European Cells and Materials Vol.54 2025 (pages 91–114) DOI: 10.22203/eCM.v054a07 ISSN 1473-2262

Review

METAL-ORGANIC FRAMEWORKS (MOFS) FOR BONE TREATMENT AND MINERALIZATION

Hani Nasser Abdelhamid[1,*]

[1]Department of Chemistry, Faculty of Science, Imam Mohammad Ibn Saud Islamic University (IMSIU), 11623 Riyadh, Saudi Arabia

Abstract

Metal-organic frameworks (MOFs) have emerged as a flexible class of porous materials with tunable physicochemical properties, making them well-suited for biomedical applications, particularly bone regeneration and biomineralization. This review analyzes recent advances in MOF-based methodologies for bone tissue engineering, highlighting various MOFs, particularly biologically-based metal-organic frameworks (BioMOFs) and bioactive MOFs, and their roles in mimicking natural mineralization processes. MOFs can be applied as carriers for biomineralizing multiple biological targets, such as proteins, enzymes, bacterial cells, and viruses, enabling controlled encapsulation, protection, and functional delivery. Considerable focus is placed on the mechanisms by which MOFs promote osteogenesis and angiogenesis, including the pH-responsive or enzyme-activated release of osteoinductive ions such as calcium (Ca^{2+}), magnesium (Mg^{2+}), zinc (Zn^{2+}), and strontium (Sr^{2+}) from frameworks composed of alkaline-earth and transition-metal ions. MOF-based materials can be used to treat various bone disorders, including osteoporosis, osteomyelitis, bone malignancies, and diabetic bone anomalies, through several proposed mechanisms, including drug delivery, immunomodulation, antibacterial effects, and neovascularization promotion. Integrating MOFs with hydrogels, electrospun membranes, and functionalized three-dimensional (3D) scaffolds yields synergistic effects that enhance bone tissue regeneration. Challenges were discussed, including biocompatibility, biodegradability, and ion toxicity. Hopefully, this review provides insights into prospective methodologies for the systematic design of multifunctional MOF platforms for clinical use in orthopedic and regenerative medicine.

Keywords: MOFs, mineralization, bioMOF, bone treatment.

***Address for correspondence**: H. N. Abdelhamid, Department of Chemistry, Faculty of Science, Imam Mohammad Ibn Saud Islamic University (IMSIU), 11623 Riyadh, Saudi Arabia. Email: hnabdelhamid@imamu.edu.sa.

Introduction

Bone disorders encompass many conditions that affect the skeletal system's integrity, architecture, and function [1,2]. These problems may arise from genetic predispositions, metabolic irregularities, infections, aging, or trauma, frequently resulting in compromised bone formation, excessive bone resorption, or structural degradation [3–5]. Prevalent bone disorders encompass osteoporosis (OP), osteopenia, osteomalacia, Paget's disease, and osteogenesis imperfecta. Osteoporosis is the most common bone condition, defined by reduced bone mineral density and heightened fracture risk, especially in the elderly and postmenopausal women [6]. Osteopenia is a precursor to osteoporosis, characterized by subnormal bone density. Osteomalacia, vitamin D insufficiency, causes bone weakening due to impaired mineralization. Paget's disease of bone entails aberrant bone remodeling, causing enlarged and deformed bones, whereas osteogenesis imperfecta is a genetic illness that impairs collagen (Col) synthesis, resulting in fragile bones and recurrent fractures [7]. These illnesses undermine skeletal integrity, decreasing mobility and quality of life [8]. With increasing global life expectancy, the incidence of bone-related diseases is rising, underscoring the need for enhanced diagnostic techniques and novel therapeutic approaches, such as biomaterials and targeted drug-delivery systems for bone regeneration and repair [9–12].

Osteoporosis (OP) is a significant global health issue, accounting for more than 50 % of all instances of tissue loss due to disease or injury [9]. If untreated, it can lead to significant deterioration of the musculoskeletal system, significantly decreasing a patient's quality of life [13]. The World Health Organization (WHO) estimates the global prevalence of OP at 19.7 %, whereas osteopenia affects roughly 40.4 % of the population [14,15]. These conditions are more prevalent in low-income countries, with rates of 22.1 %, compared with 14.5 % in industrialized countries. Gender-specific statistics reveal that 10.6 % of males are affected by osteoporosis, while 44.8 % exhibit osteopenia.

The prevalence among women is significant: 24.8 % have osteoporosis, and 39.4 % have bone loss. The prevalence is particularly high among postmenopausal women, with 27.4 % diagnosed with osteoporosis and 42.1 % suffering from osteopenia.

Metal-organic frameworks (MOFs), also referred to as porous coordination polymers (PCPs) or porous coordination networks (PCNs), are a class of hybrid porous materials characterized by their exceptionally high surface areas and tunable pore sizes [16–19]. Owing to these structural features, MOFs have found widespread applications in various fields, including adsorption [20,21], sensing [22,23], self-cleaning textiles [24], and catalysis [25]. MOFs exhibit enzyme-like activity [26], making them particularly attractive for biomedical applications [27]. When integrated with biological molecules, MOFs form metal-biomolecule frameworks (MBioFs) [28]. Various MOF-biological composites have been developed using proteins, viruses, bacteria, and yeast cells [29–32]. One prominent application of these composites is the encapsulation of enzymes within MOFs, which has enabled technologies such as single-enzyme biofuel cells used in self-powered biosensing platforms [33]. MOFs can be biodegradable, enabling safe, biocompatible use in biomedical applications [34–36].

Zeolitic imidazolate frameworks (ZIFs) represent a distinct subclass of MOFs known for their exceptional thermal and chemical stability [37]. Among them, ZIF-8 is one of the most extensively studied. Composed of zinc (Zn) ions and 2-methylimidazole (HmIm) linkers, ZIF-8 exhibits a robust framework structure. This material has been applied in diverse areas, including drug delivery [38], gene delivery [39], hydrogen generation [40], dye-sensitized solar cells [41], carbon dioxide capture [42], and biosensing [43]. Its three-dimensional (3D) structure and pH-responsive degradability make ZIF-8 particularly suitable for biomedical applications, including controlled, on-demand drug release [44]. In addition, ZIF-8-based composite microcarriers have shown potential to support the adhesion and proliferation of human mesenchymal stem cells (hMSCs) [45]. *In vivo* studies have validated the adaptability and efficacy of MOF in facilitating bone regeneration, addressing infections, targeting bone cancers, and mitigating osteoporosis [46].

This review highlighted advances in MOF research and their biomacromolecular composites for therapeutic applications in osteoporosis (Fig. 1). It covered several types of MOFs, including calcium (Ca)-MOF, magnesium (Mg)-MOF, zinc (Zn)-based MOF, zirconium (Zr)-MOF, and their bimetallic MOFs. It outlined the mechanisms of osteoporosis, various synthesis methods for MOFs and MOF-based composites, and ultimately discusses the primary challenges and future directions to enhance the utility of MOFs in osteoporosis treatment. It also addressed the interface between biomolecules and MOF, emphasizing strategies for synthesizing biomolecule-ZIF-8 biocomposites and processing them into different forms, such as hydrogels, 3D scaffolds, or injectable inks via electrospinning, 3D printing, and other methods (Fig. 1).

Analysis Publications in MOFs for Biomedical Application

Examining the Scopus database using the query TITLE-ABS-KEY (MOFs AND mineralization OR bone) highlights the growing academic interest in MOFs in bone biology and mineralization (Fig. 2). Since the inaugural publication in 1996, the volume of related articles has been sparse, with only a few studies emerging between 1996 and 2015. The tendency began to change in 2016, marked by a steady increase in annual production. This trend signifies growing interest in the biological applications of MOFs, especially in bone tissue engineering, biomineralization, and osteogenic therapy. The rise in publications over the last four years likely signifies advancements in nanotechnology, biomaterials research, and MOF-based drug delivery systems, making MOFs increasingly relevant in regenerative medicine.

The research is distinguished by its interdisciplinary nature, encompassing contributions from various scientific fields (Fig. 2). The predominant proportion of articles is in Materials Science (17.1 %), followed by Chemistry (15.9 %), Chemical Engineering (14.8 %), and Engineering (13.5 %). These figures significantly focus on the material design, synthesis, and modification of MOFs for biological applications. Moreover, Environmental Science (10.4 %) is notably significant, indicating potential interdisciplinary insights, perhaps in biomimetic or sustainable material innovation. Biomedical fields are prominently represented, with Biochemistry, Genetics, Molecular Biology, and Medicine each accounting for 8.5 % of the total literature. Including Pharmacology and Pharmaceutics (2.5 %) emphasizes the interest in MOFs for drug transport and therapeutic targeting in bone settings. Disciplines such as Physics, Agricultural Sciences, and Computer Science are present, though to a lesser extent, indicating a varied research foundation (Fig. 2). The Scopus data demonstrate that MOF-related research on mineralization and bone is experiencing tremendous growth and interdisciplinary expansion (Fig. 2). Integrating new material synthesis, biomedical applications, and regenerative potential establishes MOFs as a promising frontier in bone healing, drug delivery, and tissue engineering. This interdisciplinary momentum is expected to continue, with future studies likely to explore clinical applications, biofunctionality, and long-term safety of MOF-based systems in bone-related therapies.

Biomedical Applications of MOFs

Recent progress in MOFs has led to their growing use in bone tissue engineering, owing to their adjustable structures, biocompatibility, and ability to deliver drugs in a controlled manner. Xue *et al.* [47] revealed that MOFs can

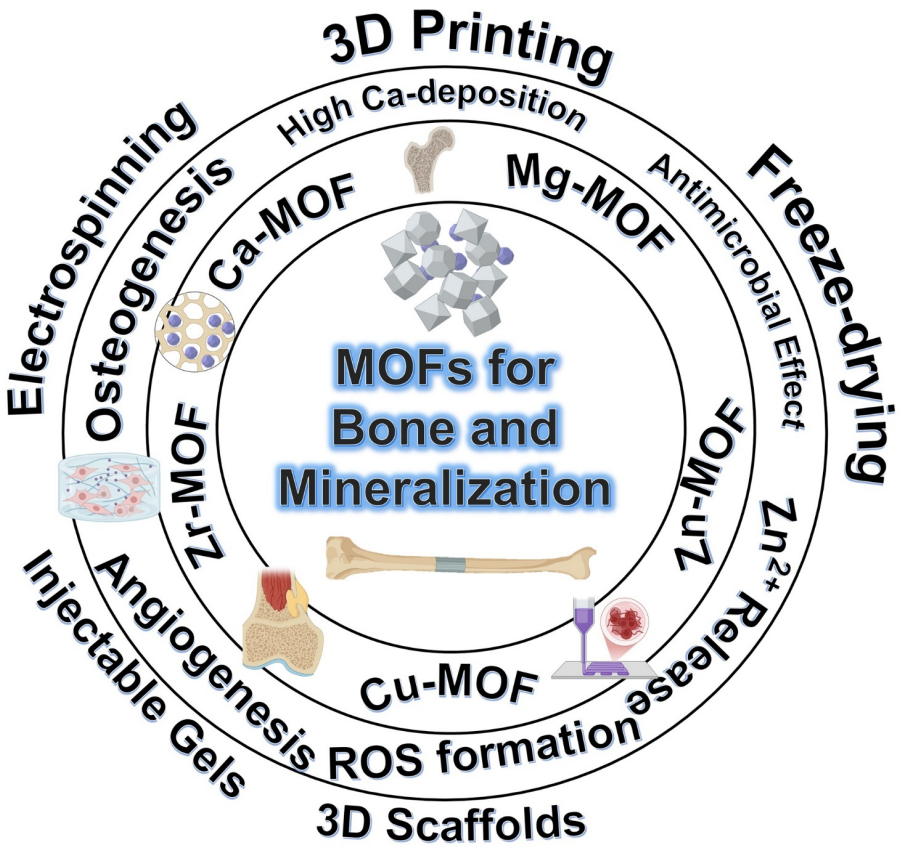

Fig. 1. Overview of MOF-based bone and mineralization applications.

attract bone marrow mesenchymal stem cells (BMSCs) via pH-responsive release of Zn^{2+}, thereby creating a favorable microenvironment for osteoblast development and facilitating bone and vascular regeneration. Toprak *et al.* [48] contained bone morphogenetic protein-6 (BMP-6) within ZIF-8, resulting in a prolonged release profile that markedly improved bone regeneration. Feng *et al.* [49] encapsulated microRNAs in ZIF-8 to enhance their stability, cellular uptake, and endosomal escape, thereby advancing the therapeutic applications of MOFs in osteogenesis and angiogenesis. Li *et al.* [50] encapsulated ZIF-8 with deferoxamine (DFO), demonstrating that the regulated release of DFO and Zn^{2+} markedly enhances angiogenic and osteogenic activity. Kang *et al.* [51] created exosome-functionalized magnesium-organic frameworks that synergistically integrate the osteogenic and anti-inflammatory properties of magnesium ions, gallic acid (GA), and exosomes derived from human adipose stem cells, enhancing scaffold functionality and biocompatibility. MOFs improved the osteogenic microenvironment [52].

Lao *et al.* [53] developed metformin-loaded ZIF-8 nanoparticles (NPs) incorporated into methacrylated gelatin (Gel) hydrogels for diabetic bone regeneration models. The simultaneous release of metformin and Zn^{2+} from this composite interrupted the reactive oxygen species (ROS)-inflammation cycle and facilitated bone repair. Similarly, Al-Baadani *et al.* [54] integrated alendronate (ALN)-loaded ZIF-8 into electrospun nanofibers, resulting in an innovative composite that promotes bone regeneration and suppresses osteoclast activity, presenting a viable strategy for addressing osteoporotic abnormalities. ZIF-8 nanoparticles are doped with cerium (Ce) ions, loaded with alendronate sodium, and coated with poly(sodium 4-styrenesulfonate) to form Aln/PSS@ZIF-8:Ce for osteoporosis treatment [55]. The nanoparticles can be uniformly distributed and remain stable at pH 7.4, gradually releasing Aln and Ce ions at pH 6.8, thereby potentially offering antioxidative action in oxidative stress microenvironments. The *in vitro* study demonstrates that the nanoparticles can enhance osteogenic differentiation and biomineralization while limiting osteoclast formation and bone resorption via suppressing reactive oxygen species generation, mitogen-activated protein kinase, and nuclear factor κ-B signaling pathways. Following intravenous administration in osteoporotic mice, the Aln/PSS@ZIF-8:Ce nanoparticles, owing to their nanoscale characteristics, decreased bone loss and retard the progression of osteoporosis. Furthermore, the nanoparticles demonstrated excellent cytocompatibility *in vitro* and favorable histocompatibility *in vivo*, exhibiting no adverse reactions. Aln/PSS@ZIF-8:Ce nanoparticles were effective biomaterials for normalizing osteoporotic microenvironments and postponing the pro-

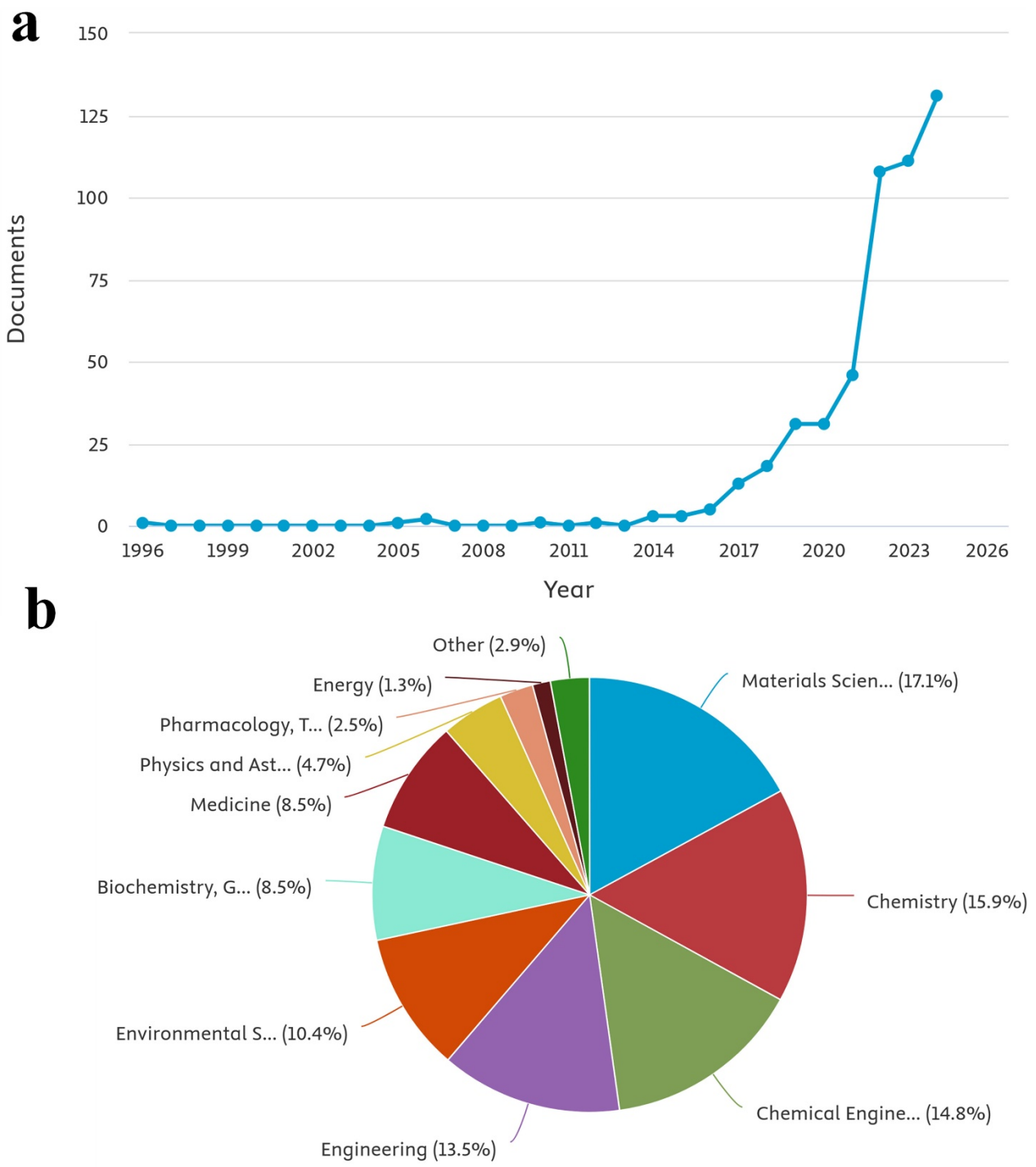

Fig. 2. Scopus analysis. (**a**) Publications per year. (**b**) Files for words "MOFs AND mineralization or Bone". Access July 2025. Query: TITLE-ABS-KEY(MOFs + mineralization or bone); https://www.scopus.com/pages/home#basic.

gression of osteoporosis, while also indicating potential applications in other inflammation-related disorders [55].

Numerous studies underscore the synergistic interactions between MOFs and bioactive substances. Xu *et al.* [56] demonstrated that integrating exosomes with MOF-modified scaffolds enables dual release of copper (Cu) ions and exosomes, thereby promoting angiogenesis and osteogenesis. They produced MOF composites by incorporating dimethyloxalylglycine (DMOG) into materials institute of lavoisier (MIL)-88 and amalgamating it with γ-poly-l-glutamic acid (PLGA), thereby promoting vascularized bone regeneration through the sustained release of DMOG and Fe^{3+} ions [57]. Zheng *et al.* [58] used Mg-MOF scaffolds to modulate macrophage polarization and enhance the bone-healing microenvironment, thereby promoting angiogenesis and osteogenesis. Mg-MOF74 exhibited enhanced

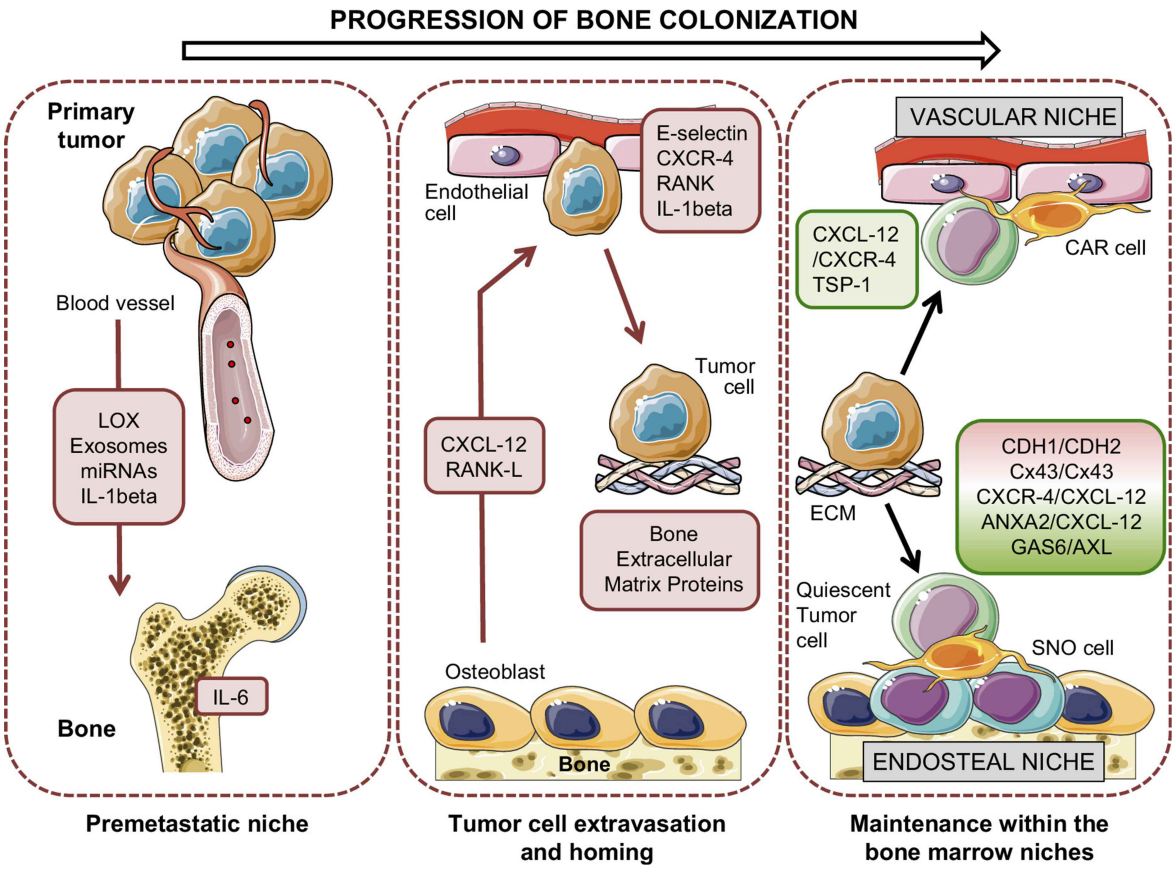

Fig. 3. Schematic representation of the stepwise process of bone colonization by tumor cells. Physiol Rev. 2021; 101: 797–855 [90]. Copyright © 2021, The American Physiological Society.

biological interactions and prolonged magnesium release, facilitating bone and blood vessel growth [59]. A multifunctional medication (Ket@Mg-MOF-74) utilizes Mg-MOF-74 to encapsulate ketoprofen (Ket) to comprehensively treat osteoporotic pain, bone loss, and inflammation [60]. Mg-MOF-74 was synthesized, and physicochemical analysis demonstrated its superior physical and chemical stability. Ket@Mg-MOF-74 was synthesized via post-synthetic modification, confirming a high loading capacity for ketoprofen. Experiments on drug and ion release demonstrated that Ket@Mg-MOF-74 exhibited effective regulated release of ketoprofen and magnesium in solution. *In vitro* cell tests showed that the compound medication significantly diminished the expression of pain-related genes associated with cyclooxygenase 2 (COX2), markedly enhanced the expression of osteogenic cytokines, and substantially reduced the secretion of pro-inflammatory substances. Consequently, Ket@Mg-MOF-74 is regarded as a promising analgesic for osteoporotic bone pain, possessing anti-inflammatory properties and the ability to promote bone growth [60].

Reports have also emerged regarding innovative hydrogel-based MOF platforms. Sun *et al.* [61] created a MOF-infused hydrogel for bone healing that simulates hypoxic conditions by cobalt (Co) ion release, promoting vascular and bone tissue development. ZIF-8-modified hydrogel improved bone adhesion, mechanical strength, angiogenesis, and osteogenesis, while providing antibacterial qualities to mitigate postoperative infection risks [62]. pH-responsive MOF hydrogels selectively released biomolecules in acidic conditions, thereby modulating inflammation and facilitating bone regeneration and vascularization [63].

Biologically-Based MOFs (BioMOFs)

Biologically-based MOFs (BioMOFs), or metal-biomolecule frameworks (MBioFs), constitute a subclass of MOFs that incorporate biomolecules such as nucleobases, amino acids, peptides, proteins, cyclodextrins (CDs), and porphyrins into their structures [28,64]. They provide significant biological compatibility and expand their prospective applications in biology, medicine, and materials science [36,65,66]. Nucleobases like adenine exhibit superior solubility and coordination properties compared to guanine, offering significant promise for the development of BioMOFs. BioMOF, such as ZnBDCA, contains zinc and a mixed linker of adenine and benzene-1,3-dicarboxylate, exhibits a DNA-helix-like topology, and demonstrates its capability for biomolecular detection [67]. Amino acid-derived BioMOFs can be constructed through combina-

tions with chemical ligands. $Zn_4(5\text{-mtz})_6(L\text{-Ala})_2 \cdot 2DMF$ was synthesized using amino acids such as l-alanine (l-Ala), d-alanine (d-Ala), l-serine (l-Ser), and l-valine (l-Val) in conjunction with the 5-methyltetrazole (5-Hmtz) ligand [68]. Peptides, especially short chains like dipeptides and tripeptides, form diverse and dynamic metal-peptide frameworks (MPF) [69]. Creating protein-based BioMOFs, specifically protein crystalline frameworks (PCFs), is more complex due to proteins' complexity [70]. Porphyrins and metalloporphyrins, particularly TCPP (meso-tetra(4-carboxyphenyl)porphine (H_4TCPP)), OCPP (5,10,15,20-tetrakis(3,5-biscarboxylphenyl)porphyrin), and 5,10,15,20-tetrakis(3,5-dicarboxyphenyl)porphine [71], have been shown as linkers for the manufacture of BioMOFs [72]. Cyclodextrin (CD)-based BioMOFs utilize the hydrophobic cavities of cyclic glucose molecules to encapsulate guest molecules [73,74].

A diverse array of BioMOFs has been engineered by integrating biomolecules and auxiliary ligands to fulfill specific applications in drug administration, molecular recognition, catalysis, and chiral separation. For example, other adenine-based BioMOFs, such as ZnBTCA [75,76] and BioMOF-100 [77]. Meanwhile, PCN-530, which utilizes a triazine-based auxiliary ligand, has also been used for molecular recognition [78]. Amino acid-derived BioMOFs such as $Zn_4(5\text{-mtz})_6(L\text{-Ala})_2 \cdot 2DMF$ and its variants incorporating d-alanine, l-serine, and l-valine have been synthesized with tetrazolate co-ligands for molecular recognition and enantiomer separation [68]. Furthermore, peptide-based BioMOFs, such as CuII(GHG) derived from the tripeptide Gly-l-His-Gly, have been employed for chiral drug separation [79]. Protein-integrated BioMOFs, such as Zn-ferritin, using ferritin and benzenehydroxamic acid derivatives as ligands, function catalytically, particularly in enzymatic processes [80]. Porphyrin-based BioMOFs, such as $[Zn_{16}(H_2O)_8(Mn^{III}Cl\text{-OCPP})_4]$ and CZJ-6, derived from biscarboxylphenyl and dicarboxyphenyl porphyrins, respectively, demonstrate efficacy in olefin epoxidation and biomimetic catalysis [71]. Other BioMOFs, including MOF-1201 and MOF-1203, constructed from l-lactate and acetate, have been utilized in food safety detection [81]. In contrast, PCN-222, derived from zirconium and TCPP (meso-tetra(4-carboxyphenyl)porphyrin), serves as a photocatalyst for water treatment and as an electrochemical sensor [82]. γ-cyclodextrin MOF (γ-CD MOFs) exhibited the distinctive cavity architecture of γ-CD for the enantioselective separation of chiral aromatic alcohols [74]. These examples collectively demonstrate the many structural strategies and extensive functional range of BioMOF.

MOFs for Biomimetic Mineralization

ZIFs, a subclass of MOFs, can be synthesized using various methods tailored to suit different applications and conditions. Traditional solvothermal synthesis has been widely employed for fabricating ZIF-8 crystals [37], but more recent advances have introduced simpler, more environmentally friendly routes. One-pot synthesis at room temperature in aqueous media has gained popularity, as it eliminates the need for high temperatures, organic solvents, or multistep procedures. This approach is particularly advantageous for encapsulating thermally sensitive biomolecules such as proteins, viruses, and whole bacterial cells.

Several parameters influence the morphology and structural features of the resulting biocomposites, particularly the binding affinity between zinc ions and the biomolecule. For example, the tobacco mosaic virus (TMV), a tubular plant virus of 300 nm × 18 nm dimensions with a proteinaceous shell, can act as a multivalent scaffold to locally concentrate zinc ions, thereby accelerating mineralization and enabling precise morphology control [83]. DNA, primarily as a cross-linking agent, can further modulate ZIF-8 growth, for example, by enhancing crystal formation on magnetic particles [84]. Peptides and proteins serve as particularly effective biomineralization agents. For instance, γ-poly-L-glutamic acid (PLGA), a peptide-based polymer, has been used to transform conventional 3D microporous ZIF-8 structures into 2D mesoporous spindle-shaped MOFs (2D MSMOFs), facilitating specific structural control and enhancing the activity of encapsulated biomolecules [85]. These biocomposites also protect sensitive proteins, preserving their functionality under denaturing conditions and improving controlled release behavior, which is crucial for drug and gene delivery applications.

Protein-mediated ZIF-8 mineralization has been thoroughly studied to optimize encapsulation efficiency and functionality. Peptides and proteins with negative charges bind effectively to zinc ions, promoting nucleation and crystal formation through electrostatic interactions [86]. Conversely, positively charged peptides (with isoelectric point pI >7.5) lead to the formation of alternate crystal phases, such as the diamond phase dia-$Zn(HmIm)_2$ [86]. Studies report encapsulation efficiencies ranging from 75 % to nearly 100 % for proteins like bovine serum albumin (BSA) and insulin [87]. Further, ternary phase diagrams reveal that the synthesis process can yield five distinct ZIF-8-related crystal phases, including new phases such as ZIF-CO_3-1. Enzyme immobilization within ZIF-8 can follow either de novo synthesis or post-synthetic modification [88]. In de novo methods, enzymes are incorporated during crystal growth, offering superior confinement and protection. However, this can lead to lower encapsulation yields. Conversely, post-synthetic loading involves adsorbing enzymes into pre-formed ZIF-8 pores, which may limit structural integration but can increase loading capacity. The encapsulation approach can significantly affect the enzyme's bioactivity. For example, rapid enzyme-triggered nucleation methods outperformed slower co-precipitation methods, yielding more active biocatalysts [88]. Insulin was

Table 1. Summary of common bone diseases.

Bone disease	Definition	Primary causes	Key characteristics	Ref.
Paget's disease	A chronic bone disorder with abnormal bone remodeling	Genetic factors, viral infections	-Enlarged -Deformed bones -Bone pain -Joint stiffness	[7]
Osteoporosis	A condition characterized by decreased bone density and increased fracture risk	Aging, hormonal changes (e.g., menopause), calcium/vitamin D deficiency	-Fragile bones -High fracture risk	[94]
Osteopenia	A precursor to osteoporosis with lower-than-normal bone density	Same as OP, aging, poor nutrition	-Mild bone loss -Asymptomatic	[95]
Osteomalacia	Softening of bones due to defective bone mineralization	Vitamin D deficiency, phosphate deficiency	-Bone pain -Muscle weakness -High fracture risk	[96]
Osteogenesis imperfecta	A genetic disorder causing brittle bones	Genetic mutation affecting collagen production	-Frequent fractures -Short stature -Bone deformities	[97]
Osteomyelitis	Infection of the bone, often bacterial	Open fractures, surgery, bloodstream infections	-Bone pain -Fever -Inflammation -Pus formation	[98]
Bone tumors	Abnormal growth of bone tissue can be benign or malignant	Genetic mutations, radiation exposure	-Swelling -Localized pain - Pathological fractures	[99]
Rickets	A childhood disease involving bone softening	Severe vitamin D deficiency	-Bone deformities - Delayed growth - Bowed legs in children	[100]
Avascular necrosis	Bone tissue death due to loss of blood supply	Trauma, steroid use, alcohol abuse	-Joint pain -Limited mobility -Eventual bone collapse	[101]

also encapsulated in ZIF-8 particles, offering a promising therapeutic vehicle for diabetes management. At concentrations below 30 μg/mL, insulin@ZIF-8 has shown biocompatibility and sustained release profiles [89]. Similarly, six enzymes, e.g., glucose oxidase (GOx), catalase (CAT), horseradish peroxidase (HRP), cytochrome c (Cyt C), alcohol dehydrogenase (ADH), and urate oxidase (UOx), have been encapsulated into ZIF-8. The results showed that rapid nucleation methods preserved bioactivity, whereas slow co-precipitation led to inactive materials [88].

MOFs for Bone Therapy

Bone diseases encompass several conditions that affect bone integrity, architecture, and function (Table 1). Osteoporosis is a prevalent bone disease characterized by reduced bone density, increasing the risk of fractures, especially in the spine, hips, and wrists. It primarily arises from age, hormonal changes such as menopause, and calcium or vitamin D deficiencies. Osteopenia is a similar disorder characterized by a moderate decrease in bone mass and often serves as a precursor to osteoporosis. Although usually asymptomatic, it is frequently detected on bone density scans.

Osteomalacia denotes the softness of bones resulting from impaired bone mineralization, typically attributable to deficiencies in vitamin D or phosphate (Table 1). It results in ostealgia, myopathy, and an increased susceptibility to fractures. Paget's disease, another chronic disorder, is characterized by aberrant bone remodeling, leading to larger, deformed bones. This ailment may be associated with ge-

netic predispositions or viral infections and frequently manifests as bone pain and joint rigidity. Osteogenesis imperfecta is an uncommon hereditary condition that impairs collagen synthesis, leading to fragile bones prone to fractures. Patients may further have reduced height, bone abnormalities, and auditory impairment. Osteomyelitis is an infectious bone disease caused mainly by bacteria that enter through open fractures, surgical interventions, or the circulation. It is generally associated with osseous discomfort, pyrexia, inflammation, and, in some cases, purulence.

Bone tumors, whether benign or malignant, originate from atypical proliferation of bone tissue (Fig. 3) [90]. Causes encompass genetic abnormalities and radiation exposure, while symptoms frequently manifest as localized discomfort, edema, or pathological fractures. Rickets in children is characterized by bone weakening and abnormalities, such as bowed legs, primarily due to severe vitamin D deficiency. Avascular necrosis is a disorder characterized by the death of bone tissue resulting from a deficiency in blood flow, which may be caused by trauma, corticosteroid usage, or excessive alcohol intake [90]. This results in arthralgia, diminished mobility, and ultimately skeletal collapse if not addressed.

Orthopedic research is essential for enhancing musculoskeletal health and formulating therapeutic approaches for various bone-related conditions, improving patient quality of life [91]. Nonetheless, there exists an urgent need for creative strategies to tackle intricate clinical issues, including significant bone abnormalities, joint inflammation, bone infections, and harm caused by bone cancers [90]. Traditional materials used in orthopedic procedures often exhibit inherent limitations, including inadequate bioactivity, low mechanical strength, and limited integration with host tissue. These deficiencies have generated heightened interest in developing sophisticated biomaterials to overcome them.

As the population ages, OP is increasingly prevalent, significantly impacting patients' quality of life and their families, making the prevention and treatment of osteoporosis a prominent issue [92,93]. The prevailing conventional approach to treating osteoporosis involves oral anti-osteoporosis medicine, which has limitations, including first-pass metabolism and gastrointestinal side effects. Simultaneously, OP may lead to microbial infections and necessitate promoting angiogenesis for bone repair, among other requirements that are frequently unmet by traditional therapies, with the potential for resistance to oral antibiotics [92,93].

MOFs have advanced bone therapy (Table 2) [46,93,102]. They have attracted significant interest in OP treatment owing to their distinctive characteristics, including adjustable porosity, large surface area, and the ability to encapsulate and release therapeutic chemicals and bioactive ions. Zn-based MOFs, e.g., ZIF-8, exhibited remarkable biocompatibility and efficacy in bone tissue engineering [103]. A significant application entails ZIF-8-modified porous titanium (Ti) surfaces that enhance osteogenesis and exhibit antibacterial properties via prolonged zinc ion release [104]. A separate study developed simvastatin-loaded ZIF-8 nanocapsules (about 238 nm in diameter, with an encapsulation efficiency of 87.4 %) for targeted administration to bone tissue, markedly improving drug solubility and bioavailability while promoting bone regeneration [105].

Iron-based MOF, such as MIL-100(Fe), was modified with poly(acrylic acid) (PAA)-grafted MIL-100(Fe) as a carrier for magnesium ions, facilitating sustained Mg^{2+} administration to aid in the repair of osteoporotic bone defects [106]. Magnesium (Mg) ions were encapsulated into the cages of MIL-100(Fe) (i.e., Mg@MIL-100(Fe)). The modification of Mg@MIL-100(Fe) with poly(acrylic acid) (PAA) effectively inhibited the leakage of Mg ions, thereby substantially enhancing the Mg loading capacity. The cytotoxicity assessment of the osteoblast-like cell line MG-63 indicated that Mg@MIL-100(Fe)-PAA exhibited biocompatibility and marginally enhanced cell growth. Moreover, the alkaline phosphatase (ALP) assay indicated that Mg@MIL-100(Fe)-PAA might alter the temporal progression of cell differentiation, potentially expediting bone healing. The findings demonstrated the potential of MOFs for bone healing [106].

Alkaline Earth-Based MOFs

Alkaline earth-based MOFs are effective biomaterials for several applications [112–114]. Alkaline earth MOFs, comprising divalent metal ions such as magnesium (Mg^{2+}), calcium (Ca^{2+}), strontium (Sr^{2+}), and barium (Ba^{2+}), have attracted increasing attention for biomedical applications owing to their biocompatibility, tunable porosity, and degradability. In contrast to numerous transition-metal-based MOFs, alkaline-earth MOFs offer reduced toxicity and greater physiological relevance, especially for calcium and magnesium, which are vital components of human biology [113]. These MOFs exhibit significant potential for drug delivery, as their extensive surface area and tunable pore environments facilitate the encapsulation and controlled release of therapeutic compounds, often in response to specific stimuli, such as pH or enzyme activity [115]. For example, Ca-MOFs and Mg-MOFs have been investigated for pH-responsive delivery of chemotherapeutics such as doxorubicin (DOX), facilitating targeted action in tumor microenvironments. Furthermore, Sr-based MOFs have exhibited efficacy in bone regeneration by facilitating osteogenesis and acting as localized drug transporters. In tissue engineering, Ca-MOFs and Sr-MOFs are essential scaffolds or ion-releasing platforms that facilitate bone cell proliferation and mineralization [116]. Alkaline-based MOFs are being investigated for bioimaging applications, in which their structures can integrate fluorescent or contrast agents, and for antimicrobial therapy via the transport

Table 2. MOFs-based materials for bone treatment.

MOFs	Compositions	Synthesis procedure	Conditions	Tests	Cells	Assessment	Ref.
ZIF-8	Zn Hmim Polycaprolactone/ collagen (PCL/Col)	Hydrothermal	37 °C for 6 h	Bone regeneration Osteogenic differentiation Blood vessel formation	L929 fibroblasts	93 % of Zn^{2+} release at pH 5.5. Cell proliferation of 1.2-fold over that in the Col group	[47]
Ket@Mg-MOF-74	Mg 2,5-dihydroxyterephthalic acid Ketoprofen	Hydrothermal	120 °C for 24h	Mg release Viability Quantitative real-time PCR (qPCR)	MG63 cells		[60]
ZIF-8	Zn Hmim	Hydrothermal	Stirred at RT overnight	Osteogenic activity and antibacterial effect Viability	MG63 human osteosarcoma cell line	Drug loading, 20.95 %	[104]
Mg-loaded MIL-100(Fe) with poly(acrylic acid)	Fe BTC PAA	Solvothermal	30 °C for 5 min 30 s	Mg release MTT ALP assay	Human osteosarcoma cells MG-63	Mg release of 84.7 % and 87.0 % at 96 h and 192 h	[106]
Ca-MOF	Ca Glycyrrhizic acid	Stirring	Stirring till precipitation	Immunofluorescent staining Micro-CT analysis	293T/D cells 293T and HKC-8 cells	EE and LE of hydrocortisone load on GC are 96.7 % and 38.7 % Viability 100 %	[107]
Mg-MOF	Mg Biphenyl-3,4′,5-tricarboxylate Denosumab (DSB)	Ultrasonication	20-min ultra-sonication at irradiation power of 450 W	Releasing Mg ions for bone formation MTT assay	MG63 cells	DSB release of 72 %, 8 h	[108]
MgCu-MOF74	Mg Cu Ketoprofen	Solvothermal	125 °C for 24 h	Cell counting kit-8 (CCK-8) assay Alkaline phosphatase (ALP) activity COL secretion	SaOS-2 human osteosarcoma cells	Ketoprofen loading, 18.55 % Viability >90 %	[109]
ZIF-8@RAPA	Zn Hmim RAPA	Hydrothermal	Stirring at room temperature for 5 min, and static standing for 55 min	Macrophage RAW 264.7 and the zebrafish embryo	Macrophage RAW 264.7 and the zebrafish embryo	Drug-loading rate 11.53 % Release of 68.23 % at pH 5.5 RAW264.7 cell survival rate of 95.3 % Zebrafish survival rates, 80 %	[110]
MOF 801/gelatin	$ZrCl_4$ Formic acid Fumaric acid	Hydrothermal	120 °C for 24 h	Antioxidant and anti-inflammatory properties, MTT crystal violet assay, alizarin red, and ALP activity assays induce calcium mineralization and alkaline phosphatase enzyme production	Osteoblast-like cells (MG-63)	Zr release, 0.45 mg/L after 24h	[111]

EE, encapsulation efficiency; LE,loading efficiency.

European Cells and Materials Vol.54 2025 (pages 91–114) DOI: 10.22203/eCM.v054a07

Table 3. Mechanism proposed for bone and mineralization using MOF-based materials.

Mechanism	MOF role/action	Therapeutic effect	Ref.
Angiogenesis	Cu^{2+}, Co^{2+}, Zn^{2+} induce VEGF expression	Enhances vascularized bone regeneration	[56]
Immunomodulation	Macrophage polarization	Reduces inflammation, promotes regeneration	[58]
Antibacterial effects	Metal ion release disrupts bacteria	Prevents infection (e.g., osteomyelitis)	[60]
Drug/gene delivery	Encapsulation & controlled release; pH/ROS/ enzyme-triggered systems	Sustained local therapy, targeted delivery	[115]
Osteogenesis	Release of Ca^{2+}, Mg^{2+}, Zn^{2+}, Sr^{2+}, Cu^{2+}; activation of BMP/Smad, Wnt/β-catenin, MAPK	Stimulates osteoblast differentiation & bone formation	[118]
Antioxidant activity	Catalase, i.e., ROS breakdown; ROS scavenging	Protects osteoblasts, maintains redox balance	[118]

of antibacterial chemicals or the inherent antimicrobial activity of the metal ions.

Substantial advancements have been achieved in Mg-based MOFs concerning multifunctional systems. For instance, Mg-MOF-7 achieved a drug loading capacity above 20 wt % with ketoprofen, enabling concurrent management of osteoporotic pain and bone regeneration via Mg^{2+} release [60]. Denosumab-loaded magnesium MOF nanocomposites (250 nm) were engineered to address osteoporosis by delivering immunotherapy and facilitating structural restoration, enabled by the synergistic action of denosumab and magnesium ions [108]. An alternative method involved incorporating Mg-MOFs with alendronate into bisphosphonate-functionalized gel scaffolds (200 nm) to facilitate dual release and promote bone repair [117]. Utilized multifunctional magnesium (Mg) and cerium (Ce) ion-based MOFs via a hydrothermal method to fabricate a three-dimensional (3D) bioprinted scaffold, aimed at efficiently scavenging ROS and sustainably releasing Mg^{2+} to enhance skeletal muscle engineering (SME) and repair age-related bone defects [118]. Under oxidative stress, the scaffolds inhibited senescence of loaded BMSCs and facilitated M2 macrophage polarization in RAW 264.7 cells, thereby enhancing BMSC osteogenic development. Furthermore, Mg^{2+} release enhanced aldehyde dehydrogenase 3A1 expression via activation of the nuclear factor E2-related factor 2 (Nrf2) signaling pathway, thereby delaying BMSC senescence. Incorporating the Wnt/β-catenin agonist SKL2001 into the scaffolds significantly amplified these effects. The composite scaffolds expedited the healing of critical-sized calvarial lesions in an elderly rat model. The efficacy of enhancing the SME to postpone BMSC senescence by multifunctional Mg-Ce-MOF and SKL2001-based 3D-bioprinting scaffolds, thereby offering a viable approach for facilitating the repair of age-related bone defects [118].

Magnesium-based MOF (Mg-MOFs) are significant due to their intrinsic function in bone mineralization [108]. The synergetic effect of Ca-MOF and Mg-MOF (Ca/Mg-MOF) nanoparticles, when integrated into a hydrogel scaffold, can manifest in several formats: sprayable, injectable, and as a coating material for orthopedic implants (Fig. 4**a**) [119]. Moreover, nanoengineered hydrogels markedly improve osteogenic differentiation and mineral deposition of preosteoblast cells relative to control groups and individual MOFs. The osteogenic property is due to the cumulative release of Ca^{2+} and Mg^{2+}, which reached 62.89 % $\pm$ 3.05 and 18.60 % $\pm$ 0.65, respectively, by day 8. Micro-computed tomography and histological examination of a rat model with critical-size bone defects indicate that the bioactive hydrogel markedly enhances new bone growth without administering supplementary pharmacological molecules. These findings highlight the clinical importance of nano-engineered mineral-based hydrogels in facilitating osteogenesis and expediting bone repair [119].

Ca-ALN MOF, a rod-shaped MOF (100 $\times$ 100 $\times$ 1000 nm) was infused with alendronate (ALN) and integrated into chitosan/gelatin (CHS/Gel) scaffolds, which shows the capacity to modulate bone formation through the co-delivery of Ca^{2+} and medicinal agents [120]. The scaffold served as a multifunctional dual-delivery system, releasing calcium ions and alendronate to modulate bone growth. Ca-ALN nanoparticle-loaded CHS/Gel scaffolds were effectively produced using a freeze-drying method. The physicochemical characteristics of scaffolds modified by incorporating nanoparticles indicated that nanoparticles led to reduced porosity, less swelling, and a lower degradation rate. The release profile results showed that the NPs-loaded CHS/Gel scaffolds could concurrently release ALN and Ca ions due to NP decomposition. The incorporation of nanoparticles (NPs) into the CHS/Gel scaffold resulted in an increase in alkaline phosphatase (ALP) activity and the amount of deposited calcium, as well as osteogenesis gene markers. The results indicate that the NPs-loaded CHS/Gel scaffold may improve the differentiation of human adipose tissue-derived mesenchymal stem cells, presenting a promising strategy for bone repair. Another system utilizing Ca-glycyrrhizin MOF (Pm-GCH, 110 $\pm$ 9 nm in size) with a core-shell morphology was reported (Fig. 4**b**) [107]. A new nanoparticle drug system (Pm-GCH) featuring a core-shell architecture was developed. MOFs, composed of glycyrrhizic acid (G) and calcium ions (Ca^{2+}) encapsulating hydrocortisone (H), constituted the core of the nanoparticles. The shells comprised platelet membrane vesicles and achieved significant encapsulation (96.7 %) and loading efficiency (38.7 %) for glycyrrhizic acid and

Table 4. Challenges and proposed solution.

Challenge	Reason	Explanation	Possible solutions
Biocompatibility & biosafety	Uncontrolled ion release, immune activation	Toxicity, inflammation, coagulation, and uncertain long-term safety	Optimize ion release kinetics, surface modifications, and conduct long-term *in vivo* studies
Degradation control	Degrades too quickly or too slowly	Mismatch with the bone healing cycle; poor mineralization consistency	Engineer MOFs with pH-sensitive or enzyme-responsive degradation; design composites with controlled dissolution
Limited osteogenic capacity	Weak stimulation of mineralization; burst ion release	Short-term bioactivity, insufficient sustained osteogenic signaling	Combine MOFs with hydroxyapatite, bioactive glass, or polymers for synergistic mineralization
Manufacturing Issues	Use of toxic solvents, poor reproducibility, and high cost	Solvothermal synthesis is not scalable or safe	Develop green, solvent-free, or aqueous synthesis; standardize scalable production methods
Mechanical limitations	Weak structural strength, rapid loss upon degradation	Inadequate compressive strength for bone; scaffold collapse risk	Reinforce with polymers, collagen, or 3D printing composites; design hybrid MOF@ceramic scaffolds
Regulatory rules	Lack of standards, limited preclinical data	No FDA guidelines; insufficient large-animal or human studies	Establish toxicity standards, perform long-term studies, and foster academic-industry collaboration

hydrocortisone, delivering both anti-inflammatory and anti-osteoporotic benefits via regulated drug release. The natural platelet membrane imparts Pm-GCH with excellent biocompatibility and facilitates immune evasion. Moreover, influenced by inflammatory chemotactic stimuli, platelet membranes facilitate Pm-GCH in the nonspecific localization of renal inflammatory sites. In an acidic inflammatory environment, GCH gradually decomposes, releasing glycyrrhizic acid and hydrocortisone. Glycyrrhizic acid impedes the inactivation of hydrocortisone, concurrently inhibits the activity of phospholipase A2 (PLA2) and the classical activation pathway of complement C2, obstructs the synthesis of inflammatory mediators, exerts an anti-inflammatory effect, and augments the efficacy of hydrocortisone in the management of steroid-resistant nephrotic syndrome (SRNS). Additionally, glycyrrhizic acid mitigates osteoporosis resulting from prolonged glucocorticoid administration. The results suggest that Pm-GCH is a viable therapeutic approach for SRNS [107].

Bimetallic MOFs derived from cerium and strontium (Ce/Sr-MOFs). These metal-organic frameworks (100–200 nm in size) were applied to titanium implants and functionalized with p-xylylenebisphosphonate (PXBP), facilitating the release of therapeutic ions (Ce^{3+} and Sr^{2+}) and pharmaceuticals to enhance osteogenesis via both catalytic and biological mechanisms (Fig. 4**c**) [121]. An increased level of reactive oxygen species (ROS) in the bone microenvironment is characteristic of osteoporosis, frequently leading to the dysfunction of bone-associated mesenchymal stem cells (MSCs), which induces MSC senescence and significantly diminishes their osteoblastic capacity. This study presents the *in situ* fabrication of a bone microenvironment-responsive biologically-based metal-organic framework (BioMOF) coating on titanium surfaces by the coordination of p-xylylenebisphosphonate (PXBP) with Ce/Sr ions using a hydrothermal approach. The AHT-Ce/SrMOF implants utilize the attached Ce and Sr ions to exhibit on-demand superoxide dismutase and catalase-like catalytic activities, effectively decomposing reactive oxygen species in mesenchymal stem cells and restoring their mitochondrial functions. *In vitro* studies demonstrated that AHT-Ce/SrMOF implants significantly activated the AMP-activated protein kinase (AMPK) signaling pathway in MSCs and reduced ROS levels. Conversely, MSCs cultured on AHT-Ce/SrMOF implants exhibited markedly elevated expressions of the mitochondrial fission marker (DRP1), mitochondrial fusion markers (MFN2 and OPA1), and mitophagy markers (PINK1 and LC3) compared to the AHT-CeMOF and AHT-SrMOF groups, suggesting that the BioMOF could enhance mitochondrial function in MSCs to counteract senescence. *In vivo* assessments demonstrated that BioMOF-coated titanium implants may restore mesenchymal stem cell function at the implant site and enhance new bone formation, thereby improving osteointegration in osteoporotic rats. This research can improve implant-mediated fracture healing in clinical settings [121]. Likewise, Ca/Sr-based MOFs modified with the same bisphosphonate were engineered to release Ca^{2+} and Sr^{2+}, thereby promoting bone growth and mitigating the degenerative effects of osteoporosis (Fig. 4**d**) [122]. It can be used to treat bone demineralization, a characteristic of osteoporosis, by delivering several components, including alkaline-earth cations and bisphosphonate compounds, to maintain normal bone density. Multicomponent BioMOFs that simultaneously release many components at a regulated rate present a compelling solu-

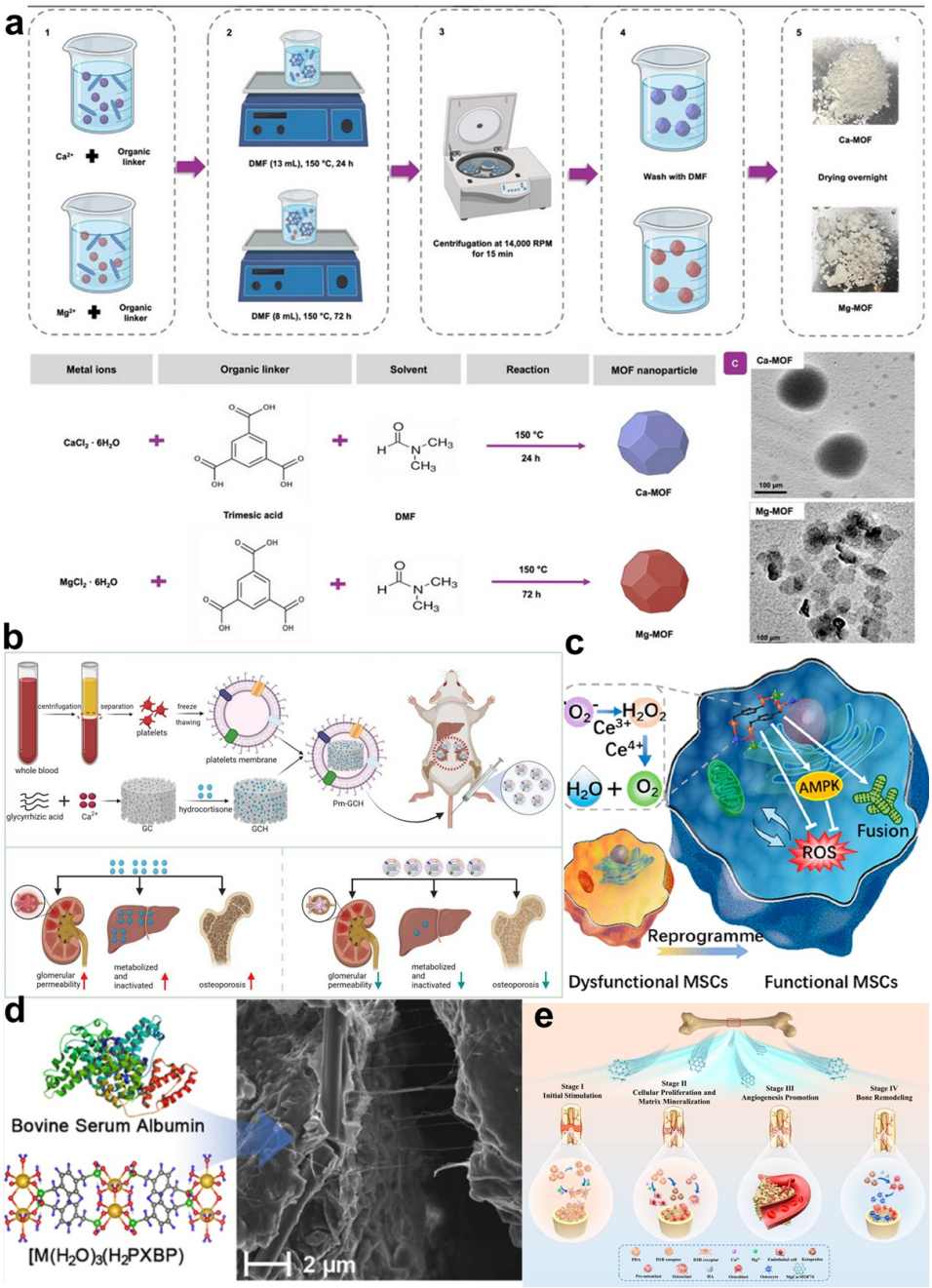

Fig. 4. Alkaline earth-based MOFs for bone treatment. (**a**) Using a schematic illustration of the synthesis pathway for Ca-MOF and Mg-MOF nanoparticles. Calcium and magnesium ions are combined with organic ligands in a DMF solvent under controlled conditions. The resulting mixtures are subjected to centrifugation and repeated washing to eliminate unreacted precursors and by-products. The final step involves collecting and drying the precipitated MOF nanoparticles for subsequent applications. Proposed reaction mechanism for the formation of MOF nanoparticles, TEM micrographs of the synthesized Ca-MOF and Mg-MOF nanoparticles, figure reprinted from Ref. [119]. (**b**) Pm-GCH, figure reprinted from Open Access Ref. [107]. This article is licensed under a Creative Commons Attribution 4.0 International License Copyright © 2021, The Author(s). (**c**) AHT-Ce/SrMOF. Figure reprinted with permission from [121]. (**d**) MOF for biomerazliatin, figure reprinted with permission from Ref. [122], Copyright © 2022 American Chemical Society. (**e**) Ket@MgCu-MOF74/Ti coatings, figure reprinted from Open Access [109] © 2025 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/). Copyright © 2019 American Chemical Society.

tion. We present two BioMOFs, consisting of strontium and calcium ions interconnected by p-xylylenebisphosphonate molecules, which release these three constituents and exhibit no cytotoxicity towards human osteosarcoma cells.

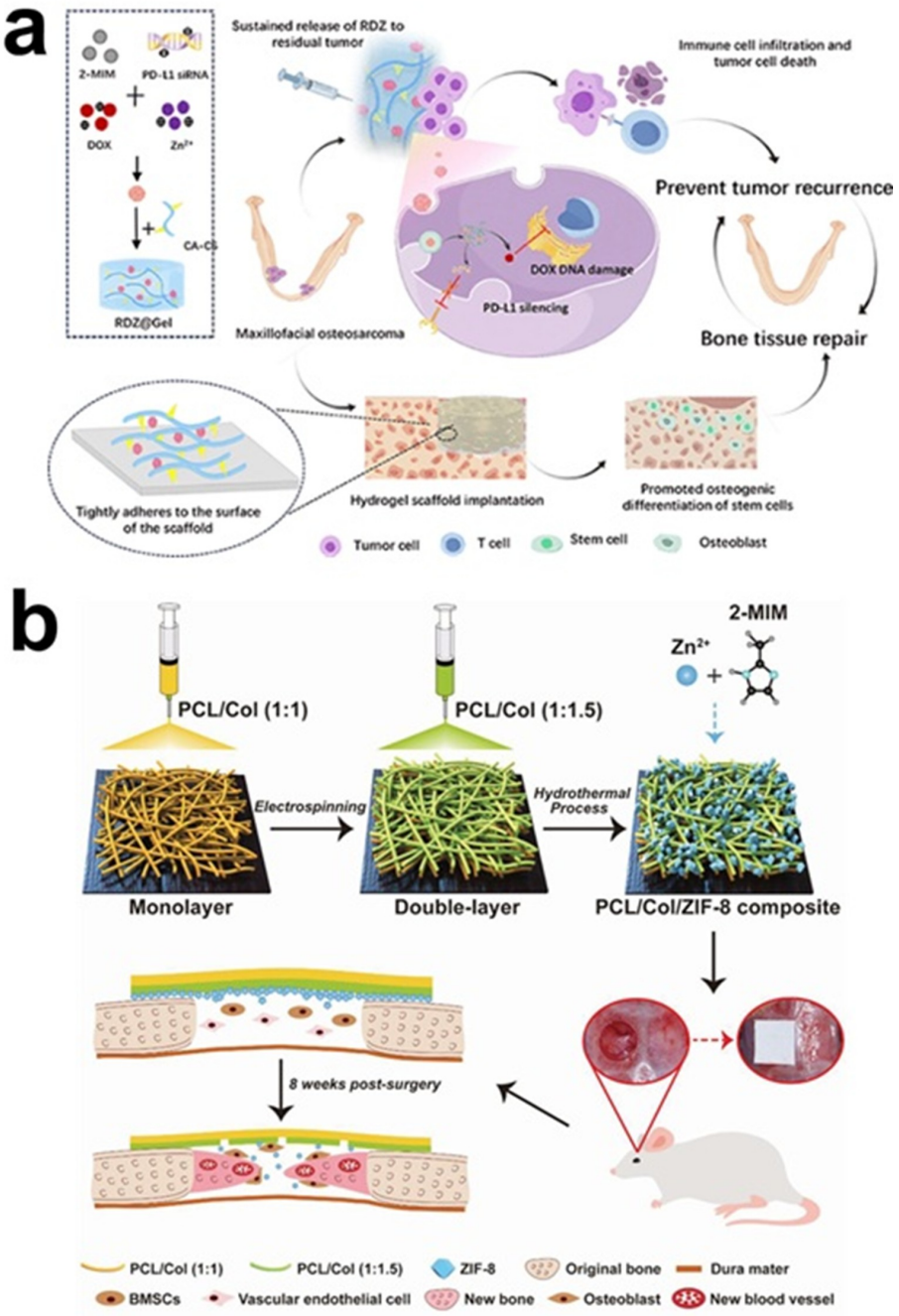

Fig. 5. ZIF8-based materials for bone treatment. (**a**) Gel, Fig. reprinted with permission from Ref. [129] Copyright © 2025 American Chemical Society. (**b**) PCL/Col/ZIF-8 composite membrane for guided bone regeneration [47] © 2021 Wiley-VCH GmbH.

Altering the Sr^{2+}/Ca^{2+} ratio in these BioMOFs results in a distinctive ion-dissolution rate in simulated bodily fluid; coupled with their protein-adsorption capacity, this characteristic is essential for future advancements in drug-release regulation and mineral-formation enhancement. The one-pot synthesis of these bioMOFs illustrates the efficacy of MOF design methodologies [122].

A bimetallic Mg-Cu-based MOF, exemplified by MgCu-MOF74, was also reported for bone repair [109]. These structures provide significant water stability and facilitate dual ion release (Mg^{2+} and Cu^{2+}), with Cu^{2+} aiding antibacterial activity and Mg^{2+} promoting osteogenic responses (Fig. 4**e**). This property makes them particularly advantageous in scenarios that require concurrent infection control and bone repair [109]. The system develops a titanium-based implant coating that combines drug-controlled release with ionic microenvironment modulation, exhibiting antibacterial and bone-regenerative capabilities. Ketoprofen, a medication with superior analgesic characteristics, was incorporated into MgCu-MOF74 powder, and the Ket@MgCu-MOF74 powder was effectively affixed to the titanium alloy surface by dopamine-mediated

adhesion. The maximum loading capacity of ketoprofen in MgCu-MOF74 is 18.55 %, demonstrating an effective, controlled release profile. The findings indicated that MgCu-MOF74/Ti and Ket@MgCu-MOF74/Ti coatings improved osteogenic efficacy by augmenting alkaline phosphatase activity, collagen production, and extracellular matrix (ECM) mineralization. The release of Mg^{2+} and Cu^{2+} generated an alkaline environment, imparting antibacterial characteristics. In conclusion, the MOF facilitated the regulated release of ketoprofen, while the composite coating can enhance osteogenic differentiation of osteoblasts and bolster the antibacterial properties of titanium alloy implants [109]. Cu-MOF74 without Mg^{2+} demonstrated the most calcium deposition and increased production of bone sialoprotein and osteopontin [123]. The results illustrate the dual functional effectiveness of Cu-MOF-74/PCL/HAp scaffolds in facilitating infection control and bone repair. The adjusted concentrations of Cu-MOF-74 (0.05–0.2 %) efficiently harmonize antibacterial and osteogenic capabilities, offering a potential approach for the healing of bone defects in clinical applications [123].

Alkaline-based MOFs for elements such as Ca^{2+} or Mg^{2+} offered several advantages. Their extensive applicability distinguishes them. They play a crucial role in bone reconstruction and repair, promoting osteogenesis and angiogenesis, exerting antibacterial effects, and exhibiting anti-inflammatory properties. Mg-MOF was made from magnesium chloride and gallic acid and subsequently integrated into gelatin microspheres to form Gel@Mg-MOF composite microspheres [124]. The biocompatibility of the composites was assessed by toxicity and adhesion studies, utilizing gelatin's biocompatibility, controlled release, and biodegradability. Additionally, the osteogenic and angiogenic capabilities of the Gel@Mg-MOF microspheres, as well as their ROS-scavenging ability, were evaluated. The findings indicate that regulated Mg^{2+} release from Gel@Mg-MOF microspheres stimulates osteogenic activity in RBMSCs and improves angiogenic potential in human umbilical vein endothelial cells (HUVECs). The composite microspheres containing gallic acid demonstrated antioxidative effects. The findings indicate that Gel@Mg-MOF microspheres may provide adequate support for repairing bone defects and have potential for clinical application [124].

Zinc-Based MOF

ZIF-8 films, consisting of nanoscale zeolitic imidazolate framework-8 (nanoZIF-8) and microscale (microZIF-8) crystals, were synthesized on porous titanium substrates via hydrothermal and solvothermal techniques, respectively [104]. The cytocompatibility and functioning of nanoZIF-8 and microZIF-8 films on titanium substrates were assessed using several *in vitro* experiments. MG63 human osteosarcoma cells were cultivated on coated surfaces to evaluate cell proliferation via the cell counting kit-8 (CCK-8) assay and cell adherence via fluorescent labeling with FITC-phalloidin and DAPI; the cells were thereafter analyzed under a microscope. The osteogenic potential was assessed by quantifying alkaline phosphatase (ALP) activity and osteocalcin (OCN) expression using enzymatic and the enzyme-linked immunosorbent assay (ELISA) assays, respectively. Furthermore, extracellular matrix mineralization was assessed using alizarin red staining, and quantitative real-time polymerase chain reaction (qRT-PCR) was utilized to examine the expression of critical osteogenic genes, including *ALP*, *Runx2*, *OCN*, and *BMP-2*. The antibacterial efficacy against Streptococcus mutans was evaluated using scanning electron microscopy (SEM) to examine bacterial adherence and morphology on surfaces, alongside an agar disk diffusion experiment to measure the inhibitory zones produced by ZIF-8 suspensions. These tests thoroughly assess the biocompatibility, osteogenic activity, and antibacterial effectiveness of MOF-coated titanium products. Biocompatibility evaluations indicated that the nanoZIF-8 coating showed positive interactions with cells, but the microZIF-8 coating negatively affected MG63 osteoblast-like cells.

In comparison to untreated titanium and alkali- and heat-treated titanium surfaces, the nanoZIF-8 coating markedly enhanced ALP activity, facilitated extracellular matrix mineralization, and increased the expression of osteogenic markers, including ALP and Runx2, in MG63 cells. The nanoZIF-8 coating suppressed the multiplication of Streptococcus mutans. The findings indicate that nanoscale ZIF-8 MOF films possess significant promise as bioactive coatings for bone tissue engineering applications [104].

Moreover, alendronate-encapsulated ZIF-8 nanoparticles (130 ± 30 nm) integrated into electrospun nanofibers exhibited synergistic release of alendronate and Zn^{2+}, thereby enhancing both anti-osteoporotic and osteoinductive effects [54]. Additional advancements encompass the development of magnesium phosphate bone cement augmented with ZIF-8, which improved the cement's mechanical strength and facilitated osteogenesis by ion release [125]. Likewise, 3D-printed scaffolds containing ZIF-8 particles (about 300 nm) facilitated controlled zinc ion release to enhance bone regeneration [126]. A bone-targeted formulation, ZOL-modified ZIF-8 (50 nm), was developed to release drugs, particularly in the acidic microenvironments associated with bone disease, offering opportunities for localized treatment of osteoporosis [127]. Additionally, BioMOF-1, a zinc-based metal-organic framework, was applied to titanium surfaces to produce BioMOF-1@AHT-1 composites (300–500 nm), which exhibited superior thermal stability, improved Zn^{2+} release, and greater biocompatibility for combating bone loss [128].

Doxorubicin (DOX) and programmed death-ligand 1 small interfering RNA (PD-L1 siRNA) were initially encapsulated within ZIF-8 to produce a very stable nanocomplex, RNA-DOX@ZIF-8 (RDZ, Fig. 5**a**) [129]. A mul-

tifunctional hydrogel (Gel@RDZ) was subsequently synthesized by combining RDZ with catechol-modified chitosan in a uniform manner. Gel@RDZ demonstrates a substantial drug-loading capacity, superior viscoelasticity, and robust scaffold adherence. The Gel@RDZ-coated scaffold group exhibited enhanced bone regeneration efficacy in a rat femoral defect model. In a murine osteosarcoma recurrence model, Gel@RDZ demonstrated optimal immune cell infiltration, significantly reduced tumor recurrence, and greatly enhanced the tumor-killing efficiency of CD8+ T cells. Consequently, creating a multifunctional hydrogel system (Gel@RDZ) offers an extensive therapeutic approach for postoperative maxillofacial osteosarcoma [129].

Rapamycin (RAPA) is widely used in biological research and therapeutic settings owing to its potent anticancer, immunosuppressive, and neuroprotective properties. Nonetheless, the direct injection of RAPA may result in considerable adverse effects, such as pronounced immune suppression, increased susceptibility to infections, and the potential for tumorigenesis. To overcome these constraints, ZIF-8 was recognized for its stability and biocompatibility as a drug delivery vehicle [110]. It was infused with rapamycin to create a composite system (ZIF-8@RAPA). The ZIF-8@RAPA particles exhibited a distinct dodecahedral morphology, an average particle size of 82 ± 4.7 nm, and a substantial drug-loading capacity of 11.53 %. *In vitro* drug release tests indicated that RAPA was released in a sustained and regulated way. Structural stability studies in phosphate-buffered saline (PBS) showed that ZIF-8@RAPA remained stable for 6 weeks, followed by slow degradation, leading to the development of microcrystals (dia(Zn)) by the 8th week, likely influenced by phosphate ions in the medium. Biocompatibility evaluations with RAW 264.7 macrophages and zebrafish embryo models demonstrated that the ZIF-8@RAPA system displayed concentration-dependent toxicity, maintaining a favorable safety profile at concentrations below 100 μg/mL. The structural evolution and degradation behavior of ZIF-8@RAPA, reinforcing its viability as a secure and efficient drug delivery system for biological applications [110].

An innovative electrospun asymmetric double-layer membrane consisting of polycaprolactone/collagen (PCL/Col) has been enhanced with MOF crystals for bone tissue engineering (Fig. 5**b**) [47]. The membrane has two separate functional layers: a barrier layer and a layer functionalized with MOF. Optimizing the PCL/Col weight ratio (1:1 and 1:1.5) refined mechanical properties and degradation rates, achieving a balance between structural integrity and bioresorbability. The membrane exhibited a 49.9 % drop in tensile strength under wet conditions and total breakdown within 12 weeks. The incorporation of MOF crystals into the membrane enabled pH-responsive release of Zn^{2+} ions, which are known for their role in promoting osteogenesis and angiogenesis. *In vitro* experiments indicated that the barrier layer successfully prevents fibrous tissue invasion, whilst the MOF-containing layer markedly improves osteogenic and angiogenic cellular responses. *In vivo* experiments using a rat calvarial defect model showed that the MOF-modified membrane facilitates bone repair and angiogenesis at 8 weeks post-implantation. Moreover, significant angiogenic activity was observed in a chick chorioallantoic membrane (CAM) model, indicating enhanced efficacy compared with commercial collagen membranes. This multifunctional PCL/Col-MOF composite membrane is a promising approach for directed bone regeneration, providing physical barrier qualities and bioactivity to enhance neovascularization and osteoinduction in bone defect healing [47].

Gao *et al*. [130] demonstrated that nano-ZIF-8 promotes the differentiation of rat BMSCs into osteoblasts by endocytosis-mediated stimulation of the MAPK signaling pathway, thereby validating its dual osteogenic actions *in vitro* and *in vivo*. Zhang *et al*. [131] enclosed DMOG within nano-ZIF-8, resulting in a sustained release that markedly improved osteogenesis and angiogenesis through effective drug delivery. A biomimetic multifunctional scaffold consisting of Zn-modified MOF-818 (Zn-MOF-818) infused with deferoxamine (DFO), gelatin methacryloyl (GelMA) hydrogel, and demineralized bone matrix (DBM) effectively scavenges excess ROS, enhances angiogenesis, and modulates immune responses [132]. Incorporating Zn markedly improves the superoxide dismutase and catalase-like activities of MOF-818, hence augmenting ROS-scavenging efficacy. Zn-MOF-818 interrupts the detrimental intracellular loop of mitochondrial failure and reactive oxygen species accumulation by promoting mitophagy, maintaining mitochondrial function, and upregulating antioxidant genes. Moreover, Zn-MOF-818 promotes macrophage polarization toward the M2 phenotype and mitigates inflammation, thereby establishing a favorable immunological milieu for the osteogenic differentiation of BMSCs. The release of DFO, an activator of the hypoxia-inducible factor 1-alpha (HIF-1α) pathway, and Zn^{2+} from Zn-MOF-818, together with the secretion of numerous cytokines from DBM (including bone morphogenetic proteins (BMPs) and vascular endothelial growth factors), promotes angiogenesis and osteogenesis. This scaffold simultaneously addresses many variables, presenting a promising strategy for treating steroid-induced femoral head necrosis (SONFH) [132].

Zirconium-Based MOFs

A zirconium-based metal-organic framework, designated as MOF-801, was synthesized and integrated into a gelatin matrix as an osteoconductive agent to produce a nanocomposite bone scaffold by the freeze-drying process [111]. The biological activity of the fabricated scaffolds was assessed using MTT, alizarin red, crystal violet, and

ALP assays. Incorporating MOF-801 nanoparticles into the scaffolds increased their compressive strength to 15 ± 0.05 MPa. The nanocomposite samples containing MOF-801 nanoparticles exhibited advantageous bioactive properties, as evidenced by their ability to form apatite on their surfaces when immersed in simulated body fluid (SBF). The Zr ion and fumarate release investigations demonstrated sustained release profiles from the gelatin matrix, resulting in antioxidant and anti-inflammatory characteristics. The MTT assay results confirmed the biocompatibility of scaffolds containing up to 5 % w/w MOF-801, whereas the crystal violet assay demonstrated adequate cell confluency and adhesion. Ultimately, alizarin red and ALP activity experiments showed that an increase in MOF-801 may stimulate calcium mineralization and Alkaline Phosphatase enzyme synthesis in MG-63 cells, hence affirming the potential of the produced scaffolds for bone tissue engineering applications [111]. A teriparatide (TRP) formulation suitable for oral delivery, utilizing biocompatible metal-organic framework nanoparticles (MOF-808 NPs) co-loaded with TRP and functionalized with transferrin targeting ligands (M@P@T NPs) [133]. The engineered nanoporous structure and transferrin surface modification effectively safeguard TRP from acidic and enzymatic breakdown under hostile gastrointestinal conditions, while facilitating the regulated release of TRP in the phosphate-rich circulation. By overexpressing transferrin receptors (TfR) on intestinal epithelial cells, the nanosystem promotes receptor-mediated transcellular transport, enabling effective systemic delivery of TRP with enhanced oral bioavailability. Following 1 month of oral administration of low-dose M@P@T to osteoporosis model mice, therapeutic effects akin to those observed with subcutaneous TRP injections were noted, including enhanced bone mineral density, improved trabecular architecture, and a marked reduction in osteoporosis symptoms. The findings indicate that this MOF-based oral TRP approach is promising for enhancing and streamlining osteoporosis treatment [133].

Another Zr-MOF, i.e., UiO-66 nanocrystals, was produced and studied, exhibiting uniform shape and a highly crystalline structure [134]. The nanocrystals were subsequently integrated into an alginate/methyl cellulose (AL/MC) hydrogel at varying concentrations, and printing conditions were tuned based on the nanocrystals' physicochemical attributes. Optimized under particular conditions, AL/MC/UiO-66 was employed as a bioink to 3D bioprint scaffolds incorporating MC3T3-E1 preosteoblasts. Cell viability and osteogenic differentiation properties were evaluated. The findings indicated that AL/MC scaffolds containing 2 % (w/v) UiO-66 nanocrystals greatly enhanced osteogenic differentiation, as evidenced by high ALP activity and increased expression of osteogenic markers (Runx2, COLI, OCN) [134]. The wet-spun chitosan scaffolds, including fosfomycin-loaded UiO-66 nanocrystals (CHI/UiO-66/FOS) exhibited a fibrous mesh structure with integrated microscale fibers and enhanced mechanical strength [135]. *In vitro* antibacterial investigations showed that CHI/UiO-66/FOS scaffolds had bactericidal efficacy against *Staphylococcus aureus*. Furthermore, the scaffolds demonstrated biocompatibility with MC3T3-E1 pre-osteoblasts, greatly enhancing the expression of osteogenesis-related genes and promoting extracellular matrix mineralization *in vitro*. UiO-66 MOFs exhibit dual functionality, and CHI/UiO-66/FOS scaffolds have considerable potential for further investigation as an alternative strategy for treating infected bone defects, such as osteomyelitis [135]. Composite scaffolds of poly-3-hydroxybutyrate-zein and UiO-66 were produced via electrospinning [136]. The scaffold with 2 wt % UiO-66 demonstrated the most favorable characteristics. Including 2 wt % UiO-66 decreases the fiber diameter and water contact angle by approximately 54 nm and 20°, respectively, while enhancing surface roughness and crystallinity. UiO-66 markedly improved ultimate tensile stress and Young's modulus by almost 90 % and 101 %, respectively. It enhanced the biomineralization of the scaffold and accelerated the breakdown rate. Incorporating UiO-66 significantly enhanced survivability, proliferation, attachment, ALP activity, and ECM mineralization, along with upregulation of *COL1*, *Runx2*, and *OCN* genes in MG-63 cells cultured on the scaffolds. In summary, the integration of UiO-66 not only strengthened the composite scaffold but also promoted osteogenesis, rendering it a favorable choice for bone tissue engineering applications [136].

Advantages of MOFs

MOF-based composites have been synthesized using advanced methodologies such as freeze-drying, 3D printing [133], papermaking, and electrospinning [134,135], enabling the creation of diverse shapes, including aerogels [137], sheets [21], and 3D scaffolds [138]. The diverse structures and functions underscore the remarkable potential of MOFs in both traditional and advanced biomedical applications [139]. A responsive hydrogel system incorporating carboxymethyl chitosan (CMCS), dextran (DEX), 4-formylphenylboronic acid (4-FPBA), and Mg-GA MOFs was reported [140]. The injectable self-healing hydrogel establishes a dual-crosslinked network, integrating the MOF and enabling on-demand release responsive to ROS and pH levels associated with periodontitis. The synergistic effects of the hydrogel containing MOFs enabled several functions, including high antibacterial activity, immunomodulation, and enhanced bone regeneration in periodontitis. The *in vivo* and *in vitro* experiments confirmed the system's effectiveness in suppressing the expression of inflammation-related genes and proteins, thereby promoting periodontal bone regeneration. The hydrogel system using MOFs demonstrated potential as a therapeutic approach for overcoming obstacles in periodontitis-related bone regeneration [140].

3D-printed composite scaffold featuring extensive interconnected porosity and diverse bioactivities through the integration of magnesium-copper dual-MOF (MgCu-MOF74), gallic acid (GA), and polylactic acid (PLA) [141]. MgCu-MOF74 demonstrates antioxidant capabilities, regulated metal ion release, and osteo-angiogenic characteristics. The composite scaffold exhibited superior mechanical properties and degradation characteristics ideal for bone regeneration. The integration of GA and dual-ion synergy facilitated significant multicellular modulation by promoting macrophage polarization, inducing angiogenesis mediated by endothelial cells, stimulating the morphological maturation of Schwann cells, and enhancing the osteogenic differentiation of BMSCs, while substantially improving intercellular crosstalk to optimize the local multidimensional microenvironment. *In vivo* investigations further validated that the scaffold successfully promotes the healing of steroid-associated osteonecrosis (SAON)-related bone deformities by leveraging the synergistic interactions among the immunological, angiogenic, and neurogenic microenvironments. This study presented an approach to addressing refractory SAON-related bone deformities, emphasizing the scaffold's ability to influence multiple cell types and restructure intricate microenvironments [141]. The viability of 3D-printed multi-material structures for intricate tissue engineering applications, while establishing an advanced framework for creating intelligent biomaterials that simultaneously tackle biological regeneration and inflammation management [142].

MOFs possess a high specific surface area, significant porosity, regulated degradation, and diverse composition; they serve not only as carriers for controlled drug release [143]. They fulfill various functions in treating OP and microbial infections by releasing metal ions, offering intrinsic advantages, necessitating prolonged treatment [92]. Incorporating flavonoids into MOFs and injectable hydrogels resulted in a 72% enhancement in new bone production *in vivo* [144]. Although further study is needed to validate long-term therapeutic efficacy, our findings demonstrate the significant potential of flavonoid-functionalized biomaterials for bone regeneration [144]. Iron-based MOF was reported to promote bone regeneration by enhancing osteogenesis and mitigating oxidative stress [145]. *In vitro*, ferric (Fe)-MOF enhanced the expression of osteogenesis-related genes and proteins while facilitating the decomposition of hydrogen peroxide into oxygen and water, thus mitigating ROS accumulation that hinders osteoblast functionality. *In vivo*, Fe-MOF suspensions in rat femoral defects and MOF-loaded hydrogel scaffolds in rabbit cranial defects enhanced bone repair relative to controls. These findings indicate that MOF facilitates bone regeneration by neutralizing ROS and activating the bone morphogenetic protein (BMP) pathway, highlighting its potential as a therapeutic biomaterial for repairing substantial bone defects [145].

MOFs offer multifunctional properties. Magnesium/copper MOF (Mg/Cu-MOF) coatings were synthesized and affixed to pure zinc [146]. The findings demonstrated that the degradation rate and aqueous stability of Mg/Cu-MOF coatings can be modulated by adjusting the Cu^{2+} feeding ratio. As the coating and zinc substrate deteriorated, an alkaline microenvironment was enriched with Zn^{2+}, Mg^{2+}, and Cu^{2+}. The extracts enhanced calcium phosphate deposition, osteoblast development, and endothelial cell vascularization. Of these, Mg/Cu1 had the most superior overall performance. The improved antibacterial efficacy of Mg/Cu1 was evidenced both *in vitro* and *in vivo*, demonstrating much higher bacteriostatic activity against Gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia coli* relative to the bare sample. The bimetallic Mg/Cu-MOF coating effectively integrates multifunctionality into a Zn membrane and provides a viable platform for enhancing bone regeneration, thereby facilitating the application of Zn-based materials as barrier membranes in oral clinical trials [146].

MOFs facilitate bone therapy in various mechanisms (Table 3). They enhanced osteogenesis by releasing osteoinductive ions, e.g., Ca^{2+}, Mg^{2+}, Zn^{2+}, Sr^{2+}, and Cu^{2+}, and by activating essential signaling pathways, while facilitating angiogenesis through pro-vascular ions such as Cu^{2+} and Co^{2+}. They are antioxidants that neutralize ROS, thereby safeguarding osteoblasts from oxidative stress. Their antibacterial properties inhibit infections, while their porous, adjustable architectures enable controlled delivery of drugs, genes, and growth factors, often in response to stimuli such as pH or ROS. Moreover, MOFs regulate immune responses to establish a pro-regenerative milieu. They are used to treat specific bone disorders—such as osteoporosis, osteomyelitis, bone malignancies, and diabetic bone defects—through targeted drug delivery, antibacterial properties, immunomodulation, and the promotion of angiogenesis.

Challenges

MOFs exhibit high performance in biomedical applications. However, critical challenges, such as cytotoxicity, long-term biosafety, and scalability, should be investigated. Some of these challenges are summarized in Table 4 [147]. The toxicity of MOFs can be mitigated through surface modification and the formation of hybrid composites. Notwithstanding their potential, obstacles persist, including achieving sufficient stability under physiological conditions, controlling degradation rates, and conducting comprehensive *in vivo* toxicity evaluations. Future research will likely focus on hybrid, stimuli-responsive MOF systems and on integrating MOFs with biopolymers or hydrogels to improve therapeutic efficacy. Alkaline-earth MOFs constitute a multifaceted and increasingly significant foundation for advancing biological technologies.

MOFs have garnered heightened interest in bone regeneration and mineralization due to their adjustable chemistry, porosity, and capacity to release osteogenic ions [148]. Nonetheless, numerous obstacles persist before its clinical application. Biocompatibility and biosafety are critical issues, as unregulated ion release or interactions with blood proteins may induce inflammation, coagulation, or immunological reactions (Table 4) [149]. The manageability of degradation poses challenges, as MOFs often disintegrate rapidly or slowly, leading to inadequate osteogenic support or prolonged retention as foreign substances. Their osteogenic potential is constrained compared to genuine bone-like materials, as many MOFs cannot sustain prolonged mineralization and merely provide transient ion release. From a manufacturing standpoint, conventional solvothermal synthesis utilizes hazardous solvents such as dimethyl formamide (DMF) and is characterized by inadequate reproducibility and scalability. Mechanically, pure MOFs have insufficient compressive strength and stability for load-bearing bone scaffolds, with their strength suppressed rapidly upon degradation. Additionally, regulatory and translational obstacles remain, characterized by the absence of established safety standards, inadequate long-term animal research, and restricted industrial scalability (Table 4). To address these challenges, research should concentrate on environmentally sustainable and reproducible synthesis techniques, the formulation of composites utilizing polymers or bioactive ceramics to enhance strength and osteogenesis, the execution of extensive biosafety evaluations, and the establishment of regulatory frameworks in conjunction with economically viable production methods.

Conclusions

Metal-organic frameworks represent a rapidly advancing field in the development of bioinspired materials for bone tissue engineering and biomineralization. The structural tunability, elevated surface area, and modular synthesis of MOFs facilitate the integration of bioactive metals (e.g., Mg, Ca, Zn, Sr) with medicinal compounds for regulated release and multifunctional efficacy. This study illustrates how several types of MOFs, such as BioMOFs, bioactive MOFs, and hybrid MOF composites, have been designed to promote the mineralization of proteins, viruses, and microbial cells, thereby providing novel pathways for the development of bone-mimicking microenvironments. The ability of MOFs to influence biological responses, including enhancing osteoblast development, promoting angiogenesis, and treating bone infections, makes them highly beneficial for addressing complex bone problems. Moreover, MOF-based systems hold promise for addressing the limitations of existing therapeutics by enabling responsive drug delivery and immunomodulatory functions. The advancement of therapeutically relevant MOF systems will depend on addressing challenges related to long-term biocompatibility, degradation dynamics, and scalable synthesis. Advancements in surface functionalization, ion doping, and the integration of composites with scaffolds or hydrogels will be crucial for improving therapeutic efficacy and patient safety. Through sustained interdisciplinary collaboration, MOFs are poised to significantly advance bone regeneration, regenerative medicine, and precision orthopedics.

List of Abbreviations

3D, three-dimensional; 4-FPBA, 4-formylphenylboronic acid; ADH, alcohol dehydrogenase; AL/MC, alginate/methyl cellulose; ALN, alendronate; ALP, alkaline phosphatase; BMSCs, bone marrow mesenchymal stem cells; BMP, bone morphogenetic protein; BMP-6, bone morphogenetic protein-6; BioMOFs, biologically-based metal-organic frameworks; PCFs, protein crystalline frameworks; CAM, chick chorioallantoic membrane; CAT, catalase; CD, cyclodextrin; CHS, chitosan; CMCS, carboxymethyl chitosan; COX2, cyclooxygenase 2; Cyt C, cytochrome c; DBM, demineralized bone matrix; DEX, dextran; DFO, deferoxamine; DMOG, dimethyloxalylglycine; DOX, doxorubicin; ELISA, enzyme-linked immunosorbent assay; GA, gallic acid; Gel, gelatin; GelMA, gelatin methacryloyl; GOx, glucose oxidase; hMSCs, human mesenchymal stem cells; HRP, horseradish peroxidase; HUVECs, human umbilical vein endothelial cells; Ket, ketoprofen; MBioFs, metal-biomolecule frameworks; MIL, materials institute of lavoisier; MOFs, metal-organic frameworks; MPF, metal-peptide frameworks; MSMOFs (2D MSMOFs), 2D mesoporous spindle-shaped MOFs; nanoZIF-8, nanoscale zeolitic imidazolate framework-8; OCN, osteocalcin; OCPP, 5,10,15,20-tetrakis(3,5-biscarboxylphenyl)porphyrin; OP, osteoporosis; PAA, poly(acrylic acid); PCNs, porous coordination networks; PCPs, porous coordination polymers; PCL/Col, polycaprolactone/collagen; PBS, phosphate-buffered saline; PLA, polylactic acid; PLGA, γ-poly-l-glutamic acid; qRT-PCR, quantitative real-time polymerase chain reaction; ROS, reactive oxygen species; SAON, steroid-associated osteonecrosis; SBF, simulated body fluid; SEM, scanning electron microscopy; SME, skeletal muscle engineering; SONFH, steroid-induced femoral head necrosis; SRNS, steroid-resistant nephrotic syndrome; TCPP, meso-tetra(4-carboxyphenyl)porphine (H_4TCPP); TfR, transferrin receptors; TMV, tobacco mosaic virus; TRP, teriparatide; UOx, urate oxidase; WHO, World Health Organization; ZIFs, zeolitic imidazolate frameworks; HmIm, 2-methylimidazole; NPs, nanoparticles; PXBP, p-xylylenebisphosphonate; RAPA, rapamycin; CCK-8, cell counting kit-8; Mg, magnesium; Ca, calcium; Ba, barium; Zn, zinc; Sr, strontium; Zr, zirconium; Ce, cerium; Ala, alanine; Val, valine; Ser, serine; Cu, copper; Ti, titanium; Co, cobalt; Fe, ferric; BTC, benzene-1,3,5-tricarboxylate; AMPK, AMP-activated protein kinase; PD-L1 siRNA,

programmed death-ligand 1 small interfering RNA; DMF, dimethyl formamide; ECM, extracellular matrix.

Artificial Intelligence Declaration

AI tools were used only for language editing tasks, e.g., rephrasing, grammatical correction, and readability enhancement. No artificial intelligence help was employed for data analysis, result interpretation, or scientific content creation. The authors are fully responsible for the integrity and precision of the scientific content provided.

Availability of Data and Materials

All data are presented in the manuscript.

Author Contributions

HNA conducted writing—review & editing, writing—original draft, visualization, validation, supervision, software, resources, project administration, methodology, investigation, funding acquisition, formal analysis, data curation, and conceptualization.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgments

Not applicable.

Funding

This work was supported and funded by the Deanship of Scientific Research at Imam Mohammad Ibn Saud Islamic University (IMSIU) (grant number IMSIU-DDRSP2501).

Conflict of Interest

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

References

[1] Rodan GA, Martin TJ. Therapeutic approaches to bone diseases. Science. 2000; 289: 1508–1514. https://doi.org/10.1126/science.289.5484.1508.

[2] Feng X, McDonald JM. Disorders of bone remodeling. Annual Review of Pathology. 2011; 6: 121–145. https://doi.org/10.1146/annurev-pathol-011110-130203.

[3] Zaimi M, Grapsa E. Current therapeutic approach of chronic kidney disease-mineral and bone disorder. Therapeutic Apheresis and Dialysis: Official Peer-Reviewed Journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy. 2024; 28: 671–689. https://doi.org/10.1111/1744-9987.14177.

[4] He Z, Peng Q, Bin W, Zhao L, Chen Y, Zhang Y, *et al*. Nucleic acid aptamers in orthopedic diseases: promising therapeutic agents for bone disorders. Bone Research. 2025; 13: 71. https://doi.org/10.1038/s41413-025-00447-8.

[5] Chen Y, Guo B, Ma G, Cao H. Sensory nerve regulation of bone homeostasis: Emerging therapeutic opportunities for bone-related diseases. Ageing Research Reviews. 2024; 99: 102372. https://doi.org/10.1016/j.arr.2024.102372.

[6] Si J, Wang C, Zhang D, Wang B, Zhou Y. Osteopontin in Bone Metabolism and Bone Diseases. Medical Science Monitor: International Medical Journal of experimental and Clinical Research. 2020; 26: e919159. https://doi.org/10.12659/MSM.919159.

[7] Rendina D, Falchetti A, Diacinti D, Bertoldo F, Merlotti D, Giannini S, *et al*. Diagnosis and treatment of Paget's disease of bone: position paper from the Italian Society of Osteoporosis, Mineral Metabolism and Skeletal Diseases (SIOMMMS). Journal of Endocrinological Investigation. 2024; 47: 1335–1360. https://doi.org/10.1007/s40618-024-02318-1.

[8] Tanvir MAH, Khaleque MA, Kim GH, Yoo WY, Kim YY. The Role of Bioceramics for Bone Regeneration: History, Mechanisms, and Future Perspectives. Biomimetics. 2024; 9: 230. https://doi.org/10.3390/biomimetics9040230.

[9] Karasik D, Rivadeneira F, Johnson ML. The genetics of bone mass and susceptibility to bone diseases. Nature Reviews. Rheumatology. 2016; 12: 323–334. https://doi.org/10.1038/nrrheum.2016.48.

[10] Zhou Z, Feng W, Moghadas BK, Baneshi N, Noshadi B, Baghaei S, *et al*. Review of recent advances in bone scaffold fabrication methods for tissue engineering for treating bone diseases and sport injuries. Tissue & Cell. 2024; 88: 102390. https://doi.org/10.1016/j.tice.2024.102390.

[11] Meng X, Wang WD, Li SR, Sun ZJ, Zhang L. Harnessing cerium-based biomaterials for the treatment of bone diseases. Acta Biomaterialia. 2024; 183: 30–49. https://doi.org/10.1016/j.actbio.2024.05.046.

[12] Yang DH, Nah H, Lee D, Min SJ, Park S, An SH, *et al*. A review on gold nanoparticles as an innovative therapeutic cue in bone tissue engineering: Prospects and future clinical applications. Materials Today. Bio. 2024; 26: 101016. https://doi.org/10.1016/j.mtbio.2024.101016.

[13] Yao Q, He L, Bao C, Yan X, Ao J. The role of TNF-α in osteoporosis, bone repair and inflammatory bone diseases: A review. Tissue & Cell. 2024; 89: 102422. https://doi.org/10.1016/j.tice.2024.102422.

[14] Salari N, Ghasemi H, Mohammadi L, Behzadi MH, Rabieenia E, Shohaimi S, *et al*. The global prevalence of osteoporosis in the world: a comprehensive systematic review and meta-analysis. Journal of Orthopaedic Surgery and Research. 2021; 16: 609. https://doi.org/10.1186/s13018-021-02772-0.

[15] WHO. Fragility fractures. 2024. Available at: https://www.who.int/news-room/fact-sheets/detail/fragility-fractures (Accessed: 20 November 2025).

[16] Zhou HC, Long JR, Yaghi OM. Introduction to metal-organic frameworks. Chemical Reviews. 2012; 112: 673–674. https://doi.org/10.1021/cr300014x.

[17] Furukawa H, Cordova KE, O'Keeffe M, Yaghi OM. The chemistry and applications of metal-organic frameworks. Science. 2013; 341: 1230444. https://doi.org/10.1126/science.1230444.

[18] Trickett CA, Helal A, Al-Maythalony BA, Yamani ZH, Cordova KE, Yaghi OM. The chemistry of metal-organic frameworks for CO_2 capture, regeneration and conversion. Nature Reviews Materias. 2017; 2: 17045. https://doi.org/10.1038/natrevmats.2017.45.

[19] Furukawa H, Ko N, Go YB, Aratani N, Choi SB, Choi E, *et al.* Ultrahigh porosity in metal-organic frameworks. Science. 2010; 329: 424–428. https://doi.org/10.1126/science.1192160.

[20] Abdellah AR, Abdelhamid HN, El-Adasy ABAAM, Atalla AA, Aly KI. One-pot synthesis of hierarchical porous covalent organic frameworks and two-dimensional nanomaterials for selective removal of anionic dyes. Journal of Environmental Chemical Engineering. 2020; 8: 104054. https://doi.org/10.1016/j.jece.2020.104054.

[21] Abdelhamid HN. Surfactant assisted synthesis of hierarchical porous metal-organic frameworks nanosheets. Nanotechnology. 2019; 30: 435601. https://doi.org/10.1088/1361-6528/ab30f6.

[22] Abdelhamid HN, Talib A, Wu HF. One pot synthesis of gold-carbon dots nanocomposite and its application for cytosensing of metals for cancer cells. Talanta. 2017; 166: 357–363. https://doi.org/10.1016/j.talanta.2016.11.030.

[23] Abdelhamid HN, Wu HF. Nanoparticles Advanced Drug Delivery For Cancer Cells. In Keservani, R.K., Sharma, A.K. (eds.) Nanoparticulate Drug Delivery Systems (pp. 121–144). 1st edn. Apple Academic Press: New York. 2019.

[24] Emam HE, Abdelhamid HN, Abdelhameed RM. Self-cleaned photoluminescent viscose fabric incorporated lanthanide-organic framework (Ln-MOF). Dyes and Pigments. 2018; 159: 491–498. https://doi.org/10.1016/j.dyepig.2018.07.026.

[25] Kassem AA, Abdelhamid HN, Fouad DM, Ibrahim SA. Metal-organic frameworks (MOFs) and MOFs-derived CuO@C for hydrogen generation from sodium borohydride. International Journal of Hydrogen Energy. 2019; 44: 31230–31238. https://doi.org/10.1016/j.ijhydene.2019.10.047.

[26] Zhang X, Li G, Wu D, Li X, Hu N, Chen J, *et al*. Recent progress in the design fabrication of metal-organic frameworks-based nanozymes and their applications to sensing and cancer therapy. Biosensors & Bioelectronics. 2019; 137: 178–198. https://doi.org/10.1016/j.bios.2019.04.061.

[27] Damian-Buda AI, Alipanah N, Bider F, Sisman O, Neščáková Z, Boccaccini AR. Metal-organic framework (MOF)-bioactive glass (BG) systems for biomedical applications-A review. Materials Today. Bio. 2024; 30: 101413. https://doi.org/10.1016/j.mtbio.2024.101413.

[28] Imaz I, Rubio-Martínez M, An J, Solé-Font I, Rosi NL, Maspoch D. Metal-biomolecule frameworks (MBioFs). Chemical Communications: Chem Comm/the Royal Society of Chemistry. 2011; 47: 7287–7302. https://doi.org/10.1039/c1cc11202c.

[29] Doonan C, Riccò R, Liang K, Bradshaw D, Falcaro P. Metal-Organic Frameworks at the Biointerface: Synthetic Strategies and Applications. Accounts of Chemical Research. 2017; 50: 1423–1432. https://doi.org/10.1021/acs.accounts.7b00090.

[30] Kempahanumakkagari S, Kumar V, Samaddar P, Kumar P, Ramakrishnappa T, Kim KH. Biomolecule-embedded metal-organic frameworks as an innovative sensing platform. Biotechnology Advances. 2018; 36: 467–481. https://doi.org/10.1016/j.biotechadv.2018.01.014.

[31] Riccò R, Liang W, Li S, Gassensmith JJ, Caruso F, Doonan C, *et al*. Metal-Organic Frameworks for Cell and Virus Biology: A Perspective. ACS Nano. 2018; 12: 13–23. https://doi.org/10.1021/acsnano.7b08056.

[32] Li S, Dharmarwardana M, Welch RP, Benjamin CE, Shamir AM, Nielsen SO, *et al*. Investigation of Controlled Growth of Metal-Organic Frameworks on Anisotropic Virus Particles. ACS Applied Materials & Interfaces. 2018; 10: 18161–18169. https://doi.org/10.1021/acsami.8b01369.

[33] Li X, Li D, Zhang Y, Lv P, Feng Q, Wei Q. Encapsulation of enzyme by metal-organic framework for single-enzymatic biofuel cell-based self-powered biosensor. Nano Energy. 2020; 68: 104308. https://doi.org/10.1016/j.nanoen.2019.104308.

[34] Zhang T, Yu Y, Lu Y, Tang H, Chen K, Shi J, *et al*. Bridging biodegradable metals and biodegradable polymers: a comprehensive review of biodegradable metal-organic frameworks for biomedical application. Progress in Materials Science. 2026; 155: 101526. https://doi.org/10.1016/j.pmatsci.2025.101526.

[35] Zhang T, Yu Y, Yuan W, Ren Z, Cheng Y, Wu S, *et al*. Photothermally controlled ICG@ZIF-8/PLGA coating to modify the degradation behavior and biocompatibility of Zn-Li alloy for bone implants. Regenerative Biomaterials. 2025; 12: rbaf001. https://doi.org/10.1093/rb/rbaf001.

[36] Li S, Lin Y, Mo C, Bi J, Liu C, Lu Y, *et al*. Application of metal-organic framework materials in regenerative medicine. Journal of Materials Chemistry. B. 2024; 12: 8543–8576. https://doi.org/10.1039/D4TB00226A.

[37] Park KS, Ni Z, Côté AP, Choi JY, Huang R, Uribe-Romo FJ, *et al*. Exceptional chemical and thermal stability of zeolitic imidazolate frameworks. Proceedings of the National Academy of Sciences of the United States of America. 2006; 103: 10186–10191. https://doi.org/10.1073/pnas.0602439103.

[38] Xiang J, Li Z, Tseng S, Li T, Wang L, Li Z, *et al*. Multifunctional MOF microneedle patch with adsorbed exosomes for enhanced diabetic wound healing. Materials Today. Bio. 2025; 33: 102076. https://doi.org/10.1016/j.mtbio.2025.102076.

[39] Abdelhamid HN, Dowaidar M, Hällbrink M, Langel Ü. Gene delivery using cell penetrating peptides-zeolitic imidazolate frameworks. Microporous and Mesoporous Materials. 2020; 300: 110173. https://doi.org/10.1016/j.micromeso.2020.110173.

[40] Abdelhamid HN. Salts Induced Formation of Hierarchical Porous ZIF-8 and Their Applications for CO_2 Sorption and Hydrogen Generation via $NaBH_4$ Hydrolysis. Macromolecular Chemistry and Physics. 2020; 221: 2000031. https://doi.org/10.1002/macp.202000031.

[41] Abdelhamid HN, El-Zohry AM, Cong J, Thersleff T, Karlsson M, Kloo L, *et al*. Towards implementing hierarchical porous zeolitic imidazolate frameworks in dye-sensitized solar cells. Royal Society Open Science. 2019; 6: 190723. https://doi.org/10.1098/rsos.190723.

[42] Abdelhamid HN. Zinc hydroxide nitrate nanosheets conversion into hierarchical zeolitic imidazolate frameworks nanocomposite and their application for CO_2 sorption. Materials Today Chemistry. 2020; 15: 100222. https://doi.org/10.1016/j.mtchem.2019.100222.

[43] Zhang J, Tan Y, Song WJ. Zeolitic imidazolate frameworks for use in electrochemical and optical chemical sensing and biosensing: a review. Microchimica Acta. 2020; 187: 234. https://doi.org/10.1007/s00604-020-4173-3.

[44] Sun CY, Qin C, Wang XL, Yang GS, Shao KZ, Lan YQ, *et al*. Zeolitic Imidazolate framework-8 as efficient pH-sensitive drug delivery vehicle. Dalton Transactions: an International Journal of Inorganic Chemistry/RSoC. 2012; 41: 6906–6909. https://doi.org/10.1039/c2dt30357d.

[45] Asadniaye Fardjahromi M, Razmjou A, Vesey G, Ejeian F, Banerjee B, Chandra Mukhopadhyay S, *et al*. Mussel inspired ZIF8 microcarriers: a new approach for large-scale production of stem cells. RSC Advances. 2020; 10: 20118–20128. https://doi.org/10.1039/D0RA04090H.

[46] Yang Y, Wang Y, Zhou Y, Zhang X, Chen Y, Lu B, *et al*. Mapping the landscape of metal-organic frameworks in orthopedics: a review. MedMat. 2025; 2: 118–132. https://doi.org/10.1097/mm9.0000000000000017.

[47] Xue Y, Zhu Z, Zhang X, Chen J, Yang X, Gao X, *et al*. Accelerated Bone Regeneration by MOF Modified Multifunctional Membranes through Enhancement of Osteogenic and Angiogenic Performance. Advanced Healthcare Materials. 2021; 10: e2001369. https://doi.org/10.1002/adhm.202001369.

[48] Toprak Ö, Topuz B, Monsef YA, Oto Ç, Orhan K, Karakeçili A. BMP-6 carrying metal organic framework-embedded in bioresorbable electrospun fibers for enhanced bone regeneration. Materials Science & Engineering. C, Materials for Biological Applications. 2021; 120: 111738. https://doi.org/10.1016/j.msec.2020.111738.

[49] Feng H, Li Z, Xie W, Wan Q, Guo Y, Chen J, *et al*. Delivery of therapeutic miRNAs using nanoscale zeolitic imidazolate framework for accelerating vascularized bone regeneration. Chemical Engineering Journal. 2022; 430: 132867. https://doi.org/10.1016/j.cej.2021.132867.

[50] Li Y, Zhu J, Zhang X, Li Y, Zhang S, Yang L, *et al*. Drug-Delivery Nanoplatform with Synergistic Regulation of Angiogenesis-Osteogenesis Coupling for Promoting Vascularized Bone Regeneration. ACS Applied Materials & Interfaces. 2023; 15: 17543–17561. https://doi.org/10.1021/acsami.2c23107.

[51] Kang Y, Xu C, Meng L, Dong X, Qi M, Jiang D. Exosome-functionalized magnesium-organic framework-based scaffolds with osteogenic, angiogenic and anti-inflammatory properties for accelerated bone regeneration. Bioactive Materials. 2022; 18: 26–41. https://doi.org/10.1016/j.bioactmat.2022.02.012.

[52] Zheng W, Meng Z, Zhu Z, Wang X, Xu X, Zhang Y, *et al*. Metal-Organic Framework-Based Nanomaterials for Regulation of the Osteogenic Microenvironment. Small. 2024; 20: e2310622. https://doi.org/10.1002/smll.202310622.

[53] Lao A, Wu J, Li D, Shen A, Li Y, Zhuang Y, *et al*. Functionalized Metal-Organic Framework-Modified Hydrogel That Breaks the Vicious Cycle of Inflammation and ROS for Repairing of Diabetic Bone Defects. Small. 2023; 19: e2206919. https://doi.org/10.1002/smll.202206919.

[54] Al-Baadani MA, Xu L, Hii Ru Yie K, Sun A, Gao X, Cai K, *et al*. *In situ* preparation of alendronate-loaded ZIF-8 nanoparticles on electrospun nanofibers for accelerating early osteogenesis in osteoporosis. Materials & Design. 2022; 217: 110596. https://doi.org/10.1016/j.matdes.2022.110596.

[55] Yao K, Zhang Q, Weng L, Li S, Zheng X, Hu L, *et al*. Cerium-Doped, Alendronate-Loaded, Metal–Organic Framework Nanodrug for Delayed Osteoporosis Progress. ACS Applied Nano Materials. 2024; 7: 28504–28518. https://doi.org/10.1021/acsanm.4c05640.

[56] Xu C, Kang Y, Dong X, Jiang D, Qi M. Integration exosomes with MOF-modified multifunctional scaffold for accelerating vascularized bone regeneration. Chinese Chemical Letters. 2023; 34: 107528. https://doi.org/10.1016/j.cclet.2022.05.042.

[57] Xu C, Kang Y, Guan S, Dong X, Jiang D, Qi M. Iron-based metal–organic framework as a dual cooperative release system for enhanced vascularization and bone regeneration. Chinese Chemical Letters. 2023; 34: 107825. https://doi.org/10.1016/j.cclet.2022.107825.

[58] Zheng Z, Chen Y, Guo B, Wang Y, Liu W, Sun J, *et al*. Magnesium-organic framework-based stimuli-responsive systems that optimize the bone microenvironment for enhanced bone regeneration. Chemical Engineering Journal. 2020; 396: 125241. https://doi.org/10.1016/j.cej.2020.125241.

[59] Zhu Z, Jiang S, Liu Y, Gao X, Hu S, Zhang X, *et al*. Micro or nano: Evaluation of biosafety and biopotency of magnesium metal organic framework-74 with different particle sizes. Nano Research. 2020; 13: 511–526. https://doi.org/10.1007/s12274-020-2642-y.

[60] Ge Y, Wang K, Li H, Tian Y, Wu Y, Lin Z, *et al*. An Mg-MOFs based multifunctional medicine for the treatment of osteoporotic pain. Materials Science & Engineering. C, Materials for Biological Applications. 2021; 129: 112386. https://doi.org/10.1016/j.msec.2021.112386.

[61] Sun Y, Liu X, Zhu Y, Han Y, Shen J, Bao B, *et al*. Tunable and Controlled Release of Cobalt Ions from Metal-Organic Framework Hydrogel Nanocomposites Enhances Bone Regeneration. ACS Applied Materials & Interfaces. 2021; 13: 59051–59066. https://doi.org/10.1021/acsami.1c16300.

[62] Liu Y, Zhu Z, Pei X, Zhang X, Cheng X, Hu S, *et al*. ZIF-8-Modified Multifunctional Bone-Adhesive Hydrogels Promoting Angiogenesis and Osteogenesis for Bone Regeneration. ACS Applied Materials & Interfaces. 2020; 12: 36978–36995. https://doi.org/10.1021/acsami.0c12090.

[63] Dong W, Zhao S, Wang Y, Zhou X, Jiang J, Dang J, *et al*. Stimuli-responsive metal–organic framework hydrogels endow long carbon fiber reinforced polyetheretherketone with enhanced anti-inflammatory and angiogenesis and osteogenesis. Materials & Design. 2023; 225: 111485. https://doi.org/10.1016/j.matdes.2022.111485.

[64] McKinlay AC, Morris RE, Horcajada P, Férey G, Gref R, Couvreur P, *et al*. BioMOFs: metal-organic frameworks for biological and medical applications. Angewandte Chemie. 2010; 49: 6260–6266. https://doi.org/10.1002/anie.201000048.

[65] Giménez-Marqués M, Hidalgo T, Serre C, Horcajada P. Nanostructured metal–organic frameworks and their bio-related applications. Coordination Chemistry Reviews. 2016; 307: 342–360. https://doi.org/10.1016/j.ccr.2015.08.008.

[66] Rojas S, Devic T, Horcajada P. Metal organic frameworks based on bioactive components. Journal of Materials Chemistry. B. 2017; 5: 2560–2573. https://doi.org/10.1039/C6TB03217F.

[67] Cai H, Xu LL, Lai HY, Liu JY, Ng SW, Li D. A highly emissive and stable zinc(ii) metal-organic framework as a host-guest chemopalette for approaching white-light-emission. Chemical Communications: Chem Comm/the Royal Society of Chemistry. 2017; 53: 7917–7920. https://doi.org/10.1039/C7CC03350H.

[68] Li MY, Wang F, Gu ZG, Zhang J. Synthesis of homochiral zeolitic metal-organic frameworks with amino acid and tetrazolates for chiral recognition. RSC Advances. 2017; 7: 4872–4875. https://doi.org/10.1039/C6RA27069G.

[69] Zhang JB, Li N, Gu ZG, Zhang J. Multilevel Chiral Semiconductor Metal-Peptide Framework Thin Film for Highly Circularly Polarized Visible Photodetection. Journal of the American Chemical Society. 2025; 147: 26674–26683. https://doi.org/10.1021/jacs.5c07024.

[70] Yang G, Zhang X, Kochovski Z, Zhang Y, Dai B, Sakai F, *et al*. Precise and Reversible Protein-Microtubule-Like Structure with Helicity Driven by Dual Supramolecular Interactions. Journal of the American Chemical Society. 2016; 138: 1932–1937. https://doi.org/10.1021/jacs.5b11733.

[71] Yang X, Wu C. Metalloporphyrinic Framework Containing Multiple Pores for Highly Efficient and Selective Epoxidation. Inorganic Chemistry. 2014; 53: 4797–4799. https://doi.org/10.1021/ic500531k.

[72] Zhao M, Wu CD. Biomimetic Activation of Molecular Oxygen with a Combined Metalloporphyrinic Framework and Co-catalyst Platform. ChemCatChem. 2017; 9: 1192–1196. https://doi.org/10.1002/cctc.201601606.

[73] Liu J, Bao TY, Yang XY, Zhu PP, Wu LH, Sha JQ, *et al*. Controllable porosity conversion of metal-organic frameworks composed of natural ingredients for drug delivery. Chemical Communications: Chem Comm/the Royal Society of Chemistry. 2017; 53: 7804–7807. https://doi.org/10.1039/c7cc03673f.

[74] Hartlieb KJ, Holcroft JM, Moghadam PZ, Vermeulen NA, Algaradah MM, Nassar MS, *et al*. CD-MOF: A Versatile Separation Medium. Journal of the American Chemical Society. 2016; 138: 2292–2301. https://doi.org/10.1021/jacs.5b12860.

[75] Cai H, Li M, Lin XR, Chen W, Chen GH, Huang XC, *et al*. Spatial, Hysteretic, and Adaptive Host-Guest Chemistry in a Metal-Organic Framework with Open Watson-Crick Sites. Angewandte Chemie International Edition. 2015; 54: 10454–10459. https://doi.org/10.1002/anie.201502045.

[76] Sun RW, Zhang M, Li D, Zhang ZF, Cai H, Li M, *et al*. Dinuclear Gold(I) Pyrrolidinedithiocarbamato Complex: Cytotoxic and Antimigratory Activities on Cancer Cells and the Use of Metal-Organic Framework. Chemistry: a European Journal. 2015; 21: 18534–18538. https://doi.org/10.1002/chem.201503656.

[77] An J, Farha OK, Hupp JT, Pohl E, Yeh JI, Rosi NL. Metal-adeninate vertices for the construction of an exceptionally porous metal-organic framework. Nature Communications. 2012; 3: 604. https://doi.org/10.1038/ncomms1618.

[78] Zhang M, Lu W, Li JR, Bosch M, Chen YP, Liu TF, *et al*. Design and synthesis of nucleobase-incorporated metal-organic materials. Inorganic Chemistry Frontiers. 2014; 1: 159–162. https://doi.org/10.1039/c3qi00042g.

[79] Navarro-Sánchez J, Argente-García AI, Moliner-Martínez Y, Roca-Sanjuán D, Antypov D, Campíns-Falcó P, *et al*. Peptide Metal-Organic Frameworks for Enantioselective Separation of Chiral Drugs. Journal of the American Chemical Society. 2017; 139: 4294–4297. https://doi.org/10.1021/jacs.7b00280.

[80] Sontz PA, Bailey JB, Ahn S, Tezcan FA. A Metal Organic Framework with Spherical Protein Nodes: Rational Chemical Design of 3D

Protein Crystals. Journal of the American Chemical Society. 2015; 137: 11598–11601. https://doi.org/10.1021/jacs.5b07463.

[81] Yang J, Trickett CA, Alahmadi SB, Alshammari AS, Yaghi OM. Calcium l-Lactate Frameworks as Naturally Degradable Carriers for Pesticides. Journal of the American Chemical Society. 2017; 139: 8118–8121. https://doi.org/10.1021/jacs.7b04542.

[82] Meng AN, Chaihu LX, Chen HH, Gu ZY. Ultrahigh adsorption and singlet-oxygen mediated degradation for efficient synergetic removal of bisphenol A by a stable zirconium-porphyrin metal-organic framework. Scientific Reports. 2017; 7: 6297. https://doi.org/10.1038/s41598-017-06194-z.

[83] Luzuriaga MA, Welch RP, Dharmarwardana M, Benjamin CE, Li S, Shahrivarkevishahi A, *et al*. Enhanced Stability and Controlled Delivery of MOF-Encapsulated Vaccines and Their Immunogenic Response *In Vivo*. ACS Applied Materials & Interfaces. 2019; 11: 9740–9746. https://doi.org/10.1021/acsami.8b20504.

[84] Zhou Z, Gao Z, Shen H, Li M, He W, Su P, *et al*. Metal-Organic Framework *in Situ* Post-Encapsulating DNA-Enzyme Composites on a Magnetic Carrier with High Stability and Reusability. ACS Applied Materials & Interfaces. 2020; 12: 7510–7517. https://doi.org/10.1021/acsami.9b23526.

[85] Chen G, Huang S, Kou X, Zhu F, Ouyang G. Embedding Functional Biomacromolecules within Peptide-Directed Metal-Organic Framework (MOF) Nanoarchitectures Enables Activity Enhancement. Angewandte Chemie. 2020; 59: 13947–13954. https://doi.org/10.1002/anie.202005529.

[86] Zou D, Yu L, Sun Q, Hui Y, Tengjisi, Liu Y, *et al*. A general approach for biomimetic mineralization of MOF particles using biomolecules. Colloids and Surfaces. B, Biointerfaces. 2020; 193: 111108. https://doi.org/10.1016/j.colsurfb.2020.111108.

[87] Carraro F, Velásquez-Hernández MJ, Astria E, Liang W, Twight L, Parise C, *et al*. Phase dependent encapsulation and release profile of ZIF-based biocomposites. Chemical Science. 2020; 11: 3397–3404. https://doi.org/10.1039/C9SC05433B.

[88] Chen G, Kou X, Huang S, Tong L, Shen Y, Zhu W, *et al*. Modulating the Biofunctionality of Metal-Organic-Framework-Encapsulated Enzymes through Controllable Embedding Patterns. Angewandte Chemie. 2020; 59: 2867–2874. https://doi.org/10.1002/anie.201913231.

[89] Hoop M, Walde CF, Riccò R, Mushtaq F, Terzopoulou A, Chen XZ, *et al*. Biocompatibility characteristics of the metal organic framework ZIF-8 for therapeutical applications. Applied Materials Today. 2018; 11: 13–21. https://doi.org/10.1016/j.apmt.2017.12.014.

[90] Clézardin P, Coleman R, Puppo M, Ottewell P, Bonnelye E, Paycha F, *et al*. Bone metastasis: mechanisms, therapies, and biomarkers. Physiological Reviews. 2021; 101: 797–855. https://doi.org/10.1152/physrev.00012.2019.

[91] Walsh MC, Takegahara N, Kim H, Choi Y. Updating osteoimmunology: regulation of bone cells by innate and adaptive immunity. Nature Reviews. Rheumatology. 2018; 14: 146–156. https://doi.org/10.1038/nrrheum.2017.213.

[92] Li J, Yin S, Zhou L, Nezamzadeh-Ejhieh A, Pan Y, Qiu L, *et al*. Advances in the study of metal-organic frameworks and their biomolecule composites for osteoporosis therapeutic applications. Biomaterials Science. 2024; 12: 5912–5932. https://doi.org/10.1039/D4BM01081G.

[93] Li M, Yin S, Lin M, Chen X, Pan Y, Peng Y, *et al*. Current status and prospects of metal-organic frameworks for bone therapy and bone repair. Journal of Materials Chemistry. B. 2022; 10: 5105–5128. https://doi.org/10.1039/D2TB00742H.

[94] Anish RJ, Nair A. Osteoporosis management-current and future perspectives-A systemic review. Journal of Orthopaedics. 2024; 53: 101–113. https://doi.org/10.1016/j.jor.2024.03.002.

[95] Reid IR, McClung MR. Osteopenia: a key target for fracture prevention. The Lancet. Diabetes & Endocrinology. 2024; 12: 856–864. https://doi.org/10.1016/S2213-8587(24)00225-0.

[96] Álvarez-Rivas N, Lugo-Rodríguez G, Maneiro JR, Iñiguez-Ubiaga C, Melero-Gonzalez RB, Iglesias-Cabo T, *et al*. Tumor-induced osteomalacia: a systematic literature review. Bone Reports. 2024; 21: 101772. https://doi.org/10.1016/j.bonr.2024.101772.

[97] Jovanovic M, Marini JC. Update on the Genetics of Osteogenesis Imperfecta. Calcified Tissue International. 2024; 115: 891–914. https://doi.org/10.1007/s00223-024-01266-5.

[98] Yang Z, Lin B, Ren H, Liu Y, Huang K, Guo Q, *et al*. Risk factors for osteomyelitis: a systematic review and meta-analysis. International Journal of Surgery. 2025; 111: 5606–5622. https://doi.org/10.1097/JS9.0000000000002811.

[99] Guan Y, Zhang W, Mao Y, Li S. Nanoparticles and bone microenvironment: a comprehensive review for malignant bone tumor diagnosis and treatment. Molecular Cancer. 2024; 23: 246. https://doi.org/10.1186/s12943-024-02161-1.

[100] Biasucci G, Donini V, Cannalire G. Rickets Types and Treatment with Vitamin D and Analogues. Nutrients. 2024; 16: 416. https://doi.org/10.3390/nu16030416.

[101] Kubisa MJ, Kubisa MG, Pałka K, Sobczyk J, Bubieńczyk F, Łęgosz P. Avascular Necrosis of the Talus: Diagnosis, Treatment, and Modern Reconstructive Options. Medicina. 2024; 60: 1692. https://doi.org/10.3390/medicina60101692.

[102] Mi B, Xiong Y, Zhao Y, Lin Z, Lu L, Liu G, *et al*. Metal–Organic Framework-Integrated Composites for Bone Tissue Regeneration. Advanced Functional Materials. 2024; 34: 2308656. https://doi.org/10.1002/adfm.202308656.

[103] Abdelhamid HN. Zeolitic Imidazolate Frameworks (ZIF-8) for Biomedical Applications: A Review. Current Medicinal Chemistry. 2021; 28: 7023–7075. https://doi.org/10.2174/0929867328666210608143703.

[104] Chen J, Zhang X, Huang C, Cai H, Hu S, Wan Q, *et al*. Osteogenic activity and antibacterial effect of porous titanium modified with metal-organic framework films. Journal of Biomedical Materials Research. Part A. 2017; 105: 834–846. https://doi.org/10.1002/jbm.a.35960.

[105] Wang X, Miao D, Liang X, Liang J, Zhang C, Yang J, *et al*. Nanocapsules engineered from polyhedral ZIF-8 templates for bone-targeted hydrophobic drug delivery. Biomaterials Science. 2017; 5: 658–662. https://doi.org/10.1039/C6BM00915H.

[106] Yu YS, Hsu CH, Cheng PH, Wu KCW, Liu CH. Poly(acrylic acid)-grafted metal-organic framework carrying Mg ions for bone repair. Materials Chemistry and Physics. 2022; 292: 126840. https://doi.org/10.1016/j.matchemphys.2022.126840.

[107] Li J, Zhao M, Xiang X, He Q, Gui R. A novel biomimetic nanomedicine system with anti-inflammatory and anti-osteoporosis effects improves the therapy efficacy of steroid-resistant nephrotic syndrome. Journal of Nanobiotechnology. 2021; 19: 417. https://doi.org/10.1186/s12951-021-01165-z.

[108] Alsaikhan F, Mahmoud MZ, Suliman M. 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. Frontiers in Bioengineering and Biotechnology. 2023; 11: 1153969. https://doi.org/10.3389/fbioe.2023.1153969.

[109] Duan Z, Yao Y, Liu J, Tan Y, Wang Q, Fang M, *et al.* Enhanced Osteogenesis and Antibacterial Properties of Ketoprofen-Loaded MgCu-MOF74-Coated Titanium Alloy for Bone Implant. Journal of Functional Biomaterials. 2025; 16: 222. https://doi.org/10.3390/jfb16060222.

[110] Liu F, Liang Z, Zhang Y, Qin S, Zhang S, Zhang T, *et al.* Evaluation of the potential application of RAPA-based delivery: Structural evolution and biocompatibility of monodispersed nano-ZIF-8@RAPA. Materials Today Communications. 2025; 47: 113163. https://doi.org/10.1016/j.mtcomm.2025.113163.

[111] Moris H, Ghaee A, Sharifloo MM, Hosseini I, Nouri-Felekori M. Gelatin-zirconium based metal-organic framework (MOF 801)

nanocomposite scaffold for bone tissue engineering. Ceramics International. 2024; 50: 23986–23998. https://doi.org/10.1016/j.ceramint.2024.04.129.

[112] Salcedo-Abraira P, Fernández-Grajera M, Guerrero-Román FA, Rodríguez-Diéguez A, Luque-Agudo V, González-Martín ML, *et al*. Calcium Medronate-Based Metal-Organic Frameworks as Multifunctional Biomaterials. Crystal Growth & Design. 2025; 25: 1415–1422. https://doi.org/10.1021/acs.cgd.4c01478.

[113] Xian S, Lin Y, Wang H, Li J. Calcium-Based Metal–Organic Frameworks and their Potential Applications. Small. 2021; 17: 2005165. https://doi.org/10.1002/smll.202005165.

[114] Jha CB, Singh C, Varshney R, Singh S, Manna K, Mathur R. Development of novel aspartic acid-based calcium bio-MOF designed for the management of severe bleeding. Materials Advances. 2023; 4: 3330–3343. https://doi.org/10.1039/D3MA00061C.

[115] An J, Miao Y, Xu Y, Huang Y, Wang H, Wang J, *et al*. Biodegradable Ca-MOF Nanoplatform with Intracellular H_2O_2-Triggered CO Release to Augment Mitochondrial Ca^{2+} Overload for Synergistic Cancer Therapy. Inorganic Chemistry. 2025; 64: 19525–19531. https://doi.org/10.1021/acs.inorgchem.5c04034.

[116] Perivolaris A, Galanakos S, Xamonaki N, Pavlos D. Alkaline earth metal (Ca, Sr)-organic frameworks (MOFs) in orthopedic conditions management. Chemical Paper. 2025: 79. https://doi.org/10.1007/s11696-025-04467-w.

[117] Li J, Wu J, Liu F, Li X, Yu P, Pan H, *et al*. Magnesium-Organic Framework-Loaded Bisphosphonate-Functionalized Gel Scaffolds for Enhanced Bone Regeneration. ACS Biomaterials Science & Engineering. 2023; 9: 6849–6859. https://doi.org/10.1021/acsbiomaterials.3c01080.

[118] Sun X, Xu X, Zhao X, Ma J, Wang T, Yue X, *et al*. Three-Dimensional Bioprinted Scaffolds Loaded with Multifunctional Magnesium-Based Metal-Organic Frameworks Improve the Senescence Microenvironment Prompting Aged Bone Defect Repair. ACS Nano. 2025; 19: 22141–22162. https://doi.org/10.1021/acsnano.5c03023.

[119] Choi CE, Liang C, Shamiya Y, Lee SJ, Paul A. Co-Delivery of Ca-MOF and Mg-MOF Using Nanoengineered Hydrogels to Promote *In Situ* Mineralization and Bone Defect Repair: *In Vitro* and *In Vivo* Analysis. Advanced Healthcare Materials. 2025. (online ahead of print) https://doi.org/10.1002/adhm.202502630.

[120] Dousti M, Golmohamadpour A, Hami Z, Jamalpoor Z. Ca-AlN MOFs-loaded chitosan/gelatin scaffolds; a dual-delivery system for bone tissue engineering applications. Nanotechnology. 2024; 35: 145101. https://doi.org/10.1088/1361-6528/ad0ef4.

[121] Chen M, Wang D, Li M, He Y, He T, Chen M, *et al*. Nanocatalytic Biofunctional MOF Coating on Titanium Implants Promotes Osteoporotic Bone Regeneration through Cooperative Pro-osteoblastogenesis MSC Reprogramming. ACS Nano. 2022; 16: 15397–15412. https://doi.org/10.1021/acsnano.2c07200.

[122] Matlinska MA, Ha M, Hughton B, Oliynyk AO, Iyer AK, Bernard GM, *et al*. Alkaline Earth Metal-Organic Frameworks with Tailorable Ion Release: A Path for Supporting Biomineralization. ACS Applied Materials & Interfaces. 2019; 11: 32739–32745. https://doi.org/10.1021/acsami.9b11004.

[123] Zhu T, Ni Q, Wang W, Guo D, Li Y, Chen T, *et al*. Cu-MOF-Decorated 3D-Printed Scaffolds for Infection Control and Bone Regeneration. Journal of Functional Biomaterials. 2025; 16: 83. https://doi.org/10.3390/jfb16030083.

[124] Luo Z, Ma J, Wang Y, Du Y, Liu Y, Zhang W, *et al*. Application of Mg-MOF-loaded gelatin microspheres with osteogenic, angiogenic, and ROS scavenging capabilities in bone defect repair. International Journal of Biological Macromolecules. 2024; 280: 135721. https://doi.org/10.1016/j.ijbiomac.2024.135721.

[125] Wang X, Qiu X, Pei J, Zhao D, Yan Y. Fabrication of magnesium phosphate bone cement with enhanced osteogenic properties by employing zeolitic imidazolate framework-8. Journal of Materials Research. 2022; 37: 2761–2774. https://doi.org/10.1557/s43578-022-00663-6.

[126] Zhong L, Chen J, Ma Z, Feng H, Chen S, Cai H, *et al*. 3D printing of metal-organic framework incorporated porous scaffolds to promote osteogenic differentiation and bone regeneration. Nanoscale. 2020; 12: 24437–24449. https://doi.org/10.1039/D0NR06297A.

[127] Pan Y, Wang J, Jiang Z, Guo Q, Zhang Z, Li J, *et al*. Zoledronate combined metal-organic frameworks for bone-targeting and drugs deliveries. Scientific Reports. 2022; 12: 12290. https://doi.org/10.1038/s41598-022-15941-w.

[128] Wu J, Jiang S, Xie W, Xue Y, Qiao M, Yang X, *et al*. Surface modification of the Ti surface with nanoscale bio-MOF-1 for improving biocompatibility and osteointegration *in vitro* and *in vivo*. Journal of Materials Chemistry. B. 2022; 10: 8535–8548. https://doi.org/10.1039/D2TB01311H.

[129] Zhou J, Lin G, Fu X, Qiu S, Zhang Y, Chen X, *et al*. ZIF-8-Modified Multifunctional Hydrogel Loading siRNA and DOX for Postoperative Therapy of Maxillofacial Osteosarcoma and Bone Repair. ACS Applied Materials & Interfaces. 2025; 17: 17990–18002. https://doi.org/10.1021/acsami.4c21331.

[130] Gao X, Xue Y, Zhu Z, Chen J, Liu Y, Cheng X, *et al*. Nanoscale Zeolitic Imidazolate Framework-8 Activator of Canonical MAPK Signaling for Bone Repair. ACS Applied Materials & Interfaces. 2021; 13: 97–111. https://doi.org/10.1021/acsami.0c15945.

[131] Zhang X, Chen JY, Pei X, Li YH, Feng H, He ZH, *et al*. One-Pot Facile Encapsulation of Dimethyloxallyl Glycine by Nanoscale Zeolitic Imidazolate Frameworks-8 for Enhancing Vascularized Bone Regeneration. Advanced Healthcare Materials. 2023; 12: e2202317. https://doi.org/10.1002/adhm.202202317.

[132] Bai L, Zhang X, Shen W, Wang P, Yin X, Liu J, *et al*. Multifunctional Scaffold Comprising Metal-Organic Framework, Hydrogel, and Demineralized Bone Matrix for the Treatment of Steroid-Induced Femoral Head Necrosis. Small. 2025; 21: e2407758. https://doi.org/10.1002/smll.202407758.

[133] Wei R, Hu S, Wang J, Lei Q, Jiang Z, Wang B, *et al*. Oral delivery of teriparatide utilizing biocompatible transferrin-engineered MOF nanoparticles for osteoporosis therapy. Materials Today. Bio. 2025; 35: 102318. https://doi.org/10.1016/j.mtbio.2025.102318.

[134] Mujtaba AG, Altunay BB, Pinarbasi B, Topuz B, Yilgor P, Karakeçili A. Zr-based metal-organic framework nanocrystals improve the osteoinductivity and osteogenicity of alginate/methyl cellulose bioink. International Journal of Biological Macromolecules. 2025; 313: 144255. https://doi.org/10.1016/j.ijbiomac.2025.144255.

[135] Karakeçili A, Topuz B, Ersoy FŞ, Şahin T, Günyakti A, Demirtaş TT. UiO-66 metal-organic framework as a double actor in chitosan scaffolds: Antibiotic carrier and osteogenesis promoter. Biomaterials Advances. 2022; 136: 212757. https://doi.org/10.1016/j.bioadv.2022.212757.

[136] Ghasemi S, Esmaeili M, Dinari M, Dabiri A, Karbasi S. UiO-66 Metal-organic Framework (MOF) as an Osteogenic Stimulant in the Poly-3-hydroxybutyrate-zein/UiO-66 Electrospun Composite Scaffold for Bone Tissue Engineering Applications. Journal of Polymers and the Environment. 2025; 33: 2001–2028. https://doi.org/10.1007/s10924-025-03521-8.

[137] Shao G, Huang X, Shen X, Li C, Thomas A. Metal-Organic Framework and Covalent-Organic Framework-Based Aerogels: Synthesis, Functionality, and Applications. Advanced Science. 2024; 11: 2409290. https://doi.org/10.1002/advs.202409290.

[138] Abdelhamid HN, Sultan S, Mathew AP. 3D printing of cellulose/leaf-like zeolitic imidazolate frameworks (CelloZIF-L) for adsorption of carbon dioxide (CO_2) and heavy metal ions. Dalton Transactions: an International Journal of Inorganic Chemistry/RSoC. 2023; 52: 2988–2998. https://doi.org/10.1039/D2DT04168E.

[139] Kumi M, Kpomah B, Ejeromedoghene O, Takyiwaa AG, Ehizo-

jie OA. 3D-Printed metal organic frameworks-based supramolecular hydrogel as biological materials. Supramolecular Materials. 2025; 4: 100100. https://doi.org/10.1016/j.supmat.2025.100100.

[140] Luo Q, Yang Y, Ho C, Li Z, Chiu W, Li A, *et al.* Dynamic hydrogel-metal-organic framework system promotes bone regeneration in periodontitis through controlled drug delivery. Journal of Nanobiotechnology. 2024; 22: 287. https://doi.org/10.1186/s12951-024-02555-9.

[141] Li Y, Guo Y, Cheng Y, Liu X, Li H, Liu C, *et al*. Dual-metal-organic framework and gallic acid incorporated 3D-printed scaffolds: Revolutionizing refractory bone defect repair through immune-angiogenic-neurogenic synergy. Materials Today. Bio. 2025; 35: 102323. https://doi.org/10.1016/j.mtbio.2025.102323.

[142] Han Y, Jia X, Yang Y, Guo P, Li C, Zhang Y, *et al*. Study of bioactive 3D-printed scaffolds incorporating zinc-based MOF for bone defect repair and anti-inflammatory applications. Materials Today. Bio. 2025; 32: 101884. https://doi.org/10.1016/j.mtbio.2025.101884.

[143] Zhao Z, Wang C, Liu A, Bai N, Jiang B, Mao Y, *et al.* Multiple applications of metal-organic frameworks (MOFs) in the treatment of orthopedic diseases. Frontiers in Bioengineering and Biotechnology. 2024; 12: 1448010. https://doi.org/10.3389/fbioe.2024.1448010.

[144] Huzum B, Lungu II, Alexa O, Sirbu PD, Cionca VD, Corciova A, *et al.* Nanotechnology in Osteogenesis and Inflammation Management: Metal-Organic Frameworks, Metal Complexes, and Biomaterials for Bone Restoration. Biomedicines. 2025; 13: 1597. https://doi.org/10.3390/biomedicines13071597.

[145] Xue Y, Xu W, Zhao D, Du Z, Jiang H, Lv H, *et al*. Biomimetic peroxidase MOF-Fe promotes bone defect repair by inhibiting TfR2 and activating the BMP2 pathway. Biology Direct. 2024; 19: 30. https://doi.org/10.1186/s13062-024-00473-2.

[146] Chen K, Wang Y, Tang H, Niu X, Yang H, Bai Y, *et al*. Fabrication of a Nanoscale Magnesium/Copper Metal-Organic Framework on Zn-Based Guided Bone Generation Membranes for Enhancing Osteogenesis, Angiogenesis, and Bacteriostasis Properties. ACS Applied Materials & Interfaces. 2024; 16: 5648–5665. https://doi.org/10.1021/acsami.3c16970.

[147] Fan Y, Long C, Cai Y, Hu Y, Peng L. Functionalized metal-organic framework and MOF-derived materials for bone regeneration applications. Frontiers in Bioengineering and Biotechnology. 2025; 13: 1645657. https://doi.org/10.3389/fbioe.2025.1645657.

[148] Liu Y, Wang S, Quan C, Luan S, Shi H, Wang L. Metal-organic framework-based platforms for implantation applications: recent advances and challenges. Journal of Materials Chemistry. B. 2024; 12: 637–649. https://doi.org/10.1039/D3TB02620E.

[149] Chen Y, Gao F, Li Y, Zeng D, Liu B, Liu L, *et al*. Recent advances in the synthesis and biomedical applications of multifunctional organic frameworks (MOFs, COFs, HOFs): A review. Journal of Alloys and Compounds. 2025; 1030: 180923. https://doi.org/10.1016/j.jallcom.2025.180923.

Editor's note: The Scientific Editor responsible for this paper was Yang Liu.

Received: 1st August 2025; **Accepted**: 26th November 2025; **Published**: 31st December 2025