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REVIEW

Advancements and Challenges in the Application of Metal-Organic Framework (MOF) Nanocomposites for Tumor Diagnosis and Treatment

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Abstract: Nanoscale metal-organic frameworks (MOFs) offer high biocompatibility, nanomaterial permeability, substantial specific surface area, and well-defined pores. These properties make MOFs valuable in biomedical applications, including biological targeting and drug delivery. They also play a critical role in tumor diagnosis and treatment, including tumor cell targeting, identification, imaging, and therapeutic methods such as drug delivery, photothermal effects, photodynamic therapy, and immunogenic cell death. The diversity of MOFs with different metal centers, organics, and surface modifications underscores their multifaceted contributions to tumor research and treatment. This review is a summary of these roles and mechanisms. The final section of this review summarizes the current state of the field and discusses prospects that may bring MOFs closer to pharmaceutical applications.

Keywords: metal-organic frame, oncotherapy, photothermal effect, tumor immunity, drug delivery

Introduction

Nanomaterials demonstrate potential in diverse sectors, particularly within biomedicine, enabling interdisciplinary partnerships across materials science, physics, and chemistry. Integrating biological materials has substantially enhanced our comprehension of crucial life processes, presenting an innovative platform to investigate complex biological phenomena and characterize their corresponding molecular pathways.[1–5] However, the complex intricacies of biomedicine pose a challenge for single-component organic and inorganic materials in terms of their biological functionality while ensuring biocompatibility,[6] as well as tackling concerns like cell or tissue toxicity.[7–9]

To tackle this issue, scientists have deliberately dispersed nanoscale organic and inorganic components throughout a polymer matrix, granting the composite material unique physical, chemical, and biological characteristics. The seminal 1989 study by Hoskins and Robson signaled the beginning of solid porous polymer materials.[13] Expanding on an innovative idea, Yaghi et al[14] produced an organic-inorganic hybrid substance featuring several pores, using the organic ligand BTC, and the transition metal ion Co^{2+}. This revolutionary product, known as an organic-metal structure, frequently incorporates metal ions or clusters that create a central metal core, alongside organic ligands. The structured pores and significant specific surface areas of these materials have gained considerable attention from the academic community. Researchers have, through the modulation of metal central nodes and associated organic ligands, yielded an array of MOFs with diverse structures and functions. This diversified class of MOFs includes but is not limited to UIO-

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66-Ce,[15,16] Isoreticular Metal-Organic Framework (IRMOF),[17,18] Materials of Institut Lavoisier (MIL),[19,20] Zeolitic imidazolate framework (ZIF),[21,22] Coordination Pillared-Layer (CPL),[23,24] and Porous Coordination Network (PCN).[25,26] The versatility of these MOFs is underpinned by the rich interplay of their structures and compositions. MOFs have various functionalities conferred by their diverse structures and compositions. They are currently utilized in several domains including nonlinear optics,[27,28] biochemical sensing,[29,30] catalysis,[31,32] biological targeting,[33,34] and drug delivery.[35–37] Particularly, MOFs have proven to be highly significant in the field of targeted drug delivery. The considerable benefits of their elevated specific surface area permit the entrapment of diverse anti-tumor and antibacterial agents. Additionally, methods of modifying the surface and other approaches bolster the biocompatibility and precision of the delivery system toward the targeted site, thus tempering possible damage to regular tissue cells.[38,39] The nanoscale dimensions of MOF materials enable them to bolster tissue penetration in tumor environments and augment drug bioavailability. As a result, they address the limitations associated with natural drug compounds, which are characterized by limited bioavailability and tissue penetration.[40] The use of nano-MOF materials in drug delivery, particularly in targeted therapies, has become a significant area of research. Researchers are constantly synthesizing and using a wide range of organic ligands, including multidentate ligands,[41,42] phenolic ligands,[43,44] and phosphorylated ligands,[45,46] by dispersing them within the appropriate matrices to produce nano-MOF materials[47–54](Figure 1).

Amid the rapid evolution of the global economy and the accelerating pace of daily life, the incidence and mortality of chronic diseases, particularly tumors, have risen relentlessly. Tumors have now taken over the mantle of the second most common disease category, behind cardiovascular diseases. In the early stages of these diseases, clinical manifestations are often imperceptible, facilitating their insidious progression from the primary site to the adjacent tissue environment. This progression is associated with a trajectory of heterogeneous evolution[55] and the establishment of an immunosuppressive tumor microenvironment,[56] thereby enhancing the malignancy of the neoplasm. In many cases, the tumor has spread to distant sites by the time overt symptoms appear, posing an existential threat to the individual.

As a result, researchers from a variety of scientific disciplines have embarked on a proactive quest to address the global conundrum posed by tumors. This collective endeavor hinges on two main dimensions: early detection of malignant tumors and precise, late-stage therapeutic intervention. MOF materials, with their aptitude for biological targeting, high biocompatibility, and skillful surface functionalization, have emerged as an outstanding modality in the fight against malignant tumors. This includes their prominent role in the early diagnosis of malignant tumors using biological imaging and fluorescence-based methods.

Subsequently, nano-MOF materials have gradually entered the field of tumor therapeutics, primarily through their key contribution to drug delivery systems. However, the adoption of simplistic approaches to anti-tumor drug delivery has led to multi-drug resistance, exacerbated by the evolutionary heterogeneity of tumor cells,[57] thereby diluting the therapeutic efficacy of drug delivery. To solve this challenge, researchers synthesized a variety of nanocomposites based on MOF materials, in which different metal centers and organic ligands were discovered, and more convenient and efficient MOF synthesis methods were developed. These innovations in methods also provide a research basis for studying the biological activity of MOFs in the future. For example, more and more researchers have modified the surface of MOFs in the synthesis process to improve the sensitivity and specificity of MOFs in tumor diagnosis and treatment in combination with different tumor-targeting or treatment mechanisms. These multifaceted composites encompass various therapeutic modalities, including photodynamic therapy,[58] photothermal effects[59] and immunogenic cell death within the scope of tumor treatment.[60–62] Such multi-dimensional interventions have the potential to improve prognosis and increase survival for affected individuals.

Given this, this review attempts to summarize the synthesis of MOFs, early diagnosis of tumors, targeted therapy, and intervention. To the best of our knowledge, existing scholarship, while embracing MOF materials within the broader biomedical spectrum, has often relegated the discourse on tumor diagnosis and treatment to a tangential annex within the biomedical ambit. Conspicuously absent from previous investigations is a systematic synthesis of early tumor diagnostics and the puzzles associated with such diagnostic strategies. This review attempts to fill this gap by providing a holistic panorama of the relevant facets of the field.

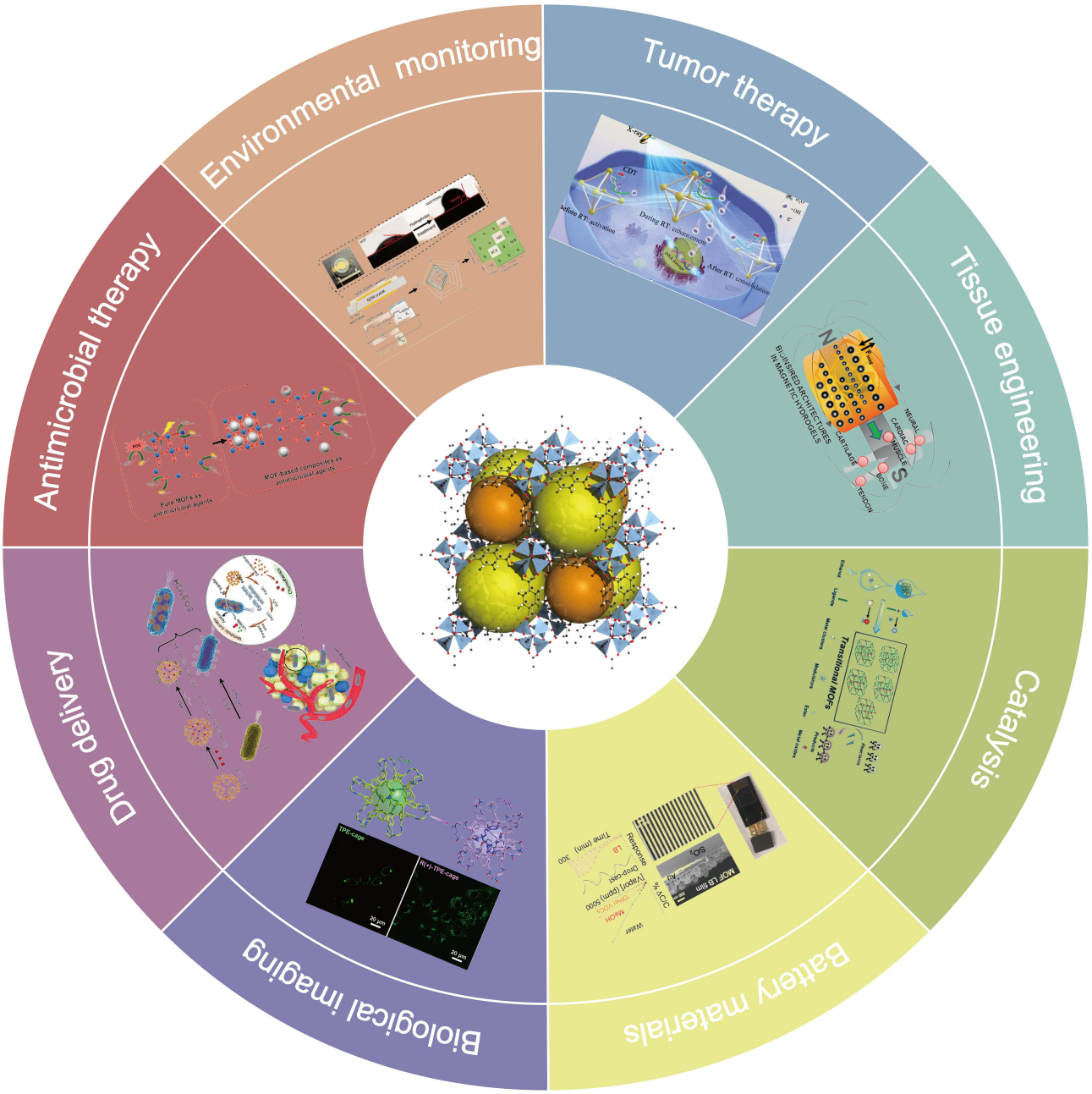

Figure 1 Schematic diagram of the application of MOF materials in different fields. Adapted from Cao, Y., Fu, M., Fan, S., Gao, C., Ma, Z., & Hou, D. Hydrophobic MOF/PDMS-Based QCM Sensors for VOCs Identification and Quantitative Detection in High-Humidity Environments. ACS *Appl Mat Inter.* 2024;16(6), 7721–7731. Copyright © 2024 American Chemical Society. Pardo, A., Gómez-Florit, M., Barbosa, S., Taboada, P., Domingues, R. M. A., & Gomes, M. E. (2021). Magnetic Nanocomposite Hydrogels for Tissue Engineering: Design Concepts and Remote Actuation Strategies to Control Cell Fate. *ACS nano*, 15(1), 175–209. Copyright © 2021 American Chemical Society. Andrés, M. A., Vijjapu, M. T., Surya, S. G., Shekhah, O., Salama, K. N., Serre, C., Eddaoudi, M., Roubeau, O., & Gascón, I. (2020). Methanol and Humidity Capacitive Sensors Based on Thin Films of MOF Nanoparticles. *ACS Appl Mater Interfaces*, 12(3), 4155–4162. Copyright © 2020 American Chemical Society. Wang, P., Li, X., Zhang, P., Zhang, X., Shen, Y., Zheng, B., Wu, J., Li, S., Fu, Y., Zhang, W., & Huo, F. (2020). Transitional MOFs: Exposing Metal Sites with Porosity for Enhancing Catalytic Reaction Performance. *ACS Appl Mater Interfaces*, 12(21), 23968–23975. Copyright © 2020 American Chemical Society. Dong J, Pan Y, Yang K, et al. Enhanced biological imaging via aggregation-induced emission active porous organic cages. *ACS nano.* 2022;16(2):2355–2368. Copyright © 2022 American Chemical Society. Wang JW, Chen QW, Luo GF, et al. A self-driven bioreactor based on bacterium-metal-organic framework biohybrids for boosting chemotherapy via cyclic lactate catabolism. *ACS nano.* 2021;15(11):17870–17884. Copyright © 2021 American Chemical Society. Li R, Chen T, Pan X. Metal–organic-framework-based materials for antimicrobial applications. *ACS Nano.* 2021;15(3):3808–3848. Copyright © 2021 American Chemical Society.[47–54]

Synthesis of Metal-Organic Frame Materials

The synthesis of MOFs encompasses various methods, each hailing from diverse scientific disciplines. Remarkably, identical MOFs can be produced through differing techniques, influencing their physical and chemical attributes, thus impacting their biomedical utility. This section provides a concise overview of common synthesis methods.

One-Pot Synthesis of the MOFs

The one-pot synthesis method usually dissolves the reaction precursors in the solvent and carries out the related synthesis reaction under stirring, Liu et al[63] used $ZrCl_4$ and H4btec to synthesize basic MOFs (UiO-66-(COOH)2) in the system of acetic acid as solvent, CuNCs@Tb@UiO-66-$(COOH)_2$ was synthesized on basic MOFs by a one-pot method to detect Cu^{2+} content in water samples, providing an effective platform for the detection of heavy metal ions. Qing Li et al[64] synthesized ZIF-8 using Zn $(NO_3)_2 \cdot 6H_2O$ and 2-MIM in a one-pot method, and in the same method synthesized GOD @ Cu-ZIF-8 in Zn $(NO_3)_2 \cdot 6H_2O$ and $Cu(NO_3)_2 4H_2O$ systems. These composite MOFs can break the tumor immunosuppressive microenvironment, stimulate covert antigen exposure, and in turn mediate the tumoricidal effect of CD8-positive T lymphocytes.

The main advantages of one-pot synthesis of MOFs are simple operation, low cost, and low requirements for experimental equipment, And the yield is also relatively large, Reagents can be continued during the reaction, Ensure the normal occurrence of reactions and the safety of the reaction system, However, the limitations of this method are also more obvious, Low purity of the synthesized MOFs, Tend to contain more magazines, Therefore, if high-precision synthetic MOFs are needed, MOFs are generally not selected, Meanwhile, the remaining material on the MOFs may disturb the downstream experimental validation, Therefore require a more careful determination of the characterization of the MOFs, To ensure the normal conduct of the downstream experiments for the.

Synthesis of MOFs by Hydrothermal Method

Hydrothermal method for the synthesis of MOFs is that the reaction mixture is in a relatively closed system using pressure or heat in a related synthesis, By mixing the reactants in an autoclave, the MOF nanomaterials were synthesized at a certain temperature. The MIL- 53 (Al) @ AC material was synthesized by hydrothermal method, to improve the thermal stability and chemical stability of the composite system, and finally improve the performance of the MIL-53 material. The results of FESEM, EDS, TEM, and XPS show that the composite MOF system has good porosity and drug-loading capacity, and has certain adsorption effects on most cephalosporin antibiotics[10](Figure 2). Huanxuan Li et al[65] using $FeCl_2.4H_2O$, Cu $(NO_3)_2.3H_2O$, and DHTA dissolved in a mixed solution of DMF and ethanol, And transferred the resulting mixture to a Teflon-lined stainless steel autoclave for synthetic FeCu-MOF, The bimetal MOF material can more effectively remove water from methylene blue waste than the monumental MOF material et al[66] mixed Zn $(NO_3)_2$ and H2BDC in DMF, MOF-5 by hydrothermal synthesis, and compared with the one-pot synthesis of MOF-5, the results

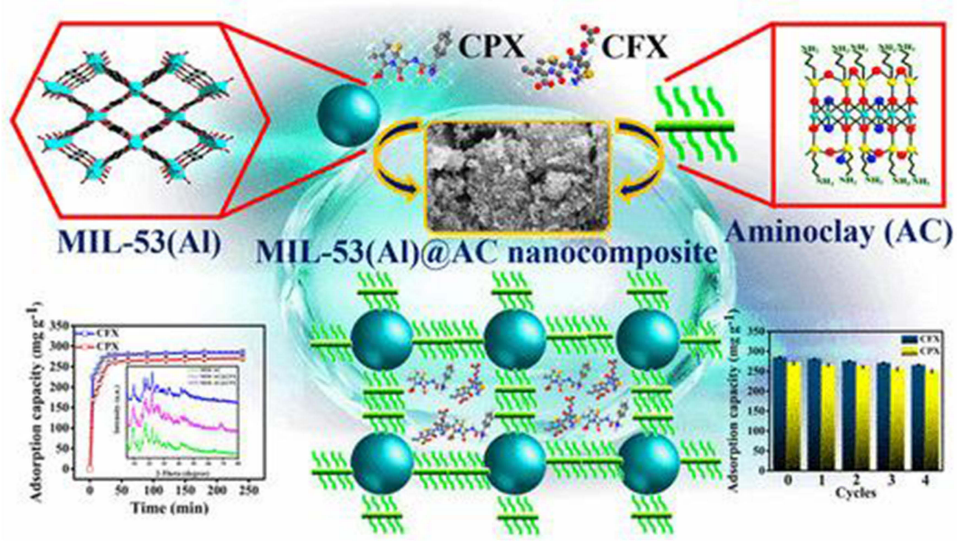

Figure 2 MIL-53 (Al)MOF schematic diagram of the manufacturing process. Reprinted with permission from Imanipoor J, Mohammadi M. Porous aluminum-based metal-organic framework-aminoclay nanocomposite: sustainable synthesis and ultrahigh sorption of cephalosporin antibiotics. *Langmuir.* 2022;38(18):5900–5914. Copyright 2022 American Chemical Society.[10]

show that hydrothermal synthesis of crystallinity is better than the one-pot synthesis, this is mainly because compared with the one-pot method, the hydrothermal method requires the reaction system under a certain high pressure, high-pressure reaction conditions are conducive to the solubility of the precursor material in the solvent to promote the occurrence of the reaction. Hydrothermal synthesis of MOFs has good thermal stability and crystallinity, at the same time the specific surface area of MOFs is higher than the pot synthesis of MOFs, making the biological application of the material and drug loading capacity better than other reaction methods of MOFs, but hydrothermal synthesis also has more expensive, poor controllability disadvantages, at the same time, unlike ideal, in the reality of artificial high-pressure system pressure value often change in the reaction process of tightening, and this uncertain pressure conditions may affect the performance of the product.[67]

Electrochemical Synthesis of MOFs

Electrochemical synthesis refers to the method of constructing MOF films on the matrix by electrooxidation or electro-reduction. Zhaowei Sun[68] synthesized Cu-MOF on the matrix surface by electrochemical deposition. Then, the modified electrode was immersed in HAuCl4 solution and AuNP reduction on the Cu-MOF surface at 0.5V, and a composite membrane of Au NPs / MOF was formed on the electrode. Ameloot[69] depends on the metal ions produced by the anode metal plate in the reaction, and metal ions on the matrix by electrochemical synthesis Cu-MOF, while the reaction conditions control variable study found that when the voltage in the range of 2.5V to 25V, the metal ion concentration in the system will gradually increase, and the higher concentration of the crystal formed on the matrix will be smaller, and if water is added in the reaction system, will hinder the formation of MOF, make the larger crystals on the matrix.

Method of electrochemical synthesis method is the main advantage of the simple operation process, fast reaction speed, and can adjust the reaction system voltage, and the concentration of metal ions to adjust the thickness of MOFs, but at the same time because the method depends on the electrochemical reaction, so can only build on conductive substrate MOF film, this disadvantage limits the wide application of electrochemical synthesis method.[70]

Application of NMOFs in Tumor Diagnosis

The imperative for accurate diagnostics of tumors underpins the treatment and monitoring strategies for oncological conditions. The quest for methods that are reliable, sensitive, rapid, and efficient for the detection of cancer biomarkers or live neoplastic cells cannot be overstated. Despite the utility of conventional imaging modalities, such as X-ray, computed tomography (CT),[71] magnetic resonance imaging (MRI),[72] positron emission tomography (PET),[73] PET-CT,[74] and photoacoustic imaging (PAI),[75] there remains a concerted effort to enhance these techniques. Innovations such as plasma resonance,[76] gel electrophoresis,[77] colorimetric assays,[78] and fluorescence detection[79] have been developed to discern tumorous tissues that manifest anomalous bioactive substance expression. While traditional methods offer direct macroscopic observation of tissues, these novel approaches aim to detect tumor-specific molecular expressions. However, each of these methodologies comes with its own set of constraints, which has propelled a substantial body of research towards the refinement of detection techniques. Within this research milieu, nanoporous metal-organic frameworks (NMOFs) have emerged as a material of significant promise in tumor diagnostic applications, owing to their multifaceted advantages. Subsequent sections will delineate the role of NMOFs in tumor diagnostics, addressing their utility in bioimaging.[80,81]. In the field of bioimaging, NMOFs play more of a developer role, with more powerful performance and targeting ability than conventional developers, or NMOFs with their own luminescence ability are directly involved in bioimaging. These development agents often enter the body through tail vein injection and enrich in the site of malignant tumor through corresponding targeting effects. These mechanisms are often related to the acidic microenvironment of tumor cells and the enrichment effect of tumor vascular space, and targeted diagnosis of malignant tumor combined with corresponding imaging methods.

Application of MOF Materials in Magnetic Resonance Imaging of Malignant Tumors

In the preceding decades, magnetic resonance imaging (MRI) has ascended to an indispensable role in clinical diagnostics, leveraging the fundamental principles of nuclear magnetic resonance.[82] MRI's non-invasive nature, coupled with its sub-millimeter spatial resolution, enables detailed anatomical visualizations and functional assessments without

compromising tissue integrity. The technique's superior tissue contrast and penetration depth render it particularly advantageous for tumor detection and treatment monitoring.[83]

The generation of MRI signals hinges on the nuclear magnetic resonance (NMR) signals of water protons within the tissue. Yet, the inherent signal contrast between pathologic and healthy tissues often falls short of lesion identification. Herein lies the utility of contrast agents, designed to modulate the relaxation times (T1 and T2) of water molecules in afflicted tissues, thus amplifying the delineation between normal and diseased states.[83] T1 is the longitudinal relaxation time and T2 is the transverse relaxation time. MRI analyzes the data by accepting the signal of relaxation and reveals a picture of the impact.[84] Due to the inherently low resolution of MRI, better imaging clarity often requires a large dose of developer Optimal MRI contrast agents typically embody paramagnetic or superparamagnetic properties, furnished by elements such as gadolinium (Gd), iron (Fe), and manganese (Mn). For enhancing T1-weighted images, paramagnetic metals like Gd and Mn are preferred, whereas superparamagnetic Fe is sought for T2-weighted enhancements. Consequently, NMOFs imbued with these metals present as prime candidates for constructing MRI contrast agents. Pioneering this avenue, Lin et al in 2006 identified a Gd-based MOF exhibiting a longitudinal relaxation rate surpassing that of contemporaneous commercial T1 agents, marking a significant stride in MRI enhancement.[85] Subsequent research proliferated, particularly focusing on Gd-based MOFs. For instance, Yin et al synthesized a novel Gd-Ru complex, which outperformed the commercial agent Gd-DTPA in MRI contrast efficiency.[86] However, the cytotoxicity associated with in vivo Gd^{3+} release necessitated alternative strategies, prompting a shift towards Mn-based MOFs. In 2008, Lin et al harnessed reverse-phase microemulsion techniques to produce manganese-containing NMOFs, achieving moderate T1 relaxation with controllable morphologies.[87] Despite the superior imaging capabilities of Gd^{3+}, MOFs as carriers for Mn^{2+} offered a platform for both in vivo and in vitro imaging applications. Evaluations of Mn^{2+}-based MOFs through MTT assays affirmed their biocompatibility; even at elevated concentrations, these MOFs exhibited negligible cytotoxicity in various cell lines over 24 to 48 hours.[88] Recently, Chen et al advanced this domain by developing Mn^{2+} haemoglobin-based MOFs, significantly enhancing both MRI imaging and therapeutic outcomes in tumor applications.[89] So far clinically approved MRI contrast agents (CAs) have not been investigated systematically for the visualization of loading and release from MOF NPs. Konstantin Böll studied the loading and release of six clinically recognised CAs from MOF MIL-100 (Fe) in a clinical MRI environment. Standard procedures from sample preparation to MRI methods were developed for this purpose. The results were reproduced and validated by inductively coupled plasma atomic emission spectrometry (ICP-AES) and thiocyanate testing. The macrocyclic CA gadoteric acid glucosamine was identified as the best candidate CA for labelling MIL-100 (iron).

Application of MOF Materials in Computed Tomography of Malignant Tumors

Computed tomography (CT) emerges as a non-invasive radiological technique that affords three-dimensional visualization of internal structures, distinguished by its high spatial and temporal resolution.[89] The operational principle of CT imaging resides in the differential attenuation of X-rays, which is augmented by contrast agents comprised of elements with high atomic numbers, yielding pronounced X-ray absorption capabilities; this group includes iodine, gold, barium, bismuth, and gadolinium. The challenge, however, Challenges are relatively homogeneous attenuation values for various tissues, high side effects and high cost of contrast media.[90] Currently, the contrast agents used in CT clinics are mainly based on elemental iodine preparations, which are often toxic or costly.[91]

To ameliorate this limitation, contrast agents harboring high atomic number elements, known for their potent X-ray attenuation, are employed to enhance the visualization of target tissues against adjacent structures.[92] MOFs that incorporate high Z-number metal cluster nodes, such as hafnium (Z=72) and zirconium (Z=40), have been engineered. These MOFs exploit the photoelectric effect, where Hf(IV) and Zr(IV) cations serve as efficient antennae, absorbing X-ray photons and subsequently emitting swift electrons.[93] Investigative studies by Lin et al assessed two NMOFs, Zr-uio and Hf-uio, for their utility as CT contrast agents, noting substantial metal content (37 wt% Zr and 57 wt% Hf) and consequent contrast enhancement.[93] Furthermore, the element gold (Au), with its eminent atomic number and superior X-ray attenuation coefficient, emerges as an exemplary candidate for CT contrast agents. Boyes et al innovated by amalgamating GdMOF nanoparticles with gold nanoparticles (AuNPs), crafting highly stable hybrid composites, with the

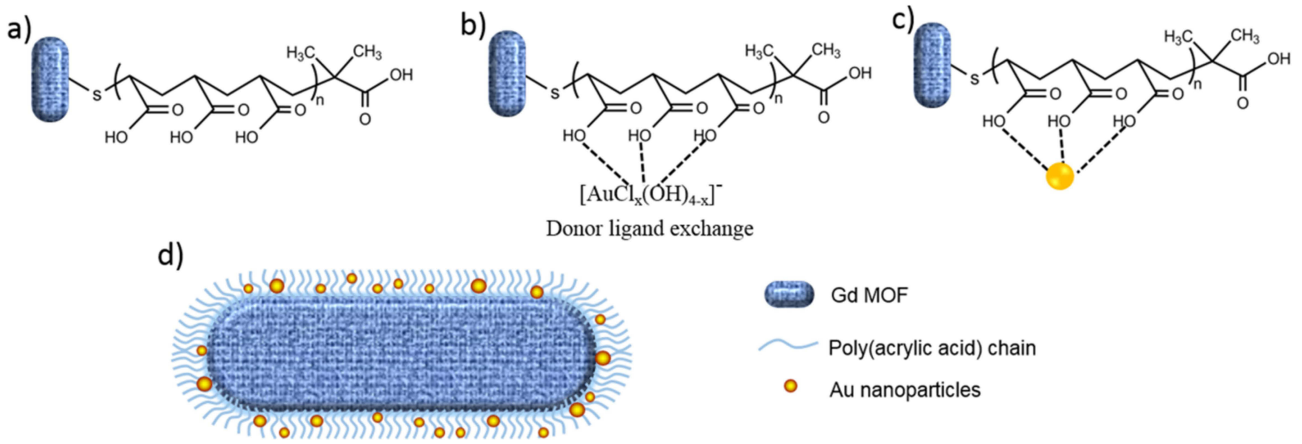

Figure 3 The synthetic strategy for fabricating hybrid GdMOF-PAA-Au nanostructures involves a sequential multi-step process: (**a**) the initial deposition of poly(acrylic acid) (PAA) onto the surface of gadolinium metal-organic framework (GdMOF) nanostructures, (**b**) the subsequent adsorption of gold (Au) ions onto the PAA-functionalized GdMOF nanostructures, and (**c**) the reduction of the Au ions, culminating in the formation of gold nanoparticles (AuNPs) firmly entrapped within the PAA matrix on the nanostructure's surface. (**d**) A schematic delineation of the hybrid nanostructure is presented, where the GdMOF core is depicted in blue, the entangled PAA chains in blue, and the incorporated AuNPs are illustrated in gold, demonstrating the complex's structural composition and the spatial distribution of its constituents. Reprinted with permission from Tian C, Zhu L, Lin F, Boyes SG. Poly(acrylic acid) Bridged gadolinium metal-organic framework-gold nanoparticle composites as contrast agents for computed tomography and magnetic resonance bimodal imaging. *ACS Appl Mater Inter.* 2015;7(32):17765–17775. Copyright 2015 American Chemical Society.[11]

synthesis intermediated by polyacrylic acid, as depicted in Figure 3 [11] When chelated with MOFs, gold demonstrates exceptional contrast enhancement, markedly outperforming conventional agents in efficacy.

In the advancement of computed tomography (CT) contrast agents, researchers have extended their investigations beyond the traditional high atomic number elements, exploring the potential of MOFs with integrated contrast-enhancing moieties. Xie et al developed a novel class of MOF nanocrystals, designated as UiO-PDT, which encapsulate iodine-boron-dipyrromethene (BODIPY) within their lattice. Comprehensive studies were undertaken to evaluate the biosafety and contrast efficacy of these nanocrystals, revealing no significant acute or subacute toxicity at injection doses up to 100 mg kg^(−1).[94] In vivo CT imaging demonstrated the preferential accumulation of UiO-PDT nanocrystals within the tumor sites of hepatoma-bearing rats, offering distinct delineation from surrounding connective tissues and organs. Concurrently, Farha et al pioneered the synthesis of a bismuth-based MOF, termed bismuth-NU-901 (Bi-NU-901), employing a hot solvent fabrication technique. Remarkably, in vitro assessments of Bi-NU-901 disclosed a sevenfold enhancement in contrast intensity relative to isoreticular zirconium MOFs, and a striking fourteenfold increase in contrast ratio in comparison to commercially available CT contrast agents, underscoring the potential of this novel bismuth MOF in CT imaging applications.[95]

In summary, most of the research on CT contrast agents has been limited to improving contrast performance, and there is a lack of research on reagent biosafety and cost control.

Application of MOF Materials in PET of Malignant Tumors

Positron emission tomography (PET) represents a sophisticated functional imaging modality that utilizes metabolically active substances labeled with ephemeral radionuclides for diagnostic imaging.[96] PET is distinguished by its superior detection sensitivity and deep signal penetration when compared to other imaging techniques. Nanoscale MOFs embedded with positron-emitting radioisotopes emerge as optimal agents for PET applications.[74,97]

The work of Hong et al introduced an nMOF complexed with the positron-emitting isotope zirconium-89 (^89Zr), specifically targeting MDA-MB-231 cells (triple-negative breast cancer cells, overexpressing nucleolin). Their construct, ^89Zr-UiO-66Py PGA-PEG-F3, exhibited robust radiochemical stability and retained material integrity within various biological media. PET scans facilitated the in vivo mapping of ^89Zr-UiO-66Py PGA-PEG-F3's biodistribution and enabled the detection of 8.2±0.3% of the total injected dose per gram of tumor tissue at 2 hours post intravenous administration. Complementing this, Liu et al reported on a different MOF system for PET, employing the radioisotope copper-64 (^64Cu) and the framework ZIF-8, noting an enhancement in biosafety profiles. Their findings also highlighted

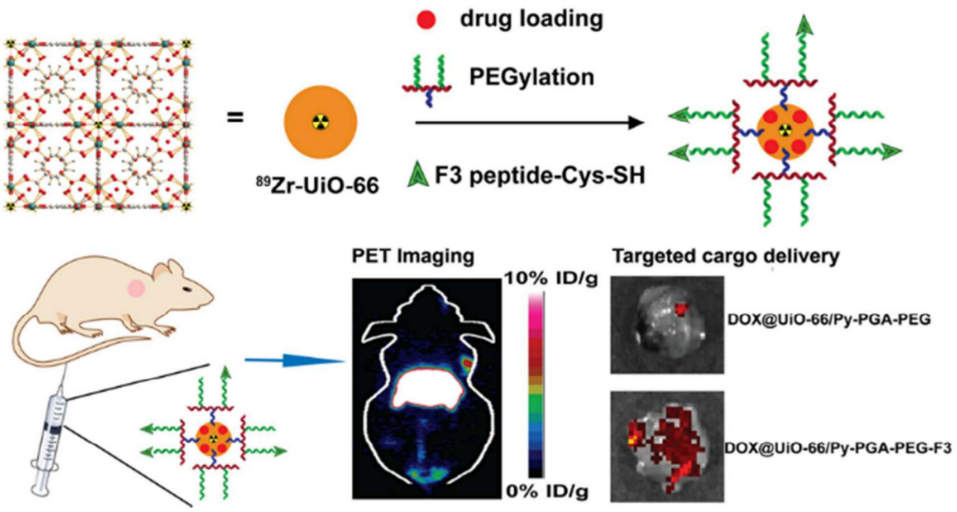

Figure 4 89Zr-Uio-66 for the treatment of tumors and PET imaging. Reprinted with permission from Duan D, Liu H, Xu M, et al. Size-controlled synthesis of drug-loaded zeolitic imidazolate framework in aqueous solution and size effect on their cancer theranostics in vivo. ACS Appl Mater Inter. 2018;10(49):42165–42174. Copyright © 2018 American Chemical Society.[12]

a correlation between nanoparticle size and diagnostic or therapeutic efficacy; smaller nanoparticles yielded improved imaging resolution, whereas larger counterparts were more effective in tumor treatment[12] (Figure 4).

Application of MOF Materials in PAI of Malignant Tumors

Photoacoustic imaging (PAI) represents an emergent, non-ionizing biomedical imaging modality, capitalizing on the photoacoustic effect inherent in light absorbers.[98] The technique synergistically marries the superior selectivity of optical imaging with the extensive penetration capabilities of ultrasound, thereby transcending the limitations imposed by light scattering and extending the boundaries of high-resolution optical imaging.[98]

Contrast agents commonly used in PAI include: organic dye molecular contrast agents, noble metal contrast agents, carbon nanomaterial contrast agents, and metal oxides. The recent deployment of NMOFs as PAI contrast agents has been propelled by their desirable characteristics: expansive porosity, adjustable pore dimensions, copious metal coordination sites, and substantial capacity for guest molecule accommodation. These traits facilitate their engineering as dual-function agents, adept in both PAI contrast and therapeutic delivery. Initially, scientists tried using common biological dyes in combination with MOFs, and achieved superior shared properties by exploiting the high loading properties of MOFs. Illustratively, Chen et al crafted multifunctional MOF nanoparticles employing MIL-100 (Fe) for PAI-directed concurrent chemo- and photothermal therapy.[99] Their methodology encompassed the use of polydopamine (PDA)-coated curcumin iron-based MOF to enhance colloidal robustness and biocompatibility, thereby bolstering PAI and photothermal conversion efficiencies. Further, the nanocomposites were modified with hyaluronic acid (HA)-linked PDA to selectively engage CD44-overexpressing tumor cells, culminating in an integrated approach for PAI facilitation and photothermal treatment. Complementarily, Yuan et al constructed a novel metal-organic nanotherapeutic, Cu-THQNPs, by coordinating tetrahydroxyanthraquinone (THQ), an organic dye, with $Cu^{\wedge 2+}$ ions, which serves as a dual-mode agent for PAI-guided photothermal/chemotherapy within the NIR-II window (1000 to 1350 nm).[100] This material exhibited exemplary photothermal attributes and PAI efficacy in the NIR-II regime. Furthering this innovation, He et al engineered a nanoscale porphyrin-palladium MOF (Pd-MOF), interspersed with finely distributed Pd atoms, capable of transporting potent reducing agents such as hydrogen, making it suitable for PAI-steered hydrothermal tumor therapy. The Pd-MOF demonstrated formidable efficacy in tumor-targeted hydrogen delivery, endorsing its utility in therapeutic applications.[101]

Application of MOF Materials in Fluorescence Imaging of Malignant Tumors

Fluorescence bioimaging stands as a distinguished technique, predicated on the excitation of fluorophores through photon absorption at discrete wavelengths, followed by photon emission at longer, higher-energy wavelengths.[102] However, the

method grapples with challenges in quantifying fluorescence intensity within biological entities, encumbered by auto-fluorescence, tissue signal attenuation, and inadequate light penetration in superficial tissues. Such challenges have spurred intense research into fluorescent materials to bolster optical imaging, particularly for deep tissue and intracellular applications.[103]

Advancements in this domain have been notably marked by the advent of luminescent MOFs, lauded over the past two decades for attributes including substantial payload capacities, tunable surface chemistries for enhanced pharmacokinetics, and variable sizes and structures.[104] Research has yielded a plethora of MOF constructs with luminescent capabilities, ranging from those incorporating fluorescent dyes or drugs to those intrinsically luminescent. Lanthanide-incorporated MOFs have elicited considerable interest due to their precise and stable emission, pronounced Stokes shifts, protracted fluorescence lifetimes, and the capacity for improved spectral and temporal differentiation from background auto-fluorescence.[105] Indocyanine green (ICG) is the only organic fluorophore in the near-infrared region (NIR) approved by FDA for medical application. However, the poor water solubility, insufficient fluorescence imaging specificity and sensitivity to tumor limit its clinical application in cancer diagnosis. A novel stratagem reported by Wuttke et al involves the encapsulation of fluorescein within lipid-coated MOFs,[106] producing MOF@lipid nanoparticles that harmonize the virtues of liposomes with porous entities, safeguarding dye molecules within MOF cavities while mitigating premature release and enhancing colloidal stability. In vivo trials have shown these fluorescein-laden nanoparticles to concentrate within T24 human bladder cancer cells, exhibiting potent emission profiles.

Furthermore, fluorescence imaging efficacy has been augmented through specialized tactics such as aggregation-induced emission and quenching. Liu et al engineered a biocompatible nanoscale zirconium porphyrin MOF (NPMOF) that leveraged high porphyrin loading for efficacious fluorescence imaging and therapy guidance.[107] In the burgeoning sphere of biological imaging sensors, DNA-based intracellular systems have made significant headway. Gao et al introduced a groundbreaking photo-activated locomotion mechanism over gold nanoparticle surfaces, triggered by photolysis, which reduces the pre-activation requisites in vivo. The mechanism encompasses enveloping nanoparticles within a dissociable ZIF-8 MOF, facilitating the autonomous pinpointing of target DNA sequences. The experimental data underscore the composite nano-system's precision and specificity in microRNA-21 identification, heralding a versatile paradigm for fluorescence-based tumor cell sensing and imaging[108] (Figure 5).

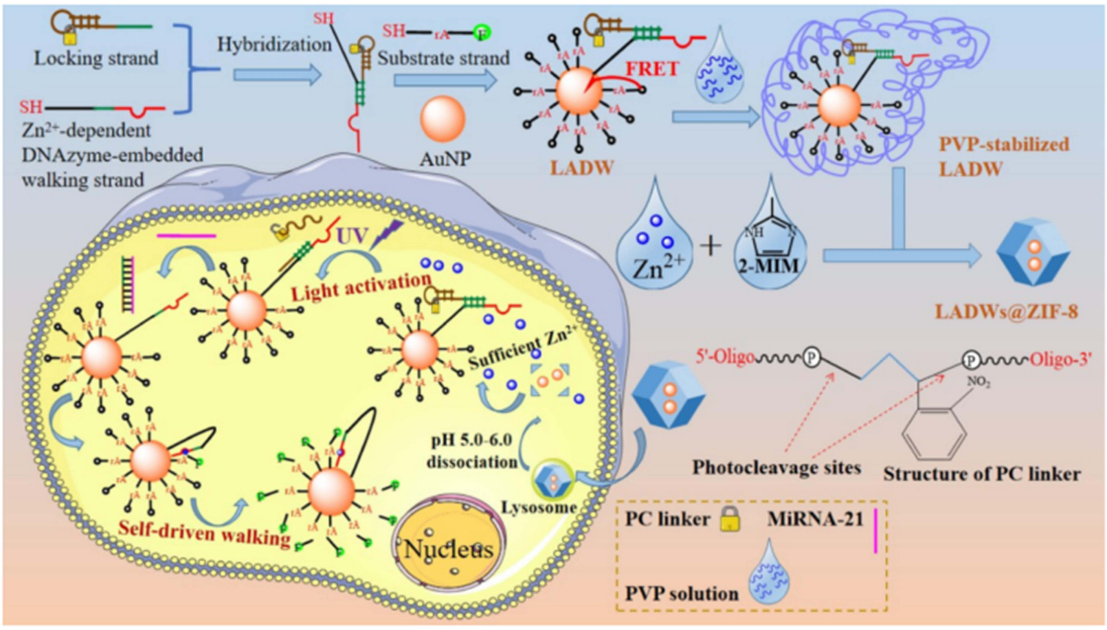

Figure 5 A ZIF-8-based platform for self-driven tumor DNA imaging sensing schematic diagram of the manufacturing process. Reprinted with permission from Gao J-L, Liu Y-H, Zheng B, et al. Light-activated and self-driven autonomous DNA nanomachine enabling fluorescence imaging of MicroRNA in living cells with exceptional precision and efficiency. *ACS Appl Mater Inter.* 2021;13(27):31485–31494. Copyright 2021 American Chemical Society.[108]

The integration of luminescent properties into MOFs has significantly expanded their utility in biomedical imaging, particularly through the inclusion of lanthanide-based MOFs, which are well-suited for fluorescence imaging modalities. Meng et al have exemplified this application by employing a lamellar europium MOF (EuMOF) to create a theranostic nano platform, facilitating simultaneous microwave thermo-chemotherapy and fluorescence imaging.[109] Their studies revealed that the EuMOF@ZIF/AP-PEG nanocomposite maintained robust fluorescence up to six hours post-in situ administration.

Furthermore, the biomedical field has recently embraced up-conversion luminescent nanoparticles (UCNPs), which possess the remarkable ability to transmute near-infrared (NIR) radiation into visible light. These nanoparticles enhance the repertoire of bio-probes by mitigating autofluorescence interference in optical imaging conducted in vivo and by reducing the risk of light-induced damage in cellular cultures and live subjects. The unique optical characteristics of UCNPs present them as a transformative element in the domain of optical imaging, aligning with the overarching goal of minimizing phototoxic effects while maximizing imaging clarity.[110,111] NMOFs is no longer just a carrier for fluorescent dyes. However, It is crucial to note that local delivery and imaging confirmation of drug distribution within the tumor are still lacking in the case of MOFs nanomaterials.

Application of MOF Materials in Multi-Modal Imaging of Malignant Tumors

Contemporary imaging modalities, including fluorescence, magnetic resonance imaging (MRI), and computed tomography (CT), each present a unique set of advantages and inherent limitations. Fluorescence imaging boasts high sensitivity yet suffers from limited penetration depth. MRI offers exquisite three-dimensional soft tissue delineation, albeit with constrained planar resolution. CT excels in visualizing osseous structures and calcifications but exhibits reduced sensitivity to soft tissues.[112] The reliance on single-modality imaging techniques offers an incomplete diagnostic picture, significantly impeding the efficacy of oncological diagnostics. Nonetheless, the convergence of these disparate imaging technologies can surmount individual limitations, yielding a composite diagnostic vista replete with detailed and reliable pathological insights—critical for the precise diagnosis and treatment of cancer. Within this multidisciplinary framework, nMOFs provide a versatile platform conducive to the integration of multiple imaging modalities.[113] For instance, Tang et al synthesized core-shell nanocomposites that harness upconversion luminescence (UCL) and MRI by encapsulating MOFs (MIL-101 (Fe)) around UCNPs.[114] These composites have demonstrated effective tumor-site enrichment and commendable UCL/MRI performance 24 hours following intravenous administration.

Further, Bai et al crafted novel core-shell PB@MIL-100 (Fe) bimetallic organic framework (d-MOF) nanoparticles, which feature an inner PB MOF core and an outer MIL-100(Fe) MOF shell, endowing them with efficacy as contrast agents for T1/T2 bimodal MRI and fluorescence optical imaging (FOI). These nanoparticles are also responsive to acidic environments, facilitating the release of encapsulated artemisinin for enhanced tumor therapy.[115]

The evolution of imaging modalities has not halted at dual-modality; the advent of MOFs with high payload capacities has paved the way for tri-modal imaging platforms, offering superior capabilities. Chen et al developed a multifunctional nanoplatform employing hyaluronic acid (HA) and indocyanine green (ICG)-engineered MIL-100 (Fe) nanoparticles (MOF@HA@ICG NPs), which enable imaging across MR, PA, and FL modalities, effectively overcoming the challenges of limited penetration depth and sensitivity inherent to single-mode imaging.[116] Wang et al, in their pursuit of comprehensive diagnostics and therapy, introduced an all-encompassing strategy for the synthesis of bimetallic-ligand MOFs, specifically Fe/TM-MOFs, incorporating $Fe^{\wedge 3+}$ and $Tm^{\wedge 3+}$ ions with 2-methylimidazole and metabenzoic acid ligands. These MOFs exhibit a potent Fenton catalytic effect by reacting with H_2O_2 to generate free radicals for tumor treatment, while simultaneously enabling fluorescence imaging, photothermal imaging, and MRI.[117]

MOFs are garnering considerable interest in the realm of biomedical imaging, standing out as potential multifunctional agents by their synthetic adaptability and dual capacity for imaging and therapeutic delivery. The imaging functionalities of MOFs may be inherent to their structure or introduced via post-synthetic incorporation of guest molecules within their pores or on their surfaces. Additionally, the structural pliability of MOFs permits facile hybridization with an array of other nanomaterials, enhancing their application scope. The intrinsic versatility of MOFs allows for the integration of diverse imaging modalities within a single particulate entity, thereby establishing a platform for multimodal imaging agents.

Multimodal Killing and Therapeutic Effects of MOFs on Tumor Cells

Malignant neoplasms present a formidable challenge in contemporary medicine, characterized by high incidence, poor prognostic outcomes, and a propensity for recurrence. Compounded by lifestyle factors and societal pressures, malignancies are increasingly affecting younger demographics, constituting a global health issue.[118–120] Conventional treatments in clinical oncology—chemotherapy,[121] radiotherapy,[122] and surgical excision[123]—each bear their own set of constraints. Chemotherapeutic approaches are often compromised by the emergence of drug-resistant cellular clones due to tumor heterogeneity, necessitating escalated drug concentrations that concurrently escalate cytotoxic risks, thus presenting a therapeutic conundrum.[124–126] The utility of radiotherapy is circumscribed by its inexactitude, inefficiency, and substantial adverse effects.[127,128] Surgical interventions, while standard, are frequently challenged by the invasive and metastatic nature of malignant cells, raising the risk of residual disease and subsequent recurrence.

In light of these limitations, there has been a pivot towards less invasive, non-toxic, and more manageable therapeutic modalities such as thermodynamic therapy, photodynamic therapy, and immunotherapy. Yet, these innovative approaches are not without their limitations. For instance, chemodynamic therapy is often stymied by an inability to generate sufficient hydrogen peroxide within the tumor microenvironment.[129] Photodynamic therapy's efficacy is limited by the instability of photosensitizers within tumor tissues and the requirement for higher oxygen levels, which is at odds with the hypoxia typical of tumor metabolic reprogramming.[130] Immunotherapy's potential is frequently undermined by an immunosuppressive milieu fostered by tumor-associated immune cells and the evasion of immune surveillance by tumor cells.[128,129] Consequently, the scientific community remains engaged in the development of more efficacious treatment strategies to augment therapeutic outcomes in oncology[131,132] (Figure 6).

The advancement of nanomaterial research has catalyzed the synthesis and implementation of novel material types in oncological therapy, mitigating some of the limitations inherent in traditional treatment modalities and offering innovative directions for clinical cancer management.[133–135] MOFs, owing to their extensive specific surface area, permeability, and well-ordered porous structures, have emerged as a prominent class of materials in the realm of tumor-targeted therapy. The versatility of MOFs is demonstrated through a spectrum of applications, including but not limited to targeted drug delivery, integration with photodynamic therapy for the conveyance of photosensitizers, and leveraging photothermal effects to potentiate the immune response against neoplastic cells (Table 1).[51,135–142]

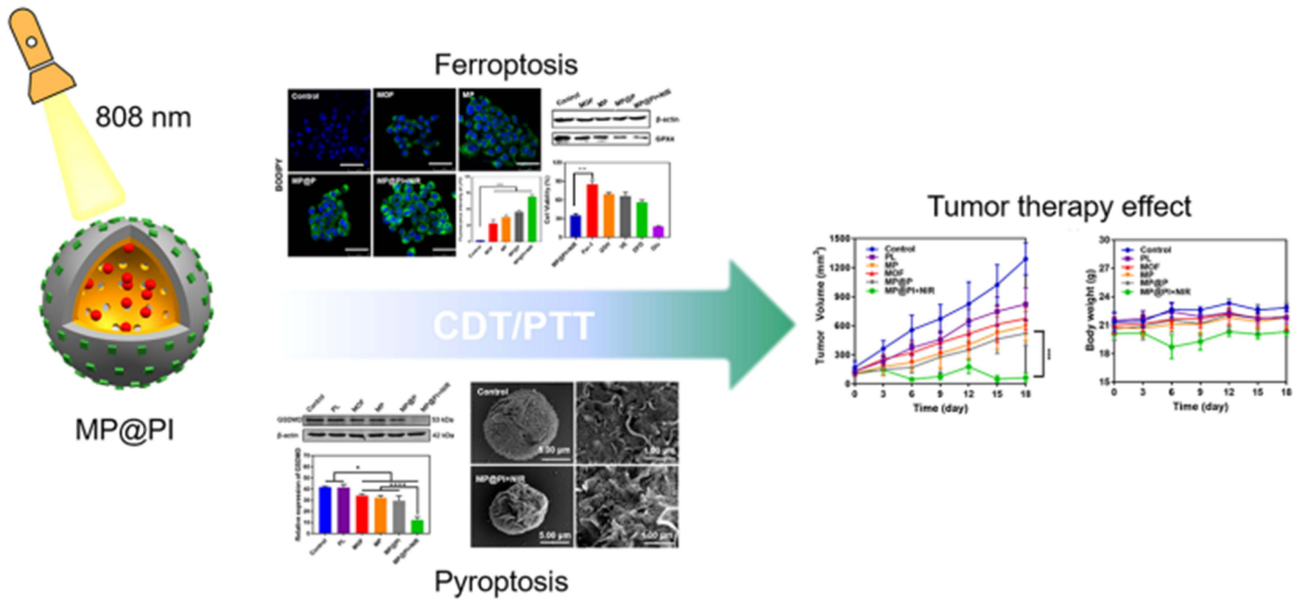

Figure 6 Schematic diagram of the MP@PI synthesis strategy and characterization of the bimodal MOF system with chemical power-photothermal effect. Reprinted with permission from Deng H, Zhang J, Yang Y, et al. Chemodynamic and photothermal combination therapy based on dual-modified metal-organic framework for inducing tumor ferroptosis/pyroptosis. *ACS Appl Mater Inter.* 2022;14(21):24089–24101. Copyright 2022 American Chemical Society.[131]

Table 1 Summary of the Tumor-Killing Effects of Different MOF-Based Nanocarriers

Material	Synthetic Method	Applications	Therapeutic Agents	Refs.
Zr-MOF	Hydrothermal method	Chemical therapy	5-FU	[135]
DOX@H-PMOF@mem	A pot of method	Chemical therapy	DOX	[136]
(DOX and ICG) @H-PMOF@mem	A pot of method	Chemotherapy, photodynamic therapy, the photothermal effect of the three modes of synergistic therapy	DOX	[51]
CMT NPs	–	Photothermal therapy (an indirect boost to immunotherapy)	Polypeptide tuftsin	[137]
Mn-IR825@PDAPEG	A pot of method	Photothermal therapy	–	[138]
DOX-ZIF-8/CQD	–	Chemotherapy, photodynamic therapy, the photothermal effect of the three modes of synergistic therapy	DOX	[139]
Hf@H2DBP	Hydrothermal method	Photodynamic therapy	H2DBP	[140]
PCN-224	–	Photodynamic therapy	TCPP	[141]
ZIF-8@AuNCs@DOX	–	Chemotherapy with synergistic photodynamic therapy	AuNCs@DOX	[142]

MOFs Treat Tumors by Targeted Drug Loading

Xi-Yu Sun et al ingeniously crafted a functionalized MOF, UiO-67-CDC, employing zirconium tetrachloride and 9H-carbazole-2,7-dicarboxylic acid via hydrothermal synthesis. Subsequently, they modified UiO-67-CDC by substituting the Lewis base sites with two methyl groups, thereby engendering a positively charged framework, UiO-67-CDC-(CH3)2. This modified Zr-MOF exhibited a pronounced affinity for the chemotherapeutic agent 5-fluorouracil (5-FU), achieving an impressive drug loading rate of 56.5%. Simulating physiological conditions, the UiO-67-CDC-(CH3)2@5-FU complex showcased commendable stability and responsiveness in a liquid medium with a pH of 7.4, indicative of its potential for targeted drug delivery within the bloodstream.[136] At the same time, the targeting vector has good degradation ability in an acidic environment, which gives the composite system a good tumor targeting effect. As we all know, tumor cells undergo a large number of anaerobic glycolysis processes due to the Warburg effect, which will form a local lactic acid microenvironment around tumor tissues, so that UiO-67-CDC-(CH3)2@5-FU will release drugs in response to the change of Ph after entering tumor blood vessels from the blood circulation, and play a targeted role in tumor cells.

In a parallel study, Xin Sun et al synthesized ZIF-8 nanoparticles by solvating zinc nitrate hexahydrate and 2-methylimidazole in methanol, followed by centrifugation and surface modification with polyvinylpyrrolidone (PVP) in dimethylformamide. This precursor was then integrated with zirconium tetrachloride and tetrakis (4-carboxyphenyl) porphyrin to fabricate a hybrid porphyrin MOF (H-PMOF), onto which doxorubicin (DOX) was loaded to construct a tumor-targeted, controlled-release system. To extend the MOF complex's circulatory longevity, a biomimetic approach was employed, enrobing DOX@H-PMOF with a breast cancer cell membrane to yield the DOX@H-PMOF@mem complex, thereby enhancing biocompatibility and mediating immune evasion. Efficacy assessment through in vivo and in vitro studies confirmed that DOX-loaded MOF materials significantly augmented the bioavailability of the chemotherapeutic drug and impeded the onset of tumor chemoresistance, exhibiting potent anticancer activity. Moreover, the MOF composite's capacity to mitigate liver and lung metastases—common in breast cancer—was evaluated. While the standalone chemotherapeutic delivery system exhibited moderate efficacy against metastatic progression, the tri-modal targeted system (DOX and indocyanine green (ICG))@H-PMOF@mem, synergizing chemotherapy with photodynamic and photothermal therapies, demonstrated substantial inhibitory effects on the metastatic spread of breast cancer.[51]

Long-term basic research and clinical retrospective research show that the maximum role of MOFs drug carriers in the body's blood circulation is largely related to the structure, particle size and charge of the loaded drugs. For example, when the particle size is 20nm-200nm, it can effectively reduce the recognition, phagocytosis and presentation of foreign nanoparticles by immune cells of the body, thus improving the peripheral circulation time. At the same time,

nanoparticles carrying a small amount of negative charge will also effectively prolong the circulation time and improve the targeting effect on tumor cells. After a long-term meta-analysis, it is known that DOX,[137–139] curcumin,[143] fluorouracil[140] and other drugs have the least systemic adverse effects, so MOFs loaded with these drugs can be used as potential clinical anti-tumor drugs, but it requires the joint efforts of long-term immunotoxicity, cell tissue toxicity and multi-center clinical research, and it is expected that in the future.

Targeted MOFs Combined with Photothermal Effects to Treat Tumors

Hongmi Zou et al synthesized carbonized magnetic nanoparticles (CM NPs) by subjecting Fe nanoparticles to high-temperature carbonization within a tube furnace under an argon atmosphere for five hours. The resultant CM NPs were subsequently treated with 30% hydrogen peroxide and functionalized with the peptide tuftsin to yield CMT NPs. The CMT NPs are carbonized from Mil-100 (Fe) at high temperatures and retain their original magnetism. On the one hand, the MOF system actively accumulates in tumor tissues by magnetism; on the other hand, tumor angiogenesis involves the signal transduction process of many cytokines, so it takes a long time. Therefore, many newly formed tiny capillaries in tumor tissues are not tight histologically, allowing particles with a particle size of 100nm-2mm to enter and passively accumulate in tumor tissues, which is called the EPR effect. Therefore, the compound system uses the dual targeting mechanism to target tumor cells and play the roles of photothermal effect and immunogenic death. Experimental validation revealed that these composite nanoparticles possess efficient photothermal conversion properties, with temperatures reaching up to 57.5°C upon 808 nm laser irradiation. Notably, the photothermal efficiency, quantified at 27.08%, displayed a strong dependence on the nanoparticle concentration and irradiation duration. While this efficiency trails that of gold-based composites, the tuftsin moiety within the CMT NPs facilitates the polarization of macrophages towards a pro-inflammatory M1 phenotype within the tumor microenvironment, augmenting the secretion of cytokines and the recruitment of T and B lymphocytes to the tumor site, thus enhancing the immunogenic assault on retinoblastoma cells.[144]

In parallel, Yang et al constructed a self-assembled MOF using $Mn^{\wedge 2+}$ as the metallic core and PTAIR825 as the organic linker. The stability of this MOF under photothermal conditions was further enhanced by surface modification with polydopamine and polyethylene glycol, yielding Mn-IR825@PDAPEG nanoparticles. These self-assembled nanoparticles demonstrated potent photothermal conversion and tumor ablation capabilities when subjected to 808 nm laser irradiation.[145] Complementing these findings, Tian et al developed a multifaceted nanoparticle system by encapsulating graphene quantum dots (GQD) and the chemotherapeutic agent doxorubicin (DOX) within the ZIF-8 MOF matrix, creating DOX-ZIF-8/CQD nanoparticles. The composite leverages the exceptional photothermal properties and upconversion potential of GQDs, allowing for precise control over photothermal conversion via adjustments in near-infrared (NIR) intensity and exposure time. Additionally, the photothermal activity of the GQDs enhances the pH responsiveness of ZIF-8, concurrently facilitating the release of DOX.[145] This study corroborates the promising therapeutic potential of MOF-based platforms in realizing synergistic chemo-photothermal treatments for malignancies.[141,147,148] Graphene quantum dots (QDs) have good biocompatibility and low tissue cytotoxicity, and a composite material system is constructed with MOFs, which can use its good drug loading activity to organically combine QDs,[149] MOF and photosensitizer to play a synergistic role in killing tumor cells. For example, in clinical practice, More and more doctors began to use natural photosensitizers such as indocyanine green for angiography,[150] fibrosis therapy[151] and tumor photothermal therapy.[142] However, this treatment strategy still has some limitations, such as poor biocompatibility and targeting ability, so we can choose to combine it with MOF, graphene quantum dots and other materials to build a targeted photothermal therapy system to cooperate with tumor killing.[151]

Targeted MOFs Combined with Photodynamic Therapy to Treat Tumors

Lu et al pioneered the synthesis of a nanoscale MOF utilizing a hydrothermal method with hafnium tetrachloride (HfCl4) and a porphyrin derivative, H2DBP. This novel MOF serves as a dispersal platform for photosensitizers, effectively mitigating aggregation and self-quenching while enhancing the production of singlet oxygen species in the vicinity of tumor tissues. Such advancements bolster the efficacy of photodynamic therapy (PDT) in oncological applications. In vivo investigations revealed a notable reduction in tumor volume in half of the treated mice, with the remainder

achieving complete tumor eradication.[152] The integration of PDT with MOF-based targeting platforms is thus recognized as a promising avenue in cancer therapy, drawing significant research interest. Current explorations extend beyond hafnium-based MOFs to other metal centers such as zirconium,[153] manganese,[154] and iron,[155] broadening the scope of MOF applications in PDT.

Park et al synthesized the spherical MOF material PCN-224 by coordinating Zr6 clusters with (4-carboxyphenyl) porphyrin (TCPP), featuring tunable sizes to enhance tumor permeability and uptake, thereby facilitating drug accumulation and tumor eradication.[156] Park also proposed surface modifications, such as the conjugation of targeting moieties like folic acid, which may potentiate the tumor-targeting and PDT effects of the system.[157–159] The innovation of encapsulating photosensitizers within MOFs or employing surface modifications and core-shell structures has transcended the constraints of using solely porphyrin-based photosensitizers, fostering the development of intricate MOF complexes. For example, Zhang et al[160] introduced gold nanoclusters (AuNCs) as photosensitizers within a pH-responsive ZIF-8@AuNCs@DOX composite, where the acidic tumor microenvironment triggers the disintegration of ZIF-8, releasing AuNCs and DOX for combined PDT and chemotherapy. This targeting system mainly targets tumor cells by acid response. Because ZIF-8 has good degradation efficiency in an acidic environment, photosensitizer and chemotherapy drug DOX are released in tumor tissue after contacting the acidic microenvironment of tumor tissue for targeted tumor killing and treatment.

Furthering this multidisciplinary approach, Chen and collaborators synthesized Cu-TCPP (Al) and Pt nanoparticles using a hydrothermal method, yielding a surface-modified composite, (Cu-TCPP (Al)-Pt). This composite nanosystem, delivering NH2-PEG-FA, targets tumor cells for cytotoxicity. The Cu^II active center within the system depletes glutathione levels in tumor cells, amplifying reactive oxygen species (ROS)-induced damage, while the Pt nanoparticles catalyze the conversion of hydrogen peroxide to oxygen. This dual action not only disrupts tumor cell glycolysis but also counters the reprogramming of immune cells caused by the hypoxic tumor microenvironment,

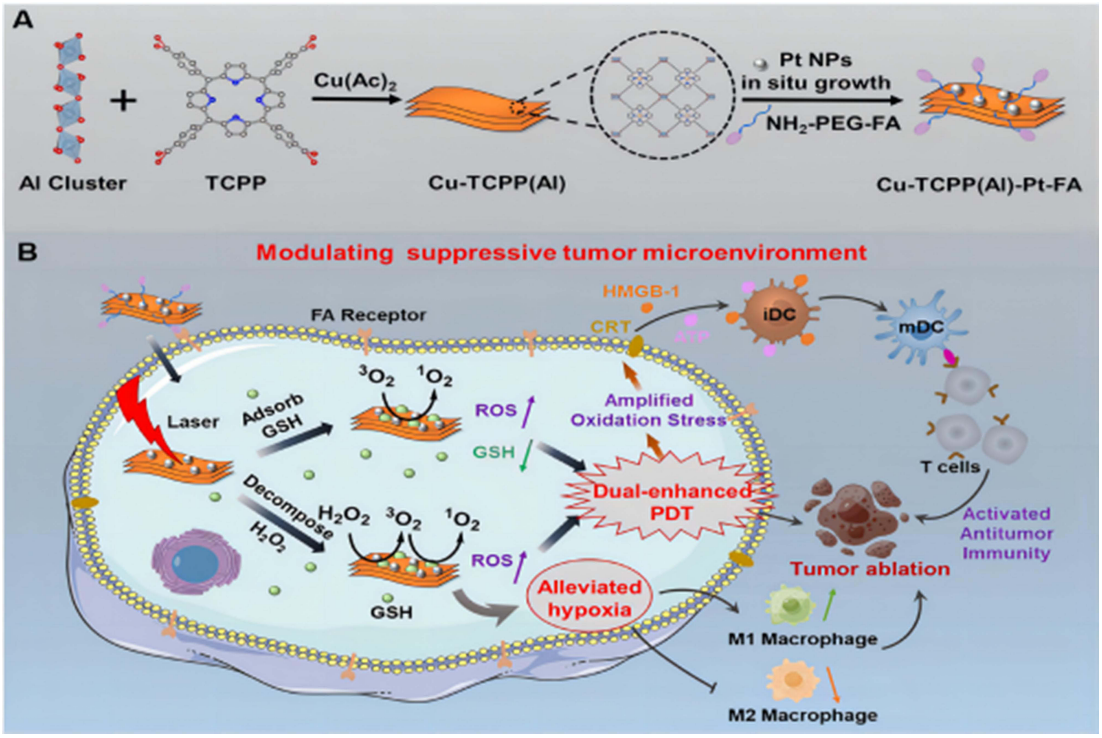

Figure 7 Schematic of (**A**) the fabrication process and (**B**) Cu-TCPC (Al) -Pt-FA stimulates the development of tumor immunity by depleting glutathione in cancer cells to enhance the effects of ROS and catalyzing O2 production by Pt NPs to reduce the inhibitory effect of tumor-induced hypoxic microenvironment on immune cells. Reprinted with permission from Chen Z, Wu Y, Yao Z, et al. 2D Copper(II) metalated metal-organic framework nanocomplexes for dual-enhanced photodynamic therapy and amplified antitumor immunity. *ACS Appl Mater Inter.* 2022;14(39):44199–44210. Copyright 2022 American Chemical Society.[161]

enhancing the immune response and curtailing tumor cell immune evasion and epithelial-mesenchymal transition[161] (Figure 7).

Conclusively, MOFs have become integral to the design of drug delivery systems, leveraging their structurally ordered porosity, extensive surface area, and permeability for effective drug loading. These characteristics facilitate the integration of MOFs with a spectrum of therapeutic modalities-including chemotherapy, photodynamic, and photothermal therapies construct targeted delivery systems aimed at malignancies, enabling multifaceted and multivalent attack strategies on tumor cells. However, empirical evidence indicates that MOF-based targeting systems, when used in isolation, may not ensure the complete eradication of tumors in vivo. Given the rapid proliferation capability of residual neoplastic cells, incomplete tumor removal can precipitate recurrence and augment patient suffering. Enhancing tumor ablation may therefore necessitate a multimodal cooperative targeting approach. As delineated in the synthesis of the tripartite treatment paradigms above, employing MOFs as a co-delivery platform for a dual-mode or even tri-mode amalgamation of chemotherapy, photodynamic, and photothermal therapies demonstrates superior efficacy in tumor cell destruction compared to monotherapy applications.[162–164]

Conclusions

MOFs, a burgeoning class of porous nanomaterials, have captivated the scientific community with their varied composition, customizable architectures, expansive surface areas, porosity, and commendable biocompatibility. These attributes have rendered them exceedingly versatile for the conveyance of diverse functional entities—ranging from ions to proteins, enzymes, photosensitizers, chemotherapeutic agents, and targeted antigens.[165–168] The strategic functionalization of MOF nanomaterials has been pivotal in enhancing their target specificity—active or passive—toward neoplastic tissues, thereby revolutionizing the targeted diagnostic and therapeutic paradigms for malignancies. Consequently, a proliferation of MOF-based intelligent nano-targeting platforms has emerged, addressing the difficult needs in global oncological diagnostics and therapeutics. Concurrently, innovations in clinical methodologies for malignant pathologies —encompassing photodynamic therapy, photothermal effects, and immunogenic cell death—have somewhat alleviated the onus on treatment regimes. In summary, MOF has demonstrated superior performance in tumor diagnostics, especially in bioimaging, due to its special structure. From fluorescence imaging, MRI, CT, etc., excellent performance MOF materials have appeared in various imaging modalities. There are many improvements to commercial visualizers, such as MOF-loaded visualizers or the use of metallic MOFs to meet the demand, all of which have demonstrated significant performance improvements. At the same time, many studies show that the combination of nano-metal core-shell constructed with metals, especially precious metals, and MOFs will effectively improve the photothermal effect and the efficiency of photodynamic therapy of MOFs, damage tumor cells more effectively to promote the immunogenic death of tumors and play a better role in tumor treatment. Moreover, the properties of the composite can be further improved effectively by changing the types, structures, and surface modification of the surface metal core-shell to achieve better therapeutic effects.[2,4,169]

Outlook

Although through the joint research of many scientists from different fields, MOF materials have been proven to apply to many tumors and play a role in targeted diagnosis and treatment. However, the inherent limitations of these nascent monotherapies, coupled with the heterogeneity of tumor cell evolution,[170] metabolic reprogramming,[171] and immunosuppressive microenvironments,[172] preclude the complete eradication of tumor cells. To surmount these impediments, researchers have advocated employing MOFs as multifaceted platforms, synergizing with photodynamic and photothermal therapies to enhance malignancy ablation. Prior studies intimate that composite constructs with MOFs may rectify certain monotherapy defects, bolstering the antineoplastic efficacy—yet not achieving total tumor eradication. Building on previous scholarly work, the author posits that MOF-constructed nano-platforms, when applied in a multimodal targeted therapeutic regimen—encompassing chemotherapy, photodynamic, and photothermal treatments —might eclipse the efficacy of singular targeted approaches.

Notwithstanding the promising laboratory milestones of MOF-centric diagnostic and therapeutic platforms, the transition to clinical applications is fraught with hurdles. MOF composites' complex synthesis, surface modification, and functionalization processes impede their large-scale production and clinical translation. Residual chemical moieties from synthesis, with potential cytotoxicity, remain a concern.[173,174] Moreover, despite extensive research documenting low cytotoxicity and favorable biocompatibility of MOF composites, these studies are limited by their brief duration. Given MOFs' limited biodegradability, the implications of prolonged human body residence remain to be elucidated through comprehensive basic or clinical investigations.[172] Furthermore, the simulation of MOF circulation in peripheral blood, typically modulated by pH and temperature, fails to account for the complexity of human blood. Enhancing MOF circulation time and evading immune detection are paramount challenges. Strategies to mitigate these challenges include downsizing MOFs or implementing biomimetic modifications, which may effectively reduce immune system recognition and presentation by neutrophils and macrophages. However, the potential aggregation of MOFs in peripheral blood, which could heighten immunogenicity and compromise tumor-targeting efficacy, must be contemplated. A thorough and systematic exploration of in vivo metabolic pathways and degradation processes of MOFs is imperative. Although some researchers have examined the degradation of individual MOF materials via bioimaging, multiple dosages required for targeted tumor therapy necessitate a granular understanding of MOF metabolism and degradation to schedule disparate administration intervals for various MOF composites-preventing MOF accumulation and subsequent bodily harm.

Confronting these challenges in the MOF domain is an onerous scientific endeavor, encompassing synthesis, characterization, application, and mechanistic studies of MOFs. Innovating simplified synthesis detection techniques and refining related strategies are quintessential for expediting MOF research. In an exemplary study, Zhiling Zheng[175] leveraged machine learning to construct a chemical assistant for MOF synthesis prediction, which has significantly streamlined the synthesis process. The chemical assistant's profound integrative and analytical capabilities hold promise for dissecting the impact of synthesis variables on MOF physicochemical properties, potentially elucidating the nexus between MOF nanomaterials' biosafety, biocompatibility, and synthetic methodologies[176] (Figure 8). At the same time,

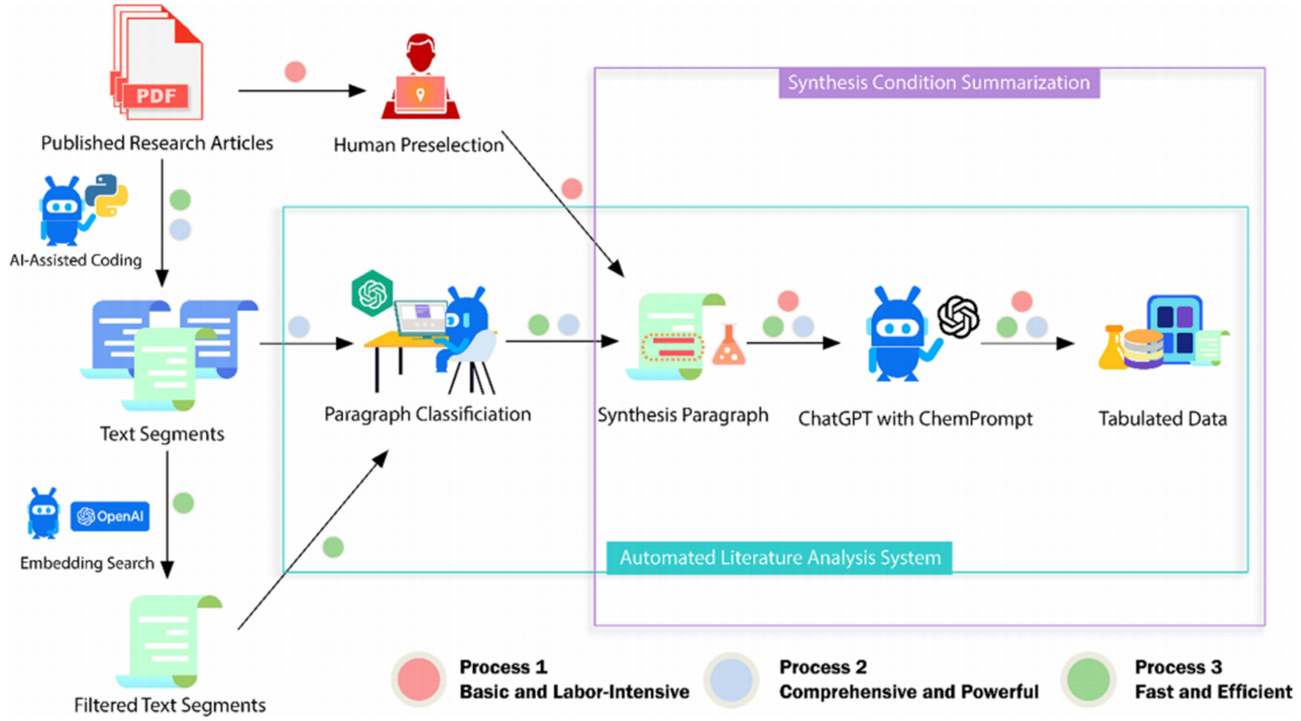

Figure 8 ChatGPT Schematic of the chemical assistant workflow, efficiently performing text mining using ChatGPT and ChemPrompt, and using machine learning to summarize the effects of MOF synthesis conditions on MOF crystallization from published research articles. Reprinted with permission from Zheng Z, Zhang O, Borgs C, Chayes JT, Yaghi OM. ChatGPT chemistry assistant for text mining and the prediction of MOF synthesis. *J Am Chem Soc*. 2023;145(32):18048–18062. Copyright 2023 American Chemical Society.[176]

using artificial intelligence to predict the synthetic results of MOFs is the result of further cross-integration between computer science, medicine, material science, chemistry, and other different disciplines, and it is also the general trend of continuous development in many fields. As far as medicine is concerned, MOFs not only have a broad application prospect in targeted diagnosis and treatment of tumors but also have a pivotal position and transformation potential in many clinical two disciplines, such as tissue engineering, regenerative medicine, and bone science. For example, researchers such as Kai Huang[163] synthesized a metal-organic framework material QCSMOF-Van with curcumin as the substrate and vancomycin and quaternary ammonium chitosan. The composite system was encapsulated in a hydrogel formed by methacrylic anhydride-modified gelatin and methacrylic anhydride-modified sodium alginate oxide by free radical polymerization and Schiff base reaction. The nano-composite system can exert good antibacterial and anti-inflammatory activities. By interfering with the polarization of macrophages, macrophages can secrete cytokines such as vascular growth factors. In tumor diagnosis, the current main clinical challenges are partially unclear resolution, poor imaging capability, and high cost. Most studies related to MOFs have demonstrated higher performance than commercialized developers. However, there is a lack of focus on production costs. Finding a low-cost contrast agent with superior performance is an important task for MOF research and could significantly reduce healthcare costs worldwide.

In conclusion, this review synthesizes the burgeoning applications of MOF-based nano-composite materials within oncological diagnostics and therapeutics. Drawing upon the collective insights of myriad investigations, it is evident that intelligent nano-platforms engineered from MOFs—leveraging their exceptional porosity and minimized biotoxicity—markedly surpass conventional methodologies when integrated with targeted modalities such as photothermal therapy, photodynamic therapy, and chemotherapy for malignancies. These platforms demonstrate significant potential in improving diagnostic and treatment paradigms for cancer.

Notwithstanding the substantial challenges that impede clinical translation, the field has witnessed considerable advancements in MOF-based targeted cancer diagnostics and therapies, evolving through rigorous research and innovation. The advent of intelligent technologies, such as ChatGTP within chemical synthesis, presages a transformative era, suggesting that the strategic deployment of such intelligent chemical assistants could expedite MOF synthesis substantially.

The past decades have seen an escalation in the deployment of nanotechnology in biomedicine, signaling a paradigm shift as medical research pivots towards the nanomaterial domain, propelled by interdisciplinary collaboration. This review posits that intelligent MOF targeting platforms are poised to assume a pivotal role in the clinical landscape for cancer diagnostics and therapeutics. Progressing from unimodal MOF applications to dual- or multimodal therapies, intelligent MOF-based diagnostic and treatment strategies are anticipated to emerge as innovative clinical modalities, enhancing the management of malignancies.

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Disclosure

The authors declare no conflicts of interest in this work.

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