



Metal-organic frameworks for antibacterial therapy: a mini-review on microenvironment-responsive strategies and recent advances

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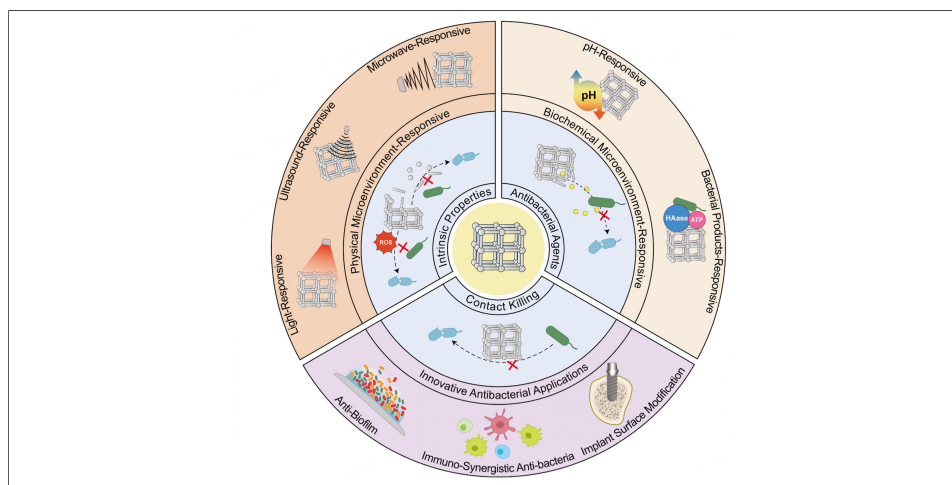
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Abstract

Non-antibiotic antibacterial agents can significantly reduce the risk of bacterial drug resistance, but they face limitations such as poor tissue penetration, insufficient *in vivo* stability, and significant side effects. Metal-organic frameworks (MOFs), as a novel class of porous functional materials, exhibit broad application prospects in the antibacterial field due to their highly tunable structures, large specific surface areas, and precisely controllable pore systems. This review introduces the antibacterial mechanisms of MOFs, explores their responsive antibacterial strategies within the bacterial infection microenvironment, and summarizes their applications in biofilm eradication, immuno-synergistic antibacterial therapy, and implant surface modification. Finally, it discusses the biocompatibility and biosafety of MOFs, addresses the existing deficiencies in this field, and outlines future directions.

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INTRODUCTION

Bacterial infection represents a major global public health challenge, posing a severe threat to human health^[1,2]. Broad-spectrum antibiotics are widely used to treat such infections; however, their overuse can induce bacterial drug resistance, reducing antibacterial efficacy and increasing the prevalence of drug-resistant infections, which imposes a heavy economic burden on global healthcare systems^[3-6]. Therefore, there is an urgent need to develop safe and effective novel antibacterial strategies.

In recent years, non-antibiotic antibacterial agents, such as metal-based nanoparticles (NPs), have garnered increasing attention from researchers. While they lower the risk of bacterial drug resistance and enhance antibacterial efficiency, they suffer from limitations such as poor tissue penetration and insufficient *in vivo* stability^[7-12]. More critically, the microenvironment of *in vivo* bacterial infection is complex and dynamic, yet current antibacterial agents generally lack microenvironment-responsive capabilities, resulting in poor therapeutic controllability and low treatment efficacy^[13]. Furthermore, the formation of bacterial biofilms further complicates treatment, as their dense extracellular polymeric substances significantly reduce the penetration efficiency of antibacterial drugs, providing a protective barrier for the bacteria^[14,15].

Metal-organic frameworks (MOFs) are a novel class of porous functional materials formed by the self-assembly of metal centers and organic linkers through coordination bonds. They feature highly tunable topological structures, large specific surface areas, and precisely controllable pore systems, offering unique advantages in antibacterial applications^[16]. Their intrinsic antibacterial properties, cargo-loading capabilities, and responsiveness to infection microenvironments facilitate effective bacterial elimination, thereby offering a multidimensional strategy to overcome drug-resistant infections and enhance therapeutic efficacy^[17-20].

Given the advantages and promising prospects of MOFs in antibacterial therapy, this review introduces their antibacterial mechanisms and analyzes their responsive therapeutic strategies in physical and biochemical microenvironments. It also summarizes recent innovative antibacterial applications of MOF composite materials and discusses their biocompatibility and biosafety. While several reviews have summarized the landscape of antibacterial MOFs, they often focus on drug delivery. This review provides a more clinically oriented perspective on *in vivo* infection microenvironments, highlighting recent progress toward practical applications.

ANTIBACTERIAL MECHANISMS OF MOFS

The antibacterial efficacy of MOFs is mediated through three mechanisms: intrinsic antibacterial properties, loaded antibacterial agents, and contact killing.

The antibacterial activity of MOFs frequently originates from their intrinsic physicochemical properties. First, MOFs can serve as sophisticated reservoirs for the controlled release of antibacterial metal ions (e.g., Zn²⁺, Cu²⁺, Ag⁺) or organic ligands. Amer *et al.* synthesized a bimetallic MOF, Fola-Zn-HKUST, that releases both Zn²⁺ and Cu²⁺, demonstrating significant antibacterial efficacy^[21]. [Figure 1A] Duan *et al.* constructed carMOF using the antibiotic carbenicillin (car) as the organic ligand^[22]. The carMOF was then coated onto mesoporous silica nanoparticles (MSNs) loaded with a β -lactamase inhibitor, creating a co-delivery system (MSN@carMOF) that synergistically enhanced the antibacterial effect against Methicillin-resistant *Staphylococcus aureus* (MRSA)^[22] [Figure 1B]. Moreover, certain MOFs display photodynamic antibacterial activity arising from their unique frameworks. Chen *et al.* synthesized PCN-224(Zr/Ti), which generates reactive oxygen species (ROS) under visible light, thereby achieving potent antibacterial effects^[23].

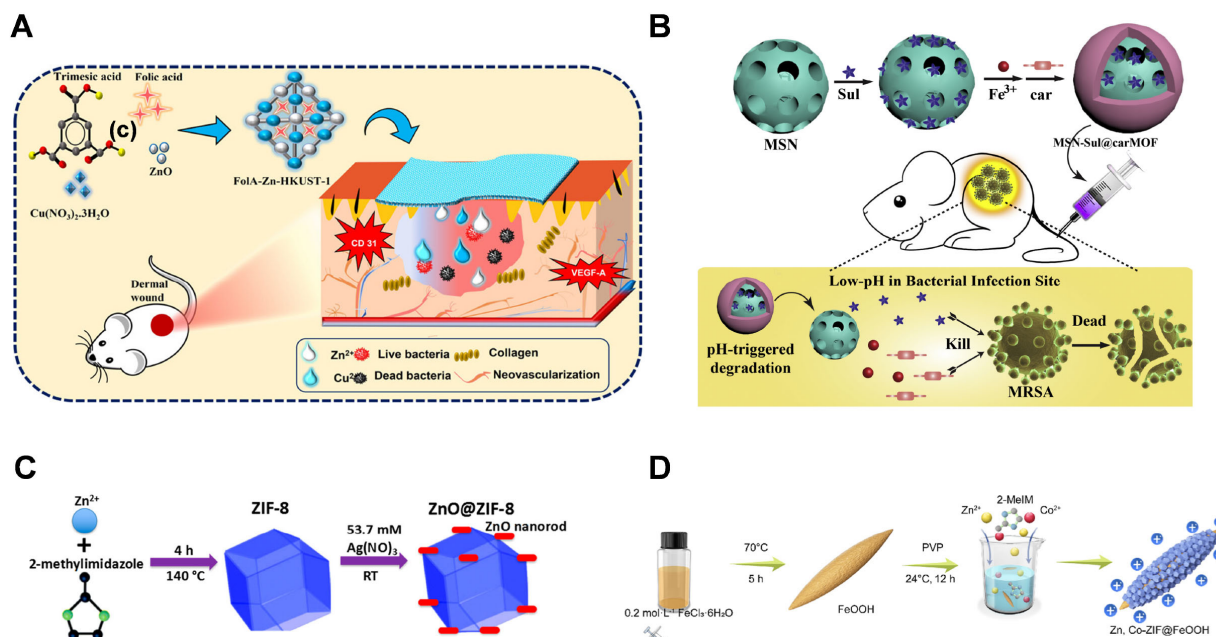


Figure 1. (A) Schematic illustration of the synthesis and structure of FoIA-Zn-HKUST-1. Reproduced with permission^[221]. Copyright 2023, American Chemical Society. (B) Schematic illustration of the synthesis and antibacterial strategy of MSN@carMOF. Reproduced with permission^[222]. Copyright 2021, Elsevier. (C) Schematic illustration of the synthesis and structure of ZnO@ZIF-8. Reproduced with permission^[25]. Copyright 2018, American Chemical Society. (D) Schematic illustration of fabrication process of Zn, Co-ZIF@FeOOH. Reproduced with permission^[26]. Copyright 2024, American Chemical Society.

Second, leveraging their large specific surface area and regular pore structure, MOFs possess high guest-loading capacity and can serve as delivery vehicles for antibacterial agents such as antibiotics and metal-based NPs. Acharya *et al.* synthesized BIO-MOF-100, which exhibits efficient co-loading capability for three anti-tuberculosis drugs, overcoming the limitations of traditional drug delivery systems in co-loading hydrophilic/hydrophobic drugs^[24]. Redfern *et al.* fabricated ZnO@ZIF-8 by embedding zinc oxide (ZnO) nanorods into Zeolitic imidazolate framework-8 (ZIF-8)^[25]. ZnO@ZIF-8 demonstrated potent activity against uropathogens and can be incorporated into silicone to fabricate antibacterial catheters^[25] [Figure 1C].

Third, MOFs can exert a bactericidal effect through "contact killing". This mechanism can be categorized into two primary modes of bacterial membrane disruption: direct physical damage and physicochemical interference. Yi *et al.* developed Zn, Co-ZIF@FeOOH. This material's sharp nanostructures can physically pierce bacterial cell membranes, while the Zn, Co-ZIF NPs on the surface of FeOOH can release antibacterial metal ions (Zn²⁺ and Co²⁺) and induce charge perturbation in the membrane, further enhancing the antibacterial effect^[26] [Figure 1D].

MICROENVIRONMENT-RESPONSIVE ANTIBACTERIAL STRATEGIES OF MOFS

The microenvironment of bacterial infection is a dynamic system including diverse physical and biochemical factors, regulated by endogenous biomediators and external conditions^[13,27]. Bacterial activity can markedly alter the local microenvironment. A neutral milieu may shift to weak acidity due to accumulated metabolic by-products^[28]. Moreover, Bacteria also secrete enzymes such as lipases and hyaluronidase (HAase), along with energy sources such as adenosine triphosphate (ATP)^[13,29,30]. These microenvironmental changes can cleave specific chemical bonds or functional groups, offering a basis for designing stimulus-responsive systems^[31].

This chapter divides the microenvironment into the physical microenvironment (light, ultrasound, and microwave) and the biochemical microenvironment (pH and bacterial products), respectively, elucidating the responsive therapeutic strategies of MOFs and analyzing how they improve antibacterial efficiency and biocompatibility.

Physical microenvironment-responsive MOFs

Light-responsive MOFs

Light-responsive MOFs based on photodynamic therapy:

Photodynamic Therapy (PDT) involves irradiating a photosensitizer with a specific wavelength of light to generate ROS, which have antibacterial capabilities^[32,33]. ROS are a class of highly chemically reactive oxygen-containing species, primarily including superoxide anions ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), hydroxyl radicals ($\bullet OH$), and singlet oxygen (1O_2), which have significant oxidative damaging effects on bacteria and other microorganisms^[34]. The essential elements for achieving PDT are the photosensitizer, light of a specific wavelength, and an oxygen substrate. Photosensitizers play a core role in PDT; however, most of them have poor water solubility and stability, and are prone to aggregation, self-quenching, and degradation in physiological media, which greatly limits the efficiency of PDT^[11,12,35]. Therefore, to achieve efficient delivery and protection of photosensitizers, researchers have constructed PDT-based light-responsive MOFs.

Porphyrins and their derivatives are among the most widely used photosensitizers^[19,33]. PCN-224 is a widely studied porphyrin MOF, composed of zirconium (Zr) and tetrakis (4-carboxyphenyl) porphyrin (TCPP). Research has found that PCN-224 not only possesses excellent PDT performance but also exhibits good loading capacity for vancomycin (Van). Under visible-light irradiation, Van/PCN can generate ROS and simultaneously release vancomycin, demonstrating a synergistic antibacterial effect between the antibiotic and PDT^[19].

Near-infrared (NIR) light has strong tissue penetration and good biocompatibility. However, due to its lower energy, its ability to activate photosensitizers is relatively poor^[36-39]. Upconversion nanoparticles (UCNPs) have unique anti-Stokes luminescence properties, capable of emitting high-energy ultraviolet and visible light upon excitation by low-energy NIR light, thereby enhancing the activation of photosensitizers^[40]. Tan *et al.* combined UCNPs and PCN-224(Pt) to form a core-shell structure and loaded it with the NIR dye IR808, constructing an NIR light-responsive PDT nanoplatfrom (UMOF(Pt)/IR808)^[41]. PCN-224(Pt) is formed by the coordination of Zr and Pt-TCPP. Through cascaded energy transfer from IR808 to PCN-224(Pt), UMOF(Pt)/IR808 exhibited excellent ROS generation capability under low-power-density (0.4 W/cm^2) NIR light irradiation, showing outstanding antibacterial effects against MRSA^[41] [Figure 2A].

Light-responsive MOFs based on photothermal therapy:

Photothermal therapy (PTT) involves using a photothermal agent to convert absorbed light energy into heat, causing localized hyperthermia that denatures bacterial proteins, thereby rapidly destroying the structure and function of bacteria. It has advantages such as low side effects, non-invasiveness, and low propensity for inducing drug resistance, giving it broad clinical application prospects^[42,43].

Polydopamine (PDA) is a widely used photothermal agent. It is a high-molecular-weight biopolymer formed by the oxidative polymerization of dopamine (DA) monomers, possessing high photothermal conversion efficiency and good biocompatibility^[44-46]. He *et al.* synthesized ultrafine silver NPs (AgNPs) within the porous structure of cyclodextrin-based MOFs (CD-MOF) and coated the surface with a PDA shell^[47]. Under

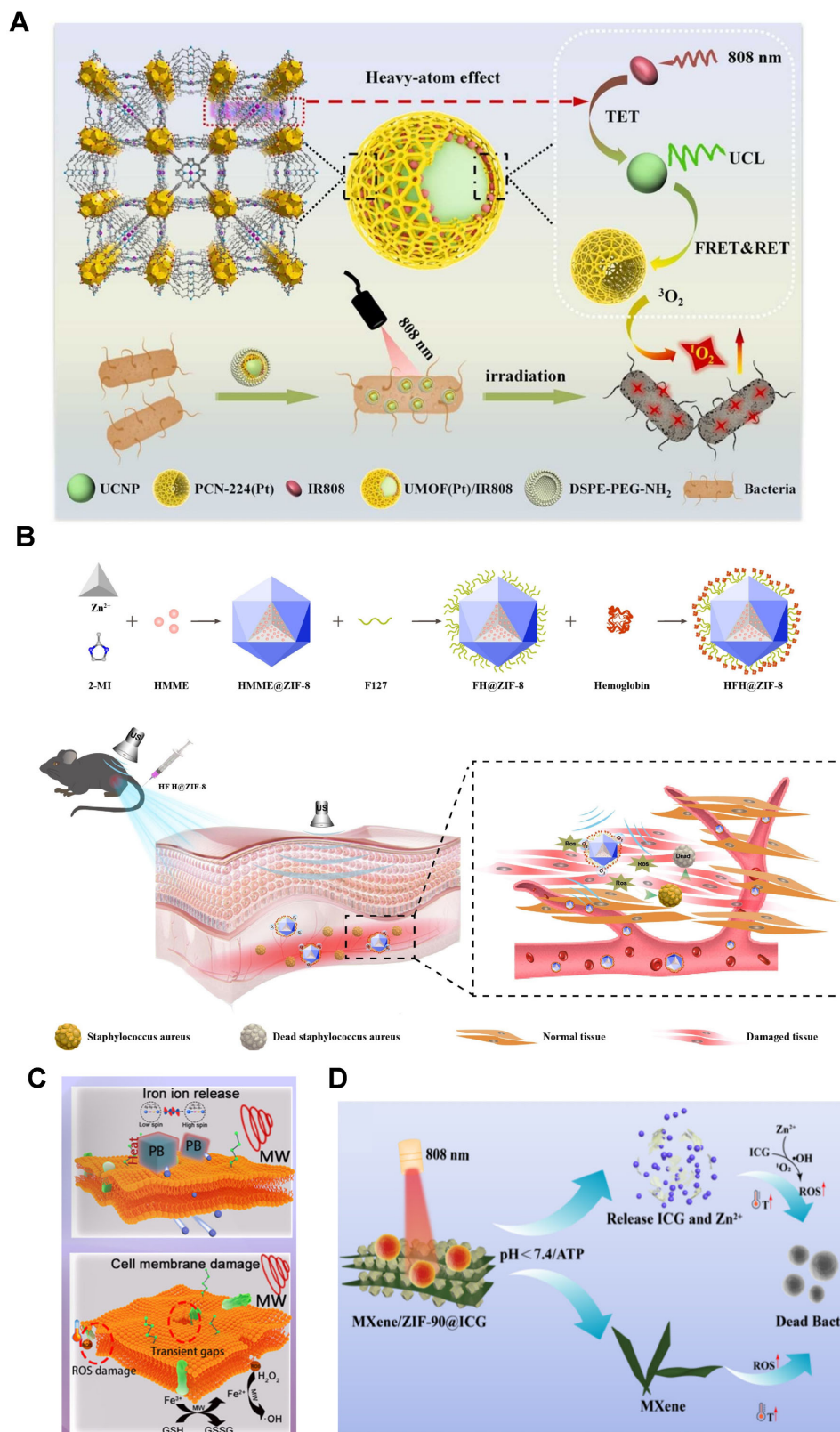


Figure 2. (A) Schematic illustration of the structure and antibacterial strategy of UMOF(Pt)/IR808. Reproduced with permission^[41]. Copyright 2023, Elsevier. (B) Schematic illustration of the synthesis and antibacterial strategy of HFH@ZIF-8. Reproduced with permission^[56]. Copyright 2022, Elsevier. (C) Schematic illustration of the microwave-responsive antibacterial strategy of PB. Reproduced with permission^[64]. Copyright 2023, Elsevier. (D) Schematic illustration of the antibacterial strategy of MXene/ZIF-90@ICG. Reproduced with permission^[70]. Copyright 2024, American Chemical Society.

808 nm NIR light irradiation, the PDA shell not only generated localized hyperthermia but also accelerated the release of Ag^+ through the photothermal effect, thus achieving synergistic antibacterial effects of PTT and Ag^+ ^[47].

Fang *et al.* grew HKUST-1 *in situ* on the surface of $\text{Ti}_3\text{C}_2\text{T}_x$ to obtain an HKUST-1@ $\text{Ti}_3\text{C}_2\text{T}_x$ (HK@MX). HK@MX exhibited synergistic antibacterial effects from both PTT and Cu^{2+} ^[48]. Furthermore, the numerous slit structures on its surface enhanced the adsorption of bacteria, further improving its antibacterial performance^[48].

Ultrasound-responsive MOFs

Ultrasound is a mechanical wave with a frequency higher than 20 kHz. Its non-invasiveness, deep penetration (≥ 10 cm), high controllability, and low cost make it a highly promising external stimulus^[49,50]. Sonodynamic Therapy (SDT) involves activating a sonosensitizer accumulated at the infection site with ultrasound, inducing ROS generation to exert an antibacterial effect^[51]. SDT significantly overcomes the limitation of poor tissue penetration (≤ 1 cm) in PDT, demonstrating unique advantages in the treatment of deep-seated infections^[52]. However, traditional sonosensitizers suffer from low bioavailability, poor stability, and insufficient ROS generation efficiency, which severely restricts their *in vivo* application^[52-55]. MOFs can effectively load and protect sonosensitizers, preventing their degradation in the physiological environment and thus fully unleashing the therapeutic potential of SDT.

Geng *et al.* loaded the sonosensitizer hematoporphyrin monomethyl ether (HMME) into ZIF-8 and modified its surface with hemoglobin, constructing the HFH@ZIF-8 nanoplatfrom^[56]. ZIF-8 can effectively prevent the degradation of HMME *in vivo*, while hemoglobin can transport and supply oxygen, providing sufficient oxygen for SDT and thereby enhancing the efficiency of ROS generation^[56] [Figure 2B].

Wang *et al.* combined a porphyrin MOF (HNTM) with Ti_3C_2 , constructing a hybrid nanomaterial HN- Ti_3C_2 with a Schottky heterojunction^[57]. HNTM can respond to ultrasound to generate abundant electron-hole pairs, while Ti_3C_2 facilitates the rapid transfer of electrons, leading to the generation of a large amount of ROS. It demonstrated an antibacterial efficiency of up to 99.75% against MRSA^[57].

Microwave-responsive MOFs

Microwave is an electromagnetic wave with a wavelength between 1 mm and 1 m. It has advantages such as strong operability, deep penetration, and minimal side effects, making it suitable for treating deep tissue infections^[58,59]. Microwave-responsive antibacterial MOFs have good application potential in the biomedical field due to their ability to absorb and convert microwave energy. It exhibits two therapeutic mechanisms: (1) Microwave Dynamic Therapy (MDT): Catalyzing ROS generation; (2) Microwave Thermal Therapy (MTT): Generating localized hyperthermia at the infection site^[60,61].

Due to the low energy of microwaves (10^{-3} eV), it is difficult to directly induce electron transitions to catalyze ROS generation^[62]. Zheng *et al.* found that under the synergistic effect of Na^+ and pulsed microwave radiation, the MDT performance of a cerium-based porphyrin MOF (CeTCPP) in a NaCl solution was significantly enhanced^[63]. Under the constantly changing microwave field of pulsed microwave radiation, the tribovoltaic effect occurs between CeTCPP and water molecules, thereby inducing electron transitions and generating ROS^[63].

Wei *et al.* developed a Na^+ -inserted Prussian blue (PB) microwave-responsive material, which demonstrated a synergistic effect of MTT and MDT^[64]. PB is a mesoporous MOF that can achieve efficient antibacterial

effects through dielectric loss under microwave irradiation. After the insertion of Na^+ into PB from a NaCl solution, the spin state of iron ions in PB changed irreversibly, which accelerates the release of iron ions during microwave irradiation. Furthermore, microwave irradiation can also increase the permeability of the bacterial membrane, promoting the entry of released iron ions into the bacteria. These iron ions then react with intracellular H_2O_2 through a Fenton-like reaction to generate ROS, while simultaneously accelerating the consumption of bacterial glutathione (GSH), achieving a highly efficient antibacterial effect^[64] [Figure 2C].

Biochemical microenvironment-responsive MOFs

pH-responsive MOFs

Under physiological conditions, the pH of blood and normal tissue microenvironments is maintained at neutral ($\text{pH} \approx 7.4$). However, at the site of a bacterial infection, enhanced bacterial metabolic activity releases lactic acid, carbon dioxide, and other acidic metabolites, causing the local microenvironment to become weakly acidic ($\text{pH} \approx 5.5$)^[28,65]. Based on this, researchers have constructed pH-responsive MOFs that can precisely release antibacterial components in response to changes in pH.

ZIF-8 is one of the most commonly used pH-responsive MOFs^[66]. Soltani *et al.* synthesized gentamicin-loaded ZIF-8 (GEN@NZIF-8) NPs^[20]. Under acidic conditions, the 2-methylimidazole ligand of ZIF-8 undergoes protonation, which weakens its coordination with Zn^{2+} , thereby accelerating the collapse of the ZIF-8 framework and the release of the guest molecules. Experiments showed that the release rate of gentamicin in acetate buffer solution ($\text{pH} = 5.0$) was significantly higher than that in phosphate buffer solution ($\text{pH} = 7.4$), demonstrating excellent pH-responsive properties^[20].

Wang *et al.* used a hierarchically porous B-UiO-66 to load the natural antibacterial substance eugenol (Eu) and further chelated it with Zn^{2+} to construct Eu@B-UiO-66/ Zn ^[67]. Eu@B-UiO-66/ Zn uses the chelation ability between eugenol and Zn^{2+} as a pH-responsive switch: in an alkaline environment ($\text{pH} = 8.0$), the phenolic hydroxyl group of eugenol is deprotonated, enhancing the electron-donating ability of the oxygen atom and thus promoting stable coordination between Zn^{2+} and eugenol. In an acidic environment ($\text{pH} = 5.8$), the protonation of the phenolic hydroxyl group leads to the disassembly of the metal-monophenol network, thereby triggering the release of eugenol and Zn^{2+} . Eu@B-UiO-66/ Zn achieves sustained antibacterial effects through the pH-responsive synergistic release of eugenol and Zn^{2+} ^[67].

Bacterial products-responsive MOFs

During an infection, bacteria secrete various specific products into the surrounding environment (e.g., HAase, ATP), which can serve as "biological switches" to regulate drug delivery.

Zhang *et al.* constructed a PCN-224-Ag-HA system responsive to bacterial HAase. The Ag^+ -loaded PCN-224 possesses both Ag^+ release and PDT capabilities^[29]. At the site of bacterial infection, the HA is degraded by the bacteria-secreted HAase, exposing the positively charged PCN-224- Ag^+ . This allows it to bind to bacteria through electrostatic interactions, thereby fully exerting the synergistic antibacterial effects of Ag^+ release and PDT^[29].

ATP is the most abundant energy source for microbial metabolism and an essential metabolite for maintaining the life activities of viable microorganisms^[30]. Some zeolitic imidazolate frameworks (ZIFs) have a unique responsiveness to ATP. As an unstable high-energy compound, ATP has a strong coordination ability and can compete with imidazole ligands for coordination with Zn^{2+} , thereby triggering an ATP-responsive structural collapse^[68-70]. Based on this, Ding *et al.* loaded the photosensitizer indocyanine

green (ICG) into ZIF-90 and combined it with the photothermal agent MXene-NH₂ nanosheets, constructing a pH/ATP dual-responsive MXene/ZIF-90@ICG composite material^[70]. Under NIR light irradiation, an acidic microenvironment (pH = 5.5) and an ATP microenvironment (0.5 mM) can accelerate the collapse of ZIF-90, releasing Zn²⁺ and ICG. MXene/ZIF-90@ICG can be used to prepare a nano-antibacterial spray for responsive therapy in a bacterial infection microenvironment^[70] [Figure 2D].

INNOVATIVE ANTIBACTERIAL APPLICATIONS OF MOF COMPOSITE MATERIALS

MOF composite materials represent a highly versatile platform for addressing the challenge of clinical bacterial infections. Their multifunctionality renders them potent candidates for engineering antibacterial therapeutic systems. Among the numerous applications, anti-biofilm therapy, immuno-synergistic antibacterial therapy, and implant surface modification have garnered significant attention and demonstrate more promising potential for clinical translation.

MOFs in anti-biofilm therapy

Biofilm is a widespread, dynamic, and complex multicellular community of surface-attached microorganisms embedded in an extracellular polymeric substance^[71,72]. It provides effective protection for bacteria and enhances their resistance to antibacterial agents^[14,15].

Inhibiting initial bacterial adhesion is the primary defense against the development of biofilms. By designing various MOF coatings or films, it is possible to effectively prevent initial bacterial adhesion and kill bacteria that have already attached, thereby preventing biofilm formation. Skvortsova *et al.* covalently immobilized CuBTC on a polypropylene (PP) film surface, successfully constructing a smart, self-activating antibacterial coating^[73]. This coating can respond to the bacterial infection marker GSNO by releasing the antibacterial free radical NO•, providing a solution for preventing catheter-related infections on surfaces such as intravenous or urinary catheters^[73].

Extracellular Polymeric Substances (EPS) are the core structure of a biofilm, composed of lipids, extracellular DNA (eDNA), proteins, and polysaccharides. In addition to providing structural support, they can also form a physical barrier and enhance the drug resistance of the biofilm^[71]. Therefore, developing MOF composite material that can effectively degrade or penetrate the EPS barrier has become an important strategy in anti-biofilm therapy.

eDNA is a key component that connects bacteria and other EPS components, playing a crucial role in biofilm formation, structural stability, and drug resistance^[74-76]. Gokhale *et al.* encapsulated selenium (Se) NPs in ZIF-8 to construct Se@ZIF-8 NPs, which can degrade eDNA within the EPS, effectively disrupting the biofilm structure of *Serratia marcescens*^[77].

To address the issue of poor penetration of •OH and other ROS in the EPS, Jia *et al.* designed a H₂O₂ self-supplying nanopatform, CaO₂/HKUST-1@l-Arg^[78]. They encapsulated CaO₂ NPs within the HKUST-1 framework and loaded the NO donor drug L-Arginine (l-Arg) onto its surface. CaO₂ NPs react with water to continuously generate a large amount of H₂O₂, which then generates •OH through Fenton-like reaction. Meanwhile, H₂O₂ catalyzes the conversion of l-Arg to NO, which further generates the more potent antibacterial agent ONOO⁻. Additionally, NO also inhibits the synthesis and stability of EPS by reducing c-di-GMP levels, thereby weakening the protective effect of EPS^[78].

Nanomotors are nanoscale devices that achieve active movement in various liquid environments by converting different forms of energy into mechanical motion^[79]. Guo *et al.* deposited Au NPs onto one half of

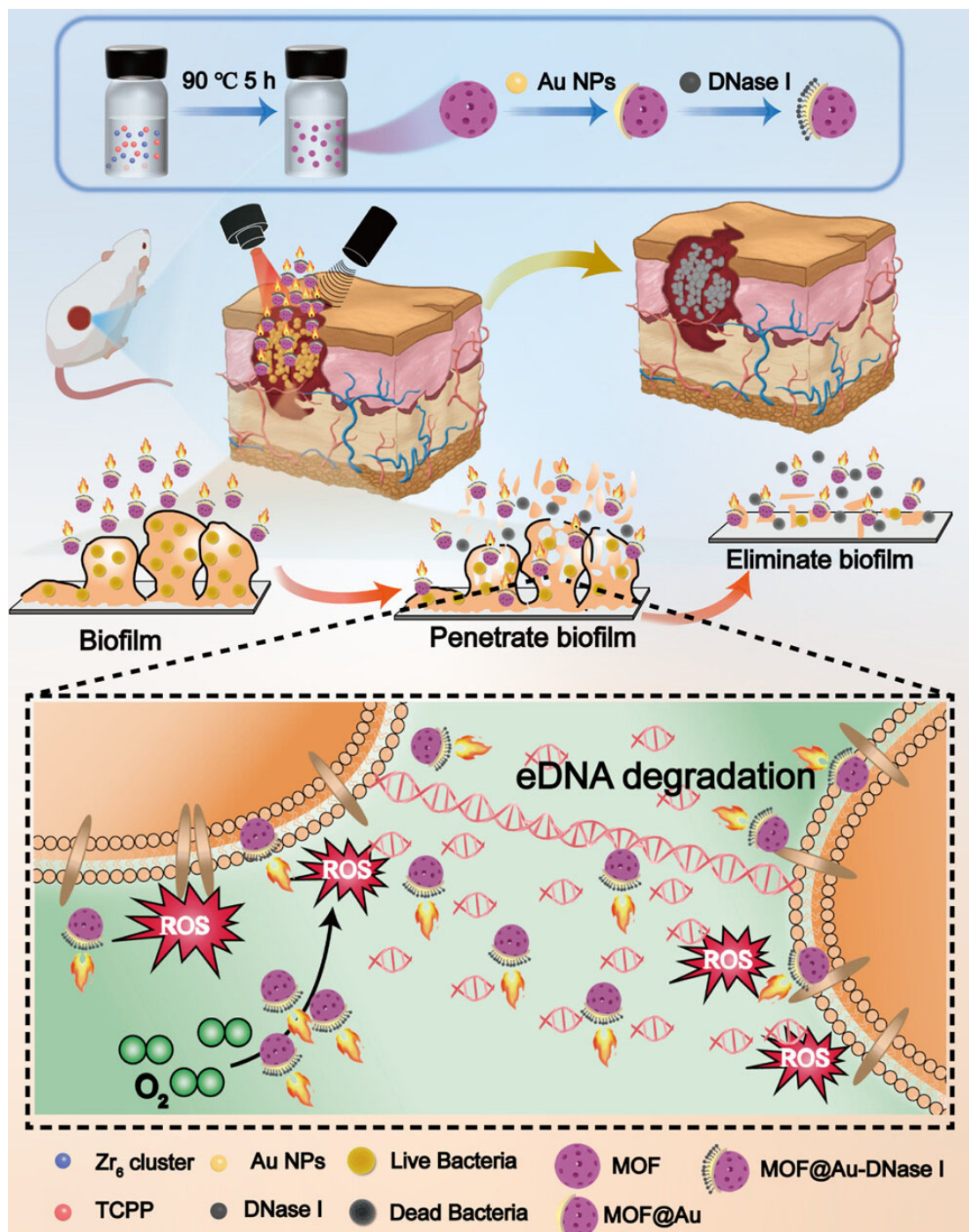


Figure 3. Schematic illustration of the synthesis and anti-biofilm strategy of MOF@Au-DNase I NPs. Reproduced with permission^[74]. Copyright 2023, American Chemical Society.

the surface of a zirconium-based porphyrin MOF and then covalently attached deoxyribonuclease I (DNase I) to the surface, constructing MOF@Au-DNase I NPs nanomotors^[74]. Under NIR light irradiation, this material can rapidly penetrate deep into the biofilm within 15 min. This material exerts its effect through a triple-synergistic mechanism: DNase I-mediated eDNA degradation, NIR light-driven active penetration, and the ROS generation from the SDT effect, thereby achieving efficient elimination of the biofilm and bacteria^[74] [Figure 3].

MOFs in immuno-synergistic antibacterial therapy

The biofilm microenvironment has immunosuppressive properties^[80]. The encapsulated bacteria-associated antigens (BAAs) are difficult to expose, leading to impaired antigen recognition and dysfunctional antigen-presenting cells (APCs), which in turn results in a failed immune response^[81,82]. Furthermore, metabolic products within the biofilm, along with the acidic and hypoxic microenvironment, further induce immune cell dysfunction. For example, they polarize pro-inflammatory M1 macrophages towards anti-inflammatory M2 macrophages, significantly weakening the phagocytic and bactericidal capacities of macrophages^[82-84].

Luo *et al.* reported a MnO₂-loaded Cu-MOF (MCM). MnO₂ can catalyze endogenous H₂O₂ to generate O₂, thereby reversing the hypoxic microenvironment within biofilms^[85]. This reoxygenation shifts bacterial metabolism from glycolysis to aerobic respiration, enhancing bacterial cuproptosis-like death. The reversal of the hypoxic microenvironment not only promotes dendritic cell maturation but also induces macrophage polarization toward the pro-inflammatory M1 phenotype, significantly enhancing the phagocytic activity and chemotactic response of immune cells, thereby reversing the immunosuppressive state and improving antibacterial efficacy^[85].

Hydrogen sulfide (H₂S), a key gas-signaling molecule involved in host-pathogen interactions, has emerged as a crucial therapeutic target for immunomodulation^[86]. Yang *et al.* reported a bismuth-based MOF (Bi-MOF). Based on the high affinity of bismuth for sulfur, Bi-MOF can efficiently scavenge intracellular H₂S, blocking the S-sulfhydration of HIF-1 α in macrophages, thereby inhibiting HIF-1 α degradation and enhancing its post-transcriptional stability^[87]. Experiments showed that Bi-MOF can induce metabolic reprogramming in macrophages, significantly enhancing their antibacterial and immunomodulatory functions. It reverses the immunosuppressive state in a macrophage-dependent manner, ultimately establishing immune memory against bacterial infections^[87] [Figure 4].

Research shows that bacteria can inhibit oxidative stress by synthesizing H₂S to evade immune killing^[88,89]. To address this immune evasion mechanism, Ge *et al.* designed hafnium-based UiO-66 NPs loaded with aurintricarboxylic acid (A@UHf NPs)^[90]. The piezoelectrically enhanced hafnium-based UiO-66 boosts photocatalytic ROS generation by tilting the band structure, while aurintricarboxylic acid blocks endogenous H₂S production by inhibiting cystathionine γ -cleaving enzyme. The combined effect of ROS burst and H₂S inhibition disrupts the redox homeostasis of the bacterial biofilm, inducing ferroptosis-like death in bacteria. Simultaneously, it activates the polarization of neutrophils in the infection microenvironment towards the N1 phenotype, thereby remodeling the antibacterial immune response^[90].

MOFs in implant surface modification

Titanium has excellent biocompatibility and mechanical properties, making it a commonly used implant material in orthopedics and dentistry. To enhance the antibacterial and osseointegration capabilities of titanium implants, surface modification based on MOFs has recently become a research hotspot. However, titanium is biologically inert, and its surface lacks the organic groups necessary for binding with MOFs^[91]. Therefore, various pre-treatment strategies are employed to improve the bonding of MOFs to the titanium surface.

Alkali-heat treatment, which involves immersing titanium in a sodium hydroxide solution at high temperature, can create a sponge-like nanostructure on its surface and form Ti-OH groups, thereby increasing the loading sites for MOFs^[92,93]. Studies show that an alkali-heat treatment enables the *in-situ* growth of a ZIF-8 film on titanium substrates, ensuring a stable bond^[94]. Additionally, micro-arc oxidation is another common pretreatment method. In this technique, titanium is used as the anode to create a porous

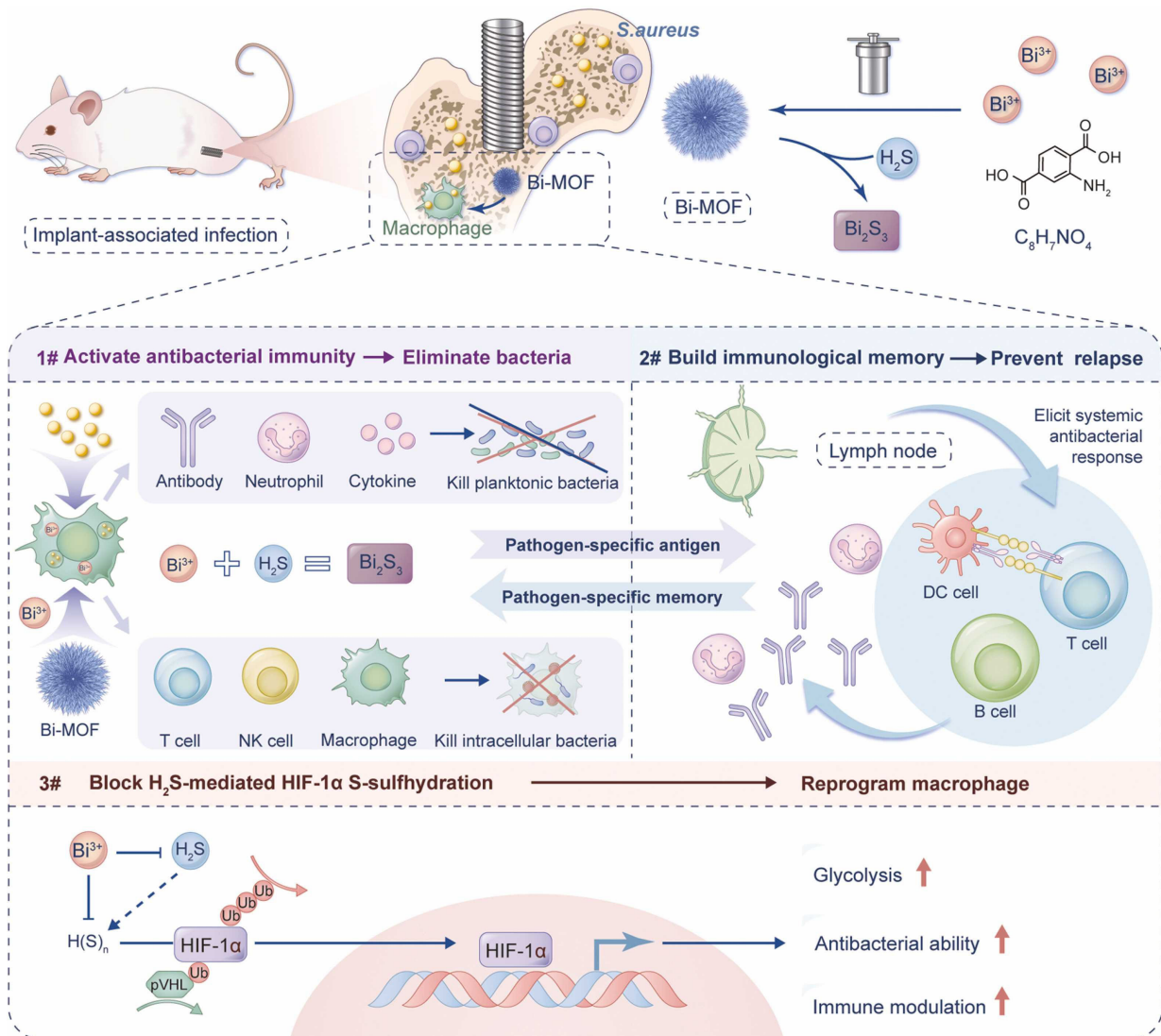


Figure 4. Schematic illustration of the synthesis and immuno-synergistic antibacterial strategy of Bi-MOF. Reproduced with permission^[87]. Copyright 2024, Elsevier.

ceramic oxide coating via micro-arc discharge in an electrolyte at high voltage^[95]. Experiments have shown that micro-arc oxidation can increase the effective loading sites of the titanium surface, facilitating efficient, uniform loading of ZIF-8^[96].

In addition to pretreating the titanium surface, an intermediate layer can be introduced between the titanium and MOFs to enhance their bonding stability. PDA, for instance, spontaneously polymerizes on the titanium surface and promotes the adhesion of MOFs through its excellent adhesive properties^[97]. Si *et al.* immobilized methyl vanillate (MV)-loaded ZIF-8 onto a PDA-modified titanium alloy surface, which exhibited excellent tribocorrosion resistance, antibacterial activity, and osteogenic effects^[97].

Titania nanotubes (TNTs) possess a controllable nano-topography and excellent drug-loading capacity, along with inherent antibacterial and osteogenic activity^[98,99]. Wang *et al.* fabricated TNTs on a titanium surface via electrochemical anodization and subsequently modified them with naringin (Nar)-loaded ZIF-8. The resulting TNT-ZIF-8@Nar coating demonstrated significant antibacterial performance and effectively promoted osteogenic differentiation and implant osseointegration^[100] [Figure 5].

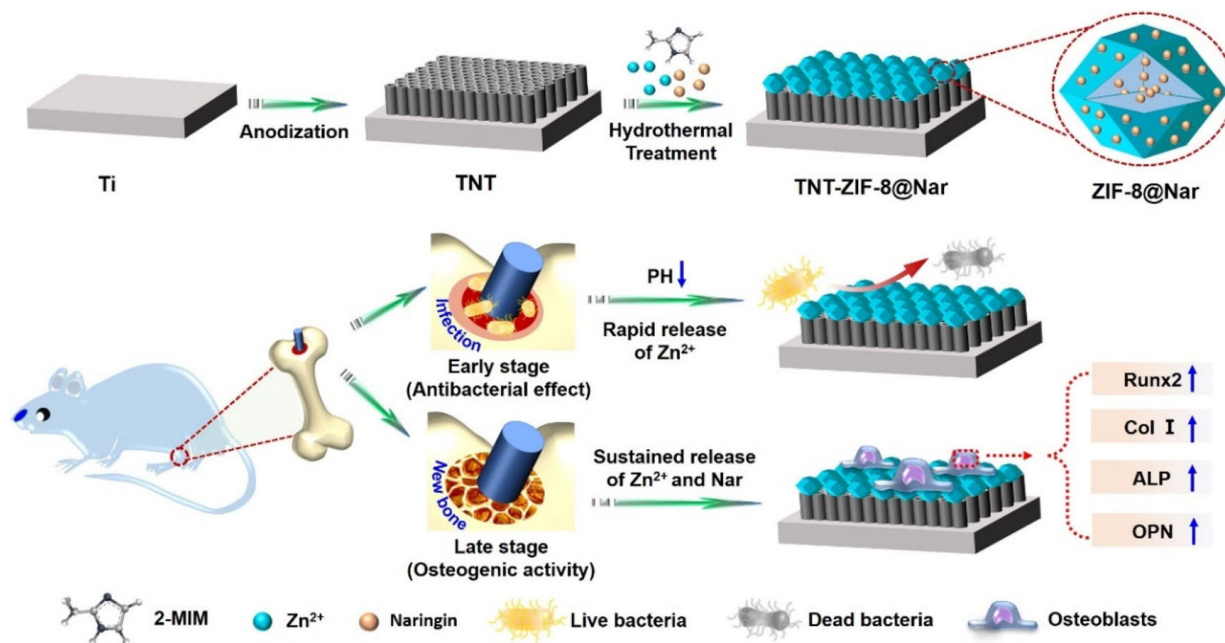


Figure 5. Schematic illustration of the synthesis and antibacterial strategy of TNT-ZIF-8@Nar. Reproduced with permission^[100]. Copyright 2022, American Chemical Society.

BIOCOMPATIBILITY AND BIOSAFETY OF ANTIBACTERIAL MOFs

Despite the excellent antibacterial performance of MOFs demonstrated *in vitro* and in animal models, their clinical translation still faces significant biosafety challenges^[101]. Therefore, advancing the clinical application of antibacterial MOFs hinges on a comprehensive understanding of their biosafety. This involves defining their dose-dependent therapeutic window, investigating potential sources and mechanisms of toxicity, and developing effective strategies to enhance their biocompatibility.

Potential sources of MOF-associated toxicity

Both the therapeutic efficacy and toxic side effects of antibacterial MOFs exhibit concentration effects, requiring an optimal balance between the effective antibacterial concentration and a safe concentration - a concept known as the "therapeutic window"^[102,103]. Ideally, an antibacterial MOF should exhibit minimal toxicity to host cells at concentrations effective for pathogen eradication, thereby presenting a wide therapeutic window. Zhu *et al.* reported that 3D-printed scaffolds incorporating Cu-MOF-74 achieved an optimal balance between antibacterial efficacy and osteogenic potential at Cu-MOF-74 concentrations of 0.05%-0.2%. However, at concentrations $\geq 0.5\%$, cytotoxic effects were observed^[104]. Similar conclusions have been drawn from studies on Ag-MOFs. *In vitro* cytotoxicity testing on Vero cell lines demonstrated a concentration-dependent decrease in cell viability, suggesting their safe application is confined to specific concentration ranges^[105].

The width of the therapeutic window for antibacterial MOFs is influenced by several factors. First, the type of metal center and its release kinetics are critical. While metal ions with high antibacterial activity (e.g., Cu^{2+} , Ag^+) are highly effective, their excessive and rapid release can lead to cytotoxicity. The toxic mechanism often involves the generation of reactive oxygen or nitrogen species, which damage cell membranes, DNA, and proteins, ultimately leading to cell death. Moreover, it may disrupt normal ionic homeostasis of the cells and interfere with intracellular physiological processes, thereby leading to cytotoxicity^[106,107].

The effect of organic ligands on biosafety should not be overlooked. Many antibacterial MOFs, such as HKUST-1 and ZIF-8, employ artificially synthesized ligands, including 1,3,5-benzenetricarboxylic acid (1,3,5-H₃BTC) and 2-methylimidazole^[108,109]. Upon the degradation of these MOFs, the biosafety and metabolic pathways of these small-molecule ligands must be carefully considered.

Strategies for enhancing biocompatibility

Selecting low-toxicity metals is a primary strategy for improving the biosafety of MOFs. Ettliger *et al.* conducted a comprehensive review and roughly ranked the cytotoxicity of MOFs containing various metals^[110]. MOFs containing metals such as Ca, Bi, and Eu were identified as the least cytotoxic, followed by those containing Ti, Fe, Co, Al, and Cr, which exhibited slightly higher toxicity. Moderately cytotoxic MOFs containing Zr, Mg, Gd, Ni, and Zn, whereas those containing Cu and Mn demonstrated the highest levels of cytotoxicity^[110].

The use of bio-derived or biocompatible molecules as ligands to synthesize MOFs, known as Bio-MOFs, offers a promising approach to address the potential toxicity^[111]. Organic ligands such as gallic acid^[112], fumaric acid^[113], tannic acid^[114] and cyclodextrin^[115] have been successfully used to synthesize various Bio-MOFs with excellent biocompatibility. CD-MOF, which are renewable, non-toxic, and edible, have demonstrated high safety profiles in the field of drug delivery^[115].

Furthermore, surface modification, which involves coating MOFs with a layer of biocompatible molecules, can effectively shield them from adverse interactions with biological systems, thereby reducing cytotoxicity and immunogenicity. Modification of MOFs with materials such as chitosan^[116] and hyaluronic acid^[117], can effectively mitigate cytotoxic effects and improve both dispersibility and structural stability.

CONCLUSIONS

With their tunable structures and capacity for functional integration, MOFs offer unique advantages in the antibacterial field and hold significant potential for addressing various infectious diseases. Despite remarkable achievements, challenges still exist: (1) The degradation products of some MOFs may exhibit cytotoxicity. Current research has primarily focused on their short-term biocompatibility in animal models, while their long-term safety and clinical suitability in humans require further investigation. (2) The interactions between MOFs and immune cells are complex and not yet fully elucidated. (3) Although antibacterial MOFs have shown excellent efficacy against drug-resistant bacteria, their impact on the expression of drug-resistance genes needs further exploration.

The translation from laboratory to clinical practice presents significant challenges. For instance, the large-scale, standardized, and cost-effective production of MOFs remains a major barrier, demanding the development of greener and more efficient synthesis protocols that ensure stability and reproducibility^[118]. Furthermore, the *in vivo* fate of MOFs is critically influenced by their interaction with the physiological environment. In a biological environment, NPs adsorb various biomolecules onto their surface, forming a layer known as protein corona^[119]. The protein corona can alter the stability of MOFs and reduce the targeting capability, thereby severely limiting therapeutic efficacy^[120].

In summary, MOFs offer a broad research and development landscape in the antibacterial field. Future studies should focus on enhancing their biosafety, conducting in-depth analyses of their antibacterial mechanisms, and advancing their clinical translation. These efforts will further promote them as a critical platform to address the drug-resistance crisis and complex infections.

DECLARATIONS

Authors' contributions

Conception, organization, and initial manuscript drafting: Li, Z.; Zhao, N.

Conceived the work: Wang, X.; Yu, T.; Li, Z.; Zhao, N.

Organized the content and prepared the draft manuscript: Li, Z.; Zhao, N.; Hu, N.; Zhang, Y.

Supervised the work: Han, B.; Wang, X.; Yu, T.;

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All authors contributed to the writing and revision of the manuscript.

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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