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Metal-organic frameworks functionalized biomaterials for promoting bone repair

Chaoqian Zhao [a,1], Chaoqin Shu [a,1], Jiangming Yu [b,**], Yufang Zhu [a,c,*]

[a] State Key Laboratory of High Performance Ceramics and Superfine Microstructure, Shanghai Institute of Ceramics, Chinese Academy of Sciences, Shanghai, 200050, PR China

[b] Department of Orthopaedics, Tongren Hospital, Shanghai Jiaotong University, Shanghai, 200336, PR China

[c] Center of Materials Science and Optoelectronics Engineering, University of Chinese Academy of Sciences, Beijing, 100049, PR China

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ABSTRACT

Bone defects induced by bone trauma, tumors and osteoarthritis greatly affect the life quality and health of patients. The biomaterials with numerous advantages are becoming the most preferred options for repairing bone defects and treating orthopedic diseases. However, their repairing effects remains unsatisfactory, especially in bone defects suffering from tumor, inflammation, and/or bacterial infection. There are several strategies to functionalize biomaterials, but a more general and efficient method is essential for accomplishing the functionalization of biomaterials. Possessing high specific surface, high porosity, controlled degradability and variable composition, metal-organic frameworks (MOFs) materials are inherently advantageous for functionalizing biomaterials, with tremendous improvements having been achieved. This review summarizes recent progresses in MOFs functionalized biomaterials for promoting bone repair and therapeutic effects. In specific, by utilizing various properties of diverse MOFs materials, integrated MOFs functionalized biomaterials achieve enhanced bone regeneration, antibacterial, anti-inflammatory and anti-tumor functions. Finally, the summary and prospects of on the development of MOFs-functionalized biomaterials for promoting bone repair were discussed.

1. Introduction

Bone defects caused by various trauma, tumor, congenital abnormality and osteoarthritis have a direct impact on the human's life and health, and surgical implantation of appropriate biomaterials is the most effective strategy for treating and repairing these defects [1–3]. Traditionally, autogenous, allogeneic and xenogeneic bone grafts are common candidates for clinical therapies, but problems of sources availability, pathogens transmission and immune rejection have limited their applications [4–6]. The artificial implants with favorable biocompatibility and excellent mechanical property, have been the most preferred options. However, the bone repair effect of most artificial implants remains unsatisfactory, especially in bone defects suffering from tumor, inflammation, and/or bacterial infection [7–10]. In addition, certain bone diseases in special situations sometimes require functionalized particles for their therapeutic effects as well [11,12]. Therefore, it is essential to enhance the functional properties of biomaterials to improve bone repair and therapeutic effects.

To date, numerous studies have demonstrated that the functionalization of biomaterials is one of the most effective strategies for solving these problems and enhancing bone repair and therapeutic effects [11–18]. For example, strontium (Sr) has been proposed to dope into various biomaterials and released locally for a long time to promote new bone formation, exhibiting a prospects in bone tissue engineering [15]. Surface modification and BMP-2 loading on three-dimensional PCL scaffold significantly increased the long-term retention of BMP-2, osteoblast proliferation and osteogenic differentiation [13]. Nanofibrous scaffolds were designed to promote bone regeneration by integrating magnesium doped MBG, fusion protein osteocalcin-osteopontin-biglycan, silk fibroin and nerve growth factor for facilitating accelerated bone formation [17]. Due to the presence of oxygen vacancies and structural defects, black bioceramics produced by magnesium thermal reduction exhibited promising photothermal functionality and excellent antitumor activity against bone tumors,

* Corresponding author. State Key Laboratory of High Performance Ceramics and Superfine Microstructure, Shanghai Institute of Ceramics, Chinese Academy of Sciences, Shanghai, 200050, PR China.

** Corresponding author.

E-mail addresses: yjm_st@163.com (J. Yu), zjf2412@163.com (Y. Zhu).

[1] These authors contributed equally to this work.

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Abbreviation

BMP	Bone morphogenetic protein
β-TCP	β-calcium phosphate
HA	Hydroxyapatite
HKUST	Hong Kong University of Science and Technology
MIL	Material Institut Lavoisier
MOFs	metal organic frameworks
MBG	mesoporous bioglass
NIR	Near-infrared
PCL	Polycaprolactone
PCN	Porous coordination network
PEEK	Polyetheretherketone
PLGA	Poly (lactic-co-glycolic) acid
PLA	Polylactic acid
ROS	Reactive oxygen species
TCPP	*meso*-tetrakis(4-carboxylatephenyl)porphyrin
UiO	Universitetet i Oslo
ZIF	Zeolitic imidazolate framework

while retaining high bioactivity and regenerative capacity for bone repair [14]. Antioxidant epigallocatechin gallate was coated on the PCL surface to improve the anti-oxidative and ROS scavenging properties of biomaterials for bone tissue engineering [18]. Therefore, significant progresses had been made in functionalizing biomaterials and developing novel functional biomaterials with enhanced bone regeneration and therapeutic functions [8–12,16,19].

Among these, MOFs materials with many outstanding properties have immense prospects for improving the functionalization of biomaterials. To be specific, MOFs are a class of porous hybrid materials, which are synthesized by the coordination between metal ions/clusters and organic ligands [20–22]. Compared with other porous materials, MOFs are distinguished by their highly adjustable compositions owing to the possible utilizations of abundant metal ions/clusters and organic ligands [23–25]. Furthermore, MOFs possess high specific surface and tunable pore structure, which allows guest molecules to be captured, loaded and transported, as well as contributing to improving the ion transport capacity and catalytic activity [25–27]. Depending on the choice of ions, MOFs like MIL-101 (Fe-based MOF) exhibited peroxidase-like catalytic properties and microwave thermal therapy [28]. Additionally, ligands like porphyrin with excellent photoactivity may impart the photodynamic and photocatalytic properties to MOFs materials [29,30]. More importantly, MOFs materials have the ability to form coatings or 3D structures combined with other materials, allowing for a wider range of applications [31,32]. Therefore, in the past decades, MOFs have been widely applied in the fields of energy [26], catalysis [33], sensing [34], chemical separation [35] and biomedicine [36,37].

Encouragingly, a variety of studies reported that biocompatible MOFs materials had been widely applied for biomedical fields, such as drug delivery, disease treatment and tissue repair [19,38]. Specifically, MOFs had the superb capacity for drug delivery due to their high specific surface and tunable pore structure, which resulted in unique effects in the treatment of diseases and promotion of bone repair [39–43]. For example, Sr-based MOFs as the drug carrier could deliver ketoprofen with a sustained release manner, which was utilized to treat osteoarthritis [39]. Levofloxacin-loaded ZIF-8 coating was deposited on Ti substrate by a cathode electrophoresis method, which improved the antibacterial effect and osteogenic activity of Ti implant for potential orthopedic application [42]. ZIF-8 loaded with cisplatin and BMP-2 was assembled on the 3D-printed gelatin scaffold, which not only efficiently released cisplatin and inhibited tumor growth, but also possessed good osteogenesis activity to promote new bone formation [43]. In addition, MOFs could also show therapeutic functions and promote tissue repair by the controlled degradation and sustained release of bioactive ions [44–48]. For example, Sr/Ca-based MOFs were proved to have great potential in the treatment of osteoporosis owing to the release of therapeutic Ca^{2+} and Sr^{2+} from MOFs during the biodegradation process [44]. Mg/HCOOH and Sr/HCOOH MOFs could regulate the expression of inflammation-associated genes by controlled releasing of Mg^{2+} and Sr^{2+}, showing great promise for reducing osteoarthritis and promoting bone formation [46,47]. Due to the excellent antibacterial activity of Zn^{2+}, Cu^{2+} and Ag^{+}, Zn, Cu and Ag-based MOFs were developed to combat infections [45]. And it also demonstrated that ZIF-8 could promote cell proliferation, extracellular matrix mineralization and expression of osteogenic genes due to the release of Zn^{2+}, which made it be a promising candidate for bone tissue engineering [48]. Furthermore, some MOFs have special physical and chemical properties that enable them to be stimulated under specific physical fields, thereby performing therapeutic functions [49,50]. For example, porphyrin-based MOFs was reported for photodynamic therapy of tumors due to the fact that singlet oxygen generated on porphyrin under NIR irradiation induce the apoptosis of tumor cells [49]. And in another report, the rapid production of ROS ($^1O_2$) by CuTCPP (Cu-MOF) under 660 nm light would destroy the bacterial membrane and increase its permeability, which made it exhibit superior therapeutic effect for periodontitis [50]. Therefore, MOFs for bone tissue engineering could be classified according to metal ions as Co-based, Cu-based, Fe-based, Mg-based, Mn-based, Sr-based, Ti-based, Zn-based and Zr-based MOFs, as well as according to microstructures as ZIF, MIL, PCN, Uio and HKUST-series MOFs. Anyway, MOFs materials are promising candidates for the orthopedic applications in bone repair and treatments of infection, tumors, inflammatory and osteoporosis.

Besides, MOFs had the ability to form coatings on the biomaterials or combine with other materials to form 3D structures, which could functionalize biomaterials to improve their biocompatibility, control their degradation, enhance their osteogenic properties and endow them with functionalities such as antibacterial, anti-inflammatory and anti-tumor properties [42,51–57]. Hence, the MOFs-functionalized strategies have great potential to integrating bone repair and therapeutic functions into biomaterials. In this review, we mainly summarized recent progresses on the MOFs-functionalized biomaterials for promoting bone repair, including MOFs-functionalized biomaterials with enhanced bone regeneration, antibacterial function, anti-inflammatory function and anti-tumor function (Fig. 1). Finally, the summary and prospects on the development of MOFs-functionalized biomaterials for promoting bone repair were discussed.

2. MOFs-functionalized biomaterials with enhanced bone regeneration

The key to successful bone repair lies in the host response of body to the implanted biomaterials, i.e., the ability of the implanted biomaterials with responses to guide the surrounding tissues of bone defects in a direction favorable to repair [58–60]. If the implanted biomaterials have good biocompatibility, osteogenesis, osteoinductivity, osteoconductivity and osseointegration ability, they can stimulate the proliferation and differentiation of bone mesenchymal stem cells, as well as promote mineralization and new bone formation, thereby resulting in successful bone repair [61,62]. Interestingly, the functionalization strategy can enable the implanted biomaterials to possess specific surface structure, physical and chemical properties, and consequently activate initial cells behaviors, thereby allowing the biomaterials to enhance bone regeneration capacity [11–14,16,18]. The unique physicochemical properties of MOFs materials, such as the cargo delivery capacity, releasing ability (ions and ligands) and the formability, place them in a superior position from the functionalized strategies of biomaterials [31,32,63]. According to the metal ions types, MOFs can be classified into Zn-based, Mg-based, Cu-based, Fe-based, Zr-based MOFs, and so on [23–25]. As shown in Table 1, there are a variety of MOFs materials used for the functionalization of diverse biomaterials for the osteoporotic treatment,

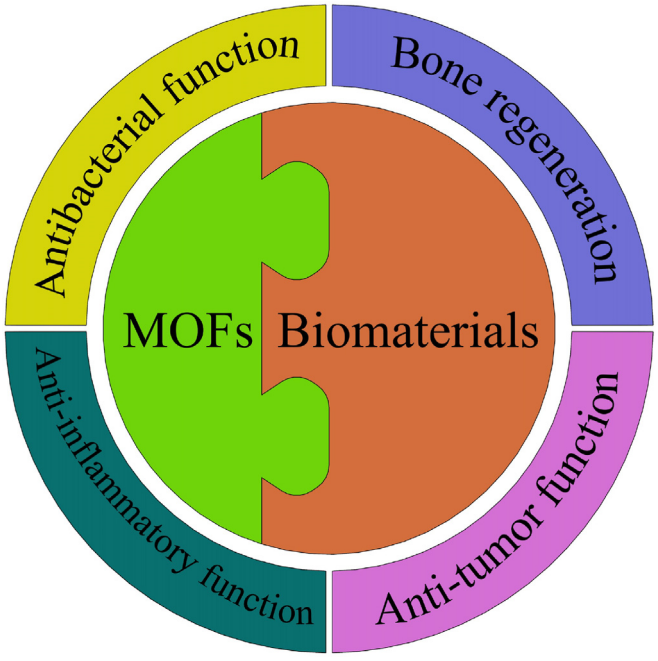

Fig. 1. MOFs-functionalized biomaterials with enhanced bone regeneration, antibacterial function, anti-inflammatory function and anti-tumor function.

tendon-bone regeneration and bone defects repair.

Among these MOFs, Zn-based MOFs are the most studied materials for functionalizing biomaterials in bone tissue engineering [48,64,72]. Zn-based MOF could be employed for regulating the surface properties of biomaterials, such as corrosion resistance, hydrophilicity and degradation, consequently enhancing bioactivity and biocompatibility [51,64]. Mg alloys have good mechanical properties, bioactivity, biocompatibility and osteoinductivity, but the poor corrosion resistance leads to their rapid degradation and excessive release of Mg^{2+}, which seriously affects the biocompatibility and limit their applications [100]. To improve the corrosion resistance of Mg alloys, the authors of Ref. [64] constructed a novel bio-MOF-1 (Zn-based MOF) coating on the surface of AZ31B Mg alloys by a hydrothermal method. Alkaline cleaning and grafting silane coupling were performed with the aim of obtaining a large number of amino groups on the magnesium alloy, resulting in a better bonding force between the Mg alloy substrate and the MOFs coating. The compact and homogeneous MOFs coating was formed on the surface of Mg alloy and effectively enhanced the corrosion resistance of Mg alloy. Additionally, the bio-MOF-1 coating could improve the rapid mineralization ability and cell viability, i.e., bioactivity and biocompatibility.

MOFs materials are self-assembled from ions and ligands in a specific solution environment, and the weak metal-ligand coordination bonding allows them to be prone to degradation [101]. Numerous studies demonstrated that ZIF-8 materials had controlled degradability, implying that ZIF-8 functionalized biomaterials had the ability to release ions and thus could promote bone repair via ion microenvironment regulation [52,65,67]. For example, ZIF-8/PCL/dicalcium phosphate dihydrate composite scaffolds was fabricated via extrusion-based 3D printing technology for promoting osteogenic differentiation and bone regeneration [65]. In this work, with the controlled release of Ca^{2+} from dicalcium phosphate dihydrate and Zn^{2+} from ZIF-8, the 3D printed composite scaffold significantly facilitated cell proliferation and differentiation behaviors, and new bone formation in rabbits. Further, researchers investigated the effects of ions released from ZIF-8 functionalized composite scaffolds on osteogenesis and angiogenesis [66,67]. For example, the authors of Ref. [67] developed an electrospun asymmetric double-layer PCL/collagen membrane modified by ZIF-8 crystals to accelerate bone regeneration by the enhancement of osteogenic and angiogenic activity. The composite scaffold firstly was fabricated by an electrospinning method using a polymer blending solutions of PCL and collagen, and then ZIF-8 crystals were synthesized in situ on one side of the double-layer membrane using a hydrothermal strategy. Water contact angle of the ZIF-8 crystal layer (65.0 ± 5.2°) was larger than that of the PCL/Col (52.9 ± 5.6°) and Col (41.7 ± 4.4°) membranes, indicating that MOFs layer improved the hydrophilic property of scaffold. The Zn^{2+} slowly released from ZIF-8 could promote cells growth and bone formation-related genes expression of bone mesenchymal stem cells, as well as the angiogenesis activity of human umbilical vein endothelial cells. In vivo findings indicated that the composite membrane had outstanding bone formation and remarkable vascularization after 8 weeks post-surgery, suggesting an accelerated role of ions released from ZIF-8 in the vascularized bone regeneration process.

Interestingly, Zn-based MOFs also possess high specific surface, high porosity and excellent biocompatibility, which have a natural advantage in the cargo delivery for improving bone regeneration [63,68,102]. For example, the authors of Ref. [68] fabricated a BMP-6-loaded MOFs/PCL composite fibers by electrospinning method for enhancing bone regeneration. The scaffolds were achieved by one-pot rapid crystallization of BMP-6-encapsulated ZIF-8 nanocrystals firstly, and followed by electrospinning the mixed solution of PCL and ZIF-8 nanocrystals. The encapsulation of BMP-6 inside the ZIF-8 crystal structures didn't greatly alter the morphology and size of MOFs. BMP-6 molecules had a high encapsulation efficiency (98%) for the ZIF-8 nanocrystals, with the biological activity retaining and the release lasting up to 30 days. And the prolonged and sustained release of BMP-6 had a positive impact on osteogenic differentiation of mouse embryo osteoblast precursor cells, as well as on the generation of well-mineralized, new bone formation in a rat cranial defect. Additionally, the combination of drugs and ions released from MOFs materials, could be also applied for promoting osteogenesis and angiogenesis, and ultimately bone tissue regeneration [69,70,103]. Ti alloys have good mechanical properties, biocompatibility and corrosion resistance, but poor bioactivity, osteogenic and angiogenic properties significantly limited their applications in bone repair [104]. Considering that dimethyloxalylglycine was a small molecular drug that was successfully used to promote angiogenesis, the authors of study [70] loaded dimethyloxalylglycine into ZIF-8 modified Ti implants to enhance the angiogenic and osteogenic activities. On one hand, the ZIF-8 modified Ti implants showed excellent wettability, which may facilitate cell adhesion. On the other hand, the Zn^{2+} and dimethyloxalylglycine could be slowly released from the ZIF-8 modified Ti implants to stimulate cell responses.

Apart from Zn-based MOFs, other MOFs were also used to functionalize biomaterials to improve the biocompatibility, bioactivity, osteogenesis, and angiogenesis. Similarly, these MOFs have the capacities to regulate the surface properties of biomaterials and release ions to assist the functionalization of biomaterials [75–78]. Although bioceramic materials exhibited excellent bioactivity, osteoinductivity and osteoconductivity, some bioceramics, such as β-Ca_2SiO_4, had an excessively rapid biodegradable rate, thus impairing biocompatibility. Therefore, the MOFs material of PCN-224 (Zr-based MOFs) coating was proposed to deposit on the surface of 3D-printed β-Ca_2SiO_4 scaffold by a hydrothermal method [77]. Due to the MOFs coating, the zeta potentials of β-Ca_2SiO_4 were increased from 15.6 mV of to 30.8 mV, demonstrated the improvement of chemical stability. In addition, the surface of the hydrothermally treated composite scaffolds was rougher, with more densely distributed new nanoscale particles and micrometer-sized pores. And detailed biological results supported that the scaffolds with MOFs coating could increase cell differentiation, new bone formation and accelerated calvarial defect repair. In addition, a Cu-MOF-74/PCL coating was constructed on the surface of Mg Alloy for enhancing the corrosion resistance and biocompatibility [78]. It was clearly observed that the as-prepared HKUST-1 exhibited a crystal structure, while the MOF-folic acid showed a less regular morphology, which was ascribed to the fact that the stabilizer folic acid was coordinated with the Cu nodes

Table 1
MOFs for functionalizing biomaterials and enhancing bone regeneration.

MOFs categories	Specific MOFs	Characteristics of MOFs	MOFs functionalized Biomaterials	Functionality of MOFs	Ref.
Zn-based MOF	Bio-MOF-1	Thickness: 190 μm	MOFs coating on Mg alloy by hydrothermal synthesis method	Controlling degradation to improve bioactivity	[64]
	ZIF-8	Size: 70–80 nm; Thickness: about 22 nm	MOFs/Chitosan coating on Mg alloy by electrospinning method		[51]
		Size: 266.5 nm	(Core-shell-Structured ZIF-8@HA)/PLA scaffold by 3D printing	Releasing ions to improve osteogenesis	[52]
		Size: 300–600 nm	MOFs/PCL/dicalcium phosphate dihydrate scaffold by 3D printing technology		[65]
		Size: 0.25–0.5 μm	MOFs/catechol−chitosan hydrogel	Releasing ions to improve osteogenesis and angiogenesis	[66]
		Size: 200–300 nm	MOFs/PCL/Collagen Membrane		[67]
		Size: MOFs of 83 nm ± 18, BMP-6-loaded MOFs of 68 nm ± 15 nm	(BMP-6-loaded MOFs)/PCL membranes	Releasing BMP-6 to improve osteogenesis	[68]
		Surface area: MOFs of 1392 m^2/g, dexamethasone-loaded MOFs of 1244 m^2/g; Size: both of them are about 60 nm	(Dexamethasone-loaded MOFs)/Silk fibroin coating on Ti	Releasing drug to improve osteogenesis	[69]
		Size: 300 nm; Contact angles: MOF of 32.8 ± 3.7°, dimethoxyglycine-loaded MOFs of 31.6 ± 2.6°	Dimethoxyglycine-loaded MOFs coating on Ti	Releasing ion and drug to improve osteogenesis and angiogenesis	[70]
		Size: MOFs of 120 ± 25 nm, alendronate-loaded MOFs of 130 ± 30 nm	alendronate-loaded MOFs on electrospun nanofibers	Releasing drug and Zn^{2+} to improve anti-osteoporosis and osteoinductive properties for osteoporotic bone defects repair	[71]
	Zn-MOF	Size: about 120 nm;	Raloxifene-loaded MOFs coating on Ti		[72]
Fe-based MOF	Fe-MIL-88 B	Pore size: 5 nm; Size: 50 & 200 nm	Alendronate-loaded Fe–MOF encapsulated in porous hydroxyapatite	Releasing drug for osteoporotic bone defects repair	[73]
Mg-based MOF	Mg-MOF-74	Pore size: MOFs of 6–11 nm, icariin-loaded MOFs of 1.5–5 nm	Icariin-loaded MOFs and silk fibroin solution injected into 3D-printed Ti alloy scaffold	Releasing icariin and Mg^{2+} for inducing osteointegration by osteoimmunomodulation	[74]
	Mg-MOF-74	Contact angles: 0°; Size: 10–20 μm	MOFs coating on Mg alloy by hydrothermal synthesis method	Controlling degradation and improving bioactivity	[75]
Zn–Cu MOF	Zn–Cu MOF	Pore size: 10.9 nm; Surface area: 6 m^2/g; Size: 60 nm	MOFs coating on electrospinning PLA scaffold	Improving bioactivity and releasing Cu^{2+}	[76]
Zr-based MOF	PCN-224	Zeta potentials: 27.9–30.8 mV	MOFs coating on the surface of 3D-printed β-Ca_2SiO_4 scaffold	Controlling degradation to improve bioactivity and osteogenesis	[77]
Cu-based MOF	folic-acid-modified HKUST-1	Size: 1–1.5 μm	MOFs/PCL coating on Mg alloy by solvent evaporation method	Controlling degradation to improve bioactivity and releasing Cu^{2+}	[78]
	HKUST-1	Size: 53.96 ± 12.53 nm; Surface area : 1194.77 m^2/g; Pore size: 2.122 nm	(nitric oxide (NO) loaded MOFs)-PCL/Gelatin coaxial scaffolds by electrospinning technology	Releasing ions and NO to improve angiogenesis and tendon regeneration	[79]
Zn-MOF + Cu-MOF	ZIF-11; HKUST-1	HKUST-1: Zeta potential: 54.23 ± 0.04; Size: 1480 nm ZIF-11: Zeta potential: −6.33 ± 0.02; Size: 1990 nm	ZIF-11/PLA + HKUST-1PLA scaffolds by electrospinning technology	Releasing ions to promote tendon and bone regeneration	[80]

during modification, partly inducing the disintegration of the HKUST-1 MOF. The pH and Mg^{2+} concentration of solution immersed by MOFs-modified Mg alloy was stabilized at a low level, which indicated that the coating had excellent corrosion resistance combined with electrochemical tests. Meanwhile, the release of Cu^{2+} showed a lower concentration at the first 10 days, and then started to increase slightly. As expected, the MOFs coating promoted cell viability and differentiation of osteoblastic cells due to the good barrier property of coating and the release of Cu^{2+}.

More importantly, these MOFs possess the ability to deliver cargo and release ions, which enables them to functionalize biomaterials for tendon-bone regeneration [79,80]. For example, the authors of Ref. [79] developed a coaxial scaffold that NO-loaded HKUST-1 (Cu-based MOF) was encapsulated into PCL/Gelatin, for tendon repair. Excitingly, this scaffold not only enhanced the tubular formation capability of endothelial cells in vitro, but significantly increased the blood perfusion near the injured tendon in vivo, resulting in accelerating the maturity of collagen and recovery of biomechanical strength of the regenerated tendon tissue. In addition, the authors of Ref. [80] constructed ZIF-11(Zn-based MOF)/PLA and HKUST-1/PLA composites scaffolds by electrospinning technology for tendon and bone regeneration. The fiber filaments successfully encapsulated MOF particles, meanwhile the crystal structure in the fiber was similar to the pure crystal. Due to the sustained release of Cu^{2+} and Zn^{2+}, the HKUST-1 and ZIF-11 could promote the process of angiogenesis and osteogenesis in vitro, respectively. More importantly, the composite scaffold could achieve the synchronous regeneration of multiple tissues at the interface of damaged tendon and bone, including tendon, fibrocartilage and bone tissue by the rat rotator cuff tear model.

Additionally, due to the cargo delivery and ions release properties of MOFs, MOFs-functionalized biomaterials have great potential for the treatment of osteoporosis and promotion of bone regeneration [71–74]. The authors of Ref. [74] constructed a novel hierarchical bio-functionalized 3D-printed porous Ti6Al4V scaffold with enhanced osteoporotic osseointegration through osteoimmunomodulation (Fig. 2). The icariin-loaded Mg-MOF-74 was encapsulated in biomimetic extracellular maxtrix-like structure that could control the release of icariin and Mg^{2+} (Fig. 2 (C)). Silk fibroin network acted as a platform for

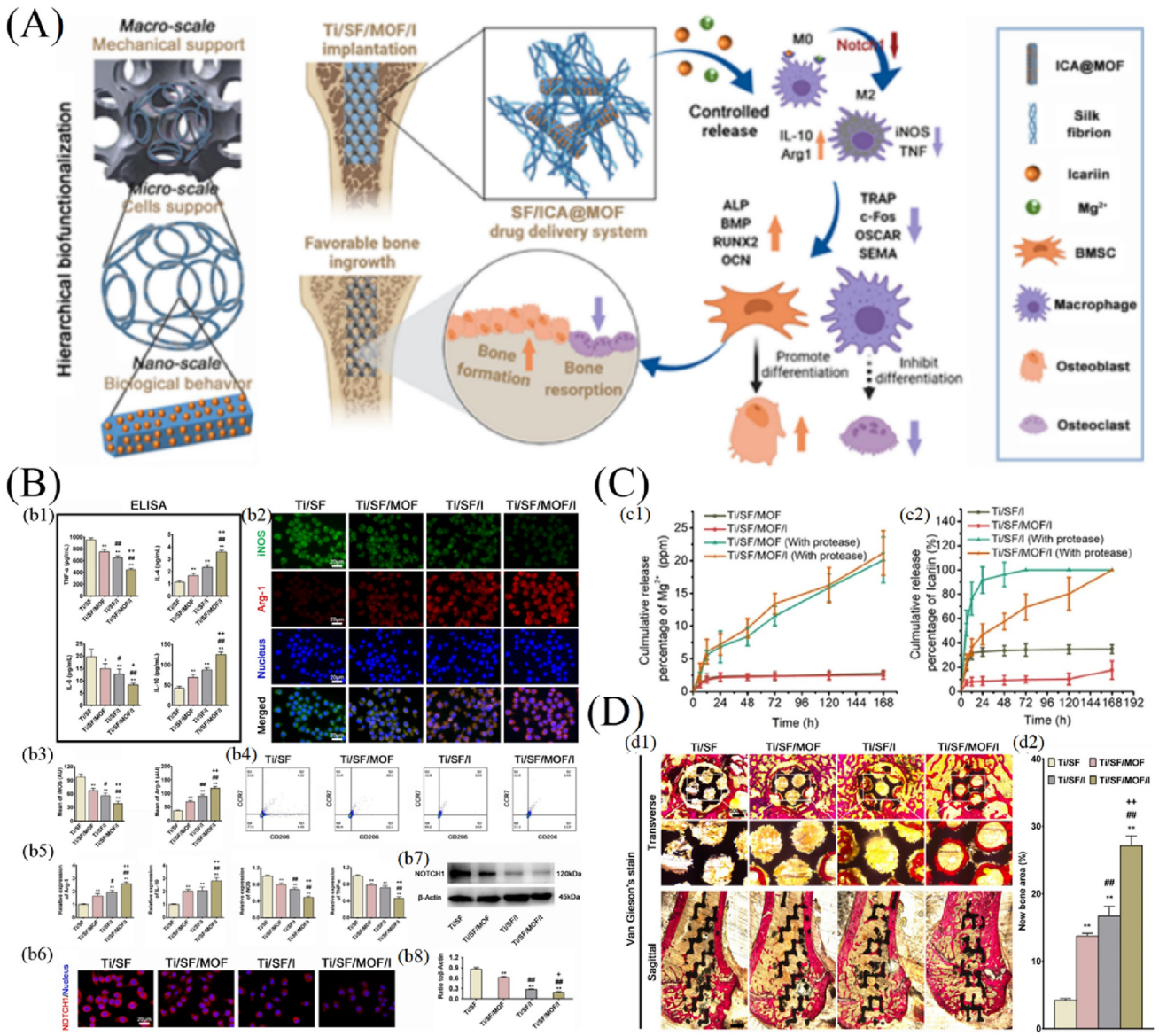

Fig. 2. Novel biofunctionalized 3D-printed Ti6Al4V scaffold for osteoporotic osseointegration, (A) Schematic diagram of improving osseointegration by scaffold. (B) In vitro polarization evaluation of Raw264.7 cells, (b1) ELISA results, (b2) Immunofluorescent staining, (b3) Quantitative analysis of iNOS and Arg-1, (b4) Polarization by flow cytometry, (b5) RT-qPCR results, (b6) Immunofluorescent staining of Notch1, (b7) Expression of Notch1 by western blot, (b8) Expression of Notch1 protein. (C) Controlled release of icariin (c1) and Mg^{2+} (c2). (D) Staining of undecalcified sections, (d1) Van Gieson's staining of undecalcified sections, (d2) Quantitative analysis of van Gieson's staining data (reprinted with permission from Ref. [74]).

biofunctionalization, and effectively realized the load of Mg-MOF-74 in Ti implant. The results indicated that the pores of the MOF, especially the narrow slit-like holes, were filled or blocked by drug molecules after drug loading. Furthermore, it found that the sustained release of icariin and Mg^{2+} from the hierarchical scaffold could significantly facilitate the polarization of M0 macrophages to M2-type by inhibiting notch1 signaling pathway and induce the secretion of anti-inflammatory cytokines (Fig. 2 (B)). It also demonstrated that abundant new bone was formed at peripheral and internal sites of the biofunctionalized scaffold after implantation into the distal femur in osteoporotic rats (Fig. 2 (D)). Thus, hierarchical implants containing controlled-release systems significantly improve bone metabolism and improve osseointegration between scaffold and osteoporotic bone, and have great potential to treat osteoporosis and improve geriatric orthopedic osseointegration.

In summary, MOFs, such as Zn-based MOFs, Mg-based MOFs, Cu-based MOFs and Zr-based MOFs, and so on, with the functions of cargo delivery, ions release and surface modification, were employed to functionalize biomaterials in the form of coating or composites to improve their biocompatibility, bioactivity, osteogenesis and angiogenesis, thereby promoting bone regeneration, tendon-bone repair, and osteoporosis treatment. Nevertheless, the biocompatibility, drugs delivery ability, degradability of MOFs-functionalized biomaterials are still worthy of further investigations due to the limitations of MOFs materials like the stability and degradability in solutions.

3. MOFs-functionalized biomaterials for bone repair with antibacterial function

In clinical orthopedics, the bone implant-related infections caused by bacterial adhesion and biofilm formation on the surface of implants, are considered as an intractable and serious issue [105,106]. Systemic administration of antibiotics is often employed to achieve the antibacterial effects, but unsatisfactory for eradicating the formed bacterial biofilm, and the overuse of antibiotics may induce the formation of

multidrug-resistant bacteria [8,107]. And it was proved that many strategies like loading antibiotics on/into the implants for local release, could effectively prevent the biofilm formation and implant-related infections, and promote bone repair [105,107,108]. Nevertheless, the drug utilization efficiency and releasing period of time were required to be further improved for facilitating the antibacterial activity and osteogenic capacity. In addition, other antibacterial strategies such as ion-mediated, physical-based and combined approaches also exhibited significant advantages against implant-related infections, especially in the case of drug-resistant bacteria [109–111]. Therefore, it is necessary to introduce a platform that can functionalize biomaterials to integrate these antibacterial strategies. Excitingly, MOFs materials have numerous properties that allow them to deliver drugs, release ions and perform physical antibacterial functions under the differently physiological conditions, thus making them be more suitable for functionalizing biomaterials (see Table 2).

Due to the excellent functions of ions release and drugs delivery, Zn-based MOF materials like ZIF-8, are particularly suitable for functionalizing biomaterials [42,81–85]. ZIF-8 has the ability to release Zn^{2+} that could transport across bacterial membranes via ion channels, thus triggering a disturbing effect on bacteria. The authors of Ref. [81] prepared nanoscale and micro-scale ZIF-8 coatings on the surface of porous Ti by the hydrothermal and solvothermal methods, respectively, to improve the osteogenic and antibacterial activity. The SEM images showed a microscale ZIF-8 film with a crystal size of over 10 μm, and a nanoscale ZIF-8 film with a crystal size of 200–300 nm. The XRD patterns of the nanoZIF-8 and microZIF-8 crystals matched very well with that of the simulated one, indicating that the crystalline products were in pure phase. The Zn^{2+} were slowly released from both coatings, but the amount generated from the nanoscale ZIF-8 coating was obviously less than that of the other one. Moreover, the nanoscale ZIF-8 coating not only better enhanced the Ti substrates' biocompatibility, alkaline phosphatase activity, extracellular matrix mineralization and bone differentiation-associated genes expression of MG63 cells, but also better inhibited the growth of *Streptococcus mutans*. Therefore, the actions of Zn^{2+} and the nanoscale topography, synergistically contributed to enhancing the osteogenic activity and antibacterial property. Similarly, ZIF-8 has the property of antibiotics delivery, thus giving the MOFs-modified scaffolds antibacterial activity. For example, the authors of Ref. [83] fabricated the 3D-printed bioglass scaffolds functionalized by vancomycin-loaded ZIF-8 with a pH-responsive antibacterial effect for the infected bone repair applications. There was no significant statistical difference in the porosity of the scaffolds before and after the vancomycin-loaded ZIF-8 deposition, suggesting that the vancomycin-loaded ZIF-8 deposition did not influence the porosity of the scaffolds. Distinctly, the vancomycin-loaded ZIF-8 were deposited on the bioglass particles and gaps among the bioglass particles, and such scaffolds presented a faster vancomycin release rate due to the higher sensitivity of ZIF-8 to weakly acidic environment. As a result, a significant inhibitory effect was exhibited on *Staphylococcus aureus*. More crucially, the scaffolds could promote cell proliferation and the osteogenesis-related genes expression of rat bone marrow mesenchymal stem cells.

Additionally, ZIF-8 can be triggered by physical effects to produce

Table 2
MOFs-functionalized biomaterials for bone repair with antibacterial function.

MOFs categories	Specific MOFs	Characteristics of MOFs	MOFs functionalized Biomaterials	Functionality of MOFs	Ref.
Zn-based MOF	ZIF-8	Size: microZIF-8 of 10 μm, nanoZIF-8 of 200–300 nm; Coating thickness: 10 μm	MOFs coatings on Ti acquired by a hydrothermal method and a solvothermal method	Releasing ions for antibacterial effect; Improving osteogenic activity	[81]
		Zeta potential: 19.4 mV; Size: about 300 nm	Ag^{+}-loaded MOFs coating on PEEK		[82]
		Zeta potentials: ZIF-8 of +22.6, levofloxacin-loaded ZIF-8 of +8.8 mV; Size: ZIF-8 of 136 ± 28 nm, levofloxacin-loaded ZIF-8 of 189 ± 35 nm	Levofloxacin-loaded ZIF-8 coating on Ti by the cathode electrophoresis deposition	Releasing drugs for antibacterial effect; Improving osteogenic activity	[42]
		–	(Vancomycin-loaded MOFs)@BG/PCL scaffold fabricated by 3D printing		[83]
		Thickness: 80 μm; Contact angle: ZIF-8 of 67.63° ± 0.15°, Iodine-loaded ZIF-8 of 60.43° ± 1.52°	Iodine-loaded MOFs coating on Ti alloy by a hydrothermal method	Releasing iodine and providing photocatalytic effect for antibacterial properties; Improving osteogenic activity	[84]
		Size: 226.2 ± 5.3 nm;	(Platelet derived growth factor-loaded MOFs- polydopamine)/Collagen hydrogel perfusing in PLGA-TCP scaffolds	Delivering platelet derived growth factor to promote bone regeneration; Polydopamine with photothermal effect for antibacterial efficacy	[85]
Zr–Mg-based MOF	MOF-801	Coating thickness: Zr-MOF0, Zr-MOF1, and Zr-MOF2 were 5.38 μm, 9.63 μm, and 14.13 μm	F-doped MOFs coating on Ti by solvothermal method	Releasing ions for antibacterial effect; Improving osteogenic activity	[86]
Ti-based MOF	MIL-125	Surface area: 44.2866 m^2/g; Pore size: 8.2772 nm	La-doped MOFs and hydroxyapatite coating on Ti by electrochemically deposition		[87]
		Surface area: 78.1089 m^2/g; Pore size: 6.6086 nm	Ce-HA-modified MOFs coating on Ti by electrochemical deposition method		[88]
Zn–Mg-based MOF	Zn–Mg-MOF74	Size: 2–3 μm; Contact angle: 0°	Dexamethasone-Loaded (MOFs coating on PEEK by hydrothermal method)	Releasing Zn^{2+}, Mg^{2+} and dexamethasone to improve antibacterial and osteogenic properties	[54]
Co-based MOF	ZIF-67	Size: ZIF-67 of 168 ± 14 nm, osteogenic growth peptide-loaded MOFs 189 ± 21 nm	Osteogenic growth peptide -loaded MOFs on Ti implants	Releasing Co^{2+} and osteogenic growth peptide to improve antibacterial and osteogenic properties	[89]
	Co-SIM-1	–	MOFs/PLA fiber scaffold manufactured by electrospinning technology	Releasing Co^{2+} to improve antibacterial	[90]
Cu-based MOF	HKUST-1	Size: 217.3 ± 34.4 nm; Zeta potentials: Hkust-1 of −11.9, F-Hkust of −13.6 mV	(Folic acid-modified MOFs)/Pectin/polyethylene oxide scaffold by electrospinning method	Releasing Cu^{2+} and folic acid improve antibacterial and osteogenic properties	[53]
Fe-based MOF	Fe-MOF	Surface area: 395 m^2/g; Size distribution peaked at 3.58 nm	Isoniazid@MBG/Fe-MOF/PCL scaffold fabricated by 3D printing	Controlling degradation to release drug for osteoarticular tuberculosis	[91]

antibacterial property as well, thereby functionalizing biomaterials with physical antibacterial functions. For example, the authors of Ref. [84] constructed an iodine-loaded MOFs onto the Ti implant to achieve responsive iodine release and intracellular ROS under the NIR irradiation for synergistic antibacterial effect. The ZIF-8 was immobilized on micro arc oxidized Ti by a hydrothermal method, and then iodine was successfully loaded onto MOFs using a vapor deposition process. Interestingly, with the loading of MOFs and iodine, the contact angles of the Ti implants declined, indicating the increase of hydrophilicity. The composite coating promoted the cells proliferation and osteogenic differentiation of human bone marrow stromal cells in vitro, as well as improved new bone formation of infected bone tissue and osseointegration condition of the coated implants in an intramedullary rat model. In addition, the antibacterial results demonstrated that the combination of NIR-triggered iodine release and ZIF-8-mediated oxidative stress of ROS greatly inhibited the activity of *Staphylococcus aureus* and fought implant infections by taking advantage of the excellent absorption capacity of ZIF-8 and its inherent photocatalytic properties, indicating that the increased antibacterial effect without compromising the osteogenic potential of the MOFs-modified implants.

Other MOFs materials with degradability, the ions release ability and cargo delivery property, such as Cu, Co, Zr and Fe-base MOFs, may also be utilized for functionalizing biomaterials. MOFs materials possessed good degradability, so the drug release from the scaffold could be promoted through the modulation of degradability [54,91]. For example, the authors of Ref. [91] constructed isoniazid@MBG/Fe-MOF/PCL scaffolds by 3D printing for treating osteoarticular tuberculosis. As a first-line drug, isoniazid with better biofilm penetration can inhibit and kill *Mycobacterium tuberculosis*, which makes it the optimal choice against osteoarticular tuberculosis. The introduction of MOF particles into MBG scaffolds does not chance its macrostructure, but MBG/MOF scaffolds are denser than MBG scaffolds. The scaffolds with the pore diameter of 400 μm and the compressive strength of 3–7 MPa, had good biocompatibility and apatite-forming abilities in vitro. In addition, the rapid degradation of MOFs in MBG/MOFs scaffolds provides more diffusion channels for INH drugs, so the drug release rate and pH microenvironment of MBG/MOFs scaffolds can be controlled based on MOFs content. Therefore, the release of drugs from the scaffold can be regulated by the degradability of the MOFs materials to improve the antibacterial capacity.

In addition, MOFs materials could functionalize biomaterials with combating infections and bone repair through the strategy of ion release [86–88,90]. For example, fluorine-doped MOF-801 (Zr-based MOF) was proposed to functionalize the surface of Ti by using a solvothermal method for promoting the antibacterial and osteogenic properties [86]. The corrosion potential of Zr-MOF0, Zr-MOF1, and Zr-MOF2 samples showed a shifting to a negative direction as compared to that of Ti, which suggested the negative influence of fluorine on the corrosion resistance of Zr-MOF. The addition of fluorine can increase the defects of Zr-MOF and the porosity. Hence, fluorine-doped Zr-MOF samples are more easily attacked by anions and degraded more easily. The fluorine-doped MOF-801 coating showed stable release behaviors of F^- and Zr^{4+}. On the one hand, the release of F^- from the MOF-modified Ti could promote the cell proliferation and alkaline phosphatase activity of mouse embryo osteoblast precursor cells, as well as the expressions of osteogenesis-associated genes. On the other hand, the ability of MOF-801 against both gram-positive *Staphylococcus aureus* and gram-negative *Escherichia coli* was improved with the increase of the content of fluorine doping and the release of F^-. In addition, the authors of Ref. [87,88] used a similar approach to construct La and Ce doped MIL-125 (Ti-based MOF) coatings on the surface of Ti alloys, thereby achieving the good biocompatibility, antibacterial property and osteogenic activity due to the sustained release of ions.

Interestingly, the combination of ions release and drug delivery for MOFs-functionalized scaffolds could improve the repair effect of infected bone defects [53,54,89]. For example, the authors of the study [89] designed an osteogenic growth peptide-loaded ZIF-67 (Co-based MOF) coating on the surface of Ti implant to improve the antibacterial and osteogenic properties. The release of Co^{2+} and osteogenic growth peptide from ZIF-67 improved the antibacterial and osteogenic properties, respectively, thus this MOFs-functionalized biomaterials could be used for infected bone defects. Additionally, the authors of Ref. [54] fabricated dexamethasone-loaded Zn–Mg MOF-74 coating on PEEK implant with antibacterial, osteogenic and angiogenic properties to promote bone regeneration (Fig. 3 (A)). Specifically, the dexamethasone-loaded coating was prepared by using a polydopamine interlayer to bond Zn–Mg MOF-74 onto PEEK, and following to load dexamethasone into the MOFs. The surface of the PEEK sample was covered with a dense crystal coating with rod-shaped grains with a size of around 2−3 μm, which showed a rougher surface compared to the PEEK and PEEK−PDA samples. The PEEK implants with the multifunctional coating provides superior hydrophilicity (80 to 0°) and induces the alkaline microenvironment on the surface with the release of Mg^{2+}, Zn^{2+} and dexamethasone (Fig. 3 (B)), resulting in potent antibacterial properties against both *Escherichia coli* and *Staphylococcus aureus*. Meanwhile, the Mg^{2+} released from the coating could promote the neovessel formation of human umbilical vein endothelial cells, and the released Mg^{2+}, Zn^{2+} and dexamethasone contributed synergistically to the outstanding bioactivity and osteogenic differentiation ability of rat bone marrow mesenchymal stem cells. Most importantly, PEEK implants coated with the Zn–Mg MOF-74 coating had potent antibacterial (Fig. 3 (C)) and angiogenic abilities, and facilitated the formation of new bone around the PEEK implant and a stronger osseointergration, as in vivo demonstrated by the rat subcutaneous infection model, chicken chorioallantotic membrane model and rat femoral drilling model (Fig. 3 (D)).

In conclusion, the antibacterial and osteogenic dual functions of MOFs-functionalized biomaterials were realized by the various properties of MOFs materials, such as degradability, drug delivery, ions release and their combined utilization. Furthermore, the increase of antibacterial capacity contributed to facilitating osteogenesis, i.e., the inhibition and removal of infections from bone tissue being helpful for repair. Regardless of the antibacterial strategy used, it is essential to achieve controlled properties, such as the sustained release of ions and drugs, and the regulation of photothermal effect. Although numerous studies had achieved good antibacterial effects and osteogenesis capacity, there were still some problems with antibacterial controllability, especially in the stability of the MOFs itself used for functionalized biomaterials. Therefore, the degradability of MOFs materials needs to be further studied and explored to better functionalize biomaterials with dual functions of against infections and promoting bone repair.

4. MOFs-functionalized biomaterials for bone repair with anti-inflammatory function

Immune cells, like macrophages and B cells, are critical to the growth, development and repair of bone tissue, as evidenced by their elimination of apoptotic cells and antigens, and their interactions with bone tissue cells [2,112–116]. The inflammatory processes, including pro-inflammatory and anti-inflammatory response, are normal responses of the immune system to aberrant stimuli in the body, and are present in fractures, bone tumors, bone infections and osteoarthritis at different degrees [2,114]. Generally, a prolonged pro-inflammatory process results in dysfunction or delayed progress of bone repair, meanwhile long-term or chronic inflammation is also strongly associated with various diseases which impede bone repair [114]. To combat inflammation, various strategies have been developed, including regulation of macrophages behaviors during bone repair, clearance of bacteria in bone infections, removal of substances causing inflammation, and anti-inflammatory drug delivery for chronic inflammation [39,114,117,118]. MOFs materials have the ability to load and release drugs, small molecules and ions, making them suitable for anti-inflammatory treatments in bone tissues (see Table 3). Local release of small molecules or drugs is more effective than systemic administration, so MOFs-functionalized biomaterials can be applied for inflammatory bone defects.

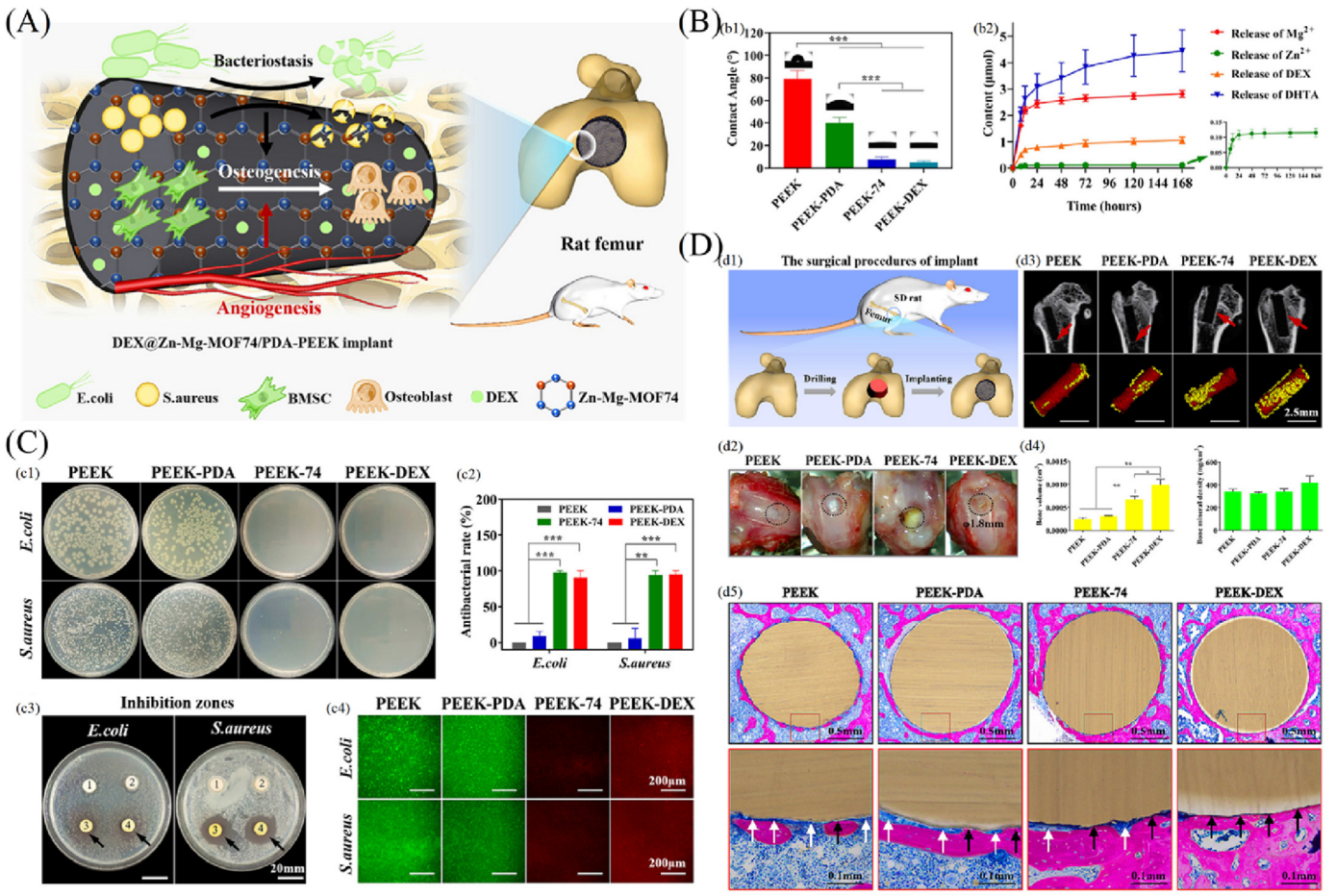

Fig. 3. PEEK implant with Zn–Mg MOF coating for promoting bone regeneration. (A) Schematic diagram. (B) Water contact angles (b1) and cumulative release profiles (b2). (C) Antibacterial activity of the different samples, (c1) Antibacterial tests against *E. coli* and *S. aureus*, (c2) Antibacterial rates, (c3) Evaluation of inhibition zones, (c4) Live/dead fluorescence images. (D) Results of the rat femoral model, (d1) 3D diagram of implant procedures, (d2) Establishing osteogenic models of different implants, (d3) Micro-CT analysis, (d4) Quantification of new bone volume and new bone mineral density, (d5) Femur tissue sections staining (reprinted with permission from Ref. [54]).

The injection of particles like MOFs materials with drug delivery capacity, are more suitable for mild osteoarthritis than scaffold materials [39,40,46,95]. For example, the authors of [39,46] found that Sr-MOF with different ligands could serve as the carriers to deliver ketoprofen drug for osteoarthritis. Additionally, the researchers of another work [40] developed a pH-responsive and hyaluronic acid-conjugated MIL-100 (Fe-based MOF) loaded with protocatechuic acid for osteoarthritis therapy. Protocatechuic acid, an anti-inflammatory polyphenol isolated from plants, has an ability to significantly down-regulate levels of markers for inflammatory factors. Compared to that in the solution at pH 7.4, the Fe^{3+} released in acidic solution increased, indicating MIL-100 display an acid-triggered degradation behavior, and it could be beneficial for pH-sensitive drug release at osteoarthritis site. Furthermore, the degradation of MIL-100 and the release of the anti-inflammatory protocatechuic acid were significantly accelerated and increased under acid conditions (pH = 5.6), suggesting that the drug release may be attributed to the pH-induced disassembly of nanoparticles. Moreover, the hyaluronic acid-conjugated MIL-100 loaded with protocatechuic acid down-regulated the inflammatory markers expression of osteoarthritis, and enhanced the expression of cartilage-specific markers, which exhibited a significant potential in alleviating the osteoarthritis and accelerating cartilage regeneration.

Besides, the MOFs-functionalized scaffold can be used for the anti-inflammation of the bone defect repair, where the ions can play antibacterial, osteogenic and angiogenic roles, and the ligands such as gallic acid and fumaric acid can play anti-inflammatory roles [86,92,93]. Gallic acid and fumaric acid significantly had the ability to alleviate ROS-induced inflammation in macrophages by eliminating excessive intracellular ROS. In specific example, the authors of Ref. [92] constructed an exosome-loaded Mg-gallic acid-MOF/PLGA scaffold fabricated by an electrospinning method with osteogenic, angiogenic and anti-inflammatory properties for accelerated bone regeneration (Fig. 4 (A)). The surface of the PLGA scaffold was smooth and uniform, but after the addition of Mg-gallic acid-MOF, the fibrous membrane became rougher. With the increase of Mg-gallic acid-MOF, the zeta potentials had a decreasing trend, which indicated that the chemical stability was reduced gradually. The composite scaffold had the ability to release the exosome, gallic acid and Mg ions slowly and controllably (Fig. 4 (B)). The cell experiments showed that the composite scaffold effectively suppressed pro-inflammatory mediator expression in lipopolysaccharide-induced RAW264.7 mouse macrophages (Fig. 4 (D)), as well as promoted the cells proliferation, osteogenic activity and angiogenic effect of human bone marrow-derived mesenchymal stem cells and human umbilical endothelial cells. Furthermore, the in vivo experiments with rat calvarial defect model also showed that the composite scaffolds promoted new bone formation (Fig. 4 (C)) and satisfactory osseointegration. Thus, this study takes full advantage of the degradation and loading properties of MOFs to enhance the osteogenic, angiogenic and anti-inflammatory abilities of the biomaterials, providing valuable new insights for functionalizing biomaterials.

For infected bone defects accompanied by inflammation, MOFs materials with drug delivery and ion release capacity are better choices for combating inflammation, either directly treating the inflammation, or

Table 3
MOFs-functionalized biomaterials for bone repair with anti-inflammatory function.

MOFs categories	Specific MOFs	Characteristics of MOFs	MOF functionalized Biomaterials	Functionality of MOFs	Ref.
Mg-based MOF	Mg-gallic acid-MOF	Zeta potentials: MOFs of +10.9 ± 0.5 mV, exosome-loaded MOFs of −23.3 ± 0.7; Surface area: MOF of 229.4 m^2/g, exosome-loaded MOFs of 154.5 m^2/g	Exosome loading on MOFs/PLGA scaffold fabricated by electrospinning method	Releasing exosome, gallic acid and ion to improving osteogenesis, anti-inflammatory and angiogenesis properties	[92]
	Mg(H2gal)	Surface area: 228.7 m^2/g; Pore size: 8.1 nm; Size: 100 nm	(CaP-modified MOF)/Collagen scaffold	Releasing ions and gallic acid to improving osteogenesis, angiogenesis and anti-inflammatory properties	[93]
Zr-based MOF	MOF-801	–	F-doped MOFs/Ti by solvothermal method	Releasing fumaric acid for anti-inflammatory effect; Releasing fluoride ions for bone regeneration	[86]
	UiO-66	–	(Fosfomycin-loaded UiO-66)/chitosan scaffolds by wet spinning	Releasing fosfomycin against bacteria and inflammation	[55]
Zn–Mg-based MOF	Zn–Mg-MOF74	–	Dexamethasone-Loaded (MOFs coating on PEEK by hydrothermal method)	Releasing drugs for anti-inflammatory effect; Improving osteogenic activity	[54]
	ZIF-8	Size: 60 ± 20 nm; Surface area: ZIF-8 of 1827 m^2/g, vancomycin -encapsulated ZIF-8 of 1559 m^2/g	(Vancomycin encapsulated ZIF8)/chitosan scaffolds prepared by wet spinning	Releasing vancomycin	[94]
Co-based MOF	ZIF-67	–	Osteogenic growth peptide -loaded MOFs on Ti implants	Releasing Co^{2+} and osteogenic growth peptide to improve anti-inflammatory, antibacterial and osteogenic properties	[89]
Fe-based MOF	MIL-100	Size: 123.4 nm; Zeta potential: MOF of −9.3 mV, hyaluronic acid-conjugated MOF of −12.1 mV, MOF with protocatechuic acid of −21mV	Hyaluronic acid-conjugated MOFs mixing with protocatechuic acid	Loading and releasing protocatechuic acid for anti-inflammatory effect and osteoarthritis treatment	[40]
Sr-based MOF	Sr/FA-MOF; Sr/TPA-MOF	–	Ketoprofen loading into MOFs	Releasing ketoprofen for anti-inflammatory effect and osteoarthritis treatment	[39, 46]
Zr-based MOF	Zr-MOF	Size: about 200 nm	Pt nano particle-loaded MOFs modified by Au, QDs and polydopamine	Carriers of catalyst for releasing H_2 and consuming ROS to treat osteoarthritis	[95]

killing the bacteria to reduce the inflammatory response [54,55,89,94]. The clinical drug of dexamethasone, an anti-inflammatory glucocorticoid, was widely applied for inducing osteogenic differentiation of bone marrow-derived mesenchymal stem cells. For example, the authors of Ref. [54] constructed a dexamethasone-loaded Mg–Zn-MOF74 composite coating on the surface of Ti implant for meeting the multifunctional requirement of antibacterial, angiogenic, anti-inflammatory and osteogenic capacities. The sustained release of Mg^{2+} and Zn^{2+} contributed to promoting antibacterial and angiogenic properties, whereas the release of dexamethasone facilitated anti-inflammatory and osteogenic capacities, synergistically enhancing bone repair and regeneration. Additionally, an osteogenic growth peptide-loaded ZIF-67 (Co-based MOF) coating was fabricated on the Ti implant to improve the antibacterial, anti-inflammatory and osteogenic properties [89]. TiO_2 nanotubes were prepared on the Ti surface by electrochemical anodization, and then osteogenic growth peptide-loaded ZIF-67 coating was prepared on the surface using one-pot synthesis. Massive of ZIF-67 crystals appeared on the Ti implant surfaces after electrophoresis deposition treatment. The elastic modulus of the ZIF-67 coated Ti substrates is about 16 GPa, which is closed to the tensile elastic modulus of human femurs. The contact angles of Ti, titanium dioxide nanotubes, titanium dioxide nanotubes-ZIF-67, and osteogenic growth peptide-loaded titanium dioxide nanotubes-ZIF-67 were 68.9 ± 7.3°, 19.7 ± 3.8°, 34.3 ± 2.7°, and 35.5 ± 4.2°, respectively. This indicated that the osteogenic growth peptide-loaded titanium dioxide nanotubes-ZIF-67 surfaces were more hydrophilic than Ti and titanium dioxide nanotubes groups, facilitating cell adhesion, proliferation, and finally promoting bone generation. The release of Co^{2+} enhanced the antibacterial activity of ZIF-67-modified Ti implant against *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus mutans* and methicillin-resistant *Staphylococcus aureus* in vitro, as well as improved the in vitro anti-inflammatory properties due to the catalytic scavenging effect of Co^{2+} on ROS, resulting in the down-regulating and up-regulating pro-inflammatory and anti-inflammatory associated genes of macrophages, respectively. And the sustained release of osteogenic growth peptide from ZIF-67-modified Ti implants promoted the cell viability and bone formation-related genes expression of bone mesenchymal stromal cells. In vivo studies further revealed that the implants modified by growth peptide-loaded ZIF-67 presented strong antibacterial and anti-inflammatory properties at the early stage of implantation, as well as enhanced the formation of new bone and the osseointegration of bone implants at the late stage. Therefore, this multifunctional Ti implant combining osteoimmunomodulatory and antibacterial effects was a promising candidate for implant-associated infectious and inflammatory bone regeneration.

In numerous physiological and pathological conditions, such as bone tumor, bone infection, and osteoarthritis, inflammation is prevalent and has a profound impact on the repair and regeneration of bone tissue. It was clear that MOFs materials with numerous properties such as drug delivery and degradability, could endow MOFs-functionalized biomaterials with anti-inflammatory, antibacterial and osteogenic capacities by ingenious design of ions, ligands and drugs and their synergistic actions, which ultimately enhanced anti-inflammatory therapy and bone repair. Even so, further investigations and improvements were needed in terms of controlled released of ions, ligands and drugs, as well as the bone repair and anti-inflammatory effects and mechanisms.

5. MOFs-functionalized biomaterials for bone repair with anti-tumor function

Bone cancer causes great sufferings for patients and has significant influence on their normal lives as well. Involving the invasion of tumors into bone tissue, bone tumors are classified as either primary tumors or metastatic tumors [119,120]. Treatments for bone tumors are frequently determined by the location and size of the tumors, with common approaches including chemotherapy, radiotherapy, and surgical resection [121]. Despite the concerted efforts of scientists and clinicians, cancer still is an insurmountable challenge. Hence, other novel anti-tumor therapies have been developed, such as chemodynamic therapy,

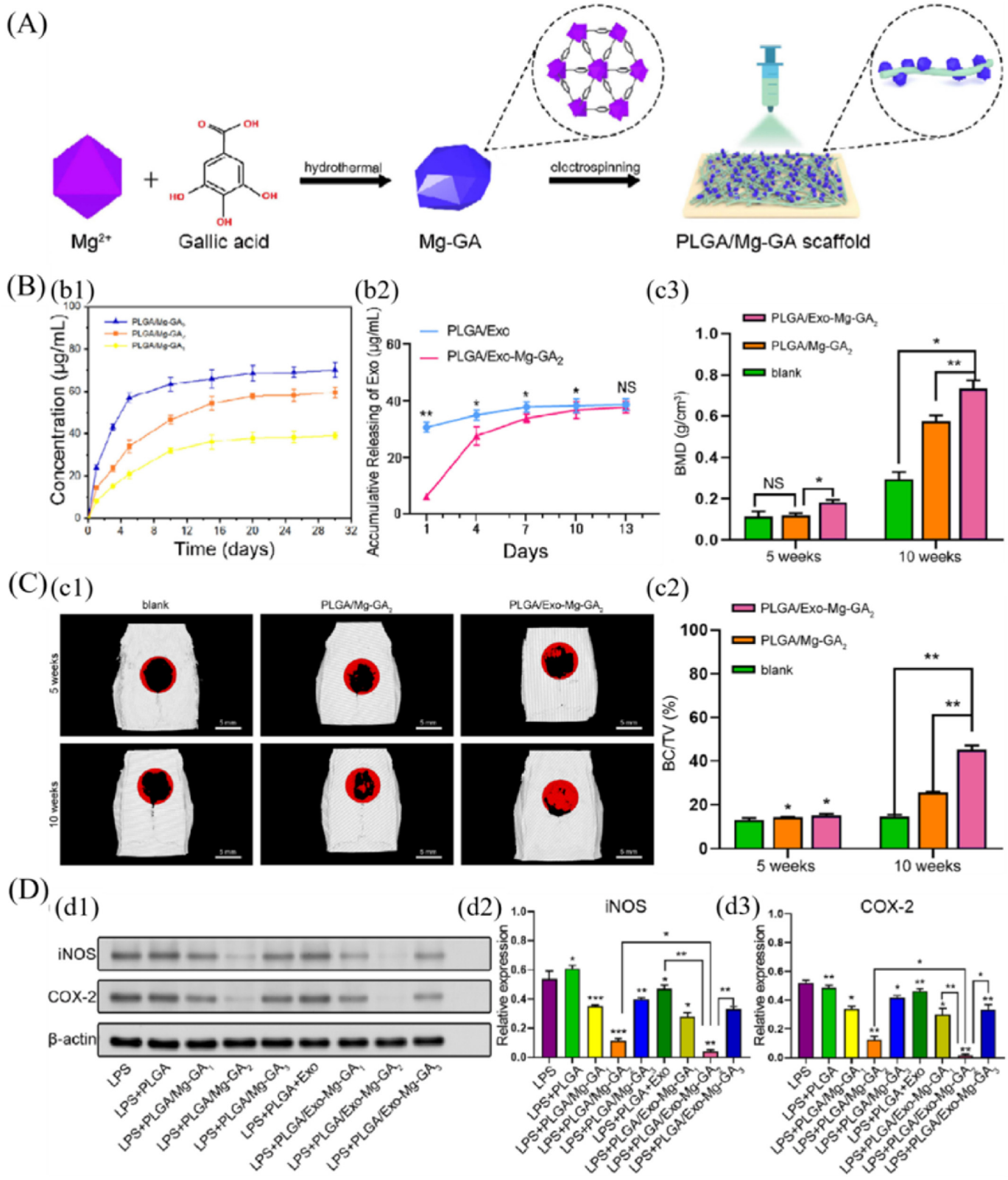

Fig. 4. Exosome-loaded Mg-gallic acid-MOF/PLGA scaffold fabricated by electrospinning method with multi properties for accelerated bone regeneration. (A) Fabrication and characterization of Mg-gallic acid MOF composite scaffolds. (B) Release curves of ion and exosome, (b1) Mg^{2+} and (b2) exosome. (C) Micro-computed tomography analysis of scaffolds on in vivo bone regeneration at 5 weeks and 10 weeks post-surgery. (c1) Three dimensional micro-CT images of rat calvarial defect areas. (c2) BV/TV ratio of composite scaffolds. (c3) BMD ratio of composite scaffolds. (D) Anti-inflammatory related genes expression. (d1) Western blot analysis of iNOS and COX-2 expression in RAW264.7 cells cultured on composite scaffolds for 3 days, relative expression of iNOS (d2) and COX-2 (d3) (reprinted with permission from Ref. [92]).

Table 4
MOFs-functionalized biomaterials for bone repair with anti-tumor function.

MOFs categories	Specific MOFs	Characteristics of MOFs	MOFs functionalized Biomaterials	Functionality of MOFs	Ref.
Zn-based MOF	ZIF-8	Size: Doxorubicin-loaded MOFs of 95.8 ± 4.7 nm, MOFs encapsulating in polyethylene glycol-folic of 106.3 ± 3.9 nm	Doxorubicin-loaded MOFs encapsulating in polyethylene glycol-folic	Drug delivery for treating osteosarcoma	[96]
		Size: about 50 nm; Zeta potentials: −19.3 ± 0.4 mV; Surface area: ZIF-8 of 1400 cm^2/g, cisplatin-loaded ZIF-8 of 1380 cm^2/g	Cisplatin-loaded ZIF-8, BMP-2-loaded ZIF-8 and HA assembling on 3D-printed gelatin scaffold	Drug and growth factor delivery	[43]
		Size: 56.77 ± 13.98 nm; Surface area: 1613 m^2/g Pore size: 1.347 nm	Phenamil-loaded MOFs dropping onto gelatin scaffold	Providing photothermal effect after sintering and releasing phenamil	[97]
Fe-based MOF	MIL-100	Size: D-arginine-loaded MOFs encapsulated in hyaluronic acid, 117 nm	D-arginine-loaded MOFs encapsulated in hyaluronic acid	Increasing ROS and releasing D-arginine for treating osteosarcoma	[98]
Mg-based MOF	Mg-MOF-74	Contact angles: about 10°	Mg-MOF74 and Sr-substituted hydroxyapatite coating on Ti substrates	Providing alkaline microenvironment and releasing ions	[56]
Co-based MOF	Co-TCPP	Sheet size: about 400 nm; Sheet thickness: 10–20 nm	MOFs-modified calcium phosphate cement	Providing photothermal effect and releasing Co^{2+}	[99]
Cu-based MOF	Cu-TCPP	Coating thickness: about 50 nm	MOFs coating on 3D printed β-TCP scaffold	Providing photo-thermal effect and releasing Cu^{2+}	[57]

photothermal therapy, magnetothermal therapy and immunotherapy strategy, etc. [121,122]. Even so, in some cases, surgical resection is unable to completely eradicate the tumor cells, and the large bone defects caused by surgical resection need to be repaired. In addition, systemic chemotherapy or radiotherapy has side effects of damage and toxicity to normal tissues. Therefore, development of biomaterials, such as particles and scaffolds, with local anti-tumor capacity are essential and urgent for bone tumor treatment [9,120,122]. Encouragingly, MOFs materials have the ability to deliver drug, release ions and exhibit physical responsiveness due to their high porosity, alterable constitute and controlled stability, which can be used for functionalizing biomaterials and giving them the dual functions of anti-tumor and bone repair (see Table 4).

Among the MOFs for functionalizing biomaterials, Zn-based MOFs are more studied, which is derived from their excellent biocompatibility and drug delivery ability [43,96,97]. For example, the authors of Ref. [43] developed a ZIF-8-modified gelatin-based implant fabricated by 3D printing, which had the ability to responsively release anti-cancer drug (cisplatin) and growth factor (BMP-2) for anti-tumor therapy and osteogenesis, respectively (Fig. 5). The polydopamine-hybridized ZIF-8 MOFs with adhesive property were firstly synthesized by catechol-controlled chemistry, which were served as the nanocarriers for encapsulating BMP-2 and cisplatin (Fig. 5 (a1)). It could be seen that the hybridization of polydopamine greatly enhanced the structural stability of the ZIF-8 nanoMOFs, which overcame the innate instability of pure ZIF-8, and therefore enhanced their potential for long-term drug release in physiological environment. And then the scaffold was constructed by alternatively assembling BMP-2 and cisplatin-encapsulated ZIF-8 MOFs with polydopamine-decorated hydroxyapatite nanoparticles on a 3D-printed gelatin scaffold by a polydopamine-assisted LBL assembly strategy (Fig. 5 (a2)). After ZIF-8 nanoMOFs alone were assembled on the scaffold, the strut surface of the ZIF-8-gelatin scaffold was covered with spherical-shaped nanoparticle. The adhesive catechol motifs available on the inorganic ZIF-8 nanoMOFs and HA NPs facilitated effective self-assembly to form the multifunctional composite coatings on the scaffold with hierarchical architectures. The scaffolds revealed an intelligent degradability that was sensitive to the tumor environment, i.e., the greater the acidity, the quicker the release of BMP-2 and cisplatin (Fig. 5 (a3)). Furthermore, due to the release of the cisplatin, the scaffold possessed more outstanding anti-tumor property than other groups by in vitro and in vivo evaluations (Fig. 5 (B)). Also, the scaffolds were confirmed to promote the cell proliferation and bone formation-associated genes expression of rat bone marrow stromal cells, and accelerate new bone formation due to the sustained release of BMP-2. In addition, on the basis of the cargo delivery capacity of ZIF-8, the authors of the literature [97] introduced a photothermal effect derived from ZIF-8 to enhance the repair of tumor-caused bone defects. The sintered ZIF-8 nanoparticles with porphyrin-like macrocycles structure were synthesized by the calcination of ZIF-8 under N_2 atmosphere, which exhibited good photothermal efficacy and drug delivery ability. As an activator of bone morphogenetic protein pathways, phenamil was encapsulated into ZIF-8 before loading onto gelatin nanofibrous scaffolds, and the loaded phenamil exhibited a sustained and NIR-triggered release profile. The scaffold could promote cell proliferation and osteogenic differentiation-related genes expression of C2C12 cells due to the release of phenamil. More importantly, the anti-tumor results revealed that the photothermal effect of the scaffolds could kill MG-63 cells in vitro and inhibit subcutaneous tumor growth in vivo.

Other MOFs, such as Mg, Co and Cu-based MOFs, were also used to functionalize biomaterials and enhance their anti-tumor and osteogenic properties [56,57,99]. For example, the authors of Ref. [56] constructed a composite coating of Mg-MOF74 and strontium-substituted hydroxyapatite on the surface of titanium for improving the local osteosarcoma treatment. It was demonstrated that superficial Mg-MOF74 could rapidly degrade, especially in the acidic microenvironment induced by osteosarcoma, and the alkaline microenvironment induced by the released Mg^{2+} could effectively kill the surrounding Saos-2 cells. After that, the exposed Sr-HA coating had great potential to promote the proliferation and osteogenic differentiation of osteoblasts. Therefore, this study provided a strategy to achieve anti-tumor function through the alkaline microenvironment generated by the rapid degradation of MOFs. In addition, MOFs-functionalized biomaterials could be equipped with anti-tumor function by the option of MOFs ligands, such as porphyrin with photothermal properties [57,99]. For example, inspired by the photothermal anti-tumor effect of Cu-TCPP nanosheets, the authors of Ref. [57] successfully prepared a Cu-TCPP coating on β-TCP scaffold by using 3D printing technology and in situ growth method. The strut surfaces of the TCP scaffolds were homogeneously covered by a large area of orange-red Cu-TCPP. Interestingly, the 20Cu-TCPP-TCP scaffolds could degrade and release bioactive ions continuously in the Tris-HCl solution. The β-TCP scaffold with Cu-TCPP coating exhibited excellent photothermal effect under the irradiation of NIR light in both dry and wet conditions, especially in wet states simulating the physiological environment up to 60 °C. And β-TCP scaffolds with 20Cu-TCPP showed extremely good killing performance with about 10% cell viability under NIR light power density of 1.0 W cm^{-2} and irradiation time of 10 min. Similarly, the scaffold with Cu-TCPP coating could translate NIR light into thermal energy, which ablated bone tumor tissue and suppressed subcutaneous bone tumor tissue growth in nude mice. At the same time,

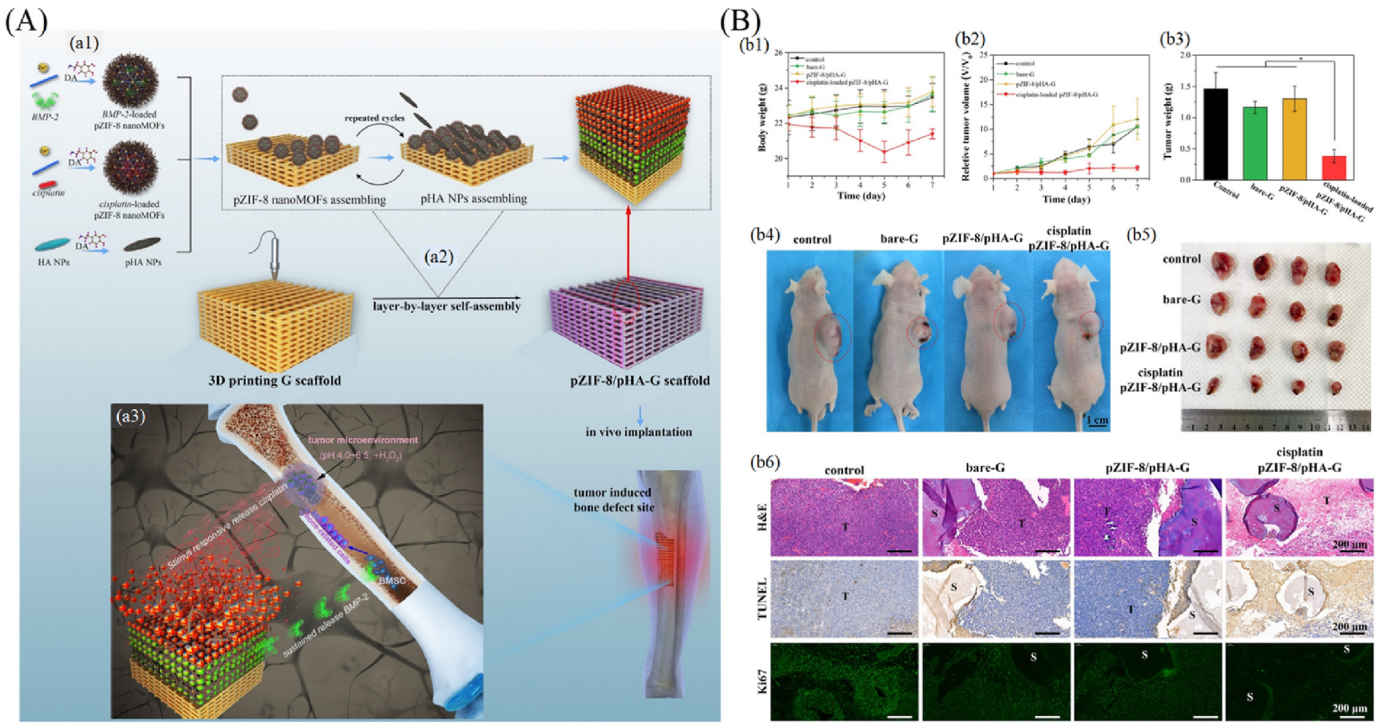

Fig. 5. 3D-printed scaffold modified by ZIF-8 for anti-tumor therapy and bone regeneration. (A) Schematics of fighting cancer and improving bone formation by functionalized implant. (a1) Synthesis process of ZIF-8 MOFs, (a2) 3D printing of scaffold, and (a3) Scaffold served as an intelligent drug delivery system. (B) In vivo antitumorefficiencies, (b1) Changes of body weights, and (b2) relative tumor-growth curves, (b3) Representative images of tumor-bearing mice (b4) and excised tumors (b5). (b6) H&E staining, TUNEL staining and Ki67 immunofluorescent analysis (reprinted with permission from Ref. [43]).

the scaffolds with Cu-TCPP coating could support the attachment of human bone marrow stromal cells and human umbilical vein endothelial cells, and significantly stimulate the expression of osteogenesis and angiogenesis-associated genes. Further, the scaffold with Cu-TCPP coating could effectively promote new bone formation and bone regeneration in vivo. Therefore, MOFs-functionalized biomaterials with photothermal effects achieved the integration of bone-formation bioactivity, angiogenic activity and anti-tumor ability, providing a new horizon for the development of biomaterials that simultaneously treated bone tumors and repaired bone defects.

Of course, for classical radiotherapy and chemotherapy in which scaffold materials may not be necessary, particles may exert a greater anti-tumor effect [96,98]. High-dose radiation therapy was useful for unresectable osteosarcoma that is a common bone cancer with a high rate of lung metastasis, yet it also leads to serious side effects. Therefore, the authors of Ref. [98] developed a D-arginine-loaded MIL-100 (Fe-based MOF) that could sensitize osteosarcoma to radiotherapy. D-arginine, a metabolically inert enantiomer of L-arginine, had the ability to produce NO. The final nanoparticles were obtained by conjugating MIL-100 nanoparticles with hyaluronic acid and then encapsulated by D-arginine. The MOFs not only was a nanocarrier for delivering D-arginine to tumors, but also increased the levels of free radicals that might work synergistically with NO to alleviate hypoxia and kill the tumors. Additionally, the D-arginine-loaded MIL-100 nanoparticles enhanced the therapeutic effect of radiotherapy on tumors in mice and effectively prevented their metastasis to lungs, as well as reduced the toxicity of the MIL-100 nanoparticles in mice.

In conclusion, it was clear that MOFs materials possessed numerous abilities such as drug delivery and physical responsiveness, thus making MOFs-functionalized biomaterials exhibit significant potential in tumor-caused bone defects. In specific anti-tumor strategies, tumor tissue could be eradicated by the direct killing effect of drugs and microenvironment changes induced by ions release and photothermal properties of ligands, especially the antitumor effect induced by physical stimulation showing great potential. Even so, there were few researches on this area, and thereby more antitumor therapies needed to be introduced, such as magnetothermal, sonodynamic, photodynamic and combined therapies. In addition, introducing other endogenous and exogenous stimuli to trigger antitumor properties would provide new ideas and new directions for the development of new antitumor biomaterials.

6. Limitations of MOFs-functionalized biomaterials for biomedical applications

In general, MOFs materials were less stable or more degradable in aqueous environments because they are composed of metal ions and ligands by the weak coordination bonds [101]. In addition, the presence of large amounts of inorganic salts and organic matter in the human physiological environment, and acidic or alkaline environments would also promote the degradation of MOFs [51,57]. Therefore, the degradation of MOFs would lead to a burst release of metal ions or ligands, which can result in poor biocompatibility; and when the MOFs material degrades, it may lose its function [54,92]. Furthermore, the bone tissue may not require large amounts of metal ions in the early stages, whereas there was a greater need for metal ions in the mid to late stages, with the degradation of the MOFs been largely complete. Thus, it would lead to a mismatch between the MOFs-functionalized biomaterials and the bone repair. Therefore, it had a requirement to improve the long-term stability and control the degradability of MOFs materials to exert continuous functions.

MOFs materials had high specific surface and porous structures, which gives them great advantages in drug delivery [39–43]. However, the release of drugs was generally more in the early stage and less in the late, which could not provide a stable and continuous release to match the actual demands [54,74]. This was mainly because the loading principle of MOFs materials for drugs was physisorption action, with the release of drugs satisfying the concentration diffusion law and being more difficult to achieve controlled release [123,124]. In addition, the

loading rate of MOFs materials on drugs or small molecules was generally not high, and pure physisorption action hardly contributed to improving the loading rate further. As mentioned above, the degradation of MOFs materials also affected the sustained release of drugs. Designing new MOFs materials with larger specific surface and improving the structural stability and drug loading rate of MOFs were effective methods to increase the drugs loading of MOFs. In addition, the development of intelligent sustained release systems with microenvironmental response may be another ideal direction to facilitate the drug delivery capacity [40,41,43].

Functionalized strategies of MOFs for biomaterials mainly included coatings and composites. The main functions of coatings were to protect the substrate materials, like magnesium alloys [51,64,75], or to enhance the bioactivity of biomaterials, like titanium alloys and PEEK [54,70,74,84]. Although the corrosion resistance and bioactivity were improved to some extent, the overall promotion is limited as the bond between the MOFs and the substrate material is weak. In composites form of MOFs and biomaterials, the combination of MOFs and biomaterials was often a mechanical mixture without chemical bond. MOFs materials only played roles in the release of ions or drugs, with no significant enhancements to the biomaterial, such as mechanical properties and corrosion resistance. Researches were carried out to address these issues. For example, a polydopamine coating was prepared on the substrate materials as a transition layer and then MOFs material was synthesized on the coating, which did improve the bonding to some extent [54]. There was also research into functionalizing a layer of polymer on the surface of the MOFs materials and using the polymer to interact with the biomaterial, thus improving the bonding [43]. In conclusion, functionalizing the surface of MOFs materials or biomaterials, and then using MOFs materials to functionalize biomaterials will effectively improve the binding state of MOFs to biomaterials.

The majority of the aforementioned studies revealed that MOFs materials were biocompatible and less cytotoxic. However, MOFs materials were still potentially toxic due to the existence of metal ions and organic ligands, especially heavy metals [125]. And toxicity of MOFs was the most urgent issue to be addressed prior to clinical studies. The authors of the study [126] evaluated the cytotoxicity of 14 kinds of MOFs, including MIL-127, MIL-100, MIL-88 A and ZIF-8, and so on. It displayed that MOFs nanoparticles exhibited low cytotoxicity, with the less toxic being the Fe-based MOFs, and the more toxic being the Zr-based and Zn-based MOFs nanoparticles. In another study, the ranking order of cytotoxicity was Mn-based MOF-74 > Cu-based MOF-74 > Zn-based MOF-74 > Mg-based MOF-74 > Ni-based MOF-74 > Co-based MOF-74 [125]. Collectively, the biocompatible metal (such as Mg) induced less cytotoxicity, while the transition metal (such as Cu and Mn) with high ROS generation or coordination ability with biomolecules made strong cytotoxicity. Therefore, the priority was the selection of less toxic metal ions in designing of MOFs. Other strategies like surface functionalization had the same effectiveness. For example, grafting of folic acid on the surface of Zr-fumarate MOF had the ability to reduce selective cytotoxicity and improves immune system compatibility in nanoscale drug delivery [127]. Due to the diversity of structures and species of MOFs, as well as the complexity of the internal environment of organisms, the toxicity of MOFs was not only associated with composition, morphology, size and stability, but also the tolerance of biological tissues [125,128]. MOFs-functionalized scaffolds are excellent candidates for biomedical applications, the toxicity of various MOFs needs to be thoroughly evaluated, as well as the long-term toxicity.

Bone repair remains suboptimal with most artificial implants, especially in bone defects with tumors, inflammation, and/or bacterial infections. With high porosity, high specific surface and variable composition, MOFs materials have natural advantages in drug loading and sustained release of ions. MOFs are better candidates for functionalization of biomaterials without loading capacity, while the advantages of MOFs materials are relatively diminished for porous materials such as mesoporous materials. Hence, MOFs materials are the best choice for functionalization of biomaterials that do not have porous structure and need to be loaded with drugs. However, the use of MOFs materials increases the biological validation and the process cost in addition to the cost of the material preparation process. Therefore, the basic logic of cost-effectiveness of these biomaterials is whether the beneficial effects of the use of MOFs far outweigh the biological validation and process cost.

7. Summary and prospects

Due to the complexity of bone repair, higher demands are placed on biomaterials, such as anti-inflammatory, anti-tumor and antibacterial functions in addition to the basic osteogenic and angiogenic abilities. MOFs materials possess inherent advantages in functionalizing biomaterials due to their flexible compositions, excellent microstructure and controlled degradability. Specifically, MOFs enhance the biocompatibility, osteogenic, angiogenic, anti-tumor, anti-inflammatory and antibacterial activities of biomaterials through the sustained release of ions and drugs, the physical triggering action and the combined effects, and so on. The MOFs-functionalized biomaterials possess above multiple functions by combining various properties of MOFs, enabling the integration of therapy and restoration, and had increasing prospects in bone tissue engineering. Nevertheless, there are still various problems, such as the biodegradability and biocompatibility of MOFs materials, and deep-seated mechanisms of affecting cells behaviors, so more in-depth research on MOFs with novel function are needed to improve bone repair and treatment effects in different scenarios.

For the MOFs used in facilitating bone regeneration, researchers have explored the Zn-based MOF in depth, while MOFs based on other elements, such as Ca, Mg, Sr and Cu, deserve more attentions and explorations. However, special attention needs to be paid to the biocompatibility of these elements, especially the heavy metal elements. In addition, the mechanism of MOFs on bone tissue is mainly focused on the role of metal ions, ignoring the effect of MOFs crystals themselves and other degradation products, as well as the changes in physicochemical properties of biomaterials after functionalization of biomaterials, such as hydrophilicity, hydrophobicity, surface charge, roughness, etc. Due to the limitations of MOFs materials like the stability and degradability in solutions, the biocompatibility, drug delivery ability, degradation property and integration state of MOFs-functionalized biomaterials are still worthy of further research and improvement.

Although numerous studies had demonstrated that MOFs-functionalized biomaterials achieved good osteogenesis and antibacterial effects, there were still some problems that were not solved. The poor stability and fast degradability of the MOFs of functionalizing biomaterials caused the sudden release of ions and drugs at the initial stage, which affected the long-term release, biocompatibility and antibacterial property. Therefore, MOFs materials with antibacterial functions needed to be further studied and explored to better functionalize biomaterials with dual functions of against infections and promoting bone repair. Furthermore, researchers had focused more on release and degradation behavior of MOFs-functionalized biomaterials in simulated infected tissues (low pH environment), while studies on the antibacterial and osteogenic properties under physiological environments with continuously changing pH were neglected. In addition to the introduction of metal ions, organic ligands and drugs, the surface charge, surface microstructure, catalytic properties, and photothermal properties also contributed to the antibacterial performance, so it was important to explore the effects of physical and chemical properties of MOFs-functionalized biomaterials on the antibacterial performance. Moreover, due to the drug resistance, the introduction of new functional MOFs materials, especially physically triggered-based strategies, was the preferable option besides improving drug utilization.

Since inflammation exists in the bone trauma and pathological environment, attentions need to be paid to its impact on bone repair and healing in different scenarios. Chronic inflammation, such as arthritis,

severely interferes with the quality of life of patients, so it is crucial to achieve long-lasting drug delivery for curing it. MOFs can achieve long-term treatment of inflammation by loading anti-inflammatory drugs, but further improvements in drug loading efficiency and sustained release capacity are needed. In addition, MOFs-functionalized biomaterials can achieve anti-inflammatory effects by releasing ions to modulate the behavior of immune cells or ligands with anti-inflammatory effects to scavenge excess free radicals, but attention needs to be paid to the degradability and long-lasting property of MOFs materials. Therefore, further investigations are needed in the aspects of controlled release of ions, ligands and drugs, as well as bone repair and anti-inflammatory effects and mechanisms. Considering the catalytic activity exhibited by MOFs materials to ROS, catalytic properties should be introduced into the future design strategies for the functionalizing biomaterials to scavenge excess free radicals, modulate inflammation and promote bone repair.

In terms of tumor-induced bone defects, MOFs-functionalized biomaterials can well manipulate the release kinetics and photothermal properties through endogenous or exogenous physicochemical triggering, so as to better use the biochemical substances in the pathological environment for tumor treatment. Although, numerous studies show that MOFs-functionalized biomaterials exert excellent antitumor properties and bone repair properties, they were performed independently in vivo experiments, ignoring their interactions. Therefore, MOFs-functionalized biomaterials should not only focus on protecting normal cells and killing cancer cells individually, but also on how to recognize them intelligently in situ and understand their interactions. In spite of the difficulties, it is absolutely necessary to build an in situ defect model of bone tumor to illustrate the interaction of anti-tumor effect and bone repair. In addition, although the anti-tumor effect induced by physical stimulation showed great potential, more therapies needed to be introduced, such as magnetothermal, sonodynamic, photodynamic and combined strategies due to the paucity of research in this area.

The currently known MOFs materials have more or less problems, such as, the toxicity of heavy metals and ligands, the insufficient functionality carried by themselves, and the degradation of MOFs materials. Therefore, the development of MOFs materials with new functions is the key to give biomaterials excellent bone repair and therapeutic functions. To address the toxicity issues, functional MOFs can be constructed using endogenous or bioactive molecules as ligands and metal ions with high biocompatibility (e.g. Fe, Ca, Zn, etc.) as metal nodes, which are of great benefit to avoid the toxicity of MOFs. Severe aggregations can lead to additional toxic effects, and preventing the aggregation and premature clearance of MOFs during circulation is another challenge that needs to be addressed. Surface functionalization and size control are often used to address this drawback, which can be achieved by controlling the diameter of MOFs in the nanoscale range by modulating synthetic methods or other physicochemical strategies, surface functionalizing MOFs with polymers, supramolecular macrocyclic compounds, and modulating the surface potential and bonding force with other entities. The functionality of MOFs materials is often insufficient, such as drug loading capacity, which needs to be addressed by the development of new MOFs. Precise design of metal ions and ligands is required to prepare smart MOFs materials with suitable pore structures and microenvironmental response. The current mechanism studies for most of the sustained release systems are mostly speculative, while the underlying mechanisms are very important for intelligent sustained release systems. Therefore, the mechanisms of intelligent drug release need to be thoroughly investigated and explained. This can be elaborated and summarized by conducting studies on the effects of endogenous stimuli (including pH, glutathione, adenosine triphosphate, glucose, enzymes, H_2S, etc.) and exogenous stimuli (including light, temperature, pressure, etc.) on stimulus-responsive drug delivery systems. The development of multi-stimulus responsive drug delivery systems has become a trend, because they have more functions attributing to multi-level modifications compared to single-stimulus ones. In addition, since in vitro degradation is difficult to simulate the real degradation results, the degradation mechanisms and pathways of MOFs need to be studied systematically in vivo.

In conclusion, the future research should focus on exploring the MOFs used for functionalizing biomaterials in various aspects, especially in designing MOFs materials with new functions by comprehensively exploring the matching and selection of ions and ligands, and studying the physicochemical and biological properties of MOFs. Furthermore, the exploration of the MOFs-functionalized biomaterials should focus not only on the MOFs and the biomaterials themselves, but also on the biological behavior of each component and the synergistic effects among the different components. It is more crucial to comprehensively elucidate the interrelationship between the composition, structure and properties of MOFs-functionalized biomaterials, as well as the long-term in vivo biological behaviors such as in vivo stability, pharmacokinetics and biological distribution. Therefore, considering designing MOFs-functionalized biomaterials, more attentions should be paid to their long-term efficacy and clinical translation potential rather than just their excellent therapeutic properties in vivo and in vitro.

Credit authors statement

Chaoqian Zhao: Writing–original draft, Resources, Validation, Funding acquisition. Chaoqin Shu: Resources, Writing–original draft. Jiangming Yu: Conceptualization, Writing–review & editing, Funding acquisition. Yufang Zhu: Conceptualization, Supervision, Writing–review & editing, Funding acquisition.

Declaration of competing interest

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

Data availability

Data will be made available on request.

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