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Nanoscale MOF-Based Composites for Cancer Treatment

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Recently, the use of porous nanomaterials with large mesopores, tunable porosity, and high surface area has drawn particular interest in the treatment and imaging of cancer. Adding additional pores to nanostructures alters therapeutic agent loading capacity and controlled release. It enhances optoelectronic and optical features suitable for tumor treatment. For many years, the leading cause of disease-related death has been cancer, which seriously threatens human health. Nanoscale-metal-organic frameworks are thought to have potential applications in the treatment and biomedical imaging of various tumors due to the rapid advancement of nanomedicine. Since their high surface area and porosity, ability to be customized in size, numerous physicochemical properties, ease of surface functionalization, and simplicity in synthesis, metal-organic frameworks (MOFs), an emerging porous organic-inorganic hybrid material, have gained popularity in recent years. These characteristics make them ideal carriers for cancer theragnostic applications. Although significant research has been done for the potential use of nanoscale MOFs (NMOFs) in cancer diagnostic and therapeutics, more information regarding the stability, in-vivo clearance, toxicology, and pharmacokinetics is still needed to enhance the use of NMOFs in cancer diagnostic and therapeutic. Different techniques using NMOFs are systematically summarized, including chemotherapy, photodynamic therapy (PDT), photothermal therapy (PTT), chemodynamical therapy (CDT), radiotherapy (RT), and the combined therapy methods. Finally, a brief conclusion and outlook for biomedical applications of this special field is provided.

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INTRODUCTION

Clinic-based cancer diagnoses can provide a detailed disease pathology and progression, leading to more accurate diagnosis, extended life expectancy, and improved patient well-being. Optical imaging (OI) [1], magnetic resonance imaging (MRI) [2], computed tomography (CT) [3], positron emission tomography (PET) [4], and photoacoustic imaging (PA) are the most common imaging modalities utilized for cancer detection nowadays [5]. These methods of assessing image quality and diagnostic effectiveness are substantially degraded due to flaws, including limited sensitivity, shallow penetration depth, and insufficient tissue contrast [6, 7]. Chemotherapy, radiation, photothermal therapy (PTT), and photodynamic therapy (PDT), on the other hand, are often used in cancer treatment modalities. Extremely toxic side effects, poor selection, and ineffective targeting are drawbacks of chemotherapy as a main cancer treatment strategy [8-10]. Radiotherapy-based X-rays have drawbacks despite their capacity to destroy cancer cells, such as their restricted penetration into tissue, serious toxic and adverse effects, and limited uses [11]. PTT has drawbacks, such as difficult operation, heavy reliance on photothermal agents, and restricted therapeutic range [12]. O2 levels in tumor sites and photosensitizer (PS) sensitization effectiveness can affect PDT's effects [13, 14]. Imaging technologies

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enhance cancer patients' diagnostic and therapeutic capabilities. For accurate cancer theragnostic, methods of treatment and imaging techniques are merged to form an intelligent "all-in-one" complex [15-17]. Numerous nanomaterials have been created thanks to advances in synthetic technologies and surface modification techniques to satisfy the unique requirements of concurrent imaging diagnosis and effective cancer theragnostic [18-21]. The most effective cancer therapeutic platforms are usually based on the following fundamental properties [22]: 1) the ability to encapsulate both imaging agents and therapeutics due to the high cargo loading capacities, and 2) the significance of the enhanced permeability and retention (EPR) effect; they are excellent for intravenous delivery and significant tumor accumulation (passive targeting). Because of their nanoscale size, simple surface functionalization features can improve cancer cell targeting (active targeting) and decrease endothelial reticular system clearance. To satisfy the rising need for cancer theragnostic, researchers are also investigating superior multipurpose platforms.

Coordination polymers known as metal-organic frameworks (MOFs) are created and generated with a porous hybrid structure that combines metal ions or ion clusters as nodes and organic ligands as linkers for various applications [23-27]. MOFs, in particular nanoscale MOFs (NMOFs), have drawn a lot of attention recently for use in the delivery of drugs and the diagnosis of diseases [28-34]. MOFs have the following distinct advantages over conventional nanoplatforms [35-41]: (a) Creating varied characteristics, such as distinct shapes and compositions, adaptable sizes, diverse composition types, and multiple physical properties, established easy by fine-tuning the metal node and organic ligand configurations; (b) They are more capable of loading a wide range of cargo molecules, from small organic molecules to biomacromolecules, due to their high surface areas and significant porosities; (c) Strong coordination properties of metal nodes and adaptable substituent types on organic ligands are often used to enhance the colloidal stability and tumor accumulation of MOFs. These features provide a strong guarantee for surface decoration, particularly in nanoparticle interaction [42-44]; MOFs have active targeting and optical detection properties thanks to the use of luminescent molecules and targeting groups [45, 46]. These MOFs can carry biological functions via macromolecules that are bound to their surfaces, such as proteins, peptides, and nucleic acids [47, 48]. To achieve controlled drug release and lessen premature release, MOFs' surfaces are equipped with supramolecular macrocycles [49-57], and (d) On-demand degradation of MOFs is ensured by coordination bonds that are both stable and weak [58]. Theragnostic platforms for cancer treatment have been identified as potential uses for MOFs due to their unique characteristics (Figure 1) [59].

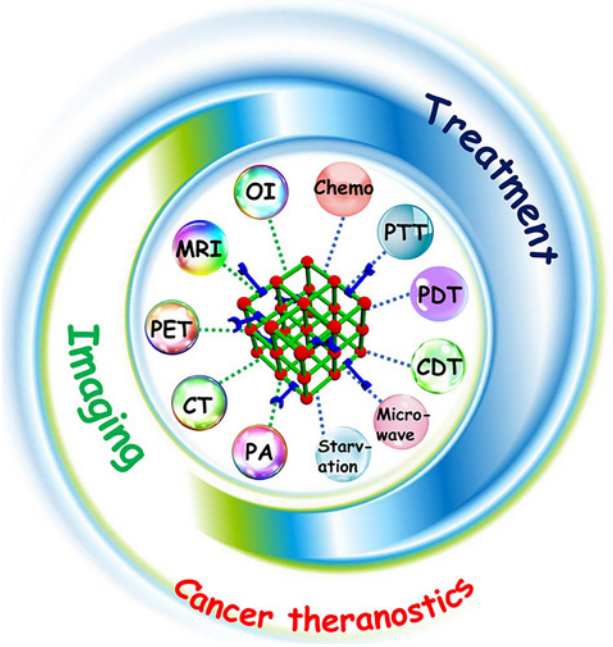

Figure 1: Illustration of MOFs as Theragnostic Platforms in Cancer Diagnosis and Treatment [59]. (License: This is an open access article distributed under the terms of the Creative Commons CC BY license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.)

In this review, we present the most recent progress of NMOFs as promising nanocarriers for drug delivery in biomedical applications. First, we summarize synthetic of NMOFs and biomedical imaging, including MRI, CT, OI, and PET. Then, we discuss recent biomedical applications of NMOF for intracellular delivery of drugs and cancer treatment. Finally, challenges and prospects are summarized to guide future researchers to engineer and explore MOFs as novel drug delivery systems for biological applications.

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Synthetic of NMOFs

Only a few NMOFs utilized the same materials during the early stages of MOF development. For biomedical purposes, controlling nanoscale particle size should be a top priority. NMOFs can be produced under specific circumstances thanks to the progress in nanotechnology. It is possible to synthesize NMOFs using various techniques, including ionic liquid microemulsions, continuous flow manufacturing, hydrothermal syntheses mediated by surfactants, and modulator-based chemistry [60]. Synthesis can be achieved with significant yield using microwave ultrasound. Despite the short time needed, not all MOFs can use it. Ionic liquid microemulsions, a successful and ecologically benign technique for producing MOFs with diameters less than 10 nm, lose their efficiency when the organic ligands of NMOFs are not water-soluble. Continuous flow production is a viable option for larger-scale synthesis, but microfluidic reactors can also generate small MOFs. Removing the surfactant and modulator was also a step in the hydrothermal syntheses mediated by surfactants and the modulator-assisted synthesis technique. It can be difficult to get rid of the modulator and surfactant. During the synthetic process, consideration is given to variables such as temperature, time to reaction, pH, and others that affect the nucleation and growth of nano-MOFs. Externally controlled synthetic processes have successfully created the nano-MOFs mentioned earlier, regardless of their size or shape. Apart from external factor regulations, an internal factor regulation was created for self-limiting growth. Through self-limiting growth, the Gd-Ru nanoscale coordination polymers (NCPs) could grow until their final particle size was approximately 200 nm in diameter [61]. In other words, as nanotechnology and synthetic technology advance, nano-MOFs become increasingly simple. Sometimes, the post-synthetic modification of MOFs results in increased bioactivity, catalytic activity, gas sorption capability, and more durable physical properties [62].

Biomedical Imaging

Magnetic Resonance Imaging

The high diagnostic sensitivity and quality of NMOFs have led to their consideration as potential MRI agents. Lin et al., demonstrated the first effective use of NMOFs as MRI contrast agents [63]. The Eu, Gd-NMOFs@SiO2, altered T2-weighted contrasts and converted them into nanoparticles, emphasizing their potential as T-1-T2 dual-modal imaging probes. Recent research aims to create MRI contrast agents that respond to stimuli, with the aim of possibility in imaging-guided precision therapy and early detection sensitivity. It was shown by Ray et al., [64] that magnetic Fe3O4@IRMOF-3/FA may be used to deliver anticancer drugs as well as T2-weighted solid MRI contrast agents, proving that Fe3O4 can provide potent contrast in T2. The targeted reagent, FA, was used and was conjugated to the NMOF surface. HeLa and NIH3T3 cells were not contaminated by Fe3O4@IRMOF-3/FA in cell viability assays. Lin et al., [65] claim that the tumor microenvironment is acidic and overexpressed with glutathione (GSH). The Fe3O4-ZIF-8 MRI contrast agent that responds to pH and GSH was successfully created. By breaking down Fe3O4-ZIF-8, they redirected the nanoparticles into tumor tissues, causing a significant inverse contrast enhancement between T2 and T1 tissues, which resulted in an enhanced T2-like response.

Computed Tomography

CT has become a popular tool for treating and detecting cancer thanks to its enhanced spatial resolution, deep tissue penetration, and 3D visualization [66]. The high Z element concentration in NMOFs made them a suitable choice for CT contrast agents [67]. Regarding contrast materials in CT imaging, gold nanoparticles are preferred due to their high absorption of X-rays coefficient [68, 69]. Shang et al., [70] developed tiny core-shell nanoparticles known as Au@MIL-88 (Fe). The altered nanocomposites could improve CT scans and increase the visibility of T2-weighted MRI features. To include several image-enhancing processes in an individual multimodal imaging system, Au@MIL-88(Fe) was employed as a further imaging agent.

Positron Emission Tomography

PET imaging outperforms other techniques regarding sensitivity, ability to penetrate deeper into the tissue, and quantitative capability. As a result, it is frequently used as a diagnostic tool in preclinical and clinical research [71]. Rarely do cancer cells selectively target PET imaging agent FDG. The radioactive MOF nanomaterial 89Zr-UiO-66/Py-

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PGA-PEG-F3 was developed and fabricated by Chen et al., [72]. F3 peptides were effective as tumor-targeting molecules due to their strong binding with tumor cells. NMOFs had a significant amount of DOX loading capacity. This study examined the possibility of drug delivery through NMOF-based tumor targeting. The safety study in vivo exhibited no acute, medium, or chronic toxicity.

Optical Imaging

Due to OI's high resolution and sensitivity, it is increasingly used in biological and medical research. Due to their desirable water solubility, NMOFs have been used extensively in OI. Fe3O4@OCMC@ IRMOF-3/FA, a powerful magnetic NMOF, was developed by Chowdhuri et al., [73] for optical imaging and medication tracking. Zirconium-porphyrin MOFs (NPMOFs) were proven to be the best system for OI-guided therapy by Liu et al., [74] Although it was hydrophobic and had the propensity to aggregate, porphyrin produced a powerful fluorescence. By retaining the photostability of the porphyrin, NPMOFs were able to overcome these drawbacks. Ryu et al., [75] showed that dye-NMOFs might be used to conduct fluorescence imaging of human cells by successfully encapsulating colored molecules within the pores of NMOFs. UiO-66@ DOPA-LB, which Zhang et al., recently showed to have better biostability and can survive longer than before, is a viable nanocarrier for imaging agents [76]. Early diagnosis of tiny tumor lesions using NIR dye led to the identification of UiO-66@ DOPA-LB-IR-800.

Cancer Therapy

Nanoscale Metal-Organic Frameworks in Radiotherapy

Radiotherapy (RT) is an effective treatment for the removal of tumors. At different stages of cancer treatment, approximately 50% of patients require a minimum of one RT session [77]. However, conventional radiotherapeutic methods lack cancer cell-specificity and risk producing serious adverse effects. It is crucial to enhance RT's effectiveness in tumor tissues while minimizing its adverse impacts on healthy tissues. The potent X-ray attenuation abilities of High-Z NMOFs made them a viable option for enhancing tumor fading in RT-induced cases [78]. Ni et al., [79] reported that Hf-DBB-Ru served as a mitochondria-targeted NMOF for radio dynamic therapy (RT-RDT). Strong mitochondrial targeting characteristics of Hf-DBB-Ru were made possible by Ru (bpy) 32+.

Nanoscale Metal-Organic Frameworks for Photodynamic Therapy

Medical organizations from all over the world are currently very concerned about cancer treatments. PDT is a novel, non-invasive treatment that only targets and kills cancer cells. Compared to traditional surgery and chemotherapy, it offers several benefits. In PDT therapy, tissue oxygen, photosensitizers, and light are the first three intrinsically non-toxic substances [80]. Reactive oxygen species (ROS), particularly singlet oxygen, are produced when the photosensitizers interact with the surrounding oxygen after entering the body by co-localizing light. Tumor cell autophagy, apoptosis, and necrosis are caused by damage to organelles and the plasma membrane. Other tissues and organs will not experience any negative effects, and there will not be any production of ROS for parts not illuminated. PDT is less invasive, exhibits no drug resistance, and is more selective than conventional tumor treatments. It also has fewer side effects [81]. However, many photosensitizers are hydrophobic, which impairs tumor localization and results in photosensitizer aggregation, reducing the effectiveness of PDT. It is vital to develop regulated photosensitizers that can raise ROS levels in a certain quantity to enhance PDT's effectiveness. The periodic porous framework of NMOFs is notable because it prevents photosensitizers from self-agglomerating and self-quenching, promotes the distribution of highly cytotoxic ROS, and enhances the efficiency of PDT. NMOFs are beneficial in PDT because of their greater biocompatibility and passive targeting capabilities of EPR.

Nanoscale Metal-Organic Frameworks for Photothermal Therapy

PTT is a less invasive, quicker healing, and stimuli-responsive cancer therapy than chemotherapy or surgery. In contrast to PDT, PTT is a photothermal agent (PTA)-mediated process that does not require oxygen or ROS. After being stimulated by a certain wavelength of light, the PTAs revert to their initial form, produce vibrational energy to create heat, and

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quickly induce hyperthermia to kill tumor tissues [82, 83]. In the past ten years, the formation of PTAs has garnered much interest. Researchers are looking for PTAs with improved tumor uptake, photothermal conversion efficiency, blood circulation timings, and NIR light absorption to boost PTT.

Nanoscale Metal-Organic Frameworks for Synergistic Chemotherapy and Photodynamic Therapy

The sort of cancer treatment that is most frequently employed is chemotherapy. Chemotherapeutic medications typically have detrimental short- and long-term consequences since only a limited quantity may reach the tumor site [84]. Additionally, multidrug resistance frequently impairs the effectiveness of therapeutic interventions. Significant concerns about using PDT with synergistic chemotherapy to overcome the drawbacks mentioned above and provide superior anti-tumor outcomes have been expressed. PDT can inhibit the active efflux translocator and aid drug accumulation within cells by introducing cytotoxic ROS. The efficacy of the therapeutic effect and tumor eradication can be greatly enhanced by the synergistic chemo-PDT. In addition, chemotherapy effects may make the tumor more sensitive to PDT [85, 86]. Wang et al., [87] created an intelligent delivery system after researching the MIL-101(Fe) class of small-sized NMOFs. The anti-tumor drug dihydroartemisinic (DHA) and the photosensitizer methylene blue (MB) were combined in the study. Polylactic acid (PLA), an enzyme respondent, was coated into the nanocomposites to achieve controlled cargo release and minimize side effects. The PEG on the outer layer was changed to improve hydrophilicity and biocompatibility. The MOFs-MB-DHA@PLA@PEG (MMDPP) were selectively degraded in the tumor tissue and were pH and enzyme sensitive. DHA's anti-tumor properties and Fe ion-catalyzed O2 in the tumor environment through H2O2 contributed to the PDT impact of the NMOFs. Incubation with free DHA raised the number of dead cells in MOFs-DHA and MOFTs by around 1.2 more than in free MB. The significant improvement in the therapeutic impact of chemotherapy and PDT is attributed to MIL-101. After undergoing MMDPP irradiation at 650 nm, the cell viability of cells was significantly reduced to 17.6 percent, which indicated a greater amount of cell death caused by chemo-PDT synergistic therapy. During the 15-day observation period, the MMDPP group successfully killed the tumor. It prevented any recurrence, demonstrating efficient tumor growth suppression in vivo. The results of the experiments indicated that MMDPP had significant potential for clinical use by demonstrating synergistic chemo-PDT to increase therapeutic efficacy significantly. Sharma et al., [88] created magnetic responsive nanocarriers (M-NMOFs) utilizing FeCl3 and 2-amino terephthalic acid to co-load doxorubicin (DOX), an anticancer medication, and the photosensitizer methylene blue (MB). The combination of chemotherapy with PDT may have an anti-tumor effect due to the superparamagnetic properties of M-NMOFs, which may be utilized for delivering PD/M-NMOF to tumor cells in vitro in magnetic conditions. At the same dose, PD/M-NMOF was shown to be more dangerous than free DOX, DOS-only loaded M-NMOFS (D/MM-NOF), and MB-only loaded but unloaded. The therapeutic efficiency of PD/M-NMOF may be enhanced by magnetic conditions.

Nanoscale Metal-Organic Frameworks in Combination Cancer Therapy

Generally speaking, tumors cannot be effectively removed using the individual cancer therapy approach. Combining two or more treatments has been recognized as a successful approach to treating cancer, owing to the lower incidence of side effects and enhanced anticancer effectiveness. The ability of NMOFs to multimodally load was crucial for adopting combination treatment based on those molecules. Numerous treatment combinations, such as RT/immunotherapy based on NMOFs, dual chemotherapy medicines, chemotherapy/siRNAs, chemotherapy/PDT, and PDT/immunotherapy, have recently been explored for both in vitro and in vivo tumor therapies. The use of one chemotherapy drug often necessitates a high dose, leading to adverse side effects caused by dual treatments. Using nanoscale ZIF-90, Zhang et al., [89] developed a co-delivery platform for two chemical medicines that reduced toxicity and produced efficient therapeutic synergy. By affixing DOX to the surface of nanoscale ZIF-90 and delivering 5-FU into the framework's pores, this co-delivery technique was created. Additionally,

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ZIF-90's structure showed more stability at higher pH levels compared to lower ones. Because tumor locations have an acidic environment, 5-FU@ ZIF-90-DOX administered DOX and 5-Fu while concurrently attacking cancer there.

Chemotherapy/siRNAs

Certain genes can be silenced by RNA interference (RNAi), a post-transcriptional gene silencing technique targeting specific sequences. Currently, it alters genes associated with diseases, such as MDR genes [90]. Ovarian cancer cells' cisplatin resistance can be successfully overcome by RNAi-mediated MDR gene silencing [91-93]. Several NMOFs have been developed to deliver chemotherapeutic medications and siRNAs that specialize in targeting MDR to chemo-resistant tumor cells to combat MDR. To co-deliver cisplatin, He et al., [94] reported using UiO NMOFs. For ovarian cancer cells, it combined siRNAs to reverse MDR. Cisplatin's prodrug was contained within the pores of the UiO. In contrast, pooled siRNAs stuck to metal ions on the surfaces of the NMOFs. The effectiveness of MDR silencing genes was improved by UiO's protection of siRNAs from degradation by nuclease and aid in their uptake. Similar strategies were used by Chen et al., [72] to spread pooled siRNAs and eliminate MDR in Taxol-resistant breast cancer cells using Se/Ru@MIL-101-(P+V) siRNA nanoparticles. The MIL-101 featured a large surface. The anti-tumor properties of selenium-based complexes were exceptional, while ruthenium (Ru) anticancer medications had negligible systemic toxicity [95, 96]. Based on in vivo research, Se@MIL-101-(P+V) siRNA can effectively halt cancer development in a xenograft model using MCF-7/T cells.

Chemotherapy / Photodynamic Therapy or Photothermal Therapy

PDT is significantly constrained in its use due to the hypoxia of the tumor environment. As a result, NMOFs can reduce tissue hypoxia and increase its efficacy. The hypoxia-activated prodrug, pirolazamide, can be easily loaded, as noted by Liu et al., [97] who developed TPZ/Hf/TCPP/PEG. This study demonstrated the possibility of combining PDT and chemotherapy using NMOF-based platforms. The recent development of A@UiO-66-H-P NMOFs by He et al., [98] enabled the combination of hypoxia-activated chemotherapy and NFOF (Non-Organic Molecule Function Cell Death Test)-based PDT. Because of the large surface area and a phosphate concentration gradient between the plasma and the cells in A@UiO-66-H-P nanoparticles, NMOFs are well-suited for prodrug loading and regulated product release. Additionally, using PTT in conjunction with chemotherapy showed an anticancer impact. He et al., eventually developed the multipurpose core-shell Au@Cu3(BTC)2 nanoparticles, which had outstanding photothermal characteristics and a high DOX loading efficiency [98]. The selection of Au nanoparticles as the most suitable materials for this NMOF was based on their exceptional biocompatibility and high sensitivity. Cu3(BTC)2 was chosen to increase the photothermal impact due to its excellent stability, low toxicity, and powerful NIR absorbance. The cytotoxicity of Au@Cu3(BTC)2 nanoparticles was not significantly influenced by their high concentration, which still managed to kill A549, beas-2b MCF-7, and HeLa cells in vitro. The safety of the A549 xenograft model was established in an in vivo study that did not demonstrate any significant weight loss. This work has drawn more attention to the creation of more adaptable theragnostic platforms based on NMOFs.

Photodynamic Therapy / Radiotherapy

The potential of RT is significantly constrained by severe toxicity. The significant improvement in anticancer effectiveness and the reduction of systemic toxicity associated with RT has resulted in a growing interest in its use alongside other therapeutic approaches [99, 100]. The successful creation of a new NMOF that incorporates PDT and RT in the breast cancer model was reported by Liu et al., [78] In this NMOF platform, the TCPP was used as both a PDT PS and radiosensitizer, improving the killing of tumors with its potent X-ray attenuation capability via Hf4 RT. These NMOFs have also shown tumor targeting thanks to their EPR action.

Photodynamic Therapy / Immunotherapy

PDT effectively eliminates nearby tumors but is unable to manage distant metastases. Despite showing promising anticancer efficacy, immunotherapy has only been effective in a small number of patients,

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particularly when immune checkpoint inhibitors are used. Additionally, it does not work well on tumors with weak immune systems. Lu et al., [101] showed that PDT-induced immunogenic cell death caused by NMOF gave them the potential to be used to improve cancer immunotherapy. Recent studies on the effects of combining PDT and immunotherapy on both distant and local tumors in animal models have produced excellent anticancer efficacy. The immune checkpoint is indoleamine 2,3-dioxygenase (IDO). To load an IDO inhibitor (IDOi), Lu et al., [102] created the TBC-Hf chlorin-based NMOF. Combining immunotherapy with NMOF-enabled PDT in a synergistic manner produced an anticancer impact. Local tumors were removed, and systemic effects of the combo treatment were seen in mouse breast and colorectal cancer models. According to mechanistic studies, IDOi@TBC-Hf (PDT) therapy boosted T-cell infiltration in the tumor microenvironment. As shown in the present study, NMOFs may improve cancer immunotherapy. Primary and metastatic lung tumors were reduced using similar methods [97].

Radiotherapy / Immunotherapy

The local immunomodulatory action of RT modifies the microenvironment of radioactively irradiated tumors when paired with immune checkpoint inhibition. Two Hf-based NMOFs, Hf6-DBA and Hf12-DBA, were created as extremely efficient radio-enhancers to produce both local and distant rejection of colorectal cancers in animal models, according to Ni et al., [103] . These NMOFs paired the anti-PD-L1 antibody with NMOF-mediated RT. Lu et al., found malignancies in both local and systemic regions in colorectal and breast cancer animal models. It also explained how to use IDOi and RD-RDT treatment with NMOF support [104].

Other Nanoscale Metal-Organic Frameworks for Cancer Theragnostic

For the first time, Liu and colleagues employed a core-shell MOF as a contrast agent to direct cancer photothermal treatment [105]. The nanoplatforms MRI and photothermal conversion characteristics were achieved using a core of Mn-IR825 MOF, while PEG was rapidly modified to achieve the desired physiological stability. Both in vitro and in vivo tests were done to verify the biocompatibility and photothermal therapy effectiveness of the Mn-IR825@PDA-PEG nano platform. It might degrade in vivo and have rapid renal excretion system clearance. The finished product demonstrated the therapeutic formulation has immense promise for in vivo therapy for cancer. A NMOF composed by hafnium and tetracids (4-carboxyphenyl) porphyrin (TCPP) was also reported. Due to Hf 4+'s inherent ability to act as a radio-sensitizer to enhance radiation therapy and the organic building block of TCPP's capacity to act as a photosensitizer for photodynamic therapy, these formulations combined radiation therapy and photodynamic therapy in a single system. The experiments revealed that the nano platform developed had significant anti-tumor efficacy due to its combination of photodynamic and radiation therapy and good biocompatibility thanks to the PEG polymers' outer coating. Additionally, the modal mouse's metabolic system eliminated this multifunctional MOF-based nano platform without any apparent damage to healthy organs. Core-shell MOF nanocomposites are gaining more attention for their practical, accurate, and efficient diagnosis. The MOF created by Yang and colleagues can perform dual-modal imaging of malignancies in both vitro and in vivo [106]. The inner core of the MOF was made up of magnetic gadolinium (III) ions and 1,1′-dicarboxyl ferrocenes (Fc). A SiO2 outer shell was also connected to the target ligand RGD's high luminescence and targeting abilities, as well as those of the fluorescent dye RBITC. The creation of dual-modal T1- and T2-weighted MRI in vivo was made possible by the pre-synthesis of Fc-Gd@SiO2(RBITC)-RGD nanocomposites, offering a flexible platform for targeting and imaging diagnostic devices. Their water-dispersion capacity, stability, and cytotoxicity were excellent. The conjugation of Lactobionic acid on the surface of the NMOF MA-HfMOFPFC- Ni-Zn allows Sakamaki et al., to determine that it can precisely target cancer cells. Three cancer cell lines were shown to be actively targeted by this effective drug delivery method. However, the MCF-10a cell line was not significantly harmed. It will be clear how toxic metal accumulation will affect therapeutic MOF dosages during in vivo studies once the excretion mechanisms of the pertinent elements are determined. The chlorin-based nano-MOFs (MA-HfMOF-PFC-Ni-Zn) showed stronger PDT effects

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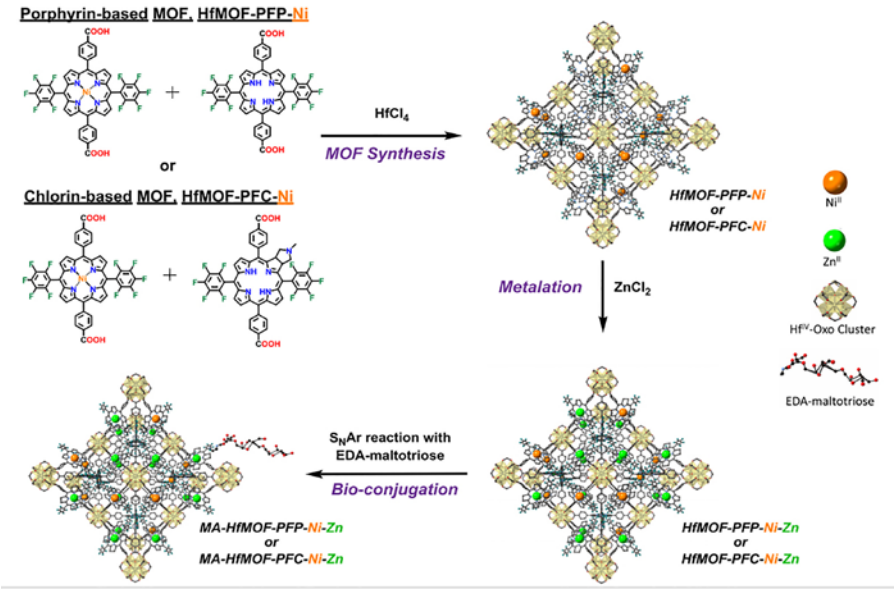

Figure 2: Synthesis of HfMOF-PFP-Ni-Zn and HfMOF-PFC-Ni-Zn [107]. (Re-print permission: Permission/License is granted for this work.)

than porphyrin-based nano-MOFs (MA-HfMOF-PFP-Ni-Zn). Figure 2 shows the synthesis steps [107].

Deng et al., developed a Zr-Fc MOF nanosheet (Figure 3) based on the Fenton reaction for combined PTT and CDT to cure cancer. The absorption band of the nanosheet, which ranges from 350 to 1350 nm, is constant. It has a remarkable photothermal conversion efficiency of 53% at 808 nm. This nanosheet is a highly effective photothermal agent for PTT, according to both in vitro and in vivo results. The nanosheet has shown to be a successful Fenton catalyst for CDT's OH production. Next, in vitro testing is done to confirm the combined action of PTT and CDT. The degradation reaction of MB demonstrates that heat can increase OH production, implying that PTT can raise CDT. However, it is established that CDT and PTT are both administered together. In vitro and in vivo therapeutic effects have been achieved through the synergistic interaction of PTT and CDT [108].

A powerful Cu-based Fenton-like agent called PCN-224(Cu)-GOD@ MnO2 was developed by Wang et al., (Figure 4). The MnO2 layer deposited on the PCN-224(Cu) surface might break down and produce O2 due to the excess H2O2 in the

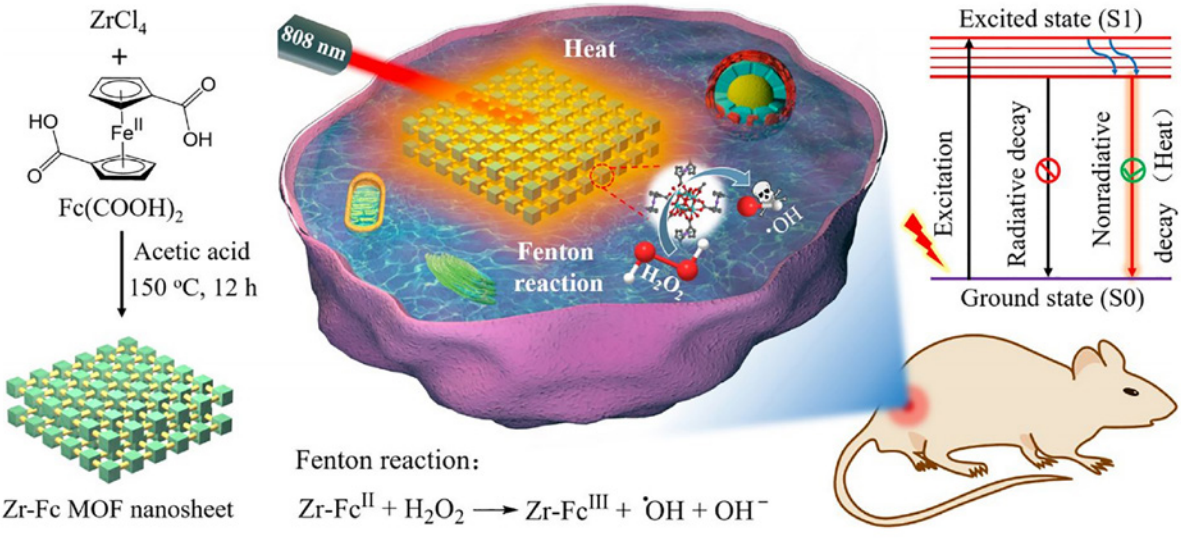

Figure 3: Synthesis of the Zr-Fc MOF Nanosheet and Illustration of Synergetic PTT and Fenton Reaction-Based CDT [108]. (Re-print permission: Permission/License is granted for this work.)

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TME. The oxygen produced might activate the enzymes in GOD, increasing the production of H2O2 necessary for the Fenton-like reaction. This would lead to the formation of toxic OH in the TME through oxidation of Cu2+ in PCN-224(Cu)-GOD, which also reduces GSH absorption. Using the Russell mechanism, the Cu+ could be combined with O2 and H2O to create one O2. The TCPP ligand and Mn present in PCN-224(Cu)-GOD@MpO2 serve as accurate anti-tumor treatment guidance, making it an effective agent for in vivo fluorescence imaging and T1-weighted MRI [109].

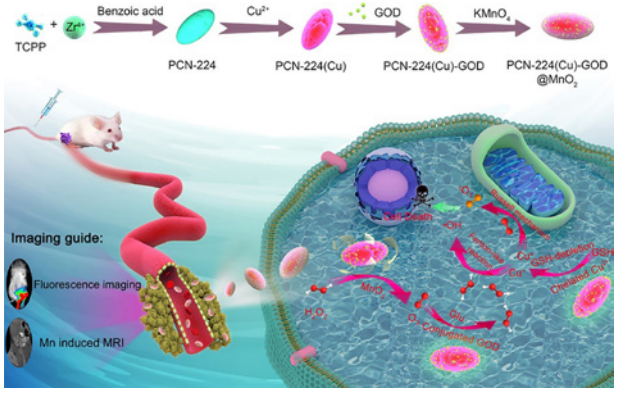

Figure 4: Schematic illustration of the main synthesis procedures and anti-tumor mechanism of PCN-224(Cu)-GOD@MnO2 NMOFs [109]. (Re-print permission: Permission/License is granted for this work.)

Current Trends and Future Perspectives

The emergence of interdisciplinary nanotechnology in biology over the past few decades has dramatically expanded the scope of biomedical and pharmaceutical research methods. Numerous nanomaterials were created and developed, each with unique physicochemical properties that served as a versatile platform for various applications. The use of nanotechnology as contrast agents for bioimaging modalities, tailored drug delivery platforms for localized and species-specific therapies, and diagnostic imaging agents are just a few of the potential elements that have developed from nanotechnological intervention. Nanocomposites, which mix two different materials with a dual purpose to improve medication delivery and treatments, have been used enormously in recent studies. We now have a greater understanding of targeted treatments and biomedical diagnostics, notably in the therapy of cancer and other infectious illnesses, thanks to the invention and development of these dual or multimodal nanocomposites. The diagnostic and therapeutic potential of NMOFs, along with their bulk counterparts, such as MOFs, is expanding. Recently, both NMOFs and MOFs-based novel strategies for cancer-targeted drug delivery and imaging have shown great promise. The system offers excellent biocompatibility, stability, and high efficacy for many drugs against a wide variety of cancers. However, there are also some limitations, such as complex methods of synthesis, poor immunological response, complex drug loading process, and low clearance rate. Diagnostically, the use of both NMOFs and MOFs has shown dark magnetic resonance and negative image contrast, which will create further limitations for their potential clinical use. Moreover, the complexity of the body or cellular environment also creates challenges for precise drug transport and release at desirable sites of action. The transport of drug systems through biological membranes, including the blood-brain barrier, also poses a significant challenge, and much work is needed to be done in this area to enhance the future of NMOFs and MOFs in cancer diagnosis and treatment.

DISSCUSION

During the past few decades, MOFs have been extensively studied for various applications because of their well-defined structure, high surface area, high porosity, tunable pore size, and easy functionalization. In particular, exploring MOFs as a nanocarrier for drug delivery in biomedical applications has attracted great interest in recent years. Currently, various molecules have been investigated as therapeutic agents for disease treatment, such as anticancer drugs, nucleic acids, and proteins. In the present review, we summarized four strategies commonly used to functionalize MOFs with therapeutic agents for drug delivery. They include surface adsorption, pore encapsulation, covalent binding, and functional molecules as the building blocks. The van der Waals interaction, π–π interaction, and hydrogen bonding are the main forces involved in surface adsorption and pore encapsulation approaches. Functional molecules are covalently bound to the framework through inorganic metal clusters or organic linkers by the covalent binding

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method. Moreover, functional molecules can be incorporated into the framework as organic ligands. Then, we thoroughly discussed the recent progress of biological applications of MOF nanocarriers for drug delivery. Benefiting from the unique advantages of MOFs, many drug molecules have been efficiently delivered by MOF nanoparticles. In this section, we selected drugs, nucleic acids, and proteins for discussion. Despite notable progress in this field, several challenges remain to be solved. First, although many functionalization methods have been reported, they all possess some limitations. For instance, molecules incorporated by surface adsorption and pore encapsulation tend to leak gradually owing to weak interaction forces. Covalent binding provides stronger interactions, but it requires complex synthetic procedures and may influence the activity of functional molecules. On the other hand, the organic ligands suitable for MOF synthesis are usually rigid and highly symmetrical, which makes it difficult to directly utilize biomolecules as building blocks. Such limitations call for the development of advanced functionalization strategies to incorporate a wide variety of potential therapeutic agents into MOFs to explore their clinical applications. Second, the kinetics of drug loading and release, in vivo toxicity, degradation mechanism, and pharmacokinetics of MOF nanoparticles are still under study. Further investigations are required to rationally design MOF–drug conjugates with enhanced biostability, biocompatibility, and therapeutic efficacy. In conclusion, MOFs possess unique properties and show great promise for intracellular drug delivery to treat diseases. In the future, efforts should be focused on overcoming the noted challenges to fully realize the potential of MOFs as drug delivery systems in clinical applications.

CONCLUSION

Developing novel nano-MOFs and functional building blocks is a priority in the biomedical industry. If the expected potentiality of imaging, therapeutic, or theragnostic effects was realized, functional building blocks could be added, as mentioned in the introduction above. Another effective way to increase the scope of using existing nano-MOFs is to realize their full potential from a multidisciplinary perspective. However, this requires close cooperation between researchers from various fields. Fe-based nano-MOFs that react to TME may offer a unique opportunity for in situ tumor therapy with high tumor selectivity and specificity. Making smaller nano-MOFs requires the urgent development of new synthetic techniques. As smaller nano-MOFs are better suited for integrating biomolecules, particularly in a FRET-based bioassay, it is widely acknowledged that they have greater applicability than larger ones. Although these materials have been shrunk to the nanometer scale, it is still very difficult to manufacture sub-20 nm nano-MOFs. Nano-MOFs require a range of soluble and stable solutions to be used in biological applications. The use of functional ligands on NMOFs' surfaces is crucial because it can enhance cell uptake, targetability, and blood circulation. The interaction of nanomaterials with cells, which affects how they accumulate in various organs and circulate throughout the body, is greatly influenced by the surface chemistry of the materials. Nano-MOF-based nanomedicine in tumor locations requires the use of new techniques for surface modification that can increase both accuracy and collection ratio. More work is required to create adaptable, non-toxic, and biocompatible nano-MOFs. Using bioactive substances as surface modifiers or endogenous organic links and body component constitutive parts as building blocks would be preferable to lower the risk of side effects. Using nano-MOFs as nanocarriers necessitates significant chemical instability, which can harm the release of therapeutic drugs or hinder their handling by the body's metabolic system to prevent endogenous accumulation. Furthermore, nano-MOFs and their composites have been shown to have short-term safety in various aspects, such as biodistribution, metabolism, pharmacokinetics, and physiology. However, their potential accumulation, clearance behavior, or pathway are poorly understood. Their relationship and the reproductive or immune system are still uncertain. Animal models must still be used to do systematic research on long-term biosafety. These problems call for the interaction of specialists from several disciplines and include multidisciplinary study areas, including chemistry, biology, and medicine. There is still much room for inventive research in the developing field

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of engineering multifunctional nano-MOFs for biomedical applications, supposing that all of the aforementioned difficulties can be quickly resolved.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS APPROVAL

Not applicable.

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