Metal–Organic Framework Composites for Theragnostics and Drug Delivery Applications

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Among a plethora of nano-sized therapeutics, metal-organic frameworks (MOFs) have been some of the most investigated novel materials for, predominantly, cancer drug delivery applications. Due to their large drug uptake capacities and slow-release mechanisms, MOFs are desirable drug delivery vehicles that protect and transport sensitive drug molecules to target sites. The inclusion of other guest materials into MOFs to make MOF-composite materials has added further functionality, from externally triggered drug release to improved pharmacokinetics and diagnostic aids. MOF-composites are synthetically versatile and can include examples such as magnetic nanoparticles in MOFs for MRI image contrast and polymer coatings that improve the blood-circulation time. From synthesis to applications, this review will consider the main developments in MOF-composite chemistry for biomedical applications and demonstrate the potential of these novel agents in nanomedicine. It is concluded that, although vast synthetic progress has been made in the field, it requires now to develop more biomedical expertise with a focus on rational model selection, a major comparative toxicity study, and advanced targeting techniques.

1. Introduction

The rapidly emerging field of nanomedicine represents the next great technological revolution in battling diseases, particularly in the area of personalized medicine. Nanopharmaceuticals combining disease treatment with diagnostic aids are being developed at a rapid pace, spanning diverse disease areas such as neurological (e.g., Parkinson’s and Alzheimer’s diseases) and oncological malignancies. Cancer, in particular, is the leading cause of death in the industrial age, after cardiovascular disease.[1] It is estimated that, in 2018, 18.1 million new cancer patients were reported, including 9.6 million deaths.[2] Despite advances in diagnosis, early detection, and cancer therapies, current treatments frequently require surgical procedures and other invasive methods such as radiation or chemotherapy, which are often associated with significant unwanted side-effects.[3,4] While there has been significant improvement in the overall patient survival rate and treatment of some cancers over the past decades, there are still many cancers with high unmet clinical needs which would benefit from improvements in treatment, such as pancreatic adenocarcinoma (PDAC) and lung carcinomas. PDAC is the fourth leading cause of cancer-related death in Western societies, with 5-year survival rates of less than 7%.[5] PDAC tumors are aggressive, often non-resectable, and difficult to treat with conventional chemotherapy; current treatment centers around gemcitabine, gemcitabine plus nab-paclitaxel, and combination therapy FOLFIRINOX (5-FU, leucovorin, irinotecan, oxaliplatin).[6] Lung cancer is the leading cause of cancer-associated deaths worldwide, with non-small cell lung cancer (NSCLC) constituting about 85% of lung cancer cases, and platinum-based combination chemotherapy is considered the first-line therapy for patients with advanced NSCLC.[7,8] Problems with these current treatment options include insufficient drug delivery to the tumor site, issues with cell-membrane penetration, drug degradation and drug solubility problems, and off-target toxicity resulting in undesirable side effects. The emerging field of nanomedicine seeks to address these issues by transporting drug molecules using vehicles that can protect drugs from degradation and deliver them safely and efficiently to the tumor site, minimizing off-target events.[9–12] Among the wide set of proposed drug delivery vehicles, metal–organic frameworks (MOFs) were proposed recently for this application.[13–17] MOFs are porous crystalline materials consisting of metal ions or clusters coordinately interconnected by organic linkers. The resultant void space within these materials provides exceptionally high surface areas of up to 8000 m² g⁻¹.[18–21] The chemical ease with which the metallic nodes or ions and the organic linkers can be combined allows for fine-tuning of the pore properties, including optimizing pore size and volume, but also surface chemistry and therefore the host-guest (i.e., MOF-drug) interactions. Therefore, MOFs have been widely explored in the past for multiple applications, including gas adsorption and separation, heterogeneous catalysis,[22] and sensing.[23,24]
On account of their large internal pore volumes, MOFs are a step forward in the development of drug carriers. The loading capacities of drugs inside MOFs surpass those of any other drug delivery vehicle, showing values as high as 2 g of drug per gram of empty MOF,\cite{14,25} that is, loading capacities >66 wt\%, whereas the release of drugs from a MOF can be slow and controlled, avoiding a therapeutically inactive burst-release.\cite{13,17,26,27} Advances in synthesis, such as those of modulated syntheses of Zr-MOFs, allow for the MOF particle size to be tuned between sub 100 to 200 nm for drug delivery.\cite{28,29} MOFs containing biocompatible metals such as Zn, Fe, or Zr (LD50 of 0.35, 4.1, 0.45 g kg\(^{-1}\), respectively) and organic linkers such as terephthalic acid, 1,3,5-benzenetricarboxylate, and 2-methylimidazole (LD50 of 1.13, 5.5, and 8.5 g kg\(^{-1}\), respectively) are also many times unstable at acidic pH or in the presence of phosphates, providing an effective clearance pathway of the delivery vehicle from the patient's body.\cite{30} Furthermore, MOFs can be directly assembled from therapeutic ingredients, such as the antitumoral BioMOFs\cite{31} and cisplatin-based nanoscale coordination polymers (NCPs).\cite{32} The high drug-loading capacities, controlled drug release, and optimal stability of MOFs can potentially contribute to minimize the side effects in cancer patients and to improve the treatment efficacy. We note that, at this point, no MOF-based formulation has been approved by drug agencies yet.

In addition to the advantageous properties of MOFs for drug delivery applications, their performance can be improved by including a guest material into an MOF, or encapsulating a MOF in a host material, creating MOF-composites,\cite{33–35} For this review, we will consider a MOF-composite to be a material that contains a MOF and at least one other supramolecular or nanoscale material; that is to say, we are not considering here a drug@MOF particle a MOF-composite. Commonly, composites will feature nanoparticles (NPs) for stimulated release or imaging,\cite{36,37} polymers or hydrogel matrices,\cite{38,39} as well as biomolecules. Due to the ease of the assembly and the large pore space, we will mostly see MOFs as the host material, but in some examples, the MOFs themselves will be encapsulated in larger assemblies. In the former case, we will distinguish between i) impregnation composites, where the guest is inside the porosity of the framework; ii) encapsulation composites, where multiple hosts, which are larger than the pores, are within the crystallite matrix but do not occupy the porosity; and iii) core–shell composites, in which an MOF crystallite is grown around a single host.

This review will introduce the reader to the broad field of MOF composites and their applications in cancer therapy and diagnostics (Scheme 1 and Table 1). Indeed, most preclinical studies have been carried out using cancer models and, therefore, throughout this review, although we emphasize cancer therapeutics, we will also touch on other indications. While we have found that the field of biomolecule/MOF composites is broadly covered by reviews,\cite{40–42} we find that especially non-biological composites are underrepresented in reviews. Non-biological composites feature more varied synthetic approaches than biological composites and are in general more responsive to external stimuli and diagnostic techniques. We will focus this review mainly on nanoparticle-MOF composites—denoted NP@MOF—and MOF–polymer composites, but we will also briefly introduce composites featuring biological materials.

2. MOF Composites

2.1. NP@MOF Composites

Nanoparticles are among the most used encapsulation guests in MOF-composites due to their wide versatility and adjustable surface chemistry, with applications ranging from drug delivery to catalysis, sensing, and gas storage.\cite{11,13,35,43} Here, we will focus on the use of magnetic, plasmonic, and optically active nanoparticles.

2.1.1. Magnetic NPs

The inclusion of magnetic NPs (MNP) into MOFs for drug delivery has two principle applications. On the one hand, the use
of magnetophoretic therapy uses external magnetic fields for targeting a composite or NPs to a particular site. On the other hand, magnetic NPs can be used for magnetic resonance imaging (MRI), where superparamagnetic NPs can reduce the spin-spin T₂*-relaxation time, leading to enhanced contrast in T₂*-weighted images. We note here that for drug delivery purposes exclusively MNPsbased on Fe are used.

**MNP@MOF for Magnetophoretic Therapy:** The first example of hosting MNPs in MOFs for drug delivery applications was brought by Ke et al. in 2011.⁴⁴ They described the synthesis of a Fe₃O₄@HKUST-1(Cu) composite, by encapsulating Fe₃O₄ nanorods (NRs) in HKUST-1(Cu) (HKUST-1(Cu), Cu₃ 1,3,5-benzene-tricarboxylate) using a bottle-around-ship approach. Subsequently, they loaded the composite with nimesulide, a pancreatic cancer drug, achieving a loading capacity of 0.2 g of drug per gram of composite (16 wt%). They determined the sample magnetization to be either 1.54 or 0.92 emu g⁻¹ at room temperature in a 10 T field, depending on the loading content of Fe₃O₄ (Figure 1A). This was strong enough to separate the NPs from a suspension using a small magnet. The nimesulide drug was completely released over 11 days in a physiological saline solution at 37 °C.

Despite the limited use of HKUST-1(Cu) in biomedical applications due to its toxicity and stability—HKUST-1(Cu) is hydrolytically unstable and contains toxic Cu(II) ions—more proof-of-principle work has been done using HKUST-1(Cu) for magnetophoretic therapy. For example, Silvestre et al. grew HKUST-1(Cu) layers on magnetic silica nanobeads using liquid phase epitaxy, resulting in a composite that was suggested for drug delivery.⁴⁵ Extending this idea, the inclusion of FDA-approved Fe₃O₄ into MOFs with better biocompatibility and water stability has often been employed since, for example, by Yang et al. in a “Litchi-like” Fe₃O₄@MIL-100(Fe) (MIL-100(Fe), Fe₃O(H₂O)₂OH 1,3,5-benzenetricarboxylate) composite.⁴⁶ as well as others obtaining similar results.⁴⁷–⁵⁰

Another early example of MNP@MOF composites for magnetically guided therapy was reported by Wu et al.⁵¹ They showed a very different synthesis technique, by impregnating pre-synthesized ZIF-8(Zn) (ZIF-8(Zn), Zn 2-methylimidazole) and MIL-53(Al) (MIL-53(Al), Al(OH) terephthalate) with Fe(acac)₃, followed by the pyrolysis of Fe(acac)₃@MOF at 300 °C in an N₂ stream. This yielded ultra-small γ-Fe₂O₃ NPs inside the MOFs, with a strong magnetization of 6.3 and 6.1 emu g⁻¹ for γ-Fe₂O₃@ZIF-8(Zn) and Ibuprofen-loaded γ-Fe₂O₃@MIL-53(Al), respectively. Due to the small window size of ZIF-8(Zn) (3.4–4.2 Å), only the MIL-53(Al) variant was loaded with the Ibuprofen (1.3 nm size). Again, the materials can be easily separated from a solution using an external magnetic field. The complete release of Ibuprofen from γ-Fe₂O₃@MIL-53(Al) in physiological saline buffer at 37 °C took place after 7 days. We note here that due to the toxic nature of Al, this proof-of-principle study would have to be extended to other drugs and MOFs.

More recently, Pinna et al. synthesized large Fe₃O₄-containing polymeric magnetic particles (PMPs) and encapsulated these in MIL-88A(Fe) (MIL-88A(Fe): Fe(III) fumarate) for the magnetophoretic delivery of dopamine (DA) for Parkinson’s disease.⁵² The resultant particle size could be tuned between 8 and 86 µm in size, depending on how many MOF layers were formed around the PMP. Their large particle size may seem surprising but is nonetheless desirable as it causes the particles upon nasal delivery to adhere to the olfactory nerve region, preventing them from entering the lungs. They also obtained DA loadings in the composite of 0.61 g g⁻¹ (38 wt%), with a burst-release in 1 mM PBS (phosphate-buffered saline) during the first 6 h, followed by a slower release due to diffusion of DA through the pore network. They confirmed the biocompatibility of the composites using a trypan blue exclusion assay on brain cancer PC12 cells, indicating only limited toxicity for multilayer PMP@MIL-88A(Fe) particles. Finally, the DA levels were assessed using

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**Scheme 1.** MOF composites and their applications in cancer therapy and diagnostics.
Table 1. A comparative review of theragnostic drug delivery MOF composites.

| Composite material                      | MOF chemistry     | Pore size (window size, if applicable) [nm] | Drug (size) [nm] | Toxicity (IC50 if stated in paper) | Ref. |
|----------------------------------------|-------------------|---------------------------------------------|------------------|------------------------------------|------|
| Fe₃O₄@HKUST-1(Cu)                      | Cu₄ bct          | 1.1–1.4                                      | Nimesulide (1.1) | ++                                 | [44] |
| MagPrep silica@HKUST-1(Cu)             | Cu₄ bct          | 1.1–1.4                                      | N/A              | ++                                 | [45] |
| Fe₃O₄@MIL-100(Fe)                      | Fe₂O(OH)(H₂O)₂ bct | 2.4–2.9 (0.6–0.9)                            | Dox (1.5)        | ++                                 | [46] |
| Fe₃O₄@MIL-100(Fe)                      | Fe₂O(OH)(H₂O)₂ bct | 2.4–2.9 (0.6–0.9)                            | Ibuprofen* (1.3) | ++                                 | [47] |
| Fe₃O₄@MIL-100(Fe)                      | Fe₂O(OH)(H₂O)₂ bct | 2.4–2.9 (0.6–0.9)                            | Dox (1.5)        | ++                                 | [48] |
| Fe₃O₄@MIL-100(Fe)                      | Fe₂O(OH)(H₂O)₂ bct | 2.4–2.9 (0.6–0.9)                            | Dox (1.5)        | ++                                 | [49] |
| γ-Fe₂O₃@SiO₂@HKUST-1(Cu)               | Cu₄ bct          | 1.1–1.4                                      | Letrozole (1.2)   | ++++                               | [50] |
| γ-Fe₂O₃@MIL-100(Fe)                    | Al(OH)bdc        | 0.85                                         | Ibuprofen (1.3)   | +++                                | [51] |
| γ-Fe₂O₃@MIL-100(Fe)                    | Al(OH)bdc        | 0.85                                         | Anthracene (1.1)  | [52] |
| AuNR/polyoxometalate@MIL-101(Cr)       | Al(OH)(1,4-ndc)   | 0.9–1                                         | N/A              | 4.45 µg/mL, MCF-7                  | [53] |
| AuNR@ZIF-8(Zn)                         | Zn₂-MIM          | 1.2 (0.34)                                   | N/A              | +++                                | [54] |
| AuNR@ZIF-8(Zn)                         | Zn₂-MIM          | 1.2 (0.34)                                   | N/A              | +++                                | [55] |
| CuS@ZIF-8(Zn)                          | Zn₂-MIM          | 1.2 (0.34)                                   | N/A              | +++                                | [56] |
| CuS@ZIF-8(Zn)                          | Zn₂-MIM          | 1.2 (0.34)                                   | N/A              | +++                                | [57] |
| AuNR@MOF-545(Zr)                       | Zr₂O₃(OH)₄ tetracarboxyphenoxyphosphin | 3.7 | Camptothecin (1.3) | [58] |
| AuNR@NU-901(Zr)                        | Zr₂O₃(OH)₄ tetra(p-benzoic acid) | 3.1 | N/A | 4.45 µg/mL, MCF-7 | [59] |
| NaYF₄@MIL-101-NH₂(Fe)                  | Fe₂O(OH)(H₂O)₂ bct | 2.9–3.4 (1.2–1.7)                            | N/A              | +++                                | [60] |
| NaYF₄@PCN-224(Zr)                      | Zr₂O₃(OH)₄ tetracarboxyphenoxyphosphin | 2.2 | N/A | 4.45 µg/mL, MCF-7 | [61] |
| NaYF₄:Yb³⁺/Er³⁺@MIL-100(Fe)            | Zr₂O₃(OH)₄ tetracarboxyphenoxyphosphin | 2.2 | N/A | 4.45 µg/mL, MCF-7 | [62] |
| NaYF₄:Yb³⁺/Er³⁺@ZIF-8(Zn)              | Zn₂-MIM          | 1.2 (0.34)                                   | N/A              | +++                                | [63] |
| C₉₀@ZIF-8(Zn)                          | Zn₂-MIM          | 1.2 (0.34)                                   | N/A              | +++                                | [64] |
| Fe₃O₄@C-dot@IRMOF-3(Zn)                | Zn₂O bdc-NH₂      | 1.9 (1)                                       | Dox (1.5)        | 10 µg mL⁻¹, HeLa                   | [65] |
| AuNc@ZIF-8(Zn)                         | Zn₂-MIM          | 1.2 (0.34)                                   | Dox (1.5)        | +++                                | [66] |
| PPy@MIL-100(Fe)                        | Fe₂O(OH)(H₂O)₂ bct | 2.4–2.9 (0.6–0.9)                            | Dox (1.5)        | +++                                | [67] |
| PPy@MIL-53(Fe)                         | Fe(OH)bdc        | 0.85                                         | Dox (1.5)        | +++                                | [68] |
| PPy@MIL-100(Fe)                        | Fe₂O(OH)(H₂O)₂ bct | 2.4–2.9 (0.6–0.9)                            | Dox (1.5)        | +++                                | [69] |
| Fe-soc-MOF@Ppy                         | Fe₂O 3.3, 5.5′ azobenzenetetracarboxylate | 0.67 | N/A | 4.45 µg/mL, MCF-7 | [70] |
| MIL-100(Fe)@PDA                        | Fe₂O(OH)(H₂O)₂ bct | 2.4–2.9 (0.6–0.9)                            | Curcumin (1.9)   | +++                                | [71] |
| ZIF-8(Zn)@PDA                          | Zn₂-MIM          | 1.2 (0.34)                                   | Dox (1.5)        | +++                                | [72] |
| ZIF-8(Zn)@PDA                          | Zn₂-MIM          | 1.2 (0.34)                                   | Dox (1.5)        | +++                                | [73] |
| PDA@MIL-100(Fe)                        | Fe₂O(OH)(H₂O)₂ bct | 2.4–2.9 (0.6–0.9)                            | Dox (1.5)        | +++                                | [74] |
| PDA@MIL-100(Fe)                        | Fe₂O(OH)(H₂O)₂ bct | 2.4–2.9 (0.6–0.9)                            | Dox (1.5)        | +++                                | [75] |
| PDA@MIL-100(Fe)                        | Fe₂O(OH)(H₂O)₂ bct | 2.4–2.9 (0.6–0.9)                            | Dox (1.5)        | +++                                | [76] |
| PDA@MIL-100(Fe)                        | Fe₂O(OH)(H₂O)₂ bct | 2.4–2.9 (0.6–0.9)                            | Dox (1.5)        | +++                                | [77] |
| PDA@MIL-100(Fe)                        | Fe₂O(OH)(H₂O)₂ bct | 2.4–2.9 (0.6–0.9)                            | Dox (1.5)        | +++                                | [78] |
| PDA@MIL-100(Fe)                        | Fe₂O(OH)(H₂O)₂ bct | 2.4–2.9 (0.6–0.9)                            | Dox (1.5)        | +++                                | [79] |
| PDA@MIL-100(Fe)                        | Fe₂O(OH)(H₂O)₂ bct | 2.4–2.9 (0.6–0.9)                            | Dox (1.5)        | +++                                | [80] |
| MCo@PDA hydrogel                       | Mn3[Co(CN)6]₂     | N/A                                          | N/A              | +++                                | [81] |

(Continued)
Table 1. Continued.

| Composite material | MOF chemistry | Pore size (window size, if applicable) [nm] | Drug (size) [nm] | Toxicity (IC50 if stated in paper) | Ref. |
|--------------------|---------------|---------------------------------------------|-----------------|-----------------------------------|------|
| Fe-soc-MOF@ICG     | Fe(OH)2O3,3',5,5'-azobenzene-tetra-carboxylate | 0.67            |                 |                                   | [100]|
| Cypate@MIL-53(Fe)  | Fe(OH)2 bdc   | 0.85                                        |                 | 2.12 μm, AS49I, 785 nm           | [101]|
| PAN@UiO-66(Zr)     | Zr2O5(OH)2 bdc | 0.8–1.2                                     | Fluorescein* (1.1) | +                                 | [104]|
| PAA@ZIF-8(Zn)      | Zn 2-MIM      | 1.2 (0.34)                                  | Caffeine* (0.8)  | ++                                | [103]|
| MIL-100(Fe)@Heparin| Zr5O4(OH)4 bdc-NH2 | 0.8–1.2                                  | Resorufin (1.0)  | +                                 | [105]|
| UiO-66-NH2(Zr)@PNIPAM | Zr6O4(OH)4 bdc-NH2 | 0.8–1.2                                  | Caffeine* (0.8)  | +                                 | [106]|
| PB@MIL-100(Fe)     | Fe(OH)2O3(H2O)2 bdc | 2.4–2.9 (0.6–0.9) | Artemisinin (0.9) | ++                                 | [106]|
| PCN-224(Zr)@MnO2   | Zr6O4(OH)4  | 2.2                                         |                 |                                   | [107]|
| Fe3O4@UiO-66-NH2/graphdiyne | Zr5O4(OH)4 bdc-NH2 | 0.8–1.2                                  | Dox (1.5)       | +                                 | [108]|
| ZIF-8(Zn)/Graphene oxide | Zr5O4(OH)4 bdc-NH2 | 0.8–1.2                                  | Fluorescein* (1.1) | +                                 | [109]|
| Zr(IV) disuccinatocisplatin | Zr disuccinatocisplatin |                                   | Cisplatin (0.5)  | 1.2 μm, AS49 cell                  | [112]|
| NCP@DOPA:DOPC/DSPE-PEG | Zn biphosphonate |                                   | Cisplatin (0.5)  | 9.3 μm, CT26                       | [115]|
| Zn(II) biphosphonate |                                   |                                   | Oxaliplatin (0.5) | 10.5 μm, CT26                    | [116]|
| NCP@DOPA:DOPC/DSPE-PEG | Zn-cis,cis,trans-[Pt(NH3)2Cl2(OCONHP(O)(OH)2)2] |                                   | Cisplatin (0.5)  | 1.3 μm, Procainamide (1.4)        | [116]|
| MIL-100(Fe)@DOPC   | Zr6O4(OH)4 bdc | 2.4–2.9 (0.6–0.9) | ++                |                                   | [111]|
| MIL-101(Cr)@DOPC   | Cr3O4(OH)H2O3 bdc | 2.9–3.4 (1.2–1.7) | ++                |                                   | [112]|
| Uio-66(Zr)@DOPA    | Zr5O4(OH)4 bdc | 0.8–1.2                                     | ++                |                                   | [114]|
| BUT-10(Zr)@DOPA    | Zr5O4(OH)4  | 1.2–1.6                                     | ++                |                                   | [115]|
| ZIF-4(Zn)@DOPC     | Zn imidazole  | 0.5 (0.25)                                  | Curcumin (1.9)   | ++                                | [113]|
| Uio-66(Zr)-DPCG    | Zr2O4(OH)4 bdc | 0.8–1.2                                     | +                 |                                   | [116]|
| HKUST-1(Cu)-DPCG   | Cu2 bdc       | 1.1–1.4                                     | +++               |                                   | [114]|
| MIL-101(Cr)-DPCG   | Cr2O4(OH)H2O3 bdc | 2.9–3.4 (1.2–1.7) | +                 |                                   | [133]|
| UiO-66(Zr)@TPP     | Zr5O4(OH)4 bdc | 0.8–1.2                                     | Dichloroacetate (0.4 nm) | +                                | [112]|
| Tyrosinase@PCN-333(Al) | Al3O4,4,4',4''-s-triazine-2,4,6-triyltribenzoate | 3.4–5.5 (2.6–3) | Paracetamol* (0.9) | +                                 | [123]|
| siRNA@NU-1000(Zr)  | Zr4O4(OH)4  | 3.6                                         | +                 |                                   | [125]|
| CRISPR/Cas9@ZIF-8(Zn) | Zn2-MIM      | 1.2 (0.34)                                  | Cisplatin (0.5)  | 45.8 μm, SKOV-3                    | [126]|
| Zn(II) biphosphonate |                                   |                                   | +                 |                                   | [129]|
| NCP@DOPA:DOPC/siRNA/DSPE-PEG | Zn biphosphonate |                                   | Cisplatin (0.5)  | +                                 | [127]|
| ssDNA@IRMOF-74(Ni) | Zn 2,4-dihyroxystephathalate | 1.5                                     | +                 |                                   | [130]|
| mRNA@UiO-66(Zr)    | Zr5O4(OH)4 bdc | 0.8–1.2                                     | +                 |                                   | [131]|
| siRNA@MIL-100(Fe)  | Fe5O4(OH)H2O3 bdc | 2.4–2.9 (0.6–0.9) | +                 |                                   | [132]|

Model drugs are highlighted with an *. Toxicity data based on MOF toxicity as analyzed by Ruyra et al. on zebrafish embryos, where "-" represents little toxicity and "++++" represents high toxicity.144 btc, 1,3,5-benzenetricarboxylate; bdc, 1,4-benzenedicarboxylate; 2-MIM, 2-methylimidazole; bdc-NH2, 2-aminobenzenedicarboxylate.
Figure 1. A) Room-temperature magnetization curves of nimesulide-loaded Fe₃O₄@HKUST-1, denoted 1-NIM and 2-NIM. 1-NIM has a Fe₃O₄NR mass contribution of 5.4 wt%, while that for 2-NIM is 3.7 wt%. Inset shows the separation of 1-NIM from the solution using a small magnet. Reproduced with permission.[44] Copyright 2011. Royal Society of Chemistry. B) MR images of HeLa cells incubated with different concentrations of Fe₃O₄@UiO-66; C) T₂-weighted MR images of Kunming mouse at several time points after injection with Fe₃O₄@UiO-66; D) T₂-weighted MR images of the tumor in Kunming mice bearing Fe₃O₄@UiO-66. B–D) Reproduced with permission. [54] Copyright 2016, Royal Society of Chemistry.

high-pressure liquid chromatography electrochemical detection (HPLC-EC), both in the extracellular and the intracellular region. The authors found higher intracellular DA levels when using PMP@MIL-88A(Fe) with respect to the control and free DA delivery, whereas the extracellular concentration of DA was reduced compared to free DA delivery. All this suggests a reduction in the risk of side-effects arising from DA oxidation in the extracellular medium.

**MNP@MOF as MRI Contrast Agents**: The use of MNPs as MRI contrast agents is widespread, with several examples both for paramagnetic and superparamagnetic NPs as T₁ and T₂*-contrast agents, respectively.[37] While Peller et al. have produced a comprehensive NMOF for MRI imaging review recently,[53] in this review we will focus only on MNP@MOF based systems.

An important early contribution was made by Zhao et al., who synthesized an Fe₃O₄@UiO-66(Zr)-NH₂ (UiO-66-NH₂(Zr), Zr₆O₄(OH)₄ 2-aminoterephthalate) core–shell composite.[54] The resultant particles were of 241 nm in size and had a respectable BET area of 150 m² g⁻¹ as well as a high saturation magnetization of 51.58 emu g⁻¹; further, they achieved a loading capacity of 66.3 wt% for doxorubicin (Dox). While the pore size of UiO-66(Zr) of 8.5 Å is probably too small to allow for Dox (1.5 nm size) to enter the internal porosity,[27,55] the authors reported an interparticle mesopore size of 3.5 nm which could host Dox molecules. Given the fact, however, that Dox was loaded post-synthetically, such a high loading capacity is surprising and raises the question if Dox is adsorbed into the framework or simply attached to the external surface of the MOF. After 41 days, 36.1% and 21.6% of Dox was released at pH 4.0 and pH 5.0, respectively. Interestingly, Dox-loaded Fe₃O₄@UiO-66-NH₂(Zr) (Fe₃O₄@UiO-66-NH₂(Zr)/Dox) showed similar therapeutic efficacy to that of the free Dox when running in vitro studies in the HeLa cancer cell line. Crucially, however, Fe₃O₄@UiO-66-NH₂(Zr)/Dox was used in vivo as a contrast agent for MR imaging on HeLa-bearing Kunming mice. Injection of Fe₃O₄@UiO-66-NH₂(Zr) into the tail vein of the mice resulted in a significant darkening in T₂*-weighted images, 1 and 9 h after injection in the tumor (Figure 1C,D). Additionally, Fe₃O₄@UiO-66(Zr) exhibited a concentration-dependent image contrast (Figure 1B). While we note that the authors did not comment on the poor stability of UiO-66(Zr) in phosphate-buffered saline (PBS),[13] this study presents a breakthrough in the development of theragnostic Fe₃O₄@MOF systems, and similar Fe₃O₄@MOF composites have been reported by Wu et al.[56] Chowdhuri et al.,[57] and Nejadshafiee et al.[58] for UiO-66(Zr), IRMOF-3(Zn), and a curcumin-based Bio-MOF(Zn), respectively.

Extending on MRI contrast, Sene et al. reported a γ-Fe₂O₃/MIL-100(Fe) composite that was capable of serving as an image contrast agent in vivo.[59] Rather than containing NPs within the MOF matrix, this composite was synthesized by co-precipitating citrate-capped γ-Fe₂O₃ NPs (7 ± 3 nm in size) with MIL-100(Fe) NPs (130 ± 30 nm in size), resulting in the γ-Fe₂O₃ NPs attached to the external surface of the MIL-100(Fe) crystallites. They showed outstanding paramagnetic properties, with a relaxivity r₂ of 93 ± 4 mm⁻¹ s⁻¹, comparable to commercial MRI contrast agents such as Endorem and Sinerem, and a very high magnetization saturation of 62 A m² kg⁻¹. They also achieved a Dox loading capacity of 14 wt%, with a sustained release over 25 days. Incubation of prostate cancer PC3 cells with γ-Fe₂O₃/MIL-100(Fe) caused negligible cell death, indicating good biocompatibility of the composite. In contrast, Dox-loaded γ-Fe₂O₃/MIL-100(Fe) exhibits good therapeutic efficacy, with cell viability decreasing to 33%, 52%, and 78% for 100, 50 and 10 µg mL⁻¹ composite concentrations, respectively, significantly higher than free Dox treatment. Finally, they demonstrated in vivo efficacy for MRI imaging by injecting 90 µL of γ-Fe₂O₃/MIL-100(Fe), at 12 mg mL⁻¹ in a PBS-BSA medium, into mice. This generated a signal decrease in T₂*-weighted MRI images corresponding to a signal-to-noise reduction of 52%.
2.1.2. Plasmonic NPs

Plasmonic NPs have been of interest to drug delivery since the early 2000s, following the application of gold nanorods (AuNRs) in photothermal therapy.[60] The process, known as plasmonic photothermal therapy (PPTT), uses the strong surface plasmon resonance absorption (SPR) of noble metal nanoparticles, to convert light energy into highly localized heating.[61–65] Gold nanorods are used most often due to near-infrared (nIR) SPR modes allowing for relatively deep tissue penetration.[60]

The integration of plasmonic nanoparticles into MOFs for biomedical applications was first considered by Khaletskaya et al., who demonstrated the model drug anthracene release from a toxic AuNR@[Al(OH)(1,4-naphthalenedicarboxylic acid)] core–shell composite under nIR-irradiation.[66] Later, Roch-Marchal et al. synthesized an AuNP/polyoxometalate/MIL-101(Cr) (MIL-101(Cr):Cr3(OH)(H2O)2O terephthalate) impregnation composite with potential catalytic and biomedical applications.[67] However, the first major systematic study was carried out by Li et al. on AuNR@ZIF-8(Zn) core–shell composites.[68] In this study, they used polyvinylpyrrolidone (PVP)-capped AuNRs to seed ZIF-8(Zn) growth, resulting in a core–shell morphology. We note here that PVP is a common NP surface ligand for MOF encapsulation.[43] In the composite, they observed a mesoporous volume (with pore sizes between 4 and 9 nm), which was attributed to multidomain growth of ZIF-8(Zn) shells on the AuNR cores, suggesting the ability to uptake larger drug molecules than otherwise allowed by the narrow ZIF-8(Zn) pore-window size of 3.4–4.2 Å.[69] They then demonstrated photothermal energy conversion using a 0.1 mg mL$^{-1}$ AuNR@ZIF-8(Zn) solution and an 808 nm nIR laser (1 W cm$^{-2}$), resulting in a large temperature increase from 25 to 50 °C within 5 min. Dox-loaded AuNR@ZIF-8(Zn) exhibited both pH and light-dependent release, with roughly four times as much Dox released at pH 5.5 compared to pH 7.4 in the dark, and roughly six times as much Dox released under nIR-irradiation at pH 5.5 (Figure 2C). The composite was studied in vivo on Balb/c mice injected with 1 million 4T1 cells, a murine breast carcinoma line. Once the tumor volume had grown to 100 mm$^3$, the mice were injected with 200 µL of either Dox/PBS (1 mg mL$^{-1}$) or AuNR@ZIF-8(Zn)/Dox (1.5 mg mL$^{-1}$). During the nIR-irradiation, the tumors heated up from 36.2 to 52.4 °C, while nIR-irradiation on a PBS control group did not raise the tumor temperature. Overall, the authors reached a very promising tumor suppression level of 90% for the AuNR@ZIF-8(Zn)/Dox-nIR system, compared to 58% for the “photothermal only” AuNR@ZIF-8(Zn)/nIR system and 30% suppression in AuNR@ZIF-8(Zn)/Dox without nIR light. Equally, high cell viability of 4T1 cells treated with AuNR@ZIF-8(Zn) in the dark suggested good biocompatibility and low cellular toxicity of the composite.

While this is the first major study in the field, we note here that a similar AuNR@ZIF-8(Zn) system was reported earlier by Fang et al.,[70] with a substantially thinner ZIF-8(Zn) shell, and later by Zhang et al.,[71] obtaining similar results. Additionally, CuS@ZIF-8(Zn) nanoparticles with plasmon resonance bands at 1000 nm have been explored for drug delivery applications.[72,73] Moving to other MOF systems, Zeng et al. encapsulated polyethylene glycol (PEG)-functionalized AuNRs using the porphyrin-based MOF-545(Zr) (MOF-545(Zr):Zr 6O8 tetracarboxyphenylporphyrin), resulting in a core–shell morphology.[74] They achieved a 25 wt% loading capacity for camptothecin (CPT). This respectable loading capacity is not surprising, given that MOF-545(Zr) has much larger apertures sizes and pores than ZIF-8(Zn), which makes claims that the drug is adsorbed into the porosity of the framework more believable. The composite exhibited strong photothermal energy conversion demonstrated by nIR-irradiation under 10 min which heated a 0.1 mg mL$^{-1}$ sol of AuNR@MOF-545(Zr) in water from room temperature to 73.4 °C. Due to its porphyrinic organic linker, the composite was also capable of generating reactive oxygen species (ROS, $O_2^*$) under UV-irradiation. This photodynamic therapy (PDT) was used here synergistically with PPTT and chemotherapy to induce cell death. They based their study on CPT@AuNR@MOF-545(Zr), demonstrating the therapeutic
action of PDT and PPTT using CCK-8 assays. However, the strongest efficacy was found for the synergistic PDT/PPTT/CPT treatment, which killed ≥90% of cells at a particle concentration of 120 μg mL⁻¹. Further, they extended their study to in vivo on BALB/c mice injected subcutaneously with 4T1 cells. They found that CPT@AuNR@MOF-545(Zr) NPs aggregated at the tumor site 24 h post-injection without any specific targeting functionalities and therefore most likely via the enhanced permeability and retention (EPR) effect. The bio-distribution was measured using inductively-coupled plasma atomic emission spectroscopy (ICP-AES) on Au, which showed that, mainly, the tumor and the liver were targeted. nIR-irradiation on the tumor raised the local temperature from 28.5 to 54.8 °C compared to a very small temperature increase in the control group. Later, Osterrieth et al. produced a similar composite featuring AuNRs at the core and pyrene-based MOF NU-901(Zr) as a shell. While the chief application on this composite was size-selective Raman spectroscopy, NU-901(Zr) has been used for drug delivery before, suggesting that this composite might be used as a plasmonic release agent as well.

2.1.3. Upconverting Nanoparticles

Upconverting nanoparticles (UCNPs) have been suggested for bioimaging applications due to their unusual optical properties. Simply put, an upconversion process involves emission from a shorter wavelength than the one used to create an excited state. Li et al. encapsulated Yb and Er-doped NaYF₄ within MIL-101-NH₂(Fe) (MIL-101-NH₂(Fe), FeO(OH)(H₂O)₂, 2-aminoterephtalate), giving core–shell UCNP@MIL-101-NH₂(Fe) nanostructures. Excited at 980 nm, the upconversion properties of the UCNP caused emission at 520, 540, and 654 nm. Additionally, due to the presence of paramagnetic heavy ions in the UCNP, UCNP@MIL-101-NH₂(Fe) could serve as T₁-relaxation agents, while the MIL-101-NH₂(Fe) moiety served as a spin-spin relaxor, reducing the T₂⁎-relaxation time of water from 2047 to 5.6 ms. This effect could be observed in an MRI as well, with T₂⁎-weighted images appearing considerably darker and the effect being concentration-dependent. Subsequently, the NPs were additionally conjugated with folic acid (FA), which targets folate receptors (FR) overexpressed in human epidermoid carcinoma KB cells. Confocal microscopy revealed that, after 24 h, FA-modified UCNP@MIL-101-NH₂(Fe) was uptaken by KB cells but not for FR-negative MCF-7 cells, suggesting an active targeting pathway. In vivo experiments on KB-bearing BALB/c mice using luminescence imaging revealed a preferential targeting to the tumor by the FA-modified UCNP@MIL-101-NH₂(Fe), while unmodified NPs did not, giving further evidence for an active-targeting pathway. T₂⁎-weighted MRI imaging in a 3 T field showed 35% image darkening in the tumor. Finally, the biodistribution of UCNP@MIL-101-NH₂(Fe), analyzed using yttrium detection with ICP-AES and ICP-MS on dissolved organs, showed that the majority of yttrium was found in the liver and the spleen, suggesting that these organs take up the composite most. The yttrium concentration of FA-decorated UCNP@MIL-101-NH₂(Fe) was substantially higher in the tumor than bare UCNP@MIL-101-NH₂(Fe), which is consistent with previous findings of active targeting. Further work on comparable UCNP@MOF systems with similar applications has been done by He et al. using PCN-224(Zr) with a larger porosity and PDT-active porphyrin linkers, Deng et al. using the biofriendly MIL-100(Fe), and Chowdhuri et al. using ZIF-8(Zn).

2.1.4. Quantum Dots

Quantum dots have recently attracted a great deal of interest due to their strongly luminescent properties for bioimaging. Due to their inherent biocompatibility, C-dots, 0D carbon species, are of particular interest to theragnostics. He et al. synthesized C-dots (2 nm) using a microwave-assisted method and subsequently encapsulated them using ZIF-8(Zn), resulting in 110 nm particles with sodalite structure. The encapsulation morphology could not be confirmed using transmission electron microscopy (TEM) due to the small size of the C-dots and poor carbon-on-carbon contrast. However, photoluminescence (PL) measurements showed that C-dots were incorporated into the ZIF-8(Zn) matrix. They achieved a 0.3 g g⁻¹ loading for 5-fluorouracil (5-FU) (23 wt%), with a drug release in PBS that is strongly pH-dependent: 92% released after 2 days at pH 5.5, compared to 67% at pH 7.4. We note that 5-FU (0.5 nm) is a much smaller molecule than Dox (1.5 nm). On account of the flexibility of the ZIF-8(Zn) pore, it is conceivable that the drug entered the porosity of ZIF-8(Zn). MTT assays on HeLa cells showed that pristine C-dot@ZIF-8(Zn) NPs were biocompatible, while 5-FU loaded C-dot@ZIF-8(Zn) had a similar therapeutic efficacy to “free” 5-FU—this could suggest loading on the external surface of ZIF-8(Zn). Similar examples of quantum dot@MOF encapsulation have been demonstrated by Chowdhuri et al. using C-dots, and by Cao et al. using ultra-small luminescent gold nanoclusters.

2.2. Polymer@MOF Composites

2.2.1. Polypyrrole@MOF

Polypyrrole (PPy) is a nIR-active polymer that has long been investigated for biomedical applications on account of its good bio-compatibility (IC₅₀: 4.16 mg mL⁻¹; U251 cell line). Zhu et al. synthesized PPy NPs using a microemulsion method and subsequently encapsulated them using PVP and MIL-100(Fe) (Figure 3). The MOF shell thickness could be tuned through the reaction and time and had a final size of approximately 107 nm, as measured by dynamic light scattering (DLS) in water. The composite had broad absorption in the nIR-range, between 700–1100 nm, which is consistent with the presence of PPy in the composite. At a concentration of 0.1 mg mL⁻¹, PPy@MIL-100(Fe) could raise the water temperature by 38 °C under 0.5 W cm⁻² nIR-irradiation after 5 min. They obtained a Dox loading capacity of roughly 13 wt%, with a Dox release that was strongly pH-dependent, with roughly twice as much Dox released at pH 5 compared to pH 7. Importantly, the deliverable amount further increased by approximately a third in the first 2
h of the release curve under photothermal action, demonstrating triggered release from the composite. MTT assays demonstrated good biocompatibility of the pristine composite, as well as therapeutic action of the Dox-loaded NPs. At a concentration of 0.3 mg mL\(^{-1}\), PPy@MIL-100(Fe)/Dox caused roughly 50% cell death in HeLa cells after 48 h; however, under additional nIR-irradiation, the cell viability was dropped to 25%. At the same time, PPy@MIL-100(Fe), without Dox, exhibited no cytotoxicity under nIR-irradiation, suggesting that the added cytotoxicity comes from triggered drug release rather than a photothermal ablation of cells. A number of other PPy/MOF composites have been synthesized in order to exploit the photothermal properties of PPy for drug release. Similar to the work done by Zhu et al., Huang et al. and Chen et al. achieved Dox release from a PPy@MIL-33(Fe) and PPy@MIL-100(Fe) under nIR-action. Different particle morphology was chosen by Cai et al., who grew PPy layers on Fe-soc-MOF, but they obtained similar results to the studies described above. 

### 2.2.2. Polydopamine@MOF

Polydopamine (PDA) is a mussel-inspired polymer consisting of the polymeric oxidation products of dopamine. In recent years, PDA has found numerous applications in drug delivery and biomedical applications on accounts of the relative easy synthesis and biocompatibility (LD\(_{50}\) of 0.48 g kg\(^{-1}\)). Its ability to grow on numerous solid supports has also made it an interesting candidate for the development of NP@MOF composites, by acting as a protective layer around an NP and as an encapsulation agent. Zhang et al. synthesized a PDA/MIL-100(Fe) composite for an extensive theragnostic study, after synthesis of MIL-100(Fe), they loaded it with curcumin, reaching a 33 wt% loading capacity. Subsequently, they grafted a hyaluronic acid (HA)/PDA co-polymer (HA-PDA) on the external surface of the MIL-100(Fe). The change in external surface chemistry was monitored using zeta potential measurements as well as TEM and SEM, which determined a final particle size of \(80\) nm. MIL-100(Fe)/HA-PDA was able to achieve good photothermal energy conversions of up to 21% efficiency, comparable to that of AuNRs. pH-dependent drug release was consistent with similar studies, suggesting a faster release at acidic pH-levels due to the dissolution of the MIL-100(Fe). In vitro experiments on CD44-overexpressing HeLa and A549 cells demonstrated the targeting capabilities of MIL-100(Fe)/HA-PDA, due to the favorable interactions between HA and CD44. Further, upon irradiation with nIR light, cells treated with MIL-100(Fe)/HA-PDA/curcumin exhibited lower survival rates than in dark, suggesting a phototherapeutic effect. This study also included in vivo experiments that demonstrated photothermal imaging capabilities due to the strong nIR-absorption of PDA. Ex vivo harvested tumors showed that MIL-100(Fe)/curcumin was not as well targeted to tumors as MIL-100(Fe)/HA-PDA/curcumin, again suggesting targeting by HA.

### 2.2.3. Other nIR Dyes

While PPy and PDA account for the majority of photothermal therapy studies using MOFs, other dyes have been used as well. Cai et al. used indocyanine green (ICG) by conjugating it on the external surface of Fe-soc-MOF (Fe-soc-MOF, Fe\(_3\)O\(5\cdot3\cdot5\cdot5\cdot\)-azobenzene tetracarboxylate), showing both PDT and PPTT activity. Yang et al. immobilized cypate, a related dye, in a MIL-53(Fe) (MIL-53(Fe), Fe(OH)\(_2\) terephthalate) matrix, yielding a multimodal imaging and therapy platform. Similar to the PDA work described above, polyaniline (PAN) has a high nIR-absorption cross-section, which was used in a UiO-66(Zr)/PAN composite to raise the temperature of the local tumor environment.

### 2.2.4. Other Polymers

Ren et al. synthesized a novel polyacrylic acid (PAA)/MOF composite, thereby improving the poor aqueous stability of PAA NPs. They encapsulated PAA NPs into ZIF-8(Zn), getting an exceptional Dox-loading capacity of 1.9 g g\(^{-1}\) (66 wt%); however, given the pore size of ZIF-8(Zn), Dox is very likely to be adsorbed on the external surface. The loaded composite exhibited pH-dependent drug release as well as good biocompatibility in breast cancer MCF-7 cells. Bellido et al. coated the external surface of MIL-100(Fe) with heparin, which improved multiple pharmacokinetic and therapeutic parameters. The heparin coating improved the colloidal stability of the MOFs and reduced the recognition by phagocytic innate immune cells, which suggests a lowered inflammatory response.

A very creative and innovative study was carried out by Sada et al., who grafted the thermoresponsive polymer poly-NIPAM (PNIPAM) on the external surface of UiO-66-NH\(_2\)(Zr) NPs. PNIPAM switches from an “open,” extended state at a temperature below 32°C to an aggregated state above its cloud point. This thermal modulation
of the aggregation state of the polymer allowed the researchers to achieve remarkable control over the drug release properties: In the cold state at 25 °C, fast drug release kinetics were observed, while at 40 °C, when the polymer blocks the external pore access, no release was observed. While this study may have only been proof-of-principle, it is certainly a unique contribution and it will be interesting to see if similar, more clinically relevant studies using PNIPAM will appear.

2.3. Other Non-Biological Composites

Alongside NPs and polymers, more exotic non-biological hosts in MOF composites have been proposed. For example, Wang et al. synthesized a theragnostic Prussian Blue PB@MOF core–shell composite, with dual nIR and pH-dependent drug release properties and MRI contrast capabilities.[106] Liu et al. reported a theragnostic glutathione-responsive fluorescence “switch” for PDT by growing MnOx on a porphyrinic Zr-based MOF PCN-224(Zr) (PCN-224: Zr6O4(OH)4 tetracarboxyphenylporphyrin).[107] Furthermore, two studies have reported the encapsulation of 2D carbon materials into MOFs; one exploits graphdiyne (GDY) as a drug adsorbent,[108] whereas the other utilizes graphene oxide as a photothermal agent.[109]

2.4. Biominolecule-MOF Composite

Biominolecule encapsulation into MOFs is a rapidly emerging field with wide applications from drug delivery to sensing and actuation.[40] A comprehensive review on biominolecule@MOF composites would be outside the scope of this publication, so we only list a few examples that we consider relevant here. We direct the interested readers to excellent reviews written by Zhuang et al.,[40] Mu et al.,[41] and Chu et al.[110] which focuses on biomineralization strategies for drug delivery applications especially.

2.4.1. Lipid-MOF Composites

MOF-lipid composites are usually MOF NPs that have a lipid layer assembled around them to improve colloidal stability and cellular uptake.[111–114] Pioneering work on MOF-lipid composites has been carried out by Huxford-Phillips et al.[112] who synthesized a La-based nanoscale coordination polymer (NCP) containing the cisplatin-prodrug disuccinato-cisplatin (DCSP). The resultant particles were capped with 1,2-dioleoyl-sn-glycero-3-phosphate (DOPA) and further coated using 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-(polyethylene glycol) (DSPE–PEG) in a lipid bilayer. Additionally, an anisamidine (AA) sigma-receptor targeting vector was added to the PEG-chain, and the resultant composites were more potent than free cisplatin against sigma-overexpressing NSCLC cell lines. Based on this work, Liu et al. synthesized more biofriendly NCPs (Zn-based NCP, Zn(II)-biphosphonate) and coated them with a similar lipid bilayer.[115] The resultant composites had significantly higher antitumoral efficacy on CT26 colon cancer, H460 non-small-cell lung cancer, and AsPC-1 pancreatic cancer-bearing mice, compared to the free drugs. He et al. developed this work even further by encapsulating the NCP in a porphyrin-containing pyrrolipid for additional PDT functionality in head and neck cancer treatment.[116] Interestingly, the above studies have all been carried out using NCPs, closely related cousins of MOFs, that do not necessarily exhibit porosity. However, very similar lipid bilayers have been used to stabilize the external surface of Fe,[111] Cr,[111] Zr,[112] and Zn-based MOFs.[113] Even wider chemical versatility was achieved by Zhu et al. through direct coordination of phenolic-lipids to metal clusters.[114] Haddad et al. extended on this idea by conjugating the lipophilic cation triphenylphosphonium (TPP) to UiO-66(Zr) for direct targeting of the mitochondria in cells.[117] The authors demonstrate dichloroacetate (DCA) delivery in MCF-7 breast cancer cells in a rare example of intracellular targeting using MOFs.

2.4.2. Protein-MOF Composites

While lipids are typically coated around MOF NPs, MOF–protein composites are usually formed from a bottle-around-ship encapsulation of a protein by a MOF. This nature-inspired “biomineralization” protocol was first demonstrated by Liang et al. in the encapsulation of the bovine serum albumin (BSA) in ZIF-8(Zn), which improved its thermal and chemical stability within the MOF.[118] Biomineralization strategies using ZIF-8(Zn) have been employed multiple times, recently, to deliver biologically sensitive proteins and protect them from degradation.[119–121] Alternatively to biomineralization, Liang et al. showed a tyrosinase@PCN-333(Al) composite created by infiltrating pre-synthesized PCN-33(Al) (Al2O 4,4,4′-s-triazine-2,4,6-triyl-trienzoate) with tyrosinase. This composite is capable of oxidizing the prodrug Paracetamol into 4-acetamido-o-benzoquinone, which is capable of generating ROS and is thus cytotoxic.[122] They achieved considerable tumor suppression after 7 days in HeLa cancer-bearing mice, which they attribute to the oxidative stress created of the generated ROS.

2.4.3. Nucleotide-MOF Composites

Delivery of other, nucleic acid-based macromolecules such as interfering RNA (RNAi) opens up the opportunity for selective inhibition through gene-targeted therapies.[123] Among the most widely studied nucleotides for gene silencing are small interfering RNA (siRNA), which inhibit their target mRNA via incorporation into the RNA-induced silencing complex (RISC) and through the action of the catalytic RISC protein argonaute 2 which cleaves the mRNA, thus inhibiting protein expression, which work by binding to RNA during the gene expression step, thus inhibiting protein expression.[124] siRNA has a poor biostability and is inherently unable to cross the cell membrane due to its high molecular weight and negative charge, and therefore requires a delivery system.[125–127] Although different MOFs have been used previously, the pore sizes and pore windows were too narrow for the diffusion of siRNA to the internal porosity. In contrast, Teplensky et al. loaded siRNA into
The mesoporous NU-1000(Zr), by impregnating pre-synthesized NU-1000(Zr) (Figure 4A),[125] They demonstrated that the siRNA was inside the MOF porosity using fluorescence lifetime imaging (FLIM) and enzymatic degradation studies that showed the MOF was able to protect the siRNA from digestion. The in vitro efficacy of siRNA@NU-1000(Zr) was then demonstrated by knocking-down the expression of the fluorescence protein mCherry in HEK293-mC cells. This produced mixed results, with mCherry-expression in some cases being suppressed effectively, while in others, no change was observed (Figure 4B). Flow cytometry of Alexa Fluor 647 tagged siRNA delivered by NU-1000(Zr) revealed that siRNA@NU-1000(Zr) was indeed internalized by the cells but had no downstream effect (Figure 4C). Based on previous studies, the authors hypothesized that while the endocytosis of siRNA@NU-1000(Zr) is successful, entrapment of the composite NPs in endosomes degrades the siRNA before it gets released to the cytoplasm.[17,128] To support this hypothesis, the authors added co-factors such as proton-sponge to the cells that are known to destroy endosomes/lysosomes, therefore, aiding the release of the siRNA cargo into the cytoplasm and, consequently, observed a significant increase in the suppression of mCherry expression (Figure 4D). Various other nucleotide@MOF delivery systems have been reported for other applications, such as the delivery of the gene-editing tool CRISPR/CAS9,[129] siRNA@NCP,[127] ssDNA@IRMOF-74(Ni), using a toxic metal,[130] mRNA using UiO-66(Zr),[131] and MIL-100(Fe).[132] The delivery of mRNA using MIL-100(Fe) in particular is promising due to its biocompatibility.
and its comparatively good stability in phosphate-containing solutions.

3. Conclusions

MOF-composite materials have high potential in drug delivery applications due to their high flexibility, rich chemistry, and relative ease of synthesis. The main groups of composites include nanoparticles with magnetic, plasmonic, and luminescent properties but also polymer-MOF and biomolecule-MOF composites. Among magnetic nanoparticles, they are usually located inside a MOF-matrix through a core–shell encapsulation. They can be used for magnetophoretic therapy as well as diagnostic tools by providing T2*-image contrast. FeO₃-based drug formulations are in part already FDA approved, which leads us to consider that MOF composites featuring such NPs would be commercially available first. Similarly, plasmonic nanoparticles such as AuNPs are often core–shell encapsulated. These are nIR-absorbing and have a very high photothermal energy conversion, allowing local heating and spatiotemporal control over drug release. Then, composites featuring luminescent NPs such as quantum dots or UCNPs can be used as diagnostic tools due to their strongly emissive properties. However, the toxic nature of many UCNPs and quantum dots may lead to them being considered prohibitively dangerous in treatment. Polymer–MOF composites exist in both MOF@polymer and polymer@MOF morphologies. The primary purpose of the polymer coatings is to improve pharmacokinetics but also polymeric NPs such as PPy and PDA also exhibit photothermal energy conversion. Similar to FeO₃, many biofriendly polymers are FDA approved, which could lead to such composites becoming the first to go into human trials. Finally, biomolecule–MOF composites, as lipid bilayer coatings on MOFs or protective MOF shells on sensitive proteins and siRNA, have been developed. While exciting and rapidly emerging, this field still lacks strong evidence to prove whether it will become therapeutically viable in the future.

In general, huge efforts on the synthesis of more and more refined MOF systems have been reported in the literature by numerous groups. However, despite their important advances, we consider that the Achilles’ heel of these studies resides on the limited biomedical expertise, which can be detrimental for their translation to the clinic. Unfortunately, only a few studies transcend the proof-of-principle stage and move toward in vivo drug delivery, which confirms that the field is still driven by novel and interesting synthesis. The reduced understanding of comprehensive biocompatibility and pharmacokinetics data demonstrates this. With the field of drug delivery and MOFs growing, greater collaboration with drug delivery experts and pharma industry will be very welcome. This will clarify what needs a drug-delivery MOF–composite would have to fulfill. Further, we consider the delivery of existing MOF systems to be too reliant on passive targeting via the enhanced permeation and retention (EPR) mechanism. In the light of recent studies about deficiencies of this kind of tumor entry, we believe further characterization of active uptake pathways and studies utilizing antibody-targeting vectors should be expanded on.

Due to the advent of personalized medicine, we anticipate a strong growth in biomolecule–MOF composites for specific gene silencing therapies. We would also expect many of the above “binary” composites—those featuring one guest and one MOF—to be eventually replaced by even more flexible complex composites; for instance, those featuring magnetic targeting capabilities with gene delivery and optical diagnostic functions. On the whole, we consider this field to be highly relevant to modern nanomedicine and we look forward to following its advance in the future.

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Conflict of Interest

The authors declare no conflict of interest.

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