Nanoscale Metal–Organic Frameworks and Their Nanomedicine Applications

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Abundant connectivity among organic ligands and inorganic metal ions makes the physical and chemical characters of metal-organic frameworks (MOFs) could be precisely devised and modulated for specific applications. Especially nanoscale MOFs (NMOFs), a unique family of hybrid nanomaterials, with merits of holding the nature as the mainstay MOFs and demonstrating particle size in nanoscale range which enable them prospect platform in clinic. Adjustability of composition and structure allows NMOFs with different constituents, shapes, and characteristics. Oriented frameworks and highly porous provide enough space for packing therapeutic cargoes and various imaging agents efficiently. Moreover, the relatively labile metal-ligand bonds make NMOFs biodegradable in nature. So far, as a significant class of biomedically relevant nanomaterials, NMOFs have been explored as drug carriers, therapeutic preparation, and biosensing and imaging preparation owing to their high porosity, multifunctionality, and biocompatibility. This review provides up-to-date developments of NMOFs in biomedical applications with emphasis on size control, synthetic approaches, and surfaces functionalization as well as stability, degradation, and toxicity. The outlooks and several crucial issues of this area are also discussed, with the expectation that it may help arouse widespread attention on exploring NMOFs in potential clinical applications.

Keywords: nanoscale MOFs, drug carriers, nanomedicine, biosensing and imaging, therapeutic preparation

INTRODUCTION

During the past 2 decades, the merging of nanotechnology and medicine has confirmed the biomedical behaviour of a series of nanomaterials and improved some of them effectively in clinic (Banerjee et al., 2020). A large number of nanomaterials have been obtained with expansive dimension scope from several nanometers to hundreds of nanometers, and the great majority of these nanomaterials have exhibited bright prospects in clinic, for example drug delivery, photodynamic therapy, thermal therapy, chemotheraphy, and biomedical sensing and imaging (Coughlan et al., 2017; Yang B et al., 2019; Mir et al., 2020; Wen et al., 2021).

As a burgeoning and fascinating stream of organic–inorganic hybrid materials, Metal-organic frameworks (MOFs) are consist of inorganic metal ions/clusters and multipoint organic bridging linkers (Li S Y et al., 2017). In light of the diversity of the connections among organic linkers and metal ions, the physical and chemical characters of MOFs could be rationally controlled and regulated for particular applications, especially when minimizing the size to nanoscale regime make it a foreground platform in biomedicine (Lismont et al., 2017;
Wu and Yang, 2017). Nanoscale MOFs (NMOFs) stand for a special class of hybrid nanomaterials. The merits of sustaining the properties and structural various as bulk MOFs and maintaining the size at the nanometer level let NMOFs perfectly capable applying in biomedical sciences (Lu et al., 2018a; Zhou et al., 2018; Bieniek et al., 2020; Li et al., 2020). Moreover, Compared with existing nanocarriers, NMOFs possess several potential advantages which make them have a wider application prospect for biomedicine: 1) structural and compositional adjustability permitting to build NMOFs owning diverse constitution, shapes, and characteristics; 2) oriented frameworks and high porosity provide enough space for lade therapeutic agents and various imaging efficiency; and 3) weaker coordination bond make them easily to be biodegraded.

In this review, the main focus is to highlight the recent research progress of NMOFs in the biological area, including the development of NMOFs in targeted drug delivery and cancer therapy, biomedical sensing and imaging as well as the toxicity, degradation, and stability of this class of novel hybrid nanomaterials (Figure 1). First, the general strategies to functionalize NMOFs for biomedicine-available considerations are briefly summarized, including pore encapsulation, and surfaces functionalization. Then, recent biomedical applications of NMOFs are discussed, including NMOFs as nanocarriers for intracellular delivery of drugs; as phototherapeutic agents for cancer therapy; and as fluorescent probes for biomedical sensing and imaging. Additionally, the outlooks and several crucial issues of this area are also mentioned with the expectation of stimulating more attention on investigating the potential of NMOFs for clinical applications.

**NANOSCALE METAL–ORGANIC FRAMEWORKS**

Nanoscale metal-organic frameworks (NMOFs), a peculiar class of metal-organic self-assembly materials, integrate the merits of beneficial property of bulk MOFs and nanomaterials. First, highly porous and large channels enable NMOFs loading imaging agents and/or therapeutic preparations efficiently meanwhile by covalent attachment the construction units—whether metal ions/cluster or organic ligands—both can be used to payload imaging cargoes and/or drugs (Chen D et al., 2017; Hang et al., 2017; Yin et al., 2017; Cao et al., 2021). For example, by choosing construction units or decorating imaging components, NMOFs-based diagnostic and therapeutic agents have been extensively developed and used for magnetic resonance imaging (MRI) (Chowdhuri et al., 2016), computed tomography (CT) (Tian et al., 2015), positron emission tomography (PET) (Zhao et al., 2016a), and optical imaging (Yang S P et al., 2017). Second, appropriate selection and functionalization of organic linkers and building blocks allows NMOFs to load and release imaging agents and drugs components in steerable patterns both spatially and temporally, emphasizing their latent roles on theranostic platforms (Ni et al., 2020a). The inorganic metal components on NMOFs also make them attractive contrast medium for biomedical optical applications. So far, therapeutic construction units have been encapsulated into NMOFs for particular treatment. Such as, using photosensitizers as construction groups permit the NMOFs effective for photodynamic therapy (PDT), meanwhile, high-Z metal ions-containing NMOFs materials possess excellent X-ray attenuation ability could be used as radiosensitizer to improve field radiotherapy (RT) (Nazari et al., 2016). Third, the adjustable skeleton stability of NMOFs in physical surroundings permits to obtain activated or controlled-release nanocarriers. Additionally, many sorts of NMOFs have been certificated with low cytotoxicity ensures them applications in vivo. Also, in light of the comparatively weaker metal-ligand coordinate bonds, the NMOFs are biodegradable in nature (Morris et al., 2017). These exceptional merits of the NMOFs make them a promising platform for biomedical field.

**FIGURE 1** | Schematic diagrams of NMOFs in biomedicine.
Synthesis and Design Strategies of Nanoscale Metal–Organic Frameworks-Based Nanomedicine

For biomedical applications, the first attention should be paid to scaling down particle size within nanoscale (Cai M et al., 2020). As porous nanomaterials, NMOFs could be designed with a limitless array of inorganic and organic components. Normally, to acquire nanoscale MOFs, two factors should be considered: 1) limiting the supramolecular assembly; a process that usually results in the formation at nanoscopic locations and 2) supporting nucleation against crystal growth. Currently in literature, controlled synthetic techniques of NMOFs gradually have been divided into four categories: nanoprecipitation, solvothermal synthesis, surfactant-assisted approach, and reverse microemulsion method (Rieter et al., 2008; Liu et al., 2012; Baa et al., 2019). In these methods, reactant ratio, temperature, pH, reaction conditions, etc. factors affect the growth and nucleation of NMOFs during the synthetic progress (Zhao et al., 2018). NMOFs occupy various merits over traditional nanomedicines for example their structural diversity, their loading capacity, and their biodegradability. A great deal of NMOFs has been certified as bioimaging agents both in vivo and in vitro (Cai et al., 2015). Researchers have used two general approaches to construct NMOFs-based nanomedicine, as shown in Figure 2: one is incorporating active groups into the skeleton or loading active agents into the channels and pores of the NMOFs; the other one is surface modification of as-synthesized NMOF by silica coatings or organic polymers to improve their stabilities, slightly regulated their physicochemical characteristics, and afford extra functionality and biocompatibility. For pore encapsulation strategy: NMOFs as a host material can prevent the loaded substrates from leaching, as well as providing them a protective environment against external adverse factors. Surfaces functionalization strategy for NMOFs can meet the specific requirements and acquire the expected function, which is extremely significant in clinic. However, these two strategies require that NMOFs and the substrate are stable under synthetic conditions.

Incorporating or loading the therapeutic agents within NMOFs: Molecular nature of NMOFs can give materials various characters. The moderate synthetic conditions and tunable components of NMOFs allow for the capacity of therapeutic and imaging agents while at the same time guaranteeing effective delivery to internal specific cells (Simon-Yarza et al., 2018). Generally, there are two general categories for cargo loading in NMOFs: incorporating cargoes directly during particle synthesis and postsynthetic loading. Additionally, complementary of these two strategies can also be applied for merging multiple biomedically relevant groups and NMOFs to develop theranostic agents.

In the method of direct incorporation, bioactive agents (the metal notes or the linkers) can be incorporated within NMOFs directly during their self-assembling process. The most commonly used therapeutic preparations based-MOFs are generally have fairly good stability in water solution such as Zr-MOF (Abánades Lazaro et al., 2020), porphyrinic MOF (Li et al., 2021), zeolitic imidazolate frameworks (ZIF) (Pan et al., 2017), and Fe-MOF (Cui et al., 2021). Although extremely high agents loading with equidistribution could be achieved by direct incorporation method, but the physic-chemical characters and morphology of these materials require to be adjusted separately. Apart from being incorporated directly, biomedically relevant units can also be imported within NMOFs in the synthesis process by object encapsulation. Various agents with different properties have been used to encapsulate into NMOFs by this strategy for example proteins, small particles, dyes, and drugs (Kumar et al., 2015). But, this method can only achieve a lower drug loading, and that...

FIGURE 2 | Approaches described in this article for constructing NMOFs-based nanomedicine.
the release kinetics of the drug from the NMOF and the skeleton decomposition rate may be extraordinary different.

Postsynthetic loading is another loading method for encapsulating biomedically relevant molecules within NMOFs. After obtaining highly porous NMOFs with specific physiochemical properties, the active units are then packed into the NMOFs via covalent or noncovalent surface conjugation. Covalent postsynthetic modification is realized by functional groups in NMOFs react with bioactive reagents (Nguyen et al., 2010). As a case, a BDC-NH₂ (2-amino terephthalic acid) group including NMOFs has been used to link contrast medium and chemotherapeutic agents via covalent conjugation (Huang et al., 2006). Noncovalent surface conjugation offers another effective way for loading drugs and an extraordinary load amount with 1.4 g of ibuprofen/g was achieved in MOF-101 (Horcajada et al., 2006).

Surfaces functionalization of NMOFs: Surfaces functionalization of NMOFs to meet the specific requirements and acquire the expected function is extremely significant in clinic. The controlled manipulation of the external surface of NMOFs improves the water dispersibility, reduces nonspecific binding with plasma protein, and appends other components to specific areas or to add extra functionalities or groups (Horcajada et al., 2006; Alexis et al., 2008).

Since NMOFs are formed by ligands and ions, the primary task is to decorate a connector on ligands before MOF assembly and then covalently bonding the specific agent with the connector on the superficies of the as-synthesis NMOFs (Zhu et al., 2018). For example, as the organic ligand in UiO-66, 1,4-benzenedicarboxylic acid without connector lead to the resultant UiO-66 cannot be functionalized by covalent modification. Conversely, 2-azido terephthalic acid, the organic linkers of UiO-66-N₃, where the azide group could react with the alkane group by click reactions to modify the desired agent on the surface of MOF. Finally, a dibenzylcyclooctyne terminal DNA sequence successful bonded with the surface of UiO-66-N₃ without any internal change in the whole chemical transformation process (Morris et al., 2014).

The second strategy is using the chelating ability of metal ions and target molecule to connect the specific agents on the MOF surface directly (Wang et al., 2017; Wang et al., 2019). Surface defects of NMOFs, such as the unsaturated coordinative metal sites (CUS), give NMOFs the ability to combine with target molecules by coordination. At present, different functional group-terminal ligands have been incorporated to NMOFs by coordinating to the metal-sites through external secondary modification including phosphonate, carboxylate, phenyl, and histidine groups. For example, both phosphonate and carboxylate groups can bonding with Zr ions in Zr-based MOFs, thus decorating the surface of the Zr-based MOF with terminal phosphate-modified DNA successfully (Röder et al., 2017). His-tags can be easily fabricated in peptides or proteins greatly expanding the range of targeted molecule-functionalized MOFs. Phenolic capped linkers also can generate the coordination bonds to modify MOF a stable material via postsynthetic (covalent) modification (Wang et al., 2015). A great variety of ions have been certified to be able to chelate with phenolic units to afford stable 5-member ring including Fe, Zr, Cr, Cu, Zn, Co, In, Eu, and Al.

Surface coating provides another convenient way to modify NMOFs with their structural integrity and porosity unchanged. During surface coating process, some factors should be considered: 1) biofriendly synthesise without any poisonous substance; 2) prevent the targeting molecule invading into the nanocarrier; 3) reduce interference with entrapped drugs; 4) keep drug release capacity; 5) improve the stability of particle colloidal, and 6) stable under physiological environment. So far, silica coating and lipid coatings have been considered the most effective strategies for NMOFs surface coating, especially for stabilizing physiologically unstable NMOFs. For promoting process of the silica coating, firstly the surface of NMOFs is decorated with a polymer, like polyvinylpyrrolidone (PVP). For instance, Lin and co-workers have obtained a series of NMOFs by silica coating (Rietier et al., 2008). Authors represented an universal way to acquire different silica shells thickness on the surface of Ln(BDC)₁₅(H₂O)₂ ( Ln = Gd³⁺, Eu³⁺, or Tb³⁺, BDC = 1,4-benzenedicarboxylate); Tb₂ (DSCP)₃(H₂O)₁₂ (DSCP = C₆H₅N(CH₃)₂; diaminedichlorodisuccinonitri); Mn₆(BTC)₀(⁶)H₂Oₖ (BTC = 1,3,5-trimesic acid), and Cr₃F(H₂O)₉(OBTC)₃·nH₂O (where n is ~25). Eventually, they loaded dipicolinic acid (DPA), Pt-based drugs, acetylcarnosine-glycerine-aspartate (RGD) peptide, and optical imaging contrast agent (BODIPY) into nanoscale materials stabilized with silica shell for biological application. Although silica coating method seems to be a widespread approach for various materials, it is hard to gain flimsy silica shells. Furthermore, weakly basic coating condition is incompatible with material. Lipid coating is not only available for slowing down the kinetics of releasing cargos but also efficient for imparting biocompatibility (Wuttke et al., 2015). The Mirkin group used the lipid ligand 1,2-dioleoyl-sn-glycerol-3-phosphate (DOPA) to transfer a family of ZrIV-based NMOFs facilely be functionalized to be able to chelate with 1,4-benzenedicarboxylate; Tb₂ (DSCP)₃(H₂O)₁₂ (DSCP = C₆H₅N(CH₃)₂; diaminedichlorodisuccinonitri); Mn₆(BTC)₀(⁶)H₂Oₖ (BTC = 1,3,5-trimesic acid), and Cr₃F(H₂O)₉(OBTC)₃·nH₂O (where n is ~25). Eventually, they loaded dipicolinic acid (DPA), Pt-based drugs, acetylcarnosine-glycerine-aspartate (RGD) peptide, and optical imaging contrast agent (BODIPY) into nanoscale materials stabilized with silica shell for biological application. Although silica coating method seems to be a widespread approach for various materials, it is hard to gain flimsy silica shells. Furthermore, weakly basic coating condition is incompatible with material. Lipid coating is not only available for slowing down the kinetics of releasing cargos but also efficient for imparting biocompatibility (Wuttke et al., 2015). The Mirkin group used the lipid ligand 1,2-dioleoyl-sn-glycerol-3-phosphate (DOPA) to transfer a family of ZrIV-based NMOFs facilely be dispersed and suspended in solvents with low polarity by easily surface encapsulation. Differ from artificial lipid layers, exosomes which have membrane structures similar with cell membranes, are usually used by cells for communication purposes. The Wuttke and co-workers coated exosomes on MIL-88A surface successfully to investigate the sustained-release of calcein in HeLa cells (Illes et al., 2017). Although a significant progress have been achieved in NMOFs modification, there are still unsolved problems in aspect of concrete characterization of targeting/coating stability and efficiency (Meng et al., 2016; Abánades Lázaro et al., 2017). In addition, for fulfilled potential of NMOF-based therapeutic and imaging agents, rigorous in vivo and in vitro researches are acquired.

**NANOMEDICINE APPLICATIONS OF NANOSCALE METAL–ORGANIC FRAMEWORKS**

Unique molecular architecture and versatile functionalities make NMOFs potential platforms for drug delivery, cancer therapy, biomedical sensing, and imaging applications (Velásquez-Hernández et al., 2020). In this section, the parameters of
NMOFs before the biomedical applications of NMOFs will be discussed and the recent research progress related to nanomedicine applications of NMOFs in clinical is summarized in the context of translational medical research.

**Parameters of Nanoscale Metal–Organic Frameworks in Biomedicine**

Although most NMOFs have the characteristics of high surface areas, tunable pore size, crystallinity, thermal stability, and so on, but for medical applications, some strict parameters should be considered (McKinlay et al., 2010). Once MOFs are utilized in biologically and medical applications, characteristics like stability, biodegradability, and toxicity need to be addressed further.

**Stability:** Before the successful applications of NMOFs in diagnosis and treatment, the stability in the physiological surrounding of NMOFs should be discussed. By scanning electron microscope (SEM), high-resolution transmission electronic microscope (HRTEM), X-ray diffraction (XRD), and other experimental characterization methods, the stability of NMOFs in water solution, buffer solution, and different pH conditions could be evaluated. Although few NMOFs are obtained from the aqueous phase, most of them are still stable in the aqueous solution, including UiO MOF series, PCN MOF series, Ni-CPO-27, Cr-MIL-100, Cr-MIL-101, MIL-125, CAU-1, and ZIP-8 (Yang et al., 2011; Jeazet et al., 2012; Liu et al., 2015). Lin groups obtained a nanosensor on account of fluorescein isothiocyanate (FITC) conjugated UiO-68 (F-UiO) for pH sensing in cell (He et al., 2014a). The fluorescein FITC is pH sensitive and shows pH-dependent ratiometric fluorescence changes, certifying its ability to sense the pH in cells. F-UiO exhibited unaltered hexagonal plate morphology after incubating in Hank’s Balanced Salt Solution (HBSS) for 24 h. Negligible FITC dye leaching experiment and XRD patterns indicate that the structural of F-UiO was stable in cell.

**Degradation:** Biodegradability of MOFs is another important issue that needs to be emphasized in terms of biological application (Wu et al., 2018). By compared the release mechanism of drug in NMOFs with two other coating methods, Amorín-Ferré and co-workers found that NMOFs with a formula of \([\text{Co(bix)(3,5-dbsq)}(\text{3,5-dbcat})]\) (bix = 1,4-bis(imidazol-1-ylmethyl)benzene) could be designed in spherical structures with a diameter of 150–200 nm, where 3,5-dbsq and 3,5-dbcat\(^2\) are respectively the semiquinonate radical and catecholate forms of 3,5-di-tert-butyl-1,2-benzoquinone (dbq) (Amorín-Ferré et al., 2013). Physical encapsulated drugs within NMOFs will be released by free diffusion, but covalently bond drugs within the structures can only be governed by slow particle degradation. Detailed description of this situation in the case of MIL-100(Fe) nanor or microparticles confirmed the gradual formation of dense forms in the process of degradation in a simulated physiological environment. Also, the excretion and degradation mechanism proved that the Fe-MOFs could be quickly segregated by organism and then eliminated and biodegraded safely.

**Toxicity:** For the ultimate biomedical goal of NMOFs in clinical, toxicity issues should be solved by a more reasonable safe-by-design approach. As MOFs consist of metal ions/cluster and organic linkers, some nontoxic or low-toxic inorganic metal ions and organic ligands should be selected to produce NMOFs for reducing of toxicity from the source. As kinds of essential microelements to human body, Cu, Zn, Fe, Mn, Mg and Zr metal ions, have been heavily applied in NMOFs assembly with acceptable toxicity decided by oral lethal dose 50 (LD50), i.e., 350 μg kg\(^{-1}\) for Zn, 25 g kg\(^{-1}\) for Cu, 30 g kg\(^{-1}\) for Fe, 4.1 g kg\(^{-1}\) for Zr, and 1.5 g kg\(^{-1}\) for Mn (Amorín-Ferré et al., 2013; Wu and Yang, 2017). As for exogenous organic linkers, terephthalic acid (LD50 = 5 g kg\(^{-1}\)), fumaric acid (LD50 = 10.7 g kg\(^{-1}\)), trimesic acid (LD50 = 8.4 g kg\(^{-1}\)), terephthalic acid (LD50 = 5 g kg\(^{-1}\)), 5-aminoisophthalic acid (LD50 = 1.6 g kg\(^{-1}\)), 2,6-naphthalenedicarboxylic acid (LD50 = 5 g kg\(^{-1}\)), isonicotinic acid (LD50 = 5 g kg\(^{-1}\)), 1-methylimidazole (LD50 = 1.13 g kg\(^{-1}\)), and 2-methylimidazole (LD50 = 1.4 g kg\(^{-1}\)), are normally significant for bioapplications. Horcajada and co-workers did outstanding works on screening the general toxicity and cytotoxicity of a range of NMOFs in mice (Tamames-Tabar et al., 2014). In their experiment, three Fe-based NMOFs could be rapidly absorbed by mononuclear phagocytic system organs after intravenous injection. The Maspoch group systematically described in vivo toxicities of a series of NMOFs such as MIL-88A, MIL-88B-4CH\(_3\), MIL-100, MIL-101, NOTT-100, HKUST-1, ZIF-7, ZIF-8, MOF-74 family (\(M = \text{Ni}, \text{Co}, \text{Cu}, \text{Mg}, \text{Zn}, \text{and Mn}\)), UiO-66, UiO-66-NH\(_2\), UiO-67, and MOF-5 (Ruyra et al., 2015). The authors found that NMOF toxicity has a strong correlation with metal toxicity as well as particles shape/size.

**Synthesis and Design Strategies of Nanoscale Metal–Organic Frameworks-Based Nanomedicine**

Drug delivery have appeared as an important field of research due to the unacceptable fact that traditional delivery patterns usually refer to large doses resulting in toxic side-effects by systemic circulation at unexpected targets (Li W et al., 2017). As efficient drug delivery vehicle, some requirements should be addressed, such as 1) controlled release the active agents; 2) maximum degradation and possibility to be surface modified by the delivery vehicle; 3) could be detected by diverse imaging techniques; 4) with high drug loading capacity; 5) toxicity and biocompatibility. The merits of diversified structural components and abundant performance make NMOFs have higher drugs loading ability, controlled release ability, and are easily modified by active agents (Al Haydar et al., 2017). Another aspect that has proved MOFs more attractive as drug delivery carriers is that a sole MOF can be quickly segregated by load multiple active agents as some of these materials exhibit a dual hydrophilic/hydrophobic pore structure. Table 1 summarizes the drug release ability of various NMOFs as drug carriers. In NMOFs as carriers for targeted drug delivery system, two factors involve loading efficiency and stimulus-responsive drugs release should be discussed.

**Loading efficiency:** Thanks to their porous structure, NMOFs have a more drug loading efficiency compared to conventional materials. The loading agents can range from small molecules to...
proteins. Perfect NMOF therapeutic preparations typically have larger pore size and excellent aqueous stability, such as Zr-MOF series, ZIF series, porphyrinic MOF series, and Fe-MOF series larger pore size and excellent aqueous stability (Cai et al., 2019; He et al., 2019; Abánades Lázaro and Forgan, 2019; Cai X et al., 2020; Sun et al., 2020). Horcajada groups demonstrated a family of non-toxic iron (III) carboxylate NMOFs as degradable drug carriers to transport various drugs that are hard to deliver by other nanocarriers, such as MIL-53, MIL-88A, MIL-88B, MIL-89, MIL-100 and MIL-101-NH2 (Horcajada et al., 2010). As drug carriers, their loading efficiency was detected by four commonly anticancer or antiviral drugs (azidothymidine triphosphate (AZT-TP), busulfan (Bu), cidofovir (CDV) and doxorubicin (doxo)), which, except the latter, could not be successfully encapsulated using existing nanocarriers. The drug loading experiment showed that the NMOFs serve as a remarkable molecular ‘sponges’. For example, up to 25, 21, 16 and 29 wt% of Bu, AZT-TP, CDV and doxo could be loaded into MIL-100. Moreover, a remarkable capacity of 42 wt% can be obtained for AZT-TP and CDV with MIL-101-NH2.

Expect for single drug delivery, MOFs also can be serving as a nanocarrier for drug co-delivery to improve clinical effects. For example, Lin group successfully loaded siRNA and cisplatin together into UiO-NMOFs via encapsulation and surface coordination, respectively (He et al., 2014b). Cisplatin loading capability is up to 12 wt%. Later, Liu and co-workers decorated selenium (Se) and ruthenium (Ru) NPs and loaded siRNAs in the surface of MIL-101 successfully (Chen Q et al., 2017). The combination of Se/Ru-NMOFs and siRNA not only can significantly improve the therapy efficacy but also has high tumor-targeted, enhances antitumor efficacy, and reduces systemic toxicity in vivo. Recently, a multifunctional NMOF-based drug delivery system was obtained by Kong groups for targeting hyperphosphorylated tau (Zhao et al., 2020). As shown in Figure 3A, by post-synthetic modification of the surface of Fe-MIL88B-NH2 with 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA) and 5-amino-3-(pyrrolo [2,3-c]pyridin-1-yl)isoquinoline (defluorinated MK6240, DMK6240) methylene blue (MB), a drug system namely Fe-MIL-88B-NH2-NOTA-DMK6240/MB was prepared successfully. The cytotoxicity of this drug system was evaluated in SH-SY5Y cells using the MTT method. The result demonstrates that almost 83% of SH-SY5Y cells were still alive 24 h of incubation with 100 μg/ml of Fe-MIL-88B-NH2-NOTA-DMK6240 (Figure 3B). The 80% cell survival rate illustrates

| TABLE 1 | The drug release ability of various NMOFs as drug carriers. |
|----------|-----------------|-----------------|-----------------|
| NMOFs    | Drugs            | Loading effective (wt%) | Ways to stimulate drug release | Refs                   |
| MIL-53  | ATP-TP; Bu; CDV; Doxorubicin (doxo) | 0.24 of AZT-TP, 14.3 of Bu | - | Horcajada et al. (2010) |
| MIL-88A | 0.6 of AZT-TP, 8.0 of Bu, 2.6 of AZT-TP, 8.0 of CDV | - | - | He et al. (2014a) |
| MIL-89  | 9.8 of Bu, 14 of CDV | - | - | Chen Q et al. (2017) |
| MIL-100 | 25 of Bu, 21 of AZT-TP, 16 of CDV, 29 of doxo | - | - | Zhao et al. (2020) |
| MIL-100-NH2 | 42 of AZT-TP, 41.9 of CDV | - | - | Lu K et al. (2016) |
| UIO-MOFs | cisplatin        | 12 | - | Chen W H et al. (2018) |
| SeRu@MIL-101 | siRNAs    | 13.93 | - | Li P et al. (2018) |
| Fe-MIL-88B-NH2 | 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA) 5-amino-3-(pyrrolo [2,3-c]pyridin-1-yl)isoquinoline (defluorinated MK6240, DMK6240) methylene blue (MB) | 15 of MB | - | Tian et al. (2015) |
| ZIF-8  | DOX             | 15 | pH | Zheng et al. (2016) |
|         | 3-MA            | 19.798 | pH | Chen W H et al. (2018) |
|         | glucose oxidase (GOx), insulin | 15.6 of GOx, 52.3 of insulin | ROS, Glucose, pH | Zhao et al. (2020) |
| NU-1000 | insulin         | 40 | - | Chen W H et al. (2018) |
| NU-1000x (x = 3, 4, 5, 6, 7) | Lactate dehydrogenase (LDH) | - | - | Li P et al. (2018) |
| ZIF-90 | Rhodamine B (RHB)  | - | ATP-responsive | Deng et al. (2017) |
|         | sgRNA, CRISPR/Cas9 | - | ATP-responsive | Yang X et al. (2019) |
| ZJU-64 | MTX             | 13.45 | Temperature, pH | Lin et al. (2016) |
| ZJU-64-CH3 | MTX        | 10.63 | Temperature, pH | Lin et al. (2016) |
| UIO-66-NH2 | 5-fluorouracil (Fu) | - | Temperature, Zn2+ | Tien et al. (2015) |
| Bio-MOF-1 | Procarinamide     | - | - | An et al. (2009) |
| MIL-101 | BODIPY          | 5.6-11.6 | Pressure, 37°C | Taylor-Pashow et al. (2009) |
| Zr-based-MOF | didclofenac sodium (DS) | 58.80 | - | Jiang et al. (2016) |

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that Fe-MIL88B-NH$_2$-NOTA-DMK6240/MB can effectively protect neurons from death (Figure 3C).

In addition to improve the loading efficiency of NMOFs by multiple coordination between the active compound and metal sites, physisorption by soaking the as-synthesized NMOFs nanocarriers into drug-containing solutions is another method to improve load efficiency of NMOFs. For example, Zou groups combined the synthesis of ZIFs and the encapsulation of target organic molecules in one pot (Zheng et al., 2016). The anticancer drug doxorubicin (DOX) guest molecules which adsorbed into the frameworks of ZIF-8 nanoparticles could be targeted delivery efficient without premature release. Besides doxorubicin, an autophagy inhibitor 3-methyladenine (3-MA) also could be capped in ZIF-8 via one-pot synthesis (Chen W H et al., 2018). The experiment showed that a remarkable capacity of 19.798 wt% can be achieved for 3-MA with ZIF-8 nanoparticles.

Larger molecule delivery encounters more challenges because of their size, surface charge, and component effects including peptides and proteins (Kato et al., 2019). The protein loading efficiency could be significantly improved by immersing NMOFs with a bigger channel size into a protein-containing solution to do physical adsorption (Lian et al., 2017). Farha groups immobilized insulin in NU-1000 due to the larger one-dimensional pores of NU-1000 (mesopores with size “∼30 Å and micropores with size “∼12 Å in diameters), and acquired a high loading of “∼40 wt% in only 30 min (Chen X et al., 2018). The surplus insulin can be digested by pepsin and denatured by stomach acid. Conversely, when using NU-1000 as a nanocarrier for oral delivery of insulin, insulin@NU-1000 not only can keep the wholeness of insulin in gastric acid but also can prevent pepsin from entering the insulin to limit proteolysis simultaneously. Subsequently, they expanded the pore apertures of a series of Zr-based MOFs (termed NU-1000x, x = 3, 4, 5, 6, 7) from 3.3 to 6.7 nm. The expanded NU-1000x MOF structures were used to incorporate the lactate dehydrogenase (LDH) and then demonstrated the use of the captured protein in a cell-free biosynthetic catalytic system (Li B et al., 2018).

Stimulus-responsive release: Although the terms of lower toxic, higher loading ability, and available organism permeability enable NMOFs as outstanding drug carriers, but the issues of premature drug release of NMOFs as nanocarrier is also extremely significant. Typically, stimuli-responsive factors of NMOFs are pH, biomolecules, temperature, and so on. Furthermore, loaded drugs of NMOFs could be activated by diverse stimuli (Lu K et al., 2016). For instance, acidic property of tumor tissue enables pH is one of the extensively studied stimuli for drug release. Willner and co-workers used ZIF-8 NMOF loaded glucose oxidase (GOx) and insulin, and the GOx-mediated aerobic oxidation of glucose yield H$_2$O$_2$ and gluconic acid (Chen Y et al., 2018). The high intracellular concentration of biomolecules in cell also can control drug release such as glutathione (GSH), adenosine triphosphate (ATP), and enzyme. Among numerous factors controlling drug release, disulfide bonds with GSH response is usually considered. Higher GSH level promote the reducing of the disulfide bond and finally set the drugs free. As an extremely important compound for organism, ATP usually used to offer energy and then promote biological processes deeper. Mao and
workers reported the first case of using nanoscale ZIF-90 to specific subcellular mitochondria and image dynamics of mitochondrial ATP in cells (Deng et al., 2017). After embedding Rhodamine B (RhB) in ZIF-90, RhB/ZIF-90 nanoprobe with fluorescence is able to monitor the ATP level fluctuation in a various scope of cellular processes. Later, ZIF-90 with ATP-responsive platform was developed by the same group to deliver cytosolic protein and clustered regularly interspaced short palindromic repeats-associated protein 9 (CRISPR/Cas9) genome editing, as shown in Figure 4A (Yang X et al., 2019). An interesting finder is a slower green fluorescent protein (GFP) release was observed when treated the ZIF-90/GFP in 10 mM phosphate-buffered saline, which is differ to ZIF-8-based protein release with pH-responsive (Figure 4B). Intracellular delivery studies indicated that the ZIF-90/protein nanocarriers can deliver abundant of proteins into the cytosol, regardless of protein size and molecular weight (Figure 4C). Because of the competitive coordination between ATP and Zn²⁺, the ZIF-90/protein nanocarriers decompose in the existence of ATP and release protein. Such as, compared with non-treated HeLa cells, ZIF-90/protein treatment efficiently inhibited GFP expression in HeLa-GFP cells up to 40%, indicating an effective CRISPR/Cas9 genome editing upon ZIF-90/protein delivery (Figure 4D).

In general, release efficiency of drug molecules in temperature-responsive nanocarriers is more susceptible to temperature changes in living organisms. Sada groups reported an example of polymer-modified MOF tethering thermoresponsive polymer poly (N-isopropylacrylamide) (PNIPAM), showing thermally ON-OFF controllable behavior (Nagata et al., 2015; Chen et al., 2019). Two Zinc-based MOFs with formula Zn₁₆(ad)₈(TP)₈O₂(H₂O)₈·4HTP·36DMF·16H₂O (DMF = N,N-Dimethylformamide) were designed by Qian groups (ad = adenine, H₂TP = [1,1′:4′,1″-terphenyl]-4,4″-dicarboxylic acid for ZJU-64, and 2′,5′-dimethyl-[1,1′:4′,1″-terphenyl]-4,4″-dicarboxylic acid for ZJU-64-CH₃) for loading anticancer drug methotrexate (MTX) (Lin et al., 2016). By an easy impregnation method, anticancer drug MTX could be incorporated into NMOFs and loading capacity of ZJU-64 is 13.45 wt%, of ZJU-64-CH₃ is 10.63 wt%. Furthermore, equal amounts of MTX drugs released from MTX-loaded ZJU-64 and ZJU-64-CH₃ at 37°C took 72 h at 60 °C only need about 1.5 and 6 h, proving a lurking application of ZJU-64 and ZJU-64-CH₃ as temperature sensitive drug nanocarriers. Sometimes a single factor is not enough to stimulate the drug release efficiency of NMOFs due to the complexity of organism. Multiple stimuli-responsive MOFs can be served as a better choice to increase drug release efficiencies. Yang and co-workers constructed the first example of mono-disperse mechanized NMOFs by post modification mechanism using stimuli responsive molecules in which pillarene-based supramolecular switches act as gatekeepers (Tan et al., 2015). This nanocarrier has exhibited pH- and/or competitive binding-triggered responded drug release. Deeper research on NMOFs-based nanocarriers with multipoint stimulus response have also been did by the same group in which carboxylatopillar [5]arene (CP5) cyclic structure act as locker. Electrostatic interaction
between quaternary ammonium salt with positive charge that was coated on UiO-66-NH₂ and the negatively charged CP5 cycles could produce [2]pseudorotaxanes as multipoint stimulus response to control drug release.

With the extensive research of NMOFs in the field of nanomedicine, some other factors that affect drug release also have been reported (Oh et al., 2015). Such as ion-responsive MOFs (Taylor-Pashow et al., 2009). Moreover, pressure has been adopted for dominating drug release. Latterly, Qian groups designed a Zr-based MOF with high model drug diclofenac sodium (DS) loading amount up to 58.80 wt% (Jiang et al., 2016). The DS release kinetics could be controlled by regulating the pressure, resulting in a continual release between 2-8 days.

**Nanoscale Metal–Organic Frameworks as Phototherapeutic Agents for Cancer Therapy**

Cancer is one of the major diseases detrimental to health and is a major public health problem worldwide. With the enormous progress made in cancer biology in the past few decades, a large number of anticancer therapeutics have been brought to the clinic including small molecule inhibitors, antibodies, chemotherapeutics, and nucleic acid drugs. However, owing to poor therapeutic effects, high risk of recurrence, intolerable side effects, and other reasons, conventional treatments often fail to meet clinical needs. Recently, phototherapeutic agents are widely used to treat cancer. However, due to the poor tissue penetration of light, pure phototherapy can only be used for superficial treatment. Adjustable structure, functional capabilities, biocompatibility, and biodegradability of NMOFs have made them a promising platform for cancer therapy. Noteworthy is the use of X-ray scintillating MOFs that constructed from metal cluster nodes of high atomic numbers (Z = 72 for Hf and Z = 40 for Zr). The Hf(IV) and Zr(IV) cations in the SBU act as antennas for X-ray photons and converting them to fast electrons through the photoelectric effect. The generated electrons scintillate/excite multiple anthracene-based optical emitters in the MOF through inelastic scattering, leading to efficient generation of detectable photons in the visible spectrum. Most importantly, NMOFs have the ability to preferentially deposit in tumors by enhancing permeability and retention (EPR) effect (Yang et al., 2020). In particular, the integration of photosensitizer to NMOFs not only addresses the limitations of photosensitizers, including aggregation, self-quenching, and uncontrollable in vivo but also improves loading efficiency, stability, and reduces cytotoxicity. Table 2 summarizes the form of cancer treatment of various NMOFs as phototherapeutic agents for cancer therapy.

**Photothermal therapy (PTT):** PTT is a popular noninvasive method for converting the incident light energy into heat for degrading tumors or killing cancer cell effectively via a light absorbing agent (Ni et al., 2020b). For NMOFs, three methods can be adopted for assembly multifunctional NMOF-based therapy for enhanced PTT. First, enhanced photothermal conversion efficiency by functionalizing the SBUs and bridging linkers of NMOFs. Second, incorporate the functional moieties into the framework of NMOFs via post-synthetic modification or
self-assembly from pre-modified linkers for the combination therapies. Third, by encapsulated the multifunctional agents into NMOF frameworks, the treatment efficiency of PTT could be improved. For example, Prussian blue (PB) is a prototype of mixed-valence hexacyanoferrate with a formula of $\text{Fe}^{III}_4 \cdot \text{Fe}^{II}(\text{CN})_6 \cdot n\text{H}_2\text{O}$ (Fu et al., 2012). Biosafety and wider absorption range of PB NPs make it outstanding phototherapeutic agents that can be embedded in the structure of MOFs to formed nanocomposites for PPT. Chen and coworkers obtained a multifunctional PB@MIL-100(Fe) dual-MOFs nanomaterial for combined chemotherapy and PTT and steps for the synthesis of dual-MOFs therapeutic nanoparticle (Wang B et al., 2016). Subsequently, Zhang and coworkers acquired PB@mSiO$_2$–PEG with a high antitumor drug DOX loading (Su et al., 2016). Biosafety and wider absorption range of PB NPs make it outstanding phototherapeutic agents that can be embedded in the structure of MOFs to formed nanocomposites for PPT. Chen and coworkers obtained a multifunctional PB@MIL-100(Fe) dual-MOFs nanomaterial for combined chemotherapy and PTT and steps for the synthesis of dual-MOFs therapeutic nanoparticle (Wang B et al., 2016). Subsequently, Zhang and coworkers acquired PB@mSiO$_2$–PEG with a high antitumor drug DOX loading (Su et al., 2016). Biosafety and wider absorption range of PB NPs make it outstanding phototherapeutic agents that can be embedded in the structure of MOFs to formed nanocomposites for PPT. Chen and coworkers obtained a multifunctional PB@MIL-100(Fe) dual-MOFs nanomaterial for combined chemotherapy and PTT and steps for the synthesis of dual-MOFs therapeutic nanoparticle (Wang B et al., 2016). Subsequently, Zhang and coworkers acquired PB@mSiO$_2$–PEG with a high antitumor drug DOX loading (Su et al., 2016).

Besides PB, NIR-absorbing polymer polyaniline (PAN) also exhibit strong absorption coefficients and excellent photostability that could be incorporated in the channels of NMOFs to construct nanocomposites for PTT upon NIR laser irradiation. Jing and co-workers synthesized a nanoscale polymer-MOF hybrid named UiO-66@PAN, in which PAN had the NIR-absorbing ability (Wang D et al., 2016). The UiO-66@PAN is effective for PTT based cancer treatment both in vivo and in vitro. As a result of higher photothermal transformation efficiency and outstanding biocompatibility, Polypyrrole (PPy) incorporated nanomaterial has been proved to be efficient for PTT. The fabrication process of PPy@MIL-100 was shown in Figure 5A, in which PPy and FeCl$_3$·6H$_2$O acted as a catalyst and PVP as stabilizer. The PPy core acts as a PTT agent while an organic PAI agent for deep tissue imaging. The MIL-100 shell was applied for loading DOX drugs. It was suggested that polypyrrole was formed by Fe(III) ions induced oxidative polymerization of PPy, then the combination of Fe(III) ions and polypyrrole surface promoted the formation of MIL-100 shell on PPy. Moreover, PPy@MIL-100 supported pH- and light controlled drug release, dual-modal imaging, and combined PTT and chemotherapy (Figures 5B,C). Besides this, Wang groups reported a dual-modal imaging core-shell nanomaterial PPy@MIL-100 for combined chemotherapy and PTT (Chen R et al., 2017). Indocyanine green (ICG) is the NIR optical dye and can be used for clinical applications. For example, Chen groups designed a multifunctional nanoplatform MOF@HA@ICG based on hyaluronic acid (HA) for imaging-guided PTT (Cai et al., 2017). However, the lacked of sensitivity and specificity in cancer treatment limited its application.

Photodynamic therapy (PDT): Photodynamic therapy (PDT) is more effective anticancer treatment that depends on nontoxic photosensitizer (PS) to yield reactive oxygen species (ROS) to inhibit cancer cells (Horne and Cronjé, 2017). The first way of
constructing NMOFs for PPT is using the nontoxic photosensitizer as building blocks. In 2014, Lin and co-workers first literates a Hf-porphyrin NMOFs with formula of $\text{Hf}_6(\mu_3-O)_4(\mu_3-OH)_4$(DBP)$_6$($\text{H}_2\text{DBP}=5,15$-di($p$-benzoato)-porphyrin) by a solvothermal strategy, as a significant photosensitizer for PDT (Lu et al., 2014). Thanks to position separation of porphyrin ligands, $\text{Hf}_6(\mu_3-O)_4(\mu_3-OH)_4$(DBP)$_6$ could efficiently generate $^1\text{O}_2$ to enhance intersystem crossing by heavy Hf centers, and realize $^1\text{O}_2$ invasive from the interior of MOFs to the cell through porous nanoplates, as shown in Figures 6A,C. Porous NMOF structure impelled $\text{Hf}_6(\mu_3-O)_4(\mu_3-OH)_4$(DBC)$_6$ remarkable PS loading up to 77 wt%. Moreover, in NMOF-treated group with 180 J cm$^{-2}$ light dose, two quarters mouse had their tumors eradicated while the other two achieved 98% tumor regression, on contrary, the ligand control failed to inhibit the tumor growth at the same dose (Figure 6E). Then, the same group used another hematoporphyrin derivative 5,15,20-tetrakis (4-carboxyphenyl) porphyrin (H$_4$TCPP) is a commercially available photosensitizer applied in PDT (Bůžek et al., 2017). The symmetrical molecular structure of TCPP and the strong coordination ability of its four carboxyl groups to metal ions could facilitate the formation of MOF structure. Liu groups obtained a NMOF Hf-TCPP composed by Hf$^{4+}$ and TCPP and proved the ability for efficient PDT by intravenous injection (Liu et al., 2016). Hf-TCPP displayed spherical morphology structure and TCPP in Hf-TCPP act a photosensitizer to allow PDT. In addition, strong X-ray attenuation ability of Hf$^{4+}$ could act as a radio-sensitizer to enhance radiotherapy (RT). Zhou group reported a series of Zr$^{IV}$-based porphyrinic NMOF (PCN-224) with different sizes (Park et al., 2015). The author indicated that modifying the surface of PCN-224 with folic acid could improve cell uptake of NMOFs and exhibited higher PDT efficacy.

Dithienylethene derivative, 1,2-bis(2-methyl-5-(pyridin-4-yl)thiophen-3-yl)cyclopent-1-ene (BDPTE) could serve as a photochromic switch to adopt reversible $6\pi$ electrocyclic reaction under photoirradiation at distinct wavelengths. The switch effect of BDPTE induced by light isomerization show special absorption characteristics, and can supply diverse energy transfer ways for photosensitizers to generate $^1\text{O}_2$. Meanwhile, dipyridyl head in BPDTE make it possible for forming pillar-layer
structure with TCPP to produce $^1$O$_2$. Zhou groups constructed Zn(II) based MOF (Zn-TCPP-BPDTE) by solvothermal reaction of TCPP (no metal), BPDETE, and Zn(NO$_3$)$_2$·6H$_2$O. In Zn-TCPP-BPDTE, paddlewheel-type Zn cluster linked TCPP via Zn-O bonds and linked BPDETE through the Zn-N bonds (Park et al., 2015). Upon UV irradiation, Zn-TCPP-BPDTE could present switch effect owing to the photochromic property of BPDETE. Moreover, the "on" state of Zn-TCPP-BPDTE without impacting the $^1$O$_2$ generation of TCPP, but the BPDETE in "off" state of Zn-TCPP-BPDTE extinguished the $S_1$ state of TCPP to decrease $^1$O$_2$ generation. Later, they used the same technique obtained a UiO-66 NMOF-based $^1$O$_2$ generation platform in which 1,2 bis(5-(4-carboxyphenyl)-2-methylthien-3-yl) cyclopent-1-ene (BCDTE) as the photochromic switch and TCPP ligand as the PS (Park et al., 2016a). The cytotoxicity test showed that PDT cytotoxicity in the "on" state of BCDTE doped Uio-66 is ~90%, while in the "off" state only 10%. This result proved the method of encapsulating photochromic molecules and PSs together into NMOFs to regulate $^1$O$_2$ generation efficacy and finally impact in vitro PDT.

Ligand exchange offers another way for fabricating NMOFs for PDT. Xie and co-workers incorporated the carboxyl-modified diiodo-substituted BODIPYS (12-BDP) into Uio-66 to elaborate the PDT into the product of Uio-PDT through solvent-assisted ligand exchange (Wang et al., 2016a). Structural analysis shows that there was 12.5 mol% of benzenedicarboxylate linker was exchanged by carboxy-12-BDP in Uio-PDT and affording a PS loading of 31.4 wt%. Both Uio-PDT and carboxy-12-BDP had the ability of crossing the cell membrane to accumulate in the cytoplasm through Confocal laser scanning microscopy study. The penetration of light affects efficiency of NMOFs for PDT as well as the building blocks in anticancer treatment. Compared with visible light and near-infrared, X-rays have stronger penetrability in organism and have been widely employed in cancer treatment (Song et al., 2018). Lin and co-workers did outstanding work on efficiently converting X-ray to visible-light luminescence of NMOFs for PDT. In 2014, they first designed and synthesized X-ray Hf/Zr-based MOFs with formula of $M_6$ ($\mu_5$-O)$_4$ ($\mu_5$-OH)$_4$ (carboxylate)$_{12}$ ($M = \text{Hf or Zr}$) (Wang et al., 2014). The high atomic number of $[\text{M}_6]$-clusters in the SBUs acts as effective X-ray antenna by absorbing X-ray photons and transforming them into fast electrons. Once the $[\text{M}_6]$-clusters assimilated X-rays in the energy range of 20–200 keV, the outer electrons of $M^{4+}$ were emitted in the form of fast electrons to produce visible light. The X-ray-induced emission spectra exhibited that the emission peaks of $M_6$ ($\mu_5$-O)$_4$ ($\mu_5$-OH)$_4$ (carboxylate)$_{12}$ was in the visible range of 400–600 nm. Obviously, this visible light had potential for serve as a PDT light source. In 2017, they built two Hf-based nanomaterials Hf-BPY-Ir or Hf-BPY-Ru as powerful PSs for effective X-PDT of colon cancer models in which $[\text{Hf}_6\text{O}_9\text{(OH)}_2\text{(HCO}_3\text{)}_3]$ as SBUs and Ir [bpy (ppy)$_2$]$^+$ or $[\text{Ru (bpy)}_3]^2+$ as ligands (bpy = 2,2′-bipyridine, ppy = 2-phenylpyridine) (Lan et al., 2017). Hf-BPY-Ir was obtained by reacting [Ir (ppy)$_2$]Cl$_2$ and Hf-based MOF in a post-synthesis modification strategy ($H_3\text{BPY} = 4',6'-\text{dibenozylo}[-2,2'-\text{bipyridine}]4$-carboxylic acid). Similarly, Hf-BPY-Ru nanomaterial were designed using Ru (bpy)$_2$Cl$_2$. Heavy Hf atoms in the SBUs absorb X-rays efficiently and transfer the energy to Ir [bpy (ppy)$_2$]$^+$ or $[\text{Ru (bpy)}_3]^2+$ units to lead to PDT by generating ROS. The fabricated cell experiment showed that these two nanomaterials had an excellent inhibitory effect on CT26 and MC38 cells in vitro, while in vivo experiments proved the efficient penetration of X-rays into tumor to enable efficient deep PDT which was performed in amice.

Combined theranostic strategies: Although PTT and PDT can strengthen by diverse strategies; the effect of monotherapy is still not satisfactory. Up to now, cancer treatment has gradually shifted from monotherapy to combination therapy which means integrating of two or more treatments for synergistic effects (Zhang et al., 2020). In 2016, Lin and co-workers obtained IDOi@TBC-Hf nanomaterial with chlorin derivative, 5,10,15,20-tetra (phenzoato) chlorin (H$_2$TBC) and Hf$_6$(μ$_5$-O)$_4$ (μ$_5$-OH)$_4$ in which IDOi was loaded (Lu Y et al., 2016). Through the combination of NMOF-enabled PDT and IDOi-based immunotherapy, IDOi@TBC-Hf platform makes a possible cancer therapy strategy. Mechanistic studies suggested that ROS were generated upon irradiation after the local injection of IDOi@TBC-Hf leading immunogenic cell death and the release of tumor associated antigen. Subsequently, the same group obtained a series of IDOi-loaded NMOFs as a treatment therapy that synergized checkpoint blockade immunotherapy and low doses of X-ray-excited PDT to acquire effective local control and abscopal effects in mice models, including DBP-Hf ($H_2$DBP = 5,15-di-p-phenzoato)porphyrin), TBP-Hf ($H_2$TBP = 5,10,15,20-tetra-p-phenzoato)porphyrin), DBA-Hf$_6$ and DBA-Hf$_{12}$ ($H_2$DBA = 2,5-di-p-phenzoato)aniline) (Lu et al., 2018b). The combination of X-ray-induced PDT and immunotherapy can not only reduce the possible various effects of local X-ray radiation but also eradicate both treated primary tumors and untreated distant tumors efficiently via systemic antitumor immune responses.

The major defects of chemotherapy are intolerable side effects, systemic toxicity, and multidrug resistance. When united the PDT and chemotherapy, PDT-induced photochemical internalization can significantly improve the efficacy of chemotherapy (Ni et al., 2018). Such as the encapsulation of anticancer drug DOX into the NMOF with photodynamic effect not only could meet high loading rate of DOX but also could facilitate the induction of $^1$O$_2$ production because of the high content of PS in the NMOFs. Lee and co-workers produced a core-shell structure g-$C_3$N$_4$@ZIF-8 for DOX drug delivery (Chen et al., 2015). The anticancer efficacy of g-$C_3$N$_4$@ZIF-8 enhanced significantly by combination DOX with g-$C_3$N$_4$. Besides ZIF-8, PCN-222 was also used as a nanocarrier for loading DOX and PDT (Liu et al., 2017). 109 wt% loading rate of DOX was obtained due to the larger pore channel (1.75V 1.75 nm). In addition, $^1$O$_2$ production could be facilitated by the high concentrations of porphyrin (59.8 wt%) in the PCN-222. Similarly, Roy and co-workers developed a combination of PDT and chemotherapy by incorporated MB and DOX into the micropores of MIL-88B (Sharma et al., 2017). In order to effectively strengthen the antitumor effect, Wang and co-workers obtained F127-MnO$_2$-ZIF@DOX/C$_3$N$_4$ nanomaterial with integration of chemotherapy.
and aerobic PDT, which had a fairly good curative effect on hypoxic tumors (Zhang Q et al., 2018). Particularly, the g-C3N4 PS and the DOX drugs were incorporated into the ZIF-8 by electrostatic interactions finally obtained F127-MnO2-ZIF@DOX/C3N4 nanomaterial (Figure 7A). F127 improved the biocompatibility the nanomaterial, promoting its accumulation in cancer (Figure 7B). ZIF-8 offered pH-responsive characteristics for the nanomaterial: releasing DOX under acidic conditions, reducing side effects, and reducing nonspecific drug release (Figure 7C). In addition, the loaded MnO2 nanodots could continuously catalyze the decomposition of endogenous H2O2 to produce O2, and greatly enhance the PDT effect.

**Nanoscale Metal–Organic Frameworks as Fluorescent Probe for Biomedical Sensing and Imaging**

Biomedical sensing and imaging have been proved as prospecting pattern for detection multiple complexes selectively and rapidly as well as environmental safety (Dong et al., 2019). Luminescent characteristics together with size/shape selective sorption properties of NMOFs make them potential fluorescent probe for biomedical sensing and imaging under different mechanisms. So far, various NMOFs were explored for detecting DNA/RNA, enzyme activity and small-biomolecules, as well as magnetic resonance imaging (MRI), X-Ray computed tomography (CT), positron emission tomography (PET) and optical imaging, which are useful techniques for clinical diagnosis.

Biomedical sensing: Through overcoming the self-quenching and leaching problems of many small molecular biosensors, NMOF-based sensors realize high sensitivity, high precision, and high resolution in subcellular bioprobes. Recently, a lot of studies have reported to describe the NMOFs as sensitive and selective sensors for screening biological macromolecules like nucleic acids (Yang Y et al., 2017), and proteins (Xu et al., 2017), small biomolecules including glucose (Chen et al., 2016), amino acids (Wang et al., 2015), and so on in cellular and subcellular sensing, as shown in Table 3.

The most exciting stories of the biomolecular sensing applications of NMOFs have been found from screening nucleic acid molecules, such as DNAs and RNAs. The detecting of DNAs and RNAs by NMOFs were mainly realized by anchoring NMOFs to nucleic acid molecules detectors. For instance, in order to detect the human immunodeficiency virus (HIV-1), a N,N’-bis(2-hydroxyethyl) dithiooxamidato containing NMOF named [Cu(H2dtoa)] has been synthetized (Zhu et al., 2013). The sensing mechanism of this detecting platform is to regenerate the photoluminescence intensity of the carboxyfluorescein (FAM)-labeled probe DNA by binding specific DNA with MOFs. With the similar quenching principle, NMOF with formula of [Cu3(Cmdcp)2

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*FIGURE 7 | (A) The schematic illustration of the fabrication of F127-MnO2-ZIF@DOX/C3N4 and F127-MnO2-ZIF@DOX/C3N4 with 1O2 generation enhancing the chemo-photodynamic therapy. (B) In vitro evaluation of 1O2 generation of FMZ/DC in H2O2 solution (10–4 m) under pH = 5. (C) The pH-responsive release of DOX from FMZ/DC determined by UV–vis spectrophotometry. Source: (Xu et al., 2017).*
TABLE 3 | Various NMOFs as sensitive and selective sensors for screening biological macromolecules.

| NMOFs | Probe units | Biomolecules | Detection limit | Detection mechanism | Refs |
|-------|-------------|--------------|----------------|---------------------|------|
| [Cu(H2dtoa)] | FAM-labeled probe | HIV-1 (DNA), Thrombin | - | PET | Zhu et al. (2013) |
| [Cu(Cmdcp)] | FAM-labeled probe | HIV-1 (dsDNA) and Sudan virus RNA, Ebola virus RNA | 196 pM for DNA, 73 pM for RNA | PET | Yang et al. (2015) |
| [La4(Cmdcp)(H2O)9] | - | - | - | - | Qin et al. (2016) |
| [La4(Cmdcp)(H2O)9] | FAM-labeled probe | P-DNA | - | - | Yang S P et al., 2017, Zhao et al. (2016a), Zhao et al. (2016b) |
| [La2(Cbdcp)3(H2O)10] | FAM-labeled probe | DNA or RNA | - | PET | Yang S P et al., 2017, Zhao et al. (2016a), Zhao et al. (2016b) |
| [Zn(Cbdcp)2(H2O)2] | FAM-labeled probe | HIV-1 (DNA), FAM-labeled probe Glycine (Gly) and Serine (Ser) | 75 ppb | - | Fang et al. (2014), Mejia-Ariza et al. (2017), Zhao H X et al. (2016), Ling et al. (2015) |
| [Cu(mal)(bpy)] | FAM-labeled probe | glycine (Gly) and serine (Ser) | 0.81 μg ml⁻¹ for Gly, 1.51 μg ml⁻¹ for Ser | - | Li S Y et al. (2017) |
| [Cd(L)(bpy)] | FAM-labeled probe | π-conjugated naphthyl moiety | 23.72 μM⁻¹ for D-PEN, 10.13 μM⁻¹ for L-PEN | - | Zhang W et al. (2018) |
| [Cd(L)(bpy)] | FAM-labeled probe | ROS | - | - | Xu et al. (2016) |
| Zr2O2(OH)8(H2O)4(TTA)6 | - | NZF and TNP Antibiotics | 58 ppb NZF, 23 ppb TNP | Electron transfer and energy transfer | Wang et al. (2016b) |
| Zr2O2(OH)8(H2O)4(TTA)6 | - | NZF Antibiotics | 58 ppb NZF, 23 ppb TNP | Electron transfer and energy transfer | Wang et al. (2016b) |
| [Cd(L)2(6-NDC)2] | DMF·H2O | - | 75 ppb | - | Zhao et al. (2017) |
| [Cd(L)2(BPDC)2] | DMF·9H2O | - | 60 ppb | - | Zhao et al. (2017) |

(dps)4·(H2O)4(SO)2 | (H2CmdcpBr = N-carboxymethyl-3,5-dicarboxylypyridinium bromide; dps = 4,4′-dipyridyl sulphide) was also used for detecting of HIV-1 double-stranded DNA (dsDNA) and Sudan virus RNA (Yang et al., 2015). Later, the research group used lanthanides ions and the identical inorganic linker to obtained ([La4(Cmdcp)6(H2O)9])n and ([Dy(Cmdcp)(H2O)9]NO3)·2H2O)n with water stability (Qin et al., 2016). The coordinated water molecules and free NO3⁻ anions on the channels of [Dy(Cmdcp)(H2O)9]NO3)·2H2O)n can induce electrostatic and hydrogen bonding interactions with FAM-tagged probe DNA. Moreover, the transient complex formed by NMOFs and FAM-tagged probe DNA served as high efficiency and selectivity fluorescent probes for sensing Ebola virus RNA. MOF ([La4(Cmdcp)6(H2O)9])n can absorb FAM-tagged probe DNA and quench the fluorescence of FAM through a photo-induced electron transfer (PET) process. Similarly, other water-stable NMOFs ([La2(Cbdcp)3(H2O)10])n (H2CmdcpBr = N-(4-carboxybenzyl)-3,5-dicarboxylypyridinium bromide), ([Zn(Cbdcp)2]H2O)n [Cu(ddbb)2]n (H2ddbbBr = 1-(3,5-dicarboxybenzyl)-4,4′-bipyridinium bromide) and ([Cu(ddbb)2(H2O)2])·10H2O)n also have been reported for sensing virus DNA or RNA by absorbing FAM-tagged probe DNA and inhibited the fluorescence of FAM by PET (Zhao et al., 2016a; Zhao et al., 2016b; Yang S P et al., 2017). Additionally, Uio-66-NH2, UIo-66, MIL-101, MIL-88A, ([La2 (TDA)3]·2H2O)n (TDA = 2,2′-thiodiacetic acid), [Gd (TIA)(HCOO)]n (TIA = 5-triazole isopthalate), Cd(L)-HDMA2 (DMF)(H2O)3 and Zn(L)-HDMA2 (DMF)(H2O)3 (H2L = bis-(3,5-dicarboxy-phenyl) terephthalamide, DMA = N,N-dimethylacetamide) (Fang et al., 2014; Ling et al., 2015; Zhao H X et al., 2016; Mejia-Ariza et al., 2017) have also been used as fluorescent probes for DNA/RNA and is able to distinguish complementary and mismatched target sequences with good selectivity and sensitivity. Besides biological molecular DNA/RNA, proteins can also be identified by NMOFs. MOF [Cd (ATC)(H2O)2]n (ATC = 2-aminothephalic acid) has...
recently been proposed as a molecular sensing platform for the fluorescence quenching based detection of bovine serum albumin (anti-BSA) through activate -COOH/-NH2 groups followed by the attachment of proteins (Kumar et al., 2014). Limit of detection or the proposed detection is found to be 7 mg/ml that is comparable to the quantum dot based detections.

Besides the DNA/RNA and proteins biological macromolecular, NMOFs can also serve as fluorescence sensors to distinguish amino acids (Wang and Wei, 2016). Pioneering work on amino acids recognition includes the detection of dipicolinic acid (DPA) molecules, a structural constituent of bacillus anthrasis spores and many other virulent bacteria. Particularly, MOF named \[
\text{[Cu(mal)(bpy)]\cdot2H_2O} \\quad (\text{mal = D, L-malic acid})
\] was constructed by Kong groups, a fluorescence probe experiment indicated that this MOF could act as fluorescence sensor to recognize glycine (Gly) and serine (Ser) and with low detection limits 0.81 μg ml\(^{-1}\) for Gly and 1.51 μg ml\(^{-1}\) for Ser (Li Y et al., 2017). The sensing principle is that fluorophore-labeled ssDNA can be adsorbed in \[
\text{[Cu(mal)(bpy)]\cdot2H_2O}
\] and then quenching of the fluorescence. In term of chiral precursors 4,4\'-((naphthalene-1,4-dicarboxonyl)bis (azanediyl))dibenzoic acid (H\(_2\)L) and bpy, a 3D homochiral LMOF \[
\text{[Cd(L)(bpy)]\cdotDMA\cdot5H_2O} \quad \text{n}
\] was successfully obtained by Zhang and co-works and can be used as detecting platform for distinguishing D/L-penicillamine (PEN) by the π-conjugated naphthyl groups as fluorescent emission center (Zhang W et al., 2018). Once excited \[
\text{[Cd(L)(bpy)]\cdotDMA\cdot5H_2O} \quad \text{n}
\] under 340 nm, a quite strong fluorescence was obtained. By adding the D-PEN or L-PEN into this platform, the luminescence intensity quenched obviously. The linear range of this fluorescence sensor is from 20 to 167 μM, and the detection limits of D-Pen and L-Pen are 23.72 μM\(^{-1}\) and 10.13 μM\(^{-1}\), respectively.

A variety of diseases cause hypoxia. PDT, radiation therapy and other common cancer treatment are all heavily oxygen-dependent treatments, so intracellular ROS sensing is greatly important and necessary. A phosphorescence/fluorescence dual-emissive NMOF was designed by Lin groups, namely, R-Uio, which could be used as an intracellular ROS detector (Xu et al., 2016). The R-Uio was stable, porous, crystalline, and dual emissive (Figures 8A,B). The mix-ligand R-Uio including an oxygen-responsive phosphorescent ligand, Pt-5,15-di
The advent of biomedical imaging

Biomedical imaging: The advent of biomedical imaging

Antibiotics are mainly used for infections caused by bacteria. Antibiotic resistance not only has a serious impact on human and animal health, but also can be widely spread as antibiotic wastes (Zhu et al., 2018). Due to the rapid response, highly selectivity and sensibility, the biosensors based on fluorescent MOF for antibiotic detection became popular. By adopting high-Z ions Zr4+ and fluorescent inorganic linkers H3TTNA (5′,6′,6″-trimethyl-[1,1′,3′,1″-terphenyl]-4,4′-dicarboxylic acid) and H3TTNA (6,6′,6″-bis-(2,4,6-trimethylbenzene-1,3,5-triyl)tris (2-naphthoic acid)), two Zr-MOFs Zr4+-containing NMOFs as MRI contrast agents was constructed by Zhou groups, namely Gd(BDC)1.5(H2O)2 (Rieter et al., 2006). Gd(BDC)1.5(H2O)2 nanopartical shows an r1 relaxivity of 35.8 s⁻¹ per mm Gd³⁺ or ≈1.6 × 10⁷ mm⁻¹ s⁻¹ on a per NMOF basis. The r1 relaxivity level of Gd(BDC)1.5(H2O)₂ is approximately an order of magnitude higher than the usually used technology Omniscan. Recently, by a hydrothermal treatment of Gd³⁺ and Ru(II)[4,4′-(COOH)₂ bipyridyl (bpy)₁₂Cl₂ (L₉), Yin groups acquired a kind of nanomaterial based on Gd³⁺ and L₉Ru precursors and used for MRI, namely Gd-Ru (Wang Y M et al., 2016). SEM and TEM images indicated that Gd-Ru is in globular structures of regular shape and uniform size in a mean diameter of 138 nm. Higher MRI contrast efficiency was acquired by Gd-Ru in contrast to the commercial MRI contrast Gd–DTPA (DTPA, diethylenetriamine pentaacetic acid). Although Gd³⁺ based nanomaterial have shown good MRI ability, but the possible release of toxic Gd³⁺ ions from Gd³⁺-based nanoparticles hinders their deeper exploration for MRI. To settle the problem of toxicity of Gd-based NMOFs, Mn²⁺-based NMOFs have been extensively investigated. As an example, Lin and coworkers designed Mn-BDC and Mn-BTC NMOFs for an optional MRI contrast media by reverse-phase microemulsion techniques at room temperature and a surfactant-assisted procedure at 120°C with microwave heating (Zhao et al., 2017).
The $r_1$ and $r_2$ relaxivities of Mn–BDC NMOF were 5.5 and 80.0 mm$^{-1}$ s$^{-1}$ on a per Mn basis, respectively.

The T2-weighted MRI contrast media is generally superparamagnetic iron oxides (SPIOs) which cause negative image enhancement. Not long ago, a series of ironcarboxylate NMOFs were synthesized by Horcajada and co-workers as T2-weighted contrast media (Horcajada et al., 2010). The size of these NMOFs range from 50 to 350 nm, matching known bulk phase materials of MIL-53, MIL-88A, MIL-88Bt, MIL-89, MIL-100, MIL-101-NH$_2$, PEG-MIL-88A and PEG-MIL-100 exhibited high $r_2$ relaxivity on a per metal basis and negative enhancement of the liver and spleen was observed after injection of MIL-88A. By incorporating Fe$_3$O$_4$ nanoparticles into the Uio-66, Fu groups acquired a core–shell nanomaterial Fe$_3$O$_4$@Uio-66 (Zhao S N et al., 2016), as shown in Figure 9A. Drug DOX was used to assessment the drug loading ability of the Fe$_3$O$_4$@Uio-66 and incorporated into the framework of Fe$_3$O$_4$@Uio-66 to obtain Fe$_3$O$_4$@Uio-66-DOX. The generated Fe$_3$O$_4$@Uio-66-DOX can not only act as nanoplateform for simultaneous drug delivery, but also can serve as a contrast media for T2-weighted MRI (Figure 9B).

Moreover, Fe$_3$O$_4$@Uio-66-DOX could effectively inhibit the growth of tumor, and the MRI of HeLa-tumor bearing mice injected with Fe$_3$O$_4$@Uio-66-DOX revealed obvious darkening effect in the tumor area (Figure 9C).

X-Ray Computed Tomography Imaging (CT). CT imaging is a noninvasive clinical diagnosis technique for 3D visualization of internal structures of a scanned object by X-ray attenuation. Contrast agents with high-Z ions, such as small molecular contrast media including iodinated aromatic molecules and barium sulfate, normally exhibit strong X-ray attenuation (Kalra et al., 2004). For the high-Z elements can be facile merged into the frameworks of NMOFs with extremely high payloads, NMOFs have been a prospective contrast platform for CT. At present, lots of NMOFs with high-Z ions have been obtained and applied as possible CT contrast media. Two NMOFs (Zr-Uio and Hf-Uio) with high loadings of Zr (37 wt%) and Hf (57 wt%) were developed by Lin and co-workers and finally their potential applications as CT contrast agents were demonstrated (Dekrafft et al., 2012). The Zr and Hf NMOFs with corresponding atomic number of 40, 72 respectively making those potential candidates as CT contrast agents. Due to strong X-ray absorbance, Au nanoparticles also could be used as contrast media for CT imaging. Tian groups described an Au nanorod-incorporated core–shell material named Au@MIL-88(Fe) could serve as a multi-mode diagnostic system to provide high resolution image in either MRI or CT imaging by microemulsion method in DMF (Shang et al., 2017). The as-prepared Au@MIL-88(A) nanomaterials in a well-defined star-like morphology structure had high monodispersity and homogeneity. Both CT and MRI induced by Au@MIL-88(Fe) contrast agents showed distinct tumor boundaries with high penetration depth and spatial resolution. Liu groups used IR825 as organic linker to coordinate with Mn$^{2+}$ and Hf$^{4+}$ ions for preparing core–shell NMOFs to act as multi-mode imaging agents (Yang Y et al., 2017). In the NMOF, Mn$^{2+}$ ion and Hf$^{4+}$ ion are acted as a MRI contrast media; high-Z element Hf$^{4+}$ ion can enhance CT signal and radio-sensitization, and the ligand IR825, is used as a photothermal agent due to the strong NIR absorption.

Positron Emission Tomography (PET). PET is X-ray functional imaging method with superior detection sensitivity (as low as picomolar scope) and stronger signal penetration. In PET, the radionuclides emitted by positrons gather on the target organ, producing a pair of gamma ray photons that can be trapped by sensitive detector panels. Hong and co-workers have done outstanding work on exploring nanomaterial for PET imaging. Recently, they obtained $^{89}$Zr-containing NMOF for PET (Chen X et al., 2017). Besides the $^{89}$Zr was loading into the framework of Uio-66, the surfaces of the nanomaterial were functionalized by pyrene-derived PEG further. PET scans traced the organ distribution of $^{89}$Zr-Uio-66/Py–PGA-PEG-F3 in vivo and detected an 8.2 ± 0.3% total injected dose per Gram of tumor after intravenous injection for 2 h.

Optical Imaging. Optical imaging, a kind of fluorescence technique, is widespread in biomedicine. Generally excited dye molecules by visible light in organism and produce luminescence.
Highly sensitive and minimally invasive make the optical imaging widely used in clinic.

Recently, by incorporated Yb³⁺ and phenylene-derived photosensitizers, Foucault-Collet and co-workers created unique near-infrared-emitting Yb³⁺-containing NMOFs (Foucault-Collet et al., 2013). Accompanied by being engulfed by cells and reserved in cytoplasm, Yb³⁺-based NMOFs emit the number of photons per unit volume that higher enough to realize the real-time imaging of HeLa and NIH 3T3 cells. Li and co-workers constructed core-shell nanomaterial with integrate of single NaYF₄: Yb, Er upconversion nanoparticles (UCNPs) into Fe-MIL-101-NH₂ to realize luminescent/magnetic dual-mode imaging (Li et al., 2015). The UCNP@Fe-MIL-101-NH₂ was further surface-functionalized with PEG and PEG-folic acid (FA) to improve the biocompatibility. A significant KB tumor contrast could be observed after intravenous injection for 24 h in vivo optical imaging. Furthermore, the dyes with optical activity were also inserted within the skeleton of NMOFs either by post synthetically or as an object species to realize the optical imaging. For example, a case of hyaluronic acid (HA) incorporated MIL-100 (Fe) NMOFs were developed by Cai and co-workers (Figures 10A,B). By inserting the indocyanine green (ICG) NIR dye into the NMOFs to realize image-induced PPT [94], this material exhibited a strong load capacity of ICG (40 wt%), high optical stability, and strong NIR absorbance (Figures 10C,D). FL images of the in vivo and in vitro certified that MOF@HA@ICG had excellent uptake capacity of CD44-positive MCF-7 cells (Figures 10E,F).

CONCLUSION AND OUTLOOK

In the last few years, substantial improvement has been achieved in applying NMOFs for drug delivery, cancer therapy and biomedical sensing and imaging. Various NMOFs-based nanomedicine have been intelligently designed and proved to be effective and powerful for clinic both in vivo and in vitro. In this review, we have comprehensively discussed the update achievements of NMOFs in clinic from a broader vision including applying NMOFs as nanocarriers, anti-cancer therapeutic agents, biosensors and molecular imaging probes as well as well-established synthetic methods for the strengthening their functional capabilities and extending their potential nanomedicine applications. Furthermore, some key issues of NMOFs including controlled synthesis, surface modification, toxicity, biocompatibility, stability, and therapeutic/imaging efficacy before the biomedical applications of NMOFs also are addressed in this review. Despite the sustainable growing interest and impressive accomplishment has been obtained in this area, the development of NMOFs as drug delivery, cancer therapy and biomedical sensing and imaging agents is still in its infancy contrasted to other nanocarriers.

Generally, it can be seen that NMOFs hold obvious superiority compared with other nanoformulations in nanomedicine applications because of their intrinsic characteristics including highly porous and large channels, structural adjustability/...
multifunctionality, as well as low toxicity and biocompatibility. Nevertheless, such nanomedical system has boundedness, such as complicated hierarchy for targeted drug delivery without eliminated or undergoes degradation, pure efficiency of phototherapy and photodynamic therapy, difficult fabricating for sensor device and so on. Consequently, there is still defiance in this field and deeper and constant exploration is needed. From a viewpoint of synthetic strategy, one of the biggest challenges is to explore new synthetic methods for the fabrication of smaller-size NMOFs on account of smaller NMOFs has better applicability than larger ones. Still, the smaller NMOFs are better for the integration of biomolecules, particularly in FRET. From the point view of applications, further efforts should be paid to prepare versatile biocompatible and low-toxicity NMOFs. Besides that, chemical instability of NMOFs is essential. Additionally, although lots of researches have proved the short-term safety of NMOFs in vitro or in vivo studies, the long-term chronic toxicity effects, pathway, and clearance behavior of NMOFs are rarely explored.

In brief, multi-functional NMOFs engineering for nanomedicine is a newly burgeoning field. There is still a large innovative research space in this exciting area. For better applied the NMOFs in disease diagnosis and treatment of clinic application, additional breakthroughs needed to acquire for solving all obstacles mentioned above in the near future.

**AUTHOR CONTRIBUTIONS**

DZ conceived and wrote the paper; WZ and Z-HW provide partial figures; HX made suggestions to improve the paper.

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