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摘要集 Abstract Collection



TABLE OF CONTENTS

PLENARY LECTURES

Biodegradable Polymers: Applications in Biomedicine and Medical Fields	001
Bio-Inspired Materials, In Vitro Models, and Multiplexed Nanomedicine for Brain Regeneration: Building the Experimental Ecosystem	
Towards Transforming Neurotherapeutics	002
Artificial Intelligence for Materials Science: Transforming Research Paradigms	003
Translating research in soft materials into the clinic	004
Toxicological Effects and Safety of Biomaterials at Nanoscales	005
Engineering Inorganic Nanoparticles and Nanocomposites to Guide Cellular Behaviour	006
Multipotent Polymers for Transcytosis-enabled Active Extravasation and Penetration of Tumors: Design and Clinical Translation	007
Engineered viscoelasticity in cellular microenvironments	008

KEYNOTE SPEECHES

3D Printing of Biomaterials and Translation (ID:26003)	009
Multifunctional Biomaterials Supporting Bone and Osteochondral Tissue Regeneration (ID:26027)	010
The Power of Small: Nanodiamonds Driving Next-Generation Natural Hydrogel Composites for the Fabrication of Bone Substitutes (ID:26023)	011
Development of Covalent Targeting Therapeutics Based on <i>In Vivo</i> Click Chemistry (ID:26019)	012
Bioprinted interfacial complex constructs for advanced healthcare applications (ID:26022)	013
Engineering Advanced Biomaterials for Cancer Therapy: Toward Integrated Therapeutic and Regenerative Strategies (ID:26011) ---	014
Hyaluronan-based strategies bridging immunomodulation and musculoskeletal regeneration (ID:26017)	015
Harnessing Wound Dressing Physicochemical Properties for Chronic Ulcer Prognosis (ID:15031)	016
From Formulation to Preclinical Translation: A Bioinspired Calcium Phosphate Adhesive for Fragility Fracture Repair (ID:26025) --	017
Cell-Assembled extracellular Matrix (CAM): a true bio-material for tissue engineering (ID:26013)	018
Ultrasound-Responsive Antibacterial Materials (ID:26016)	019
Engineering Neural-like Fiber Tissues for Central and Peripheral Nerve Regeneration (ID:26024)	020
In Vivo Transport Mechanism and Clinical Translation of Drug Delivery Systems (ID:26020)	021

INVITED & ORAL

Materialomics Engineering to decode environmental cues for stem cell immunomodulation using Interpretable Intelligent Algorithms (ID:14714)	022
AI-Driven Rational Design of an Orally Administered Engineered Probiotic System for Targeted Obesity Therapy (ID:14785) ---	023
AI-guided screening of antimicrobial peptide (ID:14952)	024
Multifunctional Dendrimer Nanogels: A Versatile Platform for Next-Generation Cancer Therapy and Immunotherapy (ID:14978) ---	025
AI for biomaterials: From foundation model to closed-loop discovery of functional polymers (ID:15062)	026
Data-Driven De Novo Design of Super-Adhesive Hydrogels for Underwater Applications (ID:15070)	027
Designing Interactive Peptide Materials in Biological Systems for Controlling Immune Cell Function (ID:15099)	028
Counting three popular available wound dressings (Atrauman, N-A, and Kaltostat) with PD-U and PD-PS to enhance their physicochemical and biocompatibility properties (ID:15103)	029
A few-shot learning workflow for identification of antimicrobial peptides against <i>Acinetobacter baumannii</i> (ID:15263)	030
Advances in the field of biodegradable metals (ID:15166)	031
Sequential-Gelation Hydrogel with Spatio-Temporal Control Reshapes the Degenerative Microenvironment for Intervertebral Disc Regeneration (ID:14708)	032
Rare-Earth modified biodegradable Zn alloys with Ti alloys-level strength and enhanced osteogenesis (ID:14742)	033
Study on the degradation and metabolic behavior of an assembled magnesium alloy suture anchor (ID:14760)	034
Neutrophil-Mediated Inflammatory Response and Regulation in Zinc-Based Implants (ID:14804)	035
TWIP/TRIP metastable beta Ti and Zr Alloys for biomedical applications (ID:14817)	036

Transformation-induced strengthening and controlled degradation in Zn–Li alloys designed for bioresorbable implants applications (ID:14819) -----	037
Antibacterial Design for Medical Metal Surfaces (ID:14846)-----	038
Study on crevice corrosion behavior of biodegradable pure zinc at bone fixation interfaces (ID:14861) -----	039
Laser Powder Bed Fusion of β -metastable Ti–12Mo: processing–microstructure relationships towards high-strength TWIP/TRIP Ti for biomedical applications (ID:15015) -----	040
Built-in Electric Field-Driven Membrane Disruption in Ultrasound-Activated Dual-Vacancy Piezoelectric Heterojunctions (ID:15020) -----	041
Biodegradable Zinc-Lithium-Copper Alloys for Orthopaedic Implants (ID:15094) -----	042
Biodegradable intermetallic compounds (ID:15164) -----	043
Rinse-Triggered Thermoresponsive Dental Implant for On-Demand Biofilm Clearance and Tissue Integration (ID:15165) ----	044
Semiconductor biomaterials for antibacterial (ID:15184) -----	045
Multi-Scale Engineering of Additively Manufactured Biodegradable Zinc (ID:15185) -----	046
Biomedical liquid metal micro/nano-robots (ID:15188) -----	047
Additively manufactured biodegradable molybdenum for biomedical applications (ID:15196) -----	048
Gradient-Based High-Throughput Optimization of Titanium Implant Coatings for Enhanced Osseointegration (ID:15200) ----	049
Thermoelectric Glycyrrhizic Acid Hydrogel for Periodontitis Treatment (ID:15212) -----	050
Microwave-Triggered Co-Delivery of Heat and Nitric Oxide Platform for Long-term Treatment of Deep-Seated Infections (ID:15236) -----	051
Self-assembled copper-amino acid nanoleaves for targeted treatment of deep-seated bacterial infections via chemodynamic therapy and cuproptosis-like death (ID:15237) -----	052
Natural-Polymers Based Membranes for Bone Tissue Regeneration (ID:14844) -----	053
Navigable Wood Pulp-Based Hemostatic Sponge for Non-Compressible Hemostasis (ID:14791) -----	054
pH-Compensatory 4arm-PLGA/Sr-BG Composite Patches Mediate Immune Microenvironment for Scarless Abdominal Wall Regeneration (ID:14810) -----	055
Supramolecular Microsphere with Dynamic ECM-Mimicking Behavior Regulate iNSC Fate for Traumatic Brain Injury Repair (ID:14870) -----	056
Integrating Natural Polymers and Bioactive Molecules: From Tissue Engineering and Controlled Drug Release to Disease Modeling (ID:14918) -----	057
Design and Application of Marine Silicon-Derived Bone Repair Materials (ID:14968) -----	058
Sustainable lipid-rich biomaterial obtained via detergent-free decellularization of fish skin (ID:15034) -----	059
Photocrosslinkable Polymers for Tissue Regeneration (ID:15713) -----	060
Near-Infrared Activated Hydrogenated TiO ₂ Nanoscale Honeycomb Surface Structure for Effective Staphylococcus aureus Biofilm Elimination and Enhanced Osteogenic Performance (ID:14923) -----	061
Design of Functional Bioceramic Scaffolds for Bone Tissue Engineering (ID:14790) -----	062
Bioinspired Hierarchical High-performance Bioceramics (ID:14832) -----	063
Bio-active glass for regenerative medicine (ID:14835) -----	064
Bioelectro-adhesive coupled biomaterials for tissue regeneration (ID:14841) -----	065
Bioceramics-enhanced patch activates epicardial epithelial-to-mesenchymal transition for cardiac repair (ID:14851) -----	066
Functional Material-Enabled Wireless Electrical Stimulation for Regulation of Stem Cell Fate and Brain Injury Repair (ID:14852) -----	067
Polyphosphate-based inorganic wax with combined hemostatic and osteogenic functions for bone repair (ID:14858) -----	068
Bioprocessing-Inspired Nanoparticle-Induced Liquid Precursor Strategy for Collagen Mineralization and Dentin Repair (ID:14871) -----	069
Development of Bioceramic-based Viscoplastic Materials for Bone Hemostasis and Osteogenesis (ID:14883) -----	070
Inorganic biomaterials for innervated tissue regeneration (ID:14898) -----	071
Research on Microenvironmental Regulation by Biomimetic Organic-Inorganic Composite Materials for Tissue Repair (ID:14901) -----	072
Silicate biomaterials-induced bone marrow organoids for tissue regeneration (ID:14906) -----	073
Binary Metal Co-doped Hierarchical Layered Piezoelectric Bioceramics for the Repair of Tumor-Associated Bone Defects (ID:15168) -----	074
Construction and Application of Composites of Polysaccharides and Inorganic Nanoparticles (ID:15104) -----	075
Heterostructure in Tissue Engineering (ID:14774) -----	076
Application of Microfluidic Organ-on-a-Chip Technology in Atherosclerosis Treatment and Regenerative Medicine (ID:14786) -----	077
Spatiotemporally Designed 2D Nanoarchitected Composites as Drugless Therapeutics (ID:14856) -----	078
A Multifunctional SIS-dECM-Based Hydrogel Integrating Anti-Inflammatory Activity and Mucosal Repair for Ulcerative Colitis Therapy (ID:14863) -----	079
A 3D-Printed Stent with Polydopamine-Modified Hydrogel Coating for Enhanced Anchorage in Acute Colorectal Obstruction (ID:14865) -----	080
ECM-Derived Biomimetic adhesive Patch Regulating the Inflammatory Microenvironment to Accelerate Oral Ulcer Healing (ID:14889) -----	081
Cross-Scale Composite Imaging Bioprobes for Tumor Boundary Identification (ID:14911) -----	082
Snail-inspired Decellularized Extracellular MatrixGlycosaminoglycan Hydrogel for Wound Healing (ID:14955) -----	083
Engineered Anti-Senescence Trachea With Post-Transplanted Regenerative Homeostasis (ID:14977) -----	084

AI-assisted volumetric 3D bioprinting of vascularized full-thickness skin (ID:14986) -----	085
NIR-Programmable Stealth 2D Black Phosphorus Nano-Biointerfaces for Deep Tumor Penetration and Photoimmunotherapy (ID:14989) -----	086
Immunomodulatory Fibrous Scaffold with Dual Enzyme-Mimic Activities Prevents Postsurgical Tumor Recurrence (ID:15000) -----	087
Porous PLLA Piezoelectric Nanofibers: Fabrication and Application for In Vivo Microenvironment Modulation (ID:15035) -----	088
Piezoelectric PLLA nanofibers with sonochemical effects: A novel safe/efficient strategy for atrial fibrillation ablation (ID:15038) -----	089
Engineered human alveolar lung-on-a-chip model (ID:15089) -----	090
Multimodal synergistic anti-tumor based on Pin1-inhibiting nanocomposites (ID:15155) -----	091
Nanoenergetic Converters with Coupled Energy Cascade for On-Demand Microwave Dynamic Therapy (ID:15231) -----	092
High-resolution 3D printed hydrogels for tissue regeneration (ID:14711) -----	093
Customized Hydrogel Dressing Addresses Biomechanical Heterogeneity across Specific Wounds (ID:14741) -----	094
Hydrogel-Based Cell Mechanical Microenvironment Engineering and Mechano-therapies for Soft Tissue Regeneration (ID:14743)-----	095
Engineered coacervates as emerging liquid biomaterials (ID:14812) -----	096
Dynamic hydrogels with metal-coordination bonds (ID:14820) -----	097
Injectable extracellular matrix-like electroactive hydrogels for sequential treatment of ischemic stroke (ID:14859) -----	098
Biomedical DNA hydrogels and microgels (ID:14864) -----	099
A Robust Bio-Supportive Hydrogel Patch for Full-Thickness Repair of Gastroesophageal Defects (ID:14869) -----	100
Engineering stable unfolded protein adhesives via polyelectrolyte locking for robust and rapid tissue sealing (ID:14897) -----	101
Multiscale structure engineering of injectable hydrogels: from design to clinical translation (ID:14908) -----	102
Fast-gelling adhesive epidermal electrode for accurate physiological signal monitoring and real-time brain control flight (ID:15047) -----	103
Cygb-loaded hydrogel synergizes antioxidant-autophagy-driven neural regeneration (ID:15056) -----	104
Metabolically and Electrically Instructive Hydrogels for Spinal Cord Injury Repair (ID:15065) -----	105
Hydro/aerogels for Flexible Human-Machine Interfaces and Wearable/Implantable Therapy (ID:15073) -----	106
Chitosan-Silica Hybrid Hydrogels with Siloxane Network Formation: Chemical Control in Dual-Network Assembly (ID:15081)-----	107
Melatonin rhythm-mimicking smart hydrogel for circadian clock regulation and promotion of intervertebral disc regeneration (ID:15085) -----	108
Comparative Analysis of 2D and 3D Cell Culture Platforms: Perspective and Experimental Validation Across 33 Cell Lines (ID:15091) -----	109
Mechanical Forces from Intercellular Peptide Self-Assembly Drive Spheroid Formation (ID:15101) -----	110
An Intelligent Redox-Responsive Mn-Based NanoplatforM for MRI-Guided Disulfidptosis in Pancreatic Cancer (ID:14720) -----	111
Coordination-Driven Metallo-Supramolecular Assembly Enables Imaging-Guided Photothermal Therapy with STING Activation and IDO-Reversed Immunosuppression (ID:14732) -----	112
Bioactive nanomotor enabling efficient intestinal barrier penetration for colorectal cancer therapy (ID:14749) -----	113
Myogenic nano-adjuvant for systematic sarcopenia via mitochondrial homeostasis modulation in macrophage-myosatellite metabolic crosstalk (ID:14753) -----	114
Deep-brain magnetothermal stimulation in freely moving mice using ferrimagnetic vortex nanorings (ID:14757) -----	115
Carrier-Free Nanodrug against Bacterial Mixed Infection for Accelerated Wound Healing (ID:14779) -----	118
Wireless Piezoelectric Nanostimulator Promotes hiPSC Cardiomyocyte Differentiation and Maturation (ID:14789) -----	119
Hijacking Helicobacter pylori: trojan horse nanoparticles for gastric infection therapy (ID:14837) -----	120
Biomimetic nanomedicines with glycan modification for the enhanced treatment of pathogenic infections (ID:14839) -----	121
Por-Ca ²⁺ -ZOL Bone-Targeting Sonosensitizing Nanodrug for Synergistic Sonodynamic Therapy and Osteolysis Inhibition in Osteosarcoma (ID:14915) -----	122
Selective Induction of Cancer Cell Pyroptosis by Erbium Nanotuner Enhances Potent Anti-Cancer Immunity (ID:14956) -----	123
Small Solutions to a Big Problem: Nanotherapy Against Helicobacter pylori (ID:14969) -----	124
Disulfidptosis Mediated Immunotherapy Integrated with Neural Regeneration in Postoperative Glioblastoma (ID:15023) -----	125
Advancing microRNA Therapeutics: Nanocarrier Platforms for Mesothelioma Treatment (ID:15060) -----	126
Engineering Neuroprotection: Biodegradable Dendrimers as Delivery Vectors for Stroke Therapeutics (ID:15095) -----	127
Hierarchically Engineered Multifunctional Fe ₃ O ₄ @Au Nanoparticles with Magnetic Responsiveness and Bioactive Surface Functionalization (ID:15137) -----	128
A ROS-Responsive NanoplatforM for Discriminating and Regulating Multiple Reactive Oxygen Species in Real Time (ID:15161) -----	129
Synergistic Photothermal-Immunotherapy of Breast Cancer via Zn ²⁺ -Enhanced AUTAC Delivery for IDO Degradation (ID:15213) -----	130
UltrasMall Magnetic Resonance Probes for Precision Diagnosis of Kidney Diseases (ID:15393) -----	131
Interface/Dipole Polarized Antibiotics-Loaded Fe ₃ O ₄ /PB Nanoparticles for Non-Invasive Therapy of Osteomyelitis Under Medical Microwave Irradiation (ID:14717) -----	132
3D Bioprinting of Bone Organoids Using Bone Matrix-Inspired Bioinks for Bone Regeneration (ID:14719) -----	136
M2 macrophage-derived exosome-functionalized fibrous scaffolds regulate the foreign body response and the coupling of angio/osteoclasto/osteogenesis (ID:14724) -----	137

Mesenchymal Stem Cells and Macrophages Crosstalk for Vascularized Bone Regeneration (ID:14727) -----	138
Aqueous-responsive self-contractive and self-compressive silk screws (ID:14734) -----	139
A dynamic enhanced electrical stimulation system coordinates non-neural cells via single-input cues for neuro-vascularized bone regeneration (ID:14736) -----	140
Gradient Intrafibrillar Mineralized Collagen Scaffold Promotes Osteochondral Regeneration by Enhancing Differentiation of SCRG1 ⁺ Progenitor Cells (ID:14765) -----	141
Chiral Nanotopography Potentiate Stem Cell-Derived Extracellular Vesicles to Enhance Osteogenesis (ID:14766) -----	142
Time-Sequential and Multi-Functional 3D printing scaffold for Repairing of Challenging bone defect (ID:14778) -----	143
Multifunctional Selenium-Polyurea Coated Zinc Alloys Sequentially Orchestrate Immune-Osteogenic Microenvironment for Bone Regeneration (ID:14796) -----	144
Sequential Theragenerative Biomaterials for Postsurgical Osteosarcoma Treatment and Bone Repair (ID:14797) -----	145
Curvature–Degradation Coupling Drives Cellular Functions and Osteointegration in Additively Manufactured Biodegradable Zn-Mg Scaffolds (ID:14803) -----	146
Antioxidant Nanozymes Engineered M2-Exosomes Break the Oxidative Stress–Innate Immune Disorder Loop to Enable Diabetic Bone Regeneration (ID:14867) -----	147
Regenerating aged bone marrow via a nitric oxide nanopump (ID:14886) -----	148
Temperature-Controlled Fabrication of Bioactive Calcium Phosphate Mineralized Microgels for Minimally Invasive Bone Regeneration (ID:14900) -----	149
Ultrasound-Driven Regulation of Catalysis–Immunity via an In Situ-Doped Sonocatalyst Coating for Infectious Bone Defect Repair (ID:15039) ----	150
Dual-functional 3D-printed polyetheretherketone scaffolds with immunomodulatory nano-calcium silicate/interleukin-4 coating synergistically enhance osteogenesis through macrophage M2 polarization and NF- κ B pathway suppression (ID:15063) -----	151
GDYO@Pt-Based Schottky Engineering Promotes Cranial Bone Regeneration through Piezoelectric Stimulation and Oxidative Stress Regulation (ID:15090) -----	152
3D-printed hybrid PCL composites for osteoporotic bone regeneration (ID:15152) -----	153
A Real-World Evidence–Based China Strategy for the Treatment of Osteonecrosis (ID:15194) -----	154
Gut Microbiome–Cartilage Axis-on-a-chip to Reveal the Effect of Probiotics on Osteoarthritis (ID:14792) -----	155
AI-Engineered Exosomes Restore Chondrocyte Metabolic Activity Through Sustained Drug Release to Treat Osteoarthritis (ID:14828) -----	156
Development of Tissue-Engineered Tracheal Scaffold Based on Multi-Modified Prussian Blue Nanoparticles and Its Application in Repairing Long-Segment Tracheal Defects (ID:14890) -----	157
A Personalized Dual-Track Strategy for Meniscus Replacement: From Bioactive Resorbable Scaffolds to Functionalized Non-Biodegradable Prostheses (ID:14942) -----	159
From disease model to therapeutic insight: An engineered hydrogel reveals the role of matrix viscous dissipation in intervertebral disc degeneration (ID:14946) -----	160
3D Printed Silk Reinforced Meniscus Implant (ID:14964) -----	161
3D printing programmed diagnostic and therapeutic bioactive “all-in-one” microspheres with multistimuli responsiveness for cartilage regeneration (ID:15003) -----	162
Zinc-Modified Nanocomposite Hydrogels as Active Platforms for Irisin-Mediated Cartilage Repair (ID:15005) -----	163
Kartogenin-loaded Aminated Hollow Mesoporous Prussian Blue Nanozyme-reinforced Hydrogel Remodels Senescent Microenvironment via ROS Scavenging and STING Inhibition to Promote Cartilage Regeneration (ID:15045) -----	164
Continuous mechanical-gradient scaffold with on-demand distributed Mn ²⁺ /Mg-HA@Fe ₃ O ₄ for osteochondral repair (ID:15059) -----	165
Bioactive 3D Printing Bioink Enabling Personalized Tissue Defect Repair (ID:15098) -----	166
Manipulating neural cell behaviors and their niche via injectable, photothermally welded 3D nanofibrous microspheres for neuroid tissue construction (ID:14937) -----	167
Bridging immune-neurovascular crosstalk via the immunomodulatory microspheres for promoting neural repair (ID:14759) -----	168
Mechanical and Bioactive Adhesive Hydrogels Facilitating Transected Peripheral Nerve Regeneration through AKT Pathway Modulation (ID:14776) -----	169
A biodegradable and restorative peripheral neural interface for the interrogation of neuropathic injuries (ID:14801) -----	170
Promoting retinal ganglion cell regeneration with targeted liposome-based delivery of MHY1485 for optic nerve repair(ID:14873) -----	171
Interface-Optimized 3D-Bioprinted Neural Constructs with Coordinated Mechanical Compatibility and Electrical Coupling for Spinal Cord Injury Repair (ID:14951) -----	172
A Hematoma Microenvironment-Responsive Keratin Nanosystem for Synergistic Neuroprotection and Repair after Intracerebral Hemorrhage (ID:14965) -----	173
3D Bioprinted Functional Living Nerve-like Construct for Spinal Cord Injury Regeneration (ID:14970) -----	174
Bio-orthogonal Engineered Chitosan Platform for Enhanced Mesenchymal Stem Cells Delivery and Function in Peripheral Nerve Repair (ID:15007) -----	175

Targeting VEGFR2 inhibition within a spatially-confined conduit promotes nerve self-resolution and alleviates mechanical allodynia (ID:15179) ----	176
Nerve-bone crosstalk in response to bone-guided biomaterials (ID:15643) -----	177
Tailored Endothelialization with Cell Membranes Accelerates Remodeling of Small-diameter Vascular Grafts (ID:15204) -----	178
A Redox-Active and Electroactive Hydrogel for Post-Infarct Myocardial Repair (ID:14751) -----	179
Bioresorbable Bead for Transient Embolization in Knee Osteoarthritis: In Vivo and In Vitro Evaluation (ID:14777) -----	180
Functional surface design strategies for accelerating endothelialization (ID:14782) -----	181
Bioengineering cardiomyocytes with biophysical instructive cues and macrophages crosstalking (ID: 14788) -----	182
A novel biomimetic nanofibrous cardiac tissue engineering scaffold with adjustable mechanical and electrical properties based on poly(glycerol sebacate) and polyaniline (ID:14833) -----	183
Myofibroblasts drive early vascular graft failure in hyperlipidemia (ID:15048) -----	184
Role and regulation of lipid-handling smooth muscle cell subtype in vascular grafts (ID:15050) -----	185
Fabrication and performance of biodegradable self-powered small-diameter vascular grafts (ID:15076) -----	186
Balloon-Mediated In-situ Biomimetic Photo-crosslinking (BMIBP) for Stent-Free Vascular Remodeling (ID:15083) -----	187
Balloon-mediated Endovascular Adhesive Tape (BEAT) for Improving Vascular Regeneration (ID:15092) -----	188
Suture-free biomimetic polymeric venous valves for peripheral interventional therapy (ID:15162) -----	189
Plaque-specific Adhesive Balloons Coated with Calcium Phosphate Nanoparticles Loaded with Rapamycin for Atherosclerosis Therapy (ID:15242) -----	190
Iron Oxide Nanoprobes and Clinical Translation (ID:14746) -----	192
Engineering nuclear medicine imaging probes: Radiolabeling strategies, pharmacokinetic profiling, and ratiometric functional sensing (ID:14715) ---	193
ROS-responsive Nanoplatforms for Atherosclerosis Photoacoustic Diagnosis and Endothelial Cell-Macrophage Crosstalk Regulation (ID:14794) -----	194
A Tunable Alginate-Decellularized ECM Hybrid Hydrogel for Modulating Mammary Epithelial Cell States (ID:14847) -----	195
Construction of Bioactive Materials for Cancer Immunotherapy (ID:15042) -----	196
Near-infrared-II-driven Z-scheme heterojunction for dual-mode imaging guided tumor synergistic therapy (ID:15057) -----	197
Dynamic MPI Visualization of PD-L1 Expression to Optimize Gemcitabine and Anti-PD-L1 Combination Therapy in Pancreatic Cancer Organoids and Orthotopic Models (ID:15067) -----	198
A Bio-imaging Guided Multifunctional Hydrogel for Postoperative Photothermal therapy in Pancreatic Ductal Adenocarcinoma (ID:15077) -----	199
Biomimetic electrical microenvironment on PVTF and its effects on osteogenesis (ID:15046) -----	200
Multimodal defect-rich nanoreactor triggers sono-piezoelectric tandem catalysis and iron metabolism disruption for implant infections (ID: 14740) -----	201
Clinical-Translatable Interface Design for Degradable Magnesium Implants: A Composite Coating to Coordinate Early Stability and Late-Stage Resorption (ID:14758) -----	202
H2-Mediated Regulation of the Inflammatory Microenvironment via a Poly(lipoic acid)-Based Coating on Titanium Implants (ID:14793) -----	203
Surface engineering NiTi alloy with tunable wettability for optimized cellular response in cardiovascular applications (ID:14811) -----	204
Layer-by-Layer Polyelectrolyte Surface Coatings for Cardiac Applications: Physicochemical and Biological Evaluation (ID:14813) -----	205
Integrated immunotherapy for infectious trauma (ID:14848) -----	206
Fabrication of Novel Antibacterial PEO Coatings on Biomedical Pure Mg and Investigation of Their Degradation and Antibacterial Properties (ID:14947) -----	207
Functionalizing Implant Surfaces/Interfaces for Bioadaptive Modulation of the Bone Implantation Microenvironment (ID:14958) --	208
ROS-Responsive Titanium Implant Coatings Enhance Osteoporotic Osseointegration via Microenvironment Remodeling and Mitochondrial Repair (ID:15001) -----	209
Electron Pump and Photon Trap Effect-Derived Selective Antitumor of Fe-Ppy@CaO ₂ -Modified PEEK for Bone Tumor Therapy (ID:15084) -----	210
Nano-interfacial Engineering on Biomaterial and Their Diverse Biomedical Applications (ID:15183) -----	211
An Immunocompatible Conductive Hydrogel via Anion- π Interlocking as an Injectable Bridge for Sustained Bioelectronic Interfacing (ID:15206) -----	212
Immunocompatible interface material for implantable devices (ID:15211) -----	213
Instant Bioanalysis (ID:15190) -----	214
A Novel Strategy for Immunological Evaluation of Recombinant Collagen Medical Devices from a Regulatory Science (ID:15408) -----	215
Study of malignant phenotypes and acquired chemoresistance via tumor organoids in the biomimetic matrices (ID:14729) -----	216
A Fiber-Based Closed-Loop Theranostic System for Real-time Biomarker Monitoring and On-demand Gas Therapy (ID:14822) ----	217
3D Artificial Skin Model as a Novel Strategy for the Diagnosis of Amyotrophic Lateral Sclerosis (ID:14974) -----	218
Tailor-Made Metal-Organic Frameworks via Molecular Engineering for Selective Recognition and Extraction of Bilirubin from Liver Failure Patients' Blood (ID:15030) -----	219
Study on pre clinical evaluation method of absorbable PLLA/HA bone fixation device based on degradation activity coupling analysis(ID: 15072) -----	221

Functional iron oxide nanoparticles cross-linked hydrogel for craniofacial bone regeneration (ID:14722) -----	222
Therapeutic Effects and Mechanisms of Mesenchymal Stem Cell-Derived Exosomes in Regenerative Dentistry (ID:14728) -----	223
3D-Architected Scaffolds Derived from Extracted Natural Teeth for Alveolar Bone Reconstruction (ID:14755) -----	224
Antimicrobial, Remineralization, And Infiltration: Advanced Strategies For Interrupting Dental Caries (ID:14917) -----	225
Clinically Informed Photothermally Activated Nanoplatform Rejuvenates the Senescent Microenvironment for Periodontal Regeneration (ID:14966) -----	226
Bioactive Dentin Scaffolds as a Driver for the Osteogenic Commitment of CGF Cells (ID:15012) -----	227
Mastication-induced electrical stimulation activates Prg4 ⁺ chondroprogenitors for osteoarthritis therapy (ID:15178) -----	228
Chrono-Controlled Biomaterial Platforms for Mitochondria-Targeted Cuproptosis and Immuno-Metabolic Cancer Therapy (ID:14738) ----	229
IL-10 immunotherapy for mouse MASH disease via Lipid nanoparticles delivery system (ID:14764) -----	230
Near-Infrared Photothermal-Responsive Drug Delivery Hydrogel Based on Zero-Dimensional Peptide Nanobundles Composite PEG in Antitumor Research (ID:14818) -----	231
Lipid nanoparticle-mediated selective modulation of M2 macrophages for improved cancer immunotherapy (ID:14821) -----	232
Inhalable Ce nanozyme-backpacked phage aims at ischemic cerebral injury by M1-microglia (ID:14831) -----	233
Engineering pirfenidone-loaded silk fibroin hydrogels to prevent fibrosis recurrence through sustained, site-activated drug release and ECM remodeling across 2D and 3D models (ID:14840) -----	234
Smart Dendrimer Nanogels Boost mRNA-Based Cancer Therapy via Synergistic Glycolysis Inhibition and Immune Activation (ID:14924) ----	235
Dual-drug loaded electrospun scaffolds serving as breast implant coatings (ID:15027) -----	236
A dual-sensitive nanogel for spatiotemporal co-delivery of aPD and GSK3787 to enhance ICB therapy (ID:15037) -----	237
Pressure-driven microinjection (PMI) of porous-coated balloon for ultrafast endoluminal drug delivery across biological barriers (ID:15043) ----	238
Targeted Protein Degradation (ID:15044) -----	239
Tumor microenvironment targeting for glioblastoma multiforme treatment via hybrid cell membrane coating supramolecular micelles (ID:15054) ----	240
Cationic lipid-modified PEG-PLGA nanoparticles facilitate effective dendritic cell reprogramming to alleviate T cell-mediated autoimmunity in EAE (ID:15058) -----	241
Breaching Intracellular Barriers: Biomaterial Interface Design for Smart drug delivery (ID:15157) -----	242

POSTER

Bioactive Magnesium Incorporated Biomaterials for Bone Defects Repair (ID:14845) -----	243
Mechanochemically-reprogrammed stem cell exosomes reconcile the biogenesis-internalization trade-off to resolve pulmonary fibrosis (ID:14935) -----	244
Constructing targeted organic nanoparticles via supramolecular pre-assembly guided disulfide exchange polymerization (ID:15061) ----	246
Additively Manufactured Magnesium Alloy Scaffolds with Tailored Degradation Kinetics for Bone Defect Repair (ID:15172) -----	247
Study on the Photothermal-Immunological Synergistic Therapeutic Effects of IFN- γ Aptamer-Modified Silk Fibroin Hydrogel for Diabetic Wounds (ID:15377) -----	248
Nanodots-mediated mitochondrial biogenesis intervening fibroblasts senescence for idiopathic fibrotic pulmonary therapy (ID:14814) -----	249
Trigger and Purge: A Pyroptosis-Senescence Coupling Strategy Followed by Senolytic Clearance for Colorectal Cancer Therapy (ID:14815) ----	250
Mechanism Study of Magnesium Alloy Endothelialization-Promoting Coating (ID:15160) -----	251
Metabolic osteoimmune biodegradable Zn-Mn alloys: high strength-ductility and in situ ascular-osteogenic coupling (ID:15174) ----	252
Bio-Integrated Core-Shell Textiles for Passive Radiative Cooling and Self-Powered Thermoelectric Antibacterial Protection (ID:15246) -----	253
A Novel Strategy for Achieving Immunomodulation and Osseointegration of Titanium Alloys: Boron-Doped Porous Coating Modification (ID:15290) -----	254
Osseointegration enhanced by the Ca-P absorption function of Zr element in the Mg alloy (ID:15299) -----	255
Two-dimensional FeCu-Metal-Organic-Framework Boosts Peroxidase Activity for Antibacterial Application (ID:15446) -----	256
Zn ion-implanted absorbable Fe for accelerated degradation and mitigated neointimal hyperplasia (ID:15458) -----	257
Antibacterial Efficacy and Molecular Mechanisms of Cobalt Porphyrin-Mediated Sonodynamic Therapy Against Anaerobic Bacteria (ID:15460) -----	258
Engineering An Ultrathin, Self-Assembled Supramolecular Coating for Long-term Corrosion Modulation of Biodegradable Mg (ID:15465) ----	259
Potential of Biodegradable Magnesium Alloys for Large Bone Defects Treatment (ID:15581) -----	260
Bioinspired Fibrin-Trapping Microspheres Enable Supra-Physiological Clot Formation under High-Pressure Hemostasis (ID:14730) -----	261
A Biodegradable Janus Sponge for Negative Pressure Wound Therapy (ID:14731) -----	262
Development of a Novel Biodegradable and Self-Lubricating Double-J Ureteral Stent (ID:14737) -----	263
Achieving Superadaptive Vascular Occlusion with Deformable Microspheres: An Ethanol-Triggered Embolization System (ID:14762) -----	264
Synthesis and Applications of Supra-Natural β -Sheet-Based Polypeptides (ID:15244) -----	265

Silk-Protein-Based Smart 3D Printing Manufacturing (ID:15324) -----	267
Tailored Biodegradable Copolymers with Random-Block Architecture for High-Performance Absorbable Tissue Ligation Clip (ID:15373) -----	269
Injectable ROS-Scavenging Porous α -Tocopheryl Succinate-Loaded PPDO Microspheres for Immunomodulatory Soft-Tissue Remodeling (ID:15476) -----	270
Latent Photodegradable Polyesters Enabled by Nitrobenzyl-Based Triggers for Controlled End-of-Life Behavior (ID:15495) -----	271
Construction of Bioactive Glass Composite Coating and Its Application in Bone Repair Research (ID:14931) -----	272
Multifunctional Hollow Manganese Silicate Nanoparticles for the Treatment of Acute Lung Injury and <i>Pseudomonas aeruginosa</i> Pulmonary Infection (ID:14997) -----	273
Preparation and Properties of Bioinspired Bone Repair Materials (ID:15075) -----	274
A hydrogel engineered with semiconductive MnPSe ₃ nanosheets as an integrative sonosensitizer/Fenton-like catalyst/nutrient for melanoma postoperative care (ID:15385) -----	275
A Senescent Metabolism-Targeting Hierarchical Scaffold Restores NAD ⁺ Homeostasis and Redox Balance for Aged Bone Repair (ID:15386) -----	276
Engineering Metal-Organic Framework System for Light-Free Antibacterial Photodynamic Therapy (ID:14912) -----	277
Coordination Self-Assembled Nanoplatfor for Augmented Photothermal/Chemodynamic Therapy and Antimetastatic Immunity (ID:15443) -----	278
Double-layer electrospun membrane with antibacterial, anti-inflammatory, and antioxidant functions for tendon injury repair (ID:15512) -----	279
A Therapeutic Strategy Integrating Ultrasound-Guided Microwave Ablation with Nanocomposite Hydrogels to Enhance Autophagy and Suppress Tumor Growth in Hepatocellular Carcinoma (ID:14748) -----	280
Biodegradable Janus sonozyme with continuous reactive oxygen species regulation for treating infected critical-sized bone defects (ID:14750) -----	281
Deep Eutectic Solvent-Enabled Network Pre-Organization for Time-Programmable 4D Eutectogels in Articular Cartilage Repair (ID:14768) -----	282
Tannic Acid-Enhanced Polyacrylamide/Hyaluronic Acid (TA@PAM/HA) Dual-network Hydrogel Patches for Repairing Annulus Fibrosus Defects After Discectomy (ID:14773) -----	283
Poly(ectoine)-Based Adhesive Hydrogel with Antimicrobial and Anti-Inflammatory Properties for Wound Treatment (ID:14775) ----	284
An Ultra-Tough Bone Adhesive as Potential Clinical Solution for Complex Fracture Fixation and Healing (ID:14787) -----	285
Ultra-Robust Ionic Biogel Enabled by Multiscale Structural Design of Silk Fibril Reinforcement and DES-Induced Synergy (ID:14919) -----	286
Body fluid-triggered adhesive hydrogels for emergency hemostasis and alveolar regeneration (ID:14976) -----	287
Assembly of a hierarchical hydrogel-based biomaterial for suppressing the neo-vascularization of the nucleus pulposus (ID:15033) -----	288
Piezoelectric Injectable Anti-adhesive Hydrogel to Promote Endogenous Healing of Tendon Injuries (ID:15195) -----	289
Biodegradable hydrogel adhesives based on o-phthalaldehyde-amine crosslinking for rapid wound closure and hemostasis (ID:15389) -----	290
Dynamic GelMA-UPy Bioinks for Multimodal 3D Bioprinting (ID:15416) -----	291
Ultra-robust Silk-based Eutectogels Engineered via Polymeric Reconstruction and Supramolecular Network Reinforcement (ID:15488) -----	292
A Mild Base-Free SuFEx Strategy for β -Sultams Construction (ID:15497) -----	293
Injectable Nanoparticle-Glycopeptide Composite Hydrogel Regulates Macrophage Polarization for Anti-Inflammatory Therapy via Oxidative Stress Alleviation and Metabolic reprogramming (ID:15521) -----	294
Powering STING and Reversing IDO: A Metallo-Supramolecular Nanoplatfor for Imaging-Guided Photothermal Tumor Immunotherapy (ID:14733) -----	295
Inhalable Nanovaccine Based on Bioengineered Bacteria-Derived Membrane Vesicles Against Lung Metastasis (ID:14781) -----	296
Engineering M2 macrophage-derived exosomes modulate activated T cell cuproptosis to promote immune tolerance in rheumatoid arthritis (ID:14903) -----	297
Polymer-Grafted Liposomes to Overcome Drug Resistance in Triple-Negative Breast Cancer: Insights from an Orthotopic Model (ID:15240) -----	298
A cascade enzyme system based on the catalase-like activity of Co-MQDs for enhanced visualized tumor combination therapy (ID:15442) -----	299
Dual Antibiotics-Based pH-Responsive Carrier-Free Nanodrug against Bacterial Mixed Infection for Accelerated Wound Healing (ID:15457) -----	300
Macromolecular MRI Contrast Agent Based on Polyaspartic Acid-grafted-Dopamine Polymer and Its Application in Animal Studies for Noninvasive Assessment of Renal Injury (ID:15470) -----	301
DLP-Printed Scaffold Based on Natural-synthetic Polymers for Bone Regeneration (ID:14784) -----	302
Pre-vascularized poly (ether- ketone -ketone) scaffold mediates vascular-bone coupling regeneration (ID:14800) -----	303
Metabolic-engineered probiotic-OMV as nanovaccine mediating sequential immunomodulation for chronic bone infection immunotherapy (ID:14834) --	304
3D-printed Strontium-incorporated β -TCP Bioceramic Triply Periodic Minimal Surface Scaffolds with Enhanced Angiogenic and Osteogenic Properties (ID:14850) -----	305
Multi-scale Engineering of Biodegradable Zn-Based Porous Fusion Cages via Additive Manufacturing for Improved Load-bearing Ability and Spinal Fusion (ID:14905) -----	306
An All-in-One Microenvironment-Responsive Multifunctional Enzyme-Linked Hydrogel for Diabetic Bone Defects Regeneration (ID:14913) -----	307
Injectable Calcium Phosphate as a Bioactive Platform for Osteogenic and Anti-Inflammatory Modulation in Osteoarthritis (ID:14973) -----	308
Chitosan/Hydroxyapatite Nanocomposite Scaffolds for Targeted Osteoarthritis Therapy through Immunomodulatory Mechanisms	

(ID:15151) -----	309
A spatiotemporally adaptive scaffold coordinating sequential osteosarcoma clearance and bone regeneration (ID:15285) -----	310
Diabetic and nondiabetic BMSC–derived exosomes affect bone regeneration via regulating miR-17-5p/SMAD7 axis(ID:15396) -----	311
Re-Editing the Bone Metabolic Niche with a Cascade-Catalytic Scaffold to Boost Repair via Enhanced Mitochondrial Bioenergetics and Osteoimmunomodulation (ID:15399) -----	313
Regulation of Molecular and Supramolecular Chirality on Osteogenic Differentiation in Biomimetic Microenvironment (ID:15445) -----	314
PT1-Loaded Targeting System for Regulating Bone Defect Repair in Femoral Head Necrosis (ID:15485) -----	315
Responsiveness of diabetic mesenchymal stem cells to advanced glycation end products and to the antioxidant effect of N-Acetylcysteine (ID:15490) -----	316
AI-Empowered Bone Organoid Fabrication:Principles and Applications (ID:15502) -----	317
EXO/Hydrogel System for Sequential Regulation of Endogenous Hyaline Cartilage Regeneration (ID:14709) -----	318
Multimodal Mechanoadaptive Artificial Synovial Fluid Drives In-Situ Engineering of Anti-Pyrototic Extracellular Vesicles to Arrest Preclinical Osteoarthritis (ID:14752) -----	319
Construction of a Smart Biomaterial Scaffold for Piezoelectric Regulation of Stem Cell Fate and Its Application and Mechanism in Tracheal Regeneration (ID:15257) -----	320
Viscoelastic polyurethane based on subject object interaction for temporomandibular joint disc repair (ID:15261) -----	321
Preparation and Performance Characterization of Multifunctional Tissue Repair Bioink Loaded with Cell Membrane Vesicles (ID:15520) -----	322
Ferromagnetic nanoparticles enhance the piezoelectric effect of silk fibroin scaffolds to promote osteochondral repair (ID:15029) ---	323
Hierarchical Fiber-Hydrogel Nerve Guidance Conduits with Spatially Programmed Phage Nanofibrillar Ligands Promote Peripheral Nerve Regeneration (ID:15284) -----	324
Transdermal NIR-II Photothermal Neuromodulation Combined with Metabolite-Mediated Immunoregulation for Deep Nerve Regeneration (ID:15401) -----	325
Label-Free Raman Microscopy Identifies Neuronal Internalization of PMMA Nanoparticles in a Microfluidic Platform (ID:15644) -----	326
Harnessing High Glucose Stress-Primed HUVECs-EVs:Microgel Delivery of Enriched Regenerative Cargo for Diabetic Flap Repair (ID:14769) -----	327
3D bioprinted vessels from peripheral blood:reinforced fibrin bioinks containing human endothelial progenitors-derived cells (ID:15016) -----	328
Accelerated Degradation Behavior of Biodegradable Vascular Stents in a Biomimetic Fluid Field (ID:15413) -----	329
Mechanically Adaptive Injectable Adhesives for Endovascular Embolotherapy (ID:15483) -----	330
Conductive Microneedle Patch Based on the Multi-dimensional Synergy of “Matrix Homeostasis-Electrical Coupling-Vascularization” for Ameliorating Ventricular Remodeling:Effects and Mechanisms (ID:15507) -----	331
Gas-Boosted Ca ²⁺ -Mediated Tumor Microenvironment Remodeling for Enhanced Sonodynamic Therapy and Osteosarcoma Cancer Treatment (ID:14721) -----	332
STAT3 interference-driven nanomodulators reverse lipid metabolism-associated chemoresistance and potentiate metalloimmunotherapy in breast cancer (ID:14885) -----	333
Carrier-Free Nano-PROTACs Enhance Tumor Therapy:Targeted Degradation + Photodynamic-Immunometabolic Effect (ID:14930) -----	334
CPIB- from light energy to chemical substance activating the immune microenvironment to treat tumor (ID:15053) -----	336
A Copper-Avicularin Nanoassembly Triggers Cooperative Cuproptosis, Disulfidptosis and Ferroptosis for Potent Tumor Suppression (ID:15071) -----	337
Highly Sensitive In Situ SERS Microneedle Probes (AuNPs/PMMA) for AChE Diagnostics (ID:15228) -----	338
Engineered sEVs promotes ECM1 degradation in TNBC (ID:15229) -----	339
Electro-nanoautopsy:a nanoscale approach to imaging intracellular structures and biomaterials (ID:15467) -----	340
Bead-on-String Non-metallic Nanoprobes with Enhanced Magnetic Resonance Imaging Sensitivity for Imaging-Guided Therapy of Colitis (ID:15506) -----	341
CD47-Targeted Liposomal Chemotherapy Upregulates CD47 Expression and Induces Microsatellite Instability to Enhance Cancer Immunotherapy (ID:15516) -----	342
Effect of different high-pressure gases on the crystallization behavior of polylactic acid stereocomplex crystallites and homo-crystallites (ID:15241) -----	343
Robust and Multifunctional Biogels Derived from Natural Proteins Engineered via Silk Nanofibril Reinforcement and Swelling-Assisted Solvent Enhancement (ID:15450) -----	344
A Dual-layer Electrospun Membrane for Islets Encapsulation and Transplantation to Treat T1D (ID:15453) -----	345
All-Peptide Zwitterionic Hydrogel Dressings for Diabetic Wound Therapy (ID:15466) -----	346
In Vivo NMR Relaxation Study of Human Skin:the Effect of Moisturization (ID:15515) -----	347
Peptide Amphiphile-Mediated Assembly and Fusion of Anisotropic Amorphous Particles for Enamel Remineralization (ID:14754) -----	348
Spatiotemporal-adaptive Magnetoelectric Hydrogel Promotes Scarless Wound Healing (ID:14860) -----	349

EGCG-Zn Metal-Polyphenol Network for Periodontitis Microenvironment Remodeling and Bone Regeneration (ID:14879) -----	350
Mechanistic study of stress-relaxing amyloid-like hydrogels in promoting bone regeneration through the mechanical and biochemical synergistic remodeling of the periodontal pathological microenvironment (ID:14921) -----	351
Piezoelectric Nanofibers Synchronize Mitochondrial Dynamics and Immune Responses for Regeneration of Infected Wounds (ID:15214) -----	352
A Study on the Regulation of Osteogenic Properties of A Magnetically Coupled CFO@BFO/ β -TCP Composite Scaffold (ID:15243) -----	354
Water in Dentin Bonding (ID:15336) -----	355
Magnetoelectric Responsive CFO-BFO Core-Shell Nanoparticles Modulate Macrophage Reprogramming for Superior Infected Periodontal Tissue Regeneration (ID:15438) -----	356
In vitro cytocompatibility, antibacterial properties, and hemocompatibility of MAO-Zn/PLA composite films for potential guiding bone regeneration (ID:15452) -----	357
Tuning zinc oxide Nanostructures on PLLA Piezoelectric Nanofibers for Self-Powered Infection Control and Oral Mucosal Regeneration (ID:15481) -----	358
Synergistic Therapeutic Mechanisms of GelMA Microneedle-Delivered Ce6-HA-Fe ₃ O ₄ Nanoparticles for Oral Squamous Cell Carcinoma (ID:14816) -----	359
Phenylboronic Acid-Modified Polyvinylamine for Efficient Intracellular Protein Delivery (ID:14853) -----	360
Stress-trained microalgae robots with probiotics backpack and intestinal brake for inflammatory bowel disease management (ID:14866) -----	361
Hydroxylated dendrimer nanogels co-deliver drugs and cytokines for chemimmunotherapy of glioma (ID:14928) -----	362
Biomimetic Exosome-Camouflaged pH-Responsive Dendrimer Nanogels as a Therapeutic Vaccine against Pancreatic Cancer through Reprogramming of Multiple Cell Types (ID:14941) -----	363
Modified Chitosan Hydrogel Enables Non-Invasive Targeted Delivery of Collagen-Polyphenol Complex for Basal Layer Repair of Thin Endometrium and Fertility Restoration (ID:15143) -----	364
Efficient Synthesis of Protein-Polymer Conjugates with Open-Air Fabrication and Facile Purification Driven by the Thermoresponsive Protein-Polymer Conjugate (ID:15296) -----	365
Butyrate-Conjugated Dual-Responsive Polymeric Nanoplatform for Colon-Targeted Drug Delivery and Enhanced Therapy of Inflammatory Bowel Disease (ID:15365) -----	366
Directional Microinjection Driven by Porous Metamaterials for Robust and Conformal Drug Delivery in Deep Tissues (ID:15433) -----	367
Polyphenol Polymer/Cationic Hydroxyethylcellulose Nanocomplexes for Anti-Breast Cancer Effects (ID:15472) -----	368
Mitochondria-targeted Cationic Hydroxyethylcellulose Gene Delivery System for Cancer Therapy (ID:15473) -----	369
Dendrigrated Poly-L-Lysine modified hydroxyethyl cellulose for non-viral gene delivery (ID:15474) -----	370
Curcumin polymer-decorated cationic hydroxyethylcellulose nanocomplexes for lung cancer therapy (ID:15477) -----	371
Hyaluronic Acid-Modified LNPs Utilize Neutrophil Hitchhiking for Targeted Treatment of Bone-Metastatic 4T1 Tumors (ID:15480) -----	372
Bilayer Microneedles Patch Potentiate Methotrexate Therapy in Psoriasis via Hypoxia/ROS Microenvironment Remodeling (ID:15489) -----	373
Click-Crosslinked Hyaluronic Acid Dressings Incorporating an SDF-1 Mimetic Peptide Enable Concurrent Recruitment of hMSCs and mMSCs for Improved Wound Healing (ID:15494) -----	374
Dual-Aggregation-Enhanced Photodynamics of NIR-II Photosensitizer for Targeted Therapy of Mucosal Mycoses (ID:15500) -----	375
Bioorthogonal PROTAC-Mediated Protein Degradation to Modulate Macrophage Phenotype and Lipid Metabolism for Atherosclerosis Therapy (ID:15505) -----	376

Biodegradable Polymers: Applications in Biomedicine and Medical Fields

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Poly(lactic acid) (PLA) and poly(-amino acid) (PAA)-based absorbable polymers can be completely degraded in the human body into lactic acid or amino acids, exhibiting excellent biosafety. Our research group has developed a series of PLA materials with controllable microstructures via the ring-opening polymerization (ROP) of lactide. We have also synthesized a series of PAA materials through the ROP of N-carboxyanhydrides (NCA) derived from amino acids. Using PLA as the raw material, we have developed Class III medical devices including absorbable fracture internal fixation devices, artificial bone, and aesthetic microspheres, obtaining 6 NMPA medical device registration certificates. Employing PLA or PAA as drug carriers, we have pioneered novel tumor-targeted drug delivery strategies, such as chain self-amplifying drug release, coagulation-hypoxia dual targeting, and ultrasound-activated prodrugs. These strategies have enhanced therapeutic efficacy while reducing adverse effects. Furthermore, we have developed PLA and PAA based delivery systems for vaccines mRNA, which achieved significant efficacy in tumor immunotherapy as well as virus-infection prevention. Several delivery systems are in pre-clinical evaluation.

Bio-Inspired Materials, In Vitro Models, and Multiplexed Nanomedicine for Brain Regeneration: Building the Experimental Ecosystem Towards Transforming Neurotherapeutics

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The brain is one of the most challenging tissues for therapeutic intervention due to its extreme cellular specialization, limited intrinsic regenerative capacity, and tightly regulated barriers that restrict access to neural tissue. Neuroprotective strategies continue to be challenged by the need to intervene early in rapidly evolving pathological microenvironments, while repair efforts face the complex interplay between neurons, glial populations, vascular components, and extracellular matrix architecture that is profoundly disrupted after injury or disease. Unlike peripheral tissues, the CNS lacks robust mechanisms for axonal regrowth and remyelination, and damage often triggers maladaptive responses - such as inflammation, gliosis, and altered metabolic signalling - that further compromise function. Traditional drug delivery approaches are insufficient to navigate these multifactorial constraints, and current in vitro and in vivo models struggle to capture the biological context needed to evaluate therapeutic mechanisms with precision. As a result, advancing brain regeneration demands not isolated solutions, but integrated technological ecosystems capable of controlling microenvironments, guiding cellular behaviour, and coordinating molecular interventions across multiple spatial and temporal scales.

At the nanoBiomaterials for Targeted Therapies Group, we have been exploring "smart" biomaterials, designed at the nanoscale with controlled architectures and functionalities, to provide, in situ and in a targeted manner, the signals required to promote nervous tissue repair and restore function.

Building on this foundation, we are advancing bio-inspired biomaterials that recapitulate key features of the brain extracellular matrix, using tailored polymer chemistries¹ and controlled architectures² to recreate the biochemical and biophysical cues that guide neural and glial behaviour. By engineering microenvironments that mimic the composition, softness, anisotropy, and signalling landscape of native brain tissue, we aim to identify new molecular and cellular targets that emerge only when cells are placed in more physiologically relevant contexts. These same platforms enable the testing of novel therapeutic candidates under conditions that more accurately reflect the remodelling, remyelination, and inflammatory dynamics of the injured CNS, as demonstrated by our bioengineered astrocyte-oligodendrocyte in vitro models. In parallel, we are developing multiplexed nanomedicine systems, including fully biodegradable dendritic carriers and self-assembled multi-siRNA nanocaged architectures, capable of delivering combinations of nucleic acids with spatial and temporal precision. These nanoscale systems allow us to modulate multiple pathways simultaneously, ranging from neuroprotection to neuroregeneration, creating more efficient and synergistic strategies to drive functional regeneration in the brain.

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Artificial Intelligence for Materials Science: Transforming Research Paradigms

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Materials science has been facing the problems of high system complexity, low degree of data standardization, and long research chain, which also reveals the limitations of the traditional research paradigm. AI technology is good at handling high-dimensional and multi-scale data, and is able to discover the complex correlation between parameters, which provides a possible solution to the current dilemmas of materials science research.

In this report, we demonstrate that AI technology may transform the materials research paradigm combining data-driven and AI-driven approaches. Based on our work, this new paradigm is defined by three key sub-paradigms: We see the Foundation as a Deep Fusion of Data, Models, and Compute.^[1] The Core Methodology is a Symbiotic Drive of Data and Knowledge. And the ultimate Goal is End-to-end Materials Development. This trinity is what truly forms the new paradigm for our field. AI may be able to bring a new future for materials science research that is “without clear understanding” but fast-moving.

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Translating research in soft materials into the clinic

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Abstract

Soft matter is widely used in medicine, in products ranging from eye drops and topical ointments to injectable delivery systems. These materials are often designed to act as inert carriers or to provide a specific physical function, such as lubrication or barrier formation. In this talk, I will describe how the properties of simple hydrocolloids can be engineered to move beyond passive roles, enabling them to exhibit added biological functionality and, in some cases, to actively participate in processes such as wound healing.

The lecture will show how subtle control over polymer chemistry, structure, and assembly across multiple length scales can be used to tune interactions with cells, tissues, and biological fluids, thereby creating materials that modulate inflammation, support tissue repair, or enhance drug residence time. Drawing on examples from ophthalmology, wound care and mucosal delivery, I will illustrate how these concepts have been translated into clinically used products — including the nasal and oral barrier sprays that are now available internationally.

The journey from a laboratory observation to a regulated, clinically-deployed product is rarely linear. It demands sustained interplay between fundamental science, formulation engineering, regulatory strategy, manufacturing scale-up and clinical evaluation. A central theme of the talk will therefore be the importance of defining intended use and clinical claims at an early stage, as these fundamentally determine regulatory classification, development strategy and routes to market. Drawing on more than fifteen years of work at the University of Birmingham — and on the five products we have taken from concept through to first in human trial — I will reflect on how scientific design, regulatory planning and commercial strategy must be developed in parallel to maximise the likelihood of successful translation.

I hope to leave the audience with a candid picture of both the scientific opportunities and the operational realities of taking a soft material from the laboratory bench to the clinic, and to highlight where stronger collaboration between academic groups, hospitals and industry can accelerate progress for patients.

Toxicological Effects and Safety of Biomaterials at Nanoscales

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Most nano-biomaterials are the particulate forms that are self-assembled from atoms' aggregates, ions' aggregates, or molecules' aggregates. The aggregation makes their chemical activities, biological or toxicological effects of the nanoscale particulates show big difference from their original forms as atoms, ions or molecules, respectively. Biomaterials at nanoscales have been rapidly developing and applying in the clinic. However, Nanotoxicology integrates fundamental chemical or biomaterial principles with biological insights to elucidate the mechanisms underlying the toxicological effects of materials at nanoscales. As a rapidly evolving frontier in biomaterials and nanomedicines, nanotoxicology has reshaped our understanding of toxicity, with broad implications across toxicology, biomaterials, medicine, and drug delivery, etc. This talk aims to expand the boundaries of classical toxicology by addressing the mechanisms underlying toxicological phenomena of biomaterials at nanoscales, we discuss our recently uncovered underlying mechanisms in vivo, like size-effect, surface-effect, interface-effects, the ETR effects in ADME, target molecules, metabolic dynamics, penetrating bio-barriers, and therapeutic outcome, etc., that have redefined the paradigms of nanoscale biomaterials, and to advance next-generation biomaterials or revolutionary medicines.

Engineering Inorganic Nanoparticles and Nanocomposites to Guide Cellular Behaviour

Abstract: Inorganic nanomaterials offer unique opportunities to move beyond passive biomaterials toward systems that more actively interact with and influence cellular behaviour. This lecture will discuss how engineered inorganic nanoparticles and nanocomposite systems can be used to modulate key stem cell processes, including adhesion, osteogenic differentiation, and angiogenesis.

Focusing on mesoporous silica nanoparticles as a model system, I will highlight how parameters such as particle architecture, ion doping, core-shell design, and surface functionalization can be tuned to control cell-material interactions. These design strategies enable the presentation of biochemical cues and the adjustment of physicochemical properties relevant for cellular responses.

In addition, I will discuss the integration of nanoparticles into hydrogel systems, where they can act as structural components or crosslinking elements. This approach allows modulation of material properties such as mechanics and dynamic behaviour, which in turn influence cell behaviour.

Examples will be presented in the context of bone regeneration and osteosarcoma, illustrating how these material design strategies can be applied in biologically relevant settings.

Multipotent Polymers for Transcytosis-enabled Active Extravasation and Penetration of Tumors: Design and Clinical Translation

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Tumor-targeted drug delivery is a critical modality in cancer therapy; however, it faces the dilemma of "abundant publications but few clinically approved drugs." This is primarily attributed to the limited clinical efficacy of delivery systems, coupled with challenges in their quality-controlled manufacturing (QCM) and in vivo safety characterizations, which collectively impede clinical translation. To address this, our team focuses on the rational design of drug-delivery polymers oriented toward clinical application. Leveraging polymer-mediated transcytosis, we established a tumor-actively delivering drug mechanism: Transcytosis-enabled Active Extravasation and Penetration (TAEP) of tumors, which transcends the limitations of the traditional Enhanced Permeability and Retention (EPR) effect and significantly improves drug delivery efficiency and therapeutic outcomes. Furthermore, we proposed the "Multipotent Polymers" strategy, which drastically simplifies the architecture and composition of delivery systems, thereby facilitating their QCM and in vivo characterizations. Building on these principles, we established guidelines for functional integration and methods for nanoparticle property modulation, creating safe, efficient, and scalable drug delivery systems. Consequently, three nano-drug candidates have secured five Investigational New Drug (IND) approvals (China/US) and entered clinical trials (Phase I/II), with two Orphan Drug Designations granted.

Engineered viscoelasticity in cellular microenvironments

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Introduction issues are viscoelastic materials whose mechanical properties evolve dynamically with time as cells perform key physiological functions. The mechanical properties of biomaterials are known to influence fundamental cellular process, including cell migration, cell growth and cell differentiation. Most of the work to understand the mechanical properties of substrates on mesenchymal stem cell (MSC) differentiation has made use of pure elastic materials. Cells probe their environment by pulling forces and receiving mechanical feedback through membrane receptors. However, viscoelastic materials respond dynamically to force, and so viscoelasticity plays a fundamental role in the differentiation of mesenchymal stem cells and hence in the design of regenerative biomaterials.

Results & Discussion We will use surfaces of controlled viscosity in our pathway to engineer and understand the viscoelastic properties of the ECM. We use supported lipid bilayers that are functionalised with either RGD (integrin binding) or HAVDI (cadherin binding) to demonstrate the molecular clutch is engaged on surfaces of high enough viscosity and, importantly, that it is weakened upon N-cadherin binding, controlled by the competition between vinculin and β -catenin for actin filaments. We then introduced substrates of controlled elasticity and viscosity, first in 2D using polyacrylamide hydrogels that were further patterned using fibronectin and then in 3D using PEG-hydrogels functionalised with fibronectin. We will discuss the unexpected interplay between viscoelasticity, cell adhesion and molecular clutch engagement. We introduce Brillouin microscopy as a way to follow the evolution of the viscoelastic properties of cells and the engineered hydrogels in 3D in a non-invasive way and in real time.

This talk will include our work engineering hydrogels with controlled elastic and viscous

properties, and how cells respond to controlled viscoelasticity in 2D and 3D, including patterning and confinement. We explain the response to viscoelastic materials through a variation of the molecular clutch model, where integrins transduce the dynamic properties of the ECM to engage to the actin cytoskeleton through focal adhesions. We introduce the role of piezo1 to enable mechanotransduction in soft viscoelastic environments.

Conclusions: We demonstrate the role of viscoelasticity in cell mechanotransduction and introduce strategies to incorporate this property in the design of biomedical hydrogels.

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3D Printing of Biomaterials and Translation: from tissue regeneration to Anti-senescence

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Abstract:

3D printing technology is one of the most promising technologies in the fields of tissue engineering and regenerative medicine, which can stack multiple components (materials, cells, etc.) layer by layer in three-dimensional space to construct complex and accurate structures. Therefore, for the construction of tissue regeneration scaffolds, 3D printing methods have far surpassed other traditional manufacturing methods. How to construct personalized tissue regeneration scaffolds with different compositions, structures, and functions through smart design and 3D printing technology is a research focus in the field of regenerative medicine. We have conducted a series of research work to meet the needs of biomimetic and functional 3D printing scaffolds, from material design, structural regulation, functional modification, and multi cell printing of artificial tissues. We have developed various 3D printing tissue regeneration scaffolds with excellent biological functions. Firstly, we prepared a series of biomimetic bioceramic scaffolds with excellent tissue repair performance by regulating the macro/micro structure of 3D printed scaffolds. Macroscopically, through precise model design, printing out scaffolds with biomimetic lotus root and natural bone multi-level structures can effectively promote vascularized bone regeneration. At the micro level, by combining microbial catalysis and other technologies with 3D printing technology, a 3D printed scaffold with a specific micro nano structure is constructed, significantly improving the osteogenic performance of the scaffold. In addition, for the regeneration and construction of complex tissues/organs, it is necessary to develop biomimetic scaffolds with a regular arrangement of multiple cells. Furthermore, the anti-senescence property of silicon-based bioceramic scaffolds were for the first time explored, and the concept of “silicate anti-senescence” (SAS) was proposed. Therefore, we further extend 3D material printing to 3D multicellular printing and anti-senescence properties, by regulating the composition of inorganic bioinks, designing cell spatial distribution, and constructing multicellular scaffolds that simulate different complex tissues. The bioceramics-based 3D printing offers excellent tissue regeneration and anti-senescence functions both in vivo and in vitro.

Multifunctional Biomaterials Supporting Bone and Osteochondral Tissue Regeneration

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Key words: nanoparticles, hydrogels, scaffolds, drugs, regeneration

Introduction: Although bone has considerable regeneration ability, infected or critical-size bone defects do not heal spontaneously and need special therapies and/or tissue engineering approach. Biomaterials that support bone tissue regeneration and healing should first be designed to eradicate pathogenic bacteria, provided that surrounding tissues are populated with such species, followed by facilitating osteogenic cell signalling and bone tissue expression processes. Our aim is to design multifunctional biomaterials that, depending on the needs, can either assure mechanical support or play a role of the artificial extracellular matrix (ECM). In addition, they can release drugs to treat infected tissues and/or deliver biologically active molecules that are beneficial for tissue regeneration and healing.

Materials & Methods: Our toolbox includes biocompatible polymers, lipids, and ceramics, which we synthesise and process into nano-metric objects, porous scaffolds, or highly hydrated matrices. In particular, we focus on degradable polyesters or polyanhydrides, whose degradation times in the body can be adapted to the clinical need. Moreover, we use fatty acids as drug carriers, biopolymers (gellan gum, gelatine, alginates) as injectable matrices or ceramic biomaterials (phosphates, carbonates, bioglasses) to process them into composite scaffolds. We also use the enzymatic mineralisation approach of hydrogels to generate nanocomposites that mimic bone tissue ECM. Obtained biomaterials are fully characterised from the point of view of chemical composition, structure, microstructure, physicochemical properties and on *in vitro* and *in vivo* models.

Results & Discussion: Our titania and zirconia scaffolds, whose pores are decorated with nano-/microparticle drug carriers of antibiotics or sodium alendronate, are dedicated to treat infections and stimulate natural regenerative abilities of the organism to finally integrate with bone tissues [1,2]. Other types are made of biodegradable polymers, so their disappearance from the treated lesion is correlated with the growth of native tissue [3,4]. We found that the deposition of calcium phosphates, collagen, or sulphated hyaluronan on polymer scaffolds promotes osteogenic cell differentiation and the healing of osteochondral defects [3,4]. We also develop biomaterials dedicated to infected bone in the form of polymeric micro-/nanoparticles loaded with antibiotics or antibacterial peptides [1,2,5,6]. They can be used as a component of injectable matrices, membranes, or immobilised on the

pore walls of scaffolds. Our biomaterials release the drugs in a controlled manner from 3 days to 4 weeks adjusted to medical requirements. We also propose an indirect 3D printing technique based on the sacrificial mould method, combined with enzymatic mineralisation to produce hydrogel-based scaffolds for osteochondral tissue regeneration [7].

Conclusions: We provide evidence that the biomaterials developed are favourable for the treatment of bone tissue defects and osteochondral tissue engineering.

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The Power of Small: Nanodiamonds Driving Next-Generation Natural Hydrogel Composites for the Fabrication of Bone Substitutes

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The engineering of hydrogels as 3D extracellular environments with controlled properties has the potential of predefining the response of osteoblasts towards bone regeneration, transforming static biomaterials into active, instructive scaffolds able to guide cell fate and accelerate functional bone repair. The fabrication of biomimetic constructs guiding such cellular response emerged towards combining current knowledge on bone structure, nanotechnology, natural origin biomaterials, and bio-inspired fabrication, to synergistically recapitulate parts of the hard tissue native complexity. Nanodiamonds represent an emerging type of carbon nanomaterials with recognized while underexplored potential in the development of composites for tissue regeneration¹⁻³.

Key words: hydrogel composites, nanodiamond, electrospinning, 3D (bio)printing, bone regeneration

Introduction: This work discusses the potential of nanodiamonds to be used as nanofillers for the engineering of acellular and cellular scaffolds based on natural-origin hydrogels, while addressing the most critical hurdles in bone tissue engineering – mechanical reinforcing and bioactivity, simultaneously resolving the elaboration of formulations for electrospinning and 3D printing or bioprinting.

Materials & Methods: Carboxylated nanodiamonds (cNDs) are explored as nanofillers for the fabrication of microfibrillar and 3D (bio)printed hydrogels such as gelatin, alginate, gellan, including when combined with other nanofillers such as biosilica and apatites (Fig. 1.). The presented examples include (i) 3D printed acellular scaffolds obtained from a paste-like formulation with low amounts of cNDs and high concentration of hydrogel-bioactive mineral phase and (ii) nanostructured multicomponent bioinks with cNDs and magnesium-doped nanohydroxyapatite⁴.

Results & Discussion: Examples will showcase the effect on the microstructural modifications, rheological properties, on the local mechanical properties, on the shape stability and osteoblasts response, when cNDs are combined with cell-responsive or bioinert hydrogels in low viscosity and high viscosity acellular and bioinks formulations^{2,4,5}. Increased surface stiffness, cell

adhesion, homing, osteogenic differentiation, extracellular matrix formation and load bearing are often associated with the supplementation with low amount of cNDs of both hydrogels and composites.

Conclusions: cNDs have excellent potential as nanofiller enhancing the properties of 3D (bio)printed natural hydrogels as extracellular environments for bone regeneration. Further studies and optimization, including the cytotoxicity after the scaffold is biodegraded are needed to confirm their promise.



Fig. 1. Nanodiamond-based hydrogel composites fabricated through green electrospinning, 3D printing using thick paste inks and bioprinting with low viscosity bioinks.

PersOC4Reg project is acknowledged.

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Development of Covalent Targeting Therapeutics Based on In Vivo Click Chemistry

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ABSTRACT: Highly coordinated, multiple non-covalent interactions between a therapeutic agent and its target are pivotal for achieving high specificity and stable binding. However, the complexity of these interactions necessitates intricate and protracted processes for drug screening and design. In contrast, covalent bonds offer superior binding stability without requiring complex structural optimization. Notably, in vivo click chemistry enables the specific formation of covalent bonds within biological environments. Building on this principle, our work focuses on developing "covalent-type" targeted drugs by leveraging in vivo click chemistry. In our initial studies, we achieved a breakthrough by selectively installing clickable handles at lesion sites, thereby establishing a corresponding targeted drug delivery system. Currently, we are advancing the development of "covalent targeted drugs" that utilize highly biocompatible macromolecules; upon undergoing a click reaction, these agents directly induce cell death for cancer therapy.

Bioprinted interfacial complex constructs for advanced healthcare applications

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Abstract

This paper reports on the biofabrication of functional, mechanoactive composite bioinks with encapsulated living cells (bone, adipose and Wharton jelly derived mesenchymal stem cells) via extrusion bioprinting for interfacial tissue engineering including vascularized bone and osteochondral grafts. We first designed and prepared bioinks containing an elastic, extrudable polymeric network matrix comprising biomimetic biomaterials including gelatin, elastin, gellan gum, methylcellulose combined with inorganic osteoinductive materials such as nanohydroxyapatite, functionalized bioactive glass, and laponite. The developed hydrogel-based inks were examined for their printability, rheological properties, thermal behavior, crystallinity, water uptake and degradation rate. The constructs were assessed biologically in vitro for their osteogenic, osteoclastogenic, angiogenic and chondrogenic capacity, as well as for their antibacterial activity. The bioprinted constructs indicate printing accuracy values of up to 75%, with the composite bioinks being higher. The bioinks demonstrate excellent capability regarding extrusion printability at extrusion pressures of 30-100 kPa, favoring high cell survival rates. Rheological analysis of the bioinks reveals >90% viscosity recovery. The gene expression of relevant osteogenic, osteoclastogenic, angiogenic and chondrogenic markers, as well as the biochemical markers and the extracellular matrix collagen and glycosaminoglycans were significantly elevated in the composite bioinks. Mechanical stimulation of the cell-encapsulated constructs by means of a bioreactor demonstrated significantly increased cell activity, particularly towards osteogenesis, angiogenesis and antiosteoclastogenesis. The bioprinted constructs were implanted in a subcutaneous mouse model for two weeks, indicating the absence of adverse immunological reactions.

Engineering Advanced Biomaterials for Cancer Therapy: Toward Integrated Therapeutic and Regenerative Strategies

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New-generation biomaterials are redefining cancer therapy, moving beyond single-function approaches towards integrated platforms that combine therapeutic efficacy with tissue regeneration. This paradigm is particularly important for aggressive malignant tumours such as melanoma and bone tumours, in which treatment failure is often caused by therapeutic instability, tumour recurrence and, in skeletal sites, the failure of functional tissue regeneration. One of the main limitations of photothermal therapy (PTT) is the intrinsic instability of high-performance agents such as black phosphorus (BP), which rapidly undergo oxidative degradation under physiological conditions. To overcome this barrier, a bioactive glass–black phosphorus (BG–BP) nanoplatform has been designed, in which the inorganic matrix stabilises the quantum structures derived from BP whilst enhancing photothermal conversion efficiency. This system allows for prolonged and predictable tumour ablation in melanoma, accompanied by modulation of the tumour microenvironment, inhibition of angiogenesis and metastatic spread, as well as gene expression profiles associated with improved outcomes.

Starting from this strategy, the concept was extended to bone cancer through the design of a multifunctional 3D scaffold based on sphene (SPH, CaTiSiO₅) and bioactive glass, further functionalised with BP-derived nanocomposites. This platform combines effective photothermal ablation of the tumour with the promotion of osteogenic regeneration. In vivo studies demonstrate a significant inhibition of tumour growth and invasiveness, a reduction in systemic disease burden and improved bone repair, without detectable systemic toxicity.

Taken together, these findings mark a paradigm shift towards ‘active’ and programmable biomaterials capable of coordinating complex therapeutic responses, opening the way to a new generation of integrated cancer therapies at the interface with regenerative medicine.

Hyaluronan-based strategies bridging immunomodulation and musculoskeletal regeneration

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Matrix biopolymers are fundamental building blocks for engineering advanced functional materials in biomedical applications. Among them, hyaluronan stands out due to its ubiquitous presence in mammalian tissues and its unique combination of physicochemical and biological properties. Its molecular structure is particularly amenable to a broad spectrum of chemical modifications, enabling precise tuning of viscoelastic behaviour, degradability, and bioactivity. When pristine or semisynthetic derivatives of hyaluronic acid are combined with collagen or other matrix proteins, their capacity to form composite materials further expands, offering a wide palette of mechanical and biological characteristics suited for regenerative medicine.¹

This talk will explore the design and application of semisynthetic hyaluronan derivatives and their composites, beginning with the underlying chemistry of derivatization. Building on this foundation, the talk will highlight how these materials can be tailored for biofabrication strategies targeting musculoskeletal tissues, with a particular focus on cartilage², bone³, and the intervertebral disc. Emphasis will be placed on how collagen–hyaluronan combinations can modulate cell-instructive properties and introduce controlled microscopic architecture—approaches that not only mimic the biochemical composition of native extracellular matrix but also recapitulate essential structural cues.

Beyond structural and biological design, the talk will address an increasingly important research dimension: how biomaterials influence the immune system. While macrophages have long been central to studies of immune–biomaterial interactions, neutrophils—often the first responders after implantation—play a decisive role in shaping the early inflammatory environment and, ultimately, the trajectory of healing. The second part of the talk will therefore focus on emerging methods to characterize neutrophil responses to biomaterials and on the relevance of these interactions for tissue regeneration.⁵

Recent work investigating human neutrophil responses to protein-coated biomaterials will be presented as an example of how subtle variations in protein presentation can dramatically alter experimental outcomes.⁶ Studies comparing foetal bovine serum (FBS) and type I collagen coatings on widely used 3D-printable and implantable polycaprolactone constructs revealed that even low concentrations of FBS significantly modified neutrophil behaviour—affecting metabolic activity, membrane integrity, inflammatory signalling, and early metabolic profiles. In contrast, type I collagen induced distinct shifts in metabolite patterns, particularly in

glycolytic intermediates, tricarboxylic acid cycle-related metabolites, and urea cycle components, while exerting relatively limited effects on ROS production compared to PCL alone. These findings underscore the need for careful control and interpretation of protein exposure in vitro, as it strongly shapes observed immune responses.

Taken together, insights from chemistry, biofabrication, and immunomodulation converge toward a unified vision: establishing design principles that harness the interplay between material properties and immune dynamics to create next-generation biomaterials for improved and predictable tissue regeneration.

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Harnessing Wound Dressing Physicochemical Properties for Chronic Ulcer Prognosis

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Introduction,

Wound dressings are the devices of choice for the management of acute and chronic wounds. Dressings are engineered either as tulle to protect the wound from mechanical insults or as hydrogels to control excessive volumes of exudate [1]. The aim of this work was to: (i) study the levels of exudate biochemical and cellular biomarkers relevant to tissue healing in chronic wounds of different clinical outcomes and (ii) assess the potential of different dressings to be used, upon retrieval from the wound, as prognostic tools for their evaluation.

Materials & Methods

Exudates and wound dressings were collected from 60 patients affected by chronic ulcers (i.e. venous leg ulcers and foot ulcers) over three visits (Vn). The following dressings were considered: (i) Atrauman, a tulle dressing made of polyester fibres coated with triglycerides; (ii) N-A, a cellulose tulle; (iii) Aquacel, a carboxymethylcellulose hydrogel. Wound areas were measured and categorised for closure of 70%, 30% and 0.0% ($\pm 20\%$). At the first visit (V1), only exudates were collected by swab. At any subsequent visit, both exudate and retrieved dressing samples were collected. Exudates were analysed for macrophage phenotypes (M1: iNOS⁺ cells at V2 and M2: CD206⁺ cells at V3) by immunofluorescence using confocal microscopy and the M2/M1 ratio was calculated. Another set of samples was analysed for TNF α , IL-6 and PDGF-BB by ELISA kits as well as for collagen levels by Picrosirius Red staining. Data were analysed against a reduction of the wound area.

Results & Discussion: A statistically significant higher linearity of wound area reduction ($r^2=0.951\pm 0.047$, $p<0.0001$) was observed in patients with an area closure of $71.0\pm 21.7\%$ over three visits compared to those showing an area reduction of $33.7\pm 19.1\%$ ($r^2=0.596\pm 0.261$) and those with no significant area change ($0.0\pm 17.1\%$, $r^2=0.340\pm 0.333$). When data were analysed per type of dressing, most of patients treated with Atrauman fell in the categories of patients with higher wound area reduction (55%) compared to only 13% in the case of N-A and 39% in the case of Aquacel. The M2/M1 macrophage ratio was estimated as a parameter of pro-regenerative versus pro-inflammatory phase. However, when patients' groups were analysed a statistically insignificant increase of the ratio was unexpectedly found in patients showing no reduction of the wound area (Fig 1A). The data became significantly different when the exudates of wounds treated with Atrauman were assessed (Fig 1B). A number of studies have reported that the role of M2 macrophages is still

not completely elucidated [2] and that higher levels of these macrophages have been found in diabetic chronic ulcers [3]. All the other parameters analysed showed no statistically significant differences (data not shown), but a trend towards a reduction of IL-6 levels in the eluate of Atrauman dressing was observed in patients with no area closure (Fig. 1C). Finally, Atrauman showed also to be suitable to detect the presence of collagen in wounds (Fig 1D). However, quantitative measurement showed no significant differences between patients with area reduction against those with no significant reduction (data not shown). The tested cellulose dressings did not show a reliable prognostic potential.

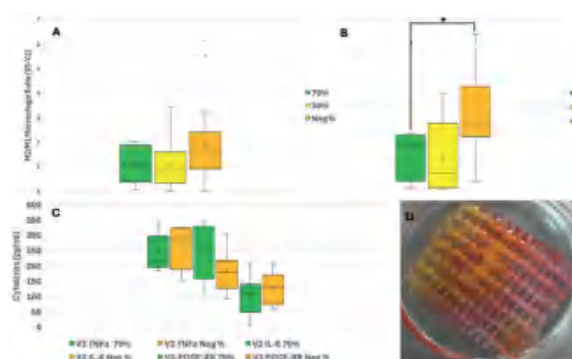


Fig. 1. Levels of cellular and biochemical biomarkers in chronic ulcers. (A) Exudate M2/M1 ratio in patients' groups, (B) Exudate M2/M1 ratio in patients' groups treated with Atrauman ($*p<0.05$), (C) Exudate IL-6 absorbed by Atrauman in all patients' groups, (D) Collagen staining of a retrieved Atrauman dressing.

Conclusions:

Atrauman can be interrogated to provide clinicians with predictive values of healing/non-healing: M2/M1 ratio and IL-6 appears to be suitable prognostic biomarkers of wound healing.

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From Formulation to Preclinical Translation: A Bioinspired Calcium Phosphate Adhesive for Fragility Fracture Repair

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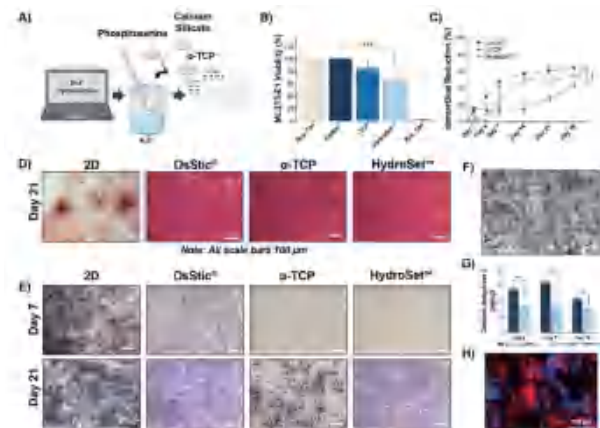
Keywords: bioinspired adhesives, bone stabilisation/repair

Introduction: Fragility and osteoporotic fractures remain difficult to stabilise with conventional metallic fixation, particularly in comminuted and poor-quality bone. A phosphoserine-modified calcium phosphate cement (PM-CPC), OsStic®, was developed as an injectable, bioresorbable bone adhesive capable of bonding wet cortical and cancellous surfaces while engaging bone repair pathways [1]. This keynote will present OsStic® development from formulation and scale-up through *in vitro* and *in vivo* evaluation.

Materials & Methods: A DoE approach was used to optimise α -TCP/phosphoserine/liquid ratios to achieve targeted rheology, setting behaviour, compressive strength, and bone-to-bone bond strength within clinically acceptable windows, and to assess robustness to ten-fold increases in powder volume. The optimised PM-CPC was then examined by *in vitro* and *in vivo* studies. Pre-osteoblast MC3T3-E1 and human MSCs were used to assess cytocompatibility, proliferation, biomineralisation and expression of osteogenic markers relative to α -TCP and HydroSet™ controls. RAW 264.7 macrophages were used to characterise osteoclastogenesis, sealing zone formation and biomarker release (CAII, TRAP and MMP-9) on OsStic® versus control cements. Translational performance was evaluated in mini-pig dental implant stabilisation and ovine long-bone defect models, focusing on early mechanical fixation, interfacial strength and new bone formation at and within the adhesive.

Results & Discussion: DoE analysis identified the optimal PM-CPC (Fig.1A) that satisfied target ranges for setting (60-200 s), compressive strength (≥ 10 MPa) and adhesive strength (≥ 2.5 MPa), with comparable performance at 1 g, 5 g and 10 g scales. ISO 10993-5-compliant extraction tests showed no cytotoxicity (Fig.1B), while direct-contact assays demonstrated superior attachment quality and proliferation kinetics (Fig.1C) on OsStic® versus α -TCP and HydroSet™, corroborated by SEM, LIVE/DEAD™ and actin–nuclei staining. Osteoblast cultures on OsStic® exhibited extensive biomineralisation (Fig.1D) and increased expression of ALP (Fig.1E), osteopontin, osteocalcin and BMP-2, and osteoclast assays revealed multinucleated cells (Fig.1F) with well-defined sealing zones (Fig.1G) and elevated CAII release (Fig.1H) on the PM-CPC surface compared with controls. In dental and long-bone models, OsStic® provided immediate mechanical stabilisation, sustained gains in torque and

pull-out strength and substantial new bone volume within and around OsStic®, consistent with progressive



replacement rather than long-term material persistence.

Fig. 1. A) PM-CPC optimisation via DoE was carried out, producing a final material that satisfied the clinical requirements for setting, handling and mechanical properties. B) Pre-osteoblast cell viability (indirect culture) confirmed no material-related cytotoxicity. C) Pre-osteoblast proliferation (direct culture) demonstrated superior kinetics on the PM-CPC. D) Alizarin Red staining confirmed significant biomineralisation. E) ALP staining demonstrated earlier ALP induction on the PM-CPC compared to both controls. F) SEM image of mature osteoclasts on PM-CPC surface. G) CAII ELISA demonstrated significantly higher release levels of this key functional marker on the PM-CPC at all timepoints. H) F-actin and DAPI staining showing a large mature osteoclast with significant sealing zone activity.

Conclusions: OsStic® is not only a wet-field adhesive that meets handling requirements but also a transient, cell-instructive interface that integrates into the osteoblast–osteoclast feedback loop. The keynote will use OsStic® to show how surgical constraints, preclinical evidence and device-level design can redefine fragile bone fixation as time-limited support that restores control to physiological bone turnover.

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Cell-Assembled extracellular Matrix (CAM): a true bio-material for tissue engineering

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Key words: Extracellular matrix, tissue engineering, vascular, cell culture.

Introduction: Unfortunately, even the most inert synthetic polymers are recognized by the innate immune system as a foreign body to be destroyed. In many applications, this foreign body reaction will cause complications like obstructive fibrosis and thrombosis as a result of the chronic inflammation it generates. In addition, synthetic materials are prone to infection and have non-physiologically high stiffness. An alternative approach is to use biological materials to provide a scaffold that the body can recognize and work with. However, this means that the body's adaptive and innate immune system will also recognize and destroy, respectively, xenogeneic proteins and extracellular matrix (ECM) proteins that have been denatured (i.e., damaged). This is why animal-derived implants are treated with powerful crosslinking agents, making them unrecognizable to the cells but transforming them in a sort of foreign material. This also explains why extracellular matrix proteins that have been chemically solubilized and re-assembled are rapidly degraded after implantation. Another alternative is to have human cells assemble an ECM in vitro that can be used as a strong, unprocessed, completely biological, human scaffold for tissue engineering and/or surgical repair.

Materials & Methods: In the right environment, normal, adult, human, skin fibroblasts can lay down extracellular matrix on their culture substrate to form a robust sheet of material we call the CAM for Cell-Assembled extracellular Matrix. These sheets can be used directly, by folding, rolling, cutting, or other means, or they can be cut into threads to produce human textiles by weaving, knitting, or braiding. We have also developed culture conditions that allow the production of CAM sheets by ovine skin fibroblasts with properties very similar to their human counterpart in order to establish an immunocompetent large-animal model to evaluate CAM-based constructs in more clinically relevant conditions.

Results & Discussion: The first prototype of woven human vascular grafts produced by weaving CAM threads displayed supraphysiological strength (burst pressure > 5000 mmHg at an I.D. of 4.2 mm and suture retention strength > 600 gf) as well as low transmural permeability in the 10 ml/cm.cm² range. Subcutaneous implantation of human threads in nude rats revealed that the material integrated rapidly and persisted for at least 10 months. Aortic implantations on miniaturized human

vascular grafts showed persistence of the graft for 12 months and regeneration of the luminal surface. However, aneurysms of the native aorta at the anastomosis and calcifications of the graft highlighted the limitations of the graft's miniaturization that produced an even stronger, hence stiffer, graft.

Allogeneic ovine CAM threads were implanted subcutaneously and persisted for at least 6 months. After a mild inflammatory reaction, the material was completely remodeled into a dense cellularized thread with no signs of inflammation at 6 months. In contrast, human CAM threads, even decellularized, caused a massive immune response that was not resolved at 6 months, underlining the need for an immunologically-matched animal model. Ovine woven vascular grafts displayed similar mechanical properties and were implanted in the carotid artery of allogeneic sheep, using standard surgical techniques, for 4 weeks without any adverse events. The assembly parameters were modified to lower its supraphysiological strength, and its design was modified to facilitate its use as an arteriovenous shunt between the carotid artery and the jugular vein (I.D. 6 mm, beveled edges). Allogeneic arteriovenous shunts were implanted for up to 8 weeks and successfully punctured at 1 month with no adverse events. Regeneration of the luminal surface was observed with smooth muscle cell migration and differentiation, as well as endothelium formation. Calcification of the CAM was also observed in areas where the CAM threads were highly compressed. Investigations are underway to determine the cause of this reaction and to produce less tightly woven grafts.

Conclusions: CAM-based human textiles can be used for a variety of applications. Woven vascular grafts show high mechanical strength, long persistence, and promising regeneration potential but need to be further improved. Thanks to a textile approach, the properties of the human textiles can be further tuned to improve outcomes.



Fig. 1. CAM sheet and woven grafts (ovine).

Ultrasound-Responsive Antibacterial Materials

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Abstract:

This report presents a strategy using ultrasound as a remote, on-demand switch to trigger antibacterial responses at localized infection sites, addressing the limitations of antibiotics, such as drug resistance and off-target toxicity. The fundamental mechanisms rely on ultrasound cavitation, which generates reactive oxygen species, mechanical forces, and thermal effects. By engineering piezoelectric heterojunctions (e.g., BiFeO₃/Ti₃C₂ and Zn(OH)F/CaF₂), interfacial charge separation is dramatically enhanced, boosting sonodynamic sterilization of deep-seated infections like osteomyelitis and periodontitis. Furthermore, multifunctional integration is demonstrated through a BTO/berberine nanoparticle system that couples sonocatalysis with anti-inflammatory and osteogenic activities, enabling simultaneous infection clearance and bone regeneration. Additionally, an ultrasound-triggered sonothermal platform on metal implants is developed for controlled nitric oxide release, achieving synergistic killing of methicillin-resistant *Staphylococcus aureus* with >99.99999% efficiency. These findings show that smart ultrasound-responsive materials can fundamentally transform the treatment paradigm for infectious diseases through deep, targeted, and multi-mechanism therapy.



Prof. Shuilin Wu – Brief Biography

Prof. Shuilin Wu is a Boya Distinguished Professor at the School of Materials Science and Engineering, Peking University. He is a recipient of the National Outstanding Youth Science Fund and the National Science Fund for Excellent Young Scholars. He has been recognized as a Highly Cited Researcher by Clarivate (2023–2025) and listed among the World's Top 2% Scientists by Stanford University and Elsevier, including the Career-long Impact list. Prof. Wu serves as a Fellow and council member of the Chinese Society for Biomaterials and is the Chair-elect of its Medical Metallic Materials Division. He is also an editorial board member of several journals, including *Bioactive Materials* and *Rare Metals*. His research focuses on medical metals, bone tissue engineering, smart responsive antibacterial materials, and traditional Chinese medicine-inspired materials for treating bacterial infections. He has published over 300 papers as corresponding author in journals such as *Nature Communications*, *Science Advances*, and *Advanced Materials*, with total citations exceeding 33,000 and an H-index of 101. He holds more than 30 authorized Chinese invention patents.

Engineering Neural-like Fiber Tissues for Central and Peripheral Nerve Regeneration

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Neural injury remains a significant challenge in clinic due to the limited regeneration capacity of neurons, the multiple types of cellular dysfunctions, and the impairment of multidimensional microenvironment. Biomaterials-based regenerative medicine strategies, which utilize multimodal signals from bioactive materials to regulate complex cellular behaviors and functions, have shown great potential in neural injury repair. In our study, we developed a series of functionalized aligned fibrin-based nanofibrous hydrogels (fAFGs), which were modified with multifunctional factors, such as bioactive peptides, magnetic, and conductive nanomaterials to construct better regenerative microenvironment with multi-signal synergy. The fAFGs could effectively regulate multiple cell types involved in nerve regeneration in vitro and in vivo, thereby accelerating motor functional recoveries in rat, canine, and primate models. In addition, we also constructed neural-like living fiber tissues in a "bottom-up" manner. Our results demonstrate that the engineered neural-like fiber tissues significantly improve the regenerative niche, modulate neurogenesis and axonal regeneration, and thereby promote the self-organization of functional neural networks, leading to substantial recovery of motor and sensory functions in rats with spinal cord injury.

Xiumei Wang is a professor at the school of Materials Science and Engineering, Tsinghua University. She is primarily engaged in fundamental research on biomaterials and the development of biomedical material products, including the research and clinical translation of regenerative materials for tissues such as nerves, bones, and cartilage. She published over 230 SCI-indexed papers in international journals including *Nature Communications*, *Science Advances*, *Bioactive Materials*, and *Biomaterials*. She is the executive member of the Chinese Society for Biomaterials and served the co-Editor-in-Chief of *Tissue Engineering Part C* and the editorial member of *Frontier of Materials Science*, *Regenerative Biomaterials*, *Biomaterials Research*. She was honored the Commemorative Medal for the 70th Anniversary of the Founding of the People's Republic of China, the 2011 Second Prize of the National Natural Science Award, the 2024 First Prize of the Military Science and Technology Progress Award, the 2023 Special Jury Gold Medal and Gold Medal at the Geneva International Exhibition of Inventions, the 2021 First Prize of the Chinese Materials Research Society Science and Technology Award, the 2021 First Prize of the Chinese Medical Science and Technology Award, the 2014 First Prize of the Shandong Provincial Science and Technology Progress Award, and "Outstanding Talent of the New Century" of the Ministry of Education.

Report title: In Vivo Transport Mechanism and Clinical Translation of Drug Delivery Systems

Prof. Yucai Wang (王育才)

Report content: Drug delivery systems represented by polymeric microspheres, liposomes and lipid nanoparticles (LNPs) have achieved industrial breakthroughs in the treatment of various diseases, and dozens of delivery carrier-based drugs have been approved globally. However, intravenously administered drug delivery still suffers from low delivery efficiency. The core scientific issue lies in the fact that delivery vehicles must cross multiple hierarchical physiological barriers in vivo, including organ clearance, vascular barriers and cellular uptake. Current research mostly focuses on material construction, property optimization and single-organ regulation, while lacking understanding of systemic regulatory mechanisms in vivo, resulting in an unpredictable relationship between material design and delivery efficiency.

To address these issues, we established a high spatiotemporal-resolution in vivo imaging platform to systematically dissect the in vivo transport and clearance patterns of polymeric delivery materials. We revealed the basement membrane barrier in tumors and developed strategies to overcome it. We also discovered the "adjacent vascular enhanced permeation effect" in avascular tumor metastases. Furthermore, we found that the in vivo fate of delivery vehicles is determined not only by material properties, but also by a multi-organ synergistic regulatory network. On this basis, we established a correlation model between material structure and in vivo behavior, developed organ-selective delivery materials and systemic regulation strategies, driving the transition of delivery systems from empirical optimization to predictable design.



Personal profile: Prof. Yucai Wang is a recipient of the National Science Fund for Distinguished Young Scholars (2020) and a selected member of the National High-Level Overseas Talents Program for Young Scholars (2015). He joined the School of Life Sciences at the University of Science and Technology of China in September 2015. He has led or participated in numerous projects, including NSFC International Cooperation and Exchange Programs, Major Research Plan Integration Projects, Key Programs and General Programs; the National Key R&D Program "Nanotechnology Special Project" and "Transformative Projects"; and the Strategic Priority Research Program of the Chinese Academy

of Sciences. For many years, he has been engaged in research on drug delivery, with more than 100 papers published as corresponding author in journals including *Science*, *Nature Nanotechnology* (2), *Nature Materials*, and *Nature Biomedical Engineering* (3). He has led six Category 1 innovative drugs to obtain clinical approval, of which two have entered Phase II clinical trials.

Materiomics Engineering to decode environmental cues for stem cell immunomodulation using Interpretable Intelligent Algorithms

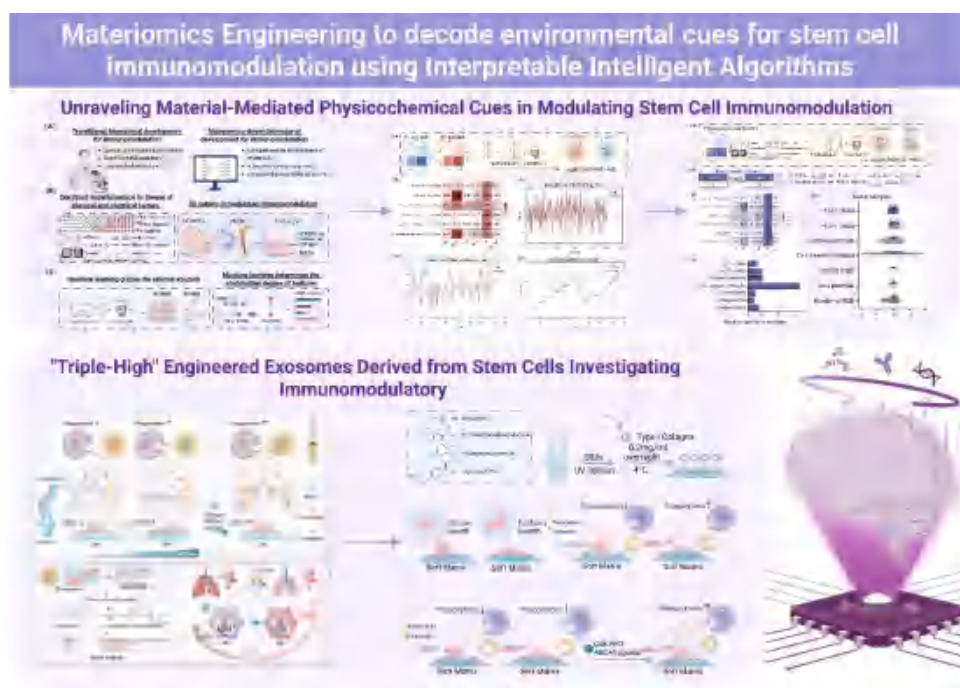
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Keywords: Interpretable Intelligent Algorithms, immunomodulation, environmental cues, exosome

Abstract: Hydrogels that mimic the extracellular matrix (ECM) create microenvironments with various physicochemical cues to markedly steer stem cell fate, prioritizing immunomodulatory and regenerative functions. Understanding how biomaterial cues regulate cell fate involves inherent complexities, such as multi-parameter interactions and nonlinear relationships, which require extensive sample collection, labor, and costs. This work introduces a materiomics platform that integrates high-throughput data and artificial intelligence for the systematic evaluation and accurate prediction of optimal stem cell niche features, thereby enhancing the immunomodulatory potential of mesenchymal stem cells (MSCs). Machine learning algorithms based on this database successfully identify the most effective hydrogel formulations, enhancing stem cell immunomodulatory efficacy while pinpointing matrix stiffness as a dominant environmental cue that shapes macrophage phenotype. Bioinformatics analyses confirm exosomes as key mediators linking matrix stiffness to stem cell immune regulation. Matrix stiffness serves as a strategy for exosome engineering. Exosomes from soft matrices show high yield and therapeutic efficacy, whereas those from stiff matrices exhibit superior delivery efficiency. Notably high delivery efficiency of stiff matrix-derived exosomes arises from stiffness-induced robust expression of the ATP-binding cassette transporter A1 (ABCA1) in MSC, which increases exosome membrane cholesterol. This mechanism generates “Triple-high” engineered exosomes, combining high yield efficacy and delivery capability. In pulmonary fibrosis, a condition characterized by difficult drug delivery due to structural remodeling and biological barriers, these exosomes demonstrate enhanced delivery of therapeutic agents to lung tissues. Interpretable machine learning identifies GLOD4 as a key exosome protein for treating pulmonary fibrosis. In summary, this study highlights artificial intelligence as a multidimensional tool that offers new solutions for biomaterial design and MSC-based therapy with significant potential in tissue engineering.



AI-Driven Rational Design of an Orally Administered Engineered Probiotic System for Targeted Obesity Therapy

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Keywords:

AI-driven design; Engineered probiotics; Oral delivery; GLP-1; Obesity

Background: The clinical management of obesity is currently hampered by the limitations of traditional pharmacotherapies, including poor patient compliance and high rebound rates. While probiotics represent a promising alternative, their therapeutic efficacy is severely restricted by the lack of precision in strain selection, insufficient metabolic potency, and the inability to survive gastric transit. Addressing these multi-dimensional challenges requires a shift from empirical screening to artificial intelligence (AI)-driven rational design.

Methods: We established an integrated AI framework to construct a synergistic therapeutic system. Initially, through extensive AI-based analysis of public metagenomic datasets, *Lactococcus lactis* was identified as a key commensal species significantly depleted in the gut of obese individuals and selected as the optimal biological chassis. Subsequently, leveraging a knowledge-graph-based inference model, we pinpointed a potent, non-endogenous GLP-1 secretion-inducing factor and genetically engineered *L. lactis* to heterologously express this bioactive factor for restoring satiety signaling. To ensure precise ileal targeting and overcome physiological barriers, an AI-screening algorithm was further utilized to identify an optimal encapsulation material capable of shielding the engineered bacteria from the harsh gastric environment, including low pH and bile salts.

Results: The resulting engineered probiotic system demonstrated high viability and stability under simulated gastrointestinal conditions. In high-fat diet (HFD) induced obese mouse models, oral administration of the encapsulated engineered *L. lactis* exerted significant therapeutic effects. The treatment successfully targeted the distal intestine, triggered endogenous GLP-1 secretion, and effectively reduced body weight and adipose tissue accumulation. Furthermore, the therapy improved glucose tolerance and insulin sensitivity while remodeling the gut microbiota toward a healthy phenotype. Notably, the system showed a favorable safety profile and minimized weight rebound compared to conventional pharmacological controls.

Conclusion: This study demonstrates a proof-of-concept for an AI-designed living therapeutic that integrates microbiome restoration, targeted metabolic intervention, and advanced material delivery. By overcoming physiological barriers through engineering, this platform offers a novel, potent, and safe strategy for the long-term management of obesity.

AI-guided screening of antimicrobial peptides

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Key words: Machine learning, Antimicrobial peptides, infection

Introduction: Antimicrobial peptides represent a potential alternative for combating multidrug-resistant bacterial infections. The arbitrary combination of peptide sequences constitutes a vast library of potential peptides, making the systematic screening of highly effective antimicrobial peptides from such an immense search space a highly challenging research problem. Leveraging an artificial intelligence framework, we developed a novel machine learning pipeline (SMEP) that integrates empirical judgment, classification, ranking, and regression models. This approach achieved, for the first time, high-throughput screening of antimicrobial peptides across the entire peptide library. On this basis, we further developed a few-shot learning-based pipeline (FSLSMEP) to identify potent antimicrobial peptides targeting *A. baumannii*.

Results & Discussion: Across the entire hexapeptide search space, we introduce our data-driven method to identify optimal peptide candidates. The core outcome of this work is a plug-and-play machine-learning framework that enables global search across a vast pool of peptides. Using SMEP, we predicted and selected the 10 peptides with the lowest predicted minimum inhibitory concentrations (MICs) from a comprehensive hexapeptide library comprising 64 million sequences for experimental validation. All 10 peptides exhibited antimicrobial activity (MIC < 160 µg/mL), with the three best peptides achieving MIC values below 10 µg/mL. Without modifying any model parameters, we tested the pipeline's screening capability on full libraries of heptapeptides (1.28 billion sequences, 13 days), octapeptides (25.6 billion sequences, 22 days), and nonapeptides (512 billion sequences, 27 days), achieving a success rate of 98.2% (54/55). Beyond MIC, we further evaluated the drug-like properties of three selected hexapeptides. In vitro tests demonstrated that these antimicrobial peptides possess broad-spectrum antimicrobial activity, low biotoxicity, a membrane-disrupting bactericidal mechanism, and a low propensity for inducing resistance. In vivo tests revealed potent bactericidal efficacy against both acute and chronic pneumonia in mouse models, with bacterial killing rates of 99.8% and 98.1%, respectively.

The FSLSMEP further enables screening of antimicrobial peptides that target specific strains under very limited strain-specific training data. In the study, this pipeline effectively scans through the entire libraries of hexapeptides, heptapeptides, and octapeptides, encompassing tens of billions of candidates, despite the extreme scarcity of available training data. Comprising classification, ranking, and regression modules integrated, each module is trained using a few-shot learning strategy involving pre-training and multiple fine-tuning steps, while incorporating similar and true data for fine-tuning. This methodology mitigates potential overfitting concerns arising from the small size of the training samples and enhances the predictive capability of the pipeline. The results highlight the robustness and versatility of the methodology, demonstrating its effectiveness in identifying AMPs against *A. baumannii* and *C. albicans*, with low off-target toxicity and negligible susceptibility to drug resistance. Additionally, the EME7(7) exhibits efficacy in controlling *A. baumannii* infections within a mouse pneumonia model, notably without inducing kidney injury — a contrast to the observed effects of polymyxin B.

Conclusions: Both the in vitro and in vivo evaluations confirmed the functionality of the identified leading AMPs. These results highlight the potential of our automated computational framework for addressing the challenge of a global increase in antibiotic resistance and a depleted antibiotic-discovery pipeline. Furthermore, SMEP is designed as a generic approach that can be easily repurposed to search for varied functional therapeutic peptides across the near-infinite repertoire of peptide sequences, facilitating the discovery of new drugs.

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Multifunctional Dendrimer Nanogels: A Versatile Platform for Next-Generation Cancer Therapy and Immunotherapy

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Abstract

This report highlights recent advancements in the design and application of dendrimer-based nanogels (DNGs) as multifunctional platforms for cancer therapy and immunotherapy. Through a series of innovative studies, our team has developed stimuli-responsive DNGs capable of co-delivering therapeutic agents, nucleic acids, and immunomodulators with high precision and efficiency. Key developments include: (1) redox-responsive dendrimer nanogels for ultrasound-enhanced chemoimmunotherapy of pancreatic cancer via endoplasmic reticulum stress amplification and macrophage polarization; (2) low-generation dendrimer nanogels for safe and efficient DNA delivery and gene therapy; (3) pH/ROS-responsive DNGs for co-delivery of chemotherapeutic drugs and cytokines to overcome the blood-brain barrier in glioma treatment; and (4) mannose-functionalized DNGs for dual-action mRNA vaccine delivery and glycolysis inhibition in melanoma. These DNG platforms exhibit excellent biocompatibility, targeted delivery, controlled release, and potent antitumor immune activation. Collectively, our work demonstrates the versatility and translational potential of smart dendrimer nanogels in integrating multiple treatment modalities—including chemotherapy, gene therapy, immunotherapy, and metabolic intervention—for enhanced and personalized cancer therapy.

Key words: dendrimer, nanogels, cancer therapy, immunotherapy, responsiveness

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AI for biomaterials: From foundation model to closed-loop discovery of functional polymers

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Abstract: We propose a foundation-to-automation workflow for data-efficient biomaterial discovery. PerioGT, a periodicity-aware polymer foundation model, reaches state-of-the-art performance on 16 downstream benchmarks. Building on PerioGT, PolyCLOVER performs closed-loop optimization in a ~100,000-candidate poly(β -amino ester) space and identifies three potent polymeric antibiotics.

Key words: polymer, foundation model, self-supervised learning, antimicrobial resistance, polymeric antibiotics

Introduction: Deep learning has transformed chemical research and accelerating the discovery of new functional molecules and materials. Yet, despite rapid progress in small-molecule and biomolecular domains, polymer science remains comparatively under-served by generalizable deep learning frameworks. Polymer modelling often faces two coupled bottlenecks—inadequate representation of complex polymer structures and severe scarcity of labelled data—which together limit the robustness and transferability of data-driven methods.

Recent efforts have advanced polymer representation learning using handcrafted descriptors, sequence-based encodings, and graph-based models. However, existing self-supervised learning (SSL) approaches simplify polymers into small-molecule-like inputs (e.g., treating repeating units as standard molecular graphs or SMILES), discarding the *periodicity* that fundamentally distinguish polymers from small molecules. Moreover, polymer properties often depend on additional conditions such as molecular weight or compositional ratios in copolymers. To address this, we introduce a periodicity-aware polymer foundation model, PerioGT, which integrates chemically grounded priors into SSL. PerioGT constructs a periodicity prior via a chemical knowledge-driven sampling mechanism (periodicity augmentation), and injects this prior into pretraining through contrastive learning. To support diverse polymer settings, we also adopt a modular graph augmentation strategy that uses virtual nodes to encode additional polymer attributes and experimental conditions, enabling explicit relational modelling.

A unified polymer foundation model is not only valuable for benchmark prediction tasks, but also serves as a key enabler for practical discovery workflows. Antimicrobial resistance (AMR) has become a major global health threat, motivating the development of antibacterial strategies beyond classic antibiotics. Synthetic polymeric antibiotics are promising alternatives. However, discovery in this area remains largely empirical: complex antimicrobial mechanisms, high structural diversity, and poorly

standardized data make it difficult to establish reliable structure–activity relationships.

Building on the periodicity-aware foundation provided by PerioGT, we further develop an automated, data-efficient discovery framework, PolyCLOVER, for iterative identification of polymeric antibiotics with high antibacterial potency and low toxicity. Within a predefined combinatorial polymer space, an ensemble multi-task predictor evaluates candidate performance, uncertainty, and diversity, recommends informative candidates for synthesis and testing, and iteratively improves through closed-loop updates. This closed-loop design is particularly suited to polymer discovery, where the chemical search space is vast, labels are expensive, and robust navigation requires both strong priors and systematic experimental refinement.

Results & Discussion: PerioGT delivers state-of-the-art performance across 16 downstream polymer property prediction tasks, indicating strong transferability. Starting from a combinatorial library of approximately 100,000 poly(β -amino ester) candidates, PolyCLOVER integrates multi-stage SSL, active learning, and high-throughput experiments to efficiently navigate the search space under limited labelled data. Within ~20 days, it identifies three lead compounds that self-assemble into stable antimicrobial nanoparticles (SANPs). These SANPs exhibit potent activity against multidrug-resistant pathogens, with minimum inhibitory concentrations (MICs) of 4 $\mu\text{g/mL}$ against *Staphylococcus aureus* and 8 $\mu\text{g/mL}$ against *Acinetobacter baumannii*. Moreover, the nanoparticles can function as antibiotic carriers/adjuvants that restore bacterial sensitivity to penicillin G, and in vivo studies confirm efficacy both as monotherapy and in combination with antibiotics.

Conclusions: This foundation-to-automation paradigm outlines a practical blueprint for future biomaterials development, where models can be customized to target desired functions and constraints (e.g., bioactivity, efficacy, safety) and continuously improved via experiment-driven feedback to accelerate the creation of next-generation biomaterials.

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Data-Driven De Novo Design of Super-Adhesive Hydrogels for Underwater Applications

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Key words: data-driven design, adhesive hydrogels, machine learning, underwater adhesion

Introduction: Rational design of soft materials is hindered by complex multiscale structure–property relationships and the vast combinatorial design space of polymer compositions.[1] Achieving strong, rapid and durable adhesion in underwater environments remains particularly challenging for biomaterials and marine applications.[2] Conventional hydrogel development relies largely on empirical trial-and-error approaches, limiting predictive power and optimization efficiency. Here, we establish a data-driven framework that integrates protein sequence mining, statistically guided polymer synthesis and machine learning optimization to enable de novo design of high-performance underwater adhesive hydrogels.[3] We test whether sequence patterns evolved in natural adhesive proteins can be quantitatively encoded into polymer composition descriptors and translated into rational hydrogel formulations with superior adhesion.

Materials & Methods: A total of 24,707 adhesive proteins from 3,822 organisms were collected from the NCBI database. After multiple sequence alignment, amino acids were grouped into six functional classes, and pairwise frequencies were converted into relative composition descriptors for polymer design. Based on 180 bioinspired formulations, hydrogels were synthesized via free-radical polymerization. Underwater adhesive strength (F_a) was evaluated by tack tests. Gaussian process and random forest models were trained to correlate monomer composition with adhesion, and batched sequential model-based optimization was applied to iteratively propose improved formulations over three rounds.

Results & Discussion: Among the 180 data mining–driven hydrogels, multiple samples exhibited adhesive strengths exceeding 100 kPa, with a maximum of 147 kPa, already outperforming many reported underwater hydrogels. Control experiments based on non-adhesive protein datasets resulted in significantly weaker adhesion, confirming the specificity of the extracted sequence features. Machine learning optimization substantially enhanced performance beyond the original dataset. The best-performing hydrogel achieved underwater adhesion exceeding 1 MPa in saline, representing an order-of-magnitude improvement over conventional systems. Model interpretation revealed that hydrophobic and aromatic

monomers promote interfacial water exclusion, while moderate cationic content enhances electrostatic interactions with negatively charged substrates; excessive hydrophilicity increases swelling and reduces effective contact. Optimized hydrogels exhibited increased viscoelasticity, toughness and energy dissipation, contributing synergistically to robust and repeatable adhesion. The materials demonstrated strong adhesion to diverse substrates, maintained performance in seawater, and showed excellent durability under repeated attachment–detachment cycles, highlighting their practical applicability.

Conclusions: This work demonstrates a scalable data-driven paradigm for soft-material discovery by bridging biological sequence information, statistical polymer synthesis and machine learning optimization. The framework enables efficient navigation of complex compositional spaces and delivers super-adhesive hydrogels with underwater adhesion exceeding 1 MPa. Beyond adhesive systems, this strategy provides a generalizable route for rational design of functional biomaterials guided by biological data and computational intelligence.



Fig. 1. (a) Conceptual scheme of the proposed approach integrating data mining (DM), experimentation, and machine learning (ML) to design high-performance adhesive hydrogels. (b) Comparison of underwater adhesive strength between previously reported hydrogels and newly developed hydrogels in this study.

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Designing Interactive Peptide Materials in Biological Systems for Controlling Cell Function

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Targeted modulation of cellular functions through chemical assemblies holds transformative potential for treating cancer and infectious diseases. This talk highlights our lab's interdisciplinary approach integrating computational design, molecular engineering, and biomaterials to develop cell-specific therapeutic platforms. We present one key advance in our lab: In situ immune cell regulation: Using programmable biomaterials (e.g., peptide hydrogels and inhalable nanoparticles) to spatially control immune activity, enhancing antitumor responses and promoting tissue regeneration. Central to these advances is our TransSAFP platform, a deep learning-driven pipeline for de novo design of multifunctional self-assembling peptides (SAFPs). These innovations—predictive peptide design and immune-engineering biomaterials—demonstrate the power of molecular engineering to bridge chemistry, materials science, and biomedicine, offering novel therapeutic avenues for precision oncology and infectious disease management.

Key words: peptide, biomaterials, self-assembly (3-5 key words)

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Counting three popular available wound dressings (Atrauman, N-A, and Kaltostat) with PD-U and PD-PS to enhance their physicochemical and biocompatibility properties

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Introduction: Wound dressings have remained the primary treatment modality for wound healing over many years; however, numerous substantial treatments exist that can expedite this process. The market offers a wide variety of wound dressings, which are employed by the healthcare community. However, to enhance their function and quality, it is not always necessary to synthesize entirely new dressings; instead, improving functionality through coating existing dressings to augment their physicochemical and biological properties is advantageous. Such enhancements can maintain moisture, prevent simultaneous loss of mass and moisture, control inflammation, and stimulate keratinocyte migration. PD-U (Phenodrive-U) (based on carboxybetaine) and PD-PS (Phenodrive-PS) (based on phosphoserine) are two components produced by the Tissue Click company. These materials possess hydrophilic properties that enhance exudate absorption and inflammation control. Several studies have demonstrated that combining different hydrogels, such as poly carboxybetaine hydrogel, can improve hydrophilicity, bioadhesion resistance, wound closure, and reduce inflammation markers. Additionally, phosphoserine has been shown to aid diabetic wound healing through immunomodulation (M1 to M2) and to accelerate wound closure.

Aim: The present study aims to enhance the physicochemical and biological characteristics of three distinct wound dressings: Atrauman (a tulle-based synthetic polymer), N-A (a tulle-based methyl cellulose), and Kaltostat (a composite of alginate). This objective is accomplished through the application of a dry coating technique utilizing pd-u and pd-ps.

Material and Methods: For coating wound dressings, 1 vial (1mg) of PD-U and 1 vial (1mg) of PD-PS were dissolved in 10 ml of 75% ethanol. Then Atrauman, N-A, and Kalt stat, which are commercially available and cut to 1 cm × 1 cm, were transferred to the 24-well plate. To each wound dressing (1*1 cm), 200 ul of PD-U and PD-PS were added separately and incubated in the Luminar cabinet overnight to dry completely. After 24 hours, they were assessed for coating confirmation with SEM, release of material into body fluid over the 48 hours using the Bradford assay, swelling after, evaporation, and body mass at 48 hours. Biocompatibility with incubation-coated wound dressing with the Monocyte cell line (U937, ATCC) for 48 hours

Results and discussion: Results from SEM demonstrated proper coating of both material PD-U and PD-PS for N-A and Kaltostat across different layers. However, for Atrauman, it was observed that the material was already coated by the manufacturer and was washed with a coating solution on different parts. The swelling rate among controls, those coated with PD-U, and those coated with PD-PS did not exhibit any significant changes in the three different dressings after 48 hours. Conversely, the vaporisation test indicated that coated Kaltostat with PD-U and PD-PS could help preserve fibre moisture ($P < 0.05$). In the biocompatibility experiment, it was shown that the three types of wound dressings coated with PD-U significantly decreased inflammation (both M1 and M2 phenotypes) ($P < 0.001$) compared to the control group. However, the coated wound dressing with PD-PS, despite visibly reducing inflammation, did not demonstrate any statistically significant changes.

Conclusion: Atrauman, due to the previously applied coated dressing, may remove earlier layers after reapplication, rendering it unsuitable as a dressing. Coating N-A with PD-U and PD-PS can reduce inflammation; however, it does not influence the physicochemical properties. The most optimal dressing to enhance physicochemical and biocompatibility properties is Kaltostat coated with PD-U.

A few-shot learning workflow for identification of antimicrobial peptides against *Acinetobacter baumannii*

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Key words: Large model, pipeline, AMP.

Introduction: *Acinetobacter baumannii*, a formidable gram-negative bacterium, poses a significant threat as it readily causes nosocomial infections and exhibits multidrug resistance. Despite its clinical importance, the available reports on antimicrobial peptides targeting this pathogen are notably scarce. Addressing this limitation and leveraging artificial intelligence tools for efficient identification of anti-*A. baumannii* peptides become critical challenges.

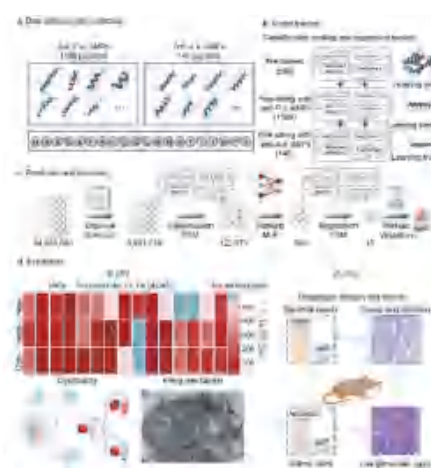
Materials & Methods: The deep learning pipeline was trained with pre-training and multiple fine-tuning. The peptides were designed by the deep learning pipeline. And they were measured with their antimicrobial property *in vitro* and *in vivo*.

Results & Discussion: In this study, we present an innovative small-sample learning pipeline (FSLSMPEP) specifically crafted to discern antimicrobial peptides capable of effectively combating *A. baumannii*. The pipeline is trained on a mere 148 data points, demonstrating its capability to systematically scan the extensive hexapeptide, heptapeptide, and octapeptide libraries, each containing tens of billions of candidate sequences. This approach mitigates potential overfitting concerns associated with the limited training dataset, thereby enhancing the predictive capacity of the pipeline. The peptides identified through this methodology exhibit potent activity against diverse *A. baumannii* strains, achieving an impressive recognition success rate of 91.1%. Furthermore, these peptides demonstrate low cytotoxicity and a reduced likelihood of inducing drug resistance. Notably, the lead peptide proves efficacious in treating *A. baumannii* infections in a mouse pneumonia model without causing nephrotoxicity, showcasing superior therapeutic effects compared to commercial polymyxin B, which serves as the last line of defense in human medicine. This research establishes a novel standard paradigm for harnessing machine learning methodologies under conditions of limited available data.

Conclusions: In conclusion, FSLSMPEP proved effective in mining potent anti-*A. baumannii* AMPs from the whole hexapeptide, heptapeptide, and octapeptide libraries, even with limited true data. The wet-laboratory experiment validated the robustness of the EME pipeline, achieving a mining success rate of 91.1% (41/45) in discovering AMPs. Both the *in vitro* and *in vivo* tests showcased the functionality of the leading compounds, which displayed strong antimicrobial activity against diverse *A. baumannii* strains,

with no discernible tendency to induce drug resistance. Particularly, the leading heptapeptide, EME7(7), exhibited therapeutic outcomes comparable to polymyxin B in the *A. baumannii* infected acute pneumonia mouse model, without causing kidney injury as observed with polymyxin B. In addition to identifying AMPs targeting *A. baumannii*, this methodology was successfully applied to discover AMPs effective against *C. albicans*. This novel approach holds remarkable promise for accelerating the discovery of effective antimicrobial agents and addressing the pressing challenge of antibiotic-resistant pathogens. Furthermore, the versatility of FSLSMPEP makes it easily adaptable for various functional-peptide discovery tasks, particularly in fields grappling with data limitations. In addition, constrained by computational power, whole-library scanning approaches are challenging to implement in longer peptide sequence spaces. To address this issue, an AMP generation module could be incorporated prior to FSLSMPEP. This module generates manageable-sized candidate libraries of AMPs—such as one-billion-scale peptides—followed by whole-library screening. By this approach, similar screening methods enable exploration of larger peptide libraries.

Fig. 1. Overview of the FSLSMPEP.



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Advances in the field of biodegradable metals

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Biodegradable metals (Mg-, Zn-, Fe-, and emerging Mo-based alloys) represent transformative temporary implant materials enabling in vivo resorption after tissue repair, eliminating secondary surgery and long-term foreign-body risks. In contrast to the previously well-developed biodegradable polymers (PLA, PLGA, PCL), biodegradable metals show distinct differences in mechanical, degradation, biological and imaging properties. Biodegradable metals possess high strength, elastic modulus and load-bearing capacity, degrading via corrosion to release bioactive ions that promote osteogenesis and angiogenesis, with excellent radiopacity. Biodegradable polymers exhibit low strength and modulus, degrading through hydrolysis to produce acidic products, which may cause local inflammation. Biodegradable polymers are bioinert and radiolucent, suitable for drug delivery and soft tissue scaffolds, while biodegradable metals are preferred for load-bearing orthopedic and cardiovascular implants. Recent advances span alloy design, additive manufacturing (AM/L-PBF/SLM), surface modification, animal testing and clinical translation. Manufacturing breakthroughs include extrusion/L-PBF comparisons and PEO post-treatment for Zn/Fe/Mo alloys. Clinical translation advances with Mg bone screws, Zn-Cu stents, Fe-based vascular stents, and Mo-based neurovascular devices entering trials. Key challenges remain: precise degradation-healing matching, uniform corrosion, and long-term ion biocompatibility. Future directions target multi-functional alloy design, in situ monitoring, and personalized AM implants for orthopedics, cardiovascular, and neurointerventional applications. In this talks, we will present you our recent works on Mg-, Zn-, Fe-, and emerging Mo-based alloys, and propose the future research directions in the field of biodegradable metals.

Sequential-Gelation Hydrogel with Spatio-Temporal Control Reshapes the Degenerative Microenvironment for Intervertebral Disc Regeneration

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Chronic low back pain, primarily caused by intervertebral disc degeneration (IVDD), is characterized by the degradation of the extracellular matrix (ECM) within the nucleus pulposus (NP), driven by oxidative stress, chronic inflammation, and cellular senescence. A significant limitation of current injectable therapies is the poor diffusion and retention of materials within the high-pressure, enclosed NP environment. Inspired by both the blood coagulation process and the native ECM, we developed a sequential injectable hydrogel system based on cerium-ion (Ce^{3+}) metal-phenolic networks (MPNs). Initially, an ECM-mimetic HPTC hydrogel was engineered, where the TA- Ce^{3+} network demonstrated potent reactive oxygen species (ROS) scavenging, anti-inflammatory modulation, and, crucially, the ability to actively reduce local oxygen concentration. This function helps restore a hypoxic niche, activating the HIF-1 α pathway to mitigate cellular senescence and promote ECM biosynthesis. To overcome the delivery challenge, we further designed a dual-network HAD-HPTC hydrogel. This system mimics the coagulation sequence of "initial diffusion and infiltration followed by stable solidification," enabling comprehensive precursor distribution and delayed in situ gelation. This intelligent delivery platform retains all the biofunctions of HPTC while significantly enhancing its distribution homogeneity and retention stability within the degenerated discs of large animal models. Consequently, the HAD-HPTC hydrogel demonstrated superior efficacy in preserving disc structure and promoting tissue regeneration in vivo. This study presents a novel integrated strategy that simultaneously addresses the dual challenges of functional microenvironment modulation and efficient spatial delivery for regenerative IVDD therapy.

Rare-Earth modified biodegradable Zn alloys with Ti alloys-level strength and enhanced osteogenesis

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Key words: Zn alloys, rare earth elements, strengthening, osteogenesis, bone implants

Introduction: High strength and robust osteogenic capability are rarely achieved simultaneously in biodegradable materials for orthopedics. Building upon previously developed 500 MPa level Zn-Li-Mn ternary system, this study utilizes trace rare-earth (RE) elements to achieve a breakthrough in both mechanical and biological performance.

Materials & Methods: We designed and fabricated a new family of Zn-0.8Li-0.1Mn-RE quaternary alloys (ZLM-RE, RE=Y, Gd, Eu, Nd, Sm). Considering that RE elements are non-essential to the human body, we limited their content to 0.3 or 0.5 wt%, forming only a minor fraction of intermetallic phases, as supported by previous in vivo biocompatibility evaluations of Zn-RE systems. We systematically investigated their mechanical properties, microstructural evolution, and strengthening mechanisms, followed by comprehensive characterization of their electrochemical corrosion behavior, cytocompatibility, and osteogenic functionality. Using a critical-sized bone defect model, we further evaluated the in vivo degradation kinetics and bone regeneration performance of the ZLM-RE implants and elucidated their underlying osteogenic mechanisms.

Results & Discussion: By incorporating Y, Gd, Eu, Nd, and Sm into the Zn-Li-Mn alloy, REZn11-13 intermetallic phases are formed within the equiaxed Zn regions. These phases suppress dynamic recrystallization, generating a bimodal grain structure that, together with the original eutectoid ultrafine lamellae (LiZn₄+Zn), synergistically enhances mechanical strength. Among the developed alloys, Zn-0.8Li-0.1Mn-0.5Y (ZLM-0.5Y) achieves an ultimate tensile strength of 772 MPa, approaching the level of Ti-6Al-4V while retaining biodegradability. Moreover, the YZn₁₃ phase, with its intermediate electrochemical potential between Zn and LiZn₄, serves as a “potential-buffering” electrode that reduces galvanic corrosion current density, improves degradation uniformity, and subsequently regulates Zn ion release. This controlled release enables Zn to exert its osteogenic effect within an optimal concentration window, thereby significantly enhancing new bone formation. The released ions activate the Rap1 signaling pathway, resulting in a two-fold increase in bone regeneration compared to Ti-6Al-4V implants.

Conclusions: Collectively, these findings establish the Zn-Li-Mn-Y alloy that uniquely integrate ultrahigh strength with potent osteoinductive activity, providing a promising platform for next-generation load-bearing orthopedic implants.

Study on the degradation and metabolic behavior of an assembled magnesium alloy suture anchor

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Key words: Magnesium alloy, Suture anchor, Assembled structure, Degradation behavior, Metabolic behavior

Introduction: Biodegradable magnesium and its alloys have shown potential in promoting tendon-bone healing, making them promising materials for suture anchors. However, their application is challenged by the premature loss of mechanical strength due to eyelet degradation and by uncertainties regarding the *in vivo* metabolic behavior of their alloying elements.

Materials & Methods: To address these challenges, this study developed an assembled-structure Mg-Zn-Y-Nd-Zr (ZE21C) suture anchor. *In vitro* mechanical assessments and immersion tests were conducted alongside *in vivo* rat patellar ligament-tibia model. Comprehensive characterization utilizing SEM, micro-XRF, western blotting, Micro-CT and histology was employed to evaluate biomechanical stability, degradation behavior and elemental metabolic pathways over a 12-week period.

Results & Discussion: Mechanical tests revealed stable fixation with a pull-out force of 123.11 ± 5.92 N and fracture strength of 213.34 ± 3.60 N, ensuring no risk of anchor breakage under physiological loads. *In vivo* analysis revealed differential degradation kinetics: the threaded region degraded rapidly to facilitate osteogenesis, whereas the eyelet retained structural integrity to maintain fixation. Metabolic tracking indicated that while Mg was rapidly absorbed, Zn and Nd exhibited slower metabolic rates and accumulated locally. This accumulation was attributed to the degradation-induced microenvironment, which influenced the expression of cation-permeable channel proteins. Otherwise, successful fibrocartilage regeneration and gas cavity resolution were observed without implant failure.

Conclusions: The assembled magnesium alloy anchor effectively balances mechanical durability with biological integration. By elucidating the specific metabolic mechanisms of alloying elements and validating the reliability of the assembled design, this study provides a critical framework for the optimization and clinical application of biodegradable magnesium implants.

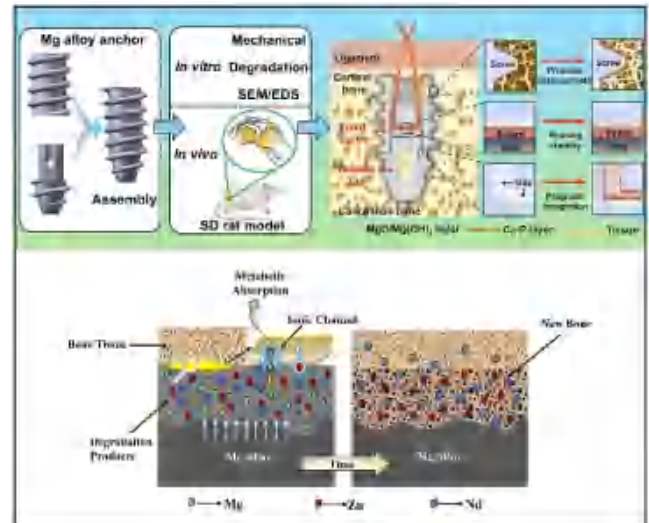


Fig. 1. Graphical Abstract

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Neutrophil-Mediated Inflammatory Response and Regulation in Zinc-Based Implants

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Key words: Zinc-based implants; Single-cell sequencing; Inflammatory response; Neutrophils

Introduction: Zinc-based metals have emerged as promising materials for bone repair and regeneration due to their excellent biocompatibility, tunable biodegradability, and multifunctional bioactivity. As the initial responders in the acute inflammatory phase, neutrophils regulate the resolution of inflammation by producing specialized mediators. However, the mechanisms by which neutrophils mediate the inflammatory response after zinc-based implant placement remain incompletely elucidated. This study employed single-cell transcriptomic technology to investigate the crosstalk mechanism between neutrophils and macrophages around zinc-based implants, aiming to provide a theoretical basis for the optimized design of zinc-based implants.

Materials & Methods: This study was divided into three groups: Zn group, Ti group, and Sham group. A rat femoral intramedullary implantation model was established. Peri-implant bone marrow tissues were collected 3 days postoperatively for single-cell transcriptomic sequencing. Seurat clustering, differential gene analysis, and CellChat analysis were used to decipher the characteristics, functions, and ligand-receptor interaction networks of cell subsets. Combined with HE staining, IHC, immunofluorescence staining, and material surface characterization, the material-tissue interactions and immune response features were comprehensively evaluated.

Results & Discussion: Single-cell transcriptomic analysis constructed a high-resolution cellular atlas of the peri-implant bone marrow microenvironment, identifying 10 major cell populations (neutrophils, macrophages, B cells, T cells, etc.). Compared with the Ti group, the Zn group exhibited reduced proportions of macrophages and neutrophils. Neutrophils were classified into four subsets (*Cd177*⁺Neu, *Ifit1bl*⁺Neu, *RatNP-3b*⁺Neu, and *Prtn3*⁺Neu). Among them, the proportion of the *Prtn3*⁺Neu subset was elevated in the Zn group, which enhanced tissue repair ability through the osteoclast differentiation pathway. Macrophages were divided into four subsets (*Hp*⁺Mac, *Apoe*⁺Mac, *RT1-Ba*⁺Mac, and *Eno3*⁺Mac). The Zn group was dominated by *Hp*⁺Mac, whereas the Ti group had a higher proportion of *Apoe*⁺Mac. Cell crosstalk analysis revealed that the *Ifit1bl*⁺Neu neutrophil subset formed a strong interaction with the *Eno3*⁺Mac macrophage subset via the Lgals9-Ighm ligand-receptor axis in the Zn group, promoting M2 polarization of macrophages.

In contrast, the interaction between *Cd177*⁺Neu and *Apoe*⁺Mac in the Ti group relied on the C3-Itgam axis, which tended to induce a pro-inflammatory response.

Conclusions: Zinc-based implants reshape the local immune microenvironment by regulating the heterogeneity of neutrophils and macrophages as well as their intercellular interaction networks, thereby promoting inflammation resolution and bone regeneration. The core mechanism is the M2 polarization regulation mediated by the Lgals9-Ighm axis between *Ifit1bl*⁺Neu and *Eno3*⁺Mac. This study provides new insights into the immunomodulatory design of biodegradable zinc-based bone implants.

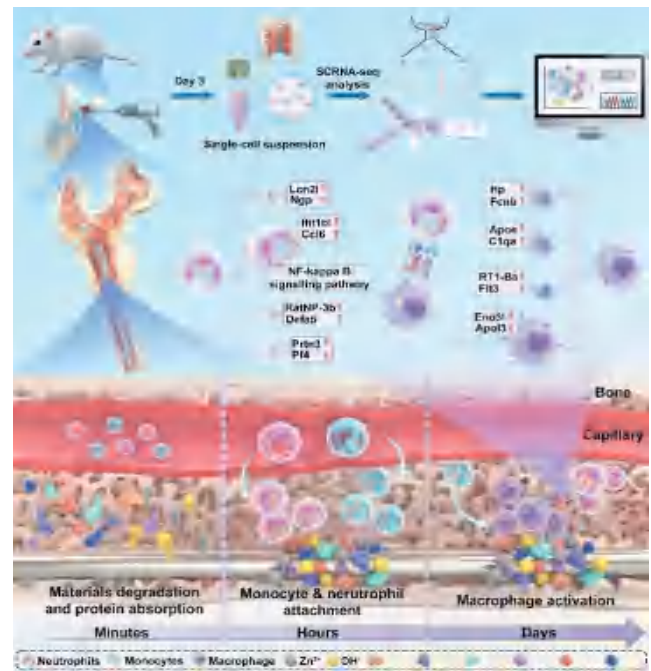


Fig. 1. Schematic illustration of neutrophil-macrophage crosstalk towards Ti versus Zn implants in the bone microenvironment, determined by single-cell transcriptomics.

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TWIP/TRIP metastable beta Ti and Zr Alloys for biomedical applications

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ABSTRACT

Twinning-Induced Plasticity (TWIP) and Transformation-Induced Plasticity (TRIP) mechanisms enhance ductility and strain-hardening in BCC alloys, as demonstrated in metastable Ti [1–4] and Zr [5,6] alloys, known for excellent biocompatibility. However, the yield strengths of TWIP/TRIP alloys are generally limited compared to high-strength Ti alloys due to the need for critical resolved shear stresses (CRSS) for twinning and martensitic transformation to be lower than for dislocation slip [4]. To address this, secondary phase engineering within the metastable beta matrix has been proposed to strengthen TWIP/TRIP BCC alloys (Ti and Zr) while preserving ductility [2,4]. This work presents two proof-of-concept cases for biomedical implant applications: (i) a TWIP/TRIP Ti alloy strengthened by isothermal omega phase precipitation [2,4]; and (ii) a TWIP Zr alloy strengthened by a quenched-in body-centered tetragonal (BCT) phase. In the case of Ti-12Mo alloy, controlled isothermal omega phase precipitation achieved an 80% increase in yield strength while maintaining >30% elongation to failure through TRIP/TWIP effects. In the Zr-Nb TWIP alloy, the introduction of a BCT phase in the solution-treated state increased the yield strength to 1.2 GPa, with a low elastic modulus of 70 GPa and a TWIP assisted ductility.

Keywords: TWIP; TRIP; Ti alloy; Zr alloy; Omega phase; body-centered tetragonal (BCT) phase

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Transformation-induced strengthening and controlled degradation in Zn–Li alloys designed for bioresorbable implants applications

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Abstract: Binary Zn-Li alloys are a new metallic system that has shown promising mechanical properties for bioresorbable stent applications. Their favorable mechanical performance is primarily associated with the formation of LiZn₄ phases and the eutectoid microstructure. Aging studies at 37 °C on Zn-0.8Li and Zn-0.8Li-0.1Mn model alloys demonstrate that progressive transformation from β -LiZn₄ to α -LiZn₄ leads to significant strengthening, with kinetics controlled by Li diffusion. The addition of Mn extends the transformation process, enhancing the mechanical stability of the alloys. Furthermore, the degradation behavior of Zn-Li and Zn-Li-Mn alloys was evaluated under both static and simulated cyclic conditions. The combined results provide insight into microstructural evolution, transformation-induced strengthening, and controlled in vitro degradation in Zn-Li alloys, offering guidance for the development of next-generation bioresorbable implants with improved mechanical performance and controlled degradation behavior.

Key words: Zn-Li alloys, phase transformation, mechanical strengthening, degradation behavior, bioresorbable implants

Antibacterial Design for Medical Metal Surfaces

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Key words: Medical metal, Antibacterial, Surface modification

Introduction: Failure of biomedical metal implants is mainly attributed to periprosthetic joint infection (PJI) and aseptic loosening, as material surfaces struggle to simultaneously achieve long-lasting antibacterial activity and stable tissue integration in the complex *in vivo* environment. Although PJI occurs in only 1-2% of cases, it imposes a substantial clinical burden; biofilms can increase bacterial tolerance to antimicrobials by up to a thousand-fold. The conflict between bactericidal “aggressiveness” and the “mild” microenvironment required for tissue integration is pronounced, highlighting the need for surface antibacterial designs that are long-lasting, broad-spectrum, and low in resistance risk without compromising mechanical reliability or corrosion/wear resistance.

Materials & Methods: Biomedical metal substrates were modified using surface nanostructuring and composite coating approaches to achieve synergistic antibacterial and osteogenic functions. First, a micro/nanostructured surface layer was fabricated via dealloying to tailor surface morphology and bioactivity. Second, antibacterial coatings were constructed by designing heterojunction structures to enhance antimicrobial performance. Third, antibacterial thin films were deposited through surface coating processes to form continuous functional layers. These routes collectively enabled the preparation of multifunctional metal materials with improved antibacterial efficacy and osteoinductive potential.

Results & Discussion: By constructing surface nanostructures and composite antibacterial coatings, this study successfully achieved a synergistic enhancement of “antibacterial activity–osteogenic promotion” on biomedical metals. The results demonstrate that the modified surface exhibits pronounced bacteriostatic/bactericidal effects against common pathogens and effectively suppresses bacterial adhesion and biofilm formation. Meanwhile, biocompatibility assessments indicate low cytotoxicity, improved adhesion, spreading, and proliferation of osteoblasts, and upregulated osteogenesis-related indicators, including ALP activity, mineralized nodule formation, and the expression of RUNX2 and OCN. Mechanistic discussions suggest that nanostructures reduce bacterial colonization through physical disruption and interfacial regulation, whereas heterostructures/functional coatings enable sustained antibacterial performance by enhancing interfacial charge transfer, inducing ROS generation, or

achieving synergistic ion release. The combination of these effects not only lowers infection risk but also creates a more favorable microenvironment for osteogenesis. In addition, the coating adhesion stability and corrosion/wear resistance were generally maintained or improved, supporting long-term implantation; however, further optimization of long-term durability and performance consistency under complex *in vivo* conditions is still required to facilitate clinical translation.

Conclusions: The integration of surface antibacterial strategies (nanostructures, functional coatings, and heterostructures) helps inhibit bacterial adhesion and biofilms while enabling osteogenic, anti-inflammatory, and corrosion-resistant functions on the same interface, broadening pathways for multifunctional implant surfaces.

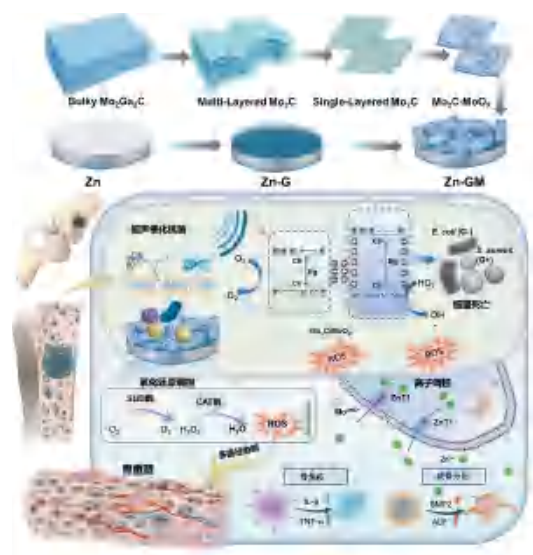


Fig. 1. A Mo_2C – MoO_x nano-heterojunction was constructed via etching and controllable oxidative heat treatment, and a heterojunction composite coating was further assembled on the zinc substrate through gelatin crosslinking.

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Study on crevice corrosion behavior of biodegradable pure zinc at bone fixation interfaces

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Biodegradable zinc alloys are regarded as promising novel materials for orthopedic repair due to their moderate degradation rate and favorable biocompatibility. However, the presence of crevice structures at the fixation interfaces of bone implants often leads to severe crevice corrosion, resulting in accelerated localized degradation. To date, the mechanism of crevice corrosion in zinc and its alloys remains unclear. This study aims to elucidate the mechanism of crevice corrosion in zinc alloys and to investigate the influence of crevice width on the corrosion behavior. The results indicate that as the crevice width increases from 0.1 mm to 1 mm, the corrosion rate of the zinc alloy within the crevice initially decreases and then rises, with the most severe corrosion shifting from the interior to the exterior of the crevice. At narrower crevice widths, the most pronounced corrosion occurs near the crevice mouth, where corrosion pit depths can exceed 90 μm , while the interior experiences milder corrosion, primarily due to the alkaline environment formed within the crevice which inhibits the corrosion process. This study enriches the understanding of the degradation mechanisms of zinc alloys and provides a theoretical reference for the design of controllable degradation in such materials.

Laser Powder Bed Fusion of β -metastable Ti-12Mo: processing–microstructure relationships towards high-strength TWIP/TRIP Ti for biomedical applications

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Ti-12Mo is a metastable β titanium alloy that can exhibit combined transformation-induced plasticity (TRIP) and twinning-induced plasticity (TWIP), offering an attractive strength–ductility balance and strong work-hardening potential. These features, together with the corrosion resistance and biocompatibility generally associated with β -Ti systems, have motivated growing interest for load-bearing biomedical components.

Additive manufacturing, and in particular laser powder bed fusion (LPBF), is increasingly considered for patient-specific medical devices. However, transferring TRIP/TWIP characteristics to LPBF-produced metastable Ti alloys remain challenging. The complex thermal gradients and cyclic heating-cooling inherent to LPBF can degrade ductility and suppress TRIP/TWIP effects.

This proof-of-concept study aims to establish evidence and a process–structure–property framework for LPBF-processed Ti-12Mo produced from a pre-alloyed powder. A matrix of LPBF parameter sets is explored to generate distinct solidification and thermal histories. The resulting alloys are assessed in terms of chemical homogeneity and defects, β grain morphology/texture and secondary phase precipitation, deformation mechanisms and macroscopic mechanical response.

A secondary goal is to identify processing pathways that enable the tunable coexistence of TRIP/TWIP signatures with controlled stiffness/strength levels, without need for further post-processing.

Keywords: metastable β -Ti; LPBF; ω precipitation; TRIP/TWIP; biomedical devices.

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Built-in Electric Field-Driven Membrane Disruption in Ultrasound-Activated Dual-Vacancy Piezoelectric Heterojunctions

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Key words:

Built-in electric field (BIEF); Electric-field-driven membrane disruption; Dual-vacancy engineering; Ultrasound activation; Implant-associated infection

Introduction:

Implant-associated infections, exacerbated by antibiotic resistance, remain difficult to eradicate. At the nano-bio interface, ultrasound-activated piezoelectric coatings are widely studied, yet bactericidal outcomes are still predominantly interpreted through reactive oxygen species (ROS), heating, or cavitation, while interfacial built-in electric fields (BIEFs) are rarely treated as a quantitatively designable antibacterial modality. We ask whether an ultrasound-amplified BIEF at a defect-engineered heterojunction can cross a membrane-stability threshold and directly initiate physical membrane failure.

Here, we introduce a dual-vacancy piezoelectric heterojunction coating ($\text{BaTiO}_{3-x}/\text{MoS}_{2-x}$) that directionally amplifies the ultrasound-activated BIEF. We demonstrate that an effective BIEF ~ 0.4 V/nm is sufficient to drive a permeabilization-to-rupture transition of lipid bilayers, establishing BIEF-driven physical membrane disruption as a primary, programmable antibacterial mechanism. Importantly, this mechanism enables rapid bacterial clearance and improved outcomes in an infected-implant model.

Materials & Methods:

DFT calculation; Synthesis of $\text{BTO}_{3-x}/\text{MoS}_{2-x}$; COMSOL Multiphysics; GROMACS simulation; Protein Leakage Assay; Cell Membrane Permeability Assay; In Vivo Osteogenic Experiment;

Results & Discussion:

1. A conceptual shift: elevating BIEF from an auxiliary effect to a quantitatively controllable primary antibacterial driver. We establish an explicit field-threshold framework for ultrasound piezoelectric antibacterial systems, demonstrating that membrane disruption can be initiated by BIEF itself rather than being solely attributed to ROS/cavitation.

2. Defect-engineered nanointerface design: a dual-vacancy piezoelectric heterojunction coating that amplifies BIEF under ultrasound. DFT-guided screening identifies the $\text{BaTiO}_{3-x}/\text{MoS}_{2-x}$ heterojunction as an optimal architecture where coupled oxygen and sulfur vacancies reshape interfacial polarization and electrostatics. The coating exhibits enhanced piezoresponse and charge-transport behaviour, enabling directional field amplification at the heterointerface.

3. Quantitative, multi-scale mechanism linking materials physics to membrane failure. Multiscale

modelling and membrane assays provide quantitative evidence that an effective BIEF of ~ 0.4 V/nm drives lipid-bilayer destabilization and water-channel formation, matching staged experimental readouts from permeability increase to irreversible rupture. Surface-potential mapping shows an ultrasound-induced upshift in surface potential and enhanced local potential contrast, consistent with a reshaped interfacial electrostatic landscape.

4. Biological relevance and translational potential for implant infection therapy. The coating achieves rapid killing of *Staphylococcus aureus* under ultrasound (99.6% within 15 min) and retains substantial activity even when hydroxyl radicals are scavenged or cavitation is suppressed, supporting BIEF-driven killing as a primary pathway. In a rat infected-implant model, ultrasound-activated $\text{BaTiO}_{3-x}/\text{MoS}_{2-x}$ rapidly reduces peri-implant bacterial burden and promotes a bone-healing-favourable microenvironment without evident systemic toxicity.

Conclusions:

In summary, this work elevates the BIEF as a quantitatively controllable dominant antibacterial pathway, establishing a generalizable material design paradigm for developing physicochemical synergistic antibacterial implants targeting drug-resistant implant-associated infections.

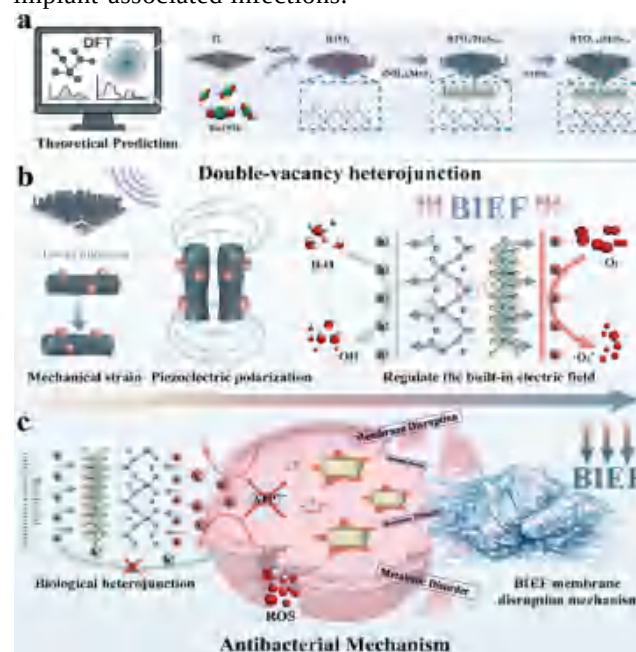


Fig. 1. BIEF-driven membrane disruption in ultrasound-activated dual-vacancy piezoelectric heterojunctions.

Biodegradable Zinc-Lithium-Copper Alloys for Orthopaedic Implants

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Key words: Biodegradable Zinc alloys, biomaterials, tissue engineering

Introduction: Biodegradable orthopaedic implants are attracting increasing attention as they eliminate the need for secondary surgery, thereby reducing infection risks and patient discomfort. An ideal biodegradable implant must exhibit appropriate mechanical strength, a moderate degradation rate, and excellent biocompatibility [1]. Among biodegradable metals, zinc (Zn)-based alloys have shown promise due to their moderate degradation rate; however, challenges remain regarding their mechanical strength and biocompatibility [2][3]. This study explores novel Zn-based alloys for orthopaedic implants, focusing on their in vitro biodegradation and biocompatibility.

Materials & Methods: The Zn alloys with Lithium (Li) and Copper (Cu), in four varying compositions (A, B, C, and D) were characterized for their biodegradation behaviour via a 30-day immersion test in simulated body fluid (SBF) using SEM, ICP-MS, and XRD analyses. Biocompatibility was evaluated including cell viability via MTT assays, oxidative stress via ROS production and NO measurements, and ALP activity for osteogenic potential. In biocompatibility experiments, ICP-MS was also used to analyse the mass of metallic ions absorbed by cells.

Results & Discussion: The corrosion behaviour of Zn-Li-Cu alloys was assessed via a 30-day immersion test. SEM imaging (Fig. 1a) revealed corrosion morphology of the alloys. XRD (Fig. 1b) identified Zn, CuZn₄, and LiZn₄ as key phases in degradation. ICP-MS (Fig. 1c) details corrosion rates of these alloys.

Biocompatibility evaluation showed pre-osteoblastic cell MC3T3-E1 viability >70% at 50% extract (Fig. 1d-f), while only the extract concentration lower than 25%, fibroblast cell L929 did not suffer significant difference (Fig.1g-i). ROS and NO levels remained stable, and ALP activity increased after 14 days. Osteoblast cells treated with Zn-Li-Cu alloy extract has a higher cell viability than treated with Zn-Ca, Zn-Sr, Zn-Mn, Zn-Fe, and Zn-Ag alloy extracts [4], reinforcing Zn-Li- Cu alloy has better biocompatibility for bone cells and potential for orthopaedic applications.

Conclusions: Zn-Li-Cu alloys exhibit moderate

biodegradation rates and excellent biocompatibility, making them promising candidates for biodegradable orthopaedic implants. Further investigations on microstructure, mechanical properties, and in vivo performance are necessary to evaluate their long-term safety and clinical feasibility.

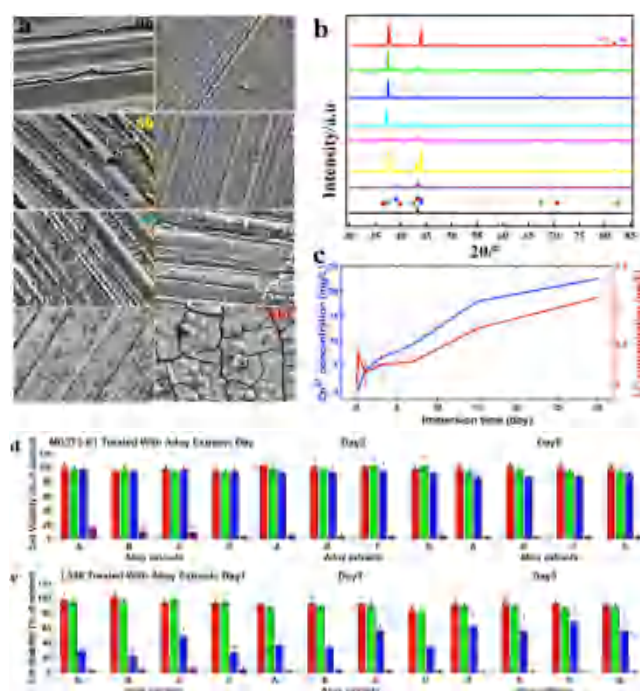


Fig. 1. Biodegradation characterization: (a) biodegradation morphology, (b) biodegradation products analyses and (c) the released Zn²⁺ and Li⁺ concentration in SBF for 30 days' immersion. Biocompatibility evaluation: cell viability of (d) MC3T3-E1 and (e) L929 treated with alloy extracts for 1, 3, and 5 days.

Acknowledgements

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Biodegradable intermetallic compounds

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Intermetallic compounds (IMCs) exhibiting high strengths and appropriate degradation rates remain scarcely available. We develop a novel biodegradable LiZn₄-IMC demonstrating a degradation rate of 0.21 mm/year and a high strength of 438 MPa, which exhibits potential for orthopedic applications. In 0.9 % NaCl solution, the degradation products comprise water-soluble Li⁺ and Zn²⁺ ions, as well as depositions of Zn(OH)₂, ZnO, and Zn₅(CO₃)₂(OH)₆. With the extension of time, pitting corrosion due to dealloying of Li transitions to uniform corrosion. The synergistic action of Li⁺/Zn²⁺ ions endows the IMC with favorable biocompatibility and excellent antibacterial properties.

Rinse-Triggered Thermoresponsive Dental Implant for On-Demand Biofilm Clearance and Tissue Integration

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Key words: Titanium, dental implant, biofilm clearance, tissue integration, *in vivo*

Introduction: The persistent challenge of bacterial infection in dental implants, compounded by the limitations of current antimicrobial strategies, such as microbiome disruption and compromised tissue integration, motivates the search for smarter, more clinically adaptable solutions. Routine oral rinsing creates a transient temperature gradient across the implant, cooling the vulnerable transgingival region to ~30 °C while the intraosseous portion remains at 37 °C. This study investigates whether this physiological cue can be harnessed to design a minimalist, thermoresponsive implant coating that dynamically switches function with daily patient behavior.

Materials & Methods: Using a single polymer (MPEG) grafted onto titanium, we achieve a surface that becomes superhydrophilic at rinsing temperature (enabling on-demand bacterial removal) and reverts to a cell-favorable conformation at body temperature (promoting soft and hard tissue integration).

Results & Discussion: The coating preserves surface chemistry needed for soft- and hard-tissue integration, shows no bactericidal activity, and retains performance after sterilization, 90-day artificial-saliva aging, and implantation-mimetic mechanical challenge. *In vitro*, a 25 °C rinse removed 89–97% of established biofilms of *S. aureus*, *A. actinomycetemcomitans*, *P. gingivalis*, and

P. intermedia compared with rinsed titanium controls. We demonstrated efficacy across three *in vivo* models: (i) a rabbit peri-implantitis model, where MPEG plus weekly rinses reduced biofilm to ~6% of titanium controls; (ii) dogs receiving commercial screw-type implants to benchmark our system, where biofilm fell to ~7% of rinsed titanium; and (iii) a prospective human oral-exposure study using removable retainers (n=4), where MPEG-grafted discs accumulated ~5-18% of biofilm on matched titanium at 15-30 days with fewer pathogenic taxa.

Conclusions: These results establish a minimalist, rinse-activated strategy for on-demand biofilm clearance while improving peri-implant tissue integration, advancing a path from bench to rabbit-dog-human translation.

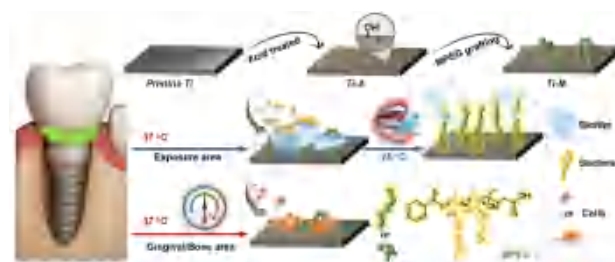


Fig. 1 Schematic illustration of the preparation of the functionalized titanium implant.)

Semiconductor biomaterials for antibacterial

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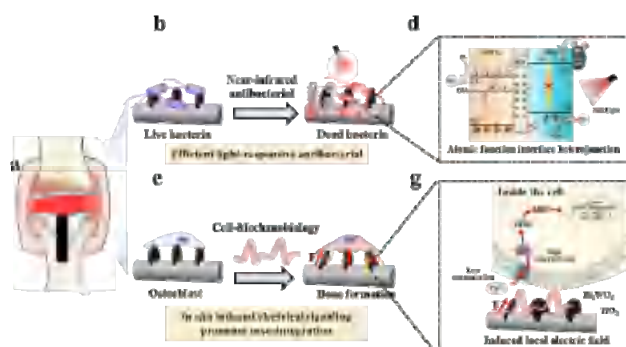
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Key words: piezoelectric heterojunction, photodynamic therapy, antimicrobial implant, bone regeneration

Introduction

Conventional titanium implants frequently encounter the severe dual challenges of delayed osseointegration and susceptibility to postoperative bacterial infections. While semiconductor heterojunctions have been extensively utilized in energy conversion, their potential within regenerative medicine particularly utilizing piezoelectric heterojunctions to remodel the implant microenvironment remains largely unexplored. This study proposes a novel design strategy to construct a TiO₂/Bi₂WO₆ piezoelectric heterojunction array featuring light-mechanobiological-electrical coupling effects, aiming to simultaneously resolve implant infection and tissue repair barriers through non-invasive photoelectric mechanisms.



Scheme 1. Schematic illustration of the dual-functional therapeutic mechanisms of the TiO₂/Bi₂WO₆ piezoelectric heterojunction implant.

Materials & Methods

The TiO₂/Bi₂WO₆ array was fabricated on titanium substrates via sequential alkaline thermal activation and in situ solvothermal synthesis. Its morphology, broadband optical absorption, and localized electromechanical properties were characterized using SEM, UV-Vis, and PFM. Biological efficacy was evaluated via in vitro antibacterial plate assays and an in vivo rat femoral defect model.

Results & Discussion

As illustrated in the schematic mechanisms (Scheme 1), the therapeutic efficacy relies on a dual-action light-mechanobiological-electrical coupling. Under NIR irradiation, the synergistic interplay of engineered oxygen vacancies and the intrinsic electric field drive rapid charge separation, generating massive ROS and

localized heat for bacterial eradication. Concurrently, the mechanical traction of adhering cells deforms the piezoelectric interface, spontaneously inducing a localized electric field that stimulates intracellular Ca²⁺ influx, activates the PI3K-AKT pathway, and upregulates osteogenic genes. Experimental characterizations (Figure 1) physically and biologically validate this paradigm. SEM reveals Bi₂WO₆ nanocrystals intimately anchored onto the TiO₂ nanowire scaffold. UV-Vis spectroscopy confirms a significantly broadened NIR absorption profile, while PFM distinctly records classic amplitude and phase loops, verifying the robust localized piezoelectricity of the interface. Functionally, in vitro agar plate assays demonstrate that the photothermal/photodynamic synergy of the heterojunction eradicates bacterial colonies nearly completely under NIR exposure. Correspondingly, in vivo Micro-CT 3D reconstructions definitively establish that the TiO₂/Bi₂WO₆ implant significantly accelerates dense new bone formation and facilitates superior osseointegration compared to the pristine Ti control.

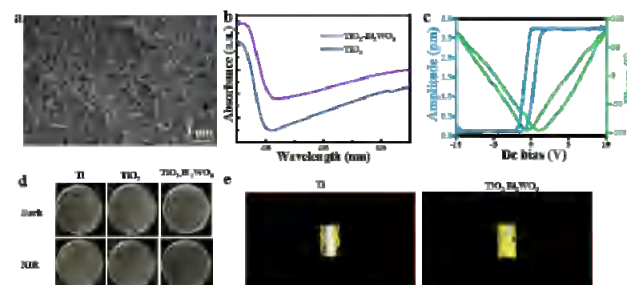


Figure 1. Comprehensive Evaluation of the Physical, Chemical, and Biological Properties of the TiO₂/Bi₂WO₆ Piezoelectric Heterojunction Implant. (a) Morphological characterization. (b) Optical properties. (c) Local piezoelectric response. (d) In vitro antibacterial performance. (e) In vivo bone integration analysis.

Conclusions

The TiO₂/Bi₂WO₆ piezoelectric heterojunction seamlessly integrates NIR-responsive in vitro antibacterial efficacy with mechanobiologically-driven in vivo osteogenesis. This interface provides a highly translatable design paradigm for next-generation smart orthopedic devices.

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Multi-Scale Engineering of Additively Manufactured Biodegradable Zinc

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Key words: Additive Manufacturing; Biodegradable Metals; Degradation; Mechanical Properties; Bioactivity

Introduction: With the continuous increase in the number of patients with musculoskeletal disorders worldwide, clinical problems such as bone defects, osteochondral defects, and fractures have become increasingly prominent. Due to the hierarchical structure and significant individual differences of human bone tissue, there is an urgent demand for personalized design and functionally gradient construction of bone implants. Traditional manufacturing processes can hardly meet such diversified and complex requirements, whereas additive manufacturing technology exhibits unique advantages in fabricating customized bone implants. In recent years, biodegradable metallic materials with favorable biocompatibility and in vivo degradability have attracted increasing attention. The combination of additive manufacturing and biodegradable metals is expected to simultaneously satisfy the comprehensive requirements of bone repair materials in terms of mechanical properties, bioactivity, and degradation behavior. Nevertheless, this interdisciplinary field is still in its infancy, and its performance is co-determined by multi-scale factors including composition, microstructure, and macrostructure. It is urgent to reveal the intrinsic correlation mechanisms and carry out systematic regulation and optimization studies.

Materials & Methods: Laser Powder Bed Fusion (LPBF) was employed to fabricate additively manufactured biodegradable metallic materials. Process optimization and compositional design were applied to tailor the microstructure of the materials, so as to improve their forming quality and mechanical properties. Subsequently, typical porous structures were designed, and their mechanical, degradation, and biological performances were systematically investigated to reveal the mechanism by which mesoscopic structural design affects the overall properties. Functionally gradient structures were adopted to regulate the degradation behavior and fatigue performance. On this basis, structurally and functionally integrated implants were designed for clinical scenarios of osteochondral and subchondral bone repair, and animal experiments were conducted to verify the tissue repair efficacy.

Results & Discussion: High compressive strength-ductility ZnMg eutectic binary alloys and high tensile strength-ductility ZnMnMg ternary alloys were separately developed. The additively manufactured

ZnMg eutectic alloy achieved a compressive yield strength of 600 MPa and remained unbroken at a compressive strain exceeding 60%, far exceeding the compressive performance requirements of human load-bearing bones. For the additively manufactured ZnMnMg ternary alloy, multi-scale strengthening and toughening were realized via the dual second phases of $\text{Mg}_2\text{Zn}_{11}$ and MnZn_{13} . For the first time, the additively manufactured biodegradable metal exhibited a tensile strength of 290 MPa and an elongation of more than 20%, meeting the tensile mechanical property requirements for bone implant devices. By using functionally gradient structures, the flow distribution of liquid inside the porous structure was regulated, decoupling the positive correlation between porosity and degradation rate. The initiation sequence of fatigue cracks in porous pure zinc was controlled, and the fatigue life was improved. A full-thickness bone defect model was established in Bama miniature pigs. Through the novel strategy of porous zinc-hydrogel bilayer scaffolds, dual gradients of mechanics and bioactivity were achieved, simultaneously promoting cartilage and bone regeneration.

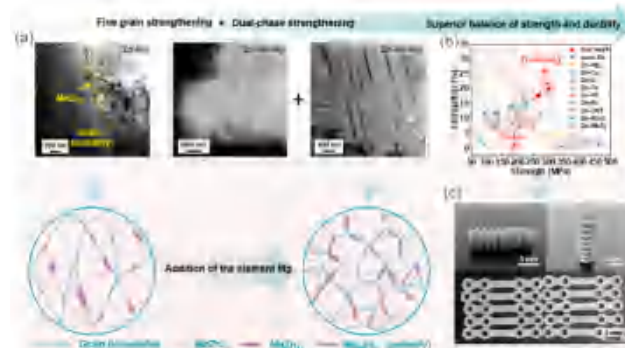


Fig. 1. Strengthening mechanisms of AM Zn alloy

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Biomedical liquid metal micro/nano-robots

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Key words: biomedical micro/nanorobots, liquid metal, surface functionalization, structural functionalization

Introduction: Biomedical micro/nanorobots (MNRs) refer to miniature functional devices with dimensions ranging from the micrometer to nanometer scale that can actively move in vivo or in biological fluids, or be controllably manipulated under external fields.¹ Owing to their navigability, sensing capability, and task-execution capacity, they offer a new technological route toward more precise diagnosis and therapy in confined spaces that are inaccessible to conventional instruments. Gallium based liquid metals (Ga-LMs), as an emerging class of soft active matter, feature a low melting point, deformability and reconfigurability, excellent electrical and thermal conductivity, and favorable biocompatibility, and have therefore become an important building platform for next generation biomedical micro/nanorobots.² However, to meet the demands of in vivo applications in complex physiological environments, liquid metal micro/nanorobots typically require systematic design along two main lines, namely surface functionalization and structural functional modification. We address two key challenges by proposing corresponding design and construction strategies along these two directions, thereby enabling controllable locomotion and functional implementation of liquid metal micro/nanorobots in biological tissue environments.

Results & Discussion: In terms of surface functionalization, we load functional units such as two-dimensional photocatalytic materials,³ metallic catalytic components,⁴ bioenzymes,⁵ and magnetic particles⁶ to enable effective actuation and motion regulation of LMs under diverse stimuli including light, chemical substrates, and magnetic manipulation. Meanwhile, the formation of heterostructures between the LM and composite constituents further strengthens electron transport and interfacial reaction capability, thereby extending therapeutic efficacy in antibacterial and antitumor applications. In addition, coupling drug payloads with controllable motile behaviors enables precise delivery functions such as targeted accumulation and on site release.

In terms of structural functional modification, by constructing anisotropic architectures such as rod-like and spiky structures, the interfacial contact force and the traction and translocation capability of LM-MNRs during locomotion across complex biointerfaces are enhanced. These structural designs also provide tunable mechanical stimulation, which strengthens physical

interactions with tissue cells or microorganisms and thereby enhances mechanical killing and localized intervention performance.

Conclusions: In summary, through synergistic surface and structural functionalization, we transform LMs from active material carriers into an integrated structure–function microdevice platform that combines controllable actuation, environmental adaptability, and functional execution, thus laying a foundation for their broad in vivo applications.

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Additively manufactured biodegradable molybdenum for biomedical applications

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Key words: Biodegradable metal, molybdenum, additive manufacturing, vascular stent, bone scaffold

Introduction: Recently, molybdenum (Mo) is being explored to be a new biodegradable metal, which exhibits superior mechanical properties and an ideally uniform degradation mode [1]. However, it is difficult to be processed through traditional deformation or machining due to its high strength & hardness. Additive manufacturing (3D-printing) is a good way to get rid of this dilemma [2]. Here, Mo components (bulk, thin-wall) were directly fabricated with fine Mo powder through selective laser melting (SLM). Systemic analyses considering the forming quality, microstructure, mechanical properties, *in vitro* degradation behavior and biocompatibility were performed. Then, *in vivo* implantation evaluations of typical 3D-printed devices (vascular stent, porous bone scaffold) were successively carried out. This work possibly opens a new era of 3D-printed Mo-based structural parts for biomedical applications.

Materials & Methods: First, bulk Mo components were fabricated with Mo powder through SLM. Microstructure, *in-vitro* corrosion behavior and biocompatibility of the as-obtained Mo were thoroughly investigated to get the most fundamental information. Then, thin-wall devices (vascular stent and porous bone scaffold) were directly 3D-printed using the optimized printing parameters. Next, the feasibility of the aforementioned devices was generally evaluated both *in vitro* and *in vivo*, by using proper cell models and animal models. Overall, the first-hand information on Mo 3D-printing and its biomedical applications was provided.

Results & Discussion:

(i) For 3D-printed bulk Mo: Ineluctable hot cracks were found in SLMed bulk Mo, and those defects accelerated the initial corrosion (one order of magnitude higher), showing a different corrosion mode and evolution pattern compared to those of traditionally metallurgical bulk Mo (Fig. 1). Still, SLMed Mo exhibited good hemocompatibility, and mouse/rat-derived mesenchymal stem cells have certain tolerance to its extract.



Fig. 1 Corrosion mechanism of SLMed Mo compared to bulk Mo.

(ii) For 3D-printed vascular stent: Mo-based thin-strut ($\leq 100 \mu\text{m}$) stents were successfully obtained through an optimized single-track laser melting route, which exhibited a nearly full-dense and crack-free microstructure. Vessel related cells were well adhered and spread on SLMed Mo, and it exhibited a low risk of hemolysis and thrombus. The stent was compatible to vessel tissues in rat abdominal aorta, and it provided sufficient support in a vein graft animal model as an



Fig. 2 Schematic diagram showing 3D-printed Mo stents and their applications

extravascular stent (Fig. 2).

(iii) For 3D-printed bone scaffolds: Mo-based porous scaffolds were successfully manufactured, with their loading capacity being adjusted through porosity control. They can provide sufficient support in a certain period (~ 3 mon.) without obvious strength reduction after 1-month corrosion. They exhibited good cytocompatibility *in vitro* and decent osteoconduction capacity *in vivo*, comparable to those of TC4 scaffolds.

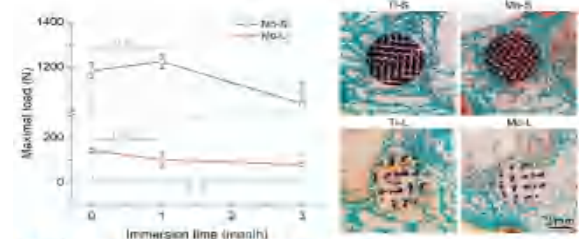


Fig. 3 Mechanical retention of 3D Mo scaffolds and histopathological results *in vivo*.

However, no established bioactivity was observed.

Conclusions: Mo-based thin-wall devices were successfully fabricated through additive manufacturing, and they exhibited promising performances regarding the aspects of mechanical strength, corrosion behavior and biocompatibility. However, more research is needed in this field to reveal more information.

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Gradient-Based High-Throughput Optimization of Titanium Implant Coatings for Enhanced Osseointegration

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Key words: High-throughput screening; Titanium; Antibacterial; Osteoimmunomodulation

Introduction: Bacterial infection and implant loosening are the two major causes of clinical implant failure. Surface functionalization of titanium-based implants has attracted considerable attention because of its high controllability and broad applicability [1]. However, conventional fabrication methods are inefficient for screening large parameter sets, and discontinuous parameter selection may overlook optimal conditions, thereby limiting understanding of the structure–function relationship between material architecture and biological performance. To overcome these limitations, high-throughput screening (HTS) was introduced. A continuously graded nanowire coating was fabricated on titanium surfaces in a single step using a sequential microdroplet method. Multicellular functional screening then identified the optimal nanowire dimension for osseointegration [2]. Based on this surface, a gradient phase-transition lysozyme (PTL) coating was further constructed. Comprehensive evaluation of its antibacterial and osseointegration properties provided an effective strategy to address the challenge of balancing these two functions in implant materials.

Materials & Methods: Using a custom-built high-throughput platform, a gradient nanowire coating with continuously varied dimensions was fabricated on titanium (Ti) surfaces in one step by delivering 2.5 M NaOH at 0.5 mL/h via sequential droplet technology. The responses of macrophages (MΦs), endothelial cells (ECs), and bone marrow mesenchymal stem cells (BMSCs) to the gradient surface were evaluated to identify the optimal nanowire structure for osseointegration. A gradient PTL coating with continuously varied thickness was then constructed on the optimized nanowire surface by sequentially depositing a mixture of equal volumes of 0.5 mg/mL lysozyme and 50 mM TCEP. Assessment of bacterial and cellular responses identified the optimal PTL thickness, which provided strong antibacterial activity while preserving cellular function.

Results & Discussion: 1. High-throughput material fabrication was employed to precisely construct gradient nanowire coatings on Ti surfaces, with nanowire diameters continuously increasing from 8.7 to 43.2 nm. 2. Specific small-sized nanowires were found to regulate the TLR-PI3K/Akt signaling pathway, promoting MΦs polarization toward the pro-healing M2 phenotype, thereby enhancing ECs angiogenesis and BMSCs osteogenic differentiation. Meanwhile, MΦs established

a favorable immune microenvironment that further supported angiogenesis and osteogenesis.

3. Composite coatings that simultaneously preserved PTL and nanowire morphology were shown to synergistically enhance both osseointegration and antibacterial performance.

4. The mechanism by which nanowire-PTL composite coatings activate macrophage-mediated bacterial phagocytosis through the TLR4-NF-κB axis was elucidated, enabling effective infection suppression while preserving osseointegration.

Conclusions: To address the critical challenge of rapidly constructing and optimizing functionalized titanium-based implants, this study employed high-throughput fabrication and screening to precisely prepare gradient nanowire and gradient PTL coatings on titanium surfaces. These coatings optimized osseointegration, conferred potent antibacterial activity through PTL incorporation, and modulated the local immune microenvironment, thereby achieving a balance between antibacterial efficacy and osseointegration. This study provides an innovative strategy and experimental foundation for overcoming the conflict between antibacterial activity and biocompatibility.

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Thermoelectric Glycyrrhizic Acid Hydrogel for Periodontitis Treatment

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Abstract: As a chronic inflammatory disease with high global incidence, periodontitis seriously threatens human oral and even systemic health. Herein, a novel thermoelectric Cu₂Se(CuSe)/SnSe₂@GA material with high antibacterial properties was prepared. The heterogeneous interface formed between Cu₂Se and SnSe₂ causes phonon scattering and additional carrier transport channels. Internal electric field constructed by the thermoelectric effect effectively hinders the recombination of carriers, which brings higher power factor ($ZT=0.025$ at 450K) to the material. Under the co-excitation of 808 nm near-infrared light and ultrasound, excellent antibacterial properties has been shown. (>98.37% against *S. aureus* and >99.54% against *P. gingivalis*). Furthermore, the combination of glycyrrhizic acid modified hydrogel can significantly down-regulate the expression level of macrophage pro-inflammatory factor (TNF- α) by 68%, reduce the damage of inflammation to alveolar bone. This work establishes a new paradigm of thermoelectric hydrogel for tissue regeneration and resolves critical limitations in antibacterial therapies.

Key words: thermoelectric hydrogel, antibacterial, periodontitis, synergistic excitation, photo-sonodynamic therapy

Introduction: Periodontitis, affecting nearly 90% of the global population, is triggered by oral microbial dysbiosis and pathogenic biofilms[1]; traditional mechanical and antibiotic therapies suffer from incomplete pathogen elimination and adverse effects, while emerging photo/ultrasonic-responsive strategies are limited by low ROS generation[2]. Thermoelectric (TE) materials, capable of heat-electricity interconversion, showing promise for antibacterial therapy[3]. For periodontitis treatment, TE materials face core challenges of low in vivo temperature gradients and biocompatibility issues, while Cu₂Se and SnSe₂ exhibit complementary TE properties[4]. To address the above limitations, this study constructs a Cu₂Se(CuSe)/SnSe₂ heterojunction TE system, which generates local thermal effects and activates an internal TE field under 808 nm NIR and ultrasound synergy; the photo-ultrasonic-thermoelectric coupling achieves excellent antibacterial effects against *S. aureus* and *P. gingivalis*. A Cu₂Se(CuSe)/SnSe₂@Glycyrrhizic acid (GA) hydrogel is further fabricated and has been evaluated in a rat periodontitis model confirm the hydrogel possesses outstanding anti-inflammatory activity and favorable in vitro/in vivo biocompatibility.

Materials & Methods: Raw materials including Cu₂Se, SnSe₂, and glycyrrhizic acid (GA) were commercially sourced for material preparation. The Cu₂Se(CuSe)/SnSe₂ heterojunction was fabricated via mechanical ball milling, followed by spark plasma sintering (SPS). Acile self-assembly method was used to synthesize the Cu₂Se(CuSe)/SnSe₂@GA hydrogel.

Characterization represented by morphological and microstructural features, photothermal/sonothermal property were characterized. Key thermoelectric parameters were measured via standardized test systems.

The in vitro antibacterial efficacy of the synthesized materials against key periodontal pathogens *S. aureus* and *P. gingivalis* was evaluated via the spread-plate method. Furthermore, biocompatibility tests were carried out to verify the biosafety of the therapeutic platform. A rat periodontitis model was established using male Sprague-Dawley (SD) rats. After treatment intervention, the anti-periodontitis efficacy was evaluated.

Results & Discussion: The successful synthesis of Cu₂Se(CuSe)/SnSe₂ was observed in detail by transmission electron microscopy. Study have also demonstrated that Cu₂Se(CuSe)/SnSe₂ exhibited superior photo-ultrasonic thermal conversion performance, reaching 56.7 °C after 5 min of co-stimulation—much higher than pure SnSe₂ (45°C) and Cu₂Se (34°C). We also characterized the thermoelectric performance of the p-type

Cu₂Se/n-type SnSe₂ heterojunction (Cu₂Se(CuSe)/SnSe₂) over 300–450 K. The key results demonstrate that the heterojunction thermoelectric figure of merit (ZT) reaches a maximum of ~ 0.025 at 450 K with a continuous upward trend as temperature increases.

The antibacterial efficiency of Cu₂Se(CuSe)/SnSe₂ under 808 nm near-infrared light alone was only 55.23%. In the case of US treatment, there was no obvious change in the number of colonies compared with the control group. However, under the synergistic effect of infrared and ultrasound, Cu₂Se(CuSe)/SnSe₂ can achieve an antibacterial rate for over 99%.

Mechanism analysis (Figure 1) showed that the combined stimulation of infrared and ultrasound has a synergistic effect to promote the efficient production of electron-hole pairs. On the other hand, thermoelectric potential at both ends of the heterojunction effectively inhibiting the recombination of electron-hole pairs, the long-term relaxation promote high ROS production, thereby exhibiting excellent antibacterial ability.

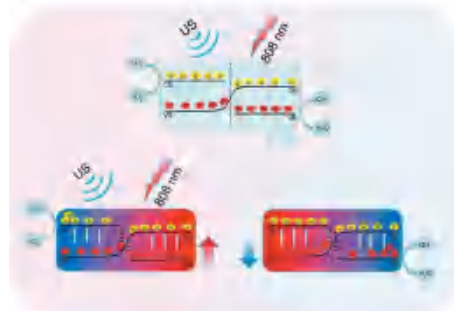


Figure 1 Schematic illustration of photo-ultrasonic-thermoelectric synthetic antibacteria mechanism.

A self-assembled Cu₂Se(CuSe)/SnSe₂@GA hydrogel have been synthesized. In vitro assays validated excellent biosafety: the hydrogel achieved 94.2% and 97.8% viability of mouse gingival fibroblasts at day 1 and day 3, respectively, with a relative hemolysis rate below 5% that complies with international biomedical standards.

Conclusions: This work synthesized a thermoelectric Cu₂Se(CuSe)/SnSe₂ heterojunction with excellent photo-ultrasonic responsiveness and low thermal conductivity, which achieved a ZT value of 0.025 at 450 K. The synergistic photo-ultrasonic-thermoelectric effect endowed Cu₂Se(CuSe)/SnSe₂ with antibacterial rates of 98.37% against *S. aureus* and 99.54% against *P. gingivalis*. Moreover, the synthesized Cu₂Se(CuSe)/SnSe₂@GA hydrogel exhibited excellent therapeutic efficacy and reliable in vitro/in vivo biocompatibility in a rat periodontitis model. This study provides a feasible strategy for the in vivo antibacterial application of thermoelectric materials and the clinical treatment of periodontitis.

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Microwave-Triggered Co-Delivery of Heat and Nitric Oxide Platform for Long-term Treatment of Deep-Seated Infections

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Microwave thermal therapy (MTT) offers an effective approach to target deep infections, elevating local temperatures to eliminate pathogens. However, the low thermal tolerance of biological tissues poses a safety concern, and microorganisms often exhibit thermotolerance by producing heat shock proteins and other protective factors that mitigate thermal damage. Herein, a microwave-responsive platform ($\text{Ti}_3\text{C}_2\text{T}_x\text{-CS-RSNO}$) is successfully prepared through electrostatic interaction with chitosan, which not only retains the high microwave thermal conversion efficiency of $\text{Ti}_3\text{C}_2\text{T}_x$ but also enables the simultaneous release of NO under microwave heating, significantly lowering the temperature required to kill bacteria. $\text{Ti}_3\text{C}_2\text{T}_x\text{-CS-RSNO}$ rapidly heats under microwave irradiation, enabling controlled NO release and achieving 99.97% antibacterial efficacy against *Staphylococcus aureus* at a lower temperature (48°C). It also demonstrates sustained NO release at physiological temperature (37°C), maintaining high antibacterial activity over extended periods. With excellent antibacterial efficacy and biocompatibility, this work provides a promising solution for the long-term treatment of deep-seated infections.

Key words: microwave thermal therapy; $\text{Ti}_3\text{C}_2\text{T}_x$; nitric oxide gas therapy; long-term treatment; deep-seated infections

Introduction: Chronic osteomyelitis, often caused by *Staphylococcus aureus*, is a persistent infection that can lead to severe complications, including bone damage and treatment-resistant recurrence¹. Conventional treatments, like surgical debridement and long-term antibiotics, face limitations such as antibiotic resistance and difficulties in eradicating deep lesions. Microwave thermal therapy (MTT) has shown promise for targeting deep infections by elevating local temperatures², but safety concerns arise from potential tissue damage at high temperatures. To enhance antibacterial efficacy, we developed a microwave-responsive composite ($\text{Ti}_3\text{C}_2\text{T}_x\text{-CS-RSNO}$), combining $\text{Ti}_3\text{C}_2\text{T}_x$ with S-nitrosothiols (RSNOs). This composite enables effective heat and NO co-delivery, lowering the required temperature for bacterial eradication and providing sustained NO release at physiological temperature (37°C), which prevents infection recurrence. This approach offers a novel strategy for the long-term treatment of deep-seated infections like chronic osteomyelitis.

Materials & Methods:

Preparation of $\text{Ti}_3\text{C}_2\text{T}_x\text{-CS-RSNO}$: Synthesized by acid etching and ultrasonic exfoliation of Ti_3AlC_2 , followed by chitosan coating and subsequent loading of RSNO onto the $\text{Ti}_3\text{C}_2\text{T}_x\text{-CS}$ composite through stirring in an ice bath (Figure 1a).

Results & Discussion:

Successfully synthesized and characterized the $\text{Ti}_3\text{C}_2\text{T}_x\text{-CS-RSNO}$ composite, with structural and elemental analysis confirming the stepwise assembly via electrostatic interactions (Figure 1b-f).

The composite achieved a 99.97% bactericidal rate against *S. aureus* under microwave irradiation at a synergistic temperature of only 48°C, demonstrating enhanced efficacy and safety.

Sustained nitric oxide release at 37°C maintained a 99.76% antibacterial rate over 12 hours, showing potential for long-term inhibition and prevention of recurrence. Severe membrane depression and rupture of bacteria in the $\text{Ti}_3\text{C}_2\text{T}_x\text{-CS-RSNO}$ group indicate that the released NO directly disrupts bacterial structure.

Excellent deep-tissue microwave penetration with minimal heating of intervening tissue.

Outstanding biocompatibility, with hemolysis rates below 5% and no adverse effects on osteoblast proliferation or morphology.

Conclusions: In summary, we developed a novel microwave-responsive platform ($\text{Ti}_3\text{C}_2\text{T}_x\text{-CS-RSNO}$) for synergistic heat/NO delivery. It overcomes conventional thermal therapy limits by enabling potent, low-temperature antibacterial efficacy via combined thermal action and NO-mediated membrane disruption. Sustained NO release and excellent biocompatibility highlight its strong potential for treating persistent deep-tissue infections like chronic osteomyelitis.

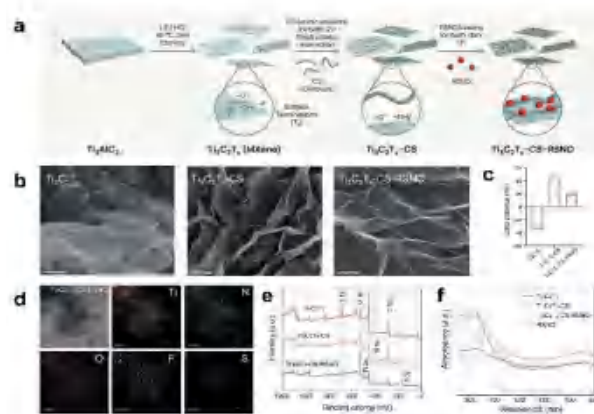


Fig. 1. Preparation and Characterization of $\text{Ti}_3\text{C}_2\text{T}_x\text{-CS-RSNO}$.

(a) Schematic illustration of the preparation procedures of $\text{Ti}_3\text{C}_2\text{T}_x\text{-CS-RSNO}$. (b) SEM images of $\text{Ti}_3\text{C}_2\text{T}_x$, $\text{Ti}_3\text{C}_2\text{T}_x\text{-CS}$ and $\text{Ti}_3\text{C}_2\text{T}_x\text{-CS-RSNO}$ (scale bar = 500 nm). (c) Zeta potential of $\text{Ti}_3\text{C}_2\text{T}_x$, $\text{Ti}_3\text{C}_2\text{T}_x\text{-CS}$ and $\text{Ti}_3\text{C}_2\text{T}_x\text{-CS-RSNO}$. (d) TEM element mapping of $\text{Ti}_3\text{C}_2\text{T}_x\text{-CS-RSNO}$ (scale bar = 1 μm). (e) XPS spectra of $\text{Ti}_3\text{C}_2\text{T}_x$, $\text{Ti}_3\text{C}_2\text{T}_x\text{-CS}$ and $\text{Ti}_3\text{C}_2\text{T}_x\text{-CS-RSNO}$. (f) UV-vis spectra of $\text{Ti}_3\text{C}_2\text{T}_x$, $\text{Ti}_3\text{C}_2\text{T}_x\text{-CS}$ and $\text{Ti}_3\text{C}_2\text{T}_x\text{-CS-RSNO}$, and RSNO.

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Self-assembled copper-amino acid nanoleaves for targeted treatment of deep-seated bacterial infections via chemodynamic therapy and cuproptosis-like death

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Key words: self-assembled nanoparticles, targeting delivery, chemodynamic therapy, cuproptosis, antibacterial

Introduction: Since the discovery of penicillin in 1928, antibiotics have played a crucial role in combating bacterial infections. However, due to the enormous selective pressure resulting from the indiscriminate abuse of antibiotics, antimicrobial resistance has become a global public health threat. To tackle this crisis, it is of particular importance to develop alternative non-antibiotic therapies. Transition metal ions such as Cu^{2+} possess broad-spectrum bactericidal activity, yet their application in treating deep-seated infections is limited by easy deactivation by protein chelation and poor targeting capability. Herein, hyaluronic acid (HA)-modified copper-N-acetyl-L-cysteine (NAC) nanoleaves (CNH NLs) are developed to enable targeted delivery of Cu^{2+} to infection sites. CNH NLs remain stable under physiological conditions but readily disassemble in the acidic infection microenvironment, triggering rapid Cu^{2+} release. The released Cu^{2+} disrupts bacterial membranes, depletes glutathione, promotes reactive oxygen species (ROS) generation and induces cuproptosis-like bacterial death, exhibiting potent activity against both planktonic bacteria and biofilms. The therapeutic efficacy of CNH NLs is further validated in murine keratitis and pneumonia models, demonstrating their potential for treating deep-seated bacterial infections.

Materials & Methods: CNH NLs were synthesized via a self-assembly reaction between CuSO_4 and NAC, followed by HA modification. The nanostructures were characterized using TEM, SEM, AFM, XRD, UV-vis spectroscopy and XPS. Cu^{2+} release was quantified by ICP-MS, and catalytic activity was evaluated by EPR and chromogenic assays. Antibacterial performance was assessed using plate counting, Live/Dead staining, SEM/TEM imaging, membrane potential and biofilm eradication studies. Biocompatibility was evaluated through CCK-8 cytotoxicity and hemolysis assays. Finally, therapeutic efficacy and biosafety were investigated in vivo using MRSA-induced bacterial keratitis and *P. aeruginosa*-induced lung infection mouse models.

Results & Discussion: CNH NLs exhibited potent antibacterial activity through chemodynamic therapy and cuproptosis-like death. Specifically, CNH NLs possessed high copper loading and released Cu^{2+} in a pH-dependent manner. The released Cu^{2+} disrupted

bacterial membrane potential, increased membrane permeability, and promoted Cu^{2+} influx into bacterial cytoplasm. Intracellular copper overload depleted GSH and reacted with H_2O_2 to generate toxic ROS, leading to bacterial death. Transcriptomic analysis further revealed that copper bound to lipoylated proteins in the TCA cycle, inducing aggregation of lipoylated proteins, loss of iron-sulfur cluster proteins, accumulation of LPO products, and decreased PDH activity, ultimately triggering cuproptosis-like bacterial death. Based on these mechanisms, CNH NLs exhibited strong antibacterial and antibiofilm activity at low doses with negligible cytotoxicity, hemolysis and acute systemic toxicity. HA modification enabled targeted accumulation of CNH NLs at infection sites. In murine MRSA-induced keratitis, CNH NLs retained in infected corneas for over 8 h and effectively eliminated bacteria. In a murine *P. aeruginosa*-induced pneumonia model, CNH NLs accumulated in infected lungs within 2 h and remained for over 24 h after intravenous injection, showing potent antibacterial efficacy. In contrast, free Cu^{2+} displayed limited antibacterial activity and poor therapeutic performance in infection models.

Conclusions: HA-modified copper-amino acid nanoleaves enable targeted Cu^{2+} delivery to infection sites and achieve potent antibacterial activity through combined chemodynamic therapy and cuproptosis-like mechanisms. The nanoplatform demonstrates strong efficacy against deep-seated bacterial infections with favorable biosafety, highlighting its potential as a non-antibiotic antibacterial strategy. These findings suggest that targeted copper-based nanomedicines may represent a promising therapeutic approach for the clinical treatment of deep-seated bacterial infections.

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Natural-Polymers Based Membranes for Bone Tissue Regeneration

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Key words: polymeric membranes, osseointegration, controlled drug delivery.

Introduction: Among all functional materials, membranes represent a special class due to their main property – selectivity. Largely synthesized from a practical necessity, water filtration for the production of drinking water, they began to be widely used in other fields such as petrochemical industry, electronics, gas separations, etc. Due to this remarkable property – selectivity – they have been used since the beginning of the field in medicine. The first application of membranes in medicine and which has saved millions of lives to date is hemodialysis [1]. Another recent application is related with osseointegration and regeneration of bone tissue [2]. Here, will be presented the results related with various polymeric membrane materials based on natural polymers for this type of application.

Materials & Methods: Several types of membranes will be presented – cellulose acetate (functionalized with sericine, resveratrol, activated crown ethers with calcium ions or composite with hydroxyapatite or magnetic nanoparticles) and chitosan (functionalized with activated crown ethers with calcium ions or composite with layered double hydroxide or hydroxyapatite), all prepared by phase-inversion method. Reported composite membranes has also the ability for controlled drug delivery of various active pharmaceutical substances like antibiotics (clindamycin phosphate) or anti-inflammatory (sodium diclofenac) [3-5].

Results & Discussion: All synthesized membranes were fully structural characterized through FT-IR, XPS, Raman, thermal analysis NMR and imagistic through SEM in order to prove the synthesis and to evaluate all chemical interactions and properties. For evaluating the biological properties of membranes for designed applications, two main tests were performed – in vitro tests using MC3T3-E1 preosteoblasts cell lines [6, 7], respectively biomineralization tests. Performed tests showed a more pronounced non-cytotoxic character of functionalized membranes and high ability for biomineralization in case of composite membranes. Also, drug delivery tests were conducted for membranes with this ability showing an advantage for preventing

infections at the implantation site (in the case of antibiotic release) or preventing inflammation (in the case of sodium diclofenac). A comparison with advantages and disadvantages of all synthesized materials and commercial available polymeric membranes will also be presented.

Conclusions: All presented materials proved their advantages in the field of membranes for osseointegration and bone tissue regeneration, some of them with additional properties like controlled drug delivery at the implantation site. The use of natural polymers for this kind of application is a continuous research field, future challenges being related with the design of biodegradability in order to optimise the materials properties in the osseointegration timeline or the ability of membrane materials to have additional functions like local treatment of tumours.

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Navigable Wood Pulp-Based Hemostatic Sponge for Non-Compressible Hemostasis

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Key words: Antimicrobial materials, hemostasis, porosity

Introduction: Non-compressible bleeding, often occurring in deep and irregular wounds, poses significant challenges for traditional compression methods. Existing expandable hemostatic materials struggle to balance rapid expansion with adequate elastic recovery, while the lack of intraoperative navigation and postoperative traceability often leads to imprecise placement and difficulties in locating residual fragments. Therefore, developing a novel hemostatic material capable of rapidly conforming to wound cavities while enabling real-time visual tracking throughout the treatment process is of critical importance. To address this need, this study developed a multifunctional integrated hemostatic sponge based on natural wood pulp.

Materials & Methods: An expandable wood pulp-based hemostatic sponge was prepared and structurally optimized for millisecond-level expansion. Functionalization with EDTA-scintillator complexes enabled dual-channel imaging, while iodine ions provided antimicrobial activity. Its hemostatic efficacy, imaging function, and biocompatibility were systematically evaluated in relevant models.

Results & Discussion: Through structural optimization, a wood pulp sponge with a hierarchical pore structure was obtained, exhibiting a compressive modulus of approximately 15 kPa, a strain recovery rate exceeding 96%, and a water absorption rate of 0.42 g/cm³/s. In Bama pig liver and spleen injury models, WPSS reduced hemostasis time to 43 s and 40 s, respectively, and decreased blood loss by more than 98% compared to the blank control group. The stable anchoring of scintillators enabled clear green fluorescence emission at 515 nm under UV excitation, as well as X-ray radiopacity comparable to that of commercial X-ray contrast agents, achieving in vitro imaging guidance and in vivo traceable localization. The loaded iodine ions exhibited an antibacterial rate exceeding 99% against *S. aureus* and *E. coli*.

Conclusions: This study successfully developed a multifunctional wood pulp-based hemostatic sponge (WPSS) for non-compressible hemorrhage. The structurally optimized sponge demonstrated rapid hemostasis, significant blood loss reduction, and over 99% antibacterial activity. It enabled dual-channel imaging for in vitro guidance and in vivo tracing, combined with excellent biocompatibility.

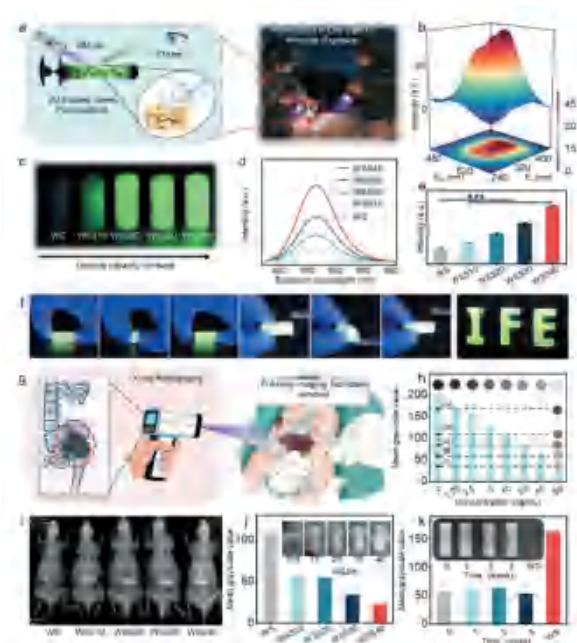


Fig. 1. Visible-light navigation in vitro and X-ray tracing in vivo properties of wood sponge.

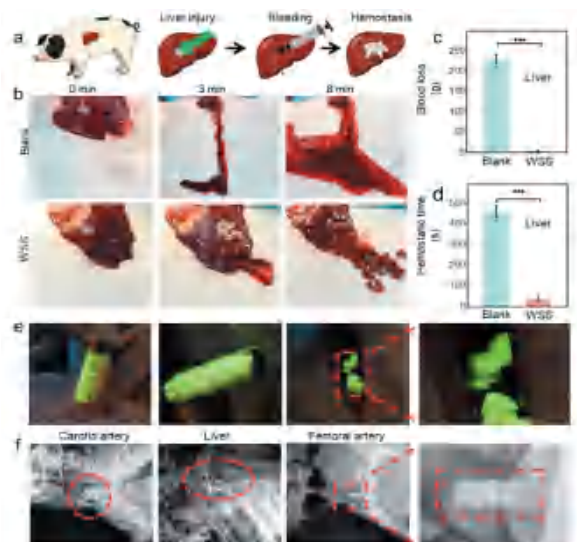


Fig. 2. Hemostatic and imaging performance of the wood sponge in vivo.

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pH-Compensatory 4arm-PLGA/Sr-BG Composite Patches Mediate Immune Microenvironment for Scarless Abdominal Wall Regeneration

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Key words: Hernia patch, Poly (lactic-co-glycolic acid), Bioglass, fibrosis mechanism, Immune microenvironment.

Introduction: Poly (lactic-co-glycolic acid) (PLGA) has become a core patch material for the repair of abdominal wall defects due to its excellent biocompatibility; however, the accumulation of acidic degradation products leads to chronic inflammation and fibrosis¹. Moreover, existing downstream targeted intervention strategies are prone to inducing adverse reactions². Strontium-doped bioglass (Sr-BG) can release alkaline ions to neutralize acidic products and regulate the immune microenvironment. Addressing the defects of PLGA, this study fabricates a novel 4aPB patch by compositing Sr-BG with 4arm-PLGA and combining 3D printing fused deposition modeling (FDM) technology. It aims to clarify the upstream regulatory mechanism of chronic inflammation-driven fibrosis, optimize the degradation characteristics of PLGA to resolve the problems of chronic inflammation and fibrosis, provide a new strategy for the performance optimization of PLGA-based repair materials, and promote the clinical translation of immunomodulatory biomaterials in abdominal wall repair.

Materials & Methods: Line-PLGA and 4arm-PLGA were synthesized via ring-opening polymerization, with their molecular weights regulated to ensure the consistency of linear segment lengths. Sr-BG was prepared by the sol-gel method. Subsequently, a novel 4aPB patch was constructed by compounding Sr-BG with 4arm-PLGA followed by FDM 3D printing technology. In vitro experiments were performed to investigate the regulatory effects of the 4aPB patch RAW 264.7 and NHDFs. In vivo experiments were conducted to evaluate the key driving role of the 4aPB patch in anti-fibrotic repair of abdominal wall defects using a rat model.

Results & Discussion: Gel permeation chromatography (GPC) and ¹³C NMR confirmed the successful synthesis of Line-PLGA and 4arm-PLGA. Degradation studies demonstrated that the 4aPB patch exhibited a slower degradation profile; after 56 days of immersion, the pH of the solution remained stable at 7.1, with concurrent sustained release of bioactive ions. In vitro assays confirmed that the 4aPB patch effectively promoted the migration and collagen production of NHDFs. Notably, PLGA degradation products did not directly induce NHDFs differentiation into myofibroblasts, while the 4aPB patch attenuated macrophage M1-type polarization

and migration induced by PLGA degradation products. In vivo findings revealed that chronic inflammation triggered by PLGA degradation products initiated a positive feedback loop between macrophage recruitment and inflammatory responses, ultimately resulting in macrophage accumulation. Subsequent polarization toward the M2 phenotype led to excessive secretion of TGF- β , thereby promoting myofibroblast differentiation and fibrotic tissue formation. In contrast, the 4aPB patch effectively disrupted this cascade by promoting early M2 macrophage polarization, and gradually reduced the populations of both M1 and M2 macrophages, thus accelerating tissue regeneration and mitigating fibrosis.

Conclusions: This study developed a 3D-printed 4aPB patch with immunomodulatory effects, confirming its efficacy in scarless repair. It improved PLGA degradation, blocked macrophage cascade recruitment, alleviated fibrosis, and accelerated abdominal wall regeneration. With well-defined components and excellent performance, 4aPB showed great clinical translation potential in abdominal wall repair.

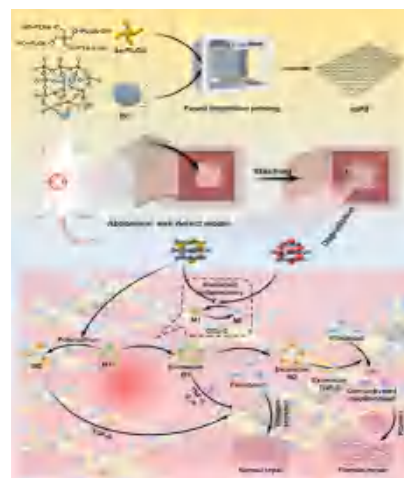


Fig. 1. Schematic diagram of 4aPB with immunomodulatory effects promoting scarless abdominal wall regeneration.

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Supramolecular Microsphere with Dynamic ECM-Mimicking Behavior Regulate iNSC Fate for Traumatic Brain Injury Repair

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Key words: Microsphere, Polyrotaxane, Dynamic ECM-Mimicking, Traumatic Brain Injury, Neural stem cell

Introduction: The exogenous neural stem cells (NSC) transplantation faces multiple challenges, including low post-transplantation survival, limited retention at the injury site, and uncontrollable differentiation behaviours. These limitations indicate that the therapeutic efficacy of NSC-based approaches is constrained not solely by intrinsic cellular properties, but more importantly by the absence of a beneficial extracellular microenvironment capable of continuously supporting and guiding cell behaviours. Under physiological conditions, the brain extracellular matrix (ECM) provides not only structural support but also dynamic biochemical and mechanical cues that tightly regulate NSC fate decisions. However, within the damage cavity of traumatic brain injury (TBI), the ECM undergoes extensive degradation and aberrant remodelling, resulting in severe disruptions in mechanical support, biochemical signalling, and dynamic regulatory capacity. This pathological niche is inherently unfavourable for the long-term survival and functional differentiation of transplanted stem cells. Therefore, designing an artificial scaffold that recapitulates the dynamic characteristics of the native ECM and effectively directs NSCs toward functional neuronal phenotypes represents a critical scientific challenge for advancing TBI therapy [1-2].

Materials & Methods: Mono-azide-functionalized β -cyclodextrin and acrylated poloxamer were first self-assembled through host-guest interactions, followed by microfluidic-assisted UV irradiation to generate supramolecular polyrotaxane (PR) microspheres featuring topological dynamic networks. Subsequently, alkene-functionalized RGD ligands were conjugated onto the microsphere surface via click chemistry, enabling a dynamically tunable cell-adhesive interface that more faithfully recapitulates the coordinated evolution of mechanical and biochemical cues in native ECM.

Results & Discussion: In this study, a supramolecular microsphere system with dynamic ECM properties was constructed based on microfluidic technology. The biocompatibility of the supramolecular microspheres was verified by CCK-8 and live/dead staining assays. NSCs were three-dimensionally co-cultured with the microspheres for 3 and 7 days, followed by protein extraction and analysis. The results showed that Nestin expression was significantly maintained at day 3, indicating effective preservation of neural stem cell stemness. At day 7, western blot analysis revealed

upregulated MAP2 expression and downregulated GFAP expression, suggesting that the PR microspheres promoted the differentiation of NSCs toward neurons while inhibiting astrocytic differentiation. Further in vivo experiments demonstrated that, compared with transplantation of NSCs alone, transplantation of NSCs together with PR microsphere significantly enhanced the co-localization of HuNu and NeuN immunofluorescence, indicating that a greater proportion of transplanted cells differentiated into neurons. Furthermore, enhanced colocalization of PSD95 and VGLUT-1 suggested improved neural regeneration and synaptic connections. In addition, behavioural tests demonstrated improved motor function recovery in mice treated with NSCs and PR microspheres. However, the long-term stability, biosafety, and durability of functional improvement of the NSC transplantation together with microsphere remain to be further validated. In addition, the molecular mechanisms by which dynamic mechanical cues regulate NSC fate require more systematic investigation.

Conclusions: We successfully developed a supramolecular microsphere system based on a PR topology that effectively mimics the dynamic mechanical properties of the ECM. In vitro experiments demonstrated that these PR microspheres significantly regulate the directed differentiation of NSCs toward neurons by providing dynamic mechanical cues. Furthermore, in vivo studies revealed that the combined transplantation of PR microspheres and iNSC also resulted in markedly improved differentiation towards neurons, which subsequently enhanced neural plasticity as well as the motor functional recovery, compared with transplantation of NSCs alone. In summary, the supramolecular PR microsphere system with dynamic ECM properties not only shows promising potential as NSC carriers to promote neural tissue repair after TBI, but also highlights the important role of mimicking ECM dynamic mechanical cues in regulating cell fate to promote tissue repair and regeneration.

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Integrating Natural Polymers and Bioactive Molecules: From Tissue Engineering and Controlled Drug Release to Disease Modeling

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Key words: scaffold, disease modeling, neurodegeneration, nasal gels,

Introduction: The field of tissue engineering is critically limited by the scarcity of biomaterials that can accurately mimic the native extracellular matrix while directing specific cellular functions. In parallel, drug development is hindered by the lack of physiologically relevant human models for pre-clinical testing. To address these challenges, this work harnesses the inherent bioactivity and biocompatibility of natural polymers, specifically hyaluronic acid (HA)¹. This polymer was engineered for three distinct purposes: (1) as supportive scaffolds for skin tissue regeneration, (2) as microenvironments for *in vitro* disease modeling, and (3) as carriers for controlled drug delivery.

Materials & Methods: HA was chemically modified *via* two distinct strategies to achieve different crosslinking capabilities and physicochemical properties, offering versatile platforms tailored to specific biomedical applications. First, methacrylated HA (MEHA) was synthesized by reacting HA with methacrylic anhydride. Second, tyramine-modified HA (HA-Tyr) was prepared through carbodiimide-mediated coupling. MEHA was processed *via* 3D printing using ROKIT Invivo 4D2. The resulting MEHA patches for skin regeneration were functionalized with mesenchymal stem cell-derived small extracellular vesicles (MSC-sEVs) and characterized for their physicochemical, morphological, and mechanical behavior. Both *in vitro* and *in vivo* studies (diabetic mouse model of pressure ulcers) were performed. Similarly, MEHA platforms integrated with electrospun poly-L-lactide (PLLA) were characterized and used *in vitro* as skin tissue analogues for studying central nervous system (CNS) disorders. Finally, for CNS-targeted therapies, HA-Tyr was enzymatically crosslinked and functionalized with natural extracts for intranasal drug delivery. Their performance, along with their *in vitro* and *in vivo* behaviors, was also assessed.

Results & Discussion: *In vitro*, MSC-sEVs enhanced proliferation, migration, and regenerative gene expression in human endothelial cells and dermal fibroblasts. In diabetic mice, treatment with MSC-sEV-loaded patches significantly improved wound closure, epithelization, angiogenesis, and innervation, harnessing the regenerative paracrine activity of MSCs. Prompted by these positive results and considering that peripheral skin mirrors certain aspects of CNS pathophysiology, a

patient-derived 3D innervated skin model was developed. This model provided a physiologically relevant human platform for investigating CNS disorders under standardized conditions while minimizing the need for repeated biopsies. It successfully recapitulated key disease features, including the activation of specific biomarkers. The 3D system enabled more sensitive discrimination of disease profiles and better replicated *in vivo*-like cellular interactions. Finally, an HA-Tyr hydrogel for intranasal delivery of neuroprotective plant extracts was developed. *In vitro*, the hydrogel protected preneuronal cells from neurotoxin insult by reducing oxidative stress. *In vivo*, intranasal administration in a Parkinsonian mouse model improved motor coordination and behavioral outcomes, indicating neuroprotection *via* anti-inflammatory and antioxidant mechanisms.

Conclusions: This work demonstrates the remarkable versatility of HA as a platform for biomedical applications, showing how targeted chemical modifications and processing techniques yield tailored solutions for distinct clinical needs through established structure-property-function relationships. By employing two different functionalization strategies, hydrogels with fundamentally different physicochemical properties, suited to specific applications, were developed. MEHA, processed *via* 3D printing, served as an effective scaffold for skin regeneration when loaded with MSC-sEVs, significantly improving wound healing outcomes. The same MEHA platform, when integrated with electrospun PLLA, was repurposed as a patient-derived 3D innervated skin model for investigating neurodegenerative disease pathophysiology. Meanwhile, HA-Tyr hydrogels, optimized for intranasal delivery, demonstrated neuroprotective effects. Together, these findings establish a continuous translational pipeline, from skin regeneration to disease modeling to therapeutic intervention, unified by a single biomaterial platform. This property-driven approach to hydrogel design underscores the potential of chemically versatile HA to address diverse biomedical challenges, bridging tissue engineering, disease modeling, and targeted drug delivery within a coherent materials science framework.

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Design and Application of Marine Silicon-Derived Bone Repair Materials

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Key words: marine biosilica, diatoms; , siliceous sponges, bone defect model.
bone regeneration, rotator cuff injury

Introduction: As one of the most abundant elements on Earth, silicon (Si) possesses multiple biological effects, including promoting osteogenesis, angiogenesis, and collagen synthesis. Terrestrial silicon primarily exists in rocks and sand in the forms of silicon dioxide and silicates. However, these forms lack bioactivity and contain significant impurities, making them difficult to utilize effectively in biomedical applications. Although synthetic silica and silicate bioceramics have been used for tissue regeneration and disease treatment, their high cost and low production yield severely limit the widespread application of silicate-based biomaterials. Life originated in the ocean, and marine biosilicon, found in organisms such as diatom^[1] and siliceous sponge^[2], has garnered significant attention as a novel class of natural siliceous resources. Despite their different evolutionary paths and morphologies compared to higher organisms like humans, these primitive and ancient marine siliceous organisms exhibit a biological homology in their utilization of silicon. These natural siliceous organisms possess ideal biocompatibility, complex and precise multi-level micro/nano structures, excellent mechanical properties, and unique physicochemical characteristics, making them highly promising biomaterials. Therefore, the focus of this work is how to effectively utilize and rationally design marine biogenic silicon for the repair of complex tissues and organs such as tendons and bone.

Materials & Methods: Inspired by the photosynthetic capability of diatoms, we used bioprinting technology to construct a cross-species symbiotic system by combining *Chaetoceros* (a genus of diatom) and tendon stem/progenitor cells (TSPCs). The regenerative effect of this cross-species scaffold on the tendon-bone injury interface was investigated in a rabbit rotator cuff injury model. Furthermore, inspired by the remarkable flexibility of siliceous sponges, we proposed a biomass reuse strategy. Natural, discarded flexible sponge skeletons were hydrothermally mineralized in an alkaline calcium solution to construct a calcium silicate micro-nano layer *in situ* on their surface, thereby transforming them into flexible bioceramic scaffolds with desirable bioactivity. The repair capacity of these scaffolds was evaluated in a rabbit cranial

Results & Discussion: In the cross-species symbiotic scaffold, *Chaetoceros* acts as a continuous “oxygen pump” through photosynthetic oxygen production and releases silicon ions as an active “silicon source” upon degradation, creating a biomimetic microenvironment. This facilitates bidirectional “acclimatization” for tendon and bone, inducing TSPC differentiation and maturation by activating the MAPK/cAMP/circadian rhythm signaling pathways. Subcutaneous implantation in rats confirmed good biocompatibility, with the material primarily accumulating and metabolizing in the liver and kidneys. Studies in the rabbit rotator cuff injury model demonstrated that the cross-species scaffold improved shoulder joint motor function, restored tissue mechanical strength, alleviated local hypoxia, and effectively promoted regeneration at the tendon-bone interface. Additionally, the bioceramics derived from the natural siliceous sponge skeleton exhibited excellent flexibility, allowing for arbitrary cutting and shaping. The hydrothermal mineralization process successfully activated the inert sponge skeleton, enabling it to release bioactive ions such as calcium and silicon, leading to outstanding osteogenic and angiogenic activity *in vitro*. Experiments in a rabbit cranial bone defect model also confirmed that this scaffold could achieve efficient vascularized bone regeneration.

Conclusion: This study respectively utilized marine biosilicon materials from diatoms and siliceous sponges. By employing techniques such as bioprinting and hydrothermal mineralization, we successfully constructed a cross-species symbiotic scaffold and a flexible bioceramic scaffold. Leveraging their unique advantages, these scaffolds achieved efficient repair of tendon-bone interfaces and cranial bone defects, offering new insights for the application of marine biosilicon in regenerative medicine.

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Sustainable lipid-rich biomaterial obtained via detergent-free decellularization of fish skin

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Keywords: detergent-free decellularization, modulatory biomaterials, wound healing, omega-3 fatty acids, fish skin.

Introduction: Decellularized skin has gained increasing attention in wound care, overcoming the poor bioactivity offered by conventional dressings [1]. Fish are especially attractive as a source of xenogeneic skin because of their collagen-rich extracellular matrix (ECM), high omega-3 content, and reduced disease transmission risks [2]. Fish skin is also a common by-product of the fishery and food industries. This work aims to produce a tissue-engineered construct from fresh mackerel skin using a detergent- and enzyme-free decellularization treatment. This procedure was designed to minimize damage to the architecture and composition of the native ECM – essential for recruiting host cells and supporting tissue regeneration *in vivo*. The novel acellular fish skin was systematically compared with a conventional detergent-based decellularized fish skin [3]. We have extensively assessed the molecular composition, architecture, and biomechanical properties of the skin-derived constructs. Our investigation led to a biomaterial suitable for tissue regeneration, namely for wound healing applications.

Materials & Methods: Atlantic mackerel (*S. scombus*) skins were provided by Casa D'Oro (Porto, Portugal) – a local restaurant that sources whole fish from the harbor. Only fish caught and delivered on the same morning were used, ensuring minimal time between capture and skin processing. The flesh was removed, and the skins were transported to the laboratory on ice. Skins were washed with water to eliminate debris and were decellularized using a detergent- and enzyme-free protocol consisting of sequential washes in hypertonic saline buffers and high concentrations of sodium chloride (NaCl). As a control, a Triton X-100-based protocol was employed in parallel. Decellularized skins were evaluated in terms of residual DNA and ECM components (including collagens, elastin, glycosaminoglycans, and lipids). Structural preservation was evaluated by histological staining (Hematoxylin and Eosin; PicroSirius Red; Masson's Trichrome; DAPI) and high-resolution microscopy (Atomic Force Microscopy; Scanning/Transmission Electron Microscopy). Uniaxial tensile testing and viscoelastic measurements were also performed to assess mechanical properties.

Results & Discussion: Both decellularization techniques significantly reduced cellular and nuclear content, while retaining the dense collagen- and elastin-rich 3D network. Compositional analysis revealed that the detergent-free approach better preserved glycosaminoglycans and lipids. Both molecules are highly leachable, especially when in contact with surfactants. Our aim was to reduce their leaching to a minimum, since they are important for wound healing,

modulating inflammation, and promoting tissue repair. Structural evaluation showed that both skins displayed an intact and organized architecture, consisting of: (i) a thin, continuous epidermis, (ii) a fibrillar dermis, and (iii) a porous hypodermis characterized by stromal and adipose compartments. The presence of a 3D porous, interconnected ECM, observed in our study, is important to facilitate cell infiltration and integration after *in vivo* implantation. Mechanical testing indicated a comparable viscoelastic profile across the two tested groups, despite an increase in the tensile strength and overall stiffness of the decellularized skins.

Conclusions: This work demonstrates that a detergent- and enzyme-free decellularization protocol yields a fish skin-derived tissue construct with preserved architecture, enhanced retention of bioactive soluble components, and suitable mechanical properties for tissue engineering and regenerative applications. Owing to its compositional and structural advantages over conventional detergent-based treatments, this material will be evaluated as a platform for the development of next-generation wound dressings that combine long-term mechanical support with intrinsic anti-inflammatory and pro-regenerative cues.

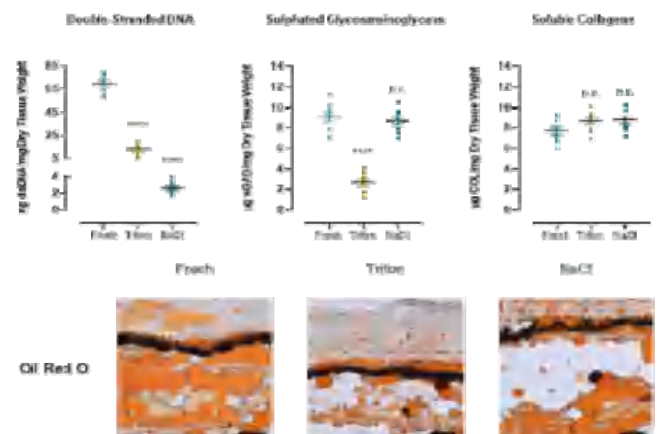


Fig. 1. Top: Molecular quantification of double-stranded DNA, glycosaminoglycans, and collagens (n=3, N=3). Mean ± SEM. One-way ANOVA. Sidak's Multiple Comparison Test. **** $p < 0.0001$. Bottom: Oil Red O histological staining of neutral lipids. Scale bar: 50 μ m.

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Photocrosslinkable Polymers for Tissue Regeneration

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Key words: biomaterials, bone regeneration, photocrosslinkable polymers, tissue engineering

Introduction: Photocrosslinkable polymers are polymers that can be solidified from liquid upon light exposure. They have been employed to fabricate tissue engineered constructs due to the mild conditions for crosslinking, highly tunable mechanical and structural modifiability, printability, biodegradability and biocompatibility. These biomaterials can maintain their structural integrity after biofabrication and provide topological, biochemical, and mechanical cues to guide cellular behaviors by creating a biomimetic microenvironment. The emphasis of this talk is placed on how photocrosslinkable polymers can be used to achieve regeneration of diseased or damaged tissues, for example, their fabrication into various scaffolds (electrospun fibers, microspheres, and 3D printed scaffolds) to reconstruct hard tissues like bone as well as soft tissues such as skin (Figure 1).

Materials & Methods: At the microscale, a microfluidics-assisted approach was used to generate GelMA-based microspheres encapsulating mesenchymal stem cells (MSCs), enabling injectable cell delivery and formation of a cell-supportive microenvironment [1]. At the fibrous scale, electrospinning was employed to fabricate periosteum-mimicking scaffolds (PMBA) composed of GelMA, Arg-UPEA, and nHAMA, followed by photocrosslinking to form a mechanically robust and bioactive fibrous network [2]. At the macroscale, extrusion-based 3D printing was utilized to construct bone scaffolds using a photocrosslinkable nanocomposite ink consisting of PmLnDMA and nHAMA, allowing precise control over scaffold architecture and composition [3].

Results & Discussion: At the microscale, GelMA microspheres provided a favorable microenvironment for MSC survival, spreading, migration, proliferation, and osteogenic differentiation, demonstrating their effectiveness in enhancing cell-based bone regeneration. At the fibrous scale, the electrospun PMBA scaffolds rapidly solidified upon light exposure and exhibited tunable mechanical properties and degradation behavior. The biomimetic fibrous structure, together with sustained release of bioactive components, promoted coupled osteogenesis and angiogenesis, mimicking the function of native periosteum. At the macroscale, the 3D printed nanocomposite scaffolds formed an inorganic-organic co-crosslinked network within 140 s, significantly improving mechanical strength and bioactivity. These scaffolds provided structural support and enhanced osteogenic performance for bone defect repair.

Conclusions: Photocrosslinkable polymers represent a powerful and versatile platform for tissue regeneration by enabling the fabrication of biomimetic scaffolds with tunable properties under mild conditions. Through integration of microfluidics, electrospinning, and 3D printing technologies, these materials can be structured across multiple length scales to regulate cellular behavior and support tissue formation. This platform is adaptable to a wide range of applications, including reconstruction of hard tissues such as bone and soft tissues such as skin, as well as other tissues including cartilage, blood vessels, tendon, and nerve.

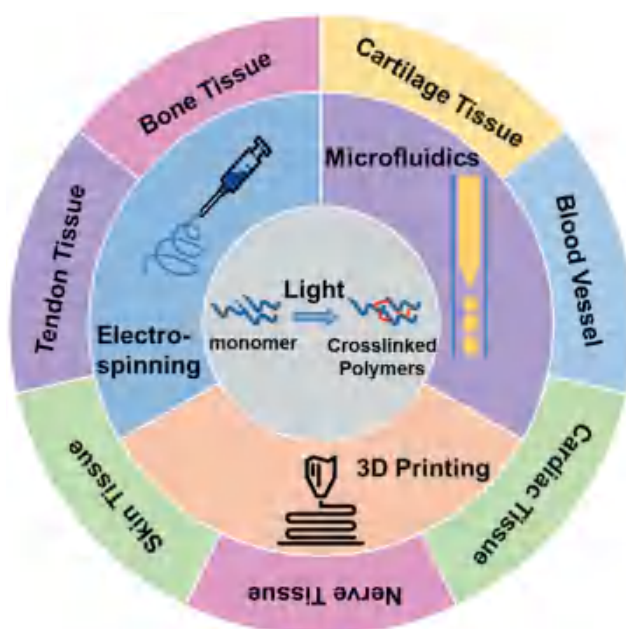


Fig. 1. Fabrication and application of photocrosslinkable polymers

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Near-Infrared Activated Hydrogenated TiO₂ Nanoscale Honeycomb Surface Structure for Effective Staphylococcus aureus Biofilm Elimination and Enhanced Osteogenic Performance

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Keywords: Antibacterial biomaterials, bone-to-implant integration, surface treatment

Introduction: Post-implantation infections in orthopedics present substantial challenges, primarily due to limited antibiotic efficacy and the necessity to eradicate bacteria while promoting successful bone integration. The prevalence of biofilm formation on implant surfaces further complicates treatment, as existing approaches seldom achieve both objectives without resorting to complex additives. In contrast to conventional coatings that require antibiotic incorporation or intricate fabrication, our agent-free hydrogenated titanium dioxide (TiO₂) nanoscale honeycomb surfaces (H-NCs) deliver an efficient and scalable solution for infection control and bone integration. H-NCs are directly fabricated onto titanium substrates. We leverage oxygen vacancies, defined as absent oxygen atoms within the TiO₂ lattice, to enhance near-infrared (NIR) light absorption and facilitate increased reactive oxygen species (ROS) production, thereby inducing mild hyperthermia. The 90 nm honeycomb architecture is intentionally engineered to influence macrophage polarization to establish an osteoimmune microenvironment at the bone-implant interface that supports both immune regulation and bone healing.

Methods: H-NCs were fabricated on titanium implants through polystyrene sphere templating, followed by calcination and hydrogen plasma treatment to generate oxygen vacancies. This approach reduces the TiO₂ bandgap, allowing for NIR activation without altering the composition of the titanium implant or necessitating additional antimicrobial agents. Furthermore, both *in vitro* and *in vivo* assessments were conducted to confirm the biosafety and antibacterial efficacy of the modified surface.

Results: Our strategy enabled rapid, agent-free elimination of 99.94% of *Staphylococcus aureus* *in vitro* and 91.58% *in vivo* after only 15 minutes of NIR exposure. At the same time, the engineered surface promoted macrophage polarization toward a pro-healing phenotype, which supports osteogenesis (bone formation) and improved bone-to-implant integration. These results show that H-NCs can address infection and integration challenges through a simple, translatable surface modification, without the need for exogenous antimicrobial agents.

Conclusions: This work presents an antibiotic-free strategy against implant infections while promoting osseointegration, offering strong potential for clinical translation. This surface modification technique could reduce reliance on antibiotics and lower infection rates in orthopedic surgeries, potentially leading to faster recovery times and fewer complications for patients.

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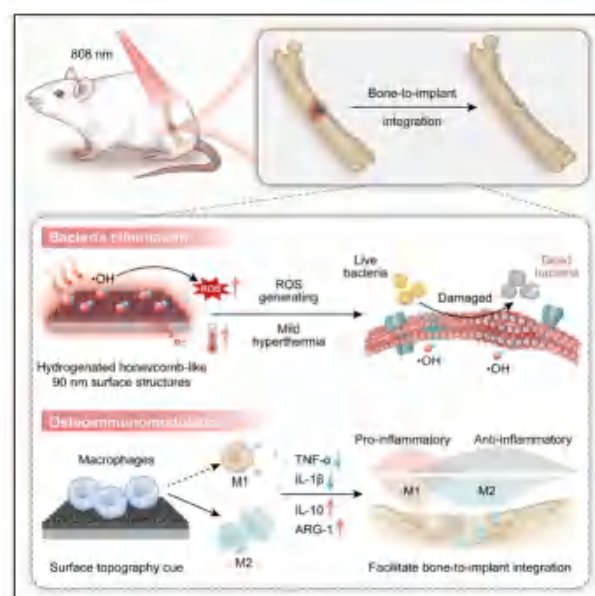


Fig. 1. Schematic of H-TiO₂ honeycomb nanopatterns on Ti implants enabling NIR-activated antibacterial action via ROS generation and mild hyperthermia and promoting osseointegration via immunomodulation.

Design of Functional Bioceramic Scaffolds for Bone Tissue Engineering

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At present, due to the increasing number of bone defect cases caused by population aging, traffic and sports accident, traumas, bone tumors et al., the clinical demand for bone repair materials has also been increasing every year. Clinical bone repair materials are expected to meet the requirements of shape, structure, and function reconstruction to achieve the purpose of precision medicine and personalized medicine. Among the preparation methods of personalized bone repair materials that match bone defect shape, structure, etc., 3D printing technology with the characteristics of precise manufacturing is undoubtedly the best choice.

In terms of the selection of bone repair materials, bioceramics, such as bioglasses, silicates, have advantages in bone function reconstruction due to their functions such as biodegradation, osteoinduction, and osteoconduction. However, for the repair and treatment of pathological bone tissue defects, pure bioceramics lack the functions of therapy or regulation of pathological microenvironment, resulting in unsatisfactory bone tissue repair effects.

Therefore, combining therapeutic or microenvironment regulation components with bioceramic scaffolds can endow the scaffolds with the functions of therapy or microenvironment regulation and improve the bone tissue repair performance. This presentation will introduce the related works of our group in the design of functional bioceramic composite scaffolds for bone tissue engineering in recent years¹⁻⁴.

Key words: bioceramic-based scaffolds, disease therapy, microenvironment regulation, bone tissue engineering

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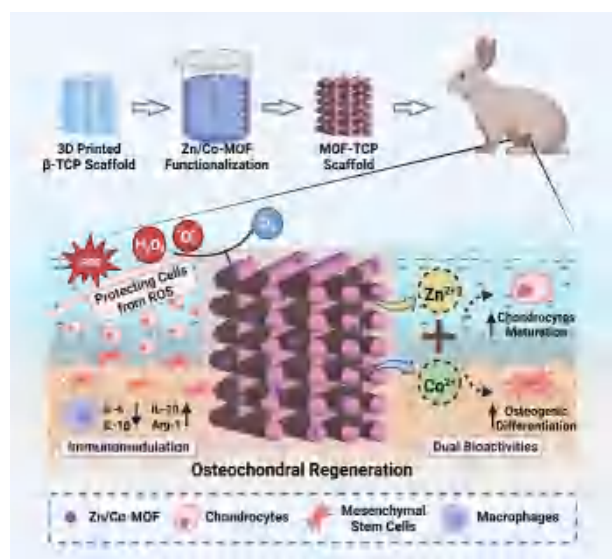


Fig. 1. Illustration diagrams of MOF-TCP scaffolds in treating osteochondral defects caused by OA.

Bioinspired Hierarchical High-performance Bioceramics

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Keywords: Bioceramics; Bioinspired microstructure; Tough and strong; Tissue regeneration; Bioactivity

Introduction: The effective repair of complex tissue injuries—such as extensive bone defects and tendon damage—is a major clinical challenge¹. Despite recent advances in the bioactivity and degradability of biomaterials, optimizing their mechanical performance, particularly the balance between strength and toughness, remains a bottleneck, limiting their use in high-stress environments².

This limitation stems largely from an insufficient understanding of multi-scale structure–property relationships in material design. Nature, however, provides excellent blueprints. Natural materials like bone (with its Haversian system), nacre (brick-and-mortar structure), and fish scales (Bouligand structure) exhibit exceptional mechanical properties due to their sophisticated hierarchical architectures³⁻⁴. These systems achieve a perfect balance of strength and toughness.

Consequently, drawing inspiration from these natural designs to create bioinspired materials with multi-level structures is a vital strategy for developing next-generation implants capable of complex tissue repair.

Materials & Methods : This study employs a combination of mineralization-self-assembly and 3D printing techniques to construct bioinspired hierarchical architectures, specifically mimicking the "brick-and-mortar" structure of nacre and the fibrous bundle structure of tendons. By precisely tailoring the micro-to-macro structural features of the materials, we achieve the hierarchical organization of bioceramics, thereby balancing their mechanical properties with bioactivity.

Results & Discussion : Experimental results demonstrate that the constructed bioinspired hierarchical architectures significantly enhance the mechanical performance of the materials. In the nacre-mimetic structured samples, the material exhibits superior interlayer energy dissipation and crack deflection mechanisms, resulting in flexural strength and fracture toughness that are significantly higher than those of traditional bioceramics. In the tendon-mimetic fibrous bundle structures, interface engineering enhances the overall toughness and deformability, effectively preventing brittle fracture. Furthermore, the introduction of porous structures increases the specific surface area and permeability, providing a favorable microenvironment for cell adhesion and nutrient transport. Preliminary cellular assays validate its excellent biocompatibility and osteogenic activity. Further structure-property relationship studies reveal that the hierarchical architecture plays a pivotal role in stress mitigation, crack blunting, and cellular response regulation, highlighting the unique advantages of bioinspired designs in synergistically improving mechanical and biological performance.

Conclusion : By incorporating bioinspired hierarchical architecture design, this study successfully fabricated bioceramic materials that integrate high strength, high toughness, and favorable bioactivity. The results confirm that the precise construction of multi-scale structures is the key to achieving synergistic optimization of material properties. This strategy not only overcomes the mechanical limitations of traditional bioceramics but also provides both a theoretical foundation and a technical pathway for developing next-generation, high-performance tissue repair materials.

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Bio-active glass for regenerative medicine

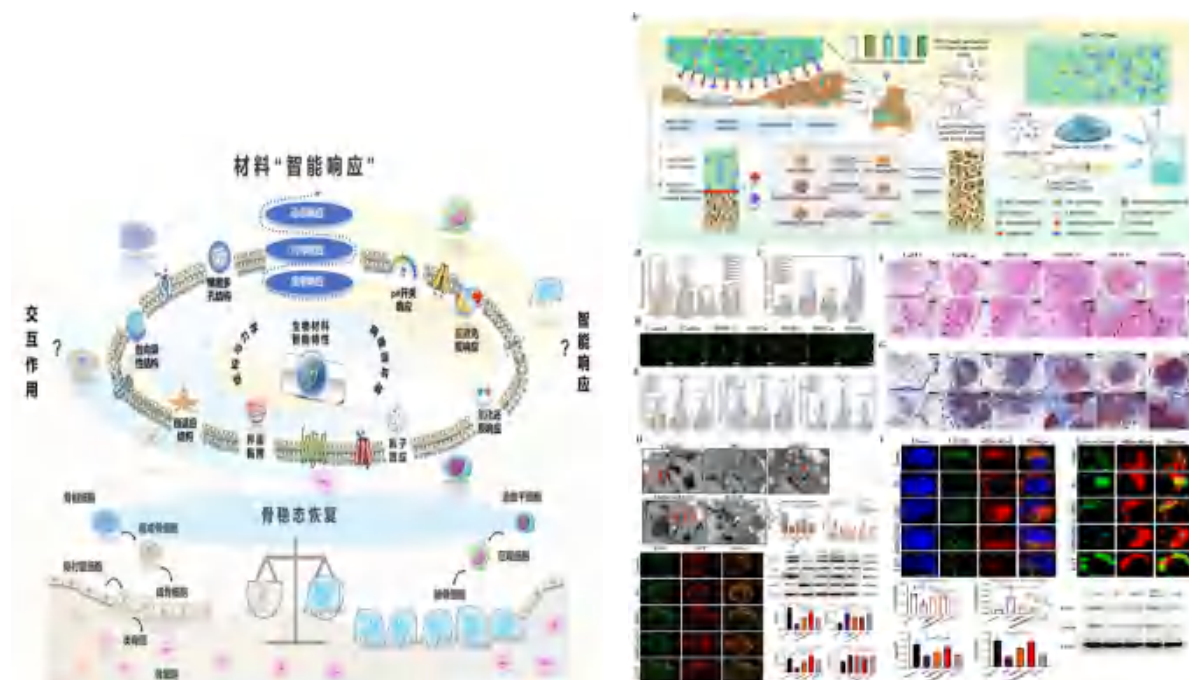
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Abstract:

The fragility of carbon-based life reflects the fragility of life. As the second largest element on Earth, silicon is particularly important for the origin of life, not only participating in the formation of oxygen on Earth, but also has a wide range of applications in the biomedical field, which can effectively compensate for the vulnerability of carbon-based life. It is a new generation of tissue engineering materials with active induction of tissue regeneration and functional reconstruction, and its outstanding advantage lies in actively intervening in cell function, promoting neovascularization and promoting the directional differentiation of stem cells. (1) Composition design responsiveness: by boron-oxygen (2) Dynamic environmental responsiveness: After the material comes into contact with the body, it forms high alkalinity in the early stage through ion release, which leads to apoptosis of surrounding cells, which is the basis for the destructive reconstruction formed by the confrontation between the material and the pathological microenvironment, and then inhibits the rapid release of ions with the formation of calcium and phosphorus mineralization, forming a regenerative microenvironment conducive to tissue reconstruction. The idea of "suppressing first and then promoting" improves the adaptive responsiveness of the pathological microenvironment and creates a regenerative microenvironment. Therefore, it can meet the major clinical needs of complex bone disease bone defects for local blood supply restoration, chronic wound infection control, and promotion of tissue healing, and the inefficiency of hemostasis and difficulty in tissue healing for acute traumatic hemorrhage. Therefore, silicon-based life maintains the cellular homeostasis of carbon-based life, which provides a new idea for tissue regeneration and repair in pathological environment.



Bioelectro-adhesive coupled biomaterials for tissue regeneration

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Tissue repair materials are crucial elements for achieving tissue repair, regeneration, and functional reconstruction, directly impacting the lives and health of hundreds of millions of people. Biological functional adaptability and interface integration are fundamental to the effective repair of damaged tissues by these materials. However, current tissue repair materials face three major barriers: (1) Functional mismatch: A contradiction between the physicochemical properties of existing materials and their biological functions; (2) Interface integration dilemma: Insufficient bonding strength at the material-tissue interface; (3) Inefficient R&D models: Traditional trial-and-error methods suffer from long development cycles and a lack of systematic evaluation systems. These issues have led to clinical bottlenecks characterized by the short service life and suboptimal therapeutic efficacy of various materials currently in use.

To address these critical challenges in the field of life and health, we have established an "adhesion-electricity coupling" system. Breaking away from traditional static design thinking and centering on polyphenol chemistry, we leveraged the relationship between dynamic mussel adhesion and electron transfer in biological systems to effectively couple bioelectrical signal conduction with polyphenol chemistry within biomaterials. We uncovered the synergistic mechanism between polyphenol chemistry and tissue endogenous electric fields and proposed a new "interface adhesion-electrical signal coupling" dual-driven paradigm for tissue repair. Based on this, we developed polyphenol-mediated adhesion-electricity coupling hydrogel systems, achieving translational applications in fields such as bone regeneration and brain-computer interfaces.

Bioceramics-enhanced patch activates epicardial epithelial-to-mesenchymal transition for cardiac repair

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Engineered cardiac patches (ECPs) introduced functional factors that offer a promising strategy for the treatment of myocardial infarction (MI). Silicate bioceramics have received widespread attention because of their great potential in the tissue repair field. Inspired by the biological functions of inorganic ions on the cardiovascular system, we prepared an ECP containing lithium magnesium silicon bioceramics (LMS) particles. The release of multiple bioactive ions from LMS-containing ECPs could facilitate the functionalization and intercellular communication between cardiomyocytes (CMs). Furthermore, it was demonstrated that the LMS-containing ECPs could promote epicardial cell epithelial-to-mesenchymal transition (EMT) through the Notch pathway and paracrine, which efficiently repaired damaged CMs. *In vivo*, the regenerative microenvironment induced by LMS-containing ECPs restored normal electrical impulse propagation across scar tissue, activated islands of surviving myocardium, and improved cardiac function.

Key words: myocardial infarction, cardiac patch, bioceramics, epicardial cell, epithelial-to-mesenchymal

Introduction: The epicardial EMT is crucial for endogenous repair following MI [1-2]; however, this process is often limited and transient [3]. Functional cardiac patches applied to the epicardium have been shown to activate endogenous repair mechanisms post-MI [4]. Therefore, an epicardium-targeted functional cardiac patch holds promise for enhancing epicardial cell-mediated myocardial regeneration by providing a biomimetic microenvironment and modulating EMT-related signaling pathways [5].

Materials & Methods: (1) fabrication and characterization of a scaffold incorporating LMS bioceramic particles; (2) Construction of a functional cardiac patch by seeding CMs onto the scaffold to evaluate its biological effects; (3) establishment of an epicardial cell-CMs co-culture model to examine the patch-mediated enhancement of cardiac repair via EMT; (4) *In vivo* assessment using the MI model, combined with RNA-seq and flow cytometry, to elucidate the therapeutic outcomes and underlying mechanisms.

Results & Discussion: The LMS bioceramic-scaffold releases bioactive ions to enhance CMs maturation and activates the Notch pathway to promote epicardial EMT and paracrine repair. *In vivo* results revealed that the

LMS-based functional cardiac patch induced a regenerative microenvironment, which restored electrical signal propagation and promoted revascularization in the infarcted area, ultimately improving cardiac function. Transcriptomic analysis further reveals that the patch enhances energy metabolism, myocardial contraction, and angiogenesis via the epicardial Notch pathway, enabling effective myocardial repair.

Conclusions: This study constructed a bioceramics-enhanced ECP, which could promote cardiac repair by activating epicardial EMT, providing a promising strategy for MI repair.

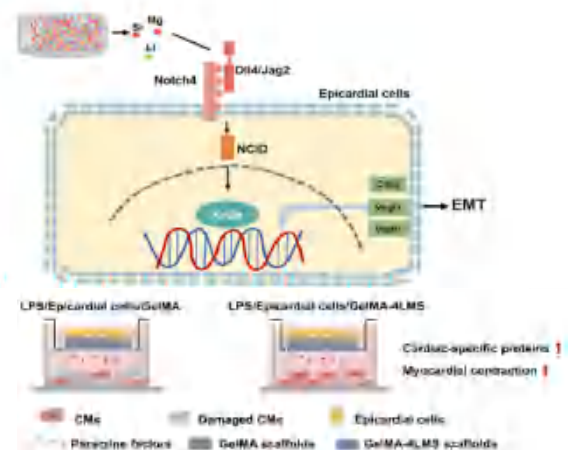


Fig. 1. Schematic diagram of the potential signal pathway of epicardial cells induced EMT by bioceramics-enhanced patch.

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Functional Material-Enabled Wireless Electrical Stimulation for Regulation of Stem Cell Fate and Brain Injury Repair

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Traumatic brain injury (TBI) is the leading cause of disability and death among young adults worldwide. At present, there are no treatments that can effectively reverse or slow the progression of TBI due to the limited regenerative capacity of adult neurons. After injury, damaged neurons are cleared, and glial cells proliferate to form scars, resulting in neurological dysfunction at the site of injury. Stem cell-based therapy is a promising approach for repair of brain tissues through replacing the damaged neurons with newly differentiated ones. However, the therapeutic performance of this approach is considerably restricted due to the difficulties in directing the transplanted cells to differentiate into functional neurons within the injured microenvironments. Electrical stimulation is a viable approach for improving the effects of NSC-based therapies, as it can influence various cellular processes, including proliferation, migration, division, differentiation, apoptosis and necrosis. However, it is great challenge to effectively apply the electrical stimulation to the implanted stem cells as they are in a movable state in vivo.

Here, I will talk about our recent work related to controlling the neuronal differentiation of stem cells using functional materials such as piezoelectric materials for promoting the repair of brain injuries. By precisely tuning the material-cell interaction, we are able to attach these functional materials to the membrane of neural stem cells. These functional materials can generate wireless electrical stimuli when exposed to external physical fields such as ultrasound to precisely activate the voltage-gated ion channels on the membrane. After delivery to the injury site, the stem cells can be induced to differentiate into functional neurons. The enhanced neuronal differentiation of stem cells facilitates the repair of injured brain and the restoration of behavioural and cognitive functions of animal TBI models.

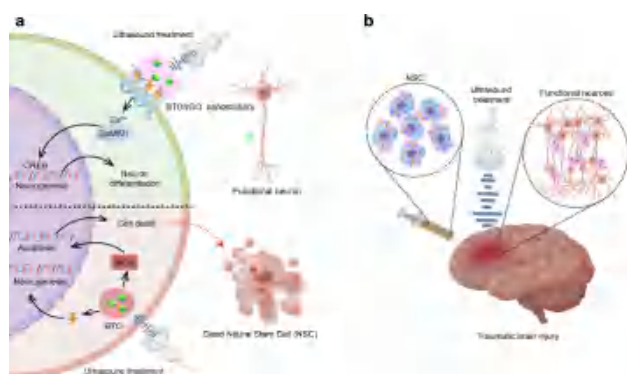


Figure 1. Piezoelectrical nanostickers facilitated the differentiation of NSCs into functional neurons. (b) The

application of piezoelectrical nanostickers in NSC-based therapy for TBI treatment.

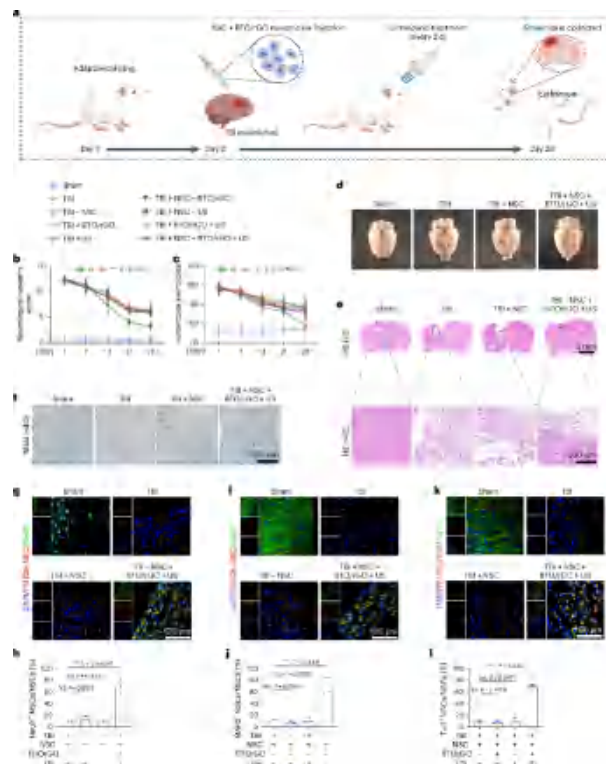


Figure 2. Piezoelectrical nanostickers promoted the therapeutic performance of NSCs for TBI treatment.

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Polyphosphate-based inorganic wax with combined hemostatic and osteogenic functions for bone repair

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Key words: polyphosphate, bone wax, bone repair, blood occlusion

Introduction: Effective management of bone defects in orthopedic surgery requires materials that can simultaneously achieve rapid hemostasis and promote bone regeneration. Conventional bone waxes are widely used to control bleeding but are biologically inert, non-degradable, and may impair bone healing or increase infection risk.¹ While bioactive ceramics and hydrogels can support osteogenesis, they lack the handling characteristics and occlusion efficiency required for intraoperative use.^{2,3} Inorganic polyphosphates (polyP) are emerging bioactive materials due to their biodegradability, osteogenic potential, and role in coagulation.^{4,5,6} However, their application in wax-like, shapeable formats has not been previously demonstrated. This study presents a novel inorganic, ion-regulated polyphosphate-based wax designed to integrate hemostatic performance with osteogenic activity.

Materials & Methods: A wax-like co-doped polyphosphate (CoPPW) was synthesized by chelating sodium polyphosphate with divalent cations (Ca^{2+} , Mg^{2+} , and Sr^{2+}) to induce controlled coacervation. By tuning cation type and molar ratios, the rheological properties were adjusted from gel-like to stiff, shapeable wax-like states. Material characterization included rheological testing, ion release, degradation behavior, and occlusion strength compared to commercial bone wax. In vitro biocompatibility and osteogenic performance were assessed using human bone marrow-derived mesenchymal stem cells (h-BMSCs) via proliferation

assays, ALP and Alizarin Red staining, qPCR, and transcriptomic analysis. In vivo performance was evaluated using a rabbit femoral defect model, with micro-CT and histological analyses performed at 4 and 8 weeks post-implantation.

Results & Discussion: The optimized Mg/Sr co-doped formulation exhibited high viscosity, excellent shapability, and occlusion capability compared to commercial bone wax, requiring approximately twice the pressure to initiate fluid leakage. The material demonstrated controlled degradation over weeks with sustained release of Mg^{2+} and Sr^{2+} ions. In vitro studies showed enhanced h-BMSC proliferation, osteogenic differentiation, and mineralization relative to bone wax. Transcriptomic and pathway analyses revealed significant upregulation of osteogenesis-related genes and activation of the PI3K/Akt and ECM-receptor interaction pathways, alongside activation of complement and coagulation cascades. In vivo, CoPPW achieved rapid hemostasis and significantly improved bone regeneration, with nearly complete defect healing observed at 8 weeks, while commercial bone wax-treated defects remained largely unhealed.

Conclusions: This work introduces the new fully inorganic, polyphosphate-based wax that combines effective hemostasis with strong osteogenic bioactivity. Through ion-regulated coacervation, the material achieves clinically relevant handling properties while actively promoting bone regeneration via controlled ion release and pathway activation. The demonstrated in vivo performance highlights CoPPW as a promising alternative to conventional bone wax for orthopedic and trauma surgery.

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Bioprocessing-Inspired Nanoparticle-Induced Liquid Precursor Strategy for Collagen Mineralization and Dentin Repair

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Abstract: Non-collagenous proteins (NCPs) critically regulate the precise integration of flexible collagen fibrils and rigid inorganic minerals in organisms. However, the ill-defined and low-contrast polymeric NCPs analogues obscure the corresponding molecular mechanisms. Here, electron-dense gold nanoclusters (AuNCs) functionalized with specific carboxyl ligands are proposed as the multi-functional NCPs analogues to both mediate and visualize collagen mineralization process. Molecular dynamic simulation and in vitro mineralization results show that carboxyl ligands modified AuNCs can induce the formation of liquid precursors, but their stability and crystallization behavior strongly depend on the ligand rigidity. Interestingly, AuNCs with short-chain rigid ligands stabilize the precursors, which infiltrate into the confined spaces of collagen fibrils in a “gap-to-overlap” sequence, ultimately achieving co-localization with intrafibrillar minerals in overlap zones. In contrast, AuNCs with long flexible ligands promote calcium phosphate crystallization, resulting in rapid extrafibrillar mineralization. Importantly, two distinct precursors types that participate in collagen mineralization process via dissolution-reassembly interconversion are identified, in which particulate liquid precursors directly infiltrate collagen fibrils, while aggregated droplets serve as transient, dissolvable ion reservoirs. Building on this knowledge, using gold nanoparticles (AuNPs-COOH) with slightly larger particle size as the NCPs, we achieve synergistic dentin regeneration and antibacterial therapy, which not only restore the hierarchical architecture and mechanical properties of dentin, but also exhibits dual antibacterial functionalities activated by near-infrared (NIR) light. This study provides molecular insights into the biomineralization mechanism of collagenous tissues and a robust bioprocessing-inspired platform for designing next-generation materials.

Keywords: Biomineralization, Collagen, Gold nanocluster, Dentin, Calcium phosphate

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Development of Bioceramic-based Viscoplastic Materials for Bone Hemostasis and Osteogenesis

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Key words: Bioceramic, hemostasis, osteogenesis

Introduction: Intraoperative bleeding associated with bone defects often impairs surgical outcomes. Traditional hemostatic bone wax acts as a passive, non-degradable barrier; whose biological inertness typically triggers inflammation and hinders bone regeneration. To overcome the limitations of bioinert bone wax, absorbable alternatives composed of bioceramic particles and absorbable polymer matrices have been attempted. However, in clinical practice such as endoscopic orthopedic procedures the applied hemostatic agent is deserved to resist washout in dynamic aqueous environments, adhere firmly to bleeding bone surfaces, and form an in-situ physical matrix for dual hemostatic and osteogenic functions. To address this need, we prepared self-setting, fluid-resistant composite candidate: magnesium phosphate-based bone putty (MPP). This material is formulated by magnesium oxide (MgO) and dipotassium hydrogen phosphate (K_2HPO_4) dispersed in a pregelatinized starch-polyethylene glycol (PEG) matrix. MPP can undergo rapid acid-base reactions in aqueous environments to in-situ form magnesium phosphate matrix, which converts the putty-like paste into a bone-like solid in bleeding area.

Materials & Methods: Briefly, MgO, K_2HPO_4 , and pregelatinized waxy starch powder were thoroughly mixed using a vortex mixer and poured into a beaker. Subsequently, molten PEG was added into the as-prepared powders and manually stirred to form an initial paste-like mixture in a 60 °C water bath environment. The mixture was then transferred to a mortar for manual grinding and shaping, ultimately yielding a uniform, highly moldable bone wax-like composite, designated as MPP.

2 g of MPP was manually kneaded for 30 s at room temperature (22–25°C) to simulate the preoperative manipulation process of bone wax. During this procedure, the plasticity, handling properties, and adhesion to surgical gloves were recorded and visually compared with those of commercial medical bone wax. Furthermore, in vitro tests such as underwater adhesion, liquid sealing, hemocompatibility, and cytocompatibility were carried to verify MPP prospects in dynamic aqueous environment. In vivo tests were also applied using rat calvarial defect. The defect areas were scanned by high-resolution micro-computed tomography. Three-dimensional reconstructions were analyzed for bone volume/total volume (BV/TV), trabecular

thickness (Tb.Th), and trabecular number (Tb.N). Specimens were then stained with haematoxylin and eosin (H&E) and Masson's trichrome to assess new bone formation and collagen deposition.

Results & Discussion: We developed a self-setting absorbable bone wax MPP that achieves rapid in-situ crystallization of magnesium phosphate phases via the reaction of MgO with K_2HPO_4 triggered by PEG-water exchange. This transition converts an intraoperatively moldable paste into a solid, providing immediate hemostatic barrier and an absorbable matrix for bone ingrowth. The as-formed matrix exhibit promising adhesive stability under dynamic water flow and degraded gradually, with mass loss increasing from $22.44 \pm 1.97\%$ on day 1 to $34.52 \pm 2.55\%$ on day 7. Besides, MPP exhibited stronger coagulation activation than bone wax, along with a low hemolysis rate of $3.24 \pm 1.36\%$ and enhanced osteoblast adhesion, proliferation, and alkaline phosphatase (ALP) expression. Compared to conventional non-resorbable bone wax, MPP showed superior hemostatic efficacy and significantly higher de-novo bone volume at 4 and 8 weeks. Its moldability, rapid setting, and structural stability in dynamic aqueous environments make it a multifunctional, osteoconductive hemostat with strong translational potential.

Conclusions: In this study, a ready-to-use MPP was developed by combining MgO and K_2HPO_4 with pre-gelatinized starch and PEG as an alternative to reported bone hemostatic agents. Compared to traditional bone wax, MPP not only retained excellent handling and defect-sealing capabilities, but also provided temporary mechanical support and promoted bone regeneration, as confirmed in both in vitro and in vivo studies. More importantly, MPP putty could be easily manipulated to fit irregular bone defects and maintained strong adhesion and structure integrity under both static and dynamic physiological fluid conditions. Self-setting was achieved through the exchange of PEG and water, inducing magnesium phosphate crystal network formation that served as a temporary scaffold for hemostasis and bone growth. As bone healing progressed, MPP gradually degraded while simultaneously enhancing bone formation, showing superior outcomes compared with control groups.

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Inorganic biomaterials for innervated tissue regeneration

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Key words: Inorganic biomaterials, 3D bioprinting, Silicate biomaterials, Tissue regeneration, Innervation

Introduction: Neural networks are densely distributed throughout many tissues and organs, which plays an essential role in tissue regeneration and functional recovery. Numerous neuropeptides and neurotrophic factors secreted from the neural system have been confirmed to be beneficial to tissue repair. However, the requirement of regenerating the neural components within the injury sites have been largely overlooked during the past decades. Inorganic biomaterials have been proved to promote various tissue regeneration, owing to the positive effects of bioactive ions (Si, Zn, Ca, etc.) on osteogenesis, angiogenesis and neurogenesis. Moreover, the spatial topology structures of biomaterials can also provide physical cues to modulate cell behaviors.

Results & Discussion: Hence, we have developed several silicate biomaterials with excellent bioactivities, and in combination with advanced manufacturing technology (including electrospinning, 3D printing and 3D bioprinting) to fabricate tissue regenerating scaffolds. The results showed that silicate biomaterials-based scaffolds could obviously promote tissue regeneration with neural integration. Besides, the physical cues of scaffolds also activated the PI3K-Akt signal pathway to promote the osteogenic differentiation of bone mesenchymal stem cells (BMSCs) and neurogenesis, resulting in innervated bone regeneration.

Conclusions: Taken together, biomaterials with innervation properties can not only recapitulate the physiological microenvironment of damaged tissues but also rapidly integrate with host neural networks, resulting in accelerated functional tissue regeneration.

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Research on Microenvironmental Regulation by Biomimetic Organic-Inorganic Composite Materials for Tissue Repair

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Key words: biomimetic structure, tissue microenvironment, biomaterials, regeneration, tissue engineering

Introduction: Pathological microenvironments are highly heterogeneous. Multiple factors, including mechanics, biochemical cues, immune responses, and metabolic states, are tightly coupled and dynamically evolving, thereby decisively shaping cell fate, inflammatory cascades, and the progression of tissue repair. Consequently, achieving predictable intervention and programmable regulation of the microenvironment remains a major challenge in biomedicine. Biomedical materials can remodel local cellular microenvironments across molecular, nanoscale, and macroscopic levels; however, their regulatory effects are closely related to material composition, hierarchical architecture, interfacial chemistry, and mass-transport behaviors. These considerations have driven the development of biomimetic organic-inorganic composite materials.

Materials & Methods: Based on organic-inorganic co-assembly reactions, we regulated the biomimetic mineralization and hybrid construction of calcium phosphate inorganic ion oligomers to establish a multi-scale, designable biomimetic material platform. (1) Biomimetic hybrid membrane materials were constructed to enable stage-specific and precise regulation of cellular metabolic behaviors during repair through interfacial chemistry and mass-transport modulation¹. (2) By controlling the mineralization pathway and spatial distribution of inorganic ion oligomers, biomimetic osteogenic hydrogels and osteochondral gradient hydrogels were fabricated to reconstruct tissue-level hierarchical structures and mechanical properties^{2,3}. (3) By tuning organic-inorganic hybrid building blocks to integrate rigidity and flexibility, multi-tissue adaptive hemostatic sponges were developed to match the mechanical environments and irregular cavities of different tissues⁴.

Results & Discussion: (1) The biomimetic hybrid membrane can recognize dominant cell populations at different repair stages and precisely modulate cellular metabolic states, thereby coordinating key processes such as macrophage-mediated inflammatory regulation and stem-cell osteogenic differentiation to achieve temporally optimized microenvironments¹. (2) Biomimetic osteogenic hydrogels and osteochondral gradient hydrogels synergistically reconstruct tissue-hierarchical mechanics and repair microenvironments in space, promoting ordered transitions in critical cellular behaviors and enhancing regenerative efficiency via coupling of

inflammation modulation with pro-regenerative signaling^{2,3}. (3) The multi-tissue adaptive hemostatic sponge, leveraging the tunable rigid-soft characteristics of the organic-inorganic composite structure and rapid fluid exchange, enables effective hemostasis and local microenvironment stabilization in complex injury scenarios, providing favorable conditions for subsequent repair⁴.

Conclusions: This multi-scale biomimetic organic-inorganic composite material system offers a materials-based pathway for multidimensional, spatiotemporal precise regulation of complex pathological microenvironments and provides new insights for advancing tissue repair and regenerative therapeutic strategies.

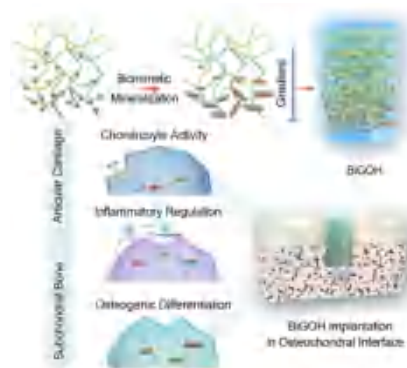


Fig. 1. Schematic illustration of Organic-Inorganic Composite Hydrogel with Biomimetic Structural Gradient for Osteochondral Regeneration in Osteoarthritis.

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Silicate biomaterials-induced bone marrow organoids for tissue regeneration

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Introduction:

The emergence of bone marrow organoids (BMOs) holds promise for addressing bone-related deficiencies, although maintaining BMOs homeostasis is still challenging, and their efficacy for tissue regeneration remains uncertain. Silicate biomaterials can provide distinctive biochemical clues by releasing bioactive ions, which are beneficial for regulating stem cell behaviors. In this study, harnessing the bioactivities of silicate biomaterials, we engineered functional BMOs through the culture of mesenchymal stem cells (MSCs) and endothelial cells in a chemically defined medium, incorporating with calcium silicate nanowires (CS) and magnesium silicate nanospheres (MSS).

Key words: bone marrow organoids, magnesium silicate, calcium silicate, homeostasis, tissue regeneration

Materials & Methods: We introduced silicate biomaterials in BMOs culture system to enhance the development and function maintenance of BMOs in terms of vascular network, mesenchymal compartment, and recruitment of HSCs. In addition, we performed rabbit *in vivo* osteochondral repair experiments to evaluate the performance of BMOs in repairing skeletal system injuries.

Results & Discussion:

The resulting BMOs demonstrated robust preservation of endothelial networks, increased self-renewal of the mesenchymal compartment, and positive effects on hematopoietic stem cells. Co-culture experiments revealed that the engineered BMOs can significantly improve the activities of chondrocytes, MSCs, and Schwann cells, pivotal for tissue regeneration. Furthermore, the silicate biomaterials upregulated gene expression and signaling pathways in the domains of osteogenesis and angiogenesis. In a rabbit osteochondral repair model, BMOs induced by MSS notably enhanced osteochondral regeneration. Our findings underscore the pivotal role of silicate biomaterials in enhancing BMOs homeostasis and functionality, making these engineered BMOs a compelling strategy for tissue regeneration.

Conclusions:

we successfully prepared functional BMOs for tissue regeneration. Attributed to the release of bioactive ions, the BMOs induced by CS or MSS exhibit prolonged interconnected endothelial networks and mesenchymal

compartment structure. The CS and MSS also enhanced the recruitment and function maintenance of HSCs. Compared to CS, MSS showed superior performance in promoting BMOs' development and activity. Co-culture experiments of BMOs and cells related to tissue regeneration indicated that BMOs possess a significantly stimulatory effect on the differentiation of tissue regeneration-related cells. RNA sequencing revealed that organoids significantly upregulated the gene expression and signaling pathways related to tissue development. The *in vivo* study suggested that functional BMOs, especially those with MSS, significantly enhanced osteochondral regeneration, offering an effective paradigm for applying BMOs to repair skeletal system injuries. This work highlights the potential of integrating silicate biomaterials into organoids development to advance tissue repair strategies.

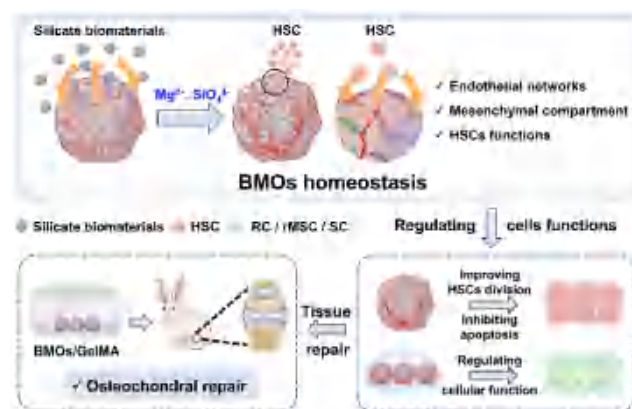


Fig. 1. Schematic illustration of the development and application of the functional BMOs induced by CS or MSS. This strategy, based on silicate biomaterials, effectively maintains BMOs homeostasis and regulates cellular functions, thereby offering potential for repairing skeletal system-related defects

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Binary Metal Co-doped Hierarchical Layered Piezoelectric Bioceramics for the Repair of Tumor-Associated Bone Defects

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Key words: KNN, Bone tumor, Sonodynamic therapy, Conch shell, BCP scaffold

Introduction: Osteosarcoma surgical treatment has always faced the dilemma of tumor recurrence and the regeneration of defective bone tissue. It is imperative to develop an implant with both antitumor and osteogenic properties. Recently, ultrasound (US)-triggered sonodynamic therapy based on piezoelectric nanomaterials has shown great potential in tumor treatment. Thus, we proposed an unprecedented strategy for bone tumor treatment by endowing biphasic calcium phosphate (BCP) bioceramics with an antitumor function via the incorporation of (Mn, Co) co-doped potassium sodium niobate (Mn, Co-KNN), a type of piezoelectric nanomaterials.

Materials & Methods: inspired by the natural structure of conch shells, Mn, Co-KNN/BCP composite scaffold was designed as a cross-lamellar biomimetic conch shell structure to enhance mechanical properties. Through the digital light processing three-dimensional(3D) printing technology, Mn, Co-KNN nanoparticles were observed to be uniformly dispersed on the surface and within the conch shell-biomimetic BCP scaffold.

Results & Discussion: The piezocatalytic experiments demonstrated that the Mn, Co-KNN/BCP biomimetic scaffold could generate various types of reactive oxygen species under US, exhibiting effective piezocatalytic activity. And the piezocatalytic activity increased with the proportion of Mn, Co-KNN in the composite scaffold. For the treatment of tumor-induced bone defects in rabbit femoral condyles, the tumor volume in the Mn, Co-KNN/BCP group was significantly smaller than that of the control group after 4 weeks. Furthermore, DR analysis revealed that almost all conch shell-biomimetic scaffolds maintained good structural integrity during implantation.

Conclusions: It was demonstrated that the Mn, Co-KNN/BCP scaffold prominently inhibited tumor growth and provided effective mechanical support. These results indicate that the 3D-printed Mn, Co-KNN/BCP biomimetic scaffold is promising as a novel functional scaffold for treating bone defects following surgical resection of osteosarcoma.

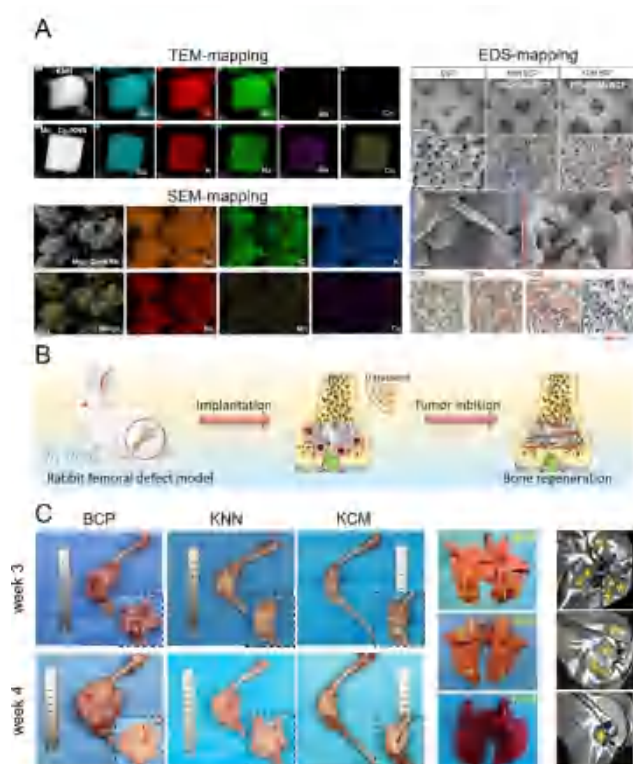


Fig. 1. Material characterization and in vivo result. (A) Confirmation of incorporation of Mn and Co element into the bioceramic; (B) Design of the animal experiment; (C) in vivo anti-tumor result of the Mn, Co-KNN/BCP bioceramic.

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Construction and Application of Composites of Polysaccharides and Inorganic Nanoparticles

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csbm@csbm.org.cn**Introduction**

Biocomposites of polysaccharides and inorganic nanoparticles have attracted increasing attention in biomedical field due to their satisfying performances. As an important type of natural polymers, polysaccharides with favorable biocompatibility, stability, and bioactivity are considered as ideal candidates to fabricate multifunctional platforms for diverse biomedical applications. On the other side, inorganic nanoparticles are widely utilized based on their unique physicochemical properties. Furthermore, morphological design is considered to achieve enhancement in corresponding properties and performances. Therefore, taking advantage of morphological design, hybrids of polysaccharides and inorganic nanoparticles are expected to produce desirable properties and performances.



Fig. 1. Design and construction of composites of polysaccharides and inorganic nanoparticles for biomedical applications.

Results & Discussion

In this work, polysaccharides with the advantages of good biocompatibility, biodegradation, and regeneration are combined with inorganic nanoparticles to prepare polysaccharide-based materials for biomedical applications. We focus on the construction strategies including surface modification, wrapping, and template strategies. The morphology effect of these composites on their biological functions and performances is discussed. We highlight the design concept and the underlying structure-activity relationships between the morphology and performance. Based on the morphology-dependent findings, star-shaped, 1D, Janus, and rough nanohybrids with fascinating properties were rationally fabricated and utilized for enhanced therapeutic effects. Integrating the

advantages of both components, the intriguing nanohybrids and hybrid systems with unique morphology demonstrate synergistic properties. On the basis of the morphology-dependent findings, star-shaped, 1D, Janus, and rough nanohybrids with fascinating properties were rationally fabricated and utilized for enhanced therapeutic effects. Subsequently, we discuss other composite systems of polysaccharides and inorganic nanoparticles and their biomedical applications. Finally, we propose the future opportunities and challenges for developing advanced composites of polysaccharides and inorganic nanoparticles in biomedical applications. In addition, excellent imaging functions such as fluorescence, photoacoustic, and magnetic resonance imaging could be realized to guide the therapy. Furthermore, these composites can also be used for antibacterial applications due to their distinct physical and chemical properties.

Conclusions

The rational design and preparation of these polysaccharide-based biocomposites provide new strategies for the construction of multifunctional theranostic systems, and will also be beneficial to the study of the interaction between nanomaterials and biological systems. These composites can combine the advantages of inorganic nanoparticles and organic components, and the resulting materials with special morphologies can achieve better anti-cancer effects in chemotherapy, gene therapy and photothermal combined therapy, and realize imaging-guided therapy. With a better understanding of the characteristics of both components and morphology effects, a series of polysaccharide-inorganic composites could be fabricated to achieve more synergistic effects. It is hoped that the rational design of these composites would light the way for safe and efficient biomedical applications.

Key words: polysaccharides, inorganic nanoparticles, morphology effect, biomedical applications

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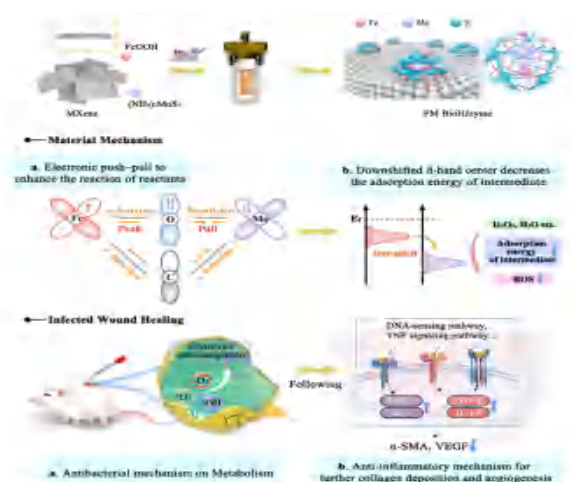
Heterostructure in Tissue Engineering

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Enter the body of your paper here in two column format. Abstract must be one page. The main text should include **Introduction, Materials & Methods, Results & Discussion**, and **Conclusions**. Type should be 12 points for the Title and 10 points for the author and body sections. Times New Roman is the only font for use. Title and headings should be highlighted in bold.

Key words: Heterostructure, regeneration, biomaterials, tissue engineering

Scheme 1. Schematic illustration of the preparation and functionality of FM BioHJzyme. (In the part of Materials Mechanism, the O from the H_2O_2 , O_2 , H_2O ; the C from MXene; the Fe and Mo from FeMoS_4).



Introduction: Pathogenic infections pose a persistent threat to global public health, necessitating innovative antibacterial strategies with well-defined disinfection pathway. The antibacterial efficiency is confined in the contradiction between reactants adsorption and intermediates desorption. Here, the $\text{FeMoS}_4/\text{MXene}$ bio-heterojunction enzyme (FM BioHJzyme) is proposed and constructed. Under the inspiration of near-infrared light (NIR), the heterostructures between the FeMoS_4 and MXene facilitates efficient electron-hole separation with localized electron accumulation at FeMoS_4 sites. Crucially, the electronic push-pull effect induced by Mo polarizes oxygen-containing reactants (H_2O_2 , H_2O , O_2) toward Fe active centers, enabling sequential electron capture for reactive oxygen species (ROS) generation. The results also reveal an enhancement in electron density at Fe sites compared to FeS/MXene controls, which is accompanied by a downshift in the Fe d-band center that reduces intermediates adsorption energy. The therapeutic efficacy is systematically evaluated using an *S. aureus*-infected full-thickness skin defect model. The bi-modulated FM BioHJzyme exhibits favorable antibacterial efficiency under NIR irradiation, while subsequent wound healing is facilitated through collagen deposition and angiogenesis in the following absence of NIR irradiation. This work offers a deep insight into the intricate mechanism-performance relationship of BioHJzyme platform in catalytic anti-bacterial application and proposes a sustainable approach of mechanism-guided materials design.

Materials & Methods: Synthesis of FeMoS_4 and FM BioHJzyme: Single-layered MXene was prepared via ultrasonic stripping method. For

FM synthesis, 400 mg ammonium tetrathiolylbolyblylate ($(\text{NH}_4)_2\text{MoS}_4$) was dispersed in deionized (DI) water, followed by addition of 140 mg iron oxyhydroxide (FeOOH). Subsequently, 200 mg MXene was introduced into the mixed solution and sonicated for 20 min. The dispersion was hydrothermally treated at 160 °C for 10 min in a sealed reactor. The resulting product was centrifuged at 8000 rpm for 10 min, with the supernatant discarded and the precipitate collected as FM BioHJzyme. The FeMoS_4 control group was synthesized through an identical procedure excluding MXene addition. Synthesis of BC, Fe-BC, and FM-BC: Bacterial cellulose (BC) membranes were biosynthesized using acetobacter xylinum (ATCC 23767) cultured in yeast-glucose-chloramphenicol (YGC) agar medium. The medium was refreshed every 48 h for 14 days. Harvested BC films were purified by boiling in 2.5% NaOH solution at 80 °C for 3-4 h, followed by five DI water rinses under boiling conditions. For Fe-BC fabrication, FeMoS_4 nanoparticles ($200 \mu\text{g mL}^{-1}$) were incorporated into the YGC medium during bacterial culture. FM-BC was prepared analogously using FM BioHJzyme instead of FeMoS_4 .

Results & Discussion: $\text{FeMoS}_4/\text{MXene}$ BioHJzyme exhibited robust enzyme-mimetic properties to improve ROS yield. Under NIR irradiation, the electron-hole separation occurred between MXene and FeMoS_4 owing to the heterostructure. Furthermore, in the phase of FeMoS_4 , the added Mo pushed adjacent reactants (H_2O_2 , H_2O , and O_2) closer to Fe by electronic push-pull effect, making the feedstocks more likely to capture electrons. Additionally, the decreased d-band center owing to the added Mo weakened the adsorption energy of intermediates enhancing the ROS production, resulting in the excellent antibacterial efficiency. Followed, in the absence of NIR irradiation, the FM showed favorable anti-inflammatory and angiogenic property.

Conclusions: Collectively, this work enhanced the understanding of the intricate catalytic antibacterial mechanism in the BioHJzyme platform, verified the mechanism-performance relationship, and provided a mechanism-guided materials design. The FM can also be applied as a formation of wound dressing presenting the same remediation effect, providing a transformative strategy for developing adaptive wound management systems.

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Revealing the Role of Zinc Ions in Atherosclerosis Therapy via an Engineered Three-Dimensional Pathological Model

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Introduction: Atherosclerosis (AS)-related cardiovascular diseases are a top global killer, with vascular stenting as a key intervention. The field has shifted to zinc-based alloys, but zinc ions' effects on vascular cells remain unclear, and current evaluations (costly low-throughput animal models, simplistic cell assays) are limited. We integrate microfluidic chips and tissue engineering to develop a 3D biomimetic AS model (multiple cells, lipid accumulation, inflammation) for efficient, cost-effective analysis. Our goal is to clarify zinc ions' molecular mechanisms in intimal hyperplasia, inflammation, and vascular remodeling, informing Zn-based stent design to regulate diseased vessel repair, accelerate clinical translation, and bridge basic research with medical applications.

Key words: atherosclerosis models; biodegradable vascular stents; layered arterial walls; zinc ions evaluation; zinc-based alloys.

Materials & Methods:

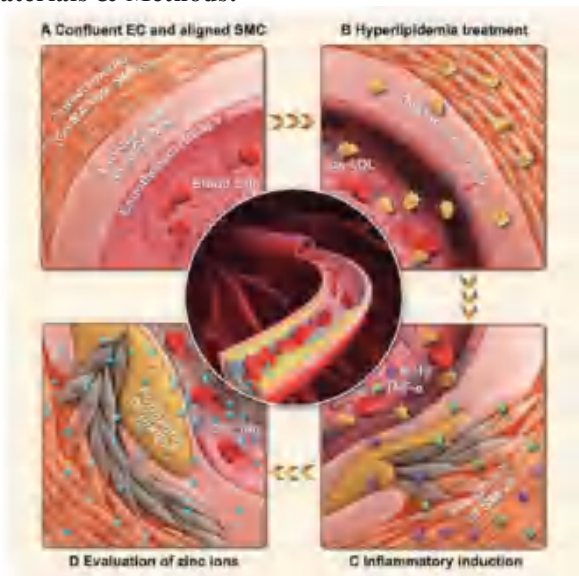


Fig. 1. Schematic illustration of the 3D AS model based on the layered arterial walls using GelMA hydrogel to investigate the molecular mechanisms and cellular reactions towards zinc ions at various concentrations.

Results & Discussion:

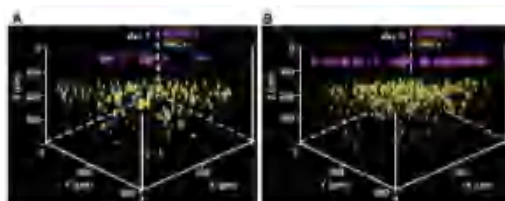


Fig. 2. Distribution of HUVECs (purple) and SMCs (yellow) in the constructed arterial model.

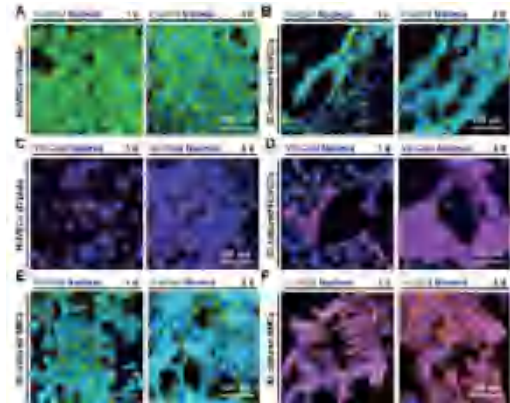


Fig. 3. Comparison of the biological performances of HUVECs and SMCs in 2D monolayer cultures and healthy arterial wall models: (A, B) Arrangement of F-actin in HUVECs; (C, D) Expression of VE-Cad in HUVECs; (E, F) Arrangement of F-actin and α -SMA expression in SMCs.

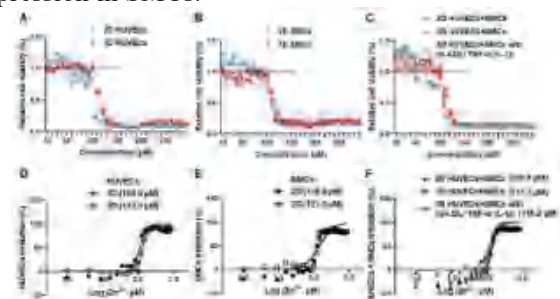


Fig. 4. Sensitivity of 3D-cultured individual cells, normal arterial wall models, and constructed pathological arterial wall models to Zn^{2+} , with 2D-cultured cells as controls.

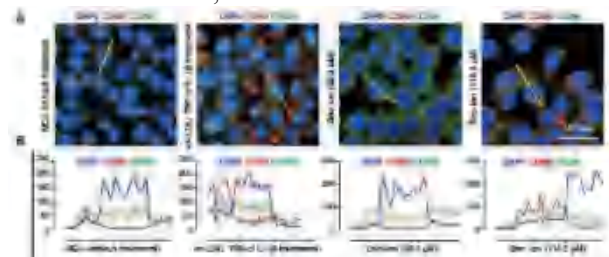


Fig. 5. The effects of ox-LDL, TNF- α , and IL-1 β on M1 and M2 polarization of macrophages (MCs) after treatment with zinc ions at different concentrations (20.0 μ M and 116.2 μ M).

Conclusions:

- 3D biomimetic AS models recapitulate key pathological features.
- Zn^{2+} exerts biphasic effects on ECs.
- Zn^{2+} inhibits DNA synthesis in 3D AS models via G0/G1-to-S phase arrest
- KEGG identifies SLC30A1/HMOX1 as potential targets.

Spatiotemporally Designed 2D Nanoarchitected Composites as Drugless Therapeutics

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Keywords: 2D Nanoarchitectures, Nanotherapeutics, Drugless, Synergistic therapy

Introduction: The rapid development of nanotechnology has brought new opportunities and challenges to biomedicine. Among them, 2D nanomaterials with a variety of special properties (conductivity and specific surface area), high designability and controllability stand out as a comprehensive "toolbox". These materials can be allosteric, or surface modified by energy band engineering and van der Waals heterojunctions to meet various therapeutic needs. In view of the pathological microenvironment, the material should be adjusted accordingly to achieve the effect of precise treatment.

Materials & Methods: We explored the transformation of two-dimensional materials (MoSe_2) into three-dimensional nano-flower architectures, doped with Pt nanodots. Finally, a layer of PEG was coated for good biocompatibility towards collaborative treatment of breast cancer. In another work, single-layer/few layer Ti_3C_2 MXene nanosheets were peeled off and Cu_2O nanoparticles were generated using in-situ oxidation method for photothermal assisted treatment of tumors (Fig. 1). Finally, Ag-doped MnO_2 nanoflowers were loaded into natural fish skin acellular matrix hydrogel for bacterial infection wound repair (Fig. 2).

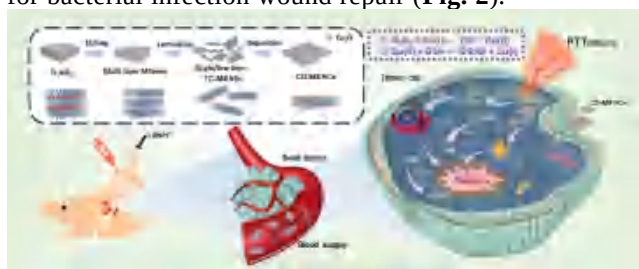


Fig. 1. Schematic illustrating the design and fabrication progress of $\text{Cu}_2\text{O}/\text{MX}$ nanocomposites (CO-MX NCs).^[1]

Results & Discussion: (1) Pt- MoSe_2 -PEG presented exceptional light-assisted photothermal (PTT) and photodynamic (PDT), as well as light-augmented chemodynamic (CDT) modalities for synergistic trimodal therapies against breast carcinoma;^[2] (2) A method based on transition metal oxide (TMOs)-decorated MXenes were enriched as drug-like nanoarchitectonics for enriched nanocatalytic CDT. (3) The TMO-encapsulated Fd-AM biohydrogel successfully delivered both antibacterial and antioxidant

effects, supporting tissue regeneration (angiogenesis) in MRSA-infected wounds.

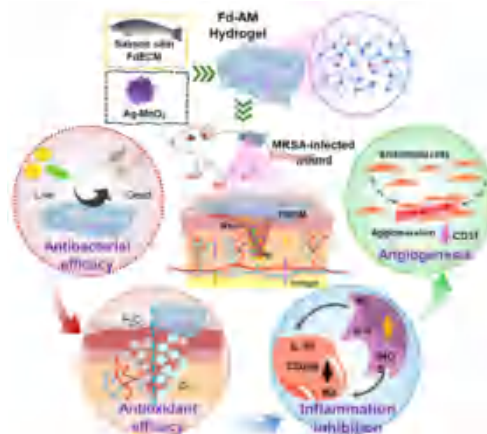


Fig. 2. Schematic diagram showing the antibacterial, infection control, promoting cell migration, angiogenesis, and macrophage polarization.^[3]

Conclusions: These studies confirmed that through rational nanostructure design, such as morphology regulation, heterogeneous recombination, and biocompatibility modification, multifunctional nanoplateforms that respond to pathological microenvironments can be constructed. We have respectively achieved photo-enhanced synergistic treatment, drug-free catalytic treatment and antibacterial antioxidant synergistic repair, demonstrating the broad potential of engineered nanomaterials in precise tumor treatment and wound regeneration of infection.

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A Multifunctional SIS-dECM-Based Hydrogel Integrating Anti-Inflammatory Activity and Mucosal Repair for Ulcerative Colitis Therapy

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Key words: SIS-dECM, hydrogel, Ulcerative Colitis, anti-inflammatory, mucosal repair

Introduction: Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by persistent colonic mucosal inflammation and tissue injury, highlighting the need for topical therapies that simultaneously suppress inflammation and promote mucosal repair.

Materials & Methods: Based on the excellent bioactivity of small intestinal submucosal acellular matrix (SIS-dECM) and the mucosal adhesion characteristics of dopamine modified hyaluronic acid (HA-DA), we developed a novel composite hydrogel (SIS-dECM/HA-DA) for targeted rectal administration in UC.

Results & Discussion: SIS-dECM/HA-DA hydrogel demonstrated good biocompatibility and strong mucosal adhesion, enabling effective local retention after rectal administration. In DSS-induced colitis, it significantly attenuated inflammation by reducing pro-inflammatory cytokine levels and promoting macrophage polarization toward an anti-inflammatory phenotype. Meanwhile, the hydrogel restored tight junction protein expression, improved mucosal barrier integrity, and contributed to the rebalancing of gut microbiota.

Conclusions: In summary, the SIS-dECM/HA-DA hydrogel achieves effective mucosal repair in UC by synergistically modulating inflammatory responses, epithelial barrier integrity, and intestinal microbiota, demonstrating its promise for targeted local therapy.

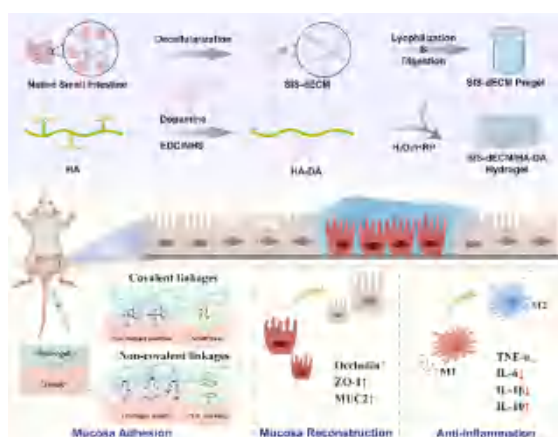


Fig. 1. Schematic diagram of the application of SIS-dECM/HA-DA hydrogel in the rectal treatment of ulcerative colitis in mice.

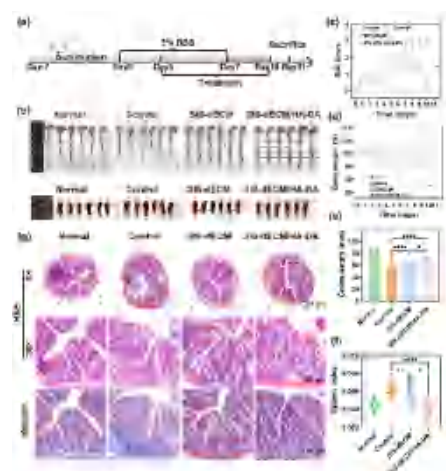


Fig. 2. Evaluation of the therapeutic effect of SIS-dECM/HA-DA hydrogel in the DSS-induced UC mice.

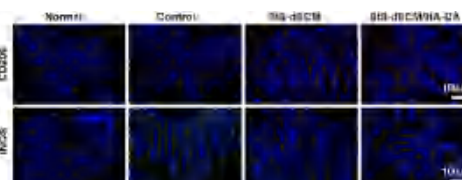


Fig. 3. SIS-dECM/HA-DA hydrogel alleviated the inflammatory response in DSS-induced UC mice.

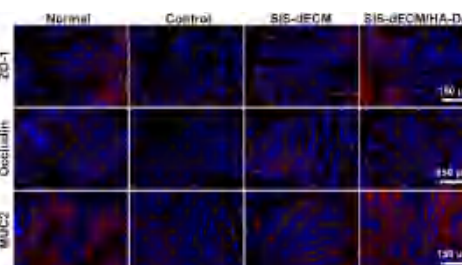


Fig. 4. SIS-dECM/HA-DA hydrogel repaired the intestinal mucosal barrier of DSS-induced UC mice.

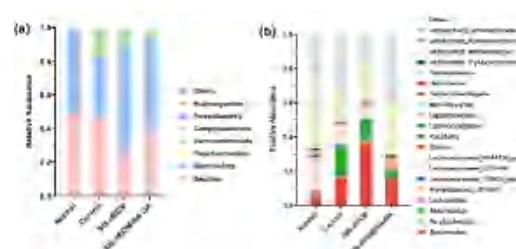


Fig. 5. SIS-dECM/HA-DA hydrogel improved the intestinal microbiota of DSS-induced UC mice.

A 3D-Printed Stent with Polydopamine-Modified Hydrogel Coating for Enhanced Anchorage in Acute Colorectal Obstruction

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Key words: Acute colorectal obstruction, Intestinal stent, Hydrogel, 3D printing, Anti-migration

Introduction: Endoscopic stent placement is an established effective intervention for relieving acute malignant obstruction secondary to colorectal tumours^[1]. However, clinically used stents are frequently associated with complications such as tumours ingrowth and stent migration, which limit their long-term efficacy^[2,3].

Materials & Methods: In this study, we developed a novel 3D-printed flexible tubular intestinal stent coated with polydopamine (PDA)-enhanced sodium alginate/polyacrylamide (SA/PAM) hydrogel (hereafter referred to as PSP hydrogel). The stent itself acts as a physical barrier to inhibit tumours ingrowth, whereas the PSP hydrogel coating markedly improves tissue adhesion^[4], thereby enhancing the overall performance of the stent system.

Results & Discussion: The modified hydrogel demonstrates excellent compressive strength (>45 kPa) and superior tissue adhesiveness (>10 kPa), along with stable binding to the stent surface. The coated stent exhibits sufficient flexibility and can expand effectively to restore patency in constricted intestinal segments upon deployment. Compared with uncoated stents, the hydrogel-coated version shows a significantly higher anti-migration force (>7 N) and a markedly reduced migration distance (<1 mm).

Conclusions: These findings indicate that the viscous PSP hydrogel-coated intestinal stent holds promising potential for clinical application in the management of acute colorectal obstructions.

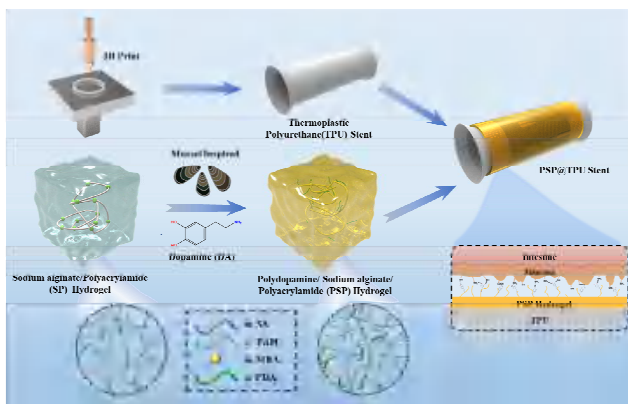


Fig. 1. Preparation process of PSP coated hydrogel and the PSP@TPU coated stent



Fig. 2. (a) Comparison of macroscopic morphology of SP and PSP coated hydrogel; (b) 3D printed polymer stent; (c) PSP hydrogel-coated intestinal stent

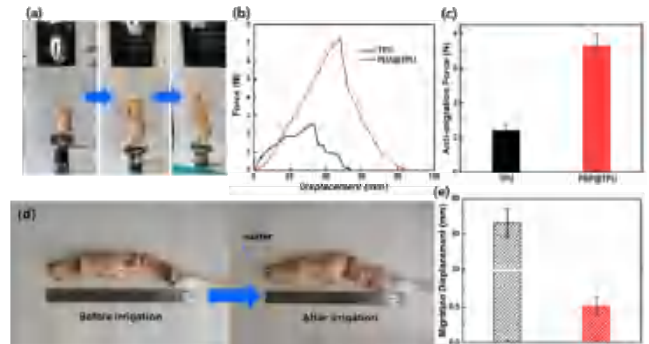


Fig. 3. (a) The anti-migration force test; (b) anti-migration force-displacement curves and (c) maximum anti-migration force before and after coating; (d) Anti-migration displacement test; (e) Comparison of migration distance of stents in pig rectum.

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ECM-Derived Biomimetic adhesive Patch Regulating the Inflammatory Microenvironment to Accelerate Oral Ulcer Healing

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Key words: ECM, Adhesive, Oral ulcer, Biomimetic, Inflammatory microenvironment

Introduction: The effective management of oral ulcers is hindered by the constantly moist oral environment and the persistently dysregulated inflammatory microenvironment¹. Inspired by the hierarchical architecture of native mucosa, we engineered a biomimetic bilayer patch designed to achieve “homologous repair” through synergistic tissue regeneration and immune modulation. Compositionally mimicking the bioactive lamina propria, the patch features a bioadhesive inner layer enriched with dopamine-modified esophageal mucosa decellularized extracellular matrix (eECM-DA) to specifically recapitulate the native biochemical niche, embedded within hyaluronic acid methacrylate (HAMA) networks loaded with dexamethasone (Dex). Structurally mimicking the protective epithelial barrier, this inner matrix was coupled with a hydrophobic ethylcellulose (EC) backing that shield against saliva erosion. After contact with the moist oral environment, this bilayer patch (EDH/EC-Dex) quickly contacted the wound surface and displaced interfacial water to achieve robust wet adhesion. Functionally, by integrating the homologous eECM microenvironment with therapeutic Dex, the patch actively reprograms the inflammatory milieu by modulating JAK-STAT signaling and antioxidant networks, driving inflammation resolution and promoting the orderly regulation of the ulcer microenvironment (**Fig.1**). In a rat oral ulcer model, EDH/EC-Dex patches demonstrated superior efficacy in accelerating re-epithelialization and functional recovery compared to commercial products. This work introduced immune-modulatory, ECM-derived platform, offering a paradigm shift for oral ulcer management and broader tissue engineering applications.

Materials & Methods: A tunable adhesive and mechanically controllable EDH/EC-Dex bilayer patch was constructed through a controlled photocuring process. The hydrogel was characterized for its physicochemical properties. Both in vitro and in vivo experiments were conducted to evaluate the patch's efficacy in promoting oral ulcer wound healing.

Results & Discussion: Through the interactions between the hydrogel and the tissue surface, the lap-shear adhesion strength was measured to be 9.63 ± 0.45 kPa, and the hydrogel could adhere to the rat oral mucosa for over 4 h. The composite hydrogel exhibited low energy dissipation, with compressive modulus of 120.70 ± 4.66 kPa. Furthermore, its synergistic anti-inflammatory effect with Dex and significant

promotion of oral mucosal healing were validated in a rat oral ulcer model.

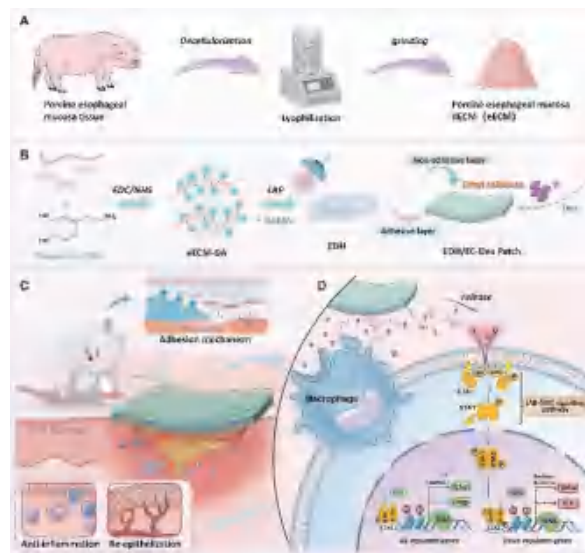


Fig. 1. Schematic illustration of the EDH/EC-Dex patch for oral ulcer repair.

Conclusions: In summary, we engineered a biomimetic bilayer patch that recapitulates both the structural hierarchy and compositional niche of native mucosa to enable homologous repair. By coupling a Dex-loaded, DA-modified eECM/HAMA bioactive matrix mimicking the lamina propria with a hydrophobic EC protective backing mimicking the epithelial barrier, the EDH/EC-Dex system overcomes the challenge of wet tissue adhesion while providing a stable window for therapy. Mechanistically, this compositionally biomimetic platform actively reprograms the inflammatory microenvironment by modulating the JAK-STAT pathway, thereby driving macrophage polarization toward a reparative phenotype and resolving the cytokine storm. In a rat oral ulcer model, the EDH/EC-Dex patches validated this design by maintaining stable adhesion for over 4 h, significantly reducing CD11b⁺ cell infiltration, and accelerating epithelial regeneration compared to commercial products. This work highlighted the paradigm of using structurally and chemically biomimetic strategies to integrate adhesion, regeneration, and immune modulation, offering a promising solution for refractory mucosal injuries.

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Cross-Scale Composite Imaging Bioprobes for Tumor Boundary Identification

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“Biomedical Boundarics” or “Boundarics in Biomedicine” is a cutting-edge interdisciplinary discipline involving multiple fields (e.g., bioscience, medicine, chemistry, materials science, and information science) dedicated to investigating and solving key scientific questions in the formation, identification, and evolution of living organism boundaries [1,2]. Specifically, it encompasses three levels: (1) the boundary between the living organism and the external environment; (2) internal boundary within living organism; and (3) the boundary related to disease in living organism. The advancement of research in biomedical boundarics is of great scientific significance for understanding the origin of life, the interaction between internal and external environments, and the mechanism of disease occurrence and evolution, thus providing novel principles, technologies, and methods for early diagnosis and prevention of major diseases, personalized drug development, and prognosis assessment, etc.

In this talk, we will discuss the details of new advances on biomedical boundarics driven by an identification of tumor boundary, particularly on composite imaging bioprobe materials.

Keywords: Boundarics, tumor boundary, composite imaging bioprobes

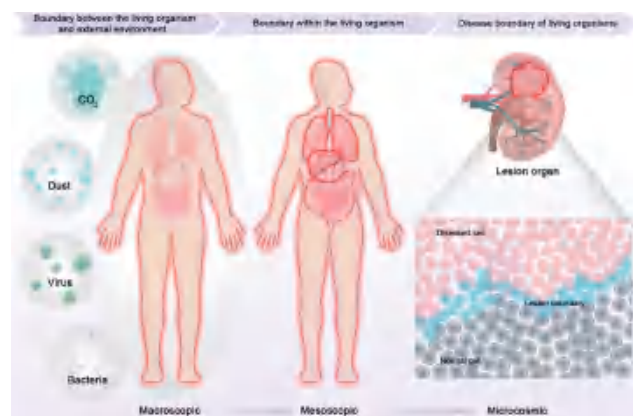


Figure 1. Schematic illustration of biomedical boundaries.

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Snail-inspired Decellularized Extracellular Matrix/Glycosaminoglycan Hydrogel for Wound Healing

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Key words: decellularized extracellular matrix, wound healing, regeneration, biomaterials, tissue engineering

Introduction: Decellularized extracellular matrix (dECM) is a biomaterial derived from biological tissues by removing cellular components such as nucleic acids while preserving the three-dimensional structure and chemical composition of the natural extracellular matrix. It possesses a microenvironment and growth factors similar to those of the cellular matrix, which can promote cell proliferation and migration^[1]. The glycosaminoglycan from snail mucus (A. fulica glycosaminoglycan, AFG) can regulate the inflammatory microenvironment of wounds and accelerate wound healing. Inspired by the using of snails to apply on wounds, this study constructed a composite hydrogel wound dressing based on porcine skin dECM and AFG (dECM/AFG) to promote wound healing and regulate the inflammatory microenvironment (Figure 1).

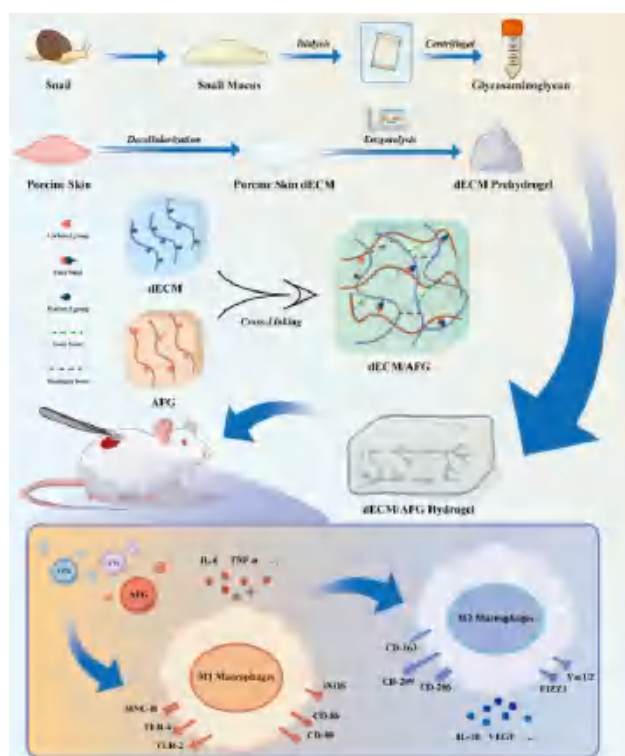


Fig. 1. Schematic diagram of the preparation of dECM/AFG hydrogel and its promotion of wound repair.

Materials & Methods: By using hydrogen bonding, electrostatic interaction and chemical bond formation in a solution with a specific pH, the surface anionic-rich AFG was combined with partially hydrolyzed positively charged dECM to construct dECM/AFG hydrogel. The physicochemical properties of the dECM/AFG hydrogel were characterized, and its wound healing promoting effect and the regulatory role in the inflammatory microenvironment were investigated through in vitro and in vivo experiments.

Results & Discussion: The composite hydrogel material showed obvious effect on wound healing. In the treatment of mouse skin wound model, the experimental group treated with dECM/AFG at a high level of mucosaccharide concentration (0.75% wt) for 9 days showed a wound healing rate of 99.6%, which was significantly better than the healing effect of other groups. Masson staining and immunohistochemistry of wound tissue showed that the wound tissue after dECM/AFG treatment had less tissue proliferation and lower inflammatory response.

Conclusions: The dECM/AFG hydrogel wound dressing constructed in this paper can be applied to the wound to promote wound healing and reduce the inflammatory reaction during wound recovery, and is expected to become a new strategy for wound treatment.

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Engineered Anti-Senescence Trachea With Post-Transplanted Regenerative Homeostasis

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Key words: Long-segmental trachea defects, Senescence, Post-transplanted dysfunction, Tissue-engineered trachea

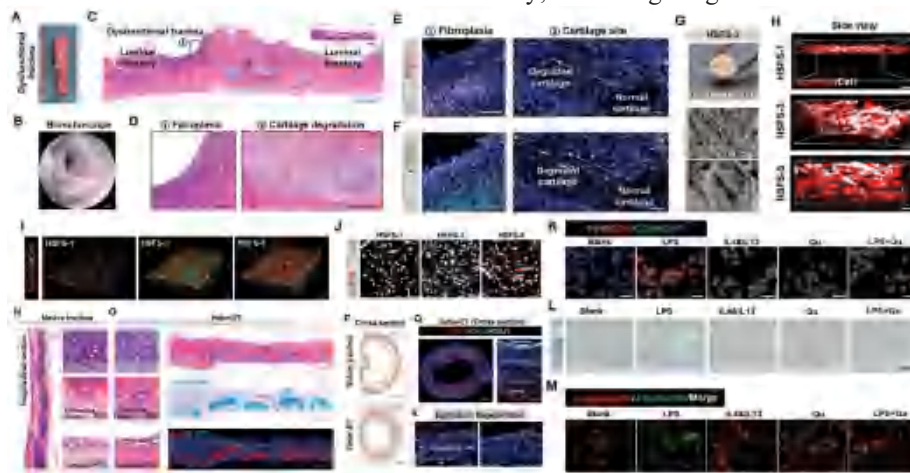
Introduction: Senescence disrupts normal cellular functions and is characterized by permanent cell cycle arrest and the secretion of large amounts of harmful factors. In addition to the cellular level, with the accumulation of senescence, cell proliferation decreases, and tissue regenerative homeostasis is disturbed; thus, tissue repair is impaired. The occurrence and progression of a series of clinically important degenerative diseases like osteoarthritis are related to senescence. The physiological integrity and regenerative potential of grafts e.g., allogeneic kidneys and artificial vascular grafts ultimately determines graft survival conditions, which were also associated with senescence. In the field of tracheal transplantation, although engineered tracheae mimicking natural structures are being developed, after orthotopic transplantation, the tracheal function was found to be decreased to varying degrees with fibroplasia, cartilage degradation, and loss of epithelial regeneration; however, whether these degenerative changes are related to senescence remains unknown. Therefore, this study focused on exploring the relationship between functional loss and tissue senescence after tracheal substitute transplantation and proposed useful solutions.

Materials & Methods: First, we analyzed the post-transplantation dysfunction of the engineered trachea constructed based on traditional silk fibroin (SF) scaffolds. Based on the analysis results, we first optimized the development pattern of chondrocytes by introducing enhanced SF membrane films into the original non-woven fiber scaffold, thereby constructing a hybrid scaffold with "fiber-film" structure to form tracheal cartilage rings. At the same time, quercetin was

loaded into the fibrous connective tissue rings for sustained release, thereby inducing an immune cascade to restrain senescence. Finally, based on the above dual anti-senescence design, the two kinds of rings were stacked to form Hebe-ET (anti-senescence engineered trachea), which was then transplanted in New Zealand rabbits to verify long-term functional maintenance.

Results & Discussion: Based on the analysis of the failed trachea, two key factors were identified: 1) Poor cell contact within the cartilage rings led to endogenous senescence of chondrocytes; 2) There was an imbalance of the immune-senescence cascade in the fibrous connective tissue. Thus, the enhanced SF films served as the hydrophilic matrix, promoting cell proliferation and cell-to-cell contact, while the non-woven short fibers endow the scaffold interconnected pores, allowing the chondrocytes to fully penetrate and interact, thereby delaying the senescence process (Fig G-J). In the fibrous connective rings, quercetin induced macrophage polarization by alleviating oxidative stress and mitochondrial-targeted protective effects, and by remodeling the immune microenvironment, it promoted the rejuvenation of cartilage, endothelial, and fibroblasts (Fig K-M). Based on the above dual anti-senescence design, Hebe-ET showed no functional deterioration 12 weeks after transplantation, demonstrating stable mechanical properties, mature cartilage phenotype, transverse vascular network, and epithelial coverage on the inner wall (Fig N-K).

Conclusions: In response to the critical challenge of functional failure after engineered tracheal transplantation, this study identified cellular senescence as the core mechanism and focused on two key factors to create Hebe-ET, which has highly natural-like morphology and multi-functional tissue regeneration ability, achieving long-term functional maintenance.



AI-assisted volumetric 3D bioprinting of vascularized full-thickness skin

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Key words: Volumetric bioprinting, Bioink, Tissue engineering

Introduction: Artificial skin provides a new strategy for the repair and functional reconstruction of deep wounds that are difficult to heal. However, the key bottleneck of existing tissue or 3D bioprinted skin lies in the difficulty of accurately reconstructing a full-thickness skin with both structural and functional vascularization.

Materials & Methods: This study proposes the use of AI assisted volumetric bioprinting for rapid and accurate construction of vascularized full-thickness skin. By accurately designing the epidermal layer, vascular containing dermis layer, and adipose layer to match the real skin structure using AI, rapid vascularization can be achieved by adding multiple cells.

Results & Discussion: Successfully prepared composite bioinks based on silk protein, achieving stable layering of multiple materials; At the same time, rapid integrated volumetric bioprinting of multi-material and multi-cell layered bioinks has been achieved, which can quickly reconstruct complex multi-layer skin models within 60 seconds.

Conclusions: This study breaks through the bottleneck of multi-material and multi-cell volumetrical bioprinting, providing a theoretical basis for the rapid and accurate reconstruction of vascularized full-thickness skin.

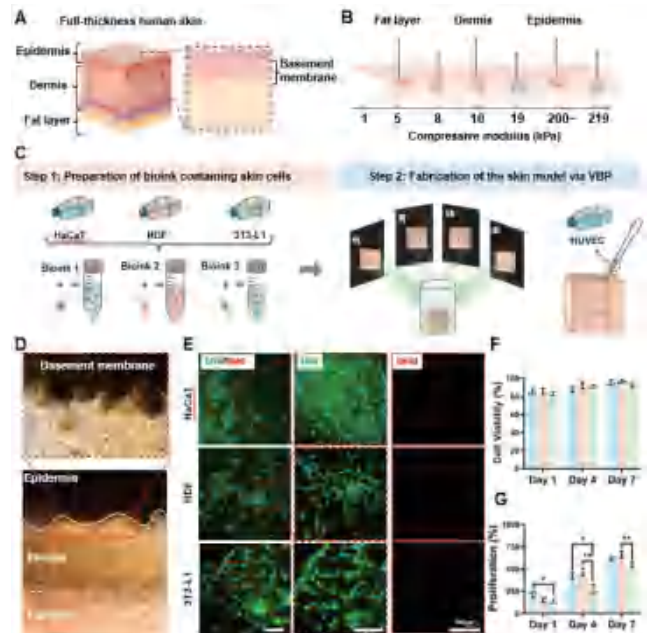


Fig. 1 Multi-materials and multi-cell volumetric bioprinting of full-thickness skin.

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NIR-Programmable Stealth 2D Black Phosphorus Nano-Biointerfaces for Deep Tumor Penetration and Photoimmunotherapy

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Key words: black phosphorus nanosheets, protein corona, light activatable nanoplatfrom, tumor penetration, photoimmunotherapy

Introduction: Two-dimensional black phosphorus (BP) nanosheets hold great promise for biomedical applications due to their high surface area, strong near-infrared (NIR) absorption, and efficient singlet oxygen ($^1\text{O}_2$) generation. However, their clinical translation is hindered by two major barriers: rapid protein corona formation upon administration, which alters their biological fate, and poor tumor penetration, limiting therapeutic efficacy. While PEGylation enhances circulation stability, it often triggers the “PEG dilemma”—reducing cellular uptake and deep tumor penetration¹. Moreover, conventional coatings lack adaptability for multistage delivery. Thus, intelligent systems that dynamically modulate protein corona for immune evasion and enable on-demand deshielding for tumor infiltration are urgently needed.

Materials & Methods: We engineered a light-activatable nanoplatfrom (PTPBP) by self-assembling BP with an ROS-responsive block copolymer (PEI_{1.8k}-TK-PEG_{5k}) (Fig.1a). Upon NIR irradiation, BP-generated ROS cleave the thioketal (TK) linker, detaching PEG and exposing cationic PEI for enhanced tumor penetration (Fig.1b). The system co-loaded with Mn²⁺ (STING agonist) and Indoximod (IDO inhibitor) enables combined photoimmunotherapy (Fig.1c). Mechanistic insights—including protein corona modulation, charge conversion, and immune activation—were validated via proteomics, molecular dynamics, multimodal imaging, and in vivo studies in orthotopic 4T1 breast tumor models.

Results & Discussion: Our surface stealth strategy proactively manages the protein corona, enriching complement inhibitory proteins while depleting opsonins, thereby attenuating immunogenicity and increasing tumor accumulation by 3.4-fold. Upon NIR irradiation at the tumor site, BP-generated ROS cleave the TK linker, detaching the PEG shield to expose cationic PEI. This spatiotemporal charge conversion facilitates programmable interactions with biointerfaces, promoting transvascular extravasation, deep tumor penetration, cellular uptake, and lysosomal escape. By co-loading Mn²⁺ and Indoximod, PTPBP@Mn²⁺/Indoximod enables synergistic photoimmunotherapy by inducing immunogenic cell

death (ICD), activating the cGAS-STING pathway, and inhibiting the IDO metabolic checkpoint. In orthotopic breast cancer models, this strategy potently inhibits primary and metastatic tumors and establishes long-term immunological memory.

Conclusions: In summary, we developed PTPBP, an intelligent nanoplatfrom with NIR-programmable 2D black phosphorus nano-biointerfaces, designed to overcome sequential biological barriers: systemic stability, tumor accumulation, and deep penetration. Key innovations include: (1) a stealth-by-design strategy enhancing circulation and tumor targeting; (2) NIR-triggered charge conversion decoupling circulation and penetration; and (3) synergy of PDT, STING activation, and IDO inhibition to boost antitumor immunity. This work establishes a framework bridging nano-bio interfaces and immune reprogramming for next-generation precision nanotherapeutics in oncology and beyond.

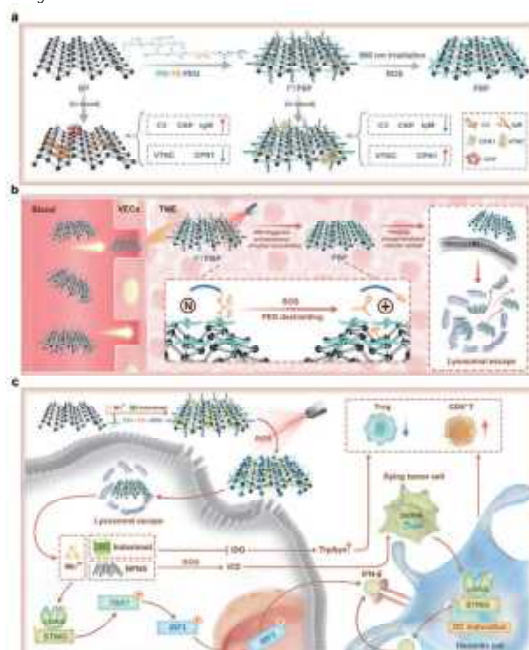


Fig. 1. Schematic mechanism of protein corona management and controlled charge conversion of light-activatable PTPBP for enhanced tumor accumulation, penetration and photoimmunotherapy.

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Immunomodulatory Fibrous Scaffold with Dual Enzyme-Mimic Activities Prevents Postsurgical Tumor Recurrence

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Key words: electrospun, immune niche, immunomodulation, implantable scaffold, postsurgical tumor treatment

Introduction: Surgery is still the preferred clinical strategy for most patients with solid tumors. However, severe local immunosuppression after surgical resection further increases the incidence of relapse and metastases. To address this clinical challenge, implantable scaffolds have been developed for postsurgical tumor treatment and immunomodulation. However, these scaffolds are loaded with immune stimulants to enhance antitumor immunity, which is costly and complicated.

Surface functionalization of electrospun fibrous scaffolds with nanoparticles represents an ideal approach, as it not only increases the nanoparticle bioavailability but also leverages the scaffold architecture to facilitate immune cell recruitment and local immune modulation. Due to the mixed-valence states of Mn, MnO_x nanomaterials could serve as nanozymes with catalase (CAT)-, peroxidase (POD)-, and oxidase-like activities. Additionally, MnO_x has been shown to promote dendritic cell (DC) maturation and macrophage polarization toward M1 phenotype. But the inherent antitumor therapeutic effects and immunomodulatory properties of the scaffold have not been explored.

Materials & Methods: The PCL fibrous scaffold was fabricated by electrospinning. The PCL@PDA (PP) scaffold was prepared by decorating the PCL scaffold with a polydopamine layer. The PCL@MnO_x (PM) scaffold was prepared by the reaction of the PP scaffold with the KMnO₄ solution.

Results & Discussion: The PM scaffolds exhibited POD-like and CAT-like dual enzyme-mimic activities. Compared with the PCL and PP scaffolds, the PM scaffolds efficiently generated reactive oxygen species in the presence of both H₂O₂ and GSH, while an obvious O₂ release was observed in H₂O₂ solution following incubation. Taken together, PM scaffolds possessed the potential to induce tumor cell immunogenic cell death (ICD) via toxic ·OH generation and alleviate hypoxia within the tumor microenvironment (TME).

PM scaffolds effectively upregulated the population of M1 macrophages, compared with the PCL and PP counterparts. An obvious increase in mature DCs was observed after treatment with PM scaffolds, confirming the immunoadjuvant effect of the MnO_x-functionalized scaffolds.

PM scaffolds could effectively induce tumor cell ICD, leading to the release of tumor-associated antigens (TAAs). In addition, a substantially elevated infiltration of immune cells was observed in the PM scaffold compared with PCL and PP scaffolds. The porous structure of the PM scaffolds and the TAAs released are supposed to favor immune cell infiltration.

PM scaffolds can effectively reshape the immunosuppressive TME by alleviating hypoxia. The released TAAs and the Mn²⁺ in the TME, facilitate efficient activation of immune cells, which collectively contribute to the potent antitumor immunity.

In the mouse tumor resection model, PM scaffolds could effectively inhibit postsurgical tumor recurrence with excellent biosafety in vivo.

Conclusions:

We present a MnO_x nanozyme-functionalized electrospun fibrous scaffold as a promising strategy to inhibit postsurgical tumor relapse by harnessing its inherent physicochemical and immunomodulatory properties. This work establishes a new paradigm for implantable biomaterials thereby providing a translatable strategy for effective postoperative cancer therapy.

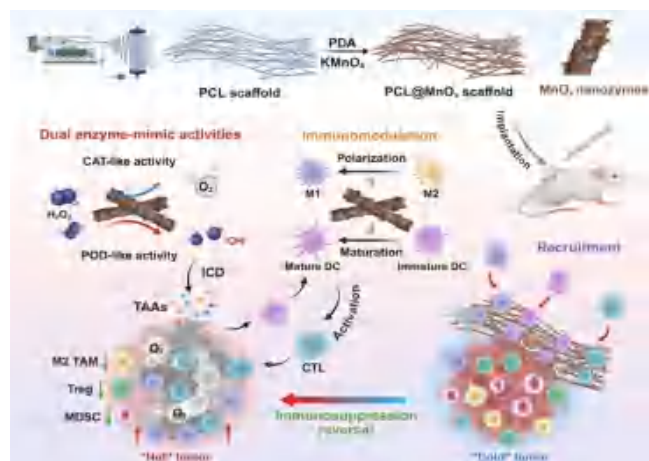


Fig. 1. Schematic illustration of the preparation of the PM scaffold for the recruitment and activation of immune cells and inhibition of postsurgical tumor recurrence.

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Electrospun Hybrid Nanofibers Enable Robust Sonopiezoelectric-Driven Antitumor Immunity

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Abstract

Sonodynamic therapy based on piezoelectric biomaterials has emerged as a research hotspot in tumor treatment due to its deep tissue penetration and spatiotemporal controllability. However, current limitations in inorganic or hybrid systems regarding metabolic clearance difficulties and biotoxicity hinder clinical translation. Poly-L-lactic acid (PLLA) combines intrinsic piezoelectric properties with biosafety, yet its insufficient piezoelectric performance caused by the lack of effective crystallization control methods fails to meet sonodynamic therapeutic requirements. Previous research revealed that solvent induction could enhance PLLA fiber crystallinity and form porous structures to improve fiber-microenvironment interfacial interactions. Based on this finding, we propose a two-step strategy of "oriented spinning, porous crystallization": 1) Design a disentangled polymer/solvent/non-solvent ternary system to achieve low molecular chain entanglement and high orientation through high-speed stretching and dynamically regulated phase separation; 2) Investigate stress-constrained solvent-assisted high-temperature crystallization mechanisms to elucidate how porous fiber morphology and high crystallinity enhance piezoelectric response. The ultrasound-responsive PLLA piezoelectric fibers will leverage porous structures to boost reactive oxygen species (ROS) yield. The antitumor efficacy was validated using animal models, to achieve a piezoelectric constant and porous morphology that meets therapeutic requirements (tumor inhibition rate > 80%) with controlled metabolic outcomes.

Key words: regeneration, biomaterials, tissue engineering (3-5 key words)

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Piezoelectric PLLA nanofibers with sonochemical effects: A novel safe/efficient strategy for atrial fibrillation ablation

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Abstract

Atrial fibrillation (AF) is an arrhythmia caused by rapid, disorganized atrial electrical signals, featuring high incidence, strong elderly susceptibility, and severe complications. Current clinical drugs have limited efficacy and many side effects, while first-line catheter ablation carries risks like severe pain, acute pericarditis, and atrioesophageal fistula—creating an urgent need for a safer, low-pain, and controllable ablation strategy.

Poly(L-lactic acid) (PLLA), an FDA-approved long-term implantable material, boasts high safety, low cost, and piezoelectricity. Under ultrasonic stimulation, it generates reactive oxygen species (ROS) via interfacial electron transfer, critical for myocardial cell death.

In this work, we combined highly oriented electrospinning, solvent-induced recrystallization, and high-temperature annealing to endow PLLA nanofibers with high crystallinity and porous morphology, ensuring stable piezoelectric performance and mesoporous structure for electron transfer. Ultrasound mediation achieved in situ ROS accumulation and myocardial cell death, with animal experiments confirming effective implantation and sustained piezoelectricity.

This project integrates degradable biomaterials with piezoelectric-sonochemical effects to develop a minimally invasive, precise AF ablation technology. Aligned with precision medicine and clinical needs, it offers a new interventional solution for AF and potential extension to other arrhythmias, holding significant scientific and clinical value.

Key words: regeneration, biomaterials, tissue engineering (3-5 key words)

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Engineered human alveolar lung-on-a-chip model

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Key words: Lung-on-a-chip, Blood-air barrier, stretchable biological membrane

Introduction: We have developed an alveolar chip designed for respiratory disease modeling and therapeutic assessment, which accurately replicates the biomechanical and structural features of the human alveolar microenvironment[1]. The pivotal components comprise a stretchable biological membrane and a negative pressure-driven device. The stretchable biological membrane serves to emulate the multi-alveolar architecture, whereas the negative pressure-driven device supplies negative pressure to the chip, thereby simulating the process of respiration. Within this lung-on-a-chip model, we have successfully established a blood-air barrier, induced pulmonary edema, and endeavored to achieve its resolution.

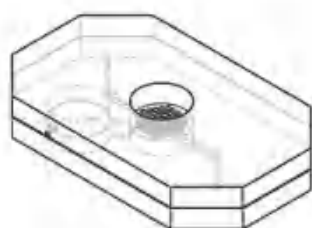


Fig. 1. Lung-on-a-chip

Materials & Methods: The main structure of the lung organ-on-a-chip is constructed using PDMS, and the stretchable biological membrane at its core is divided into two components: one is PDMS with superior mechanical elasticity, and the other is GelMA hydrogel exhibiting excellent biocompatibility[2]. GelMA hydrogel is dripped onto the pores of the plasma-treated membrane scaffold, where it forms a thin film within the pores owing to liquid surface tension. Subsequent photocuring yields a fully formed biomimetic membrane.

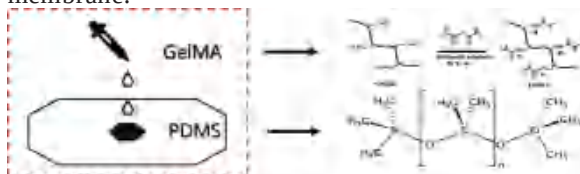


Fig. 2. stretchable biomembrane

Results & Discussion: Within the lung-on-a-chip, we replicated the alveolar structure by seeding A549 cells and HUVECs on the upper and lower surfaces of a stretchable biomembrane, respectively, and established a gas-blood barrier through gas-liquid interface culture.

Additionally, we employed high-dose IL-2[3] Induce pulmonary edema in a lung-on-a-chip model within a short-term period.



Fig. 3. Modeling and Simulation of Alveolar Structure



Fig.4. blood-air barrier

Conclusions: By employing lung-on-a-chip technology, we replicate the biomechanical and structural features of the human alveolar microenvironment to construct a model for respiratory diseases. Moreover, we are dedicated to advancing multidisciplinary integration and AI empowerment in subsequent research, with the goal of rendering lung-on-a-chip more visually accessible and platform-based.

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Multimodal synergistic anti-tumor based on Pin1-inhibiting nanocomposites

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Key words: Targeted therapy, Pin1 inhibitor, Drug delivery, Multi-effect synergy

Abstract: Cancer is difficult to treat due to its high genetic heterogeneity, and its growth and metastasis are regulated by multiple signaling pathways. However, there is a lack of drugs in clinical practice that can simultaneously block these oncogenic signaling pathways. To effectively treat cancer, it is necessary to develop new therapeutic targets and conduct combination therapy. Pin1 is a unique peptidyl-prolyl isomerase that can promote tumorigenesis by activating a series of oncogenic signaling pathways. Targeting Pin1 represents a new tumor treatment strategy. The research team identified specific inhibitors of Pin1 such as ATRA [1, 2], but they have druggable shortcomings such as short half-life, which limits their anti-tumor efficacy. We used supercritical fluid technology and self-assembly methods to prepare single-drug-loaded polylactic acid, and polylactic acid-polyethylene glycol nanospheres, as well as dual-drug-loaded human serum albumin nanoparticles carrying Pin1 inhibitors. We systematically studied their sustained-release performance, pharmacokinetic performance, cell uptake, and biosafety in vitro and in vivo, and investigated their anti-tumor growth and metastasis efficacy and underlying mechanism at the cellular, molecular, and animal levels. The results show that drug-loaded nanospheres have high drug encapsulation efficiency, can be taken up by cancer cells, can effectively sustained-release drugs, and have excellent pharmacokinetic properties and biosafety. Drug-loaded nanospheres efficiently inhibit cancer growth and metastasis by simultaneously acting on a series of signaling pathways that regulate cancer cell growth and metastasis, and are expected to provide a new method for the clinical treatment of solid tumors such as liver cancer [3-5]. In addition, we prepared biomimetic mineralized nanoparticles co-loaded with Pin1 inhibitor and photothermal agent by self-assembly method, and studied the synergistic inhibition of Pin1 inhibitor and photothermal agent combination on the proliferation of breast cancer under low-temperature photothermal conditions. Through a series of experiments, we examined the induction of drug-loaded nanoparticles on breast cancer immunogenic cell death and the inhibition on tumor recurrence, and explored their synergistic mechanism. The results showed that drug-loaded nanoparticles could significantly enhance the synergistic anti-breast cancer effect of Pin1 inhibitor and photothermal agent under low temperature photothermal

conditions, significantly increase the induction of low temperature photothermal on breast cancer immunogenic cell death, enhance the inhibitory effect on the expression of multiple oncogenic signaling pathways, and play the role of cancer vaccine. This study is expected to provide a new method for the multi-effect synergistic elimination of tumors and prevention of recurrence through targeted therapy, low-temperature photothermal therapy, and immunotherapy.

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Nanoenergetic Converters with Coupled Energy Cascade for On-Demand Microwave Dynamic Therapy

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Key words: microwave dynamic therapy, thermoelectric effect, nanoenergetic converter, energy cascade, tumor therapy

Introduction: Microwave dynamic therapy (MDT) holds promise for cancer treatment, but its efficacy is constrained by low microwave (MW) energy density and poor MW absorption of conventional sensitizers. This study aims to develop $\text{Ti}_3\text{C}_2@\text{CoFeMOF}@\text{CaO}_2$ nanoenergetic converters (MMC-NCs) that overcome these limitations through a coupled energy cascade strategy, enabling enhanced reactive oxygen species (ROS) generation for synergistic antitumor and antibacterial therapy.

Materials & Methods: MMC-NCs were fabricated by assembling CaO_2 nanospheres and CoFeMOF nanoparticles onto Ti_3C_2 MXene nanosheets. Material characterization was performed using TEM, SEM, XPS, and UV-Vis spectroscopy. MW absorption capacity was evaluated by dielectric loss and reflection loss measurements. The thermoelectric effect was investigated through electrochemical analysis and DFT calculations. ROS generation was evaluated via multiple fluorescence probes (DCFH-DA, ABDA, TEMP, DMPO). *In vitro* antitumor and antibacterial activities were assessed in 4T1 cells and against *S. aureus*. *In vivo* efficacy was validated in 4T1 tumor-bearing mice with intratumoral *S. aureus* infection.

Results & Discussion: MMC-NCs exhibited enhanced MW absorption (RL=-12.93 dB at 1.73 GHz, $\approx 94.91\%$ absorption) due to improved dielectric loss from $\text{Ti}_3\text{C}_2/\text{CoFeMOF}$ interfacial polarization. Under MW irradiation, CoFeMOF generated localized hyperthermia ($\Delta T = 37.6^\circ\text{C}$ at 6 mg/mL), creating a thermal gradient across the $\text{Ti}_3\text{C}_2/\text{CoFeMOF}$ heterostructure (Fig. 1). This induced a built-in electric field via the thermoelectric effect of Ti_3C_2 , as confirmed by DFT calculations showing electron transfer from Ti_3C_2 (work function 3.94 eV) to CoFeMOF (4.28 eV). The built-in electric field promoted electron-hole separation, enabling electron-mediated ROS production ($\cdot\text{OH}$ and $^1\text{O}_2$) by reacting with $\text{H}_2\text{O}_2/\text{O}_2$ supplied from CaO_2 degradation in the acidic TME. MMC-NCs also depleted glutathione, disrupting antioxidant defenses. *In vitro*, MMC+MW reduced 4T1 cell viability to $\approx 53\%$ and showed potent antibacterial activity ($\text{MIC}=31.25\ \mu\text{g/mL}$ under MW irradiation). *In vivo*, MMC+MW achieved significant tumor inhibition and eliminated *S. aureus* in infected tumors, with better efficacy in bacteria-positive groups, confirming that antibacterial action enhances antitumor outcomes.

Conclusions: MW-responsive nanoenergetic converters MMC-NCs were constructed, which overcame the intrinsic limitations of conventional MDT through a coupled energy cascade, mediating ROS storm for potent tumor inhibition. MW irradiation was initially transformed by MMC-NCs to localized thermal energy, subsequently converted it into directional electrical energy, and finally activated interfacial redox reactions, thereby optimizing MW absorption and addressing the low quantum energy challenge of MDT. Importantly, MMC-NCs not only exhibited robust tumor suppression performance both *in vitro* and *in vivo*, but also achieved complete eradication of *S. aureus* in infected tumors, showcasing dual therapeutic functionality. This study establishes a prospective paradigm for the design of precision nanoenergetic converters and offers an innovative strategy to optimize MW energy utilization and overcome inherent energy density limitations of MW photons, thereby substantially improving MDT efficacy.

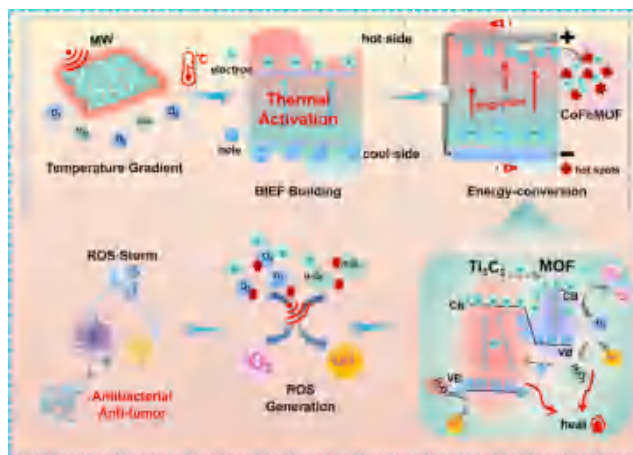


Fig. 1. Schematic illustration of the energy conversion process and ROS generation capacity of MMC-NCs.

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High-resolution 3D printed hydrogels for tissue regeneration

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Key words: Hydrogel, 3D printing, High-resolution, Tissue engineering, Regenerative medicine

Introduction: Tissue engineering requires biomaterials that integrate multi-functions such as structural support, bioactivity, and directional guidance. This study addressed the challenge of developing a multifunctional composite hydrogel system via 3D printing, aiming to combine tunable mechanical properties, microenvironment modulation, and topological guidance for organized cell/axon growth, using spinal cord repair as a representative application to validate performance.

Materials & Methods: Two functional hydrogels were designed: gelatin methacryloyl-poly(ethylene glycol) diacrylate (GM-PEGDA) for robust structural support, and gelatin methacryloyl-RADA4-IKVAV (GM-RA4IV) modified with laminin-derived peptides to enhance cell adhesion and bioactivity. High-resolution digital light projection 3D printing was used to fabricate the GM-3Dpro scaffold—GM-PEGDA with well-defined parallel channels, which were then infused with GM-RA4IV to form the composite structure. Liposome nanospheres (siRNA@LNPs) targeting PTEN were prepared via microfluidics for molecular regulation. Hydrogel properties (mechanical strength, swelling, degradation) and 3D print precision were characterized; in vitro biocompatibility (with PC12 and dorsal root ganglion cells) and in vivo functionality (rat model) were evaluated via microscopy, immunohistochemistry, and sequencing.

Results & Discussion: GM-RA4IV exhibited required multifunctionality: low swelling to avoid tissue compression, gradual degradation matching tissue regeneration, and bioactive peptides that suppressed inflammation and promoted neurite outgrowth. 3D-printed GM-3Dpro maintained high structural integrity and precise channel architecture, effectively guiding oriented cellular/axon growth—addressing the lack of directional control in non-3D-printed GM-RA4IV. GM-PEGDA alone, while mechanically stable, lacked bioactivity; the combination of GM-3Dpro and siRNA@LNPs further enhanced functional performance. Notably, the system's core strengths lay in the synergy between the multifunctional hydrogel's bioactivity and 3D printing's structural precision, though its efficacy in non-neural tissues or large-scale fabrication remains to be explored.

Conclusions: This work validates that multifunctional hydrogel design paired with 3D printing enables the creation of integrated biomaterials with tailored structure and bioactivity. The GM-3Dpro system serves as a versatile platform for tissue engineering, with potential beyond neural repair. Future efforts should expand hydrogel compositional diversity and optimize 3D printing scalability to unlock broader applications in regenerative medicine.

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Customized Hydrogel Dressing Addresses Biomechanical Heterogeneity across Specific Wounds

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Key words: tailored wound repair, wound biomechanics, mechanical modulation, reverse design, mechanomedicine

Introduction: Wound healing remains challenging, especially for chronic wounds showing impaired contraction and closure by tension-induced stress concentration at the wound edge. Although mechanically-assisted therapies have great promise, the bottleneck persists in developing tailored solutions by optimizing the heterogeneous stress distribution for individual wounds. Central to this is the absence of both specific wound features acquisition and corresponding customized design of external mechanical loading. Hence, an actionable and user-centric tool is needed for primary wound care providers, who may barely solve the biomechanical complexities but also benefit from technology innovations for improved healing.

Materials & Methods: The mechanical modulation provided by mechanically active-modulating dressing (MAD) is enabled by PNIPAM hydrogel that adheres to the skin around the wound and contracts upon its phase transition temperature to resolve stress concentration at the wound edge and further aid wound contraction. The resulting contraction force can be transferred to induce wound contraction via adhesive coatings on the MAD.

Results & Discussion: We propose a personalized strategy capable of accelerating wound closure by customizing external mechanical modulation according to specific wound features. MAD delivering stimulus-responsive, programmed contraction is developed to alleviate localized stress concentration to aid wound contraction (Fig. 1a). To address the biomechanical heterogeneity, reflected by different profiles of stress distribution, across wounds (Fig. 1b), we integrate AI-enabled image processing and data-driven inverse design to solve the key challenges in wound feature extraction and customized MAD design (Fig. 1c). As demonstrated in the technical roadmap (Fig. 1d), image segmentation is adopted to extract wound features (i.e., size and body region) from wound photos. The acquired features are then sent to an inverse design network, where the relationship between optimized MAD parameters (i.e., size and Young's modulus) and wound features is established based on experimental and modeling data. The resulting output provides the customized MAD parameters designed to maximize contraction of the given wound. To ensure clinical applicability, MADs are tailored on demand from pre-fabricated, large-area sheets with

varied moduli, and periodically replaced following an optimized schedule to adapt to evolving wound status. All these functions are integrated into a smartphone app to enable user-centered wound care. The proposed strategy demonstrates promising repair outcomes in chronic wound models and large animal models, highlighting its potential for enhancing wound repair in clinical translation.

Conclusions: We have innovated a personalized wound repair strategy that employs AI algorithm to analyze wound characteristics (i.e., size and body region) from photo taking, and establishes a data-driven inverse design framework based on mechanics to customize MAD parameters (i.e., size and Young's modulus). Further, to facilitate alignment with established clinical wound care workflows involving regular change of dressings, we have optimized a periodic replacement schedule to tune mechanical loading to the evolving wound features (e.g., size). Placing patient-centric care at the core, an accessible app streamlining wound feature analysis, customized MAD design and using guidance is developed. Preliminary outcomes evidenced by enhanced efficacy in treating chronic diabetic wounds and findings from large animal models, offer a compelling case for the clinical potential of our strategy. Building upon our findings, we recognize the immense potential for further basic understandings and technological advances in terms of rational design, dynamic modulation and scar prevention to more aptly suit real-world wound care.

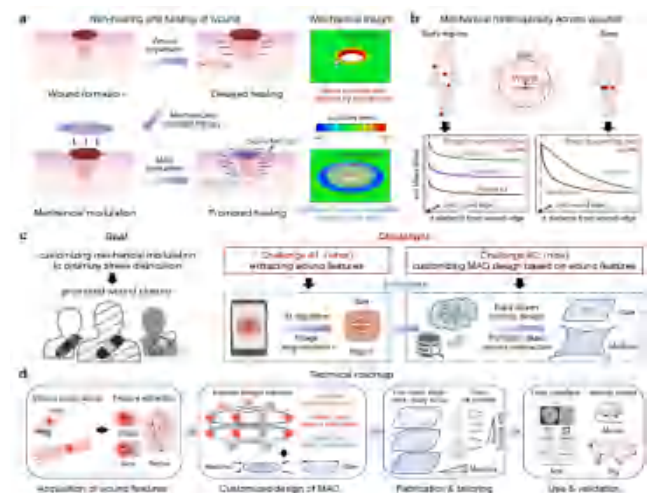


Fig. 1. Customized design of mechanically active-modulating dressings (MADs) to address biomechanical variance across wounds to promote closure.

Hydrogel-Based Cell Mechanical Microenvironment Engineering and Mechano-therapies for Soft Tissue Regeneration

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Key words: multi-functional hydrogels, micro/nano-fabrication, cell mechanical microenvironment, mechanotransduction

Introduction: The extracellular matrix (ECM) in native tissues generally exhibits various mechanical properties or some mechanical stimuli may be delivered to the cells through the ECM, which play critical roles in development and tissue regeneration. As such, advanced hydrogels and fabrication approaches have been developed to manipulate biophysical cues to recapitulate the mechanical microenvironment where cells reside in vivo^{1, 2}. Our studies address the technical challenges in cell mechanical microenvironment engineering, aiming to reveal the regulatory effects and underlying mechanisms of mechanical cues in the cell microenvironment on cellular behavior, thereby providing a theoretical foundation for development of advanced mechano-therapies for soft tissue regeneration.

Materials & Methods: We designed a microscale non-contact magnetic-driven collagen hydrogel system, constructing a cell microenvironment with oriented fibrous structures and mechanical stretching to regulate myoblast differentiation. Meanwhile, we also developed a collagen-based hydrogel platform, which was capable of mimicking strain-enhanced stress relaxation (SESR) in native skeletal muscles and separating the effects of mechanical strain and stress relaxation. Besides, we constructed a matrix stiffness gradient at the cellular scale, and elucidated the mechanism by which matrix stiffness gradients at the periodontal ligament (PDL)-alveolar bone (AB) enthesis regulate mesenchymal stem cell immunophenotypes during interfacial tissue regeneration.

Results & Discussion: Structure and mechanical strain of the ECM synergistically promoted alignment and maturation of C2C12 myoblasts, which was driven by the dynamics of YAP/TAZ and the structure of the microtubule network³. A specific nonlinear viscoelastic feature (i.e., SESR) was observed in normal skeletal muscles, which however was almost absent in diseased skeletal muscles from Duchenne muscular dystrophy (DMD) mice. The underlying mechanobiology mechanisms of SESR in skeletal myogenesis could be explained by effects of SESR on integrin-focal adhesion kinase signalling, actin cytoskeleton polymerization-mediated MRTF nuclear localization

and nuclear mechanotransduction⁴. These studies had important implications for the treatments of soft tissue injuries and diseases, as it could help researchers develop new therapies that target the tissue's mechanical properties.

Stiffness gradient strength (SGS) at PDL-AB enthesis in periodontitis was lower than that in health. MSCs residing at PDL-AB enthesis in periodontitis showed a pro-inflammatory phenotype. Low SGS minimized the ability of cell polarization in guiding this phenotype, which was probably driven by the reduced polarization of integrin $\beta 1$ clusters and myosin IIB, leading to H4K16ac localization-dependent chromatin opening that facilitated TLR3 gene expression⁵. This study provided a new insight into the design principles of natural soft-hard tissue interfaces, and offered guidelines for biomimetic strategies to rationally engineer such interfaces for tissue engineering and regenerative medicine applications.

Conclusions: Combining with multidisciplinary fields, multi-functional hydrogels have been widely developed for recapitulating ECM mechanics. Mechanical cues are important and distinct parameters of the microenvironment that guide cell behavior and fate, showing great promises in design of tissue engineering scaffolds and construction of in vitro tissue models for regenerative medicine applications.

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Engineered coacervates as emerging liquid biomaterials

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Key words: liquid-liquid phase separation; coacervates; biomaterials

Introduction: Liquid-liquid phase separation (LLPS) has emerged as a fundamental organizational principle in biological systems. Coacervates are highly concentrated condensed liquid phases (or droplets) enriched with molecules, formed through liquid-liquid phase separation (LLPS). A wide variety of synthetic coacervates have been developed to investigate the mechanisms of LLPS. However, less attention has been paid to the broader application potential of these synthetic coacervates.

Results & Discussion: Our research group is dedicated to developing general design strategies for modular liquid-liquid phase separation biomaterials (coacervates). We explore the advantages and functional mechanisms of coacervates and coacervate-to-hydrogel phase transitions in fields such as cell/tissue biomimetics [1-2], drug delivery [3-4], and tissue engineering and regenerative medicine [5-6], to emphasize how synthetic coacervates can be applied as liquid biomaterials in diverse biomedical contexts.

For example, **interfacial wetting endows coacervates with unique advantages for biomedical delivery by enabling spontaneous spreading and deep infiltration into complex biological interfaces.** Owing to their ultralow interfacial tension and strong interfacial

interactions, coacervates can efficiently wet and penetrate diverse interfaces, such as epithelial tissues, cartilage surfaces, bacterial biofilms, and mucus layers, overcoming the diffusion and access limitations of conventional aqueous formulations. This high-efficiency wetting capability facilitates a wide range of therapeutic benefits, including enhanced tissue adhesion for wound healing, superior joint lubrication for cartilage repair, and robust antibacterial activity through the effective penetration of biofilms. As a result, coacervate-based systems provide a versatile platform for addressing otherwise inaccessible biological barriers.

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Dynamic hydrogels with metal-coordination bonds

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Synthetic hydrogels are water-swollen polymer networks that provide a simplified and controllable environment for three-dimensional (3D) cell culture, mimicking certain features of the extracellular matrix (ECM). However, most hydrogels are purely elastic and lack the dynamic behavior of native tissues. To address this limitation, dynamic and self-healing hydrogels have been developed using reversible crosslinks, including metal-coordination interactions inspired by biological systems. These reversible bonds enable tunable mechanical properties, ranging from stiff, covalent-like interactions to softer, supramolecular networks.

Here, we present a versatile method for synthesizing multi-arm poly(ethylene glycol) (PEG) functionalized with the bisphosphonate, alendronic acid (ALA), as a metal-coordinating ligand and RGD peptides to enhance cellular interactions. By exploiting coordination interactions between these ligands and a range of metal ions, the introduction of Mg^{2+} , Ca^{2+} , Sr^{2+} , Mn^{2+} , Fe^{2+} , Zn^{2+} , or Cu^{2+} generated transient hydrogel networks that exhibited diverse mechanical and dynamic behaviors, including tunable stiffness, rapid stress relaxation, and self-healing. This work establishes a universal strategy for designing hydrogels with highly tunable and dynamic mechanical properties, offering strong potential for applications in regenerative medicine and tissue engineering.

Key words: dynamic hydrogels, metal-coordination bonds, bisphosphonate

Injectable extracellular matrix-like electroactive hydrogels for sequential treatment of ischemic stroke

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Key words: regeneration, biomaterials, tissue engineering, electroactive hydrogels

Introduction: Ischemic stroke can cause local blood flow interruption in brain tissue, leading to damage to neurons and glial cells and permanent loss of neurological function. Injectable hydrogels can be implanted directly into the stroke cavity through minimally invasive surgery, mimicking the mechanical properties of normal brain tissue by adjusting the crosslinking density, and serving as a drug delivery system [1]. Conductive hydrogels can mimic neurotransmitters generated between neurons, promoting signal transduction and communication by enhancing conductive integration, and influencing the differentiation and development of precursor neurons [2]. In order to achieve multifunctional hydrogels that match the physical and chemical properties of brain tissue, new design strategies are needed to achieve early-stage antioxidant, anti-apoptotic and anti-inflammatory effects, as well as later-stage neurorepair functions, providing long-term effective treatment for stroke.

Materials & Methods: Gelatin-polyaniline conductive materials were synthesized via chemical oxidative free radical grafting polymerization, and an electroactive multifunctional hydrogel simulating the extracellular matrix was prepared. Antioxidant nanoparticles loaded with piracetam were introduced to form a microenvironment-responsive multifunctional hydrogel formulation. The microstructure and mechanical properties of the hydrogel were evaluated using scanning electron microscopy and rheological testing. The biocompatibility and metabolic activity on hippocampal cells were analyzed using live/dead cell staining and CCK-8 cell viability assays. A photothrombus-induced cerebral ischemia mouse model was constructed, and the hydrogel was injected into the ischemic area. HE staining and speckle imaging techniques were used to elucidate the effects and mechanisms by which the electroactive multifunctional hydrogel promotes tissue repair and angiogenesis in the ischemic cerebral region.

Results & Discussion: Figure A shows the successful preparation of the multifunctional hydrogel. Figure B, scanning electron microscopy results, indicates that the hydrogel has a uniform porous structure. Figure C shows that the hydrogel has good injectability. Figure D shows that the hydrogel has good electrical conductivity.

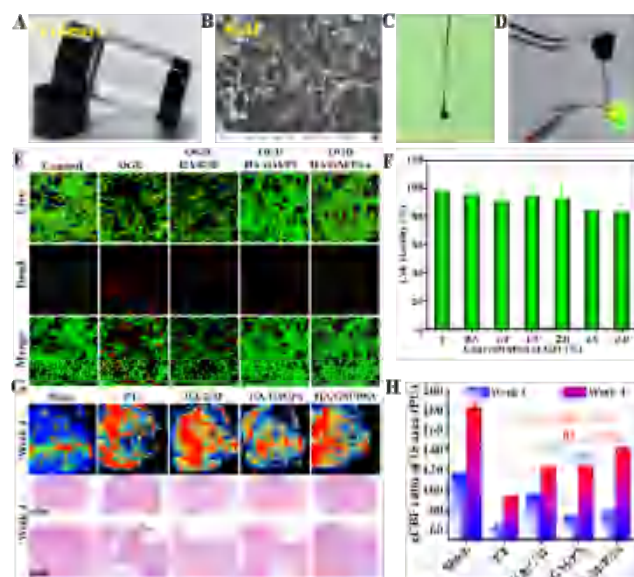


Figure E, live/dead staining of hippocampal cells, and Figure F, hippocampal cell viability results, indicate that the HA/GM/PSA hydrogel has good biocompatibility. Figure G, speckle imaging and HE staining results, show that the HA/GM/PSA hydrogel effectively promotes angiogenesis and tissue repair in ischemic brain regions, demonstrating its good tissue repair function in ischemic areas.

Conclusions: This study successfully developed an electroactive multifunctional hydrogel that mimics the extracellular matrix and incorporated antioxidant nanoparticles and neurorepair drugs, endowing the hydrogel with excellent physicochemical properties and biocompatibility. Based on the combined experimental results, this electroactive multifunctional hydrogel demonstrates great potential in the treatment of ischemic stroke and is a safe and effective biomedical material.

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Biomedical DNA hydrogels and microgels

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Microcapsules composed of synthetic polymeric matrices have attracted considerable attention in delivering oral probiotics. However, existing polymeric microcapsules demonstrate inadequate acid resistance and adaptability, as well as deficiency in the inflamed colon-specificity and uncontrolled release of probiotics therein. Herein, a DNA microcapsule is prepared as a probiotic-transporting micromotor through photo-crosslinking of hyaluronic acid methacrylate and acrydite-modified A-/C-rich oligomers within the microfluidically generated droplets in the presence of nitric oxide-cleavable crosslinker and gas donor manganese carbonyl (MnCO). As the microcapsules traverse stomach, duodenum, and ultimately colon, the formation and dissociation of A-motif and i-motif structures instigate a reversible shrinking-swelling transition of microcapsules to preserve probiotic viability. Subsequently, the microcapsules exhibit chemotaxis towards inflamed colon site, driven by a gas-generating reaction between MnCO and elevated reactive oxygen species. Following disintegration of the microcapsules, triggered by endogenous nitric oxide, probiotics are released to reshape the dysbiosis of intestinal microflora. This advanced delivery system offers significant promise for the effective clinical management of inflammatory bowel disease.

Key words: DNA micromotors, probiotic delivery, inflammatory bowel disease

Introduction: To improve the acid tolerance of oral probiotics, various encapsulation strategies have been established to create a physical barrier between the probiotics and the adverse conditions of the GI tract. Of particular interest is the encapsulation of probiotics within microspheres made of polymeric matrices with a moderate crosslinking degree. Such networks provide a natural extracellular polymeric substance (EPS)-like environment to maintain the bioactivity and proliferation of probiotics, as well as additional possibilities for biofunctionalization. However, to date, the existing probiotic microspheres exhibit suboptimal probiotic survival rates, primarily due to the inadequate acid resistance and limited acid adaptability of conventional polymeric scaffolds. Although a higher crosslinking degree in the polymeric networks of microcapsules better restricts the intrusion of H⁺ ions into the encapsulated probiotics, this persistently high crosslinking degree concurrently hinders essential substance exchange during metabolism and impairs the release rate of probiotics in the colon. Therefore, there is a significant impetus to develop probiotic microcapsules with an acid-adaptive crosslinking degree. Specifically, these microcapsules achieve a high crosslinking degree exclusively in the acidic GI tract, while then revert to a low degree at the target site of the mildly basic colon—a design that remains unexplored.

Conclusions: In summary, an acid-resistant probiotic DNA microcapsule, EcN/CO@HAD, was produced through photo-crosslinking of HAMA and acrydite-modified A-/C-rich oligomers within the microfluidically generated droplets in the presence of NO-cleavable crosslinker, APD, and CO donor, MnCO. When these microcapsules reached the stomach (~pH 2) and the duodenum (~pH 5) successively, the A- and C-rich sequences formed stable A-motif and i-motif structures, respectively, inducing an apparent microcapsule contraction to create a dense physical barrier between EcN and GI fluid. In this context, the microcapsules preserved the viability of EcN until they reached the colon (pH > 7), where the DNA motifs reverted to individual chains, resulting in the restoration of crosslinking degree and particle size, which is amenable to eliminating the trade-off between increased crosslinking for acid resistance and reduced permeability for nutrient or metabolite exchange in probiotic DNA microcapsules. This reversible shrinking-swelling transition, mediated by acid-adaptive feature of A-/i-motif sequences, improved the protective effect of microcapsules on probiotics, and the survival rates of probiotics were as high as 87.7% and 99.4% under acidic conditions at pH 2 and pH 5, respectively. Subsequently, the microcapsules containing MnCO demonstrated inflamed colonic region-specificity, achieved by the chemotaxis of the microcapsules towards elevated concentration of ROS at the inflamed colonic tissue. Note that during the reaction between MnCO and ROS, the generated CO gas acted as a driving force for the chemotactic mobility of microcapsules and a potent anti-inflammatory immunomodulator for M2 macrophage polarization simultaneously. The large-sized probiotic DNA microcapsules (> 300 µm) are unable to penetrate the gastrointestinal epithelial barrier to access the bloodstream or other organs, thus promising minimal off-target effects. Eventually, the microcapsules bearing NO-cleavable crosslinker APD disintegrated to enable the controlled release of EcN at the inflamed colonic site with elevated NO levels, so that EcN reshaped the dysbiosis of the intestinal microflora. The effective therapeutic efficacy of EcN/CO@HAD microcapsules against DSS-induced IBD was clearly demonstrated with the overall recovery of body weight, DAI value, as well as colon length and structure through reducing ROS level, altering pro-inflammatory response, and improving richness and diversity of probiotics. The analysis results of DEGs in the colon tissues by high-throughput RNA-sequencing further revealed the origin of intestinal barrier repair. In short, EcN/CO@HAD microcapsules down-regulated genes primarily linked to inflammatory response and immune cell activities, while up-regulated genes predominantly associated with the biosynthesis, metabolism, and proliferation of colonic epithelial cells.

Notably, unlike the market-approved probiotic powders and enteric capsules frequently utilized in clinical settings, which often exhibit poor acid resistance, the acid-resistant probiotic DNA microcapsules clearly outperformed these products in terms of cytoprotection. While previously

reported encapsulation systems have shown some improvement in probiotic viability compared to market-approved products, the conventional polymers generally exhibit inadequate acid resistance and limited acid adaptability^{14,15,67}. Indeed, the acid resistance of conventional microcapsules or polymeric coatings is primarily dominated by the crosslinking degree. A higher degree of crosslinking in polymeric networks more effectively restricts the penetration of H⁺ ions into encapsulated probiotics. However, a persistently high crosslinking degree of conventional systems may impede the bioactivity of probiotics. The probiotic DNA microcapsules developed in this study incorporate A-/C-rich DNA sequences, which exhibit acid-adaptive properties, characterized by a higher crosslinking degree under acidic conditions but a lower crosslinking degree when reverted to neutral conditions (Fig. 2a–d). The significance of these characteristics lies not only in its ability to mitigate persistent high crosslinking degree-associated adverse effects, but also in its effectiveness in protecting the encapsulated EcN from the hostile environments. Moreover, the conventional systems lack essential features of intelligent delivery systems, particularly the ability to exhibit chemotaxis towards inflamed colonic sites and to enable responsive release of probiotics. In contrast, our probiotic DNA microcapsules introduces several innovative aspects through addressing these challenges, which can be succinctly summarized as follows: (1) The probiotic DNA microcapsules are engineered with acid-adaptive sequences, enabling reversible crosslinking and shrinking-swelling transitions. This unique design provides enhanced acid resistance, ensuring effective cytoprotection during GI transit. (2) These microcapsules function as intelligent site-specific micromotors, demonstrating chemotactic movement towards inflamed colonic tissues with elevated ROS concentrations. This targeted motility significantly enhances probiotic bioavailability and colonization at inflammatory sites. (3) These microcapsules can disintegrate specifically in response to the overproduction of inflammatory signaling molecules at the colonic inflammation site. This stimulus-responsive disintegration enables targeted probiotic release, facilitating direct intervention in the dysbiotic intestinal microbiota at the precise location of inflammation.

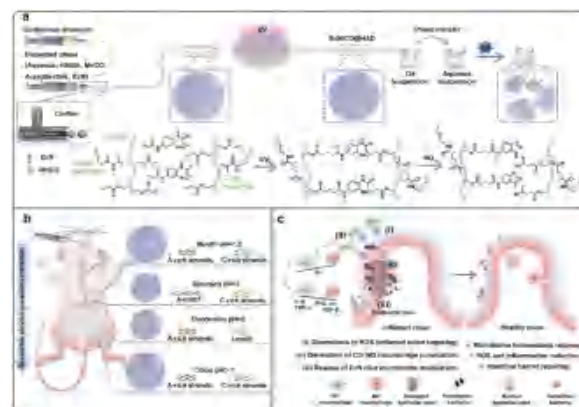


Fig. 1. a Preparation of EcN/CO@HAD microcapsules via a droplet microfluidic technology. b Reversible shrinking-swelling transition of EcN/CO@HAD microcapsules induced by formation/dissociation of A-motif and i-motif structures in the GI tract. c Therapeutic mechanisms of EcN/CO@HAD microcapsules in model mice with DSS-induced colitis.

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A Robust Bio-Supportive Hydrogel Patch for Full-Thickness Repair of Gastroesophageal Defects

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Key words: Polyvinyl alcohol (PVA) hydrogel; Gastroesophageal defects; Full-thickness repair; Gastric perforation; Esophageal perforation; Tracheoesophageal fistula

Introduction: Gastroesophageal (GE) defects, such as gastric perforations (GP), esophageal perforations (EP), and complex tracheoesophageal fistulas (TEF), pose formidable clinical challenges due to gastric acid erosion and mechanical peristaltic stress, leading to high leakage, recurrence, and mortality[1]. Conventional hydrogels lack sufficient mechanical stability and regenerative capacity[2]. This study developed a robust bio-supportive (RBS) hydrogel patch to achieve immediate sealing and full-thickness GE tissue regeneration, addressing unmet clinical needs.

Materials & Methods: RBS patches were fabricated via repeated freeze-thaw, salt fractionation, and wet annealing of polyvinyl alcohol (PVA), forming a double-disc, porous structure. Physicochemical (FTIR, XRD, Raman, SEM), mechanical, degradation, and biocompatibility tests were performed. Therapeutic efficacy was validated in multiple animal models, including rat GP, rabbit EP/TEF, and beagle dog GP/EP models, with histological and imaging evaluations.

Results & Discussion: Physicochemical characterization confirmed the RBS patch's well-defined structure: SEM revealed a uniform porous network ($\approx 10 \pm 0.5 \mu\text{m}$ pore diameter), XRD demonstrated a typical crystalline peak at 19.5° ensuring structural stability, and FTIR/Raman verified hydrophilic functional groups contributing to weakly bound water retention. Mechanical tests showed superior performance: toughness reached $13.18 \pm 0.57 \text{ MJ/m}^3$ ($20\times$ higher than natural GE tissues), maximum stress of $5.64 \pm 0.47 \text{ MPa}$, and 75% elastic recovery rate after 10 compression cycles, enabling resistance to GE peristaltic stress. Degradation tests in simulated GE environments (gastric acid + lipase) showed $\leq 10\%$ mass loss over 30 days, matching tissue healing cycles. Biocompatibility assays confirmed no cytotoxicity—live/dead staining showed great cell viability for fibroblasts, vascular endothelial cells, and gastric mucosal epithelial cells co-cultured with RBS leachates. In preclinical models, the RBS patch achieved 100% survival rate in rat GP and rabbit EP/TEF groups, with HE/immunohistochemical staining confirming intact mucosal (CK-19/CK-14⁺), submucosal (CD31⁺ angiogenesis, LYVE-1⁺ lymphangiogenesis), and

muscular ($\alpha\text{-SMA/Myosin-6}^+$) regeneration. Importantly, beagle dog models validated consistent efficacy with no postoperative complications, overcoming translational barriers. These results confirm the RBS patch's structural-design synergy (porous network + crystallinity + bound water) directly supports its superior repair performance, addressing critical limitations of conventional hydrogels.

Conclusions: We developed an RBS hydrogel patch for immediate fluid-tight closure and full-thickness tissue regeneration. Fabricated from highly crystalline PVA hydrogel, the RBS patch has a double-disc architecture, inherent porous network and weakly bound water. The double-disc design ensures superior sealing and deformation resistance; high crystallinity confers exceptional mechanical strength and long-term acid/enzyme resistance. Moreover, its porous microstructure and weakly bound water synergistically promote cellular adhesion, migration and tissue infiltration for functional repair. In rat and rabbit models, the RBS patch achieved complete healing of GP, EP and TEF, with intact mucosal, submucosal and muscular layers regeneration. Its efficacy and safety were further validated in beagle dog models, highlighting clinical translation potential. This RBS patch serves as a versatile bio-supportive technology for GE defects and a promising platform for tissue repair in dynamic physiological environments.

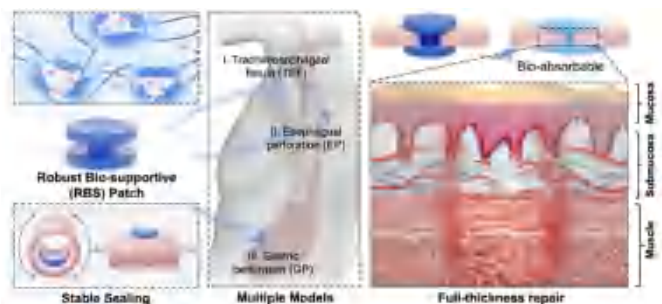


Fig. 1. Schematic illustration of the RBS patch applied for full-thickness repair of various gastroesophageal (GE) defect models.

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Engineering stable unfolded protein adhesives via polyelectrolyte locking for robust and rapid tissue sealing

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Key words: protein, hydrogel, tissue adhesive (3-5 key words)

Introduction: Bioadhesives are essential for surgery, offering a suture-less alternative for tissue attachment and hemorrhage control. While marine organisms achieve robust underwater adhesion via surface-exposed hydrophobic domains in intrinsically disordered proteins, replicating this in common proteins remains difficult. In native states, common proteins bury their hydrophobic residues within compact tertiary structures. Although chemical denaturants can expose these groups, the resulting unfolded states are metastable and prone to rapid "hydrophobic collapse" or aggregation in aqueous environments.

Here, a universal polyelectrolyte-locking strategy is presented.¹ By utilizing highly charged, flexible polyelectrolytes, the metastable unfolded conformation of proteins is stabilized. This dual-function approach maintains interfacial hydrophobicity for blood displacement and reinforces cohesion through chain entanglement, providing a robust framework for rapid tissue sealing.

Materials & Methods:

Materials: Bovine serum albumin (BSA), polyacrylic acid (PAA, and Tris(2-carboxyethyl)phosphine (TCEP) were used as primary components.

Adhesive synthesis: Unfolded bovine serum albumin (UBSA) was prepared by reducing disulfide bonds with 50 mM TCEP for 15–20 min. The UBSA-PAA adhesive was formed by mixing the unfolded protein with PAA (5–9 w/v%).

Characterization: Molecular dynamic (MD) simulations analyzed the radius of gyration and surface hydrophobicity. Surface properties were assessed via water contact angle (WCA) and TOF-SIMS.

Mechanical and in vivo testing: Adhesion strength was evaluated using ASTM standards for lap-shear, T-peel, and burst pressure. Hemostatic efficacy was validated in rat liver incision and femoral artery injury models.

Results & Discussion:

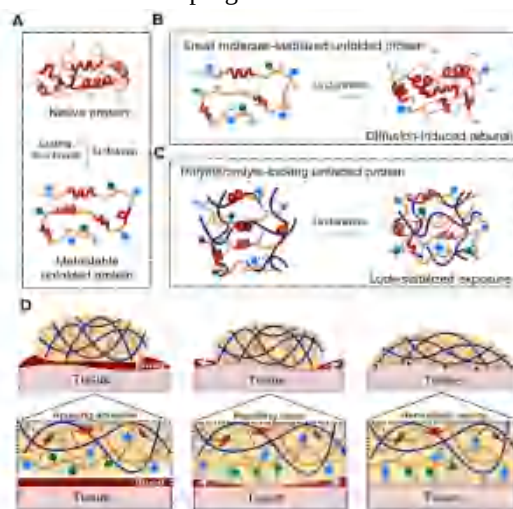
Molecular locking mechanism: MD simulations confirmed that UBSA exhibits a larger R_g (3.27 nm) and higher hydrophobic surface area compared to native BSA. PAA stabilizes this state through a 90% increase in hydrogen bond formation and 56% stronger total interaction energy compared to native protein complexes.

Adhesion performance: UBSA-PAA demonstrated a shear strength of 63.07 ± 6.52 kPa and a burst pressure of 151.7 ± 15.6 mmHg, surpassing commercial fibrin glue and withstanding physiological arterial pressures.

In vivo hemostasis: In severe liver hemorrhage models, the adhesive achieved sealing within 10 s, reducing blood loss by 95.1% compared to fibrin glue. In femoral artery models, complete hemostasis was reached within 50 s.

Biocompatibility: The system maintained >90% cell viability and showed a mild inflammatory response comparable to clinical standards, with complete biodegradation occurring within 8 weeks.

Conclusions: The polyelectrolyte-locking strategy successfully transforms common, cost-effective proteins into high-performance bioadhesives. By stabilizing unfolded protein chains, the adhesive achieves a unique synergy of interfacial hydrophobicity and bulk cohesion. This generalizable framework offers a promising platform for developing marine-like adhesives for



emergency trauma care and advanced surgical applications.

Fig. 1. Design of stable unfolded protein-based adhesive, and adhesion mechanism.

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Multiscale structure engineering of injectable hydrogels: from design to clinical translation

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Key words: injectable hydrogels, liquid liquid phase separation, two-photon polymerization lithography, tissue engineering (3-5 key words)

Introduction:Injectable hydrogels have emerged as a cornerstone of modern minimally invasive therapy, offering a unique platform for the delivery of drugs, cells, and bioactive factors with minimal surgical trauma. Their inherent high water content, excellent biocompatibility, and efficient mass transport properties make them ideal candidates for functional implants and tissue regeneration scaffolds. However, the therapeutic efficacy of these materials is fundamentally dictated by their hierarchical architecture.

Precise engineering across molecular and micro-scales is essential to tune the macroscopic performance of hydrogels. Molecular-level cross-linking determines gelation kinetics, degradability; and mechanical integrity; and microscale porosity is the primary driver for cell infiltration and host-tissue integration. Despite the proliferation of sophisticated "smart" materials in literature, achieving simultaneous and reproducible control over these multiscale features remains a formidable technical challenge.

Furthermore, a significant "valley of death" exists between laboratory innovation and clinical reality. While the research heat surrounding hydrogels continues to intensify, their clinical translation remains disproportionately stagnant. This lag is often attributed to complexities in scalable manufacturing, stringent regulatory requirements, and the lack of long-term "in vivo" performance data.

Materials & Methods: PEG-based injectable hydrogels were synthesized by optimizing end-group functionalization and screening crosslinkers to ensure tunable gelation kinetics and degradation profiles. For microstructural engineering, an aqueous two-phase system (ATPS) was employed to fabricate injectable microspheres with varied microporous architectures. Additionally, sub-micron precision hydrogel particles were produced using projection two-photon lithography. Finally, the therapeutic efficacy and biocompatibility of these multiscale-engineered platforms were rigorously

validated across diverse animal models to evaluate their potential for tissue regeneration and clinical application.

Results & Discussion: Our findings demonstrate that multiscale engineering significantly enhances both the functional performance and clinical viability of injectable hydrogels. The optimized PEG-based hydrogels exhibited precise in vivo gelation and programmable degradation profiles, serving as effective radiotherapy spacers for cervical and prostate cancers. **Notably, our cervical cancer spacer achieved NMPA approval as a world-first, marking a major milestone in the clinical translation of injectable biomaterials.**

At the micro-scale, structural control via phase separation enabled the fabrication of microspheres with unique bicontinuous architectures. Validated in both small and large animal models, these structures were shown to significantly accelerate host-cell infiltration and promote scarless tissue repair, surpassing the performance of conventional porous scaffolds.

Finally, at the sub-micron level, we successfully integrated projection two-photon lithography with a thermal inhibition initiation system. This approach achieves sub-micron resolution with a throughput 3-4 orders of magnitude higher than traditional two-photon polymerization. This leap in manufacturing efficiency addresses a major bottleneck in the high-resolution fabrication of complex biomimetic scaffolds.

Conclusions: Collectively, these results provide a robust framework for designing next-generation injectable biomaterials that are both structurally sophisticated and clinically translatable.

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Fast-gelling adhesive epidermal electrode for accurate physiological signal monitoring and real-time brain control flight

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Abstract:

Conductive hydrogel electrodes are vital components for achieving human-machine interfaces. However, the inherent trade-off between high conductivity and favorable mechanical/adhesive properties remains a significant challenge for hydrogel-based epidermal electrodes. Here, we developed a multifunctional MXene/WPU/PAA (MWA) hydrogel electrode that combines robust mechanical properties, strong adhesion, and excellent conductivity. The introduced MXene nanosheets can induce free-radical polymerization, resulting in fast gelation (<5min) at room temperature. Theoretical analyses reveal that MXene nanosheets form abundant hydrogen bonds with polymer chains, thus enhancing the cross-linking density and mechanical strength of the hydrogel electrode. The MWA hydrogel can form a stable skin-electrode interface, enabling high-fidelity multimodal physiological signal monitoring, like sEMG, ECG, and EOG. The MWA hydrogel exhibits outstanding adhesion under repeated cycles and in simulated sweat conditions, with a higher signal-to-noise ratio than Ag/AgCl electrodes. Furthermore, the MWA hydrogel electrode demonstrates precise scalp EEG monitoring, enabling wireless drone flight control via real-time brainwave decoding. This work provides insight into MXene-polymer interactions and offers a promising strategy for developing next-generation, high-performance hydrogel electrodes.

Key words: conductive hydrogel, MXene nanosheets, fast-gelling, epidermal electrodes, human-machine interfaces

Introduction: Herein, we successfully developed a rapid-gel-forming MXene-based hydrogel for constructing stable interfaces in epidermal electronics. The conductive hydrogels were formulated from MXene nanosheets, waterborne polyurethane (WPU), and polyacrylic acid (PAA), referred to as MXene/WPU/PAA (MWA) hydrogels (Fig. 1d). The incorporation of MXene nanosheets served as catalysts for the radical polymerization, enabling rapid gelation without external energy input. This approach enhances molding efficiency and enables rapid deployment of a soft hydrogel electrode. This demonstrates that the developed hydrogel holds excellent potential for long-term human health monitoring and real-time human-machine interaction applications¹.

Conclusions: In summary, a robust and multifunctional MXene/WPU/PAA hydrogel electrode has been successfully developed, integrating superior mechanical strength, high adhesion, and excellent electrical properties. MXene induced rapid gelation at room temperature (< 5min), improving the manufacturing efficiency of hydrogel electrodes. The optimized MWA hydrogel demonstrates a stable, low-impedance skin-electrode interface, enabling multimodal physiological signal monitoring, including sEMG, ECG, and EOGs². More importantly, the electrodes enable real-time brainwave-controlled drone operation³, validating their potential in human-in-the-loop applications.

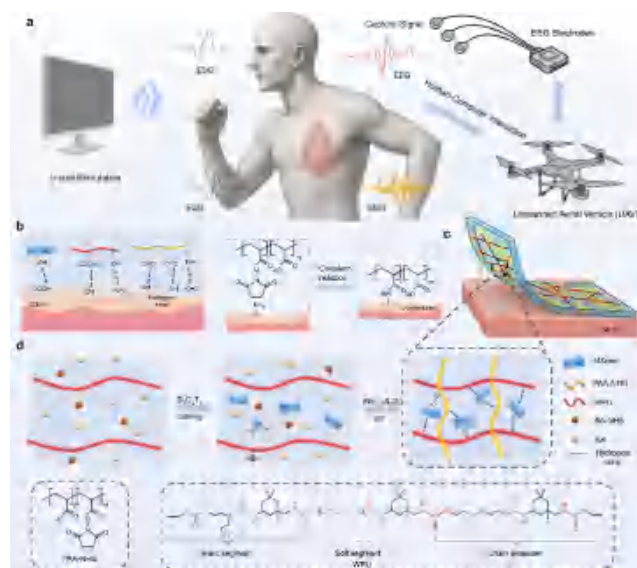


Fig. 1. MXene-reinforced fast-forming adhesive hydrogels for continuous electrophysiological monitoring.

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Cygb-loaded hydrogel synergizes antioxidant-autophagy-driven neural regeneration

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Key words: regeneration, biomaterials, oxidative stress, mitochondrial autophagy, metabolism.

Introduction: Peripheral nerve injury (PNI) presents a significant clinical challenge, often resulting in incomplete functional recovery due to a hostile post-injury microenvironment. A key pathological driver is sustained oxidative stress, which amplifies secondary damage by triggering lipid peroxidation, inflammation, and apoptosis, thereby crippling endogenous repair processes. Targeting this oxidative cascade, particularly by scavenging excess reactive oxygen species (ROS), is a promising neuroprotective strategy. The endogenous protein cytoplasmic globulin (CYGB) has gained much attention due to its excellent antioxidant properties, which can alleviate such damages [1]. However, its clinical translation is hampered by rapid clearance and poor bioavailability when delivered conventionally. Herein, we developed quaternary ammonium salt chitosan/sodium alginate (HACC/SA) hydrogel assembled solely through physical interactions. This platform enables the sustained and responsive delivery of native, bioactive CYGB directly to the injury site. The released CYGB effectively quenches ROS, alleviates oxidative stress, and provides metabolic support, ultimately remodeling the inhibitory milieu to promote axonal regeneration and functional recovery in a PNI model.

Materials & Methods:

- 1.The spatiotemporal expression of CYGB after sciatic nerve injury was dynamically profiled in a rat model.
- 2.A CYGB-overexpressing Schwann cell line (RSC96) was generated to validate its antioxidant role via the Nrf2/Keap1 pathway under oxidative stress.
- 3.HACC/SA composite hydrogels were fabricated, characterized, and screened for optimal mechanical properties and biocompatibility.
- 4.The antioxidant and mitochondrial regulatory functions of CYGB@HSA were confirmed in vitro.
- 4.The therapeutic effect of CYGB@HSA was evaluated in a rat peripheral nerve injury model, assessing molecular pathways, histology, and functional recovery.

Results & Discussion:

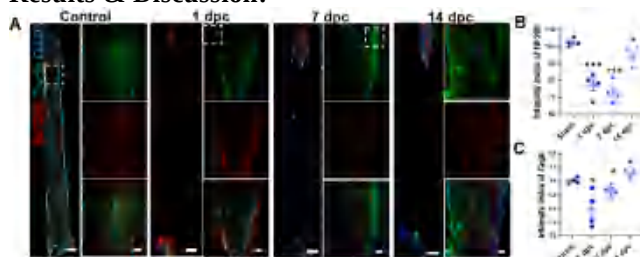


Fig. 1. Spatiotemporal dynamics expression of Cygb

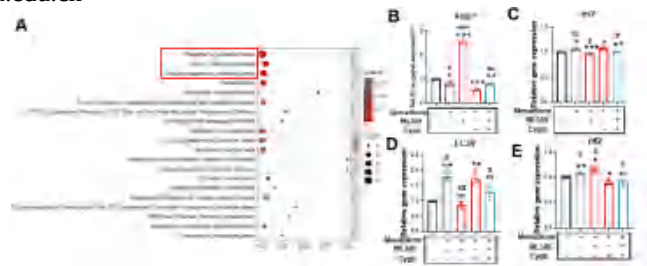


Fig. 2. Cygb-dependent activation of Nrf2/Pink1-Parkin signaling crosstalk.

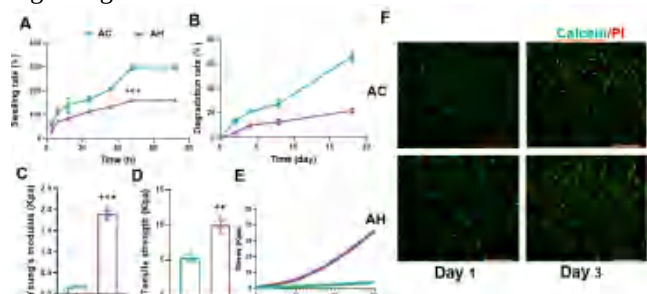


Fig. 3. Characterization, mechanical properties, and antioxidant effect of Cygb@HSA.

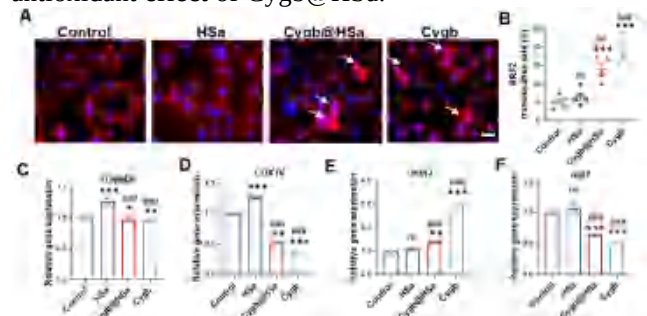


Fig. 4. Cygb@HSA protect mitochondrial function to maintain RSC96 cell homeostasis.

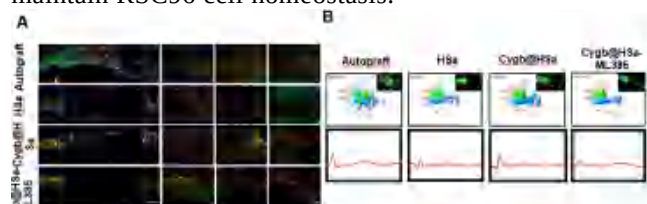


Fig. 5. Cygb@HSA promote nerve regeneration and functional recovery.

Conclusions: Cygb@HSA colloidal hydrogel remodels mitochondrial homeostasis through the Nrf2/Pink1 signaling axis, restores mitochondrial energy production, and thereby promotes axon reconstruction and functional recovery.

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Metabolically and Electrically Instructive Hydrogels for Spinal Cord Injury Repair

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Key words: spinal cord injury, hydrogels, magnetoelectric generator, neural stem cells

Introduction: Spinal cord injury (SCI) results in a hostile microenvironment characterized by oxidative stress, metabolic dysfunction, inflammation, and glial scarring, all of which impede neuronal regeneration. Increasing evidence highlights the importance of metabolic regulators and epigenetic modulators in directing neural stem cell (NSC) fate decisions. Parallel studies demonstrate that electrical stimulation (ES) activates Wnt/ β -catenin signaling and enhances axonal growth and synaptic reconnection. However, conventional wired electrodes are mechanically mismatched and invasive. Here, we present two advanced hydrogel systems: (1) a dual-crosslinked neuroinductive hydrogel for controlled release of IP_6 and Mg^{2+} to metabolically and epigenetically instruct NSCs; and (2) a soft magnetoelectric hydrogel generator (Mag-e-Gel) that wirelessly delivers localized ES under a rotating magnetic field (RMF) to promote neural regeneration.

Materials & Methods: The dual-network hydrogel was engineered using dynamic covalent crosslinking and metal coordination bonds, enabling injectability, swelling resistance, and spinal cord-matched mechanical compliance. IP_6 and Mg^{2+} were anchored within the matrix and gradually released via reversible coordination interactions. NSCs were encapsulated within the 3D scaffold and transplanted into a rat SCI model. Moreover, the Mag-e-Gel consisted of a phase-separated architecture, i.e., a continuous polythiophene-rich electroconductive network embedded within a supramolecular, cell-adaptive matrix. Under RMF exposure, the system generated localized microcurrents in the pericellular microenvironment. NSC differentiation, axonal outgrowth, signaling pathway activation, histone acetylation, and tissue-type plasminogen activator (t-PA) expression were evaluated in vitro and in rodent and canine SCI models.

Results & Discussion: IP_6 release triggered AMPK phosphorylation, elevating intracellular ATP levels and inducing ER-mediated Ca^{2+} release, consistent with AMPK-mediated neurogenic regulation reported in SCI repair. The Ca^{2+} /CaMK2 cascade promoted phosphorylation and nuclear translocation of p300, enhancing histone acetylation and activating neuron-associated genes while suppressing astrocytic differentiation. Magnesium ions further stabilized metabolic function and reduced oxidative stress,

aligning with prior findings that ionic modulation supports neural repair and limits secondary injury. In vivo, NSC-laden hydrogels promoted robust neuronal regeneration, axonal reconnection, and functional motor recovery. The immunomodulatory and vascular-supportive properties of the scaffold helped preserve neuroinductive signaling within the injured niche.

As for the wireless electrical modulation via Mag-e-Gel, which generated localized microcurrents under RMF, overcoming mechanical limitations of conventional electrodes. The induced ES activated Wnt/ β -catenin signaling, a key pathway in neuronal differentiation and axonal regeneration after SCI. Upregulation of t-PA reduced fibrotic scarring and enhanced axonal extension. In both rat and canine models, Mag-e-Gel significantly improved synaptic reconnection and motor function recovery. These findings align with growing evidence that conductive hydrogels and endogenous NSC manipulation synergistically enhance spinal repair. Importantly, the soft, cell-encircling conductive network enables precise pericellular electrical modulation, which may better mimic physiological bioelectric cues.

Conclusions: Together, these systems demonstrate a next-generation paradigm integrating metabolic reprogramming and bioelectric modulation within a mechanically compliant, cell-adaptive scaffold. This strategy offers a promising avenue for stem cell-based, minimally invasive SCI therapy.

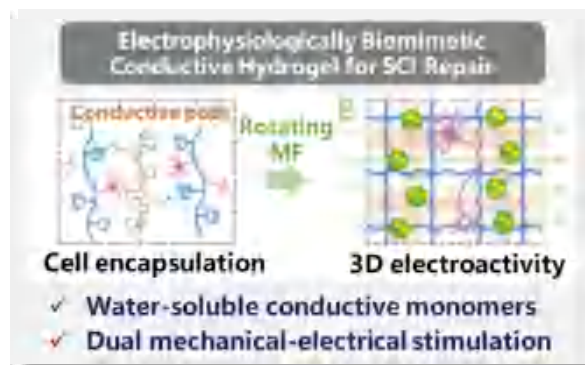


Fig. 1. Mag-e-Gel for SCI repair.

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Hydro/aerogels for Flexible Human-Machine Interfaces and Wearable/Implantable Therapy

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Flexible bioelectronics utilizing polymer-based hydro/aerogel soft materials are revolutionizing for human-machine interfaces and chronic disease therapy. By mimicking the softness and biocompatibility of human tissues, these polymeric materials enable seamless integration with the body, advancing healthcare significantly. Hydrogels, known for their high water content, offer an ideal platform for biosensing due to their biocompatibility and softness similarity to natural tissues. They enhance the accuracy and comfortability of continuous monitoring, making it possible to track vital signals in real-time. This is crucial for early diagnosis and proactive management of healthcare conditions. Aerogels, on the other hand, bring unique advantages like ultra-low density, high porosity, and exceptional thermal insulation. Their lightweight and conformable nature facilitate targeted interventions, such as localized signal monitoring and controlled drug delivery. This precision approach to therapy ensures maximum efficacy with minimal side effects, transforming the treatment of diseases like diabetes and neuropathies. In summary, hydro/aerogels-based flexible electronics are a breakthrough technology, offering tailored solutions for human-machine integration and chronic disease management. Their integration into biosensors and therapeutic devices is poised to improve treatment outcomes, enhance diagnostic capabilities, and ultimately revolutionize the future of healthcare.

Key words: soft matter, hydrogels, aerogels, flexible electronics

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Chitosan-Silica Hybrid Hydrogels with Siloxane Network Formation: Chemical Control in Dual-Network Assembly

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Decoupling mechanical rigidity from dynamic reversibility is a fundamental challenge in adaptive soft matter. Herein we report hydroxyl-selective siloxane network formation within chitosan hydrogels via orthogonal reaction pathways, yielding hybrid organic-inorganic materials with precisely controlled dual-network topology. By kinetically differentiating dynamic Schiff base formation (targeting amino domains) from acid-catalyzed sol-gel condensation (targeting hydroxyl domains), we engineered a dual-network architecture with independently tunable viscoelastic properties. Spectroscopic and rheological analyses reveal that the in-situ sol-gel process creates a rigid silica percolation network, reinforcing the storage modulus by > 400-fold (~500 kPa) without perturbing the organic phase's reversible dynamics. This unique topology enables high-efficiency self-healing (87.6%) and exceptional stability (95% retention). Our findings elucidate structure-property relationships in dual-crosslinked hybrids, establishing a generalizable framework for designing robust, adaptable materials where strength and dynamics are no longer mutually exclusive.

Melatonin rhythm-mimicking smart hydrogel for circadian clock regulation and promotion of intervertebral disc regeneration

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Keywords: Intervertebral disk degeneration, circadian clock, melatonin, repair and regeneration

Introduction

Intervertebral disk degeneration (IVDD) is a leading cause of low back pain and other spine-related diseases¹. Recent research has highlighted that disruptions of circadian rhythm can disturb the normal metabolism of disc cells, leading to increased apoptosis, autophagy, inflammation, and accelerate extracellular matrix degradation, which in turn exacerbates IVDD progression. In this study, we investigated whether modulating the intrinsic circadian clock could promote intervertebral disc repair²⁻⁴.

Materials & Methods

This study investigates the role and mechanisms of circadian clock in IVDD, focusing on degenerative annulus fibrosus (AF) tissues from patients and rat models, as well as in rat annulus fibrosus cells (AFCs). The effects of cyclic melatonin release on circadian clock-related proteins were assessed, and ultimately, its reparative effects were explored using a rat intervertebral disc (IVD) acupuncture degeneration model.

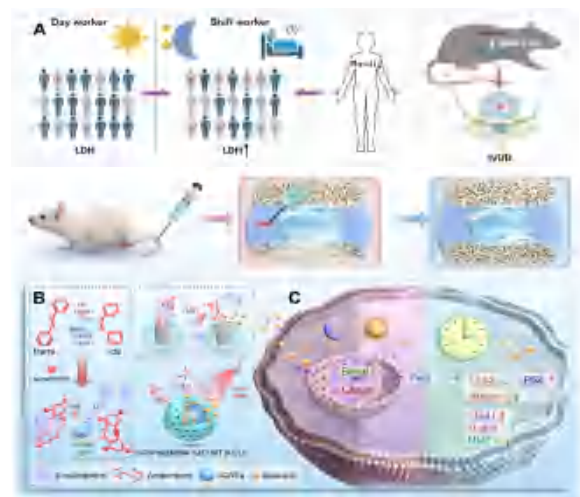
Results & Discussion

Timed high concentration release of melatonin was controlled release from the composite hydrogel by cyclic NIR irradiation. The cyclic release of melatonin can play an obvious antioxidant function. And it can effectively regulates the circadian clock of AFCs by upregulating the expression levels of BMAL and CLOCK proteins. This regulation subsequently downregulates excessive autophagic flux markers, such as LC3 and Beclin-1, in the microenvironment of IVDD, inhibits apoptosis, and ultimately promotes the expression of matrix-associated proteins Collagen 1, Collagen 2 and Aggrecan. In rat degenerated discs model, the composite hydrogel can delay disc degeneration by restoring the homeostasis of circadian clock. In summary, this study reveals the feasibility of using the circadian clock as a therapeutic target for IVDD and offers a novel therapeutic avenue through cyclically releasing melatonin, which provides a new perspective for the treatment of IVDD.

Conclusions

This study established a strong correlation between disc degeneration and the circadian clock, with circadian clock genes playing a pivotal role in matrix synthesis and degradation within disc cells. Disruption of these genes

leads to disturbances in matrix metabolism and accelerates disc degeneration. A novel composite hydrogel with photo-responsive, ROS scavenging, and anti-leakage properties was developed to regulate circadian rhythms in IVD cells. *In vitro* results demonstrated that this hydrogel restored the endogenous circadian clock and promoted ECM secretion. *In vivo* studies further confirmed its ability to enhance IVD repair by regulating the circadian clock of AFCs. This approach offers a promising strategy for circadian rhythm modulation in IVDD, with potential applications extending beyond IVD repair to broader tissue regeneration contexts.



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Comparative Analysis of 2D and 3D Cell Culture Platforms: Perspective and Experimental Validation Across 33 Cell Lines

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Enter the body of your paper here in two column format. Abstract must be one page. The main text should include **Introduction, Materials & Methods, Results & Discussion, and Conclusions**. Type should be 12 points for the Title and 10 points for the author and body sections. Times New Roman is the only font for use. Title and headings should be highlighted in bold.

Key words: 3D cell culture, polyisocyanide hydrogel, collagen matrix, translational oncology

Introduction: Conventional two-dimensional (2D) cell culture is widely used in biomedical research due to its simplicity and low cost; however, it fails to recapitulate the structural, biochemical, and mechanical complexity of native tissues. This limitation contributes to poor translational predictivity in oncology drug development. The key scientific question addressed in this study is whether a robust, scalable, and broadly applicable three-dimensional (3D) culture system can overcome the cell-type specificity and reproducibility limitations of existing 3D models while remaining compatible with standard experimental workflows.

Materials & Methods: A comparative analysis was performed using 2D monolayer cultures and 3D culture platforms across 33 cell lines derived from multiple tissue origins. A hybrid 3D culture system was developed by combining synthetic polyisocyanide (PIC) hydrogels with low concentrations of collagen. Cell growth, morphology, and structural organization were evaluated using standard imaging approaches. The platform's compatibility with high-throughput screening and downstream molecular analyses was also assessed.

Results & Discussion: The PIC–collagen hybrid system supported near-universal 3D growth across the diverse panel of cell lines, overcoming the cell-type dependence commonly observed in spheroid-based or scaffold-only systems. Compared with 2D monolayers, cells cultured in 3D displayed pronounced architectural differences, including enhanced cell–cell interactions and spatial organization that more closely resembled in vivo tumour structures. While 3D culture improved structural relevance, the results highlight that morphological changes alone are insufficient; molecular and phenotypic characterization remains essential to determine physiological relevance. The system demonstrated high

reproducibility, scalability, and compatibility with standard imaging and multi-omics workflows, supporting its practical utility.

Conclusions: This study demonstrates that the PIC–collagen hybrid hydrogel provides a cost-effective, scalable, and broadly applicable 3D culture platform capable of supporting diverse cell types. By bridging the gap between simplistic 2D models and complex in vivo systems, this approach enhances the physiological relevance of in vitro tumour models while maintaining experimental practicality. Future studies should integrate comprehensive molecular and functional analyses to further validate translational relevance and expand applications in drug screening and cancer biology.

Mechanical Forces from Intercellular Peptide Self-Assembly Drive Spheroid Formation

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This work presents a general strategy for engineering cell spheroids with capillary-like structures using intercellular self-assembly of peptide nanofibers. [1] These nanofibrous materials induce mechanical changes in the extracellular matrix (ECM), activate mechanotransduction pathways, and enhance cellular morphogenesis, resulting in dynamic 3D spheroids with improved cell-cell and cell-matrix interactions. By promoting the formation of capillary-like structures within tumor spheroids, we develop models that closely mimic human tissue physiology. Our results demonstrate that tumor spheroids with capillary-like structures display gene expression profiles that closely match those of patient-derived tumors, underscoring their relevance for cancer research. Furthermore, these spheroids, including those derived from an islet cell line, exhibit significantly increased functionality, such as enhanced insulin secretion in response to glucose stimulation, highlighting their potential for diabetes research and regenerative medicine applications. This work advances our understanding of tissue engineering and provides a robust platform for studying complex cellular interactions and therapeutic responses. By highlighting the critical role of capillary-like structure formation in engineered tissues, our findings pave the way for innovative strategies to address significant challenges in drug delivery and cancer therapy, ultimately enhancing patient care and treatment outcomes.

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An Intelligent Redox-Responsive Mn-Based Nanoplatfrom for MRI-Guided Disulfidptosis in Pancreatic Cancer

Objective: Pancreatic cancer is one of the deadliest malignancies, characterized by insidious onset, rapid progression, and resistance to conventional chemo- and radiotherapy. Its pathological microenvironment typically exhibits pronounced desmoplastic reactions, low immune infiltration, and high metabolic plasticity, all of which hinder therapeutic efficacy and interfere with imaging recognition. Notably, pancreatic tumors with co-upregulation of GLUT1 and SLC7A11 synergistically enhance glucose and cystine uptake, fueling NADPH-driven glutathione synthesis to counteract oxidative stress. Under glucose deprivation, NADPH generation is impaired, cystine cannot be efficiently reduced, leading to abnormal accumulation of protein disulfide bonds and ultimately triggering disulfidptosis. This mechanism reveals a metabolic vulnerability in pancreatic cancer and suggests new avenues for imaging-guided metabolic intervention. However, disulfidptosis, as a redox-dependent and dynamically evolving form of programmed cell death, is challenging to detect by conventional imaging modalities and lacks an efficient nanosystem for precise induction.

Methods: We developed a tumor microenvironment-responsive manganese-based nanocomposite (Pht@HMnO₂-HA), loading the GLUT1 inhibitor phloretin (Pht) and utilizing hyaluronic acid (HA) for targeted delivery. The nanoplatfrom was systematically characterized via TEM, Zeta potential analysis, and XPS to confirm its structure and responsiveness. We evaluated Mn²⁺ release, MRI signal enhancement, and redox-regulating capacity. In vitro assays assessed metabolic intervention by measuring glucose uptake, NADPH levels, and cystine accumulation. Disulfidptosis was further evaluated through F-actin staining, Western blotting, and transcriptome sequencing to detect cytoskeletal collapse, disulfide bond aggregation, and activation of related signaling pathways. In vivo, a subcutaneous pancreatic cancer xenograft model was employed to monitor dynamic MRI signal changes and assess imaging performance. Therapeutic efficacy and disulfidptosis pathway activation were evaluated by tumor volume measurement, TUNEL and Ki-67 immunohistochemistry, and Western blot analysis.

Results: The Pht@HMnO₂-HA nanosystem demonstrated robust pH/GSH responsiveness, enabling Mn²⁺ release in the tumor microenvironment for enhanced MRI contrast, while synergistically inhibiting glycolysis via Pht and inducing pronounced oxidative stress. In vitro, the system suppressed NADPH production, promoted cystine accumulation, and effectively induced disulfidptosis. In vivo, it enabled high signal-to-noise ratio tumor imaging and significantly suppressed tumor growth, accompanied by activation of disulfidptosis-associated pathways.

Conclusion: This study proposes a theranostic strategy targeting the metabolic vulnerability of pancreatic cancer. The designed Mn-based nanoplatfrom precisely induces disulfidptosis and enables MRI visualization, offering a promising pathway for functional imaging-guided precision therapy.

Keywords: Mn-based nanoplatfrom; Redox-responsive nanomaterials; Disulfidptosis; MRI-guided therapy; Pancreatic cancer

Coordination-Driven Metallo-Supramolecular Assembly Enables Imaging-Guided Photothermal Therapy with STING Activation and IDO-Reversed Immunosuppression

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Key words: biomaterial, self assembly, cancer therapy, theranostics

Introduction: Photothermal therapy (PTT), while promising, faces significant clinical limitations. These include incomplete tumor ablation, which can lead to recurrence, and the presence of an immunosuppressive tumor microenvironment (TME) that hinders systemic antitumor immunity. A key immunosuppressive mechanism involves the upregulation of indoleamine 2,3-dioxygenase (IDO). Conversely, activating the stimulator of interferon genes (STING) pathway is a potent strategy to stimulate innate immunity and reverse immunosuppression, but its efficacy is often constrained by inefficient and tumor-specific delivery of activators. To address these interconnected challenges, we developed a multifunctional metallo-supramolecular nanoplatfrom designed to synergize imaging-guided PTT with targeted immunoregulation for enhanced anticancer therapy.

Materials & Methods: A manganese-based metallo-supramolecular nanoplatfrom, designated MCTG, was constructed via a one-pot, coordination-driven self-assembly process. The platform was formed using Mn^{2+} ions, a cysteine-derived organic ligand, and concurrently loaded with the IDO inhibitor 1-methyltryptophan (1-MT) and the near-infrared photosensitizer indocyanine green (ICG). The resulting nanoparticles were characterized for size, morphology, and stability. Their intrinsic capabilities for T1-weighted magnetic resonance (MR) and photoacoustic (PA) imaging were validated in vitro. The photothermal conversion efficiency and photostability under 808 nm laser irradiation were quantitatively assessed. In vitro studies evaluated cellular uptake, photothermal cytotoxicity, and induction of immunogenic cell death (ICD). In vivo efficacy was investigated using murine tumor models, where the nanoparticles were administered intravenously, followed by MR/PA imaging-guided PTT.

Results & Discussion: The synthesized MCTG nanoparticles exhibited uniform size, excellent colloidal stability, and pronounced MR/PA contrast, enabling precise imaging-guided tumor localization. They demonstrated a high photothermal conversion efficiency and remarkable structural stability upon repeated laser irradiation. In vivo, under 808 nm laser illumination, MCTG mediated effective tumor ablation and triggered pronounced ICD, as evidenced by the surface exposure of calreticulin and release of high-mobility group box 1 (HMGB1). Concurrently, the degradation of the nanostructure within the TME led to the release of its components. The released Mn^{2+} ions potently activated the STING pathway, amplifying proinflammatory cytokine signaling. Simultaneously, the sustained release of 1-MT effectively suppressed IDO activity, alleviating local immunosuppression. This synergistic

immunoregulation—STING activation combined with IDO inhibition—resulted in a profound remodeling of the TME. This was confirmed by significant enhancement of dendritic cell (DC) maturation in tumor-draining lymph nodes and a marked increase in the infiltration of cytotoxic T lymphocytes (CTLs) into tumors. Consequently, robust systemic antitumor immunity was elicited, contributing to strong inhibitory effects on both primary and distant tumors.

Conclusions: In summary, we have successfully constructed a multifunctional metallo-supramolecular nanoplatfrom, MCTG, via a straightforward coordination self-assembly strategy. This platform seamlessly integrates capabilities for dual-modal imaging, highly efficient photothermal therapy, and synergistic immunomodulation within a single agent. By concurrently activating the STING pathway with Mn^{2+} and inhibiting the IDO pathway with 1-MT, MCTG effectively reverses the immunosuppressive TME and potentiates systemic antitumor immunity following photothermal ablation. This work presents a promising combinatorial paradigm that addresses the major limitations of conventional PTT, showing significant potential for the treatment of metastatic and recurrent cancers.

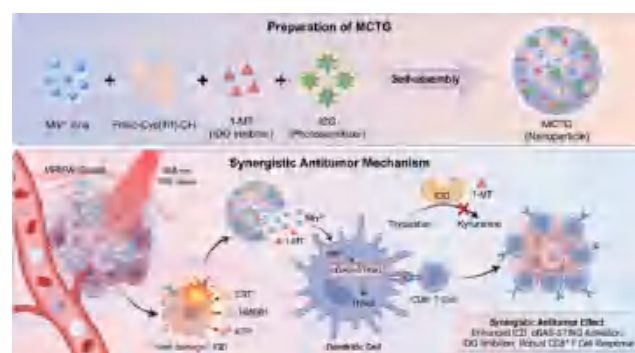


Fig.1. Synthesis of MCTG nanoparticles and mechanism in cancer diagnosis and treatment.

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Bioactive nanomotor enabling efficient intestinal barrier penetration for colorectal cancer therapy

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Key words: colorectal cancer, oral drug delivery system, nanomotor, intestinal barrier penetration

Introduction: Oral drug delivery systems possess inherent advantages in colorectal cancer (CRC) therapy, yet their efficacy is often severely compromised by the complex intestinal barrier—particularly the mucus layer and epithelial barrier—resulting in suboptimal therapeutic outcomes and challenges in clinical translation. This study aims to develop a bioactive nano-motor driven by both thermophoresis and gas, enhancing CRC treatment efficiency through efficient penetration of the intestinal barrier.

Materials & Methods: This study utilized mesoporous silica nanoparticles (MSN) as a carrier and poly(dopamine) (PDA) loaded with the nitric oxide (NO) donor BNN6 as the driving element. Through the Pickering emulsion method, Janus-structured MSN/PB was constructed. After loading cisplatin (CP), it was camouflaged with *Lactobacillus rhamnosus* GG cell wall (CWL) to prepare the CMPBC nanomotor. Structural and physicochemical properties were characterized via TEM, dynamic light scattering, and FTIR. Intestinal barrier penetration performance and mechanisms were investigated using microfluidic chips, Transwell models, Western blot, and KEGG pathway analysis. Systematically evaluated the nanomotor's in vitro/in vivo cytotoxicity, targeted distribution, antitumor efficacy, and biosafety.

Results & Discussion: This study developed a biomimetic Janus nanomotor (CMPBC) that targets IgA highly expressed in the CRC intestinal segment via coated *Lactobacillus rhamnosus* cell walls. Upon near-infrared laser activation, this motor generates dual propulsion from self-thermophoresis and NO gas, synergistically penetrating the intestinal mucus layer (with efficiency increased by 2.9-fold). Released NO reversibly modulates tight junction proteins, significantly enhancing paracellular pathway transport efficiency (3.5-fold increase). In vivo experiments demonstrate marked CMPBC accumulation at CRC sites (5.7-fold increase), achieving a 98.6% tumor suppression rate while inhibiting metastasis and regulating gut microbiota.

Conclusions: This work successfully engineered a bio-chemotactic dual-drive nanomotor that autonomously penetrates the intestinal mucus layer and reversibly opens epithelial tight junctions via NO signaling, thereby overcoming two major physiological barriers to oral drug delivery. This strategy enhanced cisplatin delivery efficiency by 3.5-fold, demonstrating outstanding antitumor efficacy and biosafety in vivo, providing an

innovative platform for targeted oral therapy of CRC and other gastrointestinal diseases.

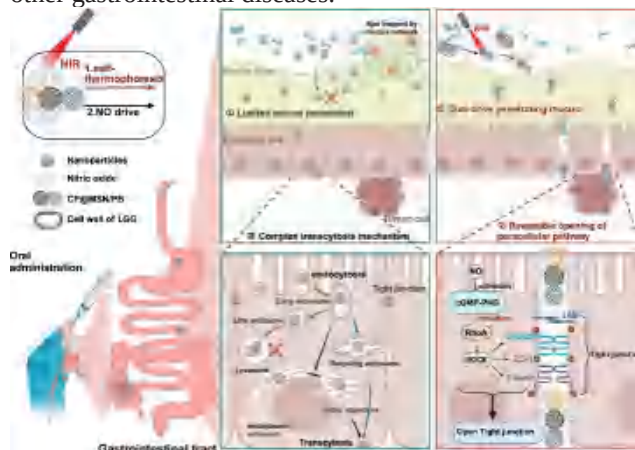


Fig. 1. Schematic comparison of nanoparticles (NPs) for CRC treatment by passive diffusion and dual-driven nanoparticles for enhanced intestinal mucus and epithelial penetration.

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Myogenic nano-adjuvant for systematic sarcopenia via mitochondrial homeostasis modulation in macrophage-myosatellite metabolic crosstalk

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Abstract: The decline in skeletal muscle mass and muscle strength linked to aging, also known as sarcopenia, is strongly associated with disability, traumatic injury, and metabolic disease in elderly patients. Meanwhile, sarcopenia increases the risk of adverse perioperative complications including implant dislocation, infection, loosening, and poor wound healing. Mitochondrial dyshomeostasis in the immune-myosatellite metabolic crosstalk is one of the major pathological factors in sarcopenia. To reduce the incidence of perioperative complications in elderly patients with sarcopenia, we designed and developed a nano-adjuvant based on two-dimensional layer double hydroxide (LDH) for sustained improvement of systemic sarcopenia. Construction of MgAlCo-LDH@UA (MACL@UA) nano-adjuvant was performed by introducing cobalt in magnesium-aluminum LDH and further loading urolithin A (UA). The release of magnesium ions and UA promoted myocyte proliferation, angiogenesis and improved mitochondrial homeostasis. Al acted as an immunomodulatory adjuvant to enhance the metabolic crosstalk between macrophages and myosatellite cells, and prompted macrophage-derived glutamine nourishment. Animal experiments confirmed that vaccination with MACL@UA in systemic sarcopenia and intensive perioperative vaccination with MACL@UA significantly enhanced quadriceps muscle mass in rats. This nano-adjuvant offers a solution for long-term improvement of sarcopenia and short-term significant reduction of perioperative complications in elderly patients, with promising prospects for clinical application and commercial translation.

Key words: myogenic nano-adjuvant, systematic sarcopenia, mitochondrial homeostasis, metabolic crosstalk

Introduction: Please clearly characterize the scientific question investigated in the study.

Materials & Methods: Please briefly explain the materials and methods applied in the study.

Results & Discussion: Please concisely present the results of significant positive and negative findings in the study.

Conclusions: Please concisely state the conclusions and include recommendations for future study, and implications and significance of the data presented.

Table X. Caption.

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Fig. X. Caption.

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Deep-brain magnetothermal stimulation in freely moving mice using ferrimagnetic vortex nanorings

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Abstract: Magnetothermal neuromodulation is a minimally invasive, deep-brain accessible, and tether-free technique. The precisely timed activation of thermosensitive ion channels, such as TRPV1, with local heat generated using magnetic nanoparticles is crucial for efficient neuromodulation. Nevertheless, this technique is greatly hindered by its long stimulus-response time and high safety risks due to the poor heat-generating performance of the nanomediators. Herein, we report the establishment of a ferrimagnetic vortex iron oxide nanoring (FVIO)-mediated magnetothermal neurostimulation technique that is efficient and safe. The FVIOs successfully triggered Ca^{2+} influx into HEK293T cells and cortical neurons. In vivo magnetothermal stimulation in the central nucleus of the amygdala of mice further demonstrated that FVIOs evoked fear behaviors with an average latency of 2.51 s. More importantly, FVIOs-mediated stimulation not only exhibited negligible histopathological alterations and proinflammatory cytokine expression but also successfully elicited fear behaviors in transgene-free mice. The FVIO-mediated efficient and safe neuromodulation has the potential for future neuroscience exploitation and neurological disease treatment.

Key words: Magnetic nanomaterials, TRPV1, magnetogenetics, wireless neuromodulation

Introduction: Magnetothermal neurostimulation is emerging as a powerful technique for gaining insight into intricate brain circuits and performing therapeutic investigations of neurological disorders, given its distinct advantages, such as minimal invasiveness, tether-free operation, deep brain accessibility, and high spatial resolution. In this technique, biocompatible magnetic nanoparticles are utilized as nanoheaters to generate heat locally through the hysteresis loss process under an alternating magnetic field (AMF). The increase in local temperature can activate the thermosensitive ion channels that are overexpressed on the cell membrane and trigger an influx of calcium (Ca^{2+}) into neurons, thereby modulating neural activity.

Current techniques still suffer from low activation efficiency and high required dosages of nanoheaters, leading to an unexpectedly long stimulus-response time and potential safety concerns. According to the principles of magnetothermal neurostimulation, the precisely timed activation of a single neuron depends on both the expression level of thermosensitive ion channels and the heating efficiency of the nanoparticles under an AMF. Transient receptor potential cation channel subfamily V member 1 (TRPV1), the

thermosensitive ion channel most commonly used in neuromodulation, can be activated by local heat ($> 43^\circ\text{C}$)-induced conformational changes in the channel pore. Moreover, the rate of TRPV1 opening increases exponentially with increasing surrounding temperature. Because an increase in TRPV1 expression in vivo requires viral vector-mediated gene transfection, which comes with safety risks, the key to quickly and safely activating TRPV1 lies in boosting the heat-generating performance of magnetic nanoparticles. Unfortunately, the superparamagnetic iron oxides (SPIOs) and ferritin protein widely used in magnetothermal neurostimulation show poor thermal conversion efficiency due to their superparamagnetic nature and minimal hysteresis loss. In addition, an AMF with a high amplitude (H) and frequency (f) is frequently needed to improve the heat-generating ability of the nanoheater. Nevertheless, less improvement has been achieved because of the biologically acceptable limit ($H \times f \leq 5 \times 10^9 \text{ A} \cdot \text{s}^{-1}$). Recognizing the above limitations, developing a high-performance magnetic nanoparticle-mediated stimulation technique is a valuable approach for realizing efficient and safe magnetothermal neuromodulation.

Significant efforts have been made to synthesize various magnetic nanoparticles with enhanced heat-generating performance given their wide application in magnetic hyperthermia, controlled drug delivery, cell signal transduction activation, and magnetothermal neurostimulation. The thermal conversion efficiency of nanoparticles is commonly evaluated using the specific absorption rate (SAR), which mainly depends on the intrinsic magnetic properties of the nanoparticles. Despite tuning their composition, shape, size, and surface chemistry of various magnetic nanoparticles, most exhibit relatively low SAR values ranging from 250–1000 W g^{-1} . As a result, these nanoparticles take more time to reach the threshold temperature and activate TRPV1, leading to long latency times ($\approx 14.7 \text{ s}$) for behavior onset. Applying a high dose of magnetic nanoparticles is an alternative method to reduce the heating time. Nevertheless, using excessive amounts of nanoheaters increases the risk of non-negligible safety issues in the brain, such as dopamine neuron damage, homeostatic disruption, and inflammatory responses. We previously reported that novel biocompatible ferromagnetic vortex-domain iron oxide nanorings (FVIOs) exhibit an ultrahigh SAR of greater than 3000 W g^{-1} because of their unique vortex-to-onion magnetization reversal phenomenon upon AMF exposure. As such, FVIOs are likely to be high-performance nanoheaters that facilitate quick activation of TRPV1, which might provide an

opportunity to establish a highly efficient and safe magnetothermal neurostimulation technique.

In the present study, we comprehensively investigated FVIO-facilitated magnetothermal neurostimulation *in vitro* and *in vivo*. The newly designed FVIOs with an anti-His antibody coating triggered Ca^{2+} influx in TRPV1-expressing HEK293T cells and cortical neurons with a low Fe concentration. *In vivo* magnetothermal stimulation in the central nucleus of the amygdala (CeA) further demonstrated that FVIO treatment quickly evoked fear behaviors in mice, exhibiting a response time that was 2.3-fold faster than that in the SPIO-treated group. Overall, the lowest effective dose of FVIOs was 0.05 μg *in vivo*, 16.7-fold less than the effective dose of SPIOs. The aim of this work is to establish an efficient and safe FVIO-facilitated magnetothermal neuromodulation technique, which is expected to be a powerful tool for future neuroscience investigations and therapeutic applications to neurological disorders.

Materials & Methods:

Calcium imaging *in vitro* and fluorescence change quantification were performed as follows. The TRPV1 His-expressing HEK293T cells were washed three times in PBS and incubated with Fluo-4 for 30 min at 37°C. Then, the cells were rewashed with PBS. Next, the anti-His-FVIOs solution (1 mg mL⁻¹) was added to the culture medium of TRPV1-expressing cells on a dish for 15 min incubation. The unbound FVIOs in cell culture medium were washed and removed with calcium imaging buffer and then imaged in calcium imaging buffer before and during AMF treatment. A magneTherm system with a live-cell coil was employed to provide an AMF at 290 kHz and 20 mT. Calcium fluorescence imaging was performed on a confocal laser microscope system at 20 × magnification. The fluorescence intensities (F_t) during AMF exposure were normalized to the average baseline fluorescence (F_0) to calculate the relative fold change F_t / F_0 . The F_0 for each examined cell was obtained for the first 20 s before AMF treatment. Responsive cells and the standard deviations of signals were determined during the stimulation period. The cultured TRPV1His-expressing cortical neurons that bound with FVIOs were also magneto-thermally stimulated for calcium imaging experiment as the protocol.

The AMF exposure was set to 20 mT and 290 kHz for the magnetothermal genetic stimulation experiment. Cameras automatically recorded animal behaviors, and their movement trajectories were analyzed using Any-Maze software. Total freezing time during each trial was used as an index of fear behaviors and converted to a percentage for analysis. The same contexts (odors, wall, color, flooring, and sound-attenuating cabinet) were used to minimize contextual freezing. The percentage of freezing time spent during each FVIOs-treated trial was compared

across groups (including SPIOs-treated, without AMF exposure).

Results & Discussion:

The 3,4-dihydroxyhydrocinnamic acid (DHCA)-coated FVIOs (DHCA-FVIOs) with an average diameter of 52 nm were first synthesized. Moreover, 20 nm DHCA-SPIOs were prepared as controls. Scanning electron microscopy revealed that the DHCA-FVIOs had a uniform ring shape with an average outer diameter, inner diameter, and thickness of 52, 18, and 15 nm, respectively. For precisely targeted magnetothermal stimulation, DHCA-FVIOs and DHCA-SPIOs were further covalently bound to anti-His antibodies using a EDC/NHS coupling reaction to enable TRPV1 targeting via an extracellular 6 × His epitope tag on the transfected cells. The covalent binding of the antibodies to the nanoparticles was confirmed using infrared spectroscopy and zeta potential measurement. Moreover, the powder X-ray diffraction patterns confirmed the cubic inverse spinel phase of Fe_3O_4 in both FVIOs and SPIOs.

Induction heating measurements were then performed with the FVIOs using an induction heating system, in which the temperature changes in the samples were recorded by an optical fiber probe. And the applied AMF had a frequency (f) of 275 kHz and an amplitude (H) of 20 mT. The calculated SAR of the FVIOs was approximately 3462 W g⁻¹, which is 10.78 times greater than that of the SPIOs (321 W g⁻¹). The superior heat-generating ability of the FVIOs can be attributed to the significantly increased hysteresis loss during the vortex-to-onion magnetization reversal process in response to AMF exposure.

FVIO-mediated magnetothermal activation of TRPV1 was systematically investigated through *in situ* Ca^{2+} imaging in cultured 293T cells, where Ca^{2+} influx indicates the opening of the TRPV1 channel and increased cellular activity. The fold changes in the intracellular fluorescence intensity (F_t/F_0) of the Ca^{2+} indicator Fluo-4 were recorded under different experimental conditions. Intense green fluorescence corresponding to the intracellular Ca^{2+} signal was observed upon AMF exposure. After treatment with anti-His-FVIOs, the F_t/F_0 of the TRPV1-expressing HEK293T cells increased with prolonged AMF exposure, which was attributed to successful heat-triggered Ca^{2+} influx. This increase in fluorescence induced by Ca^{2+} influx was observed only in TRPV1-expressing cells that were activated by anti-His-FVIOs-mediated magnetothermal stimulation and in the group treated with agonist capsaicin. The cells in the negative control group were cultured in media containing the antagonist capsazepine, and no significant difference in fluorescence intensity was observed during anti-His-FVIO-mediated magnetothermal stimulation. Moreover, the control groups, including the TRPV1 non-expressing group, the

FVIO-treated group, and the AMF-treated group, exhibited negligible Ca^{2+} -dependent changes in fluorescence intensity.

Behavioral changes in the mice in response to different doses of the nano-mediator were investigated using magnetothermal activation of the CeA. 0.05 μg of anti-His-FVIOs induced freezing behavior in mice in response to AMF application. The percentage of freezing time was greater during the AMF application period than during the AMF OFF period. However, none of the mice showed fear behaviors when injected with the same dose of SPIOs. Further studies revealed that the SPIOs could magnetothermally evoke significant freezing responses only at doses greater than 0.80 μg , which was 16-fold greater than the dose of FVIOs needed to elicit a response. Moreover, no significant differences in freezing behaviors were noted in the control groups with or without FVIO injection, AMF application, and TRPV1 overexpression. The latency to fear response of the mice was also recorded to analyze the temporal resolution of magnetothermal neurostimulation. Notably, FVIO (0.05 μg)-treated mice exhibited a fear behavioral response with an average latency time of 2.51 s, which was 2.3-fold faster than 5.77 s of the SPIO (0.80 μg)-treated group. Compared with the previously reported latency time of tens of seconds in mouse experiments, FVIO-mediated stimulation has been demonstrated to be a superior technique for improving the temporal resolution of in vivo magnetothermal neuromodulation.

Conclusions: We established the FVIO-mediated magnetothermal neurostimulation technique by systematically investigating the effect of FVIOs dose on stimulus-response time and the in vitro and in vivo biosafety, as well as exploring the effectiveness of using this system for long-term, repeated stimulation and magnetothermal regulation in the deep brains of transgene-free mice. Benefiting from the superior heat-generating performance of the FVIOs, anti-His antibody-coated FVIOs triggered Ca^{2+} transients in both transfected 293T cells and cortical neurons at a minimum Fe concentration of 51 $\mu\text{g mL}^{-1}$, which was 20.27-fold lower than the Fe concentration in the SPIOs. In vivo magnetothermal stimulation of the CeA in freely moving mice demonstrated that the mice treated with FVIOs at the optimal dose of 0.05 μg had a short latency to fear behavior response of approximately 2.51 s, which was 2.3 times faster than that of the SPIO-treated mice under the same AMF conditions. Furthermore, FVIO-mediated magnetothermal stimulation was safer and allowed long-term control of the freezing behaviors of mice for more than 60 days. Even in nongenetically modified mice, 0.28 μg of FVIOs was able to activate the endogenous TRPV1 in the CeA and elicit fear behaviors. Overall, we believe that the FVIO-mediated efficient and safe neuromodulation technique

established in this study has potential for future neuroscience and therapeutic applications.

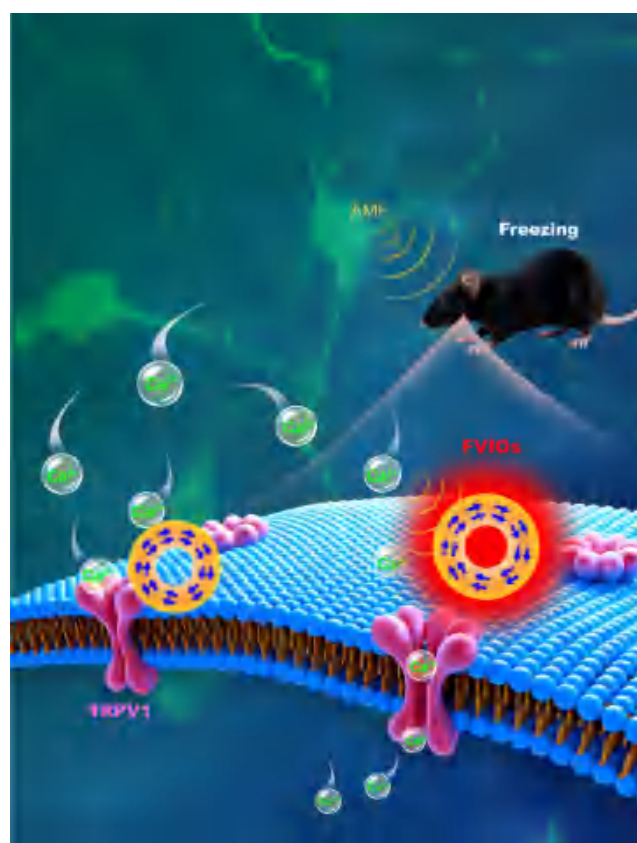


Fig. 1. The ferrimagnetic vortex iron oxide nanoring (FVIO) magnetothermally triggered Ca^{2+} influx into TRPV1-expressing neurons in deep brain and facilitated efficient and safe modulation of freezing behavior of freely moving mice.

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Carrier-Free Nanodrug against Bacterial Mixed Infection for Accelerated Wound Healing

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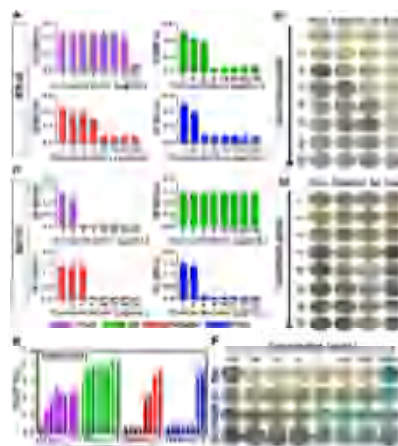
Key words: carrier-free nanodrug, bacterial mixed infection, wound healing.

Introduction: Bacterial mixed infection is a key challenge hindering wound healing. Single antibiotics struggle to exert synergistic bactericidal effects against both Gram-positive (G^+) and Gram-negative (G^-) bacteria simultaneously, while long-term high-dose treatment is prone to causing toxicity and drug resistance. Traditional nanocarriers, known for their permeability and targeting ability, but they suffer from issues such as low drug loading and carrier's toxicity. To address this challenge, this study developed a pH-responsive carrier-free nanodrug (PBN), which enables the synchronous release of two antibiotics through molecular self-assembly, aiming to precisely eliminate multidrug-resistant bacteria, enhance therapeutic efficacy, and reduce side effects.

Materials & Methods: PBN was prepared via an oil-in-water emulsion template method, in which polymyxin B (PMB) and borneol ester (BF) were linked through a Schiff-base bond. The efficacy of PBN in clearing mixed infection in vitro was validated using multidrug-resistant *P.aeruginosa* (MDR-PA) and multidrug-resistant *S.aureus* (MDR-SA). The antibacterial mechanism of PBN was investigated by observing bacterial morphology, measuring bacterial surface charge, and detecting leakage of bacterial intracellular contents. Finally, an in vivo mixed-infection model was established with MDR(SA/PA) to verify the ability of PBN to eliminate bacteria and promote wound healing.

Results & Discussion: In combating MDR-SA, PBN primarily exerts its effect through BF, while PMB plays a dominant role against MDR-PA. When addressing MDR(SA/PA), the efficacy of PBN surpasses that of both the single-drug groups and the physically mixed groups. Antibacterial mechanism studies revealed that PBN can aggregate on the bacterial surface through electrostatic adsorption, affecting bacterial membrane potential, inducing membrane depolarization, disrupting its integrity, and leading to leakage of bacterial intracellular contents. In a mouse model of mixed bacterial wound infection, PBN group exhibited almost no bacterial residue and demonstrated the fastest wound healing rate.

Conclusions: PBN can be released in response at the infected site, eliminating mixed infections and accelerating wound healing, which helps patients get

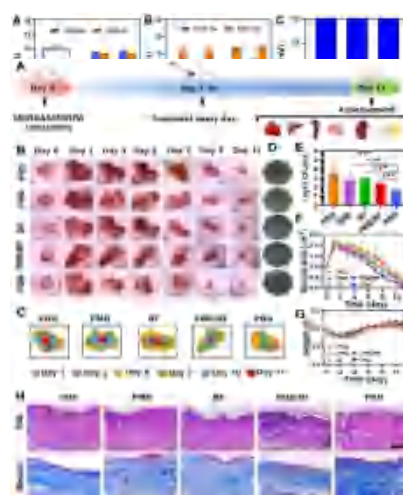


rapid recovery.

Fig. 1. Evaluation of in vitro antibacterial activity of PBN on MDR-SA, MDR-PA and MDR(SA/PA).

Fig.2. Antibacterial mechanism study of PBN.

Fig.3. In vivo study of PBN for the treatment of bacterial mixed infections.



Wireless Piezoelectric Nanostimulator Promotes hiPSC Cardiomyocyte Differentiation and Maturation

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Key words: iPSC-derived cardiomyocytes, Piezoelectric material, Barium titanate nanoparticles, Regenerative Medicine

Introduction: iPSC-derived cardiomyocytes (iPSC-CMs) show dual promise for myocardial repair and drug testing. However, inconsistent differentiation efficiency and immature phenotypes limit their practical applications.

Piezoelectric materials can produce electrical stimulation under mechanical vibrations or ultrasound (US) irradiation based on the piezoelectric effect.

By utilizing piezoelectric barium titanate nanoparticles to intervene in iPSC-to-cardiomyocyte differentiation, we established a wireless platform that mimics endogenous electrical signals, obviating traditional wired stimulation approaches.

This study aims to investigate whether the piezoelectric nanoparticle-based stimulator can enhance the efficient differentiation and maturation of iPSC-derived cardiomyocytes (iPSC-CMs), while elucidating its underlying molecular mechanisms regulating cellular electrophysiology, metabolism, and structural development.

Materials & Methods: We constructed a BaTiO₃@PDA core-shell structure, utilizing its piezoelectric properties, biocompatibility, and interfacial adhesion for efficient ultrasound-to-electrical signal conversion. Multi-scale characterization confirmed its morphology, crystal structure, piezoelectricity, and elemental composition, alongside assessments of antioxidant capacity, cellular uptake, and biosafety.

During cardiac differentiation, piezoelectric stimulation was applied from day 7. On day 14, cTnT immunofluorescence and contraction area ratios were analyzed to assess early differentiation efficiency.

Terminal maturation was evaluated on day 21, including:

- Structural maturity:** α -actinin sarcomere spacing (via immunofluorescence) and expression of cardiac genes (TNNI3, TNNI1, TNNNT2, MYH6, MYH7) by qPCR/IF.
- Electrophysiology:** Field potentials and conduction velocity (MEA, Axion Biosystems™).
- Calcium handling:** Rhod-2 AM-based calcium transient amplitude.
- Metabolic function:** OCR and ECAR (Seahorse analyzer), supplemented by qPCR analysis of metabolic (PPAR α , PGC-1 α , FATP6) and mitochondrial (mt-CO2, ND1, SDHA) genes.

Results & Discussion: The diameter of the BTO nanoparticles was about 200 nm. The phase and

amplitude hysteresis loops demonstrated the good piezoelectric properties of BTO nanoparticles. Successful polydopamine (PDA) coating on barium titanate (BTO) nanoparticles was conclusively verified by SEM elemental mapping, zeta potential analysis, and FTIR spectroscopy. This enhancement correlated with reduced reactive oxygen species (ROS) levels (decreased by 38% vs control, $p < 0.01$) and increased cellular uptake efficiency ($82 \pm 4\%$ vs $65 \pm 5\%$, $p < 0.05$).

Quantitative CCK-8 analysis guided the optimization of stimulation parameters, yielding a final protocol consisting of four daily 5-minute ultrasound exposures (100 mW/cm^2) with concurrent $20 \mu\text{g/mL}$ PDA@BTO nanoparticles.

On day 14, cTnT⁺ cell population in the ultrasound-stimulated PDA@BTO group showed a significant 1.7-fold increase ($p < 0.001$) compared to controls, accompanied by a 36% increase in contraction area ratio ($68 \pm 3\%$ vs. $50 \pm 2\%$, $p < 0.01$), indicating effective promotion of early cardiac differentiation.

By day 21, significant structural maturation was observed, demonstrated by well-organized sarcomeres with increased α -actinin striation spacing ($1.92 \pm 0.05 \mu\text{m}$ vs control $1.68 \pm 0.07 \mu\text{m}$, $p < 0.01$). Key cardiac structural genes were coordinately upregulated.

Electrophysiological functionality significantly improved, with increased conduction velocity ($22 \pm 1 \text{ cm/s}$ vs control $16 \pm 1 \text{ cm/s}$, $p < 0.01$) and more regular calcium transients displaying heightened amplitudes ($F/F_0 = 3.1 \pm 0.2$ vs 2.3 ± 0.1 , $p < 0.001$), indicating enhanced excitation-contraction coupling.

Metabolic maturation was evidenced by a 42% increase in OCR ($p < 0.01$) and elevated expression of metabolic regulators (PGC-1 α : 3.5-fold, PPAR α : 2.8-fold, FATP6, $p < 0.01$). Additionally, mitochondrial gene expression was upregulated (mt-CO2: 2.1-fold, ND1: 1.9-fold, SDHA), further confirming enhanced oxidative capacity.

Collectively, these results demonstrate comprehensive cardiomyocyte maturation spanning structural organization, electrophysiological function, and metabolic activity following stimulation.

Conclusions:

This study validates the feasibility of piezoelectric nanomaterials for regulating cardiac regeneration. Their wireless nature overcomes the limitations of conventional wired electrodes, laying the groundwork for subsequent in vivo transplantation.

Hijacking *Helicobacter pylori*: trojan horse nanoparticles for gastric infection therapy

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Key words: biomaterials, bioengineering, cholesterol chemotaxis, chitosan nanoparticles

Introduction: Nearly half of the world's population is infected by the Gram-negative bacterium *Helicobacter pylori*, responsible for several gastric disorders, as chronic gastritis, peptic ulcers and 90% of gastric cancer cases [1]. Eradication is now recommended to all infected patients, but the available antibiotic regimens fail mainly due to high resistance rates [2]. Bioengineered strategies can deliver new options to outsmart this gastric pathogen. *H. pylori* relies on host cholesterol for survival: the bacterium must actively extract it from the gastric cells and incorporate it into its membrane [3], a mechanism that enhances antimicrobial resistance. Further, cholesterol extraction supports immune evasion by disrupting the lipid rafts, which impairs immune signalling and leads to chronic inflammation [3]. *H. pylori* has positive chemotaxis towards this sterol [3] and, due to its central role in gastric infection and pathobiology, cholesterol is appealing for developing “trojan horse” antimicrobials. We previously validated this rational using cholesterol functionalized gold nanoparticles [4]. Building on this proof-of-concept study, we aim to develop biocompatible cholesterol-grafted chitosan nanoparticles (Chol-cNP) targeting the *H. pylori* cholesterol dependence. This bioengineered approach (nanoparticles) is expected to prevent bacterial metabolism of cholesterol, while physically disrupting the bacteria membrane, a strategy less prone for resistance development.

Materials & Methods: Chol-cNP were produced in a in-house designed microfluidics system [5] and were optimized using different Chol initial concentrations (1 mg/mL (Chol1-cNP) and 2 mg/mL (Chol2-cNP)). The obtained nanoparticles, as well as bare chitosan nanoparticles (cNP), were characterized regarding morphology by Transmission Electron Microscopy (TEM), size and concentration by Nanoparticle Tracking Analysis (NTA) and molecular composition by Attenuated Total Reflectance-Fourier Transform Infrared spectroscopy (ATR-FTIR). The *in vitro* antimicrobial performance was assessed using the highly pathogenic *H. pylori* J99 strain (ATCC® 700824) by colony forming units (CFU) counting after incubation with the nanoparticles for 24 h, 37°C and in agitation (150 rotations per minute). Cytotoxicity was evaluated by resazurin assay, using the MKN28 (JCRB0253™) gastric cell line in accordance with the ISO10993-5:2009.

Results & Discussion: TEM analysis revealed spherical Chol2-cNP and these had an average size of 186 ± 2 nm, larger than cNP (147 ± 10 nm). ATR-FTIR confirmed successful cholesterol grafting. Chol2-cNP were bactericidal at the highest concentration tested (10^{11} nanoparticles/mL) (Fig. 1) and cytocompatible (cell metabolic activity >70%).

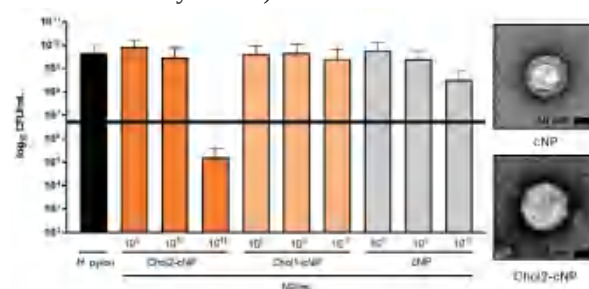


Fig. 1. CFU after incubation and nanoparticle TEM images (50000x magnified). Line - bactericidal threshold.

Conclusions: Chol-cNP were bactericidal and biocompatible. These *in vitro* studies support advancement of this strategy towards future therapeutic development for *H. pylori* gastric infection management.

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Biomimetic nanomedicines with glycan modification for the enhanced treatment of pathogenic infections

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Metabolic glycoengineering of cell membrane-coated nanoparticles represents a versatile platform for creating advanced biomimetic therapeutics. This approach exploits natural biosynthetic pathways to install non-natural functional ligands—such as glycans and lipids—onto the glycocalyx of source cells, thereby engineering their derived membrane coatings. We demonstrate the power of this strategy through three distinct applications: (1) Heparin-modified cellular nanosponges with enhanced surface density show improved inhibition of SARS-CoV-2. (2) Ganglioside-enriched nanosponges, fabricated from metabolically engineered THP-1 cell membranes, exhibit high binding capacity for botulinum neurotoxin (BoNT), serving as a potent nano-antidote. (3) Glycan-modified intestinal epithelial cell membrane-camouflaged nanosponges enhance oral treatment efficacy against cholera toxin (CT)-induced secretory diarrhea. Collectively, this metabolic engineering methodology enables the rational design of a broad-spectrum countermeasure against diverse pathogens and toxins, transcending their varied structures and mechanisms of action.

Key words: regeneration, biomaterials, tissue engineering (3-5 key words)

Introduction: In recent decades, therapeutic nanoparticles have been developed to improve the efficiency of disease diagnosis, treatment, and prevention. Among various platforms, cell membrane-coated nanoparticles, made by wrapping natural cell membranes onto synthetic polymeric cores, have attracted a great deal of attention. This platform stands out because of its ability to replicate the highly complex cellular functionalities to create new therapeutic modalities. Clearly, functionalities beyond the natural properties of cell membranes, if added, would significantly expand the application of this novel class of nanoparticles. To introduce additional functionalities, a metabolic glycoengineering strategy is developed that allows the ligand to participate in natural oligosaccharide or lipid synthesis pathways for expression onto the cell membrane. These non-natural conjugates hijack natural biosynthesis pathways, participate in the relevant cellular metabolic processes, and subsequently anchor to the glycocalyx of cell surfaces to control the cellular properties. The glycocalyx is a complex formed by glycans and sugar conjugates covering the outer side of the cell membrane, which jointly participate in regulating various physiological functions.

Materials & Methods: Inspired by the complex glycocalyx components on the cell surface, such as glycosaminoglycans, glycoproteins, and glycolipids, we developed a series of metabolic glycoengineering strategies to modify the surface glycan of biomimetic nanomaterials.

Results & Discussion: We first developed a cellular nanosponge based on the azido-expressing host cell membranes, followed by conjugating heparin to the nanosponge surfaces. The results showed that increasing surface heparin density on the cellular nanosponges could promote their inhibition against SARS-CoV-2, a strain of coronavirus that causes COVID-19. We further developed a glycan-modified cellular nanosponge that serves as a biomimetic nano-antidote against the detoxification of botulinum toxin (BoNT), a potent neurotoxin that poses a significant threat as a biowarfare weapon and a potential bioterrorist tool. Specifically, we increased the expression levels of gangliosides on THP-1 cells through metabolic engineering and then collected the modified THP-1 cell membrane and coated it onto synthetic polymeric cores. Our findings demonstrated that higher levels of gangliosides on the cellular nanosponges result in greater binding capacities with BoNT. Moreover, we reported an intestinal epithelial cell membrane-camouflaged cellular nanosponge with glycan modification for the enhanced oral treatment of secretory diarrhea caused by cholera toxin (CT), a key exotoxin protein secreted by Gram-negative bacterium *Vibrio cholerae* after colonizing in the intestinal tract of infected patients.

Conclusions: These innovative works have provided a broad-spectrum countermeasure against the intoxication of various bacterial exotoxins or viral infections, regardless of their diverse structures and complex mechanisms of action.

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Por- Ca^{2+} -ZOL Bone-Targeting Sonosensitizing Nanodrug for Synergistic Sonodynamic Therapy and Osteolysis Inhibition in Osteosarcoma

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Key words: osteosarcoma; sonodynamic therapy; bone-targeting; zoledronic acid; osteolysis inhibition

Introduction: Osteosarcoma (OS) is a common primary malignant bone tumor with a high risk of recurrence and metastasis. Drug resistance and hyperactive osteoclast-mediated osteolysis are major factors driving disease progression. Sonodynamic therapy (SDT) can generate reactive oxygen species (ROS) under ultrasound irradiation of sonosensitizers (e.g., porphyrins) to kill tumor cells, but conventional sonosensitizers are limited by poor water solubility and weak tumor targeting^[1]. Zoledronic acid (ZOL), a clinically used bisphosphonate for osteolytic lesions, can inhibit osteoclast activity, yet its poor solubility and systemic toxicity restrict therapeutic application^[2]. To overcome these limitations, we developed a bone-targeting sonosensitizing nanodrug, Por- Ca^{2+} -ZOL (PZC), using a small-molecule co-assembly strategy. PZC improves bioavailability and tumor accumulation, and upon ultrasound irradiation, enables synergistic osteosarcoma treatment through enhanced SDT, Ca^{2+} overload, and inhibition of osteolytic metabolism.

Materials & Methods: PZC was constructed by small-molecule co-assembly of a porphyrin sonosensitizer (Por), Ca^{2+} , and zoledronic acid (ZOL)^[3]. Morphology, particle size, solubility, and stability were characterized by physicochemical methods, while molecular simulation and spectroscopy were used to confirm coordination interactions. Ultrasound-triggered ROS generation, mitochondrial damage, apoptosis, cellular uptake, and intracellular retention were evaluated in osteosarcoma cells. In vivo pharmacokinetics, tumor accumulation, therapeutic efficacy, and biosafety were assessed in orthotopic osteosarcoma and bone metastasis models by histology, immunohistochemistry, and micro-CT.

Results & Discussion: PZC formed uniform and stable nanospheres (~60 nm) with improved aqueous solubility. Coordination among Por, Ca^{2+} , and ZOL was verified by molecular simulation and spectroscopic analysis. Under ultrasound irradiation, PZC generated enhanced ROS, inducing mitochondrial damage and apoptosis in osteosarcoma cells. It also showed energy-dependent cellular uptake and prolonged intracellular retention. In vivo, PZC exhibited prolonged circulation, effective tumor accumulation, and good biosafety. Ultrasound-activated PZC significantly inhibited tumor growth, reduced osteolysis, and preserved bone architecture in both orthotopic and bone metastasis models, as

confirmed by histological and micro-CT analyses. These results indicate that PZC enables synergistic tumor suppression and bone protection.

Conclusions: We developed a multifunctional bone-targeting sonosensitizing nanodrug PZC that integrates SDT enhancement, Ca^{2+} overload-mediated cytotoxicity, and ZOL-based osteolysis inhibition. PZC showed effective anti-osteosarcoma activity and bone-protective effects in vivo, providing a promising strategy for osteosarcoma treatment.



Fig. 1. Experimental Study on Ultrasound-Enhanced Bone-Targeting Sonosensitizer PZC for OS Eradication and Osteolysis Suppression.

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Selective Induction of Cancer Cell Pyroptosis by Erbium Nanotuner Enhances Potent Anti-Cancer Immunity

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Key words: tumor-selective pyroptosis, erbium, lysosomal disruption, tumor microenvironment remodeling, anti-cancer immunity

Introduction: Pyroptosis, an immunogenic programmed cell death, is a robust way to activate anti-cancer immunity. However, it is very challenging to induce pyroptosis in cancer cells while sparing normal cells selectively. Herein, an Er^{3+} -containing nanoparticle is screened from the whole series of lanthanides for boosting pancreatic cancer immunotherapy by selectively inducing cancer cell pyroptosis. To elicit tumor-specific inflammatory cell death, a tumor-targeting nanoplatfrom, termed the Erbium–RSL3 Inflammasome-Activating System (ERIS), was designed, invoking the “Greek goddess of discord” to unleash discord within tumors. ERIS has been proven to induce pyroptosis through lysosomal rupture, facilitated by a strong interaction between Er^{3+} and lysosomal phospholipid membranes, as evidenced by a 3.2-fold increase in GSDMD-N cleavage and a 12.2-fold increase in LDH release compared with controls. This localized inflammatory assault subverts tumor growth and promotes anti-cancer immune responses. Therefore, ERIS demonstrates remarkable tumor suppression with minimal systemic side effects across different pancreatic cancer models, achieved through pyroptosis-induced immune activation and remodeling of the immunosuppressive tumor microenvironment. This study identifies Er^{3+} -based nanomedicine as a new class of cell-selective pyroptosis nanotuner, offering a unique opportunity to enhance the efficacy of cancer immunotherapies.

Materials & Methods: Tannic acid, erbium chloride hexahydrate, and other lanthanide chlorides were purchased from Aladdin Reagent Co., Ltd (Shanghai, China). Dulbecco's modified Eagle's medium (DMEM), fetal bovine serum (F801-500), normal cell lines (L929, EC), and pancreatic carcinoma cell lines (KPC, L3.6.PL, PANC1, Bxpc-3, PAN02, PAN02-Luci) were offered by Baidi Biotechnology Co., Ltd (Shanghai, P. R. China). L-alpha-Dipalmitoyl phosphatidylcholine (DPPC) was provided by AVT (Shanghai, P. R. China) Pharmaceutical Tech Co. The Calcein-AM/PI cell viability/cytotoxicity assay kit and LDH release assay kit were obtained from Beyotime Biotechnology (Shanghai, China).

Results & Discussion: In this work, we put forward an Erbium–RSL3 Inflammasome-Activating System (ERIS) to selectively induce cancer cell pyroptosis and subsequent immune activation. Firstly, a nanoplatfrom based on a biocompatible metal-phenolic network was fabricated for the loading of various RE ions (Scheme 1a). Er^{3+} -containing nanoparticle (Er NP) was identified from the entire lanthanide series as the first to exhibit potent cytotoxicity toward pancreatic cancer cells while showing low toxicity to normal cells. The tumor-specific cytotoxicity of ERIS is underpinned by a dual-selectivity mechanism. Firstly, ERIS exhibits a preferential accumulation capability, resulting in significantly higher internalization in tumor cells compared to normal cells. Furthermore, the internalized Er^{3+} possesses a unique affinity for the phosphate headgroups of lysosomal phospholipids, thereby specifically triggering lysosome rupture and pyroptosis in cancer cells. To further enhance cancer cell pyroptosis, the GPX4 inhibitor RSL3 was integrated into Er^{3+} -loaded nanoparticles. In vitro and in vivo experiments indicated that RSL3 could amplify Er^{3+} -induced cell pyroptosis by inhibiting GPX4 (Scheme 1b). Notably, Er^{3+} -induced cancer cell pyroptosis effectively activated anti-cancer immunity, enabling highly efficient cancer immunotherapy through TME reprogramming, cytotoxic T cell-mediated killing, and central memory T cell (Tcm)-driven immune recall (Scheme 1c). This research provides an essential inspiration for boosted cancer immunotherapy with minimal side effects by selectively

inducing cancer cell pyroptosis.

Conclusions: In summary, an Er^{3+} -containing nanoparticle was screened from the entire lanthanide series that selectively induced pyroptotic cell death in pancreatic cancer cells without apparent cytotoxicity to normal cells. To achieve pyroptosis-triggered boosted cancer immunotherapy, tumor-targeted Er^{3+} and GPX4 inhibitor RSL3 co-delivered nanoparticles (ERIS) were successfully prepared. After incubating PAN02 cells with ERIS, Er^{3+} efficiently accumulates in cancer cells, leading to lysosomal rupture due to its strong binding to phospholipid phosphate groups on lysosomal membranes. Lysosomal rupture activated the NLRP3/Caspase-1/GSDMD pathway, triggering pyroptosis in cancer cells. RSL3 was verified to amplify Er^{3+} -induced pyroptosis by inhibiting GPX4 and disrupting membrane lipid metabolism. Furthermore, ERIS-induced pyroptosis led to the release of intracellular contents, including pro-inflammatory cytokines. The in vivo therapeutic efficacy of ERIS was evaluated on both subcutaneous and orthotopic pancreatic carcinoma models. Notably, upon triggering pyroptotic cell death in PAN02 cells, ERIS could effectively activate tumor immunogenicity and remodel the immunosuppressive TME to boost pancreatic cancer immunotherapy, as confirmed by enhanced CD8⁺ T cell infiltration, reduced immunosuppressive Treg cell populations, and promoted durable immune memory formation. By selectively inducing pyroptosis in cancer cells, ERIS could remarkably inhibit tumor growth with minimal off-target toxicity. This work demonstrated that Er^{3+} -containing nanoparticles selectively induced pyroptosis in cancer cells while sparing normal cells for the first time, providing a unique inspiration and strategy for pyroptosis-triggered cancer immunotherapy with minimal off-target toxicity.

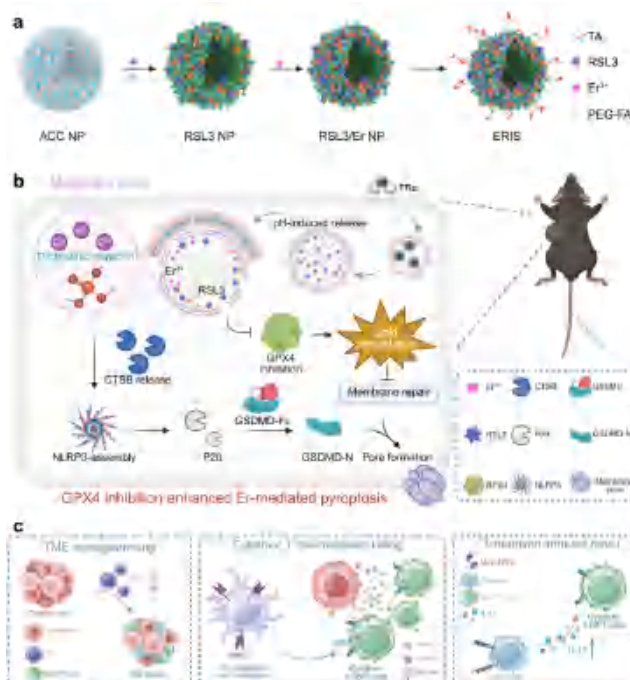


Fig. 1. Tumor-targeting Er^{3+} -containing nanoparticles for cancer immunotherapy via Er^{3+} -mediated pyroptosis amplified by GPX4 inhibition. (a) Synthesis of ERIS via formation of metal-phenolic networks. (b) ERIS induced Er^{3+} -mediated pyroptosis via lysosomal rupture, a process amplified by GPX4 inhibition. (c) ERIS activated anti-cancer immunity through TME reprogramming, cytotoxic T cell-mediated killing, and Tcm-driven immune recall.

Small Solutions to a Big Problem: Nanotherapy Against *Helicobacter pylori*

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Key words: biomaterials, targeted therapies, nanoparticles, antimicrobial peptides, bioengineering

Introduction: *Helicobacter pylori* infection is the main risk factor for the development of various gastrointestinal diseases, ranging from chronic gastritis to gastric cancer. In fact, nearly 90% of gastric cancer cases are linked to this Gram-negative pathogen, the only bacterium classified as carcinogenic by the International Agency for Research on Cancer (IARC). *H. pylori* colonizes the gastric mucosa of over 50% of the global population.

The current treatment consists of a combination of two to three broad-spectrum antibiotics and a proton pump inhibitor. However, antibiotic-based therapy still fails in 10 to 40% of infected patients [1,2].

This presentation will highlight different bioengineering strategies explored by our group using nanoparticles (NPs) as alternatives to conventional antibiotics for *H. pylori* eradication, namely: i) Lipid NPs [3]; ii) Cholesterol coated gold NPs, that specifically target *H. pylori* by exploiting its auxotrophic dependence of cholesterol [4]; iii) Antimicrobial peptide (AMP) coated chitosan NPs, developed using a simple and efficient microfluidic device, which enables the bioconjugation of AMPs onto chitosan NPs during their formation via thiol-norbornene (TNPC) "photoclick" chemistry [5].

Materials & Methods: Lipid-NPs, Cholesterol-NPs & AMP-NPs were designed, optimized and evaluated against *H. pylori* strains according to references [3], [4] and [5], respectively.

Results & Discussion:

Lipid NPs were able to target and kill *H. pylori* both *in vitro* and *in vivo*, without affecting other bacteria in the gut microbiome. Cholesterol NPs specifically kill *H. pylori* supporting the development of a "trojan horse" therapeutic strategy based on *H. pylori* cholesterol autotrophy. AMP-NPs, although not specific to *H. pylori*, can effectively kill the bacterium upon contact.

All developed NPs kill *H. pylori* by disrupting its membrane, as observed by scanning electron microscopy (SEM) and/or transmission electron microscopy (TEM).

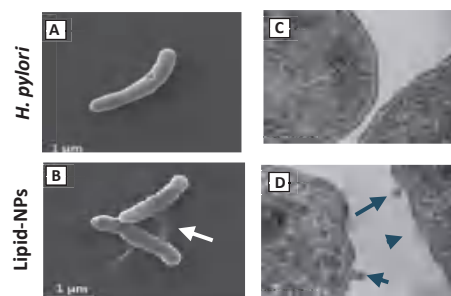


Fig. 1. SEM (left; scale bars: 1μm) and TEM (right; scale bars: 50nm) micrographs of *H. pylori* J99 (A, C) after Lipid NPs exposure (B, D).

Conclusions: All developed NPs are promising for the development of gastric infection treatments. A simple and versatile microfluidic system to obtain AMP-conjugated chitosan NP was developed.

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Disulfidptosis Mediated Immunotherapy Integrated with Neural Regeneration in Postoperative Glioblastoma

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Key words: Postoperative glioblastoma, disulfidptosis, Neural microenvironment repair, immunogenic cell death.

Introduction: Postoperative glioblastoma remains highly recurrent, and existing immunotherapeutic strategies are fundamentally constrained by the central nervous system, where effective immune activation frequently disrupts neural homeostasis and impairs functional recovery. In particular, therapies that induce tumour cell death often exacerbate postoperative neuroinflammation, demyelination, and neurological deficits.

Materials & Methods: We engineered a locally injectable immunotherapeutic platform consisting of a tumour membrane-coated copper-quercetin nanocomplex with glucose oxidase (GOx) loading embedded in an alginate-calcium hydrogel for sustained retention in the post-resection cavity. The system induces disulfidptosis in residual glioma cells through glucose oxidase-driven metabolic perturbation and copper-mediated redox stress. In parallel, quercetin modulates postoperative neuroinflammatory signaling to support oligodendrocyte lineage maturation and remyelination.

Therapeutic efficacy and neural recovery were evaluated in an orthotopic postoperative glioblastoma model using survival analysis, immune profiling, histological assessment, behavioural testing, and single-nucleus RNA sequencing of peritumoural tissue.

Results & Discussion: The treatment significantly suppressed tumour recurrence and prolonged survival. Mechanistically, disulfidptosis triggered coordinated exposure and release of damage-associated molecular patterns, promoting dendritic cell maturation and cytotoxic T cell infiltration while reducing immunosuppressive myeloid populations. Concurrently, the platform mitigated postoperative neuroinflammation and enhanced oligodendrocyte differentiation and remyelination in peritumoural regions, resulting in improved neurological function. Transcriptomic analysis revealed simultaneous activation of antitumour immune programs and restoration of myelination-related gene networks, demonstrating that immune activation and neural repair were mechanistically coupled rather than mutually exclusive. Importantly, no increase in neurotoxicity or functional impairment was observed, highlighting the advantage of integrating tumour cell death with neural repair.

Conclusions: This work establishes a dual-functional postoperative immunotherapy that integrates disulfidptosis with active neural microenvironment repair, overcoming a longstanding trade-off in CNS cancer treatment.

The findings support a new therapeutic paradigm in which immune activation and postoperative neural recovery are co-engineered, offering a strategy for function-preserving immunotherapy in glioblastoma and other neurological malignancies. Future studies will focus on optimizing death-repair coupling mechanisms, long-term functional outcomes, and translational validation.



Fig.1 Schematic illustration of the CGP-Gel platform for postoperative glioblastoma therapy integrating disulfide-dependent cell death and neural repair.

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Advancing microRNA Therapeutics: Nanocarrier Platforms for Mesothelioma Treatment

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INTRODUCTION

Mesothelioma is a highly aggressive cancer of the lung lining, primarily caused by asbestos exposure. Australia has one of the highest per capita incidences due to widespread historical asbestos use. Despite advances in immunotherapy, effective treatment remains limited, with low response rates. We have previously identified microRNA-16 (miR-16) as a potent tumour suppressor in mesothelioma,^{1,2} capable of enhancing immunotherapy efficacy.³ While a Phase I clinical trial of miR-16 replacement therapy showed promise, it highlighted the need for improved delivery systems.

METHODS

We evaluated three nanocarrier platforms, small extracellular vesicles (sEVs) derived from normal mesothelial cells, nanodiamonds, and layered double hydroxides (LDHs) for the delivery of miR-16 into mesothelioma cells. Nanocarriers were characterized using transmission electron microscopy (TEM) and zeta potential analysis. Internalization into mesothelioma cells was assessed via Tie2 confocal microscopy. Functional assays were conducted to assess the effects on cell proliferation, cell cycle progression, and apoptosis.

RESULTS AND DISCUSSION

All nanocarriers showed stable physicochemical profiles and successfully delivered miR-16 into mesothelioma cells. sEVs remained highly stable (size <100 nm) after six months and exhibited sustained internalization. LDHs displayed hexagonal plate-like morphology with hydrodynamic sizes around 104.2 ± 5.5 nm and strong positive surface charge ($+38.7 \pm 1.0$ mV), suggesting good colloidal stability. Nanodiamonds (5–20 nm) were prone to aggregation upon storage but could be re-dispersed by sonication. All delivery systems demonstrated comparable tumour-suppressive effects, including reduced proliferation, cell cycle arrest, and increased cell death in mesothelioma cells.

CONCLUSION

Our findings demonstrate that sEVs, LDHs, and nanodiamonds are all effective nanocarriers for miR-16 delivery in mesothelioma. These systems show strong potential for further development in RNA-based therapeutic strategies for this incurable cancer.

Key words: microRNA, Nanocarriers, sEVs, Nanodiamonds, LDHs (3-5 key words)

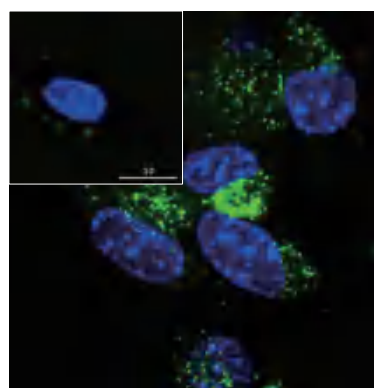


Figure 1, microRNA internalized mesothelioma cells.

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Engineering Neuroprotection: Biodegradable Dendrimers as Delivery Vectors for Stroke Therapeutics

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Key words: mRNA therapy, Botulinum Neurotoxins, Drug delivery, Nanomedicine, Neurosciences

Introduction: Stroke is the 3rd cause of death worldwide and a leading cause of long-term disability. Ischemic stroke, the most prevalent type, occurs when the blood supply to the brain is occluded, resulting in neuronal death. Nevertheless, current therapies are not applicable to most patients and only mitigate the effects of occlusion by restoring the blood-flow, lacking neuroprotective properties.

Therefore, herein we investigated our family of proprietary fully-biodegradable dendrimers (PEG-GATGE) [1] as delivery vectors of two neuroprotective therapeutics that aim to: (A) improve neuronal survival by delivering mRNA encoding for the brain-derived neurotrophic factor (BDNF mRNA), and (B) reduce glutamate excitotoxicity by delivering the catalytic domain of Botulinum Neurotoxin type A (BoNT/A-LC).

Materials & Methods: Dendrimer-BDNF mRNA nanoparticles (dendriplexes) were characterized in terms of size, polydispersity, zeta-potential (DLS), and mRNA complexation (SYBRGold). Dendriplexes' internalization and cytocompatibility were assessed in mice embryonic cortical neurons. Hemocompatibility was evaluated in human blood (hemolysis and clotting assays). A mice stroke model (pMCAO) was used to study dendriplexes performance in vivo, after IV administration.

The recombinant BoNT/A-LC was produced in a bacterial expression system and purified (IMAC and SEC). Dendrimer-LC nanoparticles (DETOX) were characterized by DLS as described above, and the LC-loading efficiency was quantified using a slot-blot assay with Cy5-labeled LC. The catalytic activity of DETOX was assessed in mice cortical neurons by ICC and WB against the LC target (cSNAP-25). Neurons exposed to oxygen-glucose deprivation (OGD) were used as an in vitro stroke model to evaluate the neuroprotective potential of DETOX by quantifying glutamate levels in the culture medium. A 3D full-human blood-brain barrier (BBB) model [2] was used to study DETOX permeability.

Results & Discussion:

Dendrimer-BDNF mRNA nanoparticles (Dendriplexes) exhibited suitable physico-chemical properties for the proposed strategy, with sizes below 100 nm, a positive

net charge, and high mRNA complexation efficiency (> 80 %). Also, in vitro studies revealed dendriplexes excellent internalization capacity without causing cytotoxicity in primary cortical neurons. The system's hemocompatibility was also demonstrated, which is significant for systemic administration. In vivo, dendriplexes were able to reach the brain, particularly the infarcted area, where increased BDNF expression was observed. This demonstrates the dendrimer's great ability to protect and effectively deliver mRNA to the lesioned brain after systemic administration.

For the dendrimer-BoNT/A LC nanoparticles (DETOX), the catalytically active LC domain (50 kDa) was successfully produced with ~99 % purity. DETOX nanoparticles, with sizes below 100 nm and positive charges, achieved up to 84 % LC-loading efficiency. These nanosystems markedly enhanced SNAP-25 cleavage (the LC target) in neurons compared to LC alone and BoNT/A, without inducing cytotoxicity, and demonstrated a faster onset of action than the full-length neurotoxin. Importantly, DETOX capacity to reduce glutamate exocytosis was demonstrated in an in vitro model of ischemia (OGD), supporting our initial concept for this stroke treatment. Moreover, DETOX nanoparticles showed their remarkable ability to permeate an innovative 3D full-human BBB in vitro model [3]. The proof-of-concept will be assessed in a mice stroke model, where DETOX-induced neuroprotection will be evaluated.

Conclusions: Together, these results point to the versatility of the explored dendrimers as promising drug delivery systems for neuroprotection in stroke. Given their excellent biocompatibility and ability to cross the BBB, their extrapolation to the treatment of other neurological conditions is foreseeable.

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Hierarchically Engineered Multifunctional Fe₃O₄@Au Nanoparticles with Magnetic Responsiveness and Bioactive Surface Functionalization

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Key words: magnetic nanoparticles, gold functionalization, chitosan, folic acid, carboplatin

Introduction: Multifunctional nanobiomaterials with controllable physicochemical properties and tunable biointerfaces are gaining importance in regenerative medicine and advanced biomedical engineering. Magnetic nanoparticles offer unique opportunities for remote manipulation and imaging, while surface functionalization enables modulation of cellular interactions. However, achieving reproducible magnetic performance together with stable and biologically active surface architecture requires careful control over both core synthesis and hierarchical functionalization. In this study, we report a magnetite-based nanoplatform obtained via rapid ammonia-induced coprecipitation, followed by gold decoration and functionalization with a chitosan–folic acid (CS–FA) conjugate, with or without carboplatin (CBPT) incorporation. The system was designed to combine magnetic responsiveness, improved surface chemistry for ligand immobilization, and active folate-receptor-mediated targeting.

Materials & Methods: Fe₃O₄ nanoparticles were synthesized by rapid alkalization of aqueous Fe²⁺/Fe³⁺ salts using NH₄OH under inert atmosphere. Gold was deposited onto the magnetic cores via citrate-assisted reduction, yielding Fe₃O₄@Au nanoparticles. A CS–FA conjugate was synthesized via carbodiimide-mediated coupling and subsequently immobilized onto the Fe₃O₄@Au surface. In the therapeutic variant, carboplatin was incorporated within the polymer matrix, resulting in Fe₃O₄@Au–CS–FA–CBPT nanostructures. Physicochemical characterization included FTIR, XRD, XPS, TEM, Raman spectroscopy, and vibrating sample magnetometry (VSM). Biological assessment was performed using NIH:OVCAR-3 human ovarian adenocarcinoma cells. Label-free 3D holotomographic imaging (Nanolive 3D Cell Explorer) was applied to investigate nanoparticle–cell interactions.

Results & Discussion: Rapid ammonia co-precipitation yielded highly crystalline Fe₃O₄ nanoparticles with quasi-spherical morphology in the nanometric range and narrow size distribution. XRD confirmed phase-pure magnetite without detectable crystalline impurities. Surface-sensitive analysis demonstrated efficient and

reproducible gold deposition on magnetic cores. FTIR and XPS analyses confirmed successful formation of the CS–FA conjugate and its immobilization on the Fe₃O₄@Au surface. Characteristic amide-related bands and surface chemical shifts indicated stable polymer–ligand integration. Incorporation of carboplatin did not disrupt structural integrity of the nanoplatform. Magnetic measurements revealed magnetically soft behavior with negligible coercivity and remanence at room temperature, consistent with superparamagnetic characteristics desirable for biomedical applications. Although a moderate reduction in saturation magnetization was observed after gold and polymer functionalization, the system retained strong magnetic responsiveness.

Holotomographic imaging suggested uptake of Fe₃O₄@Au-based systems by OVCAR-3 human ovarian adenocarcinoma cells. These observations remain qualitative and will be validated in extended biological studies.

Conclusions: The rapid ammonia-based synthesis provides a reproducible and high-quality magnetic core suitable for advanced surface engineering. The resulting Fe₃O₄@Au–CS–FA and Fe₃O₄@Au–CS–FA–CBPT nanoplatforms integrate magnetic responsiveness, folate-mediated targeting capability, and chemotherapeutic loading within a structurally stable system. The presented results demonstrate the feasibility of constructing a multifunctional, magnetically controllable platform for various biomedical applications, including ovarian cancer theranostics.

Acknowledgments: Waldemar Tokarz (Faculty of Physics and Applied Computer Science) and Marta Gajewska (Academic Centre for Materials and Nanotechnology) from the AGH University of Krakow are kindly acknowledged for their assistance with VSM and TEM analyses.

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A ROS-Responsive Nanoplatfom for Discriminating and Regulating Multiple Reactive Oxygen Species in Real Time

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Introduction: Abnormal accumulation of reactive oxygen species (ROS) can induce oxidative damage to lipids, proteins, and nucleic acids, acting as a common driver of neurodegenerative disorders, cardiovascular diseases, and cancer. However, accurate identification and quantification of ROS remain challenging due to the similar physicochemical properties of major species—superoxide anions ($O_2^{\cdot-}$), hydroxyl radicals ($\cdot OH$), and singlet oxygen ($^1O_2$)—as well as their transient nature, short lifetimes, and low steady-state concentrations.

Materials & Methods: Herein, we report a ROS-responsive nanoplatfom (UCNP- C_{60}) for real-time monitoring and *in situ* scavenging of excessive ROS. UCNPs functionalized with 3-aminophenylboronic acid (UCNP-APBA) were conjugated to hyaluronic acid-modified fullerenes (HA- C_{60}) *via* ROS-cleavable boronate ester linkages.

Results & Discussion: The strong UV-visible absorption of fullerenes initially quenches upconversion luminescence (UCL), while excessive ROS-mediated bond cleavage releases fullerenes and restores UCL for dynamic ROS tracking. Released fullerenes, with highly conjugated structures and strong electron affinity, efficiently scavenge ROS, restoring cellular redox balance. UCNP- C_{60} achieves detection limits of 0.40 μM for $\cdot OH$ and 0.44 μM for $O_2^{\cdot-}$, with excellent linearity across broad concentration ranges ($\cdot OH$: 0.40–2000 μM ; $O_2^{\cdot-}$: 0.44–200 μM).

Conclusions: The nanoplatfom offers a highly integrated approach for ROS visualization and regulation, and providing a promising tool for early diagnosis and precise treatment of oxidative stress-related diseases.

Keywords: Reactive oxygen species; Upconversion luminescence; Turn on; Biosensor

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Synergistic Photothermal-Immunotherapy of Breast Cancer via Zn²⁺-Enhanced AUTAC Delivery for IDO Degradation

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Key words: Tumor, Immunity, Metal coordination,
Targeted protein degradation,

Introduction: In breast cancer treatment, limited response to immunotherapy due to IDO-mediated immune escape remains a significant clinical challenge. Currently, targeted protein degradation (TPD) has emerged as a promising therapeutic strategy capable of precisely degrading proteins involved in tumor immune evasion, offering a novel approach to overcome this barrier. However, the application of TPD is largely constrained by its poor drug-like properties, low bioavailability, and inadequate tumor targeting. To address these limitations, we developed a tumor-specific photo-immunomodulatory nanodelivery system by loading a novel Zn-coordinated guanine-modified AUTAC molecule—designed for targeted degradation of IDO—onto polydopamine nanoparticles. This system enables controlled release in the tumor microenvironment and integrates photothermal effects with immune regulation, providing a feasible strategy to counteract immune escape and enhance antitumor efficacy.

Materials & Methods: 1. Preparation and Characterization of Nanoparticles: Polydopamine nanoparticles (PDA) were synthesized via a hydrothermal method and characterized for size, charge, and stability. Their drug release profile was assessed in vitro. 2. In Vitro Pharmacodynamic Evaluation: Cytotoxicity and cellular uptake of the nanoparticles were evaluated. The targeted degradation of IDO protein and its underlying mechanism were investigated using Western blot analysis. 3. In Vivo Therapeutic Efficacy Assessment: Antitumor activity was evaluated in a murine breast cancer model. Immune responses were analyzed via Western blot, flow cytometry, and ELISA.

Results & Discussion: The Zn-coordinated, guanine-modified AUTAC molecule was successfully loaded onto polydopamine nanoparticles, forming PP@GN-Zn with a uniform spherical morphology. The nanoparticles exhibited a hydrodynamic diameter of 116.7 ± 1.1 nm, a zeta potential of -19.3 ± 0.4 mV, and maintained excellent colloidal stability in various physiologically relevant media over 24 hours. In vitro studies demonstrated efficient cellular uptake of PP@GN-Zn by 4T1 cells with favorable biocompatibility. Upon laser irradiation, the combination treatment induced significant apoptosis/necrosis (total ~69.1%), comprising 7.26%

early apoptosis and 61.86% late apoptosis/necrosis. Notably, it reduced IDO expression by approximately 60% compared to photothermal therapy alone. Confocal microscopy and flow cytometry analysis revealed that the treatment effectively activated autophagy. Furthermore, the released Zn²⁺ ions facilitated the binding of the AUTAC molecule to IDO, subsequently inducing K63-linked polyubiquitination and leading to sustained IDO degradation for immunomodulation.

In vivo, PP@GN-Zn combined with laser irradiation significantly inhibited tumor growth and metastasis in a 4T1 breast cancer model. Immune profiling demonstrated that this strategy effectively degraded tumoral IDO, promoted dendritic cell maturation, increased the population of effector T cells, and enhanced the expression of pro-inflammatory cytokines (IL-6, IL-2, IL-12, TNF- α , and IFN- γ). Collectively, these results indicate that the nanosystem successfully alleviates immunosuppression and activates potent anti-tumor immunity.

Conclusions: In summary, we have developed a tumor-targeted photothermal-immunomodulatory nanosystem by coordinating a novel Zn²⁺-binding, guanine-modified AUTAC molecule with polydopamine nanoparticles. This system enables responded release of AUTAC for targeted IDO degradation and combines it with photothermal therapy to remodel the immunosuppressive tumor microenvironment. As a result, it effectively inhibits both primary tumor growth and metastasis in breast cancer, offering a promising strategy to overcome the delivery and bioavailability challenges associated with targeted protein degraders.

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Ultrasmall Magnetic Resonance Probes for Precision Diagnosis of Kidney Diseases

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Key words: Magnetic Resonance Imaging (MRI), Iron oxide nanoparticles (SPIONs), Kidney imaging.

Introduction: Magnetic resonance imaging (MRI) is a widely used non-invasive diagnostic tool, but its gadolinium-based contrast agents (GBCAs) pose a risk of nephrotoxicity. Although gadolinium ions are chelated to reduce toxicity and primarily excreted via urine, trace amounts can persist in the body and even accumulate in brain tissue after repeated use. This underscores the need for safer alternatives, especially for kidney disease diagnosis.

Iron oxide nanoparticles (SPIONs) offer a promising solution due to their excellent biocompatibility, multifunctionality, and tunable properties. They have been applied in cell labeling, drug delivery, and imaging, with growing interest in their use as MRI contrast agents.

The kidney's glomerular filtration barrier imposes strict size constraints: molecules under 6 nm are freely filtered, while those above 8 nm are retained. Thus, precise size control of nanoparticles is essential for targeted renal imaging. By optimizing both size and surface characteristics, iron oxide nanoparticles enable safe and effective visualization of kidney tissue.

In summary, developing size-tunable and biocompatible iron oxide nanoparticles represents a promising strategy for next-generation renal MRI contrast agents, offering a safer alternative to gadolinium-based formulations.

Materials & Methods: Utilizing microfluidic reactor technology, this study achieves the controlled and uniform synthesis of iron oxide nanoparticles via a coprecipitation method, where ligands are introduced for in-situ modification 10 seconds after the initiation of the reaction, and the product is continuously collected at room temperature.

Results & Discussion: Transmission electron microscopy (TEM) characterization revealed that the synthesized nanoparticles exhibited uniform morphology with a size of approximately 5 nm (Fig.1). Relaxivity measurements were performed using a ligand-to-iron concentration ratio of 1:1 at magnetic field strengths of clinical 3.0 T MRI systems, comparing the as-synthesized ultrasmall nanoparticles with Magnevist. The results demonstrated that the obtained

material exhibited superior longitudinal relaxivity ($r_1 = 6.1 \text{ mM}^{-1} \cdot \text{s}^{-1}$) and transverse relaxivity ($r_2 = 55.37 \text{ mM}^{-1} \cdot \text{s}^{-1}$) compared to Magnevist (Fig.2). Furthermore, in vivo biodistribution studies in Sprague-Dawley (SD) rats revealed high signal intensity in the kidney, indicating favorable renal imaging capability (Fig.3).

Conclusions: Please concisely state the conclusions and include recommendations for future study, and implications and significance of the data presented.

Fig. 1. TEM images



Fig. 2. T1 and (H) T2 relaxation efficiency-iron concentration curve of SPIONs aqueous solutions under 3.0 T main magnetic fields respectively.

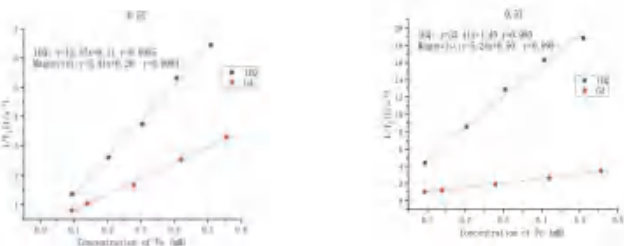
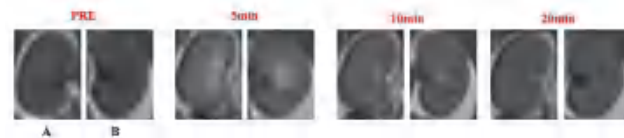


Fig. 3. MRI scans of the right (A) and left (B) kidneys acquired at indicated time intervals post-injection of the



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**Interface/Dipole Polarized Antibiotics-Loaded Fe₃O₄/PB
Nanoparticles for Non-Invasive Therapy of Osteomyelitis
Under Medical Microwave Irradiation**

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Abstract: Due to their poor light penetration, photothermal therapy and photodynamic therapy are ineffective in treating deep tissue infections, such as osteomyelitis caused by *Staphylococcus aureus* (*S. aureus*). Here, a microwave (MW)-responsive magnetic targeting composite system consisting of ferric oxide (Fe₃O₄)/Prussian blue (PB) nanoparticles, gentamicin (Gent), and biodegradable poly(lactic-co-glycolic acid) (PLGA) is reported. The PLGA/Fe₃O₄/PB/Gent complex is used in combination with MW thermal therapy (MTT), MW dynamic therapy (MDT), and chemotherapy (CT) to treat acute osteomyelitis infected with *S. aureus*. The powerful antibacterial effect of the PLGA/Fe₃O₄/PB/Gent is determined by the synergistic effects of heat and reactive oxygen species (ROS) generated by the Fe₃O₄/PB nanoparticles under MW irradiation and the effective release of Gent at the infection site via magnetic targeting. The antibacterial mechanism of the PLGA/Fe₃O₄/PB/Gent under MW irradiation is analyzed using bacterial transcriptome RNA sequencing. The MW-induced heat and ROS reduce the activity of protein transporters on the bacterial membrane, impair the transport of various ions, and accelerate phosphate metabolism. This cascade leads to increased bacterial membrane permeability, damage to ribosomes and DNA, and efflux of intracellular proteins, thus effectively killing the bacteria both in vitro and in a rodent osteomyelitis model, presenting a novel non-invasive strategy for deep-tissue infection therapy.

Key words: osteomyelitis, microwave therapy, Prussian blue, reactive oxygen species, magnetic targeting, synergistic antibacterial therapy

Introduction: *Staphylococcus aureus* osteomyelitis is a deep-seated bone infection notorious for its high recurrence and resistance to treatment, primarily due to biofilm formation and limited antibiotic penetration. Photothermal and photodynamic therapies, while effective for superficial infections, fail in this context due to the poor penetration depth of light. Microwave irradiation, with its superior tissue penetration, offers a promising physical modality. However, its efficacy relies on efficient energy transducers. Herein, we designed a magnetically targetable, microwave-responsive nanocomposite (PLGA/Fe₃O₄/PB/Gent). The core innovation lies in the interface/dipole polarized Fe₃O₄/PB nanoparticles,

which serve not only as a magnetically guidable carrier but also as a potent microwave sensitizer capable of concurrently generating localized heat (for MTT) and reactive oxygen species (for MDT). Encapsulating these drug-loaded nano-sensitizers within a biodegradable PLGA matrix enables sustained release and protection. We hypothesize that under medical microwave irradiation, this system will synergistically deliver MTT, MDT, and targeted chemotherapy (CT) to the infection site, effectively disrupting biofilms and eradicating bacteria through a multi-mechanistic attack, as elucidated by bacterial transcriptomic analysis.

Materials & Methods:

1. Synthesis of Fe₃O₄/PB/Gent NPs: Fe₃O₄ magnetic nanoparticles were synthesized via a solvothermal method. A Prussian blue (PB) shell was grown in situ on the Fe₃O₄ surface. Gentamicin (Gent) was loaded onto the nanoparticles via electrostatic adsorption and coordination, forming Fe₃O₄/PB/Gent.

2. Fabrication of PLGA/Fe₃O₄/PB/Gent Complex: The Fe₃O₄/PB/Gent nanoparticles were encapsulated into poly(lactic-co-glycolic acid) (PLGA) using a double emulsion-solvent evaporation method to form monolithic composite microspheres.

3. Material Characterization: Size, morphology, and structure were analyzed by TEM, SEM, XRD, and FTIR. Magnetic properties were measured using VSM. Drug loading and in vitro release profiles were quantified via HPLC.

4. Microwave-Responsive Properties: The temperature rise (for MTT evaluation) and ROS generation (using DCFH-DA probe for MDT evaluation) of the composite under 2.45 GHz medical microwave irradiation at various power densities were systematically measured.

5. In Vitro Antibacterial and Anti-biofilm Studies: The synergistic bactericidal effects of MTT+MDT+CT against planktonic and biofilm-embedded *S. aureus* were assessed by colony counting, Live/Dead staining, and SEM observation of bacterial morphology.

6. Transcriptomic Analysis: *S. aureus* treated with PLGA/Fe₃O₄/PB/Gent under MW irradiation was subjected to RNA sequencing to analyze differentially expressed genes and elucidate the antibacterial mechanism at the molecular level.

7. In Vivo Osteomyelitis Therapy: A rat model of acute *S. aureus* osteomyelitis was established. The PLGA/Fe₃O₄/PB/Gent microspheres were administered via intravenous injection with an external magnet placed

over the infected femur for magnetic targeting. Transcutaneous microwave irradiation was applied periodically. Efficacy was evaluated by micro-CT (bone destruction), histological staining (H&E, Gram), bacterial burden count, and systemic toxicity assessment.

Results & Discussion:

1. Material Design and MW-Activated Properties:

Successful fabrication of the core-shell $\text{Fe}_3\text{O}_4/\text{PB}$ structure and its PLGA encapsulation was confirmed. The composite exhibited strong superparamagnetism, enabling effective magnetic targeting. Under MW irradiation, it demonstrated rapid and efficient heating ($\Delta T > 30^\circ\text{C}$) and significant ROS generation, confirming its dual MTT/MDT capability. Gent release was significantly accelerated by MW-induced hyperthermia.

2. Potent Synergistic Antibacterial Efficacy *In Vitro*:

The combination treatment (PLGA/ $\text{Fe}_3\text{O}_4/\text{PB}/\text{Gent}$ + MW) showed superior efficacy compared to any single or dual therapy mode (MTT, MDT, or CT alone). It achieved >99.9% reduction in planktonic bacteria and effectively eradicated mature biofilms, demonstrating a clear synergistic effect.

3. Mechanism Elucidated by Transcriptomics:

RNA-seq analysis provided a pivotal insight into the antibacterial mechanism. MW-induced heat and ROS from $\text{Fe}_3\text{O}_4/\text{PB}$ led to widespread bacterial metabolic dysregulation. Key findings included: (i) Downregulation of genes encoding membrane protein transporters (for ions, amino acids), impairing nutrient uptake and homeostasis. (ii) Disruption of phosphate metabolism, affecting energy cycles. (iii) Damage to ribosomal RNA and DNA replication machinery, indicated by stress response gene upregulation. (iv) Increased membrane permeability, corroborated by the upregulation of efflux pump genes and protein leakage assays. This multi-target attack explains the potent bactericidal effect.

4. Effective Treatment of *In Vivo* Osteomyelitis:

The magnetically targeted PLGA/ $\text{Fe}_3\text{O}_4/\text{PB}/\text{Gent}$ complex successfully accumulated at the infection site. With non-invasive MW irradiation, the treatment group showed near-complete bacterial clearance, significant reduction in bone abscesses and inflammatory infiltration in histology, and notable preservation of bone architecture in micro-CT, far outperforming the control and free Gent groups. No significant systemic toxicity was observed.

Conclusions: We have developed a novel magnetically targetable, microwave-responsive nanocomposite (PLGA/ $\text{Fe}_3\text{O}_4/\text{PB}/\text{Gent}$) that integrates microwave thermal therapy (MTT), microwave dynamic therapy (MDT), and antibiotic chemotherapy (CT) for the non-invasive treatment of deep-tissue osteomyelitis. The interface/dipole polarized $\text{Fe}_3\text{O}_4/\text{PB}$ core acts as an

efficient MW sensitizer, enabling synergistic heat and ROS generation. Bacterial transcriptome analysis uniquely revealed that the combined MW/ROS stress cripples bacterial viability by disrupting membrane transport, ion homeostasis, and core biomolecular synthesis. This work not only presents a highly effective therapeutic platform but also provides an in-depth molecular-level understanding of its action mechanism, paving the way for next-generation physical-field-enhanced antimicrobial strategies.

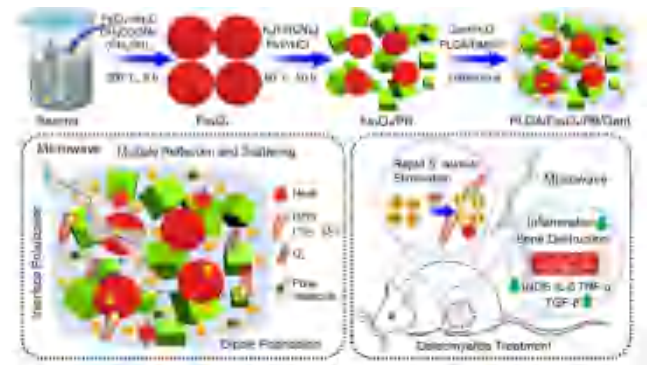


Fig. 1. Schematic diagram of microwave-responsive magnetically targeted composite PLGA/ $\text{Fe}_3\text{O}_4/\text{PB}/\text{Gent}$ combined with MTT/MDT/CT for eradication of acute osteomyelitis infected by *S aureus*.

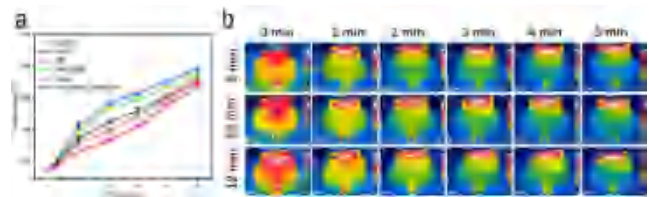
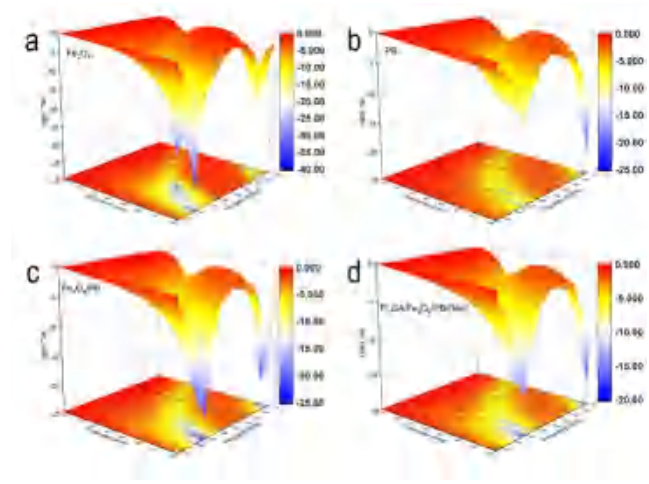


Fig. 2. (a) Microwave heating curves of Fe_3O_4 , PB, $\text{Fe}_3\text{O}_4/\text{PB}$, Gent and PLGA/ $\text{Fe}_3\text{O}_4/\text{PB}/\text{Gent}$; (b) microwave thermal test of PLGA/ $\text{Fe}_3\text{O}_4/\text{PB}/\text{Gent}$ at different pork tissue thickness.



[illegible]

a

GO Enrichment Analysis (PF02, WW, Venn, Control, WW, Control)

b

GO Enrichment Analysis (PF02, WW, Venn, Control, WW, Control)

Figure 2 displays two horizontal bar charts, (a) and (b), showing GO enrichment analysis results. Chart (a) represents the 1000 most downregulated genes, and chart (b) represents the 1000 most upregulated genes. The y-axis lists various biological processes, and the x-axis shows the number of genes (0 to 100). The bars are color-coded: red for 'Lipid Metabolism', blue for 'Protein Metabolism', green for 'Carbohydrate Metabolism', and purple for 'Other'. In chart (a), 'Lipid Metabolism' and 'Protein Metabolism' show significant enrichment. In chart (b), 'Lipid Metabolism' and 'Protein Metabolism' also show significant enrichment, with 'Carbohydrate Metabolism' also being prominent.

a

Control Gent PLGA/Fe₃O₄/PB/Gent PLGA/Fe₃O₄/PB/Gent+MW

X-ray images

b

Control Gent PLGA/Fe₃O₄/PB/Gent PLGA/Fe₃O₄/PB/Gent+MW

Masson's trichrome staining

Alizarin Red staining

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3D Bioprinting of Bone Organoids Using Bone Matrix-Inspired Bioinks for Bone Regeneration

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Key words: Hydroxyapatite; 3D Bioprinting; Bone Matrix-Inspired; Bioinks; Bone Organoids; Bone Defect Repair

Introduction: Critical-sized bone defects remain challenging to repair due to insufficient vascularization, incomplete osteogenesis, and dysregulated immune microenvironments, highlighting the need for innovative regenerative strategies. Bone organoids—three-dimensional microtissue units that recapitulate aspects of bone structure and function—have shown promising in vitro osteogenic potential and preliminary in vivo repair capability. Inspired by the organic–inorganic hybrid architecture of native bone extracellular matrix, we developed a series of bone matrix–mimicking composite bioinks and successfully fabricated large-scale bone organoids with intrinsic self-mineralization capacity. Building upon this platform, we further incorporated functional components such as aloe vera extract and nanoclay, and employed 3D bioprinting to construct multifunctional bone organoids possessing integrated self-mineralization, immunomodulatory, angiogenic, and osteoinductive properties. Their regenerative performance in bone defect repair was systematically evaluated.

Materials & Methods: A series of bioinks were developed to construct bone organoids. For example, GelMA/AlgMA served as the base matrix, supplemented with hydroxyapatite particles to enhance osteoconductivity, aloe vera extract to introduce endogenous immunomodulatory activity, and nanoclay to optimize the rheological behavior and structural stability of the bioinks. Extrusion-based 3D bioprinting was used to fabricate macroscopic honeycomb scaffolds resembling Haversian canal–like networks. For in vitro studies, human bone marrow mesenchymal stem cells (hBMSCs) and human umbilical vein endothelial cells (HUVECs) were co-encapsulated to assess cell viability, osteogenic differentiation, vascular formation, and macrophage polarization. For in vivo evaluation, printed bone organoids were implanted into critical-sized calvarial defects in SD rats, followed by μ CT, histological staining, and immunohistochemistry at 8 weeks to assess bone regeneration.

Results & Discussion: The printed constructs exhibited excellent pore interconnectivity and mechanical integrity, supporting uniform cell adhesion and distribution. In vitro results demonstrated significantly enhanced osteogenic gene expression and mineralization of hBMSCs, as well as improved capillary-like network

formation by HUVECs. The aloe vera–based matrix

promoted M2 macrophage polarization and reduced pro-inflammatory cytokine expression, establishing a pro-regenerative immune microenvironment. In vivo, the bioprinted organoids markedly increased new bone volume, defect bridging, and vascular density, with superior tissue integration compared to GelMA controls.

Conclusions: This study introduces a family of bone matrix–inspired composite bioinks enabling the fabrication of bone organoids with integrated osteogenic, angiogenic, and immunoregulatory functions. The multifunctional organoids provide a promising and effective strategy for the treatment of complex bone defects in tissue engineering.

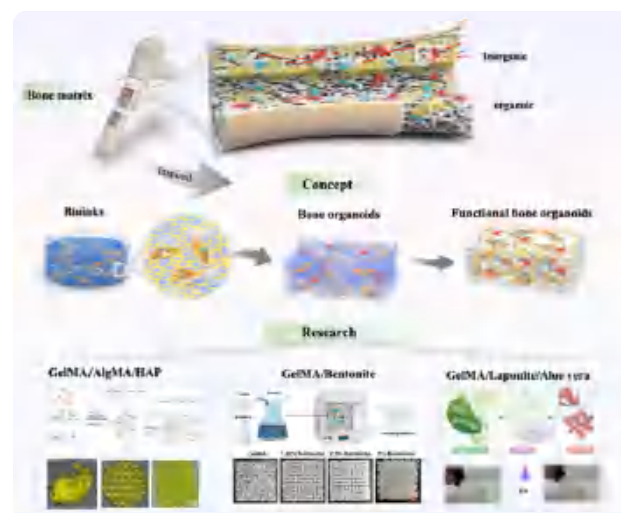


Fig. 1. Schematic illustration of bone–matrix–inspired composite bioinks used to engineer multifunctional bone organoids.

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M2 macrophage-derived exosome-functionalized fibrous scaffolds regulate the foreign body response and the coupling of angio/osteoclasto/osteogenesis

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Key words: Exosome, fibrous scaffold, FBR, angiogenesis, osteogenesis

Introduction: The foreign body response (FBR) is a complex immunological process. Designing scaffolds that can regulate the innate immune response and promote vascularized bone regeneration holds promise for bone tissue engineering.

Materials & Methods: Combining physical and biological cues into the scaffold, M2 macrophage-derived exosome-functionalized electrospun nanofibrous scaffold (PP-Exo) was fabricated. The cellular uptake of exosomes by target cells and its effects on cell functions such as tube formation by endothelial cells, osteogenic differentiation of BMSCs, and macrophage polarization *in vitro*. The FBR mediated by exosome-functionalized scaffolds was studied by subcutaneous implantation in mice. This study investigated whether M2 macrophage-derived exosomes functionalized nanofibrous scaffold could mediate vascularized bone regeneration via rat cranial bone critical-sized defects model.

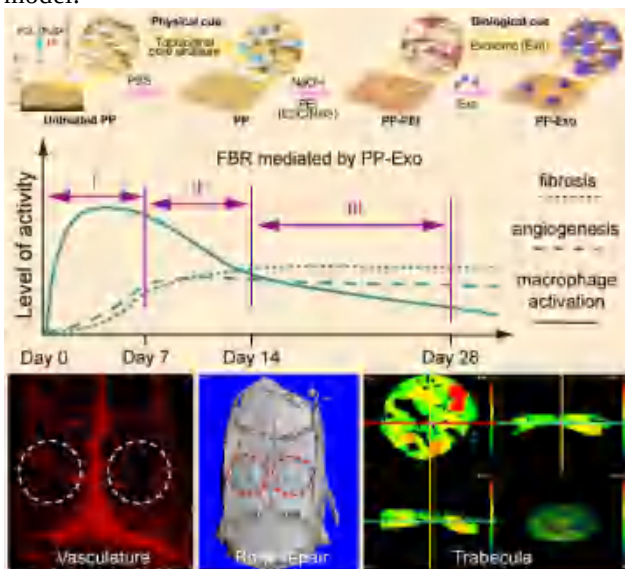


Fig.1. Schematic diagram of the preparation of PP-Exo scaffolds and their effects in regulating foreign body responses and mediating vascularized bone regeneration.

Results & Discussion: M2 macrophage-derived exosomes were successfully immobilized on the

electrospun nanofibrous scaffold by surface modification with cationic PEI. *In vitro* cell experiments showed that exosomes could promote tube formation of HUVECs, osteogenic differentiation of BMSCs, and anti-inflammatory macrophage polarization of RAW264.7. Animal experiments demonstrated that the exosome-functionalized fibrous scaffolds efficiently dampened the inflammatory response via the activation of M2 macrophages to enable sustained anti-dysfunctional angiogenesis and anti-fibrotic development. Micro-CT analysis demonstrated that the exosome-functionalized PP-Exo scaffolds were comparable with the commercial Bio-Gide in terms of bone augmentation and trabecular microarchitecture, almost closing the bone defects after 10 weeks of repair. Histological staining results indicated that the PP-Exo scaffold showed a significantly higher frequency of the type H bone vessel subtype, coupling angiogenesis, and osteogenesis.

Conclusions: M2 macrophage-derived exosomes could activate anti-inflammatory M2 macrophages to direct the development of a regenerative immune niche during the FBR. The PP-Exo scaffold could regulate the coupling of neoangiogenesis, osteogenesis, and osteoclastogenesis by stimulating the formation of type H vessels, ultimately mediating vascularized bone regeneration. We believe that these findings will contribute to the design and new paradigm of scaffolds in orthopedics and maxillofacial surgery.

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Mesenchymal Stem Cells and Macrophages Crosstalk for Vascularized Bone Regeneration

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Key words: Mesenchymal stem cells, Macrophages, Co-culture, Bone regeneration

Introduction: Conventional bone regeneration strategies are often hindered by insufficient vascularization and a lack of robust osteogenic signaling. Although mesenchymal stem cells (MSCs) are widely used in bone tissue engineering due to their osteogenic capacity, emerging evidence highlights the indispensable role of macrophages in orchestrating both angiogenesis and osteogenesis. Therefore, co-culturing MSCs with macrophages is emerging as a promising strategy to achieve more complete and functional bone regeneration by leveraging the strengths of both.

Materials & Methods: Macrophages and MSCs were co-cultured in vitro and their reciprocal effects were investigated by ALP activity, alizarin red staining and cytokine quantification with ELISA. A three-dimensional co-culture system was further established by encapsulating macrophages and MSCs in a gelatin methacryloyl (GelMA) hydrogel. This construct was implanted into femoral bone defects in a rat model to assess its regenerative efficacy. Proteomic analyses were conducted to identify key molecular mediators between the crosstalk between MSCs and macrophages, followed by functional validation using siRNA knockdown techniques.

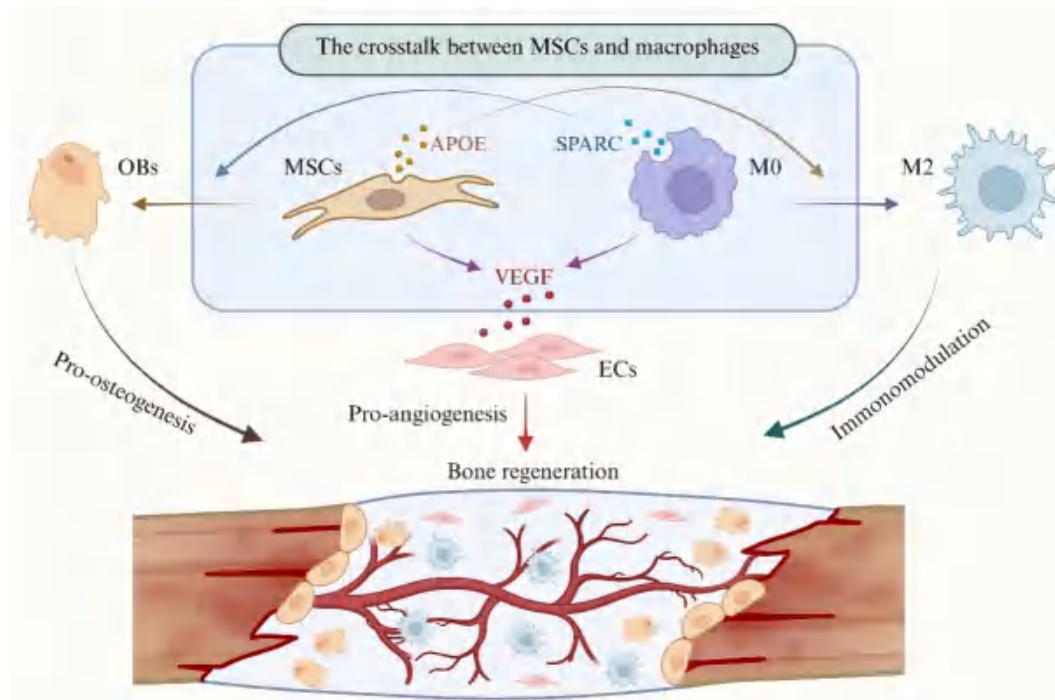
Results & Discussion: Our in vivo results demonstrated that the co-culture constructs, irrespective of the specific macrophage-to-MSC ratio, significantly enhanced early-stage vascularization and bone formation compared to constructs containing either cell type alone. Proteomic analysis revealed a reciprocal molecular axis underlying this synergy whereby macrophage-derived apolipoprotein E (APOE) was identified as a key promoter of MSC osteogenic differentiation, while MSC-secreted SPARC was crucial for driving macrophage polarization toward a pro-regenerative M2 phenotype. Functional knockdown experiments confirmed the essential roles of both APOE and SPARC in this bidirectional crosstalk.

Conclusions: This study establishes a novel co-culture-based strategy that effectively leverages the synergistic crosstalk between MSCs and macrophages to promote vascularized bone regeneration. In addition, an APOE/SPARC signaling axis was demonstrated to coordinate osteogenesis and immunomodulation.

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Fig. 1.



Aqueous-responsive self-contractive and self-compressive silk screws

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Key words: silk fibroin, biomaterials, shape memory, bone regeneration

Introduction: Shape memory materials (SMMs) show promises in medical devices, but traditional thermally responsive SMMs have issues like imprecise temperature control and tissue damage risk [1]. Silk fibroin, a natural biomaterial derived from silk, has emerged as an ideal candidate in the field of SMMs due to its exceptional physicochemical properties and biocompatibility. Here, we manufactured aqueous-responsive self-contractive and self-compressive silk screws (SCCSSs) for internal fixation of fractures using a methanol-free process.

Materials & Methods: A rigid silk fibroin material was obtained by slowly evaporating a silk fibroin solution dissolved in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) under high-humidity conditions. The material was then endowed with super-contraction properties through a wet-stretching process and subsequently machined into screws. The mechanical properties of SCCSSs were conducted using a tensile testing machine. As an application example, we implanted SCCSSs into the medial malleolus fracture site of beagles. The screws contracted under the influence of body fluids and blood, generating contractile stress and promoting fracture healing.

Results & Discussion: Figure 1. a shows photos and application illustrations of SCCSSs. The SCCSSs exhibit a unique switch-on behaviour, where super-contraction is triggered only upon reaching a critical hydration threshold (Figure 1.b). This property ensures that the SCCSSs do not undergo premature contraction when exposed to fluids such as saline during surgical implantation. Four hours after hydration, the SCCSSs exhibited significant axial contraction and radial expansion (Figure 1.c), which helped promote fracture closure and enhance contact stability with surrounding bone tissue. The screws demonstrated good mechanical and aqueous-responsive contraction properties (Figure 1.d). When implanted at the medial malleolus fracture site in a beagle dog, a significant reduction in the fracture gap was observed on X-ray three days postoperatively (Figure 2. a, b). Three months postoperatively, compared with the normal silk screws, the SCCSSs showed good osteogenic properties (Figure 2.c).

Conclusions: This paper develops aqueous-responsive self-contractive and self-compressive silk screws (SCCSSs) with excellent mechanical properties. When implanted at the fracture site, it can spontaneously contract under the influence of blood and body fluids, promoting fracture healing. The emergence of SCCSSs broadens the application prospects of silk fibroin materials in the biomedical field.

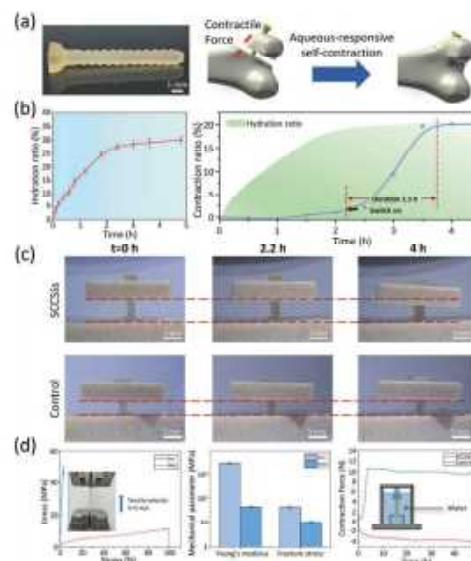


Fig. 1. (a) Schematic diagram of the application of SCCSSs (b) Hydration and contraction ratios of SCCSSs (c) Photographs of the contraction process of SCCSSs (d) Mechanical properties of SCCSSs.

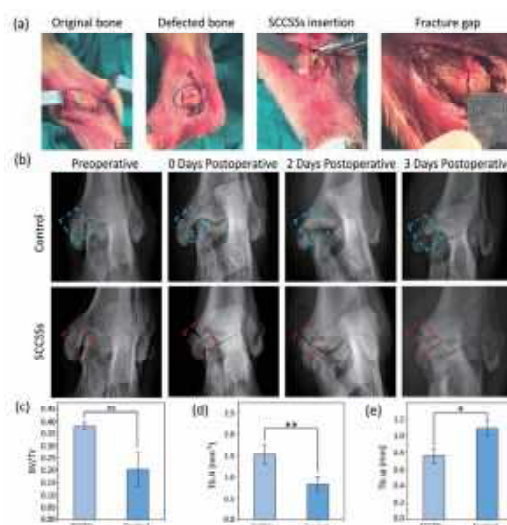


Fig. 2. (a) Surgical implantation process of SCCSSs (b) Comparison of X-ray images of SCCSSs and normal silk screws within three days post-surgery (c) Bone volume fraction (BV/TV) (d) Trabecular number (Tb.N) (e) Trabecular separation (Tb.Sp).

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A dynamic enhanced electrical stimulation system coordinates non-neural cells via single-input cues for neuro-vascularized bone regeneration

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Introduction: The interplay between angiogenesis and neurogenesis is critical for osteogenesis, yet its regulatory mechanisms remain poorly understood. Electrical stimulation has emerged as a promising strategy for bone regeneration; however, divergent electrophysiological responses between neural and non-neural cells limit its effectiveness. This study presents a dynamically enhanced electrical stimulation system designed to promote bone regeneration through a single-input modality, independent of direct neural signaling.

Key words: Electric stimulation, Single-input bioelectronic regulation, Conductive polyurethane membranes, Neuro-vascularized regeneration

Materials & Methods: A bioelectronic platform was developed by integrating conductive aniline trimer-based polyurethane (FPAT) membranes with non-invasive electrical stimulation (ES). Finite element analysis was used to evaluate the generated electric potentials. *In vitro* studies assessed the responses of mesenchymal stem cells (MSCs) and endothelial cells. *In vivo* evaluation was performed using periosteum-deficient murine femoral defect models, including denervated conditions. Bone regeneration was quantified by longitudinal analysis of callus formation.

Results & Discussion: Finite element analysis confirmed that the FPAT/ES system produced targeted electric potentials capable of simultaneously modulating MSCs and endothelial cells. The optimized FPAT1/ES protocol significantly enhanced vascularized bone regeneration by activating calcium signaling and inducing paracrine neurotransmitter secretion from MSCs. *In vivo*, callus volume ratios increased from 53.13% at 4 weeks to 101.94% at 8 weeks. Complete neurovascular bone regeneration was achieved within 8 weeks in periosteum-deficient defects, with outcomes comparable to autograft transplantation. Denervated models demonstrated that electrical stimulation promotes osteogenesis independently of direct neural input.

Conclusions: Dynamically enhanced electrical stimulation using FPAT membranes and ES effectively promotes vascularized bone regeneration without neural dependence. This bioelectronic strategy offers mechanistic insight into electro-sensitive tissue repair and a promising therapeutic approach for complex bone defects.

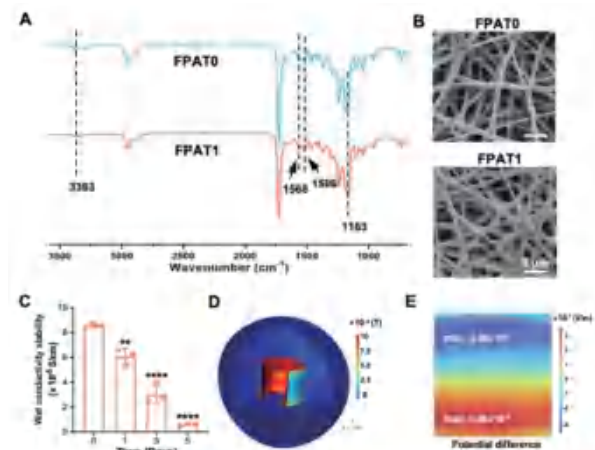


Fig. 1. Characterization of FPAT membranes and finite element analysis of FPAT membranes combined with ES.

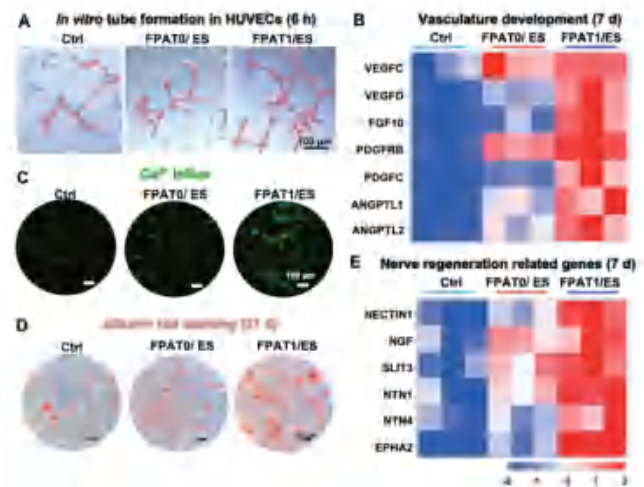


Fig. 2. *In vitro* evaluation of angiogenesis and osteogenesis in HUVECs and MSCs.

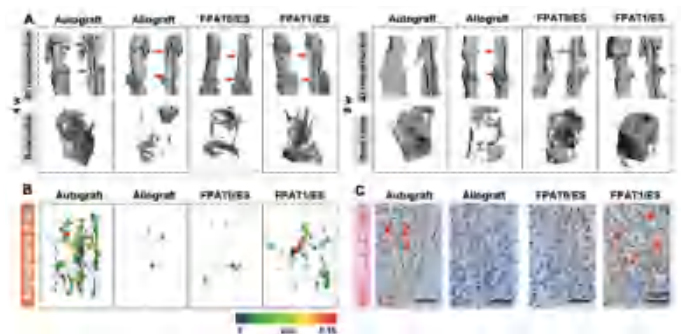


Fig. 3. *In vivo* healing efficacy of neuro-vascularized bone regeneration.

Gradient intrafibrillar mineralized collagen Scaffold Enhances Functional Osteochondral Regeneration through SCRG1⁺ Progenitor Cell Recruitment

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The repair of osteochondral defects remains a critical challenge in orthopedic surgery. A key limitation lies in the inability of current biomimetic scaffolds to simultaneously replicate macro- and microscale structural features, hindering functional tissue regeneration. Herein, by the self-assembly of ultra-small calcium phosphate polymer-induced liquid-precursor (CaP-PILP) and collagen molecule, we engineered a biomimetic scaffold featuring gradient mineral distribution with intrafibrillar mineralization. In a New Zealand rabbit model, the scaffold significantly enhanced simultaneous regeneration of cartilage and subchondral bone tissues in New Zealand rabbit model. Within the regenerative microenvironment, we found that the scaffold promotes osteochondral repair, which is associated with activation of ERK/TGF- β signaling and an increased commitment of SCRG1⁺ progenitor cells toward osteochondral lineages. Collectively, the integrated gradient mineralization scaffold builds the gradient microstructure of the natural osteochondral interface through biomimetic construction, achieving the dual functional integration of physical support and biological induction, providing an innovative treatment strategy that combines biomimetic reconstruction and functional remodeling for osteochondral defect repair.

Chiral Nanotopography Potentiate Stem Cell-Derived Extracellular Vesicles to Enhance Osteogenesis

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Key words: Extracellular vesicle, Chiral nanotopography, Stem cell, Bone regeneration.

Introduction: Stem cell-secreted extracellular vesicles (EVs) are promising cell-free therapies for tissue regeneration, such as bone repair. However, how mirrored asymmetric surface programs the composition of EVs derived from mesenchymal stem cells (MSCs) and selectively enhances osteogenic differentiation remains poorly understood.¹

Materials & Methods: (1) Chiral nanotopography synthesis & characterization: Three types of nano topography with controlled chirality, including left-handed, right-handed, and achiral racemic structure, were synthesized using a glancing angle deposition (GLAD) system. The physicochemical properties of the structure were characterized via circular dichroism (CD) and SEM (Fig. 1a-d). (2) EV isolation and characterization: EVs were harvested from MSCs cultured on different substrates in an EV-depleted medium over 14 days using SEC (Izon ICO-35). The EVs were characterized by TEM and NTA (Fig. 1e), Exo-Check Exosome Antibody Array (Fig. 1f), and miRNA sequencing (Fig. 1g and h). (3) *In vitro* studies: MSCs were treated with each EV type. Osteogenic marker expression was quantified by qPCR and histological staining. (4) *In vivo* tests: Critical-sized bone defects (CSBDs, 3 mm) in femora were created in 12-week-old male Sprague-Dawley rats (n = 5/group). Bone regeneration was assessed via micro-CT and histological analyses.

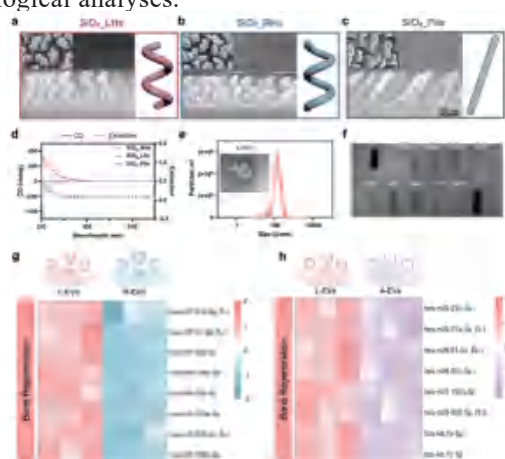


Fig. 1. Characterization of chiral topological structures and EVs. SEM images of chiral topological structures: (a) SiO₂-LHs, (b) SiO₂-RHs, and (c) SiO₂-Pils. Scale bar = 100 nm. (d) CD and extinction spectra of chiral topological structures. (e) TEM images and NTA results of L-EVs. Scale bar = 100 nm. (f) Exo-Check exosome antibody array results. miRNA

sequencing results in (g) L-EVs vs R-EVs. (h) L-EVs vs A-EVs.

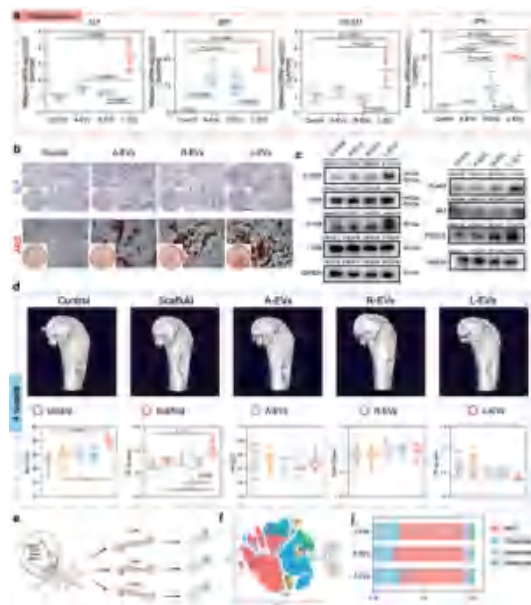


Fig. 2. In vitro and in vivo evaluation of EVs. (a) Osteogenic marker gene expression in human MSCs treated with different EVs. (b) ALP and ARS staining. Scale bar = 2 mm (inset) and 500 μ m (enlarged view). (c) Western blot results. (d) 3D reconstructed micro-CT images and quantitative analysis. (e) Schematic of sample preparation for single cell sequencing. (f) TSNE visualization. (g) Proportion of osteogenesis-related cells.

Results & Discussion: *In vitro*, L-EVs significantly upregulated osteogenic markers (Fig. 2a), increased mineral deposition (Fig. 2b), and enhanced p38/ERK and PI3K/Akt signaling (Fig. 2c). *In vivo*, scaffolds with L-NPs resulted in the fastest bone regeneration, as evidenced by the greatest bone volume and most robust tissue integration (Fig. 2d). Single-cell sequencing results revealed a higher proportion of osteocytes in the L-EVs group (Fig. 2e-j).

Conclusions: We demonstrate for the first time that nanoscale chiral topologies profoundly influence stem cell-derived EVs, with SiO₂-LHs endowing L-EVs with superior osteogenic potential. This enantioselective activation of osteogenic signaling underscores the strategic significance of chirality as a key design parameter for next-generation regenerative biomaterials.

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Time-Sequential and Multi-Functional 3D printing scaffold for Repairing of Challenging bone defect

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Key words: bone regeneration, MgO₂/PLGA 3D printing scaffold, time-sequential and multi-functional

Introduction: Bone defects caused by trauma, infection, tumor, osteoporosis, etc., remain major challenge. Osteosarcoma (OS) is the most commonly occurring primary bone malignant tumor. The clinical postsurgical OS treatment faces big challenges for the staged therapeutic requirements of early anti-tumor, anti-bacterial, and long-lasting osteogenesis. However, the traditional bone defect repair materials, such as autogenous bone, allogeneic bone, artificial bone, have obvious limitations and are insufficient in antibacterial, antitumor and osteogenic activities. Therefore, it is of great significance to develop new treatment options to suppress tumor recurrence, inhibit bacterial infection, and promote bone regeneration in a time sequential way. Thus, we designed MgO₂/PLGA composite scaffolds by low-temperature rapid prototyping (LT-RP) 3D printing technology to realize the sequential release of H₂O₂ and Mg²⁺ to exert multiple functions. Fig.1 is a schematic representation of the preparation of MgO₂/PLGA scaffolds and their mechanism for postsurgical osteosarcoma treatment.

Materials & Methods: First, MgO₂ was compounded with PLGA and dissolved in 1,4-dioxane. A series of MgO₂/PLGA scaffolds with different mass ratios were fabricated via 3D printing method. Then the composition, structure, mechanical properties, and degradation performance of the scaffolds were characterized. Second, in vitro cellular and molecular biology assays were conducted to investigate the biocompatibility, osteogenic activity, and antitumor properties of the scaffolds. Finally, in vivo animal experiments were performed to evaluate the scaffolds' efficacy in inhibiting tumor growth and promoting bone defect repair.

Results & Discussion: The MgO₂/PLGA scaffolds with different MgO₂ contents were prepared and characterized. The scaffold with 20 wt% MgO₂ (20MP) is verified with desired mechanical properties, as well as exhibits staged release behavior of bioactive elements with hydrogen peroxide (H₂O₂) release for the first 3 weeks, and long-lasting Mg²⁺ release for 12 weeks. The 20MP scaffold was demonstrated to exert multiple functions in a time-sequential manner. In the first stage, the released H₂O₂ efficiently inhibited bacterial infection, and suppressed tumor recurrence through CDT-mediated cancer apoptosis and ferroptosis, along with activating anticancer immune microenvironment by M1 polarization of macrophages. In the second stage, the released Mg²⁺ could efficiently promote

differentiation and mineralization of BMSCs by activating Wnt3a/GSK-3β/β-catenin signaling pathway and creating osteopromotive immune microenvironment by M2 polarization of macrophages. The therapeutic efficiency was further verified in an OS postsurgical recurrence mouse model and bone defect rat model in vivo. The comprehensive studies demonstrated that the as-designed MgO₂/PLGA composite scaffolds exhibited excellent anti-tumor, antibacterial, and osteogenic activities, highlighting the great potential of our novel strategy for clinical applications in postsurgical OS treatment.

Conclusions: In summary, we designed MgO₂ as the multi-functional component to fabricate MgO₂/PLGA composite bone scaffolds by 3D printing. The time-sequential release of ROS and Mg²⁺ in the scaffolds led to the time-sequential dynamic realization of their different functions. In the ROS-dominated microenvironment, the effect of ROS was more pronounced than that of Mg²⁺, and the anti-tumor function was achieved by promoting apoptosis and ferroptosis in tumor cells. And in the stage of Mg²⁺ dominated microenvironment, the effect of Mg²⁺ displays the function of promoting osteogenesis by promoting the M2-type polarization of macrophages and the differentiation of osteoblasts. It is concluded that this biodegradable composite scaffold, endowed with time-sequential and multifunctional bioactivities, exhibits great clinical application potential for repairing intractable bone defects after surgical resection of osteosarcoma.

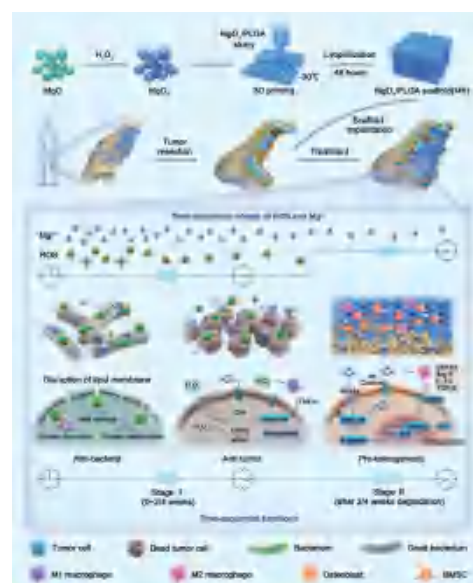


Fig. 1. The preparation of MgO₂/PLGA scaffolds and mechanism for postsurgical osteosarcoma treatment.

Multifunctional Selenium-Polyurea Coated Zinc Alloys Sequentially Orchestrate Immune-Osteogenic Microenvironment for Bone Regeneration

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Key words: selenium-containing polyurea, degradable zinc alloy, osteogenesis, immune regulation

Introduction: Large bone defects remain a clinical challenge. While autologous bone grafting causes donor-site injury, and titanium scaffolds require secondary removal, biodegradable zinc alloys offer promising alternatives. However, burst release of Zn^{2+} triggers inflammation and impedes peri-implant bone formation. Alloying and surface modifications only partially alleviate Zn^{2+} burst and face issues like complex fabrication, poor stability, weak interfacial bonding. Furthermore, Current coatings can enhance osteogenic activity, but fail to modulate the bone immune microenvironment, which is essential for osseointegration of implants. Thus, a simple, stable surface modification that limits Zn^{2+} release while synchronously regulating immunity and osteogenesis is urgently needed. Selenium is an essential element that participates in antioxidant defense and immune regulation but requires controlled release to avoid toxicity. Here, a new selenium-containing polyurea (SePUA) was designed. It suppresses Zn^{2+} burst, controls selenium release, and improves surface hydrophilicity. This multifunctional interface orchestrates the immune-osteogenic microenvironment by suppressing early inflammation, advancing M2 macrophage polarization, and enhancing MSC osteogenesis, thereby promoting bone regeneration around zinc alloys.

Materials & Methods:

1. Fabrication of SePUA-Zn0.8Li: Zinc alloys were sanded, ultrasonically cleaned, and immersed in a solution of SePUA for 3 h, and air-dried.
2. Characterization: TOF-SIMS, SEM, ICP, water contact angles and nano-scratching tests were used to analyse surface morphology and degradation. Cytocompatibility and osteogenic potential of hBMMSCs and immune response of macrophages were evaluated.
3. *in vivo* Studies: Rat femoral defect models were used to assess bone regeneration at 4 and 8 weeks, with micro-CT, histological staining, and single-cell sequencing analysis to explore mechanisms.

Results & Discussion:

1. The SePUA coating demonstrated uniform selenium distribution, improved surface hydrophilicity, and strong mechanical adhesion on Zn0.8Li alloy.
2. SePUA coating effectively modulated the degradation of Zn0.8Li alloy by suppressing the burst release of Zn^{2+} , improving corrosion resistance, while demonstrating

favorable biocompatibility.

3. *in vitro*, SePUA modification enhanced the osteogenic differentiation of hBMMSCs and exerted immunomodulatory effects by reducing intracellular ROS and shifting macrophages polarization to anti-inflammatory M2.

4. SePUA modification effectively enhanced peri-implant bone regeneration *in vivo*. Mechanically, SePUA-Zn0.8Li inhibited chemotaxis and maturation of neutrophil, promoted M2 polarization of macrophages by activating the KEAP1-NRF2-SEPP1 axis and suppressing NF- κ B p65 pathway, and upregulated NR2F2 to enhance hBMMSCs stemness and promote osteogenic differentiation.

Conclusions: A multifunctional bioactive SePUA was innovatively synthesized, enabling a facile and stable surface modification of zinc alloys and additionally enhancing their surface hydrophilicity. Simultaneously, the multifunctional bioactive SePUA interface integrates Zn^{2+} release control, immunomodulation, and osteogenesis, thereby coordinating immune responses and bone tissue regeneration around zinc-based implants. This innovative surface modification technology overcomes key limitations in the clinical translation of zinc alloys and expands their potential clinical applications.

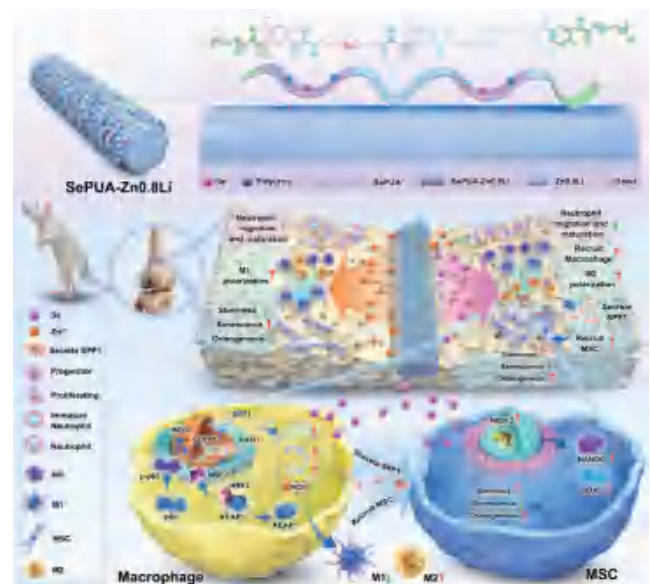


Fig. 1. Conceptual illustration of SePUA-Zn0.8Li construction and mechanism of its promotion on bone regeneration.

Sequential Theragenerative Biomaterials for Postsurgical Osteosarcoma Treatment and Bone Repair

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Key words: Osteosarcoma, sequential bioactivities, theragenerative

Introduction: Osteosarcoma (OS) is the most commonly occurring primary bone malignant tumor. The current clinical standard treatment for bone tumors comprises a combination of neoadjuvant chemotherapy and surgical resection. The bottleneck is that the current clinical strategy does fulfill the time-sequential treatment requirement for postsurgical inhibition tumor recurrence and repairing the bone defect. Therefore, it's of great significance to develop new treatment options to suppress tumor recurrence, inhibit bacterial infection, and promote bone regeneration.

Materials & Methods: Magnesium peroxide (MgO_2) nanoparticle was designed as multi-functional component to fabricate bone scaffolds as the depot of H_2O_2 and Mg^{2+} . To realize the sequential release of H_2O_2 and Mg^{2+} to exert multiple functions, the low-temperature 3D printing technology was employed to fabricate MgO_2/PLGA composite scaffolds with hierarchical pore structures.

The structure, mechanic property, H_2O_2 and Mg^{2+} release of the MgO_2/PLGA with different MgO_2 content was fully characterized. The in vitro anticancer activity was tested with 143B cells, antibacterial property with *E. coli* and *S. aureus*, osteogenic property with human bone mesenchymal stem cells (hBMSCs). And evaluation of in vivo performance with subcutaneous tumor recurrence model, subcutaneous bacterial infection model and rat critical skull defect model.

Results & Discussion: The scaffold with 20 wt% MgO_2 (20MP) is verified with desired mechanical properties, as well as exhibits staged release behavior of bioactive elements. The compressive strength of 20MP is 5.3 ± 0.14 MPa. The degradation of 20MP could release hydrogen peroxide (H_2O_2) for the first 3 weeks, and long-lasting Mg^{2+} release for 12 weeks.

At the first stage, the released H_2O_2 could efficiently inhibit bacterial infection and initiate chemodynamic therapy to induce apoptosis and ferroptosis in tumor cells, along with activating the anticancer immune microenvironment by M1 polarization of macrophages. At the second stage, the Mg^{2+} subsequently enhances bone repair by activating the Wnt3a/GSK-3 β /catenin signaling pathway to promote osteogenic differentiation of hBMSCs and create osteopromotive immune microenvironment by M2 polarization of macrophages.

Conclusions: The multifunctional MgO_2 composite materials can effectively prevent infection, inhibit tumor recurrence, and repair bone defects, representing an innovative integrated treatment strategy for osteosarcoma after surgery.

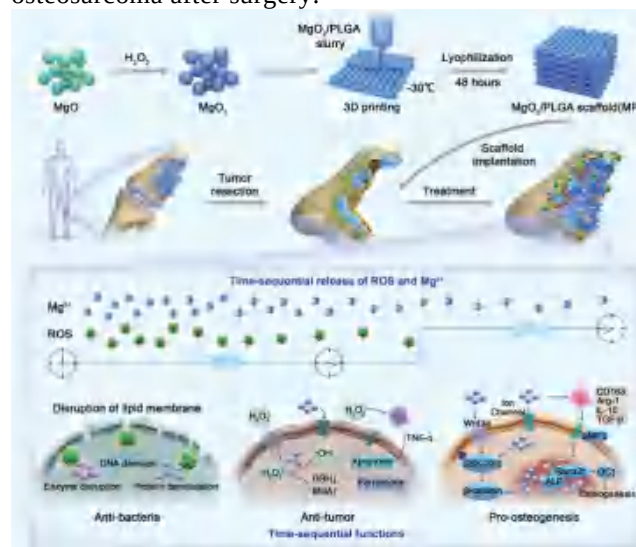


Fig. 1. Schematic representation of the preparation and time-sequential actions of innovative MgO_2/PLGA scaffolds.

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Curvature–Degradation Coupling Drives Cellular Functions and Osteointegration in Additively Manufactured Biodegradable Zn-Mg Scaffolds

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Key words: Biodegradable Zn; bone implants; Curvature

Introduction: Surface curvature is known to be a key regulator of cellular mechanobiology and bone tissue regeneration, yet its interaction with bioactive implant materials remains poorly understood. By introducing Calabi–Yau manifolds and TPMS inspired architectures into additively manufactured biodegradable Zn-Mg scaffolds, this work expands the accessible curvature space and demonstrates that curvature-regulated Zn^{2+} release reshapes cellular responses and enables uniform osteointegration. We believe these findings provide a fundamental framework for integrating geometry and bioactive degradation, with broad implications for the rational design of biodegradable implants, regenerative biomaterials, and architected biosystems.

Materials & Methods: Gyroid and Calabi–Yau manifolds isosurfaces of Zn scaffolds were fabricated using a laser powder bed fusion. Immersion tests were performed in SBF balanced salt solution (37 °C, pH 7.4) for 28 days, following the ASTM-G31-72 standard. Simulations were performed with a uniform triangular mesh (maximum element size 0.05 mm). The concentration field was obtained from the nodal solutions, and contour plots were generated to visualize the spatial distribution of Zn^{2+} ions. Afterwards, femoral condyle defects were surgically created and implanted with scaffolds of three architectures0.

Results & Discussion:

Results from Ti scaffolds indicate that mean curvature, rather than Gaussian curvature, governs the spatial organization of osteogenesis. Bone formation were mainly concentrated in concave regions with negative mean curvature, whereas convex surfaces exhibited weaker integration. Mechanobiologically, concave surfaces provide stable adhesion sites and enhance cytoskeletal tension, thereby activating downstream signals related to osteogenic differentiation.

While geometry governs osteogenesis in inert materials such as Ti, Biodegradable Zn transforms the curvature variations into spatial gradients of ion release and mineral deposition. The key properties of Zn as a bone implant material contain mechanical strength, biodegradation, and bioactivity. Among them, degradation is the most defining feature of biodegradable metals, as its rate, products, and resulting ion release directly influence both biological responses and mechanical integrity. Extensive alloy design studies have aimed to balance these properties, yet

conventionally processed bulk Zn materials still degrade too slowly for clinical applications (Fig.1).

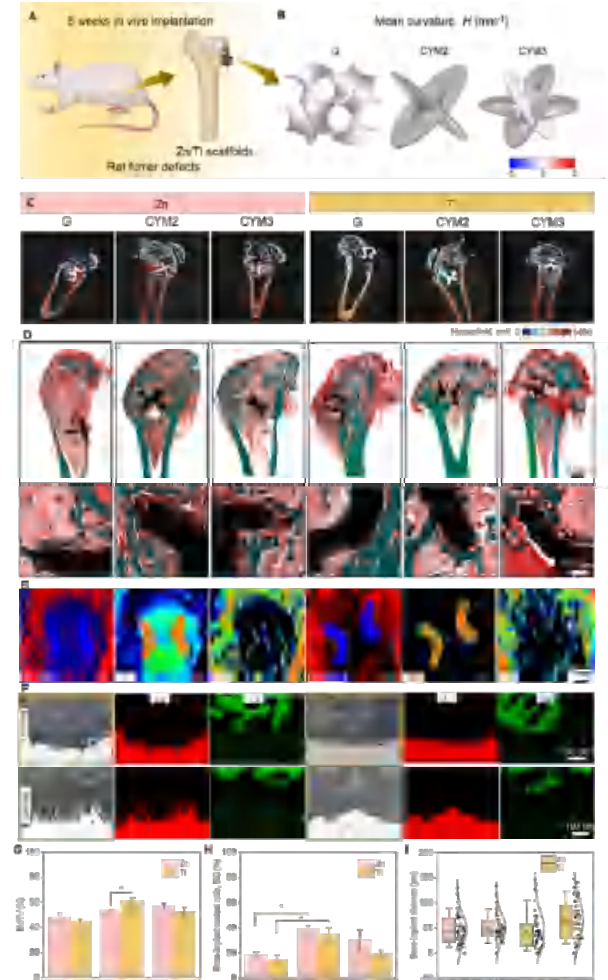


Fig. 1 In vivo evaluation of bone regeneration using Zn and Ti scaffolds.

(a) Schematic illustration of the femoral condyle defect model and implantation procedure. (b) Distribution maps of mean curvature for implanted architectures. (c) Representative micro-CT images showing new bone formation after 8 weeks. (d) Goldner trichrome staining showing mineralized bone (green) and osteoid tissue (orange) surrounding the implants. (e) XRF elemental mapping of bone–implant interfaces. (f) Representative SEM and elemental distribution images at concave and convex regions. (g) Quantitative bone volume fraction (BV/TV) analysis and (h) bone–implant contact ratios for three architectures in Zn and Ti.

Conclusion

In this study, we identified the curvature–degradation coupling effect of Zn scaffolds, which link structural geometry with local biochemical environments and bone regeneration outcomes.

Antioxidant Nanozymes Engineered M2-Exosomes Break the Oxidative Stress–Innate Immune Disorder Loop to Enable Diabetic Bone Regeneration

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Abstract: Diabetic bone defects represent a prototypical microenvironment-driven regenerative failure, in which oxidative stress and immune dysregulation form a self-amplifying inflammatory loop that compromises bone regeneration. Herein, we introduced an engineered exosome ($\text{Mn}_3\text{O}_4@\text{M2E}$) based on antioxidant Mn_3O_4 nanozymes modified M2 macrophage exosome (M2E) that orchestrated redox balance and innate immunomodulation (inhibiting NETs formation and driving macrophages M2 polarization) for comprehensive treatment of diabetic bone defect.

Key words: anti-oxidative stress, immunomodulation, engineered exosomes

Introduction: Accelerating the healing of diabetic bone defects remains a critical challenge to be addressed. The reason is that the extreme pathological microenvironment such as local high glucose, oxidative stress, immune dysregulation and chronic inflammation seriously affecting bone metabolic processes. Therefore, there is an urgent need to develop innovative therapeutic strategies that can improve the pathological microenvironment to accelerate the regeneration and repair of diabetic bone defect.

Exosomes derived from M2 macrophage (M2-Exo) inherit the immunomodulatory functions of maternal cells, enabling them to participate in immune regulation, alleviate inflammatory reactions, thereby reducing pathological damage and accelerating tissue repair. However, given the complexity of the pathological microenvironment and the susceptibility of exosomes to oxidative stress damage, a single intervention strategy based on M2-Exo may have limited efficacy in the repair of diabetic bone defect. Therefore, antioxidant nanozymes engineered M2-Exo is expected to break through the limitations of single intervention, which not only effectively reduces the oxidative damage of the diabetic microenvironment on bioactivity of M2-Exo, but also achieves synergistic treatment through spatiotemporal coupling.

Materials & Methods: Mn_3O_4 was encapsulated with DSPE-PEG-MAL for maleimide functionalization. M2-Exo was extracted from the culture supernatant of M2 macrophages by ultracentrifugation, followed by treating with TCEP for thiol functionalization. As illustrated in Fig. 1a-1b, maleimide-functionalized Mn_3O_4 was integrated onto the surface of thiol-functionalized M2-Exo through thiol-maleimide reaction, thus obtaining $\text{Mn}_3\text{O}_4@\text{M2E}$.

Results & Discussion: $\text{Mn}_3\text{O}_4@\text{M2E}$ suppresses the aberrant formation of neutrophil extracellular traps (NETs) by inhibiting ROS-PAD4 axis, thereby preventing NETosis-driven inflammatory amplification (Fig. 1c-1d). In parallel, the redox-buffered exosomal cues reprogram macrophages towards pro-regenerative M2-phenotype, collectively breaking the hostile pro-inflammatory status (Fig. 1e-1f). Under the synergistic effects of antioxidant stress and immunomodulation, $\text{Mn}_3\text{O}_4@\text{M2E}$ adequately accelerates the impaired bone regeneration in a diabetic bone defect model (Fig. 1g-1h).

Conclusions: $\text{Mn}_3\text{O}_4@\text{M2E}$ breaks the vicious cycle of diabetic pathological microenvironment by creating a synergism invulnerable to the complications incurred by excessive oxidative stress, dysregulated immune homeostasis, and detrimental inflammatory response, thereby reconstructing a pro-regenerative microenvironment for bone repair.

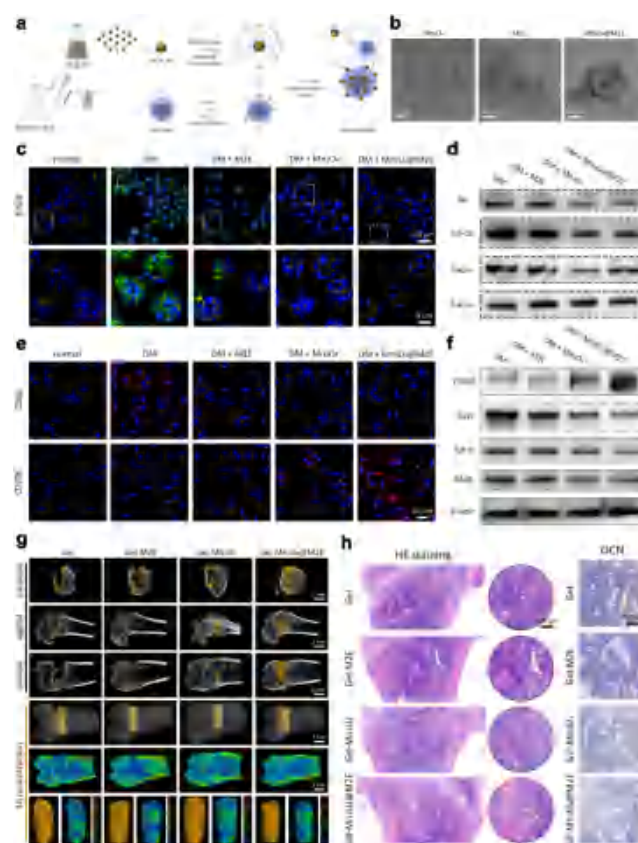


Fig. 1 (a-b) Fabrication and TEM characterization. (c-d) Inhibition of diabetes-induced NETosis. (e-f) Regulation of macrophages M2 polarization. (g-h) Bone regeneration *in vivo*.

Regenerating aged bone marrow via a nitric oxide nanopump

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Key words: aged bone marrow, senescent LepR^+ cells, no nanopump, regenerate

Introduction: Resident leptin-receptor-expressing (LepR^+) cells senesce in the aged bone marrow impairs the regenerative capacity of osteo- and other lineages of cells.

Materials & Methods: In this study, a LepR^+ cell-targeting nitric oxide (NO) nanopump with in vivo self-controlled turn-on ability was constructed to rejuvenate the LepR^+ cells in the aged bone marrow. The ability of NO nanopumps to scavenge excess H_2O_2 and release NO in situ within aged bone marrow was assessed using in vivo fluorescent probe imaging and a live-cell workstation. Furthermore, to evaluate the NO nanopump's impact on aged bone marrow, its effects were assessed via in vitro aging-related β -galactosidase, alkaline phosphatase, alizarin red, and oil red O staining, alongside in vivo micro-computed tomography and immunofluorescence staining. Finally, RNA sequencing and extracellular acidification rate detection explored the mechanism by which NO rebuilds aged bone marrow.

Results & Discussion: The nanopump co-entrapped hydrophobic chemiluminescence substrate and NO donor into the matrix of amphiphilic polymer through a nanoprecipitation process. The chemiluminescence substrate in the NO nanopump automatically reacts with the accumulated H_2O_2 in the aged bone marrow and then directly transfers the chemical energy to the NO donor to induce in situ NO release. The NO produced in situ within the aged bone marrow triggered the regeneration of the osteoblastic and the other niches in vivo through activating the glycolysis signaling in the senescent LepR^+ cells.

Conclusions: LepR^+ cells senescence is a driver of aging-induced bone marrow homeostasis collapse. The self-activating CB-NPs exhibited strong H_2O_2 scavenging and NO production in the aged BM, which rejuvenates senescent LepR^+ cells through activating glycolysis and contributes to reestablishing the homeostasis of aging-induced BM collapse. Our study proposes a new strategy to apply NO-containing nanomedicines to counter aging-related diseases.

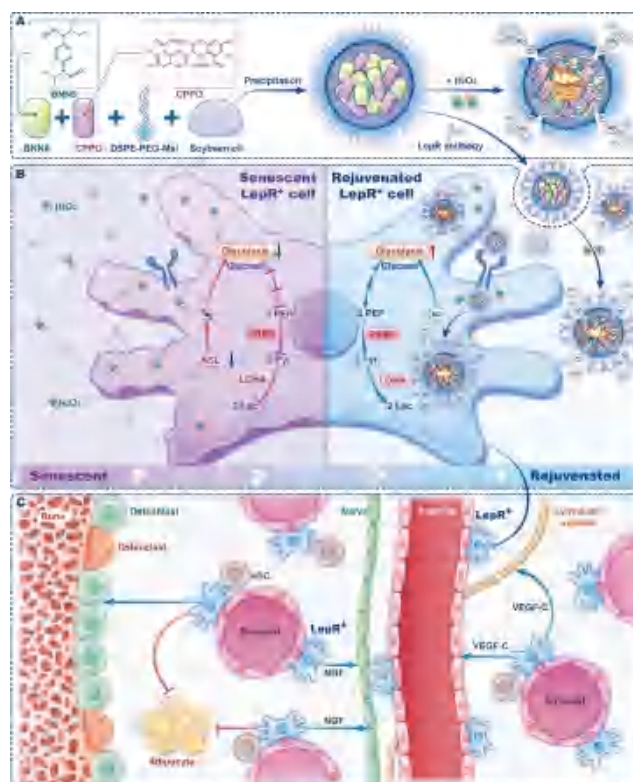


Fig. 1. The process to re-establish homeostasis in aging-induced bone marrow collapse via the rejuvenation of senescent LepR^+ cells with the NO nanopump.

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Temperature-Controlled Fabrication of Bioactive Calcium Phosphate Mineralized Microgels for Minimally Invasive Bone Regeneration

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Key words: bone tissue engineering, microgels, gellan gum, brushite, temperature control

Introduction: The development of injectable biomaterials for bone regeneration requires overcoming the trade-off between structural stability and injectability. Although high-concentration polysaccharide solutions offer robust scaffolds, their processing into microscale carriers is technologically challenging because of high viscosity [1]. Furthermore, bioinert polymers, like gellan gum, require functionalization to support cell anchorage [2]. This study addresses these limitations by developing a temperature-controlled emulsification strategy to fabricate highly concentrated gellan gum/alginate microgels mineralized with brushite, with the aim of creating a cytocompatible and bioactive system for bone defects.

Materials & Methods: Composite microgels were synthesized using a custom-designed temperature-controlled water-in-oil (W/O) emulsification system. The aqueous phase, comprising gellan gum (Gelzan, Sigma-Aldrich), sodium alginate (Sigma-Aldrich), and phosphate precursors (Na_2HPO_4 , Avantor Performance Materials), was processed at elevated temperatures to ensure consistent droplet formation. The emulsion was stabilized in canola oil with sorbitan monooleate surfactant (SPAN 80, Sigma-Aldrich), followed by ionotropic gelation with calcium chloride ($\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$, Avantor Performance Materials) and washing. The physicochemical properties were evaluated via SEM/EDS, XRD, FTIR, and ICP-OES. Cyto-compatibility and cell-material interactions were assessed using osteoblast-like MG63 cells in dynamic culture conditions, using AlamarBlue assays and fluorescence microscopy (phalloidin/DAPI staining).

Results & Discussion: Using the developed temperature-controlled setup, we obtained monodisperse microgels with spherical morphology and average sizes not exceeding 100 μm , effectively managing the high viscosity of the polymer phase. Physicochemical analysis confirmed the *in situ* precipitation of a brushite phase within the hydrogel matrix. Biological evaluation using MG63 osteoblast-like cells confirmed high cyto-compatibility across all microgel groups. However, incorporation of brushite is essential for cell adhesion. While cells formed unattached aggregates in the

presence of nonmineralized microgels, the mineralized microgels stimulated significantly higher metabolic activity driven by calcium ion release. Crucially, fluorescence microscopy demonstrated that a sufficient mineral load enables direct cell adhesion, with the actin cytoskeleton tightly enveloping the spherical microgels,



confirming their potential as osteoconductive carriers (Fig.1).

Fig. 1. Phalloidin/DAPI staining of MG63 osteoblast-like cells cultured with fabricated microgels: control (A), nonmineralized microgels (B), mineralized microgels (C). Scale bar=100 μm .

Conclusions: We validated that regulating the temperature is a crucial factor for the effective emulsification of viscous polysaccharide biopolymers, allowing for the generation of regular, injectable carriers. The incorporation of a bioactive brushite phase is critical for transforming the bioinert hydrogel into an osteoconductive scaffold that supports MG63 osteoblast-like cell adhesion. The developed system combines the benefits of injectability with enhanced biological performance, offering a promising platform for minimally invasive bone tissue engineering.

ACKNOWLEDGMENT

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Ultrasound-Driven Regulation of Catalysis–Immunity via an In Situ-Doped Sonocatalyst Coating for Infectious Bone Defect Repair

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Key words: infectious bone defect, immunosenescence regulation, sonocatalytic therapy

Introduction: Infectious bone defects pose a persistent challenge in orthopedic surgery due to biofilm-associated antibiotic resistance, leading to chronic infection and implant failure. Sonocatalytic therapy (SCT) offers a “drug-free” antibacterial strategy through ultrasound-activated generation of reactive species. Among these, nitric oxide (NO) has emerged as a critical signaling molecule generated via ultrasound-driven catalytic reduction of nitrate (NO_3^-), which not only disrupts bacterial biofilms but also interferes with bacterial metabolism without inducing resistance. However, persistent inflammation and oxidative stress after infection clearance often trigger cellular senescence and promote the senescence-associated secretory phenotype (SASP), which exacerbates tissue inflammation and impairs bone regeneration. We hypothesize that a microenvironment-responsive sonocatalytic platform capable of switching from NO-mediated antibacterial activity to spontaneous ROS scavenging-mediated anti-senescence regulation could simultaneously eradicate infection and rejuvenate osteoimmune microenvironments. To validate this hypothesis, we engineered a 3D-printed polyetherketoneketone (PEKK) scaffold coated with a defect-rich Ru-doped LaMnO_3 sonosensitizer (Ru–LMO/PEKK) designed to dynamically regulate infection and immunosenescence.

Materials & Methods: Ru–LMO catalysts were synthesized via a solvothermal reductive route and deposited onto PEKK scaffolds by in situ self-assembly. Ultrasound-triggered NO generation and spontaneous ROS scavenging were characterized using electrochemical and fluorescent assays. In vitro experiments assessed antibacterial efficacy against methicillin-resistant *Staphylococcus aureus* (MRSA), modulation of macrophage polarization, oxidative stress, and expression of senescence markers (β -galactosidase, p16, γH2AX). Density functional theory (DFT) simulations elucidated the pH-dependent NO_3^- reduction pathway, while transcriptomic and metabolomic analyses elucidated antibacterial and immune rejuvenation mechanisms. In vivo studies in rat infected bone defect models evaluated infection eradication, inflammatory resolution, and bone regeneration outcomes.

Results & Discussion: Ru–LMO/PEKK scaffolds exhibited well-confined Ru nanoclusters homogeneously dispersed within the defect-rich LMO matrix, forming

abundant oxygen vacancies that facilitated ultrasound-driven electron transfer. In acidic infectious conditions, Ru–LMO catalyzed NO_3^- reduction to NO, achieving >99% biofilm removal. Under neutral conditions after infection clearance, the catalyst switched to enzyme-mimetic antioxidative activity, which scavenged intracellular ROS and consequently suppressed SASP-associated cytokines, thereby restoring the osteogenic capacity of BMSCs. This redox modulation further promoted M2 macrophage polarization and upregulated osteogenic gene expression. In vivo, Ru–LMO/PEKK scaffolds effectively eradicated MRSA infection and promoted bone regeneration by alleviating cellular senescence and enhancing vascularization within 8 weeks.

Conclusions: This study demonstrates that Ru–LMO/PEKK scaffolds provide a sequential “dynamic antibacterial–static regenerative” response driven by infection microenvironment. The redox-switching mechanism couples ultrasound-activated NO release for biofilm eradication with antioxidative and anti-senescence regulation that suppresses SASP and rejuvenates osteogenic function. These findings support our hypothesis that a sonocatalytic platform with environment-responsive dual behavior can simultaneously eliminate infection and promote bone repair.

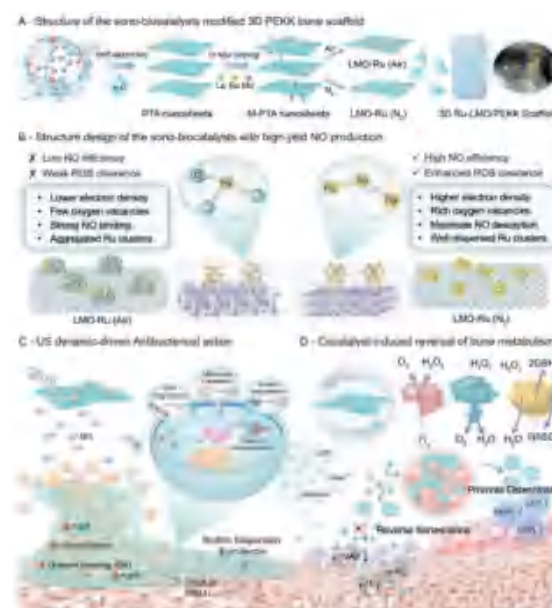


Fig. 1. The design and mechanism of the Ru–LMO/PEKK sonocatalytic scaffold for infection eradication and osteoimmune rejuvenation.

Dual-functional 3D-printed polyetheretherketone scaffolds with immunomodulatory nano-calcium silicate/interleukin-4 coating synergistically enhance osteogenesis through macrophage M2 polarization and NF- κ B pathway suppression

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Key words: PEEK, Bone regeneration, Macrophage polarization, Polydopamine, 3D-printing.

Introduction: Polyetheretherketone (PEEK) is a promising biomaterial for orthopedic implants due to its bone-mimetic mechanical properties, but its bioinertness and pro-inflammatory responses limit osseointegration. This study engineered 3D-printed PEEK scaffolds functionalized with a polydopamine (PDA)-assisted nano-calcium silicate (n-CS) and interleukin-4 (IL-4) coating (PEEK/PCS/IL-4) to synergistically modulate immune responses and osteogenesis for improved bone defect repair (Fig. 1).

Materials & Methods: Porous PEEK scaffolds were fabricated via fused deposition modeling (FDM). Surface modification involved PDA-mediated sequential immobilization of n-CS and IL-4. In vitro assays evaluated cytocompatibility, osteogenic differentiation (using hBMSCs), angiogenic potential (HUVECs), and macrophage polarization (RAW264.7 cells). In vivo assessments included rat subcutaneous implantation for immunomodulation and rabbit femoral defect models for osseointegration, analyzed via micro-CT, histology, and biomechanical testing. RNA sequencing and western blotting elucidated molecular mechanisms.

Results & Discussion: The PEEK/PCS/IL-4 scaffolds sustainedly released Ca^{2+} , SiO_3^{2-} , and IL-4 over weeks. In vitro, they enhanced hBMSCs spreading, alkaline phosphatase activity, mineralization, and osteogenic gene expression (e.g., RUNX2, OPN). HUVECs exhibited improved migration and tubule formation, indicating pro-angiogenic effects. Macrophages polarized toward M2 phenotype, with elevated TGF- β 1 and suppressed TNF- α , correlating with non-canonical NF- κ B pathway inhibition (reduced RelB and NF- κ B2). Conditioned medium from PEEK/PCS/IL-4-primed macrophages amplified hBMSCs osteogenesis, confirming immune-osteogenic coupling. In vivo, the scaffolds reduced fibrous encapsulation, promoted M2 polarization, and enhanced bone regeneration (increased BV/TV, Tb.N, BMD) and osseointegration strength in rabbit models.

Conclusions: The PDA-assisted n-CS/IL-4 coating transforms bioinert PEEK into a bioactive platform, synergistically enhancing osteogenesis through

immunomodulation (via M2 polarization and NF- κ B suppression), angiogenesis, and bone regeneration. This strategy offers a transformative approach for load-bearing bone defect repair.

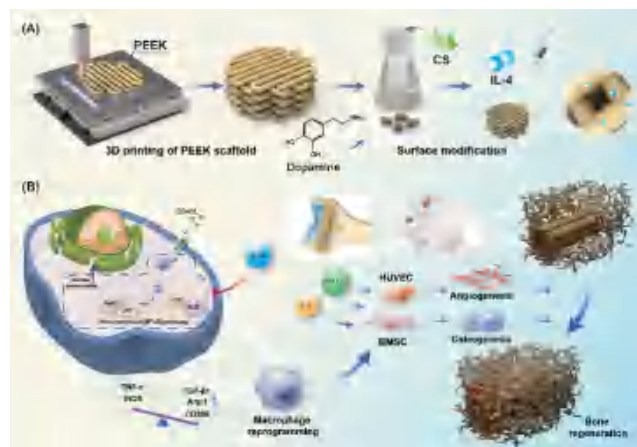


Fig. 1. Schematic illustration. (A) 3D-printing and modification of PEEK/PCS/IL-4 scaffolds. (B) The mechanism by which PEEK/PCS/IL-4 promotes bone regeneration.

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GDYO@Pt-Based Schottky Engineering Promotes Cranial Bone Regeneration through Piezoelectric Stimulation and Oxidative Stress Regulation

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Key words: Graphdiyne oxide, Schottky junction, piezoelectric stimulation, oxidative stress, bone regeneration

Introduction: Piezoelectric stimulation, as a non-invasive therapeutic approach, can modulate cellular metabolism and promote bone regeneration. However, excessive reactive oxygen species (ROS) generation and hypoxia-induced oxidative stress in the bone defect microenvironment may compromise the therapeutic efficacy of electrical stimulation. Therefore, developing narrow-bandgap piezoelectric materials with both efficient piezoelectric stimulation and ROS scavenging capabilities is of great importance.

Materials & Methods: (1) Preparation and characterization of Pt-modified graphdiyne oxide (GDYO@Pt): The material structure was characterized using transmission electron microscopy, infrared spectroscopy, X-ray diffraction, and X-ray photoelectron spectroscopy; (2) Piezoelectric property evaluation: the piezoelectric performance of the material was assessed using piezoresponse force microscopy and finite element analysis; (3) Piezocatalytic evaluation: the piezocatalytic capability was evaluated using electron paramagnetic resonance spectroscopy, gas chromatography, and a dissolved oxygen meter; (4) Assessment of cell proliferation and piezoelectric stimulation: cell proliferation was evaluated by CCK-8 assay and live/dead staining, while the piezoelectric stimulation behavior of the material on cells was assessed using an electrochemical workstation; (5) Evaluation of cellular oxidative stress: the oxidative stress level in cells was evaluated using gas chromatography, hypoxia fluorescent probes, and reactive oxygen species assay kits; (6) Assessment of osteogenic activity: osteogenic differentiation behavior was evaluated using alkaline phosphatase assay kits, alizarin red staining, and PCR technology; (7) Investigation of in vivo bone regeneration: the degree of bone defect repair was assessed using Micro-CT and histological section staining (HE and Masson); (8) Evaluation of in vivo oxidative stress: the oxidative stress level was evaluated using ROS probes, oxygen indicators, and NRF2 immunohistochemistry.

Results & Discussion: Cellular experiments demonstrated that ultrasound-activated GDYO@Pt can modulate the membrane potential, calcium ion influx,

and the levels of hydrogen, oxygen, and ROS in bone marrow mesenchymal stem cells, confirming the piezo-catalytic synergistic effect. Animal experiments showed that GDYO@Pt-loaded thermosensitive hydrogel, upon ultrasound activation, achieved bone defect repair by promoting osteogenic differentiation, angiogenesis, and immune regulation.

Conclusions: This piezo-catalytic dual-functional platform innovatively integrates piezoelectric stimulation with oxidative stress regulation, directionally generating therapeutic hydrogen and oxygen during the piezoelectric process to construct a low oxidative stress microenvironment conducive to osteogenesis, thereby providing a new paradigm for bone defect repair. This mechanism can be extended to diverse regenerative applications, including articular cartilage repair, neural axon regeneration, and skin wound healing, demonstrating universal applicability. Thus, elucidating the spatiotemporal regulatory principles of electrochemical coupling on cell fate and establishing quantitative structure-activity relationships among band structures, interfacial reaction kinetics, and biological responses will critically guide the development of next-generation intelligent bone repair materials.

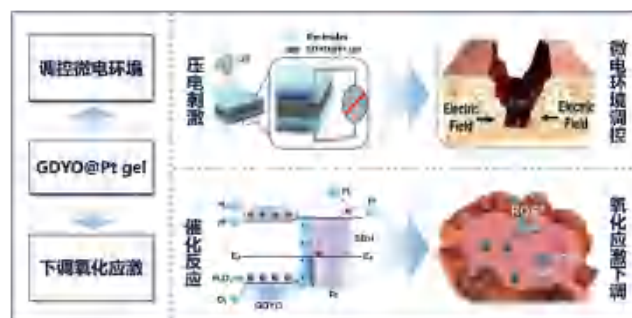


Fig. 1. Schematic illustration of the mechanism and workflow of piezoelectric stimulation and oxidative stress modulation based on GDYO@Pt gel.

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3D-printed hybrid PCL composites for osteoporotic bone regeneration

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Key words: Bone regeneration, 3D scaffolds, Osteoporosis

Introduction

Osteoporosis is a chronic, progressive, and systemic skeletal disorder characterized by reduced bone mass and microarchitectural deterioration, resulting in increased bone fragility and a heightened risk of fractures. The growing clinical burden associated with osteoporotic fractures has prompted the development of innovative therapeutic strategies that not only restore structural integrity but also actively promote bone regeneration. In this context, advances in three-dimensional printing (3DP) have enabled the fabrication of highly precise, patient-specific scaffolds tailored to individual anatomical and pathological needs [1].

To further enhance biological performance, hybrid systems integrating bioinspired materials have gained increasing attention. In particular, Inulin-g-poly(D,L-lactide) (INU-PLA) has shown promise as a functional additive in bone tissue engineering (BTE) applications. This study reports the development of a novel hybrid 3D-printed scaffold composed of PCL, INU-PLA, and strontium-doped nano-hydroxyapatite (SrHA), designed to synergistically enhance bioactivity, mechanical performance, and osteogenic differentiation. Additionally, the scaffold incorporates raloxifene, an anti-osteoporotic drug, enabling localized and sustained drug delivery to further stimulate bone regeneration. The overarching objective is to engineer multifunctional 3D-printed scaffolds capable of providing both structural support and therapeutic action for the effective treatment of osteoporotic fractures.

Materials & Methods

For the *in vitro* studies, 7F2 morphology was assessed by staining cell membrane with CellMask™ and 4',6-diamidino-2-phenylindole (DAPI) after 24 hours according to manufacturer instructions. Furthermore, cell proliferation assays were performed using Cell Counting Kit8 (CCK-8) at different time points (1, 3, 7, 14 and 21 days). Additionally, the effect of PCL scaffolds on osteogenic differentiation was evaluated by measuring early and later markers of differentiation such as alkaline phosphatase (ALP) and osteocalcin (OCN).

Results & Discussion

Cell adhesion assessed 4 hours after seeding showed that IP5 increased scaffold hydrophilicity, thereby enhancing cell attachment in both loaded and unloaded systems. CellMask™ and DAPI staining confirmed good cell

spreading and uniform distribution on R0_IP5 and R0_IP5_Sr-nHA scaffolds, indicating high biocompatibility and strong cell-material interactions. Cell viability evaluated at 1, 3, 7, 14, and 21 days revealed no cytotoxic effects. Notably, scaffolds containing Sr-doped hydroxyapatite exhibited consistently higher viability than those with non-doped HA, in both loaded and unloaded conditions, confirming the beneficial role of strontium in improving biocompatibility.

Analysis of osteogenic markers (ALP and OCN) at 3, 7, 14, and 21 days demonstrated a significant upregulation in scaffolds incorporating strontium-substituted hydroxyapatite compared to controls and PCL scaffolds without strontium ($p < 0.001$), indicating enhanced osteogenic differentiation over time.

Conclusions

This study demonstrates the strong potential of PCL-based hybrid scaffolds for bone tissue engineering applications, especially in the treatment of osteoporosis-related defects, through the integration of PCL with bioinspired materials (INU-PLA and Sr-HA) using advanced FFF 3D printing technology.

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A Real-World Evidence–Based China Strategy for the Treatment of Osteonecrosis

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Key words: osteonecrosis of the femoral head, bioceramic rod, meta-analysis, hip preservation, β -tricalcium phosphate

Introduction: Osteonecrosis of the femoral head (ONFH) is a progressive orthopedic disorder caused by vascular disruption and subsequent bone necrosis, frequently leading to collapse of the femoral head and hip joint failure. Conventional hip-preserving treatments, including core decompression and bone grafting, have demonstrated inconsistent clinical outcomes. A treatment strategy based on bioceramic rod-mediated revascularization has been developed to promote intraosseous blood supply reconstruction and bone regeneration. To evaluate the clinical effectiveness, safety, and therapeutic potential of this approach, we conducted a systematic review and meta-analysis of published clinical studies, providing real-world evidence to support a China-derived strategy for ONFH treatment.

Materials & Methods: A comprehensive literature search was conducted in PubMed, Embase, and CNKI databases for studies published between January 2011 and July 2023. Studies involving patients treated with bioceramic rod implantation for ONFH were included if they reported clear clinical outcomes and had a follow-up duration of at least six months. Reviews, case reports, conference abstracts, and studies lacking defined efficacy criteria were excluded. Two independent investigators performed study selection, data extraction, and quality assessment. Randomized controlled trials were evaluated using the modified Jadad scale, while case series were assessed according to the Oxford Centre for Evidence-Based Medicine criteria. Primary outcome measures included Harris Hip Score (HHS) improvement rate, while secondary outcomes included hip excellent and good rate, femoral head stability rate, femoral head survival rate, and hip replacement rate. Meta-analysis was conducted using R statistical software.

Results & Discussion: A total of 36 clinical studies were included after screening 374 retrieved records. These studies involved 1965 patients and 2222 hips treated with bioceramic rods. The average patient age was approximately 40 years, with a mean follow-up duration of 20.44 months, and the majority of cases

were classified as ARCO stage II. Meta-analysis demonstrated significant clinical improvement following treatment. The overall HHS improvement rate reached 33.93%, while the excellent and good outcome rate was 83.70%. Radiographic evaluation showed a femoral head stability rate of 88.91% and a femoral head survival rate of 84.42%, with an overall hip replacement rate of 7.97%. Correlation analysis revealed that postoperative improvement in hip function strongly predicted long-term hip preservation outcomes. Early-stage treatment achieved significantly better results than treatment in more advanced disease stages. Comparative analyses indicated that bioceramic rod implantation provided superior functional improvement and hip-preserving efficacy compared with core decompression and showed favorable outcomes compared with autologous bone grafting.

Conclusions: The findings from this systematic review and meta-analysis provide strong real-world evidence supporting the clinical effectiveness of bioceramic rod-mediated revascularization in ONFH treatment. The technique demonstrates significant improvement in hip function and high rates of femoral head preservation. These results support the development of a real-world evidence-based China strategy for osteonecrosis treatment, offering a safe, minimally invasive, and effective approach for hip preservation. Further multicenter prospective studies and long-term follow-up are warranted to strengthen the evidence base and optimize treatment strategies.

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Gut Microbiome–Cartilage Axis-on-a-chip to Reveal the Effect of Probiotics on Osteoarthritis

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Key words: organ-on-a-chip; gut–cartilage axis; osteoarthritis; probiotic metabolite; cartilage organoids

Introduction: Osteoarthritis (OA) is a highly prevalent joint condition and no therapies can halt or reverse OA progression, necessitating the development of models to reveal OA mechanisms and test potential disease-modifying drugs. Emerging evidence points to a significant relationship between gut microbiome and cartilage health through the gut microbiome–cartilage axis (GMCA). This study introduces a novel human cell-derived, microphysiological GMCA-on-a-chip (GMCAoC) platform, hypothesized to be capable of modeling inflammatory OA and evaluating the preventive and therapeutic effects of gut probiotics on cartilage degradation.

Materials & Methods: Combining 3D printing and soft lithography, we engineered a GMCAoC system consisting of two modules connected that enabled gut-cartilage crosstalk (**Fig. 1**). First, human mesenchymal stem cells were injected into the cartilage module to form articular cartilage organoids (COs) in the microwells. A stable O₂ gradient established by regulating the flow rates of hypoxic/aerobic culture media. Four days post-injection of Caco-2 cells onto the porous membrane, a tight intestinal epithelium was established, which was subsequently colonized by *Bifidobacterium bifidum* (obligate anaerobic) and *Lactobacillus plantarum* (aerobic). The probiotic metabolites were comprehensively analyzed by liquid chromatography-mass spectrometry. After coupling the gut and CO modules and culturing for 14 days, the COs were challenged with the proinflammatory cytokine IL-1 β (10 ng/mL) for 48 h to construct an inflammatory OA model. After withdrawing IL-1 β , COs were cultured with/without gut microbiome metabolites for another 48 h. Statistical analysis was conducted using Student's *t*-test ($N \geq 3$), with statistical difference denoted by * ($P < 0.05$), ** ($P < 0.01$), and *** ($P < 0.0001$).

Results & Discussion: With optimized microchannel heights of microchannels, a biomimetic oxygen gradient could be established. A stable co-culture of BB and LP on the integrated intestinal epithelium was achieved. The on-chip cultured COs displayed more uniform morphology and larger diameters (~26% larger) than those in static culture. Exposure to probiotic metabolites further increased the average CO diameter, alongside elevated COL2 and SOX9 expression. Notably, co-cultured COs exhibited superior anti-inflammatory properties, with IL-6 secretion levels

being ~60% of that of non-co-culture group and lower expression levels of inflammatory and degenerative marker genes. After IL-1 β withdrawal and probiotic metabolite treatment, IL-6 secretion decreased to 63% of the initial levels within 48 hours, a response not observed in the untreated group. This therapeutic effect was corroborated by the lower expression of IL-6 and MMP13 and rescued COL2 expression in the COs. Notably, we verified these therapeutic effects on “diseased” COs established with human OA patient-derived chondrocytes (**Fig. 2**). Multi-omics profiling revealed that probiotic metabolites promoted cartilage anabolism via PI3K/AKT-MAPK modulation, upregulating COL2A1, SOX9, and ACAN while suppressing MMP13 and ADAMTS4. The regulatory effects were context dependent: at baseline, probiotic metabolites increased p-AKT and p-ERK expression; under IL-1 β challenge, they reduced pro-inflammatory p-p38 levels while maintaining/restoring p-AKT/p-ERK expression, mitigating inflammation and preserving cartilage matrix.



Fig. 1 Recapitulation of gut microbiome–cartilage axis on GMCAoC.

Fig. 2 Therapeutic effects of probiotic metabolites in OA patient-derived cartilage organoids.

Conclusions: The GMCAoC platform effectively models the interplay between gut microbes and articular cartilage under healthy and OA-like conditions, demonstrating its potential in elucidating OA mechanisms and developing targeted probiotic treatments to modify disease progression.

AI-Engineered Exosomes Restore Chondrocyte Metabolic Activity Through Sustained Drug Release to Treat Osteoarthritis

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Key words: osteoarthritis, artificial intelligence, drug screening, exosome, cellular metabolism

Introduction: Osteoarthritis (OA) lacks treatments that provide durable repair. Post-traumatic OA (PTOA) is an important OA subtype.¹ The challenge in its treatment lies in effectively identifying and delivering drugs capable of regulating inflammatory intraarticular environment and restoring cellular repair activity after trauma. We built an AI drug screening system to screen drugs for different subtypes of OA and ultimately selected methylprednisolone acetate (MPA) as a candidate for drug delivery. Exosomes, as extracellular vesicles and natural nanosized drug carriers, were used to deliver MPA for treating acute-phase inflammation and realize long-term efficacy. These engineered exosomes (MPA-EXOs) were found to inhibit inflammation and restore chondrocyte metabolic activity effectively. Furthermore, the MPA-EXO platform significantly prolonged the therapeutic effects of MPA in vivo, providing a new strategy for OA treatment.

Materials & Methods:

The AI model was built on the DrugAssist model and has been trained specifically for OA drug screening. Stem cell-derived exosomes were produced in a bioreactor (REGEN-αGEEK) and purified via size exclusion chromatography (Izon Science). MPA was loaded by co-incubation, with the loading efficiency quantified by HPLC for 28 days. In vitro, the MPA-EXOs were validated using 2D chondrocyte models and 3D cartilage organoids. Additionally, we constructed an in vivo PTOA model in rabbits and evaluated the long-term efficacy of MPA-EXO treatment at 8 and 16 weeks.^{2,3}

Results & Discussion: AI screening results showed that MPA has therapeutic effects in OA subtypes associated with mechanical overloading, inflammation, and metabolic disorders. We successfully loaded MPA into exosomes using a co-incubation method. In in vitro experiments, we achieved sustained MPA release for up to 28 days in PBS solution. Cartilage organoid experiments showed that MPA-EXOs effectively reduced the release of inflammatory/degenerative factors such as MMP3, MMP13, and IL-6, enhanced cartilage cell metabolism, and inhibited cartilage hypertrophy and apoptosis. In the rabbit PTOA model, the untreated group showed significant osteophyte formation and joint effusion 8 and 16 weeks after joint trauma, while the MPA-EXO treatment group showed

similar joint function and cartilage condition to the sham group.

Conclusions: This study demonstrates that MPA-EXOs significantly extended the duration of MPA delivery, enabling sustained anti-inflammatory effects and promoting cartilage matrix regeneration. The MPA-EXO system supports long-term OA treatment via a single intra-articular injection.

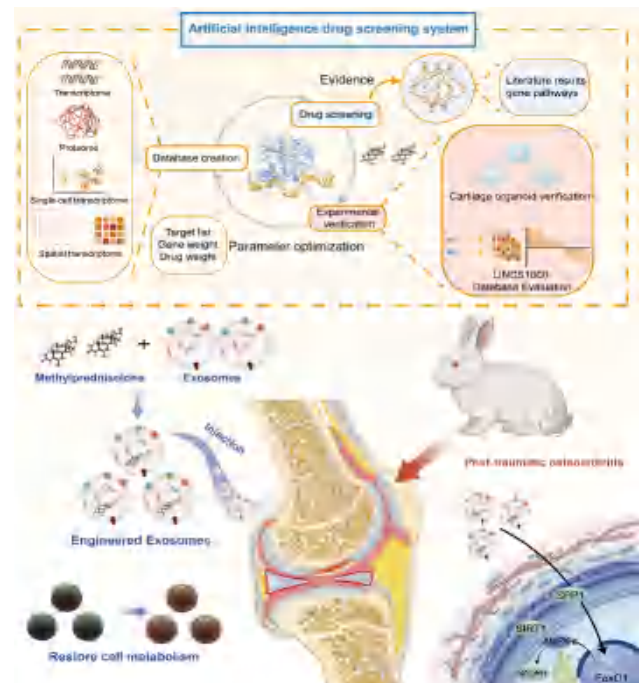


Fig. 1. Establishment of an OA-targeted drug delivery system loaded with the AI-screened drug of MPA. As the lead drug candidate, MPA was loaded in exosomes for in vitro and in vivo testing. The resulting MPA-EXOs effectively restored chondrocyte metabolism and alleviated PTOA in a rabbit model.

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Development of Tissue-Engineered Tracheal Scaffold Based on Multi-Modified Prussian Blue Nanoparticles and Its Application in Repairing Long-Segment Tracheal Defects

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Abstract: The repair of long-segment tracheal defects (LTD) remains a clinical challenge. Although tissue engineering technology provides a potential solution, it still faces problems such as high risk of infection, severe inflammatory response, and insufficient vascularization. Studies have shown that multi-modified Prussian blue (PB) nanoparticles can simultaneously achieve antibacterial, anti-inflammatory, and pro-angiogenic functions. This study proposes to prepare zinc ion (Zn) modified PB nanoparticles (ZnPB) and nitric oxide (NO) modified ZnPB nanoparticles (ZnPB-NO), utilizing their synergistic effects of antibacterial, anti-inflammatory, and pro-angiogenic properties to address the bottleneck issues in LTD repair. Specifically, ZnPB and ZnPB-NO nanoparticles will be loaded onto acellular dermal matrix to construct a scaffold system with both cartilage regeneration and vascularized connective tissue regeneration functions. The antibacterial and anti-inflammatory properties of ZnPB and ZnPB-NO can effectively control infection and inflammation during tracheal regeneration, while the pro-angiogenic effect of ZnPB-NO further optimizes the in situ repair effect of regenerated trachea. The strategy based on multi-modified PB nanoparticles proposed in this study aims to break through the technical bottlenecks of existing tissue-engineered trachea in vascularization, anti-infection, and anti-inflammation, providing a new direction for LTD repair.

Key words: Biomedical materials, Prussian blue nanoparticles, Surface modification, Tracheal reconstruction, Tissue engineering

Introduction:

Extensive tracheal defects caused by trauma, malignancy, or congenital abnormalities remain life-threatening and difficult to repair^[1]. Although tissue-engineered tracheas (TET) show promise, their clinical translation is limited by insufficient vascularization, infection, and excessive inflammation, which often lead to tissue necrosis and graft failure^[2]. Existing therapeutic strategies, including growth factors and antibiotics, present limitations such as short half-lives, adverse effects, and antibiotic resistance^[3, 4]. Therefore, multifunctional materials capable of simultaneously promoting angiogenesis while suppressing infection and inflammation are urgently needed.

Here, we prepared zinc ion (Zn) modified PB

nanoparticles (ZnPB) and nitric oxide (NO) modified ZnPB nanoparticles (ZnPB-NO), utilizing their synergistic effects of antibacterial, anti-inflammatory, and pro-angiogenic properties to address the bottleneck issues in LTD repair. These nanoparticles were incorporated into biomimetic acellular dermal matrix-based TET scaffolds. This study evaluates their biocompatibility and multifunctional therapeutic effects in vitro and in vivo, aiming to improve tracheal reconstruction.

Materials & Methods:

Zinc-doped Prussian blue nanoparticles (ZnPB NPs) were synthesized and functionalized with nitric oxide to obtain ZnPB-NO NPs, followed by physicochemical characterization. The nanoparticles were incorporated into acellular dermal matrix (ADM) to fabricate ZnPB/ADM and ZnPB-NO/ADM porous scaffolds. In vitro biocompatibility was evaluated using cell viability assays. Antibacterial activity, anti-inflammatory effects, reactive oxygen species (ROS) scavenging, and pro-angiogenic capacity were assessed through standard microbiological and cellular experiments. In vivo performance was evaluated using both a rabbit neck implantation model to assess vascularization and an in situ tracheal transplantation model to investigate graft integration. Histological and immunohistochemical analyses were performed to evaluate angiogenesis, infection, inflammation, and cartilage preservation after transplantation.

Results & Discussion:

TEM images of ZnPB nanoparticles showing uniform morphology and nanoscale size distribution. EDS confirms the elemental composition of ZnPB. SEM images exhibited interconnected porous microstructures. **(Figure 1a, 1b)**. The synthesized ZnPB/ADM and ZnPB-NO/ADM exhibited strong antibacterial activity and significant suppression of inflammatory cytokine expression, accompanied by effective scavenging of reactive oxygen species. Importantly, ZnPB-NO/ADM markedly enhanced endothelial cell proliferation and angiogenic behavior, confirming their pro-vascular potential **(Figure 1c-1e)**. The TET constructs promoted rapid vascular infiltration in the rabbit neck implantation model, with increased microvessel density compared with controls. Histological analyses revealed improved tissue integration and enhanced cartilage and vascular regeneration **(Figure 1f)**. By simultaneously addressing infection, inflammation, oxidative stress, and vascular

deficiency, this strategy overcomes key limitations of conventional tissue-engineered tracheas and supports stable graft survival and functional repair.

Conclusions:

This study innovatively developed multifunctional composite scaffolds, ZnPB/ADM and ZnPB-NO/ADM, with antibacterial, anti-inflammatory, and pro-vascular functions, and systematically evaluated their application in tracheal tissue engineering. Through in vitro and in vivo experiments, we confirmed that these scaffolds effectively improve the growth environment of tracheal cartilage and promote cartilage tissue regeneration in pathological conditions characterized by infection, inflammation, oxidative stress and microvascular damage. Both ZnPB/ADM and ZnPB-NO/ADM exhibited significant antibacterial, anti-inflammatory, and ROS scavenging activities. Specifically, ZnPB/ADM improved the inflammatory environment and supports chondrocyte regeneration, while ZnPB-NO/ADM, by releasing NO, effectively promoted the proliferation, migration, and tube formation of HUVECs, accelerating in vivo vascularization of TET. This study provides new solutions for addressing the issues of infection, inflammation, and vascularization that TET face during the in situ transplantation for the repair of long-segment tracheal defects, enhancing their potential for clinical application in such defects.

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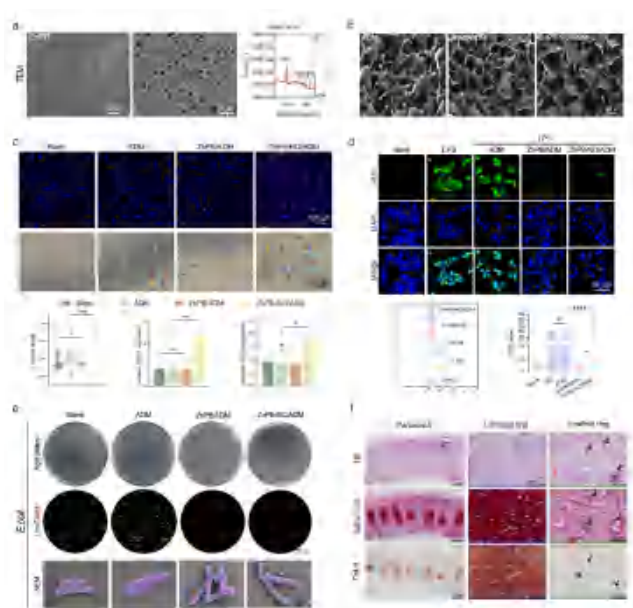


Figure 1. (a) Transmission electron microscopy (TEM) and Energy-dispersive X-ray spectroscopy (EDS) of ZnPB. (b) Scanning electron microscopy (SEM) images of ADM, ZnPB/ADM, and ZnPB-NO/ADM scaffolds. (c) Pro-angiogenic effects in vitro. (d) ROS-scavenging and anti-oxidative effects. (e) Antibacterial performance against *E. coli*. (f) Histological evaluation of in vivo tracheal regeneration.

A Personalized Dual-Track Strategy for Meniscus Replacement: From Bioactive Resorbable Scaffolds to Functionalized Non-Biodegradable Prostheses

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Key words: meniscus repair, 3D bioprinting, dual-zone scaffold, polycarbonate urethane, selective laser sintering

Introduction: Meniscus injuries are among the most frequent orthopaedic issues, significantly increasing the risk of post-traumatic knee osteoarthritis (OA). The loss of meniscal tissue leads to altered joint mechanics and pathological angiogenesis, where vascular endothelial growth factor (VEGF)-mediated vessel ingrowth contributes to cartilage degradation. Current clinical solutions often fail to provide a "one-size-fits-all" treatment, as patient needs vary drastically depending on the stage of joint degeneration. To address this gap, we proposed a dual-track strategy based on personalized medicine: (i) a bioactive, resorbable scaffold to promote tissue regeneration in early-stage OA, and (ii) a functionalized non-biodegradable prosthesis designed for mechanical unloading in advanced OA cases.

Materials & Methods: For the resorbable track, a high-concentration collagen bioink (125 mg/mL) was processed using an extrusion-based 3D bioprinter (Rokit in vivo 4D2) (1). A dual-zone approach was implemented to mimic the native meniscus architecture, incorporating bevacizumab (BVZ)-loaded Poly(lactic-co-glycolic acid) (PLGA) microparticles specifically to target OA. The microparticles were prepared *via* w/o/w double emulsion and integrated into the collagen matrix (2). For the non-biodegradable track, patient-specific prostheses were fabricated using Polycarbonate Urethane (PCU). Two additive manufacturing techniques were compared: Fused Deposition Modeling (FDM) and Selective Laser Sintering (SLS) (using a Sharebot SnowWhite). To overcome the inherent hydrophobicity and high surface roughness (unsintered powder) of SLS-printed PCU, various post-processing steps were evaluated: thermal treatment, plasma surface modification, and chitosan coating.

Results & Discussion: The 3D printed dual-zone collagen scaffolds exhibited excellent shape fidelity and load-bearing capacity immediately after printing, maintaining structural integrity for 28 days in culture. The BVZ-loaded microparticles provided a sustained release of the anti-angiogenic agent, which significantly inhibited HUVEC-driven capillary network formation (reduction in vessel area and length) without affecting cell viability.

Regarding the non-resorbable approach, SLS proved to be the most efficient fabrication method, reducing the processing time for a meniscus prototype from 17.2 hours (FDM) to only 1.2 hours, with superior geometric precision. While thermal treatments were insufficient to significantly reduce surface roughness, plasma treatment had a transformative effect, shifting the PCU surface from highly hydrophobic to extremely hydrophilic (dramatic reduction in contact angle). This functionalization was identified as a mandatory step to enable the stable attachment of bioactive coatings (e.g., chitosan or dendrimers), facilitating the interaction between the inert synthetic polymer and the biological environment.

Conclusions: We successfully validated a comprehensive dual-track strategy for meniscal loss. By combining advanced 3D bioprinting of natural polymers for regeneration with high-precision additive manufacturing and surface engineering of synthetic polymers for mechanical unloading, we provide a versatile toolkit for preventing osteoarthritis across



different patient profiles. Future work will focus on optimizing the long-term stability of bioactive coatings on the non-resorbable implants.

Fig. 1. Anatomical shape dual zone collagen meniscus as reported in (1).

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From disease model to therapeutic insight: An engineered hydrogel reveals the role of matrix viscous dissipation in intervertebral disc degeneration

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Key words: Intervertebral disc degeneration; Viscous dissipation; Extracellular matrix; Mechanotransduction; Cellular senescence.

Introduction: Intervertebral disc degeneration (IVDD) is associated with the accumulation of senescent cells and pathological remodelling of the extracellular matrix (ECM) [1]. However, the causal relationship between nucleus pulposus (NP) viscoelastic properties, cellular senescence dynamics, and disc homeostasis remains incompletely defined, representing a key knowledge gap in IVDD therapeutics [2]. Here, we demonstrate that degenerated human NP tissue exhibits a significant increase in cellular senescence, which positively correlates with a marked shift in its liquid-to-solid transition properties (viscoelasticity). Using artificial ECM models, we further show that reduced ECM viscous dissipation drives cellular senescence by aberrantly inactivating Yes-associated protein (YAP) via impaired mechanotransduction. Treatment with a YAP agonist in vivo restored NP cell (NPC) mechanotransduction, reduced cellular senescence during IVDD, and demonstrated that restoring normal mechanotransduction is a promising therapeutic strategy for IVDD (Fig. 1).

Materials & Methods: We established a comprehensive experimental framework combining clinical specimens and animal models. This included analysis of clinical NP samples (n = 14) and rat IVDD models. We then developed two artificial ECMs simulating the ECM of degenerated and normal NP tissues to investigate whether reduced ECM viscous dissipation directly induces NP cellular senescence.

Results & Discussion: Our integrated clinical and animal model data demonstrate that IVDD progression is accompanied by a progressive decrease in NP viscous dissipation and a concomitant accumulation of senescent cells. In vitro results indicated that during IVDD, declining ECM viscous dissipation impairs mechanotransduction in NPCs, thereby inhibiting YAP activation. The inactivation of YAP subsequently disrupts nuclear membrane integrity, resulting in increased cytoplasmic dsDNA, which activates the cGAS-STING pathway and drives NPC senescence. The senescence of NPCs induced by these events changed the components of the ECM, which may further reduce viscous dissipation, potentially creating a vicious cycle of “viscous dissipation reduction-cellular senescence-changes of ECM components”. By

pharmacological activation of YAP and implantation of biomimetic hydrogels, we mitigate this cycle and delay IVDD progression (Fig. 2&3). These findings underscore the potentially detrimental contribution of reduced ECM viscous dissipation to NPC senescence during IVDD progression, and offer insights for developing effective treatments for aging-related diseases.

Conclusions: Decreased ECM viscous dissipation inactivates YAP via the reduced ITGB1/FAK/YAP mechanotransduction. Then the inactivation of YAP compromises NE integrity and activates the cGAS-STING signalling pathway, ultimately inducing NPC senescence. Both YAP agonists and biomimetic hydrogels could effectively restore YAP activity and partly suppressed cellular senescence during IVDD

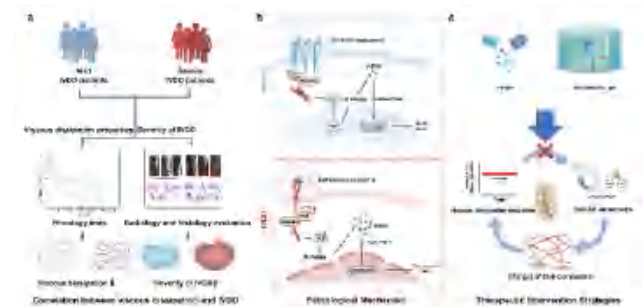


Fig. 1. Mechanotransduction recovering strategies offer a potential treatment for IVDD. a, Correlation between viscous dissipation and IVDD. **b,** Pathological Mechanism of IVDD; **c,** Therapeutic Intervention Strategies for IVDD by reducing the vicious cycle of “viscous dissipation reduction-cellular senescence-changes of ECM components”.

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3D Printed Silk Reinforced Meniscus Implant

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Introduction: The knee meniscus, a fibrocartilage structure with a complex anisotropic extracellular matrix (ECM) of circumferentially aligned collagen fibers and radial networks, is critical for load distribution and joint stability. Its limited self-healing capacity makes injury management challenging, as current clinical options like meniscectomy can lead to osteoarthritis, while as allografts and existing synthetic scaffolds (e.g., CMI, ACTIFIT) have limitations. This study addresses the need for a functionally biomimetic meniscal scaffold. Inspired by the meniscus's fibrous microstructure, we developed a novel 3D-printed composite scaffold using polycaprolactone (PCL) continuously reinforced with natural silk fibers via an in-situ impregnation technique. This continuous silk-reinforced composite (CSRC) scaffold design aims to provide the necessary mechanical support and synergistic bioactivity to guide regeneration.

Materials & Methods: *Bombyx mori* silk yarns were used to reinforce PCL. A custom fiber feeder was integrated into a 3D-bioprinter for in-situ impregnation, printing scaffolds with alternating circumferential and radial filament layers to mimic native collagen architecture. Scaffolds with varying silk content (4/11 wt.%) and UHMWPE-reinforced controls were fabricated, corresponding to Silk1x/Silk3x-PCL. A variety of materials characterizations, i.e. SEM, DMTA, and biological assessments *in vitro* and *in vivo* i.e. dynamic cell-material culture, were conducted.

Results & Discussion: The 3D-printed CSRC scaffolds successfully replicated the anisotropic architecture of the natural meniscus. Tensile modulus in the circumferential direction reached up to 898 MPa for Silk3x-PCL, and scaffold anisotropy (circumferential vs. radial modulus) increased from 1.58 (PCL) to 3.72 (Silk3x-PCL), matching native tissue levels (100-300 MPa). Suture pull-out resistance was also enhanced. Critically, CSRC scaffolds demonstrated viscoelastic behavior akin to native meniscus. They displayed a higher instantaneous modulus and faster stress relaxation (τ) under compressive creep. FE analysis confirmed that CSRC scaffolds better distribute load and reduce localized deformation and stress. Cyclic compression tests showed stable energy dissipation over 1000 cycles, confirming fatigue resistance.

In vitro, CSRC scaffolds supported enhanced SMSC adhesion, viability, and proliferation compared to PCL. Meniscus-related gene expression (*COL1*, *SOX9*) was significantly upregulated on CSRC scaffolds. *In vivo*,

CSRC scaffolds elicited a milder inflammatory response and promoted better tissue integration and cell infiltration.

The dynamic mechanical stimulation experiment and the transcriptomic analysis revealed that the biomimetic mechanics of the Silk1x-PCL scaffold actively modulate SMSC's fate. Gene expression related to mechano-transduction, cytoskeleton, and ECM was significantly differential. Notably, the PI3K-Akt signaling pathway, crucial for cell survival and chondrogenesis, was significantly enriched.

Conclusions: We successfully developed a biomimetic meniscus scaffold using 3D-printing. This scaffold exhibits viscoelastic mechanics, robust mechanical performance, and excellent biocompatibility, promoting SMSC activity and tissue integration *in vivo*. Crucially, its biomimetic mechanical stimuli could activate the PI3K-Akt mechano-transduction pathway in SMSCs, directing them toward a chondrogenic phenotype. This study presents a promising strategy for meniscus tissue engineering.

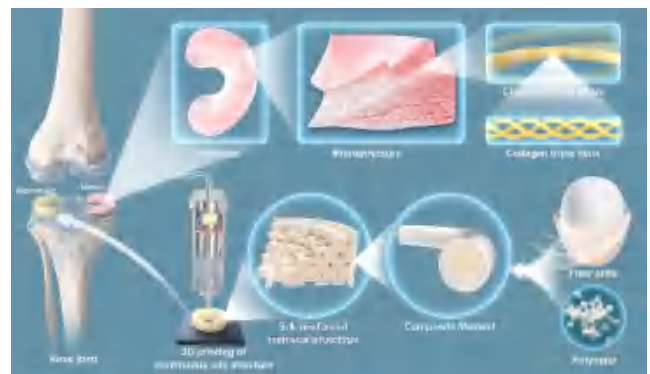


Fig. 1. Schematic illustration of biomimetic design and fabrication for a meniscus scaffold.

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Key words: meniscus, fibrocartilage, structural biomaterial, fiber reinforced composite, mechano-transduction

3D printing programmed diagnostic and therapeutic bioactive “all-in-one” microspheres with multistimuli responsiveness for cartilage regeneration

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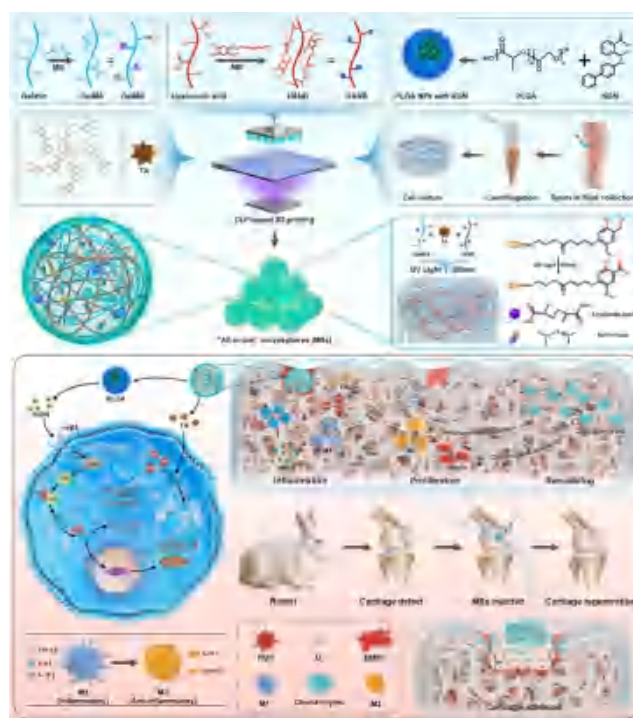
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Introduction: Direct injection of stem cells is a desirable minimally invasive strategy for cartilage repair. However, the adverse immune microenvironment, low cell viability, short joint retention and undirected differentiation significantly limit their therapeutic efficacy and clinical implementation. Hence, the bioactive “all-in-one” microspheres (MSs) integrated with synovial fluid-derived mesenchymal stem cells (SF-MSCs) and kartogenin (KGN)-loaded poly (lactic-co-glycolic acid) (PLGA) nanoparticles were fabricated by a novel digital light processing (DLP)-based 3D printing technology for microenvironmental remodeling, prolonged drug delivery and stem cell differentiation.

Key words: 3D printing, microspheres, KGN, cartilage regeneration

Materials & Methods: A novel DLP-based 3D printing technology was used to fabricate dual-logic-based bioactive “all-in-one” microspheres integrated with synovial fluid-derived mesenchymal stem cells (SF-MSCs) and KGN-loaded PLGA nanoparticles for minimally invasive cartilage regeneration. The molecular mechanisms of the bioactive “all-in-one” MS culture system to promote SF-MSCs chondrogenic differentiation was explored. The in vivo cartilage repair performance was further evaluated.

Results & Discussion: DLP-based 3D printing can print thousands of microspheres in a few seconds and maintain high cell viability without shear force effects. The hydroxyl group of TA on the surface of microspheres can form hydrogen bonds with the amino groups exposed on the cartilage, thereby fixing the microspheres and facilitating the long-term joint retention of stem cells (**Fig.1**). Then, the GelMA/HANB/TA bioink can scavenge ROS and the colloidal network of GelMA provides bioactive motifs for matrix metalloproteinase (MMP)-induced degradation to show “diagnostic” logic. For a therapeutic perspective, KGN-loaded PLGA nanoparticles incorporated into microspheres could be sustained-released to promote cell migration, SF-MSCs’ proliferation and chondrogenic differentiation. Transcriptome sequencing revealed that the mechanism of printed MSs can promote the proliferation and chondrogenic differentiation of SF-MSCs via CCN1/CYR61-mediated activation of the downstream integrin/PI3K/Akt signaling pathways. Animal studies



also shown that the printed MSs effectively facilitated cartilage repair.

Fig. 1. A schematic of the fabrication of bioactive “all-in-one” microsphere for cartilage repair.

Conclusions: In summary, we have developed a novel bioactive “all-in-one” MS culture system for stem cell delivery and sustained drug release via DLP- based 3D printing. the printed MSs can promote SF-MSCs chondrogenic differentiation via cysteine-rich protein 61 (CCN1/ CYR61)-mediated activation of the downstream integrin/PI3K/Akt signaling pathways. In vivo studies showed that the printed MSs with tissue adhesive ability facilitate the long- term joint retention of stem cells and promote cartilage regeneration.

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Zinc-Modified Nanocomposite Hydrogels as Active Platforms for Irisin-Mediated Cartilage Repair

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Key words: osteoarthritis, hydrogels, cartilage regeneration, biomaterials, tissue engineering

Introduction: Osteoarthritis (OA) affects over 240 million people worldwide and is characterized by progressive cartilage degeneration and limited regenerative capacity [1]. Irisin, a myokine released during physical activity, has demonstrated chondroprotective and anabolic effects, including stimulation of type II collagen synthesis [2]. However, effective local delivery strategies are lacking. This study aimed to develop an injectable nanocomposite hydrogel designed to actively support cartilage regeneration while delivering irisin locally.

Materials & Methods: Hydrogels were formulated using methacrylated hyaluronic acid (HAmE) and PEG-DA, enriched with Zn-Mg modified forsterite particles (Mg_2SiO_4 , $\text{Mg}_{1.5}\text{Zn}_{0.5}\text{SiO}_4$, $\text{Mg}_1\text{Zn}_1\text{SiO}_4$, $\text{Mg}_{0.5}\text{Zn}_{1.5}\text{SiO}_4$, and Zn_2SiO_4) at different concentrations (0.1% and 1% w/v). Primary human chondrocytes were cultured on hydrogels, and the most promising ceramic formulation was subsequently loaded with irisin (25-150 ng/ml). We assessed proliferation (Alamar Blue), chondrogenic gene expression (SOX9, ACAN, COMP, COL2A1) by qRT-PCR, and extracellular matrix deposition via Alcian Blue staining.

Results & Discussion: All formulations demonstrated biocompatibility and supported chondrocyte viability. Increased ceramic content (1% vs 0.1%) enhanced cell proliferation (Figure 1A). Among the tested groups, the Zn_2SiO_4 formulation showed the most pronounced pro-chondrogenic profile, significantly upregulating SOX9, ACAN, COMP, and COL2A1 expression (Figure 1B). Irisin further enhanced proliferation (Figure 2A) and gene expression (Figure 2B), and increased proteoglycan deposition (Figure 3), with 100 ng/ml producing the most stable and sustained chondrogenic response. The data reveal a clear synergistic interaction between zinc-mediated bioactivity and irisin signalling.

Conclusions: The Zn_2SiO_4 1% (w/v) hydrogel loaded with 100 ng/ml irisin demonstrated optimal in vitro regenerative performance, combining controlled release, bioactive stimulation, and minimally invasive administration. Ongoing studies are evaluating safety and therapeutic efficacy in animal models of induced osteoarthritis to support future clinical translation.

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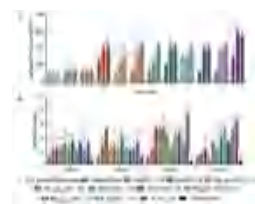


Fig. 1. Cellular proliferation (A) and chondrogenic gene expression (B) of human primary chondrocytes seeded on HAmE/PEG-DA hydrogels enriched with Zn-Mg modified forsterite particles at 0.1% and 1% w/v for 21 days.

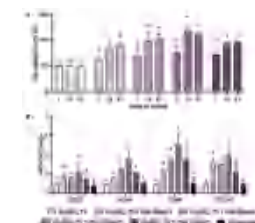


Fig. 2. Cellular proliferation (A) and chondrogenic gene expression (B) of human primary chondrocytes seeded on Zn_2SiO_4 1% (w/v) hydrogels loaded with 25-150 ng/ml of Irisin for 21 days.

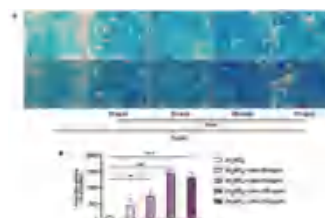


Fig. 3. Representative histological staining (A) and quantitative analysis (B) of extracellular matrix deposition of human primary chondrocytes seeded on Zn_2SiO_4 1% (w/v) hydrogels loaded with 25-150 ng/ml of Irisin for 21 days.

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Kartogenin-loaded Aminated Hollow Mesoporous Prussian Blue Nanozyme-reinforced Hydrogel Remodels Senescent Microenvironment via ROS Scavenging and STING Inhibition to Promote Cartilage Regeneration

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Key words: cartilage regeneration, senescent microenvironment, nanozyme-reinforced hydrogel, ROS scavenging, STING inhibition

Introduction: Bone cartilage defects are common and challenging clinical problems, often leading to osteoarthritis and ultimately damaging joint function. Currently, there is no effective therapy that can prevent or reverse the progression of this lesion. Therefore, it is urgent to develop effective early intervention strategies to promote cartilage regeneration.

Methods: The successful synthesis of NH₂-HMPB nanozymes was verified by various methods such as SEM, TEM, and HAADF-STEM. The successful construction of NH₂-HMPB nanozymes loaded with Kartogenin (KGN) (NH@K nanozymes) was verified by XPS. The scavenging ability of reactive oxygen species of NH₂-HMPB nanozymes was detected by EPR. In cell experiments, it was verified that NH@K nanozymes promote cell proliferation, cell recruitment ability, promote cartilage differentiation, have antioxidant stress effects, mitochondrial protection ability, inhibit the cGAS-STING pathway, and have anti-cell aging effects. RNA sequencing analysis predicted that NH@K nanozymes participate in regulating signaling pathways related to cartilage formation and inflammation. Finally, a rat bone cartilage defect model was established to verify the cartilage regeneration ability.

Results: An injectable dual-functional hydrogel system enhanced by NH@K nanozymes (HAMA-NH@K hydrogel) was successfully prepared. The cGAS-STING signaling pathway promotes inflammatory response and inhibits cartilage regeneration. HAMA-NH@K hydrogel promotes extracellular matrix reconstruction and cartilage regeneration in both in vivo and in vitro experiments.

Conclusion: HAMA-NH@K hydrogel can reshape the aging microenvironment, inhibit the cGAS-STING signaling pathway, promote

cartilage regeneration, and provide a new potential strategy for the treatment of bone cartilage defects.

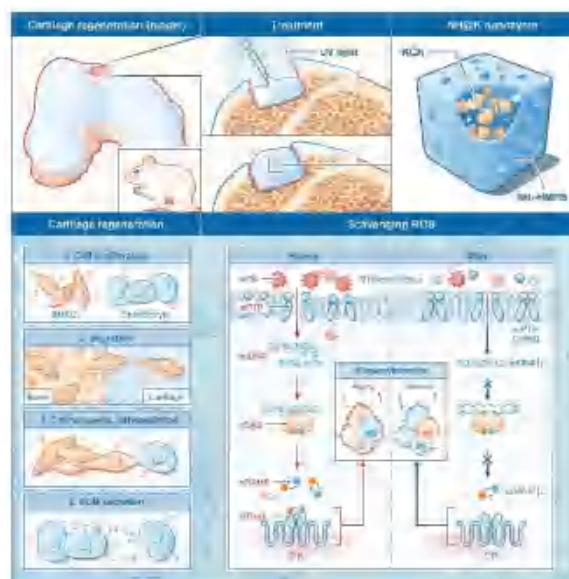


Figure 1 Schematic illustration of HAMA-NH@K hydrogel promotion of cartilage regeneration.

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Continuous mechanical-gradient scaffold with on-demand distributed $\text{Mn}^{2+}/\text{Mg-HA}@\text{Fe}_3\text{O}_4$ for osteochondral repair

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Introduction

Traditional layered gradient scaffolds for osteochondral repair face stress concentration and delamination due to interlayer mechanical discrepancies, while existing continuous gradient scaffolds suffer from single functional components and inadequate spatial regulation, failing to meet regional differentiated needs^[1,2]. This study developed a continuous magnetic-mechanical gradient hydrogel with on-demand functional components to address these limitations and explore its synergistic mechanism in full-thickness osteochondral regeneration^[3].

Materials & Methods

Magnetic particles (FMHM) were fabricated by depositing magnesium-doped hydroxyapatite on Fe_3O_4 nanoparticles and grafting carbon-carbon double bonds. The continuous gradient scaffold (CGGel) was prepared via magnetic field-induced gradient distribution of FMHM in poly(ethylene glycol) diacrylate/sodium alginate solution, followed by thermal polymerization and Mn^{2+} crosslinking, with uniform (UGel) and hierarchical gradient (HGGel) scaffolds as controls. Physicochemical characterization, *in vitro* cell experiments (BMSCs, HUVECs), and *in vivo* evaluations on rat osteochondral defect models (with/without gradient magnetic field) were conducted.

Results & Discussion

CGGel exhibits continuous gradients in mechanics, magnetism, and element distribution (with $\text{Fe}/\text{Mg}/\text{Ca}$ and Mn presenting inverse gradients). *In vitro*, Mn^{2+} promotes the chondrogenic differentiation of BMSCs, while Mg-HA and Fe_3O_4 enhance the osteogenic differentiation of BMSCs and the expression of angiogenesis-related genes in HUVECs, respectively. CGGel outperforms UGel and HGGel in promoting chondrogenic differentiation (upregulated SOX9 and Col-II) and osteogenic differentiation (elevated ALP and Runx2), which may be attributed to gradient-modulated YAP1 expression (YAP1 negatively regulates chondrogenic differentiation and positively regulates osteogenic differentiation)^[4]. Animal experimental results demonstrate that the continuous gradient scaffold CGGel significantly promotes the functional regeneration of full-thickness osteochondral defects in rat knee joints; when combined with a gradient magnetic field, it achieves the smoothest cartilage surface, the highest new bone volume fraction, and the optimal collagen distribution.

Conclusions

This hydrogel enhances full-thickness osteochondral regeneration by mimicking natural gradients and regulating YAP1-mediated mechanotransduction, with gradient magnetic field further improving efficacy. Future studies should refine component distribution precision and conduct long-term preclinical trials, providing a novel strategy for gradient tissue repair.

Key words: continuous mechanical gradient, manganese, Mg-doped hydroxyapatite, osteochondral repair, YAP1

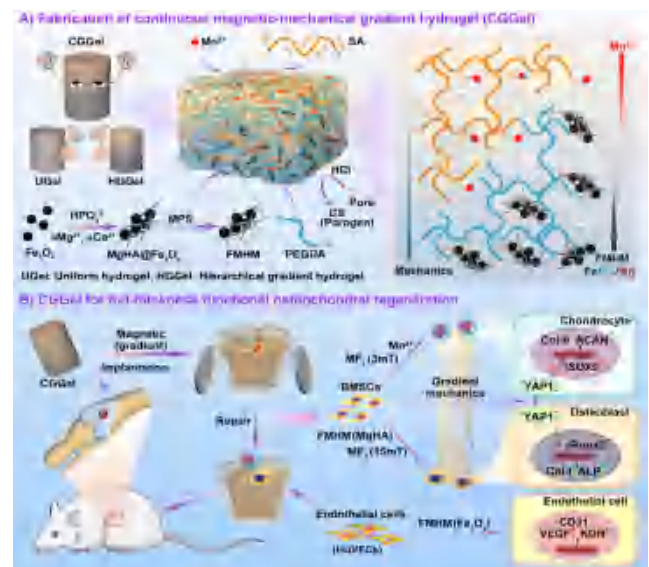


Fig. 1. Fabrication and biomedical application of continuous gradient scaffold.

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Bioactive 3D Printing Bioink Enabling Personalized Tissue Defect Repair

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There is an urgent clinical need for the repair of tissue damage caused by cartilage defects, osteoarthritis (OA), tumor resection, and bacterial infections. Tissue engineering techniques are seen as a promising solution to this challenge, but there is currently a lack of 3D printed bioinks for different pathological microenvironments. This study aims to address the core issue of achieving tissue regeneration under various pathological conditions.

To tackle this challenge, we optimized the synthesis process and successfully developed novel bioactive bioinks, including naringin-gelatin bioink, rutin-silk fibroin bioink, pea protein isolate bioink, nano-composite immune silk fibroin bioink, and degraded fucoidan bioink, etc. Naringin-gelatin effectively enhances the structural fidelity of 3D bioprinting while facilitating efficient cartilage regeneration. Rutin-silk fibroin significantly promotes cartilage tissue regeneration under oxidative stress conditions. Pea protein isolate, as a novel bioink material, shows superior cartilage regeneration effects compared to gelatin. The degraded fucoidan bioink maintains excellent printability while exhibiting high mechanical strength and multifunctional bioactivities, including antioxidant and antibacterial properties, thereby achieving a synergistic integration of load-bearing support and regulation of complex pathological microenvironments. Through a series of 3D bioprinting experiments, these bioinks have demonstrated high fidelity and bioactivity. Overall, our research provides new possibilities for cartilage defect repair and tissue regeneration, paving the way for advancements in personalized medicine and tissue engineering.

Key words: tissue engineering; 3D printing; Bioink; Tissue repair

Manipulating neural cell behaviors and their niche via injectable, photothermally welded 3D nanofibrous microspheres for neuroid tissue construction

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Key words: Nanofibrous microspheres, Photothermal welding, Neural stem cells, Oligodendrocytes, Neuroid tissue

Introduction: Neuroid tissue plays an imperative role to serve as an in-vitro model in the study of complex nervous systems. However, its construction mainly relies on the formation of stem cell autonomous clusters, which have limitations in controllable repetition of structural and functional characteristics and insufficient spatial specificity. In order to advance the precision and functionality of in-vitro construction of neuroid tissue, electrospun fiber-based materials have been explored to sought for possibility in creating neuroid tissues. The fibrous networks simulate the topological and biomechanical properties of ECM, providing mechanical support and signal transduction to regulate cell adhesion, migration, and organoid maturation. Among others, bionic nanofiber microspheres are expected to be systematically explored their applications in regulating stem cell activity and constructing neuroid tissues.

Materials & Methods: We have carried out research on the construction of neuroid tissues using the nanofibrous microspheres. Uniaxially aligned nanofibers welded with or without NGF-loaded microparticles were successfully obtained by electrospinning and electrospray. Then, short fibers were electrosprayed to produce injectable nanofibrous microspheres. After 7 days of co-culturing with neural stem cells (NSCs), immunofluorescence staining was carried out. Furthermore, to explore how oligodendrocytes (OLGs) regulate myelin formation, they were co-cultured with PCL nanofibrous microspheres for 7 days to facilitate their adhesion and adaptation to the scaffold microenvironment. Then, NSCs were introduced into the OLGs-microsphere co-culture system for an additional 7 days of co-culture. The self-assembly of single cells and the formation of multi-cell aggregates were investigated using immunofluorescence staining.

Results & Discussion: The basic structure of biocompatible nanofibrous microspheres comprises short fibers that can form a 3D biomimetic network. In a proof-of-concept demonstration (Fig. 1), the nanofibrous microspheres promoted the creation of 3D clusters of NSCs and supported their differentiation. When engineering the microspheres with the capacity for controlled release of NGF, the differentiation of NSCs was controlled to yield a greater proportion of neurons in comparison to astrocytes. Moreover, such microspheres facilitated co-culture of both OLGs and NSCs, contributing to the increased formation of myelin

around the NSC-differentiated neurons, indicating the success replication of mutual interactions between different types of neural cells. Finally, the construction of neuroid tissues were achieved by self-assembling single or multiple microspheres with co-culture of oligodendrocytes and neurons.

Conclusions: Nanofibrous microspheres serve as a biomimetic platform that bridges in vitro simplicity and in vivo complexity, enabling controlled modulation of neural cell fate and tissue organization. By integrating NSCs differentiation, OLGs myelination, and multicellular self-assembly, this system recapitulates staged processes of neural development and regeneration. Their capacity to support NSCs-OLGs interactions mimicking myelination within these neural-like tissues underscores utility in modelling both normal development and pathological states. It supports the self-assembly of single cells and multicellular aggregates into diverse neural-like tissues, whose cellular interactions and structural configurations closely approximate in vivo neural tissue complexity.

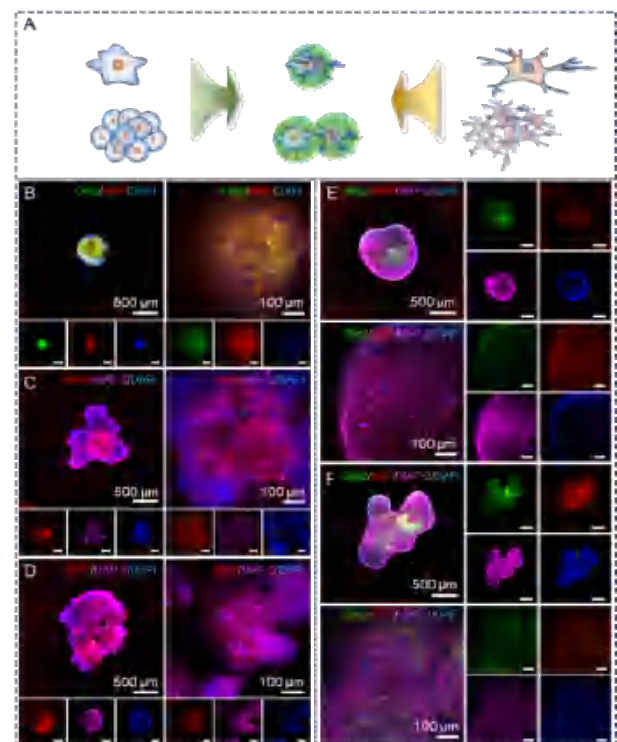


Fig. 1. Self-assembly of neuroid tissues on nanofibrous microspheres: single- and dual-cell systems. (A) Schematic illustration. (B-F) Immunofluorescent staining and high-magnification observations.

Bridging immune-neurovascular crosstalk via the immunomodulatory microspheres for promoting neural repair

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Key words: Immune modulating microsphere, Ischemic stroke, Crosstalk, Angiogenesis, Neurogenesis

Introduction: The crosstalk between immune cells and the neurovascular unit plays a pivotal role in neural regeneration following central nervous system (CNS) injury. Maintaining brain immune homeostasis is crucial for restoring neurovascular function after stroke. In this study, an interactive bridge was developed via an immunomodulatory hydrogel microsphere to link the interaction network between microglia and the neurovascular unit, thereby precisely regulating immune-neurovascular crosstalk and achieving neural function recovery.

Results & Discussion: This immunomodulatory crosstalk microsphere (MP/RIL4) was composed of microglia-targeted RAP12 peptide-modified interleukin-4 (IL-4) nanoparticles and boronic ester-functionalized hydrogel using biotin-avidin reaction and air-microfluidic techniques. We confirmed that the immunomodulatory microspheres reduced the expression of pro-inflammatory factors including IL-1 β , iNOS, and CD86, while upregulating levels of anti-inflammatory factors such as IL-10, Arg-1, and CD206 in microglia. In addition, injection of the MP/RIL4 significantly mitigated brain atrophy volume in a mouse model of ischemic stroke, promoted neurobehavioral recovery, and enhanced the crosstalk between immune cells and the neurovascular unit, thus increasing angiogenesis and neurogenesis of stroke mice.

Conclusions: In summary, the immunomodulatory microspheres, capable of orchestrating the interaction between immune cells and neurovascular unit, hold considerable therapeutic potential for ischemic stroke and other CNS diseases.

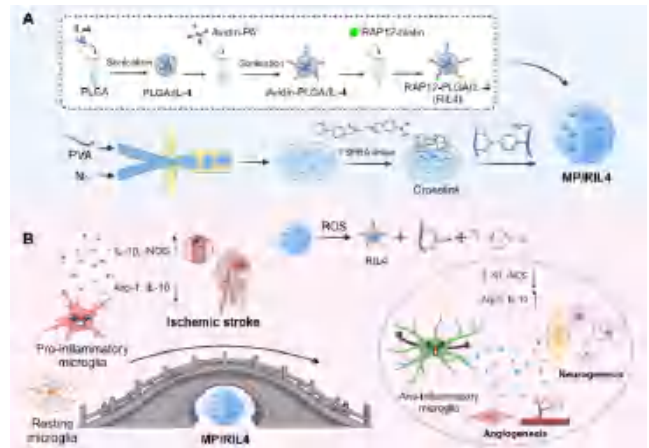


Fig. 1. Schematic diagram of immunomodulatory microsphere (MP/RIL4) for bridging immune neurovascular crosstalk. (A) Preparation of the immunomodulatory microsphere (MP/RIL4). RAP12 modified nanoparticle with IL-4 was prepared via biotin-avidin reaction, and the boronic ester-functionalized PVA microspheres were fabricated using air-microfluidic technique and crosslinking with TSPBA. MP/RIL4 was obtained by adding the RIL4 nanoparticles into the lyophilized MP microspheres through negative pressure suction. (B) MP/RIL4 promoted the polarization of microglia to anti-inflammatory phenotype in vitro and in vivo, and improved neurogenesis and angiogenesis of ischemic stroke mice. The schematic diagram was created with BioRender.com.

Mechanical and Bioactive Adhesive Hydrogels Facilitating Transected Peripheral Nerve Regeneration through AKT Pathway Modulation

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Abstract

Peripheral nerve injury often leads to chronic pain and motor dysfunction due to delayed regeneration. Tissue adhesives have emerged as potential alternatives to surgical sutures, but their clinical translation is hindered by weak adhesion (<10 kPa) and insufficient bioactivity. Herein, we developed GP-DA@Lip@QK, an injectable hydrogel adhesive composed of dopamine-modified tetra-armed poly(ethylene glycol) succinimidyl carbonate (Tetra-PEG-SC), fish gelatin, and VEGF-mimetic peptide (QK)-loaded nanoliposomes. This hydrogel exhibits ultrafast gelation (195 – 276 s, tunable by gelatin concentration), robust adhesion (lap shear strength: 14.1 ± 2.6 kPa vs. 10.2 ± 1.1 kPa for fibrin glue), and sustained QK release (80% over 72 h). In vivo, GP-DA@Lip@QK promoted macrophage polarization to the M2 phenotype (CD206⁺/CD68⁺ ratio: $2.3 \times$ control) and angiogenesis (CD31⁺ vessels: 22.6 ± 2.6 vs. 12.6 ± 0.9 in sham). In rat sciatic nerve transection models, the treated group showed enhanced axon regeneration (NF200 density: 85% of intact nerves), myelination (G-ratio: 0.46 ± 0.014), and functional recovery (SFI: -46.8 vs. -80.7 for untreated). RNA-seq revealed activation of VEGF/ERK pathways in Schwann cells, confirming dual mechanisms of immunomodulation and vascularization. This multifunctional hydrogel addresses the limitations of current adhesive materials and provides a clinically feasible approach for sutureless peripheral nerve repair.

Key words: Bioadhesives, peripheral nerve regeneration, macrophage regulation, neovascularization, AKT pathway

Introduction: Peripheral nerve injury is a critical public health issue causing pain, limb dysfunction, and even permanent disability, especially for long-distance defects. Autologous nerve transplantation, the gold standard for long-distance defects, suffers from donor scarcity, neuroma formation, and nerve mismatch. Tissue adhesives have been proposed as promising alternatives to surgical sutures for nerve repair due to their minimally invasive nature and ability to create a favorable regenerative microenvironment. However, existing adhesives are limited by weak tensile/adhesion strength and inadequate bioactivity, failing to simultaneously meet the requirements of instant adhesion, biocompatibility, and pro-regenerative capacity.

Nerve regeneration requires orderly reconstruction of vascular endothelial cells, Schwann cells, macrophages, and axons. Macrophages are early recruited to the injury site, releasing VEGF to promote angiogenesis, which further guides Schwann cell migration and axon regeneration. Thus, constructing bioadhesives with pro-angiogenic and anti-inflammatory properties is crucial for nerve repair. VEGF is a potent angiogenesis promoter but is limited by high cost, short half-life, and dose-dependent side effects. QK, a VEGF-mimetic peptide, offers a stable and low-immunogenic alternative, but controlled release is needed for sustained efficacy. Herein, we designed GP-DA@Lip@QK by integrating dopamine-modified PEG, gelatin, and QK-loaded nanoliposomes to achieve robust adhesion, immunomodulation, and sustained pro-angiogenic signaling, addressing the unmet needs in peripheral nerve repair.

Materials & Methods: Tetra-PEG-SC, fish gelatin, dopamine hydrochloride, lecithin, cholesterol, and QK peptide (Ac-KLTWQELYQLKYKGI-NH₂, purity >95%) were used as raw materials. Cell lines (RSC96, HUVEC, RAW264.7) were purchased from the Cell Bank of the Chinese Academy of Sciences. Sprague-Dawley (SD) rats (6 – 8 weeks old, 200 – 220 g) were used for in vivo experiments.

Preparation of GP-DA@Lip@QK Hydrogel

QK-loaded nanoliposomes (Lip@QK): Lecithin (160 mg) and cholesterol (40 mg) were dissolved in dichloromethane, evaporated to form a lipid film, and hydrated with QK aqueous solution ($5 \mu\text{g/mL}$). Sonication and extrusion through $0.45 \mu\text{m}$ and $0.22 \mu\text{m}$ filters

yielded Lip@QK.

Dopamine-modified Tetra-PEG (DA-PEG-(SC)₄): Tetra-PEG-SC was reacted with dopamine to obtain DA-PEG-(SC)₄ with a catechol grafting degree of ~25%.

Hydrogel fabrication: DA-PEG-(SC)₄ was mixed with fish gelatin solutions (250, 300, 350 mg/mL) to form GP-DA-250, GP-DA-300, and GP-DA-350. GP-DA-300 (GPD) was selected for further modification. GPD@QK (2 mg QK mixed with gelatin) and GPD@Lip@QK (20 mg Lip@QK mixed with gelatin) were prepared.

Characterization
Gelation time, morphology (SEM), porosity, mechanical properties (compressive strength, shear strength), rheological behavior, and QK release (ELISA) were characterized. Cytocompatibility (CCK-8, live/dead staining), macrophage polarization (DCFH-DA assay for ROS), and angiogenesis (tube formation assay) were evaluated in vitro.

In Vivo Experiments

Rat sciatic nerve transection models (5 mm defect) were established and divided into 5 groups: sham, transected, surgical suture, GPD, GPD@QK, and GPD@Lip@QK. Hydrogel ($20 \mu\text{L}$) was injected around the nerve stumps. At 8 weeks post-surgery, nerve regeneration was assessed by Masson staining, immunofluorescence (S100, NF200, CD31, CD68, CD206), TEM, and functional recovery (sciatic function index, SFI; gastrocnemius wet weight ratio). RNA-seq was performed on Schwann cells cultured with GPD@Lip@QK extract.

Results & Discussion: Hydrogel Characterization

GPD (GP-DA-300) exhibited optimal properties: gelation time (217 s), porosity ($46.7\% \pm 1.7$), compressive strength (1.2 MPa at 93% strain), and shear strength (34 kPa). Lip@QK had a mean size of 167 nm and zeta potential of -42.8 mV, with an encapsulation efficiency of 93.2%. GPD@Lip@QK showed sustained QK release (80% over 72 h) and maintained mechanical stability, with $G' > G''$ over a wide frequency range.

Biocompatibility and Bioactivity

In vitro, GPD@Lip@QK extract promoted RSC96 and HUVEC proliferation (cell viability >100% at 5 days) and inhibited LPS-induced ROS production in RAW264.7 cells (ROS level reduced by 50%). Tube formation assay showed GPD@Lip@QK significantly increased HUVEC tube formation (22.6 ± 2.6 vessels vs. 12.6 ± 0.9 in control) via activation of VEGFR2/ERK/AKT pathways.

In Vivo Nerve Repair

Histology: GPD@Lip@QK reduced collagen deposition (Masson staining) and promoted neovascularization (CD31⁺ vessels: 22.6 ± 2.6). Macrophage polarization to M2 was enhanced (CD206⁺/CD68⁺ ratio: $2.3 \times$ control).

Nerve regeneration: S100 (Schwann cells) and NF200 (axons) expression was highest in GPD@Lip@QK, with axon density reaching 85% of intact nerves. TEM showed thicker myelin sheaths ($1.28 \pm 0.04 \mu\text{m}$) and lower G-ratio (0.46 ± 0.014) compared to other groups.

Functional recovery: GPD@Lip@QK improved SFI (-46.8 vs. -80.7 for transected) and maintained gastrocnemius wet weight (injury/control ratio: ~90%). RNA-seq identified upregulation of neurodevelopment-related genes (Cldn4, Tph1) and activation of Wnt/PI3K-AKT/MAPK pathways.

Conclusions: GP-DA@Lip@QK hydrogel integrates ultrafast gelation, robust wet adhesion, sustained QK release, immunomodulation, and pro-angiogenic activity. It effectively promotes peripheral nerve regeneration by regulating macrophage polarization, enhancing angiogenesis, and activating VEGF/ERK/AKT pathways. Future studies will focus on optimizing gelation/degradation rates for clinical applicability and evaluating efficacy in larger nerve defects. This work provides a multifunctional bioadhesive platform for sutureless peripheral nerve repair, with great potential for clinical translation.

A biodegradable and restorative peripheral neural interface for the interrogation of neuropathic injuries

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Abstract: Neurological diseases affect millions of people worldwide and encompass a wide range of disorders that impact the nervous system, including the brain, spinal cord, and peripheral nerves. In the treatment of these conditions, electrical stimulation plays a crucial role as an essential nonpharmacological therapy. Techniques such as deep brain stimulation, spinal cord stimulation, and peripheral nerve stimulation have shown promise in managing symptoms and improving outcomes. However, current clinical electrical therapies often face limitations, such as being confined to intraoperative or percutaneous stimulation, which restricts the duration of treatment and poses risks of infection. Additionally, monitoring the early-stage healing of severe traumatic nerve injuries is essential to gather physiological and pathological information for timely interventions and optimal clinical outcomes. Traditional diagnostic methods relying on physical examinations, imaging tools, and intraoperative electrophysiological testing present great challenges in continuous and remote monitoring. While implantable peripheral nerve interfaces provide direct access to nerve fibers for precise interrogation and modulation, conventional non-degradable designs pose limited utilization in nerve injury rehabilitation. To address these challenges, we propose a fully biodegradable, self-electrified, and miniaturized device composed of dissolvable galvanic cells based on biodegradable metals ^[1]. This device not only stimulates calcium activity and promotes the secretion of neurotrophic factors in Schwann cells but also facilitates peripheral nerve regeneration in rat models. Moreover, our research has led to an intriguing discovery regarding silicon nanomembranes (Si NMs), traditionally known for their stability as semiconductor materials. Through an investigation of thickness changes as a function of soaking time of a patterned array of Si NM squares in buffer solutions, we have found that Si NMs exhibit unique hydrolysis behaviors highly dependent on device dimensions and surface chemistry ^[2]. Building upon this knowledge, we have developed Si NM-based signal recording electrode arrays with tunable dissolution lifetimes, achieved through meticulous geometrical designs. Furthermore, we introduce a biodegradable and restorative neural interface for wireless real-time tracking and electrical stimulating the recovery of long-gap nerve injuries ^[3]. Leveraging machine learning techniques, this electronic platform deciphers nerve recovery status and identifies traumatic neuroma formation at the early phase, enabling timely intervention and significantly improved therapeutic

outcomes. The biodegradable nature of the device eliminates the need for retrieval procedures, reducing infection risks and secondary tissue damage. This research sheds light on bioresorbable multifunctional peripheral nerve interfaces for probing neuropathic injuries, offering vital information for early diagnosis and therapeutic intervention.

Key words: nerve regeneration, biodegradable biomaterials, neural interface

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Promoting retinal ganglion cell regeneration with targeted liposome-based delivery of MHY1485 for optic nerve repair

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Key words: Liposome Targeted delivery MHY1485
Retinal ganglion cells Regeneration

Introduction: Optic neuropathy, a condition characterized by the progressive degeneration of retinal ganglion cells (RGCs), leads to irreversible vision loss and currently lacks a cure^[1]. RGCs, which are responsible for transmitting visual information from the retina to the brain, have limited regenerative capacity, particularly after optic nerve damage^[2]. Current therapies for promoting RGC regeneration, often involving nanoparticle delivery of neuroprotective agents^[3], face challenges in overcoming ocular barriers and ensuring effective drug delivery to the retina^[4]. To address this, targeted drug delivery systems, such as Tet1-functionalized liposomes, have emerged as promising strategies. Tet1, a peptide that specifically binds to RGCs^[5], can be used to enhance the delivery of therapeutic agents like MHY, an mTOR activator known to promote RGC regeneration^[6]. This study aims to investigate whether Tet1-functionalized liposomes can effectively deliver MHY to RGCs, activate the mTOR pathway, and promote RGC survival and regeneration, potentially offering a new approach to treating optic neuropathy.

Materials & Methods: Tet1-Cys was conjugated to DSPE-PEG2k-Mal using a “click” reaction, purified via dialysis, and lyophilized. Liposomes were prepared by thin-film hydration followed by sonication. Lipid mixtures were evaporated, rehydrated with PBS, and stored at 4°C. MHY-loaded liposomes were purified by ultrafiltration. DIO-labeled liposomes were injected into normal rats. Fluorescence from liposomes was quantified to assess RGC targeting efficiency. RGC survival was quantified by counting Tuj-1 and DAPI-positive cells. Axon regeneration was assessed by tracking axons with CTB labeling.

Results & Discussion: Tet1-liposomes are approximately 50 nm in size, negatively charged, and exhibit significant retinal retention. Fluorescently labeled liposomes showed strong co-localization with RGCs, with an RGC uptake rate of 68.97%, compared to 21.58% for unmodified liposomes. MHY-loaded Tet1-liposomes significantly improved RGC axonal regeneration and survival rates, while reducing glial cell activation and levels of pro-inflammatory cytokines.

Conclusions: MHY1485-loaded Tet1-liposomes significantly promote RGCs survival and stimulate axonal regeneration after optic nerve injury. Tet1-modification

enhances liposomal penetration across the inner limiting membrane, improving retinal distribution and retention. RGC-targeting specificity of Tet1-liposomes boosts MHY1485 uptake by RGCs while minimizing off-target accumulation in glial cells. Targeted mTOR activation by MHY1485 in RGCs suppresses glial reactivity and inflammation, contributing to a neuroprotective micro-environment.

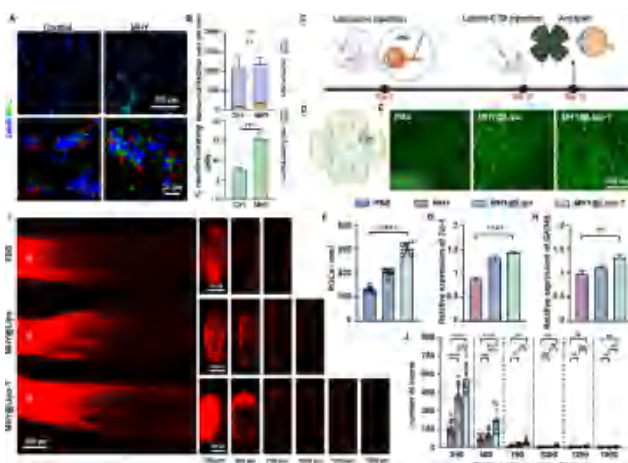


Fig. 1. In vivo evaluation of neuroprotective effects for MHY loaded liposomes in rats 14 days post-ONC. (A) Images of retinal cultures in vitro on day 7. (B) Quantification of the total number of retinal cells and neurite-bearing cells. (C) Time course of the experiment. (D) Schematic description of imaging retinal regions. (E) Confocal images showing RGCs survival. (F) Quantification of Tuj-1+ cells. (G-H) Relative expression of Tuj-1 and GAP43 in the entire retina at 7 days post-ONC. (I) z-stack images of optic nerves. (J) Quantification of the number of axons.

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Interface-Optimized 3D-Bioprinted Neural Constructs with Coordinated Mechanical Compatibility and Electrical Coupling for Spinal Cord Injury Repair

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Key words: spinal cord injury repair, neural stem cells, 3D bioprinting living construct, dynamic and conductive hydrogel, interface optimization.

Introduction: Spinal cord injury (SCI) remains a major clinical challenge due to the limited regenerative capacity of the central nervous system and the inability to reconstruct functional neural circuits across lesions. Although various biomaterial-based strategies have been explored, restoring meaningful connectivity between disrupted pathways remains difficult.

Neural stem cell (NSC)-laden engineered constructs offer a promising strategy by providing intrinsic regenerative potential and promoting local neurogenesis. These living implants enhance neuronal differentiation and axonal extension within the construct. However, despite improved intra-construct regeneration, overall functional recovery remains limited. The primary barrier lies at the host–implant interface, where insufficient integration prevents effective synaptic coupling and restricts connectivity between endogenous and transplanted neural networks.

Thus, SCI repair should be reframed as a biointerface integration challenge rather than solely a tissue replacement approach. Beyond geometrical compatibility, successful integration requires coordinated mechanical matching to reduce interfacial stress and electrical coupling to ensure signal continuity.

Here, we develop an interface-optimized engineered neural construct to enhance structural and functional integration, enabling improved neural circuit reconstruction after SCI.

Materials & Methods: GelMA and dopamine modified hyaluronic acid (HADA) were employed as biomimetic matrix components to construct a structurally stable hydrogel network enriched with hydrogen bonding interactions. Trehalose was introduced as a mechanical modulation unit to regulate network dynamics and achieve modulus matching through hydrogen-bond reconfiguration. Black phosphorus nanosheets (BP) were incorporated to establish a biomimetic ion–electron hybrid conductive pathway.

Mechanical and electrical properties were benchmarked against native rat spinal cord tissue to determine the optimal formulation (GHBT). Adhesion strength, conductivity, and interfacial impedance were evaluated. Molecular dynamics simulations and finite element analysis were performed to elucidate the electromechanical coupling mechanisms. NSC-laden constructs (GHBT@NSC) were fabricated via 3D bioprinting for in vitro and in vivo studies.

Results & Discussion: The optimized GHBT hydrogel exhibited mechanical modulus and electrical conductivity closely matching those of native spinal cord tissue. Enhanced interfacial adhesion and reduced impedance suggested improved electromechanical coupling at the tissue–implant boundary. Computational simulations confirmed that trehalose-mediated hydrogen bond modulation enabled adaptive mechanical behavior, while BP incorporation established continuous conductive pathways within the network.

In vitro, NSCs encapsulated within GHBT demonstrated enhanced neuronal differentiation, axonal extension, and neural network maturation, indicating that the mechanically and electrically adaptive microenvironment promotes functional lineage commitment. Notably, improved interface-crossing neurite extension was observed, suggesting strengthened biological integration across boundaries.

Following implantation into a 4-mm complete transection rat SCI model, GHBT@NSC significantly enhanced neural regeneration, electrophysiological recovery, and locomotor improvement. Histological analysis revealed suppressed early interfacial inflammation and scar formation, robust mid-stage axonal infiltration across the implant–host interface, and late-stage reconstruction of continuous neural circuits with increased functional synaptic connectivity.

Collectively, these findings demonstrate that electromechanical interface adaptation enables structural and functional integration, ultimately facilitating effective neural circuit reconstruction after SCI.

Conclusions: We developed a 3D-bioprinted neural construct with coordinated mechanical compatibility and electrical coupling that significantly enhances host–implant integration, neural regeneration, and functional recovery. This interface-optimized strategy provides an effective approach for spinal cord injury repair.

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A Hematoma Microenvironment-Responsive Keratin Nanosystem for Synergistic Neuroprotection and Repair after Intracerebral Hemorrhage

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Key words: intracerebral hemorrhage, iron chelation, keratin, neuroprotection, microenvironment-responsive

Introduction: The treatment of intracerebral hemorrhage (ICH) and the subsequent secondary brain injury remains a significant clinical challenge. The adverse hematoma microenvironment, characterized by iron overload and a damaged extracellular matrix, impedes neural repair. This study aimed to develop a novel therapeutic strategy by constructing a hematoma microenvironment-responsive nanosystem for the synergistic goals of in situ iron chelation, neuroprotection, and neural regeneration.

Materials & Methods: Human hair keratin (K) was extracted, and DOPA-modified keratin (DOPA-K) was synthesized. A hematoma-targeting peptide (FBP-K33AQTY, FBP) was designed. Bexarotene-loaded K/DOPA-K nanoparticles were prepared via ultrasonic precipitation, and FBP was grafted onto their surface. The nanosystem's pH/Fe³⁺ dual-responsive structural transitions were characterized in vitro using TEM, CD, and FT-IR. Its hematoma-targeting ability, iron chelation, degradation, and biosafety were evaluated in vivo in an SD rat ICH model using small-animal imaging, fluorescence staining, and Prussian blue staining. The therapeutic efficacy was assessed through hematoma volume analysis, immunofluorescence for neuroinflammation (CD86/CD163), neuronal apoptosis (TUNEL-NeuN), and behavioral tests..

Results & Discussion: The nanosystem was successfully constructed with a high drug loading rate (70%) and demonstrated a programmed structural transition: pH-responsive swelling and drug release, followed by Fe³⁺-coordinated hydrogel formation. DOPA modification significantly enhanced Fe³⁺ chelation via O-Fe bonds, forming a stable, porous gel (porosity 49.92%) that supported neural cell growth. In vivo, the nanoparticles targeted the cerebral hematoma within 2 hours, significantly reduced iron deposition, and formed stable hydrogel chelates that persisted for 1-3 days before being completely metabolized within 7 days without Fe³⁺ re-release. In the ICH rat model, this system accelerated hematoma resolution, downregulated the pro-inflammatory marker CD86, and upregulated the

anti-inflammatory marker CD163. This led to significantly reduced neuronal apoptosis, enhanced neuroregeneration, and improved functional motor recovery, with the DOPA-K group showing superior outcomes.

Conclusions: This study successfully constructed a hematoma-targeted, pH/Fe³⁺ dual-responsive keratin nanosystem. By enabling precise hematoma targeting, prolonged iron chelation, and a programmed structural transformation from nanoparticles to a neuro-supportive hydrogel, the system achieves synergistic neuroprotection and repair post-ICH. With excellent biocompatibility and safety, this work provides a theoretical foundation for designing microenvironment-responsive carriers and offers a novel and promising therapeutic strategy for treating intracerebral hemorrhage.

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3D Bioprinted Functional Living Nerve-like Construct for Spinal Cord Injury Regeneration

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Key words: neural stem cells, hydrogels, 3D bioprinting, next-generation living constructs, spinal cord injury

Introduction: Spinal cord injury (SCI) leads to severe neurological dysfunction and substantial socioeconomic burdens. Current treatments are limited by the hostile injury microenvironment characterized by inflammation, neuronal loss, and glial scar formation.

Neural stem cell (NSC) transplantation offers benefits but faces challenges like low cell survival and poor differentiation in an inflammatory environment. Successful regeneration relies on reconstructing a supportive microenvironment resembling the disrupted stem cell niche.

3D bioprinting technology enables precise fabrication of tissue-mimetic architectures, offering new opportunities for neural regeneration and recovery. Our previous studies demonstrated that 3D-bioprinted living nerve-like constructs composed of NSC and ECM-mimetic hydrogels refine the regenerative niche and promote long-distance neural repair.^{1, 2}

Here, we propose a next-generation functional neural construct platform based on advanced hydrogel bioinks and integrated multi-modal bioactivation strategies to further enhance SCI repair efficacy. This strategy holds translational potential for advancing SCI therapy.

Materials & Methods: Gelatin and hyaluronic acid served as the foundational matrices for developing next-generation functional bioinks through diverse chemical modifications integrated with advanced nanomaterials, neural electrodes, and optimized fabrication strategies. Comprehensive physicochemical and biofunctional characterizations were conducted to evaluate hydrogel performance and elucidate advanced mechanisms of cell – matrix interactions. Engineered neural constructs were fabricated via 3D bioprinting and implanted into a rat SCI model with a 4-mm complete transection to assess regenerative efficacy and decode biomaterial-mediated neural repair mechanisms.

Results & Discussion: The advanced bioink platform enabled the integration of multiple functional strategies within engineered neural constructs. First, a dynamic network combined with functionalized peptides established a mechanotransduction-mediated three-dimensional microenvironment to enhance neural network self-organization. Building upon this structural cue, metabolic preconditioning through bioactive nanocarriers stabilized NSC energy homeostasis and improved cellular resilience. Meanwhile, mechanical and electrical interface adaptation strengthened

host-implant integration and promoted electrophysiological continuity across lesion sites. In parallel, microenvironmental remodeling via multifunctional nanostructures attenuated inhibitory signals and supported regenerative niche reconstruction. Furthermore, the incorporation of neural electrodes generated cyborg-like neural constructs capable of enhanced bioelectronic communication. Collectively, these coordinated strategies synergistically regulated neural development within engineered tissues and markedly improved regenerative efficacy in spinal cord injury models.

Conclusions: We developed a next-generation 3D-bioprinted functional neural construct based on integrated bioink design and coordinated multi-modal regulatory strategies. This platform-driven approach advances engineered neural tissue development and deepens the understanding of advanced cell-matrix interaction mechanisms underlying NSC neurodevelopment, providing a comprehensive regenerative strategy for spinal cord injury repair.

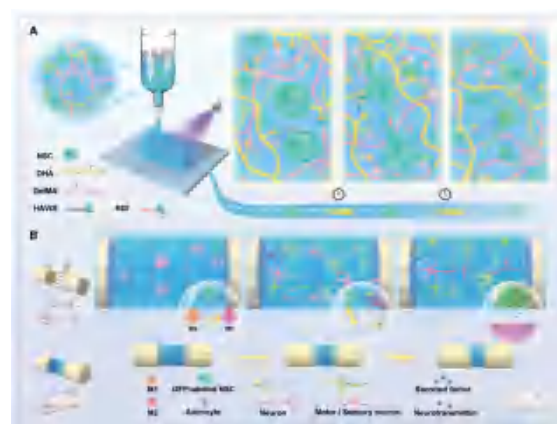


Fig. 1. Scheme showing the fabrication of the 3D bioprinted living nerve-like fibers and the remodeling of the newborn functional network in vivo.

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A Bio-orthogonal Engineered Chitosan Platform for Enhanced Mesenchymal Stem Cells Delivery and Function in Peripheral Nerve Repair

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Introduction Mesenchymal stem cells (MSCs) hold significant potential for the clinical treatment of various diseases, demonstrating particularly promising therapeutic efficacy in neurological disorders and injuries. However, current MSC-based therapies primarily rely on delivery methods such as systemic or local injection and encapsulation within hydrogels. These approaches often suffer from a lack of stable cell anchoring sites, leading to high cell loss, poor in situ retention, and low cell survival rates, thereby compromising the therapeutic outcomes of MSCs^[1]. To address these limitations, we have developed a tissue-engineered MSC-chitosan material platform through bioorthogonal reactions, enabling covalent conjugation between cells and the biomaterial. Furthermore, we systematically investigated how this covalent integration affects MSC functionality, with the aim of enhancing the overall therapeutic efficacy of MSC-based therapies.

Key words: mesenchymal stem cells, chitosan, bio-orthogonal, covalent conjugation, peripheral nerve regeneration

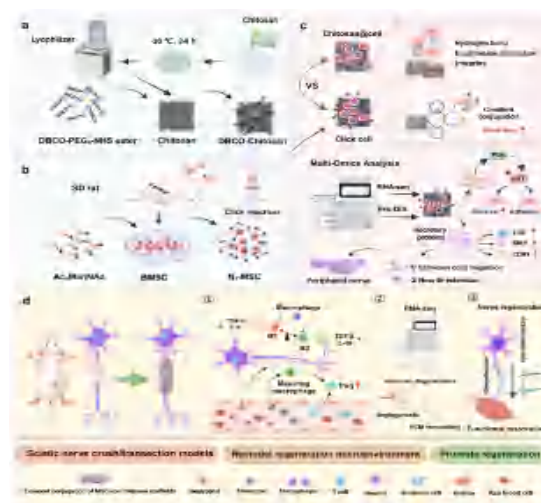
Materials & Methods: In this study, an engineered chitosan-MSC covalent conjugation platform was developed via strain-promoted azide-alkyne cycloaddition (SPAAC) to achieve enhanced and stable anchoring of MSCs onto chitosan-based materials. Optimization of modification conditions via controlled experiments to enable subsequent bioorthogonal reactions. Subsequently, azide-modified MSCs were co-cultured with DBCO functionalized chitosan scaffolds to establish a covalent MSC-chitosan conjugation platform. Multi-omics analysis of the impact of covalent crosslinking on MSC functional regulation. Finally, covalently conjugated MSC-chitosan materials were implanted into rat models of sciatic nerve injury. To evaluate the nerve repair efficacy of covalently conjugated MSCs, assessments were performed at 6 weeks post-sciatic nerve crush injury and at 12 weeks post-10-mm sciatic nerve gap injury, respectively.

Results & Discussion: This study successfully established a covalently conjugated engineered MSC-chitosan platform. *In vitro* studies demonstrate that covalent conjugation effectively enhances the retention of MSCs on chitosan-based biomaterials. Multi-omics analyses reveal that, covalent conjugation promotes MSC adhesion and survival by activating the

PI3K-AKT signaling pathway, while simultaneously upregulating the secretion of multiple neuroregeneration-promoting proteins. *In vivo*, bioorthogonal chemistry-mediated MSC delivery significantly improves the in-situ retention of transplanted MSCs following neural injury, enabling real-time modulation of the regenerative microenvironment during the early post-injury phase—including accelerated Wallerian degeneration, enhanced angiogenesis, immunomodulation, and extracellular matrix remodelling. Long-term functional assessments confirm that bioorthogonal chemistry-mediated MSC therapy robustly facilitates neural regeneration and functional recovery.

Conclusions: In summary, we developed an MSC-chitosan platform via bioorthogonal chemistry-mediated covalent conjugation. This strategy effectively enhances the retention, survival, and secretion of bioactive factors of MSCs on the material surface through covalent binding. This approach achieved favourable outcomes in promoting nerve regeneration for neural injury repair. This approach not only enhances the therapeutic efficacy of MSC-chitosan-based materials in neural injury repair but also offers novel insights for material-based applications in regenerative medicine.

Fig. 1. Schematic of covalent conjugation of MSCs to chitosan scaffolds regulating biological behavior of MSCs and promoting nerve regeneration in peripheral nerve injury.



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Targeting VEGFR2 inhibition within a spatially-confined conduit promotes nerve self-resolution and alleviates mechanical allodynia

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Key words: Traumatic painful neuroma; Mineralized collagen; GelMA microspheres; VEGFR2; Neuroinflammation

Introduction

The study investigates the pathophysiology of stump neuromas, which are nonfunctional redundant tissues that cause neuropathic pain through disorganized axonal regeneration, pathological angiogenesis, scar hyperplasia, and chronic neuroinflammation. Current therapeutic strategies inadequately address these underlying mechanisms, particularly the excessive production of reactive oxygen species resulting from dysregulated vascular proliferation and activation. The scientific question focuses on whether targeting pathological angiogenesis via a novel biomaterial platform can stop the regrowth of nerve end interface and prevent neuropathic pain.

Materials & Methods

GelMA microspheres (MPs) were covalently functionalized with methacryloyl-modified anti-VEGFR2 peptides (MAVP) to inhibit angiogenesis. These functionalized microspheres were fabricated into linear arrays using 3D printing and integrated into a progressively spatial-constrictive conduit. The system was evaluated in a sciatic nerve ligation model and a stump neuroma model to assess its effects on neuroinflammation, angiogenesis, and pain-related signaling.

Results & Discussion

In the sciatic nerve ligation model, the GelMA^{MAVP} MPs system demonstrated significantly superior analgesic efficacy compared to the conventional VEGFR2 inhibitor vandetanib. In the stump neuroma model, treatment effectively normalized the peripheral nerve end interface by inhibiting neovascularization, M1 macrophage polarization, and fibrotic scar formation. Additionally, the microspheres distributed in nerve stumps indirectly downregulated pain-related proteins (TRPA1/CGRP) in dorsal root ganglia and suppressed spinal microglial activation. These findings highlight the platform's ability to sustain VEGFR2 phosphorylation suppression and coordinated mechanotransduction signaling, thereby inhibiting neuroinflammatory responses and pathological angiogenesis.

Conclusions

This study presents a comprehensive and safe

vascular-targeted strategy that promotes self-resolution of the nerve end interface and prevents neuropathic pain. The GelMA^{MAVP} MPs system offers a promising approach to address the underlying pathophysiology of stump neuromas. Future research should explore long-term efficacy, translational potential in larger animal models, and clinical applicability for neuropathic pain management. The findings underscore the significance of targeting pathological angiogenesis as a therapeutic avenue for neuroma-related pain.

Fig. 1. Schematic illustration of targeted VEGFR2 inhibition within a spatially-confined conduit for the treatment of neuropathic pain.

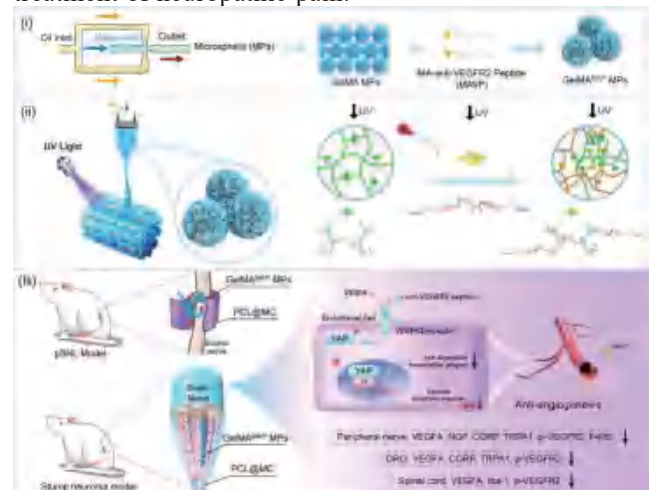
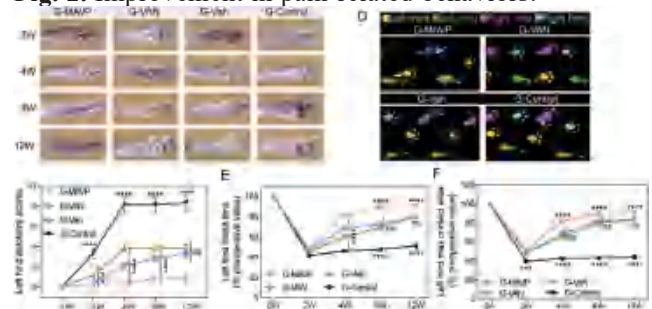


Fig. 2. Improvement in pain-related behaviors.



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Nerve-bone crosstalk in response to bone-guided biomaterials

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Key words: biomaterials, kefir, nerve-bone crosstalk, bone regeneration.

Introduction: Bone regeneration is a multifactorial process coordinated by neural and osteogenic interactions. Despite bone's intrinsic regenerative capacity, large defects remain a global orthopedic challenge, often associated with chronic pain and socioeconomic burden [1]. Current biomaterial-based strategies have improved bone tissue engineering (TE) outcomes, but remain largely osteogenic, frequently neglecting the role of the peripheral innervation in bone repair. The peripheral nervous system (PNS) is a key regulator of bone repair, with early nerve sprouting preceding vascularization and ossification. Impaired neural signaling compromises callus formation and is associated with delayed or non-union fractures [2]. Therefore, next-generation biomaterials should modulate multicellular crosstalk within the regenerative microenvironment [2]. In this context, kefir, a microbial exopolysaccharide, presents promising physicochemical and biological properties for TE applications [3]. This study proposes a kefir-based biomaterial microphysiological system (MPS) aimed at supporting neural integration and modulating nerve-bone crosstalk during bone regeneration.

Materials & Methods: The biocompatibility of kefir hydrogels at 5%, 2%, and 1% (w/v) was assessed using human osteoblasts (HOBs) and sensory neurons derived from dorsal root ganglia (DRGs). Neurite outgrowth was quantified using the AxoFluidic software [4]. Alkaline phosphatase (ALP) activity in HOB was evaluated at days 7, 14 and 21. Engineered 3D bone microtissues (EBM) were created by encapsulating HOB in kefir hydrogels and subsequently characterized.

Results & Discussion:

Preliminary findings demonstrate that kefir-based biomaterials support neuronal viability and neurite outgrowth. HOB cultured in these biomaterials exhibited enhanced metabolic activity and increased ALP levels at day 7. Furthermore, EBM demonstrated improved structural organization and cell morphology compared with control conditions (Fig. 1).

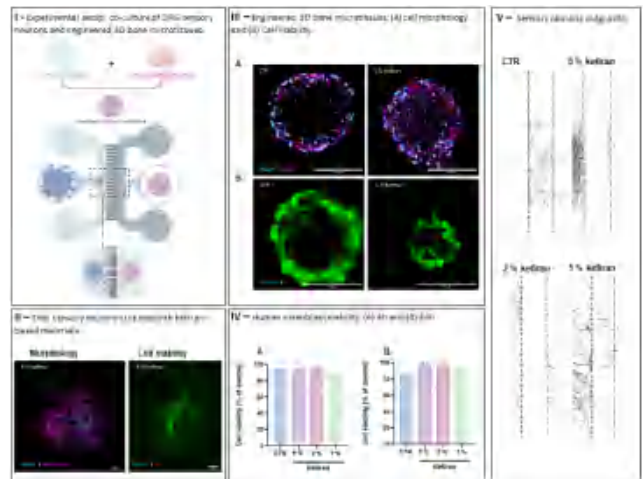


Fig. 1. Experimental assessment of kefir-based biomaterials in neuronal and osteogenic *in vitro* models.

Conclusions: These findings position kefir-based biomaterials as a novel strategy for promoting neural integration and modulating nerve-bone crosstalk during bone regeneration. Ongoing work aims to explore broader implications of this approach, particularly the influence of inflamed EBM on sensory neurons activity.

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Tailored Endothelialization with Cell Membranes Accelerates Remodeling of Small-diameter Vascular Grafts

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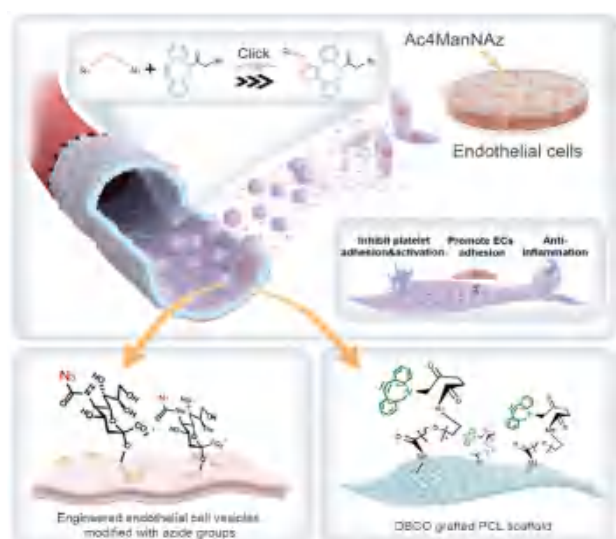
Current gold standard for the replacement of small-diameter blood vessel (ID<4 mm) is still to utilize the autologous vessels of patients due to the limitations of small-diameter vascular grafts (SDVG) on weak endothelialization, intimal hyperplasia and low patency. Herein, we create a SDVG with the tailored endothelialization by applying the engineered endothelial cell vesicles to camouflaging vascular grafts for the enhancement of vascular remodeling. The engineered endothelial cell vesicles were modified with azide groups (ECVs-N₃) through metabolic glycoengineering to precisely link the vascular graft made of PCL-DBCO via click chemistry, and thus fabricating ECVG (ECVs modified SDVG), which assists inhibition of platelet adhesion and activation, promotion of ECs adhesion and enhancement of anti-inflammation. Furthermore, *In vivo* single-cell transcriptome analysis revealed that the proportion of ECs in the cell composition of ECVG surpassed that of PCL, and the tailored endothelialization enabled to differentiate endothelial cell into some specific EC clusters. One of the specific cluster, Endo_C5 cluster, was only detected in ECVG. Consequently, our study integrates the engineered membrane vesicles of ECVs-N₃ from native ECs for tailored endothelialization on SDVG by circumventing the limitations of living cells, and paves a new way to construct the alternative

Key words: Small-diameter blood vessel, Tailored endothelialization, Endothelial Cell Vesicles, Click chemistry, Vessel remodeling

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endothelialization in vessel remodeling following injury.

A Redox-Active and Electroactive Hydrogel for Post-Infarct Myocardial Repair

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Abstract: Free radical scavenging and electrical coupling reconstruction are two critical issues in the early and late stages of myocardial pathology following myocardial infarction. This study developed an integrated nanoparticle, PEDOT@PMOF, which functions as a redox-active nanozyme and conductive nanofiller within a cell-affinity hydrogel platform for acute MI treatment. The material demonstrates favorable catalytic activity, and the incorporation of PEDOT enhances its conductivity. This work presents a novel dual-therapy strategy combining ROS scavenging and electrical coupling reconstruction for future applications.

Key words: hydrogel, nanozyme, electroactive, myocardial infarction

Introduction: Following myocardial infarction, cardiomyocyte injury leads to reactive oxygen species (ROS) accumulation, exacerbating damage and expanding the infarct area. Subsequent fibrosis further disrupts electrical conduction.¹ While metal-organic framework (MOF)-based nanozymes offer promising ROS regulation by mimicking natural enzymes, their insulating organic ligands limit applications in tissue repair.² To address this, a conductive composite nanozyme was synthesized. It features a manganese porphyrin MOF core, which mimics SOD2 activity, coated with a polydopamine adhesion layer and conjugated with conductive poly(3,4-ethylenedioxythiophene) (PEDOT). This design integrates antioxidant and electroactive properties. The resulting nanofiller was incorporated into a cell-affinity hydrogel, creating a multifunctional system for myocardial repair. This combined strategy of ROS scavenging and electrical coupling restoration presents a promising therapeutic approach for post-infarction healing.

Materials & Methods: Redox-active and electroactive nanofillers (PEDOT@PMOF) were fabricated through a polydopamine-assisted in situ assembly approach. The SOD2-mimic metal ligand TCPP-Mn was utilized as a ligand to coordinate with zirconium-oxo clusters via its peripheral carboxylate groups, forming a highly porous MOF structure. Then the MOF particles were pretreated in an alkaline dopamine solution, allowing spontaneous self-polymerization of dopamine to form a uniform PDA nanocoating. Finally, electrostatic interactions and π - π stacking between PEDOT and the PDA-rich PMOF surface facilitated stable anchoring, producing the integrated electroactive nanofiller PEDOT@PMOF. And the hydrogel TAlg is composed of cysteine-terminated cell adhesion peptide T16 grafted with double

bond-functionalized alginate.

Results & Discussion: Extensive in vitro characterization under various oxidative stress conditions confirmed that PEDOT@PMOF exhibits potent catalytic activity and effective ROS scavenging. The presence of the T16 peptide within the hydrogel scaffold promoted neonatal rat cardiomyocyte adhesion, spreading, cytoskeletal organization, and robust calcium transients, all indicative of improved cardiomyocyte maturation and electromechanical coupling. In vivo, administration of the TAlg/PEDOT@PMOF hydrogel in a rat MI model resulted in significant therapeutic benefit: during the early post-MI phase, its ROS-scavenging capacity mitigated oxidative injury and preserved viable cardiomyocytes within the peri-infarct zone; in the subsequent reparative phase, its electroconductive properties facilitated reestablishment of intercellular electrical communication, markedly reducing susceptibility to arrhythmia.

Conclusions: This study represents an innovative advancement in the integration of SOD-mimetic MOF nanozymes with conductive polymers, achieving improved catalytic and electroactive performance through synergistic material design. From the acute reduction of oxidative stress to the progressive reestablishment of stable electrical conduction, this synergistic strategy holds substantial promise as a next-generation therapeutic platform for cardiac tissue regeneration.

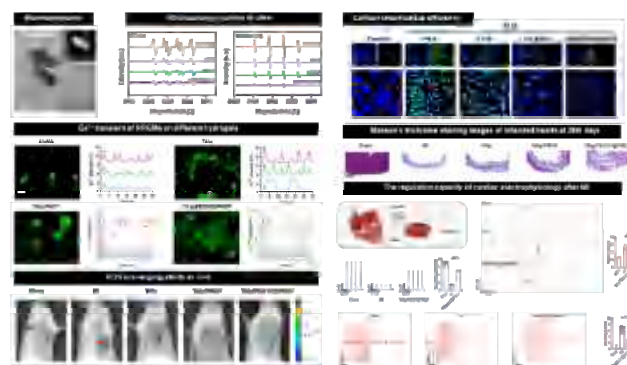


Fig. Material structure, in vitro and in vivo properties, and cardiac function recovery experimental data.

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Bioresorbable Bead for Transient Embolization in Knee Osteoarthritis: In Vivo and In Vitro Evaluation

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Key words: Transient embolization, enzymatic degradation, biocompatible microspheres, knee osteoarthritis, resorbable biomaterial

Introduction: Knee osteoarthritis (KOA) imposes a significant clinical burden, affecting approximately 15% of the global adult population¹ and substantially impairing mobility. Genicular artery embolization (GAE) can arrest neoangiogenesis to inflamed nociceptive subchondral bone and synovium and prevent the pathologic reinnervation that serves as a driver of pain, which can significantly improve pain symptoms and function in patients with mild-to-moderate knee osteoarthritis². Current GAE therapies utilize non-degradable embolic agents that generate persistent fragments, leading to non-target embolization and chronic inflammatory responses. This study pioneers a fully resorbable microsphere technology designed to eliminate long-term implant retention risks while maintaining therapeutic efficacy.

Materials & Methods: A starch-based Bioresorbable Bead (BRB) was synthesized through a patent-protected crosslinking strategy with inorganic phosphate. In vitro degradation were quantified using human serum α -amylase incubation assays (37°C, pH 7.4). In vivo evaluations involved bilateral auricular artery embolization in New Zealand rabbits, with histological assessment via hematoxylin-eosin (H&E) staining at 7 days post-procedure. Vascular occlusion efficacy was documented through macroscopic imaging.

Results & Discussion: The BRB platform exhibited α -amylase-dependent enzymatic hydrolysis in vitro, achieving >95% mass loss while generating low-molecular-weight oligosaccharides, indicating a biocompatible metabolic clearance pathway. In vivo studies demonstrated complete microsphere resorption within the 7-day observation period. H&E analysis revealed no residual foreign materials, granuloma formation, or significant lymphocyte infiltration in the embolized target tissues, indicating excellent biocompatibility and minimal acute inflammatory response. Precise distal arteriolar occlusion was consistently achieved in the rabbit ear model, with no evidence of non-target embolization or proximal reflux. This rapid, enzyme-mediated degradation profile and favorable tissue response contrast sharply with permanent embolics, effectively mitigating the risks of chronic vessel wall inflammation, foreign body reaction, and long-term ischemic sequelae.

Conclusions: As the first China-developed transient embolic agent to receive FDA Breakthrough Device Designation for KOA, the BRB platform enables effective, residue-free vascular occlusion with subsequent enzymatic clearance and metabolic assimilation. Its rapid resorption kinetics, predictable enzymatic degradation pathway, and demonstrated biocompatibility represent a significant paradigm shift in embolotherapy for KOA, moving away from permanent implants towards transient, biologically integrated solutions. Future work will focus on validating therapeutic efficacy in reducing synovial neovascularization and pain in a translational porcine KOA model and initiating first-in-human (FIM) clinical trials to assess safety and clinical outcomes for pain relief in KOA.

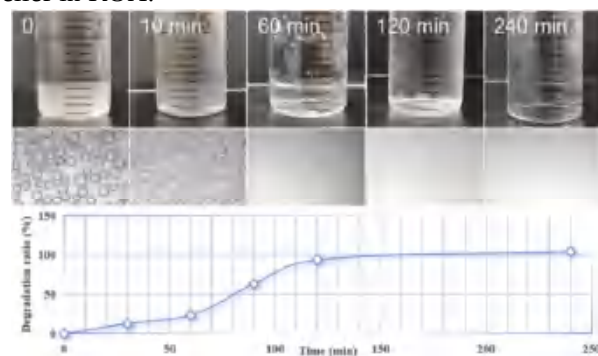


Fig. 1. In vitro degradation Performance of the BRB.

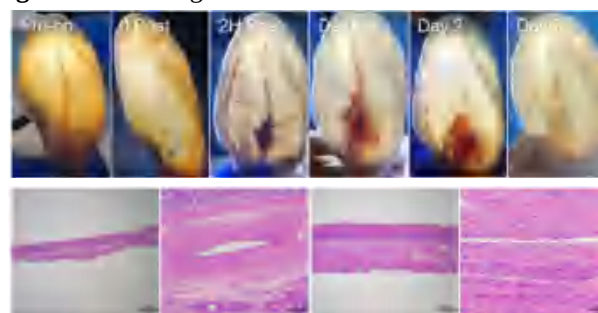


Fig. 2. Rabbit ear images and H&E-stained sections (Day 7) after embolization with the BRB.

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Functional surface design strategies for accelerating endothelialization

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Introduction: Left atrial appendage occluders are critical medical devices for preventing stroke in patients with atrial fibrillation. Adverse events related to device-related thrombosis after implantation can lead to severe complications such as systemic embolism. This is primarily attributed to the poor biocompatibility of occluder materials and the slow endothelialization of their surfaces. Functional coatings represent an effective strategy to improve material biocompatibility. However, the large surface area and complex structural design of occluders, combined with significant shear forces during catheter delivery, pose major challenges for coating applications.

Materials & Methods: In our recent research, we have developed multiple novel surface design strategies aimed at accelerating endothelialization of left atrial appendage occluders. These strategies include:

1. Chemical coatings: A UV-curable multifunctional coating preparation technology was developed to achieve long-term stability and functional synergy by integrating polyethyleneimine (PEI), silane coupling agents, and cell adhesion peptides.
2. An optimized microgroove design composed of continuous droplet-like structures was developed. This unique structural configuration effectively constrains cell migration directionality and suppresses backward cell migration. When these microgrooves were arranged on the occluder membrane surface, they significantly enhanced the collective migration efficiency of endothelial cells, accelerating cellular and tissue coverage of the surface.

Results & Discussion: Our findings demonstrate that these specific physical microstructures or chemical designs endow coatings with excellent mechanical properties. Functional molecules immobilized on the surface through microtopography or chemical fixation improve hemocompatibility and expedite endothelial cell coverage. Furthermore, canine in vivo animal data show that these novel surface designs significantly accelerate endothelialization of left atrial appendage occluders. **Conclusions:** These advancements offer promising clinical benefits, including reduced incidence of device-related thrombosis and shortened postoperative anticoagulation therapy duration.

Key words: regeneration, biomaterials, tissue engineering (3-5 key words)

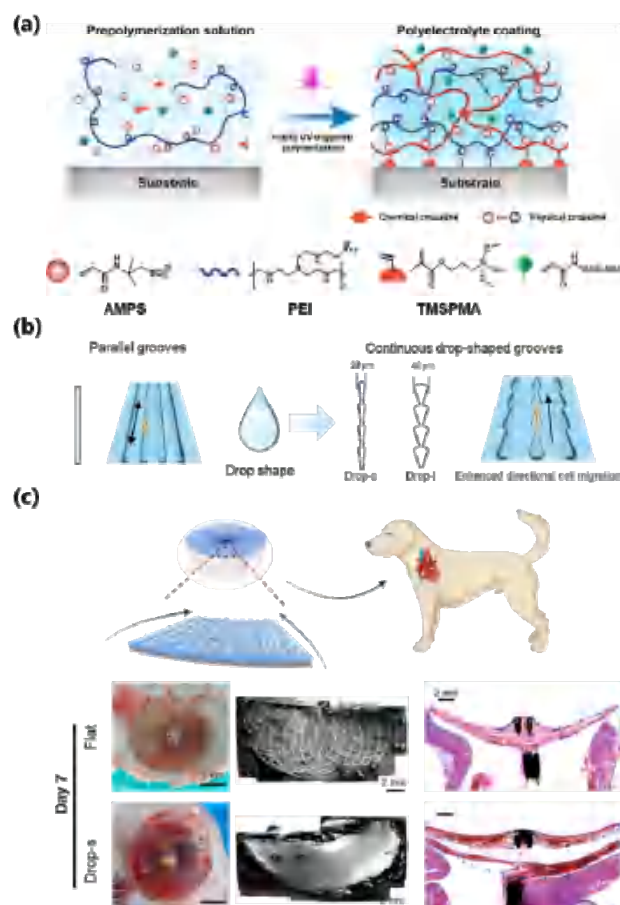


Fig. 1. Schematic of a Novel Functional Surface Design for the Left Atrial Appendage Occluder.

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Bioengineering cardiomyocytes with biophysical instructive cues and macrophages crosstalking

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Key words: cardiomyocytes; macrophages; tensile stimulation; biophysical factors; immune modulation

Introduction: Myocardial infarction is one of the leading causes of death worldwide¹. Bioengineering myocardial tissue, as an alternative to damaged myocardial tissue, is widely investigated in the cardiac field. In the human body, the myocardial microenvironment is rich in biophysical factors such as mechanosensory and electrical signals, as well as biological factors. Immune cells play also an important role in cell-cell communications and tissue homeostasis. Firstly, we integrated key biophysical factors, such as anisotropic topography, mechanosensing and electrical signals by combining cell-seeded melt electrowritten (MEW) scaffolds with an electromechanically responsive interpenetrating hydrogel network. Furthermore, we investigated the effects of macrophage density and polarization on cardiomyocyte function in a 2D co-culture system. Since the heart is a constant dynamic contractile environment, we also investigated the effect of dynamic mechanical stimulation on macrophage polarization.

Materials & Methods: MEW scaffolds were fabricated by using Polycaprolactone (PCL, Mn 80,000) and characterized with scanning electron microscopy (SEM). Electromechanical-responsive interpenetrating networks composed of mechano-responsive polyisocyanide (PIC)² and electroconductive (2-(methacryloyloxy) ethyl dimethyl-(3-sulfopropyl) ammonium hydroxide (SBMA) hydrogels with methacrylated collagen peptides (COPMA) as a micro-crosslinker. The murine cardiomyocyte cell line HL-1 was seeded on the MEW scaffolds for pre-alignment. Then, the PIC-SBMA-COPMA (conductive-PIC) hydrogels were added into cell-seeded scaffolds. Murine macrophages (Raw 264.7) were seeded on scaffolds and stimulated by a shaking device at 0.5 Hz, for 4 hours/day for 3 days. Macrophages in different polarization phenotypes (M0, unpolarized; M1, classically activated; M2, alternatively activated) and cell densities (5% and 50%) were co-cultured with HL-1 for 3 days. Cardiac calcium activity was used to monitor cell activity *in vitro* by genetically encoded GCaMP8s calcium indicator. Macrophage phenotype was assessed by iNOS and Arg1.

Results & Discussion: SEM analysis showed that the MEW fibers were aligned (Figure 1A). HL-1 in different electromechanical environments showed different calcium transient amplitudes and frequency (Figure 1B). Macrophages seeded on scaffolds were well attached (Figure 1C). Direct shaking stimulation promoted macrophage into M2 polarization (Figure 1C). Cardiomyocytes co-cultured with 5% M2 had stronger calcium transient amplitudes (Figure 1D). We found that the fibrous MEW scaffolds significantly induced cardiomyocyte alignment, resulting in regulating the synchronicity of cardiomyocyte calcium transient. Calcium transient activity was promoted with either increasing electromechanical properties of the matrices and macrophage interactions. Moreover, applying dynamic stimulation could promote macrophage polarization.

Conclusions: In summary, we developed engineered 3D *in vitro* models that integrated biophysical and/or immunomodulatory cues to regulate cell behavior, including cardiomyocyte calcium transient activities and macrophage polarization. Our ultimate goal is to develop engineered myocardial tissue with a close biomimicry to native heart.

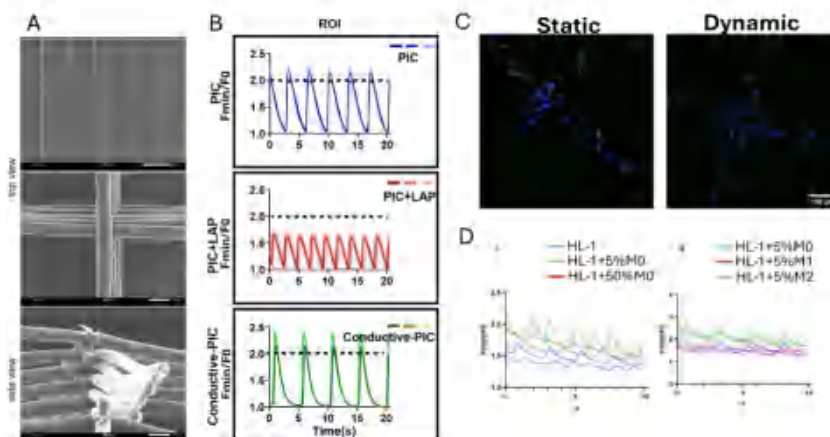


Figure 1. A) SEM images of MEW scaffolds. B) Analysis of intracellular calcium changes based on GCaMP8s HL-1 cultured in PIC, conductive-PIC and PIC-LAP as control, respectively. Fmin: fluorescent signal of real time; F0: fluorescent signal of minimum. C) Immunofluorescence staining of DAPI, Arg1 and iNOS. D) HL-1 coculture with i) 5%,50% M0 and ii) 5% M0, M1, M2. Analysis of intracellular calcium changes based on GCaMP8s.

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A novel biomimetic nanofibrous cardiac tissue engineering scaffold with adjustable mechanical and electrical properties based on poly(glycerol sebacate) and polyaniline

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Key Words: cardiac tissue engineering, electroactive scaffold, poly(glycerol sebacate)

Introduction: Myocardial infarction remains a leading cause of heart failure worldwide, with limited regenerative capacity of native cardiac tissue. Current therapeutic strategies are often inadequate due to complications and poor long-term outcomes. Cardiac tissue engineering has emerged as a promising approach to regenerate functional myocardial tissue by integrating cells, bioactive molecules, and biomaterial scaffolds. An ideal cardiac scaffold should not only provide structural support and degrade in a controlled manner but also mimic the anisotropic architecture, mechanical elasticity, and electrical conductivity of native myocardium to facilitate synchronous contraction and electrical signal propagation^[1]. However, most existing biomaterials lack the necessary electroactivity or possess inappropriate stiffness, limiting their clinical applicability. To address these challenges, this study developed a novel biomimetic nanofibrous scaffold by combining the elastic and biodegradable PGS with the conductive PANI, aiming to create a tunable platform that closely replicates the mechanical and electrical microenvironment of natural heart tissue.

Materials & Methods: PGS prepolymer was synthesized via polycondensation reaction. The electrospinning solution was prepared by dissolving PVA in deionized water, followed by blending with PGS prepolymer and HFIP. Various concentrations of PANI were incorporated into the mixture. Both random and aligned nanofibrous scaffolds were fabricated using a custom electrospinning setup. Subsequently, the fibrous mats were thermally crosslinked at 120°C for 48 hours, followed by sequential washing in water and ethanol to remove PVA and residual solvents. Scaffold morphology was characterized by SEM. Chemical structure, thermal behavior, hydrophilicity, and electrical conductivity were analyzed using FTIR, DSC, contact angle measurements, and cyclic voltammetry, respectively. Mechanical properties were evaluated under both dry and wet conditions via uniaxial tensile testing. In vitro degradation was assessed in lipase-containing PBS. Biocompatibility was examined using H9c2 rat cardiomyocytes for cell viability, adhesion, proliferation, and alignment. In vivo host response and degradation behavior were investigated by subcutaneous implantation in Wistar rats for up to 8 weeks, followed by histological

analysis.

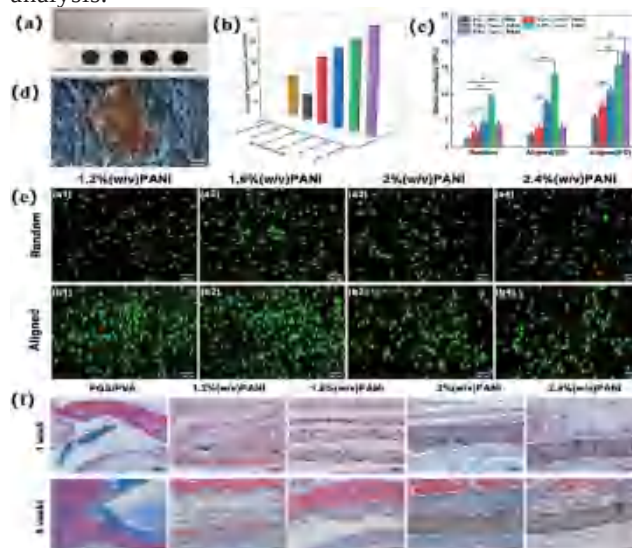


Fig. 1. Characterization results of the composite scaffolds based on PGS and PANI

Results & Discussion: As demonstrated in Fig. 1., scaffolds exhibited uniform nanofibrous structures with fiber diameters in the sub-micron range. PANI incorporation enhanced electrical conductivity and reduced degradation rates. The elastic modulus under wet conditions (0.65–2.18 MPa) matched native myocardium. Aligned fibers showed anisotropic mechanical behavior. H9c2 cells adhered, proliferated, and aligned along fibers, with optimal outcomes at 1.6% PANI. In vivo implantation results indicated good biocompatibility, with mild inflammatory response, progressive cell infiltration, collagen deposition, and scaffold integration into host tissue.

Conclusions: A tunable PGS/PANI nanofibrous scaffold with biomimetic mechanical and electrical properties was successfully developed. The scaffold supports cardiomyocyte alignment and exhibits excellent biocompatibility, demonstrating strong potential as a functional cardiac patch for myocardial regeneration.

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Myofibroblasts drive early vascular graft failure in hyperlipidemia: a novel therapeutic target via anti-fibrotic nanomodification

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Key words: small-diameter vascular grafts, vascular graft failure, single-cell RNA sequencing, macrophage-to-myofibroblast transition, myofibroblasts

Introduction: Neointimal hyperplasia following the implantation of small-diameter vascular grafts is a major cause of graft failure, a process markedly accelerated in the pathological microenvironment of coexisting hyperlipidemia. However, the cellular origins and mechanistic drivers of early neointimal formation in this pathological setting remain incompletely defined. This study aims to identify the key cellular contributors and underlying mechanisms driving early intimal hyperplasia in small-diameter vascular grafts under hyperlipidemic conditions and explores potential therapeutic targets to improve graft performance.

Materials & Methods: A hyperlipidemic rat model was established via a high-fat diet, followed by implantation of extracellular matrix-based vascular grafts. Two weeks post-implantation, histological analyses were performed to assess intimal hyperplasia and collagen deposition. Single-cell RNA sequencing (scRNA-seq) was applied to characterize the cellular heterogeneity during early graft regeneration. Key cellular phenotypes were validated by immunofluorescence co-localization and genetic lineage tracing. Pseudotime trajectory analysis and gene ontology (GO) enrichment analyses were conducted to explore macrophage phenotypic transitions and their contribution to neointimal remodeling. In addition, a lipid nanoparticle-based delivery system was employed to administer microRNA as an interventional therapy to validate our findings.

Results & Discussion: Hyperlipidemic environment markedly aggravates early neointimal hyperplasia and collagen deposition in vascular grafts. Contrary to the traditional view that vascular smooth muscle cells (SMCs) are the primary drivers of neointimal formation, scRNA-seq and immunofluorescence analyses demonstrate that a subset of contractile myofibroblasts with high *Tagln* expression (*Tagln*^{hi} myofibroblasts) constitutes the predominant cell population within the hyperplastic neointima. Notably, these myofibroblasts co-express macrophage marker genes, consistent with macrophage-to-myofibroblast transition (MMT) described in organ fibrosis. Further analysis identifies a distinct macrophage subset that is significantly expanded under hyperlipidemic conditions. This subset exhibits hallmark MMT features, including enrichment of fibrosis-related

GO pathways and a marked increase in α -SMA⁺CD68⁺ double-positive cells in the neointima. Pseudotime trajectory analysis reconstructs a continuous transition from circulating blood-derived macrophages to MMT-like cells and subsequently toward *Tagln*^{hi} myofibroblasts. Collectively, these findings indicate that MMT contributes to early neointimal remodeling and that hyperlipidemia amplifies this fibrotic transition, leading to enhanced collagen deposition and neointimal hyperplasia. Based on this mechanism, we designed a localized antifibrotic therapeutic strategy: functionalizing vascular grafts with lipid nanoparticles loaded with antifibrotic miR-29b. *In vivo* experiments demonstrate that this approach effectively attenuated early neointimal hyperplasia and collagen deposition, confirming the feasibility of targeting this fibrotic pathway.

Conclusions: Our study elucidates the central role of *Tagln*^{hi} myofibroblasts and MMT in early neointima formation following vascular graft implantation, revealing that hyperlipidemia exacerbates graft fibrosis and early neointimal hyperplasia by driving MMT. Based on this mechanism, we developed an efficient localized antifibrotic therapeutic strategy, which provides a novel direction and theoretical foundation for improving the long-term patency of vascular grafts. These findings provide mechanistic insight and support a potential strategy to improve long-term graft patency.

Acknowledgements: This work was supported by the National Natural Science Foundation of China (Grant No. 12372311).

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Role and regulation of lipid-handling smooth muscle cell subtype in vascular grafts

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Key words: arteriovenous transplantation, intimal hyperplasia, vascular smooth muscle cell, phenotypic switch

Introduction: Small-caliber vascular grafts often fail under arterial pressure and shear stress due to maladaptive remodeling, leading to intimal hyperplasia (IH) and restenosis^[1]. A central driver is the stress-induced phenotypic switching of vascular smooth muscle cells (VSMCs), which is frequently accompanied by lipid metabolic dysregulation and foam cell-like transdifferentiation.^[2,3] This study focuses on the pathological alterations triggered by mechanical stress subsequent to arteriovenous transplantation. Using single-cell omics technology, we accurately identify and target the stress-induced VSMC subpopulations associated to lipid metabolism. Our findings provide more precise and effective intervention targets and therapeutic strategies to improve the long-term patency rates of vascular grafts and reduce the risk of restenosis.

Materials & Methods: To investigate the mechanical regulation of vascular remodeling, we established interposition graft models in mice: vein-to-artery (jugular vein grafted into the carotid artery, high-pressure/high-tensile) and artery-to-vein (carotid artery grafted into the jugular vein, low-pressure/low-tensile) groups. On postoperative day 3, single-cell RNA sequencing (scRNA-seq) was performed to generate a transcriptomic atlas. Functional enrichment of differentially expressed genes (DEGs) revealed distinct VSMC subpopulation alterations. Pseudotime trajectory analysis delineated tensile force-driven phenotypic switching in graft VSMCs. Lipid metabolism signature genes identified a key high-metabolic VSMC subpopulation. Finally, we inferred pathway activities in classical lipid metabolism routes and integrated them with a core gene set from the high-metabolic VSMC subpopulation to construct a drug-target network for screening activators of lipid metabolic function.

Results & Discussion: High-pressure/high-tensile vein-to-artery grafts rapidly adapted to hypertensive hemodynamics, exhibiting enhanced VSMC proliferation, osteogenic calcification, and myogenic features consistent with maladaptive remodeling and accelerated IH. In contrast, low-pressure/low-tensile artery-to-vein grafts displayed a protective profile distinct from conventional ox-LDL-induced foam cells. These grafts showed coordinated upregulation of lipid uptake, cholesterol biosynthesis, and reverse cholesterol transport (RCT) capacities, establishing a metabolic equilibrium that preserved VSMC homeostasis and limited

transdifferentiation toward synthetic or macrophage-like phenotypes. Pseudotime trajectory analysis confirmed tensile force as a key driver of phenotypic switching, with low mechanical stress favoring a high-metabolic, lipid-handling VSMC subpopulation.

Drug-target network analysis prioritized Mesalamine (5-ASA)—a PPAR γ activator and COX-2 (*Ptgs2*) inhibitor used in inflammatory bowel disease—as a lead candidate. Since its mechanism of action aligns with our finding objective, our results underscore its potential for drug repurposing. These findings challenge the conventional paradigm of uniform phenotypic switching in vascular remodeling, revealing mechanical stress as a tunable metabolic switch: high tensile force promotes detrimental intimal hyperplasia, whereas low tensile force maintains lipid metabolism homeostasis and exerts cytoprotection by preserving phenotypic stability.

Conclusions:

Our graft models uncover a mechanosensitive, lipid metabolically active VSMC subpopulation under low tensile force that enhances lipid metabolism (including RCT) to resist pathological remodeling—contrasting with high-stress-driven maladaptation. Through scRNA-seq, pseudotime analysis, and drug-target network prioritization, we nominate Mesalamine as a promising PPAR γ activator to mitigate lipid accumulation and phenotypic switching in VSMCs under mechanical stress. These findings highlight a potential link between hemodynamics and lipid metabolic reprogramming in early vascular graft remodeling, suggesting PPAR γ modulation as a strategy to limit intimal hyperplasia.

Acknowledgements

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Fabrication and performance of biodegradable self-powered small-diameter vascular grafts

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Key words: small-diameter vascular graft, electrical stimulation, biodegradable, self-powered, regeneration

Introduction: Small-diameter vascular grafts (SDVGs) (< 6 mm) face significant challenges in the treatment of coronary artery and peripheral vascular diseases. The existing grafts are prone to thrombosis and calcification problems, which lead to the failure of SDVG implantation. Electrical stimulation (ES) can promote vascularization and tissue repair by regulating cell membrane potential and influencing cell behavior [1-2]. This study developed a self-powered and biodegradable electronic SDVG based on the principle of primary battery. Through continuous and stable *in vivo* ES, it effectively promoted the adhesion and growth of human umbilical vein endothelial cells (HUVECs). The animal model preliminarily verified the patency and biocompatibility of the electronic SDVG. This research provides a new strategy for promoting rapid endothelialization and inhibiting thrombosis, and demonstrates great potential in the field of SDVGs.

Materials & Methods: In this study, polycaprolactone (PCL) and poly(lactic acid-co-caprolactone) (PLCL) were used as the base materials, combined with zinc-molybdenum (Zn-Mo) metal electrodes to construct an electronic SDVG. The tensile stress and burst pressure of the materials were tested using a universal material testing machine; the microscopic morphology and hydrophilicity were characterized by scanning electron microscopy (SEM) and contact angle measuring instrument. The electrodes were placed in PBS to evaluate the *in vitro* degradation behavior and voltage stability. In the *in vitro* experiments, the blood compatibility was evaluated through platelet adhesion experiments, and HUVEC proliferation, migration, and tube formation experiments were conducted using to assess the effect of ES on HUVEC function. The *in vivo* experiments included a rat subcutaneous implantation model and a rat abdominal aorta *in situ* transplantation model to evaluate tissue compatibility, voltage stability, and vascular patency.

Results & Discussion: The electronic SDVG has excellent tensile mechanical properties, with a burst pressure of 2472.5 ± 292.5 mmHg, which is much higher than that of natural blood vessels and demonstrates good mechanical performance. In terms of electrical properties, the initial voltage of the electrode is 0.949 V, and it remains at 0.231 V after 100 days of degradation in PBS, showing continuous and stable electrical performance. The *in vitro* blood compatibility of the electronic vascular graft indicates that ES

inhibit platelet adhesion to a certain extent, and implantation in the body may prevent platelet aggregation and the formation of blood clots. In cell experiments, the electronic SDVG significantly promotes the proliferation, migration, and tube formation ability of HUVECs. In the subcutaneous implantation experiment in rats, it was found that the ES group with the graft had more capillary formation on the surface of the scaffold after 4 weeks of implantation, and the H&E staining results showed good cell infiltration. The graft had good biocompatibility. Within 4 weeks after being implanted under the skin, the voltage of this electronic SDVG remained at 0.805 V, dropping by only 0.14 V. This indicated that the voltage was stable after being implanted in the body. The electronic SDVG was implanted into the abdominal aorta of rats, and the electronic SDVG was well connected to the natural abdominal aorta, with a smooth blood flow. After 2 months of *in vivo* transplantation, the SDVG was analyzed and found to be unobstructed. Under the stereomicroscope, the outer layer of the SDVG was covered with tissue, and the electrode morphology remained good. The voltage was 0.790 V after 2 months of implantation, which was only 0.16 V lower than the initial voltage of 0.949 V, proving that the electronic SDVG can achieve long-term voltage stability after implantation in the body. The H&E staining results showed that the cell infiltration of the electronic SDVG was good.

Conclusions: This study successfully developed a degradable electronic SDVG based on Zn-Mo electrodes. The SDVG not only possesses the mechanical properties required for clinical applications, but also can provide continuous and stable self-powered stimulation. The electronic SDVG has good blood compatibility and can significantly promote the proliferation, migration, and tube formation ability of HUVEC. It also exhibited excellent tissue compatibility and antithrombotic ability *in vivo*. The design of this electronic SDVG provides a new strategy for solving the problems of rapid endothelialization and long-term patency of SDVGs.

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Balloon-Mediated In-situ Biomimetic Photo-crosslinking (BMIBP) for Stent-Free Vascular Remodeling

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Key words: drug-coated balloon, heparin, biomimetic layer, photo-crosslinking, , vascular remodeling.

Introduction:

Drug-coated balloon (DCB) angioplasty avoids permanent implants but frequently suffers from elastic recoil, thrombosis, and restenosis due to balloon-induced endothelial denudation and the absence of sustained mechanical stabilization^[1]. Loss of the native endothelial interface exposes thrombogenic substrates and amplifies inflammatory cascades, driving maladaptive vascular remodeling. Rapid reconstruction of an endothelial-mimicking luminal barrier that restores thromboresistance and interfacial stability remains a key unmet need in balloon-based intervention.

Most current strategies rely on drug elution or bulk hydrogel coverage and face challenges in the vascular lumen, including shear stress, anatomical variability, and limited interfacial anchoring^[2]. Here, we propose a balloon-mediated in situ biomimetic photo-crosslinking (BMIBP) strategy to construct a heparin-based endothelial-mimicking layer under red-light activation during angioplasty. Combining dynamic interfacial crosslinking with anticoagulant and barrier functions can enable transient mechanical reinforcement and promote stent-free vascular stabilization.

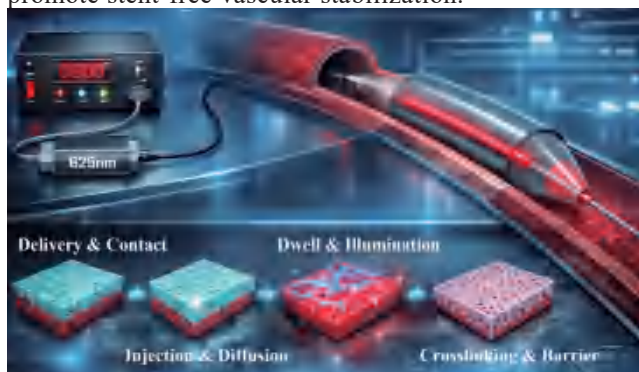


Fig. 1. Balloon-Mediated In-situ Biomimetic Photo-crosslinking platform.

Materials & Methods:

Furan-modified heparin (Hep-F) was photo-activated under 625 nm irradiation to enable light-triggered Schiff-base crosslinking with tissue amines. The precursor was loaded into a porous balloon coating, allowing compression-assisted delivery and in situ crosslinking through an integrated optical fiber during angioplasty.

Barrier function was evaluated by monocyte adhesion and inflammatory factor permeation assays. Mechanical

reinforcement was quantified by nanoindentation and radial compression testing. Anticoagulant activity was assessed as supportive evidence of functional retention. Therapeutic performance was further examined in rat abdominal aorta acute injury and restenosis models.

Results & Discussion:

Red-light activation enabled rapid interfacial crosslinking of Hep-F, resulting in markedly enhanced surface retention compared with non-irradiated controls under simulated shear conditions, indicating stable anchoring within a dynamic vascular environment. Functionally, the crosslinked barrier significantly reduced monocyte adhesion and inflammatory factor permeation. Anticoagulant assays confirmed retention of heparin bioactivity. In contrast, non-crosslinked Hep-F showed partial but unstable effects, highlighting the necessity of effective interfacial anchoring. Mechanically, photo-crosslinking doubled the interfacial modulus (~150 kPa to ~300 kPa) and increased radial compression resistance by ~40-50%, resulting in substantial suppression of elastic recoil ex vivo. In vivo, the crosslinked group exhibited minimal thrombus formation, reduced inflammatory cytokine expression, improved early lumen preservation, and significantly attenuated restenosis at 4 weeks (<10% vs. ~20% in injury group). Together, these findings demonstrate coordinated biological and mechanical stabilization mediated by the endothelial-mimicking barrier.

Conclusions:

This study demonstrates that red-light-triggered in situ crosslinking enables stable reconstruction of an endothelial-mimicking luminal barrier during balloon angioplasty. The crosslinked interface provided coordinated anticoagulant retention, inflammatory shielding, and transient mechanical reinforcement, resulting in improved lumen preservation and reduced restenosis in vivo. These findings support a barrier-first strategy for vascular stabilization without permanent scaffolds.

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Balloon-mediated Endovascular Adhesive Tape (BEAT) for Improving Vascular Regeneration

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Key words: Drug-coated balloon, Bioactive coating, Endothelium adhesion, Vascular regeneration

Introduction: Drug-coated balloons (DCBs) represent a promising modality for cardiovascular intervention. However, the physical injury during balloon angioplasty inevitably disrupts the endothelium, creating an urgent need for the rapid sealing of injured vascular. Furthermore, unmatched drug delivery in conventional DCBs collectively limits their therapeutic efficacy. To address these challenges, we develop a swelling-resistant and bioactive adhesive coating based on poly(thioctic acid) end-capped with epigallocatechin gallate (PTAE). This PTAE material achieves robust, instant wet adhesion to the vascular lumen. Moreover, it provides sustained release of bioactive thioctic acid (TA), which acts as a potent antioxidant to reduce oxidative stress and create an anti-inflammatory microenvironment. This PTAE bioactive coating presents a promising strategy that integrates immediate injury sealing with biological regulation for vascular regeneration.

Materials & Methods: The PTAE material was synthesized via a sequential strategy that combined thermal polymerization with UV-induced end-capping using epigallocatechin gallate (EGCG). Adhesion and Stability: Molecular adhesion forces were quantified using atomic force microscopy (AFM), and mechanical stability was evaluated via ex vivo burst pressure tests on bovine arteries. Adhesion and Stability: Molecular adhesion forces were quantified using atomic force microscopy (AFM), and mechanical stability was evaluated via ex vivo burst pressure tests on bovine arteries. In Vitro Assays: The biological activity of the coatings was assessed through reactive oxygen species (ROS) scavenging assays, and the behavior of smooth muscle cells (SMCs) was analyzed using transcriptome sequencing. In Vivo Evaluation: A rat abdominal aortic injury model was employed to evaluate immediate vascular sealing efficacy, acute inflammatory responses, and neointimal hyperplasia after balloon angioplasty.

Results & Discussion: The UV-induced polymerization and EGCG end-capping drastically reduced the residual monomer content, generating exceptional storage stability and minimal premature degradation compared to thermal-polymerized controls. During application, the highly hydrophobic backbone of PTAE expels interfacial water, allowing carboxyl groups to form dense hydrogen bonds with the endothelial glycocalyx. Under hydrated conditions, the PTAE patch achieved a reliable burst pressure of 126.08 ± 25.57 mmHg. Beyond mechanical sealing, the PTAE material serves as a highly effective

biomedical platform that continuously neutralizes reactive oxygen species, thereby establishing an anti-inflammatory microenvironment conducive to tissue repair. Transcriptomic profiling revealed that the controlled release of bioactive TA downregulates key inflammatory cascades, such as the p38 MAPK pathway, thereby inhibiting pathological SMC proliferation and migration. In vivo, the PTAE-coated balloon successfully restored normal blood flow immediately after arterial rupture without requiring surgical sutures. Over a two-week observation period, the PTAE coating significantly inhibited neointimal hyperplasia and promoted the formation of a nearly complete endothelial layer.

Conclusions: The PTAE adhesive coating establishes a highly reliable paradigm for endovascular therapy by successfully integrating immediate mechanical injury sealing with long-term biological regulation. It effectively suppresses pathological SMC phenotypic switching and significantly promotes endothelial regeneration. Future studies will focus on validating this promising interventional platform in large animal models to facilitate clinical translation.

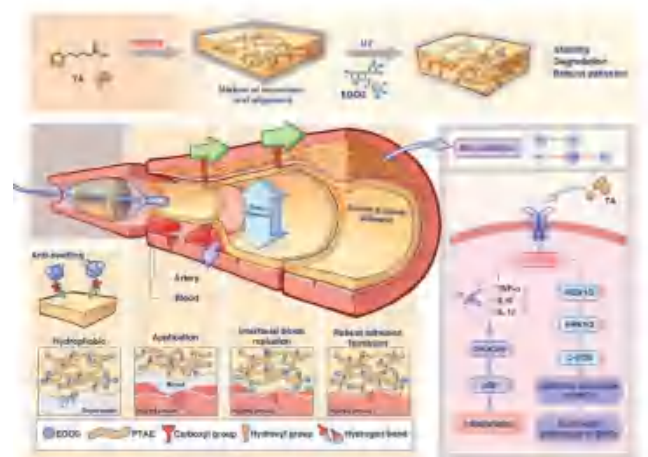


Fig. 1. Schematic illustration of the bioactive PTAE adhesive coating.

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Suture-free biomimetic polymeric venous valves for peripheral interventional therapy

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Key words: Chronic venous insufficiency; venous valve; electrospinning; suture-free; Polymeric valve;

Introduction: Chronic venous insufficiency (CVI), a debilitating clinical disorder driven primarily by venous valve incompetence, remains largely unaddressed by current standard-of-care treatments, compression therapy and open surgery, neither of which achieves durable functional valve reconstruction ^[1]. Inspired by transcatheter aortic valve replacement yet uniquely tailored to the low-pressure, low-flow physiology of venous systems, we report a first-in-class suture-free biomimetic polymeric interventional venous valve, fabricated via an integrated one-step strategy, combining nitinol shape-memory alloy frames with electrospinning. **Materials & Methods:** The interventional venous valve consists of three components: a nitinol stent frame, polymer leaflets, and a sealing skirt. The stent was laser-machined from nitinol tubing, featuring upper and lower annular grid segments connected by 2 straight rods. And then electrospinning was performed. The spinning solution was electrospun onto the aluminum foil to form the first polymer film layer. The nitinol stent was then sleeved onto the polymer film surface, and the spinning solution was electrospun again onto the stent surface and the base of the first leaflet layer to form the second film layer. No obvious stratification was observed between the two layers in the leaflet region. After that the two film layers were sintered at 80°C for 30 min to fuse into a single integrated layer. Finally, the valve height and leaflet morphology were trimmed to be highly biomimetic to human venous valves.

Results & Discussion: This approach directly deposits polymer leaflets and skirts onto straight stent rods without suturing, enabling submicron precision in tuning leaflet thickness (50–200 μm), biomimetic arc-shaped free edges, and flexible customization of mono-, bi- or tri-leaflet configurations. *In vitro* characterization and computational simulations of the optimized bileaflet design (100–150 μm thickness, 10–12/22 mm dimensions) demonstrated exceptional physiological performance: opening at <5 mmHg, rapid closure in <0.5 s, and robust stability even under extreme pressure (300 mmHg), alongside optimal hemodynamics and antithrombotic properties that resolve key design trade-offs for venous valves. Critical preclinical validation in a porcine model confirmed the device's biosafety, hemocompatibility and interventional feasibility: the valve (10 mm $\times$ 30 mm) was crimped to 4 mm, delivered via a 12-Fr sheath through the left external jugular vein, and accurately

deployed in the target superficial femoral vein under DSA guidance. Immediate and 3-h post-implantation assessments verified stable anchoring, intact leaflet function and improved venous hemodynamics. Gross and histological analyses of explanted devices revealed excellent structural integrity, absent surface thrombosis and negligible acute inflammatory infiltration.

Conclusions: This minimally invasive platform thus provides a transformative solution for functional venous valve replacement in CVI.

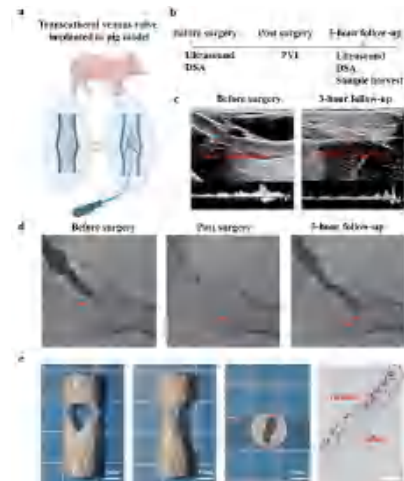


Fig. 1. *In vivo* evaluation of interventional venous valves in a porcine model. (a) Schematic illustration of interventional delivery and orthotopic implantation of the venous valve. (b) Preoperative Doppler ultrasound image showing left SFV diameter (7–8 mm) and significant venous reflux; postoperative image showing improved hemodynamics with stable unidirectional blood flow. (c) Preoperative DSA image showing baseline venous reflux; postoperative DSA image showing no obvious contrast medium reflux immediately and 3 h post-implantation. (d) Fluoroscopic image of the valve during controlled deployment under fluoroscopic guidance, showing stable positioning with no jumping or displacement. (e) Gross morphological observation of the explanted valve at 3 h post-implantation, demonstrating intact structural integrity, good leaflet morphology, and no surface thrombosis, tearing, or perforation. (f) HE staining showing no acute thrombus deposition or massive inflammatory cell adhesion on the valve surface.

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Plaque-specific Adhesive Balloons Coated with Calcium Phosphate Nanoparticles Loaded with Rapamycin for Atherosclerosis Therapy

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Abstract

Drug-coated balloons (DCBs) represent a significant clinical innovation in the management of atherosclerosis, offering a superior alternative to traditional stents by eliminating the need for permanent foreign implants. However, their therapeutic effectiveness is critically compromised by the high blood flow rates in arterial vasculature, which result in brief drug residence times at the lesion site. Furthermore, non-selective drug transfer can inadvertently affect healthy vascular tissue. Drawing inspiration from the natural mechanisms of vascular calcification, where calcium phosphate preferentially accumulates at atherosclerotic plaques, this study developed a novel rapamycin-loaded calcium phosphate nanoparticle (CaP@Rapa) coating for angioplasty balloons. This amorphous calcium phosphate coating serves as a highly potent, plaque-specific anchor in arteries, facilitating the direct adhesion of rapamycin to plaques to enhance local drug concentrations. In addition to its anchoring capability, the acidic microenvironment of atherosclerotic plaques triggers a pH-sensitive, sustained release of the drug directly into vascular smooth muscle cells (VSMCs). To comprehensively evaluate its *in vivo* therapeutic efficacy, we utilized a rabbit iliac artery atherosclerosis model, which authentically mirrors human pathological progression. Results demonstrated that the CaP@Rapa coating substantially reduced plaque volume, decreased intimal hyperplasia, and mitigated local inflammation. To further substantiate its translational potential, the intervention was tested in a clinically relevant pig coronary atherosclerosis model, which yielded significant improvements in vascular lumen diameter and reductions in neointimal growth. By overcoming the limitations of standard DCBs, this plaque-focused adhesive strategy offers a highly effective, targeted therapeutic tool for atherosclerosis management, paving the way for future clinical trials.

Key words: Drug-coated balloons, Calcium phosphate, Rapamycin, Atherosclerosis

Introduction

Atherosclerosis is a primary driver of life-threatening cardiovascular diseases, characterized by the accumulation of lipids and cholesterol in arterial walls that form obstructive plaques^{1,2}. While percutaneous coronary intervention (PCI), particularly stenting, has advanced vascular treatment, it remains hindered by elevated restenosis rates^{3,4}. Drug-coated balloons (DCBs) emerged to deliver drugs directly to the arterial wall without leaving residual foreign materials⁵; however, the rapid arterial blood flow severely limits the

duration of drug residence, undercutting their therapeutic efficacy⁶.

The primary scientific question investigated in this study is whether the natural propensity of calcium phosphate to accumulate at atherosclerotic plaques can be leveraged to create a plaque-specific drug anchoring system. During atherosclerosis, vascular smooth muscle cells (VSMCs) transform into an osteogenic phenotype, promoting mineralization and calcium phosphate deposition^{7,8}. By exploiting this affinity, we propose an amorphous calcium phosphate-based delivery mechanism to anchor rapamycin directly to lesions. We hypothesize that an amorphous CaP@Rapa coating will provide enhanced biodegradability, plaque-specific adhesion, and pH-responsive sustained drug release in the acidic plaque microenvironment, thereby suppressing VSMC proliferation and overcoming the limitations of conventional DCBs.

Materials & Methods

CaP@Rapa nanoparticles were synthesized via *in situ* generation within high glucose Dulbecco's Modified Eagle Medium (DMEM). Rapamycin, featuring abundant hydroxyl groups, provided nucleation sites for calcium phosphate formation upon the addition of calcium chloride. The resulting nanoparticles were isolated via centrifugation. The coating was applied to balloons using a high-frequency ultrasonic spraying technique, ensuring a uniform distribution with an intended rapamycin dosage of 0.8 µg/mm².

Nanoparticle and coating characteristics were evaluated using Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), Energy-Dispersive Spectroscopy (EDS), and Fourier-transform infrared spectroscopy (FT-IR). *In vitro* assessments included measuring hemocompatibility via hemolysis assays and determining pH-responsive drug release profiles using high-performance liquid chromatography (HPLC).

To evaluate *in vivo* efficacy, a rabbit atherosclerosis model was established using a combination of a 2% high-cholesterol diet and balloon-induced iliac artery injury. Arteriography and digital subtraction angiography (DSA) were used to guide the CaP@Rapa-coated balloon to stenotic sections. Coating transfer and retention were quantified using a fluorescent Cy3 marker and *In Vivo* Imaging Systems. Finally, therapeutic validation was expanded to a porcine coronary artery model, mirroring human cardiovascular anatomy, to assess macroscopic lumen recovery and histological tissue responses.

Results & Discussion

Characterization and *In Vitro* Efficacy: CaP@Rapa synthesis yielded uniformly distributed, amorphous nanoparticles with an average diameter of approximately 250

nm. The ultrasonic application produced a robust coating roughly 4.4 μm thick with an enhanced surface roughness that facilitates vascular wall adhesion. In vitro testing confirmed exceptional biocompatibility; the coating exhibited a hemolysis ratio of only 1.2% and did not upregulate vascular calcification markers (OPN and Runx2). Crucially, the nanoparticles demonstrated pH-responsive behavior, releasing 61% of rapamycin in an acidic environment (pH 6.2) compared to 34% at physiological pH (7.4) over 72 hours. Cellular assays revealed that CaP@Rapa was rapidly endocytosed by VSMCs, leading to a profound suppression of cellular proliferation and migration via the targeted downregulation of the mTOR signaling pathway.

In Vivo Outcomes: In the rabbit iliac artery model, tracking of Cy3-labeled CaP@Rapa confirmed plaque-specific adhesion, with significantly higher fluorescence detected at atherosclerotic lesions compared to healthy vessel segments. Liquid Chromatography-Mass Spectrometry (LC-MS) proved that the CaP@Rapa coating maintained substantial drug concentrations in vascular tissues up to seven days post-procedure, whereas free drug levels were nearly imperceptible. Following intervention, CaP@Rapa-coated balloons substantially suppressed atherosclerotic plaque growth and increased the arterial lumen diameter within two weeks. Histological analyses (SMA, H&E, and Masson's trichrome) showed marked reductions in intima thickness, intimal/media ratios, and collagen deposition. Furthermore, the treatment orchestrated a favorable inflammatory environment, significantly downregulating macrophage (CD68) and neutrophil (Ly6G) infiltration, alongside drops in pro-inflammatory cytokines like TNF- α and IL-1 β .

The translational viability of these results was solidified in the porcine coronary model, where DSA and tissue staining confirmed increased vascular lumen diameters and significantly diminished neointimal growth without inducing systemic toxicity in major organs.

Conclusions

This study establishes the CaP@Rapa-coated balloon as a highly effective, biomimetic intervention for atherosclerosis therapy. By utilizing amorphous calcium phosphate as an anchor, the system achieves plaque-specific adhesion and extended, pH-responsive intracellular drug delivery. This successfully limits VSMC proliferation and reduces localized inflammation, resulting in mitigated plaque accumulation and decreased restenosis.

Given the outstanding biocompatibility and efficacy demonstrated in both rabbit and highly clinically relevant porcine models, it is strongly recommended that this technology progress toward human clinical trials. The implications of this research are substantial; by ensuring targeted, sustained drug delivery that spares healthy tissues, CaP@Rapa-coated balloons offer a much safer and reliable alternative to current interventional cardiovascular therapies.

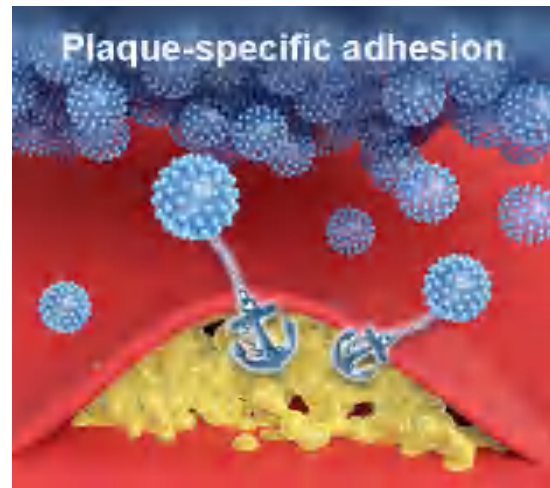
Fig. 1. Schematic illustration of atherosclerosis treatment through the use of CaP@Rapa-coated balloons, demonstrating plaque-specific adhesion and pH-responsive sustained drug release.

Fig. 2. Characterization of CaP@Rapa nanoparticles and the balloon coating process, including TEM, SEM, and EDS analyses, alongside in vitro hemolysis and pH-responsive release profiles.

Fig. 3. Evaluating the inhibitory impact of CaP@Rapa on VSMCs in vitro, highlighting enhanced cellular uptake, reduced viability, restricted migration, and mTOR pathway suppression.

Fig. 4. The effects of balloon coatings on arterial intimal hyperplasia in the atherosclerosis rabbit model, evaluated via DSA and Oil Red O staining.

Fig. 5. Histological and immunohistochemical analysis of



intimal hyperplasia and inflammatory marker reduction (CD68, Ly6G) in the rabbit iliac artery post-treatment.

Fig. 6. Therapeutic effects and quantitative analysis of luminal loss using CaP@Rapa-coated balloons in a porcine coronary atherosclerosis model.

Fig. 7. Histological examination of systemic tissue responses confirming the in vivo biocompatibility and safety of the CaP@Rapa intervention.

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Iron Oxide Nanoprobcs and Clinical Translation

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Due to their excellent magnetic properties and biocompatibility, iron oxide nanoparticles are currently the most promising inorganic nanomaterials for clinical translation. However, achieving the clinical translation of nanomaterials, particularly inorganic nanomaterials, still requires addressing numerous challenges, such as controllable and large-scale production of nanomaterials, as well as preclinical safety evaluation. This presentation will focus on our recent progress in the mass production of high-quality iron oxide nanoparticles, their application as magnetic resonance contrast agents for imaging, and their preclinical safety evaluation.

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Engineering nuclear medicine imaging probes: Radiolabeling strategies, pharmacokinetic profiling, and ratiometric functional sensing

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Key words: nuclear medicine imaging, radiolabeling, pharmacokinetics, ratiometric imaging, molecular probes

Introduction: The development of clinically translatable nuclear medicine imaging probes is limited by challenges in radiolabeling stability, unpredictable in vivo pharmacokinetics, and the inability to quantitatively sense pathological microenvironments. Our study addresses three key scientific questions: (1) how to establish a universal and mild radiolabeling strategy for inorganic nanomaterials; (2) how physicochemical properties regulate the biodistribution and liver–nanoparticle interactions of radiolabeled nanoprobe; and (3) whether dual-radionuclide ratiometric imaging can quantify in vivo glutathione (GSH) levels with high specificity.

Materials & Methods: Iron oxide nanoparticles were modified using polyethylene glycol ligand to enable stable radiolabeling with SPECT/PET isotopes. In vivo pharmacokinetic behavior was evaluated by quantitative SPECT imaging, combined with size- and surface-variant nanoparticle libraries. Liver uptake, retention, and distribution were analyzed through in vivo SPECT imaging and in vitro cell incubation. For functional sensing, a dual-isotope $^{177}\text{Lu}/^{125}\text{I}$ ratiometric probe was synthesized via a cleavable GSH-responsive linker to enable energy-resolved gamma-ray detection.

Results & Discussion: The ligand anchoring radiolabeling strategy demonstrated high radiochemical stability across multiple inorganic nanoplateforms and allowed seamless integration of multimodal imaging capabilities (Figure 1). Pharmacokinetic studies revealed that nanoparticle size and surface modification are determinants of hepatic accumulation and elimination, establishing design rules for safer nuclear imaging agents. The dual-isotope ratiometric probe achieved precise quantification of GSH levels in vivo, where the $^{177}\text{Lu}/^{125}\text{I}$ signal ratio exhibited linear responsiveness to GSH concentration, enabling reliable redox imaging

even in complex tissue environments.

Conclusions: These works provide a unified framework that links radiochemistry, nanomaterial design, pharmacokinetic profiling, and functional sensing for nuclear medicine imaging probes. The findings support rational optimization of probe safety, stability, and physiological performance, and highlight ratiometric nuclear imaging as a promising strategy for quantitative assessment of disease-associated microenvironments. Future studies will focus on clinical translation, long-term biosafety evaluation, and the integration of AI-assisted probe design to accelerate precision molecular imaging.

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ROS-responsive Nanoplatforms for Atherosclerosis Photoacoustic Diagnosis and Endothelial Cell-Macrophage Crosstalk Regulation

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Key words: atherosclerosis, π -conjugated polymer, photoacoustic diagnosis, self-assembling nanoparticles

Introduction: As one of the primary causes of cardiovascular disease globally, atherosclerosis is typically characterized by aberrant lipid buildup and chronic vascular inflammation, resulting from deleterious cellular crosstalk between endothelial cells and macrophages. Nonetheless, in the absence of discernible symptoms, it is difficult to recognize early atherosclerosis with conventional imaging techniques. Upon reaching an advanced stage, the rupture of the susceptible plaque may result in acute arterial occlusion, significantly increasing the risk of mortality. Consequently, it is imperative to accurately identify and promptly treat atherosclerosis in its early stages.

Materials & Methods: A smart ROS-responsive theranostic self-assembled nanoplatform (PA/HFLCD) has been developed for photoacoustic diagnosis and endothelial cell-macrophage crosstalk regulation of early atherosclerosis. Conjugated polymers (PFDPP-Se) are synthesized by palladium-catalyzed arylation polymerization reaction. The antioxidants linolic acid and ferrocene are grafted on low molecular weight heparin, while oxidized dextran is conjugated with β -cyclodextrin, which can self-assemble into PFDPP-Se loaded nanoparticles simultaneously utilizing hydrophilic-hydrophobic and host-guest interaction.

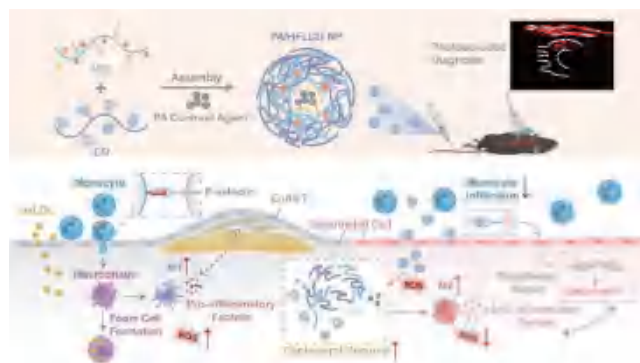


Fig. 1. Diagrammatic illustration of PA/HFLCD for photoacoustic diagnostics and modulation of the plaque inflammation.

Results & Discussion: First, the photoacoustic spectrum of PA/HFLCD was measured, revealing an optimal excitation wavelength of 720 nm and a linear correlation between photoacoustic intensity and PA/HFLCD concentration. Subsequently, PA/HFLCD was injected

into ApoE^{-/-} mice with established atherosclerotic models, and photoacoustic signals from plaques at the aortic arch were detected. Twelve hours post-injection, distinct photoacoustic signals were observed at the aortic arch plaque site, confirming the potential of PA/HFLCD for non-invasive photoacoustic diagnosis. Furthermore, excellent therapeutic effects were further validated by various staining of aortic valve sections. Eventually, the therapeutic mechanism of PA/HFLCD was investigated through RNA-seq analysis.

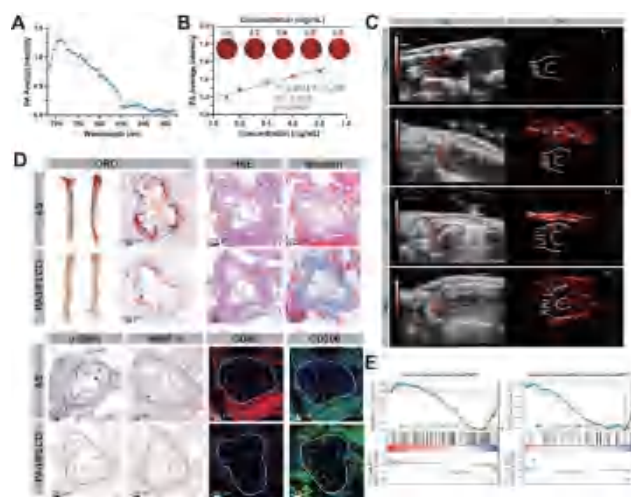


Fig. 2. Relevant data concerning the application of PA/HFLCD in photoacoustic imaging diagnostics and atherosclerosis treatment.

Conclusions: A smart responsive nanoparticle loaded with π -conjugated polymers has been developed, enabling non-invasive photoacoustic diagnosis and early treatment of atherosclerosis in vivo, which offers novel insights for the integrated diagnosis and treatment of other inflammatory diseases.

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A Tunable Alginate-Decellularized ECM Hybrid Hydrogel for Modulating Mammary Epithelial Cell States

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Key words: Tunable Hybrid Hydrogel; Epithelial-Mesenchymal Transition (EMT); Label-free Three-Dimensional Raman Imaging; Matrix Remodeling / ECM Remodeling; Disease Modeling.

Introduction: Extracellular matrix (ECM) signals critically guide cell behaviors like epithelial-mesenchymal transition (EMT). However, independently controlling ECM biochemical composition and physical stiffness in 3D, and quantifying subsequent remodeling non-destructively, remains challenging. This study developed an integrated platform to decouple and investigate the roles of these properties in directing mammary epithelial cell fate.

Materials & Methods: A hybrid hydrogel system combining alginate (mechanical scaffold) with cell-derived decellularized ECM (dECM) was created. Stiffness was tuned via alginate concentration. dECM from TGF- β 1-activated fibroblasts (adECM, tumor-like) or untreated fibroblasts (ndECM, normal-like) was incorporated. Mammary epithelial cells were cultured in 3D within hydrogels of varying composition (alginate-only, ndECM, adECM) and stiffness. Confocal Raman microscopy enabled label-free, quantitative 3D imaging of ECM components (e.g., collagen, laminin).

Results & Discussion: In soft RGD-alginate hydrogels, cells formed stable epithelial structures without spontaneous EMT, providing a baseline. Incorporating adECM into soft gels induced partial EMT and enhanced cellular response to TGF- β 1, unlike ndECM or alginate-only controls. Increasing stiffness synergized with adECM to robustly drive EMT. The platform successfully decoupled biochemical (dECM type) and biophysical (stiffness) cues, revealing their interplay. Raman imaging proved effective for high-content, non-destructive 3D analysis.

Conclusions: We developed a robust platform combining tunable hydrogels and Raman imaging to decouple and quantitatively assess ECM properties in 3D. This emphasizes the need to consider both matrix composition and mechanics in regenerative strategies. The platform is valuable for building predictive disease models and designing regenerative biomaterials. Future work should extend it to other tissues and utilize it for long-term live-cell dynamics monitoring.

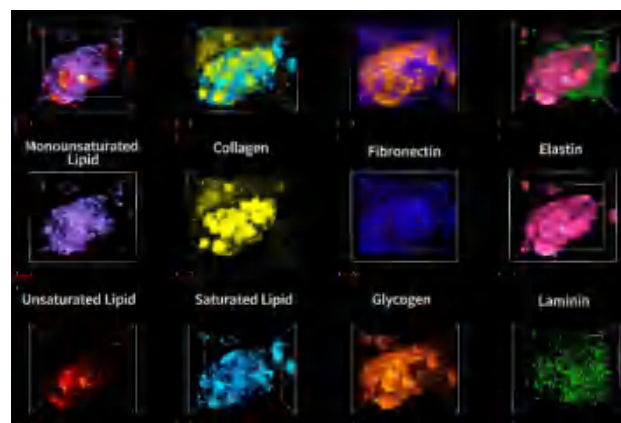


Fig.1. Raman Profile of MET State in Breast Tumor Organoid.



Fig. 2. 3D In Situ Analysis of the Extracellular Matrix.

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1. P. Barros da Silva, Xiaoyu Zhao, Sílvia J. Bidarra, Diana S. Nascimento, Vernon LaLone, Bianca N. Lourenço, Joana Paredes, Molly M. Stevens,* and C. C. Barrias*, Adv. Healthcare Mater. 2024, 2401032

Construction of Bioactive Materials for Cancer Immunotherapy

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Key words: immunotherapy, radiotherapy-driven vector, cellular senescence, tumor microenvironment

Introduction: Cancer immunotherapy has achieved remarkable clinical breakthroughs, yet its efficacy is limited by low response rates and severe immune-related adverse events. These challenges stem from poor tumor immunogenicity, an immunosuppressive tumor microenvironment (TME), and off-target effects of immunotherapeutic agents. To address these issues, we developed a series of nanomedicines tailored to enhance the safety and effectiveness of cancer immunotherapy.

Materials & Methods: Two complementary strategies were employed. First, we self-assembled senescence-inducing agents and senescence-associated secretory phenotype (SASP) modulators into orally administrable nanocrystals. This design ensures spatiotemporal synchronization of senescence induction and modulation within tumor cells, leveraging the appearance of senescence-associated self-antigens and the release of immunogenic SASP factors (Fig.1). Second, to mitigate off-target side effects, we analyzed the alteration of chemokines in irradiated tumors and engineered cell membranes with tropism toward these chemokines. These membranes were used to construct a radiotherapy-driven nanoplatform that capitalizes on the deep penetration and precision of radiation to deliver immunotherapeutic agents specifically to the tumor site (Fig.2).

Results & Discussion: The nanocrystals effectively induced cellular senescence in tumor cells while simultaneously regulating the SASP, leading to enhanced tumor immunogenicity and remodeling of the immunosuppressive TME. This dual action amplified the antitumor immune response and improved the efficacy of subsequent immunotherapy in preclinical models [1]. The radiotherapy-driven nanocarrier demonstrated precise homing to irradiated tumors guided by the upregulated chemokine gradient. This targeted delivery significantly increased the local concentration of immunomodulators, potentiated the synergistic effect of radio-immunotherapy, and markedly reduced systemic toxicity [2]. Together, these findings highlight the potential of combining senescence manipulation and radiation-guided delivery to overcome

key limitations of current immunotherapies.

Conclusions: Our research provides innovative bioactive materials and strategies to tackle the low response and high toxicity challenges in tumor immunotherapy. The oral nanocrystals offer a clinically translatable approach to reprogram the TME via senescence modulation, while the radiotherapy-driven vector enables precise spatiotemporal control of drug delivery. Future studies will focus on optimizing these platforms for combination with diverse immunotherapies and advancing them toward clinical translation. These materials hold significant promise for improving patient outcomes in cancer treatment.

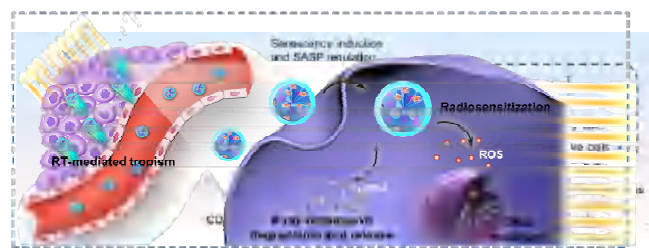


Fig. 1. Schematic illustration that nanocrystals enhance antitumor immune response through enhancing the expression of MHC-I and release of DAMPs as well as restoring the immunosuppressive TME in orthotopic 4T1 tumor-bearing mouse models.

Fig. 2. Schematic illustration of engineering nanoplatform with RT-mediated tropism, responsive release and radiosensitization for the radioimmunotherapy of glioblastoma.

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Near-infrared-II-driven Z-scheme heterojunction for dual-mode imaging guided tumor synergistic therapy

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Key words: Z-scheme heterojunction; Synergistic therapy; Photocatalysis; Dual-mode imaging

Introduction: Targeting the unique tumor microenvironment (TME), characterized by acidity, hypoxia, and hydrogen peroxide (H₂O₂) overexpression, is crucial for effective cancer treatment [1]. While photodynamic (PDT), photothermal (PTT), and chemodynamic therapy (CDT) show promise, their efficacy is limited by insufficient oxygen (O₂) supply and antioxidant glutathione (GSH)^[2]. Z-scheme heterojunction photocatalysts, known for efficient charge separation and strong redox potentials, offer a potential solution by splitting water to generate O₂^[3]. Herein, we designed an acid-responsive Z-scheme heterojunction nanoplatform for multimodal imaging-guided synergistic therapy under near-infrared-II (NIR-II) light.

Materials & Methods: The acid-responsive polyethyleneglycolated MoS₂/CoFe₂O₄ Z-scheme heterojunction (MSCO-PEG) was synthesized via a two-step hydrothermal method. Its physicochemical properties were characterized by TEM, XRD, XPS, etc. Photoelectrochemical properties, reactive oxygen species (ROS)/O₂ generation, GSH depletion, and photothermal performance were evaluated in vitro. The biocompatibility and combined therapeutic efficacy (PTT/PDT/CDT) were assessed using 4T1, HeLa, and AGS cancer cells. The dual-mode photoacoustic (PA) and magnetic resonance (MRI) imaging capability and in vivo antitumor performance were investigated in 4T1 tumor-bearing mice.

Results & Discussion: MSCO-PEG exhibited a successful heterojunction structure with excellent NIR-II absorption and a high photothermal conversion efficiency (41.16%). Notably, the constructed Z-scheme facilitated a “step-like” charge transfer under 1064 nm irradiation, amplifying the edge redox potentials. This mechanism significantly enhanced the photocatalytic splitting of H₂O to O₂ and the generation of superoxide radicals (•O₂⁻), alleviating tumor hypoxia and boosting PDT. Simultaneously, MSCO-PEG displayed peroxidase-/catalase-like activity for CDT and could effectively deplete GSH to promote ROS accumulation. In vitro, MSCO-PEG showed low cytotoxicity to normal

cells but potent killing effect on cancer cells upon NIR-II irradiation due to the synergistic PTT/PDT/CDT. Furthermore, MSCO-PEG served as an effective contrast agent for both PA and MR imaging, allowing for monitoring of tumor accumulation with peak enrichment at 24h post-injection. In vivo studies confirmed that MSCO-PEG + laser treatment achieved complete tumor ablation via the synergistic effects, guided by the dual-mode imaging, with no observable systemic toxicity.

Conclusions: We successfully developed a bioinspired Z-scheme heterojunction nanoplatform, MSCO-PEG, which responds to the acidic TME. Its unique “step-like” charge transfer mechanism under NIR-II light amplifies photocatalytic performance for O₂ self-supply and ROS generation. Integrating enhanced CDT, efficient PTT, and dual-mode imaging guidance, MSCO-PEG achieves highly effective tumor synergistic therapy. This work provides a promising strategy for advancing photocatalytic nanomedicine in targeted cancer treatment.

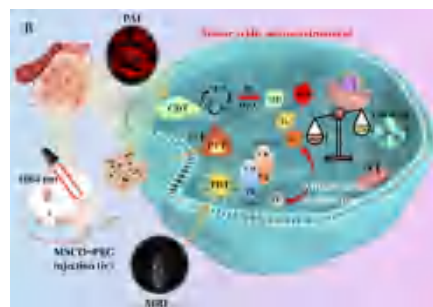


Fig. 1. Schematic illustration.

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Dynamic MPI Visualization of PD-L1 Expression to Optimize Gemcitabine and Anti-PD-L1 Combination Therapy in Pancreatic Cancer Organoids and Orthotopic Models

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Introduction: Pancreatic ductal adenocarcinoma (PDAC) exhibits poor response to immune checkpoint blockade due to its immunosuppressive microenvironment. Chemotherapy such as gemcitabine (GEM) has been reported to modulate PD-L1 expression; however, the dynamic temporal changes of PD-L1 following chemotherapy and the optimal timing for anti-PD-L1 administration remain unclear. In this study, we established pancreatic cancer organoids and orthotopic mouse models to investigate the temporal regulation of PD-L1 expression after GEM treatment. A PD-L1-targeted magnetic nanoparticle probe was developed for magnetic particle imaging (MPI) to dynamically visualize PD-L1 expression in vivo. Our results demonstrated that GEM significantly upregulated PD-L1 expression in a time-dependent manner, reaching peak levels at 72 h post-treatment. Sequential administration of anti-PD-L1 antibody at the PD-L1 expression peak significantly improved antitumor efficacy compared to simultaneous treatment. These findings suggest that MPI-guided dynamic monitoring of PD-L1 enables precise optimization of chemo-immunotherapy scheduling and provides a potential strategy for personalized treatment in PDAC.

Materials & Methods: Human pancreatic cancer organoids were established in a three-dimensional culture system and treated with gemcitabine, after which PD-L1 expression was evaluated at different time points. A PD-L1-targeted magnetic nanoprobe was constructed using superparamagnetic iron oxide nanoparticles as the magnetic core, followed by physicochemical characterization and in vitro validation of targeting specificity. An orthotopic pancreatic tumor model was then established in mice, and gemcitabine was administered prior to intravenous injection of the targeted nanoprobe at designated time points for magnetic particle imaging. MPI signal intensity within

the tumor region was quantitatively analyzed to assess dynamic changes in PD-L1 expression in vivo. Based on MPI-determined peak PD-L1 expression, a sequential treatment regimen was designed in which anti-PD-L1 antibody was administered at the peak time point, and therapeutic efficacy was evaluated through tumor growth monitoring, survival analysis, and assessment of immune cell infiltration.

Results & Discussion: Gemcitabine induced a time-dependent increase in PD-L1 expression in pancreatic cancer organoids and orthotopic tumors, peaking at 72 hours as confirmed by magnetic particle imaging. MPI signals correlated with ex vivo protein analyses, supporting its reliability for non-invasive dynamic monitoring in vivo. Sequential administration of anti-PD-L1 antibody at the peak expression time significantly improved tumor suppression and survival compared with concurrent treatment, whereas simultaneous therapy showed no significant synergy, highlighting the importance of treatment timing optimization.

Conclusions: This study demonstrates that GEM dynamically regulates PD-L1 expression in pancreatic cancer. MPI-based non-invasive imaging enables real-time visualization of PD-L1 changes and identifies the optimal therapeutic window for immune checkpoint blockade. Sequential chemo-immunotherapy guided by molecular imaging significantly enhances antitumor efficacy. Future studies should investigate the molecular mechanisms underlying PD-L1 upregulation and validate this strategy in patient-derived models to facilitate clinical translation.

Key words: pancreatic cancer; organoids; magnetic particle imaging; immunotherapy

A Bio-imaging Guided Multifunctional Hydrogel for Postoperative Photothermal therapy in Pancreatic Ductal Adenocarcinoma

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Key words: Pancreatic ductal adenocarcinoma, hydrogel, photothermal therapy, postoperative complications, immune response

Introduction:

Pancreatic ductal adenocarcinoma (PDAC) surgery is plagued by postoperative complications (1) and recurrence, driven by an immunosuppressive microenvironment (2). Here, we introduce a Ultraviolet (UV)-responsive hydrogel (Mxenes-Cy7/GelMA) for the pancreatic resection bed, evaluating its efficacy in preventing complications and inhibiting distant tumor growth via photothermal therapy (PTT).

Materials & Methods: Mxenes-Cy7/GelMA was prepared by incorporating MXenes and Cy7 into GelMA. In vitro photothermal cytotoxicity was assessed in KPC cells. In an orthotopic PDAC mouse model, post-resection mice received Mxenes-Cy7/GelMA + UV. Postoperative bleeding and pancreatic fistula were evaluated by blood loss, hemoglobin, and ascitic α -amylase/lipase. To assess systemic immunity, KPC-Luc cells were subcutaneously re-implanted into the flank one day post-resection. Tumor growth at both sites was monitored by BLI and caliper measurements.

Results & Discussion: In vitro, Mxenes-Cy7/GelMA exhibited stable photothermal performance (Fig. 1A) and induced significant tumor cell death upon NIR irradiation (Fig. 1B). In vivo, UV-cross-linked hydrogel on the pancreatic stump significantly reduced postoperative bleeding at 10 and 15 min (Fig. 2A-D) and lowered ascitic α -amylase/lipase levels, indicating effective PF prevention comparable to fibrin sealant (Fig. 2E-F). Immunofluorescence showed decreased IL-6 and increased TGF- β in residual tissue (Fig. 2G-H). Crucially, in the distant tumor model, Mxenes-Cy7/GelMA PTT significantly reduced Bioluminescence imaging (BLI) signals and tumor volumes at both primary and distant sites versus surgery alone at day 14 (Fig. 3A-D). Body weight in both treated groups remained comparable and significantly higher than untreated controls (Fig. 3E).

Conclusions: Mxenes-Cy7/GelMA hydrogel effectively manages postoperative complications—hemostasis, PF prevention, and local inflammation—following PDAC resection. Local PTT further activates systemic antitumor immunity to suppress distant tumor growth, offering a comprehensive strategy to improve surgical outcomes and prevent recurrence in PDAC.

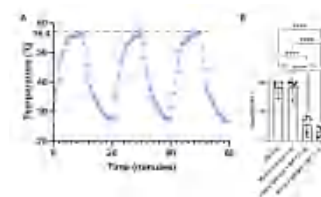


Fig. 1. (A) On-off heating curve. (B) KPC cell viability.

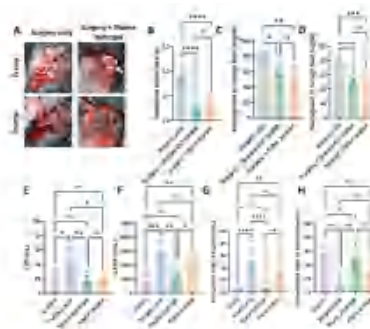


Fig. 2. Prevention of postoperative complications. (A) Macroscopic views of pancreatic stump. (B) Blood loss (n=5). (C) Hemoglobin in lavage fluid at 10 and 15 min (n=5). (D) Serum amylase and lipase at day 3 (n=5). (E) Semi-quantitative IF analysis of IL-6 and TGF- β (n=5).

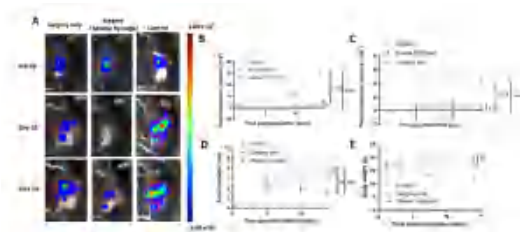


Fig. 3. PTT inhibition of tumors. (A) Representative BLI images. (B) BLI at orthotopic site (n=5) and (C) subcutaneous site (n=5). (D) Subcutaneous tumor diameters (n=5). (E) Body weight (n=5).

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Biomimetic electrical microenvironment on PVTF and its effects on osteogenesis

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Key words: PVTF, Electrical microenvironment, Osteogenic responses

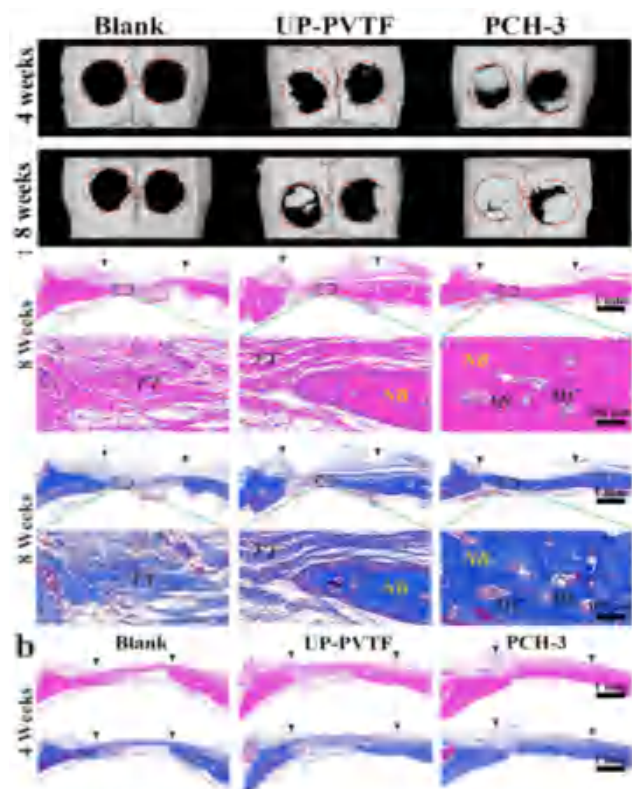
Introduction: Bone tissue possesses intrinsic electroactivity. During its injury repair process, the electrical microenvironment can enhance regeneration by influencing cellular behaviours such as migration and differentiation. Utilizing electroactive materials to construct a biomimetic electrical microenvironment at the material-cell interface to regulate cellular behavior and enhance repair outcomes represents one of the current effective strategies in bone tissue engineering. In natural bone tissue, cells reside within an ECM rich in collagen and hydroxyapatite, where bioelectric signals likely generate or transmit through these components to influence cellular behaviour. This process may differ from the mediation mechanisms and repair outcomes observed on artificial material surfaces. The natural ECM contains abundant functional groups such as hydroxyl, amino, and carboxyl groups, forming the most fundamental active constituents. Together with macromolecules like collagen and hydroxyapatite, these elements constitute extracellular microenvironments at different levels. Although collagen and hydroxyapatite possess some electroactivity, they are difficult to directly assemble into high-intensity, controllable bioinspired electrical microenvironments in vitro. Therefore, this study utilizes the ferroelectric polymer poly(vinylidene fluoride-trifluoroethylene) (PVTF) as the substrates, amines groups, collagen (COL) and its composites with hydroxyapatite (HA) were surface-modified onto PVTF, so that the electrical cues could be transmitted in a more biomimetic manner. The surface composition and electrical properties were investigated, exploring their regulation and mechanisms of action on stem cell osteogenic differentiation and macrophage immune polarization behaviours were also evaluated.

Materials & Methods: amines groups, collagen (COL) and its composites with hydroxyapatite (HA) were surface-modified onto the film through monoethanolamine (MEA) treatment, polydopamine (PDA) adhesion, and solvent evaporation coating methods, creating composite films with diverse surface biomimetic electrical microenvironments.

Electroactive PVTF films were prepared via solution casting and subjected to contact polarization. Subsequently, monoethanolamine treatment was employed to modify amino groups on the surface, establishing an amino-based bioinspired electrical microenvironment; adhesive polydopamine was used to

modify COL onto the PVTF surface via a static deposition method, constructing a collagen-based biomimetic electrical microenvironment; a biomimetic electrical microenvironment based on collagen and hydroxyapatite was further constructed by modifying the surface of amino-functionalized PVTF with COL/HA composite layers via solvent evaporation film formation and genipin.

Results & Discussion: Amine groups modification of PVTF could effectively promote protein adsorption and subsequent stem cells and macrophages responses. Further modification of COL reduces surface potential and then promoted the osteogenic differentiation of stem cells. At optimal condition, the biomimetic electrical microenvironment based on COL/HA showed much improved osteogenesis and reduced infectious responses. The new bone formation reached up to 3.7 times in comparison with blank control.



Conclusions: It is observed that such construction of biomimetic electrical microenvironment could effectively improve the stem cells and macrophage responses, and eventually improve osteogenesis.

Multimodal defect-rich nanoreactor triggers sono-piezoelectric tandem catalysis and iron metabolism disruption for implant infections

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Key words: Infectious bone defect; Lead-free piezoelectric material; Sonodynamic therapy

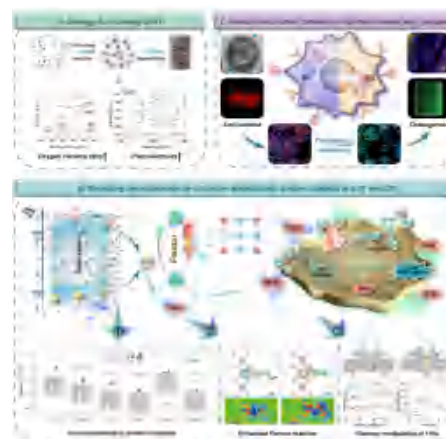
Introduction: Implant-associated infections (IAIs) and large bone defect reconstruction present persistent challenges in orthopaedics. Conventional implants lack inherent antibacterial properties, rendering them vulnerable to bacterial colonization and subsequent failure. Amid growing antibiotic resistance, developing effective antibiotic-free antibacterial materials has become critical. Chemodynamic therapy (CDT), which employs Fenton reactions to produce hydroxyl radicals ($\cdot\text{OH}$), is constrained by limited Fe^{2+} and H_2O_2 supply. Thus, engineering smart biomaterials that efficiently drive Fenton catalysis while promoting bone regeneration is essential for integrated infection control and bone repair.

Materials & Methods: We constructed a bio-piezoelectric nanoreactor (TH-BFBT) based on bismuth ferrite-barium titanate (BF-BT), utilizing a sono-piezoelectric tandem catalysis strategy to overcome the catalyst and substrate limitations of traditional CDT. $\text{Ba}^{2+}/\text{Ti}^{4+}$ -doped BF-xBT solid solutions were synthesized via solid-state reaction, with composition (x) screening to optimize band structure and oxygen vacancy (OV) content. Under ultrasound (US) stimulation, the material generates a built-in electric field that separates electron-hole pairs, enhances charge migration, promotes H_2O_2 dissociation, and reduces the Fe^{3+} -to- Fe^{2+} reduction barrier, thereby significantly boosting $\cdot\text{OH}$ production and enabling long-lasting CDT.

Results & Discussion: We developed an oxygen-vacancy-rich piezoelectric nanoreactor (TH-BFBT) that enables sono-piezoelectric tandem catalysis for sustained antibacterial and osteogenic effects (Fig. 1). The material demonstrated high piezoelectricity and oxygen vacancy concentration (Fig. 1A), facilitating self-supplied H_2O_2 generation and enhanced $\text{Fe(III)}/\text{Fe(II)}$ cycling under ultrasound. This synergy bypassed traditional Fenton limitations, enabling long-lasting chemodynamic therapy (Fig. 1B). Furthermore, sustained Fe(II) accumulation disrupted bacterial iron metabolism, inducing ferroptosis-like death, while the piezoelectric microenvironment promoted M1-to-M2 macrophage polarization and bone regeneration (Fig. 1C). These results establish a noninvasive strategy combining tandem catalysis with immunomodulation to treat implant-associated

infections.

Conclusions: This study developed a US-responsive piezoelectric nanoreactor for effective IAI treatment. The BFBT material initiates sono-piezodynamic and chemodynamic tandem catalysis under US, where self-supplied H_2O_2 from SPT fuels a sustained Fenton reaction, substantially enhancing ROS generation. Oxygen vacancies further facilitate Fe(III) reduction, accelerating $\text{Fe(III)}/\text{Fe(II)}$ cycling and enabling a self-sustained catalytic process. Transcriptomics revealed that prolonged Fe(II) exposure disrupts the two-component system in *S. aureus*, dysregulating iron metabolism and triggering ferroptosis-like death. Beyond antibacterial activity, BFBT modulates post-infection inflammation by promoting macrophage polarization toward an M2 phenotype, thereby supporting bone repair through electrically driven immunomodulation. In vivo studies confirmed that TH-BFBT significantly enhances new bone formation in infected rat models following US stimulation, attributable to its combined ROS-mediated antibacterial action, ferroptosis induction, and osteo-immunomodulatory effects. This work advances



the design of lead-free piezoelectric biomaterials for infection control and regenerative applications, with potential relevance beyond orthopaedics.

Fig. 1. Multimodal defect-rich nanoreactor triggers sono-piezoelectric tandem catalysis and iron metabolism disruption for implant infections.

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Clinical-Translatable Interface Design for Degradable Magnesium Implants: A Composite Coating to Coordinate Early Stability and Late-Stage Resorption

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Key words: magnesium alloy; composite coating; programmed degradation; clinical translation

Introduction: Degradable magnesium (Mg) implants require high mechanical integrity during the initial bone-healing period (3–6 months) followed by controlled resorption^[1]. Current surface strategies largely delay corrosion in a monotonic manner and lack programmable temporal control^[2]. This study proposes a hydroxyapatite (HA) conversion layer + Parylene C outer barrier composite coating (MHP/MHP composite interface) to actively synchronize implant degradation with staged bone repair.

Materials & Methods: An HA conversion layer and a Parylene C hydrophobic outer film were sequentially deposited on Mg-Zn-Zr-Mn alloy screws to form the composite coating (MHP)^[3]. Bare Mg (M), HA-only (MH), and Parylene C-only (MP) served as controls. Coating morphology, composition, and phase were characterized by SEM/EDS/XRD. In-vitro immersion assessed corrosion kinetics, hydrogen evolution, and mechanical retention. Cytocompatibility and osteogenic activity were evaluated using adhesion assays and osteogenic marker expression. A 24-month goat tibia implantation and a randomized clinical trial provided long-term interfacial imaging and safety outcomes.

Results & Discussion: The MHP coating exhibited robust interfacial bonding and surface hydrophobicity. In vitro, MHP demonstrated distinct two-stage degradation: within 12 weeks, volume retention >95%, and mechanical property retention >95%, markedly outperforming controls, confirming strong early corrosion shielding. Subsequent weeks showed a controlled transition to accelerated resorption. Cell studies indicated that MHP supported firm adhesion, spreading, and significant up-regulation of early and late osteogenic markers, evidencing osteoinductive potential. In goats, no radiographically detectable gas pockets were observed in the first 6 months, and a stable bone-implant interface was maintained before gradual replacement by new bone. Clinical imaging confirmed sound fracture healing without radiolucent zones or gas shadows, and all safety indices remained within normal ranges.

Conclusions: The HA/Parylene C composite interface enabled programmed temporal corrosion control, delivering reliable mechanical support during critical healing and orderly bio-resorption thereafter. Combined preclinical and preliminary clinical evidence supports this strategy as a promising pathway for next-generation Mg implants with

translatable degradation staging for orthopedic use.

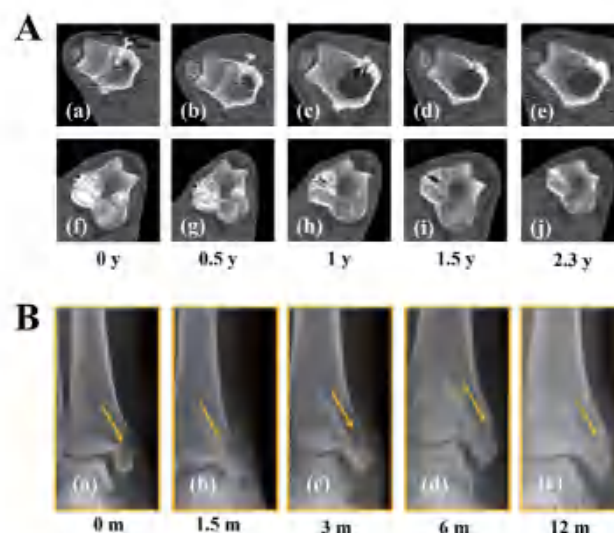


Fig.1. A: CT images of the surgical bones of two goats at different time points (immediately after surgery, 0.5 years, 1 year, 1.5 years, and 2.3 years); B: X-ray examination results of the patient's left ankle fracture at different follow-up times (immediately after surgery, 1.5 months, 3 months, 6 months, and 12 months).

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H₂-Mediated Regulation of the Inflammatory Microenvironment via a Poly(lipoic acid)-Based Coating on Titanium Implants

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Key words: tissue regeneration, molecular hydrogen, gas therapy, antibacterial, Ti implant

Introduction: The inflammatory microenvironment of peri-implantitis severely compromises peri-implant tissue regeneration and frequently results in implant failure. Molecular hydrogen (H₂) has demonstrated remarkable antioxidant and immunomodulatory effects in this context, thereby significantly promoting tissue regeneration. However, its lack of intrinsic antibacterial activity and uncontrolled release behavior hinder its further clinical application.

Materials & Methods: To address these limitations, a poly(lipoic acid)-based antibacterial polymer (pLAP) was synthesized to encapsulate H₂ donors on Ti surfaces. By copolymerizing aminated and phenylated lipoic acid at tunable ratios, pLAP balanced antibacterial activity, affinity, and biocompatibility. Its amino groups conferred antibacterial effects, while disulfide bond cleavage enabled polymer degradation and sustained H₂ release in inflammatory microenvironments, thereby reducing oxidative stress and promoting tissue regeneration.

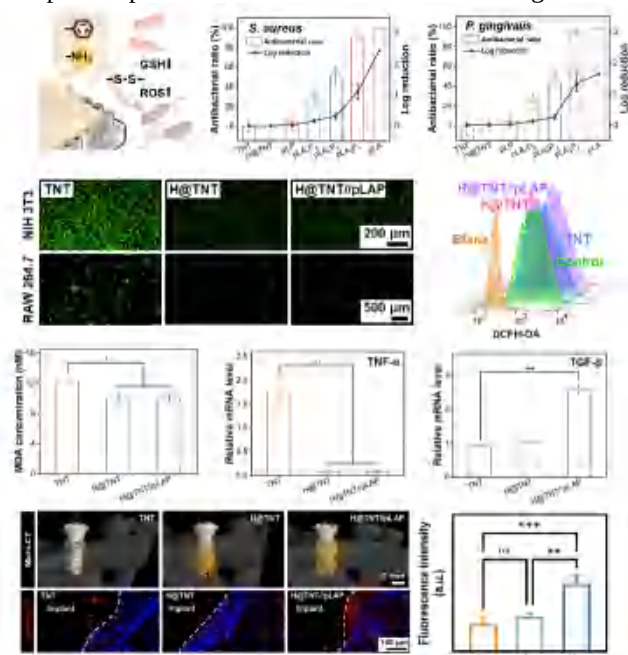
Results & Discussion: Herein, a poly(lipoic acid)-based antibacterial polymer (pLAP) was designed and synthesized to encapsulate H₂ donor-loaded TiO₂ nanotube (H@TNT), thereby constructing a bifunctional Ti implant coating (H@TNT//pLAP) with combined antibacterial activity and sustained H₂ release for enhanced tissue regeneration (Fig. 1).



Fig. 1. Schematic illustration of preparation and mechanism of H@TNT//pLAP.

In vitro antibacterial assays confirmed antibacterial rates of approximately 90.71% and 94.62% against

Staphylococcus aureus and *Porphyromonas gingivalis*, respectively. H₂ release kinetics demonstrated that the pLAP effectively encapsulated H₂. Antioxidant and immunomodulatory evaluations further confirmed that the released H₂ effectively scavenged ROS and promoted macrophage M2 polarization. Importantly, a rat peri-implantitis model validated the significant



therapeutic efficacy of the H@TNT//pLAP *in vivo*.

Fig. 2. Evaluation of the therapeutic efficacy of H@TNT//pLAP in peri-implantitis.

Conclusions: A H₂-releasing Ti implant coating was successfully developed, exhibiting strong antibacterial, antioxidant, and pro-regenerative effects. This strategy enables stable remodeling of the peri-implant inflammatory microenvironment and shows significant potential for clinical management of peri-implantitis.

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Surface engineering NiTi alloy with tunable wettability for optimized cellular response in cardiovascular applications

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Key words: NiTi alloy, plasma modification, atomic layer deposition, biocompatibility, protein adsorption

Introduction: Nickel–titanium (NiTi) alloys are widely applied in cardiovascular implants due to their unique superelastic and shape-memory properties; however, their long-term use is limited by nickel-related cytotoxicity [1]. Surface engineering is a key strategy to improve biocompatibility. Among the most promising approaches are aerosol-assisted atmospheric pressure plasma deposition (APPD) and atomic layer deposition (ALD), both enabling the formation of silicon-based surface layers with distinct physicochemical characteristics [1]. This study addresses plasma-based and ALD-derived coatings regulate protein adsorption behavior, surface mechanical properties, and biological responses. By correlating surface chemistry, wettability, mechanics, and protein conformation with cellular response, the work provides insight into the role of surface modification strategy in optimizing NiTi-based cardiovascular implants [2].

Materials & Methods: NiTi discs were used as substrates. Surface modification was performed using two approaches: ALD and APPD. Silicon-based coatings were deposited by ALD using tetramethoxysilane and water, in parallel, hydrophilic, hydrophilic/hydrophobic, and hydrophobic surfaces were obtained by APPD using hexamethyl disiloxane (HMDSO) and perfluorooctyl triethoxysilane (PFOTES) as precursors with controlled oxygen incorporation. Surface roughness, wettability, and surface free energy were evaluated before and after protein adsorption. Protein-surface interactions were analyzed by ATR–FTIR (Attenuated Total Reflectance - Fourier Transform Infrared Spectroscopy). Mechanical properties and wear resistance were assessed by nanoindentation and scratch testing. Biocompatibility was evaluated in vitro using Normal Human Dermal Fibroblasts, with fluorescence staining and analysed with confocal laser scanning microscopy.

Results & Discussion: Both surface modification strategies influenced the physicochemical and biological response. Plasma deposition enabled effective tuning of wettability, while ALD produced uniform and stable coating. Protein adsorption altered surface roughness and wettability, with the strongest effects observed for hydrophobic plasma coatings. ATR–FTIR analysis revealed partial protein unfolding on hydrophobic surfaces, whereas hydrophilic plasma coatings and ALD-derived coating better preserved protein secondary structure. Mechanical testing confirmed sufficient

hardness (**Tab. 1**) and adhesion for all coatings, with higher homogeneity and resistance observed for ALD layers. In vitro studies showed enhanced fibroblast adhesion and cytoskeletal organization on hydrophilic plasma and ALD-modified surfaces, while hydrophobic coatings resulted in reduced cell spreading.

Conclusions: The results confirm that the method of surface modification critically determines the biological performance of NiTi alloys. Hydrophilic plasma-treated and ALD-deposited silicon-based surfaces preserved protein structure and promoted favorable cellular responses, whereas hydrophobic coatings induced protein unfolding and reduced cell spreading. Plasma modification offers high tunability of surface properties, while ALD provides high uniformity, superior chemical and mechanical stability. These findings underline the importance of surface chemistry control in designing hemocompatible NiTi implants. Future work should address long-term and dynamic blood-contact conditions.

Table 1. Results of the hardness test

Sample (type of coating)	Average indenter penetration depth [nm]	Average hardness [MPa]	Mean Young's modulus [GPa]
NiTi + APDD hydrophilic	152,1	1290	27,1
NiTi + APPD mixed	90,1	3571	57,5
NiTi + APPD hydrophobic	94,6	3154	55,0
NiTi + ALD	78,0	4872	62,5

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Layer-by-Layer Polyelectrolyte Surface Coatings for Cardiac Applications: Physicochemical and Biological Evaluation

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Key words: layer-by-layer assembly, surface modification, polyelectrolyte coatings

Introduction: Surface modification of implantable materials offers a direct and effective strategy to tailor implant functionality. Among available approaches, the layer-by-layer (LbL) assembly technique provides exceptional versatility in designing multifunctional coatings with tunable physicochemical properties [1]. In this work, LbL films were engineered for drug-eluting cardiac patches, aiming to enhance local therapeutic release while maintaining cytocompatibility.

Materials & Methods: Two polymer pairs were selected for LbL assembly. As the state-of-the-art reference system, chitosan (Chi) and chondroitin sulfate (CS) were used. As an alternative, thermoresponsive pairs were introduced: N-Isopropylacrylamide (NIPAM) -grafted chitosan (Chi-g) and NIPAM-grafted alginate (Alg-g) (Table 1). Coatings were fabricated in two thickness variants: 6 bilayers (6 bi) and 12 bilayers (12 bi), in both non-crosslinked and crosslinked forms. A bilayer is described as two layers - one positively charged and one negatively charged. Crosslinking was performed using an N-hydroxysuccinimide (NHS)/ 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) activation system. The resulting films were characterized for thickness and surface roughness, wettability, followed by cell culture studies to evaluate biological response.

Table 1. List of polycations and polyanions

Polyelectrolyte	Acronym	Charge	Concentration [mg/ml]
Chitosan	Chi	Positive	0.5
Chondroitin sulfate	CS	Negative	1.0
Chitosan-g-PNIPAM	Chi-g	Positive	0.5
Alginate-g-PNIPAM	Alg-g	Negative	1.0

Results & Discussion: All coatings were successfully deposited on the substrate surface. Crosslinked films exhibited greater thickness compared to their non-crosslinked counterparts, consistent across both bilayer numbers (Fig. 1). Water contact angle measurements revealed clear differences in surface wettability depending on polymer composition, number of bilayers, and crosslinking. (Fig. 2) Coatings based on the Chi/CS system exhibited lower contact angle values, indicating more hydrophilic surfaces, particularly for crosslinked films. Cell studies revealed that the coatings supported cell adhesion and viability, with differences in cellular behaviour reflecting the underlying polymer

chemistry and surface morphology.

Fig. 1. Thickness of polyelectrolyte multilayers.

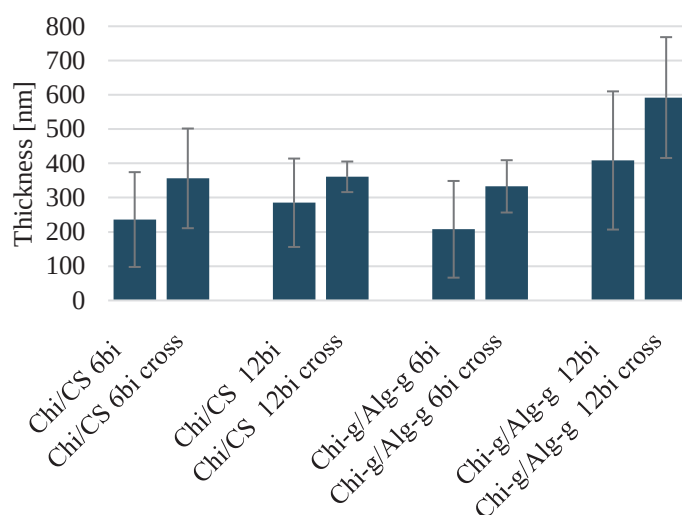
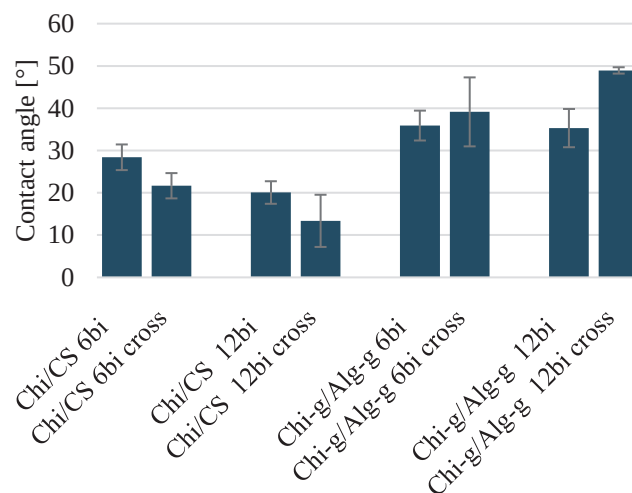


Fig. 2. Water contact angle of polyelectrolyte multilayers.



Conclusions: Layer-by-layer polyelectrolyte coatings enable precise control over surface thickness and wettability through polymer selection, bilayer number, and crosslinking.

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Integrated immunotherapy for infectious trauma

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Key words: Macrophage, antibacterial, tissue repair, biomaterials

gradually endows the bone implant material with antibacterial and osteogenic properties.

Introduction:

In the complex and dynamic clinical context of infected trauma, where persistent pathogen invasion, a dysregulated inflammatory response, and compromised tissue regeneration create a vicious cycle, achieving precise and adaptively control over the innate immune response is paramount. Macrophages, as the regulators at the intersection of inflammation and tissue repair, are central to this challenge. Their remarkable plasticity, allowing them to polarize into pro-inflammatory (M1) or anti-inflammatory (M2) phenotypes, presents a potential way for biomedical engineering interventions aimed at restoring the healing cascade.

Materials & Methods: The surface modification of Polyetheretherketone(PEEK) was applied to endow it with superior ability of immune regulation.

Results & Discussion:

Our works focus on precisely orchestrate macrophage phenotype, which include:

- 1. Activation of M1:** Pyrrole monomers were polymerized *in situ*. Through gentle photothermal stimulation, the phagocytic function of M1 macrophages was controlled, resulting in a material surface with immune and antibacterial functions. The material demonstrated excellent repair effects in bacterial infection models of the skin and femur.
- 2. Reprogramming of M2:** Once infection is contained, unchecked M1 activity becomes detrimental. A mitochondrial function regulation material was constructed, which specifically inhibited the key metabolic enzyme ALOX12 for M1 macrophage polarization, alleviated lipid peroxidation, promoted autophagy of damaged mitochondria mediated by ANT1/OPTN, reprogrammed M1 macrophages into M2, and promoted the repair of brain and bone injuries.
- 3. Sequential Programming for Adaptive Therapy:** Based on the differences in enzymes involved in metabolism in the infection microenvironment and the repair microenvironment, an adaptive macrophage phenotypic reprogramming surface was constructed. This surface regulates macrophages in response to the adaptive microenvironment in a time-dependent manner, and

Conclusions:

1. A strategy for gently activating M1 macrophage damage molecular patterns (DAMPs) was proposed.
2. M2 reprogramming materials was constructed for tissue repair.
3. The materials sequentially orchestrating of M1 and M2 were constructed for integrated immunotherapy for infectious trauma

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Fabrication of Novel Antibacterial PEO Coatings on Biomedical Pure Mg and Investigation of Their Degradation and Antibacterial Properties

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Abstract: Currently, the fabrication of antibacterial plasma electrolytic oxidation (PEO) coatings on pure magnesium primarily relies on doping with antibacterial elements. However, this approach often leads to a contradiction among antibacterial efficiency, degradation performance, and biosafety, thereby hindering practical application. In this study, two methods were employed to enhance the degradation resistance and antibacterial properties of PEO coatings while ensuring biosafety. The first method involved the preparation of a Cu-containing composite coating on pure magnesium via PEO combined with hydrothermal deposition. This composite coating consisted of a PEO layer and a deposition layer composed of CuHPO_4 and $\text{Cu}_3(\text{PO}_4)_2$. The Cu-containing deposition layer effectively sealed the micro-pores on the PEO coating surface. Furthermore, the Cu^{2+} ions released during degradation promoted the formation of $\text{Ca}_{19}\text{Cu}_2(\text{PO}_4)_{14}$ deposits on the surface. These two factors contributed to the composite coating exhibiting significantly superior degradation resistance compared to the single PEO coating. Due to a “fast-then-slow” Cu^{2+} release profile, the Cu-containing composite coating achieved an antibacterial rate of 99.89% in the early stage of service. In the later stage, the release rate decreased to an appropriate level, facilitating cell growth and proliferation. The second method utilized zinc plating followed by PEO to fabricate a PEO coating containing ZnO and $\text{Zn}_3(\text{PO}_4)_2$. Compared to the Zn-free PEO coating, the Zn-containing PEO coating demonstrated better degradation resistance and a lower degradation rate due to its greater thickness and the higher chemical stability of ZnO compared to MgO . During co-culture with bacteria, the release of Zn^{2+} ions and the reactive oxygen species (ROS) generated by ZnO acted synergistically to kill bacteria, effectively inhibiting bacterial counts at the lesion site and improving the success rate of implantation surgery. Simultaneously, the release of Zn^{2+} and Mg^{2+} ions promoted the proliferation and osteogenic differentiation of bone marrow mesenchymal stem cells. These findings provide a valuable reference for the design of antibacterial coatings on magnesium alloy implant materials.

Key words: Magnesium; Plasma electrolytic oxidation (PEO); Degradation; Antibacterial; Cu; Zn

Functionalizing Implant Surfaces/Interfaces for Bioadaptive Modulation of the Bone Implantation Microenvironment

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Key words: bone implant, surface/interface engineering, microenvironment modulation, catalytic therapy, bioadaptive materials

Introduction: Bone defect repair under complex pathological conditions, such as diabetes and infection, faces the fundamental challenge of a severely dysregulated local microenvironment at the implantation site, characterized by intertwined factors like sustained hypoxia, excessive oxidative stress, chronic inflammation, and immune dysregulation.^[1] Traditional biomaterials often underperform in such hostile settings. This study, building upon the paradigm shift towards adaptive and smart implants, aims to develop intelligent bone implant materials capable of dynamically sensing and actively remodeling the pathological microenvironment through advanced surface/interface engineering.^[2-4]

Materials & Methods: Two types of functionalized interfaces were designed and fabricated based on our previous work:^[2-4] 1) Bionically catalytic and self-adaptive interfaces created by immobilizing enzyme-mimetic nanocatalysts or biocatalysts to form responsive coatings. 2) Programmed delivery interfaces fabricated using degradable polymers or metallic systems (e.g., Mg-based) in multilayer/core-shell structures, loaded with therapeutic gas precursors, metal ions, and bioactive molecules. Materials were characterized by SEM, XPS, and *in vitro* degradation tests. Biological efficacy was systematically evaluated using cell models (osteoblasts, macrophages under high-glucose/inflammatory stimulation) and animal models of diabetic or infectious bone defects.

Results & Discussion: *In vitro*, the bionically catalytic interfaces effectively catalyzed the generation of antibacterial ROS under simulated pathological conditions and switched to producing pro-osteogenic substances as the microenvironment normalized, demonstrating a “self-adaptive” functionality. The programmed delivery interfaces, particularly those based on biodegradable metals like Mg, exhibited sequential release profiles: rapid initial antibacterial activity, sustained release of therapeutic ions (e.g., Mg^{2+} , Zn^{2+}) and hydrogen (H_2) to mitigate oxidative stress and inflammation, and prolonged osteogenic stimulation. *In vivo* results in diabetic rat models with infected bone defects showed that these functionalized implants significantly reduced early inflammation, alleviated local hypoxia, promoted M2 macrophage polarization, and ultimately enhanced new bone formation and defect closure compared to traditional implants. The discussion integrates these findings,

highlighting how the engineered surfaces mediate a transition from biomimetic to truly bioadaptive behaviors, precisely regulating the immunomodulation-osteogenesis coupling via integrated catalytic and delivery effects.

Conclusions: This study successfully developed smart bone implant interfaces with microenvironment-responsive properties. By integrating dual strategies of “enzymatic-catalysis regulation” and “temporal delivery of active agents”, these interfaces can actively reverse the pathological microenvironment into a pro-regenerative state, significantly improving bone repair under complex conditions. This work provides a new design concept for next-generation “intelligent” and adaptive bone implant materials. Future research will focus on the translational optimization of these synergistic systems.



Fig. 1. Schematic demonstration of the functionalization of bone implants for bioadaptive surfaces and interfaces that interact proactively with host implantation microenvironments.

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ROS-Responsive Titanium Implant Coatings Enhance Osteoporotic Osseointegration via Microenvironment Remodeling and Mitochondrial Repair

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Key words: ROS-responsive coating, osteoporotic bone regeneration, titanium implants, mitochondrial damage repair, nicotinamide mononucleotide

Introduction: Osteoporosis (OP) is a metabolic bone disorder characterized by reduced bone mass, increased bone fragility, and microarchitectural deterioration. Titanium-based implants are widely used for bone defect repair due to their superior mechanical strength and biocompatibility. However, under osteoporotic conditions, excessive reactive oxygen species (ROS) accumulation and mitochondrial dysfunction impair osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs) and enhance osteoclast activity. Consequently, titanium implants often exhibit compromised osseointegration, poor stability, and an increased risk of loosening in OP patients. The present study addresses the scientific question of whether mitochondrial-targeted surface functionalization of titanium implants can restore redox homeostasis and improve osteoporotic osseointegration.

Materials & Methods: A dual-network hydrogel coating with mitochondrial repair capability was fabricated on titanium substrates. Nicotinamide mononucleotide-loaded amorphous calcium carbonate nanoparticles (NMN@CaCO₃) were incorporated into a lipoic acid-modified gelatin (LAMG) and sodium alginate (S) hydrogel system to form a bioadhesive and controlled-release coating (GSC). In vitro assays evaluated cytocompatibility, ROS-scavenging capacity, NAD⁺ restoration, mitochondrial membrane potential, and osteogenic protein expression (Runx2, Col1, Opn, and SIRT1) in BMSCs. In vivo performance was assessed using an osteoporotic rat model. Oxidative stress levels in peri-implant bone were analyzed, while micro-computed tomography (micro-CT) quantified bone volume fraction (BV/TV) and trabecular thickness (Tb.Th). Tartrate-resistant acid phosphatase (TRAP) staining was performed to evaluate osteoclast activity.

Results & Discussion: The GSC coating demonstrated favorable biocompatibility and sustained NMN release in vitro. It effectively scavenged ROS, restored intracellular NAD⁺ levels, and improved mitochondrial membrane potential in BMSCs. Osteogenic markers (Runx2, Col1, Opn) and SIRT1 expression were significantly upregulated, indicating enhanced osteogenic differentiation. In vivo, coated implants reduced oxidative stress in osteoporotic bone defects and significantly increased BV/TV and Tb.Th compared

to unmodified controls. TRAP staining revealed suppressed osteoclast activity around the implant site. No adverse inflammatory or cytotoxic responses were observed. These findings suggest that mitochondrial-targeted redox modulation synergistically promotes bone formation while inhibiting bone resorption under osteoporotic conditions.

Conclusions: This study demonstrates that a mitochondrial repair-oriented dual-network hydrogel coating can substantially enhance osseointegration of titanium implants in osteoporotic bone. By restoring NAD⁺ metabolism and alleviating oxidative stress, the functionalized implant promotes osteogenesis and suppresses osteoclast-mediated bone resorption. Future studies should investigate long-term implant stability, large-animal validation, and translational optimization for clinical application. This strategy provides a pathophysiology-responsive approach for improving implant performance in compromised bone microenvironments and holds significant potential for osteoporosis-related bone defect repair.

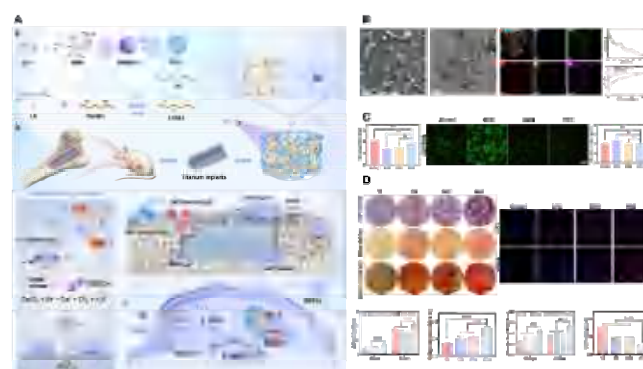


Fig. A) Schematic illustration of the construction strategy a) and the mechanism for enhancing osteoporotic osseointegration b) of ROS-responsive titanium implant coatings. **B)** Characterization (SEM, XRD, etc) of NMN@CaCO₃ NPs. **C)** Intracellular NAD⁺/NADH and ROS levels in BMSCs. **D)** Osteogenic differentiation, immunomodulatory and anti-osteoclastic effects of GSC-modified Ti implants.

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Electron Pump and Photon Trap Effect-Derived Selective Antitumor of Fe-Ppy@CaO₂-Modified PEEK for Bone Tumor Therapy

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Key words: Bone tumor, polyetheretherketone, electron pump, photon trap, immunomodulation

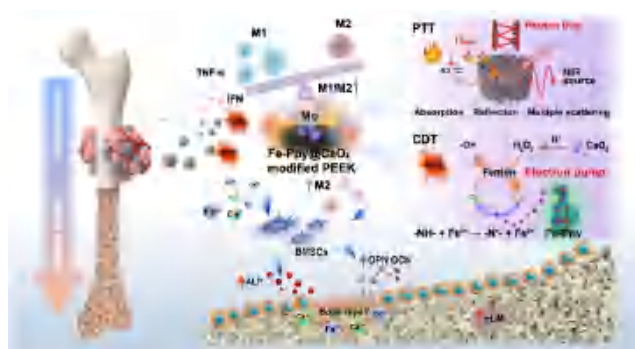
Introduction: Bone tumors with high mortality and disability have become a major clinical challenge. Herewith, it is necessary to design materials for bone tumor therapy and bone repair. Polyetheretherketone (PEEK) is a class of FDA-approved hard tissue replacement materials that can be implanted into bone defect sites for treatment after bone tumor resection. And the immune response mediated by macrophages is essential for tumor clearance and later osteogenesis. Effective combination of immunomodulation with CDT and PTT is attractive to improve the antitumor efficacy and bone repair. Herewith, endowing PEEK with enhanced synergistic therapeutic functions is an effective strategy to address key issues in bone tumor therapy.

Materials & Methods: The mechanism of long-lasting reactive oxygen species (ROS) generation and effective photothermal conversion was studied by •OH generation determination, elemental state analysis, infrared thermal images, and simulation calculation. The modified PEEK with the above physicochemical properties and immunomodulation has been studied for antitumor and osteogenesis *in vitro* and *in vivo*.

Results & Discussion: Fe-doped polypyrrole (Fe-Ppy) and CaO₂ are constructed on sulfonated polyetheretherketone (SP) to form a multistage-responsive coating. The coating achieves long-lasting antitumor through chemodynamic therapy (CDT), photothermal therapy (PTT), and combined immunotherapy. Fe-Ppy acts as an electron pump to replenish Fe²⁺ through oxidizing -NH- to -N⁺-, which lasts the Fenton reaction and persistently produces reactive oxygen species (ROS) in the tumor microenvironment (TME). CaO₂ selectively provides exogenous H₂O₂ in response to TME to boost the electron cycle. Stronger near-infrared light absorption due to Fe doping and more photon traps caused by porous structure-induced scattering and refraction diminishment improve the photothermal conversion of modified SP. Furthermore, long-lasting ROS and effective photothermal conversion enhance M1 activation to secrete TNF-α and IFN to kill tumor cells. After tumor therapy, Fe-Ppy@CaO₂-modified SP could adaptively switch the macrophage to M2 and promote

osteogenesis with the abolishment of TME and NIR stimulation.

Conclusions: The modified PEEK can efficiently kill tumor through long-lasting ROS, enhanced photothermal conversion, and strong M1 phenotype activation. And after tumor elimination, it polarizes macrophages switching to the M2 phenotype with the abolishment of a weak acid environment and NIR-II stimulation, thereby promoting new bone formation in bone tumor models. This provides a good candidate material for tumor therapy and bone repair.



Graphic abstract. Fe-Ppy and CaO₂ are constructed on sulfonated polyetheretherketone for tumor therapy and bone repair. In the TME, Fe-Ppy acts as electron pump, and porous structure traps photons, causing long-lasting ROS, enhanced photothermal conversion, and M1 activation, which synergistically kills tumors as CaO₂ responds to the TME. After tumor treatment, it adaptively switches macrophage to M2 and promotes osteogenesis.

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Nano-interfacial Engineering on Biomaterial and Their Diverse Biomedical Applications

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Key words: Nano-interfacial engineering, Bone implants, Antibacterial, Osseointegration, Nanozyme

Introduction: Advanced functional nanomaterials and surface engineering hold immense potential for revolutionizing disease management and tissue repair. However, existing biomaterials, including bioactive ceramics and titanium alloys used as bone implants, still face limitations such as insufficient bioactivity and poor antimicrobial performance. Their effective application requires overcoming the complexity of biological microenvironments through precise multifunctional designs and intelligent responsiveness to pathological signals. This study presents innovative solutions ranging from smart nano-formulations for disease therapy to macro-implant surface nanotechnology for enhanced bone regeneration and infection control.

Materials & Methods: We developed a diverse toolkit of nano-interfacial strategies: 1) Manganese-based nanozymes with triple enzyme-mimic activities and Co^{3+} -rich hydroxide nanosheets were engineered for crystalline and viral pathologies. 2) Silicon-based hydroxyapatite nanocarriers were synthesized for the synergistic treatment of osteomyelitis. 3) For macro-scale implants (Ti/Ti alloys and ceramics), customized surface nanotechnology was employed to introduce specific nanostructures. This included the precise control of light absorption characteristics to enable photodynamic antimicrobial functions. The surface topography and biological material-host interactions were evaluated using advanced spectroscopic, microscopic, and cellular assays.

Results & Discussion: Our integrated nano-engineering approach yielded significant results across multiple biomedical fronts. The manganese-based nanozyme effectively treated acute gout by degrading MSU crystals and suppressing inflammation^[1]. The trivalent cobalt nanosheets demonstrated potent antiviral efficacy against SARS-CoV-2^[2]. Addressing bone defects, the silicon-based hydroxyapatite carriers cleared infections while promoting tissue regeneration^[3]. On the macro-implant surfaces, the introduced nanostructures significantly enhanced cellular functions and osseointegration through the "nano effect." Furthermore, the achieved photodynamic antimicrobial function provided a new dimension for infection control, drastically reducing bacterial colonization without compromising biocompatibility^[4,5]. These modifications optimized the interface between the material and the

biological body, significantly improving bone repair efficiency.

Conclusions: Nano-interfacial engineering, both at the particulate and macro-surface levels, provides a powerful platform for addressing complex pathological challenges. By tailoring nanostructures and surface properties, we have successfully enhanced the antimicrobial performance, bioactivity, and osseointegration of various biomaterials. These findings underscore the clinical potential of nanotechnology in promoting bone tissue integration and disease therapy, offering significant implications for the development of next-generation intelligent implants.

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An Immunocompatible Conductive Hydrogel via Anion- π Interlocking as an Injectable Bridge for Sustained Bioelectronic Interfacing

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Key words: Anion- π interactions; Injectable conductive hydrogel; Bioelectronic interfaces; Anti-FBR

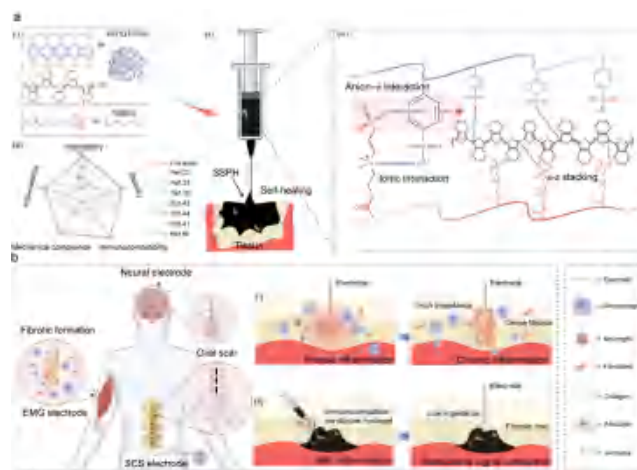
Introduction: Implantable bioelectronic devices hold great promise for neural recording, stimulation, and disease treatment. However, their long-term performance is often compromised by the mechanical and biological mismatch between rigid devices and soft tissues, which can lead to interfacial damage, chronic inflammation, and fibrotic encapsulation. Constructing a compliant and biologically adaptive interface is therefore critical for stable tissue-device communication. Here, we present an injectable conductive hydrogel formed by blending PEDOT:PSS with the zwitterionic polymer PSBMA. Driven by anion- π interactions together with ionic and hydrophobic interactions, the hydrogel is designed to serve as an immunocompatible bridge between bioelectronic devices and biological tissues.

Materials & Methods: The conductive hydrogel was prepared by directly mixing PEDOT:PSS and PSBMA in aqueous solution, followed by spontaneous gelation through noncovalent intermolecular interactions. Its injectability, self-healing capability, mechanical compliance, and electrochemical properties were systematically characterized. The interfacial performance of the hydrogel was further evaluated through in vitro biocompatibility studies and in vivo implantation or stimulation tests, with particular attention to tissue integration, inflammatory response, and electrical signal transmission.

Results & Discussion: The hydrogel first showed homogeneous gelation after simple mixing of PEDOT:PSS and PSBMA, indicating the formation of a robust supramolecular network. This dynamic network endowed the material with excellent injectability and rapid structural recovery after shear, making it suitable for minimally invasive delivery. Meanwhile, the hydrogel combined soft tissue-matched mechanical compliance with stable electrical conductivity, satisfying the key requirements for implantable bioelectronic interfaces. When introduced as an interfacial bridge, it reduced the mechanical mismatch between rigid electrodes and surrounding tissues, thereby improving interfacial contact. Importantly, the hydrogel enabled efficient bidirectional signal transmission between bioelectronic devices and biological tissues. In vivo studies further demonstrated

that the zwitterionic hydrogel interface alleviated local inflammation and tissue damage, supporting stable long-term communication at the tissue-device interface. In a spinal cord stimulation (SCS) model, the hydrogel-assisted interface further exhibited reliable electrical stimulation performance in vivo, highlighting its potential for long-term implantable bioelectronics.

Conclusions: An anion- π -interlocked injectable conductive hydrogel was developed from PEDOT:PSS and PSBMA for bioelectronic interface engineering. By integrating injectability, self-healing behavior, mechanical compliance, stable conductivity, and zwitterion-enabled immunocompatibility, the hydrogel serves as an effective bridge between rigid bioelectronic devices and soft tissues. Its ability to support bidirectional signal transmission and effective spinal cord stimulation in vivo highlights its promise for long-term implantable bioelectronics.



Scheme 1. Design of the injectable tissue bridge and its interfacing applications.

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Immunocompatible interface material for implantable devices

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Key words: Implants, Immunocompatible surface, foreign body response.

Introduction: Implantation of biomaterials inevitably triggers a foreign body reaction, wherein the host immune system attempts to isolate the implant through fibrous encapsulation. This chronic inflammatory response culminates in the formation of a dense, avascular collagenous capsule that walls off the material from surrounding tissue. Such fibrotic encapsulation severely compromises device performance by impeding molecular exchange, altering mechanical properties, and ultimately limiting the functional longevity of implantable medical devices across diverse clinical applications.

Materials & Methods: This work aims to improve the immunocompatibility of implant–tissue interfaces, a central challenge in biomaterials. We first developed a human serum albumin–based immunocompatible interface strategy and demonstrated that the long-term immunomodulatory performance of albumin coatings critically depends on interfacial stability. Only biointerfaces capable of resisting competitive protein displacement *in vivo* can sustain suppression of inflammatory responses.

To address the requirements of implantable bioelectronics, we further developed conductive polymers with immunomodulatory side chains, enabling the integration of electrical functionality with improved immunocompatibility at the device–tissue interface.

Moving beyond conventional surface modification, we then developed elastomeric materials with intrinsic immunocompatibility. A hydrophobic elastomer capable of *in-situ* forming a superhydrophilic anti-fouling interface was shown to mitigate chronic inflammation and fibrotic encapsulation after implantation.

Moreover, we then developed an intrinsically immunocompatible fully hydrophobic elastomer (EVADE) by introducing immunomodulatory moieties into the polymer backbone. Mechanistic studies revealed that EVADE suppresses fibrotic responses by modulating host innate immune alarm signals, particularly the S100A8/A9 pathway, providing molecular insight into material-driven immune regulation.

Building on this concept, we further developed a structurally heterogeneous elastomer (PURE) that combines high elasticity with adaptive immunomodulatory interfaces through phase separation–mediated surface reconstruction. PURE

exhibits further enhanced anti–foreign body response performance compared with EVADE, enabling long-term suppression of fibrotic encapsulation *in vivo*.

Results & Discussion: These results show that the immunocompatibility of implant materials can be systematically improved through rational materials design. From stabilizing albumin-based biointerfaces to developing intrinsically immunocompatible elastomers, our studies demonstrate that material composition and structure can actively regulate host immune responses. In particular, modulation of the S100A8/A9 innate immune pathway and adaptive immunomodulatory interfaces enabled effective suppression of fibrotic encapsulation.

Conclusions: To address the challenge of immune incompatibility at implant–tissue interfaces, we developed a series of material strategies, including stable biointerfaces, immunomodulatory conductive polymers, and intrinsically immunocompatible elastomers. These approaches demonstrate that rational materials design can effectively regulate host immune responses and suppress fibrotic encapsulation for implantable biomaterials.

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Instant Bioanalysis

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Key words: Microfluidic Chip, Surface-Enhanced Fluorescence, Fluorescent Probe, Disease Diagnostics, Rapid Detection

Introduction: Instant bioanalysis is pivotal for early-stage and point-of-care diagnostics, yet its performance is frequently compromised by complex biological matrices, severe signal attenuation, and a heavy reliance on sophisticated laboratory equipment. To address these bottlenecks, this work focuses on the fundamental scientific question: "How to systematically enhance the efficiency of signal transduction and readout?". We transitioned from traditional single-concentration act-of-diagnosis to "Mechanism-Tool-Application" framework, aiming to push the limits of sensitivity and information dimensionality in decentralized clinical settings.

Materials & Methods: Our approach integrates three synergistic layers: a) Signal Transduction: We elucidated luminescence kinetic regulation mechanisms and developed plasmon-enhanced fluorescence (pGOLD) platforms to overcome the intrinsic limits of quantum yield; b) Probe Design: A modular, AI-driven strategy was implemented for the rational design of chemical probes, utilizing deep learning to predict and optimize molecular structures with large Stokes shifts and high brightness; c) Analytical Framework: We constructed a multidimensional phenotypic analysis method that shifts the focus from "isolated indicator detection" to "comprehensive functional state parsing."

Results & Discussion: Ultra-sensitivity: The pGOLD platform achieved femtomolar detection limits and single-copy sensitivity, showing 97.6% consistency with genomic sequencing in over 1,000 clinical samples; Readout Efficiency: AI-optimized probes demonstrated a 100-fold reduction in detection limits compared to traditional gold immunochromatography, enabling robust visual interpretation without complex optics; Clinical Impact: the developed technologies have been adopted by global giants like Beckman Coulter and authorized by the US FDA and EU CE.

Conclusions: We have established a closed-loop research paradigm from physical mechanism discovery to industrial translation. By breaking the physical constraints of signal transduction and the empirical limits of probe development, this work provides a systematic solution for high-performance, instrument-free bioanalysis. Our future directions aim to extend this framework to in-situ protein microenvironment analysis in deep tissues, bridging the gap between in-vitro diagnosis and in-vivo functional imaging.

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A Novel Strategy for Immunological Evaluation of Recombinant Collagen Medical Devices from a Regulatory Science Perspective: From Humanized Model Construction to Full-Cycle Risk Prediction

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Key words: Recombinant Collagen; Immunological Evaluation; Regulatory Science; Humanized Transgenic Mouse; Full-Cycle Risk Prediction;

Introduction: Recombinant collagen medical devices are widely used in regenerative medicine due to their excellent biocompatibility and bioactivity. However, as exogenous protein materials, their potential immunogenicity remains a core challenge in regulatory evaluation. Traditional evaluation methods rely on wild-type rodent models, which suffer from significant species-specific interference (i.e., "xenogeneic recognition"), often leading to false-positive results. Furthermore, there is a lack of systematic predictive tools for material degradation products and long-term in vivo interactions. Guided by the principles of regulatory science, this study aims to explore a scientific and systematic new method for immunological evaluation of recombinant collagen by constructing precise evaluation tools, innovating evaluation paradigms, and establishing a full-cycle risk prediction system. This addresses the industry pain point of "insufficient suitability of evaluation methods for continuous in vivo interaction."

Materials & Methods: Tool Innovation: A humanized type III collagen transgenic mouse model (hCOL3A1) was constructed using CRISPR/Cas9 technology on a C57BL/6J background. Immune tolerance was induced via embryonic exposure to eliminate species barriers, with expression verified by qPCR and mass spectrometry.

Paradigm Reconstruction: We proposed a "Six-Layer Progressive" evaluation strategy. This involved a comparative study (wild-type vs. transgenic mice) across 10 groups, including investigational materials (multi-dose), marketed controls, and negatives. Dynamic monitoring of humoral immunity (IgG/IgM/IgE), cytokine profiles (Luminex), complement activation, and lymphocyte subsets was conducted over 180 days to capture acute, sub-chronic, and delayed immune responses.

Risk Prediction: A full-cycle safety system was integrated, combining in vitro enzymatic degradation proteomics to match human tissue profiles with 52-week chronic toxicity studies in rats to assess long-term biocompatibility and tumorigenic potential.

Results & Discussion:

Model Efficacy: The transgenic model successfully eliminated species artifacts. While wild-type mice

exhibited significant secondary immune responses (false positives) against recombinant collagen, transgenic mice maintained negligible antibody titers and no memory B-cell activation, confirming the material's intrinsic low immunogenicity.

Strategy Validation: The "Six-Layer" approach effectively differentiated immune profiles, demonstrating that recombinant collagen possesses superior immunocompatibility compared to animal-derived counterparts and exhibits a controllable, dose-dependent safety profile.

Long-Term Safety: Proteomic analysis revealed that degradation products of the recombinant collagen perfectly matched human skin proteomes. The 52-week chronic toxicity study showed no material-related adverse effects on organ coefficients or weight gain. Observed tumors were statistically confirmed as spontaneous background events in SD rats, unrelated to the test material.

Conclusions: This study successfully developed a robust regulatory science framework comprising a humanized animal model, a multidimensional "Six-Layer Progressive" evaluation paradigm, and a full-cycle risk prediction system. By resolving the critical issues of species difference and long-term uncertainty, this approach shifts the evaluation focus from simple safety screening to a closed-loop assessment of safety, efficacy, and quality. It provides essential methodological support and new tools for the global registration, standardization, and clinical translation of recombinant collagen and other protein-based medical devices.

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Study of malignant phenotypes and acquired chemoresistance via tumor organoids in the biomimetic matrices

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Tumor progression is a long-term developing process along with multiple malignant phenotypes (eg., proliferation, invasion, acquired chemoresistance and stemness), which can be significantly promoted by the tumor niche. Thus, it is essential to understand the complex interactions between tumor cells and the tumor niche for the rational development of effective treatment methods. However, both two-dimensional monolayer cell culture and in vivo animal models have their inherent limitations, such as lack of proper cell-ECM interactions and uncontrollable variables. By their heterogeneous simulation of tumor processes, 3D organoids can better recapitulate real tumor characteristics and more realistic responses to distinct factors. In recent years, our group has established heterogeneous organoids of diverse cancer types in the recreating tumor-stroma niche by using alginate cryogels to mimic the porous ECM, providing tunable mechanical properties and introducing matrix-bound growth factors [1-7]. The tumor organoids in the biomimetic ECM promoted malignant phenotypes in proliferation, migration, EMT, apoptosis and drug resistance, in accordance with clinical evidence. The multi-omics analyses combined with molecular biological experiments were also applied to reveal functioned interactions to activate signaling pathways and to identify possible targets for drug development [8-13]. Our system would represent a new paradigm of cancer progression studies using in vitro 3D organoids in a biomimetic ECM, in order to develop novel therapeutic strategies and evaluate preclinical treatments.

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A Fiber-Based Closed-Loop Theranostic System for Real-time Biomarker Monitoring and On-demand Gas Therapy

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Key words: Closed-loop, electrochemical sensing, fibers

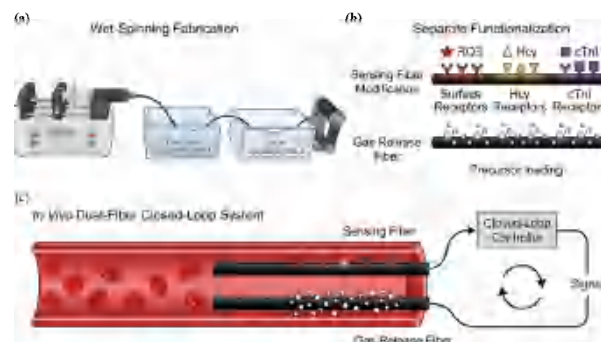
Introduction: Chronic diseases such as cardiovascular disorders and non-healing wounds require continuous monitoring and timely intervention, yet conventional strategies separate diagnosis from therapy, causing delayed responses. Implantable flexible bioelectronics offer a promising solution by enabling long-term, real-time sensing and treatment with improved precision. Among various substrates, fibers provide superior mechanical compliance, conformability, and tissue compatibility compared to rigid devices. Here, we develop a fiber-based closed-loop theranostic system using chitosan/single-walled carbon nanotube composite fibers. Through ligand- or enzyme-based functionalization, the fibers enable detection of inflammatory biomarkers (H_2O_2 , Hcy, cTnI) and controlled gas-drug release to achieve integrated closed-loop regulation.

Materials & Methods:

Chitosan (CS)-carbon nanotube (SWCNT) conductive fibers were fabricated through wet spinning for electrochemical sensing. Enzyme catalysis and applied potential were used to trigger the release of oxygen (O_2) and hydrogen sulfide (H_2S), and a closed-loop circuit was constructed.

Results & Discussion: Through process optimization, we successfully fabricated CS-CNT fibers with a uniform diameter of 0.1 mm and a linear resistance of approximately 5 k Ω /cm, providing a stable and flexible scaffold for the system. The integrated sensing platform achieved high sensitivity with well-defined linear detection ranges for cTnI (0.001–100 ng/mL), Hcy (4–40 μM), and H_2O_2 (10–200 μM), covering clinically relevant windows associated with chronic inflammation and cardiac stress. In addition, the miniaturized hardware enables real-time monitoring of these biomarkers and supports wireless data transmission via Bluetooth.

Conclusions: This study established a theranostic platform prototype using conductive fibers as a flexible structural support. The platform integrates multi-biomarker sensing with wireless communication electronics, achieving a high level of functional integration while maintaining good mechanical compatibility. The proposed fiber-scaffolded architecture provides a practical basis for further developing closed-loop bioelectronic systems capable of



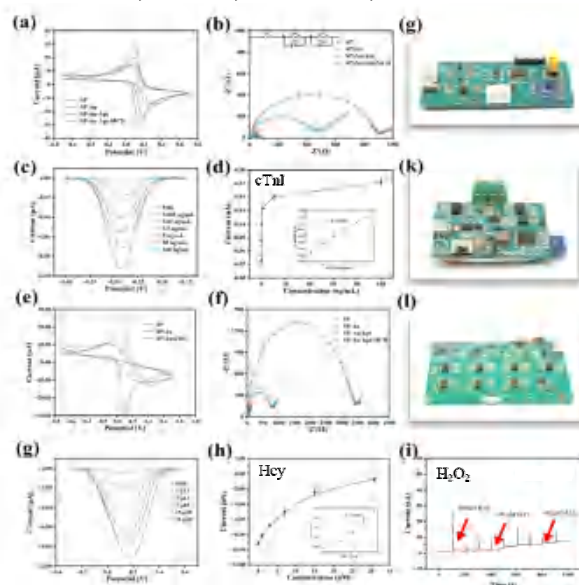
real-time monitoring and on-demand therapy.

Fig.1. Schematic illustration of the fabrication, functionalization, and in vivo application of a fiber-based closed-loop theranostic system.

Fig.2. Electrochemical characterization of the fiber-based sensing system and corresponding signal acquisition electronics.

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3D Artificial Skin Model as a Novel Strategy for the Diagnosis of Amyotrophic Lateral Sclerosis

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Key words: pyroptosis, nerve degeneration, 3D printed artificial skin, ALS, diagnosis

Introduction: Amyotrophic lateral sclerosis (ALS) is a severe adult-onset neurodegenerative disease with limited treatment approaches [1]. Growing evidence indicates that the pyroptosis-related NOD-like receptor pyrin domain containing protein 3 (NLRP-3) inflammasome plays a crucial role in ALS pathogenesis and has recently been associated with TAR DNA-binding protein 43 (TDP-43) aggregates, which contribute to motor neuron degeneration in the central nervous system (CNS) [2]. Several studies have also shown that degeneration of cutaneous nerves reflects neurodegenerative processes occurring in the CNS [3]. Although skin biopsy is widely adopted in clinical practice, the procedure is invasive and it requires multiple patients' tissue removals. For this reason, here, a 3D innervated skin model together with an artificial interstitial fluid (ISF) was developed, which serves as an efficient source of inflammatory biomarkers and complements traditional sources such as blood and urine.

Materials & Methods: A 3D innervated artificial skin model was developed by combining 3D printing with methacrylated hyaluronic acid (MeHA), used to better reproduce the dermis/epidermis structure, and electrospinning of polylactic acid (PLA) to mimic skin innervation. The 3D skin construct was then populated with a pre-neuronal cell line (SH-SY5Y) and fibroblasts isolated from skin biopsies of ALS patients with different disease progression rates (Slow and Fast). The 3D skin model was characterized from chemical, physical, and morphological perspectives [swelling assay, scanning electron microscopy (SEM), and degradation analysis]. Cell viability, cell morphology, and the expression of pyroptosis biomarkers (p-TDP-43, NLRP-3, interleukin (IL)-18, IL-6 and nitrites) were performed using spectrophotometric assays, SEM, ELISA, and fluorescence imaging.

Results & Discussion: Morphological and physicochemical characterization showed that 3D

innervated artificial skin possesses an adequate porosity for cell colonization and an enhanced structural stability. Biological results revealed an increase of p-TDP-43, NLRP-3, IL-18, IL-6 and nitrites in 3D skin of ALS patients, thus indicating pyroptosis activation linked to neurodegeneration. Particularly, the findings in this study revealed that pyroptosis cascade could be used as a biomarker for better monitoring ALS progression and severity in ALS patients. Artificial ISF allowed to understand IL-6 and nitrites increased by increasing ALS disease. Furthermore, both Slow and Fast ALS progressors released higher IL-18 levels thus suggesting IL-18 is a relevant diagnostic marker of ALS disease. Finally, p-TDP-43 is also a marker of ALS aggressiveness because its expression increases by increasing ALS severity.

Conclusions: The overall findings highlight the value of this platform for biomarker discovery, disease stratification, and preclinical therapeutic testing, providing proof of concept that engineered human skin models can serve as translational tools for ALS research. In the near future, this approach may support the development of cutaneous biosensor strategies aimed at monitoring disease progression in a minimally invasive manner, reducing diagnostic delay and enabling more personalized patient management.

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Tailor-Made Metal-Organic Frameworks via Molecular Engineering for Selective Recognition and Extraction of Bilirubin from Liver Failure Patients' Blood

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Abstract: Overcoming the albumin-bilirubin binding barrier to achieve specific recognition and high-efficiency capture of blood bilirubin remains a major clinical challenge in treating liver-failure patients. We propose a molecular-engineering strategy: programming UiO-66's coordination environment with carboxylic-acid ligands to create "bilirubin-exclusive traps." The experimental results confirm these frameworks rapidly enrich albumin-bound bilirubin via van der Waals/electrostatic effects. Internal Zr- μ_3 -OH sites form directional Zr-pyrrole coordination with bilirubin, while narrow apertures (7.6 Å) physically exclude albumin, breaking the "barrier" without displacement. Hydrogen-bond networks and π - π stacking strengthen specificity. The computed adsorption energy ($\Delta E_{\text{ads}} = -3$ eV) indicates spontaneous, diffusion-limited capture. In simulated blood, HA-UiO-66 achieved a 97.9% removal rate with negligible albumin loss. Clinical tests showed a single-pass total bilirubin reduction 251% higher than commercial BS330-resin, with albumin leakage $\leq 2.58\%$ (vs $\geq 8.53\%$). This unveils molecularly engineered MOFs as a viable clinical platform for blood purification.

Key words: Metal-organic Frameworks; Bilirubin Capture; Blood Purification

Introduction: Liver failure—triggered by multiple insults and manifested as jaundice, coagulopathy, hepatic encephalopathy and ascites—carries a mortality $>30\%$ and remains a global public-health threat. At present, artificial liver-assisted therapy is an important supportive method for liver failure, and plasma adsorption purification type artificial liver is widely used. However, the existing resin adsorption columns have problems such as poor adsorption selectivity and low total bilirubin (TBil) removal efficiency, and may lead to the loss of beneficial components such as albumin, immunoglobulin and complement, further aggravating the condition. For example, the widely used BS330 column (Jafron Biomedical Co., Ltd., China) in China lowers TBil by only $\Delta \approx 200$ $\mu\text{mol/L}$ per session, corresponding to a 20~40 % removal efficiency restricted to the free fraction; albumin-bound bilirubin (Bil) remains virtually untouched. This limitation stems from the inability of existing sorbents to disrupt the nanomolar affinity between Bil and serum albumin. Therefore, the development of hemodialysis materials that can break through the binding force between albumin and Bil, have high Bil selectivity, and do not remove beneficial components has become an urgent problem to be solved.

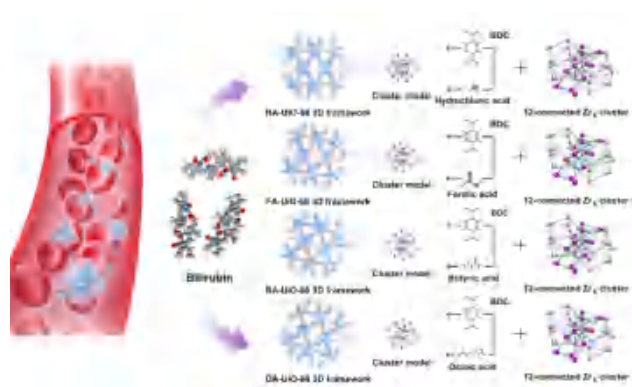
Materials & Methods: This first-in-human case series resolves the long-standing trade-off between aggressive TBil removal and essential-protein loss inherent to commercial hemodialyzers. In blood drawn from ten liver failure patients, a single pass through the engineered MOF extracted 251% more TBil than the BS330-resin (per unit mass) while reducing albumin leakage to $\leq 2.58\%$ (versus $\geq 8.53\%$ for BS330). The data demonstrate quantitative disruption of the albumin-Bil complex and establish the highest TBil-adsorption capacity yet reported for clinical blood purification. The breakthrough is realized through a "molecular-engineering-assisted functionalization" strategy: monodentate carboxylates of tunable chain length (C0-C8) are exploited as minimum engineering units to competitively replace BDC ligands, precisely programming the density and local strain of Zr- μ_3 -OH nodes. The resulting UiOs series behaves as a bilirubin-exclusive trap. The lead candidate, HA-UiO-66, integrates three synergistic features: Size-exclusion gating—an ultramicropore distribution centred at ~ 7.6 Å admits bilirubin (6.7 Å) yet blocks albumin (~ 6 nm). Directed pre-concentration-short-range van-der-Waals and electrostatic fields enrich the albumin-bilirubin complex at the crystal surface within milliseconds. Chemoselective docking-upon entry, the tetrapyrrole group forms a highly specific Zr-pyrroolate coordination ($\Delta E_{\text{ads}} = -3.0$ eV, DFT), reinforced by a dense hydrogen-bond tapestry and π - π stacking that act as cooperative "molecular locks". Consequently, HA-UiO-66 sequesters 97.9 % of bilirubin from simulated blood while rejecting 100% of albumin. When challenged with whole blood from liver failure patients ($n=10$, TBil ≥ 200 $\mu\text{mol/L}$), the material delivers a 2.5-fold higher TBil capture capacity than BS330 (per unit mass) after 3 h and leaves plasma albumin below the detection limit of clinical assays ($\leq 2.58\%$ loss). These results establish HA-UiO-66 as a next-generation sorbent that breaks the "albumin-binding barrier" and set a new benchmark for TBil removal in clinical hemodialysis.

Results & Discussion: In summary, this work delivers three conceptual breakthroughs: (1) We developed a nano-scale bilirubin-specific capture trap, overcoming the critical trade-off between bilirubin removal and protein loss by pure physical means: In clinical hemoperfusion, pathological TBil is typically reduced by only 20~40%. Here, we introduce an "inside-out" strategy: by programming the ligand environment we implant dense Zr- μ_3 -OH nodes—exclusive docking sites for the bilirubin tetrapyrrole skeleton—while simultaneously engineering a

7.6 Å pore aperture that is slightly larger than the 6.7 Å linear span of bilirubin yet far smaller than the 6 nm size of albumin. This concerted action spontaneously dissociates the albumin-bilirubin complex at the engineered UiO-66 nanoporous framework surface and instantaneously traps the freed pigment via Zr-pyrrolate coordination, requiring no external energy input. Consequently, 97.9 % of bilirubin is captured from simulated blood, while albumin is rejected with ≈ 100 % selectivity. (2) We innovatively formulated a molecular engineering strategy for nanocrystalline frameworks, achieving precise customization of MOF nanoporous architectures: Using HCl, formic, butyric, and octanoic acids as “minimum-engineering units” to competitively displace BDC, we precisely tune the density and strain field of Zr- μ_3 -OH nodes, thereby encoding engineered UiO-66 nanocrystals that exhibit both high affinity and high selectivity toward blood bilirubin. The newly engineered UiO-66 nanoporous framework exhibits a spontaneous, ultrafast adsorption free energy, providing the kinetic basis for millisecond-scale bilirubin capture. (3) Our pioneering clinical assessment yielded unprecedented performance—a 251% improvement in total bilirubin capture capacity versus a minimal albumin loss of $\leq 2.58\%$ —setting a world record: the developed nano HA-UiO-66 is, for the first time, evaluated ex vivo in blood from liver failure patients (n=10). Compared with the commercial IER, the developed HA-UiO-66 delivers a 251% increase in TBil capture per unit mass while leaving plasma albumin virtually unchanged ($\Delta \leq 2.58\%$). This study constitutes the inaugural demonstration that the clinical “high-efficiency bilirubin clearance vs. essential-protein loss” trade-off can be broken and establishes a global benchmark for single-session bilirubin removal in clinical hemoperfusion.

Conclusions: In this study, by employing a monodentate-carboxylate ligand-engineering strategy, we systematically tuned the coordination environment of UiO frameworks, generating hierarchical porosity and well-defined Zr- μ_3 -OH sites. Multiscale characterization, batch adsorption and DFT calculations jointly reveal the structure-property relationships governing Bil capture: HA-UiO-66 forms directional Zr-pyrrole coordination with the Bil tetrapyrrole core, while sub-nanometre apertures physically exclude Alb; additional hydrogen bonding and π - π stacking further strengthen the complex. In a single-pass clinical test using blood from ten liver-failure patients, HA-UiO-66 achieved 2.51-fold higher TBil removal than styrene-divinylbenzene-based anion exchange resin in the commercial BS330 column with $\leq 2.58\%$ Alb loss, breaking the long-standing trade-off between bilirubin clearance and essential-protein depletion. These findings provide both mechanistic insight and a translational roadmap for the rational design of next-generation MOF-based sorbents for selective blood purification.

Fig. 1. Molecularly engineered synthesis routes of the developed UiO-66 nanoporous frameworks and their



Bil-capture process.

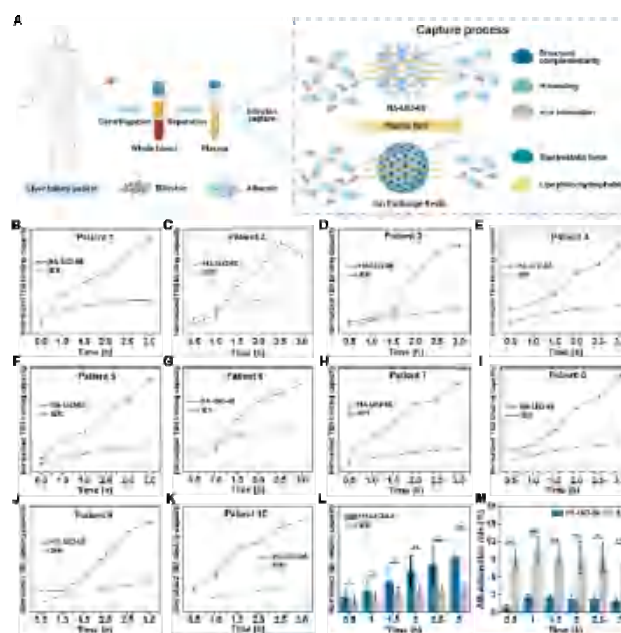


Fig. 2. A) Schematic of the clinical testing protocol (partially rendered with BioRender.com). B-K) Time-resolved removal of TBil (≥ 200 $\mu\text{mol/L}$) from the plasma of 10 liver failure patients within 3 h using nano HA-UiO-66 or commercial IER (each column represents an individual patient). L) Normalized TBil capture capacity and M) human Alb loss rate for nano HA-UiO-66 versus commercial IER. (Data are expressed as mean $\pm$ SD; ns = not significant, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; $n = 10$)

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Study on pre clinical evaluation method of absorbable PLLA/HA bone fixation device based on degradation activity coupling analysis

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Key words: polylactic acid, hydroxyapatite, bone fixation instruments, mechanical degradation, biological evaluation

Introduction: Absorbable bone fixation devices provide significant clinical advantages for treating common fractures by eliminating the need for secondary removal surgery, unlike permanent metal implants. Currently, most commercial devices are made from pure polylactic acid (PLA), which has limitations in mechanical strength and bioactivity. In contrast, composites of L-polylactic acid (PLLA) and hydroxyapatite (HA) offer enhanced mechanical and biological performance. Given the complex in vivo environment, evaluating material degradation and strength retention under mechanical stress is critical. This study aims to establish a preclinical evaluation method that assesses degradation behavior and bioactivity changes under load-bearing conditions, offering guidance for the design and assessment of similar medical devices.

Materials & Methods: In this study, an absorbable PLLA/HA composite bone fixation device was evaluated under dynamic physiological loading using a feedback-controlled fatigue testing machine. A simulated clinical fracture model — exemplified by a human unilateral tibial compression setup — was constructed with the device assembled onto polyurethane bone blocks in a clinically relevant configuration. Real-time stress feedback was recorded via sensors to investigate polymer degradation behavior under variable loading (Fig. 1). Degradation outcomes were compared with those from a traditional static, non-loading model. The target instrument was also used to fix and repair the femoral fracture model in rabbits, and compared with the degradation model in vitro.

Results & Discussion: In vitro degradation results showed that dynamic stress significantly accelerated the degradation rate of PLLA and PLLA/HA composites through the effects of microcrack propagation, fatigue fracture, interfacial shear and changing the degradation microenvironment. The attenuation range of mechanical properties (such as bending strength and shear strength) increased by 10%-20% compared with the static condition (Fig. 2). Mechanical loading significantly affected the biological activity in the degradation process through the coupling effect of physics and chemistry. The degradation rate and mode were significantly different from the static condition used in conventional research. In vivo degradation results showed that the molecular weight decay rate predicted by the dynamic loading model (42% at 5 weeks) was

close to the data at 8 weeks in vivo (40%), which could provide a prediction close to the truth to a large extent.

Conclusions: This study presents a feasible approach for assessing bioactivity changes in polymer/calcium-phosphorus composite devices under mechanical degradation, addressing the lack of load-bearing degradation characterization in current preclinical evaluation systems. This new composite evaluation method supports the R&D and regulatory approval of similar devices, advancing industry development.



Fig. 1. Schematic diagram of cyclic mechanical loading degradation model of bone nail and bone plate.

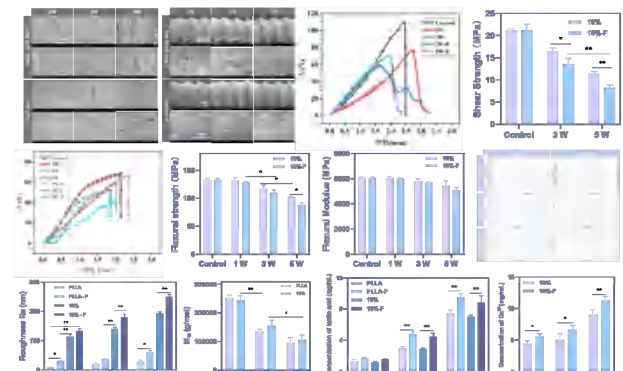


Fig. 2. In vitro mechanical loading degradation test results.

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Functional iron oxide nanoparticles cross-linked hydrogel for craniofacial bone regeneration

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Key words: iron oxide nanoparticles, hydrogel, craniofacial bone regeneration, angiogenesis

Introduction: Craniofacial bone defects are a major clinical challenge, with current treatments like autografts and allografts having significant limitations. While hydrogels show promise in tissue engineering, traditional ones often lack both mechanical strength and effective biological cues for bone regeneration. This study explores whether vinyl-functionalized iron oxide (Fe_2O_3) nanoparticles can be used as covalent crosslinkers in methacrylated gelatin (GelMA) hydrogels to improve their mechanical properties and simultaneously promote angiogenesis and osteogenesis for effective craniofacial bone repair.

Materials & Methods: Fe_2O_3 nanoparticles, modified with vinyl groups using 3-(trimethoxysilyl) propyl methacrylate (MPS), served as crosslinkers in a free-radical polymerization with GelMA to form a hybrid hydrogel. The material was characterized by SEM, mechanical testing, and swelling analysis. In vitro, BMSC were used for osteogenesis (ALP, Alizarin Red) and HUVEC for angiogenesis (migration, tube formation). In vivo, efficacy was tested in a 5 mm rat cranial defect model, with regeneration assessed by micro-CT and histology at 4, 8, and 12 weeks.

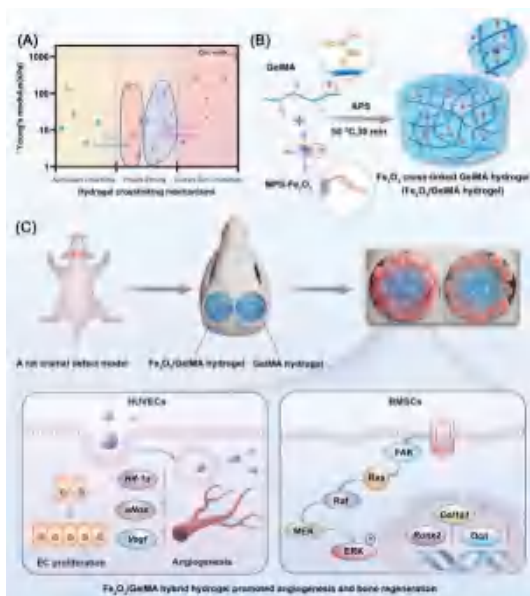


Fig. 1. Construction of Fe_2O_3 /GelMA hybrid hydrogel for craniofacial bone defect repair.

Results & Discussion: The study synthesized MPS- Fe_2O_3 to crosslink GelMA, creating Fe_2O_3 /GelMA

hydrogel with enhanced mechanical properties. It supported BMSC and HUVEC adhesion, promoting osteogenesis and angiogenesis in vitro. In a rat cranial defect model, it improved neovascularization and bone formation, achieving near-complete closure in 12 weeks. Fe_2O_3 nanoparticles acted as structural hubs and bioactive ion sources, stimulating pathways like HIF-1 α . The hydrogel's covalent bonds enhanced mechanical and biological properties, promoting BMSC adhesion and osteogenesis. In vivo, it showed controlled biodegradation, tissue integration, and excellent biocompatibility with no organ damage or inflammation. Fe_2O_3 's magnetic properties offer potential for magnetothermal therapy and MRI tracking, broadening clinical applications.

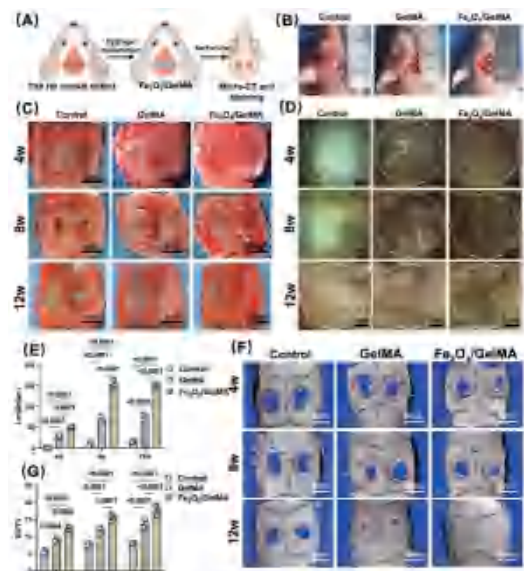


Fig. 2. Fe_2O_3 /GelMA hydrogel promoted angiogenesis and subsequent osteogenesis in a rat cranial defect model.

Conclusions: This study developed a Fe_2O_3 nanoparticle-crosslinked GelMA hydrogel that balances mechanical stability and bioactivity in bone tissue engineering. The nanoparticles act as crosslinkers and bioactive agents, enhancing angiogenesis and osteogenesis. The hydrogel effectively promoted regeneration of critical-size craniofacial bone defects in vivo.

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Therapeutic Effects and Mechanisms of Mesenchymal Stem Cell-Derived Exosomes in Regenerative Dentistry

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Key words: Temporomandibular joint osteoarthritis; Extracellular vesicles; Osteoclasts; Subchondral bone; Macrophages

Introduction: Temporomandibular joint osteoarthritis (TMJOA) is a prevalent degenerative oral disease and remains one of the most difficult joint disorders to manage clinically. It is marked by progressive cartilage degradation, subchondral bone remodelling, and chronic inflammation. Mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) have recently gained attention for their potential to modulate osteoarthritis pathology. However, their application in TMJOA is still limited, and the mechanisms underlying their therapeutic effects are not fully defined.

Materials & Methods: A rat TMJOA model was established to evaluate the therapeutic effects of human umbilical cord MSC-derived extracellular vesicles (hUCMSC-EVs) on cartilage integrity, subchondral bone structure, and synovial inflammation. In vitro, osteoclast differentiation and macrophage polarization assays were used to explore cellular mechanisms. miRNA sequencing and proteomic analyses were conducted to identify key molecular cargo and downstream targets, followed by functional validation using miRNA mimic and siRNA knockdown approaches.

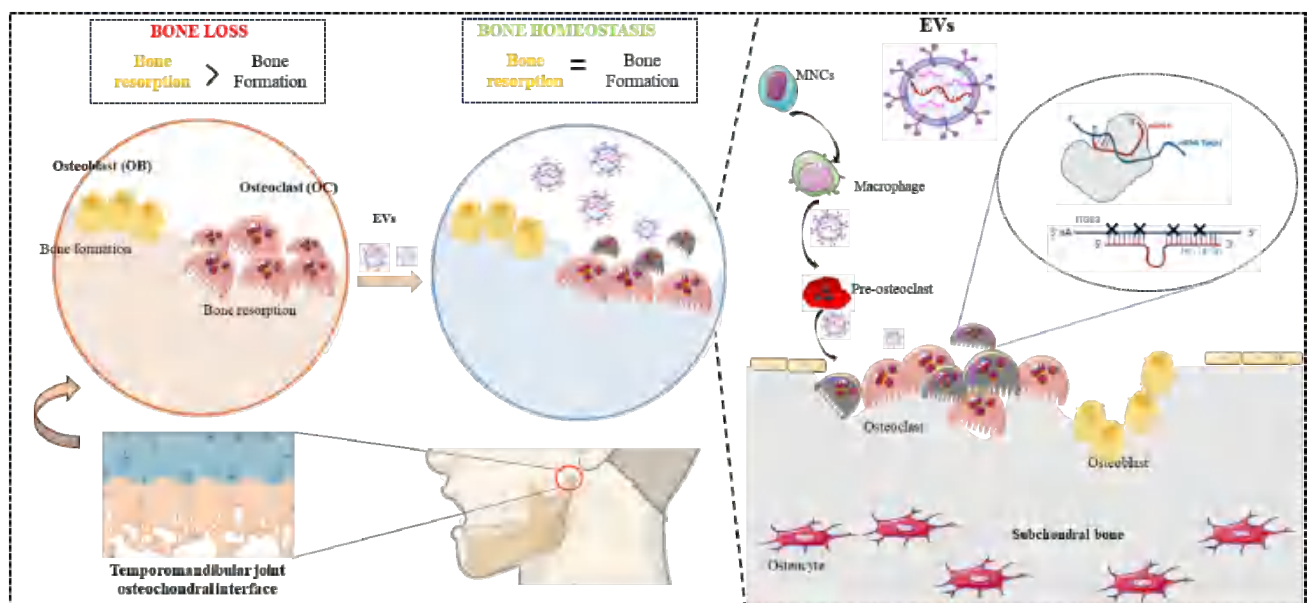
Results & Discussion: The results demonstrated that hUCMSC-EVs treatment significantly reduced osteoclast (OC) activity and regulated macrophage polarization by transferring let-7a-5p and PTX3, which further suppressed the expression of integrin $\beta 3$ (ITG $\beta 3$) of osteoclasts and MAPK signaling pathways. In a rat TMJOA model, intra-articular injection of hUCMSC-EVs demonstrated protective effects on both subchondral bone and cartilage, primarily through the suppression of osteoclast and macrophage activities. Consequently, these results highlight the potential of hUCMSC-EV-based therapies as promising and effective approaches for the treatment of TMJOA.

Conclusions: These findings support hUCMSC-EV-based therapy as a promising and effective strategy for the treatment of TMJOA.

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Fig. 1.



3D-Architected Scaffolds Derived from Extracted Natural Teeth for Alveolar Bone Reconstruction

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Key words: Alveolar bone defects, extracted natural teeth, digital light processing, bioceramic scaffolds, finite element analysis

Introduction: The materials and design of scaffolds play a crucial role in promoting bone regeneration in alveolar bone defects. Extracted natural teeth have been considered potential graft biomaterials for treating bone defects. This study aimed to verify the feasibility and effectiveness of repairing alveolar bone defects using extracted natural teeth through biomechanical modeling, additive manufacturing preparation, and *in vitro* experiments.

Materials & Methods: This study selected and collected extracted natural teeth (ET) to prepare bone tissue engineering scaffolds with different structures using DLP-based additive manufacturing technology. Key issues such as the dispersion, sintering characteristics, mechanical properties, and biocompatibility of scaffolds during the DLP manufacturing process were systematically investigated. The biomechanical behaviors of scaffolds with different structures (trabecular, diamond, gyroid, hexagonal void) were compared and analyzed using Finite Element Analysis (FEA) and Computational Fluid Dynamics (CFD). Finally, through *in vitro* mineralization experiments, the apatite-forming ability of the extracted natural tooth scaffolds was tested to verify their biological performance.

Results & Discussion: The results demonstrated that 50 vol% solid loading slurry with 2 wt.% dispersant dosage was regarded as the optimal high-solid loading and low-viscosity slurry, and 1200 °C was the optimum sintering temperature. The simulation results show that the G-scaffold exhibited excellent osteogenic space maintenance as well as mass transport properties. The mechanical properties and mineralization behavior both indicated that ET scaffolds possess excellent biomechanical properties for alveolar bone defect repair.

Conclusions: This study confirmed that extracted natural teeth are available to fabricate bioceramic scaffolds via DLP-based additive manufacturing techniques and exhibit superior clinical potential for the repair of alveolar bone defects. The work provides foundational validation for the future clinical application of patient-customized ET scaffolds in the treatment of bone defects.

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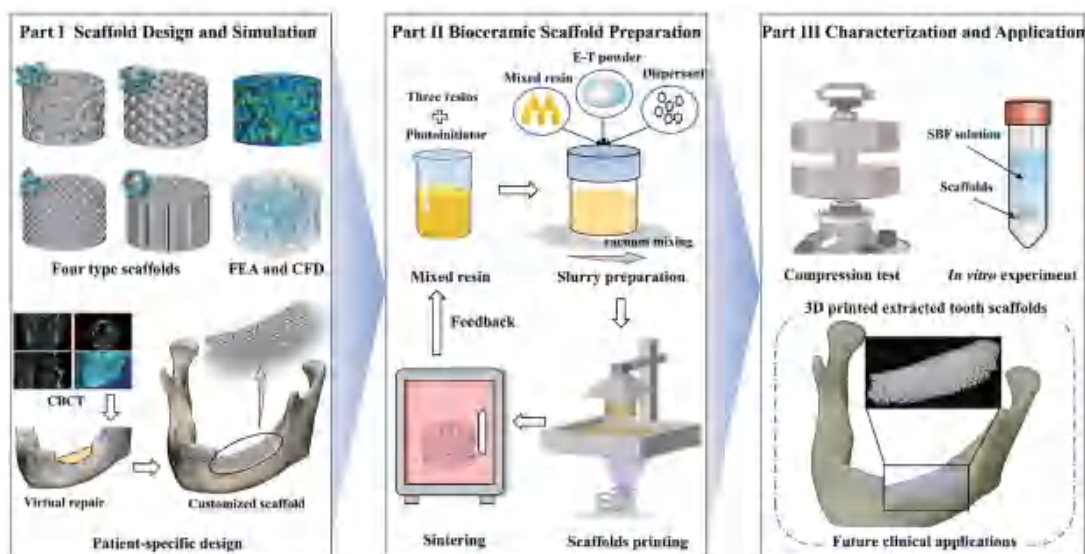


Fig. 1. Schematic illustration of the DLP-based extracted tooth scaffolds for alveolar bone defects.

Antimicrobial, Remineralization, And Infiltration: Advanced Strategies For Interrupting Dental Caries

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Key words: dental caries; remineralization; antibacterial; infiltration

Introduction: Dental caries is the most prevalent chronic oral disease worldwide and arises from biofilm-mediated acid production that disrupts the dynamic balance between demineralization and remineralization. Traditional therapies typically focus on either antibacterial control or mineral restoration, failing to address the ecological-mineral coupling mechanism underlying lesion progression. We herein introduce the concept of Interrupting Dental Caries (IDC) as a minimally invasive early-intervention strategy aiming not merely to halt disease progression but to actively reconstruct biofilm homeostasis and mineral balance. Considering the “core microbiome” theory of caries, we further propose a dual-dynamic equilibrium model, in which synchronized regulation of microbial ecology and biomineralization is essential for effective caries interruption. To implement this strategy, a bifunctional amyloid hydrogel, PTB@CPC/ACP, was developed to synergize antimicrobial regulation with amelogenesis-mimetic remineralization.

Materials & Methods: The PTB@CPC/ACP hydrogel incorporates antimicrobial cetylpyridinium chloride (CPC) and remineralizing amorphous calcium phosphate (ACP) within an amyloid-inspired matrix. The material fulfills three IDC requirements: antibacterial modulation of cariogenic biofilms, biomimetic mineralization emulating enamel matrix protein function, and high permeability enabling infiltration and sealing of subsurface lesions. Antibacterial activity, mechanical recovery, and remineralization depth were evaluated using biofilm assays, nano-mechanical testing, and micro-CT. In vivo experiments assessed biosafety and therapeutic validity.

Results & Discussion: PTB@CPC/ACP exhibited significant inhibition of biofilm adhesion (>70%), deep lesion infiltration, and effective remineralization restoring enamel-like crystallinity and mechanical properties. The hydrogel sealed demineralized regions and prevented lesion progression while maintaining biocompatibility in vivo. Compared with single-function

antimicrobial or remineralizing treatments, the combined strategy achieved superior caries arrest by simultaneously modulating microbial activity and mineral recovery.

Conclusions: This study advances the IDC framework by integrating antimicrobial regulation, biomimetic remineralization, and lesion infiltration under a dual-dynamic equilibrium paradigm targeting both the cariogenic core microbiome and mineral balance. The PTB@CPC/ACP hydrogel provides a clinically translatable platform capable of stabilizing lesions, preserving tooth structure, and partially restoring native composition. Future studies should investigate long-term microbiome modulation, clinical effectiveness in diverse lesion stages. This work establishes a conceptual and material foundation for next-generation multifunctional caries-intervention therapies with significant preventive and public health implications.

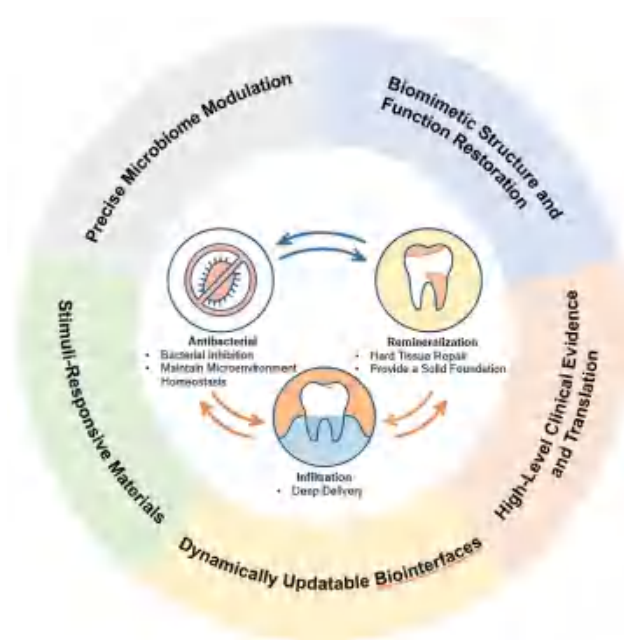


Fig. 1. Integration mechanisms and future prospects of the antimicrobial-remineralization-infiltration synergistic strategy.

Clinically Informed Photothermally Activated Nanoplatform Rejuvenates the Senescent Microenvironment for Periodontal Regeneration

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Key words: Periodontal regeneration; Senescence; Nanoplatform; Microenvironment; Osteogenesis

Introduction: Age-related periodontitis is a leading cause of tooth loss in the elderly population, yet periodontal regeneration remains largely ineffective in aged patients^[1]. Increasing evidence indicates that this failure cannot be explained solely by reduced stem cell osteogenic potential, but is closely associated with a deteriorated periodontal microenvironment characterized by oxidative stress, chronic inflammation, and disrupted regenerative signalling. However, which microenvironmental alterations dominantly constrain regeneration in aged human alveolar bone remains insufficiently validated, limiting the rational design of effective biomaterials. Importantly, such multifactorial and dynamic microenvironmental dysfunction cannot be adequately addressed by conventional biological therapies alone, highlighting the need for biomaterials capable of simultaneously modulating oxidative, inflammatory, and osteogenic cues^[2]. Therefore, identifying senescence-driven microenvironmental barriers through clinical validation and developing responsive biomaterial systems to remodel these barriers represent a critical strategy for restoring periodontal regeneration in aging.

Materials & Methods: Clinical alveolar bone specimens from young and aged individuals were analyzed for senescence markers, inflammatory cytokines, and osteogenic potential. Guided by these clinically identified features, a photothermally activated nanocomposite (AuNR@BMP2@MPNs, AuBM) was engineered using gold nanorods as the photothermal core with a metal-polyphenol network of epigallocatechin gallate (EGCG), Fe³⁺, and BMP2. Physicochemical properties, photothermal performance, and stimulus-responsive release were characterized. Senescence was induced in mouse bone marrow mesenchymal stem cells (BMSCs) using H₂O₂ to evaluate antioxidant, anti-inflammatory, and osteogenic responses under near-infrared (NIR) irradiation. Therapeutic efficacy was evaluated in a doxorubicin-induced aging periodontitis model in C57BL/6 mice by nanoplatform treatment.

Results & Discussion: Clinical analyses revealed that aged alveolar bone exhibited elevated senescence markers and pro-inflammatory cytokines with impaired osteogenic potential, identifying senescent microenvironmental dysregulation as a dominant regenerative barrier. AuBM nanocomposites displayed a uniform core-shell structure with high BMP2 loading efficiency and pH/NIR-responsive release. EGCG-mediated antioxidant effects reduced intracellular reactive oxygen species and suppressed senescence-associated secretory phenotype factors, including IL-1 β , IL-6, and TNF- α ,

in senescent BMSCs. Synergistic BMP2 delivery and mild photothermal stimulation enhanced osteogenic gene expression (Runx2, OPN, OCN) and matrix mineralization. AuBM combined with NIR irradiation promoted alveolar bone regeneration in aging-associated periodontitis, evidenced by increased BV/TV, reduced osteoclast activity, attenuated inflammation, and downregulation of p16 and IL-1 β .

Conclusions: This study establishes a clinically informed biomaterials strategy for periodontal regeneration in aging. By integrating clinical identification of senescence-driven microenvironmental barriers with photothermally activated metal-polyphenol nanocomposites, AuBM rejuvenates the aged periodontal microenvironment and restores osteogenic capacity, highlighting the potential of responsive biomaterials to address age-associated regenerative challenges.

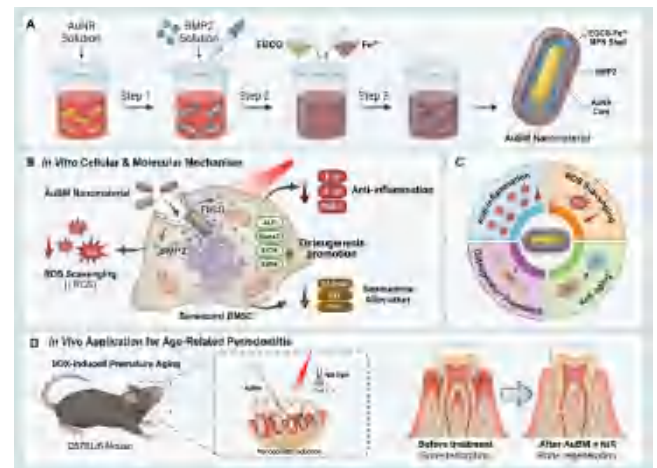


Fig. 1. Schematic of the AuBM nanocomposite. (A) Synthesis of the core-shell structure. (B) Mechanism: ROS scavenging and osteogenesis promotion via BMP2 and photothermal effect. (C) Multifunctionality summary. (D) Application in an aging periodontitis model.

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Bioactive Dentin Scaffolds as a Driver for the Osteogenic Commitment of CGF Cells

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Key words: Dentin, biomaterials, tissue engineering

Introduction: Concentrated Growth Factors (CGF) represent a fibrin-based biomaterial rich in growth factors, produced by centrifuging venous blood at varying speeds using the Silfrudent device [1]. Recognized as a novel autologous biological matrix, CGF has been shown to enhance *in vivo* bone regeneration and stimulate osteoblast differentiation [1,2]. Within this framework, the osteogenic differentiation of CGF-derived primary cells has been previously investigated by combining CGF with hydroxyapatite-silicon scaffolds [3]. In the present study, we utilized dentin scaffolds to further evaluate the osteogenic potential of CGF-derived primary cells.

Materials & Methods: CGF was prepared from the blood sample. Briefly, each blood sample was centrifuged, and the CGF was used for the experiments. After three days, CGF was chopped into small pieces to improve the release of primary cells; these pieces were plated on Dentin scaffolds and cultured with L-DMEM (Basal medium) or Osteogenic Medium (L-DMEM with 10 mM β -glycerophosphate, BGP, and 100 μ M ascorbic acid 2-phosphate, AA) for 21 days. The cellular viability of primary cells cultivated on Dentin scaffolds was determined by MTT assay, and the matrix mineralization was evaluated through alizarin red staining and mRNA quantification of osteogenic differentiation markers by real-time PCR.

Results & Discussion: The MTT assay (Fig.1) shows that hBMSCs cultured on dentin scaffolds display a progressive increase in cell viability over time compared with cells maintained in standard 2D conditions, with values consistently higher than the control, although not statistically significant. These findings indicate that the dentin scaffold supports cell proliferation. To assess the osteoinductive capacity of the dentin scaffold, an Alizarin Red assay was performed (Fig.2A). As reported, CTR represents hBMSCs in 2D culture, BM refers to cells seeded on the scaffold for 21 days in basal medium, and OM to cultures exposed to osteogenic medium. The percentage of mineralized matrix normalized to DNA content shows that hBMSCs grown on dentin scaffolds in BM exhibit significantly higher mineral deposition compared to controls (Fig.2B). These results indicate that dentin scaffolds enable hBMSCs to generate a mineralized structure even without osteogenic inducers. To further characterize scaffold-mediated osteogenesis, the expression

of RUNX2, Osteocalcin (OCN), and COL1A1 was quantified in BM and OM conditions (Fig.3A), together with the expression of stem cell markers CD105 and CD45 (Fig.3B). The reduced expression of CD105 and CD45 in cells cultured on dentin compared with controls, combined with the significantly increased levels of osteogenic genes in scaffold-incubated cells, confirms that dentin scaffolds actively promote osteogenic differentiation while reducing the stemness profile of hBMSCs.

Conclusions: In conclusion, our study demonstrated that dentin scaffolds are non-cytotoxic and support the adhesion, growth, and proliferation of CGF-derived cells. Notably, these scaffolds promote osteogenic differentiation, highlighting their potential as future biomaterials for CGF-based tissue regeneration applications.

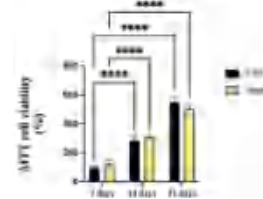


Fig.1. MTT assay hBMSCs cultured on dentin scaffolds.

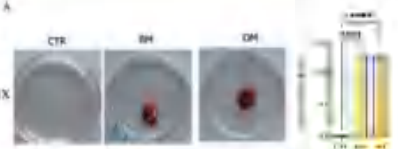


Fig.2. Alizarin Red assay (A) and the percentage of mineralized matrix (B).



Fig.3. Real-time PCR of osteogenic differentiation markers (A) and stem cell markers (B).

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Mastication-induced electrical stimulation activates Prg4⁺ chondroprogenitors for osteoarthritis therapy

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Abstract: Osteoarthritis (OA) is a whole-joint degenerative disease primarily driven by excessive mechanical overloads. However, current therapeutic strategies lack effective interventions that modulate biomechanical cues to halt cartilage degeneration. We found that piezoelectric poly L-lactic acid alone, though effective in knee OA, was insufficient in temporomandibular joint (TMJ) due to its distinct inflammatory microenvironment and cell types. In light of this, we developed mastication-driven magnesium incorporated piezoelectric nanofibers (MagPie) that can release Mg²⁺, neutralize pH and work as electrical stimulator. During in vitro experiments, MagPie under applied force exerted pronounced growth-promoted and anti-inflammatory effects on chondrocytes. In a rat model of TMJOA induced by overloading, MagPie in conjunction with mastication-derived joint loads successfully restored the damaged osteochondral unit. Crucially, through single-cell transcriptional sequencing, we identified an electrical-sensitive Prg4⁺ cell population that is essential for articular cartilage regeneration. Mechanistically, MagPie-activated Prg4⁺ cells enhanced anabolic activity via the ECM-mediated FAK-PI3K-Akt axis and ameliorated the arthritic microenvironment by shifting macrophage polarization toward an anti-inflammatory phenotype. Genetic ablation of *Prg4* blunted the therapeutic efficacy of MagPie. Overall, this study unveils a fundamental mechanism of electrosensitive tissue repair and proposes a “trash-to-treasure” strategy that harnesses joint overloading to activate endogenous electrical-sensitive Prg4⁺ cells for OA treatment.

Key words: piezoelectric materials, temporomandibular joint osteoarthritis, tissue engineering

Introduction: TMJ, a unique joint in the craniofacial system that is essential for normal masticatory functions, is one of the most frequently affected sites of OA [1]. Current therapeutic approaches for TMJOA generally focus on alleviating symptoms rather than reversing disease progression. Therefore, it is imperative to develop a comprehensive strategy that can eliminate the effects of overloads on the articular surface, reconstruct the entire joint microenvironment and restore the structural integrity of both cartilage and subchondral bone. In this study, we hypothesized that a piezoelectric film could utilize joint overloading to produce more charges and Mg²⁺ on the condylar surface, thus improving arthritic microenvironment and facilitating TMJ cartilage repair. To verify our hypothesis, we attempted to (i) develop magnesium incorporated piezoelectric nanofibers (MagPie), which could release Mg²⁺, neutralize pH and work as

electrical stimulator at the same time, (ii) demonstrate the effects of the MagPie under overloading on cartilage repair in vitro and in vivo, (iii) elucidate the key cell populations and underlying mechanism in TMJOA electrotherapy through single-cell transcriptional sequencing.

Materials & Methods: Electrospun films were characterized by XRD, DSC, SEM, EDS, degradation and piezoelectric tests. Biological properties were analyzed through scratch assays, PCR, immunofluorescence and WB. Mechanistic investigations focused on identifying electrical-sensitive cell populations through scRNA-seq and validating the role of Prg4⁺ chondroprogenitors using AAV-mediated knockdown approaches.

Results & Discussion:

1. MagPie effectively neutralized acidic degradation by-products, thereby improving the arthritic microenvironment.
2. MagPie exerted synergistic therapeutic effects and effectively promoted condylar cartilage repair in ADD-induced TMJOA rats.
3. Sequencing analysis revealed that MagPie implantation significantly expanded the Prg4⁺ cell population, enhanced their differentiation, and upregulated fibrocartilage markers, thereby facilitating the repair and reconstruction of the cartilage matrix.

Conclusions:

This study demonstrates that the biodegradable MagPie device can simultaneously regenerate cartilage and modulate joint inflammation in TMJOA by activating Prg4⁺ chondroprogenitors.

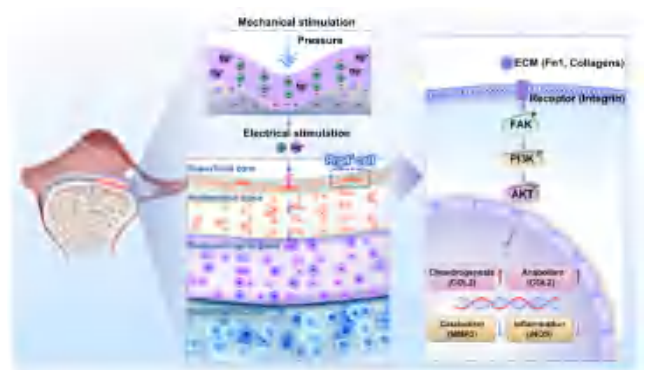


Fig. 1. Mechanism of MagPie in the treatment of TMJOA

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Chrono-Controlled Biomaterial Platforms for Mitochondria-Targeted Cuproptosis and Immuno-Metabolic Cancer Therapy

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Key words: chrono-controlled hydrogel, sequential drug release, immunogenic cuproptosis, metabolic reprogramming, tumor immunotherapy

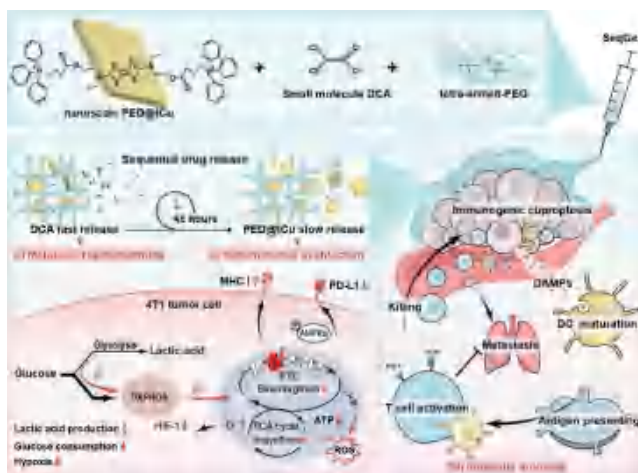
Introduction: The mode of cancer cell death critically determines therapeutic efficacy and antitumor immune activation. Conventional chemotherapies predominantly induce apoptosis, which lacks immunogenicity and fails to elicit durable immune responses. Recently, cuproptosis, a copper-dependent mitochondrial cell death modality, has emerged as a promising strategy to induce immunogenic cell death (ICD). However, insufficient mitochondrial copper delivery and tumour metabolic plasticity limit its therapeutic potential. This study aims to address these challenges by integrating mitochondria-targeted copper complexes with chrono-controlled biomaterial delivery systems to amplify immunogenic cuproptosis and remodel the tumour immune microenvironment.

Materials & Methods: A mitochondria-targeted copper dithiocarbamate (TPP-CuET) was designed by conjugating triphenylphosphonium to enhance mitochondrial copper accumulation and trigger robust cuproptosis. To further overcome metabolic resistance, an injectable PEG-based chrono-controlled hydrogel platform (SeqGel) was developed to sequentially deliver dichloroacetate (DCA) and TPP-CuET-loaded polymeric nanosheets (PED@tCu). DCA was rapidly released to reprogram tumour metabolism from glycolysis to oxidative phosphorylation, followed by sustained release of PED@tCu for mitochondrial targeting. Cellular, molecular, and immunological evaluations were performed in vitro, while antitumor efficacy, metastasis suppression, and immune activation were assessed in murine 4T1 triple-negative breast cancer models.

Results & Discussion: The mitochondria-targeted copper complex TPP-CuET achieved enhanced mitochondrial copper accumulation (29.0% vs 19.4% for CuET), providing a robust foundation for inducing immunogenic cuproptosis. Building on this mechanism, a chrono-controlled hydrogel platform (SeqGel) enabled sequential metabolic intervention to overcome tumour metabolic plasticity. Sequential delivery markedly suppressed mitochondrial complex II activity from 116.1 to 10.1 U/mg protein, enforcing mitochondrial dependency and sensitizing tumour cells to cuproptosis. This metabolic-mitochondrial coordination resulted in pronounced immune remodelling, characterized by a 55.6% reduction in PD-L1 expression and a 157.7% increase in MHC I expression, thereby enhancing antigen presentation. In murine 4T1 models, SeqGel achieved

76.2% tumour regression and effectively suppressed lung and lymph-node metastasis, demonstrating potent chrono-metabolic immunotherapy enabled by biomaterial design.

Conclusions: This work establishes a biomaterial-enabled chrono-metabolic immunotherapy strategy that integrates mitochondrial targeting, cuproptosis induction, and immune microenvironment remodelling. By synchronizing metabolic reprogramming with immunogenic cell death, the proposed platform overcomes tumour metabolic plasticity and immune suppression. These findings highlight the potential of chrono-controlled biomaterials as powerful tools for next-generation immuno-metabolic cancer therapies and provide new design principles for regenerative and translational biomaterials.



Scheme 1. SeqGel orchestrates chrono-metabolic immunotherapy through sequential release of DCA and PED@tCu: metabolic reprogramming toward OXPHOS, followed by cuproptosis induction and immune activation.

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IL-10 immunotherapy for mouse MASH disease via Lipid nanoparticles delivery system

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Key words: Lipid nanoparticles; IL-10 mRNA; MASH

Introduction: With the increasing prevalence of obesity, patients with nonalcoholic fatty liver disease have the potential to progress to metabolic dysfunction-associated steatohepatitis (MASH). Currently, pharmacological treatments for MASH remain challenging. Interleukin-10 (IL-10) is a dimeric anti-inflammatory cytokine that plays a crucial role in preventing inflammatory and autoimmune diseases. In preclinical studies involving hepatitis C virus (HCV) infection or inflammatory bowel disease (IBD), IL-10 therapy demonstrated significant efficacy in mouse models; however, it failed to show similar effectiveness in clinical trials. The major challenges associated with IL-10 therapy include the insufficient therapeutic effect observed at low doses and the occurrence of adverse effects at high doses, both in patients and healthy volunteers. Therefore, the key limitation in applying IL-10 therapy for MASH treatment lies in the lack of an innovative drug delivery system.

Materials & Methods: LNPs were synthesized using the thin-film hydration method followed by ultrasonication. MASH mouse models were established by feeding mice with a methionine- and choline-deficient (MCD) diet.

Results & Discussion: In this study, we present a novel strategy for delivering IL-10 mRNA specifically to mouse hepatocytes using an LNP delivery system. Four types of functionalized LNPs were prepared: LNP-Methoxy (LNP-Met), LNP-Amino (LNP-Ami), LNP-Carboxyl (LNP-Car) and LNP-Maleimide (LNP-Mal). SEM revealed that all four LNP formulations exhibited spherical vesicular morphologies (Fig. a). Comparable hydrodynamic diameters, ζ -potentials and encapsulation efficiencies were also observed (Fig. b-d). IVIS revealed Mal modification enhanced the accumulation of LNP-Mal in the liver (Fig. e). Moreover, CLSM images confirmed that LNP-Mal exhibited the highest level of internalization in hepatocytes (Fig. f). Furthermore, LNP-Mal/IL-10 mRNA was used for MASH therapy in MCD diet-induced mouse models. ALT levels were significantly reduced in LNP/IL-10 mRNA-treated mice (Fig. g and h). Effective expression and release of IL-10 mRNA within the liver microenvironment (Fig. i) ameliorated hepatic steatosis (Fig. j) and fibrosis (Fig. k).

Conclusions:

These results indicate that LNP-mediated IL-10 mRNA delivery represents a promising therapeutic strategy with significant potential for targeted hepatocyte delivery and MASH treatment.

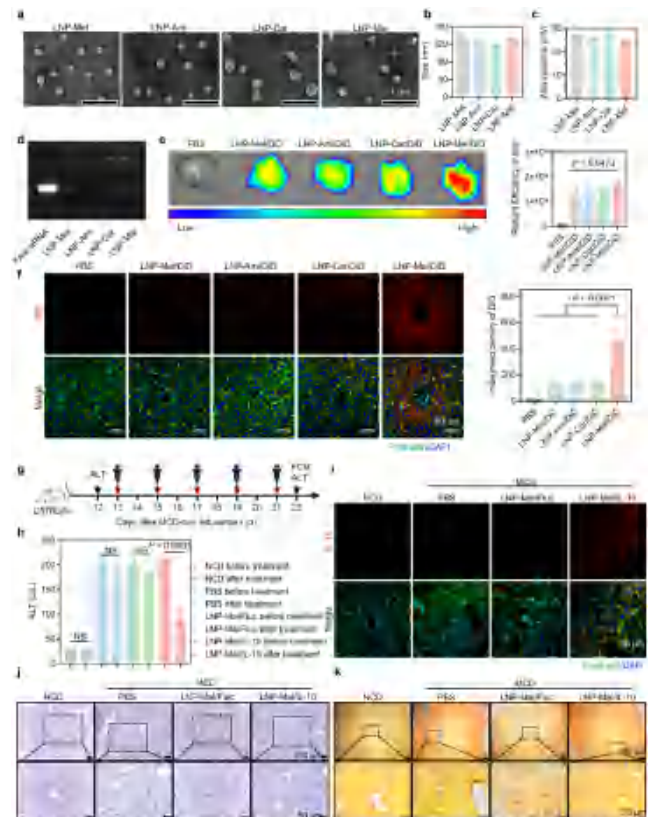


Fig. 1. LNP-Mal/IL-10 mRNA improves the nano-therapeutic effect on MASH disease. **a**, SEM images of LNP-Met, LNP-Ami, LNP-Car and LNP-Mal loaded with siNC. **b** and **c**, Characterization of LNPs particle size (**b**) and zeta potential (**c**) of LNPs. **d**, Encapsulation efficiency of LNP/siRNA. **e**, Representative IVIS fluorescent image of LNPs/DiD signal in the liver (left) and statistical analysis (right). **f**, Confocal images (left) of liver sections collected 24 h after intravenous administration of LNPs/DiD, together with quantification of DiD integrated density (right). **g**, Schematic illustration demonstrating LNP-Mal/IL-10 mRNA treatment in MASH mice. **h**, Serum ALT levels on days 12 and 22 following MCD diet feeding. **i**, Expression and release of LNP-Mal/IL-10 mRNA in mouse livers on day 21 after MCD diet feeding. **j,k**, H&E (**j**) and Sirius Red (**k**) staining of liver sections after treatment with PBS, LNP-Mal/Fluc mRNA or LNP-Mal/IL-10 mRNA.

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Near-Infrared Photothermal-Responsive Drug Delivery Hydrogel Based on Zero-Dimensional Peptide Nanobundles Composite PEG in Antitumor Research

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Abstract: Combined chemo-photothermal therapy can overcome the limitations of monotherapy and enhance therapeutic efficacy via additive or synergistic effects. However, its clinical translation is largely hindered by the lack of on-demand and controllable drug release. Herein, a temperature-responsive zero-dimensional peptide nanobundles with multi-thiol groups was synthesized, and then covalently cross-linked with maleimide-functionalized 4-arm polyethylene glycol. By optimizing the ratio and concentration of the two components, a nanocomposite hydrogel 3-PEG-8S with optimal thermo-responsiveness was fabricated. Subsequently, doxorubicin and graphene oxide were incorporated into 3-PEG-8S to construct a near-infrared photothermal-responsive hydrogel (PGD) for controlled drug delivery. Both in vitro and in vivo results demonstrated that PGD exhibited excellent photothermal performance, superior photothermal recyclability, precise NIR-triggered drug release behavior, and remarkable synergistic anti-tumor efficacy upon repeated NIR irradiation.

Key words: biomaterials, zero-dimensional, peptide, antitumor, drug delivery

Introduction: Malignant tumors severely threaten human health, with the global female cancer incidence rate reaching 30% in 2020. Traditional single-modality therapies, such as chemotherapy, surgical resection, and radiotherapy, still inevitably face limitations such as off-target effects, low bioavailability, and severe systemic toxicity. Chemo-photothermal combination therapy shows advantages, ablating tumors and enhancing drug uptake to improve efficacy. However, the current chemotherapy-photothermal synergistic therapy is largely constrained by the inability to perform controlled drug release on demand.

In order to achieve efficient chemotherapy-photothermal synergistic therapy, it is very important to develop a new release platform that is highly compatible with biological tissues, capable of efficiently and controllably multiple release of therapeutic drugs, and has good biodegradability. We designed to cross-link zero-dimensional peptide nanobundles with four-arm polyethylene glycol to construct a temperature-responsive nanocomposite hydrogel 3-PEG-8S (P). P redoped graphene oxide and doxorubicin to construct an efficient photothermal chemotherapy synergistic composite hydrogel platform PGD with controllable multiple drug release.

Materials & Methods:

1. Preparation experiment of PGD

Peptide 1-8S was synthesized by solid-phase peptide standard synthesis. 1-8S self-assembled in water to form zero-dimensional peptide nanobundles (8S). According to the molar ratio of 1:1, 8S was put into PEG to form a hydrogel P. Then, graphene oxide and doxorubicin were incorporated to P form PGD hydrogel.

2. The antitumor experiment of PGD hydrogel in vivo

The mice were randomly divided into 9 groups: PBS, PBS + 808 nm laser, DOX, GO, P, PG, PG + 808 nm laser, PGD and PGD + 808 nm laser. Then, hydrogel was injected into the tumor. For the light group, the tumor site was illuminated once every 3 days, and the illumination was performed four times for 16 days. Finally, three mice were randomly selected from each group to continue to observe and record the survival time of the mice.

Results & Discussion:

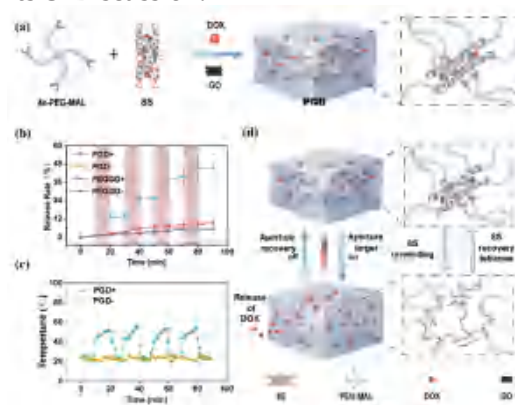


Fig. 1. (a) The schematic diagram of PGD preparation. (b) Drug release curves of PEGD and PGD under. (c) Photothermal curve of PGD. (d) The schematic diagram of drug release mechanism of PGD.

The data show that PGD hydrogel releases more doxorubicin when the temperature rises under laser irradiation, which indicates that the mechanism of releasing doxorubicin is that the temperature rise of the hydrogel caused by near-infrared light irradiation leads to 8S unwinding, the crosslinking degree of the hydrogel network decreases, the network pore size becomes larger, and doxorubicin diffuses and releases from the hydrogel.

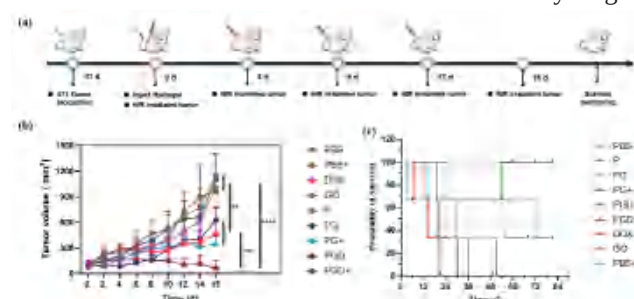


Fig. 2. (a) Program diagram of anti-tumor experiment. (b) The tumor volume of 9 groups. (** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$). (c) Survival curve of mice in 9 groups.

PGD was injected into the tumor tissue of mice, and the tumor growth was inhibited by the combination of near-infrared photothermal controlled release drugs and photothermal effect. After 16 days of treatment, the PGD treatment group had the best therapeutic effect. The survival time of the mice was observed later, and no mice died in the PGD group after two months. The above data indicate that PGD + in the chemotherapy-phototherapy synergistic treatment group has the best tumor treatment effect.

Conclusions: In general, the near-infrared photothermal response drug controlled release hydrogel PGD shows the application potential and prospect of nano-biocomposites based on peptide nanomaterials and biopolymers in the field of biomedical engineering. It is expected to cope with the complex and changeable in vivo environment, promote the development of nanocomposites and the transformation of biomaterials.

Lipid nanoparticle-mediated selective modulation of M2 macrophages for improved cancer immunotherapy

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Key words: M2 macrophages, Lipid nanoparticle, Caspase-1, Gene modulation, Immunotherapy

Introduction: Due to tumor immunosuppressive microenvironment, tumor-associated macrophages (TAMs) predominantly display a pro-tumorigenic M2 phenotype^[1]. Therefore, functional modulation of M2 macrophages is an attractive target for immunotherapy. Caspase-1, as an effector protein of inflammasomes, can regulate cell inflammation, death, and related cytokines secretion^[2]. In M2 macrophages, caspase-1-mediated regulation of inflammatory factors represents one of the key mechanisms underlying the formation of immunosuppressive microenvironment^[3]. Improving the efficiency of targeted delivery to M2 macrophages is crucial for effectively modulating antitumor immune responses. Although surface modification with ligand molecules enables M2 macrophage targeting, the efficacy of such ligands is often compromised in complex *in vivo* environments. Therefore, developing novel targeting strategies remains essential. The intracellular delivery of most nanoparticles is an energy-dependent process. Macrophage polarization states lead to pronounced differences in cellular energy metabolism^[4]. However, the relationship between this metabolic heterogeneity and the efficacy of nanoparticle-based drug delivery remains poorly understood and warrants further investigation.

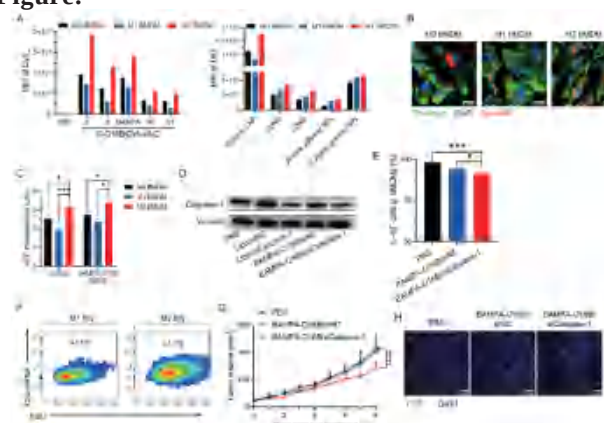
Materials & Methods: We systematically evaluated the uptake efficiency of various lipid nanoparticles by macrophages with distinct polarization phenotypes and analyzed the correlation between these differential uptake patterns and associated cellular metabolic profiles. Subsequently, we developed a BAMPA-O16B lipid-based delivery system to encapsulate and deliver caspase-1 siRNA for tumor therapy and further elucidated the underlying molecular mechanisms.

Results & Discussion: The results demonstrated that the vast majority of energy-dependent drug delivery systems exhibit higher accumulation in high-energy M2-type macrophages. Further analysis using lipid nanoparticles revealed that this energy-driven uptake mechanism is independent of phagocytic receptors on M2 macrophages surface. We screened a degradable lipid nanoparticle RNA delivery system (BAMPA-O16B/siCaspase-1) capable of efficiently delivering caspase-1 siRNA into M2 macrophages to achieve effective gene expression silencing. The administration of BAMPA-

O16B/siCaspase-1 not only reduced caspase-1 expression, suppressed cellular pyroptosis, and cytokine secretion, but also promoted macrophage polarization toward anti-tumor phenotype, ultimately contributing to tumor growth inhibition.

Conclusions: Our study uncovers a metabolism-guided mechanism that governs macrophage-specific nanoparticle internalization by linking lipid dynamics with cellular energy states. We developed a versatile siRNA delivery platform capable of selectively targeting tumor-infiltrating M2 macrophages for caspase-1 silencing and cancer therapy. This strategy provides a new avenue for designing next-generation macrophage-focused RNA nanotherapeutics for cancer immunotherapy.

Figure:



(A) The uptake of different nanoparticles by M0, M1, and M2 BMDMs. (B) CLSM images of BMDMs treated with BAMPA-O16B/Cy5-siNC. (C) The concentration of ATP in BMDMs. (D) Caspase-1 protein levels. (E) IL-1β⁺ cells in BMDMs treated with BAMPA-O16B/siCaspase-1. (F) Cy5⁺ cells in M1 and M2 macrophages at tumor tissues. (G) Tumor growth curves. (H) The distribution of CD8⁺ T cells in tumor after treatment.

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Inhalable Ce nanozyme-backpacked phage aims at ischemic cerebral injury by M1-microglia hitchhiking

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Key words: regeneration, biomaterials, tissue engineering
(3-5 key words)

Introduction: There is a desperate need for precise nanomedications to treat ischemic cerebral injury. Yet, the drawbacks of poor-delivery efficiency and off-target toxicity in pathologic parenchyma for traditional antioxidants against ischemic stroke result in inadequate brain accumulation. M13 bacteriophages are highly phagocytosed by M1-polarized microglia and can be carried towards the neuroinflammatory sites.

Materials & Methods: Here, we developed a bio-active, inhalable, $\text{Ce}_{0.9}\text{Zr}_{0.1}\text{O}_2$ -backpacked-M13 phage (abbreviated as CZM) and demonstrated how M13 bacteriophages were taken up by different phenotypes' microglia.

Results & Discussion: With the M1 microglia's proliferating and migrating, CZM can be extensively and specifically delivered to the site of the ischemic core and penumbra, where the surviving nerve cells need to be shielded from secondary oxidative stress and inflammatory cascade initiated by reactive oxygen species (ROS). With non-invasive administration, CZM effectively alleviates oxidative damage and apoptosis of neurons by eliminating ROS generated by hyperactive M1-polarized microglia.

Conclusions: Here, a secure and effective strategy for the targeted therapy of neuroinflammatory maladies is offered by this research.



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Engineering pirfenidone-loaded silk fibroin hydrogels to prevent fibrosis recurrence through sustained, site-activated drug release and ECM remodeling across 2D and 3D models

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Introduction

Fibrosis, driven by dysregulated wound healing and chronic inflammation, underlies fibroproliferative diseases, causing ~45% of global deaths through excessive extracellular matrix (ECM) deposition, myofibroblast activation, epithelial-mesenchymal transition (EMT), and mitochondrial dysfunction. Pirfenidone (PFD), an FDA-approved antifibrotic, is limited by poor pharmacokinetics. Urothelial fibrosis, with a high recurrence rate, exacerbates bladder dysfunction. In this work, we have engineered an injectable silk fibroin-based hydrogel that mimics the soft tissue modulus for sustained, enzyme-responsive PFD release, evaluating its effects across fibroblast recurrence models, 2.5D C2C12/RAW macrophage coculture fibrosis models, and 3D spheroid models.

Methods

Hydrogels with a physiological modulus of ~5 kPa were synthesized, and their physicochemical properties were characterized. Fibrosis recurrence model was induced in human fibroblasts using lipopolysaccharide (LPS), while inflammatory crosstalk in the C2C12 myoblast-RAW macrophage coculture (2.5D model) was established through LPS stimulation, which promotes the pro-inflammatory phenotype in RAW cells. SV-HUC cells were cultured on Matrigel for 15 days to generate 3D spheroids, where fibrosis was induced using a cocktail of LPS and TNF- α . Key fibrogenic gene and protein markers, mitochondrial function, and EMT progression were evaluated. Additionally, the mechanobiological cellular stiffness was also assessed using atomic force microscopy.

Results

The hydrogel demonstrated *in situ* injectability, undergoing sol-to-gel transition at physiological temperature, with sustained drug release maintained for up to seven days. The hydrogel exhibited profibrotic enzyme-responsive drug release, thereby regulating ECM remodeling. In the fibroblast recurrence model, treatment with PFD-loaded hydrogel resulted in significant reductions in fibroblast hyperproliferation, reactive oxygen species formation, and the expression of collagen I and α -SMA, highlighting the importance of sustained release. The 2.5D C2C12/RAW macrophage cocultures revealed suppressed myofibroblast transition, diminished collagen deposition, upregulated myogenesis genes, ameliorated mitochondrial dysfunction, and reduced monolayer stiffness. In 3D urothelial spheroids,

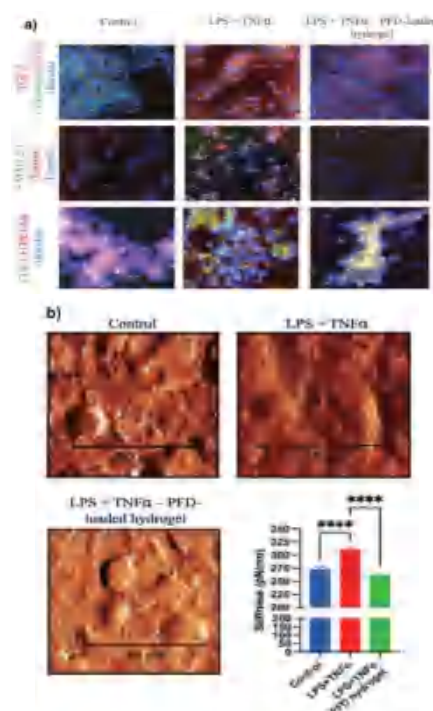
the hydrogel markedly downregulated EMT-associated proteins (TGF- β and vimentin) and focal adhesion kinase (FAK), a mechanosensor elevated in fibrosis, highlighting biomechanically regulated signaling via tissue-mimicking mechanical properties.

Conclusion

This multifunctional hydrogel disrupts fibrosis by synchronizing sustained PFD delivery with disease progression, targeting biochemical (EMT, ROS, mitochondrial repair), biomechanical (stiffness normalization), and regenerative pathways across 2D/2.5D/3D models. By addressing the limitations of the free drug, it offers a promising translational strategy for reversing urothelial fibrosis and preventing recurrence.

Keywords: Site-activated hydrogel, ECM remodeling, disease modeling.

Figures



a) Immunostaining of 2D and 3D models, b) Stiffness analysis using AFM

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Smart Dendrimer Nanogels Boost mRNA-Based Cancer Therapy via Synergistic Glycolysis Inhibition and Immune Activation

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Key words: dendrimers; nanogels; cancer immunotherapy; mRNA vaccine; glycolysis inhibition

Introduction: Development of functional vehicles for safe and efficient mRNA delivery into immune cells (e.g., dendritic cells, DCs) remains to be challenging, and most of the mRNA-based vaccines just act on immune cells for improved anticancer immunity without additional input to tackle cancer cells, ultimately limiting the anticancer efficacy. Therefore, there is an urgent need to design multifunctional mRNA delivery platforms that integrate immune activation with metabolic intervention for more effective cancer treatment.

Materials & Methods: Man-conjugated G3 PAMAM dendrimers through dual H_2O_2 /pH-responsive boronate ester bond were used as the macromonomers to be crosslinked with FBA-PEG-FBA through Schiff base bonding, thus forming pH-responsive DNGs via a microemulsion method. The DNGs were used to deliver gp100 mRNA as a potential nanovaccine.

Results & Discussion: The DNGs with a size of 45.7 nm show excellent colloidal stability and cytocompatibility and allow dual-actions for DC-targeted mRNA delivery and cancer cell glycolysis inhibition. In a subcutaneous mouse melanoma model, the DNG/mRNA vaccine exerted glycolytic inhibition effect and triggered robust antitumor immune responses to suppress the tumor growth, especially in combination with anti-PD-L1 antibody-mediated immune checkpoint blockade. Meanwhile, the local vaccination of the vaccine enabled effective tumor occurrence prevention.

Conclusions: With the Man-mediated targeting specificity to DCs and metabolic intervention to cancer cells, the DNGs allow dual-actions for DC-targeted mRNA delivery and cancer cell glycolysis inhibition, respectively. We show that in a subcutaneous mouse melanoma model, the DNG/mgp100 vaccine triggers robust antitumor immune responses to suppress the tumor growth, especially in combination with aPD-L1 antibody-mediated ICB. Meanwhile, local muscular vaccination of the DNG/mgp100 vaccine effectively slows down the tumor occurrence and development. Therefore, the developed DNG-based mRNA delivery vaccine holds a great promise both as a therapeutic and prophylactic nanovaccine, and should be extendable to tackle other cancer types for improved mRNA cancer vaccine development.

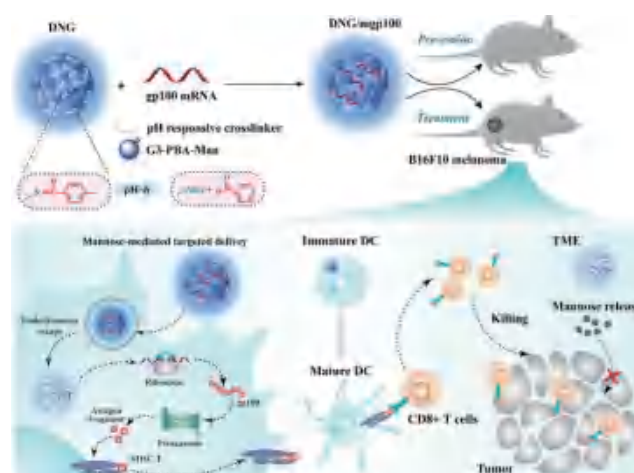


Fig. 1. Synthesis of DNG-based mRNA vaccine and the proposed dual-action mechanism.

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Dual-drug loaded electrospun scaffolds serving as breast implant coatings.

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Key words: electrospinning, drug delivery, polycaprolactone, breast cancer

Introduction: Breast implant-associated complications, including surgical site infection and capsular contracture, pose significant clinical challenges. Local drug delivery systems that simultaneously address multiple complications represent an attractive strategy. We have developed coaxially electrospun polycaprolactone (PCL) nanofibres incorporating ciprofloxacin (CIP) in the shell and tamoxifen (TMX) in the core, forming dual-drug loaded patches with potential antimicrobial, anticancer, and antifibrotic properties, which could be used as coatings for commercially available silicone implants.

Materials & Methods: Core-shell nanofibres were fabricated by coaxial electrospinning. CIP, a broad-spectrum fluoroquinolone active against *Pseudomonas aeruginosa* and *Staphylococcus* species, was incorporated into the PCL shell; TMX was incorporated into the PCL core. Four patch variants were prepared: TMX+CIP+, TMX+CIP-, TMX-CIP+, and drug-free controls. Fibre morphology was characterised by scanning electron microscopy (SEM) and surface hydrophobicity assessed by water contact angle. Antimicrobial activity in *E.coli* was evaluated over 8 days. Anticancer and cytotoxic effects were assessed in MCF-7 human breast cancer cells following 24 h exposure.

Results & Discussion: Coaxial electrospinning enables preparation of dual-drug loaded patches (Fig.1a) which resemble tissue paper macroscopically (Fig.1b) and extracellular matrix microscopically (Fig.1c). In microbiological assays, CIP-loaded patches (TMX+CIP+ and TMX-CIP+) demonstrated antibacterial activity for up to 8 days, with the most effect observed during the first 48 hours (Fig. 1d). Anti-cancer effect of TMX was confirmed in MCF-7 cells (human breast cell line) following 24 h exposure to TMX-loaded patches (TMX+CIP+ and TMX+CIP-; Fig. 1e).

Conclusions: Coaxially electrospun PCL nanofibres represent a promising platform for localised co-delivery of CIP and TMX, providing simultaneous antimicrobial, anticancer, and potentially antifibrotic effects. Further optimisation of drug loading, release kinetics, and rigorous cytotoxicity assessment alongside in vivo evaluation are required before clinical translation.

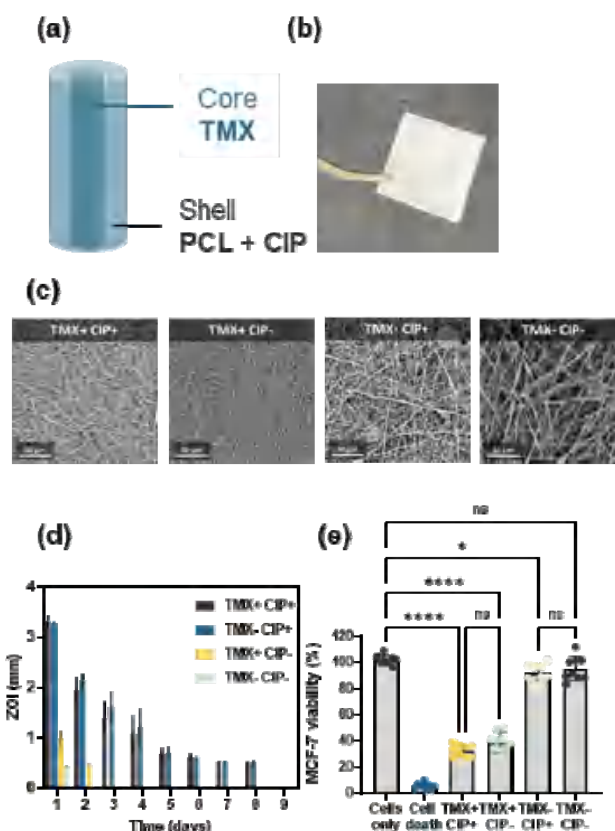


Fig. 1. Coaxially electrospun coatings were prepared, bearing tamoxifen (TMX) in the core and ciprofloxacin (CIP) mixed with polycaprolactone (PCL) in the shell (a). A digital photograph (b) presents the gross morphology of produced implants, while scanning electron microscopy (SEM) (c) visualises the intertwined fibres resembling extracellular matrix. CIP-loaded coatings showed antimicrobial effect over 8 days (d). TMX reduced MCF-7 viability significantly, suggesting potential anticancer effect (e).

A dual-sensitive nanogel for spatiotemporal co-delivery of aPD-1 and GSK3787 to enhance ICB therapy

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Introduction: The clinical efficacy of immune checkpoint blockade (ICB) therapy is often limited by the immunosuppressive tumor microenvironment (TME). While combining checkpoint inhibitors with agents that remodel the TME is a key strategy to enhance efficacy, the efficient co-delivery and spatiotemporal coordination of these drugs remain a significant challenge. This study investigates a novel nanoplatform designed to achieve the sequential, site-specific delivery of an anti-PD-1 antibody (aPD-1) and a PPAR δ antagonist (GSK3787) to overcome this limitation.

Materials & Methods: A linear-dendritic nanogel (DNG) was synthesized using previously described Thiol-Ene Chemistry [1]. Its PEG shell, inspired by the protein corona, was designed to physically adsorb aPD-1. The nanogel core was engineered with an "AND-gate" logic, responding only to the dual stimuli of acidic pH and esterase, to encapsulate GSK3787. Drug release profiles were characterized in vitro under simulated TME conditions. The cellular uptake, biodistribution, and anti-tumor efficacy of the DNG@(GSK3787+aPD-1) system were evaluated in a murine melanoma model. Immune cell infiltration within tumors and systemic immune responses were analyzed by flow cytometry.

Results & Discussion: The DNG system demonstrated "AND-gate" controlled release, ensuring that aPD-1 was preferentially released only upon encountering the acidic and enzyme-rich TME. Following this initial release, the GSK3787-loaded nanogel core was efficiently internalized by tumor cells. In vivo, the system achieved high tumor accumulation. Treatment with DNG@(GSK3787+aPD-1) significantly suppressed tumor growth in the melanoma model. This potent anti-tumor effect was attributed to the sequential drug action: aPD-1 first relieved T-cell inhibition, while GSK3787 delivered into tumor cells inhibited the PPAR δ /ANGPTL4 pathway. This dual action resulted in a remodeled immune microenvironment, characterized by increased cytotoxic T lymphocyte infiltration, a reduced regulatory T cell population, and the induction of a systemic anti-tumor immune response.

Conclusions: This study presents an innovative nanogel-based co-delivery strategy that effectively combines ICB with TME modulation. By enabling the spatiotemporal release of aPD-1 and a PPAR δ antagonist, the system successfully overcomes ICB resistance in a melanoma model. The findings also provide new insights into the role of tumor cell-intrinsic PPAR δ signaling as a key regulator of the immune

landscape. This approach offers a promising strategy for enhancing cancer immunotherapy and warrants further investigation.

Key words: nanogel, immune checkpoint blockade, PPAR δ antagonist, dual-responsive delivery, tumor immune microenvironment

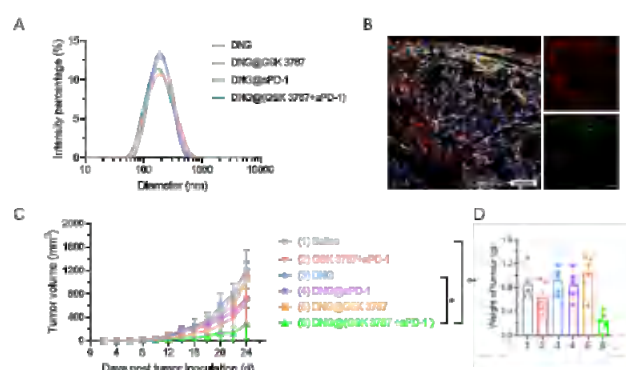


Fig. 1. Characterization and anti-tumor efficacy of DNG. (A) No significant change in particle size before and after drug loading; (B) The nanocarrier penetrates deep into tumor tissue for drug delivery, with red fluorescence representing the hydrophobic drug and green fluorescence representing the antibody; (C) Tumor growth curves under different treatment groups; (D) Comparison of tumor weights.

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Pressure-driven microinjection (PMI) of porous-coated balloon for ultrafast endoluminal drug delivery across biological barriers

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Key words: porous coating; biological barrier; drug delivery across barriers; balloon catheter; precise medicine

Introduction: Biological barriers in lumen systems, composed of basement membranes, tight cellular junctions, and glycosaminoglycan networks, play a critical role in maintaining tissue homeostasis by preventing pathogen invasion. However, these highly selective structures, severely restrict drug transport, particularly across nanoscale intercellular gaps. Although nanomedicines have been engineered through size control, surface charge modulation, and ligand functionalization to enhance barrier penetration, their delivery remains largely dependent on passive diffusion and systemic circulation, leading to inefficient accumulation at target sites. Physical strategies, including microneedles, iontophoresis, and electroporation, offer active and localized barrier disruption. Yet, their clinical translation is limited by tissue damage, invasiveness, and the risk associated with implanted or residual materials. Therefore, an ideal and versatile barrier penetration strategy faces several challenges: (i) precise drug accumulation at lesion sites, (ii) rapid and robust penetration across complex biological barriers, and (iii) compatibility with existing medical devices, without inducing vascular injury or long-term tissue damage.

Materials & Methods: The PLEL spongy coating was prepared via ultrasonic spray of a PLEL/PVP/BP solution (CH₂Cl₂:ethanol, 1:1), followed by UV crosslinking for 5 min and immersion in DI water to form a microporous structure, then dried under nitrogen. SEM was used to characterize the microstructure. For ex vivo evaluation, the coating was applied to fresh pig aortas under controlled pressures for 60 s, and penetration of functional agents was assessed by CLSM. For balloon-based delivery, PLEL coatings were applied to balloons and tested on rat vessels, intestines, and tracheas under 1-3 atm pressure. Tissue cryosections were imaged with fluorescence microscopy to measure penetration depth.

Results & Discussion: We report a pressure-driven microinjection (PMI) platform based on a compressible porous coating for ultrafast, localized, and minimally invasive drug delivery across biological barriers. Unlike passive diffusion systems, PMI actively propels drug solutions by compressing the porous structure under

pressure, enabling rapid liquid extrusion and transient opening of tight junctions for robust barrier penetration. The platform achieved efficient and safe delivery of diverse agents under low pressures. Notably, bovine serum albumin penetrated endothelial barriers to a depth of 150 μm at 100 kPa within 60 s. Small-molecule penetration depth scaled with the square root of pressure, consistent with Darcy's law, allowing precise depth control. Enhanced macromolecule delivery at higher pressures further suggested pressure-responsive endothelial mechanics. When integrated with an interventional balloon, the porous-coated system enabled ultrafast endoluminal drug delivery in vivo, suppressing inflammation and promoting endothelial regeneration after angioplasty. Overall, the PMI strategy establishes a controllable, device-compatible approach for efficient drug transport across complex biological barriers.

Conclusions: We developed a PMI strategy with compressible porous coatings for rapid, controllable drug delivery across biological barriers. Macromolecules like BSA penetrated vessels $>150\ \mu\text{m}$ in 60 s, with depth tunable via Darcy's law. Enhanced transport under higher pressure relied on transient stretching of elastic cell layers, enabling efficient convection with minimal endothelial damage. Balloon integration enabled endoluminal delivery to vessels, intestines, and trachea, and OI delivery suppressed inflammation and neointima formation post-angioplasty.

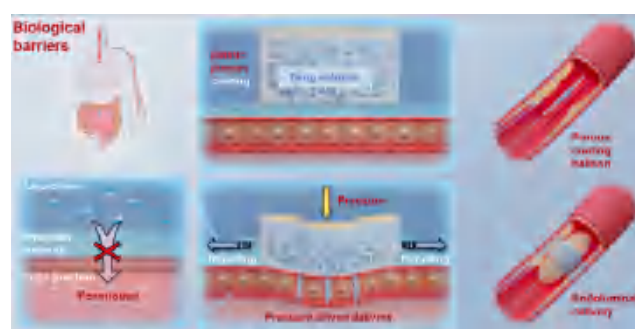


Fig. 1. Schematic illustration of the PMI strategy.

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Targeted Protein Degradation

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Abstract: Protein homeostasis is essential for cellular function, and its disruption contributes to diseases such as cancer, inflammation, and neurodegeneration. Inducing the degradation of pathogenic proteins has therefore emerged as an effective therapeutic strategy. Approaches such as proteolysis-targeting chimeras (PROTACs) and lysosome-targeting chimeras (LYTACs) enhance proteasomal or autophagic degradation and show considerable promise. However, small-molecule degraders often exhibit limited target selectivity, short circulation half-lives, and susceptibility to resistance, and none has yet been approved for clinical research. To overcome these limitations, our group developed a series of targeted protein degradation nanoplateforms, including NanoTAC, CoroTAC, and MitoTAC. These platforms employ multivalent ligand coordination to improve target engagement, activate autophagy in situ, and extend circulation time, thereby enhancing degradation efficacy. Taking the mutant p53 protein (mutp53) as an example, we engineered biomimetic nanoreceptors (NRs) that combine specific protein binding with autophagy activation, achieving effective degradation in vitro and in a patient-derived xenograft ovarian cancer model. Notably, these platforms achieve superior efficacy with up to a 25-fold reduction in antibody dosage, highlighting strong translational potential.

Key words: Targeted protein degradation, Drug delivery, Disease therapy

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Tumor microenvironment targeting for glioblastoma multiforme treatment via hybrid cell membrane coating supramolecular micelles

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Glioblastoma multiforme (GBM) is one of the most common primary intracranial tumors in the central nervous system with poor prognosis, high invasiveness, risk of recurrence and low survival rate. Thus, it is urgent and vital to develop drug effective delivery systems that efficiently to traverse the blood – brain barrier and targeted transport therapeutic agents into the GBM tumor site for the treatment of brain tumors. Recently, amphiphilic cucurbit[7]uril-polyethylene glycol-hydrophobic Chlorin e6 (CB[7]-PEG-Ce6) polymer was designed, prepared, and self-assembled into micells (CPC) in an aqueous solution, and chemo drug methyl-triazeno-imidazolecarboxamide (MTIC), loaded into the cavity of CB[7] was subsequently coated with hybrid membrane mUMH (HMC3 membrane: macrophage membrane: U87MG membrane = 1:1:2) to afford mUMH@CPC@MTIC. The surface hybrid membrane mUMH potentially enhance the targeted delivery of CPC@MTIC to GBM tissue. Bioactive MTIC was released from the cavity of CB[7] in response to the high spermine level in GBM tumor microenvironments for effective tumor chemotherapy. The biomimetic mUMH@CPC@MTIC exhibited superior antitumor efficacy against GBM in mice. These findings provide new strategies for the design of biomimetic nanoparticle-based drug delivery systems and promising therapy of GBM.

Key words: Hybrid cell membrane, Biomimetic coating, Glioblastoma multiforme, Targeted drug delivery, Controlled drug release

Introduction: central nervous system (CNS), and the five-year median survival time for patients with GBM is less than two years [1,2]. Currently, the clinical treatment for GBM is surgical resection accompany with chemotherapy or radiotherapy [3-5]. Unfortunately, the survival time of the patients had not been significantly improved due to the tight junctions between tumor cells and brain cells, making it rare to completely resect the GBM tumor [6]. More importantly, the presence of the intrinsic blood-brain barrier (BBB) would prevent the entrance of chemo drugs into the CNS, resulting in low bioavailability, high toxicity of the drug, and high recurrence rate of GBM [7,8]. Therefore, developing a novel drug delivery system with high targeting efficiency to GBM is in a highly clinical needed [9,10].

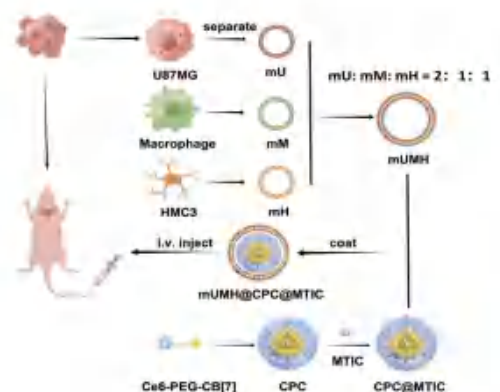
Materials & Methods: Recently, amphiphilic cucurbit[7]uril-polyethylene glycol-hydrophobic Chlorin e6 (CB[7]-PEG-Ce6) polymer was designed, prepared, and self-assembled into micells (CPC) in an aqueous solution, and chemo drug methyl-triazeno-imidazolecarboxamide (MTIC), loaded into the cavity of CB[7] was subsequently coated with hybrid membrane mUMH (HMC3 membrane: macrophage membrane: U87MG membrane = 1:1:2) to afford mUMH@CPC@MTIC.

Results & Discussion: The surface hybrid membrane mUMH potentially enhance the targeted delivery of CPC@MTIC to GBM tissue. Bioactive MTIC was released from the cavity of CB[7] in response to the high spermine level in GBM tumor microenvironments for effective tumor chemotherapy. The biomimetic mUMH@CPC@MTIC exhibited superior antitumor efficacy against GBM in mice.

Conclusions: In summary, we have proposed a new strategy to fabricate biomimetic nanomicelles systems for targeted and controlled released chemotherapy of GBM. Hybrid membrane mUMH (HMC3 membrane:

macrophage membrane: U87MG membrane = 1:1:2) exhibited higher intracellular uptake capability and target ability to U87MG in comparison to the single cell membrane. And after internalization by cancer cells, MTIC can be released from the cavity of CB[7] in

response to the overproduced spermine. Therefore, mUMH@CPC@MTIC provided a potential biomimetic nanomicelle-based drug delivery systems for synergistic GBM treatment. This study also offers a promising strategy



Scheme. Design of tumor microenvironment targeting for glioblastoma multiforme treatment via hybrid cell membrane coating supramolecular micelles.

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Cationic lipid-modified PEG-PLGA nanoparticles facilitate effective dendritic cell reprogramming to alleviate T cell-mediated autoimmunity in EAE

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Key words: Multiple sclerosis, Dendritic cell, CLAN platform, CD40, LKB1.

Introduction:

Multiple sclerosis (MS) is a chronic autoimmune disease characterized by dysregulated T-cell responses and neuroinflammation, while current therapies remain limited by modest efficacy and adverse effects. Here, we developed CLAN, a modular nanodelivery platform that silences *CD40* and *LKB1* in dendritic cells (DCs) to induce immune reprogramming and restore immune homeostasis. This strategy provides a promising therapeutic approach for MS and other T cell-mediated autoimmune diseases.

Materials & Methods:

1. A CLAN/siCD40+siLKB1 nanocarrier was constructed using a double-emulsion solvent evaporation method to achieve the co-encapsulation of siCD40 and siLKB1.
2. The siRNA delivery efficiency of CLAN, its gene-silencing efficacy, and its regulatory effects on the DC phenotype were first evaluated *in vitro*, followed by *in vivo* assessment of its biodistribution, targeting capability, and biosafety.
3. In the EAE mouse model, the therapeutic efficacy of CLAN/siCD40+siLKB1 was evaluated under both prophylactic and post-onset treatment regimens by assessing disease onset and clinical severity.
4. The underlying molecular mechanisms by which it regulates immune homeostasis were investigated using flow cytometry, RNA sequencing, histopathological staining, and cell co-culture assays.

Results & Discussion:

CLAN/siCD40+siLKB1 demonstrated efficient delivery, favorable biosafety, and potent immunomodulatory effects both *in vitro* and *in vivo*. This nanocarrier enables efficient co-delivery of siCD40 and siLKB1 to dendritic cells (DCs), achieving synergistic dual-gene silencing and reprogramming DCs toward a tolerogenic phenotype, as evidenced by reduced antigen-presentation and costimulatory molecules, increased tolerogenic markers, enhanced differentiation of naïve CD4⁺ T cells into Tregs, and suppressed Th1/Th17 polarization. *In vivo*, CLAN efficiently targeted DCs and showed favorable biodistribution and biocompatibility. Furthermore, in the EAE model, CLAN effectively delayed disease progression and alleviated central nervous system inflammatory infiltration and demyelination under both prophylactic and therapeutic treatment settings.

Conclusions:

CLAN is an efficient, safe, and modular nanocarrier that enables targeted co-delivery of siCD40 and siLKB1 to DCs. By coordinately silencing these genes, CLAN reprograms DCs toward a tolerogenic phenotype, restores T-cell immune homeostasis, and alleviates the onset and progression of EAE.

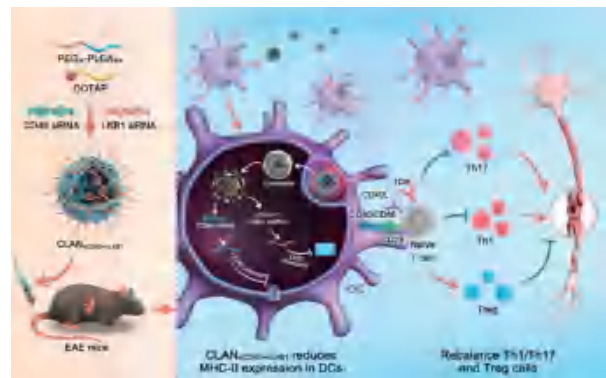


Fig. 1. Schematic of modulation of the Th1/Th17/Treg balance mediated by CLANsiCD40+siLKB1.

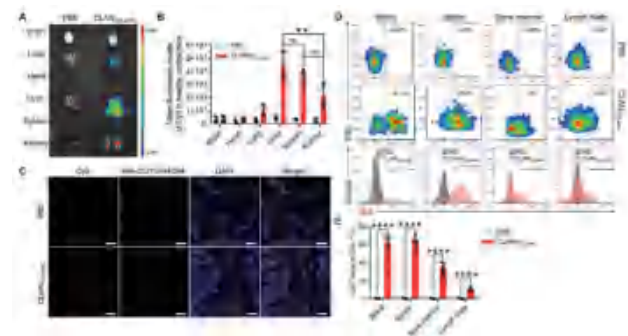


Fig. 2. The particles simultaneously deliver siRNA into DCs *in vivo*

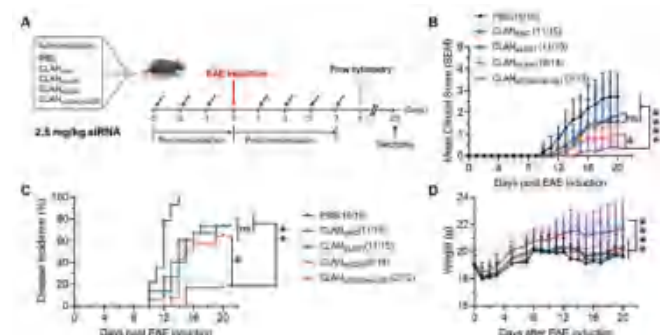


Fig. 3. CLANsiCD40+siLKB1 suppresses EAE onset and progression in a murine model.

Breaching Intracellular Barriers: Biomaterial Interface Design for Smart Drug Delivery

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Key words: regeneration, polymer brushes, drug delivery, intracellular barriers

Introduction: The clinical translation of advanced therapeutics, including nucleic acids, proteins, and immunomodulators, is often hindered by a series of extra- and intra-cellular barriers. These barriers range from non-specific interactions in the bloodstream and poor accumulation at target sites to the more formidable challenges of cellular internalization, endosomal escape, and controlled release within the correct subcellular compartment. A fundamental understanding and precise engineering of the biomaterial interface are therefore critical to overcoming these obstacles and enabling the next generation of smart drug delivery systems that can sense and respond to their environment for precise therapeutic intervention.

Materials & Methods: To address these challenges, we have developed a range of biomaterial interfaces with tailored architectures and functionalities. This includes the synthesis of well-defined cationic polymer brushes, such as poly(dimethylaminoethyl methacrylate) (PDMAEMA) and poly(2-methacryloyloxyethyltrimethylammonium chloride) (PMETAC), via surface-initiated atom transfer radical polymerization (SI-ATRP) from various nanomaterial cores (e.g., silica nanoparticles, carbon nanotubes). The interactions of these brushes with nucleic acids (siRNA, plasmid DNA) and complex biological media were characterized using surface plasmon resonance (SPR), in situ ellipsometry, and dynamic light scattering (DLS). Furthermore, we engineered more complex systems, such as block copolymer brushes for enhanced serum stability and designed inorganic nanoparticles (e.g., AgFeS₂) and extracellular vesicles (MSC-EVs) for combined therapeutic modalities, characterizing their material properties and biological performance using a suite of in vitro and in vivo models, including flow cytometry, confocal microscopy, and transcriptomic/metabolomic analysis.

Results & Discussion: Our investigations revealed that the high density and confined architecture of cationic polymer brushes create a unique "crowded" environment that enables the exceptionally stable capture of siRNA through multivalent electrostatic interactions, as opposed to the weaker binding observed on low-density coatings. We demonstrated that the subsequent release of nucleic acids is governed by a competitive binding mechanism within the cytoplasm, where highly charged biomacromolecules like glycosaminoglycans and cytosolic RNA displace the payload. This understanding guided the design of a charge-shifting polymer brush (CS-PMETAC) that modulates its binding affinity in response to endosomal pH, enabling sustained intracellular siRNA delivery and prolonged gene knockdown. Expanding on this interfacial design principle, we developed more complex platforms: (i) polymer brush-coated carbon nanotubes for the sequential, spatiotemporally controlled delivery of siRNA (siPD-L1) and plasmid DNA (pOX40L) to reprogram immune checkpoints in the tumor microenvironment, effectively reversing local and systemic immunosuppression in gastrointestinal cancer. (ii) Iron-based ternary chalcogenide nanoparticles (AgFeS₂) that integrate photothermal therapy, ferroptosis, and immunogenic cell death into a single system for the synergistic treatment of triple-negative breast cancer. (iii) Engineered mesenchymal stem cell-derived extracellular vesicles (nor@MSC-EVs) loaded with an Arg1 inhibitor to simultaneously correct metabolic and immunological disorders in psoriasis by scavenging disease-specific self-antigens. These examples illustrate how precise interface design, whether synthetic or

bio-derived, can be adapted to breach specific intracellular barriers for a given disease.

Conclusions: This body of work (references 1-10) establishes that the rational design of biomaterial interfaces is paramount for overcoming complex intracellular barriers. By moving from fundamental studies of polymer brush interactions to the development of multi-functional, stimuli-responsive nanocarriers and bio-inspired vesicles, we have demonstrated the potential of this approach to create smart drug delivery systems. These systems not only enhance therapeutic efficacy in challenging disease models like cancer and autoimmune disorders but also provide a platform for understanding and modulating complex biological pathways. Future work will focus on the clinical translation of these technologies, with an emphasis on long-term biosafety, scalable manufacturing, and the exploration of new combinatorial therapies.

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Bioactive Magnesium Incorporated Biomaterials for Bone Defects Repair

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Key words: Magnesium, Bone regeneration, Biomaterials

Introduction: Bone defect as a result of diseases and traffic accidents is one of the most detrimental medical issues due to its high disability and morbidity. Conventional treatment for large bone defects is to use bone grafts harvested from the patients or compatible donors for bone fixation and regeneration; however, this common practice is still associated with several limitations, including unmatched shape, disease transmission, and additional morbidity. Bioactive Magnesium (Mg) has been widely studied in orthopedic implants on account of its comparable mechanical properties, biocompatibility, excellent biodegradability, and osteopromotive effects during degradation.

Materials & Methods: Our group has developed a series of Mg Incorporated biomaterials for bone repair. For example, we proposed a remote-controllable self-deploying and bioactive scaffold fabricated by a low temperature rapid prototyping 3D-printing technology, which comprises of shape memory polyurethane (SMPU) as the thermal-responsive matrix and magnesium (Mg) as the photothermal and bioactive fillers. In addition, we also developed a unified bilayer Mg-containing membranes featuring a reinforced dual-crosslinking interface between barrier and porous layers through a homogeneous isomeric in-situ fabrication strategy.

Results & Discussion: Through in vivo studies, the scaffold demonstrated the functions of remote-controllable bone regeneration including the no-contact recovery, tightly supporting ability and promoted new bone growth. The membrane's superior mechanical strength (~157 MPa in dry state and ~8.6 MPa in wet state) ensures its long-term degradation stability and bioactivity in vivo. In a rat critical-sized cranial defect model, the membranes significantly outperformed clinical collagen membranes, achieving ~2.5-fold greater bone volume regeneration after 8 weeks.

Conclusions: Based on above results, we envision these Mg Incorporated biomaterials have huge potentials for effective tissue regeneration and functional reconstruction.

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Mechanochemically-reprogrammed stem cell exosomes reconcile the biogenesis-internalization trade-off to resolve pulmonary fibrosis

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Abstract: Matrix stiffness serves as a pivotal biophysical cue that profoundly dictates exosome biogenesis and cellular internalization, yet often creates a functional trade-off that impedes clinical translation. Herein, we developed a mechano-chemo-transductive strategy to engineer mesenchymal stem cell (MSC) exosomes endowed with robust biogenesis and superior delivery potency. Specifically, we revealed that MSCs cultured on soft matrices secreted a significantly elevated exosome yield and demonstrated enhanced competence to drive macrophage towards anti-inflammatory M2 polarization. Conversely, stiff matrices upregulated ATP-binding cassette transporter A1 (ABCA1) expression, enriching exosomal membrane cholesterol and facilitating cellular internalization by recipient cells. By taking advantages of these unique mechano-responses, we engineered MSCs via substrate softening combined with ABCA1 modulation to generate mechanochemically reprogrammed exosomes with concurrently enhanced yield and internalization efficiency. In a murine model of pulmonary fibrosis characterized by restrictive biological barriers, inhaled mechanochemically reprogrammed exosomes treatment demonstrated superior lung retention and deep tissue penetration. Furthermore, they effectively orchestrated immune homeostasis by repolarizing alveolar macrophages to reverse fibrotic remodeling and restore lung function. Collectively, by reconciling the intrinsic trade-off between biogenesis and cellular uptake, this strategy represents a paradigm shift in exosome engineering and paves the way for next-generation therapeutics against refractory fibrotic diseases.

Key words: Mechano-chemo-transduction, Engineered exosomes, Pulmonary fibrosis, Macrophage reprogramming, Inhalation delivery, ABCA1

Introduction: Mesenchymal stem cell (MSC)-derived exosomes hold immense therapeutic potential, but their clinical translation is severely hindered by low isolation yields and poor delivery efficiency¹. Although culturing MSCs on soft matrices significantly increases exosome yield and anti-inflammatory properties, it inadvertently compromises their cellular internalization capacity compared to those derived from stiff matrices². By integrating transcriptomic and biomechanical analyses, we discovered that the mechanosensor ABCA1 regulates exosomal cholesterol composition, with elevated cholesterol being the critical driver for superior cellular internalization³. Leveraging this mechanistic insight, we developed a novel mechano-chemo-transductive strategy that combines soft matrix culturing with chemical

ABCA1 activation to non-invasively enrich exosomal cholesterol⁴. This combinatorial approach successfully reconciles the persistent trade-off between production and delivery, yielding engineered exosomes with simultaneously enhanced productivity, robust immunomodulatory efficacy, and superior internalization for accelerated clinical translation.

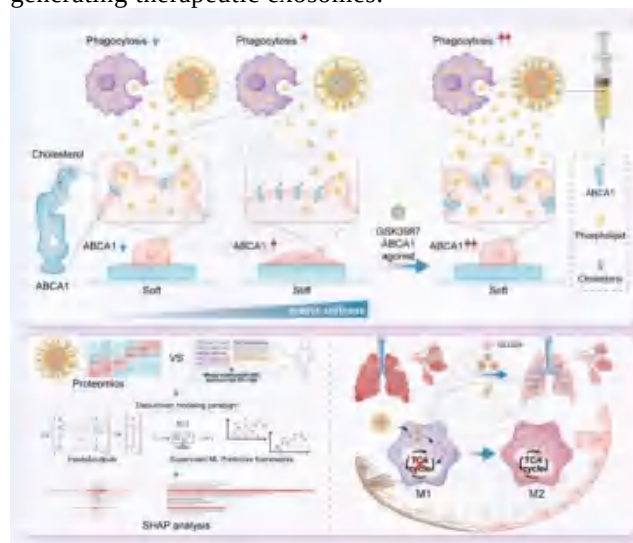
Materials & Methods: To investigate the mechanobiological regulation of exosome function, we fabricated polyacrylamide hydrogels with decoupled tunable stiffness and cultured human mesenchymal stem cells (MSCs) on these precisely engineered substrates. MSC-derived exosomes were systematically isolated and rigorously characterized utilizing dynamic light scattering, transmission electron microscopy, and advanced data-independent acquisition (DIA) proteomic profiling to elucidate their biophysical and molecular signatures. In vitro cellular assays, including quantitative real-time PCR, Western blotting, and confocal microscopy, were employed alongside machine learning-assisted bioinformatics to evaluate the cellular internalization and immunomodulatory effects of these exosomes on polarized macrophages. To experimentally validate our multi-omics predictions, we constructed and transfected GLOD4-overexpressing plasmids into both murine macrophages and TGF- β 1-induced human alveolar epithelial cells to assess target-specific phenotypic reversal. The in vivo biodistribution and therapeutic efficacy of the engineered vesicles were subsequently evaluated utilizing a bleomycin-induced murine pulmonary fibrosis model via intratracheal administration and real-time whole-animal fluorescence tracking. Final therapeutic outcomes were comprehensively confirmed through histological assessments of lung architecture, combined with extensive multiplex ELISA profiling of bronchoalveolar lavage fluid to quantify the resolution of the pathological inflammatory microenvironment.

Results & Discussion: Mesenchymal stem cell (MSC)-derived exosomes offer tremendous therapeutic promise, yet their clinical translation is hindered by a persistent trade-off where soft culture matrices yield abundant, highly immunomodulatory vesicles that unfortunately suffer from cholesterol-deficient membranes and poor cellular internalization. Through systematic transcriptomic screening and decoupled hydrogel platforms, we identified the ATP-binding cassette transporter A1 (ABCA1) as a pivotal

mechanosensor that directly links extracellular matrix stiffness to intracellular lipid metabolic reprogramming and exosomal cholesterol efflux. We demonstrated that while stiff matrices promote ABCA1-mediated cholesterol enrichment for superior cellular uptake, they concurrently compromise exosome secretion yield and the intrinsic quality of the anti-inflammatory payload. To surmount this biomechanical dichotomy, we developed a novel mechano-chemo-transductive strategy combining the high-yield, soft-matrix culture of MSCs with pharmacological ABCA1 agonism to non-invasively elevate exosomal membrane cholesterol. This combinatorial reprogramming successfully restored the macrophage delivery efficiency of soft-matrix exosomes to levels comparable to their stiff-matrix counterparts, fully unleashing their robust immunomodulatory potential. By integrating human clinical transcriptomics with machine learning algorithms, we further identified Glyoxalase Domain Containing 4 (GLOD4) as the critical functional cargo within these engineered exosomes, acting as an inflammation-responsive molecular switch. In a bleomycin-induced pulmonary fibrosis model, these mechanochemically-reprogrammed exosomes exhibited prolonged pulmonary retention and profoundly reversed fibrotic progression by resolving macrophage-driven inflammation and arresting alveolar epithelial-mesenchymal transition. Ultimately, this multidimensional engineering paradigm successfully resolves the critical production-delivery bottleneck, offering a translatable blueprint for maximizing the clinical efficacy of exosome-based nanomedicines in treating refractory fibrotic diseases.

Conclusions: In summary, we have unveiled the pivotal role of ABCA1 in governing the stiffness-dependent regulation of exosomal lipid composition and internalization efficiency. Capitalizing on this mechanism, we devised a combinatorial engineering strategy integrating soft matrix culture with chemical agonism to overcome the inherent trade-off in natural exosomes, characterized by a dichotomy between cargo potency and delivery efficiency. This mechanochemically-reprogrammed approach yielded engineered exosomes with robust pulmonary retention and potent immunomodulatory activity. Moreover, advanced machine learning analysis of clinical datasets pinpointed GLOD4 as the indispensable therapeutic payload enriched within soft matrix derived exosomes responsible for abrogating macrophage inflammation and reversing epithelial-mesenchymal transition. Collectively, our study presents a paradigm shift from passive isolation to rational exosome reprogramming, and offers a potent non-invasive therapeutic modality for a broad spectrum of fibrotic pathologies that reconciles yield biological activity and target cell uptake (Figure 1)

Fig. 1. Schematic illustration of the mechano-chemo-transductive engineering strategy for generating therapeutic exosomes.



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Constructing targeted organic nanoparticles via supramolecular pre-assembly guided disulfide exchange polymerization

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Polymerization-induced self-assembly (PISA) enables the construction of multicomponent polymers but typically requires harsh conditions and yields nondegradable C–C backbones.¹ In contrast, supramolecular assembly proceeds under mild conditions yet suffers from limited stability in complex environments. Developing a strategy that combines structural stability with controllable multicomponent assembly under aqueous conditions remains challenging. Herein, we report a supramolecular preassembly-guided disulfide exchange polymerization strategy for the controlled construction of structurally defined multicomponent polymers. Functional monomers are first organized into ordered aggregates through supramolecular interactions, followed by dynamic disulfide exchange to stabilize the assemblies via covalent linkage while enabling continuous regulation of nanoparticle size. Molecular dynamics simulations reveal stable aggregate formation in water and identify a pronounced S–S distance peak at ~0.6 nm, corresponding to a pre-reactive contact state that facilitates disulfide exchange. Using methylene blue and mannose as model components, we prepared size-tunable bifunctional polymeric nanoparticles exhibiting macrophage-targeting capability and photodynamic antibacterial activity, achieving efficient intracellular bacterial eradication. This strategy provides a mild and programmable platform for constructing multifunctional polymer nanomaterials through dynamic covalent chemistry integrated with supramolecular preorganization.

Key words: Self-assembly, Disulfide exchange, Molecular dynamics simulation, Nanoparticles

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Additively Manufactured Magnesium Alloy Scaffolds with Tailored Degradation Kinetics for Bone Defect Repair

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Key words: Bone regeneration; Magnesium alloy; Additive manufacturing; Degradation kinetics; Immunomodulation.

Introduction: The quantitative influence of magnesium alloy degradation kinetics on bone regeneration remains inadequately elucidated, and the host response at the material-bone interface necessitates comprehensive investigation. This study engineered magnesium alloy scaffolds with tunable degradation profiles to delineate the intrinsic relationship between degradation behavior and osteogenic efficacy.

Materials & Methods: Porous magnesium alloy scaffolds exhibiting fast, moderate, and slow degradation rates (designated as LP, MP, and HP groups, respectively) were fabricated via additive manufacturing through modulation of printing power. Comprehensive materials characterization, in vivo implantation in rabbit femoral condyle defects, proteomic profiling, and in vitro cellular assays were systematically conducted.

Results & Discussion: HP-Mg exhibited uniformly refined grains with diminished secondary phases, conferring superior corrosion resistance. In vitro degradation coupled with finite element analysis demonstrated that HP-Mg scaffolds provided enhanced mechanical strain distribution and degradation resistance, establishing a structural template permissive for cellular adhesion. In vivo, HP-Mg maintained superior mechanical integrity and facilitated robust bone regeneration. Proteomic analysis revealed enrichment of mechanotransduction and immunomodulatory cascades. In vitro, HP-Mg potentiated BMSCs adhesion and stress fiber formation via pFAK activation and YAP nuclear translocation, promoting osteogenic and pro-angiogenic phenotypes; pathway inhibition attenuated osteogenic differentiation.

Conclusions: Slow-degrading HP-Mg scaffolds achieve synchronized coupling between degradation, mechanical support, and bone regeneration through mechano-transduction-mediated osteogenesis and angiogenesis. This work establishes a "mechanical-chemical-biological" paradigm for engineering next-generation bone repair biomaterials.

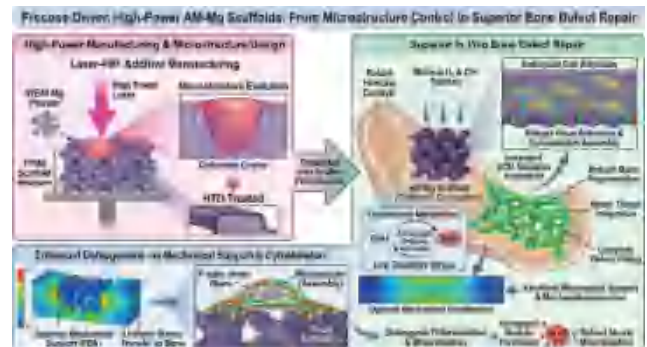


Fig. 1. Laser power-driven AM-Mg scaffolds: From microstructure control to superior bone defect repair.

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Study on the Photothermal-Immunological Synergistic Therapeutic Effects of IFN- γ Aptamer-Modified Silk Fibroin Hydrogel for Diabetic Wounds

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Abstract

The healing of diabetic wounds faces enormous challenges due to the dysfunctional microenvironment caused by drug-resistant bacterial infection,insufficient angiogenesis and excessive inflammatory factors.This project proposes "targeted antibacterial,intelligent anti-inflammatory,and pro-angiogenic" triple-pronged strategy.This study innovatively introduces IFN- γ aptamer and photothermal Cypate into silk fibroin (SF) to construct multifunctional DNA-SF hydrogels with dual network to target IFN- γ /TNF- α .This smart system dynamically releasing Cypate can kill E.Coli and S. aureus effectively by synergistic photothermal effect and precisely capture dual inflammatory factors (IFN- γ /TNF- α) inhibit LPS-induced L929 cells to apoptosis, and induces macrophage M2 polarization.This project aims to achieve intelligent materials by modifying SF with aptamers and enables multi-target synergistic regulation to increase wound healing from passive repair to active modulation.This will provide a new paradigm for developing intelligent,responsive tissue regeneration materials targeting multiple inflammatory factors.

Key words:Cypate;IFN- γ Aptamer;Silk Fibroin; IFN- γ /TNF- α .

Nanodots-mediated mitochondrial biogenesis intervening fibroblasts senescence for idiopathic fibrotic pulmonary therapy

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Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal interstitial lung disease characterized by repetitive alveolar epithelial cell injury, aberrant fibroblast activation, and excessive extracellular matrix deposition. Current therapeutic options remain limited with only two FDA-approved drugs showing modest survival benefits but unable to reverse disease progression. This study investigates the role of fibroblast senescence in IPF pathogenesis and develops innovative iridium-based nanodots (Ir-NADs) to counteract this process through mitochondrial biogenesis regulation. We established a bleomycin-induced pulmonary fibrosis model confirming p16-mediated senescence as a critical pathway in fibrogenesis. Transcriptomic analysis revealed profound alterations in mitochondrial function and cellular senescence pathways. The designed Ir-NADs exhibited exceptional reactive oxygen species scavenging capabilities and mitochondrial targeting properties. In vitro experiments demonstrated that Ir-NADs effectively reduced senescence markers in fibroblasts and improved mitochondrial function. In vivo therapeutic administration of Ir-NADs significantly attenuated bleomycin-induced pulmonary fibrosis, improved lung function parameters, and reduced collagen deposition. Mechanistic studies revealed that Ir-NADs promoted mitochondrial biogenesis through activation of the PGC-1 α pathway while inhibiting p16-mediated senescence. This dual-action mechanism positions Ir-NADs as a promising innovative therapeutic strategy for IPF treatment by simultaneously addressing mitochondrial dysfunction and cellular senescence.

Key words: idiopathic pulmonary fibrosis, fibrotic pulmonary, nanodots

Trigger and Purge: A Pyroptosis-Senescence Coupling Strategy Followed by Senolytic Clearance for Colorectal Cancer Therapy

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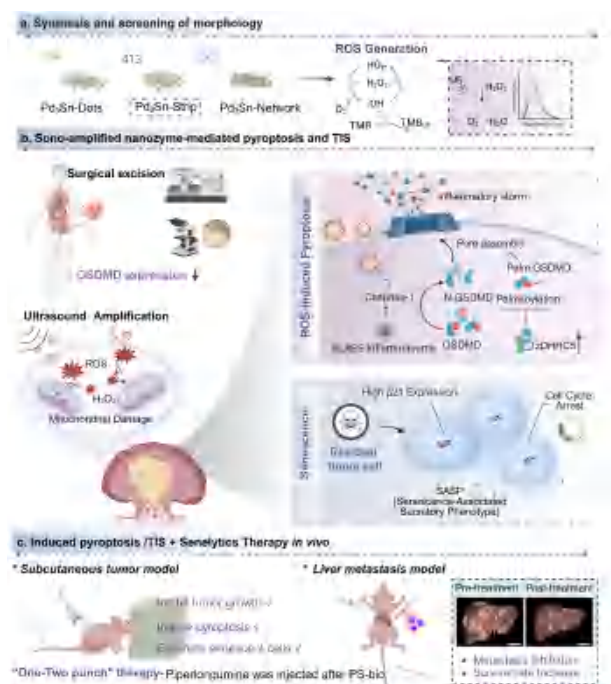
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Abstract

Pyroptosis is an inflammatory form of programmed cell death that can eradicate tumor cells and stimulate antitumor immunity. However, under sublethal oxidative stress, many cancer cells fail to complete pyroptotic execution and instead enter therapy-induced senescence (TIS), characterized by high p21 expression and a reinforced senescence-associated secretory phenotype (SASP) that fuels chronic inflammation and tumor relapse. Here, we develop an ultrasound-responsive Pd₃Sn-Strip nanozyme (PS-bio) and combine it with the senolytic agent piperlongumine (PL) to couple pyroptosis induction with senescent-cell clearance for colorectal cancer therapy. Notably, Pd₃Sn, as a topological semimetal intermetallic, provides intrinsically high electrical conductivity and robust charge-transport characteristics, which favor rapid redox cycling and efficient electron transfer during catalytic reactions; together with facet regulation, this electronic advantage amplifies multienzyme-mimicking catalysis under ultrasound. PS-bio exhibits superior oxidase-, peroxidase-, and catalase-like activities that are further boosted by ultrasound, enabling efficient H₂O₂ activation and broad-spectrum ROS generation. The resulting oxidative stress activates the NLRP3 – caspase-1 – GSDMD cascade and promotes zDHHC5-dependent S-acylation of GSDMD, thereby facilitating its membrane targeting and pore formation to execute canonical pyroptosis. Meanwhile, a fraction of surviving cells undergoes stable growth arrest with elevated p21, persistent DNA damage, and a pronounced SASP. PL selectively eliminates these senescent cells, markedly reducing SASP cytokines and mitigating the pro-tumorigenic consequences of TIS. Overall, this work establishes a “trigger-and-purge” strategy integrating an ultrasound-amplified topological-semimetal nanozyme with senolytic therapy to synchronize ROS-driven pyroptosis and TIS clearance, offering a promising approach for durable colorectal cancer treatment.

Key words: topological semimetal, Pd₃Sn nanozyme, ultrasound amplification, pyroptosis, senolytic therapy

Graphical abstract



Mechanism Study of Magnesium Alloy Endothelialization-Promoting Coating

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Key words: Magnesium alloy ; Endothelialization; Oxidative phosphorylation

Introduction: Biodegradable magnesium alloy stents are promising for cerebrovascular intervention, but their rapid degradation often compromises mechanical support and delays endothelialization. The effects of their degradation products on vascular repair remain unclear. This study investigates how coated magnesium alloy extracts influence HUVEC function and whether they regulate endothelialization via mitochondrial oxidative phosphorylation (OXPHOS).

Materials & Methods: HUVECs were cultured in coated magnesium alloy extracts. Cell proliferation was assessed by CCK-8. OCR and ECAR were measured using Seahorse analysis. Metabolite levels were quantified by ELISA. Transcriptomic and non-targeted metabolomic analyses were performed to identify changes in gene expression and metabolite profiles.

Results & Discussion: Magnesium alloy extracts significantly enhanced HUVEC proliferation and increased OCR. Multi-omics analysis revealed elevated levels of citrate, succinate, thiamine, and Lyso PC, indicating activation of mitochondrial OXPHOS.

Conclusions: Coated magnesium alloy degradation products promote endothelialization by activating OXPHOS, enhancing ATP supply, and supporting cell proliferation, migration, and angiogenesis.

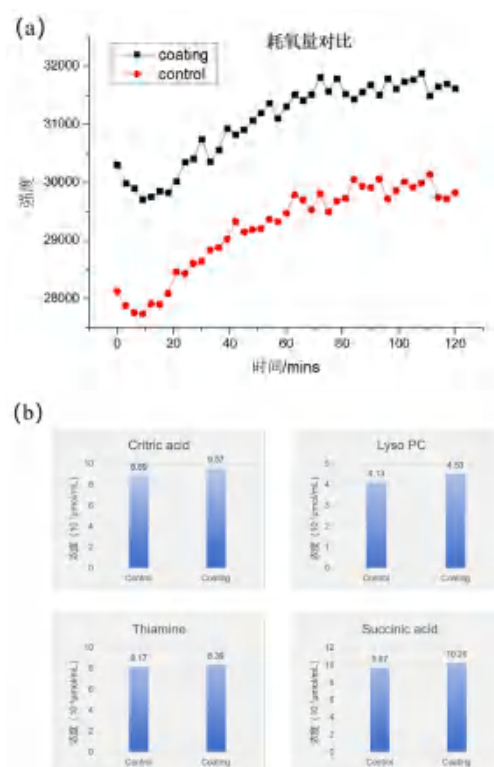


Fig. 1. HUVECs were cultured in conventional medium and coated magnesium alloy extracts : (a) Seahorse energy metabolism analysis showed a significantly increased OCR in the experimental group. (b) Elisa results revealed significant upregulation of key metabolites, including citrate, succinate, thiamine, and lysophosphatidylcholine (Lyso PC), in the experimental group.

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Metabolic osteoimmune biodegradable Zn-Mn alloys: high strength-ductility and in situ ascular-osteogenic coupling

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Key words: Biodegradable Zn alloy; Osteo/angiogenesis activity; PI3K/Akt signaling pathway, Bone defect repair; Genetics and proteomics

Introduction: Driven by the demand for sustainable, safe, and cost-effective medical materials, design of biodegradable metals increasingly aims to achieve higher strength and biofunctionality with less alloying. Addressing these challenges, this study aims to develop novel Zn-based alloy that integrates high strength-ductility, high strengthening efficiency (SE), and enhanced biofunctionality.

Materials & Methods: The design objective is to achieve YS > 350 MPa, SE > 5, and EL > 40%, while limiting the total content of alloying elements to less than 1 wt.% in Zn alloys. Beyond mechanical enhancement, the study focuses on systematically evaluating the antibacterial activity, angiogenic potential, and osteogenic capacity of the alloys through comprehensive in vitro and in vivo investigations. Furthermore, integrated genomics and proteomics approaches are employed to uncover the underlying biological mechanisms associated with their osteoimmunomodulatory behavior. This work is intended to provide a new strategy for designing next-generation Zn-based orthopedic implants with synergistic mechanical and biological performance.

Results & Discussion: Driven by the demand for sustainable, safe, and cost-effective medical materials, design of biodegradable metals increasingly aims to achieve higher strength and biofunctionality with less alloying. This study proposes a high strengthening-efficiency (high-SE) design strategy and develop novel Zn-0.8Mn-0.1Mg and Zn-0.8Mn-0.1Li alloys. With total alloying additions below 1 wt.%, these alloys achieve yield strength of 369~397 MPa, elongation of 42~57%, and remarkable strengthening efficiency (SE) of 6.4~6.8. These SE values represent the highest level among high strength-ductile Zn alloys (YS > 300 MPa, EL > 40%). Benefiting from the synergistic release of Zn²⁺, Mn²⁺, and Li⁺/Mg²⁺ ions, both the alloys exhibit superior antibacterial activity, cytocompatibility, controlled degradation rates, and *in vivo* osteogenesis, demonstrating excellent degradation-osteogenesis coupling effect. Notably, Zn-0.8Mn-0.1Mg further enhances osteogenesis by activating the PI3K/Akt/HIF-1 α signaling axis, which coordinates cascades of immunomodulation (e.g., IGF2, P2rx5), anti-inflammation (e.g., Nfkb α inhibition), and cellular energy metabolism (e.g., Ndufaf3), resulting in a more pronounced osteogenic effect. This work establishes

a new paradigm for high-efficiency alloy design, achieving simultaneous breakthroughs in mechanical and biofunctionality, offering a promising framework for next-generation Zn-based orthopedic implants.

Conclusions: This study demonstrates that a high-strengthening-efficiency (high-SE) design strategy, with total alloying elements below 1 wt.%, successfully overcomes the typical trade-offs in biodegradable metals: strength vs. ductility, antibacterial activity vs. cell viability, degradation rate vs. bone-implant contact. The developed Zn-0.8Mn-0.1Mg and Zn-0.8Mn-0.1Li alloys exhibit the highest SE values among Zn alloys with YS > 350 MPa and EL > 40%. *In vivo*, their degradation rates are 0.17~0.25 mm/y, bone implant contact rates are 76.3~74.2%, and new bone volume fractions reach 44.5~46.3%, exhibiting excellent degradation-osteogenesis coupling effects. Notably, Zn08Mn01Mg exhibits better osteogenic effect by activating the PI3K/Akt/HIF-1 α signaling pathway, which coordinates cascades of immunomodulation, anti-inflammation, and cellular energy metabolism. This work validates feasibility of the high-SE strategy for synergistically optimizing mechanical and biological functions in biodegradable metals. Leveraging its inherent advantages in cost, processability, and biosafety, this strategy sets a new direction for developing clinically translatable, next-generation Zn-based implants.

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Bio-Integrated Core-Shell Textiles for Passive Radiative Cooling and Self-Powered Thermoelectric Antibacterial Protection

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Key words: silk fibroin spheres, radiative cooling, thermoelectric antibacterial, coaxial electrospinning, personal thermal management

Introduction: With the accelerating pace of global warming and the increasing frequency of heatwaves, there is a growing need for energy-efficient personal thermal management (PTM) solutions. Conventional cooling systems such as air conditioning contribute significantly to global energy consumption and greenhouse gas emissions, highlighting the importance of developing sustainable alternatives. Among the various strategies, passive radiative cooling offers a promising zero-energy solution for regulating body temperature. However, integrating multiple functionalities such as cooling, antibacterial protection, and biocompatibility into a single textile material has remained a significant challenge. In this study, we present a bio-integrated coaxial electrospun textile consisting of a polyoxymethylene/bismuth telluride (POM/Bi₂Te₃) core and a cellulose/silk fibroin (Cel/SFS) shell. This textile successfully decouples the optical and thermoelectric functionalities, offering enhanced performance in passive cooling and antibacterial protection.

Materials & Methods: The textile was fabricated using a coaxial electrospinning method, where the core consisted of POM and Bi₂Te₃, and the shell was formed from a combination of cellulose acetate and silk fibroin spheres (SFS). The coaxial design allows for the functional and optical properties to be separated, with the core focusing on thermoelectric activity and the shell enhancing the textile's solar reflectance and MIR emissivity. The Bi₂Te₃ material was chosen for its excellent thermoelectric properties, which generate a reactive oxygen species (ROS) under the temperature gradient between human skin and ambient temperature. The Cel/SFS shell improves the textile's optical performance by increasing solar reflectance and maintaining high MIR emissivity, ensuring effective cooling. The fabrication process was carefully optimized to ensure good mechanical durability, biocompatibility, and air permeability.

Results & Discussion: The textile demonstrated impressive optical properties, achieving an average solar reflectance of 93.17% and an average emissivity of 93.39%. These values are crucial for enhancing passive cooling, allowing the textile to reflect solar radiation and emit excess heat efficiently in the mid-infrared spectrum. The POM/Bi₂Te₃ core was shown to generate a thermoelectric driving force, triggering the production

of ROS and exhibiting a 99.55% antibacterial efficiency against *Staphylococcus aureus*. Theoretical simulations and experimental results indicated that the textile's cooling power peaked at 102.55 W/m² during the day and 110.21 W/m² at night, offering a substantial reduction in temperature under both conditions. The outdoor tests confirmed a temperature drop of up to 5.161°C under sunny conditions and 4.614°C under cloudy conditions, outperforming conventional cotton fabrics. Furthermore, the textile retained excellent mechanical strength, with a significant improvement in deformation resistance compared to pure POM fibers. The microstructure, including micropores and mesopores, allowed for improved air and moisture permeability, ensuring comfort during wear.

Conclusions: This study introduces a new class of bio-integrated core-shell textiles that combine passive radiative cooling, self-powered thermoelectric antibacterial protection, and biocompatibility. The coaxial electrospun textile with a POM/Bi₂Te₃ core and a Cel/SFS shell effectively addresses the functional-optical coupling challenge by decoupling these properties. With outstanding passive cooling performance, a high antibacterial ratio, and favourable mechanical properties, this textile holds great promise for applications in personal thermal management, outdoor work, and medical protection. Moreover, its sustainable design, relying on bio-based materials and scalable production, supports the global trend toward environmentally friendly materials and energy-saving technologies. Future research will focus on optimizing the textile's washability, long-term durability, and expanding its applications in extreme environments and wearable medical devices.

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A Novel Strategy for Achieving Immunomodulation and Osseointegration of Titanium Alloys: Boron-Doped Porous Coating Modification

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Key words: Micro-arc oxidation, Hierarchical porous coatings, Boron incorporation, Immune regulation, Osseointegration

Introduction: Ti-19Zr-10Nb-1Fe (TZNF) is a β -type titanium alloy with excellent mechanical properties and biocompatibility [1,2]. To mitigate its surface bioinertness and the risk of aseptic loosening after implantation, the construction of surface topographies is essential [3]. Early inflammatory responses critically influence subsequent osseointegration, making it necessary to investigate the combined effects of such surfaces on macrophages and osteoblasts.

Materials & Methods: In this study, micro/nano-hierarchical porous coatings were fabricated on TZNF alloys via micro-arc oxidation. The surface morphology and chemical composition were characterized using SEM, AFM, XRD, and XPS. The physicochemical properties of the coatings were evaluated through scratch testing, tensile testing, microhardness measurements, and contact angle analysis. In vitro inflammatory responses and osteogenic performance were assessed using RAW264.7 and MC3T3-E1 cells, while in vivo inflammatory response and osseointegration were investigated using a rat femoral defect model.

Results & Discussion: The coatings were primarily composed of rutile and anatase TiO_2 , along with oxides of alloying elements and B_2O_3 . With increasing treatment voltage, the micro/nano pore size and surface roughness increased, while the chemical composition remained largely unchanged. The coatings exhibited strong adhesion to the substrate and improved surface hardness and corrosion resistance.

In vitro co-culture with RAW264.7 and MC3T3-E1 cells showed that the M300V hierarchical porous structure modulated inflammatory factor release, established a pro-osteogenic immune microenvironment, and

promoted osteoblast proliferation and differentiation. In vivo results further demonstrated that the M300V structure regulated the early inflammatory microenvironment and enhanced the long-term stability of the implant.

Conclusions: Please concisely state the conclusions and include recommendations for future study, and implications and significance of the data presented.

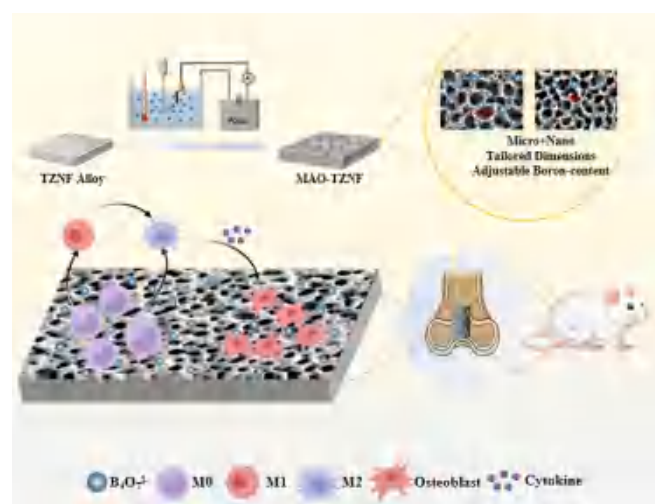


Fig. 1. Schematic illustration of TZNF with boron-doped hierarchical porous ceramic coating.

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Acknowledgments

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Osseointegration enhanced by the Ca-P absorption function of Zr element in the Mg alloy

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INTRODUCTION:

Enhanced osseointegration is crucial for improving the stability of implants and reducing the risk of infection, thereby contributing to the success rate of implant restorations. The ability of an implant to form hydroxyapatite on its surface after implantation is typically one of the key criteria for evaluating its osseointegration capacity. In this study, alloying was employed to introduce a dispersed distribution of Zr elements into the Mg alloy. Leveraging the strong adsorption effect of Zr elements on calcium ions and phosphate ions, the Mg alloys demonstrated autonomous adsorption of calcium ions and phosphate ions during degradation in simulated body fluids, alongside self-thickening of the surface hydroxyapatite layer.

METHODS:

The Mg-Zn-Nd-Zr alloy was cast at 690 °C and extruded with extrusion ratio of 64:1 at 390 °C.

Samples with a diameter of 10 mm and a thickness of 2.5 mm were machined by electrical discharge wire cutting with the radial direction of the specimen parallel to the radial direction of the extruded bar. The samples were suspended and immersed in Hank's solution at 37 °C. The ratio of Hank's solution to the surface area of the samples was 20 mL: 1 cm². The solution was replaced every 24 hours. The morphology of the corrosion products on the sample surface was observed by a scanning electron microscope (SEM, FEI Inspect F50) equipped with field emission energy dispersive spectroscopy (EDS).

RESULTS:

Fig.1 shows the corrosion product morphology of the Mg-2Zn-0.5Nd-0.5Zr alloy after immersion in Hank's solution for 28 days. A corrosion product layer consisting of numerous uniformly distributed spherical particles was observed on the sample surface. This layer was primarily composed of calcium phosphate salts and reached a thickness of up to 10.5 µm.

Table 1 presents the compositional analysis of the spherical corrosion products on the sample surface. The surface layer was found to be primarily composed of Ca, P, and O. The atomic ratio of Ca to P in the corrosion product layer was calculated to be 1.58, a value close to that of hydroxyapatite (1.67).

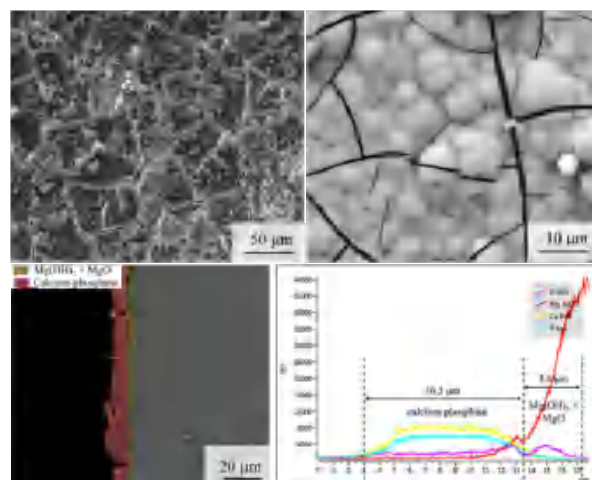


Fig. 1: Corrosion product morphology of the Mg-2Zn-0.5Nd-0.5Zr alloy after immersion in Hank's solution for 28 days.

Table 1. The compositional analysis of the spherical corrosion products on the sample surface.

	C	O	Mg	P	Ca
wt%	11.50	35.12	3.59	16.35	33.44
at%	20.55	47.08	3.16	11.32	17.89

DISCUSSION & CONCLUSIONS:

Metal oxides and hydroxides bind water molecules in aqueous solution and undergo decomposition of water complexed on the surface to form surface hydroxyl groups. Surface hydroxyl groups can complex with anions or cations in solution, resulting in adsorption. ZrO₂ is a strong adsorbent, showing strong adsorption effects on calcium ions and phosphate ions in aqueous solution [1, 2]. The incorporation of dispersed Zr-containing nanophases into the magnesium alloy, which upon oxidation generates ZrO₂, enhances the adsorption of calcium and phosphate ions, leading to the formation of a uniform hydroxyapatite layer on the surface.

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Two-dimensional FeCu-Metal-Organic-Framework Boosts Peroxidase Activity for Antibacterial Application

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Introduction: The overuse of antibiotics results the presence of drug-resistant bacteria, which seriously threatens life and health and leads to medical burden. Metal-organic frameworks (MOFs) possess great potential to replace biological enzymes for antibacterial purposes, but suffer from low density of active sites. Herein, we develop a new class of confinement growth technology for constructing two-dimensional (2D) MOFs nanosheets (NH₂-BDC-Cu, Fe NSs, BDC) with high active site exposure ratio for significantly enhancing reactive oxygen species (ROS) production, promoting the antibacterial efficiency of drug-resistant bacteria. Experimental shows that the as-made 2D NH₂-BDC-Cu, Fe NSs exhibits 6.6-folds higher than that of NH₂-BDC-Cu, Fe nanopowders (NPs) for the ROS production. Thus, NH₂-BDC-Cu, Fe NSs possess the excellent antibacterial kinetics of 100% for both *Staphylococcus aureus* (*S. au*) and *Escherichia coli* (*E. coli*) in 1 h, which is significantly higher than that NH₂-BDC-Cu, Fe NPs and biomaterials reported before. The in vivo experiments exhibit that NH₂-BDC-Cu, Fe NSs promote the wound healing, as confirmed with a wound healing rate of 100 % on 10 days, which is obviously higher than that of NH₂-BDC-Cu, Fe NPs. Overall, this work proposes a new strategy of constructing NH₂-BDC-Cu, Fe NSs for increasing the antibacterial efficiency, which brings the significant promise for developing advantage catalyst with high antibacterial performance.

Materials & Methods: 0.192g CuSO₄ and 0.336g FeSO₄·7H₂O were added into the mixed solution of dimethylformamide (10 mL) and H₂O (5mL), followed by ultrasonic dispersion for 10 min. Subsequently, 20 mg of hexadecyl trimethyl ammonium bromide and 0.217 g of 2-aminoterephthalic acid were added into the above solution. The mixed solution was further sonicated for 10 min. And then, the coordination reaction was carried out under 120°C for 10 h. Finally, the precipitate was obtained by filtration and washing with water.

Results & Discussion: Through a confinement growth strategy, bimetallic MOFs nanosheets (NH₂-BDC-Cu, Fe NSs) were synthesized, which increases the number of active sites and exhibits high efficiency of the •OH production. The Density Functional Theory (DFT) calculations shows that the Fe element is the adsorption site of H₂O₂, while the introduction of Cu element promotes the desorption of •OH from catalytic surface.

NH₂-BDC-Cu, Fe NSs possess the excellent antibacterial kinetics for *S. au* and *E. coli* in vitro by triggering oxidative stress induced disordered metabolic process and intracellular stress. NH₂-BDC-Cu, Fe NSs could effectively eliminate bacterial infection, hence reduce inflammation and accelerate wound healing, which are remarkably superior to NH₂-BDC-Cu NSs, NH₂-BDC-Fe NSs and NH₂-BDC-Cu, Fe NPs.

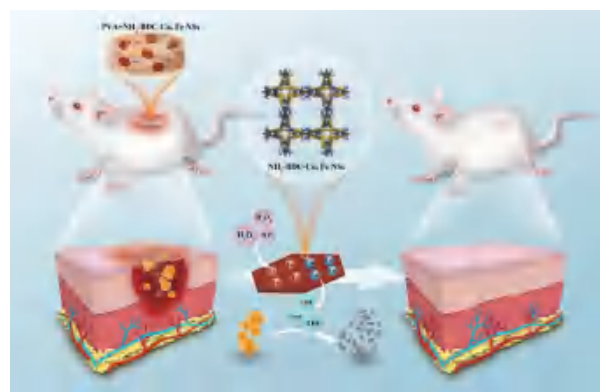


Fig. 1. The principle of NH₂-BDC-Cu, Fe NSs for the infected skin defect treatment.

Conclusions: This work brings a new method for the self-assembly of NH₂-BDC-Cu, Fe NSs nanoenzyme with high exposure rate of active sites for the purpose of increasing the ROS formation kinetics, which further promote the antibacterial efficiency. The research findings offer the significant promise for developing biomaterial-based solutions for tissue anti-infection.

Key words: metal-organic frameworks, two-dimensional, self-assembly, antibacterial, wound healing

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Zn ion-implanted absorbable Fe for accelerated degradation and mitigated neointimal hyperplasia

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Key words: Iron, Zinc, Biodegradable, Ion implantation, Neointimal hyperplasia

Introduction: In recent years, Fe-based stents have achieved significant progress in the field of vascular intervention. However, biodegradable pure iron degrades slowly, and the biocompatibility at the cell-material interface still needs to be further improved.

Materials & Methods: In this study, a functionalized Zn/Fe surface was fabricated by ion implantation. The corrosion mechanism was elucidated through electrochemical measurements and long-term immersion tests. In vitro cell experiments were conducted to simulate the material-cell interface and to evaluate the beneficial effects of the co-release of Zn and Fe ions. In vivo corrosion behavior and neointimal response were assessed using a rat carotid artery (CCA) implantation model.

Results & Discussion: The Zn/Fe surface exhibited a three-layer structure from the exterior to the interior. The outermost layer was an O-rich layer (5–8 nm), containing multiphase oxides. The subsurface layer was a Zn-rich implanted layer (50–70 nm), in which nanoscale Zn was uniformly dispersed within the Fe matrix, forming numerous Zn–Fe micro-galvanic cells. The innermost region was a radiation-affected zone characterized by a high density of deep dislocations.

This structure resulted in a staged corrosion behavior. At the initial stage of corrosion, Zn–Fe galvanic corrosion occurred, leading to the release of Zn^{2+} with antioxidant effects. This process provided a favorable microenvironment for vascular repair. The release of trace amounts of Zn^{2+} reduced the sensitivity of endothelial cells to high concentrations of Fe^{2+} , thereby alleviating oxidative stress and promoting endothelial cell adhesion and proliferation.

During the late stage of corrosion, the radiation-affected zone exhibited a high electrochemical driving force due to its high defect density. Consequently, Zn/Fe maintained long-term corrosion sensitivity. After immersion for 7, 30, and 120 days, the corrosion rates were 7.4, 5.4, and 3.1 times higher than that of pure iron, respectively.

The biological responses of Zn/Fe were evaluated using a rat CCA model. The Zn/Fe group exhibited a mild inflammatory response, and the endothelialization rate was comparable to that of pure iron. Notably, Zn/Fe significantly reduced neointimal hyperplasia. The lumen loss rate decreased by 36.1% compared with pure iron after 56 days of implantation.

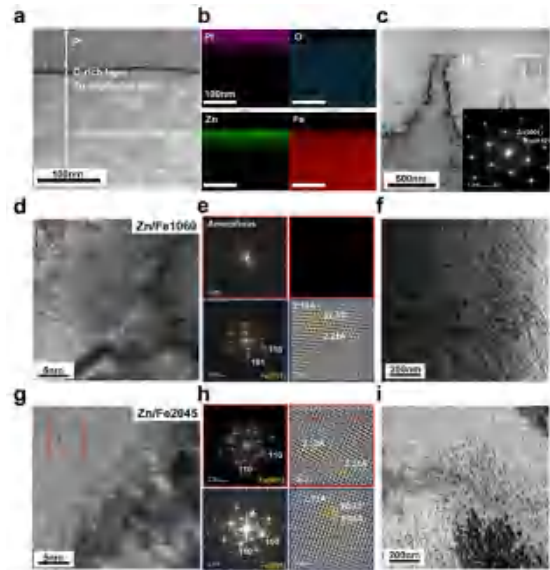


Fig. 1. High-resolution transmission electron microscopy characterization of Zn/Fe.

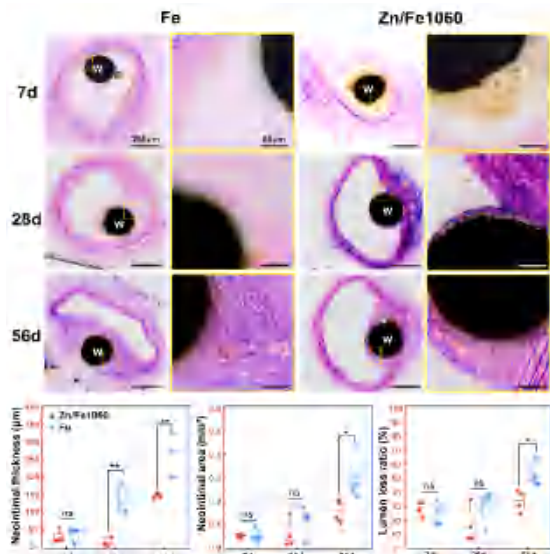


Fig. 2. H&E staining and quantitative results of neointimal hyperplasia in the CCA of rats after Zn/Fe implantation

Conclusions: Zn ion implantation is an effective method for increasing degradation rate and improving biocompatibility of absorbable pure Fe, providing valuable insights for the development of novel functionalized iron-based medical device scaffolds.

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Antibacterial Efficacy and Molecular Mechanisms of Cobalt Porphyrin-Mediated Sonodynamic Therapy Against Anaerobic Bacteria

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In this study, cobalt porphyrin was investigated as a sonosensitizer for sonodynamic therapy (SDT) against anaerobic bacteria. The antibacterial efficacy of cobalt porphyrin-mediated SDT was evaluated under ultrasonic irradiation, and the underlying molecular mechanisms were systematically explored.

Key words: cobalt porphyrin, anaerobic bacteria, sonodynamic therapy

Introduction: SDT is a noninvasive therapeutic modality. However, the hypoxic microenvironment within deep infection sites suppresses ROS generation, thereby compromising the therapeutic efficacy of SDT. Porphyrin-based compounds are employed as sensitizers owing to their excellent ROS-producing capacity. Among them, cobalt porphyrins possess unique redox properties and catalytic activities, making them promising candidates for SDT applications. Nevertheless, their antibacterial activity against anaerobic bacteria and the molecular mechanisms remain poorly explored.

Materials & Methods: Cobalt porphyrin (CoP-4) was synthesized using standard metalloporphyrin coordination methods, while zinc porphyrin (ZnP-4) was used as a control.

Results & Discussion: CoP-4 exhibited characteristic porphyrin absorption and concentration-dependent GSH consumption, unlike ZnP-4. It also mediated H_2O_2 -derived radical generation, confirming dual oxidase/peroxidase-like activity. EPR and UV-vis results further verified the CoP redox cycle and key intermediate, thereby sustaining catalytic cycle. Under ultrasound, CoP-4 generated substantial levels of ROS. Consequently, CoP-4+US induced bacterial oxidative damage and potent in vitro antibacterial activity. In addition, it effectively alleviated *P. gingivalis*-infected periodontitis in the rat model, validating its therapeutic efficacy.

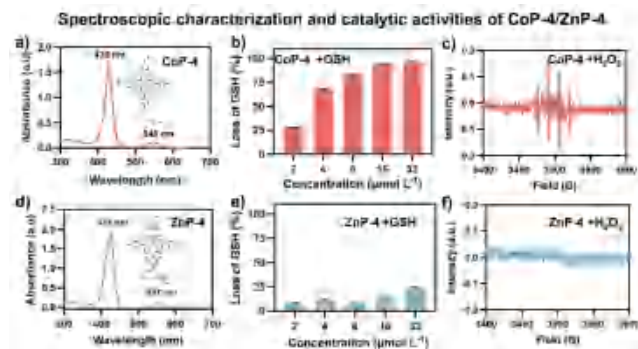


Fig. 1. (a,d) UV-vis spectra, (b,e) GSH consumption, and (c,f) EPR of H_2O_2 -induced radicals of CoP-4/ZnP-4.

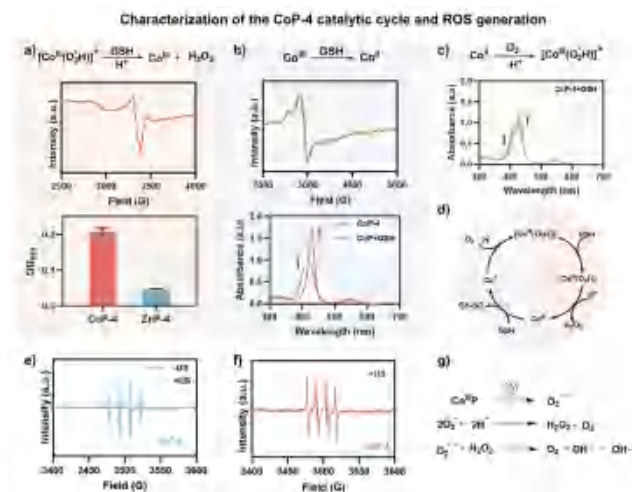


Fig. 2. (a-d) Proposed catalytic cycle of CoP-4. (e, f) EPR spectra of ROS generated by ZnP-4 and CoP-4 under ultrasound. (g) Proposed reaction pathways for ROS generation by CoP-4.

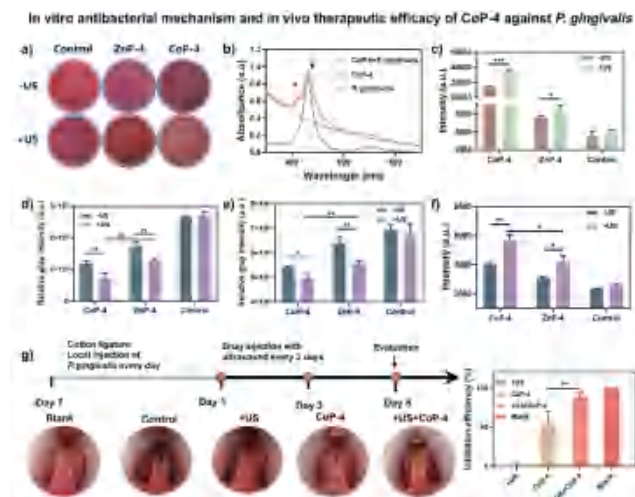


Fig. 3. (a) Antibacterial activity of control, ZnP-4, and CoP-4 with or without US. (b) UV-vis spectra of CoP-4 in the presence of *P. gingivalis*. (c-f) Intracellular ROS, DNA damage, protein damage, and membrane damage in treated bacteria. (g) In vivo treatment schedule, representative images, and inhibition efficiency.

Conclusions: In summary, the catalytic activities of CoP-4 were characterized, and its antibacterial mechanism against *P. gingivalis* was elucidated. In contrast, ZnP-4 lacks comparable redox catalytic activity. These results support the potential of CoP-4 as a sonosensitizer for the treatment of periodontitis.

Engineering An Ultrathin, Self-Assembled Supramolecular Coating for Long-term Corrosion Modulation of Biodegradable Mg

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Key words: Biodegradable Mg, supramolecular coating, ultrathin coating, corrosion modulation

Introduction: Biodegradable Mg is a promising lightweight metallic material with high reactivity, yet its rapid corrosion in aqueous environments severely limits practical applications. Although surface coatings are widely employed for corrosion control, constructing an ultrathin, compact, and stable protective layer on highly reactive Mg surfaces remains challenging. In this work, an ultrathin supramolecular self-assembled coating was developed through a high-throughput screening-guided strategy to improve corrosion modulation and enhance interfacial electrochemical stability.

Materials & Methods:



Fig. 1. Synthesis of Supramolecular Self-assembled Coating

Phenolic compounds can form supramolecular coatings through self-assembled deposition in the presence of catalysts, under base-catalyzed conditions, or via photocatalysis. These coatings exhibit broad substrate adaptability and can uniformly cover a wide range of substrates.

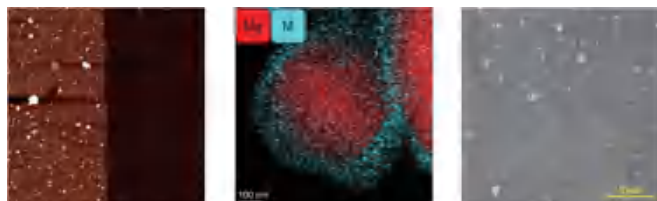


Fig. 2. Morphological characterization of the coating
AFM scratch measurements revealed that the single coating had a thickness of ~25 nm. TEM images further showed that the coating uniformly covered the Mg particles without inducing noticeable corrosion of the substrate, while SEM images revealed nanoparticles of different sizes distributed on the coating surface, suggesting a possible nanoparticle deposition mechanism.

Results & Discussion:

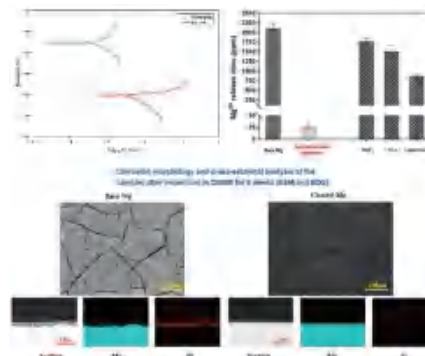


Fig. 3. Corrosion resistance analysis of the coating
The coating showed a higher corrosion potential and lower corrosion current density than bare Mg. Immersion, SEM, and EDS results further confirmed its excellent corrosion resistance during both short-term and long-term exposure.



Fig. 4. *In vitro* and *in vivo* evaluation

Live/Dead staining showed good cytocompatibility of the coated Mg compared with bare Mg. *In vivo*, OCT and XRM analyses further demonstrated good bioefficacy, no obvious restenosis, and markedly suppressed degradation after 3 months.

Conclusions: In summary, the supramolecular coating formed a uniform ultrathin layer on Mg, providing enhanced corrosion resistance. Both *in vitro* and *in vivo* results demonstrated good cytocompatibility, favorable bioefficacy, and suppressed degradation, highlighting its potential for biodegradable Mg-based implants.

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Potential of Biodegradable Magnesium Alloys for Large Bone Defects Treatment

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Key words: magnesium alloy, biodegradation, bone, osseointegration.

Introduction: Regenerative medicine based on Mg alloy implants is considered a modern approach to address bone defects. It represents a promising alternative to traditional grafting strategies by potentially mitigating complications such as limited supply [1].

Also, devices made by biodegradable magnesium alloys could be potential solutions in case of large bone defects due to their tunable biodegradation and better mechanical properties than currently used bioceramics or biocomposites.

In line with this global topic, attention is devoted to an innovative manufacturing route for biodegradable structures made by magnesium alloys for the treatment of large bone defects [2,3].

The mechanical properties, biodegradation in simulated body fluids, surface properties, and cytotoxicity were evaluated to determine whether the developed structures are suitable for consideration as future solutions for large bone defects.

Materials & Methods: Experimental research on various biodegradable magnesium alloys will be presented. The first approach will follow their chemical composition and microstructural aspects, following by biofunctional testing in order to identify their degradation pattern and their mechanical properties. Also, different solution for modulate their biodegradation by surface modifications and coatings with bioceramics and biocomposites will be presented. The geometry for the biodegradable structure was designed based on Autodesk Inventor® Professional 2021 [4]. Final evaluation of the new designed biodegradable structure was made on cell cultures and animal testing.

Results & Discussion: From a technical point of view, by analyzing mechanical suitability, one can immediately conclude that the new biodegradable structure exhibited superior behavior compared to the simple implant, as they minimized the stress-shielding effect. Structure exhibit mechanical properties much closer to that of human bone (131–205 MPa), a fact that proved an important design feature and the possibility of adjusting the structure's mechanical properties to match those of natural bone. A comparison with advantages and disadvantages of all synthesized materials will also

be presented.

Conclusions: Three-dimensional magnesium-based structures are considered an important step because they can have precise bone defect geometry, high porosity grade, anatomical pore shape, and mechanical properties close to the human bone. In addition, magnesium has been proven in in vitro and in vivo studies to influence bone regeneration and new blood vessel formation positively. We emphasized the microstructure, mechanical properties, biodegradation behavior, and biocompatibility of each study and made a basis for the researchers who want to start to apply the regenerative potential of magnesium-based structures in future biofunctional testing and future clinical trials.

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Bioinspired Fibrin-Trapping Microspheres Enable Supra-Physiological Clot Formation under High-Pressure Hemostasis

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Abstract: Rapid control of high-pressure hemorrhage requires fast fibrin and platelet capture. We develop hydroxyapatite(HAp)-modified gelatin microspheres (GHMPs-10) that enrich fibrinogen, recruit platelets and swell to occlude channels. GHMPs-10 withstand ~ 191.5 mmHg, shorten hemostasis time and reduce blood loss versus commercial powders, forming tough hydrogel clots with clear clinical translational potential.

Key words: gelatin microspheres, hydroxyapatite, fibrinogen recruitment, blood clot mechanics, high-pressure hemostasis

Introduction: Uncontrolled high-pressure bleeding is a major cause of death in surgery and trauma, where pulsatile pressure and high shear often prevent timely formation of stable clots.[1] An effective high-pressure hemostat should concentrate plasma proteins, enrich fibrinogen, recruit platelets, and provide a tough scaffold that resists shear.[2,3] Hydroxyapatite (HAp) combines protein adsorption with platelet activation,[4] suggesting that exposing HAp on gelatin microspheres could intensify fibrinogen capture and platelet adhesion while the gelatin matrix swells to compress and occlude channels. Here we design HAp-modified gelatin microspheres (GHMPs-10) to enrich fibrinogen, recruit platelets and red cells and form tough, elastic blood-material clots under high-pressure bleeding.

Materials & Methods: Gelatin-HAp microspheres were fabricated by water-in-oil emulsification, characterized by spectroscopy, microscopy, particle sizing, rheology and thermal analysis, and evaluated both in vitro and in rat bleeding models for coagulation performance, blood-cell and protein interactions, degradation, cytocompatibility, hemocompatibility and systemic biosafety.

Results & Discussion: Gelatin microspheres (GMPs) were prepared to give spherical, porous particles, then doped with 10 or 50 wt% HAp to obtain GHMPs-10 and GHMPs-50. Rheology at 37 °C showed that 10 wt% HAp increased storage modulus compared with GMPs, whereas excessive HAp (50 wt%) partially disrupted the gelatin network, indicating that GHMPs-10 provides the best balance between stiffness and integrity for resisting vascular pressure.

In vitro coagulation tests in calcified and anticoagulated whole blood demonstrated that all microspheres accelerated clotting versus blank controls, but GHMPs-10 achieved the lowest blood clotting index and complete clarification within 1 min. Inverted-tube and burst-pressure assays further showed that GHMPs-10 formed cohesive blood gels that remained intact for at

least 30 min and withstood ~ 191.5 mmHg, outperforming GMPs and GHMPs-50. Mechanistic studies revealed that GHMPs-10 selectively adsorbed fibrinogen and plasma proteins, exhibited a swelling ratio of $\sim 718\%$, and promoted dense adhesion of RBCs and platelets, thereby generating a tough, self-recovering composite clot. In rat liver, tail, and femoral artery injury models, GHMPs-10 significantly shortened hemostasis time, reduced blood loss, and promoted more orderly tissue repair than gauze or a commercial powder. Biosafety studies confirmed low hemolysis, minimal cytotoxicity, rapid in vivo degradation, and absence of systemic toxicity, supporting the translational potential of GHMPs-10 for managing high-pressure hemorrhage.

Conclusions: This study addresses high-pressure bleeding using GHMPs-10 that selectively capture fibrinogen and platelets while rapidly swelling to occlude channels, forming elastic blood-material clots that resist washout, shorten time, increase burst pressure, reduce blood loss, and are biosafe.

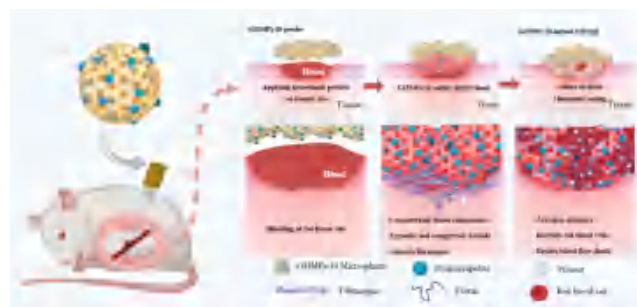


Fig. 1. GHMPs-10 are applied as a powder to bleeding wounds, rapidly absorb blood, and adhere as a hydrogel seal.

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A Biodegradable Janus Sponge for Negative Pressure Wound Therapy

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We developed a novel biodegradable, amphiphilic sponge with a Janus pore architecture for NPWT. The two-layer design features a dense, hydrophobic upper layer for mechanical support and a loose, hydrophilic lower layer for superior exudate absorption and moisture maintenance. The sponge provides broad-spectrum antibacterial activity. In a rat skin defect model, the sponge outperformed a commercial NPWT dressing by preventing tissue adhesion and significantly accelerating wound healing, demonstrating its promise as an advanced, multifunctional wound dressing.

Key words: Janus sponge, NPWT, Wound healing

Introduction: Negative pressure wound therapy is a prominent treatment, using suction to remove exudate and promote healing. Current clinical options primarily being porous polyurethanes. These can cause issues, such as tissue ingrowth leading to re-injury during dressing changes, and do not optimally support all wound healing phases. To address adhesion, dressings like PICO use a silicone membrane, but this can delay epithelialization. Multi-layer architectures have shown promise in better matching healing stages. Inspired by this, we developed a novel biodegradable Janus sponge for NPWT. The sponge features a dual structure: a dense, hydrophobic upper layer with small pores for protection and support under negative pressure, and an elastic, hydrophilic lower layer with large pores for high exudate absorption and maintaining a moist wound environment. The biodegradability eliminates painful, disruptive dressing changes in later stages. Silver sulfadiazine is incorporated for antimicrobial protection. This design aims to support the entire wound healing process in NPWT, as evaluated in a rat skin defect model.

Materials & Methods: A Janus sponge was fabricated for NPWT. The material was synthesized from PCL, PLLA and PEG via copolymerization with hexamethylene diisocyanate. The sponge was created by freeze-drying. It featured a dense, hydrophobic top layer and a porous, hydrophilic bottom layer. The sponges were loaded with antimicrobial silver sulfadiazine. Material properties were analyzed using FTIR, NMR, GPC, TGA, DSC, SEM, and mechanical tests. Sponge performance was then evaluated through a series of in vitro and in vivo experiments, including antibacterial assays, cytocompatibility tests, degradation studies, hemostatic assessment in a rat liver model, and a comprehensive in vivo wound healing study on full-thickness skin defects under NPWT, followed by histological and immunohistochemical analysis.

Results & Discussion: The synthesized biodegradable polyurethanes exhibited excellent mechanical strength,

thermal stability, and tunable hydrophilicity, showing optimal flexibility. Freeze-drying fabricated Janus sponges with a dense hydrophobic top layer and a porous hydrophilic bottom layer. These sponges demonstrated high porosity (~86%), superior fluid absorption (19.5x its weight), robust compression resistance, excellent cytocompatibility, and effective hemostasis. The sponges displayed potent antibacterial activity against *E. coli* and *S. aureus*. In a rat full-thickness wound model under negative pressure, the Janus sponge significantly outperformed a commercial PU foam. It accelerated wound closure, promoted collagen deposition and angiogenesis (increased CD31), reduced inflammation (decreased IL-6), and critically, prevented tissue adhesion and secondary injury during treatment due to its biodegradability, supporting the entire healing process.

Conclusions: We developed biodegradable amphiphilic Janus sponges for NPWT. Its dual-layer structure—a hydrophilic bottom for exudate absorption and a hydrophobic top for mechanical support—prevents tissue adhesion and eliminates traumatic dressing changes. The sponge demonstrates excellent biocompatibility, fluid uptake, and antibacterial activity. In vivo, it reduces inflammation, promotes angiogenesis, and significantly accelerates wound healing under negative pressure, showing great promise for clinical application.

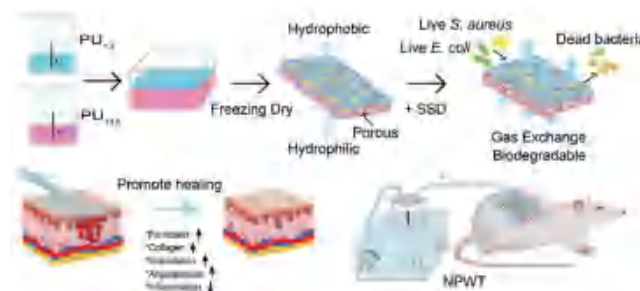


Fig.1. Schematic illustration of Bi@Janus bilayer sponge and the dressing application for NPWT in a full-thickness defect model.

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Development of a Novel Biodegradable and Self-Lubricating Double-J Ureteral Stent

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Abstract: Targeting the clinical challenge of ureteral strictures, this study developed a self-lubricating and biodegradable ureteral stent based on alternating ABA-PEG multiblock copolymers. By adjusting the PEG/ABA ratio, mechanical strength, surface lubricity, and degradation profiles could be tailored. This work offers a promising material strategy for next-generation ureteral stents with improved patient comfort and reduced need for secondary removal.

Key words: Ureteral stent, Biodegradation, Self-lubricating, Multiblock copolymers

Introduction: The double-J ureteral stent, a cornerstone in the management of ureteral obstruction and hydronephrosis, is nonetheless hampered by complications attributable to its permanent, non-degradable structure.^[1] The double-J ureteral stent is widely utilized in urological procedures but remains limited by complications arising from its non-degradable nature.^[2] Although biodegradable polymers such as PLA and PLGA have been explored as alternatives, their clinical application is often constrained by uncontrolled degradation rates and insufficient surface lubricity.^[3,4] To address these challenges, this study develops a self-lubricating, biodegradable stent based on ABA-PEG multiblock copolymers, which allow precise regulation of hydrophilic-hydrophobic balance and hydrolytic cleavage sites. The stent is fabricated via micro-precision extrusion, exhibiting tunable mechanical strength, enhanced lubricity, and controlled degradation behavior, thereby offering a promising strategy for next-generation ureteral implants with improved biocompatibility and functional performance.

Materials & Methods: ABA-PEG multiblock copolymers were synthesized through sequential ring-opening polymerization and polycondensation. Ureteral stents were fabricated via micro-extrusion and thermal molding. The mechanical properties, in vitro degradation, surface lubricity, and biocompatibility of the stents were systematically characterized.

Results & Discussion: The ABA-PEG multiblock copolymer was successfully synthesized via ring-opening polymerization followed by polycondensation. This material demonstrated excellent comprehensive properties, fully meeting the mechanical requirements for ureteral stents, with its tensile strength and elasticity conforming to clinical standards. Surface characterization revealed a significant reduction in the friction coefficient upon hydration, along with a low

water contact angle and a smooth surface morphology, indicating favorable hydrophilicity, lubricity, and potential resistance to bacterial adhesion.

Both in vitro/vivo biocompatibility assessments showed that the material elicited only a mild inflammatory response, confirming its good biosafety. Degradation studies indicated a near-linear mass loss profile in simulated urine, suggesting a controllable degradation process. Owing to its hydrophilic nature, the degradation fragments resisted aggregation and could be efficiently cleared by urine flow, effectively mitigating the risk of lumen occlusion. Furthermore, the material exhibited notable antibacterial activity against *E. coli* and *S. aureus* and significantly reduced calcification and stone formation in animal models.

Conclusions: In conclusion, this study demonstrates that the synthesized ABA-PEG multiblock copolymer exhibits notable improvements in mechanical strength, surface lubricity, controllable degradation, antibacterial activity, and resistance to encrustation. These properties collectively establish a solid material foundation for advancing the design of self-lubricating, biodegradable ureteral stents, showing promising potential for clinical application.



Fig. 1. Schematic illustration of a novel self-lubricating double-J stent with uniform degradation from surface to core

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Achieving Superadaptive Vascular Occlusion with Deformable Microspheres: An Ethanol-Triggered Embolization System

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Key words: embolization, polyurethane, embolic agent

Introduction: Transcatheter arterial embolization (TAE) is a cornerstone of interventional oncology, primarily aimed at blocking blood flow to diseased tissues by injecting embolic material into the target vessel via a catheter. However, conventional embolic agents, such as polyvinyl alcohol (PVA) microspheres, often lead to incomplete occlusion and vessel recanalization due to their rigid structure and inability to conform to the irregular vasculature of tumors, necessitating repeated interventions. To address this limitation, we developed a novel sequential embolization system. This study explores the unique property of polyurethane, which swells into a gel upon exposure to ethanol. By fabricating deformable microspheres and employing a synergistic physical-chemical embolization mechanism with ethanol, we achieved more complete and durable vascular occlusion.

Materials & Methods: Multiblock polyurethane (PU) was synthesized via step-growth polymerization, using poly(ϵ -caprolactone) (PCL) and poly(ethylene glycol) (PEG) as soft segments, linked by hexamethylene diisocyanate (HDI). The polymer was characterized by NMR and GPC. Microspheres were fabricated using an optimized emulsion-solvent evaporation method, with polyvinyl alcohol (PVA) as an emulsifier. Particle size distribution and morphology were analyzed via laser diffraction and scanning electron microscopy (SEM). The ethanol-response was quantified by measuring changes in storage modulus (G') and loss modulus (G'') with rheology, and morphological transformation was observed in vitro. Preliminary biocompatibility was assessed through hemolysis and cytotoxicity assays.

Results & Discussion: The synthesized PCL-PEG PU exhibited excellent film-forming and elastic properties. Microspheres with particle sizes ranging from 100 to 300 μm were successfully prepared using the O/W emulsion solvent evaporation method. These microspheres were spherical with a porous internal structure. Importantly, exposure to anhydrous ethanol triggered a rapid softening transition, with G' decreasing by over 70% within minutes, confirming their designed ethanol-responsive deformability. This allowed the microspheres to shift from a stable state for delivery to a highly compliant state for better vessel wall conformation. In vitro occlusion models showed that the sequential protocol—first deploying microspheres for mechanical blockage followed by ethanol

injection—resulted in a denser, gap-free embolic cast compared to microspheres alone. Ethanol not only plasticized the microspheres but also acted as a sclerosing agent, promoting vascular fibrosis for long-term occlusion. The material exhibited minimal hemolytic activity and acceptable cytotoxicity, indicating promising biocompatibility.

Conclusions: We have successfully developed a proof-of-concept, smart embolization system based on ethanol-responsive PCL-PEG PU microspheres. This system introduces a novel sequential treatment approach that combines the benefits of mechanical embolization and chemical sclerosis. The microspheres' unique ethanol-triggered deformability addresses the critical issue of poor vessel conformity associated with current agents. Future work will focus on comprehensive in vivo evaluation in established tumor embolization models to validate efficacy in preventing recanalization and inhibiting tumor growth.

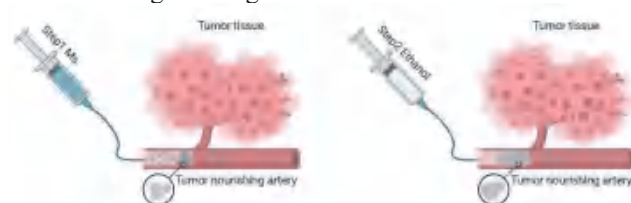


Fig. 1 Schematic of embolization for arterial

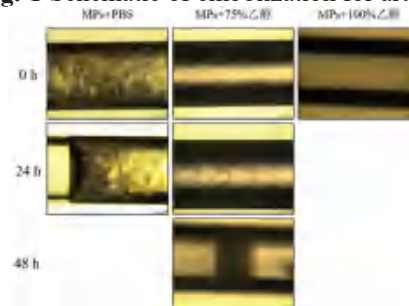


Fig. 2 The simulation of intravascular delivery of embolic microspheres in different solvents at 37°C

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Title: Synthesis and Applications of Supra-Natural β -Sheet-Based Polypeptides

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Key words: Spider silk, Bionic assembly, Supernatural β -sheet based polypeptides

Introduction: Synthetic polypeptide materials, sharing the peptide backbone with natural proteins, exhibit exceptional biocompatibility and tunable secondary structures, holding substantial promise for functional protein mimicry and biomedical applications¹. Especially, β -sheet-based polypeptides serve as fundamental building blocks that enable modular assembly of protein-like architectures and exquisite hierarchical materials². Research on their assembly holds critical significance in high-performance materials science³, functional nanomaterial engineering⁴, and mechanistic studies of protein folding and aggregation⁵. This represents the pivotal pathway for advancing from synthetic polypeptides to protein-mimetic architectures. However, how the β -sheet secondary structures undergo further assembly to form higher-order architectures remains largely unexplored. Moreover, current research on β -sheet peptide assembly remains confined to local-scale secondary structure modulation. For instance, modular construction of spider silk-mimetic proteins by linking multiple β -sheet sequences via covalent linkers has been attempted⁶. However, precise control over intermolecular packing, hierarchical organization, and crystal structures in these silk-like β -sheet architectures remains elusive. Additionally, studies have engineered precise side-chain modifications to stabilize multiple β -sheet motifs, enabling the construction of functional β -barrel-like architecture⁷. Other research utilizes local steric hindrance from side chains to suppress amyloid fibril transformation. However, these strategies suffer from limited sequence generality. The main challenge in β -sheet peptide assembly lies in achieving controllable manipulation of intramolecular and intermolecular hydrogen bonding across entire polypeptide structures. This is critical to prevent aggregation and amyloid fibrillization driven by β -sheet's inherent strong hydrophobicity and highly extended hydrogen-bonding networks, ultimately enabling modular and controllable assembly of β -sheet domains.

Materials & Methods:

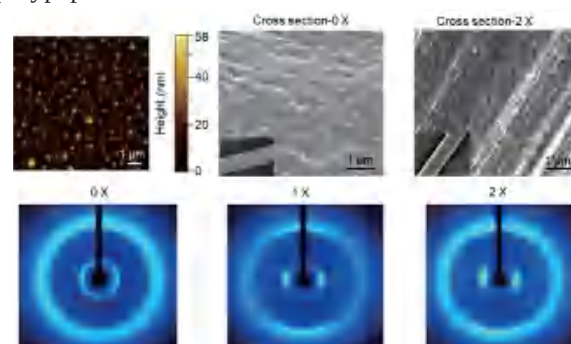
- (1) Synthesis and assembly behavior: Chemical synthesis pathways for linear and dendritic β -sheet polypeptides, self-assembly kinetics, and phase transition mechanisms;
- (2) Application performance validation: Functional evaluation of biomimetic nanochannels assembled from linear polypeptides and high-strength fibers derived from dendritic β -sheet polypeptides;
- (3) Experimental condition optimization: Regulation of structural formation by temperature/pH/solvent systems;
- (4) Structure-property correlation analysis: Multi-level

structural resolution via cryo-EM and X-ray scattering techniques to establish structure-performance relationships for mechanical/transport properties.

Results & Discussion: Viewed from the surface section of the fiber, bionic silk has a multi-scale hierarchical structure, and one fiber is composed of many microcosmic nanofibers. WAXD quantitatively confirmed that higher draw ratios enhance both crystallinity and structural uniformity of the fibers. The above results are microscopically consistent. SEM characterization revealed that the cross-section of unstretched samples (0X) exhibited disordered packing with irregular interfaces, showing no directional alignment. In contrast, the fibers with 2X stretch displayed further orientation along the drawing direction with denser, fused packing.

Conclusions: Synthetic polypeptides, featuring protein-like backbones, tunable secondary structures, and excellent biocompatibility, are ideal materials for biomimetic applications. Among them, β -sheet polypeptides serve as a key foundation for constructing high-performance materials, functional nanomaterials, and studying protein folding. However, the mechanism governing their precise assembly into higher-order structures remains unclear. Existing strategies suffer from limitations like poor sequence generality, aggregation propensity, and difficulty in achieving precise hierarchical assembly. To address this, we propose strategies like multiblock design and spherical initiator templates, achieving modular assembly by regulating intramolecular pre-organization and intermolecular stacking. This approach solves the critical challenge of balancing controllable β -sheet folding against abnormal aggregation. It holds promise for spider silk-mimetic fibers with controlled hierarchy, providing a new platform to bridge the gap between natural protein complexity and synthetic scalability

Fig. 1. The formation and crystal structure of β -sheet polypeptide fibers.



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Silk-Protein-Based Smart 3D Printing Manufacturing

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Oral presentation

Keywords: Silk material, Bioink, 3D printing, Vat polymerization

1. Introduction

Currently, the application of natural hydrogels in tissue engineering is constrained by their poor printability and limited ability to mimic the in vivo microenvironment. To address these challenges, this study explores silk fibroin as a model material, investigating its modification and composite processing strategies to enhance its printability and broaden its application scope via 3D printing technology. This study addresses the poor printability and limited biomimicry of natural hydrogels in tissue engineering by exploring silk fibroin as a model material. We focus on modifying and formulating photopolymerizable silk fibroin-based hydrogel inks for high-precision 3D printing. Using minimal surface designs, we fabricate structured soft tissue scaffolds and investigate how internal architectures influence scaffold performance. Our goal is to develop customizable biomimetic scaffolds with enhanced mechanical properties and permeability through synergistic regulation of material composition and topological design. Additionally, we examine the effects of hybrid hydrogel inks on printing accuracy and propose a novel precision evaluation method using ink-responsive light recognition over long distances. By optimizing energy input through work curve measurements, we aim to achieve high-resolution ($<100\ \mu\text{m}$) 3D fabrication of photopolymerized silk fibroin. Ultimately, this research advances the industrial translation of silk fibroin-based hydrogels for tissue engineering applications.

2. Results and discussion

In recent years, significant progress has been made in both three-dimensional (3D) printing technologies and the exploration of silk as an ink to produce biocompatible constructs. Combined with the unlimited design potential of 3D printing, silk can be processed into a broad range of functional materials and devices for various biomedical applications. The ability of silk to be processed into various materials, including solutions, hydrogels, particles, microspheres, and fibers, makes it an excellent candidate for adaptation to different 3D printing techniques. This review presents a didactic overview of the 3D printing of silk-based materials, major categories of printing techniques, and their prototyping mechanisms and structural features. In addition, we provide a roadmap for researchers aiming to incorporate silk printing into their own work by summarizing promising strategies from both technical and material aspects, to relate state-of-the-art silk-based material processing with fast-developing 3D printing technologies. Thus, our focus is on elucidating the techniques and strategies that advance the development of precise assembly strategies for silk-based materials. Precise printing (including high printing resolution, complex structure realization, and printing fidelity) is a prerequisite for the digital design capability of 3D printing technology and would broaden the application era of silk, such as complex biomimetic tissue structures, vasculatures, and transdermal microneedles.

Among the different 3D printing techniques, Digital Light Processing (DLP) exhibits the unique advantage of high printing precision. However it faces significant

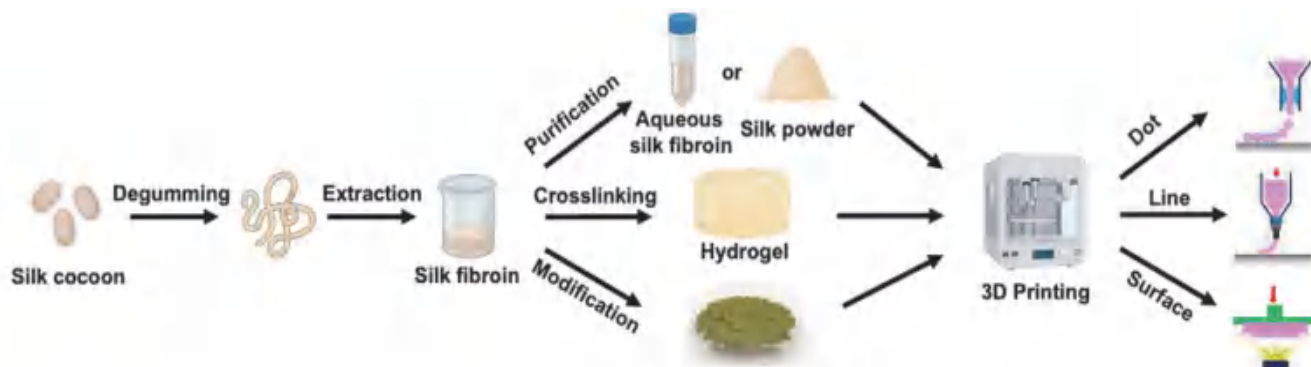


Figure 1 General methodologies for 3D printing of Silk-based materials [1].

challenges in printing ultra-soft hydrogels due to their weak mechanical properties and the lack of robust accuracy evaluation systems. Here, we overcome these limitations by introducing silk sericin (SS) - a protein recovered from alkaline thermal degumming water - as a sustainable bioink. Through glycidyl methacrylate (GMA) modification, we developed methacrylated silk sericin (SerMA) with enhanced curability while preserving its inherent biocompatibility. A "Height Gradient Screening" approach was innovatively applied to the Jacob's working curve, enabling precise determination of cured depth under real world printing conditions by addressing light scattering and self-focusing effects. Furthermore, we proposed the "Tangent Cylindrical Model", a novel framework to quantify localized printing errors across dynamic illumination source spacings, achieving resolutions as fine as 300 μm channel gaps and 400 μm hole structures-surpassing current capabilities for weak hydrogels. The printed SerMA constructs demonstrated excellent cytocompatibility (L929 cell viability >95 % over 168 h) and supported cell adhesion/spreading, validated via Live/Dead assays and F-actin staining. This work not only expands the DLP material library to include recovered, mechanically fragile proteins but also establishes a universal methodology for high-precision printing of soft biomaterials, with direct implications for tissue engineering, microfluidics, and biosensing.

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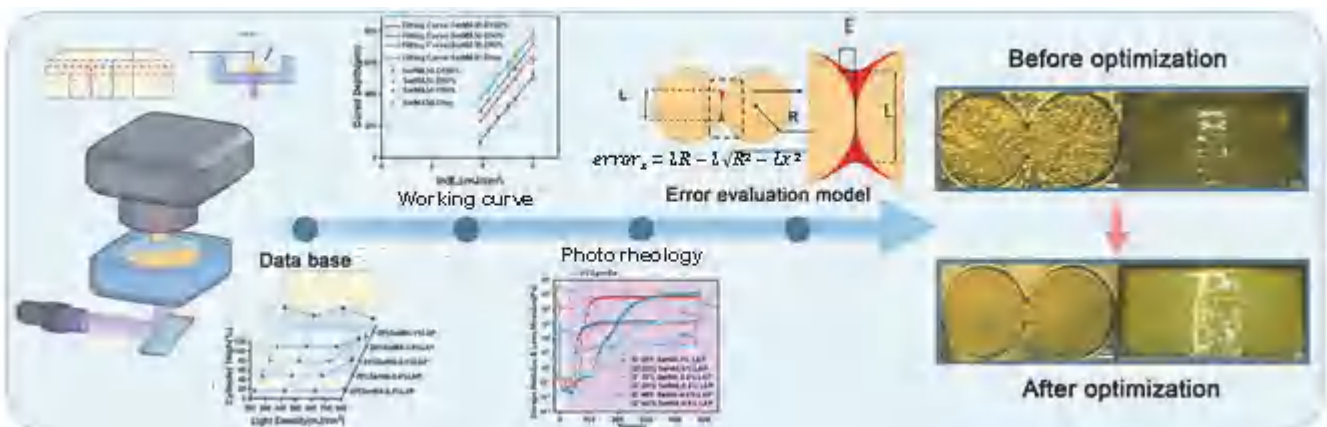


Figure 2 DLP printing strategy of Methacrylated silk sericin (SerMA) [2].

Tailored Biodegradable Copolymers with Random-Block Architecture for High-Performance Absorbable Tissue Ligation Clip

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Key words: tissue ligation clip, biodegradable, PLCL-b-PLLA copolymer, random-block architecture

Introduction: Tissue ligation clips are essential devices in laparoscopic surgery. Hem-o-lok clips are widely used, but their non-degradable polyoxymethylene requires either secondary removal or permanent implantation, increasing long-term foreign-body risks. Developing biodegradable polymers with an optimal balance of flexibility and strength would enable absorbable Hem-o-lok-shaped clips with significant clinical potential. Poly(L-lactide-r-ε-caprolactone)-b-poly(L-lactide) copolymer (PLCL-b-PLLA) with a combined random-block architecture is designed to achieve a comprehensive balance between mechanical strength and flexibility. The tissue ligation clips of PLCL-b-PLLA are expected to exhibit both good rebound ability and strong closure force, while their absorbable nature enables swift removal of pathological tissues and gradual degradation during the healing process.



Fig. 1. Schematic of the material design and application of the novel absorbable tissue ligation clip.

Materials & Methods: PLCL-b-PLLA copolymers with varying monomer ratios were synthesized via two-step ring-opening polymerization using L-lactide and ε-caprolactone. Tissue ligation clips were fabricated by injection molding.

Results & Discussion: ¹H-NMR and FTIR spectra confirmed the presence of both random and block

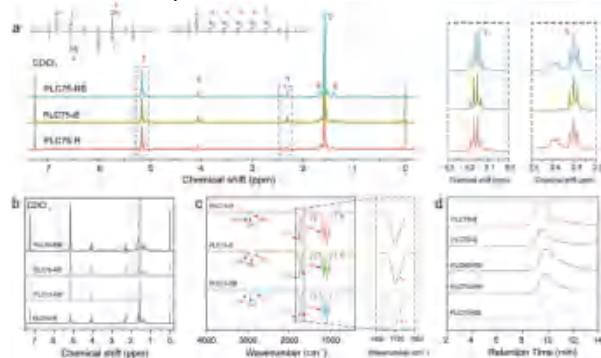


Fig. 2. The characterizations of PLCL-b-PLLA.

structures in the PLCL-b-PLLA copolymer, as evidenced by characteristic peak splitting and absorption bands. Each GPC profile displayed a single and well-defined peak, indicating the single polymer species rather than blends. These results confirmed the successful synthesis of PLCL-b-PLLA copolymers.

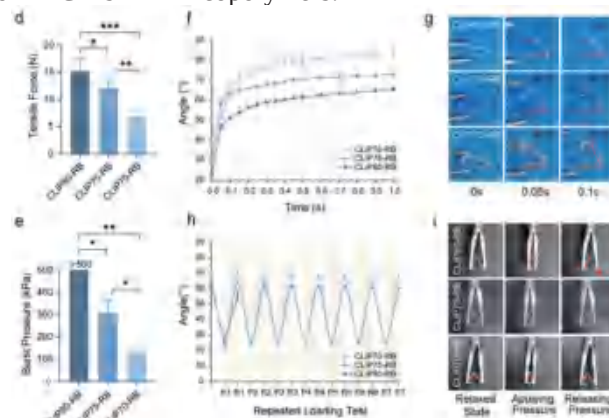


Fig. 3. Mechanical performance and rebound behavior of Hem-o-lok-shaped tissue ligation clips.

The tensile forces of CLIP80-RB, CLIP75-RB and CLIP70-RB were 15.25 ± 2.46 N, 12.04 ± 1.39 N and 6.80 ± 1.26 N. CLIP80-RB and CLIP75-RB offered a safer performance margin. All the three clips were reliable as the withstanding pressures were far exceeding normal physiological blood pressure. CLIP75-RB and CLIP70-RB showed superior elastic recovery and operational stability, which were essential for reliable handling in clinical procedures. The PLC75-RB was ultimately selected to satisfy both the closure strength and elastic rebound requirements of tissue ligation clips. In a rabbit unilateral nephrectomy model, CLIP75-RB effectively occluded the renal artery, vein, and ureter, demonstrating its functional performance.



Fig. 4. Surgical procedure using CLIP75-RB for ligation in rabbits.

Conclusions: PLCL-b-PLLA was developed as a tailored biodegradable copolymer featuring a random-block architecture that integrates the flexibility of PLCL with the high strength of PLLA. CLIP75-RB demonstrated sufficient closure force and good rebound ability prior to degradation, fulfilling the functional requirements for tissue ligation.

Injectable ROS-Scavenging Porous α -Tocopheryl Succinate-Loaded PPDO Microspheres for Immunomodulatory Soft-Tissue Remodeling

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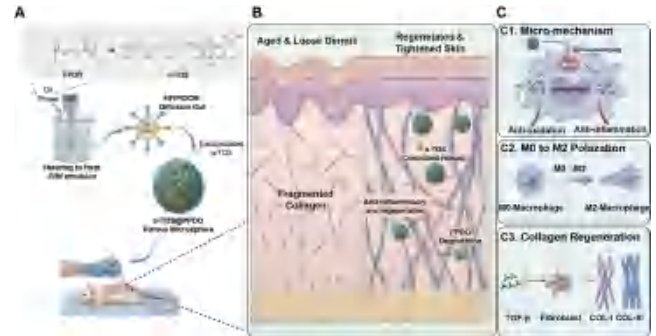
Key words: soft-tissue filler, PPDO microspheres, ROS scavenging, immunomodulation, collagen remodeling

Introduction: Injectable soft-tissue fillers are widely used for contour correction and volume augmentation, but most current systems mainly act as passive bulking materials. Excessive post-implant oxidative stress and persistent inflammation can impair tissue integration, limit long-term volume retention, and compromise regenerative remodeling. We therefore designed a bioactive filler that couples structural support with reactive oxygen species (ROS) regulation and immunomodulation.^{1,2}

Materials & Methods: Porous poly(p-dioxanone) (PPDO) microspheres were fabricated by emulsion-solvent evaporation and loaded with α -tocopheryl succinate (α -TOS), then dispersed in a carboxymethyl cellulose (CMC) hydrogel to obtain an injectable composite filler. Microsphere morphology, physicochemical properties, injectability, and α -TOS release were characterized. Cytocompatibility, intracellular ROS regulation, macrophage polarization, and collagen-related gene expression were evaluated in vitro, followed by subcutaneous implantation in rats to assess filler retention, inflammatory remodeling, and collagen deposition.

Results & Discussion: The α -TOS@PPDO microspheres showed uniform porous spherical morphology with mean diameters of about 53–60 μ m and preserved α -TOS loading without compromising structural integrity. The composite filler was smoothly extruded through a 26G needle under less than 15 N and exhibited shear-thinning behavior, while sustaining α -TOS release for nearly 70 days. Encapsulation markedly reduced the cytotoxicity of free α -TOS while retaining antioxidant activity. In LPS-stimulated cells, α -TOS@PPDO suppressed intracellular ROS accumulation, promoted reparative M2 macrophage polarization, downregulated IL-1 β and TNF- α , upregulated IL-10, and restored COL I/COL III expression. After subcutaneous implantation, the filler formed a stable depot, showed acceptable tissue tolerance, alleviated excessive inflammatory responses, and promoted more sustained collagen deposition and dermal reconstruction than free α -TOS or PPDO alone.

Conclusions: Injectable α -TOS@PPDO/CMC fillers combine structural persistence with controlled antioxidant delivery, enabling ROS scavenging, favorable macrophage regulation, and long-term collagen remodeling. The system is a promising candidate for next-generation regenerative soft-tissue fillers and warrants further optimization toward translational and defect-specific studies.



Scheme 1. Fabrication strategy, therapeutic concept, and proposed regenerative mechanism of the α -TOS@PPDO injectable filler.

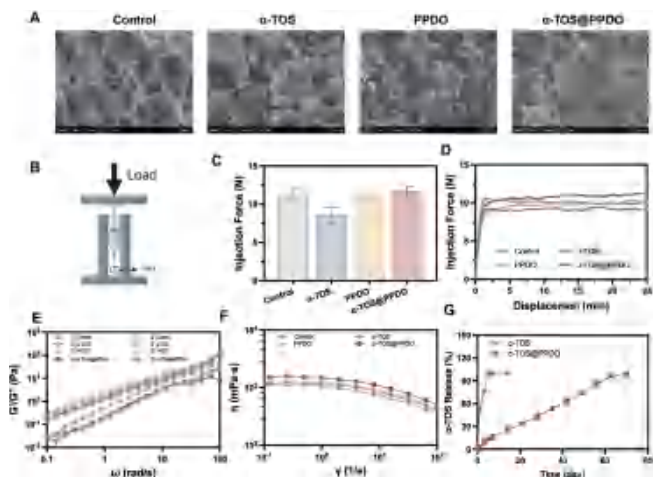


Fig. 2. Selected characterization of the filler system, including microstructure, injectability, rheology, and sustained α -TOS release.

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Latent Photodegradable Polyesters Enabled by Nitrobenzyl-Based Triggers for Controlled End-of-Life Behavior

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Key words: photodegradable polyester, nitrobenzyl trigger, controlled degradation, biodegradable polymer, end-of-life behavior

Introduction: The development of polymeric materials that remain stable during use but degrade in a controlled manner after disposal is an important strategy for sustainable materials design. Conventional biodegradable polymers often undergo continuous degradation once exposed to environmental conditions, which may limit long-term performance during their service life. To overcome this limitation, latent degradation systems that can be activated only when needed have attracted increasing attention.

In this study, we designed a light-responsive polyester system containing a nitrobenzyl-based photolabile trigger. The polymer is stable under ambient conditions before activation, but upon UV irradiation, the photolabile unit is cleaved, inducing chain scission and switching the material from a degradation-off state to a degradation-on state. This approach enables programmed degradation behavior and offers potential as an environmentally responsible alternative to conventional polymeric materials.

Materials & Methods: A nitrobenzyl-based photolabile initiator, PR-OH, was synthesized and used to prepare photodegradable polyesters through ring-opening polymerization of ϵ -caprolactone (CL) and L-lactide (LA). In addition, urethane-based reinforced polymer structures were prepared to expand the material platform beyond simple linear polyesters.

The photodegradation behavior of PR-OH was investigated by ^1H NMR spectroscopy after irradiation at 254, 365, and 405 nm. The degradation kinetics were evaluated by comparing the spectral changes in the aromatic region and determining the apparent rate constants. The photodegradable behavior of the polymers was further examined after UV irradiation, and their subsequent hydrolytic degradation in distilled water was analyzed over time. Mechanical properties including Young's modulus, tensile strength, and elongation at break were also measured to evaluate the structural performance of the polymer materials before degradation.

Results & Discussion: PR-OH showed photodegradation behavior under UV irradiation, with 365 nm being the most effective wavelength. The

photolabile initiator was successfully incorporated into polyester chains, and the resulting polymers remained stable before irradiation. After UV exposure, the polymers became more susceptible to hydrolysis, indicating that light irradiation effectively activated the degradation process. In addition, the reinforced polymer structures maintained useful mechanical properties before activation, suggesting that the system can provide both stability during use and controllable degradation after disposal.

Conclusions: A latent photodegradable and biodegradable polyester system incorporating a nitrobenzyl-based photolabile unit was successfully developed. The material remained stable before irradiation and could be switched into a degradable state upon light exposure. After photodegradation, the polymers exhibited enhanced hydrolytic degradation, confirming effective on-demand activation of the degradation process.

This study demonstrates the feasibility of combining phototriggered activation with biodegradable polyester design to achieve controllable end-of-life behavior. The proposed system may provide a useful platform for sustainable polymeric materials that require both service-life stability and post-use degradability. Future studies will focus on expanding the structural diversity of the polymer system and optimizing degradation efficiency under practical irradiation conditions.

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Construction of Bioactive Glass Composite Coating and Its Application in Bone Repair Research

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Key words: Bioactive Glass, Composite Coating, Bone Repair

Introduction: Due to their multifunctional properties in immunomodulation, antibacterial activity, and pro-angiogenic effects, bioactive glass coatings offer a novel research approach for addressing complex bone defect environments. Taking bioactive glass coatings as the 切入点, in-depth investigations into how their composition, structure, and ion release behavior influence the bone repair process hold significant scientific value and clinical translation potential for advancing the development of high-performance bone repair implant materials.

Materials & Methods: Different concentrations of polylysine (EPL) were incorporated into a prepolymer of double-bonded poly(citrate ester) (PCA). The amino groups in EPL underwent a Michael addition reaction with the double bonds in PCA under aqueous conditions. Subsequently, CuBGN was synthesized via the sol-gel method and added to the system at a specific ratio. After freeze-drying, a multifunctional poly(citrate ester) (PBE) composite material was obtained. The PBE composite was then formulated into liquids of varying concentrations, spin-coated onto the surface of Zn metal, and thermally cured to produce the Zn@PBE material.

Results & Discussion: The Zn@PBE material demonstrated excellent performance in MRSA-infected bone defects. In terms of antibacterial activity, the incorporation of EPL and CuBGN significantly enhanced the bacteriostatic rate, with bacterial survival rates much lower than those of the control group. Regarding immunomodulation, the material inhibited the expression of pro-inflammatory cytokines (TNF- α , IL-6, IL-1 β) while promoting the secretion of the anti-inflammatory cytokine IL-10, inducing macrophage polarization towards the M2 phenotype. In angiogenesis experiments, the material extract promoted the migration and tube formation of HUVECs, and in vivo CD31 staining showed an increased density of new blood vessels. In terms of osteogenesis, ALP and ARS staining confirmed enhanced osteogenic differentiation and mineralization, and abundant new bone formation was observed in vivo. Through its multiple synergistic effects, Zn@PBE effectively addresses complex infected bone defects.

Conclusions: In this study, a polycitrate-based multifunctional coating integrating EPL antimicrobial peptides and CuBGN bioactive glass was constructed on

the surface of zinc (Zn@PBE), successfully achieving the organic integration of antibacterial, anti-inflammatory, pro-angiogenic, and pro-osteogenic properties. Through multi-mechanism synergy, this material effectively addresses the complex microenvironment of MRSA-infected bone defects, offering a novel strategy for the design of next-generation bone repair implant materials.

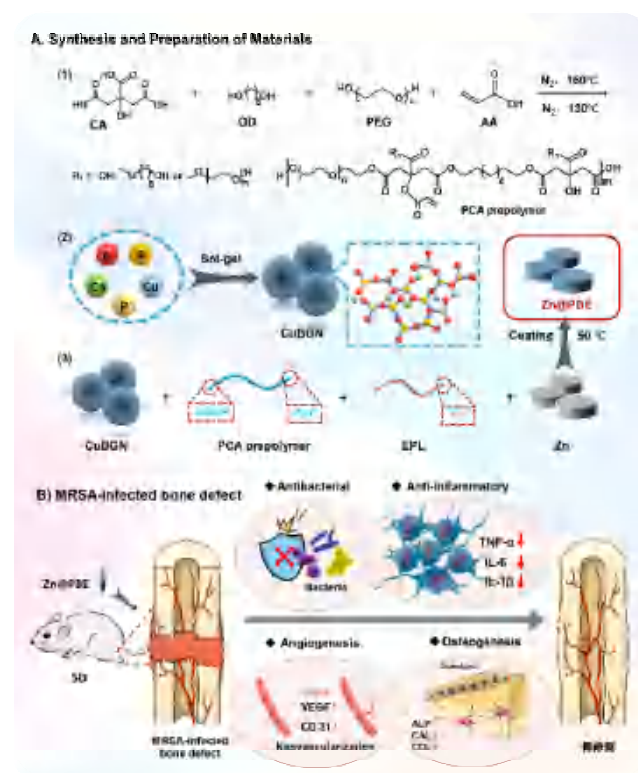


Fig. 1. Construction of bioactive glass composite coating and its application in bone repair research.

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Multifunctional Hollow Manganese Silicate Nanoparticles for the Treatment of Acute Lung Injury and *Pseudomonas aeruginosa* Pulmonary Infection

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Key words: acute lung injury, manganese silicate, antioxidant, anti-inflammation, lung repair

Introduction: Acute respiratory distress syndrome (ARDS) is a life-threatening lung condition marked by severe inflammation, increased reactive oxygen species (ROS), and alveolar-capillary barrier disruption, causing high morbidity and mortality.^[1] The clinical treatment options for ARDS are mainly restricted to supportive care, and pharmacological interventions have shown limited therapeutic benefit.^[2] Nanomaterial-based therapeutics have emerged as promising strategies for inflammatory lung diseases due to their multifunctional regulatory capacity. In particular, manganese-based nanomaterials have attracted increasing attention for their enzyme-mimicking activity, enabling ROS scavenging and immune response regulation.^[3] Meanwhile, silicate-based biomaterials are recognized for releasing bioactive Si ions that support tissue regeneration. Based on the above, Mn-Si nanomaterials with multiple biofunctions, including ROS scavenging, immune regulation, and tissue repair, are expected to become promising candidates for treating acute lung injury (ALI) and ARDS.

Materials & Methods: Hollow manganese silicate (MS) nanospheres were synthesized via a hard-template hydrothermal strategy. The antioxidant and immunomodulatory properties of MS were evaluated in lung epithelial cells and macrophages under inflammatory and oxidative stress conditions by assessing intracellular ROS, cell viability, cytokine production, macrophage polarization, and epithelial junction integrity. Next, an LPS-induced acute lung injury model was established to investigate the therapeutic effects of MS on inflammation regulation, oxidative stress alleviation, and alveolar-capillary barrier protection. Moreover, gentamicin-loaded MS (MS-GM) was further developed and evaluated in a *Pseudomonas aeruginosa*-induced pulmonary infection model to assess its synergistic antibacterial and anti-inflammatory efficacy in vivo.

Results & Discussion: MS nanospheres exhibited uniform hollow structures (~100 nm) with both Mn(II) and Mn(III) valence states, which support effective ROS scavenging activity. In vitro, MS decreased intracellular oxidative stress and pro-inflammatory cytokine secretion induced by LPS and H₂O₂, and encouraged M2 macrophage polarization. In vivo, MS notably reduced LPS-induced lung injury, evidenced by less

inflammatory cell infiltration, decreased protein leakage in bronchoalveolar lavage fluid, lower levels of pro-inflammatory cytokines, reduced oxidative stress, and improved histopathological structure. In the *Pseudomonas aeruginosa* infection model, MS-GM demonstrated enhanced bacterial clearance, lessened infection-related inflammation, and exhibited superior therapeutic effects.

Conclusions: This study presented a nanotherapeutic strategy based on MS hollow nanospheres for the treatment of ALI and acute pulmonary infection. By integrating ROS scavenging, immune regulation, and protection of the alveolar-capillary barrier, MS nanospheres effectively reduced LPS-induced acute lung injury. Furthermore, their drug-loading capacity enabled synergistic treatment of *Pseudomonas aeruginosa*-induced acute pulmonary infection by combining intrinsic bioactivity with antibiotic effects. This study presented a promising strategy of nanomedicine application for the management of inflammatory lung diseases.

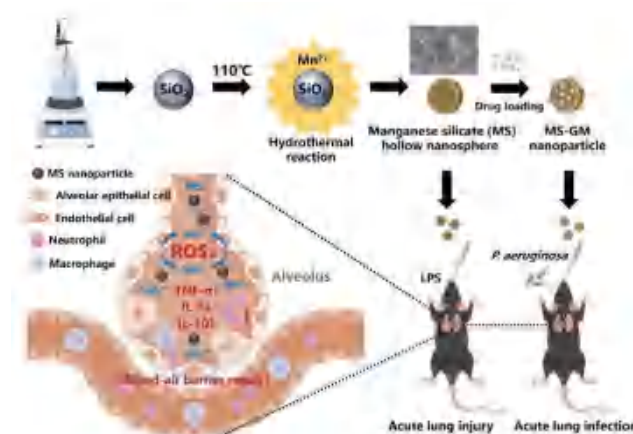


Fig. 1. Multifunctional manganese silicate (MS) hollow nanospheres for treating acute lung injury (ALI) and *Pseudomonas aeruginosa* pulmonary infection.

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Preparation and Properties of Bioinspired Bone Repair Materials

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Key words: bioinspired strategy, mechanical performance, bone tissue engineering

Introduction: Preparation of bone repair materials with good bioactivity and mechanical properties has been a hot topic in biomaterial research. In particular, the different bone defect sites have specific mechanical requirements for the corresponding bone repair materials. Therefore, the design and preparation of mechanically matched bioactive materials have great significance for bone-repairing effect.

Materials & Methods: Inspired by the relationship between the hierarchical structure and excellent mechanical properties of natural materials, high-performance bioinspired bone repair materials are developed through natural structure-mimetic or biotemplate methods combining with bioactive inorganic components.

Results & Discussion: For the development of load-bearing bone repair materials, inspired by the fiber-oriented microstructure and biomineralization process of bone, we successfully fabricated the bone-inspired hydroxyapatite-based bioceramics via directional assembly and biomimetic mineralization strategies. Such bone-inspired bioceramics showed good strength and elastic modulus similar to cortical bone, overcoming the mismatch of mechanical performance between the traditional bioceramics and bone tissue. In addition, high-strength mineralized calcium phosphate/bamboo composite scaffolds were prepared in combination of biotemplated approach and biomimetic mineralization. The porous structure of biotemplate and the calcium phosphate components endowed the mineralized scaffolds with good cell transport and osseointegration properties. Besides, in view of the repair of thin-wall bone tissue such as skull and orbital bone, the flexible bioactive ceramics were developed by low-temperature hydrothermal mineralization of discarded natural sponge. The flexible bioactive ceramics not only met various processing operations in

the surgical of thin-wall bone tissue, but also could effectively accelerate the regeneration of blood vessels and bone tissue.

Conclusions: By constructing bioinspired hierarchical structure or using natural biotemplates, we successfully developed three high-performance bioinspired biomaterials for the repairing of different bone defect sites, which also proved the construction of hierarchical structure in biomaterials is of great significance to tissue engineering.

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A hydrogel engineered with semiconductive MnPSe₃ nanosheets as an integrative sonosensitizer/Fenton-like catalyst/nutrient for melanoma postoperative care

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Key words: hydrogel; semiconductive MnPSe₃ nanosheet; dynamic therapy; melanoma inhibition; wound healing

Introduction: Simultaneous tumor recurrence inhibition and wound healing is of paramount significance for patients who undergo melanoma surgery¹. Most of the reported approaches for combined tumor treatment/skin repair involve chemotherapy, PTT, and photodynamic therapy (PDT), which are not satisfactory due to the therapeutic resistance and toxic side effects of drugs, nonspecific heating on surrounding skin tissues, phototoxicity, and poor tissue permeability of light². Therefore, developing an effective yet simple platform that meets the comprehensive therapeutic demands of postoperative care in clinical melanoma treatment remains a significant challenge.

Materials & Methods: A sodium alginate-based composite hydrogel dressing was developed, incorporating 2D semiconductive MnPSe₃ nanosheets (MPS NSs) as an integrated inorganic sonosensitizer, Fenton-like catalyst, and nutrient agent for combined sonodynamic therapy (SDT)/chemodynamic therapy (CDT) and wound healing promotion following melanoma surgery. First, the MPS NSs not only respond to ultrasound stimulation to undergo electron transfer reactions, generating ¹O₂ for SDT of residual melanoma cells, but also catalyze endogenous H₂O₂ to produce •OH via a Fenton-like reaction under the acidic tumor microenvironment (TME), enabling CDT. Second, the high-valence manganese species (Mn³⁺/Mn⁴⁺ in MPS NSs react with glutathione (GSH) to remodel the highly reduced TME, thereby effectively amplifying reactive oxygen species (ROS)-mediated cell death during combined SDT/CDT. Third, the phosphorus and selenium elements released from MPS NSs act as nutrients to collectively promote endothelial cell migration and proliferation, upregulate the expression of angiogenesis-related genes, and ultimately accelerate wound healing.

Results & Discussion: Probe-based assays demonstrated that MPS NSs possess the ability to ROS under ultrasound stimulation while also depleting GSH. After being incorporated into the hydrogel, their ROS-generating capacity was retained, along with the sustained release of nutrients such as phosphorus and selenium. In vitro cellular assays showed that the composite hydrogel effectively promoted the proliferation and migration of endothelial cells and

exhibited no cytotoxicity toward fibroblasts. Under ultrasound stimulation and simulated tumor microenvironment conditions, the composite hydrogel exerted a combined therapeutic effect, effectively killing melanoma cells. In a nude mouse tumor-bearing model, the composite hydrogel combined with ultrasound treatment significantly inhibited tumor recurrence. Meanwhile, in a diabetic mouse wound model, the composite hydrogel effectively accelerated chronic wound healing and demonstrated favourable biosafety.

Conclusions: Such multifunctional SA-MPS hydrogel dressing without complex integrations capable of potently suppressing postoperative melanoma recurrence and facilitating wound healing holds great application potential for postoperative care.

Graphic

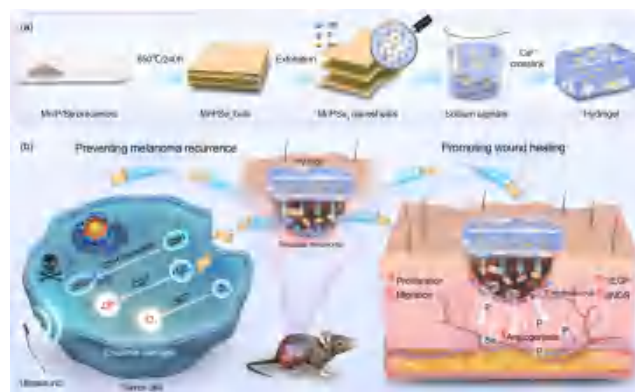


Fig. 1. Schematic illustrations of the synthesis process and proposed therapeutic effects of SA-MPS hydrogel.

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A Senescent Metabolism-Targeting Hierarchical Scaffold Restores NAD⁺ Homeostasis and Redox Balance for Aged Bone Repair

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Keywords: Senescence, Aged bone repair, NAD⁺ Scaffold, Metabolic modulation

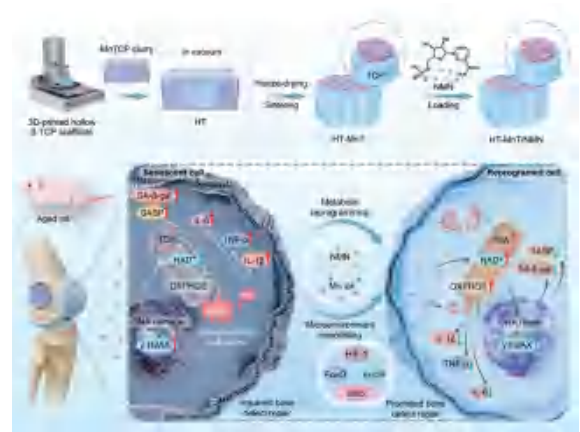
Introduction: The accelerating global aging population has increased the incidence of senescence-related bone metabolic disorders, with impaired bone repair capacity stemming from metabolic network dysregulation: NAD⁺ decline leads to mitochondrial dysfunction and osteoblast senescence, while redox imbalance causes reactive oxygen species accumulation that disrupts bone remodeling. NMN, as an NAD⁺ precursor, restores energy metabolism and alleviates osteoblast senescence, whereas manganese ions scavenge reactive oxygen species (ROS) via Mn-SOD, jointly improving the osteogenic microenvironment. However, achieving sustained co-delivery of both agents is essential for optimal therapeutic effects, highlighting the need for a delivery system that enables prolonged release to promote aged bone repair.

Materials & Methods: A hierarchically structured ceramic scaffold was fabricated by loading the NAD⁺ precursor NMN onto MnTCP ceramic rods and combining them with β -TCP hollow tube scaffolds using a dual-directional freezing method. The study investigated the regulatory effects of this scaffold on the proliferation and differentiation of aged bone marrow-derived mesenchymal stem cells (BMSCs), as well as on mitochondrial function and the bone microenvironment. Furthermore, an aged SD rat femoral defect model was employed to explore the scaffold's efficacy in promoting aged bone repair and its underlying repair mechanisms.

Results & Discussion: The hierarchically structured bioceramic scaffold significantly elevates NAD⁺ levels in senescent cells through sustained release of NMN, restores mitochondrial homeostasis, and repairs DNA damage, thereby alleviate cellular senescence. The concurrently released manganese ions effectively scavenge excessive reactive oxygen species in the bone microenvironment, ameliorate oxidative stress, and promote the differentiation of BMSCs into osteoblasts. In vivo repair experiments using an aged SD rat femoral defect model further

demonstrate that this scaffold system significantly enhances new bone formation and mineralization in aged bone defect regions, offering a new strategy for bone regeneration in the aging population.

Conclusions: This study designed a composite bioceramic scaffold capable of regulating both energy metabolism and antioxidant function in senescent cells. By delivering the NAD⁺ precursor NMN, the scaffold effectively elevates endogenous NAD⁺ levels in senescent cells, activates mitochondrial energy metabolism pathways, repairs DNA damage, and restores cellular physiological functions. Simultaneously, it significantly scavenges excessive ROS in the bone defect microenvironment, alleviating the detrimental effects of oxidative stress on osteogenic activity. Through this dual mechanism, the bioceramic scaffold demonstrates substantial repair efficacy in an aged bone defect model, offering a novel strategy for synergistic metabolic-immune regulation in aged bone regeneration.



Graphics

Schematic illustration of the construction of HT-MnT/NMN scaffold system and its ability to reprogram the senescent bone metabolic microenvironment for promoting aged bone defect repair.

Engineering Metal-Organic Framework System for Light-Free Antibacterial Photodynamic Therapy

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Key words: biofilm infections, photodynamic therapy, metal-organic framework, chemiluminescence, cascade reaction

Introduction: Photodynamic therapy provides a non-antibiotic bactericidal approach, yet its efficacy is limited by poor light penetration and hypoxia. In this nanosystem, glucose oxidase loaded onto the MOF catalyzes glucose to generate hydrogen peroxide, which subsequently reacts with manganese dioxide in a cascade. The resulting cascade alleviates hypoxia via O_2 production and activates luminol-based chemiluminescence (CL), which excites the embedded porphyrin photosensitizer to generate deep-tissue ROS without external light. This self-sufficient strategy synergistically enhances antibacterial efficacy by overcoming both light penetration and O_2 limitations. In a *S. aureus*-infected subcutaneous abscess model, the system achieves potent biofilm eradication and efficient bacterial clearance. By integrating oxygen self-supply, cascade enzymatic catalysis, and endogenous CL-triggered photosensitization into a single nanoplatform, this work presents a laser-free PDT strategy against deep biofilm infections.

Materials & Methods: PCN-224 with an ellipsoid shape was synthesized following the previous literature with some modifications. 60 mg of $ZrOCl_2 \cdot 8H_2O$, 15 mg of tetrakis (4-carboxyphenyl) porphyrin, and 0.56 g of benzoic acid were dissolved in 10 mL of dimethylformamide (DMF). The mixture was stirred (400 rpm) and heated to $90^\circ C$ for 1 h. After cooling to room temperature, the PCN-224 product was collected by centrifugation (14000 rpm, 20 min) and washed with DMF and deionized water. PL was prepared by loading luminol onto PCN-224, followed by the coating of MnO_2 to form PLM, and subsequent immobilization of glucose oxidase to yield the final PLMG nanocomposite.

Results & Discussion: Based on PCN-224, the PLMG composite was constructed via sequential loading of luminol, in-situ MnO_2 growth, and GOx immobilization. Structural and elemental analyses confirmed successful fabrication. Efficient chemiluminescence resonance energy transfer from luminol to PCN-224 was verified. The composite demonstrated synergistic GOx/ MnO_2 -driven O_2 generation and corresponding singlet oxygen production, with all integrated components being essential for optimal self-illuminating photodynamic activity. *In vitro* assays demonstrated that PLMG combined with glucose achieves potent antibacterial activity through a cascade reaction generating ROS, with

all components (GOx, luminol, MnO_2) being essential, and the system is effective against both Gram-positive and Gram-negative bacteria. As confirmed by viability assays and imaging, the PLMG+G treatment achieved >99.9% eradication of *S. aureus* biofilms, significantly outperforming PLMG alone. This demonstrates that exogenous glucose is essential to fuel the cascade reaction for effective biofilm disruption. *In vivo* results demonstrated that the PLMG+G treatment achieved near-complete bacterial eradication and significantly accelerated wound healing in a *S. aureus*-infected mouse model. Histological analysis confirmed that this glucose-fuelled catalytic cascade effectively suppressed inflammation and enhanced tissue repair.

Conclusions: The designed MOF system enables self-sustained O_2 generation and chemiluminescence-triggered photodynamic therapy, which overcomes hypoxia and light penetration barriers, achieving complete biofilm eradication and accelerated wound healing in a *S. aureus* infection model.

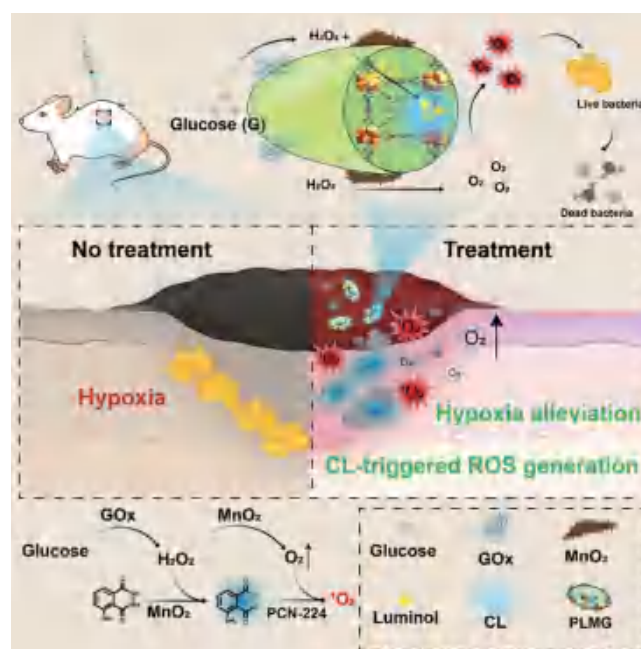


Fig. 1. Schematic illustration of O_2 self-supplying and self-illuminating process of PLMG in response to exogenous Glucose to enhance PDT.

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Coordination Self-Assembled Nanoplatfom for Augmented Photothermal/Chemodynamic Therapy and Antimetastatic Immunity

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Key words: luteolin; coordination self-assembly; carrier-free nanoparticles; synergistic therapy; tumor metastasis

Introduction: The efficacy of photothermal therapy (PTT) and chemodynamic therapy (CDT) for cancer treatment is significantly limited by the tumor microenvironment's antioxidant defenses, such as glutathione (GSH), and thermoresistance mechanisms. Additionally, conventional nanocarriers often suffer from low drug loading, premature leakage, and carrier-induced toxicity. To overcome these challenges, this study aimed to develop a carrier-free nanoplatfom that integrates high drug loading, self-amplifying therapy, and immune activation for enhanced antitumor and antimetastatic effects.

Materials & Methods: A carrier-free nanoplatfom (LF@HA NPs) was constructed through the coordination self-assembly of luteolin (Lut) and Fe^{3+} ions, followed by surface modification with hyaluronic acid (HA) to enhance stability and active targeting. The nanoparticles were characterized for their physicochemical properties, photothermal performance, GSH depletion, and dual-responsive drug release. In vitro studies evaluated cellular uptake, cytotoxicity, reactive oxygen species (ROS) generation, and immunogenic cell death (ICD) in 4T1 cells. In vivo studies assessed the biodistribution, antitumor efficacy, immune response, and metastatic inhibition in 4T1 tumor-bearing mouse models.

Results & Discussion: The LF@HA NPs achieved exceptional encapsulation (90.46%) and drug loading (85.86%) efficiencies. HA modification improved dispersibility and enabled active targeting, resulting in uniform particles with a size of 23.55 nm. The nanoplatfom exhibited excellent photothermal conversion and dual-responsiveness to GSH and near-infrared (NIR) laser, enabling controlled drug release. In vitro, LF@HA NPs with NIR irradiation effectively depleted GSH, generated ROS, inhibited HSP90 and HIF-1 α expression, and induced significant ICD, as evidenced by calreticulin exposure and HMGB1 release. In vivo, LF@HA NPs demonstrated superior tumor accumulation and achieved a 94.01% tumor inhibition rate when combined with NIR. This synergistic therapy activated systemic antitumor immunity, increasing CD4 $^{+}$ and CD8 $^{+}$ T cell populations, and effectively suppressed lung metastasis in a mouse model.

Conclusions: This study successfully developed a novel carrier-free LF@HA nanoplatfom that addresses the

limitations of conventional nanocarriers. By combining high drug loading, self-amplifying PTT/CDT, and immune activation, the platform demonstrates a potent strategy for eradicating primary tumors and inhibiting distant metastasis. The results highlight the potential of natural product-based coordination nanomedicines for advanced cancer therapy. Future studies will focus on evaluating the platform's efficacy across diverse tumor models and optimizing its therapeutic safety with mild-photothermal protocols.

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Double-layer electrospun membrane with antibacterial, anti-inflammatory, and antioxidant functions for tendon injury repair

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Key words: tendon injury; nanoparticles; double-layer electrospun membrane; tendon repair; tissue engineering

Introduction: Tendon injuries seriously affect people's quality of life. Currently, surgery is the main treatment for repairing tendon ruptures and alleviating clinical symptoms. However, due to the low number of cells and blood vessels, tendons have limited self-regenerative ability, resulting in poor treatment efficacy^[1]. Adhesions often occur due to oxidative stress, local inflammation, and tendon sheath infections, and these complications can lead to poor mechanical performance of the tendon after healing^[2]. The current clinical treatments for tendon repair, including surgical suturing, autografts or allografts, and permanent artificial prostheses, all have unavoidable drawbacks^[3]. Therefore, it is necessary to find new treatments to promote tendon regeneration. Tissue engineering and electrospun nanofiber membranes provide a new direction for tendon repair, but their purely physical barrier is insufficient to meet regenerative needs, and single-layer membranes are difficult to achieve precise delivery of active substances. In this study, we designed a double-layer electrospun membrane to promote tendon injury repair.

Materials & Methods: The outer layer is prepared by electrospinning a mixture of poly- ϵ -caprolactone (PCL) and polyhexamethylene biguanide hydrochloride (PHMB) to create a PCL-PHMB fiber membrane, serving as a physical barrier with antibacterial and anti-adhesive functions; the inner layer is combining procyanidins (PC) and zinc acetate dihydrate to synthesize nanoparticles, and incorporating ZnO-PC nanoparticles into PCL/gelatin membrane. The experimental design includes the preparation, performance characterization of nanoparticles and electrospun membranes, *in vitro* functional validation, and application and evaluation in *in vivo* animal models. First, the microstructure, tensile mechanical properties, porosity, and other physical indicators of the electrospun membranes were characterized. Then, the *in vitro* functions of the electrospun membranes in cell proliferation, migration, and oxidative stress were explored. Finally, a rat Achilles tendon rupture model was established, and the effects of the bilayer electrospun membranes on *in vivo* tendon injury repair were assessed through histological staining, immunohistochemical staining, tendon mechanical testing, gait analysis, and other methods.

Results & Discussion: Experimental results show that ZnO-PC nanoparticles were successfully synthesized. The electrospun membranes exhibited good mechanical properties, and biocompatibility results indicated that the hemolysis rates were all below 5%, meeting the application requirements for medical biomaterials. PCL-PHMB membranes demonstrated excellent antibacterial properties. *In vitro* functional experiments proved that the inner PGZn₈ membrane can promote the proliferation and migration of tendon stem cells, effectively reduce ROS production, and modulate the immune microenvironment toward M2 anti-inflammatory phenotypes. Subsequently, after 4 and 8 weeks of *in vivo* repair, H&E, Masson, and Sirius Red staining results showed that the PCL-PHMB_{0.5}@PGZn₈ double-layer membrane group effectively inhibited adhesion between the tendon and surrounding tissues, improved collagen fiber alignment, and increased COL I content. Immunohistochemical staining results indicated that the PCL-PHMB_{0.5}@PGZn₈ group promoted the expression of tendon-related factors SCX and TNMD, and suppressed inflammatory responses. Regenerative mechanical testing and gait analysis results showed that the PCL-PHMB_{0.5}@PGZn₈ group improved tendon healing strength and promoted functional recovery.

Conclusions: In summary, this study provides a double-layer electrospun membrane with antibacterial, anti-inflammatory, and antioxidant functions. Both *in vivo* and *in vitro* experiments have demonstrated that this bilayer membrane is expected to not only achieve physical isolation but also enable localized drug delivery and functional synergy, offering a new type of repair material with greater clinical application potential for tendon regeneration.

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A Therapeutic Strategy Integrating Ultrasound-Guided Microwave Ablation with Nanocomposite Hydrogels to Enhance Autophagy and Suppress Tumor Growth in Hepatocellular Carcinoma

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Key words: Hydrogel, Microwave ablation, Autophagy, Arsenic trioxide, Hepatocellular carcinoma

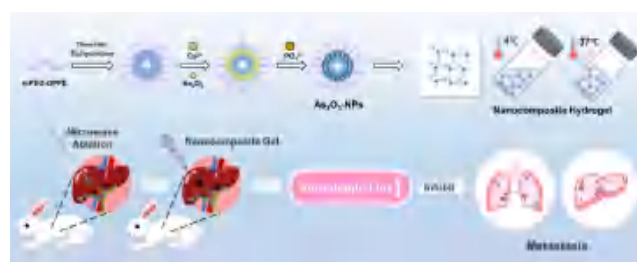
Introduction: Microwave ablation (MWA) is an effective radical therapy for hepatocellular carcinoma (HCC), but it carries a high risk of local tumor recurrence. This study developed a drug delivery system using arsenic trioxide (As_2O_3)-loaded nanoparticles encapsulated in a thermoresponsive hydrogel (ANPs-Gel) to combine with MWA, aiming to enhance antitumor efficacy and prevent recurrence in a rabbit VX2 liver tumor model.

Materials & Methods: As_2O_3 NPs were encapsulated in an injectable thermoresponsive hydrogel (ANPs-Gel). Efficacy was evaluated in a rabbit hepatic VX2 tumor model, with ultrasound (US) and contrast-enhanced ultrasound (CEUS) used to monitor tumor response and angiogenesis. In vitro and in vivo experiments assessed autophagy induction, tumor cell death, and suppression of epithelial-mesenchymal transition (EMT).

Results & Discussion: In vitro results demonstrated that the combination of MWA-like thermal stress with ANPs-Gel significantly enhanced autophagy induction in HCC cells, as evidenced by increased autophagosome formation and elevated autophagy-related proteins, leading to promoted tumor cell apoptosis and death. Simultaneously, EMT was markedly suppressed, with upregulation of epithelial markers and downregulation of mesenchymal ones. In the in vivo rabbit VX2 model, the MWA + ANPs-Gel group exhibited superior tumor growth inhibition compared to MWA alone or ANPs-Gel alone, with significantly reduced tumor volumes, delayed or prevented recurrence, and improved animal survival rates. US and CEUS imaging confirmed complete ablation zones with minimal residual perfusion and markedly decreased angiogenesis in the combination group. Histological and molecular analyses corroborated enhanced autophagy, EMT suppression, and reduced microvessel density. The thermoresponsive hydrogel played a critical role by ensuring prolonged drug

retention at the tumor site, minimizing systemic exposure and off-target effects. Mechanistically, the synergy arises from MWA-induced heat facilitating hydrogel gelation and drug release, while As_2O_3 modulates autophagy to amplify cell death and block EMT-driven metastasis. Compared to conventional approaches, this integrated strategy offers targeted, sustained chemotherapy adjunct to ablation, addressing key limitations like recurrence. However, translation to humans may require further optimization, considering differences in tumor biology and ablation parameters.

Conclusions: The integration of ultrasound-guided microwave ablation with the thermoresponsive ANPs-Gel nanocomposite hydrogel represents a promising therapeutic strategy for hepatocellular carcinoma. By effectively inducing autophagy to promote tumor cell death, suppressing EMT to limit invasion and metastasis, and inhibiting angiogenesis and tumor growth, this approach significantly outperforms standalone treatments in preclinical models, while demonstrating good biocompatibility and reduced recurrence risk. These findings support its potential for clinical translation as an advanced, multimodal therapy to improve long-term outcomes in HCC patients through precise, autophagy-targeted interventions.



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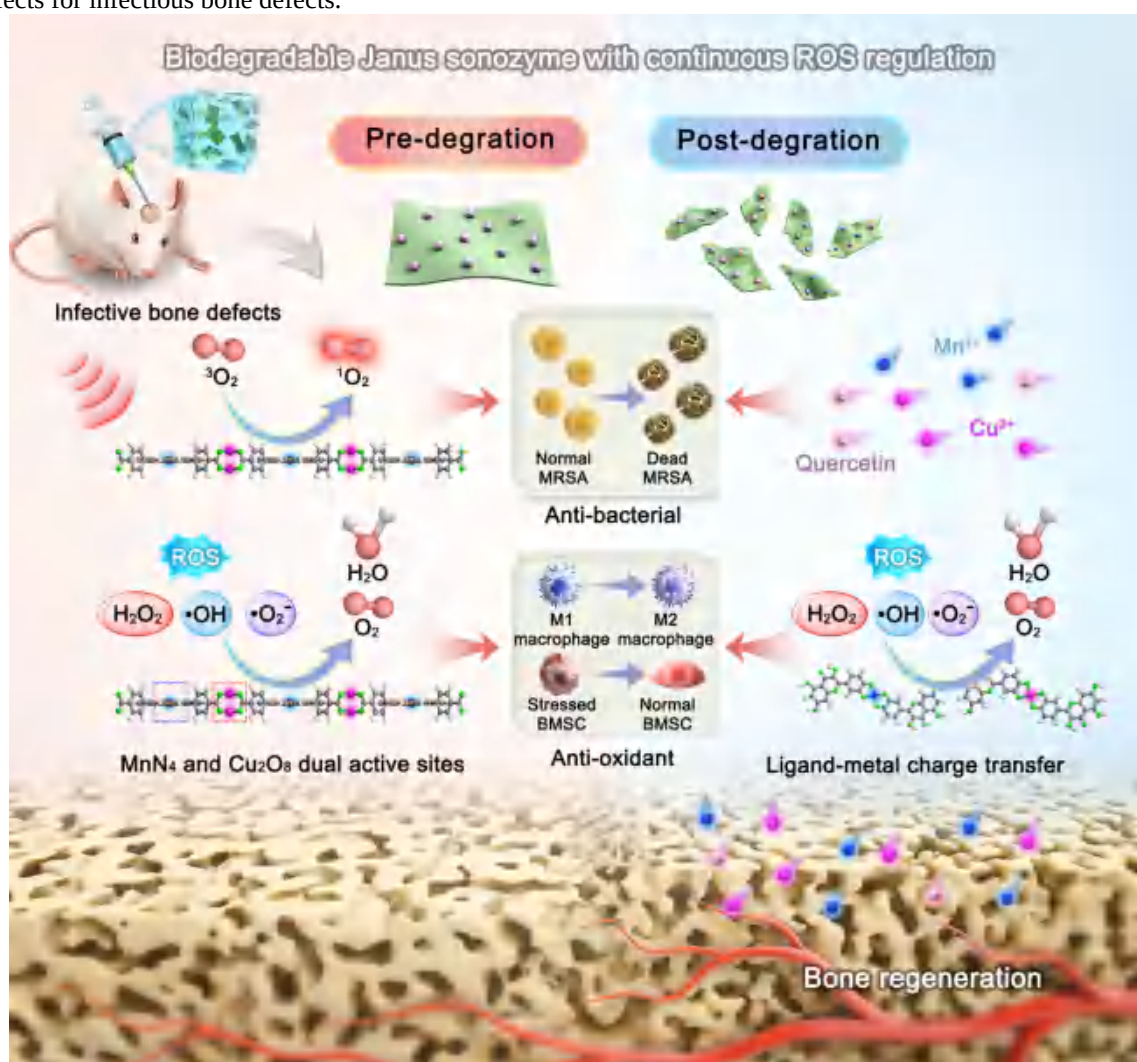
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Biodegradable Janus sonozyme with continuous reactive oxygen species regulation for treating infected critical-sized bone defects

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Critical-sized bone defects are usually accompanied by bacterial infection leading to inflammation and bone nonunion. However, existing biodegradable materials lack long-term therapeutical effect because of their gradual degradation. Here, a degradable material with continuous ROS modulation is proposed, defined as a sonozyme due to its functions as a sonosensitizer and a nanoenzyme. Before degradation, the sonozyme can exert an effective sonodynamic antimicrobial effect through the dual active sites of MnN_4 and Cu_2O_8 . Furthermore, it can promote anti-inflammation by superoxide dismutase- and catalase- like activities. Following degradation, quercetin-metal chelation exhibits a sustaining antioxidant effect through ligand-metal charge transfer, while the released ions and quercetin also have great self-antimicrobial, osteogenic, and angiogenic effects. A rat model of infected cranial defects demonstrates the sonozyme can rapidly eliminate bacteria and promote bone regeneration. This work presents a promising approach to engineer biodegradable materials with long-time effects for infectious bone defects.



Graphic abstract. Schematic representation of the mechanism via which the Janus sonozyme treats infected critical-sized bone defects. Before degradation, the sonozyme can exert an effective sonodynamic antimicrobial effect through the dual active sites of MnN_4 and Cu_2O_8 . Furthermore, it can promote anti-inflammation by superoxide dismutase- and catalase- like activities. Following degradation, quercetin-metal chelation exhibits a sustaining antioxidant effect through ligand-metal charge transfer, while the released ions and quercetin also have great self-antimicrobial, osteogenic, and angiogenic effects.

Deep Eutectic Solvent-Enabled Network Pre-Organization for Time-Programmable 4D Eutectogels in Articular Cartilage Repair

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Key words: Deep eutectic solvents; network pre-organization; 4D hydrogels; viscoelastic remodeling; cartilage regeneration

Introduction:

Achieving long-term stable tissue regeneration and functional restoration under complex in vivo mechanical environments, such as articulating joints, remains a fundamental challenge. The key bottleneck lies not in introducing dynamic behaviors per se, but in enabling biomaterials to intelligently evolve over time, continuously delivering mechanical and biochemical cues matched to different stages of tissue repair while maintaining controllability and clinical translatability. Current dynamic hydrogels predominantly rely on dynamic chemical bonds or reversible covalent crosslinking, which often suffer from synthetic complexity, high environmental sensitivity, and limited predictability of network evolution, thereby restricting their long-term in vivo applications^[1].

Materials & Methods: A deep eutectic solvent (DES)-based pre-organized gelation strategy was developed to fabricate dynamic hydrogels without relying on dynamic chemical bonds. DES components rich in hydrogen bonding and electrostatic interactions were introduced to pre-organize polymer chains prior to and during gelation. The resulting DES-polyacrylamide hydrogels were characterized for network topology and viscoelastic properties. Bone marrow-derived mesenchymal stem cells (BMSCs) were dynamically encapsulated, and their behavior was evaluated under sustained physiological loading in vitro and in vivo.

Results & Discussion:

DES acted as a molecular-level network pre-organizer, cooperatively regulating polymer chain entanglement and reversible supramolecular interactions, thereby directly programming the topology and viscoelastic response of the hydrogel network. This strategy enabled independent modulation of stiffness, viscoelastic dissipation, and biological functionality within a single material system. Mechanistic studies revealed that DES-mediated pre-organization decisively governed stress relaxation kinetics and long-term viscoelastic remodeling behavior, thereby establishing a clear physical basis for time-programmable 4D dynamic hydrogels. Under sustained mechanical loading, the injectable DES-polyacrylamide hydrogel underwent controllable viscoelastic remodeling and spontaneously evolved into a macroporous structure, promoting mass transport, multicellular spheroid formation, and chondrogenic differentiation of BMSCs without exogenous growth factors. In vivo, the mechanically active joint environment enabled this 4D dynamic

microenvironment to precisely match the temporal requirements of osteochondral regeneration, resulting in coordinated reconstruction of hyaline cartilage-like tissue and continuous subchondral bone.

Conclusions: This work establishes deep eutectic solvents as a versatile platform for network pre-organization and gelation programming, allowing the prediction and rational design of time-dependent behaviors, structural evolution pathways, and cell fate regulation of 4D dynamic hydrogels from the material design stage. The proposed paradigm provides a powerful and generalizable strategy for developing regenerative biomaterials tailored for complex mechanical environments.

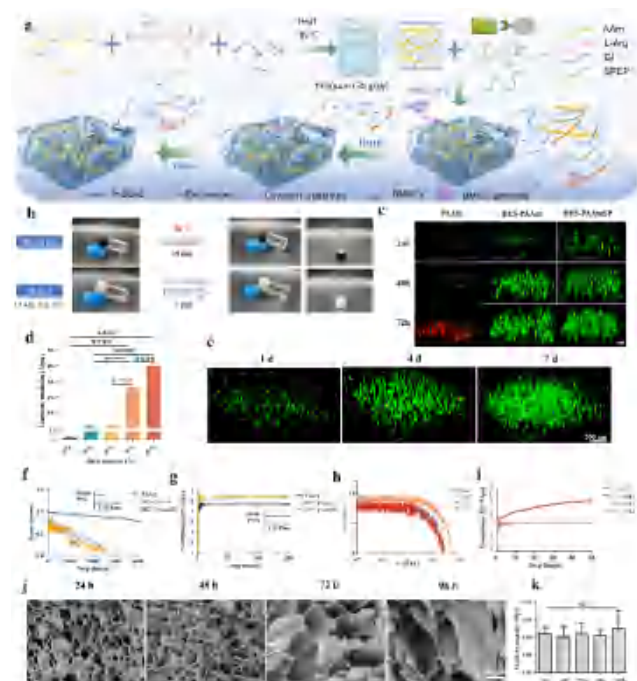


Fig.1. Preparation and characterization of 4D DES-PAAmSP hydrogels.(a) DES-mediated gelation schematic.(b) Optical images of PAAm and DES-PAAmSP hydrogels.(c) 3D live/dead confocal images of BMSC-laden hydrogels.(d) Elastic modulus versus DES content.(e) Time-dependent confocal images of BMSC-laden DES-PAAmSP hydrogels.(f–i) Stress relaxation and creep behaviors with varied SPEP content.(j) SEM images of time-dependent microstructural evolution.(k) Small-strain elastic modulus over time (ns).

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Tannic Acid-Enhanced Polyacrylamide/Hyaluronic Acid (TA@PAM/HA) Dual-network Hydrogel Patches for Repairing Annulus Fibrosus Defects After Discectomy

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Introduction: Lumbar discectomy alleviates nerve compression but leaves a persistent annulus fibrosus (AF) defect within a postoperative oxidative stress microenvironment, synergistically accelerating intervertebral disc degeneration (IDD) and risk of reherniation^[1,2]. Current closure devices are bioinert, lacking the ability to actively modulate this hostile healing environment. This study aims to develop a multifunctional, bioactive patch that seamlessly integrates robust mechanical sealing with potent antioxidant activity.

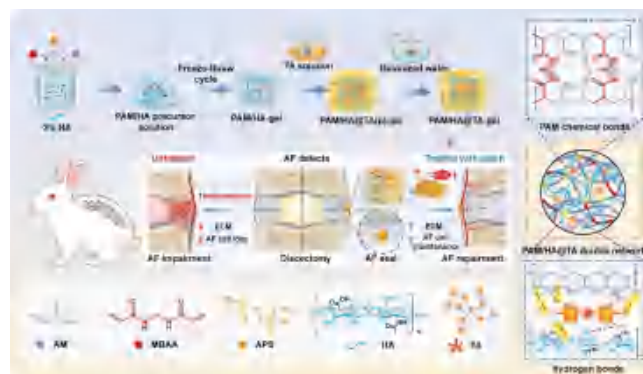
Materials & Methods: We engineered a dual-network (DN) hydrogel by integrating a covalently crosslinked polyacrylamide (PAM) network with a physically crosslinked hyaluronic acid (HA) network, dynamically bridged via multi-point hydrogen bonds formed by the natural polyphenol tannic acid (TA). The synthesis involved in-situ polymerization followed by TA solution immersion. Comprehensive characterization included FTIR, XPS, SEM, compressive/cyclic mechanical testing, and lap-shear adhesion assays. The ROS scavenging capacity was quantified by DPPH and ABTS assays. In vitro biocompatibility, cytoprotection against tert-butyl hydroperoxide (TBHP)-induced oxidative stress, and ECM metabolism regulation in human AF cells (hAFCs) were evaluated. Efficacy was validated in a rabbit lumbar disc puncture-degeneration model over 12 weeks using MRI (Disc Height Index, Pfirrmann grade) and histological (H&E, Masson's, Alcian blue) analyses.

Results & Discussion: Structural analyses confirmed successful TA integration and hydrogen-bond mediated network densification. The optimized PAM/HA@TA hydrogel exhibited a high compressive modulus (98.73 kPa), strength (1.34 MPa), and exceptional energy dissipation ($2.74 \text{ kJ} \cdot \text{m}^{-3}$) with rapid elastic recovery (79.23%). It demonstrated strong bioadhesion (196.7 kPa) suitable for defect sealing. TA conferred remarkable antioxidant activity, achieving 61.5% DPPH and 98.5% ABTS⁺ radical scavenging within 30 minutes. In vitro, PAM/HA@TA effectively protected hAFCs from TBHP-induced damage: it scavenged intracellular ROS, restored mitochondrial membrane potential, reduced apoptosis by 21.7%, and rebalanced ECM metabolism by upregulating COL-1/aggreacan while downregulating MMP-13/ADAMTS-5. The hydrogel showed excellent cytocompatibility and hemocompatibility. In the rabbit model, the PAM/HA@TA patch significantly outperformed the defect control, maintaining near-normal disc height and

hydration on MRI, and yielding superior histological scores with preserved AF/NP structure and proteoglycan content at 8 and 12 weeks.

Conclusions: We successfully developed a simple yet effective DN hydrogel patch that unifies biomechanical competence and interfacial adhesion with intrinsic antioxidant bioactivity. By physically sealing the AF defect and simultaneously quenching pathological ROS, PAM/HA@TA creates a conducive microenvironment for tissue repair, effectively mitigating post-discectomy degeneration in vivo. This strategy presents a clinically translatable and promising solution for improving long-term outcomes after lumbar disc surgery.

Key words: Intervertebral disc degeneration; Annulus fibrosus repair; Double-network hydrogel; Tannic acid; Antioxidant



Graphical abstract

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Poly(ectoine)-Based Adhesive Hydrogel with Antimicrobial and Anti-Inflammatory Properties for Wound Treatment

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Key words: adhesion, ectoine, dopamine, hydrogel, wound healing

Introduction: For hydrogel dressing, the interfacial adhesion is a great challenge because of the destruction from interface residual blood and tissue exudate. The interfacial water layer often results in poor adhesion to contact surfaces in humid environments. Besides, the growing resistance of bacteria has prioritized the search for improved antibacterial strategies. To overcome the interface dehydration and antimicrobial challenges, we have developed a poly(ectoine methacrylate) (PEMA)-based hydrogel dressing combined with Jelleine-I antimicrobial peptide (J-I AMP). EMA has a strong ability to complex water molecules due to its unique and highly polar molecular structure, however, its roles in absorbing interfacial water have not been well explored. Besides, it has been widely used due to anti-inflammatory properties. J-I AMP was a typical amphiphilic AMP, which has strong antibacterial activity and low toxicity.^[1]

Materials & Methods: AAm, NIPAAm, EMA, and DMA were used to prepare P(AAm-co-NIPAAm-co-EMA-co-DMA) hydrogel through UV-initiated radical polymerization, and the solvent was deionized water. Then, the J-I AMP was covalently linked to the hydrogel via EDC and NHS.

Results & Discussion: The PEMA-based hydrogel demonstrated superior adhesion to glass and pigskin compared to the other hydrogel groups. Furthermore, we assessed hydrogels with varying ratios of EMA and DMA, confirming that these monomers indeed improved the adhesion strength, and the content of NIPAAm was found to significantly influence adhesion strength. It should be noted that the adhesion strength of the J-I AMP-modified hydrogel was slightly lower than that of the PEMA-based hydrogel without modification, probably due to the hydrated J-I AMP, which changes surface chemistry and hence adhesion. Additionally, the PEMA-based hydrogel showed strong adhesion to mouse skin, heart, liver, spleen, lungs, kidneys, stomach, intestines, and bones. Rheological testing demonstrated that the hydrogel had stable internal structures and good viscoelasticity and resistance to deformation. The results of the tensile test indicated the hydrogel had high toughness and strong fatigue resistance. The hydrogel exhibited good cytocompatibility and anti-inflammatory properties, which reduced the expression of inflammatory cytokines in vitro and in vivo. J-I AMP-modified hydrogels had good antibacterial effects.

Conclusions: We successfully designed and developed an adhesive, tough, antimicrobial, and anti-inflammatory hydrogel as a wound dressing. EMA acted as the main adhesive component to absorb interfacial water, while NIPAAm with short hydrophobic alkyl chains disrupted the hydration layer, and hence, the hydrogel could expose catechol groups of DMA to interact directly with the substrate surface, resulting in good wet adhesion. J-I AMP was incorporated into the main chain of the hydrogel by covalent bonds, which prevented the uncontrolled release and improved antimicrobial persistence. This study employs a novel monomer capable of effectively removing interfacial water, thereby offering an alternative approach for addressing dopamine adhesion failure. Moreover, the adhesive hydrogel sped up the healing of infected wounds in vivo, which showed promising applications in biomedicine.

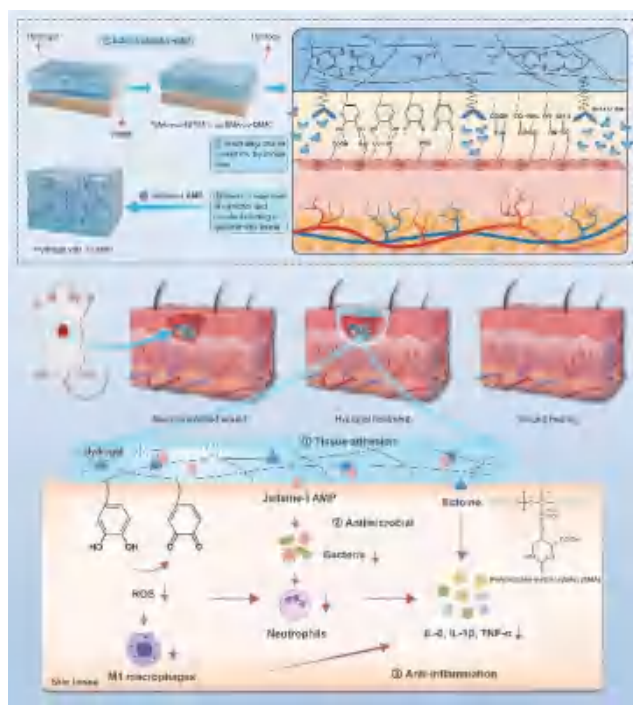


Fig. 1. Schematic illustration of the adhesion mechanism and wound treatment of poly(ectoine)-based hydrogel.

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An Ultra-Tough Bone Adhesive as Potential Clinical Solution for Complex Fracture Fixation and Healing

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Introduction: Complex fractures, especially comminuted intra-articular types, remain a major clinical challenge due to the limitations of conventional internal fixation methods. Bone adhesives offer a promising alternative, but existing materials bone adhesives are hindered by an inherent trade-off among strong wet-state adhesion, biocompatibility, and inherent osteogenic activity. To address this critical gap, we developed a dual-bionic, organic-inorganic hybrid hydrogel adhesive. This material is designed to simultaneously achieve robust adhesion in bloody environments and actively promote bone regeneration, offering an integrated bioactive strategy for complex fracture repair.

Materials & Methods: The adhesive, termed CPA, was synthesized by integrating caffeic acid-grafted collagen (CAC), aminated laponite (ALAP), and tetra-armed polyethylene glycol succinimidyl succinate (tetra-PEG-SC). Mechanical performance was evaluated through compression, tensile, and fatigue testing. Adhesive strength was quantified on wet porcine bone using lap-shear and face-to-face mechanical tests, with commercial cyanoacrylate (CA) as a control. In vitro biological assessments included cytocompatibility (NIH-3T3), hemocompatibility, antioxidant activity (DPPH assay), angiogenesis, and osteogenic differentiation. In vivo efficacy was rigorously validated using a novel rabbit radius comminuted fracture model. Fracture healing was monitored at 4, 8, and 12 weeks via radiography, micro-CT, histological analysis, and three-point bending biomechanical tests (Figure 1).

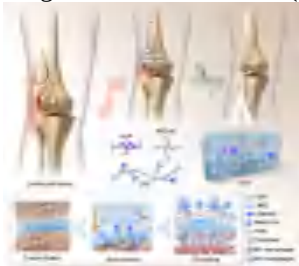


Figure 1. Schematic illustration for the preparation and characterization of the bone adhesive.

Results & Discussion: The CPA hydrogel exhibited rapid, tunable gelation (0.5–3 min), high compressive strength (~14.5 MPa at 90% strain), and exceptional tensile strength (~170 kPa). It demonstrated superior wet adhesion to bone surfaces, achieving a lap-shear strength (152.1 ± 7.3 kPa) comparable to CA, while

maintaining structural integrity. The uniform dispersion of ALAP through multiple cross-linking (covalent, ionic, hydrogen bonding, Mg^{2+} -catechol chelation) was key to its enhanced mechanical and adhesive properties. In vitro, CPA showed excellent cytocompatibility and hemocompatibility, potent antioxidant activity (>90% DPPH scavenging), and significantly promoted HUVEC migration/tube formation and BMSC osteogenic differentiation. In vivo, CPA effectively stabilized comminuted fragments in the challenging rabbit radius model. Micro-CT and histology revealed that CPA accelerated the healing process, leading to significantly higher BMD and BV/TV, complete cortical reconstruction by 8 weeks, and successful medullary canal recanalization. In contrast, control and CA groups showed delayed healing, fragment displacement, or impaired union due to poor degradability. The biomechanical strength of CPA-repaired bones at 12 weeks approached that of native bone. The osteogenic mechanism is attributed to CPA's ability to mitigate oxidative stress and modulate macrophage polarization towards a pro-healing M2 phenotype, thereby fostering a conducive osteogenic microenvironment (Figure 2).



Figure 2. Coronal tomographic images (denoted by the blue border) and three-dimensional reconstructed images (denoted by the yellow border) acquired from CT scans at 4, 8, and 12 weeks.

Conclusions: We have successfully developed a novel ultra-tough bone adhesive that uniquely integrates robust wet adhesion, matched degradation, excellent biocompatibility, and inherent osteogenic activity. This dual bionic design, leveraging organic-inorganic network reinforcement and bioactive components, enables stable fragment fixation and actively accelerates the healing of complex fractures. The CPA hydrogel represents a promising and innovative clinical strategy for fracture repair, potentially reducing reliance on traditional metal hardware.

Keywords: bone adhesive, osteogenesis, complex fracture, mechanical strength, laponite

Ultra-Robust Ionic Biogel Enabled by Multiscale Structural Design of Silk Fibril Reinforcement and DES-Induced Synergy

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Natural biogels have attracted significant attention as building blocks for advanced materials, owing to their exceptional flexibility, functionality and biocompatibility. To enhance the mechanical properties of gel materials, the strength and toughness of gels have been effectively improved by designing double-network structures, high-density uniform crystalline domain structures, and hierarchical fiber-reinforced structures. Among them, hierarchical fiber-reinforced structures, inspired by natural hydrogels, generally exhibit exceptional strength, toughness, and fatigue resistance due to their multiscale architecture, which integrates microscopic fibrils with molecular-scale crystalline units. However, several developed methods for manufacturing biomimetic fibril-structured gels, such as confined drying, mechanical training, exogenous fibril incorporation, and combinations of unidirectional freeze-casting with post-treatments (e.g., salting out, solution displacement, and annealing), although effectively improving the mechanical properties of the gels, usually involve complex, time-consuming, and energy-intensive processes, posing significant challenges for scalable production. Moreover, the stability of gel material performance in complex environments is also a highly challenging issue. Therefore, biogels that combine mechanical robustness and multifunctionality is highly valuable for developing promising flexible functional gels. In this work, we design a tough, fatigue-resistant and multifunctional ionic biogel with a distinctive multiscale structure through synergistic structural engineering, intended for wearable self-powered human-interactive sensing. By simply incorporating a silk fibril-deep eutectic solvent dispersion into an aqueous polymer solution, a hierarchical fiber-reinforced structure, a crystalline cross-linked network, and multiple functionalities are simultaneously integrated into the biogel in a single processing step. The engineered ionic biogel exhibited exceptional mechanical performance, achieving a remarkable combination of high stretchability (>620% elongation), strength (~4.25 MPa), and toughness (~12.35 MJ/m³). The stretch-induced fibril alignment further endowed the biogel with superior crack tolerance (fracture energy of 112.41 KJ/m²) and fatigue resistance (fatigue threshold of 2286 J/m²), surpassing most reported biogel systems. Beyond mechanical robustness, the biogel demonstrated multifunctional characteristics including high ionic conductivity (0.94 S/m), remarkable environmental stability over extended periods, and good recyclability. This scalable manufacturing strategy has produced multifunctional resilient ionic biogels with multiscale hierarchical structures at the micro, nano and molecular levels simultaneously, exploring promising strategies for developing bioinspired structural gels and promoting their practical applications in fields such as bioengineering and flexible electronics.

Keywords: Ionic biogel, Multiscale structure, Mechanical robustness, Multifunctionality

Body fluid-triggered adhesive hydrogels for emergency hemostasis and alveolar regeneration

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Key words: adhesive hydrogel, wound closure, rapid hemostasis, lung regeneration

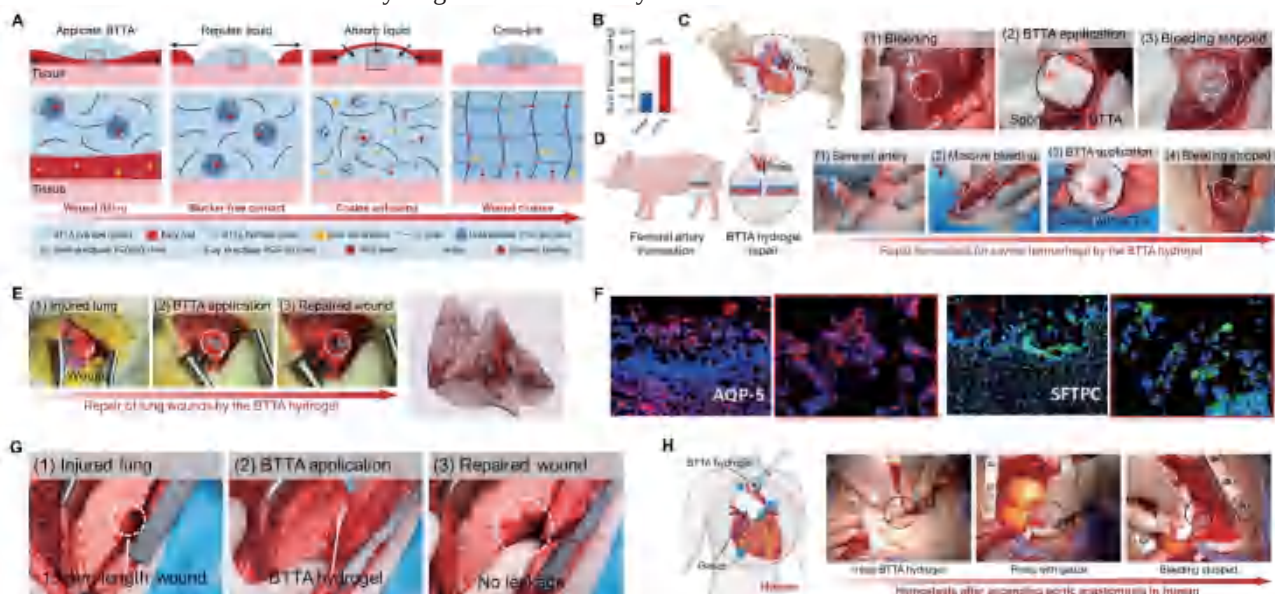
Introduction: Adhesive hydrogels are emerging products used for surgical and wound closure, with the potential to become the next generation of suture alternatives. However, existing products perform poorly in achieving hemostasis during severe bleeding and in promoting tissue regeneration. This study aims to develop a tissue-adhesive hydrogel capable of rapid emergency hemostasis and facilitating lung regeneration.

Materials & Methods: The body fluid-triggered tissue adhesive (BTTA) hydrogel was prepared by dispersing polyethylene glycol succinimidyl glutarate (PEG-SG) and polylysine (PL) in glycerol. Its application effectiveness was validated in rat and large animal (pig and sheep) models of lung wounds, femoral artery and cardiac massive hemorrhage. Finally, the hydrogel has been applied in real-world clinical patients and demonstrated excellent efficacy.

Results & Discussion: Upon wound contact, the glycerol momentarily repels the fluid on the tissue surface, preventing the hydrated layer from interfering with adhesion and facilitating full contact between the dispersed PEG-SG and the tissue surface (**Figure A**). The BTTA hydrogel withstood a burst pressure of over 350 mmHg, which is approximately three times greater than that of the commercial adhesive CoSeal™ (**Figure B**). Experiments on different large animals, which are anatomically and physiologically similar to humans, demonstrated that this BTTA hydrogel can effectively

seal femoral and cardiac wounds and rapidly stop bleeding within 30 seconds (**Figure C-D**). For the first time, an adhesive hydrogel was used for rapid hemostasis in a completely transected large animal femoral artery without blocking proximal blood flow. A rat lung wound model demonstrated the excellent lung repair effects of the BTTA hydrogel, which prevented long-term air leakage, significantly reducing inflammation and hemorrhage (**Figure E**). The PL component within the BTTA hydrogel promotes cell migration to the wound site. During the lung repair process, cells were observed migrating into the BTTA hydrogel, identified as type I and type II alveolar epithelial cells (**Figure F**), indicating that the hydrogel facilitates in situ alveolar regeneration. The ability of the BTTA hydrogel to promote lung wound closure and lung regeneration was further validated in a large animal model where the BTTA hydrogel significantly inhibited fibrous capsule formation (**Figure G**). The clinical application of hemostasis in ascending aortic anastomosis patients further demonstrates the hemostatic efficacy and clinical feasibility of the BTTA hydrogel (**Figure H**).

Conclusions: This study developed a body fluid-triggered adhesive hydrogel with ultra-strong wet adhesion properties, capable of rapidly closing wounds and stopping bleeding, while also promoting in situ alveolar regeneration. The ultra-strong performance was achieved through simple FDA-approved materials, providing a new approach for wound closure and regeneration. This approach shows great potential for clinical translation and application.



Assembly of a hierarchical hydrogel-based biomaterial for suppressing the neo-vascularization of the nucleus pulposus

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Keywords: intervertebral disc regeneration, nucleus pulposus, decellularized extracellular matrices, anti-angiogenic biomaterials, hydrogels.

Introduction: The in-growth of new blood vessels via neo-vascularization within the nucleus pulposus (NP) is a pathological feature associated with intervertebral disc (IVD) degeneration, a medical condition that culminates in disruption of the tissue's avascular microenvironment [1]. This work aims to engineer a hierarchical hydrogel-based biomaterial capable of rebuilding the biologically responsive, though anti-angiogenic character of a healthy NP. Our approach integrates three major building blocks combined into an interpenetrating network (IPN): (i) a physically crosslinked hydrogel from decellularized NPs sourced from bovine tails; (ii) a chemically crosslinked hydrogel containing elastin-like recombinamers (ELRs); and (iii) thrombospondin-1 (TSP-1). The performance of the IPNs was improved by decorating ELRs with RGD-binding and metalloproteinase (MMP)-sensitive domains. The anti-angiogenic glycoprotein TSP-1 was selected due to its ability to bind fibrillar collagens [2]. Our group has demonstrated that TSP-1 is abundant in the matrisome of fetal NPs [3], where it suppresses neo-vascularization. Its expression, however, is reduced with aging and disease.

Materials & Methods: Bovine NPs were isolated from whole IVDs collected from tails and decellularized with a 0.1% SDS-based treatment to remove cells and dsDNA. A physical hydrogel was obtained through the digestion of the decellularized NPs in 3% acetic acid and 1 mg/mL pepsin, followed by pH neutralization. TSP-1 was added at 20 mg/mL and 50 mg/mL concentrations. ELRs were prepared with azide (N_3)-modified RGD-binding, as well as cyclooctyne (CYC)-modified MMP-sensitive motifs. The building blocks were blended *in situ* and placed at 37°C for both physical crosslinking and N_3 -CYC “click” reaction. IPNs were characterized by their biomechanical behavior, swelling capacity, and degradation kinetics. *In vitro* studies with primary human fibroblasts were carried out, while the anti-angiogenic capacity was assessed with the chick chorioallantoic membrane (CAM) model.

Results & Discussion: Decellularization removed most cells and dsDNA from the NPs, allowing for the assembly of a collagen-rich physical hydrogel upon digestion with acetic acid and pepsin. TSP-1 bound acetic acid-soluble collagens *in situ*, as confirmed by the modifications in the FT-IR spectra bands, in particular the amide I, II, and III regions. TSP-1 conjugation provoked a dose-dependent,

synergistic suppression of blood vessels in CAMs treated with pro-angiogenic factors. Inhibition of vascularization in hydrogels containing the anti-angiogenic glycoprotein confirmed retention of its bioactivity after incorporation (Fig. 1). IPNs exhibited tunable porosity and viscoelastic properties due to the presence of different percentages of ELRs. Higher percentages improved mechanical stiffness and resistance to degradation, addressing the limitations observed in the physically crosslinked hydrogel. Because collagens play an active role in water retention, a crucial parameter for NP homeostasis, a balanced 50:50 ratio of physical and chemical hydrogels was used to achieve the optimal IPN formulation. All IPNs supported metabolic activity and cell viability.

Conclusions: This work presents a regenerative strategy to preserve NP avascularity and mitigate the progression of IVD degeneration. Combining decellularized ECMs with ELRs enabled the creation of a biologically active construct that emulated the architectural and mechanical aspects of the native NP. In addition, the anti-angiogenic function of TSP-1 restored the inhibitory barrier against vascular invasion *in vivo*.

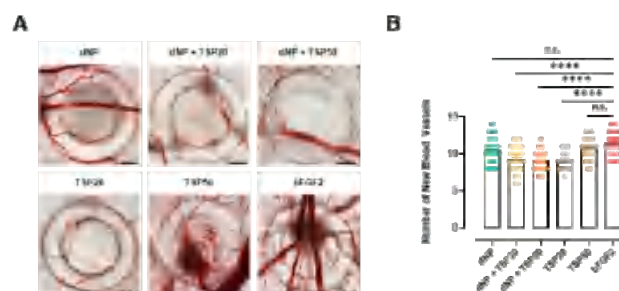


Fig. 1. (A) *Ex ovo* images of the CAMs. Scale bar: 50 μm. Magnification: 20x. (B) Number of new vessels growing towards the inoculation site (n = 15-28, N = 3). Mean ± SEM. One-way ANOVA. Sidak's Multiple Comparison Test. **** $p < 0.0001$. dNP: Decellularized NP. TSP20: 20 mg/mL TSP-1. TSP50: 50 mg/mL TSP-1.

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Piezoelectric Injectable Anti-adhesive Hydrogel to Promote Endogenous Healing of Tendon Injuries

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Key words: piezoelectric stimulation, injectable anti-adhesive hydrogel, tendon adhesion, tendon repair

Introduction: Achilles tendon rupture has become a common sports injury nowadays, but tendon repair is still a challenge in the clinical practice. Tendon adhesion, which results from exogenous healing, is a crucial problem impairing tendon repair. Meanwhile, insufficient endogenous healing from the tendon stem cells, makes tendon repair even more difficult.

Materials & Methods: The bioabsorbable natural materials carboxymethyl chitosan (CMCS) and hyaluronic acid (HA) are employed to form the injectable anti-adhesive hydrogel (IAH), which can effectively inhibit adhesion and inflammatory response both in vitro and in vivo. The piezoelectric property of the PE-IAH originates from annealed poly-L-lactic acid (PLLA) short nanofibers. PLLA is cut into short fibers and incorporated with the IAH to form a PE-IAH that can achieve both piezoelectric stimulation and anti-adhesion effect, while retaining the injectable properties of IAH.

Results & Discussion: The physical barrier and anti-inflammatory effect of the IAH reduced the exogenous healing from the tissue around the tendon, providing suitable immune microenvironment for the tendon endogenous healing. The piezoelectric PLLA short fibers in the PE-IAH could generate piezoelectric stimulation under US excitation, which were demonstrated to promote the proliferation and differentiation of endogenous TSPCs into tenocytes, and rebuilt the extracellular matrix through the synthesis and secretion of collagen. In addition to promoting tendon healing, the synergistic effect of piezoelectric stimulation and the IAH also greatly reshaped the biomechanical function of the tendon and restored the movement function of rats with tendon rupture.

Conclusions: This strategy provides a more efficient and safer new method for clinical treatment, which is expected to improve the rehabilitation effect and life quality of patients with tendon injuries.

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Biodegradable hydrogel adhesives based on *o*-phthalaldehyde-amine crosslinking for rapid wound closure and hemostasis

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Key words: hydrogels, rapid gelation, tissue adhesion, wound closure, hemostasis

Introduction: Medical tissue adhesives have received increasing attention as an emerging class of wound closure materials. Nevertheless, major challenges including poor biocompatibility, weak tissue adhesion, undesired degradation behavior, limited functionality still remain.

Materials & Methods: A type of hydrogel adhesives were facilely prepared by mixing OPA-terminated 4-armed poly(ethylene glycol) and amine-/hydrazide-containing natural and synthetic polymers as well as their derivatives. The mechanical properties, tissue adhesion property, biodegradation behaviors, and biocompatibility were investigated. The efficiencies of the hydrogel adhesives in the sutureless wound closure, anastomotic sealing and hemostasis in diverse animal models were evaluated.

Results & Discussion: In our recent studies, a new strategy for catalyst-free, rapid hydrogel formation under physiological condition was developed via the *o*-phthalaldehyde (OPA) and amino groups (primary amines, hydrazine groups) condensation [1]. A tissue adhesion mechanism of the formation of stable phthalimidine moieties between the OPA groups in the hydrogel and the primary amines in the tissues was proposed, which mediates the formation of seamless hydrogel-tissue interface and strong tissue adhesion [2]. The hydrogel exhibited excellent biocompatibility, and the biodegradation of the hydrogels could be tuned by introduction of stimuli-responsive cleavable bonds such as disulfide bonds into the crosslinking network. In diverse animal models including full-thickness skin incision, organ injury bleeding and dura mater defect models, the hydrogels achieved robust sutureless closure and repair of skin incision, rapid hemostasis of organ injury, as well as sealing and effective repair of dura mater defects [2,3].

Conclusions:

A type of biodegradable and biocompatible hydrogels adhesives were developed via the OPA-amine condensation. The hydrogels exhibited good biocompatibility and tunable biodegradation behaviors. A new mechanism on hydrogel-tissue adhesion was disclosed, leading to the formation of firmly adhered interfaces. In various animal wound models, the

hydrogels achieved robust suture wound closure, efficient sealing of dura matter defects and rapid hemostasis. The results have shown strong potential of the hydrogel adhesives in clinical wound treatments.

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Dynamic GelMA-UPy Bioinks for Multimodal 3D Bioprinting

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Key words: Dynamic bioink, 3D bioprinting, 3D cell culture, Ureidopyrimidinone

Introduction: Gelatin methacryloyl (GelMA) is one of the most widely used bioinks for 3D bioprinting because of its photocrosslinkability, biocompatibility, and inherent cell-adhesive motifs. However, conventional GelMA still exhibits limited printability and forms a relatively static covalent network, which restricts shape fidelity, adaptability to multimodal printing, and the ability to recapitulate the dynamic extracellular matrix (ECM). Although increasing polymer concentration can improve printability, it often results in higher viscosity, greater extrusion-induced stress, and reduced cell compatibility. To overcome these limitations, dynamic supramolecular ureidopyrimidinone (UPy) units were introduced into GelMA. The reversible quadruple hydrogen bonding of UPy enhances shear-thinning behavior, structural recovery, and print fidelity, while also providing a more dynamic and cell-responsive microenvironment for 3D cell culture.

Materials & Methods: GelMA-UPy was synthesized by reacting GelMA with UPy-NCO in anhydrous DMSO under N₂, followed by purification and vacuum drying. Its structure was characterized by NMR and FTIR, while mechanical and rheological properties were evaluated by mechanical testing and rheology. Printability was assessed by extrusion and DLP printing. For biological evaluation, cells were encapsulated in GelMA-UPy and analyzed for viability and morphology by FDA/PI and F-actin/DAPI staining.

Results & Discussion: GelMA-UPy was successfully synthesized, as confirmed by NMR, MS, and FTIR. Compared with GelMA, GelMA-UPy exhibited improved shear-thinning behavior, enhanced mechanical performance (1.7-fold higher compressive modulus and 3-fold higher compressive strength), reduced swelling, and slower early-stage degradation. In addition, the incorporation of UPy generated a hierarchical porous structure, which increased scaffold porosity. In terms of printing performance, GelMA-UPy enabled the stable fabrication of complex, large-scale scaffolds by extrusion printing and showed improved suitability for DLP printing after optimization of the MA/UPy ratio. Among all formulations, the bioink with MA/UPy = 0.65:0.30 achieved the best balance between printability and bioactivity. Moreover, GelMA-UPy better supported MSCs spreading and long-term viability than GelMA,

highlighting its potential as a high-performance bioink for tissue engineering.

Conclusions: A UPy-functionalized GelMA bioink was successfully developed, exhibiting enhanced mechanical strength, printability, and bioactivity through reversible UPy hydrogen bonding (Fig. 1). The optimized MA/UPy ratio of GelMA-UPy enables compatibility with multimodal bioprinting, highlighting its strong potential for tissue engineering and regenerative medicine.

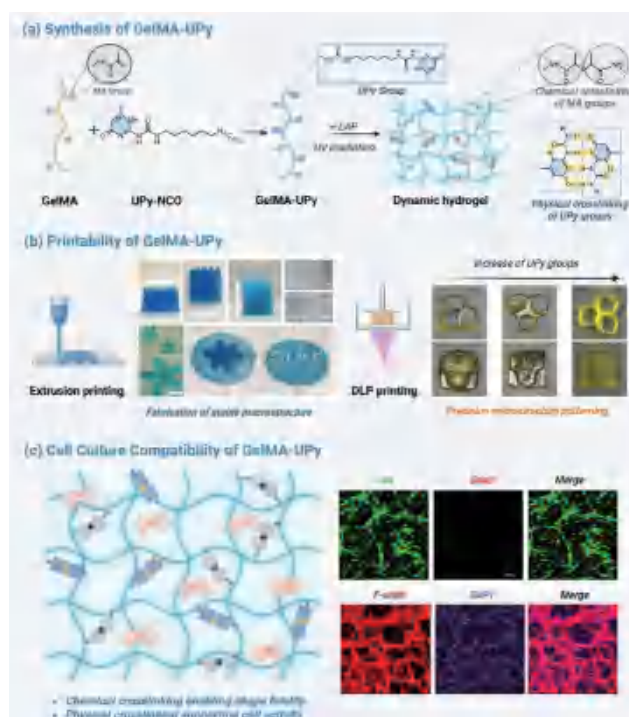


Fig. 1. Schematic illustration of the GelMA-UPy bioink for multimodal 3D printing and cell culture.

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Ultra-robust Silk-based Eutectogels Engineered via Polymeric Reconstruction and Supramolecular Network Reinforcement

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Natural polymer-based gel materials are promising candidates for advanced sustainable applications. Silk fibroin (SF), derived from *Bombyx mori*, has been widely explored as a high-performance biomaterial owing to its favorable chemical processability, good biocompatibility, and biodegradability. However, conventional silk fibroin-based biogels typically suffer from poor mechanical properties, which significantly limits their practical use in complex scenarios. Moreover, conventional silk processing involves time-consuming, complicated, and energy-intensive dissolution using irritative solvents or solution. Here, mechanically robust silk-based eutectogels were designed and fabricated via a sustainable one-pot strategy in which a zinc-based functional deep eutectic solvent (DES) composed of ZnCl₂, lactic acid, and acrylic acid was developed for disrupting the compact architecture of degummed silk fibers, yielding a silk fibroin dispersion. Concurrently, Zn²⁺-induced in-situ polymerization of acrylic acid without the need for photo initiators enabled polymeric reconstruction through the molecular-level integration of silk fibroin and polyacrylic acid phases. Notably, strong interactions among the DES components and silk fibroin integrated the supramolecular network into the resulting eutectogel, synergistically contributing to its ultra-robust mechanical performance. The obtained eutectogel exhibited a tensile strength of 11.4 MPa, an elongation at break of 910%, and a toughness of 46.6 MJ/m³. Furthermore, the thermal stability of the DES imparted superior environmental adaptability, as evidenced by remained mechanical properties under both high and subzero temperatures. This strategy is extendable to other biopolymers, such as cellulose and gelatin, offering a general route for engineering biomaterials via structural reconfiguration.

Keywords: Silk fibroin, Eutectogel, mechanical robustness, polymeric reconstruction, supramolecular network reinforcement

A Mild Base-Free SuFEx Strategy for β -Sultams Construction

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Introduction: Click chemistry has become an important tool for the design and functionalization of biomedical materials because of its efficiency, selectivity, and operational simplicity [1]. β -Sultams are attractive bioactive motifs, but their synthesis usually relies on harsh conditions or prefunctionalized substrates, which limits their broader use in biomolecular and biomaterial design [2]. **Materials & Methods:** Here, we report a mild, base-free SuFEx strategy promoted by silica gel for the one-step construction of β -sultams from primary amines and ethenesulfonyl fluoride. The reaction proceeds under simple conditions and is applicable to a range of structurally diverse amines, including bioactive molecular scaffolds. **Results & Discussion:** This method enabled efficient construction of diverse β -sultam-containing molecules with broad substrate compatibility and functional group tolerance. It was also applicable to late-stage modification of bioactive molecules. These features suggest its potential as a molecular platform for preparing bioactive building blocks relevant to antibacterial materials and functional biomaterial systems. **Conclusions:** This work provides a practical route to β -sultam construction and expands the chemical toolbox for future biomedical material design, especially for bioactive and responsive material platforms.

Key words: β -Sultams; SuFEx click chemistry; silica gel promotion; bioactive molecules

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Injectable Nanoparticle–Glycopeptide Composite Hydrogel Regulates Macrophage Polarization for Anti-Inflammatory Therapy via Oxidative Stress Alleviation and Metabolic reprogramming

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INTRODUCTION

Macrophage polarization plays a pivotal role in the development of inflammatory diseases, where an imbalance between pro-inflammatory M1 and anti-inflammatory M2 phenotypes drives chronic inflammation and tissue damage. Strategies that modulate oxidative stress and cellular metabolism have emerged as effective means to regulate macrophage function. Injectable nanomaterial-based hydrogels offer localized delivery and biocompatibility, making them ideal platforms for immune modulation. Here, we developed an injectable nanoparticle–glycopeptide composite hydrogel that integrates chlorogenic acid–Mn²⁺ nanoparticles with an ECM-mimicking hydrogel to regulate macrophage polarization in situ. This system not only alleviates oxidative stress but also reduces the proportion of M1 macrophages via metabolic reprogramming, providing a promising approach for inflammation control via targeted metabolic and immune modulation.

METHODS AND RESULTS

Initially, the preparation process of CGA-Mn nanoparticles was optimized, and the optimal synthesis ratio was determined. These nanoparticles exhibited pH-responsive release of CGA under weakly acidic conditions. Subsequently, the nanoparticles were incorporated into a glycopeptide hydrogel GRgel¹ constructed via dynamic imine bond crosslinking. The resulting composite hydrogel demonstrated a well-defined three-dimensional porous structure, self-healing capability, as well as good hemocompatibility and cytocompatibility. In vitro functional studies further revealed that CGA-Mn@GRgel¹ could effectively eliminate both intracellular and extracellular ROS, while maintaining mitochondrial membrane potential and ATP levels in macrophages under inflammatory conditions, thereby exerting anti-inflammatory effects mediated through metabolic regulation.

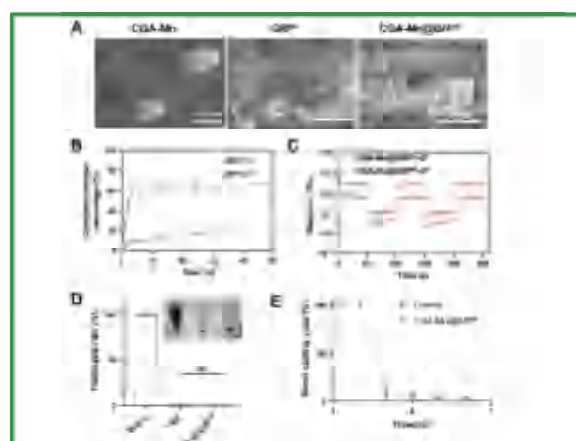


Figure 1. The injectable hydrogel is composed of a composite system integrating CGA-Mn nanoparticle with a glycopeptide-based hydrogel matrix. The nanoparticles are capable of disassembling in the weakly acidic microenvironment of injured tissues, thereby enabling the controlled release of bioactive components. The hydrogel exhibits self-healing properties and demonstrates good hemocompatibility.

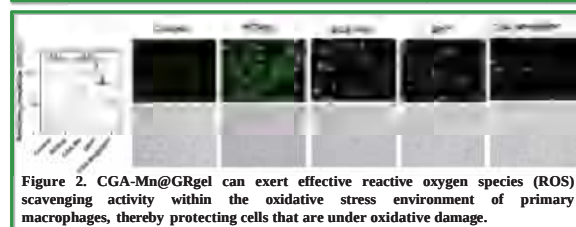


Figure 2. CGA-Mn@GRgel can exert effective reactive oxygen species (ROS) scavenging activity within the oxidative stress environment of primary macrophages, thereby protecting cells that are under oxidative damage.

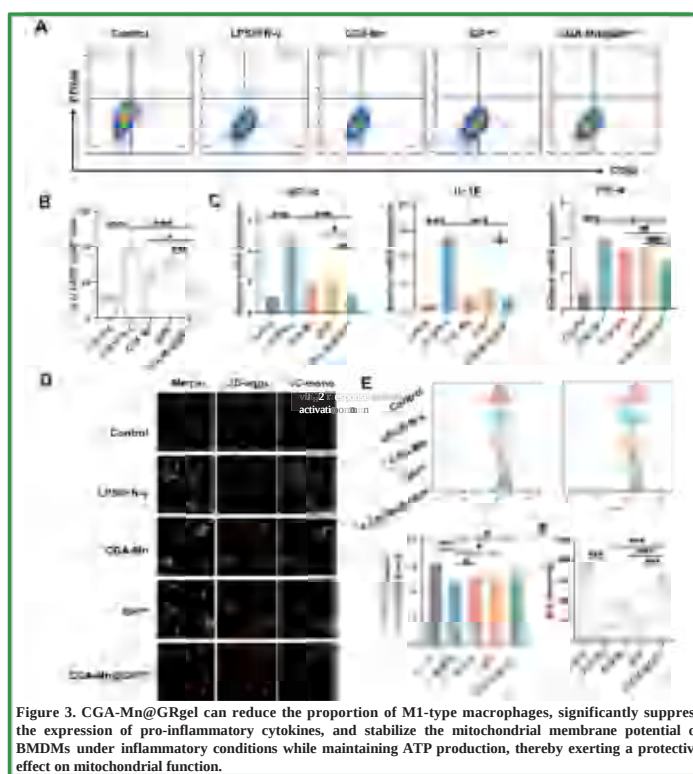


Figure 3. CGA-Mn@GRgel can reduce the proportion of M1-type macrophages, significantly suppress the expression of pro-inflammatory cytokines, and stabilize the mitochondrial membrane potential of BMDMs under inflammatory conditions while maintaining ATP production, thereby exerting a protective effect on mitochondrial function.

CONCLUSIONS

In summary, this project takes advantage of the coordination between the carboxyl groups of chlorogenic acid and Mn²⁺ to construct CGA-Mn nanoparticles via a chelation reaction. These nanoparticles were subsequently incorporated into a glycopeptide hydrogel to develop an injectable in situ therapeutic platform. This injectable hydrogel system exhibits antioxidative stress, anti-inflammatory, and metabolic regulatory effects, thereby providing a novel strategy for metabolic regulation-based interventions in inflammatory diseases.

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Powering STING and Reversing IDO: A Metallo-Supramolecular Nanoplatfom for Imaging-Guided Photothermal Tumor Immunotherapy

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Key words: amino acid, self assembly, cancer therapy, theranostics

Introduction: Photothermal therapy (PTT), while promising, faces significant clinical limitations. These include incomplete tumor ablation, which can lead to recurrence, and the presence of an immunosuppressive tumor microenvironment (TME) that hinders systemic antitumor immunity. A key immunosuppressive mechanism involves the upregulation of indoleamine 2,3-dioxygenase (IDO). Conversely, activating the stimulator of interferon genes (STING) pathway is a potent strategy to stimulate innate immunity and reverse immunosuppression, but its efficacy is often constrained by inefficient and tumor-specific delivery of activators. To address these interconnected challenges, we developed a multifunctional metallo-supramolecular nanoplatfom designed to synergize imaging-guided PTT with targeted immunoregulation for enhanced anticancer therapy.

Materials & Methods: A manganese-based metallo-supramolecular nanoplatfom, designated MCTG, was constructed via a one-pot, coordination-driven self-assembly process. The platform was formed using Mn^{2+} ions, a cysteine-derived organic ligand, and concurrently loaded with the IDO inhibitor 1-methyltryptophan (1-MT) and the near-infrared photosensitizer indocyanine green (ICG). The resulting nanoparticles were characterized for size, morphology, and stability. Their intrinsic capabilities for T1-weighted magnetic resonance (MR) and photoacoustic (PA) imaging were validated in vitro. The photothermal conversion efficiency and photostability under 808 nm laser irradiation were quantitatively assessed. In vitro studies evaluated cellular uptake, photothermal cytotoxicity, and induction of immunogenic cell death (ICD). In vivo efficacy was investigated using murine tumor models, where the nanoparticles were administered intravenously, followed by MR/PA imaging-guided PTT.

Results & Discussion: The synthesized MCTG nanoparticles exhibited uniform size, excellent colloidal stability, and pronounced MR/PA contrast, enabling precise imaging-guided tumor localization. They demonstrated a high photothermal conversion efficiency and remarkable structural stability upon repeated laser irradiation. In vivo, under 808 nm laser illumination, MCTG mediated effective tumor ablation and triggered pronounced ICD, as evidenced by the surface exposure of calreticulin and release of high-mobility group box 1 (HMGB1). Concurrently, the degradation of the nanostructure within the TME led to the release of its components. The released Mn^{2+} ions potently activated the STING pathway, amplifying proinflammatory cytokine signaling. Simultaneously, the sustained release of 1-MT effectively suppressed IDO activity, alleviating local immunosuppression. This synergistic

immunoregulation—STING activation combined with IDO inhibition—resulted in a profound remodeling of the TME. This was confirmed by significant enhancement of dendritic cell (DC) maturation in tumor-draining lymph nodes and a marked increase in the infiltration of cytotoxic T lymphocytes (CTLs) into tumors. Consequently, robust systemic antitumor immunity was elicited, contributing to strong inhibitory effects on both primary and distant tumors.

Conclusions: In summary, we have successfully constructed a multifunctional metallo-supramolecular nanoplatfom, MCTG, via a straightforward coordination self-assembly strategy. This platform seamlessly integrates capabilities for dual-modal imaging, highly efficient photothermal therapy, and synergistic immunomodulation within a single agent. By concurrently activating the STING pathway with Mn^{2+} and inhibiting the IDO pathway with 1-MT, MCTG effectively reverses the immunosuppressive TME and potentiates systemic antitumor immunity following photothermal ablation. This work presents a promising combinatorial paradigm that addresses the major limitations of conventional PTT, showing significant potential for the treatment of metastatic and recurrent cancers.

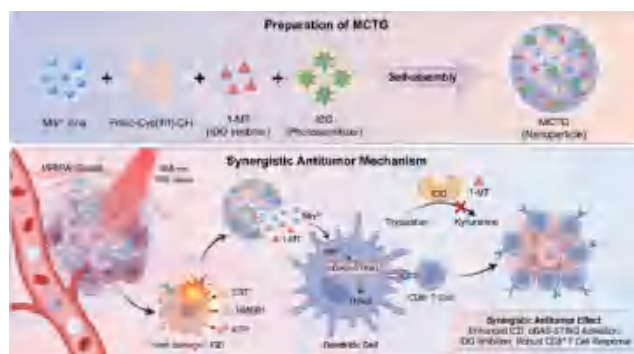


Fig.1. Synthesis of MCTG nanoparticles and mechanism in cancer diagnosis and treatment.

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Inhalable Nanovaccine Based on Bioengineered Bacteria-Derived Membrane Vesicles Against Lung Metastasis

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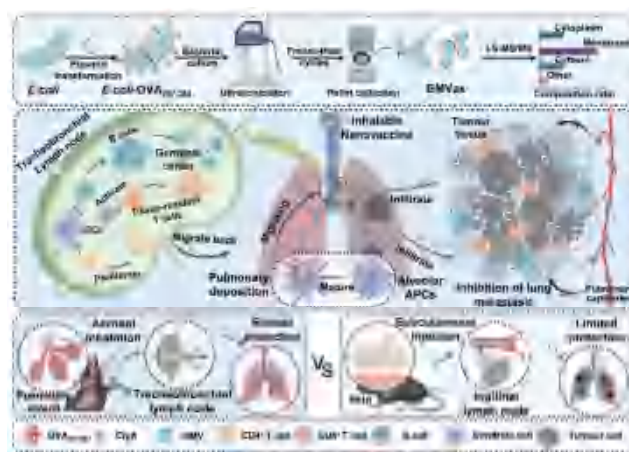
Key words: Genetically Engineered Bacteria, Membrane Vesicles, Inhalable Nanovaccine, Lung Metastasis, Cancer Immunotherapy

Introduction: Inhalable mucosal vaccines offer a compelling strategy for cancer immunotherapy by directly targeting the lungs, a primary site of metastatic colonization. Unlike subcutaneous vaccination, which mainly induces systemic immunity, pulmonary immunization engages lung-resident antigen-presenting cells and mucosal immune networks, enabling rapid local immune activation while also supporting systemic immune memory. However, the efficacy of inhalable vaccines is often limited by insufficient antigen stability, poor mucosal penetration, and inefficient antigen presentation. Bacterial membrane vesicles (BMVs) are nanoscale vesicles derived from bacterial membranes that retain intrinsic immunostimulatory components and can be genetically engineered to display defined antigens. Importantly, BMVs exhibit natural mucosal barrier-penetrating capability, making them particularly suitable for pulmonary delivery. Together, their strong immunogenicity, genetic editability, and mucosal permeability position BMVs as a promising platform for inhalable cancer vaccines targeting lung metastasis.

Materials & Methods: Engineered *E. coli* expressing the ClyA-OVA₂₅₇₋₂₆₄ fusion protein were generated by cloning a codon-optimized sequence into the pBAD vector and transforming it into *E. coli* TOP10. BMVs were isolated from bacterial lysates through ultrasonication, freeze-thaw cycles, and differential centrifugation, followed by resuspension in PBS. Vesicle size, zeta potential, morphology, stability, and endotoxin levels were systematically characterized using DLS, TEM, and standard biochemical assays.

Results & Discussion: We developed an inhalable nanovaccine (BMVax) based on membrane vesicles derived from engineered *E. coli* expressing OVA₂₅₇₋₂₆₄ (Scheme 1). BMVax displayed a uniform nanoscale size, excellent colloidal stability, and preserved intrinsic immunostimulatory properties. In vitro, BMVax markedly enhanced antigen uptake and cross-presentation, leading to robust activation of antigen-specific T cells. Pulmonary immunization with BMVax induced potent immune responses in tracheobronchial lymph nodes, including significant increases in germinal center B cells (5.8-fold), mature dendritic cells (2.5-fold), and follicular helper T cells (4.9-fold). In lung tissue, tissue-resident CD8⁺ T cells and antigen-specific CD8⁺ T cells increased by 3.9-fold and 2.7-fold, respectively. Notably, inhalation immunization also elicited systemic

immunity, as splenic CD8⁺ T cells exhibited elevated TNF- α and IFN- γ production upon antigen restimulation. In a B16-OVA melanoma lung metastasis model, BMVax achieved an 83.3% complete prevention rate, with minimal metastatic burden observed 30 days post tumor challenge. Compared with subcutaneous vaccination, inhaled BMVax significantly enhanced immune activation in lung-draining lymph nodes and promoted superior recruitment and functionality of antigen-specific T cells in lung tissue. Subcutaneous administration failed to activate tracheobronchial lymph node immunity and showed limited therapeutic efficacy, resulting in substantial pulmonary tumor nodules.



Scheme 1. Schematic illustration of the inhalable nanovaccine leveraging bioengineered bacteria-derived membrane vesicles against lung metastasis

Conclusions: This study presents BMVax, an inhalable nanovaccine derived from genetically engineered bacterial membrane vesicles, as a powerful platform for pulmonary cancer immunotherapy. By integrating antigen delivery and intrinsic adjuvanticity within a single vesicle, BMVax efficiently activates both local mucosal and systemic immune responses. Inhaled BMVax demonstrated superior preventive and therapeutic efficacy against lung metastasis compared with conventional subcutaneous vaccination. Its straightforward production, strong immunogenicity, and effective mucosal penetration highlight the translational potential of BMVax as a next-generation inhalable cancer vaccine for the treatment of metastatic tumors.

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Engineering M2 macrophage-derived exosomes modulate activated T cell cuproptosis to promote immune tolerance in rheumatoid arthritis

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Key words: rheumatoid arthritis, immune tolerance, cuproptosis, exosome, nanomedicine

Introduction: Rheumatoid arthritis (RA) is an autoimmune disease driven by aberrant T cell activation. Current immunosuppressive therapies lack specificity and risk systemic immune suppression. Inducing antigen-specific immune tolerance while halting inflammatory progression remains a major challenge. Here, we developed a targeted nanomedicine to selectively eliminate activated T cells and promote durable immune tolerance.

Materials & Methods: M2 macrophage-derived exosomes (M2-Exos) were isolated and loaded with ultrafine copper sulfide nanoparticles (CuS NPs), citrullinated peptide antigen (CitP), and rapamycin (Rapa) via sonication, forming M2Exo@CuS-CitP-Rapa (M2CPR). Physicochemical properties were characterized by TEM, NTA, DLS, and UV-vis. In vitro studies used CTLL2 (T cell line), RAW264.7, and BMDCs. In vivo efficacy was evaluated in a collagen-induced arthritis (CIA) mouse model. Targeting, biosafety, and immune cell profiles were assessed via imaging, histology, flow cytometry, and ELISA.

Results & Discussion: M2CPR exhibited uniform size (~142 nm) and high loading efficiency. It selectively accumulated in inflamed joints of CIA mice and showed good biosafety. In vitro, M2CPR induced cuproptosis in activated CTLL2 cells but not in resting T cells, due to their enhanced mitochondrial respiration. This led to phagocytosis by macrophages and TGF- β release. Combined with Rapa, M2CPR promoted differentiation of tolerogenic dendritic cells (tDCs) and Tregs, establishing an antigen-specific immune tolerance cycle. In vivo, M2CPR significantly reduced arthritis scores, paw swelling, pro-inflammatory cytokines (TNF- α , IL-1 β , IL-17), and increased anti-inflammatory cytokines (IL-10, TGF- β). Flow cytometry confirmed elevated Tregs and tDCs in M2CPR-treated mice.

Conclusions: We successfully engineered M2-Exos to deliver CuS NPs, CitP, and Rapa for targeted RA therapy. M2CPR selectively eliminates activated T cells via cuproptosis and induces robust antigen-specific immune tolerance without broad immunosuppression. This strategy offers a novel paradigm for RA treatment and potential application in other autoimmune diseases. Future studies should focus on clinical translation and long-term tolerance monitoring.

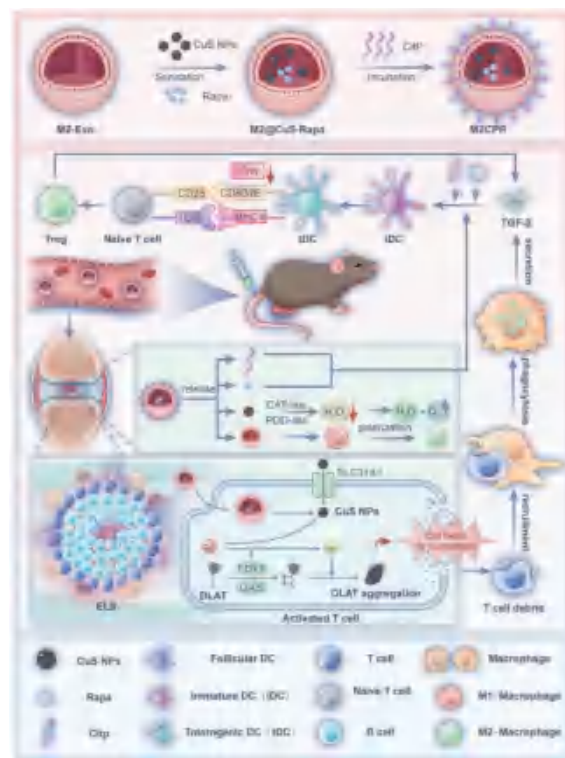


Fig. 1. Therapeutic Process Diagram of M2CPR.

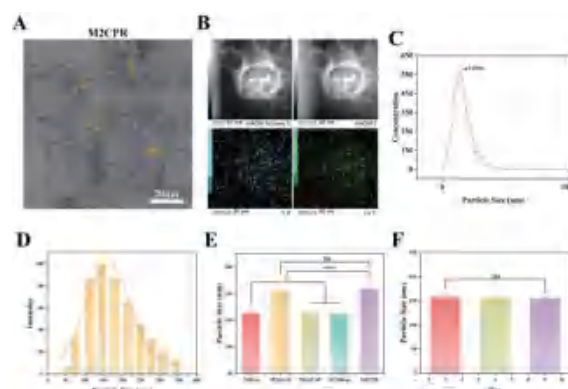


Fig. 2. Characterization of M2CPR. (A) TEM image, (B) Elemental mapping of Cu and S in M2CPR, etc.

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Polymer-Grafted Liposomes to Overcome Drug Resistance in Triple-Negative Breast Cancer: Insights from an Orthotopic Model

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Key words: triple-negative breast cancer, multidrug resistance, polymer-grafted liposomes

Introduction: Triple-negative breast cancer (TNBC) is an aggressive subtype lacking hormone receptors and HER2, often linked to epidermal growth factor receptor (EGFR) overexpression. A key challenge in TNBC therapy is multidrug resistance (MDR), which reduces the efficacy of standard chemotherapeutics. While liposomal formulations improve drug delivery, their ability to overcome MDR remains limited. Incorporating polymers into liposomes offers enhanced drug loading, stability, and cellular uptake.

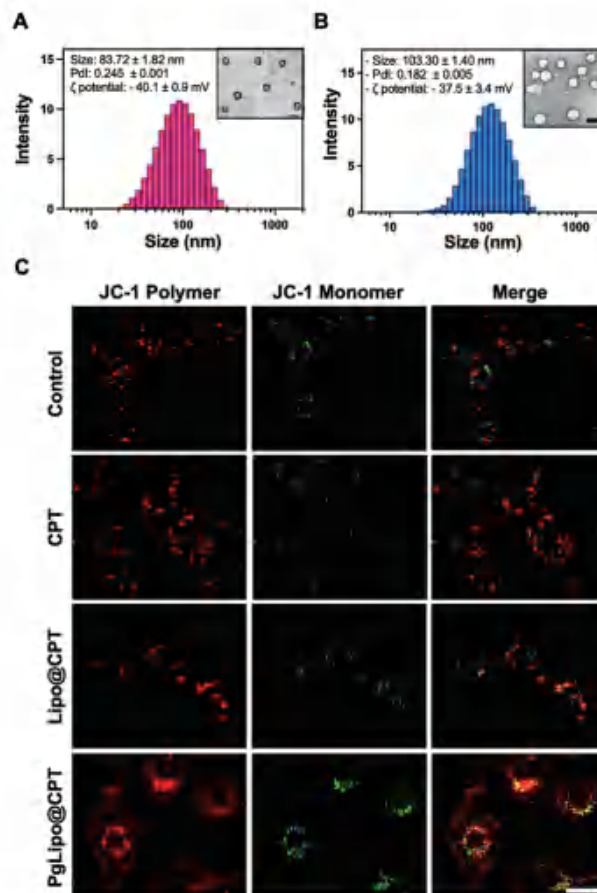
Materials & Methods: EGF peptide was conjugated with lipid and analyzed by NMR. The liposomes and polymer-grafted liposomes encapsulating camptothecin (PgLipo@CPT) were prepared by the thin-film hydration method. They were then characterized by DLS and TEM for size, zeta potential, and stability. Cytotoxicity was evaluated by CCK-8 assay. The uptake of PgLipo@CPT into breast cancer cells was evaluated by confocal microscopy and flow cytometry. To detect the cell death signal, the mitochondrial potential was evaluated by mitochondrial membrane potential indicator, JC-1. The DNA damage was confirmed with anti- γ -H2AX antibody via confocal microscopy.

Results & Discussion: In this study, we developed PgLipo@CPT to overcome TNBC-associated MDR. PgLipo@CPT showed a uniform spherical morphology (80–100 nm) with encapsulation and loading efficiencies of 18.01% and 9.69%, respectively. In MDA-MB-231/MDR cells, PgLipo@CPT exhibited superior cellular uptake and cytotoxicity compared to free CPT and conventional liposomes. Confocal microscopy revealed increased intracellular accumulation and marked mitochondrial damage after PgLipo@CPT treatment. In an orthotopic TNBC mouse model, PgLipo@CPT achieved >80% tumor inhibition relative to controls and ~50% compared to standard liposomes, with minimal systemic toxicity confirmed by stable body weights and normal histology of major organs.

Conclusions: Overall, these results demonstrate that EGFR-targeted polymer-integrated liposomes offer an efficient strategy to overcome MDR in TNBC and hold strong potential for translational cancer therapy.

Figure 1. Physicochemical characteristics of Lipo@CPT (A) and PgLipo@CPT (B). Representative

images of mitochondrial membrane potential after the treatment (C).



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A cascade enzyme system based on the catalase-like activity of Co-MQDs for enhanced visualized tumor combination therapy

Kai Long, Xinxin Yuan, Chang Yin, Zhi Yuan*

Abstract

Catalytic therapy based on natural enzymes and nanozymes is a highly promising cancer treatment strategy. Glucose oxidase (GOx) is a natural enzyme, which can decompose glucose in tumor cells to produce gluconic acid and hydrogen peroxide (H_2O_2) in the presence of oxygen, thereby inducing tumor starvation therapy. However, the hypoxic tumor microenvironment severely limits its therapeutic efficacy. To address the oxygen supply issue and enhance treatment outcomes. Herein, by in-situ introducing cobalt atoms at one end of the MQDs, we obtained the quantum dot CM, which retains the outstanding properties of MQDs while exhibiting significantly enhanced CAT-like activity and photothermal performance. CM and GOx were loaded onto persistent luminescence nanoparticles (ZGGC PLNPs) and modified with human serum albumin (HSA) to construct an enzyme cascade system, Z-CM/GOx-HSA, for visualized tumor therapy. Afterglow imaging confirmed the system's enrichment at the tumor site, guiding the initiation of photothermal therapy (PTT) and achieving a temperature increase of about 20 °C. At the tumor site, CM decomposes the overexpressed H_2O_2 into oxygen, alleviating tumor hypoxia, while accelerating GOx-mediated glucose breakdown to starve the tumor and generate additional H_2O_2 . The newly formed H_2O_2 is then continuously split by CM, creating a positive-feedback loop that markedly amplifies the synergistic photothermal/catalytic therapeutic effect. Z-CM/GOx-HSA exhibited remarkable tumor-killing efficacy, with a tumor inhibition rate of 93.7%, far superior to single-treatment strategies. Moreover, its non-autofluorescent visualization capability allows for real-time monitoring of the therapeutic process. Overall, this visualized enzyme cascade system effectively enhances tumor therapeutic efficacy and demonstrates excellent biosafety, providing strong support for visualized tumor catalytic combination therapy.

Keywords: Nanozyme, Catalase-like activity, Enzyme cascade system, Combined photothermal/catalytic therapy, Visualized tumor therapy



Dual Antibiotics-Based pH-Responsive Carrier-Free Nanodrug against Bacterial Mixed Infection for Accelerated Wound Healing

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Abstract

Bacterial co-infections hinder wound healing. To overcome limitations of antibiotics and carriers, we developed a pH-responsive carrier-free nanodrug to target resistant G^+ and G^- bacteria.

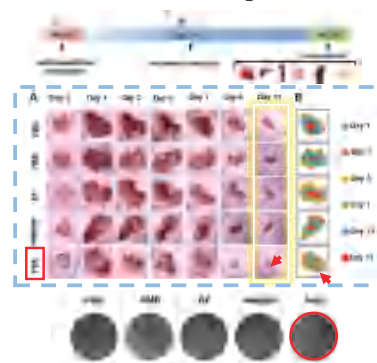
Methods

Carrier-free nanodrug self-assembles via a Schiff-base linkage between PMB and BF



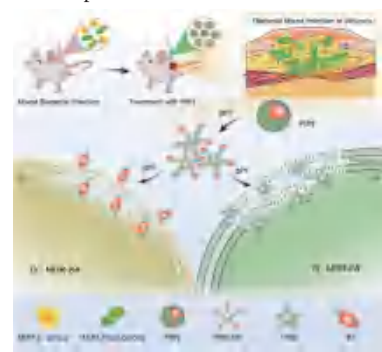
Results

In a mouse model with mixed-bacterial wound infection, the nanodrug group showed nearly no bacterial residue and the fastest wound healing.



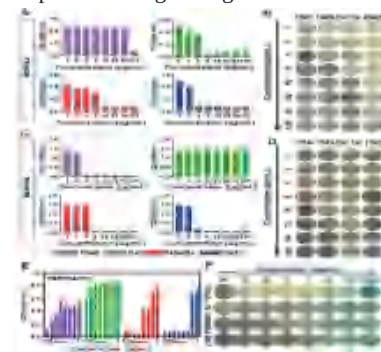
Hypotheses

Drugs for G^+ and G^- bacteria are self-assembled into carrier-free nanodrug for acid-responsive release at infection sites.



Results

Against G^+ , BF is dominant; against G^- , is PMB. For co-infections, the particle outperforms single-drug.



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Macromolecular MRI Contrast Agent Based on Polyaspartic Acid-grafted-Dopamine Polymer and Its Application in Animal Studies for Noninvasive Assessment of Renal Injury

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Key words: Iron-based contrast agents, nanoparticles, magnetic resonance imaging, biomaterials

Introduction: Acute kidney injury (AKI) is a common clinical condition, mainly characterized by a sudden decline in kidney function. Early diagnosis is crucial for improving patient prognosis. Traditional methods for assessing renal function, such as serum creatinine and urine output measurement, often lag behind the actual occurrence of kidney injury. Therefore, there is an urgent need to develop more sensitive and non-invasive diagnostic tools. In recent years, novel iron-based contrast agents have attracted attention for their applications in imaging technologies, especially showing potential in the diagnosis of AKI. Iron-based contrast agents are mainly composed of nanoscale iron particles, which have good biocompatibility and safety. Compared with traditional gadolinium-based contrast agents, iron-based contrast agents show higher contrast in various imaging techniques, effectively enhancing renal imaging. This type of contrast agent can enter the bloodstream via intravenous injection and accumulate in the renal tubules and renal interstitium.

Materials & Methods: First, synthesize polyaspartic acid (PASP) as the base polymer, and introduce dopamine for chemical modification through reaction, ensuring the reaction is complete. Polymerization is carried out under appropriate solvent and catalyst conditions, and unreacted monomers and by-products are removed using a precipitation method. The structure and properties of the synthesized product are confirmed by methods such as NMR. The reaction is generally controlled at room temperature to 60 °C, lasting from several hours to 24 hours, using specific acid or base catalysts. The molar ratio of reactants PASP and DAF_e is controlled between 1:1 and 1:3. The product is purified through cooling, filtration, and washing to ensure the removal of impurities.

Results & Discussion: Current experimental results show that iron-based contrast agents have superior imaging performance compared to traditional contrast agents and significantly reduce indicators of kidney injury (such as serum creatinine and blood urea nitrogen). Imaging analysis indicates that this contrast agent can clearly depict kidney structures and provide important diagnostic information. At the same time, experiments with low-toxicity cell culture traditional imaging agents show that MRI scans of the kidneys clearly reflect cell-level results, indicating that

iron-based contrast agents can provide early imaging information of the kidneys before kidney function declines, thereby helping doctors identify the risk of AKI at an early stage.

Conclusions: This study synthesized a novel iron-based contrast agent using the co-precipitation method, which shows good application prospects in the non-invasive diagnosis of acute kidney injury. Its safety and imaging capabilities make it an important tool for future renal imaging, and it possesses good stability and sensitive imaging response.

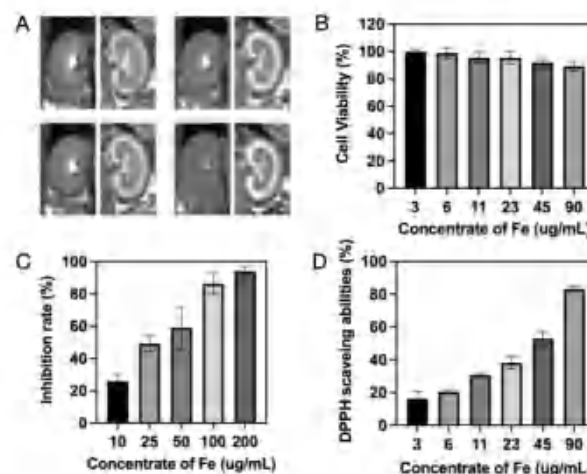


Fig. 1. Figure A shows the imaging effects of the material in normal and injured kidneys. In normal kidneys, the material is almost completely metabolized after 3 hours, while in injured kidneys, material accumulation occurs due to filtration obstruction and can still be observed in MRI after 12 hours. Figure B shows the cellular safety verification of the material. Even at concentrations exceeding 90 μ g/ml, cell viability remains above 80%, indicating that the surface material has good biocompatibility. Figures C and D show the ABTS and DPPH antioxidant tests, respectively, and the results indicate that as the material concentration increases, the antioxidant capacity gradually strengthens.

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DLP-Printed Scaffold Based on Natural-synthetic Polymers for Bone Regeneration

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Key words: biomaterials; digital light processing; bone tissue engineering; bone regeneration

Introduction: Tissue-engineered scaffolds are one of the effective methods for the treatment of bone defects, whose structure and function are essential for bone regeneration. Digital light processing (DLP) printing technology has been widely used in bone tissue engineering (BTE) for its high printing resolution and gentle printing process. Synthetic polymers, one of the commonly used bio-inks, with satisfactory printability and mechanical properties, usually lack sufficient adhesion to cells and tissues.

Materials & Methods: Here, a BTE scaffold with composite composition is successfully prepared by DLP printing technology. Not only can the scaffold facilitate the adhesion and proliferation of cells, but also effectively promote the osteogenic differentiation of mesenchymal stem cells in an osteoinductive environment. Moreover, the scaffold in vivo guide new bone growth towards the interior of the defect.

Results & Discussion: In brief, the gelatin dis-solved in phosphate buffered saline (PBS) at 40° to prepare 10% gelatin solution. After adding methacrylic anhydride (MA) drop by drop into gelatin solution, stir it with magnetic force for three hours at 40°C and 300 rpm, and then a white porous foam was prepared after dialyzed against distilled water for 5 days at 40 °C and lyophilized. GelMA (5% (w/v)), PEGDA (10% (w/v)) and F127DA (5% (w/v)) were dissolved in PBS added with Lithium Phenyl (2,4,6-trimethylbenzoyl) Phosphinate (LAP, 0.25% (w/v)) and Tartrazine (0.05% (w/v)), then the bio-ink composed of 5% GelMA/10% PEGDA/5% F127DA (GPF) were prepared. And the preparation method of another bi-ol-ink of 10% PEGDA/5% F127DA (PF) was the same.

Conclusions: The composite scaffold prepared by DLP printing technology provides a new approach to the clinical treatment of bone defects.

Pre-vascularized poly (ether- ketone -ketone) scaffold mediates vascular-bone coupling regeneration

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Key words: Poly (ether- ketone -ketone), Microvascular network, Bone regeneration

Introduction: The rapid establishment of blood supply is essential for the effective repair of large bone defects. Conventional autologous or allogeneic bone grafting techniques are frequently compromised by central necrosis due to the inadequate vascularization, which severely impedes vascularized bone regeneration. To overcome this limitation, we developed a pre-vascularized poly (ether- ketone -ketone) (PEKK) composite scaffold (PVP) by inducing umbilical vein endothelial cells (UVECs) to form a functional microvascular network in vitro. Furthermore, the role of bone marrow mesenchymal stem cells (BMSCs) in facilitating microvascular formation was systematically investigated and the regenerative efficacy of the PVP scaffold in a rabbit model of segmental femoral defect was also evaluated.

Materials & Methods: Porous PEKK scaffolds were fabricated via fused deposition modelling and subjected to surface sulfonation. Extracellular matrix (ECM) was extracted from bovine cancellous bone and used as a hydrogel to encapsulate UVECs and BMSCs. This cell-laden ECM hydrogel was then seeded into the porous PEKK scaffolds. Following 7 days of in vitro co-culture, a pre-vascularized construct was successfully generated.

Results & Discussion: The ECM derived from bovine cancellous bone preserved essential bioactive components, including collagen, glycosaminoglycans, and elastin, and effectively recapitulated the biochemical cues of native bone tissue. Within the ECM hydrogel, sprouting of UVECs was observed and after co-culture with BMSCs for 7 days, UVECs self-assembled into a three-dimensional capillary-like network within the scaffold. Notably, a synergistic interaction was observed between UVECs and BMSCs through a bidirectional paracrine signalling loop. BMSCs secreted vascular endothelial growth factor and angiopoietin-1, promoting endothelial cell proliferation and vessel stabilization, while UVECs reciprocally enhanced osteogenic differentiation of BMSCs by secreting bone morphogenetic protein-2, leading to upregulated expression of key osteogenic markers (RUNX2 and OCN). This mutual reinforcement significantly enhanced both angiogenesis and

osteogenesis in vitro. Upon implantation into critical-sized segmental femoral defects in rabbits, the PVP scaffold markedly accelerated new bone formation compared to controls, highlighting its regenerative potential.

Conclusions: The porous structure of PEKK provides sufficient space for the vascular ingrowth, while the bone-derived ECM retains the key biological clues that support the adhesion, migration and tube formation of endothelial cells. Through 7-day co-culture with BMSCs, UVECs formed a stable, three-dimensional pre-vascularized network within the scaffold. The bidirectional paracrine crosstalk between UVECs and BMSCs establishes a positive feedback loop that simultaneously enhances vascularization and osteogenic differentiation. Implantation studies confirmed that the PVP scaffold significantly promotes bone regeneration in vivo, offering a promising strategy for the treatment of large bone defects.

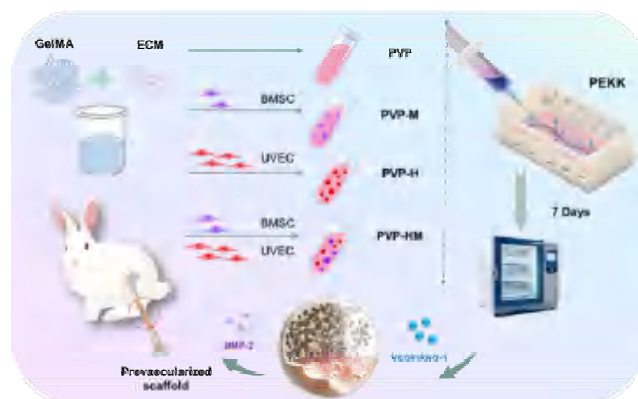


Fig. 1. Schematic diagram of PEKK scaffold with a microvascular network promoting the repair of segmental bone defects in rabbits.

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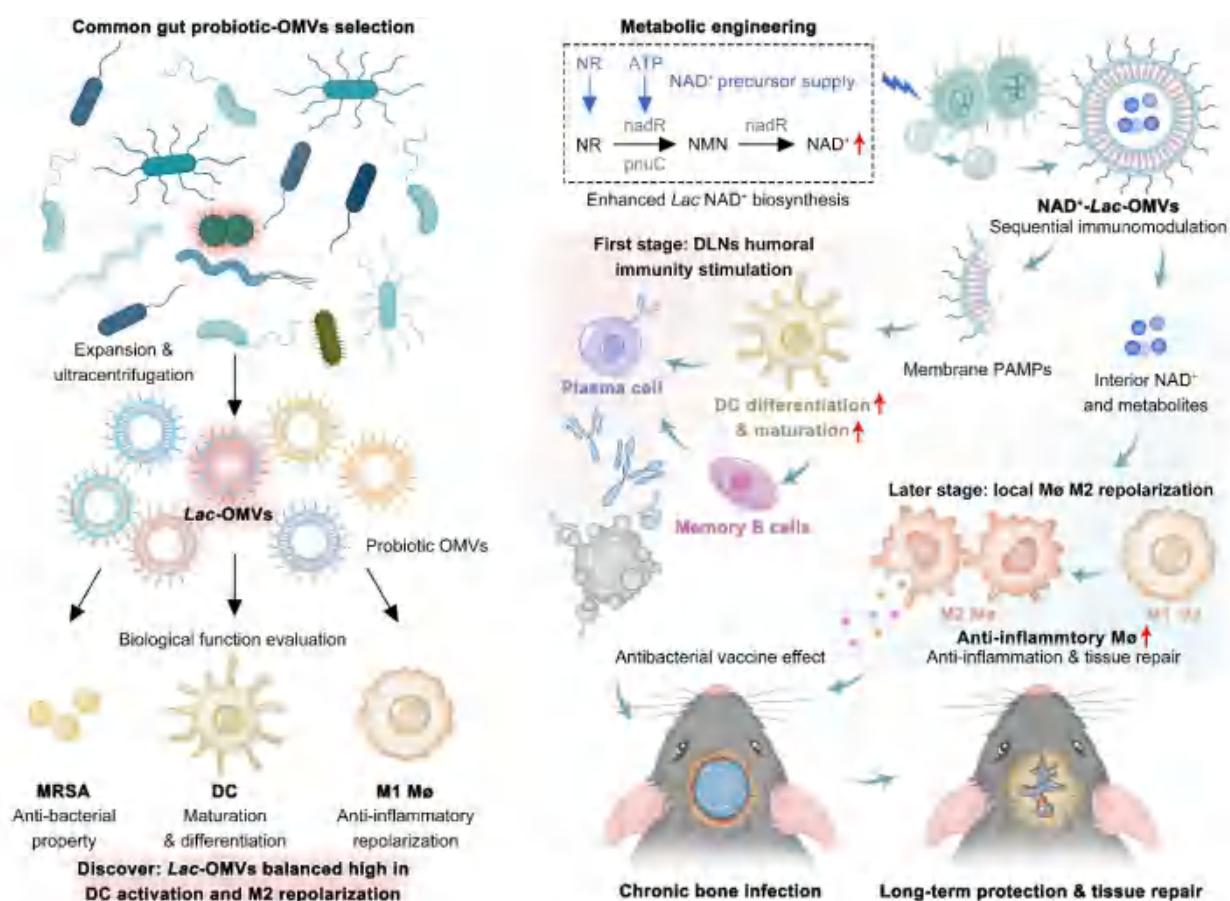
Metabolic-engineered probiotic-OMV as nanovaccine mediating sequential immunomodulation for chronic bone infection immunotherapy

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Chronic, drug-resistant bone infection, predominantly caused by methicillin-resistant *Staphylococcus aureus* (MRSA), features an immunosuppressive niche enabling persistent infection and impaired bone healing. Thus, specific treatment requires initial antibacterial immune activation against infection, followed by reshaping an anti-inflammatory microenvironment for later bone repair. Here, we screened out *Lactococcus lactis* outer membrane vesicles (Lac-OMVs) as natural nanovaccine capable of this sequentially biphasic immunomodulation. Lac-OMVs uniquely combined potent first-stage dendritic cell (DC) activation conducting antibacterial immunity with later-stage superior inflammatory macrophage repolarization to an anti-inflammatory phenotype for bone repair. Mechanistically, we discovered enrichment of the NR→NMN→NAD⁺ nicotinamide metabolism pathway within Lac-OMVs, with NAD⁺ as a key anti-inflammatory mediator. Leveraging this, we metabolically engineered NAD⁺-enriched Lac-OMVs (NAD⁺-Lac-OMVs) via targeted culture condition optimizing. The resulting nanovaccine executed biphasic action: (i) Early-stage DC activation established robust humoral immunity, protecting against primary and recurrent MRSA challenge; (ii) Later-stage targeted intracellular NAD⁺ delivery reprogrammed inflammatory macrophages at defect site, resolving inflammation and establishing a pro-osteogenic microenvironment for efficient bone repair. A single-dose, metabolically enhanced OMV nanovaccine administration offers a promising strategy for sequentially integrated antibacterial immunotherapy and regenerative therapy against intractable MRSA-related chronic bone infection



Scheme 1 Schematic of the screening and engineering strategy. Partly created in BioRender. (i) Initial screening of seven gut probiotic-derived OMVs for key functionalities: antibacterial activity, DC activation, and macrophage reprogramming towards an anti-inflammatory phenotype. (ii) Identification of Lac-OMVs exhibiting superior performance across all three functionalities. (iii) Vesicular metabolomic sequencing revealed NAD⁺ -core-enriched nicotinamide metabolites as potential mediators of Lac-OMVs' anti-inflammatory efficacy. (iv) Metabolic engineering cultivation to produce NAD⁺ -enriched OMVs (NAD⁺ -Lac-OMVs), developed into a potent OMV based antibacterial nanovaccine with enhanced anti-inflammatory properties.

3D-printed Strontium-incorporated β -TCP Bioceramic Triply Periodic Minimal Surface Scaffolds with Enhanced Angiogenic and Osteogenic Properties

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Key words: Strontium; β -tricalcium phosphate; Triply periodic minimal surface; Osteogenesis; Angiogenesis

Introduction: Reconstructing bone defects remains a significant challenge in clinical practice, driving the urgent need for advanced artificial grafts. To achieve vascularized bone regeneration, scaffolds must combine high porosity, enhanced strength, and excellent bioactivity. In this study, we employed DLP-based 3D printing to systematically investigate Sr concentration gradients (0, 2.5, 5.0, 10.0 mol%) in TPMS-structured β -TCP scaffolds for the first time, aiming to identify the optimal Sr dose for vascularized bone regeneration



Fig. 1. Schematic representation of the fabrication and biological function of Sr-incorporated β -TCP bioceramic TPMS scaffolds.

Materials & Methods: Initial characterization focused on microstructure, element distribution and compressive strength. Subsequently, we systematically evaluated cell viability, adhesion, and migration, while comparing the angiogenic and osteogenic properties of scaffolds with different Sr contents in vitro, thereby identifying the optimal Sr incorporation concentration. To further validate these findings, we established a rat femoral condylar defect model, which comprehensively demonstrated the enhanced vascularized bone regeneration potential of Sr-incorporated β -TCP bioceramic TPMS scaffolds in vivo.

Results & Discussion: The unique TPMS structure of the Sr-TCP scaffold contributes to superior mechanical strength (compressive strength up to 1.44 MPa at 80% porosity) while maintaining high porosity, ultimately facilitating effective space maintenance and promoting cell recruitment necessary for bone regeneration. In vitro assays revealed that the Sr-TCP scaffold dose-dependently stimulated osteogenic differentiation and mineralization in MC3T3-E1 cells, while also significantly enhancing the angiogenic capacity in HUVECs. In vivo studies indicated that the scaffold demonstrated synergistic osteogenic and angiogenic effects in rat femoral condylar defects, leading to marked improvements in bone healing.

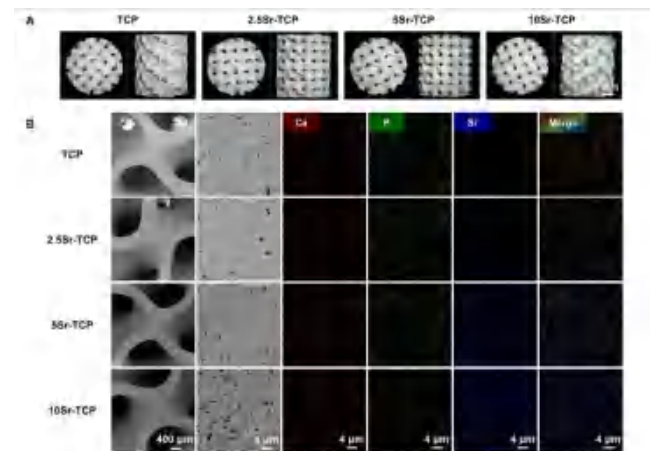


Fig. 2. Characterization of TCP and Sr-TCP scaffolds.

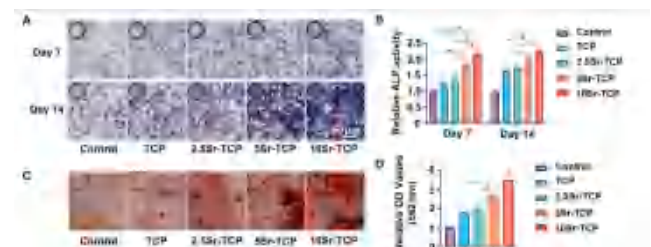


Fig. 3. In vitro osteogenic differentiation of TCP and Sr-TCP scaffolds in MC3T3-E1 cells.



Fig. 4. Micro-CT analysis of the impact of TCP and Sr-TCP scaffolds on in vivo bone regeneration.

Conclusions: Collectively, the Sr-incorporated TPMS-structured TCP scaffold represents a highly promising biomaterial for promoting vascularized bone regeneration, with 10 mol% Sr confirmed as the optimal concentration for achieving desired outcomes.

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Multi-scale Engineering of Biodegradable Zn-Based Porous Fusion Cages via Additive Manufacturing for Improved Load-bearing Ability and Spinal Fusion

Abstract: Interbody fusion cages are critical in spinal decompression and fusion procedures for restoring normal vertebral curvature and rebuilding spinal stability. Current cages exhibit limitations such as biomechanical mismatches and insufficient osseointegration. To address these challenges, for the first time, the biodegradable Zn-based interbody fusion cages that offer load-bearing mechanical strength, controlled degradation rates, excellent biocompatibility, and enhanced fusion efficiency are developed. Advanced additive manufacturing is employed to integrate optimized alloying elements, heterogeneous microstructures, and interpenetrating porous designs. The eutectic Zn-3Mg alloy cage, designed with gyroid unit cells and reinforcing ribs, achieves compressive strength comparable to cortical bone while maintaining good ductility and low elastic modulus. *In vitro* degradation tests demonstrate a balanced co-release of Zn^{2+} and Mg^{2+} , which mitigates the inhibitory effects of excessive Zn^{2+} on cell proliferation while promoting osteogenic differentiation. Moreover, Zn-3Mg extracts effectively counteract the estrogen deficiency-induced impairment of osteoblast differentiation and suppress osteoclast formation. An anterior cervical discectomy and fusion (ACDF) goat model further confirms that Zn-3Mg cages exhibit excellent biocompatibility and osseointegration, facilitating superior bone ingrowth and mechanical interlocking with endplates. By synergizing the benefits of biodegradable metals with advanced additive manufacturing techniques, Zn-3Mg cage represents a compelling alternative to conventional cages.

An All-in-One Microenvironment-Responsive Multifunctional Enzyme-Linked Hydrogel for Diabetic Bone Defects Regeneration

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Introduction

The repair of bone defects in diabetes mellitus (DM) remains a significant challenge due to complex pathological mechanisms involving systemic and local factors. Diabetic patients typically exhibit systemic skeletal metabolic abnormalities, such as reduced bone density and compromised bone quality(1). The pathological microenvironment in DM bone defect areas is characterized by hyperglycemia, chronic inflammation, vascular dysfunction, and immune dysregulation(2). The imbalance between osteoblast and osteoclast activity further complicates bone defect repair in DM(3). Furthermore, clinical management often fails to address the combined effects of DM-induced chronic inflammation and acute inflammation triggered by bone injury, leading to disrupted macrophage polarization and immune dysregulation, which further hinder bone repair(4). Currently, the repair of DM bone defects is not recognized as a distinct pathological entity and is treated as separate conditions, highlighting the urgent need for strategies to modulate the microenvironment and enhance bone regeneration in DM.

Materials and Methods

A microenvironment-responsive all-in-one strategy for repairing DM bone defects was proposed (Fig.1.). To address the unique microenvironment of DM bone defects, a glucose (Glu)/ROS-responsive multifunctional hydrogel (AAT-ZCG) was designed, integrating tannic acid (TA)-mediated dynamic borate ester bonds and a cascade nanozyme (ZCG) based on cerium-zoledronic acid-glucose oxidase. This strategy simultaneously targets hyperglycemia, inflammation, vascular dysfunction, immune dysregulation, and osteoclast/osteoblast imbalance in a concise way.

Results and discussion

The AAT-ZCG hydrogel leverages wet adhesion and self-healing to stably localize in diabetic bone defects. It responds to the pathological microenvironment, triggering cascade reactions that lower glucose and eliminate ROS. In vitro and in vivo, it promotes BMSC osteogenesis, inhibits osteoclasts, restores bone metabolism, enhances HUVEC angiogenesis, and modulates immunity via macrophage polarization. RNA sequencing reveals upregulation of FoxO1, a key bone metabolism regulator. In diabetic rats, the hydrogel shows biocompatibility and degradability, significantly enhancing bone regeneration and defect healing over

controls. Despite these advantages, future work should explore glucose regulation mechanisms and employ large animal models for critical-sized defects to increase clinical relevance.

Conclusions

In conclusion, this all-in-one microenvironment-responsive multifunctional enzyme-linked hydrogel overcomes the limitations of traditional therapies with single efficacy or complex compositions, offering a concise and efficient integrated approach for diabetic bone defect regeneration.

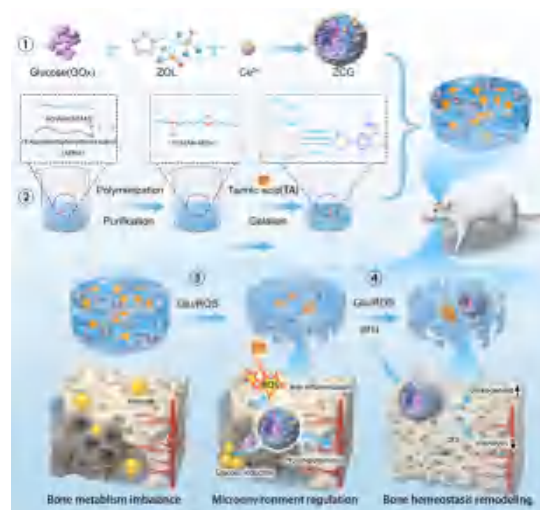


Fig.1. Schematic illustration of the construction and application of all-in-one microenvironment-responsive multifunctional enzyme-linked.

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Injectable Calcium Phosphate as a Bioactive Platform for Osteogenic and Anti-Inflammatory Modulation in Osteoarthritis

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Key words: injectable biomaterials; bone tissue regeneration; calcium phosphates; inflammation treatment; drug loaded biomaterials.

Introduction: Osteoarthritis is a degenerative musculoskeletal disorder characterized by progressive cartilage degradation, subchondral bone remodeling, and chronic inflammation, ultimately leading to pain and functional impairment. Current therapeutic strategies mainly rely on systemic administration of anti-inflammatory and anti-resorptive drugs, which are often associated with limited local efficacy and undesirable side effects. In this context, locally injectable biomaterials capable of modulating both osteogenic and inflammatory pathways represent a promising alternative. Calcium phosphate-based systems, owing to their intrinsic osteoconductivity, biocompatibility, and injectability, offer an attractive platform for targeted delivery and bioactive modulation within the joint microenvironment^{1,2}. Here, we investigate a bioactive injectable calcium phosphate system designed to promote osteogenic activity while attenuating inflammatory responses relevant to osteoarthritis progression.

Materials & Methods: Here, three formulations of injectable calcium phosphate (CaP) materials were developed and investigated as carriers for different classes of therapeutic compounds. Specifically, these included a bisphosphonate (alendronate), an anti-inflammatory drug (diclofenac sodium), and a natural bioactive molecule (Harpagoside). Quantitative biological assays were performed to evaluate the osteoinductive potential and anti-inflammatory behaviour of the drug-loaded CaP systems. Additionally, cellular morphology and interactions with the biomaterials were examined using scanning electron microscopy (SEM) and confocal microscopy to assess cell adhesion, spreading, and structural features.

Results & Discussion: Across all three formulations, the drug-loaded CaP materials demonstrated clear osteoinductive behaviour, particularly during the later stages of osteogenic differentiation. This suggests that the presence of therapeutic compounds did not impede, and may even support, the bone-forming capacity of the injectable matrices. Furthermore, all compositions exhibited significant anti-inflammatory activity *in vitro*,

confirming their potential to reduce inflammatory responses associated with bone lesions. Microscopy investigations revealed favorable cell-material interactions, with morphological features consistent with healthy cell adhesion and spreading, reinforcing the biological compatibility and functional performance of the developed systems.

Conclusions: The present findings demonstrate that injectable calcium phosphate formulations can effectively modulate osteogenic and inflammatory responses relevant to osteoarthritis. The investigated systems exhibited intrinsic bioactivity, promoting osteogenic markers while attenuating pro-inflammatory signals within the pathological microenvironment. These results support the potential of calcium phosphate-based injectable platforms as minimally invasive strategies for localized treatment of osteoarthritis, offering a promising alternative to conventional systemic therapies.

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Chitosan/Hydroxyapatite Nanocomposite Scaffolds for Targeted Osteoarthritis Therapy through Immunomodulatory Mechanisms

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Key words: Osteoarthritis, 3D scaffolds, chitosan, hydroxyapatite, *in vitro* inflammatory response

Introduction:

Significant attention has been devoted to chitosan (CS)-based materials reinforced with inorganic bioactive components such as hydroxyapatite (HA) for the treatment of musculoskeletal disorders, including osteoarthritis (OA). Beyond cartilage degeneration, OA is characterized by subchondral bone remodeling and a persistent inflammatory microenvironment that contributes to disease progression. In this context, CS/HA composites are particularly attractive due to their excellent biocompatibility, controlled biodegradability, minimal foreign body reaction, and intrinsic bioactivity. In this study, we developed three-dimensional (3D) porous CS/HA nanocomposite scaffolds and evaluated their potential as targeted therapeutic platforms for osteoarthritis. The scaffolds were fabricated through a combination of sol-gel processing and freeze-drying techniques to obtain an architecture suitable for cell infiltration and tissue interaction. Particular attention was placed on investigating their immunomodulatory properties and their ability to regulate inflammatory responses *in vitro* using relevant bone cell models. The overall aim was to assess the potential of these bioactive scaffolds as immunoregulatory systems for targeted osteoarthritis therapy.

Materials & Methods: CS/HA composite scaffolds were fabricated by *in situ* sol-gel synthesis of HA in the CS matrix. Four different compositions of samples by considering the 0, 50, 60 and 70% v/v of HA amount respect to composite were produced. Briefly, viscous CS solution [Middle molecular weight; the degree of deacetylation (DD) = 75–85%] was prepared by dissolving chitosan in 0.1 M acetic acid (AA, 99%) solution (1.5% wt) at 40°C. The CS/HA biocomposites were prepared as 3D scaffolds by combining *in situ* sol-gel approach with freeze-drying technology. Morphological properties of CS/HA composite scaffolds at different compositions were studied by scanning electron microscopy SEM (Quanta FEG200-FEI, The Netherlands). Biological investigations were performed at different time points of cell-material interaction. Cell viability, expressed as percent of Alamar Blue reduction, was evaluated in according to the manufacturer's protocol. The effect of CS/HA scaffolds on osteogenic differentiation of hMSCs was evaluated by measuring early and later markers of differentiation such as alkaline phosphatase (ALP) and osteocalcin (OCN), respectively. The effect of CS/HA scaffolds on inflammatory response

in basal conditions was also evaluated by quantifying the secretion of pro-inflammatory and anti-inflammatory cytokines using commercial ELISA kits (Affimetrix Italia, SRL) according to the manufacturer's instructions.

Results & Discussion:

Scanning electron microscopy (SEM) analyses confirmed that HA crystals were homogeneously embedded within the CS matrix at lower inorganic contents. However, at higher HA concentrations (60 and 70% v/v), partial aggregation of HA was observed, with crystals exhibiting a needle-like morphology protruding from the polymeric network. This structural feature is consistent with the intrinsic crystallization behavior of HA and contributed to increased surface roughness and bioactive exposure. From a biological perspective, scaffolds containing higher inorganic fractions (60 and 70% v/v) elicited a favorable cellular response. While enhanced osteogenic differentiation of human mesenchymal stem cells (hMSCs) toward an osteoblastic phenotype was observed, particular attention was given to the immunomodulatory effects of the composites. Notably, CS/HA scaffolds with higher HA content significantly influenced cytokine production, promoting the expression of anti-inflammatory mediators (IL-4 and IL-10) while reducing levels of the pro-inflammatory cytokine TGF- β .

These findings suggest that increasing the inorganic component not only enhances bioactivity but also contributes to the modulation of the inflammatory microenvironment, supporting the potential application of CS/HA nanocomposite scaffolds as immunoregulatory platforms for targeted osteoarthritis therapy.

Conclusions: This study highlights the potential of CS/HA nanocomposite scaffolds as bioactive platforms for targeted osteoarthritis therapy. Increasing the HA nanoparticle content within the CS matrix enhanced the biological performance of the scaffolds, promoting a favorable cellular response while modulating inflammatory signaling. In particular, higher inorganic fractions contributed to the upregulation of anti-inflammatory mediators and the attenuation of pro-inflammatory cytokine expression. Overall, these findings support the use of CS/HA composites as immunoregulatory biomaterials capable of influencing the inflammatory microenvironment associated with osteoarthritis, thus representing a promising strategy for targeted therapeutic intervention.

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A spatiotemporally adaptive scaffold coordinating sequential osteosarcoma clearance and bone regeneration

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Abstract: Osteosarcoma is an aggressive bone malignancy, and post-resection repair requires aligning local tumor control with subsequent bone regeneration within the defect. Here, radially aligned three-dimensional (3D) fibrous scaffold integrating calcium peroxide (CaO_2) and black phosphorus (BP) within melt electrowritten polycaprolactone (PCL) framework ($\text{CaO}_2/\text{BP}/\text{PCL}$) was fabricated enabling spatiotemporally adaptive therapy. Built from fully degradable, biocompatible components, the scaffold integrates topographic guidance with degradation-driven ionic and redox cues and programmable photothermal modulation to coordinate immune, neural, vascular, and osteogenic events for post-tumor bone repair.

Key words: melt electrowritten scaffold; spatiotemporally adaptive therapy; tumor ablation; bone regeneration

Introduction: Effective eradication of residual tumor depends on persistent cytotoxic and immune-activating cues, while bone reconstruction hinges on timely inflammatory resolution and osteogenic regeneration. Reconciling these opposing requirements within a single therapeutic platform remains a formidable challenge in musculoskeletal oncology. Here, we developed a radially aligned $\text{CaO}_2/\text{BP}/\text{PCL}$ scaffold assembled by stacked adhesion of CaO_2/PCL and BP/PCL layers. By coupling degradation-driven ionic and redox with near-infrared (NIR)-programmable photothermal modulation spanning high-temperature ablation and mild hyperthermia, the scaffold supports stage-specific regulation that supports early residual tumor eradication with immune activation, and subsequently orchestrates immune remodeling, neurovascular ingrowth, and vascularized osteogenesis.

Materials & Methods: $\text{CaO}_2/\text{BP}/\text{PCL}$ scaffold was fabricated by melt electrowriting. By precisely controlling NIR irradiation intensity, anti-tumor, anti-inflammatory, pro-angiogenic, neurogenic, and osteogenic effects were evaluated *in vitro*. In addition, *in vivo* anti-tumor and bone regeneration efficacy were assessed in subcutaneous tumor resection and bilateral cranial defect models.

Results & Discussion: Transmission electron microscopy (TEM) confirmed successful synthesis of CaO_2 NPs and BP NSs (Fig.1a, b), while scanning electron microscopy (SEM) revealed radially aligned fiber arrays with uniform diameters of $ca. 22.88 \pm 4.94 \mu\text{m}$ for scaffolds (Fig.1c, d). Functionally, the scaffolds induced extensive tumor cell death, promoted M1 macrophage polarization, markedly enhanced neurite extension, endothelial network formation, and ALP

activity and mineral deposition (Fig.1e-i). *In vivo*, scaffolds markedly reduced bioluminescence signals and excised tumor weights, and achieved pronounced bone regeneration at 8 weeks (Fig.1j-l). These findings support a clinically compatible framework.

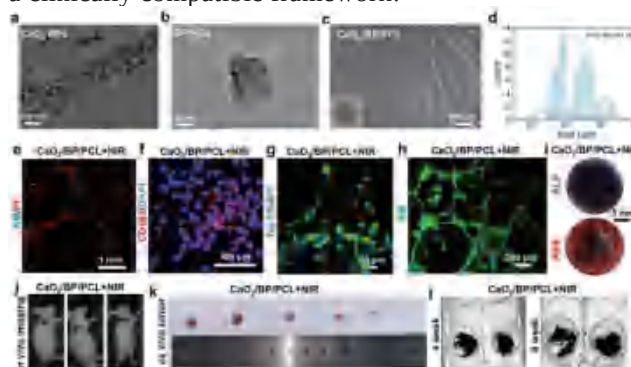


Fig. 1. (a, b) TEM images of CaO_2 NPs and BP NSs. (c, d) SEM images and fiber diameter distributions of $\text{CaO}_2/\text{BP}/\text{PCL}$. (e-h) CLSM images of live/dead-stained 143B cells (e), CD163 expression in RAW264.7 cells (f), neurite extension from PC12 cells (g), and tubular networks formed by HUVECs on Matrigel (h). (i) ALP and ARS staining of BMSCs. (j) *In vivo* chemiluminescence images of osteosarcoma-bearing mice at days 12. (k) *Ex vivo* images of tumors. (l) micro-CT images in the calvarial defect area.

Conclusions: In summary, we developed a radially aligned, melt-electrowritten $\text{CaO}_2/\text{BP}/\text{PCL}$ scaffold that enables spatiotemporally adaptive therapy after tumor surgery by coupling degradation-driven ionic and redox cues with NIR-programmable photothermal modulation. Immediately after implantation, CaO_2 -associated oxidative cues together with ablation-range photothermal stimulation support local control of residual tumor cells. Along the postoperative timeline, the scaffold shifts toward regeneration by providing sustained Ca/P ionic cues and mild hyperthermia that favor a pro-reparative microenvironment, neurovascular ingrowth, and osteogenic maturation, resulting in effective post-resection tumor control and markedly improved bone repair *in vivo*.

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Diabetic and nondiabetic BMSC-derived exosomes affect bone regeneration via regulating miR-17-5p/SMAD7 axis

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Key words: Diabetic bone disease, Exosomes, GelMA hydrogel, miR-17-5p, SMAD7

Introduction:

Diabetes mellitus (DM), particularly type 2 diabetes mellitus (T2DM), represents one of the most prevalent metabolic disorders worldwide^[1]. Diabetic bone disease (DBD), one of the common complications of diabetes mellitus, characterized by impaired fracture healing, compromised implant osseointegration, and diminished bone regenerative capacity^[2]. Bone marrow stromal cells (BMSCs) are the principal osteoprogenitors governing bone homeostasis and can differentiate into osteoblasts to repair and regenerate bone. Studies have shown that the chronic hyperglycemic milieu of T2DM profoundly compromises their function^[3], but how T2DM conditions alter the intercellular communications underlying this impairment remains incompletely understood.

Exosomes have emerged as pivotal mediators of paracrine intercellular signaling, transferring a diverse repertoire of bioactive cargo, including proteins, lipids, and non-coding RNAs, from donor to recipient cells^[4]. MicroRNAs (miRNAs), one of the most functionally significant components of the exosomal cargo^[5], regulate gene expression at the post-transcriptional level. BMSC-derived exosomes (BMSC-Exos) have been demonstrated to recapitulate many of the regenerative properties of their parent cells and have attracted considerable interest as cell-free therapeutic agents for bone repair^[6]. Nevertheless, whether and how diabetic conditions alter the miRNA composition and functional efficacy of BMSC-Exos has not been systematically investigated.

Smad7, one of the target genes of miR-17, functions as a negative feedback regulator of the TGF- β /BMP pathway by antagonizing receptor-activated SMAD signaling, thereby suppressing osteoblast differentiation^[7]. Dysregulation of SMAD7 has been implicated in impaired bone formation^[7]; however, its regulation by exosomal miRNAs under diabetic conditions has not been previously explored.

Our study aimed to investigate whether the diabetic microenvironment alter the miRNA cargo of BMSC-derived exosomes in a manner that impairs their osteoinductive capacity, and if so, through what molecular mechanism does this occur? Our findings provide mechanistic insight into diabetic bone disease and to establish a rational foundation for the development of exosome- and miRNA-based cell-free therapeutics for bone regeneration in diabetic patients.

Materials & Methods:

1. Cell culture and identification

Rat osteoblasts (rOBs) were isolated from the calvaria, and rBMSCs were isolated from femurs of Sprague-Dawley rats

2. Exosome Isolation and Characterization

rBMSCs were cultured in normal-glucose (5.5 mM glucose, NG group) or high-glucose (33 mM glucose, HG group) medium for 48 hours, cell supernatant was collected and exosomes were isolated by sequential differential ultracentrifugation. Characterization was performed by nanoparticle tracking analysis (NTA) for size distribution, transmission electron microscopy (TEM) for morphological assessment, and western blot for exosomal marker expression (CD63, CD81, HSP70).

3. Exosome Uptake Assay

Exosomes were fluorescently labeled with PKH67 and co-cultured with rOBs for 24 hours. Cellular uptake was subsequently visualized by fluorescence microscopy.

4. miRNA Microarray Profiling and Target Gene Prediction

NG-Exos and HG-Exos pooled from three independent rBMSC cultures were submitted for exosomal miRNA sequencing. Differentially expressed miRNAs were visualized by volcano plot and heatmap. The downstream targets of miRNA were cross predicted from four bioinformatic databases, overlapping candidates were identified via Venn diagram analysis and further confirmed by dual luciferase reporter assay.

5. Transfection of miRNA Mimics/Inhibitors and Smad7 Overexpression Vector

miR-17 levels of rOBs were upregulated or downregulated by transfection with miR-17 mimic/ inhibitor, respectively. A pcDNA-Smad7 plasmid was employed for SMAD7 overexpression. All transfections were performed using Lipofectamine 2000.

6. Fabrication of Exosome-Loaded Hydrogel and In Vitro Release Analysis

Gelatin methacryloyl (GelMA) was mixed with 200 μ g NG-Exos, HG-Exos, or an equivalent volume of PBS to achieve a final exosome concentration of 200 μ g/mL and crosslinked under 405-nm UV light to form the hydrogel in situ. To evaluate exosome release kinetics, PKH67-labeled exosomes were incorporated into 5%, 10%, or 15% (w/v) GelMA hydrogels and immersed in PBS. Supernatants were collected every 2 days over a 14-day period; fluorescence intensity was measured at 502 nm to generate cumulative release profiles at each concentration.

7. Animal Experiments

Male Sprague-Dawley rats were randomly assigned to either the type 2 diabetes mellitus (T2DM) group (n=12) or the non-diabetic control group (n=12). Bilateral calvarial defects (5-mm diameter) were created using a trephine bur and filled with 60 μ L of 15% (w/v) exosome/PBS-loaded GelMA hydrogel. Postoperatively, miR-17 agomir or antagomir was formulated with *in vivo*-jetPEI and locally injected into the peri-defect area. Animals were

euthanized and skulls were harvested at 4 weeks post-surgery.

Results & Discussion:

1. rBMSCs, rOBs, HG-Exos, and NG-Exos were successfully isolated and identified. Both HG-Exos and NG-Exos secreted by rBMSCs could be internalized by rOBs.

2. HG-Exos Impair Osteoblast Function Compared to NG-Exos
Co-culture experiments revealed that NG-Exos significantly promoted migration and osteogenic differentiation of rOBs. In contrast, HG-Exos compromised the above effects, indicating that a diabetic micro-environment impairs the pro-osteogenic and pro-migration cargo of BMSC-derived exosomes.

3. miRNA Profiling Identifies miR-17-5p as a Key Differentially Expressed Cargo

Fifty-five significantly differentially expressed miRNAs between NG-Exos and HG-Exos were identified, among which miR-17-5p was one of the most markedly downregulated species in HG-Exos. PCR confirmed a significant reduction of miR-17-5p in the skulls of T2DM rats compared with control rats *in vivo*, and a significant reduction in HG-Exos-treated rOBs compared with NG-Exos-treated rOBs *in vitro*.

4. miR-17-5p Directly Targets and Suppresses Smad7

Bioinformatic analysis identified *Smad7* as a high-confidence target of miR-17-5p. Dual-luciferase reporter assays confirmed that miR-17-5p directly binds to the 3'UTR of *Smad7* and suppresses its transcriptional activity. Consistent with this, miR-17 mimic transfection in rOBs led to significant downregulation of SMAD7 at both mRNA and protein levels, while miR-17 inhibitor produced the opposite effect.

5. miR-17-5p Promotes Osteogenesis via SMAD7/TGF- β Signaling Suppression

Gain- and loss-of-function experiments demonstrated that miR-17 mimic transfection significantly enhanced osteogenesis of rOBs, whereas miR-17 inhibitor produced opposing effects, recapitulating the inhibitory phenotype of HG-Exos. Overexpression of SMAD7 reversed the pro-osteogenic effects of miR-17 mimic, confirming that miR-17-5p promotes osteogenesis at least in part through suppression of SMAD7-mediated inhibition of TGF- β /BMP signaling.

6. GelMA Hydrogel Enables Sustained Exosome Delivery *In Vitro*

Exosome release profiling from GelMA hydrogels of varying concentrations (5%, 10%, 15% w/v) demonstrated a concentration-dependent release pattern: 5% GelMA exhibited initial burst release, whereas 15% GelMA provided the most sustained and controlled release over 14 days. Accordingly, 15% GelMA was selected as the optimal scaffold for subsequent *in vivo* experiments, as it best preserved exosome bioactivity while affording prolonged local delivery.

7. NG-Exos-Loaded GelMA Promotes Calvarial Bone Repair *In Vivo*, While HG-Exos-Loaded GelMA Impairs Defect Healing in Diabetic Rats

Compared with the HG-Exos/GelMA or PBS/GelMA groups, NG-Exos/GelMA significantly promoted bone repair and regeneration of T2DM rat calvarial defect. Conversely, HG-Exos/GelMA-treated defects showed impaired bone regeneration comparable to the PBS/GelMA group, corroborating the *in vitro* findings. IHC further demonstrated elevated SMAD7 expression in HG-Exos-treated and untreated diabetic defects,

which was markedly reduced in NG-Exos-treated specimens.

8. Local Delivery of miR-17 Agomir Rescues Impaired Bone Regeneration in Diabetic Defects

Local injection of miR-17 agomir at HG-Exos/GelMA-treated calvarial defect sites in diabetic rats significantly improved bone regeneration and reduced local SMAD7 levels. In contrast, miR-17 antagomir administration in NG-Exos-treated non-diabetic defects significantly attenuated bone repair, reducing osteogenic outcomes to levels comparable to the diabetic control group. These *in vivo* findings collectively validate the miR-17-5p/SMAD7 axis as a functionally significant and therapeutically targetable pathway governing BMSC exosome-mediated bone regeneration under diabetic conditions.

Conclusions:

In nondiabetic conditions, BMSC-derived exosomes (NG-Exos) promoted osteogenesis and migration of rOBs *in vitro* and bone regeneration in rats with T2DM *in vivo*, whereas, in diabetic conditions, exosomes from BMSCs (HG-Exos) impaired the migration of rOBs and undermine the osteogenic promotion effect of MSC-Exos on rOBs *in vitro* and bone regeneration in rats *in vivo*.

Moreover, miR-17-5p level was downregulated in HG-Exos and HG-Exo-co-cultured rOBs and the skulls of rats with T2DM, which further disinhibited SMAD7 expression and resulted in poor bone regeneration. Overall, diabetic BMSC-derived exosomes attenuate the promotion effect of MSC-Exos in bone regeneration via the miR-17/SMAD7 axis, providing support for the miR-17-5p/SMAD7 axis as a promising therapeutic target to treat DBD.

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Re-Editing the Bone Metabolic Niche with a Cascade-Catalytic Scaffold to Boost Repair via Enhanced Mitochondrial Bioenergetics and Osteoimmunomodulation

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Key words: Bone repair; Lactate metabolism; Scaffold; Enzymatic catalysis; Metabolic modulation

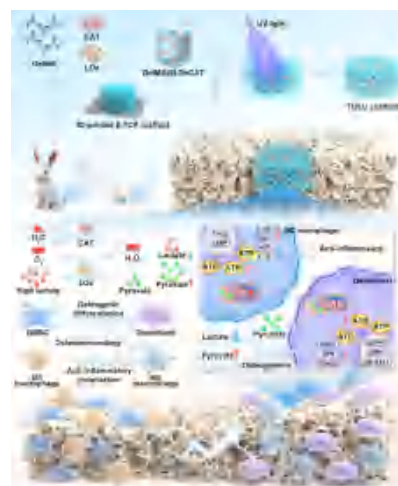
Introduction: Bone defects caused by trauma, osteoporosis, tumor surgery and other reasons affect millions annually and severely reduce quality of life. While autografts, allografts and xenografts are clinical gold standards, they suffer from donor shortage, immune rejection and disease transmission risks. Bioactive ceramic bone substitutes such as β -TCP, bioglass and hydroxyapatite have become promising alternatives due to their adjustable mechanics, processability and biocompatibility. Bioceramic scaffolds support bone repair by providing structural stability, enabling cell infiltration via porous structures and releasing bioactive ions to boost bone regeneration. However, current strategies rarely consider the interaction between cellular metabolism and the healing microenvironment. Metabolic reprogramming and metabolite changes regulate cell fate and regeneration, yet their application is underexplored. Therefore, developing regenerative scaffolds that modulate cellular metabolism in the bone microenvironment is a promising and innovative strategy for enhanced bone repair.

Materials & Methods: A cascade enzymatic scaffold (TGLC) was designed. The scaffold consists of a 3D-printed β -tricalcium phosphate (β -TCP) structure infused with a gelatin methacryloyl (GelMA) hydrogel co-immobilizing lactate oxidase (LOx) and catalase (CAT). Specifically, LOx catalyzes the conversion of lactate into pyruvate, thereby depleting accumulated metabolites while generating a beneficial precursor that fuels mitochondrial bioenergetics. Simultaneously, CAT decomposes the byproduct hydrogen peroxide (H_2O_2) into oxygen (O_2), sustaining LOx catalytic efficiency, preventing uncontrollable side reaction and mitigating oxidative stress. Under lactate-rich conditions, the TGLC enhanced cellular oxidative phosphorylation (OXPHOS) process and adenosine triphosphate (ATP) production, boosting the proliferation and osteogenic differentiation of bone mesenchymal stem cells (BMSCs), meanwhile it induced macrophage M1-to-M2 anti-inflammation polarization through such metabolic reprogramming, fostering a pro-regenerative immunoregulatory microenvironment.

Results & Discussion: The TGLC scaffold offers mechanical support and osteoconductivity, and the cascade enzymes enable sustained catalytic activity for efficiently converting accumulated lactate into pyruvate.

This metabolic remodeling enhanced mitochondrial OXPHOS and adenosine triphosphate (ATP) production in BMSCs, activating signaling pathways like MAPK, cAMP, and JAK-STAT to promote proliferation and osteogenic differentiation. Concurrently, it also drove macrophage polarization toward the M2 anti-inflammatory phenotype, upregulated OXPHOS process, FoxO and cAMP signaling pathways, thereby fostering a positive osteoimmune microenvironment that could regulate inflammatory cytokine secretions benefiting in osteogenesis.

Conclusions: This cascade enzymatic system demonstrates the therapeutic potential of this metabolic intervention and opens up a new paradigm for dealing with impaired healing in challenging bone defects via a promising catalytic treatment approach. It highlights the potential of engineering functional biomaterials to construct pro-regenerative metabolic niches, correct cellular energy metabolism, and harness beneficial immunoregulatory microenvironments.



Graphic

Fig. 1. Schematic illustration of the construction of TGLC scaffold system and its cascade enzymatic effect and bone microenvironment metabolism-modulating mechanisms for promoting bone defect repair

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Regulation of Molecular and Supramolecular Chirality on Osteogenic Differentiation in Biomimetic Microenvironment

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Key words: molecular chirality, supramolecular chirality, biomimetic microenvironment, hydrogel, osteogenic differentiation

Introduction: Chirality is a pivotal determinant in stem cell differentiation, yet discerning the individual effects of chirality across different scales within native 3D environments remains challenging. Here, a strategy is employed using nanostructures with controlled chirality to precisely assess the impact of molecular and supramolecular chirality on mesenchymal stem cell (MSC) osteogenic differentiation. Intriguingly, MSCs encapsulated within these chiral fibers displayed osteogenic differentiation that was predominantly influenced by higher-order supramolecular chirality rather than molecular chirality. Specifically, supM-nanofibrils significantly promoted MSC commitment to the osteoblast lineage, whereas supP-nanofibrils lacked this osteoinductive potential. Additionally, we observed subtle positive and negative modulations of MSC osteogenic differentiation by L- and D-enantiomeric molecular chirality, respectively. Our study presents a strategy for chiral hydrogel design and delineates how supramolecular chirality surpasses molecular chirality in directing MSC osteogenesis within 3D hydrogels, highlighting the potential of chiral biomaterials in bone tissue engineering.

Materials & Methods: Here, we manipulated the chiral inversion of supramolecular nanofibers within hydrogels by altering the aromatic side chains of the building blocks. This approach enables the creation of distinct chiral fibrous hydrogels: LsupP and DsupP (where supP indicates supramolecular right-handed helix), and LsupM and DsupM (where supM denotes supramolecular left-handed helix).

Results & Discussion: Compared to molecular-level chirality, supramolecular chirality substantially alters the nanofibrillar architecture, thereby significantly enhancing interactions with integrins and other mechanosensitive receptors, thus effectively activating downstream mechanosignaling cascades. These findings highlight the pronounced impact of molecular and supramolecular chirality on MSC osteogenic differentiation. We extended investigation to evaluate in vivo osteogenic potential of MSCs encapsulated within chiral hydrogels. MSCs were integrated into hydrogels

and implanted into rat femoral defects.

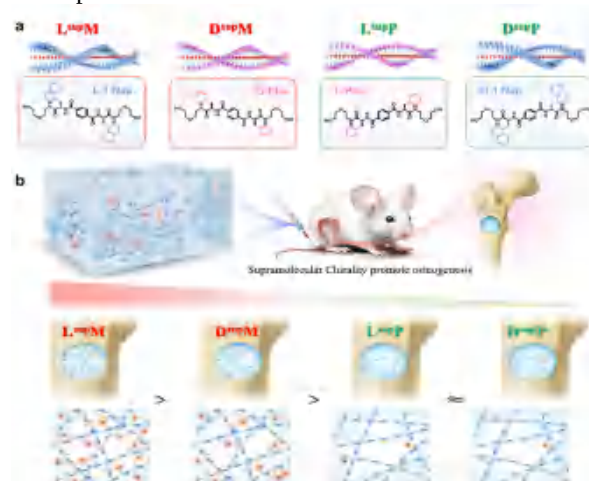


Fig. 1. Schematic illustration of self-assembly mode and higher-order supramolecular chirality promote mesenchymal stem cells osteogenesis. (a) Molecular structure of designed amino acids derivatives and the self-assembly mode. (b) 3D hydrogel mode and both in vitro and in vivo experiments have showed that the osteogenic differentiation capacity of MSCs is predominantly influenced by the higher-order supramolecular chirality.

Conclusions: We engineered four chiral hydrogels to meticulously investigate the distinct impacts of molecular and supramolecular chirality on the osteogenic differentiation of MSCs within 3D scaffolds. Supramolecular chirality exerts a more significant influence on osteogenic differentiation than molecular chirality, which suggests that the modulation of aromatic side chains is a potent approach to control the helical bias in supramolecular hydrogels, providing an avenue for design of biomaterials with tailored chiral properties to direct stem cell fate and enhance bone tissue regeneration.

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PT1-Loaded Targeting System for Regulating Bone Defect Repair in Femoral Head Necrosis

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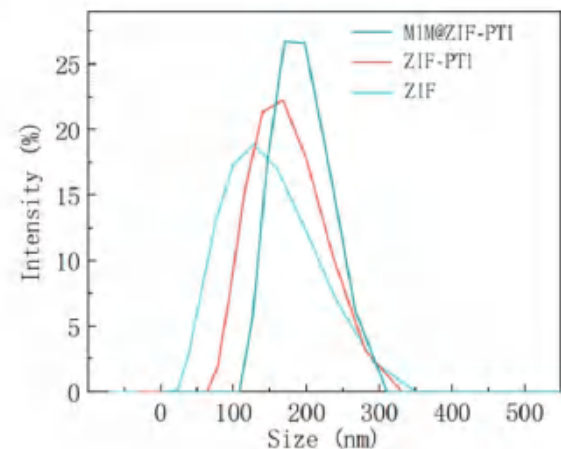
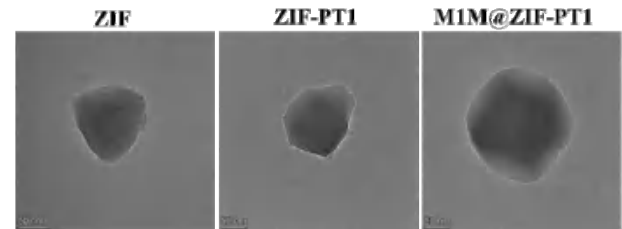
Key words: ONFH; macrophage polarization; AMPK; ZIF-8 nanoparticle; bone tissue engineering

Introduction: Osteonecrosis of the femoral head (ONFH) is driven by ischaemia and chronic M1-dominated macrophage polarisation, creating an inflammatory microenvironment that prevents bone healing and repair. No approved therapy is able to corrects this imbalance. Opal multiplex immunohistochemistry confirmed that the M1/M2 ratio scales with Ficat staging severity, implicating macrophage immunometabolism as a key target [1]. AMPK activation redirects macrophage fuel use from glycolysis toward oxidative phosphorylation, promoting M1-to-M2 repolarisation [2]. The direct AMPK α activator PT1, however, is limited by poor aqueous solubility, enzymatic lability, and restricted access to avascular necrotic tissue. We therefore engineered M1M@ZIF-PT1/GelMA-HAP: M1 macrophage membrane-coated, pH-responsive ZIF-8 nanoparticles embedded in a 3D-printed GelMA-hydroxyapatite scaffold for site-specific immunomodulation and concurrent osteogenesis.

Materials & Methods: PT1-loaded ZIF-8 was coated with M1 macrophage membranes and characterised by TEM, DLS, zeta potential, and pH-triggered release. M1M@ZIF-PT1 was incorporated into GelMA-HAP scaffolds. In vitro, polarised THP-1/BMSC co-cultures were assessed for M1/M2 polarisation by flow cytometry and AMPK/mTOR/glycolytic signalling by Western blot and RT-qPCR. In vivo, a corticosteroid-induced rabbit ONFH model underwent scaffold implantation via core decompression, with sacrifice at 2, 6, and 12 weeks for micro-CT, histology, Opal multiplex immunohistochemistry, and transcriptomics.

Results & Discussion: M1M@ZIF-PT1 (~200 nm, core-shell) showed pH-responsive PT1 release and M1-selective uptake via CD47-mediated immune evasion. PT1 activated AMPK α , suppressed mTOR and downregulated LDHA/Glut1/PKM2, reducing M1 markers (iNOS, TNF- α , IL-1 β) and elevating M2 markers (CD206, IL-10, TGF- β), with consequent enhancement of BMSC osteogenic differentiation. In the rabbit ONFH model, M1M@ZIF-PT1/GelMA-HAP is expected to produce the largest number of M1-to-M2 shift at 2 weeks, accelerated vascularisation at 6 weeks, and superior BV/TV at 12 weeks compared with that of control group. These findings are consistent with the broader principle that metabolic reprogramming governs

macrophage functional polarisation[3], and support the



potential of immunometabolic intervention as a strategy for inflammatory bone diseases [4].

Fig.1. TEM morphology and DLS size distributions of ZIF, ZIF-PT1, and M1M@ZIF-PT1.

Conclusions: M1M@ZIF-PT1/GelMA-HAP resolves ONFH inflammation and promotes bone repair via targeted PT1 delivery, AMPK-driven metabolic reprogramming, and osteoinductive scaffold architecture, establishing the PT1-AMPK-mTOR-glycolysis axis as a translational immunometabolic target for hip-preserving surgery.

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Responsiveness of diabetic mesenchymal stem cells to advanced glycation end products and to the antioxidant effect of N-Acetylcysteine

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Key words: Diabetes, Bone marrow mesenchymal stem cell, oxidative stress, antioxidant

Introduction: Type 2 diabetes mellitus (T2DM) increases the fracture risk and impairs bone healing, posing persistent challenges for treating its skeletal complications [1]. Hyperglycemia promotes advanced glycation end products (AGEs) accumulation, impairing bone cell functions, including those of bone marrow mesenchymal stem cells (BMSCs)- key cells in bone homeostasis and promising candidates in cell therapies and tissue-engineered bone repair [2]. AGEs induce reactive oxygen species (ROS) overproduction, shifting cellular redox toward a pro-oxidant state [3]. However, the effects of AGEs and AGEs-induced OS on T2DM-BMSCs are poorly defined. Moreover, N-Acetylcysteine (NAC), a potent antioxidant, mitigates OS in non-diabetic BMSCs [4], but remains underexplored against AGEs-induced OS in T2DM-BMSCs. This study therefore aimed to investigate the effects of the AGEs on select functions and ROS generation in BMSCs harvested from longstanding T2DM versus non-diabetic microenvironment, as well as the antioxidant potential of NAC on AGEs-induced ROS. Diabetic and non-diabetic BMSCs were harvested from T2DM model rats (ZDF rats) and their LEAN littermates, respectively.

Materials & Methods: ZDF-BMSCs and LEAN-BMSCs were culture with AGEs-BSA varying from 0 to 200µg/mL for 48 hours. Cytotoxicity was assessed by cell number counting (CyQUANT). Proliferation was measured over 10 days, and migration was performed using Boyden chambers. Intracellular ROS (iROS) and mitochondrial ROS (mROS) in the presence of AGEs were detected by DCFD-DA and DHE probe, respectively. To evaluate the capacity of NAC to reduce AGEs-induced ROS production in BMSCs, cells were pre-treated (12 hours prior) or co-treated (concurrently with AGEs) with NAC (2.5-10mM).

Results & Discussion: (1) Cytotoxicity: AGEs up to 200µg/mL did not affect LEAN-BMSC number but significantly ($p<0.01$) reduced ZDF-BMSC number by 55%. (2) Proliferation: the addition of AGEs resulted in a significant reduction of proliferation in both cell types over 10 days, with a more pronounced effect at 200µg/mL. (3) Migration: AGEs decreased the number of migrated cells by 59.1% (LEAN-BMSCs) and 45.5% (ZDF-BMSCs). (4) ROS generation: AGEs significantly

increased iROS (by 270%) in both LEAN- and ZDF-BMSCs, with no effect on mROS, indicating a cytoplasmic localization of AGEs-induced ROS. NAC pre-treatment mitigated AGEs-induced iROS generation in a dose-dependent manner in both cell populations (>40% at 10mM), while NAC co-treatment reduced iROS by 70% and 28% in LEAN-BMSCs and ZDF-BMSCs, respectively.

Conclusions: Our study showed that AGEs impair diabetic BMSC expansion and functionality in an exacerbated manner. AGEs-induced OS appears to play a key role in this impairment, while NAC can reduce OS in the context of T2DM. These findings emphasize the detrimental effects of the diabetic microenvironment and the importance of developing strategies to enhance the regenerative capacity of diabetic BMSCs in cell-based therapies by protecting them from OS.

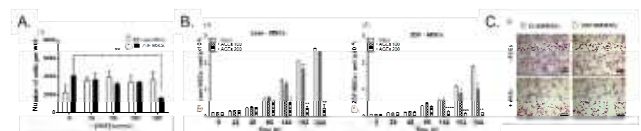


Fig 1. Impaired cell survival, proliferation and migration of BMSCs exposed to AGEs.

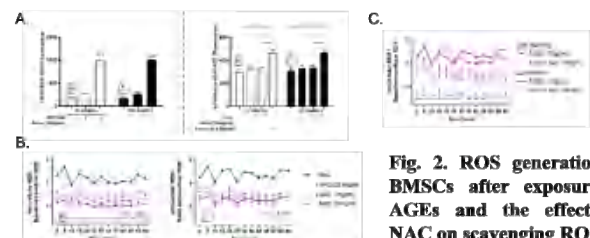


Fig. 2. ROS generation in BMSCs after exposure to AGEs and the effects of NAC on scavenging ROS.

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AI-Empowered Bone Organoid Fabrication: Principles and Applications

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Key words:

Materials biology; repair and regeneration; bone repair materials; bioprinting; bone-like organs

Introduction:

Bone-related diseases such as osteoporosis and osteoarthritis pose serious threats to human health, and their high-quality repair remains a critical challenge in medicine. Our previous research, grounded in material-biological effects, developed engineered synthetic hydrogel matrices as replacements for traditional Matrigel, enabling the construction of highly biomimetic bone organoids with self-mineralization and vascularization characteristics. Nevertheless, bone organoid fabrication still faces key challenges: poor reproducibility due to the absence of standardized construction strategies, limited functional recapitulation caused by insufficient cell maturation, and low scalability efficiency resulting from reliance on manual operations. To address these bottlenecks, we focused on AI-empowered fabrication approaches by introducing an organoid-specific large model O-GPT and proposing the "AI Virtual Organoids (AIVOs)" framework. Machine learning algorithms were employed to achieve precise prediction of material properties and optimization of fabrication parameters. Through this digitalized system, we aim to overcome the major barriers in intelligent bone organoid manufacturing, thereby providing a scientific paradigm for bone regeneration research and clinical translational applications.

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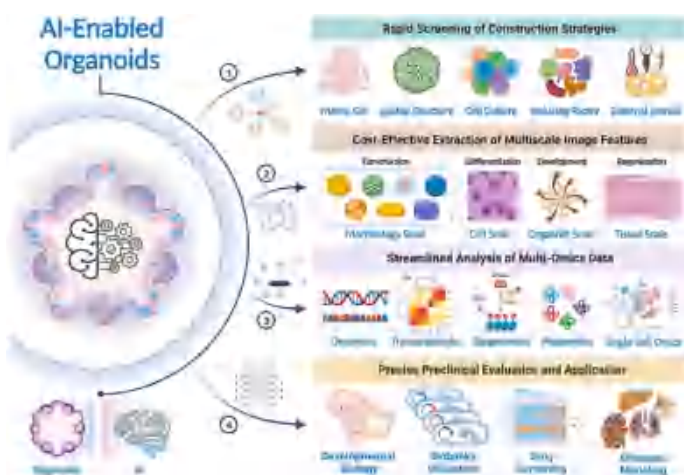


Fig. 1. Caption.

EXO/Hydrogel System for Sequential Regulation of Endogenous Hyaline Cartilage Regeneration

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Articular cartilage repair remains a clinically significant challenge due to its limited regenerative capacity and vulnerability to inflammation-induced damage and fibrocartilage formation. Current therapeutic strategies frequently fail to enhance intrinsic repair capacity or overcome the dual barriers of injury/inflammation-driven fibrosis and insufficient hyaline cartilage regeneration, often yielding suboptimal outcomes. Here, we developed an exosome-integrated hydrogel system for temporally programmed drug delivery. Kartogenin (KGN) and halofuginone (HF) were encapsulated into human umbilical cord MSC-derived exosomes (EXO_{KGN}/EXO_{HF}). EXO_{HF} was specifically immobilized in GelMA hydrogel via CP05-CD63 binding, while EXO_{KGN} was incorporated unbound. This design achieved rapid release of EXO_{KGN} versus sustained retention of EXO_{HF} for sequential therapeutic action. The rapidly released EXO_{KGN} initiated bone marrow-derived mesenchymal stem cell (BMSC) migration and chondrogenic differentiation in the repair process. Concurrently, the sustained release of EXO_{HF} demonstrated anti-inflammatory and anti-fibrotic effects during later regenerative phases. This sequential release profile—first promoting BMSC recruitment and chondrogenesis, then suppressing inflammation and fibrocartilage formation—synergistically enhanced hyaline cartilage repair. Importantly, we identified that HF dynamically modulates inflammatory chemokines through the cGAS-STING pathway, maintaining a pro-regenerative microenvironment. In conclusion, our exosomal dual-drug hydrogel with sequential release successfully coordinated chondrogenesis promotion and inflammation/fibrosis suppression, significantly enhancing hyaline cartilage regeneration. Also revealed was HF's cGAS-STING immunomodulatory mechanism, demonstrating strong potential for clinical translation.

Multimodal Mechanoadaptive Artificial Synovial Fluid Drives In-Situ Engineering of Anti-Pyroptotic Extracellular Vesicles to Arrest Preclinical Osteoarthritis

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Abstract: Effective early interventions for knee protection in exercise enthusiasts and pre-clinical symptomatic knee osteoarthritis (OA) patients are lacking. Abnormal mechanical loading initiates a dual pyroptotic loop between chondrocytes and macrophages, converting healthy cartilage to pathology. Herein, we engineered a multifunctional artificial synovial fluid, pPBA@MN UM6@Co (PMUC), to deliver graded protection and repair of early pathogenetic cartilage. Intra articular PMUC builds a persistent hydration layer via water bonding, mimicking native synovial fluid, markedly enhancing lubrication and dissipating mechanical stress. When abnormal stress provokes ultra early cartilage lesions, the ensuing ROS ($\cdot\text{OH}$) surge cleaves boronate esters and glycosidic bonds in PMUC, releasing mannose (Man) and UM6@Co (UC) nanocomplexes. Activation of the hexosamine biosynthetic pathway (HBP) suppresses Caspase-3(CAS3)-GSDME-mediated pyroptosis in chondrocytes while promoting in situ formation and engineering of extracellular vesicle (EV) derived from resident and synovial macrophages. These EVs, functioning as intercellular messengers within the articular cavity, collectively disrupt the chondrocyte-macrophage pyroptosis loop and facilitate matrix regeneration. Proteins including XIAP and OTULIN present in EVs play essential roles in inhibiting the dual-pyroptosis loop. In high-load exercise and early OA rat models, PMUC prevented further erosion and healed existing defects, achieving full cartilage regeneration and restored locomotor performance within eight weeks. By coupling adaptive lubrication with stress triggered immune-metabolic modulation, PMUC offers the first stage specific strategy that simultaneously protects healthy joints and repairs silent OA, filling a critical clinical gap for exercise enthusiasts and early-stage patients.

Key words: artificial synovial fluid; extracellular vesicles; exercise enthusiasts; pre-clinical symptomatic knee osteoarthritis.

Introduction: Please clearly characterize the scientific question investigated in the study.

Materials & Methods: Please briefly explain the materials and methods applied in the study.

Results & Discussion: Please concisely present the results of significant positive and negative findings in the study.

Conclusions: Please concisely state the conclusions and include recommendations for future study, and implications and significance of the data presented.

Table X. Caption.

Graphics(the graphics should be clear, and its resolution should be 600 dpi)

Fig. X. Caption.

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Construction of a Smart Biomaterial Scaffold for Piezoelectric Regulation of Stem Cell Fate and Its Application and Mechanism in Tracheal Regeneration

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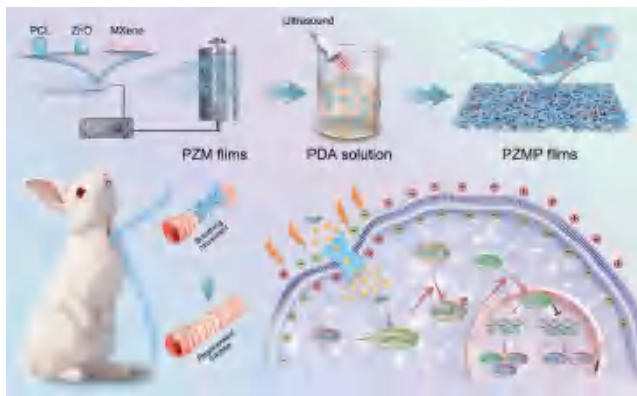
Key words: Tracheal regeneration, Piezoelectric scaffold, Signaling seesaw, Tissue engineering

Introduction: Long-segment tracheal defects lack effective repair strategies. Conventional scaffolds fail to actively guide functional cartilage regeneration^[1]. This study develops an active piezoelectric tissue engineering strategy to navigate bone marrow mesenchymal stem cell (BMSC) fate and drive functional tracheal regeneration.

Materials & Methods: We electrospun a piezoelectric composite scaffold (PZMP) comprising polycaprolactone (PCL), zinc oxide (ZnO), MXene, and polydopamine (PDA). After physicochemical characterization, we evaluated BMSC differentiation, calcium transients, and pathway inhibition in vitro under dynamic loading. *In vivo* structural and biomechanical repair efficacy was assessed using a rabbit segmental tracheal defect model.

Results & Discussion: PZMP exhibited stable piezoelectricity (Fig. 1). Dynamically loaded PZMP significantly upregulated chondrogenic and downregulated osteogenic markers in BMSCs versus PCL scaffolds. Real-time imaging confirmed piezoelectric stimulation induced transient calcium influx, which was blockable by voltage-gated calcium channel (VGCC) inhibitors. *In vivo*, PZMP achieved superior repair, improving survival, reducing restenosis, and regenerating tissue with near-native biomechanics (Fig. 2).

Conclusions: PZMP promotes functional tracheal regeneration by piezoelectrically regulating the VGCCs/ Ca^{2+} axis, which modulates the RUNX1/RUNX2 signal seesaw to precisely guide BMSC differentiation. This intelligent, endogenous energy-converting biomaterial presents a promising approach for clinical long-segment tracheal reconstruction.



Graphics

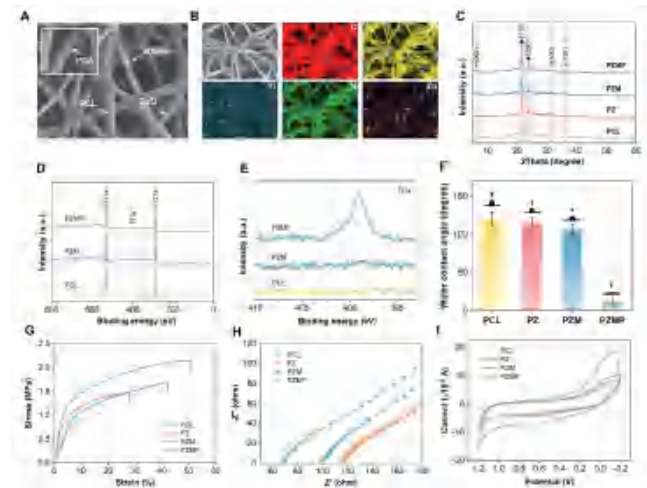


Fig. 1. Physicochemical characterization of the PZMP composite scaffolds. (A-B) SEM morphology and corresponding EDS elemental mapping; (C-E) XRD patterns, XPS survey spectra, and high-resolution N 1s spectra; (F) Water contact angle analysis; (G) Stress-strain curves; (H-I) Electrochemical impedance spectroscopy (EIS) and cyclic voltammetry (CV) curves.

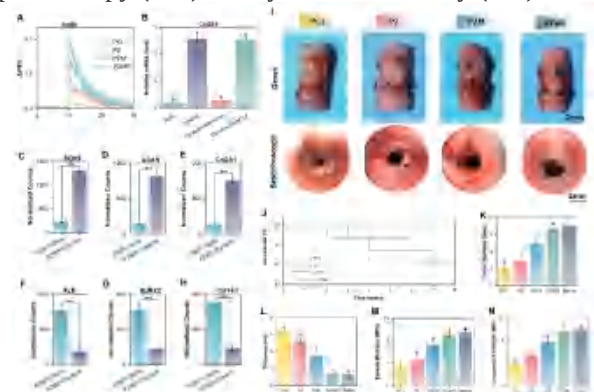


Fig. 2. *In vitro* differentiation mechanism and *in vivo* tracheal repair efficacy of the PZMP scaffolds. (A-B) Piezoelectric-induced calcium influx and VGCC inhibition; (C-H) Upregulation of chondrogenic and downregulation of osteogenic/fibrotic markers under dynamic loading; (I-J) Gross/bronchoscopic evaluation and 8-week survival rate; (K-N) Morphological (diameter, thickness) and biomechanical properties of the regenerated trachea.

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Viscoelastic polyurethane based on subject object interaction for temporomandibular joint disc repair

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Keywords: Organizational replacement; Polyurethane; Temporomandibular joint; viscoelasticity

Introduction: The temporomandibular joint (TMJ) is the only movable joint in the face and essential for oral function. TMJ discs buffer mechanical loads and lubricate joint movements through their viscoelastic properties, protecting condylar bone and cartilage. Developing artificial substitutes with matching mechanical properties is an ideal approach for treating disc injuries. Polyurethane elastomers are promising candidates due to their excellent elasticity, long-term lubricity, and fatigue resistance; however, their viscoelasticity requires further tuning to match actual joint motion frequencies. Host-guest interactions, as a dynamic non-covalent bonding strategy, enable precise viscoelastic design through reversible crosslinking between molecular segments.

Materials and Methods: This study developed a β -cyclodextrin/adamantane host-guest polyurethane elastomer for artificial TMJ discs. Dynamic viscoelasticity was tuned via host-guest ratios to match high-frequency joint motion. 3D scanning enabled fabrication of biomimetic discs matching native morphology and mechanics. Finite element analysis and animal experiments evaluated mechanical protection of bone-cartilage tissue and mechanisms of joint function recovery.

Result and Discussion: The β -cyclodextrin/adamantane host-guest inclusion creates a molecular-level damping system. Under cyclic loading, dynamic hysteresis enhances intermolecular friction for efficient energy dissipation. The material exhibits frequency-dependent softening behavior that closely matches natural disc viscoelasticity. Post-implantation, the artificial disc effectively disperses cartilage surface shear stress (~40% reduction) and alleviates strain energy concentration at the bone-cartilage interface, significantly reducing secondary injury risk through mechanical microenvironment reshaping.

Conclusion: This study successfully developed a host-guest polyurethane artificial disc with dynamic viscoelasticity matching native tissue frequency responses, effectively reconstructing joint mechanical distribution and restoring physiological function. This design offers new materials and theoretical foundations for TMJ disc replacement and repair.

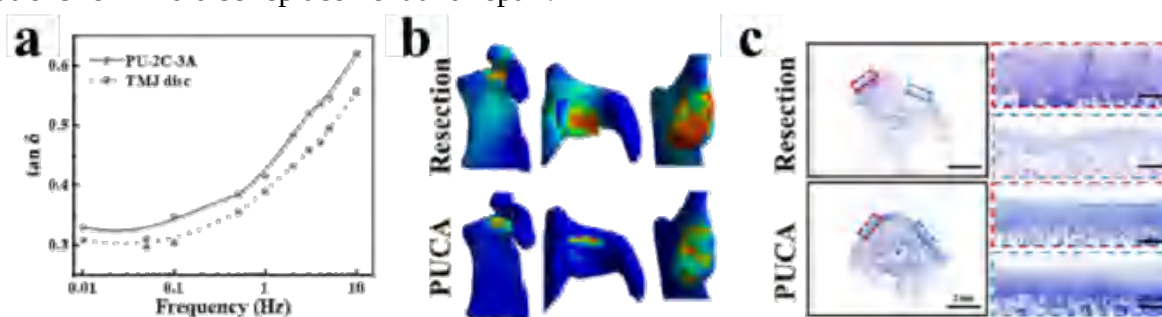


Figure 1 (a) Loss factors ($\tan \delta$) of polyurethane and natural joint discs; (B) Finite element analysis of joint stress in artificial joint disc implantation; (c) Methylamine blue staining of condylar bone cartilage tissue implanted with artificial joint disc

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Preparation and Performance Characterization of Multifunctional Tissue Repair Bioink Loaded with Cell Membrane Vesicles

Hunan University

Mengyi Yu Hairong Liu Zheng Zhou Wenkai Zhao Chenxuan Zhou

ABSTRACT

Articular cartilage repair remains a formidable clinical challenge due to its limited self-healing capacity, the oxidative stress associated with the post-injury pathological microenvironment, and the high risk of infection. Herein, we developed a multifunctional bioink based on sericin, a highly biocompatible natural biomaterial, to simultaneously promote cartilage regeneration and modulate the adverse microenvironment after injury. Sericin was methacrylated with methacrylic anhydride to obtain photocrosslinkable sericin (SerMA), which was further functionalized with chondrocyte membrane-derived vesicles through acrylate-polyethylene glycol-succinimidyl ester conjugation. The retained membrane proteins, including CD44 and integrins, endowed the bioink with enhanced bioactivity for cell adhesion and proliferation. In addition, the natural polyphenol punicalagin was loaded into the membrane vesicles to construct bioactive cell-mimetic capsules. Owing to its abundant phenolic hydroxyl groups, punicalagin exhibited potent reactive oxygen species scavenging capability, with a clearance efficiency of up to 93%, and broad-spectrum antibacterial activity by disrupting bacterial membrane integrity, achieving antibacterial rates above 90%. Under 405 nm blue-light irradiation, the bioink rapidly crosslinked and displayed excellent printability, shape fidelity, and cytocompatibility. In a nude mouse subcutaneous ectopic model, the SerMA-mCMVs hydrogel promoted the formation of typical cartilage lacuna-like structures, along with enhanced proteoglycan and type II collagen deposition. More importantly, in a rat knee osteochondral defect model, the PUN8@SerMA-mCMVs bioink achieved complete neo-cartilage coverage of the defect, increased type II collagen expression by 3.1-fold, and restored an intact tidemark. Collectively, this study presents a biomimetic and multifunctional bioink capable of integrating pro-regenerative and microenvironment-regulating functions, thereby providing a promising strategy for cartilage tissue engineering and translational repair of articular cartilage defects.

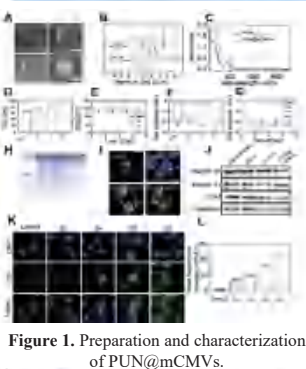
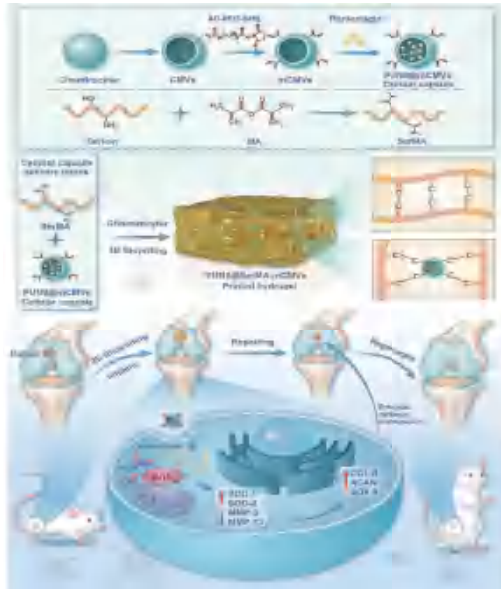


Figure 1. Preparation and characterization of PUN@mCMVs.

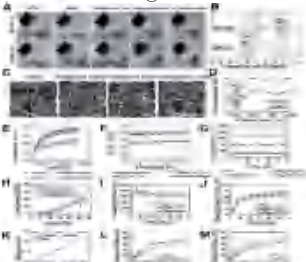


Figure 2. Fabrication and characterization of SerMA and PUN@SerMA-mCMVs.

1. PUN-loaded modified membrane vesicles (PUN@mCMVs) were fabricated by mixing mCMVs with PUN at a 1:1 mass ratio, followed by sonication, repeated extrusion, and ultracentrifugation, yielding uniform nanovesicles with a size of 125.67 ± 1.64 nm.
2. TEM imaging showed a typical closed cup-shaped structure, confirming successful drug encapsulation.
3. The engineered vesicles preserved key chondrocyte-derived membrane proteins and exhibited efficient cellular uptake with cytoplasmic localization.

1. SerMA, LAP, and PUN@mCMVs were blended to form a bioink precursor and rapidly photocrosslinked under 405 nm blue light to obtain the PUN@SerMA-mCMVs composite hydrogel.
2. The hydrogel exhibited a highly porous 3D network with pore sizes of 100–150 nm and porosity above 70%, together with sustained release behavior without burst release and oxidative stress-responsive cargo release.

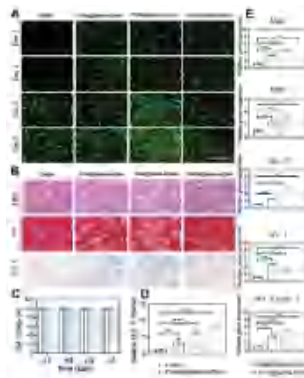


Figure 3. Biocompatibility of PUN@SerMA-mCMVs.

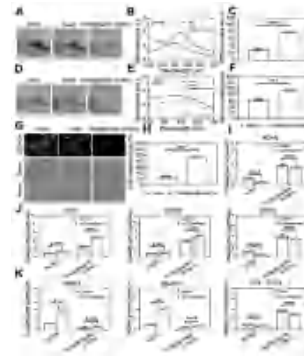


Figure 4. Antioxidant activity of PUN@SerMA-mCMVs.

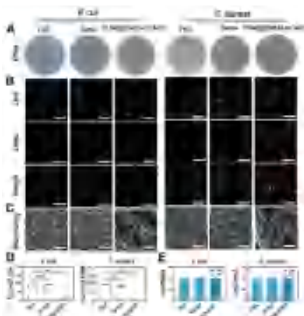


Figure 5. Evaluation of antibacterial performance.

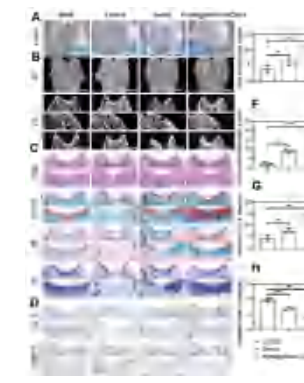


Figure 6. Assessment of cartilage repair.

1. PUN8@SerMA-mCMVs (800 $\mu\text{g/mL}$) most effectively promoted chondrocyte proliferation, with the highest cellular metabolic activity observed at all time points.
2. PUN@SerMA-mCMVs significantly upregulated SOX9 and ACAN expression, enhanced COL II expression, and reduced COL I expression, thereby increasing the COL II/COL I ratio and supporting maintenance of the hyaline cartilage phenotype.

1. PUN8@SerMA-mCMVs effectively scavenged ROS by releasing punicalagin-derived phenolic hydroxyl groups as hydrogen donors for free radical neutralization.
2. In parallel, it upregulated antioxidant genes (SOD1, SOD2) and downregulated catabolic genes (MMP-3, MMP-13) in chondrocytes, thereby reducing oxidative stress and inhibiting cartilage matrix degradation.

1. Plate counting and live/dead staining verified the potent antibacterial performance of PUN8@SerMA-mCMVs.
2. SEM images showed intact and smooth bacteria in the control and SerMA groups, whereas bacteria in the PUN8@SerMA-mCMVs group displayed membrane rupture, cytoplasmic leakage, and polymer-associated aggregation, consistent with the membrane-disruptive antibacterial mechanism of punicalagin.

1. PUN8@SerMA-mCMVs enabled complete defect coverage by neo-tissue with a smooth surface and good integration with adjacent native cartilage, resulting in significantly improved ICRS macroscopic scores.
2. Micro-CT and 3D reconstruction further confirmed effective defect filling and restoration of a cartilage-like contour.
3. Meanwhile, the hydrogel suppressed matrix metalloproteinase expression, thereby reducing oxidative stress- and inflammation-mediated cartilage degeneration.

Ferromagnetic nanoparticles enhance the piezoelectric effect of silk fibroin scaffolds to promote osteochondral repair

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Keywords: magnetic nanoparticles, silk fibroin scaffold, piezoelectric effect, osteochondral, stem cell

Abstract

Background

Silk fibroin scaffolds (SFCs) that exploit piezoelectricity for osteochondral repair have been hampered by both insufficient electromechanical output and a pro-inflammatory joint microenvironment that erodes therapeutic efficacy[1, 2].

Methods

we developed an intra-articular implantable scaffold with enhanced piezoelectricity, called FENS@MF, via covalently integrating ultradispersible magnetic nanoparticles (MNPs) into SFCs via EDC/NHS crosslinking.

Results

Under magnetically controlled stimulation, FENS@MF generates an ~8.5-fold increase in output voltage, a threefold enhancement in tensile strength, and undergoes only 15.65% degradation by protease XIV over 15 d, thereby sustaining potent electromechanical signaling. *In vitro*, it markedly

upregulates chondrogenic (COL2, SOX9), osteogenic (RUNX2, BMP2), and angiogenic (VEGF, eNOS) markers, while inducing M1-to-M2 macrophage polarization to attenuate inflammation. In rat osteochondral defect models, FENS@MF outperforms conventional SFC and FENS scaffolds, achieving cartilage and subchondral bone regeneration with bone mineral density and trabecular thickness comparable to autologous grafts. FENS@MF enhances the piezoelectric effect by responding to the magnetic field (MF) and absorbing electromagnetic waves, and cooperates with magnetic stimulation and immune microenvironment regulation to achieve efficient osteochondral regeneration. Enhanced piezoelectric signals may drive SOX9-mediated chondrogenesis through activation of p38 MAPK phosphorylation (upregulation of COL2/ACAN) and trigger osteogenic differentiation through β -catenin nuclear translocation (upregulation of RUNX/BMP2).

Conclusions

This study is the first to integrate the piezoelectric effect, magnetic stimulation and immunomodulation, which breaks through the limitation of a single functional scaffold, establishes a ‘structure-function-signal’ paradigm for intelligent osteochondral repair, and provides a multifunctional platform for functional tissue regeneration.

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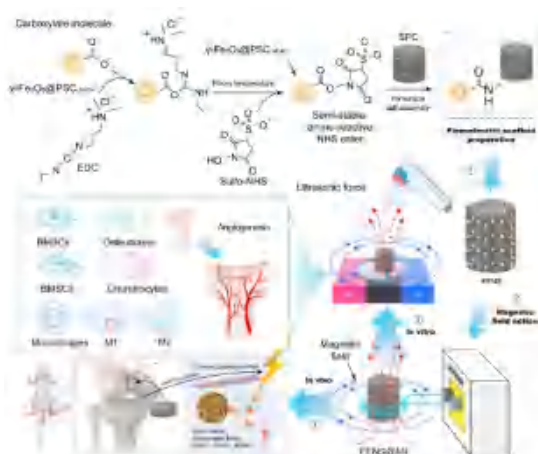


Figure 1. Schematic diagram of the construction of iron-based nanoparticle enhanced silk fibroin (SF) piezoelectric scaffold

Hierarchical fiber-hydrogel nerve guidance conduits with spatially programmed phage nanofibrillar ligands promote peripheral nerve regeneration

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Abstract: Peripheral nerve regeneration requires integrating topographical and biochemical cues, but soluble neurotrophic factors suffer from rapid degradation. Here, we report a hierarchical fiber-hydrogel nerve guidance conduit (NGC) enabled by spatially programmed recombinant phage nanofibrillar ligands. Displaying bioactive motifs on pIII proteins provides ultra-stable, localized signaling that circumvents free peptide fragility. The NGC combines aligned PCL nanofibers (phage-RGD) for prolonged adhesive guidance (>15 days) with a GelMA hydrogel (phage-RGD/RGI) for sustained BDNF-mimetic stimulation. These ligands induce anabolic metabolic reprogramming in Schwann cells to fuel proliferation. In a 10-mm rat sciatic nerve defect, the conduit restored 76.15% CMAP alongside robust axonal regeneration and remyelination.

Key words: Peripheral nerve regeneration; recombinant phages; nanofibrillar ligands; NGC

Introduction: Treating peripheral nerve injury (PNI) remains challenging due to autograft morbidity and the rapid degradation of soluble neurotrophic factors in passive nerve guidance conduits (NGCs). The extremely short in vivo half-life of free factors (e.g., <10 minutes for BDNF), coupled with rapid diffusion, completely precludes the sustained signaling essential for macroscopic repair. To overcome this, we designed a bio-instructive hierarchical NGC. By employing recombinant M13 phages as ultra-stable, multivalent nanofibrillar ligands via pIII protein display, we aimed to provide sustained, spatially localized signaling to drive Schwann cell metabolic reprogramming and facilitate robust nerve regeneration.

Materials & Methods: Recombinant phage-RGD and phage-RGI were engineered using the M13KE system to display an integrin-binding RGD motif (with VPFYSHS/GGG spacers) or a BDNF-mimetic peptide (RGI) flanked by KpnI/EagI sites. SCs were treated with a 1:1 phage mixture (10^7 PFU mL/each) for 5 days for untargeted metabolomic analysis and compared to a phage-free control. Bilayer PCL fibrous films were electrospun from 12% (w/v) solution in TFE (14 kV, 1 mL/h), with collector speed reduced from 1200 to 200 rpm to form aligned inner and random outer layers. For composite fabrication, 10% (w/v) GelMA prepolymer co-loaded with phage-RGD and phage-RGI (50 °C) was injected into cylindrical molds (1.5 mm × 1 cm) and photocrosslinked 6s to obtain NGC.

Results & Discussion: TEM confirmed engineered phages retained wild-type filamentous structures, verifying pIII display preserves self-assembly. In vitro, they robustly enhanced SCs proliferation (10^5 - 10^7 PFU/mL). Metabolomics revealed this is fueled by a

dual-action anabolic reprogramming where phages serve as both signaling ligands and intracellular biomass reservoirs. Specifically, treatment upregulated nucleotide precursors (uracil, 1.83-fold; 2'-deoxyinosine, 2.51-fold), neuroregenerative spermidine (1.70-fold), and antioxidant γ -glutamylcysteine (4.67-fold). Concurrently, accumulated di/tri-peptides suggest potential lysosomal capsid degradation, hypothesized to provide an exogenous nutrient pool to meet the intensive demands of SC proliferation (Fig. 1).

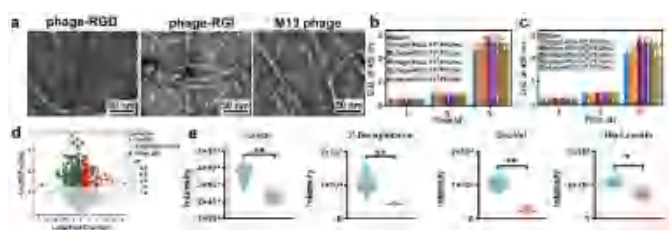


Fig. 1. (a) TEM images of phage-RGD, phage-RGI and M13 phage. (b, c) CCK-8 proliferation assays of SCs treated with respective phage. (d) Differentially expressed metabolites (DEMs) between phage-treated and control groups. (e) Relative abundances of uracil, 2'-deoxyinosine, Glu-Val, and His-Leu-Ala.

In vitro plaque assays confirmed the ultra-stable retention of phages on PCL fibers (<1% release over 15 days), validating their function as stably anchored nanofibrillar ligands rather than transient soluble cues. Translating this persistent signaling to a 10-mm rat sciatic nerve defect, the hierarchical NGC drove robust electrophysiological recovery. While bare PCL yielded a limited compound muscle action potential (CMAP) of 3.96 mV, topographical phage-RGD functionalization increased this to 8.42 mV. Strikingly, the GelMA lumen co-encapsulating phage-RGD&RGI achieved a peak CMAP of 11.62 mV, restoring 76.15% of autograft performance (Fig 2).

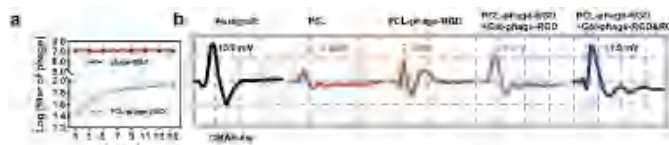


Fig. 2. (a) Release kinetics of phage-RGD from PCL scaffolds over 15 days versus a free phage-RGD control. (b) Representative CMAP waveforms at 8 weeks.

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Transdermal NIR-II Photothermal Neuromodulation Combined with Metabolite-Mediated Immunoregulation for Deep Nerve Regeneration

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Abstract: Deep peripheral nerve regeneration remains hindered due to inflammatory infection, neurotrophic factor deficiency, and slow axonal growth kinetics. Herein, we developed an innovative nerve conduit fabricated with indole-3-propionic acid (IPA)-functionalized and polydopamine-coated Au nanorods cluster (AuNR@PDA-IPA, API) loading on parallel fiber film of PLGA, exhibiting NIR-II photo-responsiveness for spatiotemporally precise neuromodulation. API convert deep-penetrating NIR-II light (1064 nm) to localized heat ($\sim 43^\circ\text{C}$) and non-invasively activate TRPV1 channels in Schwann cells to trigger Ca^{2+} -mediated neurotrophic expression. Meanwhile, the newly introduced gut metabolite IPA cooperate with PDA potently scavenges ROS, suppresses NF- κB activation and promotes M2 polarization of macrophages, thereby reshaping the neuro-regenerative microenvironment. Concurrently, the results demonstrate that the API-PLGA conduit enhances VEGF-driven angiogenesis and activates Schwann Cells to upregulate the expression s of neurotrophic factors and myelin-related proteins. This work pioneers a non-invasive bioelectronic paradigm, which merges spatiotemporally photothermal neuromodulation with immune-metabolic reprogramming for precision neural reconstruction.

Key words: Nerve Regeneration; NIR-II irradiation; Polydopamine; Gold nanorods; Indole-3-propionic acid;

Introduction: Although multifunctional nerve guidance conduits (NGCs) integrating various strategies are developed, achieving spatiotemporally precise neuromodulation within deeply located neural tissues *in situ* presents a significant challenge. Through orchestrated tripartite regulation of “anti-inflammatory–angiogenic–neuroregenerative”, the conduit enables robust axonal regrowth, re-myelination, and functional recovery in peripheral nerve defects, offering a transformative strategy for the repair of deeply located neural tissue.

Materials & Methods:

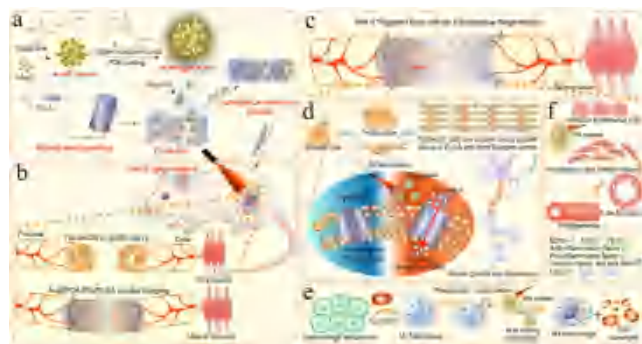


Figure 1. Schematic of AuNR@PDA-IPA (API)-PLGA conduit nerve repair under NIR-II: (a) Fabrication process of API-PLGA conduit; (b) conduit bridge a sciatic

nerve defect of rat; (c) NIR-II triggered multi-cellular collaborative regeneration at the site of nerve transection; (d) NIR-II-triggered bio-effects of API, including activating TRPV1 channel in SCs and enhancing neurotrophic factor expression and axonal myelination; (e) API mitigate the inflammatory response by scavenging ROS, promoting macrophage polarization toward M2 phenotype, and modulating the expression of key inflammatory cytokines; (f) API under NIR-II activate vascular endothelial cells and promoting microvascular regeneration

Results & Discussion:

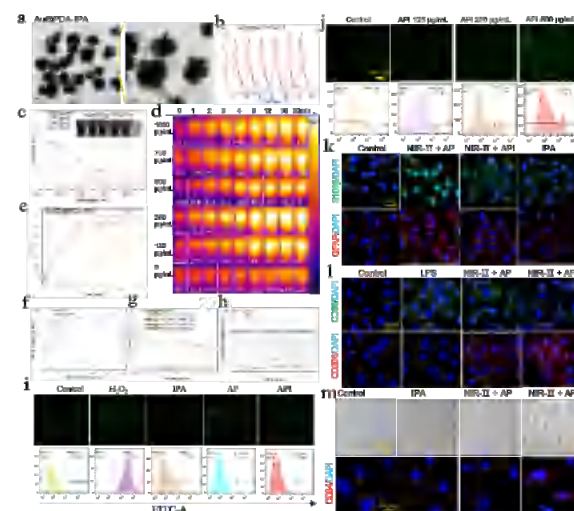


Fig 2. (a) TEM image of API. (b) Photothermal cycle curve of 500 $\mu\text{g/mL}$ API under NIR-II (1064 nm, 1 W/cm^2) light for 6 times. (c) UV-vis-NIR absorbance spectra of API. (d) The corresponding real-time thermal images of API dispersions. (e) Photothermal curves of API dispersions under NIR-II. (f) The ABTS $\cdot^+$ scavenging rate after API and AP treatment with different concentrations ($n = 3$). (g) UV-vis absorption spectra of API treated with different concentrations of H_2O_2 for 24 hours. (h) IPA release curve of API under intermittent NIR-II irradiation or simulated reactive oxygen species environment (1 mM H_2O_2) for 12 hours. Immunofluorescence staining images and flow cytometry analysis results of (i) different groups' RAW264.7 intracellular ROS levels and (j) intracellular Ca^{2+} level of RSC96 cells. (k) CLSM images of S100 β and GFAP protein in RSC96 cells. (l) CLSM images of CD86 and CD206 protein in RAW264.7 cells. (m) Images of tube formation by HUVECs after coinubation with API, AP and IPA under NIR-II irradiation for 6 h and CLSM images of CD34 in HUVECs. ($n = 3$, data represent mean $\pm$ SD)

Conclusions: In summary, we developed an innovative artificial nerve conduit composed of AuNR@PDA-IPA/PLGA, effectively promoting axonal regeneration and functional motor-sensory recovery. The conduit features a hyperbranched black-body structure, which facilitates plasmonic coupling and efficient NIR-II photothermal conversion. This process activates TRPV1 channels, induces calcium influx, and triggers neuronal action potentials to stimulate proximal nerve regeneration and facilitate distal reinnervation. Simultaneously, the neuroprotective IPA activates Schwann cells, upregulates S100, GFAP, BDNF and NGF expression, collectively accelerating axonal growth and myelination. The IPA-PDA coating confers anti-inflammatory and ROS-scavenging capabilities. This nerve conduit overcomes key limitations of conventional approaches, offering a breakthrough strategy for innovative treatment of deep peripheral nerve injuries.

Label-Free Raman Microscopy Identifies Neuronal Internalization of PMMA Nanoparticles in a Microfluidic Platform

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Key words: Raman Microscopy; PMMA particles; periprosthetic tissues; microfluidics; dorsal root ganglia

Introduction: Poly(methyl methacrylate) (PMMA) is widely used as a bone cement in joint arthroplasties. Over time, mechanical wear generates debris that accumulates in periprosthetic tissues, contributing to chronic inflammation characterized by dense innervation and macrophage infiltration [1]. Although the biological effects of PMMA wear debris have been extensively studied in macrophages [2], the interactions of nano-sized PMMA particles (PMMA NPs) with sensory neurons remain poorly understood. This study focuses on the use of label-free confocal Raman microscopy to investigate PMMA NPs–neurons interactions in a physiologically relevant model.

Materials & Methods: Compartmentalized microfluidic cultures of embryonic dorsal root ganglia (DRG) explants were used to selectively expose axonal terminals to PMMA NPs, mimicking the spatial organization of the periprosthetic niche. Given their role in transmitting sensory signals from the peripheral to the central nervous system, DRGs provide a physiologically relevant platform to assess nerve-fiber sprouting and neuronal responses. Label-free confocal Raman microscopy was employed to chemically characterize and detect PMMA NPs within neuronal compartments, providing a means to assess their interaction with neurons based on their specific vibrational fingerprints.

Results & Discussion: Confocal Raman microscopy enabled the label-free detection of PMMA NPs in DRG tissue by identifying polymer-specific bands (~818 and 2849 cm⁻¹) that were absent in untreated controls. Broadening of the 2800-3000 cm⁻¹ region further supported the internalization of PMMA NPs within the DRG (Fig. 1).

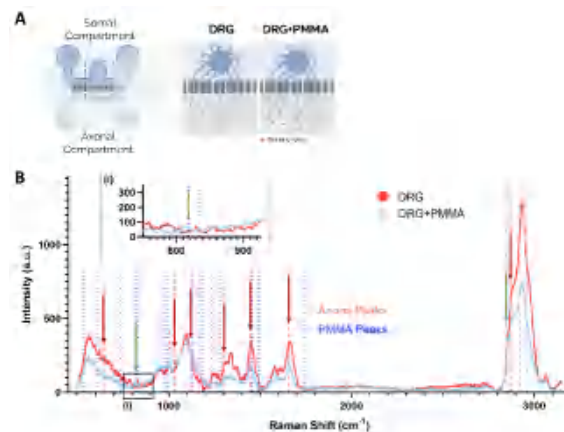


Fig. 1. Neuronal internalization of nano-sized implant-derived PMMA particles. (A) Microfluidic platform. (B) Confocal Raman microscopy detection of PMMA signatures in axonal compartments.

Conclusions: These findings establish label-free confocal Raman microscopy, combined with a microfluidic platform, as a robust platform for exploring nanoparticle-neuron interactions. By enabling direct chemical detection of implant-derived nanodebris within sensory neurons, this approach overcomes key limitations of fluorescence-based strategies and provides reliable molecular specificity. The demonstration of neuronal access to PMMA NPs supports that implant-derived particles may directly engage the nervous system, offering new insight into mechanisms potentially underlying persistent periprosthetic pain.

Acknowledgements: This work was supported by the Funding Neuro-skeletal group (Centro 8089901H22) and the MOBILisE_Plus project, co-funded by the European Union through the NORTE 2030 Regional Program of the European Regional Development Fund (FEDER), under the operation with the code NORTE2030-FEDER-01801000. The authors acknowledge the support of i3S Scientific Platforms: ALM, Bioimaging, HEMS, PPBI-Portuguese Platform of Bioimaging (PPBI-POCI-01-0145-FEDER-022122), BN, and TraCy.

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Harnessing High Glucose Stress-Primed HUVECs-EVs: Microgel Delivery of Enriched Regenerative Cargo for Diabetic Flap Repair

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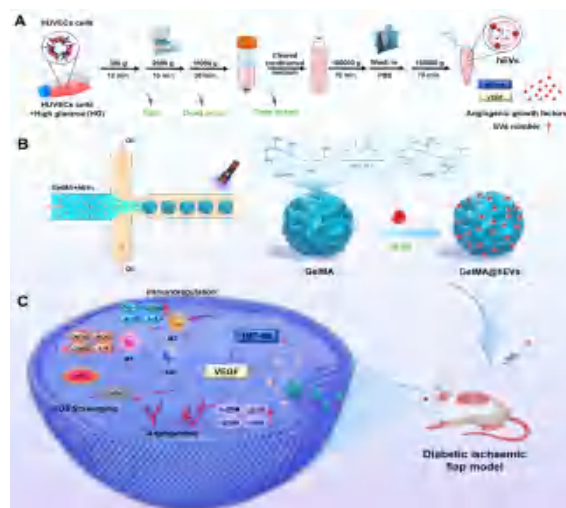
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Abstract

Diabetic ischaemic flaps pose a major clinical challenge due to intertwined pathological barriers: impaired angiogenesis, excessive oxidative stress, and persistent inflammation, which collectively lead to poor tissue repair. To address this challenge, this study developed a therapeutic platform integrating high glucose (HG)-preconditioned HUVECs-derived extracellular vesicles (hEVs) with microfluidically fabricated gelatin methacryloyl (GelMA) microgels (GelMA@hEVs). HG preconditioning enhanced hEVs secretion and enriched pro-regenerative molecules (HIF-1 α , VEGF) and proteins involved in angiogenesis-related pathways. GelMA microgels with uniform morphology were stable in physiological conditions, while showed rapid degradation in ischaemic microenvironments. The platform sustained hEVs release, exhibited excellent biocompatibility, promoted endothelial cell proliferation, migration, and tube formation critical for vascularization, scavenged reactive oxygen species, and modulated macrophage polarization toward a pro-reparative phenotype. Mechanistically, these therapeutic effects relied on activating the HIF-1 α /VEGF pathway, a core axis for angiogenesis dysregulated in diabetes. In diabetic ischaemic flap models, GelMA@hEVs significantly improved flap survival, restored vascular perfusion, and facilitated tissue regeneration without systemic toxicity. Altogether, this work provides a translatable strategy for diabetic ischaemic flap repair by employing in situ tissue engineering approach involving engineered EVs as bioactive factors and microgel as the scaffold.

Keywords:

HUVECs-derived extracellular vesicles; Angiogenesis; Microgels; Inflammation regulatory; Diabetic ischaemic flap regeneration



Scheme 1. Schematic illustration of GelMA@hEVs microgels promoting diabetic ischaemic flap regeneration.

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3D bioprinted vessels from peripheral blood: reinforced fibrin bioinks containing human endothelial progenitors-derived cells

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Key words: carrageenan, endothelial cells, 3D bioprinting, vascular graft, fibrin-based hydrogels

Introduction: The prevalence of vascular diseases as a leading cause of mortality highlights the need for artificial vascular models. To overcome the limitations of conventional therapies, 3D bioprinting emerges as an innovative tissue engineering approach [1]. Fibrin is a fibrous protein involved in the coagulation cascade that polymerizes in the presence of calcium ions and undergoes crosslinking to form a gelatinous network [2]. Endothelial progenitor cells are mononuclear cells derived from bone marrow that have the ability to migrate into the peripheral circulation and differentiate into mature endothelial cells, thereby contributing to endothelialisation and revascularization [3]. Alginate is a polysaccharide found in brown algae whose low toxicity and non-immunogenicity make it a biocompatible material [4], whereas carrageenan is a natural polysaccharide extracted from red algae known for its thickening and stabilizing properties in the presence of potassium ions [5]. The aim of this work is the assessment of the incorporation of these polysaccharides on hydrogels based on plasma-derived fibrin and human endothelial cells differentiated from peripheral blood progenitor cells in order to evaluate their suitability as a bioink for the bioprinting of vascular grafts.

Materials & Methods: Mononuclear cells were isolated from peripheral blood of healthy donors by Ficoll-Hypaque density gradient centrifugation. The fraction enriched in CD34⁺ cells by immunomagnetic separation with microbeads was cultured in medium supplemented with specific endothelial growth factors for its in vitro differentiation. Human blood plasma, different concentrations of alginate and carrageenan were combined for the synthesis of the hydrogels in which the endothelial cells were embedded. To evaluate the performance of these bioinks, the gels were subjected to rheological, printability, stability and cytotoxicity assays.

Results & Discussion: Immunofluorescence characterization of the culture derived from the CD34⁺ enriched subpopulation revealed the expression of the mature endothelial cell marker CD31 (Fig. 1a). Rheological analysis showed that bioink viscosity decreased with increasing shear rate, consistent with the shear-thinning behaviour required for extrusion. Furthermore, the incorporation of alginate exerted a directly proportional effect on hydrogel viscosity due to

an increase in the molecular weight of the hydrogel (Fig. 1b). Regarding the consistency of the bioinks, the addition of carrageenan improved the structural integrity of the hydrogel, thus enabling the fabrication of luminal three-dimensional cylinders, resembling the architecture of a native blood vessel (Fig. 1c,d).

Conclusions: This study raises the feasibility of a bioink that incorporates patient-derived native cells for the manufacturing of autologous vascular grafts, thereby avoiding immune rejection, which represents a promising step towards the treatment of vascular diseases.

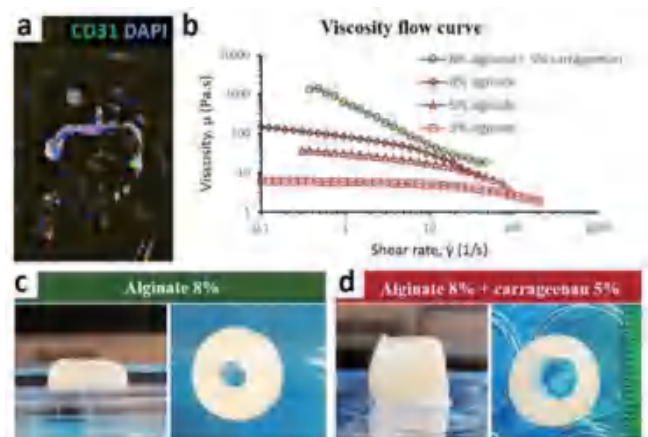


Fig. 1. (a) Phenotype characterization of endothelial cells derived from CD34⁺ enriched fraction. (b) Viscosity flow curves of the bioinks. (c,d) Frontal and top views of the printed construct without and with carrageenan.

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Accelerated Degradation Behavior of Biodegradable Vascular Stents in a Biomimetic Fluid Field

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Key words: biodegradable vascular stents, biomimetic fluid field, degradation behavior, molecular weight

Introduction: Traditionally, *in vitro* degradation studies of biodegradable vascular stents are predominantly conducted in static liquid environments. However, recent studies indicate that dynamic fluid flow can significantly accelerate the degradation behavior of biomaterials[1-3]. Because stents are continuously exposed to dynamic blood flow *in vivo*, static models may fail to accurately predict their actual degradation kinetics. The primary scientific question investigated in this study is how a dynamic, biomimetic fluid field simulating human hemodynamic conditions alters the degradation behavior of cardiovascular stents compared to conventional static environments.

Materials & Methods: To address this scientific question, we designed and constructed a custom testing system capable of simulating the physiological human blood flow environment. Biodegradable vascular stents were deployed into this dynamic biomimetic fluid system(made of Nanjing Recongene), while a control group was maintained in a traditional static liquid environment. Stent samples were extracted from both systems at predetermined degradation time points. Subsequently, comprehensive characterizations were performed to evaluate the physical and chemical properties of the degraded stents, with a specific focus on measuring the changes in molecular weight and crystallinity. The biodegradable vascular stent was fabricated by our 3D4-axis printing equipment, using PLCL as the material.

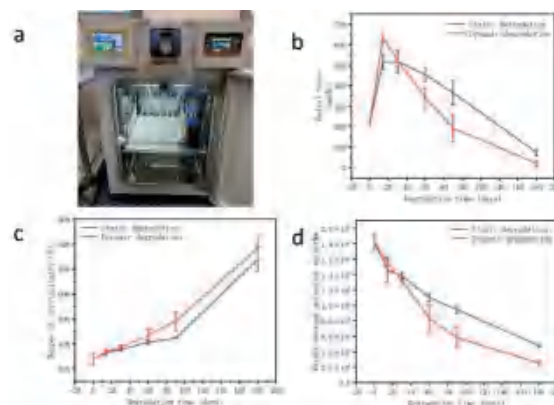
Results & Discussion: The comparative analysis revealed significant disparities in the degradation profiles between the dynamic and static environments. Most notably, we found that under the simulated human blood flow conditions, the molecular weight of the stents decreased at a markedly faster rate. Alterations in crystallinity were also observed at earlier time points, corresponding to the accelerated breakdown of the polymer matrix. The continuous fluid flow likely facilitated mass transfer and the rapid removal of local degradation products, thereby expediting the degradation processes. These findings provide strong positive evidence that the biomimetic fluid field plays a critical role in accelerating material degradation.

Conclusions: A simulated human blood flow environment significantly accelerates the degradation process of biodegradable vascular stents, primarily evidenced by a more rapid decline in molecular weight. Our findings provide a novel and crucial direction for future *in vitro* degradation studies of biodegradable vascular implants. Furthermore, this study establishes a vital theoretical and practical basis for the design and construction of specialized research testing equipment. For future studies, we recommend incorporating varying physiological parameters (e.g., shear stress) into the dynamic system to further elucidate the localized degradation mechanisms and optimize stent design.

Fig. 1. Schematic diagram of 3D-printed degradable vascular stent.



Fig. 2. Devices and Results



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Mechanically Adaptive Injectable Adhesives for Endovascular Embolotherapy

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Key words: injectable adhesive; mechanical adaptation; vascular occlusion; vascular endothelialization

Introduction: An aneurysm is a pathological dilation of the arterial wall caused by hemodynamic stress. Clinically, metallic coil embolization is widely used; however, poor sealing, low packing density, and mechanical mismatch with the vessel wall often result in heterogeneous stress distribution and compromised hemodynamics. Injectable hydrogels offer a promising alternative due to their excellent lumen conformability and volumetric filling capacity; however, their clinical application remains limited by weak tissue adhesion, risk of post-implantation displacement, and uncontrolled swelling that may compress adjacent vasculature. In this study, we developed a mechanically adaptive, injectable adhesive based on polyelectrolyte complexes (PECs). The material consists of PEC microparticles dispersed in a biocompatible oil-phase carrier, enabling catheter-based delivery. Upon delivery to the target site, the adhesive conforms precisely to the aneurysm morphology and undergoes rapid in situ gelation via interfacial solvent exchange. In vitro and in vivo studies demonstrated complete aneurysm occlusion, sustained embolic stability for 14 days without detachment or migration, and favorable biomechanical integration with native tissue. The adhesive matches the mechanical properties of the tissue, reduces local inflammation, and promotes endothelial repair, providing a promising strategy for aneurysm treatment.

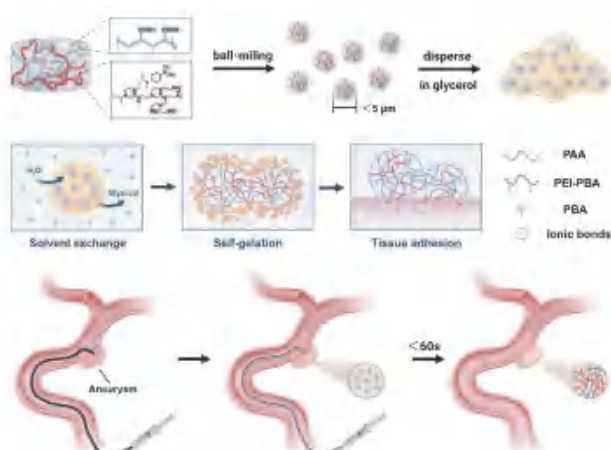


Fig. 1. Schematic illustration of the preparation and application of the injectable adhesive.

Materials & Methods: In this study, a Michael addition reaction was employed to graft phenylboronic acid

groups onto the polyethyleneimine (PEI) molecular chain, thereby synthesizing the phenylboronic acid-modified cationic polymer PEI-PBA. Subsequently, the PEI-PBA solution was mixed with a polyacrylic acid (PAA) solution at a predetermined mass ratio. Through electrostatic interactions between the two polyelectrolytes, a polyelectrolyte complex (PEI-PBA/PAA, PEAB) was self-assembled. The resulting complex was then subjected to freeze-drying to remove the solvent, followed by ball milling to produce uniform microparticles. Finally, the powder was redispersed in glycerol to obtain the final injectable adhesive formulation.

Results & Discussion: In this study, we developed a mechanically adaptive, injectable adhesive based on polyelectrolyte complexes. The introduction of phenylboronic acid groups reinforced the crosslinking network via covalent and hydrophobic interactions, significantly enhancing the material's mechanical properties and tissue adhesion. The maximum tensile strength of PEAB reached 1.19 N—approximately 2.4-fold and 9.3-fold higher than that of PEI-PAA complexes and sodium alginate hydrogel, respectively—and its elastic modulus reached 10^5 Pa within 5 min of water exposure, matching that of vascular tissue. In an ex vivo circulation model, PEAB achieved effective lumen filling and stable occlusion, remaining firmly adhered to the vessel wall after 7 days of circulation. Additionally, PEAB significantly reduced intracellular ROS levels. In a rat carotid aneurysm pouch model, it provided stable embolization, alleviated inflammatory responses, and promoted vascular repair, indicating strong potential for clinical application.

Conclusions: The injectable adhesive developed in this study matches the mechanical modulus of the tissue, enabling effective filling and occlusion. Its excellent tissue-adhesive properties allow for stable attachment to the vascular wall. Furthermore, the adhesive has the potential to modulate local inflammation and promote endothelial repair, highlighting its significant therapeutic potential for the treatment of aneurysms.

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Conductive Microneedle Patch Based on the Multi-dimensional Synergy of "Matrix Homeostasis-Electrical Coupling-Vascularization" for Ameliorating Ventricular Remodeling: Effects and Mechanisms

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Adverse ventricular remodeling after myocardial infarction (MI) is a major driver of heart failure and involves extracellular matrix disruption, impaired electrical coupling, and insufficient angiogenesis, which are difficult to address with single-modality therapies. Herein, we developed an MMP-2/9-responsive conductive microneedle patch for localized and synergistic post-MI intervention. The patch integrates a conductive hydrogel matrix with scar-penetrating microneedles and an enzyme-responsive QK peptide delivery system, enabling simultaneous restoration of matrix homeostasis, repair of electrical conduction, and promotion of angiogenesis. Upon implantation into infarcted myocardium, the patch scavenged aberrantly elevated MMP-2/9 to attenuate pathological matrix degradation, while enzyme-triggered release of the VEGF-mimetic QK peptide activated pro-angiogenic signalling. Meanwhile, the conductive matrix enhanced Cx43-mediated intercellular electrical coupling in the infarct border zone. In vitro and in vivo studies collectively demonstrated that this multifunctional platform reduced MMP-2/9 activity, increased Cx43 expression and microvascular density, improved cardiac function, and lowered the incidence of ventricular arrhythmias in MI rats. Collectively, these findings establish a responsive conductive microneedle platform for coordinated regulation of the post-infarction microenvironment and provide a promising therapeutic strategy for preventing heart failure after MI.

Key words: Conductive microneedle patch; Responsive drug delivery; Synergistic therapy; Ventricular remodeling

Gas-Boosted Ca^{2+} -Mediated Tumor Microenvironment Remodeling for Enhanced Sonodynamic Therapy and Osteosarcoma Cancer Treatment

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Key words: sonodynamic therapy, osteosarcoma therapy, gas therapy, Ca^{2+} overload, immunotherapy

Introduction: Osteosarcoma (OS) treatment is hindered by tumor recurrence, metastasis, and an immunosuppressive tumor microenvironment (TME). Sonodynamic therapy (SDT), despite its deep-tissue penetration, suffers from limited reactive oxygen species (ROS) generation due to hypoxia and glutathione overexpression. Furthermore, achieving precise and sustained delivery of hydrogen sulfide (H_2S) to enhance SDT remains challenging. .

Materials & Methods: Tin chloride dihydrate, Polyvinylpyrrolidone (PVP), Cetyltrimethylammonium bromide (CTAB), tetraethoxysilane (TEOS), 3-aminopropyltriethoxysilane (APTES).

Results & Discussion: We developed an innovative ultrasound-activable nanoplatform, termed C-S-AH Gel, which integrated C@MHD nanoparticles (NPs) and SnO_{2-x} -FA NPs within a hydrogel matrix for synergistic gas therapy (GT), sonodynamic therapy (SDT), and Ca^{2+} overload therapy. The released H_2S alleviated hypoxia and disrupted mitochondrial function, dramatically amplifying ROS production, while Ca^{2+} overload further augmented tumor cell killing. This cascade process not only induced potent cancer cell apoptosis and immunogenic cell death (ICD) but also promoted dendritic cell (DC) maturation and cytotoxic T lymphocyte infiltration. Moreover, the C-S-AH could induce immune memory to prevent recurrence under US stimulation. We demonstrated that the development of this ultrasound-activable C-S-AH presented a significant avenue for the engineering of innovative tumoricidal materials, enabling a synergistic therapeutic strategy with high biosafety for the treatment of OS.

Conclusions: The C-S-AH platform, as an innovative synergistic therapy approach, provides a novel solution for the treatment of OS. This platform exhibited remarkable anti-tumor efficacy and robust immunomodulatory functions. Specifically, the C@MHD NPs induced calcium ion overload through the sustained release of calcium ions, while simultaneously releasing H_2S to reverse the immunosuppressive TME. This dual action effectively activated systemic anti-tumor immune responses and exacerbated mitochondrial damage. The SnO_{2-x} -FA NPs, with their engineered oxygen vacancy structure and narrow bandgap, demonstrated excellent electron transport capacity and active sites. Under US irradiation, C-S-AH

platform significantly enhanced the efficiency of ROS generation. The accumulation of large amounts of ROS within tumor cells triggered lethal oxidative stress, leading to tumor cell death via the apoptotic pathway. Notably, the ICD induced by this therapeutic process effectively promoted the maturation of DCs and significantly enhanced the infiltration of $\text{CD}8^+$ T cells. In vivo experimental results confirmed the significant therapeutic efficacy of this treatment system, as evidenced by marked tumor regression and activation of immune effector pathways. Furthermore, the apoptosis induced by the C-S-AH platform elicited persistent immune memory, effectively suppressing tumor recurrence.

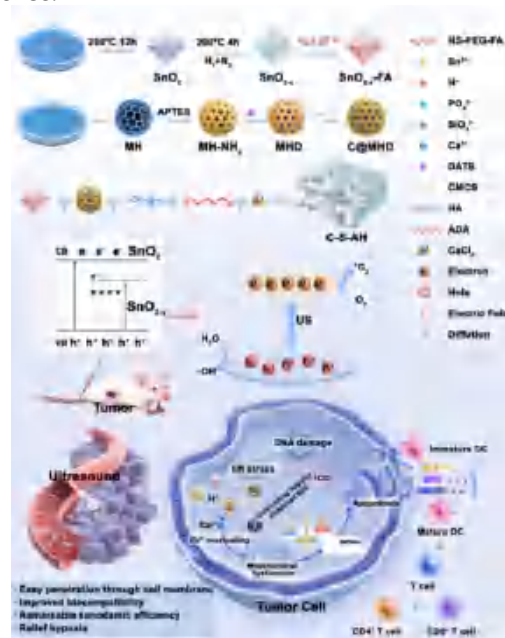


Fig. 1. Schematic illustration of the synthesis of C-S-AH.

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STAT3 interference-driven nanomodulators reverse lipid metabolism-associated chemoresistance and potentiate metalloimmunotherapy in breast cancer

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Clinical evidence has suggested that persistent STAT3 activation and alteration in lipid metabolism correlate with pathological progression in patients with breast cancer, driving resistance to chemotherapy. Herein, we showed that hydrogen sulfide (H₂S), an endogenous gas signaling molecule, sensitized breast cancer to chemotherapy by suppressing STAT3 signaling-mediated lipid metabolism and enhancing tumor immunogenicity via methylation regulation. Moreover, we further identified nickel ion (Ni²⁺) as a novel immune agonist for potent metalloimmunotherapy by screening typical transition metal ions. The construction of an activable nanoplatform through a mild biomineralization method enabled the controllable delivery of metal ions and H₂S gas, which increased the sensitivity of breast tumors to chemotherapy via metabolic modulation by STAT3 signaling and elicited systemic anti-tumor immunity by inducing cancer cell pyroptosis and mobilizing multiple immune cells. Moreover, the combination treatment with nanodrugs and chemotherapeutic agents significantly improved the responsiveness of breast tumors to immune checkpoint blockade (ICB) therapy. The synergistic effect of the αPD-1 antibody inhibited the progression of both primary and metastatic tumors. The efficacy of the combined therapy was also validated in a humanized drug-resistant xenograft breast tumor model. Our work emphasized the great potential of bioactive gas transmitter and nutrient metal ion for reversing the dual dilemmas of chemoresistance and low immunogenicity in breast cancer, and thus provided a nanosensitization strategy to synergize with multiple clinical treatment modalities.

Key words: Breast cancer, H₂S, metalloimmunotherapy, lipid metabolism, STAT3, chemotherapy, αPD-1

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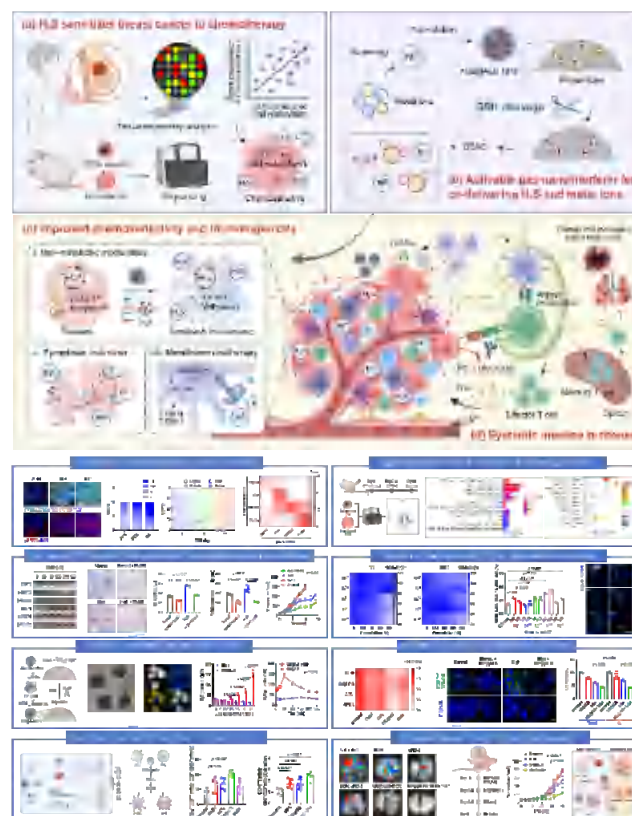


Fig. 1. STAT3 interference-driven nanomodulators reverse lipid metabolism-associated chemoresistance and potentiate metalloimmunotherapy in breast cancer. (a) After confirming the correlation between persistent STAT3 activation and elevated lipid metabolism with pathological progression and chemoresistance in breast cancer, H₂S was found to sensitize breast tumor to chemotherapy via metabolism and immunogenicity modulation. (b) Ni²⁺ ions were screened as a novel immune agonist, and NiS@ALB with GSH-activated H₂S release was synthesized via a mild biomineralization reaction. (c) Therapeutic mechanisms of the gas-metabolic nanointerferers to potentiate the chemosensitivity and immunogenicity in breast cancer. (d) A potent systemic anti-tumor immune response was elicited in combination with various clinical interventions, such as chemotherapy and ICB, to suppress breast tumor progression and metastasis.

Carrier-Free Nano-PROTACs Enhance Tumor Therapy: Targeted Degradation + Photodynamic-Immunometabolic Effect

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Key words: PROTAC, Adenosine 2A receptor, BRD4, immunosuppressive tumor microenvironment, programmed cell death protein ligand 1

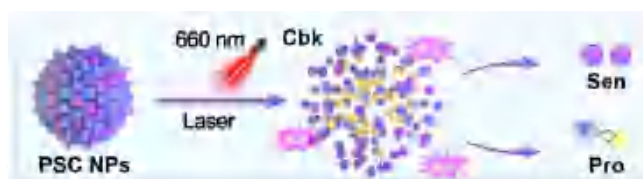
Introduction: Programmed death-ligand 1 (PD-L1) is a direct transcriptional target of BRD4. BRD4 inhibitors can reprogram the tumor immune microenvironment by downregulating both constitutive and interferon gamma (IFN- γ)-induced PD-L1 expression. However, these inhibitors often trigger feedback upregulation of BRD4 protein and exhibit pan-BET inhibitory activity. Compare to conventional inhibitors, proteolysis-targeting chimeras (PROTACs) hijack the endogenous ubiquitin-proteasome system (UPS) to degrade target proteins, demonstrating superior potency, selectivity, and tunable reversibility. Furthermore, adenosine A2a receptor (A2AR) expression is upregulated in various malignant tumors, including lung adenocarcinoma (LUAD), and its expression level is closely associated with patient prognosis. Several A2AR antagonists have been shown to effectively reduce the infiltration of immunosuppressive cells while promoting the activation and function of dendritic cells (DCs) and T cells. Nevertheless, systemic administration of both PROTACs and A2AR antagonists faces considerable challenges, such as poor aqueous solubility, unfavorable pharmacokinetic profiles, limited tissue permeability, dose-limiting toxicity, and off-target effects. Therefore, developing novel delivery strategies is crucial to enhancing tumor specificity and bioavailability in the context of BRD4 degradation and A2AR inhibition.

Materials & Methods: In this work, to identify potential therapeutic targets for LUAD, genes with high expression in LUAD tissues were mined and predicted with the aid of the Gene Expression Omnibus (GEO) Database. To validate these *in silico* findings, paired tumor and adjacent normal lung tissue samples were collected from LUAD patients, and immunofluorescence assays were employed to analyze differentially expressed molecules in these tissues. Carrier-free Nano-PROTACs (designated as PSC NPs) were fabricated via the self-assembly of BRD4-targeted PROTAC (Pro), A2AR antagonist (Sen), and photosensitizer (Cbk) using a one-pot synthesis strategy. The physicochemical properties of these nanoparticles were systematically characterized using multiple technical approaches, including TEM, SEM, and FTIR, and their antitumor efficacy was validated both *in vitro* and *in vivo*.

Results & Discussion: PSC NPs were successfully fabricated with uniform particle size distribution and spherical morphology. These nanoparticles exhibited high accumulation in tumor sites, enabling efficient BRD4 protein degradation and PD-L1 downregulation, thereby alleviating the immunosuppressive TME. Notably, besides serving as a component of PSC NPs, the photosensitizer Cbk also initiated PDT, which not only achieved tumor ablation but also induced ICD to stimulate antitumor immune responses. Furthermore, the incorporated Sen efficiently blocked the A2AR signaling pathway, reprogramming the adenosine-mediated immunosuppressive microenvironment. Ultimately, through the synergistic effects of selective protein degradation, immunometabolic regulation, and PDT, PSC NPs significantly suppressed the growth of primary, distant, and metastatic lung adenocarcinoma lesions.

Conclusions: In this study, we introduced nano-PROTACs that integrate protein-targeted degradation, reprogram immunosuppression, and PDT, featuring a straightforward synthesis method and high loading capacity of active pharmaceutical ingredients (APIs). This work presents a novel paradigm for the synergism of target protein degradation and immunotherapy through a self-assembly strategy, potentially facilitating the biomedical application of PROTACs in tumor treatment.

Fig. 1. Illustration of PSC NPs for tumor therapy.



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Chloroplast-derived pro-inflammatory battery: from light energy to chemical substance activating the immune microenvironment to treat tumor

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Abstract: Tumor development is closely linked to inflammatory responses. Generally, chronic inflammation promotes tumor progression, while acute inflammatory responses initiate anti-tumor immune responses. Extracellular ATP can serve as an effective signaling factor, inducing acute inflammatory responses. Herein, a strategy utilizing the ATP-synthesizing properties of chloroplasts through dual modification of the chloroplast interior and surface is proposed. Specifically, photoacids are encapsulated within the chloroplast, and M1 macrophage membranes are coated on the chloroplast surface, while simultaneously loading POM-1. This method transforms chloroplasts into targeted and highly efficient pro-inflammatory energy conversion machines (CPIB), thereby activating the tumor's immune microenvironment and exerting immunotherapeutic effects.

Key words: Photosynthesis, immunotherapy, ATP, photoacids.

Introduction: As is well known, cancer is a highly malignant disease. There are many treatment methods for cancer, among which immunotherapy is a very effective one. In immunotherapy, dendritic cells (DCs) play a crucial role in initiating cancer immunotherapy by processing tumor antigens. The progression of tumors is closely linked to inflammatory responses; chronic inflammation promotes tumor progression and treatment resistance, while the induction of acute inflammatory responses typically stimulates the maturation of dendritic cells (DCs) and antigen presentation, thereby initiating an anti-tumor immune response. After tumor cells undergo immunogenic death (ICD), the released ATP molecules bind to P2RX7 on dendritic cells (DCs), promoting DC maturation. This is because ATP, as a signaling molecule, activates the NLRP3 inflammasome, which further activates DCs, inducing an acute inflammatory response. These inflammatory responses contribute to activating the anti-tumor immune response. However, although extracellular ATP has a strong pro-inflammatory effect, its concentration is regulated by the ATP-adenosine pathway. After ATP is released extracellularly, CD39 hydrolyzes it into ADP and AMP, and then CD73 dephosphorylates AMP into adenosine. Accumulated extracellular adenosine (eADO) binds to downstream purine receptors, acting on immune effector cells to reduce their toxicity to tumor cells, ultimately exerting an immunosuppressive effect. Considering that ATP is one of the main products of plant photosynthesis, we hypothesize that increasing the concentration of

extracellular ATP and decreasing the concentration of extracellular ADO in the tumor microenvironment through photosynthesis can activate the tumor immunosuppressive microenvironment, using ATP to transform "cold" tumors into "hot" tumors, thereby inducing an anti-tumor immune response. There are already many research examples of using photosynthetic ATP to treat diseases. Lin Xianfeng's research group fused thylakoids with the cell membrane, using ATP, NADPH, and other substances produced by photosynthesis to regulate intracellular energy metabolism, thereby reversing cellular aging and degeneration. Zhang Xianzheng's research group proposed and constructed a highly efficient intracellular light-driven system (HELIOS) that can generate cytoplasmic electrons, thereby significantly increasing intracellular ATP levels under light. He Qiang and Li Junbai's team recently constructed a phosphorylated nanorobot system with directional movement capabilities and in-situ ATP synthesis function for the precise treatment of energy metabolism disorders. However, these studies require complex manipulation of the extracted thylakoids, leading to the loss of thylakoid surface membrane proteins and photosynthetic pigments, thus reducing photosynthetic efficiency. Furthermore, these methods rely on chemotherapy drugs and radiotherapy to induce ICD in tumor cells, with significant side effects. Inspired by these methods, we hope to leverage the ATP synthesis properties of chloroplasts through photosynthesis. By modifying both the internal and surface of chloroplasts, we aim to transform them into highly efficient energy conversion and pro-inflammatory machines, thereby activating the tumor's immune microenvironment and exerting an activating effect on immunotherapy.

Materials & Methods:

Materials: Chloroplast, M1 macrophage membrane, photoacid, POM-1, DSPE-PEG-SH,

Methods: First, photoacids were encapsulated into chloroplasts using ultrasound. Then, M1 macrophage membranes loaded with POM-1 were wrapped around the surface of the chloroplasts by extrusion.

Results & Discussion:

Since photosynthesis in chloroplasts is enhanced by photoacids, and the loaded CD39 inhibitor can act on the ATP-ADO axis, the applied external light source can promote ATP production and trigger the activation of tumor immunity after the CPIB reaches the tumor immunosuppressive microenvironment, thereby treating

the tumor.

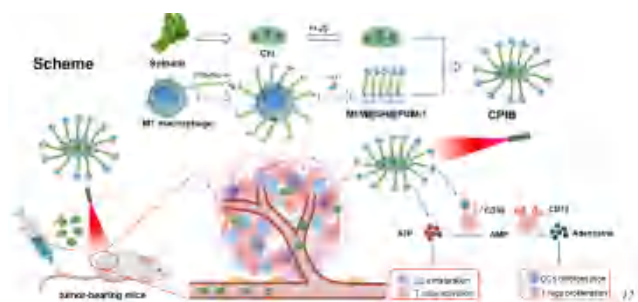


Figure1. Schematic illustration of preparation of CPIB and its mechanism of tumor treatment

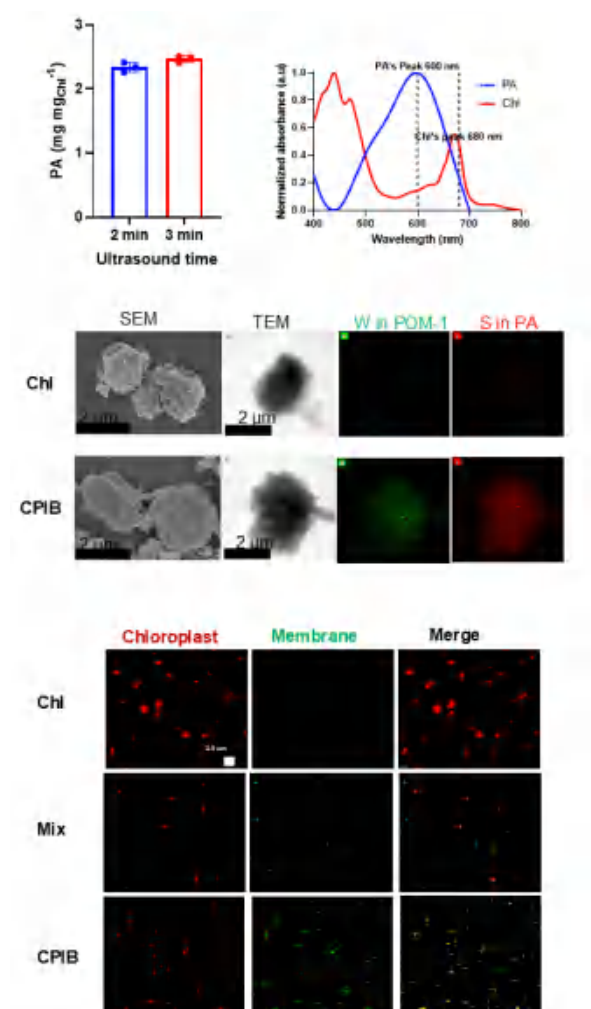


Figure2. Preparation and Characterization of CPIB

Conclusions: CPIB can effectively improve the tumor immune microenvironment and activate tumor immunotherapy. It presents a novel approach: using naturally derived plant organelles as raw materials, enhancing their natural photosynthetic function through physical and chemical methods, and applying this to the

treatment of cancer. This strategy offers a way to leverage the power of nature to treat diseases. The advantages of this approach lie in the fact that many natural sources are renewable and inexpensive, and good biocompatibility is also an advantage. The key lies in how to rationally and efficiently modify these materials to target the specific characteristics of the disease.

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A Copper-Avicularin Nanoassembly Triggers Cooperative Cuproptosis, Disulfidptosis and Ferroptosis for Potent Tumor Suppression

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Abstract

As a form of autonomously regulated cell death, cuproptosis requires copper ions (Cu^{2+}) and functional mitochondrial metabolism. The efficacy of cuproptosis, however, is inherently limited in tumor cells due to their predominant reliance on glycolysis (the Warburg effect) and elevated intracellular glutathione (GSH)/nicotinamide adenine dinucleotide (NADPH) levels. Herein, copper-avicularin metallophenolic nanoparticles (CuAL MPNs) were developed via a simple effective approach to overcome the cuproptosis resistance by orchestrating a coordinated attack on three cell death pathways. When

internalized by tumor cells, CuAL MPNs could inhibit GLUT4-mediated glucose uptake, deplete NADPH, which also trigger disulfidptosis. Meanwhile, copper ions released from CuAL MPNs simultaneously induce cuproptosis through mitochondrial protein aggregation and drive ferroptosis via Fenton-like reactions. This triple-pathway activation results in profound tumor suppression in 4T1-bearing mice with minimal systemic toxicity, establishing a new paradigm for cancer therapy through integrated metabolic intervention and metal-induced cytotoxicity.

Key words: Cuproptosis, Disulfidptosis, Metabolic Intervention, Redox Homeostasis.

Introduction:

- The Promise of Cuproptosis: A novel cell death pathway driven by mitochondrial copper overload offers new hope for cancer therapy.
- The Problem: Tumor cells resist cuproptosis via robust antioxidant defenses. They upregulate glucose uptake to fuel NADPH production and synthesize high levels of glutathione (GSH), which effectively buffers copper ions and neutralizes oxidative stress.
- Our Strategy: To overcome this resistance, we designed a nanoplatform that simultaneously disables these defenses while delivering a copper payload, triggering a coordinated, self-reinforcing cell death cycle.

Materials & Methods: CuAL MPNs were prepared via coordination self-assembly by mixing CuCl_2 , PVP, and avicularin under pH5.6 conditions, followed by 12 hours of reaction at room temperature. The resulting nanoparticles were purified via ultrafiltration and obtained as a blue solid after freeze-drying.

Conclusions: We successfully developed a GSH-responsive nanoplatform, CuAL MPNs, by co-assembling copper ions with the glucose transporter inhibitor avicularin. This metabolic intervention strategy effectively dismantles the antioxidant defenses of tumor cells, leading to potent antitumor efficacy with an excellent in vivo biosafety profile.

Results & Discussion:

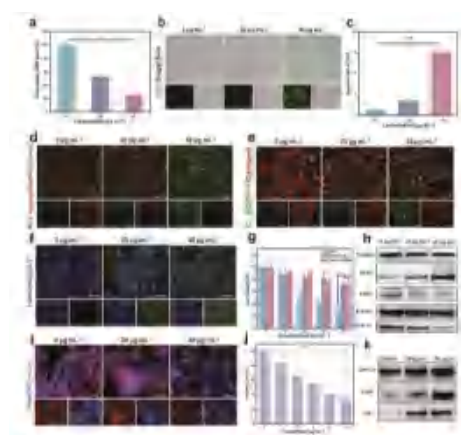


Figure 1&2. CuAL MPNs dose-dependently depleted intracellular GSH, induced oxidative stress and mitochondrial damage (b-e), triggered cuproptosis characterized by DLAT aggregation and FDX1 downregulation (f, h), and caused cytoskeletal disruption with increased $\text{NADP}^+/\text{NADPH}$ ratio (i-k); these effects were partially reversed by copper chelator TTM (g), confirming the crucial role of copper-induced cell death.

Highly Sensitive In Situ SERS Microneedle Probes (AuNPs/PMMA) for AChE Diagnostics

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Abstract: Acetylcholinesterase (AChE) is a critical biomarker for motion sickness. To overcome the limitations of traditional ex vivo assays like ELISA, which suffer from cumbersome procedures and prolonged turnaround times, this study engineered an AuNPs/PMMA microneedle SERS sensor. Based on an enzyme-triggered "signal-on" mechanism, the AChE-catalyzed product induces the conversion of the probe DTNB into a strongly Raman-active molecule, TNB. This design aims to achieve highly sensitive and rapid in situ detection of the target biomarker within the subcutaneous interstitial fluid (ISF). Experimental characterizations confirmed that the microneedles possess excellent penetration capability (fracture force ~ 4.8 N, penetration depth ~ 709 μm) and exceptional biocompatibility, with micro-wounds completely self-healing within 35 minutes. The sensor requires a mere 30-minute reaction time to accomplish the detection, exhibiting an outstanding linear response ($R^2 = 0.9962$) to AChE across a broad dynamic range of 1 to 1000 mU/mL, alongside remarkable anti-interference capabilities. In an SD rat model of motion sickness, in situ Raman spectroscopy precisely captured the pathological surge of subcutaneous AChE. Notably, the absolute concentration determined in situ by the microneedles (~ 537.8 mU/mL) was highly consistent with the traditional ex vivo ELISA gold standard (545.0 ± 35.0 mU/mL). In summary, this sensor successfully overcomes the technical bottlenecks associated with traditional sampling and delayed analysis. Featuring minimally invasive in situ acquisition, rapid and highly sensitive responses, and an accuracy comparable to conventional ELISA, this platform provides a highly translatable paradigm for the non-invasive tracking of in vivo biochemical indicators and the design of high-performance molecular diagnostic devices.

Keywords: Surface-Enhanced Raman Scattering (SERS), Molecular Probes, Microneedle Sensors, In Situ Detection, Acetylcholinesterase (AChE).

Engineered sEVs enhances promotes ECM1 degradation in TNBC

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Introduction:

Triple-negative breast cancer (TNBC) exhibits high expression of programmed death ligand-1 (PD-L1) and elevated extracellular matrix protein 1 (ECM1), the latter correlating with poor patient survival. We identified apigenin, a dietary flavonoid, promotes ECM1 ubiquitination via the E3 ligases FZR1, URB3, and URB5. To harness these findings therapeutically, we developed a TNBC-targeted delivery system with selective ECM1 degradation.

Materials and Methods:

Small extracellular vesicles (sEVs) were engineered to overexpress programmed death protein-1 (PD-1) (sEV-PD-1) to target PD-L1-expressed TNBC cells. sEV-PD-1 uptake was evaluated in vitro and biodistribution assessed in vivo. Apigenin was loaded into sEV-PD-1 (sEV-PD-1-Api) to achieve tumor-selective ECM1 degradation. In mouse models of TNBC, we assessed ECM1 levels, and antitumor efficacy of sEV-PD-1-Api.

Results and Discussion:

sEV-PD-1 exhibited strong TNBC targeting in vivo and significantly increased uptake by TNBC cells in vitro. Loading apigenin into sEV-PD-1 generated sEV-PD-1-Api, which specifically delivered apigenin to tumors and induced selective ECM1 degradation only within tumor tissue. In mouse models, sEV-PD-1-Api demonstrated more potent anti-tumor activity than sEV-PD-1 and control vehicles. These data support apigenin's role in promoting ECM1 ubiquitination via FZR1, URB3, and URB5, and affirm sEV-PD-1 as an effective TNBC-targeting vehicle.

Conclusion:

sEV-PD-1-Api is an innovative therapeutic strategy with selective ECM1 degradation in TNBC. By reducing ECM1 through apigenin-mediated ubiquitination, sEV-PD-1-Api achieves enhanced antitumor efficacy and tumor specificity. These findings highlight strong potential for clinical translation of sEV-PD-1-Api as a therapy for TNBC.

Key words: Triple negative breast cancer; Small extracellular vesicles; ECM1; Apigenin

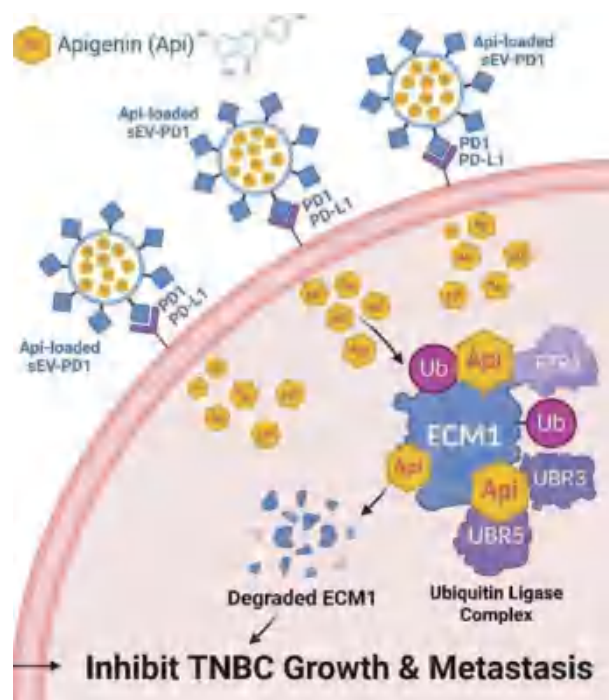


Figure. A schematic diagram showing the anti-TNBC mechanism of sEV-PD-1-Api

Electro-nanoautopsy: a nanoscale approach to imaging intracellular structures and biomaterials

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Key words: Nanoscale bio-imaging, intracellular imaging, atomic force microscopy, cytoskeleton.

Introduction: Nanoscale intracellular analysis is essential for understanding biological processes, disease mechanisms, and biomaterials-based therapeutic development. However, existing nanoscale tools such as atomic force microscopy (AFM) have limitations. AFM live-cell imaging preserves cell dynamics but restricts high-resolution probing of subcellular structures and biomaterial localization and effects due to the intact plasma membrane. AFM combined with fixed-cell methods can alter cellular morphology, protein structure, and function, introducing artifacts that hinder assessment of biomaterial effects.

Materials & Methods: Here, we present cellular electro-nanoautopsy, a novel method that selectively removes the plasma membrane while preserving the three-dimensional cellular architecture and intracellular components in their native state. This approach combines optimized pulsed electric field (PEF) parameters with a detergent- and fixative-free buffer, resulting in an intact, membrane-free “cell cadaver” suitable for intracellular high-resolution AFM imaging.

of nanocarriers and nanomaterial–cell interactions. Here, we will show nanoscale images of the cytoskeleton network structure in its native state, as well as the preservation of its functionality by imaging molecular protein transport after cell membrane removal. This technique bridges the gap between live-cell dynamics and subcellular resolution, offering a unique platform for characterizing intracellular structures and biomaterial distribution at the nanoscale.

Conclusions: Cellular electro-nanoautopsy offers new opportunities for precision nanomedicine, drug delivery research, and intracellular diagnostics by enabling high-resolution AFM imaging of preserved intracellular environments without the constraints of an intact plasma membrane.

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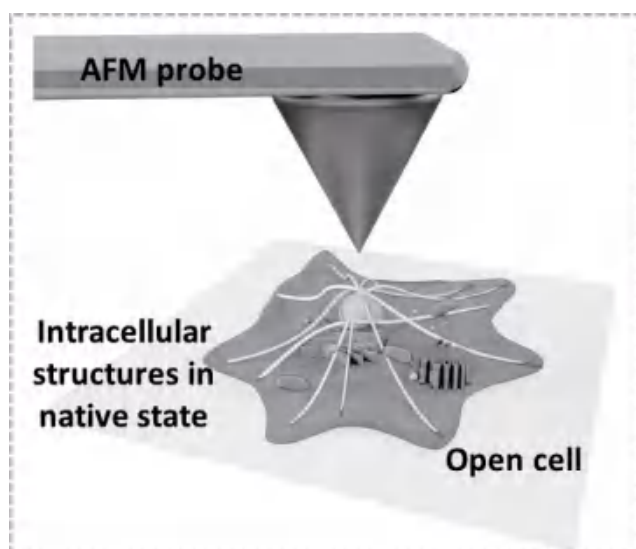


Fig. 1. Electro-nanoautopsy method. The cellular membrane is selectively removed, and intracellular materials are preserved in their native state.

Results & Discussion: Cellular electro-nanoautopsy provides direct access to intracellular targets and preserves their functionality, enabling advanced studies

Bead-on-String Non-metallic Nanoprobes with Enhanced Magnetic Resonance Imaging Sensitivity for Imaging-Guided Therapy of Colitis

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Key words: non-metallic nanoprobes, bead-on-string nanoprobes, magnetic resonance imaging, ulcerative colitis

Introduction: Inflammatory bowel disease (IBD), exemplified by ulcerative colitis (UC), is a class of chronic, relapsing gastrointestinal disorders for which curative therapies remain unavailable. The development of nanotheranostic agents that integrate both diagnostic and therapeutic functions remains a major challenge in UC management. Conventional gadolinium-based magnetic resonance imaging (MRI) contrast agents are limited by potential nephrotoxicity and the absence of therapeutic capability. In this study, a TEMPO-grafted block copolymer is synthesized and self-assembled to a non-metallic MRI nanotheranostic carrier encapsulating the natural polyphenol tannic acid (TA), aiming to achieve integrated UC therapy and inflammation assessment. Notably, the resulting nanostructure exhibits a bead-on-string morphology (TA@WNPT), distinct from the conventional spherical counterpart (TA@SNPT). By systematically comparing the MRI performance of nanoprobes with distinct morphologies, we further elucidated the influence of nanoparticle morphology on relaxivity.

Materials & Methods: Specifically, polymerization-induced self-assembly (PISA) was first employed using 2-(perfluorooctyl)ethyl methacrylate (HFDMA) and 2-(perfluorohexyl)ethyl methacrylate (FHMA) as monomers, with 2,2,6,6-tetramethyl-4-piperidyl methacrylate (TEMP) as a functional component, to successfully prepare bead-on-string nanoparticles (WNPT) and spherical nanoparticles (SNPT). Under hydrogen peroxide stimulation, TEMP is oxidized to the paramagnetic nitroxide radical TEMPO, thereby endowing the nanoprobes with MRI capability and reactive oxygen species (ROS) scavenging functionality. Subsequently, the natural polyphenol TA, which possesses pronounced antioxidant, antibacterial, and anti-inflammatory activities, was loaded onto the two types of nanoparticles via electrostatic interactions, yielding TA@WNPT and TA@SNPT, respectively.

Results & Discussion: Incorporating TEMPO not only imparts intrinsic paramagnetism for efficient T₁-weighted MRI but also facilitates ROS scavenging, while TA provides complementary antioxidant and anti-inflammatory activities. Compared with the spherical formulation, the bead-on-string TA@WNPT demonstrates higher relaxivity, enabling high-contrast

lesion visualization and real-time therapeutic monitoring. Furthermore, TA@WNPT effectively alleviate mucosal inflammation and restore intestinal barrier integrity through by modulating the TNF and IL-17 pathways and suppressing downstream NF-κB and MAPK signaling, while the prebiotic properties of TA further promote gut microbiota rebalancing. Treatment with TA@WNPT also mitigates ameliorates anxiety-, depression-, and cognition-related behavioral deficits in colitis mice, highlighting its regulation of the gut-brain axis.

Conclusions: Together, these findings establish a safe and effective non-metallic MRI nanotheranostic platform that integrates MRI with multimodal therapy, offering a promising strategy for the comprehensive management of inflammatory bowel disease.

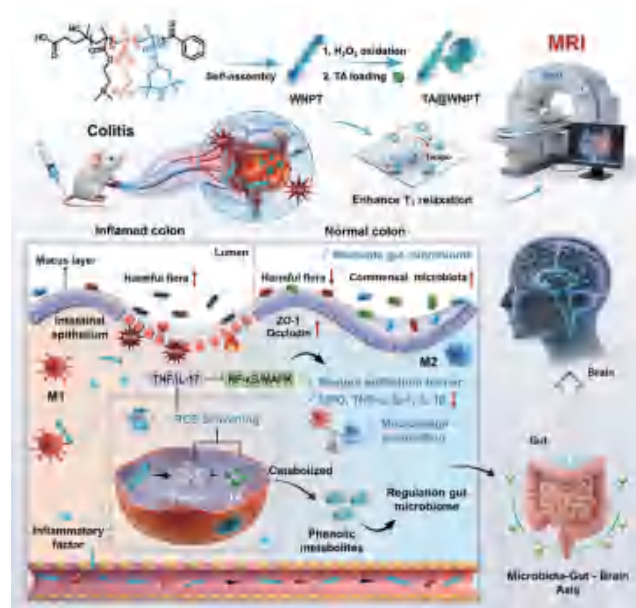


Fig. 1. Schematic illustration of MRI-guided colitis therapy and disease monitoring using the nanoprobes in mice.

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CD47-Targeted Liposomal Chemotherapy Upregulates CD47 Expression and Induces Microsatellite Instability to Enhance Cancer Immunotherapy

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Introduction: Colorectal cancer (CRC), particularly the microsatellite-stable (MSS) subtype, exhibits poor responsiveness to immunotherapy due to its low immunogenicity and an immunosuppressive tumor microenvironment. The standard FOX chemotherapy regimen (5-fluorouracil and oxaliplatin) paradoxically induces both beneficial microsatellite instability (MSI) and detrimental upregulation of CD47, an immune checkpoint that enables tumor immune evasion. To harness the immunogenic benefits of FOX while mitigating CD47-mediated immunosuppression, we developed a CD47 antibody-armed liposome (α L-FOX) co-delivering 5-FU and oxaliplatin, designed to function as a chemotherapeutic feedback modulator for enhanced CRC immunotherapy.

Materials & Methods: α L-FOX was synthesized via thin-film hydration followed by post-insertion of CD47 antibodies. Particle size, zeta potential, and drug loading were characterized. In vitro cellular uptake, CD47 expression, and cytotoxicity were assessed. Phagocytosis was evaluated using RAW264.7 and bone marrow-derived macrophages (BMDMs) co-cultured with CT26-GFP cells. In vivo biodistribution and tumor accumulation were monitored using an IVIS imaging system. Therapeutic efficacy was evaluated in both ectopic and metastatic CT26 tumor-bearing BALB/c mice, with assessments including tumor growth, survival, immune cell infiltration, and systemic toxicity.

Results & Discussion: α L-FOX exhibited uniform size (~100 nm), negative surface charge, and stable drug loading. FOX treatment upregulated CD47 expression in CRC cells, which enhanced subsequent α L-FOX uptake via a self-promoted targeting mechanism. α L-FOX significantly improved macrophage-mediated phagocytosis, promoted M1 macrophage polarization, and increased MHC-II expression on antigen-presenting cells. In vivo, α L-FOX achieved rapid and sustained tumor accumulation, with enhanced retention following repeated dosing, validating its cascade-targeting capability. In both ectopic and metastatic CRC models, α L-FOX at half the standard FOX dose significantly suppressed primary tumor growth, prevented lung metastasis, and achieved 100% survival, with no detectable systemic toxicity or hemolysis. Mechanistically, α L-FOX increased intratumoral infiltration of CD8⁺ T cells and dendritic cells, while reducing M2 macrophages and splenomegaly.

Conclusions: We have developed a CD47 antibody-armed liposomal platform that leverages chemotherapy-induced CD47 upregulation for self-amplifying tumor targeting and simultaneously

reverses CD47-mediated immune evasion. This feedback-modulating nanotherapeutic strategy synergizes chemotherapy with innate and adaptive immune activation, achieving potent antitumor efficacy with reduced toxicity. The α L-FOX platform represents a promising approach for converting immunotherapy-resistant MSS-type CRC into an immunologically responsive phenotype, with broad implications for combination cancer therapy.

Key words: Colorectal cancer, CD47 antibody, Liposome, Chemotherapy, Immunotherapy

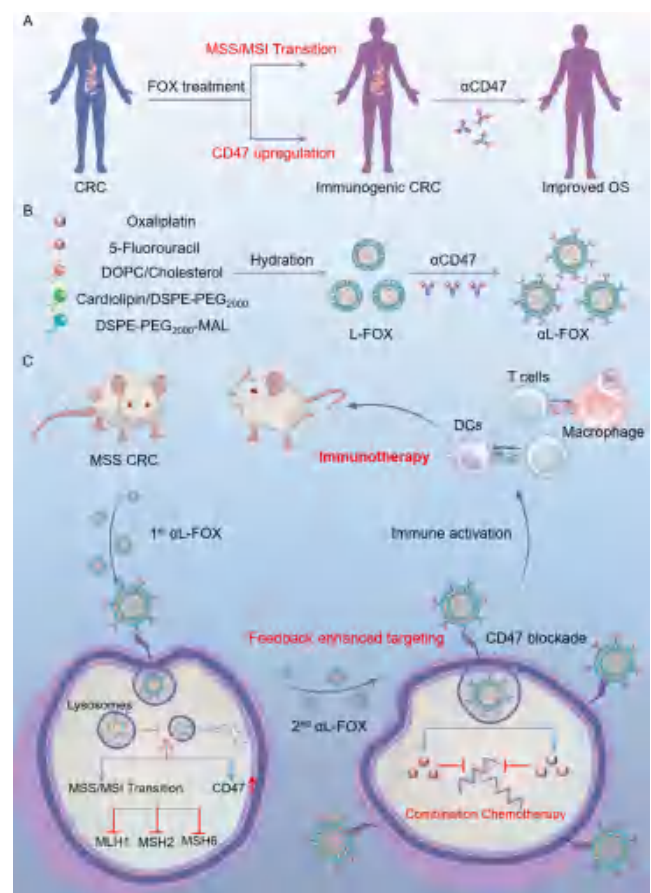


Fig. 1. Schematic illustration of CD47 antibody-armed FOX regimens to sensitize colorectal cancer immunotherapy by MSS/MSI transition and CD47 upregulation.

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Effect of different high-pressure gases on the crystallization behavior of polylactic acid stereocomplex crystallites and homo-crystallites

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Key words: Polylactic acid (PLA); Multiple crystal forms; High-pressure gases

Introduction: Polylactic acid (PLA), a semi-crystalline polyester, has emerged as the predominant polymer in biomedical engineering owing to its exceptional biocompatibility and non-toxicity of degradation byproducts. The crystallization of PLA has a decisive impact on the final properties of its products, which has made in-depth exploration of the crystallization process of PLA a hot research topic in the field of polymers. This study investigated the crystallization behavior of HCs and SCs in PLA under high-pressure N₂ for the first time, and analyzed the lamellar arrangement of HCs and SCs. By analyzing the effects of different pressures on the lamella growth of PLA's HCs and SCs. The reason for the occurrence of birefringence in crystals has been revealed.

Materials & Methods: The molecular weight of PLLA is 1.6×10^5 , whose brand is L175, purchased by Total Corbion. The molecular weight of PDLA is 7×10^4 , whose brand is D070, purchased by Total Corbion. The dichloromethane (CH₂Cl₂, analytical reagent) was purchased by Chengdu Changlian Chemical Reagent Co. Ltd. N₂ with a purity of 99.9999% was purchased by Chengdu Qiaoyuan Gas Co., Ltd. The samples were made by solution casting. After weighing PDLA and PLLA, stir and dissolve them in CH₂Cl₂. After waiting for the solution to dissolve evenly, drop the solution onto a cleaned glass slide. Place it in a fume cupboard for 24 h, and then dry it in vacuum for 1 week. Heat samples to 240 °C for 3 min to eliminate the residual crystals, and then rapidly cool the sample to the isothermal crystallization temperature within 3 min for 2 h.

Results & Discussion: Firstly, use CLSM to observe the height changes on the surface of the SC crystals. Under air, the height change of SCs was around 2 μm. The height of SCs formed under N₂ is above 3 μm.

Further utilizing AFM to characterize the morphological changes of SCs, under air conditions, as the isothermal crystallization temperature increased, the branching growth of SCs became incomplete. In figure b₃, b₄ and b₅ the observed SCs had similar areas, indicating that with the increase of pressure, more molecular chains were used for the growth of crystal height, resulting in higher crystal height and incomplete branching of SCs formed under N₂.

In Figure c, the HCs with obvious birefringence could have a clear arrangement of lamella. However, in the enlarged image of SCs without birefringence, the

arrangement of lamellae cannot be clearly seen. Seen in figure d, the SCs exhibited a slight birefringence phenomenon. From its AFM image and enlarged image, it could be seen that the lamella of SCs shown radial arrangement, thus exhibiting birefringence.

Conclusions: SCs were formed by two types of molecular chains, and N₂ made it difficult for complete branching development. With the increase of pressure, the height of SCs increased, and there was a slight birefringence phenomenon on SCs, which was due to the preferred orientation of the internal lamella. The lamellar arrangement of SCs without birefringence was unclear, while the clear lamellar arrangement could be observed on the surface of HCs, which exhibited obvious birefringence phenomenon.

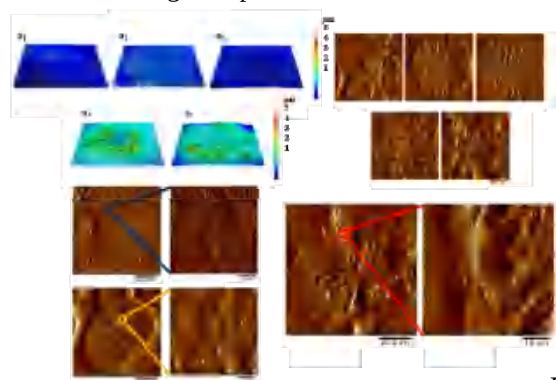


Figure
Different crystal images in PDLA/PLLA mixture. (a) CLSM images of PDLA/PLLA mixture crystallized at (a₁) 130 °C, (a₂) 140 °C, (a₃) 150 °C under air and (a₄) 150 °C under 4 MPa N₂, (a₅) 150 °C under 8 MPa N₂. (b) AFM images of PDLA/PLLA mixture crystallized at the same condition with a. (c) AFM images of PDLA/PLLA mixture crystallized at 130 °C under air, (c₁) HC crystal and (c₂) SC crystal. (d) Enlarged AFM image of SC crystals formed by the crystallization of PDLA/PLLA mixture at 150 °C under 8MPa N₂.

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Robust and Multifunctional Biogels Derived from Natural Proteins Engineered via Silk Nanofibril Reinforcement and Swelling-Assisted Solvent Enhancement

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Flexible electronics are essential for smart healthcare due to their wearability. Gelatin, a natural polymer, is a promising gel matrix to fabricate the epidermal electrodes due to its unique combination of advantageous properties, including exceptional biocompatibility, controlled biodegradability, nontoxicity, cost-effective scalability, and superior gelation capability. However, conventional gelatin-based gels employing water, organic solvents or ionic liquids as dispersion media suffer from inherent limitations including poor environmental adaptability, high production cost and potential toxicity concerns, which underscores the urgent need for innovative fabrication approaches that can construct gelatin-based biogels with robust mechanics, multifunctionality and environmental sustainability.

Gelatin was utilized to serve as gel matrix in this work. Natural silk nanofibrils (SNFs) were chosen as nanofibrous strengthening elements and was prepared according to the literature [1]. SNFs at varying mass ratios (2, 4, 6 wt% to gelatin) were dispersed in citric acid solution (pH=5.25). Gelatin was then added and stirred to obtain a uniform precursor. This solution was cast in a mold at 4 °C for 1 h to form the original biogels, which were soaked in water subsequently. Finally, solvent exchange in a deep eutectic solvent (composed of 2 mol glycerol and 1 mol choline chloride) for different durations yielded the designed multifunctional biogels (named BioGel-SNFSE).

The mechanically robust and multifunctional BioGel-SNFSE were developed through a synergistic strategy integrating natural silk nanofibril reinforcement and swelling-assisted solvent enhancement. This strategy enabled nanoscale and molecular restructuring, drastically improving mechanics compared with traditional gelatin hydrogels, including an 804% increase in tensile strain (reaching a final value of 247%), 987% increase in modulus (1.6 MPa), 8306% increase in strength (3.1 MPa), 54413% increase in toughness (2.9 MJ/m³), and demonstrating superior fracture resistance (fracture energy: 12.6 kJ/m²). Stretch-induced alignment further boosted performance, including 14166% stronger tensile strength (5.3 MPa), 6679% higher elastic modulus (10.1 MPa) and greater fracture energy (24.1 kJ/m²). The BioGel-SNFSE also exhibited low impedance, adhesion, environmental

stability, self-healing, UV resistance, and biodegradability, making it ideal for high-quality (SNR ≥ 24 dB) and long-term monitoring (13 days) of ECG during daily activities and exercise.

In summary, a robust multifunctional protein-based biogel with hierarchical structures was developed via SNFs reinforcement and swelling-assisted DES enhancement. This work establishes a novel paradigm for designing advanced multifunctional biogels for next-generation epidermal bioelectronics.

Key words: natural protein-based biogels, silk nanofibril reinforcement, swelling-assisted solvent enhancement, electrophysiological recording

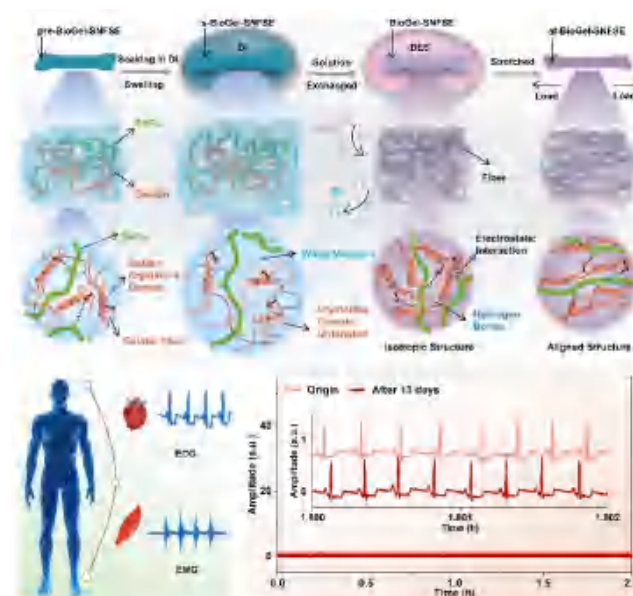


Fig. 1. The design and applications of this work.

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A Dual-layer Electrospun Membrane for Islets Encapsulation and Transplantation to Treat T1D

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Key words: diabetes, transplantation, biomaterials

Introduction: Type 1 diabetes (T1D) is a chronic metabolic disease resulting from the autoimmune destruction of pancreatic islets, with its treatment strategies attracting attention throughout the world [1]. Islets transplantation therapy has been proven to be an effective method for T1D patients. As one of the methods to protect the islets transplanted, macroencapsulation is prominent for advantages such as physical isolation of immune cells and easily retrieval [2]. However, macro transplantation devices have universal defects such as the inefficient exchange of nutrients and obstacles of oxygen diffusion, leading to core islets necrosis. In addition, the survival and function of islets are facing the challenge of immune rejection during long-term transplantation [3]. Therefore, the development of novel macroencapsulation devices that can overcome these defects is the key to islets transplantation for the treatment of T1D. In this study, we designed and construct a dual-layer electrospun membrane with great hydrophilicity. The diameters of fibers and the pore size of the inner-layer membrane is at the nanometer level, while those of the outer-layer membrane are at the micrometer level. The membrane can be utilized to construct a macroencapsulation device for islet transplantation.

Materials & Methods: The composition of the membrane is poly-ε-caprolactone (PCL) and type IV collagen (COL IV). The experimental content included the preparation, physical and chemical performance characterization such as mechanical properties, surface microstructure, water contact angle, surface protein adhesion, and selective permeability and *in vitro* and *in vivo* functional verification and evaluation of the electrospun membranes. The selective permeability of the dual-layer electrospun membrane was evaluated using 40 kDa-Dextran to simulate VEGF and 150 kDa-Dextran to simulate Immunoglobulin G (IgG).

Results & Discussion: The mechanical strength of the dual-layer electrospun membrane is superior to that of the inner-layer or outer-layer membrane alone, with a tensile strength of 6.71 ± 0.19 MPa and an elastic modulus of 56.97 ± 2.02 MPa, enabling effective protection of the islets encapsulated. Quantitative characterization of the surface microstructure observed with scanning electron microscope revealed that the inner-layer pore size is less than 1 μm, which can effectively dispute the infiltration of immune cells and immunoproteins; the outer-layer pore size is 2.6 ± 0.16

μm, allowing the penetration of oxygen and nutrients. According to existing studies, the differential pore sizes between the inner and outer layers are conducive to vascularization [4]. In addition, the introduction of COL IV significantly enhances the hydrophilicity of the electrospun membrane, effectively reducing the adhesion of immune cells and immunoproteins. *In vitro* biocompatibility experiments demonstrate that the electrospun membrane exhibits good cytocompatibility and maintains cell viability; *in vivo* compatibility indicates that the membrane has good biosafety. The dual-layer electrospun membrane showed favourable release behaviour for 40 kDa-Dextran, while for 150 kDa-Dextran, the release amount was less than 5% in 48 hours. These results indicate that the dual-layer electrospun membrane possesses favourable selective permeability, permitting the diffusion of oxygen, nutrients, and metabolites, while effectively preventing the invasion of immunoproteins.

Conclusions: In this study, a dual-layer electrospun membrane for pancreatic islets encapsulation and transplantation was fabricated, exhibiting excellent biocompatibility, efficient mass exchange capability, and the favorable mechanical properties that help maintain its morphology *in vivo* and protect the encapsulated islets. More importantly, the membrane possesses good hydrophilicity, appropriate pore size, and selective permeability, offering a potential solution to the issues of fibrosis induced by islet transplantation, facilitate long-term mass exchange the long-term safety of implantable devices. This provides a new choice for the treatment of T1D. Future studies will further validate the glucose-lowering capability of the islet transplantation device based on this membrane.

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All-Peptide Zwitterionic Hydrogel Dressings for Diabetic Wound Therapy

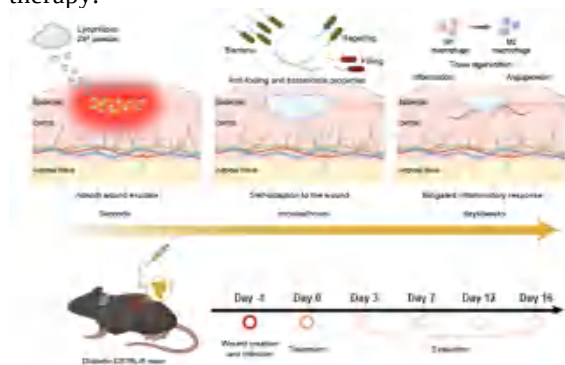
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Key words: polypeptide hydrogel, zwitterionic, diabetic wound healing

Introduction: Diabetic wounds represent a persistent clinical challenge due to chronic hyperglycemia, sustained inflammation, and impaired tissue regeneration. Conventional dressings often suffer from inadequate adhesion, susceptibility to bacterial infection, and secondary tissue damage upon removal, underscoring the urgent demand for advanced materials that combine biocompatibility, multifunctionality, and minimal invasiveness. Zwitterionic polypeptides composed of alternating glutamic acid and lysine (EK), both abundant in the human body, have been demonstrated to exhibit excellent antifouling properties and to effectively mitigate foreign body responses in non-human primates, establishing them as an ideal platform for implantable biomaterials. Building upon this foundation, we herein report an all-peptide zwitterionic hydrogel dressing designed specifically for diabetic wound therapy. By engineering an alternating EK polypeptide network, the hydrogel achieves precisely tunable enzymatic degradability while maintaining superior resistance to nonspecific protein adsorption. The incorporation of RGD motifs and antimicrobial peptides further endows the scaffold with enhanced cell adhesion, intrinsic antibacterial activity, and immunomodulatory functions. Moreover, the lyophilized formulation enables rapid in situ gelation upon contact with wound exudate, ensuring conformal coverage and eliminating the risk of secondary injury associated with dressing changes. Collectively, this system promotes angiogenesis, suppresses inflammation and scarring, and holds substantial promise for diabetic wound therapy.



Materials & Methods: The multifunctional peptide hydrogel was synthesized through a stepwise solution-phase peptide coupling strategy. Briefly,

protected lysine and glutamic acid derivatives were first coupled using EDCI/HOBt to obtain a protected EK dimer, followed by partial deprotection with trifluoroacetic acid (TFA) to expose reactive functional groups. Subsequently, the integrin-binding RGD peptide, bearing appropriate protecting groups, was conjugated to the EK backbone via further EDCI/HOBt-mediated amidation to yield the EK - RGD intermediate. After complete deprotection under acidic conditions, an antimicrobial peptide sequence was introduced through additional coupling reactions to form the final multifunctional peptide conjugate. The purified peptide was then lyophilized and rehydrated, allowing rapid self-assembly into a hydrogel driven by noncovalent interactions, including hydrogen bonding, electrostatic interactions from zwitterionic residues, and hydrophobic effect.

Results & Discussion: The EK-RGD polypeptide demonstrates excellent gelation properties, maintaining stable rheological behavior even after lyophilization and subsequent rehydration, which supports its practical utility as a ready-to-use lyophilized powder. In an infected diabetic wound model, PeptiGel significantly accelerates wound closure. Histological analysis further reveals that PeptiGel effectively reduces local inflammation, controls bacterial burden, promotes robust angiogenesis, and prevents excessive scar formation. Collectively, these results underscore the multifunctional therapeutic potential of this all-peptide zwitterionic hydrogel for managing complicated diabetic wounds.

Conclusions: Based on the favorable antifouling and immunomodulatory properties of zwitterionic EK polypeptides, we developed an all-peptide zwitterionic hydrogel dressing for diabetic wound therapy. The alternating EK network enables tunable enzymatic degradability, while incorporation of RGD and antimicrobial peptides confers enhanced cell adhesion, antibacterial activity, and immunomodulation. The lyophilized formulation allows rapid in situ gelation upon contact with wound exudate, minimizing secondary injury. In vivo, this system effectively promotes angiogenesis, suppresses inflammation, and reduces scarring. Collectively, this all-peptide zwitterionic hydrogel represents a promising multifunctional platform for diabetic wound management with strong potential for clinical translation.

In Vivo NMR Relaxation Study of Human Skin: the Effect of Moisturization

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Key words: skin state, Low-field NMR relaxation, water mobility

Introduction:

The skin is the largest organ of the human body and has the most extensive surface area in contact with the environment. It serves multiple functions: protecting internal organs, regulating body temperature, and synthesizing vitamin D. The condition of the skin reflects the overall state of the body. One of the most important property of the skin is the water content and state of water in it. Low-field NMR equipped with a single-sided probe, the NMR-MOUSE (Mobile Universal Surface Explorer), is well-suited for studying the skin.[1] This method is very promising providing useful data about aging and diseases of skin without non-invasive way.

Materials & Methods:

In the literature the most often applied method is the measurement of the apparent transverse relaxation time of the water content in skin.[2] The classical CPMG pulse sequence is used, in general.[3] Due to the high field gradient of the NMR MOUSE device, diffusion significantly influences the relaxation rate and may even dominate it. The classical Hahn-echo experiment is particularly sensitive to diffusion effects compared to CPMG due to its longer echo times.[4]

Bruker© NMR Profiler was employed controlled by a 20 MHz Minispec relaxometer. The probe was able to detect the mobility of the protons approximately 1, 3 and 5 mm deep under the skin. The Hahn-echo experiments refer to the rotation (T_2) and translation mobility of water (D) according to the following equation:

$$I = \sum_{i=1}^n I_{0i} \left\{ -\left(\frac{t}{T_{2i}}\right) - \left(\frac{2}{3}\right) G^2 \gamma^2 t^3 D_i \right\} \quad (1)$$

Results & Discussion:

Figure 1 illustrates that two types of water can be identified at a depth of 3 mm in the studied samples. It verifies that the Hahn-echo experiment emphasizes the translation motion of the moisture content of human skin. The amount of faster-moving water is higher in older individual, and the fitted diffusion coefficient is approximately twice as large as that in the younger individual. This observation aligns with expectations since collagen and hyaluronic acid content decreases with age, since the water mobility is primarily determined by its bonding to collagen.

We applied an intensive moisturization with a hydration gel available on the market on forearm skin of one persons After five-day treatment the amount of faster-moving water significantly decreased, however its

diffusion rate did not change. The diffusion rate of slower-moving water slightly decreased, indicating that gel's effect was not simply increasing the water content.

Conclusions.

It should be noted that the hydration properties of human skin are not exclusively determined by age. They also depend on factors such as gender, skincare habits, environmental conditions, workplace exposure, and overall skin health.

Systematic investigations and the creation of a comprehensive database will aid in the medical characterization of human skin. Since the NMR mouse measures about one cm² area of the skin it can detect local injury or symptoms of illness. The described experiment meets standard diagnostic requirements: it is painless, non-destructive, and takes less than half an hour.

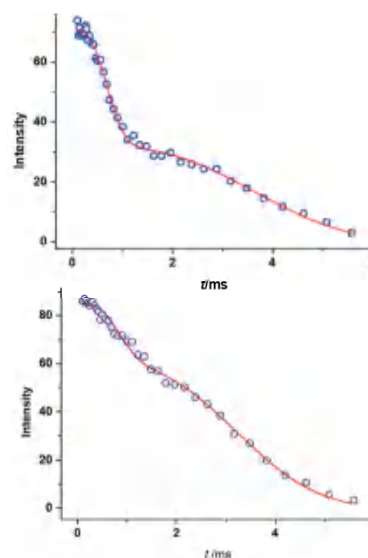


Fig. 1. The Hahn-echo profile of a 70 years (upper) and 25 years (lower) old male person, fitted by equation (1)

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Peptide Amphiphile-Mediated Assembly and Fusion of Anisotropic Amorphous Particles for Enamel Remineralization

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Abstract: Enamel remineralization remains a significant challenge due to the difficulty of restoring the native hierarchical structure and mechanical properties. This study introduces rationally designed peptide amphiphile (PA) molecules that bind to amorphous calcium phosphate (ACP) particles via electrostatic interactions, imparting anisotropic properties that drive the formation of spindle-shaped aggregates. PA further regulates crystallization into well-aligned hydroxyapatite (HAP) bundles and mediates ordered deposition and fusion on the enamel surface. This process constructs a continuous crystalline-amorphous mineralization front, ensuring epitaxially oriented growth that reproduces the natural enamel structure. Mechanical performance is effectively restored, and the mineral layer thickness can be increased through cyclic remineralization

Key words: Enamel remineralization, peptide amphiphile, amorphous calcium phosphate, hydroxyapatite,

Introduction: Tooth enamel is a highly mineralized, acellular tissue that cannot self-repair after damage. Current clinical therapies like fluoride treatment and composite resins fail to restore its complex hierarchical structure and may lead to secondary issues like fluorosis or microleakage. While previous attempts used organic molecules to regulate HAP growth, they often failed to reconstruct the original architecture. This study aims to develop a general strategy using PA to promote the fusion of amorphous precursors with crystals, forming a continuous mineralization front for enamel regeneration.

Materials & Methods: A rationally designed peptide amphiphile (PA, $C_{11}H_{23}CO-KDDDDKDDDD$) was used. Healthy human enamel was etched with 37% phosphoric acid for 30 s to mimic caries. Samples were immersed in modified simulated body fluid (m-SBF) with or without PA molecules. Techniques included TEM, SEM, HRTEM, XRD, and AFM to monitor mineral evolution and structure. Nanoindentation was used to measure hardness (H), elastic modulus (E), and creep behavior.

Results & Discussion: (1) PA-Mediated Assembly: PA molecules bind to ACP particles, creating “chemical anisotropy” that drives them to assemble into spindle-shaped aggregates rather than disordered clusters. (2) Mineralization Front: A crystalline-amorphous growth front with a continuous structure was successfully constructed at the atomic level, enabling epitaxial growth. (3) Structure Reconstruction: After 3 days, the remineralized enamel

showed a fish scale-like pattern and rod/interrod orientation indistinguishable from native enamel. (4) Mechanical Restoration: The hardness (4.12 GPa) and elastic modulus (88.52 GPa) of the remineralized layer were nearly identical to natural enamel (H: 4.14 GPa, E: 90.97 GPa), significantly outperforming the control group.

Conclusions: The study demonstrates that PA molecules play multiple essential roles in enamel remineralization by regulating the assembly, fusion, and crystallization kinetics of ACP. By successfully constructing a biomimetic mineralization front, the complex hierarchical structure and mechanical properties of enamel can be precisely reconstructed from the nanoscale to the macroscale. This strategy offers significant potential for future practical applications in clinical enamel repair.

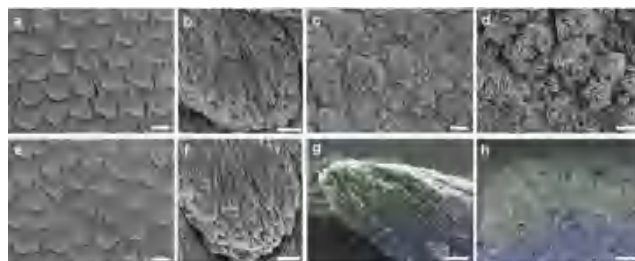


Fig. 1. (a,b) SEM images of acid-etched enamel showing a fish scale-like structure and a magnified view of individual enamel rods. Enamel remineralized in m-SBF (c,d, h) without PA and (e-g) with PA. The morphological features of the enamel remineralized in PA-containing m-SBF were similar to those of natural enamel, whereas the structure of the enamel remineralized just in m-SBF was disordered. (g) Cross-sectional view of the remineralized enamel presenting a well-organized structure, and the newly formed HAP with a native enamel rod orientation, while (h) exhibits a spherical structure. The green area is remineralized, and the blue area is native.

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Spatiotemporal-adaptive Magnetoelectric Hydrogel Promotes Scarless Wound Healing

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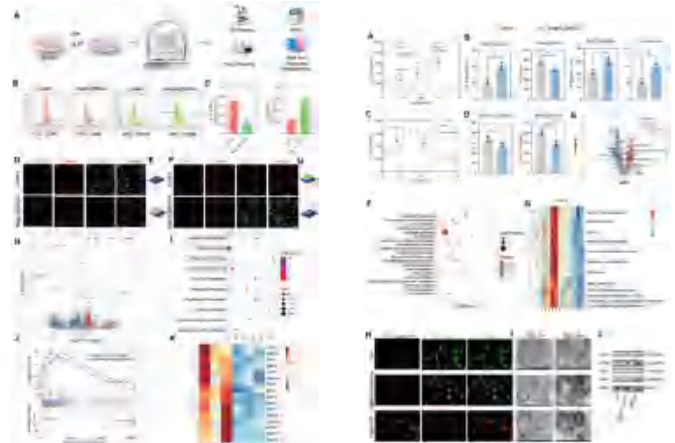
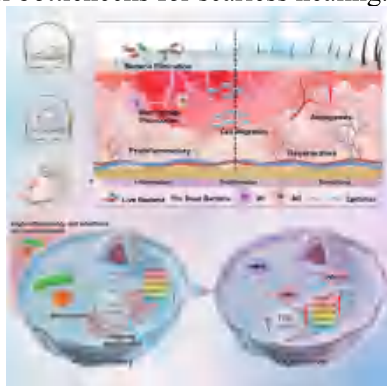
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Objective

Chronic infected wounds suffer from persistent inflammation and macrophage metabolic dysregulation. Current biomaterials are functionally monotonic and lack stage-specific regulation. In this study, we developed a non-invasive magnetoelectric hydrogel with spatiotemporal adaptability to co-target two core pathological bottlenecks for scarless healing.

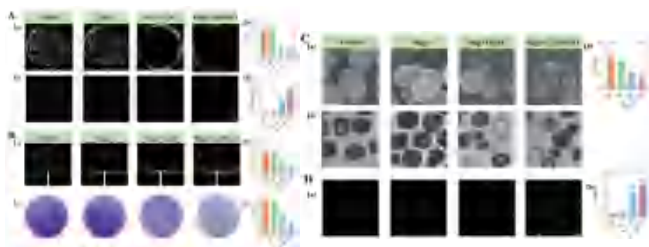


Phenotype shift: CD206⁺ (M2) cells increased from 20% to 60%; CD86⁺ (M1) cells reduced from 18% to 5% (flow cytometry) Metabolic switch: OXPHOS enhancement and Glycolysis suppression.

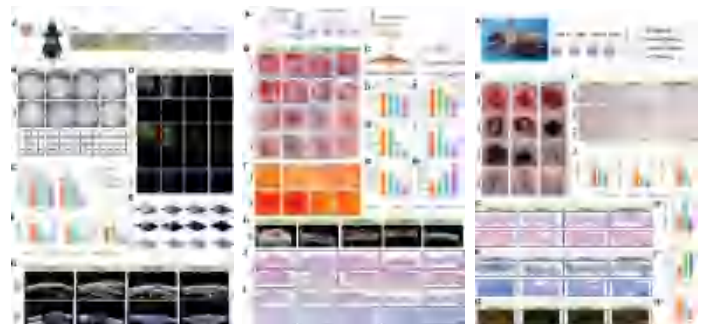
Results



We synthesised the magnetoelectric CFO-BFO nanoparticles and incorporated with rGO nanosheets into GelMA matrix to construct the C@B/rGO magnetoelectric hydrogels.



92% antibacterial rate against *S. aureus* (CFU assay)
Disrupts biofilm formation (crystal violet staining: OD₅₉₀ reduced by ~80% vs. control)
Mechanism: Magnetoelectrically induced ROS (DCFH-DA staining: ROS level ~3x higher than control)



1. Mouse (infected wounds): 70% scar area reduction.
2. Rabbit ear (HS model) : Scar Elevation Index (SEI) reduced from 2.5 to 1.2; scar thickness reduced by ~60%.
3. Mini Bama pig: Outperforms clinical growth factor gel (Beifuji): Smooth skin with hair regeneration; collagen I/III ratio matches normal skin

Conclusion

The magnetoelectric hydrogel achieves spatiotemporal adaptive regulation: eliminates pathogens in inflammation phase and drives macrophage glycolysis→OXPHOS reprogramming in remodeling phase and validated across three preclinical models for scarless healing.

EGCG-Zn Metal-Polyphenol Network for Periodontitis Microenvironment Remodeling and Bone Regeneration

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Abstract

Introduction: Periodontitis is driven by pathogenic biofilm accumulation and dysregulated host immune responses, characterized by excessive reactive oxygen species (ROS) and inflammatory cytokines, leading to periodontal tissue destruction and alveolar bone loss[1]. Conventional therapies mainly focus on infection control but are insufficient to modulate inflammation or promote regeneration. Therefore, multifunctional biomaterial strategies for periodontal microenvironment remodeling are urgently needed. Metal-polyphenol networks (MPNs) represent a promising platform for this purpose[2].

Materials & Methods: An epigallocatechin gallate-zinc (EGCG-Zn) metal-polyphenol network was fabricated via a one-step coordination strategy and encapsulated in a thermosensitive poloxamer hydrogel poloxamer to form an injectable, sustained-release system[3]. Antibacterial activity, intracellular ROS levels, inflammatory mediator expression, and osteogenic differentiation were evaluated *in vitro*. A ligature-induced periodontitis model was used to assess antibacterial efficacy, inflammation resolution, and alveolar bone regeneration *in vivo*. Transcriptomic analysis was conducted to investigate underlying mechanisms.

Results & Discussion: The EGCG-Zn MPN hydrogel showed effective antibacterial activity by disrupting bacterial membranes and inducing quinone-mediated damage. *In vitro*, the system significantly suppressed ROS overproduction and inflammatory cytokine expression, while promoting osteogenic differentiation through bone immune regulation. *In vivo* treatment markedly reduced bacterial burden, alleviated periodontal inflammation, and enhanced alveolar bone regeneration. Transcriptomic analysis indicated that these effects were associated with

mitochondrial restoration, as EGCG-Zn reversed lipopolysaccharide-induced downregulation of mitochondrial genes (*MT1*, *MT2*, and *ATP6*), thereby inhibiting oxidative stress and supporting osteogenic gene expression.

Conclusions: EGCG-Zn metal-polyphenol network effectively remodels the periodontal microenvironment by integrating antibacterial, antioxidative, anti-inflammatory, and osteogenic functions through mitochondrial restoration, offering a promising strategy for periodontal regeneration.

Key words: Periodontitis treatment; Metal-polyphenol network; Mitochondrial restoration; Immunomodulation; Bone regeneration

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Mechanistic study of stress-relaxing amyloid-like hydrogels in promoting bone regeneration through the mechanical and biochemical synergistic remodeling of the periodontal pathological microenvironment

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Key words:

bone regeneration, stress relaxation, amyloid-like hydrogel, mechanical and biochemical synergy, antioxidant

Introduction:

Inflammatory bone defects involve biochemical and mechanical microenvironmental dysregulation. We developed PTLFG, a lactoferrin-based amyloid hydrogel biomimicking the stress relaxation of the extracellular matrix. By coupling tunable mechanical kinetics with ROS scavenging, PTLFG restores homeostasis and drives bone regeneration via mechanosensing-guided pathways.

Methods:

PTLFG-F and PTLFG-S were synthesized via protein self-assembly with tunable stress relaxation. Indirect co-culture isolated biochemical signaling, while direct culture evaluated the synergy of mechanical signal on BMSC osteogenesis.

Results & Discussion:

1. PTLFG hydrogels assemble into uniform porous networks via cysteine-triggered protein unfolding. Intermolecular β -sheet hydrogen bonds, rather than reversible disulfide bonds, provide reductant-resistant stability and superior structural integrity.

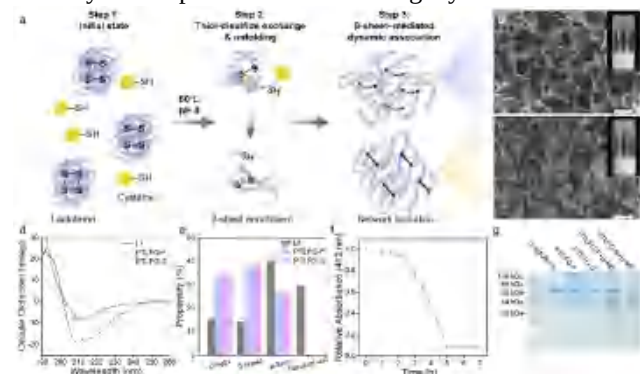


Fig. 1. Characterization of PTLFG-F and PTLFG-S

2. PTLFG-F/S feature stiffness-decoupled stress relaxation ($t_{1/2}$ = 40 s vs. 277 s) to biomimic ECM dynamics [1]. These platforms also scavenge intracellular ROS and promote cell recruitment, establishing the biochemical basis for restoring microenvironmental homeostasis.

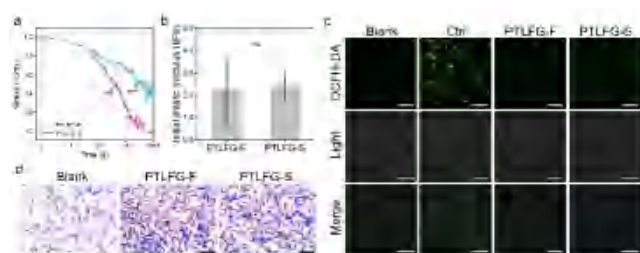
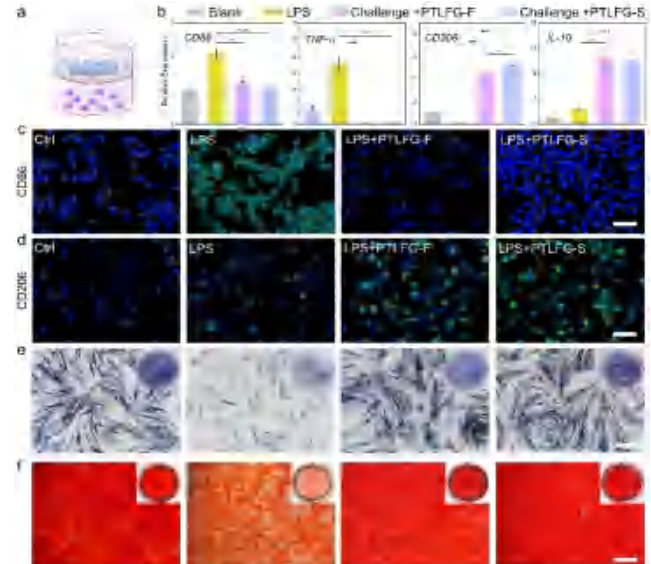


Fig. 2. Mechanical and biological performance.

3. Indirect co-culture suggests PTLFG-F and PTLFG-S exert comparable biochemical effects, promoting M2 macrophage polarization and rescuing BMSC osteogenesis under inflammatory challenge.

Fig. 3. PTLFG induces M2 polarization and rescues



inflammatory BMSC osteogenesis.

4. Direct culture indicates PTLFG-F outperforms PTLFG-S, suggesting fast stress relaxation likely drives BMSC osteogenesis.

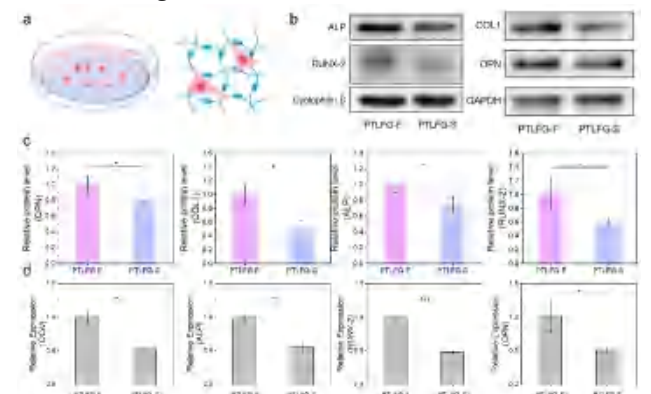


Fig. 4. Osteogenic protein and gene expression

Conclusions:

β -sheet-stabilized PTLFG restores the biological baseline via ROS scavenging and immunomodulation. Fast stress relaxation likely drives BMSC osteogenesis, offering a promising dual-functional strategy for inflammatory bone regeneration.

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Piezoelectric Nanofibers Synchronize Mitochondrial Dynamics and Immune Responses for Regeneration of Infected Wounds

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ABSTRACT: Mitochondria play a central role in coordinating wound repair by integrating bioenergetic activity with immunometabolic signaling. Although electrical cues are known to influence mitochondrial behavior, most existing methods depend on implanted electrodes. Besides, how electrical stimulation precisely regulates the fate of mitochondrial function during infection remains incompletely defined. In this study, we use piezoelectric poly(L-lactic acid) (PLLA) nanofibers upon ultrasound stimulation to act as a wireless interface for spatiotemporally precise mitochondrial regulation during infected wound repair. During the inflammatory stage, piezoelectric activation led to a rapid mitochondrial Ca^{2+} influx and membrane depolarization within seconds, followed by a minute-scale rise in mitochondrial reactive oxygen species (ROS). This sequence initiated the Ca^{2+} -ROS-mtDNA-STING cascade, enhancing antimicrobial activity via cytosolic DNA sensing and promoting mitochondrial fission associated with proinflammatory defense. As healing progressed to the proliferative phase, electrical cues from the nanofibers shifted cellular metabolism and drove macrophage polarization toward a regenerative phenotype, as indicated by a higher Arg1/iNOS ratio and lower IL-6 and TNF- α expression, while promoting mitochondrial fusion and tissue remodeling. In vivo experiments confirmed that these time-scaled mitochondrial responses facilitated the immune response, angiogenesis, and epithelial regeneration, resulting in markedly accelerated closure of infected wounds. Collectively, this work demonstrates how piezoelectric charges regulate mitochondrial Ca^{2+} , ROS, and mtDNA, identifying mitochondria as spatiotemporal mediators of electrostimulation-driven immune reprogramming, offering a wireless bioelectronic strategy to overcome chronic infection barriers and promote functional tissue regeneration.

Key words: mitochondrial dynamics, electrical stimulation, mtDNA, piezoelectrics, immune responses, wound repair

Introduction: This study investigates the scientific question of how electrical stimulation precisely regulates the fate of mitochondrial function and subsequent immunometabolic reprogramming during the repair of infected wounds. While electrical cues are known to influence mitochondrial behavior, most existing platforms rely on invasive implanted electrodes or external power supplies. The research aims to bridge the gap in understanding the multiscale mechanisms that

connect material-induced physical cues with specific organelle-level signaling pathways.

Materials & Methods:

Material Fabrication: Piezoelectric poly(L-lactic acid) (PLLA) nanofibers were fabricated using an electrospinning protocol, with collector speed and a two-step annealing process adjusted to enhance fiber alignment and β -phase crystallinity.

Characterization: The structural, mechanical, and electrical properties were evaluated using SEM, XRD, DSC, FTIR, and a precision electrometer to confirm stable piezoelectric responses under ultrasound (US) stimulation.

In Vitro Assays: L929 fibroblasts and macrophages were cultured on the scaffolds and stimulated with US to monitor mitochondrial Ca^{2+} influx, membrane potential, ROS production and mtDNA leakage.

In Vivo Model: A 6 mm full-thickness *S. aureus*-infected dermal wound model was established in Balb/c mice to evaluate wound closure, epithelial regeneration, and immune cell infiltration under daily 10-minute US treatment.

Results & Discussion:

Mitochondrial Cascade: Piezoelectric activation triggered a sequential Ca^{2+} -ROS-mtDNA-STING cascade, where rapid Ca^{2+} influx and membrane depolarization occurred within seconds, followed by ROS elevation and mtDNA release.

Biphasic Regulation: The treatment synchronized a transition from a proinflammatory defense phase (enhanced M1 polarization and bacterial clearance on Day 2) to a regenerative phase (enhanced M2 polarization, angiogenesis, and collagen remodeling by Day 4).

Accelerated Healing: *In vivo* results showed the piezo+US group achieved a 96.6% wound closure rate by Day 10, significantly outperforming all control groups

Conclusions:

Main Conclusions: The study demonstrates that piezoelectric PLLA nanofibers act as a wireless bioelectronic interface that effectively "switches" mitochondrial dynamics to coordinate immune responses and promote functional tissue regeneration.

Implications & Significance: This work identifies mitochondria as spatiotemporal mediators of electrostimulation-driven immune reprogramming,

offering a wireless strategy to overcome chronic infection barriers in wound care.

Future Recommendations:

Further investigation is needed to identify the primary molecular sensor at the material-cell interface responsible for mechanoelectric transduction. Next-generation designs should incorporate feedback regulation for real-time sensing and self-adjustment of electrical cues in heterogeneous tissue environments. Future work should combine high-resolution spatiotemporal omics to further reveal the dynamic mechanisms of the therapeutic phase transitions in various immune cell types.

Graphics

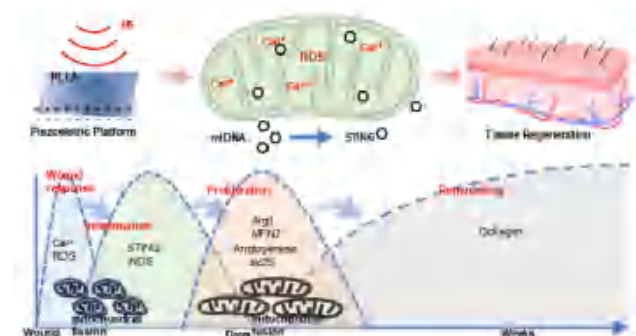
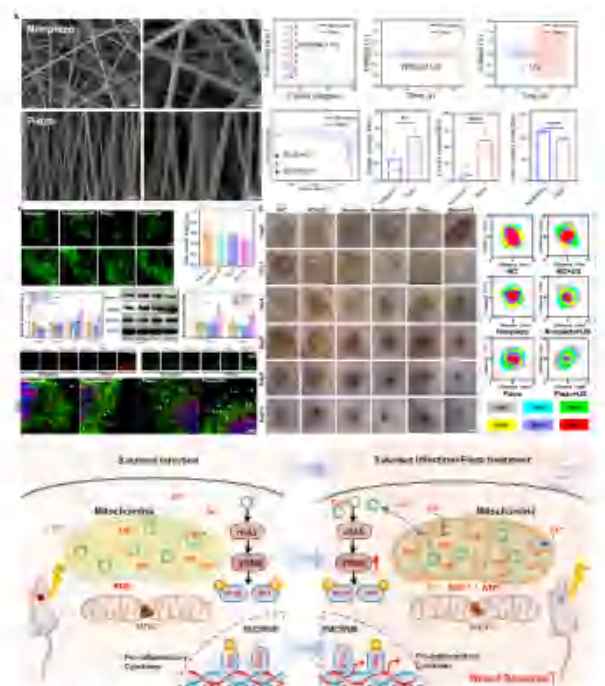


Fig. 1. Piezoelectric PLLA nanofibers synchronize mitochondrial dynamics and immune responses to accelerate infected wound regeneration. A Material Characterization. B Mitochondrial and Molecular Reprogramming. C In Vivo Therapeutic Efficacy. Bottom: Mechanistic Schematic: Illustration of the "electrometabolic switch" where piezoelectric cues enhance the cGAS-STING-mediated immune response and ATP production, thereby overcoming chronic infection barriers to drive functional tissue repair.



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A Study on the Regulation of Osteogenic Properties of A Magnetically Coupled CFO@BFO/ β -TCP Composite Scaffold

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Key words: Magnetoelectric effect, 3D-printed ceramic scaffold, vertical bone augmentation

Introduction: Vertical bone augmentation requires scaffolds with strong space maintenance and osteogenesis-angiogenesis coupling capabilities. While 3D-printed β -TCP scaffold featuring a triple-periodic minimal surface (TPMS) topology provide mechanical stability and interconnected porosity, they function as passive supports and lack active microenvironmental regulation. Since restoring the local electrical microenvironment can promote bone regeneration and magnetoelectric materials allow remote modulation under magnetic fields, this study investigates whether integrating magnetoelectric coupling with a 3D-printed TPMS β -TCP scaffold can actively regulate the microenvironment and enhance vertical bone regeneration.

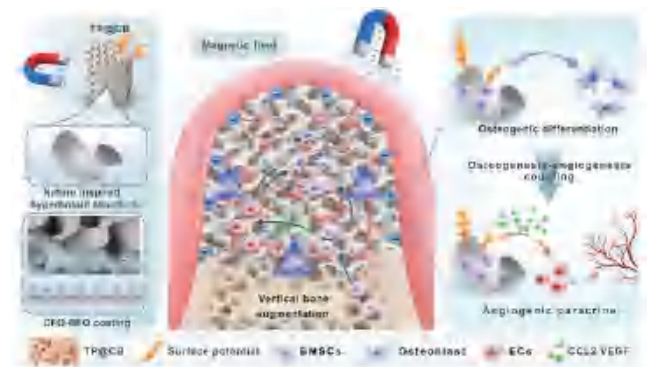
Materials & Methods: The TPMS-structured β -TCP scaffold was fabricated by DLP printing, and CFO-BFO NPs were uniformly immobilized on its surface via a PLA-mediated coating process to form the magnetoelectric TPMS@CFO-BFO (TP@CB) scaffold. The magnetic and magnetoelectric coupling properties of TP@CB were evaluated using VSM, PFM, and EPR. BMSCs adhesion, osteogenesis, and angiogenesis were characterized using SEM, ALP/ARS staining, and tube formation assays. RNA-seq and Western blot identified the molecular coupling mechanisms. The efficacy of TP@CB efficacy for vertical bone augmentation was further confirmed in both rat calvarial defect models and a large-animal (beagle dog) mandibular model.

Results & Discussion: Under magnetic field stimulation, TP@CB significantly promoted the early adhesion and subsequent osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs). Furthermore, by activating the Ca^{2+} -PI3K-Akt signaling pathway, TP@CB enhanced the pro-angiogenic potential of bone marrow mesenchymal stem cells, thereby promoting endothelial cell migration and tubular structure formation. In vivo experiments further demonstrated that TP@CB established a magnetoelectric microenvironment conducive to osteogenic-angiogenic coupling under external magnetic field stimulation. Meanwhile, the ordered pore structure of TP@CB provided spatial support for new bone and blood vessel formation, ultimately promoting healing of critical bone defects in rat cranial bone (including under inflammatory

conditions) and achieving vertical bone augmentation in beagle jawbones.

Conclusions: In this study, we developed a novel magnetoelectric-coupled 3D-printed β -TCP scaffold that combines a TPMS structure with magnetoelectric-coupled CFO-BFO nanoparticles, providing a new regenerative strategy for vertical bone augmentation. Under the influence of an external magnetic field, the scaffold generates a stable magnetoelectric microenvironment that significantly enhances the early adhesion and osteogenic differentiation capacity of bone marrow-derived mesenchymal stem cells (BMSCs), while simultaneously enhancing their osteogenesis-angiogenesis coupling ability. Furthermore, the ordered TPMS pore structure provides the necessary spatial support and mechanical stability for vertical bone augmentation while synergizing with the magnetoelectric coupling effect to significantly promote the sequential growth of new bone and blood vessels. This significantly improves the bone augmentation treatment outcomes for vertical bone defects.

Fig.1 Abstract.



Water in Dentin Bonding

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Key words: demineralized dentin matrix, interface-confined water, dentin bonding

Introduction: Resin restorations are secured to dental tissues through bonding, forming a bonding joint that consists of an adhesive layer connected to the resin and a hybrid layer integrated with the dentin [1]. While the adhesive layer remains relatively stable, the hybrid layer is more prone to degradation due to multiple defects that arise during the bonding process [2]. The defective hybrid layer is produced by insufficient infiltration of adhesives in the demineralized dentin matrix (DDM), which is attributed to difficulty in water replacement [3]. The complete replacement of the water in the DDM by adhesives is considered to be the basic way to eliminate the defects in the hybrid layer and solve the durability problem [4]. Therefore, water in DDM and how does it influence adhesive infiltration need to be revealed in depth.

Materials & Methods: Water in DDM was characterized through hydration dynamics and dielectric responses, using low-field nuclear magnetic resonance (LF-NMR) and broadband dielectric spectroscopy, with direct visualization by in situ liquid-phase atomic force microscopy (LP-AFM). To regulate the confined water, strategies were developed. Utilizing the endogenous negatively charged groups within the DDM as pseudo-nucleation sites, ionic clusters or free cations and anions was applied to facilitate the rapid in situ deposition of nanoparticles. Alternatively, the highly anionic DDM can serve as a natural 3D template for electrostatic assembly. Cationic polymers were used to sequentially assembled onto the DDM. A more biomimetic strategy was inspired by the native mineralization-modulating role of the demineralized dentin during dentinogenesis, lanthanum ion (La^{3+}) was treated as a pretreatment.

Results & Discussion: Rehydration kinetics and dielectric spectroscopy reveal that interface-confined water formation governs matrix electronegativity and dielectric response. The deposited particles effectively mask the negative charges, which is a key step in reducing hydration [5]. Specific coordination ions (e.g., Ag^+ , Cu^{2+}) can directly complex with these anionic groups to form coordination compounds. This interaction not only neutralizes the surface charge but also directly weakens the hydration layer, thereby promoting dehydration [6]. The cationic polymers assembled onto the DDM to form a stable polyelectrolyte complex, which rapidly and efficiently eliminates hydration and dramatically improves adhesive penetration [7]. Via a lanthanum ion (La^{3+}) pretreatment, this approach achieves significant DDM dehydration within seconds, which works by inducing the rapid aggregation of non-collagenous proteins and the crystallization of

thermodynamically stable $\text{Ca}_8\text{La}_2(\text{PO}_4)_6\text{O}_2$ [8].

Conclusions: A unifying principle emerges from these diverse strategies: the effective release of interface-confined water directly results in improved adhesive infiltration and bonding durability. This principle not only underpins the targeted dehydration approaches described above but also provides a mechanistic explanation for the efficacy of other established dentin bonding strategies, such as pre-adhesion mineralization, which also enhance bonding outcomes, at least in part, through the critical step of demineralized dentin dehydration. This reformed perspective paves the way for solving the persistent scientific challenge of water management, thereby advancing dentin bonding towards greater predictability and durability.

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Magnetoelectric Responsive CFO-BFO Core-Shell Nanoparticles Modulate Macrophage Reprogramming for Superior Infected Periodontal Tissue Regeneration

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Key words: Magnetoelectric nanoagents, Periodontitis, Antibacterial, Macrophage reprogramming, Osteogenesis

Introduction: Clinical management of periodontitis requires addressing both bacterial infection and the deficient osteogenic microenvironment to optimize tissue regeneration. Electroactive biomaterials have demonstrated promise in bone regeneration, but are insufficient to enduringly synergize antibacterial properties with optimal immunomodulatory and tissue remodeling effects within the complex inflammatory microenvironment. Here, this study proposes an efficient, dynamic magnetoelectric conversion-based therapeutic strategy, which integrates antibacterial activity and immunomodulation to optimize periodontal tissue regeneration.

Materials & Methods: In this study, core-shell structured magnetoelectric $\text{CoFe}_2\text{O}_4\text{-BiFeO}_3$ nanoparticles (CFO-BFO NPs) were fabricated. In vitro, the osteogenic differentiation of periodontal ligament stem cells (PDLSCs) and the antibacterial activity against *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, and *Staphylococcus aureus* were evaluated under magnetic field stimulation. RNA sequencing (RNA-seq) was performed to investigate the immunomodulatory mechanisms, with validation of the PI3K-Akt signaling pathway in macrophage polarization. In vivo, the therapeutic efficacy was assessed in a *P. gingivalis*-mediated periodontitis mouse model.

Results & Discussion: Magnetoelectric CFO-BFO NPs significantly enhance osteogenesis of periodontal ligament stem cells (PDLSCs) and exhibit potent antibacterial activity in vitro. Crucially, magnetoelectric coupling stimulation can program macrophage from the M1 to M2 phenotype via the PI3K-Akt signaling pathway, thereby enhancing osteogenesis. Moreover, magnetoelectric CFO-BFO NPs can also alleviate tissue inflammation and accelerate infected periodontal bone regeneration in *Porphyromonas gingivalis* (*P. gingivalis*)-mediated periodontitis mice models. After 4 weeks of treatment, the bone volume fraction (BV/TV) in the magnetoelectric CFO-BFO NPs group approached healthy levels.

Conclusions: This study pioneers the application of magnetoelectric coupling materials for periodontitis treatment and provides a novel strategy for enhancing the therapeutic effects of electroactive biomaterials on periodontitis.

***In vitro* cytocompatibility, antibacterial properties, and hemocompatibility of MAO-Zn/PLA composite films for potential guiding bone regeneration**

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Abstract

In order to evaluate the application potential of micro-arc oxidized Zn foil (MAO-Zn)/Poly(lactic acid) (PLA) composite films in guiding oral bone regeneration (GBR) from the perspective of material composition, its cytocompatibility, antibacterial properties, and hemocompatibility were investigated. The cytocompatibility was evaluated using Human gingival fibroblasts (HGF) and MC3T3-E1 cells by CCK-8 method. For PLA film, the viability of the above two types of cells was 87.6% and 84.5%, respectively, and their morphology was normal. However, PLA has no antibacterial ability. In contrast, the inhibition ratio of Zn foil and MAO-Zn foil against *Staphylococcus aureus* reached 48.56% and 48.19%, and their inhibition ratio against *Porphyromonas gingivalis* reached 76.6% and 80.99%, respectively, after co-culturing with bacterial suspension for 24 h. While the cells viability from these two groups was only 10.38%, 9.13% for HGF and 67.31%, 8.90% for MC3T3-E1 cells, after culturing with the original extract for 5 days. The abnormal morphology also implied their toxicity. Under the protection of PLA for composite film, it avoided direct contact between Zn foil or MAO-Zn foil and surrounding cells, also realized long-term sustained release of Zn^{2+} . The composite film showed the bacterial inhibition ratio of 81.09% and 89.85%, respectively. Meanwhile, the morphology of the above two types of cells was normal after co-culturing on the surface of the composite film for 24 h. Moreover, it upregulated the expression levels of osteogenesis-related genes (COLL- α , OCN, ALP, RUNX2). The hemolysis ratio of the composite film was less than 2%. Although the cells viability in the 1:9 diluted extract was 91.54% and 87.46%, while that in the original extract was only 8.75% and 3.36%. It is still necessary to further reduce its toxicity by subsequent adjusting its composition and structure. This study provides experimental basis and theoretical reference for further enhancing the application potential of this kind of composite film in the field of GBR membrane.

Key words: micro-arc oxidized Zn foil, Poly(lactic acid), composite films, cytocompatibility, antimicrobial properties

Tuning zinc oxide Nanostructures on PLLA Piezoelectric Nanofibers for Self-Powered Infection Control and Oral Mucosal Regeneration

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Key words: Oral wound healing; Electrospun nanofiber; Low intensity pulsed ultrasound, Piezoelectric effect

Introduction: Oral ulcers are prevalent inflammatory lesions with limited treatment options^[1,2], largely due to persistent inflammation, weak tissue adhesion, and poor retention in the dynamic oral environment^[3,4]. Herein, we developed a ZnO/PLLA piezoelectric nanocomposite dressing capable of providing antibacterial, immunomodulatory, and bioelectrical cues for oral mucosal regeneration, and systematically investigated how ZnO morphology influences its piezoelectric properties and biological performance.

Materials & Methods: Morphology-tunable ZnO nanostructures, including hollow, nanoparticle, nanorod, and nanowire architectures, were synthesized via a water-content-regulated hydrothermal method using ZIF-8 as the precursor (**Fig.1**). These ZnO structures were incorporated into aligned electrospun PLLA membranes, followed by corona poling to obtain piezoelectric fibrous dressings. The membranes were comprehensively characterized by SEM, EDS, XRD, FTIR, DSC, wettability, mechanical, piezoelectric, degradation, and Zn²⁺ release analyses. Their cytocompatibility, hemocompatibility, antibacterial, antioxidative, immunomodulatory, cell migration, and angiogenic properties were evaluated in vitro, and therapeutic efficacy was further assessed in a rat model of full-thickness buccal mucosal defects.

Results & Discussion: Structural characterization showed that the hollow ZnO/PLLA membrane (HZIP) exhibited improved fiber alignment, enhanced crystallinity, and stronger piezoelectric output than the other groups. Under low-intensity pulsed ultrasound (LIPUS) stimulation, HZIP generated the highest localized electrical response and ROS signal, indicating superior sono-piezoelectric activity. This enhancement was accompanied by remarkable antibacterial and antibiofilm effects against *S. aureus*, *E. coli*, and *P. gingivalis*. Meanwhile, all membranes exhibited good cytocompatibility and hemocompatibility (**Fig.2**). In vitro, ultrasound-activated HZIP significantly promoted fibroblast migration and endothelial angiogenesis, reduced intracellular oxidative stress, and modulated the inflammatory microenvironment by suppressing M1 macrophage polarization while promoting the M2 phenotype. Transcriptomic analysis further revealed that HZIP under ultrasound regulated multiple pathways associated with tissue repair and inflammation control, including PI3K-Akt, ErbB, Hippo, and JAK-STAT

signalling. Consistent with these findings, the HZIP+US group achieved the best therapeutic outcome in a rat full-thickness buccal mucosal defect model, as evidenced by accelerated wound closure, enhanced collagen deposition, and improved neovascularization. These results highlight the therapeutic potential of morphology-engineered piezoelectric nanocomposite membranes for oral mucosal regeneration.

Conclusions: Morphology-engineered HZIP membranes enabled self-powered, stage-adaptive oral wound repair by integrating piezoelectric stimulation, antibacterial activity, and sustained Zn²⁺ release. This “morphology-bioactivity” strategy enhanced mucosal regeneration in vivo and provides a promising design framework for clinically translatable oral wound dressings.

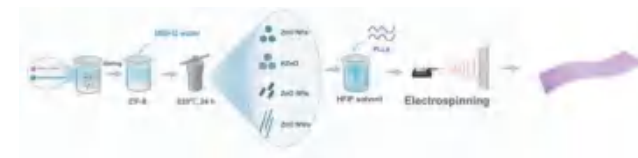


Fig.1. Schematic diagram of preparation of PLLA/ZnO piezoelectric nanocomposite membranes.

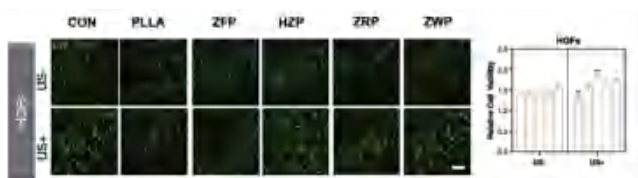


Fig.2. In vitro biocompatibility and hemocompatibility of PLLA/ZnO. Representative live/dead fluorescence images and quantitative relative cell viability of HGFs after co-culture with different membranes (CON, PLLA, ZFP, HZIP, ZRP, ZWP) under LIPUS untreated (US-) and treated (US+) conditions, indicating live (green) and dead (red) cells, Scale bar: 200 μ m. Data are shown as the mean $\pm$ standard deviation (n=3). *p < 0.05, ***p < 0.001, ****p < 0.0001.

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Synergistic Therapeutic Mechanisms of GelMA Microneedle-Delivered Ce6-HA-Fe₃O₄ Nanoparticles for Oral Squamous Cell Carcinoma

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Key words: Drug delivery system; hydrogel microneedle; nanoparticle; oral squamous cell carcinoma

Introduction: Oral squamous cell carcinoma (OSCC) has emerged as a major clinical challenge in oral medicine due to its highly aggressive biological behavior, high rates of recurrence and metastasis, and the significant functional and esthetic impairment often associated with treatment. Although multimodal treatment has improved patient survival to some extent, substantial limitations remain. Furthermore, the unique tumor microenvironment (TME) of OSCC exacerbates therapeutic resistance. Therefore, the development of a novel therapeutic platform that can precisely target local lesions, overcome TME-associated barriers, and achieve synergistic multimodal therapy holds significant clinical value and research importance.

Materials & Methods: This study aims to develop a localized microneedle (MN) delivery system based on gelatin methacryloyl (GelMA), integrating photodynamic therapy (PDT) and chemodynamic therapy (CDT). The MN system enables precise drug delivery, while hyaluronic acid (HA)-mediated tumor targeting and the catalytic properties of magnetic nanoparticles synergistically enhance therapeutic efficacy.

Results & Discussion: Scanning electron microscopy (SEM) demonstrated that the MN array was well-organized with sharp tips (height: 950 μm ; base diameter: 360 μm). In vitro degradation studies showed a 45% degradation rate at 24 h, and nanoparticle release exhibited a biphasic pattern characterized by an initial rapid release followed by sustained release. Transmission electron microscopy (TEM) revealed that the nanoparticles were square-like with a uniform size distribution (15 ± 5 nm).

Conclusions: GelMA MNs enable painless, localized delivery of Ce6-HA-Fe₃O₄ nanoparticles, enhancing intratumoral accumulation and reducing systemic toxicity. PDT/CDT synergy complements ROS generation and improves therapeutic efficacy. This local targeting added synergistic therapy platform provides a promising strategy for precise, minimally invasive OSCC treatment.

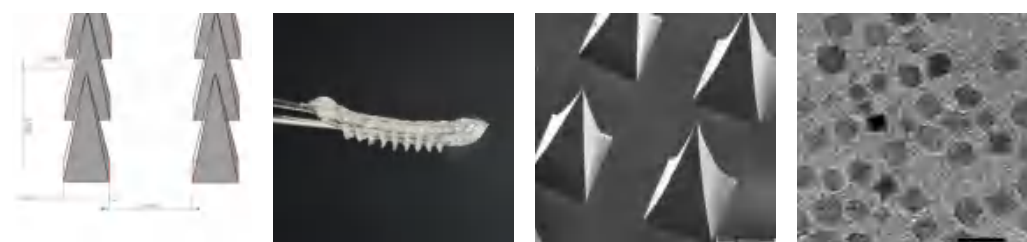


Figure 1 (A) Schematic illustration of the PDMS mold design. (B) Macroscopic of GelMA hydrogel microneedles. (C) SEM of GelMA hydrogel microneedles. (D) TEM of HA-Fe₃O₄ nanoparticles.



Figure 2 Schematic illustration of GelMA hydrogel microneedle degradation in vitro at 0 h, 24h, 48h, 72h.

Phenylboronic Acid-Modified Polyvinylamine for Efficient Intracellular Protein Delivery

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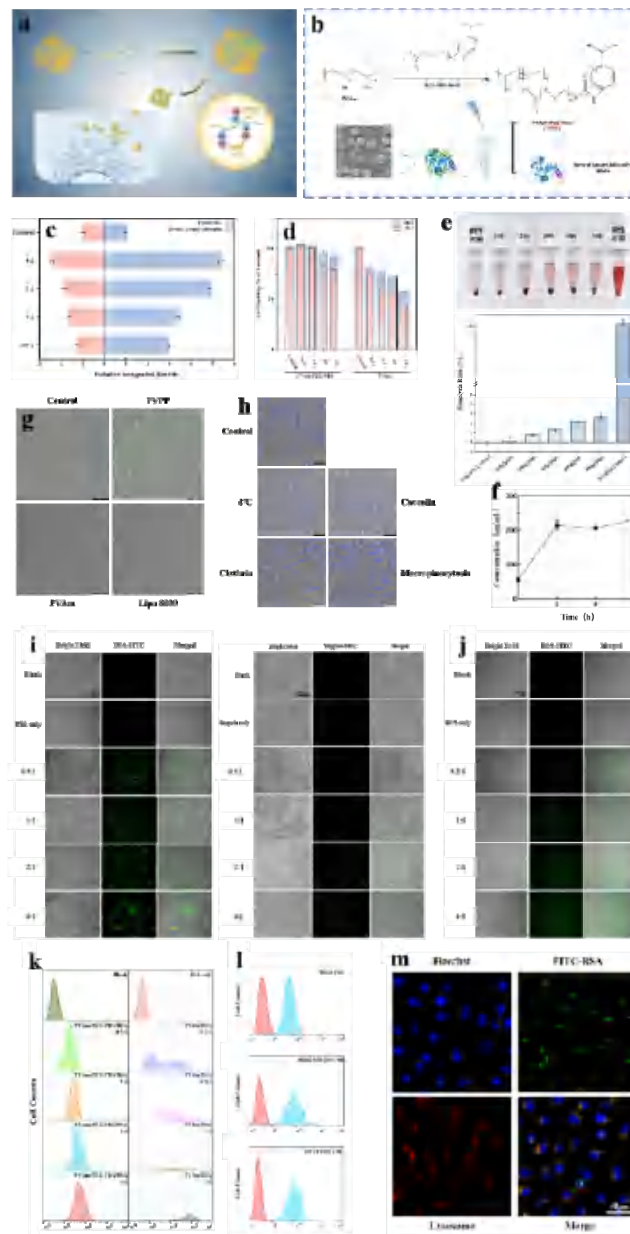
Key words: Protein carrier, Polyvinylamine, Phenylboronic Acid, Cytosolic delivery

Introduction: Due to the difficulty of proteins freely penetrating biological membrane barriers to achieve intracellular targeted delivery and exert their effects, developing efficient delivery systems is a critical issue that urgently needs to be addressed. This study constructed a delivery carrier based on the linear cationic polymer polyvinylamine (PVAm). By grafting polyethylene glycol (PEG), which possesses both biocompatibility and water solubility, a amphiphilic backbone was formed. The introduction of phenylboronic acid (PBA) functional units enabled efficient binding to proteins through its dynamic covalent bond characteristics and multiple intermolecular interactions. The carrier demonstrated excellent biocompatibility and successfully delivered proteins to various cell types. Both qualitative and quantitative assays revealed high transfection efficiencies, with glucose-responsive controlled protein release achievable. These findings indicate that this carrier provides a novel strategy for intracellular protein delivery.

Materials & Methods: A PVAm-PEG-PBA delivery carrier was synthesized by chemically modifying polyvinylamine with polyethylene glycol and phenylboronic acid through a side-chain amine derivatization method.

Results & Discussion: The PVAm-PEG-PBA delivery system enables efficient intracellular delivery of proteins into various cell types. It achieves high transfection efficiency while maintaining low physiological toxicity, demonstrating excellent biocompatibility and safety. This system facilitates the highly efficient delivery of diverse proteins with minimal toxicity.

Conclusions: This PVAm derivative holds potential as an intracellular protein delivery vehicle, offering promise as a more efficient, safer, and cost-effective protein carrier.



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Stress-trained microalgae robots with probiotics backpack and intestinal brake for inflammatory bowel disease management

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Abstract: Inflammatory bowel diseases (IBD) are frequently characterized by heightened levels of ROS and profoundly dysregulated gut microbiota. Here, we introduce the stress-trained biohybrid robots with braking system, termed “EcN@PDA@HP,” which effectively scavenge ROS and modulate gut microbiota using metabolites and probiotics for the treatment of IBD. *Haematococcus Pluvialis* (HP) produces astaxanthin (AST) under stress, during which its cell wall thickens to resist the stomach environment and retains the motility characteristics of microalgae, allowing itself and its cargo to remain active and quickly pass through the harsh gastric acid barrier. The combination of *Escherichia coli* Nissle 1917 (EcN) modified with polydopamine (PDA) and HP is achieved through host-guest interaction, resulting in the formation of EcN@PDA@HP. Owing to PDA's robust adhesive properties of PDA, EcN@PDA@HP exhibit prolonged retention time in the inflamed intestines, thereby enhancing both the antioxidant effect of astaxanthin and the bacteriotherapy potential of EcN. The therapeutic effects are demonstrated in murine models, including inflammation mitigation, macrophage reprogramming, ROS scavenging, and restoration of the intestinal barrier and microbiota.

Key words: microalgae robots, braking system, ROS scavenging, bacteriotherapy

Introduction: Inflammatory bowel disease (IBD), encompassing ulcerative colitis and Crohn's disease, is critically linked to reactive oxygen species (ROS) overaccumulation and gut dysbiosis^[1,2]. Excessive ROS disrupt intestinal barrier integrity through lipid peroxidation and DNA damage, while microbial imbalance perpetuates inflammation and metabolic dysfunction^[3,4]. Although antioxidants counteract ROS-mediated pathology, their therapeutic potential is limited by poor oral stability, nonspecific biodistribution, and short intestinal retention.

Micro/nanorobots have emerged as promising candidates for biomedical delivery, with green algae-based systems offering unique advantages including autonomous propulsion, autofluorescence imaging, and scalable production^[5]. However, conventional algal robots face challenges in gastric acid resistance and sustained intestinal retention. *Haematococcus pluvialis* (HP), a stress-tolerant microalga, thickens its cell wall under harsh conditions and biosynthesizes astaxanthin (AST)—a potent antioxidant activating superoxide dismutase (SOD), catalase (CAT), and ascorbate peroxidase (APX) pathways^[6]. Despite AST's therapeutic potential, its bioavailability remains constrained by gastrointestinal degradation.

IBD progression further correlates with depletion of beneficial microbiota and pathogenic bacterial overgrowth^[7]. While probiotic supplementation shows therapeutic promise, its efficacy is compromised by gastric acid inactivation and poor colonic colonization.

Materials & Methods: Briefly, *Haematococcus Pluvialis* (HP) can biosynthesize a large amount of astaxanthin under stress conditions (nitrogen starvation, continuous light and weak acid), thickens its cell wall to resist the stomach environment, retain its self-motility characteristics, allowing it to remain active and quickly pass through the harsh gastric acid barrier. Then probiotic *Escherichia coli* Nissle 1917 (EcN) is functionalized with polydopamine (PDA) to enhance its intestinal the adhesion time and it is referred to as “EcN@PDA”. Subsequently, host and guest molecules were respectively introduced onto HP and EcN, resulting in the formation of HP-EcN hybrid microrobots (EcN@PDA@HP) through host-guest interactions.

Results & Discussion: Due to the strong motility characteristics of HP and acid-resistant properties acquired through training, these hybrid microrobots can rapidly traverse the adverse stomach environment, avoiding affecting the activity of AST and EcN. Next, when the HP-EcN hybrid microrobots reach the intestine, the PDA on the EcN surface significantly prolongs the microbots' retention time in the inflamed intestines, thereby facilitating sustained release of AST and prolonged colonization by EcN. In the murine model of dextran sulfate sodium (DSS)

-induced acute and chronic colitis and, the intelligent stimulation-responsive mucoadhesive probiotic EcN@PDA@HP shows obvious remediation effect. Thus, the HP-EcN hybrid microrobots equipped with an intelligent brake system remarkably inhibited DSS-induced acute and chronic colitis, and *S. Typhimurium* (STm)-induced colitis, including macrophage reprogramming, reduced apoptosis levels in the colon epithelium, intestinal barrier restoration, alleviated intestinal inflammation, ROS scavenging, and gut microbiota modulation.

Conclusions: our research introduced oral hybrid microalgae robots (EcN@PDA@HP), which provide unique mobility performance and braking functions, and are specifically designed to treat IBD by clearing ROS and regulating gut flora. This multifaceted approach shows great potential for clinical translation and paves the way for further research in this field.

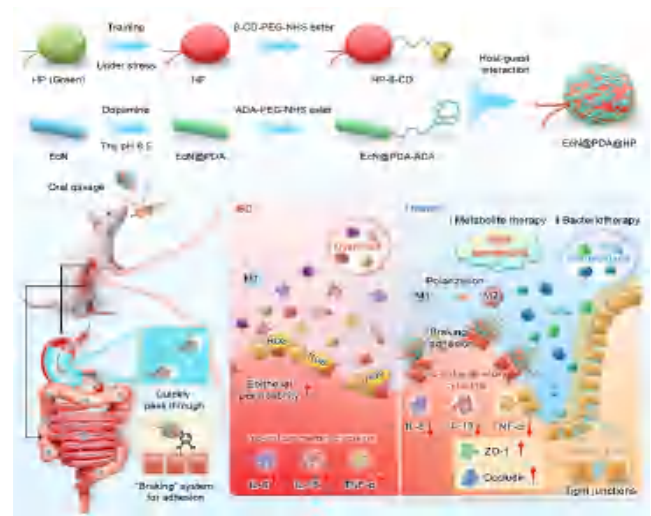


Fig. 1. Schematic illustration of EcN@PDA@HP robots preparation and their mechanism for IBD treatment.

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Hydroxylated dendrimer nanogels co-deliver drugs and cytokines for chemoimmunotherapy of glioma

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Key words: dendrimers, nanogels, cytokine, chemotherapy, immunotherapy

Introduction: Glioma, one of the most aggressive primary tumor types, poses severe challenges in clinical management. The complex structure of brain hinders precise surgical resection, resulting in a high recurrence rate.¹ In addition, the blood-brain barrier (BBB) prevents approximately 98 % of small molecular drugs and 99.9 % of macromolecular therapeutics from reaching tumor sites while also limiting immune cell infiltration.² Although nanodelivery systems have shown promise in crossing the BBB, clinical translation is hindered by complex manufacturing processes, high costs, and poor batch-to-batch stability. Tirapazamine (TPZ) offers selective killing of hypoxic tumor cells but suffers from limited BBB penetration and an immunosuppressive tumor microenvironment (TME).³ Immunotherapy, particularly cytokine therapy such as interferon-gamma (IFN- γ), can modulate immune responses and synergize with chemotherapy.⁴ However, free cytokines have a narrow therapeutic window and short half-life. Here, we address the need for a straightforward, develop a dual pH/reactive oxygen species-responsive dendrimer nanogel (DNG) platform based on generation 3 poly (amidoamine) (G3 PAMAM) dendrimers for co-delivery of the hypoxia-activated prodrug TPZ and the immunomodulatory cytokine IFN- γ .

Materials & Methods: This DNG platform was constructed by crosslinking G3 PAMAM dendrimers that were surface-modified with phenylboronic acid (PBA) and glycidol with dual PBA-terminated poly(ethylene glycol) (PBA-PEG-PBA) via a reverse microemulsion method. The formed DNGs were then loaded with TPZ through physical encapsulation and surface complexed with IFN- γ via dendrimer terminal PBA group-mediated ionic and cation- π interactions to form a co-delivery system of DNG-TPZ/IFN- γ for chemoimmunotherapy of glioma based on the hypoxic and immunosuppressive microenvironment of glioma.

Results & Discussion: Material characterization confirmed the successful synthesis of DNG-TPZ/IFN- γ with an average diameter of 72.5 nm, demonstrating favorable stability and biosafety. *In vitro* release assays revealed pH/ROS-responsive release profiles of TPZ and IFN- γ . Cellular experiments demonstrated that DNG-TPZ/IFN- γ significantly induced tumor cell apoptosis under hypoxic conditions, promoted M1

polarization of macrophages and maturation of dendritic cells. In an orthotopic mouse glioma model, DNG-TPZ/IFN- γ effectively penetrated the BBB, exhibiting superior tumor suppression and potent immune activation, thereby significantly prolonging mouse survival.

Conclusions: Through rational design, we crosslinked hydroxyl-terminated low-generation PAMAM dendrimers to form pH/ROS dual-responsive DNGs, which enabled co-loading of chemotherapeutic drugs and cytokines with small size and excellent colloidal stability. Leveraging the BBB-crossing capability of hydroxylated DNGs and the enhanced permeability and retention effect, we achieved targeted delivery of TPZ/IFN- γ for glioma treatment. The hypoxic TME was exploited to activate TPZ for tumor cell killing, while IFN- γ concurrently triggered immune responses, achieving efficient chemoimmunotherapy of orthotopic glioma.

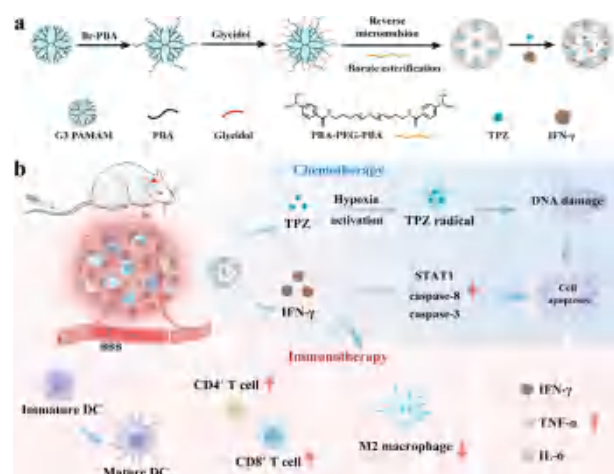


Fig. 1. (a) Synthesis of DNGs-TPZ/IFN- γ and (b) action mechanisms of the co-delivered TPZ and IFN- γ for synergistic chemoimmunotherapy of orthotopic glioma.

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Biomimetic Exosome-Camouflaged pH-Responsive Dendrimer Nanogels as a Therapeutic Vaccine against Pancreatic Cancer through Reprogramming of Multiple Cell Types

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Key words: dendrimer nanogels; exosome; nanovaccine; chemotherapy; antigen presentation

Introduction: Cancer remains a severe global health burden with a continuously increasing incidence. Although cancer vaccines exhibit distinct advantages over conventional therapies, their clinical efficacy is severely limited by challenges including inefficient antigen cross-presentation. Nanovaccines represent a promising strategy to address these obstacles, among which exosomes serve as an ideal antigen source due to their ability to deliver abundant antigens and favorable biocompatibility. Meanwhile, dendrimer nanogels (DNGs) possess versatile favorable properties and represent an excellent platform for the construction of multifunctional nanovaccines. In this study, an exosome-camouflaged DNG vaccine (Au-DNGs/CpG@Exo) was developed, loaded with the drug Toy, gold nanoparticles (Au NPs) and adjuvant CpG, featuring pH/ROS-responsive drug release and homologous targeting. Au NPs can reshape the tumor microenvironment and enable CT imaging-guided therapy. This vaccine can simultaneously modulate multiple cell types including cancer cells, tumor-associated macrophages (TAMs) and dendritic cells (DCs), achieving tumor killing, efficient antigen presentation and reversal of the immunosuppressive microenvironment, thereby providing a novel direction for cancer therapy.

Materials & Methods: Generation 3 (G3) poly(amidoamine) (PAMAM) dendrimers partially conjugated with Toy via dual pH- and reactive oxygen species (ROS)-responsive borate ester bonding were used as macromolecular monomers, and terephthalaldehyde-polyethylene glycol-benzaldehyde (FBA-PEG-FBA) was employed as a crosslinker to prepare pH-responsive DNGs using a microemulsion technique. The formed DNGs were in-situ loaded with Au NPs through sodium borohydride reduction of Au salt and the immunoadjuvant CpG through electrostatic interaction. The created Au-DNGs/CpG were camouflaged with Exos derived from pancreatic cancer cells to form an Exo-biomimetic DNG vaccine system (Au-DNGs/CpG@Exo), which was thoroughly characterized in terms of physicochemical properties and in-vitro and in-vivo evaluations of cytotoxicity, cellular uptake, antigen presentation, tumor therapeutic effects and immune responses.

Results & Discussion: The formed Au-DNGs/CpG@Exo have a size of 111.6 nm and pH-responsive Toy release property under a TME-mimetic environment. The nanovaccine enables homologous tumor targeting delivery of Toy to mediate chemotherapy for immunogenic cell death (ICD) induction, and delivery of adjuvant/Exo-derived antigens to DCs for triple ICD-, adjuvant- and antigen-mediated

maturation. Meanwhile, the loaded Au NPs remodel the immunosuppressive microenvironment through macrophage M1 repolarization/lysosomal dysfunction to boost immune activation. Such biomimetic DNGs enable effective tumor inhibition and recurrence prevention in a pancreatic tumor mouse model, and may be developed as a therapeutic nanovaccine to tackle other cancer types through reprogramming of multiple cells.

Conclusions: We developed an innovative exosome-camouflaged dendrimer nanogel nanovaccine Au-DNGs/CpG@Exo, which is colloiddally stable and exhibits pH-responsive drug release in the tumor microenvironment. This nanovaccine integrates chemotherapy, tumor targeting, DC maturation, TAM repolarization and lysosomal dysfunction regulation to achieve combined antitumor immunity, reverses the immunosuppressive microenvironment, and effectively inhibits primary tumors and tumor recurrence in a pancreatic tumor mouse model. This work demonstrates the promising potential of DNG-based nanovaccines in overcoming inefficient antigen cross-presentation, immunosuppressive TME and insufficient multi-cell type reprogramming.

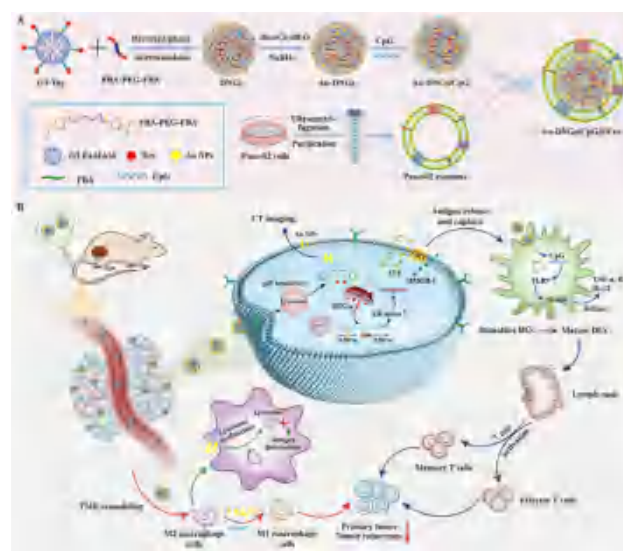


Fig. 1. (A) Preparation and (B) antitumor mechanism of biomimetic Exo-DNG vaccine (Au-DNGs/CpG@Exo).

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Modified Chitosan Hydrogel Enables Non-Invasive Targeted Delivery of Collagen-Polyphenol Complex for Basal Layer Repair of Thin Endometrium and Fertility Restoration

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Abstract

Repairing the thin endometrium (TE) remains a significant clinical challenge due to basal layer damage, vascular insufficiency, and the inherent difficulty of delivering therapeutics across endometrial biological barriers. To address this, we present a hierarchical delivery strategy designed to overcome these barriers for non-invasive, deep tissue repair. We engineered a composite system comprising recombinant human type III collagen (RC) loaded into SNAC-grafted chitosan (SCS) nanoparticles, which are encapsulated within a tissue-adhesive hyaluronic acid hydrogel (HDAHgel@SCS/RC). This design synergizes the sustained-release properties of the hydrogel matrix with the enhanced permeability of the nanoparticles, enabling prolonged retention and deep penetration of bioactive macromolecules into the endometrial stroma. In a rat TE model, the composite hydrogel significantly promoted endometrial regeneration—characterized by thickened endometrium, stromal reconstruction, and robust neovascularization—thereby restoring fertility. This work not only presents a clinically relevant strategy for treating thin endometrium but also establishes a versatile biomaterial platform capable of overcoming tissue barriers for regenerative protein delivery.

Key words: Hydrogels; Drug delivery system; Endometrial repair

Efficient Synthesis of Protein–Polymer Conjugates with Open-Air Fabrication and Facile Purification Driven by the Thermoresponsive Protein–Polymer Conjugate

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Introduction: Protein-polymer conjugates represent a next-generation class of biomacromolecules with extensive applications in protein therapeutics, drug delivery, and biocatalysis. However, current synthesis methods are limited by stringent deoxygenation requirements, complex purification processes, and poor compatibility with diverse monomers and proteins. This study aims to develop a universal strategy that enables open-air polymerization and facile purification for protein-polymer conjugate synthesis.

Materials & Methods: A thermoresponsive deoxygenation agent, GOX-PDEGMA, was synthesized by conjugating glucose oxidase (GOX) with an ATRP initiator followed by in situ polymerization of di(ethylene glycol) methyl ether methacrylate (DEGMA). The conjugate was characterized by MALDI-TOF-MS, SDS-PAGE, NMR, and DLS. For protein-polymer conjugate synthesis, various proteins (HSA, IFN, Herceptin, LYS) were modified with ATRP initiators and polymerized under open-air conditions using GOX-PDEGMA (1 μ M), glucose, sodium pyruvate, and copper wire. Five methacrylate monomers (OEGMA, DMAEMA, HEMAP, MPC, HPMA) were tested. Reaction kinetics were monitored by NMR and GPC. Protein structure and activity were assessed by CD spectroscopy and bioactivity assays.

Results & Discussion: GOX-PDEGMA exhibited LCST phase transition at 21–23°C, enabling >99% removal efficiency via simple centrifugation post-reaction. The system demonstrated excellent polymerization control with linear molecular weight evolution and preserved end-group fidelity for block copolymer synthesis. As shown in Fig. 1, GPC traces revealed a progressive shift in retention time from 10 to 60 min, corresponding to an increase in molecular weight (M_w up to 158.9 kDa, $\bar{D}=1.23$), indicating good polymerization control. All five monomers successfully polymerized on protein surfaces. CD spectroscopy confirmed preservation of secondary structure (>90% α -helix content), and bioactivity assays showed 61.1–86.4% activity retention. GOX-PDEGMA remained recyclable for three cycles with >50% enzymatic activity. The strategy scaled efficiently from 10 μ L to 100 mL and proved compatible with 96-well plate format. Importantly, the method was successfully applied to therapeutic proteins including interferon- α , trastuzumab, and lysozyme.

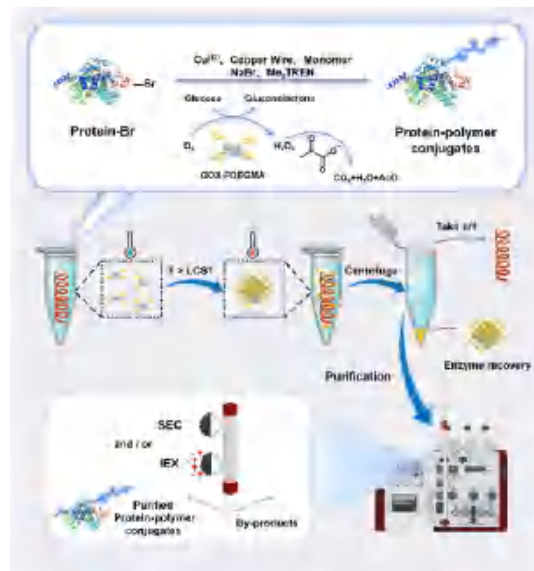


Fig. 1. GPC traces of HSA-POEGMA conjugates over reaction progress (10–60 min), showing progressive shift to higher molecular weight with increasing reaction time.

Conclusions: This study presents the first application of protein-polymer conjugates to overcome challenges in their own synthesis. The thermoresponsive GOX-PDEGMA-based strategy enables open-air fabrication, one-step purification, reagent recyclability, and broad compatibility with monomers and therapeutic proteins across scales. This platform offers significant potential for developing long-acting protein therapeutics and antibody-based drugs.

Key words: oxygen-tolerant ATRP, protein-polymer conjugate, thermoresponsive purification, therapeutic proteins, biomaterials

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Butyrate-Conjugated Dual-Responsive Polymeric Nanoplatfom for Colon-Targeted Drug Delivery and Enhanced Therapy of Inflammatory Bowel Disease

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Key words: inflammatory bowel disease, drug delivery, nanoparticle, butyrate, polymer

Introduction: Inflammatory bowel disease (IBD) is a chronic gastrointestinal disorder with a growing global prevalence. The emergence of novel therapeutic agents, together with currently approved drugs, has significantly reshaped the therapeutic landscape. However, achieving efficient drug delivery to the inflamed intestinal mucosa remains a major challenge, despite its critical importance for improving therapeutic efficacy and minimizing systemic side effects. Therefore, the development of colon-targeted, mucoadhesive drug delivery systems is of considerable importance and clinical relevance.

Materials & Methods: An oral butyrate-conjugated polymer nanoplatfom (PSBA) was developed for co-delivery of magnolol (Mag) and butyrate in IBD. PSBA polymers with varying butyrate contents were synthesized to optimize drug release behavior. Mag-loaded nanoparticles (PSBA@Mag) were prepared and evaluated for gastrointestinal stability and pH/redox-responsive release. The bio-adhesive and colonic retention was also assessed. Therapeutic efficacy was investigated in DSS-induced colitis mice with mechanisms further analyzed by transcriptomics, metabolomics, and gut microbiota profiling.

Results & Discussion: PSBA were successfully synthesized and self-assembled into uniform nanoparticles (~80–180 nm) with high drug loading and encapsulation efficiency. Mag-loaded nanoparticle, PSBA@Mag, significantly improved the cytocompatibility and hemocompatibility of free magnolol, while enabling efficient cellular uptake and sustained colonic pH-responsive release.

In vivo, PSBA@Mag exhibited enhanced colonic retention and bioadhesion in colitis mice. It markedly alleviated disease severity in both DSS- and TNBS-induced models, outperforming free drug and control polymers. Mechanistically, PSBA@Mag restored epithelial barrier integrity, normalized inflammatory cytokines, and increased short-chain fatty acid levels. Multi-omics analyses further revealed suppression of TNF/MAPK inflammatory pathways, improvement of lipid metabolism, and partial restoration of gut microbiota composition and diversity.

Conclusions: We developed a butyrate-rich, colonic pH/redox dual-responsive polymer (PSBA) for efficient

magnolol (Mag) delivery and colitis treatment. PSBA enabled ~10% drug loading, improved biocompatibility, and achieved pH/redox-triggered release with enhanced colonic retention and bioadhesion. PSBA@Mag exhibited potent anti-inflammatory and antioxidant effects, promoted epithelial repair, and improved therapeutic outcomes in DSS and TNBS colitis models. Mechanistically, it restored SCFA levels, epithelial barrier function, and gut microbiota homeostasis. Overall, this butyrate self-supplying nanoplatfom shows strong potential for colon-targeted combinational therapy of IBD, with further optimization and safety evaluation warranted.

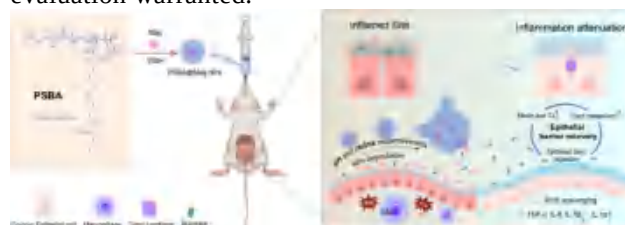


Fig. 1. Magnolol-incorporated pH and redox dual responsive butyrate-based polymeric nanoparticles (PSBA@Mag) as an oral nanomedicine to treat inflammatory bowel disease by improving epithelial barrier repair and inflammation mitigation.

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Directional Microinjection Driven by Porous Metamaterials for Robust and Conformal Drug Delivery in Deep Tissues

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Key words: biological barriers, drug delivery, jets, porous materials, ultrasonic cavitation

Introduction:

While biotherapeutics are widely utilized, their *in vivo* bioavailability is severely restricted by physiological barriers. Effectively delivering therapeutic macromolecules into deep tissues represents a major challenge. Thus, developing rapid, conformal transportation strategies that adapt to individualized anatomical geometries remains a critical unmet need. Existing delivery approaches face distinct inherent limitations: nanomedicine-based passive diffusion is often hindered by inefficient localized accumulation, whereas physical intervention strategies, such as conventional ultrasonic cavitation, are compromised in complex internal environments by severe energy attenuation and multi-directional acoustic flow. Here, we propose a directional microinjection strategy driven by a Janus porous metamaterial (JPM) to construct a localized acoustic-energy-harvesting platform under remote mild ultrasound activation. Combining structural cavitation reinforcement with directional liquid microjets can enable transient barrier opening without compromising tissue integrity and promote robust, conformal biotherapeutics delivery in deep tissues.

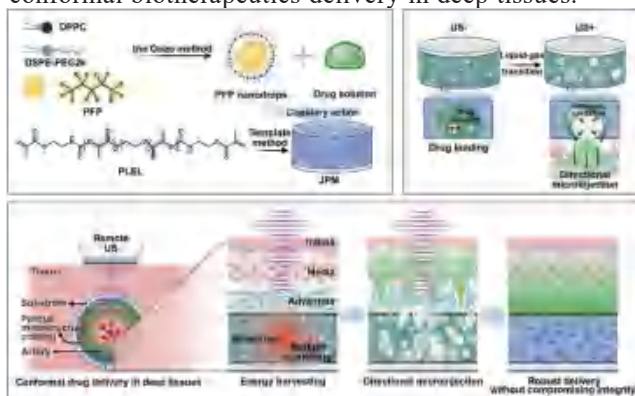


Fig. 1. Directional microinjection driven by JPM-amplified cavitation.

Materials & Methods:

By simultaneously incorporating perfluoropentane (PFP) and biotherapeutics within the porous metastructure, the JPM leverages mild ultrasound irradiation to trigger ultrasonic cavitation amplification, the generated directional microjets subsequently drive the conformal delivery of the drug payload.

Cavitation enhancement was quantified by microbubble observations and acoustic energy modeling. Penetration capability was evaluated using a laser

scanning confocal microscope to assess the delivery of diverse therapeutic agents across various tissue barriers. Furthermore, *in vivo* conformal delivery behavior and therapeutic efficacy were examined through adventitia and intima injury models.

Results & Discussion:

The porous JPM metastructure was prepared using a phase-separation-based template method, exhibiting a distinct Janus configuration with a low surface pore area in the top region and a highly interconnected porous network within the down region. This structure exhibited a remarkable acoustic confinement effect, under mild ultrasound excitation, a 20 μm -thick metamaterial film generated a microjet displacement of up to 2.02 mm, representing a 2-fold increase compared to conventional electrospun films. Utilizing this cavitation driven microinjection, the system achieved a 30-fold enhancement in BSA-FITC delivery efficiency across a 100 μm -thick dense pericardium within 5 minutes. *In vivo*, the JPM-mediated conformal delivery of miR-22 demonstrated exceptional vascular remodeling efficacy: it reduced adventitial hyperplasia by 64% in an adventitia injury model, and drastically slashed neointima thickness by 89% compared to the injury groups. Furthermore, applying the metastructure coating onto the surface of an interventional balloon revealed that remote ultrasound actuation for merely 3 cycles enabled macromolecules to uniformly and completely penetrate the intima and media.

Conclusions:

This study demonstrates that the ultrasound-activated JPM enables ultrafast and conformal trans-barrier microinjection of biotherapeutics into deep tissues. The localized acoustic-harvesting structure provided amplified cavitation and directional liquid jets, resulting in non-destructive macromolecular penetration and enhanced vascular regeneration *in vivo*. These findings not only support a cavitation-driven strategy for robust, barrier-preserving drug delivery, but more importantly, demonstrate the metastructure's excellent integration with medical balloon devices. By facilitating precise interventional therapies, this JPM platform paves a new avenue for conformal trans-barrier delivery and opens exciting opportunities for untapped clinical applications.

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Polyphenol Polymer/Cationic Hydroxyethylcellulose Nanocomplexes for Anti-Breast Cancer Effects

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Key words: Epigallocatechin gallate (EGCG), Hydroxyethylcellulose, Breast cancer, Drug/Gene Delivery System

Introduction: Breast cancer is one of the most prevalent cancers worldwide (1) and remains a leading cause of cancer-related mortality among women (2). Epigallocatechin gallate (EGCG), a major green tea polyphenol, exhibits anticancer activity by inhibiting proliferation and metastasis and regulating apoptosis-related genes, including FAS upregulation and Bcl-2 downregulation. However, its clinical application is limited by poor stability and low bioavailability. To overcome these limitations, we developed EGCG-conjugated multifunctional nanocomplexes for sialic acid-overexpressing cancer-targeted delivery.

Materials & Methods: pPBA-EG polymer was synthesized by grafting EG-phenylboronic acid (PBA) conjugates onto poly(methyl vinyl ether-alt-maleic anhydride) (pMVMA) polymer. A cationic hydroxyethyl cellulose derivative (HECP2k) polymer was used as the gene/drug delivery carrier. For complex formation, pPBA-EG was first mixed with Bcl-2 siRNA or pDNA in ultrapure water by vortexing. The pre-mixture was then slowly added dropwise to HECP2k or HECP2k@Dox solution. All mixtures were gently pipetted and incubated to allow complex formation, yielding pPBA-EG containing nanocomplexes. This sequential assembly improved EG stability while preserving the high transfection efficiency of HECP2k. Anticancer efficacy was evaluated in breast cancer cell line MDA-MB-231 and doxorubicin-resistant breast cancer cell line MDA/Dox-RES.

Results & Discussion: Physicochemical characterization of the nanocomplexes was performed by measuring particle size distribution and zeta potential to evaluate cellular uptake efficiency. DLS analysis confirmed a uniform nanoscale size of approximately 200–300 nm, which is favorable for efficient cellular internalization. The nanocomplexes exhibited positive zeta potential values, while a noticeable reduction in surface charge was observed after pPBA-EG inclusion, indicating successful surface modification without compromising colloidal stability. Compact nucleic acid condensation was verified by agarose gel electrophoresis and a PicoGreen assay. The nanocomplexes showed minimal cytotoxicity and effectively overcame drug resistance through enhanced cellular uptake via sialic acid targeting in MDA-MB-231 cells, while also exhibiting potent anticancer effects in Dox-resistant cancer cells. Furthermore, MDA-MB-231 cells treated with the nanocomplexes showed significant upregulation of the FAS gene and downregulation of the Bcl-2 gene, indicating apoptosis-mediated cell death induced by siRNA, Dox, and EG (Figure 1).

Conclusions: In conclusion, the pPBA-EG/HECP2k@Dox/siRNA nanocomplexes enabled efficient co-delivery of Dox, siRNA, and EG while improving EG stability and cellular uptake through sialic acid targeting. This multifunctional platform effectively induced apoptosis and overcame drug resistance, demonstrating strong potential as a therapeutic strategy for sialic acid-overexpressing breast cancer.

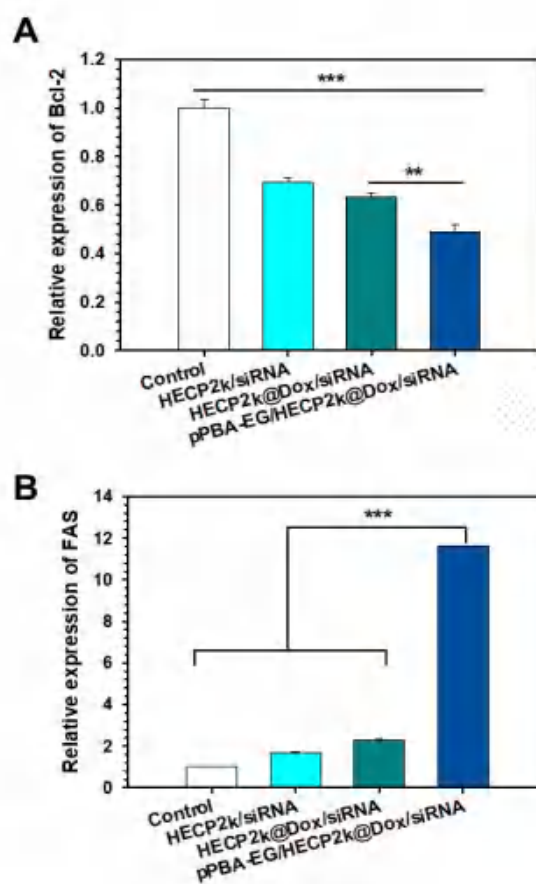


Fig. 1. qPCR analysis of apoptosis-related gene expression in MDA-MB-231 cells. (A) Bcl-2 and (B) FAS mRNA levels. Gene expression levels were normalized to GAPDH, and analyzed using the $2^{-\Delta\Delta CT}$ method. (Statistical significance: *P < 0.05, **P < 0.01, ***P < 0.001.)

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Mitochondria-targeted Cationic Hydroxyethylcellulose Gene Delivery System for Cancer Therapy

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Key words: Mitochondria, Mitochondria targeting, Mitochondrial gene delivery

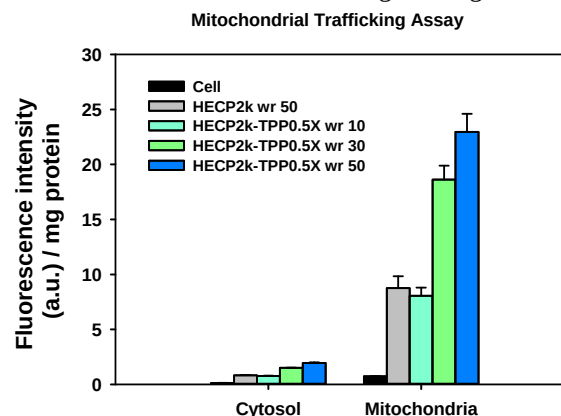
Introduction: Mitochondria serve as central metabolic hubs in cancer cells, making mitochondrial targeting an attractive therapeutic strategy by overcoming drug efflux, disrupting energy metabolism, and restoring apoptosis [1]. However, this approach is limited by the high negative membrane potential and hydrophobic inner membrane of mitochondria [2]. Triphenylphosphonium (TPP) is a representative targeting moiety that enables efficient permeation and accumulation within mitochondria. Accordingly, a TPP-conjugated, biocompatible cellulose-based cationic polymer system was developed to enhance anticancer efficacy.

Materials & Methods: As a biocompatible cationic gene carrier, hydroxyethyl cellulose was oxidized and conjugated with polyethyleneimine (Mw 2000) according to previously reported methods (3). The synthesized HEC2k polymer was subsequently conjugated with various ratios of TPP and characterized by ¹H NMR and GPC. Polyplex formation with pDNA was evaluated using agarose gel electrophoresis and dynamic light scattering. In vitro cytotoxicity was assessed by the MTT assay in HeLa cells. Cellular uptake of polyplexes formed with YOYO-1 labeled pDNA was quantified by flow cytometry. Mitochondrial and cytosolic fractions were isolated using a mitochondrial fractionation kit via differential centrifugation, and intracellular localization was analyzed using a microplate reader and normalized by a BCA assay.

Results & Discussion: ¹H NMR analysis confirmed successful TPP conjugation to HEC2k synthesized at 0.5X, 1X, and 2X molar ratios relative to PEI, corresponding to HEC2k:TPP ratios of 1:0.56, 1:1.40, and 1:2.50, respectively. GPC analysis further verified the molecular weight increase after TPP conjugation and confirmed successful purification. MTT assays showed noticeable cytotoxicity for HEC2k-TPP 1X and 2X, whereas HEC2k-TPP 0.5X exhibited acceptable biocompatibility and was therefore selected for subsequent experiments. Agarose gel electrophoresis demonstrated stable polyplex formation from a polymer/pDNA weight ratio of 0.5. DLS analysis revealed stable particle sizes of approximately 200–300 nm with a positive zeta potential of around +40 mV. Flow cytometry demonstrated cellular uptake

efficiencies above 90% across all tested polymer/pDNA weight ratios (10–50), exceeding those of HEC2k. Mitochondrial trafficking assays indicated comparable mitochondrial accumulation to HEC2k at a weight ratio of 10, whereas substantially enhanced mitochondrial accumulation was observed at weight ratios of 30 and 50.

Conclusions: In this study, a TPP-conjugated, biocompatible cellulose-based cationic polymer was developed for mitochondria-targeted gene delivery. The optimized HEC2k-TPP system showed efficient polyplex formation, high cellular uptake, and enhanced mitochondrial accumulation with acceptable biocompatibility. These results indicate its potential as an effective mitochondria-targeted gene delivery



platform for cancer therapy.

Fig. 1. Quantification of intracellular mitochondrial trafficking at various weight ratios

Figure 1 shows quantitative mitochondrial trafficking of HEC2k-TPP 0.5X in HeLa cells. No significant difference was observed in the cytosolic fraction. In contrast, mitochondrial accumulation was comparable to HEC2k at a weight ratio of 10 but increased more than twofold at ratios of 30 and 50.

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Dendrigrated Poly-L-Lysine modified hydroxyethyl cellulose for non-viral gene delivery

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Key words: gene delivery systems, hydroxyethyl cellulose, dendrigrated poly-L-lysine, serum stability

Introduction: Non-viral gene delivery systems have been studied as safer alternatives to viral vectors; however, widely used polycations such as polyethyleneimine exhibits high cytotoxicity and poor biodegradability despite their high transfection efficiency. Cellulose-based polymers offer excellent biocompatibility and structural tunability but generally exhibit limited gene delivery efficiency. A hydroxyethyl cellulose–dendrigrated poly-L-lysine (HECDGL) was designed as a biodegradable polymeric gene carrier that integrates a polysaccharide backbone with efficient nucleic acid condensation capability.

Materials & Methods: Hydroxyethyl cellulose was oxidized to introduce aldehyde groups, followed by reductive amination to conjugate DGL, yielding HECDGL conjugates with different grafting densities (HECDGL1X and 2X). Polymer synthesis was confirmed using ^1H NMR spectroscopy and gel permeation chromatography. Polyplexes were prepared via electrostatic complexation with plasmid DNA. DNA condensation was assessed by agarose gel retardation assays, while particle size and zeta potential were measured using dynamic light scattering. Polyplex morphology was visualized by transmission electron microscopy. Cytotoxicity was assessed using MTT assays, and in vitro transfection efficiency was evaluated by luciferase reporter assays in both no serum and serum conditions with normalization to total protein content determined by BCA assays.

Results & Discussion: ^1H NMR and GPC analyses confirmed the successful conjugation of DGL onto the HEC backbone, with controlled grafting densities for HECDGL1X and 2X. Both conjugates efficiently formed nanoscale polyplexes with pDNA, exhibiting complete DNA retardation in agarose gel electrophoresis. Dynamic light scattering revealed stable polyplexes occurred at pDNA weight ratios of 5 or higher; particles showed average diameters in the range of 150–300 nm and zeta potentials of +8 to +24 mV, which were further confirmed by TEM imaging showing compact, spherical structures. Cytotoxicity studies demonstrated both HECDGL1X and 2X exhibited lower toxicity compared to DGL. In no serum condition, synthesized polyplexes achieved meaningful gene expression levels, although their transfection efficiency was slightly lower than that of PEI25k and DGL controls; they showed higher transfection efficiency in the serum condition.

Conclusions: The HECDGL provides a biocompatible gene delivery platform that partially preserves the

transfection efficiency of conventional polycations while reducing cytotoxicity. These results demonstrate the potential of DGL as an effective alternative to PEI in polysaccharide-based delivery systems, with its dendritic structure expected to improve cellular uptake and enhance gene delivery performance.

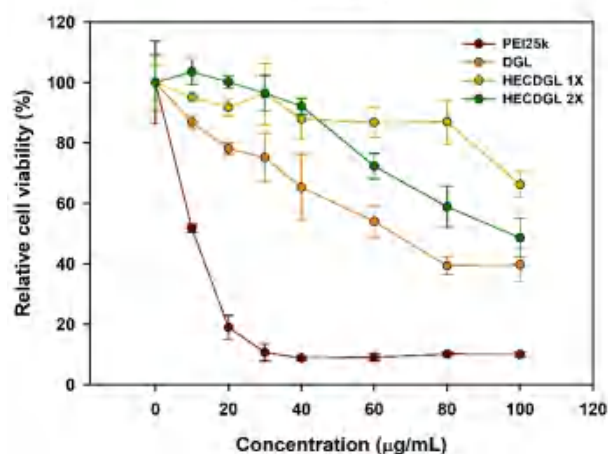


Fig. 1. MTT assay results of HECDGL polymers on HeLa cells; PEI25k and DGL were used as controls.

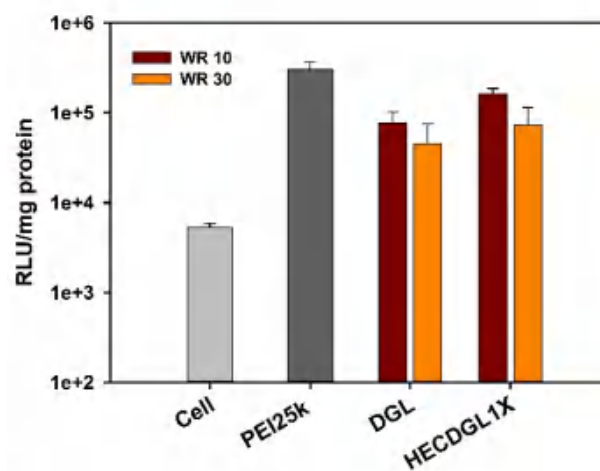


Fig. 2. Transfection efficiency of HECDGL1X and 2X polyplexes in HeLa cells in serum condition, 10% FBS (weight ratio, wr=10, 30); PEI25k (wr=1) and DGL (wr=10, 30) were used as controls.

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Curcumin polymer-decorated cationic hydroxyethylcellulose nanocomplexes for lung cancer therapy

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Key words: curcumin, phenylboronic acid, gene-drug co-delivery, cancer therapy, polyplex

Introduction: Lung cancer is a fatal disease with low survival rates, due to late diagnosis and therapeutic resistance. (1) In particular, the multidrug resistance inherent to lung cancer significantly limits the efficacy of existing therapies. Curcumin, a polyphenolic compound, has been reported to inhibit P-glycoprotein expression, thereby increasing intracellular drug accumulation and inducing cancer cell death. (2) Accordingly, a polymer-based gene-drug nanocomplex delivery strategy is proposed to improve low solubility and chemical stability of curcumin.

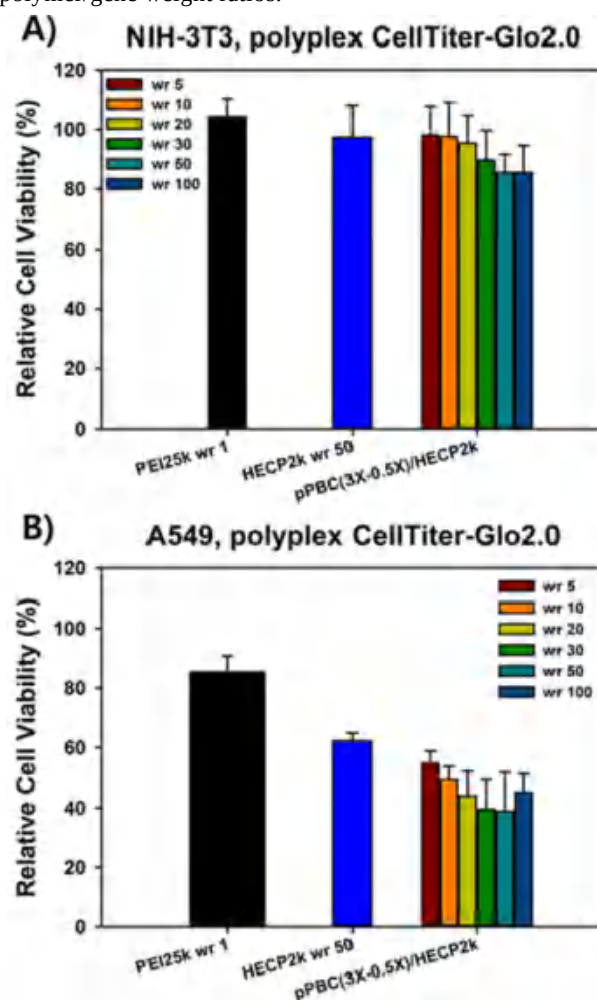
Materials & Methods: A polymeric delivery platform was designed by functionalizing a polymer backbone with phenylboronic acid (PBA) groups and conjugating curcumin to form polyPBA-CUR (pPBC). A gene-polymer polyplex was first prepared using a cationic polymer and therapeutic gene, followed by surface coating of pPBC to enable simultaneous gene and curcumin delivery. The chemical composition of pPBC was analyzed by ^1H NMR, and curcumin-PBA interaction was qualitatively assessed by absorption spectroscopy. Polyplex morphology and size variation before and after pPBC coating were evaluated using transmission electron microscopy and dynamic light scattering. Cytotoxicity was assessed using the CellTiter-Glo assay, cellular uptake and apoptosis were analyzed by flow cytometry in representative cancer cell lines.

Results & Discussion: The degree of conjugation during pPBC synthesis was confirmed by ^1H NMR, revealing PBA and curcumin substitution levels of 54.5% and 7.3% per pMVMA backbone unit, respectively. Compared to free curcumin with a maximum absorbance at 430 nm, pPBC exhibited a red-shifted absorbance peak at 490 nm, indicating curcumin-boronic ester conjugation. Transmission electron microscopy and dynamic light scattering showed the formation of spherical polyplexes with stable hydrodynamic sizes of approximately 200 nm after pPBC coating. In cytotoxicity assays, pPBC polymer alone showed high cell viability (>90%) in both NIH-3T3 and A549 cells, whereas pPBC-coated polyplexes selectively reduced the viability of A549 lung cancer cells to 44% while maintaining >80% viability in normal cells. Furthermore, cellular uptake efficiency increased from approximately 80% for uncoated polyplexes to up to 92% following pPBC coating.

Conclusions: This study presents a polymer-based gene-drug co-delivery platform that enables stable curcumin conjugation and enhanced intracellular delivery. The system exhibits

selective cytotoxicity toward lung cancer cells while maintaining low toxicity in normal cells. This approach offers a promising strategy to improve the therapeutic potential of hydrophobic anticancer agents.

Fig. 1. Cytotoxicity evaluation of pPBC coated polyplexes in normal and cancer cell lines. Relative cell viability of (A) NIH-3T3 normal fibroblasts and (B) A549 lung cancer cells after treatment with pPBC coated polyplexes at various polymer/gene weight ratios.



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Hyaluronic Acid-Modified LNPs Utilize Neutrophil Hitchhiking for Targeted Treatment of Bone-Metastatic 4T1 Tumors Zixin Liao, Ye Cao*, Hong Wang *

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Key words: Lipid nanoparticles; Drug delivery; Gene therapy; Neutrophil hitchhiking

Introduction: To address challenges such as chemotherapy resistance and poor targeting in breast cancer bone metastasis treatment, this study developed an efficient bone marrow-targeted drug delivery system. We constructed hyaluronic acid (HA)-modified lipid nanoparticles (BP-HLNPs) co-loaded with Bcl-2 siRNA and paclitaxel (PTX). These LNPs were further integrated with neutrophil hitchhiking to achieve efficient drug accumulation in the bone marrow.

Materials & Methods: LNPs co-encapsulating PTX and Bcl-2 siRNA were prepared using a microfluidic method. HA was then attached to the surface via electrostatic adsorption. The cellular uptake, lysosomal escape capability, and in vitro anti-tumor activity of the nanoparticles were validated using the 4T1 breast cancer cell model. Leveraging the bone marrow homing property of aged neutrophils, we constructed an LNP-neutrophil delivery system (BP-HLNP@NEs). A 4T1 breast cancer bone metastasis model in Balb/c mice was established to assess bone marrow targeting ability and anti-tumor efficacy.

Results & Discussion: The optimal preparation conditions were N/P=8, flow rate ratio=5, and drug-to-lipid ratio = 1:30 (w:w). The resulting HA-modified BP-HLNPs had a particle size of (177.28 ± 2.41) nm, a polydispersity index of (0.198 ± 0.10) , and a siRNA encapsulation efficiency of $(91.37 \pm 0.47)\%$, with good physiological stability. BP-HLNPs enabled efficient CD44 receptor-mediated cellular uptake $(62.64 \pm 0.84)\%$ and completed lysosomal escape within 6 h. Optimal binding with neutrophils occurred at 37°C for 0.5 h with a particle-to-cell ratio of 1:20000, achieving a binding efficiency of $(98.64 \pm 2.34)\%$. In vivo, BP-HLNP@NEs reduced non-specific liver and spleen uptake, increased bone marrow accumulation to $(50.26 \pm 1.29)\%$, inhibited bone metastasis proliferation, alleviated bone erosion, and blocked bone-to-lung metastasis. Mechanistically, the system synergistically downregulated Bcl-2, inhibited the NF-κB/P-gp pathway, upregulated Caspase-3, induced mitochondrial depolarization, and promoted ROS accumulation, leading to efficient tumor cell apoptosis.

Conclusions: In summary, we successfully developed an HA-modified, dual-drug loaded LNP-neutrophil delivery system that overcomes the bone marrow delivery barrier and significantly enhances bone marrow targeting and antitumor efficacy. By synergistically combining chemotherapy and gene therapy, this system reverses drug resistance, induces tumor apoptosis, and exhibits favorable biosafety and bone-protective effects. This biomaterial-enabled neutrophil-hitchhiking platform offers a promising strategy for the targeted treatment of breast cancer bone metastasis and other bone marrow malignancies

Bilayer Microneedles Patch Potentiate Methotrexate Therapy in Psoriasis via Hypoxia/ROS Microenvironment Remodeling

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Key words: psoriasis, hypoxia, microneedles, methotrexate, nanozymes

Introduction: Psoriasis is a chronic inflammatory skin disease characterized by epidermal keratinocyte hyperproliferation and dermal inflammatory cell infiltration. The high oxygen consumption of keratinocytes and inflammatory cells, together with diffusion limitation caused by epidermal thickening, renders psoriatic lesions hypoxic. Hypoxia is further coupled with excessive reactive oxygen species (ROS) generated by inflammatory infiltration, forming a vicious cycle that drives disease progression. In this study, we found that the hypoxia microenvironment markedly reduces keratinocyte sensitivity to methotrexate (MTX), a classical anti-psoriasis drug¹. To overcome this limitation, we developed biphasic-release bilayer microneedles patch, in which the rapidly MTX-releasing proximal base layer targeted the epidermis for early intervention, while the nanozyme-loaded ROS-responsive hydrogel distal tips penetrated into the dermis to continuously reduce ROS level and alleviate hypoxia, thereby enhanced the therapeutic efficacy of MTX. This microneedle system provides a new strategy for psoriasis treatment.

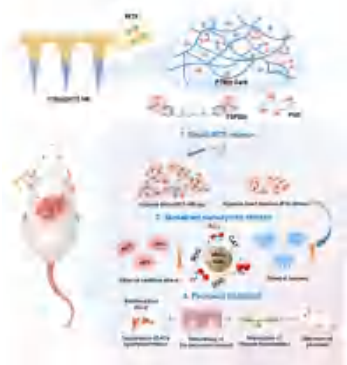


Fig.1. Schematic illustration of the bilayer microneedles patch for psoriasis treatment.

Materials & Methods: Manganese dioxide nanozymes (MnO₂ NMs) were prepared via a facile one-pot method. The bilayer microneedles patch was fabricated through a three-step micro-molding process. The distal tips were composed of ROS-responsive hydrogel formed by the crosslinking between polyvinyl alcohol (PVA) and TSPBA (a boronic acid-containing compound), and loaded with MnO₂ NMs. The proximal base layer was consisted of polyvinyl pyrrolidone (PVP) loaded with MTX. Biphasic-release behavior was evaluated by ICP-MS and UV-Vis. Finally, in vivo therapeutic

efficacy of microneedles patch were evaluated by H&E staining, immunofluorescence staining, immunohistochemical staining, flow cytometry, and ELISA in an imiquimod-induced mouse psoriasis model.

Results & Discussion: In vitro cell experiments and transcriptomic analysis showed that, compared with normoxic conditions, hypoxia weakened the inhibitory effect of methotrexate on keratinocytes. MnO₂ nanozymes exhibited excellent ROS-scavenging and oxygen-generating capabilities. Owing to its rapidly dissolving base and ROS-responsive hydrogel tip, the microneedles patch showed a biphasic drug-release profile, enabling rapid MTX release within 5 min and sustained MnO₂ nanozyme release over 48 h. In vivo studies further demonstrated that microneedle treatment reduced ROS levels in lesional tissue, downregulated the expression of the hypoxia marker HIF-1 α , the proliferation-associated marker Ki-67, and the inflammatory cytokines TNF- α and IL-17A, and promoted Treg cell expansion as well as M2 macrophage polarization. By relieving hypoxia and thereby enhancing the therapeutic efficacy of methotrexate, this microneedles patch achieved the greatest alleviation of psoriatic symptoms, outperforming the methotrexate-only group, with epidermal thickness reduced to a level comparable to that of the normal group.

Conclusions: In summary, we identified hypoxia as a key pathological factor limiting the therapeutic efficacy of MTX in psoriasis. To overcome this limitation, we developed a bilayer microneedles patch that integrated rapid epidermal MTX delivery with sustained dermal nanozyme release. This patch remodeled the hypoxia/ROS microenvironment, restored immune homeostasis, and enhanced the therapeutic efficacy of MTX against psoriasis. This work provides a new therapeutic strategy for psoriasis treatment.

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Click-Crosslinked Hyaluronic Acid Dressings Incorporating an SDF-1 Mimetic Peptide Enable Concurrent Recruitment of hMSCs and mMSCs for Improved Wound Healing

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Key words: Click-crosslinked hydrogel, SDF-1 mimetic peptide, Stem cell recruitment, Wound healing, Tissue regeneration

Introduction: Stem cell-based wound healing is often limited by insufficient recruitment and retention of stem cells at the injury site, leading to suboptimal regenerative outcomes. In particular, the lack of a sustained chemotactic gradient restricts effective cell homing and long-term therapeutic efficacy. Although biomaterial-based dressings have been explored as delivery platforms to overcome these limitations, maintaining both sustained chemotactic signaling and structural stability remains challenging. In this study, we developed a click-crosslinked hyaluronic acid (Cx-HA) dressing incorporating an SDF-1 mimetic peptide (SMP) to enhance stem cell recruitment and improve tissue regeneration.

Materials & Methods: Hyaluronic acid was chemically modified and crosslinked via click chemistry using DBCO and azide functional groups to form a structurally stable dressing (Cx-HA). The hydrogel precursor solution was cast into a mold, followed by crosslinking and subsequent lyophilization to obtain a porous dressing structure. SMP was physically incorporated into the dressing to enable sustained release and formation of a chemotactic gradient. The physicochemical properties of the dressing were characterized using standard analytical methods. In vitro migration assays using mesenchymal stem cells (MSCs) were conducted to evaluate chemotactic effects. For in vivo evaluation, the dressing was applied to a full-thickness skin wound model, and human mesenchymal stem cells (hMSCs) were intravenously injected via the tail vein. Subsequently, tissues were harvested at predetermined time points for histological and molecular analyses.

Results & Discussion: The Cx-HA dressing exhibited high structural stability and maintained its integrity under physiological conditions. Sustained release of SMP significantly enhanced MSC migration compared to controls, indicating effective chemotactic signaling. In vivo results demonstrated accelerated wound closure, improved retention of injected stem cells, and enhanced tissue regeneration, including increased collagen deposition and angiogenesis.

Immunofluorescence analysis revealed increased expression of CXCR4, CD29, and CD31 at the wound site, indicating sequential activation of chemotaxis, cell adhesion, and angiogenesis. In particular, enhanced CD29 expression suggested improved stem cell retention within the regenerated tissue. Gene expression analysis by RT-PCR further confirmed the upregulation of these markers over time, supporting coordinated stem cell-mediated regenerative responses. Notably, SMP showed comparable or superior efficacy to SDF-1, highlighting its potential as a stable and effective alternative chemotactic factor for regenerative applications.

Conclusions: The SMP-incorporated Cx-HA dressing effectively promotes stem cell recruitment and enhances wound healing by improving cell migration, retention, and subsequent tissue regeneration. In particular, the sustained release of SMP contributes to the formation of a stable chemotactic microenvironment, supporting enhanced collagen deposition and angiogenesis at the wound site. However, further studies are required to evaluate the maturity and long-term functionality of newly formed blood vessels to fully validate its therapeutic potential and clinical applicability.

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Dual-Aggregation-Enhanced Photodynamics of NIR-II Photosensitizer for Targeted Therapy of Mucosal Mycoses

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Key words: aggregation-induced emission; second near-infrared; photodynamic therapy; fungal infection; phage display

Introduction: Mucosal mycoses are difficult to treat precisely because pathogenic fungi coexist with commensal microorganisms that are essential for local homeostasis. Although photodynamic therapy (PDT) is effective against microbes, its clinical translation for mucosal fungal infections is limited by poor selectivity and collateral damage to beneficial microbiota. We therefore sought to develop a fungus-targeted photodynamic platform that selectively eradicates *Candida albicans* while preserving surrounding commensals.

Materials & Methods: A *Candida albicans*-binding filamentous phage (R9) was identified by phage display and electrostatically assembled with a second near-infrared (NIR-II) aggregation-induced emission (AIE) photosensitizer, TPASN, to construct R9@T. The platform was characterized by optical spectroscopy, zeta potential analysis, FTIR, and electron microscopy. Targeting and antifungal activity were evaluated by fluorescence colocalization, colony counting, live/dead staining, and ROS assays under 660 nm irradiation. Mechanistic studies included molecular simulation and transcriptomic profiling. Therapeutic efficacy and microbiota preservation were assessed in murine models of fungal vaginitis and oral candidiasis.

Results & Discussion: R9@T selectively accumulated on *C. albicans* but showed negligible binding to *Lactobacillus* or mammalian cells. Under 660 nm irradiation, R9@T eradicated >99.9% of fungi *in vitro* within 5 min, outperforming free TPASN and the non-targeted control R0@T. Mechanistically, its enhanced photodynamic activity arose from a hierarchical dual-aggregation process: TPASN first aggregated on the phage scaffold, restricting intramolecular motion and promoting intersystem crossing; subsequent R9-mediated accumulation on the fungal surface further amplified local ROS generation and shortened the ROS working distance. Compared with free TPASN, R9@T produced approximately 2-fold higher type I/II ROS signals and triggered stronger oxidative-stress and metabolic-collapse signatures in transcriptomic analysis. In both fungal vaginitis and oral candidiasis models, R9@T-based PDT reduced fungal burden, alleviated inflammation, improved tissue repair, and maximally preserved local

beneficial microorganisms.

Conclusions: This work establishes a phage-guided, dual-aggregation-enhanced photodynamic strategy for precision treatment of mucosal mycoses. By coupling fungal targeting with spatially confined ROS generation, R9@T achieves potent antifungal efficacy while minimizing disruption of commensal microbiota, providing a promising design paradigm for microbiome-sparing anti-infective therapy.

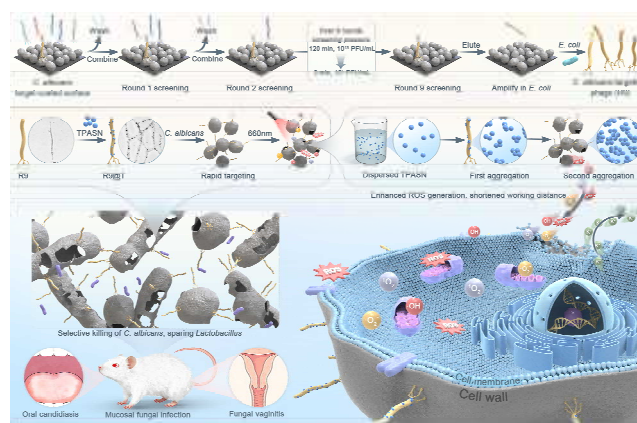


Fig. 1. Scheme 1. Schematic illustration of the screening of *C. albicans*-targeting phage (R9), the synthesis process of R9@T, its enhanced fungicidal activity via a dual-aggregation mechanism, and the applications of R9@T in the selective elimination of *C. albicans* in murine models of fungal vaginitis and oral candidiasis, while preserving beneficial *Lactobacillus*.

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Bioorthogonal PROTAC-Mediated Protein Degradation to Modulate Macrophage Phenotype and Lipid Metabolism for Atherosclerosis Therapy

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Abstract

Atherosclerosis is a progressive inflammatory disease in which macrophages play a central role in plaque formation and destabilization. Current anti-inflammatory drugs, such as statins and monoclonal antibodies, exhibit limited efficacy due to resistance, systemic immunosuppression, and their inability to target “undruggable” proteins. Proteolysis-targeting chimeras (PROTACs) provide an event-driven strategy for selective protein degradation, enabling sustained therapeutic effects and overcoming resistance. Trim24, an E3 ubiquitin ligase involved in Stat6 acetylation and macrophage polarization, represents a promising therapeutic target; however, systemic degradation may cause off-target toxicity owing to broad tissue expression. To address this, we developed a macrophage-specific bioorthogonal PROTAC (Bio-PROTAC) system for targeted Trim24 degradation. In this design, tetrazine-modified mannose (Man-Tz) selectively labelled macrophages and reacted with trans-cyclooctene–caged dTRIM24 (TCO-dTRIM24-TCO), ensuring localized release within plaque-associated macrophages. The released dTRIM24 triggered Trim24 degradation, thereby reprogramming macrophages toward an anti-inflammatory state, reducing ox-LDL uptake, and promoting cholesterol efflux via the PPAR γ –ABCA1 pathway. Consequently, plaque burden was alleviated in an atherosclerosis model. This study demonstrates that integrating bioorthogonal chemistry with PROTAC technology enables precise, efficient, and safe therapeutic modulation of atherosclerosis.

Keywords: Atherosclerosis; Macrophage; Trim24; PROTACs; Bioorthogonal chemistry

Introduction

Atherosclerosis, a chronic cardiovascular disease driven by dyslipidemia and inflammation, is characterized by plaque formation and life-threatening complications like myocardial infarction and stroke [1]. Inflammatory M1 macrophages play a pivotal role in disease progression, as they exacerbate inflammation, promote necrotic core formation, and reduce plaque stability—making macrophage polarization modulation a promising therapeutic strategy [2].

Current anti-inflammatory therapies (e.g., statins, canakinumab) rely on passive inhibition, with limitations including drug resistance, adverse effects, and difficulty targeting “undruggable” proteins [3]. Proteolysis-targeting chimeras (PROTACs) offer an “event-driven” alternative by inducing ubiquitination and degradation of pathogenic proteins, addressing these drawbacks. Trim24, an E3 ubiquitin ligase, restrains M2 polarization (anti-inflammatory) by regulating Stat6 acetylation, emerging as a key therapeutic target. The Trim24-degrading PROTAC dTRIM24 shows potential but risks off-target toxicity via systemic delivery [4].

Bioorthogonal chemistry (e.g., tetrazine-trans-cyclooctene reaction) enables precise drug delivery through “artificial targets” without disrupting endogenous processes. Herein, we designed a bioorthogonal PROTAC (Bio-PROTAC) system: mannose-tetrazine (Man-Tz) selectively targets macrophages, forming surface “artificial targets” that react with TCO-protected dTRIM24, facilitating site-specific release. This triggers Trim24 degradation, promoting M2 polarization, reducing ox-LDL uptake, and enhancing cholesterol efflux via the PPAR γ –ABCA1 pathway—ultimately suppressing atherosclerosis and stabilizing

plaques. This integration of bioorthogonal chemistry and PROTAC technology addresses systemic delivery challenges, advancing precision therapy for cardiovascular disease (Fig. 1)

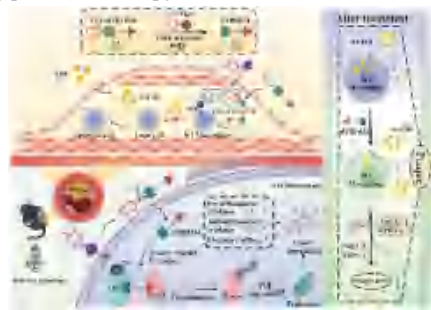


Fig. 1 Targeted bioorthogonal activation of TCO-dTRIM24 via Man-Tz on plaque macrophages induces Trim24 degradation, reprograms macrophages toward an anti-inflammatory phenotype, and suppresses atherosclerotic plaque progression.

Materials & Methods

To achieve selective dTRIM24 release, macrophages overexpressing the mannose receptor (CD206) in atherosclerotic plaques were targeted [5]. Trans-cyclooctene (TCO)-protected dTRIM24 (TCO-dTRIM24-TCO) and mannose-tetrazine (Man-Tz) were synthesized per reported methods. The former releases dTRIM24 upon click reaction with tetrazine (Tz), while the latter serves as a macrophage-targeting moiety. Both compounds were purified and characterized via ¹H NMR, LC-MS, and HPLC. Man-Tz, synthesized via amidation, exhibited a 7:3 ratio of α - to β -anomers. TCO-dTRIM24-TCO, prepared by reacting dTRIM24 with TCO-PNP, was confirmed by a characteristic TCO olefin peak (~5.5 ppm) in ¹H NMR, yielding a bioorthogonal PROTAC prodrug with dual TCO modifications.

The click-triggered release efficiency was evaluated by incubating 1.0 mM TCO-dTRIM24-TCO with 3 mM Man-Tz in PBS (pH=7.4) (Figure 2C). HPLC analysis showed nearly complete consumption of TCO-dTRIM24-TCO within 30 minutes, with ~37% converted to active dTRIM24 (Figure 2D). Molecular docking revealed TCO-dTRIM24-TCO had a lower binding energy (-5.591 kcal/mol) to VHL/Trim24 than dTRIM24 (-7.942 kcal/mol) (Figures 2A, 2B), confirming its stable prodrug state. Both compounds remained stable in PBS for at least 3 hours.

Macrophage targeting was verified using RAW 264.7 macrophages (Figure 2E). Following co-incubation with Man-Tz and treatment with TCO-Cy5, RAW 264.7 macrophages exhibited strong red fluorescence, while human umbilical vein endothelial cells (HUVECs) showed no significant enhancement. Quantitative analysis (Figure 2F) confirmed Man-Tz's specific binding to macrophages, which was abolished by D-mannosamine pre-incubation. This validated the bioorthogonal system's macrophage specificity.

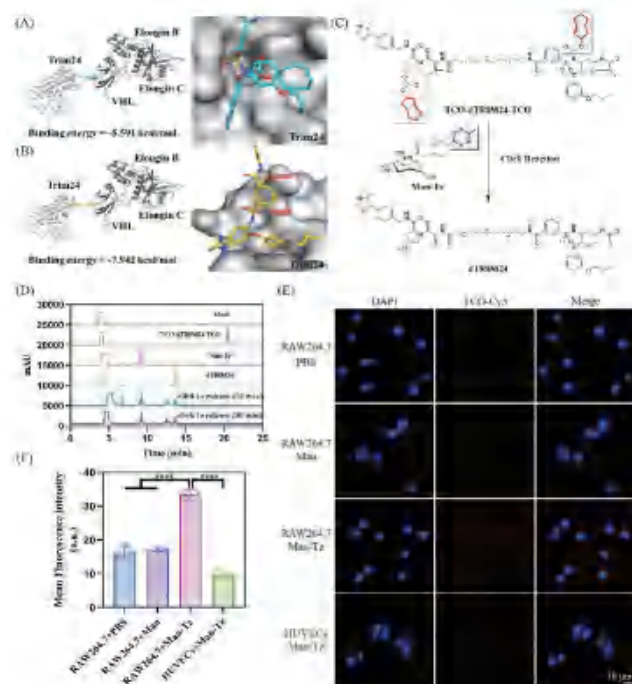


Figure 2: Summary of the binding energies and conformations of TCO-dTRIM24-TCO and dTRIM24 within the Trim24-VHL complex, the click-to-release reaction between TCO-dTRIM24-TCO and Man-Tz and its monitoring, and confocal fluorescence imaging with quantification of Man-Tz macrophage targeting. (A) Binding energy of TCO-dTRIM24-TCO in the Trim24-VHL complex and its conformation on Trim24. (B) Binding energy of dTRIM24 in the Trim24-VHL complex and its conformation on Trim24. (C) Schematic illustration of the click-to-release reaction between TCO-dTRIM24-TCO and Man-Tz. (D) Monitoring the reaction between TCO-dTRIM24-TCO and Man-Tz. (E) Confocal fluorescence imaging of the Man-Tz macrophage-targeting assay.

(F) Quantification of fluorescence intensity from (E), shown as a bar graph. Values are shown as mean $\pm$ SD (n = 3).

Results & Discussion

We evaluated the *in vivo* therapeutic efficacy of Bio-PROTAC against atherosclerosis. ApoE^{-/-} mice were fed a high-fat, high-cholesterol diet for 8 weeks (Figure 3A), and atherosclerotic plaque burden in the entire aorta and abdominal root sections was assessed by Oil Red O staining. Results showed that Bio-PROTAC treatment markedly reduced the total plaque area. In contrast, mice treated with saline or TCO-dTRIM24-TCO exhibited extensive aortic plaques, indicating that TCO-protected dTRIM24 remained pharmacologically inert *in vivo* and did not influence plaque formation (Figure 3B). Quantitative analysis demonstrated Oil Red O-positive areas of 38%, 45%, and 30% in the free dTRIM24, TCO-dTRIM24-TCO, and Bio-PROTAC groups, respectively, compared to 48% in the saline control. This indicated that Bio-PROTAC treatment markedly reduced plaque burden, showing a ~38% reduction compared with the saline control group (48% vs. 30%) and a ~33% reduction relative to the TCO-dTRIM24-TCO group (45% vs. 30%) (Figure 3C). Consistently, lipid deposition in abdominal aortic sections was approximately 20% and 21% in the saline and TCO-dTRIM24-TCO groups, respectively, whereas Bio-PROTAC administration significantly decreased lipid accumulation to 5% (Figure 3D and 3E). Collectively, these Oil Red O staining results demonstrated that Bio-PROTAC effectively suppressed the progression of atherosclerotic plaques.

We further performed immunofluorescence analysis to evaluate macrophage infiltration and Trim24 protein levels within atherosclerotic plaques, aiming to elucidate the *in vivo* targeted degradation of plaque-associated Trim24 mediated by Bio-PROTAC. The results showed that Bio-PROTAC treatment markedly reduced the positive area of CD68 and Trim24 in abdominal aortic sections (CD68: $5.69 \pm 0.35\%$; Trim24: $5.05 \pm 0.82\%$) (Figure 3F-H). A consistent reduction was also observed in aortic valve sections (CD68: $4.10 \pm 0.23\%$; Trim24: $2.28 \pm 0.12\%$) (Figure 3I-K),

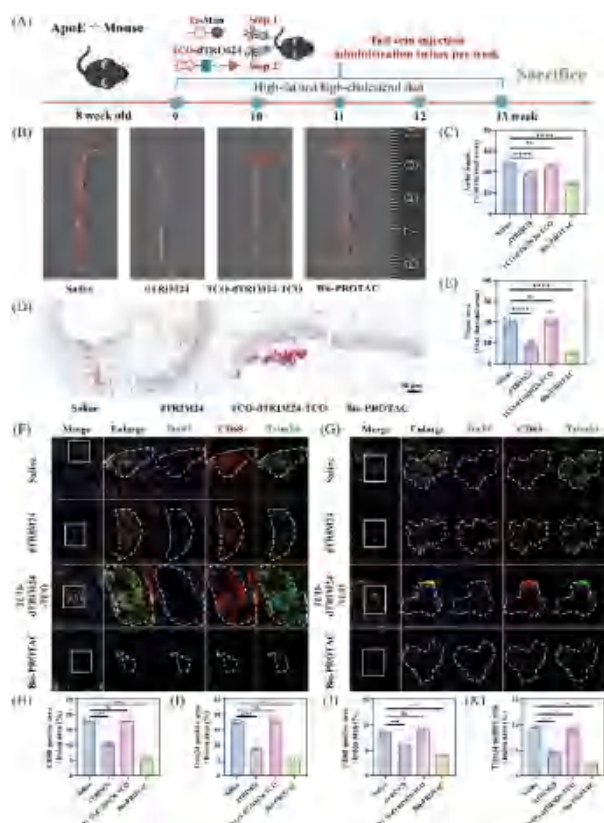


Figure 3: Effects of Bio-PROTAC on atherosclerotic plaque formation in ApoE^{-/-} mice. (A) Diagram depicting the atherosclerosis mouse model and the Bio-PROTAC treatment regimen. (B) Representative Oil Red O-stained images of aortas from ApoE^{-/-} mice subjected to various treatments. (C) Quantification of total aortic plaque burden expressed as the percentage of Oil Red O-positive area. Values are shown as mean $\pm$ SD ($n = 3$). (D) Oil Red O-stained images of abdominal aortic sections from ApoE^{-/-} mice under different treatment conditions. (E) Quantitative assessment of plaque area in abdominal aortic sections based on Oil Red O staining. Values are shown as mean $\pm$ SD ($n = 3$). (F) Fluorescence images of abdominal aortic sections stained with CD68 (red) and Trim24 (green) antibodies. (G) Quantitative analysis of CD68 fluorescence. (H) Quantitative analysis of Trim24 fluorescence. (I) Fluorescence images of aortic valve sections stained with CD68 (red) and Trim24 (green) antibodies. (J) Quantitative analysis of CD68 fluorescence. (K) Quantitative analysis of Trim24 fluorescence. Data in panels (H, I, K, L) are represented as the proportion of fluorescence-positive area relative to the plaque area. Values are shown as mean $\pm$ SD ($n = 3$).

Conclusions

The Bio-PROTAC platform provides a highly specific and effective strategy for the treatment of atherosclerosis. By enabling localized activation of dTRIM24 within lesions, it minimizes systemic off-target effects while promoting macrophage polarization toward the anti-inflammatory M2 phenotype and enhancing cholesterol efflux. These changes

translate into substantial inhibition of aortic plaque formation. This study establishes Bio-PROTAC as a promising therapeutic approach that integrates targeted protein degradation with site-specific drug activation, offering a novel avenue for precise and efficacious atherosclerosis therapy.

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