Metal-organic Frameworks: Preparation, Sensing, Drug Delivery, Imaging and Therapy

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Abstract: Metal-organic frameworks (MOFs) materials have been widely used in biomedical field due to their unique physical-chemical properties. This review summarized the preparation methods for MOFs, including hydrothermal or solvothermal method, microwave synthesis, ultrasonic synthesis, mechanical method and aerosol method. The MOFs synthesized by hydrothermal method exhibit uniform morphology. Moreover, the properties of MOFs can be controlled by changing the concentration of precursors, the types of solvents and catalysts. For the mechanical method, MOFs can be obtained by the mixing and grinding of raw materials in a small amount of solvent without external heating. This method is applied for the large-scale production of MOFs due to the simple operation, high yield and low energy consumption. With the advantages of large specific surface area, high porosity, easy modification, low toxicity and biodegradability, this review also focused in various biomedical applications of MOFs, such as fluorescence sensing, drug delivery, bioimaging and tumor therapy.

1 INTRODUCTION

Metal-organic frameworks (MOFs) are crystalline porous materials with three-dimensional periodic structure constructed by coordination bonds between metal ions or ion clusters and organic molecules (Jiang, Alezi, Eddaoudi 2021). MOFs, firstly proposed by O.M. Yaghi et al. in 1995, are also known as porous coordination polymers (Yaghi, Li 1995). MOFs have experienced a stage three generations with rapid development. In the early preparation, the pore size and stability were limited for the first generation of MOFs. The significantly improved stability of frameworks is achieved for the second generation of MOFs, and the frameworks of MOFs also remained their integrity even after removing the guest molecules. For the third-generation MOFs, the shrinkage and expansion of frameworks further is attained. And the broad pore size of MOFs, from micropore to mesopore are realized. Compared with the traditional nanomaterials, MOFs offer the larger specific surface area, high porosity, framework flexibility and the controlled pore size by adjusting the length of organic ligands (Lin, Zhang, Chen 2021, Kim, Hong 2021, Pallach et al 2021). Moreover, the uncoordinated unsaturated metal sites can be provided for surface modification. This allows MOFs is easily modified and functionalized. Due to their unique characters, MOFs have been considered as a promising absorbent or catalyst in gas storage and separation, catalysis, membrane materials and other fields (Wu, Lin, Ge, Wu, Xu 2013, Yang, Gates 2019, Li, Wang, Sun, Lollar, Li, Zhou 2018). Moreover, MOFs have good biodegradability and biocompatibility, which can be used as drug carrier, contrast agent as well as nano enzyme (Sun et al 2020, Li et al 2020, Robison et al 2019). Therefore, MOFs play a vital role in the biomedical field. This article describes the preparation methods and various applications in different branches of biomedical field for MOFs.

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2 PREPARATION FOR MOFS

To obtain MOFs with various structures and functions for various application, different synthesis methods of MOFs have been proposed. The main methods include hydrothermal or solvothermal method, microwave synthesis, ultrasonic synthesis, mechanical method and aerosol method and so on. The synthesized MOFs have a variety of morphologic features, including crystal and amorphous forms, which makes MOFs play different functions in various fields and have broad prospects.

2.1 Hydrothermal and Solvothermal Methods

The hydrothermal or solvothermal method is one of the most common preparation routes for MOFs. Firstly, the raw materials including metal salts, organic ligand and additives were dissolved in water or organic solvent. Then the mixture was heated at a certain temperature and pressure in reaction kettle and MOFs products can be obtained. Kandiah et al. synthesized the UiO-66-NH2 by dissolving ZrCl4 and NH2-H2BDC in dimethylformamide (DMF). The precursor solution was heated in an oven at 80 °C for 12 hours and kept at 100 °C for 24 hours. The final product was obtained by washing and purifying (Kandiah et al 2010). Besides reaction kettle commonly used in MOFs preparation, Motegi et al. synthesized MOFs of zirconium-based UiO-66 under the nitrogen atmosphere using a standard reflux device (Figure 1). (Motegi et al 2017) The synthesized MOFs showed excellent hydrothermal stability. This simple synthesis method can be scaled up to 1 L and further scaled up to allow industrial production of high-quality, uniform crystalline UiO-66 materials.

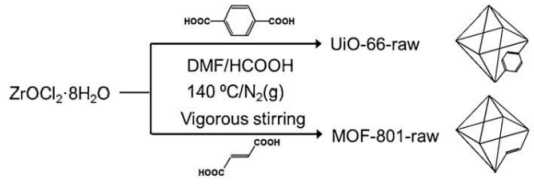

Figure 1: The schematic diagram of MOFs synthesis by conventional reflux solvothermal method.[13]

2.2 Microwave Synthesis

Microwave synthesis of MOFs refers to the reaction process forming coordination bonds between metal ions and organic ligands through the vibration and friction of molecules of precursor solution under microwave irradiation. In 2006, Zheng et al. synthesized cubic Zn-MOF (MOF-5) with lengths ranging from 200 nm to 4 μm by microwave assisted method for the first time (Ni, Masel 2006). On the basis of this work, many MOFs have been successfully prepared by microwave synthesis. For example, Li and colleagues reported the synthesis of Zn-MOF (ZIF-7) using microwave assisted strategy, in which diethylamine was added to further accelerate the synthesis of ZIF-7, resulting in a significant increase in the synthesis efficiency (Li et al 2010). Taddei et al. reported the high-quality microwave-assisted synthesis methods for large-scale preparation of UiO-66, offering a possible way for industrial production and commercialization of MOFs (Figure 2). (Taddei et al 2017)

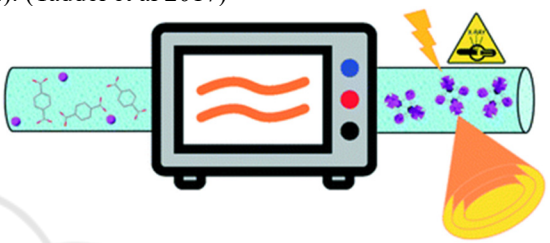

Figure 2: The schematic diagram of MOFs synthesis by a continuous-flow microwave reactor (Taddei et al 2017).

2.3 Ultrasonic Synthesis

In addition to microwave-assisted synthesis, ultrasound-assisted synthesis is also widely used in the preparation of MOFs. Ultrasonic wave can not only facilitate the dissolution of metal salts, organic ligand and additives, but also promote the binding between metal ions and ligands due to the local transient heating and vibration of solution caused by its cavitation. Moreover, this reaction is only carried out in very small individual reaction units, therefore, MOF with small particle size were easily synthesized. Jun Teng et al. designed and developed a novel small-sized (about 95 nm) multilayer porous MOFs (HPMOFs) by combining external ultrasound with the inherent competitive binding between Co and Zn of bimetallic Co/Zn-ZIF materials (Figure 3) (Teng et al 2018). The competitive binding between two metal ions in bimetallic MOFs was interfered with ultrasonic in this strategy, in which the two metal ions not only act as the building units of HPMOF, but also the regulator of structure and size for HPMOF nanocrystals. Thus, the small nanocrystals MOFs with excellent selectivity and stability was achieved.

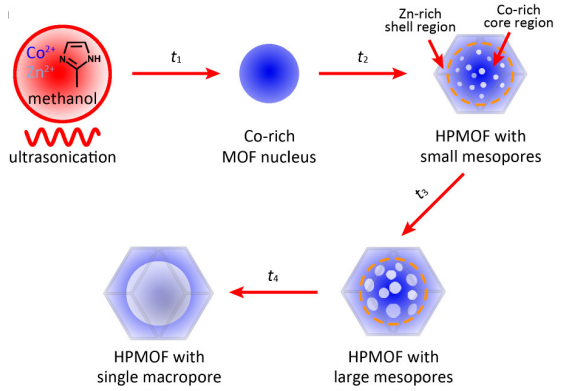

Figure 3: Growth strategy for the synthesis of MOFs (Teng et al 2018).

2.4 Mechanical Method

Mechanical method, first proposed by James et al. in 2006, refers that the solid phase precursor can be extruded and grinded by the use of external mechanical force, resulting in sufficient contact between metal ions and ligands (Figure 4) (Yuan et al 2010). With ball milling method, James et al. quickly synthesized Cu-MOFs using copper acetate and 4-picolinic acid as raw materials, which pioneered the mechanical chemical synthesis of MOFs. Julien et al. reported Zn-MOFs-74 by mechanical grinding (Julien et al 2016). X-ray diffraction analysis (XRD) results of products with different grinding time showed that the longer the grinding time, the better the crystallinity of products and the more significant the characteristic peak.

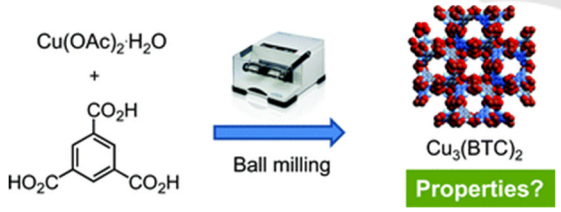

Figure 4. The schematic diagram of Cu-MOFs synthesis by ball milling (Yuan et al 2010).

2.5 Aerosol Method

For the spray pyrolysis or aerosol flow strategy, the precursor solution was transformed from liquid to nano/micro droplets or aerosols using spray tools, and transported to the heating region by the mean of flowing carrier gas. Under high temperature, final nanomaterials can be prepared by the condensation and reaction of reactants due to rapidly volatilization of the solvent in the droplets. In this process, each droplet can act as a single reactor in which do not interfere with each other, leading to a good dispersion of MOFs. In 2013, Arnau et al. synthesized Cu-MOF (HKUST-1, MOF-199) with hollow sphere structure by spray method.20 Additionally, based on this method, Arnau et al. also synthesized NOTT-100, MIL-88A, MOF-14, UiO-66 and other MOFs. In 2018, Ceren et al prepared a spherical porous Zr-MOFs (UiO-66-NH2) by continuous-flow spray-drying (Figure 5) (Avci-Camur et al 2018). By adjusting the concentration of acetic acid as an additive, the specific surface area and water absorption values of the resulting microbeads were comparable to those obtained using other methods. In addition, this work demonstrates the possibility of spray drying for large-scale production of high yield UiO-66-NH2. Spray pyrolysis has become a green method for rapid preparation of MOFs, offering a bright prospect in the synthesis of MOFs and other nanomaterials (Garzón-Tovar et al 2016).

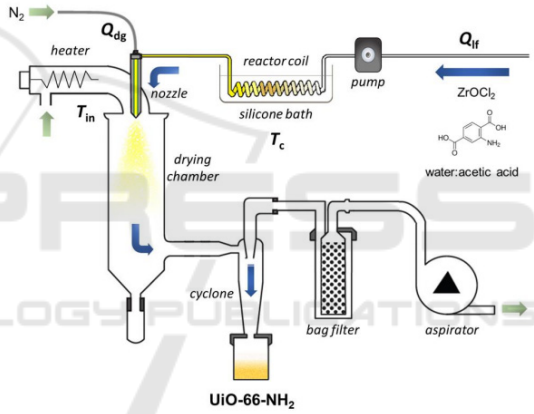

Figure 5. The schematic diagram of the set-up for the aqueous continuous-flow spray-drying synthesis of Zr-MOFs (Avci-Camur et al 2018).

3 APPLICATIONS IN SENSING, DRUG DELIVERY, IMAGING, AND THERAPY FOR MOFS

With the potential of adjustable pore structure, large surface area, large internal pore volume, and multifunctional surface modification, MOFs have been widely used in biomedical applications, such as fluorescence sensor, drug delivery, bioimaging, and tumor therapy (Figure 6) (Lai et al 2021)

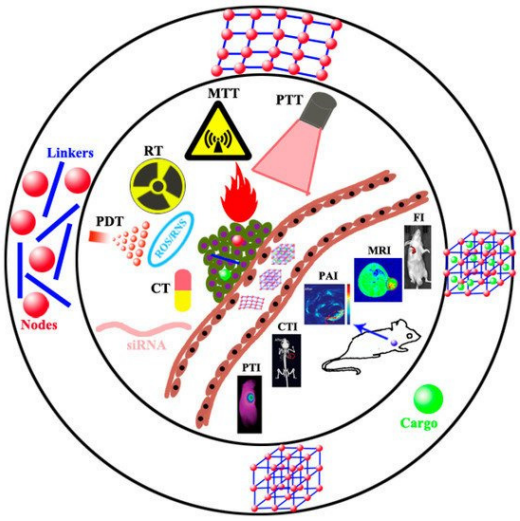

Figure 6: Biomedical applications of MOFs. (Lai et al 2021).

3.1 Fluorescence Sensor

Fluorescent sensing materials, as the core materials of light-emitting diodes and various solid-state sensors, are widely applied in our daily life. It is known that many small organic molecules can emit fluorescence. The introduction of these small molecules or functional groups into the pore structure of MOFs can not only control the fluorescence properties of materials, but also explore the luminescence and electron transport mechanism of materials. Therefore, the design and synthesis of MOFs with fluorescence properties have attracted more attention in recent years. Researches have shown that amino functionalized UiO-66 can selectively probe phosphate ions in aqueous solution, with obvious fluorescence response in the range of 5-150 μM, and a good linear relationship between fluorescence intensity and phosphate ion concentration (Zhao et al 2015). The theoretical detection line can reach up to 1.25 μM, which is far below the emission standard of phosphate ions. Similarly, azide (-N3) and nitro (-NO2) functionalized UiO-66 (UiO-66-N3 and UiO-66-NO2) can also be used as fluorescent probes for rapid and selective detection of H2S, even below the concentration of H2S in the human body (Bai et al 2016).

3.2 Drug Delivery

MOFs, as a drug delivery platform, have attracted considerable attention in recent years due to their unique properties. The stable porous structure and large specific surface area favor the load of a large number of drug molecules by physical adsorption or bonding reactions. The toxicity of MOFs can be controlled by changing the type of ions. In addition, the coordination bonds can degrade in a low pH environment. MOFs can be passively targeted at tumor sites by enhanced permeability and retention (EPR) effect. Moreover, the targeting of MOFs can be increased by functional surface modification, such as cell membranes, proteins, organic polymers and so on. For the MOFs-based drug delivery system, the selectivity to lesions and selective aggregation of drugs can be improved, which can reasonably control the distribution of drugs in vivo, and avoid the toxic and side effects caused by unnecessary drug diffusion. In addition, the usage of nano-drug delivery platform can also regulate the biological metabolism of drugs and control drug release by chemical switch, leading to the improved efficiency of drug treatment. It is expected to achieve controlled release of drugs when some small drug molecules are encapsulated in MOFs with low toxicity.

Furthermore, some studies have shown that the combination of different organic functional groups in the structure of MOFs can achieve the regulation of the types of drug loading and sustained release effects. Cunha et al. found that the loading capacity of UiO-66-X (X = H, CH_3, NH_2, NO_2, Cl, Br) modified by different organic functional groups was very different for different drug small molecules (Cunha et al 2013). In 2017, Deng group found that the type and content of functional groups modified on the organic ligand of MIL-101 (Fe) can affect the slow-release effect of the drug by changing the interaction between small molecules and pore channels (Dong et al 2017).

3.3 Bioimaging

MOFs can be used as contrast agents in biological imaging to enhance the imaging signal of magnetic resonance (MRI), fluorescence imaging (FOI) and X-ray computed tomography (CT). The high-resolution images for the structure of the living body structure can be provided by the detection the radiofrequency signals of protons inside organisms using external magnetic fields, gradient fields and radio waves. The contrast ratio of images can be further improved due to the change in the transverse and longitudinal relaxation rates of protons by the usage of MOFs.

MRI contrast agents include two types: one is a positive contrast agent that shortens the longitudinal relaxation time (T1) of the water proton, and the other is a negative contrast agent that reduces the transverse relaxation time (T2) of the water proton (Wu, Jiang, Roy 2016). MRI contrast agents were evaluated by the

longitudinal and transverse relaxation rates of protons (r1 and r2), and the type of contrast agents can be determined by the ratio of r2/r1. The contrast agent is positive or T1 relaxation when r2/r1 is small, which usually contains paramagnetic transition metal ions (such as Gd^{3+} or Mn^{2+}). In the case of large r2/r1, the contrast agent is negative or called T2 relaxation, and often contain superparamagnetic materials. Lin et al. reported a Gd-based MOFs as a T1 imaging contrast agent with a r1 of 35.8 $mM^{-1}s^{-1}$.(Rieter et al 2006) Moreover, such nanoparticle also exhibits T2 imaging capability with a r2 of 55.6 $mM^{-1}s^{-1}$. Horcajada et al. synthesized Fe^{3+}-MOFs (MIL-88A) with a r2 of about 50 $mM^{-1}s^{-1}$, which reveals the promising application for T2 magnetic resonance imaging as contrast agent (Lin, Rieter, Taylor 2009).

FOI has been extensively used in the diagnosis of tumors and diseases because of its non-invasive ability to distinguish diseased tissues. At present, FOI using MOFs can be achieved by recombination with fluorescent particles or by linking and adsorbing fluorescent molecules. Tang et al. designed a MOFs coated upconverting nanoparticles ($NaYF_4$: Yb, Er@Fe-MIL) that exhibit both the fluorescence characteristics of the core and the T2-weighted magnetic resonance imaging characteristics of the MOFs shell (Tang et al 2015). In addition, MOFs also have the inherent fluorescence properties. It is reported that $Mn_3[Co(CN)_6]_2@SiO_2$ exhibits green fluorescence at 488 nm single photon excitation, and blue fluorescence at 720 nm two-photon excitation. This two-photon fluorescence imaging show a greater penetration depth, less photobleaching and light damage and higher resolution than single-photon fluorescence imaging (Huang et al 2013).

CT imaging refers that the fault or cross section image of the detected object can be drawn using the attenuation signal of X-ray in different beam paths. The improved contrast of CT imaging is achieved by using the contrast agent with high X-ray attenuation. Lin et al. prepared two MOFs with high Zr (37 wt%) and Hf (57 wt%), respectively (Dekrafft et al 2012). Zr with an atomic number of 40 and Hf with an atomic number as high as 72 can be used as a component of CT contrast agent. MOFs, modified with PEG with an enhanced biocompatibility, showed negative enhancement of CT signal in liver and spleen after intravenous injection of 15 minutes on *in vivo* CT imaging of mice. Zhang et al. reported a MOFs nanocrystal (UiO-PDF) with iodine-boron dipyrrolimethylene (I_2-BDP) that can be used as CT contrast agent. In addition, the CT imaging capabilities of MOFs by combining with other CT contrast agents such as noble metal material can be realized (Zhang et al 2017).

The performance of contrast agent with the high ordinal number metal can be effectively improved. Meanwhile, MOFs with controllable particle size can be selectively enriched in tumor sites by EPR effect, which can further improve the diagnostic efficiency of tumor.

3.4 Photothermal, Photodynamic, Microwave Hyperthermia, And Synergistic Therapy

3.4.1 Photothermal Therapy

Photothermal therapy mean that the thermal damage and apoptosis of tumor cells due to the local warming of tumor sites occur by the usage of near-infrared (NIR) laser irradiation. The photothermal agents that easily accumulate in tumor sites are usually selected as auxiliary agents in clinical practice, because of simple tumors is insensitive to the absorption of near infrared golden light. Common photothermal agents include metal compounds (MoS2, Co9Se8), noble metal nanomaterials (gold nanoparticles), carbon nanomaterials (graphene), organic fluorescent dyes (IR825, ICG) and MOFs. Particularly, MOFs have attracted wide attention due to their functionalization and biodegradation. Cai et al. developed a MIL-100 (Fe) nMOF using hyaluronic acid (HA) as a surface modification for targeted therapy of tumors.35 The MOFs loaded with the indocyanine green (ICG) also was used for image-guided photothermal tumor therapy, which exhibited high ICG loading (40%), strong NIR absorption and photostability. In vitro and in vivo studies clearly revealed that MOFs@HA@ICG with a good photothermal therapeutic effect showed high cellular uptake in MCF-7 cells and increased accumulation in xenograft tumors.36 In addition, Wang et al. reported a polymer-MOF hybrid that is Zr MOF (UiO-66) particle modified by polyaniline (PAN) (UiO-66@PAN) as a nanoplatform for photothermal therapy of tumors. Under laser irradiation, the temperature of UiO-66@PAN solution at a concentration of 100 μg mL-1 increased to 57.2 °C, which was sufficient to effectively kill malignant tumor cells. In cell experiments, this platform shows non-cytotoxicity in mouse colon cancer CT26 and human colon cancer HTC116 cell lines. However, the cell death rate reached 70 % after laser irradiation. In vivo experiments shows that tumors treated with UiO-66@PAN and NIR radiation completely retreated

after 10 days, demonstrating the promising prospect of UiO-66@PAN for photothermal therapy of tumors.

3.4.2 Photodynamic Therapy

Photodynamic therapy (PDT) is an important method in clinical treatment of tumor. In the PDT, oxygen can be converted into reactive oxygen species (ROS) using photosensitizers under laser irradiation, resulting the tumor cell death. PDT, with high selectivity, small side effects, no trauma and restorability, has attracted more attention in the clinical. Lu et al. synthesized Al-Mn mixed MOFs (Mn-MOF) with Mn as the active center to enhance the photodynamic effect.37 The ROS produced by Mn-MOF under light irradiation can be detected using ROS detection reagent, DCFH as a probe. It is confirmed that the fluorescence intensity of ROS probe increased threefold after irradiation, indicating that Mn-MOF has good photosensitivity and can be used as a photosensitizer of PDT.

Based on the easy modification and functionalization of MOFs materials, Zhang et al. reported a simple and universal strategy for the enhancement of PDT (Zhang et al 2018). The platinum nano-enzymes with high catalase activity and stability can be uniformly decorated in the photosensitizer MOF. Therefore, the formation of singlet oxygen for hypoxic tumor sites under laser irradiation is promoted by the release of O_2 activated by H_2O_2 catalyzed by platinum nano-enzymes, resulting tumor cells death.

3.4.3 Microwave Hyperthermia

Microwave hyperthermia of tumor (MWT) also is a treatment method that induces apoptosis by means of local heating at the tumor site. Compared with photothermal therapy, a lot of heat can be generated by the high-speed oscillatory friction between polarized ions and dipoles in the radiation zone induced by high-speed alternating electric field generated by microwave (MW) as a heat source in the microwave hyperthermia. Microwave hyperthermia has the advantages of low cost, low toxicity and small wound. However, the tumor cannot be accurately located by a single microwave therapy. Meanwhile, the temperature changes of the edge zone caused by the gradient of the thermal field is not enough to eliminate the tumor cells, resulting in the occurrence of recurrence. To solve this problem, the concept of microwave sensitizer was proposed. Microwave sensitizer exhibit high microwave-heat conversion efficiency, which is based on the ion domain limitation. Compared with inorganic nanomaterials, many studies have proved that MOFs materials can be used as excellent microwave sensitizer in clinical microwave hyperthermia of tumors. Zhou et al. prepared Zr-MOF-PEG-TPP@DOX with mitochondrial targeting ability as MW sensitizer, by loaded chemotherapy drug doxorubicin (DOX) with a porous zirconium-based MOF nanocubes (Zr-MOF, UiO-66) modified by triphenyl phosphate (TPP) and polyethylene glycol (PEG).39 The local temperature of H22 tumor-bearing mice treated with Zr-MOF-PEG-TPP@DOX increase to 50.8 °C after 5 min microwave irradiation, which meets the requirements of local temperature rise for thermal therapy. Tumor growth also proved the good tumor inhibition effect of this nanoplatform.

3.4.4 Synergistic Therapy

Besides the catalytic activity, photosensitivity or microwave sensitization of MOFs, combine with different therapies, the good loading performance and functionalization of MOF materials can be used to achieve the synergistic treatment, which can effectively enhance the lethality for tumors. For instance, MOF materials loaded with chemotherapy drugs (such as adriamycin, cisplatin), cooperated with chemotherapy, hyperthermia and kinetic therapy, become an effective synergistic treatment. Ma et al. reported that Zr-MOF with degradation and release of terephthalic acid in acidic tumor microenvironment, was used to inhibit carboxylic anhydrase (CAIX) induced by hypoxic factor HIF-1α.40 Moreover, Zr-MOF loaded with the chemotherapy drug quercetin (QU) can also improve the radiotherapy sensitivity of QU used for the inhibition of hypoxic factor, which realizes the inhibition of hypoxic and chemotherapy. As one of the important research fields in clinical tumor treatment, the combination of immunotherapy and MOF materials has attracted more attention. Lin et al. reported a novel dihydroporphyrin-based MOF nanomaterial (TBC-Hf), which encapsulated with an inhibitor of IDOi for the immunomodulatory enzyme IDO within the framework (Figure 7).41 The synthesized IDOi@TBC-Hf can be used for the synergistic treatment of photodynamic therapy and immunotherapy. Based on this treatment, the effective tumor suppression in colorectal cancer models is achieved, and increased T cells in the tumor microenvironment were detected after inhibiting IDO and activating the immune system, which provides a new idea for the clinical treatment of cancers.

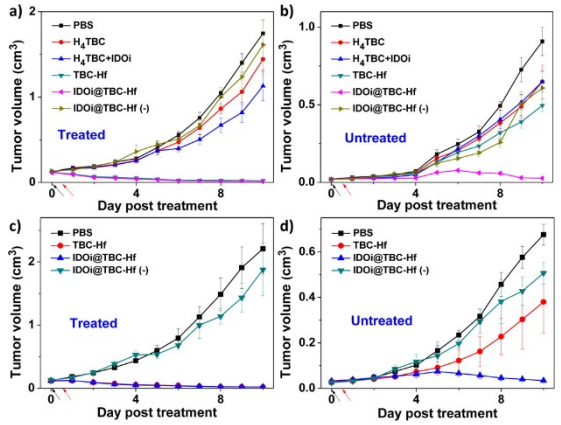

Figure 7: In vivo anticancer efficacy of IDOi@TBC-Hf.41.

4 CONCLUSIONS

The unique properties of MOF, such as tunable pore structure, large surface areas, high drug loading, easy modification and functionalization, make it a potential candidate in the biomedical field. This review provides a more systematic understanding for the preparation methods and bio-applications of MOFs. However, limitation and challenges still exist for MOF, such as standardization of preparation methods, large-scale preparation, biocompatibility and biodegradability. These factors limit the application of MOF in biological field. Therefore, a simple and stable preparation strategy with uniform size and high yield of biocompatible MOFs is urgently developed. Additionally, compared to biomedical application of MOFs, the research on the biological effect of MOF materials have received less attention. Therefore, it is of great significance to clarify the biological effect of MOF materials for safe application. In summary, although the research based on MOF has made great progress, it still faces challenges related to its toxicology, clinical application and large-scale production technology.

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