

# Progress in the Development of Metal-Organic Frameworks (MOFs) for Medical Imaging of Tumors: Prospects and Challenges

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**Abstract:** Metal-organic frameworks (MOFs) are an emerging class of porous nanomaterials for tumor imaging owing to their tunable porosity, exceptionally high surface area, confinement effect, and high density of active sites, which collectively enable superior loading efficiency, signal amplification, and multifunctionality compared with conventional nanoplateforms. This review is a general overview of the advances that have been conducted in the development of imaging agents based on MOFs, with the perspective of their use in different imaging modalities such as magnetic resonance imaging (MRI), positron emission tomography (PET), fluorescence imaging, and computed tomography (CT). All the peculiarities of MOFs, including the possibility to introduce a metal, adjust the surface, and combine different imaging methods into one are described in detail. We also discuss the application of MOFs to tumor targeting and drug delivery and how this system can be functionalized to allow targeting of tumors and the possibility of personalized therapy. Despite these advantages, major barriers including complex synthesis, limited physiological stability, potential toxicity, scalability issues, and regulatory constraints continue to widen the bench-to-bedside gap and hinder the clinical translation of MOF-based imaging systems. New technologies in the design of MOFs, including hybrid and multifunctional MOFs, present new possibilities to improve imaging sensitivity, resolution, and therapeutic success. Future perspectives including theranostic integration and potential clinical applications of MOF-based imaging platforms are also discussed. Finally, despite the presence of multiple challenges, MOFs can be used to revolutionize the field of tumor imaging and enhance the process of cancer diagnosis and treatment with more sensitive, targeted, and personalized strategies.

**Keywords:** metal-organic frameworks, tumor imaging, multimodal imaging, drug delivery, personalized medicine

## Introduction

Early tumor detection remains a major cause of cancer prognosis and therapeutic success, as diagnosis at advanced stages is frequently associated with metastasis, limited treatment options, and reduced survival rates.<sup>1-3</sup> Current clinical imaging modalities, including computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and ultrasound, play essential roles in tumor diagnosis and monitoring. However, they still suffer from important limitations such as inadequate sensitivity for micro-invasive lesions, limited molecular specificity, radiation exposure, high operational cost, and insufficient differentiation between benign and malignant tissues.<sup>4-9</sup> These limitations highlight the growing need for advanced imaging platforms capable of improving tumor-selective detection, signal sensitivity, and multimodal diagnostic performance.

Recently, metal-organic frameworks (MOFs) gained a lot of interest in different fields like catalysis, imaging, and drug delivery.<sup>10-13</sup> Especially MOFs have attracted considerable attention for overcoming the limitations of conventional imaging systems due to tunable porosity, exceptionally high surface area, confinement effect, structural versatility, and high density of active sites. These properties enable efficient loading of imaging agents, enhanced signal amplification, and multifunctional integration within a single nanosystem.<sup>12,13</sup> Furthermore, MOFs can be engineered with imaging-

active metals, fluorescent probes, targeting ligands, and stimuli-responsive components, making them attractive platforms for MRI, PET, CT, fluorescence imaging, and multimodal tumor imaging applications.<sup>14–20</sup> The advantages and disadvantages of imaging modalities are given in Table 1.

Even though these imaging modalities have been found to be effective in the detection of tumors, these modalities have limitations in regard to detecting tumors at an early stage, specificity and in certain cases sensitivity especially when the tumors are in the micro-invasive or minimal stages of development. Consequently, a vast clinical gap exists in the need to apply more sophisticated methods, which can enhance tumor early detection and define its biology better. A potential area of future research is the application of molecular imaging agents with the ability to give both anatomical and functional information on tumors on a molecular basis. As an example, molecular imaging biomarkers have demonstrated the capability to identify early-stage cancers and an option of detecting tumors at subclinical disease stage, which could enable interventions to be performed at earlier stages.<sup>4</sup>

The latter advanced methods such as the implementation of MOFs are actively being studied to address the shortcomings of the existing imaging technologies.<sup>12,13</sup> MOFs possess high surface area, tunable structures, and favorable functionalization capability, making them promising platforms for tumor imaging and drug delivery applications. Recent developments in MOF-based imaging agents demonstrate that they have the potential to increase the sensitivity and specificity of tumor detection and could help to overcome some of the major limitations of the traditional imaging modalities.<sup>14</sup> In the last couple of years, MOFs were identified as a promising imaging platform because they feature tunable metal-organic coordination, high porosity, and large surface areas in addition to the capacity to introduce imaging-active metals or functional linkers.<sup>15</sup> MOF-based nanoplateforms have demonstrated considerable potential as contrast agents for MRI, PET, fluorescence, and hybrid imaging applications.<sup>16</sup> Analysis of these publications shows a significant increase in MOFs publications in the last five years and demonstrates imaging as one of the most popular areas of its application, indicating an increase in interest and a possible direction of translation.<sup>17</sup>

Despite the rapid expansion of MOF-related literature, most existing reviews primarily focus on general theranostic applications, drug delivery systems, or broad biomedical uses of MOFs. Comparatively, fewer reviews critically evaluate the specific progress of MOF-based platforms in tumor imaging from the perspective of multimodal imaging integration, imaging-active metal engineering, and clinical translation challenges. In addition, limited attention has been given to the relationship between MOF structural design, imaging performance, biosafety, and translational feasibility.

Therefore, the present review specifically focuses on the recent progress of MOF-based systems for tumor imaging across MRI, PET, CT, fluorescence, and multimodal imaging applications, with particular emphasis on structure–property relationships, imaging-active metal incorporation, smart surface functionalization, and translational barriers limiting clinical implementation. Unlike previous reviews, this article also highlights the emerging bench-to-bedside challenges associated with biosafety evaluation, large-scale synthesis, reproducibility, regulatory approval, and long-term clinical applicability of MOF-based imaging agents.

## MOFs: Structure and Properties

MOFs are crystalline porous materials obtained by the coordination of metal nodes (ions or clusters) and organic linkers (ligands) into a repeating network structure with known porosity and a high surface area,<sup>21</sup> as illustrated in Figure 1. The connectivity centers become the metal nodes which are commonly known as the secondary building units (SBUs) and the organic linkers connect the nodes in one, two or three dimensions to create the extended structures.<sup>22</sup> The size and shape of the pore, their connection, and the topology of the whole MOF can be adjusted to diverse metal ions/clusters, different linker molecules, and modified post-synthetically.<sup>23</sup> In common MOFs, the metal nodes may be isolated metal ions (eg,  $\text{Zn}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Fe}^{3+}$ ) or metal oxo/hydroxide clusters (eg,  $\text{Zr}_6\text{O}_4(\text{OH})_4$ ).<sup>24,25</sup> The organic linkers tend to be carboxylate or imidazolate or phosphonate or other multidentate ligands that bind to the metal centers to determine the topology of the structure.<sup>26</sup>

The versatility of MOFs is that by changing the metal node or the linker, or both, the properties (chemical stability, pore environment, functional groups, guest-binding capacity) of the material can be changed.<sup>23</sup> Zirconium-based MOFs (Zr-MOFs) have been found to be an especially strong and highly studied category due to the strong Zr–O interactions, excellent hydrolytic stability, and good biocompatibility.<sup>16,24</sup> Examples include the UiO-series (UiO –66, UiO –67), MOF –808, and the NU –1000, all of which are Zr-based scaffolds that find applications in biomedical applications.<sup>24</sup>

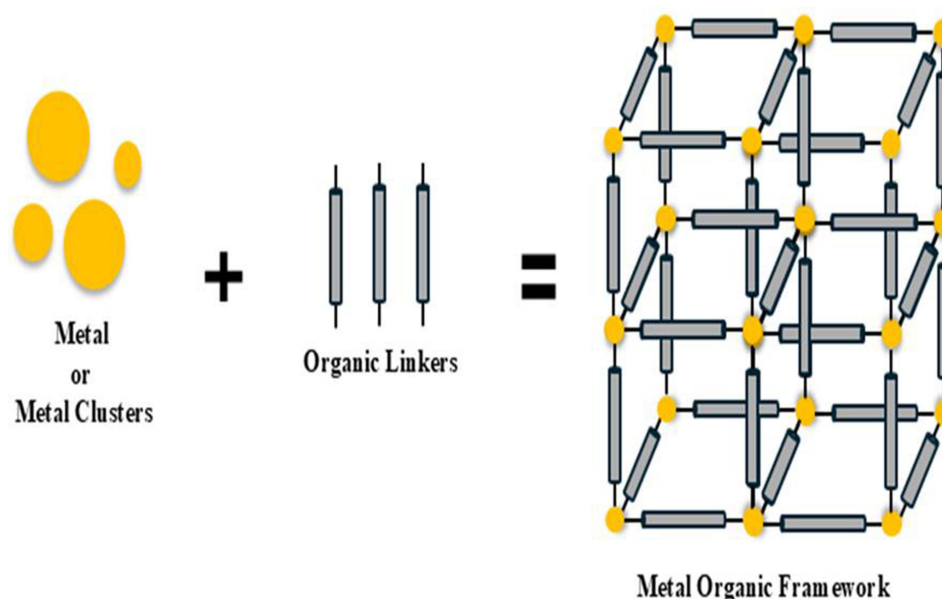
**Table 1** Comparison of Major Medical Imaging Modalities for Tumor Diagnosis and Monitoring

| Imaging Modality   | Principle                                                                          | Major Advantages                                                                                                                                                                                                                  | Major Disadvantages                                                                                                                                                                                                                                       | Typical Clinical Applications in Oncology                                      | Relevance to MOF (Metal-Organic Framework) Based Imaging Agents                                                                     |
|--------------------|------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| CT                 | Uses X-ray attenuation to generate cross-sectional anatomical images               | <ul style="list-style-type: none"> <li>Fast image acquisition</li> <li>High spatial resolution</li> <li>Excellent visualization of bone and lung structures</li> <li>Widely available and relatively low cost</li> </ul>          | <ul style="list-style-type: none"> <li>Exposure to ionizing radiation</li> <li>Limited soft tissue contrast</li> <li>Requires iodinated contrast agents that may cause nephrotoxicity or allergic reactions</li> <li>Low molecular sensitivity</li> </ul> | Tumor localization, staging, detection of metastases, image-guided biopsy      | MOFs containing high atomic number metals (eg, Hf, Zr, Bi) can improve CT contrast enhancement                                      |
| MRI                | Uses magnetic fields and radiofrequency pulses to detect proton relaxation signals | <ul style="list-style-type: none"> <li>Excellent soft tissue contrast</li> <li>No ionizing radiation</li> <li>Multiplanar imaging capability</li> <li>Functional imaging possible (diffusion, perfusion, spectroscopy)</li> </ul> | <ul style="list-style-type: none"> <li>Long scanning time</li> <li>High operational cost</li> <li>Lower sensitivity compared with nuclear imaging</li> <li>Contraindicated in some patients with metallic implants or claustrophobia</li> </ul>           | Brain tumors, soft tissue tumors, liver lesions, tumor characterization        | Paramagnetic MOFs containing gadolinium (Gd), Manganese (Mn), or iron (Fe) can serve as MRI contrast agents with tunable relaxivity |
| PET                | Detects gamma rays generated from positron-emitting radionuclides                  | <ul style="list-style-type: none"> <li>Very high sensitivity</li> <li>Enables quantitative molecular and metabolic imaging</li> <li>Early detection of tumor activity before anatomical changes occur</li> </ul>                  | <ul style="list-style-type: none"> <li>Exposure to ionizing radiation</li> <li>Poor spatial resolution compared with CT/MRI</li> <li>Expensive instrumentation and radiotracer production</li> <li>Short half-life of radionuclides</li> </ul>            | Tumor metabolism assessment, staging, therapy monitoring, recurrence detection | Radioisotope-labeled MOFs can act as multifunctional PET probes for targeted tumor imaging                                          |
| Ultrasound Imaging | Uses high-frequency sound waves reflected by tissues                               | <ul style="list-style-type: none"> <li>Real-time imaging</li> <li>Portable and inexpensive</li> <li>No ionizing radiation</li> </ul>                                                                                              | <ul style="list-style-type: none"> <li>Operator dependent</li> <li>Limited penetration through bone or air</li> <li>Lower soft tissue contrast</li> </ul>                                                                                                 | Guided biopsy, abdominal and thyroid tumor imaging                             | MOF-based nanoplateforms may enhance acoustic contrast and theranostic applications                                                 |

(Continued)

Table 1 (Continued).

| Imaging Modality                         | Principle                                                                          | Major Advantages                                                                                                                                                                                                                     | Major Disadvantages                                                                                                                                                                                                                                | Typical Clinical Applications in Oncology                                      | Relevance to MOF (Metal-Organic Framework) Based Imaging Agents                                     |
|------------------------------------------|------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| Optical/Fluorescence Imaging             | Detects emitted fluorescent or bioluminescent signals                              | <ul style="list-style-type: none"><li>• Very high sensitivity</li><li>• Real-time intraoperative imaging</li><li>• Low cost and easy operation</li></ul>                                                                             | <ul style="list-style-type: none"><li>• Limited tissue penetration</li><li>• Autofluorescence interference</li><li>• Mainly preclinical or intraoperative use</li></ul>                                                                            | Image-guided surgery, molecular imaging, preclinical tumor studies             | Fluorescent dye-loaded MOFs provide multifunctional imaging and drug delivery capabilities          |
| Multimodal Imaging (eg, PET/CT, PET/MRI) | Combines anatomical and functional imaging techniques                              | <ul style="list-style-type: none"><li>• Provides complementary structural and molecular information</li><li>• Improved diagnostic accuracy</li></ul>                                                                                 | <ul style="list-style-type: none"><li>• High cost</li><li>• Complex instrumentation and data integration</li></ul>                                                                                                                                 | Comprehensive tumor diagnosis and therapy monitoring                           | MOFs are highly suitable for multimodal platforms due to tunable composition and multifunctionality |
| MRI                                      | Uses magnetic fields and radiofrequency pulses to detect proton relaxation signals | <ul style="list-style-type: none"><li>• Excellent soft tissue contrast</li><li>• No ionizing radiation</li><li>• Multiplanar imaging capability</li><li>• Functional imaging possible (diffusion, perfusion, spectroscopy)</li></ul> | <ul style="list-style-type: none"><li>• Long scanning time</li><li>• High operational cost</li><li>• Lower sensitivity compared with nuclear imaging</li><li>• Contraindicated in some patients with metallic implants or claustrophobia</li></ul> | Brain tumors, soft tissue tumors, liver lesions, tumor characterization        | Paramagnetic MOFs containing Gd, Mn, or Fe can serve as MRI contrast agents with tunable relaxivity |
| PET                                      | Detects gamma rays generated from positron-emitting radionuclides                  | <ul style="list-style-type: none"><li>• Very high sensitivity</li><li>• Enables quantitative molecular and metabolic imaging</li><li>• Early detection of tumor activity before anatomical changes occur</li></ul>                   | <ul style="list-style-type: none"><li>• Exposure to ionizing radiation</li><li>• Poor spatial resolution compared with CT/MRI</li><li>• Expensive instrumentation and radiotracer production</li><li>• Short half-life of radionuclides</li></ul>  | Tumor metabolism assessment, staging, therapy monitoring, recurrence detection | Radioisotope-labeled MOFs can act as multifunctional PET probes for targeted tumor imaging          |



**Figure 1** Diagrammatic representation of synthesis and structure of a MOF. The MOF itself is built by self-assembling two key elements, namely the Metal Ions or Metal Clusters (symbolized by the yellow circles) and the Organic Linkers (symbolized by the grey rods). The obtained structure is a highly organized, porous and three-dimensional MOF in which metal centers serve as nodes and organic linkers serve as connecting struts.

Copper based MOFs (Cu-MOFs) (eg, HKUST-1) are also widespread; copper paddlewheel units have been employed due to their flexibility of coordination and the availability of open metal sites.<sup>27</sup> Fe based MOFs (Fe-MOFs) are also being investigated to be used in biomedicine because of magnetic/paramagnetic properties of Fe that can be used in imaging and therapies.<sup>28,29</sup>

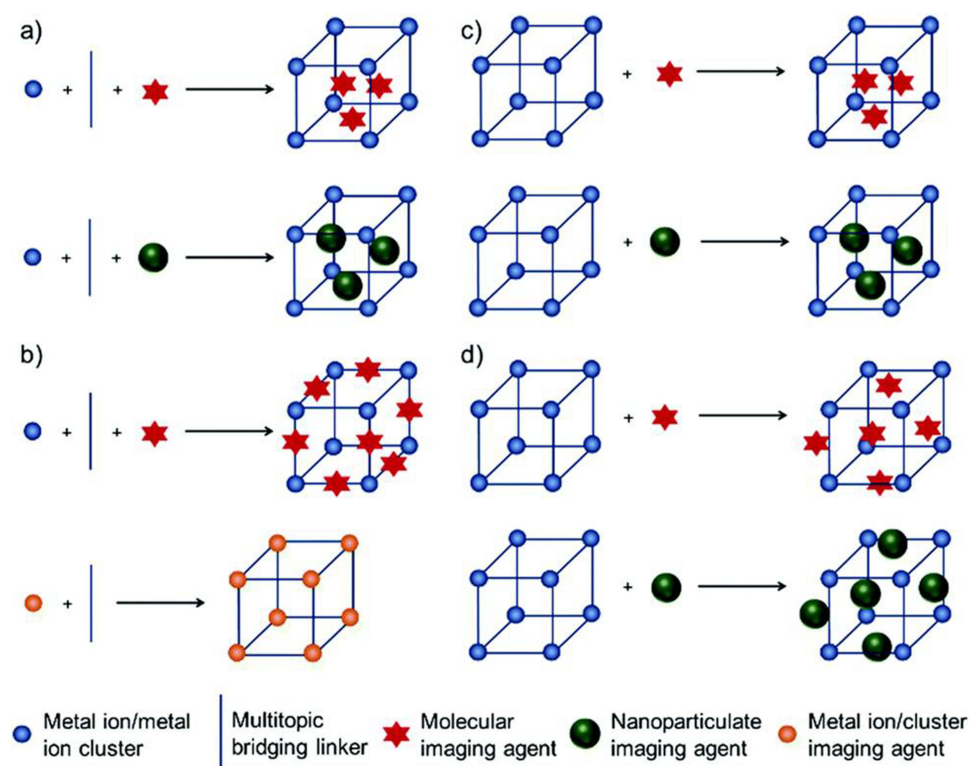
The metal node type also determines stability, geometry of coordination as well as imaging-relevant characteristics (such as paramagnetism to take advantage of MRI, metal X-ray absorption to take advantage of CT contrast, radionuclide compatibility to take advantage of PET). Likewise, the targeting moieties, fluorescent dyes, responsive groups (pH, enzyme), or radiolabels can be installed on the organic linker based on its choice and functionalization. The linkers also determine the size of the pore, uptake of the guests, surface chemistry and biocompatibility in general.<sup>30</sup> Besides, topology (connectivity of nodes and linkers) and pore environment (size, shape, functionality) determine the interaction between the guests (imaging agents, drugs, contrast molecules) and the framework. MOFs have been optimized to biomedical imaging by post-synthetic modifications (eg, ligand exchange, metal-node doping, surface coating).<sup>31</sup> The synthesis approaches for MOFs with imaging capabilities are shown in Figure 2.<sup>12</sup> The main properties of MOFs relevant to tumor imaging are given in Table 2.<sup>23,25,32–39</sup>

## Applications of MOFs in Tumor Imaging

### Role in Different Imaging Modalities

#### MRI

MRI remains a central non-invasive modality for tumor diagnosis due to its high soft-tissue contrast and absence of ionizing radiation. However, clinically used T1 contrast agents, predominantly  $Gd^{3+}$ -based chelates, suffer from limited relaxivity, non-specific biodistribution, and potential nephrogenic systemic toxicity in patients with impaired renal clearance.<sup>40,41</sup> These limitations have encouraged the development of MOF-based contrast agents as high-density and structurally tunable MRI platforms. The efficacy of MR contrast agent is dictated fundamentally by the Solomon-Bloembergen-Morgan theory, where proton relaxivities ( $r_1$  and  $r_2$ ) are described based on various molecular and electronic properties, including the number of inner-sphere water molecules ( $q$ ), water lifetimes ( $\tau_M$ ), rotational correlation times ( $\tau_R$ ), and electronic relaxation times ( $T_{1e}$  and  $T_{2e}$ ). SBM theory dictates that optimal tuning of  $\tau_R$  and  $\tau_M$  is vital towards improving T1-weighted contrast efficacy. The same principles are used in MOFs, where these



**Figure 2** Principal approaches for the fabrication of MOFs with imaging functionalities: (a) in situ encapsulation of imaging agents during MOF synthesis; (b) integration of imaging agents as intrinsic structural components, including organic linkers, metal ions, or metal clusters; (c) postsynthetic incorporation of imaging agents within the porous architecture of the MOF; and (d) postsynthetic surface functionalization of MOF particles with imaging units.<sup>12</sup>

relaxation properties can be adjusted using the rigidity, architecture, and metal-node coordination environment of the framework.<sup>42–44</sup> However, it should be noted that relaxivity is highly sensitive to the intensity of the magnetic field, and all the obtained values for  $r_1$  need to be clearly defined as depending on field strength (eg, at 1.5 T, 3.0 T, or higher). It can be observed that  $r_1$  values for Gd-based compounds are lower as the magnetic field increases because of decreased relaxation efficiency.<sup>41,43,45</sup>

MOFs have an edge over traditional chelates owing to the high capacity for metal ions, the ability to tune porosity, and the elongation of water diffusion paths, all of which contribute to the increased ability of paramagnetic centers to

**Table 2** Key Properties of MOFs Relevant to Tumor Imaging

| Key Property of MOFs                   | Description                                                                                                      | Relevance to Tumor Imaging                                                                                                                                                  | Representative Examples/Findings                                                                                                              | References |
|----------------------------------------|------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|------------|
| High surface area                      | MOFs possess extremely high internal surface areas, often reaching several thousand $\text{m}^2 \text{g}^{-1}$ . | Enables high loading capacity for imaging agents such as contrast dyes, radionuclides, fluorescent probes, and metal ions. Enhances interaction with biological systems.    | MOFs exhibit surface areas exceeding $6500 \text{ m}^2 \text{g}^{-1}$ , making them highly suitable for multifunctional imaging applications. | [23,25,32] |
| Tunable porosity and pore architecture | MOF pore size, connectivity, and internal channels can be precisely controlled.                                  | Facilitates controlled loading/release of imaging agents, improves biodistribution, pharmacokinetics, and tumor retention. Supports multimodal imaging agent incorporation. | Porosity-tunable MOFs with systematically modified pore structures regulate guest accessibility and functionality.                            | [33,34]    |

(Continued)



Table 2 (Continued).

| Key Property of MOFs                           | Description                                                                                                    | Relevance to Tumor Imaging                                                                                       | Representative Examples/ Findings                                                                                                                              | References |
|------------------------------------------------|----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Surface functionalization capability           | MOF surfaces can be modified through PEGylation, peptide conjugation, glycoproteins, or protective shells.     | Improves colloidal stability, circulation time, tumor targeting, and reduces immunogenicity and rapid clearance. | Functionalization with folate ligands, RGD peptides, pH-responsive linkers, and stealth coatings enhances tumor-specific accumulation and imaging specificity. | [32,35]    |
| Biocompatibility and nanoscale permeability    | Nanoscale MOFs possess adaptable biological interfaces and tunable physicochemical properties.                 | Enhances penetration into tumor tissues and compatibility with imaging-guided tumor diagnosis.                   | Nanoscale MOFs exhibit high biocompatibility, high surface area, and defined porosity suitable for imaging-guided tumor applications.                          | [35]       |
| Optical properties (fluorescence/ NIR imaging) | MOFs can incorporate luminescent linkers, fluorescent dyes, or quantum-dot-like structures.                    | Enables fluorescence imaging, near-infrared (NIR) imaging, and image-guided surgery for tumor visualization.     | Functional MOFs containing fluorescent dyes or luminescent linkers have been designed for optical imaging and intraoperative tumor margin visualization.       | [36,37]    |
| Multimodal imaging capability                  | MOFs can simultaneously integrate multiple imaging agents within one platform.                                 | Allows combined MRI, fluorescence, PET, or CT imaging for improved sensitivity and diagnostic accuracy.          | MOFs have been developed as multifunctional platforms integrating fluorescence and MRI for enhanced tumor detection.                                           | [36,37]    |
| Metal-node tunability                          | Imaging performance depends strongly on the type of metal node or dopant incorporated into the MOF structure.  | Determines imaging modality compatibility, signal intensity, stability, and biocompatibility.                    | Gd <sup>3+</sup> -MOFs for MRI, <sup>64</sup> Cu/ <sup>89</sup> Zr-MOFs for PET imaging, and iodine/gold-containing MOFs for CT imaging.                       | [36–39]    |
| Hydrolytic and structural stability            | Certain metal nodes such as Zr <sup>4+</sup> provide high hydrolytic stability under physiological conditions. | Maintains structural integrity during circulation and imaging, reducing premature degradation or metal leakage.  | Zr-based MOFs are widely recognized for their excellent in vivo stability and safety profile.                                                                  | [25,39]    |
| Enhanced relaxivity and imaging sensitivity    | High metal loading and optimized MOF architecture improve imaging signal efficiency.                           | Produces stronger imaging contrast and enhanced tumor detection sensitivity.                                     | MOFs provide superior MRI relaxivity compared with traditional contrast agents.                                                                                | [39]       |
| Controlled biological behavior                 | Linker chemistry and external surface groups can regulate interactions with biological systems.                | Influences cellular uptake, circulation, clearance, and tumor accumulation.                                      | Linker engineering and surface-group modification are critical for modulating biological behavior.                                                             | [32]       |

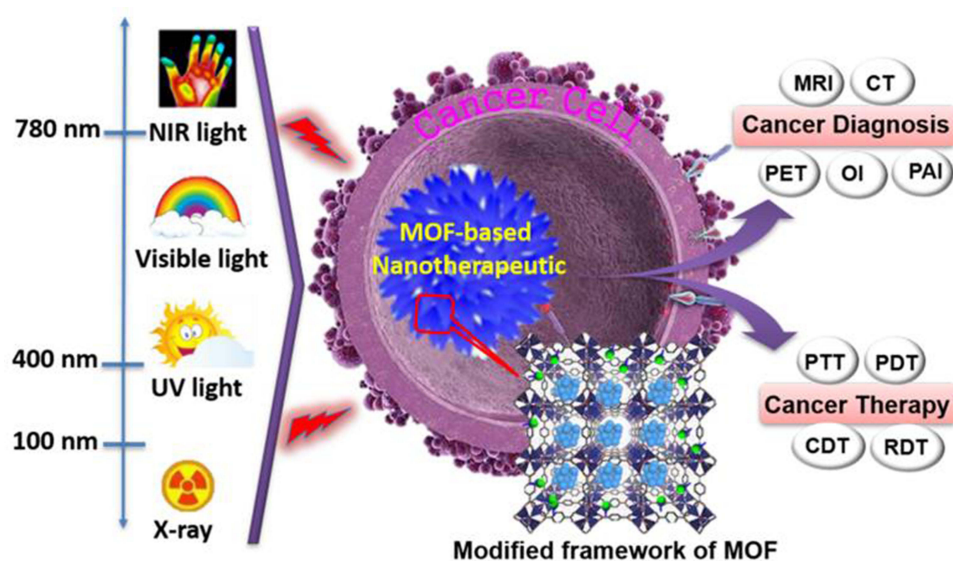
interact with water molecules, resulting in better efficiency in proton relaxation processes. For instance, PEGylated Mn-MOF-74 nanocrystals showed  $r_1$  values ranging from 8.08 to 13.5 M<sup>-1</sup>s<sup>-1</sup> along with strong signal intensity enhancement in tumor tissue using T1-weighted MRI images.<sup>46</sup> However, recent developments show that rational pore engineering boosts the MRI capabilities even more. The hierarchical pores in Gd MOFs facilitate diffusion of water molecules to internal coordinating sites. As a result, the effective amount of water molecules available to participate in the process is increased, thus improving  $\tau M$ .<sup>47</sup> In the same way, multifunctional Gd-MOF nanosystems have also been prepared for microwave-responsive MRI guided treatment of cancer patients exhibiting high contrast enhancement owing to optimal structure and composition of such multifunctional nanosystems.<sup>48</sup> Metal ion selection is very important in terms of

relaxivity and safety. Fe containing MOF compounds are gaining more attention as safer substitutes to Gd based compounds because of their good biocompatibility and natural metabolism, however, low magnetic moment necessitates structural optimization.<sup>35</sup> Furthermore, surface modification techniques like PEGylation and targeting using specific ligands increase circulation time, minimize uptake by the reticuloendothelial system, and promote selective uptake of the agent in tumors, thereby increasing the local relaxivity of the agent indirectly.

Despite these advances, clinical translation is limited by physicochemical instability under physiological conditions. MOF degradation can alter SBM-relevant parameters such as  $\tau_M$  and  $q$  through metal ion leaching or framework collapse, resulting in reduced relaxivity and potential toxicity. Moreover, aggregation in biological media can unpredictably alter  $\tau_R$ , leading to inconsistent imaging performance. Therefore, reproducible synthesis, stability optimization, and standardized reporting of relaxivity under defined magnetic field strengths are essential for future clinical translation. The MOFs developed as dual or even multimodal imaging (MRI and fluorescence or PET) facilitate the provision of anatomic and functional information, enhancing the detection, delineation and response to therapy are illustrated in Figure 3.<sup>49</sup> Moreover, a hypoxia-resistant and persistent O<sub>2</sub> self-supplementing nanoplatform was developed to achieve enhanced synergistic phototherapy under the guidance of Fluorescence/Multispectral Optoacoustic Tomography/CT/MR quadruple-modal imaging. The system was constructed using Pt-decorated gold nanoparticles with MOFs serving as the inner template is shown in Figure 4.<sup>50</sup>

### Positron Emission Tomography (PET)

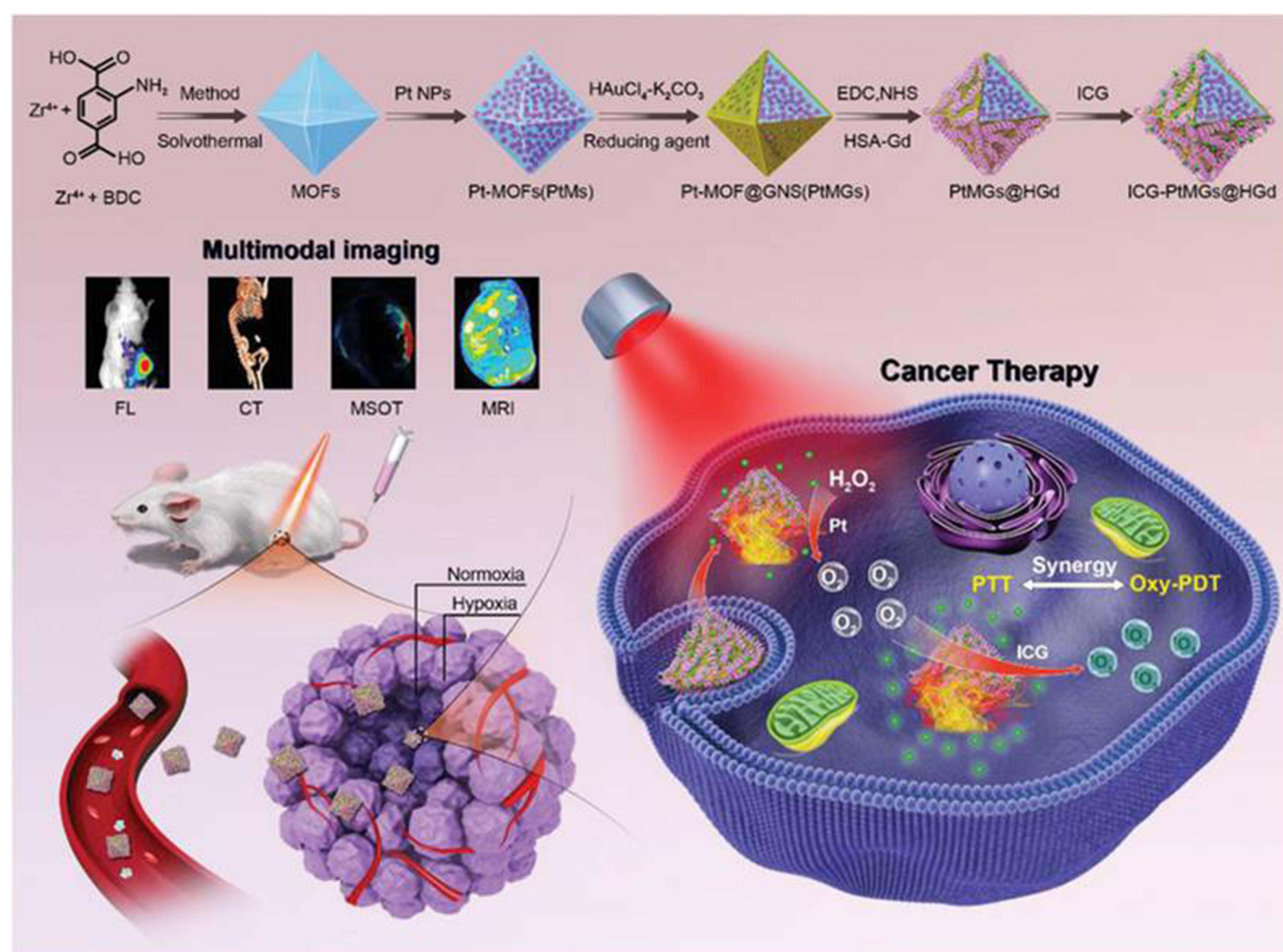
PET is a highly sensitive molecular imaging modality that enables quantitative visualization of tumor metabolism and biological activity through positron-emitting radionuclides such as Fluorine-18 (<sup>18</sup>F), <sup>64</sup>Cu, and <sup>89</sup>Zr.<sup>15,51</sup> Conventional PET tracers, however, often suffer from rapid systemic clearance, limited tumor specificity, and suboptimal tumor-to-background ratios, particularly for small-molecule agents and some antibody fragments.<sup>15</sup> In recent years, MOFs have emerged as promising nanoplatforms for PET imaging due to their tunable porosity, high surface area, and modular architecture enabling radionuclide incorporation via intrinsic or extrinsic strategies.<sup>52,53</sup> Intrinsic radiolabeling involves direct incorporation of radionuclides into the MOF framework during synthesis, often through coordination with metal nodes or secondary building units (SBUs). For example, <sup>89</sup>Zr integration into Zr-based MOFs has been demonstrated via framework coordination, improving radiochemical stability and reducing radionuclide leaching under physiological conditions.<sup>52</sup> In contrast, extrinsic labeling typically relies on post-synthetic surface modification using chelators such as DOTA, NOTA, or desferrioxamine (DFO), followed by radionuclide complexation (notably <sup>89</sup>Zr–DFO systems widely



**Figure 3** Schematic depiction of MOF-based nanotherapeutics for cancer theranostics.<sup>49</sup>

**Abbreviations:** MRI, Magnetic Resonance Imaging; CT, Computed Tomography; PET, Positron Emission Tomography; OI, Optical Imaging; PAI, Photoacoustic Imaging.





**Figure 4** Schematic illustration of the ICG-PtMGs@HGd nanoplateforms as  $\text{H}_2\text{O}_2$ -driven oxygenator for Fluorescence/Multispectral Optoacoustic Tomography/CT/MRI multimodal imaging guided enhanced PDT and PTT synergistic therapy in a solid tumor.<sup>50</sup> PDT; photodynamic therapy, PTT; photothermal therapy, ICG-PtMGs@HGd; Pt-decorated MOF@GNSs with human serum albumin-chelated gadolinium and loaded with indocyanine green.

used in immunoPET). Although post-synthetic strategies provide synthetic flexibility and targeting versatility, *in vivo* stability can be compromised due to transchelation with endogenous metal-binding ligands.<sup>51</sup>

Recent studies suggest that MOF-based PET probes may improve tumor accumulation and prolong circulation time compared to some small-molecule tracers due to enhanced retention and multivalent loading capacity.<sup>53</sup> However, reported extremely high tumor-to-background enhancements should be interpreted cautiously, as PET signal intensity is primarily governed by radionuclide-specific activity and radiochemical stability rather than total metal loading. Thus, the key advantage of MOFs is not simply high metal content, but rather their ability to achieve high radioactivity-per-particle loading, while enabling multifunctional surface engineering and multimodal imaging integration.<sup>53</sup> Radiochemical stability remains a major translational challenge. In particular,  $^{89}\text{Zr}$  dissociation from unstable frameworks can lead to nonspecific bone uptake due to strong affinity of free Zr ions for phosphate-rich tissues, a well-recognized phenomenon in Zr-based immunoPET chemistry.<sup>51</sup> Similarly, acidic and reductive tumor microenvironments can accelerate partial MOF degradation and radionuclide leakage, emphasizing the importance of stability testing in serum, plasma, and competitive biological media for accurate PET interpretation.<sup>52</sup> Targeted PET imaging using antibody- or peptide-functionalized MOFs is increasingly explored for tumor-specific delivery and enhanced imaging contrast.<sup>15</sup> However, MOF nanoparticles (often 50–200 nm) are significantly larger than classical immune PET constructs such as  $^{89}\text{Zr}$ -trastuzumab, which may alter pharmacokinetics.

## Fluorescence Imaging

The high-resolution, real-time visualisation of tumors or tumor margins through fluorescence contrast agents is possible using fluorescence imaging. Recent developments have shown that MOFs have the potential to be highly promising fluorescence agents due to their special internal architecture, tunable pore structure and ability to incorporate or encapsulate fluorescent moieties such as quantum dots (QDs). MOF-based fluorescence agents are characterised by the combination of the merits of MOF scaffolds, namely, high surface area, structural stability, and flexibility of functionalisation, and the optical characteristics of fluorescent dyes, lanthanide centres or QDs, thereby improving the sensitivity and specificity of tumour imaging.<sup>12,54,55</sup>

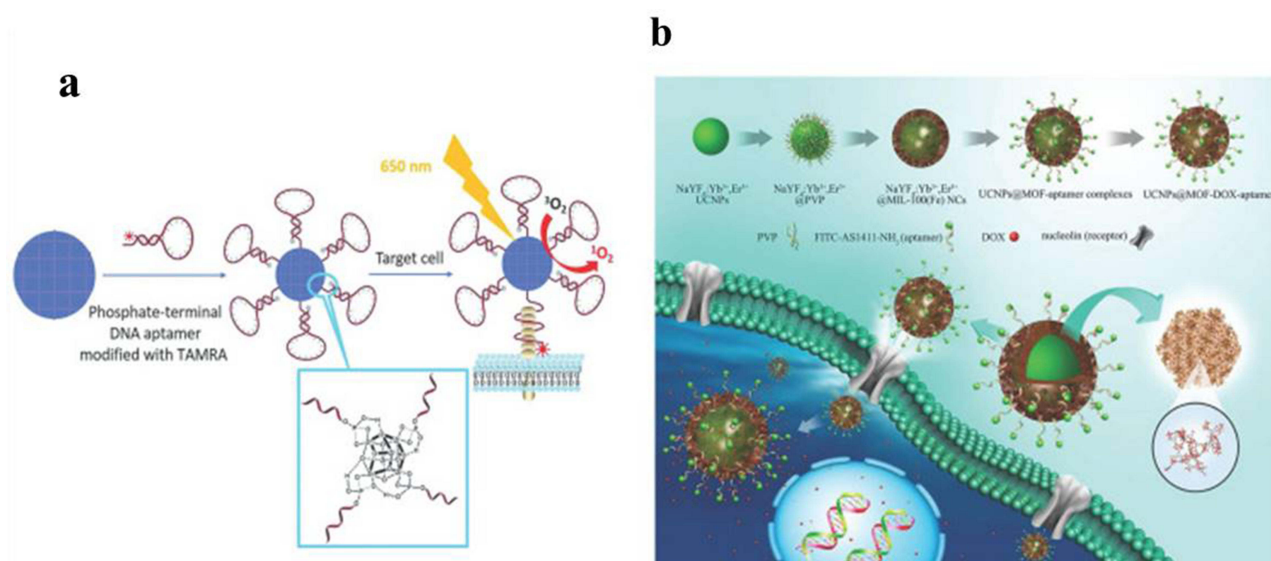
MOFs functionalised with QDs or using QDs concepts (so-called QD-MOF hybrids) have been designed to use as tumour imaging contrast agents. As an illustration, a survey on QD which comprises MOF hybrid systems shows how the aggregation of QDs in MOF matrices can be reduced, they can be made more photostable, and more efficient tumour-imaging agents.<sup>56</sup> In these systems, localisation and stabilisation of the fluorescent QDs are performed by the MOF in a biocompatible environment, which allows an increase in fluorescence emission and tumour-targeting performance (with surface functionalisation, eg, peptides, antibodies).

The advantages of MOF based fluorescence agents in fluorescence guided surgery are especially attractive. In surgery, FGS can be used to see tumour margins in real time under the fluorescence light during the resection of tumours. Tumour-targeting ligand (folate, RGD peptides) functionalised MOFs will accumulate within tumour tissue and lead to a tumour-to-background fluorescence ratio that helps to better excise the target tumour tissue and minimise the amount of tumour tissue remaining.<sup>57</sup> According to a more recent review of MOF applications in imaging-guided tumour diagnosis, MOFs have the ability to enhance tumour targeting, image delineation and be utilised as dual or multi-modal fluorescence-based agents.<sup>35</sup>

Moreover, MOF based fluorescence agents tend to have greater photostability, increased payload of fluorophore and controlled release kinetics as compared to free dyes.<sup>58</sup> Since fluorophores can typically be rapidly photobleached or distributed non-specifically by themselves, the photostability and biodegradation of dyes and fluorophores in MOF pores can be used to preserve dyes and fluorophores, and dyes from quenching and degradation, and design stimuli-controlled release (eg, pH, enzyme) to tumour microenvironment specificity.<sup>59</sup> Moreover, the modularity of MOF synthesis can allow both combinations of fluorescence imaging with therapeutic and other imaging modalities (eg, MRI, CT). A MOF platform could, eg, have a fluorescent QD moiety and a paramagnetic metal center attached to it, thus supporting intraoperative fluorescent guidance and preoperative MRI imaging.<sup>60,61</sup> Such a multimodal property is beneficial in tumor therapy - a single imaging agent (the MOF) performs many functions, enhancing clinical practice and diagnostic efficiency.<sup>62</sup>

Nevertheless, along with these encouraging properties, there are still some challenges to clinical translation of MOF based fluorescence imaging agents. These are the possible toxicity of metal constituents or QDs (particularly, heavy metal based QDs), the biocompatibility and clearance, the absence of aggregation or instability in physiological media, the efficient tumor targeting and retention, and the in vivo safety with the application of FGS. It is noted in literature that reproducibility of nanoscale synthesis, stable surface modification, and depth of fluorescence penetration in vivo (particularly of near-infrared emission) are major challenges to next-generation clinical usage.<sup>35</sup> The schematic illustration of phosphate-terminal DNA aptamer conjugation onto a Zr-MOF nanoparticle quencher for target-induced imaging and photodynamic therapy and synthesis procedure, drug-loading process, and receptor-mediated endocytosis pathway of targeted UCNPs@MOF core-shell nanocomposites (NCs) is shown in Figure 5.<sup>62</sup>

Fluorescence imaging in metal-organic frameworks (MOFs) is increasingly categorized into two optical windows: the first near-infrared window (NIR-I, 650–900 nm) and the second near-infrared window (NIR-II, 1000–1700 nm). NIR-I fluorophores have been widely used due to relatively mature dye chemistry and detector availability; however, their clinical utility is limited by significant photon scattering, shallow tissue penetration, and high tissue autofluorescence, which collectively reduce imaging contrast in deep-seated tumors. In contrast, NIR-II imaging provides substantially improved spatial resolution, higher signal-to-noise ratio, and deeper tissue penetration due to reduced photon scattering and lower tissue absorption at longer wavelengths.<sup>63–68</sup> Recent advances demonstrate that MOF-based fluorescent platforms can be engineered to incorporate NIR-II emitters or act as nanocarriers for NIR-II dyes, enabling enhanced



**Figure 5** (a) Schematic illustration of phosphate-terminal DNA aptamer conjugation onto a Zr-MOF nanoparticle quencher for target-induced imaging and photodynamic therapy. (b) Schematic illustration of the synthesis procedure, drug-loading process, and receptor-mediated endocytosis pathway of targeted UCNPs@MOF core-shell nanocomposites (NCs). The insets show enlarged views of the porous cavities of MIL-100(Fe) and its partial coordination structure, respectively.<sup>62</sup>

tumor visualization beyond several centimeters of tissue depth. This transition from NIR-I to NIR-II systems is particularly important for accurate tumor delineation and real-time intraoperative imaging.<sup>69,70</sup> Importantly, integrating NIR-II functionality into MOFs also facilitates multimodal imaging when combined with MRI or PET-active components, supporting theranostic applications in oncology.<sup>71</sup>

## CT

CT is a technique of imaging that is used in clinical practice with the highest frequency, allowing high-resolution images of internal structures without invasiveness.<sup>72</sup> It is based on X-ray absorption to produce high-resolution cross-sectional body images. Although CT imaging is widely used, there are some limitations to the imaging technology especially the contrast resolution and specificity of the imaging of the soft tissue or tumor. MOFs are new promising materials in improving CT imaging because of their distinctive structural characteristics, composition manageability and combination of diverse imaging modalities. The potential use of MOFs as CT contrast agent is gaining more attention due to the bonding of metal ions that have high X-ray absorption properties.<sup>73</sup> Metals with a high atomic number (Z) tantalum (Ta), iodine, barium (Ba), and gadolinium (Gd) have a high level of X-ray absorption, which is very required in enhancing contrast in CT images.<sup>74,75</sup>

Tunable porosity and surface functionality is one of the key benefits to using MOFs as CT contrast agents. It is possible to design MOFs to ensure a regulated release of metal ions into the bloodstream to have long-lasting and high-contrast imaging of tumors. Likewise, Gd-based MOFs have been investigated as dual-modal contrast agents, with the possibility to have both CT and MRI images of the same system.<sup>62,76–78</sup> This Gd ions addition improves the X-ray absorption properties of the MOF and also allows the MRI contrast to be improved, providing the benefits of multimodal imaging. The metal ions that are embedded in MOFs are critical towards the improvement of their work as CT contrast agents. These metal ions have a decreasing X-ray absorption depending on Z with atoms of higher values of Z attenuating X-ray better resulting in better image contrast.<sup>79</sup> MOFs made of metal of higher atomic numbers like Ta, iodine, and Ba have a better X-ray attenuation than the traditional iodine based agents.<sup>80,81</sup>

Clinically used iodinated contrast agents typically show a CT attenuation efficiency on the order of ~20–40 HU per mg I/mL (or equivalent iodine molar concentrations) at standard clinical tube potentials (120 kVp), with the exact value depending strongly on scanner calibration, beam hardening, filtration, and spectrum shape. This dependence arises from the strong energy dependence of iodine's K-edge (~33.2 keV) and the polychromatic nature of clinical X-ray beams.<sup>82,83</sup> By comparison, the



high-Z nanomaterials provide improved X-ray absorption owing to their higher atomic number and mass attenuation coefficients. For instance, gold nanoparticles are known to offer excellent CT contrast, usually giving about 4.8–5.4 HU/mM (equivalent to a few tens of HU per mg/mL depending on various parameters and voltage), particularly at clinical voltages of 120 kVp.<sup>82,84</sup> In a similar way, bismuth nanoparticles have excellent X-ray attenuation properties because of the high atomic number of Bi ( $Z = 83$ ). It is shown both experimentally and in vivo that bismuth nanoparticles possess very effective CT contrast properties (hundreds of HU from clinically feasible doses), usually outperforming standard iodinated contrast agents for the same amount of injected material.<sup>83</sup> Regarding CT contrast agents based on MOFs, it is clear that the effective attenuation properties will be greatly determined by the use of high atomic number metals as nodes, including hafnium (Hf), Zr, Ta, and bismuth (Bi). The reason is that, thanks to the porosity of the MOFs and their very high metal content, MOFs can attain enhanced effective attenuation due to their concentration levels compared to traditional iodine-based materials. However, CT signal intensity is influenced not only by concentration but also by particle dispersion, aggregation state, hydration environment, and X-ray energy dependence.<sup>85–88</sup>

An interesting development in these recent works is the shift from traditional monofunctional MOFs to hybrid MOFs that are capable of performing multiple functions or responding to environmental stimuli. Prior work has concentrated mainly on zirconium-containing MOFs due to their superior hydrolytic resistance, stability, and higher loading efficiency, which makes them suitable for biomedical applications.<sup>16</sup> However, in recent years, research tends to be focused on the utilization of hybrid and biomimetic MOFs by including various additives such as polymers, cell membranes, peptides, or responsive linkers, addressing concerns like the immune system response, lack of sufficient specificity toward cancer cells, and inadequate stability.<sup>24</sup> In addition, iron and manganese based MOFs also received significant attention due to their improved biocompatibility and decreased toxicity in comparison to gadolinium MOFs. It is interesting that Mn based MOFs can exhibit excellent redox property and produce  $Mn^{2+}$ , thus realizing MRI and degradation-dependent imaging.<sup>24</sup> Fe-based MOFs are also extensively investigated due to their good degradation properties in biological systems, providing potential for clinical use in drug delivery and imaging applications.<sup>16</sup> Such trends are evident in other recent literature studies that focus on developing translational MOFs with improved biocompatibility, imaging capabilities, multimodality, and personalized theranostics, among others.<sup>89</sup>

## Multimodal Imaging Using MOFs

The development of MOFs-based integrated metal-organic structures in combination with several imaging modalities has become a groundbreaking solution in tumor diagnostics. Researchers are obtaining improved diagnostic accuracy and improved clinical results by incorporation of MOFs into other imaging modalities, which include MRI, PET, and fluorescence imaging. The high surface area, biocompatibility, and customizable porous structures of MOFs make them the best to be used in multimodal imaging. They can be readily conjugated with contrast agents or radionuclides into imaging agents that are more comprehensive in analyzing the tumor and accurately localizing it.<sup>90,91</sup>

One application of MOFs has the potential to be in dual-modality imaging, where two or more imaging modalities are used in series to exploit the complementary nature of the two. As an example, MOFs like palladium (Pd)-hafnium-based (Pd@Hf-EDB) have been able to improve CT and photoacoustic imaging (PAI) at the same time. This dual-modality system increases contrast in addition to facilitating the precise tracing of tumor boundaries thereby increasing the overall diagnostic accuracy.<sup>90</sup> This technology is also revolutionizing the manner in which tumors are detected, staged, and monitored because it provides both structural and functional understanding about tumors.

Furthermore, recent developments, as well, resulted in development of hybrid imaging agents, in which MOFs are used alongside other nanoparticle platforms in multimodal applications. Namely, nanoparticles that have been created using core-shell MOFs have been utilized to enhance the stability and bioavailability of the contrast agents. These bimodal systems have the ability to apply in both MRI and fluorescence imaging, which allows them to track the tumors in real-time, as well as deliver therapeutic agents that are targeted.<sup>92</sup> The flexibility of MOFs in these hybrid designs has not limited MOFs to imaging but also can be used in other fields like theranostics, where diagnostics and therapy are on the same platform.

The use of MOFs in theranostics has been particularly able to be useful in cancer therapy. Porphyrin-based MOFs are being integrated into imaging systems to detect tumors and at the same time perform photodynamic or photothermal therapy by their nature of inherent fluorescence. Such MOFs as those based on Zr-based porphyrin scaffolds not only

enable visualization of tumors using fluorescence but also permit the delivery of energy to cancer cells using this scaffold to achieve therapeutic effects.<sup>93</sup> The possibility to monitor the actual performance of the treatment and at the same time deliver therapeutic agents is a major breakthrough in individual cancer therapy.

Moreover, MOFs integration along with PET is an effective way of molecular imaging of cancer. Recently, MOF-based PET imaging using radiolabeled metal centers has been developed, which offers high resolution pictures on tumor location at the molecular scale.<sup>94</sup> The associated benefits of these PET-MOF agents are that they can identify small tumors or metastasis that may be overlooked by other conventional methods of imaging and therefore an early detection and intervention are feasible.

Nevertheless, no matter how promising all these developments are, a number of obstacles are still present in the process of extending the MOF-based multimodal imaging systems beyond the laboratory to the clinical environment. The problems of the stability, biodegradation and possible toxicity of MOFs should be resolved to make them safe to use in human beings.<sup>95</sup> It is important to note that the growth of biocompatible MOFs, as well as control release mechanisms of both imaging agents and therapeutic drugs, is essential to their clinical success. Moreover, a mass production of MOFs that will streamline its synthesis to enhance efficiency and reduce the cost of production will be necessary to enable massive clinical usage.

## Tumor Targeting and Drug Delivery Potential MOF Functionalization for Tumor Specificity

The surface modification of MOFs is critical in increasing their selectivity to tumor therapy and diagnosis. It is feasible to enhance the selective tumor marker binding and minimise off-target effects on tumor cells, by functionalizing MOFs with tumor-specific ligands, including peptides, antibodies, and small molecules. Tumor-associated antigens that are over-expressed have become a target of MOF functionalization because smaller molecules (peptides) can readily access these antigens. As an example, a recent study has emphasized targeting fibroblast activation protein (FAP) and transforming growth factor beta (TGF) as peptides therapy and imaging tools of tumors that can be upregulated in several cancers.<sup>96,97</sup> When conjugated to MOFs, these peptides can be used to achieve better targeting and longer retention at the tumor locations thereby facilitating more effective drug delivery and tumor imaging.

Antibodies are also a great potential in tumor targeting as they are very specific with considerable affinity towards the cancer antigens. Both the diagnostic and therapeutic uses of antibody-conjugated MOFs have been pioneered through the development of the antibody-conjugated MOFs. This was demonstrated in a study by Anderluzzi et al, 2024 which showed that antibody-based MOF functionalization targeted the tumor vasculature, such as the membrane-bound enzyme CD13.<sup>98</sup> In addition to making the targeting process more efficient, this method also boosted the therapeutic activity of the conjugated drugs using the biological characteristics of MOF materials.

Besides, small molecules like epidermal growth factor receptor (EGFR) and integrin 21 beta 3 have been incorporated into MOFs to target them more effectively in tumor targeting. They enable the accurate targeting of chemotherapeutic agents as recent research demonstrates the ability of MOF-based systems to deliver specific types of tumors.<sup>99,100</sup> The targeted delivery of such molecules, reduction of systemic toxicity as well as the pharmacokinetics of encapsulated drugs can be achieved through functionalization of MOFs with these molecules.

The presence of tumor-targeting peptides and small molecules in MOFs further increases the ability of the material to serve in selective targeting. The recent advances of the application of peptide-related approaches, including those demonstrated by Mathieu et al, 2024, reflect the benefits of supramolecular assembly of peptides onto MOFs to reach high specificity to tumor-associated antigens, including HER2, which is a powerful marker in breast cancer.<sup>101</sup> This method leads to a higher bioavailability of drugs in the tumor site and is much more beneficial to the outcome of therapeutic effect. Moreover, these peptide-functionalized MOFs have high tumor penetration and retention, proving their applications in the further treatment and diagnostics of cancer.<sup>102</sup>

Combination of MOFs and tumor-targeting ligands will transform cancer treatment, offering highly specific, highly effectual and versatile platform of drug delivery and diagnostic imaging. Promising opportunities of MOF-based systems in precision medicine can be maximized by further studies on surface modification methods and ligand choices.

## MOFs as Drug Delivery Carriers in Tumor Imaging

The exceptional structural properties of MOFs – their high porosity, large internal surface-areas, tuneable pore sizes and surface chemistries – have made them very desirable as delivery vectors of therapeutic agents or imaging probes in tumor therapy and imaging. MOFs are an optimal system to encapsulate or adsorb drugs or contrast agents as reviewed articles have highlighted and therefore combining diagnostic imaging with therapeutic delivery (theranostics) in a single system.<sup>103</sup>

MOFs have been engineered to carry out small-molecule chemotherapeutics or photosensitizers, radionuclides, fluorescent probes or magnetic contrast agents, in the tumour imaging and therapy context. As an example, Yang et al, 2021 discuss nano-MOFs as drug carriers and indicate that the high drug containing capacity is due to the large pore volume and the versatile chemical nature of the structure.<sup>104,105</sup>

The loading may be carried out via physical encapsulation (via pores or voids), via adsorption on surfaces, via covalent conjugation to MOF linkers, or via post-synthetic alteration of the surface. Khafaga et al, 2024 remark that MOF functionalisation allows better stability, drug solubility and bioavailability.<sup>106</sup> In tumour imaging, imaging moieties can also be conjugated to such drug-loaded MOFs such that the distribution, accumulation and release of the therapeutic agent can be tracked in vivo. The article by Patil et al, 2024 about the stimuli-responsive MOFs that integrate targeted delivery and imaging and cargo release.<sup>20</sup>

## pH-Responsive Drug Release

One of the most important processes through which MOFs release cargos in tumour environments takes advantage of the acidity of the tumour microenvironment (pH) in comparison with normal tissues (eg, pH = 6.57.0 vs pH = 7.4). MOFs, like zeolitic imidazolate frameworks (ZIFs), have been known to degrade when subjected to acidic pH and release drugs. As an example, dihydroartemisinin (DHA) was delivered in a tumour-therapy setting using an acid-responsive ZIF-8 system.<sup>107,108</sup> To validate the utility of pH-responsive MOFs in general, Guillen et al, 2022 showed a pH-stimuli thin film of MIL-88B(Fe) to release ibuprofen.<sup>109</sup>

More broadly, Yan et al, 2021 provide an overview of environmental-sensitive MOFs that prevent the premature release of drug into the blood and instead, cause release of their cargo only at the tumour locations upon stimuli, eg, low pH.<sup>108</sup> This mechanism assistance in tumour imaging/therapy encompasses enhancement of tumour accumulation (through the enhanced permeability and retention effect) and local delivery of contrast or therapeutic agent, thus enhancing imaging specificity and decreasing systemic side effects. Due to their porous structures, MOFs exhibit high drug-loading capacity, facile surface functionalization, and favorable biocompatibility. As a result, numerous MOF-based stimuli-responsive drug delivery systems have been developed, leading to considerable advances in recent years. Schematic illustration of MOFs-based stimuli-responsive system for drug delivery is shown in Figure 6.<sup>110</sup>

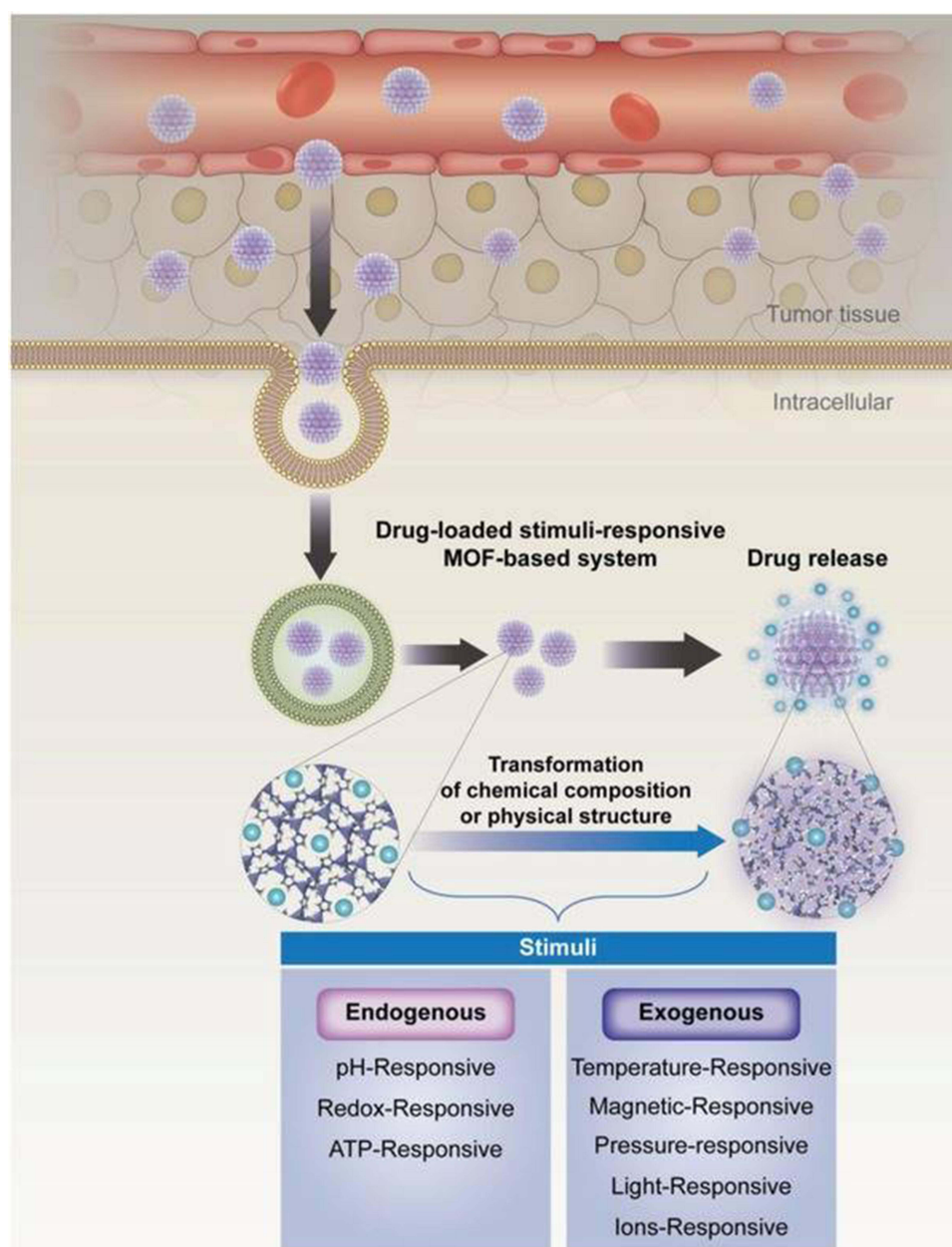
## Enzyme-Responsive Drug Delivery

Besides the pH, endogenous enzymes or tumor-overexpressed biomolecules can serve as stimuli to MOF-based release systems. A growing review is enzyme-immobilised MOFs, in which tumor microenvironment triggers enzymatic catalysis of drug release by MOF carriers.<sup>111</sup> Indicatively, a clickable PEG phosphate ligand attached to a Zr based MOF (UiO 66) allowed the release of drug to be controlled in the presence of certain enzymes.<sup>112</sup> These enzyme responsive systems will be able to enhance selectivity of release (only in tumour or peritumour regions of high enzyme concentration) and hence enhance contrast between tumour and normal tissue in imaging or better therapeutic index in therapy.

## Specific Drug Discharge Processes

In addition to passive accumulation and release of tumours, MOFs have been engineered to be actively targeted to tumour cells or tumour vessels. It is done through conjugation of ligands (eg, antibodies, aptamers, peptides) to the MOF surface, which identify tumour specific markers. As an example, Wang et al showed aptamer-functionalised Fe-based MOF, which targeted tumour cells.<sup>113</sup> In a different report, an aptamer-functionalised Fe<sub>3</sub>O<sub>4</sub> at MOF nanocarrier facilitated simultaneous fluorescence imaging and targeted delivery of drugs to triple-negative breast cancer cells.<sup>114</sup> Such targeting in the imaging setting enhances the concentration of the imaging/therapeutic payload in tumor tissue,





**Figure 6** Schematic illustration of MOFs-based stimuli-responsive system for drug delivery.<sup>110</sup>

thereby enhancing contrast and potentially decreasing off-target background. Kong et al, 2024 present a review of MOFs in tumor-targeted drug delivery systems, including the focus on active targeting.<sup>115</sup>

### Acquisition of Tumour Imaging

The delivery of the therapeutics, release, and accumulation of the payload of imaging probes into tumors can be imaged on the same platform when therapy or imaging probes are loaded into MOFs. A study explains the combination of imaging (eg, MRI, fluorescence, CT) with drug delivery of such theranostic MOFs, which allows them to monitor the release and therapeutic response in real-time.<sup>116,117</sup> The Advances, applications, and challenges of MOFs in tumor imaging: from single-modal systems to multifunctional theranostic platforms are given in Table 3.<sup>12,35,37,38,118–120</sup>

**Table 3** Advances, Applications, and Challenges of MOFs in Tumor Imaging: From Single-Modal Systems to Multifunctional Theranostic Platforms

| MOF/MOF-Based System<br>(Evolutionary Category)                             | Imaging Modality (Tumor)/<br>Application                         | Key Findings/Advantages<br>(Multimodal Integration Emphasized)                                                                                                                                                                                                      | Limitations/Challenges<br>(Clinical Translation Barriers)                                                                                  | Reference |
|-----------------------------------------------------------------------------|------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Pt-decorated nanoscale MOF<br>(NMOF-545@Pt)                                 | CT/MRI/Photoacoustic imaging<br>(PAI) + imaging-guided therapy   | Demonstrates true multimodal integration (CT–MRI–PAI); Pt enhances X-ray attenuation (CT), accelerates T <sub>1</sub> relaxation (MRI), and boosts photoacoustic signal; enables imaging-guided synergistic therapy (PTT + RT) with strong tumor inhibition in vivo | Concerns regarding Pt-related long-term toxicity, biodistribution heterogeneity, and incomplete clearance pathways                         | [118]     |
| Early-generation nanoscale MOFs<br>(generic platform)                       | MRI/CT/PET/optical/PAI (proof-of<br>-concept multimodal imaging) | Establishes MOFs as universal multifunctional carriers due to high porosity, tunable chemistry, and ability to load imaging agents; foundational step toward multimodal imaging platforms                                                                           | Limited physiological stability, partial degradation in vivo, insufficient targeting specificity, and incomplete pharmacokinetic profiling | [12]      |
| MOF-based smart nanoplateforms<br>(hybrid/engineered systems)               | CT/MRI/PET and emerging<br>multimodal imaging systems            | Incorporation of metals/dopants and functional coatings enables signal amplification and tumor targeting; supports integration of imaging with drug delivery and theranostics                                                                                       | Biocompatibility, immunogenicity, off-target accumulation, and reproducibility of complex architectures remain unresolved                  | [119]     |
| Theranostic MOF nanocomposites<br>(imaging + therapy integrated<br>systems) | Multimodal imaging + imaging-<br>guided therapy                  | Enables single-platform diagnosis + therapy + monitoring; high loading capacity; programmable release; facilitates precision oncology approaches                                                                                                                    | High synthetic complexity, batch-to-batch variability, instability under physiological conditions, and incomplete toxicological profiling  | [120]     |
| Metal-based MOFs for MRI (Gd, Fe,<br>Mn systems)                            | MRI contrast enhancement                                         | Fe- and Mn-based MOFs provide safer alternatives to Gd-based agents with improved biodegradability; enhanced relaxivity and tumor accumulation via nanosizing and surface modification                                                                              | Metal ion leakage risk (Gd), partial degradation, unclear long-term fate, and regulatory safety concerns                                   | [38]      |
| Dye-loaded MOF optical imaging<br>systems                                   | Fluorescence/luminescence<br>tumor imaging                       | MOF porosity protects fluorophores from quenching and degradation; enhances signal stability and tumor accumulation; supports optical imaging-guided tracking                                                                                                       | Limited tissue penetration depth, photobleaching, and poor deep-tumor imaging performance                                                  | [12]      |
| MOF–metal hybrid nanocomposites                                             | MRI/CT/PAI + therapy<br>(multimodal theranostics)                | Synergistic combination of MOF porosity with metallic imaging/therapeutic functions enables enhanced contrast and multifunctional therapy                                                                                                                           | Structural complexity, reproducibility issues, unclear metabolism, and long-term toxicity concerns                                         | [118]     |
| Radiolabeled MOFs/isotope-doped<br>MOFs                                     | PET/PET-MRI multimodal imaging                                   | Combines ultra-high PET sensitivity with MOF structural tunability, enabling early tumor detection and quantitative imaging                                                                                                                                         | Radiolabel instability, radiotoxicity, rapid clearance challenges, and regulatory barriers                                                 | [37]      |
| Stimuli-responsive MOF systems (pH/<br>redox/hypoxia)                       | Imaging-guided drug delivery +<br>therapy                        | Tumor microenvironment-responsive activation enables spatiotemporal imaging and controlled therapeutic release, improving selectivity                                                                                                                               | Tumor heterogeneity limits predictability; in vivo validation still limited; stability and reproducibility concerns                        | [35]      |

|                                                               |                                                 |                                                                                                                                                 |                                                                                                                            |       |
|---------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|-------|
| Targeted MOFs with engineered pore size and surface chemistry | Multimodal imaging + targeted delivery          | Surface functionalization improves tumor accumulation, circulation time, and imaging contrast enhancement; tunable drug/imaging payload loading | Protein corona effects, instability in blood circulation, and trade-off between targeting efficiency and clearance         | [37]  |
| Imaging-guided MOF drug delivery systems                      | Multimodal imaging + chemotherapy monitoring    | Enables real-time tracking of drug distribution, uptake, and therapeutic response; supports dose optimization through imaging feedback          | Premature drug leakage, systemic toxicity risk, and poor clinical translation evidence                                     | [35]  |
| Integrated theranostic MOFs                                   | Fully integrated imaging + therapy + monitoring | Represents next-generation “all-in-one” nanoplatforms combining diagnosis, treatment, and monitoring to reduce systemic exposure                | High system complexity increases failure risk; biological heterogeneity limits reproducibility and clinical predictability | [119] |

## Prospects of MOFs in Tumor Imaging

### Enhanced Sensitivity and Resolution

A highly attractive application of MOFs to tumour imaging is that it has the potential to show improved sensitivity and resolution relative to established contrast or imaging agents. This is because of their characteristic structural, chemical and functional tunabilities, which all combine to generate superior signal generation, superior contrast-noise and spatial resolution in imaging modalities.<sup>121–123</sup>

To begin with, MOFs have the potential to deliver higher amounts of imaging-active (eg, paramagnetic metal ions to be used in MRI, heavy elements to be used in CT, fluorophores to be used in optical imaging) amounts of imaging-active components per particle than many other conventional agents. For example, nanoscale MOFs (NMOFs) have large internal pore volumes, high density of metal-ion group and adjustable organic linkers, which enable high concentrations of imaging moieties to be loaded or incorporated.<sup>12,38,62</sup> The high loading can be translated to the higher signal per nanoparticle or dose which can increase the sensitivity ie the capacity to detect low concentration of target tissue or small tumours.

Secondly, the tunable surface chemistry and structure of MOFs facilitate enhanced targeting and retention in tumour tissues, which enhances signal specificity and resolution of tumour versus background.<sup>103,124</sup> The fact that it is possible to functionalize MOF surfaces with targeting ligands (eg, peptides, antibodies) or effectively use enhanced permeability and retention effects implies that imaging contrast can be better localized to malignant tissue, enhancing tumor to normal tissue contrast and hence increasing effective resolution.<sup>35,62</sup> Further, the porosity of MOFs allows imaging agents to be stabilized by the porous structure and thus not lost by quenching or degradation during their transit to the tumor site, retaining signal integrity.<sup>12</sup>

Thirdly, the MOFs enable multimodal imaging, which brings together various imaging modalities (eg, MRI + optical + CT) within a single nanoparticle platform. This multimodality has the capability to offer complementary contrast modalities (eg, high spatial resolution MRI, high sensitivity optical, or high-density CT) and hence can enhance the overall resolution: anatomical, functional or molecular.<sup>38,125</sup> An example is a MOF particle that can contain a paramagnetic metal cluster to provide MRI and a fluorophore to provide fluorescence imaging, to allow a macro-scale imaging of the particle and microscopic localization.<sup>37</sup>

Moreover, the fine size and shape control of MOFs at the nanoscale can have a direct effect on imaging resolution. Particles between 20–200nm can extravasate into tumour interstitium yet not be quickly eliminated by the kidney or mononuclear phagocyte system. Tumor penetration and uniform distribution, which can be improved by adjusting MOF size, morphology and surface charge, are factors that can lead to high -resolution imaging of tumor heterogeneity. As it is observed in the review by Duman et al, 2021 NMOFs do tend to have tunable sizes and structures as compared to other nanocarriers.<sup>12</sup>

Moreover, mechanistically, MOFs permit amplification of signals based on principles of clustering of contrast agents, confinement and improved relaxivity (in MRI). To give an example, the high local concentration of paramagnetic centres in a MOF can be used to provide higher relaxivities (ie a larger effect per unit metal) than free ionic contrast agents in MRI applications.<sup>12,38</sup> The increased relaxivity implies that smaller doses can be used to produce the same (or better) contrast and this improves sensitivity and reduces background interference.

Lastly, the background and off-target signal are also reduced with the help of MOFs which indirectly leads to better resolution. Since MOFs may be passively loaded or passively functionalized to stay silent until they arrive at the tumor microenvironment (as in stimuli-responsiveness), the difference in tumor and normal tissue is better defined, and small lesions may be detected.<sup>31,108,126</sup> Even though this mechanism is adjacent to those of drug-delivery, it plays a role in imaging towards the future of high spatial resolution, and the detection limits of imaging. According to reviews by Hou et al 2024, MOFs are important such that they are crucial to tumor cell targeting, identification, imaging, among other things in the tumor-diagnostic scheme.<sup>35</sup>

### Biocompatibility and Safety

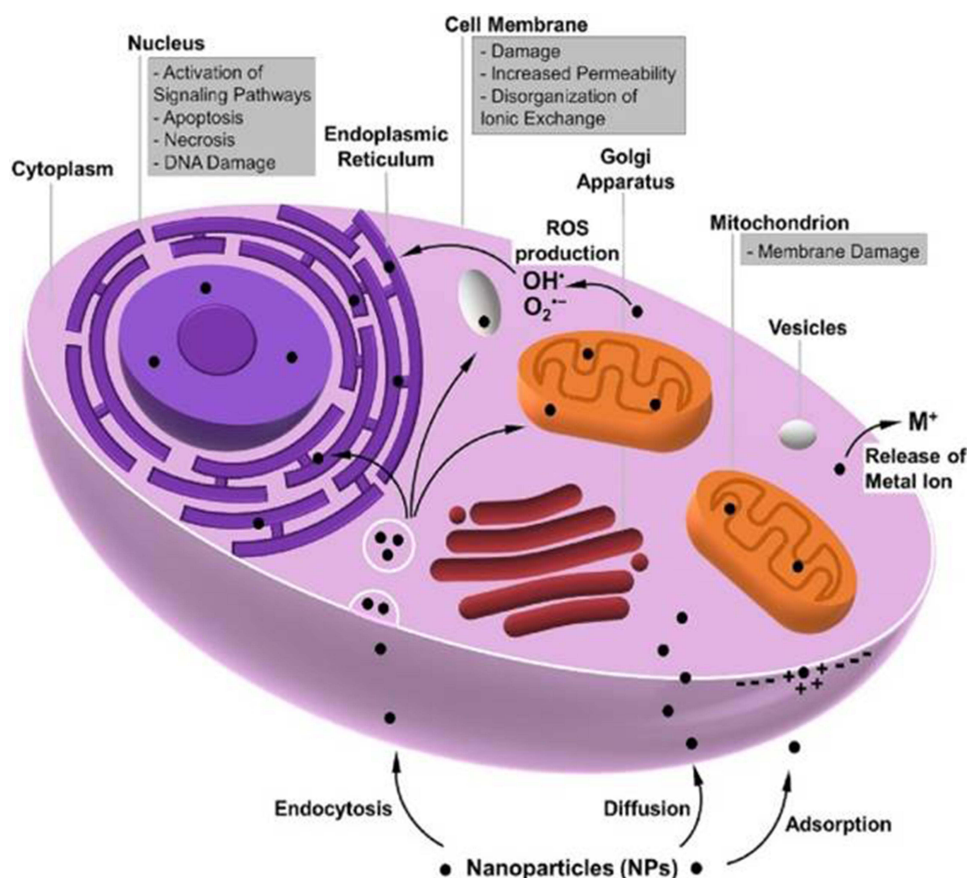
Tumor-imaging translation of MOFs biocompatibility and safety profile is a major consideration. The biocompatibility of MOFs is highlighted in a number of recent reviews to be dependent upon a variety of design factors - the type of metal ion used, ligand chemistry, particle-size distribution, surface functionalization, colloidal stability and the degradation/clearance routes of these particles in the biological host.<sup>28,127,128</sup>

MOFs constructed with biologically favorable metals (like Fe, Zn or Mg), ligands that are benign should have reduced cytotoxicity and have more favorable biodistribution properties. As one example, MOFs containing what is deemed as an essential metal in the body eg, Fe, Zn and Mg have been reported by Singh et al, 2021 to have a better biocompatibility.<sup>127</sup> Further approaches to minimise immune recognition, oxidative stress and damage of healthy tissues are surface functionalization (eg, PEGylation) and size/shape control.<sup>13,128</sup>

In terms of in vivo stability and clearance, MOFs should be stable enough to fulfill the imaging task (contrast generation and tumor targeting) but degradable to achieve clearance to prevent accumulation and toxicity over time.<sup>35,129,130</sup> Framework stability (strength of metal-ligand bonds), particle size, and vulnerability to physiological circumstances (eg, pH, ionic strength, enzymatic environment) determine biodegradability of nano-MOFs. Singh et al, 2021 synthesis reported in-vivo biodistribution, organ accumulation, clearance dynamics and immune responses of different MOFs.<sup>127</sup>

It has been demonstrated that some MOFs can be eliminated through a renal or hepatobiliary clearance route depending on size and surface characteristics. Nevertheless, most of the studies are at the small-animal scale, and long-term destiny (weeks to months) is less characterized. A 2024 study by Zhuang et al, 2025 points out that nanoscale MOFs multiscale profiling of biocompatibility, toxicity, inflammation and organ damage is yet to be explored.<sup>131</sup>

Having a tumor-imaging carrier, MOFs have a favorable safety profile when well-designed (compared to traditional imaging agents), and thus may have a lower systemic toxicity profile, in particular, should they release toxic contrast particles or non-specifically accumulate.<sup>12,120</sup> This justifies one of the major opportunities of MOFs in tumor imaging: that these carriers can combine high imaging capability with biological risk tolerability. Nevertheless, complete translation requires standardized toxicity assays, scalable and repeatable production in good-manufacturing-practice (GMP) conditions, and strict in-vivo clearance/accumulation information. Schematic illustration of the primary mechanisms underlying MOF-induced toxicity is shown in Figure 7.<sup>132</sup>



**Figure 7** Schematic illustration of the major mechanisms associated with MOF-induced toxicity. MOF-related toxicity may arise during cellular internalization processes, including endocytosis, diffusion, and membrane adsorption, potentially leading to membrane damage. Following internalization, MOF nanoparticles (MOF NPs) may also induce intracellular toxicity through reactive oxygen species (ROS) generation, thereby affecting cellular organelles such as mitochondria and the nucleus.<sup>132</sup>



## Scalability and Cost-Effectiveness

The viability of the implementation of MOF based imaging agents in clinical applications is based on not just on the performance and safety but also on the cost of production, scalability and economic feasibility. One of the key benefits of MOFs is their modular chemistry and tunable synthesis, which theoretically can be cost-effectively manufactured as opposed to less complex tailored nanoparticle systems.<sup>23</sup> However, there is still a problem of practical up-scaling.

The recent large-scale MOF production analyses suggest that although it is possible to produce at pilot-scale (kilogram) scale, production at multi-kilogram to ton scale is still limited by the design of the reactor, its yield, cost of purification/activation, solvent consumption, and shaping/housing of materials.<sup>131</sup> To illustrate, Chakraborty et al, 2024 outline the so-called techno-economic analyses and life-cycle assessments that MOFs should undergo in order to reach commercial status.<sup>133</sup>

MOFs have high active contrast agent loading per particle (lowering dose) and can incorporate many functions (theranostic) which could lower the overall cost of the agents and enhance cost-efficiency per diagnostic result.<sup>78,134</sup> Tunability of MOF chemistry can potentially allow the use of relatively cheap metals/ligands instead of the rare earth elements or highly engineered QDs, lowering the cost of raw materials.<sup>25,135</sup>

The modular assembly has a potential of simplifying regulatory and manufacturing pipelines (when standardized), which in the longer term may help to lower the unit-cost relative to a custom nano-agent.

Nevertheless, the cost-effectiveness of real clinical implementation will remain to be based on the requirements of reproducible purity, batch-to-batch reproducibility, stability, shelf-life, regulatory, and imaging efficiency. Summary: although MOFs have potential in the cost-effective and scalable production of imaging-agents, scalable and GMF-compatible production of imaging-agents on a large scale (biomedical imaging) has yet to be demonstrated.

## Recent Advances and Innovations in MOF Development

### Advancements in MOF Synthesis Techniques

In the recent past, there has been a significant positive shift in synthetic methods to develop biocompatible and stable MOFs, specifically designed to be used in biomedical imaging. As an illustration, mechanochemical, microwave-assisted and sonochemical pathways permit more reproducible and faster MOF generation that requires fewer solvents and less severe conditions and enhances scalability and minimizes toxic by-products.<sup>32,136</sup>

At the same time, machine-learning-supported design pipelines have recently been developed to predict MOF biocompatibility and toxicity by metal-ligand combinations that allow pre-selection of MOFs to be used in vivo.<sup>137</sup>

Together with these synthetic improvements, modifications in post-synthetic functionalization (eg, PEG-ylation, biomolecule-anchoring, surface-coating) have improved colloidal stability, bio-distribution and circulatory lifetime of MOFs in physiological media.<sup>138,139</sup> The surface engineering is needed to avoid premature aggregation or forming of protein corona both of which worsen imaging performance. These developments, together, empower the synthesis toolkit to allow MOFs with enhanced crystallinity, size/shape control, and increased adaptability to tumor-imaging applications.

### Novel MOF Structures to Improve Imaging

MOF structural design innovations have brought in hybrid and multifunctional structures that enhance imaging ability. An example is hybrid MOFs, in which two or more different metal nodes are combined, or in which the core and shell are MOFs and the core can offer a contrasting feature (eg, MRI-active metal) and the shell can include a fluorophore or imaging probe.<sup>35,140,141</sup>

Multimodal MOFs have been designed to accommodate multimodal imaging agents eg, to incorporate in a single MOF scaffold, MRI, fluorescence and CT contrast. This allows co-registration of imaging, superior fidelity of tumor delineation and functional/molecular imaging. The biomedical MOF domain is a field of research where reviews highlight these imaging and therapy-integration design advances.<sup>142</sup> Besides, the stability of MOFs in physiological conditions has been enhanced by choosing metal-linker nodes with high stability (eg, Zr based MOFs) or through surfaces of biocompatible shells, which increases the usability of MOF in tumor imaging in vivo.<sup>22</sup>

## Nanotechnology Interrelation

Combination of MOFs with other nanotechnology components (eg, nanoparticles, quantum dots, upconversion nanoparticles, liposomes) has provided additional opportunities to carry out targeted tumor imaging with increased precision and resolution. To illustrate, MOF shell hybrids, in which a MOF shell surrounds or decorates a magnetic or plasmonic nanoparticle result in combined functionalities: improved MR contrasting of the nanoparticle with a MOF shell and high payload and functionalization capacity of the MOF cage. According to the review by Chandra et al, 2025 the so-called smart nano-hybrid MOFs are the systems that combine MOFs and nanoparticles to deliver drugs, catalyze and image in cancer.<sup>143</sup>

Similarly, hybrid platforms with up-conversion nanoparticles (UCNPs) and MOFs enable near-infrared excitation and deep-tissue imaging, in which the MOF scaffold increases stability and surface functionalization.<sup>35,144</sup> These incorporations allow better tumour targeting (through ligand functionalisation of the hybrid surface), enhance signal amplification (through a high agent loading within the MOF) as well as imaging resolution (through synergistic contrast mechanisms). MOFs chemistry and nanotechnology is offering potent platforms that are awaiting further development to advanced tumor imaging, namely; high contrast, multi-modal read-out, and smart targeting, although the transition of these complex systems into clinical practice has not yet been realized.

## Challenges and Limitations in MOF-Based Tumor Imaging

There are a number of challenges and limitations associated with the application of MOFs to medical imaging of tumors. To start with, the biocompatibility and stability of nanoscale MOFs in physiological conditions is a problem: nanoparticles can be readily degraded or aggregated in blood, and this can cause unpredictable clearance, off-target retention, and imprecise imaging contrast. As an example, Liu et al, 2022 emphasize that MOFs showed desirable properties in terms of porosity and tunable composition to be used in bioimaging but, at the same time, their behavior in biological fluids needs powerful control.<sup>62</sup> MOF-based imaging probes have low biological targets (eg, endothelial transport, tumor interstitial pressure, reticuloendothelial system uptake) which limit targeting efficiency and tumor accumulation. In spite of surface functionalisation, several MOF-based systems fail to reach sufficient tumor uptake over background tissue and this lowers imaging specificity and sensitivity. According to Hou et al, 2024 MOF-nanocomposites have been used in tumor diagnosis with a tendency to lack optimal delivery to the tumor location.<sup>35</sup>

Despite the encouraging relaxivity improvement and multiple functionalization of MOFs as MRI contrast agents, however, there are still some problems left to solve. Most MOFs that contain gadolinium, for instance, pose certain health risks due to metal ion leaching, because free  $Gd^{3+}$  is known to cause nephrogenic systemic fibrosis.<sup>40,145–148</sup> Similarly, Mn- and Fe-based MOFs may undergo partial degradation in physiological environments, resulting in instability, altered relaxivity, and unpredictable pharmacokinetic behavior.<sup>88,149–151</sup>

Another serious problem is the possibility of aggregating nanoparticles in biological media, which can destabilize the dispersion of MOFs and facilitate their clearance by the RES, thus reducing tumor targeting. In addition, the reproducibility of the imaging signals from magnetic MOFs highly depends on particle size, surface chemistry, and metal coordination geometry. Despite recent advances in surface modification to improve stability and circulating time, the lack of long-term toxicity data continues to be an issue.<sup>88,151–153</sup>

Although the advantages offered by PET imaging with MOF nanoparticles include efficient radiolabeling and multimodal imaging, some practical and biological challenges hinder their clinical applications.<sup>88,152–154</sup> Radiolabeled MOFs might undergo radiolabels detachment or disintegration under physiological conditions, causing background signals or radiation exposure.<sup>88,119,155</sup> Furthermore, since the use of PET tracers like  $^{64}Cu$  or  $^{89}Zr$  demands fast labeling and injection processes, it becomes difficult to develop large-scale protocols for the mentioned materials.<sup>154,156</sup> Although surface modification could increase the stability of MOFs in vivo, issues connected with their safety, biodistribution, hepatotoxicity, or clearance mechanisms still raise questions.<sup>119,153,157</sup> Besides that, introducing radioactivity into multifunctional hybrid MOFs makes the material structure more complicated and decreases its reproducibility.<sup>125,152,154</sup>

CT-oriented MOFs containing high-atomic-number elements such as Hf, Zr, iodine, or gold demonstrate improved X-ray attenuation and imaging contrast; however, several limitations hinder their biomedical translation.<sup>132,158–160</sup> The incorporation of heavy-metal components may increase the risk of long-term metal accumulation and organ toxicity,

particularly in the liver and spleen following repeated administration.<sup>132,159–161</sup> Additionally, several of the CT-responsive MOFs are known to have comparatively slower rates of biodegradation, which could further complicate their clearance. As compared to other techniques such as MRI and PET, CT is known to be less sensitive at the molecular level, necessitating a higher dose of nanoparticles for obtaining adequate levels of contrast enhancement.<sup>158–160</sup>

There are manufacturability and reproducibility problems. It is not easy to synthesis MOFs in the nanoscale with even size, uniform surface chemistry and stability; translation could be compromised by batch-to-batch variations. According to the review by Patil et al, 2024 there are difficulties in the reliable engineering of stimuli-responsive MOFs to use them in cancer applications.<sup>20</sup> Lastly, there is a long way to translation to clinical use due to regulatory, scalability, cost and long-term evaluation challenges. While many proof-of-concept studies exist, the path from bench to bedside for MOF-based tumor imaging is limited by the lack of standardization and comprehensive in vivo safety/imaging data (eg, biodistribution, pharmacokinetics).<sup>37</sup>

The chance of degradation products of MOFs in vivo is important in establishing their biosafety properties, especially when MOFs are utilized for biomedical purposes that demand systemic delivery. After MOFs are degraded in vivo, they produce metal ions and organic linkers whose distribution in the body is greatly influenced by their tendency to bind to particular tissues in the body. For example, the metal ions from the degradation of Zr-MOFs have a strong tendency to bind to biological tissues containing phosphates.<sup>16,24,162</sup> This is due to the effect of strong coordination of Zr-O-P, which may lead to retention and even skeletal deposition, as has been seen before in cases involving free Zr in the context of nuclear imaging.<sup>163,164</sup> Apart from the change in metal ions' distribution, the structure of the MOF nanoparticles might trigger an immunological response. Nano-crystals have the ability to activate intrinsic immunity, such as macrophage uptake and activation of inflammasome, especially if their structures allow lysosomal retention.<sup>165</sup> These interactions can result in either temporary or permanent inflammation due to the presence of cytokine production and the accumulation of immune cells in the vicinity.<sup>165,166</sup> More significantly, studies have reported that surface treatments, such as PEGylation and biomimetic coating, effectively limit protein absorption and hence immunogenicity.<sup>167,168</sup>

## Future Directions and Opportunities

Considering the advancements being made in the realm of tumor imaging using MOF materials, a few possibilities for future research in this area can be pointed out. In the first place, the advancement of surface modification or functionalization appears as a highly interesting area for achieving improved tumor targeting abilities of MOFs. By adding some specific targeting ligands (such as antibodies or peptides) which recognize tumor markers, the ability of the MOFs to interact selectively with cancerous tissues is enhanced, thus leading to an increase in accuracy and lower off-target effects.<sup>38,130,169</sup> The next potential trend is stimuli-responsive MOFs, where imaging agents or therapeutic drugs can be released in response to biological stimuli, eg, pH, redox potential or enzyme activity within tumor microenvironment. This innovation can greatly enhance the accuracy of imaging and treatment by making sure that imaging agent is only activated at the tumor site instead of systemic toxicity and specificity of imaging. The development of MOFs capable of responding to stimuli like acidity or hypoxia in tumors is on the increase with research indicating that such systems can provide high-resolution imaging and significantly reduce adverse effects.<sup>170,171</sup>

The other promising area of research is hybrid MOFs, the integration of MOFs with other nanomaterials (graphene, carbon nanotubes, or gold nanoparticles). These hybrids can provide the synergistic advantages, including increased stability, multimodal imaging features, and better therapeutic effect. As an example, the hybrid MOFs have been generated to enhance the biocompatibility and stability of the MOFs in addition to enabling greater variety of imaging methods to be used, including PET in conjunction with MRI.<sup>172,173</sup> The potential opportunity is the development of multifunctional MOFs. Scientists are now working on the development of MOFs that combines imaging with therapy into a unified system, which is commonly known as theranostic agents. By enabling the simultaneous imaging and therapy of tumors (eg, chemotherapy, photothermal therapy or gene therapy), these multifunctional platforms can save the patient several treatments.<sup>174,175</sup> Such a two-fold role can contribute to the increased individualization of cancer treatment and its effectiveness. The recent literature has also attracted attention to theranostic MOFs, the potential of which extends to imaging and photodynamic therapy, which can be employed to personalize medicine.<sup>176</sup>

The important direction is to nanostructure MOFs in an attempt to increase their stability and minimize possible toxicity. To enable MOFs to make a jump towards a clinical use, they have to be reproducibly synthesized, and their biodegradation needs to be predictable and safe. It will be essential to advance in the preparation of stable, biocompatible MOF nanoparticles that will not be subject to aggregation and degradation under physiological conditions. Furthermore, to develop MOFs that break down in the body without acting as long-term negatives, scientists are looking into the utilization of biodegradable links and metal nodes.<sup>177</sup> MOF-based tumor imaging has potential that can be achieved through clinical translation. The barriers to entry of regulatory bodies, scalability and a better standardization of MOF production will play a key role in their usage in clinical settings. The forthcoming research needs to be directed toward the large-scale preclinical studies, multicenter clinical studies as well to determine the long-term safety, efficacy, and functioning of MOFs in real-life medical conditions.

## Conclusion

MOFs have emerged as highly adaptable nanoplatforms for tumor imaging because their tunable metal–organic interfaces enable precise control over contrast performance, payload loading, biodegradability, and targeting behavior. While many traditional contrast agents usually suffer a compromise between signal enhancement ability and potential toxicity issues, MOFs provide an inherently programmable modality that combines high sensitivity with controllable drug delivery, selective targeting of cancer tissues, and multifunctional theranostics. In this way, MOFs can be considered to have a unique role in clinical practice, especially with regard to multimodal and image-guided oncology. Recent research suggests that MOFs are shifting from the traditional single-component form to more stable hybrids with increased biocompatibility. Among these approaches, hybrid MOFs with biomimetic and surface modifications show promise in reaching the clinic earlier by addressing significant hurdles such as rapid clearance and nontargeted accumulation in the body. At the same time, Fe/Mn-based MOFs are replacing Gd-containing MOFs due to greater biodegradability. Despite substantial progress, several limitations continue to hinder clinical implementation, including reproducibility of synthesis, long-term safety evaluation, pharmacokinetic uncertainty, and regulatory standardization. Overall, this review highlights that future advances in MOF-based tumor imaging will depend not only on improved imaging performance, but also on the development of clinically translatable, scalable, and biologically predictable nanoplatforms supported by rigorous interdisciplinary validation.

## Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

## Ethical Approval and Consent to Participate

Not Applicable. This is a review paper and does not involve direct research on humans or animals.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. All the authors listed meet the criteria for authorship as per the ICMJE guidelines, read the final manuscript and agree to publish this work.

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