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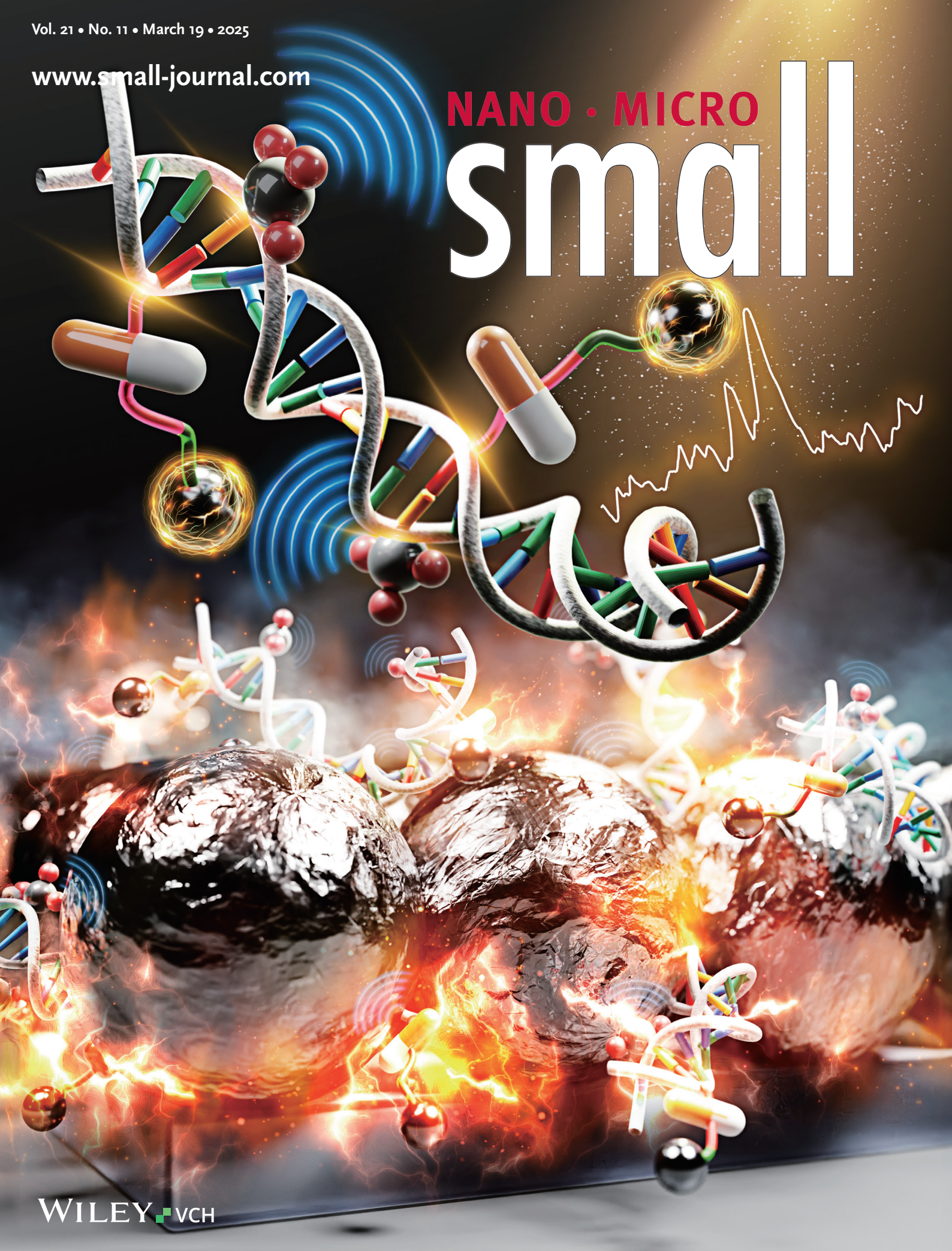

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REVIEW

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Material-Mediated Immunotherapy to Regulate Bone Aging and Promote Bone Repair

Pengfei Xue, Jiayi Wang, Yu Fu, Hongyan He, Qi Gan, and Changsheng Liu**

As the global population ages, an increasing number of elderly people are experiencing weakened bone regenerative capabilities, resulting in slower bone repair processes and associated risks of various complications. This review outlines the research progress on biomaterials that promote bone repair through immunotherapy. This review examines how manufacturing technologies such as 3D printing, electrospinning, and microfluidic technology contribute to enhancing the therapeutic effects of these biomaterials. Following this, it provides detailed introductions to various anti-osteoporosis drug delivery systems, such as injectable hydrogels, nanoparticles, and engineered exosomes, as well as bone tissue engineering materials and coatings used in immunomodulation. Moreover, it critically analyzes the current limitations of biomaterial-mediated bone immunotherapy and explores future research directions for material-mediated bone immunotherapy. This review aims to inspire new approaches and broaden perspectives in addressing the challenges of bone repair and aging by exploring innovative biomaterial-mediated immunotherapy strategies.

1. Introduction

Bone defects caused by fractures, trauma, and surgeries significantly impact the health and quality of life of the elderly. As people age, the decline in bone regenerative capacity, which refers to the natural degenerative changes in bone tissue over time leading to reduced bone remodeling and repair efficiency, makes the repair of bone defects in the elderly even slower. In addition, common conditions like osteoporosis, a pathological bone disease characterized by decreased bone density and quality that increases the risk of fractures and further complicates the healing process, exacerbate this issue.[1] Osteoporosis leads to decreased bone density and quality, making bones more susceptible to fractures and complicating the healing process after a fracture. Whether opting for conservative treatment or surgical intervention, elderly patients often face several severe complications. These complications may include postoperative infections, chronic pain, and mobility impairments, further reducing their quality of life.[2] Therefore, developing and exploring effective strategies to promote rapid healing of bone defects in the elderly, as well as managing addressing both bone aging and osteoporosis appropriately, is particularly important. This not only helps improve the speed and quality of fracture healing but also helps reduce the occurrence of complications, thereby improving the overall health status of the elderly.

Currently, bone defect repair in elderly patients remains a major clinical challenge due to the limitations of traditional treatment strategies. Autografts and allografts, which are widely used in clinical practice, are associated with complications such as donor site morbidity and immune rejection, while metallic implants pose risks of infection and implant failure.[3] In addition, current pharmacological treatments for osteoporosis, including bisphosphonates (BP) and monoclonal antibodies, have limitations such as delayed bone healing and adverse effects. These challenges highlight the urgent need for novel strategies that can accelerate bone healing and modulate the local immune environment to improve clinical outcomes.[4]

Bone regeneration is a complex biological process that includes multiple stages such as inflammatory response, tissue repair, and bone tissue remodeling.[5] A moderate immune response can create a favorable microenvironment for bone

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healing.[6] However, dysregulation of the immune system may lead to the continuous production of pro-inflammatory mediators by macrophages and other immune cells. These mediators can disrupt the homeostasis of the repair area, thereby hindering the normal repair and regeneration of bone tissue. When such an imbalance in the immune response occurs, the bone repair process may completely fail, leading to complications in treatment and prolonged recovery times.[7] A healthy immune environment supports the smooth transition from inflammation to repair and then to remodeling, ensuring that bone tissue can recover its original structure and function.[8] In-depth research into "bone immunology" and exploring mechanisms to regulate the immune microenvironment are crucial for developing new therapeutic strategies.

Arron and Choi first introduced the concept of "bone immunology" in their study on the regulation of osteoclast activation by T lymphocytes.[9] As research in bone immunology has deepened, it has been shown that bone regeneration is a complex multi-system process involving the skeletal and immune systems. Takayanagi defined bone immunology and emphasized its interdisciplinary nature, elaborating on the extensive interactions between bone and immune system cells.[10] Okamoto and others have proposed that bone immunology focuses on the interactions between macroscopic and microscopic systems and their mechanisms in health and disease states, providing a comprehensive overview of the field.[11] As research on the interactions between the skeletal system and immune cells continues to deepen, the field of bone immunology has developed strategies focusing on using biomaterials to modulate the local immune environment, aiming to shift from pro-inflammatory states to tissue states that promote healing and regeneration.[12] In the response to bone injury, the immune system regulates the local immune environment by initiating an inflammatory response, which promotes tissue repair and regeneration. This process involves the activation and recruitment of immune cells, clearance of damage and pathological factors, and the restoration of bone tissue homeostasis through inflammation regulation, ultimately supporting bone regeneration.[13]

Recent advances in biomaterial-mediated immunotherapy have provided new opportunities for clinical bone repair. Several bioactive materials, including immunomodulatory hydrogels, bioengineered nanoparticles, and functionalized scaffolds, have been developed to modulate inflammatory responses and enhance bone healing. Some of these technologies have entered preclinical and clinical evaluation, demonstrating promising potential in enhancing bone regeneration through immune regulation.[14]

In this review, we comprehensively and systematically discuss materials that mediate immunotherapy to promote bone repair and regulate bone aging. The article first explores immunotherapeutic strategies in bone repair and aging, and how key immune cells regulate the microenvironment of bone repair. It then discusses the application of manufacturing technologies such as 3D printing, electrospinning, microfluidic technology, and artificial intelligence (AI) in supporting immunotherapy. Following this, the article categorizes material-mediated bone immunotherapy from three perspectives: drug delivery systems, bone tissue engineering materials, and coating materials. Finally, we summarize the achievements of biomaterial-mediated bone immunotherapy to date and highlight the challenges that still need to be overcome, including the potential role of AI in addressing these challenges (**Scheme 1**).

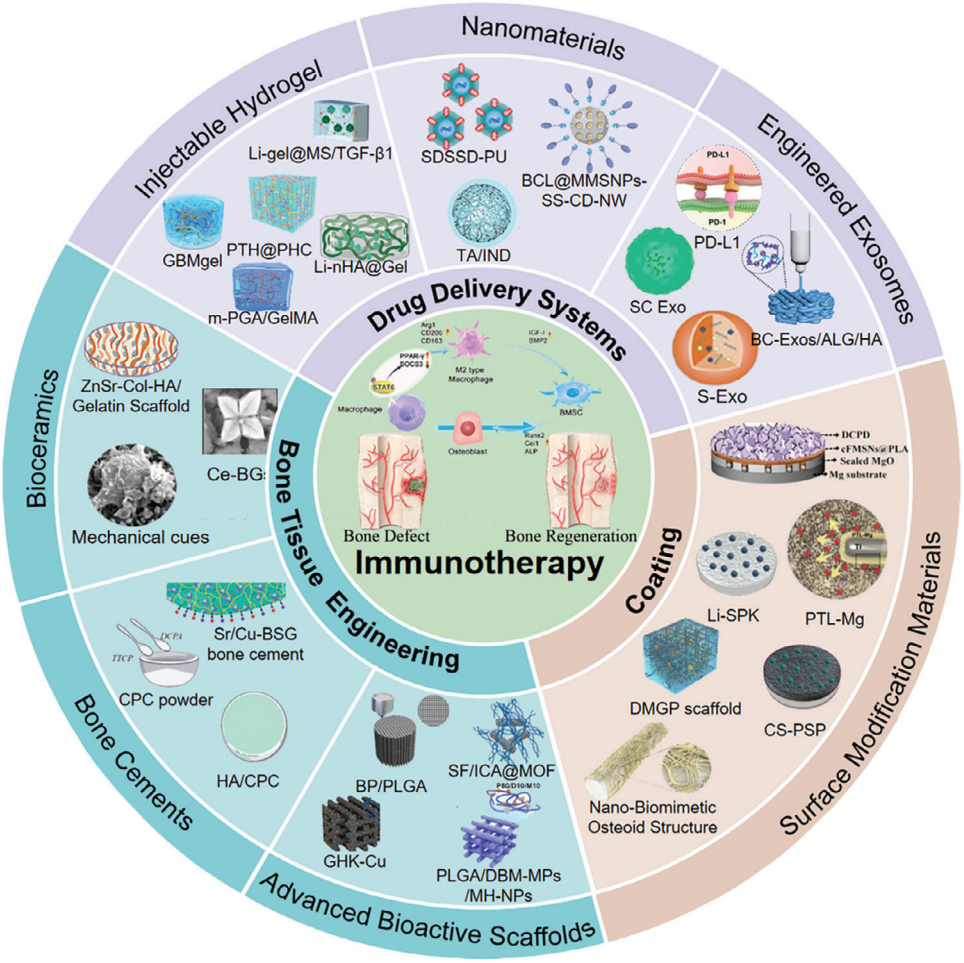
2. The Role of Immunotherapy in Bone Repair and Aging Regulation

2.1. Characteristics of the Bone Aging Microenvironment

To maintain the integrity and mechanical stability of bone microstructure, a continual process of bone remodeling occurs in the body, where old bone is absorbed by osteoclasts and replaced by osteoblasts with new bone. This process is controlled by various biological regulatory pathways to ensure proper cellular function within bone tissue. However, as cells age, some remain metabolically active but cease mitosis, entering a state known as "senescent cells."[15] Cellular aging leads to a decline in stem cell function, causing tissue homeostasis disruption and regenerative impairments.[16] Moreover, senescent cells inhibit the function of adjacent normal cells through paracrine actions. These cells secrete a large number of factors that inhibit tissue regeneration, known as the senescence-associated secretory phenotype (SASP), including matrix metalloproteinase-12 (MMP12), interleukin-6 (IL-6), interleukin-8 (IL-8), and plasminogen activator inhibitor-1 (PAI-1). In addition, aging biomarkers such as P16, P21, and P53—key regulators of cell cycle arrest and senescence—are involved in these processes, further contributing to the decline in regenerative capacity.[17]

The persistent halt in the cell cycle and the unique pro-inflammatory secretory phenotype of various cells create a senescent microenvironment, which through negative feedback mechanisms exacerbates the dysfunction of bone cells, significantly reducing the self-repair capacity of bone tissue, leading to accelerated bone loss.[18] Over time, the accumulation of senescent cells in joint tissues causes the tissues to gradually lose the ability to participate in long-term tissue regeneration through cell proliferation. This accumulation not only affects the function of bone tissue but also increases the risk of osteoporosis.[19]

Osteoporosis is a common disease that becomes apparent with bone aging, characterized by significant changes in the bone microenvironment. These changes include markedly elevated levels of reactive oxygen species (ROS), highly reactive chemicals that can directly damage bone cells and degrade the bone matrix, thereby inhibiting bone formation. In addition, a low environmental pH increases the tendency for bone resorption while inhibiting the deposition of minerals, further weakening the bone structure.[20] In terms of immune regulation, there is an overactivation of T cells and an imbalance between regulatory T cells (Treg) and T helper cells (Th). This immune imbalance leads to the overexpression of osteoclast-promoting cytokines IL-6, IL-17, tumor necrosis factor α (TNF-α), and receptor activator of nuclear factor κB ligand (RANKL), which together promote the formation and activation of osteoclasts, leading to excessive bone resorption, further accelerating bone loss, and ultimately making bones fragile and prone to fractures. These combined factors make the osteoporotic bone microenvironment a pathological immune environment, posing a serious threat to the health of the elderly.[20,21]



Scheme 1. Material-mediated immunotherapy for bone repair and aging regulation: drug delivery systems, bone tissue engineering materials, and coatings. GBMgel: Reproduced with permission.[74] Copyright 2024 The Authors. Advanced Healthcare Materials published by Wiley-VCH. BCL@MMSNPs-SS-CD-NW: Reproduced with permission.[105] Copyright 2021 The Authors. Published by American Chemical Society. SC Ex: Reproduced with permission.[133] Copyright 2022 The Authors. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd. Nano-Biomimetic Osteold Structure: Reproduced with permission.[192] Copyright 2021 Elsevier. All rights reserved. PTL-Mg: Reproduced with permission.[189] Copyright 2022 The Authors, Published by Elsevier. DMGP scaffold: Reproduced with permission.[193] Copyright 2022 Wiley-VCH.

2.2. Key Immune Cells in Regulating the Bone Repair Microenvironment

As age increases, bone aging leads to a decline in bone regenerative capacity, slowing down bone repair in the elderly. The characteristics of the bone aging microenvironment include reduced cellular function and local cytokine changes, which significantly impact the bone repair process. Bone regeneration is a complex process involving multiple stages such as inflammation, repair, and remodeling. Bone regeneration and repair depend on a healthy immune microenvironment, with proper regulation of the acute inflammatory response being key to healing, driven by the immune system's fine-tuning of the repair process.[5,8] In bone repair, injured cells and ECM fragments release damage-associated molecular patterns (DAMPs), while invading microbes release pathogen-associated molecular patterns (PAMPs). Both types of molecules can cause local inflammation, prompting tissue-resident immune cells to secrete inflammatory factors and recruit more immune cells to the injury site, thus playing a key role in the bone repair process.[22] The immune system is divided into innate and adaptive immunity based on reaction kinetics and function. Innate immunity acts as the primary responder, involving neutrophils, dendritic cells, monocytes, and macrophages. When these cells cannot eliminate the threat, the adaptive immunity's B cells and T cells intervene to specifically clear the foreign invasion.[23]

2.2.1. Neutrophils

Neutrophils far outnumber any other immune cells found in human blood and heavily infiltrate damaged tissues. They are direct effector cells in antibacterial responses, closely associated with innate immunity. Current research is continually exploring how neutrophils regulate homeostasis beyond infection.[24] In bone regeneration and repair, they are typically the first immune cells recruited to the injury site, responsible for phagocytizing pathogens and clearing debris, while also releasing signaling

molecules that trigger acute inflammatory responses.[25] In addition, neutrophils can recruit monocytes and macrophages by secreting inflammatory cytokines.[26] Neutrophils are also involved in bone regeneration and can directly inhibit the function of osteoblasts, leading to reduced bone formation.[27]

2.2.2. Dendritic cells

Dendritic cells (DCs) are a type of functional antigen-presenting cell that act as a bridge between innate and adaptive immune responses, thus playing a crucial role in promoting immune defense and maintaining tolerance.[28] Dendritic cells phagocytize and process antigens, presenting endogenous antigens to CD8+ T cells via MHC class I molecules and exogenous antigens to CD^{4+} T cells via MHC class II molecules. They effectively activate T cell immune functions and initiate immune responses.[29] Therefore, DCs are considered to indirectly influence inflammation-related bone loss by regulating T cell functions.

2.2.3. Monocytes and Macrophages

Monocytes are precursors to macrophages and dendritic cells, typically circulating for about a day before leaving the bloodstream to mature into macrophages in tissues.[30] Following bone tissue injury, circulating monocytes are massively recruited to the injury site through chemokine and cytokine signals, where they collaborate with resident macrophages, exhibiting significant phenotypic and functional changes during inflammation and subsequent tissue healing.[31] Inflammatory monocytes (IM) are recruited to inflammatory sites via integrins and chemokine receptors such as CCR2 and CCR5, responding to inflammatory cytokines like monocyte chemoattractant protein (MCP), and promote inflammation to peak concentrations within about 48 h after injury.[32] Anti-inflammatory monocytes (AM) help resolve inflammation and promote matrix modeling, angiogenesis, and prevent fibrosis by secreting cytokines such as TGF-β and IL-10.[33]

Macrophages can be broadly categorized into two main subtypes based on their activation state: pro-inflammatory M1 macrophages and anti-inflammatory M2 macrophages. M1 macrophages secrete reactive chemicals, phagocytize apoptotic neutrophils and necrotic tissue debris, clear pathogens, and produce growth factors like VEGF and FGF. However, excessive activation or prolonged mobilization of M1 can impair tissue healing and lead to further tissue damage.[34] Anti-inflammatory M2 macrophages help maintain tissue homeostasis and can be further subdivided into M2a, M2b, and M2c based on cell surface markers, activators, and cytokine expression.[35] The M2a phenotype is induced by the action of IL-4 and IL-13 on IL-4Rα, leading to increased expression of CD206, arginase, and TGF-β. The M2b phenotype is generated by the action of IgG-immune complexes and IL-1R ligands, increasing IL-10 production while decreasing IL-12 production, thus playing an anti-inflammatory role. The M2c phenotype is formed under the influence of IL-10 or glucocorticoids, characterized by high expression of IL-10, low expression of IL-12, and an increased presence of the surface receptor CD163.[36]

Overall, monocytes transform into macrophages with diverse functions after bone tissue injury, with M1 dominating initial defense and inflammatory responses, while M2 plays a crucial role in wound healing and tissue repair. Both M1 and M2 macrophages are indispensable for bone self-healing, and targeted, timely modulation of these macrophages can promote healing.[37]

2.2.4. T Cells

T cells, derived from hematopoietic stem cells and part of the adaptive immune system, play a crucial role in bone remodeling and regeneration by producing a variety of cytokines and growth factors. T cells are categorized based on surface molecule differences; for instance, CD^{4+} T cells, or helper T cells, are further divided into Th1, Th2, Th17, and regulatory T cells (Tregs), each characterized by distinct functions due to different cytokines.[8b,38]

Naive T cells can differentiate into either Th1 or Th2 cells. Th1 cells primarily eliminate intracellular pathogens by secreting interferon-gamma (IFN-γ), IL-2, and TNF-α, whereas Th2 cells promote B cell activation and the clearance of extracellular pathogens by producing IL-4, IL-5, IL-6, and IL-10.[39] Studies have also found that RANKL is primarily expressed by Th1 cells.[40]

Th17 cells are the most effective T cells in inducing osteoclastogenesis, expressing cytokines including IL-17A, IL-17F, IL-22, IL-26, and IFN-γ. These cells promote the expression of M-CSF and RANKL in osteoblasts and stromal cells, increase RANK expression in osteoclast precursors, and produce RANKL and TNF-α.[41]

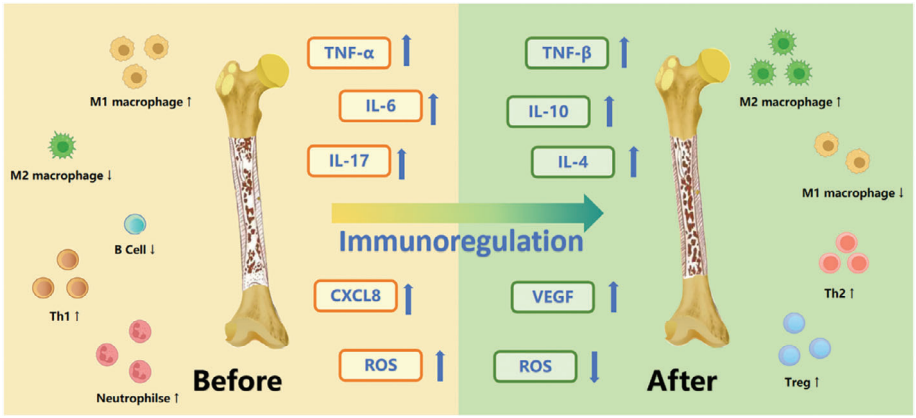
Regulatory T cells, a type of T cell with immunosuppressive effects, maintain immune tolerance and systemic balance by secreting cytokines such as TGF-β and IL-4. Tregs also directly enhance the function of osteoblasts, promoting their differentiation and inhibiting osteoclastogenesis.[42] These cells are also recruited to inflammatory sites to mitigate inflammation and regulate the immune response after injury.[43]

2.2.5. B Cells

B cells originate from hematopoietic stem cells and are a crucial source for the synthesis and secretion of antibodies, playing an important role in adaptive immunity.[44] B cells closely collaborate with the immune system, with their differentiation and maturation occurring in the bone marrow. During the development of B cells, hematopoietic stem cells provide a stable microenvironment for B cell differentiation through the action of cytokines and signaling molecules such as RANKL, CXCL12, and IL-7, promoting the formation and maturation of B cells. This phenomenon is particularly evident in conditions related to bone loss, such as osteoporosis and rheumatoid arthritis.[45]

2.2.6. Interactions and Temporal Sequence of Immune Cells in Bone Repair

In bone repair, the interactions and timing of immune cells are highly coordinated. During the acute inflammation phase



Scheme 2. Key immune regulatory roles in contrasting normal and aging bone microenvironments.

(Day 1–3), neutrophils are the first responders, performing phagocytosis and releasing inflammatory cytokines to recruit monocytes and macrophages. Macrophages play a key role in the subsequent repair phase, with M1 macrophages responsible for clearing pathogens and necrotic tissue, while M2 macrophages secrete anti-inflammatory cytokines to promote tissue repair and bone formation.[36,46] Meanwhile, dendritic cells and T cells also become active. Dendritic cells activate T cells to initiate adaptive immune responses, while T cells regulate the immune response by secreting cytokines, thereby driving the bone repair process.[47] In the remodeling phase (Day 7 and beyond), regulatory T cells (Tregs) play a crucial role in immune tolerance, inhibiting excessive immune responses and preventing chronic inflammation and fibrosis, ensuring proper bone repair. B cells further modulate the immune environment by secreting cytokines, supporting the repair process.[8b,48] Overall, immune cells interact in a precise temporal sequence, effectively regulating inflammation and promoting tissue repair and reconstruction during bone healing.

To better illustrate the differences in immune regulation between normal and aging bone microenvironments, **Scheme 2** highlights the key immune cell interactions and their roles in maintaining or disrupting bone homeostasis.

2.3. Immune Therapeutic Strategies for Bone Repair and Aging

The immune system plays a crucial role in regulating bone aging. By modulating immune responses, it can slow down bone degeneration, improve the bone microenvironment, and promote the regeneration and repair of bone tissue. Immune responses can be broadly classified into two categories: direct immune responses and indirect immune responses. Direct immune responses occur when biomaterials directly interact with immune cells, such as macrophages and dendritic cells, triggering inflammation or immune activation. On the other hand, indirect immune responses involve signals mediated through neural pathways, where the immune system is influenced by neural signals from the local environment or even distant organs.[49] Currently, researchers have been exploring how to regulate immune responses by controlling the polarization of immune cells toward an anti-inflammatory state to promote bone repair and regulate bone aging. Existing research mentions several common immunomodulation methods, each based on different types of stimuli and corresponding mechanisms. The first category is physical signals, such as when implants like hydroxyapatite (HAp) or titanium materials are implanted into the human body, the immune system naturally attempts to intervene. The physical properties of the implant provide key signals and indicators that trigger immune responses, with most studies focusing on the reaction of macrophages.[50] The second category is chemical signals, where the chemical composition of the implant is a key factor influencing the foreign body response. Inorganic cues from metals, ceramics, and organic biomaterials (such as metal ions and ceramics) and their functional groups are used to control the interaction between the implant and the immune system to achieve immunomodulation. The third category is biological signals, which regulate the immune response directly through cytokines, genes, extracellular substances, and stem cells, typically providing more effective methods of immune regulation. These biological factors have been used to regulate inflammation and promote tissue homeostasis.[50a]

In this context, this article categorizes immunotherapy methods based on different materials, with a focus on how these materials are used to achieve bone repair and regulate bone aging. It is important to note that biomaterials can achieve immunotherapy for bone repair and aging through a variety of fundamental mechanisms. The safest and most effective immunotherapy requires precisely delivering stimulation signals to the correct cells at the right location and time, to avoid toxic overstimulation in healthy tissues or incorrect programming of immune responses.[51] In material-mediated immunotherapy, three main categories of materials are used to promote bone repair and regulate bone aging. First, immunomodulatory drug delivery systems, including injectable hydrogels, functionalized nanomaterials, and engineered exosomes, can effectively release immunomodulators locally at the injury site, enhancing the immune response and promoting bone repair. The second category is bone tissue engineering materials, such as bioceramics, bone cement, and other scaffold materials, which are widely used to fill bone defects and promote cell growth, aiding in the development of new bone tissue. Finally, coating materials, such as apatite, are primarily used to improve the integration of implant materials with

natural bone tissue, promoting bone integration and improving therapeutic outcomes.

3. Adjunctive Techniques

In addition to continuous innovations aimed at enhancing bone repair materials, auxiliary technologies have also been developed to improve the mechanical properties of biomaterials, optimize the microstructure of scaffolds, and enhance their bioactivity. This section introduces several promising auxiliary technologies: 3D printing, electrospinning, and microfluidic techniques.

3.1. 3D Bioprinting

The application of 3D printing technology in the biomedical field is progressively expanding, notably advancing the repair of bone defects through the fabrication of living cells and precise tissue structures. 3D printing overcomes the limitations of traditional manufacturing techniques such as freeze-drying and gas foaming by using precise computer-aided design (CAD) to create bone tissue engineering scaffolds with complex internal structures. This technology supports various printing methods, such as extrusion printing, stereolithography, selective laser sintering, and inkjet printing, each with specific material requirements and indications.[20]

Nonetheless, this technology still faces challenges, such as selecting appropriate biocompatible materials, controlling shear forces and photothermal effects during the printing process, and meeting the constraints of complex biological demands.[52] In addition, scalability remains a major hurdle, as many successful preclinical applications fail to translate into large-scale production suitable for clinical use.[53] Regulatory challenges also hinder clinical adoption, as establishing standardized quality control protocols and gaining FDA or EMA approval for bio-printed constructs require extensive validation and long-term safety assessments. Addressing these challenges is crucial for transitioning 3D bioprinting from experimental research to routine clinical practice.[54]

3.2. Electric Field-Assisted Techniques

Electrospinning is a technique for fabricating bone tissue engineering microfibers or nanofibers by applying an electric field between a syringe and a collector. This method can generate continuous fibers with large surface area, high porosity, and good bioactivity, offering significant advantages over traditional bone tissue engineering scaffolds.[55] Electrospinning can also be used to manufacture three-dimensional scaffolds, where the pore size of electrospun fibers can be controlled by adjusting the voltage and concentration of the spinning solution to create tissue engineering scaffolds with defined micro/nanostructures in fiber dimensions.[56] In addition to assisting in material fabrication, electrical stimulation has shown in animal experiments and clinical treatments to promote osteogenesis, vascularization, and anti-inflammatory effects. Mechanisms include promoting the proliferation and osteogenic differentiation of mesenchymal stem cells (MSCs), activating endothelial cells to produce new blood vessels, and inducing macrophages to transition from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype.[57]

Despite its potential, electrospinning faces several limitations in clinical translation. The scalability of electrospun scaffolds remains a challenge due to the low production rate of conventional electrospinning processes. Generating uniform, reproducible fiber structures at a large scale while maintaining bioactivity is difficult. In addition, the integration of electrospun scaffolds into existing surgical or minimally invasive procedures requires further optimization.[58]

3.3. Microfluidic Technology

Microfluidic technology involves the control, manipulation, and analysis of fluids at microscopic scales, capable of manipulating fluids on the sub-millimeter level.[59] Using osteoporotic bone defects as a disease model, injectable hydrogel microspheres based on droplet microfluidics offer an excellent option for minimally invasive treatment.[60]

Moreover, microfluidic technology has unlimited application prospects, ranging from simple cell culture chips to organ chips.[59] Organ chips, also known as "tissue chips," are advanced platforms based on microfluidic systems for constructing and simulating miniature organ models in vitro. These chips can replicate physiological and pathological responses of human organs, especially in the development of bone and joint chips, where they can simulate complex physiological processes, cellular interactions, the impact of biochemical factors, and mechanical stimuli, thereby deepening the understanding of the health and disease states of bones and joints.[61] For example, Sheyn and others developed a bone chip system for studying osteogenic differentiation in vitro. This system integrates optical imaging technologies, allowing for real-time monitoring of MSC survival, proliferation, and differentiation without terminating the culture. Studies have shown that the flow system significantly enhances cell survival and proliferation rates and promotes osteogenic differentiation compared to static cultures.[62] Li et al. used microfluidic organ chip technology to simulate the bone microvascular environment by cultivating and observing bone marrow endothelial cells (BMEC), exploring the pathogenesis of steroid-induced osteonecrosis and the effects of different pharmaceutical interventions.[59] These technologies can also be applied to immunomodulatory strategies in bone repair and aging treatments.

However, the fabrication of microfluidic chips, particularly those with complex multichannel designs, remains time-consuming and costly, limiting their widespread clinical adoption. In addition, the standardization of microfluidic platforms is still lacking, making it difficult to compare results across different studies. Overcoming these barriers will be essential for translating microfluidic technologies into routine clinical applications for bone repair and tissue engineering.[63]

Building upon the discussion of advanced technologies in bone repair, the following section introduces a variety of materials that play a critical role in material-mediated immunotherapy. These materials are integral to regulating bone aging, promoting

Table 1. Overview of materials for immunotherapy in bone aging and repair.

Main topic	Subtopic		Key points
Immunomodulatory drug delivery systems	Injectable hydrogel	Stimulus-responsive hydrogels	Stimulus-responsive hydrogels enable precise, localized drug delivery for bone repair by responding to specific physiological stimuli.
		Multifunctional drug delivery hydrogels	Multifunctional hydrogels enhance bone regeneration by enabling targeted drug delivery, carrying metal ions, stem cells, and antioxidants, and promoting cell migration and inflammation regulation.
		Hydrogels utilizing advanced manufacturing technologies	Advanced manufacturing technologies enable customized hydrogels for enhanced bone repair with bioactive substances and tailored properties.
	Functionalized nanomaterials	Nanomaterials for drug delivery	Nanomaterials improve bone repair through targeted and controlled drug delivery using bone-affinity substances and peptides.
		Nanomaterials with intrinsic therapeutic activity	Nanomaterials with intrinsic therapeutic activity promote bone repair by stimulating osteogenesis and modulating the immune environment.
	Engineered exosomes		Engineered exosomes, especially those derived from BMSCs, play a key role in bone repair by promoting osteogenic differentiation, immunomodulation, and enhancing tissue integration.
Bone tissue engineering materials	Bioceramics	Mesoporous bioactive glass	MBG scaffolds promote bone repair via drug release, macrophage modulation, and surface enhancements.
		Hydroxyapatite	Hydroxyapatite scaffolds' bioactivity and bone repair can be enhanced through doping, pore size adjustments, and structural design.
		Other bioceramic materials	Other bioceramics promote bone regeneration and repair through different mechanisms.
	Bone cements		Bone cements like CPC and TSC enhance bone repair and regeneration, with modifications improving their osteogenic, immunomodulatory, and mechanical properties.
	Advanced bioactive scaffolds		Advanced bioactive scaffolds, including metal and natural biomaterials, enhance bone regeneration and immunomodulation through controlled release of therapeutic agents.
Coating materials	Inorganic coatings		Inorganic coatings, such as hydroxyapatite and graphene oxide, enhance the bioactivity and immune modulation of metal implants, promoting bone regeneration and reducing inflammation.
	Organic coatings		Organic coatings enhance implant biocompatibility and bone integration by modulating immune responses and promoting regeneration.

bone repair, and play an essential role in immune modulation, particularly in influencing key immune cells. Their specific properties and mechanisms are summarized in **Table 1**. The table categorizes these materials based on their unique functions, providing a comprehensive overview of their potential in enhancing bone health through immunomodulatory strategies. The focus of the entire manuscript is particularly on the three core areas: drug delivery systems, bone tissue engineering materials, and coating materials, all of which are pivotal in facilitating bone repair and immune modulation.

4. Immunomodulatory Drug Delivery Systems

In this section, we will delve into the analysis of immunomodulatory drug delivery systems, discussing how these systems regulate the immune environment through precise control of drug release. In addition, we will explore specific nanomaterials that not only carry and release drugs but also directly promote bone tissue regeneration due to their inherent immunomodulatory activities.

4.1. Injectable Hydrogel

Hydrogels, due to their three-dimensional hydrophilic networks and excellent ability to mimic the extracellular matrix (ECM), have been extensively researched and applied in the fields of tissue engineering, wound healing, and drug delivery. These properties not only facilitate cell proliferation and differentiation but also enable localized drug loading and release, thereby promoting tissue regeneration.[64]

4.1.1. Stimulus-Responsive Hydrogels

In the field of bone repair and aging regulation, stimulus-responsive hydrogels demonstrate unique capabilities by

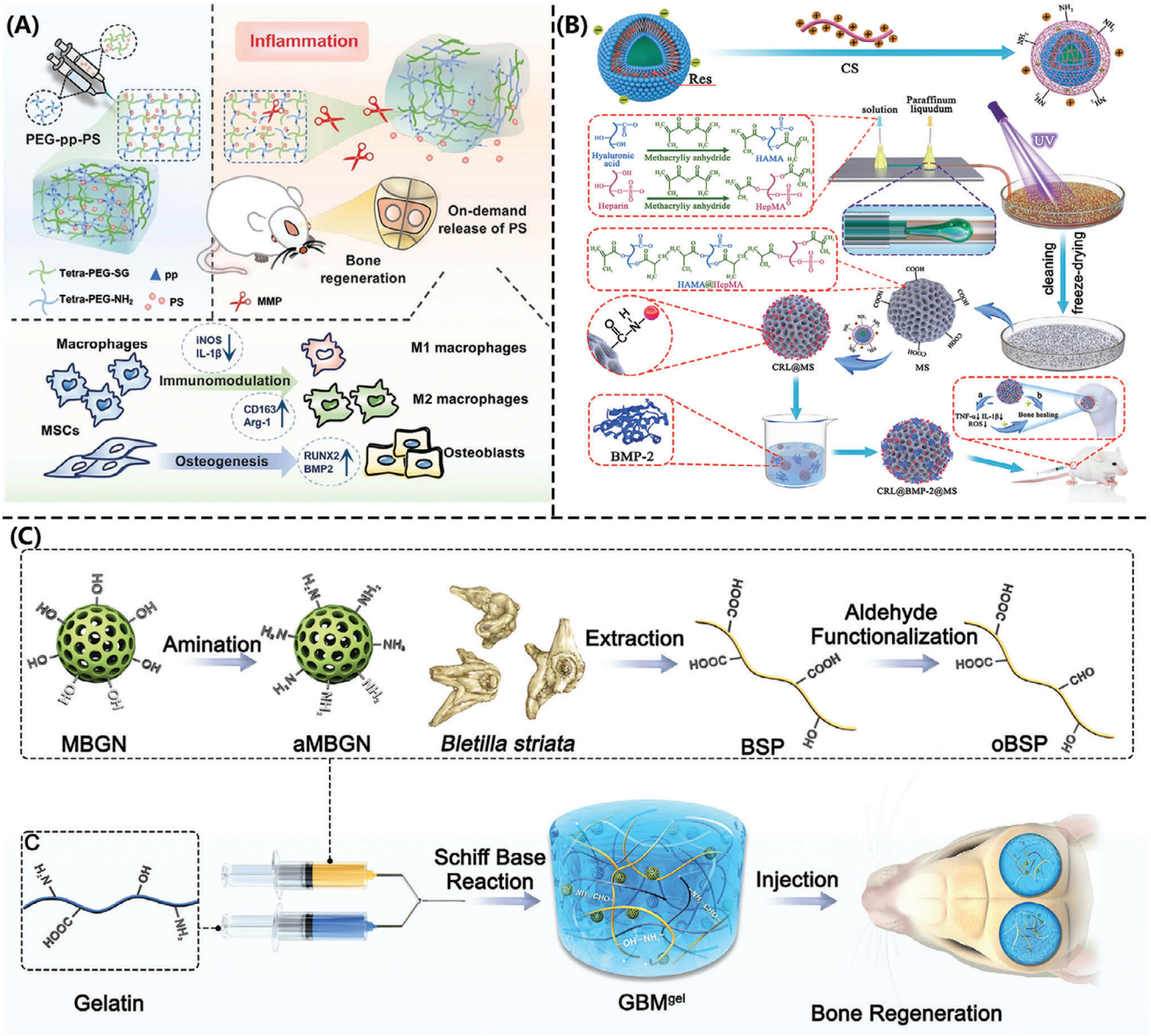


Figure 1. Hydrogel materials for regulating bone aging/promoting bone repair. A) Schematic of the fabrication process for an MMP-responsive, PS-encapsulated injectable hydrogel (PEG-pp-PS) for rat calvarial bone defect regeneration. Reproduced with permission.[68] Copyright 2024 The Authors. Advanced Science published by Wiley-VCH. B) Composite schematic diagram of CRL@ BMP-2@MS. Reproduced with permission.[93] Copyright The Author(s). Published by Elsevier. C) Schematic of the construction and application of the inorganic–organic double-cross-linked hydrogel for enhanced bone regeneration. Reproduced with permission.[74] Copyright 2024 The Authors. Advanced Healthcare Materials published by Wiley-VCH.

altering their physical structure or chemical properties in response to specific physiological or environmental stimuli such as temperature changes, pH variations, or enzymatic actions.[65] Unlike traditional hydrogels that exhibit unstable and arbitrary drug release, inflammation-responsive hydrogels facilitate precise localized drug delivery, ensuring maximum therapeutic efficacy in modulating the bone defect environment.[66] In bone injuries, levels of matrix metalloproteinases (MMPs) increase across various stages of inflammation and bone remodeling. Therefore, developing hydrogel systems that intelligently respond to MMP levels to release therapeutic agents on demand represents an effective strategy for enhancing bone repair and addressing age-related bone degeneration.[67] For example, Zhang et al. designed an MMP-responsive injectable hydrogel specifically engineered for the precise release of phosphatidylserine (PS). This was achieved by integrating an MMP-cleavable peptide (pp) into a tetra-arm polyethylene glycol (PEG) network, enabling precise drug delivery upon inflammatory stimulation. In their study, PS was encapsulated within the scaffold to form a PEG-pp-PS network, which could be activated by MMPs during the early stages of inflammation, releasing a significant amount of PS and continuing until the later stages of bone repair[68] (**Figure 1A**). Ultrashort peptides, known for their excellent biological functions, safety, and lower synthesis costs, also play

a significant role in stimulus-responsive hydrogels.[69] Zhang et al. developed a biomimetic ultrashort peptide nanofiber hydrogel triggered by ultrasound, using self-assembling ultrashort peptide technology. The ultrasound-initiated hydrogel formed through coordination bonds between the carboxyl groups of alginate and calcium ions.[70] Under ultrasound treatment, these coordination bonds are disrupted, leading to the degradation of the hydrogel and the release of the encapsulated nanofibers.[71] The nanofibers release in a time-dependent manner, activating mitochondrial glycolysis and the tricarboxylic acid cycle, suppressing the production of reactive oxygen species, and enhancing the polarization of M2 macrophages. This promotes the secretion of BMP-2 and IGF-I by M2 macrophages, significantly accelerating the differentiation of bone marrow mesenchymal stem cells into osteoblasts.[70]

Although stimulus-responsive hydrogels hold potential for bone repair, they face challenges in drug release predictability due to variations in enzyme activity, pH, and inflammation across patients. Furthermore, controlling long-term stability and degradation is essential, as many hydrogels degrade too quickly or inconsistently in vivo. Future research should focus on developing hydrogels with better stability and predictable degradation, tailored to individual patients, to ensure consistent and effective bone regeneration.

4.1.2. Multifunctional Drug Delivery Hydrogels

Recently, multifunctional hydrogels have been developed to serve various roles in drug delivery and tissue regeneration, showing particular promise in targeted delivery systems and carriers for metal ions, stem cells, and antioxidants.

Over the past few years, precisely controlled structured biomaterials have been extensively utilized in drug delivery and tissue regeneration. The development of timed and targeted noncellular material strategies has proven especially advantageous for endogenous bone repair and fracture healing.[66a,72] The extracellular matrix-like properties of hydrogels mean they can promote cell migration and adhesion, making them widely used as biomaterials.[73] Targeted delivery hydrogels, by incorporating specific ligands or antibodies, identify and target specific cells or biomarkers in damaged bone tissue, ensuring precise delivery of therapeutic molecules to the site of bone injury. This enhances the precision and efficiency of treatments for bone repair and age-related bone regulation, making them suitable for scenarios requiring precise control of inflammatory responses. For example, Wang et al. developed a gelatin-*Bletilla striata* polysaccharide-mesoporous bioactive glass hydrogel (GBMgel), by crosslinking amino silane-modified mesoporous bioactive glass (aMBGN) with aldehyde-functionalized *B. striata* polysaccharide (oBSP) and gelatin through a Schiff base reaction. This hydrogel can target macrophages and induce their polarization, thereby activating the endogenous bone repair process[74] (Figure 1C).

In addition to targeted delivery, some hydrogels function as carriers for metal ions or stem cells, playing a crucial role in enhancing bone regeneration. Li et al. developed an injectable lithium-heparin hydrogel (Li-gel) containing gelatin-heparin microspheres (MS/TGF-β1) loaded with TGF-β1. The Li-gel serves not only as a delivery vehicle for MS/TGF-β1 but also promotes osteogenesis through the release of lithium ions.[75] Luo et al. utilized a thiolated hyaluronic acid hydrogel as a carrier, doped with lithium ion (Li^+) modified nano-hydroxyapatite (Li-nHA), forming the Li-nHA@Gel immunomodulatory biomaterial platform. This platform promotes the polarization of M2 macrophages by continuously releasing lithium ions to activate specific signaling pathways.[76] Researchers have also developed Au-MSNs, which are gold nanoparticle (AuNP) loaded mesoporous silica nanoparticles, that can promote macrophage polarization toward the M2 phenotype, enhancing anti-inflammatory effects and thus facilitating bone repair.[77] For instance, Li et al. designed microgel carriers for the delivery of skeletal stem cells (SSCs), enhancing their immunomodulatory properties through mechanical activation. In vivo, these microgels facilitate the differentiation of SSCs into immunomodulatory subpopulations by localized release, effectively suppressing inflammation and promoting tissue repair.[78]

Reportedly, the microenvironment during bone injury, such as low oxygen tension and high levels of ROS, can impede bone healing.[79] Thus, to address the oxidative stress that impedes bone healing during injuries, some hydrogels are specially designed to incorporate antioxidants. Chen et al. integrated manganese dioxide (MnO_2)-coated calcium phosphate microspheres and fibroblast activation protein inhibitors (FAPi). This hydrogel utilizes the redox activity of MnO_2 to eliminate hydrogen peroxide, generating oxygen to improve the oxidative stress environment in the bone defect area and continuously releasing FAPi to modulate the local immune response, promoting polarization of macrophages toward the M2 phenotype.[80] Zhou et al. developed a novel diffusion-dependent self-release (DDSR) hydrogel by polymerizing the natural antioxidant lipoic acid (LA), controlling the hydrogel's degradation rate to achieve sustained release of LA from the hydrogel backbone, maintaining antioxidant and anti-inflammatory effects for about four months. In addition, the DDSR hydrogel can also serve as a carrier, loading bone-inducing nano-hydroxyapatite, further accelerating the repair of osteoporotic bone.[81]

Multifunctional hydrogels are promising for targeted drug delivery and bone regeneration, but controlling drug release remains a significant challenge due to varying degradation rates in vivo. These variations impact drug bioavailability, while mechanical stability needs improvement for supporting load-bearing defects. The complex synthesis process also hinders reproducibility and clinical adoption.

4.1.3. Hydrogels Utilizing Advanced Manufacturing Technologies

In recent years, the development of hydrogels developed using advanced manufacturing technologies, such as 3D printing, nanotechnology, and microfluidic techniques, have been designed to precisely match the specific anatomical structures of patients or replicate complex extracellular matrices at the microscale. These innovations allow for the integration of bioactive substances, enhanced mechanical properties, and tailored degradation rates, resulting in highly customized scaffold solutions for bone repair and regeneration.[82]

However, due to the limited cell permeability at the core of pure hydrogels, incorporating effective bioactive substances remains a critical challenge in their design.[83] For example, methacrylated

gelatin (GelMA), which contains cell-adhesive RGD sequences, offers lower immunogenicity and enhanced moldability compared to traditional proteins like collagen and gelatin.[84] Similarly, platelet-rich plasma (PRP), an autologous biomaterial rich in growth factors such as PDGF, TGF-β, IGF, and CXCL12, provides a cost-effective and efficient option.[85] Therefore, Jiang et al. used 3D printing with Digital Micromirror Device technology to combine biogenic GelMA and blood-derived PRP, successfully constructing a composite hydrogel scaffold. Studies have shown that GelMA hydrogel containing 20% PRP (20% PRP-GelMA) can effectively promote the proliferation, migration, osteogenic, and chondrogenic differentiation of bone marrow mesenchymal stem cells (BMSCs) in vitro, as well as enhance the polarization of M2 macrophages, and increase the expression of Arg1 and CD206.[86]

In another approach, tetra-armed polyethylene glycol (tetra-PEG) is an ideal choice due to its uniform network, high mechanical strength, and low immunogenicity, making it well-suited for integration with nanotechnology in the construction of composite hydrogels.[87] Building on this concept, Sun et al. utilized nanotechnology to integrate short-chain chitosan (CS) and nano-hydroxyapatite (nHAp) into a tetra-PEG network, creating a composite hydrogel (PEG/nHAp/CS, PHC) through chemical crosslinking that effectively promotes M2 macrophage polarization by antagonizing the TLR4/NF-κB signaling pathway.[88] Fu et al. used EDTA-2Ca/GDL as a crosslinker to develop a novel alginate/graphene oxide/silk/nano-hydroxyapatite (Alg/GO/Ser/nHApp) nanocomposite hydrogel.[89] This composite hydrogel exhibits excellent mechanical strength and biocompatibility, capable of inducing M2 macrophage polarization via silk and directly promoting osteogenic activity through nano-hydroxyapatite.[90]

Expanding on the use of microfluidic technology, Zhao and others developed microfluidic hydrogel microspheres (GelMA-BP-Mg) by chelating Mg^{2+} and grafting BP on the surface of methacrylated gelatin (GelMA-BP) microspheres. This design endows the microspheres with active capture of Mg^{2+}, minimally invasive injectability, sustained release, and osteotargeting capabilities, effectively enhancing their ability to activate osteoblasts and endothelial cells while inhibiting osteoclasts, optimizing bone repair and regeneration processes.[91] Zhao et al. also combined microfluidic technology with solid-phase peptide synthesis (SPPS) to effectively prepare GelMA microspheres integrated with biological signals (GelMA-S-B). This method uses microfluidics to precisely control the loading of composite peptides and the formation of microspheres, ensuring the uniform distribution and sustained release of bioactive peptides, thus enhancing the microspheres' functionality in promoting bone repair and angiogenesis.[92]

Finally, designing programmable release hydrogel microspheres is an effective strategy, as demonstrated by Cai et al., who employed chemical grafting condensation reactions and microfluidic technology. This system integrates chitosan, resveratrol liposomes, hydroxypropyl methylcellulose, and heparin methacrylate networks. It is capable of rapidly releasing resveratrol to suppress acute immune responses while promoting the sustained release of BMP-2, thus effectively supporting bone repair and regeneration[93] (Figure 1B and **Table 2**).

Despite advances in hydrogel manufacturing technologies, challenges remain in clinical translation, especially with regard to scalability and reproducibility. The complex fabrication methods required for these hydrogels hinder large-scale production. Overcoming these issues is crucial for their widespread clinical application, ensuring that they can be used effectively in bone repair procedures.

4.2. Functionalized Nanomaterials

In recent times, the application of nanotechnology and nanomaterials in the field of bone regeneration has experienced substantial growth. Nanomaterials typically refer to materials with at least one dimension in the nanoscale, or 1–100 nm.[94] To optimize bone regeneration, it is crucial that the biomaterials used should mitigate the host's adverse immune response and effectively regulate the immune process to promote healing. This requires a shift from traditional inert biomaterials to materials with immunomodulatory capabilities.[13a,95] Therefore, the design concept of modern nanomaterials should incorporate "bone immunoregulation" systems.[96] Nanoparticles as drug delivery systems have shown great potential. They can be used to design efficient delivery systems targeted at bone, carrying drugs, vesicles, or nucleic acids and other therapeutic molecules.[97] In addition, some nanomaterials themselves possess therapeutic activity.

4.2.1. Nanomaterials for Drug Delivery

With the surge in development of nanodrugs for bone repair, many nanodrug delivery systems have been designed to efficiently deliver various drugs to the site of bone injury, increasing drug concentration while reducing side effects.[98] Among these, targeted drug delivery systems enhance their therapeutic effects through specific surface modifications with ligands.[99]

There are two main methods to achieve targeting capabilities for bone tissue: one is utilizing substances that naturally have an affinity for hydroxyapatite, such as BP and oligopeptides, where the unique P—C—P bond structure in bisphosphonates and oligopeptides allows them to bind strongly to the hydroxyapatite in bone tissue; the other method involves selectively targeting bone-related cells, typically using surface-functionalized mesoporous silica nanoparticles or specific targeting ligands like peptides, to achieve precise drug delivery and cellular regulation.[100] First is to use substances with a natural affinity for hydroxyapatite. Zhong et al. developed BP-activated self-assembling keratin nanoparticles, which harness keratin's pro-coagulant and immunomodulatory properties while maintaining its native conformation. These nanoparticles specifically target bone fractures, enhancing bone repair and modulating the immune response to accelerate the healing process.[4a] Ren et al. developed a dual-targeting nanocarrier, CH6-PAMAM-C11, by modifying a G4.0 PAMAM dendrimer with the C11 peptide and CH6 aptamer. The nanocarrier demonstrated strong bone-targeting capabilities, showing high affinity for hydroxyapatite and osteoblasts, making it a promising candidate for delivering drugs to bone. Its potential for treating osteoporosis through enhanced bone targeting and immune modulation is particularly noteworthy.[101]

Table 2. Hydrogel materials used for mediating immunotherapy to promote bone repair/regulate bone aging.

Hydrogel materials	Crosslinking type	Loading materials	Release mechanisms	Drug release mode	Refs.
Tetra-PEG	Chemical	PS encapsulated in PEG network through MMP-cleavable peptide integration	MMP-responsive cleavage	On-demand release upon inflammatory stimulation	[68]
Self-assembling ultrashort peptide	Physical	Peptide nanofibers released through ultrasound-induced degradation of coordination bonds	Ultrasound-triggered release	Time-dependent release	[70]
Gelatin, *B. striata* polysaccharide, aMBGN	Chemical	aMBGN and *B. striata* polysaccharides integrated within the gelatin network	Specific interaction with macrophages and controlled release via key signaling pathways	Targeted release to modulate macrophage activity	[74]
Lithium-heparin gel	Chemical	TGF-β1 encapsulated in gelatin-heparin microspheres	Controlled release facilitated by ionic interactions and microsphere degradation	Sustained release to maintain prolonged therapeutic levels	[75]
Thiolated hyaluronic acid	Chemical	Li^+ modified nano-hydroxyapatite (Li-nHA) encapsulated in thiolated hyaluronic acid hydrogel	Continuous release of lithium ions	Sustained release to activate specific signaling pathways	[76]
Microgels (specific composition unspecified)	Chemical	SSCs encapsulated within microgels through localized delivery	Localized release for immunomodulation	Local release to modulate the immune environment and promote tissue repair	[78]
m-PGA, GelMA	Chemical	FAPi encapsulated in MnO_2-coated CaP microspheres using dopamine-assisted deposition and $KMnO_4$ oxidation methods	MnO_2 decomposes H_2O_2 to produce oxygen, while CaP microspheres degrade to release FAPi	Sustained release responsive to acidic microenvironment	[80]
DDSR hydrogel	Chemical	Lipoic acid and nHA encapsulated into DDSR hydrogel	Controlled degradation of hydrogel to release LA and nHA over time	Sustained release for about 4 months, providing antioxidant and anti-inflammatory effects	[81]
GelMA	Chemical	PRP encapsulated in GelMA hydrogel via photo-crosslinking	Designed for localized and sustained release of growth factors from PRP	Controlled release to promote osteochondral regeneration	[86]
Tetra-PEG	Chemical	CS and nHAp encapsulated in tetra-PEG network through chemical crosslinking	Modulated by interaction within the tetra-PEG network	Targeted release to enhance osteogenesis and immunomodulation	[88]
Alginate, GO	Chemical	Silk fibroin and nHAp encapsulated in alginate and GO hydrogel through chemical crosslinking	Controlled release structured for mechanical strength and biological compatibility	Continuous release to facilitate bone formation	[89]
Chitosan, hydroxypropyl methylcellulose, heparin methacrylate	Chemical	Resveratrol liposomes encapsulated by chemical grafting condensation; BMP-2 incorporated within the hydrogel network	Phase-dependent release (early and sustained)	Rapid release of resveratrol and sustained release of BMP-2	[93]

Second is the approach of selectively targeting bone-related cells. Hosseinpou et al. used surface-functionalized mesoporous silica nanoparticles (MSN-CC), specifically designed with a core-cone structure to efficiently load and target deliver miRNA-26a to macrophages, where the loaded nanoparticles (MSN-CC-miRNA-26a) achieve cell internalization mediated by specific receptors, thus precisely regulating macrophage behavior to promote the osteogenesis process by reducing the expression of pro-inflammatory cytokines.[102] In addition, due to their potential low immunogenicity, high affinity, ease of bioconjugation and synthesis, and lower cost, peptides are attractive targeting ligands.[103] Sun et al. successfully developed an osteoblast-targeted delivery system using the SDSSD peptide (Ser-Asp-Ser-Ser-Asp), which specifically targets osteopontin to recognize osteoblasts. Through SDSSD peptide-modified polyurethane (PU) nanomicelles, siRNA/microRNA are encapsulated and delivered to osteoblasts[104] (**Figure 2A**). Zhou et al. utilized targeting peptides to develop BCL-loaded mesoporous silica and Fe_3O_4 composite nanoparticles (BCL@MMSNPs-SS-CD-NW). This system magnetically delivers BCL to bone injury sites, with a NW targeting peptide modified with adamantane on the outer layer. Intracellular glutathione (GSH) cleaves disulfide bonds, releasing BCL, which induces macrophages to polarize into the M2 type and promotes osteogenic differentiation[105] (Figure 2B,C). Moreover, Peng et al. proposed a novel nanoplatform called RSV@DTPF, which utilizes resveratrol (RSV), a natural

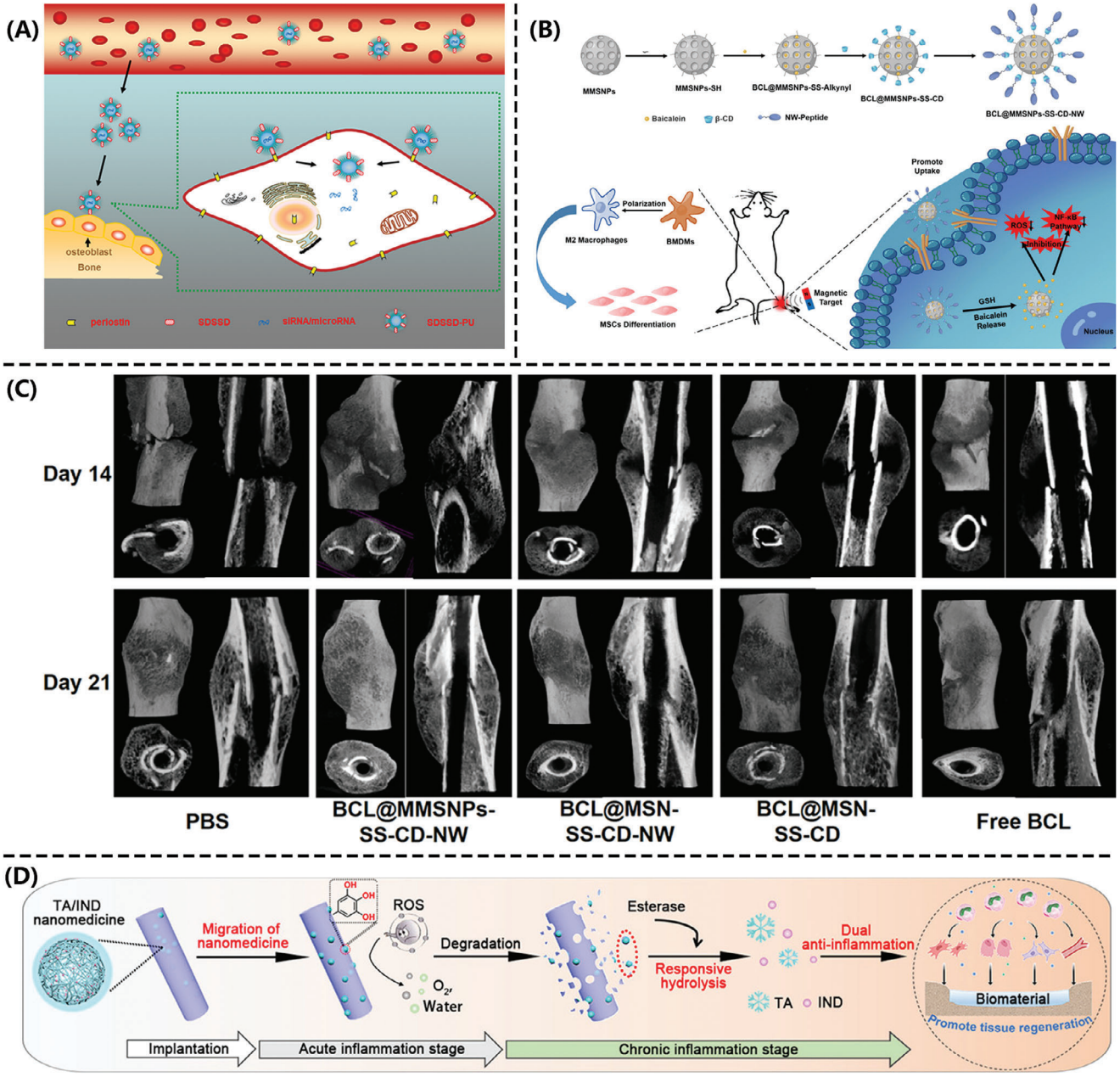


Figure 2. Functionalized nanomaterials for regulating bone aging/promoting bone repair. A) Schematic diagram of the SDSSD-PU delivery system. Reproduced with permission.[104] Copyright 2016, American Chemical Society. B) Schematic of MMSNPs-SS-CD-NW nanoplatform preparation and their action principles. Reproduced with permission.[105] Copyright 2021 The Authors. Published by American Chemical Society. C) Micro-CT 3D reconstructions, longitudinal slices, and cross-sectional images at days 14 and 21 post-fracture treatment with composite-targeted nanoparticles. Reproduced with permission.[105] Copyright 2021 The Authors. Published by American Chemical Society. D) Schematic of spatio-temporal strategies using amphiphilic nanomedicines. Reproduced with permission.[111] Copyright 2022, American Chemical Society.

compound derived from traditional Chinese medicine. When intracellular ROS concentrations increase, the disulfide bond breaks and releases RSV, enabling targeted and controlled release.[106]

Beyond targeting, loading immunomodulators is also an important, simple, and effective strategy, although improper release patterns can trigger side effects.[107] For example, directly loaded anti-inflammatory drugs often present issues with initial burst release and short release duration.[108] This may lead to excessive suppression of M1 macrophage activity, which is detrimental to tissue repair.[109] In addition, a short drug release period can only temporarily alleviate acute inflammation in the early stages but fails to provide continuous protection against chronic inflammation later on.[110] He et al. developed a spatiotemporal strategy based on amphiphilic nanodrugs, synthesizing a prodrug from tannic acid (TA) and indomethacin, and using Fe^{3+}

to cross-link on a PCL nanofiber scaffold. This system regulates the immune response at different stages, initially controlling the release of reactive oxygen species to mitigate acute inflammation and promote macrophage transition from M1 to M2 phenotype, while in the later stages of scaffold degradation, it increases the release of inflammatory-responsive drugs to adapt to chronic inflammation[111] (Figure 2D).

4.2.2. Nanomaterials with Intrinsic Therapeutic Activity

Advancements in nanotechnology have led to the creation of nanomaterials with inherent therapeutic properties that both promote bone formation and modulate the immune environment, offering dual-functional benefits for enhanced bone repair and regeneration. Certain nanoparticles inherently possess the ability to promote bone formation and limit bone resorption activities due to their unique structures and compositions. For example, superparamagnetic iron oxide nanoparticles coated with hydroxyapatite (SPIO@HA) exhibit a dual effect by simultaneously stimulating osteoblast growth and inhibiting osteoclast formation.[112] T-cell depleting nanoparticles based on mesoporous silica have also been developed to improve the pathological immune environment in osteoporotic bone tissue.[113]

Recent research has increasingly turned its attention to incorporating naturally occurring compounds with therapeutic properties into nanomaterials, with a particular focus on their potential to enhance bone repair and regulate bone aging by modulating the immune environment. Among various bioactive molecules, catechins, a type of polyphenol found in green tea, have been reported to promote osteogenic activity in mesenchymal stem cells.[114] Catechins typically function as effective antioxidants, scavenging free radicals to produce anti-inflammatory effects and achieve immunomodulatory action.[115] Kong et al. designed self-assembling iron-catechin nanoparticles based on the coordination reaction between iron ions and catechins. These particles show intracellular pH responsiveness and can release catechins in acidic lysosomal environments to promote osteogenic differentiation and resist inflammation by modulating macrophages toward M2 polarization, effectively reshaping the osteoimmune environment.[116] In addition, calcium ions (Ca^{2+}) can accelerate osteogenic differentiation of MSCs, and calcium-based biomaterials are widely used for bone repair.[114a,117] Squalene, a long-chain monounsaturated fatty acid extracted from shark neural tissues, has been shown to have potential in inhibiting inflammation and regulating the immune environment, with its effects inversely correlated with inflammatory responses.[115a,118] Therefore, Ma et al. developed calcium squalene nanoparticles as dual-functional materials for osteoinduction and immunoregulation. These particles can decompose intracellularly to release bone-promoting calcium ions and anti-inflammatory squalene, thus promoting osteogenesis of mesenchymal stem cells in vitro, alleviating macrophage inflammation induced by lipopolysaccharide in vivo, and demonstrating superior bone regeneration capabilities in bone defect repair models compared to either Ca^{2+} or squalene alone[119] (**Table 3**).

When these nanomaterials or exosomes, which will be discussed later, are locally implanted, there is a possibility they may enter the systemic circulation, influenced by factors such as particle size, surface charge, and degradation rate. This can lead to interactions with immune cells beyond the local site, potentially affecting global immune responses. On the one hand, this systemic distribution can be beneficial, promoting immune modulation and enhancing bone regeneration by affecting distant immune cells and tissues.[120] However, unintended immune activation or systemic inflammation could occur, potentially compromising the bone healing process. In addition, the distribution and clearance of these materials in the body must be carefully considered, as excessive retention in organs like the liver or spleen may reduce their therapeutic efficacy.[121] Therefore, while these advanced materials offer significant promise for bone regeneration, future research should focus on optimizing their design for localized activity, minimizing off-target effects, and ensuring safe and efficient delivery through careful immune modulation.

4.3. Engineered Exosomes

Recently, therapeutic interventions using exosomes with immunomodulatory functions to promote bone tissue repair have gained increasing attention.[122] Exosomes are key extracellular vesicles in intercellular communication, typically ranging from 40 to 160 nm in size and secreted by most eukaryotic cells.[123] Compared to easily inactivated cytokines, exosomes offer a wide range of sources, high stability, good biocompatibility, low immunogenicity, and excellent delivery and therapeutic effects.[124]

Our initial focus will be to explore the role that exosomes derived from BMSCs play in facilitating bone repair and regulating bone aging. Studies indicate that BMSCs primarily exert their regulatory effects on inflammation or bone immunomodulation through paracrine mechanisms.[125] As carriers of paracrine secretions, BMSC-derived exosomes contain a variety of biological signaling molecules such as proteins, lipids, and small RNAs, which can be delivered to target cells to perform immunomodulatory functions.[126] Notably, Exos can promote the polarization of macrophages from the M1 to the M2 phenotype, thereby enhancing their immunomodulatory functions.[127] Zhang et al. successfully isolated mesenchymal stem cell-derived exosomes (MSC-Exo) and designed a bioactive 3D porous polylactic acid exosome scaffold with bone immunomodulatory and osteogenic differentiation properties, effectively reducing the production of pro-inflammatory markers and reactive oxygen species.[128] Fan et al. developed an implant functionalized with BMSC-derived Exos using TA-modified sulfonated polyetheretherketone (SPEEK) surface to achieve immunomodulation and accelerate bone integration. This material uses the polyphenol groups in TA to fix Exos to the PEEK surface through reversible hydrogen bonding, creating a 3D porous structure to improve the loading and release efficiency of Exos.[129] Xu et al. used viral vectors to transfer Smurf1-shRNA to BMSCs to prepare engineered exosomes (S-Exos), which were fixed to the micro-arc oxidized Ti6Al4 V surface using polyethyleneimine (PEI), creating a dual-functional coating (Ti-MAO@PEI-S-EXO). S-Exos released in this system activate the BMP/Smad signaling pathway in BMSCs as well as promote macrophage M2 polarization, thereby enhancing integration with bone tissue[130] (**Figure 3A**).

In addition to exosomes derived from BMSCs, several other examples also highlight the potential of exosomes in bone re-

Table 3. Nanomaterials used for mediating immunotherapy to promote bone repair/regulate bone aging.

Nanomaterials	Size [nm]	Preparation method	Loaded bioactive agents	Drug release	Targeting strategies	Refs.
MSN-CC	≈200	Synthesis involving cetyltrimethylammonium chloride, triethanolamine, chlorobenzene, and tetraethyl orthosilicate, followed by surface phosphonate modification and PEI coating	miRNA-26a	Through transfection of miRNA-26a into macrophages and osteoprogenitor cells	Via the delivery of miRNA-26a to macrophages to modulate osteogenesis	[102]
Mesoporous silica	≈100	Sol-gel method followed by etching to form mesopores	miRNA-26a	Controlled release via pH-sensitive degradation	Functionalization with a specific peptide that targets osteoblasts	[104]
MMSNPs	≈100	Synthesized with sulfhydrylation and amination, using β-cyclodextrin to block mesoporous channels.	BCL	Cleavage of disulfide linker by GSH	Magnetic targeting and NW peptide targeting to macrophages	[105]
MMSNPs (Fe_3O_4@MSN core)	–	MMSNPs were synthesized using a solvothermal method, involving a mixture of CTAB, deionized water, ethanol, ammonia, and TEOS	BCL	Triggered by intracellular GSH	Utilizes a peptide targeting strategy	[111]
Fe-cat NPs	40–150	Fe–cat NPs are synthesized using a one-pot room temperature method, involving the reaction of iron ions with catechin	Catechin.	pH-responsive, released under acidic conditions typical of lysosomes	The nanoparticles target bone repair, promoting osteogenesis and immunomodulation	[111]
Calcium nervonate nanoparticles	150–200	Nanoprecipitation method using calcium acetate and nervonic acid	Calcium and nervonic acid	pH-responsive release in acidic environments	Enhanced osteogenesis and immunomodulation for bone repair	[119]

pair and regeneration. Lin et al. obtained exosomes enriched with PD-L1 (Exos) from genetically engineered human umbilical vein endothelial cells (HUVEC), which specifically inhibit T cell activation and induce MSCs toward osteogenic differentiation. By embedding these exosomes into an injectable hydrogel, a delayed release at the fracture site was achieved, effectively suppressing excessive local inflammatory responses and promoting tissue healing[131] (Figure 3B). Chen et al. explored the role of miR-142-3p contained in regulatory T cell-derived exosomes (TregD-Exos) in bone repair, finding that they effectively promote osteogenic differentiation of BMSCs and angiogenesis of HUVEC. TregD-Exos deliver signals through miR-142-3p, activating the TGFBR1/SMAD2 pathway, thus enhancing the osteogenic capacity of BMSC and the functions of HUVEC, including proliferation, migration, and vasculogenesis.[132] Exosomes from Schwann cells (SC Exo) might also have potential for immunomodulatory bone regeneration. Hao et al. developed a nerve tissue-engineered hydrogel encapsulated with Schwann cell-derived exosomes, where the SC Exo system continuously released in vivo, effectively coordinating nerve innervation, immunomodulation, vascularization, and osteogenesis, significantly enhancing bone regeneration[133] (Figure 3C).

Moreover, exosome-biomaterial composites can exhibit synergistic effects, such as bioceramics that positively induce exosomes. Sun et al. used 3D printing to manufacture a porous scaffold containing beta-tricalcium phosphate (β-TCP) induced macrophage exosomes (BC-Exos), which continuously release exosomes and recruit bone marrow mesenchymal stem cells and endothelial cells by regulating macrophage polarization and chemokine expression.[134] In addition, Chen and colleagues found that BCP ceramics with submicron structures are particularly effective at promoting macrophages to produce exosomes containing miR-142a-5p (B1-Exos). These exosomes significantly activate the PTEN/AKT signaling pathway in MSCs, thereby enhancing osteogenic differentiation.[135]

Recent studies have explored the application of traditional Chinese medicine-derived compounds, such as Icariin (ICA) and Pueraria lobata, in enhancing bone repair through innovative delivery systems like exosomes. Yu et al. prepared sEV-ICA by isolating milk-derived extracellular vesicles (sEV) and loading them with Icariin (ICA) to enhance its bioavailability and osteogenic effects, thereby improving the therapeutic efficacy of ICA in bone defect repair.[136] Similarly, Zhan et al. utilized Pueraria lobata-derived exosome-like nanovesicles (PELN) to deliver active ingredients that regulate the gut microbiome metabolite TMAO, promote autophagy, and enhance osteogenic differentiation of hBMSCs, offering a promising strategy for improving osteoporosis treatment[137] (**Table 4**).

Despite the potential of exosomes for immunomodulatory promotion of bone repair, significant challenges remain, including the lack of clinical approval, assessing immunogenicity, enhancing bioavailability, targeting exosomes to bone tissue, and variability depending on their source cells' state and microRNA stability.[124b] Furthermore, standardization and large-scale

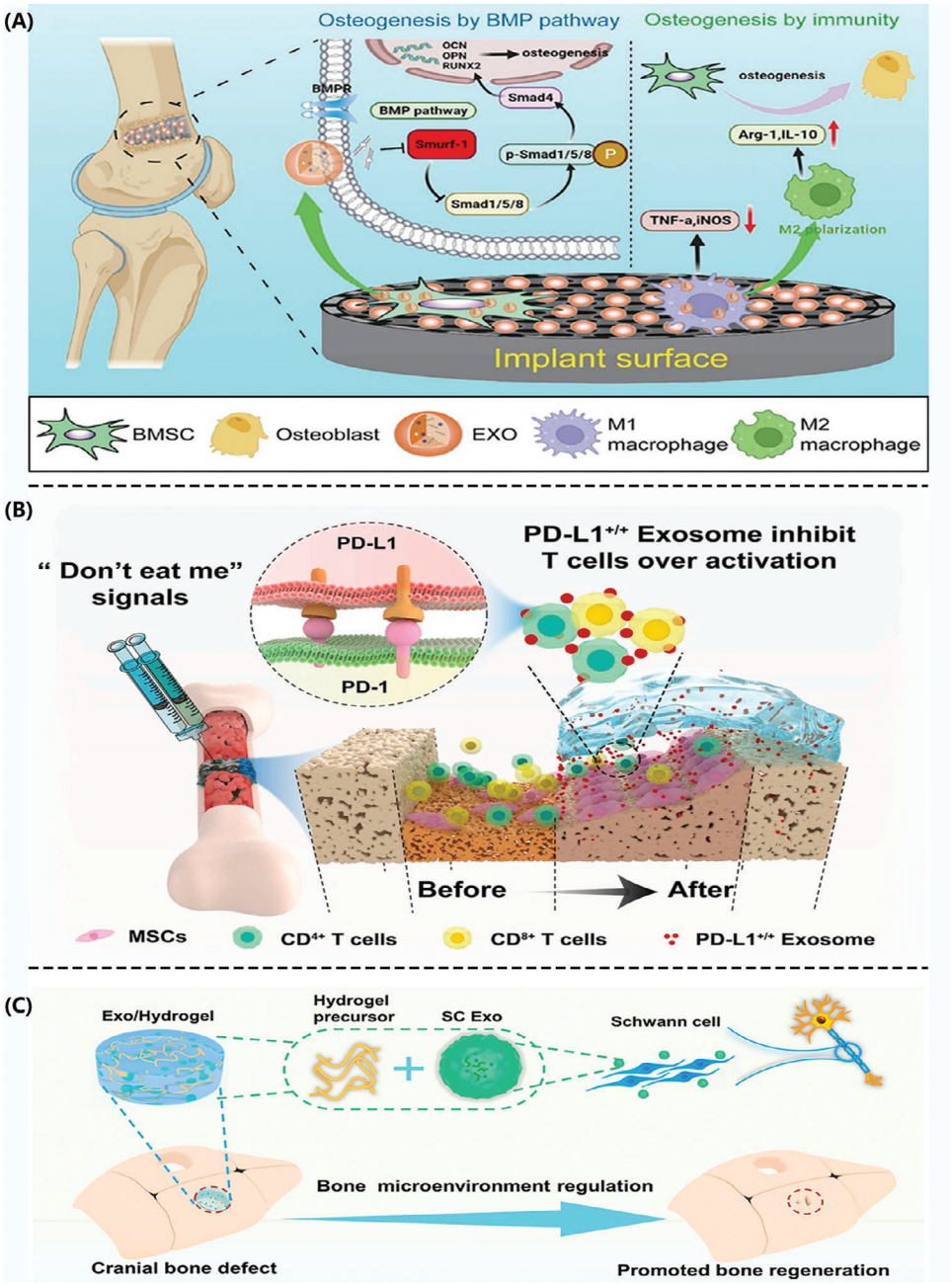


Figure 3. Exosomes for regulating bone aging/promoting bone repair. A) Mechanism of Ti-MAO@PEI-S-EXO to promote osteogenesis. Reproduced with permission.[130] Copyright 2022, American Chemical Society. B) Schematic of the therapeutic process for fracture healing using exosomal PD-L1. Reproduced with permission.[131] Copyright2021 The Authors. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd. C) Schematic of SC Exo isolation and Exo/Hydrogel construction. Reproduced with permission.[133] Copyright 2022 The Authors. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd.

production pose major hurdles, as exosome isolation, purification, and quality control remain technically complex and inconsistent across different studies. In addition, ensuring targeted delivery and controlled release within bone tissue remains difficult due to rapid clearance and limited tissue penetration. The mechanisms underlying exosome-mediated immune modulation and bone regeneration are still not fully understood, requiring further studies to optimize their therapeutic potential.

5. Bone Tissue Engineering Materials

In recent years, tissue engineering has opened new avenues for bone repair and the regulation of bone aging by leveraging the controlled release of exogenous progenitor cells and biofactors.[138] Scaffolds with good mechanical strength, appropriate degradation rates, and optimized biocompatibility, especially those rapidly evolving in osteogenic activity, have become a

Table 4. Engineered exosomes used for mediating immunotherapy to promote bone repair/regulate bone aging.

Engineered exosomes	Size [nm]	Origin cell	Loaded bioactive agents	Drug release	Targeting strategies	Refs.
MSC-Exo	≈100	MSCs	miRNAs, proteins	Controlled by enzymatic reaction, featuring a burst release followed by a sustained release phase, tailored to the inflammatory environment of the injury site	Enhanced osteogenesis and immunomodulation	[128]
MSC-Exos	≈100	MSCs	miRNAs, proteins	Slow release for prolonged interaction	Promotes macrophage M2 polarization and osteogenic differentiation	[129]
S-Exos	≈120	BMSCs	Proteins, miRNAs, BMP signaling pathway activators	Slow and sustained, ensuring prolonged interaction and efficacy	Promotes macrophage M2 polarization and activates the BMP/Smad signaling pathway to enhance osseointegration	[130]
BC-Exos	≈100	β-TCP	Specific proteins, miRNAs	Initial rapid burst within one day, followed by sustained long-term release	BC-Exos modulate macrophage polarization, enhance osteogenesis and immunomodulation	[131]
TregD-Exos	≈100	Tregs	miR-142-3p	Controlled by esterase-sensitive mechanisms, gradual release varies with inflammation conditions	Promotes osteogenesis and angiogenesis, aiding in bone repair	[132]
SC-Exo	≈120	SCs	mRNAs, small RNAs, proteins, lipids	Burst release in the first week, slow release thereafter	Promotes macrophage M2 polarization and osteogenic differentiation and activates the TGF-β1/SMAD2/3 signaling pathway to enhance osseointegration	[133]
BC-Exos	≈110	Macrophages (RAW 264.7)	miRNAs, proteins (e.g., BMP2, VEGFA, PDGF-BB)	Burst release within one day, followed by long-term sustained release; retention rate ≈80% after one month	Promotes macrophage M2 polarization and osteogenic differentiation and ctivates BMP2/Smad signaling pathway to enhance osseointegration	[134]
BC-Exos	≈100	Macrophages	miRNAs, proteins specific to macrophages	Sustained, ensuring prolonged interaction and efficacy	Promotes macrophage M2 polarization and activates BMP/Smad signaling pathway to enhance osseointegration	[135]

focal point in bone tissue engineering research.[139] This section will discuss the application of bioceramics, bone cements, and advanced bioactive scaffolds in immunoregulation. These materials are used to fill bone defects and serve as matrices for cell growth, facilitating the formation of new bone tissue, and have been widely applied in the treatment of bone aging and bone injuries.

5.1. Bioceramics

Bioceramics are widely used in bone tissue engineering due to their ability to release bioactive ions such as silica, which exhibit high biological activity.[140] In this section, we specifically explore the applications and advancements of mesoporous bioactive glass (MBG) and HAp in enhancing bone repair and regeneration, as well as in regulating bone aging, focusing on their roles in modulating immune responses and promoting osteogenesis.

5.1.1. Mesoporous Bioactive Glass

MBG significantly enhances bioactivity and has the capability to release drugs, growth factors, and proteins. This makes it a focus in bone regeneration research, with improvements in surface topologies, compositing with polymers, or combining with anti-inflammatory agents to further enhance osteogenic capabilities.[141] Despite these advancements, the impact of MBG content on macrophage inflammatory behavior and its

promotion of bone repair and regeneration has not been extensively studied. Thus, Liu and colleagues explored the effects of scaffolds with different MBG contents (0%, 10%, 20%, and 40%) based on poly(lactic-*co*-glycolic acid) (PLGA) on macrophage polarization, immune responses, and cytokine secretion. The results indicated that scaffolds with 10% MBG content significantly promoted angiogenesis and osteogenesis.[142] Building on these findings, Qi and others added GO nanosheets to BG, endowing the porous scaffold surface with better hydrophilicity and roughness, creating a surface-modified three-dimensional (3D) porous bioactive glass (BG)/GO scaffold.[143] In another approach, MBG scaffolds fabricated using PU sponges as templates, whose 3D structure enhances cell infiltration and drug carrier functionalities, facilitate the ingrowth and osteogenic differentiation of bone marrow mesenchymal stem cells.[144] Furthermore, Shi and colleagues developed a composite scaffold based on mesoporous bioactive glass and hyaluronan methacrylate (HAMA), manufactured using a PU sponge template to mimic the three-dimensional porous structure of natural bone, enhancing macrophage M2 polarization and anti-inflammatory functions by modulating N2 neutrophils[145] (**Figure 4A**). To further advance the potential of MBG scaffolds, researchers have also explored their use in spatiotemporal drug delivery. For example, Lin and colleagues' design of a graded macro/mesoporous bioactive glass scaffold, implementing a time-release system for the rapid release of IL-8 and prolonged release of BMP-2.[146] In addition, hydrogen gas (H_2), as an emerging anti-inflammatory agent, is capable of selectively neutralizing highly oxidative radicals such as hydroxyl radicals, and has also been incorporated into the design with MBG scaffolds.[147] For example, Chen and colleagues developed a novel material—polyhydroxyalkanoate (PHA) encapsulated calcium silicide nanoparticles (CSN) loaded mesoporous bioactive glass scaffold (termed CSN@PHAMBG), designed for the localized and sustained release of a large amount of hydrogen (up to 911 mL g^{-1} CSN).[148] Finally, nanoscale bioactive glass scaffolds (BGS) have been introduced into the design, proven to effectively promote osteogenic activity near the cranial bones.[149]

MBG has shown great promise for bone regeneration, but challenges remain in optimizing degradation rates, enhancing immune modulation, and improving mechanical properties. The impact of MBG on macrophage polarization and chronic inflammation requires further investigation. Future studies should focus on refining the composition of MBG to enable controlled degradation and more effective immunoregulation, leading to better clinical outcomes.

5.1.2. Hydroxyapatite

Aside from bioactive glass, HAp remains one of the most a widely used orthopedic bioceramic material, known for its biocompatibility, osteoconductivity, and osteoinductivity.[150] In optimizing HAp-based biomaterials, key factors such as particle size, morphology, and crystallinity must be considered.[151] To improve HAp's bioactivity, several strategies have been used, including elemental doping, heat treatment, and material cladding.[152] For instance, Zhong and others used a strategy of inorganic ion doping, successfully synthesizing zinc and strontium co-doped hydroxyapatite (ZnSr-Col-HAp) through a biomimetic approach using a collagen template. Activation of the OSM signaling pathway plays a dominant role in the early expression of osteogenic genes, while direct stimulation by Zn^{2+}/Sr^{2+} is more effective in later stages through the activation of the Nfatc1/Maf and Wnt signaling pathways.[153] In another study, Zhao et al. developed a micro/nanostructured (MNS) hydroxyapatite bioceramic that optimizes osteoporotic bone formation by adjusting nHAp nanoparticle loading, and promotes bone regeneration while delaying bone aging through immune microenvironment modulation, particularly macrophage polarization and inflammatory response regulation.[154]

The importance of scaffold design was also demonstrated, as smaller pore sizes (100–400 µm) typically stimulate the polarization of M1 macrophages, promoting cell invasion and angiogenesis.[155] Conversely, larger pore sizes (400–800 µm) tend to facilitate the differentiation of M2 macrophages, which assists in the attachment and spread of osteoblasts and ensures adequate nutrient and oxygen transport.[156] Therefore, by adjusting the pore size of the scaffold, effective modulation of M2 macrophages can be achieved, enhancing repair and anti-inflammatory processes, while minimizing adverse host reactions.[157] Xiong and others fabricated 3D printed HAp bioceramic scaffolds with varying pore sizes, finding that a 600 µm pore size provided the optimal microenvironment.[158]

Challenges in optimizing hydroxyapatite for bone regeneration include controlling degradation rates and improving mechanical strength. HAp's brittleness and limited osteogenic performance hinder its broader use. Future research should focus on improving HAp's mechanical properties and its ability to degrade at predictable rates, ensuring better integration with bone tissue and enhanced osteogenic potential.

5.1.3. Other Bioceramic Materials

In addition to MBG and HAp, various other bioceramic materials, such as biphasic calcium phosphate (BCP), akermanite, and calcium-magnesium silicate, have shown significant potential in promoting bone regeneration, osteochondral repair, and regulating bone aging through various mechanisms. For instance, previous studies have reported that BCP ceramics with whisker surface structures exhibit favorable bone regeneration and bone defect repair capabilities.[159] Specifically, Peng and others found that the nanowhisker structure of this material can activate specific biological processes through mechanical stress, inducing a shift in macrophages from the M1 to the M2 phenotype[160] (Figure 4B,C). In another study, Deng et al. developed a 3D-printed akermanite bioceramic scaffold integrated with hair-derived antioxidative nanoparticles/microparticles, effectively promoting osteochondral regeneration and regulating bone aging by scavenging reactive oxygen species and stimulating chondrocyte proliferation and osteogenic differentiation.[161] Furthermore, Namdar et al. explored the advantages of doping calcium-magnesium silicate bioceramics (e.g., diopside, akermanite) with ions such as Sr^{2+}, Cu^{2+}, and Ba^{2+}, significantly enhancing their mechanical properties, osteogenesis, angiogenesis, and antibacterial performance, positioning them as superior bone substitutes compared to traditional bioceramics.[162]

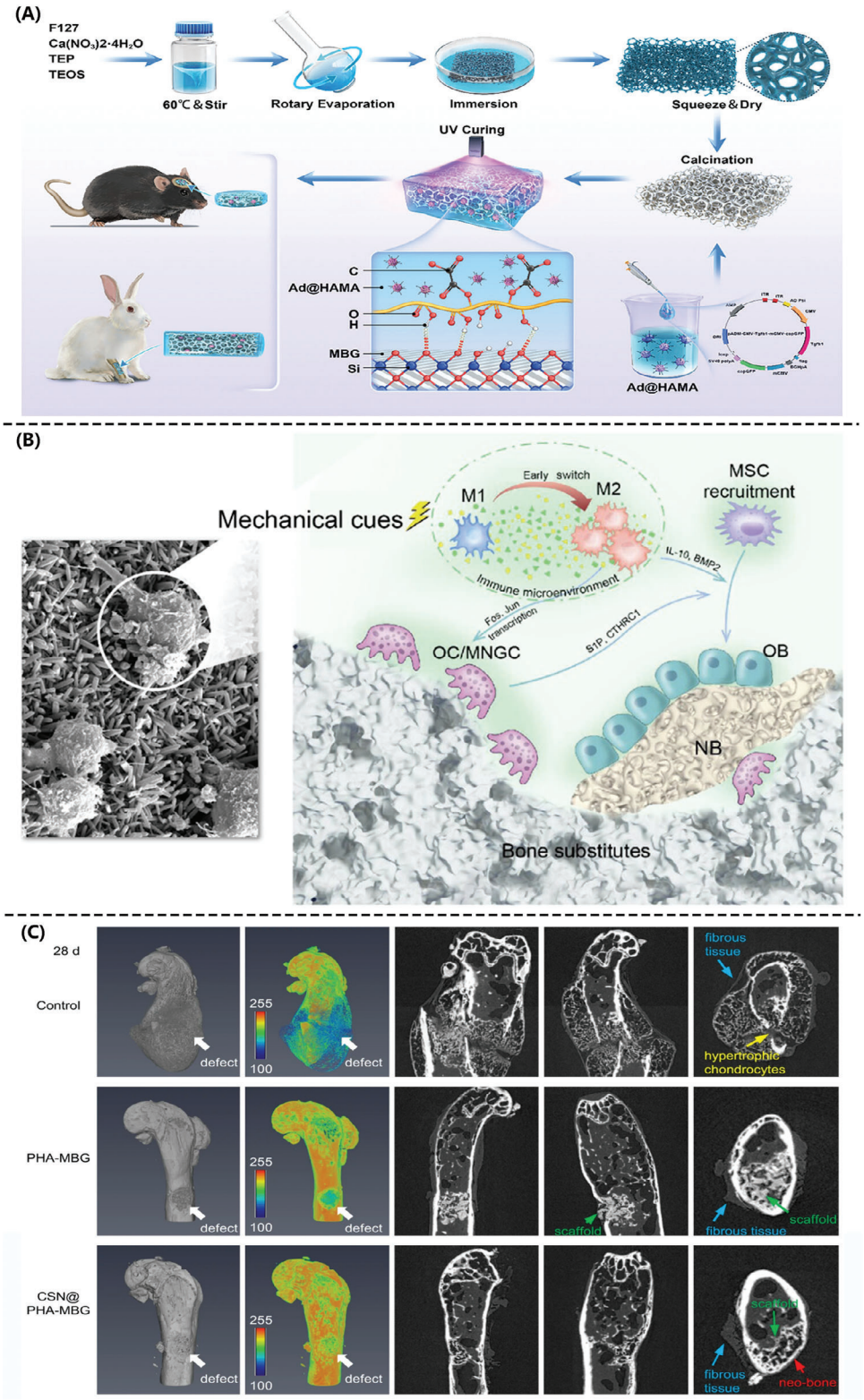


Figure 4. Bioceramics for regulating bone aging/promoting bone repair. A) Schematic diagram of Ad@H/M preparation and application. Reproduced with permission.[145] Copyright 2024 The Authors. Advanced Healthcare Materials published by Wiley-VCH. B) Schematic of bone substitute-generated immune microenvironment impact on bone defect repair. Reproduced with permission.[160] Copyright 2023, American Chemical Society. C) Representative SRμCT images of neo-tissues at day 28 after control, PHA-MBG, or CSN@PHA-MBG treatment. Reproduced with permission.[160] Copyright 2023, The Author(s).

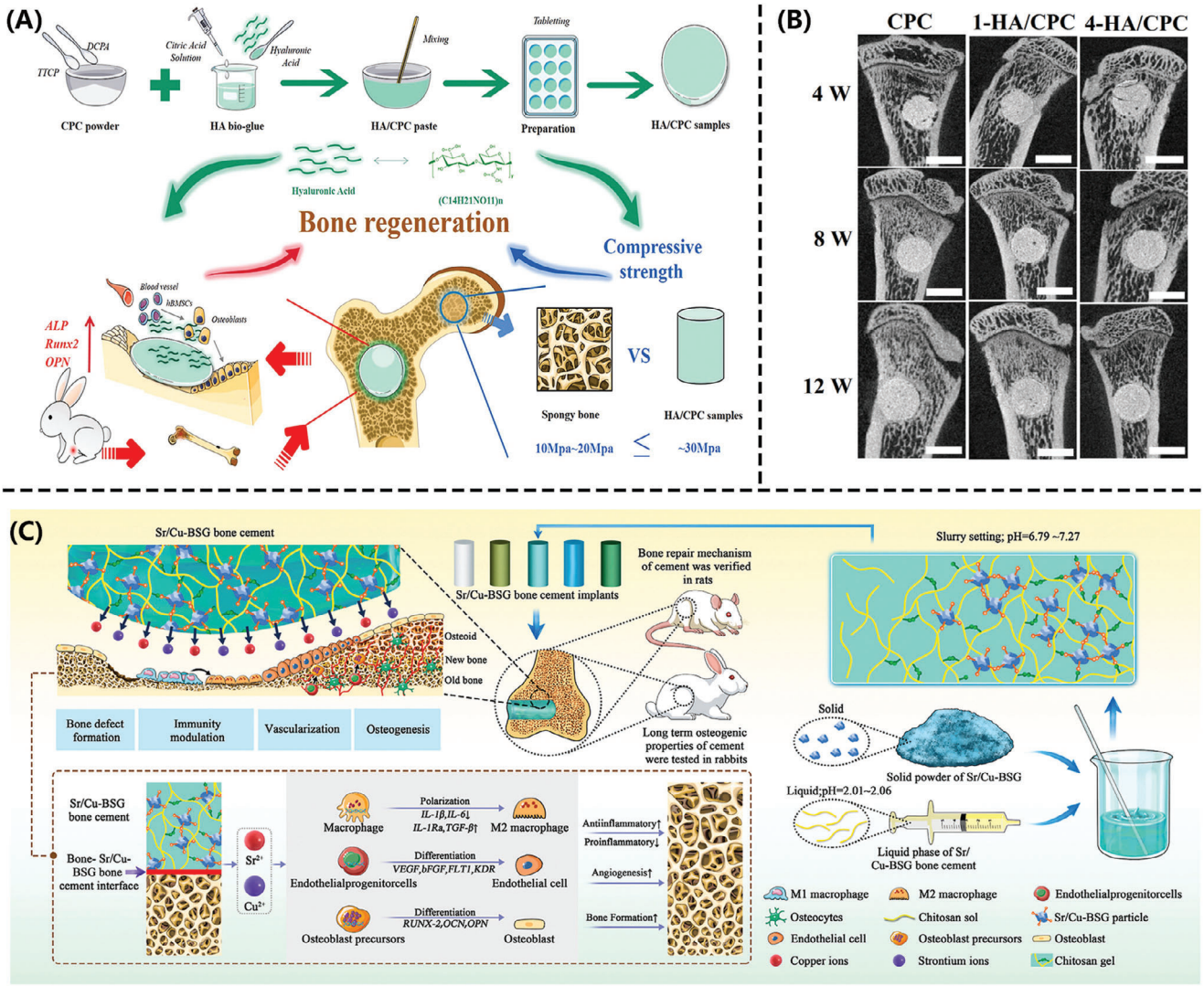


Figure 5. Bone cements for regulating bone aging/promoting bone repair. A) Schematic of hyaluronic acid's effect on calcium phosphate bone cement (CPC). Reproduced with permission.[169] Copyright 2021 The Authors. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd. B) Sagittal images by micro-CT imaging of the area surrounding cement implants. Reproduced with permission.[169] Copyright 2021 The Authors. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd. C) Schematic of bone defect repair with Sr/Cu-BSG bone cement. Reproduced with permission.[173] Copyright 2022 The Authors. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd.

5.2. Bone Cements

Injectable bone cements are renowned for their excellent moldability and are widely used in minimally invasive surgeries to fill and repair orthopedic traumas, especially those with irregular shapes.[163] Clinically, the most commonly used injectable bone cements include traditionally bioinert polymethyl methacrylate (PMMA) cement and currently utilized biologically active calcium phosphate cement (CPC).[164] Among these, CPC is highly biocompatible, resorbable, and osteoconductive, extensively used as a bone graft substitute and drug delivery system.[165] Based on the final hydration products at 37 °C, CPC can be classified into apatite or brushite ($CaHPO_4 \cdot 2H_2O$) cements. Specifically, apatite forms when the pH of the cement paste is above 4.2; below 4.2, brushite is preferentially formed.[166] Compared to apatite, brushite cements are more resorbable under physiological conditions, allowing for quicker replacement by new bone tissue.[167] Despite these benefits, the brittleness and weak osteogenic performance of CPC, along with its insufficient bonding strength and poor mechanical properties, limit its broader application.[168] To address these limitations, Cui et al. found that adding hyaluronic acid as an additive could improve the physicochemical properties and osteoinductivity of CPC, making it suitable for immunomodulatory treatment of bone defects[169] (**Figure** 5A,B). Similarly, the effects of tricalcium silicate cement (TSC) on osteogenesis have also been extensively studied. For instance, in pursuit of its immunomodulatory effects, Wan et al. discovered that TSC induces polarization of murine bone marrow-derived macrophages (mBMDM) to the M2 type, enhancing the osteogenic potential of co-cultured murine bone

marrow mesenchymal stromal cells (mBMMSC), thus promoting new bone formation and immunomodulation in an in vivo bone defect model.[170]

However, commonly used bone cements typically fail to form interconnected porous structures in situ, which are crucial for cell adhesion, ingrowth, and subsequent osteogenic differentiation and vascular remodeling.[171] To overcome this challenge, Tan et al. developed a magnesium microsphere-based injectable bone cement (MMSC) that can solidify to form a 3D porous scaffold and possesses excellent biodegradability to continuously support tissue growth. MMSC effectively upregulates anti-inflammatory genes and promotes polarization of M2 type macrophages by releasing magnesium ions, thus triggering positive immunomodulation and enhancing osteogenesis.[172] Moreover, considering the triple functions of strontium (Sr) and copper (Cu) in regulating inflammation, angiogenesis, and osteogenesis, Li et al. also developed a new type of bone cement composed of strontium and copper-doped borosilicate glass (Sr/Cu-BSG). This innovative cement regulates the expression of anti-inflammatory and pro-inflammatory genes in macrophages by controlling the release of Sr and Cu ions, achieving immunomodulatory effects while also enhancing the activity of angiogenic and osteogenic genes[173] (Figure 5C).

Currently, bone cements face issues like brittleness, inadequate porosity, and uncontrolled ion release, limiting their performance in load-bearing applications. Future research should focus on improving mechanical strength, enhancing porosity for better cell infiltration, and fine-tuning ion release for improved bone integration.

5.3. Advanced Bioactive Scaffolds

In bone tissue engineering, various biomaterials such as silk fibroin, cellulose nanocrystals, peptides, enzymes, polydopamine, and cell membrane derivatives are widely used to manufacture scaffolds with immunomodulatory functions. These scaffolds are designed for the localized delivery of bioactive cations, growth factors, small molecules, platelet-rich plasma, cytokines, drugs, and DNA/RNA as immunomodulatory factors.[174] Among these, metal scaffolds, especially titanium alloy scaffolds, are widely adopted due to their excellent mechanical properties, good biocompatibility, and chemical stability. For instance, Li et al. embedded an alginate hydrogel containing icariin and mineralized collagen into a 3D-printed porous titanium alloy scaffold, forming an AMCI/PTi composite scaffold.[175] Similarly, Wang et al. developed a hierarchically biofunctionalized 3D-printed porous Ti6Al4 V scaffold, which constructs a biomimetic ECM within microscale interconnected pores. In addition, at the nanoscale, the drugs icariin and Mg^{2+} were incorporated into Mg-MOF-74 (ICA@MOF) and encapsulated within an ECM-like structure, achieving controlled release of these components.[176]

Beyond titanium-based scaffolds, magnesium-based implants have also gained significant attention due to their biodegradability and immunomodulatory properties. Studies have shown that biodegradable magnesium intramedullary nails (Mg-IMN) promote endogenous CGRP and H-type vessel expression by releasing magnesium ions, thereby accelerating fracture healing in osteoporotic bone. This highlights the immunomodulatory function of biodegradable metals like magnesium, playing a crucial role in coupling angiogenesis and osteogenesis.[177] Another study demonstrated that degradable magnesium implants can mitigate the progression of medication-related osteonecrosis of the jaw (MRONJ)-like lesions by upregulating VEGF and CGRP-mediated angiogenesis, further confirming the immunoregulatory potential of magnesium-based implants.[178]

Building on these findings, researchers have explored other metal-based scaffolds with immunomodulatory potential. In another approach, Miao et al. fabricated a porous 3D-printed SrTCP scaffold by doping Sr ions into TCP, utilizing the positive effects of strontium ions on angiogenesis and bone regeneration, particularly by modulating the polarization state of macrophages to enhance the secretion of angiogenic factors such as VEGF and PDGF-bb.[179] Moreover, Zhou et al. manufactured a 3D-printed silk-based scaffold with sustained release of copper peptide (a copper ion-specific binding tripeptide), showing similar therapeutic effects to free copper ions but with lower toxicity[180] (**Figure 6A**).

Beyond metal scaffolds and their associated metal ions, natural proteins and compounds, such as flavonoids, are also extensively used in the manufacture of scaffolds. These biomaterials, due to their excellent biocompatibility and ability to promote tissue regeneration, have become an important component in tissue engineering. For example, fibrinogen (Fg) is typically considered a pro-inflammatory protein that can promote bone repair, and Vasconcelos et al. found that a porous scaffold made of fibrinogen (Fg-3D) implanted in rat femoral defects effectively promoted bone and periosteum repair while inducing local and systemic immunomodulatory responses.[181] Similarly, modification of collagen scaffolds is also a strategy, and Song et al. developed a DNA-crosslinked collagen scaffold (DNA-Col), enhancing its effectiveness in bone defect repair by enhancing interactions with regulatory T cells (Tregs).[182] In addition, Hu et al. developed a 3D porous biodegradable scaffold based on Poly(HEMA-co-3APBA)/LUT, which prolongs the release period of luteolin through reversible boronate ester bonds while maintaining its bioactivity.[174]

Apart from the natural and synthetic biomaterials mentioned, PLGA is widely used in 3D-printed bone scaffolds due to its good biocompatibility and tunable biodegradability, but its low osteoinductivity, limited mechanical properties, and potential inflammatory responses due to acidic degradation remain major limitations.[183] To address these issues, Long et al. developed a composite 3D-printed scaffold composed of PLGA and black phosphorus (BP)[184] (Figure 6B). Furthering this approach, Yuan et al. developed a hierarchically biofunctionalized 3D-printed scaffold constructed from PLGA mixed with decellularized bone matrix microparticles (DBM-MPs) and multifunctional magnesium hydroxide nanoparticles (MH-NP), simulating the bone microenvironment of the natural bone healing process[185] (Figure 6C).

While advanced bioactive scaffolds show promise for bone regeneration and immune modulation, challenges remain in controlling biodegradation, understanding immune microenvironment regulation, and balancing mechanical strength with bioactivity. Further optimization of material design and functional integration is crucial for clinical application.

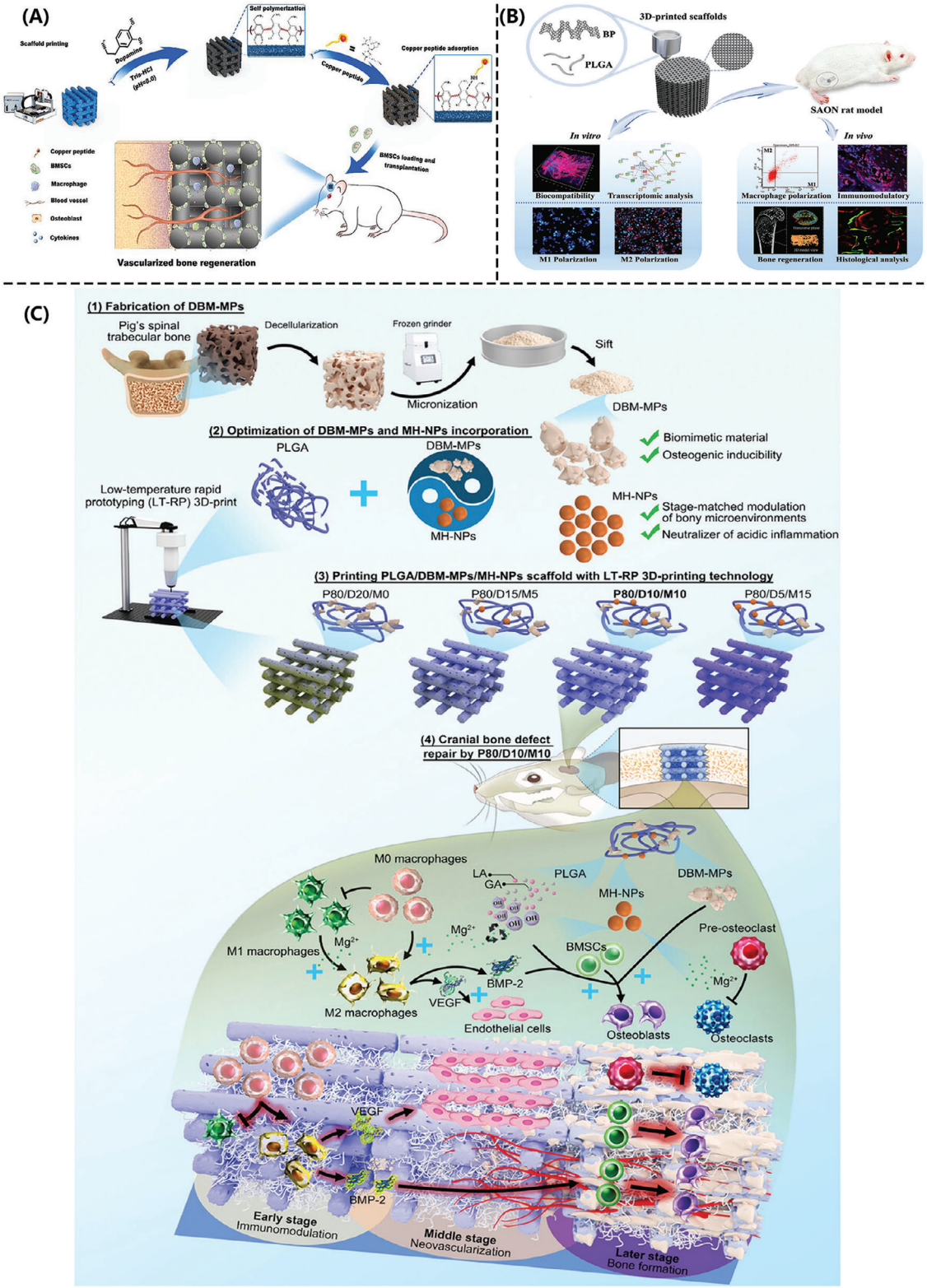


Figure 6. Advanced bioactive scaffolds for regulating bone aging/promoting bone repair. A) Schematic of GHK-Cu-incorporated 3D scaffold fabrication for vascularized bone regeneration. Reproduced with permission.[180] Copyright 2021 Elsevier B.V. All rights reserved. B) Schematic of 3D-printed PLGA/BP scaffolds. Reproduced with permission.[184] Copyright 2023 The Authors. Advanced Science published by Wiley-VCH. C) Schematic of a novel 3D-printed PLGA/DBM-MPs/MH-NPs scaffold (P80/D10/M10) for enhanced endogenous bone regeneration. Reproduced with permission.[185] Copyright 2023 The Authors. Advanced Science published by Wiley-VCH.

6. Coating Materials

To enhance the performance of implants and address their bioinert issues, researchers utilize coating technologies to modify the surface topography of implants, increase biocompatibility, and impart new functions such as promoting bone regeneration, regulating inflammatory responses, and improving angiogenesis. These surface modifications not only enable better integration with surrounding bone tissue but also activate specific biological signaling pathways, creating an immune microenvironment conducive to bone formation and repair. In this context, both organic and inorganic coatings have been extensively developed and explored, each offering unique advantages in enhancing the biological activity of implants. Composite materials are categorized into either the organic or inorganic group based on their primary components. This section delves into the application of these organic and inorganic coatings on implants, highlighting their roles in utilizing immunotherapy to regulate bone aging and promote bone repair.

6.1. Inorganic Coatings

Among inorganic coating materials, hydroxyapatite is one of the most commonly used. For instance, Jiang explored the effects of a biomimetic hydroxyapatite coating on macrophages, finding that the coating could suppress the expression of the inflammatory cytokine TNF-α and promote the expression of BMP-2 and VEGF, thus aiding in angiogenesis and osteogenic differentiation.[186] Currently, metal implants are the most widely used biomaterials in orthopedic surgeries, but their bioinertia does not induce new bone growth. For example, in the application of titanium based implants, due to their inherent lack of bioactivity, these implants often struggle to achieve stable bone-implant integration.[187] To overcome this limitation, various surface modification methods have been developed to enhance their performance. For example, Bai et al. developed a microporous TiO_2 coating prepared through micro-arc oxidation and subsequent annealing processes, decorated with hydroxyapatite HA nanoparticles. By adjusting the annealing temperature, they modified the physical (such as morphology and wettability) and chemical (such as composition and crystallinity of the composites) characteristics of the coating, where the MAO coating treated at 650 °C (MAO-650) showed excellent biocompatibility, including promoting the proliferation and differentiation of osteoblasts and endothelial cells while inhibiting macrophage inflammatory responses.[188] In addition to hydroxyapatite coatings, other functional coatings have also been developed to further improve implant performance. Jiang et al. developed a functional coating on the titanium substrate by depositing lysozyme phase change material doped with different concentrations of magnesium chloride ($MgCl_2$). The coating prepared with a 5×10^{-3} M solution of magnesium chloride (PTL-Mg5) showed the best effects on modulating macrophage polarization and inflammatory cytokine release, creating a favorable immune microenvironment for bone formation[189] (**Figure 7A**). Moreover, graphene oxide (GO) is also used for surface modification of titanium materials; Su et al. applied GO on titanium surfaces using dopamine to form a Ti-GO coating. This coating displayed good biocompatibility and promoted the expression of osteogenic genes and extracellular matrix mineralization in human mesenchymal stromal cells (hMSC). Moreover, the Ti-GO coating regulated macrophage polarization and cytokine expression by activating the Toll-like receptor pathway, manipulating immune responses under physiological and simulated acute inflammatory conditions, and fostering a bone-forming environment.[190] Furthermore, Li et al. developed a three-layer structured coating with self-healing and bone immunomodulatory functions, applied to magnesium-based bone implants. This coating includes an inner layer of MgO, a middle layer containing curcumin-encapsulated mesoporous silica nanocarriers (cFMSNs), and an outer layer of anhydrous dicalcium phosphate. The sustained release of curcumin effectively regulates the immune microenvironment, particularly with a higher proportion of cFMSNs in the coating[191] (Figure 7D).

6.2. Organic Coatings

In the realm of organic coatings, various innovative strategies have been used to enhance the biocompatibility and functionality of implant surfaces. Among these, biomimetic coatings have also shown promise in improving implant integration. For instance, Bai et al. developed a biomimetic implant coating that forms an MNS titanium dioxide fibrous network on the titanium surface, mimicking the natural ECM and bone healing hematoma of the host. The MNS enhanced immunomodulatory effects on BMSC, improving the bone immune microenvironment by regulating multiple inflammation-related signaling pathways and showing better bone integration than standard nanostructured (NS) and original titanium implants.[192] Building on the theme of enhancing immunomodulatory effects, liposomes, as a cost-effective immunomodulator, are used to activate immune cells to address the bioinertia of metal implants. Zhang et al. developed a novel multifunctional liposome-methacryloyl gelatin (GelMA) coating, directly applied to bone implants using electrospinning technology to modulate the immune response and promote bone regeneration. This coating structure is stable, maintaining its integrity for at least four weeks under various storage conditions, and effectively releases liposomes, regulating inflammation and enhancing the osteogenic activity of human mesenchymal stromal cells.[193] Similarly addressing the challenges associated with implant materials, due to their high degradation rate, the clinical applications of magnesium and its alloys are limited.[194]

Polyether ether ketone (PEEK) is also a commonly used implant material in orthopedics, but its surface may trigger adverse inflammatory reactions, affecting bone integration. To improve the success rate of PEEK implants, To tackle this issue, biofunctionalizing its surface to achieve immunomodulation is a key strategy for improving bone integration. Su et al. coated the surface of sulfonated PEEK with lithium-doped bioactive glass nanospheres (Li/BGs) to improve the bone integration of PEEK implants and increase their success rate.[195] Wu et al. further advanced this approach by using polydopamine (PDA) to fix Cu-Sr double-layered bioactive glass nanoparticles (CS-BGNs) on the PEEK surface, implementing a novel spatiotemporal immunomodulation strategy. The CS-BGNs exhibit a double-layered core-shell structure, enabling controlled and sequential release of copper (Cu^{2+}) and strontium (Sr^{2+}) ions, where Cu^{2+}'s rapid release promotes early antibacterial and tissue

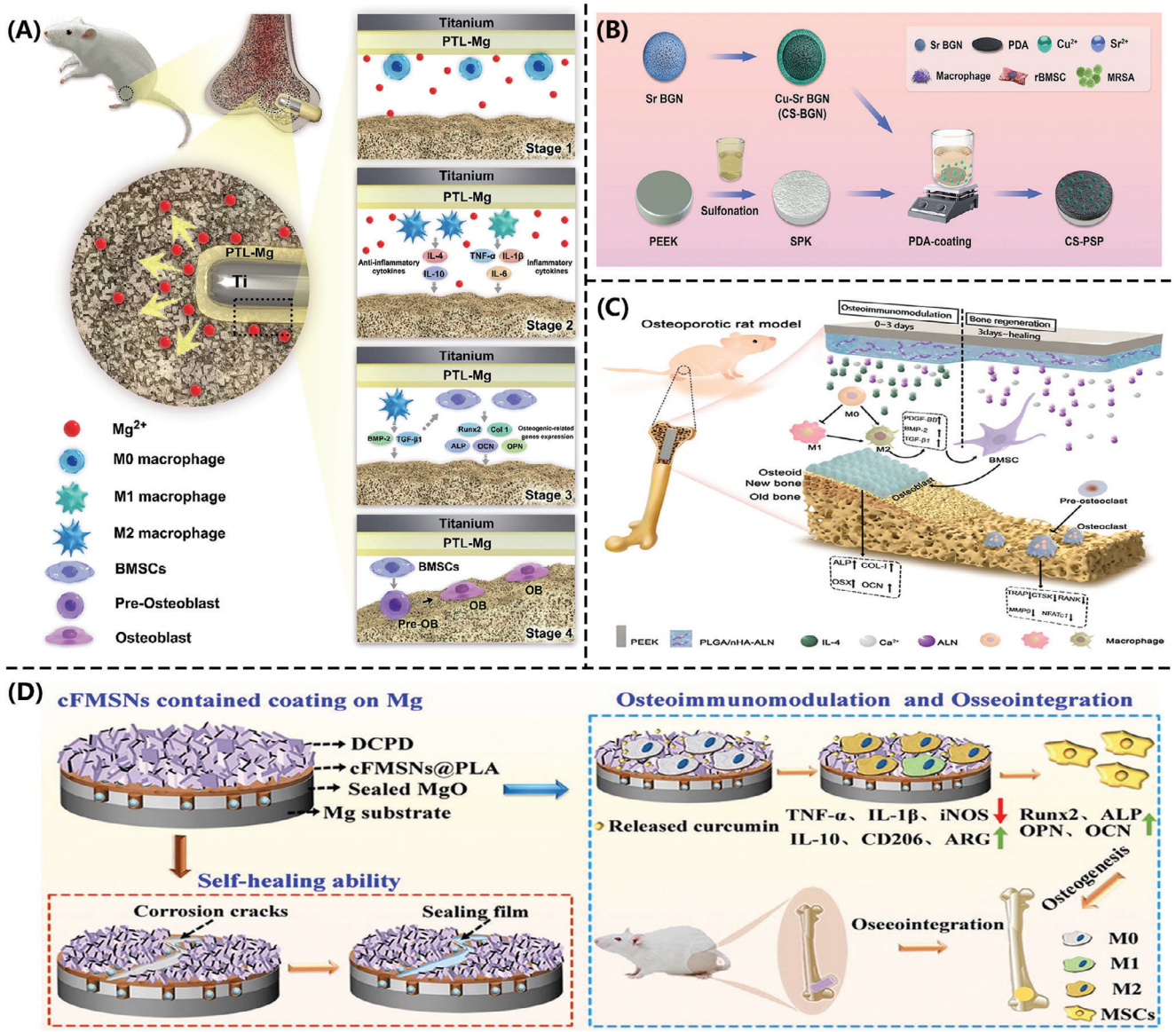


Figure 7. Coating materials for regulating bone aging/promoting bone repair. A) Schematic of immunomodulatory osteointegration with PTL-Mg coated Ti. Reproduced with permission.[189] Copyright 2022 The Authors. Published by Elsevier. B) Scheme of CS-BGNs-PDA-coated sulfonated PEEK (CS-PSP) preparation. Reproduced with permission.[196] Copyright 2023 Wiley-VCH. C) Schematic of the programmed surface on PEEK. Reproduced with permission.[197] Copyright 2022 The Authors. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd. D) Schematic of the fabrication process for the cFMSNs-coated Mg. Reproduced with permission.[191] Copyright 2020 Elsevier B. v All rights reserved.

healing activities, while Sr^{2+}'s delayed release aids in long-term bone integration[196] (Figure 7B). Adding to these advancements, Zheng et al. designed a programmable surface on the PEEK substrate by combining poly(caprolactone-*co*-lactide) with alendronate and nano-hydroxyapatite, followed by N_2 plasma treatment and loading with IL-4, creating a sequence-controlled functionality that promotes bone immunomodulation and regeneration, co-releasing IL-4, alendronate, and calcium ions to achieve immunomodulatory effects[197] (Figure 7C).

Moving beyond metal implants, coating materials are also commonly used for surface modification of implant scaffolds. Hoemann et al. explored the effects of chitosan coatings on the bone integration and angiogenesis of poly(ϵ-caprolactone) bioplastic scaffolds, finding that a non-inflammatory chitosan coating (99% deacetylation chitosan) promoted cartilage infiltration and bone integration, while doping with pro-inflammatory chitosan microparticles (83% DDA) induced mild bone resorption and accelerated angiogenesis.[198] In another innovative approach, Inspired by diatoms and mussels, Xiao et al. constructed multifunctional coatings on various substrates using epigallocatechin gallate (EGCG) and PEI through a silane coupling bridge. This coating, through the synergistic effects of EGCG and PEI, promoted silica precipitation, enhancing antioxidant and immunomodulatory capabilities, while also promoting angiogenesis and osteogenesis[199] (**Table 5**).

Table 5. Coating materials used for mediating immunotherapy to promote bone repair/regulate bone aging.

Coating materials	Preparation method	Loaded bioactive agents	Drug release	Targeting strategies	Refs.
TiO_2-HA	Micro-arc oxidation (MAO) followed by annealing at different temperatures (250, 450, and 650 °C)	HA nanoparticles which include calcium and phosphorus	Controlled by the release of Ca and P ions from the coating	Enhanced osseointegration due to superhydrophilicity and increased surface roughness which promote osteogenesis and angiogenesis	[188]
PTL-Mg	PTL deposition, $MgCl_2$ immersion (2.5×10^{-3}, 5×10^{-3}, and 10×10^{-3} M)	Mg^{2+}	Controlled release of Mg^{2+} ions, initial burst release in first 3 d, sustained release over 21 d	Achieved through creating an osteoimmunomodulatory environment, promoting macrophage polarization to M2 phenotype, enhancing osteogenesis	[189]
GO	Alkaline treatment with 5 M NaOH, dopamine coating, immersion in 0.25 mg mL^{-1} GO solution	Not specified	None specified	Achieved by manipulating macrophage polarization and inflammatory response to enhance osteogenesis	[190]
PLA, DCPD, MgO, cFMSNs	Synthesis of FMSNs (CTAB, TEOS, EA, NaOH, HCl, APTES, NaF, curcumin), MAO (Na_3PO_4, $Ca(OH)_2$, NaOH), spin-coating PLA and cFMSNs, DCPD deposition	Curcumin	Controlled release of curcumin	Enhanced osseointegration through osteoimmunomodulation	[191]
MNS	Alkali treatment (5 M NaOH, 48 h)	Not specified	Not applicable	Promotes osteogenesis and angiogenesis, modulates macrophage polarization (M1 to M2)	[192]
DFO/MnCO@GelMA-PLA/HA	FDM 3D printing of PLA scaffold, alkali treatment, HA coating, GelMA hydrogel infusion with DFO@PCL nanoparticles and MnCO nanosheets, UV crosslinking	DFO, MnCO	Sustained release of DFO and Mn^{2+}, initial burst release followed by a prolonged release over several weeks	Enhances osteoimmunomodulation, promotes M2 macrophage polarization, angiogenesis, and osteogenesis	[193]
PLA, DCPD, MgO, cFMSNs	Synthesis of FMSNs (CTAB, TEOS, EA, NaOH, HCl, APTES, NaF, curcumin), MAO (Na_3PO_4, $Ca(OH)_2$, NaOH), spin-coating PLA and cFMSNs, DCPD deposition	Curcumin	Controlled release of curcumin	Enhanced osteoimmunomodulation and osseointegration	[195]
Cu-Sr BGNs/PDA functionalized PEEK	Synthesis of Cu-Sr BGNs, sulfonation of PEEK, polydopamine (PDA) coating, chelation of Cu-Sr BGNs onto PDA-coated PEEK	Cu^{2+}, $Sr^{2}+$	Rapid release of Cu^{2+} in early stage, sustained release of Sr^{2+}	Modulates macrophage polarization, enhances osseointegration, prevents infection	[196]
PLGA/nHA-ALN with IL-4 grafting	Solvent evaporation of PLGA/nHA-ALN on PEEK, N_2 plasma immersion ion implantation (PIII), IL-4 solution immersion	ALN, IL-4	Initial burst release of IL-4 in first 3 d, sustained release of ALN and Ca^{+} over several weeks	Modulates macrophage polarization (M1 to M2), enhances osteogenesis, suppresses osteoclastogenesis	[197]
99% DDA chitosan, 83% DDA chitosan	Layer-by-layer (LbL) deposition on PCL scaffolds, followed by chitosan coating with different degrees of deacetylation	Not specified	Not applicable	Enhances angiogenesis and osteogenesis, modulates inflammation to promote cartilage and bone formation	[198]
EGCG/PEI-silica	Layer-by-layer assembly of EGCG/PEI and silicic acid on PCL scaffolds	Not specified	Sustained release of Si ions over 28 d	Enhances osteogenesis and angiogenesis by modulating immune microenvironment, promoting macrophage polarization to M2 phenotype	[199]

Surface coatings enhance implant integration and immunomodulation, but challenges persist in maintaining long-term stability, controlled bioactive release, and patient-specific adaptability. Their durability under physiological stress requires further study, as degradation may reduce effectiveness. Optimizing immune modulation while preventing off-target effects remains a critical goal for future research.

7. Summary

In this review, we systematically evaluate materials mediating immunotherapies to promote bone repair and regulate bone aging. Studies have shown that meticulously designed materials to modulate the bone immune microenvironment can significantly enhance bone repair efficiency and regulate bone aging. Particularly, strategies mediated by these materials have demonstrated potential in animal models to promote bone regeneration by regulating macrophage polarization from M1 to M2, activating specific T cell responses, and optimizing the local release of cytokines. Moreover, advanced manufacturing technologies such as 3D printing, electrospinning, microfluidics, and AI further enhance the functionality of these materials, allowing them to more precisely mimic the natural bone microenvironment and improve therapeutic outcomes.

However, several shortcomings exist in the current research on material-mediated immunotherapy. First, the mechanisms underlying bone aging are not fully understood. In addition, while current research has made progress in modulating the polarization of macrophages from M1 to M2, little is known about the roles and regulatory mechanisms of other key immune cells, such as T cells and B cells, in bone regeneration. Furthermore, current immunomodulatory strategies largely depend on pharmacological interventions and do not fully utilize the inherent bioactivity of the biomaterials for immunoregulation. This over-reliance on pharmaceuticals may limit the long-term efficacy and biosafety of treatments, as it could lead to unnecessary side effects and drug tolerance issues. Future research needs to develop and utilize novel biomaterials with natural bioregulatory functions to improve the durability and safety of treatments.

As our understanding of the immune system's role in bone regeneration deepens, emerging technologies are providing novel insights into the complex interactions between immune cells and biomaterials. With the rapid development of biological technologies such as single-cell sequencing and spatial transcriptomics, an increasing number of immune cell subtypes and surface receptors involved in bone repair are being identified. These finer biological insights provide new opportunities for biomaterials to be more precisely engineered to modulate immune responses.[200] For instance, biomaterials can be designed to selectively target specific immune cell populations or exploit receptor–ligand interactions to enhance therapeutic efficacy.[201] In addition, high-throughput sequencing data can be integrated with machine learning models to predict patient-specific immune responses, allowing for the development of personalized biomaterial-based therapies.[202] By leveraging these advanced techniques, next-generation biomaterials can be more intelligently designed to achieve precise immune modulation, ultimately improving bone regeneration outcomes and expanding their clinical applications.

AI offers promising solutions to these challenges. AI, the ability of computers or robots to perform tasks typically accomplished by humans, has shown enormous potential in disease research and diagnosis over the past decade, particularly in enhancing image analysis capabilities, reducing human workload, and improving diagnostic objectivity and consistency.[203] For example, various methods have been developed for the prevention and risk assessment of osteoporosis, such as reliably predicting fracture risk using bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA).[204] Machine learning algorithms automate training to assess the osseointegration of materials with surrounding bone tissue and have achieved over 82% accuracy in diagnosing osteoporosis, making them highly suitable for population screening.[205] In addition, combining other clinical risk factors with fracture risk assessment tools (FRAX), the Garvan Fracture Risk Calculator, and the QFracture scoring system can further improve prognostic accuracy.[206] Beyond diagnosing diseases, AI is also used for the precision manufacturing and implantation of biomaterials. Utilizing CAD and computer-aided manufacturing (CAM) systems provides advanced visualization tools and 3D modeling capabilities, such as virtual reality. These technologies enable surgeons to perform precise preoperative planning, including virtual surgical simulations and implant designs for specific patients. The completed virtual model can also be imported into intraoperative navigation systems to ensure the accurate placement of implants, thereby increasing the success and safety of surgeries.[207] Overall, integrating clinical and basic medical data with artificial intelligence technology represents the future direction in the diagnostics and treatment of bone aging and bone repair.

Future research should focus on developing novel multifunctional biomaterials that not only simulate the bone microenvironment but also actively regulate the behavior of various immune cells such as T cells and B cells. To gain deeper insight into the role of the immune system in bone repair, we can utilize microfluidic technology to precisely construct organ chips that simulate the complex microenvironment of bone tissue and monitor interactions between immune cells and bone cells in real-time. In addition, by integrating machine learning or deep learning algorithms with AI, we can analyze and predict the effects of different biomaterials and design parameters on immune cell behavior, thereby optimizing material design and treatment strategies. Furthermore, by combining advanced biosensor technology, we can develop smart scaffolds that dynamically respond to local environmental changes during bone repair processes, such as pH changes and mechanical stress, providing dynamic, customized therapeutic strategies. Such smart scaffolds can adjust the treatment modality during the therapy process based on the specific needs of the bone defect site, for instance, by automatically regulating drug release in response to the severity of the inflammatory response, thereby more effectively promoting bone tissue regeneration and repair.

Researchers should also strive to enhance the immunomodulatory functions of materials through drug-free strategies, where materials influence immune cell behavior directly through their inherent physical and chemical properties without relying on pharmacological interventions. For example, researchers can improve material surfaces through nanotechnology, such as by adjusting surface nanostructures or chemical modifications to

enhance interactions between materials and cells, more effectively activating or inhibiting specific immune cell functions. This includes inducing macrophages to polarize toward tissue-repairing M2 types, or activating specific T cell responses against pathological states. Furthermore, by integrating advanced biosensors and responsive systems, these materials can evolve into intelligent therapeutic platforms capable of monitoring and responding to physiological changes during the bone repair process, such as pH variations or mechanical pressures, and thus release bioactive molecules on demand. This adaptive functionality not only accelerates the repair process of bone defects but also regulates immunotherapeutic responses to prevent and treat age-related osteoporosis, providing comprehensive protection for bone health. Such platforms will offer a novel, highly personalized treatment strategy for bone tissue engineering.

8. Conclusion

In conclusion, this review highlights the categorization of materials mediating immunotherapies for bone repair and aging regulation, focusing on the use of hydrogels, drug delivery systems, and tissue engineering scaffolds. While these materials show great promise in modulating the bone immune microenvironment and enhancing bone regeneration, challenges remain, including a limited understanding of bone aging mechanisms and the need for more advanced biomaterials that leverage inherent bioactivity rather than relying on pharmaceuticals.

Future studies should aim to uncover the molecular and cellular processes underlying bone aging, with a particular emphasis on how the aging immune system influences bone regeneration. Advanced techniques like single-cell RNA sequencing and spatial transcriptomics can provide detailed immune cell activity maps, enabling more targeted immunomodulatory strategies. In addition, developing bioactive biomaterials with inherent immune-regulating properties, rather than passive drug carriers, could significantly enhance therapeutic outcomes. Engineering scaffolds with tunable mechanical and biochemical properties that dynamically respond to the healing process may further improve bone regeneration. Integrating smart technologies, such as biosensors within biomaterials, could allow real-time monitoring of inflammation and bone remodeling for more precise treatments. Machine learning-driven predictive models can optimize biomaterial design and personalize therapies based on patient-specific immune responses. To facilitate clinical translation, efforts should focus on scalable manufacturing, ensuring reproducibility, and addressing regulatory challenges, as many promising biomaterial-based immunotherapies remain at the preclinical stage.

Advancing research in these areas will drive the development of next-generation biomaterials that not only enhance bone regeneration but also regulate the aging immune microenvironment, paving the way for more effective and personalized treatments.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

biomaterials, bone aging, bone defects, immunotherapy

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[1] T. Wang, S. Huang, C. He, *Cell Proliferation* **2022**, *55*, e13323.
[2] X. Xing, H. Huang, X. Gao, J. Yang, Q. Tang, X. Xu, Y. Wu, M. Li, C. Liang, L. Tan, L. Liao, W. Tian, *ACS Appl. Mater. Interfaces* **2022**, *14*, 3885.
[3] a) C. Liu, Z. Ren, Y. Xu, S. Pang, X. Zhao, Y. Zhao, *Scanning* **2018**, *2018*, 9216314; b) J. Zhang, Y. Jiang, Z. Shang, B. Zhao, M. Jiao, W. Liu, M. Cheng, B. Zhai, Y. Guo, B. Liu, *Bioact. Mater.* **2021**, *6*, 4027.
[4] a) J. Zhong, X. Hu, J. Dong, Y. Chen, B. Liu, M. Hao, H. Xie, C. Ke, Z. Peng, *Chem. Eng. J.* **2024**, *489*, 151265; b) K. Atieh, B. Miles, J. Mackey, A. Mehta, *Eur. Heart J.* **2024**, *45*, ehae666; c) 马. 婧. 张博涵, *解放军医学院学报* **2024**, *45*, 326.
[5] T. A. Einhorn, L. C. Gerstenfeld, *Nat. Rev. Rheumatol.* **2015**, *11*, 45.
[6] Z. Chen, A. Bachhuka, S. Han, F. Wei, S. Lu, R. M. Visalakshan, K. Vasilev, Y. Xiao, *ACS Nano* **2017**, *11*, 4494.
[7] a) R. J. O'Keefe, J. Mao, *Tissue Eng., Part B.* **2011**, *17*, 389; b) X. Han, J. Shen, S. Chen, Z. Cai, Y. Zhu, W. Yi, K. Li, W. Cai, B. Tao, W. Cui, *Biomaterials* **2023**, *295*, 122057.
[8] a) Z. Chen, A. Bachhuka, F. Wei, X. Wang, G. Liu, K. Vasilev, Y. Xiao, *Nanoscale* **2017**, *9*, 18129; b) N. Yang, Y. Liu, *Int. J. Med. Sci.* **2021**, *18*, 3697.
[9] J. R. Arron, Y. Choi, *Nature* **2000**, *408*, 535.
[10] H. Takayanagi, *Nat. Rev. Immunol.* **2007**, *7*, 292.
[11] K. Okamoto, T. Nakashima, M. Shinohara, T. Negishi-Koga, N. Komatsu, A. Terashima, S. Sawa, T. Nitta, H. Takayanagi, *Physiol. Rev.* **2017**, *97*, 1295.
[12] A. Przekora, *Int. J. Mol. Sci.* **2019**, *20*, 435.
[13] a) S. Franz, S. Rammelt, D. Scharnweber, J. C. Simon, *Biomaterials* **2011**, *32*, 6692; b) W.-J. Hu, J. W. Eaton, T. P. Ugarova, L. Tang, *Blood* **2001**, *98*, 1231.
[14] a) C. Dou, J. Li, J. He, F. Luo, T. Yu, Q. Dai, Y. Chen, J. Xu, X. Yang, S. Dong, *Bioact. Mater.* **2021**, *6*, 4697; b) L. Kuang, J. Huang, Y. Liu, X. Li, Y. Yuan, C. Liu, *Adv. Funct. Mater.* **2021**, *31*, 2105383.
[15] a) U. Herbig, M. Ferreira, L. Condel, D. Carey, J. M. Sedivy, *Science* **2006**, *311*, 1257; b) Y. Zhao, X. Peng, D. Wang, H. Zhang, Q. Xin, M. Wu, X. Xu, F. Sun, Z. Xing, L. Wang, *Adv. Sci.* **2022**, *9*, 2204535; c) A. M. McDermott, S. Herberg, D. E. Mason, J. M. Collins, H. B. Pearson, J. H. Dawahare, R. Tang, A. N. Patwa, M. W. Grinstaff, D. J. Kelly, *Sci. Transl. Med.* **2019**, *11*, eaav7756.
[16] a) M. P. Baar, R. M. Brandt, D. A. Putavet, J. D. Klein, K. W. Derks, B. R. Bourgeois, S. Stryeck, Y. Rijksen, H. van Willigenburg, D. A. Feijtel, *Cell* **2017**, *169*, 132; b) A. K. Palmer, M. Xu, Y. Zhu, T. Pirtskhalava, M. M. Weivoda, C. M. Hachfeld, L. G. Prata, T. H. van Dijk, E. Verkade, G. Casaclang-Verzosa, *Aging Cell* **2019**, *18*, e12950.
[17] N. Basisty, A. Kale, O. H. Jeon, C. Kuehnemann, T. Payne, C. Rao, A. Holtz, S. Shah, V. Sharma, L. Ferrucci, *PLoS Biol.* **2020**, *18*, e3000599.

[18] a) B. Lozano-Torres, A. Estepa-Fernández, M. Rovira, M. Orzaez, M. Serrano, R. Martinez-Manez, F. Sancenon, *Nat. Rev. Chem.* **2019**, *3*, 426; b) A. Hernandez-Segura, J. Nehme, M. Demaria, *Trends Cell Biol.* **2018**, *28*, 436.
[19] D. J. Baker, T. Wijshake, T. Tchkonia, N. K. LeBrasseur, B. G. Childs, B. Van De Sluis, J. L. Kirkland, J. M. Van Deursen, *Nature* **2011**, *479*, 232.
[20] C. Lei, J. H. Song, S. Li, Y. N. Zhu, M. Y. Liu, M. C. Wan, Z. Mu, F. R. Tay, L. N. Niu, *Biomaterials* **2023**, *296*, 122066.
[21] W. Zhang, K. Dang, Y. Huai, A. Qian, *Front. Endocrinol.* **2020**, *11*, 523780.
[22] a) A. Kaczmarek, P. Vandenabeele, D. V. Krysko, *Immunity* **2013**, *38*, 209; b) S. Akira, H. Hemmi, *Immunol. Lett.* **2003**, *85*, 85.
[23] R. Medzhitov, C. A. Janeway Jr., *Curr. Opin. Immunol.* **1997**, *9*, 4.
[24] G. L. Burn, A. Foti, G. Marsman, D. F. Patel, A. Zychlinsky, *Immunity* **2021**, *54*, 1377.
[25] E. Kolaczkowska, P. Kubes, *Nat. Rev. Immunol.* **2013**, *13*, 159.
[26] A. Kovtun, S. Bergdolt, R. Wiegner, P. Radermacher, M. Huber-Lang, A. Ignatius, *Eur. Cells Mater.* **2016**, *32*, 152.
[27] I. Allaeys, D. Rusu, S. Picard, M. Pouliot, P. Borgeat, P. E. Poubelle, *Lab. Invest.* **2011**, *91*, 905.
[28] J. Liu, X. Zhang, Y. Cheng, X. Cao, *Cell Mol. Immunol.* **2021**, *18*, 2461.
[29] a) A. Alloatti, F. Kotsias, J. G. Magalhaes, S. Amigorena, *Immunol. Rev.* **2016**, *272*, 97; b) P. Guermonprez, J. Valladeau, L. Zitvogel, C. Théry, S. Amigorena, *Annu. Rev. Immunol.* **2002**, *20*, 621.
[30] T. Deller, *Zytologie, Histologie und mikroskopische Anatomie: das Lehrbuch*, 5th ed., Elsevier, München **2018**.
[31] a) M. E. Ogle, C. E. Segar, S. Sridhar, E. A. Botchwey, *Exp. Biol. Med.* **2016**, *241*, 1084; b) A. Das, M. Sinha, S. Datta, M. Abas, S. Chaffee, C. K. Sen, S. Roy, *Am. J. Pathol.* **2015**, *185*, 2596.
[32] a) N. Ruparelia, J. Godec, R. Lee, J. T. Chai, E. Dall'Armellina, D. McAndrew, J. E. Digby, J. C. Forfar, B. D. Prendergast, R. K. Kharbanda, *Eur. Heart J.* **2015**, *36*, 1923; b) S. L. Deshmane, S. Kremlev, S. Amini, B. E. Sawaya, *J. Interferon Cytokine Res.* **2009**, *29*, 313.
[33] a) H. Braley-Mullen, K. Chen, Y. Wei, S. Yu, *J. Immunol.* **2001**, *167*, 7111; b) R. de Waal Malefyt, J. Abrams, B. Bennett, C. G. Figdor, J. E. de Vries, *J. Exp. Med.* **1991**, *174*, 1209.
[34] a) P. J. Murray, T. A. Wynn, *Nat. Rev. Immunol.* **2011**, *11*, 723; b) W.-K. Wu, O. P. Llewellyn, D. O. Bates, L. B. Nicholson, A. D. Dick, *Immunobiology* **2010**, *215*, 796; c) T. Glaros, M. Larsen, L. Li, *Front. Biosci.* **2009**, *14*, 3988.
[35] P. Italiani, D. Boraschi, *Front. Immunol.* **2014**, *5*, 116283.
[36] R. J. Miron, M. Bohner, Y. Zhang, D. D. Bosshardt, *Periodontol. 2000* **2024**, *94*, 9.
[37] a) C. Shi, E. G. Pamer, *Nat. Rev. Immunol.* **2011**, *11*, 762; b) J.-L. Sun, K. Jiao, L.-N. Niu, Y. Jiao, Q. Song, L.-J. Shen, F. R. Tay, J.-H. Chen, *Biomaterials* **2017**, *113*, 203.
[38] J. Zhu, W. E. Paul, *Blood* **2008**, *112*, 1557.
[39] L.-W. Lai, K.-C. Yong, Y.-H. H. Lien, *Kidney Int.* **2012**, *81*, 983.
[40] Y. Liu, L. Wang, T. Kikuiri, K. Akiyama, C. Chen, X. Xu, R. Yang, W. Chen, S. Wang, S. Shi, *Nat. Med.* **2011**, *17*, 1594.
[41] a) I. E. Adamopoulos, C.-c. Chao, R. Geissler, D. Laface, W. Blumenschein, Y. Iwakura, T. McClanahan, E. P. Bowman, *Arthritis Res. Ther.* **2010**, *12*, 1; b) I. E. Adamopoulos, E. P. Bowman, *Arthritis Res. Ther.* **2008**, *10*, 1.
[42] G. Mori, P. D'Amelio, R. Faccio, G. Brunetti, *J. Immunol. Res.* **2013**, *2013*, 720504.
[43] T. J. Murphy, N. N. Choileain, Y. Zang, J. A. Mannick, J. A. Lederer, *J. Immunol.* **2005**, *174*, 2957.
[44] T. Nagasawa, *Nat. Rev. Immunol.* **2006**, *6*, 107.
[45] a) M. C. Horowitz, J. A. Fretz, J. A. Lorenzo, *Bone* **2010**, *47*, 472; b) M. Kanematsu, T. Sato, H. Takai, K. Watanabe, K. Ikeda, Y. Yamada, *J. Bone Miner. Res.* **2000**, *15*, 1321; c) W. Sun, N. Meednu, A. Rosenberg, J. Rangel-Moreno, V. Wang, J. Glanzman, T. Owen, X. Zhou, H. Zhang, B. F. Boyce, *Nat. Commun.* **2018**, *9*, 5127.
[46] F. Martinez, *F1000Prime Rep.* **2014**, *6*, 10.
[47] C. A. Ambarus, S. Krausz, M. van Eijk, J. Hamann, T. Radstake, K. A. Reedquist, P. P. Tak, D. Baeten, *J. Immunol. Methods* **2012**, *375*, 196.
[48] I. Könnecke, A. Serra, T. El Khassawna, C. Schlundt, H. Schell, A. Hauser, A. Ellinghaus, H.-D. Volk, A. Radbruch, G. N. Duda, *Bone* **2014**, *64*, 155.
[49] J. Kubackova, J. Zbytovska, O. Holas, *Eur. J. Pharm. Sci.* **2020**, *142*, 105139.
[50] a) B. Zhang, Y. Su, J. Zhou, Y. Zheng, D. Zhu, *Adv. Sci.* **2021**, *8*, e2100446; b) K. M. Hotchkiss, G. B. Reddy, S. L. Hyzy, Z. Schwartz, B. D. Boyan, R. Olivares-Navarrete, *Acta Biomater.* **2016**, *31*, 425; c) D. J. Misiek, J. N. Kent, R. F. Carr, *J. Oral Maxillofac. Surg.* **1984**, *42*, 150.
[51] C. Backlund, S. Jalili-Firoozinezhad, B. Kim, D. J. Irvine, *Annu. Rev. Immunol.* **2023**, *41*, 153.
[52] C. Dong, G. Tan, G. Zhang, W. Lin, G. Wang, *Front. Bioeng. Biotechnol.* **2023**, *11*, 1133995.
[53] a) N. Lindner, A. Blaeser, *Front. Bioeng. Biotechnol.* **2022**, *10*, 855042; b) S. Chameettachal, S. Yeleswarapu, S. Sasikumar, P. Shukla, P. Hibare, A. K. Bera, S. S. R. Bojedla, F. Pati, *J. Indian Inst. Sci.* **2019**, *99*, 375.
[54] a) F. Gilbert, C. D. O'Connell, T. Mladenovska, S. Dodds, *Sci. Eng. Ethics* **2018**, *24*, 73; b) L. Phoebe, A. Faulkner, *Eur. J. Risk Regul.* **2017**, *8*, 441.
[55] a) L. Dejob, B. Toury, S. Tadier, L. Gremillard, C. Gaillard, V. Salles, *Acta Biomater.* **2021**, *123*, 123; b) T. Jiang, E. J. Carbone, K. W.-H. Lo, C. T. Laurencin, *Prog. Polym. Sci.* **2015**, *46*, 1.
[56] R. A. Surmenev, S. Shkarina, D. S. Syromotina, E. V. Melnik, R. Shkarin, I. I. Selezneva, A. M. Ermakov, S. I. Ivlev, A. Cecilia, V. Weinhardt, *Eur. Polym. J.* **2019**, *113*, 67.
[57] L. Leppik, K. M. C. Oliveira, M. B. Bhavsar, J. H. Barker, *Eur. J. Trauma Emerg. Surg.* **2020**, *46*, 231.
[58] a) J. L. Hernandez, M.-A. Doan, R. Stoddard, H. M. VanBenschoten, S.-T. Chien, I. T. Suydam, K. A. Woodrow, *Front. Biomater. Sci.* **2022**, *1*, 928537; b) K. Dziemidowicz, Q. Sang, J. Wu, Z. Zhang, F. Zhou, J. M. Lagaron, X. Mo, G. J. Parker, D.-G. Yu, L.-M. Zhu, *J. Mater. Chem. B.* **2021**, *9*, 939.
[59] T. Li, Y. Liu, Q. Zhang, W. Sun, Y. Dong, *Exp. Ther. Med.* **2021**, *22*, 1070.
[60] a) Z. Zhao, Z. Wang, G. Li, Z. Cai, J. Wu, L. Wang, L. Deng, M. Cai, W. Cui, *Adv. Funct. Mater.* **2021**, *31*, 2103339; b) X. Han, M. Sun, B. Chen, Q. Saiding, J. Zhang, H. Song, L. Deng, P. Wang, W. Gong, W. Cui, *Bioact. Mater.* **2021**, *6*, 1639; c) J. Wu, G. Li, T. Ye, G. Lu, R. Li, L. Deng, L. Wang, M. Cai, W. Cui, *Chem. Eng. J.* **2020**, *393*, 124715.
[61] C. Du, J. Liu, S. Liu, P. Xiao, Z. Chen, H. Chen, W. Huang, Y. Lei, *Small Methods* **2024**, *8*, 2400436.
[62] D. Sheyn, D. Cohn-Yakubovich, S. Ben-David, S. De Mel, V. Chan, C. Hinojosa, N. Wen, G. A. Hamilton, D. Gazit, Z. Gazit, *Microfluid. Nanofluidics.* **2019**, *23*, 1.
[63] X. Liu, A. Sun, J. Brodský, I. Gablech, T. Lednický, P. Vopařilová, O. Zítka, W. Zeng, P. Neužil, *Sci. Rep.* **2024**, *14*, 28793.
[64] a) S. Yue, H. He, B. Li, T. Hou, *Nanomaterials* **2020**, *10*, 1511; b) P. Gupta, K. Vermani, S. Garg, *Drug Discovery Today* **2002**, *7*, 569; c) X. Bai, S. Lü, Z. Cao, C. Gao, H. Duan, X. Xu, L. Sun, N. Gao, C. Feng, M. Liu, *Chem. Eng. J.* **2016**, *288*, 546; d) Y. Zhang, T. Yu, L. Peng, Q. Sun, Y. Wei, B. Han, *Front. Pharmacol.* **2020**, *11*, 622.
[65] M. Zhang, W. Hu, C. Cai, Y. Wu, J. Li, S. Dong, *Mater. Today Bio* **2022**, *14*, 100223.
[66] a) K. Lavanya, S. V. Chandran, K. Balagangadharan, N. Selvamurugan, *Mater. Sci. Eng., C.* **2020**, *111*, 110862; b) H. Zhang, L. Wang, J. Cui, S. Wang, Y. Han, H. Shao, C. Wang, Y. Hu,

X. Li, Q. Zhou, *Sci. Adv.* **2023**, *9*, eabo7868; c) A. Bordbar-Khiabani, M. Gasik, *Int. J. Mol. Sci.* **2022**, *23*, 3665.
[67] a) I. Luchian, A. Goriuc, D. Sandu, M. Covasa, *Int. J. Mol. Sci.* **2022**, *23*, 1806; b) S. A. Schoonraad, M. L. Trombold, S. J. Bryant, *Biomacromolecules* **2021**, *22*, 1065; c) E. Hardy, C. Fernandez-Patron, *Front. Physiol.* **2020**, *11*, 500305.
[68] M. Zhang, T. Yu, J. Li, H. Yan, L. Lyu, Y. Yu, G. Yang, T. Zhang, Y. Zhou, X. Wang, D. Liu, *Adv. Sci.* **2024**.
[69] M. Ni, S. Zhuo, *RSC Adv.* **2019**, *9*, 844.
[70] F. Zhang, M. Lv, S. Wang, M. Li, Y. Wang, C. Hu, W. Hu, X. Wang, X. Wang, Z. Liu, Z. Fan, J. Du, Y. Sun, *Bioact. Mater.* **2024**, *31*, 231.
[71] a) J. L. Aparicio-Collado, N. García-San-Martín, J. Molina-Mateo, C. Torregrosa Cabanilles, V. Donderis Quiles, A. Serrano-Aroca, R. Sabater i Serra, *Colloids Surf., B* **2022**, *214*, 112455; b) X. Yin, L. Yan, D. J. Hao, S. Liu, M. Yang, B. He, Z. Liu, *Int. J. Pharm.* **2020**, *582*, 119303.
[72] a) Z. Li, F. Cai, J. Tang, Y. Xu, K. Guo, Z. Xu, Y. Feng, K. Xi, Y. Gu, L. Chen, *Bioact. Mater.* **2023**, *24*, 346; b) Q. Zhang, X. Wang, G. Kuang, Y. Yu, Y. Zhao, *Research* **2022**, *2022*, 9784510.
[73] P. Yang, Y. Ju, X. Liu, Z. Li, H. Liu, M. Yang, X. Chen, L. Lei, B. Fang, *Mater. Today Bio* **2023**, *23*, 100875.
[74] J. Wang, L. Zhang, L. Wang, J. Tang, W. Wang, Y. Xu, Z. Li, Z. Ding, X. Jiang, K. Xi, L. Chen, Y. Gu, *Adv. Healthcare Mater.* **2024**, *13*, 2303851.
[75] D. Li, Z. Yang, X. Zhao, Y. Luo, W. Zhou, J. Xu, Z. Hou, P. Kang, M. Tian, *Chem. Eng. J.* **2022**, *435*, 134991.
[76] Y. Luo, Z. Yang, X. Zhao, D. Li, Q. Li, Y. Wei, L. Wan, M. Tian, P. Kang, *Mater. Today Bio* **2024**, *25*, 100976.
[77] H. Liang, C. Jin, L. Ma, X. Feng, X. Deng, S. Wu, X. Liu, C. Yang, *ACS Appl. Mater. Interfaces* **2019**, *11*, 41758.
[78] P. L. Li, D. F. Chen, X. T. Li, R. C. Hao, Z. D. Zhao, Z. L. Li, B. F. Yin, J. Tang, Y. W. Luo, C. T. Wu, J. J. Nie, H. Zhu, *Bioact. Mater.* **2024**, *34*, 204.
[79] a) J. Li, C. Deng, W. Liang, F. Kang, Y. Bai, B. Ma, C. Wu, S. Dong, *Bioact. Mater.* **2021**, *6*, 3839; b) H. Aro, E. Eerola, A. Aho, J. Niinikoski, *J. Surg. Res.* **1984**, *37*, 202.
[80] Q. Chen, J. Li, F. Han, Q. Meng, H. Wang, Q. Wei, Z. Li, F. Li, E. Xie, X. Qin, S. Chen, W. Wang, C. Liu, B. Li, F. Han, *Adv. Funct. Mater.* **2022**, *32*, 2201067.
[81] X. Zhou, R. Lu, M. Jia, H. Lai, X. Xiao, Y. Yao, T. Yuan, P. Li, S. Zhang, *Chem. Mater.* **2024**, *36*, 3381.
[82] a) R. Williams, I. M. Khan, K. Richardson, L. Nelson, H. E. McCarthy, T. Analbelsi, S. K. Singhrao, G. P. Dowthwaite, R. E. Jones, D. M. Baird, H. Lewis, S. Roberts, H. M. Shaw, J. Dudhia, J. Fairclough, T. Briggs, C. W. Archer, *PLoS One* **2010**, *5*, e13246; b) D. J. Huey, J. C. Hu, K. A. Athanasiou, *Science* **2012**, *338*, 917.
[83] a) S. P. Nukavarapu, D. L. Dorcemus, *Biotechnol. Adv.* **2013**, *31*, 706; b) Y. J. Chuah, Y. Peck, J. E. J. Lau, H. T. Hee, D.-A. Wang, *Biomater. Sci.* **2017**, *5*, 613.
[84] K. Yue, G. Trujillo-de Santiago, M. M. Alvarez, A. Tamayol, N. Annabi, A. Khademhosseini, *Biomaterials* **2015**, *73*, 254.
[85] S. M. Muir, N. Reisbig, M. Baria, C. Kaeding, A. L. Bertone, *Am. J. Sports Med.* **2019**, *47*, 1955.
[86] G. Jiang, S. Li, K. Yu, B. He, J. Hong, T. Xu, J. Meng, C. Ye, Y. Chen, Z. Shi, G. Feng, W. Chen, S. Yan, Y. He, R. Yan, *Acta Biomater.* **2021**, *128*, 150.
[87] a) Y. Zhang, N. Ding, T. Zhang, Q. Sun, B. Han, T. Yu, *Front. Chem.* **2019**, *7*, 682; b) D. Li, J. Zhou, M. Zhang, Y. Ma, Y. Yang, X. Han, X. Wang, *Biomater. Sci.* **2020**, *8*, 3138.
[88] B. Sun, H. Wang, B. Xiao, H. Yan, H. Wu, R. Zhang, Y. Zhang, W. Yuan, X. Wang, C. Shi, *Chem. Eng. J.* **2023**, *476*, 146743.
[89] M. Fu, J. Li, M. Liu, C. Yang, Q. Wang, H. Wang, B. Chen, Q. Fu, G. Sun, *Int. J. Nanomed.* **2023**, *18*, 1875.
[90] a) E. Bressan, L. Ferroni, C. Gardin, L. Sbricoli, L. Gobbato, F. S. Ludovichetti, I. Tocco, A. Carraro, A. Piattelli, B. Zavan, *J. Transl. Med.* **2014**, *12*, 296; b) Y. S. Cho, M. Quan, N.-U. Kang, H.-J. Jeong, M. W. Hong, Y. Y. Kim, Y.-S. Cho, *Eur. Polym. J.* **2020**, *134*, 109814; c) M. Farokhi, F. Mottaghitalab, S. Samani, M. A. Shokrgozar, S. C. Kundu, R. L. Reis, Y. Fatahi, D. L. Kaplan, *Biotechnol. Adv.* **2018**, *36*, 68; d) D. Zhang, Q. Chen, Y. Bi, H. Zhang, M. Chen, J. Wan, C. Shi, W. Zhang, J. Zhang, Z. Qiao, *Nat. Commun.* **2021**, *12*, 5327.
[91] Z. Zhao, G. Li, H. Ruan, K. Chen, Z. Cai, G. Lu, R. Li, L. Deng, M. Cai, W. Cui, *ACS Nano* **2021**, *15*, 13041.
[92] Z. Zhao, R. Li, H. Ruan, Z. Cai, Y. Zhuang, Z. Han, M. Zhang, W. Cui, M. Cai, *Chem. Eng. J.* **2022**, *436*, 135176.
[93] W. Cai, X. Xu, Y. Jiang, K. Cheng, F. Liu, C. Song, D. Guo, Z. Hu, Z. Liu, Z. Liu, *Mater. Today Adv.* **2023**, *18*, 100381.
[94] D. N. Karunaratne, *J. Natl. Sci. Found. Sri Lanka* **2007**, *35*, 149.
[95] a) N. Mokarram, R. V. Bellamkonda, *Ann. Biomed. Eng.* **2014**, *42*, 338; b) D. F. Williams, *Biomaterials* **2009**, *30*, 5897.
[96] M. Shi, Z. Chen, S. Farnaghi, T. Friis, X. Mao, Y. Xiao, C. Wu, *Acta Biomater.* **2016**, *30*, 334.
[97] M. W. Tibbitt, J. E. Dahlman, R. Langer, *J. Am. Chem. Soc.* **2016**, *138*, 704.
[98] a) R. O. Rodrigues, P. C. Sousa, J. Gaspar, M. Bañobre-López, R. Lima, G. Minas, *Small* **2020**, *16*, 2003517; b) Y. Kohl, M. Biehl, S. Spring, M. Hesler, V. Ogourtsov, M. Todorovic, J. Owen, E. Elje, K. Kopecka, O. H. Moriones, *Small* **2021**, *17*, 2006012.
[99] a) T. Zhang, Z. Lu, L. Zhang, Y. Li, J. Yang, J. Shen, J. Wang, Y. Niu, Z. Xiao, L. Chen, *Chin. Chem. Lett.* **2020**, *31*, 3135; b) L. Guo, N. He, Y. Zhao, T. Liu, Y. Deng, *Theranostics* **2020**, *10*, 3206.
[100] S. Yamashita, H. Katsumi, N. Hibino, Y. Isobe, Y. Yagi, K. Kusamori, T. Sakane, A. Yamamoto, *J. Controlled Release* **2017**, *262*, 10.
[101] M. Ren, Y. Li, H. Zhang, L. Li, P. He, P. Ji, S. Yang, *J. Mater. Chem. B.* **2021**, *9*, 2831.
[102] S. Hosseinpour, H. Dai, L. J. Walsh, C. Xu, *Nanomaterials* **2023**, *13*, 1755.
[103] L. D. Field, J. B. Delehanty, Y. Chen, I. L. Medintz, *Acc. Chem. Res.* **2015**, *48*, 1380.
[104] Y. Sun, X. Ye, M. Cai, X. Liu, J. Xiao, C. Zhang, Y. Wang, L. Yang, J. Liu, S. Li, C. Kang, B. Zhang, Q. Zhang, Z. Wang, A. Hong, X. Wang, *ACS Nano* **2016**, *10*, 5759.
[105] W. Zhou, Z. Lin, Y. Xiong, H. Xue, W. Song, T. Yu, L. Chen, Y. Hu, A. C. Panayi, Y. Sun, F. Cao, G. Liu, L. Hu, C. Yan, X. Xie, W. Qiu, B. Mi, G. Liu, *ACS Appl. Mater. Interfaces* **2021**, *13*, 56944.
[106] H. Peng, X. Qiu, M. Cheng, Y. Zhao, L. Song, B. Zhu, Y. Li, C. Liu, S. Ren, L. Miao, *Chem. Eng. J.* **2023**, *476*, 146615.
[107] Y. Chandorkar, R. K, B. Basu, *ACS Biomater. Sci. Eng.* **2018**, *5*, 19.
[108] U. Bhardwaj, R. Sura, F. Papadimitrakopoulos, D. J. Burgess, *J. Diabetes Sci. Technol.* **2007**, *1*, 8.
[109] J. L. Dziki, S. F. Badylak, *Curr. Opin. Biomed. Eng.* **2018**, *6*, 51.
[110] a) J. Tan, Z. Deng, G. Liu, J. Hu, S. Liu, *Biomaterials* **2018**, *178*, 608; b) G. Pan, S. Liu, X. Zhao, J. Zhao, C. Fan, W. Cui, *Biomaterials* **2015**, *53*, 202.
[111] M. He, Q. Wang, Y. Feng, X. Gao, C. He, J. Li, W. Zhao, W. Tian, C. Zhao, *ACS Appl. Mater. Interfaces* **2022**, *14*, 13991.
[112] M. Li, S. Fu, Z. Cai, D. Li, L. Liu, D. Deng, R. Jin, H. Ai, *Regener. Biomater.* **2021**, *8*, rbab027.
[113] X. Yang, F. Zhou, P. Yuan, G. Dou, X. Liu, S. Liu, X. Wang, R. Jin, Y. Dong, J. Zhou, *Bioact. Mater.* **2021**, *6*, 3150.
[114] a) F. Viti, M. Landini, A. Mezzelani, L. Petecchia, L. Milanesi, S. Scaglione, *PLoS One* **2016**, *11*, e0148173; b) X. Li, Q. He, J. Shi, *ACS Nano* **2014**, *8*, 1309.
[115] a) N. Lewkowicz, P. Piątek, M. Namiecińska, M. Domowicz, R. Bonikowski, J. Szemraj, P. Przygodzka, M. Stasiołek, P. Lewkowicz, *Cells* **2019**, *8*, 786; b) Q. Li, J. Chen, X. Yu, J.-M. Gao, *Food Chem.* **2019**, *301*, 125286.
[116] Y. Kong, F. Liu, B. Ma, W. Wang, L. Li, X. Xu, Z. Sun, H. Yang, Y. Sang, D. Li, G. Li, C. Liu, S. Wang, H. Liu, *Nano Res.* **2021**, *15*, 1153.

[117] A. M. Barradas, H. A. Fernandes, N. Groen, Y. C. Chai, J. Schrooten, J. Van de Peppel, J. P. Van Leeuwen, C. A. Van Blitterswijk, J. De Boer, *Biomaterials* **2012**, *33*, 3205.
[118] Q. Ma, T. Sun, S. Li, J. Wen, L. Zhu, T. Yin, K. Yan, X. Xu, S. Li, J. Mao, *Plant J.* **2020**, *104*, 662.
[119] W. Ma, W. Wang, F. Liu, Y. Kong, B. Xia, H. Yang, H. Zhao, L. Wang, K. Li, Y. Li, Y. Sang, H. Liu, X. Wang, J. Qiu, *Composites, Part B* **2023**, *255*, 110612.
[120] a) C. E. Vantucci, L. Krishan, A. Cheng, A. Prather, K. Roy, R. E. Guldberg, *Biomater. Sci.* **2021**, *9*, 1668; b) M. A. Ansari, M. Thiruvengadam, B. Venkidasamy, M. N. Alomary, A. Salawi, I.-M. Chung, M. A. Shariati, M. Rebezov, presented at Seminars in Cancer Biology **2022**.
[121] a) G. Ye, F. Bao, X. Zhang, Z. Song, Y. Liao, Y. Fei, V. Bunpetch, B. C. Heng, W. Shen, H. Liu, *Nanomedicine* **2020**, *15*, 1995; b) S. Verma, A. J. Domb, N. Kumar, *Nanomedicine* **2011**, *6*, 157.
[122] B. Corradetti, D. Gonzalez, I. M. Pinto, R. S. Conlan, *Front. Media* **2021**, *9*, 714743.
[123] J. Dai, Y. Su, S. Zhong, L. Cong, B. Liu, J. Yang, Y. Tao, Z. He, C. Chen, Y. Jiang, *Signal Transduction Targeted Ther.* **2020**, *5*, 145.
[124] a) Y.-J. Liu, C. Wang, *Cell Commun. Signaling* **2023**, *21*, 77; b) I. V. Zhivodernikov, Y. V. Markina, T. V. Kirichenko, M. A. Popov, A. M. Markin, *Front. Immunol.* **2023**, *14*, 1309015.
[125] M. Á. Brennan, P. Layrolle, D. J. Mooney, *Adv. Funct. Mater.* **2020**, *30*, 1909125.
[126] a) J. Fan, C.-S. Lee, S. Kim, C. Chen, T. Aghaloo, M. Lee, *ACS Nano* **2020**, *14*, 11973; b) L. Li, Y. Zhang, J. Mu, J. Chen, C. Zhang, H. Cao, J. Gao, *Nano Lett.* **2020**, *20*, 4298.
[127] W. Liu, Y. Rong, J. Wang, Z. Zhou, X. Ge, C. Ji, D. Jiang, F. Gong, L. Li, J. Chen, *J. Neuroinflammation* **2020**, *17*, 1.
[128] Y. Zhang, M. Huo, Y. Wang, L. Xiao, J. Wu, Y. Ma, D. Zhang, X. Lang, X. Wang, *J. Biol. Eng.* **2022**, *16*, 22.
[129] L. Fan, P. Guan, C. Xiao, H. Wen, Q. Wang, C. Liu, Y. Luo, L. Ma, G. Tan, P. Yu, L. Zhou, C. Ning, *Bioact. Mater.* **2021**, *6*, 2754.
[130] H. Xu, Q. Chai, X. Xu, Z. Li, W. Bao, Z. Man, W. Li, *ACS Appl. Mater. Interfaces* **2022**, *14*, 46161.
[131] Z. Lin, Y. Xiong, W. Meng, Y. Hu, L. Chen, L. Chen, H. Xue, A. C. Panayi, W. Zhou, Y. Sun, F. Cao, G. Liu, L. Hu, C. Yan, X. Xie, C. Lin, K. Cai, Q. Feng, B. Mi, G. Liu, *Bioact. Mater.* **2022**, *13*, 300.
[132] L. Chen, Y. Xiong, Y. Hu, C. Yu, A. C. Panayi, W. Zhou, F. Cao, Y. Sun, M. Liu, G. Liu, H. Xue, L. Hu, B. Mi, G. Liu, *Chem. Eng. J.* **2022**, *427*, 131419.
[133] Z. Hao, L. Ren, Z. Zhang, Z. Yang, S. Wu, G. Liu, B. Cheng, J. Wu, J. Xia, *Bioact. Mater.* **2023**, *23*, 206.
[134] Y. Sun, B. Zhang, D. Zhai, C. Wu, *NPG Asia Mater.* **2021**, *13*, 72.
[135] F. Chen, X. Li, Y. Xiao, X. Zhu, X. Chen, X. Zhang, *Mater. Des.* **2024**, *241*, 112903.
[136] X. Yu, M. Dong, L. Wang, Q. Yang, L. Wang, W. Han, J. Dong, T. Liu, Y. Kong, W. Niu, *Drug Delivery* **2023**, *30*, 2169414.
[137] W. Zhan, M. Deng, X. Huang, D. Xie, X. Gao, J. Chen, Z. Shi, J. Lu, H. Lin, P. Li, *J. Controlled Release* **2023**, *364*, 644.
[138] a) L. Kock, C. C. van Donkelaar, K. Ito, *Cell Tissue Res.* **2012**, *347*, 613; b) E. A. Makris, A. H. Gomoll, K. N. Malizos, J. C. Hu, K. A. Athanasiou, *Nat. Rev. Rheumatol.* **2015**, *11*, 21.
[139] a) Y. Zhang, X. Dou, L. Zhang, H. Wang, T. Zhang, R. Bai, Q. Sun, X. Wang, T. Yu, D. Wu, *Bioact. Mater.* **2022**, *11*, 130; b) T. Yu, L. Zhang, X. Dou, R. Bai, H. Wang, J. Deng, Y. Zhang, Q. Sun, Q. Li, X. Wang, *Adv. Sci.* **2022**, *9*, 2203734; c) X. Ren, X. Chen, Z. Geng, J. Su, *Chem. Eng. J.* **2022**, *446*, 137133.
[140] G. L. Koons, M. Diba, A. G. Mikos, *Nat. Rev. Mater.* **2020**, *5*, 584.
[141] a) M. Feito, L. Casarrubios, M. Oñaderra, M. Gómez-Duro, P. Arribas, A. Polo-Montalvo, M. Vallet-Regí, D. Arcos, M. Portolés, *Colloids Surf., B.* **2021**, *208*, 112110; b) L. Cao, W. Weng, X. Chen, Y. Ding, Y. Yan, H. Li, H. Zhao, J.-W. Shin, J. Wei, F. Ji, *Composites, Part B.* **2015**, *77*, 454.
[142] Y. Liu, S. Zhang, X. Zhang, L. Ji, H. Yu, J. Wang, C. Liu, *Composites, Part B.* **2024**, *272*, 111202.
[143] X. Qi, Y. Liu, X. Yin, R. Zhao, W. Zhang, J. Cao, W. Wang, W. Jia, *Composites, Part B.* **2023**, *257*, 110673.
[144] J. Zhang, S. Zhao, Y. Zhu, Y. Huang, M. Zhu, C. Tao, C. Zhang, *Acta Biomater.* **2014**, *10*, 2269.
[145] W. Shi, Y. Feng, J. Tang, Y. Xu, W. Wang, L. Zhang, X. Jiang, Z. Ding, K. Xi, L. Chen, Y. Gu, *Adv. Healthcare Mater.* **2024**, *13*, 2304585.
[146] D. Lin, Y. Chai, Y. Ma, B. Duan, Y. Yuan, C. Liu, *Biomaterials* **2019**, *196*, 122.
[147] a) I. Ohsawa, M. Ishikawa, K. Takahashi, M. Watanabe, K. Nishimaki, K. Yamagata, K.-I. Katsura, Y. Katayama, S. Asoh, S. Ohta, *Nat. Med.* **2007**, *13*, 688; b) G. Zhou, E. Goshi, Q. He, *Adv. Healthcare Mater.* **2019**, *8*, 1900463.
[148] S. Chen, Y. Yu, S. Xie, D. Liang, W. Shi, S. Chen, G. Li, W. Tang, C. Liu, Q. He, *Nat. Commun.* **2023**, *14*, 7783.
[149] F. Zhao, W. Xie, W. Zhang, X. Fu, W. Gao, B. Lei, X. Chen, *Adv. Healthcare Mater.* **2018**, *7*, e1800361.
[150] a) B. Ma, J. Han, S. Zhang, F. Liu, S. Wang, J. Duan, Y. Sang, H. Jiang, D. Li, S. Ge, *Acta Biomater.* **2018**, *71*, 108; b) S. L. Aktuğ, S. Durdu, E. Yalçın, K. Çavuşoğlu, M. Usta, *Mater. Sci. Eng., C.* **2017**, *71*, 1020.
[151] a) O. R. Mahon, D. C. Browe, T. Gonzalez-Fernandez, P. Pitacco, I. T. Whelan, S. Von Euw, C. Hobbs, V. Nicolosi, K. T. Cunningham, K. H. Mills, *Biomaterials* **2020**, *239*, 119833; b) Y. Li, Y. Wang, Y. Li, W. Luo, J. Jiang, J. Zhao, C. Liu, *ACS Biomater. Sci. Eng.* **2019**, *6*, 320; c) G. Yang, H. Liu, X. Hu, Z. Chen, T. E. Friis, J. Wang, Y. Xiao, S. Zhang, *Nanoscale* **2017**, *9*, 5794.
[152] a) H. Shi, X. Ye, J. Zhang, T. Wu, T. Yu, C. Zhou, J. Ye, *Bioact. Mater.* **2021**, *6*, 1267; b) J. He, X. Hu, J. Cao, Y. Zhang, J. Xiao, D. Chen, C. Xiong, L. Zhang, *Carbohydr. Polym.* **2021**, *253*, 117198; c) A. Shavandi, A. E.-D. A. Bekhit, Z. F. Sun, A. Ali, *J. Biomimetics, Biomater. Biomed. Eng.* **2015**, *25*, 98.
[153] Z. Zhong, X. Wu, Y. Wang, M. Li, Y. Li, X. Liu, X. Zhang, Z. Lan, J. Wang, Y. Du, S. Zhang, *Bioact. Mater.* **2022**, *10*, 195.
[154] R. Zhao, T. Shang, B. Yuan, X. Zhu, X. Zhang, X. Yang, *Bioact. Mater.* **2022**, *17*, 379.
[155] a) J. Filipowska, K. A. Tomaszewski, Ł. Niedźwiedzki, J. A. Walocha, T. Niedźwiedzki, *Angiogenesis* **2017**, *20*, 291; b) J. R. García, A. J. García, *Drug Delivery Transl. Res.* **2016**, *6*, 77.
[156] X. Zheng, L. Xin, Y. Luo, H. Yang, X. Ye, Z. Mao, S. Zhang, L. Ma, C. Gao, *ACS Appl. Mater. Interfaces* **2019**, *11*, 43689.
[157] M. M. Alvarez, J. C. Liu, G. Trujillo-de Santiago, B.-H. Cha, A. Vishwakarma, A. M. Ghaemmaghami, A. Khademhosseini, *J. Controlled Release* **2016**, *240*, 349.
[158] S. Xiong, Y. Zhang, J. Zeng, J. Zhou, S. Liu, P. Wei, H. Liu, F. Yi, Z. Wan, L. Xiong, B. Zhang, J. Li, *Mater. Today Bio* **2024**, *24*, 100929.
[159] a) C. Feng, Y. Wu, Q. Li, T. He, Q. Cao, X. Li, Y. Xiao, J. Lin, X. Zhu, X. Zhang, *Adv. Funct. Mater.* **2022**, *32*, 2204974; b) Y. Zhu, K. Zhang, R. Zhao, X. Ye, X. Chen, Z. Xiao, X. Yang, X. Zhu, K. Zhang, Y. Fan, *Biomaterials* **2017**, *147*, 133.
[160] H. Peng, T. Ling, Y. Zhang, T. Xie, X. Pei, K. Zhou, A. Chen, J. Chen, X. Zhu, X. Zhang, Z. Zhou, *ACS Appl. Mater. Interfaces* **2023**, *15*, 9120.
[161] C. Deng, Q. Zhou, M. Zhang, T. Li, H. Chen, C. Xu, Q. Feng, X. Wang, F. Yin, Y. Cheng, C. Wu, *Adv. Sci.* **2022**, *9*, e2105727.
[162] A. Namdar, E. Salahinejad, *Coord. Chem. Rev.* **2023**, *478*, 215001.
[163] N. Suhm, A. Gisep, *J. Orthop. Trauma* **2008**, *22*, S121.
[164] a) J. Zhang, W. Liu, V. Schnitzler, F. Tancret, J.-M. Bouler, *Acta Biomater.* **2014**, *10*, 1035; b) K. L. Low, S. H. Tan, S. H. S. Zein, J. A. Roether, V. Mouriño, A. R. Boccaccini, *J. Biomed. Mater. Res., Part B.* **2010**, *94B*, 273.
[165] a) W. Wang, K. W. Yeung, *Bioact. Mater.* **2017**, *2*, 224; b) S. V. Dorozhkin, *Int. J. Mater. Chem.* **2011**, *1*, 1.

[166] J. C. Elliott, *Structure and Chemistry of the Apatites and Other Calcium Orthophosphates*, Elsevier, Amsterdam **2013**.
[167] Z. Sheikh, Y. L. Zhang, L. Grover, G. E. Merle, F. Tamimi, J. Barralet, *Acta Biomater.* **2015**, *26*, 338.
[168] L. Li, X. Peng, Y. Qin, R. Wang, J. Tang, X. Cui, T. Wang, W. Liu, H. Pan, B. Li, *Sci. Rep.* **2017**, *7*, 45204.
[169] X. Cui, C. Huang, Z. Chen, M. Zhang, C. Liu, K. Su, J. Wang, L. Li, R. Wang, B. Li, D. Chen, C. Ruan, D. Wang, W. W. Lu, H. Pan, *Bioact. Mater.* **2021**, *6*, 3801.
[170] Q.-Q. Wan, J.-L. Sun, Y.-X. Ma, L. C. Noble, Y. Dong, Z.-H. Feng, J.-T. Gu, Y.-R. Wang, W.-R. Wang, B. E. Bergeron, K. Jiao, F. R. Tay, L.-N. Niu, *Appl. Mater. Today* **2021**, *24*, 101145.
[171] Y. Lai, Y. Li, H. Cao, J. Long, X. Wang, L. Li, C. Li, Q. Jia, B. Teng, T. Tang, *Biomaterials* **2019**, *197*, 207.
[172] S. Tan, Y. Wang, Y. Du, Y. Xiao, S. Zhang, *Bioact. Mater.* **2021**, *6*, 3411.
[173] S. Li, L. Zhang, C. Liu, J. Kim, K. Su, T. Chen, L. Zhao, X. Lu, H. Zhang, Y. Cui, X. Cui, F. Yuan, H. Pan, *Bioact. Mater.* **2023**, *23*, 101.
[174] Y. Hu, L. Tang, Z. Wang, H. Yan, X. Yi, H. Wang, L. Ma, C. Yang, J. Ran, A. Yu, *J. Controlled Release* **2024**, *365*, 889.
[175] S. Li, Y. Cui, H. Liu, Y. Tian, Y. Fan, G. Wang, J. Wang, D. Wu, Y. Wang, *Mater. Today Bio* **2024**, *24*, 100943.
[176] W. Wang, Y. Xiong, R. Zhao, X. Li, W. Jia, *J. Nanobiotechnol.* **2022**, *20*, 68.
[177] N. Zheng, J. Xu, Y. C. Ruan, L. Chang, X. Wang, H. Yao, J. Wang, R. Zhang, Q. Xue, N. Tang, T.-Y. Ong, J. Schilcher, R. J. O'Keefe, L. Qin, *Mater. Today* **2022**, *52*, 43.
[178] W. Y. Zhu, J. Guo, W. F. Yang, Z. Y. Tao, X. Lan, L. Wang, J. Xu, L. Qin, Y. X. Su, *J. Orthop. Transl.* **2022**, *33*, 153.
[179] Q. Miao, X. Yang, J. Diao, H. Ding, Y. Wu, X. Ren, J. Gao, M. Ma, S. Yang, *Mater. Today Bio* **2023**, *23*, 100871.
[180] M. Zhou, X. Wu, J. Luo, G. Yang, Y. Lu, S. Lin, F. Jiang, W. Zhang, X. Jiang, *Chem. Eng. J.* **2021**, *422*, 130147.
[181] D. M. Vasconcelos, R. M. Gonçalves, C. R. Almeida, I. O. Pereira, M. I. Oliveira, N. Neves, A. M. Silva, A. C. Ribeiro, C. Cunha, A. R. Almeida, C. C. Ribeiro, A. M. Gil, E. Seebach, K. L. Kynast, W. Richter, M. Lamghari, S. G. Santos, M. A. Barbosa, *Biomaterials* **2016**, *111*, 163.
[182] J.-H. Song, J.-T. Gu, G.-P. Dang, Z.-T. Li, C. Lei, L. Li, Z. Mu, F. R. Tay, K. Jiao, L.-N. Niu, *Chem. Eng. J.* **2023**, *474*, 145318.
[183] F. Sun, X. Sun, H. Wang, C. Li, Y. Zhao, J. Tian, Y. Lin, *Int. J. Mol. Sci.* **2022**, *23*, 5831.
[184] J. Long, Z. Yao, W. Zhang, B. Liu, K. Chen, L. Li, B. Teng, X. F. Du, C. Li, X. F. Yu, L. Qin, Y. Lai, *Adv. Sci.* **2023**, *10*, e2302539.
[185] Y. Yuan, Y. Xu, Y. Mao, H. Liu, M. Ou, Z. Lin, R. Zhao, H. Long, L. Cheng, B. Sun, S. Zhao, M. Zeng, B. Lu, H. Lu, Y. Zhu, C. Chen, *Adv. Sci.* **2024**, *11*, e2306428.
[186] J. Jiang, W. Liu, Z. Xiong, Y. Hu, J. Xiao, *Biomater. Adv.* **2022**, *134*, 112640.
[187] Y.-T. Sul, *Biomaterials* **2003**, *24*, 3893.
[188] L. Bai, Z. Du, J. Du, W. Yao, J. Zhang, Z. Weng, S. Liu, Y. Zhao, Y. Liu, X. Zhang, X. Huang, X. Yao, R. Crawford, R. Hang, D. Huang, B. Tang, Y. Xiao, *Biomaterials* **2018**, *162*, 154.
[189] Y. Peng, J. Yang, W. Fu, Q. Gao, S. Yao, C. Peng, S. Hou, *Mater. Today Adv.* **2022**, *14*, 100234.
[190] J. Su, Z. Du, L. Xiao, F. Wei, Y. Yang, M. Li, Y. Qiu, J. Liu, J. Chen, Y. Xiao, *Mater. Sci. Eng., C.* **2020**, *113*, 110983.
[191] B. Li, R. Huang, J. Ye, L. Liu, L. Qin, J. Zhou, Y. Zheng, S. Wu, Y. Han, *Chem. Eng. J.* **2021**, *403*, 126323.
[192] L. Bai, P. Chen, Y. Zhao, R. Hang, X. Yao, B. Tang, C. Liu, Y. Xiao, R. Hang, *Biomaterials* **2021**, *278*, 121162.
[193] J. Zhang, D. Tong, H. Song, R. Ruan, Y. Sun, Y. Lin, J. Wang, L. Hou, J. Dai, J. Ding, H. Yang, *Adv. Mater.* **2022**, *34*, 2202044.
[194] M. P. Staiger, A. M. Pietak, J. Huadmai, G. Dias, *Biomaterials* **2006**, *27*, 1728.
[195] X.-J. Su, S. Liu, S.-C. Huo, F. Wang, Q.-X. Song, H.-X. Shen, S.-H. Huang, C. Zhu, K. Wang, *Mater. Des.* **2024**, *238*, 112646.
[196] Y. Wu, S. Huo, S. Liu, Q. Hong, Y. Wang, Z. Lyu, *Adv. Healthcare Mater.* **2023**, *12*, e2301772.
[197] Y. Zheng, A. Gao, J. Bai, Q. Liao, Y. Wu, W. Zhang, M. Guan, L. Tong, D. Geng, X. Zhao, P. K. Chu, H. Wang, *Bioact. Mater.* **2022**, *14*, 364.
[198] C. D. Hoemann, J. R. Gonzalez, J. Guzman-Morales, G. Chen, E. Jalali Dil, B. D. Favis, *Bioact. Mater.* **2022**, *10*, 430.
[199] S. Xiao, J. Wei, S. Jin, X. Xia, L. Yuan, Q. Zou, Y. Zuo, J. Li, Y. Li, *Adv. Funct. Mater.* **2022**, *33*, 2208968.
[200] T. Zhao, Z. Chu, J. Ma, L. Ouyang, *J. Funct. Biomater.* **2022**, *13*, 103.
[201] K. Y. Yang, M. Ku, K. O. Lui, *J. Leucocyte Biol.* **2020**, *108*, 1593.
[202] W. Yang, Y. Wang, K. Mo, W. Chen, X. Xie, *Sci. Rep.* **2024**, *14*, 29493.
[203] A. Shmatko, N. Ghaffari Laleh, M. Gerstung, J. N. Kather, *Nat. Cancer* **2022**, *3*, 1026.
[204] a) D. M. Black, J. A. Cauley, R. Wagman, K. Ensrud, H. A. Fink, T. A. Hillier, L. Y. Lui, S. R. Cummings, J. T. Schousboe, N. Napoli, *J. Bone Miner. Res.* **2018**, *33*, 389; b) W. D. Leslie, S. N. Morin, *Curr. Osteoporosis Rep.* **2020**, *18*, 115; c) E. Juliet, M. Compston, *Lancet* **2019**, *393*, 364.
[205] a) A. Krishnaraj, S. Barrett, O. Bregman-Amitai, M. Cohen-Sfady, A. Bar, D. Chettrit, M. Orlovsky, E. Elnekave, *J. Am. Coll. Radiol.* **2019**, *16*, 1473; b) B. S. Mackay, K. Marshall, J. A. Grant-Jacob, J. Kanczler, R. W. Eason, R. O. Oreffo, B. Mills, *Biomed. Phys. Eng. Express* **2021**, *7*, 052002.
[206] a) T. V. Nguyen, *Osteoporosis Sarcopenia* **2018**, *4*, 2; b) C. Beaudoin, L. Moore, M. Gagné, L. Bessette, L. Ste-Marie, J. Brown, S. Jean, *Osteoporosis Int.* **2019**, *30*, 721; c) G. E.-H. Fuleihan, M. Chakhtoura, J. A. Cauley, N. Chamoun, *J. Clin. Densitom.* **2017**, *20*, 397.
[207] J. Parthasarathy, *Ann. Maxillofac. Surg.* **2014**, *4*, 9.

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