

Metal semiconductor materials in bone diseases: properties, applications, and future perspectives

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Abstract

The objective of bone tissue engineering is to develop innovative biomaterials and stimulation strategies to promote bone regeneration. Bioelectric materials play a crucial role in this domain owing to their inspiration of the inherent piezoelectric properties of bone. This review explores the progress made in utilizing metal semiconductor materials for bone tissue engineering, focusing on their operating mechanisms, various material classifications, and the ways they foster bone regeneration. First, the working principles of metal semiconductor materials are discussed, with an emphasis on the importance of bioelectric phenomena in regulating cell behavior. Owing to their roles in mimicking the electrophysiological microenvironment to promote bone regeneration, we highlight various types of metal semiconductor materials, such as metallic semiconductor materials, piezoelectric materials, and conductive biomaterials. Personalized and specific materials, including conductive smart scaffolds, modified implant surfaces, and those that target bone tissues, promote osseointegration and exert antibacterial properties, serving diverse applications in bone tissue engineering. Additionally, to improve implant biocompatibility and osseointegration, the use of metal semiconductor materials in the design of orthopedic implants has shown promising clinical application prospects. Finally, looking forward to the future applications of metal semiconductor materials in bone engineering, integrating multiple functions, personalized medicine, and biodegradable materials, as well as the application of nanotechnology and 3D printing techniques, may arise to satisfy clinical requirements. This review also presents the biological characteristics of metal semiconductor materials and their recent applications in treating bone diseases, while also discussing innovative concepts for their design and development.

Keywords: Metal semiconductor materials; Bone tissue engineering; Bone regeneration; Conductive biomaterials

Highlights

- This is the first comprehensive review of metal semiconductors as multifunctional bone tissue engineering platforms that integrate osteogenic, antibacterial, imaging, drug delivery, and photothermal therapy effects into a unified system.
- This study highlights the electrophysiological mechanisms by which metal semiconductors rebuild the bone microelectric field on the basis of piezoelectric/conductive properties, Ca^{2+} channel modulation, osteogenic signaling, and immune cell polarization to offer new therapeutic targets.
- A translational roadmap that features biodegradable metal semiconductors, 3D-printed personalized scaffolds, and stimuli-responsive release strategies is established to bridge laboratory research with clinical practice.
- Examples of device-integrated designs, such as surface coatings, smart scaffolds, and nanodrug carriers, that reduce stress shielding and infection risk while enhancing osseointegration are discussed.
- Future directions that emphasize interdisciplinary collaboration, long-term biocompatibility assessments, and patient-specific customization are identified to lay theoretical and technical foundations for next-generation orthopedic implants.

Background

Bone, which is a dense and highly mineralized tissue, is composed primarily of inorganic hydroxyapatite nanocrystals dispersed among organic elements, including cells and collagen fibers [1, 2]. The number of orthopedic patients characterized by inadequate bone healing and regeneration, which have been linked to a variety of health conditions, is increasing. This trend is attributed primarily to the growing number of

elderly individuals, sedentary habits, and the poor dietary choices common in urban environments [3]. Conditions such as type II diabetes [4], periodontitis [5], osteoporosis [6], osteoarthritis [7], rheumatoid arthritis [8], and metastatic osteolysis [9] are known to cause bone deterioration and loss or impair the body's ability to heal and regenerate bone after injury. Furthermore, recovery from bone defects in the context of these diseases is typically poor [4–7, 9, 10] and

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necessitates medical intervention in many instances. Osteoporosis is caused primarily by an imbalance between bone formation by osteoblasts and bone resorption by osteoclasts [11, 12]. The balance between these two processes is crucial for bone remodeling; any disruption can lead to osteoporosis. The regulation of bone mass depends on this dynamic equilibrium between osteoblast-driven bone formation and osteoclast-driven bone resorption [13–15].

In recent years, although researchers have enhanced bone repair by modulating multiple signaling pathways that promote osteoblast function or inhibit osteoclast function, healing bone defects caused by nonunion fractures, severe injuries, congenital deficiencies, cancer surgery, or infection remains a major clinical challenge [16]. Due to the sustained endeavors of scientists, various biological substances have been utilized in the repair of bone. However, the processing of synthetic bone graft substitutes into porous complex scaffolds for load-bearing implantation sites can be challenging because of their brittle and stiff nature and the inevitable degradation of mechanical durability [17, 18]. Despite significant research into the creation of scaffolds that mimic the composition, structure, and mechanical properties of natural bone, the importance of replicating the body's electrophysiological microenvironment is often overlooked [19, 20]. However, this electrophysiological microenvironment is crucial for stimulating bone regeneration and repair [21]. Given that bone is an electroactive and electroresponsive tissue and that bone degeneration under various pathological conditions is associated with significant changes in its bioelectric properties, restoring the natural electrophysiological microenvironment could promote bone healing and regeneration [22]. This restoration may be achieved through the use of metal semiconductor materials that enhance osteogenesis and angiogenesis, suppress inflammation and osteoclastogenesis, and protect against bacterial infection [23–27].

This review begins by highlighting the important function of bioelectricity in the typical physiology and healing processes of bone tissue. Subsequently, we examine the characteristics of different kinds of metal semiconductor materials and their uses in biological contexts. We subsequently focus on how metal semiconductor materials promote bone repair and regeneration through their unique bioelectric effects, which enhance osteogenesis, support angiogenesis, mitigate inflammation and osteoclastogenesis, and offer protection against bacterial infections (Figure 1). In conclusion, we examine the advancements and obstacles associated with the clinical application of metal semiconductor materials, with the hope that these materials may soon enter clinical practice to benefit patients with bone injuries.

Review

Working mechanisms of bioelectricity in bone

Bioelectricity is an indispensable factor of bone tissue, and the endogenous electric field plays a vital role in normal bone function [28]. When pressure is applied to bones, microcurrents are generated, which then initiate electrical signals that stimulate the biological processes of bone remodeling [29–31]. In several clinical trials, researchers attempted to use various electrical stimulation methods to encourage bone formation and healing [31, 32], which has resulted in advancements in the use of electrical stimulation for bone growth in

clinical applications. However, electrical stimulation is currently applied from the outside in clinical practice, and the sites where bone regeneration are needed cannot be accurately located. The compressive force on collagen causes a reorientation of the dipole moment, which results in the electrical stimulation of cells, thus creating a negative charge on the plasma membrane and triggering the opening of voltage-gated calcium (Ca^{2+}) channels [33–35]. The initial activation of these Ca^{2+} channels facilitates the entry of Ca^{2+} , subsequently triggering a series of growth factor activations, such as transforming growth factor β (TGF- β), bone morphogenetic proteins (BMPs), and vascular endothelial growth factor (VEGF) (Figure 2). Consequently, external electrical stimulation or voltage application can be used to locally enhance bone regeneration and repair extensive bone defects [36, 37].

The electric field in bone tissue, which is generated by the transmembrane potential due to differences in ion (K^+ , Na^+ , and Ca^{2+}) concentrations, affects osteoblasts, osteocytes, and osteoclasts with a strength of 40–500 mV/mm. Voltage-gated Ca^{2+} channels are crucial in the processes of osteogenesis and bone regeneration by regulating Ca^{2+} influx. During electrical stimulation (ES), these channels increase the osteogenic differentiation of osteoblasts by increasing TGF- β 1 levels. ES also stimulates additional ion channels (including Na^+ , K^+ , and Cl^- channels). In osteoclasts, ES-induced Ca^{2+} influx disrupts the cytoskeleton, thus inhibiting podosome expression and reducing bone resorption [38–41].

The process of bone healing typically encompasses four successive phases: the formation of a hematoma, the development of a fibrous callus, the creation of new bone, and the remodeling of bone tissue. This complex process requires the coordination of several physiological processes, such as inflammation suppression, immune regulation, angiogenesis, and osteogenesis [22]. During the bone healing process, bioelectricity can exert a variety of biological effects.

Osteoblast enhancement

Osteoblast differentiation and proliferation can be induced by ES, with currents that range from 5 to 100 μA and promote bone formation [42]. Bone formation and reconstruction are regulated by bioactive substances secreted by osteoblasts. The activation of calcium ion channels by ES triggers the signaling pathway involving calmodulin (CaM), calcineurin (CaN), and nuclear factor of activated T cells (NFAT). This pathway involves CaM binding to calcium ions, which activates CaN, and the dephosphorylation of p-NFAT, which then enters the nucleus to induce osteogenesis-related protein expression [43]. Calcium plays a vital role in how bone cells respond to ES since ES elevates the intracellular calcium levels by either releasing calcium from internal reserves or activating L-type channels, which permits the influx of extracellular calcium into the cell. This increase in calcium activates protein kinases or calmodulin, which results in the conversion of electrical signals into biological signals that promote gene expression and protein synthesis, thereby affecting cell proliferation and differentiation [44]. Research was conducted to examine the osteogenic influence on MC-3 T3-E1 cells through the application of pulsed electrical stimulation (PES) alongside different concentrations of BMP-2. The results indicated that the combination of PES and BMP-2 works together to promote the proliferation of MC-3 T3-E1 cells. Quantitative real-time polymerase chain reaction (qPCR) analysis indicated that this synergistic effect on osteoblast differentiation is

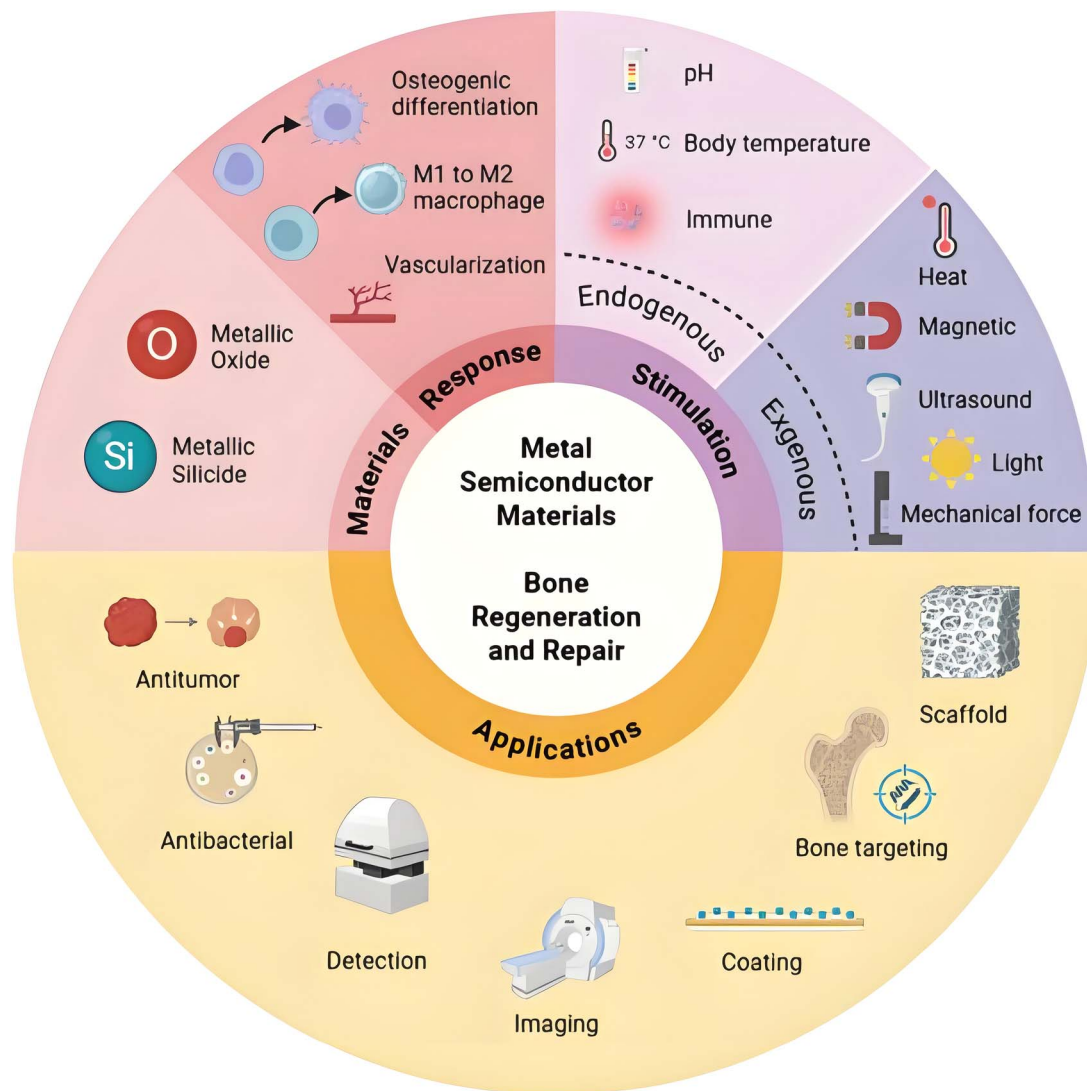


Figure 1. Overview of metal semiconductor materials for bone tissue engineering and regeneration. Created by BioRender

mediated primarily through the Smad/BMP and insulin-like growth factor 1 (IGF1) signaling pathways. Additionally, on a 3D-printed polylactic acid scaffold, the combination of PES and BMP-2 significantly promoted cell proliferation, collagen I (COL-I) and alkaline phosphatase expression, and cell mineralization [45].

Osteoclast suppression

Normal bone tissue maintains a dynamic balance between bone formation by osteoblasts and bone resorption by osteoclasts [46]. Osteoblasts are responsible for synthesizing bone collagen and facilitating mineralization, while osteoclasts are involved in the breakdown and removal of necrotic or aging bone cells. Consequently, employing ES to inhibit osteoclast activation and simultaneously enhance osteogenesis presents a promising approach for managing bone-related disorders. The research team led by Cui investigated the ability of electrical stimulation to create induced tumor-suppressing (iTTS) cells utilizing a specially designed stimulator incorporating platinum electrodes. Mesenchymal stem cells (MSCs) and Jurkat T cells underwent stimulation under optimally set parameters (50 mV/cm and 10–100 Hz for 1 h). The

conditioned medium (CM) derived from these cells exhibited tumor-suppressing properties by inhibiting tumor cell migration, 3D spheroid proliferation, and the viability of cancer tissue fragments. Additionally, CM contributed to the decrease in osteoclast maturation and facilitated osteoblast differentiation. Proteomic analysis indicated an increase in tumor-suppressing proteins, such as histone H4, in the treated cells. Functional experiments underscored Piezo1's critical role as a mediator necessary for the noted tumor-suppressing effects. Mechanistically, this mechanism differs from other techniques like mechanical vibration, as inhibiting sad1 and UNC84 domain containing 1 (SUN1) did not influence the generation of iTTS cells. These results indicate that electrical stimulation can enhance the antitumor capabilities of MSCs and T cells, thus suggesting a new strategy for cancer therapy [47].

Increased angiogenesis

Blood vessels are crucial for bone homeostasis because they provide nutrition and oxygen and support bone cell renewal and differentiation [48, 49]. Insufficient angiogenesis after bone repair material implantation can lead to nonunion and



avascular necrosis, thereby increasing the risk of reconstruction failure [50, 51]. ES can enhance endothelial cell migration and growth factor secretion, thus promoting healing [52, 53]. An innovative therapeutic strategy that involves the use of a conductive hydrogel doped with magnesium ion (Mg^{2+})-modified black phosphorus (BP) was employed to address pathological imbalances in senile bone defects. This hydrogel reprograms electrical signals, restores Mg^{2+} homeostasis, and promotes blood vessel regeneration. Moreover, the hydrogel synergistically restored chemical and bioelectric signals in the bone microenvironment, increasing VEGF and VEGFR2 expression, activating the PI3K-AKT-eNOS pathway, and enhancing angiogenesis in aged vascular endothelial cells. Additionally, the hydrogel normalized Ca^{2+} influx, increased osteogenesis-related transcription factor accumulation in the nucleus, and facilitated the osteogenic differentiation of senescent stem cells. This strategy effectively restores bone-vascular coupling to achieve the regeneration of vascularized bone in senile bone defects, thus showing therapeutic promise [54].

The immune system is crucial in bone disease development and progression, and its interaction with bone cells is essential for both bone homeostasis and pathology [55]. Cytokines secreted by immune cells, especially macrophages, have a direct influence on the immune responses of bones as well as on regenerative repair processes. Both chemical and

Implants designed to replace or repair bone tissue that is damaged owing to severe significant defects from fractures or conditions like osteoporosis and osteoarthritis are needed in the medical field. For decades, tissue engineering strategies have aimed to engineer functional and natural-like bone tissue [60]. This necessitates the use of hard, porous biomaterials that are osteoinductive (induce bone formation), osteoconductive (facilitate bone growth), and osteopromotive (promote

bone healing) [60–62]. These materials have been seeded with bone-forming and endothelial cells to recreate the bone tissue microenvironment and restore the structural integrity of the skeletal system with artificial implants, ultimately stimulating new bone growth *in situ* [63].

While metals and metalloids offer important mechanical strength and electrical conductivity, their use in bone repair remains restricted due to inadequate tissue integration and biocompatibility. Although initial *in vitro* studies have suggested that these materials are corrosion resistant, long-term exposure to the body's electrochemical environment can cause metals and metalloids to corrode and release nonbiodegradable, toxic metal ions into the surrounding fluids [64]. There have been multiple reports of infections following metal or metalloid implantation, which have been attributed to bacterial adhesion and biofilm formation on their surfaces [65]. These complications may result in significant clinical failure rates. To address these issues, various methods have been employed to improve the surfaces of metal and metalloid implants, such as applying protective coatings, creating a passivation oxide layer, using ion beam surface modification, and introducing surface texturing [66–68]. However, these methods do not fundamentally eliminate the drawbacks of metals and metalloid implants; thus, a new type of material to promote bone remodeling is urgently needed.

In recent years, metal semiconductor materials have gradually become a new research direction for promoting bone healing. Researchers are starting to investigate the application of metal semiconductor materials to repair bone tissue loss or dysfunction because of their excellent biological properties. Owing to their unique electrical, optical, ultrasonic, and thermal response characteristics, these materials offer new possibilities for the noninvasive, controllable, dynamic repair of pathological bone defects [69–71].

In bone tissue engineering, the selection of metal semiconductor materials is guided by the following six key criteria [72–74]. (1) Biomimeticism: The material should have properties that mimic those of natural bone and facilitate effective interaction with regenerating tissue, with biocompatibility, osteoconductivity, and osteoinductivity. (2) Mechanical properties: The material should possess an appropriate elastic modulus and compressive strength to facilitate bone growth while avoiding stress shielding. (3) Biodegradability: The scaffold must slowly break down and be substituted by new bone, ensuring that the degradation rate and byproducts are safe. (4) Imaging compatibility: The material should be easily imageable without altering information to enable post-operative monitoring of positioning and bone growth without interfering with native bone. (5) Histological processing: The material should enable easy cutting of histological slices without degradation. (6) Sterilization compatibility: The material should be compatible with clinically approved sterilization processes. These criteria ensure that the material effectively and safely supports bone regeneration.

Representative metal semiconductor materials

Organic materials become semiconductors only when charge carriers are injected from electrodes or created through intentional or unintentional doping [75]. Semiconducting polymeric nanomaterials are an emerging class of organic nano-optical reagents with excellent biocompatibility and are widely used in sensors and for imaging, therapy, and drug delivery applications [76–78]. Conversely, semiconductor

materials made from metals can exhibit semiconductor properties regardless of doping. Owing to the extraordinary properties inherent to and acquired by these nanomaterials, semiconducting polymeric nanomaterials have been widely used as nanoreagents in photothermal and photodynamic therapies, drug carriers, biosensors, and imaging contrast agents and are promising materials with which the difficulties in the diagnosis and treatment of diseases can be solved [79–81] (Table 1).

Metallic silicide

In the late 1960s, a groundbreaking innovation in metal semiconductor materials was the exploration of silica-based bioactive glass, which has since ignited considerable interest in examining silicon-containing biomaterials across both macroscale and nanoscale dimensions [97]. Silica-based biomaterials have been intensely scrutinized for their suitability in a variety of biomedical applications and have been shown to exhibit exceptional bioactivity, superior biocompatibility, easy surface modification, and tunable synthesis processes. However, to accelerate the transition of silicon-containing nanomedicines and biomaterials from the bench to the bedside and foresee their unanticipated clinical applications, a comprehensive understanding of their properties and biological effects is imperative [98, 99].

Silicon is a trace element that is abundant in the environment and our daily diet and is the third most prevalent element in the human body [100]. It is concentrated at the sites where bones are actively calcified and plays crucial roles in the metabolic processes of bone formation. A lack of silicon can result in abnormalities in connective and skeletal tissues. The outstanding biocompatibility of silicon, in combination with its multifaceted capabilities that can be tailored through strategic design, renders silicon-based biomaterials some of the most promising inorganic substances for an array of biomedical uses [101–105].

A new alloy based on metallic silicide (Ti-Nb-Zr-Si, TNZS) was created to overcome the challenges posed by existing biomedical titanium alloys, which trigger inflammatory responses following implantation. The electrochemical properties and biocompatibility of TNZS were evaluated in comparison to commercially pure titanium and the Ti-6Al-4V alloy. The corrosion resistance exhibited by TNZS was greater than that of pure titanium and the Ti-6Al-4V alloy when tested in both simulated inflammatory conditions and acidic environments that included hydrogen peroxide. TNZS also showed excellent biological activity for supporting cell proliferation and growth, which makes it a promising material for orthopedic applications [82].

Studies have revealed that silicon exhibits significantly altered optical characteristics when its crystal size is reduced to the exciton Bohr radius of bulk silicon (~4 nm) [98]. Considerable research has been dedicated to leveraging the superior qualities of group IV nanodiamonds, including their luminescence, enzymatic-like activity, reductive capacity, and properties relevant to therapeutics, for applications in bioimaging both *in vitro* and *in vivo*. Both silicon (Si) and germanium (Ge) nanocrystals are promising materials for bioimaging applications because of their unique optical characteristics and low toxicity [100]. Silicon nanocrystals have advanced further in their research for bioimaging applications compared to germanium nanocrystals. Both silicon and germanium nanocrystals are appropriate for

Table 1. Representative metal semiconductor materials

Metal semiconductor materials					
Material	Form	Field(s)	Biological function(s)	Advantage(s)	Ref(s)
Metallic silicide	Ti-Nb-Zr-Si (TNZS)	Cells; (severe) inflammatory media	Support cell proliferation and growth	Excellent biological activity; superior corrosion resistance	[82]
	SiNPs	Cells	Next-generation probes for long-term imaging	Outstanding water solubility and biocompatibility; elevated luminescence (photoluminescent quantum yield of 44.77%); pH/photo-/storage stability	[83]
	Si-CsPbBr ₃	Cells	Used in the first system for high-resolution tumor detection and tissue identification; potential for application in luminescence-guided surgery		[84]
Metallic oxide	CuO	Molecular; infectious conditions	Unique antibacterial mechanism: copper creates ROS and damages nucleic acids; Cu ⁺ is more effective against bacterial infections than other types of infections	Excellent cytocompatibility and marked antibacterial efficacy	[85–88]
	GaO	FEMs; clinical	Disturbs bacterial ionic balance; works against certain pathogens as antimicrobial agents; Ga-based antibacterials are in the class of metal antimicrobials; clinical treatment of cancer-related hypercalcemia	Anti-inflammatory and immunosuppressive activities	[89, 90]
	IGZO		Rapid and inexpensive detection of cardiac biomarkers	Excellent semiconducting channel (integrated with nanosheet materials to detect cTnI)	[91]
	Gallium-based antibacterials		Class of metal antimicrobials	Broad-spectrum effects; lack of resistance development; trace amounts of gallium are minimally toxic	[89]
	Ga nitrate		Clinical treatment of cancer-related hypercalcemia	No significant toxic side effects have been observed	[90, 92]
	ZnO NPs	Clinical	Various medical applications (antimicrobial, antidiabetic, anti-inflammatory, anti-aging, trauma healing, and bioimaging); therapeutic uses against bacteria, fungi, viruses, and cancer; safe for use as a medication, preservative, and antibacterial agent	Extremely small (easily absorbed by the human body); affordable; low toxicity; highly biocompatible; contact stability; tasteless and odorless; easy to prepare	[93–96]

biological imaging due to their capacity to be tailored for particular optical characteristics and their suitability for integration with biological systems. Compared with the toxicity of various traditional semiconductor quantum dots, such as those that contain harmful elements such as cadmium, lead, or mercury, the lower toxicity of these Si- and Ge-based materials makes them attractive for the development of new bioimaging agents [98]. A new biomimetic method used yeast secretion and a silicon compound to produce fluorescent silicon nanoparticles (SiNPs). These SiNPs disperse in water and are biocompatible and highly luminescent, which makes them a promising new type of fluorescent probe for long-term cell imaging. Unique properties are imparted to these SiNPs by yeast proteins, while their amino and carboxyl functionalities contribute to the stabilization of the particles, facilitating additional medical uses. This approach overcomes the limitations of traditional synthesis methods and offers a new direction for nanotechnology [83]. Liu *et al.* developed a Si-CsPbBr₃ hybrid photodetector by adding a CsPbBr₃ perovskite layer to a Si/PEDOT:PSS heterojunction, which increased its sensitivity in the 400–600-nm range and flattened the spectral response from 400 to 800 nm. This stable, flat-spectrum hybrid photodetector (PD) addresses the limitations of conventional Si-based PDs and is well suited for hyperspectral imaging (HSI). We also created a high-resolution perovskite HSI system for potential use in tumor detection and tissue identification [84]. *In vivo* studies have shown that after tumor accumulation, luminescent SiNCs are cleared after 48 h and exhibit a three-fold improvement in the signal-to-noise ratio for time-gated imaging compared with steady-state acquisition, thus demonstrating their potential for luminescence-guided surgery [106].

Moreover, studies have demonstrated the important roles of metallic silicides in the treatment of osteoporosis [107] and rheumatoid arthritis [108], the promotion of bone reconstruction [109], and the fabrication of bone prostheses [110]. Although metallic silicide has demonstrated extraordinary imaging properties in several fields, little research on its applicability to bone tumor imaging and the tracing of metastatic bone tumors has been conducted, which are potential research directions for metallic silicides in orthopedics.

Metallic oxide

Recently, increasing attention has been given to the incorporation of bioactive oxides such as Ag₂O, SrO, ZnO, CeO₂, CuO, and Ga₂O₃ into biocompatible silicate bioactive glass (SBG) and phosphate bioactive glass (PBG) [90, 111]. This doping process is used to enhance and diversify the capabilities of the bioactive glass (BG), particularly promoting angiogenesis, resisting oxidative stress, and demonstrating antimicrobial activity. The aim is to broaden their scope of application from rigid tissue regeneration to flexible tissue repair and injury recovery, in alignment with particular biomedical needs. Since the incorporation of these therapeutic agents affects the physical characteristics of the new BG, understanding their structural role and chemical surroundings within the glass network is crucial. This insight is essential, as it dictates the rate at which these agents are released into the biological medium, which directly influences the overall efficacy of the BG [112, 113].

GaO and CuO. Researchers are enhancing BGs to form SBGs or PBGs with therapeutic ions, such as those from CuO and

Ga₂O₃, to promote bone regeneration. Various BG formulations, including FastOs®BG and another with P₂O₅, CaO, Na₂O, and Fe₂O₃, which is produced by melt quenching, have been fabricated. A study examined how these elements function in the glass structure and their biological effects. *In vitro* tests revealed that Cu ions were released similarly from both BG types, whereas Ga release from SBGs was much lower than that from PBGs. This was due to the role of Cu as a network modifier and the varying roles of Ga. All glasses demonstrated cytocompatibility, and the discharge of Ga and Cu from the SBGs produced strong antibacterial effects. The most promising BG for implants and bone grafts was identified as a specific SBG formula with balanced Cu and Ga release, good cytocompatibility, and significant antibacterial activity [90]. Cu and Ga have unique ways of fighting bacteria: copper creates reactive oxygen species (ROS) and damages nucleic acids, whereas gallium interferes with the bacterial ion balance. This combination in bioactive glasses such as C3G2 and C2G3 improves their antibacterial effects compared with the effects of single-metal BGs. X-Ray photoelectron spectroscopy revealed that some Cu²⁺ in both glass types was reduced into the more effective antibacterial ion Cu⁺, which was possibly because less energy is needed for the formation of Cu₂O than CuO. This suggests that Cu⁺ is more effective against bacteria in conditions that mimic infections [85–88]. The treatment of implant infections has continued to be a serious clinical challenge, and CuO and Ga₂O₃ have demonstrated potent antimicrobial effects, thus providing new options for the treatment of orthopedic implant infections. Thus, their fabrication into prostheses or modification into prosthetic coatings may be a future application.

Several studies have proved that gallium compounds have anti-inflammatory and immunosuppressive activity [114–116], and more recent studies have shown that gallium compounds can work against certain pathogens as antimicrobial agents [117]. Moreover, recent research by Brid Murphy *et al.* has shed new light on the features of the nanosized gallium oxide surface for enhancing antimicrobial and osteointegrative responses [118]. The use of gallium compounds in clinical medicine can be further improved by obtaining a greater understanding of their mechanisms of action, drug resistance, pharmacology, and side effects [117, 119–122]. Khushaim and colleagues identified a biosensing method utilizing a field effect transistor that employs indium gallium zinc oxide (IGZO) as a highly effective semiconducting channel, which is coupled with nanosheet materials for cTnI detection. The reported compact microsystem paves the way for the rapid and inexpensive detection of cardiac biomarkers [91].

Ga-based antibacterials are metal antimicrobials that are known for their broad-spectrum effectiveness and lack of resistance development [89]. Notably, trace amounts of gallium are minimally toxic to humans and have important roles in clinical diagnostics and therapy. Additionally, gallium nitrate has been approved for the clinical treatment of cancer-related hypercalcemia, marking it the first gallium compound to be used in this context [90, 92]. Throughout treatment with these gallium compounds, no significant toxic side effects have been observed. In addition, as summarized by Peter Lakatos *et al.*, gallium nitrate was proven to inhibit bone resorption and collagen synthesis in neonatal mouse calvariae [123]. Evidence that supports this claim can be found in the work of Ying Yang *et al.* [124]. In their research, an

innovative nanoplatform that integrates graphene oxide with gallium nanoparticles (GO/Ga) was developed to address implant-related infections and bone healing challenges. It has strong *in vitro* antibacterial activity and promotes osteoblastogenesis while inhibiting osteoclastogenesis by modulating key signaling pathways. *In vivo* studies in a rat model for implant-associated osteomyelitis demonstrated the ability of this platform to reduce bone infection and osteolysis and enhance osseointegration with good biocompatibility. This nanocomposite holds promise for improving implant surfaces in bacterially infected settings and accelerating bone healing.

Although metallic silicide has not been used for the imaging of bone metastases, the conclusions drawn by Ivan *et al.* suggest that using gallium-68 citrate PET as a bone-tropic imaging biomarker in patients with metastatic castration-resistant prostate cancer (mCRPC) is feasible [125]. This research utilized ^{68}Ga -citrate PET imaging to detect bone metastases in 34 individuals diagnosed with mCRPC, with high sensitivity for bone lesions but low sensitivity for soft tissue. It also allowed the early treatment response to be monitored in a patient with small cell neuroendocrine cancer. Further studies are investigating the use of ^{68}Ga -citrate PET with MYC-targeting agents.

Ga-containing metal semiconductor materials have been used for several applications in orthopedics due to their excellent antimicrobial properties, biocompatibility, and low toxicity, and we look forward to their further development for the clinical treatment of orthopedic conditions.

Zinc oxide. Zinc oxide nanoparticles (ZnO NPs) are popular in many industries and research laboratories because of their diverse applications [126]. Compared with other metal oxide nanoparticles, their remarkably tiny size allows for easy absorption, and they are known for their affordability and low toxicity. This makes ZnO NPs suitable for a variety of medical applications, such as antimicrobial, antidiabetic, anti-inflammatory, anti-aging, wound healing, and bioimaging applications [93–96]. ZnO NPs are highly biocompatible, which enables their use in therapeutic settings to combat bacteria, fungi, viruses, and cancer [93, 127, 128]. Among the various inorganic metal oxides under investigation, such as TiO_2 , CuO , and ZnO , ZnO NPs stand out for their lower cost, superior safety, and easier preparation [129]. Materials designed for human intake to address health conditions must be nontoxic and stable when in contact with food or containers, have a pleasant taste or be tasteless, and be odorless. ZnO NPs meet these criteria, which makes them suitable for use as medications, preservatives, and antibacterial agents [130, 131]. As a result, the Food and Drug Administration has deemed ZnO NPs generally regarded as safe (GRAS) [132].

Numerous studies have confirmed that ZnO can be used as a scaffold for bone tissue engineering [133, 134] and that it has good antimicrobial capacity to promote infected bone regeneration [135]. It can also be used to fabricate prostheses and coatings and has good corrosion resistance, cytocompatibility, and antimicrobial capacity for potential biodegradable bone implant applications [136]. Several studies have also demonstrated that ZnO can promote the osteogenesis of mouse bone marrow mesenchymal stem cells (mBMSCs) [137, 138], thus providing a theoretical basis for the use of zinc oxide in orthopedics.

The robust biocompatibility, antibacterial properties, imaging capabilities, and other advantages of various metal semiconductor materials have been demonstrated upon their

introduction for biological applications. However, a common drawback of many metal semiconductors is their cytotoxicity. This is due to the release of metal ions within biological environments, as certain ions can be extremely harmful to cells. It is essential to tackle the challenges of minimizing the release of metal ions and lowering their cytotoxicity in future design, manufacturing, and application processes are critical challenges that need to be addressed.

Orthopedic applications of metal semiconductor materials

In modern orthopedics, the application of semiconductor materials is gradually becoming a highly anticipated direction of basic research, preclinical development, and clinical practice. Owing to their unique electrical, optical, ultrasonic, and thermal response properties [139–142], metal semiconductor materials provide new avenues for bone defect repair and regeneration. Metal semiconductor materials can simulate the local complex bioelectric environment and dynamically promote the repair of pathological bone defects in a controllable manner [143, 144]. These characteristics endow metal semiconductor materials with immense potential in the design and application of orthopedic implants, especially in addressing challenges with bone repair in pathological microenvironments such as those of infections, tumors, and inflammation (Table 2).

Metal semiconductor scaffolds

A promising approach for repairing huge bone defects is tissue engineering, which relies heavily on scaffolds and growth factors—two essential elements that significantly impact the effectiveness of bone regeneration. Scaffolds for bone regeneration have been engineered with bioactive features and harbor various growth factors, seed cells, medications, or genes in order that accelerate angiogenesis and osteogenesis [187]. Numerous research teams have shown great interest in ceramic nanomaterials derived from perovskite-like oxides due to their potential uses in biomedical fields [188]. Barium titanate (BaTiO_3), recognized for its significant dielectric constant and remarkable ferroelectric characteristics, ranks among the most extensively researched perovskite materials. The material's biocompatibility, piezoelectric characteristics, and nonlinear optical properties present promising opportunities for investigation in diverse biomedical applications. Notably, recent reports suggest that BaTiO_3 NPs could be used in a wide range of biomedical applications, including nonlinear imaging, drug delivery, tissue engineering, and biostimulation [146–149]. Furthermore, a scaffold made of piezoelectric $\text{BaTiO}_3/\text{Ti}_6\text{Al}_4\text{V}$ (BT/Ti) displayed excellent biocompatibility along with piezoelectric characteristics, facilitating the polarization of M2 macrophages and osteogenesis *in vitro*. In an *in vivo* setting, this scaffold enhanced the quantity of M2 macrophages and stimulated bone regeneration, particularly when subjected to low-intensity pulsed ultrasound stimulation. Mechanistic studies suggest that the BT/Ti scaffold reduces inflammation and increases energy metabolism in macrophages. This approach could improve bone healing by modulating the immune environment [150]. A recent investigation conducted by Bhaskar and colleagues revealed that the interaction between the electroactive characteristics of biomaterials and ES can promote the proliferation, migration, and maturation of osteoprogenitor cells (specifically, preosteoblasts such as MC3T3-E1) on composites based on electroactive poly(vinylidene difluoride)

Table 2. Orthopedic applications of metal semiconductor materials

Orthopedic applications of metal semiconductor materials		
Material	Form	Biological functions
Metal semiconductor scaffolds PLGA/HA/PLA-AP/phBMP-4		Harbors multiple growth factors, medications, or genes that accelerate angiogenesis and osteogenesis; enhances cell proliferation, osteogenic differentiation; promotes bone healing [145]
Barium titanate (BaTiO ₃)		A high dielectric constant coupled with outstanding ferroelectric characteristics; nonlinear imaging, drug transport, tissue engineering, and biostimulation applications [146–149]
BaTiO ₃ /Ti ₆ Al ₄ V		Piezoelectricity and biocompatibility; suppresses inflammatory signaling and activation of OXPHOS in macrophages [150]
PVDF-based BaTiO ₃ -MWCNT		Enhances adhesion, proliferation, and differentiation; promotes osteogenesis; synergistic interactions [44]
Ti/HAp/OHA-Apt		Sustains Apt19s release; improves MSC migration; promotes MSC adhesion and osteogenic differentiation; stimulates bone formation, recruitment of MSC at the implant interface [151]
IONPs		Enhances scaffold functions, stem cell differentiation, and drug tracking in bone tissue engineering applications; influences gene expression for biomineralization; increases stem cell attachment and bone differentiation; indicates the drug location to monitor bone repair processes [152]
PLLA nanofibers		Promotes chondrogenesis and cartilage regeneration; applications in osteoarthritis treatment and the regeneration of other injured tissues [153]
Surface modifications of metal semiconductor implants		
Titanium alloys		Robust mechanical strength, resistance to corrosion, excellent conductivity, and bioinert characteristics [154–156]
Si ₃ N ₄ ceramic coating on CpTi		Antibacterial and osteogenic properties; resists <i>Staphylococcus epidermidis</i> adhesion; application to Ti-alloy acetabular shells [157]
Mg alloys		Production of bone pins, screws, surgical clips, wires, sutures, and coronary stents [158–160]
Mg substrates		Alloying with elements (Ca, Zn, Cu, and Mg) to reduce Mg alloy corrosion, expedites bone fracture healing, and increases direct tissue attachment and osteoconduction [161]
Mg-Zn-Ca coated with nanohydroxyapatite and silk fibroin		Enhanced coating adhesion and corrosion resistance; good biocompatibility, promotes cell functions and bone formation; lays a foundation for the development of osteogenic implant coatings [162]
H-Si@HA		Leverages pH-responsive properties to stabilize the structure in acidic environments; mimics enzymatic activities to deplete reactive oxygen species; induces cellular autophagy to protect cells; boosts the expression of genes related to osteogenesis in bone marrow-derived stem cells (BMSCs) and SOD1 levels in osteoprogenitor cells, thereby facilitating fracture healing; modulates core mRNAs linked to osteogenesis and bone development through the regulation of autophagy [163]
PEEK-PDA-Mn		Improves cell growth and osteogenic properties for bone regeneration; increases surface roughness and hydrophilicity; improves cytocompatibility and cell spreading; increases gene expression and mineralization; enhances tissue regeneration with the modified implant; superior biocompatibility [164]
Bone-targeting metal semiconductors		
SPFeNOC		Improves the identification and management of bone metastases; targets cancerous cells and osteoclasts; efficiently kills cancer cells; high antitumor efficacy; effectively detects and eliminates metastatic bone tumors; NIR imaging, SDT, CDT, and MRI applications [165]
Bone-targeting polymer vesicles		Combines the evaluation and therapy of malignant bone tumors; provides enhanced SPECT/CT imaging contrast along with effective drug delivery; dynamically monitors tumor distribution; significantly reduces tumor size [166]
Au NR@CuS		Loaded with methotrexate for RA treatment; decorated with hyaluronic acid and vasoactive intestinal peptide for precisely targeted photothermal and pH-responsive drug therapy; combined photothermal therapy, photodynamic therapy, and chemotherapy for rheumatoid arthritis (RA) by eliminating synovial hyperplasia [167]
Multifunctional metal semiconductors		
<i>Antibacterial</i> PEO-treated Mg alloys with Cur-Fe nanoflowers		Enhanced antibacterial/tumor and bone regeneration properties; promotes protein adsorption and cell proliferation; excellent biocompatibility and corrosion resistance; strong antibacterial effects and synergistic antitumor effects [168]

(Continued)

Table 2. Continued

Orthopedic applications of metal semiconductor materials			
Material	Form	Biological functions	Ref(s)
Maxillofacial silicone with barium titanate D6 UBI ₂₉₋₄₁ peptides		Enhanced antibacterial properties against <i>S. epidermidis</i> biofilm adhesion Nanoparticles that are dual-targeted to bone and bacteria, designed for controlled release of vancomycin, exhibit remarkable antibacterial effectiveness and biocompatibility <i>in vitro</i> ; early infection treatment without cytotoxicity in a rat model	[169] [170]
AntagomiR-138-activated CHA		Reduced bacterial attachment; induced hMSCs to heal rat femur defects; hMSC-mediated vasculogenesis <i>in vivo</i>	[171]
Lactide-co-glycolide encapsulated antibiotic–biphasic calcium phosphate		Superior to other modalities in terms of quicker control of sepsis, success rate and regeneration	[172]
<i>Antitumor</i> TC@BTO		Excellent photothermal conversion and ROS generation for tumor ferroptosis; enhanced osteogenic differentiation; activates the Wnt pathway	[173]
Natural phenolic acid planted nanohybrids		Desirable properties; precise nanostructures suppress osteosarcoma growth and promote osteogenic differentiation	[174]
Ni-doped oxide semiconductor film		Stable; antitumor effects; allows cell differentiation; enhanced angiogenesis and osteointegration; offers a strategy for tumor-related therapy	[175]
<i>Biomedical imaging</i> AuNC@BSA-Gd-I SCU-15 Bone SPECT with SwiftScan		Cartilage detection; multimodal assessment of damaged cartilage Enhanced photocurrent response and detection sensitivity; potential for imaging applications Use of a CZT detector in prostate cancer patients; reliable images; improved image values; reduced inspection duration	[176] [177] [178]
<i>Biomedical detection</i> QDs capped with chitosan and OPS Oncomine Myeloid Assay GX panel		Biocompatible with different human cell sources; promotes intracellular trafficking; increases ECM mineralization; reliable bioprobe; future applications in bioimaging and biomedical implants Tested on synthetic DNA/RNA and patient specimens; 100% control variant identification rate and 80% detection rate; rapid detection and accurate diagnosis of myeloid neoplasms	[179] [180]
Metal semiconductor electroactive biomaterials <i>Piezoelectric biomaterials</i> PLLA/CMBT		Enhanced osteogenic activity; improved properties postpolarization; biodegradable; strong antibacterial and anti-inflammatory activities	[181]
Gel-PD-CMBT		Enhanced biological responses; mechanical stability; space for cellular ingrowth (porous structure); promotes osteogenic differentiation and new bone formation	[182]
PVDF with CNTs-GO PVDF with BaTiO ₃ polydopamine		Improved voltage generation and cell activity; potential for osteogenic stimulation Improved dispersion; increased piezoelectric output voltage; enhanced attachment, proliferation, and differentiation; enhanced strengthened mechanical characteristics (rigid particle strengthening, better interfacial adhesion)	[37] [21]
<i>Electroconductive biomaterials</i> Steel/Ti/Mg alloys		Suitable for orthopedic implants (especially in load-bearing bone repair); promotes cell–substrate interactions, communication, and intercellular signaling	[183, 184]
Gold-based micro-/nanomaterials		Improved conductivity, stiffness, flexibility, and biocompatibility; enhanced properties to enable drug loading and vascularization (new porous designs); composite scaffolds for bone regeneration (surface modifications to enable drug loading)	[185]
Nanomaterials (Ag/B/Cu/Mg/MoS ₂ /Pt/Sr/Ti/Zn)		Bone repair, tissue engineering	[186]

(PVDF). Barium titanate (BT; 30 wt.%) and multiwalled carbon nanotubes (MWCNTs; 3 wt.%) were incorporated into PVDF through a melt mixing process, and the ensuing biophysical stimulation studies showed that the composite (designated PVDF/30BT/3MWCNT) significantly enhances the adhesion and proliferation of MC3T3-E1 cells in non-osteogenic conditions, particularly when subjected to ES. According to the results of this investigation, this approach is a promising bioengineering strategy for bone tissue engineering [44] (Figure 3a–c).

The above studies confirm that BaTiO₃ scaffolds, owing to their piezoelectric properties, can generate electrical signals under mechanical pressure, thus exerting multiple biological functions, including facilitating the repair and regeneration of bones, enhancing the adhesion and proliferation of osteoblasts, and regulating the immune microenvironment.

In addition, a variety of metal semiconductor scaffolds are still used in orthopedic applications. Recently, Cui *et al.* developed a smart scaffold using poly(lactic-co-glycolic acid)/hydroxyapatite (PLGA/HA)/poly(L-lactic acid)-block-aniline pentamer-block-poly(L-lactic acid) (PLA-AP)/plasmid vector (pSTAR) human bone morphogenetic protein-4 (hBMP-4) for bone tissue engineering, which enabled the controlled release of hBMP-4 and Dox-regulated gene expression under electrical stimulation, thereby enhancing cell proliferation and osteogenic differentiation and promoting bone healing in a rabbit bone defect model [145] (Figure 3d). To enhance osseointegration, Wei *et al.* functionalized titanium implants with an HA coating modified with DNA aptamer 19s (Apt19s)-grafted oxidized hyaluronic acid (OHA). The Ti/HAp/OHA-Apt substrate exhibited prolonged release of Apt19s, enhanced migration of MSCs, and facilitated both MSC adhesion and osteogenic differentiation. *In vivo* tests confirmed its ability to stimulate new bone formation and MSC recruitment at the implant interface, thus providing a new approach for developing functional Ti-based materials for bone defect repair [151] (Figure 4a–b). Experiments by Lu *et al.* revealed the roles of iron oxide nanoparticles (IONPs) in improving scaffold performance, promoting stem cell differentiation, and facilitating drug monitoring in the field of bone tissue engineering. IONPs modulate gene expression for biomineralization, form composite scaffolds to increase stem cell attachment and bone differentiation, and can be used to locate drugs for monitoring bone repair processes [152] (Figure 4c–e). A biodegradable piezoelectric PLLA nanofiber scaffold promoted chondrogenesis and cartilage regeneration. Compared with control rabbits, rabbits with defects exhibited better healing with exercise. This approach of combining scaffolds and mechanical activation may be useful for osteoarthritis treatment and applicable to the regeneration of other injured tissues [153].

Based on both *in vitro* and *in vivo* research findings, there are significant immunomodulatory and angiogenic properties, alongside a limited capacity for osteoclast formation and enhanced osteogenic potential, such as the ability to regulate osteoimmunity, have profound effects that improve regeneration, which has positive implications for large defect repair.

Metal semiconductor surface-modified implants

Total hip arthroplasty and total knee arthroplasty are common orthopedic procedures [189], and the aseptic loosening of the prosthesis [190, 191] is a major cause of joint replacement failure. Titanium alloys are used in tissue engineering because

of their high mechanical strength, corrosion resistance, bioinert properties, and high conductivity [154]. Traditionally, titanium oxide has been used as a nanometer-scale passivation layer on Ti-alloy surfaces for the sake of the improvement of osteoblast adhesion, an essential factor for the reliable secure integration of implants with living bone. However, when fibrosis occurs at the bone–implant interface instead of during osseointegration, micromotion is catastrophic, which ultimately causes the release of very harmful metal ions and ache. Moreover, failed bone ingrowth into porous Ti alloys and periprosthetic infection can also lead to joint replacement failure and the need for revision [154–156]. Thus, enhancing the osteointegration potential of porous titanium alloys and increasing their resistance to bacterial adhesion are essential for decreasing the failure rates of cementless total joint replacements. These enhancements are especially important in the context of current surgical goals, which include swift recovery, rapid restoration of mobility, and performance metrics that impact surgeon and institutional reimbursement. A dense Si₃N₄ ceramic coating, measuring $15 \pm 5 \mu\text{m}$ in thickness, was created on a commercially pure titanium (CpTi) substrate using a 3D additive manufacturing technique. The coating endowed the substrate with antibacterial and osteogenic properties and was applied to Ti-alloy acetabular shells [157]. In another study, nanoparticle barium titanate (nanoBaTiO₃) polycaprolactone (PCL) was added as a coating to a Ti₁₃Nb₁₃Zr alloy, and the coated implant material significantly enhanced bone regeneration and expedited healing [192]. The addition of a metal semiconductor coating onto the surface of a Ti alloy prosthesis can significantly enhance the prosthesis's resistance to infection and promote bone healing, which considerably aids in preventing postoperative complications after arthroplasty.

Of the absorbable metals, magnesium (Mg) along with its alloys is considered one of the most promising alternatives. They have been utilized in the production of bone pins, screws, surgical clips, wires, sutures, and coronary stents [158–160]. However, a significant challenge in the application of Mg and its alloys is their relatively high degradation rates [193]. Thus, a bioactive coating designed to reduce magnesium alloy corrosion and expedite bone fracture healing was proposed. Such coatings aim to increase direct tissue attachment and osteoconduction. Bioactive agents with high potential for use in this system include zoledronate, COL-I, BMP-2, hydroxyapatite, simvastatin, and strontium. Additionally, magnesium substrates can be rendered bioactive by alloying with elements such as calcium, zinc, copper, and manganese, which are known to stimulate bone regeneration [161]. Fang *et al.* presented a biomimetic coating of nanohydroxyapatite and silk fibroin on a Mg–Zn–Ca alloy intended for use in bone implants. Layer-by-layer application via ultrasonic spray and plasma activation enhanced coating adhesion and improved corrosion resistance. The optimized nHA/SF composite coating promoted cell function and bone formation, thus demonstrating good biocompatibility and laying a foundation for the development of osteogenic implant coatings [162] (Figure 5a–f). Yuan *et al.* developed an H-silicene nanosheet (H-Si) anchored on hydroxyapatite (HA)-coated metal implants to form an H-Si@HA composite coating. This coating leverages the pH-responsive properties to stabilize the structure in acidic environments, mimics enzymatic activities to deplete reactive oxygen species, and induces cellular autophagy to protect cells. The release

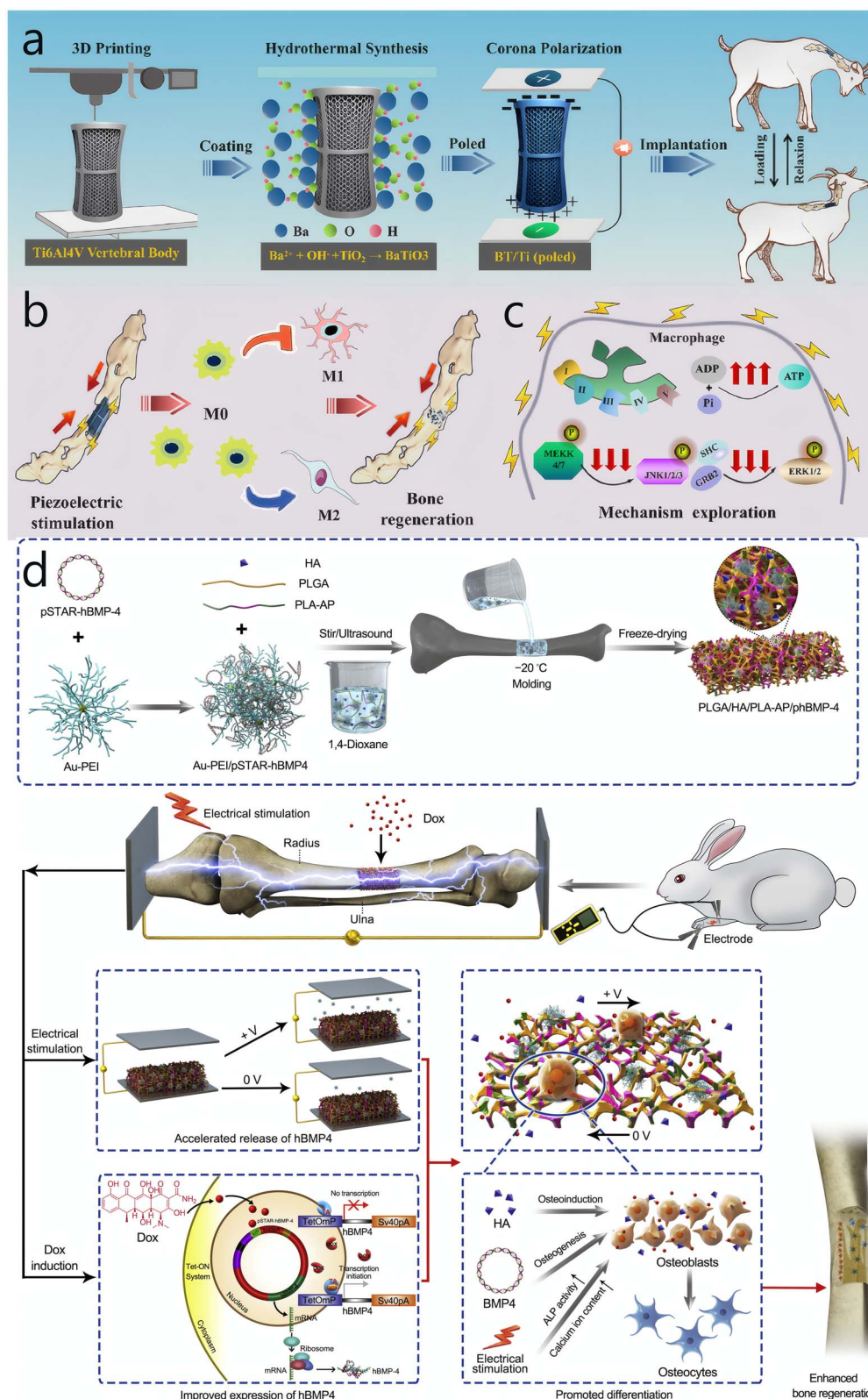


Figure 3. Metal semiconductor scaffolds can promote bone repair. **(a)** The creation of porous Ti6Al4V scaffolds that are coated with piezoelectric barium titanate and their subsequent implantation in a sheep model of en bloc cervical spondylectomy. **(b)** The use of poled piezoelectric BT/Ti artificial vertebral bodies facilitated the polarization of M2 macrophages and contributed to the bone healing process. **(c)** Stimulation from piezoelectric properties inhibited the MAPK/JNK signaling pathway and enhanced oxidative phosphorylation (OXPHOS) in macrophages. Adapted from [150] with permission. Copyright © 2023, *Biomaterials*. **(d)** Development of an intelligent electroactive scaffold for tissue engineering that can regulate the release and expression of hBMP-4, facilitating effective bone repair. Adapted from [145] with permission. Copyright © 2020, *Biomaterials*

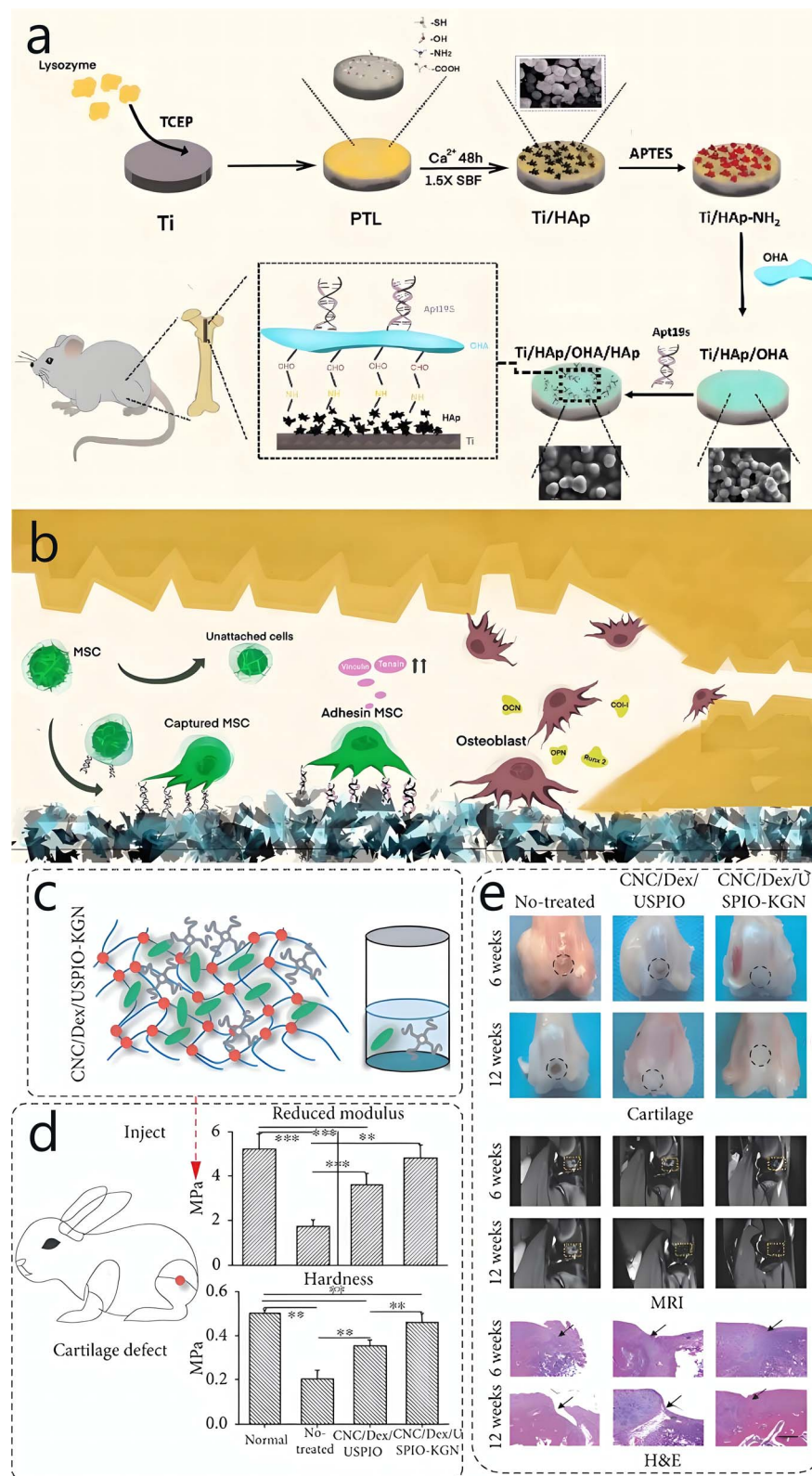


Figure 4. Incorporating aptamers and nanoparticles into metal semiconductor scaffolds significantly enhances their capacity to repair bone tissue. **(a–b)** Development of titanium-based materials functionalized with aptamers. The Apt19s released notably improved the migration of bone marrow-derived mesenchymal stem cells (MSCs) and facilitated MSC recruitment at the interface surrounding the implant, leading to the formation of new bone. Adapted from [151] with permission. Copyright © 2022, *ACS Applied Materials & Interfaces*. **(c–e)** Synthesis of CNC/Dex/USPIO-KGN and its physicochemical characteristics were examined in rabbit cartilage through *in vitro* methods. Histological analysis using H&E staining revealed that the neocartilage was seamlessly integrated with surrounding normal cartilage. Adapted from [152] with permission. Copyright © 2021, *Science Translational Medicine*

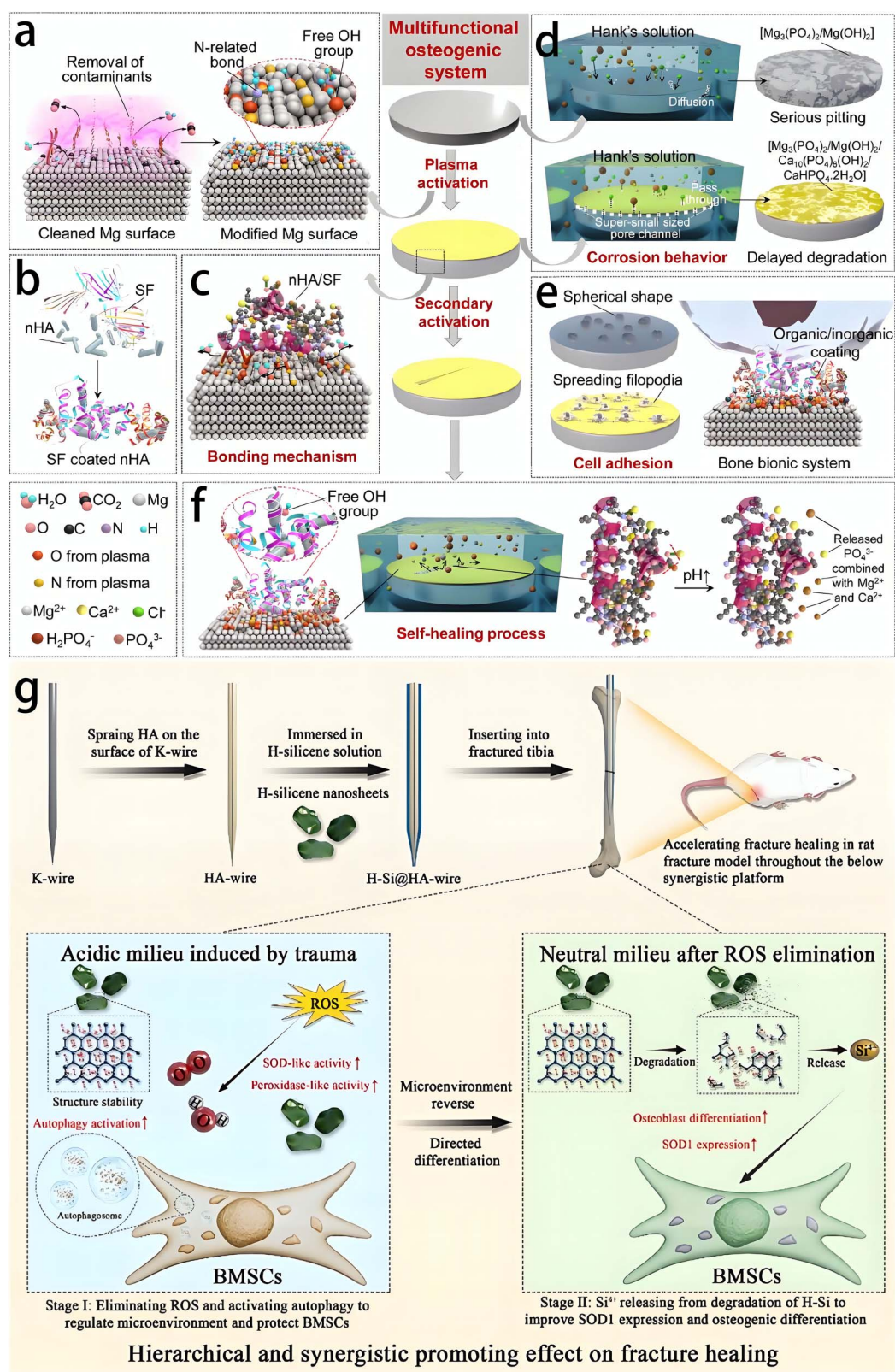


Figure 5. Metal semiconductor coatings effectively reduce oxidation and corrosion while promoting bone tissue repair. Diagrams illustrating the (a) interaction between nHA and SF, (b) influence of hybrid oxygen/nitrogen plasma activation, (c) bonding mechanism involving the coating and the substrate, (d) models of corrosion, (e) cellular behaviors, and (f) self-repair processes. Adapted from [162] with permission. Copyright © 2021, *Journal of Magnesium and Alloys*. (g) Illustration of the H-Si@HA composite coating applied to a metal implant, along with the cooperative processes involved in the suppression of reactive oxygen species (ROS), activation of autophagy, and promotion of fracture healing. Adapted from [163] with permission. Copyright © 2023, *Nano Today*

of Si^{4+} ions from degrading H-Si under neutral conditions enhances the expression of genes associated with osteogenesis in BMSCs and also increases the expression of superoxide dismutase (SOD) 1 in osteoprogenitor cells, thereby promoting fracture healing. Transcriptome sequencing revealed the ability of H-Si to modulate core mRNAs associated with osteogenesis and bone formation by regulating autophagy [163] (Figure 5g). Wang obtained similar results. A coating composed of a bioactive chemical conversion Mg–phenolic network complex (eEGCG) was gradually applied to a Mg-2Zn magnesium alloy, integrating epigallocatechin-3-gallate (EGCG) along with external Mg^{2+} .

The corrosion resistance was markedly improved on the Mg-2Zn alloy by this eEGCG coating, which also exhibited minimal hemolytic activity, sustained antioxidant properties, and moderate wettability, thus creating a stable biological environment that fostered the attachment and proliferation of rat bone marrow stromal cells (rBMSCs). Furthermore, assessments using microcomputed tomography (micro-CT), histological analysis, and elemental distribution at the interface indicated that eEGCG effectively diminished the deterioration of the Mg alloy and promoted the formation of bone tissue. These findings show that the proposed coating is a potential bioactive coating based on Mg–phenolic networks for use in biodegradable orthopedic implants [194].

In addition to Ti and Mg alloys, polyetheretherketone (PEEK) has been used extensively in biomedical engineering applications, and the ability to promote cell growth and significant osteogenic properties, consequently stimulating bone regeneration, are highly desirable for PEEK implants [195]. A PEEK implant modified with manganese (Mn) (referred to as PEEK-PDA-Mn) was created through a chemical treatment involving polydopamine (PDA). The immobilization of Mn on the PEEK surface was achieved effectively, leading to a notable enhancement in both surface roughness and hydrophilicity following the modification. When PEEK-PDA-Mn was immersed in PBS, it released Mn^{2+} . Thus, simple immersion modified the PEEK surface, thereby resulting in a modified PEEK with outstanding biocompatibility and enhanced bone tissue regeneration ability for application as an orthopedic implant in the clinic [164]. Additionally, Li *et al.* reported similar results. A hydrogel coating composed of a metal–phenolic network was created by spin-coating a blend of gelatin, iron ions, and polyphenol monomers featuring a phthalazinone structure (THPZB) onto the surface of poly(aryl ether nitrile ketone) (PPENK) based on a cyclolactam network (G/THPZB/Fe/PPENK). The residual polyphenols on the surface not only confer good adhesion ability but also promote angiogenesis and healing *in vitro* [196]. Metallic semiconductor coatings play significant roles in the fields of biomedical engineering and medical device manufacturing, particularly for improving the performance of implant materials. These coatings enhance biocompatibility by reducing inflammatory responses and foreign body reactions, a factor that is essential for the effective *in situ* integration of implants with bone tissue. These coatings enhance osseointegration by supporting the adhesion, propagation, and osteogenic differentiation of bone cells, which in turn speeds up the attachment of the implant to the adjacent bone. The antimicrobial properties of certain metallic semiconductor materials can decrease the likelihood of infections associated with implants, and their enhanced mechanical performance, including wear resistance and corrosion resistance, can extend the lifespan

of the implant. Additionally, these coatings can serve as drug delivery vehicles to enable the controlled release of therapeutic agents such as antibiotics or antitumor drugs [197], which can be beneficial for local treatment and to prevent infection.

Bone-targeting metal semiconductors

Through chemical modifications, it is possible to equip nanoparticles with the capability to specifically target bone tissue. These specialized, bone-targeting nanoparticles have great potential for diagnosing and treating bone diseases [198–200]. Generally, the surfaces of nanoparticles designed for bone targeting are made up of ligands that guide these nanomaterials to the bone tissue. Commonly used bone-targeting ligands are bisphosphonates, tetracyclines, polypeptides, and small molecule heterocycles [201–203], among which bisphosphonates are the most widely used. Bisphosphonates are effective for treating conditions such as osteitis deformans and osteoporosis but might cause side effects such as jaw necrosis and femur fractures after long-term use [204]. Peptides offer better biocompatibility but weaker bone affinity [203, 205]. In recent years, several new metal semiconductor bone-targeting materials have emerged, thus opening new directions for innovative approaches in diagnosing and treating bone tumors as well as other orthopedic diseases.

A new semiconducting polymer nanocomposite inspired by biomimetic principles (SPFeNOC) has recently been developed to simultaneously target osteoclasts and cancer cells, enhancing the diagnosis and treatment of bone metastases. This nanocomposite consists of a core that contains a semiconducting polymer and iron oxide (Fe_3O_4) nanoparticles enveloped by a hybrid membrane that mimics the surfaces of cancer cells and osteoclasts. This membrane allows for homologous targeting, thereby leading to the increased accumulation of nanoparticles at metastatic tumor sites. The synergistic effects of sonodynamic therapy (SDT) and chemodynamic therapy (CDT) result in the simultaneous destruction of both cancer cells and osteoclasts, which disrupts the cycle of bone metastasis and achieves significant antitumor effects [165] (Figure 6a–b). In the research of Zhou, a novel bone-targeting polymer vesicle that serves as an integrated diagnostic and therapeutic platform for malignant bone tumors was developed. This vesicle, known for its enhanced imaging capabilities in single-photon emission computed tomography/computed tomography (SPECT/CT) and its efficient delivery of antitumor medications, can spontaneously assemble in water from the copolymer poly(ϵ -caprolactone)67-b-poly[(L-glutamic acid)6-stat-(L-glutamic acid-alendronic acid)16] (PCL67-b-P[Glu6-stat-(Glu-ADA)16]) without requiring a cosolvent. By utilizing SPECT/CT, the authors were able to dynamically monitor drug distribution within a bone tumor rabbit model, and a significant reduction in tumor volume from $>2.0 \text{ cm}^3$ to $<0.6 \text{ cm}^3$ was observed within 11 days. Pathological assessments revealed that the tumor cells underwent substantial necrosis and apoptosis. Overall, this bone-targeting polymer vesicle offers a promising new approach for the real-time diagnosis and treatment of malignant bone tumors [166] (Figure 6c).

Materials aimed at targeting bone can be utilized for diagnosing and treating not just bone tumors, but also a range of prevalent orthopedic conditions. Huang *et al.* developed

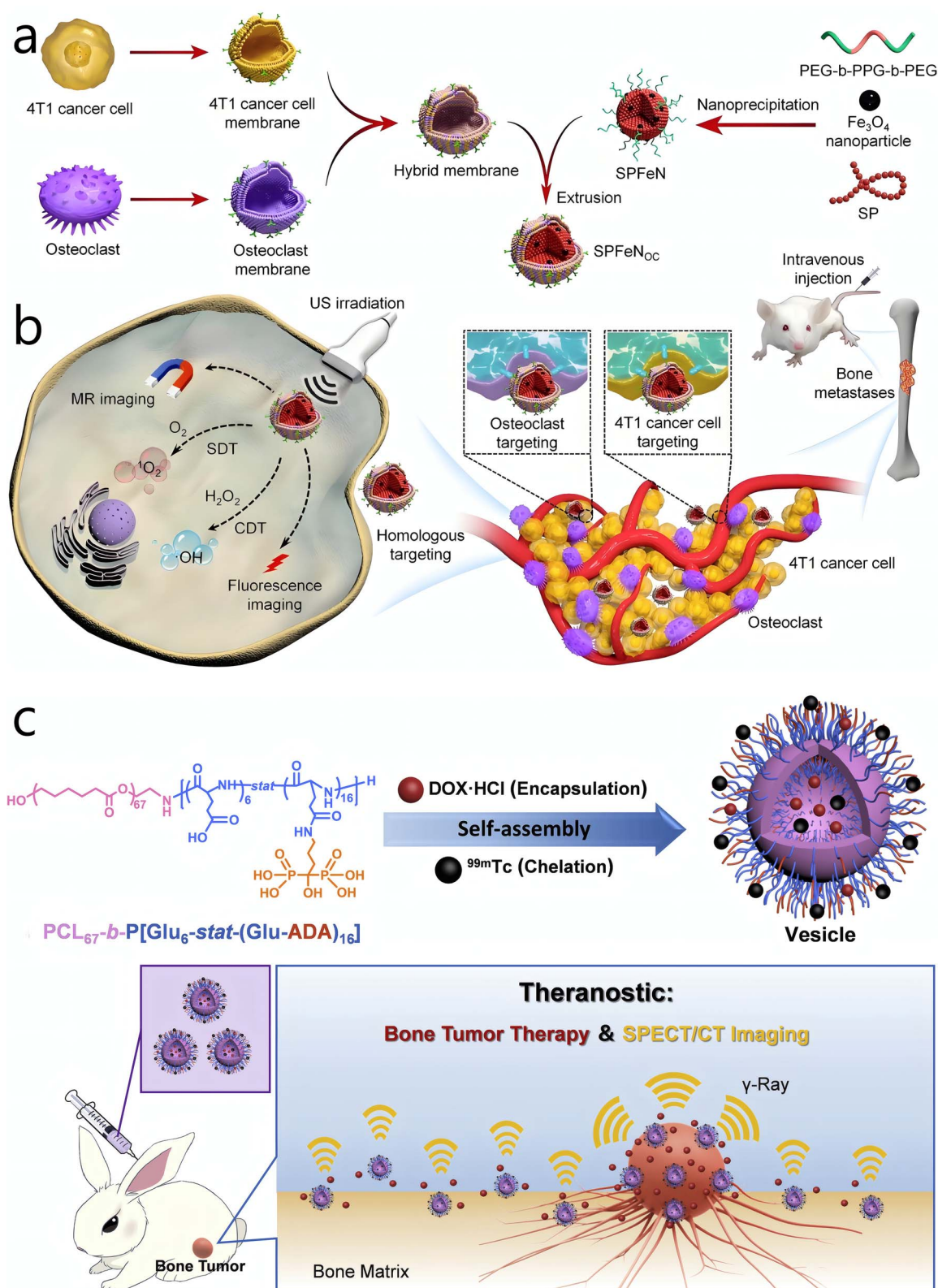


Figure 6. Bone-targeting metal semiconductor nanocomposites can assist in the diagnosis and treatment of bone tumors by exerting highly efficient tumoricidal effects. **(a-b)** A semiconducting polymer nanocomposite with dual-targeting capabilities was created to enhance theranostics for bone metastases. This innovative nanocomposite facilitates efficient targeting of tumors through its simultaneous targeting of cancer cells and osteoclasts, allowing for improved diagnosis of bone metastasis and effective inhibition of tumor growth. It achieves this by enabling dual-modal imaging at the sites of bone metastasis, in addition to providing a combined therapeutic approach against both osteoclasts and cancer cells. Adapted from [165] with permission. Copyright © 2023, *Angewandte Chemie International Edition*. **(c)** A diagram illustrating polymer vesicles designed to target bone for the concurrent diagnosis and treatment of malignant bone tumors. The ADA unit within the coronas of PCL₆₇-b-P[Glu₆-stat-(Glu-ADA)₁₆] vesicles exhibits a strong affinity for bone tissue by chelating the divalent calcium ions (Ca²⁺), particularly in bone tumors that have elevated calcium levels. The ^{99m}Tc-chelated ADA unit is suitable for SPECT imaging targeting bone tumors. Additionally, the vesicles that encapsulate the chemotherapeutic agent DOX can effectively target bone tumors for therapeutic purposes. Consequently, ^{99m}Tc-chelated DOX-loaded vesicles serve as optimal platforms for theranostics in malignant bone tumors. Adapted from [166] with permission. Copyright © 2020, *Biomaterials*

a composite consisting of a copper sulfide shell shaped like an octahedron surrounding a gold nanorod core (Au NR@CuS). This design is intended for integrated therapies that combine photothermal therapy, photodynamic therapy, and chemotherapy for rheumatoid arthritis (RA) by reducing synovial hyperplasia. They encapsulated methotrexate within the Au NR@CuS nanoparticles for RA treatment and applied coatings of hyaluronic acid and vasoactive intestinal peptide to enhance the accuracy of photothermal and pH-responsive drug delivery. Furthermore, methotrexate was incorporated into the Au NR@CuS nanoparticles, and VIP was added to the surface of these nanoparticles to boost their capability for targeted drug delivery [206].

Multifunctional metal semiconductors

Traditional biomaterials address bone regeneration unidirectionally by controlling topography and elemental composition [208]. While progress has been made in terms of the biocompatibility and osteoconductivity of these biomaterials, they cannot switch signals upon the application of an external stimulus to combat transitions in the pathological microenvironment or modulate osteogenic differentiation. In contrast, semiconductive biomaterials exhibit crystal structure phonon vibrations, controllable energy band structures, and heterojunction structures to convert light/ultrasound energy into thermal, chemical, or electrical energy [209], thereby enabling dynamic signal conversion for the spatiotemporal modulation of pathological bone defect repair [173, 175]. This has driven multidisciplinary developments. Functional semiconductive biomaterials designed to respond to various stimuli can meet medical device development requirements and improve bioactivities such as osseointegration, diagnosis and treatment of orthopedic diseases (Figure 7a–b), and antibacterial and anti-inflammatory capabilities [210].

Antibacterial effects. Biofilm infections related to implants represent a frequent and intricate issue in orthopedic surgery, diminishing the immune system's ability to eliminate pathogens, as bacteria often adhere to the solid surfaces of these implants. Once a small number of adherent bacteria attach to the implant surface, they can rapidly grow and form a biofilm, which is highly resistant to the immune system and antibiotics, thus suppressing osseointegration and potentially leading to a loose prosthesis, infectious shock, or even death [211]. Although loading antimicrobial drugs on implants can enhance antibacterial performance, there are risks and concerns in practical applications, such as the potential for drug resistance [212, 213]. Materials classified as semiconductors exhibit precisely defined and easily adjustable optical, ultrasonic, and electronic traits, allowing them to effectively react to the spatiotemporal features of diverse microenvironments. Recently, the strategy of combating biofilm without antibiotics, which leverages the responsiveness of semiconductor materials to external fields, has emerged as a significant area of research. Importantly, in the case of infected bone, the combined use of antimicrobial agents and osteogenic strategies can effectively control bacterial growth in the early stage and promote long-term bone regeneration [214].

Du *et al.* conducted a study in which they developed a biodegradable nanoflower coating of curcumin (a herbal remedy) and ferrum (Cur-Fe) on magnesium alloys treated with plasma electrolytic oxidation (PEO), aiming to improve antibacterial and tumor-fighting capabilities as well as to

support bone regeneration. The coating promotes protein adsorption and cell proliferation, with excellent biocompatibility and corrosion resistance because of its unique degradation into FeOOH nanosheets. Under simulated sunlight, the Cur-Fe coating generates ROS and produced strong antibacterial effects, thus demonstrating synergistic antitumor effects under NIR irradiation. Furthermore, the Cur-Fe nanoflower coating demonstrated great osteogenic activity due to its unique micro/nanostructure, surface chemical bonds, and release of Mg and Fe ions, which makes it a promising material for Mg-based implants in bone regeneration applications [168] (Figure 7c). A study indicated that incorporating varying concentrations of barium titanate nanoparticles into maxillofacial silicone significantly enhances its antibacterial properties against *Staphylococcus epidermidis* biofilm adhesion in a concentration-dependent manner, with no chemical interaction observed between the nanoparticles and the silicone matrix, as confirmed by Fourier-transform infrared spectroscopy and scanning electron microscopy analyses [169]. Researchers also developed a novel single-step sol-gel technique for the synthesis of mesoporous bioactive glass (MBG) scaffolds with a composition of SiO₂-CaO-P₂O₅. These scaffolds are enriched with silver nanoparticles (AgNPs) and are fabricated using rapid prototyping (RP) technology. With the aid of computer-aided design, it enables the creation of structures that feature extensive microporosity. The one-step sol-gel method promotes the transformation of silver salts into nanoparticles, which are uniformly dispersed throughout the MBG matrix. Upon implantation, the AgNPs are gradually released as the MBG scaffold degrades, thus effectively inhibiting the accumulation and growth of both gram-positive and gram-negative bacteria [215] (Figure 8a–c). A multifunctional collagen-based scaffold was created by Sadowska *et al.*, incorporating antibiotic-free CuBG nanoparticles alongside antagomiR-138. The CuBG scaffold reduced bacterial attachment, and antagomiR-138 induced hMSCs to heal rat femur defects. Combining these technologies resulted in hMSC-mediated vasculogenesis *in vivo* [171] (Figure 8d–f). In the research of Mistry *et al.*, an antibiotic–biphasic calcium phosphate granule complex additive powder gypsum binder was encapsulated with poly(lactide-co-glycolide), and several postoperative clinical radiological examinations proved the superiority of the resulting material over other modalities in terms of the success rate, sepsis control rate, and bone regeneration [172].

Although a variety of metal semiconductor materials have antimicrobial properties, existing antibiotic therapies still struggle to effectively target bone locations, leading to unsatisfactory therapeutic outcomes. Chemokine receptor D6 antibody blocking peptide (D6) and ubiquitin (29–41) (UBI_{29–41}) peptide were used to develop nanoparticles (NPs) loaded with vancomycin for controlled release that target both bacteria and bone. The mesoporous silica NPs showed high antibacterial efficacy and biocompatibility *in vitro*. In a rat model, infected with methicillin-resistant *Staphylococcus aureus*, the NPs significantly inhibited bacterial growth without causing cytotoxicity, which indicates their potential for early infection treatment. Thus, these molecule-modified NPs could be promising for the treatment of bone infections [170] (Figure 9a).

The presence of bacterial infection leading to biofilm formation during the initial postoperative phase poses a significant risk to osseointegration and a key obstacle in

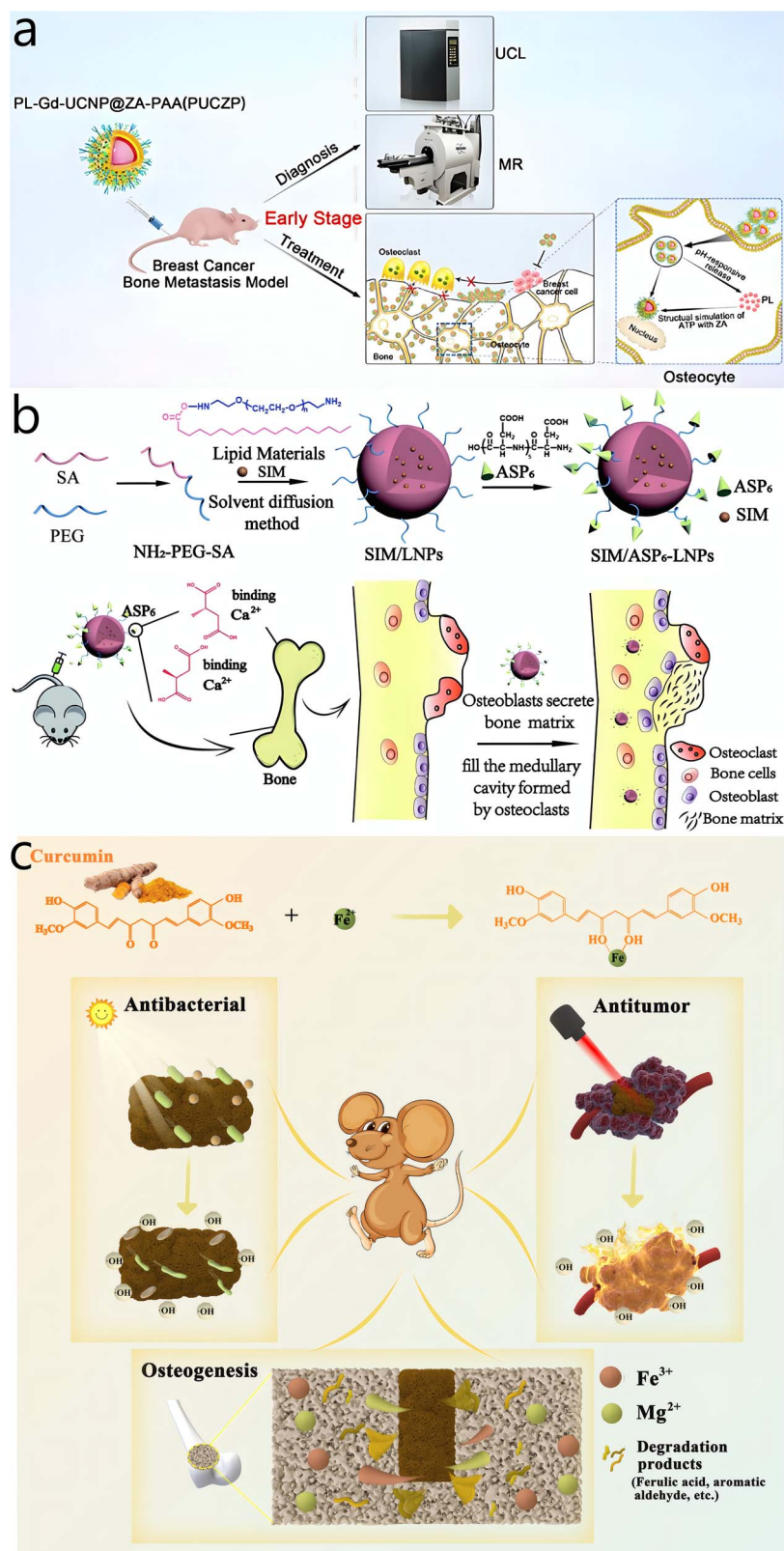


Figure 7. Metal semiconductors enable the diagnosis and treatment of both bone tumors and osteoporosis. **(a)** Diagram of PUCZP utilized for diagnosing and treating breast cancer that has metastasized to the bones. Adapted with permission from [207]. Copyright © 2019, ACS Nano. **(b)** Preparation of SIM/Asp₆-LNPs and its mechanism of osteoporosis treatment. Adapted with permission from [167]. Copyright © 2020 The Royal Society of Chemistry. **(c)** Schematic of the curcumin-Fe nanoflower coating for the treating of osteosarcoma. Adapted from [168] with permission. Copyright © 2024, Journal of Magnesium and Alloys

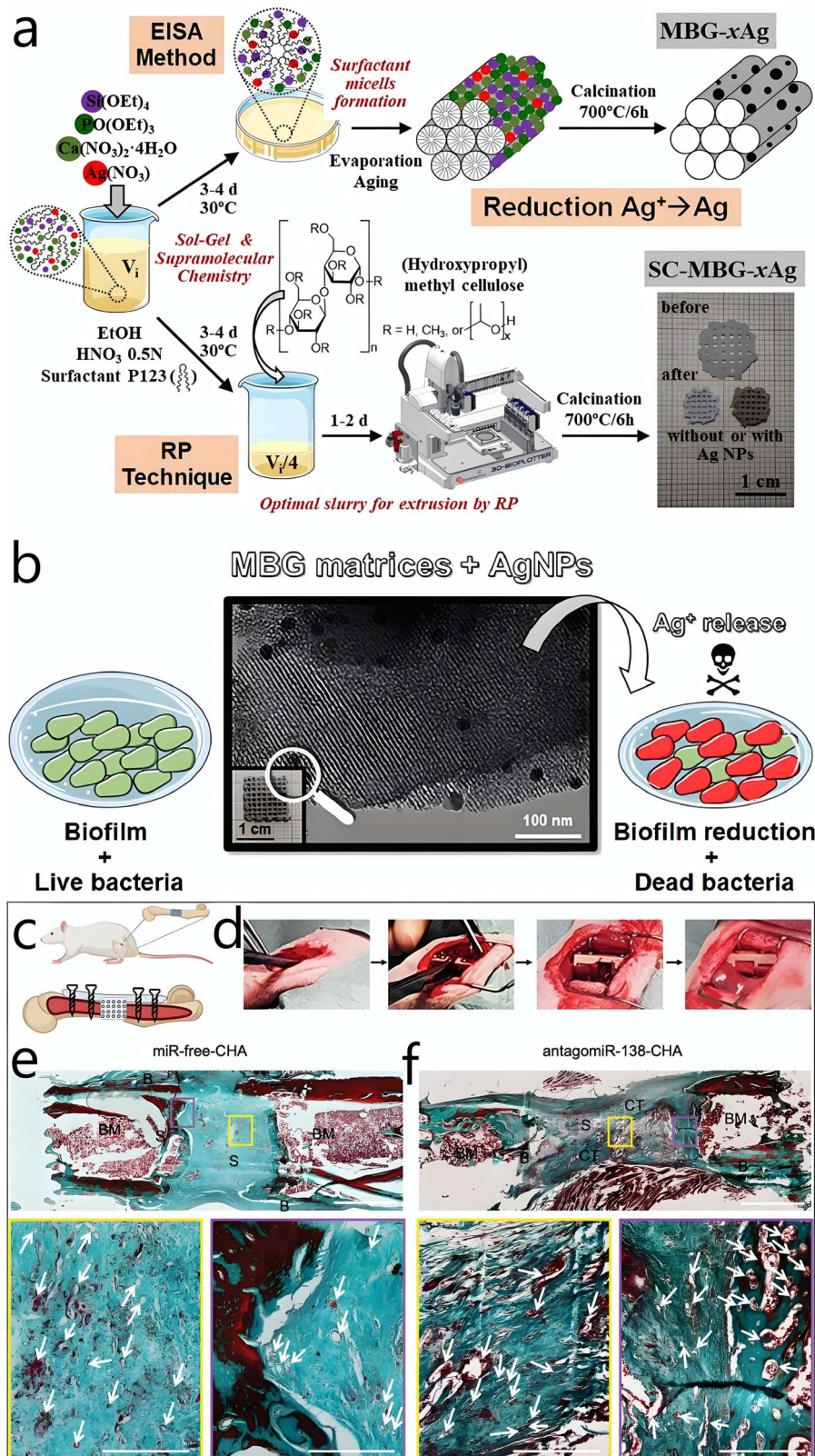


Figure 8. Metal semiconductors exhibit notable antibacterial activity and actively promote angiogenesis. **(a–b)** Diagram illustrating the synthesis methods for MBG-xAg powders and SC-MBG-xAg scaffolds. Adapted from [215] with permission. Copyright © 2023, *Materials Today*. **(c)** Transmission electron microscopy image along with a (insert) photo of an MBG-AgNP scaffold exhibiting antibacterial properties. **(d–f)** An activated CHA scaffold driven by antagomiR-138 enhanced early bone formation and vascularization within just 2 weeks following implantation in a rat femoral defect model that bears weight. Adapted from [171] with permission. Copyright © 2023, *Advanced Materials*

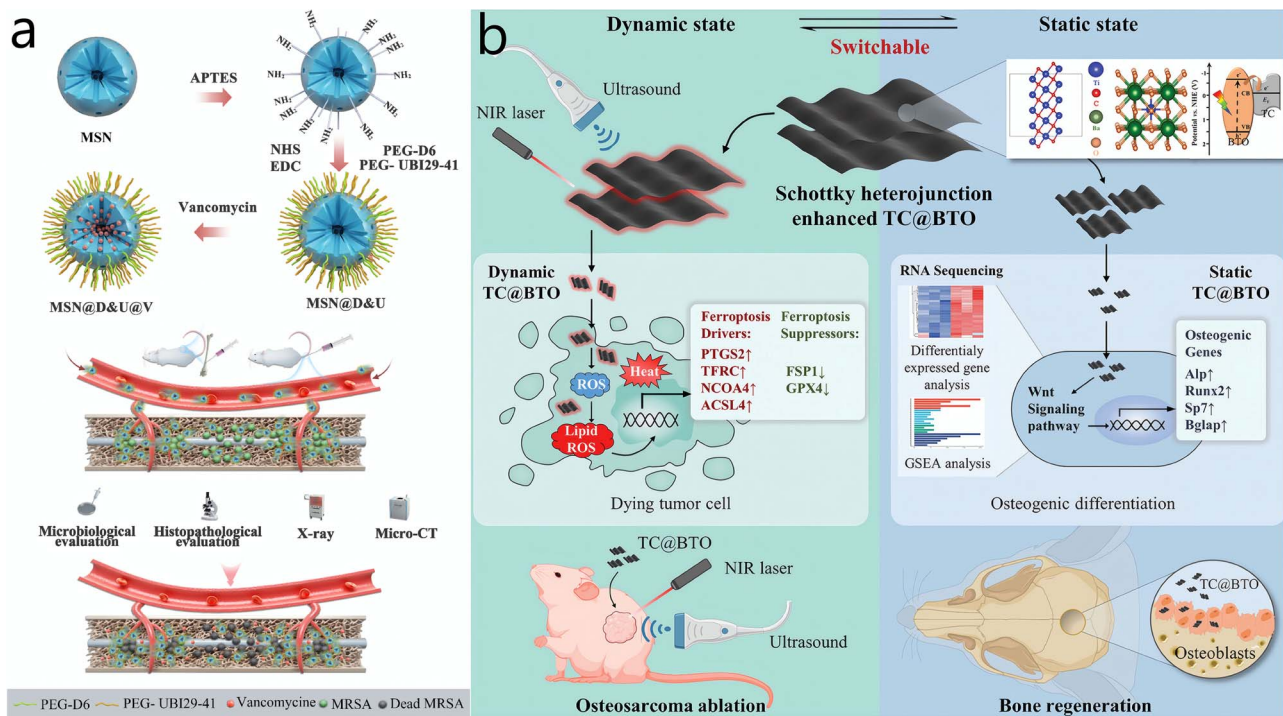


Figure 9. Bone- and bacteria-targeting metal semiconductor materials exhibit robust antimicrobial activity and, upon ultrasound stimulation, generate potent antitumor effects. (a) The creation of mesoporous silica nanoparticles (MSNs) aimed at targeting bone tissue and bacteria, along with an examination of their functions both *in vitro* and *in vivo*. Adapted from [170] with permission. Copyright © 2022, *Bioactive Materials*. (b) TC@BTO enhanced by Schottky heterojunctions for dual, adjustable sonodynamic therapy (SDT) and photothermal therapy (PTT), as well as for bone regeneration. Adapted from [173] with permission. Copyright © 2023, *Advanced Functional Materials*

implant replacement. Fortunately, semiconductor materials exhibit excellent functional responses. Strategies involving coating, drug delivery, and antibiotic bone cement have greatly enhanced antibacterial efficacy and can create a sterile microenvironment conducive to bone formation.

Antibacterial metallic semiconductors often exhibit cytotoxicity, which has been attributed to their inherent chemical properties and the release of toxic metal ions. These materials, while effective in combating bacterial infections, can also harm human cells, thereby leading to issues such as inflammation, tissue damage, and compromised healing processes. Most researchers have balanced antibacterial efficacy and cytotoxicity by employing controlled release systems that allow for the slow release of antibiotics or metal particles, thereby controlling the concentration of antimicrobial agents [216–219]. Lai *et al.* introduced an innovative method that integrates melt electrowriting and solution electrospinning to create a scaffold embedded with hydroxyapatite (HAP), which promotes osteogenesis, and roxithromycin (ROX), which is an antibacterial agent. The addition of HAP enhances the scaffold's capacity to absorb water, consequently improving cell attachment, proliferation, and differentiation. Furthermore, the controlled release of ROX produces antibacterial effects without cytotoxicity [220]. In Wang's research, GO was incorporated into a zwitterionic scaffold, which decreased the release rate and lower the cytotoxic effects of GO. Zwitterions and GO synergistically promoted the proliferation and osteogenic differentiation of rBMSCs both *in vivo* and *in vitro* [221].

Antitumor effects. The most frequently employed method for treating osteosarcoma is surgical resection. Nevertheless, two

significant complications typically emerge: the presence of remaining tumor cells and substantial bone defects. Discovering new strategies for programmatically resolving the above-mentioned issues has become a worldwide challenge [222]. Effective antitumor agents that also possess osteogenic properties are crucial for the comprehensive treatment of osteosarcoma (OS). Nonetheless, the existing clinical strategies for managing OS do not completely eliminate tumors while promoting bone formation at the same time. Recently, Lv *et al.* reported a switchable strategy in which BaTiO_3 (BTO) was integrated with atomically thin Ti_3C_2 (TC) to form TC@BTO. Under irradiation, TC@BTO shows excellent photothermal conversion and ROS generation performance to induce tumor cell ferroptosis. Under static conditions, TC@BTO enhances osteogenic differentiation by activating the Wnt signaling pathway. This work broadens the biomedical potential of Schottky heterojunction-based therapies and provides a comprehensive strategy for OS ablation and bone regeneration [173] (Figure 9b).

The study of photothermal therapy (PTT), which is a noninvasive treatment modality, for tumor suppression and ablation has made great progress in the past two decades [223]. Yao and colleagues created oxide semiconductor film implants infused with Ni nanoparticles, which exhibited a dependable photothermal effect when exposed to near-infrared light. Additionally, the film demonstrated significant antitumor efficacy both *in vitro* and *in vivo*. Furthermore, the nanostructures present on the film facilitated the differentiation of mouse embryo cells (C3H10T1/2) into osteogenic lineages, while the Ni ions released promoted angiogenesis in human umbilical vein endothelial cells. Experiments involving bone implantation also indicated improved osteointegration of the

modified Nitinol implant in live subjects. This novel multifunctional Nitinol bone implant design offers a promising strategy for the treatment of bone tumor-related defects [175]. Yang *et al.* presented an innovative single-step method for the preparation of nanohybrids with natural phenolic acid and gold nanorods. These nanohybrids have specific properties and can generate heat to fight osteosarcoma and aid in bone healing. They are produced by combining chlorogenic acid with gold nanorods, which results in nanostructures that dissolve well in water, are stable, and can control heat production. These nanohybrids kill cancer cells and inhibit tumor growth when heated and stimulate bone cell differentiation when subjected to mild near-infrared light. This approach could help surgeons remove osteosarcomas by targeting leftover cancer cells and promoting bone repair [174] (Figure 10a).

Additionally, many types of PTT agents, such as noble metal nanostructures and Cu-based semiconductor nanoparticles, have been reported [224–226]. Among these agents, noble metal nanostructures have been widely studied and show promising clinical potential because of their biocompatibility and stable photothermal effects [227].

Biomedical imaging. Among well-studied biomaterials, gold nanomaterials not only exhibit outstanding benefits as drug carriers [228], *in vitro* diagnostics, and radiosensitizers [229] but are also widely used as contrast agents for imaging, particularly for tumors [230, 231]. Lu *et al.* developed AuNC@BSA-Gd-I, along with its radiolabeled variant, for the purpose of identifying cartilage lesions, and it can be visualized using CT, MRI, and *in vivo* imaging systems applied for and gamma counting. Owing to its multimodal imaging capabilities, this nanomaterial outperforms other gold nanomaterials in terms of versatility for imaging damaged cartilage across various modalities, which makes it a valuable tool for multimodal cartilage assessment [176] (Figure 10b).

Furthermore, Cheng and colleagues created a semiconductive metal–organic framework (SCU-15) on a millimeter scale and investigated its electrical characteristics. The SCU-15 framework demonstrated an impressive charge-carrier mobility lifetime product ($\mu\tau$) of $2.18 \times 10^{-3} \text{ cm}^2 \text{ V}^{-1}$, along with a carrier diffusion length $>70 \text{ }\mu\text{m}$ when subjected to X-ray excitation, enhancing the photocurrent response and detection sensitivity. A planar 2×3 pixelated detector was constructed from this framework, which demonstrated its potential for imaging applications [177]. Funakoshi *et al.* evaluated bone SPECT with/without SwiftScan by using a cadmium–zinc–telluride (CZT) detector in prostate cancer patients. Their results showed that SwiftScan could improve image values and generate reliable images even with ultrashort acquisition times [178].

Recent developments in cation doping have broadened its possible biological uses. The most recent studies indicate that HA combined with poly(lactide-co-glycolide) acid (PLGA) is a widely favored choice for orthopedic implants, thanks to its favorable biocompatibility and flexibility. However, it is not visible in X-ray images and has limited ability to induce osteogenesis. Copper (Cu) and gadolinium (Gd) were added to HA/PLGA to improve its MRI visibility and osteogenic properties. The Cu/Gd@HA/PLGA composite was found to maintain the HA structure, enhance MRI visibility, and improve cell adhesion and proliferation. It also upregulated COL-1 and BMP-2 expression, thereby enhancing bone recovery in

rats. The study concluded that Cu/Gd@HA/PLGA composites improve MRI capabilities, osteoblast activity, and bone defect healing [232].

Biomedical detection. Numerous research efforts have indicated that metallic semiconductors serve distinct functions in medical diagnostics and gene sequencing. Salgado *et al.* validated the efficacy of hybrid semiconductor bioconjugates, which are composed of quantum dots (QDs) that are coated with chitosan and O-phospho-L-serine (OPS). These functionalized hybrid semiconductor bioconjugates showed satisfactory biocompatibility with various human cells. OPS modification promoted intracellular trafficking and increased ECM mineralization. QDs are reliable bioprobes and have potential for future applications in bioimaging and biomedical implants [179]. In order to tackle the clinical gaps associated with myeloid neoplasms, Sande and colleagues assessed the OncoPrint Myeloid Assay GX panel utilizing the Ion Torrent Genexus platform. The test was compared to two other genomic workflows and showed 100% control variant identification and an 80% detection rate for patient samples. These results hold promise for the implementation of an integrated next-generation sequencing system to rapidly detect genetic aberrations, thus facilitating accurate, genomics-based diagnosis and accelerating the development of precision therapies for myeloid neoplasms [180].

Although several researchers have already applied metal semiconductors to biomedical detection, there is still an enormous scope for their development in the field of detection, especially for orthopedic diseases.

Metal semiconductor electroactive biomaterials

Increasing attention is being given to biomimetic electroactive biomaterials that replicate the natural electrophysiological microenvironment found in healthy bone tissue, aiming to enhance bone repair. Putative mechanistic pathways by which electroactive biomaterials can mitigate bone degeneration, including the enhancement of osteogenesis and angiogenesis, the suppression of inflammation, and their antibacterial effects, have been critically examined [3, 233].

Piezoelectric biomaterials. Biomaterials that exhibit piezoelectric properties produce electrical signals when subjected to mechanical stress and can also deform under external electrical stimulation due to the reverse piezoelectric effect. These materials are non-centrosymmetric, with organic materials producing piezoelectricity through molecular dipole reorientation during deformation, whereas inorganic materials generate piezoelectricity through ionic displacement within their crystal structures under stress [234].

Novel Ca/Mn-doped BaTiO₃ (CMBT) nanofibers were combined with poly(L-lactide) (PLLA) to create piezoelectric substrates with enhanced osteogenic activity. These PLLA/CMBT composites, unlike nondegradable PVDF, are biodegradable and exhibited improved properties postpolarization. They formed a network in the matrix, which significantly increased the *in vitro* and *in vivo* performance. In contrast to non-piezoelectric PCLs, these materials demonstrate significant antibacterial and anti-inflammatory properties, which provide further advantages for bone regeneration. In summary, polarized PLLA/CMBT composites are promising candidates for bone regeneration and functional reconstruction because of their multifunctionality in

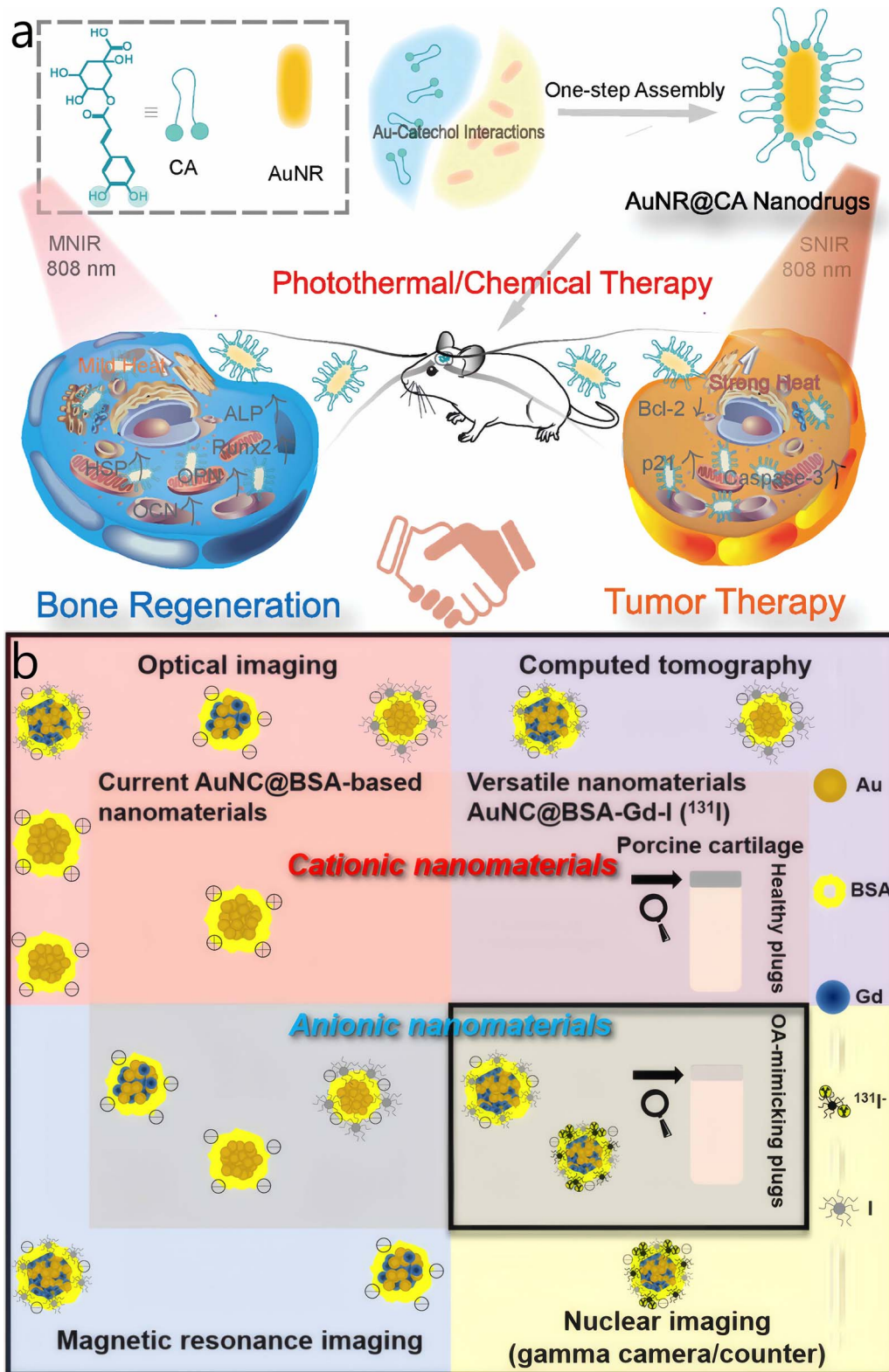


Figure 10. Antitumor and imaging capabilities of metal semiconductor materials. **(a)** a diagram illustrating the supramolecular hybrid approach for creating biomimetic catechol-based nanohybrids, featuring a one-step process for their fabrication through strong Au–catechol interactions and adjustable hyperthermia capacities, which demonstrate combined effects of tumor suppression and osteoinduction. Adapted from [174] with permission. Copyright © 2023, *Advanced Healthcare Materials*. **(b)** A diagram that contrasts AuNC@BSA-Gd-I with existing gold nanomaterials regarding their adaptability for cartilage imaging and detection. Adapted from [176] with permission. Copyright © 2024, *APL Bioengineering*

terms of electroactivity, biodegradability, and antibacterial and anti-inflammatory activities to meet the challenges of inducing osteogenesis [181] (Figure 11a). In a study by Zheng, a composite cryogel scaffold intended for bone regeneration, named Gel-PD-CMBT, was created by integrating gelatin with a conductive matrix of poly(ethylene dioxithiophene)/poly(styrene sulfonate) and incorporating calcium/manganese codoped barium titanate nanofibers as piezoelectric fillers. The incorporation of these components resulted in the development of a unified piezoelectric and conductive network within the scaffold, which enhanced charge migration and achieved a conductivity level of 0.59 S cm^{-1} . This conductive scaffold established a favorable electroactive microenvironment, which has the potential to improve biological responses. Additionally, the porous interconnected structure of the Gel-PD-CMBT scaffolds ensured not only mechanical stability but also sufficient space for the growth of cells and tissues. Furthermore, this Gel-PD-CMBT scaffold demonstrated a greater ability to encourage cellular osteogenic differentiation *in vitro*, as well as promote new bone formation *in vivo*. In conclusion, the Gel-PD-CMBT scaffold combined piezoelectricity and electrical conductivity, which can effectively restore the local electroactive microenvironment and provided an ideal platform for electrophysiological bone tissue regeneration [182] (Figure 11b–c). A PVDF membrane with CNTs and GO was prepared, and its cytotoxicity and osteogenic effects were studied. The results revealed improved voltage generation and cell activity, with the 0.8 GO-0.2 CNT-15 blend exhibiting the best performance. *In vitro*, this blend enhanced alkaline phosphatase secretion, which suggests its potential for osteogenic stimulation [37]. As previously reported by Shuai *et al.*, polydopamine was used to functionalize BaTiO₃ nanoparticles, enhancing their dispersion within PVDF scaffolds created through selective laser sintering. As a result of this functionalization, the BaTiO₃ nanoparticles achieved a uniform distribution throughout the PVDF matrix, leading to a noteworthy rise in the β phase fraction from 46% to 59%, accompanied by a 356% increase in output voltage. The modified scaffolds presented an increased in piezoelectric output voltage and enhanced cell adhesion, proliferation, and differentiation. Improved mechanical properties were also observed due to rigid particle strengthening and better interfacial adhesion [21].

However, the nonbiodegradable nature of these materials presents clinical challenges. While they serve as effective membranes or films for covering bone defects, additional surgeries are typically necessary to remove them once the defects have healed. Moreover, when these materials are employed as fillers for bone defects, their complete removal becomes impractical, as they integrate with the newly formed bone tissues [235]. Consequently, their enduring presence within the body might trigger adverse effects, such as inflammatory responses [236]. The mitigation or even elimination of these adverse reactions is a direction that needs further study.

Electroconductive biomaterials. Due to the electroactive and electroresponsive characteristics of bone, the incorporation of conductive biomaterials can enhance its regeneration. These materials facilitate electron transfer at the interface between cells and the substrate, thereby promoting cell–substrate interactions, communication, and intercellular signaling [183, 184].

Steel, titanium, and magnesium alloys are strong, conductive materials that are suitable for orthopedic implants, especially in load-bearing bone repair. New porous designs enhance their properties and enable drug loading and vascularization. Gold-based micro- and nanomaterials, which are known for their conductivity, stiffness, flexibility, and biocompatibility, have also been used in composite scaffolds for bone regeneration, with surface modifications that enable drug loading [185]. Additionally, nanomaterials such as Ag, B, Cu, Mg, Pt, Sr, Ti, Zn, and MoS₂ have been used in bone repair and tissue engineering [186].

In general, compared with nonconductive grafts, implanted conductive biomaterials significantly promote bone regeneration. This could be attributed to the fact that conductive biomaterials, particularly those that are porous, have the ability to act as mechanical and structural supports, aiding in the filling of bone defects and facilitating the homing and proliferation of osteoblasts. In addition, they can synergize with applied electrical stimulation [145, 237] or possibly with bioelectricity in the bone to accelerate the formation of new bone [238]. However, conductive grafts mechanically interact with newly formed bone, which may affect bone strength; therefore, conductive biomaterials for bone repair should have excellent mechanical properties and the ability to permanently bond with the bone or be biodegradable and absorbable during bone regeneration [69, 70, 239].

Applications and barriers to clinical translation

Bone defects resulting from infections, tumors, or other bone diseases present formidable challenges. In recent years, researchers have made significant strides in the development of 3D-printed metal semiconductor materials for bone treatment and have achieved remarkable therapeutic success [73, 240–245]. While preclinical studies have been crucial for advancing the use of 3D-printed metal semiconductor materials, clinical validation has been limited, with the majority of research focusing on animal models [246–249].

After extensive research, only a few studies have successfully applied 3D-printed materials in patients. Borni *et al.* reported a case of a 6-year-old child who underwent two previous surgeries for osteolytic extradural complicated hydatid cysts followed by intracerebral dissemination and who was admitted for recurrence. In scheduled cyst resection cranioplasty with polymethylmethacrylate, after the removal of the cysts, the flap was cast on an effective preprinted polylactic acid mold [250]. Liu conducted a comprehensive assessment of the efficacy of 3D-printed porous Ti6Al4V prostheses in treating defects caused by osteomyelitis. The findings indicated that the prostheses effectively distributed and minimized the load in both experimental models, consequently decreasing the likelihood of fractures resulting from external pressures. Although two patients faced a recurrence of infection that necessitated removal through debridement, the other six patients showed improvements in their LEFS scores. This innovative approach shows promise for wider adoption and warrants further investigation in medical practice [251].

Despite the progress that has been made in 3D-printed bone scaffolds for clinical use, some barriers remain. First, there is an insufficient availability of medical-grade materials suitable for additive manufacturing, and among those available, such as calcium phosphates and titanium, are expensive and sometimes limited in supply. Second, the cost of manufacturing patient-specific implants is high because of their unique

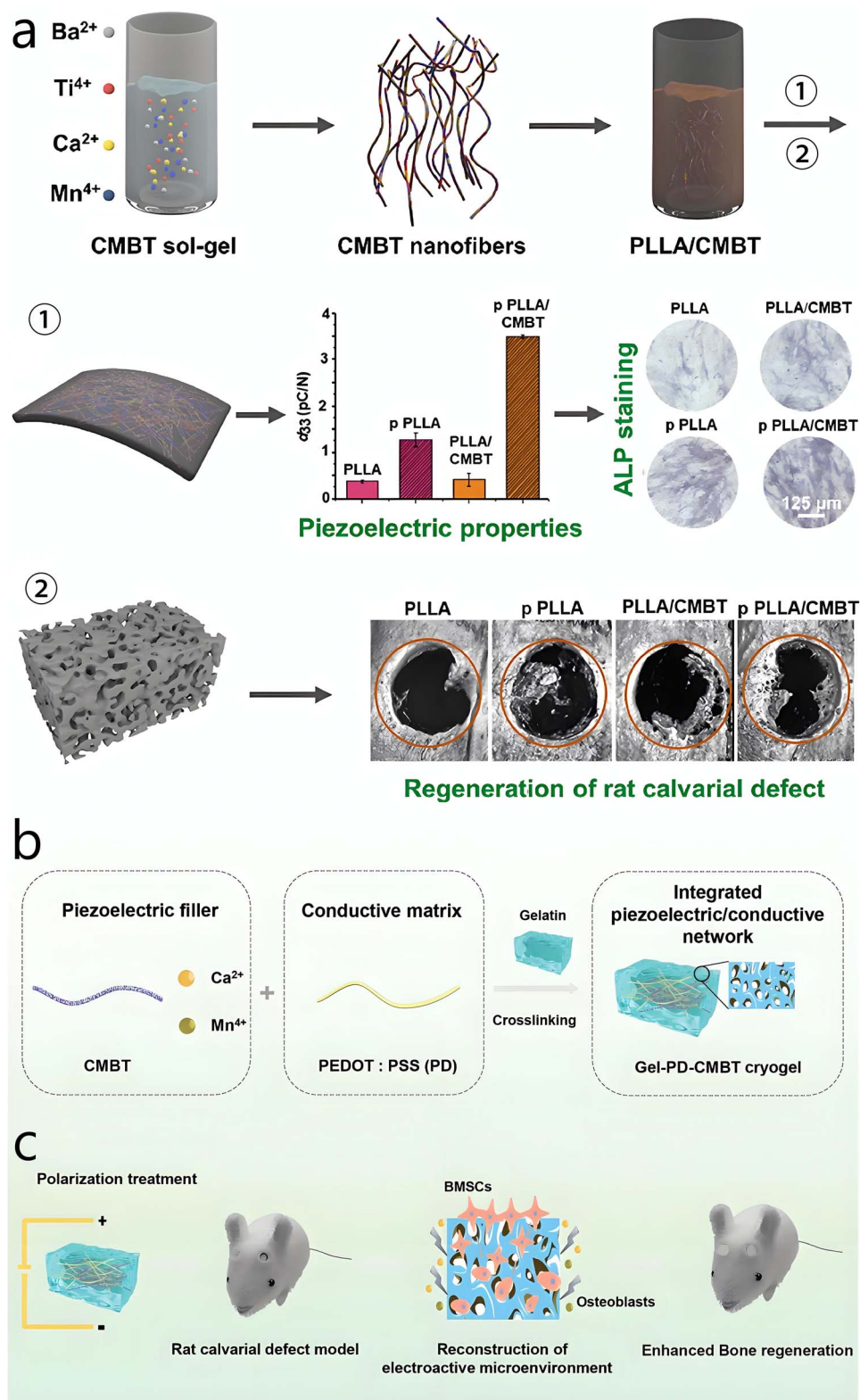


Figure 11. Piezoelectric materials can promote bone repair. **(a)** Enhancing bone regeneration through the use of composites composed of piezoelectric poly(L-lactide) and barium titanate nanofibers that are codoped with calcium and manganese. Adapted from [181] with permission. Copyright © 2022, *Composites Part B: Engineering*. **(b–c)** Diagrams illustrating how the electroactive gel-PD-CMBT composite cryogel facilitates the repair of bone defects and the process of fabricating the gel-PD-CMBT cryogel featuring an embedded piezoelectric/conductive network. Thanks to its combined piezoelectric and conductive properties, the gel-PD-CMBT cryogel restores a local electroactive microenvironment at the sites of defects, thereby promoting osteogenesis and ossification. Adapted from [182] with permission. Copyright © 2023, *Advanced Healthcare Materials*

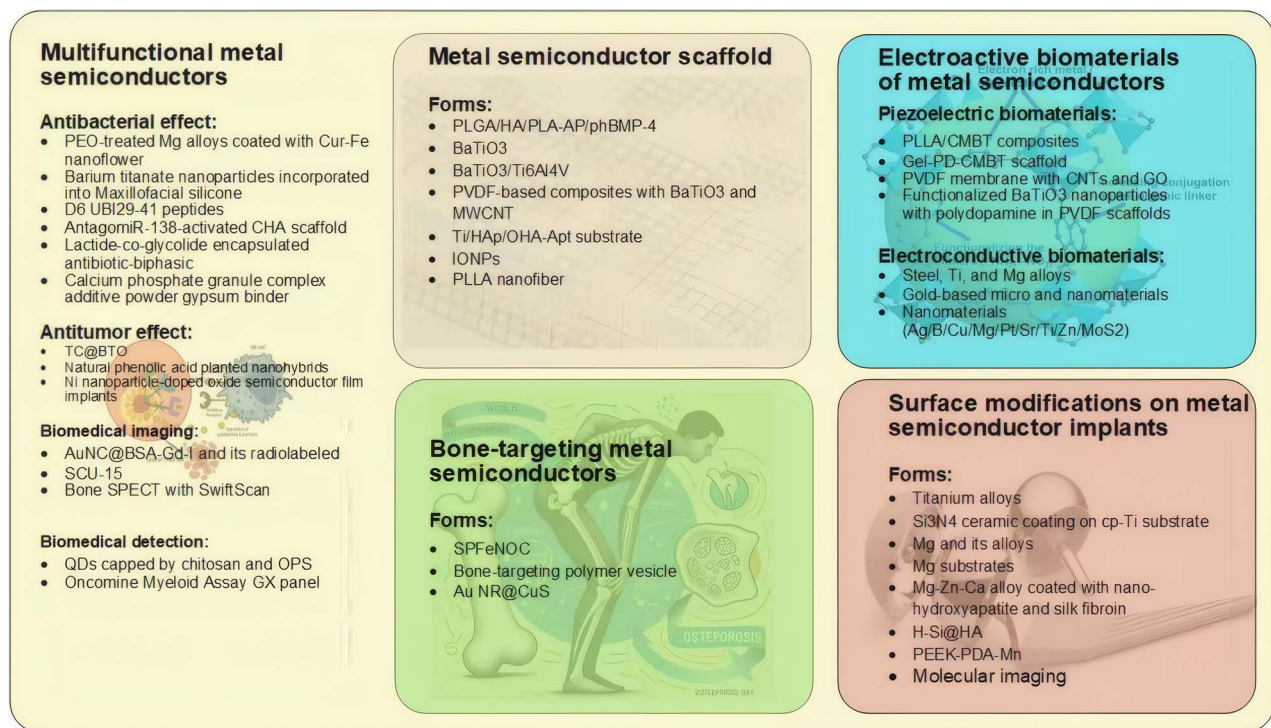


Figure 12. Summary of the orthopedic applications of metallic semiconductors

nature. Third, implementing 3D printing in hospitals requires costly and time-consuming onsite training for clinicians or assistants. Additionally, while sterilization is crucial, studies on its effects on 3D-printed scaffolds have been limited, indicating the necessity for further studies to comprehend how various sterilization processes affect these materials.

Summary and outlook

This research offers a glimpse into the application of metallic semiconductors in orthopedics and prospects for future applications. First, metallic semiconductor coatings, such as titanium and zirconium alloys, have enhanced the biocompatibility and osseointegration of implants by improving their surface properties [66–68]. Second, certain metallic semiconductor materials, such as silver and copper nanoparticles, have been proven to have antimicrobial properties that help reduce the risk of postoperative infections [85–88]. Third, metallic semiconductor nanoparticles can serve as drug carriers for the localized and controlled release of antibiotics or other therapeutic agents to promote bone healing and repair [60–62]. Metallic semiconductor materials, e.g. gold nanoparticles, can then generate heat under near-infrared light irradiation, which is used for photothermal and photodynamic therapies against bone tumors and infections [206]. Moreover, the application of metallic semiconductor materials in imaging has improved the detection of bone lesions. Contrast agents for MRI and SPECT/CT e.g. aid in more accurate diagnosis and treatment assessments. Finally, metallic semiconductor materials can be designed to respond to environmental changes (such as pH variations) for stimulus-responsive drug release or as self-healing materials [206] (Figure 12).

Although the application of metallic semiconductors in orthopedics is promising, realizing their potential and ensuring their safety and effectiveness remain challenging, and

interdisciplinary collaboration and innovation are needed. Future research may focus on developing metallic semiconductor materials with multiple functions, such as antimicrobial, drug delivery, imaging, and therapeutic capabilities integrated into a single system. Moreover, metallic semiconductor materials might be customized for personalized bone repair and regeneration strategies with a deeper understanding of specific patient needs. With nanotechnology and 3D printing approaches, researchers can precisely control the shape and structure of implants embedded in metal semiconductor materials. Given the effects of stress shielding and long-term biocompatibility, research into biodegradable metallic semiconductor materials to reduce issues associated with long-term implant presence is important. In addition, translating laboratory research findings into clinical applications requires further safety and efficacy assessments, along with close collaboration with clinical practitioners and patients. We anticipate more breakthroughs in the future as new materials and technologies emerge.

Conclusions

Metal semiconductor materials have emerged as versatile, electroactive platforms that simultaneously promote osteogenesis, angiogenesis, immunomodulation, and antibacterial activity while enabling imaging, drug delivery, and photothermal therapy. By reconstructing the native bioelectric microenvironment of bone and leveraging its tunable physicochemical properties, these materials offer a clear path toward personalized, multifunctional orthopedic implants. Future efforts should focus on biodegradable formulations, precise 3D bio-printing, rigorous long-term safety evaluations, and clinical translation to completely harness their capabilities in next-generation bone repair.

Author contribution

Wenshuang Sun (Data curation [lead], Investigation [lead], Writing—original draft [lead]), Yizhang Wu (Conceptualization [lead], Methodology [equal], Writing—review & editing [lead]), Jia Sha (Data curation [equal], Formal analysis [equal], Writing—original draft [equal]), Xueru Song (Data curation [equal], Formal analysis [equal]), Ziying Sun (Investigation [equal], Methodology [equal]), Xi Cheng (Investigation [equal], Resources [equal]), Tao Yuan (Data curation [equal], Investigation [equal]), Hong Qian (Data curation [equal], Investigation [equal]), Xiaojiang Yang (Methodology [equal], Resources [equal]), Zhao Tang (Investigation [equal], Software [equal]), Yueying Chen (Project administration [equal]), Xinrui Sun (Data curation [equal], Investigation [equal]), Liang Wang (Investigation [equal], Project administration [equal]), Jia Meng (Conceptualization [equal], Project administration [equal], Supervision [equal]), Zhongyang Lv (Conceptualization [equal], Funding acquisition [lead], Methodology [lead], Supervision [lead], Writing—review & editing [lead]), and Nirong Bao (Project administration [equal], Supervision [equal], Writing—review & editing [equal])

Conflict of interest None declared.

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