Metal-organic framework-based cancer theranostic nanoplatforms

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Abstract
The rapid development of imaging technologies provides a visual diagnostic tool for scientists and surgeons to comprehensively and accurately understand the pathogenesis and pathological processes of complicated diseases, especially cancer. Theranostic platforms integrating various imaging technologies and treatment strategies for the diagnosis and treatment of cancer have been extensively studied. Notably, metal-organic frameworks (MOFs) – an emerging porous organic-inorganic hybrid material composed of metal ions/ion clusters as nodes and organic ligands as linkers bridged by coordination bonds – have been widely used as intelligent carriers for cancer theranostics in recent years due to their fascinating properties, including facile synthesis, diverse compositions, high surface areas and porosities, tailorable sizes, multiple physicochemical properties, easy surface functionalization, and good biocompatibility. This review summarizes the recent advanced developments and achievements of MOFs as smart theranostic platforms for effective cancer diagnosis and treatment guided by monomodal imaging technologies, including optical imaging, magnetic resonance imaging, computed tomography imaging, positron emission tomography imaging, and photoacoustic imaging, and multimodal imaging technologies. Moreover, the development prospects and critical challenges of MOFs for cancer theranostics are also addressed.

KEYWORDS
cancer theranostics, disease diagnosis, monomodal imaging, multimodal imaging, porous materials

1 | INTRODUCTION

In the clinic, effective diagnosis of cancer can comprehensively and accurately reflect the pathological characteristics and progression of disease, helping to improve diagnostic accuracy, prolong the life cycle, and improve the life quality of cancer patients. At present, the typical imaging technologies used for cancer diagnosis mainly include optical imaging (OI), magnetic resonance imaging (MRI), computed tomography (CT) imaging, positron emission tomography (PET) imaging, and photoacoustic (PA) imaging. However, these common imaging technologies exhibit some intrinsic imperfections, such as low sensitivity, poor penetration depth, and low tissue contrast, which seriously reduce the
imaging quality and diagnostic effect. On the other hand, chemotherapy, radiotherapy, photothermal therapy (PTT), and photodynamic therapy (PDT) are common options for cancer treatment. Chemotherapy, as a main method in cancer treatment, faces the disadvantages of large toxic side effects, low selectivity, and poor targeting. Radiotherapy uses high-energy X-rays to kill cancer cells, but suffers from small tissue penetration, large toxic and side effects, and narrow application scope. PTT has disadvantages of complicated operation, highly depending on photothermal agents, and limited therapeutic range. The effect of PDT is susceptible to O₂ content in tumor sites and sensitization efficiency of photosensitizer (PS). Furthermore, such therapeutic strategies require the guidance of imaging technologies to achieve enhanced treatment efficacy, and more effective treatment strategies are needed to be developed for cancer diagnosis and treatment.

Integrating the multitudinous features of imaging technologies and treatment strategies into an intelligent “all-in-one” complex for imaging-guided precise cancer theranostics has become a hot research direction. With the development of synthetic technologies and surface modification strategies, numerous nanomaterials have been fabricated to meet the special demands of simultaneous imaging diagnosis and efficient treatment during cancer theranostics. In general, ideal cancer theranostic platforms should boot the following basic characteristics: high cargo loading capacities can satisfy simultaneously effective encapsulation of imaging agents and therapeutic agents; nanoscale sizes make them suitable for intravenous administration and high tumor accumulation via enhanced permeability and retention (EPR) effect (passive targeting); easy surface functionalization features can reduce the clearance of endothelial reticular system and enhance cancer cell targeting (active targeting); the platforms should be biocompatible and degradable to be metabolized by the body. Furthermore, scientists are currently exploring excellent multifunctional platforms to satisfy the ever-increasing demand for cancer theranostics.

Metal-organic frameworks (MOFs) – a fascinating and interesting class of porous hybrid coordination polymers composed of metal ions/ion clusters as nodes and organic ligands as linkers – have been designed and fabricated for miscellaneous applications, that is, gas storage/separation/adsorption, catalysis, sensing, nonlinear optics, and biomedicine fields. In recent years, MOFs, especially nanoscale MOFs (NMOFs), have received widespread attention in drug delivery and disease diagnosis. Compared with traditional nanoplatforms, MOFs possess the following unique superiorities: various features including different morphologies, tailorable sizes, diverse compositions, and multiple physicochemical properties can be effortlessly obtained by changing almost infinite combinations of metal nodes and organic ligands; high surface areas and large porosities make them easier to load various cargo molecules from small organic molecules to biomacromolecules; flexible substituent types on organic ligands and strong coordination abilities of metal nodes provide a powerful guarantee for surface decoration, for example, polymers are often used to improve colloidal stabilities and tumor accumulation of MOFs; targeting groups and luminescent molecules are employed to give MOFs active targeting and optical detection properties, respectively; biomacromolecules including nucleic acids, proteins, and peptides can be anchored to the surface of MOFs to give the biological functions; supramolecular macrocycles are equipped on the surface of MOFs to achieve controllable drug release and reduce the premature release; and stable but weak coordination bonds ensure on-demand degradation of MOFs. Therefore, MOFs have been employed as potential theranostic platforms for imaging-guided cancer treatment due to these preeminent attributes (Figure 1).

In this review, we summarize the advanced developments and achievements of MOFs as multifunctional theranostic platforms for effective cancer diagnosis and treatment guided by monomodal imaging technologies, including OI, MRI, CT imaging, PET imaging, and PA imaging, and multimodal imaging technologies in recent few years. Moreover, the development prospects and critical challenges of MOFs for cancer theranostics are also addressed, hopefully helping researchers to comprehensively understand the current status of MOFs and stimulate more fascinating developments in cancer theranostics.
| MOFs          | MOF skeleton components | Imaging strategy | Therapeutic option | Animal model                  | Administration method        | Reference |
|--------------|-------------------------|-------------------|--------------------|-------------------------------|------------------------------|-----------|
| NPMOF        | Zr₆, TCPP               | FL                | Chemotherapy, PDT  | HepG2 tumor-bearing mice      | Intravenous administration   | 34        |
| mCGP         | Zr₆, TCPP               | FL                | PDT, starvation therapy | 4T1 tumor-bearing mice | Intravenous administration   | 35        |
| mPPt         | Zr₆, PtTCP              | Phosphorescence imaging | PDT              | 4T1 tumor-bearing mice        | Intravenous administration   | 36        |
| UiO-66-NH₂-FA-5-FAM/5-FU | Zr⁴⁺, NH₂-BDC | FL | Chemotherapy | HepG2 tumor-bearing mice | Intraperitoneal injection   | 37        |
| BQ-MIL@cat-fMIL | Fe³⁺, NH₂-BDC    | FL | PTT, PDT       | HeLa tumor-bearing mice      | Intravenous administration   | 38        |
| pEGFP-C1@ZIF-8-polymer | Zn²⁺, 2-H-MeIM | FL (FITC-labeled) | –                  | Tumor-carrying zebrafish embryos, 4T1 tumor-bearing mice | Intravenous administration   | 39        |
| PS@MOF-199 NPs | Cu²⁺, BTC             | FL | PDT             | –                             | –                            | 40        |
| MIL-88A      | Fe³⁺, fumaric acid     | MRI               | Chemotherapy       | Wistar female rats            | Intravenous administration   | 45        |
| MIL/USPIO-cit | Fe³⁺, trimesic acid   | MRI               | Chemotherapy       | BALB/c mice                   | Intravenous administration   | 46        |
| Fe₃O₄@UiO-66@WP6 | Zr⁴⁺, NH₂-BDC | MRI | Chemotherapy | –                             | –                            | 47        |
| Gd-ZMOF      | Gd³⁺, H₂bpdc           | MRI               | –                  | 4T1 tumor-bearing mice        | Intravenous administration   | 48        |
| MOFs-MB-DHA@PLA@PEG | Fe³⁺, H₂BDC | MRI | Chemotherapy, PDT | U14 tumor-bearing mice         | Intravenous administration   | 49        |
| UiO-PDT      | Zr⁴⁺, H₂BDC            | CT                | –                  | Rat orthotopic hepatoma       | Intravenous administration   | 50        |
| LA-AuNR/ZIF-8 | Zn²⁺, 2-H-MeIM       | CT                | Chemotherapy, PTT   | H22 bearing BALB/c mice       | Intravenous administration   | 54        |
| Bi-NU-901    | Bi³⁺, H₂TBAPy          | CT                | –                  | –                             | –                            | 55        |
| ZIF-8/DOX@ZrO₂@IL | Zn²⁺, 2-H-MeIM | CT | Microwave thermal therapy, chemotherapy | H22 tumor-bearing mice       | Intravenous administration   | 56        |
| HUC-PENG     | Hf⁴⁺, BDC, TCPC        | CT                | PTT, PDT           | U14 tumor-bearing mice        | Intravenous administration   | 57        |
| DOX loaded AZIF-8 | Zn²⁺, 2-H-MeIM | CT | Chemotherapy | 4T1 tumor-bearing mice        | Intravenous administration   | 59        |
| Polymer-wrapped Zr-MOF | Zr⁴⁺, 1,4-BDC | PET | Chemotherapy | A431 tumor-bearing mice       | Intravenous administration   | 60        |
| O₂@UiO-66@ICG@RBC | Zr⁴⁺, 1,4-BDC | PA | PDT              | MCF-7 tumor-bearing mice      | Intravenous administration   | 63        |
| DBBC-Uio      | Hf⁴⁺, H₂DBBC           | PA                | PDT                | MCF-7 tumor-bearing mice      | Intravenous administration   | 64        |
| MGH           | Fe³⁺, BTC              | PA                | CDT, PTT, starvation therapy | 4T1 tumor-bearing mice | Intravenous administration   | 65        |
| Au@MOF-DOX   | Zn²⁺, 2-H-MeIM         | PA, thermal imaging | Chemotherapy, PTT | H22 tumor-bearing mice        | Intravenous administration   | 66        |
MOF-BASED MONOMODAL IMAGING THERANOSTIC NANOPLATFORMS

Imaging technologies, an intelligent visualization tool, provide an important guarantee for exploring the pathogenesis and characteristics of diseases, especially cancer. As a key component of imaging technologies, imaging agents play a vital role in the imaging process. However, traditional small molecule imaging agents suffer from a series of shortcomings, such as easy degradation, rapid metabolism, and high nonspecific distribution. In the past few decades, various carriers, including inorganic vehicles and organic supports, have been constructed for the addition of small molecule imaging agents to overcome the aforementioned defects, improving the diagnosis effect of diseases. Unfortunately, although significant progress has been made, the degradability, biodistribution, and metabolic mechanisms of inorganic vehicles still need to be further comprehensively studied. Meanwhile, the major disadvantages of organic supports are low loading capacity, poor targeting, and easy degradation. Considering the outstanding superiorities of facile synthetic conditions, tailorable sizes, large surface areas, tunable pore sizes, easy modifications, unique physicochemical properties, good biocompatibility, and biodegradability, MOFs have become one of the most promising candidates for cancer diagnosis. Furthermore, MOFs can also co-deliver various bioactive agents, including drugs, enzymes, genes, and gases, to achieve imaging-guided cancer theranostics. In this section, we will summarize the advanced applications of MOFs as monomodal imaging theranostic nanoplatforms in the diagnosis and treatment of cancer guided by OI, MRI, CT imaging, PET imaging, or PA imaging (Table 1).

2.1 OI theranostic nanoplatforms

OI, as a universal imaging technology for diseases diagnosis, is the conversion of light into fluorescent or phosphorescent signals by imaging agents to reflect information of organs, tissues, or cells in organisms, which possesses the advantages of facile operation, good sensitivity, and high resolution. MOF-based OI theranostic nanoplatforms can be fabricated by either selection of intrinsically luminescent metal nodes/organic ligands or encapsulation/decoration of imaging agents to pores or surface of MOFs. Moreover, due to the shallow tissue penetrability of visible light, near-infrared (NIR) dye molecules with strong penetrability and high photostability excited by NIR light have been developed to obtain enhanced OI effect.

In 2017, Yin and co-workers designed a nanoscale spindle-like zirconium-porphyrin MOF (NPMOF) using a simple one-pot synthesis strategy (ie, microemulsion method) for FL imaging-guided synergetic chemotherapy and PDT of tumors in vivo. The obtained spindle-like NPMOF, consisting of Zr6 as metal clusters and meso-tetakis(4-carboxyl)-21H,23H-porphine (TCCP) as ligand linkers with a particle size of 155 × 260 nm, was suitable for PDT because of the short diffusion distance of singlet oxygen (1O2). Moreover, the content of porphyrin in the NPMOF skeleton was up to 59.8%, which indicated the great potential of NPMOF as fluorescent imaging. The one-dimensional channel and pores sizes of 1.75 and 3.5 nm in the NPMOF were suitable for loading the antitumor drug doxorubicin (DOX) ended up with an efficient loading capacity of 109%. Subsequently, good biocompatibility of the NPMOF carrier was verified by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and zebrafish model. Importantly, in vivo FL imaging results demonstrated that NPMOF mainly accumulated in the circulatory system, lymph nodes, and tumor site, which contributed to the tumor therapy and inhibited cancer metastasis. The results of FL-guided synergistic chemotherapy and PDT in HepG2 tumor-bearing mice showed that the DOX-loaded NPMOF had satisfactory therapeutic effect and high biocompatibility to the major organs.

Zhang and coworkers reported a biomimetic cancer cell membrane-camouflaged MOF-based bioreactor (denoted as mCGP) for FL imaging-guided synergistic PDT and starvation therapy of cancer (Figure 2A). Spherical PS PCN-224, composed by Zr6 cluster and TCPP ligands, was used to load glucose oxidase (GOx) and catalase (CAT) by electrostatic interactions, followed by the coating of cancer cell membrane to construct biomimetic core-shell mCGP with a homogeneous outer lipid bilayer of 10 nm. Owing to the biomimetic surface decoration of bioreactor, the immune escape and homologous targeting abilities of mCGP would significantly improve its targeting and retention effects of tumors. Once being internalized into the tumor cells, CAT loaded in the mCGP could decompose H2O2 into O2, and GOx could promote glucose consumption, thus leading to the improvement of O2 in hypoxia microenvironment and the effective starvation therapy in tumors. Moreover, under light irradiation, O2 was converted into highly toxic 1O2, which enhanced the therapeutic efficiency of PDT. Furthermore, in vivo FL imaging results demonstrated that mCGP was effectively accumulated in the tumor sites after intravenous administration, reached a peak at 48 h and then gradually weakened (Figure 2B). Meanwhile, the outstanding effect of synergistic PDT and starvation therapy was observed in 4T1 tumor-bearing mice.

Similarly, another biomimetic theranostic nanocomposite, that is, mPPT, was also constructed by their group for phosphorescence imaging and tumor targeting therapy. In this design, mPPT was prepared by coating cancer cell membrane on Pt(II) porphyrinic-MOFs consisting of Zr6 as clusters and Pt(II) meso-tetra(4-carboxyphenyl)porphyrin (PTCPP) as ligands, showing high PS loading, homotypic targeting, and characteristics of diseases, especially cancer. As a key component of imaging technologies, imaging agents play a vital role in the imaging process. However, traditional small molecule imaging agents suffer from a series of shortcomings, such as easy degradation, rapid metabolism, and high nonspecific distribution. In the past few decades, various carriers, including inorganic vehicles and organic supports, have been constructed for the addition of small molecule imaging agents to overcome the aforementioned defects, improving the diagnosis effect of diseases. Unfortunately, although significant progress has been made, the degradability, biodistribution, and metabolic mechanisms of inorganic vehicles still need to be further comprehensively studied. Meanwhile, the major disadvantages of organic supports are low loading capacity, poor targeting, and easy degradation. Considering the outstanding superiorities of facile synthetic conditions, tailorable sizes, large surface areas, tunable pore sizes, easy modifications, unique physicochemical properties, good biocompatibility, and biodegradability, MOFs have become one of the most promising candidates for cancer diagnosis. Furthermore, MOFs can also co-deliver various bioactive agents, including drugs, enzymes, genes, and gases, to achieve imaging-guided cancer theranostics. In this section, we will summarize the advanced applications of MOFs as monomodal imaging theranostic nanoplatforms in the diagnosis and treatment of cancer guided by OI, MRI, CT imaging, PET imaging, or PA imaging (Table 1).

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FIGURE 2  (A) Schematic representation of the fabrication of mCGP and its application for FL imaging-guided synergistic PDT and starvation therapy of cancer. (B) In vivo and ex vivo fluorescence images at different times after intravenous injection of mCGP (top) and PCN-224 (bottom) in 4T1 tumor-bearing mice. Reproduced with permission.35 Copyright 2017, American Chemical Society. (C) 2D plane view of UiO-66-NH₂ and the application of UiO-66-NH₂-FA-5-FAM/5-FU for FL imaging-guided tumor therapy. Reproduced with permission.37 Copyright 2018, The Royal Society of Chemistry
and immune escape capabilities. Moreover, the O2-dependent phosphorescence effect of mPPT could be applied in achieving the assessment of O2 levels in the tumor environment, effective phosphorescence imaging, and significant tumor suppression by PDT without significant side effects. This biomimetic strategy paves a new way to develop multifunctional nanotheranostic MOFs for effective treatment of diseases.

Subsequently, Liu and co-workers reported a multifunctional nanotheranostic platform via hydrothermal method and post-synthetic modification strategy, namely UiO-66-NH2-FAMA-5-FAM/5-FU, for FL imaging and cancer therapy (Figure 2C).37 UiO-66-NH2 (formed by Zr4+ and 2-amino terephthalic acid (NH2-BDC)) with average diameters from 20 to 200 nm was obtained by adjusting the amount of benzoic acid. Considering the requirements of good dispersibility and suitable size for carrier during the treatment of diseases, 50 nm UiO-66-NH2 was selected as the reservoir for loading the drug 5-fluorouracil (5-Fu), followed by a decoration with the fluorescent reagent 5-carboxyfluorescein (5-FAM) and the targeting group folic acid (FA). As expected, FL imaging experiments showed that the obtained UiO-66-NH2-FAMA-5-FAM/5-FU possessed good FL imaging ability in living cells with high folate receptor expression and tumor-bearing mice. Moreover, such a nanoplatform with controlled drug release, excellent water solubility, good biocompatibility, and preeminent targeting, demonstrated enhanced effects in tumor diagnosis and treatment in vivo, which paves a way for the design and construction of MOF-based theranostics integrating FL imaging and chemotherapy.

Recently, Lei and coworkers structured an integrated theranostic system based on a black phosphorus quantum dot (BQ) and MIL-101-NH2 to achieve FL imaging and combined PTT and PDT of tumor.38 The octahedral spindle-like BQ-MIL@cat-MIL heterostructure with a diameter of ca. 140 nm was precisely developed via a layered MIL-101-NH2 using a stepwise in situ growth method, encapsulating the BQ as inner and CAT as outer, respectively. Subsequently, HOOC-poly(ethylene glycol)-folic acid (PEG-FA) and cyanine 3 (Cy3)-labeled caspase substrate peptide (Cy3 pep) were modified on the surface of BQ-MIL@cat-MIL by an amidation reaction to develop BQ-MIL@cat-fMIL for the improved targeting ability and visualization (Figure 3A). During 808 nm laser irradiation, the inner BQ could convert light energy into hyperpyrexia for PTT. Meanwhile, excessive H2O2 could be catalyzed by CAT in the outer layer to generate O2, and then O2 was directly transferred into the inner layer to generate O2 for PDT, which was beneficial to alleviate hypoxia in the tumor site to enhance the PDT effect. In vivo results demonstrated that BQ-MIL@cat-fMIL effectively accumulated in the tumor area after 24 h of intravenous administration, achieving an efficient tumor diagnosis and treatment effect by FL-guided synergistic PTT and PDT (Figure 3B).

Interestingly, Tang, Zhao, Wei, and co-workers designed two gene-based theranostic nanostructures, namely, pEGFP-C1@ZIF-8 and pEGFP-C1@ZIF-8-polymer, to achieve efficient plasmid DNA (pDNA) encapsulation and intracellular gene delivery.39 pEGFP-C1, as a pDNA expressing enhanced green fluorescent protein, was encapsulated in aforementioned two systems via one-pot method with some differences. For pEGFP-C1@ZIF-8 system, pEGFP-C1 was embedded into ZIF-8 MOF by biomimetic mineralization method, reaching a loading content of ≈ 2.5%. In the pEGFP-C1@ZIF-8-polymer system, polymers including nonionic polyethylene glycol (PEG), cationic polyethyleneimine (PEI) 10 and 25 kD was selected and combined with ZIF-8 and pEGFP-C1 to form pEGFP-C1@ZIF-8-PEI 10 kD, pEGFP-C1@ZIF-8-PEI 10 kD, and pEGFP-C1@ZIF-8-PEI 25 kD via coprecipitation method with loading capacities of ≈ 2.6%, ≈ 3.0%, and ≈ 3.4%, respectively, which was due to the cationic charge densities, the degrees of branching, and the electrostatic binding capacities of different polymers. Experimental studies demonstrated that pEGFP-C1@ZIF-8-PEI 25 kD system showed pH-responsive release behavior of pEGFP-C1 with less premature release, strong resistance against enzyme degradation, good biocompatibility, effective cell internalization, enhanced endosome escape performance, and superior gene delivery and expression capabilities, which was conducive to gene delivery and expression. This work paves a new way to construct efficient and biocompatible MOF-based nanoplatorms for gene therapy of diseases.

For another instance, Liu and co-workers reported an “inert” theranostic nanocomposite, namely PS@MOF-199 NPs, for FL imaging-guided PDT of tumor (Figure 3C).40 MOF-199, constructed from Cu2+ and benzene-1,3,5-tricarboxylate (BTC) triethylammonium salt ligands was applied to encapsulate synthesized PS 2-(4-[diphenylnamino]phenyl)anthracene-9,10-dione (TPAAQ) with aggregation-induced emission (AIE) property or commercial PS Ce6 with aggregation-caused quenching (ACQ) feature, reaching a high loading contents of 58 wt% for TPAAQ and 49 wt% for Ce6, respectively. And then, the two obtained nanoplatorms were coated with a F-127 layer to yield PS@MOF-199 with sizes of ≈ 150 nm (TPAAQ@MOF-199 or Ce6@MOF-199). Interestingly, under normal conditions, the photosensitization process of PS in the PS@MOF-199 was blocked due to the isolation effect of PS by MOF-199. In contrast, once the PS@MOF-199 entered cancer cells through endocytosis, it was decomposed by glutathione (GSH), and the encapsulated TPAAQ or Ce6 was released and reacted with O2, resulting in activated photosensitization process with light irradiation. Furthermore, experimental results showed that PS@MOF-199 possessed good biocompatibility, remarkable FL imaging effect, and improved therapeutic effects by PDT to both tumor-carrying zebrafish embryos and 4T1 tumor-bearing mice (Figure 3D).
**FIGURE 3**  (A) Schematic diagram of the preparation of BQ-MIL@cat-fMIL and its application in FL imaging and synergistic PTT and PDT. (B) Time-dependent in vivo FL images of HeLa tumor-bearing mice after intravenous injection of BQ-MIL@cat-fMIL. Reproduced with permission.38 Copyright 2019, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (C) Schematic of the synthesis of PS@MOF-199 NPs and its application for FL imaging-guided PDT of tumor. (D) FL images before and after intravenous injection of PS@MOF-199 NPs. Reproduced with permission.40 Copyright 2019, American Chemical Society
providing a reliable guide for monitoring the material delivery process in disease treatment.

2.2 MRI theranostic nanoplatforms

MRI is a medical imaging technology that employs radio-frequency signals generated by the complicated interactions between external magnetic field/radio-waves and the protons (typically of hydrogen atoms in water) of detected soft tissues to obtain anatomy and physiological processes of the living body.\(^{41}\) MRI has been widely used in clinical practice owing to its noninvasiveness, high spatial resolution, and deep tissue penetration.\(^{42}\) MRI contrast agents can transform the longitudinal (T1) and lateral (T2) relaxation rates of water protons in the detection site to construct images for disease diagnosis.\(^{43}\) At present, small-molecule Gd chelates, and superparamagnetic iron oxide are usually used for T1-weighted (positive signal enhancement) imaging and T2-weighted (negative signal enhancement) imaging, respectively, but they often suffer from large doses, poor water solubility, and short effective half-life. In view of this, various MOFs containing Gd, Mn, Fe, and their derivatives were developed as high resolution MRI contrast agents to improve tumor accumulation and image quality during cancer diagnosis and treatment.\(^{44}\)

For example, Gref, Horcajada, and co-workers reported several theranostic nanoplatforms based on non-toxic Fe(III)-based carboxylate MOFs (MIL-53, MIL-88A, MIL-88Bt, MIL-89, MIL-100, and MIL-101-NH\(_2\); MIL = Materials of Institut Lavoisier) via environmentally friendly medium for controllable delivery of anticancer or retroviral drugs (busulfan (Bu), azidothymidine triphosphate (AZT-TP), DOX, cidofovir (CDV), etc) and MRI effect (Figure 4A).\(^{45}\) Drug loading experiments showed that Fe(III)-based MOFs could not only encapsulate hydrophilic drugs efficiently, such as AZT-TP and CDV, but also entrap hydrophobic drugs and amphiphilic drugs, including Bu, DOX, and others. Moreover, drugs could be released in a controlled manner under physiological conditions and maintained pharmacological activity. Cytotoxicity assay, acute toxicity experiment, and in vivo subacute toxicity assays results demonstrated that Fe(III)-based MOFs possessed good biocompatibility and biosafety. Importantly, MIL-88A exhibited good T2-weighted MRI effect in the liver and spleen of Wistar female rats (Figure 4B), which revealed that Fe(III)-based MOFs could be used as nice candidates for MRI. This work opens new perspectives for the development of Fe(III)-based MOFs in the diagnosis and treatment of diseases.

Interestingly, Steunou and co-workers fabricated a biocompatible theranostic nanohybrid (denoted as MIL/USPIO-cit), with excellent colloidal stability, outstanding superparamagnetic behavior, and high drug loading capacity, for MRI-guided cancer therapy.\(^{46}\) Maghemite (\(\gamma\)-Fe\(_2\)O\(_3\)) nanoparticles (NPs) with a size of approximately 7 nm as decoration was modified on the outer surface of octahedral morphology mesoporous MIL-100(Fe) host with a diameter of approximately 130 nm by cost-effective and reliable green method to generate MIL/USPIO-cit nanohybrid. Remarkably, experimental results indicated that relaxometric value of MIL/USPIO-cit improved with the \(\gamma\)-Fe\(_2\)O\(_3\) content from 1 to 10 wt\%. When the \(\gamma\)-Fe\(_2\)O\(_3\) NPs content on the surface of MIL/USPIO-cit was 10 wt\%, the relative relaxometric value was nine times higher than that of MIL-100(Fe), which was attributed to the high saturation magnetization of the \(\gamma\)-Fe\(_2\)O\(_3\). After intravenous injection of MIL/USPIO-cit into mice, a decrease of the liver and spleen signals occurred, which was due to the outstanding T\(_2\)-weighted effect of MIL/USPIO-cit. Interestingly, after loading anticancer drug DOX, MIL/USPIO-cit exhibited great biocompatibility and high antitumor activity, making it a potential drug carrier for chemotherapy. According to the abovementioned properties, such a nanohybrid system could be applied as a promising tool for MRI-guided cancer treatment.

In 2018, our group prepared a smart theranostic nanocomposite based on Fe\(_3\)O\(_4\)@UiO-66 core-shell structure and water-soluble carboxylatopillar[6]arene (WP6) nanovalves, that is, Fe\(_3\)O\(_4\)@UiO-66@WP6, for MRI and cervical cancer treatment (Figure 4C).\(^{47}\) The core-shell nanohybrid of Fe\(_3\)O\(_4\)@UiO-66 was constructed by growing of UiO-66-NH\(_2\) shell with high loading ability of antitumor drug 5-Fu on the surface of Fe\(_3\)O\(_4\) core with superior abilities of MRI and magnetic separation effect. Subsequently, the WP6 nanovalves was equipped on the surface of Fe\(_3\)O\(_4\)@UiO-66 nanocomposite via the dynamic host-guest interactions with 1-(6-bromohexyl) pyridinium bromide (Py)-containing stalks on the UiO-66-NH\(_2\) shell, endowing the as-prepared Fe\(_3\)O\(_4\)@UiO-66@WP6 with multi-stimuli responsive drug release ability under pathological environment. Notably, such a smart theranostic nanoplatform exhibited good biocompatibility, excellent T\(_2\)-weighted MRI ability (Figure 4D,E), and superior anticancer effect on HeLa cells. Interestingly, the presence of WP6 nanovalves enabled sustained drug release over 7 days, which demonstrated the effectiveness and tunability of supramolecular nanovalves in controllable drug release. This work provides a possibility for the application of MOF-based nanocomposites equipped with supramolecular nanovalves in the diagnosis and treatment of diseases.

More interestingly, Shi, Zaworotko, and co-workers reported a stable, biocompatible Gd(III) zeolite-like MOF, namely \([\text{Gd}_{48}(\text{NO})_{48}(\text{bpdc})_{48}]_x\cdot Gx\), (denoted as Gd-ZMOF, G = guest), to enhance proton relaxation and high temperature sensitivity for monitoring cancer treatment-induced rise in temperature by MRI.\(^{48}\) Gd-ZMOF, consisting of Gd\(^{3+}\) and 2,2′-bipyridine-6,6′-dicarboxylate (H\(_2\)bpdc) ligand, exhibited a monodispersed size of approximately 100 nm, which was
Figure 4 (A) Scheme of Fe (III)-based carboxylate MOFs for imaging. (B) $T_2$-weighted magnetic resonance images of gradient echo (1, 3, 4, 6) or spin echo (2, 5) sequence of Wistar female rats in the liver and spleen regions of the control group (left) and MIL-88A treatment group (right) after 30 min of administration. dm, dorsal muscle; k, kidney; li, liver; s, spleen; st, stomach. Reproduced with permission. Copyright 2009, Springer Nature. (C) Schematic description of the construction of Fe$_3$O$_4$@UiO-66@WP6 and the application for MRI and chemotherapy. (D) Magnetic hysteresis curves of Fe$_3$O$_4$ NPs (black) and 5-Fu-loaded Fe$_3$O$_4$@UiO-66@WP6 (red), and $T_2$-weighted transverse relaxivity of Fe$_3$O$_4$@UiO-66@WP6 with a series of Fe concentrations. (E) MRI images of Fe$_3$O$_4$@UiO-66@WP6 on HeLa cells. Reproduced with permission. Copyright 2018, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (F) Schematic of the preparation of MOFs-MB-DHA@PLA@PEG and its application for $T_2$-weighted MRI and cancer therapy. (G) In vivo MRI images of U14 tumor-bearing mice after injection of the MOFs composite at 0 (1), 3 (2), 9 (3), and 24 h (4). Reproduced with permission. Copyright 2019, American Chemical Society
suitable for MRI application. Meanwhile, the structural stability of Gd-ZMOF was evaluated by thermogravimetric analysis and density functional theory (DFT) calculation, which was beneficial to decrease the toxicity risk caused by the release of Gd\(^{3+}\) cation under physiological conditions. Biodistribution results showed that Gd-ZMOF initially accumulated in the liver, spleen, and lung after intravenous administration, and finally excreted from the body, indicating the safety of the applications in vivo. According to the T\(_1\)-weighted MRI images of 4T1 tumor-bearing mice, small temperature changes, especially in the thermal therapy range (41-45\(^\circ\)C), could be visually observed through the T\(_1\) relaxivity of Gd-ZMOF, indicating that the Gd-ZMOF could be used as a magnetic resonance thermometer to monitor the rise in temperature caused by tumor therapy. Furthermore, combined with the intrinsic porous structure of the Gd-ZMOF, such a nanoplatform could be used as a theranostic nanoplatform for tumor.

For another instance, Jiang, Zhang, and co-workers constructed a pH/enzyme dual-responsive small-sized MOF (denoted as MOFs-MB-DHA@PLA@PEG) for the diagnosis and treatment of U14 tumor-bearing mice guided by T\(_2\)-weighted MRI (Figure 4F).\(^{49}\) In this system, octahedral MIL-101(Fe) with a diameter of 100 nm, constructed from Fe\(^{3+}\) as nodes and benzene-1,4-dicarboxylic acid (H\(_2\)BDC) as organic linkers, was prepared as a nanocarrier to load the antitumor drug dihydroartemisinin (DHA) and the PS methylene blue with loading rates of 75.6% and 54.5%, respectively. In addition, polyactic acid and PEG were modified on the surface of MIL-101(Fe) to achieve pH/enzyme stimuli-responsive drug release, improved biocompatibility, reduced side effects, and enhanced hydrophilicity. In the tumor microenvironment, the Fe\(^{3+}\) released from the degradation of MIL-101(Fe) skeleton could catalyze the conversion of H\(_2\)O\(_2\) to O\(_2\) and enhance the cytotoxicity of DHA, improving the effect of chemotherapy and PDT. Furthermore, the MOFs-MB-DHA@PLA@PEG (160 \(\mu\)g/mice for intravenous injection) showed high T\(_2\)-weighted MRI effect on U14 tumor-bearing mice (Figure 4G), providing a new way for the diagnosis and treatment of tumors using MOF-based nanocomposites.

### 2.3 X-ray computed tomography imaging theranostic nanoplatforms

As one of the important strategies of clinical assistant examination, CT imaging with excellent spatial resolution and deep tissue penetration is a three-dimensional (3D) grayscale imaging reconstructed by the difference of X-ray attenuation among scanned tissues, providing a favorable basis for the visualization diagnosis of cancer.\(^{50}\) Currently, high atomic number elements, such as iodine, aurum, bismuth, and barium, are often used as small molecular CT contrast agents to increase the contrast effect between the target tissue and surrounding tissue.\(^{51}\) However, due to rapid clearance, extravasation from blood and lymphatic vessels, low targeting, and high dose requirements (tens of grams), the application of small molecular CT contrast agents are severely limited.\(^{52}\) Moreover, tissues with similar densities are difficult to distinguish in CT imaging.\(^{75}\) With the rapid development of strategies for MOFs synthesis and surface functionalization, MOF-based contrast agents can solve aforementioned problems, thus enhancing the effect of cancer therapy guided by CT imaging.

For instance, Zhang, Wang and co-workers synthesized a monodispersed iodine-boron-dipyromethene (BODIPY)-containing MOF, that is, UiO-PDT, for CT imaging in the rat orthotopic hepatoma model (Figure 5A).\(^{53}\) Octahedral UiO-PDT with a size of \(\approx 70\) nm was prepared by the ligand exchange of the diiodo-substituted monocarboxyl-modified BODIPY dyes and the ligands in UiO-66. After that, experimental studies indicated that UiO-PDT exhibited good biosafety and concentration-dependent X-ray attenuation effect, giving an attenuation value of 236 HU at the concentration of 40 mg/mL and \(R^2\) of 0.997 (Figure 5B). According to the CT imaging results in the rat orthotopic hepatoma model, UiO-PDT could preferentially accumulated in the tumor sites, rather than in the surrounding connective tissues and organs, and the contour between the tumor and the surrounding tissue was completely clear after 24 h of intravenous injection, achieving the best CT imaging effect. This work offers a possibility to construct MOFs with CT imaging ability for disease diagnosis and treatment.

In 2019, Han and co-workers structured a Janus nanocomposite based on Au nanorods (NRs) and ZIF-8, that is, LA-AuNR/ZIF-8, for CT imaging and synergistic chemo-photothermal therapy of H22 bearing BALB/c mice (Figure 5C).\(^{54}\) In this system, after interacting with polyacrylic acid, ZIF-8 was installed on the Au NRs, followed by the decoration of the targeting group lactobionic acid on the side surface to prepare LA-AuNR/ZIF-8 Janus. To assess the drug delivery ability of the system, DOX as a model drug was loaded into the LA-AuNR/ZIF-8 with a loading capacity of 30% and pH/NIR stimuli-responsive release behavior. Notably, due to the presence of Au NRs in the as-fabricated system, LA-AuNR/ZIF-8 showed a photothermal conversion efficiency of 33% and strong CT contrast, suggesting good PTT ability and CT imaging ability. Thus, LA-AuNR/ZIF-8 with good biocompatibility and dual stimuli-responsive drug release exhibited effective CT imaging-guided synergistic chemotherapy and PTT of liver cancer under NIR laser irradiation.

In the same year, Farha and co-workers reported a robust bismuth (Bi)-based MOF, namely Bi-NU-901, for CT imaging.\(^{55}\) Bi-NU-901 possessing a phase feature of microporous diamond-shaped 1D channels utilized
FIGURE 5  (A) Schematic diagram of the fabrication of UiO-PDT and its application for CT imaging in rat orthotopic hepatoma model. (B) Relations between CT values of UiO-PDT and its different concentration. Reproduced with permission.53 Copyright 2017, The Royal Society of Chemistry. Schematic of the preparation of (C) LA-AuNR/ZIF-8 and its application for CT imaging-guided tumor treatment; Reproduced with permission.54 Copyright 2019, The Royal Society of Chemistry. (D) HUC-PEG and its application for CT imaging and PTT and PDT of tumor. (E) In vivo CT images of U14 tumor-bearing mice preinjection (i-iv) and after (v-viii) injection of HUC-PEG. Reproduced with permission.57 Copyright 2020, Elsevier Ltd
[Bi$_6$O$_4$(OH)$_3$(NO$_3$)$_9$(H$_2$O)](H$_2$O) as metal nodes and tetratopic 1,3,5,8-(p-benzoate)pyrene (H$_4$TBAPy) as ligands in the architecture of its skeleton. Meanwhile, from the results of nitrogen adsorption-desorption isotherms and density functional theory, the surface area, and pore size of Bi-NU-901 were calculated as 320 m$^2$/g and $\approx$ 11 Å, respectively. In vitro results showed that Bi-NU-901 possessed approximately seven times and $\approx$ 14 times better contrast intensity than the Zr-MOF with the same topology and the commercially available CT contrast agent iodoxanol, respectively. In addition, the strong stability of Bi-NU-901 in phosphate-buffered saline makes it possible for further in vivo applications. Nevertheless, the sizes, charges, morphologies, and surface functionalization (such as targeting groups) of the MOF also need to be further optimized to meet the requirements in vivo.

For another instance, Meng, Zhang, Huang, and co-workers developed a biocompatible MOF-based nanocomposite via a simple one-pot method for CT imaging-guided synergistic microwave thermal therapy and chemotherapy of tumor.$^{56}$ In this system, ZIF-8 NPs consisting of Zn$^{2+}$ and 2-methylimidazolate (2-H-MeIM) ligands, was used to cover the ZrO$_2$ shell after loading anticancer drug DOX, followed by the decoration of ionic liquid (IL) in the intrinsic pores of ZIF-8 to form ZIF-8/DOX@ZrO$_2$@IL with an average hydrodynamic size of 306.2 nm. Both in vitro and in vivo toxicity evaluation results demonstrated that ZIF-8@ZrO$_2$ showed low toxicity to L929 cells and mice due to the encapsulation of the ZrO$_2$ shell. Considering the good microwave responsiveness of IL, the microwave thermal effect of ZIF-8/DOX@ZrO$_2$@IL nanocomposites had been proven to work under microwave irradiation. Moreover, ZIF-8/DOX@ZrO$_2$@IL exhibited excellent CT imaging effect due to the high relative atomic number of Zr atoms in the ZrO$_2$ shell. Such a nanoplatform showed excellent CT imaging effect and enhanced anticancer effect by synergistic microwave thermal therapy and chemotherapy in the H22 tumor-bearing mice.

Recently, Xie, Wang, and co-workers constructed a stable core-shell structure nanocomposite integrating two types of porous materials by a self-template strategy, namely HUC-PEG, for CT imaging-guided PTT and PDT of tumor (Figure 5D).$^{57}$ HUC-PEG with a diameter of 179 nm was prepared via growing terephthalaldehyde, tetrakis (4-aminophenyl)-21H,23H-chlorin (TAPC), and NH$_2$-PEG on the surface of Hf-Uio-AM template. Owing to the coating of the PEG, HUC-PEG demonstrated good biocompatibility, enhanced clathrin-mediated cellular internalization, and high intratumor accumulation. Importantly, under 671 nm light irradiation, HUC-PEG exhibited a stable and superior photothermal conversion efficiency of 41% according to the photothermal property studies, providing prominent superiorities for PTT. Moreover, the interface effects between the core-shell structures showed improved photon utilization efficiency, increased the generation of $^{1}$O$_2$, and boosted thermal effects, enhancing the therapeutic effect of PTT and PDT. Furthermore, the excellent CT imaging effect of HUC-PEG had been proven through in vivo and in vitro experiments (Figure 5E). This work provides a feasible reference for improving the theranostic performance of MOF-based nanocomposite through interfacial effects.

### 2.4 | Positron emission tomography imaging theranostic nanoplatforms

PET imaging is a nuclear medicine imaging technology that applies the disintegration of positron-emitting nuclide to visualize the metabolic processes in the body.$^{13a}$ Compared with other imaging technologies, PET imaging exhibits the advantages of deep penetration, small dose requirements, high sensitivity, and strong quantitative abilities.$^{58}$ In general, PET imaging contrast agents contain $^{11}$C, $^{13}$N, $^{15}$O, $^{18}$F, $^{64}$Cu, $^{68}$Ga, and $^{89}$Zr, however, they often face some problems such as short half-life and poor specificity during clinical diagnosis.$^{5,7a}$ Fortunately, numerous MOF-based contrast agents were designed to enhance PET imaging effect due to the diverse ion compositions, high cargo loading, and easy functionalization capabilities.

For example, Liu and coworkers reported a sized-controlled theranostic nanohybrid (AZIF-8) using a rapid, facile and completely aqueous approach for PET imaging-guided tumor chemotherapy.$^{59}$ Spherical amorphous AZIF-8 with uniform diameters from 30 to 150 nm was precisely synthesized through the competitive coordination property of non-toxic polypropyleneamine hydrochloride (PAH) as a modulator (Figure 6a). Subsequently, DOX-loaded AZIF-8 with different diameters was obtained by simply adding DOX during the construction of AZIF-8 and exhibited similar physicochemical properties, providing advantages for assessing their size-dependent biological features. Interestingly, the authors found that the cellular uptake, intracellular drug release, and pharmacokinetics behavior were correlated with the size of DOX-loaded AZIF-8. Specifically, the 60 nm material exhibited the largest cellular/tumor uptake and prolonged blood circulation, and the smallest size DOX-loaded AZIF-8 showed the fastest drug release behavior. In addition, in vivo antitumor studies indicated that 60 nm DOX@AZIF-8 exhibited significant PET imaging effect (Figure 6b), high tumor accumulation, good biosafety and improved therapeutic efficacy in the 4T1 tumor-bearing mice, providing new possibilities to develop optimal size of MOFs for cancer theranostics.

Recently, Chen, Wang, and coworkers fabricated a nanoscale polymer-wrapped MOFs with strong physiological stability by a in situ polymerization strategy for controllable drug delivery (Figure 6c).$^{60}$ Various MOFs including
FIGURE 6  (A) TEM images of AZIF-8 NPs with different PAHs at room temperature. 0, 0.1, 0.5, 1, 2, and 4 in the images represent the molar ratio of PAHs/Zn$^{2+}$ during preparation process. (B) PET images of 4T1 tumor-bearing mice after injection of 60 nm/130 nm $^{64}$Cu-DOX@AZIF-8 at different points of time. Reproduced with permission.$^{59}$ Copyright 2018, American Chemical Society. Preparation strategy of (C) polymer-wrapped MOFs and (D) $^{64}$Cu-labeled polymer-wrapped Zr-MOF. (E) In vivo PET images at different time points after treatment. Reproduced with permission.$^{60}$ Copyright 2019, Elsevier Ltd
zirconium-based porphyrinic MOF (Zr-MOF), MIL-101(Fe), ZIF-8, and UiO-66, were selected to anchor bis[2-(methylacryloyloxy)ethyl] phosphate (BMAP) ligands and polymer coating formed by different monomers (such as N,N’-bis(acyryloyl) cystamine, acrylic acid, poly(ethylene glycol) diacrylate, fluorescein dimethacrylate, and poly(ethylene glycol) methacrylate) on the surface to obtain polymer-wrapped MOFs. Transmission electron microscopy (TEM) images showed that polymer-wrapped MOFs possessed significantly enhanced stability in phosphate buffered saline and cell culture medium RPMI-1640 compared with original MOFs. Meanwhile, the stability of polymer-wrapped MOFs was also related to the type of monomers coated on the surface. After coordination with $^{64}$Cu (Figure 6d), Zr-MOFs exhibited good PET imaging effect in A431 tumor-bearing mice. Importantly, compared to $^{64}$Cu-labelled Zr-MOF, $^{64}$Cu-labelled polymer-wrapped Zr-MOF achieved prolonged circulation and significant tumor accumulation in the tumor region due to the EPR effect (Figure 6e). The intrinsic loading capacity of MOFs allowed them to be used as theranostic nanoplatforms for PET imaging-guided disease treatment.

2.5 | Photoacoustic imaging theranostic nanoplaforms

PA, a unique noninvasive and nonionizing medical imaging detection technology, is formed by biological tissues absorbing pulsed laser to generate PA signals, which provides an important tool for the study of the morphological structures, pathological characteristics, and metabolic functions of targeting tissues. It is particularly suitable for the early diagnosis and treatment monitoring of cancer. Like other imaging technologies, MOFs are employed to achieve high imaging quality and enhanced therapeutic effect.

For example, Zhang, Liang, Li, and co-workers reported a biomimetic O$_2$-evolving MOF-based nanocomposite called O$_2$@UiO-66@ICG@RBC for PA imaging and PDT of hypoxic tumors. In this design, after modifying PS indocyanine green (ICG) via coordination reaction, biocompatible UiO-66, composed of Zr$^{4+}$ and terephthalic acid ligands, was applied to store O$_2$, followed by the modification of red blood cell (RBC) membranes to generate O$_2$@UiO-66@ICG@RBC with immune escape property because of the immunomodulatory proteins of RBC membranes. Moreover, owing to the photothermal response of ICG and the thermal instability of the RBC membranes, the initial O$_2$ produced by ICG could decompose the RBC membranes and remotely trigger the burst release of O$_2$ from UiO-66 pores under laser irradiation. It was worth noting that the elevated O$_2$ content in tumor sites given O$_2$@UiO-66@ICG@RBC strong PA imaging and enhanced PDT capabilities in vivo, providing a new perception to design MOF-based nanocomposite for the treatment of hypoxic tumors.

Recently, Dong, Yang, Meng, and co-workers synthesized a versatile bacteriochlorin-based MOF nanoshells consisting of H$_2$(μ$_3$-O)$_4$(μ$_3$-OH)$_4$ as metal nodes and 5,15-di(ρ-benzoato) bacteriochlorin (H$_2$DBBC) as ligands, namely DBBC-Uio, for PA imaging and PDT of hypoxic tumors (Figure 7A). DBBC-Uio nanoshell with a size of $\approx$ 220 nm in length and $\approx$ 4.6 nm in thickness exhibited good stability and strong NIR absorption peak at 754 nm, providing an enormous potential for PDT in deeper tumor tissues. Experimental results indicated that DBBC-Uio could not only act as PS to generate $^1$O$_2$ under NIR laser irradiation in a suitable O$_2$ microenvironment through type II mechanism of PDT, but also could generated numerous superoxide anion radical (•O$_2^-$) using type I mechanism of PDT in severe hypoxia microenvironment under NIR laser irradiation. Meanwhile, the produced •O$_2^-$ could be used as a cytotoxic anion radical to induce tumor cell apoptosis, and could also be converted into H$_2$O$_2$ and highly toxic hydroxyl radical (•OH) through the intracellular superoxide dismutase (SOD)-mediated disproportionation, thus promoting tumor apoptosis. Importantly, such a system exhibited good bio-compatibility, favorable PA imaging ability, and significant tumor growth inhibition effect in the MCF-7 tumor-bearing mice (Figure 7B,C), providing new opportunities for PDT of hypoxic solid tumor using MOF-based nanoplatforms.

Tian and co-workers reported a positive feedback MOF-based nanoamplifier for PA imaging-guided synergistic chemodynamic therapy (CDT), PTT, and starving therapy of tumor (Figure 7D). MIL-100 consisting of Fe$^{3+}$ and 1,3,5-benzenetricarboxylic acid (BTC) ligands was used to encapsulate GOx, followed by the modification of polydopamine-hyaluronic acid (HA-PDA) layer to develop MGH nanoamplifier. The accumulation of as-prepared MGH nanoamplifier at tumor sites could trigger Fenton-like/ enzymatic cascaded reaction, improving the levels of H$^+$, H$_2$O$_2$, and O$_2$ for self-enhanced chemodynamic and starving therapy and improved PA imaging of tumor (Figure 7E). Besides, the HA-PDA layer endowed MGH nanoamplifier with enhanced stability, sustainable GOx release, and photothermal effect, triggering non-toxic PDT of tumor. In vivo studies demonstrated that such a theranostic nanoplatform exhibited improved tumor accumulation, negligible side effects, and satisfactory therapeutic effect in 4T1 tumor-bearing mice (Figure 7F).

Very recently, Lin, Cheng, and co-workers designed a remote-controlled yolk–shell nanohybrid based on Au nanostar as yolk and ZIF-8 as shell, that is, Au@MOF-DOX, for PA/thermal imaging and synergistic chemo-photothermal therapy. Au nanostar with strong absorption ability in the NIR-II region was encapsulated into ZIF-8 to form 200 nm Au@MOF with photothermal conversion efficiencies of 30.2% for 808 nm and 48.5% for 1064 nm. Subsequently,
DOX was loaded into the pores of Au@MOF, indicating a high loading ratio of 29% and controlled drug release behavior. In vitro experimental results showed that Au@MOF-DOX had enhanced cytotoxic effect under 1064 nm NIR laser irradiation. Furthermore, Au@MOF-DOX displayed efficient tumor accumulation, outstanding PA/thermal imaging and preeminent tumor ablation effects in H22 tumor-bearing mice according to the in vivo results obtained in the literature.

3 | MOF-BASED MULTIMODAL IMAGING THERANOSTIC NANOPLATFORMS

As mentioned previously, monomodal imaging theranostics, including OI, MRI, CT imaging, PET imaging, and PA imaging, exhibited individual strengths during cancer diagnosis and treatment. For example, OI has the outstanding
advantages of facile operation, good sensitivity, and high resolution, but suffers from the drawbacks of low tissue penetration and poor anatomical resolution. MRI exhibited the superiorities of noninvasiveness, high spatial resolution, and deep tissue penetration, while lacks high sensitivity. CT imaging possessing excellent spatial resolution and deep tissue penetration, low soft tissue resolution defects limit its further application. PET imaging with deep penetration, small dose requirements, high sensitivity, and strong quantitative abilities showed the deficiencies of short half-life and high operational risk. PA imaging displays the features of noninvasiveness, satisfactory sensitivity, strong penetration, and high resolution, but still faces small image sizes and limited insufficient pixels (Table 2). Moreover, monomodal imaging strategies cannot reflect comprehensive pathological information, which seriously weaken the effectiveness of imaging technologies in disease diagnosis. Incorporating multiple monomodal imaging strategies and various treatments into one system for diagnosis and treatment of cancer is an exciting new opportunity. Remarkably, multimodal imaging theranostics superimposed by two or more monomodal imaging strategies, integrate the superiorities, and circumvent the limitations of monomodal imaging strategies, providing comprehensive information for cancer theranostics. Therefore, the development of multimodal imaging MOFs theranostic nanoplatforms is conducive to the precise cancer therapy (Table 3).

### 3.1 Bimodal imaging theranostic nanoplatforms

In 2015, Tang, Chen, Liu, and co-workers synthesized a PEG-functionalized core-shell theranostic nanostructure based on rare-earth-doped NaYF4:Yb,Er upconversion nanoparticles (UCNPs) core and Fe-MIL-101-NH2 shell, that is, UMP-FAs, for the treatment of KB tumor-bearing mice guided by upconversion luminescence (UCL) imaging and T2-weighted MRI. The Fe-MIL-101-NH2 shell with an octahedral morphology was coated on the hexagonal core of the Yb- and Er-doped NaYF4 UCNPs to form UCNP@Fe-MIL-101-NH2, followed by the modification of PEG-FAs conjugates as outermost layer, thus improving the biocompatibility, stability, and targeting of the obtained UMP-FAs (Figure 8A). Moreover, with the increase of Fe3+ concentration, the intensity of MRI signal gradually turned darker and was positively correlated with the concentration of Fe3+, indicating that the UMP-FAs could be applied as a contrast agent for T2-weighted MRI. Biocompatibility of UMP-FAs on the human oral squamous carcinoma cells was proved by MTT assay. Furthermore, after intravenous administration of UMP-FA for 24 h, the UCL intensity was almost 10 times higher than that of the control group (Figure 8B), and the MRI intensity at tumor site in KB tumor-bearing mice was darkened by ≈ 35% (Figure 8C), indicating high sensitivity of UCL imaging and MRI of UMP-FA in the tumor region. Such a core-shell nanocomposite integrating the advantages of both UCNPs and MOFs showed broad application prospects in multimodal imaging-guided solid tumors treatment.

Chen, Wang, Guo, and co-workers designed a multifunctional core-shell theranostic nanocomposite, that is, PB@MIL-100(Fe), consisting of Prussian blue nanocubes (PB NCs) core and MIL-100(Fe) shell, to achieve FL imaging and T1/T2-weighted MRI bimodal-guided synergetic chemotherapy and PTT (Figure 8D). Cubic-shaped PB NCs with a uniform diameter of 90 nm was coated by the biodegradable MIL-100(Fe) shell with a thickness of ≈ 50 nm via a layer-by-layer strategy. PB NCs could be used not only as imaging agent for T1/T2 bimodal MRI and FL, but also as photothermal agent for PTT. Simultaneously, MIL-100(Fe) could serve as T2-weighted MRI contrast agent and drug reservoir for loading hydrophobic anticancer drug artemisinin with a high loading capacity of 848.4 mg/g, which was attributed to the Fe3+ and high porosity of the MOF shell, respectively. In vivo experiments demonstrated that PB@MIL-100(Fe) possessed the ability of imaging-guided synergistic PTT and chemotherapy, improving the therapeutic effect in HeLa tumor-bearing mice model under NIR laser irradiation (Figure 8E,F). Subsequently, they reported another core-shell structured nanoplatorm consisting of carbon dots using Fe3O4 nanospheres as core and MIL-100(Fe) as shell for

| Imaging strategy | Advantages | Disadvantages |
|------------------|------------|--------------|
| OI | Facile operation, good sensitivity, high resolution | Low tissue penetration, poor anatomical resolution |
| MRI | Noninvasiveness, high spatial resolution, deep tissue penetration | Low sensitivity |
| CT | Excellent spatial resolution, deep tissue penetration | Low soft tissue resolution |
| PET | Deep penetration, small dose requirements, high sensitivity, strong quantitative abilities | Short half-life, high operational risk |
| PA | Noninvasiveness, satisfactory sensitivity, strong penetration, and high resolution | Small image sizes and limited insufficient pixels |
two-photon FL imaging- and T₂-weighted MRI-guided cancer chemotherapy.⁷¹ In this system, Fe₃O₄@C@MIL-100(Fe) was employed to simultaneously release the hydrophobic drug DHA encapsulated in the pores and Fe³⁺ produced by the degradation of MIL-100(Fe) shell in the tumor site, and then, the obtained Fe³⁺ was reduced to Fe²⁺ and interacted with DHA to generate toxic reactive oxygen species (ROS), resulting in cell apoptosis. In vivo studies indicated that the as-fabricated nanoplateform showed good imaging-guided tumor theranoistic effect and high biocompatibility to the major organs. Similarly, a distinctive core-shell MOF-based nanotheranostic structure, composed of PB NCs core and ZIF-8 shell, for achieving pH and NIR laser stimuli-responsive drug release, high biocompatibility, and multimodal imaging-guided visual tumor diagnosis and treatment was also reported by their group, and the effectiveness of this system was verified by in vitro and in vivo experiments.⁷² Taken together, these works provide a new direction to construct multifunctional disease theranostic systems by integrating the advantages of various functional materials.

In addition, Damirin, Liu, and co-workers reported a multifunctional tumor targeting nanocomposite with FL imaging, MRI and controlled drug release by a facile postsynthetic surface modification method for cancer diagnosis and therapy.⁷³ In this system, Fe₃O₄@C@MIL-100(Fe) was treated with T₂-weighted MRI ability to load pyrimidine analogue 5-Fu with high loading efficiency of 28%. In order to endow the nanocomposite with active targeting and FL imaging capabilities, the targeting group FA and FL agent 5-FAM were decorated on the surface of 5-Fu-loaded Fe₃O₄@C@MIL-100(Fe) as an outer layer through an amidation reaction to yield Fe₃O₄@C@MIL-100(Fe)-FA-5-FAM/5-FU. Importantly, the obtained nanocomposite showed satisfactory T₂-weighted MRI ability with a high relaxivity values of 18.8 mM/s and outstanding FL imaging effect. Meanwhile, good biocompatibility, favorable cellular uptake, and strong tumor therapeutic effect of this system had also been proven through a series of in vitro and in vivo experiment including MTT assay, cellular uptake study, and biodistribution studies, suggesting the strong possibility of Fe-based MOF in tumor diagnosis and treatment.

Interestingly, Hong and co-workers designed and prepared an intrinsically radioactive theranostic nanoplateform integrating FL, and PET imaging, that is, ⁸⁹Zr-Uio-66/Py-PEG-F3, for the treatment of triple-negative breast tumors

| MOFs | MOFs skeleton components | Imaging strategy | Therapeutic option | Animal model | Administration method | Reference |
|------|-----------------------------|------------------|-------------------|--------------|----------------------|----------|
| UMP-FAs | Fe³⁺, NH₂-BDC | UCL, MRI | - | KB tumor-bearing mice | Intravenous administration | 69 |
| PB@MIL-100(Fe) | Fe³⁺, H₂BTC | FL, MRI | Chemotherapy, PTT | HeLa tumor-bearing mice | Intravenous administration | 70 |
| Fe₃O₄@C@MIL-100(Fe) | Fe³⁺, H₂BTC | FL, MRI | Chemotherapy, PTT | HeLa tumor-bearing mice | Intravenous administration | 71 |
| CSD-MOFs@DOX | Zn²⁺, 2-H-MelM | FL, MRI | Chemotherapy, PTT | HeLa tumor-bearing mice | Intravenous administration | 72 |
| Fe-MIL-53-NH₂-FA-5-FAM/5-FU | Fe³⁺, NH₂-H₂BDC | FL, MRI | Chemotherapy | Athymic nude mice bearing glioblastoma | Intratumoral injection | 73 |
| ⁸⁹Zr-Uio-66/Py-PEG-F3 | Zr⁴⁺, BDC, benzoic acid | PET, FL | Chemotherapy | MDA-MB-231 tumor-bearing mice | Intrapertitoneal injection | 74 |
| Mn(III)-TCPP MOF | Mn³⁺, TCPP | FL, MRI | PDT | 4T1 tumor-bearing mice | Intravenous administration | 75 |
| Fe₃O₄@PAA/AuNCs/ZIF-8 NPs | Zn²⁺, 2-H-MelM | FL, MRI, CT | Chemotherapy | Mice with viable H22 ascites tumors | Subcutaneous injection | 76 |
| Au@MIL-88(Fe) | Fe³⁺, fumaric acid | CT, PA, MRI | - | U87 tumor-bearing mice | Intravenous administration | 77 |
| MOF@HA@ICG | Fe³⁺, H₂BTC | FL, MRI, PA | PTT | MCF-7 tumor-bearing mice | Intravenous administration | 78 |
| NPs@ZIF-8@Au NR-DOX | Zn²⁺, 2-H-MelM | OI, CT, PA | Chemotherapy, PTT | HeLa tumor-bearing mice | Intravenous administration | 79 |
| Gd/Yb-MOFs-Glu | Gd/Yb, BBDC | FL, MRI, CT | Chemotherapy | HeLa tumor-bearing mice | Intravenous administration | 80 |
| Cypane@MIL-53/PEG-Tf | Fe³⁺, NH₂-H₂BDC, cyanine | FL, MRI, PA | PTT, PDT | A549 tumor-bearing mice | Intravenous administration | 81 |
FIGURE 8  (A) Synthetic route to UMP-FAs. (B) FL images of KB tumor-bearing mice and major organs of the mice sacrificed 24 h after intravenous injection of targeted (left) and nontargeted (right) nanoplatorms. 1–6 represent heart, kidney, lung, liver, spleen, and tumor.  (C) T₂-weighted magnetic resonance images of KB tumor-bearing mice after injection of targeted (left) and nontargeted (right) nanoplatorms at 24 h. Reproduced with permission.69 Copyright 2015, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (D) Schematic of the fabrication of PB@MIL-100(Fe) and its application in FL imaging and T₁/T₂-weighted MRI bimodal-guided synergetic chemotherapy and PTT. (E) T₁- and (F) T₂-weighted MRI of tumor at 0 h, 10 min, 30 min, and 24 h after injection of PB@MIL-100(Fe). Reproduced with permission.70 Copyright 2016, Elsevier Ltd

(Figure 9A).74 After loading of DOX, ⁸⁹Zr-UiO-66 with intrinsic radioactivity, composed of Zr⁴⁺ as metal nodes and BDC and benzoic acid as ligand linkers, was decorated by pyrene-derived polyethylene glycol (Py-PGA-PEG) and F₃ peptide (KDEPQRRSARLSAKPAPPKPEPKPKKAKKKAK) to enhance the stability and active targeting of the resulting ⁸⁹Zr-UiO-66/Py-PGA-PEG-F₃ with a diameter of 250 nm. Notably, DOX with high loading capacity of 1 mg DOX/mg Uio-66, could serve as both anticancer drug for tumor chemotherapy and as fluorescent agent for FL imaging. In addition, the long and stable half-life advantage of ⁸⁹Zr (t₁/₂ = 78.4 h) could be used to monitor the distribution and clearance process of ⁸⁹Zr-UiO-66/Py-PGA-PEG-F₃ for up to 120 h after intraperitoneal injection in MDA-MB-231 tumor-bearing mice (Figure 9B). In vivo experimental results indicated that ⁸⁹Zr-UiO-66/Py-PGA-PEG-F₃ could serve as a biocompatible and stable drug delivery system for PET, FL imaging, and visualized tumor therapy.

Recently, Zhang and co-workers designed a multifunctional fusiform-like “inert” Mn(III)-sealed MOF theranostic nanoplatform, that is, Mn(III)-TCPP MOF, consisting of Mn₃⁺ nodes and TCPP ligands via a one-pot reaction, for T₁-weighted MRI and FL imaging and PDT of tumor via controllable ROS generation and GSH depletion (Figure 9C).75 3D structured spindle-shaped Mn(III)-sealed MOFs with good monodispersity and stability showed a uniform size of ≈ 170 × 50 × 100 nm. Owing to the strong quenching effect of Mn(III) on TCPP-based fluorescence and ROS generation, the Mn(III)-sealed MOFs showed an “inert” theranostic effect. However, at the pathologic environment of high GSH-expressed tumor, GSH could react with Mn(III)-sealed MOF scaffold to decompose it into Mn(II) and free TCPP.
FIGURE 9  (A) Schematic diagram of the preparation route and the crystal structure of $^{89}$Zr-Uio-66/Py-PGA-PEG-F3. (B) PET images of mice after injection of various agents at 0.5, 2, 24, 72, and 120 h. Reproduced with permission. Copyright 2017, American Chemical Society. (C) Schematic illustration of Mn(III)-sealed MOFs for MRI and FL imaging in cancer theranostics. (D) FL images and (E) T1-weighted magnetic resonance images of tumor sites after injection of Mn(III)-sealed MOFs at different time. (F) MRI and (G) FL images of mice after injection of Mn(III)-sealed MOFs at different time. Reproduced with permission. Copyright 2019, American Chemical Society.
ligands, which could cause the continuous TCPP ligands release, GSH depletion, and activation of TCPP-based FL and Mn(II)-based MRI. In vivo studies demonstrated that Mn(II)-sealed MOF possessed negligible side effects, enhanced $T_1$-weighted MRI/FL imaging effect (Figure 9D-G), and significant tumor growth inhibition induced by PDT on 4T1 tumor-bearing mice.

### 3.2 Trimodal imaging theranostic nanoplatorms

Wang, Li, and co-workers reported a smart theranostic nanocomposite combining FL imaging, MRI, and CT imaging strategies and stimuli-responsive drug release behavior for multimodal imaging-guided cancer diagnosis and treatment. Under ultrasonic condition, polyacrylic acid was coated on the surface of cetyltrimethylammonium bromide modified Fe$_3$O$_4$ NPs to produce Fe$_3$O$_4$@PAA, then, GSH capped Au nanoclusters (Au NCs) were introduced to the aforementioned system, followed by the growth of ZIF-8, resulting in the smart Fe$_3$O$_4$@PAA/AuNCs/ZIF-8 NPs with a diameter of $\approx 130$ nm. Subsequently, DOX as a model anticancer drug, was encapsulated into the as-prepared nanocomposite with a high loading capacity of 1.54 g/g and showed dual pH-responsive (pH 7.4 and 5.3) controlled drug release behaviors. Subsequently, in vitro results demonstrated that the CT and $T_2$-weighted MRI signals were changed with the increase of the concentration of Fe$_3$O$_4$@PAA/AuNCs/ZIF-8 NPs in HepG-2 cells, indicating that Fe$_3$O$_4$@PAA/AuNCs/ZIF-8 NPs could be applied as a promising candidate for CT imaging and MRI. Meanwhile, the fluorescence property in this system was $\approx 2.5$ times higher than that of discrete Au NCs under the same conditions, which was attributed to the aggregation effect of isopropanol and Zn$^{2+}$ on Au NCs. Furthermore, in vivo anticancer studies confirmed the theranostic ability of Fe$_3$O$_4$@PAA/AuNCs/ZIF-8 NPs for cancer diagnosis and chemotherapy through $T_2$-weighted MRI, FL imaging, and CT imaging.

Subsequently, Shang et al reported a multifunctional NMOFs composite via microemulsion method, that is, Au@MIL-88(Fe), for glioma treatment guided by CT imaging, MRI, and PAI imaging. The core-shell Au@MIL-88(Fe) with an average diameter $\approx 89$ nm was constructed by coating Au NRs into MIL-88(Fe) inner, followed by the decoration of PEG corona. Owing to the strong CT enhancement and PAI features of Au NRs and MRI effect of MIL-88(Fe), the as-prepared nanocomposite possessed high contrast abilities in CT, $T_2$-weighted MRI, and PAI. Such a nanoplatorm showed improved imaging sensitivity, high penetration depth, and spatial resolution in glioma. Moreover, high porosities and large surface areas of MIL-88(Fe) shell endowed Au@MIL-88(Fe) with high anticancer drug loading features, making it suitable for multimodal imaging and treatment in cancer theranostics.

For another instance, Liu and co-workers reported a versatile nanocomposite based on ICG-loaded MIL-100(Fe) and hyaluronic acid (HA) coating combing FL imaging, $T_2$-weighted MRI, and PA imaging strategies and PTT method, that is, MOF@HA@ICG, for tumor diagnosis and treatment in MCF-7 tumor-bearing mice (Figure 10A). MIL-100(Fe), consisting of Fe$^{3+}$ and 1,3,5-benzenetricaboxyllic acid (H$_3$BTC) ligands, was employed to encapsulate the hydrophobic NIR organic dye ICG with a high loading capacity of 40%, and exhibited MRI and PAI effects for the MOF@HA@ICG system. Meanwhile, ICG could be used as photothermal and FL agents for PTT and FL imaging. Furthermore, HA, a targeting group recognized by CD44, was coated on the surface of MOF as an outermost layer to enhance the stability and cellular uptake by CD44-positive MCF-7 cells. Both in vitro and in vivo studies demonstrated that such a MOF@HA@ICG nanoplatform combined with FL-, PA-, MRI imaging-guided PTT exhibited negligible toxicity and excellent therapeutic effect on MCF-7 tumor-bearing mice (Figure 10B-D), paving a way for the application of MOF-based nanotheranostic system in multimodal imaging-guided solid tumor therapy.

Interestingly, Kuang and co-workers reported a multifunctional heterodimer based on ZIF-8 and multiple NPs, namely NPs@ZIF-8@Au NR-DOX, for OA, CT, and PA imaging and cancer therapy by chemotherapy and PTT in HeLa tumor-bearing mice (Figure 10E). NPs@ZIF-8@Au NR-DOX bearing a diameter of $\approx 140$ nm was fabricated as carriers to load DOX, Ag$_2$S, Ag$_2$Se, or UCNPs in ZIF-8 and Au NR@PEG on the surface, which could release drugs and nanoplatforms continuously under acidic conditions due to the degradability of ZIF-8. In vivo studies showed that such a heterodimer possessed outstanding OA (Figure 10F-G), PA (Figure 10H), and CT imaging (Figure 10I) capabilities and complete tumor elimination effect without obvious side effects through synergetic PTT and chemotherapy under 808 nm laser irradiation, providing an effective reference for tumor cure (Figure 10J).

Recently, Yin, Sun, and co-workers reported an intelligent nanoscale theranostic MOF composite with good biocompatibility, active tumor targeting, stimuli-responsive drug release, and FL-, $T_1$-weighted MRI-, and CT imaging-guided visualized tumor diagnosis and precise chemotherapy (Figure 11A). Gd-NMOF, constructed from Gd$^{3+}$ and 5-boronobenzene-1,3-dicarboxylic acid (BBDC) as ligands was applied to encapsulate DOX with a loading efficiency of 43.2%, and then, the glucose layer was facilely modified on the surface of Gd-NMOF by reversible diol-borate condensation to develop biocompatible DOX@Mofs-Glu. The glucose layer on the surface of DOX@Mofs-Glu enhanced...
the active targeting ability on tumor cells through the direct interaction of glucose-glucose transported protein, and possessed pH-responsive controllable drug release of DOX via diol-borate gatekeepers. Both in vitro and in vivo experimental results indicated that this system possessed active targeting ability, and multimodal imaging to guide precise chemotherapy (Figure 11B,C). Importantly, the preparation strategy of this nanocomposite could be easily extended for the preparation of other similar nanoplatforms, such as Yb-MOF-Glu, for gastrointestinal tract CT imaging and targeted drug delivery (Figure 11D), which opens a new avenue to fabricate smart theranostic nanoplateform for multimodal imaging-guided precision treatment of diseases.

Very recently, Yang and co-workers designed a smart defective MOFs by a simple one-pot method, namely cypate@MIL-53/PEG-Tf, for FL imaging, MRI, and PA imaging and cancer therapy using PTT and PDT (Figure 11E). In this system, after the addition of organic NIR
cyanine dye into Fe^{3+}, H_2BDC as ligands was introduced to the mixture to form cypate@MIL-53, then, PEG and transferrin (Tf) were immobilized on the surface of cypate@MIL-53 to achieve good biocompatibility and active targeting ability. Meanwhile, owing to the presence of NIR cyanine dye, the obtained nanoplatfor exhibited excellent photothermal conversion effect, photostability, and ROS generation. According to the in vivo studies, cypate@MIL-53/PEG-Tf group showed high FL signals at the tumor region, which was attributed to the EPR effect (passive targeting) and Tf receptor-mediated cellular uptake of cancer cells (active targeting) (Figure 11F). Furthermore, high PA imaging and T_1-weighted MRI abilities was also observed in A549 tumor-bearing mice (Figure 11G-H). Importantly, tumor phototherapy based on PTT and PDT results demonstrated that the tumor was completely eliminated without obvious side effects, which provides a new avenue to develop smart defect MOFs for multimodal imaging-guided precise cancer theranostics.
CONCLUSION AND PERSPECTIVE

In summary, we have summarized the recent advanced developments and achievements of MOFs as multifunctional theranostic platforms in cancer diagnosis and treatment guided by monomodal imaging technologies, containing OI, MRI, CT imaging, PET imaging, and PA imaging, and multimodal imaging technologies. By integrating both imaging technologies and treatment strategies in one system, imaging-guided precise theranostic platforms based on MOFs are developed to achieve both diagnosis and treatment of tumors at the same time. To date, numerous excellent MOFs platforms have been fabricated to meet the growing special demands during cancer theranostics. As mentioned before, MOFs as smart theranostic platforms mainly rely on the unique features of diverse compositions, tailorable sizes, high surface areas and pores, strong loading capacities, easy surface modification, and degradability. Moreover, MOF-based theranostic platforms combining multimodal imaging and synergistic multiple treatment strategies have achieved important research progress in tumor diagnosis and treatment, which demonstrate the effectiveness and operability of MOFs in cancer theranostics.

Although significant progress has been obtained in laboratory research, MOFs still face serious challenges in diagnosis and treatment of cancer, which limit the further applications in clinic. First, the toxicity and biosafety of MOFs are key issues that need to be studied before clinical application. The toxicity of MOFs is closely related to their compositions, sizes, stabilities, and physicochemical properties because of the diversity of species of MOFs. Meanwhile, the tolerance of different living tissues of the body should also be considered. Therefore, a comprehensive evaluation of the toxicity of various MOFs is necessary. Many excellent studies on the toxicity of MOFs currently reported mainly focused on acute toxicity and short-term toxicity, but less studies on long-term toxicity, which requires numerous in vivo and long-term tissue accumulation studies. In addition, MOFs consisting of highly biocompatible metal ions (ie, Zn, Fe, Ca, Zr, etc) as metal nodes and endogenous molecules as organic ligands can effectively reduce their intrinsic toxicity.

Second, due to the complexities and diversities of cancer, it is necessary to develop intelligent and versatile MOFs theranostic systems to achieve precise cancer treatment. Importantly, there are significant differences between animal tumor models and actual human tumors. Many MOFs theranostic platforms exhibited outstanding antitumor capabilities in animal model, but the therapeutic effect on actual human tumors still needs comprehensive evaluation. Moreover, although currently reported active targeting ligands can partly improve the internalization abilities of tumor cells to carriers, it is still urgent to study exclusive targeting ligands that only recognize tumor cells to achieve efficient tumor clearance without side effects on normal cells. Fortunately, various functional groups on the surface of MOFs, such as -NH₂, -COOH, -N₃, ensure easy functionalization of targeting entities.

Finally, the degradation mechanisms of MOFs during metabolism process in vivo also require to be analyzed in depth to further guarantee the biosafety in cancer diagnosis and treatment. Owing to the imaging features of MOF theranostic platforms, the degradation process of MOFs can be monitored through imaging strategies, which suffers from the defects of unpredictable degradation and large space-time restriction. Therefore, the continuous accumulation of MOFs in tissues caused by multiple administrations needs to be investigated reliably and comprehensively by monitoring the long-term absorption-distribution-metabolism-excretion processes. As aforementioned, MOF-based theranostic platforms – from monomodal imaging-guided single treatment to multimodal imaging-guided multiple treatments – have made significant progress in the last decade. With the rapid development of imaging technologies and cancer treatment strategies, future work may focus on the construction of nontoxic, exclusive MOFs to achieve specific tumors clearance. As outlined in Table 2, monomodal imaging technologies possess different advantages and disadvantages. Multimodal imaging technologies that combine various advantages of monomodal imaging have drawn much attention in cancer theranostics. Moreover, the development of new imaging technologies with more superiorities by scientists will also provide a favorable guarantee for the fabrication of advanced MOF-based theranostic platforms. In short, although MOFs as theranostics in clinic still face long-term challenges, significant progress has been made. Thanks to the unique properties of MOFs that can be precisely tailored, we strongly believe that MOFs will be widely used in clinical applications in the future.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. a) R. L. Siegel, K. D. Miller, A. Jemal, Ca-Cancer J. Clin. 2020, 70, 7; b) X. Huang, Y. Liu, B. Yung, Y. Xiong, X. Chen, ACS Nano 2017, 11, 5238; c) A. S. Thakor, S. S. Gambhir, Ca-Cancer J. Clin. 2013, 63, 395.
2. Y. Cai, Z. Wei, C. Song, C. Tang, W. Han, X. Dong, Chem. Soc. Rev. 2019, 48, 22.
3. M. A. Chowdhury, *ChemBioEng Rev.* 2017, 4, 225.
4. S.-K. Sun, H.-F. Wang, X.-P. Yan, *Acc. Chem. Res.* 2018, 51, 1131.
5. X. Deng, J. Rong, L. Wang, N. Vasdev, L. Zhang, L. Josephson, S. H. Liang, *Angew. Chem., Int. Ed.* 2019, 58, 2580.
6. T. Zhao, A. E. Desjardins, S. Ourselin, T. Vercauteren, W. Xia, *Photoacoustics* 2019, 16, 100146.
7. a) V. Kumar, D. Kukkar, B. Hashemi, K.-H. Kim, A. Deep, *Adv. Funct. Mater.* 2019, 29, 1807859; b) M. Gervering, K. Herrmann, A. Helfen, C. Schliemann, W. E. Berdel, M. Eisenblätter, M. Wildgruber, *Nat. Rev. Clin. Oncol.* 2019, 16, 442.
8. a) C. Holohan, S. Van Schaeybroeck, D. B. Longley, P. G. Johnston, *Nat. Rev. Cancer* 2013, 13, 714; b) W. Q. Lin, G. Yang, S. Z. F. Phua, H. Chen, Y. Zhao, *ACS Appl. Mater. Interfaces* 2019, 11, 16391; c) J. Yang, D. Dai, X. Lou, L. Ma, B. Wang, Y.-W. Yang, *THERANOSTICS* 2020, 10, 615.
9. G. Song, L. Cheng, Y. Chao, K. Yang, Z. Liu, *Adv. Mater.* 2017, 29, 1700996.
10. J. Nam, S. Son, K. S. Park, W. Zou, L. D. Shea, J. J. Moon, *Nat. Rev. Mater.* 2019, 4, 398.
11. a) W. Fan, B. Yung, P. Huang, X. Chen, *Chem. Rev.* 2017, 117, 13566; b) M. Lismont, L. Dreesen, S. Wuttke, *Adv. Funct. Mater.* 2017, 27, 1606314.
12. a) L. Cheng, X. Wang, F. Gong, T. Liu, Z. Liu, *Adv. Mater.* 2019, 31, 1902333; b) J.-N. Liu, W. Bu, J. Shi, *Chem. Rev.* 2017, 117, 6160; c) N. Song, X.-Y. Lou, L. Ma, H. Gao, Y.-W. Yang, *Theranostics* 2019, 9, 3075.
13. a) W. Sun, S. Li, G. Tang, Y. Luo, S. Ma, S. Ma, S. J. Ren, Y. Gong, C. Xie, *Int. J. Nanomed.* 2020, 14, 10195; b) T. Kang, F. Li, S. Baik, W. Shao, D. Ling, T. Hyeon, *Biomaterials* 2017, 136, 98; c) S. M. Cohen, *Chem. Rev.* 2012, 112, 970; d) R. Vankayala, K. C. Hwang, *Adv. Mater.* 2018, 30, 1706320.
14. T. Sun, Y. S. Zhang, B. Pang, D. C. Hyun, M. Yang, Y. Xia, *Angew. Chem., Int. Ed.* 2014, 53, 12320.
15. a) H. Furukawa, O. M. Yaghi, *J. Am. Chem. Soc.* 2009, 131, 8875; b) S. Li, F. Huo, *Nanoscale* 2015, 7, 7482.
16. a) J. Wu, X. Wang, Q. Wang, Z. Lou, S. Li, Y. Zhu, L. Qin, H. Wei, *Chem. Soc. Rev.* 2019, 48, 1004; b) H. An, M. Li, J. Gao, Z. Zhang, S. Ma, Y. Chen, *Coord. Chem. Rev.* 2019, 384, 90; c) R. J. Drout, L. Robison, O. K. Farha, *Coord. Chem. Rev.* 2019, 381, 151.
17. D. I. Osman, S. M. EL-Shiekh, S. M. Sheta, O. I. Ali, A. M. Salem, W. G. Shousha, S. F. EL-Khamisy, S. M. Shawky, *Biosens. Bioelectron.* 2019, 141, 111451.
18. R. Medishetty, J. K. Zarbea, D. Mayer, M. Samoc, R. A. Fischer, *Chem. Soc. Rev.* 2017, 46, 4976.
19. a) H. Furukawa, K. E. Cordova, M. O. Keeffe, O. M. Yaghi, *Science* 2013, 341, 1230444; b) H.-C. Zhou, J. R. Long, O. M. Yaghi, *Chem. Rev.* 2012, 112, 673; c) A. C. McKinlay, R. E. Morris, P. Horcajada, G. Férey, R. Gref, P. Couvreur, C. Serre, *Angew. Chem., Int. Ed.* 2010, 49, 6260; d) S. Wang, C. M. McGuirk, A. d’Aquino, J. A. Mason, A. C. Mirkin, *Adv. Mater.* 2018, 30, 1800202; e) J. Yang, Y.-W. Yang, *Small* 2020, 16, 1906846.
20. a) Y. Wang, J. Yan, N. Wen, H. Xiong, S. Cai, Q. He, Y. Hu, D. Peng, Z. Liu, Y. Liu, *Biomaterials* 2019, 230, 119619; b) M.-X. Wu, Y.-W. Yang, *Adv. Mater.* 2017, 29, 1606134; c) S. Beg, M. Rahman, A. Jain, S. Saini, P. Midoux, C. Pichon, F. J. Ahmad, S. Akhter, *Drug Discovery Today* 2017, 22, 625; d) W. Cai, J. Wang, M. Chiu, W. Chen, C. Wu, G. Liu, *Adv. Sci.* 2019, 6, 1801526; e) C. Carrillo-Carrion, *Anal. Bioanal. Chem.* 2020, 412, 37; f) S. Begum, Z. Hassan, S. Bräse, C. Wöll, M. Tsotsalas, *Acc. Chem. Res.* 2019, 52, 1598; g) C.-Y. Sun, C. Qin, X.-L. Wang, Z.-M. Su, *Expert Opin. Drug Deliv.* 2013, 10, 89.
10.1002/anie.201909880; c) M. D. Allendorf, C. A. Bauer, R. K. Bhakta, R. J. Houk, Chem. Soc. Rev. 2009, 38, 1330.

33. S. Zhu, R. Tian, A. L. Antaris, X. Chen, H. Dai, Adv. Mater. 2019, 31, 1900321.

34. W. Liu, Y.-M. Wang, Y.-H. Li, S.-J. Cai, X.-Y. Yin, X.-W. He, Y.-K. Zhang, Small 2017, 13, 1603459.

35. S.-Y. Li, H. Cheng, B.-R. Xie, W.-X. Qiu, J.-Y. Zeng, C.-X. Li, S.-S. Wan, L. Zhang, W.-L. Liu, X.-Z. Zhang, ACS Nano 2017, 11, 7006.

36. S.-Y. Li, B.-R. Xie, H. Cheng, C.-X. Li, M.-K. Zhang, W.-X. Qiu, W.-L. Liu, X.-S. Wang, X.-Z. Zhang, Biomaterials 2018, 151, 1.

37. X. Gao, R. Cui, G. Ji, Z. Liu, Nanoscale 2018, 10, 6205.

38. J. Liu, T. Liu, P. Du, L. Zhang, J. Lei, Angew. Chem., Int. Ed. 2019, 58, 7808.

39. Y. Li, K. Zhang, P. Liu, M. Chen, Y. Zhong, Q. Ye, M. Q. Wei, H. Zhao, Z. Tang, Adv. Mater. 2019, 31, 1901570.

40. Y. Wang, W. Wu, J. Liu, P. N. Manghnani, F. Hu, D. Ma, C. Teh, B. Wang, B. Liu, ACS Nano 2019, 13, 6879.

41. M. A. Chowdhury, J. Biomed. Mater. Res., Part A 2017, 105, 1184.

42. a) W. Cai, C.-C. Chu, G. Liu, Y. X.-J. Wang, Small 2015, 11, 4806; b) K. Zhu, Y. Ju, J. Xu, Z. Yang, S. Gao, Y. Hou, Acc. Chem. Res. 2018, 51, 404.

43. Z. Zhou, L. Yang, J. Gao, X. Chen, Adv. Mater. 2019, 31, 1804567.

44. M. Peller, K. Böll, A. Zimpel, S. Wuttke, Inorg. Chem. Front. 2018, 5, 1760.

45. P. Horcajada, T. Chalati, C. Serre, B. Gillet, C. Sebrée, 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, R. Gref, Nat. Mater. 2010, 9, 172.

46. S. Sene, M. T. Marcos-Almaraz, N. Menguy, J. Scola, J. Volatron, R. Rouland, J.-M. Grenèche, S. Miraux, C. Menet, N. Guilhou, F. Gazeau, C. Serre, P. Horcajada, N. Steunou, Chem 2017, 3, 303.

47. M.-X. Wu, J. Gao, F. Wang, J. Yang, N. Song, X. Jin, P. Mi, J. Tian, J. Luo, F. Liang, Y.-W. Yang, Small 2018, 14, 1704440.

48. S.-Y. Zhang, Z.-Y. Wang, J. Gao, K. Wang, E. Gianolio, S. Aime, W. Shi, Z. Zhou, P. Cheng, M. J. Zaworotko, Chem 2019, 5, 1609.

49. C. Wang, X. Jia, W. Zhen, M. Zhang, X. Jiang, ACS Biomater. Sci. Eng. 2019, 5, 4435.

50. P. Horcajada, R. Gref, T. Baati, P. K. Allan, G. Maurin, P. Couvreur, G. Férey, R. E. Morris, C. Serre, Chem. Rev. 2012, 112, 1232.

51. H.-S. Wang, Coord. Chem. Rev. 2017, 349, 139.

52. J. D. Rocca, D. Liu, W. Lin, Acc. Chem. Res. 2011, 44, 957.

53. T. Zhang, L. Wang, C. Ma, W. Wang, J. Ding, S. Liu, X. Zhang, Z. Xie, J. Mater. Chem. B 2017, 5, 2330.

54. H. Zhang, Q. Zhang, C. Liu, B. Han, Biomater. Sci. 2019, 7, 696.

55. L. Robison, L. Zhang, R. J. Drout, P. Li, C. R. Haney, A. Brihka, H. Noh, B. L. Mehdi, N. D. Browning, V. P. Dravid, Q. Cui, T. Ismailoglu, O. K. Farha, ACS Appl. Bio Mater. 2019, 2, 1197.

56. L. Su, Q. Wu, L. Tan, Z. Huang, C. Fu, X. Ren, N. Xia, Z. Chen, X. Ma, X. Lan, Q. Zhang, X. Meng, ACS Appl. Mater. Interfaces 2019, 11, 10520.

57. X. Zheng, L. Wang, Y. Guan, Q. Pei, J. Jiang, Z. Xie, Biomaterials 2020, 235, 119792.

58. K. Lu, T. Aung, N. Guo, R. Weichselbaum, W. Lin, Adv. Mater. 2018, 30, 1707634.
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