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REVIEW

Hydrogel-Based Immunomodulatory Strategies for Infected Bone Defects Regeneration: Remodeling the Osteoimmune Microenvironment and Future Perspectives

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Abstract: Infected bone defects remain a major challenge in orthopaedic and reconstructive medicine. Conventional strategies often fail to achieve reliable long-term outcomes lack of adequately addressing the hostile osteoimmune microenvironment. In recent years, hydrogel-based biomaterials have emerged as highly promising platforms for infected bone defect regeneration due to their injectability, defect conformity, extracellular matrix-like architecture, and tunable physicochemical properties. Importantly, hydrogels are evolving from passive drug carriers into dynamic immunomodulatory systems capable of releasing bioactive agents in a controlled manner, reprogramming immune metabolism, and coordinating angiogenic and osteogenic repair. This review summarizes recent progress in hydrogel-based immunomodulatory strategies for infected bone defects from the perspective of osteoimmune microenvironment remodeling. Four major design paradigms include programmed transformation of the osteogenic microenvironment, metabolic reprogramming of the infectious niche, spatiotemporally staged immune–osteogenic regulation, and photothermal-immunomodulatory therapy. However, the translation of these systems faces challenges including biosafety concerns, batch-to-batch variability, manufacturing complexity, and regulatory intricacies. Despite these hurdles, hydrogel-based immunomodulatory platforms represent a clinically relevant strategy for integrated infection control and functional bone regeneration. Future perspectives are proposed, emphasizing multicellular osteoimmune network engineering, disease-specific precision hydrogels, and artificial intelligence (AI)-assisted biomaterial design. Overall, hydrogel-based immunomodulatory systems represent a promising direction for achieving integrated infection control and functional bone regeneration in infected bone defects.

Keywords: hydrogel biomaterials, osteoimmune microenvironment, immunometabolic regulation, stage-specific bone regeneration, multifunctional nanocomposite hydrogels

Introduction

Infected bone defects remain one of the most formidable challenges in orthopaedic and reconstructive medicine because they combine two biologically antagonistic conditions including persistent infection and impaired tissue regeneration.[1,2] Unlike aseptic bone injuries, these defects are characterized not only by loss of structural integrity, but also by bacterial colonization, biofilm formation, prolonged inflammation, oxidative stress, vascular disruption, and dysregulated bone remodeling.[3] Under such conditions, conventional clinical strategies, including systemic antibiotics, repeated debridement, bone grafting, and implant-based reconstruction, often fail to achieve predictable long-term healing.[4–6] The difficulty lies in the fact that infected bone repair is not simply a matter of filling a defect or eliminating bacteria.[7] It requires coordinated control of infection, resolution of pathological inflammation, restoration of vascular supply, and

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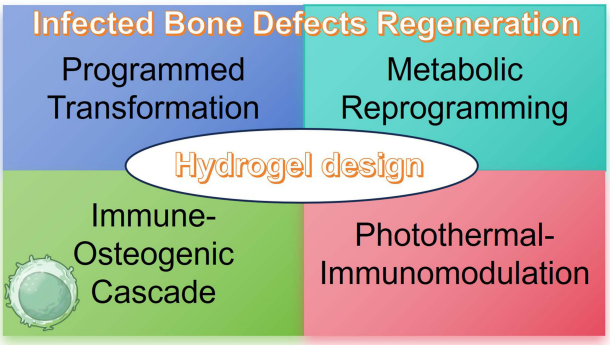
Graphical Abstract



reactivation of osteogenesis within a hostile local niche.[8] This clinical reality has driven a conceptual shift in the field from osteogenesis-centered repair toward osteoimmunology-guided regeneration.

Bone healing is now understood as a tightly regulated process governed by reciprocal interactions among immune cells, skeletal cells, stromal cells, cytokines, metabolites, and extracellular matrix cues.[9] In infected defects, this osteoimmune crosstalk becomes profoundly disturbed.[10] Excessive or unresolved inflammatory activation can suppress osteoblast function, promote osteoclast-mediated bone resorption, impair angiogenesis, and prevent the establishment of a regenerative microenvironment.[11] At the same time, premature or indiscriminate immunosuppression may weaken host defense and allow persistent bacterial survival.[12] Therefore, the key therapeutic challenge is no longer merely to promote bone formation, but to reshape the osteoimmune microenvironment.[13] This perspective has elevated immunomodulation from an auxiliary consideration to a central design principle in biomaterials for infected bone defect treatment.[14]

Among candidate biomaterial platforms, hydrogels are uniquely suited for this purpose.[15,16] Their high water content, tunable physicochemical properties, injectability, biocompatibility, and structural similarity to native extracellular matrix make them highly adaptable to irregular bone defects and local pathological niches.[17,18] More importantly, modern hydrogels are no longer viewed as passive carriers for antibiotics or growth factors.[19,20] Instead, they are increasingly engineered as dynamic and instructive systems capable of sensing local cues, releasing therapeutics in a programmed manner, interacting with immune cells, scavenging reactive oxygen species, modulating inflammatory signaling, and supporting angiogenic and osteogenic processes.[21,22] Because infected bone healing unfolds across multiple stages, hydrogels offer a particularly attractive platform for integrating responsiveness, spatial adaptability, and temporal control into a single material system.[23,24] In this sense, the therapeutic value of hydrogels lies not only in what they deliver, but in how they actively participate in microenvironmental reprogramming.[25,26] Several recent studies have mentioned the immune microenvironment of bone healing and immunomodulatory hydrogel strategies. Zhao et al focuses on the impacts of various immune cells and cytokines on the immune microenvironment in infected bone defects and summarizes hydrogel strategies targeting infection and regeneration.[27] Fu et al summarizes general advances in immunomodulatory hydrogels for bone tissue regeneration, emphasizing macrophage regulation and hydrogel design principles for enhancing bone repair.[28] Zhang et al summarized macrophage polarization mechanisms and hydrogel strategies broadly from basic immunology to translational challenges.[11] Hydrogel could achieve temporal immunomodulation of early M1 and later M2 macrophage phenotypes to promote infected bone repair.[29] Hydrogel-based immunomodulatory systems promote bone regeneration by actively reshaping the osteoimmune microenvironment rather than merely serving as osteogenic delivery matrices.[30] The novelty of this review lies in its disease-specific and mechanism-integrated framework. Rather than summarizing hydrogels simply according to material type or delivered bioactive molecules, this review reorganizes recent advances according to four functional design paradigms: programmed

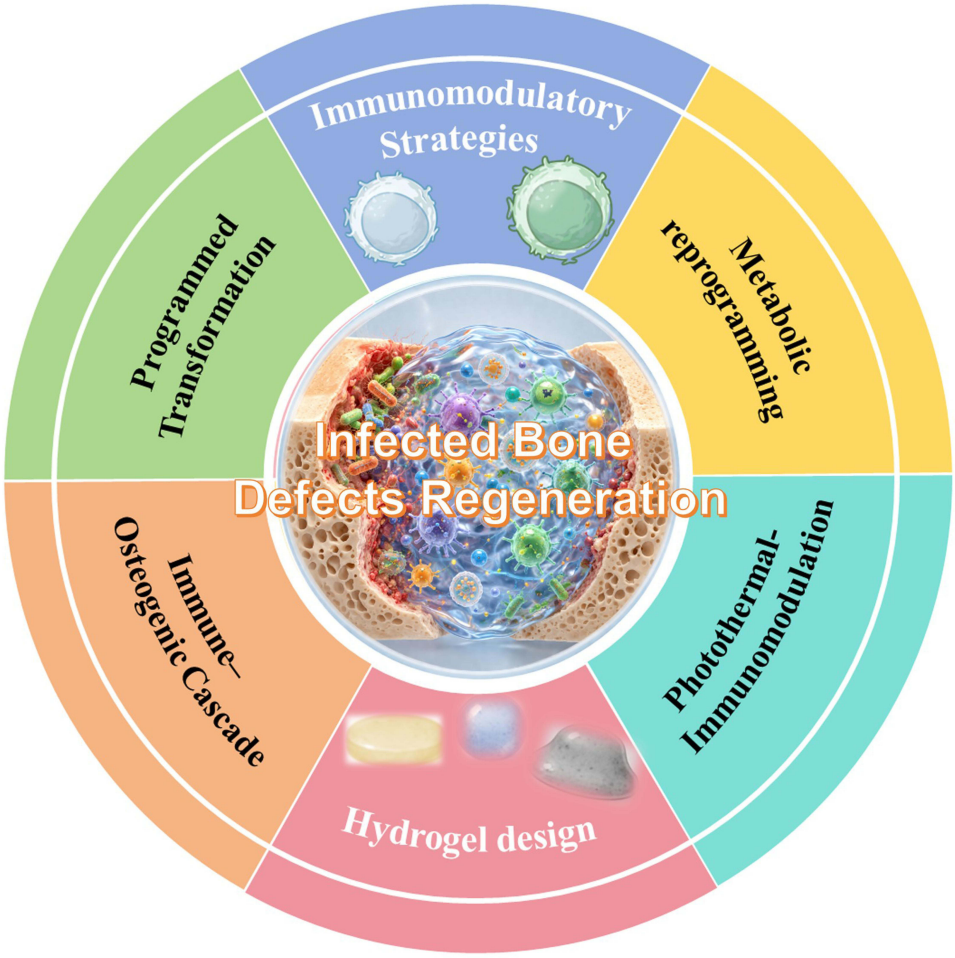


Figure 1 Scheme for hydrogel-based immunomodulatory strategies for infected bone defects regeneration.

transformation of the osteogenic microenvironment, immunometabolic reprogramming of the infectious niche, spatiotemporally staged immune–osteogenic regulation, and photothermal-immunomodulatory therapy (Figure 1). This structure highlights how advanced hydrogels are evolving from passive delivery matrices into dynamic microenvironment-regulating platforms that coordinate antibacterial defense, immune remodeling, angiogenesis, and osteogenesis in a stage-adapted manner. The related studies have been summarized in Table 1.

Design Strategies of Hydrogel-Based Immunomodulatory Systems

Hydrogel-based immunomodulatory systems for infected bone defects have rapidly evolved from passive space-filling materials or local antibiotic depots into active platforms for osteoimmune engineering.[41] Rather than merely suppressing inflammation or delivering antibacterial agents, current hydrogels are increasingly designed to dynamically reconfigure the pathological niche in a way that integrates infection control, immune regulation, vascularization, and osteogenesis.[42] Based on the representative studies discussed above, their design strategies can be understood as four highly interconnected directions (Table 2). Microenvironment-responsive and transformation-oriented hydrogels are engineered to sense pathological features such as acidity, oxidative stress, and persistent inflammation, and then adapt their behavior accordingly.[43] In this design logic, the hydrogel is not a static carrier but a responsive therapeutic platform whose function evolves with the healing stage.[44] Acid-responsive systems, conductive hydrogels, and all-in-one multifunctional networks exemplify this principle by coupling antibacterial activity with immune remodeling, angiogenesis, and osteogenic support, thereby enabling the gradual conversion of an infection-dominated hostile niche into one permissive for bone regeneration.[45] Metabolic reprogramming-based hydrogels target the immunometabolic abnormalities that

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Table 1 Hydrogel-Based Immunomodulatory Strategies for Infected Bone Defects Regeneration

Hydrogel System	Main Design Strategy	Key Immunomodulatory Mechanism	Function	Regenerative Outcome	Reference
GH-MCD (GelMA–oxidized hyaluronic acid + melatonin carbon dots)	Programmed microenvironment transformation; acid-responsive release in the infectious niche	Regulates the immune microenvironment while balancing osteogenesis and osteoclastogenesis	Faster release under acidic infection conditions; enhances cellular resistance to bacteria	Reframes infected bone repair as stage-adaptive transformation of the osteogenic microenvironment rather than static treatment.	[31]
Inflammatory microenvironment-modulated conductive hydrogel	Inflammation-responsive/conductive immunomodulatory platform	Treats the inflammatory microenvironment itself as a therapeutic target	Simultaneous infection control with conductive-matrix-assisted niche remodeling	Promotes vascularized bone regeneration by coupling infection control, immune remodeling, and angiogenesis.	[32]
C/O/Sr/MA hydrogel	All-in-one multifunctional hydrogel	Reduces inflammation and drives macrophages toward an M2 phenotype	Anti-MRSA activity; pro-angiogenic and biomineralization support via Sr^{2+}	Highlights coordinated progression from antibacterial defense to anti-inflammatory regulation to pro-regenerative remodeling.	[33]
Injectable osteomyelitis hydrogel	Metabolic reprogramming-based immunomodulation	Induces trained immunity through immunometabolic rewiring: increased succinate, ATP, lactate, HIF-1α stabilization, glycolysis, COX2/iNOS/CD86, IL-1β/IL-6/TNF-α	Captures bacteria, virulence factors, and inflammatory mediators; sustained antimicrobial activity	Converts infected marrow cavity into a niche supporting both durable immune defense and osteogenic repair.	[34]
Silk-6/ε-PL@Exo hydrogel	Macrophage metabolic reprogramming in diabetic infected defects	M2 macrophage-derived exosomes regulate HK2, inhibit excessive glycolysis and lactate accumulation, suppress NF-κB, restore M1/M2 balance	Broad-spectrum antibacterial activity against Gram-positive and Gram-negative bacteria	Shows that immunometabolic normalization can reverse a chronic inflammatory diabetic infected niche toward osteogenesis.	[35]
AOHA-RA/Lap IH	Simultaneous multi-target strategy (macrophages, bacteria, BMSCs)	Promotes M2 polarization via JAK1-STAT1 and PI3K-AKT pathways	Long-lasting RA release; antibacterial activity; injectability, self-recoverability, post-injection reinforcement	Demonstrates that infected bone repair requires concurrent control of bacteria, macrophage phenotype, and stromal osteogenic competence.	[36]
Temporal immunomodulatory hydrogel with Zn-based HAP nanoparticles	Stage-specific immune–osteogenic cascade via temporal ion release	Early inflammatory activation supports antimicrobial defense; later release profile supports pro-regenerative immune transition	Sequential ion-delivery profile converts scaffold into an active osteoimmune regulator	Establishes the concept that infected bone healing requires phase-adapted orchestration, not uniform M2-driven repair.	[37]
GCS (GelMA + sulfur quantum dot nanozymes + calcium–phosphorus oligomers)	Spatiotemporally programmed nanohybrid hydrogel	SQD-mediated ROS scavenging restores mitochondrial homeostasis and promotes M2 polarization	Three-phase program: rapid bacterial inactivation, immune/mitochondrial recovery, delayed vascular-bone coupling	Broadens stage-specific repair into a three-step antibacterial–immune–vascular/osteogenic program.	[38]
Photothermal-immunomodulatory nanohydrogel (RuO_2 + nano-hydroxyapatite)	Photothermal-immunomodulatory platform	RuO_2 scavenges ROS, reduces pro-inflammatory signaling, promotes pro-regenerative macrophage polarization	NIR-II-triggered photothermal bacterial killing	Integrates photothermal antibacterial action, immune remodeling, angiogenesis, and osteogenesis in one platform.	[39]
AMAD/MP hydrogel (alginate methacrylate/alginate-graft-dopamine /MXene)	Mild photothermal immunomodulation	Regulates M1/M2 balance and suppresses ROS-induced inflammatory status	Mild NIR thermal cue plus antibacterial support	Shows that thermal stimulation can act as an instructive regenerative cue, not merely a bactericidal adjunct.	[40]

Table 2 Major Design Strategies of Hydrogel-Based Immunomodulatory Systems for Infected Bone Defects

Design Strategy	Core Design Logic	Typical Pathological Target	Representative Functional Elements	Main Immunomodulatory Effect	Regenerative Significance
Microenvironment-responsive /transformation-oriented hydrogels	Sense pathological cues and adapt material behavior to the evolving niche	Acidity, oxidative stress, persistent inflammation	Acid-responsive release systems, conductive matrices, all-in-one multifunctional networks	Remodel the inflammatory microenvironment and coordinate antibacterial, immune, and angiogenic responses	Gradually convert an infection-dominated hostile niche into a bone-regeneration-permissive microenvironment
Metabolic reprogramming-based hydrogels	Correct dysregulated immune metabolism that sustains chronic inflammation	Abnormal glycolysis, lactate accumulation, NF-κB activation, trained immunity imbalance	Self-assembling injectable hydrogels, exosome-releasing systems, mediator-capturing matrices	Reprogram macrophage metabolism, restore immune homeostasis, and normalize inflammatory signaling	Reconstruct the infectious osteogenic microenvironment by coupling antimicrobial action with immunometabolic correction
Spatiotemporally staged immunomodulatory hydrogels	Deliver bioactive cues in a phase-adapted sequence matching different healing stages	Early infection burden and inflammation; later impaired angiogenesis and osteogenesis	Sequential release systems, programmed multistep therapeutic platforms, temporal ion/ nanoparticle delivery	Enable early antibacterial defense and immune activation, followed by inflammation resolution and macrophage repolarization	Orchestrate the transition from host defense to vascularized bone regeneration in a temporally ordered manner
Photothermal-immunomodulatory hydrogels	Integrate NIR-triggered antibacterial therapy with broader osteoimmune remodeling	Persistent infection, excessive ROS, pro-inflammatory signaling	Photothermal nanoparticles, ROS-scavenging components, osteogenic matrices	Reduce inflammatory signaling, promote macrophage polarization toward a pro-regenerative state, and rebalance the niche	Combine bacterial eradication with angiogenesis and osteogenesis, turning photothermal therapy into a regenerative cue

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sustain chronic inflammation and impaired repair.[31] In osteomyelitis and diabetic infected bone defects, advanced hydrogels have been developed to self-assemble in situ, capture bacteria and inflammatory mediators, induce trained immunity, regulate glycolytic pathways such as hexokinase 2 (HK2), reduce lactate accumulation, suppress nuclear factor kappa-B (NF-κB)-related inflammation, and restore macrophage homeostasis. These studies suggest that reconstruction of the infectious osteogenic microenvironment may require not only antimicrobial action, but also active correction of the dysregulated metabolic circuitry that underlies persistent immune dysfunction.

Spatiotemporally staged immunomodulatory hydrogels are built on the recognition that infected bone healing has fundamentally different requirements in the early and late phases. Early antibacterial defense depends on sufficiently activated innate immunity, whereas later repair requires inflammation resolution, vascular coupling, and osteogenesis. Accordingly, recent systems have been designed with sequential release profiles or programmed multistep therapeutic behavior, allowing rapid bacterial inactivation and early immune activation to be followed by reactive oxygen species (ROS) scavenging, macrophage repolarization, angiogenesis, and bone regeneration.[46] Compared with uniform immunosuppression, this strategy is more physiologically aligned because it orchestrates the transition from host defense to tissue repair in a temporally ordered manner.[47] Photothermal-immunomodulatory hydrogels represent a rapidly emerging strategy in which near infrared (NIR)-responsive antibacterial therapy is integrated with broader microenvironment remodeling.[32] In these systems, photothermal treatment is no longer viewed simply as a local bactericidal tool, but as part of a multifunctional platform that also scavenges ROS, modulates inflammatory signaling, promotes macrophage polarization toward a pro-regenerative state, and enhances angiogenesis and osteogenesis.[33] Earlier work on mild photothermal stimulation further indicates that thermal cues themselves can serve as instructive regulators of the regenerative niche, even without exogenous cytokines or cells, highlighting that photothermal responsiveness can be harnessed to coordinate antibacterial action with immune and osteogenic regulation.[48]

These functional strategies share common structural design principles. Most systems are injectable and in situ forming, enabling them to conform to irregular defects and localize treatment within the infected niche.[49,50] Many incorporate reversible or dual cross-linking networks, which provide self-healing, self-recoverability, spatial adaptability, and post-implantation mechanical reinforcement. In addition, multifunctionality is often achieved through incorporation of bioactive ions, nanoparticles, nanozymes, exosomes, conductive agents, or photothermal components, which allow the hydrogel matrix to directly influence antibacterial defense, redox balance, immune phenotype, angiogenesis, and osteogenesis.[51] Importantly, these advances show that high-performance immunomodulatory hydrogels are not created simply by adding more therapeutic ingredients, but by rationally integrating matrix architecture, responsive behavior, immune targeting, and regenerative signaling into a unified design.[52] Taken together, these studies indicate that the field is moving from static delivery to microenvironment-responsive transformation, from simple macrophage phenotype regulation to immunometabolic reprogramming, from uniform intervention to stage-adapted orchestration, and from single-function anti-infective materials to multifunctional osteoimmune engineering systems capable of supporting durable regeneration of infected bone defects.

Programmed Transformation of Osteogenesis Microenvironment

Infectious bone defects are characterized by a highly dynamic pathological niche, in which the dominant barriers to regeneration vary over time.[34,53] During the early stage, bacterial colonization and excessive ROS accumulation severely impair cell survival and tissue integration, whereas in the later stage, residual intracellular bacteria, persistent inflammation, and delayed osseointegration continue to compromise defect healing.[35,36] Xie et al proposed the concept of programmed transformation of the osteogenesis microenvironment, arguing that successful repair of infectious bone defects requires biomaterials capable of adapting to the evolving biological demands of different healing phases rather than providing a single static function throughout treatment (Figure 2).[54] They developed a multifunctional hydrogel termed GH-MCD, in which melatonin carbon dots (MCDs) were incorporated into a GelMA–oxidized hyaluronic acid hydrogel through a Schiff-base-associated network. Importantly, the hydrogel was engineered to respond to the acidic microenvironment of infectious bone defects, enabling faster release of MCDs under infection-relevant conditions and transforming the material into a microenvironment-responsive therapeutic platform rather than a passive scaffold. Mechanistically, this study emphasized that the hydrogel promotes bone repair not through a single pathway, but through

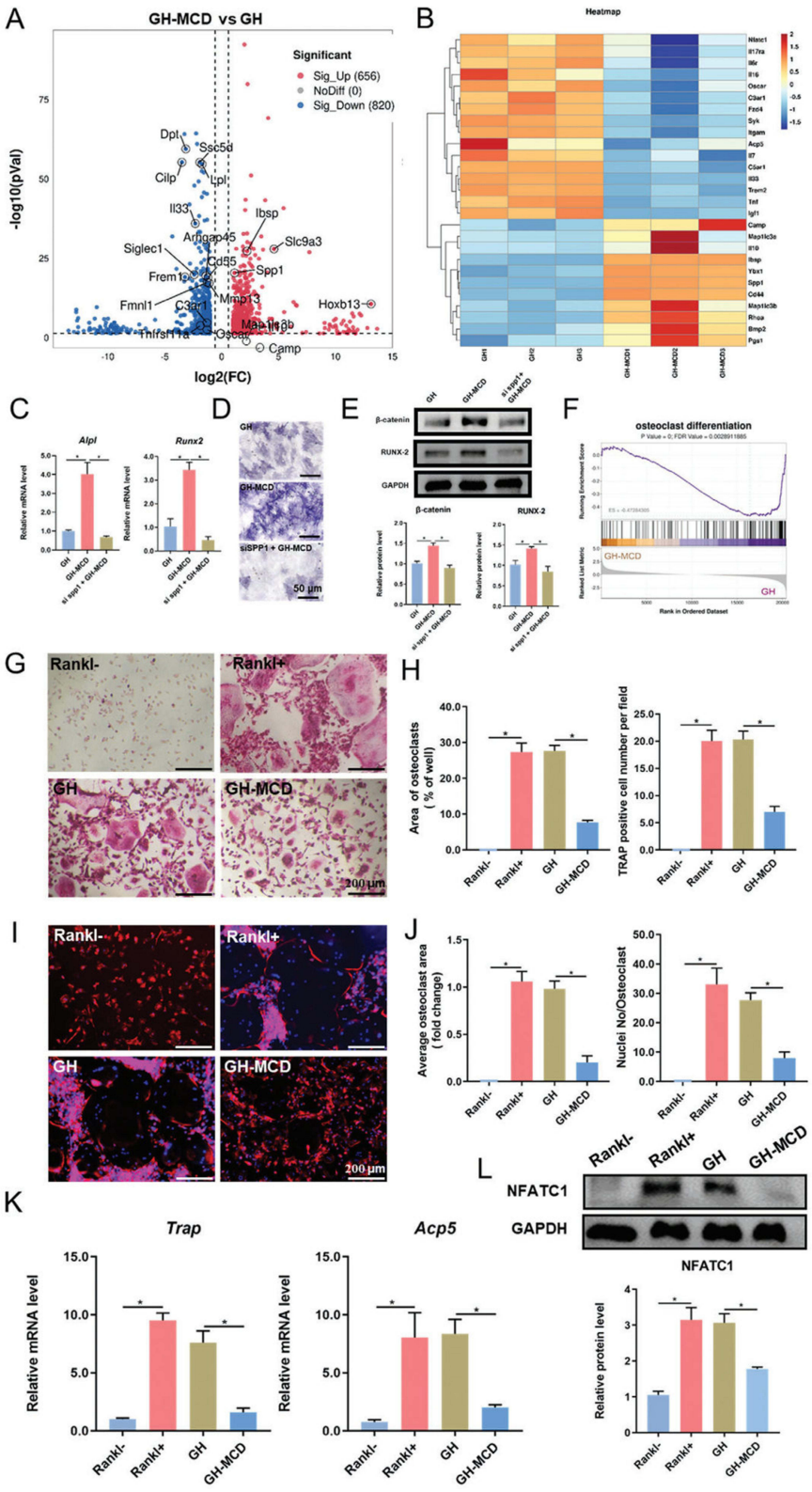

Figure 2 Programmed Transformation of Osteogenesis Microenvironment (adapted from Adv Sci (Weinh). 2025 Mar;12 (10):e2409683).[54] (**A**) Volcano plot showing differentially expressed genes between GHMCD and GH groups. (**B**) Heat map of some genes. (**C**) Gene expression of Alpl and Runx2 of the BMSCs at 5 days. (**D**) ALP staining of BMSCs at 5 days. (**E**) Protein expression of RUNX-2 and *β*-catenin at 5 days before and after Spp1 being knocked down and quantitative analysis. (**F**) Gene set enrichment analysis. (**G**) TRAP staining. (**H**) Quantitative analysis of TRAP staining. (**I**) Podosome belt formation assay. (**J**) Quantitative analysis of Podosome belt formation assay. (**K**) Genes and (**L**) protein expression during osteoclastogenesis of the BMMs at 7 days. *p < 0.05.

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programmed, stage-adaptive modulation of the regenerative microenvironment. The GH-500 MCD hydrogels killed ≈90% of the bacteria within 24 h, suggesting enhanced cellular resistance to bacteria. After 4 weeks, the bone volume fraction (BV/TV) in the GH-MCD group reached ≈25%, in contribution to the balanced osteogenesis and osteoclastogenesis. RNA-seq analysis revealed that GH-MCD regulated the immune microenvironment by downregulating genes involved in hematopoietic cell lineage, complement and coagulation cascades, platelet activation, natural killer cell-mediated cytotoxicity, B-cell receptor signaling, and osteoclast differentiation, thereby reducing immunogenicity while supporting antibacterial defense and bone regeneration. Taken together, this study exemplifies how hydrogel-based systems are evolving from static anti-infective scaffolds into dynamic platforms that program the transformation of the osteogenic microenvironment, thereby enabling more effective regeneration of infectious bone defects.[37,55]

In contrast to approaches focused primarily on bacterial killing, Yang et al highlighted the importance of simultaneously controlling infection, remodeling the immune microenvironment, and restoring vascularized bone regeneration.[14] They developed an inflammatory microenvironment-modulated conductive hydrogel for infected bone defects. In this system, the hydrogel matrix served as a defect-adaptable semi-solid scaffold, while copper nanoparticles provided multiple functions, including antibacterial activity, electrical conductivity, and immune microenvironment regulation. The rationale for introducing conductivity was to provide bioelectrical cues that may support cell communication, angiogenic activity, and osteogenic repair, whereas the copper-containing component contributed to bacterial inhibition and inflammatory niche remodeling. CuNPs-GelMA conductive hydrogel combined with electrical stimulation, significantly reduced the expression levels of M1 macrophage markers (IL-1β, CD86, IL-6) while markedly increasing the expression levels of M2 macrophage markers (IL-10, CD206, TGF-β). The significance of this work lies in its emphasis that the inflammatory microenvironment itself should be regarded as a therapeutic target rather than a passive background condition. By integrating anti-infective and immunomodulatory functions with a conductive matrix, the hydrogel broadened the concept of osteogenic microenvironment transformation from simple inflammation attenuation to a more coordinated regulation of infection control, immune remodeling, and vascularized osteogenesis. A further extension of this concept was provided by Duan et al, who described an all-in-one multifunctional injectable hydrogel (C/O/Sr/MA hydrogel) for MRSA-infected bone defects.[38] Their design explicitly framed infected bone repair as a multistep regenerative process involving antibacterial activity, immune regulation, angiogenesis, osteogenic differentiation, and biomineralization, and sought to integrate these functions within a single hydrogel system. There was no significant variation observed in CD206 expression between the HP-PVA and HP-PVA@MH hydrogels compared with the IL-4 group. However, a substantial increase was observed in CD206 expression within the HP-PVA@Fe-Que and HP-PVA@MH/Fe-Que groups. Mechanistically, the hydrogel inhibited MRSA growth and coordinated with Sr^{2+}, which was associated with reduced inflammation, a shift of macrophages toward the M2 phenotype, and enhanced vascularization and bone regeneration. In a rat MRSA-infected bone defect model, the hydrogel promoted angiogenesis, collagen deposition, and bone healing while suppressing inflammatory responses. This study therefore reinforces the idea that effective transformation of the osteogenic microenvironment requires not one dominant biofunction, but the coordinated progression from antibacterial defense to anti-inflammatory regulation and pro-regenerative remodeling.[56]

Metabolic Reprogramming Reconfigure the Infectious Osteogenic Microenvironment

In infected bone defects, successful healing depends not only on pathogen eradication, but also on reconstruction of a regeneration-permissive osteoimmune microenvironment within the bone marrow cavity.[57,58] This is especially important because the bone marrow is not merely an anatomic site of infection, but also a key niche for innate immune activation and immune memory formation.[59,60] From this perspective, Chen et al proposed that injectable hydrogels for osteomyelitis treatment should move beyond conventional local antibiotic delivery and instead reconfigure the infectious osteogenic niche through metabolic reprogramming of innate immunity (Figure 3).[61] They developed an injectable hydrogel that self-assembles in situ within the bone marrow cavity and captures bacteria, virulence factors, and inflammatory mediators through multivalent interactions, while simultaneously providing sustained antimicrobial and immunomodulatory activity.[61] By targeting the marrow cavity, the system was designed not only to control infection at

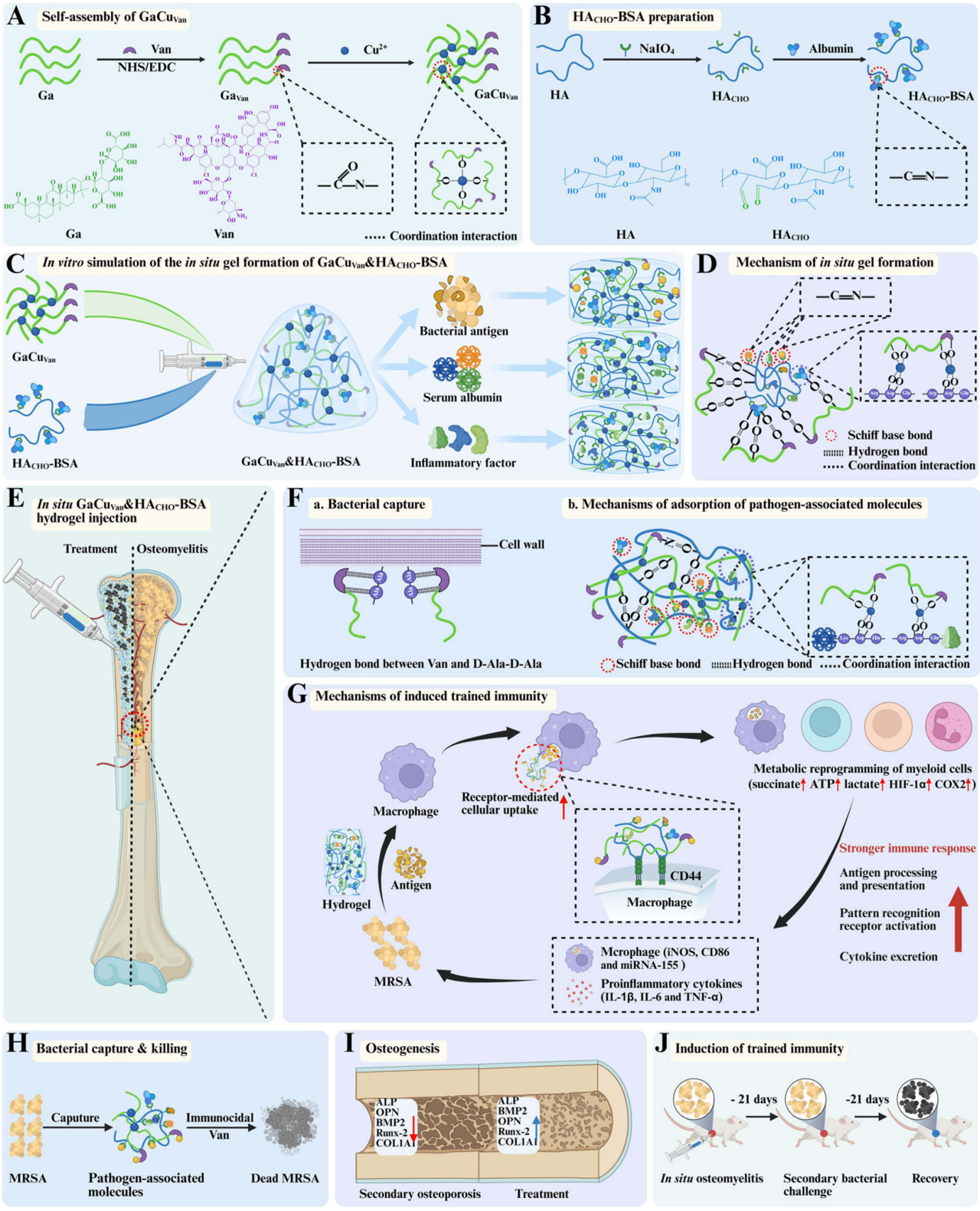

Figure 3 Metabolic reprogramming reconfigure the infectious osteogenic microenvironment (adapted from Nat Commun. 2026 Jan 13;17 (1):1613).[61] (**A**) Schematic illustration of GaCuVan self-assembly. (**B**) Schematic diagram illustrating the preparation of HACHO-BSA. (**C**) In vitro simulation of in situ gel formation of GaCuVan&HACHO-BSA hydrogel. (**D**) Mechanism of in situ gel formation. (**E**) In situ administration with GaCuVan&HACHO-BSA hydrogel. (**F**) (a) Recognition and capture of bacteria by the hydrogel via binding to specific terminal peptides on the bacterial cell wall. (b) Schematic illustrating the adsorption of bacterial antigens, serum albumin, and inflammatory factors by the hydrogel through Schiff base reactions, hydrogen bonding, and ionic coordination. (**G**) Mechanisms of induced trained immunity by the hydrogel. (**H**) Bacterial capture and bactericidal properties of the hydrogel. (**I**) Osteogenic effects of the hydrogel. (**J**) Induction of trained immunity and prevention of relapse by the hydrogel.

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its core location, but also to engage the local immune microenvironment where trained immunity is initiated.[61] Mechanistically, the significance of this work lies in demonstrating that hydrogel-mediated treatment can be coupled to immunometabolic rewiring. Pathogen-associated signals adsorbed by the hydrogel activated pattern-recognition pathways and induced metabolic changes characterized by elevated succinate, ATP, and lactate, stabilization of HIF-1α, enhanced glycolysis, and increased expression of inflammatory markers such as COX2, iNOS, and CD86, together with upregulated IL-1β, IL-6, and TNF-α.[61] Rather than representing uncontrolled inflammation, this response was interpreted as the establishment of trained immunity, enabling stronger antibacterial defense and protection against reinfection.[61] Importantly, this hydrogel did not function as a purely immune-activating system, it also promoted bone regeneration, with improved expression of osteogenic factors such as Runx-2, Osterix, OPG, COL1A1, and ALP, as well as better bone structural outcomes including increased BMD, BV/TV, and Tb.N and reduced Tb.Sp.[61] Thus, the therapeutic logic of this study lies in converting the infected marrow cavity from a site of persistent pathogen burden into a microenvironment capable of both durable immune defense and osteogenic repair.

Abnormal immune metabolism further aggravates persistent inflammation, bacterial infection, and delayed bone regeneration.[62] To solve this, Jin et al developed a multifunctional Silk-6/ε-PL@Exo hydrogel composed of modified silk fibroin, ε-polylysine, and M2 macrophage-derived exosomes, and explicitly framed the system as a strategy for macrophage metabolic reprogramming rather than simple anti-inflammatory delivery.[39] This degradable hydrogel exhibited broad-spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria, while the released M2-Exo targeted M1 macrophages and modulated the key glycolytic enzyme hexokinase II (HK2). This in turn regulated the inflammation-related NF-κB pathway, alleviated lactate accumulation, inhibited excessive glycolysis, and helped restore the M1-to-M2 balance. In a rat model, the hydrogel improved infection control, rebalanced immune responses, and accelerated bone defect healing, indicating that immunometabolic normalization can be used to convert a diabetic infected niche from a state of chronic inflammatory persistence toward one permissive for osteogenesis. Thus, this study reinforces the idea that reconstruction of the infectious osteogenic microenvironment may require not only antimicrobial activity, but also direct intervention in the metabolic circuitry of macrophages that sustains pathological inflammation. A further complementary example was provided by Du et al, who developed a multifunctional self-reinforced injectable hydrogel (AOHA-RA/Lap IH) designed to simultaneously target macrophages, bacteria, and bone marrow stromal cells (BMSCs) in infected bone defects (Figure 4).[63] The hydrogel was formed through two reversible cross-linking mechanisms, namely laponite-mediated electrostatic interactions and phenylboronic acid ester bonds between 4-aminobenzeneboronic acid-grafted oxidized hyaluronic acid and rosmarinic acid (RA), which endowed the material with injectability, self-recoverability, spatial adaptability, and post-injection mechanical reinforcement. Importantly, the hydrogel induced M2 macrophage polarization and osteogenic differentiation of bone marrow derived mesenchymal stem cells (BMSCs). Mechanistically, the macrophage-regulatory effect was linked to the JAK1-STAT1 and PI3K-AKT pathways, whereas the osteogenic effect involved calcium signaling, extracellular matrix (ECM) receptor interaction, and TGF-β signaling. Although this study did not focus explicitly on immunometabolic memory, it strongly supports the broader principle that successful reconfiguration of the infectious osteogenic microenvironment requires simultaneous control of bacteria, macrophage phenotype, and stromal osteogenic competence, rather than treatment of these pathological axes in isolation.

Spatiotemporally Stage-Specific Immune–Osteogenic Cascade

A central challenge in the treatment of infected bone defects is that the immune requirements of the early and late healing phases are fundamentally different.[40] Early after implantation, efficient pathogen clearance depends on a sufficiently activated inflammatory response, whereas later-stage repair requires resolution of inflammation and the establishment of a pro-regenerative microenvironment.[64] In this context, Jin et al reported a temporal immunomodulatory hydrogel for infected bone defect regeneration, arguing that conventional osteoimmunomodulatory strategies place excessive emphasis on M2-driven repair while underestimating the indispensable contribution of early M1-associated antimicrobial immunity (Figure 5).[29] Their work therefore reframed infected bone healing as a stage-specific immune–osteogenic cascade rather than a simple anti-inflammatory process. The hydrogel was constructed by crosslinking acrylate-modified engineered protein with oxidized sodium alginate, yielding a rapidly formed matrix intended to mimic extracellular

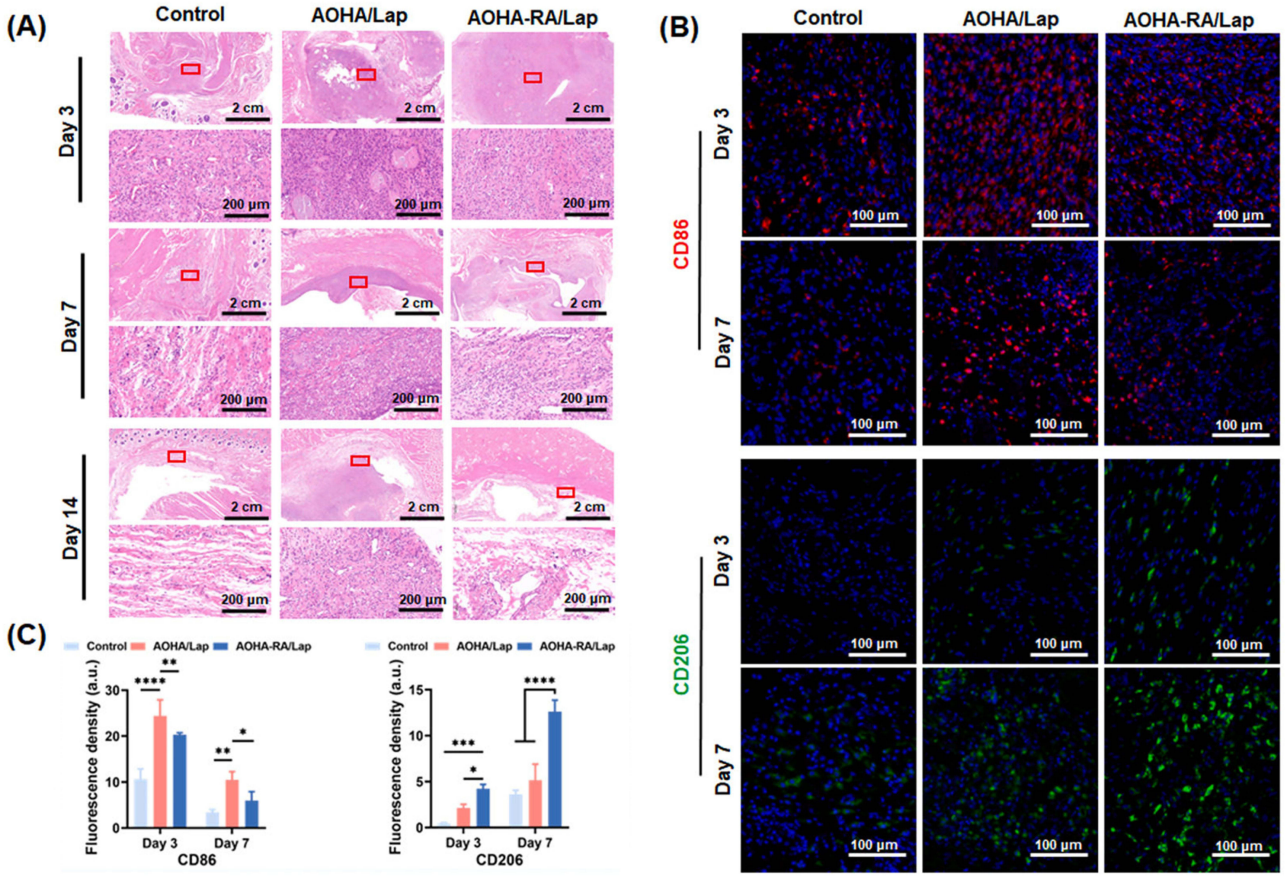

Figure 4 Subcutaneous immunoregulatory effects of the hydrogel in rats (adapted from Acta Biomater, 189 (2024) 232–253).[63] (**A**) Representative H&E staining images of subcutaneous implantation at 3, 7, and 21 d post-implantation. The image below is a high-magnification image corresponding to the red area above. (**B**) Representative immunofluorescence staining images of CD86 and CD206 within the subcutaneous tissues at 3 and 7 d post-implantation. (**C**) Corresponding statistical analysis of the fluorescence intensities of CD86 and CD206 in (**B**). *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.

matrix architecture and support cell adhesion, angiogenesis, and osteogenesis. To enable temporal regulation, they incorporated zinc-based nanoparticles mineralized with hydroxyapatite into the hydrogel network. This design is particularly important because it links hydrogel composition to a programmed ion-delivery profile, thereby converting the material from a passive scaffold into an active regulator of the osteoimmune microenvironment. Mechanistically, the key innovation of this study lies in its sequential ion release behavior, which promoted M1-associated antibacterial immunity to improve early infection control, and then supported a later pro-regenerative transition that enhanced inflammation resolution, osteogenic differentiation, and new bone formation. The hydrogel regulated infected bone healing through a temporally ordered immune–osteogenic cascade rather than uniform immunosuppression or continuous M2 polarization.

Another representative example of stage-specific regulation in infected bone defect repair was reported by Liu et al, who developed a GelMA-based nanocomposite hydrogel (GCS) co-embedded with sulfur quantum dot nanozymes (SQDs) and calcium–phosphorus oligomers (CPOs) to achieve temporally controlled therapy of infectious bone defects (Figure 6).[65] Unlike strategies that rely on uniform immunosuppression throughout healing, this system was designed to coordinate the sequential needs of the defect microenvironment. The hydrogel executed a three-phase therapeutic program. First, SQDs that were only weakly associated with the matrix were released rapidly to inactivate bacteria during the early phase. Second, SQD-mediated reactive oxygen species scavenging restored mitochondrial homeostasis and ATP synthesis, suppressed inflammation-associated protein expression, and promoted macrophage M2 polarization. Third, the more sustained delivery of calcium–phosphorus oligomers promoted vascular coupling and osteogenic differentiation during tissue regeneration. In this way, the material functioned not merely as an antibacterial depot, but as a dynamically instructive platform that linked infection control,

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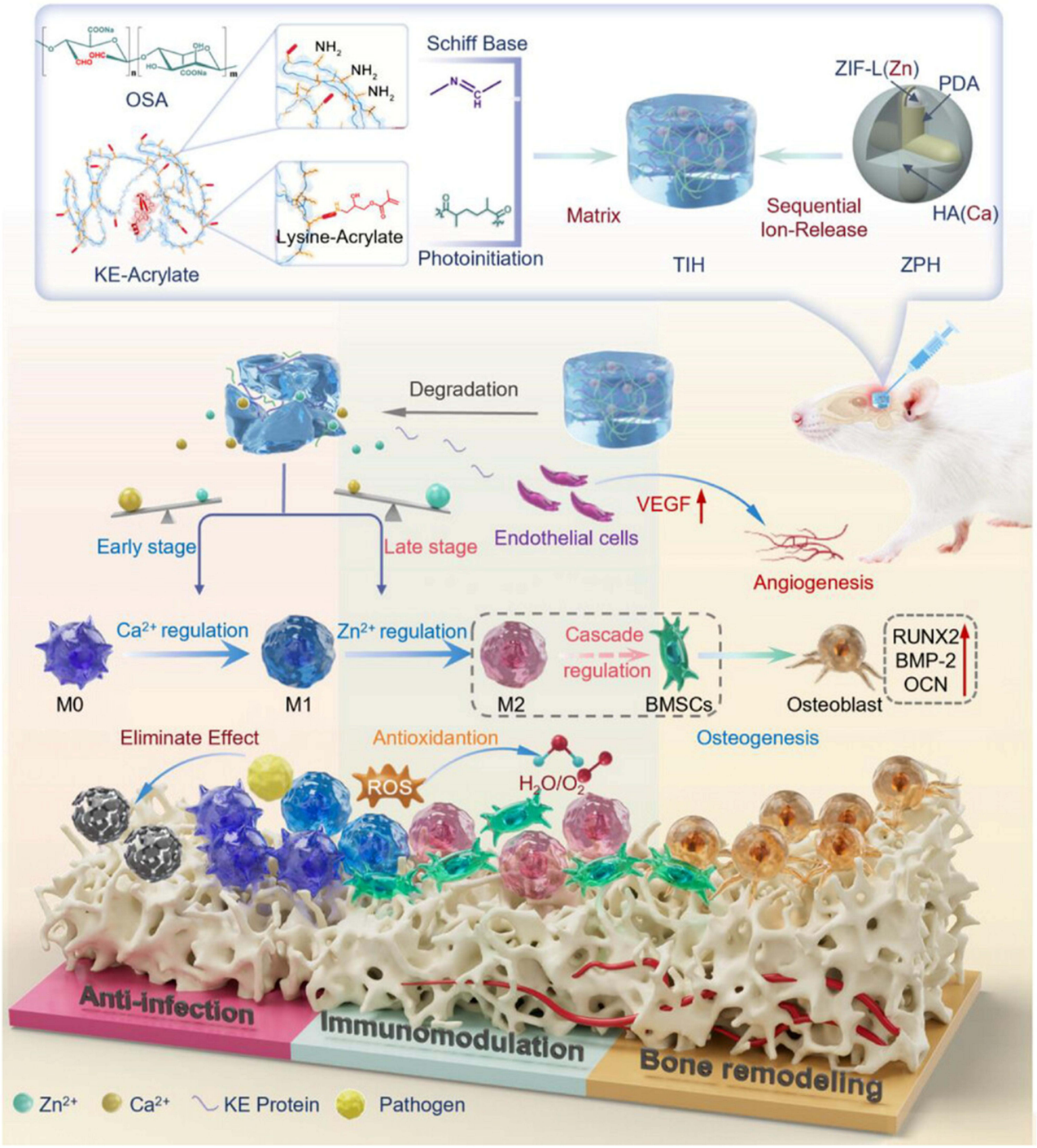

Figure 5 Stage-specific Immune–Osteogenic Cascade by Temporal Ion Release (adapted from Adv Mater. 2026 Jan;38 (2):e14419).[29]

immune remodeling, and bone repair in a temporally ordered sequence. This study therefore broadens the concept of the immune–osteogenic cascade from simple phenotype switching to a more integrated model in which programmed material dynamics orchestrate the transition from innate defense to regenerative healing in infectious bone defects.[66] Taken together, these studies highlight a paradigm shift from static immunomodulation to phase-adapted orchestration of antibacterial defense, immune remodeling, vascularization, and osteogenesis, thereby enabling more precise regeneration of infected bone defects.

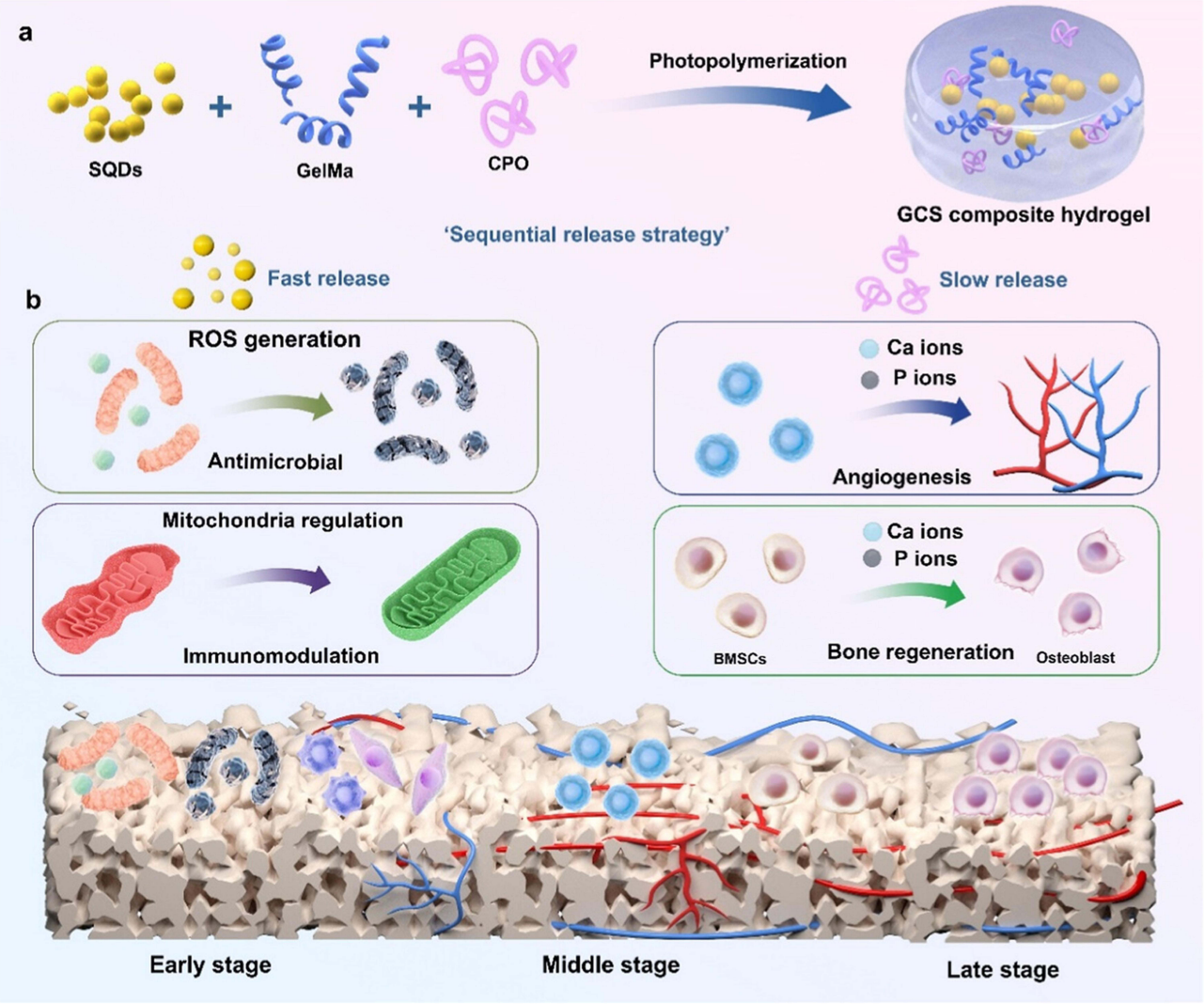

Figure 6 Preparation of CSG Nanocomposite Hydrogels (**a**) and Temporal-Controlled Therapy through Mitochondrial Homeostatic Balance Modulation of Immunity and Vascularization (**b**) (adapted from ACS Appl Mater Interfaces, 17 (2025) 51,904–51,918).[65] (**a**) Preparation of CSG Nanocomposite Hydrogels and (**b**) Temporal-Controlled Therapy of IBDs through Antimicrobial Maintenance of Mitochondrial Homeostatic Balance Modulation of Immunity and Vascularization.

Photothermal-Immunomodulation Accelerates Bone Regeneration

Photothermal therapy has emerged as a promising strategy for infected bone defects because it enables localized bacterial eradication without relying exclusively on conventional antibiotics, which is particularly valuable in the context of persistent infection and impaired tissue repair.[67–69] However, photothermal antibacterial treatment alone is often insufficient for defect healing, since excessive inflammation and oxidative stress may continue to compromise osteogenesis even after bacterial burden is reduced.[70–72] To solve this, Zhan et al developed a photothermal-immunomodulatory nanohydrogel and proposed that effective treatment of infected bone defects should integrate targeted antibacterial therapy, immune microenvironment modulation, and osteogenic support within a single platform (Figure 7).[73] The system was constructed by combining photothermal/antioxidant-responsive polymer nanoparticles containing ruthenium oxide with bioactive nano-hydroxyapatite in a hydrogel matrix. Under NIR-II laser irradiation, the hydrogel generated a potent photothermal effect that damaged bacterial membranes and disrupted bacterial metabolic activity, thereby achieving strong local antibacterial action. At the same time, the RuO_2 component scavenged excessive reactive oxygen species, reduced pro-inflammatory signaling, and helped remodel the immune microenvironment, while the hydrogel scaffold and embedded hydroxyapatite provided a favorable matrix for osteoblast adhesion, growth, and osteogenic

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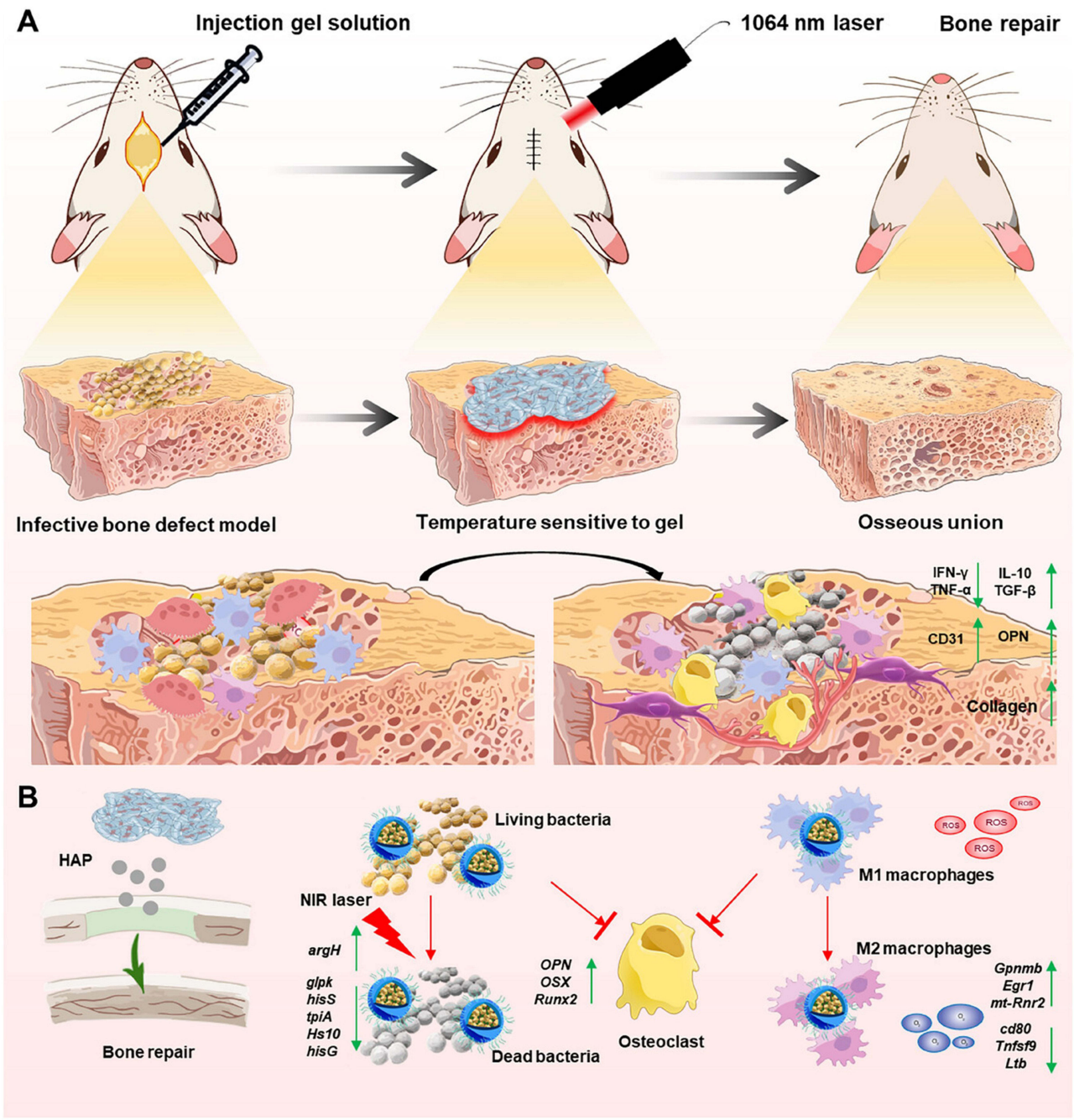

Figure 7 Photothermal-Immunomodulation Accelerates Bone Regeneration (adapted from Adv Healthc Mater, 15 (2026) e04317).[73] (**A**) Schematic diagram of the treatment of infectious bone defects with PNPs@RuO2@HAP@Gel. (**B**) Diagram explaining the mechanism of PNPs@RuO2@HAP@Gel in repairing infectious bone defects.

differentiation. Particularly, the PNPs@RuO_2@HAP@Gel/laser group exhibited significantly greater CD206 expression and a concomitant reduction in CD80-positive cells, suggesting a clear shift toward M2 macrophage polarization. The Gel/laser and PNPs@RuO2@HAP@Gel groups showed moderate levels of CD31-positive microvessels within the defect areas. This multifunctional hydrogel not only eradicated infection in a rat infected bone defect model, but also lowered pro-inflammatory cytokine levels, promoted macrophage polarization toward a pro-regenerative state, and enhanced both angiogenesis and new bone formation.

The rationale of photothermal-immunomodulation is further supported by earlier work showing that mild, rather than ablative, photothermal stimulation can actively orchestrate the regenerative microenvironment.[74] Wu et al developed an injectable and photocurable AMAD/MP hydrogel based on alginate methacrylate, alginate-graft-dopamine, and polydopamine-functionalized MXene nanosheets, and demonstrated that NIR-mediated mild thermal stimulation could synergize immunomodulation, osteogenesis, and bacterial elimination within a single hydrogel platform.[75] The optimized hydrogel exhibited favorable biocompatibility and osteogenic activity, while also establishing a more appropriate immune microenvironment by regulating the M1/M2 macrophage balance and suppressing ROS-induced inflammatory status. Notably, this mild photothermal cue was sufficient to attenuate local immune reactions and promote new bone formation without the addition of exogenous cells, cytokines, or growth factors, underscoring that thermal stimulation itself can serve as an instructive signal rather than merely a bactericidal adjunct. Although this study was not specifically designed for infected bone defects, it provides important mechanistic support for the infected-defect strategy. Thus, photothermal-immunomodulatory hydrogels are evolving from simple heat-generating antibacterial systems into microenvironment-orchestrating platforms that coordinate infection control, immune remodeling, and bone regeneration.

Current Challenges and Future Perspectives

While macrophage-centered approaches have significantly advanced infected bone defect regeneration, focusing solely on M1/M2 polarization may overlook the nuanced spectrum of immune cell states present in vivo.[76] The immune microenvironment involves dynamic interactions among neutrophils, dendritic cells, T cells, and stromal cells, each with distinct temporal and spatial contributions to both infection control and tissue repair.[77] Current hydrogel systems that target only macrophage phenotypes may insufficiently capture these complex regulatory networks, limiting translational efficacy.[78] Over-suppression of early inflammatory responses can impede bacterial clearance, whereas insufficient control of later-stage inflammation may compromise osteogenesis.[79] Stage-specific hydrogels with spatiotemporal release profiles and programmable immunomodulatory cues have shown promise in addressing this challenge, yet fine-tuning remains difficult due to inter-individual variability and the dynamic evolution of infectious niches.[80] Hydrogel systems are increasingly multifunctional, integrating antimicrobial agents, immunoregulatory molecules, metabolic modulators, photothermal components, and osteogenic factors.[81,82] While these designs enhance therapeutic efficacy, they introduce manufacturing complexity, batch-to-batch variability, and regulatory hurdles.[83] Simplifying design without compromising performance remains an ongoing challenge for clinical translation.[84] There is a notable absence of standardized metrics for evaluating immunomodulatory hydrogels, including immune readouts, mechanical properties, degradation kinetics, and in vivo performance in infected bone models.[28,85,86] This heterogeneity complicates cross-study comparisons, hampers reproducibility, and slows regulatory approval processes. Development of consensus frameworks for hydrogel characterization and preclinical testing is urgently needed.[87] The incorporation of bioactive ions, nanoparticles, exosomes, and photothermal agents raises safety concerns, including immunogenicity, cytotoxicity, and long-term persistence in tissue.[88] Regulatory pathways for combination products involving biologics, devices, and drugs are complex.[89] Early engagement with regulatory authorities and rigorous preclinical safety assessments are essential to ensure clinical viability. In addition to biochemical immunomodulation, the physical properties of hydrogels should be considered as important regulators of the osteoimmune microenvironment.[90] Hydrogels are semi-solid, water-rich three-dimensional polymer networks whose stiffness, viscoelasticity, porosity, swelling behavior, and degradation kinetics can be adjusted through polymer composition and crosslinking density.[91] An ideal immunomodulatory hydrogel for infected bone defects should provide a mechanically permissive but sufficiently supportive microenvironment.

Future hydrogel designs will increasingly adopt a systems-level approach, modulating not just macrophages but orchestrating interactions among multiple immune and stromal cell types, such as neutrophils, dendritic cells and T lymphocytes, to provide a more comprehensive overview of the osteoimmune network. By targeting the broader osteoimmune network, these platforms aim to synchronize infection clearance, inflammation resolution, angiogenesis, and bone regeneration for more robust and resilient repair outcomes. Advances in responsive and programmable hydrogels enable customization to disease-specific pathological microenvironments.[92,93] Tailoring hydrogel composition, release kinetics, and mechanical properties to match conditions such as diabetic osteomyelitis or MRSA-infected defects can enhance regeneration while minimizing off-target effects.[94,95] Integration of metabolic reprogramming and

photothermal cues further supports niche-adapted, stage-specific therapy.[96] Artificial intelligence and machine learning offer opportunities to accelerate hydrogel development.[97] By integrating large-scale omics data, imaging, and outcomes, predictive models can inform the selection of bioactive components, crosslinking strategies, and spatiotemporal release profiles. Data-driven approaches can optimize multifunctional hydrogel architectures, reduce experimental burden, and enhance the precision of immunomodulatory interventions. Although hydrogel-based immunomodulatory strategies have shown promising therapeutic effects in preclinical models of infected bone defects, their clinical translation remains limited. Therefore, future work should prioritize standardized preclinical assessment, long-term biosafety evaluation, scalable manufacturing, regulatory pathway clarification, and well-designed clinical trials to validate their safety and efficacy in patients.

Conclusion

Infected bone defects represent a uniquely challenging regenerative concern. As highlighted throughout this review, effective treatment therefore requires more than antibacterial eradication or structural defect filling alone. It demands active remodeling of the osteoimmune microenvironment so that host defense, inflammation resolution, angiogenesis, and bone regeneration can proceed in a coordinated manner. In this context, hydrogel-based immunomodulatory systems have emerged as especially promising platforms because they combine injectability, defect adaptability, extracellular matrix-mimicking properties, and the capacity for dynamic therapeutic programming. Rather than functioning as passive carriers, these hydrogels are increasingly designed as instructive biomaterials that sense pathological cues, regulate immune responses, modulate redox and metabolic states, and guide stage-specific tissue repair. Hydrogel design is evolving along programmed microenvironment transformation, immunometabolic reprogramming, spatiotemporal orchestration of immune–osteogenic cascades, and photothermal-assisted osteoimmune regulation. Importantly, the next generation of hydrogels will likely move beyond simplified macrophage-centered models toward multicellular osteoimmune network engineering, with greater emphasis on disease-specific precision design, long-term biosafety, regulatory complexity, manufacturing reproducibility, and clinical scalability. With continued progress in biomaterials science, osteoimmunology, and data-driven design, hydrogel-based immunomodulatory strategies are poised to become powerful therapeutic tools for achieving durable and clinically translatable regeneration of infected bone defects.

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Disclosure

The authors report no conflicts of interest in this work.

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