



Cite this: *Chem. Commun.*, 2025, 61, 1962

Immunoadjuvant-functionalized metal–organic frameworks: synthesis and applications in tumor immune modulation

Chen Zhao,^a Weihua Song,^b Jianing Wang,^c Xiaoying Tang^{*a} and Zhenqi Jiang^{*a}

Cancer immunotherapy, which leverages the body's immune system to recognize and attack cancer cells, has made significant progress, particularly in the treatment of metastatic tumors. However, challenges such as drug stability and off-target effects still limit its clinical success. To address these issues, metal–organic frameworks (MOFs) have emerged as promising nanocarriers in cancer immunotherapy. MOFs have unique porous structure, excellent drug loading capacity, and tunable surface modification properties. MOFs not only enhance drug delivery efficiency but also allow for precise control of drug release. They reduce off-target effects and significantly improve targeting and therapy efficacy. As research deepens, MOFs' effectiveness as drug carriers has been refined. When combined with immunoadjuvants or anticancer drugs, MOFs further stimulate the immune response. This improves the specificity of immune attacks on tumors. This review provides a comprehensive overview of the applications of MOFs in cancer immunotherapy. It focuses on synthesis, drug loading strategies, and surface modifications. It also analyzes their role in enhancing immunotherapy effectiveness. By integrating current research, we aim to provide insights for the future development of immunoadjuvant-functionalized MOFs, accelerating their clinical application for safer and more effective cancer treatments.

Received 11th December 2024,
Accepted 20th December 2024

DOI: 10.1039/d4cc06510g

rsc.li/chemcomm

1. Introduction

Cancer continues to stand as a paramount global health challenge, marked by irregular cell growth and metabolic

imbalances.¹ As the incidence and mortality rates of diverse cancer types persistently climb worldwide, the strain on health-care systems and patients intensifies. While conventional treatments like chemotherapy,² radiotherapy (RT),^{3,4} and surgery⁵ remain the prevailing methods for cancer management, there is an evident and pressing demand for innovative technologies. These advancements hold the promise of delivering better therapeutic results, minimizing side effects, and elevating the quality of life for patients.^{6–8} In this context, cancer

^a School of Medical Technology, Beijing Institute of Technology, Beijing 100081, China. E-mail: jiangzhenqi@bit.edu.cn, xiaoying@bit.edu.cn

^b Xuanwu Hospital Capital Medical University, Beijing, 100037, China

^c School of Medical Technology, the Qiushi College, Beijing Institute of Technology, Beijing 100081, China



Chen Zhao

Chen Zhao received her master's degree at Ningbo Institute of Materials Technology & Engineering, CAS. Currently, she is studying for a PhD in the School of Medical Technology, Beijing Institute of Technology. Her research interests include biomedical engineering and material science.



Jianing Wang

Jianing Wang is currently an undergraduate student in the School of Medical Technology, the Qiushi College, Beijing Institute of Technology. He majors in biomedical engineering. His research interest is fabrication and application of biomedical materials.

Highlight

immunotherapy stands out as a groundbreaking approach to cancer treatment. By leveraging the body's immune system to identify and combat cancer cells, immunotherapies have shown impressive efficacy across a range of cancer types. They are especially promising for targeting metastatic tumors, relying on enhancing or restoring both innate and adaptive immune responses to detect and eliminate malignant cells.⁹

However, tumor immunotherapy still faces challenges like the instability of the body's natural environment and the potential off-target effects of vaccines or checkpoint blockade inhibitors.¹⁰ For instance, when PD-1/PD-L1 inhibitors are administered systemically, they can lead to immune-related side effects and even autoimmunity, often with limited efficacy due to the body's clearance mechanisms.^{11,12} Additionally, immune boosters like cytosine-phosphate-guanine (CpG) oligodeoxynucleotides (ODN) struggle to penetrate cell barriers and are prone to degradation once inside the cell.^{13,14} To overcome these hurdles, nanocarriers play a crucial role by protecting these agents from degradation and facilitating their targeted delivery to antigen-presenting cells (APCs) for efficient antigen presentation to T cells.

To optimize therapeutic efficacy while minimizing side effects, significant efforts have been directed towards developing innovative nano-platforms for controlled and intelligent drug release systems. With advancements in nanotechnology, various nanocarriers such as liposomes, silica nanoparticles, micelles, and metal-organic frameworks (MOFs) have emerged.^{15–17} Among these, MOFs stand out as a promising class of nanomaterials due to their unique structure, combining inorganic nodes with organic ligands, which offer distinct advantages over other nanocarriers. Since the initial report of MOFs by Hoskins and colleagues, this field has undergone rapid development and extensive research.¹⁸ MOFs have demonstrated outstanding performance not only in areas such as gas storage,¹⁹ gas separation,²⁰ and catalysis,²¹ but also show tremendous potential in biomedical applications, particularly in drug delivery and cancer treatment.^{22,23} With in-depth studies on their synthesis, structure, and properties, MOFs have become a hot research topic in the field of nanomedicine. For instance, we previously developed H-TiO₂/C-PEG nanosheets to enhance cancer therapy through the combination of sonodynamic

and photothermal treatments. Originating from MOFs, these nanosheets were tailored with polyethylene glycol to enhance tumor targeting. They demonstrated potent therapeutic effects and improved treatment outcomes, highlighting their potential as safe and versatile strategies for cancer treatment.²⁴ In the field of immunotherapy, MOFs have garnered significant attention due to their high porosity, large surface area, and customizability. For instance, MOF-based nanoplateforms incorporating high-Z elements such as Hf⁴⁺ serve as effective carriers for radiotherapeutic agents in combination with immune adjuvants.²⁵ Furthermore, Chen *et al.* discovered that in their self-assembled nanoparticles (MOF-CpG-DMXAA), the loading capacity of CpG ODN in MOF-801 was 8.3 wt%, and the DMXAA loading was 1.5 wt%. This is significantly higher than the loading capacity of poly(L-lysine)-functionalized silica nanoparticles, which ranged from 1 to 2.25 wt%.²⁶ As research continues to advance, MOFs are poised to play an increasingly important role in revolutionizing therapeutic approaches, offering new avenues for improving patient outcomes and quality of life. Their potential in immunotherapy holds great promise, opening up exciting possibilities for the future of personalized medicine and targeted treatments.

Because of the widespread applications of MOFs in drug delivery and tumor treatment, this review categorizes MOFs used for cancer immunotherapy into groups based on their central metals: Zn-MOFs, Zr-MOFs, Fe-MOFs, Hf-MOFs, Al-MOFs, Eu-MOFs, Gd-MOFs, Dy-MOFs, Mn-MOFs, and Cu-MOFs. We also provide an overview of their synthesis methods. Subsequently, we discuss the methods of loading adjuvants into MOFs and surface modification of MOFs. In the applications section, we classify immunoadjuvant-functionalized MOFs into immune cell membrane-coated MOFs, MOFs loaded with immune factors, and metal ions for immunomodulatory MOFs, and discuss their respective applications in cancer treatment. Finally, we summarize and predict the application prospects of MOFs in tumor immunotherapy, hoping to further promote the development of MOF-mediated cancer immunotherapy (Fig. 1).

2. Synthesis of MOFs

MOFs, a type of coordination polymer (CP), are highly ordered crystalline porous materials composed of metal ions or clusters



Xiaoying Tang

Xiaoying Tang is a professor at School of Medical Technology, Beijing Institute of Technology. She is mainly engaged in scientific research and teaching in the fields of biomedical engineering and communication and information systems, and has in-depth research in biomedical signal detection and processing, medical image processing, and key technologies of magnetic resonance imaging (MRI) equipment.



Zhenqi Jiang

Zhenqi Jiang received his PhD degree at Ningbo Institute of Materials Technology & Engineering, CAS. Now, he is an assistant professor at the School of Medical Technology, Beijing Institute of Technology. His research interests include biomedical engineering and materials science.

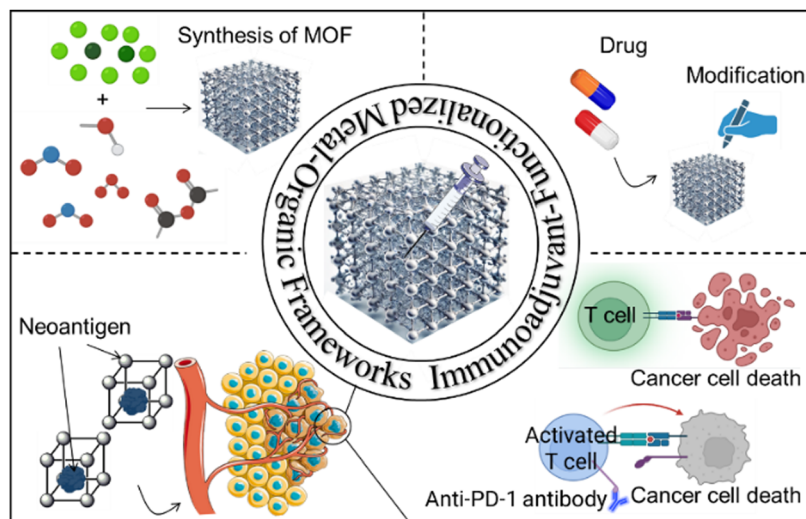


Fig. 1 Schematic illustration of the synthesis, modification, and applications of immunoadjuvant-functionalized MOFs.

and multidentate organic ligands serving as linkers.^{27,28} This unique combination of metal ions and organic ligands gives MOFs their hybrid material designation. Given the versatility of available metal ions and organic ligands, the desired functionalities of MOFs can be achieved through the selection of appropriate metals and the proper functionalization of ligands.²⁹ A major criterion when designing MOFs is to consider the toxicity of the metal ions, such as Zn^{2+} and $\text{Fe}^{2+}/\text{Fe}^{3+}$. Different metals have different applications. For example, Al-based MOFs are usually used for local administration, while Zr-MOFs are frequently applied in synthesizing MOFs in intravenous administration.³⁰ As for the biological applicability of organic ligands, the choice of metal ions and organic linkers has a direct correlation with MOF functions and stability. For instance, the choice of ligands can significantly affect the efficiency of photodynamic therapy (PDT). Therefore, macrocyclic derivatives such as porphyrin³¹ and chlorin³² are widely used as photosensitizers (PSs) in PDT. Given that the temperature and pH conditions during MOF synthesis significantly influence their morphology, reaction kinetics, and yield, it's crucial to tailor the synthesis conditions to the specific properties and desired functionalities of the MOFs. For MOFs and associated molecules sensitive to high temperatures and pressures, the synthesis processes should be conducted under mild conditions, suitable temperatures, pH level, and solvents, to preserve their bioactivity and to prevent denaturation.³³

As for the synthesis methods of MOFs, they can be categorized into the following types: (1) conventional hydro/solvothermal synthesis, (2) reverse microemulsion method, (3) sonochemical synthesis, (4) microwave-assisted hydrothermal/solvent-thermal method, (5) room-temperature one-pot synthesis, (6) electrochemical synthesis, and (7) post-synthesis methods (Fig. 2).

2.1. Zn-MOFs

Zinc is frequently employed in the construction of MOFs for cancer immunotherapy. In this context, the competitive interaction of zinc with other redox-active metals can contribute to

oxidative stress. ZIF-8 is usually synthesized through a facile one-pot procedure conducted at room temperature in order to avoid damages to the biomolecules added to the solution for encapsulation inside the nanoparticle (Fig. 3(a)). The synthesis conditions of ZIF-8 typically involve mixing followed by strong agitation at room temperature for less than 1 h,^{35–37} sometimes using ultrasonic assistance.^{34,38} Apart from in water solution, ZIF-8 can also be synthesized in methanol solution.³⁹ As for other zinc-based MOFs, the zinc salts selected are the same as those used to synthesize ZIF-8, while the reactions occur under various conditions, such as under vortex,⁴⁰ sonication in ice⁴¹ apart from agitation.⁴² Particularly, Bai *et al.* synthesized Zn/Co-MOF through stirring, and then the Zn/Co-MOF was heated to 800 °C for 12 h to become magnetic.⁴³ For Zn-MOFs designed to load with adjuvants, some use one-step synthesis, such as the synthesis of DOX-MNP,³⁷ C&H@MOF,⁴⁴ $\text{CO}_2\text{-g-C}_3\text{N}_4\text{-Au@ZIF-8}$,⁴⁵ NV-ZIF,⁴⁶ PMO^{Col} and Col@ZIF-8,⁴⁷ ICG@MOF⁴⁸ and LYS-NPS.⁴⁹

Generally, the synthesis of zinc-based MOFs is rapid and occurs under relatively mild conditions. This makes it feasible to load adjuvants *via* one-step synthesis, which is more eco-friendly and more cost-effective.

2.2. Zr-MOFs

When constructing MOFs, zirconium ions typically form Zr_6 clusters, which act as secondary building units within MOF structure. Therefore, Zr-MOFs are known for their stability and robustness, making zirconium-based MOFs advantageous for applications in cancer immunotherapy. Most notable examples of zirconium-based MOFs include UiO-66, which was synthesized by the Catalysis Group of the Chemistry Department of the University of Oslo in 2008.⁵⁴ UiO-66 is composed of terephthalic acid and zirconium-base nodes, constructed from Zr^{4+} ions and terephthalic acid serving as the linker. Similar to ZIF-8, UiO-66 is renowned for its exceptional thermal and chemical stability and biocompatibility,⁵⁵ making it an excellent candidate for

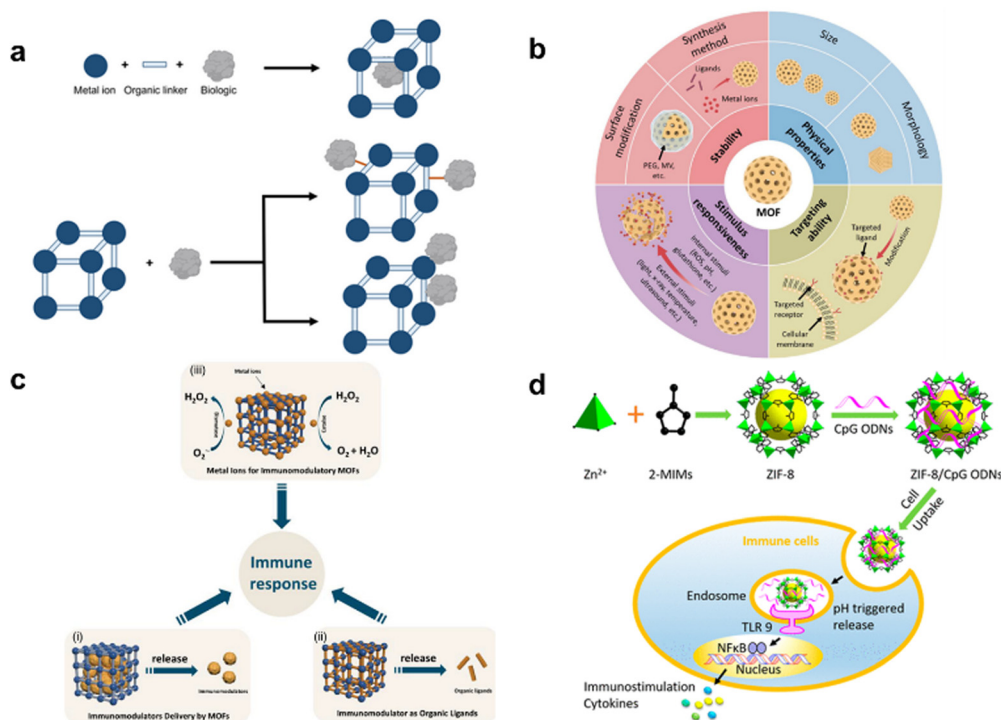


Fig. 2 Approaches for MOF design, immunoadjuvant loading, and applications, focusing on a ZIF-8-based system. (a) Loading immunoadjuvants via *in situ* encapsulation, covalent bonding, or electrostatic adsorption. (b) Design strategies for immunomodulatory MOFs. (c) Applications of MOFs in cancer immunotherapy. (d) One-step synthesis of a ZIF-8-based CpG ODN delivery system. (a) Reproduced from ref. 29 with permission from Wiley-Blackwell. (b) and (c) Reproduced from ref. 33 with permission from Wiley-VCH Verlag. (d) Reproduced from ref. 34 with permission from American Chemical Society.

applications in adsorption and catalysis.⁵⁶ Moreover, UiO-66 exhibit highly robust structure topology, allowing for various modifications of its original linker.

Zr^{4+} within the MOF can modify the biological effect of cancer vaccines, imparting properties similar to adjuvants. For instance, they can trigger the innate immune system,

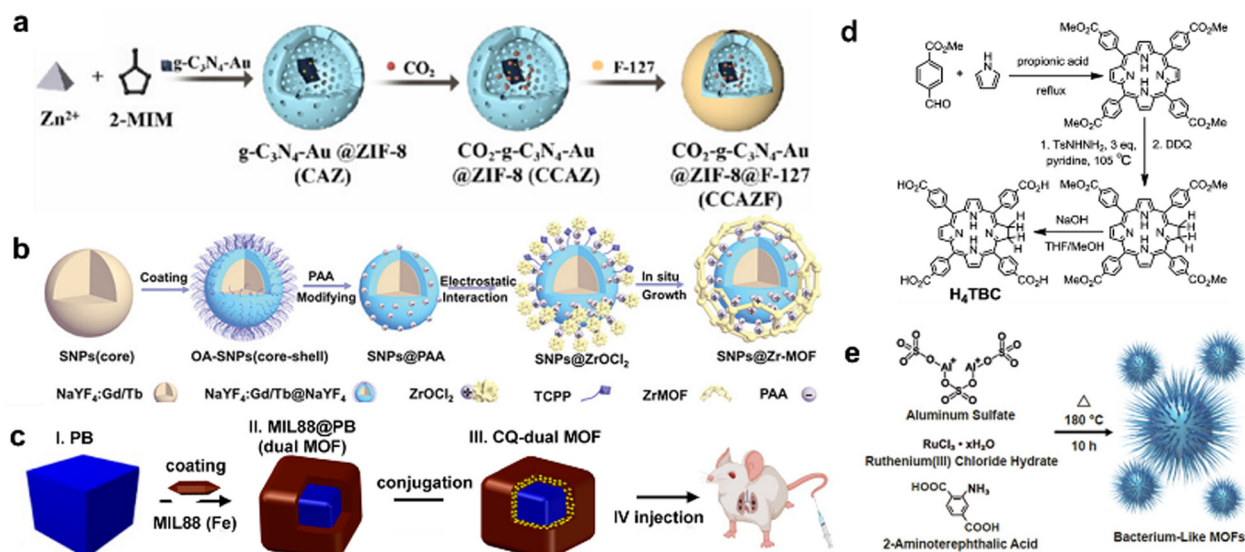


Fig. 3 Synthesis process of representative (a) Zn-, (b) Zr-, (c) Fe-, (d) Hf-, and (e) Al-based MOFs. (a) Reproduced from ref. 45 with permission from Elsevier BV. (b) Reproduced from ref. 50 with permission from John Wiley and Sons Ltd. (c) Reproduced from ref. 51 with permission from MDPI (Basel, Switzerland). (d) Reproduced from ref. 52 with permission from American Chemical Society. (e) Reproduced from ref. 53 with permission from Wiley-VCH Verlag.

facilitating an adaptive immune response. Additionally, Zr^{4+} promotes the maturation of dendritic cells (DCs), which can initiate the activation and proliferation of T lymphocytes to combat tumors. Moreover, under irradiation, Zr^{4+} can transfer soft X-ray energy to produce ROS efficiently within deep tumor tissues to assist PDT (Fig. 3(b)).⁵⁰ For example, Chen *et al.* synthesized MOF-CpG-DMXAA, which effectively deliver CpG ODNs and DMXAA to cells, synergistically improving the tumor microenvironment by reprogramming tumor-associated macrophages (TAMs), promoting DC maturation, and destroying tumor blood vessels.²⁶ Similarly, Zhao *et al.* synthesized SNPs@Zr-MOF-RB, which can efficiently produce ROS through the energy transfer from SNPs to Zr-MOF under soft X-ray irradiation.⁵⁰

Generally, the inorganic substances used to synthesize zirconium-based MOFs are ZrCl_4 or $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$. In practical applications, UiO-66 is often functionalized with amine groups to form UiO-66- NH_2 which is synthesized *via* solvothermal methods.^{55,57–59} The porous coordination network (PCN-*n*) family represents another type of zirconium-based MOF. The PCN-*n* MOFs used in tumor immunotherapy include PCN,^{60,61} PCN-222⁶² and PCN-224.⁶³ These MOFs utilize $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ as the source of Zr^{4+} , while TCPP or H_2TCPP serve as the organic ligands. Solvothermal methods are reported for the synthesis of PCN, PCN-222 and PCN-224. Specifically, PCN-224 has also been synthesized *via* ultrasonic stirring.⁶⁴ Additionally, solvothermal synthesis methods have been reported for other zirconium-based MOFs, such as TBP-MOFs (benzoporphyrin-based MOFs),⁶⁵ MOF-801,²⁶ MOF-525,⁶⁶ pMOFs,⁶⁷ ZrMOF-NH_2 ⁶⁸ and SNP@Zr-MOF .⁵⁰

The application of solvothermal methods in the synthesis of Zr-MOFs suggests that a higher energy input is required for Zr^{4+} to form MOFs with organic ligands compared to zinc.

2.3. Fe-MOFs

Fe-MOFs play a crucial role in cancer treatment due to their magnetic and catalytic properties. For instance, iron ions can catalyze hydrogen peroxide to produce hydroxyl radicals, generating ROS that can inactivate the organelles and proteins of tumor cells, leading to the aberrant accumulation necessary for Fenton reactions. This process further conduct chemodynamic therapy (CDT).⁶⁹ Additionally, the acidification of the extracellular pH can trigger the intracellular degradation of iron-based MOFs, releasing iron that leads to cell death and lysis, a process known as pyroptosis.⁷⁰ For example, Yalamandala *et al.* designed a dual MOF composed of $\text{NH}_2\text{-MIL-88B}$ and (PB)MOF in a core-shell structure (Fig. 4(c)). Fe^{2+} in $\text{NH}_2\text{-MIL-88B}$ ensures the generation of an adequate amount of $\cdot\text{OH}$ radicals, while Fe^{3+} in prussian blue (PB) exhibits catalytic activity in reducing H_2O_2 . This dual MOF not only induces cancer cell death through ROS generation but also promotes the recruitment of T lymphocytes, potentially enhancing the immune response.⁵¹

Most notable example of iron-based MOFs include the MIL-*n* series, which are types of porous metal carboxylates designed by Férey *et al.*⁷³ MIL-*n* are constructed from Fe^{3+} clusters and an

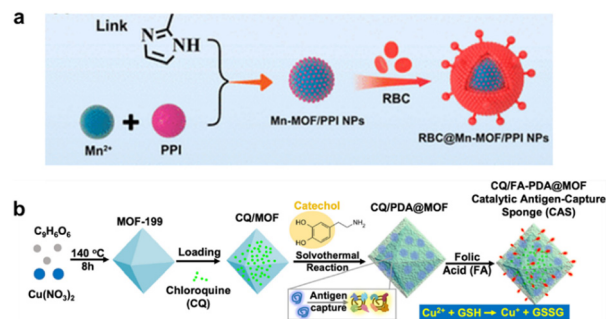


Fig. 4 Synthesis process of representative (a) Mn- and (b) Cu-based MOFs. (a) Reproduced from ref. 71 with permission from American Chemical Society. (b) Reproduced from ref. 72 with permission from Elsevier.

aromatic dicarboxylic acid as a linker (terephthalic acid), leading to a very porous structure²⁹ and high capacity for drug loading.⁷⁴

The synthesis of iron-based MOFs, such as MIL-*n*, typically requires high temperature and high pressure, sometimes with the use of microwave irradiation, while the solvent used is usually DMF or water, similar to that of Zr-MOFs. For MIL-88, the synthesis of MIL-88A^{75,76} and $\text{NH}_2\text{-MIL-88B}$ ⁵¹ has been reported to require solvothermal methods. The synthesis of MIL-89 and MIL-53 requires a solvothermal reaction in an autoclave.⁷⁵ Following a similar approach, Horcajada *et al.* synthesized MIL-100(Fe), while other reported methods to synthesize MIL-100(Fe) are involve solvothermal reactions under microwave conditions,^{39,70,74,77,78} which is similar to the synthesis of MIL-101.^{75,79–82}

Synthesis of other types of iron-based MOFs has been reported. Solvothermal methods have been employed in the synthesis of Fe-TBP⁸³ and PB MOF.⁸⁴ Specifically, Yalamandala *et al.* coated $\text{NH}_2\text{-MIL-88B}$ synthesized previously with PB MOF to form dual MOFs. $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and porphyrin can also serve as bridging ligands to form Fe-MOFs, as demonstrated in the synthesis of Fe-MOFs,⁸⁵ FeTCPP-OME,⁸⁶ iron-based composite nanoparticles⁶⁹ and PCN-224(Fe).⁸⁷ Additionally, Huang *et al.* synthesized MTO@PA/ Fe^{3+} MOF using Na_2FeCl_3 , PA and MTO *via* ultrasonication.⁸⁸

Compared to the synthesis of zirconium-based MOFs, the synthesis of iron-based MOFs requires an autoclave to provide high pressure and microwave assistance during solvothermal reactions. This demonstrates that more time and energy are needed for the construction of Fe-MOFs.

2.4. Hf-MOFs

Hafnium-based MOFs are constructed from Hf^{4+} ions, which form robust Hf_6 clusters upon coordination with organic linkers, leading to exceptionally stable structures. Notable Hf-MOFs include TBC-Hf, where TBC is a chlorin-based ligand 5,10,15,20-tetra(*p*-benzoato)chlorin, porphyrin-based MOFs DBP-Hf (5,15-di(*p*-benzoato)porphyrin linker), and TBP-Hf (5,10,15,20-tetra(*p*-benzoato)porphyrin linker).²⁹ Hf-MOFs show great promise in cancer immunotherapy when combined with radiation and checkpoint blockade. The Hf clusters within Hf-MOFs can efficiently absorb X-ray photons, leading to RT (*via* the production of $\cdot\text{OH}$ radicals) and RDT (by exciting the photosensitizers to generate O_2),²⁵ making Hf-

MOFs effective radio enhancers.⁸⁹ For an example, Lu *et al.* designed IDOi@DBP-Hf, where Hf ions within the MOF can efficiently eradicate several different types of cancer cells using extremely low doses of X-rays, and IDOi (indoleamine 2,3-dioxygenase) can reverse immunosuppression and control tumor growth. Combining together, it can overcome immunosuppression and elicit a systemic immune response against distant tumors.²⁵

Hf-MOFs are classified according to its bridging ligands, including Hf-DBP, Hf-DBA, Hf-TBC, and Hf-TBP, which are constructed starting with H₂DBP(5,15-di(*p*-benzoato)-porphyrin),^{25,90} H₂DBA(2,5-di(*p*-benzoato)aniline),^{25,89} H₄TBC(5,10,15,20-tetra(*p*-benzoato)chlorin),⁵² and H₄TBP(5,10,15,20-tetrabenzoatoporphyrin),^{25,52,91} along with HfCl₄. Choi *et al.* also used 1,4-BDC and HfCl₄ to synthesize Hf-MOFs.⁹² Their synthesis typically involves solvothermal reactions in DMF or an oil bath (Fig. 3(d)).

2.5. Al-MOFs

Aluminum is a functional metal ion that can act as an immune adjuvant to enhance immune responses against cancers.⁹³ Due to their excellent clinical safety profile, Al salts are frequently used to recruit and activate APCs and to stimulate the proliferation and activation of T cells. When integrated into MOFs, Al³⁺ can form MIL-100(Al), IL-57(Al)-NH₂MOF(2-aminoterephthalic acid linker),²⁹ among others, which have exhibit the immune adjuvant properties mentioned above. Despite the non-redox character of Al compounds, Hidalgo *et al.* synthesized MIL-100(Al), which has proven to be a powerful prooxidant *in vitro* and *in vivo* due to the Al³⁺ in the MOF promoting both iron auto-oxidation and ROS formation through their binding with superoxide radical anions.³⁹

The solvothermal method is commonly used in synthesizing aluminum-based MOF, such as solvothermal synthesis of MIL-100(Al)³⁹ and Al-TCPP⁹⁴ in DMF and that of bacterium-like MOF⁵³ in water (Fig. 3(e)).

2.6. Eu-MOFs, Gd-MOFs and Dy-MOFs

Several MOFs based on lanthanides have been reported, including europium, gadolinium, and dysprosium. Among them, studies show that Eu-MOFs can be used to deliver adjuvants and antigens for cancer immunotherapy.²⁹ Phosphatidylserine (PS) acts as a resistance against antitumor immunity, while Gd³⁺ has stronger binding affinity than Ca²⁺, which can reduce TMEM16F activity through competitive binding, inhibiting PS externalization. For example, Dai *et al.* synthesized Gd-MOF-5, where Gd³⁺ inhibits PS externalization *via* inhibiting the activity of scramblase, an enzyme that transfers PS to the outer leaflet of the plasma membrane, and Zn²⁺ overload activates endoplasmic reticulum stress for ICD induction. In combination with an immune checkpoint inhibitor, Gd-MOF-5 activated potent immune response and effectively inhibited primary and distal tumor growth.⁹⁵

In magnetic resonance imaging (MRI) applications, gadolinium can provide T1 MRI contrast, such that it is commonly used for the clinical diagnosis of bleeding-related and neoplastic diseases. For instance, Wang *et al.* synthesized Gd/Fe-MOF, where Gd and Fe ions can provide MRI contrast,⁹⁶ while

dysprosium in Dy-TCPP that Jiang *et al.* synthesized shows an excellent candidate element for T2-weighted contrast agents.⁹⁷

Among the lanthanides, the one-step synthesis methods of europium-based MOFs are reported where EuCl₃·6H₂O, GMP, and OVA (ovalbumin) construct Eu-MOF through self-assembly in solution by stirring the mixture.^{98,99} Apart from that, synthesis of Gd-MOF and Dy-MOF *via* solvothermal methods, such as the synthesis of Gd/M¹⁰⁰ and Dy-TCPP,⁹⁷ are reported. Besides, gadolinium is reported to construct MOFs combining with other metal ions *via* solvothermal methods, such as using GdCl₃ and Zn(NO₃)₂·6H₂O to synthesize Gd-MOF-5⁹⁵ and using Gd(NO₃)₂·6H₂O and FeCl₃·6H₂O to synthesize Gd/Fe-MOF.⁹⁶

2.7. Mn-MOFs

Mn-MOFs can be used as immunotherapeutic vehicles in terms of cancer treatment and the organic linker can act as the adjuvant to assist with antigen cross-presentation.²⁹ Recent studies have revealed that Mn²⁺ can activate the cGAS-STING pathway to induce cells to produce type I interferon (IFN) and inflammatory cytokines to promote DC maturation and elicit an antitumor immune response and infiltration of CTLs.^{71,101} For example, Xu *et al.* synthesized RBC@Mn-MOF/PPI which can release Mn²⁺ and PPI to work synergistically to enhance the cGAS-STING-mediated immune responses. Besides, Mn²⁺ can help transform cold tumors into “hot” ones by activating immune cells, as evidenced *via* DC maturation, cytotoxic T lymphocyte infiltration, and natural killer cell recruitment, thereby targeting primary and abscopal tumors and lung metastatic nodules (Fig. 4(a)).⁷¹ Specially, Mn-based nanomaterials also have photothermal conversion performance and Fenton catalysis ability, which indicate the huge advantages of granular Mn as a stimulator for cancer immunotherapy.

The synthesis of Mn-MOFs has been reported using various methods. MnCl₂·4H₂O has been employed in solvothermal methods in solvents like water, ethanol, and DMF.^{102,103} Alternatively, milder conditions involving ultrasonication or simple mixing and stirring have also been reported.^{71,101} Zhan *et al.* reported the solvothermal synthesis of Mn-MOF starting with ZrOCl₂, Mn-TCPP and BA in DMF.¹⁰⁴ Mn also can form MOFs with other metal ions for example, Liu *et al.* synthesized Mn/Zr-MOF *via* solvothermal methods and cation exchange reactions,¹⁰⁵ while Wu *et al.* synthesized Mn/Ca-MOF *via* mixing and stirring in double distilled water.¹⁰⁶

2.8. Cu-MOFs

The synthesis methods for copper-based MOFs primarily include solvothermal, ultrasonic, and room temperature stirring approaches (Fig. 4(b)). The solvothermal approach is used for the synthesis of MOF-199 (Chiang *et al.*),⁷² while the room temperature stirring method is employed in the synthesis of CuTtpy (Zhang *et al.*).¹⁰⁷ Cu can also form MOFs with other metal ions. Zeng *et al.* synthesized TBP-MOF(Cu) based on Cu-TBP using ZrOCl₄, BA, and acetic acid *via* solvothermal methods in DMF.⁶⁵ For Cu doping in MOFs formed with other metal ions, Hu *et al.* synthesized PCu-MOFs based on PCN-224(Fe) *via* solvothermal methods and stirring,⁸⁷ while Chen *et al.*

synthesized Cu-TCPP(Al) based on Al-TCPP through solvothermal methods.¹⁰⁸

2.9. Other MOFs

The reported synthesis approaches of cobalt-based MOFs include synthesizing ZIF-67 *via* stirring at room temperature,¹⁰⁹ Co-Fc MOF through ultrasonication methods,¹¹⁰ and constructing Ni/Co-MOF¹¹¹ and Zn/Co-MOF⁴³ with Ni and Zn. Potassium can also be applied in constructing MOFs, known as γ -CD-MOF, which is reported to be synthesized *via* incubating in water and methanol¹¹² or vaporizing the water of the solution under methanol.¹¹³ Ni *et al.* reported the synthesis of W-TBP and Bi-TBP *via* solvothermal methods where cationic W-TBP efficiently adsorbs anionic CpGs, the drug loaded with W-TBP, can facilitate their internalization by DCs to promote DC maturation.¹¹⁴ Tantalum is used as a contrast agent for computed tomography (CT) in clinics owing to its superb biocompatibility, which is reported to construct TZM nanoparticles, a kind of Ta/Zr-MOF, *via* solvothermal reaction as radiosensitizers.¹¹⁵ Titanium-based MOFs can be used as the sonosensitizer in sonodynamic therapy (SDT). MIL-125-BA, a kind of Ti-MOF, was reported to be synthesized by a solvothermal method starting with TTIP in DMF to achieve enhanced sono-immunotherapy against both primary tumors and metastatic tumors.¹¹⁶

In summary, among all the metal ions that MOFs based on, those based on zinc, potassium, and europium are synthesized under relatively mild, one-step and “green” conditions. In contrast, those based on zirconium, iron, and copper are synthesized under higher temperature, pressure, and microwave conditions, requiring more energy. Thus, it is more convenient for the former to load biomolecules and adjuvants, while the latter usually load adjuvants *via* post-synthesis approaches, or in a few cases, they are applied in cancer immunotherapy as adjuvants themselves. We summarized the key features and details of immunoadjuvant-functionalized metal-organic frameworks in Table 1.

3 Application of immunoadjuvant-functionalized MOFs

3.1. Immune cell membrane-coated MOFs

The immune cell membrane is a thin film extracted from immune cells. It retains the key proteins and biomolecules naturally present on the cell surface.¹²⁶ The extraction process includes mechanical disruption, hypotonic treatment, and differential ultracentrifugation. Nanoscale vesicles are formed through extrusion.¹²⁷ Compared to traditional biomimetic membranes, immune cell membrane-coated MOFs offer significant advantages as a new generation of therapeutic agents and drug delivery systems.¹²⁸ Due to their natural origin, they can trigger specific immune responses, effectively masquerade as targets for inflammation and tumors, and directly deliver antigens to immune cells. The interaction between positively charged MOFs and negatively charged cell membranes

facilitates the self-assembly of membrane fragments and drug-loaded cores, ultimately resulting in the formation of polydisperse aggregates through electrostatic attraction. Moreover, these coated MOFs can efficiently release their drug components, such as metal ions or other therapeutic agents, to achieve therapeutic effects. These characteristics make immune cell membrane-coated MOFs promising candidates for targeted drug delivery and immunotherapy, providing more effective and personalized treatment options for various diseases, including cancer and inflammatory conditions.¹²⁹

By leveraging immune cell membranes, which naturally elicit autoimmunity and possess surface markers for tumor recognition, MOFs can be effectively cloaked to achieve targeted delivery to sites of inflammation and tumors. This cloaking mechanism not only prolongs circulation *in vivo* and enhances biocompatibility but also facilitates key immune processes such as antigen presentation, T-cell activation, and modulation of cytokines. Immune cell membranes, rich in selectins and integrins, enable MOFs to mimic immune cell adhesion, rolling, and transmigration through endothelial barriers, guided by chemokines. This process allows membrane-coated MOFs to traverse the blood-brain barrier and accumulate at inflammation and tumor sites, utilizing immune signaling pathways to ensure precise delivery. Furthermore, MOFs' high drug-loading capacity and function as nano-sensitizers amplify their therapeutic potential across modalities like PTT, PDT, CDT, and RT. By combining immune-mimicking properties with their intrinsic versatility, MOFs emerge as a powerful platform for orchestrating multimodal treatment strategies, addressing a wide spectrum of diseases efficiently and effectively.

3.1.1. Macrophage membrane-coated MOFs. Macrophages are specialized immune cells with a sophisticated arsenal of surface membrane receptors.¹³⁰ These receptors are highly versatile, allowing macrophages to recognize and bind to a wide range of molecules, including both endogenous components produced within the host and exogenous substances from the external environment.¹³¹ This capability enables macrophages to engage with the host's natural self-components, ensuring immune homeostasis and tolerance, while also responding to foreign invaders like bacteria,¹³² viruses,¹³³ and other pathogens.¹³⁴ When macrophages encounter these different ligands, the membrane receptors play a crucial role in initiating specific cellular responses. Depending on the nature of the interaction, macrophages can phagocytose pathogens, release cytokines to signal other immune cells, or even induce programmed cell death to eliminate infected or damaged cells. This dynamic and multifaceted interaction makes macrophages central players in both innate and adaptive immunity, contributing to the body's defense mechanisms against infections, cancer, and other diseases.

Given the pivotal role of macrophage membrane receptors in immune responses, nanoparticles coated with macrophage membranes have garnered significant interest in biomedical research.^{107,135,136} These biomimetic nanoparticles can mimic the natural interactions and functions of macrophages, offering

Table 1 Summary of immunoadjuvant-functionalized MOFs in terms of their components, synthesis, and applications in tumor immune modulation

Metal elements	MOF names	Organic ligands	Synthesis methods	Ways of immunoadjuvants loading		Applications	Ref.
				Immunoadjuvants	loading		
Zinc (Zn)	ZIF-8	2-MIM	Stirring at R.T.	CpG ODNs	Attached on the MOF's surface <i>via</i> electrostatic interaction	CpG ODNs inhibit the growth of EG7-OVA tumors	Zhong <i>et al.</i> ³⁵
Zinc (Zn)	—	2-MIM	Vortex + stirring at R.T.	LOx + OXA	Encapsulated in the MOF's pores	LOx catalytically consumed lactate; OXA induce ICD to modulate the iTME and inhibit tumor growth	Wang <i>et al.</i> ⁴⁰
Zirconium (Zr)	UiO-66	BDC 4-azidobenzonic acid	Solvothermal methods	CLB + NLG919	CLB: conjugated on AuNPs through Au–thiol interaction; NLG-919; encapsulated in the MOF's pores	NLG919 suppress IDO activity to reverse suppressive TME; CLB is chemotherapeutic prodrug	Ding <i>et al.</i> ¹¹⁷
Zirconium (Zr)	PCN-222	TCPP dichloroacetic acid	Solvothermal methods	—	—	The MOF enhance the infiltration of cytotoxic T cells in the tumor site	Li <i>et al.</i> ⁷⁵
Zirconium (Zr)	PCN-224	H2TCPP BA	Stirring + ultrasonication	RAPA@BSA	Encapsulated in the MOF's pores	PCN-224 produce ROS to mediate PDT; rapamycin increases immune response and promote T cell proliferation and differentiation	Tian <i>et al.</i> ¹¹⁸
Iron (Fe)	MIL-88A	Fumaric acid	Solvothermal methods	MC DNA	Metal-phosphate and electrostatic interaction	MC DNA shows therapeutically potential in ovarian cancer	Zhao <i>et al.</i> ¹¹⁹
Iron (Fe)	MIL-100	1,3,5-BTC	Solvothermal methods (high pressure) + microwave	MTO	N/A	MTO increase CD4+ and CD8+ T cells to kill tumor cells and inhibit tumor metastasis	Ni <i>et al.</i> ⁷⁸
Iron (Fe)	MIL-101	1,4-BDC	Solvothermal methods	CpG ODNs	π - π interactions between CpG and MOF's organic ligands	CpG ODNs induce enhanced immune response	Zhang <i>et al.</i> ⁷⁹
Iron (Fe)	PB	PVP	Solvothermal methods (high pressure)	—	—	Fe ³⁺ shows catalytic activity for the reduction of H ₂ O ₂ ; MOF actuate cancer cell death and enhance T cell recruitments	Yalamandala <i>et al.</i> ⁵¹
Hafnium (Hf)	Hf-DBP	H2DBP	Solvothermal methods	Fe(III) ligands	N/A	The MOF mediate effective local therapy of hypoxic cancer with low-dose X-ray irradiation	Ni <i>et al.</i> ⁹⁰
Hafnium (Hf)	Hf-TBP	H4TBP BA	Solvothermal methods	—	—	Al ³⁺ in the MOF promote iron auto-oxidation and ROS formation	Lu <i>et al.</i> ¹²⁰
Aluminum (Al)	MIL-100(Al)	Trimethyl-1,3,5-trimesic acid	Solvothermal methods	—	—	CpG ODNs enhance CD8+ cytotoxic T lymphocyte responses	Hidalgo <i>et al.</i> ³⁹
Europium (Eu)	—	GMP	One-step synthesis stirring at R.T.	CpG ODNs	Loaded on MOF's surface	The MOF is used for contrast-enhanced MRI and induce immunogenic death of tumor cells; α -PD-1 enhance anti-tumor ability of T cells	Duan <i>et al.</i> ⁹⁸
Gadolinium (Gd)	Gd-MOF	Fumaric acid benzene-1,3,5-tricarboxylic acid	Solvothermal methods	α -PD-1	Loaded in MOF's pores	Dy ions reduce PD-L1 expression in tumor cells; the MOF realize SDT and obtain T2-weight MRI of tumor sites	Cui <i>et al.</i> ^{97,100}
Dysprosium (Dy)	Dy-TCPP	TCPP	Solvothermal methods	—	—	The MOF ameliorate tumor hypoxia and generate strong SDT effects in hypoxic tumors; CpG induce ICD and improve the therapeutic effects of anti-PD-1	Zhan <i>et al.</i> ¹²¹
Manganese (Mn)	Mn-MOF	TCPP BA	Solvothermal methods + stirring	CpG ODNs	Electrostatic absorption	The MOF promote ROS generation in cancer cells; CQ reduce cancer cell self-defense mechanism then induces autosis cell death pathway	Chiang <i>et al.</i> ⁷²
Copper (Cu)	MIL-199	1,3,5-BTC PVP	Solvothermal methods	CQ + FA	CQ: loaded in MOF's pores; FA: conjugated on the MOF's surface <i>via</i> π - π interactions	LOx and Cas9/sgSIRP improve macrophage antitumor immune responses and inhibit tumor growth	Li <i>et al.</i> ¹²²
Cobalt (Co)	ZIF-67	2-Methylimidazole	Reacting at R.T.	Cas9/sgSIRP + LOx	Encapsulated inside the MOF	OVA induce high antigen-specific IgG titers and cytokine secretion	Li <i>et al.</i> ¹¹²
Potassium (K)	γ -CD-MOF	γ -CD CTAB	Incubating	OVA	Immobilized on MOF's pores		

Table 1 (continued)

Metal elements	MOF names	Organic ligands	Synthesis methods	Ways of immunoadjuvants loading		Applications	Ref.
				Immunoadjuvants	N/A		
Tungsten (W)	W-TBP	H4TBP	Solvothermal methods	CpG ODNs	N/A	The MOF facilitate tumor antigen presentation and promote DC maturation CpG ODNs elicit strong antitumor immunity in abilateral breast cancer model	Ni <i>et al.</i> ¹²³
Tantalum (Ta)	TZM	TCPP	Solvothermal methods	—	—	The MOF induce ICD and upregulate PD-L1 expression <i>via</i> the cGAS-STING pathway	Li <i>et al.</i> ¹²⁴
Titanium (Ti)	MIL-125-BA	BA	Solvothermal methods	PFOB	N/A	The MOF enhance SDT, relieve the immunosuppressive TME and enhance immunogenic cell death	Yang <i>et al.</i> ¹²⁵

promising avenues for targeted drug delivery, vaccine development, and immunotherapy. By harnessing the unique properties of macrophage membranes, these nanoparticles hold great potential for enhancing therapeutic efficacy while minimizing side effects, thereby revolutionizing approaches to disease treatment and prevention.

Yao *et al.* presents a macrophage membrane-coated MOF-based nanoplatform (AP@ZIF-Mem) that targets glucose metabolism in triple-negative breast cancer (TNBC). By combining atorvastatin (a glycolysis inhibitor) and polydatin (a PPP inhibitor), this system effectively disrupts tumor glucose metabolism, inducing acidosis, oxidative stress, and redox imbalance. Leveraging the tumor-specific targeting and immune-evasive properties of macrophage membranes, AP@ZIF-Mem demonstrated enhanced tumor accumulation, reduced tumor growth, and inhibited metastasis. This dual-targeting approach underscores the potential of biomimetic nanoplatforms in tackling TNBC's metabolic vulnerabilities (Fig. 5(a)–(d)).¹³⁷ Cheng *et al.* subsequently employed a cobalt-based MOF to load anethole trithione into its pores using a one-pot method. Subsequently, they coated the MOF surface with a macrophage membrane. Utilizing integrin targeting, the biomimetic nanoplatform concentrates in the tumor microenvironment. The macrophage membrane serves as camouflage, enhancing the biocompatibility of the MOF and reducing the phagocytosis of the nanoplatform by immune cells.¹³⁸

In another study, Cheng *et al.* developed a platform combining the Fenton reaction and PTT based on MOF nanoparticles. These nanoparticles, termed PPy-CTD@MIL-100@MPCM (PCMM NPs), are designed to target and accumulate in tumor tissues due to their encapsulation with macrophage cell membranes. The photothermal agent, polypyrrole (PPy), within the nanoparticles accelerates the release of the therapeutic agent, cantharidin (CTD), and iron ions upon irradiation, enhancing the efficiency of both PTT and the Fenton reaction. CTD, acting as an inhibitor of the heat shock response in tumor cells, improves the therapeutic effect of PTT. The Fenton reaction, promoted by the released iron ions, helps consume excessive H₂O₂ in tumor tissues, generating hydroxyl radicals that kill tumor cells and improve the tumor microenvironment.¹⁴¹ The tumor-targeted combination therapy mediated by PCMM provides a promising approach for cancer treatment.

3.1.2. Neutrophil membrane-coated MOFs. Neutrophils serve as the body's initial defense against infections and respond to a range of inflammatory stimuli, including those associated with cancer.¹⁴² One of the key features of neutrophils is their capacity to travel to inflammatory sites. This migration is orchestrated by chemokines, danger-associated molecular patterns, lipid metabolites, and various other signaling molecules.^{143,144} However, the exact role of neutrophils in the tumor microenvironment remains controversial. Recent studies have confirmed the involvement of neutrophils in tumor cell migration and dissemination.¹⁴⁵ Additionally, neutrophils have been shown to regulate tumor cell proliferation.¹⁴⁶ Nevertheless, as research progresses, it has been demonstrated that human neutrophils can mediate antibody-dependent, cell-mediated cytotoxicity against tumor cells.¹⁴⁷

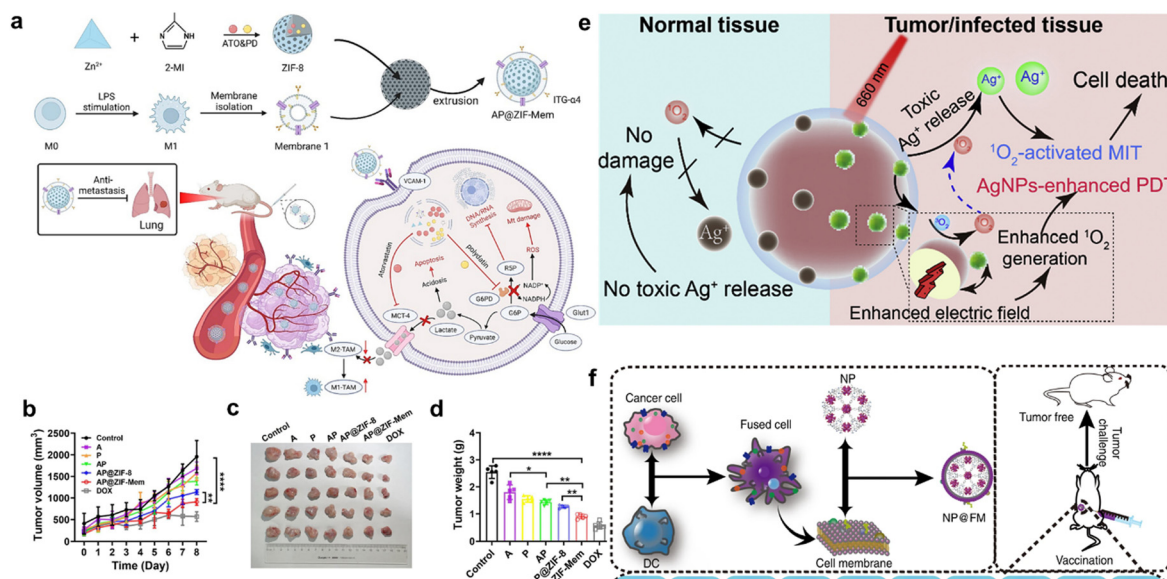


Fig. 5 (a) Schematic diagram of the preparation of macrophage-membrane-coated metal-organic framework nanoparticles (AP@ZIF-Mem) and its anti-cancer mechanism. (b) Tumor growth trends in mice subjected to various treatments. (c) Representative image of excised tumors on day 8. (d) Tumor weights measured in experimental mice. (e) Illustrative schematic of the underlying mechanisms of PCN@AgNPs@Neutrophil membrane for biomedical applications. (f) Schematic illustration of MOF@cytomembranes for tumor prevention. (a)–(d) Reproduced from ref. 137 with permission from Elsevier. (e) Reproduced from ref. 139 with permission from Elsevier BV. (f) Reproduced from ref. 140 with permission from Springer Nature.

Zhang *et al.* constructed a nanoplatfrom, termed PAM, designed to achieve on-demand release of metal ions through near-infrared (NIR) light-induced PDT for precise and efficient disease treatment. PAM integrates silver nanoparticles (AgNPs), the porphyrinic PCN, and the neutrophil membrane (NM). The inflammatory targeting ability of NM enables selective accumulation of PAM at tumor sites. Under NIR irradiation, PCN generates singlet oxygen (¹O₂), activating AgNPs to release cytotoxic Ag⁺ ions (Fig. 5(e)).¹³⁹ This interaction provides precise control over disease treatment while reducing side effects. This strategy holds promise for offering a safer and more effective tumor therapeutic approach. In another study, Cui *et al.* developed a ferric porphyrin MOF sensitive to high levels of glutathione and combined it with the immune factor porcine pancreatic elastase (PPE). They further encapsulated this combination with a neutrophil membrane to achieve specific targeting of tumors. Upon reaching the tumor site, the MOF releases MOF and PPE. During this process, PPE mimics the function of neutrophils, leading to the release of histone H1 and selectively killing cancer cells. Simultaneously, the MOF serves as an *in situ* ¹O₂ generator, inducing DNA double-strand breaks under laser irradiation, further enhancing the translocation of histone H1 from the nucleus to the cytoplasm, thereby promoting the elimination of cancer cells.¹⁴⁸ This precise therapeutic approach not only effectively eradicates cancer cells but also activates an adaptive immune response, exerting inhibitory effects on both primary and distant tumors.

Building on the aforementioned advantages, different types of immune cell membranes offer specific therapeutic mechanisms, further enriching the applications in this field. Next, we will delve into the characteristics and potential applications of Macrophage membrane-coated MOFs, Neutrophil

membrane-coated MOFs, and Dendritic cell membrane-coated MOFs.

3.1.3. Dendritic cell membrane-coated MOFs. DCs play a crucial role as APCs within the immune system.^{149,150} Upon antigen invasion, DCs located in tissues like the skin, intestines, lungs, and lymphoid organs become activated, initiating an immune response. These cells identify and capture antigens through various mechanisms, subsequently presenting them to T cells. Given their central role in immune responses, dendritic cells have become essential targets in both biomedical research and immunotherapy.¹⁵¹ Coating nanoparticles with DCs preserves the cancer cell membrane's homotypic targeting ability, while also facilitating the concurrent expression of tumor antigens and immunological costimulatory molecules.¹⁵² This strategy enhances the dendritic cell-mediated activation of both CD4⁺ and CD8⁺ T cells with antigen-specific responses.¹⁵³ For example, Ma *et al.* developed a nanoplatfrom termed aDCM@PLGA/RAPA, which integrates the activated mature dendritic cell membrane (aDCM) with rapamycin-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles. This innovative platform is designed to efficiently traverse the blood-brain barrier (BBB) and precisely modulate the immune microenvironment. Their research introduces a promising therapeutic strategy for glioma, a brain tumor with a challenging prognosis, largely attributed to the BBB and the immunosuppressive nature of the tumor microenvironment.¹⁵⁴

Building on the versatility of DCs in nanoparticle applications, researchers have expanded their use to include the incorporation of various functional agents. In this context, MOFs have emerged as a promising material for therapeutic delivery due to their high loading capacity and controlled release properties. When combined with the capabilities of

DCs, MOFs offer a novel approach to enhance immune responses and target-specific therapeutic delivery. For example, Liu *et al.* utilized biologically reprogrammed cell membranes (FM) derived from fused DCs and cancer cells (Fig. 5(f)).¹⁴⁰ They incorporated fluorescent MOFs for imaging to prepare MOF@FM nanoparticles capable of eliciting anti-tumor immune responses. MOF@FM is anticipated to provide both the antigen-presenting capabilities typical of APCs, and a sustained supply of endogenous tumor antigens sourced from fragments of the cancer cell membrane. These fragments can be recognized by DCs, stimulating their maturation and subsequently inducing T cell activation.

3.1.4. Other cell membrane-coated MOFs. Although red blood cell membranes (RMs), platelet membranes (PMs), and bacterial membranes (BMs) are not considered immune cell membranes, they possess certain immune-related functions and are widely used in cancer therapy and other drug delivery systems.¹⁵⁵ Combining these cell membranes with MOFs not only improves the system's safety and efficacy but also significantly enhances targeted therapy and immune regulation capabilities.^{156–158} RMs have the ability to circulate for extended periods, a property attributed to specific surface markers such as CD58, CD59, and CD47, along with their inherent physiological traits. These characteristics provide RMs with immune evasion capabilities, flexibility, and excellent biocompatibility.¹⁵⁹ Xu *et al.* introduces a RMS-coated manganese-based MOF (RBC@Mn-MOF/PPI) that activates the cGAS/STING pathway.⁷¹ Peng develops a RMS-camouflaged iron-based MOF nanoplatfor for combined ferroptosis-apoptosis therapy, effectively overcoming multidrug resistance by depleting glutathione, amplifying oxidative stress, and downregulating P-glycoprotein expression.¹⁶⁰

PMs exhibit unique properties that make them suitable for tumor targeting and immune evasion.¹⁶¹ Overexpressed P-selectin on platelet membranes specifically binds to the upregulated CD44 receptors on cancer cells, enabling active targeting of tumors and circulating tumor cells. Additionally, CD47 molecules on platelet membranes prevent macrophage-mediated clearance of platelet membrane-coated nanoparticles.¹⁶² Zhuang *et al.* synthesized a PMs-coated MOF nanodelivery platform for targeted siRNA delivery *in vivo*, demonstrating high silencing efficiency, antitumor efficacy, and potential for expanding siRNA applications in various diseases.¹⁶³ Liu *et al.* developed PM-camouflaged silver MOF nanoparticles (PM@MOF-Ag NPs) with enhanced targeting, immune evasion, and antitumor efficacy for triple-negative breast cancer, demonstrating effective tumor apoptosis induction and minimal organ toxicity.¹⁶⁴ Guo *et al.* developed a magnetic MOF nanoplatfor coated with platelet membranes (PmMN@Om&As). It combines immune escape, dual-targeting, and controlled drug release. The system enhances tumor-infiltrating lymphocyte activity and synergizes with PD-1 inhibitors. This approach achieves improved antitumor efficacy in hepatocellular carcinoma.¹⁶⁵

Bacteria membrane-modified nanocarriers exhibit characteristics such as immune stimulation, prolonged circulation time, and tumor imaging capabilities.^{166–168} Zhang *et al.* developed a bacterial outer membrane vesicle (OMV)-modified MOF

nanoplatform for breast cancer treatment, combining sonodynamic therapy and immunotherapy to enhance tumor targeting, immune activation, and therapeutic efficacy.¹⁶⁹ Chen *et al.* designed a photothermal bacterium (PTB)-based therapeutic platform, combining Pd nanoparticle-biomaterialized bacteria with ZIF-90/MB to enhance tumor-targeted photothermal therapy and overcome challenges in tumor targeting and heat tolerance.¹⁷⁰

3.2. MOFs loaded with immune factors

Antigens, adjuvants, vaccines, immune checkpoint inhibitors, biologics, and other immunogens play significant roles in immunology and clinical medicine. However, they still have some drawbacks. Some antigens may exhibit poor immunogenicity, adjuvants may trigger allergic or toxic reactions, and vaccine efficacy may decrease over time. Additionally, immune checkpoint inhibitors may lead to immune-related adverse events, and biologics face challenges in preparation and quality control. Fortunately, advancements in nanotechnology offer hope in addressing these challenges. One promising approach involves utilizing MOFs to encapsulate immunogens. MOFs possess highly porous structures, tunable properties, and excellent stability and biocompatibility, providing an ideal platform for controlled release and targeted delivery of immunogens. For example, Lin *et al.* encapsulated a small-molecule immunotherapy agent inhibiting indoleamine 2,3-dioxygenase (IDOi) within a chlorin-based nanoscale metal-organic framework (TBC-Hf) using the co-mixing method. IDOi@TBC-Hf leverages the PDT effect of TBC-Hf and the enhanced immune response of IDOi, which can effectively generate systemic anti-tumor immune effects. Notably, IDOi@TBC-Hf demonstrated tumor inhibitory effects in both primary and distant tumor models of colorectal cancer.⁵² Using the foundation of TBC-Hf MOF, Lin *et al.* engineered Hf-TBP/COD nanomaterials. This innovation facilitated synergistic anti-cancer effects by inducing cholesterol depletion through COD and generating ROS *via* Hf-TBP. This approach not only locally suppressed tumor growth but also stimulated systemic anti-tumor immune responses. In subcutaneous models of triple-negative breast cancer and colon cancer, Hf-TBP/COD demonstrated a remarkable tumor growth inhibition rate of 95%.⁹¹ Lin *et al.* also utilized MOFs synthesized from metal-oxo clusters and functional organic ligands as a novel carrier for cancer vaccines. Through X-ray activation, they released activated damage-associated molecular patterns and tumor antigens, while delivering CpG as pathogen-associated molecular patterns to APCs for personalized vaccine administration. This personalized vaccine has been demonstrated to expand cytotoxic T cells in tumor-draining lymph nodes, not only locally inhibiting tumor growth but also eliciting systemic anti-tumor immune responses (Fig. 6(a) and (b)).¹⁷¹

Traditional immunotherapy often targets specific cell types like DCs or T cells, which can limit its effectiveness. To overcome this limitation, Luan *et al.* developed a dual tailor-made MOF based on ZIF-8 that synergistically releases various therapeutic agents, including the photothermal agent IR820, the adjuvant R837, and the immunomodulator 1-methyl-D-tryptophan (1-MT).

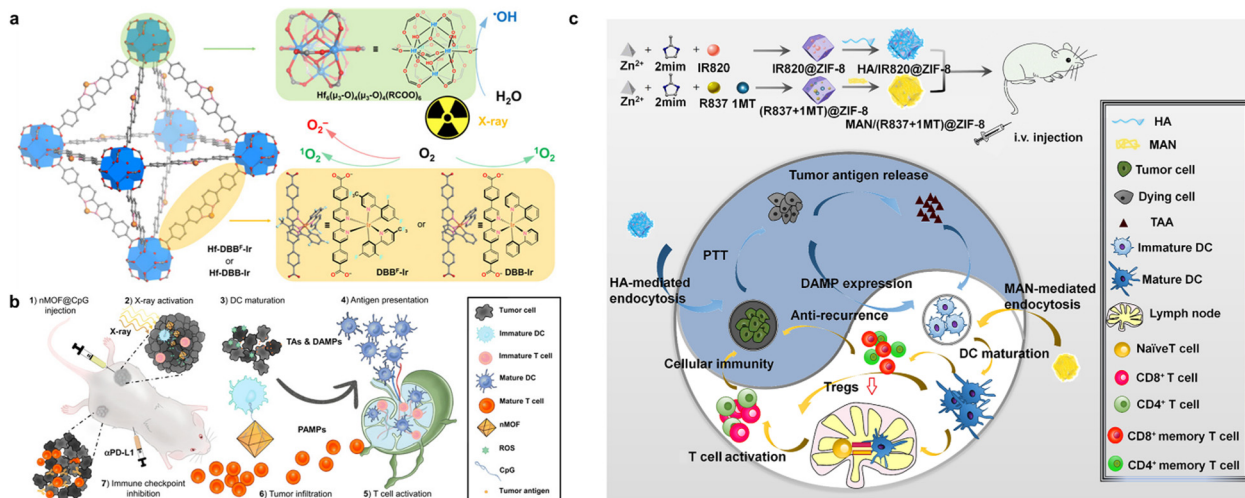


Fig. 6 (a) Schematic illustration of controlled synthesis of Hf-DBB^F-Ir and Hf-DBB-Ir, and (b) their antitumor effect. (c) Schematic representation of the synthesis process for HA/IR820@ZIF-8 and MAN/(R837 + 1-MT)@ZIF-8 nanoparticles, along with the synergistic mechanisms underlying photothermal therapy (PTT) and antitumor immunotherapy facilitated by these composite nanoparticles. (a) and (b) Reproduced from ref. 171 with permission from American Association for the Advancement of Science. (c) Reproduced from ref. 172 with permission from Elsevier BV.

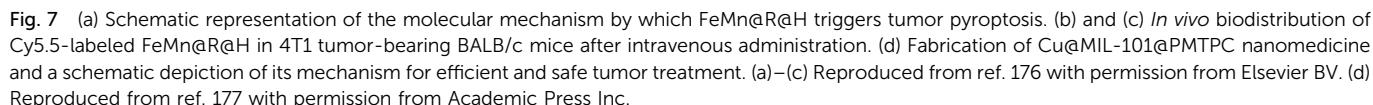
The IR820@ZIF-8 nanoparticles, modified with hyaluronic acid, are designed to target tumor cells, facilitating tumor-specific PTT and the subsequent release of tumor antigens. Conversely, the (R837 + 1-MT)@ZIF-8 nanoparticles, modified with mannan, aim to target DCs, thereby enhancing the immune response. By integrating targeted treatment of tumor cells with DC-focused immunomodulation, this approach addresses two key challenges in immunotherapy: inadequate immune activation and immune evasion. The goal of this research is to develop a more effective immunotherapeutic nanoplatform capable of modulating the functions of multiple cell types simultaneously (Fig. 6(c)).¹⁷² Similarly, they employed ZIF-8 to load HYD and MIT, aiming to induce ferroptosis in tumor cells while eliminating T cell paralysis.³⁶ In summary, the encapsulation of immunogens by MOFs offers a promising solution to the challenges encountered in traditional applications. This advancement not only revitalizes the field of immunology but also opens up new avenues for disease prevention and treatment.

3.3. Metal ions for immunomodulatory MOFs

Functional metal ions, such as aluminum, copper, and iron, serve as immunoadjuvants that can be incorporated into MOFs. This integration enhances the immune response against cancer. By leveraging the properties of MOFs, including their high surface area, tunable pore size, and capacity for high loading, the inclusion of these metal ions aims to potentiate the immune system's response to cancer cells. This approach capitalizes on the unique features of MOFs, making them promising candidates for drug delivery and immunotherapy.

In these metal ions, Copper ions play a crucial role in the activities and regulation of various immune cells, including macrophages, dendritic cells, and T lymphocytes. They interact with proteins, thereby regulating essential immune functions such as cell signaling pathways, apoptosis, and cell proliferation. Additionally, divalent copper ions possess strong oxidizing

properties, which facilitate the generation of oxygen radicals during immune responses. This oxidative environment enhances the clearance of pathogens by immune cells. Furthermore, the production of oxygen radicals activates immune cells, amplifying their activity and promoting the initiation and reinforcement of immune responses. Recently, Tsvetkov *et al.* discovered that Copper-induced cell death occurs *via* direct interaction between copper and lipoylated components of the tricarboxylic acid (TCA) cycle. This interaction initiates the aggregation of lipoylated proteins, leading to the subsequent loss of iron-sulfur cluster proteins. As a result, this mechanism induces proteotoxic stress, ultimately resulting in cell death.¹⁷³ Yu *et al.* deposited cuprous oxide on the surface of ZIF-8 for loading DNAzyme.¹⁷⁴ The Cu⁺ generated from cuprous oxide triggers a Fenton-like reaction to produce ROS. Simultaneously, Cu²⁺ produced from the Fenton-like reaction induces copper-induced cell death, while consuming intracellular glutathione (GSH) and transforming into Cu⁺ for further action. Cu⁺ not only induces CDT but also leads to copper-induced apoptosis. Additionally, DNA and Zn²⁺ combine to form a DNAzyme, which cleaves catalase-associated RNA, resulting in the accumulation of hydrogen peroxide and further enhancing combination therapy. Huang *et al.* employed MOF-199 to load buthionine-sulfoximine (BSO), catalase (CAT), and the absorption enhancer Dodecyl-beta-D-maltoside from an FDA-approved nasal formulation.¹⁷⁵ This approach was utilized to facilitate cuproptosis and subsequently enhance immunotherapy for glioblastoma. Chen *et al.* utilized Cu²⁺ as the active center and tetrakis(4-carboxyphenyl) porphyrin (TCPP) as ligands to construct Cu-TCPP(Al). Platinum was deposited on the surface of the MOF and modified with NH₂-PEG-FA. This nanomedicine achieves dual-enhanced PDT, triggering immunotherapy and reprogramming the immune-suppressive TME, thus enhancing the anti-tumor effect.⁹⁴ In previous studies, Cu²⁺ has typically been employed as a CDT agent to initiate



In conclusion, the development of MOF-mediated cancer immunotherapy represents a significant step forward in the fight against cancer. With their unique properties and versatile applications, MOFs offer exciting possibilities for improving patient outcomes and advancing the field of oncology. Continued research and innovation in this area will undoubtedly lead to groundbreaking discoveries and new treatment modalities for cancer patients.

Data availability

Based on the extensive discussion and analysis presented in this review, it is evident that MOFs hold great promise in revolutionizing cancer immunotherapy. The application of MOFs in drug delivery and tumor treatment represents a significant advancement in the field of nanomedicine. Firstly, MOFs have demonstrated exceptional potential as carriers for immunoadjuvants and therapeutic agents in cancer immunotherapy. Their high porosity, large surface area, and customizability make them ideal candidates for targeted drug delivery and controlled release systems.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors acknowledge funding from the National Natural Science Foundation of China (32101153), Young Elite Scientists Sponsorship Program by BATSA (BYESS2023244), Xuanwu Hospital Capital Medical University Nursing Special Project (HLZD2023002) and Beijing Institute of Technology Research Fund Program for Young Scholars. The authors also want to thank the Analysis & Testing Center at the Beijing Institute of Technology.

References

- J. E. Visvader, *Nature*, 2011, **469**, 314–322.
- M. M. Yan, S. Wu, Y. H. Wang, M. H. Liang, M. B. Wang, W. T. Hu, G. C. Yu, Z. W. Mao, F. H. Huang and J. Zhou, *Adv. Mater.*, 2024, **36**, 2304249.
- L. Galluzzi, M. J. Aryankalayil, C. N. Coleman and S. C. Formenti, *Nat. Rev. Clin. Oncol.*, 2023, **20**, 543–557.
- M. C. Vozenin, J. Bourhis and M. Durante, *Nat. Rev. Clin. Oncol.*, 2022, **19**, 791–803.
- F. C. Hamdy, J. L. Donovan, J. A. Lane, C. Metcalfe, M. Davis, E. L. Turner, R. M. Martin, G. J. Young, E. I. Walsh, R. J. Bryant, P. Bollina, A. Doble, A. Doherty, D. Gillatt, V. Gnanapragasam, O. Hughes, R. Kockelbergh, H. Kynaston, A. Paul, E. Paez, P. Powell, D. J. Rosario, E. Rowe, M. Mason, J. W. F. Catto, T. J. Peters, J. Oxley, N. J. Williams, J. Staffurth, D. E. Neal and T. S. G. Protec, *New Engl. J. Med.*, 2023, **388**, 1547–1558.
- I. Mellman, G. Coukos and G. Dranoff, *Nature*, 2011, **480**, 480–489.
- B. Smolarz, A. Z. Nowak and H. Romanowicz, *Cancers*, 2022, **14**, 2569.
- M. Sekhoacha, K. Riet, P. Motloung, L. Gumenku, A. Adegoke and S. Mashele, *Molecules*, 2022, **27**, 5730.
- M. Bausart, V. Pr  at and A. Malfanti, *J. Exp. Clin. Cancer Res.*, 2022, **41**, 35.
- O. Kepp, A. Marabelle, L. Zitvogel and G. Kroemer, *Nat. Rev. Clin. Oncol.*, 2020, **17**, 49–64.
- P. C. Tume, C. L. Harview, J. H. Yearley, I. P. Shintaku, E. J. M. Taylor, L. Robert, B. Chmielowski, M. Spasic, G. Henry, V. Ciobanu, A. N. West, M. Carmona, C. Kivork, E. Seja, G. Cherry, A. J. Gutierrez, T. R. Grogan, C. Mateus, G. Tomasic, J. A. Glaspy, R. O. Emerson, H. Robins, R. H. Pierce, D. A. Elashoff, C. Robert and A. Ribas, *Nature*, 2014, **515**, 568–571.
- I. Baraibar, I. Melero, M. Ponz-Sarvis and E. Castanon, *Drug Saf.*, 2019, **42**, 281–294.
- Q. Shang, Y. B. Dong, Y. Su, F. Leslie, M. J. Sun and F. H. Wang, *Adv. Drug Delivery Rev.*, 2022, **185**, 114308.
- N. Pacifici, A. Bolandparvaz and J. S. Lewis, *Adv. Ther.*, 2020, **3**, 2000129.
- C. Zhao, J. Kang, Y. Li, Y. Wang, X. Tang and Z. Jiang, *Cyborg Bionic Syst.*, 2023, **4**, 0022.
- Z. Q. Jiang, X. Han, C. Zhao, S. S. Wang and X. Y. Tang, *Int. J. Mol. Sci.*, 2022, **23**, 1923.
- C. Zhao, X. Han, S. S. Wang, Z. Y. Pan, X. Y. Tang and Z. Q. Jiang, *Adv. Healthcare Mater.*, 2023, **12**, 2201995.
- B. F. Hoskins and R. Robson, *J. Am. Chem. Soc.*, 1989, **111**, 5962–5964.
- W. D. Fan, X. R. Zhang, Z. X. Kang, X. P. Liu and D. F. Sun, *Coord. Chem. Rev.*, 2021, **443**, 213968.
- S. L. Qiu, M. Xue and G. S. Zhu, *Chem. Soc. Rev.*, 2014, **43**, 6116–6140.
- Y. Shen, T. Pan, L. Wang, Z. Ren, W. N. Zhang and F. W. Huo, *Adv. Mater.*, 2021, **33**, 2007442.
- H. L. Tian, M. Z. Zhang, G. X. Jin, Y. Jiang and Y. X. Luan, *J. Colloid Interface Sci.*, 2021, **587**, 358–366.
- S. Liang, X. Xiao, L. X. Bai, B. Liu, M. Yuan, P. A. Ma, M. L. Pang, Z. Y. Cheng and J. Lin, *Adv. Mater.*, 2021, **33**, 2100333.
- X. Han, C. Zhao, S. S. Wang, Z. Y. Pan, Z. Q. Jiang and X. Y. Tang, *J. Colloid Interface Sci.*, 2022, **621**, 360–373.
- K. D. Lu, C. B. He, N. N. Guo, C. Chan, K. Y. Ni, G. X. Lan, H. D. Tang, C. Pelizzari, Y. X. Fu, M. T. Spiotto, R. R. Weichselbaum and W. B. Lin, *Nat. Biomed. Eng.*, 2018, **2**, 600–610.
- X. J. Chen, Q. Y. Tang, J. Q. Wang, Y. Zhou, F. Q. Li, Y. X. Xie, X. A. Wang, L. Du, J. R. Li, J. Pu, Q. Y. Hu, Z. Gu and P. F. Liu, *Adv. Mater.*, 2023, **35**, 2210440.
- P. D. Fernandes, F. D. Magalhaes, R. F. Pereira and A. M. Pinto, *Polymers*, 2023, **15**, 1490.
- W. J. Zhu, J. Y. Zhao, Q. Chen and Z. Liu, *Coord. Chem. Rev.*, 2019, **398**, 113009.
- E. S. Pena, L. M. Lifshits, M. Eckshtain-Levi, E. M. Bachelder and K. M. Ainslie, *Wiley Interdiscip. Rev.: Nanomed. Nanobiotechnol.*, 2023, **15**, e1877.
- Q. Li, Y. Liu, Y. R. Zhang and W. Jiang, *J. Controlled Release*, 2022, **347**, 183–198.
- P. D. Harvey and J. Pl  , *J. Inorg. Organomet. Polym. Mater.*, 2021, **31**, 2715–2756.
- J. T. Liu, J. Huang, L. Zhang and J. P. Lei, *Chem. Soc. Rev.*, 2021, **50**, 1188–1218.
- B. J. Zhang, J. Y. Chen, Z. Zhu, X. Zhang and J. Wang, *Small*, 2024, **20**, 2307299.
- H. J. Zhang, W. Chen, K. Gong and J. H. Chen, *ACS Appl. Mater. Interfaces*, 2017, **9**, 31519–31525.
- X. F. Zhong, Y. T. Zhang, L. Tan, T. Zheng, Y. Y. Hou, X. Y. Hong, G. S. Du, X. Y. Chen, Y. D. Zhang and X. Sun, *J. Controlled Release*, 2019, **300**, 81–92.
- S. Y. Zhou, Q. Shang, J. B. Ji and Y. X. Luan, *ACS Appl. Mater. Interfaces*, 2021, **13**, 47407–47417.
- J. Lei, H. J. Wang, D. M. Zhu, Y. B. Wan and L. Yin, *J. Cell. Physiol.*, 2020, **235**, 4814–4823.
- Y. Zhang, F. M. Wang, E. G. Ju, Z. Liu, Z. W. Chen, J. S. Ren and X. G. Qu, *Adv. Funct. Mater.*, 2016, **26**, 6454–6461.
- T. Hidalgo, R. Sim  n-V  zquez, A. Gonz  lez-Fern  ndez and P. Horcajada, *Chem. Sci.*, 2022, **13**, 934–944.
- H. J. Wang, C. H. Wu, X. W. Tong and S. J. Chen, *J. Controlled Release*, 2023, **353**, 727–737.
- X. Li, X. P. Wang, A. Ito and N. M. Tsuji, *Nat. Commun.*, 2020, **11**, 3858.
- X. L. Zhang, Y. Lu, D. Jia, W. Qiu, X. B. Ma, X. L. Zhang, Z. G. Xu and F. Q. Wen, *J. Nanobiotechnol.*, 2021, **19**, 1–17.
- Z. H. Bai, L. S. Guo, J. F. Huang, H. Y. Li, G. H. An, H. M. Zheng, N. N. Wang, Z. Z. Li and Y. Q. Zhu, *Chem. Eng. J.*, 2024, **479**, 147932.
- J. Huang, Z. C. Xiao, M. Z. Lin, H. H. Zhong and X. T. Shuai, *Nano Today*, 2024, **54**, 102102.
- X. Xiao, S. Liang, Y. J. Zhao, M. L. Pang, P. A. Ma, Z. Y. Cheng and J. Lin, *Biomaterials*, 2021, **277**, 121120.
- S. K. Alsaiani, S. S. Qutub, S. C. Sun, W. Baslyman, M. Aldehaiman, M. Alyami, A. Almalik, R. Halwani, J. Merzaban, Z. W. Mao and N. M. Khashab, *Sci. Adv.*, 2021, **7**, eabe7174.
- Q. Liu, L. Wang, Y. T. Su, W. Dong, H. R. Wang, Y. Liu, H. Liu, L. X. Liu and Y. C. Wang, *Small*, 2024, **20**, 2305131.
- K. F. Wang, Y. P. Mu, S. Wang, Y. X. Song, J. Xu, X. H. Li and R. T. Wang, *Mater. Today Commun.*, 2023, **34**, 105221.
- Q. Zhao, Z. J. Gong, Z. H. Li, J. Y. Wang, J. L. Zhang, Z. F. Zhao, P. Zhang, S. H. Zheng, R. J. Miron, Q. Yuan and Y. F. Zhang, *Adv. Mater.*, 2021, **33**, 2100616.
- X. T. Zhao, Y. B. Li, L. M. Du, Z. M. Deng, M. Y. Jiang and S. J. Zeng, *Adv. Healthcare Mater.*, 2021, **10**, 2101174.
- B. N. Yalamandala, P. H. Chen, T. Moorthy, T. M. H. Huynh, W. H. Chiang and S. H. Hu, *Pharmaceutics*, 2022, **14**, 527.
- K. D. Lu, C. B. He, N. N. Guo, C. Chan, K. Y. Ni, R. R. Weichselbaum and W. B. Lin, *J. Am. Chem. Soc.*, 2016, **138**, 12502–12510.
- P. M. Chen, W. Y. Pan, Y. B. Miao, Y. M. Liu, P. K. Luo, H. N. Phung, W. W. Wu, Y. H. Ting, C. Y. Yeh, M. C. Chiang, W. T. Chia and H. W. Sung, *Adv. Funct. Mater.*, 2020, **30**, 2003764.
- J. H. Cavka, S. Jakobsen, U. Olsbye, N. Guillou, C. Lamberti, S. Bordiga and K. P. Lillerud, *J. Am. Chem. Soc.*, 2008, **130**, 13850–13851.
- Y. Wei, G. Qin, Z. Wang, C. Q. Zhao, J. S. Ren and X. G. Qu, *ACS Nano*, 2023, **17**, 5808–5820.

- 56 X. Y. Ren, Y. X. Han, Y. Q. Xu, T. G. Liu, M. Y. Cui, L. L. Xia, H. N. Li, Y. Q. Gu and P. Wang, *Coord. Chem. Rev.*, 2021, **431**, 213676.
- 57 S. Z. Ren, X. H. Zhu, B. Wang, M. Liu, S. K. Li, Y. S. Yang, H. L. An and H. L. Zhu, *J. Mater. Chem. B*, 2021, **9**, 4678–4689.
- 58 Z. J. Wang, Y. Fu, Z. Z. Kang, X. G. Liu, N. Chen, Q. Wang, Y. Q. Tu, L. H. Wang, S. P. Song, D. S. Ling, H. Y. Song, X. Q. Kong and C. H. Fan, *J. Am. Chem. Soc.*, 2017, **139**, 15784–15791.
- 59 Y. Ding, Q. Sun, Y. Gao, S. T. Zhang, C. X. Yang, Z. F. Qian, L. L. Jin, J. J. Zhang, C. Zeng, Z. W. Mao and W. L. Wang, *Adv. Mater.*, 2021, **33**, 2102188.
- 60 Z. X. Cai, F. L. Xin, Z. W. Wei, M. Wu, X. Y. Lin, X. F. Du, G. Chen, D. Zhang, Z. X. Zhang, X. L. Liu and C. P. Yao, *Adv. Healthcare Mater.*, 2020, **9**, 1900996.
- 61 Z. X. Cai, F. L. Xin, Z. W. Wei, M. Wu, X. Y. Lin, X. F. Du, G. Chen, D. Zhang, Z. X. Zhang, X. L. Liu and C. P. Yao, *Adv. Healthcare Mater.*, 2020, **9**, 1900996.
- 62 Y. T. Li, J. L. Zhou, Y. N. Chen, Q. Pei, Y. Li, L. Wang and Z. G. Xie, *Chem. Eng. J.*, 2022, **437**, 135370.
- 63 F. Hao, Z. Y. Yan and X. P. Yan, *Chemosphere*, 2022, **307**, 135680.
- 64 J. H. Tian, J. Wang, H. X. Yu, B. C. Zou, W. H. Chen, Y. L. Liu, J. S. Chen and R. P. Zhang, *Nanomedicine*, 2023, **50**, 102678.
- 65 J. Y. Zeng, M. Z. Zou, M. K. Zhang, X. S. Wang, X. Zeng, H. J. Cong and X. Z. Zhang, *ACS Nano*, 2018, **12**, 4630–4640.
- 66 R. Li, T. Bu, Y. J. Zhao, X. Y. Sun, Q. Z. Wang, Y. M. Tian, F. E. Bai and L. Wang, *Anal. Chim. Acta*, 2020, **1131**, 109–117.
- 67 Q. J. Chen, Y. Q. He, Y. Wang, C. Li, Y. J. Zhang, Q. Guo, Y. W. Zhang, Y. C. Chu, P. X. Liu, H. Y. Chen, Z. Zhou, W. X. Zhou, Z. H. Zhao, X. M. Li, T. Sun and C. Jiang, *Adv. Sci.*, 2020, **7**, 2000411.
- 68 W. N. Guo, M. Niu, Z. Z. Chen, Q. Wu, L. F. Tan, X. L. Ren, C. H. Fu, J. Ren, D. E. Gu and X. W. Meng, *Adv. Healthcare Mater.*, 2022, **11**, 2201441.
- 69 J. Li, S. J. Wang, X. Y. Lin, Y. B. Cao, Z. X. Cai, J. Wang, Z. X. Zhang, X. L. Liu, M. Wu and C. P. Yao, *Nano-Micro Lett.*, 2022, **14**, 57.
- 70 E. Ploetz, A. Zimpel, V. Cauda, D. Bauer, D. C. Lamb, C. Haisch, S. Zahler, A. M. Vollmar, S. Wuttke and H. Engelke, *Adv. Mater.*, 2020, **32**, 1907267.
- 71 M. M. Xu, Y. C. Chang, G. H. Zhu, X. Y. Zhu, X. T. Song and J. Li, *ACS Appl. Mater. Interfaces*, 2023, **15**, 17470–17484.
- 72 M. R. Chiang, W. T. Shen, P. X. Huang, K. L. Wang, W. H. Weng, C. W. Chang, W. H. Chiang, Y. C. Liu, S. J. Chang and S. H. Hu, *J. Controlled Release*, 2023, **360**, 260–273.
- 73 G. Férey, C. Serre, C. Mellot-Draznieks, F. Millange, S. Surblé, J. Dutoir and I. Margiolaki, *Angew. Chem., Int. Ed.*, 2004, **43**, 6296–6301.
- 74 H. S. Liu, C. N. Xu, M. Meng, S. Li, S. Sheng, S. J. Zhang, W. D. Ni, H. Y. Tian and Q. Wang, *Acta Biomater.*, 2022, **144**, 132–141.
- 75 P. Horcajada, T. Chalati, C. Serre, B. Gillet, C. Sebrie, T. Baati, J. F. Eubank, D. Heurtaux, P. Clayette, C. Kreuz, J. S. Chang, Y. K. Hwang, V. Marsaud, P. N. Bories, L. Cynober, S. Gil, G. Férey, P. Couvreur and R. Gref, *Nat. Mater.*, 2010, **9**, 172–178.
- 76 J. Zhao, D. P. Lu, S. Moya, H. Y. Yan, M. J. Qiu, J. Z. Chen, X. C. Wang, Y. Li, H. B. Pan, G. C. Chen and G. C. Wang, *Appl. Mater. Today*, 2020, **20**, 100701.
- 77 G. Cutrone, X. Li, J. M. Casas-Solvas, M. Menendez-Miranda, J. W. Qiu, G. Benkovics, D. Constantin, M. Malanga, B. Moreira-Alvarez, J. M. Costa-Fernandez, L. Garcia-Fuentes, R. Gref and A. Vargas-Berenguel, *Nanomaterials*, 2019, **9**, 1103.
- 78 W. D. Ni, J. Y. Wu, H. P. Fang, Y. J. Feng, Y. Y. Hu, L. Lin, J. Chen, F. F. Chen and H. Y. Tian, *Nano Lett.*, 2021, **21**, 7796–7805.
- 79 Y. Zhang, C. Q. Liu, F. M. Wang, Z. Liu, J. S. Ren and X. G. Qu, *Chem. Commun.*, 2017, **53**, 1840–1843.
- 80 X. Y. Ge, F. C. Jiang, M. H. Wang, M. Chen, Y. M. Li, J. Phipps, J. F. Cai, J. Xie, J. Ong, V. Dubovoy, J. G. Masters, L. Pan and S. Q. Ma, *ACS Appl. Mater. Interfaces*, 2023, **15**, 677–683.
- 81 Y. Yang, Q. Chen, J. Wu, T. Kirk, J. Xu, Z. Liu and W. Xue, *ACS Appl. Mater. Interfaces*, 2018, **10**, 12463–12473.
- 82 Z. J. Fan, H. X. Liu, Y. H. Xue, J. Y. Lin, Y. Fu, Z. H. Xia, D. M. Pan, J. Zhang, K. Qiao, Z. Z. Zhang and Y. H. Liao, *Bioact. Mater.*, 2021, **6**, 312–325.
- 83 G. X. Lan, K. Y. Ni, Z. W. Xu, S. S. Veroneau, Y. Song and W. B. Lin, *J. Am. Chem. Soc.*, 2018, **140**, 5670–5673.
- 84 B. N. Yalamandala, T. M. H. Huynh, M. R. Chiang, W. H. Weng, C. W. Chang, W. H. Chiang and S. H. Hu, *Adv. Funct. Mater.*, 2023, **33**, 2210644.
- 85 L. Liang, L. L. Yang, W. J. Wang, C. L. Ji, L. Zhang, Y. Y. Jia, Y. X. Chen, X. Q. Wang, J. Tan, Z. J. Sun, Q. Yuan and W. H. Tan, *Adv. Mater.*, 2021, **33**, 2102271.
- 86 Z. H. Wei, X. Q. Zhang, Z. L. Zhang, T. Y. Yong, G. T. Zhan, W. L. Lv, Z. Q. Ding, K. L. Sun, X. L. Yang and L. Gan, *Chem. Eng. J.*, 2022, **433**, 133847.
- 87 X. C. Hu, R. H. Li, J. Liu, K. Fang, C. Y. Dong and S. Shi, *Adv. Healthcare Mater.*, 2024, **13**, 2302333.
- 88 S. Huang, J. Yuan, Y. Xie, K. Qing, Z. Y. Shi, G. Y. Chen, J. Gao, H. X. Tan and W. H. Zhou, *Cancer Nanotechnol.*, 2023, **14**, 43.
- 89 K. Y. Ni, G. X. Lan, C. Chan, B. Quigley, K. D. Lu, T. Aung, N. N. Guo, P. La Riviere, R. R. Weichselbaum and W. B. Lin, *Nat. Commun.*, 2018, **9**, 2351.
- 90 K. Y. Ni, G. X. Lan, Y. Song, Z. Y. Hao and W. B. Lin, *Chem. Sci.*, 2020, **11**, 7641–7653.
- 91 W. Y. Zhen, T. K. Luo, Z. T. Wang, X. M. Jiang, E. R. Yuan, R. R. Weichselbaum and W. B. Lin, *Small*, 2023, **19**, 2305440.
- 92 E. Choi, M. Landry, N. Pennock, M. Neufeld, K. Weinfurter, A. Goforth, J. Walker and C. Sun, *Adv. Healthcare Mater.*, 2023, **12**, 2202830.
- 93 J. N. Li, W. Y. Lu, Y. N. Yang, R. Q. Xiang, Y. Ling, C. Z. Yu and Y. M. Zhou, *Adv. Sci.*, 2023, **10**, 2204932.
- 94 Z. J. Zhang, L. M. Wang, J. Wang, X. M. Jiang, X. H. Li, Z. J. Hu, Y. H. Ji, X. C. Wu and C. Y. Chen, *Adv. Mater.*, 2012, **24**, 1418–1423.
- 95 Z. Dai, Q. Y. Wang, J. Tang, M. Wu, H. Z. Li, Y. N. Yang, X. Zhen and C. Z. Yu, *Biomaterials*, 2022, **280**, 121261.
- 96 Q. Z. Wang, X. W. Zhu, X. W. Meng and H. S. Zhong, *Acta Biomater.*, 2023, **172**, 382–394.
- 97 S. Jiang, C. C. Liu, Q. J. He, K. Dang, W. W. Zhang and Y. Tian, *Nano Res.*, 2023, **16**, 9633–9641.
- 98 F. Duan, X. C. Feng, X. J. Yang, W. T. Sun, Y. Jin, H. F. Liu, K. Ge, Z. H. Li and J. C. Zhang, *Biomaterials*, 2017, **122**, 23–33.
- 99 F. Duan, J. N. Wang, Z. X. Li, T. Zhang, Z. H. Li and X. H. Zhou, *ACS Appl. Nano Mater.*, 2021, **4**, 13398–13404.
- 100 H. Cui, Y. Y. Zhao, Q. Wu, Y. You, Z. Lan, K. L. Zou, G. W. Cheng, H. Chen, Y. H. Han, Y. Chen, X. D. Qi, X. W. Meng, L. M. Ma and G. T. Yu, *Bioact. Mater.*, 2024, **33**, 532–544.
- 101 S. J. Zheng, M. F. Yang, J. Q. Luo, R. Liu, J. Song, Y. Chen and J. Z. Du, *ACS Nano*, 2023, **17**, 15905–15917.
- 102 Z. S. Xiong, M. Q. Yang, P. X. Liu, Z. Y. Tang, Y. Yang, M. X. Zhan, T. F. Chen, X. L. Li and L. G. Lu, *Adv. Funct. Mater.*, 2024, **34**, 2312919.
- 103 L. L. Dai, M. J. Yao, Z. X. Fu, X. Li, X. M. Zheng, S. Y. Meng, Z. Yuan, K. Y. Cai, H. Yang and Y. L. Zhao, *Nat. Commun.*, 2022, **13**, 2688.
- 104 G. T. Zhan, Q. B. Xu, Z. L. Zhang, Z. H. Wei, T. Y. Yong, N. N. Bie, X. Q. Zhang, X. Li, J. Y. Li, L. Gan and X. L. Yang, *Nano Today*, 2021, **38**, 101195.
- 105 F. Liu, L. L. Tan, Z. Dai, Y. Wang, L. Huang, Y. Zhang, Q. Cheng, X. Li, M. D. Liu, L. Wang and Z. Wang, *Nano Today*, 2024, **54**, 102112.
- 106 Q. Wu, L. F. Tan, X. L. Ren, C. H. Fu, Z. Z. Chen, J. Ren, T. C. Ma and X. W. Meng, *ACS Nano*, 2023, **17**, 25575–25590.
- 107 Y. Wang, D. Zhang, M. Jia, X. Zheng, Y. Liu, C. L. Wang, F. T. Lei, H. Niu and C. H. Li, *J. Drug Targeting*, 2022, **30**, 1006–1016.
- 108 Z. X. Chen, Y. F. Wu, Z. P. Yao, J. Su, Z. Wang, H. P. Xia and S. Q. Liu, *ACS Appl. Mater. Interfaces*, 2022, **14**, 44199–44210.
- 109 Y. W. Li, Y. Wei, Y. Huang, G. Qin, C. Q. Zhao, J. S. Ren and X. G. Qu, *Small*, 2023, **19**, 2301519.
- 110 X. Wang, J. L. Luo, J. Wang, J. Cao, Y. R. Hong, Q. Wen, Y. Q. Zeng, Z. Shi, G. R. Ma, T. Zhang and P. T. Huang, *ACS Appl. Mater. Interfaces*, 2023, **15**, 6442–6455.
- 111 B. Yang, H. Li, C. J. Nong, X. K. Li and S. X. Feng, *Anbio Biotechnol.*, 2023, **669**, 115117.
- 112 C. C. Li, C. X. Chen, Y. C. Wei, M. Tan, S. Zhai, J. B. Zhao, L. Wang and T. Dai, *Drug Delivery*, 2021, **28**, 2594–2602.
- 113 I. Kritskiy, T. Volkova, T. Sapozhnikova, A. Mazur, P. Tolstoy and I. Terekhova, *Mater. Sci. Eng., C*, 2020, **111**, 110774.
- 114 K. Ni, T. Luo, G. Lan, A. Culbert, Y. Song, T. Wu, X. Jiang and W. Lin, *Angew. Chem., Int. Ed.*, 2020, **59**, 1108–1112.
- 115 T. Li, M. Q. Gao, Z. F. Wu, J. J. Yang, B. H. Mo, S. T. Yu, X. Y. Gong, J. Liu, W. D. Wang, S. L. Luo and R. Li, *Adv. Sci.*, 2023, **10**, 2206779.
- 116 Y. Yang, N. Wang, Z. Wang, M. Han, F. Yan, Z. Shi and S. Feng, *Chem. Eng. J.*, 2023, **474**, 145764.
- 117 Y. Ding, Z. Q. Sun, Y. Gao, S. T. Zhang, C. X. Yang, Z. F. Qian, L. L. Jin, J. J. Zhang, C. Zeng, Z. W. Mao and W. L. Wang, *Adv. Mater.*, 2021, **33**, 2102188.

- 118 J. H. Tian, J. Wang, H. Y. Xu, B. C. Zou, W. H. Chen, Y. L. Liu, J. S. Chen and R. P. Zhang, *Nanomedicine*, 2023, **50**, 102678.
- 119 J. Zhao, D. P. Lu, S. Moya, H. Y. Yan, M. J. Qiu, J. Z. Chen, X. C. Wang, Y. Li, H. B. Pan, G. C. Chen and G. C. Wang, *Appl. Mater. Today*, 2020, **20**, 100701.
- 120 K. D. Lu, C. B. He, N. N. Guo, C. Chan, K. Y. Ni, G. X. Lan, H. D. Tang, C. Pelizzari, Y. X. Fu, M. T. Spiotto, R. R. Weichselbaum and W. B. Lin, *Nat. Biomed. Eng.*, 2018, **2**, 600–610.
- 121 G. T. Zhan, Q. B. Xu, Z. L. Zhang, Z. H. Wei, T. Y. Yong, N. N. Bie, X. Q. Zhang, X. Li, J. Y. Li, L. Gan and X. L. Yang, *Nano Today*, 2021, **38**, 101195.
- 122 Y. W. Li, Y. Wei, Y. Huang, G. Qin, C. Q. Zhao, J. S. Ren and X. G. Qu, *Small*, 2023, **19**, 2301519.
- 123 K. Y. Ni, T. K. Luo, G. X. Lan, A. Culbert, Y. Song, T. Wu, X. M. Jiang and W. B. Lin, *Angew. Chem., Int. Ed.*, 2020, **59**, 1108–1112.
- 124 T. Li, M. Q. Gao, Z. F. Wu, J. J. Yang, B. H. Mo, S. T. Yu, X. Y. Gong, J. Liu, W. D. Wang, S. L. Luo and R. Li, *Adv. Sci.*, 2023, **10**, 2206779.
- 125 Y. L. Yang, N. Wang, Z. H. Wang, M. D. Han, F. Yan, Z. Shi and S. H. Feng, *Chem. Eng. J.*, 2023, **474**, 145764.
- 126 Y. P. Zeng, S. F. Li, S. F. Zhang, L. Wang, H. Yuan and F. Q. Hu, *Acta Pharm. Sin. B*, 2022, **12**, 3233–3254.
- 127 H. L. Duan, L. J. Wang, S. Wang and Y. F. He, *Nanomedicine*, 2023, **18**, 1281–1303.
- 128 P. Gong, Y. F. Wang, P. F. Zhang, Z. G. Yang, W. Y. Deng, Z. H. Sun, M. M. Yang, X. F. Li, G. C. Ma, G. J. Deng, S. Y. Dong, L. T. Cai and W. Jiang, *Cancers*, 2021, **13**, 77.
- 129 H. N. Ding, Q. Xia, J. Q. Shen, C. Y. Zhu, Y. T. Zhang and N. P. Feng, *Colloids Surf., B*, 2023, **232**, 113607.
- 130 A. J. Boutilier and S. F. Elsawa, *Int. J. Mol. Sci.*, 2021, **22**, 6995.
- 131 S. Gordon, *Res. Immunol.*, 1998, **149**, 685–688.
- 132 G. Weiss and U. E. Schaible, *Immunol. Rev.*, 2015, **264**, 182–203.
- 133 Y. Sang, L. C. Miller and F. Blecha, *J. Clin. Cell. Immunol.*, 2015, **6**, 1–10.
- 134 D. G. Russell, L. Huang and B. C. VanderVen, *Nat. Rev. Immunol.*, 2019, **19**, 291–304.
- 135 H. M. Cao, Y. Gao, H. X. Jia, L. P. Zhang, J. J. Liu, G. E. Mu, H. Gui, Y. B. Wang, C. H. Yang and J. F. Liu, *Nano Lett.*, 2022, **22**, 7882–7891.
- 136 Y. N. Ma, W. H. Gao, Y. J. Zhang, M. Yang, X. J. Yan, Y. Y. Zhang, G. Y. Li, C. Liu, C. L. Xu and M. Z. Zhang, *ACS Appl. Mater. Interfaces*, 2022, **14**, 6358–6369.
- 137 Q. Yao, J. Ye, Y. Chen, L. Huang, L. Sun, Z. He, J. Wu, Y. Zhao, X. Zhao, A. Cai, X. Chen, H. Zheng, A. Sysa, C. Xie, R. Chen and L. Kou, *Chem. Eng. J.*, 2024, **480**, 148069.
- 138 K. Cheng, B. Liu, X. S. Zhang, R. Y. Zhang, F. Zhang, G. Ashraf, G. Q. Fan, M. Y. Tian, X. Sun, J. Yuan and Y. D. Zhao, *Nat. Commun.*, 2022, **13**, 4567.
- 139 L. Zhang, Q. Cheng, C. Li, X. Zeng and X.-Z. J. B. Zhang, *Biomaterials*, 2020, **248**, 120029.
- 140 W. L. Liu, M. Z. Zou, T. Liu, J. Y. Zeng, X. Li, W. Y. Yu, C. X. Li, J. J. Ye, W. Song, J. Feng and X. Z. Zhang, *Nat. Commun.*, 2019, **10**, 3199.
- 141 X. Cheng, Y. Liu, H. Zhou, J. K. Leng, X. F. Dai, D. Wang, K. Ma, C. H. Cui, J. J. Fu and Z. M. Guo, *Biomaterials Science*, 2021, **9**, 7862–7875.
- 142 M. A. Giese, L. E. Hind and A. Huttenlocher, *Blood*, 2019, **133**, 2159–2167.
- 143 S. Patel, S. Fu, J. Mastio, G. A. Dominguez, A. Purohit, A. Kossenkova, C. Lin, K. Alicea-Torres, M. Sehgal, Y. Nefedova, J. Zhou, L. R. Languino, C. Clendenin, R. H. Vonderheide, C. Mulligan, B. Nam, N. Hockstein, G. Masters, M. Guarino, Z. T. Schug, D. C. Altieri and D. I. Gabrilovich, *Nat. Immunol.*, 2018, **19**, 1236–1247.
- 144 A. Mócsai, B. Walzog and C. A. Lowell, *Cardiovasc. Res.*, 2015, **107**, 373–385.
- 145 J. D. Spicer, B. McDonald, J. J. Cools-Lartigue, S. C. Chow, B. Giannias, P. Kubes and L. E. Ferri, *Cancer Res.*, 2012, **72**, 3919–3927.
- 146 S. Tazzyman, S. T. Barry, S. Ashton, P. Wood, D. Blakey, C. E. Lewis and C. Murdoch, *Int. J. Cancer*, 2011, **129**, 847–858.
- 147 Z. G. Fridlender and S. M. Albelda, *Tumor Biol.*, 2012, **33**, 23.
- 148 T. T. Cui, Y. Zhang, G. Qin, Y. Wei, J. Yang, Y. Huang, J. S. Ren and X. G. Qu, *Nat. Commun.*, 2023, **14**, 1974.
- 149 R. M. Steinman and J. Banchereau, *Nature*, 2007, **449**, 419–426.
- 150 B. H. Kang and H. K. Lee, *Int. J. Mol. Sci.*, 2022, **23**, 7325.
- 151 S. H. Cheng, C. Xu, Y. Jin, Y. Li, C. Zhong, J. Ma, J. N. Yang, N. Zhang, Y. Li, C. Wang, Z. Y. Yang and Y. Wang, *Adv. Sci.*, 2020, **7**, 1903301.
- 152 F. R. Li, F. H. Li, R. Urie, E. Bealer, R. O. Ruiz, E. Saito, A. Turan, E. Yolcu, H. Shirwan and L. D. Shea, *Biotechnol. Bioeng.*, 2023, **120**, 767–777.
- 153 M. Kajihara, K. Takakura, T. Ohkusa and S. Koido, *Immunotherapy*, 2015, **7**, 1111–1122.
- 154 X. Y. Ma, L. Kuang, Y. Yin, L. Tang, Y. Zhang, Q. Fan, B. Y. Wang, Z. F. Dong, W. Wang, T. Y. Yin and Y. Z. Wang, *ACS Nano*, 2023, **17**, 2341–2355.
- 155 T. T. Hu, Y. Z. Huang, J. Liu, C. Shen, F. B. Wu and Z. Y. He, *Pharmaceutics*, 2023, **15**, 1821.
- 156 S. Y. Wang, M. X. Kai, Y. O. Duan, Z. D. Zhou, R. H. Fang, W. W. Gao and L. F. Zhang, *Angew. Chem., Int. Ed.*, 2022, **134**, e202203115.
- 157 J. M. Guo, Y. L. Yu, W. Zhu, R. E. Serda, S. Franco, L. Wang, Q. Lei, J. O. Agola, A. Nouredine, E. Ploetz, S. Wuttke and C. J. Brinker, *Adv. Funct. Mater.*, 2021, **31**, 2005935.
- 158 R. Huang, G. Q. Cai, J. Li, X. S. Li, H. T. Liu, X. L. Shang, J. D. Zhou, X. M. Nie and R. Gui, *J. Nanobiotechnol.*, 2021, **19**, 1–19.
- 159 M. Zhang, Y. H. Wang, Z. Y. Song, Y. M. Lu, H. Y. Zhao, Y. H. Wang, P. Lu and Y. T. Liu, *Clin. Med. Insights: Oncol.*, 2024, **18**, 11795549241236896.
- 160 H. B. Peng, X. C. Zhang, P. Yang, J. X. Zhao, W. Zhang, N. P. Feng, W. L. Yang and J. Tang, *Bioact. Mater.*, 2023, **19**, 1–11.
- 161 H. J. Wang, J. Z. Wu, G. R. Williams, Q. Fan, S. W. Niu, J. R. Wu, X. T. Xie and L. M. Zhu, *J. Nanobiotechnol.*, 2019, **17**, 1–16.
- 162 Q. Y. Shi, Y. Zhao, M. H. Liu, F. Y. Shi, L. X. Chen, X. R. Xu, J. Gao, H. B. Zhao, F. P. Lu, Y. J. Qin, Z. Zhang and M. L. Lian, *Small*, 2024, **20**, 2309366.
- 163 J. Zhuang, H. Gong, J. R. Zhou, Q. Z. Zhang, W. W. Gao, R. H. Fang and L. F. Zhang, *Sci. Adv.*, 2020, **6**, eaaz6108.
- 164 H. T. Liu, G. Q. Cai, S. Yuan, X. H. Zhou, R. Gui and R. Huang, *Mol. Pharmaceutics*, 2024, **21**, 3577–3590.
- 165 H. Guo, Y. P. Liu, X. Li, H. Wang, D. X. Mao, L. Y. Wei, X. T. Ye, D. Qu, J. G. Huo and Y. Chen, *ACS Nano*, 2023, **17**, 23829–23849.
- 166 Q. Long, P. Zheng, X. Zheng, W. R. Li, L. Q. Hua, Z. Q. Yang, W. W. Huang and Y. B. Ma, *Adv. Drug Delivery Rev.*, 2022, **186**, 114321.
- 167 N. Krishnan, L. J. Kubiatowicz, M. Holay, J. R. Zhou, R. H. Fang and L. F. Zhang, *Adv. Drug Delivery Rev.*, 2022, **185**, 114294.
- 168 O. Y. Kim, H. T. Park, N. T. H. Dinh, S. J. Choi, J. Lee, J. H. Kim, S. W. Lee and Y. S. Gho, *Nat. Commun.*, 2017, **8**, 626.
- 169 Z. W. Zhang, J. W. Tu, X. F. Kuang, M. Y. Shi, Y. M. Zhang, H. Li, J. S. Huang, L. Wang and H. F. Yuan, *New J. Chem.*, 2023, **48**, 367–376.
- 170 Q. W. Chen, X. H. Liu, J. X. Fan, S. Y. Peng, J. W. Wang, X. N. Wang, C. Zhang, C. J. Liu and X. Z. Zhang, *Adv. Funct. Mater.*, 2020, **30**, 1909806.
- 171 K. Y. Ni, G. X. Lan, N. N. Guo, A. Culbert, T. K. Luo, T. Wu, R. R. Weichselbaum and W. B. Lin, *Sci. Adv.*, 2020, **6**, eabb5223.
- 172 H. Y. Zhang, J. Zhang, Q. Li, A. X. Song, H. L. Tian, J. Q. Wang, Z. H. Li and Y. X. Luan, *Biomaterials*, 2020, **245**, 119983.
- 173 P. Tsvetkov, S. Coy, B. Petrova, M. Dreishpoon, A. Verma, M. Abdusamad, J. Rossen, L. Joesch-Cohen, R. Humeidi, R. D. Spangler, J. K. Eaton, E. Frenkel, M. Kocak, S. M. Corsello, S. Lutsenko, N. Kanarek, S. Santagata and T. R. Golub, *Science*, 2022, **375**, 1254–1261.
- 174 Q. Yu, J. Zhou, Y. Liu, X. Q. Li, S. Li, H. Zhou, B. Kang, H. Y. Chen and J. J. Xu, *Adv. Healthcare Mater.*, 2023, **12**, 2301429.
- 175 Q. X. Huang, J. L. Liang, Q. W. Chen, X. K. Jin, M. T. Niu, C. Y. Dong and X. Z. Zhang, *Nano Today*, 2023, **51**, 101911.
- 176 Z. G. Feng, G. Chen, M. Zhong, L. Lin, Z. Y. Mai, Y. Tang, G. M. Chen, W. Ma, G. Li, Y. Y. Yang, Z. Q. Yu and M. Yu, *Biomaterials*, 2023, **302**, 122333.
- 177 G. H. An, H. M. Zheng, L. S. Guo, J. M. Huang, C. L. Yang, Z. H. Bai, N. N. Wang, Y. Q. Zhu and W. H. Yang, *J. Colloid Interface Sci.*, 2024, **662**, 298–312.