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When metal–organic framework mediated smart drug delivery meets gastrointestinal cancers

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Cancers of the gastrointestinal tract constitute one of the most common cancer types worldwide and a ~58% increase in the global number of cases has been estimated by IARC for the next twenty years. Recent advances in drug delivery technologies have attracted scientific interest for developing and utilizing efficient therapeutic systems. The present review focuses on the use of nanoscale MOFs (Nano-MOFs) as carriers for drug delivery and imaging purposes. In pursuit of significant improvements to current gastrointestinal cancer chemotherapy regimens, systems that allow multiple concomitant therapeutic options (polytherapy) and controlled release are highly desirable. In this sense, MOF-based nanotherapeutics represent a significant step towards achieving this goal. Here, the current state-of-the-art of interdisciplinary research and novel developments into MOF-based gastrointestinal cancer therapy are highlighted and reviewed.

1. Introduction

According to the International Agency for Research on Cancer (IARC), cancer is a leading cause of death worldwide, and is predicted to account for an estimated 16.3 million deaths, by 2040.[1] Survival rates depend on the type of cancer, its stage, diagnoses, and treatment availability. As depicted in Fig. 1B, major cancers of the gastrointestinal (GI) tract represent more than one-quarter of the global cancer incidence (colon 6.1%, stomach 5.7%, liver 4.7%, rectum 3.9%, esophagus 3.2%, and pancreas 2.5%) and more than one-third of all cancer-related deaths (stomach 8.2%, liver 8.2%, colon 5.8%, esophagus 5.3%, pancreas 4.5%, and rectum 3.2%).[2] They are caused by factors arising from lifestyle and age, although a small number of cases occur due to gene inheritance disorders. According to the GLOBOCAN 2018 report, it is expected that the global number of new cases and deaths from GI cancers will increase by 58% and 73% by 2040, respectively.[3] Owing to their extraordinarily high surface area, highly tunable character, adjustable surface chemistry and functionality, and their capacity to accommodate various guest molecules, metal–organic frameworks (MOFs) have become good candidates for biological applications.[4,5] The increasing number of publications over past ten years reflects the huge potential of MOFs as drug delivery and cancer theranostic platforms (Fig. 1A).

Progress in anti-cancer therapy over the past decades has significantly improved disease outcome and mean survival time. Nonetheless, current state-of-the-art therapeutic options still suffer from serious side effects and a lack of efficacy which is dependent on the type of cancer and/or the cancer stage. Consequently, significant efforts have been put into smart strategies for non- or minimally invasive cancer treatment with the aim of achieving overall cancer regression, a reduction of the tumor size prior to surgery, preventing cancer metastasis, minimizing post-treatment cancer recurrence, and ideally achieving long-term disease remission.[6–12] When focusing exclusively on chemotherapy, current interventions do not fully exploit their potential, especially due to a lack of targeted *in situ* therapy which often results in still significant side-effects and a high treatment burden to the patient[13–16] – although improved adjuvant medication now successfully counteracts many of the side-effects, most importantly nausea.[17–19] Consequently, a targeted and side-effect free therapy with maximal mean survival times not only requires the development of significantly more effective therapeutics *per se*, but also smart and directed delivery

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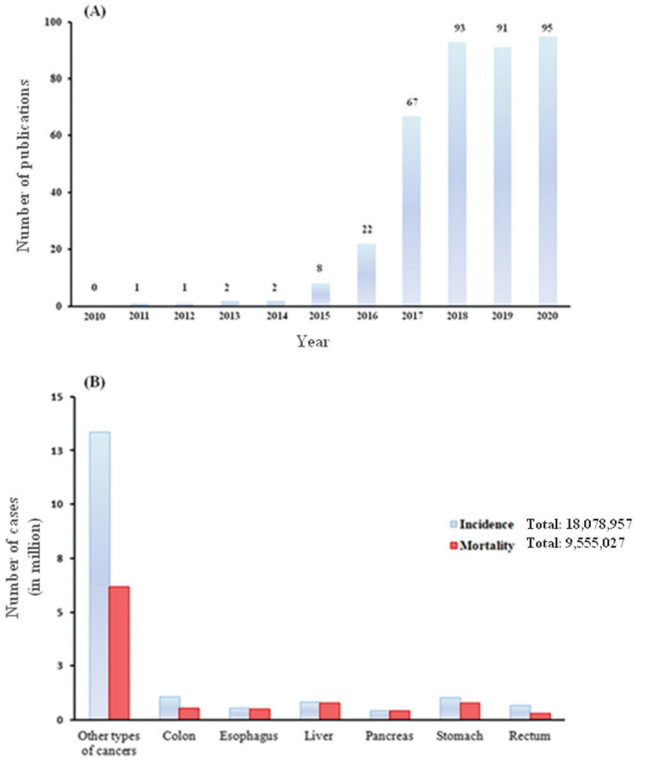

Fig. 1 (A) Number of publications published per year obtained from a simple and limited literature search using the keywords ''metal–organic framework'', ''drug delivery'', and ''cancer therapy'' (data source, Web of Science); (B) contribution of major gastrointestinal cancers to global cancer cases and deaths in 2018 (data source, GLOBOCAN 2018).

systems.[20–24] Promising approaches to achieving the aforementioned goals are nanomaterial-based drug delivery systems (DDSs),[25–29] smart DDSs (SDDSs),[30–32] photodynamic therapy (PDT),[33–36] photothermal therapy (PTT),[37–42] cancer immunotherapy (immuno-oncology),[43,44] and rational polytherapy.[45–48]

In addition, recent improvements in established radiotherapy (RT) methods[49–51] to include a significantly more focused approach have shown great promise for the treatment of particular cancer types.[52–55] The major advantages of nanoparticle-based treatments are the size-tunability of the carrier/therapeutic agent as well as the potential to engineer controlled drug release into the carrier (*i.e.* SDDS), the possibility of selectively targeting particles to aberrant cells in tissues by exploiting the excessive expression of surface molecules in cancer cells, and their easy uptake into cells.

At the present time, nanotechnology has stepped forward by nurturing new methods to advance our knowledge of cancer therapy for tackling the recognized limitations and drawbacks of treatment.[56–71] SDDSs help to regulate the speed and the site at which the encapsulated cargo is released and the degradation rate of the drug, which have led to enhanced efficiency and toxicity, and reduced side effects.[72–74] Nanoscale metal–organic frameworks (Nano-MOFs) as a mean to generate novel DDSs and progressive nanomedicines have attracted much attention.[75–80] As can be seen in Fig. 1A, there has been a dramatic increase in the number of publications dealing with MOFs for drug delivery and cancer therapy during past five years. Nano-MOFs, as emerging porous nanomaterials, have practical advantages of tunable size, shape, porosity, functionality, high loading capacity, and biodegradability which indicate a greater potential as a nano-carrier over other DDSs including liposomes, dendrimers, and micelles.[81–85] Nano-MOFs that are reasonably efficacious in DDSs, SDDSs, PDT, PTT, RT, and polytherapy, could effectively improve the quality of DDSs with regard to drug release, delivery, targeting, and toxicity.[86–90] Greater flexibility and control over Nano-MOFs would enable researchers to better employ stimuli responsive conditions or bind stimuli responsive agents for site-specific drug release and/or drug targeting.[91–101] In contrast to other excellent reviews that discuss the bioapplications of MOFs from a broad perspective, herein, the importance and applicability of Nano-MOFs in the treatment of GI cancers will be highlighted and reviewed.[102–105]

2. General principles of Nano-MOFs in drug delivery systems

2.1. Synthesis

MOFs are architecturally robust crystalline structures constructed by the combination of organic linkers and metal ions/clusters that possess pores and cavities of adjustable sizes and shapes.[106] They have constituted an increasingly important class of materials because of their wide applications in many areas such as gas storage/separation,[107,108] catalysis/photocatalysis,[109–111] and energy conversion/storage.[112,113] By taking advantage of the tailorability of MOFs, a wide range of structures with different topologies are available, which could give more opportunities for obtaining more effective nanocarriers. Pre- or post-synthetic modifications have also broadened the functional group scope of MOFs (linker).[114–122] A survey of the literature shows that the majority of MOF-related studies are focused on obtaining nano-sized crystals, usually of already-known structures, and on the control of size and morphology. When it comes to biological applications, this can be rationalized by considering the fact that nanomaterials can extend the circulation time of drugs, improve their stability, bioavailability, and selective targeting.[123] It is worth mentioning here that prior to any clinical development, it is of high importance to consider the potential toxic effects of Nano-MOFs both *in vitro* and *in vivo*. In this line, the toxicity is usually influenced by the nature of the metal ion.[124] The intrinsic properties of cells also affect the toxicity, mainly through the internalization ability of the cells.[125] Although iron-carboxylate Nano-MOFs have shown negligible toxic effects so far,[126,127] the integration of design synthesis and safety assessment are necessary to mitigate the toxic properties of the MOF.

The most widely used synthetic procedures for obtaining Nano-MOFs are microwave, sonochemical, surfactant-mediated and hydro- or solvothermal methods, forcing the components to form structures with different crystallinity from very simple building blocks.[128–135] Each method can lead to different sizes and morphologies or even topologies.[118,136] Hydro- and solvothermal synthesis are the most common methods used for obtaining nanostructures. The reaction temperature and time

along with the type of solvent are all among the factors that critically affect the nucleation stage, the formation and final morphology of the nanostructures.[126,137] However, by using these methods the size distribution of particles could not be controlled well. Because of the rapid nucleation in microwave heating, microwave-assisted synthesis usually produces particles with smaller sizes. The fast reaction times achieved with this method also offer a narrower size distribution.[138] In addition, utilizing the emulsion method can also reduce the size of the particles to the nanoscale.[139] Modulating acids (monodentate carboxylic acids such as formic acid, acetic acid, trifluoroacetic acid, benzoic acid *etc.*) could also be used to control size and shape evolution of crystals by using different molar ratios.[140–142] In this regard, the pK_a value and concentration of the modulator are important factors that affect the surface area, pore size, defects or acidity.[143–145] In a recent study, Lin and coworkers developed a one-step strategy for the controlled synthesis of diclofenac-loaded MIL-100(Fe).[146] It was demonstrated that the size of drug-loaded MOF particles could be controlled when using diclofenac as a modulating agent during the synthesis. Forgan *et al.* pursued a similar approach to incorporate up to three drugs as modulators in one-pot syntheses of UiO-66. In the protocol proposed by the authors, drugs with a phosphonate functionality (Alendronate) showed a higher affinity for binding to Zr clusters than drugs with carboxylate moieties and resulted in effective loadings, leaving the porous structure for a fourth guest (5-FU) to be loaded. Nevertheless, addition of a classic modulator (dichloroacetic acid) was necessary to the control particle size ($\sim$100 nm) and prevent aggregation.[147] Because of the strong attachment of drugs to metal (Zr) clusters in this method, the drug release profile might be affected.

2.2. Drug loading and release

The incorporation of therapeutic agents into Nano-MOFs is typically achieved either during synthesis (direct synthesis) or *via* post-synthetic modifications. In the first approach, bioactive molecules directly act as part of the framework (BioMOF);[102] thus, the distribution of drug molecules in this method is homogeneous. Furthermore, the release of the biologically active molecules in this method reduces any side effects to normal tissues. This method can also avoid the necessity for large pore sizes and volumes being required to attain high loadings; however, the drug-loaded MOF in this case may not possess high porosity.[148] Moreover, the whole procedure should be monitored to ensure that the bioactive molecule is stable under the synthetic conditions.[149,150] The addition of drug molecules during MOF synthesis has also been reported, exemplifying the versatility of one-pot methods.[151] Since the biomedically relevant agent will replace one of the MOF components (linker), the loading capacity achieved with this technique is limited.[146] In another approach to one-pot methods, the MOF is assembled around the biomolecule during synthesis.[152] This is particularly useful when the pore aperture is smaller than the size of the biomolecule.

In the second method, loading is achieved through impregnation by soaking the Nano-MOF in a solution saturated with the drug. This method requires an activation process to the remove pore-filling solvent, which occupies the nanospaces, prior to drug loading. The activation process is performed at high temperature and low pressure or by replacing the existing solvent with a solvent with a low boiling point (solvent-exchange method). In spite of the simple procedure, the distribution of drug molecules in this method cannot be easily controlled and often results in heterogeneity.[148] A range of interactions have been reported to be appropriate for post-synthetic drug loading. For example, Hu *et al.* employed electrostatic interactions to accommodate the anionic form of ibuprofen in the positively charged porous MOF-74-Fe(III).[153] A similar approach was pursued by Lin and coworkers for loading Mn^{2+} and an anionic form of ibuprofen into ZJU-16.[154] In addition, the ability to form hydrophilic/hydrophobic interactions with the confined drug impacts the loading capacity of the MOF.[155] Covalent attachment has also been reported for the incorporation of drug molecules. Pidko and coworkers successfully confined heparin molecules in the pores of MIL-101(Fe) through the complexation of heparin sulphate groups with iron atoms.[156]

Prodrugs are among examples of systems in which the drug molecules can bind to the host framework either *via* covalent or noncovalent interactions.[157–160] Recently, Yan *et al.* reported a one-pot synthesis method for doxorubicin (DOX) loading on the surface of ZIF-8. In the method developed by the authors, DOX underwent a ring opening reaction with *cis*-aconitic anhydride first to produce the DOX prodrug. Then, DOX@ZIF-8 was further conjugated with a tumor-targeting ligand (folic acid) to achieve target-specific delivery.[161] Successful drug loading requires a close match between the pore aperture and guest diameter to allow uptake. Very recently, Gu and coworkers utilized PCN-333 for the confinement of large enzyme molecules as well as a prodrug (Fig. 2A). In PCN-333 metal–oxo clusters (Al) are connected by large 4,4′,4″-*s*-triazine-2,4,6-triyltribenzoic acid (TATB) ligands, creating a porous structure that contains two mesopores: a large hexacaidecahedral cage and a smaller dodecahedral one. After impregnation with a horseradish peroxidase (HRP) aqueous solution, the authors reported that only large mesoporous cages of PCN-333 (5.5 nm) were accessible. Meanwhile, small mesoporous cages (close to metal nodes) remained empty for the indole-3-acetic acid (IAA) prodrug.[162]

Any nanotherapeutic system used for targeted delivery and controlled release should have the ability to shield the drug under physiological conditions and protect it from premature elimination, assist the drug to display its biological activity in the targeted cell only, and control the drug exposure over time, to avoid burst release.[163] Any factor that changes the structural features (either reversible or irreversible) of the MOF nanocarrier can trigger drug release. Several triggers are available in response to external stimuli, including thermal or pH changes,[164–166] magnetic field,[167] and photo irradiation.[168] As the pH values in cancer cells (pH 5.5–6.0) are known to be more acidic than in blood or normal tissues (pH 7.4), and by considering the fact that coordination bonds in most MOFs are sensitive to external pH, pH-responsive MOFs are the most extensively studied nanocarriers. However, the complexity of

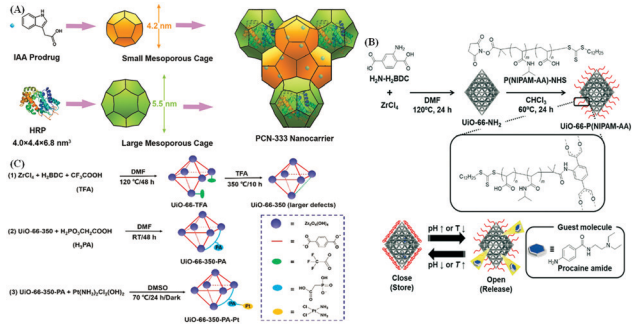

Fig. 2 (A) Simultaneous drug loading in the hierarchical porous structure of PCN-333. Adapted from ref. 162 with permission from the Royal Society of Chemistry. (B) Schematic illustration of dual-stimuli-responsive DDS based on NIPAM-AA-modified UiO-66-NH_2. Reproduced from ref. 171 with permission from the Royal Society of Chemistry. (C) Effective cisplatin loading into a defective UiO-66 through Zr–O–P linkages. Reproduced from ref. 160 with permission from the Royal Society of Chemistry.

the human body, has led to developing multi-responsive MOFs as a new alternative to conventional systems for improving the chemotherapeutic efficiencies.[169,170] For example, a dual-responsive MOF has been developed recently for the delivery of procainamide.[171] The authors integrated pH- and thermal-responsive strategies into a single drug nanocarrier, where UiO-66-NH_2 was coated with a copolymer comprising *N*-isopropylacrylamide (NIPAM) and acrylic acid (AA). In the system developed by the authors, drug release was triggered at pH values of 6.86 or higher, and at pH 4.01 when the temperature was 25 °C, whereas the release was suppressed at pH values of 4.01 or lower when the temperature was 40 °C (Fig. 2B).[171]

Beside the target environment, the release of drugs in a controlled manner will depend on the structural features of both the MOF and the drug. For example, Farha and coworkers utilized a Zr-based MOF (NU-1000) for oral insulin delivery. The acid-stable MOF capsules effectively prevented insulin from degrading against the gastric acid and released it only under conditions simulating the bloodstream (PBS).[172] In fact, Zr–O bonds are susceptible to linker exchange due to the strong affinity of Zr atoms for phosphate groups.[173,174] By considering this, Lin and coworkers used phosphonoacetic acid to create free carboxyl binding sites in defective UiO-66 for anchoring the cisplatin prodrug (Fig. 2C).[160] In addition, it has been reported that DOX loses its ability to form hydrogen bonds with host framework when exposed to acidic media due to the protonation of the carboxyl groups in its structure.[175]

2.3. General principles of Nano-MOFs in drug delivery systems

MOFs are unlocking a new frontier in cancer research. The science of building small nano- or meso-porous materials is changing the way we look at cancer, especially in diagnosis and treatment.[6,62,64,176–178] Nanoscale MOFs give the opportunity to attack cancer at the cellular and genetic levels, which holds the promise to stop cancer and dramatically changes cancer patient care.[131,179]

From a drug delivery prospective, MOFs could be polypharmeceuticals (enabling the delivery of more than one type of drug or bioactive agent simultaneously to the patient), have a higher deliverable drug capacity (the amount of drug that can be taken out of the system and delivered), and be modified to be bio-adaptive, biocompatible, bioavailable and biodegradable.[158,180–184] The more famous or promising MOF platforms that can be used in drug delivery systems and biomedical applications are shown in Fig. 3. The cargo could be entrapped in MOF pores, bonded covalently to the linker, adsorbed electrostatically (or by other weaker interactions into the pores or on the surface), or coordinated to the open metal sites.[76,185–188] In spite of the higher bioavailability in organic systems, they have the drawbacks of low drug capacity and stability.[189] Some other benefits of MOFs are (1) the ability to control the pharmacokinetics,[179,190,191] (2) matrix engineering,[192,193] and (3) possible trackability or monitoring by medical imaging.[194–197] The size of the MOF could be controlled to be under 500 nm and over 10 nm to avoid removal by mononuclear phagocyte systems and large enough to avoid rapid renal filtration.[198–201] MOFs could be designed to be stickier to the drug by incorporating functionalities.[202–205] For most drugs to be therapeutically active, they must go inside the cells. Modified MOFs carrying drug payloads can be used to facilitate the drug delivery. These amazing materials could be customized for targeted drug delivery with a large variety of ingredients including DNA, antibodies, proteins,[206] PEG, and other large and small molecules.[116,207–216] Reports indicate that

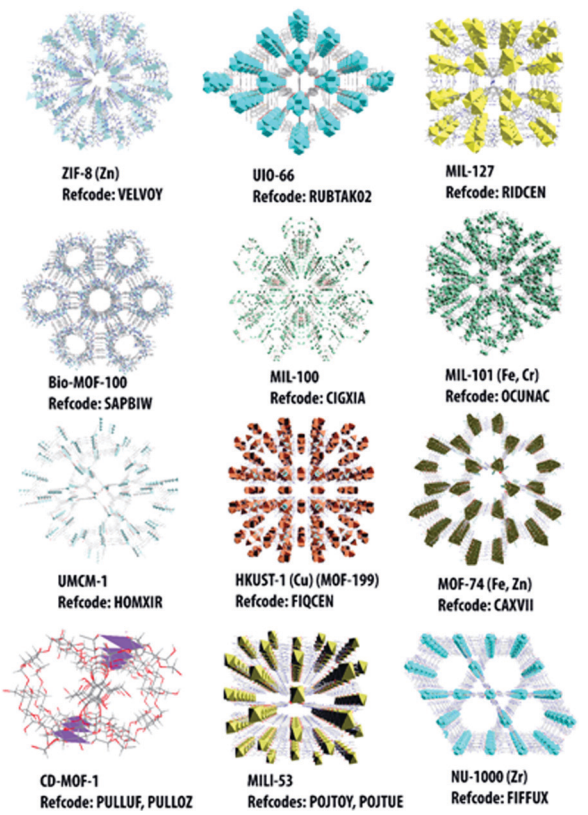

Fig. 3 Examples of common MOF platforms used in drug delivery systems and biomedical applications.

after modification, MOFs bind to the over expressed receptors on the surface of cancer cells initiating the internalization process. In this regard, PEGylated MOFs or ones equipped with gate-closing and -opening agents would also influence the pharmacokinetics of the loaded drug, the hydrophobicity, and cellular internalization.[170,217–220] Hence, MOF linkers could be modified to tune the pores, surface charge, and drug interaction along with the amount of loading and the release mechanism. One possible mechanism could be clathrin-mediated endocytosis in which, after internalization, the clathrin protein may form a cage around the developing endocytic vesicle that is then cleaved from the cell membrane. The newly formed vesicles carrying the MOF travel further inside the cell where they might be captured and fused with an early endosome. Inside the acidic endosomal conditions, the MOF could release the therapeutic cargo which induces the controlled death of a cancer cell.[221–225] This revolutionary material could enable scientists to design a unique treatment for each cancer, which is surely evolving the biomedical application and moving research from the bench to the bedside.

2.4. Nano-MOFs in cellular and animal models

In medicinal research studies, it is important to assess the cytotoxicity of the nanodrugs intended for pharmaceutical use in cancer treatment. To ensure the applicability of MOFs in treatment, it is important that the performance of the nano-drug be investigated by cellular models, for example, the cell viability assay is a simple snapshot for determining the IC_{50}. To develop drugs to prevent or target cancer cells and metastases, reliable preclinical animal models can be a solution. The overall goal is to develop valid and reliable preclinical mouse models of human cancer, which might be used as ideal models to test new therapeutic agents. In this regard, histology and genetic analysis allow the validation of the introduced model. MOFs have shown great potential in drug delivery systems.[90,97,116,126,188,194,208,216,218,226–230] A list of nano MOFs that have been used in drug delivery and cancer treatment both *in vitro* and *in vivo* are tabulated in Tables 1 and 2. Customizing MOFs by chosen functionalities could avoid recognition by a host's defense mechanism and interact with a specific stimulus, a receptor, a protein *etc.*, to treat the cancer cells. The stimulus could be an external source like different light sources, a magnet or a sonic wave, *etc.*, or be internal like pH, temperature, EPR effect, receptors, *etc.*[231–233]

3. Nano-MOFs mediated smart drug delivery in gastrointestinal cancer therapy

The diagnoses of these cancers are difficult and the outcome of treatment is totally dependent on the stage of the cancer and therapy.[234] Minimally invasive surgeries may be needed after/before chemotherapy. Dose-escalated therapies for more effective medication against drug-resistant cancers increases the impact on bio-responses, but bio-toxicity and treatment side effects would also increase much further above normal.[235–237] To treat cancers resistant to currently available chemotherapy regimes, targeted therapy drugs could open a new path as well as increasing the drug efficiency and reducing the side effects.

Recently, Nano-MOFs including medi-MOF-1,[238] UiO-66,[239–242] MIL-100,[114,243,244] ZIF-8,[119,120,245–250] MIL-101,[157,251] DBC-UiO,[252] TBC-Hf,[253] and Fe-TBP[137] *etc.* have been used to treat pancreatic cancer, liver cancer, and colorectal cancer (Tables 1 and 2). In most cases, cells may be eradicated if exposed to the targeted therapies, but mutations of the cancer cells make them invulnerable even to the targeted drugs.[254–256] PDT, radio-dynamic therapy (RDT) or PTT alone and in combination with targeted therapeutics could be a robust and highly targeted therapeutic modality to treat GI cancers.[257–263] As shown in Tables 1 and 2, Nano-MOFs could be modified to be photo/radiosensitive, to interact with specific receptors or to control pharmacokinetics, which will lead to aggregating to a greater degree in the cancerous cells. The goal is to make engineered and robust treatments available for everyone to become a solid therapy. In this regard, the targeted delivery/co-delivery of immunotherapy drugs could be of interest. PDT, radiotherapy, sonodynamic therapy, and photothermal therapy could be immunogenic adjuvant therapies, which can be used in combination with immunotherapeutic agents.[264,265] MOFs in targeted therapy are new and full of potential; hence, it is necessary to turn this potential into new applications. Given their drug-related capabilities, their use in GI cancer can create new horizons in treatment.

3.1. Pancreatic cancer

Despite the advances in pancreatic cancer treatment, the difficulty to fully treat and rehabilitate patients still stands.[96,266–271] Recently, Zhu and coworkers designed a novel bio-MOF, medi-MOF-1, with the aim of investigating its applicability as a nano-carrier for biomedical applications. In order to avoid potential side-effects, which vary in strength with the toxicity of the pharmaceutical constituents, medi-MOF-1 was designed and synthesized by utilizing less toxic substances such as Zn^{2+} and the bio-active curcumin. Curcumin's bio-activity has been well documented over the past few years and ranges from steroid behavior analogous to prednisolone to antioxidative and cell signaling modulation.[272–278] Medi-MOF-1 achieved the objectives of superior porosity and greater surface area in comparison with other bio-MOFs, and it could also act as a medicinal carrier to treat unsolved clinical dilemmas such as pancreatic cancer. In this regard, the biodegradation of medi-MOF-1 would make it a perfect candidate to co-deliver curcumin and other anticancer drugs, which could give synergetic anticancer effects for more effective cancer treatment. The cell growth proliferation effects of medi-MOF-1 were compared with Zn^{2+} and curcumin on the BxPC-3 cell line, and were found to be on a par with curcumin.[238]

Maksimenko and coworkers recently proposed another approach with the iron-based nano MIL-100 in which high drug loads were achieved by virtue of drug interactions with open metal sites.[282–286] Most importantly, the crystallinity of

Table 1 A list of MOFs applied in smart drug delivery and employed in cellular models

MOF type	Hydrodynamic size and/or Zeta value of drug loaded MOF	Cell line	Drug	Targeting agent	Stimuli	Ref.
Silica coated MIL-101	—	HT-29	Cisplatin prodrug	Cyclo(Arg-Gly-Asp-D-Phe-Lys)	pH	157
UiO-66	—	MCF-7	Dichloroacetate	Folic acid, biotin and heparin	pH	239
ZIF-90	104.7 ± 6.3 nm, −2.1 ± 1.0 mV	MDA-MB-231 TNBC	Doxorubicin	Y1 receptor ligand	ATP, pH	279
UiO-66	∼300 nm, 6.61 ± 0.106 mV	MDA-MB-231 TNBC	Doxorubicin	Py−PGA-PEG-F3	pH	241
UiO-66	85.5 ± 9.5 nm	HepG2	Iodine-attached Zn(II) porphyrinic building block	—	Light	240
ZIF-8	106.5 nm, 26 mV	HepG2 cells	Zinc phthalocyanine	—	pH	120
DUT-32	—	HeLa cells and PC-3 cells	Doxorubicin	—	pH	280
ZIF-8	>200 nm, −30.2 mV	PC-3 cells	Doxorubicin	Hyaluronic acid	pH	119
ZIF-8	—	HeLa cells	5-Fluorouracil and upconversion nanoparticles	Folic acid (FA)	pH	245
MIL-101	—	Hep-2 cells	Hexamolybdenum cluster	—	Light	251
Adeninate-based MOF	—	MG63 and U2OS cells	5-Fluorouracil	—	pH	281

Table 2 A list of Nano-MOFs applied in drug delivery and cancer treatment in animal models

MOF type	Hydrodynamic size and/or Zeta value of drug loaded MOF	Cell line	Model	Drug	Targeting agent	Ref.
ZIF-8	243 nm, −29.6 mV	CT26	*In vitro* & *in vivo* (Balb/c mice)	Glucose oxidase, tirapazamine	Erythrocyte	246
UiO-66@PAN	100 nm, 1 mV	CT26 and HCT116	*In vitro* & *in vivo* (Balb/c mice)	Polyaniline	—	242
DBC-UiO	128.5 nm, −10.2 mV	CT26 and HT29	*In vitro* & *in vivo* (Athymic male nude mice and Balb/c male mice)	5,15-Di(*p*-benzoato)-chlorin (H_2DBC)	—	252
IRMOF-3	371.7 ± 8.80 nm, −10.9 ± 0.50 mV	TNBC cells	*In vitro* & *in vivo* (Balb/c mice)	Curcumin	Folic acid	115
ZIF-8	> ∼200 nm, ∼16 mV	4T1, MCF-7, and HepG2	*In vitro* & *in vivo* (SD rats, ICR and Balb/c mice)	5-Fluorouracil	—	247
ZIF-90	104.7 ± 6.3 nm, −2.1 ± 1.0 mV	MDA-MB-231 TNBC	*In vivo* (Balb/c mice)	Doxorubicin	Y1 receptor ligand	279
UiO-66	∼300 nm, 6.61 ± 0.106 mV	MDA-MB-231 TNBC	*In vitro* & *in vivo* (Balb/c mice)	Doxorubicin	Py−PGA-PEG-F3	241
ZIF-8	—	HepG-2, A549 and MCF-7	*In vitro* & *in vivo* (Balb/c mice)	Doxorubicin	Lactobionic acid	249
Gadolinium-porphyrin MOF	19.58 mV	HepG2	*In vitro* & *in vivo* (Zebra fish)	Porphyrin	Folic acid	288
ZIF-8	116.6 ± 2.7 nm, 14.4 mV	A549	*In vitro* & *in vivo* (Kunming mice)	Cytolytic peptide melittin	—	248
ZIF-8	∼200 nm, −18.5 mV	B16F10 cells	*In vitro* & *in vivo* (Mice)	Catalase and doxorubicin	Murine melanoma cell membrane	250

MIL-100 (Fe) remained intact after drug loading. In pancreatic cancer, gemcitabine/abraxane and FOLFIRINOX are two standard treatments available. Gemcitabine (Gem) is an antimetabolite that influences cell cycle and dividing, but has side effects like peripheral neuropathy, flu-like symptoms, fatigue, *etc.* Besides, Gem is unstable, has a short half-life, and for activation needs deoxycytidine kinase (dCK) and nucleoside transporters (NTs). The mono-phosphorylated form of Gem (Gem-MP) could circumvent this issue, but it is still usable. The best way is to protect Gem-MP from decaying by smart delivery to the cancer cells. For this purpose, the biodegradability of MIL-100 (Fe) in a phosphate medium was employed as a trigger for targeted Gem-MP cargo release which was nine times more efficient in cultured pancreatic PANC-1 cells compared with the free drug.[244]

Among Fe-based MOFs, MIL-100 (Fe) is currently considered as one of the most promising Nano-MOFs for directed drug delivery because of its low toxicity, water stability, high surface area, structure malleability, and biodegradability in phosphate-containing media.[243,282–287]

Douhal and coworkers used the ship-in-a-bottle technique to prepare drug-loaded nano-carriers. Nano MIL-100 (Fe) was loaded with topotecan *via* a wet impregnation technique. Topotecan degradation occurs under conditions such as irradiation or in oxidative, basic or aqueous media. MIL-100 (Fe) effectively prevents the topotecan monomers from aggregating, prevents degradation due to environmental factors and prevents burst release. Furthermore, human pancreatic cancer cells (PANC-1) were largely insensitive to high doses of the free drug, whereas

nano-encapsulated topotecan was shown to exhibit significant antitumor activity and effectively attenuated cellular proliferation.[114]

Very recently, Lin and coworkers designed two CpG-loaded Nano-MOF carriers with a UiO-like structure, in which Hf–oxo clusters were connected to each other through $[Ir(bpy)_2(ppy)]^+$ (bpy = 2,2′-bipyridine, ppy = 2-phenylpyridine) derived dicarboxylate (DBB-Ir) bridging ligands. Fluorination of the DBB ligands increased the electrostatic interactions between cationic MOF and anionic CpGs. The antitumor efficacy of this therapeutic system was demonstrated in MC38 and Panc02 tumor models. The system was activated by X-ray irradiation, generated hydroxyl radicals from the Hf_{12} secondary building units (SBUs) and singlet oxygens from the Ir-based ligands and reinvigorated the adaptive immune system for tumor regression (Fig. 4).[289]

3.2. Liver cancer

PDT was established to limit drug consignment to specific targets within tissues and organs.[290–293] Targeting is triggered by an energy-specific light stimulus that provokes a strong reaction from photosensitizers (PS) to generate reactive oxygen species (ROSs).[292,294] Recently, Chen *et al.* introduced a new pH-responsive targeting system that utilizes a biocompatible zeolitic imidazolate framework (ZIF-8) as a nano-capsule to encase a zinc phthalocyanine (ZnPc). Complexes containing diamagnetic metals enhance intersystem crossing, having higher efficacy in ROS generation.[295] ZnPc with diamagnetic zinc would provide a propitious environment to efficiently photo-generate high levels of cytotoxic singlet oxygen atoms needed for highly efficient PDT, for which minor dark cytotoxicity was also reported. Whereas the cytotoxicity of ZIF-8 *per se* was shown to be low in the human liver carcinoma cell line HepG2, under irradiation, the potency of the nano-capsules was apparent

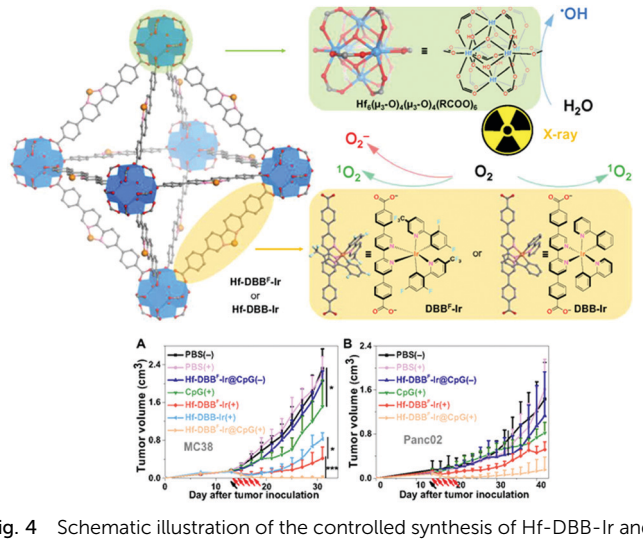

Fig. 4 Schematic illustration of the controlled synthesis of Hf-DBB-Ir and Hf-DBBF-Ir Nano-MOFs based on Hf–oxo clusters and DBBF–Ir or DBB–Ir ligands. Growth curves of (A) MC38 and (B) Panc02 tumor-bearing mice treated with CpG-loaded Nano-MOFs. Adapted from ref. 289 with permission from the American Association for the Advancement of Science.

as demonstrated by low IC_{50} values.[120] Very recently, Zhu *et al.* studied the antitumor activity of a dihydroartemisinin-loaded ZIF-8 against HepG2 cells using RNA-seq analysis. It was observed that 7090 genes are involved in the induction of cell apoptosis through a p53-mediated mitochondrial pathway and the suppression of glycolysis by inhibiting the PI3K/AKT pathway and downregulating HIF-1α expression.[296]

Recent research has shown that insertion of doped ligands into known nano-crystalline MOFs[297,298] is a suitable strategy for developing functionalized MOFs for targeted therapy. For instance, Dong and coworkers employed porphyrin ligand doping ($ZnDTPP-I_2$) to synthesize phototoxic UiO-66 and explored its application in PDT. The incorporated $ZnDTPP-I_2$ within UiO-66 was successfully used as an efficient ROS generator to treat liver cancer cells (HepG2 cells) by PDT.[240]

Despite many complications in existing chemotherapy modalities that could slow down cancer advancement, chemotherapy still plays an indispensable role in cancer treatment. A multidrug dosing regimen may extensively increase the efficiency of the treatment by having a synergistic action on drug-resistant malignancies.[299–303] Thus, the co-delivery of two or more drugs simultaneously as well as targeting and monitoring could be a more effective approach in treatment. In this regard, nano composites could lead to new approaches in the field. For instance, Yin and coworkers have investigated the *in vitro* and *in vivo* cytotoxicity of a well-tailored DDS employing multidrug chemotherapy (camptothecin, CPT). Another aspect of this DDS was the enhancement of PTT treatment features obtained by merging with a PTT agent (polydopamine) to trigger drug release locally to the targeted cells with the benefit of including polydopamine being hydrophobically modified. ZIF-8, an established Nano-MOF, was used as a drug carrier. For tracking and monitoring purposes, encapsulated $CoFe_2O_4$ nanoparticles were used as an imaging probe for T_2-weighted imaging. The anticancer potency was analyzed against a HepG2 cell line. In fact, DOX and CPT co-delivery was carefully administered in a stepwise manner by local impetus comprising pH or NIR stimulants. *In vitro* results indicated that the designed DDS has superior biocompatibility and less bio-toxicity towards non-malignant tissues. It was apparent from the outcome of the *in vivo* studies that tumor cells substantially lose their growth momentum after administration of the nano-drug; in other words, it has a pronounced beneficial effect in treating drug-resistant HepG2 cancer cells.[304]

3.3. Colorectal cancer

Non-invasive techniques such as chemotherapy may be considered more appropriate and more convenient than surgery or may act as a supplemental therapy alongside surgery for cancer treatment.[305–307] Cancers of the colon and rectum are the fourth most common cancer diagnosed and the second major cause of cancer death in the world (Fig. 1).[308,309] The level of survival in colorectal cancer is directly related to the quality of life. In developed countries, 5 year survival may reach 60%, but in poorer ones it is 30% or lower.[310] Early diagnoses and treatment of colorectal cancer favors its treatment, but stage IV is lethal. For life

extension, new chemotherapy drugs are needed to increase the survival rate, whether for detection, monitoring, tracking or cure. For example, it has been recently reported that embedding cobalt phthalocyanine nanoparticles inside MIL-101(Cr) pores greatly enhances the MOF performance for detecting CT26 cells.[311]

Targeted chemotherapy of colorectal cancer could be a blossoming procedure to eradicate tumors or cause their regression.[312–314] Recently, Lin and coworkers have introduced an innovative nano-drug-delivery platform employing an NH_2-modified Nano-MOF (MIL-101, Fe), Pt(IV) prodrug (ethoxysuccinato-cisplatin, ESCP), an imaging contrast agent (Br-BODIPY) and silyl bonded c(RGDfK) to treat colorectal cancer cells (HT-29 cell line). BODIPY and ESCP were grafted covalently to biologically increase the stability of the Nano-MOF. To overcome MIL-101(Fe) degradation and unfortunate burst release, it was coated with a thin film of silica which was developed one step further by introducing c(RGDfK) to target overexpressed $\alpha_v\beta_3$ integrin in cancerous cells. According to previous reports, ESCP was endogenously bio-reduced to Platinol by biomolecules like glutathione.[315,316] *In vitro* studies demonstrated IC_{50} = 21 μM against HT-29 cells, which was comparable to cisplatin efficiency.[157]

An immune system which is revitalized or modified efficiently in biological therapy (immunotherapy) could be employed for developing innovative therapeutic methods.[317] PDT has a pre-eminent advantage in cancer immunotherapy that could activate T-cells (T lymphocytes) against malignancies, especially, triggering an increase in response rate towards colorectal cancer therapy.[318–320] Metastatic tumors are devastating for patients; hence, immunotherapy is a great tool for treating this kind of cancer for good. A research report of Lin and coworkers was basically aimed at ascertaining the PDT efficiency of chlorine-based porphyrinic Nano-MOF (DBC-UiO) against CT26 and HT29 colon cancer cells. The *in vitro* and *in vivo* studies indicated that the photophysical attributes of DBC-UiO were of superior quality and functionality in the photo-generation of singlet oxygen ($^1O_2$) which could elevate the potency of the PDT procedure and devastate CT26 and HT29 cells through normal and immunogenic apoptosis.[252]

Recently, Xie and coworkers have employed a polyaniline (PAN) encased Nano-MOF, UiO-66@PAN, as a PTT agent to treat colon cancer cells (CT26) under local NIR laser irradiation (Fig. 5). The relative merits of UiO-66@PAN consisted of suitable dimensions and superior water-dispersible features. PAN is a photo-thermal converter (PTC) with a conversion efficiency of 21.6%, which is sufficient for cancer PTT applications, and in addition, by amalgamating PAN with UiO-66, it would gain the characteristic features of robustness, water stability and dispersibility. *In vitro* and *in vivo* investigations on the functional effectiveness of UiO-66@PAN indicated a high photo-thermal conversion efficiency in the PTT procedure, ameliorated colon cancer or malignancies.[242]

Coupling of an immunotherapy agent and PDT is another innovative approach for treatment. Lin and coworkers employed an immunotherapeutic encased in a new porous chlorin-based PS (a porphyrinic Nano-MOF, TBC-Hf), which inhibited the expression of indoleamine 2,3-dioxygenase (IDO) and generated a systemic immunity against malignant cells resulting in higher tumor-infiltrating properties of T lymphocytes. The designed targeted therapy has provided the first evidence that the encapsulated IDO inhibitor (IDOi) in nano-PDT-enabled-MOFs may appreciably boost immuno-oncology employing checkpoint blockade and have the advantage of treating drug resistant cancer cells.[253] Thereafter, in pursuit of an efficient treatment of colorectal cancer, a novel nano-PS employing a porphyrinic Nano-MOF, Fe-TBP, was used

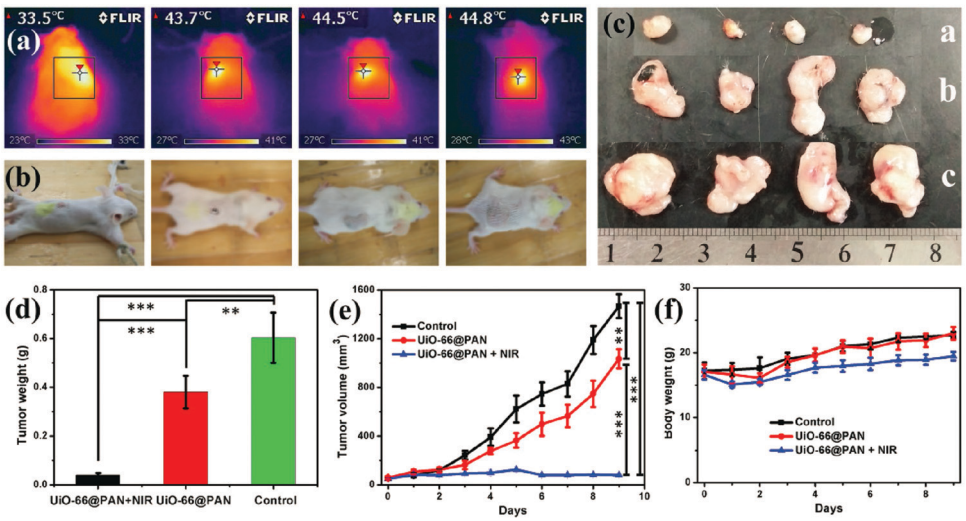

Fig. 5 *In vivo* PTT study of UiO-66@PAN. (a) Whole-body photothermal images of mice after intratumoral injection of UiO-66@PAN solution (0.1 mL, 1 mg mL^{-1}) and laser exposure (808 nm, 0.7 W cm^{-2}). (b) The mice before treatment, UiO-66@PAN combined with NIR laser treatment, UiO-66@PAN only and without treatment. (c) Representative photos of tumor dissection: (a) combination of UiO-66@PAN and NIR laser; (b) UiO-66@PAN only; and (c) without treatment. (d) Quantitative analysis of tumor weight of each group. (e) Tumor growth rates of groups after different treatments. (f) Changes in body weight of mice with CT26 tumors upon various treatments. Reproduced from ref. 242 with permission from Wiley-VCH.

to strengthen the PDT response rates by lessening hypoxia issues and increasing T-cell infiltration into malignant cells. Furthermore, a checkpoint inhibitor (anti-programmed death-ligand 1, α-PD-L1) was coupled with Fe-TBP to boost the treatment effects. *In vivo* studies indicated that abscopal effects lead to cell regression of the colorectal cancer by more than 90%.[137]

Subsequently, Lin and coworkers demonstrated the combination or integration of a porphyrinic Nano-MOF (DBP-Hf) and radiodynamic therapy (RDT) to treat deep-rooted tumors. One of the disadvantages of PDT therapy is the superficial light infiltration into malignant tissues (about 1 cm). To circumvent the problem of deep-rooted tumors, ionizing radiation (low doses of X-ray radiation) was employed to effectively generate $^1O_2$ in the tumor cells. Similarly to the previous case, a small-scale IDOi encased in TBP-Hf (IDOi⊂DBP-Hf) was utilized to prevail over checkpoint blockade and work synergistically with RDT to eradicate tumor cells. *In vitro* and *in vivo* studies on breast and colorectal cancer revealed an increase in the T cell penetration that led to a more efficient treatment of both local and off-target (distal) cancer cells (immune-mediated abscopal effects).[321]

4. Conclusions and perspectives

Cancer is not a single disease but a complex set of diseases that displays some common characteristics. MOFs alone may accomplish less than expected in cancer treatment, but by using advantages such as the flexibility of design, it is possible to prepare modified systems with different agents for specific cancer treatments. These functionalities may include targeting agents, gates, enzymes, proteins, synthetic or natural polymers, metallic or metal oxide nanoparticles, and immunotherapeutic agents. It is an innovative idea to use these assemblies to transfer drugs for possible new therapies to avoid the side effects of standard chemotherapy regimens. To circumvent many issues concerning platform design, it is of great interest to connect different cancer researches and experiences made so far, which could dramatically improve cancer treatment. New treatments are needed to decrease the mortality and morbidity rates. Survival rates could be increased through using customizedt carriers like modified MOFs that could specifically deliver drugs to the cancer cells. Literature reports also showed that MOFs are customizable for specific purposes including detection visualizing, tracking, killing and monitoring of cancers or metastases. The ultimate goal in therapy is to find a procedure to do all these operations, simultaneously. MOFs could accomplish this if different research directions merged and were directed towards concepts that have a clinical focus. To reach this goal, groups of chemists, physicists, biochemists, physiologists, oncologists, surgeons, pathologists, radiation oncologists *etc.* are needed to increase the life expectancy of a patient. MOF-based drug delivery provides a novel and targeted approach for the future of cancer therapy. Optimizing cancer treatment is focused on understanding its biology to determine the best approach, which is a multidisciplinary task. Using different tools to design new smart drugs could lead to individualized treatments and improving outcomes for patients. The emergence of MOFs has brought additional tools to the current treatment landscape and novel combinations with PDT, RT, PTT, sonodynamic therapy, and immunotherapy are on the horizon. MOFs are a promising and thriving field of research, but research is still in the early stages and requires more solid information for entering into clinical trials.

Conflicts of interest

There are no conflicts to declare.

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