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Multiscale metal-based nanocomposites for bone and joint disease therapies

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ABSTRACT

Bone and joint diseases are debilitating conditions that can result in significant functional impairment or even permanent disability. Multiscale metal-based nanocomposites, which integrate hierarchical structures ranging from the nanoscale to the macroscale, have emerged as a promising solution to this challenge. These materials combine the unique properties of metal-based nanoparticles (MNPs), such as enzyme-like activities, stimuli responsiveness, and photothermal conversion, with advanced manufacturing techniques, such as 3D printing and biohybrid systems. The integration of MNPs within polymer or ceramic matrices offers a degree of control over the mechanical strength, antimicrobial efficacy, and the manner of drug delivery, whilst concomitantly promoting the processes of osteogenesis and chondrogenesis. This review highlights breakthroughs in stimulus-responsive MNPs (e.g., photo-, magnetically-, or pH-activated systems) for on-demand therapy and their integration with biocomposite hybrids containing cells or extracellular vesicles to mimic the native tissue microenvironment. The applications of these composites are extensive, ranging from bone defects, infections, tumors, to degenerative joint diseases. The review emphasizes the enhanced load-bearing capacity, bioactivity, and tissue integration that can be achieved through hierarchical designs. Notwithstanding the potential of these applications, significant barriers to progress persist, including challenges related to long-term biocompatibility, regulatory hurdles, and scalable manufacturing. Finally, we propose future directions, including machine learning-guided design and patient-specific biomanufacturing to accelerate clinical translation. Multiscale metal-based nanocomposites, which bridge nanoscale innovations with macroscale functionality, are a revolutionary force in the field of biomedical engineering, providing personalized regenerative solutions for bone and joint diseases.

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1. Unmet medical need for bone and joint disease treatment

Bones serve load-bearing functions and provide structural support to the body. They are connected by joints, which play crucial roles in smooth, pain-free articulation. Disorders affecting human bone and joint systems are highly prevalent and substantially affect individuals, healthcare systems, and the global economy [1,2]. In 2020, musculoskeletal disorders are projected to become the second leading cause of non-fatal disability, affecting more than 163 billion people worldwide [3] (see Tables 1 and 2).

Osteoporosis is a bone disorder characterized by low bone density and degeneration of bone microarchitecture, which ultimately results in weaker bones and an increased risk of fracture [4]. It is the most prevalent bone disease and a significant public health concern. From 1990 to 2019, the global number of deaths and disability-adjusted life years attributable to low bone mineral density (also called osteopenia) increased from 207,367 to 8.6 million to 437,884 and 16.6 million, respectively [5].

Osteosarcoma (OS), the most prevalent form of bone cancer among children, has its origin in the cells responsible for bone formation [6] and typically manifests during the growth spurt in early adolescence [7]. OS most frequently manifests in the vicinity of the knee joint, particularly in the tibia (shinbone), femur (thighbone), or humerus (upper arm bone) in proximity to the shoulder [8]. The incidence rate of osteosarcoma varies depending on several factors, including age, race, and sex. The incidence rate is approximately 5.2 per year per million individuals aged 0–19 years [9]. The reported age-adjusted incidence rates per million were 1.9, 6.7, 1.9, and 2, respectively, for age groups 0–9 years, 10–24 years, 25–59 years, and 60 years or above [10]. The primary prognostic factor in OS is stage, with metastatic OS exhibiting a markedly inferior prognosis compared to localized disease. The most common metastatic site is the lung (61 %), followed by bone (15.8 %), lung and bone (13.9 %), and other sites [11]. Individuals with lung metastases have the poorest prognosis, with a survival rate of less than 30 % at the three-year mark. Fractures can potentially indicate a more aggressive condition [12]. Patients who experience fractures have a higher rate of lung metastasis, both during initial presentation and after treatment [13].

Osteomyelitis is defined as a bone infection caused by either bacteria or fungus [14]. Osteomyelitis can manifest in any bone in the human body. However, it most commonly affects the long bones of the legs and arms. The infection can disseminate to the bone via the bloodstream or from adjacent tissues [15]. Furthermore, major features of osteomyelitis include the formation of a biofilm, intracellular infection, invasion of the canaliculi network, and forming *Staphylococcus* abscess communities (SAC). Unfortunately, antibiotic treatment and immune responses often prove ineffective against bacteria in these areas, leading to the persistence of chronic recurring osteomyelitis and a shift in bone remodeling toward osteolysis [16].

Critical-sized bone defects, defined as those that are unable to heal spontaneously, is associated with a considerable disease burden [17]. Defects exceeding 2.5 cm in size present a considerable challenge to treatment and have a poor healing history [18]. These defects may arise in a number of clinical scenarios, including trauma, infection, and tumor removal [19]. The current standard of care often employs the use of bone grafts and growth factors, including vascular endothelial growth factors (VEGFs), fibroblast growth factors (FGFs), and bone morphogenic proteins (BMPs) [20]. Autologous bone grafts remain the gold standard for critical-size bone defects. However, they have limited availability and can cause potential donor-site morbidity [21]. Allografts, despite their higher availability, have lower osteoinductivity and are associated with risks of disease transmission and immune rejection [22]. Although growth factors have been demonstrated to be effective in bone healing, their utilization is constrained by several factors, including their high cost, short half-lives, slow tissue penetration, and inability to regenerate large-size bone defects [23,24].

Table 1
Stimuli-responsive MNPs and their applications in joint and bone disorders.

Stimulation	NPs	Mechanism	Disease model	Ref
Enzyme-mimic	Pt–Se NPs	Scavenge ROS and RNS to promote the transformation of M1 macrophages into the anti-inflammatory M2 phenotype	OA	[135]
	Albumin-CeO_2 NPs	Inhibit inflammation by reducing hypoxia, scavenging excessive ROS, and restoring the misbalance of M1/M2 macrophages	OA	[137]
	CeO_2@Ce6	Kill bacteria, eliminate ROS, and promote M2 polarization of macrophages	RA	[136]
	Triam-Au NPs	Enhance the FLS anti-inflammatory function and macrophage repolarization	RA	[138]
	HA@RH-CeO_X micelle	Relieve oxidative stress in M1 macrophages while inhibit TLR4 signaling, therefore promoting repolarization to M2 phenotype	RA	[139]
	HPB nanozymes	Inhibit ROS and NF-κB signaling to remodel the microenvironment to protect chondrocytes	Bone defect	[134]
	CeO_2-BG scaffold	Relieve oxidative stress, enhance mineral deposition, and promote alkaline phosphatase activity along with osteogenic gene expression	Osteomyelitis	[140]
	TiNTA-Ce NPs	Protect cells against H_2O_2-impaired cell viability and osteogenic differentiation	Osteoporosis	[142]
Light	MoS_2@CS@Dex	Extend the dwell time of Dex in the joint cavity while reducing cartilage erosion caused by TNF-α and IL-1	OA	[152]
	$Cu_{7.2}S_4$ NPs	Preserve bone and cartilage, reduce synovial invasion, thereby enhancing anti-inflammatory effects	RA	[149]
	pAuPds NPs	Promote the expression of Hsp47 and BMP2 while enhancing cell proliferation and bone regeneration	Bone defect	[156]

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Table 1 (*continued*)

Stimulation	NPs	Mechanism	Disease model	Ref
	AuNC	Bind with cytokines to inhibit the inflammatory response while enhance RvD1-induced polarization of M2 macrophages to promote bone regeneration	Bone defect	[157]
	PA/Pt NPs	Enhance targeting and anticancer activity while inhibiting bone resorption	OS	[158] [159]
	TiO_2/MoS_2/PDA/RGD nanorod arrays	Generate ROS to rapidly kill bacteria while improving cell adhesion, proliferation, and osteogenic differentiation	Osteomyelitis	[160]
Magnetic field	PM NPs	Inhibit the expression of autocrine motility factor, promote cancer cell apoptosis, and enhance bone tissue regeneration.	Bone defect, OS	[174]
	ADT-loaded magnetic nanoliposome	Intratumorally convert to H_2S bubbles that can explode to ablate tumor tissue	OS	[175]
	Ti-Fe NPs	Accelerate the formation of the extracellular mineralized matrix by increasing cell proliferation and promoting osteogenic differentiation	Bone defect	[176]
pH	Ti-ZnO-PBA-NG NPs Migel	Demonstrate good long-term capability, inhibit bacterial biofilm formation, produce ROS to activate the ERK signaling pathway to induce apoptosis in OS cells	OS	[196]
	C-TherMods	Protect normal cells while induce ROS mediated apoptosis of cancer cells	OS	[194]
	KGN@HMZC@HA	Eliminate ROS and oxygen to transform macrophages from M1 phenotype to M2 phenotype	OA	[195]
	Fe-cat NPs	Deliver catechins within cells to enhance osteogenic differentiation while inhibiting adipogenic differentiation and promotes M2 polarization of macrophages to resist inflammation	Osteoporosis	[189]
	pDA–Ag	Kill bacteria while enhancing cell adhesion, proliferation, and bone formation	Bone defect	[193]
	HMPBzyme	Inhibit the expression of HIF-1α and reduces ROS levels, thereby inhibiting oxidative damage and alleviating hypoxia to suppress inflammation and reduce cartilage degeneration	OA	[205]

Abbreviations: OA = osteoarthritis; Pt = platinum; Se = selenium; ROS = reactive oxygen species; RONS = reactive nitrogen species; MnO_2 = manganese dioxide; CeO_2 = cerium oxide; Ce6 = chlorin e6; Triam = triamcinolone; FLS = fibroblast-like synoviocytes; HA = hyaluronic acid; RH = rhein; HPB = hollow Prussian blue; BG = bioactive glass; OS = Osteosarcoma; RA = Rheumatoid arthritis; TiNTA = TiO_2 nanotube array; MoS_2 = Molybdenum disulfide; CS = chitosan; Dex = dexamethasone; Cu = Copper; S = sulfide; Au = nanogold; pAuPds = porous AuPd alloy; AuNC = gold nanocage; PA = phytic acid; TiO_2 = Titanium dioxide; PDA = polydopamine; RGD = arginine-glycine-aspartic acid; PM = Piezo-Magnetic; ADT = anethole dithiolethione; MagGel = magnetic nanocomposite hydrogels; Fe = iron; ZnO = zinc oxide; PBA = 3-carboxyphenylboronic acid; NG = naringin; KGN = kartogenin; HMZC = hollow mesoporous CeOx; Cat = catechin; AL = acetal linker; pDA = polydopamine; HMPB = hollow-structured manganese Prussian blue.

Osteoarthritis (OA) is the most common joint disease worldwide, affecting approximately 500 million people and leading to physical disability and reduced quality of life [25]. The causes of OA are multifactorial and include genetic factors, obesity, joint injury and metabolic disorders [26]. An imbalance between biochemical and mechanical factors leads to increased production of inflammatory factors in the synovial fluid, initiating the pathogenesis of OA. Inflammatory factors such as tumor necrosis factor (TNF-α) and interleukin (IL-1β) induce chondrocyte apoptosis, leading to cartilage degradation, particularly in the knee [27]. In the treatment of OA, acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for symptomatic relief, but both have associated adverse effects [28,29]. For example, NSAIDs, while effective, are associated with gastrointestinal problems ranging from dyspepsia to ulcers with complications [30].

Another type of arthritis, rheumatoid arthritis (RA) is a chronic autoimmune disease-causing inflammation of the synovial membrane, excessive autoantibody production, and cartilage and bone damage. RA incidence is estimated at approximately 0.5–1 % [31], leading to joint inflammation, polyarticular synovitis, bone erosion, cartilage degradation, impairments, and reduced quality of life [32]. Current understanding of the pathogenesis of RA is incomplete, resulting in a lack of established treatment options [33]. Early diagnosis and intervention are critical for effective treatment. Researchers are exploring new biomarkers to aid in this process. RA treatment includes drugs such as leflunomide, methotrexate, sulfasalazine, and hydroxychloroquine [34]. However, these drugs have some common side effects, including gastrointestinal disorders [35], pulmonary arterial hypertension [36], headache [37], heart failure [38], and cardiomyopathy [39]. There remains an urgent need for innovative approaches to the treatment of OA and RA.

Table 2
Different types of MNPs and their use for treating joint and bone disorders.

Material	NPs	Disease treated	Mechanism(s)	Ref
Gold	CUR-CGNPs	Osteoporosis	Inhibit RANKL signaling to suppress osteoclast differentiation	[233]
	Nanocomposite cements with AuNPs	Bone infection	Enhance the mechanical properties of bone cement, and improve antibacterial performance	[294]
	EGCG-Au-Ag	OA	Induce cartilage regeneration through anti-oxidative properties and reduction of chondrocyte apoptosis	[364]
	HA-AuNP/TCZ	RA	Protect and lubricate articular surfaces through anti-angiogenic effects, and interfere with IL-6 in the pathogenesis of RA	[388]
Silver	Chitosan/agar/Ag NPs	Osteoporosis	Maintain calcium homeostasis while eliminating ROS to promote collagen formation	[407]
	Rhizophora apiculate-Au hydrosol	OS	Strengthen oxidative stress to promote cancer cell apoptosis	[277]
	Ag NPs	Osteomyelitis	Destroy the basic skeletal structure of bacterial cell walls	[289]
	PC-miR-148b-SNP	Bone defect	Promote osteogenic differentiation of hASC and closure of mouse calvarial defects	[408]
	Ag@AMP/SF	Bone defect	Generate ROS to damage bacterial cell membranes while promoting adhesion, spreading, and proliferation of BMSCs, thereby promoting osteogenic differentiation	[325]
	FA-Ag NPs	RA	Eliminate ROS to induce M1 macrophage reduction and M2 macrophage polarization	[401]
	MgO-Ag_2O hydrogels	Bone defect	Promote the proliferation and differentiation of osteoblasts while ensuring good antibacterial ability	[326]
Iron	Ti-Fe NPs	Bone defect	Promote bone regeneration to shorten the time required for bone integration	[176]
	Fe-Cur NPs	OA	Eliminate ROS while activating Nrf2 signaling and inhibit NLRP3 signaling to reduce the production of matrix degrading proteases and inflammatory mediators	[409]
	Alendronate-IO NPs	Osteoporosis	Eliminate ROS to promote osteogenic differentiation and inhibit osteoclast differentiation	[228]
	Fe_3O_4 NPs	Bone infections	Reduce bacterial adhesion and inhibit bacterial biofilm formation while promoting the adhesion, proliferation, and differentiation of BMSCs	[296]
Cerium	TiNTA-Ce NPs	Osteoporosis	Eliminate ROS and protect cell vitality to promote osteogenic differentiation	[142]
	Cerium oxide NPs	Osteoporosis	Increase the osteogenic effect of MSCs and promote endothelial progenitor cell angiogenesis	[223]
	Cerium oxide NPs	Osteomyelitis	Eliminate ROS while killing bacteria to promote osteogenic effects	[299]
Manganese	MFC-MSN	RA	Eliminate ROS to promote M2 polarization of macrophages	[395]
	MnO_2 NPs	OA	Reduce the loss of glycosaminoglycans and the release of nitric oxide while inhibiting the inflammatory microenvironment to protect chondrocytes	[133]
	FAPi-MnO2 hydrogel	Osteoporotic bone defects	Eliminate ROS, promote M2 polarization of macrophages, and alleviate inflammation, and thereby enhancing osteogenic activities and inhibit osteoclastogenesis	[410]
Copper	CuS@PC	OA	Promote gene expression for cartilage formation, glycosaminoglycan deposition, and type II collagen formation while inhibiting IL-1β-induced extracellular matrix degradation	[380]
	CuTA@SF	Bone defect	Regulate intracellular ROS levels, upregulate the expression of EGR1, TAGLN, and CSRP1 to enhance the proliferation of BMSCs and chondrocytes, and inhibit the growth of staphylococcus aureus.	[378]

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Table 2 (*continued*)

Material	NPs	Disease treated	Mechanism(s)	Ref
Magnesium	BP-Mg	Osteoporosis	Exhibit a powerful Mg capture ability while promoting the expression of ALP, Runx2, e-NOS, and VEGF to enhance osteogenesis and vascular regeneration	[243]
	MgO NPs-carried artificial periosteal bandage	Bone defect	Promote M2 polarization of peripheral macrophages and upregulate anti-inflammatory factors such as IL-4 and IL-10, while fostering new bone formation, enhancing the proliferation and migration of endothelial cells, and promoting angiogenesis and neuronal growth	[320]
Platinum	DOX-Pt NPs	OS	Upregulate lactate dehydrogenase leakage, ROS generation, malondialdehyde, nitric oxide, and carbonylated protein levels to promote mitochondrial damage and apoptosis in cancer cells	[280]
Titanium	Ti-Fe NPs	Dental Implantation	Effectively kill bacteria while promoting the proliferation and differentiation of osteoblast-like cells	[176]
	Ti-Au NPs	Osteoporosis	Upregulate osteogenic differentiation-related genes such as COL1, Runx2, and OPN to promote osseointegration of implants	[411]
	GDY-TiO2	Implant infection	Generate ROS to kill bacteria while promoting cell adhesion, differentiation, and osteogenesis	[305]
Zinc	BSA-ZnPc	OS	Promotes NP uptake by tumor cells to induce ROS production, thereby downregulating p-AKT, p-mTOR and p65 signaling pathways, enhancing CD8 T cell-induced immune responses, promoting tumor cell autophagy, and inhibiting their proliferation and invasion	[272]
	ZG-CS NPs	RA	Downregulate inflammatory biomarkers (TNF - α, IL-6, and iNOS) and reduce oxidative stress while inhibiting inflammatory cell infiltration	[397]
	ZnO NPs	Osteoporosis	Effectively kill bacteria while promoting the proliferation, differentiation, and mineralization of osteoblast-like cells	[236]
	ZnO NPs	RA	Downregulate IL-1 β, TNF - α, IL-10, total white blood cell count, and anti-CP to improve autoimmunity	[399]

Abbreviations: OA = osteoarthritis; CUR = curcumin; CGNPs = β-cyclodextrin (CD) conjugated gold nanoparticles; DE = dendrimer-entrapped; EGCG = epigallocatechin gallate; OS = Osteosarcoma; HA = hyaluronic acid; RA = Rheumatoid arthritis; TCZ = tocilizumab; PC = photoactivated; SNP = silver nanoparticles; AMP = antimicrobial peptides; SF = silk fibroin; FA = folic acid; Agar = agarose; Cur = curcumin; IO = iron oxide; TiNTA = TiO2 nanotube array; MFC = manganese ferrite and ceria; MSN = mesoporous silica nanoparticles; FAPi = fibroblast activating protein inhibitor; CuS = cupper sulfide; PC = phosphatidylcholine; CuTA@SF = Cu-Tannic acid @ silk fibroin; CuO QDs = copper oxide quantum dots; BP = bisphosphonate; DOX = doxorubicin; GDY = graphdiyne; BSA-ZNPC = bovine serum albumin-zinc phthalocyanine; ZG-Chit = zinc gluconate-loaded chitosan; CS = chitosan; PEG = poly ethylene glycol; HAp = hydroxyapatite.

In cases of bone and joint disorders, the body's intrinsic capacity to repair damaged tissues is often insufficient, leading to discomfort and restricting the patient's mobility, locomotion, and daily activities [40]. Currently, the clinical management of bone and joint disorders predominantly necessitates surgical procedures involving grafts and scaffolds [41]. However, there is a dearth of non-invasive, efficacious therapeutic options for bone and joint regeneration [42,43]. The pursuit of advanced treatment strategies for bone and joint disorders offers considerable potential for enhancing patient outcomes and alleviating the global burden associated with these conditions.

Nanotechnology has emerged as a highly promising avenue for diagnosing and treating skeletal diseases [44–46]. Advances in biology and nanotechnology have driven the development of stem cell-based regenerative medicine by promoting cell differentiation into desired functional cells such as osteoblasts and chondrocytes [47]. Among the various methods employed to modulate stem cell behaviors, metal-based nanoparticles (MNPs) have gained significant attention as bioactive agents for bone and cartilage regeneration [48]. It is noteworthy that MNPs composed of gold (Au), silver (Ag), iron oxide (FeO), magnesium oxide (MgO), and cerium oxide (CeO) have gained widespread use due to their high biocompatibility, favorable physicochemical properties, facile surface modification, and diverse biological activities that influence cell fate [47,49]. Using MNPs in bone and cartilage grafts has demonstrated improved cartilage formation and bone regeneration [50–52]. These MNPs contribute to a favorable environment for skeletal repair and regeneration, making them a promising therapeutic approach in the field of regenerative medicine [53,54]. Moreover, they have demonstrated toxicity towards bone-derived cancer cells, further underscoring their potential therapeutic applications for treating OS [54–57].

Among the various types of NPs, MNPs offer distinctive advantages over lipid-based NPs and polymeric NPs. MNPs exhibit remarkable capabilities in targeted delivery of drugs, antibodies, growth factors, and

nucleic acids, as illustrated in Fig. 1A [58,59]. The surface of MNPs can be easily functionalized, allowing for the conjugation of single or multiple drugs and active biomolecules through a variety of interactions, including hydrogen bonding, covalent bonding, and electrostatic interactions [60–62]. Consequently, MNPs generally possess a higher drug-loading capacity than lipid-based NPs and polymeric NPs [63]. Additionally, many biocompatible compounds and substances derived from natural sources employed in the oxidation/reduction processes can be incorporated [64]. Furthermore, MNPs exhibit significant potential in delivering both hydrophobic and hydrophilic drugs with high efficiency [65], whereas polymeric NPs and lipid-based NPs are often less effective for carrying hydrophilic drugs [66].

This review aims to examine the biological functions of various MNPs, focusing on those composed of Au, Ag, iron (Fe), zinc (Zn), cerium (Ce), titanium (Ti), manganese (Mn), magnesium (Mg), and copper (Cu) as well as their nanocomposites. This analysis is based on an in-depth examination of the existing literature on the subject. While several review articles have discussed nanotechnology-based approaches for treating bone and joint disorders, focusing on different types of MNPs and different types of disorders, our review is distinctive in that it comprehensively discusses multiple types of MNPs and encompass various bone and joint disorders. Furthermore, we discuss the modification of NPs with drugs and proteins and the integration of NPs into implants, injectable hydrogels, and biofabricated scaffolds to generate nanocomposites targeting bone and joint conditions (Fig. 1B). The aim is to address significant gaps in knowledge that warrant further investigation, and to offer promising avenues for elucidating the mechanisms underlying bone and joint disorders and their interactions with MNPs, thereby facilitating the development and clinical translation of effective MNP-based treatments.

2. Metal-based biomaterials treating bone and joint diseases: from implants to NPs

Biomaterials, including metals, ceramics, and polymers, are extensively utilized in bone and joint therapies for treating tissue repair disorder conditions such as OA, RA, osteoporosis, and OS [67]. One of the first bone implants was constructed from ivory was affixed to bone with nickel-plated nails and a combination of pumice, resin, and plaster [68,69]. Subsequently, a variety of metals, including nickel (Ni), chromium (Cr), molybdenum (Mo), Mg, Fe, Mn, and Cu, and their alloys were used for bone and joint grafts [70–72]. These materials are designed to mimic

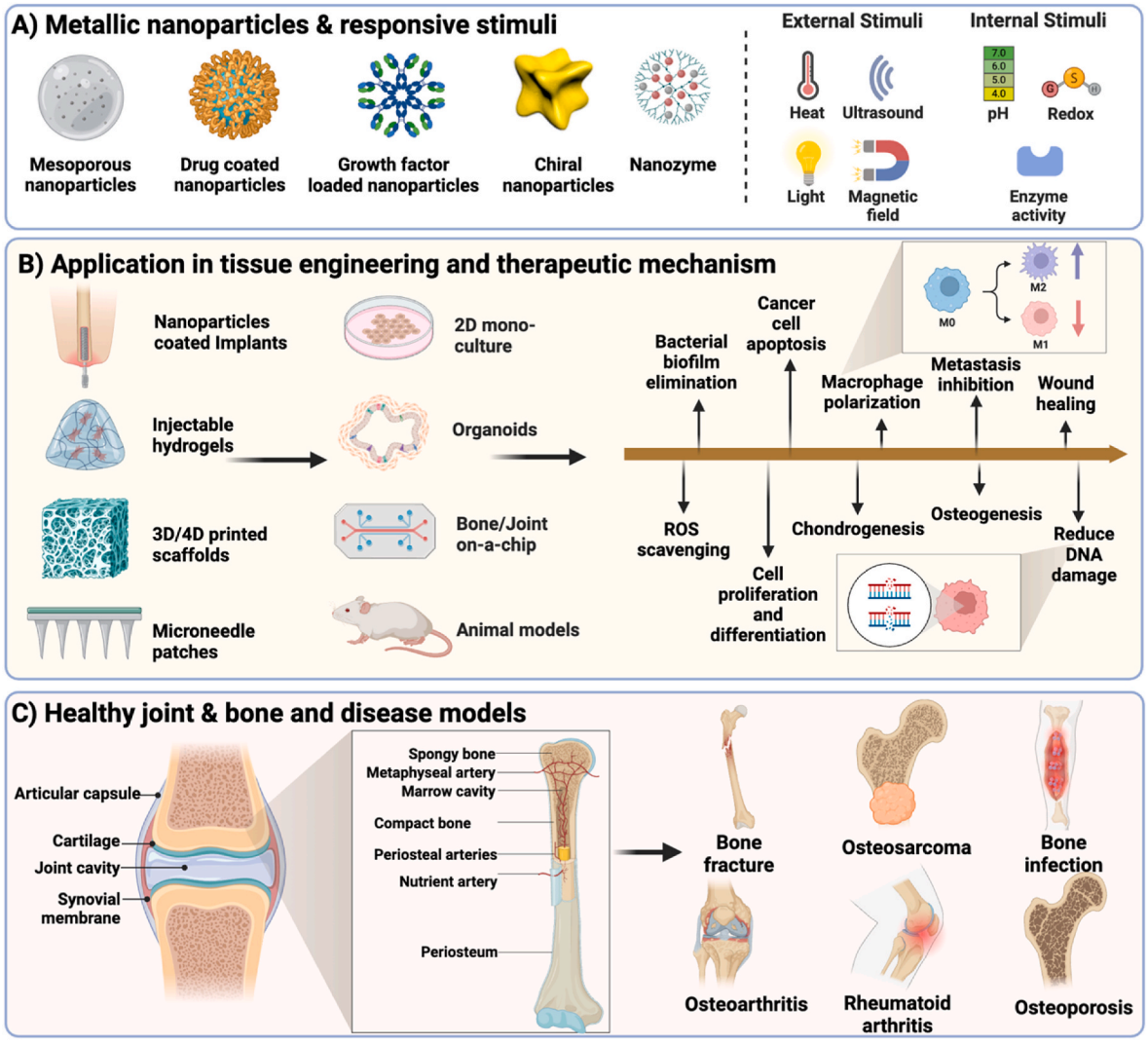

Fig. 1. NP- and nanocomposite-based approach for treating bone and joint disorders. (**A**) Cargo-loaded metal-based nanoparticles (MNPs) and highly promising metal-based/containing chiral NPs and nanozymes are shown. MNPs can respond to stimuli such as light, magnetic field, temperature, and pH. (**B**) Integration of MNP with different scaffolds in tissue engineering is demonstrated, and their therapeutic mechanisms are shown, including antimicrobial effects, induction of cancer cell apoptosis, controlled release of bioactive molecules, immunomodulation to promote tissue healing, and enhancement of stem cell differentiation. (**C**) Structure of healthy joints and bones and various relevant diseases and disorders.

native bone by balancing biocompatibility, corrosion resistance, fatigue strength, and elastic modulus, with longevity prioritized to minimize revision surgeries [68]. For instance, nickel, chromium, and molybdenum alloys are frequently employed in artificial joints due to their mechanical robustness and corrosion resistance [70,73–75]. Cobalt-based alloys have improved biocompatibility due to the presence of a protective chromium oxide layer [76]. However, their high modulus frequently causes stress shielding, which can result in bone resorption and implant loosening [77]. Austenitic stainless steel (Fe-Cr-Ni-Mo) offers excellent corrosion resistance and favorable tissue interaction [78,79], but the excessive release of cobalt, chromium, or nickel ions has been demonstrated to be deleterious to organs and blood cells [80].

Ti and its alloys (e.g. nitinol) are widely used metallic materials for dental and joint implants due to their biocompatibility and ability to promote bone regeneration [68,78,81–85]. Tantalum (Ta) is often covered by a corrosion-resistant Ta_2O_5 layer and supports osteoblast proliferation, though its high cost and mechanical mismatch with native tissue limits broader applications [86–91]. Zirconium (Zr) alloys have been found to induce the formation a bone-like apatite layer and are considered promising materials as orthopaedic implants [92,93]. Mg alloys are particularly attractive for biodegradable implants due to their biocompatibility and ability to minimize inflammatory responses and stress shielding [94–97]. The release of Mg^{2+} ions by magnesium implants has been shown to promote angiogenesis and osteogenesis [98,99]. However, their rapid corrosion in physiological environments can lead to premature mechanical failure, hydrogen gas accumulation, and local pH increases [100–102], highlighting the need for advanced strategies to control their degradation.

A key limitation of traditional metallic implants is the difficulty in incorporating bioactive molecules or cells, which is less of an issue for ceramics or polymers [103]. Furthermore, high concentrations of trace elements, such as manganese and silicon, used in alloys pose risks of toxicity, neurodegeneration, or organ damage [72,104,105]. Of particular concern are cobalt, nickel, and nickel-chromium alloys, with studies showing that nickel implantation is associated with sarcoma formation in rats [106]. These limitations, including mechanical mismatch, cytotoxic ion leaching, corrosion-related complications, and biologically inert properties, underscore the pressing need for advanced biomaterials.

In this context, MNPs have emerged as transformative solutions. MNPs address the shortcomings of metallic implants through nanoengineering. For instance, Mg-based MNPs embedded in a polymeric matrix have been shown to regulate the degradation rate of the matrix, release therapeutic Mg^{2+}, and maintain the scaffold's mechanical integrity [100,107]. Their high surface area-to-volume ratio allows for versatile loading of bioactive molecules (e.g. antibiotics, growth factors, siRNAs), thus overcoming the inherent bioinertness of most traditional metallic implants. Furthermore, MNPs interact with biomolecules present in biological fluids, altering the intrinsic properties of the original NPs [108,109]. Dynamic protein coronas on the surface of AuNPs can also result in cellular metabolic remodeling [110]. Innovative techniques, such as in situ trapping, now allow for real-time analysis of protein corona formation on MNPs, thus facilitating more rational nanomaterial design [111,112]. By integrating structural and functional characteristics with therapeutic delivery capability, MNPs hold the potential to bridge the gap between traditional bioinert implants and bioactive therapies, positioning them as promising nanocarriers for treating bone and joint diseases.

3. Stimuli-responsive MNP mechanisms for Bone and joint therapies

The continuous improvement in human life expectancy in recent decades has contributed to an increased incidence of numerous age-related disorders such as osteoporosis, osteomyelitis, bone cancer and OA. At present, no definitive treatments exist for any of these pathologies [113,114], and while various pharmacological therapeutics can be beneficial in addressing specific conditions, the side effects of these treatments influence patients' overall health and daily quality of life [115,116]. For example, the use of FDA-approved recombinant parathyroid hormone is restricted to severe cases of osteoporosis and a maximum treating time of 2 years because of the increased risk of developing OS as a side effect [117]. Similarly, oral administration of antiresorptive bisphosphonates has been reported to induce peptic ulcer and osteonecrosis of the jaw [118]. In OS and similar bone diseases, the presence of osteoid, which is denser than normal bone tissue, impedes the delivery of systemically administered drugs to the tumor. This limitation exacerbates the common side effects of systemic chemotherapy [119].

The challenge in delivering bioactive molecules and drugs to diseased bone/cartilage tissues is to achieve an optimal compromise among pharmacokinetic/pharmacodynamic parameters, the administered dose, the presence of off-target side effects, and the short- or long-term therapeutic outcome. To address these challenges, the development of advanced nanoscale carriers for the delivery of bone and cartilage therapeutics via diverse routes of administration has been a prominent area of research [44,120]. Such nanocarriers have so far been designed to modify the pharmacokinetics of drugs, improving local concentration and drug release [121]. Stimuli-responsive NPs have been investigated in recent years as an approach to bypass the characteristic burst release profile of nano formulated therapeutics or residual release during parenteral administration [122]. To achieve controlled release, stimuli-responsive NPs can be precisely tailored to respond to internal and external conditions (e.g., magnetic field, light, redox) to finetune the release of bioactive molecules such as growth factors, antibiotics, and chemotherapeutic drugs [123].

3.1. Nanozymes mimicking MNPs

Nanozymes are synthetic materials designed to mimic the enzymatic function of natural enzymes, first recognized in 2007 for their intrinsic peroxidase activity in Fe_3O_4 NPs [124]. Engineered nanozymes have many advantages, including high catalytic activity, tunable catalytic types, low cost, facile preparation, robust stability, and recyclability [125,126]. By mimicking natural enzymes such as peroxidase (POD), oxidase (OXD), catalase (CAT), and superoxide dismutase (SOD), nanozymes have been employed in various biomedical applications, encompassing disease monitoring, tumor therapy, antibacterial treatments, and inflammation-induced disease (such as OA) treatments [127]. In principle, nanozymes could possess an intrinsic capacity to effectively neutralize reactive oxygen species (ROS) and reactive nitrogen species (RNS), modulate inflammatory responses, and demonstrate properties that actively foster osteochondral regeneration [128,129].

Bone and joint disorders are characterized by perturbations in the bone microenvironment, such as ROS accumulation, hypoxia and osteoimmunology. The imbalance in ROS homeostasis is the primary cause of impaired osteochondral regeneration. Excessive ROS production inhibits the proliferation and differentiation of MSCs, disrupting the homeostasis of normal bone resorption and formation and promoting the degradation of the cartilage extracellular matrix [130–132]. Nanozymes could potentially overcome the imbalance by directly consuming local ROS. For example, manganese dioxide NPs, with a size of less than 20 nm, were found effective in scavenging ROS through penetrating the depth of cartilage explants. These NPs were observed to be present in the extracellular matrix and resident chondrocytes. Furthermore, the NPs demonstrated chondroprotective properties in cytokine-induced cartilage tissue sections, reducing the loss of glycosaminoglycans (GAGs) and the release of nitric oxide.

Biodistribution and histological analysis revealed that the NPs aggregated on the cartilage surface and co-localized with the spaces of chondrocytes, indicating that manganese dioxide NPs may be an effective method of chondroprotection for OA cartilage [133]. In another

study, hollow Prussian blue nanozymes (HPBzymes) composed of Fe-CN-Fe nano-units have shown significant protective effect on chondrocytes and delayed the progression of traumatic OA by inhibiting ROS and Rac1/nuclear factor kappa-B (NF-κB) signaling in a rat model as shown in (Fig. 2A–C) [134]. Additionally, Wei and colleagues synthesized a hybrid Pt-Se nanozyme with potent catalytic activities [135]. These nanozymes act as ROS and RNS scavengers to exert synergistic effects for OA therapy. The Pt-Se nanozyme has been demonstrated to exhibit an extremely efficacious scavenging effect on ROS and RNS levels, thereby promoting the re-polarization of M1 macrophages. The polarization of synovial macrophages towards M2 macrophages has been shown to inhibit the expression of pro-inflammatory factors and restore mitochondrial function in chondrocytes.

The efficacy of several nanozymes in treating RA has been demonstrated through the emulation of enzymes that target ROS scavenging, macrophage polarization, and the eradication of bacterial infection. For instance, a multifunctional nanocomposite was fabricated by coating photosensitizer chlorin e6 (Ce6) onto nanoceria to study the anti-inflammatory and antibacterial effects. This nanoplatform has been engineered to elicit antibacterial effects through the implementation of photodynamic therapy (PDT). The CeO_2 NPs within the nanoplatform have been shown to catalyst the reaction between superoxide and hydrogen peroxide by means of the redox cycle reaction between Ce^{3+} and Ce^{4+}. This process has been demonstrated to emulate the behavior of SOD and CAT, thereby scavenging free radicals and combating chronic inflammation and oxidative stress. Additionally, the nanoplatform is equipped with the ability to regulate the M1 and M2 phenotypes of macrophages, thereby influencing host immunity, as illustrated in Fig. 2D and E [136]. In a related study, albumin-CeO NPs were synthesized via a biomineralization process and subsequently combined with the near-infrared dye indocyanine green (ICG). The therapeutic efficacy and systemic targeting potential of the NPs were evaluated in a mouse model of collagen-induced arthritis (CIA). It was found that these NPs exhibited superior efficacy in converting the proinflammatory macrophage phenotype to an anti-inflammatory macrophage phenotype, along with high activity in scavenging active oxygen and

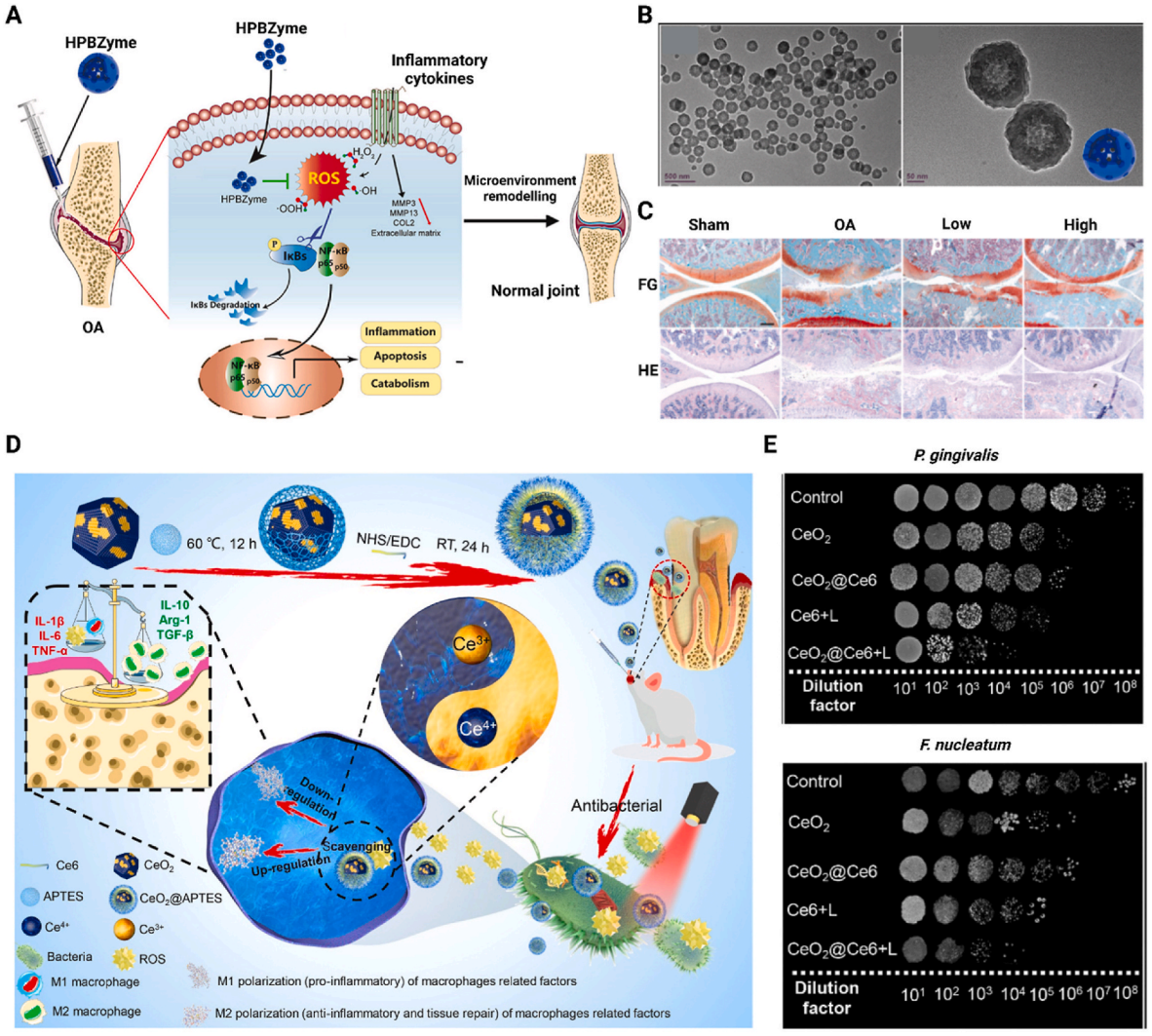

Fig. 2. Enzyme mimicking MNPs for treating bone and joint disorders. (A) Schematic diagram of the mechanism by which hollow Prussian blue nanozyme (HPBzyme) protects chondrocytes and delays arthritis. **(B)** Transmission electron microscope (TEM) images of HBPzyme. **(C)** HPBzyme delays the progression of OA *in vivo*. Low: low-dose HPBzyme group; High: high-dose HPBzyme group. HE = hematoxylin and eosin staining, FG = safranin O and fast green staining, Scale Bar = 500 μm. Adapted under the terms of the CC-BY-NY-ND Creative Commons Attribution 4.0 International license (https://creativecommons.org/licenses/by/4.0) [134]. Copyright 2021, The authors, published by Elsevier. **(D)** Schematic illustration of cerium oxide-chlorin e6 (CeO_2@Ce6) nanocomposite synthesis, and their antibacterial mechanism and modulation of macrophage polarization. **(E)** Antibacterial activity CeO2@Ce6 by colony forming unit counts of *P. gingivalis* and *F. nucleatum* biofilms with different treatments. L = light (630 nm) irradiation for 3 min per day. Adapted with permission from Ref. [136]. Copyright 2021, Elsevier. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

enzymatic activity [137]. Furthermore, using CAT-mimicking Au-Triamcinolone NPs in a study resulted in the transformation of proinflammatory M1 macrophages into anti-inflammatory M2 macrophages by increasing the expression of IL-4, IL-10, and Arg-4. These findings suggest that Au-Triamcinolone NPs may have the potential to promote an anti-inflammatory response and repolarize macrophages towards a more beneficial state in RA, which could in turn facilitate cartilage healing [138]. ROS-responsive micelle (HA@RH-CeO_X) based on ceria oxide nanozymes and HA biopolymers were designed (Fig. 3A and B), which precisely delivered nanozyme and the clinically approved RA drug Rhein (RH) to proinflammatory M1 macrophage populations in inflamed synovial tissues. Specifically, the Ce^{3+}/Ce^{4+} redox pair presented SOD-like enzymatic activity and rapidly decomposed ROS and alleviated the oxidative stress in M1 macrophages, while RH inhibited the TLR4 signaling in M1 macrophages, both of which could act in a concerted manner to induce their repolarization into anti-inflammatory M2 phenotype to ameliorate local inflammation (Fig. 3A) and promote cartilage repair as shown in Fig. 3C [139].

The integration of cerium oxide NPs (CeO_2 NPs) into bioactive glass has resulted in the establishment of a multifunctional therapeutic platform that achieves a continuous therapeutic effect against inflammation and promotes osteogenesis in the treatment of bone defects. The capacity of CeO_2 NPs to act as antioxidants is of significant importance in the alleviation of oxidative stress during the formation of bone defects [140]. Similarly, CeO_2 NPs and antibacterial Ag-reinforced hydroxyapatite (HAp) composite were found to be effective in ROS scavenging and antibacterial effects [141]. Pandey and co-workers proposed titania nanotube arrays infused with cerium NPs (TiNTA-CeNPs) as an ROS scavenging tool. TiNTA-CeNPs were shown to protect pre-osteoblasts from ROS-induced oxidative stress. The NPs have a high potential for improving osteogenesis in oxidative stress-related bone disorders when tested in osteoporotic rat models [142]. Despite the progress so far, some limitations still impede the further development and application of nanozymes [133,143,144]. For example, the large-scale production of nanozymes is susceptible to fluctuations in reaction conditions. Additionally, the catalytic activity and selectivity of nanozymes remain inferior to their natural counterparts [144].

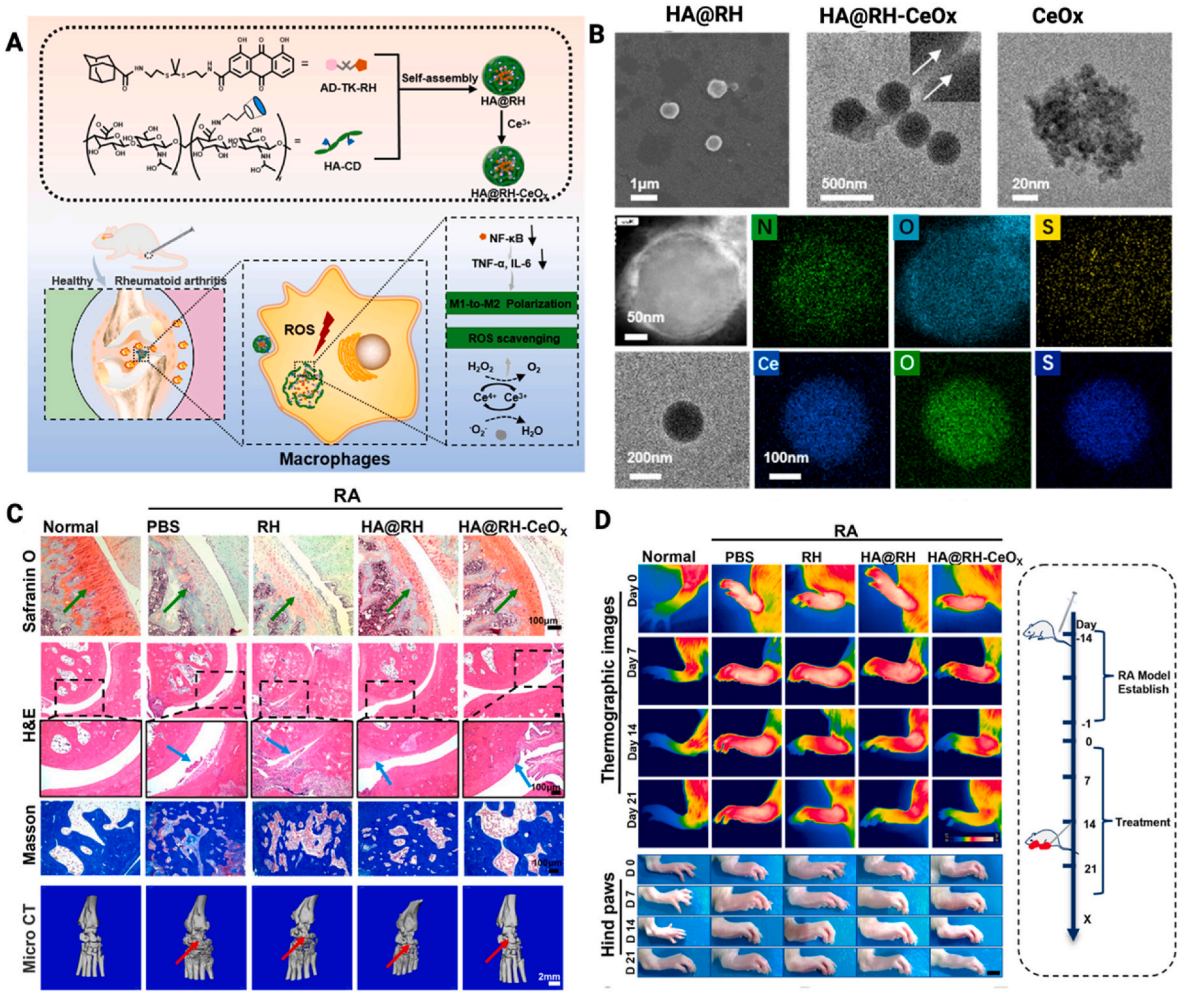

Fig. 3. Metallic nanozymes act as antioxidative and antibacterial agents. (A) Schematic of ceria oxide nanozyme micelles (HA@RH-CeOx) and their redox homeostasis normalization effects on M1 macrophages in RA microenvironment. **(B)** Scanning electron microscope (SEM)/Transmission electron microscope (TEM) images of HA@RH, HA@RH-CeOx, and CeOx; scanning transmission electron microscope (STEM) image and EDX spectra of HA@RH micelles (middle); STEM image and corresponding EDX spectra of HA@RH-CeOX micelles (bottom). **(C)** Safranin O staining of cartilage showing the HA@RH-CeOx-mediated increase in sulfated proteoglycans accumulation in cartilage matrix (green arrows). H&E staining of synovial tissues after different treatments. Blue arrows indicate the synovial fibroblast proliferation. Masson staining synovial tissues and micro-CT analysis of the bone tissues indicated rough bone surfaces due to bone erosion. **(D)** Thermal imaging of the left hind limb of CIA model mice after different treatments, and schematic illustration of the establishment of the RA model and the treatment process. Adapted with permission from Ref. [139]. Copyright 2023, American Chemical Society. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.2. Light-responsive MNPs

Light-responsive nanomaterials represent a nascent class of materials employed in non-invasive, non-contact, precise, and controllable nanodevices and in a wide range of biomedical applications, including photothermal therapy (PTT), drug delivery, and regenerative medicine [145]. The significance of these light-responsive nanomaterials is being investigated with the objective of designing light-guided nano-vehicles, modulating cellular behaviors, and regulating extracellular microenvironments [146]. Among the various types of light sources, near-infrared (NIR) light has garnered significant attention due to its capacity for deep tissue penetration, minimal damage to surrounding tissues, and convenient remote control capabilities [147]. The use of NIR for phototherapy in the treatment of inflamed joints is a promising avenue of research due to its ability to penetrate deeply into the affected area. Currently, there is significant interest among scientists in the potential of various types of nanomaterials that respond to NIR, including carbon-based nanomaterials, metal nanostructures, and metal sulfide or oxide nanostructures [148]. These nanomaterials demonstrate promise for intra-articular anti-inflammatory therapies that can provide photothermal and photodynamic therapeutic effects comparable to those observed in anticancer and antibacterial treatments [149,150].

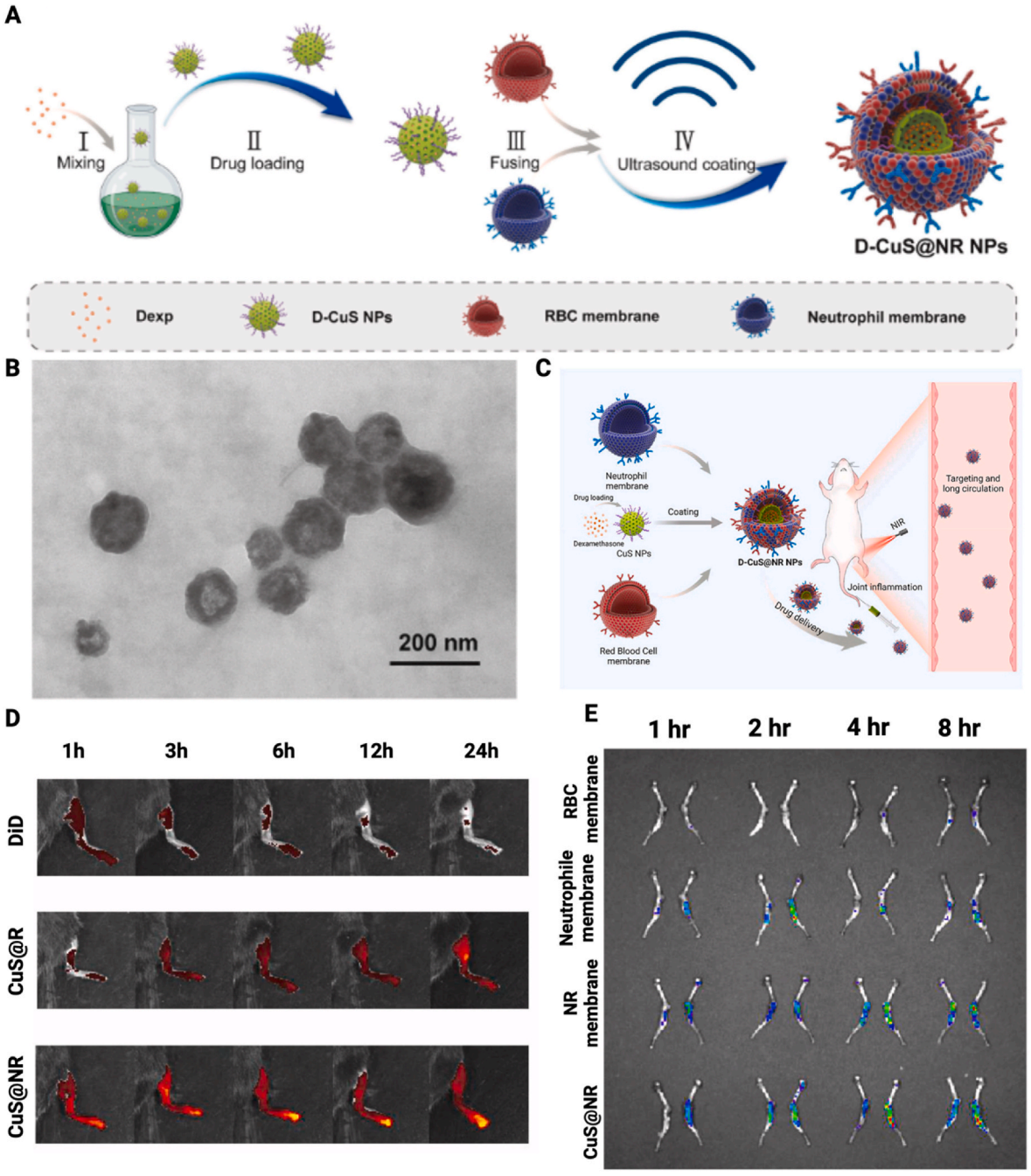

Fig. 4. Application of NIR responsive MNPs for OA treatment. (A) Preparation of neutrophil-erythrocyte membrane coated, dexamethasone sodium phosphate-loaded cupper sulfide (CuS) NPs. **(B)** TEM image of CuS@NR; NR = nanorod. **(C)** Graphical representation of synthesis and *in vivo* drug delivery of D-CuS@NR NPs *in vivo* in C57 mice. **(D)** Retention effects and biodistribution of DiD, CuS@R NPs and CuS@NR NPs in OA mice at different times (n = 3). **(E)** Targeting capacity of different NP samples examined at different times (1 h, 2 h, 4 h, and 8 h) in bone tissue of C57 mice. Adapted with permission from Ref. [154]. Copyright 2022, Elsevier.

Several studies underscore the versatility and therapeutic potential of NIR light-responsive nanomaterials in addressing joint diseases, including OA and RA, through precise and controlled drug delivery and therapeutic modulation [149,151]. A photothermal-triggered drug delivery platform based on molybdenum disulfide (MoS_2) nanosheets has been developed by researchers. The system can be used to treat OA via intra-articular injection, in which NIR is used to control the release of dexamethasone in the affected area [152]. In a further study, $Cu_{7.2}S_4$ NPs were employed as a photothermal agent for PTT and a photosensitizer for PDT. The $Cu_{7.2}S_4$ NPs, when combined with NIR irradiation, have been observed to achieve superior bone preservation outcomes while simultaneously inhibiting the progression of inflamed synovial invasion, cartilage erosion, and the expression of proinflammatory cytokines in CIA models [149]. NIR-responsive Au-NPs is another group of intensively studied light-responsive nanomaterials. Au-NPs entrapped in dendrimers coated with methotrexate (Au-DEN-MTX-IR780) were designed for RA treatment. The study findings demonstrate the biocompatibility of these NPs on both non-activated and LPS-activated RAW264.7 macrophages [153]. Similarly, NIR responsive tea-derived polyphenol modified zirconium-based porphyrin metal organic framework (TP-Au@PCN) was designed by Xu and his co-workers as a multifunctional nanoplatform for the treatment of OA. The expression of collagen type II (COL- II) and proteoglycan was observed to increase in chondrocytes treated with NPs. Injection of TP-Au@PCN effectively raised the joint temperature and controlled drug delivery under NIR excitation, which was very helpful for *in vivo* tissue growth [151]. Copper sulfide NPs coated with neutrophil-erythrocyte hybrid membranes and dexamethasone sodium phosphate NE/D-CuS were studied to understand their *in vitro* therapeutic effect in chondrocytes of the suckling mouse and *in vivo* with C57 mouse OA model (Fig. 4A–C). These biomimetic NPs improved have excellent retention time and showed good anti-inflammatory properties and biocompatibility with chondrocytes isolated from mouse (Fig. 4D and E) [154].

Beyond arthritis therapy, NIR light has also been harnessed to accelerate bone tissue regeneration. The photothermal effect triggered by NIR irradiation has the potential to achieve non-invasive and controlled cell differentiation, thereby providing a unique strategy for bone tissue regeneration [155,156]. Researchers have designed synthetic porous AuPd alloy NPs (pAuPds) as a thermotherapy agent for in situ bone regeneration via PTT. It was found that after six weeks of PTT treatment, the area of new bone covering the skull defect reached nearly 97 % [156]. Furthermore, a recent study has confirmed the efficacy of biomimetic anti-inflammatory nano capsules (BANCs) for bone tissue repair. These BANCs, when irradiated with NIR light, demonstrated enhanced efficacy in bone tissue repair through preventing inflammatory response and promoting M2 polarization in *in vivo mouse femoral defect models* [157].

Additionally, there have been notable advancements in the utilization of NIR-responsive NPs for the targeted treatment of osteolytic lesions and bone tumors. These NPs include phytic acid-capped platinum NPs [158] and trifolium-like platinum NPs (TPNs) [159]. Phytic acid-capped NPs show high specificity for HAp and a 4-fold higher accumulation in osteolytic lesions. Their anticancer properties and photothermal effects effectively inhibit bone tumor growth and associated osteolysis upon exposure to NIR light. Furthermore, when activated by NIR light, TPNs exhibit minimal cytotoxicity to normal cells while demonstrating potent cytotoxic effects against cancer cells in PC9-BALB/c mouse models, highlighting their potential for targeted cancer therapy. Recent advances in NIR-based NPs have led to the development of innovative dual light irradiation systems for the enhancement of biofilm elimination and promotion of osteointegration of implants. In this quest, Hang and colleagues developed a biocompatible nanorod array on Ti implants that incorporates TiO_2, molybdenum disulfide, polydopamine and arginine-glycine-aspartic acid. These nanoarrays have the capacity to eradicate bacteria when exposed to 808 nm NIR light. This system has the additional benefit of enhancing the osteogenic ability of implants while eradicating biofilms [160]. Another hybrid system consisting of Bi_2S_3 nanorods prepared on Ti implant and loaded with Ag_3PO_4 NPs (Fig. 5A) also showed good photothermal effects using BS as photocatalyst. Additionally, the integration of Ag_3PO_4 conferred bacteriostatic capabilities upon the implants, as evidenced in Fig. 5B–D [161]. To form stable and cost-effective photothermal films on bone implants, the researchers grew oxide semiconductor films doped with Ni NPs on $NiTiO_3$ in situ. These films have a reliable photothermal effect under NIR and excellent anti-tumor properties *in vitro* and *in vivo* [162].

The potential of multifunctional PTT, combined with chemotherapy, immunotherapy, PDT, as well as simultaneous imaging modality, has also been demonstrated by MNP-based nanoplatforms [152,153,163]. Despite their excellent photothermal efficacy, they still suffer from poor biodegradability and potential toxicity, which can cause serious side effects such as long-term organ accumulation. Furthermore, the synthesis and modification processes may employ harsh surfactants (e.g., CTAB), which could prove deleterious to human health if not completely removed. Thus, thorough investigations of pharmacokinetics, biodistribution and toxicity of MNPs-PTT agents are critically needed. Another challenge is to overcome the physical limitation of the light penetration depth, which is usually less than 1 cm under the skin, leaving deep tumors and bone beyond effective PTT treatment. To overcome this hurdle, a possible solution is the development of NIR-II responsive PTT (1000–1350 nm), which exhibits reduced tissue absorption and, consequently, enhanced potential for deeper tissue penetration [163,164].

3.3. Magnetic NPs

NPs possess a high surface-to-volume ratio, which enables them to adsorb proteins or load drugs [165]. At nanoscale, magnetic NPs exhibit superparamagnetic behavior, enabling precise aggregation in response to an external magnetic field at a specific location [166]. This targeted delivery capability is highly advantageous for gene and drug delivery [167], making magnetic NPs attractive for applications in osteoporosis [168], OS [169], bone defect [170], and OA [171], which will be discussed in detail below.

Some studies have shown promising applications of magnetic NPs in treating arthritic disorders, particularly OA. Jafari and co-workers coated magnetic NPs with polyethylene glycol (PEG) and demonstrated their ability in an *ex vivo* cartilage model under an alternating magnetic field. The application of magnetic field increased the uptake of the NPs by nearly 50-fold, suggesting that magnetic fields can potentially enhance the transport and distribution of bioactive agents within cartilage [172]. In another study, magnetic composite NP made of iron oxide NPs coated with Dir dye and PEG-polylactic acid (PLA) were studied for drug clearance efficiency (Fig. 6A and B). The results of EPR spectroscopy demonstrated that the NP retention rate was higher in 15-month-old mice compared to 5- and 10-month-old mice, indicating that age influences clearance efficiency. The age factor therefore should be considered when synthesizing magnetic composites for drug biodistribution for the treatment of OA [171]. Moreover, researchers have integrated magnetic NPs into a hybrid hydrogel for cartilage tissue engineering. For instance, Zhang and colleagues combined polyvinyl alcohol (PVA)-modified magnetic NPs with a hybrid hydrogel composed of COL-II, HA, and PEG to develop magnetic nanocomposite hydrogel for cartilage tissue engineering. Remarkably, this magnetic hydrogel demonstrated excellent responsiveness to external magnetic fields while retaining its structural integrity [173].

Additionally, other studies demonstrated the potential of magnetic NPs in the treatment of bone tumors and their efficacy in enhancing bone growth. For example, Sasikala and colleagues designed piezomagnetic NPs (PMNPs), a nanocomposite system consisting of piezoelectric barium titanate and superparamagnetic iron oxide NPs [174]. As shown in Fig. 6C and D, it was found that risedronate released from

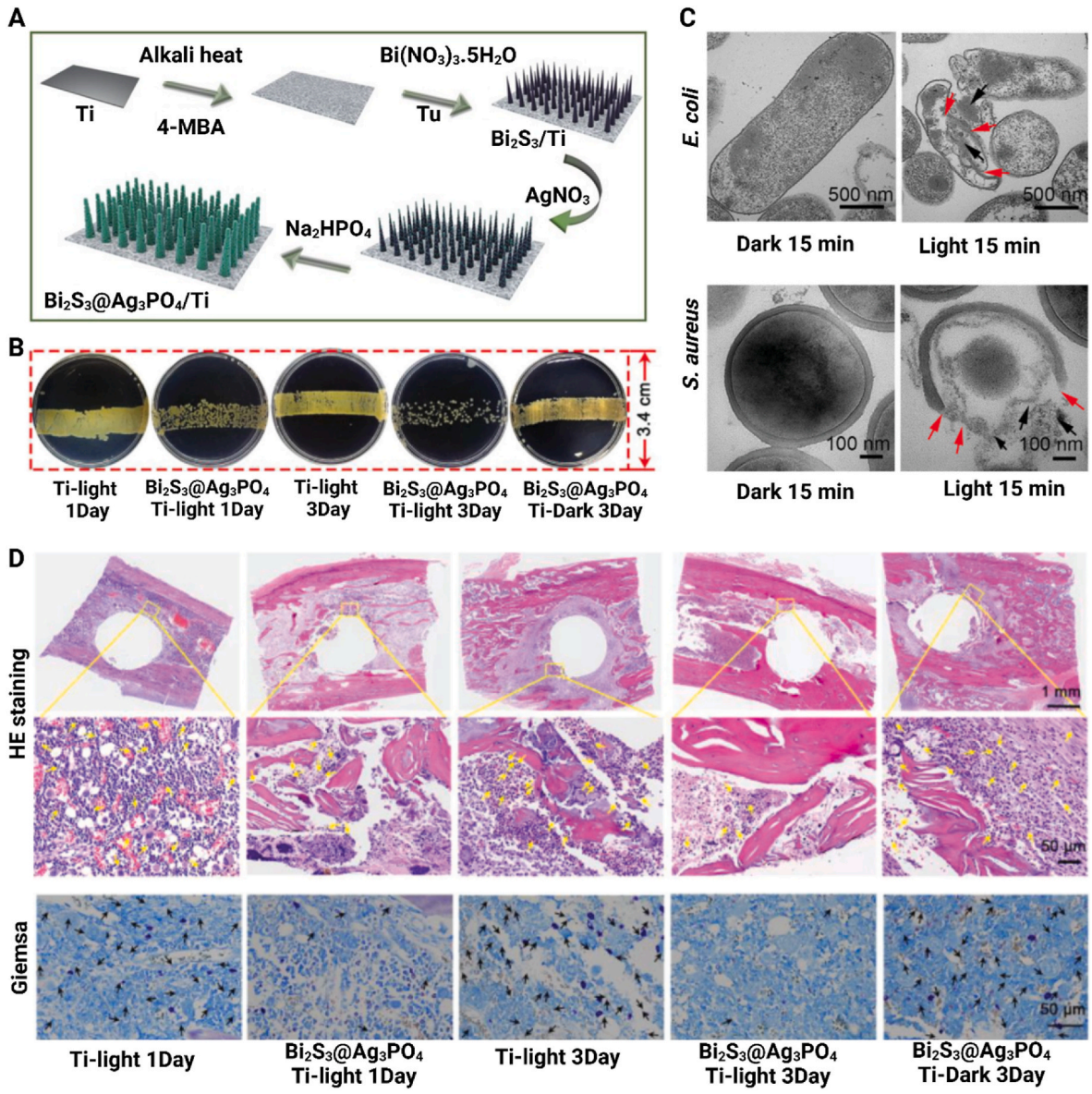

Fig. 5. Use of Bi_2S_3 nanorods for the removal of biofilms from bone implants. **(A)** Schematic illustrating the synthesis of Bi_2S_3@Ag_3PO_4 nanorod arrays on a Ti plate. **(B)** Photographs of bacteria colonies showing the antibacterial ability of Bi_2S_3@Ag_3PO_4. **(C)** Antibacterial efficiency of Bi_2S_3@Ag_3PO_4/Ti against *S. aureus* and *E. coli* with protein leakage. **D)** H&E and Giemsa staining images showing bone tissue infection (yellow arrows indicate neutrophil infiltration and necrotic cells; bacteria indicated with black arrows). Adapted with permission from Ref. [161]. Copyright 2019, Wiley-VCH. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

PMNPs under low-intensity pulsed ultrasound (LIPUS) promotes the intracellular localization of NPs in Saos-2 cells. Anethole dithiolethione (ADT)-loaded magnetic nanoliposomes (AMLs) have been found to be efficient in targeting tumor tissue when guided by an external magnetic field. AMLs treated with a magnetic field have shown significantly higher inhibition of tumor growth, which may be promising for multi-modal image-guided accurate cancer therapy [175]. Nelogi and co-workers designed Ti-chambers composed of neodymium and boron magnetic discs treated with Fe-NPs and evaluated their effects on osteoblast-like cells (MG-63) [176]. It was observed that the process of mineralization and osteogenesis was significantly more pronounced in the Ti-chambers than in the control groups. Another research study demonstrated that superparamagnetic iron oxide NPs (SPIONs) and SPIONs-loaded gel have a tissue repair effect in the incisor sockets of Sprague-Dawley rats. *In vivo* MRI images of mandible incisor sockets treated with SPIONs and SPIONs-based gel showed improved growth, indicating the effectiveness of these NPs in osteogenesis [177].

Although numerous studies on magnetic NPs for biomedical applications, including cancer therapies, drug delivery, OA, and bone defect management, have been conducted and significant achievements have been made, there is still a great deal of work to be done [178–180]. Firstly, the development of new synthesis techniques and methods is essential for the preparation of magnetic NPs with improved biocompatibility. Secondly, following the delivery of magnetic NPs to target tissue, most of these particles are often distributed within the reticulo-endothelial system, particularly in the liver and spleen. It is therefore important to develop new methods for reducing the cytotoxicity and improving the biocompatibility of the currently available magnetic NPs [181]. Another significant challenge associated with magnetic NPs is their proclivity to aggregate, coupled with the poor magnetization observed in the smallest magnetic NPs employed in biomedical applications. It is therefore paramount to establish effective large-scale synthesis protocols with precise control of the size, dispersion, and shape of the different magnetic NPs, including their appropriate

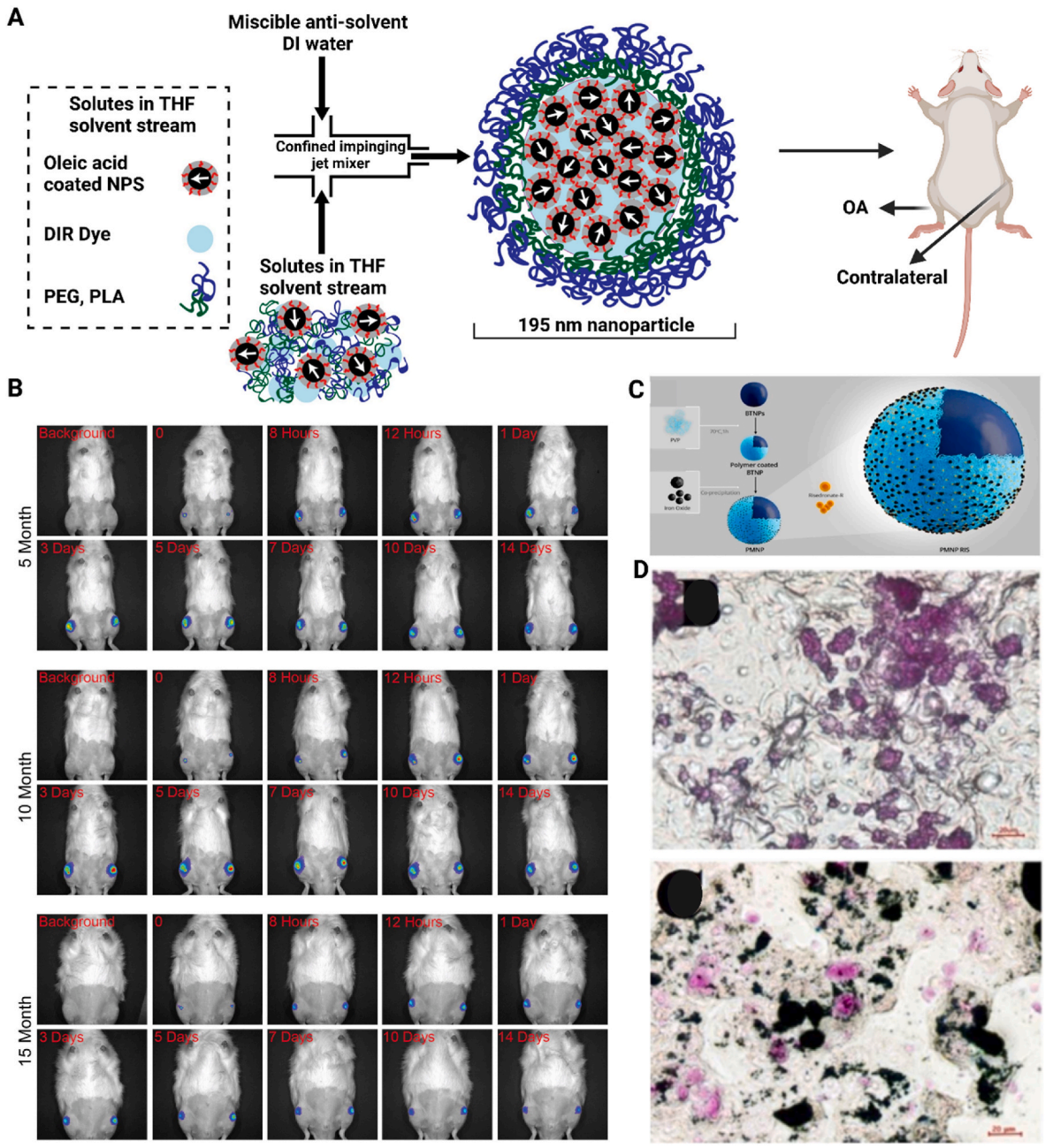

Fig. 6. Magnetic NPs for OA (A, B) and OS treatment (C, D). **(A)** Flash nanoprecipitation method for the synthesis of composite NPs. Iron oxide NPs were coated with oleic acid, DiR dye and PEG-PLA and subsequently suspended in tetrahydrofuran (THF), which was then mixed in a closed impinging jet mixer. **(B)** Representative fluorescent images showing NP clearance in rats aged 5, 10 and 15 months. Reproduced with permission from Ref. [171]. Copyright 2020, Elsevier. **(C)** Schematic illustration of the synthesis of piezo magnetic NPs. **(D)** Prussian blue staining of Saos-2 cells alone and cells treated with Piezomagnetic NPs (PMNPs) showing the intracellular localization of PMNPs (PMNPs in dark blue color due to the presence of Fe_3O_4 NPs and the cell nuclei stained in pink color using nuclear fast red staining. Reproduced under the terms of the CC-BY-NY-ND Creative Commons Attribution 4.0 International license (https://creativecommons.org/licenses/by/4.0) [174]. Copyright 2022, The authors, published by Elsevier. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

biofunctionalization, in order to overcome the aforementioned challenges [182].

3.4. pH-responsive MNPs

The acidic microenvironment is a common feature of several bone diseases and OA [183]. pH-responsive NPs are mostly developed using an acid-sensitive side chain as a functional group or attaching a pH-responsive substance [184]. As a result, pH-responsive NPs can change charge and/or hydrophilicity depending on the environmental pH, thereby inducing changes in NP behaviors such as rearrangement, solubilization, or disintegration [185,186]. The design of pH-responsive NPs typically employs either cationic or anionic substances [187]. As the pH level declines, the hydrophobicity of cationic substances increases, while the hydrophilicity of anionic substances decreases [186]. The majority of bone and joint diseases manifest in acidic environments, thus facilitating the release of drugs attached to acid-reactive groups within the pathological microenvironment [188]. Recently, some interesting pH-sensitive MNPs based on metals such as Fe, Ag, Au, Ce, Zn, Cu and metal organic frameworks (MOFs) have been designed to treat

bone-related diseases and OA, showing encouraging efficacy.

A study based on self-assembled iron-catechins NPs (Fe-cat NPs) was designed based on the synergistic reaction between iron ions and plant-derived antioxidants, the catechins [189]. It was demonstrated that Fe-cat NPs exhibited pH-responsive degradation in cells and inhibited the adipogenic differentiation of human adipose-derived stem cells (hADSCs). Furthermore, Fe-cat NPs remodeled the osteogenic immune microenvironment through resistance to inflammation and promotion of macrophage M2 polarization. Another study proposed a drug delivery system based on Fe^{3+} incorporated on the surface of nanotubes, which can effectively bind to alendronate sodium (NaAL), a bisphosphonate drug for the treatment of osteoporosis, through coordination bonds that can be formed or broken by a change in pH [190]. The Fe-modified titanium dioxide nanotubes (TNTs) enabled not only alendronate loading levels of up to 50.2 wt%, significantly higher than most previously reported drug delivery systems, but also delayed and prolonged drug release. In addition, Ahmadi and co-workers designed a smart nano system consisting of a magnetic inner core and polymeric outer shell with pH-responsive cationic cyclodextrin for targeted delivery and enhanced uptake of the anticancer drug methotrexate for the Saos-2 cell line [191].

pH-responsive strategies have also been combined with metal NPs to treat bone defects and infections. One study used a low pH-sensitive acetal linker to implant AgNPs onto TNT implants [192]. An acidic environment (pH = 5.5) facilitated the release of AgNPs from the TNT-AL-AgNPs implant more than a basic environment (pH = 7.4). 3D printed porous polyetheretherketone (PEEK) scaffolds with AgNPs trapped on the first polydopamine (pDA) layer and apatite on the second

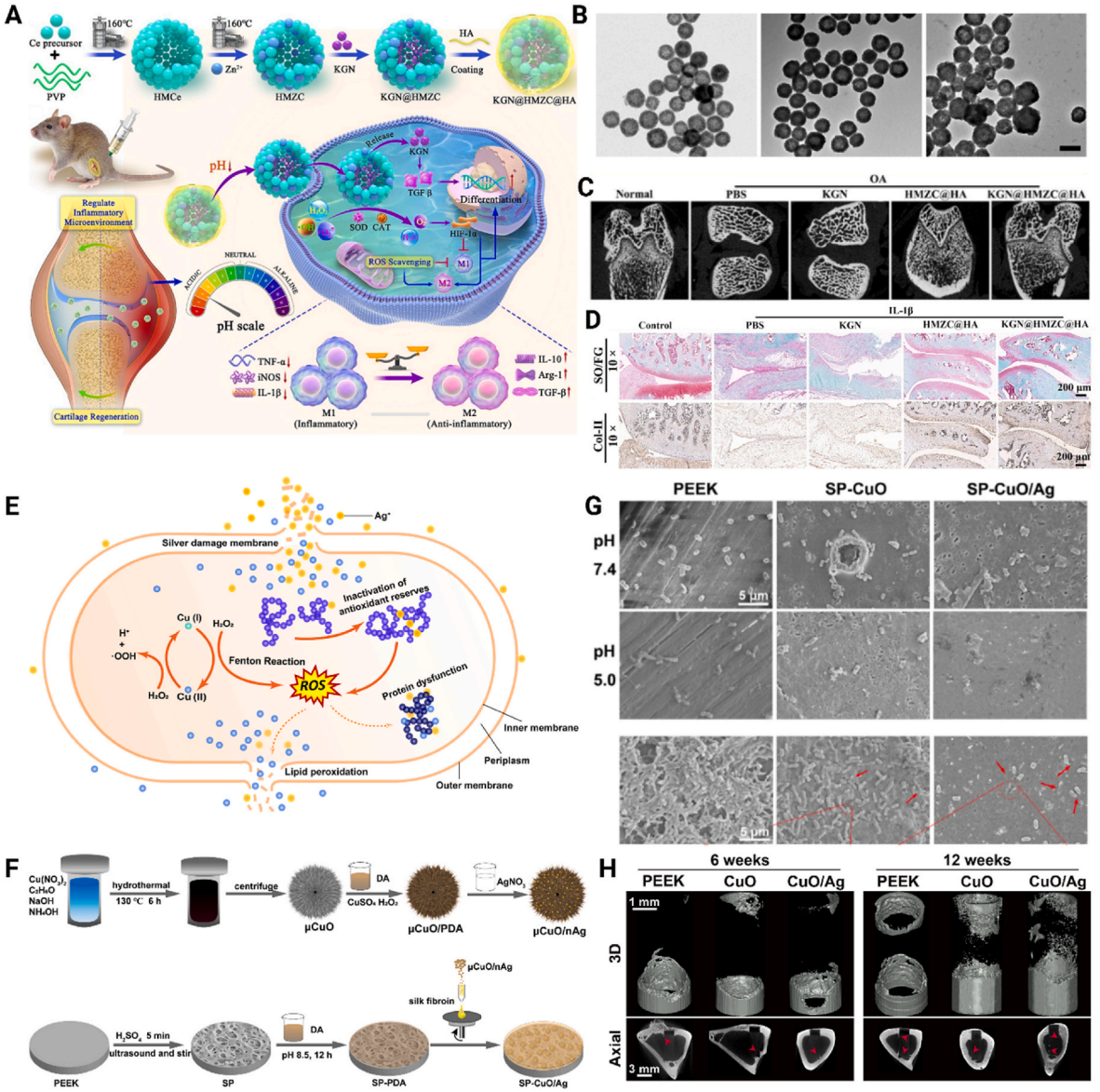

Fig. 7. pH-responsive MNPs for treating OA (A–D), osteomyelitis and bone defect (E–H). **(A)** Schematic illustration of the preparation of Zn-doped hollow mesoporous CeO (HMZC) loaded with kartogenin (KGN). **(B)** TEM images of HMCe, HMZC, and HMZC@ hyaluronic acid (HA). **(C)** Representative reconstruction images obtained from Micro-CT scans, illustrating the right knee at 28 days post-treatment. **(D)** Safranin O-fast green (SO/FG), and collagen type II immunohistochemistry staining images of knee joint tissues of normal or OA rats subjected to PBS, KGN, HMZC@HA, or KGN@HMZC@HA treatments. Reproduced with permission from Ref. [195]. Copyright 2024, Elsevier. **(E)** Schematic illustration of the synergistic bactericidal effect between copper and silver. **(F)** Schematic illustration of μCuO/nAg fabrication and surface functionalization of PEEK. **(G)** SEM images of bacterial morphology after 6 h and 7 days of sample incubation. **(H)** Micro-CT imaging and quantification of bone regeneration. Reproduced with permission from Ref. [197]. Copyright 2020, Elsevier. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

pDA layer have also been developed for bone defects treatment [193]. The unique "pDA-Ag-pDA" sandwich structure imparts to the inert PEEK scaffolds a bacteria-triggered pH-responsive ion-release behavior, i.e. the release of Ag^{+} ions from the coating increases with decreasing pH, which is associated with bacterial metabolism. Importantly, *in vivo* evaluation indicates that the Ag/apatite decorated multifunctional scaffolds exhibited attractive *in vivo* antibacterial efficacy and resulted in excellent bone ingrowth and osseointegration in an infected critical-sized bone defect.

Nanoplatforms that respond to pH levels can deliver drugs in a targeted manner for the treatment of OS and OA. A study showed that CeO-NPs enhanced chemotherapeutic activity against the OS cell line Saos-2 [194]. The delivery system comprised calcium carbonate and collagen type I containing nano-cerium oxide and doxorubicin. At pH = 6.0, the synergistic effect of the pro-oxidant CeO_2 NPs and the encapsulated doxorubicin results in nearly 100 % cell death. Another innovation involved Zn-doped hollow mesoporous CeO-NPs designed for targeted drug delivery of kartogenin (KGN) (Fig. 7A and B) [195]. The prepared NPs achieved controlled KGN release in response to the OA environment and chemically programmed the OA microenvironment. The NPs in acidic conditions showed a significantly higher cumulative release of KGN, with more than 60 % and 80 % of the encapsulated KGN being released from the nano-system at pH = 6.7 and 6.0, respectively. Overall, these pH-responsive nanoplatforms provide a promising strategy for targeted drug delivery in OA and improved cartilage growth (Fig. 7C and D) by taking advantage of the intrinsic elevated acidity levels in the affected areas. Researchers have developed a new type of zinc oxide NPs and fixed them on a titanium substrate [196]. It was found that naringin and Zn^{2+} can be easily released from the functionalized titanium substrate to the bacterial infection sites due to the acidic conditions caused by osteomyelitis. These studies highlight the potential of pH-responsive nanoplatforms in enhancing therapeutic outcomes through precise drug delivery and efficacy modulation in acidic disease microenvironments.

In the context of osteomyelitis treatment, Cu-based NPs have demonstrated efficacy in eradicating bone infections and promoting bone regeneration. Researchers have prepared a metastable $CuFe_5O_8$ nanocube (NC) as a smart catalyst with properties similar to those of the Fenton reaction. The spatial selectivity of its activity can be controlled by adjusting pH and H_2O_2 concentration. It has been demonstrated that $CuFe_5O_8$ NC is capable of catalyzing the cleavage of environmental DNA (eDNA) in biofilms, leading to disruption of its structure. In addition, lower levels of hydroxyl radicals induced pro-inflammatory macrophage polarization outside the biofilm, reversing the immunosuppressive microenvironment [198]. pH-responsive carmellose microspheres crosslinked with Cu ions, developed by an external ionic gelation method, have shown activity against *Escherichia coli* or *Candida albicans*. Consequently, changes in the pH of the medium can determine the diffusion characteristics and, therefore the release of drugs [199,200]. In another study, a research team employed silk fibroin to fabricate CuO microspheres adorned with silver NPs (nAg) on a porous PEEK surface (Fig. 7E and F). The release of Cu^{2+} and Ag^{+} at pH 5.0 resulted in the death of 99.99 % of planktonic bacteria. Furthermore, the release of metal ions at pH 7.4 promoted the production of ALP and NO, and the secretion of collagen and calcium deposition, indicating enhanced bone formation and angiogenesis (Fig. 7G and H) [197].

MOFs have a range of applications, including OA therapy, co-delivery of drugs and siRNA for inflammatory disorders, and enhanced efficacy in OS. A pH-responsive MOF system was developed, which was modified with HA and loaded with the anti-inflammatory protocatechuic acid (PCA) for treating OA. The MOF system exhibited an intelligent response to acidic conditions within the inflammatory microenvironment, resulting in the release of PCA and reduced synovial inflammation [201]. In another pH-responsive MOF material, MIL-101-NH2 was employed to synergistically deliver the anti-inflammatory drug curcumin (CCM) and siRNA targeting the hypoxia-inducible factor (HIF-2α) [202]. The MOF system released the CCM active ingredient in an acidic environment, thereby reducing the level of pro-inflammatory cytokines. As well as active siRNA targeting HIF-2α mRNA. These processes inhibited the inflammatory response and cartilage degeneration associated with OA. A team led by Kin developed folate-targeting nano formulations based on nanoscale MOFs (nMOFs) and calcium zoledronate (CaZol), a third-generation bisphosphonate widely used as an anti-resorptive agent to treat cancer bone metastasis [203]. The Fol-targeted lipid coating facilitates endocytosis of CaZol nMOFs in cancer cells, allowing CaZol nMOFs to control the release of encapsulated Zol under mildly acidic conditions. Due to the super cellular uptake and prolonged drug release kinetics, CaZol nMOFs showed higher efficacy than Zol in inhibiting cell proliferation and inducing apoptosis.

In pH-responsive drug delivery for bone and joint diseases, protonation could cause endoplasmic/lysosomal escape in nano systems, leading to autophagy and cell death. It is therefore recommended that greater attention be paid to the safety of pH-responsive NPs when investigating the efficacy of chemical group protonation. Furthermore, the application of acid-sensitive hydrazone bonds may result in cytotoxicity due to the presence of aldehyde or ketone functional groups within the therapeutic agent and cationic residues [123,204].

4. Joint & Bone disease-specific therapeutic applications of MNP-based nanocomposites

MNPs have demonstrated significant potential in the treatment of various bone and joint disorders [206]. For example, in osteoporosis, MNPs can improve the growth and density of bone due to their structural reinforcement and ability to effectively deliver therapeutic agents [207]. For patients with osteomyelitis, the incorporation of antibacterial MNPs into scaffolds can facilitate the prevention of infection and support the bone healing process [208]. In the case of OS, MNPs can be functionalized to specifically target cancer cells, thus aiding in both diagnosis and treatment [209]. Moreover, MNPs can enhance the mechanical strength of scaffolds utilized for bone defect treatment and facilitate the controlled release of growth factors, thereby promoting regeneration [210]. In OA and RA, MNPs enable targeted drug delivery to reduce inflammation and accelerate cartilage repair [211]. Overall, MNPs in hydrogels and scaffolds can enhance bioactivity, mechanical properties and therapeutic effects, thereby improving the treatment outcomes of various bone and joint diseases. These MNPs can be administered via localized or systematic approaches, as discussed below.

4.1. MNPs and MNP-based composites for treating osteoporosis

Osteoporosis is a disease that causes bones to become weak and more likely to break. In adults, bone formation is a coordinated process involving both osteogenesis (production and mineralization of new bone matrix) and osteoclast genesis (destruction of old bone) [212]. While various antiresorptive medications are used for clinical management of osteoporosis [213], the current scope of osteoporosis treatment is constrained by several significant limitations, including long-term safety concerns [214]. Bisphosphonates represent a primary treatment option for osteoporosis, which can inhibit osteoclast activity by inhibiting farnesyl pyrophosphate synthase [215]. Although bisphosphonate has the capacity to mitigate the risk of fracture and bone turnover, its impact on the growth or restoration of bone mass is minimal. Furthermore, bisphosphonate is not readily absorbed by the gut and exhibits variable bioavailability [216,217]. Raloxifene (RLX) is another antiresorptive drug, which is a selective estrogen receptor modulator capable of increasing bone mineral density. Although the intestines rapidly absorb RLX, it undergoes a prolonged pre-systemic glucuronide conjugation, resulting in relatively low absolute bioavailability [218]. Furthermore, systemic medications typically circulate throughout the body but demonstrate limited penetration into bone tissue and are rapidly

excreted. This is due to the lower blood supply to the bones than to organs such as brain, liver, or kidneys [219,220]. As a result, high doses are usually required to reach therapeutic levels, increasing the risk of systemic toxicity. To address this issue, the development of a controlled delivery platform that selectively targets bone tissue would enhance safety and efficacy [221].

There has been increased interest in using MNPs to treat bone diseases. MNPs offer a number of advantages, including protection from degradation, improved transport efficiency, enhanced pharmacokinetics and biodistribution, as well as tissue targeting capabilities. These properties make them an ideal choice for the repair of bone tissue in patients with osteoporosis [222]. A bone-targeting pH-responsive cerium oxide NPs was developed for treating osteoporosis by selectively removing mature osteoclasts without damaging pre-osteoclasts (Fig. 8A and B). The application of cerium oxide NPs has been demonstrated to enhance calcium oscillation, improve bone marrow macrophages (BMMs) proliferation and reduce the viability of mature osteoclasts through ROS generation (Fig. 8C–E) [223]. In another study, nanoceria encapsulated in mesoporous silica NPs offer antioxidant, osteogenic, and anti-osteoclastogenic properties in osteoporosis treatments. These NPs stimulated osteoblast cells to form bone matrix and exhibited antioxidant effects in MC3T3-E1 cells without the need for osteogenic supplements. Furthermore, tartrate-resistant acid phosphatase (TRAP) staining of RAW264.7 cells exposed to NPs in basal and osteogenic media with or without RANKL showed promising efficacy of the NPs as an osteoporosis treatment (Fig. 8F and G) [224].

One of the distinctive characteristics of nanoceria in redox chemistry is their capacity to transition between cerous (Ce^{3+}) and ceric (Ce^{4+})

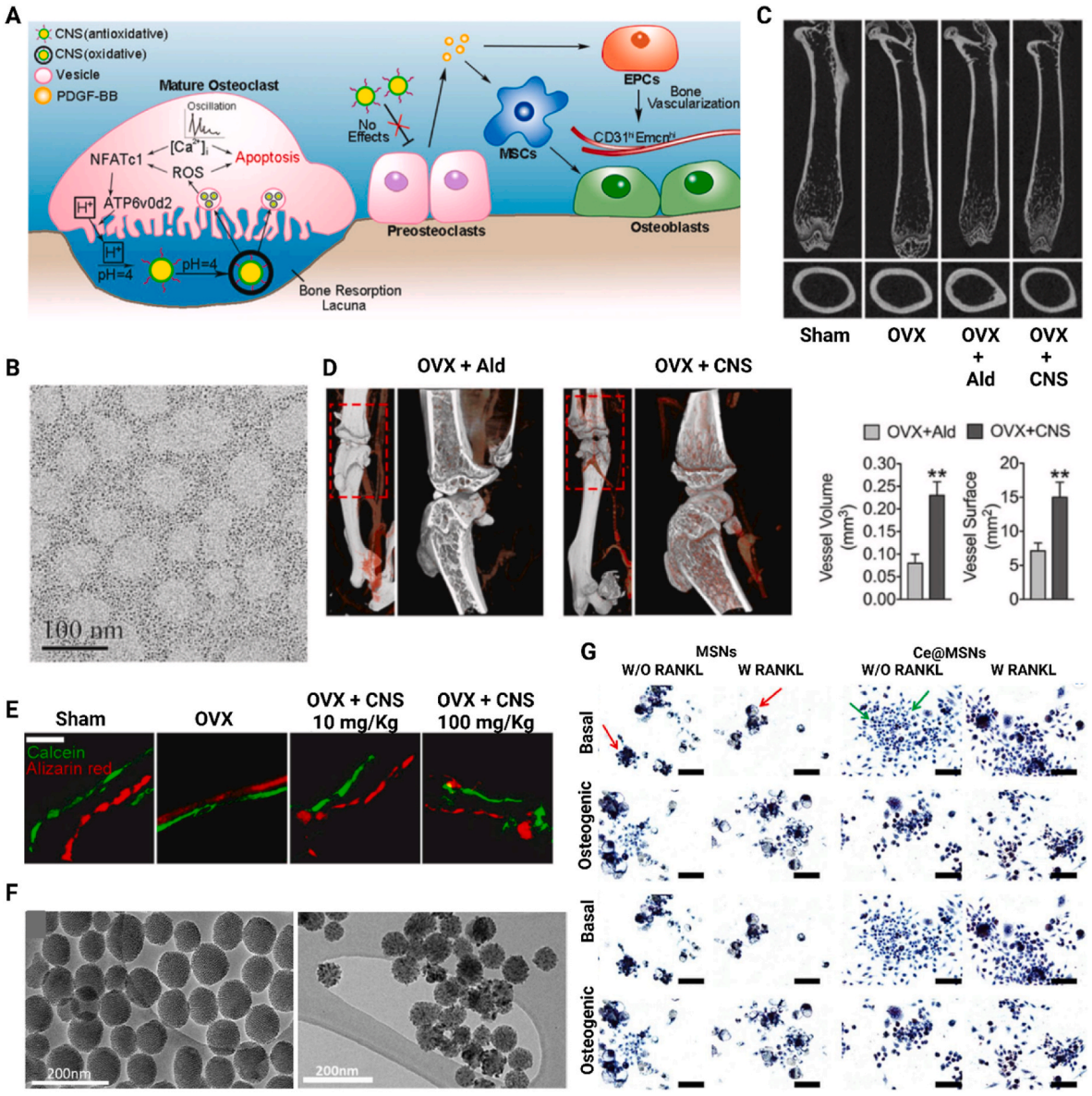

Fig. 8. Effects of cerium-based NPs in osteoporosis treatment. (A) Schematic diagram of the mechanism of cerium NPs (CNS) in the treatment of ovariectomized (OVX) mice. **(B)** TEM image of CNS. **(C)** Typical μCT image of the femur of an OVX mice. **(D)** μCT microvascular perfusion imaging of the femurs of OVX mice treated with the anti-resorptive drug alendronate (Ald) or CNS, and corresponding quantitative analysis. **(E)** Representative images of tissue sections showing double labelling with calcein and alizarin red of cortical bone in treated mice and the control group. Scale bar = 200 μm. Reproduced under the terms of the CC-BY-NY-ND Creative Commons Attribution 4.0 International license (https://creativecommons.org/licenses/by/4.0) [223]. Copyright 2021, The authors, published by Elsevier. **(F)** TEM images for mesoporous silica NPs (MSNs) and ceria-loaded mesoporous silica NPs (Ce@MSNs). **(G)** TRAP staining of RAW264.7 cells exposed to MSNs and Ce@MSNs in basal and osteogenic media with and without RANKL treatments after 3 and 7 days. Scale bar = 100 μm. Reproduced with permission from Ref. [224]. Copyright 2021, Elsevier. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

oxidation states, making nanoceria comparable to biological antioxidants such as superoxide dismutase and catalase [225]. Cerium oxide NPs doped with lanthanum ions were developed with the objective of resisting oxidative stress in osteoporotic rat models. The rat models treated with the doped cerium oxide NPs showed a significant osteogenic effect with upregulated SOD1 and CAT expression [226]. In addition, bisphosphonate and iron NPs proved beneficial in enhancing the properties of HAp for the treatment of osteoporosis. In this way a multi-functional HAp with alendronate (AL) and Fe_3O_4 was used for bone regeneration in ovariectomized (OVX) rats. The findings indicated that the multifunctional HAp was capable of inhibiting osteoclast activity, promoting osteoblast proliferation and differentiation, enhancing bone integration of the implant, and accelerating bone remodeling in OVX rats with osteoporosis [227]. A comparable study employed alendronate-loaded FeO-NPs to address postmenopausal bone loss in OVX mice. The NPs significantly regulated bone metabolism and were helpful in the scavenging of ROS [228]. In another study, dextran-coated Fe_3O_4-NPs were conjugated with bisphosphonates. Dextran-coated Fe_3O_4-NPs showed potential inhibition of osteoclasts when exposed to radiofrequency (RF) to induce thermolysis [168].

AuNPs are highly beneficial osteogenic agents. AuNPs were reported to induce osteogenic differentiation of osteoprogenitor cells such as MSCs without cell cytotoxicity and inhibit osteoclast formation [229, 230]. Vitamin D conjugated Au NPs (VGNPs) were prepared and evaluated for their anti-osteoporotic effects. VGNPs were found to inhibit the expression of ROS and the expression of genes associated with osteoclast differentiation [231]. In another study, alendronate-conjugated AuNPs (AuNPs-ALD) were tested for their ability to suppress RANKL-induced osteoclastogenesis. AuNPs-ALD inhibited osteoclast growth and showed improved bone density in OVX mice [232]. Another study

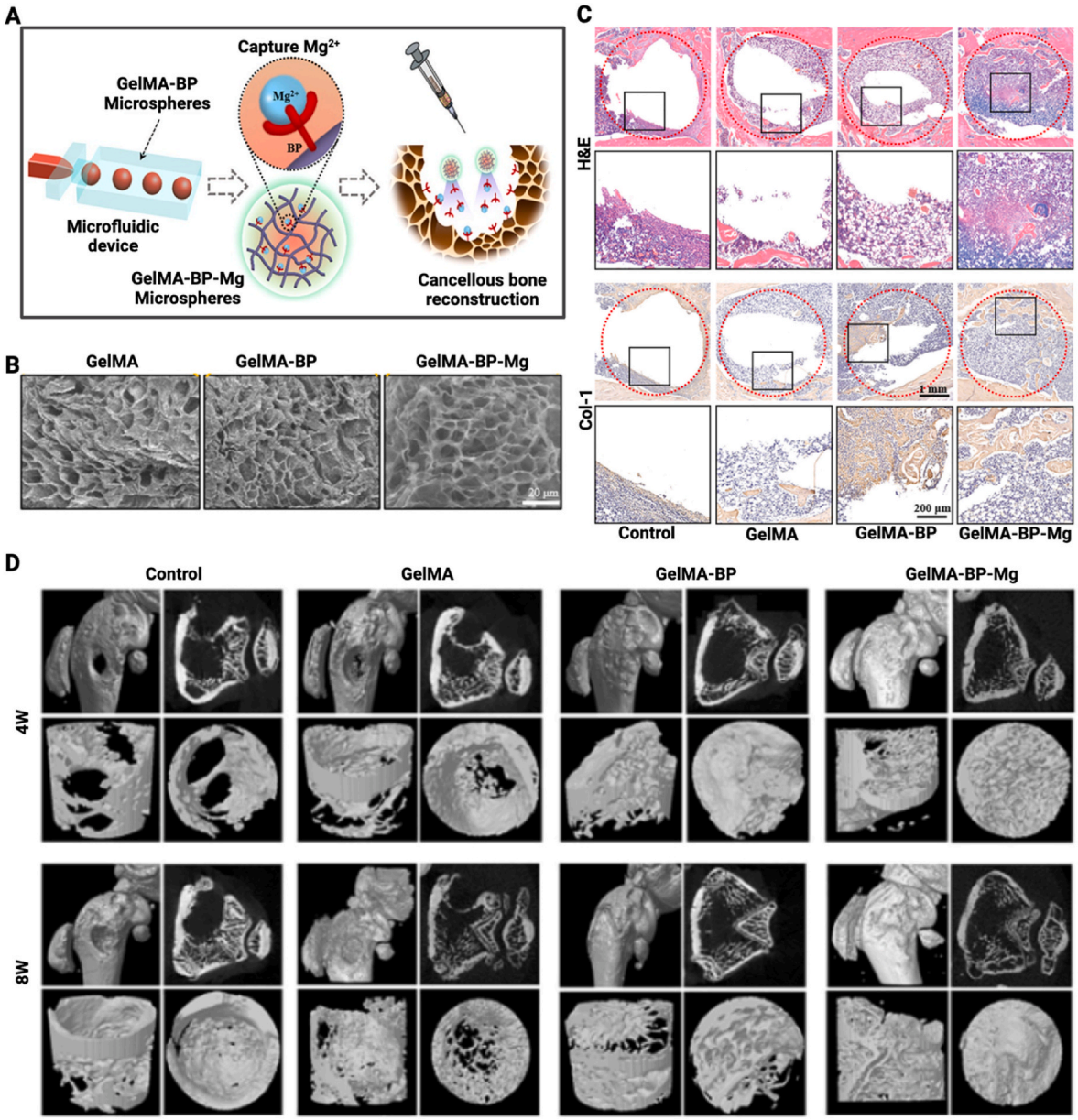

Fig. 9. MNPs encapsulated in GelMA and their use in osteoporosis. **(A)** The process of preparing Mg ion-based microspheres. **(B)** Typical SEM images of GelMA, GelMA-BP and GelMA-BP-Mg; GelMA = gelatin methacrylate, BP = bisphosphonate. **(C)** Representative micrographs of H&E staining and Col-1 IHC staining of bone tissue sections treated for 8 weeks in each group and pictures of the femoral tissue section; H&E = Hematoxylin and eosin stain, COL-1 = collagen type 1, IHC = immunohistochemistry. **(D)** Micro-CT images of rat models after 4 and 8 weeks of treatment. Adapted with permission from Ref. [243], Copyright 2021, American Chemical Society.

assessed the inhibitory impact of AuNPs in conjunction with a β-cyclodextrin and curcumin complex (CUR-CGNPs) on RANKL-induced osteoclast genesis. The presence of CUR-CGNPs reduced the expression of osteoclast-associated receptors (OSCAR), nuclear factor of activated T cells 1 (NFATc1) in BMMs and significantly improved bone density in the osteoporotic OVX mouse model [233].

Zinc can be a dopant in HAp crystals and contribute to bone formation and mineralization [234]. Zinc has been shown to stimulate the activity and proliferation of osteoblasts to accelerate bone formation and repair [235]. Studies suggest that zinc supplementation may help prevent bone loss associated with aging and conditions such as osteoporosis. It was observed that ZnO NPs can effectively stimulate the proliferation and mineralization of MG-63 cells without significant cytotoxicity [236]. Coatings of Zn-based MOFs and raloxifene on Ti-implants were investigated for their anti-osteoporotic potential. These coatings on Ti-implants boosted cell viability and osteogenic differentiation of osteoblasts within osteoporotic rat femurs, showing their therapeutic impact in osteoporotic bone injury [237].

Mg has anti-inflammatory properties and can help reduce chronic inflammation associated with osteoporosis and bone degeneration. Mg can also promote osteoblast function, thereby facilitating bone formation [127,238–241]. One such approach involved the development of a composite hydrogel containing calcium phosphate microspheres infused with MnO_2 NPs and loaded with a fibroblast activating protein inhibitor (FAPi). The experimental results demonstrated that these hydrogels effectively osteoblast proliferation and differentiation [242]. An additional innovative solution was the creation of bisphosphonate-functionalized injectable hydrogel microspheres (GelMA-BP-Mg), specifically designed for the treatment of osteoporotic defects (Fig. 9A and B). Both *in vitro* and *in vivo* experiments showed that these microspheres support osteogenesis and angiogenesis by promoting the functions of osteoblasts and endothelial cells while inhibiting osteoclast activities, as shown in Fig. 9C and D [243]. These diverse strategies illustrate promising avenues for addressing osteoporosis through tailored biomaterials and targeted therapeutic interventions, with Mg as a promising candidate.

Several challenges remain in the development of MNP therapeutics for osteoporosis, including precise bone targeting, controlled release of the cargo without off-site toxicity, and the risk of nanotoxicity [244–246]. For example, Ag NPs have been found to damage osteoblasts and osteoclasts and affect their DNA [247,248]. Different strategies have been utilized to address such challenges. For example, magnesium oxide nanocomposites that release osteogenic Mg^{2+} have been shown to enhance mineral density and activity of osteoblasts [240]. Moreover, anti-resorptive drugs (e.g. denosumab) and osteogenic ions (e.g. Mg^{2+}) in bifunctional MNPs could potentially synergistically restore bone homeostasis [249]. However, challenges persist in achieving and optimizing sustained release to circumvent excessive inhibition of osteoclast-driven remodeling and ensuring the long-term biocompatibility of non-degradable MNPs. Therefore, it is highly desirable to develop smart MNPs that respond to microenvironmental cues (e.g., pH, enzymes) for on-demand delivery in future research. Additionally, such smart MNPs can be integrated into 3D printed scaffolds for personalized repair to address patient heterogeneity.

4.2. MNPs and MNP-based composites for treating OS

OS exhibits considerable histological heterogeneity, lacks specific biomarkers, and is locally invasive and highly metastatic [119]. Collectively, these factors present a significant challenge to the treatment of OS. Despite the efficacy of chemotherapy drugs in the treatment of OS, they continue to exhibit certain disadvantages, including toxicity to normal tissues, drug resistance and rapid clearance from the blood [119,250]. Nanoplatforms are being developed to deliver drugs to tumors, enhancing efficacy and minimizing side effects. OS represents the most prevalent primary malignant bone tumor in pediatric and adolescent populations. However, the limited efficacy of chemotherapy and the emergence of drug resistance present significant treatment challenges. Recent advances in nanotechnology have led to a significant transformation in the approach to cancer therapy, particularly through the development of tumor-targeted drug delivery systems. Nanocarriers, such as MNPs, offer distinctive advantages, including prolonged circulation times and elevated drug concentrations at tumor sites. This improves therapeutic outcomes and minimizes side effects [251–256]. MNPs, including Au, cerium oxide, zinc oxide, Ag, iron oxide, titanium dioxide, and terbium oxide (Tb_2O_3), have demonstrated intrinsic anticancer properties in OS cells, suggesting their potential as stand-alone therapeutic agents [257].

In the context of OS treatment, AuNPs can be functionalized with various molecules, such as chemotherapeutics and targeting ligands, to deliver therapeutic payloads specifically to cancer cells while minimizing damage to healthy tissue [258]. AuNPs can exploit the EPR effect, which refers to the tendency of NPs to accumulate in tumors due to leaky blood vessels and impaired lymphatic drainage [259]. This phenomenon allows AuNPs to selectively accumulate in OS, enhancing the efficacy of therapeutic payloads delivered via the NPs. For example, Ma and colleagues developed a nanoplatform (Fig. 10A and B) consisting of an AuNP core with a metal-organic framework and mesoporous silica shells that are loaded with cisplatin [260]. This platform demonstrated efficacy in targeting metastatic spinal tumors and reducing bone destruction in preclinical models, as illustrated in Fig. 10C–E.

Similarly, AuNPs conjugated with cisplatin and doxorubicin have shown enhanced delivery to the nucleus of cancer cells, thereby improving their therapeutic efficacy against Saos-2 and MG-63 OS cell lines [261]. Furthermore, AuNPs stabilized with glutathione (GSH) and modified with cytarabine (CTA) have demonstrated significant anticancer activities against human OS-143B cells. These findings demonstrated that AuNPs at a concentration of 100 μg/mL diluted in a notable reduction of approximately 45 % in cell viability [262]. Continued research and development in this area have the potential to further optimize nanocarrier designs and advance personalized approaches to cancer treatment. Au nano-dendrites incorporated with programmed death receptor 1 antibodies (aPD-1) were designed for the eradication of primary and distant metastatic tumors in an OS mouse model. AuNDs + aPD-1 could destroy primary and distant metastatic OS via activating T cells and exhibited long-term immune memory to prevent tumor reinvasion and recurrence, as shown in Fig. 11E and F [263]. In a subsequent investigation, AuNPs functionalized with PEG and fused with a Tat peptide, and synthesized doxorubicin. Tumor viability assays demonstrated that PEGylated AuNPs were 100 % cytotoxic against human OS cells [264]. Sha and co-workers developed mesoporous silica NPs with alendronate loading and a Mn-doped Au core (Fig. 11A and B) [265]. The NPs exhibited remarkable tumor microenvironment-responsive drug release and efficacy in eradicating cancer cells *in vitro* (HUVEC and 143B) and *in vivo* in BALB/c Nude mice, as depicted in Fig. 11C and D.

A novel theragnostic platform for the immunotherapy and chemotherapy of OS has recently been developed, comprising macrophage loaded with dendrimer-entrapped AuNPs. This platform is capable of activating and polarizing macrophages into the M1 phenotype [266]. Moreover, Zhang and colleagues synthesized Au-nanocages coated with cancer cell membranes and loaded with a ferroptosis inducer, RSL3, with the objective of overcoming chemoresistance [267]. RSL3 induced ferroptotic cell death, while the cancer cell membrane promoted immunogenic cell death, making these Au-nanocages a promising clinical therapy of OS.

A pH-sensitive microparticle drug delivery system was designed as a combinatorial therapy and evaluated using the Saos-2 cell line. At pH 6, the combined action of CeO_2 NPs and encapsulated doxorubicin (acts as pro-oxidants), results in almost 100 % cell death [194]. In a study conducted by Alapslan and colleagues, cerium oxide NPs were prepared with dextran, and their anticancer efficacy against OS and effects on

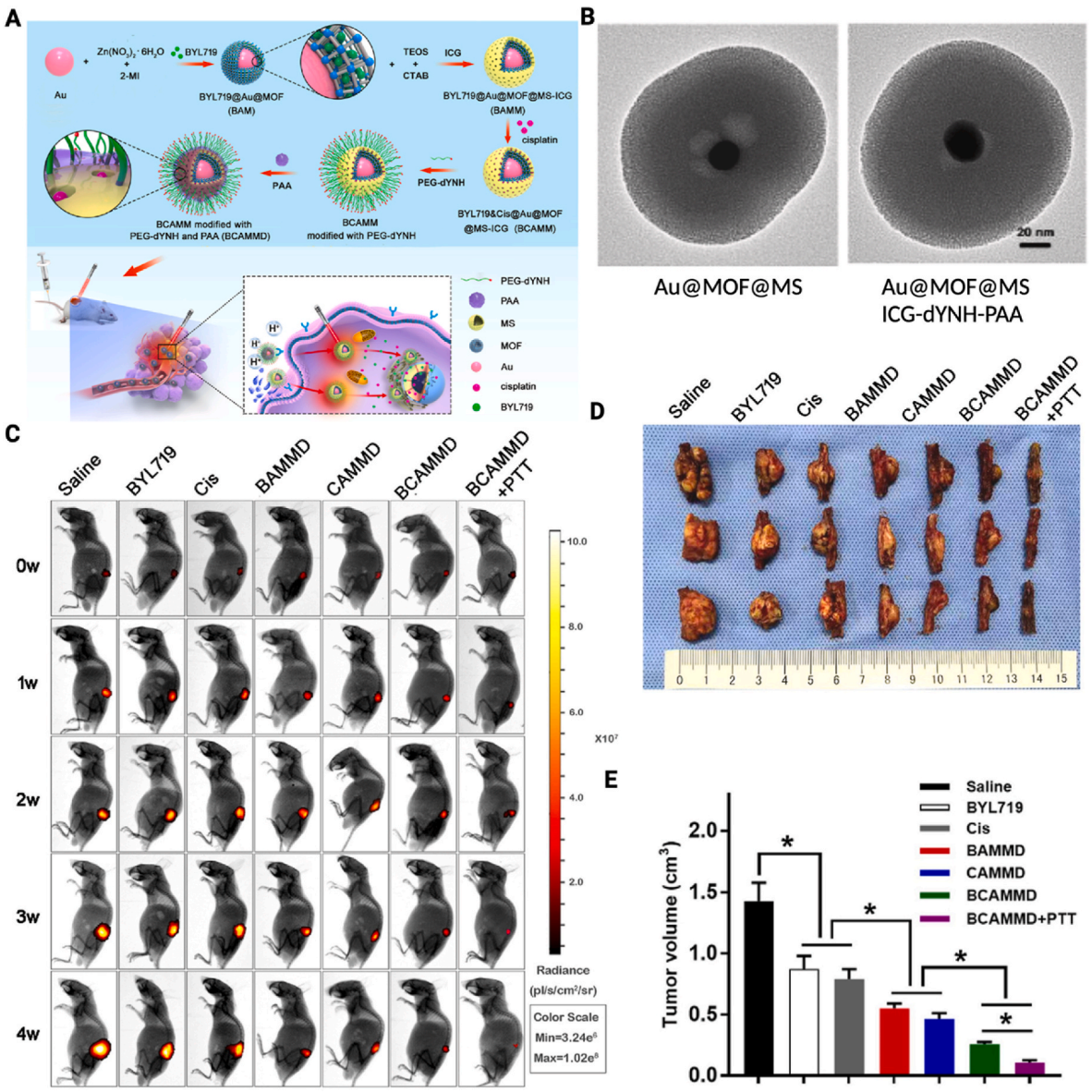

Fig. 10. Evaluation of drug coated MOFs and AuNPs in an OS mouse model. **(A)** Synthesis of Alpelisib (BYL719) and cisplatin loaded double shell NPs modified with dYNH targeting peptide (BCAMMD) and antitumor mechanisms of BCAMMD in tumor cells. **(B)** TEM images for Au@MOF@MS and Au@MOF@MS-ICC-DYNH-PAA, MOF = metal organic framework, MS = mesoporous silica, ICG = indocyanine green, PAA = poly acrylic acid. **(C)** Bioluminescence images presenting the orthotopic metastatic spinal tumors in mice. **(D, E)** Tumor volume isolated from mice in each group after different treatments. Reproduced with permission from Ref. [260]. Copyright 2021, Elsevier. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

healthy osteoblasts was evaluated in weakly acidic conditions [268]. The results demonstrated that the dextran-coated nano-cerium oxide killed a significant number of OS cells without adversely affecting osteoblast noncancerous cell line.

ZnO NPs exhibit diverse properties and can be combined with cancer inhibitors [269] and hypoxia inducers [270] and serve as chemotherapeutic nano-carriers [271] for synergistic therapeutic effects, which enhance their efficacy in treating OS, as evidenced by several recent studies. He and colleagues demonstrated that the combination of ZnO NPs and ICG-001, a β-catenin inhibitor, had a synergistic inhibitory effect on OS lung metastasis [269]. Furthermore, the study demonstrated that Zn^{+} release downregulates β-catenin expression through the HIF-1α/BNIP3/LC3B-mediated mitochondrial autophagy pathway. Similarly, He and colleagues discovered that a hypoxia-inducing agent ($CoCl_2$) augmented ZnO NP-induced cell death at 1 % hypoxia, while concomitantly impeding ZnO NP-induced cell death when accompanied by a hypoxia inhibitor (YC-1) or the suppression of HIF-1α [270]. Yu and co-workers designed and explored Zn-phthalocyanine NPs infused with bovine serum albumin (ZnPc/BSA) as a PDT tool [272]. They stated that the interaction of autophagy inhibitor with PDT inhibited OS *in vitro* (MG-63, K7M2 and HOS) and *in vivo* (Balb/c mice), indicating the possible applicability of this regimen for tumor metastasis prevention. A nanocarrier system composed of Zn-HAp NPs coated with methotrexate F127 was developed as a chemotherapeutic agent for targeting OS cells. These nanocarriers inhibited P-glycoproteins through F127 and effectively increased their antitumor effect via Zn^{2+} drug release [271].

AgNPs exhibit potent cytotoxic effects against OS cells, inducing apoptosis through multiple pathways [273]. Their small size allows effective penetration into cancer cells, where they can disrupt cellular functions and induce programmed cell death [274]. The ability of AgNPs to inhibit OS cell lines with different p53 genotypes was studied. AgNPs were discovered to directly target mitochondria and trigger apoptosis in cancer cells via p53-independent apoptosis [275]. AgNPs biosynthesized from bark extract of *Ficus benghalensis* and *Azadirachta indica*

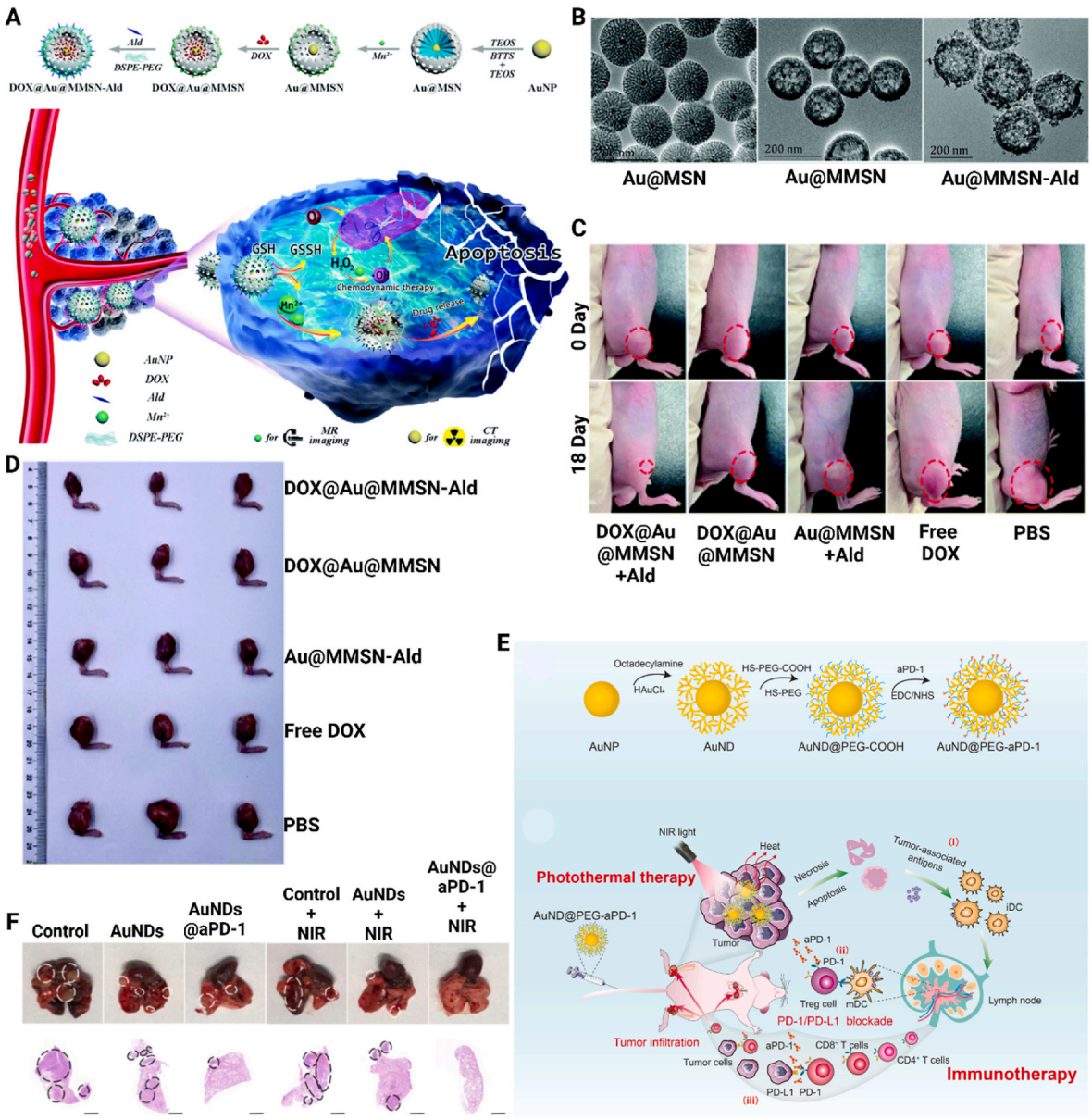

Fig. 11. MNPs for inhibition and treatment of OS. (A) Synthesis of gold core mesoporous silica NPs loaded with doxorubicin and alendronate (DOX@Au@MMSN-Ald). These NPs work as chemo-dynamic agents and help in CT/MR imaging, DOX = doxorubicin hydrochloride, MMSN = mesoporous silica NPs, Ald = alendronate. **(B)** TEM images of Au@MSN, Au@MMSN, and Au@MMSN-Ald. **(C)** Photos of tumor-bearing mice before and after treatment. **(D)** Images of excised tumors from mice in different groups after 18 days of treatment. Reproduced with permission from Ref. [265]. Copyright 2021, Royal Society of Chemistry. **(E)** Top: synthesis of AuNDs@PEG-aPD-1 by conjugating programmed receptor 1 antibody (aPD-1) and gold nanodendrites (AuNDs). Bottom: mechanism of AuNDs@PEG-aPD-1 on tumor metastasis. **(F)** Gross view appearance (top) and H&E staining (bottom) of metastatic lung nodules at the end of the intervention in each group of K7M2 tumor-bearing mice. Scar bar = 1000 μm. Reproduced with permission from Ref. [263]. Copyright 2022, Elsevier. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

demonstrated anti-proliferative potential against MG-63 cells in a dose-dependent manner [276]. A comparable study employed tannins in the biosynthesis of Ag-NPs and observed that these Ag-NPs exhibited considerable anti-cancer effects against MG-63 cells, predominantly due to the antioxidant properties of Ag [277].

New ways are being developed to use iron oxide NPs in treating OS. These NPs have been modified with different substances to target, and deliver drugs to induce cell apoptosis. Polyethyleneimine- and dextran-modified FeO NPs (PDIs) were successfully produced to transport miR-302b. The PDIs were transported to OS cells in nude mice using a magnetic field. It was demonstrated that PDIs with miR-302b exhibited anti-OS activity and could serve as a carrier for various therapeutics for OS treatment [278]. Fe_3O_4 NPs were infused with chitosan (CS) and folic acid conjugates as well as CS and succinic anhydride conjugates and loaded with doxorubicin to act as a pH-sensitive anti-OS drug. The folate acid component of the NPs was enable binding to folate receptors on the surface of MG-63 cells, facilitating higher uptake and significantly enhancing the cytotoxic effect of the NPs [169]. In another study, Fe_3O_4 NPs were successfully incorporated with pollen shells of *Pistacia vera* L. and tested for anticancer activity against MG-63 OS cells. The results demonstrated that Fe_3O_4 NPs induced expression of BAX/BCL2 and caspase-3 genes, which led to mitochondrial apoptosis of OS cells [279].

Other MNPs that have been demonstrated to be efficacious in the treatment of OS include platinum and titanium oxide. The anti-cancer efficacy of doxorubicin-loaded platinum NPs was evaluated in human U2OS cells. The viability of OS cells was impaired in a dose-dependent

manner by platinum NPs, with an increase in apoptosis and apoptotic gene expression. Furthermore, an increase in the amount of oxidative stress-induced DNA damage was observed in cells treated with platinum NPs [280].

While promising, most nano-drug delivery platforms for OS treatment are not yet ready for clinical use. Most evaluations are still at the cellular and animal level, with a long way to go before they can be used in humans [281]. The development of optimized NPs for targeted drug delivery will be contingent upon our ability to overcome a number of challenges. An ideal drug delivery system should be capable of selective accumulation in tumor sites, and further research is required to gain a deeper understanding of the OS-targeting mechanism to identify more specific target ligands. Besides, accumulation of NPs in the liver is a common issue for nanomedicine. Additionally, the limited penetration ability of light currently used for PTT towards deep tumors necessitates the development of more effective strategies [281,282]. It is also important to note that NPs can have adverse effects on stem cell functions, which should be taken into consideration in stem cell-based regenerative medicine research. For example, AgNPs displayed significant toxicity against human and rat-derived embryonic stem cells in a dose-dependent manner [283]. Moreover, NPs can cause neurotoxicity due to increased ROS production, mitochondrial dysfunction, BAX protein activation, and the release of lactate dehydrogenase [284]. It is essential to overcome these challenges to realize the widespread clinical applications of NPs in the treatment of OS and beyond.

4.3. MNPs and MNP-based composites for treating osteomyelitis

The diagnosis and treatment of osteomyelitis represent a significant challenge for medical practitioners. This condition is caused by bacteria that evade the immune system and antibiotics. Osteomyelitis is influenced by alterations in the blood vessels and manifest in various ways [285]. Current treatment options include extensive surgical debridement and antibiotic therapy, but the condition is compounded by increasing antibiotic resistance. MNPs offer extensive opportunities to design therapeutic biomaterials that show high biocompatibility and antimicrobial activity and enhance tissue regeneration [286]. Several MNPs have been found to possess antimicrobial properties and employed in the treatment of osteomyelitis, including Ag, Au, Fe, Ce, and Ti.

AgNPs have potent antimicrobial properties against a broad spectrum of bacteria, fungi, and even antibiotic-resistant strains. This ability makes AgNPs a popular choice to combat the various pathogens that cause osteomyelitis, including *Staphylococcus aureus* and *Pseudomonas aeruginosa* [287]. The significant antibacterial properties of AgNPs are attributed to their large surface area, which allows for direct absorption at bacterial cell walls. Ye and colleagues devised a porous cellulose hydrogel incorporating Ag-NPs, which exhibited remarkable antibacterial activity against both *S. aureus* and *E. coli* [288]. Hou and colleagues investigated the bactericidal mechanism of Ag/AgBr/TiO_2 nanotube array electrode against *E. coli*, and revealed that ROS induced the disruption of cell integrity and eventual bacterial death [289,290]. In a study by Qadri and colleagues, Ag-Cu-boron nanocomposites were employed against *S. aureus*-mediated bone infection in mice [291]. The researchers discovered that a dosage of 1 mg/kg was sufficient to eradicate 99 % of the bacteria responsible for causing osteomyelitis. In another study, the efficacy of AgNPs loaded onto mesoporous bioactive glass (AgNPs/MBG) was assessed in *Enterococcus faecalis*-induced infection. The sustained release of Ag^+ ions by AgNPs/MBG contributed to the disruption of the biofilm structure and demonstrated good antibacterial potential [292].

The antibacterial properties of AuNPs have been demonstrated to be promising in the treatment of bone infections and osteomyelitis. They effectively enhance the efficacy of conventional antibiotics, particularly against antibiotic-resistant bacteria such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*, which are commonly involved in bone infection [293]. Historically, PMMA has been used as a bone cement in combination with antibiotics. More recently, PMMA bone cement has been loaded with AuNPs in order to exploit their mechanical strength and antibacterial effects. A research study has demonstrated that AuNP-loaded PMMA enhances the antibacterial efficacy of bone implants [294]. *In vitro* evaluation of 3D scaffolds incorporating AuNPs, ampicillin and PVA confirms their osteoinductive properties, biocompatibility, and ability to inhibit bacterial growth in MC3T3-E1 cells, highlighting their potential in bone tissue engineering and infection control [295].

MNPs of iron, cerium and Cu have also been identified as potential candidates for the treatment of bone infection and osteomyelitis due to their unique antimicrobial properties. Gentamicin-coated Fe_3O_4 NPs integrated into a mesoporous bioactive glass (MBG) effectively controlled the release of gentamicin and prevented biofilm formation by pathogens such as *S. aureus* and *S. epidermidis* [296]. Microwave responsive Cu nanorod composites (Cu/C/Fe_3O_4-COOH) (Fig. 12A) exhibited selective affinity to bacterial surfaces, leading to efficient capture and destruction of *S. aureus* through cytoskeletal collapse and membrane rupture, as shown in the SEM images (Fig. 12B and C) [297]. Copper-cerium oxide (CuCeOx) materials, when combined with microwave irradiation, have been demonstrated to be an effective treatment for osteomyelitis caused by *S. aureus*, as depicted in Fig. 12E and F [298]. In addition, CeO NPs encapsulated within HAp and CS were prepared using the precipitation technique. The bactericidal effect of these synthesized NPs was investigated against infection in Wistar albino rats. The results revealed that the CeO NPs exhibited significant antibacterial activity and potentially disrupted the bacterial membrane structure [299]. Collectively, these NPs represent innovative approaches to combat bone infections, utilizing controlled drug delivery, magnetic targeting, microwave-induced cytotoxicity, and membrane-disrupting mechanisms to effectively address the challenges of osteomyelitis treatment.

Ti is highly biocompatible and generally well tolerated by the site where it is implanted [300] and has also a strong ability of osseointegration [301]. A study was conducted to investigate the antibacterial efficacy of Ti wire coated with Ti nanotubes loaded with gentamicin as a potential bone implant material. The Ti wires were demonstrated to be biocompatible, exhibit an elastic modulus close to that of natural bone, and serve as an alternative to conventional bone implants for the prevention of bone infection [302]. Similarly, the antibacterial potential of TNT loaded with gentamicin was evaluated in terms of its ability to prevent the adhesion of *S. epidermidis*. MC3T3-E1 cells were cultured on these nanotubes, and the results indicated that the nanotubes effectively reduced bacterial cell adhesion on the TNT surface and improved osteoblast differentiation [303]. At the same time, nanoscale HAp coated on Ti surfaces showed significant antibacterial efficacy against colonies of *S. mitis* and *S. gordoni*, highlighting their potential for the development of antibacterial bone implants [304]. Furthermore, Wang and colleagues synthesized graphdiyne-modified TiO_2 nanofibers by electrostatic self-assembly (Fig. 13A) [311]. These nanofibers exhibited long-lasting photocatalytic antibacterial activities and osteoinductive capabilities, as shown in Fig. 13B–E.

Human exposure to NPs commonly employed for antibacterial applications is inevitable. Consequently, concerns regarding their potential for toxicity are gaining prominence. These nanomaterials are engineered to interact with cells; therefore, their interactions must not have minimal negative consequences on the human body [306]. Despite the prevalence of Ag in antibacterial applications, concerns regarding its effectiveness and safety have emerged. The antimicrobial activity of Ag is transient, necessitating repeated application. Additionally, the active ionic form of Ag requires an aqueous environment to exert its effect. While the majority of studies have investigated the antimicrobial activity of Ag ions or NPs *in vitro*, only a limited number have studied Ag toxicity using *in vivo* models [291].

Research has demonstrated that Ag-Cu alloys exhibit superior

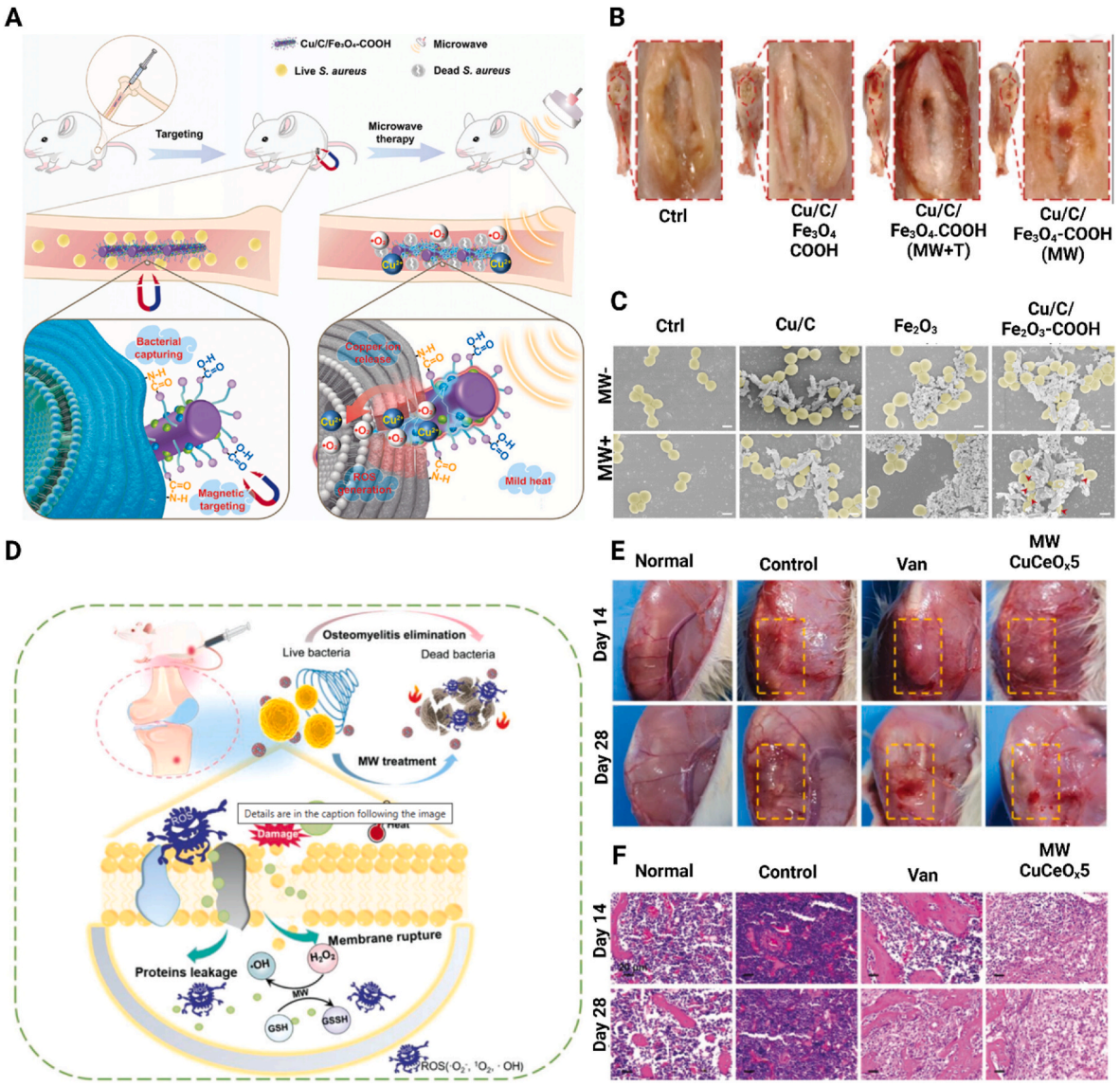

Fig. 12. MNPs and their applications in the eradication of bone infection. (A) Schematic diagram of application of Cu/C/Fe_3O_4-COOH in the treatment of *S. aureus*-induced osteomyelitis. **(B)** Macroscopic images of the infected tibia and surrounding tissue in the different groups after 7 days of treatment. **(C)** SEM images of the morphology (structure collapse and cell membrane rupture are indicated by red arrow) of *S. aureus* (Scale bar = 500 nm). Reproduced with permission from Ref. [297]. Copyright 2023, Wiley-VCH. **(D)** Schematic diagram of efficient elimination of *S. aureus* infection using CuCeOx-NPs *in vivo*. **(E)** Images of surgical site images of rat models after 2 and 4 weeks of treatment. **(F)** H&E staining of infected bone tissues after 2 and 4 weeks of treatment. Scale bar = 20 μm. Reproduced with permission from Ref. [298]. Copyright 2023, Wiley-VCH. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

antimicrobial efficacy in comparison to Ag or Cu utilized individually. However, the antimicrobial efficacy of the Ag-Cu complex is also limited by the rapid oxidation of Cu [307]. AgNPs have been observed to induce toxicity in a dose-dependent manner, resulting in oxidative stress and DNA damage, ultimately leading to cell death [308]. The intracellular aggregation of AuNPs is a plausible phenomenon due to their diminutive size, which is believed to be the underlying cause of their toxicity [309]. Many researchers have expressed concerns that the degradation of implanted NPs may lead to ROS production, apoptosis, or necrosis [310]. However, there is currently a lack of data on real-time monitoring of the potential toxic effects of MNPs. Therefore, it is critical to conduct in-depth and comprehensive studies on the long-term effects of NPs on human health and the microenvironment with regard to their size, surface chemistry, shape, quantity, and other necessary characteristics [311]. In addition, standardized protocols should be developed to obtain a comprehensive understanding of how MNPs are absorbed, distributed, and cleared by living cells or tissues through real-time pharmacokinetic studies [312].

Furthermore, MNPs can be directed to target the site of infection and loaded with antibiotics (e.g., vancomycin) or antimicrobial peptides to circumvent systemic toxicity and antibiotic resistance. For instance, magnetic NPs can be employed to generate local hyperthermia to destroy biofilms, and pH-responsive MNPs can selectively release drugs in the acidic microenvironment near the infected bone [313,314]. However, several gaps remain to be filled, including the optimization of biofilm penetration by the MNPs, the prevention of repeated infections due to incomplete bacterial eradication, and the integration of rapid antimicrobial effects with long-term bone regeneration. In addition, the potential risk of bacterial resistance to antibiotics encapsulated in nanoparticles and the lack of standardized *in vivo* infection models hinder the clinical translation of MNPs for osteomyelitis treatment. Therefore, progress in this field is expected to benefit from innovative

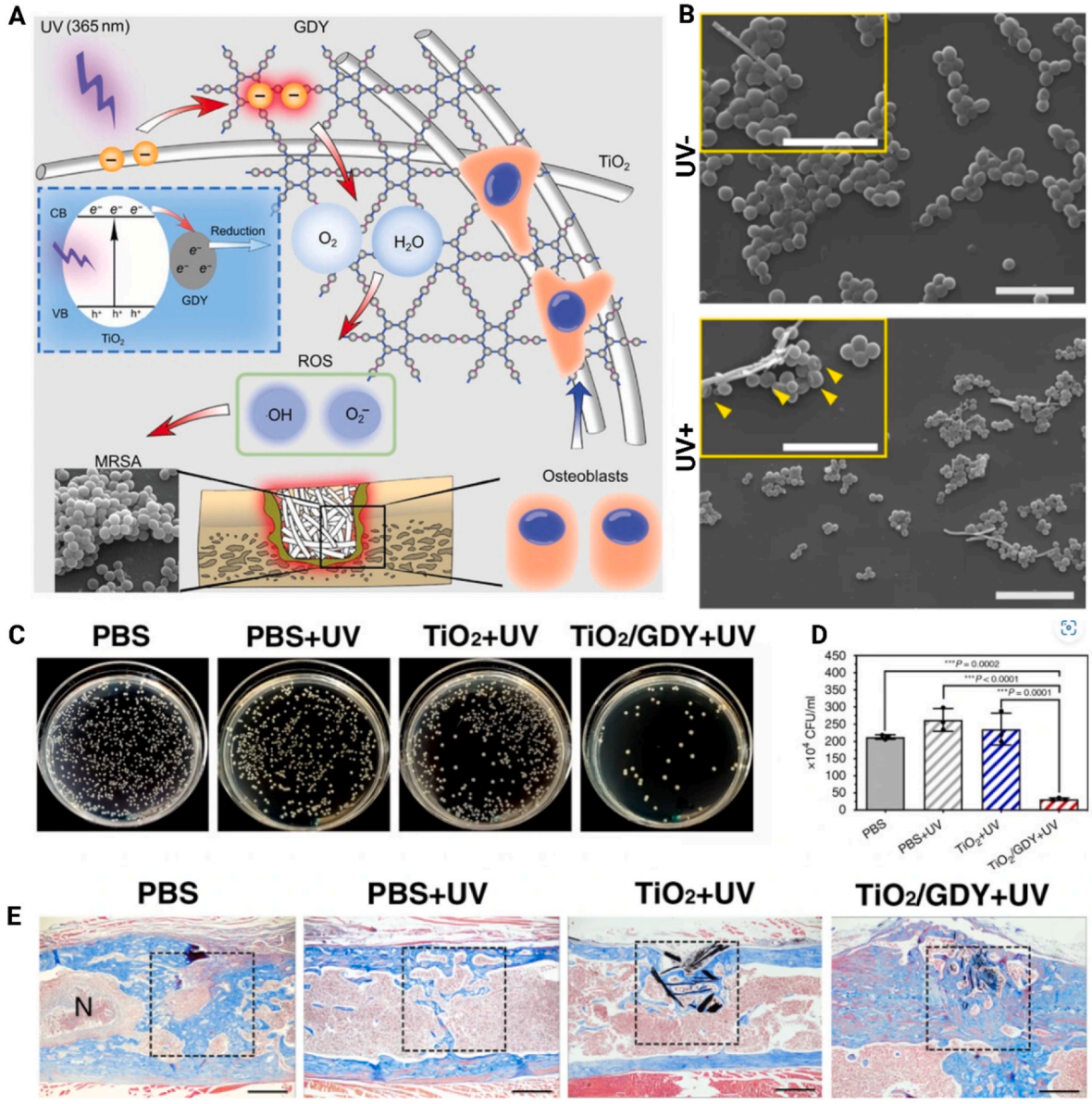

Fig. 13. Antibacterial mechanism and effect of ROS generated by graphdiyne-modified TiO2 nanofibers. (A) Schematic diagram of the graphdiyne modified titanium dioxide nanofibers (TiO2/GDY) for eradicating methicillin-resistant *S. aureus* (MRSA) and bone regeneration. **(B)** SEM image of TiO2/GDY nanofibers and MRSA with and without photocatalytic treatment. Yellow arrow: Pores on the bacterial surface. **(C, D)** Photographs of bacterial colonies and corresponding quantitative analysis after TiO2/GDY treatment of infected femurs. **(E)** Masson's staining of bone formation after 4 weeks (scale bar = 500 μm). 'N' represents necrotic tissue in the bone marrow. Reproduced under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/) [305]. Copyright 2020, The authors, published by Springer Nature. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

combinational therapeutic strategies, such as MNPs loaded with immunomodulators, and the development of imaging-compatible MNPs for real-time infection monitoring.

4.4. MNPs and MNP-based composites for treating critical-sized bone defect

Bone defects can be devastating and result in significant functional impairment or even permanent disability. At present, a plethora of biomaterials are employed in the treatment of skeletal defects. However, most of these materials are constrained by inherent limitations and are associated with complications such as corrosion, compromised cell proliferation, and bacterial adhesion. With recent advances in materials science and nanotechnology, MNPs have garnered considerable interest as they offer a wide variety of options to address the existing problems in the treatment of bone defects [206]. The physicochemical and biological properties of MNPs, when combined with implants or hydrogels, can enhance the antibacterial properties, capacity of bioactive molecule delivery, and mechanical strength of the scaffolds [52,206]. Scaffolds comprising organic and inorganic composites containing metallic elements of Mg, Ag, Fe, Ce, Sr and Zn have been developed for the effective healing of bone defects.

Like Mg alloys, Mg NPs are biodegradable and biocompatible. These NPs can be broken down in the body over time without adverse effects [315] and release ions that promote bone regeneration [316]. The use of Mg NPs has been demonstrated to enhance osteoconductivity, facilitating the attachment and growth of bone cells and integration of the implant into the surrounding bone tissue to promote regeneration.

[317]. A number of studies have demonstrated the successful applications of MgO NPs in promoting bone healing and regeneration across a range of experimental models. A hybrid hydrogel scaffold comprising HAp and MgO nanocrystals within a cysteine-modified polyglutamic acid (PGA-Cys) hydrogel has been shown to enhance the proliferation and osteogenic differentiation of BMSCs, thereby accelerating bone defect healing in diabetic rats [318]. A bilayer scaffold comprising HAp nanorods and MgO was designed for bone healing in rabbit femurs. It significantly downregulated TNF-α and IL-1β, while upregulating IL-10 and suppressing osteoclastogenesis, modifying the surrounding milieu to favor osteogenic cell recruitment [319]. MgO NPs can also promote blood vessel development and neurite outgrowth [320]. Lin and co-workers designed microspheres comprised of MgO NPs, poly (lactic-co-glycolic acid) (PLGA) biopolymer, and alginate hydrogel for in situ bone regeneration (Fig. 14A–C) [321]. The controlled release of Mg ions has been demonstrated to facilitate osteogenic differentiation of MC3T3-E1 *in vitro* and stimulate bone regeneration *in vivo*, as illustrated in Fig. 14D–F. Injectable hydrogels made from phosphocreatine-functionalized chitosan (CSMP) incorporating MgO NPs was designed to repair critical-sized bone defect. These injectable hydrogels increased calcium phosphate deposition and induced osteogenic differentiation of cells by upregulating BSP and OPN in calvarial defectes in rats [322].

Among different MNPs, AgNPs have been widely studied for treating critical-sized bone defects by preventing bacterial infections through their antimicrobial properties, enhancing osteogenesis, and improving bone fracture healing, as demonstrated in various studies involving different scaffold materials and nanocomposite formulations [323]. Zheng and colleagues designed PLGA-based composites integrated with AgNPs and BMP-2, which were proved effective in healing an infected

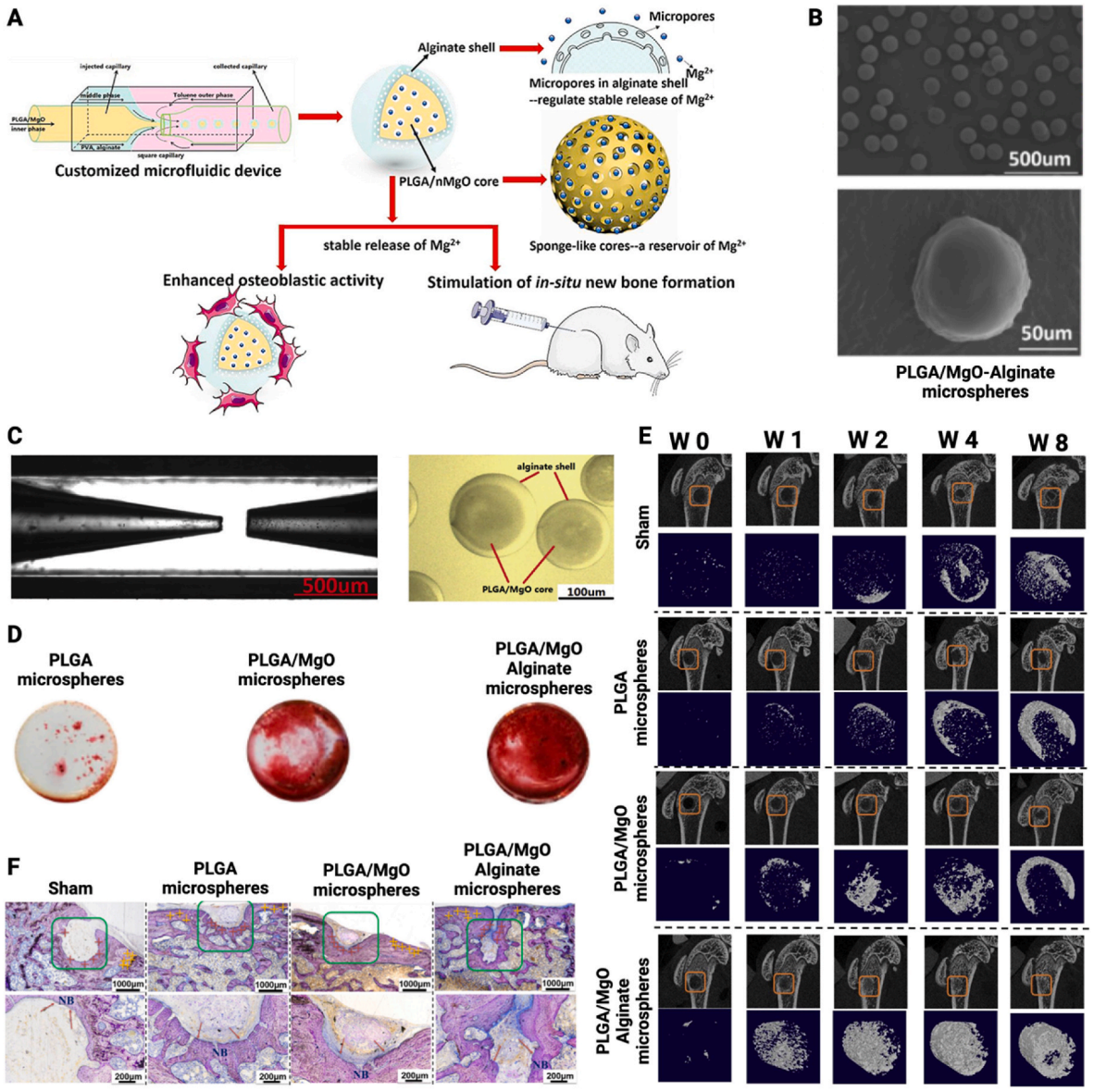

Fig. 14. MNPs and their applications for osteogenesis and treating critical-sized bone defect. (A) Graphical representation of a nano-system describing the controlled release of Mg^{2+} ions from alginate shells *in vivo* to effectively stimulate in situ bone regeneration. **(B)** SEM images of PLGA/MgO-Alginate microspheres. PLGA = poly (lactic-co-glycolic acid). **(C)** Image of the microfluidic device and microscopic image of the PLGA/MgO-alginate core-shell droplets. **(D)** Images showing the mineralization of MC3T3-E1 cells co-cultured with PLGA-based microspheres on day 21. **(E)** Micro CT images of the lateral epicondyle and 3D reconstruction model. **(F)** Giemsa staining images of newly formed bone tissue (green frame: bone defect; NB: new bone; red cross: region of interest for measuring the Young's modulus of new bone; yellow cross: measuring the Young's modulus of the surrounding mature bone by nanoindentation technique). Reproduced with permission from Ref. [321]. Copyright 2018, Elsevier. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

femoral defect in rat models within 12 weeks with eradicated bacterial infection [324]. Further advancements involved the attachment of antimicrobial peptides (AMPs) containing osteogenic fragments onto AgNPs modified with silk fibroin coatings. *In vivo* implantation of these SF-based coatings improved osseointegration at weeks 4 and 8, indicating their potential for treating bone defects [325]. Moreover, sodium alginate and polyacrylamide hydrogel loaded with MgO-Ag_2O nanocomposites exhibited excellent self-recovery and mechanical properties, while stimulating the proliferation and differentiation of Saos-2 cells [326]. Collectively, these findings highlight the versatile role of AgNPs in promoting bone regeneration and combating infections in diverse biomedical applications.

Iron oxide NPs also play an important role in treating critical-sized bone defects by enhancing scaffold functionality in several ways [206]. These NPs can promote cell adhesion, proliferation, and osteogenic differentiation, which is crucial for bone regeneration [327]. Iron oxide NPs can also contribute to scaffold biocompatibility, antibacterial properties, and mechanical integrity, supporting their effective use in bone tissue engineering applications [328]. Various types of magnetic scaffolds have been developed using iron oxide NPs for bone tissue engineering applications. Aqueous ferrofluids-coated HAp and collagen scaffolds supported human bone marrow MSCs adhesion and proliferation [329]. Polyurethane fibrous scaffolds integrated with Fe_3O_4/SrO_2 NPs and functionalized multiwall carbon nanotubes exhibited excellent biocompatibility and antibacterial properties [330]. Magnetic poly (l-lactide) nanofibers stabilized with Fe_3O_4 NPs were designed to develop a bone regeneration substrate, which supported MC3T3-E1 cell adhesion and proliferation [331]. Additionally, HAp/PLGA composite

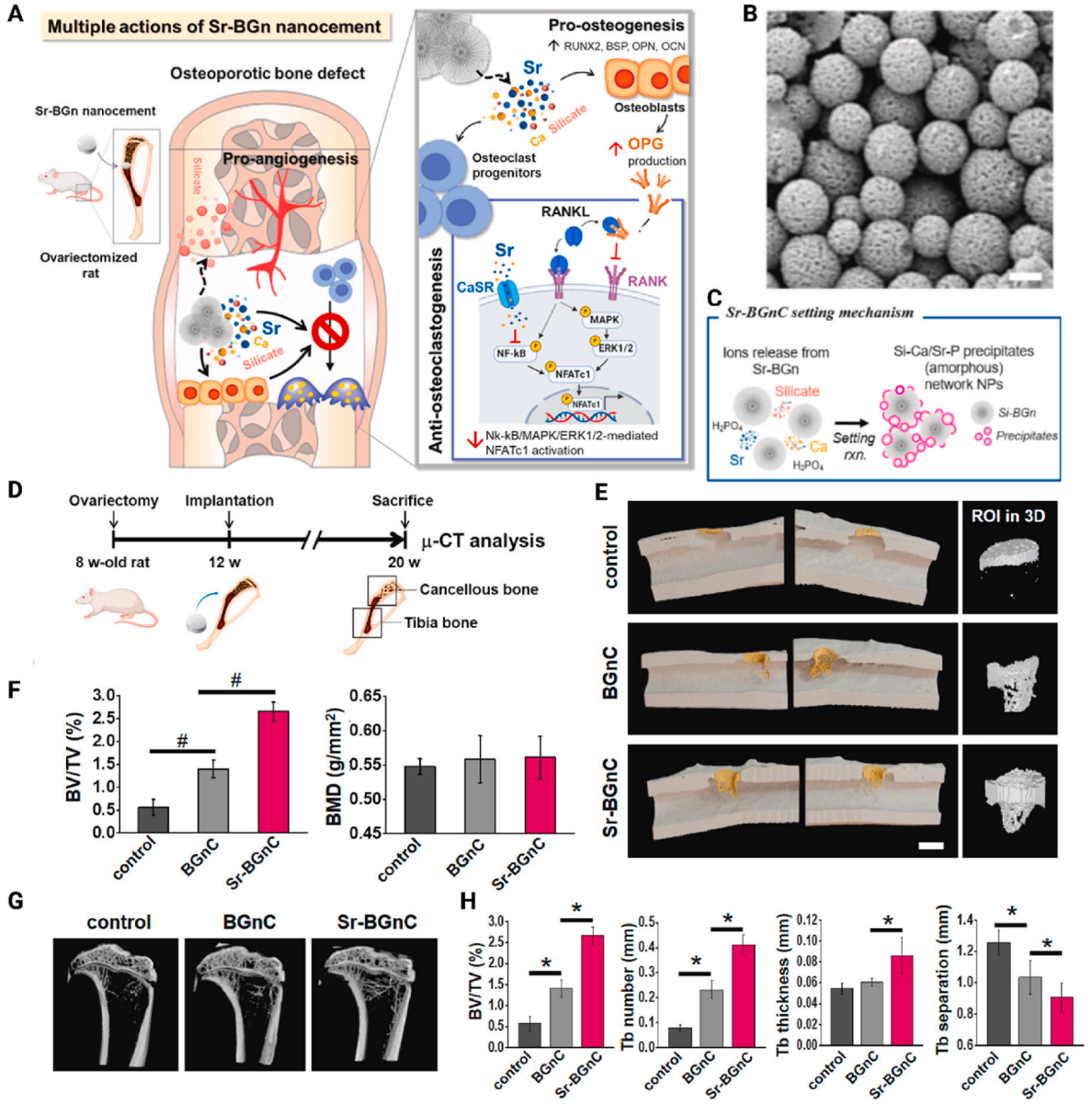

Fig. 15. Effective use of strontium-based nanocement for treating bone defects. (A) Schematic summary of the multiple-actions of strontium-based nanoscale cement (Sr-BGnC) in the regeneration of osteoporotic bone defects. **(B)** FE-SEM image for Sr-BGn. **(C)** Schematic illustration of the setting mechanism of Sr-BGnC. **(D)** Schematic timeline of the *in vivo* study. Three months after OVX induction, a hole defect was drilled on the rat tibia and the nanocement was implanted. **(E)** μCT images of the cortical bone region, with new bone formation in the false color of yellow (left, scale bar = 2 mm), and 3 D reconstruction (right). **(F)** Quantitative analysis showing the volume of new bone generated (BV/TV) and bone mineral density (BMD). **(G)** μCT images and **(H)** Quantitative analysis of the bone trabecular index (bone volume, number of trabeculae, thickness and spacing). Reproduced with permission from Ref. [335]. Copyright 2021, Elsevier. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

scaffolds modified with Fe_3O_4 NPs showed adequate porosity, high mechanical strength, and good osteogenic potential, demonstrating efficacy in healing bone defects in a rabbit ulna defect model following bone tumor excision [332].

Apart from the above-mentioned MNPs, other MNPs types, including cerium oxide, strontium, and zinc oxide NPs, also represent promising materials for bone regeneration in critical-sized bone defects. The investigation into tissue-engineered bone scaffolds modified with cerium oxide NPs revealed their potential to enhance angiogenesis by increasing the expression of the angiogenic factor VEGF in C3H/10T1/2 cells and promoting ectopic bone formation *in vivo* [333]. Moreover, CeO_2 NPs enhanced the mineralization ability of MC3T3-E1 preosteoblast cells and up-regulated key osteogenic genes such as runt-related transcription factor 2 (RUNX2), collagen I (COL1), and osteocalcin (OCN) that are crucial for maintaining bone homeostasis [334]. The Sr-doped nanoscale cement has been demonstrated to exert a dual effect on bone repair, namely the promotion of bone formation and the inhibition of osteoclast formation (Fig. 15A–C). The nanoscale cement delivery to ovariectomized tibia defective rats (Fig. 15D) demonstrated substantial bone regeneration capacity in the cortical (Fig. 15E and F) and adjacent trabecular areas as shown in (Fig. 15G and H) [335]. Similarly, multifunctional nano-layered double hydroxide (LDH) and bioactive CS scaffolds doped with $SrFe_{12}O_{19}$ NPs, were designed for in situ bone formation by effectively blocking the NF-κB signaling pathway to suppress osteoclast-mediated bone resorption and promoting the expression of COL1 proteins by osteoblasts [336]. Hybrid nanocomposites of CS, PEG, and HAp-ZnO also exhibited good biodegradability, erythrocyte compatibility, and antimicrobial activity, supporting bone tissue growth and protein adsorption [337]. Additionally, polyurethane scaffolds incorporating ZnO NPs and multi-walled carbon nanotubes exhibited anti-bacterial properties. These properties of the scaffolds enhanced osteogenic differentiation of cells and are recognized as a promising strategy for tackling osteoporosis-related bone fractures [338].

The utilization of MNPs-doped implants and hydrogels is predicted to facilitate the repair of critical-sized bone defects, with the simultaneous enhancement of both mechanical strength and osteoinductivity. For instance, iron oxide NPs doped with bioactive glass have been shown to promote angiogenesis, a critical process for vascularizing regenerated bone tissue [339]. Furthermore, 3D printed scaffolds containing MNPs showed stimuli-responsive behavior, such as adapting to mechanical stress or releasing osteogenic factors (e.g. BMP-2) in response to pH changes or magnetic fields, allowing dynamic control of bone regeneration [340]. Nevertheless, challenges remain in balancing the degradation of the scaffold and the formation of new bone, preventing chronic inflammation and fibrous encapsulation, and elucidating the cellular interactions with MNPs. Such interactions may involve rapid phagocytosis or receptor-mediated effects that can in turn trigger undesirable responses [341–344]. The prospect of combining MNPs with polymers that can be tailored (for example, dynamically crosslinked hydrogels) has been identified as a potential solution to the issue of synchronizing the degradation rate with bone formation in response to local enzymatic or mechanical cues [345,346]. In order to mitigate chronic inflammation, immunomodulatory MNPs emerged as effective biomaterials to promote pro-healing polarization of macrophage [46,111,347]. To enhance cell predictability, cell membrane-coated nanoparticles can be utilized to achieve functions such as immune evasion and prolonged blood circulation time [348]. Furthermore, MNPs can be used for the sustained, local delivery of osteogenic factors (such as BMP-2 and VEGF) for the treatment of critical bone defects [349,350].

4.5. MNPs and MNP-based composites for treating OA

OA is a degenerative disease characterized by the gradual loss of articular cartilage and chronic inflammatory responses, with damage to multiple other associated tissues. The avascular nature of the articular cartilage and its highly dense matrix impede the delivery and penetration of drugs into the tissue, resulting in low drug bioavailability. Currently, anti-inflammatory and analgesic drugs taken orally or injected into the joint encounter several issues, including poor water solubility, low cellular uptake, and premature degradation [351,352]. Clinicians often prescribe NSAIDs, including aspirin, ibuprofen, and more recently, COX-2 inhibitor such as celecoxib, to relieve pain and inflammation in OA patients, but these drugs often cause various side effects, including skin infections, gastric ulcers, mood changes, depression, and osteoporosis [353]. Given the limitations of existing treatments, there is a need for innovative and more effective interventions to repair cartilage and delay the progression of OA, while minimizing the adverse effects. Most MNPs are more stable and have longer half-lives *in vivo* than drugs and are therefore often used as drug carriers. MNPs are also excellent sustained-release systems that can continuously and steadily release the drugs contained and have a long residence time in the joint cavity [133,354].

MNPs can have catalytic activities similar to that of antioxidant enzymes (e.g., SOD and CAT), thereby effectively reducing oxidative stress and inflammation [355]. Their small particle size and high surface area to give them strong catalytic activities, and they are easy to attach to cell membranes, thereby promoting cell uptake and exerting antioxidant and anti-inflammatory effects by regulating the redox state of cells and releasing metal ions [356]. One advantage of MNPs is their ability to enter cells through various endocytic pathways, including clathrin-mediated endocytosis and caveolae-mediated endocytosis [357]. Additionally, due to the negative charge of cartilage, positively charged MNPs have a higher propensity to enter cartilage, and the retention of MNPs in cartilage tissue facilitates the gradual release of metal ions.

AuNPs have great potential in the treatment of OA, mainly due to their multiple effects on inflammatory responses, cell survival, and cartilage regeneration [358]. Studies have shown that high concentrations of AuNPs can impair the activity of chondrocytes [358], while low concentrations of AuNPs have anti-inflammatory properties and can reduce the expression of inflammatory markers such as IL-1α, TNF-β, COX-2, and NF-κB in cell cultures and animal models [359]. Previous studies have confirmed the potential of AuNPs to treat OA by reducing inflammation and promoting a shift from an inflammatory response to an anti-inflammatory response [360]. In complete Freund's adjuvant (CFA)-induced rat models of RA, treatment with AuNPs reduced the expression of inflammatory markers, including IL-1α, TNF-β, and COX-2, and inhibited the NF-κB pathway [361]. Another study using HA-modified AuNPs in OA Wistar rats indicated that these NPS reversed the deleterious effects of what on cartilage and simultaneously increased the levels of transforming growth factor alpha (TGF-α) and FGF, and anti-inflammatory cytokines [359]. Combining AuNPs with the polyphenolic compound curcumin, has demonstrated positive outcomes in cartilage repair in a mouse OA model [362]. Another study showed that AuNPs improved the delivery of chondroitin sulfate (CS) to primary goat chondrocytes, stimulating cell proliferation and the production of GAGs, collagen, and ECM [363]. In addition, epigallocatechin gallate (EGCG)-mediated AuAg nanostructures have intrinsic antioxidant properties, which significantly reduced the apoptosis rate of chondrocytes by 83.3 % and increased cell viability *in vitro* [364]. In addition to these properties, AuNPs have been found to enhance the activity of antioxidant enzymes such as SOD [365]. These multifaceted properties highlight the great potential of AuNPs as an OA therapeutic agent, targeting inflammation, oxidative stress, and cartilage regeneration pathways.

Cerium NPs (nanoceria) have multifaceted properties and hold great potential as therapeutic agents for the treatment of OA. These NPs can scavenge ROS and RNS, thereby reducing oxidative stress [366]. Nanoceria can also mimic the catalytic activity of antioxidant enzymes, which further enhances their antioxidant capacity [367]. Studies have shown that nanoceria, especially cerium oxide NPs combined with HA,

can protect chondrocytes from oxidative stress-induced apoptosis and upregulate essential cartilage ECM components such as aggrecan and collagen type II [368]. In addition, nanoceria can counteract the inflammatory effects of IL-1α on chondrocytes by increasing glycogen and proline levels [369]. In OA rat models, nanoceria can reduce apoptosis, decrease the secretion of pro-inflammatory mediators such as TNF-α, IL-1β, and COX-2, and promote the production of cartilage-derived glycoproteins and the anti-inflammatory cytokine IL-10. Nanoceria can also promote the differentiation of M0 macrophages to the M2 phenotype, which further promotes cartilage repair [370]. Integrating microRNA-224-5p onto sea urchin-shaped nanoceria were evaluated for enhanced OA gene therapy (Fig. 16A and B). These NPs were used to genetically treat OA by efficiently transfecting microRNA-224-5p and enhancing ROS-scavenging activities and cartilage formation, as shown in Fig. 16C–E [371]. Collectively, these findings indicate that nanoceria represents a promising avenue for therapeutic intervention in OA by targeting oxidative stress, inflammation, and promoting cartilage regeneration.

Mn is a trace element with therapeutic effects for the treatment of OA. Various factors contribute to their efficacy as an OA therapy, including its antioxidant properties, protection of cartilage integrity, promotion of cartilage regeneration, and the use of Mn-based NPs a drug delivery vehicle. MnO NPs can also mimic the action of SOD and POD to scavenge ROS [372,373]. Studies have shown that MnO NPs can protect chondrocytes from oxidative damage, while also assisting in the removal of ROS and reducing the loss of GAG [133]. In another study, MnO NPs combined with carboxymethyl CS and cartilage-targeting peptides were found to be effective in MRI imaging and promoting chondrogenesis of MSCs in a rat model of OA induced by medial meniscus instability [374]. Zhou and colleagues synthesized a novel hydrogel by combining manganese dioxide NPs encapsulating bovine serum albumin with HA and platelet-rich plasma gel [375]. These hydrogels helped reduce severe oxidative stress, promoted chondrocyte proliferation, and facilitated cartilage repair in a rat OA model. These studies collectively highlight the potential of MnO NPs as a potential therapeutic approach for managing OA and promoting cartilage regeneration.

Several studies have also demonstrated the role of AgNPs in OA treatment through different mechanisms. For example, AgNPs can reduce the expression of matrix metalloproteinase (MMP), highlighting their potential in alleviating cartilage degeneration [376]. In another study, researchers investigated the effects of caffeic acid-coated AgNPs on OA chondrocytes *in vitro*. The NPs were found to be biocompatible with OA chondrocytes, proving their safety in OA treatment [377]. In addition, Cu-tantalum nano catalysts infused into silk-based hydrogels promoted osteochondral regeneration in what animal model. The results showed that the hydrogels promoted what cell cell proliferation and had antibacterial and antioxidant properties. In addition, it promoted the formation of cartilage-specific extracellular matrix [378]. These studies highlight the multiple benefits of AgNP for OA treatment, including reducing inflammation, reducing MMP activities, and supporting tissue regeneration.

Other MNPs, like those based on MgO, CuS, and Fe also possess several beneficial functions that are desirable for treating OA. MgO NPs incorporated into porous scaffolds of PLGA promoted chondrogenic differentiation of MSCs and effectively reduced calcification, necrotic cell death, and the expression of inflammatory cytokines [379]. Cai and co-workers investigated the effects of CuS NPs loaded with TGF-β1 transgene in engineered MSCs (Fig. 17A–C) [380]. These biomimetic CuS NPs demonstrated promising treatment outcomes in rat OA models, including improved OARSI score (Fig. 17D and E) and increased collagen type II formation, GAG deposition, and chondrogenic gene expression (Fig. 17F and G).

In summary, for OA treatment, MNPs are frequently utilized as drug delivery vehicles due to their prolonged residence time and extended half-life within the joint cavity. MNPs loaded with antioxidants have been shown to exhibit higher *in vivo* stability in comparison to antioxidant drugs used as monotherapy for the treatment of OA. Notwithstanding the noteworthy advancements, there remain challenges to be surmounted to expedite the clinical implementation of MNPs in the treatment of OA [381]. In addition, the joint cavity, a closed space containing synovial fluid, is a crucial consideration in the design of MNP delivery systems [382]. This results in the rapid elimination of NPs from the joint cavity via the synovial membrane and the lymphatic system following intra-articular drug delivery. This necessitates multiple injections, which increases the risk of infection, toxicity, and off-target drug delivery. Consequently, further research is imperative to ascertain the long-term toxicity and biological effects of MNPs as potential OA therapies [383].

4.6. MNPs and MNP-based composites for treating RA

RA is a chronic, systemic autoimmune disease characterized by symmetric polyarthritis as the primary clinical manifestation [384]. While the exact cause of RA is unknown, the complex formation or interactions of the body's immune system components, including cytokines and effector cells, are known to be responsible for its pathogenicity. Current treatments that involve various traditional approaches, such as infliximab, adalimumab, etanercept, certolizumab, and golimumab, have shown therapeutic effects to various degrees; however, long-term use of these drugs causes several adverse effects [385]. Therefore, innovative therapeutic options for more efficacious treatment of RA with improved safety are urgently needed.

AuNPs have emerged as a promising therapeutic candidate for RA management. One study modified AuNPs with α-tocopherol succinate (α-TOS) and anti-TNF-α siRNA to prevent bone erosion and reduce cytokine expression in a mouse model of CIA [386]. AuNPs were encapsulated in liposomes modified with LGNP-CoQ10, and administered orally to CIA mice, resulting in a significant reduction in pro-inflammatory cytokines [387]. HA-AuNPs modified with tocilizumab (HA-AuNP/TCZ) also resulted in lower levels of inflammatory cell infiltration and reduced cartilage and bone degradation in CIA models [388]. Liposomes biofunctionalized with anti-IL-23 antibodies and AuNPs demonstrated compatibility with human articular chondrocytes and macrophages, which effectively reduced the production IL-17A by peripheral blood mononuclear cells from healthy donors and patients with RA [389]. AuNPs conjugated with nuclear localized peptides (Au-PsNLPs) were also evaluated for their therapeutic effects in CIA rat models. Au-PsNLPs demonstrated the ability to reduce bone and cartilage degeneration, suggesting a protective effect on rat ankle joints. Additionally, Au-NLS suppressed the expression of inflammatory and angiogenic factors involved in the progression of arthritis [390]. Another study used rutin-coated AuNPs (R-AuNPs), which showed prominent anti-arthritic expression of effect in CIA rats. R-AuNPs downregulated oxidative stress markers and the expression of key inflammatory mediators, including NF-κB and iNOS, *in vivo* [391]. In addition, CuS + MnO_2 nanocomposites functionalized with MSCs targeting peptides were developed for effective stem cell therapy for RA treatment (Fig. 18A and B). The nanocomposites demonstrated enhanced cell migration, anti-inflammatory activities and cartilage formation, which effectively reduced cartilage erosion in a rat model of RA (Fig. 18C–F) [392]. Furthermore, an octahedral Cu sulfide shell with a gold nanorod core (AuNR@CuS) was developed for the simultaneous treatment of RA with PTT, PDT, and chemotherapy to eliminate synovial hyperplasia. The results demonstrated the effective inhibition of synoviocytes and the degree of edema in CIA mice [393]. Collectively, these studies highlight the versatility and therapeutic promise of AuNPs in targeting inflammation, protecting joint structures, and advancing treatment strategies for RA.

Cerium NPs, used alone or in composites, show significant potential in the treatment of RA by reducing inflammation, scavenging harmful ROS, and supporting tissue repair [394]. For instance, manganese ferrite and CeO NPs attached to mesoporous silica NPs (MFC-MSNs) were

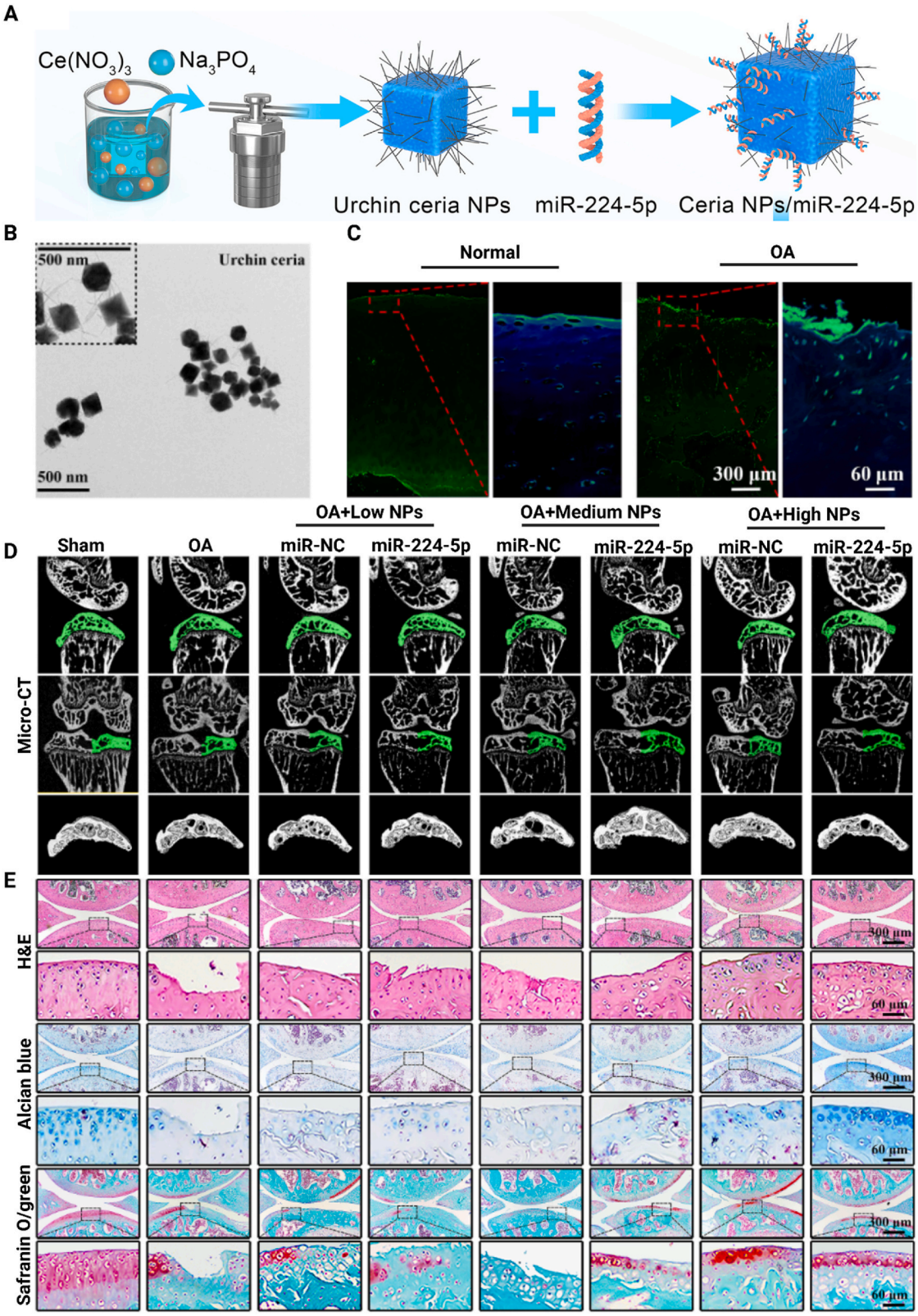

Fig. 16. MNPs and their potential for treating OA. (A) Synthesis of urchin-like ceria NPs via the hydrothermal reaction between Ce $(NO_3)_3{\cdot}6H_2O$, Na_3PO_4, and deionized water, which were then combined with miR-224-5p. **(B)** TEM images of cerium oxide NPs in the shape of sea urchins. **(C)** Localization and expression of miR-224-5p in the knee cartilage of OA patients. **(D)** Representative micro-CT images of subchondral bone of OA mice treated with different ceria NP-based therapies. **(E)** Representative cartilage sections stained with H&E, Alcian Blue, and Safranin O-Fast Green staining of the mouse knee joints. Reproduced under the terms of the CC-BY-NC Creative Commons Attribution NonCommercial License 4.0 (https://creativecommons.org/licenses/by-nc/4.0/) [371]. Copyright 2023, The authors, published by American Association for the Advancement of Science. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

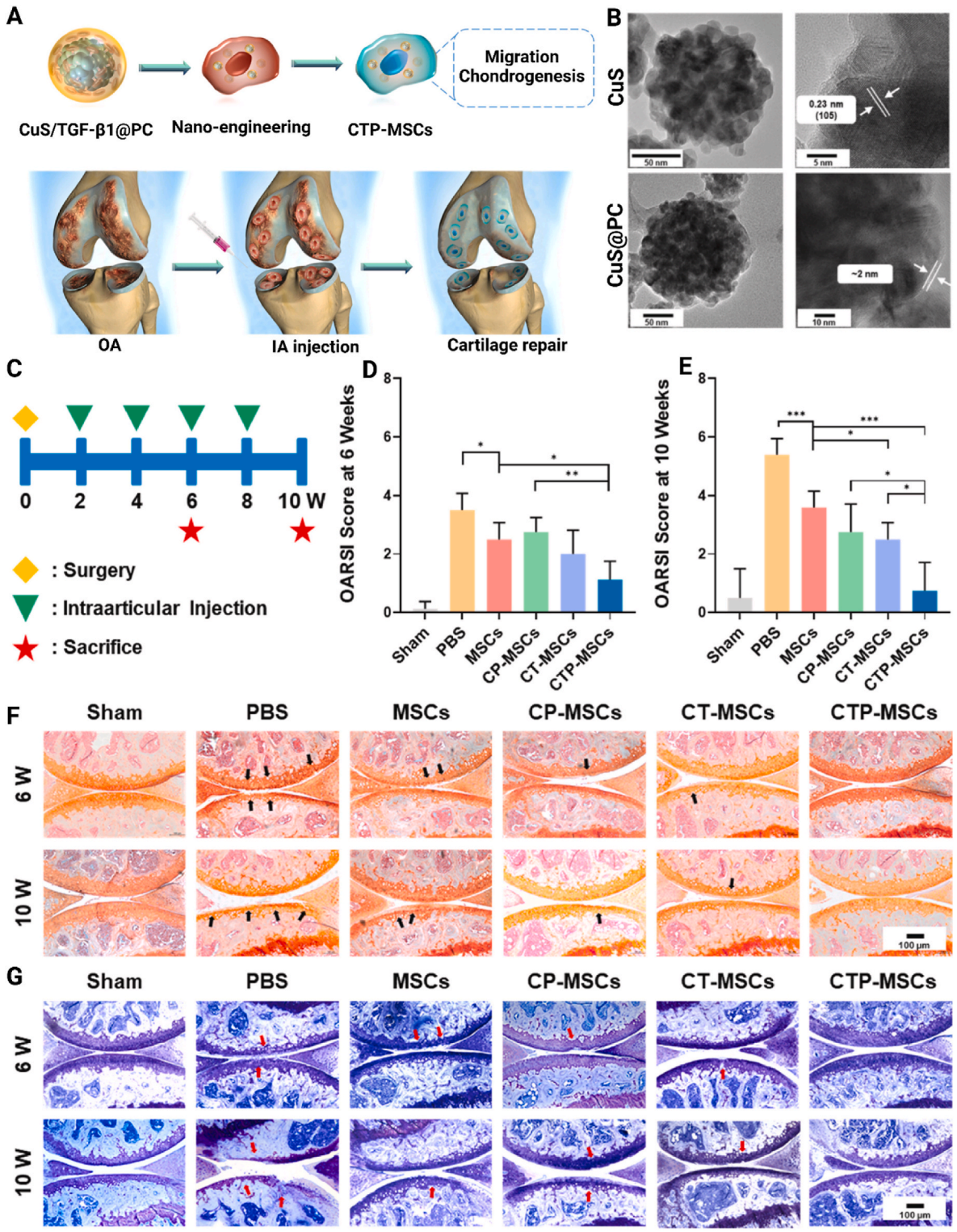

Fig. 17. Application of CuS NP-programmed MSCs for OA treatment. (A) Schematic of CuS NPs carrying plasmid DNA encoding TGF-β1, and the CuS/TGF-β1@PC (referred to as CTP) and introduction to articular joint. **(B)** TEM images of CuS-NP and CuS@PC. **(C)** Schematic diagram of the experimental design with knee joints collected at 6 and 10 weeks postoperatively. **(D)** OARSI scores measured based on histological analysis of samples collected at day 6 and **(E)** 10 weeks postoperatively. **(F)** Representative images of Safranin-O/Fast green staining, with cartilage lesions highlighted by black arrows. **(G)** Toluidine blue staining of the knee joints after different treatments, with lesions highlighted by red arrows. Reproduced under the terms of the CC-BY-NY-ND Creative Commons Attribution 4.0 International license (https://creativecommons.org/licenses/by/4.0) [380]. Copyright 2023, The authors, published by Elsevier. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

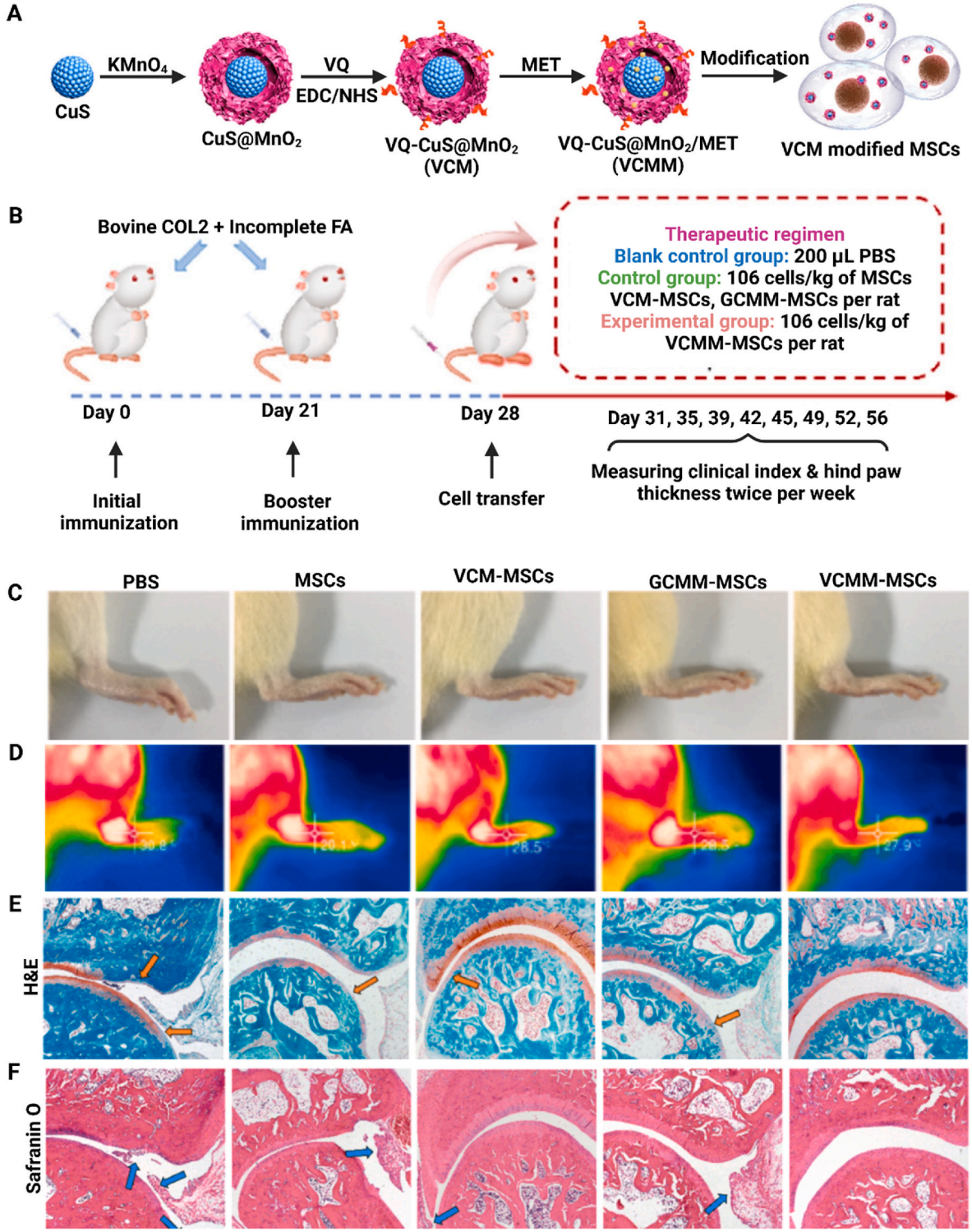

Fig. 18. Effective RA therapy by peptide-mediated nanomodification of mesenchymal stem cells. (A) Schematic of the synthesis of VQ-CuS@MnO_2/MET NPs. CuS NPs were chemically synthesized and $KMnO_4$ provided an oxidizing environment to produce CuS@MnO_2 NPs. An NH2-rich, MSC-targeting peptide (VQ) was conjugated on the NPs via EDC/NHS reaction. Finally, metformin (MET) was encapsulated in the NPs to form VQ-CuS@MnO_2/MET NPs, which were used to modify MSCs (VCMM-MSCs) for stem cell therapy. **(B)** Schematic illustration of the establishment of CIA model and therapeutic regimen of stem cell therapy using NP-modified MSCs. **(C)** Typical photographs of the rat hind paws after treatment. **(D)** Typical IR images of the hind paws. **(E)** H&E staining and **(F)** Safranine O-fast green staining. Scale bar = 200 μm. Blue and orange arrows indicate synovial inflammation and cartilage erosion, respectively. Reproduced with permission from Ref. [392]. Copyright 2022, Elsevier. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

developed and tested in adjuvant-induced arthritis models. MFC-MSNs showed beneficial effects by reducing inflammation and pathological signs in the affected joints. They also helped to scavenge ROS and convert inflammatory macrophages to an anti-inflammatory phenotype [395]. In another study, albumin-cerium oxide showed effective accumulation in RA synovial tissues. These NPs exhibited enzymatic activities, allowing them to effectively scavenge oxygen and nitrogen species in both RAW264.7 and THP-1 cells as well as alleviate joint damage in CIA mouse models [137]. Furthermore, Fe_3O_4/CeO_2 core-shell NPs capable of scavenging ROS were evaluated for their effects on J774A.1 cells. The results indicated that the cerium component of these NPs exhibited intrinsic antioxidant activity, which was effective for scavenging ROS, and showed excellent magnetic resonance imaging (MRI) performance [396].

The therapeutic potential of ZnO NPs in different formulations has been investigated in various models of RA. Researchers have used zinc gluconate-loaded chitosan NPs (ZG-CS NPs) to evaluate their effectiveness in CIA Wistar rats. The NPs reduced the severity of arthritis, as indicated by reduced joint swelling, erythema, and edema. These NPs also reduced the levels of inflammatory markers such as TNF-α, IL-1β, and oxidative stress factors such as catalase, superoxide dismutase, and glutathione [397]. The researchers developed a method for encapsulating ZnO NPs in mannose-containing liposomes and used them to treat CIA mice. It was found that the NPs promoted CCL5 degradation through NF-κB signaling and induced the conversion of immune dendritic cells (igDCs) in the spleen to tolerogenic dendritic cells (tDCs). In addition, tDCs in the spleen helped to relieve ankle swelling and inhibit ankle inflammation [398]. In another study, the researchers investigated the effect of ZnO NPs using the CFA-induced arthritis rat model. The results showed that ZnO NPs had an inhibitory effect on a variety of inflammatory mediators, including IL-1β, IL-10, and TNF-α. In addition, ZnO NPs also inhibited the autoimmune response in the rats, as evidenced by the reduced levels of anti-citrullinated protein autoantibodies [399].

AgNPs are versatile therapeutics for the treatment of RA due to their antimicrobial, anti-inflammatory, and immunomodulatory effects [400]. Silver NPs exhibit immunomodulatory properties that can help regulate the immune system's responses in RA. Yang and co-workers synthesized folic acid-modified AgNPs (FA-AgNPs) (Fig. 19A and B), which inhibited M1 macrophages and activated M2 macrophage for successful RA treatment (Fig. 19C–E) [401]. Results showed that the intracellular release of Ag^+ played an essential role in this synergistic action. The release of Ag triggering the apoptosis of M1 macrophages and facilitating the clearance of ROS, and the repolarization of M1 into M2 macrophages. Additionally, AgNPs can modulate inflammatory responses by suppressing pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [402]. In another study, bergenin-loaded and gum xanthan-stabilized Ag-NPs were studied in a CFA-induced arthritis model in what animal. The results demonstrated that BGX-AgNPs effectively alleviated articular damage and significantly reduced synovitis and inflammation in the paws. Furthermore, BGX-AgNPs exhibited inhibitory effects on the expression of Toll-like receptors 2 (TLR-2) and Toll-like receptors 4 (TLR-4). These NPs also reduced the production of inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [403]. Similarly, another study reported the synthesis of hesperidin-loaded and gum acacia-stabilized AgNPs and evaluated their efficacy against arthritic phenotypes mediated by TLR-2 and TLR-4, resulting in a lower arthritic score, mild to moderate tissue edema, and reduced degenerative effects with only moderate articular changes [404].

Although MNPs hold great promises for treatment of RA, several issues need to be resolved before they can be used as safe and effective nanomedicine. Firstly, MNPs may remain as residues in healthy tissues. Such residues can impact the diagnosis and treatment of RA complications, including pleurisy, valvulitis, interstitial pneumonia, and neurological damage. Furthermore, despite their potential for treating RA, MNPs still exhibit issues with their bioavailability. Further research is required to determine how MNPs can be used to target inflamed joints with precision. It is essential to ensure that these NPs can effectively reach the affected areas without negatively affecting healthy tissues. In conclusion, it is crucial to weigh the advantages and potential drawbacks of MNPs prior to their clinical trials as RA therapies [384,405,406].

5. Challenges and future perspectives

Bone and joint disorders encompass a wide range of conditions that affect the skeletal health and functions. The main treatment strategies for these disorders involve the use of drugs to slow down the rate of bone/cartilage loss or promote new tissue formation. However, the medications used for treating bone and joint disorders often have limited effectiveness and serious long-term side effects. MNP-based strategies could markedly augment our ability to tackle bone and joint disorders. These strategies entail the utilization of MNPs for the targeted delivery of drugs, growth factors, and siRNA to specific tissue sites, modulation of immune responses, and elimination of inflammatory and/or degenerative mediators, thereby enhancing their precision and efficacy while reducing their side effects to achieve improved patient outcomes. To realize the successful clinical translation of MNPs as novel bone and joint disease therapies, several emerging areas with the potential to overcome the current limitations of MNP-based nanomedicine are garnering increasing attention (Fig. 20).

5.1. Validating and improving MNPs with organs-on-chip (OoC)

Combining bone and joint OoC systems with MNPs provides a promising avenue for advancing targeted drug delivery and treatments for bone and joint disorders [412]. This convergence exploits the precision aspect of nanotechnology and the biological fidelity of OoC platforms to enhance a compressive understand of MNP delivery to the intricate microenvironments of bone and cartilage tissues under physiological and pathological conditions. Robust *in vitro* analyses based on bone- and joint-mimicking OoCs can illuminate the physicochemical and biological properties of MNPs in diverse tissue microenvironments, offering valuable insights for validating the MNPs' safety and efficacy. The bone- and joint-mimicking OoCs, characterized by dynamic culture conditions, serve as a versatile, high-throughput test of disorder platform to bridge current gaps in the translation of nanotechnology for treatment. These investigations will also address the ethical concerns over the use of animal models for assessing new drugs, including MNPs, and bring a paradigm shift in drug development.

5.2. MNP-enabled multifunctional approach for treatment and imaging

The use of MNPs in tissue engineering has opened new opportunities for various future clinical applications. NP research related to bone and joint disorders has shown promising results in three main areas: scaffold design and fabrication, synthesis of NPs for biomolecule delivery, and NPs for imaging [413–416]. Combining these strategies into a multifunctional system can provide the appropriate scaffolds, stimulate cellular functions through intracellular drug release, and track the delivered cells *in vivo* via bioimaging. The ability of MNPs to label cells has a significant impact on the development of new therapeutic solutions. It allows researchers to monitor cell biodistribution and function after transplantation for an extended period, which can aid in our understanding of the healing process. Researchers have already used deep learning combined with nanotomography to visualize MNPs in single cells [417]. Additionally, future research should report the number of NPs used, along with pharmacokinetic studies that investigate how NPs are absorbed, distributed, metabolized, and excreted by organisms. Moreover, it is crucial to understand the dynamics and pathways associated with MNP uptake by cells.

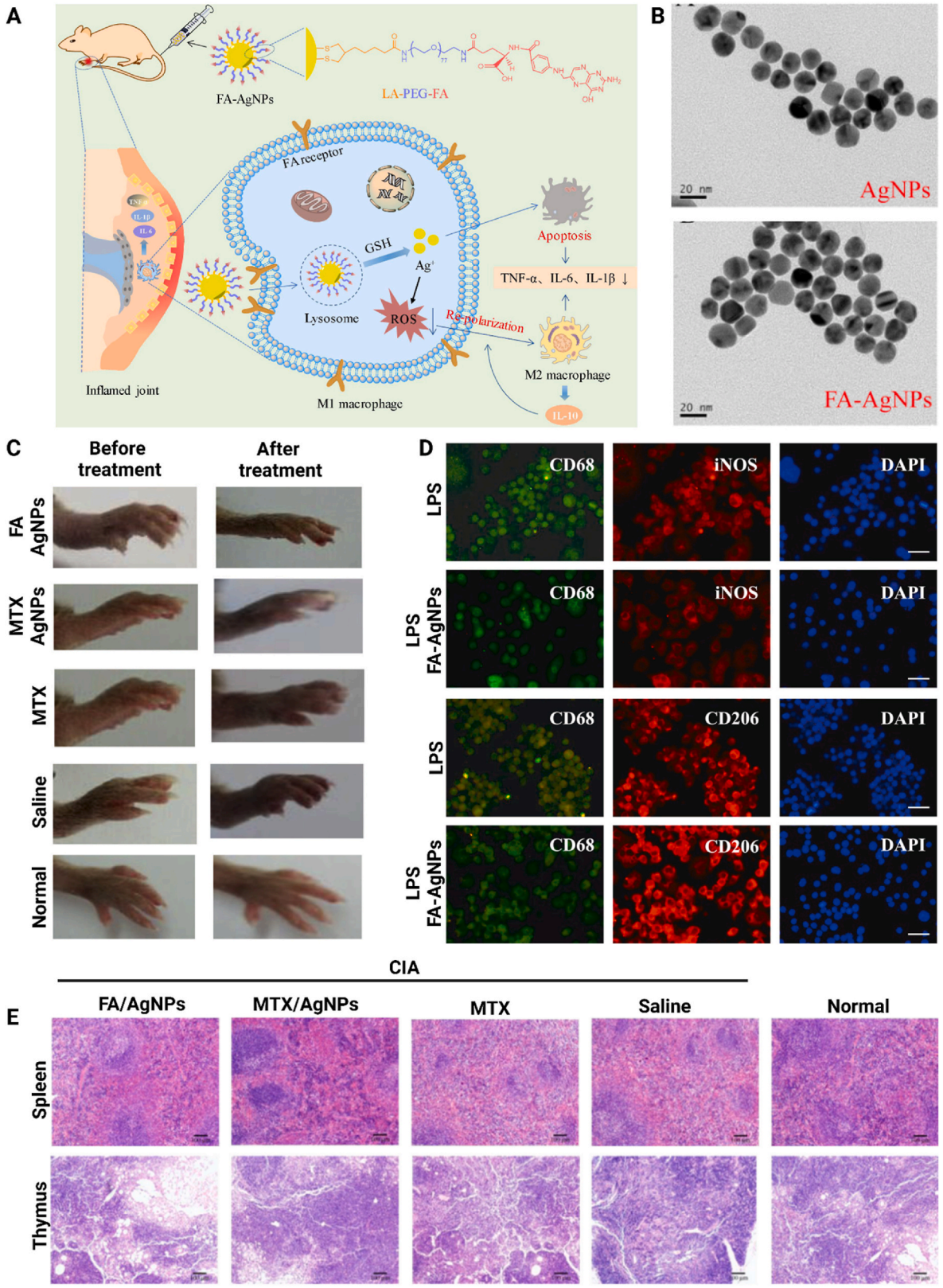

Fig. 19. Silver NPs for RA therapy via macrophage apoptosis and re-polarization. (A) Schematic illustration of the therapeutic mechanism of FA-AgNPs against RA. FA = folic acid. **(B)** TEM image of AgNPs and FA-AgNPs. **(C)** Photographs of inflamed joints before and after different treatments. **(D)** Immunofluorescence staining of CD68 (green), iNOS and CD206 (red), and nuclei (blue) on macrophages without or with treatment of FA-AgNPs. Scale bar = 100 μm. **E)** Histopathological analysis by H&E staining of spleen and thymus after various treatments. Scale bar = 100 μm. Reproduced with permission from Ref. [401]. Copyright 2021, Elsevier. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

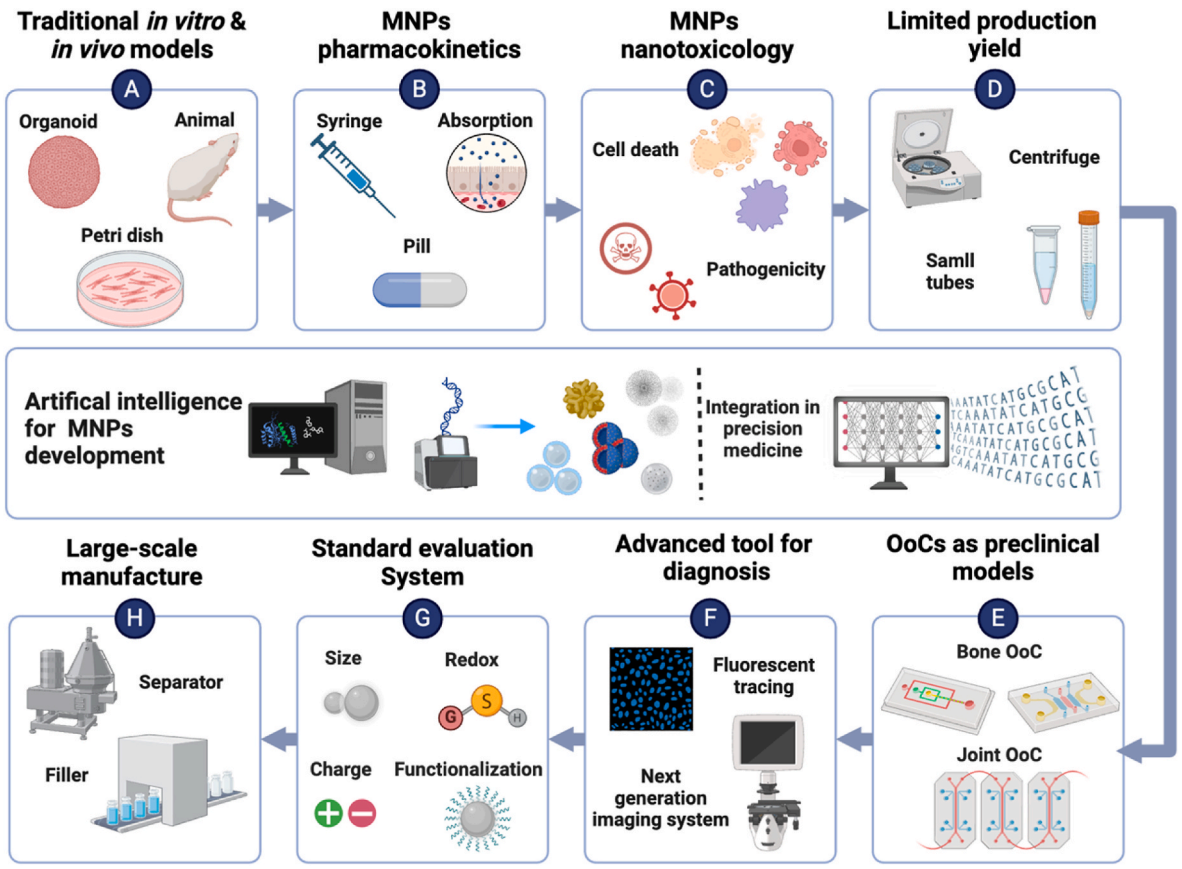

Fig. 20. Challenges and prospects of MNPs as therapeutic modalities for joint and bone disorders. The top panels depict the current challenges in the application of MNPs, including nanotoxicology, limited pharmacokinetics evaluation, and the hurdle of large-scale production of functionalized MNPs. The potential of artificial intelligence (AI) for molecular diagnostics and the benefits of combining AI with other techniques for precision medicine in bone and joint disease populations are illustrated in the middle panel. The bottom panels depict the promising applications of organs-on-chips (OoCs), advanced detection instruments, advanced assessment techniques, and industrialized production processes for future clinical translation of MNPs.

5.3. Advanced nanotoxicology evaluation

The past decade has witnessed a significant increase in research work on the biomedical applications of MNPs, but much remains unclear regarding the interactions between MNPs and living organisms as well as the underlying mechanisms. The ultrasmall size of NPs results in high chemical reactivity. Therefore, mechanistic paradigms of bulk metallic materials are inaccurate when applied to NPs. Most of previous studies have examined the potential cytotoxicity of MNPs, but further research is needed to fully understand the possible toxicological effects of MNPs. Therefore, nanotoxicology should grow alongside nanotechnology to provide safety profiles for each type of MNPs. Future studies should comprehensively characterize NPs, including their size, composition, shape, charge, application mode (immobilized in scaffolds or in a free form), and interactions with different tissue and cell types. Furthermore, when MNPs are introduced into the human body, they inevitably interact with body fluids, thereby adsorbing a variety of biomolecules. This process gives rise to the formation of a 'biomolecular corona' on the surface of the NPs, which endows them with new biological properties and thus determines biological events including cellular uptake, immune response, and biodistribution [418]. In order to standardize the data collected, it is necessary to establish a representative model for each type of NP, a toxicity testing protocol, and the composition of the protein corona.

5.4. Clinical translation of MNPs

Ensuring quality control and reproducibility during the scale-up of MNP production for clinical translation represents a significant challenge. Significant progress has been made in the preclinical evaluation and clinical trials of MNPs, with a number of MNPs already achieving regulatory approval. For instance, iron oxide nanoparticles (e.g., Ferumoxytol) are utilized clinically for MRI and anemia treatment [419]. Additionally, gold nanoparticle (AuNP)-based therapies, such as AuroShell®, are being studied in clinical trials for localized tumor ablation [420,421]. Notably, the establishment of regulatory frameworks, including the FDA's 2022 Nanotechnology Product Guide and ISO/TS 19807–1:2019 (Characterization of Nanomaterials) standards, has enhanced reproducibility, safety, and batch-to-batch consistency [422]. However, there remain challenges in scaling up laboratory-scale synthesis to cost-effective, good manufacturing practices-compliant industrial production [423]. Collaborative initiatives such as the Nanotechnology Characterization Laboratory (NCL) Consortium are actively addressing the gaps by standardizing protocols for toxicity analysis, biodistribution studies, and regulatory compliance [424].

5.5. Artificial intelligence (AI) for MNP development

The application of artificial intelligence (AI) techniques, such as machine learning and data mining, has been demonstrated to facilitate overcoming the challenges in the design and optimization of MNPs for various biomedical applications. By leveraging large datasets and computational models, AI algorithms are able to analyze the intricate relationships between NP properties, synthesis parameters, and biological reactions [425,426], and specifically to model potential outcomes. This enables researchers to identify novel design principles, optimize

synthesis protocols, and predict NP behaviors (both *in vitro* and *in vivo*) with greater precision. AI algorithms can also analyze large-scale patient datasets to identify biomarkers and patterns that can inform the selection and optimization of MNPs for specific therapeutic interventions.

6. Conclusions

Significant advances have been made in the development of MNPs for treating bone and joint disorders. This review focuses on the synthesis, characterization, and *in vitro* and *in vivo* evaluation of MNPs that were used alone, loaded with drugs and growth factors, or infused into hydrogels and scaffolds, to effectively treat osteoporosis, osteomyelitis, OS, critical-sized bone defect, OA, and RA. MNPs have been demonstrated to be a versatile platform for biomolecule delivery to enhance bone and joint repair and regeneration, and can offer superior efficacy at lower costs as compared to conventional therapies. Furthermore, MNPs can enable a plethora of novel applications and facilitate treatment techniques with increased precision, leading to more efficacious and durable implants with reduced incidences of complications such as infection. Finally, the rapidly evolving AI technology is markedly accelerating the development and translation of MNPs to enable effective, potentially personalized applications of MNPs as precision medicine for bone and joint diseases.

CRediT authorship contribution statement

Yuwen Wang: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Hasnain Jan:** Writing – original draft, Visualization, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Zheng Zhong:** Writing – review & editing, Validation, Software, Resources, Methodology, Investigation, Formal analysis. **Liangbin Zhou:** Writing – review & editing. **Kexin Teng:** Writing – review & editing. **Ye Chen:** Writing – review & editing. **Jiankun Xu:** Writing – review & editing. **Denghui Xie:** Writing – review & editing. **Dexin Chen:** Writing – review & editing. **Jiake Xu:** Writing – review & editing. **Ling Qin:** Writing – review & editing. **Rocky S. Tuan:** Writing – review & editing. **Zhong Alan Li:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Conceptualization.

Declaration of competing interest

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

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Data availability

Data will be made available on request.

References

[1] D.J. Hunter, D. Schofield, E. Callander, The individual and socioeconomic impact of osteoarthritis, Nat. Rev. Rheumatol. 10 (2014) 437–441, https://doi.org/10.1038/nrrheum.2014.44.
[2] A. Finckh, B. Gilbert, B. Hodkinson, S.-C. Bae, R. Thomas, K.D. Deane, D. Alpizar-Rodriguez, K. Lauper, Global epidemiology of rheumatoid arthritis, Nat. Rev. Rheumatol. 18 (2022) 591–602, https://doi.org/10.1038/s41584-022-00827-y.
[3] GBD 2021 Other Musculoskeletal Disorders Collaborators, Global, regional, and national burden of other musculoskeletal disorders, 1990–2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021, Lancet Rheumatol 5 (2023) e670–e682, https://doi.org/10.1016/S2665-9913(23)00232-1.
[4] T. Sözen, L. Özışık, N.Ç. Başaran, An overview and management of osteoporosis, Eur. J. Rheumatol. 4 (2017) 46–56, https://doi.org/10.5152/eurjrheum.2016.048.
[5] Y. Shen, X. Huang, J. Wu, X. Lin, X. Zhou, Z. Zhu, X. Pan, J. Xu, J. Qiao, T. Zhang, L. Ye, H. Jiang, Y. Ren, P.-F. Shan, The global burden of osteoporosis, low bone mass, and its related fracture in 204 countries and territories, 1990-2019, Front. Endocrinol. 13 (2022), https://doi.org/10.3389/fendo.2022.882241.
[6] H. Tian, J. Cao, B. Li, E.C. Nice, H. Mao, Y. Zhang, C. Huang, Managing the immune microenvironment of osteosarcoma: the outlook for osteosarcoma treatment, Bone Res 11 (2023) 1–26, https://doi.org/10.1038/s41413-023-00246-z.
[7] S.J. Taran, R. Taran, N.B. Malipatil, Pediatric osteosarcoma: an updated review, Indian J. Med. Paediatr. Oncol. 38 (2021) 33–43.
[8] H.C. Beird, S.S. Bielack, A.M. Flanagan, J. Gill, D. Heymann, K.A. Janeway, J. A. Livingston, R.D. Roberts, S.J. Strauss, R. Gorlick, Osteosarcoma, Nat. Rev. Dis. Primer 8 (2022) 77. https://doi.org/10.1038/s41572-022-00409-y.
[9] L.R. Sadykova, A.I. Ntekim, M. Muyangwa-Semenova, C.S. Rutland, J. N. Jeyapalan, N. Blatt, A.A. Rizvanov, Epidemiology and risk factors of osteosarcoma, Cancer Invest. 38 (2020) 259–269, https://doi.org/10.1080/07357907.2020.1768401.
[10] H.C. Beird, S.S. Bielack, A.M. Flanagan, J. Gill, D. Heymann, K.A. Janeway, J. A. Livingston, R.D. Roberts, S.J. Strauss, R. Gorlick, Osteosarcoma, Nat. Rev. Dis. Primers 8 (2022) 1–19, https://doi.org/10.1038/s41572-022-00409-y.
[11] R. Gorlick, K. Janeway, S. Lessnick, R.L. Randall, N. Marina, COG Bone Tumor Committee, Children's Oncology Group's 2013 blueprint for research: bone tumors, Pediatr. Blood Cancer 60 (2013) 1009–1015, https://doi.org/10.1002/pbc.24429.
[12] A.H. Aljubran, A. Griffin, M. Pintilie, M. Blackstein, Osteosarcoma in adolescents and adults: survival analysis with and without lung metastases, Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. 20 (2009) 1136–1141, https://doi.org/10.1093/annonc/mdn731.
[13] Y. Zhou, Q. Lu, J. Xu, R. Yan, J. Zhu, J. Xu, X. Jiang, J. Li, F. Wu, The effect of pathological fractures on the prognosis of patients with osteosarcoma: a meta-analysis of 14 studies, Oncotarget 8 (2017) 73037–73049, https://doi.org/10.18632/oncotarget.20375.
[14] P.R. Chapman, G. Choudhary, A. Singhal, Skull base osteomyelitis: a comprehensive imaging review, AJNR Am. J. Neuroradiol. 42 (2021) 404–413, https://doi.org/10.3174/ajnr.A7015.
[15] E.A. Masters, B.F. Ricciardi, K.L. de M. Bentley, T.F. Moriarty, E.M. Schwarz, G. Muthukrishnan, Skeletal infections: microbial pathogenesis, immunity and clinical management, Nat. Rev. Microbiol. 20 (2022) 385–400, https://doi.org/10.1038/s41579-022-00686-0.
[16] M.I. Hofstee, G. Muthukrishnan, G.J. Atkins, M. Riool, K. Thompson, M. Morgenstern, M.J. Stoddart, R.G. Richards, S.A.J. Zaat, T.F. Moriarty, Current concepts of osteomyelitis: from pathologic mechanisms to advanced research methods, Am. J. Pathol. 190 (2020) 1151–1163, https://doi.org/10.1016/j.ajpath.2020.02.007.
[17] A. Nauth, E. Schemitsch, B. Norris, Z. Nollin, J.T. Watson, Critical-size bone defects: is there a consensus for diagnosis and treatment? J. Orthop. Trauma 32 (Suppl 1) (2018) S7–S11, https://doi.org/10.1097/BOT.0000000000001115.
[18] E.H. Schemitsch, Size matters: defining critical in bone defect size, J. Orthop. Trauma 31 (Suppl 5) (2017) S20–S22, https://doi.org/10.1097/BOT.0000000000000978.
[19] A. Nauth, M.D. McKee, T.A. Einhorn, J.T. Watson, R. Li, E.H. Schemitsch, Managing bone defects, J. Orthop. Trauma 25 (2011) 462–466, https://doi.org/10.1097/BOT.0b013e318224caf0.
[20] W. Wang, K.W.K. Yeung, Bone grafts and biomaterials substitutes for bone defect repair: a review, Bioact. Mater. 2 (2017) 224–247, https://doi.org/10.1016/j.bioactmat.2017.05.007.
[21] Y.-H. Huang, A.E. Jakus, S.W. Jordan, Z. Dumanian, K. Parker, L. Zhao, P.K. Patel, R.N. Shah, Three-dimensionally printed hyperelastic bone scaffolds accelerate bone regeneration in critical-size calvarial bone defects, Plast. Reconstr. Surg. 143 (2019) 1397–1407, https://doi.org/10.1097/PRS.0000000000005530.

[22] C.E. Gillman, A.C. Jayasuriya, FDA-approved bone grafts and bone graft substitute devices in bone regeneration, Mater. Sci. Eng., C 130 (2021) 112466, https://doi.org/10.1016/j.msec.2021.112466.

[23] M. Farokhi, F. Mottaghitalab, M.A. Shokrgozar, K.-L. Ou, C. Mao, H. Hosseinkhani, Importance of dual delivery systems for bone tissue engineering, J. Control. Release Off. J. Control. Release Soc. 225 (2016) 152–169, https://doi.org/10.1016/j.jconrel.2016.01.033.

[24] H. Xu, W. Wang, X. Liu, W. Huang, C. Zhu, Y. Xu, H. Yang, J. Bai, D. Geng, Targeting strategies for bone diseases: signaling pathways and clinical studies, Signal Transduct. Target. Ther. 8 (2023) 202, https://doi.org/10.1038/s41392-023-01467-8.

[25] V.P. Leifer, J.N. Katz, E. Losina, The burden of OA-health services and economics, Osteoarthr. Cartil. 30 (2022) 10–16, https://doi.org/10.1016/j.joca.2021.05.007.

[26] I.J. Wallace, S. Worthington, D.T. Felson, R.D. Jurmain, K.T. Wren, H. Maijanen, R.J. Woods, D.E. Lieberman, Knee osteoarthritis has doubled in prevalence since the mid-20th century, Proc. Natl. Acad. Sci. U. S. A 114 (2017) 9332–9336, https://doi.org/10.1073/pnas.1703856114.

[27] S. Liu, C. Zhang, Y. Zhou, F. Zhang, X. Duan, Y. Liu, X. Zhao, J. Liu, X. Shuai, J. Wang, Z. Cao, MRI-visible mesoporous polydopamine nanoparticles with enhanced antioxidant capacity for osteoarthritis therapy, Biomaterials 295 (2023) 122030, https://doi.org/10.1016/j.biomaterials.2023.122030.

[28] G.C. Machado, C. Abdel-Shaheed, M. Underwood, R.O. Day, Non-steroidal anti-inflammatory drugs (NSAIDs) for musculoskeletal pain, BMJ 372 (2021) n104, https://doi.org/10.1136/bmj.n104.

[29] E. Roberts, V. Delgado Nunes, S. Buckner, S. Latchem, M. Constanti, P. Miller, M. Doherty, W. Zhang, F. Birrell, M. Porcheret, K. Dziedzic, I. Bernstein, E. Wise, P.G. Conaghan, Paracetamol: not as safe as we thought? A systematic literature review of observational studies, Ann. Rheum. Dis. 75 (2016) 552–559, https://doi.org/10.1136/annrheumdis-2014-206914.

[30] A. Magni, P. Agostoni, C. Bonezzi, G. Massazza, P. Menè, V. Savarino, D. Fornasari, Management of osteoarthritis: expert opinion on NSAIDs, Pain Ther 10 (2021) 783–808, https://doi.org/10.1007/s40122-021-00260-1.

[31] K. Sharif, A. Sharif, F. Jumah, R. Oskouian, R.S. Tubbs, Rheumatoid arthritis in review: clinical, anatomical, cellular and molecular points of view, Clin. Anat. N. Y. N 31 (2018) 216–223, https://doi.org/10.1002/ca.22980.

[32] Clinical Overview of Arthritis with a Focus on Management Options and Preventive Lifestyle Measures for Its Control | Request PDF, ResearchGate (n.d.). https://doi.org/10.2174/1573401318666220204095629.

[33] M. Akiyama, Y. Kaneko, Pathogenesis, clinical features, and treatment strategy for rheumatoid arthritis-associated interstitial lung disease, Autoimmun. Rev. 21 (2022) 103056, https://doi.org/10.1016/j.autrev.2022.103056.

[34] A.A. Drosos, E. Pelechas, P.V. Voulgari, Treatment strategies are more important than drugs in the management of rheumatoid arthritis, Clin. Rheumatol. 39 (2020) 1363–1368, https://doi.org/10.1007/s10067-020-05001-x.

[35] W. Wang, H. Zhou, L. Liu, Side effects of methotrexate therapy for rheumatoid arthritis: a systematic review, Eur. J. Med. Chem. 158 (2018) 502–516, https://doi.org/10.1016/j.ejmech.2018.09.027.

[36] V. Collini, M. Driussi, C. Nalli, M. Baldassi, E. Di Poi, L. Cereser, F. Giuliana, V. Patruno, D. Stolfo, G. Sinagra, M. Imazio, Leflunomide-induced pulmonary arterial hypertension: case report and review of literature, J. Cardiol. Cases 26 (2022) 148–150, https://doi.org/10.1016/j.jccase.2022.04.001.

[37] S. Mushtaq, R. Sarkar, Sulfasalazine in dermatology: a lesser explored drug with broad therapeutic potential, Int. J. Womens Dermatol. 6 (2020) 191–198, https://doi.org/10.1016/j.ijwd.2020.01.009.

[38] M.J. Ahlers, B.D. Lowery, E. Farber-Eger, T.J. Wang, W. Bradham, M.J. Ormseth, C.P. Chung, C.M. Stein, D.K. Gupta, Heart failure risk associated with rheumatoid arthritis-related chronic inflammation, J. Am. Heart Assoc. 9 (2020) e014661, https://doi.org/10.1161/JAHA.119.014661.

[39] J. Walton, M.V. Bazavan, Long term side effects of hydroxychloroquine: cardiomyopathy and heart failure, J. Am. Coll. Cardiol. 79 (2022) 2641, https://doi.org/10.1016/S0735-1097(22)03632-4.

[40] P. Kangari, T. Talaei-Khozani, I. Razeghian-Jahromi, M. Razmkhah, Mesenchymal stem cells: amazing remedies for bone and cartilage defects, Stem Cell Res. Ther. 11 (2020) 492, https://doi.org/10.1186/s13287-020-02001-1.

[41] J. Song, L. Li, L. Fang, E. Zhang, Y. Zhang, Z. Zhang, P. Vangari, Y. Huang, F. Tian, Y. Zhao, W. Chen, J. Xue, Advanced strategies of scaffolds design for bone regeneration, BMEMat 1 (2023) e12046, https://doi.org/10.1002/bmm2.12046.

[42] N. Abbasi, S. Hamlet, R.M. Love, N.-T. Nguyen, Porous scaffolds for bone regeneration, J. Sci. Adv. Mater. Devices 5 (2020) 1–9, https://doi.org/10.1016/j.jsamd.2020.01.007.

[43] J. Li, G. Chen, X. Xu, P. Abdou, Q. Jiang, D. Shi, Z. Gu, Advances of injectable hydrogel-based scaffolds for cartilage regeneration, Regen. Biomater. 6 (2019) 129–140, https://doi.org/10.1093/rb/rbz022.

[44] M. Rabiei, S. Kashanian, S.S. Samavati, H. Derakhshankhah, S. Jamasb, S.J. P. McInnes, Nanotechnology application in drug delivery to osteoarthritis (OA), rheumatoid arthritis (RA), and osteoporosis (OSP), J. Drug Deliv. Sci. Technol. 61 (2021) 102011, https://doi.org/10.1016/j.jddst.2020.102011.

[45] D. Medina-Cruz, E. Mostafavi, A. Vernet-Crua, J. Cheng, V. Shah, J.L. Cholula-Diaz, G. Guisbiers, J. Tao, J.M. García-Martín, T.J. Webster, Green nanotechnology-based drug delivery systems for osteogenic disorders, Expert Opin. Drug Deliv. 17 (2020) 341–356, https://doi.org/10.1080/17425247.2020.1727441.

[46] Y. Wang, L. Liu, Z. Le, A. Tay, Analysis of nanomedicine efficacy for osteoarthritis, Adv. NanoBiomed Res. 2 (2022) 2200085, https://doi.org/10.1002/anbr.202200085.

[47] Y. Zhang, P. Wang, H. Mao, Y. Zhang, L. Zheng, P. Yu, Z. Guo, L. Li, Q. Jiang, PEGylated gold nanoparticles promote osteogenic differentiation in *in vitro* and *in vivo* systems, Mater. Des. 197 (2021) 109231, https://doi.org/10.1016/j.matdes.2020.109231.

[48] M.A. Fernandez-Yague, S.A. Abbah, L. McNamara, D.I. Zeugolis, A. Pandit, M. J. Biggs, Biomimetic approaches in bone tissue engineering: integrating biological and physicomechanical strategies, Adv. Drug Deliv. Rev. 84 (2015) 1–29, https://doi.org/10.1016/j.addr.2014.09.005.

[49] Q. Wang, B. Chen, F. Ma, S. Lin, M. Cao, Y. Li, N. Gu, Magnetic iron oxide nanoparticles accelerate osteogenic differentiation of mesenchymal stem cells via modulation of long noncoding RNA INZEB2, Nano Res. 10 (2017) 626–642, https://doi.org/10.1007/s12274-016-1322-4.

[50] K. Qiao, L. Xu, J. Tang, Q. Wang, K.S. Lim, G. Hooper, T.B.F. Woodfield, G. Liu, K. Tian, W. Zhang, X. Cui, The advances in nanomedicine for bone and cartilage repair, J. Nanobiotechnology 20 (2022) 141, https://doi.org/10.1186/s12951-022-01342-8.

[51] J. Huang, F. Liu, H. Su, J. Xiong, L. Yang, J. Xia, Y. Liang, Advanced nanocomposite hydrogels for cartilage tissue engineering, Gels Basel Switz 8 (2022) 138, https://doi.org/10.3390/gels8020138.

[52] R. Eivazzadeh-Keihan, E. Bahojb Noruzi, K. Khanmohammadi Chenab, A. Jafari, F. Radinekiyan, S.M. Hashemi, F. Ahmadpour, A. Behboudi, J. Mosafer, A. Mokhtarzadeh, A. Maleki, M.R. Hamblin, Metal-based nanoparticles for bone tissue engineering, J. Tissue Eng. Regen. Med. 14 (2020) 1687–1714, https://doi.org/10.1002/term.3131.

[53] S. van Rijt, P. Habibovic, Enhancing regenerative approaches with nanoparticles, J. R. Soc. Interface 14 (2017) 20170093, https://doi.org/10.1098/rsif.2017.0093.

[54] A. Tautzenberger, A. Kovtun, A. Ignatius, Nanoparticles and their potential for application in bone, Int. J. Nanomedicine 7 (2012) 4545–4557, https://doi.org/10.2147/IJN.S34127.

[55] M.I. González-Sánchez, S. Perni, G. Tommasi, N.G. Morris, K. Hawkins, E. López-Cabarcos, P. Prokopovich, Silver nanoparticle based antibacterial methacrylate hydrogels potential for bone graft applications, Mater. Sci. Eng., C 50 (2015) 332–340, https://doi.org/10.1016/j.msec.2015.02.002.

[56] A. Abdal Dayem, S.B. Lee, S.-G. Cho, The impact of metallic nanoparticles on stem cell proliferation and differentiation, Nanomater. Basel Switz. 8 (2018) 761, https://doi.org/10.3390/nano8100761.

[57] D.J. Irvine, E.L. Dane, Enhancing cancer immunotherapy with nanomedicine, Nat. Rev. Immunol. 20 (2020) 321–334, https://doi.org/10.1038/s41577-019-0269-6.

[58] Neha Desai null, M. Momin, T. Khan, S. Gharat, R.S. Ningthoujam, A. Omri, Metallic nanoparticles as drug delivery system for the treatment of cancer, Expert Opin. Drug Deliv. 18 (2021) 1261–1290, https://doi.org/10.1080/17425247.2021.1912008.

[59] B. Liu, Z. Qi, J. Chao, Framework nucleic acids directed assembly of Au nanostructures for biomedical applications, Interdiscip. Med. 1 (2023) e20220009, https://doi.org/10.1002/INMD.20220009.

[60] S. Chen, Y. Wu, F. Lortie, J. Bernard, W.H. Binder, J. Zhu, Hydrogen-bonds-mediated nanomedicine: design, synthesis, and applications, macromol, Rapid Commun 43 (2022) e2200168, https://doi.org/10.1002/marc.202200168.

[61] T. Doane, C. Burda, Nanoparticle mediated non-covalent drug delivery, Adv. Drug Deliv. Rev. 65 (2013) 607–621, https://doi.org/10.1016/j.addr.2012.05.012.

[62] Y. Liu, Y. Wu, Z. Luo, M. Li, Designing supramolecular self-assembly nanomaterials as stimuli-responsive drug delivery platforms for cancer therapy, iScience 26 (2023) 106279, https://doi.org/10.1016/j.isci.2023.106279.

[63] E. Kahraman, S. Güngör, Y. Özsoy, Potential enhancement and targeting strategies of polymeric and lipid-based nanocarriers in dermal drug delivery, Ther. Deliv. 8 (2017) 967–985, https://doi.org/10.4155/tde-2017-0075.

[64] B. Priyadarshini, M. Rama, Chetan, U. Vijayalakshmi, Bioactive coating as a surface modification technique for biocompatible metallic implants: a review, J. Asian Ceram. Soc. 7 (2019) 397–406, https://doi.org/10.1080/21870764.2019.1669861.

[65] L. Gao, G. Liu, J. Ma, X. Wang, L. Zhou, X. Li, Drug nanocrystals: in vivo performances, J. Control. Release Off. J. Control. Release Soc. 160 (2012) 418–430, https://doi.org/10.1016/j.jconrel.2012.03.013.

[66] J. Ezzati Nazhad Dolatabadi, Y. Omidi, Solid lipid-based nanocarriers as efficient targeted drug and gene delivery systems, TrAC Trends Anal. Chem. 77 (2016) 100–108, https://doi.org/10.1016/j.trac.2015.12.016.

[67] M. Navarro, A. Michiardi, O. Castaño, J.A. Planell, Biomaterials in orthopaedics, J. R. Soc. Interface 5 (2008) 1137–1158, https://doi.org/10.1098/rsif.2008.0151.

[68] Q. Chen, G.A. Thouas, Metallic implant biomaterials, Mater. Sci. Eng. R Rep. 87 (2015) 1–57, https://doi.org/10.1016/j.mser.2014.10.001.

[69] L. Kunčická, R. Kocich, T.C. Lowe, Advances in metals and alloys for joint replacement, Prog. Mater. Sci. 88 (2017) 232–280, https://doi.org/10.1016/j.pmatsci.2017.04.002.

[70] E.-K. Song, J.-K. Seon, J.-Y. Moon, Y.J.- Hyoun, E.-K. Song, J.-K. Seon, J.-Y. Moon, Y.J.- Hyoun, The evolution of modern total knee prostheses, in: Arthroplasty - Update, IntechOpen, 2013, https://doi.org/10.5772/54343.

[71] D.J. Blackwood, Biomaterials: past successes and future problems, Corros. Rev. 21 (2003) 97–124, https://doi.org/10.1515/CORRREV.2003.21.2-3.97.

[72] Y. Ding, C. Wen, P. Hodgson, Y. Li, Effects of alloying elements on the corrosion behavior and biocompatibility of biodegradable magnesium alloys: a review, J. Mater. Chem. B 2 (2014) 1912–1933, https://doi.org/10.1039/c3tb21746a.

[73] M. Bonnin, A. Amendola, J. Bellemans, S. MacDonald, J. Ménétrey, The Knee Joint: Surgical Techniques and Strategies, Springer, Paris, 2012, https://doi.org/10.1007/978-2-287-99353-4.
[74] Z. Liu, H. Liu, R. Vowden, L. Hughes, D. Qi, W. Francis, G. Perino, R. Pink, J. Xiao, B. Li, Z. Xia, Combination of cobalt, chromium and titanium nanoparticles increases cytotoxicity in vitro and pro-inflammatory cytokines in vivo, J. Orthop. Transl. 38 (2023) 203–212, https://doi.org/10.1016/j.jot.2022.10.013.
[75] X. Meng, W. Zhang, Z. Lyu, T. Long, Y. Wang, ZnO nanoparticles attenuate polymer-wear-particle induced inflammatory osteolysis by regulating the MEK-ERK-COX-2 axis, J. Orthop. Transl. 34 (2022) 1–10, https://doi.org/10.1016/j.jot.2022.04.001.
[76] Q. Wang, L. Zhang, J. Dong, Effects of plasma nitriding on microstructure and tribological properties of CoCrMo alloy implant materials, J. Bionic Eng. 7 (2010) 337–344, https://doi.org/10.1016/S1672-6529(10)60265-X.
[77] M. Geetha, A.K. Singh, R. Asokamani, A.K. Gogia, Ti based biomaterials, the ultimate choice for orthopaedic implants – a review, Prog. Mater. Sci. 54 (2009) 397–425, https://doi.org/10.1016/j.pmatsci.2008.06.004.
[78] W.R. Wagner, S.E. Sakiyama-Elbert, G. Zhang, M.J. Yaszemski, Biomaterials Science: an Introduction to Materials in Medicine, Elsevier, 2020, https://doi.org/10.1016/C2017-0-02323-6.
[79] M. Talha, C.K. Behera, O.P. Sinha, A review on nickel-free nitrogen containing austenitic stainless steels for biomedical applications, Mater. Sci. Eng. C 33 (2013) 3563–3575, https://doi.org/10.1016/j.msec.2013.06.002.
[80] R.P. Brown, B.A. Fowler, S. Fustinoni, M. Nordberg, Chapter 5 - toxicity of metals released from implanted medical devices, in: G.F. Nordberg, B.A. Fowler, M. Nordberg (Eds.), Handb. Toxicol. Met, fourth ed., Academic Press, San Diego, 2015, pp. 113–122, https://doi.org/10.1016/B978-0-444-59453-2.00005-6.
[81] C. Oldani, A. Dominguez, C. Oldani, A. Dominguez, Titanium as a biomaterial for implants, in: Recent Adv. Arthroplasty, IntechOpen, 2012, https://doi.org/10.5772/27413.
[82] N. Sakaguchi, M. Niinomi, T. Akahori, J. Takeda, H. Toda, Effect of Ta content on mechanical properties of Ti–30Nb–*X*Ta–5Zr, Mater. Sci. Eng. C 25 (2005) 370–376, https://doi.org/10.1016/j.msec.2005.04.003.
[83] Y.L. Zhou, M. Niinomi, T. Akahori, Effects of Ta content on Young's modulus and tensile properties of binary Ti–Ta alloys for biomedical applications, Mater. Sci. Eng. A 371 (2004) 283–290, https://doi.org/10.1016/j.msea.2003.12.011.
[84] Z.-S. Tao, W.-S. Zhou, H.-G. Xu, M. Yang, Parathyroid hormone (1–34) can reverse the negative effect of valproic acid on the osseointegration of titanium rods in ovariectomized rats, J. Orthop. Transl. 27 (2021) 67–76, https://doi.org/10.1016/j.jot.2020.10.006.
[85] Q. Zhang, Z. Chen, Y. Peng, Z. Jin, L. Qin, The novel magnesium–titanium hybrid cannulated screws for the treatment of vertical femoral neck fractures: biomechanical evaluation, J. Orthop. Transl. 42 (2023) 127–136, https://doi.org/10.1016/j.jot.2023.08.003.
[86] K. Yuan, K. Zhang, Y. Yang, Y. Lin, F. Zhou, J. Mei, H. Li, J. Wei, Z. Yu, J. Zhao, T. Tang, Evaluation of interbody fusion efficacy and biocompatibility of a polyetheretherketone/calcium silicate/porous tantalum cage in a goat model, J. Orthop. Transl. 36 (2022) 109–119, https://doi.org/10.1016/j.jot.2022.06.006.
[87] J.A. Hanzlik, J.S. Day, Bone ingrowth in well-fixed retrieved porous tantalum implants, J. Arthroplast. 28 (2013) 922–927, https://doi.org/10.1016/j.arth.2013.01.035.
[88] L.D. Zardiackas, D.E. Parsell, L.D. Dillon, D.W. Mitchell, L.A. Nunnery, R. Poggie, Structure, metallurgy, and mechanical properties of a porous tantalum foam, J. Biomed. Mater. Res. 58 (2001) 180–187, https://doi.org/10.1002/1097-4636(2001)58:2<180::aid-jbm1005>3.0.co;2-5.
[89] H. Matsuno, A. Yokoyama, F. Watari, M. Uo, T. Kawasaki, Biocompatibility and osteogenesis of refractory metal implants, titanium, hafnium, niobium, tantalum and rhenium, Biomaterials 22 (2001) 1253–1262, https://doi.org/10.1016/s0142-9612(00)00275-1.
[90] A. Jiang, A. Yohannan, N.O. Nnolim, T.A. Tyson, L. Axe, S.L. Lee, P. Cote, Investigation of the structure of β-tantalum, Thin Solid Films 437 (2003) 116–122, https://doi.org/10.1016/S0040-6090(03)00702-8.
[91] D.M. Findlay, K. Welldon, G.J. Atkins, D.W. Howie, A.C.W. Zannettino, D. Bobyn, The proliferation and phenotypic expression of human osteoblasts on tantalum metal, Biomaterials 25 (2004) 2215–2227, https://doi.org/10.1016/j.biomaterials.2003.09.005.
[92] J. Málek, F. Hnilica, J. Veselý, B. Smola, S. Bartáková, J. Vaněk, The influence of chemical composition and thermo-mechanical treatment on Ti–Nb–Ta–Zr alloys, Mater. Des. 35 (2012) 731–740, https://doi.org/10.1016/j.matdes.2011.10.030.
[93] Y. Bai, Y.L. Hao, S.J. Li, Y.Q. Hao, R. Yang, F. Prima, Corrosion behavior of biomedical Ti–24Nb–4Zr–8Sn alloy in different simulated body solutions, Mater. Sci. Eng. C 33 (2013) 2159–2167, https://doi.org/10.1016/j.msec.2013.01.036.
[94] M. Rahman, N.K. Dutta, N. Roy Choudhury, Magnesium alloys with tunable interfaces as bone implant materials, Front. Bioeng. Biotechnol. 8 (2020), https://doi.org/10.3389/fbioe.2020.00564.
[95] W. Zhu, J. Guo, W. Yang, Z. Tao, X. Lan, L. Wang, J. Xu, L. Qin, Y. Su, Biodegradable magnesium implant enhances angiogenesis and alleviates medication-related osteonecrosis of the jaw in rats, J. Orthop. Transl. 33 (2022) 153–161, https://doi.org/10.1016/j.jot.2022.03.004.
[96] Z. Shan, X. Xie, X. Wu, S. Zhuang, C. Zhang, Development of degradable magnesium-based metal implants and their function in promoting bone metabolism (A review), J. Orthop. Transl. 36 (2022) 184–193, https://doi.org/10.1016/j.jot.2022.09.013.
[97] M.P. Staiger, A.M. Pietak, J. Huadmai, G. Dias, Magnesium and its alloys as orthopedic biomaterials: a review, Biomaterials 27 (2006) 1728–1734, https://doi.org/10.1016/j.biomaterials.2005.10.003.
[98] Y. Chen, Z. Xu, C. Smith, J. Sankar, Recent advances on the development of magnesium alloys for biodegradable implants, Acta Biomater. 10 (2014) 4561–4573, https://doi.org/10.1016/j.actbio.2014.07.005.
[99] M. Niinomi, Recent research and development in titanium alloys for biomedical applications and healthcare goods, Sci. Technol. Adv. Mater. 4 (2003) 445–454, https://doi.org/10.1016/j.stam.2003.09.002.
[100] H.S. Brar, M.O. Platt, M. Sarntinoranont, P.I. Martin, M.V. Manuel, Magnesium as a biodegradable and bioabsorbable material for medical implants, JOM 61 (2009) 31–34, https://doi.org/10.1007/s11837-009-0129-0.
[101] N.T. Kirkland, N. Birbilis, M.P. Staiger, Assessing the corrosion of biodegradable magnesium implants: a critical review of current methodologies and their limitations, Acta Biomater. 8 (2012) 925–936, https://doi.org/10.1016/j.actbio.2011.11.014.
[102] A. Atrens, M. Liu, N.I. Zainal Abidin, Corrosion mechanism applicable to biodegradable magnesium implants, Mater. Sci. Eng. B 176 (2011) 1609–1636, https://doi.org/10.1016/j.mseb.2010.12.017.
[103] J. Vaithilingam, S. Kilsby, R.D. Goodridge, S.D.R. Christie, S. Edmondson, R.J.M. Hague, Functionalisation of Ti6Al4V components fabricated using selective laser melting with a bioactive compound, Mater. Sci. Eng. C 46 (2015) 52–61, https://doi.org/10.1016/j.msec.2014.10.015.
[104] X.-N. Gu, Y.-F. Zheng, A review on magnesium alloys as biodegradable materials, Front. Mater. Sci. China 4 (2010) 111–115, https://doi.org/10.1007/s11706-010-0024-1.
[105] H. Waizy, J.-M. Seitz, J. Reifenrath, A. Weizbauer, F.-W. Bach, A. Meyer-Lindenberg, B. Denkena, H. Windhagen, Biodegradable magnesium implants for orthopedic applications, J. Mater. Sci. 48 (2013) 39–50, https://doi.org/10.1007/s10853-012-6572-2.
[106] H. Matusiewicz, Potential release of in vivo trace metals from metallic medical implants in the human body: from ions to nanoparticles–a systematic analytical review, Acta Biomater. 10 (2014) 2379–2403, https://doi.org/10.1016/j.actbio.2014.02.027.
[107] M.P. Staiger, A.M. Pietak, J. Huadmai, G. Dias, Magnesium and its alloys as orthopedic biomaterials: a review, Biomaterials 27 (2006) 1728–1734, https://doi.org/10.1016/j.biomaterials.2005.10.003.
[108] J. Ren, N. Andrikopoulos, K. Velonia, H. Tang, R. Cai, F. Ding, P.C. Ke, C. Chen, Chemical and biophysical signatures of the protein corona in nanomedicine, J. Am. Chem. Soc. 144 (2022) 9184–9205, https://doi.org/10.1021/jacs.2c02277.
[109] X. Cheng, X. Tian, A. Wu, J. Li, J. Tian, Y. Chong, Z. Chai, Y. Zhao, C. Chen, C. Ge, Protein corona influences cellular uptake of gold nanoparticles by phagocytic and nonphagocytic cells in a size-dependent manner, ACS Appl. Mater. Interfaces 7 (2015) 20568–20575, https://doi.org/10.1021/acsami.5b04290.
[110] R. Cai, J. Ren, M. Guo, T. Wei, Y. Liu, C. Xie, P. Zhang, Z. Guo, A.J. Chetwynd, P. C. Ke, I. Lynch, C. Chen, Dynamic intracellular exchange of nanomaterials' protein corona perturbs proteostasis and remodels cell metabolism, Proc. Natl. Acad. Sci. 119 (2022) e2200363119, https://doi.org/10.1073/pnas.2200363119.
[111] Y. Wang, A. Tay, Advances in enantiomer-dependent nanotherapeutics, ACS Nano 17 (2023) 9850–9869, https://doi.org/10.1021/acsnano.3c02798.
[112] Y. Wang, X. Zhang, D. Xie, C. Chen, Z. Huang, Z.A. Li, Chiral engineered biomaterials: new frontiers in cellular fate regulation for regenerative medicine, Adv. Funct. Mater. n/a (2024) 2419610, https://doi.org/10.1002/adfm.202419610.
[113] G.A. Rodan, T.J. Martin, Therapeutic approaches to bone diseases, Science 289 (2000) 1508–1514, https://doi.org/10.1126/science.289.5484.1508.
[114] W. Gu, C. Wu, J. Chen, Y. Xiao, Nanotechnology in the targeted drug delivery for bone diseases and bone regeneration, Int. J. Nanomedicine 8 (2013) 2305–2317, https://doi.org/10.2147/IJN.S44393.
[115] E. Feurer, R. Chapurlat, Emerging drugs for osteoporosis, Expert Opin. Emerg. Drugs 19 (2014) 385–395, https://doi.org/10.1517/14728214.2014.936377.
[116] E.J. Carbone, K. Rajpura, B.N. Allen, E. Cheng, B.D. Ulery, K.W.-H. Lo, Osteotropic nanoscale drug delivery systems based on small molecule bone-targeting moieties, Nanomedicine Nanotechnol. Biol. Med. 13 (2017) 37–47, https://doi.org/10.1016/j.nano.2016.08.015.
[117] G. Marcucci, G. Della Pepa, M.L. Brandi, Drug safety evaluation of parathyroid hormone for hypocalcemia in patients with hypoparathyroidism, Expert Opin. Drug Saf. 16 (2017) 617–625, https://doi.org/10.1080/14740338.2017.1311322.
[118] J.B. Nase, J.B. Suzuki, Osteonecrosis of the jaw and oral bisphosphonate treatment, J. Am. Dent. Assoc. 137 (2006) 1115–1119, https://doi.org/10.14219/jada.archive.2006.0350.
[119] A. Luetke, P.A. Meyers, I. Lewis, H. Juergens, Osteosarcoma treatment - where do we stand? A state of the art review, Cancer Treat, Rev. 40 (2014) 523–532, https://doi.org/10.1016/j.ctrv.2013.11.006.
[120] X. Zhao, L. Li, M. Chen, Y. Xu, S. Zhang, W. Chen, W. Liang, Nanotechnology assisted targeted drug delivery for bone disorders: potentials and clinical perspectives, Curr. Top. Med. Chem. 20 (2020) 2801–2819, https://doi.org/10.2174/1568026620666201019110459.
[121] G. Basha, M. Ordobadi, W.R. Scott, A. Cottle, Y. Liu, H. Wang, P.R. Cullis, Lipid nanoparticle delivery of siRNA to osteocytes leads to effective silencing of SOST and inhibition of sclerostin in vivo, Mol. Ther. Nucleic Acids 5 (2016) e363, https://doi.org/10.1038/mtna.2016.68.

[122] P. Lavrador, V.M. Gaspar, J.F. Mano, Stimuli-responsive nanocarriers for delivery of bone therapeutics - barriers and progresses, J. Control. Release Off. J. Control. Release Soc. 273 (2018) 51–67, https://doi.org/10.1016/j.jconrel.2018.01.021.
[123] S. Mura, J. Nicolas, P. Couvreur, Stimuli-responsive nanocarriers for drug delivery, Nat. Mater. 12 (2013) 991–1003, https://doi.org/10.1038/nmat3776.
[124] S. Liu, J. Xu, Y. Xing, T. Yan, S. Yu, H. Sun, J. Liu, Nanozymes as efficient tools for catalytic therapeutics, VIEW 3 (2022) 20200147, https://doi.org/10.1002/VIW.20200147.
[125] M. Zandieh, J. Liu, Nanozymes: definition, activity, and mechanisms, Adv. Mater. 36 (2024) 2211041, https://doi.org/10.1002/adma.202211041.
[126] Y. Huang, J. Ren, X. Qu, Nanozymes: classification, catalytic mechanisms, activity regulation, and applications, Chem. Rev. 119 (2019) 4357–4412, https://doi.org/10.1021/acs.chemrev.8b00672.
[127] Q. Sun, Y. Zhou, A. Zhang, J. Wu, L. Tan, S. Guo, The immunomodulatory effects and mechanisms of magnesium-containing implants in bone regeneration: a review, J. Magnesium Alloys 12 (2024) 2695–2710, https://doi.org/10.1016/j.jma.2024.05.011.
[128] L. Gao, J. Zhuang, L. Nie, J. Zhang, Y. Zhang, N. Gu, T. Wang, J. Feng, D. Yang, S. Perrett, X. Yan, Intrinsic peroxidase-like activity of ferromagnetic nanoparticles, Nat. Nanotechnol. 2 (2007) 577–583, https://doi.org/10.1038/nnano.2007.260.
[129] X. Sun, X. Xu, X. Yue, T. Wang, Z. Wang, C. Zhang, J. Wang, Nanozymes with osteochondral regenerative effects: an overview of mechanisms and recent applications, Adv. Healthc. Mater. 13 (2024) e2301924, https://doi.org/10.1002/adhm.202301924.
[130] Z. Jiang, H. Wang, Z. Zhang, J. Pan, H. Yuan, Cartilage targeting therapy with reactive oxygen species-responsive nanocarrier for osteoarthritis, J. Nanobiotechnology 20 (2022) 419, https://doi.org/10.1186/s12951-022-01629-w.
[131] F. Wauquier, L. Leotoing, V. Coxam, J. Guicheux, Y. Wittrant, Oxidative stress in bone remodelling and disease, Trends Mol. Med. 15 (2009) 468–477, https://doi.org/10.1016/j.molmed.2009.08.004.
[132] J. Huang, R. Li, J. Yang, M. Cai, Y. Lee, A. Wang, B. Cheng, Y. Wang, Bioadaptation of implants to in vitro and in vivo oxidative stress pathological conditions via nanotopography-induced FoxO1 signaling pathways to enhance Osteoimmunal regeneration, Bioact. Mater. 6 (2021) 3164–3176, https://doi.org/10.1016/j.bioactmat.2021.02.023.
[133] S. Kumar, I.M. Adjei, S.B. Brown, O. Liseth, B. Sharma, Manganese dioxide nanoparticles protect cartilage from inflammation-induced oxidative stress, Biomaterials 224 (2019) 119467, https://doi.org/10.1016/j.biomaterials.2019.119467.
[134] W. Hou, C. Ye, M. Chen, W. Gao, X. Xie, J. Wu, K. Zhang, W. Zhang, Y. Zheng, X. Cai, Excavating bioactivities of nanozyme to remodel microenvironment for protecting chondrocytes and delaying osteoarthritis, Bioact. Mater. 6 (2021) 2439–2451, https://doi.org/10.1016/j.bioactmat.2021.01.016.
[135] H. Wei, H. Huang, H. He, Y. Xiao, L. Chun, Z. Jin, H. Li, L. Zheng, J. Zhao, Z. Qin, Pt–Se hybrid nanozymes with potent catalytic activities to scavenge ROS/RONS and regulate macrophage polarization for osteoarthritis therapy, Research 7 (2024) 310, https://doi.org/10.34133/research.0310.
[136] Y. Sun, X. Sun, X. Li, W. Li, C. Li, Y. Zhou, L. Wang, B. Dong, A versatile nanocomposite based on nanoceria for antibacterial enhancement and protection from aPDT-aggravated inflammation via modulation of macrophage polarization, Biomaterials 268 (2021) 120614, https://doi.org/10.1016/j.biomaterials.2020.120614.
[137] I. Kalashnikova, S.-J. Chung, M. Nafiujjaman, M.L. Hill, M.E. Siziba, C.H. Contag, T. Kim, Ceria-based nanotheranostic agent for rheumatoid arthritis, Theranostics 10 (2020) 11863–11880, https://doi.org/10.7150/thno.49069.
[138] J.-Y. Park, S. Kwon, S.-H. Kim, Y.J. Kang, D. Khang, Triamcinolone–gold nanoparticles repolarize synoviocytes and macrophages in an inflamed synovium, ACS Appl. Mater. Interfaces 12 (2020) 38936–38949, https://doi.org/10.1021/acsami.0c09842.
[139] F. Zhou, M. Li, M. Chen, M. Chen, X. Chen, Z. Luo, K. Cai, Y. Hu, Redox homeostasis strategy for inflammatory macrophage reprogramming in rheumatoid arthritis based on ceria oxide nanozyme-complexed biopolymeric micelles, ACS Nano 17 (2023) 4358–4372, https://doi.org/10.1021/acsnano.2c09127.
[140] M. Zhang, X. Zhai, T. Ma, Y. Huang, M. Jin, H. Yang, H. Fu, S. Zhang, T. Sun, X. Jin, Y. Du, C.-H. Yan, Sequential therapy for bone regeneration by cerium oxide-reinforced 3D-printed bioactive glass scaffolds, ACS Nano 17 (2023) 4433–4444, https://doi.org/10.1021/acsnano.2c09855.
[141] A. Pandey, S. Midha, R.K. Sharma, R. Maurya, V.K. Nigam, S. Ghosh, K. Balani, Antioxidant and antibacterial hydroxyapatite-based biocomposite for orthopedic applications, Mater. Sci. Eng., C 88 (2018) 13–24, https://doi.org/10.1016/j.msec.2018.02.014.
[142] D. Shao, K. Li, T. Hu, S. Wang, H. Xu, S. Zhang, S. Liu, Y. Xie, X. Zheng, Titania nanotube array supported nanoceria with redox cycling stability ameliorates oxidative stress-inhibited osteogenesis, Chem. Eng. J. 415 (2021) 128913, https://doi.org/10.1016/j.cej.2021.128913.
[143] F. Wei, C.J. Neal, T.S. Sakthivel, S. Seal, T. Kean, M. Razavi, M. Coathup, Cerium oxide nanoparticles protect against irradiation-induced cellular damage while augmenting osteogenesis, Mater. Sci. Eng., C 126 (2021) 112145, https://doi.org/10.1016/j.msec.2021.112145.
[144] Y. Ai, Z.-N. Hu, X. Liang, H. Sun, H. Xin, Q. Liang, Recent advances in nanozymes: from matters to bioapplications, Adv. Funct. Mater. 32 (2022) 2110432, https://doi.org/10.1002/adfm.202110432.
[145] C. Li, W. Zhang, Y. Nie, X. Du, C. Huang, L. Li, J. Long, X. Wang, W. Tong, L. Qin, Y. Lai, Time-Sequential and multi-functional 3D printed MgO2/PLGA scaffold developed as a novel biodegradable and bioactive bone substitute for challenging postsurgical osteosarcoma treatment, Adv. Mater. 36 (2024) 2308875, https://doi.org/10.1002/adma.202308875.
[146] H.P. Lee, A.K. Gaharwar, Light-responsive inorganic biomaterials for biomedical applications, Adv. Sci. 7 (2020) 2000863, https://doi.org/10.1002/advs.202000863.
[147] W. Zhao, Y. Zhao, Q. Wang, T. Liu, J. Sun, R. Zhang, Remote light-responsive nanocarriers for controlled drug delivery: advances and perspectives, Small 15 (2019) 1903060, https://doi.org/10.1002/smll.201903060.
[148] G. Yang, J. Liu, Y. Wu, L. Feng, Z. Liu, Near-infrared-light responsive nanoscale drug delivery systems for cancer treatment, Coord. Chem. Rev. 320–321 (2016) 100–117, https://doi.org/10.1016/j.ccr.2016.04.004.
[149] Y. Lu, L. Li, Z. Lin, L. Wang, L. Lin, M. Li, Y. Zhang, Q. Yin, Q. Li, H. Xia, A new treatment modality for rheumatoid arthritis: combined photothermal and photodynamic therapy using Cu7.2 S4 nanoparticles, Adv. Healthc. Mater. 7 (2018) e1800013, https://doi.org/10.1002/adhm.201800013.
[150] W. Pan, C. Dai, Y. Li, Y. Yin, L. Gong, J.O. Machuki, Y. Yang, S. Qiu, K. Guo, F. Gao, PRP-chitosan thermoresponsive hydrogel combined with black phosphorus nanosheets as injectable biomaterial for biotherapy and phototherapy treatment of rheumatoid arthritis, Biomaterials 239 (2020) 119851, https://doi.org/10.1016/j.biomaterials.2020.119851.
[151] S. Xu, Y. Lin, X. Zhao, Z. Liang, Y. Hu, Z. Chen, X. Ren, X. Mei, NIR triggered photocatalytic and photothermal bifunctional MOF nanozyme using for improving osteoarthritis microenvironment by repairing injured chondrocytes of mitochondria, Chem. Eng. J. 468 (2023) 143826, https://doi.org/10.1016/j.cej.2023.143826.
[152] Y. Zhao, C. Wei, X. Chen, J. Liu, Q. Yu, Y. Liu, J. Liu, Drug delivery system based on near-infrared light-responsive molybdenum disulfide nanosheets controls the high-efficiency release of dexamethasone to inhibit inflammation and treat osteoarthritis, ACS Appl. Mater. Interfaces 11 (2019) 11587–11601, https://doi.org/10.1021/acsami.8b20372.
[153] P.K. Pandey, R. Maheshwari, N. Raval, P. Gondaliya, K. Kalia, R.K. Tekade, Nanogold-core multifunctional dendrimer for pulsatile chemo-, photothermal- and photodynamic- therapy of rheumatoid arthritis, J. Colloid Interface Sci. 544 (2019) 61–77, https://doi.org/10.1016/j.jcis.2019.02.073.
[154] X. Xue, H. Liu, S. Wang, Y. Hu, B. Huang, M. Li, J. Gao, X. Wang, J. Su, Neutrophil-erythrocyte hybrid membrane-coated hollow copper sulfide nanoparticles for targeted and photothermal/anti-inflammatory therapy of osteoarthritis, Compos. Part B Eng. 237 (2022) 109855, https://doi.org/10.1016/j.compositesb.2022.109855.
[155] J. Fu, X. Liu, L. Tan, Z. Cui, Y. Zheng, Y. Liang, Z. Li, S. Zhu, K.W.K. Yeung, X. Feng, X. Wang, S. Wu, Photoelectric-responsive extracellular matrix for bone engineering, ACS Nano 13 (2019) 13581–13594, https://doi.org/10.1021/acsnano.9b08115.
[156] X. Zhang, G. Cheng, X. Xing, J. Liu, Y. Cheng, T. Ye, Q. Wang, X. Xiao, Z. Li, H. Deng, Near-infrared light-triggered porous AuPd alloy nanoparticles to produce mild localized heat to accelerate bone regeneration, J. Phys. Chem. Lett. 10 (2019) 4185–4191, https://doi.org/10.1021/acs.jpclett.9b01735.
[157] C. Yin, Q. Zhao, W. Li, Z. Zhao, J. Wang, T. Deng, P. Zhang, K. Shen, Z. Li, Y. Zhang, Biomimetic anti-inflammatory nano-capsule serves as a cytokine blocker and M2 polarization inducer for bone tissue repair, Acta Biomater. 102 (2020) 416–426, https://doi.org/10.1016/j.actbio.2019.11.025.
[158] Z. Zhou, T. Fan, Y. Yan, S. Zhang, Y. Zhou, H. Deng, X. Cai, J. Xiao, D. Song, Q. Zhang, Y. Cheng, One stone with two birds: phytic acid-capped platinum nanoparticles for targeted combination therapy of bone tumors, Biomaterials 194 (2019) 130–138, https://doi.org/10.1016/j.biomaterials.2018.12.024.
[159] C. Wang, X. Cai, J. Zhang, X. Wang, Y. Wang, H. Ge, W. Yan, Q. Huang, J. Xiao, Q. Zhang, Y. Cheng, Trifolium-like platinum nanoparticle-mediated photothermal therapy inhibits tumor growth and osteolysis in a bone metastasis model, Small Weinh. Bergstr. Ger. 11 (2015) 2080–2086, https://doi.org/10.1002/smll.201403315.
[160] G. Zhang, X. Zhang, Y. Yang, R. Chi, J. Shi, R. Hang, X. Huang, X. Yao, P.K. Chu, X. Zhang, Dual light-induced in situ antibacterial activities of biocompatibleTiO2/MoS2/PDA/RGD nanorod arrays on titanium, Biomater. Sci. 8 (2019) 391–404, https://doi.org/10.1039/C9BM01507H.
[161] L. Hong, X. Liu, L. Tan, Z. Cui, X. Yang, Y. Liang, Z. Li, S. Zhu, Y. Zheng, K.W. K. Yeung, D. Jing, D. Zheng, X. Wang, S. Wu, Rapid biofilm elimination on bone implants using near-infrared-activated inorganic semiconductor heterostructures, Adv. Healthc. Mater. 8 (2019) 1900835, https://doi.org/10.1002/adhm.201900835.
[162] M. Yao, X. Hao, H. Shao, D. Wang, B. Li, S. Xing, X. Zhao, C. Zhang, X. Liu, Y. Zhang, F. Peng, Metallic nanoparticle-doped oxide semiconductor film for bone tumor suppression and bone regeneration, ACS Appl. Mater. Interfaces 14 (2022) 47369–47384, https://doi.org/10.1021/acsami.2c10672.
[163] Z. Lv, S. He, Y. Wang, X. Zhu, Noble metal nanomaterials for NIR-triggered photothermal therapy in cancer, Adv. Healthc. Mater. 10 (2021) e2001806, https://doi.org/10.1002/adhm.202001806.
[164] E.D. Onal, K. Guven, Plasmonic photothermal therapy in third and fourth biological windows. https://doi.org/10.48550/arXiv.1609.08871, 2016.
[165] J. Kudr, Y. Haddad, L. Richtera, Z. Heger, M. Cernak, V. Adam, O. Zitka, Magnetic nanoparticles: from design and synthesis to real world applications, Nanomater. Basel Switz 7 (2017) 243, https://doi.org/10.3390/nano7090243.
[166] M. Hao, W. Wang, A. Kumar, W.H.A. Kamaruddin, S. Saidin, N.A.N.N. Malek, J. Claverie, H. Liu, Magnetic hydroxyapatite nanobelt-stem cell hybrid spheroids

for remotely patterning bone tissues, BMEMat 2 (2024) e12059, https://doi.org/10.1002/bmm2.12059.
[167] Y. Xiao, J. Du, Superparamagnetic nanoparticles for biomedical applications, J. Mater. Chem. B 8 (2020) 354–367, https://doi.org/10.1039/c9tb01955c.
[168] M.-S. Lee, C.-M. Su, J.-C. Yeh, P.-R. Wu, T.-Y. Tsai, S.-L. Lou, Synthesis of composite magnetic nanoparticles Fe3O4 with alendronate for osteoporosis treatment, Int. J. Nanomedicine 11 (2016) 4583–4594, https://doi.org/10.2147/IJN.S112415.
[169] N. Amiryaghoubi, E.D. Abdolahinia, A. Nakhlband, S. Aslzad, M. Fathi, J. Barar, Y. Omidi, Smart chitosan–folate hybrid magnetic nanoparticles for targeted delivery of doxorubicin to osteosarcoma cells, Colloids Surf. B Biointerfaces 220 (2022) 112911, https://doi.org/10.1016/j.colsurfb.2022.112911.
[170] A. Dasari, J. Xue, S. Deb, Magnetic nanoparticles in bone tissue engineering, Nanomaterials 12 (2022) 757, https://doi.org/10.3390/nano12050757.
[171] B.D. Partain, M. Unni, C. Rinaldi, K.D. Allen, The clearance and biodistribution of magnetic composite nanoparticles in healthy and osteoarthritic rat knees, J. Controlled Release 321 (2020) 259–271, https://doi.org/10.1016/j.jconrel.2020.01.052.
[172] S. Jafari, L.O. Mair, S. Chowdhury, A. Nacev, R. Hilaman, P. Stepanov, J. Baker-McKee, S. Ijanaten, C. Koudelka, B. English, P. Malik, I.N. Weinberg, Magnetically targeted delivery through cartilage, AIP Adv. 8 (2017) 056717, https://doi.org/10.1063/1.5006156.
[173] N. Zhang, J. Lock, A. Sallee, H. Liu, Magnetic nanocomposite hydrogel for potential cartilage tissue engineering: synthesis, characterization, and cytocompatibility with bone marrow derived mesenchymal stem cells, ACS Appl. Mater. Interfaces 7 (2015) 20987–20998, https://doi.org/10.1021/acsami.5b06939.
[174] A.R.K. Sasikala, V.K. Kaliannagounder, N.R. Alluri, B.K. Shrestha, S.-J. Kim, H. Ali-Boucetta, C.H. Park, A.R. Unnithan, Development of self-powered multifunctional piezomagnetic nanoparticles for non-invasive post-surgical osteosarcoma theranogeneration, Nano Energy 96 (2022) 107134, https://doi.org/10.1016/j.nanoen.2022.107134.
[175] Y. Liu, F. Yang, C. Yuan, M. Li, T. Wang, B. Chen, J. Jin, P. Zhao, J. Tong, S. Luo, N. Gu, Magnetic nanoliposomes as in situ microbubble bombers for multimodality image-guided cancer theranostics, ACS Nano 11 (2017) 1509–1519, https://doi.org/10.1021/acsnano.6b06815.
[176] S. Nelogi, A.K. Patil, R. Chowdhary, The effect of external magnetic field on osteogenic and antimicrobial behaviour of surface-functionalized custom titanium chamber with iron nanoparticles. A preliminary research, Odontology 111 (2023) 600–607, https://doi.org/10.1007/s10266-022-00769-7.
[177] S. Hu, Y. Zhou, Y. Zhao, Y. Xu, F. Zhang, N. Gu, J. Ma, M.A. Reynolds, Y. Xia, H.H. K. Xu, Enhanced bone regeneration and visual monitoring via superparamagnetic iron oxide nanoparticle scaffold in rats, J. Tissue Eng. Regen. Med. 12 (2018) e2085–e2098, https://doi.org/10.1002/term.2641.
[178] Y. Xia, J. Sun, L. Zhao, F. Zhang, X.-J. Liang, Y. Guo, M.D. Weir, M.A. Reynolds, N. Gu, H.H.K. Xu, Magnetic field and nano-scaffolds with stem cells to enhance bone regeneration, Biomaterials 183 (2018) 151–170, https://doi.org/10.1016/j.biomaterials.2018.08.040.
[179] H. Wei, J. Cui, K. Lin, J. Xie, X. Wang, Recent advances in smart stimuli-responsive biomaterials for bone therapeutics and regeneration, Bone Res 10 (2022) 17, https://doi.org/10.1038/s41413-021-00180-y.
[180] T.S.S. Carvalho, P.M.C. Torres, J.H. Belo, J. Mano, S.M. Olhero, Bioactive magnetic materials in bone tissue engineering: a review of recent findings in CaP-based particles and 3D-printed scaffolds, Adv. NanoBiomed Res. 3 (2023) 2300035, https://doi.org/10.1002/anbr.202300035.
[181] X. Li, J. Wei, K.E. Aifantis, Y. Fan, Q. Feng, F.-Z. Cui, F. Watari, Current investigations into magnetic nanoparticles for biomedical applications, J. Biomed. Mater. Res. 104 (2016) 1285–1296, https://doi.org/10.1002/jbm.a.35654.
[182] W. Wu, C.Z. Jiang, V.A.L. Roy, Designed synthesis and surface engineering strategies of magnetic iron oxide nanoparticles for biomedical applications, Nanoscale 8 (2016) 19421–19474, https://doi.org/10.1039/C6NR07542H.
[183] M. Li, B. Yu, S. Wang, F. Zhou, J. Cui, J. Su, Microenvironment-responsive nanocarriers for targeted bone disease therapy, Nano Today 50 (2023) 101838, https://doi.org/10.1016/j.nantod.2023.101838.
[184] N. Deirram, C. Zhang, S.S. Kermaniyan, A.P.R. Johnston, G.K. Such, pH-responsive polymer nanoparticles for drug delivery, Macromol. Rapid Commun. 40 (2019) 1800917, https://doi.org/10.1002/marc.201800917.
[185] H. Ding, P. Tan, S. Fu, X. Tian, H. Zhang, X. Ma, Z. Gu, K. Luo, Preparation and application of pH-responsive drug delivery systems, J. Controlled Release 348 (2022) 206–238, https://doi.org/10.1016/j.jconrel.2022.05.056.
[186] M. Zhang, X. Chen, C. Li, X. Shen, Charge-reversal nanocarriers: an emerging paradigm for smart cancer nanomedicine, J. Control. Release Off. J. Control. Release Soc. 319 (2020) 46–62, https://doi.org/10.1016/j.jconrel.2019.12.024.
[187] J. Zhao, V.E. Lee, R. Liu, R.D. Priestley, Responsive polymers as smart nanomaterials enable diverse applications, Annu. Rev. Chem. Biomol. Eng. 10 (2019) 361–382, https://doi.org/10.1146/annurev-chembioeng-060718-030155.
[188] M. Karimi, A. Ghasemi, P. Sahandi Zangabad, R. Rahighi, S.M. Moosavi Basri, H. Mirshekari, M. Amiri, Z. Shafaei Pishabad, A. Aslani, M. Bozorgomid, D. Ghosh, A. Beyzavi, A. Vaseghi, A.R. Aref, L. Haghani, S. Bahrami, M. R. Hamblin, Smart micro/nanoparticles in stimulus-responsive drug/gene delivery systems, Chem. Soc. Rev. 45 (2016) 1457–1501, https://doi.org/10.1039/c5cs00798d.
[189] Y. Kong, F. Liu, B. Ma, W. Wang, L. Li, X. Xu, Z. Sun, H. Yang, Y. Sang, D. Li, G. Li, C. Liu, S. Wang, H. Liu, Intracellular pH-responsive iron-catechin nanoparticles with osteogenic/anti-adipogenic and immunomodulatory effects for efficient bone repair, Nano Res. 15 (2022) 1153–1161, https://doi.org/10.1007/s12274-021-3618-2.
[190] Y. Liu, C. Xie, F. Zhang, X. Xiao, pH-responsive TiO2 nanotube drug delivery system based on iron coordination, J. Nanomater. 2019 (2019) 6395760, https://doi.org/10.1155/2019/6395760.
[191] D. Ahmadi, M. Zarei, M. Rahimi, M. Khazaie, Z. Asemi, S.M. Mir, A. Sadeghpour, A. Karimian, F. Alemi, M. Rahmati-Yamchi, R. Salehi, F. Jadidi-Niaragh, M. Yousefi, N. Khelgati, M. Majidinia, A. Safa, B. Yousefi, Preparation and *in-vitro* evaluation of pH-responsive cationic cyclodextrin coated magnetic nanoparticles for delivery of methotrexate to the Saos-2 bone cancer cells, J. Drug Deliv. Sci. Technol. 57 (2020) 101584, https://doi.org/10.1016/j.jddst.2020.101584.
[192] Y. Dong, H. Ye, Y. Liu, L. Xu, Z. Wu, X. Hu, J. Ma, J.L. Pathak, J. Liu, G. Wu, pH dependent silver nanoparticles releasing titanium implant: a novel therapeutic approach to control peri-implant infection, Colloids Surf. B Biointerfaces 158 (2017) 127–136, https://doi.org/10.1016/j.colsurfb.2017.06.034.
[193] Y. Deng, X. Shi, Y. Chen, W. Yang, Y. Ma, X.-L. Shi, P. Song, M.S. Dargusch, Z.-G. Chen, Bacteria-triggered pH-responsive osteopotentiating coating on 3D-printed polyetheretherketone scaffolds for infective bone defect repair, Ind. Eng. Chem. Res. 59 (2020) 12123–12135, https://doi.org/10.1021/acs.iecr.0c02107.
[194] C. Tapeinos, M. Battaglini, M. Prato, G. La Rosa, A. Scarpellini, G. Ciofani, CeO2 nanoparticles-loaded pH-responsive microparticles with antitumoral properties as therapeutic modulators for osteosarcoma, ACS Omega 3 (2018) 8952–8962, https://doi.org/10.1021/acsomega.8b01060.
[195] J. Guo, C. Li, J. Lin, J. Fang, Y. Sun, P. Zhang, S. Li, W. Li, X. Zhang, Chemically programmed nanozyme with microenvironment remodeling for combinatorial treatment of osteoarthritis, Chem. Eng. J. 485 (2024) 149897, https://doi.org/10.1016/j.cej.2024.149897.
[196] Y. Yang, B. Tao, Y. Gong, R. Chen, W. Yang, C. Lin, M. Chen, L. Qin, Y. Jia, K. Cai, Functionalization of Ti substrate with pH-responsive naringin-ZnO nanoparticles for the reconstruction of large bony after osteosarcoma resection, J. Biomed. Mater. Res. 108 (2020) 2190–2205, https://doi.org/10.1002/jbm.a.36977.
[197] J. Yan, D. Xia, W. Zhou, Y. Li, P. Xiong, Q. Li, P. Wang, M. Li, Y. Zheng, Y. Cheng, pH-responsive silk fibroin-based CuO/Ag micro/nano coating endows polyetheretherketone with synergistic antibacterial ability, osteogenesis, and angiogenesis, Acta Biomater. 115 (2020) 220–234, https://doi.org/10.1016/j.actbio.2020.07.062.
[198] G. Guo, H. Zhang, H. Shen, C. Zhu, R. He, J. Tang, Y. Wang, X. Jiang, J. Wang, W. Bu, X. Zhang, Space-selective chemodynamic therapy of CuFe5O8 nanocubes for implant-related infections, ACS Nano 14 (2020) 13391–13405, https://doi.org/10.1021/acsnano.0c05255.
[199] M. Kejdušová, J. Vysloužil, K. Kubová, V. Celer, M. Krásna, A. Pechová, V. Vyskočilová, V. Košťál, Antimicrobial properties of microparticles based on carmellose cross-linked by Cu(2+) ions, BioMed Res. Int. 2015 (2015) 790720, https://doi.org/10.1155/2015/790720.
[200] S. Chatterjee, P. Chi-Leung Hui, Review of stimuli-responsive polymers in drug delivery and textile application, Mol. Basel Switz. 24 (2019) 2547, https://doi.org/10.3390/molecules24142547.
[201] F. Xiong, Z. Qin, H. Chen, Q. Lan, Z. Wang, N. Lan, Y. Yang, L. Zheng, J. Zhao, D. Kai, pH-responsive and hyaluronic acid-functionalized metal-organic frameworks for therapy of osteoarthritis, J. Nanobiotechnology 18 (2020) 139, https://doi.org/10.1186/s12951-020-00694-3.
[202] Z.-J. Zhang, Y.-K. Hou, M.-W. Chen, X.-Z. Yu, S.-Y. Chen, Y.-R. Yue, X.-T. Guo, J.-X. Chen, Q. Zhou, A pH-responsive metal-organic framework for the co-delivery of HIF-2α siRNA and curcumin for enhanced therapy of osteoarthritis, J. Nanobiotechnology 21 (2023) 18, https://doi.org/10.1186/s12951-022-01758-2.
[203] K.M. Au, A. Satterlee, Y. Min, X. Tian, Y.S. Kim, J.M. Caster, L. Zhang, T. Zhang, L. Huang, A.Z. Wang, Folate-targeted pH-responsive calcium zoledronate nanoscale metal-organic frameworks: turning a bone antiresorptive agent into an anticancer therapeutic, Biomaterials 82 (2016) 178–193, https://doi.org/10.1016/j.biomaterials.2015.12.018.
[204] S.J. Sonawane, R.S. Kalhapure, T. Govender, Hydrazone linkages in pH responsive drug delivery systems, Eur. J. Pharm. Sci. Off. J. Eur. Fed. Pharm. Sci. 99 (2017) 45–65, https://doi.org/10.1016/j.ejps.2016.12.011.
[205] H. Xiong, Y. Zhao, Q. Xu, X. Xie, J. Wu, B. Hu, S. Chen, X. Cai, Y. Zheng, C. Fan, Biodegradable hollow-structured nanozymes modulate phenotypic polarization of macrophages and relieve hypoxia for treatment of osteoarthritis, Small Weinh. Bergstr. Ger. 18 (2022) e2203240, https://doi.org/10.1002/smll.202203240.
[206] N. Wang, J.Y.H. Fuh, S.T. Dheen, A. Senthil Kumar, Functions and applications of metallic and metallic oxide nanoparticles in orthopedic implants and scaffolds, J. Biomed. Mater. Res. B Appl. Biomater. 109 (2021) 160–179, https://doi.org/10.1002/jbm.b.34688.
[207] A.-C. Burduşel, O. Gherasim, A.M. Grumezescu, L. Mogoantă, A. Ficai, E. Andronescu, Biomedical applications of silver nanoparticles: an up-to-date overview, Nanomater. Basel Switz. 8 (2018) 681, https://doi.org/10.3390/nano8090681.
[208] M. Vallet-Regí, D. Lozano, B. González, I. Izquierdo-Barba, Biomaterials against bone infection, Adv. Healthc. Mater. 9 (2020) e2000310, https://doi.org/10.1002/adhm.202000310.
[209] R. Khursheed, K. Dua, S. Vishwas, M. Gulati, N.K. Jha, G.M. Aldhafeeri, F. G. Alanazi, B.H. Goh, G. Gupta, K.R. Paudel, P.M. Hansbro, D.K. Chellappan, S. K. Singh, Biomedical applications of metallic nanoparticles in cancer: current status and future perspectives, Biomed. Pharmacother. Biomedecine Pharmacother. 150 (2022) 112951, https://doi.org/10.1016/j.biopha.2022.112951.

[210] S. Ghosh, T.J. Webster, Metallic nanoscaffolds as osteogenic promoters: advances, challenges and scope, Metals 11 (2021) 1356, https://doi.org/10.3390/met11091356.
[211] J. Wen, H. Li, H. Dai, S. Hua, X. Long, H. Li, S. Ivanovski, C. Xu, Intra-articular nanoparticles based therapies for osteoarthritis and rheumatoid arthritis management, Mater. Today Bio 19 (2023) 100597, https://doi.org/10.1016/j.mtbio.2023.100597.
[212] G.R. Beck, S.-W. Ha, C.E. Camalier, M. Yamaguchi, Y. Li, J.-K. Lee, M. N. Weitzmann, Bioactive silica-based nanoparticles stimulate bone-forming osteoblasts, suppress bone-resorbing osteoclasts, and enhance bone mineral density in vivo, Nanomedicine Nanotechnol. Biol. Med. 8 (2012) 793–803, https://doi.org/10.1016/j.nano.2011.11.003.
[213] M.S. LeBoff, S.L. Greenspan, K.L. Insogna, E.M. Lewiecki, K.G. Saag, A.J. Singer, E.S. Siris, The clinician's guide to prevention and treatment of osteoporosis, Osteoporos. Int. J. Establ. Result Coop. Eur. Found. Osteoporos. Natl. Osteoporos. Found. USA 33 (2022) 2049–2102, https://doi.org/10.1007/s00198-021-05900-y.
[214] W.F. Lems, H.G. Raterman, Critical issues and current challenges in osteoporosis and fracture prevention. An overview of unmet needs, Ther. Adv. Musculoskelet. Dis. 9 (2017) 299–316, https://doi.org/10.1177/1759720X17732562.
[215] W. Yuan, Z. Li, X. Xie, Z.-Y. Zhang, L. Bian, Bisphosphonate-based nanocomposite hydrogels for biomedical applications, Bioact. Mater. 5 (2020) 819–831, https://doi.org/10.1016/j.bioactmat.2020.06.002.
[216] N.M. Iñiguez-Ariza, B.L. Clarke, Bone biology, signaling pathways, and therapeutic targets for osteoporosis, Maturitas 82 (2015) 245–255, https://doi.org/10.1016/j.maturitas.2015.07.003.
[217] M.I. Carter, P.S. Hinton, Physical activity and bone health, Mo, Med. 111 (2014) 59–64.
[218] S. Zeghoud, I. Ben Amor, A. Alnazza Alhamad, L. Darwish, H. Hemmami, Osteoporosis therapy using nanoparticles: a review, Ann. Med. Surg. 86 (2012) 284–291, https://doi.org/10.1097/MS9.0000000000001467, 2024.
[219] A.A. Alhamad, S. Zeghoud, I.B. Amor, A. Zaater, A.B. Amor, A. Aouadif, A. Hemmami, E.C. Nleonui, A A short review of Nanomaterials: synthesis methods, properties, and applications: review, Algerian J. Chem. Eng. AJCE 1 (2023) 1–7.
[220] A. Herland, B.M. Maoz, D. Das, M.R. Somayaji, R. Prantil-Baun, R. Novak, M. Cronce, T. Huffstater, S.S.F. Jeanty, M. Ingram, A. Chalkiadaki, D. Benson Chou, S. Marquez, A. Delahanty, S. Jalili-Firoozinezhad, Y. Milton, A. Sontheimer-Phelps, B. Swenor, O. Levy, K.K. Parker, A. Przekwas, D.E. Ingber, Quantitative prediction of human pharmacokinetic responses to drugs via fluidically coupled vascularized organ chips, Nat. Biomed. Eng. 4 (2020) 421–436, https://doi.org/10.1038/s41551-019-0498-9.
[221] Peptide-based hydrogel for enhanced bone repair, Mater. Des. 229 (2023) 111862, https://doi.org/10.1016/j.matdes.2023.111862.
[222] W. Xinluan, L. Yuxiao, N.H. Helena, Y. Zhijun, Q. Ling, Systemic drug delivery systems for bone tissue regeneration- a mini review, Curr. Pharm. Des. 21 (2015) 1575–1583, https://doi.org/10.2174/1381612821666150115152841.
[223] C. Dou, J. Li, J. He, F. Luo, T. Yu, Q. Dai, Y. Chen, J. Xu, X. Yang, S. Dong, Bone-targeted pH-responsive cerium nanoparticles for anabolic therapy in osteoporosis, Bioact. Mater. 6 (2021) 4697–4706, https://doi.org/10.1016/j.bioactmat.2021.04.038.
[224] A. Pinna, M. Torki Baghbaderani, V. Vigil Hernández, P. Naruphontjirakul, S. Li, T. McFarlane, D. Hachim, M.M. Stevens, A.E. Porter, J.R. Jones, Nanoceria provides antioxidant and osteogenic properties to mesoporous silica nanoparticles for osteoporosis treatment, Acta Biomater. 122 (2021) 365–376, https://doi.org/10.1016/j.actbio.2020.12.029.
[225] D. Dutta, R. Mukherjee, S. Ghosh, M. Patra, M. Mukherjee, T. Basu, Cerium oxide nanoparticles as antioxidant or pro-oxidant agents, ACS Appl. Nano Mater. 5 (2022) 1690–1701, https://doi.org/10.1021/acsanm.1c04518.
[226] W. Hu, K.H.R. Yie, C. Liu, J. Zhu, Z. Huang, B. Zhu, D. Zheng, B. Yang, B. Huang, L. Yao, J. Liu, X. Shen, Z. Deng, Improving the valence self-reversible conversion of cerium nanoparticles on titanium implants by lanthanum doping to enhance ROS elimination and osteogenesis, Dent. Mater. Off. Publ. Acad. Dent. Mater. 38 (2022) 1362–1375, https://doi.org/10.1016/j.dental.2022.06.014.
[227] H. Quan, Y. He, J. Sun, W. Yang, W. Luo, C. Dou, F. Kang, C. Zhao, J. He, X. Yang, S. Dong, H. Jiang, Chemical self-assembly of multifunctional hydroxyapatite with a coral-like nanostructure for osteoporotic bone reconstruction, ACS Appl. Mater. Interfaces 10 (2018) 25547–25560, https://doi.org/10.1021/acsami.8b09879.
[228] L. Zheng, Z. Zhuang, Y. Li, T. Shi, K. Fu, W. Yan, L. Zhang, P. Wang, L. Li, Q. Jiang, Bone targeting antioxidative nano-iron oxide for treating postmenopausal osteoporosis, Bioact. Mater. 14 (2022) 250–261, https://doi.org/10.1016/j.bioactmat.2021.11.012.
[229] J. Li, J.J. Li, J. Zhang, X. Wang, N. Kawazoe, G. Chen, Gold nanoparticle size and shape influence on osteogenesis of mesenchymal stem cells, Nanoscale 8 (2016) 7992–8007, https://doi.org/10.1039/c5nr08808a.
[230] C. Yi, D. Liu, C.-C. Fong, J. Zhang, M. Yang, Gold nanoparticles promote osteogenic differentiation of mesenchymal stem cells through p38 MAPK pathway, ACS Nano 4 (2010) 6439–6448, https://doi.org/10.1021/nn101373r.
[231] H. Nah, D. Lee, J.S. Lee, S.J. Lee, D.N. Heo, Y.-H. Lee, J.B. Bang, Y.-S. Hwang, H.-J. Moon, I.K. Kwon, Strategy to inhibit effective differentiation of RANKL-induced osteoclasts using vitamin D-conjugated gold nanoparticles, Appl. Surf. Sci. 527 (2020) 146765, https://doi.org/10.1016/j.apsusc.2020.146765.
[232] D. Lee, D.N. Heo, H.-J. Kim, W.-K. Ko, S.J. Lee, M. Heo, J.B. Bang, J.B. Lee, D.-S. Hwang, S.H. Do, I.K. Kwon, Inhibition of osteoclast differentiation and bone resorption by bisphosphonate-conjugated gold nanoparticles, Sci. Rep. 6 (2016) 27336, https://doi.org/10.1038/srep27336.
[233] D.N. Heo, W.-K. Ko, H.-J. Moon, H.-J. Kim, S.J. Lee, J.B. Lee, M.S. Bae, J.-K. Yi, Y.-S. Hwang, J.B. Bang, E.-C. Kim, S.H. Do, I.K. Kwon, Inhibition of osteoclast differentiation by gold nanoparticles functionalized with cyclodextrin curcumin complexes, ACS Nano 8 (2014) 12049–12062, https://doi.org/10.1021/nn504329u.
[234] M. Molenda, J. Kolmas, The role of zinc in bone tissue health and regeneration-a review, Biol. Trace Elem. Res. 201 (2023) 5640–5651, https://doi.org/10.1007/s12011-023-03631-1.
[235] M.H. Fernandes, M.M. Alves, M. Cebotarenco, I.A.C. Ribeiro, L. Grenho, P. S. Gomes, M.J. Carmezim, C.F. Santos, Citrate zinc hydroxyapatite nanorods with enhanced cytocompatibility and osteogenesis for bone regeneration, Mater. Sci. Eng. C 115 (2020) 111147, https://doi.org/10.1016/j.msec.2020.111147.
[236] D. Wang, L. Cui, X. Chang, D. Guan, Biosynthesis and characterization of zinc oxide nanoparticles from Artemisia annua and investigate their effect on proliferation, osteogenic differentiation and mineralization in human osteoblast-like MG-63 Cells, J. Photochem. Photobiol., B 202 (2020) 111652, https://doi.org/10.1016/j.jphotobiol.2019.111652.
[237] X. Shen, K. Hii Ru Yie, X. Wu, Z. Zhou, A. Sun, A.M. Al-bishari, K. Fang, M.A. Al-Baadani, Z. Deng, P. Ma, J. Liu, Improvement of aqueous stability and anti-osteoporosis properties of Zn-MOF coatings on titanium implants by hydrophobic raloxifene, Chem. Eng. J. 430 (2022) 133094, https://doi.org/10.1016/j.cej.2021.133094.
[238] Z. Weng, J. Ye, C. Cai, Z. Liu, Y. Liu, Y. Xu, J. Yuan, W. Zhang, L. Liu, J. Jiang, X. Cheng, X. Wang, Inflammatory microenvironment regulation and osteogenesis promotion by bone-targeting calcium and magnesium repletion nanoplatform for osteoporosis therapy, J. Nanobiotechnology 22 (2024) 314, https://doi.org/10.1186/s12951-024-02581-7.
[239] L. Chang, Y. Luo, W. Li, F. Liu, J. Guo, B. Dai, W. Tong, L. Qin, J. Wang, J. Xu, A comparative study on the effects of biodegradable high-purity magnesium screw and polymer screw for fixation in epiphyseal trabecular bone, Regen. Biomater. 11 (2024) rbae095, https://doi.org/10.1093/rb/rbae095.
[240] J. Guo, H. Yao, L. Chang, W. Zhu, Y. Zhang, X. Li, B. Yang, B. Dai, X. Chen, L. Lei, Z. Chen, Y. Li, L. Zheng, W. Liu, W. Tong, Y. Su, L. Qin, J. Xu, Magnesium nanocomposite hydrogel reverses the pathologies to enhance mandible regeneration, Adv. Mater. n/a (2024) 2312920, https://doi.org/10.1002/adma.202312920.
[241] H. Zu, L. Zheng, M. Huo, K. Liu, C. Halling Dreyer, Y. Zhang, X. He, Y. Li, L. Zou, L. Huang, X. Yi, A.R. Sun, X. Meng, K. Shi, H. Cao, X. Zu, W. Tong, D. Hokiu Chow, X. Wang, Y. Lai, J. Xu, M. Ding, J. Lu, L. Qin, Tree-inspired magnesium hybrid column for preventing hip collapse in steroid-associated osteonecrosis in bipedal emus, Mater. Today (2024), https://doi.org/10.1016/j.mattod.2024.08.009.
[242] Y. Cheng, Y. Zhang, Z. Zhao, G. Li, J. Li, A. Li, Y. Xue, B. Zhu, Z. Wu, X. Zhang, Guanidinium-decorated nanostructure for precision sonodynamic-catalytic therapy of MRSA-infected osteomyelitis, Adv. Mater. Deerfield Beach Fla 34 (2022) e2206646, https://doi.org/10.1002/adma.202206646.
[243] Z. Zhao, G. Li, H. Ruan, K. Chen, Z. Cai, G. Lu, R. Li, L. Deng, M. Cai, W. Cui, Capturing magnesium ions via microfluidic hydrogel microspheres for promoting cancellous bone regeneration, ACS Nano 15 (2021) 13041–13054, https://doi.org/10.1021/acsnano.1c02147.
[244] P. Mora-Raimundo, D. Lozano, M. Manzano, M. Vallet-Regí, Nanoparticles to knockdown osteoporosis-related gene and promote osteogenic marker expression for osteoporosis treatment, ACS Nano 13 (2019) 5451–5464, https://doi.org/10.1021/acsnano.9b00241.
[245] A. Shukla, N. Dasgupta, S. Ranjan, S. Singh, R. Chidambram, Nanotechnology towards prevention of anaemia and osteoporosis: from concept to market, Biotechnology & Biotechnological Equipment 31 (5) (2017) 863–879. https://doi.org/10.1080/13102818.2017.1335615.
[246] C. Gao, D. Wei, H. Yang, T. Chen, L. Yang, Nanotechnology for treating osteoporotic vertebral fractures, Int. J. Nanomedicine 10 (2015) 5139–5157, https://doi.org/10.2147/IJN.S85037.
[247] G.V. Vimbela, S.M. Ngo, C. Fraze, L. Yang, D.A. Stout, Antibacterial properties and toxicity from metallic nanomaterials, Int. J. Nanomedicine 12 (2017) 3941–3965, https://doi.org/10.2147/IJN.S134526.
[248] C.E. Albers, W. Hofstetter, K.A. Siebenrock, R. Landmann, F.M. Klenke, In vitro cytotoxicity of silver nanoparticles on osteoblasts and osteoclasts at antibacterial concentrations, Nanotoxicology 7 (2013) 30–36, https://doi.org/10.3109/17435390.2011.626538.
[249] F. Alsaikhan, M.Z. Mahmoud, M. Suliman, Synthesis and characterization of novel denosumab/magnesium-based metal organic frameworks nanocomposite prepared by ultrasonic route as drug delivery system for the treatment of osteoporosis, Front. Bioeng. Biotechnol. 11 (2023). https://www.frontiersin.org/journals/bioengineering-and-biotechnology/articles/10.3389/fbioe.2023.1153969.
[250] C. Rodríguez-Nogales, Y. González-Fernández, A. Aldaz, P. Couvreur, M. J. Blanco-Prieto, Nanomedicines for pediatric cancers, ACS Nano 12 (2018) 7482–7496, https://doi.org/10.1021/acsnano.8b03684.
[251] S.-Y. Wang, H.-Z. Hu, X.-C. Qing, Z.-C. Zhang, Z.-W. Shao, Recent advances of drug delivery nanocarriers in osteosarcoma treatment, J. Cancer 11 (2020) 69–82, https://doi.org/10.7150/jca.36588.
[252] M. Ibrahim, R. Sabouni, G.A. Husseini, Anti-cancer drug delivery using metal organic frameworks (MOFs), Curr. Med. Chem. 24 (2017) 193–214, https://doi.org/10.2174/0929867323666160926151216.
[253] M. Soleymaniha, M.-A. Shahbazi, A.R. Rafieerad, A. Maleki, A. Amiri, Promoting role of MXene nanosheets in biomedical sciences: therapeutic and biosensing

innovations, Adv. Healthc. Mater. 8 (2019) e1801137, https://doi.org/10.1002/adhm.201801137.
[254] P.D.P. Menezes, T. de A. Andrade, L.A. Frank, E.P.B.S.S. de Souza, G. das G. G. Trindade, I.A.S. Trindade, M.R. Serafini, S.S. Guterres, A.A. de S. Araújo, Advances of nanosystems containing cyclodextrins and their applications in pharmaceuticals, Int. J. Pharm. 559 (2019) 312–328, https://doi.org/10.1016/j.ijpharm.2019.01.041.
[255] R.S. Riley, E.S. Day, Gold nanoparticle-mediated photothermal therapy: applications and opportunities for multimodal cancer treatment, Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol. 9 (2017), https://doi.org/10.1002/wnan.1449.
[256] P. Singh, S. Pandit, V.R.S.S. Mokkapati, A. Garg, V. Ravikumar, I. Mijakovic, Gold nanoparticles in diagnostics and therapeutics for human cancer, Int. J. Mol. Sci. 19 (2018) 1979, https://doi.org/10.3390/ijms19071979.
[257] B. Sha, W. Gao, Y. Han, S. Wang, J. Wu, F. Xu, T. Lu, Potential application of titanium dioxide nanoparticles in the prevention of osteosarcoma and chondrosarcoma recurrence, J. Nanosci. Nanotechnol. 13 (2013) 1208–1211, https://doi.org/10.1166/jnn.2013.6081.
[258] A.A. Vodyashkin, M.G.H. Rizk, P. Kezimana, A.A. Kirichuk, Y.M. Stanishevskiy, Application of gold nanoparticle-based materials in cancer therapy and diagnostics, ChemEngineering 5 (2021) 69, https://doi.org/10.3390/chemengineering5040069.
[259] Q. Gao, J. Zhang, J. Gao, Z. Zhang, H. Zhu, D. Wang, Gold nanoparticles in cancer theranostics, Front. Bioeng. Biotechnol. 9 (2021), https://doi.org/10.3389/fbioe.2021.647905.
[260] Y. Ma, L. Chen, X. Li, A. Hu, H. Wang, H. Zhou, B. Tian, J. Dong, Rationally integrating peptide-induced targeting and multimodal therapies in a dual-shell theranostic platform for orthotopic metastatic spinal tumors, Biomaterials 275 (2021) 120917, https://doi.org/10.1016/j.biomaterials.2021.120917.
[261] S. Iram, M. Zahera, S. Khan, I. Khan, A. Syed, A.A. Ansary, F. Ameen, O.H. M. Shair, M.S. Khan, Gold nanoconjugates reinforce the potency of conjugated cisplatin and doxorubicin, Colloids Surf. B Biointerfaces 160 (2017) 254–264, https://doi.org/10.1016/j.colsurfb.2017.09.017.
[262] K.P. Steckiewicz, E. Barcinska, K. Sobczak, E. Tomczyk, M. Wojcik, I. Inkielewicz-Stepniak, Assessment of anti-tumor potential and safety of application of glutathione stabilized gold nanoparticles conjugated with chemotherapeutics, Int. J. Med. Sci. 17 (2020) 824–833, https://doi.org/10.7150/ijms.40827.
[263] G. He, Y. Shuai, Y. Hai, T. Yang, X. Pan, Y. Liu, X. Meng, H. Yang, M. Yang, C. Mao, Integration of gold nanodendrites and immune checkpoint blockers to achieve highly efficient photothermal immunotherapy for eradicating primary and distant metastatic osteosarcoma, Mater. Today Nano 20 (2022) 100268, https://doi.org/10.1016/j.mtnano.2022.100268.
[264] R.V. Lupusoru, D.A. Pricop, C.M. Uritu, A. Arvinte, A. Coroaba, I. Esanu, M. F. Zaltariov, M. Silion, C. Stefanescu, M. Pinteala, Effect of TAT-DOX-PEG irradiated gold nanoparticles conjugates on human osteosarcoma cells, Sci. Rep. 10 (2020) 6591, https://doi.org/10.1038/s41598-020-63245-8.
[265] Z. Sha, S. Yang, L. Fu, M. Geng, J. Gu, X. Liu, S. Li, X. Zhou, C. He, Manganese-doped gold core mesoporous silica particles as a nanoplatform for dual-modality imaging and chemo-chemodynamic combination osteosarcoma therapy, Nanoscale 13 (2021) 5077–5093, https://doi.org/10.1039/D0NR09220G.
[266] F. Yin, Y. Fan, L. Xu, F. Yin, M. He, T. Xiao, X. Shi, H. Wang, Macrophages loaded with dendrimer-entrapped gold nanoparticles as a theranostic platform for CT imaging-guided combinational therapy of orthotopic osteosarcoma, Chem. Eng. J. 417 (2021) 129273, https://doi.org/10.1016/j.cej.2021.129273.
[267] C. Zhang, H. Liu, M. Gong, M. Yang, Z. Yang, Y. Xie, L. Cai, Biomimetic gold nanocages for overcoming chemoresistance of osteosarcoma by ferroptosis and immunogenic cell death, Mater. Des. 210 (2021) 110087, https://doi.org/10.1016/j.matdes.2021.110087.
[268] E. Alpaslan, H. Yazici, N.H. Golshan, K.S. Ziemer, T.J. Webster, pH-dependent activity of dextran-coated cerium oxide nanoparticles on prohibiting osteosarcoma cell proliferation, ACS Biomater. Sci. Eng. 1 (2015) 1096–1103, https://doi.org/10.1021/acsbiomaterials.5b00194.
[269] G. He, J.-J. Nie, X. Liu, Z. Ding, P. Luo, Y. Liu, B.-W. Zhang, R. Wang, X. Liu, Y. Hai, D.-F. Chen, Zinc oxide nanoparticles inhibit osteosarcoma metastasis by downregulating β-catenin via HIF-1α/BNIP3/LC3B-mediated mitophagy pathway, Bioact. Mater. 19 (2023) 690–702, https://doi.org/10.1016/j.bioactmat.2022.05.006.
[270] G. He, X. Pan, X. Liu, Y. Zhu, Y. Ma, C. Du, X. Liu, C. Mao, HIF-1α-Mediated mitophagy determines ZnO nanoparticle-induced human osteosarcoma cell death both in vitro and in vivo, ACS Appl. Mater. Interfaces 12 (2020) 48296–48309, https://doi.org/10.1021/acsami.0c12139.
[271] A. Meshkini, H. Oveisi, Methotrexate-F127 conjugated mesoporous zinc hydroxyapatite as an efficient drug delivery system for overcoming chemotherapy resistance in osteosarcoma cells, Colloids Surf. B Biointerfaces 158 (2017) 319–330, https://doi.org/10.1016/j.colsurfb.2017.07.006.
[272] W. Yu, Y. Wang, J. Zhu, L. Jin, B. Liu, K. Xia, J. Wang, J. Gao, C. Liang, H. Tao, Autophagy inhibitor enhance ZnPc/BSA nanoparticle induced photodynamic therapy by suppressing PD-L1 expression in osteosarcoma immunotherapy, Biomaterials 192 (2019) 128–139, https://doi.org/10.1016/j.biomaterials.2018.11.019.
[273] H. Katifelis, M.-P. Nikou, I. Mukha, N. Vityuk, N. Lagopati, C. Piperi, A.A. Farooqi, N. Pippa, E.P. Efstathopoulos, M. Gazouli, Ag/Au bimetallic nanoparticles trigger different cell death pathways and affect damage associated molecular pattern release in human cell lines, Cancers 14 (2022) 1546, https://doi.org/10.3390/cancers14061546.
[274] E. Zielinska, A. Zauszkiewicz-Pawlak, M. Wojcik, I. Inkielewicz-Stepniak, Silver nanoparticles of different sizes induce a mixed type of programmed cell death in human pancreatic ductal adenocarcinoma, Oncotarget 9 (2018) 4675–4697, https://doi.org/10.18632/oncotarget.22563.
[275] D. Kovács, N. Igaz, C. Keskeny, P. Bélteky, T. Tóth, R. Gáspár, D. Madarász, Z. Rázga, Z. Kónya, I.M. Boros, M. Kiricsi, Silver nanoparticles defeat p53-positive and p53-negative osteosarcoma cells by triggering mitochondrial stress and apoptosis, Sci. Rep. 6 (2016) 27902, https://doi.org/10.1038/srep27902.
[276] D. Nayak, S. Ashe, P.R. Rauta, M. Kumari, B. Nayak, Bark extract mediated green synthesis of silver nanoparticles: evaluation of antimicrobial activity and antiproliferative response against osteosarcoma, Mater. Sci. Eng., C 58 (2016) 44–52, https://doi.org/10.1016/j.msec.2015.08.022.
[277] X. Wen, Q. Wang, T. Dai, J. Shao, X. Wu, Z. Jiang, J.A. Jacob, C. Jiang, Identification of possible reductants in the aqueous leaf extract of mangrove plant Rhizophora apiculata for the fabrication and cytotoxicity of silver nanoparticles against human osteosarcoma MG-63 cells, Mater. Sci. Eng., C 116 (2020) 111252, https://doi.org/10.1016/j.msec.2020.111252.
[278] M. Gong, H. Liu, N. Sun, Y. Xie, F. Yan, L. Cai, Polyethylenimine-dextran-coated magnetic nanoparticles loaded with miR-302b suppress osteosarcoma in vitro and in vivo, Nanomed 15 (2020) 711–723, https://doi.org/10.2217/nnm-2019-0218.
[279] S. Zakhireh, Y. Omidi, Y. Beygi-Khosrowshahi, A. Barzegari, J. Barar, K. Adibkia, Synthesis and biological impacts of pollen shells/Fe3O4 nanoparticles composites on human MG-63 osteosarcoma cells, J. Trace Elem. Med. Biol. Organ Soc. Miner. Trace Elem. GMS 71 (2022) 126921, https://doi.org/10.1016/j.jtemb.2022.126921.
[280] S. Gurunathan, M. Jeyaraj, M.-H. Kang, J.-H. Kim, Tangeretin-Assisted platinum nanoparticles enhance the apoptotic properties of doxorubicin: combination therapy for osteosarcoma treatment, Nanomater. Basel Switz. 9 (2019) 1089, https://doi.org/10.3390/nano9081089.
[281] C. Li, X. Liu, L. Zhang, L. Chen, X. Shi, S. Wu, J. Zhao, Advances in bone-targeted drug delivery systems for neoadjuvant chemotherapy for osteosarcoma, Orthop. Surg. 8 (2016) 105–110, https://doi.org/10.1111/os.12238.
[282] S. Augustine, J. Singh, M. Srivastava, M. Sharma, A. Das, B.D. Malhotra, Recent advances in carbon based nanosystems for cancer theranostics, Biomater. Sci. 5 (2017) 901–952, https://doi.org/10.1039/c7bm00008a.
[283] F. Liu, M. Mahmood, Y. Xu, F. Watanabe, A.S. Biris, D.K. Hansen, A. Inselman, D. Casciano, T.A. Patterson, M.G. Paule, W. Slikker, C. Wang, Effects of silver nanoparticles on human and rat embryonic neural stem cells, Front. Neurosci. 9 (2015) 115, https://doi.org/10.3389/fnins.2015.00115.
[284] P. Rajanahalli, C.J. Stucke, Y. Hong, The effects of silver nanoparticles on mouse embryonic stem cell self-renewal and proliferation, Toxicol. Rep. 2 (2015) 758–764, https://doi.org/10.1016/j.toxrep.2015.05.005.
[285] D. Zapata, J. Higgs, H. Wittholt, K. Chittimalli, A.E. Brooks, P. Mulinti, Nanotechnology in the diagnosis and treatment of osteomyelitis, Pharmaceutics 14 (2022) 1563, https://doi.org/10.3390/pharmaceutics14081563.
[286] A.M. Ribeiro, I. Jarak, D. Costa, F. Veiga, A. Figueiras, Chapter 23 - polymeric and metal nanostructures for bone regeneration and osteomyelitis treatment, in: A. Das Talukdar, S. Dey Sarker, J.K. Patra (Eds.), Adv. Nanotechnol.-Based Drug Deliv. Syst., Elsevier, 2022, pp. 605–644, https://doi.org/10.1016/B978-0-323-88450-1.00002-8.
[287] N.A. Rosli, Y.H. Teow, E. Mahmoudi, Current approaches for the exploration of antimicrobial activities of nanoparticles, Sci. Technol. Adv. Mater. 22 (2021) 885–907, https://doi.org/10.1080/14686996.2021.1978801.
[288] D. Ye, Z. Zhong, H. Xu, C. Chang, Z. Yang, Y. Wang, Q. Ye, L. Zhang, Construction of cellulose/nanosilver sponge materials and their antibacterial activities for infected wounds healing, Cellulose 23 (2016) 749–763, https://doi.org/10.1007/s10570-015-0851-4.
[289] X. Wang, M. Zhang, T. Zhu, Q. Wei, G. Liu, J. Ding, Flourishing antibacterial strategies for osteomyelitis therapy, Adv. Sci. Weinh. Baden-Wurtt. Ger. 10 (2023) e2206154, https://doi.org/10.1002/advs.202206154.
[290] Y. Hou, X. Li, Q. Zhao, G. Chen, C.L. Raston, Role of hydroxyl radicals and mechanism of Escherichia coli inactivation on Ag/AgBr/TiO2 nanotube array electrode under visible light irradiation, Environ. Sci. Technol. 46 (2012) 4042–4050, https://doi.org/10.1021/es204079d.
[291] S. Qadri, Y. Haik, E. Mensah-Brown, G. Bashir, M.J. Fernandez-Cabezudo, B.K. al-Ramadi, Metallic nanoparticles to eradicate bacterial bone infection, Nanomedicine Nanotechnol. Biol. Med. 13 (2017) 2241–2250, https://doi.org/10.1016/j.nano.2017.05.013.
[292] W. Fan, D. Wu, T. Ma, B. Fan, Ag-loaded mesoporous bioactive glasses against Enterococcus faecalis biofilm in root canal of human teeth, Dent. Mater. J. 34 (2015) 54–60, https://doi.org/10.4012/dmj.2014-104.
[293] N. Rabiee, S. Ahmadi, O. Akhavan, R. Luque, Silver and gold nanoparticles for antimicrobial purposes against multi-drug resistance bacteria, Mater. Basel Switz. 15 (2022) 1799, https://doi.org/10.3390/ma15051799.
[294] T. Russo, A. Gloria, R. De Santis, U. D'Amora, G. Balato, A. Vollaro, O. Oliviero, G. Improta, M. Triassi, L. Ambrosio, Preliminary focus on the mechanical and antibacterial activity of a PMMA-based bone cement loaded with gold nanoparticles, Bioact. Mater. 2 (2017) 156–161, https://doi.org/10.1016/j.bioactmat.2017.05.002.
[295] A. Topsakal, S. Midha, E. Yuca, A. Tukay, H.T. Sasmazel, D.M. Kalaskar, O. Gunduz, Study on the cytocompatibility, mechanical and antimicrobial properties of 3D printed composite scaffolds based on PVA/Gold nanoparticles (AuNP)/Ampicillin (AMP) for bone tissue engineering, Mater. Today Commun. 28 (2021) 102458, https://doi.org/10.1016/j.mtcomm.2021.102458.
[296] Y.-Z. Liu, Y. Li, X.-B. Yu, L.-N. Liu, Z.-A. Zhu, Y.-P. Guo, Drug delivery property, bactericidal property and cytocompatibility of magnetic mesoporous bioactive

glass, Mater. Sci. Eng., C 41 (2014) 196–205, https://doi.org/10.1016/j.msec.2014.04.037.
[297] J. Ren, Y. Qiao, L. Jin, C. Mao, C. Wang, S. Wu, Y. Zheng, Z. Li, Z. Cui, H. Jiang, S. Zhu, X. Liu, A smart bacteria-capture-killing vector for effectively treating osteomyelitis through synergy under microwave therapy, Small Weinh. Bergstr. Ger. 20 (2024) e2307406, https://doi.org/10.1002/smll.202307406.
[298] W. Sun, C. Wang, D. Wan, Y. Zheng, S. Wu, J. Shen, Y. Zhang, X. Liu, CuCeO bimetallic oxide rapidly treats Staphylococcus aureus-infected osteomyelitis through microwave strengthened microwave catalysis and fenton-therapy, Small Methods 7 (2023) e2300203, https://doi.org/10.1002/smtd.202300203.
[299] X. Dai, X. Wang, X. Chen, L. Ye, M. Wu, Fabrication of ultrasound-mediated cerium oxide nanoparticles for the examinations of human osteomyelitis and antibacterial activity, Appl. Nanosci. 11 (2021) 2549–2560, https://doi.org/10.1007/s13204-021-02083-0.
[300] A. Bandyopadhyay, I. Mitra, S.B. Goodman, M. Kumar, S. Bose, Improving biocompatibility for next generation of metallic implants, Prog. Mater. Sci. 133 (2023) 101053, https://doi.org/10.1016/j.pmatsci.2022.101053.
[301] Y. Zhang, Z. Cheng, Z. Liu, X. Shen, C. Cai, M. Li, Z. Luo, Functionally tailored metal-organic framework coatings for mediating Ti implant osseointegration, Adv. Sci. Weinh. Baden-Wurtt. Ger. 10 (2023) e2303958, https://doi.org/10.1002/advs.202303958.
[302] K. Gulati, M.S. Aw, D. Losic, Drug-eluting Ti wires with titania nanotube arrays for bone fixation and reduced bone infection, Nanoscale Res. Lett. 6 (2011) 571, https://doi.org/10.1186/1556-276X-6-571.
[303] K.C. Popat, M. Eltgroth, T.J. Latempa, C.A. Grimes, T.A. Desai, Decreased Staphylococcus epidermis adhesion and increased osteoblast functionality on antibiotic-loaded titania nanotubes, Biomaterials 28 (2007) 4880–4888, https://doi.org/10.1016/j.biomaterials.2007.07.037.
[304] A. Murakami, T. Arimoto, D. Suzuki, M. Iwai-Yoshida, F. Otsuka, Y. Shibata, T. Igarashi, R. Kamijo, T. Miyazaki, Antimicrobial and osteogenic properties of a hydrophilic-modified nanoscale hydroxyapatite coating on titanium, Nanomedicine Nanotechnol. Biol. Med. 8 (2012) 374–382, https://doi.org/10.1016/j.nano.2011.07.001.
[305] R. Wang, M. Shi, F. Xu, Y. Qiu, P. Zhang, K. Shen, Q. Zhao, J. Yu, Y. Zhang, Graphdiyne-modified TiO2 nanofibers with osteoinductive and enhanced photocatalytic antibacterial activities to prevent implant infection, Nat. Commun. 11 (2020) 4465, https://doi.org/10.1038/s41467-020-18267-1.
[306] P. Makvandi, C. Wang, E.N. Zare, A. Borzacchiello, L. Niu, F.R. Tay, Metal-based nanomaterials in biomedical applications: antimicrobial activity and cytotoxicity aspects, Adv. Funct. Mater. 30 (2020) 1910021, https://doi.org/10.1002/adfm.201910021.
[307] M. Hans, A. Erbe, S. Mathews, Y. Chen, M. Solioz, F. Mücklich, Role of copper oxides in contact killing of bacteria, Langmuir ACS J. Surf. Colloids 29 (2013) 16160–16166, https://doi.org/10.1021/la404091z.
[308] K. Li, X. Zhao, B.K. Hammer, S. Du, Y. Chen, Nanoparticles inhibit DNA replication by binding to DNA: modeling and experimental validation, ACS Nano 7 (2013) 9664–9674, https://doi.org/10.1021/nn402472k.
[309] A.M. Alkilany, C.J. Murphy, Toxicity and cellular uptake of gold nanoparticles: what we have learned so far? J. Nanoparticle Res. 12 (2010) 2313–2333, https://doi.org/10.1007/s11051-010-9911-8.
[310] T. Gong, J. Xie, J. Liao, T. Zhang, S. Lin, Y. Lin, Nanomaterials and bone regeneration, Bone Res. 3 (2015) 15029, https://doi.org/10.1038/boneres.2015.29.
[311] E. Gibon, L.A. Córdova, L. Lu, T.-H. Lin, Z. Yao, M. Hamadouche, S.B. Goodman, The biological response to orthopedic implants for joint replacement. II: polyethylene, ceramics, PMMA, and the foreign body reaction, J. Biomed. Mater. Res. B Appl. Biomater. 105 (2017) 1685–1691, https://doi.org/10.1002/jbm.b.33676.
[312] S. Vieira, S. Vial, R.L. Reis, J.M. Oliveira, Nanoparticles for bone tissue engineering, Biotechnol. Prog. 33 (2017) 590–611, https://doi.org/10.1002/btpr.2469.
[313] K.H. Min, E.-Y. Jang, H.J. Lee, Y.-S. Hwang, J.-I. Ryu, J.-H. Moon, S.C. Lee, pH-Responsive mineralized nanoparticles for bacteria-triggered topical release of antibiotics, J. Ind. Eng. Chem. 71 (2019) 210–219, https://doi.org/10.1016/j.jiec.2018.11.027.
[314] Y. Fu, M. Zhu, A. Shi, B. Zhang, P. Xu, Stimulus-responsive antibacterial strategies for construction of anti-infection bone implants, Mater 8 (2025) 100554, https://doi.org/10.1016/j.nxmate.2025.100554.
[315] S. Agarwal, J. Curtin, B. Duffy, S. Jaiswal, Biodegradable magnesium alloys for orthopaedic applications: a review on corrosion, biocompatibility and surface modifications, Mater. Sci. Eng. C 68 (2016) 948–963, https://doi.org/10.1016/j.msec.2016.06.020.
[316] H. Zhou, B. Liang, H. Jiang, Z. Deng, K. Yu, Magnesium-based biomaterials as emerging agents for bone repair and regeneration: from mechanism to application, J. Magnes. ALLOYS 9 (2021) 779–804, https://doi.org/10.1016/j.jma.2021.03.004.
[317] A. Shanmugavadivu, S. Lekhavadhani, S. Babu, N. Suresh, N. Selvamurugan, Magnesium-incorporated biocomposite scaffolds: a novel frontier in bone tissue engineering, J. Magnes. ALLOYS 12 (2024) 2231–2248, https://doi.org/10.1016/j.jma.2024.06.001.
[318] R. Chen, H.-B. Chen, P.-P. Xue, W.-G. Yang, L.-Z. Luo, M.-Q. Tong, B. Zhong, H.-L. Xu, Y.-Z. Zhao, J.-D. Yuan, HA/MgO nanocrystal-based hybrid hydrogel with high mechanical strength and osteoinductive potential for bone reconstruction in diabetic rats, J. Mater. Chem. B 9 (2021) 1107–1122, https://doi.org/10.1039/d0tb02553d.
[319] B. Li, P. Gao, H. Zhang, Z. Guo, Y. Zheng, Y. Han, Osteoimmunomodulation, osseointegration, and *in vivo* mechanical integrity of pure Mg coated with HA nanorod/pore-sealed MgO bilayer, Biomater. Sci. 6 (2018) 3202–3218, https://doi.org/10.1039/c8bm00901e.
[320] X. Li, B. Dai, J. Guo, Y. Zhu, J. Xu, S. Xu, Z. Yao, L. Chang, Y. Li, X. He, D.H. K. Chow, S. Zhang, H. Yao, W. Tong, T. Ngai, L. Qin, Biosynthesized bandages carrying magnesium oxide nanoparticles induce cortical bone formation by modulating endogenous periosteal cells, ACS Nano 16 (2022) 18071–18089, https://doi.org/10.1021/acsnano.2c04747.
[321] Z. Lin, J. Wu, W. Qiao, Y. Zhao, K.H.M. Wong, P.K. Chu, L. Bian, S. Wu, Y. Zheng, K.M.C. Cheung, F. Leung, K.W.K. Yeung, Precisely controlled delivery of magnesium ions thru sponge-like monodisperse PLGA/nano-MgO-alginate core-shell microsphere device to enable in-situ bone regeneration, Biomaterials 174 (2018) 1–16, https://doi.org/10.1016/j.biomaterials.2018.05.011.
[322] Y. Chen, W. Sheng, J. Lin, C. Fang, J. Deng, P. Zhang, M. Zhou, P. Liu, J. Weng, F. Yu, D. Wang, B. Kang, H. Zeng, Magnesium oxide nanoparticle coordinated phosphate-functionalized chitosan injectable hydrogel for osteogenesis and angiogenesis in bone regeneration, ACS Appl. Mater. Interfaces 14 (2022) 7592–7608, https://doi.org/10.1021/acsami.1c21260.
[323] Y. Qing, L. Cheng, R. Li, G. Liu, Y. Zhang, X. Tang, J. Wang, H. Liu, Y. Qin, Potential antibacterial mechanism of silver nanoparticles and the optimization of orthopedic implants by advanced modification technologies, Int. J. NANOMEDICINE 13 (2018) 3311–3327, https://doi.org/10.2147/IJN.S165125.
[324] Z. Zheng, W. Yin, J.N. Zara, W. Li, J. Kwak, R. Mamidi, M. Lee, R.K. Siu, R. Ngo, J. Wang, D. Carpenter, X. Zhang, B. Wu, K. Ting, C. Soo, The use of BMP-2 coupled - nanosilver-PLGA composite grafts to induce bone repair in grossly infected segmental defects, Biomaterials 31 (2010) 9293–9300, https://doi.org/10.1016/j.biomaterials.2010.08.041.
[325] W. Zhou, T. Bai, L. Wang, Y. Cheng, D. Xia, S. Yu, Y. Zheng, Biomimetic AgNPs@antimicrobial peptide/silk fibroin coating for infection-trigger antibacterial capability and enhanced osseointegration, Bioact. Mater. 20 (2023) 64–80, https://doi.org/10.1016/j.bioactmat.2022.05.015.
[326] J. Liu, S. Yang, Y. Tan, X. Liu, Y. Tian, L. Liang, H. Wu, Simultaneously stimulated osteogenesis and anti-bacteria of physically cross-linked double-network hydrogel loaded with MgO-Ag2O nanocomposites, Biomater. Adv. 141 (2022) 213123, https://doi.org/10.1016/j.bioadv.2022.213123.
[327] D. Lu, X. Wu, W. Wang, C. Ma, B. Pei, S. Wu, Synthesis and application of iron oxide nanoparticles in bone tissue repair, J. Nanomater. 2021 (2021) 3762490, https://doi.org/10.1155/2021/3762490.
[328] T. Russo, R. De Santis, V. Peluso, A. Gloria, Multifunctional bioactive magnetic scaffolds with tailored features for bone tissue engineering, in: Magn. Nanoparticles Hum. Health Med., John Wiley & Sons, Ltd, 2021, pp. 87–112, https://doi.org/10.1002/9781119754725.ch4.
[329] N. Bock, A. Riminucci, C. Dionigi, A. Russo, A. Tampieri, E. Landi, V.A. Goranov, M. Marcacci, V. Dediu, A novel route in bone tissue engineering: magnetic biomimetic scaffolds, Acta Biomater. 6 (2010) 786–796, https://doi.org/10.1016/j.actbio.2009.09.017.
[330] R. Kandel, S.R. Jang, U. Ghimire, S. Shrestha, B.K. Shrestha, C.H. Park, C.S. Kim, Engineered nanostructure fibrous cell-laden biointerfaces integrating Fe3O4/SrO2-fMWCNTs induce osteogenesis and anti-bacterial effect, J. Ind. Eng. Chem. 120 (2023) 216–230, https://doi.org/10.1016/j.jiec.2022.12.028.
[331] D. Shan, Y. Shi, S. Duan, Y. Wei, Q. Cai, X. Yang, Electrospun magnetic poly(L-lactide) (PLLA) nanofibers by incorporating PLLA-stabilized Fe3O4 nanoparticles, Mater. Sci. Eng., C 33 (2013) 3498–3505, https://doi.org/10.1016/j.msec.2013.04.040.
[332] M. Li, J. Liu, X. Cui, G. Sun, J. Hu, S. Xu, F. Yang, L. Zhang, X. Wang, P. Tang, Osteogenesis effects of magnetic nanoparticles modified-porous scaffolds for the reconstruction of bone defect after bone tumor resection, Regen. Biomater. 6 (2019) 373–381, https://doi.org/10.1093/rb/rbz019.
[333] J. Xiang, J. Li, J. He, X. Tang, C. Dou, Z. Cao, B. Yu, C. Zhao, F. Kang, L. Yang, S. Dong, X. Yang, Cerium oxide nanoparticle modified scaffold interface enhances vascularization of bone grafts by activating calcium channel of mesenchymal stem cells, ACS Appl. Mater. Interfaces 8 (2016) 4489–4499, https://doi.org/10.1021/acsami.6b00158.
[334] J. Luo, S. Zhu, Y. Tong, Y. Zhang, Y. Li, L. Cao, M. Kong, M. Luo, Q. Bi, Q. Zhang, Cerium oxide nanoparticles promote osteoplastic precursor differentiation by activating the wnt pathway, Biol. Trace Elem. Res. 201 (2023) 865–873, https://doi.org/10.1007/s12011-022-03168-9.
[335] N.-H. Lee, M.S. Kang, T.-H. Kim, D.S. Yoon, N. Mandakhbayar, S.B. Jo, H.S. Kim, J.C. Knowles, J.-H. Lee, H.-W. Kim, Dual actions of osteoclastic-inhibition and osteogenic-stimulation through strontium-releasing bioactive nanoscale cement imply biomaterial-enabled osteoporosis therapy, Biomaterials 276 (2021) 121025, https://doi.org/10.1016/j.biomaterials.2021.121025.
[336] Y.-W. Ge, Z.-H. Fan, Q.-F. Ke, Y.-P. Guo, C.-Q. Zhang, W.-T. Jia, SrFe12O19-doped nano-layered double hydroxide/chitosan layered scaffolds with a nacre-mimetic architecture guide in situ bone ingrowth and regulate bone homeostasis, Mater. Today Bio 16 (2022) 100362, https://doi.org/10.1016/j.mtbio.2022.100362.
[337] A. Bhowmick, N. Pramanik, P.J. Manna, T. Mitra, T.K.R. Selvaraj, A. Gnanamani, M. Das, P.P. Kundu, Development of porous and antimicrobial CTS–PEG–HAP–ZnO nano-composites for bone tissue engineering, RSC Adv. 5 (2015) 99385–99393, https://doi.org/10.1039/C5RA16755H.
[338] B.K. Shrestha, S. Shrestha, A.P. Tiwari, J.-I. Kim, S.W. Ko, H.-J. Kim, C.H. Park, C. S. Kim, Bio-inspired hybrid scaffold of zinc oxide-functionalized multi-wall carbon nanotubes reinforced polyurethane nanofibers for bone tissue engineering, Mater. Des. 133 (2017) 69–81, https://doi.org/10.1016/j.matdes.2017.07.049.

[339] J. Crush, A. Hussain, K.T.M. Seah, W.S. Khan, Bioactive glass: methods for assessing angiogenesis and osteogenesis, Front. Cell Dev. Biol. 9 (2021). https://www.frontiersin.org/journals/cell-and-developmental-biology/articles/10.3389/fcell.2021.643781.
[340] A. Schwab, R. Levato, M. D'Este, S. Piluso, D. Eglin, J. Malda, Printability and shape fidelity of bioinks in 3D bioprinting, Chem. Rev. 120 (2020) 11028–11055, https://doi.org/10.1021/acs.chemrev.0c00084.
[341] W. Habraken, P. Habibovic, M. Epple, M. Bohner, Calcium phosphates in biomedical applications: materials for the future? Mater. Today 19 (2016) 69–87, https://doi.org/10.1016/j.mattod.2015.10.008.
[342] T.-M. De Witte, L.E. Fratila-Apachitei, A.A. Zadpoor, N.A. Peppas, Bone tissue engineering via growth factor delivery: from scaffolds to complex matrices, Regen. Biomater. 5 (2018) 197–211, https://doi.org/10.1093/rb/rby013.
[343] E. Saiz, E.A. Zimmermann, J.S. Lee, U.G.K. Wegst, A.P. Tomsia, Perspectives on the role of nanotechnology in bone tissue engineering, Dent. Mater. Off. Publ. Acad. Dent. Mater. 29 (2013) 103–115, https://doi.org/10.1016/j.dental.2012.08.001.
[344] V. Thomas, D.R. Dean, Y.K. Vohra, Nanostructured Biomaterials for Regenerative Medicine, Curr. Nanosci. 2 (n.d.) 155–177. https://doi.org/10.2174/1573413710602030155.
[345] Q. Wang, Y. Zhang, Y. Ma, M. Wang, G. Pan, Nano-crosslinked dynamic hydrogels for biomedical applications, Mater. Today Bio 20 (2023) 100640, https://doi.org/10.1016/j.mtbio.2023.100640.
[346] B. Yin, M. Gosecka, M. Bodaghi, D. Crespy, G. Youssef, J.M. Dodda, S.H.D. Wong, A.B. Imran, M. Gosecki, A. Jobdeedamrong, M. Afzali Naniz, A. Zolfagharian, Engineering multifunctional dynamic hydrogel for biomedical and tissue regenerative applications, Chem. Eng. J. 487 (2024) 150403, https://doi.org/10.1016/j.cej.2024.150403.
[347] W.T. Johnson, D. McBride, M. Kerr, A. Nguyen, M. Zoccheddu, M. Bollmann, X. Wei, R.M. Jones, W. Wang, M.N.D. Svensson, N. Bottini, N.J. Shah, Immunomodulatory nanoparticles for modulating arthritis flares, ACS Nano 18 (2024) 1892–1906, https://doi.org/10.1021/acsnano.3c05298.
[348] L. Liu, X. Bai, M.-V. Martikainen, A. Kårlund, M. Roponen, W. Xu, G. Hu, E. Tasciotti, V.-P. Lehto, Cell membrane coating integrity affects the internalization mechanism of biomimetic nanoparticles, Nat. Commun. 12 (2021) 5726, https://doi.org/10.1038/s41467-021-26052-x.
[349] M. Chen, Y. Chen, C. Wei, Nanoparticles based composite coatings with tunable vascular endothelial growth factor and bone morphogenetic protein-2 release for bone regeneration, J. Biomed. Mater. Res. 111 (2023) 1044–1053, https://doi.org/10.1002/jbm.a.37489.
[350] D.H.R. Kempen, L. Lu, A. Heijink, T.E. Hefferan, L.B. Creemers, A. Maran, M. J. Yaszemski, W.J.A. Dhert, Effect of local sequential VEGF and BMP-2 delivery on ectopic and orthotopic bone regeneration, Biomaterials 30 (2009) 2816–2825, https://doi.org/10.1016/j.biomaterials.2009.01.031.
[351] J. Majumder, T. Minko, Multifunctional and stimuli-responsive nanocarriers for targeted therapeutic delivery, Expert Opin. Drug Deliv. 18 (2021) 205–227, https://doi.org/10.1080/17425247.2021.1828339.
[352] J. Li, H. Zhang, Y. Han, Y. Hu, Z. Geng, J. Su, Targeted and responsive biomaterials in osteoarthritis, Theranostics 13 (2023) 931–954, https://doi.org/10.7150/thno.78639.
[353] M. Rahimi, G. Charmi, K. Matyjaszewski, X. Banquy, J. Pietrasik, Recent developments in natural and synthetic polymeric drug delivery systems used for the treatment of osteoarthritis, Acta Biomater. 123 (2021) 31–50, https://doi.org/10.1016/j.actbio.2021.01.003.
[354] X. Liu, C. Corciulo, S. Arabagian, A. Ulman, B.N. Cronstein, Adenosine-functionalized biodegradable PLA-b-PEG nanoparticles ameliorate osteoarthritis in rats, Sci. Rep. 9 (2019) 7430, https://doi.org/10.1038/s41598-019-43834-y.
[355] Y. Bai, X. Gong, C. Dou, Z. Cao, S. Dong, Redox control of chondrocyte differentiation and chondrogenesis, Free Radic. Biol. Med. 132 (2019) 83–89, https://doi.org/10.1016/j.freeradbiomed.2018.10.443.
[356] H. Agarwal, A. Nakara, V.K. Shanmugam, Anti-inflammatory mechanism of various metal and metal oxide nanoparticles synthesized using plant extracts: a review, Biomed. Pharmacother. 109 (2019) 2561–2572, https://doi.org/10.1016/j.biopha.2018.11.116.
[357] A.G. Bajpayee, M. Scheu, A.J. Grodzinsky, R.M. Porter, A rabbit model demonstrates the influence of cartilage thickness on intra-articular drug delivery and retention within cartilage, J. Orthop. Res. Off. Publ. Orthop. Res. Soc. 33 (2015) 660–667, https://doi.org/10.1002/jor.22841.
[358] P. Famta, M. Famta, J. Kaur, R. Khursheed, A. Kaur, G.L. Khatik, D.M. Pawde, S.N. R. Rahman, T. Shunmugaperumal, Protecting the normal physiological functions of articular and periarticular structures by aurum nanoparticle-based formulations: an up-to-date insight, AAPS PharmSciTech 21 (2020) 95, https://doi.org/10.1208/s12249-020-1636-0.
[359] M.C.B. Filho, D.P. Dos Santos Haupenthal, R.P. Zaccaron, G. de Bem Silveira, L. de Roch Casagrande, F.S. Lupselo, N. Alves, S. de Sousa Mariano, F.R.C. do Bomfim, T.A.M. de Andrade, R.A. Machado-de-Ávila, P.C.L. Silveira, Intra-articular treatment with hyaluronic acid associated with gold nanoparticles in a mechanical osteoarthritis model in Wistar rats, J. Orthop. Res. Off. Publ. Orthop. Res. Soc. 39 (2021) 2546–2555, https://doi.org/10.1002/jor.25008.
[360] D. Cabuzu, A. Cirja, R. Puiu, A.M. Grumezescu, Biomedical applications of gold nanoparticles, Curr. Top. Med. Chem. 15 (2015) 1605–1613, https://doi.org/10.2174/1568026615666150414144750.
[361] M.A. Khan, M.J. Khan, Nano-gold displayed anti-inflammatory property via NF-kB pathways by suppressing COX-2 activity, Artif. Cells Nanomedicine Biotechnol 46 (2018) 1149–1158, https://doi.org/10.1080/21691401.2018.1446968.
[362] W.N. da Silva Campos, A.E. Tognoli Leite, D.A. Sonego, M.A. de Andrade, F. D. Pizzinatto, V.S. Marangoni, V. Zucolotto, L. Nakazato, E.M. Colodel, R.L. de Souza, Synthesis and characterization of gold nanoparticles combined with curcumin and its effects on experimentally induced osteoarthritis, Cienc. RURAL 47 (2017) e20161001, https://doi.org/10.1590/0103-8478cr20161001.
[363] P. Dwivedi, V. Nayak, M. Kowshik, Role of gold nanoparticles as drug delivery vehicles for chondroitin sulfate in the treatment of osteoarthritis, Biotechnol. Prog. 31 (2015) 1416–1422, https://doi.org/10.1002/btpr.2147.
[364] S. Xu, L. Chang, X. Zhao, Y. Hu, Y. Lin, Z. Chen, X. Ren, X. Mei, Preparation of epigallocatechin gallate decorated Au-Ag nano-heterostructures as NIR-sensitive nano-enzymes for the treatment of osteoarthritis through mitochondrial repair and cartilage protection, Acta Biomater. 144 (2022) 168–182, https://doi.org/10.1016/j.actbio.2022.03.038.
[365] M. Sharifi, K. Faryabi, A.J. Talaei, M.S. Shekha, M. Ale-Ebrahim, A. Salihi, N.M. Q. Nanakali, F.M. Aziz, B. Rasti, A. Hasan, M. Falahati, Antioxidant properties of gold nanozyme: a review, J. Mol. Liq. 297 (2020) 112004, https://doi.org/10.1016/j.molliq.2019.112004.
[366] S.M. Hirst, A.S. Karakoti, R.D. Tyler, N. Sriranganathan, S. Seal, C.M. Reilly, Anti-inflammatory properties of cerium oxide nanoparticles, Small 5 (2009) 2848–2856, https://doi.org/10.1002/smll.200901048.
[367] V. Baldim, F. Bedioui, N. Mignet, I. Margaill, J.-F. Berret, The enzyme-like catalytic activity of cerium oxide nanoparticles and its dependency on Ce3+ surface area concentration, Nanoscale 10 (2018) 6971–6980, https://doi.org/10.1039/C8NR00325D.
[368] Y.-W. Lin, C.-H. Fang, F.-Q. Meng, C.-J. Ke, F.-H. Lin, Hyaluronic acid loaded with cerium oxide nanoparticles as antioxidant in hydrogen peroxide induced chondrocytes injury: an in vitro osteoarthritis model, Molecules 25 (2020) 4407, https://doi.org/10.3390/molecules25194407.
[369] S. Ponnurangam, G.D. O'Connell, I.V. Chernyshova, K. Wood, C.T.-H. Hung, P. Somasundaran, Beneficial effects of cerium oxide nanoparticles in development of chondrocyte-seeded hydrogel constructs and cellular response to interleukin insults, Tissue Eng. Part A 20 (2014) 2908–2919, https://doi.org/10.1089/ten.TEA.2013.0592.
[370] K. Dashnyam, J.-H. Lee, R.K. Singh, J.-Y. Yoon, J.H. Lee, G.-Z. Jin, H.-W. Kim, Optimally dosed nanoceria attenuates osteoarthritic degeneration of joint cartilage and subchondral bone, Chem. Eng. J. 422 (2021) 130066, https://doi.org/10.1016/j.cej.2021.130066.
[371] H. Chen, T. Ye, F. Hu, K. Chen, B. Li, M. Qiu, Z. Chen, Y. Sun, W. Ye, H. Wang, D. Ni, L. Guo, Urchin-like ceria nanoparticles for enhanced gene therapy of osteoarthritis, Sci. Adv. 9 (2023), https://doi.org/10.1126/sciadv.adf0988.
[372] P. Chen, J. Bornhorst, M. Aschner, Manganese metabolism in humans, Front. Biosci. Landmark Ed. 23 (2018) 1655–1679, https://doi.org/10.2741/4665.
[373] M.H. Tootoonchi, M. Hashempour, P.L. Blackwelder, C.A. Fraker, Manganese oxide particles as cytoprotective, oxygen generating agents, Acta Biomater. 59 (2017) 327–337, https://doi.org/10.1016/j.actbio.2017.07.006.
[374] T. Lin, Y. Zhao, J. Chen, C. Wu, Z. Li, Y. Cao, R. Lu, J. Zhang, C. Zhao, Y. Lu, Carboxymethyl chitosan-assisted MnOx nanoparticles: synthesis, characterization, detection and cartilage repair in early osteoarthritis, Carbohydr. Polym. 294 (2022) 119821, https://doi.org/10.1016/j.carbpol.2022.119821.
[375] T. Zhou, J. Ran, P. Xu, L. Shen, Y. He, J. Ye, L. Wu, C. Gao, A hyaluronic acid/platelet-rich plasma hydrogel containing MnO2 nanozymes efficiently alleviates osteoarthritis in vivo, Carbohydr. Polym. 292 (2022) 119667, https://doi.org/10.1016/j.carbpol.2022.119667.
[376] M. Ahmadi, H. Maghsoudi, G.B. Khaniki, R.H. Hosseini, P. Ahangar, The effect of Ag-NPs-Menthol on the expression of metalloproteinase in A model-like osteoarthritis, Arch. Med. Lab. Sci. 7 (2021) 1–13, https://doi.org/10.22037/amls.v7.34925, e11.
[377] Q. Lin, H. Huang, L. Chen, G. Shi, Synthesis of caffeic acid coated silver nanoparticles for the treatment of osteoarthritis, Biomed. Res.-Tokyo. 28 (2017) 1276–1279.
[378] Z. Cao, H. Wang, J. Chen, Y. Zhang, Q. Mo, P. Zhang, M. Wang, H. Liu, X. Bao, Y. Sun, W. Zhang, Q. Yao, Silk-based hydrogel incorporated with metal-organic framework nanozymes for enhanced osteochondral regeneration, Bioact. Mater. 20 (2023) 221–242, https://doi.org/10.1016/j.bioactmat.2022.05.025.
[379] K.-S. Park, B.-J. Kim, E. Lih, W. Park, S.-H. Lee, Y.K. Joung, D.K. Han, Versatile effects of magnesium hydroxide nanoparticles in PLGA scaffold-mediated chondrogenesis, Acta Biomater. 73 (2018) 204–216, https://doi.org/10.1016/j.actbio.2018.04.022.
[380] Y. Cai, C. Wu, Q. Ou, M. Zeng, S. Xue, J. Chen, Y. Lu, C. Ding, Enhanced osteoarthritis therapy by nanoengineered mesenchymal stem cells using biomimetic CuS nanoparticles loaded with plasmid DNA encoding TGF-β1, Bioact. Mater. 19 (2023) 444–457, https://doi.org/10.1016/j.bioactmat.2022.04.021.
[381] R. Mohammadinejad, M. Ashrafizadeh, A. Pardakhty, I. Uzieliene, J. Denkovskij, E. Bernotiene, L. Janssen, G.S. Lorite, S. Saarakkala, A. Mobasheri, Nanotechnological strategies for osteoarthritis diagnosis, monitoring, clinical management, and regenerative medicine: recent advances and future opportunities, Curr. Rheumatol. Rep. 22 (2020) 12, https://doi.org/10.1007/s11926-020-0884-z.
[382] X. Jiang, Y. Sun, Y. Lyu, H. Kang, J. Zhao, K. Zhang, L. Bian, Hydrogels for ameliorating osteoarthritis: mechanical modulation, anti-inflammation, and regeneration, BMEMat 2 (2024) e12078, https://doi.org/10.1002/bmm2.12078.
[383] J. Chen, L. Chen, X. Song, K. Fang, L. Sun, Applications of antioxidant nanoparticles and hydrogels in osteoarthritis: a review, Mater. EXPRESS 13 (2023) 189–205, https://doi.org/10.1166/mex.2023.2339.

[384] Y. Li, Q. Liang, L. Zhou, J. Liu, Y. Liu, Metal nanoparticles: a platform integrating diagnosis and therapy for rheumatoid arthritis, J. Nanoparticle Res. 24 (2022) 84, https://doi.org/10.1007/s11051-022-05469-5.
[385] P. Jain, K.G. Babu, A. Madhusudhan, S.R. Pulikallu, Nanotherapeutics for rheumatoid arthritis therapy, in: A. Madhusudhan, S.D. Purohit, R. Prasad, A. Husen (Eds.), Funct. Smart Nanomater. Their Theranostics Approaches, Springer Nature, Singapore, 2024, pp. 305–330, https://doi.org/10.1007/978-981-99-6597-7_11.
[386] J. Li, L. Chen, X. Xu, Y. Fan, X. Xue, M. Shen, X. Shi, Targeted combination of antioxidative and anti-inflammatory therapy of rheumatoid arthritis using multifunctional dendrimer-entrapped gold nanoparticles as a platform, Small Weinh. Bergstr. Ger. 16 (2020) e2005661, https://doi.org/10.1002/smll.202005661.
[387] J. Jhun, J. Moon, J. Ryu, Y. Shin, S. Lee, K.-H. Cho, T. Kang, M.-L. Cho, S.-H. Park, Liposome/gold hybrid nanoparticle encoded with CoQ10 (LGNP-CoQ10) suppressed rheumatoid arthritis via STAT3/Th17 targeting, PLoS One 15 (2020) e0241080, https://doi.org/10.1371/journal.pone.0241080.
[388] H. Lee, M.-Y. Lee, S.H. Bhang, B.-S. Kim, Y.S. Kim, J.H. Ju, K.S. Kim, S.K. Hahn, Hyaluronate-gold nanoparticle/tocilizumab complex for the treatment of rheumatoid arthritis, ACS Nano 8 (2014) 4790–4798, https://doi.org/10.1021/nn500685h.
[389] A.C. Lima, C.F. Campos, C. Cunha, A. Carvalho, R.L. Reis, H. Ferreira, N.M. Neves, Biofunctionalized liposomes to monitor rheumatoid arthritis regression stimulated by interleukin-23 neutralization, Adv. Healthc. Mater. 10 (2021) e2001570, https://doi.org/10.1002/adhm.202001570.
[390] S.M. Shahen, M.R. Mohamed, M.R.K. Ali, R.M. Samaka, G.M. Hamdy, R.M. Talaat, Therapeutic potential of targeted-gold nanospheres on collagen-induced arthritis in rats, Clin. Exp. Pharmacol. Physiol. 48 (2021) 1346–1357, https://doi.org/10.1111/1440-1681.13531.
[391] A. Gul, B. Kunwar, M. Mazhar, S. Faizi, D. Ahmed, M.R. Shah, S.U. Simjee, Rutin and rutin-conjugated gold nanoparticles ameliorate collagen-induced arthritis in rats through inhibition of NF-κB and iNOS activation, Int. Immunopharmacol. 59 (2018) 310–317, https://doi.org/10.1016/j.intimp.2018.04.017.
[392] Y. Lu, Z. Li, L. Li, J. Chen, X. Xu, Z. Lin, T. Zhang, Y. Zhu, C. Ding, C. Mao, Highly effective rheumatoid arthritis therapy by peptide-promoted nanomodification of mesenchymal stem cells, Biomaterials 283 (2022) 121474, https://doi.org/10.1016/j.biomaterials.2022.121474.
[393] R. Huang, C. Zhang, Y. Bu, Z. Li, X. Zheng, S. Qiu, J.O. Machuki, L. Zhang, Y. Yang, K. Guo, F. Gao, A multifunctional nano-therapeutic platform based on octahedral yolk-shell Au NR@CuS: photothermal/photodynamic and targeted drug delivery tri-combined therapy for rheumatoid arthritis, Biomaterials 277 (2021) 121088, https://doi.org/10.1016/j.biomaterials.2021.121088.
[394] M. Hosseini, M. Mozafari, Cerium oxide nanoparticles: recent advances in tissue engineering, Mater. Basel Switz 13 (2020) 3072, https://doi.org/10.3390/ma13143072.
[395] J. Kim, H.Y. Kim, S.Y. Song, S.-H. Go, H.S. Sohn, S. Baik, M. Soh, K. Kim, D. Kim, H.-C. Kim, N. Lee, B.-S. Kim, T. Hyeon, Synergistic oxygen generation and reactive oxygen species scavenging by manganese ferrite/ceria Co-decorated nanoparticles for rheumatoid arthritis treatment, ACS Nano 13 (2019) 3206–3217, https://doi.org/10.1021/acsnano.8b08785.
[396] Y. Wu, Y. Yang, W. Zhao, Z.P. Xu, P.J. Little, A.K. Whittaker, R. Zhang, H.T. Ta, Novel iron oxide–cerium oxide core–shell nanoparticles as a potential theranostic material for ROS related inflammatory diseases, J. Mater. Chem. B 6 (2018) 4937–4951, https://doi.org/10.1039/C8TB00022K.
[397] M.M. Ansari, A. Ahmad, R.K. Mishra, S.S. Raza, R. Khan, Zinc gluconate-loaded chitosan nanoparticles reduce severity of collagen-induced arthritis in wistar rats, ACS Biomater. Sci. Eng. 5 (2019) 3380–3397, https://doi.org/10.1021/acsbiomaterials.9b00427.
[398] H. Qiao, J. Mei, K. Yuan, K. Zhang, F. Zhou, T. Tang, J. Zhao, Immune-regulating strategy against rheumatoid arthritis by inducing tolerogenic dendritic cells with modified zinc peroxide nanoparticles, J. Nanobiotechnology 20 (2022) 323, https://doi.org/10.1186/s12951-022-01536-0.
[399] S.S. Gad, A.M. Fayez, M. Abdelaziz, D. Abou El-Ezz, Amelioration of autoimmunity and inflammation by zinc oxide nanoparticles in experimental rheumatoid arthritis, Naunyn-Schmiedebergs Arch Pharmacol 394 (2021) 1975–1981, https://doi.org/10.1007/s00210-021-02105-2.
[400] S. Muhammad, A. Ali, S. Zahoor, X. Xinghua, M. Hamza, M. Kashif, S. Khan, B.K. A. Khel, A. Iqbal, Synthesis of Silver Oxide Nanoparticles and its Antimicrobial, Anticancer, Anti-inflammatory, Wound Heal, 2023.
[401] Y. Yang, L. Guo, Z. Wang, P. Liu, X. Liu, J. Ding, W. Zhou, Targeted silver nanoparticles for rheumatoid arthritis therapy via macrophage apoptosis and Re-polarization, Biomaterials 264 (2021) 120390, https://doi.org/10.1016/j.biomaterials.2020.120390.
[402] H. Liu, H. Lv, X. Duan, Y. Du, Y. Tang, W. Xu, Advancements in macrophage-targeted drug delivery for effective disease management, Int. J. Nanomedicine 18 (2023) 6915–6940, https://doi.org/10.2147/IJN.S430877.
[403] K. Rao, T. Roome, S. Aziz, A. Razzak, G. Abbas, M. Imran, T. Jabri, J. Gul, M. Hussain, B. Sikandar, S. Sharafat, M.R. Shah, Bergenin loaded gum xanthan stabilized silver nanoparticles suppress synovial inflammation through modulation of the immune response and oxidative stress in adjuvant induced arthritic rats, J. Mater. Chem. B 6 (2018) 4486–4501, https://doi.org/10.1039/C8TB00672E.
[404] K. Rao, S. Aziz, T. Roome, A. Razzak, B. Sikandar, K.S. Jamali, M. Imran, T. Jabri, M.R. Shah, Gum acacia stabilized silver nanoparticles based nano-cargo for enhanced anti-arthritic potentials of hesperidin in adjuvant induced arthritic rats, Artif, Cells Nanomedicine Biotechnol. 46 (2018) 597–607, https://doi.org/10.1080/21691401.2018.1431653.
[405] S. Nasra, D. Bhatia, A. Kumar, Recent advances in nanoparticle-based drug delivery systems for rheumatoid arthritis treatment, Nanoscale Adv. 4 (2022) 3479–3494, https://doi.org/10.1039/d2na00229a.
[406] M. Zheng, H. Jia, H. Wang, L. Liu, Z. He, Z. Zhang, W. Yang, L. Gao, X. Gao, F. Gao, Application of nanomaterials in the treatment of rheumatoid arthritis, RSC Adv. 11 (2021) 7129–7137, https://doi.org/10.1039/D1RA00328C.
[407] D. Shi, B. Karmakar, H.-E. Hussein Osman, A.F. El-kott, K. Morsy, M.M. Abdel-Daim, Design and synthesis of chitosan/agar/Ag NPs: a potent and green bio-nanocomposite for the treatment of glucocorticoid induced osteoporosis in rats, Arab. J. Chem. 15 (2022) 103471, https://doi.org/10.1016/j.arabjc.2021.103471.
[408] A.T. Qureshi, A. Doyle, C. Chen, D. Coulon, V. Dasa, F. Del Piero, B. Levi, W. T. Monroe, J.M. Gimble, D.J. Hayes, Photoactivated miR-148b-nanoparticle conjugates improve closure of critical size mouse calvarial defects, Acta Biomater. 12 (2015) 166–173, https://doi.org/10.1016/j.actbio.2014.10.010.
[409] Z. Zhou, F. Gong, P. Zhang, X. Wang, R. Zhang, W. Xia, X. Gao, X. Zhou, L. Cheng, Natural product curcumin-based coordination nanoparticles for treating osteoarthritis via targeting Nrf2 and blocking NLRP3 inflammasome, Nano Res. 15 (2022) 3338–3345, https://doi.org/10.1007/s12274-021-3864-3.
[410] Q. Chen, J. Li, F. Han, Q. Meng, H. Wang, Q. Wei, Z. Li, F. Li, E. Xie, X. Qin, S. Chen, W. Wang, C. Liu, B. Li, F. Han, A multifunctional composite hydrogel that rescues the ROS microenvironment and guides the immune response for repair of osteoporotic bone defects, Adv. Funct. Mater. 32 (2022) 2201067, https://doi.org/10.1002/adfm.202201067.
[411] W.-K. Ko, S.J. Kim, D.N. Heo, I.-B. Han, S. Kim, I.K. Kwon, S. Sohn, Double layers of gold nanoparticles immobilized titanium implants improve the osseointegration in rabbit models, Nanomedicine Nanotechnol. Biol. Med. 24 (2020) 102129, https://doi.org/10.1016/j.nano.2019.102129.
[412] Y. Wang, P. Yung, G. Lu, Y. Liu, C. Ding, C. Mao, Z.A. Li, R.S. Tuan, Musculoskeletal organs-on-chips: an emerging platform for studying the nanotechnology-biology interface, Adv. Mater. n/a (2024) 2401334, https://doi.org/10.1002/adma.202401334.
[413] X. Yuan, W. Zhu, Z. Yang, N. He, F. Chen, X. Han, K. Zhou, Recent advances in 3D printing of smart scaffolds for bone tissue engineering and regeneration, Adv. Mater. 36 (2024) 2403641, https://doi.org/10.1002/adma.202403641.
[414] M. Pan, R. Zhao, C. Fu, M. Tang, J. Zhou, B. Ma, J. Liu, Y. Yang, B. Chen, Q. Zhang, Y. Wang, Tuning nanoparticle core composition drives orthogonal fluorescence amplification for enhanced tumour imaging, Nat. Commun. 15 (2024) 7824, https://doi.org/10.1038/s41467-024-52029-7.
[415] Y. Wang, J. Guo, M. Chen, S. Liao, L. Xu, Q. Chen, G. Song, X.-B. Zhang, Ultrabright and ultrafast afterglow imaging in vivo via nanoparticles made of trianthracene derivatives, Nat. Biomed. Eng. (2024), https://doi.org/10.1038/s41551-024-01274-8.
[416] M.J. Mitchell, M.M. Billingsley, R.M. Haley, M.E. Wechsler, N.A. Peppas, R. Langer, Engineering precision nanoparticles for drug delivery, Nat. Rev. Drug Discov. 20 (2021) 101–124, https://doi.org/10.1038/s41573-020-0090-8.
[417] H. Zhou, Y. Guo, T. Fu, Y. Peng, Z. Chen, Y. Cui, M. Guo, K. Zhang, C. Chen, Y. Wang, Three-dimensional label-free observing of the self-assembled nanoparticles inside a single cell at nanoscale resolution, ACS Nano 18 (2024) 19802–19813, https://doi.org/10.1021/acsnano.4c06095.
[418] R. Cai, C. Chen, The crown and the scepter: roles of the protein corona in nanomedicine, Adv. Mater. 31 (2019) 1805740, https://doi.org/10.1002/adma.201805740.
[419] L.C. Adams, P. Jayapal, S.K. Ramasamy, W. Morakote, K. Yeom, L. Baratto, H. E. Daldrup-Link, Ferumoxytol-enhanced MRI in children and Young adults: state of the art, Am. J. Roentgenol. 220 (2023) 590–603, https://doi.org/10.2214/AJR.22.28453.
[420] R. Zhang, F. Kiessling, T. Lammers, R.M. Pallares, Clinical translation of gold nanoparticles, Drug Deliv. Transl. Res. 13 (2023) 378–385, https://doi.org/10.1007/s13346-022-01232-4.
[421] D. Sung, A. Sanchez, J.D. Tward, Successful salvage brachytherapy after infusion of gold AuroShell nanoshells for localized prostate cancer in a human patient, Adv. Radiat. Oncol. 8 (2023) 101202, https://doi.org/10.1016/j.adro.2023.101202.
[422] ISO/TS 19807-1:2019, ISO (n.d.). https://www.iso.org/standard/66237.html (accessed March 30, 2025).
[423] P. Joyce, C.J. Allen, M.J. Alonso, M. Ashford, M.S. Bradbury, M. Germain, M. Kavallaris, R. Langer, T. Lammers, M.T. Peracchia, A. Popat, C.A. Prestidge, C. J.F. Rijcken, B. Sarmento, R.B. Schmid, A. Schroeder, S. Subramaniam, C. R. Thorn, K.A. Whitehead, C.-X. Zhao, H.A. Santos, A translational framework to DELIVER nanomedicines to the clinic, Nat. Nanotechnol. (2024), https://doi.org/10.1038/s41565-024-01754-7.
[424] Protocols - nanotechnology characterization lab - NCI. https://www.cancer.gov/nano/research/ncl/protocols-capabilities, 2022. (Accessed 30 March 2025).
[425] L. Nuhn, Artificial intelligence assists nanoparticles to enter solid tumours, Nat. Nanotechnol. 18 (2023) 550–551, https://doi.org/10.1038/s41565-023-01382-7.
[426] H. Tao, T. Wu, M. Aldeghi, T.C. Wu, A. Aspuru-Guzik, E. Kumacheva, Nanoparticle synthesis assisted by machine learning, Nat. Rev. Mater. 6 (2021) 701–716, https://doi.org/10.1038/s41578-021-00337-5.