



Cite this: *Chem. Soc. Rev.*, 2021,
50, 5086

The recent progress on metal–organic frameworks for phototherapy

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Some infectious or malignant diseases such as cancers are seriously threatening the health of human beings all over the world. The commonly used antibiotic therapy cannot effectively treat these diseases within a short time, and also bring about adverse effects such as drug resistance and immune system damage during long-term systemic treatment. Phototherapy is an emerging antibiotic-free strategy to treat these diseases. Upon light irradiation, phototherapeutic agents can generate cytotoxic reactive oxygen species (ROS) or induce a temperature increase, which leads to the death of targeted cells. These two kinds of killing strategies are referred to as photodynamic therapy (PDT) and photothermal therapy (PTT), respectively. So far, many photo-responsive agents have been developed. Among them, the metal–organic framework (MOF) is becoming one of the most promising photo-responsive materials because its structure and chemical compositions can be easily modulated to achieve specific functions. MOFs can have intrinsic photodynamic or photothermal ability under the rational design of MOF construction, or serve as the carrier of therapeutic agents, owing to its tunable porosity. MOFs also provide feasibility for various combined therapies and targeting methods, which improves the efficiency of phototherapy. In this review, we firstly investigated the principles of phototherapy, and comprehensively summarized recent advances of MOF in PDT, PTT and synergistic therapy, from construction to modification. We expect that our demonstration will shed light on the future development of this field, and bring it one step closer to clinical trials.

Received 24th January 2021

DOI: 10.1039/d1cs00056j

rsc.li/chem-soc-rev

1. Introduction

The history of light treatment dates back to 3000 years ago, when the ancient civilizations utilized light to treat skin cancer, rickets and vitiligo.¹ In 1903, Niels Finsen was awarded the Nobel Prize for using red light and ultraviolet (UV) light to treat smallpox pustules and cutaneous tuberculosis, which was known as the beginning of “phototherapy”.^{1,2} In 1975, Thomas Dougherty firstly demonstrated complete tumor eradication of mice, which aroused extensive investigation in this field.^{1,3} Nowadays, phototherapy refers to cell-killing treatment by certain

therapeutic agents under appropriate light irradiation. There are two distinct killing strategies: reactive oxygen species (ROS) generation and temperature increase, and the former route is named photodynamic therapy (PDT) while the latter is called photothermal therapy (PTT). Compared to traditional treatment strategies such as chemotherapy and radiotherapy, phototherapy is less invasive, highly selective and causes minimum damage to normal tissues.^{4,5} In recent decades, more and more researchers have been trying to apply phototherapy in the treatment of cancer and nonmalignant diseases, and have achieved good therapeutic efficacy.^{4,6} Therefore, phototherapy is showing great promise as an emerging type of therapeutic method.

In the case of PDT, a photosensitizer (PS) is irradiated by a certain wavelength of light, leading to the generation of highly toxic ROS, including the superoxide anion radical ($\text{O}_2^{\cdot-}$), hydroxyl radical ($\text{OH}^{\cdot}$), hydrogen peroxide (H_2O_2) and singlet oxygen ($^1\text{O}_2$). These ROS, especially $^1\text{O}_2$ and $\text{OH}^{\cdot}$, are cytotoxic oxidizing agents that can diffuse through the membrane and then directly react with many biomolecules in cells such as proteins and DNA, thus inducing cell death and tissue lesions.^{4,7} The superoxide anion radical is more like an intermediate for the generation of H_2O_2 and $\text{OH}^{\cdot}$ via Type I process in PDT, or by reacting with metal ions (e.g. Fe^{2+}), namely the Fenton reaction.⁷

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However, as the lifetime of ROS is short, the direct influence of ROS has a limited radius of action. For example, the lifetime of $^1\text{O}_2$ is around 48 ns and its diffusion in cells is approximately 20 nm.⁸ Therefore, targeted cells should be in proximity, to where ROS is generated. Besides direct cytotoxic effects, PDT also causes vascular injury and robust immune response, which depends on the interval between drug administration and light irradiation.^{6,9} A longer interval provides the PS with sufficient time to diffuse through tissues, while a shorter interval renders the accumulation of PS in vessels, thus inducing vascular stasis and thrombus formation.¹ Porphyrin and its derivatives are the most commonly used PS in clinical settings, owing to their low dark toxicity and high ROS quantum yield.¹⁰ Hematoporphyrin derivative (HPD) is the first approved PS for clinical usage by the US Food and Drug Administration (FDA), followed by Foscan[®], Levulan[®], and Radachlorin[®], *etc.* because of their excellent photochemical properties.^{2,5} Besides that, organic dyes,¹¹ quantum dots,¹² black phosphorus,¹³ red phosphorus,¹⁴ copper sulfide,¹⁵ zinc oxide,¹⁶ graphitic carbon nitride (g-C₃N₄)¹⁷ can also act as PSs. To date, PSs have been developed from bare HPD and its derivatives to those carrier-loaded PSs with long-wavelength absorption and selective accumulation. However, these properties still need further improvement.¹⁰ Other drawbacks of the existing PSs are hydrophobicity-induced aggregation, limited diffusion of ROS, oxygen dependence and undesirable penetration depth, *etc.*

Different from PDT, the mechanism of PTT is like causing a localized “fever” in the therapeutic sites. During this course, the temperature increase is triggered by light irradiation on photothermal agents (PTAs) through the nonradiative relaxation of excited electrons. The efficacy of PTA was evaluated by photothermal conversion efficiency, which refers to the ratio between the absorption (σ_{abs}) and extinction (σ_{ext}) of light, according to the following equation:¹⁸

$$\mu = \sigma_{\text{abs}}/\sigma_{\text{ext}} \quad (1)$$

Based on the final temperature, PTT can be categorized into diathermia (< 41 °C), hyperthermia (41–46 °C) and thermal ablation (> 46 °C).^{19–23} Diathermia is a relatively mild treatment that can promote tumor oxygenation by increasing blood flow, thereby sensitizing cells to radiotherapy and chemotherapy.²² Diathermia is also applied in physiotherapy for rheumatic treatment and muscle relaxation.^{19,20} In hyperthermia, heat stress causes protein denaturation and aggregation, cell membrane loosening and DNA cross-linking, which strongly affect cellular functions and finally lead to cell inactivation.^{20,21,24} However, in this temperature range, the expression of heat shock protein is higher, which is a molecular chaperone that repairs thermal damage to cells, leading to the formation of thermo-resistance.^{25,26} Moreover, hyperthermia is also able to induce the sensitization of cells towards heat,²² antibiotics,²⁷ and other therapies.²³ Thermal ablation can directly cause coagulative necrosis of cells in a few minutes, which is irreversible damage.¹⁹ Despite the high efficiency of thermal ablation, it can also affect healthy cells, induce inflammation and cancer metastasis.²⁸ When the temperature is above 60 °C, rapid necrosis of cells will occur due to enzyme

inactivation and protein denaturation.²⁹ Hence, the therapeutic temperature should be appropriately designed to achieve desirable efficacy. PTAs have several distinct types: carbon material,^{30–32} noble metal material,^{33–35} organic dyes,^{36,37} conjugated polymers,^{38,39} manganese dioxide,⁴⁰ magnetic nanoparticles,²⁰ *etc.* Similar to PSs, limited penetration depth and lack of selectivity are the main drawbacks of PTAs. To utilize sensitization, prevent thermo-resistance and reduce damage to healthy tissues, PTT requires a more elaborate design and a new therapeutic platform for combined therapy.

Metal–organic frameworks (MOFs) are emerging materials that are widely utilized in gas storage, gas separation, catalysis and medical treatment.⁴¹ The main components of the MOF are metal nodes (or metal clusters) and organic linkers (mostly carboxyl- or nitrogen-containing agents), which are joined by coordination bonds, forming one-, two- or three-dimensional networks.^{41–43} Numerous combinations of metals and linkers give rise to diverse MOFs with different structures and properties. Moreover, MOF is highly porous, with pore size ranging from the micro- to the meso-scale, providing space for guest molecules.⁴⁴ The well-defined structure of the MOF has a clear relationship with their properties, which offers guidance for future modifications.⁴¹ In terms of biomedical applications, MOFs have shown great promise in chemotherapy, phototherapy, diagnosis and imaging. Due to the tunable pore size, MOFs have been reported as efficient drug carriers. The weak coordination bonds in MOFs render the stimuli-responsive release of drugs.⁴⁵ MOFs have a large number of reactive sites,⁴⁶ which are suitable for further modifications such as targeting molecule attachment, thus greatly improving the selectivity of therapeutic nanoparticles (NPs). Under rational design, some MOFs are nontoxic and biodegradable and can be eliminated from the body with low side effects.

The study of MOFs in phototherapy started in the last decade (2010–2020) and showed a rapidly growing tendency in recent years (Fig. 1). The major functions of MOFs in phototherapy are schematically summarized in Fig. 2. MOFs can directly act as PSs

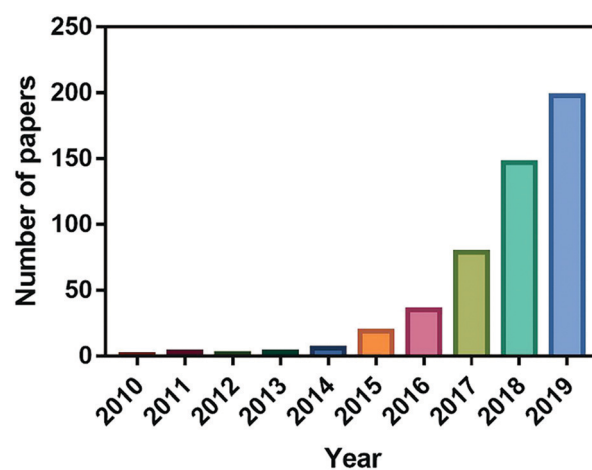


Fig. 1 The number of publications in the last decade that focused on the topic of phototherapy by using a metal–organic framework based on a Web of Science search conducted on March 31st 2020.

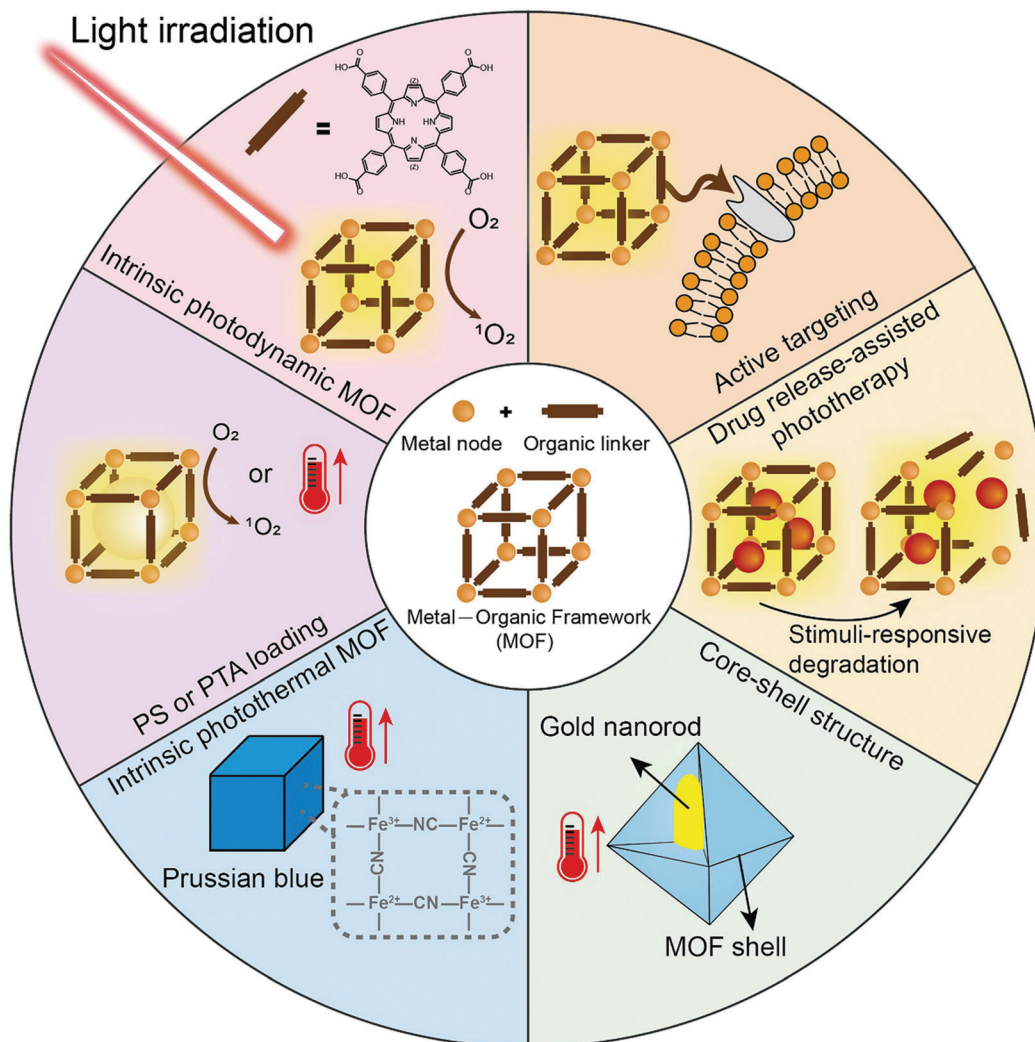


Fig. 2 Summary of the major functions of MOFs in phototherapy.

or PTAs by using photo-responsive building units,^{47–49} thus constructing intrinsic photodynamic or photothermal MOFs. They can also realize photo-responsive ability by loading phototherapeutic agents,^{50,51} or forming core-shell structures and other composites.^{52,53} The structural design and modification of MOFs can tune the light absorption^{54,55} and electron transition pathway⁵⁶ for improving the efficiency of ROS generation or temperature increase, and also help therapeutic particles to better adapt to the physiological environment through hypoxia alleviation⁵⁷ or targeting molecule attachment.⁵⁸ MOFs are also excellent platforms for combined therapy such as chemotherapy,^{59–61} starvation therapy^{62,63} and gas therapy,^{64,65} which greatly improve the therapeutic efficacy as compared to phototherapy alone. Due to the stimuli-responsive degradation of MOF, the loaded agents can be released and function in certain environments, preventing the loss during transportation.^{51,66}

In this review, we firstly illustrate the principles of phototherapy, then comprehensively summarize the recent advances of MOFs in phototherapy (including PDT, PTT and PDT–PTT synergistic therapy) from the intrinsic photo-responsive MOFs

to the modified MOFs, and then categorize the typical methods for therapy optimization. We mainly focus on how MOFs function and make a difference in each therapeutic system. Finally, we address the existing drawbacks and challenges in this rapidly growing research field.

2. Principles of phototherapy

Phototherapy is initiated by light irradiation on therapeutic agents. During this process, some incident photons impinge on chromophores and then undergo scattering, transmission, or absorption.³ As only absorbed photons can take effect in phototherapy, we use the Jablonski diagram to describe this process, as shown in Fig. 3a.^{19,67–70} Absorption occurs when an electron in the ground state (S_0) interacts with a photon with energy equal to the difference between two electronic states. The energy of the photon is then transferred to the electron, bringing the electron from the ground state to the short-lived ($\sim 10^{-6}$ s) higher-energy singlet excited state (S_1), and then the

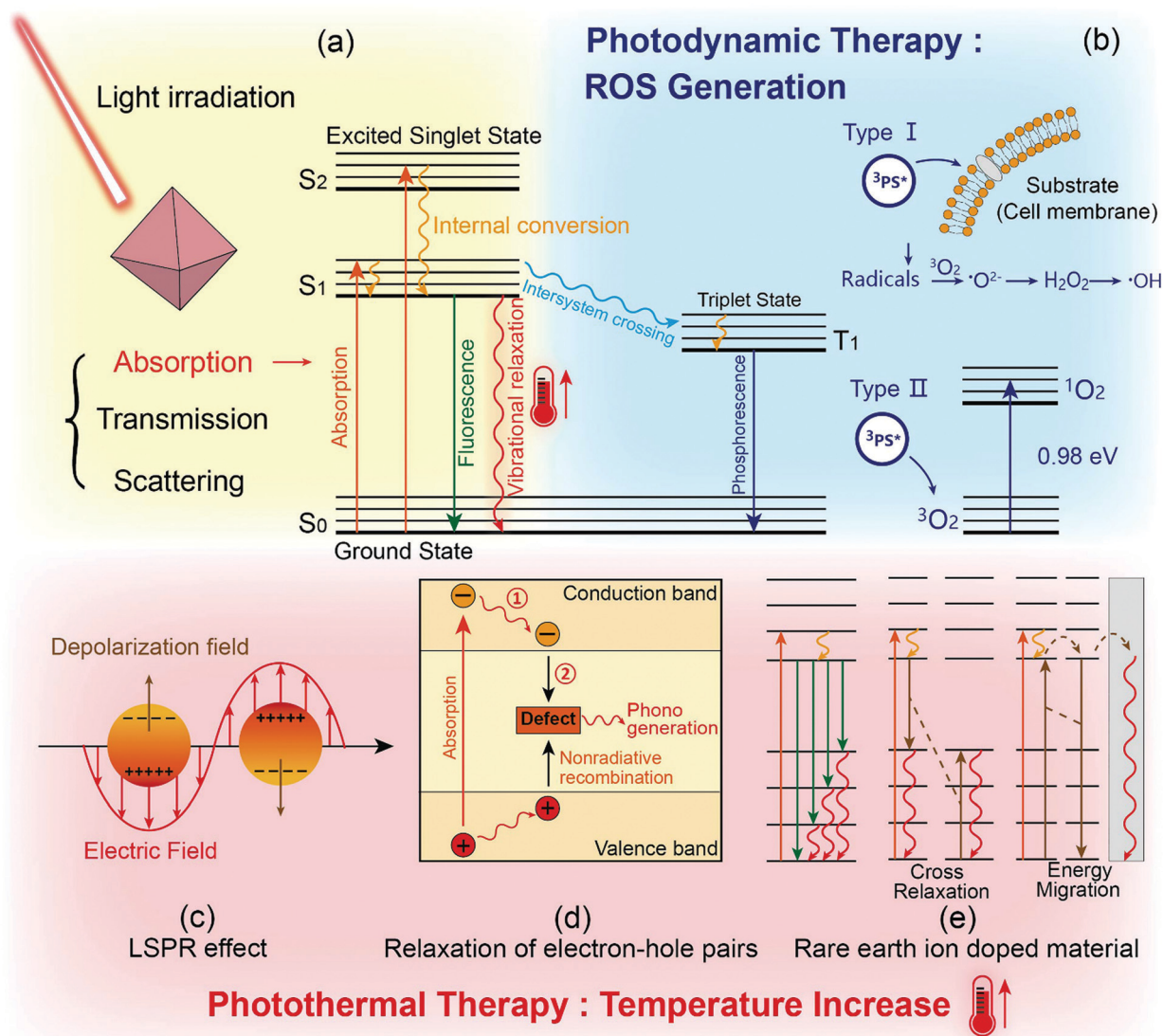


Fig. 3 Photophysics and photochemistry processes of phototherapy: (a) Jablonski diagram; (b) Type I and Type II mechanism of PDT; schematic illustration of (c) the LSPR effect, (d) relaxation of electron-hole pairs, and (e) rare earth ion doped material in PTT.

electron relaxes to the lowest vibrational level of the excited state through internal conversion.^{5,67} Internal conversion is a nonradiative process that occurs between energy states of the same spin multiplicity, which is a rapid process.⁷¹ Finally, the excited electron goes back to the ground state by three pathways: fluorescence, phosphorescence, and vibrational relaxation.^{2,67}

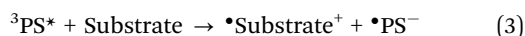
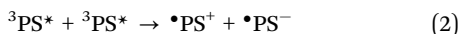
Fluorescence refers to a radiative electron transition from the lowest vibrational excited state to the ground state, which has the same spin multiplicity, inducing the release of a photon.^{3,71} In medical fields, fluorescence is mostly applied to imaging guidance including diagnostics, drug delivery, monitoring, and surgery imaging.^{9,72} For example, fluorescence imaging can be used for defining the margin between a tumor and healthy tissues, or serve as the marker of the body's response to treatment.^{9,73} After drug administration, fluorescence can monitor the location of drugs and determine the degree of drug uptake by

diseased tissues.⁷³ Hence, guidance by fluorescence imaging can provide important information about the disease and treatment. It is also helpful in understanding the mechanism and adjusting the parameters of therapy.⁷³

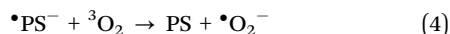
Different from fluorescence, phosphorescence emission occurs by electron transitions between energy states of different spin multiplicity. The electron firstly enters the long-lived ($\sim 10^{-2}$ s) triplet state (T_1) through a process called intersystem crossing, leading to the change in the electron spin orientation.^{3,5} Intersystem crossing is a forbidden transition caused by the interaction between the orbital angular momentum of the electron and the magnetic dipole related to the electron spin.^{3,74} Afterwards, the electron usually transfers energy by phosphorescence emission and then relaxes to the ground state. However, as the lifetime of T_1 is long, many kinds of quenchers can react with the T_1 electron before phosphorescence emission.⁷³

In high partial oxygen solvents, the electron in T_1 can transfer energy by reacting with a nearby substrate or triplet state molecules such as molecular oxygen (3O_2), thus producing ROS.^{1,3}

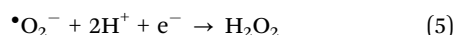
To be specific, ROS are generated through two distinct routes, namely, the Type I and Type II mechanism (Fig. 3b). In the Type I mechanism, PS in the triplet state (referred to as $^3PS^*$) transfers a proton or an electron to the nearby substrate (e.g., cell membrane, protein and lipid, etc.) or other PS molecules, which leads to the formation of a radical anion or radical cation (eqn (2) and (3)).^{1,10,75,76}



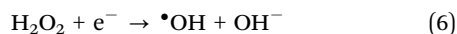
These radicals can further react with 3O_2 , thus producing $\bullet O_2^-$ (eqn (4)).



Although $\bullet O_2^-$ is not the main reactive cytotoxic agent and cannot cause much oxidative damage, it is an important intermediate in biological systems. $\bullet O_2^-$ can produce H_2O_2 through dismutation in the presence of superoxide dismutase or by one-electron reduction (eqn (5)).



Finally, H_2O_2 can generate the highly cytotoxic hydroxyl radical ($\bullet OH$) through one-electron reduction (eqn (6)).^{6,7}



In the Type II mechanism, the energy of the triplet state PS is directly transferred to 3O_2 due to the same electron spin multiplicity, which brings the 3O_2 from the ground state to the excited singlet state, thus producing 1O_2 .^{77,78} The energy gap between 3O_2 and 1O_2 is 0.98 eV, which is the energy threshold for $^3PS^*$ in PDT.³ The two types of mechanism can work simultaneously, and the ratio depends on the oxygen concentration, substrate and PS type. Generally, most PSs are based on the Type II mechanism, which results in the dependence of PDT on oxygen. The reaction product 1O_2 is the main cytotoxic component in PDT due to its high electrophilicity. The Type I mechanism is more effective in oxygen-deficient environments.^{6,76,78,79}

Vibrational relaxation is the main mechanism of light-to-heat conversion. During this process, electrons in the excited state relax to the ground state in a nonradiative way, causing the collision between the chromophore and the surrounding environment. Hence, part of the energy is released as heat.^{3,80} Generally, most PTAs such as carbon-based PTAs, organic dyes and photothermal polymers generate heat *via* this mechanism, under light irradiation at the appropriate wavelength.^{19,36,81} However, as for metals, semiconductors, and rare earth materials, the light-to-heat conversion mechanism is more complex.

For high carrier density materials such as metals, the movement of free conduction electrons can be guided by incident light, causing the polarization of electrons. The oppositely accumulated charges, in turn, form a depolarization field, which leads to the collective oscillation of electrons, namely,

surface plasmon polariton.^{18,68} The surface plasmon then decays by light emission or nonradiative transition.⁸² In the latter case, energy is dissipated in the form of heat. This phenomenon is called localized plasmon surface resonance (LSPR), which is shown in Fig. 3c. As LSPR is related to the energy redistribution in the conduction band, it is also referred to as “intragap transition”.⁶⁸ The primary control of LSPR is free electron density, which determines whether a material can have the LSPR effect in the optical region.⁸³ The LSPR frequency is slightly influenced by particle size and shape. By changing the particle morphology or introducing coupling materials, the LSPR peak can be tuned from the visible to the near-infrared (NIR) range.^{68,80} The most popular LSPR materials are noble metals, such as gold and silver, because of their suitable response of light at optical frequencies. However, LSPR is not confined to metals. Semiconductors, metal oxides and quantum dots with high carrier density can also have a photothermal effect through LSPR.⁸³ It is worth noting that enhancing the electron density through modifications can change the major electron transition from bandgap to LSPR, thus inducing the photothermal effect.^{54,84}

Another mechanism is based on the bandgap transition of electrons, which mainly appears in low electron density semiconductors. Due to the interaction of molecular orbitals, semiconductors have two broad energy bands, namely the conduction band and valence band. The former is filled with electrons while the latter has no electrons. There are no energy levels between these two bands. The energy gap between the lowest energy of the conduction band and the highest energy of the valence band is called the bandgap. If the semiconductor is irradiated by photons with energy higher than or equal to the bandgap, the electron will be excited to a higher energy level in the conduction band, leaving a hole in the valence band. The electrons and holes are referred to as “hot carriers”, due to their higher temperature than the lattice. When the energy of the photon is higher than the bandgap, the electron and hole will be “above-bandgap”, as shown in Fig. 3d. Then, in process 1, the electron and hole will relax to the band edges through vibrational relaxation, which causes the thermalization process, thus converting energy into heat.^{69,85} Hence, narrowing the bandgap can improve the photothermal effect through a longer relaxation pathway. Afterwards, the electron-hole pair will recombine near the band edge or at deep-level defect (DLD) sites (process 2).⁷⁰ During the recombination process, the excessive energy is transferred to phonon generation for the equilibrium of hot carriers and lattice, resulting in heat generation due to the crystal lattice vibration. DLD sites serve as the centers of non-radiative recombination. More DLDs lead to higher photon generation, thus increasing the photothermal effect.⁷⁰

The last type of photothermal mechanism is based on the ladder-like energy level of rare earth ions (Fig. 3e). Similarly, the nonradiative relaxation of excited electrons to the ground state can generate heat. In rare earth doped nanocrystals, when the rare earth ion content is increased, the distance to the same ions is reduced, forming electron pathways between the same ions, which is called cross-relaxation (CR).⁸⁶ CR results in the

excitation and de-excitation of two neighboring ions, and then the two excited electrons relax to the ground state to produce heat, thus improving the photothermal effect of PTAs.⁵⁶ The energy of excited electrons can also migrate between the same ions. Once the energy is transferred to a nonradiative center, the energy will be released in the form of heat.¹⁹ This process is called energy migration.

The light's wavelength is a critical factor that is related to the depth of light penetration, photon adsorption and the subsequent electron behaviors. The frequently used wavelength of light in phototherapy is red light (620–750 nm), NIR-I (750–1000 nm), and NIR-II (1000–1350 nm). For PSs, the wavelength is usually in the range of 650–800 nm, which is called the “tissue transparent window”. Tissue penetration depth in this wavelength region is 3–10 mm.² Shorter wavelengths (<600 nm) have limited therapeutic depth and will cause skin photosensitivity, while longer wavelengths (>800 nm) cannot provide enough energy for ³O₂ excitation.⁷ Since longer wavelengths of light have deeper penetration, the ideal wavelength of PDT is located in the deep-red region.⁶ To further improve the tissue penetration of PDT, the PS can be modified with upconversion nanoparticles that can absorb NIR light and emit ultraviolet (UV)-vis light for PS activation.^{87–89} In this way, NIR can be used as the light source. For PTAs, the desired wavelength is longer, which is located in the first biological window (700–980 nm) and the second biological window

(1000–1400 nm).¹⁹ The longer wavelength of light provides deep-tissue treatment because of minimal tissue absorption and scattering.⁹⁰ The absorption of PSs or PTAs is a critical factor when choosing the light source. When the irradiation wavelength is the same as the wavelength of the absorption peak, the photon absorption is enhanced. It is worth mentioning that for coordination structures, besides the interband transition mentioned above, their absorption is also influenced by various charge transfer processes such as metal-to-ligand charge transfer, ligand-to-metal charge transfer, *etc.*⁹¹ The absorptions of typical PSs, PTAs and some intrinsic photodynamic or photothermal MOFs are listed in Table 1, and are summarized according to the published literature. The absorption of a material is not constant and can be tuned by different sizes and shapes or by modifications. The disease location and tissue properties should also be considered when selecting the appropriate wavelength of light.⁶

Whether an excited electron goes through fluorescence emission, nonradiative relaxation or enters into the triplet state depends on many factors, which requires deep insight into the mechanism of photo-induced electron transitions. The ratio between radiative and nonradiative processes depends on the distance and relative orientation of chromophores.³ When the fluorescence quantum yield is low, the ratio of the other two processes is high, which means higher efficacy of phototherapy.

Table 1 Typical PSs and PTAs responding to light of specific wavelength

PSs or PTAs	Absorption under specific wavelengths of light	Ref.
Porphyrin	Strong absorption band at 400 nm (Soret band) A set of absorption bands at 600–800 nm (Q band)	5
Chlorin	630–650 nm (Q band)	
Bacteriochlorin	700–800 nm	
Methylene blue	550–700 nm	10
Rose bengal	480–550 nm	
IR780	Absorption peak at 780 nm	92
IR825	Absorption peak at 825 nm	93
Indocyanine green (ICG)	Absorption peak at 777 nm	94
1,3,6,8-Tetrakis(<i>p</i> -benzoic acid)pyrene (H ₄ TBAPy)	Absorption peaks at ~420 nm and ~330 nm	95
Tetrakis(4-carboxyphenyl)-porphyrin (TCPP)	Soret band at 419 nm	96
5,15-Di(<i>p</i> -benzoato)porphyrin (H ₂ DBP)	Q bands at 513, 548, 589, 645 nm	
	Soret band at 402 nm	55
5,15-Di(<i>p</i> -methylbenzoato)chlorin (H ₂ DBC)	Q bands at 505, 540, 566, 619 nm	
	Soret band at 408 nm	47
5,10,15,20-Tetra(<i>p</i> -benzoato) (H ₄ TBC)	Q bands at 504, 534, 591, 643 nm	
	Soret band at 420 nm	97
	Q bands at 518, 546, 600, 652 nm	
Au nanorod	LSPR peak at 520 nm	98
	Longitudinal peak in the NIR region	
Pb nanocube	Surface plasmon resonance absorption at 220–700 nm	99
Prussian blue	500–900 nm with an absorption peak at 712 nm	100
Graphene	Strong absorption in the NIR region	31
Graphene oxide	Absorption peak at 227 nm	101
Polypyrrole	700–1200 nm	102
Polydopamine	Absorption peak centered at 500–800 nm	53
PCN-224 (composed of TCPP ligand and Zr node)	Q bands at 515, 550, 591, 646 nm	96
DBP-Uio MOF (composed of H ₂ DBP ligand and Hf node)	Q bands at 510, 544, 579, 634 nm	55
DBC-Uio MOF (composed of H ₂ DBC ligand and Hf node)	Q bands at 508, 545, 592, 646 nm	47
TBC-Hf MOF (composed of H ₄ TBC ligand and Hf node)	Q bands at 520, 548, 600, 653 nm	97
Zr-Ferrocene MOF (composed of Fc(COOH) ₂ ligand and Zr node)	350–1350 nm	103
5,10,15,20-Tetrakis(4-pyridyl)-21H,23H-porphine (TPyP)	Soret band at 418 nm	104
Pd-TPyP MOF (composed of TPyP ligand and Pd node)	Soret band at 440 nm	104
	Absorption band at 800–1000 nm	

Intersystem crossing can be promoted by combining PSs with heavy atoms due to enhanced intramolecular spin-orbit coupling or intermolecular collision, namely the heavy atom effect.³ Another requirement of PDT is that the energy of the triplet state should be higher than 0.98 eV, which corresponds to the energy between $^1\text{O}_2$ and $^3\text{O}_2$.³ On the other hand, to improve the photothermal effect, intersystem crossing and fluorescence should be reduced. Chelation with metals such as Mn and Cu can quench the fluorescence and ROS generation of PSs,^{105,106} thus promoting electrons to go through nonradiative decay pathways.⁸⁰ Moreover, aggregates of PSs formed by π -stacking can decrease the triplet state lifetime and ROS quantum yield of PSs, which improves the ratio of nonradiative relaxation.^{5,80} As PDT is dependent on oxygen, reducing the oxygen content by clamping also hinders the PDT effect of PSs.¹

3. Photodynamic therapy

3.1 Intrinsic photodynamic MOF

3.1.1 Porphyrin-based MOFs. Using porphyrin and its derivatives as MOF ligands is a straightforward way to fabricate intrinsic photodynamic MOFs. The frequently-used porphyrin ligands are presented in Fig. 4, which are mostly carboxyl-containing derivatives of porphyrin, chlorin and bacteriochlorin, *etc.*^{47,55,62,97,107,108} The number of π electrons in porphyrin, chlorin and bacteriochlorin is 22, 20 and 18, respectively.⁵ The absorption of porphyrins red-shifts with the decrease in π electrons.¹⁰ Hence, the photo-response of MOFs can be tuned by using different porphyrin linkers. Compared to traditional porphyrin PSs, porphyrin-based MOFs are more efficient and potent. Firstly, porphyrins are regularly arranged in the MOF structure with high loading content, which prevents PSs aggregation. The channels and pores in MOFs render facile diffusion of $^3\text{O}_2$ and $^1\text{O}_2$. Using metal nodes such as Hf can improve intersystem crossing through the heavy atom effect, thus increasing $^1\text{O}_2$ yields. However, despite these advantages, the morphology of metal-organic nanocomposites is hard to control. The insolubility

and aggregation of PS in common solvents also add difficulty to the MOF synthesis and porosity control.^{49,109} To date, many porphyrin-based MOFs have been synthesized and applied in PDT as PSs, which are given in Table 2.

The first report of porphyrin-based MOFs for PDT was made by Lin's group.⁵⁵ They synthesized DBP-UiO constructed by 5,15-di(*p*-benzoato)porphyrin (H_2DBP) ligands and Hf nodes, with a H_2DBP loading of 77 wt%. DBP-UiO has nanoplate morphology, which was ~ 100 nm in diameter and ~ 10 nm in thickness. The high-Z ion, Hf^{4+} , promoted the intersystem crossing of the PDT system. Hence, the absorption peaks of DBP-UiO all red-shifted and the $^1\text{O}_2$ generation of DBP-UiO was at least 2 times higher as compared to H_2DBP . *In vivo* tests manifested the excellent antitumor effect of DBP-UiO, *i.e.*, the tumor decreased in size by 50 times, or was completely eradicated after PDT treatment. However, the lowest-energy Q band absorption of Hf-DBP was close to the edge of the "tissue transparent window", and its extinction coefficient was $2200 \text{ M}^{-1} \text{ cm}^{-1}$, which means the light source had limited penetration in the tissue and the light absorption of DBP-UiO was not enough as well. Therefore, Lin's group then partially reduced H_2DBP to generate H_2DBC (H_2DBC refers to 5,15-di(*p*-methylbenzoato)chlorin), which was used to fabricate DBC-UiO MOF (Fig. 5a).⁴⁷ DBC-UiO also had nanoplate morphology, which was 100–200 nm in diameter and 3.3–7.5 nm in thickness (Fig. 5b). The lowest-energy Q band of DBC-UiO red-shifted to 646 nm (Fig. 5c), and the extinction coefficient reached $24\,600 \text{ M}^{-1} \text{ cm}^{-1}$, which was 11 times higher than DBP-UiO. Moreover, DBC-UiO exhibited 3-fold higher PDT efficacy and even more potent tumor eradication than DBP-UiO in the CT26 and HT28 model. Afterwards, Lin's group fabricated TBC-Hf MOF (TBC refers to 5,10,15,20-tetra(*p*-benzoato)), and loaded IDO inhibitor (INCB24360) in it for PDT and immune-combined therapy.⁹⁷ The lowest-energy Q band of TBC-Hf was 653 nm, which was 7 nm red-shifted as compared to the DBC-UiO. The extinction coefficient also increased to $38\,500 \text{ M}^{-1} \text{ cm}^{-1}$. Their results showed that TBC-Hf had the highest ROS generation among its analogues.

After these reports from Lin's group, a growing number of reports about MOF-based PSs came out. Among them, the porous coordination network (PCN) is an important branch, which is composed of Zr clusters (mostly octahedral Zr_6 clusters) and the tetrakis(4-carboxyphenyl)-porphyrin (TCPP) ligand. Due to its excellent ROS generation ability, biodegradability and stability in aqueous solution, *etc.*,¹¹⁵ this kind of MOF is becoming the most popular photodynamic MOF as indicated in Table 2. Park *et al.* successfully fabricated PCN-224 of various sizes from 30 to 190 nm by adding different concentrations of benzoic acid (Fig. 5d).⁵⁸ When the particle size of PCN-224 was 90 nm, the cellular uptake in HeLa cells was the highest (Fig. 5e). Under the irradiation of 420 nm and 630 nm lasers, PCN-224 of 90 nm in size also had the highest PDT efficacy of around 80% in cells due to the better contact of intracellular O_2 with PSs (Fig. 5f). Then, the Zr_6 cluster was further functionalized with folic acid by coordination between the carboxyl of the folic acid and Zr_6 clusters for active targeting (Fig. 5g). In folate receptor-abundant cells such as ovarian tumors, the attachment of folic

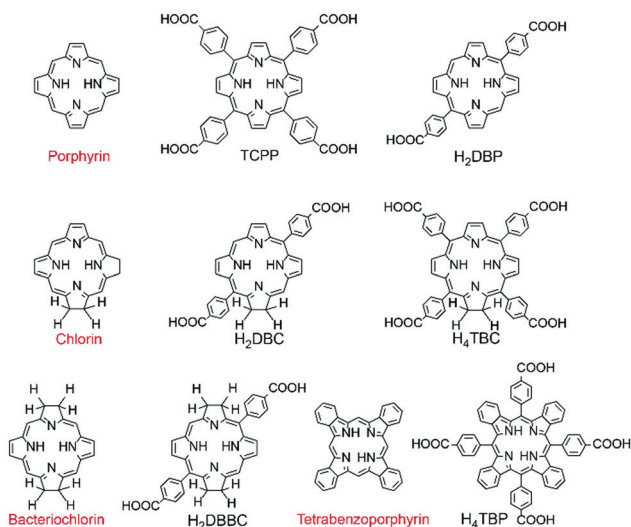


Fig. 4 Typical porphyrins and their derivatives, which have been used as MOF ligands.

Table 2 Summary of recent porphyrin-based MOFs in PDT. Particle size was measured by SEM (scanning electron microscopy), TEM (transmission electron microscopy) or DLS (dynamic light scattering)

Metal nodes	Organic ligands	Materials for decoration	Particle size	Irradiation wavelength	Additional functions	Ref.
Zr ⁴⁺	TCPP	Folic acid	30–190 nm	420 nm and 630 nm	Targeting	58
Zr ⁴⁺	TCPP	NaFY ₄ :Yb/Er, thiol-PEG	52.1 ± 9.8 nm for PCN-224	980 nm	Upconversion	96
Zr ⁴⁺	TCPP	Glucose oxidase, catalase, cancer cell membrane	227.5 nm	660 nm	Starvation therapy, targeting	62
Zr ⁴⁺	TCPP	PDA, Pt NPs, folic acid	250 nm	660 nm	O ₂ supply, targeting	110
Zr ⁴⁺	TCPP	Tirapazamine, cancer cell membrane	154.0 nm	660 nm	Bioreductive therapy, targeting, immune escape	111
Zr ⁴⁺	TCPP	Pt NPs, HOOC-PEG-COOH	90 nm	638 nm	O ₂ supply	48
Zr ⁴⁺	TCPP	L-Arg, cancer cell membrane	105 nm for PCN-224	660 nm	Gas therapy	112
Zr ⁴⁺	TCPP	Ag ions, HA	85 nm for PCN-224	Visible light	Bacteria killing	113
Zr ⁴⁺	TCPP	Apatinib, MnO ₂ , cancer cell membrane	140.5 nm	660 nm	Angiogenesis inhibition, GSH depletion, immune escape, targeting	60
Zr ⁴⁺	TCPP	CeO ₂	190 nm	638 nm	Biofilm inhibition	114
Zr ⁴⁺	TCPP	DOX, HA	~250 ± 20 nm	640 nm	Targeting, enzyme responsive drug release	115
Zr ⁴⁺	TCPP	—	4.0 nm	650 nm	Renal clearance	116
Zr ⁴⁺	TCPP	PCL	100 nm	510 nm	Bacteria killing	117
Zr ⁴⁺	TCPP	DOX, galactose, PEG	121.2 ± 3.7 nm	660 nm	Targeting, drug loading	118
Zr ⁴⁺	TCPP	α-Cyano-4-hydroxycinnamate, HA	152.4 nm	660 nm	Hypoxia alleviation, targeting, lactate-fueled respiration	119
Zr ⁴⁺	TCPP	DOX, ZnO, AS1411	161.7 nm	650 nm	Drug loading, targeting	120
Zr ⁴⁺	TCPP	MnFe ₂ O ₄ , PEG	~110 nm without PEG coating	660 nm	O ₂ supply, GSH depletion, MRI	57
Zr ⁴⁺	TCPP	PAH, MnO ₂ , DOX	72 nm for PCN-222	655 nm	Drug loading, MRI, GSH depletion	121
Zr ⁴⁺	TCPP	Pt NPs, Au NPs, folic acid	147.5 nm	671 nm	Starvation therapy, targeting	63
Zr ⁴⁺	TCPP	Alkaloid piperlongumine, cancer cell membrane	200 nm for PCN-222	660 nm	Thioredoxin reductase inhibition, targeting	61
Zr ⁴⁺	TCPP	MnO ₂ nanosheet, cell membrane	105 nm without cell membrane coating	409 nm	O ₂ supply, MRI, targeting	122
Zr ⁴⁺	TCPP	Acriflavine, cytosine-phosphate-guanine, HA	105.4 nm	670 nm	Immunotherapy	123
Zr ⁴⁺	PtTCPP	Cancer cell membrane	150.5 nm	532 nm	Homologous targeting, O ₂ sensing	124
Zr ⁴⁺	MnTCPP	—	300 × 130 nm (length × width)	660 nm	MRI, O ₂ supply	125
Zr ⁴⁺	FeTCPP	NaYb _{0.92} F ₄ :Er _{0.08} @NaYF ₄ , Au NPs	~126.4 nm	980 nm	Upconversion, O ₂ supply, starvation therapy	89
Hf ⁴⁺	H ₂ DBP	—	76.3 nm	640 nm	—	55
Hf ⁴⁺	H ₂ DBC	—	128.5 nm	640 nm	—	47
Hf ⁴⁺	H ₄ TBC	IDO inhibitor	83.2 nm for Hf-TBC	650 nm	Immunotherapy	97
Hf ⁴⁺	H ₂ DBBC	—	220 nm in size, 4.6 nm in thickness	750 nm	Photoacoustic imaging	108
Zr ⁴⁺	TBP	PEG	~50 nm	660 nm	Immunotherapy	107
Zr ⁴⁺	5,10,15,20-Tetra(<i>p</i> -benzoato)bacteriochlorin	—	117.9 ± 1.4 nm	740 nm	—	126
Hf ⁴⁺	TCPP	PEG	~130 nm	661 nm	Radiotherapy	127
Cu ²⁺	ZnTCPP	—	105 nm	600 nm	H ₂ S response	106
Al ³⁺	CuTCPP	—	—	650 nm	GSH depletion	128
Hf ⁴⁺	TCPP	Tirapazamine, DOPA-PIMA-mPEG	163 ± 5 nm	635 nm	Drug loading, computed topography imaging	129
Gd ³⁺	TCPP	—	240.7 nm	660 nm	MRI	130
Fe ³⁺	TCPP	Bovine serum albumin, sulfadiazines, MnO ₂	122 nm	660 nm	O ₂ supply, MRI	131
Mn ³⁺	TCPP	—	170 nm in length, 50 nm in width and 100 nm in thickness	660 nm	MRI, GSH depletion, optical imaging	105
Hf ⁴⁺	TCPP	Human serum albumin coated MnO ₂	105 nm	Visible light	Biofilm eradication	132
Cu ²⁺	ZnTCPP	—	—	635 nm	H ₂ S response	133
Zn ²⁺	TCPP	DOX, PEG	2 nm in thickness	660 nm	Drug loading	134
Gd ³⁺	ZnTCPP	ZnO, MnO, MgO, Fe ₂ O ₃ , CuO	—	660 nm	—	135
Fe ³⁺	TCPP	Dihydroartemisinin, CaCO ₃	382 ± 23 nm in length and 182 ± 37 nm in width	655 nm	Drug loading, MRI, oncosis therapy	136
Mn ²⁺	TCPP	—	150 nm	650 nm	O ₂ supply	137
Sm ³⁺	TCPP	Pt NPs, triphenylphosphine	~100 nm in diameter and less than 10 nm in thickness	660 nm	O ₂ supply, mitochondrion targeting	138

Table 2 (continued)

Metal nodes	Organic ligands	Materials for decoration	Particle size	Irradiation wavelength	Additional functions	Ref.
W ⁶⁺	TBP	CpG	114.0 ± 6.7 nm	650 nm	Immunotherapy	139
Fe ³⁺	TCPP	Fe ₂ O ₃ , red blood cell membrane, AS1411	110–140 nm, depending on the reaction time	660 nm	Targeting, Fenton reaction	140
Fe ³⁺	TCPP	Bovine serum albumin, sulfonamide	160 nm	660 nm	PTT, MRI	141
Zr ⁴⁺	TCPP	Gold nanorod, camptothecin	53.8 ± 2.1 nm in length and 25.2 ± 1.7 nm in width	808 nm PTT, 660 nm PDT	PTT, drug loading, fluorescence imaging	142
Zr ⁴⁺	TCPP	CuS NPs, folic acid, ICG, PAH	112 nm for PCN-224	650 nm	PTT, fluorescence imaging, photothermal imaging	143
Cu ²⁺	TCPP	—	330 nm in size and 5.1 ± 0.3 nm in thickness	808 nm PTT, 660 nm PDT	PTT, MRI, infrared thermal imaging	144
Zr ⁴⁺	FeTCPP	siRNA	210 nm in length	635 nm	Low-temperature PTT, photothermal imaging, photoacoustic imaging, computed tomography imaging	145
Zr ⁴⁺	CuTCPP	—	100 nm	660 nm	PTT	146

acid can increase the delivery efficiency of PCN-224 due to the higher cellular uptake (Fig. 5h). After folic acid modification, the PDT efficacy reached as high as 90% (Fig. 5i). Since then, PCN-224 has been widely applied as a carrier to combine PDT and other functions, which will be further discussed in Section 3.3.

Although TCPP is extensively applied as a MOF ligand, porphyrin derivatives such as H₂DBP, H₂DBC and H₄TBC reported by Lin's group also showed high ROS generation and therapeutic efficacy.^{47,55,97} Expanding the category of porphyrin-based ligands can be a promising direction for developing MOF-based PDT. Zeng *et al.* coordinated the tetrabenzoporphyrin (TBP) ligand with Zr₆ clusters, which was named TBP-nMOF (Fig. 5j).¹⁰⁷ Since benzoporphyrin had a larger π conjugation than porphyrin, the TBP-nMOF exhibited a 50 nm-red-shifted lowest-energy Q band and a 100 nm-red-shifted lowest-energy emission as compared to other porphyrin MOFs (Fig. 5k). The coordination with Zr₆ clusters also shortened the fluorescence lifetime of TBP from 3.16 ns to 2.12 ns, due to enhanced intersystem crossing (Fig. 5l). Therefore, the ¹O₂ yield of TBP-nMOF was about 8 times higher (Fig. 5m). Zhang and coworkers fabricated DBBC-UiO, which was composed of Hf⁴⁺ nodes and 5,15-di(*p*-benzoato)bacteriochlorin (H₂DBBC) ligands.¹⁰⁸ The DBBC ligand can generate ¹O₂ in an O₂-sufficient environment and also produce •O₂[−] in hypoxia through the Type I mechanism. In the presence of superoxide dismutase, •O₂[−] was partially converted into the highly cytotoxic •OH through the H₂O₂ disproportionation reaction. DBBC-UiO showed high cancer cell inhibition in both normoxia and hypoxia environments, proving that this MOF was O₂-independent, which is desirable in tumor suppression.

The tetrapyrrole structure in porphyrin has a strong tendency to coordinate metals at the central site, forming metalloporphyrin, which is denoted as MTCPP (M is the central-coordinated metal) in this review.¹⁴⁷ Metalloporphyrin ligands endow the MOF with more metal sites for synergistic functions. For example, Li *et al.* reported a MOF that can monitor O₂ fluctuation, which is composed of PtTCPP and Zr₆ clusters, and coated with a cancer cell membrane (referred to as mPPT) (Fig. 6a).¹²⁴ The cancer cell membrane gave the mPPT immune escape ability, which protected

mPPT from immune clearance due to the antigenic profile on the membrane. In an O₂-sufficient environment, the triplet phosphorescence of mPPT was quenched because the triplet PSs mainly reacted with ³O₂ to produce ¹O₂. In an O₂-deficient environment, the PDT effect was limited, giving rise to a higher phosphorescence emission (Fig. 6b). The authors manifested that mPPT in a 1% O₂ atmosphere had a 6.22-fold higher phosphorescence intensity than in 100% O₂, and can give a quick response to O₂ fluctuation (Fig. 6c and d). This property can be used to detect O₂ *in vivo* and realize phosphorescence imaging guidance. Another research group fabricated PCN-222 with Mn-porphyrin as ligands.¹²⁵ Mn chelation rendered PCN-222 with magnetic resonance imaging (MRI) ability due to the high spin quantum number and long electronic relaxation time. The longitudinal relaxivity was ~35.3 mM^{−1} s^{−1} (1.0 T). Moreover, the Mn-porphyrin can also decompose the surrounding H₂O₂, thus providing O₂ for ¹O₂ generation.

The most-reported Hf- and Zr-based porphyrin-MOF is stable, and can be directly applied as a PS. Other metal nodes such as Cu, Mn and Fe can quench the ROS generation of PS ligands, resulting in much less ROS generation than free PS ligands. These metals can respond to different stimuli in the microenvironment, which means that the MOF structure will decompose after the reaction, releasing active metal ions, PS ligands and drugs. The photodynamic activity of ligands is then restored. Hence, this kind of MOF can be used for stimulus-triggered PDT. Besides, Mn¹⁰⁵ and Gd¹³⁰ nodes can also endow MOF with imaging ability. Ma *et al.* reported Cu-MOF with ZnTCPP as ligands.¹²⁸ Cu²⁺ can respond to H₂S, which is of high content in human colon adenocarcinoma cells, and Cu²⁺ can also completely quench the fluorescence of TCPP ligands. When Cu²⁺ encountered H₂S, the Cu nodes separated from the MOF structure, restoring the photosensitivity of TCPP. Wan and coworkers fabricated a Mn(III)-TCPP MOF (Fig. 6e).¹⁰⁵ The fluorescence and ROS generation of TCPP were temporarily blocked by Mn nodes. Glutathione (GSH) is an antioxidative ROS scavenger in tumor cells, which can weaken the potency of PDT. Mn(III)-TCPP can react with intracellular GSH, thus

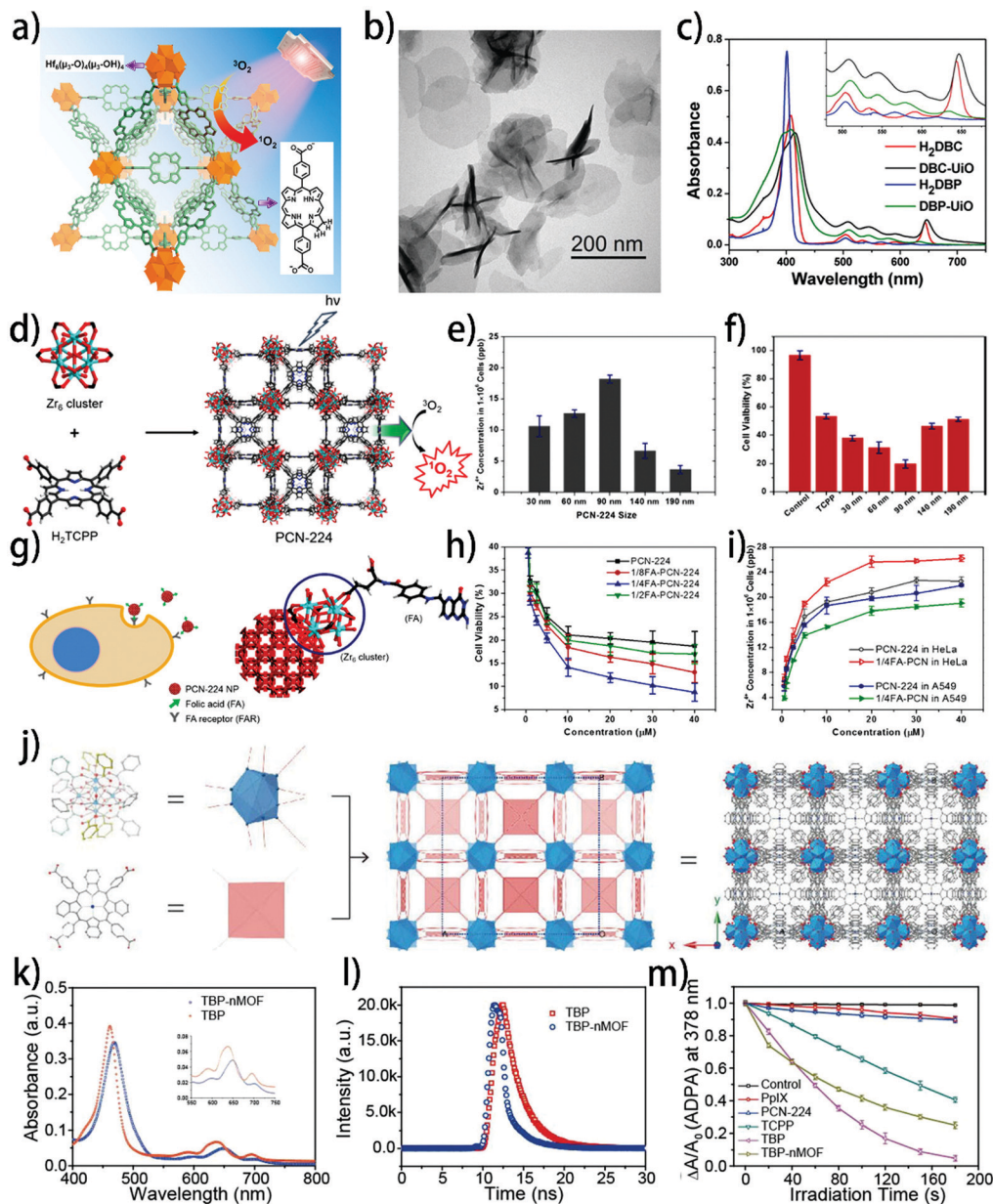


Fig. 5 (a) Schematic description of $^1\text{O}_2$ generation by DBC-UiO under LED light irradiation. (b) TEM image of DBC-UiO showing nanoplate morphology. (c) UV-vis absorption spectra of H_2DBC , DBC-UiO, H_2DBP and DBP-UiO in DMF or 0.67 mM PBS. Reprinted with permission from ref. 47. Copyright 2015 American Chemical Society. (d) 3D nanoporous structure of PCN-224 composed of a Zr_6 cluster and H_2TCPP ligand. (e) Size-dependent cellular uptake of PCN-224 after 24 h of incubation with HeLa cells. (f) PDT efficacy of different sized PCN-224 and free TCPP molecules. (g) Schematic illustration of FA functionalized PCN-224 and the proposed internalization. (h) ICP analysis of the cellular uptake of unfunctionalized and FA functionalized 90 nm-PCN-224 at various concentrations in HeLa and A549 cells. Incubation time = 24 h. (i) *In vitro* PDT efficacy of FA functionalized (FA equivalent of 0, 1/8, 1/4, 1/2) 90 nm-PCN-224 at various concentrations in HeLa cells. Irradiation at 420 nm for 30 min for PDT. Reprinted with permission from ref. 58. Copyright 2016 American Chemical Society. (j) Schematic representation of TBP-MOF, in which the 10-connected Zr_6 cluster and TBP ligand are simplified as a blue node and red plane, respectively. (k) UV-vis spectra of TBP and TBP-nMOF. Inset shows expanded views of the Q-band regions. (l) Time-resolved fluorescence decay traces of TBP and TBP-nMOF. (m) $^1\text{O}_2$ generation by PpIX, TCPP, PCN-224, TBP, and TBP-nMOF with a 660 nm LED irradiation (30 mW cm^{-2}). Reprinted with permission from ref. 107. Copyright 2018 American Chemical Society.

releasing Mn(II) , free TCPP and glutathione disulfide (GSSG) by GSH oxidation. Hence, the fluorescence and ROS generation of TCPP was restored, and the PDT efficacy was protected as well due to GSH depletion. Mn nodes can also be used for MRI. Wan *et al.* reported an Fe-TCPP MOF that was loaded with the anticancer drug dihydroartemisinin (DHA).¹³⁶ In their work,

Fe-TCPP was further covered with a CaCO_3 mineralized layer that could prevent drug leakage and TCPP toxicity during transportation. The ROS generation of TCPP was temporarily quenched by Fe nodes. In an acidic environment such as the tumor area, CaCO_3 decomposes and releases Ca^{2+} . In a high GSH environment, the exposed Fe^{3+} on Fe-TCPP is reduced to

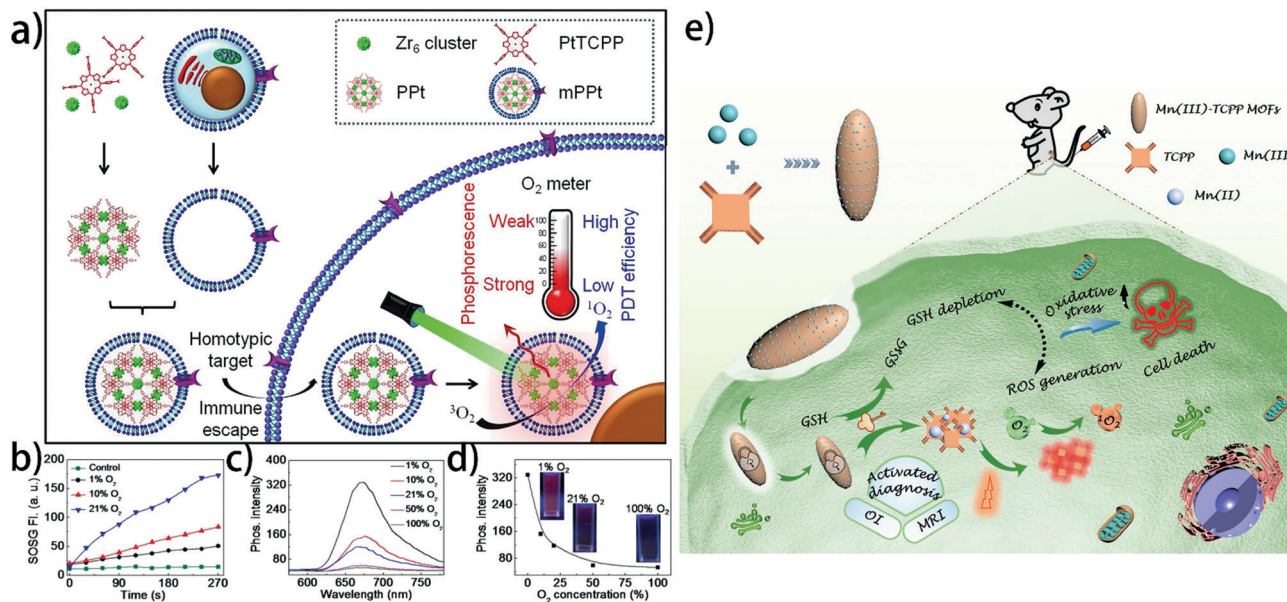


Fig. 6 (a) Preparation processes and the proposed mechanism of mPPt for cancer-targeted and phosphorescence image-guided PDT. (b) ¹O₂ generation of mPPt at various O₂ pressures. (c) Phosphorescence spectra of mPPt (5 μg mL⁻¹) under various O₂ levels. (d) The O₂ concentration-related phosphorescence changes in mPPt (5 μg mL⁻¹). Inserted: The macroscopic images of mPPt (50 μg mL⁻¹) under the irradiation of hand-held UV lamp. Reprinted with permission from ref. 124. Copyright 2018 Elsevier. (e) Schematic illustration of an endocytosis Mn(III)-sealed MOF nanosystem for MRI- and optical imaging-guided PDT by controlled ROS generation and GSH depletion after being unlocked by overexpressed GSH in tumor cells. Reprinted with permission from ref. 105. Copyright 2019 American Chemical Society.

Fe²⁺, releasing free TCPP. Fe²⁺ could activate DHA, which then generates free radicals for cancer cell killing. Moreover, as DHA could affect the Ca²⁺ pump ATPase, the Ca²⁺ from the CaCO₃ coating could enter cancer cells, leading to the increase of intracellular Ca²⁺ concentration, which could induce oncosis-like cell death. Free TCPP also restored its ROS generation. This strategy combines pH- and GSH-controlled drug activation, PDT activation and oncosis-like therapy at the same time.

3.1.2 Other photodynamic building blocks. In terms of photodynamic metal nodes, Cai and coworkers fabricated the CuTz-1 MOF composed of Cu(I) nodes and 3,5-diphenyl-1,2,4-triazole ligands, which was loaded with O₂.¹⁴⁸ F127 was coated on CuTz-1 to increase its biocompatibility. The Cu(I) and Cu(II) mixed-valence structure of MOF could induce the intervalence charge-transfer effect and d-d transition, which resulted in its absorption in the visible and NIR region. Under 808 nm NIR light irradiation, this MOF went through Type I PDT, producing •OH and •O₂⁻ through a Fenton-like reaction. Besides, the Cu(I) could react with GSH, thus reducing the ROS loss. The loaded O₂ can also help to alleviate the hypoxia in the tumor environment.

Partially substituting the normal ligands of MOF with PS agents is also a feasible way to endow MOFs with photodynamic properties. This strategy leads to mixed-ligand MOFs, and even more than one PSs can be incorporated into the non-intrinsic MOF structure through the ligand-exchange process. Wang *et al.* substituted the 2-hydroxyterephthalic acid (H₂BDC) ligand of UiO-66 with I2-BDP (carboxyl-functionalized diiodo-substituted BODIPYs) by solvent-assisted ligand exchange.¹⁴⁹ The final product was called UiO-PDT. According to inductively

coupled plasma-mass spectrometer (ICP-MS) tests, around 12.5% of BDC had been replaced, and the final content of I2-BDP was 31.4 wt%. After the ligand exchange, UiO-PDT showed an absorption peak at 524 nm, which was slightly shifted as compared to I2-BDP (528 nm). UiO-PDT presented moderate but lower ¹O₂ generation than that of I2-BDP because of the heterogeneous structure of the former. In another study, Zhao and coworkers used TCPP to substitute for the ligand of NU-1000, which was referred to as NT.¹⁵⁰ NU-1000 was composed of Zr clusters and 1,3,6,8-tetrakis(*p*-benzoic acid)pyrene (H₄TBAPy) ligand, which featured large pore sizes. About 20% of the original ligand was substituted with TCPP. After the replacement, the maximum absorption was red-shifted to 571 nm as compared to H₄TBAPy (410 nm), due to the narrowed energy gap between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). Hence, the ROS generation of NT was triggered under 650 nm light irradiation in their work. Park *et al.* *in situ* inserted BCDTE (1,2-bis(5-(4-carboxyphenyl)-2-methylthien-3-yl)cyclopent-1-ene) and TCPP into UiO-66 by a thermodynamic-controlled synthesis process to fabricate a photochromic switch of ¹O₂ generation (Fig. 7a).¹⁵¹ The photoisomerization of BCDTE could switch TCPP from the ¹O₂ quenching state to the activated state. Under UV light irradiation, BCDTE had two isomers, namely, the open form and the closed form, which had different absorptions (Fig. 7b and c). When BCDTE was in the open form, TCPP in the triplet state (T₁) could react with ³O₂ to produce ¹O₂, while the BCDTE in the closed form had another energy transfer pathway with TCPP that could hinder the reaction between TCPP and ³O₂, thus

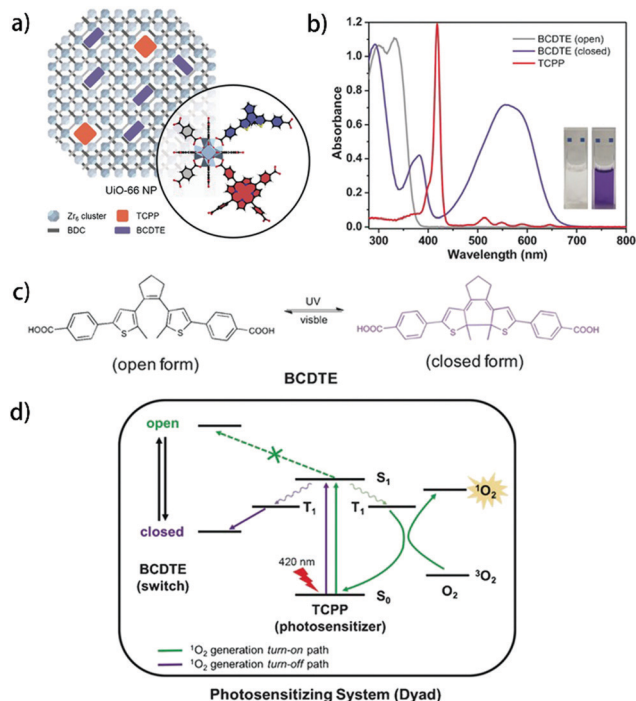


Fig. 7 (a) Defective structure of UiO-66 with inserted TCPP and BCDTE, and a proposed binding scheme of TCPP and BCDTE to a Zr₆ cluster. (b) UV/vis absorption spectra of BCDTE (30 μM) and TCPP (2 μM). Inset: Photographs of solutions of BCDTE open (left) and closed (right) isomers. (c) Chemical structures and photoisomerization of BCDTE. (d) Proposed scheme of ¹O₂ control via competitive energy-transfer pathways upon photoisomerization. Reprinted with permission from ref. 151. Copyright 2016 Wiley.

quenching ¹O₂ generation (Fig. 7d). More importantly, the ratio of BCDTE to TCPP can be tuned. When the ratio of BCDTE to TCPP was the highest, the quenching ability was the best as well. This strategy was proved to be effective in the cell model, which could serve as a protective system in PS delivery.

3.2 Modifications via photodynamic agents

Fabricating composites using PSs and non-intrinsic photodynamic MOF is another way to make MOF-based PDT agents. The reported structures include PSs encapsulation, surface attachment and core-shell structure. In this strategy, PSs are not limited to porphyrin and its derivatives. The choices of MOF are also more varied, such as ZIF-8, UiO-66 and MIL-101, *etc.* (ZIF, UiO, MIL refer to the zeolitic imidazolate framework, Universitetet i Oslo, Materials Institute Lavoisier, respectively), which are frequently used in biomedical applications. Recent advances are summarized in Table 3, and the chemical structures of typical organic linkers and encapsulated PSs are summarized in Fig. 8.^{148,151–153,155,157,158,160,161,164,179}

3.2.1 PS encapsulation. PS encapsulation is the most widely used strategy to cause non-intrinsic MOF photodynamic activity. MOF here serves as the carrier of PSs, creating a “ship in a bottle” structure. The loaded PSs should have certain functional groups, such as –COOH and –SO₃H, or have the opposite charge to the MOF.^{66,188} The loading can be achieved

through two strategies: loading during MOF synthesis and post-synthetic loading.¹⁰⁹ The advantages of PS encapsulation include the following: (i) preventing PS aggregation; (ii) blocking the contact of PSs and O₂, thus the ROS generation of PSs can be inhibited before reaching the tumor area; (iii) preventing pre-leakage of PSs during transportation; (iv) improving the tumor specificity of PSs, *etc.*^{50,157,168} In 2015, Zhang *et al.* encapsulated tetrakis(1-methylpyridinium-4-yl)porphyrin (TMPyP) in a Zn-based MOF as a PS with a loading efficiency of 32.8%.¹⁵² The final product was named PS@MOF. With methylene blue as a standard agent, the ¹O₂ yield of PS@MOF was 0.61 ± 0.05, which was higher than that of TMPyP (0.10 ± 0.02). The unshifted fluorescence emission spectra and blue-shifted phosphorescence emission spectra of PS@MOF indicated that compared to free TMPyP, PS@MOF showed the same energy gap between the higher-energy singlet excited state (S₁) and the ground state (S₀), and widened the energy gap between the triplet state (T₁) and the S₀ energy level. Hence, the energy gap between S₁ and T₁ was narrowed, which resulted in enhanced intersystem crossing. The phosphorescence quantum yield of encapsulated TMPyP was ~34%, which means that most of the triplet state PS was used for reacting with ³O₂, leading to more ¹O₂ generation. Furthermore, compared to free TMPyP, the PS@MOF composite showed much less cytotoxicity.

More and more PSs have been reported to be encapsulated in MOFs for PDT, such as chlorine e6 (Ce6), zinc phthalocyanines (ZnPc), methylene blue and rose bengal, as shown in Table 3. Taking Ce6 as an example, which is an efficient PS but suffers from aggregation-caused quenching,⁵⁰ Wang and coworkers fabricated MOF-199 (composed of Cu nodes and 1,3,5-benzenetricarboxylic acid (H₃BTC) ligands) and loaded Ce6 in the MOF with a loading efficiency of 49 wt%.¹⁶⁸ The Ce6 was in an inert state in MOF-199. After the internalization of cells, Cu(II) nodes of MOF-199 reacted with GSH, leading to the collapse of the MOF structure. Hence, the loaded Ce6 was released and contacted the intracellular O₂ to generate ROS. This GSH-controlled PS release strategy can minimize ROS loss and scavenge intracellular GSH at the same time. Xie *et al.* fabricated a O₂-Cu/ZIF-8@Ce6/ZIF-8@F127 hybrid MOF (Fig. 9a),¹⁷¹ in which the Cu²⁺-doped ZIF-8 was encapsulated by Ce6/ZIF-8@F127. The former was used as an O₂ carrier and GSH scavenger, while the latter was employed for PDT. As a typical pH-responsive MOF, ZIF-8 will collapse in the mild acid environment of the tumor area, releasing O₂, Ce6 and Cu²⁺. Due to a sufficient O₂ supply, the PDT efficacy of Ce6 was enhanced. Moreover, Cu²⁺ could go through a Fenton-like reaction, thus reducing GSH content and the product Cu¹⁺ can further generate cytotoxic •OH for better PDT efficacy. Wang *et al.* encapsulated Ce6-functionalized DNAzyme into ZIF-8 to realize imaging-guided gene-photodynamic synergistic therapy (Fig. 9b).⁵¹ ZIF-8 can improve the cellular uptake of DNA through enhanced permeability and the retention effect. In the tumor area, ZIF-8 would degrade and release Zn²⁺, which served as the DNAzyme cofactor to trigger the RNA-hydrolytic ability of DNAzyme. The mRNA, human early growth response-1, acted as the substrate for gene therapy. After the treatment of

Table 3 Summary of MOFs modified by PSs in PDT. Particle size was measured by SEM, TEM or DLS

MOF	Metal nodes	Organic ligands	Photodynamic agents	PS loading	Materials for decoration	Particle size	Irradiation wavelength	Additional functionality	Ref.
—	Zn ²⁺	H ₃ BTC	TMPyP	32.8%	GPTS, Cy3-labelled caspase-3 peptide, H ₂ N-PEG-FA	—	660 nm	Targeting, fluorescence imaging	152
ZIF-8	Zn ²⁺	2-mIm	g-C ₃ N ₄	—	DOX	60 nm	Visible light	Drug loading, fluorescence imaging	153
ZIF-8	Zn ²⁺	2-mIm	AlPcS ₄	10.6%	Catalase, cancer cell membrane	110 nm	660 nm	O ₂ supply, targeting	154
MIL-101(Fe)	Fe ³⁺	H ₂ BDC	Ce6-peptide	32.3 mg g ⁻¹	camptothecin, COOH-PEG-FA	95 nm	660 nm	Fluorescence imaging	155
ZIF-8	Zn ²⁺	2-mIm	g-C ₃ N ₄	—	NaGdF ₄ :Yb, Tm@NaGdF ₄ , PEI, carbon dots	~150 nm	980 nm	Upconversion	156
ZIF-8	Zn ²⁺	2-mIm	Methylene blue	1.97%	NaYF ₄ :60%,2%Er, catalase	~450 nm for ZIF-8	980 nm	Upconversion, O ₂ supply	157
UiO-66	Zr ⁴⁺	H ₂ BDC	ZnPc	—	Erlotinib	100 nm for UiO-66	670 nm	Targeting, drug loading	158
MIL-88	Fe ³⁺	H ₂ BDC	Methylene blue	4.3 wt%	DOX	152 nm	635 nm	Drug loading	159
—	Hf ⁴⁺	BATA	Ce6	80% (w/w)	DOX, PEG	~90 nm	660 nm	Drug loading, CT imaging	160
ZIF-90	Zn ²⁺	IcaH	2I-BodipyPhNO ₂	25.4 ± 1.0 wt%	—	<80 nm	540 nm	—	161
ZIF-8	Zn ²⁺	2-mIm	ZnPc-COOH	0.296 g g ⁻¹	CTAB	83.5 nm	670 nm	Drug loading	162
ZIF-8	Zn ²⁺	2-mIm	ZnPc	5.9 µg mg ⁻¹	—	255 nm (in PBS for 72 h)	650 nm	—	163
MIL-100	Fe ³⁺	H ₃ BTC	Ce6, TPEDC, TPETCF	49, 42 and 58 wt%	F127	340 nm (average)	White light	O ₂ supply	50
ZIF-8	Zn ²⁺	2-mIm	Rose bengal	35.3 µg mg ⁻¹	SiO ₂	93.8 ± 17.3 nm	532 nm	—	164
ZIF-90	Zn ²⁺	IcaH	Rose bengal	5.6%	SiO ₂ , NaYF ₄ :Yb/Er@NaYbF ₄ :Nd@NaGdF ₄ , DOX, PEGFA	140 nm	808 nm	Drug loading, upconversion, MRI, targeting	165
UiO-66	Zr ⁴⁺	H ₂ BDC	Photochlor	0.38%	AQ4N, PEG, <i>p</i> -azidomethylbenzoic acid	95 nm	671 nm	Drug loading, fluorescence imaging	166
ZIF-8	Zn ²⁺	2-mIm	Ce6 modified DNAzyme	10 wt%	—	167 nm	660 nm	Gene therapy	51
ZIF-8	Zn ²⁺	2-mIm	Ce6	28.3 wt%	Bovine serum albumin-MnO ₂ NPs	100 nm for Ce6@ZIF-8	650 nm	O ₂ supply, MRI	167
MOF-199	Cu ²⁺	H ₃ BTC	TPAAQ, Ce6	58 wt% and 49 wt%	F-127	150 nm	White light	GSH depletion	168
MOF-199	Cu ²⁺	H ₃ BTC	PEG conjugated TBD	—	Pt(IV) NPs	160 nm	White light	GSH depletion, drug loading, O ₂ supply	169
ZIF-8	Zn ²⁺	2-mIm	Ce6	67.4%	PVP, Au NPs	106 ± 7.3 nm	660 nm	O ₂ supply	170
ZIF-8	Zn ²⁺ , Cu ²⁺	2-mIm	Ce6	3.34 wt%	F127	95 nm	650 nm	Drug loading, oxygen delivery, GSH depletion	171
ZIF-8	Zn ²⁺	2-mIm	Ce6	—	Si-Gd NPs, DOX, HOOC-PDMAEMA-SH, PEG-FA	70 nm	630 nm	Drug loading, fluorescence imaging, MRI	172
MIL-101	Fe ³⁺	H ₂ BDC	Methylene blue	54.5%	DHA, PLA, PEG	120 nm	650 nm	MRI, drug loading, O ₂ supply	173
ZIF-8	Zn ²⁺	2-mIm	Methylene blue	5%	Catalase, PDA NPs	—	660 nm	PTT, O ₂ supply	174
ZIF-8	Zn ²⁺	2-mIm	TAPP	—	Catalase, GOx, NaYF ₄ :Yb,Tm	—	980 nm	O ₂ supply, starvation therapy	175
—	Fe ³⁺	Tannic acid	Self-assembled Ce6 and rapamycin core	13.89% for Ce6	Catalase	—	—	O ₂ supply	176
ZIF-8	Zn ²⁺	2-mIm	Ammonium methylbenzene blue	From 1.5 ± 0.2 wt% to 99.5 ± 6.0 wt%	Polyacrylic acid, AgNPs, vancomycin/NH ₂ -PEG	150 nm	650 nm	Bacteria killing, biofilm inhibition	177
ZIF-8	Zn ²⁺	2-mIm	Ce6	76.80%	HA	150 nm	660 nm	—	178
Bio-MOF-1	Zn ²⁺	H ₂ BPDC	[Ru(bpy) ₃] ²⁺ , [Ru(phen) ₃] ²⁺ , [Ru(phen) ₂ hipp] ²⁺	—	—	—	490 and 800 nm	Two-photon activation PDT	179
UiO-67	Zn ²⁺	H ₂ BPDC	[Ru(bpy) ₃] ²⁺	13.85 wt%	—	~92 nm	White light	Two-photon activation PDT	180

Table 3 (continued)

MOF	Metal nodes	Organic ligands	Photodynamic agents	PS loading	Materials for decoration	Particle size	Irradiation wavelength	Additional functionality	Ref.
ZIF-8	Zn ²⁺	2-mIm	Au ₂₅ (Capt) ¹⁸⁻	—	Fe ₃ O ₄	100 nm	808 nm	PTT	181
PB	Fe ³⁺ , Fe ²⁺	—CN ⁻	AlPc	—	PDA, bovine serum albumin	~108 nm	660 nm	PTT, MRI, photoacoustic imaging, fluorescence imaging	182
UiO-66	Zr ⁴⁺	H ₂ BDC	Ce6	5.95%	Pt, Au shell	60 nm without Au shell	808 nm, PTT, 670 nm PDT	PTT	183
UiO-66	Zr ⁴⁺	H ₂ BDC	ICG	—	Red blood cell membrane	64.7 nm	808 nm	PTT, immune escape	184
MIL-53	Fe ³⁺	H ₂ BDC	Cypate	—	PEG, transferrin	250 nm	785 nm	PTT, targeting	185
MIL-101	Fe ³⁺	H ₂ BDC	Black phosphorus	15.8 wt%	HOOC-PEG-folic acid	140 nm	808 nm, PTT, 660 nm PDT	PTT, targeting, O ₂ supply	186
UiO-68	Zr ⁴⁺	TPDC	Protoporphyrin IX	29.1 wt%	—	~120 nm (diameter), ~20 nm (thickness)	635 nm	PTT	187

DNAzyme@ZIF-8, the substrate RNA showed down-regulated expression in MCF-7 cells (Fig. 9c). Ce6 provided the MOF

imaging guidance and ROS generation. Under light irradiation, the early apoptotic ratio increased to 44.9%, which was much higher than individual PDT (33.6%) and gene therapy (19.85%).

3.2.2 Surface attachment. Besides encapsulation, PSs can also be attached to the exterior of the MOF. There are two types of surface attachment: covalent and coordinative modification, both of which are post-synthetic modifications.^{189–191} In the former strategy, the MOF should be modified with certain functional groups (e.g. —NH₂ and —COOH), which can bind the targeted agents on the surface of MOF.^{190,192} The attachment of PSs is irreversible, which can prevent the pre-leakage of agents.^{109,193} The attached functional agents should maintain their properties while on the MOF, or be released in certain environments due to the cleavage of the linkage with MOF, and then restore their function.¹⁰⁹ The latter strategy refers to binding targeted agents to the unsaturated metal sites or linkers of MOF, such as metal nodes that coordinate with solvent molecules and linkers containing functional groups that do not participate in the MOF formation.^{189,190} This strategy is more straightforward than the former and usually does not affect the topology of the MOF.¹⁸⁹ Although these two strategies have been widely applied in MOF modification, the reported surface-attached PSs on the MOF are few. Here are some examples.

Liu and coworkers firstly modified MIL-101(Fe) MOF with —NH₂ (referred to as MOF-NH₂). The amino groups were used as an anchor to attach the Ce6-labelled cathepsin B (CaB) substrate peptide.¹⁵⁵ The fluorescence of Ce6 was inhibited because the electron of the excited Ce6 was transferred to MOF-NH₂. CaB is a lysosomal cysteine endopeptidase that exhibits higher expression in cancer cells. In this therapeutic system, CaB acted as an intracellular target to trigger PDT. When in contact with CaB, the substrate peptide was cut off, then the photodynamic activity of Ce6 was restored. Moreover, MIL-101(Fe) was loaded with the anticancer drug camptothecin. This drug-release combined PDT

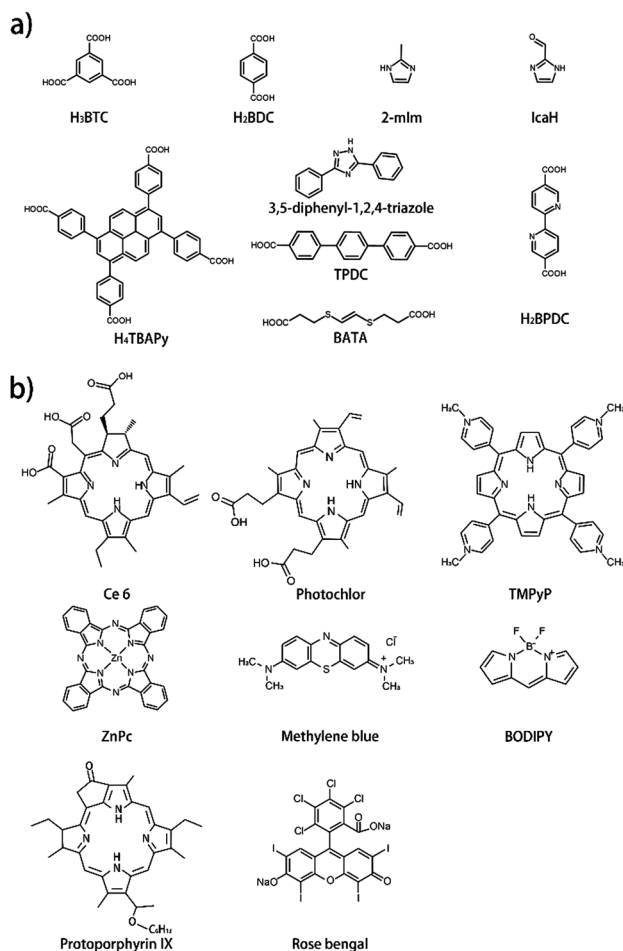


Fig. 8 Chemical structures of (a) MOF ligands and (b) PSs that can be used for MOF modification.

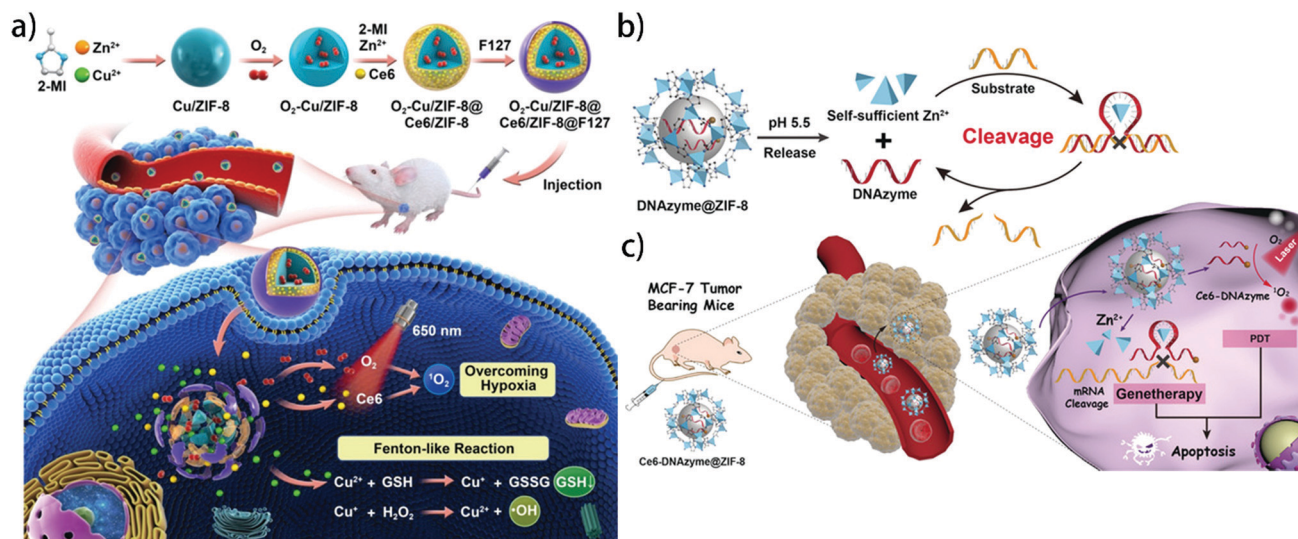


Fig. 9 (a) Schematic illustration of the fabrication process of the tumor microenvironment-responsive O_2 -Cu/ZIF-8@Ce6/ZIF-8@F127 nanoplateform for enhanced PDT and chemotherapy through GSH depletion and O_2 replenishment. Reprinted with permission from ref. 171. Copyright 2019 American Chemical Society. (b) The pH-triggered release of DNAzyme and the corresponding Zn^{2+} -ion cofactors for efficient gene silencing therapy, and an all-in-one DNAzyme@ZIF-8 nanosystem for fluorescence imaging-guided combined gene/photodynamic therapy. Reprinted with permission from ref. 51. Copyright 2019 Wiley.

can reduce drug resistance and PDT's dependence on O_2 . Nian *et al.* attached the carboxyl substituted ZnPC and anticancer drug erlotinib on N_3 -UiO-66- NH_2 by covalent modification.¹⁵⁸ ZnPC was connected to $-N_3$ via amidation and erlotinib was connected to $-NH_2$ via click chemistry. The final product, E-UiO-66-Pc, had higher ROS generation than ZnPC alone. This strategy provides accessibility for functional group-guided PS and drug surface attachment.

3.2.3 Core-shell structure. The core-shell structure refers to growing the MOF shell on the PS. The core-shell structure can combine the properties of the core and shell material while keeping the stability and activity of the inner PS core by the MOF shell protection.¹⁴² For example, Chen and coworkers synthesized a ZIF-8 shell on the $g-C_3N_4$ core, and loaded doxorubicin (DOX) in ZIF-8.¹⁵³ Under visible light irradiation, the $g-C_3N_4$ @ZIF-8 nanocomposite showed similar 1O_2 generation to that of $g-C_3N_4$, indicating that the MOF shell did not influence the properties of the $g-C_3N_4$ shell, but facilitated the diffusion of 1O_2 through the porous structure of the MOF. Moreover, the MOF shell was loaded with DOX. The drug release was responsive to an acid environment, which added more potency to the therapy. However, $g-C_3N_4$ was excited under visible light, which has limited penetration depth. To solve this problem, Yang *et al.* decorated $g-C_3N_4$ with upconversion nanoparticles and carbon dots (CDs), which were protected by the ZIF-8 shell.¹⁵⁶ Since the absorption of $g-C_3N_4$ in the visible light region was stronger than that in NIR light region, when irradiated by a 980 nm laser, upconversion nanoparticles converted NIR light to UV-vis light, thus triggering $g-C_3N_4$ to produce ROS. Simultaneously, CDs converted the UV-vis light generated from upconversion nanoparticles into blue visible light, which once again triggered $g-C_3N_4$ for a second ROS

generation. Therefore, the ROS generation of the final product was much higher than that of free $g-C_3N_4$. It was noted that this dual-model PDT system was protected by the ZIF-8 shell. As a result, the composite showed little change in particle size, even when immersed in solution for 5 days. Moreover, the outside shell of ZIF-8 also provided space to store O_2 and H_2O as the raw material for ROS production.

3.3 Optimizing the efficacy of photodynamic therapy

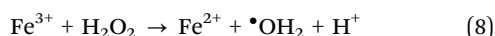
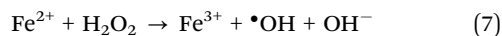
We have discussed how to synthesize a MOF-based PS based on MOF construction and PS agent selection. To successfully apply these PSs in clinical trials with potent therapeutic efficacy, the therapeutic system is not limited to ROS generation. On the other hand, is hard to cure advanced cancer with PDT alone without recurrence.¹⁹⁴ Hence, more elaborate designs of MOF-based PSs and more complex combined systems have been developed by researchers, which will be discussed in this section.

3.3.1 Utilizing the properties of the therapeutic environment.

PDT is usually applied to the tumor or bacterial infected area. Hypoxia is one typical feature of the tumor microenvironment and biofilms,^{110,195} however, excessive acidity, highly expressed GSH levels and the presence of adenosine-5'-triphosphate (ATP) also exist.¹⁹⁶ It is known that PDT is strongly dependent on oxygen concentration.^{2,67} In an oxygen insufficient area, PDT will have much less efficacy. GSH is an important antioxidant in tumor cells, which can protect cells from the attack of free radicals including ROS. Thus, the PDT efficacy will also be affected.^{197,198} One straightforward way to solve these problems is by increasing the amount of PS, however, a PS overdose could arouse serious side effects.¹²⁸ As such, researchers have made efforts to design

specific structures of MOFs or make targeted modifications to achieve self-oxygen generation and GSH depletion.

As mentioned in Sections 3.1 and 3.2, Mn(III)^{105} and $\text{Cu(II)}^{128,169}$ can reduce GSH to oxidized GSH (GSSG); Fe(II)^{57} , Mn(II)^{137} , $\text{Fe(III)}^{50,173}$ and $\text{Cu(I)}^{148,199}$ can react with both intra- and extra-cellular H_2O_2 through the Fenton or Fenton-like action to produce O_2 . Taking Fe^{3+} and Fe^{2+} as examples, the related Fenton reaction (eqn (7)) and Fenton-like reaction (eqn (8)) processes are presented below:²⁰⁰



The MOF mentioned above is H_2O_2 or GSH-responsive, which means that the material will decompose after reaching the therapeutic area. On the other hand, modifications based on these elements and other catalytical agents have also been reported, such as MnO_2 NPs and coating,^{121,122,132,201} Pt NPs,^{48,63} catalase,^{154,157,175} etc., which have similar functions. For instance, Liu and coworkers. Synthesized a MnO_2 shell on the Zr-TCPP core by mixing the MOF solution with KMnO_4 solution under vigorous stirring.²⁰¹ The MnO_2 coating quenched the ROS generation and the fluorescence of the inner core due to the fluorescence resonance energy transfer. When in contact with GSH, the MnO_2 shell was reduced to Mn^{2+} , resulting in GSH depletion and GSSG generation. Therefore, the properties of Zr-TCPP were recovered. As the consumption of MnO_2 shell was fast, it was unable to offer consistent catalyzing ability. In this regard, Yin *et al.* fabricated a core-shell structure composed of a MnFe_2O_4 core and Zr-TCPP shell, which was termed as $\text{MnFe}_2\text{O}_4@\text{MOF}$ (Fig. 10a).⁵⁷ MnFe_2O_4 features both catalase-like and GSH peroxidase-like activities. Both Fe^{2+} and Mn^{2+} firstly went through the Fenton reaction to generate Fe^{3+} and Mn^{4+} , which were further reduced by GSH and H_2O_2 to produce GSSG and O_2 , creating a reaction cycle. Therefore, the total content of Fe^{3+} and Mn^{2+} in

MnFe_2O_4 was not consumed, which leads to its continuous catalytic ability. In hypoxia, the $^1\text{O}_2$ generation of $\text{MnFe}_2\text{O}_4@\text{MOF}$ was improved due to the O_2 supply. In the presence of GSH, after 3 min of irradiation, only 17.6% of $^1\text{O}_2$ generated by $\text{MnFe}_2\text{O}_4@\text{MOF}$ was depleted by GSH, while the $^1\text{O}_2$ depletion percentage for bare Zr-TCPP was 57.4%. The MnFe_2O_4 core can also be used for MRI. Recently, Wang and coworkers annealed $\text{Mn}_3[\text{Co}(\text{CN})_6]_2$ MOF to fabricate the mesoporous $\text{Mn}_{1.8}\text{Co}_{1.2}\text{O}_4$ nanoenzyme, which was loaded with Ce6 as PS.²⁰² The nanoenzyme was coated with polydopamine (PDA) and polyethylene glycol (PEG) for better biocompatibility. The final product was named MCOPP-Ce6. The Mn atoms in the nanoenzyme served as active sites that can be used to coordinate with Ce6 molecules and decompose H_2O_2 by the Fenton reaction without self-consumption. Because of the highly porous structure of the MOF-derived nanoenzyme, the H_2O_2 decomposition rate of the composite was 0.0438 min^{-1} , which was much higher as compared to MnO_2 (0.0233 min^{-1}). The porosity of the nanoenzyme also assisted the O_2 diffusion to contact Ce6. Hence, MCOPP-Ce6 showed around 95.2% tumor cell killing in an O_2 insufficient environment.

Besides the above-mentioned strategies, Meng *et al.* found that the disulfide-containing ligand of MOF can also deplete GSH through the disulfide-thiol exchange reaction.²⁰³ In their work, the MOF (referred to as Ce6@RMOF) was composed of a disulfide-bearing imidazole ligand and Zn node. Ce6 was loaded in the MOF with a loading efficiency of $14.9 \pm 2.7\%$, which acted as the PS. Compared to the disulfide-free MOF, Ce6@RMOF showed obvious GSH depleting ability. The ligand was also responsive to low pH and $^1\text{O}_2$ due to ligand ionization. Therefore, Ce6 can be released in the presence of GSH, tumor acidity or under light irradiation. More importantly, the authors mentioned that glutathione peroxidase 4 can repair lipid peroxidation, which requires the participation of GSH. The GSH depletion (both by reacting with ROS and ligand) can inhibit this process, thus leading to cell death.

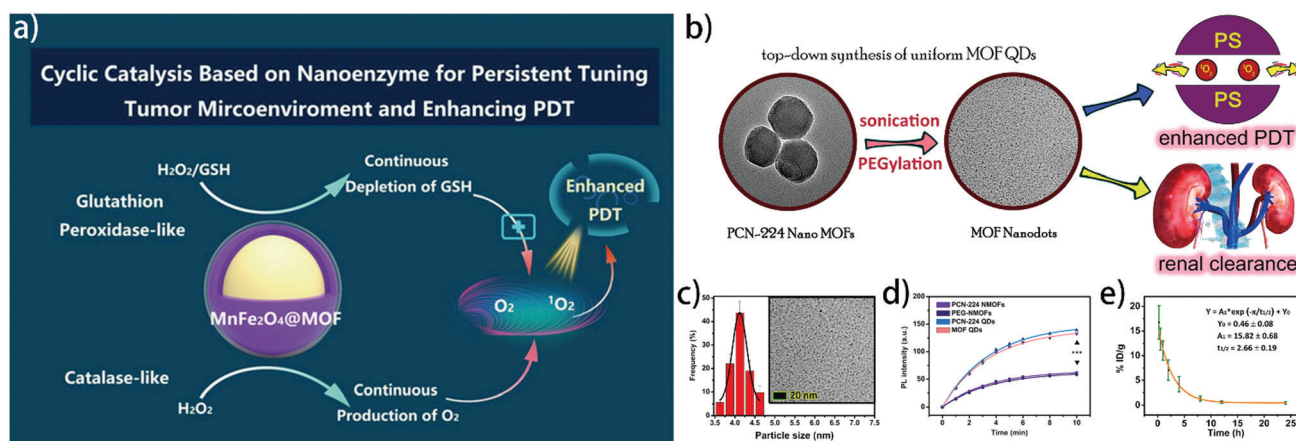


Fig. 10 (a) Schematic illustration of $\text{MnFe}_2\text{O}_4@\text{MOF}$ for persistently providing O_2 and consuming GSH to efficiently enhance PDT. Reprinted with permission from ref. 57. Copyright 2019 Wiley. (b) Schematic illustration of the rational design of MOF QDs and their usage as renal-clearable nanoagents for enhanced PDT of cancer. (c) Size distribution and TEM image of MOF QDs. (d) Light-induced ROS generation from PCN-224 NMOFs, PEG-NMOFs, PCN-224 QDs and MOF QDs. (e) Pharmacokinetics of MOF QDs from tumor-bearing mice after intravenous injection. Reprinted with permission from ref. 116. Copyright 2019 American Chemical Society.

This phenomenon is called ferroptosis, which is a newly-found contributor to PDT efficacy. Moreover, ferroptosis can be tuned by ligand content. Hence, their work inspired future researchers to consider the coexisting mechanism of PDT and find out more about the relation between PDT and the immune system.

3.3.2 Changing particle size. Particle size is another important factor that deals with ROS generation, cellular uptake, clearance from the body, and biofilm penetration. In general, due to the abnormal tumor vascularization, therapeutic NPs with a size of 5–200 nm can preferentially enter tumor tissue and be retained in it because of poor lymphatic clearance.^{204–206} This is called enhanced permeability and retention effect, which endows nano-sized therapeutic agents with a much higher drug delivery efficiency by passive targeting.²⁰⁷ When the particle size is smaller than 5 nm, the enhanced permeability and retention effect become negligible. This kind of smaller-sized particles can be cleared by the kidneys, which means they have fewer side effects, but their targeting ability is also poorer.^{206,208} On the other hand, larger-sized NPs (> 300 nm) will be recognized as “foreign substances” by the reticuloendothelial system organs such as the liver and spleen, and are retained in the body for a long time, thus increasing the risk of side effects.^{116,205} Hence, exploring the influence of particle size is necessary to simultaneously achieve higher therapeutic efficacy and fewer potential side effects.

Park *et al.* modulated the size of PCN-224 by analyzing the equilibrium of MOF formation.⁵⁸ Using benzoic acid as a competing agent that can form coordination bonds with the Zr₆ cluster, the size of PCN-224 increased with higher concentrations of benzoic acid. They also suggested that other factors included in the formation equation of PCN-224 such as TCPP concentration can also influence the diameter of the product. Their research shed light on controlling the particle size of MOF, which is beneficial for investigating the influence of particle size on PDT efficacy and cellular response. More recently, Wang and coworkers fabricated PCN-224 nanodots by sonication (PCN-224 QDs), which were further PEGylated and referred to as MOF QDs (Fig. 10b).¹¹⁶ The sonication process could attack the defect sites of PCN-224, thus resulting in smaller fragments with new defect sites, which were further attacked by ultrasound. The final MOF QDs had an average hydrodynamic diameter of 4.5 nm (Fig. 10c), which was smaller than the renal filtration threshold. Moreover, the PCN-224 QDs presented 2-fold ROS yield as compared to the nanosized PCN-224 (Fig. 10d), due to the better utilization of ¹O₂ from the interior PCN-224 nanodots. Animal tests manifested that the MOF QDs could be excreted from the mouse bodies mostly through renal clearance within 1 week, with a blood circulation half-life of 2.66 ± 0.19 h and high tumor accumulation (Fig. 10e). This strategy offered insight into the fabrication of ultrasmall MOF with high therapeutic efficacy and biosafety.

3.3.3 Combined therapy. Since it is hard to cure advanced cancers without recurrence with PDT alone, PDT can be combined with various therapies such as chemotherapy, gas therapy, starvation therapy and immunotherapy. Due to the synergistic effect between PDT and these therapies, the combined therapy usually shows a “1 + 1 > 2” effect. In this regard, MOFs can act as an

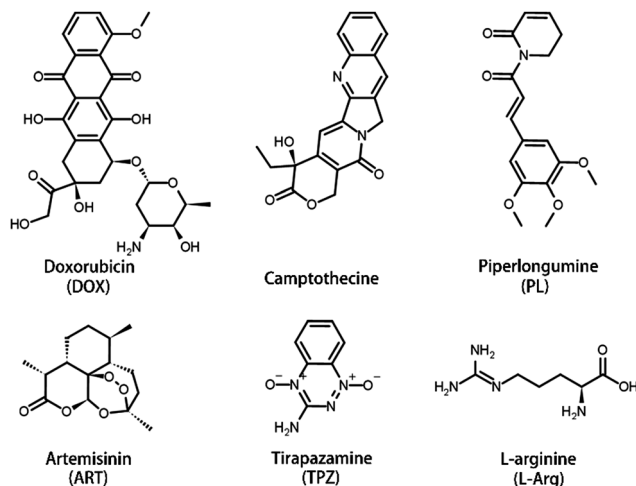


Fig. 11 Chemical structures of typical drugs and other modifying agents for MOF modification.

ideal platform for combined therapy through modification methods such as encapsulation, surface attachment, and core-shell structure, *etc.* Hence, in this part, we mainly focus on the therapeutic systems composed of MOF-based PDT and other therapies. The chemical structures of typical drugs and other modifying agents are presented in Fig. 11.^{61,111,112,115,142,266}

Chemotherapy functions by using anticancer drugs to stop or slow the growth of tumor cells.²⁰⁹ In MOF-based PDT therapeutic systems, drugs are usually loaded in photodynamic MOF. The loaded drugs are not limited to traditional anticancer drugs such as DOX and camptothecin (Fig. 11). Li *et al.* loaded hypoxia-activated tirapazamine (TPZ) in PCN-224, and coated PCN-224 with the cancer cell membrane.¹¹¹ Unlike the design of hypoxia alleviation mentioned above, this strategy further decreased the intracellular O₂ content by PDT under irradiation. This resulted in extremely low-oxygen environment-activated TPZ, which released transient oxidizing radicals to kill cancer cells. Therefore, TPZ@PCN@Mem showed better cancer cell inhibition in hypoxia, and the cancer cell viability decreased with increasing the content of TPZ. Min and coworkers incorporated apatinib in PCN-224, and coated it with MnO₂ and cancer cell membrane.⁶⁰ Angiogenesis in the tumor area will lead to tumor regrowth and metastasis. Apatinib is a vascular endothelial growth factor inhibitor that can effectively inhibit angiogenesis. Apatinib was released in the presence of GSH due to the decomposition of MnO₂. Their results showed that apatinib had little influence at the early-stage of treatment but several days later, the groups that were not treated with apatinib resumed the tumor growth, indicating that apatinib-assisted PDT had long-term tumor inhibition. Cheng *et al.* reported a cancer cell membrane-coated PCN-222 as the carrier of alkaloid piperlongumine (PL) (Fig. 12a).⁶¹ The thioredoxin/thioredoxin reductase (Trx/TrxR) system is another way that cancer cells develop to confront oxidative stress, which maintains the cellular redox homeostasis but also leads to the ROS resistance of cancer cells. The dithiol group in Trx can react with ROS through the thiol-disulfide exchange reaction, and the reduced Trx can take

electrons from NADPH catalyzed by TrxR.²¹⁰ In this regard, PL can inhibit the activity of TrxR, thus breaking the redox homeostasis in tumor cells. Hence, the ROS level in cells was promoted by 1.6 times after the treatment with PCN-PL@CM, which proved that the effect of ROS was guaranteed, and tumor cells also became more sensitive to ROS.

Starvation therapy refers to cutting off the nutrition supply of cells by glucose decomposition,^{25,211} which is usually achieved by glucose oxidase (GOx) or enzyme-like agents according to the following equation:^{25,62}



Similar to PDT, starvation therapy also requires an O₂ supply. Therefore, Li *et al.* fabricated a cascade bioreactor mCGP by encapsulating glucose oxidase (GOx) and catalase in PCN-224.⁶² PCN-224 was further camouflaged with the cancer cell membrane. Endogenous H₂O₂ was consumed by catalase to generate O₂, which was important for ROS production and glucose consumption. Simultaneously, glucose was decomposed by GOx, breaking the glucose metabolism balance of tumor cells. The H₂O₂

produced by glucose decomposition could further react with catalase for O₂ production. Therefore, this strategy presented enhanced PDT efficacy and tumor proliferation inhibition. Another

nano-reactor was made by Liu *et al.*⁶³ They made a sandwich structure where the Pt NPs were embedded between the outer PCN shell and the inner PCN core. The outer PCN was further incorporated with Au NPs (Fig. 12b). Afterwards, folic acid was incorporated for active targeting. The Pt NPs and Au NPs showed catalase-like and glucose oxidase-like activity, respectively. The tumor inhibition of the final product was 90.88%, much higher than that of folic acid attached PCN-224 (41.93%), due to the combined photodynamic and starvation therapy.

Gas therapy is an emerging therapy that uses gaseous transmitters to kill cancer cells with negligible negative effect.²¹² Gas molecules are cytotoxic under appropriate concentrations without harming normal cells.²¹³ Taking NO as an example, NO not only participates in many physiological processes, but also shows a dose-dependent anti-tumor effect. When the concentration of NO is higher than 1 μM, it can directly kill cancer cells

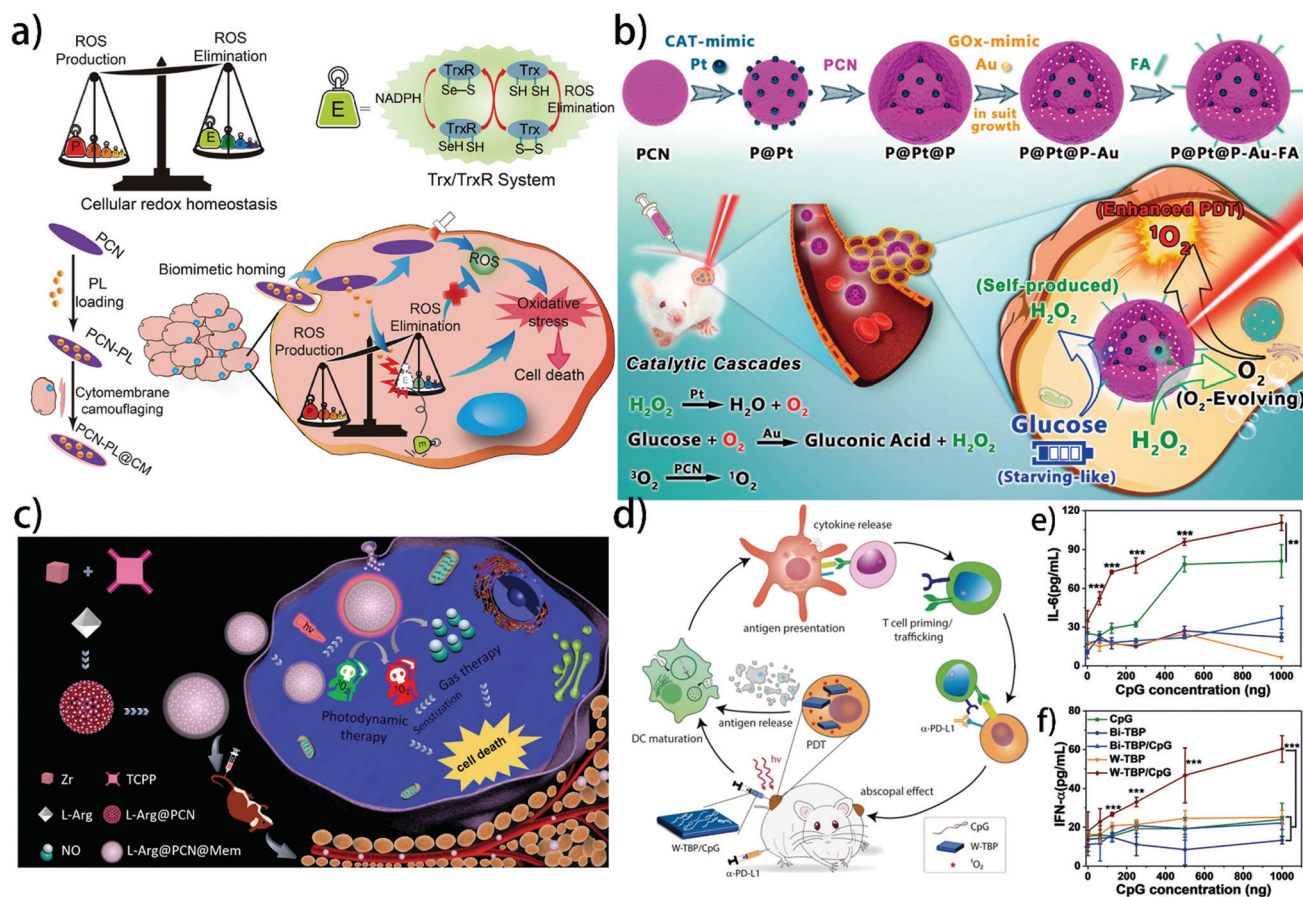


Fig. 12 (a) Schematic illustration of interfering with redox homeostasis in cancer cells for improved PDT. Reprinted with permission from ref. 61. Copyright 2019 Elsevier. (b) Schematic illustration of the catalytic cascades-enhanced synergistic cancer therapy driven by dual-inorganic nanozymes-engineered PCNs. Reprinted with permission from ref. 63. Copyright 2019 American Chemical Society. (c) Schematic illustration of L-Arg@PCN@Mem preparation and lethal mechanism of gas therapy and sensitized PDT against tumors. Reprinted with permission from ref. 112. Copyright 2018 Elsevier. (d) W-TBP/CpG promoted antigen presentation via immunogenic PDT and CpG delivery synergizes with checkpoint blockade immunotherapy to afford systemic antitumor immunity. Concentration-dependent IFN-α (e) and IL-6 (f) levels by ELISA, $n = 3$. Reprinted with permission from ref. 139. Copyright 2020 Wiley.

by mitochondria and DNA nitrosation.²¹² Moreover, NO molecules can react with $\bullet\text{O}_2^-$ to produce cytotoxic peroxynitrite (ONOO^-), which has efficient oxidizing and nitrating ability.²¹⁴ Generally, gas therapy requires the loading of gas donors or the attachment of gas molecules, and the release of gas is stimuli-triggered. Light irradiation is a suitable stimulus due to minimal side effects, and it also provides the possibility for combining gas therapy and PDT to enhance the therapeutic potency. As an ideal gas carrier, MOF is also appropriate for loading the gas donor and storing the generated gas. Wan and coworkers encapsulated biocompatible L-arginine (L-Arg) in PCN-224 as the NO donor for combined gas therapy (Fig. 12c).¹¹² Upon irradiation, the donor L-Arg can react with H_2O_2 and ROS to generate NO with a long half-life and wide diffusion range. More importantly, in a hypoxic environment, due to the free diffusion and penetration of NO, NO can sensitize tumor cells to ROS. Although NO generation consumed part of the ROS, their results showed that the combination of the released NO and PDT achieved much better therapeutic efficacy than PDT alone, almost completely eliminating the tumor. Guan *et al.* firstly synthesized the UiO-66-OH(Hf) MOF composed of Hf nodes and H_2BDC ligand.⁶⁴ Afterwards, 2I-BODIPY, which acted as a PS, was attached to UiO-66-OH(Hf) by etherification, and the gas donor, MnCO, was further coordinated to Hf cluster nodes. In the presence of oxidizing agents such as H_2O_2 and $^1\text{O}_2$, the Mn(I) in MnCO can be oxidized to Mn(II), thus releasing CO molecules. Hence, light irradiation not only triggered the PDT effect but also CO release through $^1\text{O}_2$ generation. CO can hinder the ATP generation in tumor cells by activating the oxidative phosphorylation process, thus preventing tumor cell proliferation and tumor metastasis. The selectivity of the MOF and light-controlled release of CO also prevented the side effects of CO.

Besides directly releasing cytotoxic agents to kill cancer cells as mentioned above, the response of the immune system is worth considering. In this regard, immunotherapy was put forward, which harnesses immune cells in the tumor microenvironment or host lymphoid tissues to target and eradicate tumor cells, thus preventing tumor metastasis and facilitating systemic immune surveillance.^{215,216} Generally, during PDT, the death of tumor cells will result in the release of tumor-assisted antigens, which are then presented to T cells by antigen-presenting cells (especially dendritic cells).^{139,216,217} However, the tumor can release immunosuppressive signals through the expression of proteins or interfering with the receptors on T cells, thus leading to T cell apoptosis and preventing the response of the immune system.^{107,216,218} On the other hand, tumor-assisted antigens are deficient in the tumor microenvironment, and the antigen-presenting efficiency of dendritic cells is also poor, which all hinder the immune response.^{123,139,219} Hence, several strategies have been put forward, such as blocking the inhibitory signals of T cells or improving the efficiency of antigen presentation.²¹⁶ The former is referred to as checkpoint blockade immunotherapy. These strategies usually utilize immunostimulatory agents, such as antibodies and small molecules, which can be loaded in the MOF, thus preventing their degradation and improving their targeting ability.^{215,216,220}

For checkpoint blockade immunotherapy, the commonly used checkpoints are T-lymphocyte-associated protein 4 (CTLA4), programmed cell death 1 (PD-1), programmed cell death 1 ligand (PD-L1), and indoleamine 2,3-dioxygenase (IDO), *etc.*^{215,221} Lu *et al.* loaded IDO inhibitor in a TBC-Hf MOF with a content of 4.7 wt%.⁹⁷ IDO is highly expressed in the tumor microenvironment, which can inhibit the clonal expansion of T cells, thus promoting the immune escape of tumors. The IDO inhibitor in MOF can effectively block the activity of IDO, and the combination of the TBC-Hf and the IDO inhibitor under light irradiation showed the best tumor suppression. Notably, when TBC-Hf and the IDO inhibitor were applied without light irradiation, the tumor growth was slightly inhibited, indicating that the PDT-induced tumor cell death and the following release of tumor-associated antigens are necessary for immunotherapy. Moreover, in this combined therapy, the immune cells can migrate to other tumor areas, causing a strong abscopal effect. Hence, the tumor at the untreated site can also be attacked by immune cells.

As for improving the efficiency of antigen presentation, Ni *et al.* fabricated a cationic W-TBP MOF (TBP refers to 5,10,15,20-tetra(*p*-benzoato)porphyrin), which can adsorb anionic cytosine-phosphate-guanine (CpG) (Fig. 12d).¹³⁹ CpG is a toll-like receptor agonist. When internalized by dendritic cells, CpG can bind to toll-like receptor-9, thus promoting the maturation of dendritic cells. The dendritic cells then release cytokine (*e.g.*, immunostimulatory cytokines type I Interferon ($\text{IFN-}\alpha$) and interleukin-6 (IL-6)) as the marker of maturation. Hence, the activated dendritic cells will present more tumor-associated antigens to T cells, which then prime and traffic to activate other T cells. In their work, W-TBP absorbed CpG with an efficiency of 89.9%, which is attributed to the high positive zeta-potential of W-TBP (37.2 ± 0.6 mV). The MOF carrier endowed CpG with higher internalization by dendritic cells, as evidenced by the highest dendritic maturation in Fig. 12e ($\text{IFN-}\alpha$) and Fig. 12f (tested by IL-6). The combination of PDT and CpG-induced immunotherapy showed 96.6% of tumor regression, much higher than free CpG and PDT alone. Afterwards, the authors demonstrated that this immunotherapy can be combined with checkpoint blockade immunotherapy by injecting the mice with the α -PD-L1 antibody. This combination caused a strong and consistent abscopal effect, which can take effect on distant tumors.

3.3.4 Enhancing the penetration depth. Limited penetration depth is one of the biggest shortcomings of phototherapy. Especially for PDT, the frequently used wavelength of light was 650–800 nm, which can only penetrate the tissue for 3–10 mm.² Hence, traditional PDT can only treat lesions that are superficial or within 1 cm of depth.^{6,222} Two factors cause this problem. One is that the absorption peak of most PSs is located in the visible range, which means that the longer-wavelength but deeper-penetrating light is not suitable for the excitation of these PSs.²²² Another concern is that when the wavelength of light is longer than 800 nm, the light cannot provide enough energy for the excitation of $^3\text{O}_2$.⁷ In this regard, the use of two-photon activated PSs and upconversion nanoparticles was put forward.

Most PSs are single-photon excitation PS, which means the PS can only absorb one photon under irradiation. By comparison, simultaneously absorbing two photons, namely two-photon

activation, features long-wavelength two-photon absorption, which renders deep-tissue treatment and prevents the energy loss of light.²²³ One typical example of two-photon-excited PS is the polypyridyl ruthenium complex (RCs). Zhang and coworkers encapsulated cationic RCs ($[\text{Ru}(\text{bpy})_3]^{2+}$, $[\text{Ru}(\text{phen})_3]^{2+}$ and $[\text{Ru}(\text{phen})_2\text{hipp}]^{2+}$) in anionic bio-MOF-1 by means of ion exchange.¹⁸⁰ The MOF carrier hindered the intramolecular rotation and π - π interactions of RCs, which reduced their aggregation. Moreover, bio-MOF-1 also provided an extended π -conjugation system, which improved the light harvesting ability of RCs. The single-photon activation of bio-MOF-1/RCs was measured under 490 nm light irradiation. The singlet oxygen yields of bio-MOF-1/ $[\text{Ru}(\text{bpy})_3]^{2+}$ under single-photon activation was 0.86, which was higher than that of $[\text{Ru}(\text{bpy})_3]^{2+}$ (0.81) due to the reduced aggregation of RCs. In terms of two-photon activation, the maximum two-photon activation wavelength was in the range of 800–820 nm. Under 800 nm light irradiation, owing to the stronger electron delocalization conjugate system of bio-MOF-1/ $[\text{Ru}(\text{phen})_3]^{2+}$ and bio-MOF-1/ $[\text{Ru}(\text{phen})_2\text{hipp}]^{2+}$, they had higher $^1\text{O}_2$ generation than bio-MOF-1/ $[\text{Ru}(\text{bpy})_3]^{2+}$. Therefore, the therapeutic wavelength shifted to the longer region, which rendered deeper light penetration.

Another way to improve the penetration depth of PDT is by using upconversion nanoparticles (UCNPs), which can absorb two or more low-energy photons and generate one high-energy photon.^{224,225} In this way, NIR light can be converted into visible light, thus activating PSs. The frequently used UCNPs are lanthanide-doped UCNPs^{224,226} and quantum dots.^{227,228} In MOF-based therapeutic systems, UCNPs can be attached to the surface of MOF,⁹⁶ or covered by MOF as the core material of the core-shell structure.^{89,165} For example, He *et al.* firstly fabricated a core-shell-shell UCNP ($\text{NaYb}_{0.92}\text{F}_4\text{:Er}_{0.08}\text{@NaYF}_4$) with a diameter of 29.8 ± 2.2 nm.⁸⁹ Under 980 nm laser irradiation, this UCNP can convert the light source into 524, 542 and 660 nm light, with a quantum yield of $6.55 \pm 0.34\%$, which is much higher than that of traditional UCNPs. The UCNP was then coated with the PCN-222 MOF shell (composed of Zr nodes and FeTCPP ligands) and further decorated with Au NPs. The absorption of PCN-222 was located at 554 and 646 nm, which matches well with the emission of UCNPs. Au NPs serve as glucose oxidases to trigger glucose starvation therapy and generate a large amount of H_2O_2 . The chelated Fe atom in the FeTCPP further reacted with H_2O_2 for O_2 generation. Hence, the Au NPs and PCN-222 together caused a cascade reaction, and the UCNPs also deepened the therapeutic depth of PDT. After 8 days of 980 nm light treatment, the tumor-bearing mice showed complete tumor eradication without recurrence.

3.3.5 Typical modifications towards antibacterial applications.

Bacteria-killing is another important application of PDT, and the mechanism is similar to the anticancer mechanism. Under light irradiation, bacteria are killed by ROS due to the damage of the bacterial cell membrane and the DNA inside. However, the strategies in PDT are not completely suitable for antibacterial applications due to the following reasons. Firstly, bacteria can be divided into Gram-positive (e.g., *Staphylococcus aureus*) and Gram-negative (e.g., *Escherichia coli*) bacteria. The cytoplasmic membrane of Gram-positive bacteria is covered by porous peptidoglycan and

lipoteichoic acid, which is easy for PSs to cross. Whereas, besides the cytoplasmic membrane, Gram-negative bacteria have another outer membrane that acts as a barrier to prevent the penetration of PSs.²²⁹ Therefore, traditional PDT has limited efficacy against Gram-negative bacteria. In view of this, PS requires modifications that increase the outer membrane permeability. It is known that bacteria usually bear a negative charge, hence, cationic PSs have greater affinity for bacteria. Another concern is the formation of biofilms, which is a consortium of bacteria growing compactly on living tissues or implant materials.^{230,231} The extracellular polymeric substances form a dense and protective shelter that hinders the contact of PSs and the inner bacteria.²³² The biofilm area also features acidity (pH $\sim$ 5.5) and hypoxia.¹³² Therefore, many strategies have been put forward to accommodate MOF-based PSs for antibacterial applications.

Ag ions are an important biocide that can react with biomolecules such as DNA and peptides due to their affinity for thiols, amines and phosphates, thus causing the irreversible aggregation of these biomolecules and finally leading to the inactivation of bacteria.²³³ Zhang *et al.* loaded Ag ions into PCN-224 and sealed it with surface-adaptive HA.¹¹³ The HA shell can be decomposed by hyaluronidase secreted by Gram-positive bacteria. PCN-224- Ag^+ was able to attack bacteria due to charge interaction, leading to bacterial death. Their results showed that the antibacterial abilities of PCN-224 and PCN-224-HA against methicillin-resistant *Staphylococcus aureus* (MRSA) were similar under light irradiation, suggesting that the HA coating was degraded by MRSA. After the encapsulation of Ag^+ , PCN-224-Ag-HA exhibited obvious bacterial inhibition, which was more potent than PCN-224-HA and AgNO_3 . The results confirmed that loading Ag^+ in PCN-224 was effective for bacteria-killing by the synergistic action of both Ag^+ and PDT. It also provided insight for loading other kinds of antibacterial agents in MOF-based PSs, such as Cu^{2+} and Zn^{2+} .^{234–237}

Bacterial adhesion is the initial stage of biofilm formation, which is promoted by ATP stimulated cell lysis and extracellular DNA release. At this time point, the bacteria are easily attacked by PS because of the absence of biofilm protection. In view of this, Qiu *et al.* decorated PCN-224 with CeO_2 NPs of 4 nm in size to form a shell structure on PCN-224 with L-arg as the capping agents to perform ATP deprivation and PDT (Fig. 13).¹¹⁴ The Ce^{3+} and Ce^{2+} in CeO_2 can react with ATP through the nitrogen and oxygen on adenine and triphosphate of ATP. Therefore, the biofilm formation was inhibited because of ATP deprivation, and the planktonic bacteria were subsequently killed by PDT. Results showed that after incubation with different contents of MOF@CeO_2 , the ATP content decreased with the higher concentration of MOF@CeO_2 , while the ATP content showed no obvious variation with different concentrations of PCN-224. Therefore, the decoration of CeO_2 could effectively eliminate ATP, which led to 40% of biofilm inhibition for MOF@CeO_2 ($50 \mu\text{g mL}^{-1}$). When light irradiation (638 nm) was introduced, the biofilm inhibition was 90% for MOF@CeO_2 at the concentration of $200 \mu\text{g mL}^{-1}$.

Different from the initial stage, once the biofilm forms, the inner bacteria are protected by the biofilm.²³⁸ In this case, the

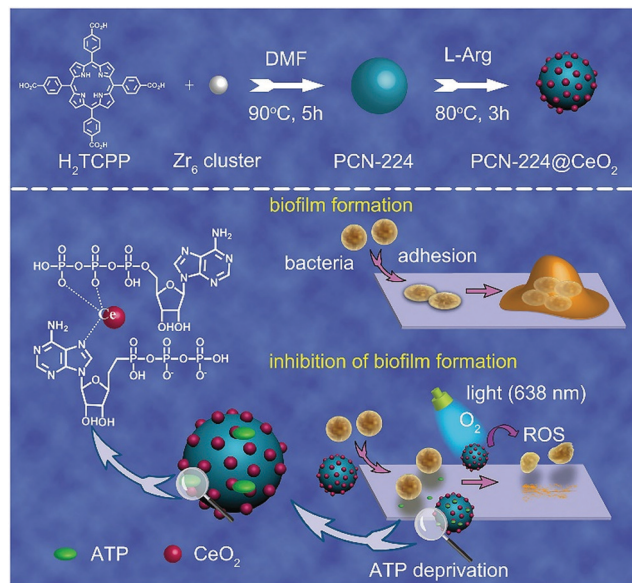


Fig. 13 Schematic illustration of the preparation process of CeO_2 -decorated PCN-224 and the inhibition of biofilm formation through the synergy of adhesion-related molecule deprivation and cytotoxic ROS generation. Reprinted with permission from ref. 114. Copyright 2019 Wiley.

diffusion of PS and ROS should be taken into consideration. Reducing the particle size of therapeutic agents is a feasible way to penetrate the biofilm. Deng and coworkers fabricated a MOF dot composed of Hf nodes and TCPP ligands, which was further covered with human serum albumin and MnO_2 .¹³² The final product was named MMNPs. The diameter of MMNPs was about 105 nm. The outer MnO_2 would degrade in the mildly acidic environment or in the presence of H_2O_2 , releasing porphyrin-based MOF and O_2 for hypoxia alleviation. The ultrasmall MOF dot was about 5 nm in size and positively charged, which had excellent penetration ability through the biofilm and a high affinity for the negatively charged bacteria. Therefore, the MMNPs showed 99% and 90% of the antibacterial ratio against *E. coli* and *S. aureus*, respectively. Compared to the bulk MOF, this MOF dot showed 12 times higher accumulation in the biofilm. Animal testing manifested that the abscesses of *S. aureus*-infected mice healed with no obvious inflammation in 5 days after MMNPs treatment and visible light irradiation.

4. Photothermal therapy

4.1 Intrinsic photothermal MOF

Intrinsic photothermal MOF refers to MOF that can be directly used as PTAs without the need for extra PTA decoration. One of the most important branches of intrinsic photothermal MOF is Prussian blue (PB) and its analogues. Other intrinsic photothermal MOF is based on (i) photothermal building units and (ii) the ligand-to-metal charge transfer mechanism to have photothermal ability. Hence, in this section, we will introduce the composition as well as typical modification methods for intrinsic photothermal MOF.

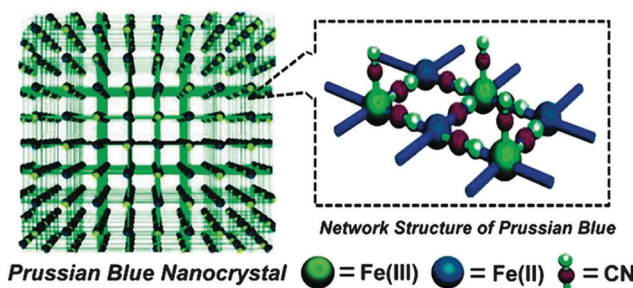


Fig. 14 Basic cubic network structure of PB. Reprinted with permission from ref. 239. Copyright 2015 Royal Society of Chemistry.

4.1.1 Prussian blue-based MOF. PB is one of the oldest synthetic MOFs that has been intensively studied.²³⁹ The chemical structure of PB is presented in Fig. 14. The carbon atom and nitrogen atom of $-\text{C}\equiv\text{N}-$ in PB is coordinated with Fe(II) and Fe(III) , respectively, creating a face-centered cubic structure.^{239,240} The PB has two categories: soluble PB ($\text{KFe}^{\text{III}}[\text{Fe}^{\text{II}}(\text{CN})_6]$) and insoluble PB ($\text{Fe}_4^{\text{III}}[\text{Fe}^{\text{II}}(\text{CN})_6]_3 \cdot n\text{H}_2\text{O}$).²⁴⁰ As for insoluble PB, depending on the coordination site of water molecules, it can be divided into coordinative type (water molecules coordinate to iron ions) and zeolitic type (water molecules occupy cavities).²⁴⁰

In biomedical applications, PB has been approved by FDA to treat radioactive exposure as clinical medicine with good biocompatibility and biosafety.^{100,241} Owing to the charge transfer between Fe(II) and Fe(III) , PB can generate heat under NIR irradiation for tumor ablation and bacteria disinfection.¹⁰⁰ The Fe(III) nodes in PB can also react with H_2O_2 and generate $\cdot\text{OH}$ through the Fenton reaction.²⁴² Moreover, the coordination between Fe(III) and water molecules in insoluble PB renders an inner-sphere longitudinal relaxation time with a longitudinal relaxivity of 0.14 mM^{-1} , which can be used for MRI-guided therapy.²⁴³

PB can directly serve as PTA in PTT. Yue *et al.* fabricated PB by mixing a solution of FeCl_3 and $\text{K}_4[\text{Fe}(\text{CN})_6]$ with citric acid as the surface capping agent.¹⁰⁰ In their work, the size of PB could be controlled by different concentrations of citric acid, ranging from 10 to 50 nm. In addition, their PB had a broad absorption band at 500–900 nm, and the absorption peak was located at 712 nm. Under 808 nm irradiation, the molar extinction coefficient was $1.09 \times 10^9 \text{ M}^{-1} \text{ cm}^{-1}$, which was slightly lower than that of Au nanorods. The temperature of PB rose to 43°C under less than 3 min of irradiation. After the PTT treatment by PB, the viability of HeLa cells was lower than 10%. However, the absorption peak of PB was near the edge of the near-infrared region (700–900 nm), and the photothermal conversion efficiency was merely 20% under 808 nm irradiation.^{54,56} The subsequent research mainly focused on improving the therapeutic efficacy by doping, etching, drug loading and auxiliary methods such as imaging guidance.

Doping is a common modifying method for PB. Up to now, the doped metal ions include Mn^{2+} ,²⁴⁴ Zn^{2+} ,^{54,245} Cu^{2+} (ref. 246) and Gd^{2+} ,^{247–249} *etc.*, which are usually located at the interstitial site or lattice site (Fig. 15a).²⁴⁹ The dopant size, distribution and concentration will affect the chemical properties of PB,

rendering PB with tunable photothermal behavior.⁵⁴ Besides, imaging guidance can also be introduced through doping. Zhu *et al.* doped Mn^{2+} in PB, and coated PB with poly(allylamine hydrochloride) (PAH), polyacrylic acid (PAA) and PEG through the layer-by-layer method.²⁴⁴ The dopant changed the electron density and orbital energy of PB. Thus, the absorption peak of PB red-shifted to 718, 730, and 768 nm, corresponding to the Mn^{2+} doping ratio of 5%, 15% and 25%, respectively. On the other hand, Mn^{2+} also increased the longitudinal relaxivity of PB, which showed much-enhanced contrast in MRI. Shou *et al.* doped 10% Zn^{2+} in PB (SPBZn(10%)), which resulted in ultra-small PB particles (3.8 ± 0.90 nm).²⁴⁵ The SPBZn(10%) showed a 1.3 times higher absorption peak than the non-doped PB. When the doping concentration changed, the photothermal conversion efficiency varied from 37.73% to 47.33%. Besides, the doped Zn^{2+} could replace Fe^{2+} , giving rise to higher Fe^{3+} concentration, and the magnetic saturation value was also improved, which was beneficial for the MRI guidance.

The pore size is another important factor that affects the photothermal performance of PB MOF and the drug-loading efficacy. Generally, the pore size of PB is smaller than 1 nm,²⁵⁰ and the loading capacity is also limited, which is not suitable for drug loading.²⁵¹ Therefore, many researchers have reported the hollow mesoporous PB (HMPB) structure by chemical etching or the hydrothermal method. Under light irradiation, the elevated local temperature can accelerate the drug diffusion. For example, Zhou and coworkers used hydrochloric acid to etch PB crystals.²⁵ Nitrogen absorption isotherms manifested that the Brunauer–Emmett–Teller (BET) surface area of PB increased from $302.56 \text{ m}^2 \text{ g}^{-1}$ to $922.14 \text{ m}^2 \text{ g}^{-1}$ with a pore diameter of 10.12 nm. Cai and coworkers synthesized HMPB by the hydrothermal method and chemical etching.²⁴¹ Afterwards,

the authors added Mn^{2+} and $[\text{Fe}(\text{CN})_6]^{2-}$ as sources to fabricate a Mn-containing PB analogue shell on both the exterior and interior surfaces of HMPB (Fig. 15b). The final product was termed as HMPB–Mn. DOX was loaded in HMPB–Mn with an efficiency of 97.5%, which was attributed to its coordination with Fe^{2+} and Mn^{2+} nodes. In an acidic environment, the $\text{Mn}-\text{C}\equiv\text{N}-\text{Fe}$ structure will decompose, thus releasing Mn^{2+} and DOX. The release efficiency of Mn^{2+} and DOX at pH 5.0 was 95% and 34.7%, respectively. The pH-induced Mn^{2+} release facilitated the MRI ability of HMPB–Mn, which showed the brightest MRI images at pH 5.0 with a molar relaxivity of $7.43 \text{ mM}^{-1} \text{ s}^{-1}$. Therefore, this pH-triggered smart therapeutic agent can be used for MRI-monitored drug release, which was synergized with PTT. In another work, Cai *et al.* loaded DOX and perfluoropentane (PFP) in HMPB.²⁵² HMPB had a higher intrinsic molar extinction coefficient at 808 nm, which could be used for photoacoustic (PA) imaging. When the temperature increased, the bubbles generated by PFP could act as the contrast agent of ultrasound (US) imaging. The combination of PA and US imaging was beneficial for the early diagnosis of cancer. Therefore, this nanoplatform combined PTT, chemotherapy and diverse imaging on the basis of HMPB, showing almost complete eradication of tumor.

The Fe^{2+} , Fe^{3+} and $-\text{CN}^-$ in PB can be active sites for coordination with therapeutic agents. One of the major applications of coordination modification is gas combined therapy. Gas therapy utilizes gas molecules (*e.g.*, CO ,²⁵³ NO ^{212,254} and H_2 ¹⁰⁴) as cytotoxic agents, which can be attached to a carrier such as MOFs and then released under certain environment conditions. Besides ROS (as mentioned in Section 3.3.3), light-induced temperature increase is also an ideal trigger for gas release. For example, Li *et al.* coordinated $\text{Fe}(\text{CO})_5$ on mesoporous PB by replacing $-\text{CN}^-$ with

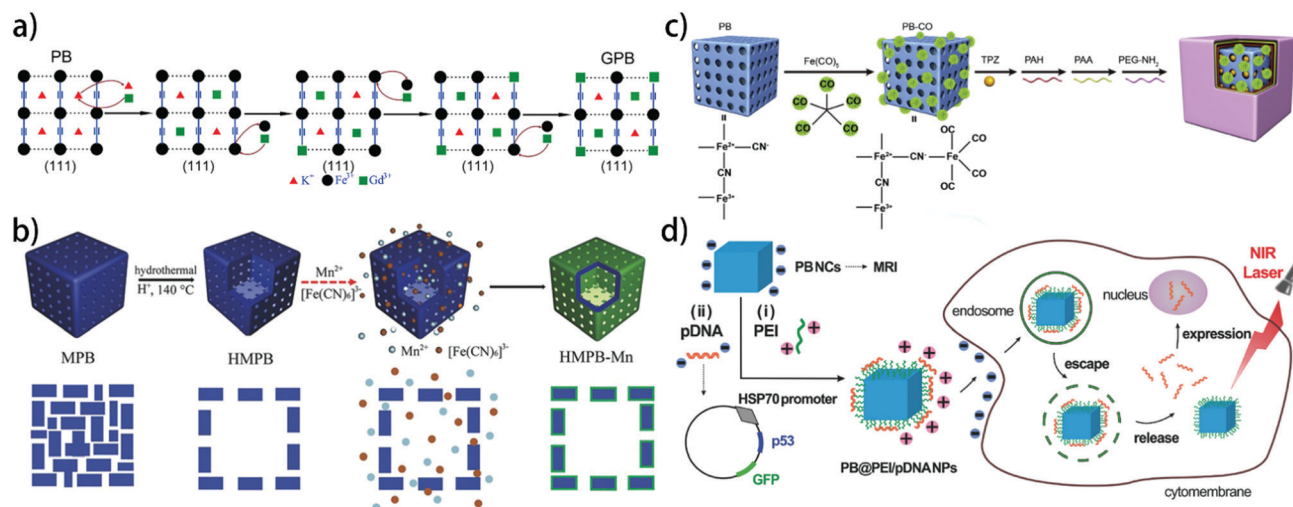


Fig. 15 Different modification methods of PB. (a) Doping: schematic of Gd^{3+} simultaneously optimizing the properties of PB nanocrystals. Reprinted with permission from ref. 249. Copyright 2016 American Chemical Society. (b) Hollow mesoporous PB: schematic illustration of the synthetic procedure of HMPB–Mn. Reprinted with permission from ref. 241. Copyright 2015 Wiley. (c) Coordination modification: schematic illustration of PB–CO–TPZ NPs with enhanced bioreductive chemotherapy and CO-mediated pro-apoptotic gas therapy. Reprinted with permission from ref. 255. Copyright 2019 Elsevier. (d) PB-based composites: schematic illustration of HSP70 promoter-based PB theranostic platform for gene therapy/PTT. Reprinted with permission from ref. 257. Copyright 2018 Wiley.

one of the CO moieties of $\text{Fe}(\text{CO})_5$.⁴⁶ CO can lead to cancer cell apoptosis by inducing mitochondria disorder. However, CO can also bind with hemoglobin and oxygen, showing acute toxicity to normal tissues. In order to avoid CO poisoning, the CO release amount was controlled by irradiation time and intensity. The CO release was suppressed in blood circulation. Only under irradiation can the photothermal effect of PB cleave the Fe–CO bond for CO release. Since CO treatment can accelerate mitochondrial respiration in the second stage, which facilitates O_2 consumption, Li *et al.* introduced hypoxia-activated TPZ in $\text{Fe}(\text{CO})_5$ and PB therapeutic system, and coated it with PAH, PAA and NH_2 -modified PEG (Fig. 15c).²⁵⁵ Another coordination method was reported by Feng *et al.* During the fabrication process of PB, the authors doped PB with sodium nitroprusside (SNP), which is a NO donor.²⁵⁶ As SNP was embedded in the crystal structure of PB, some of the Fe^{3+} nodes in PB were coordinated with NO. Afterwards, the PB was loaded with the anticancer drug docetaxel (DTX), generating DTX@m-PB–NO. Upon irradiation, the heat led to the cleavage of Fe–NO bonds, while no NO release was detected at 37 °C, indicating its safety in blood circulation. The highest NO release amount was 10.43 μM . When the NO content reached the micromolar level, it could inhibit tumor growth and metastasis by nitrosation.

Besides the above PB-based PTAs, some other PB-based composites can be derived by coating specific materials on the surface of PB or employing PB as the coating. The former can be categorized into polymer coating (PEI,²⁵⁷ PEG,^{258,259} chitosan,²⁶⁰ gelatin,²⁶¹ and PDA,²⁶² *etc.*), inorganic coating (SiO_2 ,^{251,263,264} *etc.*), and MOF coating (ZIF-8,²⁶⁵ MIL-100(Fe),^{169,266} UiO-66,²⁶⁷ *etc.*), which is mainly used for stability enhancement, drug loading, and other combined therapy. Wang *et al.* fabricated the PB@MIL-100(Fe) dual-MOF structure.²⁶⁶ The outer MOF shell was used as a carrier of anticancer drug artemisinin (ART) with a loading efficiency of 848.4 mg g^{-1} . ART was released under an acidic environment because of MIL-100 shell decomposition. Moreover, as the MIL-100 shell increased the dielectric constant of the composite NPs, the absorption peak of PB red-shifted 35 nm. Hence, the temperature of PB@MIL-100(Fe) increased 30 °C at a concentration of 0.2 mg mL^{-1} with excellent photostability. Liu *et al.* coated PB with PEI, which was loaded with pDNA by electrostatic interactions (Fig. 15d).²⁵⁷ The pDNA was HSP70–p53–GFP, wherein HSP70 has higher expression in the moderate temperature region (39–43 °C) and acted as a promoter to activate gene therapy, while p53 and GFP was the targeted tumor-suppressive gene and reporter, respectively. After the endocytosis of PB@PEI/pDNA NPs, the low heat (≤ 43 °C) can facilitate the endosomal escape of material by destroying the endosomal membrane, thus releasing the pDNA, which was then expressed to the nucleus. When the temperature was about 41 °C, HSP70 initiated the expression of p53, which resulted in tumor apoptosis. When the temperature exceeded 50 °C, the hyperthermia led to cell necrosis. Therefore, the gene therapy and PTT showed a synergistic effect, which was controlled by PB-induced heat generation.

In the latter case, the most reported strategies were to coat PB on contrast agents such as Au,^{268,269} Fe_3O_4 ,²⁷⁰ and MnO_2 ,²⁷¹ *etc.*, to enhance the imaging properties (MRI, PA imaging, and

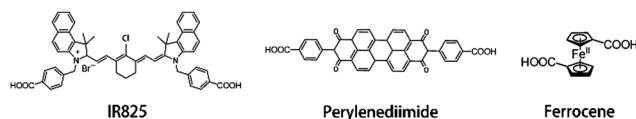


Fig. 16 Typical photothermal ligands for intrinsic photothermal MOF.

computed topography (CT), *etc.*) of PB. The core material also provides synergistic functions. Peng *et al.* coated PB on MnO_2 and encapsulated the NP with red cell membrane (RCM).²⁷² DOX was loaded within RCM by coextruding. The MnO_2 core decomposed H_2O_2 at the tumor site with O_2 generation, which resulted in RCM disruption and DOX release. Moreover, the RCM prolonged the circulation time of NPs and increased the aggregation of NPs at the tumor site, which resulted in a higher PTT temperature (59.6 °C) as compared to the non-coated samples (49.3 °C). This group also demonstrated that the PB/ MnO_2 nanocomposite has a high diamagnetic transverse relaxation time (T_2) signal intensity, which was promising in MRI and PAI.²⁷¹

4.1.2 Utilizing photothermal agents as building units. MOFs with intrinsic photothermal effect can be synthesized by employing various kinds of PTAs as ligands, as schematically shown in Fig. 16.^{49,93,103}

For instance, Yang *et al.* synthesized a MOF using Mn as nodes and IR825 as ligands, and they covered this MOF with PDA and PEG for better biocompatibility.⁹³ On the one hand, as a common NIR dye with NIR light absorption peak at 825 nm, IR825 endowed the composite with photothermal performance. Under 808 nm light irradiation, the mass extinction coefficient of MOF at 808 nm was 78.2 $\text{L g}^{-1} \text{cm}^{-1}$, and the temperature quickly rose to ~ 52 °C within 5 min. In addition, their results showed that this material possessed photothermal cycling ability. On the other hand, the Mn nodes also offered the MOF with MRI guidance. More recently, Lü *et al.* reported a Zr-PDI (PDI refers to perylenediimide) MOF with high photothermal conversion efficiency.⁴⁹ PDI can be reduced into $\text{PDI}^{\bullet-}$, which is a delocalized radical anion with red-shifted absorption compared to the PDI molecule. However, $\text{PDI}^{\bullet-}$ is unstable in ambient conditions. To solve this problem, the authors coordinated PDI with Zr_6 clusters, forming Zr-PDI MOF (Fig. 17a–c). The Zr_6 cluster was coordinated with 12 carboxyl groups, and the PDIs showed axial chirality (Fig. 17b). Zr-PDI can obtain electrons from electron donors (*e.g.*, amine vapors) through photo-induced electron transfer (PET), generating radical anion $\text{Zr-PDI}^{\bullet-}$. In this work, the PET process was performed by irradiating Zr-PDI with blue light (455 nm) in amine vapor (Fig. 17d). The absorption of $\text{Zr-PDI}^{\bullet-}$ was obviously red-shifted (Fig. 17e). Due to the shielding effect of the MOF structure, the quenching of radical anions was efficiently prevented. $\text{Zr-PDI}^{\bullet-}$ is the first reported stable isolated radical anion, which retained the high light-to-thermal conversion of $\text{PDI}^{\bullet-}$ with a photothermal conversion efficiency of 52.3% (Fig. 17f), showing great promise in PTT. More recently, Deng *et al.* used 1,1'-ferrocenedicarboxylic acid ($\text{Fc}(\text{COOH})_2$) as a ligand that was coordinated with Zr nodes.¹⁰³ The final product was termed as Zr-Fc MOF, which is a 16.4 nm thick MOF nanosheet. The PTT

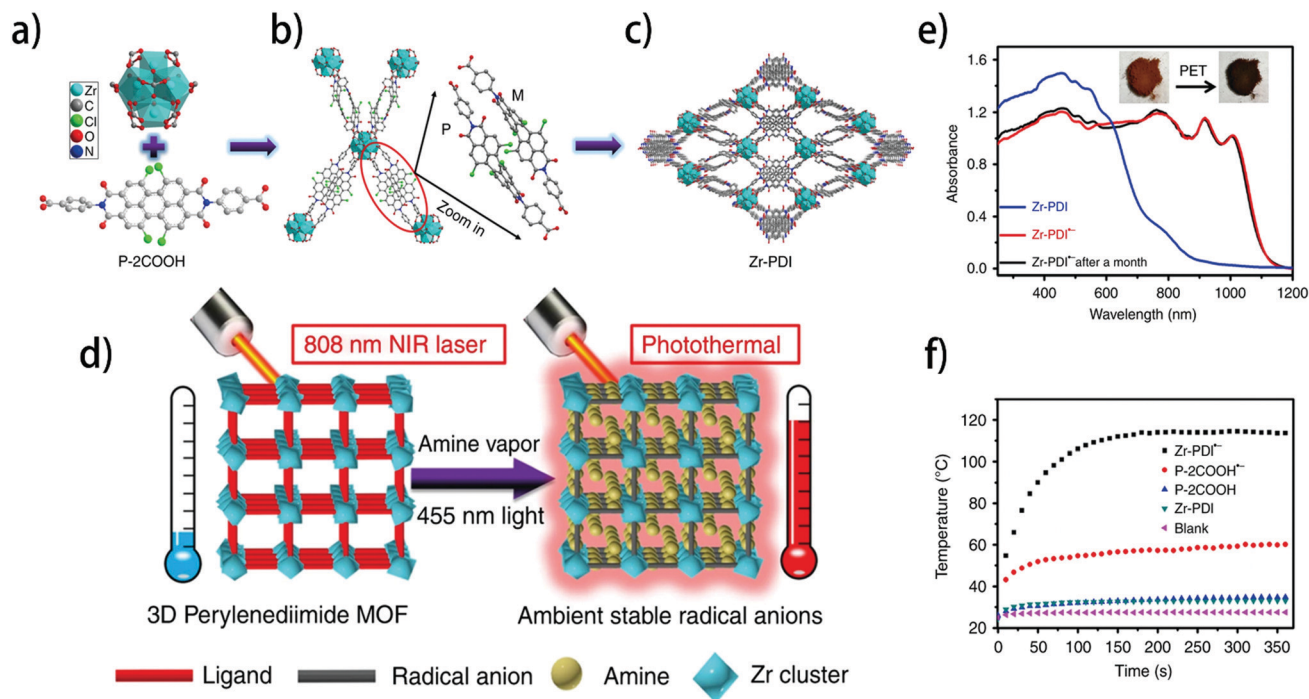


Fig. 17 (a) Structures of the Zr-cluster and P-2COOH. (b) Connection mode of the Zr-cluster (the Zr-cluster is fully coordinated by 12 carboxylate units) and the molecular arrangement of chiral P-2COOH. (c) c-Axis crystal structure of Zr-PDI. (d) UV-vis-NIR absorption of Zr-PDI, Zr-PDI^{•-} and Zr-PDI^{••-} after a month. The insets show the photographs of color changes. (e) Illustration of the colored PDI^{••-} formation and photothermal conversion of Zr-PDI^{••-}. (f) Photothermal conversion curves of Zr-PDI^{••-} films on quartz glass under laser irradiation (808 nm, 0.7 W cm⁻²). Reprinted with permission from ref. 49, Copyright 2019 Nature.

effect was attributed to the ferrocene ligand. Zr-Fc MOF showed broad absorption in the region of 350–1350 nm. Under 808 nm light irradiation, the temperature of Zr-Fc reached 92 °C in 3 min, while for Fe(COOH)₂, the highest temperature was merely 46.8 °C. This difference was derived from the greater stability of Zr-Fc MOF. Besides, the radiative decay of Zr-Fc MOF was inhibited as manifested by the fluorescence emission, which indicates that more excited photo-electrons decayed through nonradiative pathways, thus more heat was generated for PTT. Moreover, Zr-Fc can also act as a Fenton catalyst, which showed 3.3 times higher •OH production at 45 °C as compared to that at 25 °C. Hence, when incorporated in the MOF structure, the ferrocene ligand could provide chemo- and photothermal-synergistic therapy, which was simple and straightforward.

As for mixed-ligand MOFs, Zheng *et al.* incorporated tetraporphyrin (TCPC) into Hf-Uio-66 with a content of 8 wt% (referred to as TCPC-Uio).²⁷³ As a porphyrin derivative, TCPC had photodynamic activity. However, the ROS yield of TCPC-Uio was much less than the free TCPC molecule, which was probably ascribed to the weakened confinement of TCPC and the resulting aggregation. Instead, the photothermal ability of TCPC played a dominant role in this therapeutic system. Under 630 nm light irradiation, the temperature increased to 42 °C within 5 min at the lowest NPs concentration. The tumor inhibition also reached up to 90% after treatment. Therefore, the photothermal ability of porphyrin-based MOF is also worth exploring.

In terms of photothermal nodes, Zhou *et al.* reported a porphyrin-palladium MOF (Pd-MOF) composed of Pd nodes and 5,10,15,20-tetrakis(4-pyridyl)-21H,23H-porphine (TPyP) ligands for hydrogen-thermal therapy.¹⁰⁴ The photothermal effect was attributed to a single-atom Pd unit, and the photothermal efficacy was up to 44.2%. More importantly, Pd nodes have specific coordination ability with hydrogen. After hydrogenation, the obtained PdH-MOF had high hydrogen loading. The continuous hydrogen release could effectively scavenge •OH and ONOO⁻, causing the disorder of tumor energy metabolism. Hydrogen therapy also lowered the required intensity of light in PTT.²⁷⁴

4.1.3 Photothermal effect by ligand-to-metal charge transfer. For coordination structures such as MOF, the electrons go through not only interband transition, but also various charge transfer processes such as metal-to-ligand charge transfer and ligand-to-metal charge transfer, *etc.*⁹¹ Ligand-to-metal charge transfer (LMCT) occurs when the metal nodes are in a relatively low valence state. When the material is excited, the electron will move from the donor orbital of the ligand to the accepting orbital of the metal nodes.⁹¹ LMCT endows materials with strong absorption in the low-energy regions, such as the visible light and NIR light region, which facilitates photothermal ability.^{91,275} The reported combinations of metal nodes and linkers used in PTT are given in Fig. 18.^{275–277}

Liu *et al.* fabricated Fe-CPND composed of Fe³⁺ nodes and gallic acid ligand, which was protected by PVP.²⁷⁵ The Fe-CPND was 5.3 nm in size, which can be cleared by the kidneys, thus

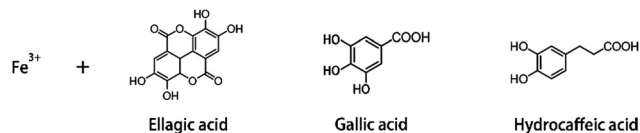


Fig. 18 Typical combinations of intrinsic photothermal MOFs based on ligand-to-metal charge transfer.

lowering the toxicity of the material. In an acidic environment, the gallic acid ligand gradually disassociated from Fe-CPND and the Fe^{3+} -gallic acid complex changed from tris- to bis-coordination, which was attributed to the change in the coordination number of gallic acid. This pH-induced structural change endowed Fe-CPND with higher longitudinal relaxivity at pH = 5.0. Hence, the MRI ability of Fe-CPND can be triggered by tumor acidity. The LMCT effect was attributed to the phenolic oxygen on gallic acid. Under 808 nm light irradiation, the temperature of Fe-CPND quickly rose to 50 °C, which significantly inhibited tumor growth. Moreover, the absorption of Fe-CPND did not change after being irradiated for 60 min, which indicates the good photostability of Fe-CPND. More recently, it has been reported that MOFs composed of Fe^{3+} metal nodes and ellagic acid²⁷⁷ or hydrocaffeic acid ligands²⁷⁶ can be used as PTAs due to the LMCT effect. Similar to the gallic acid ligand mentioned above, both ellagic acid and hydrocaffeic acid can form complexes with Fe^{3+} . The photothermal ability of this kind of MOF originated from the Fe-phenol structure, which resulted in the LMCT effect. Hence, these findings could inspire the design of MOF compositions in the future exploration of intrinsic photothermal MOF.

4.2 Modifications via photothermal agents

Photothermal MOFs can be fabricated by the encapsulation of PTAs, such as indocyanine green (ICG) and its derivatives. The chemical structures are presented in Fig. 19.^{66,185,278}

Cai *et al.* loaded indocyanine green (ICG) in HA-coated MIL-100(Fe) with a loading content of 40%.²⁷⁸ *In vitro* tests manifested that under 808 nm light irradiation for 3 min, the temperature could reach up to 70 °C, and the temperature could remain for 10 min, while free ICG solutions reached 65.47 °C after 3 min of irradiation but soon decreased due to the poor photostability of ICG. This result indicates that the

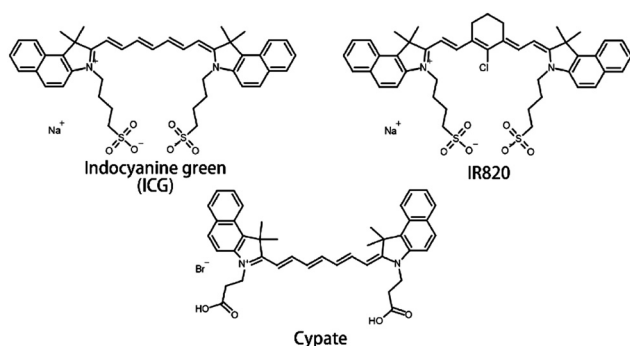


Fig. 19 Chemical structures of PTAs that can be encapsulated in MOFs.

encapsulation in MOF can improve the photothermal ability of ICG, which was ascribed to the better photostability of ICG under the protection of the MOF. Moreover, Fe nodes and HA also rendered the integration of fluorescence imaging, PA imaging and MRI guidance. Zhu *et al.* encapsulated Pd nanosheets and DOX in ZIF-8 through a one-pot strategy, and coated ZIF-8 with PDA.²⁷⁹ The Pd nanosheets acted as a PTA, which was 17 nm in size. After the encapsulation of Pd nanosheets, the particle size of ZIF-8 increased from ~150 to ~300 nm. After the coating of PDA, the photothermal conversion efficiency of the final product was 45%. Besides the photothermal effect, this material also has pH-controlled drug release ability. Zhang and coworkers used IR820 as the bond between the anticancer drug cytarabine (Ara) and ZIF-8 to improve the interaction between the model drug and MOF.⁶⁶ ZIF-8 was further covered with HA to realize active targeting through enhanced permeability and the retention effect. Due to the small molecular size and lack of strong bonding functional groups, Ara was hard to load in the MOF without leaking. In their work, the amino bond of Ara was firstly bonded with the carboxyl bond of IR820, forming a prodrug. Then, the prodrug was loaded in ZIF-8 by coordinating with the sulfonic group of IR820 with a loading content of 39.8%. In the acidic tumor area, ZIF-8 would decompose, after which the amide linkage was hydrolyzed by amidase, releasing Ara for chemotherapy. ZIF-8 also improved the photostability of IR820, which resulted in higher photothermal conversion efficacy and high-temperature increase (26.7 °C).

4.3 MOF-derived carbon materials

MOF-derived carbon materials are fabricated by MOF pyrolysis, which possess high porosity and controllable structures.^{280–282} During pyrolysis, the metal cations in the MOF are reduced to isolated metal sites, and the organic linkers are changed into carbon supports due to carbonization.²⁸³ The heteroatoms on organic linkers (*e.g.*, N atoms on the 2-mIm linkers of ZIF-8) remained on the carbon framework.^{280,284} To add more metal sites to this carbon material, metal precursors can be pre-encapsulated in the MOF before pyrolysis.²⁸⁵ Moreover, the carbon defects, metal sites and the graphitic contents can be tuned by different pyrolysis conditions.²⁸⁴ Like the traditional carbon materials, MOF-derived carbon materials also have light-to-thermal conversion ability, which can be used for PTT. More importantly, the doped metal atoms and heteroatoms can be used for single-atom catalysts.^{283,285,286} To be specific, if the organic linker contains nitrogen, a M–N–C structure (M refers to Co, Fe, Mn, Zn, *etc.*) can be generated after pyrolysis under certain environments, wherein the metal centers are coordinated with several N atoms, forming the M–N_x structure, and each metal site is isolated.²⁸⁷ Compared to the bulk or nanocatalysts, single-atom catalysts are on the atom scale, which means they have much higher efficiency than traditional catalysts.²⁸³ Therefore, single-atom catalysts have been widely applied in the O₂ reduction reaction²⁸⁸ and CO₂ reduction reaction, *etc.*²⁸⁹ In biomedical applications, it can also generate

$\bullet\text{OH}$ through the Fenton reaction, which is comparable to natural enzymes.^{287,290}

Huo *et al.* fabricated a single-atom catalyst based on an Fe-decorated ZIF-8 precursor that could combine PTT with $\bullet\text{OH}$ generation chemotherapy (Fig. 20a).²⁹⁰ The authors firstly encapsulated Fe^{III} acetylacetonate in ZIF-8 by a precursor isolation strategy, and the composite was then subjected to pyrolysis at 800 °C. After the pyrolysis, Fe atoms from Fe^{III} acetylacetonate were coordinated with neighboring N atoms, forming the $\text{Fe}_1\text{-N}_x$ structure, which was used for single-atom Fe nanocatalysts, termed as SAF NCs (Fig. 20b). The loading of the Fe single-atom was 1.54 wt%. The $\bullet\text{OH}$ production rate of this material is much higher than that of Fe_3O_4 , and the $\bullet\text{OH}$ production is accelerated in an acid environment. The $\bullet\text{OH}$ generation mechanism is shown in Fig. 20c and d. When an H_2O_2 molecule approached SAF NCs, it was firstly absorbed on the Fe atom of the Fe-N_4

structure, and then cleaved by the homolytic path, releasing a $\bullet\text{OH}$ and leaving a hydroxyl group on the Fe atom. In an acidic environment, the residual hydroxyl group can be desorbed from the Fe atom in the form of a H_2O molecule by reacting with a protonated hydrogen atom. Hence, this Fe-N_4 structure can be used for decomposing another H_2O_2 molecule. However, in a neutral environment the desorption of OH^* is much harder (Fig. 20d) due to a lack of protonated hydrogen atoms. Although the residual hydroxyl group can be attached to another H_2O_2 group through hydrogen bonding, the $\bullet\text{OOH}$ formation and desorption is hard to occur due to a high energy barrier. Hence, in a neutral environment, the catalytic activity of the single-atom catalyst is inhibited. To improve its biocompatibility, SAF NCs was further PEGylated, referred to as PSAF NCs, which could induce the ferroptosis of tumor cells. The resulting lipid peroxidation also contributed to tumor cell death. The tumor

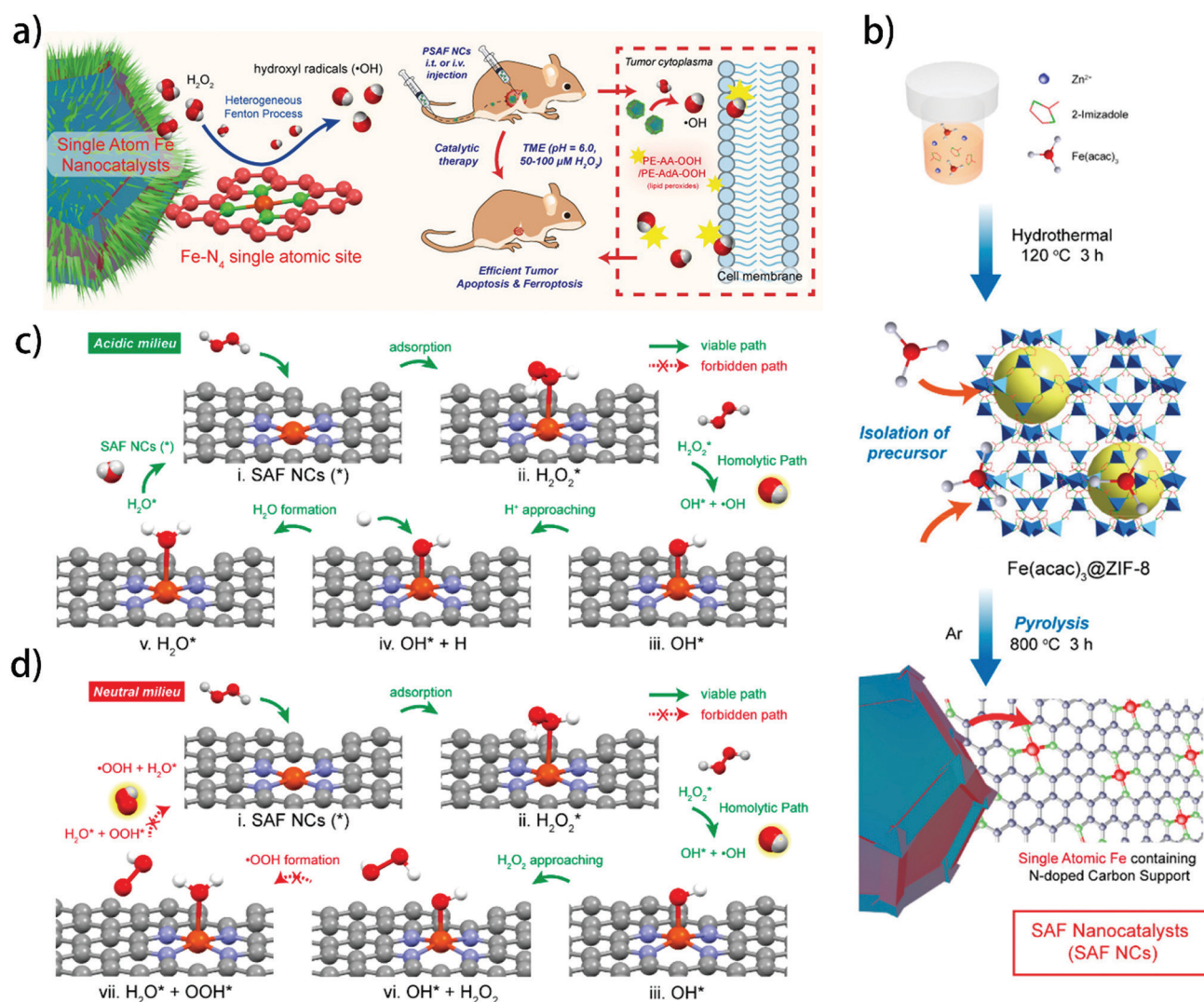


Fig. 20 (a) Schematic illustration of SAF NCs for PTT and the Fenton reaction in the tumor microenvironment. (b) Schematic diagram of the isolation-pyrolysis approach to synthesizing SAF NCs. Proposed reaction mechanism schematics for SAF NCs in the heterogeneous Fenton reaction toward generating $\bullet\text{OH}$ under (c) acidic (protonated) and (d) neutral catalytic milieu. Reprinted with permission from ref. 290. Copyright 2019 American Chemical Society.

inhibition rate of PSAF NCs without light irradiation was up to 63.5%. As for PTT, under 808 nm light irradiation, the temperature of PSAF NCs increased by 45 °C. With the assistance of PTT, PSAF NCs could achieve complete eradication of tumor.

For ion release-related applications, Yang *et al.* annealed ZIF-8 under an Ar atmosphere, 800 °C and O₂ atmosphere, 200 °C, respectively, after which the ZIF-8 was turned into ZnO-doped carbon NPs with a diameter of 50 nm.²⁹¹ Afterwards, poly(*N*-isopropylacrylamide) (PNIPAM) was coated, which served as a thermo-responsive gel layer. The final product was called ZnO-CNP-TRGL. Under 5 min of 808 nm light irradiation, the temperature of ZnO-CNP-TRGL increased to 55 °C, confirming the photothermal ability of this ZIF-8-derived carbon material. Moreover, when immersed in phosphate buffer solution (PBS), about 0.63 wt% of Zn²⁺ from ZnO-CNP-TRGL was released, which can destroy the membranes of the bacteria and cause the denaturation of proteins and enzymes. Moreover, the thermo-responsive gel layer changed from highly hydrophilic to hydrophobic when the temperature increased from room temperature to higher than the lower critical solution temperature of PNIPAM. Hence, at a higher temperature, ZnO-CNP-TRGL can form bacterial aggregations due to its hydrophobicity and the hydrophilic adhesin proteins on bacteria. The bacteria trapping process occurred at 40 °C, and the material showed complete bacterial eradication of *S. aureus* when the temperature was higher than 45 °C, due to the synergistic effect of PTT, Zn²⁺ release and bacteria trapping. Fan and coworkers *in situ* fabricated ZIF-8 on graphene oxide nanosheets, which was then carbonized under an Ar and O₂ atmosphere, successively.²⁹² The as-obtained ZnO-doped graphene was grafted with transformable thermal-responsive brushes, giving rise to TRB-ZnO@G. When the temperature rose to 56 °C by the PTT effect, the polymer brushes changed from hydrophilic to hydrophobic, which can be used for bacteria trapping. The 2D morphology of graphene nanosheets can also kill bacteria *via* physical cutting.

4.4 MOF-based composites

4.4.1 MOF-photothermal polymer composites. Polymers have been widely applied in MOF-based therapeutic systems for better stability and biocompatibility.²⁹³ Besides this property, polypyrrole (PPy),^{39,294} PDA²⁹⁵ and polyaniline (PAN),²⁹⁶ *etc.* have additional photothermal ability. In the hybridization of photothermal polymers and MOF, polymers are usually in the form of surface coating, core structure, decoration NPs or *in situ* polymerized in the pores of MOF. Zhu *et al.* synthesized PPy NPs, and introduced PVP on PPy NPs to facilitate the nucleation of MIL-100.²⁹⁴ Afterwards, DOX was loaded in MIL-100. The release of DOX was influenced by both low-pH-induced MOF decomposition and NIR irradiation-induced temperature increase. In their work, PPy served as the PTA, and its combination with MIL-100 provided feasibility for drug loading-assisted PTT. Wang *et al.* utilized UiO-66 to absorb aniline monomer through electrostatic interaction. Afterwards, the oxidizing agent, ammonium persulfate, was added to trigger the polymerization. PAN was polymerized on the surface of UiO-66, giving a smooth surface of the particle. Due to the strong absorption of PAN in the NIR region, the

maximum temperature under irradiation was 57.2 °C, and its photothermal conversion efficiency was 21.6%.

The small size of the polymer monomer makes it easy to be introduced and subsequently polymerized in the nanopores of MOF; this method is called *in situ* polymerization. By this method, it is easy to control the polymer size and generate a uniform hybrid of MOF and polymers.²⁹³ Huang *et al.* fabricated MIL-53, which has mixed-valent Fe nodes.²⁹⁷ The unsaturated coordination of the Fe³⁺ node can be used to oxidize the polymerization of Py. After the *in situ* polymerization of PPy, MIL-53 retained its structure and drug loading capacity. The DOX loading content in MIL-53 was up to 90%, and the release of DOX was triggered in an acidic environment. Under 808 nm light irradiation, the temperature increased by 22.1 °C at 0.50 mg mL⁻¹ with good photostability. The PPy@MIL-53 composite can also act as a contrast agent for MRI. Wang *et al.* firstly blended dopamine monomer with manganese acetate, which formed coordination bonds through phenolic hydroxyl groups.⁵³ Afterwards, the ligand precursor, K₃[Co(CN)₆], was added to the mixture. Hence, the dopamine monomer was loaded in the pores of MnCo MOF, which is a PB analogue. After 24 h of stirring, dopamine was *in situ* polymerized, forming the composites of PDA and MnCo, referred to as MCP, which was further attached with PEG and tumor-targeting peptide cRGD-SH (cyclic arginine-glycine-aspartic acid). Due to the π - π stacking between -C $\equiv$ N and dopamine, the absorption of MCP showed an extra absorption at 550–700 nm, which indicates that the absorption of MCP was enhanced. The photothermal conversion efficiency of MCP was 41.3%, which was higher than that of PDA NPs (36.9%). Hence, *in situ* polymerization could enhance the therapeutic efficacy of photothermal polymers, and the MnCo structure also provided feasibility for MRI and targeting molecule attachment.

4.4.2 Core-shell structure. Traditional photothermal NPs such as Au-based particles (Au nanorods,²⁹⁸ Au nanostars,^{52,299} and Au NPs^{300–302}), Pd nanocubes,⁹⁹ magnetic carbon,³⁰³ PB, and photothermal polymers, *etc.*, usually lack homogeneous targeting and drug loading capacity. Moreover, the particles also suffer from aggregation. Coating the MOF shell on the photothermal core not only makes up for these shortcomings but also improves the crystallinity of the composite.³⁰⁴ As PB- and polymer-based core-shell structures have been discussed above, we firstly take Au-based particles as an example. The photothermal ability of Au particles mainly stems from the LSPR effect under light irradiation.⁸² Li *et al.* fabricated a single gold nanorod (AuNR) of 47 nm in diameter and 12 nm in length.²⁹⁸ Afterwards, ZIF-8 was synthesized on PVP-stabilized gold nanorods and loaded with DOX. The LSPR absorption peak of AuNR@ZIF-8 shifted to ~810 nm as compared to the sole AuNR (~790 nm), which was attributed to the influence of the ZIF-8 shell. Owing to the AuNR core, the nanocomposite showed potent photothermal efficacy under 808 nm NIR light irradiation. The release of DOX was triggered by the acidic environment and NIR light irradiation because of ZIF-8 decomposition, thus enhancing the potency of therapy. Deng and coworkers reported a ZIF-8-covered Au nanostar, which was

further etched by tannic acid.⁵² The cavity between ZIF-8 and the Au nanostar was utilized to store DOX. The Au nanostar has strong absorption in the second NIR light (NIR-II) region (1000–1350 nm). Owing to the deeper penetration and larger maximum permissible exposure, the NIR-II-based PTT has better therapeutic efficacy. The composite had higher photothermal conversion efficiency under 1064 nm light (48.5%) as compared to 808 nm light irradiation (30.2%). The generated heat also dissociated the Zn–O coordination bond, thus accelerating the DOX release. Moreover, the strong absorption also provided PA imaging and infrared photothermal imaging.

Besides Au-based NPs, Deng *et al.* coated MIL-100 on magnetic carbon NPs.³⁰³ The MOF shell was PEGylated and subsequently modified with Mn carbonyl. Finally, DOX was loaded in MIL-100. The magnetic carbon core served as a PTA for PTT, and it also provided PA imaging and MRI response for imaging guidance. The $[\text{Mn}(\text{CO})_5]^+$ moiety was used as the CO source for gas therapy, and the CO capacity was 1.16% (w/w). Under 808 nm light irradiation, the temperature elevation not only accelerated the DOX release, but also triggered CO therapy. The combined CO therapy facilitated the escape of the composite from lysosomes, guaranteeing the efficacy of the drug, and also made up for the deficiency of the relatively low photothermal temperature.

4.5 Enhancing the efficacy of photothermal therapy

4.5.1 Improving photothermal conversion efficiency. Generally, for PTAs, high photothermal conversion efficiency can decrease the irradiation time, laser power density and PTA dose, thus minimizing tissue damage.³⁰⁵ Therefore, many methods have been devoted to increasing the photothermal conversion efficiency. As mentioned in Section 2, two processes are related to the photothermal effect: light absorption and nonradiative relaxation of electrons. To improve the photothermal conversion efficiency, researchers can optimize the absorption of the material or create more nonradiative pathways. To date, several strategies have been put forward as follows: (i) increasing the density of DLDs;⁷⁰ (ii) introducing more electron circuit loops through the heterostructure;³⁰⁶ (iii) narrowing the bandgap;³⁰⁷ (iv) introducing more CR pathways;⁵⁶ (v) optimizing LSPR absorption;²⁴⁹ (vi) transferring electron transition from the bandgap to the LSPR,⁵⁴ *etc.* Here, we listed some examples of enhancing the photothermal conversion efficiency of MOF-based materials.

Cai *et al.* doped Gd^{3+} in PB for the tunable LSPR and enhanced MRI ability.²⁴⁹ It is known that LSPR is based on the collective oscillations of free charge carriers. In PB, the free charge carrier mainly refers to $[\text{Fe}(\text{CN})_6]$. The position of the Gd^{3+} dopant was firstly at the interstitial site, which had no impact on the $[\text{Fe}(\text{CN})_6]$ vacancy. With the increase of Gd^{3+} concentration, the dopant position changed to the lattice site, forming the $\text{Fe}-\text{C}\equiv\text{N}-\text{Gd}$ structure. The number of $[\text{Fe}(\text{CN})_6]$ vacancies was therefore decreased. Simultaneously, the electron density and orbital energies of $-\text{C}\equiv\text{N}-$ were also affected by lattice Gd^{3+} . As a result, the LSPR absorption peak red-shifted from 710 to 910 nm. The authors adjusted the absorption peak to around 808 nm, which was beneficial for applying 808 nm irradiation, giving rise to a much enhanced photothermal efficacy.

Additionally, as a typical contrast agent, Gd^{3+} improved the MRI efficacy of PB. Moreover, the Gd-doped PB can also reduce oxidative stress by scavenging ROS.

Li *et al.* doped PB with Zn with increasing doping levels, which were called ZnPB-1, -2, and -3.⁵⁴ Fe^{2+} in PB was replaced by Zn^{2+} , forming the $\text{Fe}-\text{C}\equiv\text{N}-\text{Zn}$ structure. As shown in Fig. 21a, the structure of PB was simplified into two kinds of octahedrons with Fe located at the center ($\text{Fe}(\text{III})-\text{N}$ and $\text{Fe}(\text{III})-\text{C}$). The Zn doping gave rise to another octahedron that was centered with the Zn atom ($\text{Zn}(\text{II})-\text{C}$). Along with increasing the Zn dopant concentration, the bandgap of ZnPB decreased from 1.72 to 1.65 eV according to density functional theory, which was also proved by experimental calculations (Fig. 21b). On the other hand, the electronic density also increased with more Zn doping, which gave rise to the major electron transition changing from bandgap to LSPR. Due to the hybridization of Zn dopant and crystal structure interaction, the NIR absorption peak of PB red-shifted to the lower energy region (Fig. 21c). Owing to the narrowed bandgap and red-shifted LSPR, the photothermal conversion efficiency of Zn-doped PB reached up to 39.79% (ZnPB-3). Under 808 nm light irradiation, the temperature of ZnPB-3 could increase to above 50 °C, which is the required temperature for bacteria-killing. Moreover, the heat generated from the enhanced photothermal effect also facilitated the diffusion of interstitial Zn^{2+} , which improved the collagen deposition for wound healing. To sum up, ZnPB-3 had excellent short-term and long-term antibacterial ability against *E. coli*, *S. aureus*, and MRSA biofilm.

Yu *et al.* coated PB on NaNdF_4 particles, forming a core-shell structure (NdNP@PB).⁵⁶ During fabrication, citric acid was applied as a surfactant to provide growth sites for PB and improve the stability of NP (Fig. 21d). The ladder-like energy levels of Nd^{3+} have cross-relaxation (CR) pathways between Nd^{3+} ions. Since the CR process and the subsequent photon relaxation to the ground state can contribute to heat generation (Fig. 21e), NaNdF_4 can be used as PTA, but its photothermal conversion efficiency was merely 8.7%. One way to improve the photothermal conversion efficiency was by increasing the Nd^{3+} concentration to generate more CR pathways between the same lanthanide ions (Fig. 21f). However, increasing the doping content of Nd^{3+} to even 100% cannot provide enough photothermal effect. Therefore, new CR pathways needed to be introduced. PB has a continuous energy band. When the energy band of PB was in close contact with that of NaNdF_4 , new CR pathways with shorter distances were generated (Fig. 21g). Therefore, the nonradiative relaxation distance was much longer, leading to better PTT effects. Hence, NdNP@PB showed a much enhanced photothermal conversion efficiency of up to 60.8%, and the tumor growth inhibition of NdNP@PB was 76.7%.

4.5.2 Low-temperature photothermal therapy. Another important factor of PTT is therapeutic temperature. As high-temperature PTT will result in serious damage to ambient healthy tissue, researchers put forward the low-temperature PTT (*e.g.*, 43 °C) strategy. The main concern of low-temperature PTT is the cell's resistance to hyperthermia, which is related to a higher expression of heat shock proteins (HSPs) in the low-temperature region. Zhang and coworkers encapsulated siRNA, which is an HSP 70 inhibitor, in the Zr-ferriporphyrin MOF

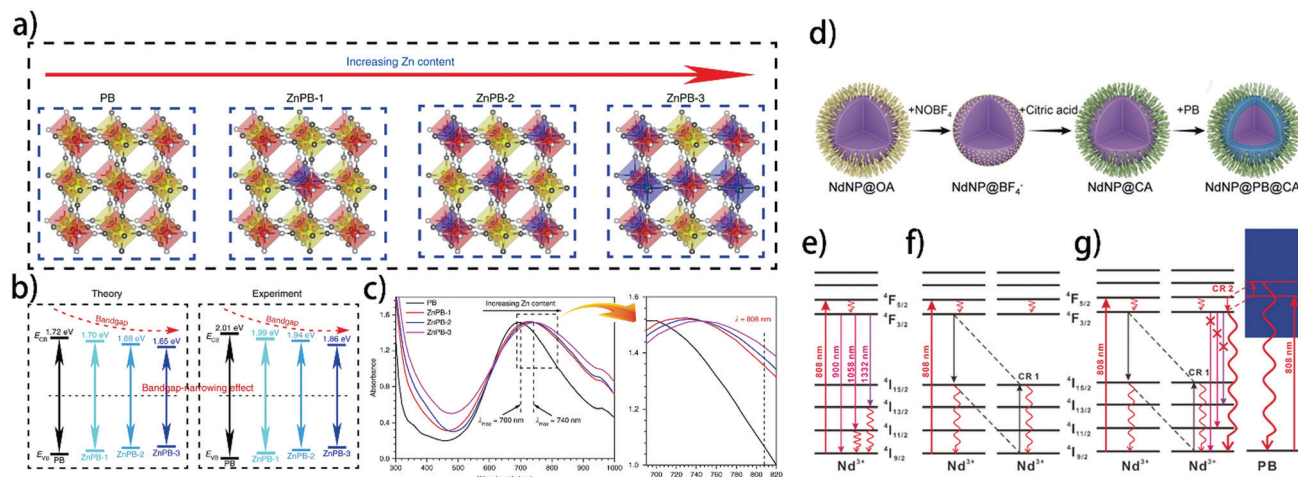


Fig. 21 (a) Simplified geometrical structure of PB and ZnPB with various doping levels (color coding: Fe(III) – red, Fe(II) – yellow, Zn – blue, N – grayish and C – dark gray). (b) Scheme of bandgap-narrowing effect with the increase of Zn-doped density by theory and experiment. (c) UV-vis-NIR spectra of PB, ZnPB-1, ZnPB-2 and ZnPB-3. Reprinted with permission from ref. 54. Copyright 2019 Nature. (d) Synthesis of NdNP@PB. Simplified diagrams of the (e) radiative and nonradiative processes in a single Nd^{3+} ion, (f) CR between Nd^{3+} ions, (g) generation of new CR pathways between Nd^{3+} ions and PB. Reprinted with permission from ref. 56. Copyright 2019 Wiley.

(siRNA/Zr-FeP) with a loading capacity of 76.13%.¹⁴⁵ Under 635 nm light irradiation, the temperature increased to 45.4 °C, and the photothermal conversion efficiency was 33.7%. The release of siRNA was triggered by tumor acidity and heat. It was observed that the expression of HSP 70 was inhibited after treatment with siRNA/Zr-FeP. Animal testing manifested that siRNA/Zr-FeP had the best therapeutic efficacy due to the inhibited thermal resistance. Another strategy is inhibiting the generation of ATP, which is related to the expression of HSP. This strategy can be used for combining PTT with starvation therapy. Zhou *et al.* loaded GOx in HMPB and coated them with HA. Upon irradiation for 5 min, the temperature reached 45 °C by HMPB.²⁵ After endocytosis, the intracellular GSH can cleave the disulfide bond between HMPB and HA, triggering the release of GOx. HMPB then decomposed H_2O_2 to increase the O_2 content for the oxidation of glucose. Results showed that after the treatment, the ATP level of HepG2 and HL-7702 cells decreased and the expressions of both HSP70 and HSP90 were dramatically inhibited. Therefore, the efficacy of low-temperature PTT was improved, and the combined starvation therapy also contributed to tumor growth suppression.

4.5.3 Drug release controlled by phase-change material.

Drug loading is a ubiquitous combined therapy for MOF-based PTT, as MOF is an ideal drug carrier and photothermal heat can accelerate the diffusion of the drug. PTT also enhances the sensitivity of chemotherapy.²⁵² Based on these properties, precise control over drug release was achieved by introducing phase-change materials (PCM) such as 1-pentadecanol,^{308,309} tetradecanol²⁹⁵ and lauric acid.³¹⁰ Only when the temperature rises above the melting point of PCM will the loaded drug be released. Therefore, in blood circulation, this strategy can realize “zero drug leakage”. Zhang *et al.* incorporated DOX and losartan with lauric acid, and encapsulated them in HMPB.³¹⁰ After 10 min of 808 nm NIR light irradiation, the

maximum temperature of the composite rose to 59.2 °C, which was above the melting point of lauric acid (44.7 °C), thus triggering the release of DOX and losartan. After 21 min of irradiation, the release rate of DOX was up to 21.9%, while almost no release was observed under 3 min of irradiation. Moreover, the released losartan could enhance the penetration of DOX by degrading extracellular matrices. Therefore, the combination of controlled-drug release and PTT gave rise to a tumor inhibition rate of up to 81.3%. Wu and coworkers covered ZIF-8 with PCM and PDA after loading DOX in the MOF.²⁹⁵ The melting point of the PCM, tetradecanol, was 38–40 °C. The photothermal ability was attributed to PDA coating. The DOX release was controlled by both NIR irradiation and pH value, and NIR light-triggered PCM degradation was more critical. Within 5 min of 808 nm light irradiation, the temperature increase in aqueous solution was 34.6 °C ($500 \mu\text{g mL}^{-1}$), which was above the melting point of the PCM shell. Additionally, the tumor acidity-induced ZIF-8 decomposition also accelerated the DOX release. Hence, the drug release amount under both NIR irradiation and pH 5.0 was up to 78%.

5. Photodynamic and photothermal synergistic therapy

Although both PDT and PTT have been reported to be efficient strategies in clinical applications, there are still some drawbacks in each therapy. First of all, due to the hypoxia in the therapeutic area, it is hard to satisfy the O_2 demand of PDT, which hinders the ROS generation.⁶⁷ As for PTT, improving photothermal conversion efficiency requires complex modification.¹⁴¹ Another concern is that to achieve sufficient ROS yield or temperature increase, the laser power density is usually high, which might cause lesions in healthy tissues.¹⁸⁷ To solve these problems,

combined therapies have been put forward, such as chemotherapy,^{263,311,312} gas therapy,^{46,112,255,256} *etc.*, which adds to the complexity of the design. As PDT and PTT can be simultaneously triggered by light irradiation, combining PDT and PTT in one therapeutic system is a promising way to overcome the disadvantages of PDT and PTT. Moreover, the heat generated by PTT can improve the blood flow, and consequently increase the ambient O₂ content to alleviate hypoxia.¹⁴⁵ On the other hand, targeted cells also become more sensitive to heat due to the interference of PDT.¹⁴⁵ Therefore, PDT and PTT can work synergistically. In this section, we will discuss how to construct PDT and PTT synergistic therapeutic systems based on MOFs.

The “all-in-one” strategy means incorporating both photo-thermal and photodynamic ability in one MOF without further modification. Han *et al.* introduced Cu²⁺ into the porphyrin ligands of PCN-224 with various doping levels (5%, 10%, 15% and 25%).¹⁴⁶ The Cu²⁺ dopant could trap electrons, thus hindering the recombination of electron-hole pairs. After the electron trapping, Cu²⁺ was reduced to Cu, which could react with holes and decrease the photocatalytic ability. Therefore, the dopant concentration should be moderate. Their results showed that PCN-224 with 10% Cu²⁺ dopant (denoted as Cu₁₀MOF) had the highest ¹O₂ generation and relatively higher absorption at 660 nm. Moreover, the d-d transition of the chelated Cu²⁺ provided the photothermal effect. Under 660 nm light irradiation, the temperature of Cu₁₀MOF was the highest (48.4 °C). Therefore, the synergistic therapy of Cu₁₀MOF exhibited 99.71% and 97.14% of bacteria-killing against *S. aureus* and *E. coli*, respectively. Li *et al.* reported a Cu-TCPP MOF nanosheet.¹⁴⁴ The thickness of the nanosheet was 5.1 ± 0.3 nm, which rendered a quicker response to light as compared to the bulk material. The PDT effect of the TCPP ligand was triggered by 660 nm laser. Owing to the d-d transition of Cu²⁺ nodes, Cu-TCPP also efficiently transforms light into heat. Under 5 min of 808 nm light irradiation, the temperature quickly increased 34.5 °C. Moreover, due to the unpaired 3d electrons of Cu²⁺ nodes, the nanosheets could be used for MRI and infrared thermal imaging.

As mentioned in Section 4.3, the high-temperature pyrolysis of MOFs can generate MOF-derived carbon materials, which features photothermal conversion ability. If the ligand is N-containing, the MOF-derived carbon material can show a porphyrin-like M-N-C structure (M denotes metal center) under appropriate pyrolysis conditions, wherein the metal cations are dispersed and each of them is coordinated with 4 pyridinic nitrogen, which is similar to the coordination environment in porphyrin.^{313–315} Therefore, the porphyrin-like structure further endows this material with PDT ability. Wang and coworkers coated ZIF-8 with mesoporous silica, followed by high-temperature pyrolysis.³¹³ Afterwards, mSiO₂ was removed by NaOH etching. This surface protection prevented the aggregation of the M-N-C structure during pyrolysis. The diameter of the as-obtained material (referred to as PMCS) was about 140 nm, and it retained the porosity of the ZIF-8 precursor. Similar to other carbon materials, PMCS had strong absorption in the NIR region. PDT and PTT were simultaneously triggered by

the 808 nm laser. The singlet oxygen quantum yield of PMCS was comparable to that of ICG, and the photothermal conversion efficiency was 33.0%. Due to the strong absorption, PMCS can serve as the contrast agent for PA imaging. The combination of imaging guidance, PTT, and PDT showed complete eradication against tumors.

Some dyes have been reported to have both ROS generation and light-to-heat conversion ability. Gao *et al.* applied UiO-66 as the O₂ carrier and coordinated ICG on the surface of UiO-66.¹⁸⁴ Afterwards, the nanoparticles were coated with red blood cell membrane. ICG served as both PS and PTA. Under 808 nm light irradiation, the temperature increased to 43.5 °C. The generated heat accelerated the diffusion of O₂ from the inner UiO-66 core, which in turn facilitated the PDT efficacy of ICG. Cypate is another organic dye that features photodynamic, photothermal, and versatile imaging abilities. Yang and coworkers introduced cypate during the fabrication process of MIL-53, denoting as CMNP.¹⁸⁵ CMNP was then coated with PEG and transferrin (referred to as CMNP-Tf). During fabrication, a cypate-Fe³⁺ precursor was firstly formed owing to the coordination bond between the carboxyl of cypate and Fe³⁺. Then after the addition of ligand solution, MIL-53, with defects, was created. The defects can be used to control the pore size of MIL-53, which increased with increasing the concentration of cypate. This method increased the druggability and bioavailability of cypate, and also avoided its photobleaching. Due to the successful loading and versatility of cypate, CMNP-Tf showed complete tumor ablation with good biocompatibility.

Lastly, to synthesize MOF-based composites with PDT and PTT dual functions, researchers usually combine the above-mentioned PSs (dye, porphyrin-based MOF, *etc.*) and PTAs (Au-based PTA and photothermal polymer, *etc.*), which all achieved superior therapeutic efficacy.^{142,182,186,267} Here, we mainly illustrate examples of multi-MOF core-shell structure. Liu *et al.* fabricated a dual MIL-101 core-shell structure by the *in situ* growth method, and decorated the outer shell with PEG-FA and cyanine 3-labelled peptide (referred to as BQ-MIL@cat-fMIL) (Fig. 22a).¹⁸⁶ The inner MIL-101 was loaded with black phosphorus dots (BQ), while the outer MIL-101 was loaded with catalase. Because of quantum confinement and edge effects, BQ is promising for combining PDT and PTT. The photosensitivity of MIL-101 resulted in a widened gap between the triplet state and the ground state of the composite, indicating that the excited BQ-MIL@cat-fMIL mainly reacted with ³O₂ rather than went through phosphorescence emission. Therefore, the ¹O₂ generation of BQ-MIL@cat-fMIL was increased to 88.3%. Moreover, the catalase in the outer shell of MIL-101 efficiently provided O₂ for the inner BQ by decomposing H₂O₂. Under 660 nm light irradiation, the apoptotic percentage was 52.1% by PDT, which was 8.7 times higher than that without catalase. On the other hand, the photothermal effect was triggered by 808 nm light, and the photothermal conversion efficiency was 23.3%, which provided 28.7% of cell apoptosis. After applying dual-light irradiation, the combination of PDT and PTT led to 75.6% of cell apoptosis.

Luo *et al.* coated PB with the UiO-66 MOF shell (Fig. 22b), which was used for bacteria-infected wound healing under

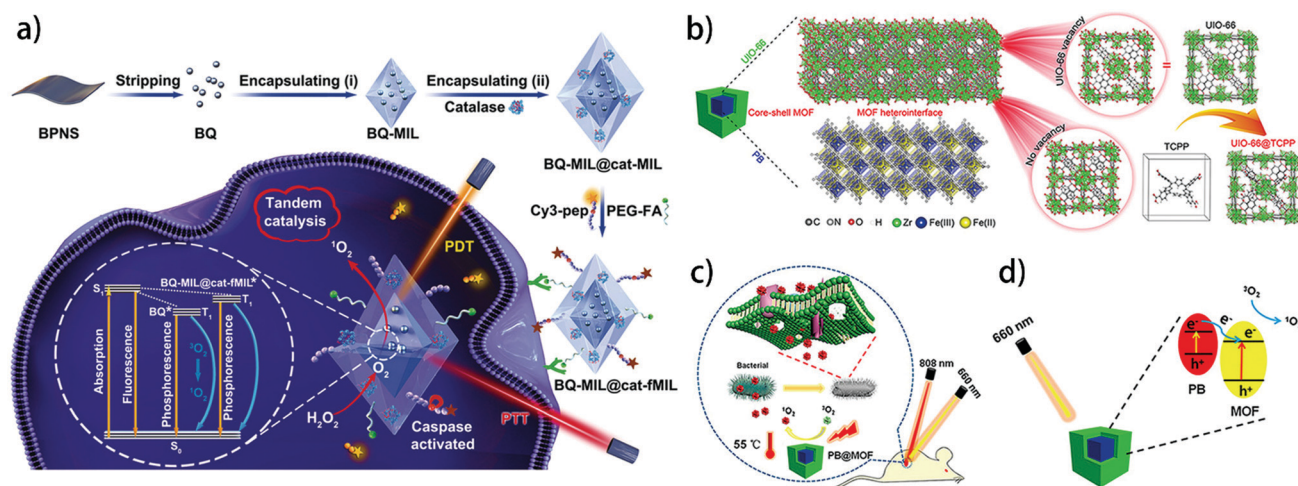


Fig. 22 (a) The stepwise assembly of BQ and catalase in MOF layers and its application as a tandem catalyst for enhanced therapy against hypoxic tumor cells. Reprinted with permission from ref. 186. Copyright 2019 Wiley. (b) Schematic illustration of the core-shell structure of PB@MOF. (c) Schematic illustration of the bacteria killing processes with the PB@MOF under dual light irradiation. (d) Schematic illustration of the rational photocatalytic mechanism for PB@MOF heterojunction photocatalysts. Reprinted with permission from ref. 267. Copyright 2019 American Chemical Society.

dual-light irradiation (660 nm light for PDT and 808 nm light for PTT (Fig. 22c)).²⁶⁷ Taking advantage of the defects in the MOF structure, the outer UiO-66 was doped with TCPP, which served as PS. The core-shell structure not only combined two therapies, but also enhanced the photocatalytic ability by forming a heterojunction structure. Both PB and TCPP-doped UiO-66 (referred to as MOF) were n-type semiconductors. Their results showed that PB had a lower CB than the MOF (Fig. 22d). Hence, the photo-induced electrons of PB could move to MOF, accelerating the photo-electron transfer and inhibiting photo-electron-hole recombination. Though the photothermal effect of PB was partially hindered by the UiO-66 shell, the temperature still exceeded 50 °C within 5 min of irradiation. Moreover, the composite released trace amounts of Fe and Zr element during degradation, which facilitated the wound healing. Therefore, this core-shell dual-MOF composite is superior for bacterial infection treatment. Under dual-light irradiation, the PB@MOF composite showed more than 99% of antibacterial efficiency against *S. aureus* and *E. coli*.

6. Conclusions and perspectives

In the last decade, the applications of MOFs in phototherapy have presented a booming trend, as illustrated in this review. Due to the tunability of the MOF structure, MOFs could directly serve as PSs or PTAs by applying photo-responsive building units, or act as the carrier of phototherapeutic agents. The periodic array of MOFs prevent the aggregation and self-quenching of PSs and PTAs, which greatly enhances their efficacy. Moreover, the active sites and cavities of MOFs make numerous modifications feasible, such as combined therapy, active targeting and imaging guidance, *etc.* To date, many complex and elaborate designs have been put forward, indicating the great potential of

MOF in phototherapy. However, to push this field forward, we have listed some issues that need to be addressed.

In spite of the advantages mentioned in this review, phototherapy still has many limitations such as O₂-dependence, inhomogeneous distribution of heat, and limited tissue penetration, *etc.* Future research on phototherapy may be combined with various therapies, including but not limited to chemotherapy, radiotherapy, gas therapy, starvation therapy and immunotherapy. Another concern is that the limited penetration is a big problem for phototherapy. Although the use of upconversion nanoparticles and two-photon activated PSs can improve the therapeutic depth, it is still difficult for phototherapy to cure deep-sited tumors or infections. Imaging guidance is another important auxiliary method in phototherapy, which can determine the location and morphology of lesions and monitor the distribution of therapeutic agents in order to provide the appropriate irradiation. More importantly, with the guidance of fluorescence, it is desirable to implant a light source in solid organs, which can be used for treating deep lesions.⁶ In view of these concerns, the MOF is an ideal carrier for these functions. To date, the combined therapy and imaging-assisted therapy based on MOFs have achieved good results. However, improvements are still needed for precise control, potent efficacy, resistance prevention and lowering tissue lesions before being applied in clinical settings.

Many researchers have mainly focused on improving the ROS yield and photothermal conversion efficiency of PSs and PTAs. However, other physiochemical properties of materials need to be taken into consideration as well, such as crystallinity, aqueous stability and degradability, *etc.* The specific mechanisms of photodynamic and photothermal effects should be further clarified, such as the electron transition pathway, and the correlation between radiative and nonradiative decays, which will shed light on the future design of MOFs with desirable ROS yields, photothermal conversion efficiency and other photo-related functions. On the other hand, the requirement of

combined therapy gives rise to the integration of various therapeutic agents, and each of them has separate functions. More studies towards the synergistic effect of these agents are needed, from synthesis to treatment mechanisms. For example, the influence on MOF morphology and crystallinity, the interface interactions of core-shell structure, the synergistic effects of the drug and ROS, *etc.* After the in-depth understanding of the underlying mechanisms, researchers can build up a comprehensive correlation between composition, structure, properties, and efficacy, which is beneficial for fabricating highly effective rather than purely structurally sophisticated medical materials.

In terms of clinical applications, the most important concern is the biosafety of materials. Unfortunately, up to now, none of these therapeutic agents have been approved by the FDA, indicating that more attempts towards improving biosafety are needed. Although there have been reports about different surface coatings to improve the stability and biocompatibility of materials, researchers still need to consider every process of materials in the body, such as drug administration, circulation in the blood flow, degradation, and elimination from the body. The related properties including biodegradability, particle size and the release of various agents during degradation should be carefully designed. Many researchers have reported the features of the therapeutic area, such as hypoxia and the generation of acidity, GSH, ATP and H₂S, *etc.*, and they have put forward various responsive methods. However, the understanding of the therapeutic area is not enough, as the real microenvironment is more complex. The immune response and physiological properties of different tumors, bacteria, biofilms and other diseases still need further investigation.

Although most reported MOF-based PSs or PTAs are aiming at cancer treatment, ROS generation and temperature increase induced by light irradiation are promising in many other fields as well. For example, many researchers have applied PDT and PTT in antibacterial applications, which can be divided into water disinfection,^{316,317} medical device sterilization,³¹⁸ wound healing,^{319,320} and implant modification,^{321–323} with light source ranging from the visible to NIR range. Moreover, the combination of PTAs and PCMs has been applied to fabricate the anticorrosion coating of magnesium alloy implants, which has light-induced self-healing ability.³²⁴ Therefore, the applications of PDT and PTT can be extended in various fields, which have different requirements for light penetration, ROS yield, and temperature increase. Besides the traditional material fabrication methods such as encapsulation and surface coating, some novel techniques such as biomineralization,^{325–327} which combines materials with bacteria and viruses, can be used in phototherapy as well. As the penetration depth of light is limited, researchers can focus on superficial diseases such as dental antibacterial applications, which can better utilize the light source. MOFs have been successfully fabricated in the form of nanoparticles, membranes,³²⁸ mixed-matrix membranes¹¹⁷ and coatings,^{329,330} which make it possible for MOF-based PSs and PTAs to adapt to different therapeutic conditions. Due to the unique structure of the MOF, it can be used as a precursor or template for fabricating new porous materials such as MOF-based carbon single-atom catalysts. Hence, on the basis of the

reported phototherapy in cancer treatment, researchers can consider using these materials in other medical applications.

In conclusion, the applications of MOFs in phototherapy have been put forward and rapidly developed in the last decade. Under rational design, MOFs can improve the efficacy of traditional phototherapy with multiple combined functions, which is now attracting more and more attention. However, although we have seen the elaborate design of MOFs and good therapeutic efficacy in recent publications, the research on MOFs in phototherapy is in its infancy. Numerous efforts are still needed before it reaches clinical trials. We believe that the applications of MOFs in phototherapy will continue to expand, and finally become an important part of medical treatment.

Abbreviations

ROS	Reactive oxygen species
PDT	Photodynamic therapy
PTT	Photothermal therapy
PS	Photosensitizer
•O ₂ [−]	Superoxide anion radical
•OH	Hydroxyl radical
H ₂ O ₂	Hydrogen peroxide
¹ O ₂	Singlet oxygen
HPD	Hematoporphyrin derivative
FDA	Food and Drug Administration
g-C ₃ N ₄	Graphitic carbon nitride
PTA	Photothermal agent
MOF	Metal-organic framework
NP	Nanoparticle
³ O ₂	Molecular oxygen
LSPR	Localized plasmon surface resonance
NIR	Near infrared
CB	Conduction band
VB	Valence band
DLD	Deep-level defect
CR	Cross relaxation
UV	Ultraviolet
SEM	Scanning electron microscope
TEM	Transmission electron microscope
DLS	Dynamic light scattering
H ₂ DBP	5,15-Di(<i>p</i> -benzoato)porphyrin
H ₂ DBC	5,15-Di(<i>p</i> -methylbenzoato)chlorin
H ₄ TBC	5,10,15,20-Tetra(<i>p</i> -benzoato)
PCN	Porous coordination network
TPDC	Terphenyl-4,4''-dicarboxylic acid
TCPP	Tetrakis(4-carboxyphenyl)-porphyrin
TBP	Tetrabenzoporphyrin or
	5,10,15,20-tetra(<i>p</i> -benzoato)porphyrin
H ₂ DBBC	5,15-Di(<i>p</i> -benzoato)bacteriochlorin
MRI	Magnetic resonance imaging
GSH	Glutathione
H ₄ TBAPy	1,3,6,8-Tetrakis(<i>p</i> -benzoic acid)pyrene
DHA	Dihydroartemisinin
H ₂ BDC	2-Hydroxyterephthalic acid

BODIPY	Boron-dipyrromethene	PNIPAM	Poly(<i>N</i> -isopropylacrylamide)
ICP-MS	Inductively coupled plasma-mass spectrometer	PBS	Phosphate buffer solution
H ₄ TBAPy	1,3,6,8-Tetrakis(<i>p</i> -benzoic acid)pyrene	PPy	Polypyrrole
HOMO	Highest occupied molecular orbital	PAN	Polyaniline
LUMO	Lowest unoccupied molecular orbital	cRGD-SH	Cyclic arginine-glycine-aspartic acid
BCDTE	1,2-Bis(5-(4-carboxyphenyl)-2-methylthien-3-yl)cyclopent-1-ene	HSP	Heat shock protein
ZIF	Zeolitic imidazolate framework	PCM	Phase-change material
UiO	Universitetet i Oslo	HA	Hyaluronic acid
MIL	Materials Institute Lavoisier	GPTS	(3-Glycidyloxypropyl)trimethoxysilane
TMPyP	Tetrakis(1-methylpyridinium-4-yl)-porphyrin	FA	Folic acid
ZnPc	Zinc phthalocyanines	AlPcS ₄	Al(III) phthalocyanine chloride tetrasulfonic acid
Ce6	Chlorine e6	2-mIm	2-Methylimidazole
H ₃ BTc	1,3,5-Benzenetricarboxylic acid	PEI	Poly(ethylenimine)
CaB	Cathepsin	BATA	Bis-(alkylthio) alkene
DOX	Doxorubicin	IcaH	Imidazole-2-carboxaldehyde
CD	Carbon dot	TPEDC	2-((4'-(2,2-Bis(4-methoxyphenyl)-1-phenylvinyl)-[1,1'-biphenyl]-4-yl)(phenyl)methylene) malononitrile
ATP	Adenosine triphosphate	TPETCF	(<i>E</i>)-2-(4-(4-(2,2-Bis(4-methoxyphenyl)-1-phenylvinyl)styryl)-3-cyano-5,5-dimethylfuran-2(5 <i>H</i>)-ylidene)malononitrile
GSSG	Oxidized glutathione	AQ4N	Banoxantrone
PDA	Polydopamine	TPAAQ	2-(4-(Diphenylamino)phenyl)anthracene-9,10-dione
PEG	Polyethylene glycol	PDMAEMA	Poly(2-(diethylamino)ethylmethacrylate)
TPZ	Tirapazamine	TPyP	5,10,15,20-Tetrakis(4-pyridyl)-21 <i>H</i> ,23 <i>H</i> -porphine
PL	Piperlongumine	PLA	Poly(lactic acid)
Tex	Thioredoxin	PVP	Poly(vinyl pyrrolidone)
TexR	Thioredoxin reductase	TAPP	5,10,15,20-Tetrakis(4-aminophenyl)porphyrin
GOx	Glucose oxidase	H ₂ BPDC	2,2'-Bipyridine-5,5'-dicarboxylic acid
ONOO [−]	Peroxonitrite	AlPc	Aluminum phthalocyanine
L-Arg	L-Arginine	PCL	Polycaprolactone
CpG	Cytosine-phosphate-guanine	PEGFA	NH ₂ -poly(ethylene glycol) modified folic acid
IFN-α	Immunostimulatory cytokines type I Interferon	CTAB	Cetyltrimethylammonium bromide
IL-6	Interleukin-6	<i>E. coli</i>	<i>Escherichia coli</i>
CTLA4	T-lymphocyte-associated protein 4	<i>S. aureus</i>	<i>Staphylococcus aureus</i>
PD-1	Programmed cell death 1		
PD-L1	Programmed cell death 1 ligand		
IDO	Indoleamine 2,3-dioxygenase		
RC	Polypyridyl ruthenium complex		
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>		
PB	Prussian blue		
PAH	Poly(allylamine hydrochloride)		
PAA	Polyacrylic acid		
HMPB	Hollow mesoporous Prussian blue		
BET	Brunauer-Emmett-Teller		
PFP	Perfluoropentane		
PA	Photoacoustic		
US	Ultrasound		
SNP	Sodium nitroprusside		
DTX	Docetaxel		
ART	Artemisinin		
CT	Computed tomography		
RCM	Red cell membrane		
PDI	Perylenediimide		
Fc(COOH) ₂	1,1'-Ferrocenedicarboxylic acid		
TCPC	Tetratopic porphyrin		
LMCT	Ligand-to-metal charge transfer		
ICG	Indocyanine green		
Ara	Cytarabine		

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work is jointly supported by the National Science Fund for Distinguished Young Scholars (no. 51925104), National Natural Science Foundation of China (no. 51871162, 51671081), Natural Science Fund of Hubei Province, (no. 2018CFA064), RGC/NSFC (N_HKU725-1616), Hong Kong ITC (ITS/287/17, GHX/002/14SZ), as well as Health and Medical Research Fund (no. 03142446).

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