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Biofunctionalized metal–organic frameworks and host–guest interactions for advanced biomedical applications

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Owing to highly favourable properties such as enormous internal surface areas, high porosity and large flexibility, when it comes to the choice of precursors and high control over their structures and porosity, metal–organic frameworks (MOFs) have emerged as promising materials for applications such as gas storage and separation, catalysis, wastewater filtration, *etc.* The applications of MOFs, despite being so lucrative materials, are very limitedly explored in biomedical applications owing to several concerns such as their biocompatibility, rate of degradation and rate of accumulation in tissues and biological systems. Newer methods are being developed to make MOFs more biologically palatable by their surface functionalization using biomolecules such as nucleic acids, amino acids and lipids. Here we present the progress in biofunctionalization methods of MOFs for improving their physical and chemical properties for biomedical applications, with special focus on their formation *via* covalent and non-covalent routes. Following this, we discuss in detail the applications of these biofunctionalized MOFs in areas of drug delivery, bio-sensing and bio-imaging. We conclude by presenting a brief outlook of the major challenges that lie ahead for mainstream usage of these materials for advanced biomedical applications.

1 Introduction

Metal–organic frameworks (MOFs) represent a new class of compounds where the metal ions (single or in clusters) are coordinated with organic linkers in a very tunable manner, giving rise to one-, two- and three-dimensional hybrid materials with some exceptional properties. Owing to their enormous internal surface areas (>6000 m^2 g^{-1}) and extremely high porosity ($\approx 90\%$ free volume) coupled with a high degree of variability of their individual components, MOFs have emerged as a promising class of crystalline porous materials.[1] MOFs are open crystalline frameworks comprising metallic centers [referred to as secondary building units (SBUs)] linked *via* organic linkers. Since the chemical space offered by such organic linkers is enormous, it has opened the door to thousands of MOFs being synthesized and studied.[1,2] As a result of these exceptional properties, MOFs are widely investigated in applications pertaining to gas storage and separation,[3–5] catalysis[6,7] and wastewater treatment.[8,9] As an example, Goyal and coworkers were able to achieve Pb adsorption of >550 mg g^{-1} from water, by doping a copper centered MOF, HKUST-1, with 5% Fe^{3+} ions, and in the process, improved the hydrolytic stability of HKUST-1 by more than 10 hours.[10]

MOFs are highly programmable materials and their hybrid organic–inorganic nature makes these materials promising candidates for biomedical applications.[11] Over the years, MOFs

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Table 1 A summary of the most widely studied MOFs, their building blocks and surface areas as discussed in this review

MOF	Metal center	Organic linker	Surface area (m^2 g^{-1})	Ref.
HKUST-1	Cu	Benzene-1,3,5-tricarboxylic acid	1099	35
MIL-88A	Fe	Fumaric acid	41.44	59
UiO-66	Zr	Benzene-1,4-dicarboxylic acid	1187	60
MIL-101(Fe)	Fe	Terephthalic acid	3739	61
MIL-101(Cr)	Cr	Terephthalic acid	4100	61
NH_2-MIL-101(Al)	Al	2-Amino terephthalic acid	2100	61
ZIF-8	Zn	2-Methylimidazole	1249–1580	62
MOF-545	Zr	Tetracarboxyphenylporphyrin	913–2248	63

have been widely explored for applications pertaining to biosensing,[12,13] bioimaging[14] and drug delivery[15] (the most commonly used MOFs for these applications, and their building blocks and surface areas as discussed in this review have been highlighted in Table 1). However, owing to the complex nature of biological systems, it becomes essential to ensure their readiness in terms of biocompatibility and biodegradability before they can be fully explored for biomedical applications. For example, since MOF precursors include metal ions, the toxicity of the cation under consideration needs to be carefully evaluated both *in vitro* and *in vivo*. Using lethal doses in rats, it has been ascertained that Ca, Mg, Fe, Zn, Ti and Zr are the most biocompatible cations for biomedical applications.[11,16] Outside of the toxicity of the building blocks of the MOF, there are several other factors that affect their biocompatibility, such as the rate of degradation, the rate of accumulation in tissues and organs and its clearance from the body.[11,17]

Of many strategies used to make these materials compatible for bioapplications, the one being increasingly applied is 'functionalization' (the introduction of different functional groups in MOFs)[18] using materials such as polymers[19] or nanoparticles.[20] Functionalization as a strategy has been successfully applied to a wide-range of materials ranging from nanobubbles[21] to nanofibers[22] to core–shell microparticles.[23] For example, Gole and colleagues exploited the alkynophilicity of Pd^{2+} ions to achieve a high loading of Pd nanoparticles in alkyne-functionalized MOFs, resulting in highly efficient heterogeneous catalysis.[24] While there are several strategies that can be employed for the functionalization of MOFs, the most widely used is postsynthetic modification, where the functionalization is carried out after the MOF is synthesized. This is an increasingly popular method since the way that MOFs are synthesized (through solvothermal reactions[25]) makes it difficult to introduce functional groups presynthesis. Additionally, owing to their high porosity, MOFs can undergo both interior and exterior functionalization unlike other materials like quantum dots, where only the surface can be modified.[26]

In the context of biomedical applications, MOFs are functionalized using biomolecules such as nucleic acids – DNA,[27] RNA,[28] lipids,[29] aptamers[30] and enzymes.[31] Biofunctionalization imparts the properties of biomaterials to the MOFs, thus stabilizing the structures of MOFs, enhances their physical and chemical properties, and facilitates an improved performance. Since each biomolecule has a set of unique properties, biofunctionalization helps in incorporating the properties of these biomolecules as well. For example, biofunctionalization using aptamers helps to improve binding to cellular targets and enhance their uptake, while that using fluorescently labelled DNA helps to improve bioimaging.[32] In this focussed review, we highlight the synthesis and characterization of biofunctionalized MOFs, with an in-depth discussion on their structural aspects. We further discuss the host–guest interactions in biofunctionalized MOFs and how they influence the physical and chemical properties, consequently affecting their biological applications. We then summarize the applications of biofunctionalized MOFs particularly focussing on drug delivery, biosensing and bioimaging (Fig. 1). Finally, we offer insights into the challenges involved in biofunctionalized MOF research and possible directions for a way forward, which can be adopted for efficient drug delivery, biosensing and bioimaging, thus making the biofuncionalized MOFs next generation tools and devices for targeted biomedical applications.

2 Formation of biofunctionalized MOFs

Controlled synthesis of MOFs is an area of active interest (Fig. 2a), because control over the pore size, shape and guest–host interactions plays a critical role in the chemical and physical properties of the material, facilitating advanced applications. Here, it becomes important to define the synthesis conditions to ensure that the fundamental building blocks of the MOF, the organic linkers, do not undergo decomposition. At the same time, the kinetics should be such that the desired phase nucleates and grows at a favourable rate.[33] Conventionally, MOFs are synthesized using a solvothermal process that involves chemical reactions taking place above the boiling point of the solvent under autogenous pressure in closed vessels. In the event that the solvent is water, the process is termed as a hydrothermal process.[33,34] For example, in the case of HKUST-1, a popular copper-centered MOF, the conventional hydrothermal synthesis involves addition of cupric nitrate hemipentahydrate in deionized water and benzene-1,3,5-tricarboxylic acid in a 1 : 1 ethanol–water mixture in appropriate stoichiometric concentrations and stirring the mixtures until they are completely dissolved. Following this, these mixtures are transferred to a stainless steel autoclave and heated in an oven at 110 °C for 18 hours. Finally, HKUST-1 is extracted by filtration by washing the suspension obtained several times with ethanol and deionized water.[10,35]

The synthesis time using conventional solvothermal methods is of the order of a couple of days. This is one of the limitations and it becomes especially important when industrial scale synthesis is desired. Thus, alternative routes of

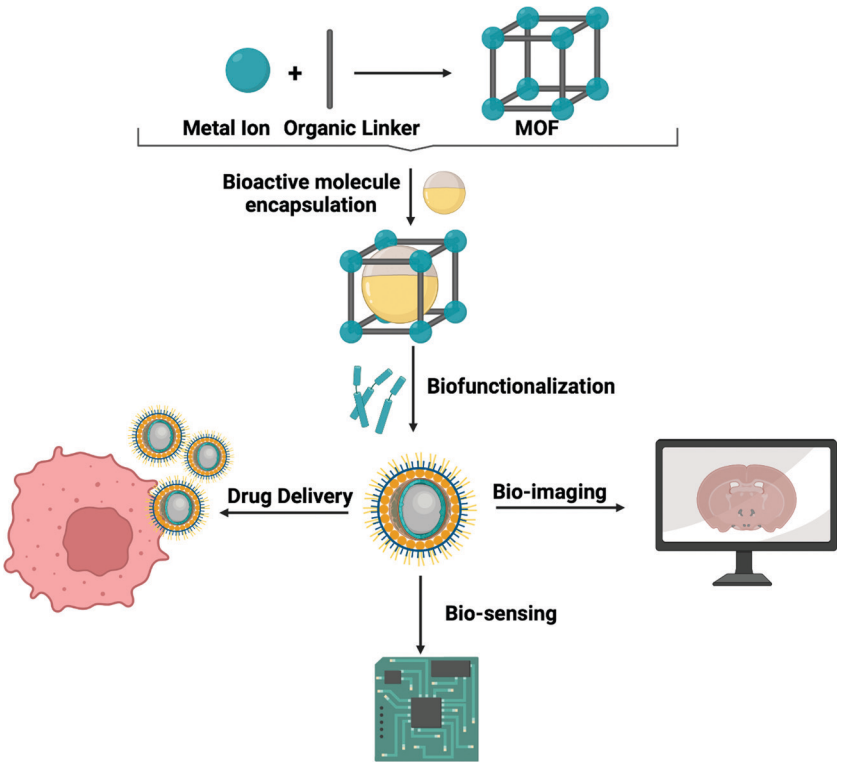

Fig. 1 A cartoon illustration of the biofunctionalization of metal–organic frameworks (MOFs) for advanced biomedical applications such as drug delivery, bio-sensing and bio-imaging. Metal ions (referred to as secondary building units) combine with organic linker molecules to yield 3D porous structures known as MOFs. MOFs can then be loaded with bioactive molecules such as drugs and functionalized with biomolecules such as nucleic acids and amino acids using covalent and non-covalent means to yield composite materials. These materials can then be used for various biological applications such as targeted drug delivery, bio-imaging and bio-sensing.

synthesis that can bring this time down are being developed (Fig. 2a). One such route is microwave-assisted synthesis.[36] Although there are some disadvantages to this method such as the temperatures being much higher than the boiling point of the solvent and there being some concerns over health and safety, this method is highly productive, gives a greater control over the morphology and produces a smaller particle size as opposed to the solvothermal process.[34,37] In this process, microwaves are generated using a magnetron, which facilitates electromagnetic interactions between mobile electric charges in the reaction solution, containing a polar solvent, cation(s) and organic ligand(s).[34,36,38] A method that has gained popularity for industrial production, taking the same order of time as microwave-assisted synthesis, but involving much milder reaction conditions, is the electrochemical method. Instead of providing the metal ions in the form of a salt, in this process, metal electrodes are used allowing for continuous, large-scale production. Metal ions are supplied to the synthesis mixture comprising the organic linker and an electrolyte by the dissolution of the electrode. Despite the obvious advantages of this method, the electrochemistry of the organic linkers used is relatively less investigated, and as a result the reactions taking place at the cathode are unknown, which is a cause of concern.[39] The first MOF to be synthesized in large-scale using the electrochemical method was HKUST-1, in a room-temperature synthesis process pioneered by BASF.[39,40] Two other methods that have gained attention as alternatives to the conventional solvothermal process are the sonochemical and mechanochemical processes. In the sonochemical method, high-intensity ultrasound is used to generate extremely high local temperatures *via* acoustic cavitation, leading to an enhancement in the reactivity of the MOF precursors.[41] The mechanochemical process is a solvent-free route to produce high dimensional connectivity that can support permanent porosity, as is required for MOFs by ball milling (grinding) the precursors.[42] Detailed discussions on the synthesis of MOFs to generate different topologies and morphologies have been provided by Stock and Biswas[33] and Al Amery and coworkers.[34]

Functionalization of MOFs can be carried out either during their synthesis or postsynthesis. However, owing to the high temperatures involved in most synthesis procedures, presynthesis functionalization could cause degradation of biomolecules such as DNA, RNA and amino acids.[18,43] Thus, most experiments focus on postsynthesis functionalization of MOFs. In the context of biofunctionalization of MOFs, postsynthetic modifications can be further classified into two categories depending on the type of interactions involved – covalent functionalization and non-covalent functionalization. (Fig. 2b).[30]

2.1 Covalent functionalization of MOFs

Covalent functionalization involves the use of reagents (biomolecules) for modifying components of the MOF postsynthesis

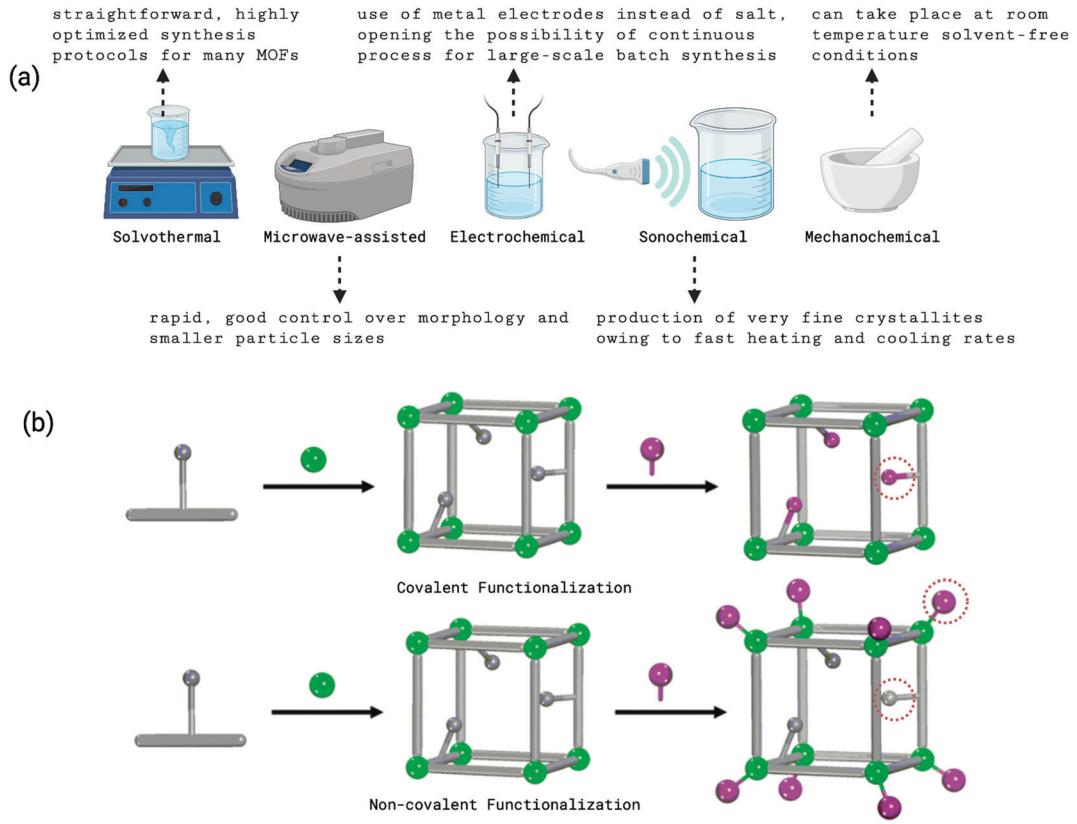

Fig. 2 (a) A schematic illustration of the various routes for the synthesis of MOFs as described in Section 2, along with their major advantages.[44] The most common route to synthesize MOFs is *via* the solvothermal process involving chemical reactions above the boiling point of the solvent. Alternate routes involve microwave-assisted synthesis (involving the use of microwaves generated from a magnetron), electrochemical synthesis (involving the application of electrochemistry principles), sonochemical synthesis (involving the use of high-intensity ultrasound) and mechanochemical synthesis (involving the use of mechanical processes such as grinding and ball-milling). (b) Generic schemes for covalent binding- and non-covalent binding-based routes for functionalization of MOFs, with differences in the bonds formed highlighted. In covalent binding, a covalent bond is typically formed between the biomolecule and the organic linker. In non-covalent binding, a non-covalent bond or coordinate covalent bond is typically formed between the biomolecule and the SBU. Reprinted (adapted) with permission from ref. 18. Copyright 2022 American Chemical Society.

by the formation of covalent bonds. In this process, the interactions take place on the organic linker and not the SBU.[18] An advantage of covalent functionalization is that covalent bonding is relatively stable, which helps in stabilizing the structure of MOFs, improving their fitness for applications such as drug delivery and biosensing.[30] For example, Morris *et al.* covalently functionalized the surface of UiO-66-N_3 MOF with oligonucleotides to develop MOF nanoparticle-nucleic acid conjugates.[45] They first synthesized the UiO-66-N_3 MOF having a cubic topology *via* the solvothermal process, following which postsynthetic modifications were carried out by reacting the MOF nanoparticles with dibenzylcyclooctyne (DBCO)-functionalized DNA. To reduce electrostatic interactions between neighboring oligonucleotides, NaCl was added to the reaction solutions to facilitate a higher surface loading of DNA. One critical conclusion here was that the size of the MOF nanoparticle plays a crucial role in the surface coverage of the oligonucleotide strands used.

Mejia-Ariza *et al.* were able to develop a DNA-sensing platform by functionalizing the surface of an iron-centered MOF, MIL-88A, using both covalent and non-covalent interactions. During the synthesis of MIL-88A *via* the solvothermal route, a small percentage of fumaric acid (the organic linker) was replaced with undecynoic acid to facilitate alkyne functionalization. The alkyne functionalized MIL-88A was further surface-functionalized using covalent interactions through a Cu-catalyzed click reaction using 3-azido-7-hydroxycoumarin. The surface functionalization was confirmed using fluorescence microscopy. The ability of functionalized MIL-88A to bind with DNA was demonstrated using non-covalent interactions as discussed in Section 2.2.[46] Kahn *et al.* with the help of DNA switching motifs were able to design pH-responsive and K^+ ion-responsive DNA-modified MOFs. The MOF under investigation consisted of zinc carboxylate clusters bridged by two organic linkers – 4,4,4-benzene-1,3,5-triyl-tribenzoic acid and amino terephthalic acid. The functionalization was achieved by first introducing carboxylic acid functionalities by reacting the amine based organic linker with succinic anhydride. Following this, amide coupling of carboxylic acid functionalities with amine-modified cytosine-rich nucleic acid was carried out to achieve the DNA-functionalized MOF. The coverage of functionalization was estimated to be of the order of 3.3 nmol mg^{-1} MOF.

Depending on the kind of motif used, Kahn and coworkers were able to control the stability under different pH and K^+ ion concentrations. In essence, the motifs acted as 'gates', which could control the release of encapsulated loads.[27] When it comes to enzymes, a covalent linkage is possible *via* the formation of a peptide bond between the free amino groups and carboxylate groups of the MOF and the enzyme.[31]

Covalent binding of biomolecules to MOF surfaces has been found to be more inefficient in terms of yield of final product, and time-consuming as opposed to non-covalent binding.[32] However, the interactions in covalent bonds are stronger, making the MOF structure more stable and strong. In covalent functionalization, as discussed in previous examples, the primary candidates are amine-tagged MOFs owing to their versatility, easy availability and chemically robust nature and aldehyde-tagged MOFs. Here, 'tagging' refers to the introduction of certain functionalities that appear as integral parts of MOFs during their synthesis, but can undergo transformations during postsynthetic functionalization.[18] These functionalizations have been commonly carried out for altering the permeability of the MOFs[47] or their hydrophobicity among other properties.[48] One very promising development in the covalent funtionalization of MOFs is *via* 'click' chemistry, where a cycloaddition reaction between an azide and an alkyne, catalyzed by Cu(I) is carried out as discussed in previous examples.[49,50]

2.2 Non-covalent functionalizations

Non-covalent (or dative) functionalizations occur when reagents (biomolecules) form dative (metal–ligand) bonds with the metallic center of the MOF postsynthesis. This type of functionalization involves hydrogen bonding, π–π interactions and electrostatic interactions as opposed to covalent interactions in the previous section.[18,30] Owing to the nature of bonding, these functionalization techniques are less time-consuming and more efficient and do not affect the intrinsic structure of the MOF, but at the expense of the strength of the interactions. Mainly intended for tuning pore functionality of the MOFs, the first example of non-covalent functionalization was during the original description of HKUST-1, where the authors discovered that the axially bound water molecules to the MOF can be removed by heating it in air above 100 °C, following which, immersing the MOF in dry pyridine causes pyridine molecules to bind to the SBU.[18,51] In possibly one of the first uses of non-covalent functionalization of a MOF for biological usage, Rosseinsky and colleagues used 4-(methylamino)pyridine vapors to functionalize HKUST-1 by binding to the coordination sites of the SBU. Following this non-covalent functionalization, they treated the MOF with nitric oxide (NO) to obtain a covalent NONOate adduct for possible storage and release of NO for biological applications.[52]

Mirkin and coworkers developed a generalizable approach for the post-synthetic surface-functionalization of MOFs using phosphate-modified oligonucleotides to impart certain chemical functionality to the MOF surfaces independent of the bulk properties. Following the solvothermal synthesis of UiO-66 MOF and phosphate-modified nucleic acids, the oligonucleotides were added in excess to a colloidal suspension of the MOF and incubated overnight. The high surface density of functionalization was achieved by salt-aging that acted as a screen to separate negatively charged oligonucleotides. Solid-state NMR and powder X-ray diffraction were carried out to confirm the functionalization and transmission electron microscopy was conducted to confirm structural preservation post functionalization. Inductively coupled plasma atomic emission spectroscopy and UV-visible spectroscopy were carried out to ascertain the extent of surface functionalization. Their approach was generalized to MIL-101 (Al-centered MOF), MIL-101 (Fe-centered MOF) and MIL-101 (Cr-centered MOF). Two interesting observations that were made were that the oligonucleotide surface coverage was directly correlated to the density of SBUs on the nanoparticle surface, which has implications in colloidal stability and particle probe performance, and there is a positive correlation between the DNA surface coverage and the bond dissociation energy of the metal–oxygen bond.[53]

Wang *et al.* loaded two water stable zirconium-MOF nanoparticles NU-100 and MOF-545 with insulin (a model protein) and functionalized them with phosphate-modified DNA to yield insulin@DNA-MOF nanoparticles. This DNA functionalization helped in stabilizing the MOF nanoparticles in high dielectric media by forming steric and electrostatic barriers. This helped in facilitating cellular entry and resulted in a ten-fold increase in cellular uptake.[54] Similarly, Abdelhamid *et al.* exploited hydrogen bonding and electrostatic interaction for adsorbing cell-penetration peptides onto ZIF-8 MOF. These functionalized MOFs were explored for applications as gene-delivery therapeutic agents.[55] Since MOFs have a conjugated π-electron system, this offers a possible hydrogen bonding source, facilitating interactions between MOFs and single-strand DNA, opening the door to bio-sensing applications. In order to probe this, Zhang *et al.* synthesized an amine-functionalized MOF, UiO-66-NH_2 made up of $Zr_6O_4(OH)_4$ oxoclusters linked by 12 NH_2-BDC ligands containing tetrahedral and octahedral cages. Single-stranded DNA and UiO-66-NH_2 MOF interact *via* π–π stacking and/or hydrogen bonding allowing detection through fluorescence imaging.[56] In a similar bio-sensing application, Xie *et al.* synthesized DNA@MOFs for sensing three conserved sequences of the Zika virus.[30,57]

In the case of enzymes, although covalent functionalization is a possibility, as discussed in Section 2.1, in most cases, non-covalent binding is the preferred route of functionalization. An example of this is work by Cao *et al.*,[58] where the HKUST-1 MOF was functionalized *via* weak interactions with Bacillus subtilis lipase (BSL2) for use as a bio-catalyst. Here, BSL2 was first modified by a non-ionic surfactant to yield a complex that was then bound to HKUST-1 by stirring in an isooctane solution for 8 hours.

3 Applications of biofunctionalized MOFs

Most biomaterials or nanomaterials poised for bioapplications have met with concerns such as the toxicology and biocompatibility. In the case of MOFs, owing to a vast chemical space of potential organic linkers and metal centers, toxicology does not

appear to be a major concern. As stated earlier, using a high dosage of MOFs in rats, it has been ascertained that there is no toxicity in certain classes of MOFs (for example, iron carboxylate MOFs), with no detrimental effects even after acute exposure. In fact, certain compounds having similar compositions to those of MOFs have been cleared for use as therapeutic agents.[64,65] As discussed by McKinlay *et al.*, one of the biggest potential drawbacks for MOFs is their chemical stability, which happens to depend on several factors such as the operating environment, temperature, pH conditions, and particle size.[66,67] The enhanced chemical instability of MOFs could actually be a desirable characteristic, as it would prevent an endogeneous accumulation of potentially toxic ions and MOF precursors in the living system.[64] Control over the physical and chemical properties of MOFs *via* biofunctionalization could ensure a stability of up to several days, or even weeks, which would be enough to ensure completion of its intended function, such as drug delivery, bio-sensing or bio-imaging.

Owing to their porosity, chemical structure, low toxicity and the ability to tune the host–guest interactions by functionalization with biomolecules, MOFs are ideal candidates for the encapsulation, targeted delivery and controlled release of bioactive molecules such as drugs (Fig. 3a).[64,68] When a MOF degrades *in vivo*, apart from the metal ions, even the linker gets released, adding to the toxicity concerns. In conventional applications of MOFs from biological perspectives, MOFs are exploited only for their porosity and surface area, and their precursors often go to waste. Due to these toxicity concerns, and the precursors not being adequately utilized, a new realm of biofunctionalization has come along, where the bioactive molecule to be delivered is used as the organic linker itself (these MOFs are termed as BioMOFs).[64,68] Examples of these bioactive linkers include adenine being used in BioMOF-100[69] and ZNBTCA[70] for drug release applications, and biomolecules such as certain amino acids[71] and peptides.[68,72] In this section, we discuss the key applications of biofunctionalized MOFs pertaining to drug delivery, bio-sensing and bio-imaging.

3.1 Drug delivery

The first use of MOFs for drug delivery was using MIL-100 (chromium center) and MIL-101 (chromium center). These MOFs were particularly chosen owing to their large pore sizes and pore volume and high specific surface areas. Using ibuprofen as a model drug, a high drug loading capacity of the order of 1.376 gram of ibuprofen per gram of MOF was observed, which is much higher compared to other commonly used porous materials such as zeolites. In the case of drug encapsulation, some amount of drug is weakly bound to the MOF surface, while the rest gets encapsulated in the pores, as a result of which, while analyzing the kinetics of release, the weakly bound drug releases quickly (in 2–8 hours), while the entire drug gets released over a larger period of time (3–6 days). However due to toxicity concerns pertaining to the use of chromium, there was a shift to iron-based MOFs.[15,73,74]

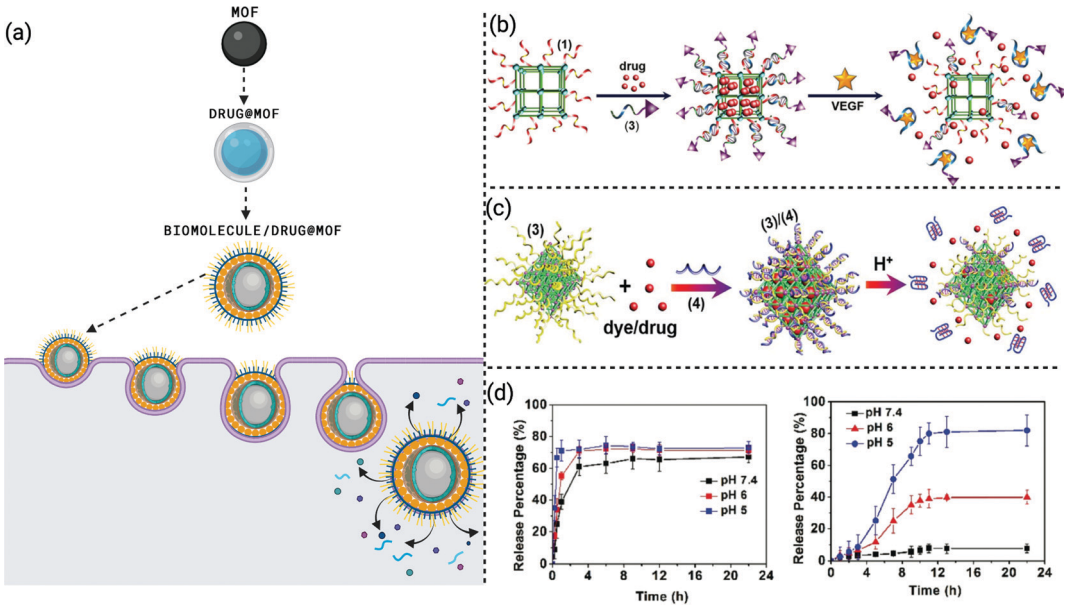

Fig. 3 (a) A schematic illustration of biofuntionalization of drug-encapsulated MOFs for improved endocytosis and targeted delivery and controlled release of drugs as described in Section 3.1. A MOF is loaded with a bioactive molecule such as a drug, and functionalized either *via* covalent or non-covalent binding to form a biomolecule-functionalized MOF composite. Owing to this biofunctionalization, the composite exhibits an enhanced cellular uptake and a more targeted delivery and controlled release of the encapsulated drug. (b) A schematic depicting the loading and release of doxorubicin from amino-triphenyl dicarboxylate-bridged zirconium MOF nanoparticles functionalized using nucleic acids. Reprinted with permission from ref. 77. Copyright 2022 Royal Society of Chemistry. (c) A schematic showing the fabrication of drug-loaded MOF nanoparticles functionalized with DNA *via* click chemistry that are pH and metal-ion responsive. Reprinted from ref. 79 under a Creative Commons Attribution 3.0 Unported Licence. (d) A comparison of the pH-responsive release of BSA/DOX and BSA/DOX@MOF nanocomposites. Reprinted with permission from ref. 80. Copyright 2022 Royal Society of Chemistry.

In conventional drug-loading applications, a MOF is introduced to a drug solution and the encapsulation occurs *via* non-covalent interactions. As discussed earlier, these interactions are relatively weak and could lead to premature release of the drug, which is a cause of concern. To alleviate these concerns, postsynthetic modifications are carried out to facilitate a covalent attachment of the bioactive molecule to the MOF. An example of this was the covalent attachment of *cis*-dichlorodiammineplatinum(II) (cisplatin) to amino-functionalized MIL-101 (Fe-centered) for chemotherapeutic applications. Cisplatin loaded to the bare amino-functionalized MIL-101 showed a release half-life ($t_{1/2}$) of 1.2 h in PBS at 37 °C, whereas the addition of a thin silica layer increased the release half-life to 14 h, serving as a perfect example of the benefits of biofunctionalization.[15,75,76]

One of the major advantages of using nucleic acid- or amino acid-functionalized MOFs is their stimuli-responsive nature. A drug-loaded MOF functionalized with appropriate biomolecules can be thought of as a locked cage. On the introduction of external, specific stimuli such as pH, temperature or light, this cage gets unlocked, leading to the release of the entrapped drug.[32] An excellent example of this idea was work by Chen and colleagues, who developed amino-triphenyl dicarboxylate-bridged zirconium MOF nanoparticles that were functionalized using nucleic acids having sequences complementary to the VEGF aptamer. These MOF nanoparticles were then loaded with doxorubicin (an anti-cancer drug) and hybridized with VEGF aptamer to obtain 'VEGF-responsive duplex nucleic acid gates' (Fig. 3b).[77] In the case of cancer cells, VEGF is often over-expressed and thus, can be exploited as a biomarker.[78] When this drug-loaded nucleic acid-functionalized MOF encounters high VEGF levels, due to the complementary sequence of the aptamer, it will bind to VEGF, facilitating the release of doxorubicin leading to a targeted delivery. Given that VEGF is over-expressed even in diseases such as rheumatoid arthritis and diabetes mellitus, a similar mechanism could be used for their treatment as well.[77] Along similar lines, the same group exploited 'click' chemistry (as discussed in Section 2.1) to synthesize stimuli-responsive DNA-functionalized MOF nanoparticles loaded with anti-cancer drugs (Fig. 3c). The first class of MOF nanoparticles developed were pH-dependent, unlocking at pH 5, leading to the release of the load, while the second class of MOF nanoparticles developed were metal-ion-dependent, where the nucleic acids got cleaved in the presence of certain metal ions. These MOFs were Mg^{2+} ion- and ATP-dependent, with their presence triggering drug release, opening the door to interesting applications in ion-sensing and logic gate-based biologically relevant systems for targeted delivery and controlled release of drugs.[79]

In standard practice, the MOF is used as a core, which is coated (or functionalized) with biomolecules, acting as a shell, for applications such as drug delivery. Liang *et al.* developed a shell@core nanocomposite system, with doxorubicin-loaded bovine serum albumin (BSA) as the core and ZIF-8 MOF as the shell. Here, ZIF-8 acts as a protective capsule, preventing the premature release of the drug at a pH of 7.4. At lower pH values (pH 5–6), ZIF-8 undergoes degradation, leading to a controlled drug release (Fig. 3d). In addition, owing to the way the nanocomposite is synthesized, the outer surface has a positive charge that helps in improving cellular uptake.[80] Ma *et al.* synthesized amino-derived MIL-101 MOF and loaded it with Au nanoparticles *in situ*, followed by immobilization with L-cysteine (Cys) to yield MIL-101(NH_2)@Au-Cys for the enrichment of N-linked glycopeptides in HeLa cell lysates and model glycoproteins. The authors synthesized the nanocomposite using a facile two-step process and exploited rapid encapsultion of Au in MIL-101(NH_2) and post-synthetic modification using Au–S bonding.[81]

Most drug delivery applications employing MOFs focus on cancer therapy as is evident from previous examples, because of the obvious limitations of conventional chemotherapeutic techniques. Most such work focusses on biomolecule@MOF composites, where the biomolecule helps in improving cellular uptake and colloidal stability, and facilitates a targeted delivery. Outside of nucleic acids and amino acids, at times even lipids are used for these biofunctionalization purposes, where the MOF is coated with a lipid layer or bilayer.[82] An example of this would be experiments by Wuttke and coworkers, who developed a MOF-lipid nanoparticle system, where the external lipid bilayer is able to prevent premature release of dye molecules encapsulated within the pores of the MOF. The lipid coating here was carried out using a controlled solvent-exchange deposition process. A high uptake of these nanoparticles in cancer cells was confirmed using fluorescence microscopy and toxicological testing indicated that these nanoparticles are neither cytotoxic nor do they have an anti-proliferative effect on carcinoma cells.[29] There are several other studies focussing on the functionalization of MOFs and their effects on drug delivery, such as studies by Dong *et al.*, who developed a MOF-based nanoplatform for efficient endo/lysosomal escape and the release of drugs into the cytosol, addressing some major obstacles in cancer treatment.[83]

3.2 Bio-sensing

Due to their hybrid inorganic/organic hybrid nature, MOFs have good luminescence properties and good control over their shape and morphology, ensuring selective absorption and emission properties opening new vistas to potential sensing applications. Their flexible porous nature allows an easy diffusion of small guest molecules (such as O_2) coupled with favourable host–guest interactions (that can be improved even more *via* postsynthetic functionalization) enabling specific molecular recognition, an excellent trait for potential bio-sensors (Fig. 4a).[12] Compared to other commonly used bio-sensors such as graphene or Au nanoparticles, MOFs have a high loading capacity, higher biocompatibility, π electron conjugated system and the possibility of funtionalization to tune host–guest chemistry.[13] Standard MOFs have poor electrical conductivity due to a mismatch in electronic levels between the metal center and the organic linker. Due to this reason, MOFs were not considered for applications pertaining to electrochemical sensing. However, over the years, a new domain of research termed as guest@MOF has emerged, focussing on the use of 'non-innocent' guest molecules to improve the electrical conductivity of the MOF,

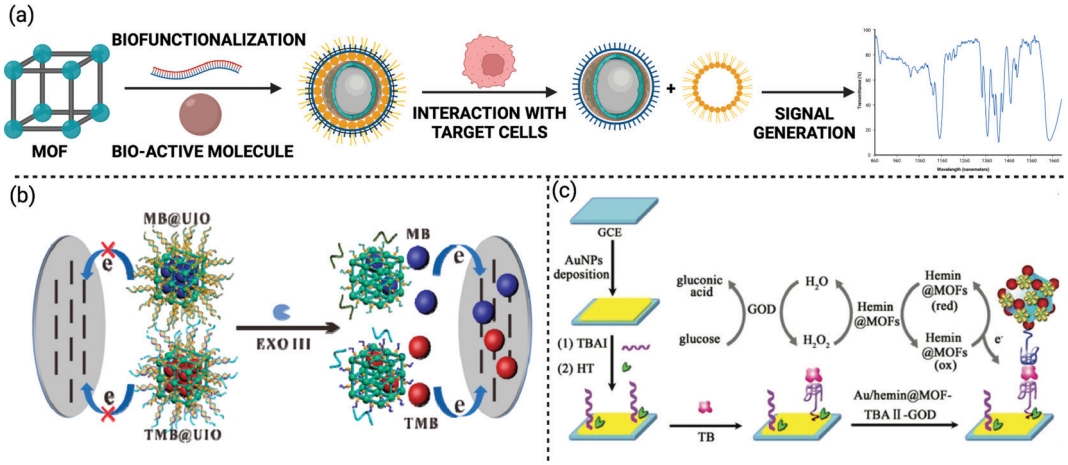

Fig. 4 (a) A schematic illustration of biofuntionalization of a MOF and its application in bio-sensing as discussed in Section 3.2. A MOF is loaded with a bioactive molecule such as a drug and functionalized with biomolecules such as nucleic acids or amino acids to form biofunctionalized MOF composites. When these composites interact with certain target cells, owing to the modified properties because of biofunctionalization, there is a release of the bioactive molecule, which leads to the generation of a signal. The generation and detection of these signals can be exploited for bio-sensing purposes. (b) The mechanism of interaction between a nucleic-acid (double-stranded DNA)-functionalized MOF and EXO III for the detection of biomarkers. Reprinted (adapted) with permission from ref. 28. Copyright 2022 American Chemical Society. (c) A schematic depicting the mechanism of action of an Au/hemin@MOF nanocomposite as an electrochemical aptasensor for the detection of thrombin. Reprinted with permission from ref. 89. Copyright 2022 Royal Society of Chemistry.

opening the chances to electrochemical sensing applications.[84–86] Specifically, biofunctionalized MOFs can be used for DNA/RNA sensing, biomacromolecule sensing, small biomolecule sensing, metal ion sensing and anion sensing.[12]

Ling and coworkers used covalent binding to develop a streptavidin-functionalized zirconium-polyphyrin MOF (PCN-222@SA) for use as an electrochemical probe. The probe was designed for DNA sensing by exploiting the triple helix DNA structure switch. The mechanism of interaction here is rather complex. The sensing platform was made by the immobilization of biotin-labelled triple-helix DNA on a graphene-modified glassy carbon electrode. This triple helix has a very large steric effect because of its hairpin structure, blocking the electrochemical MOF probe from interacting with the sensing platform. As soon as the target DNA is introduced, the hairpin DNA gets released, allowing the probe to interact with the platform. This leads to an amplification of electrolytic current through the probe, facilitating the detection of DNA.[87] Chang *et al.* were able to exploit nucleic acid functionalization of MOFs to detect multiple tumour biomarkers, which allows early, accurate cancer diagnosis. Here, UiO-66-NH_2 MOF was used as a nanocarrier to encapsulate electroactive dyes for tumor detection. This dye-loaded MOF was functionalized using double-stranded DNA that acts as a gatekeeper, preventing a premature release of the dye as seen in earlier examples (Fig. 4b). These functionalized MOFs were able to detect two biomarkers – let-7A and miRNA-21 at resolutions of 3.6 and 8.2 fM, respectively, which is comparable to techniques and strategies focussing on single biomarker detection.[28] Wu *et al.* exploited the π–π interactions between UiO-66-NH_2 MOF and a fluorescently-labelled single-stranded DNA aptamer to fabricate a MOF/DNA hybrid for detecting Hg^{2+}. Initially this hybrid system showed fluorescence; however on the introduction of Hg^{2+}, a duplex was formed, which when released from the surface of the MOF leads to the recovery of the fluorescence.[32,88]

The examples discussed above focus on the detection of DNA/RNA. However, biofunctionalized MOFs have been successfully employed in biosensing large macromolecules such as thrombin[89] and alpha-fetoprotein in human serum.[12] For example, Xie *et al.* synthesized a nano-sized MIL-88 (Fe-centered) MOF, encapsulated hemin into it and functionalized it with Au nanoparticles to develop a Au/hemin@MOF nanocomposite for use as an electrochemical aptasensor for thrombin detection. Their platform had a detection limit of 0.068 pM for the detection of thrombin (Fig. 4c).[89] MOFs have also been explored for the bio-sensing of small biomolecules such as glucose.[12,90] Huang and colleagues developed a rapid, sensitive, single-use Ag@Au-MOF composite for detecting glucose in human serum by exploiting photoluminescence properties of this composite. The mechanism of sensing essentially entails an increase in phosphorescence emission on the oxidation of glucose, the detection limit of which is greatly enhanced by Ag@Au functionalization of the MOF.[90] Using similar biofunctionalization strategies, MOFs have been used for the detection of metal ions such as Hg^{2+},[88] Fe^{2+} [91] and Cu^{2+},[92] anions such as flouride[93] and gases such as O_2[94] and H_2O_2.[95]

3.3 Bio-imaging

An excellent technique for the early diagnosis of diseases is by employing advanced bio-imaging technologies to understand the pathological characteristics of biological tissues (Fig. 5a). Bio-imaging agents are of two types – fluorescent small molecules that generate signals and image contrasting agents that enhance signal contrast. Advanced bio-imaging agents involve doped silica nanoparticles, quantum dots and gold nanoparticles.[96,97] Their structural diversity and physicochemical properties, and the

ability to tune their dimensions in the nanometer regime (essential for cellular uptake) makes MOFs attractive candidates for bio-imaging.[14] In particular, biofunctionalized MOF composites are used in fluorescence imaging (FL), magnetic resonance imaging (MRI), positron emission tomography (PET) imaging and computed tomography (CT).[75,96,98] When it comes to MRI and X-ray CT, due to biocompatibility issues of conventional contrast agents (CA), there has been a rise in the usage of metallic nanoparticles.[99,100] Owing to the presence of metal centers and the ease of functionalization of their surfaces, MOFs can potentially replace these conventional CAs.

Deng *et al.* developed ZIF-90 MOF (Zn-center and imizadolate-2-carboxylate linker) encapsulated with Rhodamine (RhB). The fluorescence of RhB, which was quenched due to the self-quenching effect of RhB/ZIF-90, was recovered on exposure to ATP due to the degradation of the RhB/ZIF-90 composite, thus serving as an intracellular ATP imaging agent.[96,101] Coming over to biofunctioalization, Yang *et al.* functionalized the surface of PCN-58 MOF[102] with alkynyl-BR-NH_2 and alkynyl-DL for bio-imaging of H_2S and Zn^{2+}, respectively. This functionalization was carried out *via* click chemistry as described in Section 2.1. These functionalized MOFs showed superior photostability and selectivity compared to conventional imaging agents and the penetration depth in the rat liver tissue was also of desirable levels (approximately 130 μm).[96,103] The examples discussed above involve fluorescence imaging, where the fluorescence of small molecules is exploited. When it comes to techniques such as CT and MRI, image contrasting agents are required. Here, Bi-, Gd-, Mn- and Fe-centered MOFs are used for high resolution imaging. That being said, some of these metals have serious toxicity concerns, limiting the applications of these MOFs for bio-imaging.[96]

Shen and colleagues employed a core–shell nanostructure as described in several previous examples to fabricate a peptide-functionalized gold nanoparticle core, with a ZIF-8 MOF shell. This peptide@MOF nanocomposite was sensitive to both pH and enzyme activity and was used for imaging lysosomal cathepsin B. Here gold nanoparticles were conjugated with Cy3-labelled peptide through covalent binding to yield Au–Cy3, following which, it was encapsulated in a ZIF-8 shell through a route that allowed the biological activity retention of the peptide towards lysosomal cathepsin B. Under acidic environments, this MOF shell degrades, exposing the Au–Cy3 core that could then be recognized by lysosomal cathepsin B with high specificity (Fig. 5b).[104] Coming to PET imaging, Chen *et al.* developed radioactive doxorubicin-loaded UiO-66 MOF nanoparticles incorporated with positron-emitting isotope zirconium-89, which was functionalized with pyrene-derived polyethylene glycol conjugated with a peptide ligand for targeting triple negative breast tumors.[106] This functionalization not only helped in a high drug loading capacity (of the order of 1 mg drug per mg of MOF), but also gave stability to the composite in biological media. Their results indicated that this non-toxic nanocomposite could serve as an '*image-guided*, *tumor-selective cargo delivery nanoplatform*'.[106]

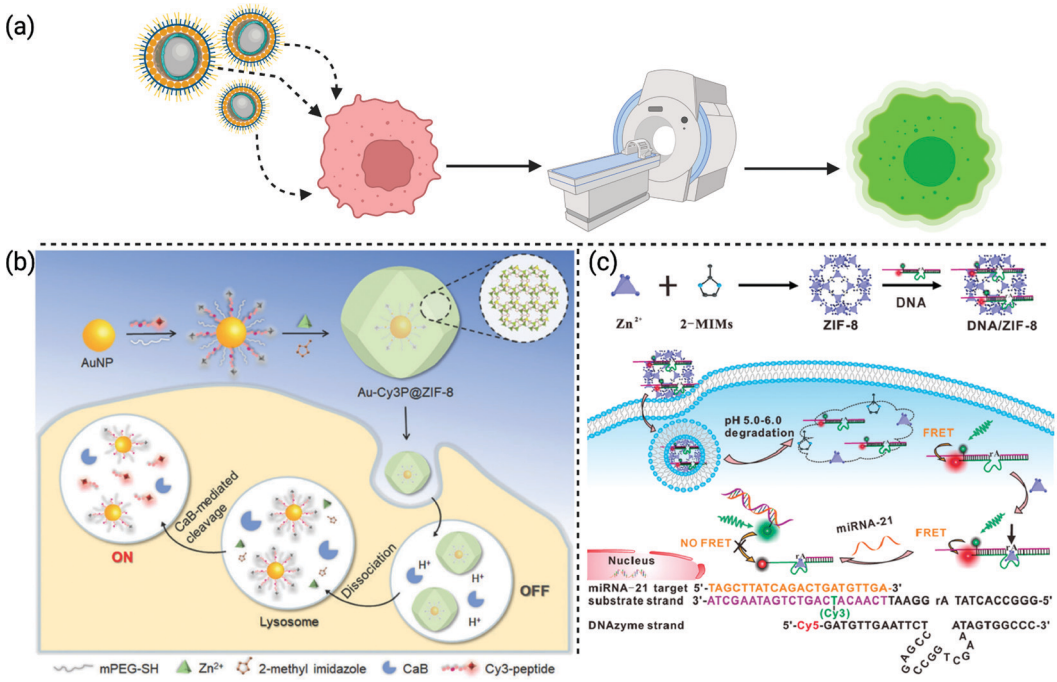

Fig. 5 (a) A schematic illustration of biofuntionalization of MOFs and its application in bio-imaging as discussed in Section 3.3. Biofunctionalized MOF composites interact with target cells (such as cancer cells) to generate signals such as fluorescence. These signals can be detected using technologies such as MRI and/or CT, opening the door to bio-imaging applications. (b) The synthesis and mechanism of action of a peptide@MOF as a dual-recognition pH and enzyme activity switch for live imaging of cells. Reprinted with permission from ref. 104. Copyright 2022 Royal Society of Chemistry. (c) The synthesis of DNA-functionalized ZIF-8 MOF and the mechanism of action of its application for fluorescence imaging of microRNA-21. Reprinted with permission from ref. 105. Copyright 2022 American Chemical Society.

In one of the most interesting applications of bio-imaging using biofunctionalized MOF composites, Chu and coworkers developed a DNAzyme-based ratiometric fluorescence strategy for imaging miRNA-21, which is an important biomarker for disease diagnosis. First a duplex probe was formed using a Cy5-labeled 8–17 DNAzyme strand and a Cy3-labeled substrate strand having a segment with the complementary strand to the target miRNA. This probe was then adsorbed onto the surface of the ZIF-8 MOF to form a probe@MOF nanocomposite. Under acidic conditions this nanocomposite degrades leading to the release of the probe, with the complementary strand-hybridizing miRNA-21 causing dissociation of the DNAzyme–substrate duplex. The DNAzyme then cleaves the substrate, leading to a change in the fluorescence resonance energy transfer, facilitating the imaging of miRNA-21 expression levels (Fig. 5c).[105]

4 Conclusions and outlook

We presented the need for biofunctionalization of MOFs and the theory behind the formation of these MOF composites and host–guest interactions that make them stable and ready for exploration in biological applications, and discussed state-of-the-art applications of these composites in drug delivery, bio-sensing and bio-imaging. Despite the promise of these materials, there are several challenges that lie ahead in their wide-range applications. The biggest challenge that one can foresee is the identification of optimum organic linkers, metal ions, and biomolecules for functionalization and guest molecules. This is primarily because the chemical space associated with each of these precursors (especially the organic linker and biomolecule) is vast, making an experimental approach to exploration near impossible. This motivates a venture into the use of computational approaches through techniques like MD,[107] DFT,[108] and/or AI/ML. Although AI/ML-based techniques are being increasingly used in materials and biological research,[109–111] it is yet to make an impact on MOF-based research. This could have to do with challenges pertaining to the lack of availability of appropriate MOF databases or issues related to the molecular representation (essentially unique ways of representing the chemical structure in a way that is understandable to a machine) of MOFs.

A second, more obvious challenge is the toxicity, biocompatibility and biodegradability of these MOFs. For example, despite superior properties, MOFs with certain metal centers such as Bi, Gd and Mn cannot be readily used for applications such as bio-imaging due to toxicity concerns. This motivates a search into the development of less toxic bioactive MOFs. Here the MOF chosen should be such that it has an intermediate chemical stability. Too high a stability implies a buildup of MOF in tissues, and too low a stability implies a failure to carry out its intended application. This is where biofunctionalization would play a major role, in tuning the stability of the MOFs, allowing better control over the release of encapsulated bioactive molecules such as drugs for drug delivery, bio-sensing- and bio-imaging-based applications.

There is a lack of understanding of the host–guest interactions of these biofunctionalized MOFs. A systematic understanding of how these biomolecules such as nucleic acids, amino acids or lipids interact with the MOF precursors would aid in a better design of composite materials for an enhanced performance in intended applications. This is a highly dynamic area of research, which is ever-evolving, and an optimized approach to the discovery, design and optimization of biofunctionalized MOF composites would go a long way in the diagnosis and treatment of clinical diseases.

Conflicts of interest

There are no conflicts to declare.

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