

Biomimetic Nanoparticles for Bone Regeneration: Construction Strategies and Therapeutic Mechanisms

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Abstract: Bone tissue is the hardest and most dynamic connective tissue in the human body, and its integrity is essential for maintaining both mechanical support and physiological functions. However, with the aging population, the incidence of fractures, osteoporosis, and bone defects has risen significantly, severely impairing patients' quality of life and creating a substantial social burden. Although autologous or allogeneic bone grafts and metallic or non-metallic implants can partially restore bone defects, their long-term efficacy is constrained by donor shortages, immune rejection, and limited regenerative capacity. Consequently, the development of efficient, precise, and biomimetic bone regeneration strategies is of great importance. In recent years, biomimetic nanoparticles have shown unique advantages in mimicking the bone microenvironment, delivering bioactive factors, and modulating cellular behavior due to their tunable structures and functions. This review summarizes the structural composition of bone tissue and its repair processes, highlights biomimetic nanoparticle construction strategies based on cell membranes, exosomes, proteins, and peptides, and discusses their roles in osteogenesis, mineralization, immune regulation, and neurovascular development. Finally, it explores their clinical translation prospects and associated challenges.

Keywords: biomimetic nanoparticles, bone regeneration, exosomes, targeting, tissue engineering

Introduction

Bone is one of the hardest tissues in the human body and constitutes the primary structural component of the skeletal system. It is characterized by a dense and rigid architecture as well as the biological capacity for continuous remodeling, thereby providing essential support and maintaining skeletal function.¹ Bone tissue comprises cellular components—such as osteoblasts, osteoclasts, and osteocytes—alongside matrix elements including collagen and hydroxyapatite. Together, these components coordinate bone formation, resorption, and mechanical maintenance.^{2,3} Structurally, bone exists in two forms: cortical bone and cancellous bone. Cortical bone is compact and rigid, responsible for bearing the majority of mechanical loads, whereas cancellous bone is spongy, enriched with bone marrow and blood vessels, and facilitates material exchange and metabolic regulation.^{4,5} In addition to structural support and enabling movement, bone performs essential physiological functions, including protection of visceral organs, regulation of calcium–phosphorus metabolism, and hematopoiesis.^{6–8} With the global trend of population aging, the incidence of musculoskeletal disorders—including fractures, osteoporosis, infections, tumors, and degenerative diseases—has markedly increased.⁹ Current estimates indicate that approximately 1.71 billion



people worldwide are affected by musculoskeletal diseases.^{10,11} These conditions compromise bone integrity by enhancing resorption, inhibiting osteogenesis, inducing local inflammation, or disrupting bone metabolism. As a result, they often cause bone injury, defects, or nonunion, severely impairing both the mechanical function and regenerative capacity of bone tissue.¹² This pathological process not only diminishes patients' quality of life but also imposes significant socioeconomic and healthcare burdens. Although several clinical strategies are currently employed to treat bone defects—such as autologous and allogeneic bone grafting, metal implants, and bone substitute materials¹³—these approaches remain limited by restricted donor availability, risks of donor-site morbidity, low rates of graft resorption and integration, immune rejection, and suboptimal restoration of bone structure and function (Table 1).^{14,15} Therefore, developing cost-effective and efficient bone regeneration strategies could yield substantial global health and economic benefits.

In recent years, advances in regenerative medicine and tissue engineering have driven bone repair strategies toward greater precision and biomimicry. The development of biomimetic materials with structural and functional similarities to native tissue has shown considerable potential for reconstructing the microstructure, mechanical properties, and biological activity of bone, thereby offering new insights and technical support for repairing complex bone defects.¹⁶ Nanoparticles (NPs), defined as solid particles with dimensions of 1–100 nm, have attracted significant attention in the biomedical field due to their high surface area, excellent biocompatibility, and ease of surface modification.¹⁷ The integration of nanotechnology with regenerative medicine has further accelerated their application in drug delivery systems, bioactive carriers, and smart responsive platforms.¹⁸ In bone repair, nanoparticles not only enable controlled delivery of growth factors or drugs by mimicking the nanoscale architecture of bone but also modulate cellular behavior and the microenvironment, thereby promoting osteogenic differentiation and tissue regeneration.^{19,20} Through strategies such as surface modification and multifunctional coupling, nanoparticles can achieve targeted delivery, controlled release, and tissue-specific repair, establishing themselves as essential materials for bone regeneration research.²¹ However, conventional nanoparticles face significant obstacles in complex physiological environments, including immune clearance, nonspecific distribution, and limited ability to regulate biological signaling.^{22–24} To address these limitations, biomimetic design principles have been increasingly applied in nanomaterial development. By mimicking the structural and functional characteristics of natural cells, tissues, or biomolecules, biomimetic nanoparticles achieve enhanced biocompatibility, targeting, and functional integration.^{25,26} Representative strategies include cell membrane coating,^{27–29} exosome-inspired nanostructures,^{30,31} and protein- or peptide-based templating.^{32–34} These approaches significantly improve nanoparticle stability and recognition *in vivo*, while endowing them with multifunctional biological activities such as osteoinduction, immunomodulation, and neurovascular regeneration. Collectively, biomimetic nanoparticles represent a promising next-generation platform for more efficient and precise bone repair and regeneration.

Table 1 Comparative Analysis of Clinical Bone Defect Repair Strategies

Method	Applicable Conditions	Advantages	Disadvantages	Ref
Autologous bone grafting	Small to moderate defects Areas requiring a strong bone-forming capacity	Excellent biocompatibility Lower risk of immune rejection	Limited sources of bone supply Donor site injury and pain Increased surgical time	[13]
Allograft bone grafting	Large defect Higher structural support requirements	Relatively abundant supply Good structural support	Slow osseointegration Bone Resorption and Nonunion Higher risk of immune rejection Contract infectious diseases	[14]
Metal implants	Fixed load-bearing sections	High mechanical strength Instant stability Mature clinical protocols	Biological inertia Secondary surgery for removal Risk of infection	[15]
Bone substitute materials	Small to moderate defects Bone Graft Supplement	Production stability Avoid damage to the supply area	Osteogenic potential depends on the host microenvironment Bone Resorption and Nonunion	[14,15]

This paper first reviews the structural composition of bone tissue and its microenvironment, along with the healing processes following bone injury. It then systematically summarizes the principal methods and design strategies for constructing biomimetic nanoparticles. Next, it highlights the mechanisms by which biomimetic nanoparticles contribute to bone regeneration. Finally, it discusses current development trends and future application prospects in bone repair, with the aim of providing valuable references and insights for the design of biomimetic nanoparticles and related biomedical research (Figure 1).

Biological Basis of Bone Tissue Regeneration and Repair

Structure and Composition of Bone

Bone is a highly specialized dynamic connective tissue composed primarily of a small population of bone cells embedded within a large bone matrix. Bone tissue is maintained by coordinated interactions among osteoblasts, osteoclasts, and osteocytes, which collectively regulate matrix deposition, resorption, and homeostatic remodeling.³⁵ The bone matrix consists of approximately 30% organic and 70% inorganic mineral components. The organic fraction is primarily composed of type I collagen, which accounts for over 90% of the organic matrix and lends bone its toughness and tensile strength. Non-collagenous proteins, such as osteopontin, osteocalcin, and proteoglycans, contribute to mineralization and mediate cell adhesion.³⁶ The inorganic fraction is primarily composed of hydroxyapatite crystals, which are regularly deposited within collagen fibrils, conferring high hardness and compressive strength to bone.³⁷ At the nanoscale, the organic and inorganic phases form a composite architecture that combines rigidity with elasticity and toughness, thereby enabling bones to withstand substantial external mechanical loads.³⁸

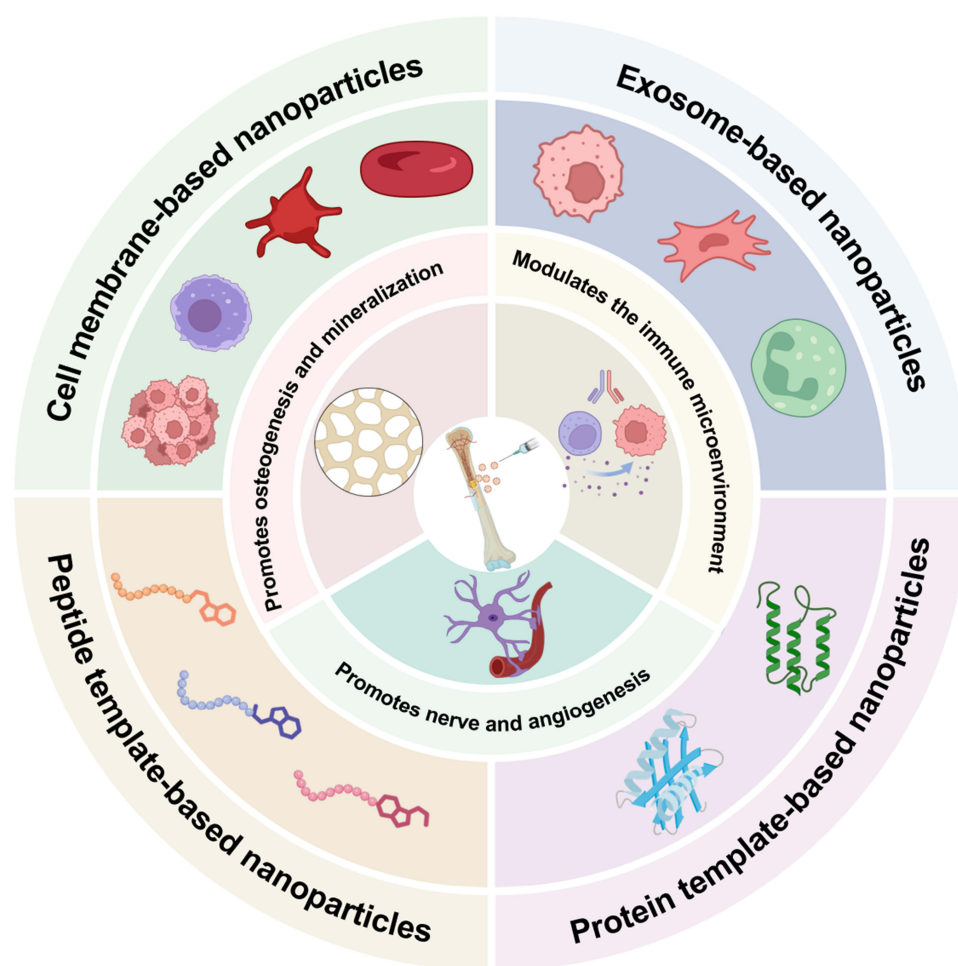


Figure 1 Strategies for Constructing Biomimetic Nanoparticles Based on Different Biological Templates and Their Role in Bone Repair and Regeneration.

Based on structural characteristics and density, bone tissue is classified into two types: compact bone and cancellous bone (Figure 2).³⁹ Compact bone, or cortical bone, is dense and rigid. Its matrix contains abundant organic substances and inorganic salts,⁴⁰ while bone cells are housed within small cavities called lacunae.⁴¹ Approximately 80% of the human skeleton is composed of cortical bone, primarily located in the shafts of long bones and in the outer layers of other bones. It serves as the main mechanical support of the body, capable of withstanding substantial tensile, compressive, and bending stresses.⁴² Mature compact bone exhibits a lamellar arrangement, penetrated by interlacing vascular and neural networks that form the Haversian system. This system, organized around osteons, provides essential nutritional and metabolic support to osteocytes.⁴³ By contrast, immature cortical bone displays a woven architecture without distinct osteons, characterized by randomly oriented collagen fibers.⁴⁴ During bone remodeling, involving resorption and new bone deposition, this woven bone is progressively replaced by mature lamellar bone with well-defined osteons.⁴³ Cancellous bone, or spongy bone, is lightweight and porous, with a honeycomb-like structure composed of interconnected trabeculae. The intertrabecular spaces are filled with bone marrow and vascular tissue.⁴⁵ Accounting for roughly 20% of skeletal mass, cancellous bone is predominantly found in the epiphyses of long bones, ribs, scapulae, and flat bones such as the cranium. Its high surface area allows effective dispersion and absorption of sudden mechanical impacts and supports elevated metabolic activity during bone remodeling.⁴⁶ Moreover, the porous structure facilitates vascularization and hematopoiesis within the bone marrow, serving as a critical foundation for homeostasis and the continuous renewal of bone tissue.⁴⁷

The bone unit is the fundamental structural and functional element of mature cortical bone, representing the highly ordered microscopic architecture of bone tissue. Each osteon consists of concentric lamellae encircling a central Haversian canal.^{48,49} These canals run longitudinally along the bone axis and contain blood vessels, lymphatic vessels, and nerve fibers that provide essential nutritional and metabolic support to compact bone.⁶ Between the lamellae lie lacunae that house osteocytes, which are interconnected by canaliculi to form a three-dimensional communication network that facilitates intercellular signaling and material exchange.⁵⁰ Different osteons are linked by transverse or oblique Volkmann's canals, establishing an interwoven vascular network that connects with the blood supply of the periosteum and bone marrow cavity.⁵¹ This intricate tubular–lamellar architecture ensures sufficient vascularization within dense cortical bone and provides the structural foundation for mechanical adaptation and microdamage repair. The ordered arrangement of osteons confers cortical bone with exceptional resistance to bending, torsion, and compression, forming the microscopic basis for balancing high strength with high toughness in bone tissue.⁵²

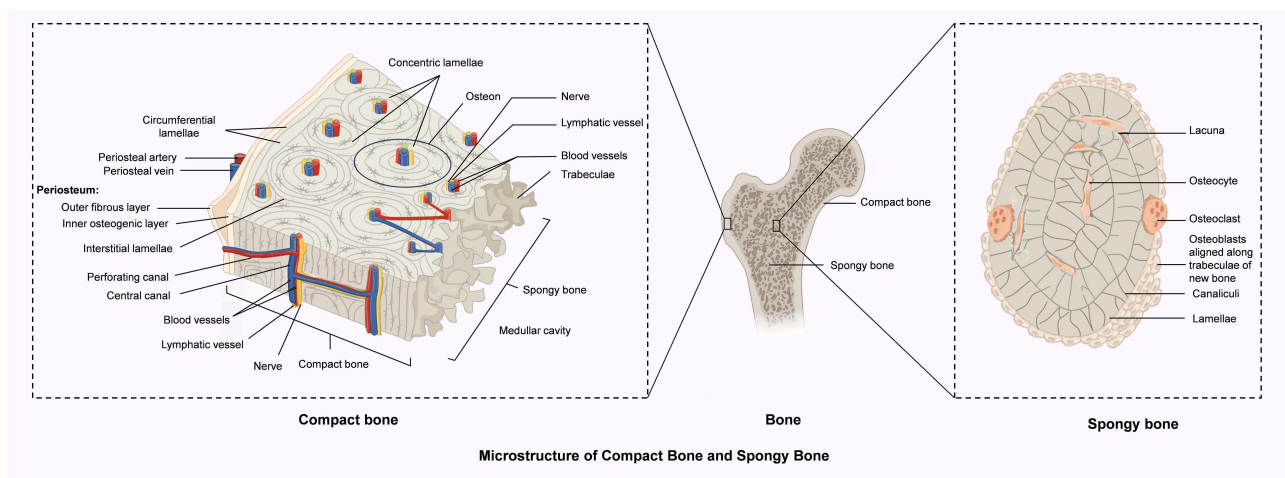


Figure 2 The Composition and Structure of Compact Bone and Spongy Bone.

The Components of the Bone Microenvironment

The Extracellular Matrix in the Bone Microenvironment

The extracellular matrix (ECM) of bone tissue is a critical component of the bone microenvironment. It not only provides a structural scaffold for cell adhesion, growth, and migration but also regulates bone development, maintenance, and regeneration by mediating mechanical signal transduction, storing bioactive factors, and influencing cell fate.⁵³ The bone ECM demonstrates high specificity and dynamic plasticity, consisting mainly of an organic matrix and inorganic minerals, whose synergistic interactions endow bone tissue with superior mechanical properties and biological activity.⁵⁴ The organic fraction represents approximately 30% of the ECM's dry weight, with type I collagen as the predominant constituent, comprising more than 90% of the organic portion. Type I collagen is the key molecule that imparts toughness and tensile strength to bone.⁵⁵ Its ordered fiber arrangement not only provides a template for mineral deposition but also regulates osteoblast adhesion and differentiation. In addition, non-collagenous proteins (NCPs), including osteopontin, osteocalcin, osteoglycin, and proteoglycans, play essential roles in bone formation and remodeling.^{56,57} These molecules participate in matrix mineralization, mediate extracellular signaling, and regulate cell–matrix interactions. The inorganic fraction is composed primarily of hydroxyapatite crystals, which are deposited along the axial orientation of collagen fibers, forming nanoscale bone plates that confer compressive strength and structural stability to bone tissue.⁵⁸ The nanostructural characteristics of the ECM—including collagen fiber diameter, spatial arrangement, and crystal size—directly affect the mechanosensing and responsiveness of osteogenic cells, thereby regulating their proliferation, differentiation, and migration.⁵⁹ Moreover, the ECM undergoes continuous remodeling during osteogenesis and resorption, reflecting its dynamic plasticity.⁶⁰ Matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) synergistically coordinate ECM degradation and reconstruction to maintain the structural and functional homeostasis of bone.⁶¹ Furthermore, the ECM functions as a reservoir and controlled-release system for diverse growth factors, including bone morphogenetic proteins (BMPs), fibroblast growth factors (FGFs), and vascular endothelial growth factor (VEGF).⁶² These factors interact with the ECM to regulate osteogenesis, angiogenesis, and the immune microenvironment, thereby promoting bone regeneration. Consequently, mimicking the composition and nanostructure of the ECM has emerged as a central strategy for the design of biomimetic nanomaterials aimed at enhancing biological functionality and improving integration in bone defect repair.

Because the ECM provides structural support, mediates biochemical signaling, and regulates the local microenvironment, current ECM-inspired biomimetic nanoparticle design strategies can be broadly categorized into two complementary approaches. The first, interfacial biomimicry, focuses on reconstructing a cell-instructive interface by incorporating ECM-derived components (eg., collagen, gelatin, and hyaluronic acid) or adhesive motifs, together with precise control over ligand density and surface physicochemical properties to promote cell adhesion, spreading, and osteogenic differentiation. The second, functional biomimicry, seeks to recapitulate key matrix functions by integrating hydroxyapatite or bone-associated ions to mimic the mineral phase and by incorporating heparinized or sulfated shells, or multivalent binding sites, to enable the spatiotemporal presentation of bioactive factors such as BMPs and VEGF. Through these combined design elements, functional biomimicry provides osteogenic and pro-angiogenic cues that more closely align with the physiological sequence of bone regeneration.

Bone Immune Microenvironment

In recent years, advances in bone biology have highlighted that bone tissue functions not only as a structural support for mechanical forces but also as a highly dynamic site of immune regulation.⁶³ The emergence of the field of “osteimmunology” has revealed the intimate spatial and functional interactions between the skeletal and immune systems, thereby defining the bone immune microenvironment (Figure 3A).^{64,65} This microenvironment comprises diverse bone cells, including osteoblasts and osteoclasts, immune cells such as macrophages, T cells, B cells, and dendritic cells, as well as their secreted cytokines, chemokines, and bone-regulatory factors. Together, these components coordinate to maintain bone homeostasis and facilitate regenerative repair following injury.⁶⁶

Under physiological conditions, the bone marrow serves as the primary site for hematopoietic and immune cell production, providing a rich cellular reservoir for intramedullary immune activity.⁷⁰ Resident immune cells, including macrophages, dendritic cells, and natural killer cells, not only mediate immune surveillance of microenvironmental changes (33872520) but also engage in cross-regulation with bone cells such as osteoblasts and osteoclasts through direct contact or paracrine

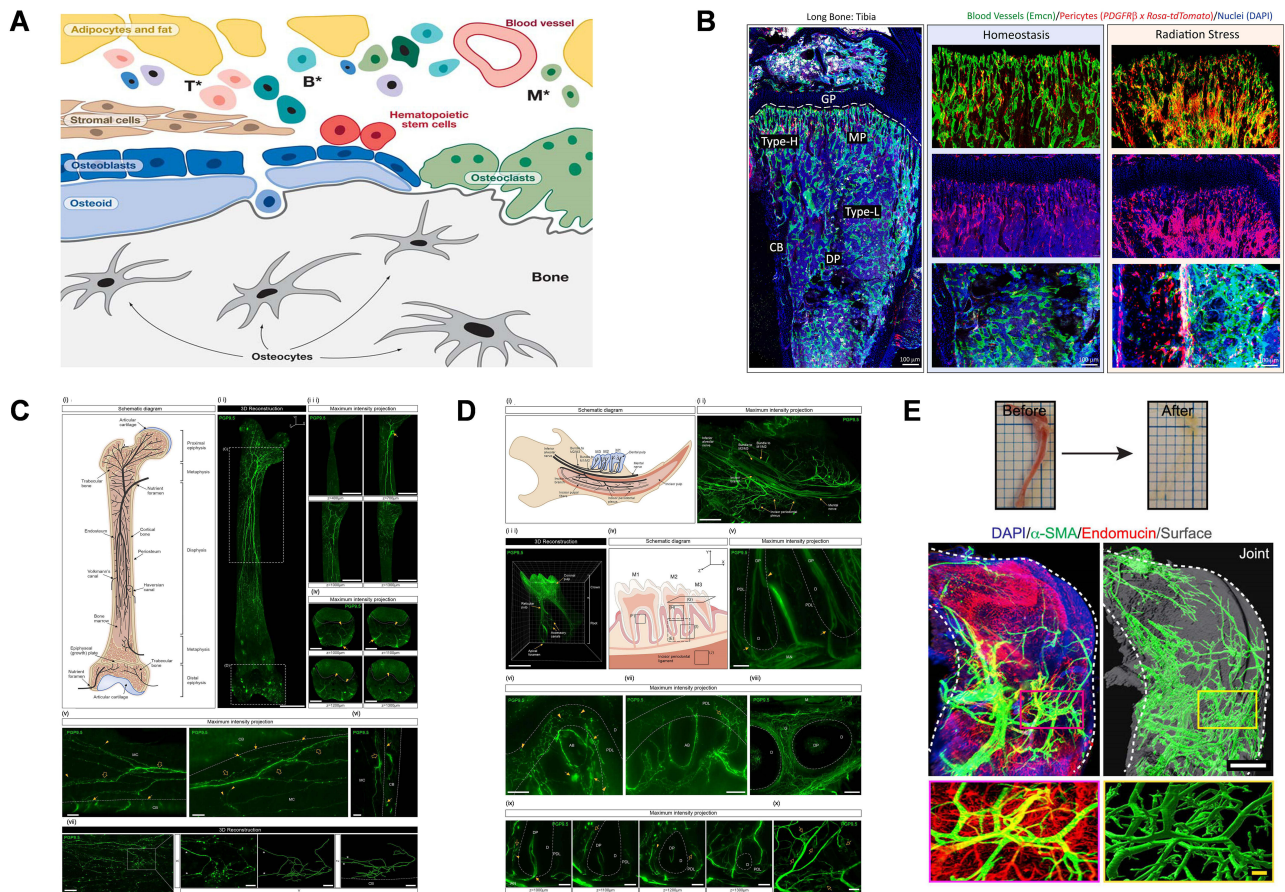


Figure 3 Composition of the Bone Microenvironment. **(A)** Bone microenvironment as a loosely compartmentalized lymphoid organ: primarily comprising T* cells (memory T cells and circulating T cells), B* cells (B cells, memory B cells, and circulating mature B cells), stromal cells, M* cells (monocytes and their derivatives), and newly formed uncalcified osteoid matrix.⁶⁵ **(B)** 3D imaging of blood vessels and perivascular cells under homeostasis and radiation stress.⁶⁷ **(C)** Neural tissue within the femur.⁶⁸ (i) A simplified schematic representation of the neuronal distribution in the mouse femur. (ii) A mosaic stitched, 3D reconstructed image of the bone marrow after surface rendering (scale bars, 1000 μ m). (iii) Insets show 300 μ m maximum intensity z-projections of PGP9.5-labeled nerve fibers are indicated in (ii). Arrow indicates the entry site of a nerve bundle into the marrow cavity (scale bars, 1000 μ m). (iv) Insets show 200 μ m z-projections of nerve fibers in the trabecular bone indicated in (ii). Nerve bundles enter through the distal epiphysis (arrows), where they branch out and terminate in the marrow cavity (arrowheads). Dotted lines indicate the growth plate (scale bars, 500 μ m). (v) 300 (left) and 200 μ m (right) z-projections of nerve fibers imaged at higher power, showing PGP9.5-labeled axons wrapping around or running parallel to blood vessels (open arrows) and branching out and terminating near the endosteum (arrows) or in the marrow cavity (arrowheads) (scale bars, 100 μ m). (vi) A 100 μ m z-projection showing PGP9.5-labeled axons following vessels in the marrow cavity (open arrows) and running through canals in the cortical bone (arrows) (scale bar, 100 μ m). (vii, left) A 3D reconstructed image of PGP9.5-labeled nerve fibers taken in the lower diaphysis (scale bar, 200 μ m). (Right) Insets show a 3D reconstruction and tracing of a cluster of complex nerve endings indicated in the white box viewed from the front (XY-plane; left) and side (YZ-plane; right). Asterisks indicate parent axons (scale bars, 50 μ m). Dotted lines indicate cortical bone. **(D)** Neural tissue within the mandible.⁶⁸ (i) A simplified schematic representation of the neuronal distribution in the mouse mandible. (ii) An 800 μ m maximum intensity z-projection showing the distribution of inferior alveolar nerve branches through the mandible (scale bar, 500 μ m). (iii) A 3D-reconstructed image of the dental pulp after surface rendering (scale bar, 500 μ m). (iv) Schematic representation indicating the location from which (v–x) were sampled and viewed. (v) A 400 μ m z-projection showing a bundle of nerve fibers that entered the molar through the apical foramen (arrows) and an accessory canal (arrowhead) (scale bar, 100 μ m). (vi) A 150 μ m z-projection showing nerve fibers running through the mandibular alveolar bone, including the marrow, and nerve terminal endings in the periodontal ligament (arrowheads). Arrows indicate PGP9.5-labeled cells in the alveolar bone (scale bar, 100 μ m). (vii) An 80 μ m z-projection showing nerve fibers running through the mandibular alveolar bone, including the marrow, and complex Ruffini-like endings in the periodontal ligament (open arrow) (scale bar, 100 μ m). (viii) A 100 μ m z-projection showing innervation of the gingiva around the tooth (scale bar, 200 μ m). (ix) 100 μ m z-projections showing a PGP9.5-labeled nerve bundle entering the apical foramen (arrow) or branching and terminating around the periodontal ligament in a “basket”-like manner around the molar root. The periodontal nerve fibers terminated as free endings (arrowheads) or Ruffini-like endings (open arrows) (scale bars, 100 μ m). (x) A 100 μ m z-projection showing complex Ruffini-like endings (open arrows) in the incisor periodontal ligament (scale bar, 500 μ m). **(E)** Light sheet imaging of intact skeletal elements identifying lymphatic vessels within the knee joint⁶⁹ (scale bar, 50 μ m).

Abbreviations: GP, growth plate; MP, metaphyseal; CB, condensed bone; DP, diaphyseal; Emcn, endomucin; PDGFR β , platelet-derived growth factor beta (scale bars, 100 μ m); CB, cortical bone; MC, marrow cavity; AB, alveolar bone; D, dentin; DP, dental pulp; G, gingiva; IAN, inferior alveolar nerve; M, muscle; PDL, periodontal ligament.

signaling. Among these interactions, the RANK–RANKL–OPG axis represents a central pathway in osteoimmune regulation. RANKL, secreted by osteoblasts and activated T and B lymphocytes, induces osteoclast differentiation and maturation.⁷¹ Osteoprotegerin (OPG), acting as a soluble decoy receptor, competitively binds RANKL and prevents its interaction with RANK, thereby inhibiting osteoclast formation and maintaining the balance between bone resorption and formation.⁷² The subtypes and polarization states of immune cells also play essential roles in shaping the bone microenvironment. Macrophages dynamically transition between M1 (pro-inflammatory) and M2 (anti-inflammatory) phenotypes depending on local stimuli.

This polarization modulates inflammatory responses^{73,74} and indirectly regulates osteoblast and osteoclast activity via cytokine secretion, thereby influencing bone remodeling.²⁵ T cells display similarly diverse functions: subsets such as Th1, Th2, Th17, and Treg exhibit complex and distinct roles in bone metabolism. By secreting specific cytokines, they regulate the balance of bone resorption and formation and contribute to bone regeneration by maintaining immune homeostasis.^{75,76} Through these synergistic interactions and cross-regulatory mechanisms, immune cells establish a multidimensional and finely tuned network within the bone immune microenvironment. Collectively, this microenvironment is essential for preserving bone tissue function. Its highly integrated immunoregulatory mechanisms not only maintain metabolic equilibrium under homeostatic conditions but also enable rapid adaptive responses to internal and external perturbations, reflecting the multifunctional regulatory system unique to bone tissue.

Because bone regeneration follows a characteristic temporal sequence of inflammation, repair, and remodeling, immune-inspired biomimetic nanoparticle design generally focuses on reshaping the regenerative microenvironment through controlled modulation of inflammatory intensity and immune cell function. One strategy is to target, or preferentially interact with, key immune cells such as macrophages in order to promote pro-repair phenotypes (eg., M2-associated polarization) while attenuating excessive inflammation, thereby creating an immune milieu more conducive to osteogenesis and angiogenesis. A complementary strategy is to incorporate stimulus-responsive release mechanisms that are tailored to defect-site microenvironmental cues, enabling the spatiotemporal separation and staged delivery of immunoregulatory signals together with osteogenic or pro-angiogenic factors.

Vascularization in the Bone Microenvironment

As a highly vascularized and metabolically active tissue, the bone microenvironment regulates the dynamic equilibrium between osteoblasts and osteoclasts through immune cell activity, while the vascular system plays a pivotal role in bone development, remodeling, and regeneration (Figure 3B).^{67,77} The intraosseous vascular network supplies oxygen and nutrients to bone tissue and efficiently removes metabolic waste, thereby preserving local homeostasis and supporting normal skeletal function.⁷⁸

Blood vessels in bone tissue are primarily located between trabeculae in cancellous bone and within the Haversian and Volkmann's canals of cortical bone, forming a complex microcirculatory system with diverse functions.⁶ Recent studies have shown that intraosseous vessels display marked structural and functional heterogeneity, particularly H-type vessels, which are strongly associated with high osteogenic activity.⁷⁹ These vessels regulate the proliferation, differentiation, and localization of bone progenitor cells through the secretion of angiogenic signaling molecules such as VEGF, Platelet-Derived Growth Factor (PDGF), and Notch ligands.⁸⁰ In parallel, vascular endothelial cells establish synergistic regulatory networks with osteoclasts and immune cells, contributing to bone remodeling and immune homeostasis.⁸¹ The intricate interplay between the vascular system and bone cells forms the so-called "vascular–bone axis." This functional unit plays a pivotal role in maintaining bone homeostasis and provides a theoretical basis and therapeutic targets for understanding bone repair and regeneration.⁸² Informed by the biological coupling between angiogenesis and osteogenesis, recent biomaterials and nanodelivery strategies have increasingly focused on improving bone defect repair by promoting vascularization, enhancing local perfusion, and coordinating pro-angiogenic and osteogenic cues in a spatiotemporally controlled manner.

Nerves in the Bone Microenvironment

Bone tissue functions not only as a critical organ for mechanical support and mineral storage but is also extensively innervated by a complex neural network.¹⁴ Anatomically, similar to the intricate vascular system within bone, neural fibers often accompany blood vessels and are widely distributed throughout cortical bone, cancellous bone, bone marrow, and the periosteum (Figure 3C and D).^{68,83,84} Through extensive branching and interconnections, these nerve fibers facilitate signal transmission and nutritional regulation across skeletal structures. Moreover, they act synergistically with bone marrow mesenchymal stem cells (BMSCs), osteoblasts, osteoclasts, and vascular endothelial cells to maintain metabolic homeostasis and dynamic equilibrium within bone tissue.⁸⁵

Intraosseous nerves consist primarily of sensory and sympathetic fibers, which together form a complex neural regulatory system involved in bone formation, continuous tissue renewal, and the modulation of repair mechanisms.⁸⁶ Sensory nerve endings release neuropeptides such as calcitonin gene-related peptide (CGRP) and substance P (SP), directly influencing the

activity of osteoblasts and osteoclasts to promote bone formation or inhibit bone resorption.⁸⁷ By contrast, sympathetic nerves indirectly suppress osteogenesis and enhance bone resorption through norepinephrine secretion, which acts on β -adrenergic receptors, thereby contributing to the inhibition of bone formation within metabolic regulation.⁸⁸ The neural network within bone tissue not only maintains metabolic balance under physiological conditions but also plays a pivotal role in bone repair. Axonal regeneration, neurotrophic factor release, and coordinated vascular reconstruction are considered essential biological events in bone regeneration.^{88,89} Therefore, advancing our understanding of neural regulatory mechanisms in bone tissue is critical for elucidating the pathophysiology of bone regeneration disorders and for developing neuro-mediated therapeutic strategies.

Building on the roles of neural signaling in bone regeneration—including cell recruitment, inflammatory regulation, and coordinated neurovascular reconstruction—recent studies have increasingly incorporated neuroregulatory principles into the design of biomimetic nanodelivery systems. One approach uses nanoplateforms to achieve the localized enrichment and controlled release of neuropeptides, such as CGRP and SP, as well as neurotrophic factors, including NGF and BDNF, thereby providing phase-appropriate neural cues during regeneration. Another strategy exploits the influence of sympathetic signaling on bone metabolism by modulating the neural-immune-bone signaling axis, thereby indirectly optimizing the regenerative microenvironment and promoting bone repair.

Lymphatic Vessels in the Bone Microenvironment

Within the bone microenvironment, the lymphatic system is a critical regulator of immunity and fluid homeostasis. Although its spatial distribution is relatively restricted compared with the vascular system, its biological functions are indispensable. Recent studies have identified abundant lymphatic structures within bone tissue, particularly in the periosteum, cancellous bone, and perimedullary regions (Figure 3E).⁶⁹ These structures maintain interstitial fluid balance, regulate local immune responses, and facilitate metabolic waste clearance.^{90–92} In addition, the lymphatic network contributes to antigen presentation, inflammatory signaling, and immune cell trafficking, thereby indirectly modulating the dynamic balance between osteogenesis and osteoclast activity.⁸⁸ Under pathological conditions such as bone injury, inflammatory disease, and tumor-related bone disorders, functional alterations in lymphatic vessels within bone or adjacent tissues can markedly reshape the local immune environment, compromising the stability of the bone regeneration microenvironment.⁹³ Therefore, elucidating the spatial distribution, structural features, and regulatory mechanisms of lymphatic vessels within the bone microenvironment is essential for advancing a systematic understanding of immune-bone interactions in both homeostasis and disease.

Given the roles of lymphatic vessels in tissue fluid drainage and immune cell trafficking, recent studies have begun incorporating lymphatic-associated processes into the design of nanodelivery systems for bone regeneration. Such strategies typically employ inflammation-responsive nanoplateforms to achieve controlled release of immunomodulatory factors, while optimizing particle size and surface physicochemical properties to enhance accumulation at the defect site. Together, these design features.

The Healing Process of Bone Tissue Injury

The healing of bone tissue is a highly dynamic and tightly regulated biological process that integrates multiple cellular and molecular signaling pathways, with the primary goal of restoring structural integrity and mechanical function.⁹⁴ Bone healing is generally classified into two types: primary (direct) healing and secondary (indirect) healing.⁹⁵

When displacement or compression at the site of bone injury is mild and occurs within a stable mechanical environment, bone repair proceeds through primary healing.⁹⁶ This process predominantly relies on intramembranous ossification, closely resembling normal bone remodeling, and is most common in flat bones such as the cranium, mandible, and clavicle.⁹⁷ Bone marrow mesenchymal stem cells, osteoblasts, and osteoclasts collectively contribute to repair. In the early phase, osteoclasts migrate to the injury site to remove necrotic and damaged matrix,⁹⁸ while BMSCs differentiate into osteoblasts under the regulation of signaling pathways such as BMPs and Wnt/ β -catenin. These osteoblasts secrete type I collagen and other extracellular matrix components, promoting hydroxyapatite deposition and gradually forming dense, lamellar bone.⁹⁹ Ultimately, the newly formed lamellae organize concentrically around the central canal, reconstructing the Haversian system of mature cortical bone and restoring both structural integrity and mechanical function.¹⁰⁰ However, in most clinical cases, inadequate stability or rigidity of external fixation devices results in displacement at the injury site. Under these conditions, bone healing typically follows the classical multi-stage

secondary healing process.¹⁰¹ Based on dynamic histological changes during regeneration, this process can be divided into four sequential stages: hematoma and inflammatory response, soft callus formation, hard callus formation, and bone remodeling (Figure 4).¹⁰²

The hematoma and inflammatory phase represent the initial and indispensable stage of bone healing.¹⁰³ Following bone injury, blood vessels in the surrounding soft tissues rupture, leading to blood extravasation and the formation of a hematoma enriched with platelets and fibrin.¹⁰⁴ This hematoma not only seals the injury site but also acts as a reservoir for bioactive factors, releasing signaling molecules such as PDGF, transforming growth factor- β (TGF- β), and VEGF to promote angiogenesis and recruit mesenchymal stem cells.¹⁰⁵ Concurrently, neutrophils, monocytes, and macrophages migrate to the site, where they remove necrotic tissue and cellular debris by secreting inflammatory mediators including IL-1 β , TNF- α , and IL-6, while simultaneously activating osteogenesis-related signaling pathways.⁹⁵ Subsequently, the process transitions into the soft callus formation phase. Under the influence of multiple growth factors in the bone microenvironment, subperiosteal osteogenic progenitors, BMSCs, and perivascular cells differentiate into chondrocytes and osteoblasts.¹⁰⁶ The locally generated hyaline cartilage matrix, rich in type II collagen and proteoglycans, provides preliminary mechanical stability and partially supports external loading.¹⁰⁷ At the same time, some BMSCs differentiate

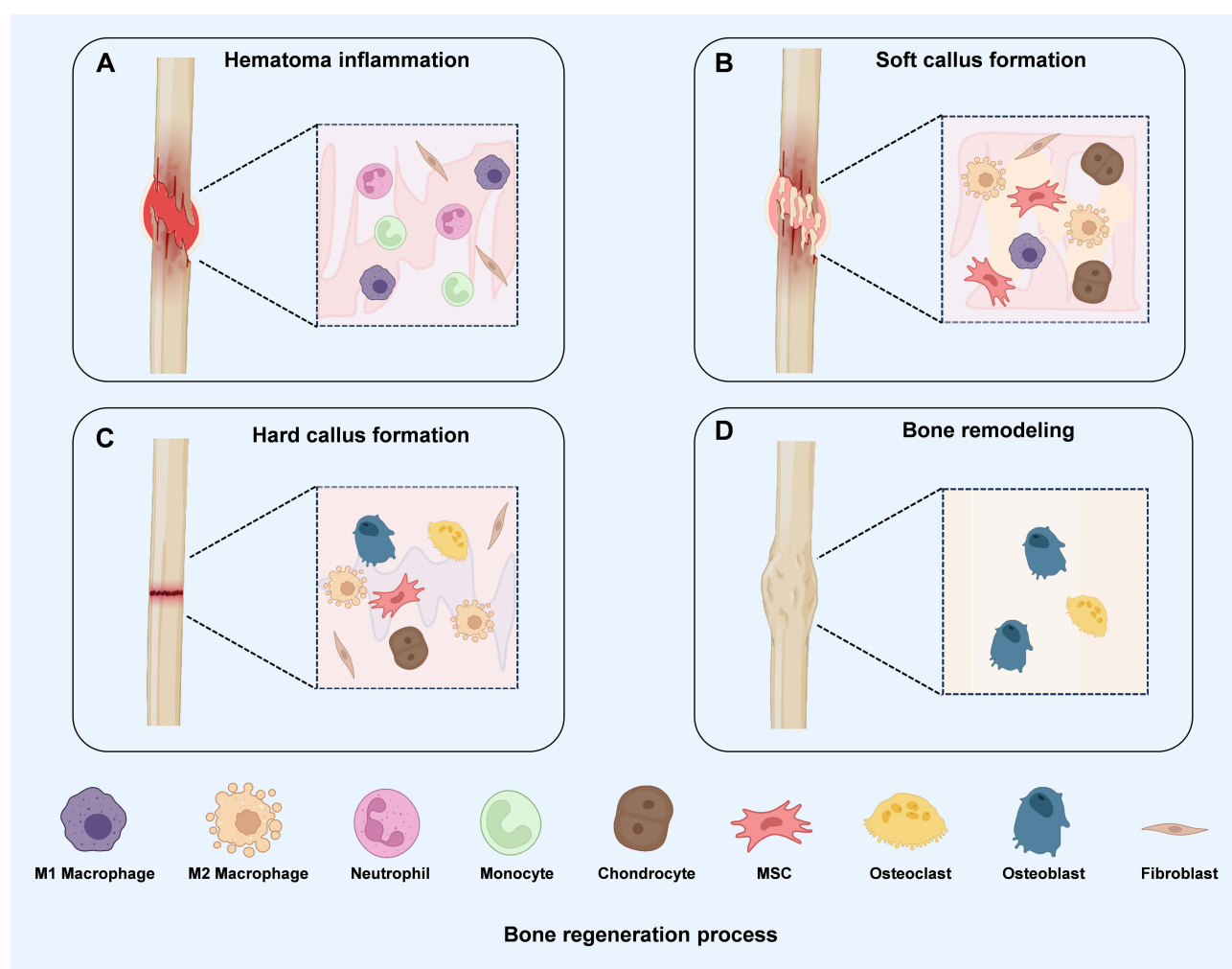


Figure 4 Schematic Diagram of Bone Tissue Injury Healing Process. **(A)** Hematoma and Inflammatory Response Phase: Following fracture, a hematoma forms at the injury site and is accompanied by infiltration of inflammatory cells, primarily neutrophils, monocytes, and M1 macrophages, along with fibroblasts, thereby initiating the early inflammatory response. **(B)** Formation of Soft Healing Tissue Phase: As the inflammatory response gradually subsides, macrophages begin to transition toward a reparative phenotype, while mesenchymal stem cells, chondrocytes, fibroblasts, and macrophages collectively contribute to soft callus formation. **(C)** Formation of Hard Healing Tissue Phase: During endochondral ossification, osteoblasts and osteoclasts, together with MSCs, chondrocytes, fibroblasts, and reparative macrophages, promote mineralized callus formation and bone consolidation. **(D)** Bone remodeling phase: Newly formed bone is further remodeled through the coordinated activities of osteoblasts and osteoclasts, gradually restoring the structural integrity and function of the injured bone.

directly into osteoblasts, depositing non-mineralized collagen matrix that serves as a scaffold for subsequent mineralization.¹⁰⁸ Meanwhile, VEGF secreted by the cartilage matrix stimulates vascular invasion into the injury site, enhancing local oxygenation and establishing conditions necessary for hard callus formation.¹⁰⁹

During the hard callus formation phase, angiogenesis further intensifies, resulting in a marked increase in local oxygen partial pressure. This enhanced oxygenation suppresses the continued differentiation of chondrocytes while simultaneously promoting osteoblast activation and bone matrix deposition.¹¹⁰ As osteogenesis progresses, hyaline cartilage is gradually replaced by calcified cartilage and ultimately by lamellar bone secreted by osteoblasts.¹¹¹ In parallel, intramembranous ossification occurs in the subperiosteal region, directly generating bone plate structures. Hydroxyapatite crystals deposit within collagen fiber interspaces, conferring high compressive strength and structural stability to the newly formed bone tissue, thereby markedly improving its mechanical properties.¹¹²

In the bone remodeling phase, osteoclasts initially resorb woven bone, after which osteoblasts deposit structurally dense lamellar bone to reconstruct the Haversian system characteristic of mature cortical bone.¹¹³ This process depends on the functional coordination between osteoclasts and osteoblasts, primarily regulated by the RANKL–RANK signaling pathway, to maintain dynamic equilibrium between bone resorption and formation.¹¹⁴ As trabeculae and cortical bone gradually align with mechanical loading, the tissue's resistance to bending, torsion, and compression markedly increases. Ultimately, the anatomical architecture and function of the medullary cavity and vascular network are restored to steady-state levels, thereby fully re-establishing the mechanical support and metabolic functions of bone tissue.¹¹⁵

The endogenous bone-healing process depends critically on the proper initiation and timely resolution of inflammation, effective vascular regeneration with restoration of tissue oxygenation, and precise coordination of osteoblast–osteoclast coupling. In clinically common pathological conditions—including aging and osteoporosis, diabetes, infection, post-tumor resection defects, and nonunion—the defect microenvironment is often characterized by persistent or dysregulated inflammation, elevated oxidative stress, impaired angiogenesis, and compromised reparative cell function. As a result, healing may remain arrested in the inflammatory or cartilaginous stages, ultimately leading to delayed union or nonunion. In this context, biomimetic nanoparticles provide several rational strategies to overcome pathological barriers to bone repair. First, immune-biomimetic and immunoregulatory designs can facilitate the transition from inflammation to repair by modulating macrophage phenotypes and limiting excessive release of inflammatory mediators. Second, strategies aimed at restoring vascularization and perfusion can enhance angiogenic–osteogenic coupling and improve local oxygenation through the delivery of pro-angiogenic factors or the incorporation of microenvironment-responsive release mechanisms triggered by hypoxia, reactive oxygen species (ROS), or pH changes. Third, ECM and mineral phase-mimetic approaches can partially compensate for the compromised osteogenic niche under pathological conditions. In more complex settings, such as infectious or tumor-associated bone disease, nanoplatfoms may further integrate antimicrobial and regenerative functions to simultaneously address pathological control and tissue reconstruction.

Strategies for Constructing Biomimetic Nanoparticles Based on Different Biological Templates

In bone tissue engineering and regenerative medicine, the development of biomimetic nanoparticles has emerged as a pivotal strategy to improve bone repair efficiency and regeneration outcomes.¹¹⁶ These nanoscale platforms achieve precise biomimicry of natural biological components through modifications in chemical composition, spatial configuration, and surface functionalization. Such designs enable high compatibility with host tissues *in vivo* while effectively replicating—or even amplifying—critical signaling pathways and biological functions involved in bone repair.²⁵ This approach not only enhances immune regulation within the bone microenvironment but also promotes osteoblast differentiation, accelerates mineralization, and enables targeted drug delivery to sites of injury. In this review, we summarize construction strategies for biomimetic nanoparticles based on diverse biological templates, including cell membrane-based, exosome-based, protein template-based, and peptide template-based systems (Table 2). Table 3 outlines the advantages and limitations of these biomimetic nanoparticle categories, providing a theoretical framework for their rational selection and optimization in bone regeneration applications.

Table 2 Comparative Analysis of Bionic Nanodelivery Strategies: Composition, Preparation, Targeting Mechanisms, and Therapeutic Functions

Biomimetic Strategy	Core Components	Biomimetic Component	Preparation Method	Targeting Mechanism	Therapeutic Function	Ref
Cell Membrane-Based Nanoparticles	PLGA liposomes	RBCs, Platelets, Tumor cells, MSCs, macrophages, OBs	Membrane extraction followed by fusion with nano-cores via extrusion or ultrasonication	Homologous targeting Inflammatory chemotaxis,	Targeted Enrichment Immune Regulation	[117]
Exosome-Based Nanoparticles	Natural or engineered exosomes	Endogenous cargo (siRNA and proteins)	Ultracentrifugation	Receptor-ligand recognition	Drug and siRNA Delivery Multipathway Microenvironment Remodeling	[118,119]
Protein Template-Based Nanoparticles	Self-assembling protein	Domains and functional groups of proteins	Solvent-free processing, emulsion polymerization, self-assembly	Receptor-mediated uptake Bone affinity retention	Drug Delivery and Controlled Release	[120]
Peptide Template-Based Nanoparticles	Self-assembling peptides	Short peptide sequence	Solid-phase synthesis and self-assembly, surface grafting, and click chemistry	Click Chemistry Sequence-Specific Recognition	Precision Signal Delivery	[121]

Table 3 Advantages and Disadvantages of Strategies for Constructing Biomimetic Nanoparticles Based on Different Biological Templates

Type	Advantages	Disadvantages	Ref
Cell membranes	Preserving the “self” markers of source cells to reduce immune clearance Natural targeting capability Excellent vector compatibility	Extraction and separation processes are complex Drug loading capacity is limited High potential toxicity	[28,122]
Exosomes	Endogenous loading mechanism enables efficient delivery of therapeutic molecules Low immunogenicity Immune evasion	Extraction and purification steps are cumbersome with low yield Components exhibit significant heterogeneity Poor stability Strict storage conditions	[116,123]
Proteins	Chemical modification enables efficient drug loading and specific targeting Easily functionalized Capable of large-scale production expansion	Potential toxicity Prone to inactivation by environmental factors	[124,125]
Peptides	Sequence design flexibility with high specificity in synthesis Low molecular weight for excellent permeability Low immunogenicity Functional diversification is achievable through amino acid residue modification	Poor stability Limited drug loading capacity	[121]

Cell Membrane-Based Nanoparticles

As natural biological interfaces, cell membranes exhibit exceptional biocompatibility. Their phospholipid bilayers encapsulate diverse functional proteins that are essential for signal transduction, cell recognition, and immune regulation.¹²⁶ Membranes derived from different cell sources preserve the key biological traits of their parent cells, including “self” markers, targeting capabilities, and specific interactions with the immune system.^{27,127} Since the 1980s, cell membranes have been extensively investigated as natural carriers for drug delivery, enabling targeted transport and

controlled release within the body.³³ More recently, techniques such as hypotonic treatment and ultrasonic extrusion have been employed to coat various nanoparticle surfaces with cell membranes. The resulting nanoplateforms integrate the biological attributes of cell membranes with the physicochemical properties of nanoparticles, establishing themselves as a cutting-edge focus in active targeted drug delivery research.²⁷ To date, this biomimetic strategy has been applied to multiple cell types, including erythrocytes,²⁸ platelets,¹²² cancer cells,¹¹⁷ and macrophages.¹¹⁷

Red blood cells (RBCs) are the most abundant and longest-circulating cells in the human bloodstream, with a lifespan of approximately 100–120 days.¹²⁸ Accordingly, they were among the earliest cell types investigated and applied in cell therapy. The erythrocyte membrane preserves multiple functional proteins, including CD47, C8bp, and HRP, which interact with signal-regulatory protein alpha (SIRP α) to transmit “self” recognition signals to the immune system, thereby suppressing phagocytic clearance by immune cells.¹²⁹ This immune evasion mechanism prolongs the *in vivo* half-life of RBCs and extends the circulation time of RBC membrane-coated nanoparticles. Moreover, the absence of a nucleus and most organelles results in minimal cytoplasmic contents, reducing interference during membrane separation and extraction. This facilitates the acquisition of structurally intact and functionally preserved membranes for nanoparticle coating.^{130,131} Ji et al developed icariin (ICA)-loaded nanoparticles (iRINPs) coated with erythrocyte membranes functionalized with the tumor-penetrating peptide iRGD, creating a biomimetic camouflage layer to overcome ICA’s limitations, including poor solubility, high hydrophobicity, and limited tumor penetration. The iRINPs significantly enhanced ICA solubility, biocompatibility, and stability while markedly reducing macrophage uptake. In a lung cancer model, they inhibited A549 cell proliferation, migration, and invasion, demonstrating superior therapeutic efficacy compared with ICA alone.²⁸ Overall, RBC membranes offer excellent biocompatibility, low immunogenicity, prolonged circulation, and facile membrane separation, making them a promising platform for biomimetic drug delivery and precision medicine. Nevertheless, additional functionalization strategies are required to overcome inherent limitations, particularly their lack of intrinsic tumor-targeting ability.

Platelets are naturally occurring, anucleate, disc-shaped cells in the bloodstream with a diameter of approximately 2–3 μm . They are released from megakaryocytes in the bone marrow during maturation.¹³² Beyond their central role in hemostasis and coagulation, platelets contribute to a range of physiological and pathological processes, including angiogenesis, immune regulation, and inflammation.^{133,134} Platelet membranes are enriched with adhesion molecules and receptors that promote preferential accumulation at ischemic or injured sites in the circulation.¹³⁵ Accordingly, platelet membrane-derived biomimetic nanoparticle delivery systems have attracted growing interest. Nevertheless, difficulties in platelet isolation and *ex vivo* processing remain major barriers to clinical translation. Hu et al developed platelet membrane-cloaked nanoparticles (PNPs) by coating poly(lactic-co-glycolic acid) (PLGA) nanoparticles with human platelet membranes. These PNPs were separately loaded with docetaxel and vancomycin, yielding the PNP-DtX1 and PNP-Vanc delivery systems. Their therapeutic efficacy was subsequently evaluated in rat models of coronary artery injury and mouse models of systemic bacterial infection. Results demonstrated that PNP-DtX1 effectively suppressed neointimal hyperplasia induced by balloon injury, while PNP-Vanc significantly reduced bacterial loads in multiple organs of infected mice (Figure 5A and B).¹²²

Tumor cells exhibit a range of distinctive biological characteristics, including unlimited proliferative capacity, immune evasion, and homing and adhesion properties mediated by specific membrane proteins.^{137,138} Exploiting these features, nanoparticles cloaked with tumor cell membranes can achieve active targeting and selective adhesion to tumor tissues, thereby improving drug delivery efficiency and antitumor efficacy.¹³⁹ For example, Meng et al engineered a peptide delivery system (SPIO NP@M-P) by encapsulating superparamagnetic iron oxide nanoparticles within lung cancer H460 cell membranes and conjugating them with a PD-L1 inhibitor peptide (TPP-1) and an MMP2 substrate peptide. This multifunctional system integrated homologous targeting, enzyme-triggered release, and magnetic resonance imaging capabilities. It significantly prolonged peptide half-life *in vivo*, enhanced T-cell activation, and inhibited tumor growth, demonstrating potential as an integrated platform for tumor diagnosis and therapy.¹¹⁷ Similarly, Wang et al first prepared ovalbumin (OVA) nanoparticles loaded with the photosensitizer Ce6 (ON) and subsequently cloaked them with B16-OVA cancer cell membranes, yielding membrane-coated nanoparticles (MON) with homotypic targeting capability. Under laser irradiation, MONs enhanced OVA antigen cross-presentation through ROS generation, effectively inducing immune cascade reactions that achieved complete tumor clearance and durable immune memory in tumor-bearing mice.

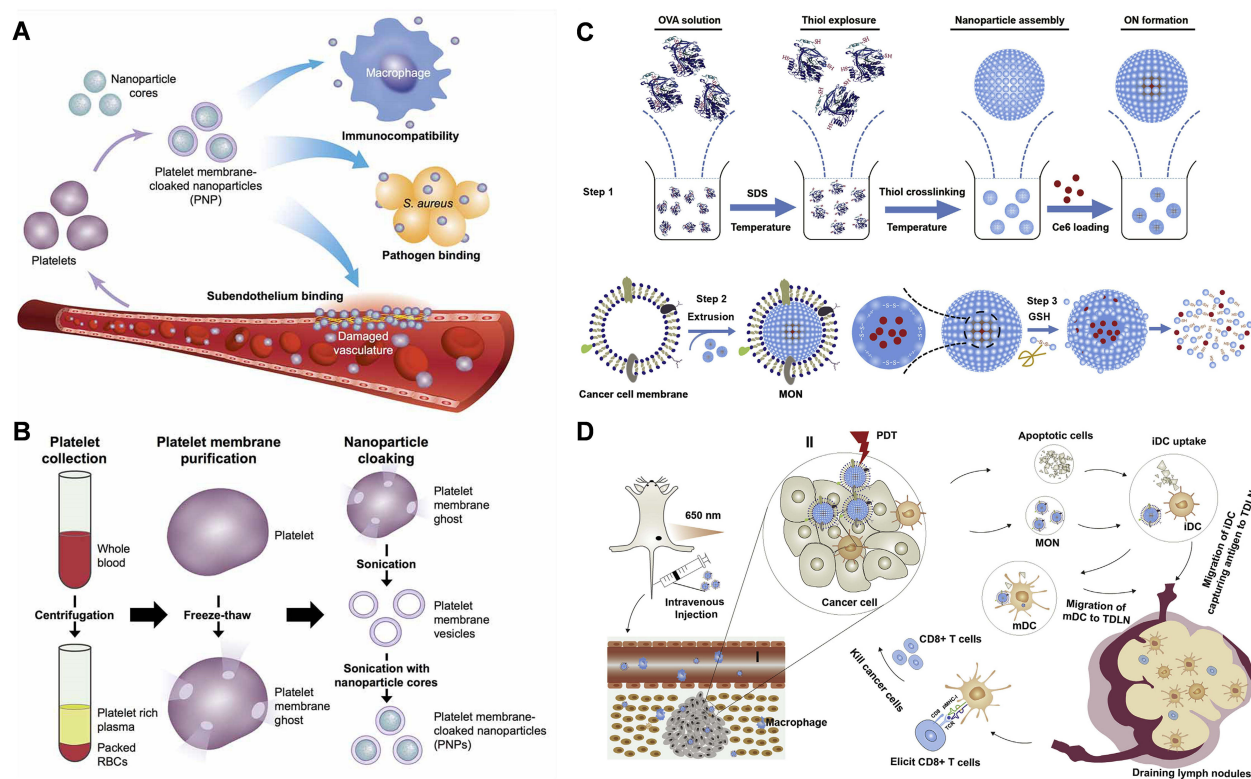


Figure 5 Strategies for Constructing Cell Membrane-Based Bionic Nanoparticles (A) Enveloping poly(lactic-co-glycolic acid) (PLGA) nanoparticles with human platelet membranes endows them with platelet-like properties, conferring immunocompatibility, endothelial cell binding, and pathogen adhesion capabilities, thereby significantly enhancing in vivo stability and targeting efficiency.¹²² (B) Schematic of membrane-coated photosensitizer nanocarrier (MON) preparation and photosensitizer nanocarrier (ON) depolymerization processes. (C) Schematic of platelet membrane-cloaked nanoparticle (PNP) preparation. (D) Schematic of MON in vivo circulation, tumor targeting, and immune response induction during photodynamic therapy.¹³⁶

Compared with conventional photodynamic therapy (PDT), this strategy substantially expanded PDT's immunological potential, offering a novel and highly efficient approach to photodynamic immunotherapy (Figure 5C and D).¹³⁶

Macrophage-coated nanoparticles exhibit remarkable immune evasion capacity due to the protective function of membrane-derived proteins, thereby extending their half-life in systemic circulation.¹⁴⁰ In addition, the abundance of inflammation-related receptors on macrophage membranes mediates their inherent chemotaxis toward inflammatory microenvironments, enabling selective nanoparticle accumulation at lesion sites and conferring tissue-targeting properties. This significantly enhances the precision of drug delivery and therapeutic efficacy.^{141,142} Lu et al developed a biomimetic anti-inflammatory nanomedicine system (MM-CEP/NLCs) for the treatment of acute lung injury by encapsulating cefpodoxime (CEP) in nanostructured lipid carriers (NLCs) coated with macrophage membranes (MMs). This platform integrates the superior physicochemical properties of nanostructured lipid carriers with the inflammatory homing and immune regulatory functions of macrophage membranes. It achieves targeted accumulation and sustained drug release at pulmonary inflammatory sites while markedly reducing lung injury parameters, including pulmonary edema, bronchoalveolar lavage cell counts, inflammatory cell infiltration, and cytokine levels, thereby demonstrating promising potential in the treatment of inflammatory diseases.²⁹

Within cell membrane-based biomimetic nanostrategies, recent studies have extended beyond conventional membrane templates—such as erythrocyte, platelet, and immune cell membranes—to incorporate membranes derived from cells directly involved in bone regeneration and remodeling. This shift enables more precise engagement of the key regulatory processes that govern the bone-defect microenvironment. In particular, stem cell membranes have attracted interest because of their lesion-homing capacity, low immunogenicity, and potential to modulate the local microenvironment. Accordingly, they have been used to enhance nanocarrier accumulation and retention at defect sites while providing a biomimetic interface for the integration of osteogenic, angiogenic, and immunomodulatory functions.^{143,144} Dong et al incorporated BMSC membrane-coated, ultrasound-responsive barium titanate nanoparticles into carboxymethyl cellulose-based hydrogels to create a dual-

functional platform for diabetic bone regeneration. This system improved repair by simultaneously reshaping the immune microenvironment and enhancing osteogenic stimulation: CMS promoted macrophage polarization from the pro-inflammatory M1 phenotype toward the pro-reparative M2 phenotype via the PI3K–Akt–mTORC1 axis, whereas the released nanoparticles generated moderate levels of ROS under ultrasound stimulation, thereby activating Wnt/ β -catenin signaling and enhancing BMSC proliferation and osteogenic differentiation.¹⁴³

Osteoblast-derived membranes represent another functionally relevant template, as their surface adhesion molecules and bone-associated receptors can improve bone-site targeting and support a more favorable osteogenic microenvironment, thereby promoting osteogenic differentiation and mineralization.¹⁴⁵ In this context, Li et al developed a bone-targeted delivery platform (OM/Cur@NPs) by coating curcumin-loaded PLGA nanoparticles with osteoblast-like membranes enriched in CXCR4 and tumor necrosis factor- α receptors. This design improved the *in vivo* stability of curcumin and increased accumulation at bone sites. In ovariectomized mice, the platform achieved greater bone enrichment and attenuated the inflammatory bone microenvironment through TNF- α neutralization, thereby exerting dual effects of promoting osteogenesis and suppressing bone resorption.¹⁴⁶

Because cell membranes are directly derived from the host organism, most cell membrane-coated nanoparticles display excellent biocompatibility, biodegradability, and low immunogenicity. Nevertheless, their potential risks cannot be ignored. Certain cellular components and secreted molecules may exert toxic effects. For example, hemoglobin in blood has been reported to induce neuronal death,¹⁴⁷ while bioactive factors released by platelets may exhibit neurotoxicity.¹⁴⁸ Therefore, comprehensive safety assessments are essential before clinical application of biomimetic cell membrane-coated nanoparticles. In addition, the structural complexity of these systems often limits their drug-loading capacity. Despite these limitations, cell membrane-coated nanoparticles hold considerable promise for active tumor targeting due to their intrinsic membrane proteins and biorecognition properties. However, their mechanisms of action and safety profiles require further systematic investigation.

Exosome-Based Nanoparticles

Exosomes (EVs) are nanoscale lipid bilayer vesicles secreted by diverse cell types to mediate intercellular communication. With diameters of approximately 30–150 nm, they are widely distributed in bodily fluids such as blood, urine, and saliva. EVs originate from intracellular multivesicular bodies (MVBs) and are released into the extracellular microenvironment through exocytosis.^{149,150} They play pivotal roles in numerous physiological and pathological processes by transporting nucleic acids, proteins, and small molecules from donor cells to recipient cells, thereby regulating cellular biology and inducing functional or phenotypic changes.^{151–153} Owing to their broad distribution, nanoscale size, and natural tropism for specific tissues and cells, EVs are increasingly recognized as promising candidates for drug delivery systems and diagnostic biomarkers.¹⁵⁴

Multiple studies have confirmed that exosomes, as key mediators of intercellular communication, possess selective recognition capabilities for specific target cells and display natural tropism toward particular tissues.¹⁵⁵ This unique ability to interact with target cells enables exosomes to play pivotal roles not only in maintaining physiological homeostasis and mediating pathological processes but also as ideal natural carriers for therapeutic agents, thereby advancing precision medicine.³⁰ Currently, drug loading into EVs is achieved through two primary strategies: indirect and direct methods (Figure 6A).^{116,123} Indirect loading exploits the endogenous biogenesis of EVs, during which therapeutic molecules are incorporated by donor cells and subsequently packaged into vesicles. This approach mainly includes two strategies: (i) co-incubation, in which donor cells are exposed to therapeutic molecules that are internalized and secreted into EVs through intrinsic uptake and secretion pathways;¹¹⁸ and (ii) genetic engineering, in which specific genes or proteins are introduced into donor cells via transfection or gene editing to direct selective packaging of RNA, proteins, or functional molecules into EVs.¹¹⁹ For example, Wang et al co-incubated paclitaxel (PTX) and doxorubicin (DOX) with breast and ovarian cancer cells, yielding exosomes enriched with these drugs.¹⁵⁶ Similarly, Liu et al overexpressed miR-20a in BMSCs, generating EVs that promoted BMSC migration, osteogenesis, and enhanced osseointegration of porous titanium alloys in osteoporotic rats.³¹ Direct loading, in contrast, bypasses donor cell metabolism by modifying EV membrane permeability to allow drug entry. This method increases loading efficiency and is particularly suited for hydrophilic or macromolecular drugs.¹⁵⁷ Common strategies include passive co-incubation and active electroporation. In passive co-incubation, isolated EVs are directly incubated with therapeutic molecules, enabling drug entry via diffusion or affinity.¹⁵⁸ For instance, Wei et al loaded DOX into BMSC-derived EVs by co-incubation, followed by desalting and dialysis, producing Exo–Dox vesicles that enhanced uptake, inhibited

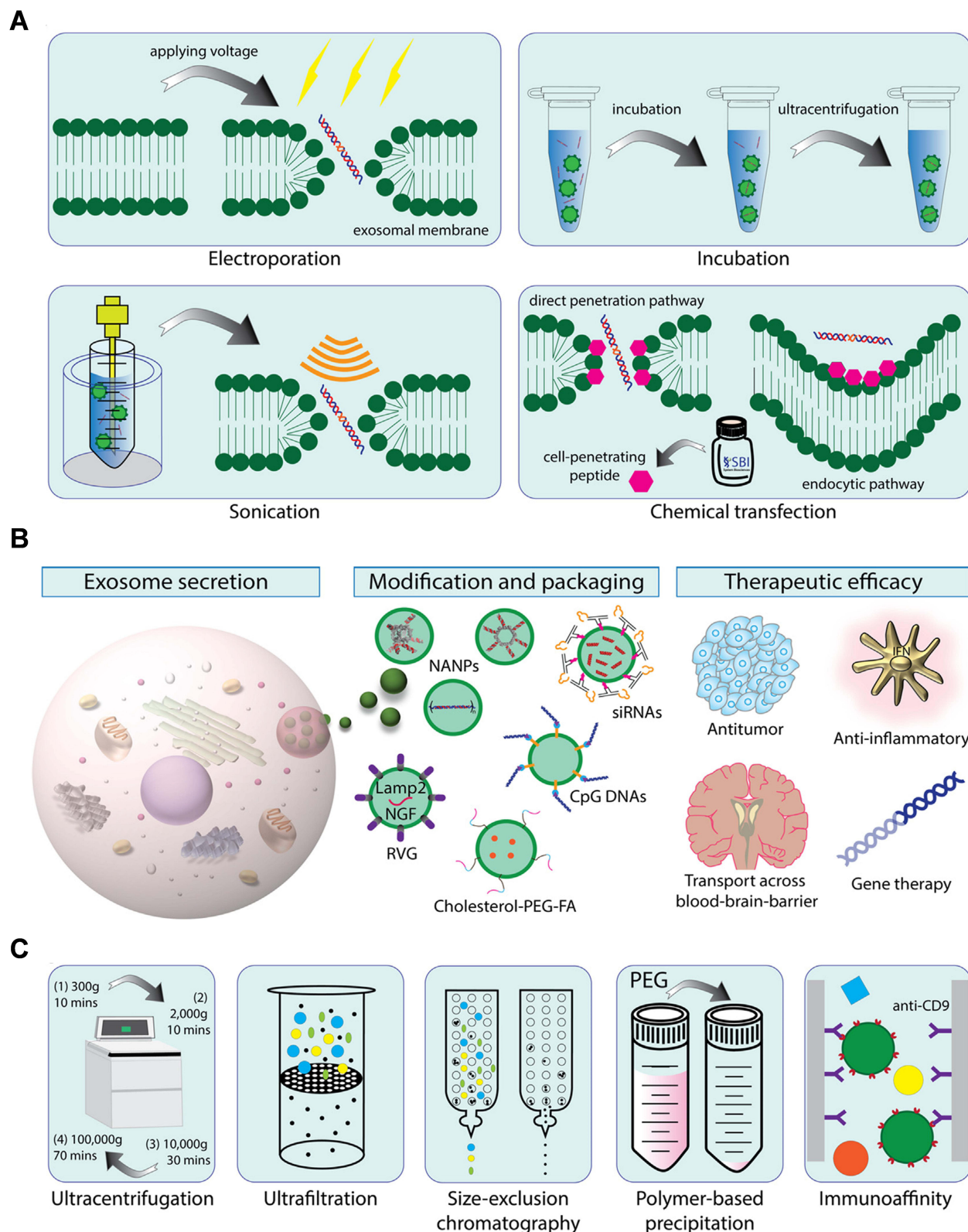


Figure 6 Different Methods for Exosome Isolation and Drug Encapsulation. **(A)** Commonly Used Exosome Isolation Method.¹⁵⁷ **(B)** Commonly Used Exosome Drug Encapsulation Methods.¹⁵⁷ **(C)** Schematic diagram of exosome-mediated delivery of different functionalized payloads. Following separation and purification, exosomes can be engineered to acquire specific targeting capabilities through surface modification or by covalent incorporation of functional motifs. Therapeutic payloads may be encapsulated within the exosomal lumen or conjugated to its surface. Upon uptake by target cells, the therapeutic motifs exert their intended effects.

osteosarcoma MG63 proliferation, and exhibited reduced cardiotoxicity in H9C2 cells.¹⁵⁹ Electroporation, by contrast, generates transient pores in EV membranes under high voltage, facilitating efficient encapsulation of hydrophilic or large molecules such as siRNA.^{157,160} Faruq et al successfully employed electroporation to load siRNA into exosomes derived from human embryonic kidney cells, achieving efficient delivery into cancer cells and establishing a standardized protocol for siRNA-based EV therapeutics (Figure 6B).¹⁶¹

Although exosome-based therapeutic strategies have not yet received clinical approval, early clinical trials have demonstrated their favorable safety profile. Once regarded merely as cellular metabolic waste, exosomes are now increasingly recognized as promising delivery platforms for diverse therapeutic agents, with their roles in intercellular communication being progressively clarified. Compared with cell membrane-coated nanoparticles, exosome-based delivery systems offer several advantages, including high endogenous loading capacity, low immunogenicity, ease of modification, and enhanced cellular internalization efficiency. Nonetheless, clinical translation remains hindered by significant challenges, such as the development of efficient separation and purification methods, scalable production processes, and appropriate storage conditions (Figure 6C). Moreover, a deeper understanding of the uptake and transport mechanisms of EVs and their subpopulations in recipient cells is essential to advance their broad application in targeted therapies.

Protein Template-Based Nanoparticles

Protein-templated nanoparticles have emerged as an important research direction in nanomedicine. This strategy exploits the three-dimensional structure, functional group distribution, and self-assembly capacity of proteins as natural templates to guide nanoparticle nucleation and ordered growth.³² By mimicking biomineralization and biomolecular assembly, such approaches enable the synthesis of nanoparticles that closely resemble natural structures in size, morphology, and functionality. Based on design strategies, these nanoparticles can be broadly classified into three categories: protein–drug conjugates, engineered therapeutic proteins, and combinatorial complex platforms utilizing protein motifs.^{124,125} Protein-templated nanoparticles offer the advantage of personalized functional design through surface modification, while also improving drug targeting and minimizing off-target effects. As a result, they show great promise in cancer therapy, bone regeneration, and precision treatment of chronic diseases.¹²⁰ Albumin, a highly soluble and stable natural protein, possesses low toxicity, excellent biocompatibility, and a long in vivo half-life.¹²⁰ Its molecular surface contains multiple functional groups amenable to chemical modification, making it an ideal carrier for drug delivery systems. Albumin-based nanocarriers effectively improve drug stability, solubility, and tissue targeting.¹⁶² Zhu et al developed a novel biomimetic bone repair material, TD-BNP@DBBM, by loading thiazolidine-2,5-dione (TD) onto bovine serum albumin nanoparticles (BNPs) and combining them with deproteinized bovine bone mineral (DBBM). Experimental findings demonstrated that TD-BNP@DBBM significantly enhanced the osteogenic differentiation of MC3T3-E1 cells and accelerated bone regeneration in a rat cranial defect model, a process potentially associated with activation of the Wnt/ β -catenin signaling pathway (Figure 7).¹⁶³ Similarly, MinJoo Kim et al employed bovine serum albumin (BSA) to modify nanoparticle surfaces for biomimetic functionalization. Compared with scaffolds containing unmodified nanoparticles, BSA-coated scaffolds exhibited superior protein adsorption capacity and controllable degradation behavior, while significantly improving MC3T3-E1 cell adhesion, proliferation, and alkaline phosphatase (ALP) activity.¹⁶⁴

Transferrin (Tf) is a natural protein widely employed in drug delivery systems. Its primary physiological role is to mediate iron transport across cell membranes by binding to transferrin receptors (TfR) on the cell surface, thereby maintaining cellular iron homeostasis and normal physiological function.¹⁶⁶ The high expression of transferrin receptors on many tumor cells allows this receptor-mediated endocytosis pathway to serve not only in regulating iron metabolism but also as an efficient targeting mechanism for drug and gene delivery.¹⁶⁷ As a result, transferrin and transferrin-derived nanoparticles show considerable promise in antitumor therapy and in facilitating drug transport across the blood–brain barrier. For example, Peng et al utilized an adenoviral vector to upregulate transferrin receptor expression in prostate cancer cells, which significantly enhanced the selective uptake and intracellular accumulation of transferrin–doxorubicin conjugates (Tf-DOX). This approach highlights transferrin’s pivotal role in precision delivery and antitumor therapy, offering novel insights for targeted cancer treatment.¹⁶⁸

Protein-templated nanoparticles generally consist of an outer surface and an inner core, a structural feature that allows drug loading through two mechanisms: adsorption of drug molecules onto the outer surface or encapsulation within the

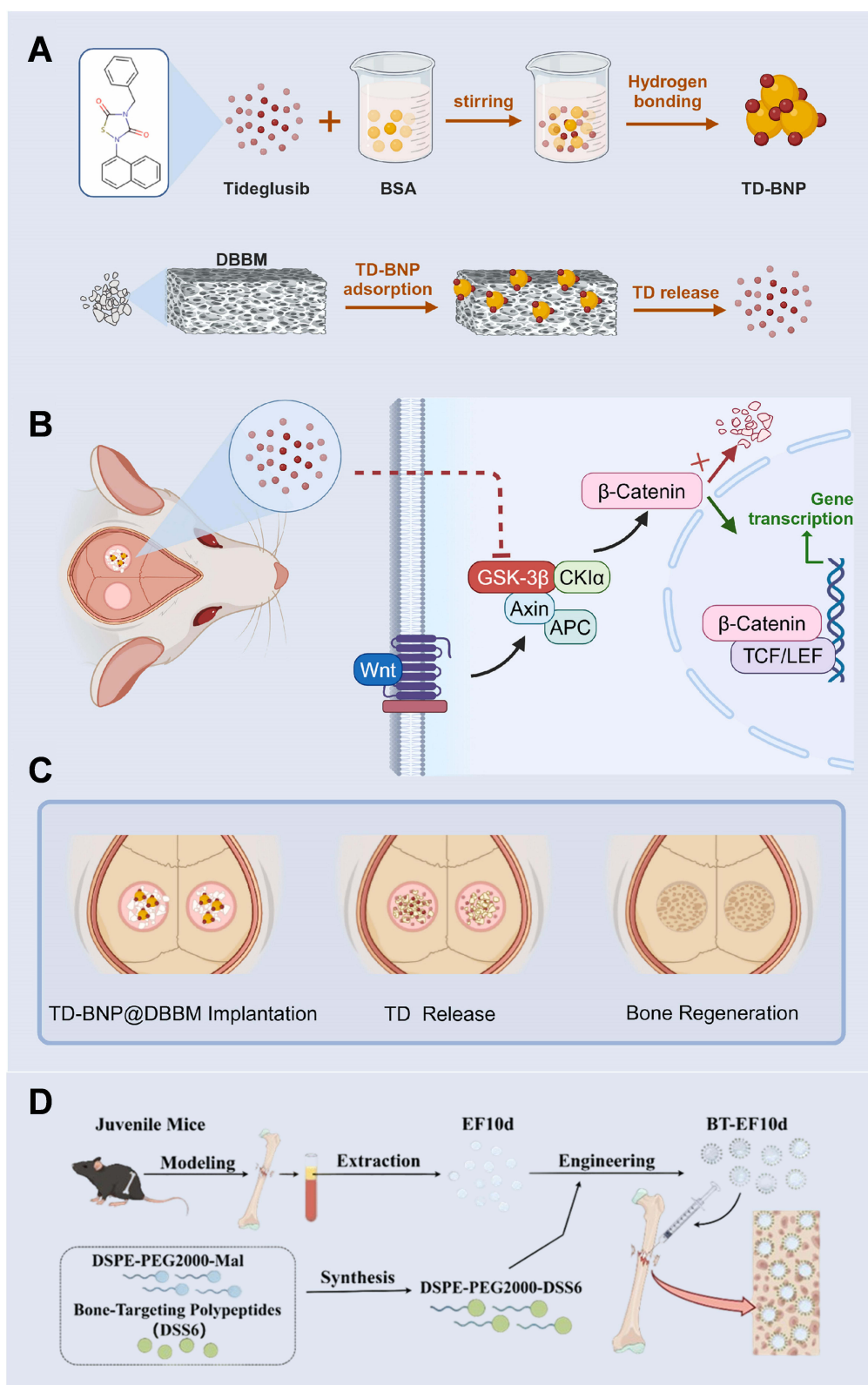


Figure 7 Schematic diagram of TD-BNP@DBBM preparation and its application in treating critical-sized cranial defects. **(A)** TD-BNP@DBBM preparation process.¹⁶³ **(B)** Mechanism of action by which TD-BNP@DBBM promotes bone regeneration.¹⁶³ **(C)** Schematic diagram of TD-BNP@DBBM application in repairing large-area bone defects in rats.¹⁶³ **(D)** Schematic diagram of the process for constructing engineered EVs for bone targeting.¹⁶⁵

inner core for storage and delivery. Modification of the protein template can further improve loading efficiency—for example, rendering albumin hydrophobic to accommodate hydrophobic drugs¹⁶⁹ or cationizing proteins to bind nucleic acids.¹⁷⁰ Once internalized by cells, these nanoparticles typically release their payload in a controlled manner through gradual protease-mediated degradation. Although proteins are often derived from endogenous molecules and therefore exhibit relatively low *in vivo* toxicity, preparation methods frequently require the use of harmful crosslinking agents, such as glutaraldehyde, to enhance stability. Consequently, the development of safer and more efficient preparation strategies remains a major challenge in this field.

Peptide Template-Based Nanoparticles

Targeting peptides are short peptide molecules that specifically recognize surface markers on cells with high affinity and selectivity.¹⁷¹ Compared with other targeting ligands, they provide multiple advantages, including higher targeting efficiency, straightforward synthesis, excellent biocompatibility, and low immunogenicity.¹⁷² In nanomedicine delivery systems, nanoparticle modification with targeting peptides markedly improves their accumulation in target tissues or cells, thereby enhancing drug delivery specificity and therapeutic efficacy.¹²¹ Consequently, a wide range of targeting peptides has been designed and applied in targeted therapies for diverse diseases, offering promising strategies for precision medicine.

DSS6 is an acidic, bone-targeting oligopeptide widely used to confer bone-selective accumulation on delivery systems. Its multiple aspartic acid residues exhibit strong affinity for hydroxyapatite within the bone mineral matrix, thereby promoting carrier localization and retention at bone surfaces.^{173,174} Accordingly, DSS6 is frequently grafted onto nanoparticles, liposomes, and extracellular vesicles as a bone-targeting module to enhance local delivery efficiency, tissue selectivity, and bioavailability in bone defect repair applications.¹⁷⁵ Using this strategy, Zheng et al developed an engineered delivery platform for aging-associated bone repair based on extracellular vesicles derived from juvenile mouse serum. Surface modification with DSS6 enhanced EV accumulation and therapeutic efficacy at bone repair sites. Compared with unmodified EVs, DSS6-engineered EVs more effectively promoted fracture healing in aged mice. Mechanistically, these engineered EVs appeared to improve mitochondrial function in senescent cells and restore the stemness of BMSCs by activating the Tomm7-mediated Pink1/Parkin mitophagy pathway, thereby remodeling the senescent bone microenvironment.¹⁶⁵

Peptides enriched in aspartic acid (Asp) display strong affinity for bone tissue due to electrostatic interactions between their carboxyl groups and calcium ions in hydroxyapatite (HAp), the primary mineral component of bone.¹⁷⁶ Studies have shown that bone-targeting efficacy is closely correlated with the number of exposed Asp residues in the peptide chain, with higher residue counts conferring greater binding affinity.¹⁷⁷ Among commonly used bone-targeting peptides, the *D*-aspartic acid octapeptide (Asp8), composed of eight Asp residues, exhibits particularly high affinity for bone tissue and is therefore widely employed in bone-targeted drug delivery and bone regeneration research.¹⁷⁸ For instance, Wang et al developed Asp8-modified dendritic platinum–copper alloy nanoparticles (Asp-DPCN) and systematically evaluated their bone-targeting and antitumor properties. Compared with unmodified DPCN, Asp-DPCN showed stronger binding to hydroxyapatite and bone fragments *in vitro* and exhibited enhanced accumulation within the bone tumor microenvironment *in vivo*. Exploiting this property, Asp-DPCN significantly increased local tumor temperatures during photothermal therapy, effectively suppressing tumor growth while reducing osteoclast-mediated bone destruction.¹⁷⁹ Similarly, the DSS6 peptide, composed of six Asp residues rich in carboxyl side chains, achieves high-affinity binding to bone tissue through strong coordination with calcium ions in hydroxyapatite crystals.^{180,181} This binding not only promotes preferential accumulation of drugs or nanocarriers in bone tissue but also elevates local drug concentrations, thereby enhancing therapeutic efficacy while minimizing systemic side effects. Zheng et al designed a bone repair platform by extracting engineered exosomes from juvenile mouse serum and modifying their surfaces with DSS6 peptides. Compared to unmodified EVs, DSS6-engineered EVs showed improved enrichment at bone repair sites, promoted osteogenesis and angiogenesis, and restored the pluripotency of BMSCs through activation of the Tomm7-mediated Pink1/Parkin mitophagy pathway, ultimately reversing the impaired microenvironment associated with aging bone.¹⁶⁵

Peptide-templated nanoparticles exhibit strong binding affinity for specific targets, along with excellent biocompatibility and low immunogenicity. Current studies indicate that these nanoparticles generally do not trigger elevated inflammatory cytokine release or induce acute toxicity in major organs, making them promising candidates for systemic administration.³³ Nonetheless, their clinical translation faces significant challenges due to the histological heterogeneity and genomic complexity of many diseases, which demand greater delivery precision and individualized therapeutic strategies. Therefore, the

development of more specific, high-affinity targeting peptides is urgently needed to improve the accuracy of delivery systems and broaden their therapeutic applications.

Mechanism of Action of Biomimetic Nanoparticles in Bone Regeneration

Bone is a mineralized connective tissue composed of osteoblasts, osteoclasts, and osteocytes. Its extracellular matrix contains both inorganic minerals and organic components, conferring high mechanical strength and toughness.¹⁸² Although bone possesses an intrinsic self-repair capacity through continuous remodeling, this ability is limited. When injury surpasses the regenerative threshold, structural and functional restoration becomes challenging.¹⁸³ Without timely and effective treatment, bone injuries can reduce mechanical strength and progress to nonunion or defects, severely compromising skeletal support and motor function.¹⁸⁴ Consequently, developing new strategies to enhance bone repair and regeneration is of great clinical significance. Traditionally, treatment has relied on autologous bone grafting, allogeneic transplantation, and artificial metallic or non-metallic implants.¹³ While these methods can partially restore structural integrity and function, long-term clinical outcomes remain suboptimal due to persistent challenges, including limited donor availability, immune rejection, risk of disease transmission, poor corrosion resistance, and susceptibility to infection.^{14,15}

Biomimetic nanoparticles have attracted growing attention in bone regeneration due to their ability to replicate the structural and compositional features of the ECM in bone tissue. By reconstructing a microenvironment analogous to the natural ECM, they facilitate osteoblast adhesion, differentiation, and mineralization, thereby accelerating new bone formation.^{20,185} Moreover, their surfaces can be readily functionalized to incorporate drugs, growth factors, or bone-targeting peptides, enabling precise delivery and controlled release.^{32,33} As a result, biomimetic nanoparticles offer distinct advantages in improving bone repair efficiency, reducing adverse reactions, and advancing clinical translation, providing innovative strategies for the treatment of bone injuries and defects. This section highlights the mechanisms through which biomimetic nanoparticles contribute to bone regeneration, including the promotion of osteogenesis and mineralization, modulation of the bone immune microenvironment, and stimulation of angiogenesis.

Promotion of Osteogenesis and Mineralization

Osteogenesis and mineralization are central biological processes in bone tissue regeneration.¹⁸⁶ This process relies on the directed differentiation of BMSCs into osteoblasts, which subsequently secrete and deposit a collagen-rich organic matrix. Hydroxyapatite crystals then nucleate on this scaffold, leading to progressive mineralization and hardening of bone tissue.¹⁸⁷ Multiple signaling pathways regulate these events synergistically. For example, the Wnt/ β -catenin pathway enhances osteoblast differentiation and proliferation,¹⁸⁸ while the BMP/Smad pathway is pivotal in inducing osteogenic differentiation and mineralization.¹⁸⁹ Additional pathways, such as MAPK and PI3K/AKT, further regulate cytoskeletal reorganization, proliferation, and differentiation.¹⁹⁰ The ECM of bone not only provides structural support but also creates a dynamic regulatory microenvironment through surface-bound growth factors and biomechanical cues, thereby exerting critical control over osteogenesis and mineralization.^{191,192} Zhang et al developed a novel biomimetic nanoparticle, ALN@BMSCM@PLGA-TK-PEG-SS31, designed for immune evasion and prolonged circulation via BMSC membrane coating, while incorporating alendronate (ALN) for bone targeting. Under oxidative stress, the Reactive oxygen species (ROS)-sensitive PLGA-TK-PEG structure ruptures to release the mitochondrial-targeting peptide SS31, thereby alleviating oxidative stress. In vitro, this nanoplatfrom suppressed RANKL-induced osteoclastogenesis under hydrogen peroxide exposure and significantly promoted BMSC osteogenic differentiation and bone formation. In vivo, in an ovariectomized mouse model, ALN@BMSCM@PLGA-TK-PEG-SS31 not only mitigated oxidative stress but also increased bone mass without significant systemic toxicity (Figure 8).¹⁹³ The BMP/Smad signaling pathway remains one of the most critical molecular regulators of bone formation. BMPs first bind to cell surface receptors, which sequentially activate Smad proteins. Phosphorylated Smads form complexes that translocate into the nucleus, where they regulate transcription of osteogenesis-related genes, thereby promoting BMSC differentiation into osteoblasts and accelerating mineralized matrix deposition.¹⁹⁴ Chen et al demonstrated that miR-486-5p from rheumatoid arthritis (RA) fibroblast-like synovial cell exosomes promotes osteoblast proliferation and differentiation by activating the BMP/Smad pathway and inhibiting Tob1.¹⁹⁵ Furthermore, miRNAs secreted by osteogenically differentiated BMSCs, including let-7a-5p, let-7c-5p, miR-328a-5p, and miR-31a-5p, modulate the competitive balance between Bmpr2/Acvr2b and Bmpr-induced Smad1/5/9 phosphorylation, thereby fine-tuning downstream Smad signaling to promote bone regeneration.¹⁹⁶

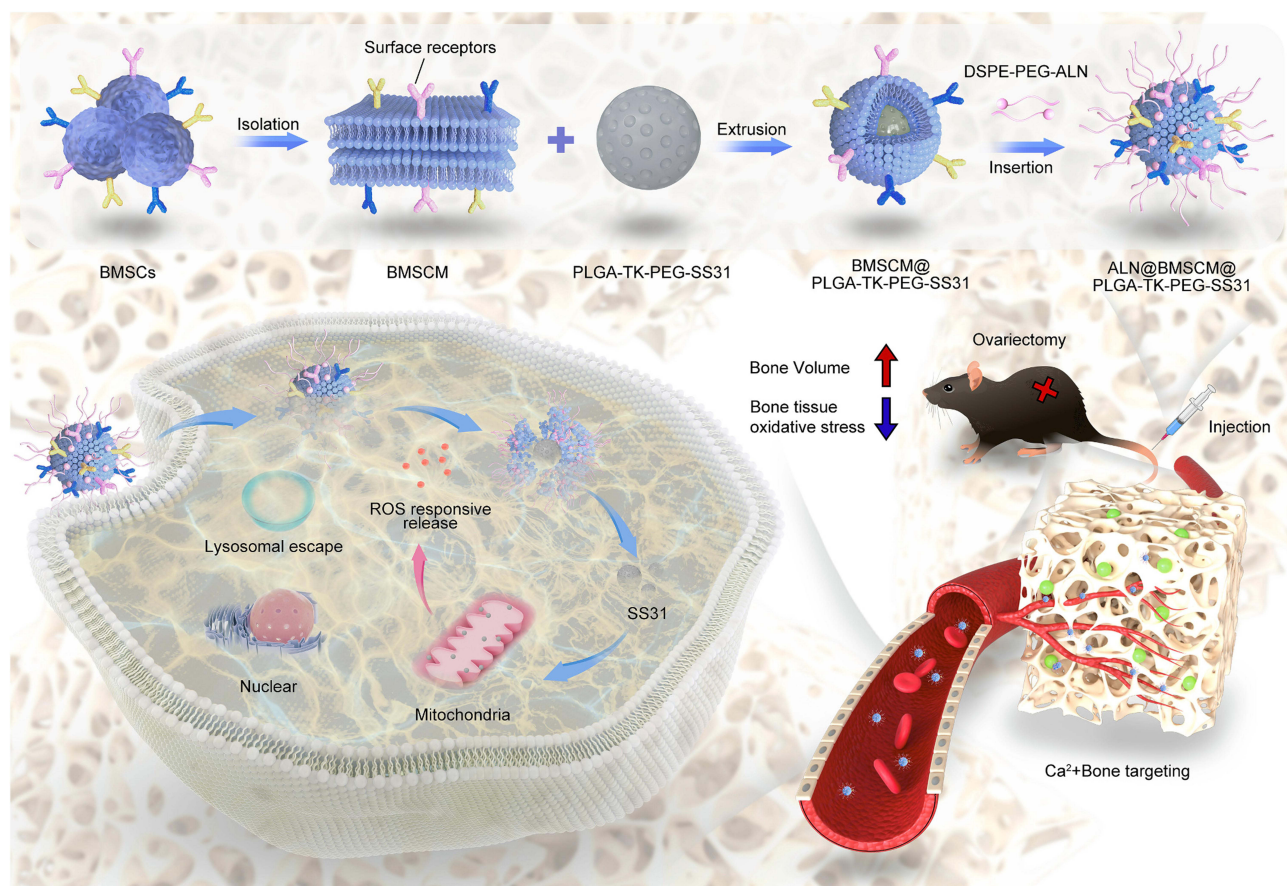


Figure 8 Schematic Diagram of the Synthesis Process of ALN@BMSCM@PLGA-TK-PEG-SS31 and Its Functional Effects Following Systemic Injection.¹⁹³

Modulating the Immune Microenvironment

Bone regeneration and repair is a complex biological process in which dynamic changes within the immune microenvironment exert critical regulatory functions.¹⁹⁷ During the early stages of repair, immune cells such as macrophages, dendritic cells, and T cells modulate the intensity and duration of inflammation by secreting cytokines and chemokines, thereby directly influencing the balance between osteogenesis and osteoclastogenesis.^{198,199} Aberrant immune responses may induce excessive inflammation or bone resorption, whereas appropriate immune modulation establishes a microenvironment favorable for osteogenesis.²⁰⁰ In recent years, biomimetic nanoparticles, owing to their structural and functional versatility, have demonstrated the ability to resolve inflammation⁷⁴ and induce macrophage polarization toward the M2 phenotype^{201,202} by modulating immune cell activation states and cytokine secretion patterns. These immunomodulatory effects further support osteogenic differentiation and tissue regeneration.²⁵ Yin et al designed a biomimetic anti-inflammatory nanocapsule (BANC), in which lipopolysaccharide-treated macrophage membranes encapsulated gold nanocages (AuNC). The membrane surface receptors neutralized excessive pro-inflammatory cytokines, suppressing pathological inflammation. Simultaneously, Resolvin D1 loaded in the nanocages was released on demand under near-infrared irradiation, driving macrophage polarization toward the M2 phenotype and thereby enhancing anti-inflammatory activity and tissue repair. In vivo femoral defect studies showed that BANC combined with boron-containing mesoporous bioactive glass scaffolds not only attenuated inflammation but also promoted sequential M2 polarization and bone regeneration.⁷⁴ Wu et al proposed a strategy targeting Icam1⁺ macrophages to address non-healing infectious bone defects. They synthesized magnetic and ultrasonically responsive iron-doped barium titanate nanoparticles (BFTO), coated with γ 3-peptide-modified engineered mesenchymal stem cell membranes (EMM) and simultaneously loaded with curcumin, forming BFTO-Cur@EMM nanoparticles. These nanoparticles disrupted bacterial biofilms under alternating magnetic fields and activated oxidative phosphorylation and osteoimmune responses in Icam1⁺ macrophages via low-intensity pulsed ultrasound. In vitro and in vivo experiments confirmed that BFTO-

Cur@EMM nanoparticles promoted macrophage polarization toward a reparative phenotype by activating the JAK2–STAT3 pathway and inhibiting the MAPK–JNK pathway, thereby enhancing the secretion of pro-angiogenic and osteogenic cytokines and facilitating bone defect repair (Figure 9).²⁰³

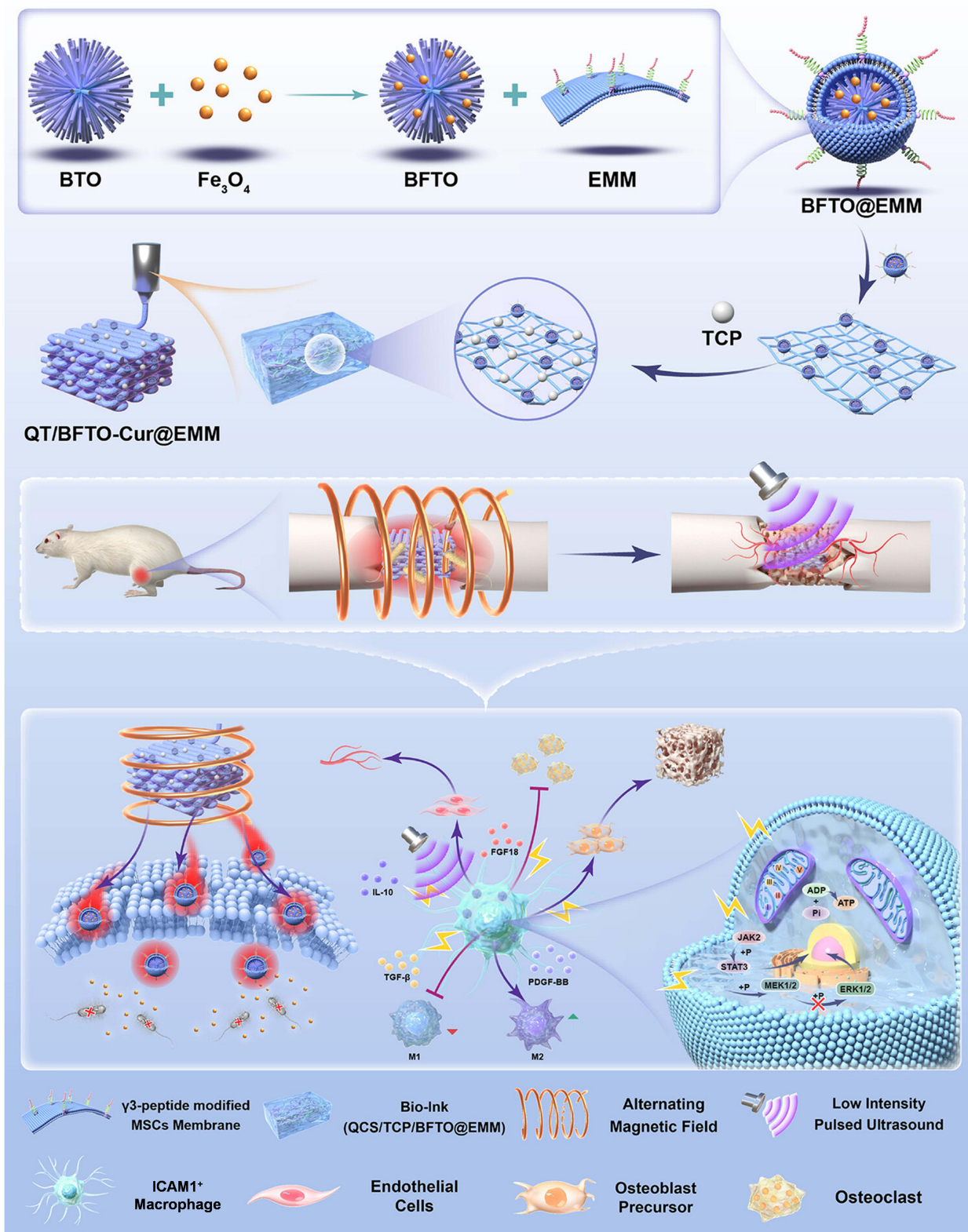


Figure 9 Bifunctional iron-doped strontium barium titanate nanoparticles (BFTO–Cur@EMM) were implanted into an infectious bone defect model. Through sequential magnetic guidance for anti-infection and ultrasound-targeted activation of Icam1⁺ macrophages, they induced bone regeneration after controlling the infection.²⁰³

Biomaterials implanted in the body often elicit immune responses primarily mediated by macrophage polarization.²⁰⁴ Persistent activation of the M1 phenotype results in chronic inflammation and impaired osseointegration,²⁰⁵ whereas enhancement of the M2 phenotype fosters an immune microenvironment favorable for bone regeneration.²⁰⁶ Thus, precise regulation of M1/M2 macrophage transition is essential for improving bone regeneration and osseointegration. Lei et al developed a tannic acid-modified sulfonated polyether ether ketone (SPEEK) implant functionalized with bone marrow mesenchymal stem cell-derived exosomes. This system enabled sustained Exo release, significantly improving material biocompatibility after cellular uptake. It further promoted M2 macrophage polarization and BMSC osteogenic differentiation by modulating the NF- κ B signaling pathway. In vivo studies confirmed its capacity to achieve effective immune modulation, robust new bone formation, and enhanced osseointegration in rat models, highlighting the therapeutic potential of BMSC-derived Exo-functionalized implants for bone immune regulation and osteogenesis.²⁰¹ Similarly, Schwann cell-derived exosomes were shown to promote M2 macrophage polarization, enhance endothelial cell tubulogenesis, and facilitate osteogenic differentiation of BMSCs.²⁰²

Promoting Neurogenesis and Angiogenesis

Bone tissue repair and regeneration depend not only on osteogenesis but also on the coordinated interactions between the vascular and nervous systems.²⁰⁷ Blood vessels supply oxygen and nutrients to bone tissue while removing metabolic waste, thereby maintaining homeostasis and supporting bone healing.^{208,209} Meanwhile, nerve fibers regulate immune responses, angiogenesis, and osteoblast activity through the secretion of neuropeptides and growth factors.¹⁴ Increasing evidence indicates that blood vessels and nerves are spatially co-localized and functionally interdependent, forming a “vascular–nerve unit” critical for bone regeneration and repair.^{6,210} Consequently, the development of biomimetic nanomaterials that promote both angiogenesis and neuroregeneration has emerged as an important strategy in bone tissue engineering. Jiang et al designed a novel miRNA-based delivery system by loading miR-21 onto metal–organic frameworks (MOFs) and encapsulating them within membranes derived from CXCR4-overexpressing bone marrow mesenchymal stem cells. Leveraging the CXCR4–SDF1 axis, this nanoplatform achieved targeted delivery to ischemic bone regions. Upon release, miR-21 silenced PTEN and activated the PI3K–AKT pathway, thereby promoting angiogenesis and vascular repair, improving blood supply, and ultimately enhancing osteogenesis. This strategy demonstrated significant therapeutic potential for glucocorticoid-induced osteonecrosis of the femoral head (GIONFH) through neovascularization.²¹¹ Yang et al revealed a pathological vicious cycle in steroid-induced osteonecrosis of the femoral head (SANFH), in which exosomes from damaged endothelial cells induced adipogenic differentiation of BMSCs. In turn, adipogenically differentiated BMSCs secreted pro-inflammatory factors, exacerbating endothelial injury, impairing angiogenesis, and hindering bone regeneration. To address this, they developed M-SiO₂@Icariin@EBHM, a biomimetic nanomaterial consisting of icariin-loaded mesoporous silica coated with a hybrid membrane from endothelial cells and BMSCs. Systemic administration enabled targeted accumulation at lesion sites, where it scavenged glucocorticoid-induced reactive oxygen species, repaired vascular endothelium, and promoted osteogenic differentiation of BMSCs. This dual mechanism effectively disrupted the cycle of endothelial injury, inflammation amplification, and impaired bone repair, significantly enhancing angiogenesis and bone regeneration, thereby delaying SANFH progression (Figure 10).²¹²

Growing evidence indicates that exosomes are promising candidates for promoting both vascular and neural regeneration. The miRNAs, proteins, and lipids they transport regulate the function of vascular endothelial and neural cells, thereby exerting dual effects during bone repair.^{213,214} To address the challenge of inadequate vascularization in large bone defect repair, Zha et al developed an acellular tissue-engineering system based on engineered exosomes. Specifically, exosomes derived from ATDC5 cells were functionalized with the anchoring peptide CP05, immobilized on 3D-printed porous bone scaffolds, and loaded with the VEGF gene. In vitro studies showed that these functionalized exosomes not only acted as osteogenic matrices to promote mesenchymal stem cell differentiation but also significantly enhanced angiogenesis through controlled VEGF release. In vivo experiments further confirmed their efficacy in inducing large-volume vascularized bone regeneration, underscoring the potential of functionalized exosomes in acellular tissue engineering.²¹⁵ In addition, exosomes can simultaneously promote vascular and neural regeneration. Su et al constructed a biomimetic periosteum PCL@PEI@exosome@aptamer (PPEA) by conjugating phosphatidylserine (PS)-targeting aptamers with Schwann cell-derived exosomes and immobilizing them on electrospun fiber surfaces, thereby

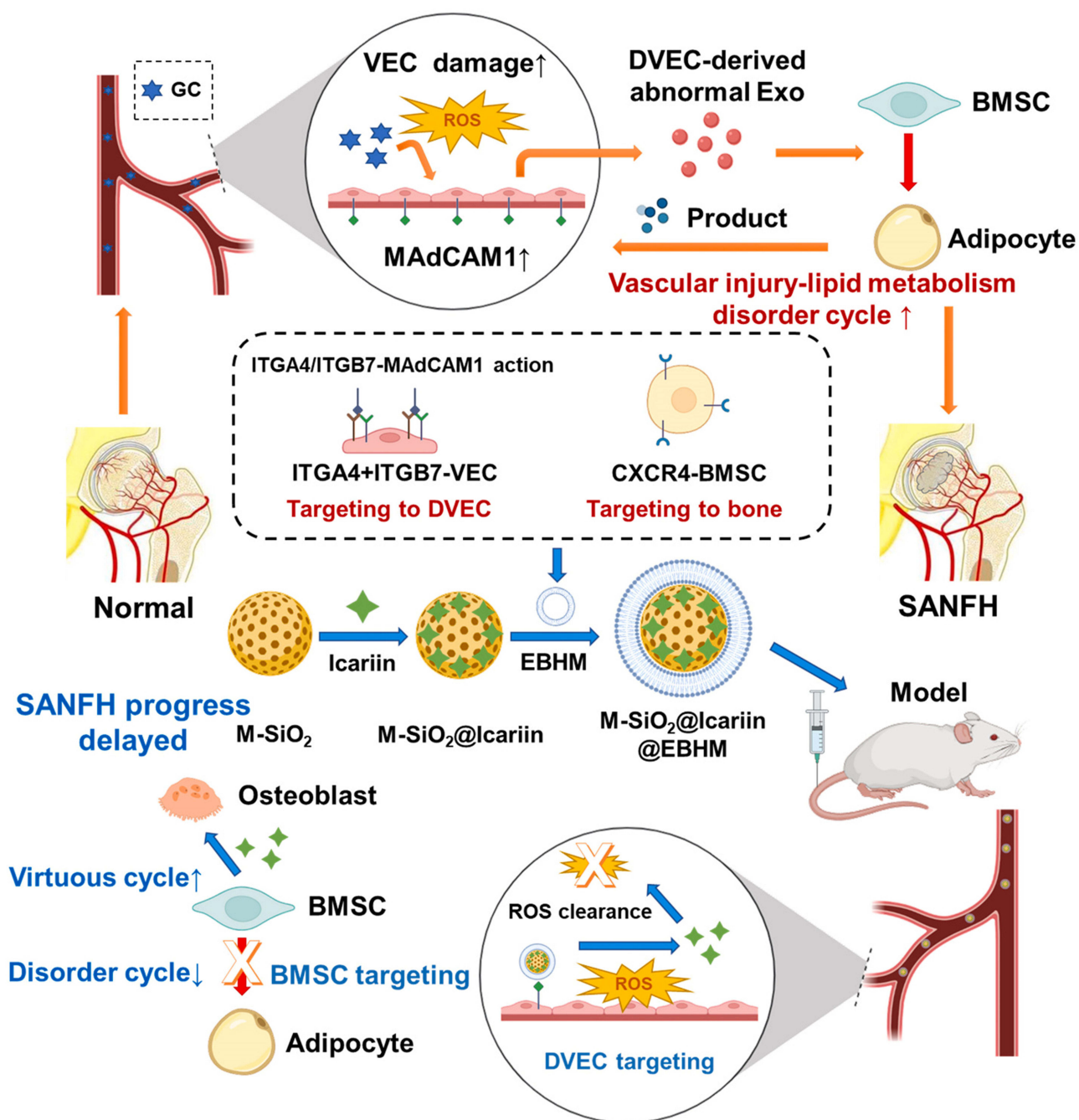


Figure 10 Pathological Mechanisms and Therapeutic Strategies for Steroid-Associated Necrosis of the Femoral Head (SANFH): Hormones and other factors induce vascular endothelial cell injury, leading to increased reactive oxygen species (ROS) production and upregulation of mucosal addressin cell adhesion molecule-1 (MAdCAM-1). This, in turn, promotes the secretion of abnormal exosomes by damaged vascular endothelial cells (DVECs), driving the formation of a vicious cycle of vascular injury and lipid metabolism disorders. Targeting this mechanism, mesoporous silica (M-SiO₂) loaded with icariin combined with engineered bone matrix (EBHM) forms M-SiO₂@Icariin@EBHM, constructed from mesoporous silica (M-SiO₂) loaded with icariin and engineered bone matrix (EBHM), exerts therapeutic effects by scavenging ROS, targeting DVECs and BMSCs, delaying SANFH progression, promoting osteogenic-related positive feedback loops, inhibiting metabolic dysfunction cycles, and regulating BMSC differentiation.²¹²

enabling precise repair of periosteal nerve injuries. Both in vitro and in vivo experiments demonstrated that Schwann cell-derived exosomes promoted neurogenesis and angiogenesis through activation of the JNK/MAPK signaling pathway, while also exhibiting osteogenic potential by upregulating neuropeptide expression.²¹⁶

Challenges and Future Prospects

Biological Safety and Toxicity

Despite their significant advantages in bone regeneration, the clinical translation of biomimetic nanoparticles still faces substantial challenges. First, rigorous and comprehensive biosafety evaluations are essential. Previous experience with nanomedicine development underscores that biosafety risks are often the primary reason for the termination of research or clinical projects. Although biomimetic nanoparticles have shown favorable biocompatibility, biodegradability, and low immunogenicity *in vitro* and in small animal studies, uncertainties remain regarding their long-term metabolism, the toxicity of degradation products, and potential immune responses *in vivo*. Therefore, systematic biosafety assessments of all nanoparticle components are indispensable. Personalized biomimetic nanoparticles—such as those derived from patient-specific cell membranes or exosomes from mesenchymal stem cells or immune cells—may offer a promising precision medicine strategy, reducing immunogenicity risks while enhancing therapeutic outcomes.

Challenges in Large-Scale Production

Scalability and reproducibility remain major barriers to clinical application due to limitations in current production processes. Present fabrication methods are largely restricted to the laboratory stage and are hampered by low yields, batch-to-batch variability, and complex preparation steps. For example, cell membrane-coated nanoparticles often suffer from high production costs and limited drug-loading capacity, while exosome-based systems face issues of heterogeneity and labor-intensive extraction. Emerging technologies, however, provide potential solutions. High-throughput microfluidic platforms enable precise microscale manipulation of liquid flow, allowing particle sorting or enrichment through acoustic forces, electric fields, or size-based separation. These platforms can shorten processing times, reduce sample consumption, and improve purity and reproducibility. Tangential flow filtration (TFF) has also been applied to exosome isolation, offering 3–5 times higher yields than ultracentrifugation while preserving structural integrity. Importantly, integrating microfluidics with TFF holds promise for achieving scalable, cost-effective production with robust quality control, thereby enhancing the clinical translation potential of biomimetic nanoparticles.

Clinical Translational and Regulatory Standards Challenges

At present, most research on biomimetic nanoparticles remains at the preclinical stage, and verification of their long-term safety and efficacy in humans requires costly large-scale clinical trials. Regulatory gaps further hinder this process. The absence of unified international standards not only delays approval procedures but also exacerbates difficulties arising from material heterogeneity and inconsistent characterization methods. Rigorous evaluation of key physicochemical parameters—such as particle size, dispersibility, and metabolic stability—is essential, yet presents far greater challenges than conventional drug assessment. Moreover, limited experience in industrial-scale production significantly restricts controllable mass manufacturing. Addressing these barriers demands close interdisciplinary collaboration to advance regulatory standards, optimize analytical and characterization techniques, and streamline manufacturing and quality control, thereby accelerating the clinical translation of biomimetic nanoparticles.

Despite these challenges, biomimetic nanoparticles hold tremendous potential in bone regeneration. Ongoing advancements in materials science, nanotechnology, and fabrication strategies are expected to enable the design of personalized nanoparticles with controllable structures, precise functionalization, and enhanced biosafety. Such progress will provide critical assurance for their successful clinical translation.

Conclusion

In recent years, biomimetic nanoparticles have emerged as an important area of research in bone regeneration because of their tunable structural and functional properties. This review summarizes the structural organization and functional characteristics of bone tissue and its microenvironment, and outlines the key stages of bone repair following injury. It further discusses major strategies for constructing biomimetic nanoparticles using diverse biological templates, including cell membranes, exosomes, proteins, and peptides. These design approaches may be used individually or in combination to integrate complementary functions and generate multifunctional platforms that better interface with the host bone microenvironment. Collectively,

biomimetic nanoparticles show broad potential to enhance osteogenesis and mineralization, modulate the immune micro-environment, and support vascular and neural regeneration, thereby providing a materials-based framework for the development of bone repair strategies. Future progress in this field will depend on establishing verifiable links between key material parameters and biological outcomes, improving scalable manufacturing, batch-to-batch consistency, and standardized characterization, and building a more rigorous evidence base for long-term biosafety and clinical translation. Such advances will be essential for the development of more translatable and personalized therapies for bone repair.

Abbreviations

NPs, Nanoparticles; ECM, Extracellular matrix; NCPs, Non-collagenous proteins; MMPs, Matrix metalloproteinases; TIMPs, Tissue inhibitors of metalloproteinases; BMPs, Bone morphogenetic proteins; FGFs, Fibroblast growth factors; VEGF, Vascular endothelial growth factor; OPG, Osteoprotegerin; PDGF, Platelet-Derived Growth Factor; BMSCs, Bone marrow mesenchymal stem cells; CGRP, Calcitonin gene-related peptide; SP, Substance P; TGF- β , Transforming growth factor- β ; RBCs, Red blood cells; SIRP α , Signal-regulatory protein alpha; ICA, Icarin; PLGA, Poly(lactic-co-glycolic acid); PNPs, Platelet membrane-cloaked nanoparticles; OVA, Ovalbumin; PDT, Photodynamic therapy; CEP, Cefpodoxime; MMs, Macrophage membranes; NLCs, Nanostructured lipid carriers; EVs, Exosomes; MVBs, Multivesicular bodies; PTX, Paclitaxel; DOX, Doxorubicin; TD, Thiazolidine-2,5-dione; BNPs, Bovine serum albumin nanoparticles; DBBM, Deproteinized bovine bone mineral; BSA, Bovine serum albumin; ALP, Alkaline phosphatase; Tf, Transferrin; TfR, Transferrin receptors; Tf-DOX, Transferrin-doxorubicin conjugates; E7, EPLQLKMC; OPN, Osteopontin; PDA, PLGA/dopamine; KGN, Kartogenin; Asp, Aspartic acid; Hap, Hydroxyapatite; Asp8, d-aspartic acid octapeptide; Asp-DPCN, Asp8-modified dendritic platinum-copper alloy nanoparticles; ALN, Alendronate; ROS, Reactive oxygen species; RA, Rheumatoid arthritis; BANC, Biomimetic anti-inflammatory nanocapsule; EMM, Mesenchymal stem cell membranes; SPEEK, Sulfonated polyether ether ketone; MOFs, Metal-organic frameworks; GIONFH, Glucocorticoid-induced osteonecrosis of the femoral head; SANFH, Steroid-induced osteonecrosis of the femoral head; PPEA, PCL@PEI@exosome@aptamer; PS, Phosphatidylserine; TFF, Tangential flow filtration.

Data Sharing Statement

No data was used for the research described in the article.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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