Bioengineering of nano metal-organic frameworks for cancer immunotherapy

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ABSTRACT

Immunotherapy techniques, such as immune checkpoint inhibitors, chimeric antigen receptor (CAR) T cell therapies and cancer vaccines, have been burgeoning with great success, particularly for specific cancer types. However, side effects with fatal risks, dysfunction in tumor microenvironment and low immune response rates remain the bottlenecks in immunotherapy. Nano metal-organic frameworks (nMOFs), with an accurate structure and a narrow size distribution, are emerging as a solution to these problems. In addition to their function of temporospatial delivery, a large library of their compositions, together with flexibility in chemical interaction and inherent immune efficacy, offers opportunities for various designs of nMOFs for immunotherapy. In this review, we overview state-of-the-art research on nMOFs-based immunotherapies as well as their combination with other therapies. We demonstrate that nMOFs are predominantly customized for vaccine delivery or tumor-microenvironment modulation. Finally, a prospect of nMOFs in cancer immunotherapy will be discussed.

KEYWORDS

cancer immunotherapy, nano metal-organic frameworks (nMOFs), bioengineering, vaccine delivery, tumor-microenvironment modulation

1 Introduction

As an alternative of conventional chemotherapy and radiotherapy, cancer immunotherapy can effectively activate specific immune cells to create a specific antitumor or immune memory effect [1, 2]. Unlike conventional treatments, cancer immunotherapy reduces multidrug resistance, mitigate cancerous cell gene mutation (generally caused by chemotherapy) and enhance therapeutic synergy with other therapies like radiotherapy, photodynamic therapy (PDT), photothermal therapy (PTT), thereby inhibiting cancer metastasis and recurrence [3]. However, challenges of cancer immunotherapy remain in terms of effectiveness and safety [4].

The major issues consist of poor immunogenicity, insufficient tumor infiltration, and off-target toxicity [5]. For example, programmed cell death 1 or its ligand 1 (PD-1/PD-L1) antibodies are insufficient to maintain long-lasting effective and safe responses to specific tumors because of the lack of tumor-cytotoxic T cells and poor infiltration. They also suffer from the risks of immunotoxicity and autoimmunity caused by the systemic administration [6, 7]. Effective antibody/vaccine delivery, tumor-microenvironment modulation and site-specific delivery based on nanotechnology have been developed to address such issues [8–11]. The vaccine delivery is to increase tumor immunogenicity, and thereby augment the response rates in PD-1/PD-L1 therapy. The multi-synergistic therapeutic effect from different important pathways can be integrated by nanocarriers [12], which can effectively deliver immunomodulators by either passive or active targeting, then release cargoes spatiotemporally via responding to extra- or intra-stimuli.

Nano metal-organic frameworks (nMOFs), an emerging class of porous nanocarriers, have become attractive tools to potentially improve stability, efficacy and safety of cancer immunotherapeutics. They are highly crystalline inorganic-organic hybrids with adjustable porosity and large specific surface areas, typically bridged between metal ions (or metal clusters) and organic ligands. Their unique components and nanostructures endow them with good capability to accommodate a wide range of therapeutics for cancer therapy, imaging, and sensing applications [13]. Therapeutic agents can be either small-molecule or macromolecular drugs, including anticancer drugs, antivirals [14] and anti-inflammatory drugs [15], antimicrobial agents [16], photosensitizers and fluorescent dyes [17], protein drugs [18], and gene drugs [19].

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For immunotherapy, nMOFs encompass several superior features over conventional nanocarriers: 1) nMOFs with high porosity, large surface area and greater tunability possess high loading efficiency of immune-related biomolecules, such as nucleic acids, antigens, antibodies and so on. GMP/Eu MOF can achieve a high ovalbumin (OVA) loading efficiency of 55% [20], while other nanocarriers e.g. upconversion nanoparticles, silica nanorattle, cationic lipid–PLGA hybrid nanoparticles can only attain 10% [21], 14.76% [22], 24.2% [23], respectively. ZIF-8 and ZIF-90 can quickly complete the load of Goat anti BSA IgG polyclonal antibody (G-IgG), with high loading efficiency, reaching 42% ± 3% and 59% ± 2% respectively [24]. The high antigen/antibody density are highly favorable for inducing immune response [25]. 2) An accurate structure of nMOFs, relative to other conventional structures, represents the most intriguing advantage for their consistency in physicochemical property and effect prediction [26, 27]. 3) As carriers, nMOFs also enable inherent superior functions without extra loading of functional agents, e.g. metal ions contained in nMOFs favor for immune stimulation or imaging functions [14, 28]. nMOFs containing Fe³⁺ or Fe²⁺ can stimulate the production of reactive oxygen species (ROS) through a Fenton reaction, regulate tumor inflammation, and recruit immune cells. Fe³⁺ or Mn²⁺ can further serve as imaging tracking indicators for diagnosis and treatment. Recent study has shown that the nMOF MIL-100 containing Fe³⁺ can induce pyroptosis in cancer cells controlled by the extracellular pH [29]. In parallel, the organic ligands in nMOFs can also play an important role in contributing the therapeutic efficacy or regulating the interaction between the host and guest, thus modulating the drug release. Specifically, PCN-224 directly employed a porphyrin derivative as its organic ligand to attenuate self-quenching and insufficient loading of photosensitizers, which facilitated singlet oxygen (¹O₂) diffusion [30]. Organic ligands imidazole of ZIF-8 can interact with H⁺ in tumor microenvironment to control the drug release [31]. 4) Besides above unique characterizations, nMOFs also have general features as conventional nanocarriers, such as convenient modification to improve the stability, the biodistribution and/or the release kinetics of immunomodulators.

This review mainly focuses on the bioengineered nMOFs in cancer immunotherapy (Scheme 1). The applications of nMOFs in traditional cancer treatments are not covered in this review as they have been discussed to a great detail in the previous review articles [32–35]. In the first part, we overview several design considerations for nMOFs-based immunotherapy, including toxicity, stability, and sensitivity. In the second part, we present advances of nMOFs in immunotherapy, which can be classified into two types: vaccine delivery (adjuvants, vaccines) and tumor-microenvironment modulation (immune checkpoint inhibitors, combination therapies). In the last section, we provide the perspectives of nMOFs in cancer immunotherapy.

Scheme 1 Bioengineered nMOFs in cancer immunotherapy. (a) Surface modification strategies of bioengineered nMOFs for prolonged circulation, specific targeting and selective release. (b) The characteristics of bioengineered nMOFs and applications in cancer immunotherapy. The applications include delivery of cancer vaccines (adjuvants, vaccines) and tumor-microenvironment modulation (immune checkpoint inhibitors, combination therapies). Cancer vaccines are developed to enhance tumor antigen presentation. Checkpoint inhibitors activate the immune system to recognize and attack tumor cells. Combination therapies integrate the immunotherapy with chemotherapy, radiotherapy, PDT, or PTT, to improve immunogenicity and modulate tumor immunosuppressive microenvironment.
2 Design considerations for nMOFs

2.1 Components and synthesis of nMOFs

A variety of metal ions and organic ligands can be selected to yield diverse structures of nMOFs. Typically, Zn\(^{2+}\), Fe\(^{3+}\), Fe\(^{2+}\), Zr\(^{4+}\), Ca\(^{2+}\), Mg\(^{2+}\), Cu\(^{2+}\), Al\(^{3+}\) and Mn\(^{2+}\) are frequently used [36]. Common ligands are carboxylates, phosphonates, sulfonates, imidazolates, amines, pyridyl and phenolates [37]. Alternatively, bio-derived ligands including aspartic acid, adenine, gallate, fumarate, muconate, and cyclodextrin are also candidates for bioMOFs, which reduce risks of side effects compared to non-biological materials [26, 38]. During synthesis, surface and inner pores can be modified with functional groups, molecules, biofilms, either by coordinating with metal ions or by covalently bonding with organic structural units [39].

In similar to other nanocarriers (e.g. micelles, liposomes, dendrimers, inorganic nanoparticles and nano-quantum dots), nMOFs can be formed via self-assembly of starting materials [40–43]. The synthesis of nMOFs can be categorized into five types:

1. conventional hydro/solvothermal synthesis,
2. reverse microemulsion method,
3. sonochemical synthesis,
4. microwave-assisted hydrothermal/solvent-thermal method,
5. room-temperature one-pot synthesis.

The most common method is the one-pot synthesis at room temperature. nMOFs with different morphologies and sizes can be obtained through the above different synthetic routes. The morphologies of diverse nMOFs were observed by transmission electron microscopy (TEM), including spherical, cubic, octahedral shape, faceted structure, hexagonal rod, hexagonal lump, hexagonal disk, square rod, plate, nanorod, nanobel, pseudo spherical, block and so on (see in [33]). Detailed synthetic protocols for miscellaneous topologies, morphology, and composite of nMOFs have been reported in the previous articles [36, 44]. Mostly adopted modulation strategies involve adjustments in composition and process parameters, temperature program, additives, and reverse microemulsions. For example, by diluting the reaction system while keeping the stoichiometry between the reactants constant, more MOF monomers can be produced, thus smaller nMOF harvested [30]. Crystal growth inhibitors, surfactants and modulators also greatly affect the sizes and shapes of nMOFs [37, 44].

Certainly, the restructuring of nMOFs morphologies and sizes is accompanied by the modulation of pore diameter. nMOFs possess high adjustable apertures (usually 0–3 nm, up to 9.8 nm) and large specific surface areas (usually ranging from 1,000 to 10,000 m\(^2\)/g) [45]. The world’s repository of small molecule crystal structures Cambridge Structural Database (CSD) have been accommodating a milestone of 850,000+ MOF entries in 2016 [46]. Figure 1 schematically represents representative nMOFs with their pore size and BET surface area.

Adjustments of linker geometry, length, ratio, and functional-groups are efficient ways to build and tune aperture [47]. The pore apertures for a series of MOF-74 (termed IRMOF-74-I to IRMOF-74-XI) ranged from 14 to 98 Å as the organic ligand structure extends [48]. By functionalizing the organic carboxylate linkers of IRMOF-1 with groups such as –Br, –NH\(_2\), –OC\(_2\)H\(_5\), –OC\(_6\)H\(_{11}\), –C\(_6\)H\(_4\), and –C\(_2\)H\(_4\), the pore size can be varied from 3.8 to 28.8 Å [26].

In terms of materials, commercialized zeolitic imidazolate frameworks (ZIF), materials of institute lavoisier (MIL), university of oslo (UIO) and porous coordination network (PCN) are typically chosen for cancer immunotherapy due to their well-established preparation protocols and hypotoxicity [49]. In addition to those materials, there are a number of novel nMOFs with excellent biocompatibility, as summarized in Table 1.

2.2 Toxicity and biocompatibility

To ensure the biosafety, nMOFs constructed by human endogenous metal ions and organic ligands are intriguing. Those ions, frequently employed, include Zn\(^{2+}\), Fe\(^{3+}\), Fe\(^{2+}\), Mg\(^{2+}\), Ca\(^{2+}\), Mn\(^{2+}\), Zr\(^{4+}\), and K\(^{+}\), their rat oral lethal dose 50 (LD\(_{50}\)) (g/kg) are 0.35, 30, 0.45, 8.1, 1, 1.5, 4.1 and 3, respectively [36, 64]. While organic ligands consist of carboxylates, phosphonates, sulfonates, imidazolates, amines, pyridyl and phenolates, amino acids, peptides, proteins, sugars, nuclear bases, porphyrins, adenine, and even commercial drugs [64, 65]. Indeed, there is not much rat oral LD\(_{50}\) data available for most of nMOFs ligands. Current data include low toxic ligands 1,4-benzenedicarboxylate (1,4-BDC, 5 g/kg), benzene-1,3,5-tricarboxylate (H\(_3\)BTC, 8.4 g/kg), 1,3-benzenedicarboxylate (1,3-BTCs, 10.4 g/kg), 1-methylimidazole (1.13 g/kg) and 2-methylimidazole (1.4 g/kg) [64, 66]. Studies have demonstrated that the toxicity of nMOFs can be controlled to an acceptable level of biological safety [67, 68].

The first study of biological functions in animal level was tested by ZIF-8, where normal doses (32 mg/kg) upon intravenous administration, led to minimal impacts on liver and renal functions, immune cells, and inflammatory factors [67]. In another study, MIL-100 evidenced biodegradable character of iron level and benzenetricarboxylic acid (BTC), even after the administration of very high doses (220 mg/kg) [69]. Although bioMOFs are built up of endogenous molecules or active ingredients, their toxicity researches are still at initial stages of development up to now.

However, most of the works rely on the design of nMOFs on toxicity of the components (metal and ligand). Extrapolating the LD\(_{50}\) value in one determined administration way to other administration routes is finite for which biodistribution will be absolutely different. Although this approach allows us to narrow down to a set of safe nMOFs, the most effective nMOFs are yet to be found. Noticeably, toxicity issues can be intimately associated with the synthesis process, especially to narrow down to a set of safe nMOFs, the most effective nMOFs are yet to be found. Noticeably, toxicity issues can be intimately associated with the synthesis process, especially...
the toxic organic solvents and reaction modulators employed during preparation. Therefore, it is important to establish a comprehensive evaluation based on animal behavior, hematology analysis, biochemistry, and histological test for a wider range of nMOFs [70].

### 2.3 Stability

Considered as a “foreign” component, nanoparticles are recognized as intruders, and can be easily cleared from the blood circulation by the reticuloendothelial system (RES) or mononuclear phagocyte system [71]. Surface modification of nMOFs plays a vital role to determine the blood circulation, half-life, biological distribution and targeting ability of nMOFs.

Relative to macromolecules, surface modification with small molecules is not favorable since they can penetrate into pores of nMOFs and affect the drug loading and release [72]. The surface modification of nMOFs with hydrophilic macromolecules not only maintains the drug release rate, but also minimizes the interaction with proteins [73]. As a result, nMOFs can passively target to tumor tissues via the enhanced permeability and retention (EPR) effect. Polyethylene glycol (PEG) and lipid are popular candidates for the surface modification of the bioengineered nMOFs in addition to exosome-modification [73–75]. Active targeting moieties can also be attached to the surface of nMOFs via post-synthetic modifications so as to reduce the non-specific distribution of drugs [59, 76, 77]. Camouflaging nanoparticles with cell membranes is a promising strategy to improve immunocompatibility [78]. The biofilms rich in outer-membrane antigens proteins can be wrapped on the surfaces of nMOFs to mediate immune escape and to reduce the non-specific distribution of drugs [59, 76, 77]. The biofilms rich in outer-membrane antigens proteins can be wrapped on the surfaces of nMOFs to mediate immune escape and to reduce the non-specific distribution of drugs [59, 76, 77].

### 2.4 Intelligent selective release

The design of intelligent selective release enables nMOFs to protect therapeutic drugs from leakage prior to reaching targets, while release immunomodulators spatiotemporally in response to inherent tumor characteristics or external stimuli.

Endogenous stimulus signals include low pH (6.5–6.8), reduced glutathione (GSH), reactive oxygen species (ROS), matrix metalloproteinases (MMP-2/9), and adenosine triphosphate (ATP) in tumor microenvironment [81–83]. Moreover, there are also many external stimulus signals such as light, heat, magnetic field, and ultrasound [84]. The sensitive designs of the nMOFs-based vaccines depend mainly on the acidic environment of lysosomes/endosomes in antigen-presenting cells (APCs). In such environment, nMOFs can be triggered to release the model antigens. This suggested that the bioengineered nMOFs could help to resist the clearance of RES. The pharmacokinetic experiments proved that the blood circulation half-life of TPZ-GOx-ZIF-8@erythrocyte membrane (t1/2 = 4.7) was approximately twice longer than that of TPZ (t1/2 = 2.4) [79]. The TPZ-loaded PCN-224 encapsulated by a 4T1 murine cancer cell membrane mainly concentrated on the tumor tissue and strengthened continually until peaking at 54 h, exhibited an excellent homologous targeting and immune evasion [80]. As summarized in Table 2, various surface modifications of nMOFs can be classified into three categories: covalent modification, non-covalent modification, and biomimetic modification.

| Table 1 | nMOFs used in cancer immunotherapy |
| Classification | Metal ion | Organic ligand | Features | Reference |
|---------------|-----------|----------------|---------|----------|
| Conventional | ZIF-8 | Zn²⁺ | 2-Methylimidazole | Degradation in response to acid Zeolite-like structure | [50] |
| MIL-100 | Fe²⁺ | 1,3,5-Benzentricarboxylic acid (H,BTC) | MRI performance in vivo | [51] |
| MIL-101 | Fe²⁺ | Terephthalic acid (1,4-BDC) | Good biocompatibility and biodegradability | [52] |
| MIL-101-NH₂ | Fe²⁺ | 2-Amino terephthalic acid | Tailorability of amino groups | [53] |
| MIL-88A | Fe²⁺ | Fumaric acid ester | Good biocompatibility and biodegradability | [54] |
| UIO-66-NH₂ | Zr₆ cluster | Amino terephthalic acid | High thermal, mechanical and chemical stability | [55] |
| HF-DBA | Hf⁴⁺ | 5,10,15,20-Tetra(p-benzoato) porphyrin (H₄TPP) | Strong X-ray absorption | [56] |
| HF-TBC | Hf⁴⁺ | 5,10,15,20-Tetra(p-benzoato) chlorin (H₄TBC) | Photosresponsive degradation | [57] |
| Zn-TCP | Zn²⁺ | Tetrakis(4-carboxyphenyl) porphyrin (TCPF) | Photosresponsive degradation | [58] |
| PCN-224 | Zr₆ cluster | Tetrakis(4-carboxyphenyl) porphyrin (TCPF) | Photosresponsive degradation | [59] |
| AI-MOF | Aluminum isopropoxide | 2-Amino terephthalic acid | As an adjuvant to enhance the immune response | [60] |
| Others | Fe²⁺-GA MOF complexes | Fe²⁺ | Gallic acid (GA) | Magnetic resonance imaging with pH activation Photothermal effects | [61] |
| Fe²⁺-GA MOF complexes | Fe²⁺ | Gallic acid (GA) | Magnify tumor oxidative stress | [62] |
| GMP/Eu³⁺ MOF complexes | Eu³⁺ | Guanine monophosphate (GMP) | Degradation in response to acid | [20] |
| Hollow Mesoporous Prussian Blue (HMPB) | Fe³⁺ | [Fe(CN)₆]³⁻ | Hollow mesoporous structure, the shell also has a large cavity Photothermal effects | [63] |
Table 2  The surface modification strategies for nMOFs

| Modification strategies | Driving force of formation | Surface Modification | Functions | Reference |
|-------------------------|-----------------------------|---------------------|-----------|-----------|
| Covalent modification   | Click chemistry             | Polyethylene glycol (PEG) | Improved colloidal stability | [85] |
| Covalent modification   | Click chemistry             | CpG oligonucleotides (CpG ODNs) | Immunostimulatory | [20] |
| Covalent modification   | Coordination                | Cycloextrin (CD) | Improved colloidal stability | [72] |
| Covalent modification   | Coordination                | Hyaluronic acid (HA) | Improved colloidal stability CD44 Targeting Cancer Cells | [59] |
| Covalent modification   | Coordination                | Calcium phosphate (CaP) | Releasing phosphate ions in response to the tumor’s weak acid environment | [55] |
| Condensation            | Phenylboronic acid (PBA)    | Response of ROS | | [86] |
| Condensation            | Silica                      | Retard the decomposition of nMOF | | [87] |
| Non-covalent modification | Hydrophilic–hydrophobic interaction | Lipid double shell | Improved colloidal stability | [74] |
| Non-covalent modification | Electrostatic interaction    | Chitosan (CS) | Improved colloidal stability | [88] |
| Non-covalent modification | Electrostatic interaction    | CpG oligonucleotides (CpG ODNs) | Immunostimulatory | [50] |
| Non-covalent modification | Electrostatic interaction    | Yeast capsules (YCs) | Protected the MOF complex from degradation by high acidity and gastrointestinal proteins | [60] |
| Non-covalent modification | Electrostatic interaction    | Polyaniline (PAN) | Improved colloidal stability Enhanced near infrared absorption | [89] |
| Non-covalent modification | π–π interaction            | Polydopamine (PDA) | Improved colloidal stability Enhanced near infrared absorption | [90] |
| Biomimetic modification | Hydrogen bonds and π–π interaction | Folic acid (Fol) ligand | Targeted folate receptors on tumor surfaces | [77] |
| Biomimetic modification | Van der Waals force         | Polyvinyl pyrrolidone (PVP) | Improved colloidal stability | [51] |
| Biomimetic modification | Van der Waals force         | Heparin | Improved colloidal stability | [91] |
| Biomimetic modification | Unmentioned                 | Erythrocyte membrane | Improved colloidal stability | [79] |
| Biomimetic modification | Unmentioned                 | Exosome | Improved colloidal stability | [75] |
| Biomimetic modification | Unmentioned                 | Cancer cell membrane | Targeted homologous tumor | [80] |
| Biomimetic modification | Unmentioned                 | Extracellular vesicles (EV) | Improved colloidal stability | [92] |
| Biomimetic modification | Unmentioned                 | Hybrid biofilms | Targeted homologous tumor Processed tumor antigens Induced immune costimulatory molecules | [93] |

Table 3  Intelligent sensitive response designs for nMOFs

| Types                          | Internal or external stimuli | Sensitive principles | Materials | Synthetic method | Payloads | Surface modification | Size (nm) | Cell/animal models | Functions | Reference |
|--------------------------------|-----------------------------|----------------------|-----------|------------------|----------|---------------------|-----------|---------------------|-----------|-----------|
| pH sensitivity                 | APCs lysosomes/ endosomes   | Imidazolate acid cleavage | ZIF-8     | Ultrasonic water bath one pot synthesis | OVA      | CpG ODNs            | 200       | RAW264.7/ Kunning mice | Subunit vaccine | [50] |
| pH sensitivity                 | APCs lysosomes/ endosomes   | Eu³⁺ and GMP coordination dissociation | GMP/Eu³⁺ complexes | Room temperature one pot synthesis | OVA      | CpG ODNs            | 30        | RAW264.7 B16-F10/ C57BL/6j mice | Subunit vaccine | [20] |
| pH sensitivity                 | APCs lysosomes/ endosomes   | Imidazolate acid cleavage | Aluminum ZIF-8 | Room temperature one pot synthesis | OVA      | CpG ODNs            | 80        | DC2.4 RAW264.7 EG7-OVA/ C57BL/6j mice | Subunit vaccine | [94] |
| Reduction sensitivity          | GSH in tumor cells          | Disulfide bond (S–S) fractures linked to amino groups | MIL-101-NH₂ | High pressure reactor hydrothermal synthesis method | CpG ODNs | OVA | 300 | DC2.4 RAW264.7 EG7-OVA/ C57BL/6j mice | Subunit vaccine | [53] |
| ROS sensitivity                | Mitochondrial H₂O₂ in tumor cells | Phenyl borate cleavage | Uio-66    | Solvothermal reaction | B(OH)₂ | ~ 50 | MDA-MB-231 | H₂O₂ probe Live cell imaging | H₂O₂ probe | [86] |
| Ion sensitivity                | Phosphate ions in lysosomes | High affinity of Fe³⁺ to phosphate ions | MIL-101 | Solvothermal reaction | CpG ODNs | 360 | RAW264.7 H22 cells/ BALB/c mice Kunning mice | Adjuvant delivery Immuno-stimulation MRI imaging diagnostic | [52] |
| Enzyme sensitivity             | HAdase in tumor cells       | Surface-bonded HA is degraded by HAdase | PCN-224   | Solvothermal reaction | DOX      | HA | 100 | Hek 293T MDA-MB-231 SCC-7 | Tumor targeting PDT combination | [59] |
3 Bioengineered nMOFs for cancer immunotherapy

3.1 Adjuvants

Immune agonists, known as adjuvants, include toll-like receptors (TLRs), interferon genes (STING), and cytokines [99]. Adjuvants can not only motivate the immunogenicity, but also guide the magnitude and types of adaptive immune responses [100]. Unmethylated cytosine-phosphate-guanine oligodeoxynucleotides (CpG ODNs) are single strands of a synthetic DNA that needs to be recognized by toll-like receptor 9 (TLR9) expressed in the endolysosomes of APCs. The activation of TLR9 initiates MyD88 signaling pathways such as MAPK and NFκB, and further induces the Th-1 immune response. CpG ODNs have been extensively used as adjuvants in allergic diseases, viral infections and cancer immunotherapy [101].

However, CpG ODNs are ineffective to penetrate through cell membranes and fragile to nuclease degradation [102]. The nucleic acid-nMOF conjugates address the issues via coordinating unsaturated metal sites on nMOFs’ surface with terminal phosphate-modified oligonucleotides [19]. Therefore, nMOFs can be utilized for the intracellular delivery and release of therapeutic nucleic acids. For instance, MIL-101 (Fe) could load CpG ODNs via the π–π interactions and promote the intracellular delivery to stimulate the immune response [52]. Inside APCs endolysosomes, phosphates will progressively replace terephthalic acid organic linkers due to the relatively high affinity of Fe³⁺ ions to phosphate ions, causing the gradual release of CpG ODNs to elicit Th-1 immune response. T2-magnetic resonance imaging (MRI) ability of MIL-101 (Fe) afforded the tracking of the labeled immune cells in vivo.

As for ZIF-8, negatively charged CpG ODNs mainly bound to ZIF-8 via electrostatic interactions [103]. The bioengineered ZIF-8 exhibited satisfactory stability in physiological environment, and could release CpG ODNs under acidic conditions of endolysosomes where TLR9 located, favorable to initiate the MyD88-dependent signal pathway.

A concept of exoskeleton was developed recently by the biomineralization of calcium phosphate (CaP) onto the surface of UiO-66-NH₂-CpG [55]. As shown in Fig. 2(a), the CaP exoskeleton played dual roles of "protection-release"; not only defending CpG ODNs against degradation in extracellular environment, but also generating high concentration of free phosphate ions in response to acidic tumor microenvironment. Once the concentration of free H₂PO₄⁻ ion reached 4 mM, CaP responds to acid environment to produce phosphate ions Competitive binding of phosphate to Zr sites (Figs. 2(d) and 2(e)).

3.2 Vaccines

Cancer vaccines, generally constituted by antigens and immune adjuvants, are devoted to improving tumor antigen presentation, and thereby educating adaptive immune response and reversing tumor immunosuppressive microenvironment. In addition to the resistance to proteases degradation [104], the delivery purposes of vaccine include the localization antigen and immune adjuvants in one identical dendritic cells (DCs) and desirable antigen cross-presentation to effectively prime CD8⁺ T cell [105].

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In 2016, Qu’s group firstly bioengineered an effective ZIF-8 subunit vaccine through a facile synthesis method. The pores of ZIF-8 were embedded protein antigen OVA, with CpG ODNs attached on ZIF-8 by electrostatic interaction (Fig. 3(a)), which enabled co-delivery and release of antigens and adjuvants in identical APCs [50]. The pH-responsive ZIF-8 facilitated the cross-presentation. The vaccine elevated TNF-α and IFN-γ secretion (Figs. 3(b) and 3(c)), mediated the productions of significantly anti-OVA IgGs (Fig. 3(d)), CD8+ CTLs and CD4+ CTLs proliferation (Fig. 3(e)), as well as more splenocytes proliferation in mice after the second exposure to the same pathogen (Fig. 3(f)).

The base-pairing loading mechanism was realized by self-assembly of lanthanide ions (Eu3+) with guanine monophosphate (GMP). In this fashion, GMP, a DNA nucleotide, was employed to enhance the interaction of CpG and MOF. Through base-pairing interaction, GMP/Eu MOF was able to firmly bind to CpG onto the surface via Watson-Crick bases in addition to the electrostatic loading mechanism. This method led to a high antigen-loading efficiency (55%, w/w) of OVA, as the
model antigen. Importantly, the coordination of CpG and MOF dissociated at pH 5.0, favorable for lysosome escape of vaccine [20]. Such bioengineered GMP/Eu MOF resulted in a superior anti-melanoma effect. The high flexibility in designing the chemical structure of ligands allows for many opportunities in the development of MOF adapted for the cargoes.

Aluminum salts have been approved as adjuvants for human vaccines due to the excellent biocompatibility and the immune response ability to many antigens [106]. On this basis, a ZIF-8 vaccine was bioengineered from OVA, CpG and aluminum adjuvants to enhance humoral and cellular immune responses [94]. The bioengineered ZIF-8 was demonstrated to enhance antigen cross-presentation since AlO(OH) can boost lysosomal swelling and the immunogenicity of ZIF-8.

In addition to the injection model, nMOFs can be bioengineered as oral administration vaccines. Interestingly, an aluminum-metal organic framework (Al-MOF) containing OVA and yeast-derived capsule (YCs) can be resistant to ambient temperature, pH and protease [60]. The bioengineered nMOF specifically eventually accumulated within mesenteric lymph nodes and produced long-lasting and strong potent mucosal immunity (secretory immunoglobulin A, S-IgA) and systemic immune response (serum IgG).

Apart from engineering the model antigen/adjuvant vaccines to increase the quantity and/or quality of T cell-mediated immunity, cytomembrane vaccines based nMOFs emerge as novel cancer immunotherapies. Zhang’s team integrated hybrid cell membranes (FMs) fused from dendritic cells (DCs) and murine breast tumor (4T1) cells into PCN-224. Antigen peptide-major histocompatibility complex (pMHC) and DC-derived costimulatory molecules can be collectively expressed on the FMs. Self-carrying multiple antigens and homologous targeted characteristics with the bioengineered PCN-224 can yield successful immunotherapy [95]. Further study founded that the PCN-224@FMs were able to home to lymph nodes and activate T cell immunity like APCs after subcutaneous injection (Figs. 4(a) and 4(b)). The percentages of CD80+ and CD86+ DCs, and the expression level of TNF-α and IL-6 in the FMs treatment group were appreciably higher than those in control groups (Figs. 4(c)–4(e)). Importantly, the hybrid membrane-enveloped PCN-224 was remarkably impressive in reducing mice mortality assigned to immune memory in situ and distal tumor treatment [93].

### 3.3 Immune checkpoint inhibitors

Programmed cell death 1 or its ligand 1 (PD-1/PD-L1) and cytotoxic T lymphocyte antigen 4 (CTLA-4) blocking are the dominant immune checkpoint inhibition (ICI) strategies. PD-1/PD-L1 inhibitors restore the ability of T cells to attack tumor cells by blocking PD-1/PD-L1 pathways. CTLA-4 inhibitors rejuvenate T cells recognition and demobilism by prohibiting interactions between CTLA-4 and its ligands B7-1 (CD80) and B7-2 (CD86) [107]. Furthermore, indoleamine 2, 3-dioxygenase (IDO) such as 1-methyl-d-tryptophan, INCB24360 and NLG919 are considered as small molecular immune checkpoints that regulate tumor metabolism to oxidize tryptophan to kynurenine and reprogram the immunosuppressive tumor microenvironment [108].

Due to the robust loading, delivery and release capacity of nMOFs, it is promising to deliver immune checkpoint inhibitors to realize effective and safe treatment. In the literature survey of this review, we found there have been reports to deliver small molecule immune checkpoint inhibitors by nMOFs. However, to the best of our knowledge, there has not been any report dealing with encapsulation of PD-1/PD-L1 or CTLA-4 macromolecular inhibitors in nMOFs for immunotherapy. Instead, multifarious combination therapies are employed together with bioengineered nMOFs to increase immunogenicity and response rates. The possible reason underlying this phenomenon may be due to the deactivation potential of the antibodies like PD-1, PD-L1 in the chemical environment of nMOFs, especially in the context of ion components. It has been established that ion components can coordinate with the protein structure and compromise the activity. The concern should be carefully addressed when we choose the encapsulation strategy. The need to achieve extracellular release of those checkpoints antibodies represents another issue that should be paid attention for their molecular target generally localizing outside the cells. The delivery of small molecule immune checkpoint inhibitors by nMOFs will be detailed in section 3.5.

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**Figure 4**  
(a) Schematic illustration of PCN-224@FM for tumor prevention. (b) Western blotting analysis of membrane-specific and intracellular protein markers in the fused cells lysate and FM. (c) The percentage of DC maturation. (d) and (e) Secretion of TNF-α and IL-6 in DC suspensions measured by ELISA kit. Reproduced with permission from Ref. [93], © Springer Nature Limited 2019.
3.4 Other antibodies

Herein, other monoclonal antibodies refer to therapeutic monoclonal antibodies targeting tumor-associated markers, such as vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), CD20, CD52 and TNF-α [109]. However, these antibodies remain issues including unstable storage, poor penetrability in tissues and tumors, possible aggregation, and decreased activity [110], even cardiotoxicity, cytokine release syndrome, infection, and autoimmune diseases [111].

To stabilize the antibodies, a facile antibody@MOFs formulation strategy has been proposed (Fig. 5). Two imidazole zeolite frameworks (ZIF-90 and ZIF-8) are self-assembled with three antibodies namely human IgG polyclonal antibody (H-IgG), goat anti-BSA IgG polyclonal antibody (G-IgG) and a commercial monoclonal antibody Adalimumab (Ada). Both the encapsulation and release (in vitro) of the antibodies in nMOFs were rapid (about 10 min and 10 s, respectively) with a high loading efficiency (53% ± 3% for H-IgG@ZIF-90, 37% ± 1% for H-IgG@ZIF-8, 59% ± 2% for G-IgG@ZIF-90, 42% ± 3% for G-IgG@ZIF-8). The antibodies that were loaded in nMOFs showed almost no aggregation and activity loss under harsh conditions, such as high temperature (75 °C), organic solvent (methanol, acetone), mechanical pressure (20 MPa pressure) and the freeze-thaw cycle for three weeks (50 ↔ 4 °C, 25 °C/min ramp rate). In addition, there was no nMOFs residue in the recovered antibodies, and the structure and activity of the recovered antibodies were found to be the same as the original ones [24].

Figure 5  Schematic illustration of in vitro protective coating strategy for antibodies preparation and applications. Reproduced with permission from Ref. [24], © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 2018.

Further studies are expected to extend the bioengineered nMOFs to tumor immunosuppressive microenvironment reprogram in the future.

3.5 Combination therapies

During ICI therapies, the host immune systems are usually confronted with poor immunogenicity and insufficient cytotoxic T lymphocyte (CTL) infiltration [112, 113]. These factors are the major reasons leading to the failure of ICI therapies. As the solution, chemotherapy, radiotherapy, PDT, and PTT, being able to stimulate immunogenic cell death (ICD), have been employed for the combination therapies [114, 115]. Without ICI, these therapies would reversely misguide tumor immune resistance causing weak antitumor immune signals. As a result, combination immunotherapy will balance the relationship between immune activation and immunosuppression [2]. In addition, nMOFs with theranostic function are promising tools to coordinate the combination immunotherapy [51, 116, 117].

In this section, we overview the most recent advances of nMOFs-based combination immunotherapy in modulating the tumor immunosuppressive microenvironment and enhancing immune systemic response.

3.5.1 Immunotherapy combined with chemotherapy

Although cytotoxic drugs are generally deemed to be immunosuppressive, some chemotherapy regimens can potentiate the effect of cancer immunotherapy. An amount of chemotherapeutics such as doxorubicin (DOX), oxaliplatin, gemcitabine, 5-fluorouracil, cyclophosphamide, fludarabine have been shown to trigger inflammation and tumor antigens release while potentiating immunostimulatory signals simultaneously [118–120]. Accordingly, the combination of immunotherapy and chemotherapy through nMOFs are capable of resolving insufficient immune response and elevating the antitumor effect [121].

As an example, a bioengineered ZIF-8 (denoted as mZCD) was cooperated with the aPD-1 antibody to create a dual inhibition of the PD-1/PD-L1 axis and mediate significant immune responses (Fig. 6(a)). Due to the ZIF-8 with porous structure and pH-sensitivity, the catalase (CAT) and doxorubicin

Figure 6  (a) Schematic illustration of mZCD as an oxygen generating biomimetic nanoplatform for tumor chemotherapy and immunotherapy. (b) Flow cytometry analysis of the PD-L1 expression in tumor tissues after treatment with mZCD, mZD, and PBS. (c) Average tumor weight for different groups. (d) Flow cytometry analysis of their corresponding percentage of CD3^+CD8^+ tumor infiltrating T cell after various treatment. Reproduced with permission from Ref. [96], © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 2018.
(DOX) can be easily embedded, protected and released. A murine melanoma membranes coating provided tumor homologous targeting and induced an immune response due to abundant antigens [96]. The oxygen generation down-regulated the expression of hypoxia-inducible factors-1α (HIF-1α) related to tumor escape, which further reduced the expression of PD-L1 (Fig. 6(b)). CD8+ T cells were substantially recruited (Fig. 6(d)) and the tumors were almost suppressed post intravenously injection with mZCD+αPD-1 (Fig. 6(c)), indicating the synergistic therapeutic effects of chemotherapy and immunotherapy.

Metabolic changes in tumor microenvironment can suppress immune cell infiltration. The increase of lipid metabolism in tumor cells interfered with T cell receptor aggregation and T cell immune synapse formation [122]. Based on this advance, Yin et al. harnessed ZIF-8 to load the anticancer drug DOX and the metabolic drug avasimibe, with a goal to realize the combination therapy of metabolic immunotherapy and chemotherapy. Avasimibe is an inhibitor of acyl coenzyme A-cholesterol acyltransferase (ACAT), while ACAT is the main enzyme for cholesterol esterification in CD8+ T cells [123]. Compared with ZIF-8 without avasimibe, such combination therapy produced more cytokines of CD8+ CTL including TNF-α and IFN-γ, suggesting that avasimibe regulated the metabolism of T cells for improved antitumor capability.

3.5.2 Immunotherapy combined with radiotherapy

Radiotherapy (RT) is a local treatment to kill tumor cells directly in clinic, which can act as an immunoregulatory adjuvant therapy [124–126]. nMOFs are fit for radiotherapy (RT) or radiodynamic therapy (RDT) domino effects in structure, where the secondary generated photons are more likely to interact with metal clusters and initiate a chain reaction. In addition, the porous structure facilitates the rapid diffusion of ROS, produced from the ionizing radiation of photosensitizer ligands. For instance, the radiosensitive nMOFs, characterized with high-Z elements and large specific surface areas, were significantly more effective than HfO2 (hafnium dioxide), Au (gold) and other heavy metal radiosensitizers. When combined with PD-L1 inhibitor, the nMOFs led to consistent abscopal responses that rejected distal tumor [127].

Adverse effects can be minimized by using tumor-targeted radiation enhancers that reduce the dose of X-rays while maintaining sufficient ionization damage [128]. Considering heavy metal hafnium (Hf) possess radiosensitivity, Lin’s research team bioengineered two nMOFs (DBP-Hf and TBP-Hf) using Hf clusters and porphyrin ligands to activate radiotherapy-radiokinetic therapy (RT-RDT) only with low-dose X-ray irradiation (Fig. 7(a)). IDO inhibitors were loaded into the porous of nMOFs to yield a synergistic immune effect [56]. The secondary building units (SBUs) of metal Hf clusters can effectively absorb X-ray photons, leading to radiotherapy, then transfer energy from X-ray photons to photosensitizers to increase O2 (Figs. 7(b) and 7(c)), finally remarkably strengthen the proportion of CD45+ leukocytes, CD4+ T and CD8+ T cells infiltrated in tumor microenvironment (Figs. 7(d)–7(f)).

3.5.3 Immunotherapy combined with photodynamic therapy

PDT relies on nontoxic photosensitizers (PSs), light and oxygen to produce cytotoxic ROS especially O2. Most PSs failed in clinical applications due to their hydrophobicity, self-aggregate tendency and no selectivity for tumor cells. A variety of nanomaterials have been constructed to deliver PSs although most of them exhibit loading instability and leaching risks [129]. The superiority of nMOFs are their crystal structure, stable skeleton and prevention capacity of non-specific phototoxicity.

There are two strategies for constructing photosensitive nMOFs. One strategy is to load PSs directly into the porous structure of nMOFs in order to avoid fluorescence quenching. After irradiation, the porous nature helps ROS to rapidly diffuse into the cellular environment, resulting in effective cytotoxicity. The other strategy is to directly employ PSs as construction units of nMOFs, which provides a high PS loading without PS self-quenching and O2 diffusion facilitation [58].

Photosensitive nMOFs have been widely developed in PDT studies [130–132]. Because of their porous structures, photosensitive nMOFs are particularly suitable for use in conjunction with immune checkpoints. For example, the organic ligands of TBC-Hf are derived from 5,10,15,20, tetra (p-benzofuran) porphyrin (TBP) with highly porous large channel structures (Fig. 8(a)), which ensure the loading of IDO inhibitors (IDOi) INC24360 to achieve combination immunotherapy (Fig. 8(b)) [57].

Figure 7  (a) Schematic illustration of the mechanisms of X-ray-induced RT–RDT by nMOFs. (b) Structure models of Hf12/Zr12 SBUs, and DBP-Hf, DBP-Zr and DBA-Hf nMOFs. (c) Structure models of Hf/Ze SBUs, and TBP-Hf and TBP-Zr nMOFs. (d)–(f) The treated and untreated tumors were collected for flow cytometry analysis and the cells were stained with CD45+PI− (d), CD45+CD3ε+CD8+PI− (e), or CD45+CD3ε+CD8+PI− (f), and gated from the total tumor cells. Reproduced with permission from Ref. [56], © Springer Nature Limited 2018.
O₂-dependent PDT coordinates cancer immunotherapy to improve an immune response, but its effectiveness is severely limited by tumor hypoxia. TBP-nMOF exhibited red-shifted absorption bands (at $\lambda > 650$ nm) due to the π-extended benzoporphyrins, which formulated a stronger infrared luminescence capacity and a high chemical stability (Figs. 8(c)–8(e)) [133]. The ROS generation from TBP-nMOF irradiation sustained even in 5% O₂ atmosphere imitated tumor hypoxic microenvironment. The combination of TBP-nMOF with α-PD-1 inhibitor further induced adaptive immune responses via stimulating secretion of chemokines, cytokines and recruiting CTL.

Another paradigm to solve hypoxia for PDT in the combination immunotherapy is the response of nMOFs to the tumor microenvironment to produce O₂ [28]. When Fe-TBP was irradiated under hypoxia, cascade reactions could be catalyzed. Abundant H₂O₂ in tumor regions was catalyzed to O₂ via Fenton reaction of metal Fe 3O clusters. When the PDT was combined with ICI, both primary and distant tumors exhibited noticeable CTL infiltration in bilateral CT26 tumors-bearing mice. The cured mice successfully resisted the tumor relapse.

3.5.4 Immunotherapy combined with photothermal therapy

PTT utilizes light absorbents accumulated within tumors to generate heat to kill tumor cells. Then, tumor antigens in the surrounding environment promote antigen uptake and presentation by APCs so as to build up host antitumor immunity [134–136]. The synergistic effect of PTT and immunotherapy can efficiently overcome inadequate activation of immune response and evasion.

Small molecular photothermal agents indocyanine green (ICG), dye cyanine (Cy) can be payloaded by nMOFs carriers to solve the problems of poor water stability and rapid internal clearance [137, 138]. Various photothermal polymers such as polyaniline (PAN), polydopamine (PDA), polypyrrole (Ppy) are loaded into nMOFs to achieve a uniform size distribution, a long-term solution stability and an intense photothermal conversion efficiency [89, 90, 139]. Among nMOFs, hollow mesoporous prussian blue nanoparticle is an excellent autogenous photothermal conversion agent [63]. The nMOF Fe-gallic acid (GA) possesses intense NIR absorption due to the strong delocalization in π-electron structure. It has been shown that OVA-Fe-GA enables to induce the maturation of dendritic cells (DC2.4) and macrophage cells (RAW264.7), suggesting promise as an in-situ vaccine combined with PTT [140].

To improve the immune response rate, Luan et al. bioengineered two ZIF-8 carriers for dual tailor-made functions, that is, specifically delivering photothermal agents and immune adjuvants to their respective target cells. One is to deliver photothermal agent IR820 to tumor cells, and the other is to deliver the TLR7 agonist imiquimod R837 with
the IDO inhibitor 1-methyl-d-tryptophan to DCs in tumor microenvironment. Thus, the two bioengineered ZIF-8 can realize fighting against invasive malignancy and rechallenged tumors via the spatiotemporally coordinated antitumor PTT and immunotherapy [141].

3.5.5 Multiple combination therapies based on immunotherapy

The size of pores in nMOFs can be modulated, and can accommodate several molecules simultaneously with multiple functions, enabling an “all in one” multi-drug combination with cancer immunotherapy. A copper porphyrin nano-metal organic framework Cu-TBP was combined with hormone-triggered chemodynamic therapy (CDT), phototriggered PDT and ICI therapy to block the tumor estrogen metabolic pathways and induce systemic antitumor immunity in the tumor phenotype with hormone imbalance [97]. Cu²⁺ can be released to undergo Fenton-like reactions and deplete estradiol (E2) that overexpressed within tumor cells, collaborated with the photo-responsive organic ligand H₄TBP producing excessive ROS (Fig. 9(a)).

nMOFs can integrate multiple probes and reagents through a green one-pot co-loading strategy [98]. For example, CuS nanoparticles, protoporphyrin IX, and DOX were added into the ZIF-8 for PTT, PDT, and chemotherapy, respectively. The Cpg was electrostatically adsorbed on the positive charged ZIF-8 surface for immunotherapy to inhibit tumor recurrence and metastasis. The outer layer connected with the polydopamine (PDA) layer was to amplify the PTT effect. Another layer of MnO₂ nanosheets was grown to “turn on” MRI in response to GSH (Fig. 9(b)). Ultimately, ZIF-8 gradually released the drugs under near-infrared triggering, slightly acidic and GSH conditions (Fig. 9(c)).

Based on the cases mentioned above, the combination immunotherapy based on bioengineered nMOFs can modulate immunosuppressive microenvironment and significantly address the side effects and insufficient systemic immune responses limitations of ICI therapies.

Nonetheless, the combination of multiple drugs may induce excessive immune activation from dialectical views. It is also essential to realize complicated interaction such as the antagonistic possibility between different agents and the potential severe side effects. These should be carefully considered in the bioengineering of nMOFs for combination immunotherapy.

4 Conclusions and future prospects

Compared with traditional counterparts, nMOFs with high structure accuracy and versatility, tunable porosity and biodegradability, are greatly expanding the nano-biomedicine avenue. With the booming of immunotherapy, the past few years has witnessed tremendous efforts in exploiting nMOFs for immunotherapy. In this subfield, those research works can be generally divided into two categories: vaccine delivery and tumor-microenvironment modulation. Immune checkpoint inhibitors, adjuvants, antigens, antibodies, chemicals, radiators, photothermals and photosensitizers can be efficiently loaded into nMOFs to mediate effective immune response while ensuring safety. To achieve an ideal loading and biodistribution, nMOFs based nanomedicine have made significant progress in the following aspects and in the future will continue to evolve: (1) optimization of the composition and structure for carrier materials; (2) Improvement of biological distribution (e.g. long circulation, tumor targeting and lymphocyte homing), controllability (e.g. intelligent sensitive designs), efficiency (e.g. combination immunotherapy, biomimetic function and theranostic platform).

Despite of the rapid progress, nMOFs for immunotherapy has been yet at its infant stage. The current strategy focuses more on the employment of nMOFs as the delivery and controlled release of immunotherapeutic molecules. To exploit the full potential of nMOFs in immunotherapy, much attention should be devoted to the critical challenges encountered during the whole process of an effective immune response. For vaccine delivery, antigen cross-presentation, lymph trafficking as well as the targeting to specific APC cells that are potent to stimulate T cells, represent the major obstacles to mediate the adaptive immune response. The incorporation of neoadtigen will definitely make the work more clinically relevant and indicative. For nMOFs intended to tumor microenvironment regulation, it is ideal to relieve the immunosuppressive microenvironment while mediating the tumor immunogenicity to initiate the antigen presentation.

In addition to the necessity of in-depth immune consideration, there are also some basic challenges that should be taken into account in the future nMOFs design for immunotherapy. Those challenges with particular concern include: i) the potential loss of structure intactness, ii) the possible compromised bioactivity

Figure 9  (a) Hormone-induced Cu-mediated ROS generation process. (b) In vitro GSH-responsive T1-weighted MRI of CuZP Mn (inset: T1-weighted images of CuZPMn at different Mn concentrations with and without GSH) (c) TEM images of CuZPMn@DOX at pH 5.0 from 30 min to 8 h and different NIR irradiation time periods from 20 to 80 min at pH 5.0. Reproduced with permission from Refs. [97], © Elsevier Inc. 2019; Ref. [98], © The Royal Society of Chemistry 2018.
due to coordination of metal ion with the immunologic therapeutics [142], iii) rational design of those immunologic therapeutics as the ligands, and iv) the inherent immune response of metal ion and ligands [143, 144]. The inter-coordination of metal ion with much of immunologic therapeutics, like antigenic peptide, PD-1 antibody and nucleotide agonists, may destroy the fundamental of nMOFs formation mechanism and thereby influence the nMOFs structure intactness. Rational design of those immunologic therapeutics, as the ligands to coordinate directly with metal ions to form MOFs structure, promises to be a solution to the above concern. Additionally, it also needs careful assessment of maintenance of the biological activities of the immunologic therapeutics for that their concomitant release with the metal ions may affect the spatial structure. The screening of metal ions and organic ligands to refine nMOFs with inherent positive immunological functions will represent an interesting branch in pursuit of immunotherapy applications.

The accurate structure and high loading of nMOFs will greatly favor for consistency evaluation and quality management in the clinical translation, arching particular advantages over other nanomaterials. To maximize the benefit of these unique properties, particular attention should be paid to the biosafety due to potential toxicities of many metal ions and ligands, particularly in the context of the major accumulation of MOFs in normal organs like liver and spleen. Minding the challenges and opportunities, the success of nMOFs in immunotherapy will undeniably rely on the multidisciplinary efforts. The first nMOF clinical trial (NCT 03444714), as a radioenhancer for radiotherapy, encourages the future confidence in pushing forward the MOFs immunotherapy.

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