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Nanoparticles of Metal-Organic Frameworks: On the Road to In Vivo Efficacy in Biomedicine

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In the past few years, numerous studies have demonstrated the great potential of nano particles of metal-organic frameworks (nanoMOFs) at the preclinical level for biomedical applications. Many of them were reported very recently based on their bioactive composition, anticancer application, or from a general drug delivery/theranostic perspective. In this review, the authors aim at providing a global view of the studies that evaluated MOFs' biomedical applications at the preclinical stage, when in vivo tests are described either for pharmacological applications or for toxicity evaluation. The authors first describe the current surface engineering approaches that are crucial to understand the in vivo behavior of the nanoMOFs. Finally, after a detailed and comprehensive analysis of the in vivo studies reported with MOFs so far, and considering the general evolution of the drug delivery science, the authors suggest new directions for future research in the use of nanoMOFs for biomedical applications.

1. Introduction

Metal-organic frameworks (MOFs) or porous coordination polymers were first reported in the late 1980s[1] and this domain started to expand continuously since the end of the 1990s.[2–4] The structure and composition of these crystalline hybrid solids can easily be tuned through the almost infinite possible combination of metal inorganic subunits (clusters, chains or layers of transition metals, 3p, lanthanides, etc.) and/or constitutive organic ligands (carboxylates, phosphonates, azolates, etc.) leading to thousands of MOFs with unique features[5–8] (and references therein). MOFs exhibit therefore highly porous structures that span over a large range of pore sizes (micro- or mesopores) or pore shapes (cages, channels, etc.), and possess either rigid or flexible frameworks. One can also further tune their polar/apolar character through the use of polar or apolar organic functionalities, often carried out through direct synthesis or postsynthesis modification on the ligand or grafted on the metal sites, which strongly impacts the sorption properties of the solids.[9] As a consequence, a large number of potential applications of MOFs have been proposed to date such as gas adsorption/storage or separation,[10–12] catalysis,[13,14] energy,[15–18] optical properties,[19] sensing,[20–22] and biomedicine,[23,24] among others.[8]

Downsizing materials to the nanoscale is also a suitable method to tackle down new applications compared to the ones of their bulk analogues,[25–33] such as in biomedicine, whereas applications of nanoparticles of metal-organic frameworks (nanoMOFs) is a rapidly developing topic of interest. Nanomaterials, due to their smaller particle size, can indeed improve the drug delivery performances for the treatment of several diseases.[24,34] Moreover, the high and regular porosity and the unique combination of well-dispersed metal sites and organic groups within the framework of nanoMOFs, combined with the low toxicity of polycarboxylic acids and selected metals (Fe, Zn, Ca, etc.), make these porous solids appealing nanocarriers for the controlled release of drugs.[9] Considering the drug delivery requirements, the best nanovectors are the ones that fulfill the following conditions[35–40]: 1) high drug entrapment (payload and efficiency), 2) controlled drug release without "burst" effect, 3) ability to target diseased cells and tissues in a highly selective manner, 4) lack of toxicity through a progressive degradation and the absence of accumulation in the body, 5) an easy engineering of the outer surface of the nanoparticles (NPs) for an improved in vivo stability and/or biodistribution (the distribution and accumulation in the different organs and tissues), and 6) possibility of NPs to be detected by imaging techniques.

In the past few years, numerous studies have demonstrated the great potential of nanoMOFs at the preclinical level for biomedical applications. Many of them were reported very recently

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based on their bioactive composition,[41] anticancer application,[7,42–49] or from a general drug delivery/theranostic perspective.[50] In this review, we aim at providing a global view of the studies that evaluated MOFs' biomedical applications at the preclinical stage, when in vivo tests are described either for pharmacological applications or for toxicity evaluation (**Table 1**). Of note, most of the nanoMOFs reaching a preclinical in vivo evaluation are those based on Fe carboxylates or Zn azolates. We first describe the current surface engineering approaches that are crucial to understand the in vivo behavior of the nanoMOFs. Finally, after a detailed and comprehensive analysis of the in vivo studies reported with MOFs so far, and considering the general evolution of the drug delivery science, we suggest new directions for future research in the use of nanoMOFs for biomedical applications.

2. Surface Modifications of NanoMOFs

So far, the great number of studies describing the potential of MOFs to be used for pharmaceutical applications contrasts with the reduced number of in vivo pharmacological efficacy studies performed to date.[51] There are several reasons why most of the physicochemical and in vitro studies dealing with MOFs in the biomedical field have not been systematically evaluated in vivo yet. Some are related to MOFs' design development itself, such as colloidal stability issues and/or lack of organ or tissue-targeting properties.[51] These challenges are already being overcome by several surface coating strategies. Similarly to what has already been demonstrated for other nanocarriers, it is possible to tune pharmacokinetics and biodistribution by incorporating motifs onto the outer surface of the nanoMOFs, and the aim of this section is to give an overview of the latest advances in this field (the most recent works are summarized in Table 1).

First, it must be noted that for isotonicity, intravenous (i.v.) administration of nanomaterials needs dispersion in an isotonic solution such as 0.9% saline or 5% glucose. Many nanoMOFs, particularly once dried, cannot be dispersed yet in these media and/or are not stable enough and tend rapidly to form aggregates, making i.v. administration not possible due to risk of embolization. In some cases, nanoMOFs could nevertheless be administered at (low) doses at which particle aggregation does not occur. For instance, Baati et al. did not observe any stability problems for low doses of iron(III) carboxylates MIL-100(Fe), MIL-88A(Fe), and MIL-88B_4CH_3(Fe) (MIL stands for Materials of Institut Lavoisier) when dispersed in glucose solution.[52] But colloidal stability of nanoMOFs still remains a major issue that makes difficult in vivo administration.[53] Selective functionalization of the external surface of nanoMOFs is thus required in view of their biomedical applications.

Apart from the colloidal stability, one major objective of the surface engineering of nanoMOFs is to also allow blood long circulating properties (i.e., "stealthness") of the NPs (**Figure 1**). Indeed, surface functionalization of NPs with hydrophilic polymers reduces opsonization, a process that involves the interaction between some proteins from the blood and the NPs, resulting in their recognition and elimination by the macrophages to the liver, spleen, and the bone marrow (i.e., the so-called reticulo-endothelial system).[51] Surface modification strategies of NPs and liposomes have indeed been proposed several years ago and polyethylene glycol (PEG) is without any doubt the best candidate. The PEGylation of polymeric NPs was first proposed in 1994 by Gref and co-workers[54] and a great number of studies dealing with PEGylation of other types of NPs have been carried out since that time.[55,56] Nevertheless, to date, Doxil represents the only FDA-approved PEGylated

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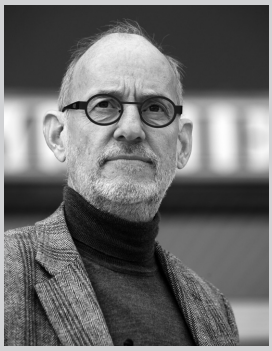

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Table 1. Recent advances on nanoMOFs' in vivo studies.

MOF	Type of study	Drug	Animal model	Route	Ref.
MIL-88A MIL-88Bt	Toxicity	–	Rat	Intravenous	[24]
MIL-100(Fe) MIL-88A(Fe) MIL-88B_4CH3(Fe)	Toxicity Pharmacokinetic Biodistribution	–	Rat	Intravenous	[52]
Cu-BTC	Anti-inflammatory effect	5-FU	Carrageenan test–induced peritonitis in mouse	Oral	[96]
GdIII-pDBI	Toxicology parameters	Doxorubicin	Mice	Intravenous	[106]
DPB-UiO	Photodynamic therapy	–	Xenograft subcutaneous tumor model in mice	Intratumoral	[48]
ZIF-8	Antitumoral Theranostic	Doxorubicin Fe_2O_3	Xenograft subcutaneous tumor model in mice	Intravenous	[132]
9 different MOFs	Toxicity	–	Zebrafish embryo	Exposition to nanoMOF solution	[104]
MIL-101	Antitumoral	Doxorubicin	Xenograft subcutaneous tumor model in mice	Subcutaneous near the tumor site	[69]
CaZol	Antitumoral	Zoledronate	Xenograft subcutaneous tumor model in mice	Intravenous	[68]
MIL-100(Fe)	Pharmacokinetic Biodistribution	Busulfan	Rat	Intravenous	[124]
CD-MOF-1	Biodistribution	Ibuprofen	Mice	Oral	[128]
meso-MOF	Antitumoral	Doxorubicin	Xenograft subcutaneous tumor model in mice	Intratumoral	[133]
ZIF-8	Antitumoral	Doxorubicin Verapamil	Xenograft subcutaneous tumor model in mice	Intratumoral	[127]
ZIF-8	Antitumoral	Camptothecin Doxorubicin Photosensitizer: CoFe2O4 nanoparticles	Xenograft subcutaneous tumor model in mice	Intravenous	[129]
MIL-100(Fe)	Antitumoral	Photosensitizer: indocyanine green	Xenograft subcutaneous tumor model in mice	Intravenous	[66]
MIL-100(Fe)	Antitumoral	Doxorubicin	Mice	Intravenous	[130]
UiO-66(Zr)	Antitumoral	Doxorubicin	Xenograft subcutaneous tumor model in mice	Intravenous	[59]
MIL-101(Fe)	Antitumoral	Unmethylated cytosine–phosphate–guanine oligonucleotides	Xenograft subcutaneous tumor model in mice	Intravenous and intratumoral	[131]
MIL-100(Fe)	Antitumoral	Gemcitabine-monophosphate	Lung metastasis model	Intravenous	[125]
ZIF-8	Cytokine production	CpG (oligodeoxynucleotides)	Mice	Intravenous	[134]
ZIF-8	Antitumoral	Doxorubicin	Xenograft subcutaneous tumor model in mice	Intravenous	[135]
ZIF-8	Antitumoral	3-Methyladenine (autophagy inhibitor)	Xenograft subcutaneous tumor model in mice	Intravenous	[136]
UiO	Photodynamic therapy	–	Rat orthotopic hematoma	Intravenous	[45]
GMP/EU (guanine monophosphate/ Europium)	Antitumoral	OVA (ovoalbumin antigen) and CpG (oligodeoxynucleotides)	Xenograft subcutaneous tumor model in mice	Not specified	[137]

liposomes for the delivery of the anticancer drug doxorubicin (Dox).[57] There is another product consisting of PEG–polylactic-*co*-glycolyc acid NPs for the delivery of paclitaxel, Genexol-PM, already approved by Korean FDA and currently in clinical trials in the US.[58] NPs coating with PEG prolongs the circulation time in the blood, allowing their distribution in other organs.

Besides, "active" targeting implies the incorporation of molecules on the surface of the nanoMOFs that are specifically designed to recognize particular receptors or antigens expressed onto the membrane of the diseased cells and tissues.[51,59,60]

In general, surface coating of NPs should fulfill some criteria to be suitable for drug delivery,[37,61] such as a) biofriendly synthesis method, without any toxic additive, b) avoid intrusion of the targeting molecule into the nanocarrier, c) preserve drug release capacity, d) lack of interference with entrapped drugs, e) improvement of particle colloidal stability, and f) stability under physiological conditions. Furthermore, in the case of nanoMOFs, the presence of a high porosity makes the surface modification even more challenging due to possible nonspecific intrusion of the molecules into the pores, blocking them, and/or decreasing drug release capacities.[61] Numerous

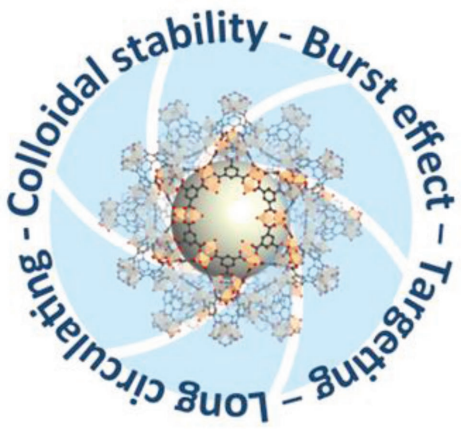

Figure 1. Surface modification of nanoMOFs directly affects colloidal stability before and after in vivo administration, drug release and burst effect, and in vivo targeting and prolonged circulation in the organism.

strategies have been proposed so far to modify the surface of nanoMOFs using a large variety of molecules, such as nucleic acids,[62,63] polymers,[44,64–66] cyclodextrins (CDs),[61] or lipids,[67,68] resulting into various degrees of improvement of the particles properties. One can classify these approaches into three categories: covalent,[61,63,64,69–79] noncovalent,[59,66,80–85] (**Table 2**) or core–shell,[20,60,67,86–93] as detailed below.

2.1. Covalent Route

Recently, Zimpel et al. have reported the covalent attachment of functional polymers, such as amino-PEG and a derived oligoamino amide named Stp10-C and constituted by two terminal groups, a primary amine and a thiol, connected via a repetitive diaminoethane motif with proton-sponge characteristics, grafted on the external surface of the mesoporous biocompatible iron carboxylate MIL-100(Fe) NPs (**Figure 2**).[64] This resulted in a successful improvement of the colloidal stability of the functionalized NPs together with satisfactory

Table 2. Covalent and noncovalent strategy for surface modifications of nanoMOFs (CD-P: cyclodextrin-phosphates; Py-PGA-PEG: pyrene-derived polyethylene glycol).

Interactions	Type of interactions	Example
Noncovalent	van der Waals	Heparin
	Electrostatic	Chitosan
	π–π stacking	Hyaluronic acid
		Py-PGA-PEG
Covalent	Coordination	CD-P
	Condensation	Amino-polymer (amino-PEG)
	"Click chemistry"	Oligonucleotides
		PEG-RGD-β-CD

cellular uptake of MIL-100(Fe) NPs functionalized with Stp-10C by murine neuroblastoma (N2A) cells. Authors showed nevertheless a negative impact of the polymer coating on MIL-100(Fe) magnetic resonance imaging (MRI) properties. Concerning PEG coating, no information was provided about its influence on macrophage uptake and thus it is not yet possible to conclude about the stealth properties of this system.[64]

Agostoni et al. reported the use of cyclodextrin-phosphates (CD-P) covalently attached to the outer surface of MIL-100(Fe) NPs through direct coordination of the phosphate groups to the Lewis iron(III) sites from the outer surface of the NPs. Cyclodextrin molecules being bulkier than the microporous windows of MIL-100(Fe) thus avoided any penetration inside the matrix of the nanoMOFs. By this method, 17 wt% of CD-P was found covalently attached to the nanoMOFs after 24 h of incubation. Upon surface functionalization, the phosphate groups led to a more negative surface charge (ζ −17 mV against −35 mV for uncoated and coated NPs, respectively) and thus a better electrostatic stabilization and a reduced aggregation of the NPs.[61] Moreover, authors demonstrated the good stability of CD-P coating in aqueous solution, where three washings did not lead to any CD-P leaching, while three washings with phosphate buffer saline (PBS) led to only 7% CD-P detachment. Similarly, it was shown that less than 10% of the total CD-P coating was released from the nanoMOFs after 24 h of incubation in PBS

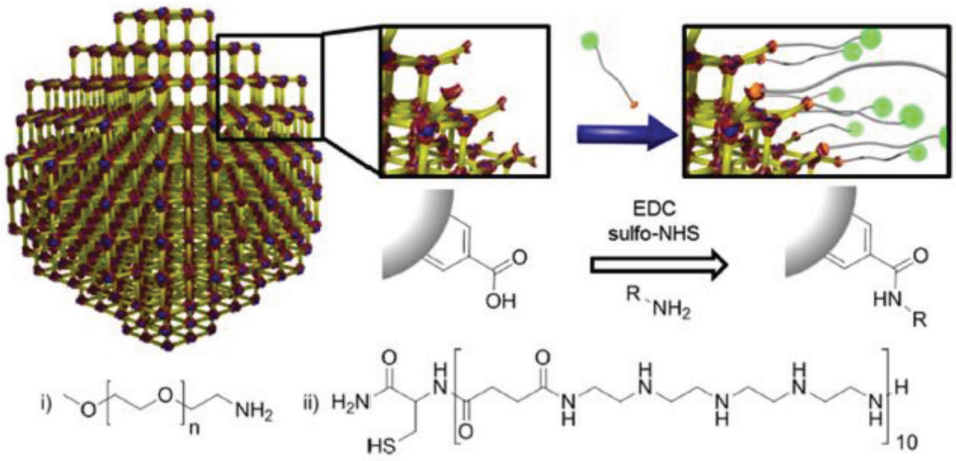

Figure 2. Schematic illustration of the coating with polymers: I) PEG and II) Stp10-C. Reproduced with permission.[64] Copyright 2016, American Chemical Society.

or in cell culture media. Loading and release of the antiretroviral azidothymidine-triphosphate was also not affected by MOF coating; in all cases drug cargo was almost entirely delivered after 24 h, under physiological simulated conditions (PBS, 37 °C). Importantly, the coating with CD-P did not cause any significant toxic effects on the cell lines (J774, MCF7 and LP-1). In addition, cellular uptake of MIL-100(Fe) NPs functionalized with mannose-bearing CD-P derivative by the human retinoblastoma cell line Y79 exhibited more than twice higher penetration inside cells as compared to uncoated NPs.[61] The benefit of such a covalent coating in vivo remains however still to be demonstrated.

Morris and colleagues, took advantage of the click chemistry route to covalently functionalize the microporous zirconium carboxylate UiO-66-N_3 NPs with oligonucleotides,[62] by a strain promoted click reaction between DNA append with dibenzylcyclooctane and azide-functional UiO-66-N_3. As a result, colloidal stability in NaCl was meaningfully improved and cellular uptake (HeLa—human cervical cancer cells) was significantly higher, whereas cell viability was not altered.

A more sophisticated system was developed by Wang et al. who prepared surface modified by the mesoporous iron(III) amino-benzenedicarboxylate MIL-101(Fe) NPs loaded with Dox. After the synthesis of the NPs, to avoid premature drug release through systemic circulation, CD and PEG chains were added by a one-pot, and organic solvent-free "green" postsynthetic procedure based on click chemistry and host–guest interactions forming PEG-RGD-β-CD-SS-MIL-101(Fe) NPs.[69] This led to a better stability in PBS and prevented from fast degradation compared to uncoated particles. Surface-modified nanoMOFs presented negligible uptake in $\alpha_v\beta_3$ integrin negative noncancerous COS7 (African green monkey kidney) cells, while NPs were internalized in $\alpha_v\beta_3$ integrin expressing HeLa (human adenocarcinoma) cells. In vivo antitumor efficacy in hepatoma H22 tumor-bearing mice was then demonstrated through tumor inhibition effect for coated NPs loaded with Dox and for free Dox, while no side effects were observed in coated NPs. Nevertheless, the main inconvenient lies here in the lack of demonstration of the effectiveness of the coating since the NPs were locally administered by subcutaneous injection, near the tumor.

Schmitt et al. have reported functionalized and hierarchically structured MOFs embedding magnetic core particles (magMOFs) through a layer-by-layer synthesis route.[73] Core/multishell particles were obtained following several steps: i) MOF growth of Cu(BA-TPDC) (BA-TPDC-bis(azidomethyl)-terphenyldicarboxylic acid) around a magnetic core, ii) click reaction of blue dye, iii) MOF growth of Cu(TPDC) (TPDC-terphenyldicarboxylic acid), iv) MOF growth of Cu(BA-TPDC), and v) finally a click reaction of the red dye was performed. In the next step, the SURMOF final product was converted into dye-loaded SURGEL (the surface-grafted gels) capsules around the magnetic core. The advantage of SURGELs results from the possibility to control the release of the dye molecule, depending on the pH of the environment. The drug loading of the MOF inner layers was carried out followed by a coating with a protective polymer layer. The resulting magMOF particles could be converted to magGEL by ethylenediaminetetraacetic acid (EDTA) treatment. Different kinetics of release were reported as a function of the pH with a maximum of release reached at pH 11 after 2 h. This product was considered for the oral administration of drugs[73] with however neither in vitro nor in vivo assays to assess the benefit of this strategy. In the same study, the growth of SURMOF films on gold-coated mica substrate was described followed by their conversion into SURGELs via click chemistry with arginine–glycine–aspartic acid (RGD) to favor cell adhesion via specific interaction with the integrin receptors of the cell membrane. GRD is well known to be able to induce adhesion of osteoblasts onto implanted surfaces and to improve bone formation. The proof of concept has been performed in vitro using osteoblast-like CAL72 cell line. The cells were seeded onto the functionalized SURGEL substrates. Finally, no toxicity was observed until 24 h and more adherent cells were observed onto functionalized SURGELs. Additionally, microfluidic shear force assay was performed which confirmed that CAL72 cells interacted stronger at the surface of functionalized SURGELs as compared to the nonfunctionalized counterpart.[74]

2.2. Noncovalent Approach

Chen et al. prepared an intrinsically radioactive microporous Zr dicarboxylate MOF UiO-66 (^{89}Zr-UiO-66) functionalized with pyrene-derived polyethylene glycol (Py-PGA-PEG) taking advantage of "click modulation."[59] The grafting on the external surface of the NPs was ensured here via strong π–π interactions between the organic moieties of UiO-66 NPs and the pyrene molecules. This strategy was also used to further attach a tumor-targeting ligand named F3 on the surface of the MOF (UiO-66/Py-PGA-PEG-F3). Additionally, NPs were loaded with Dox for the drug delivery experiments. Noteworthily, the kinetics of nanoMOFs' degradation and release of the drug were slowed down, probably due to partial blocking of the pore windows of the MOFs by the polymer, hampering the diffusion of phosphates from PBS into the pores. Moreover, drug release kinetics was dependent on the pH of the environment, and once NPs arrived at the extracellular region of the tumor, release of cargo was sped up. Despite these facts, burst release was not totally avoided with around 19% of Dox delivered within 30 min. Regarding cellular experiments, in vitro tumor cell uptake performed in the MDA-MB-231 triple-negative breast cancer cell line and L929 fibroblast showed higher cellular uptake in the MDA-MB-231 cell line compared to the L929 cell line. Empty NPs did not show any cytotoxic effect on MDA-MB-231 cells, while NPs loaded with Dox succeeded to inhibit MBA-MB-231 cell growth. Toxicity of UiO-66/Py-PGA-PEG was studied in Balb/c mice through i.v. administration of 10 and 50 mg kg^{-1} NPs. After 7 and 30 d no sign of toxicity was reported based on histological examination and evaluation of biochemical parameters. Finally, authors evaluated biodistribution by in vivo positron emission tomography imaging in a xenograft subcutaneous tumor model in mice and showed that ^{89}Zr-UiO-66/Py-PGA-PEG-F3 was faster accumulated in MDA-MB-231 tumors compared to ^{89}Zr-UiO-66/Py-PGA-PEG demonstrating that F3 ligand caused active targeting. Note that for further experiments a reduction on the size of the nanoMOFs would lead to better efficacy results since the large size of coated NPs (≈250 nm) prevented from effective internalization into tumor vasculature cells. Furthermore, blood circulation half-life of less than 2 h was reported suggesting that surface PEG density was not efficient to provide sufficient stealth properties

to the nanoMOFs. In a first attempt to prepare MOFs for oral administration, MIL-100(Fe) NPs were coated by the bioadhesive polysaccharide chitosan (CS).[80] The surface-modified NPs exhibited an improved chemical and colloidal stability under oral simulated conditions. In vitro, permeability through a model of intestinal barrier and cytotoxicity were improved, in comparison with the noncoated nanoMOFs. The viability and integrity of the intestinal barrier were investigated using an in vitro model of polarized Caco-2 monolayer cells. Systemic and mucosal immune responses were also studied, through complement activation tests and by cytokine profile, resulting in the absence of any complement activation for both coated and uncoated NPs, while cytokine production decreased from one to two orders of magnitude for the CS-coated NPs.[80,81]

Another noncovalent approach was reported by Bellido et al. through heparin coating of MIL-100(Fe) NPs.[82] The colloidal stability of these NPs was improved in water and PBS, while reduced cell recognition was also observed in vitro for the heparin-coated nanoMOFs using a macrophage cell line (J774.A1) at short time of incubation (up to 4 h), without any complement activation and reactive oxygen species production. Furthermore, surface modification preserved NP encapsulation capacities, as demonstrated with the active caffeine, while a decrease in the release kinetics compared to uncoated NPs was observed. However, the eventual benefit of these NanoMOFs in terms of pharmacokinetics and biodistribution still needs further demonstration.

Another example of noncovalent approach to decorate MOF NPs was developed recently by Cai et al. who successfully developed surface engineered MIL-100(Fe) with hyaluronic acid and indocyanine green with improved colloidal stability and good cellular uptake by cancer cells using the CD44-positive MCF-4 cell line.[66]

Qu and co-workers described the ability of noncovalent functionalized iron carboxylate MIL-101(Fe) with unmethylated cytosine–phosphate–guanine oligonucleotydes (CpG ODNs) (MIL-101(Fe)-CpG nanoconjugates) to enhance the immune response. In addition, T_2-magnetic response imaging ability was tested in vitro and in vivo.[85] CpG ODNs were adsorbed onto the MOFs by $\pi - -\pi$ interactions between the CpG ODNs and the terephthalic acid organic ligands. Regarding cellular experiments, the obtained nanoconjugates did not show any toxicity on RAW264.7 cells, even at rather highest concentration (200 µg mL^{-1}). After cell internalization, the nanoconjugates interacted with TLR9 and triggered the secretion of cytokines. Furthermore, MIL-101(Fe)-CpG nanoconjugates displayed a higher immune response comparatively to CpG ODNs alone, both in vitro and in vivo. Moreover, T_2-weighted MR images of the tumor-bearing mice, before and after subcutaneous injection of MIL-101(Fe)-CpG nanoconjugates, showed a strong signal at the site of injection, whereas the tumor position was well visible. Due to T_2-MRI ability of the nanoconjugates, it was proposed to use these nanoconjugates to track the labeled immune cells and to monitor in vivo the CpG-ODN-based drugs or vaccines.[85]

2.3. "Core–Shell" Strategies

Besides covalent and noncovalent surface modification, another strategy related to the so-called "core–shell" approach consists in the covering of the nanoMOF core by a dense coating, identified as the shell of the system.

Rieter et al. were the first to consider silica coating to form core–shell systems made of nanoMOFs to avoid a too fast degradation of the NPs in body fluids.[20] Further functionalization of silica-coated NPs was also performed using diopicolinic acid. Authors described a general method to obtain variable thickness of silica shells on the lanthanide dicarboxylate $Ln(BDC)_{1.5}(H_2O)_2$, where Ln = Eu^{3+}, Gd^{3+}, or Tb^{3+}, and BDC = 1,4-benzenedicarboxylate. They also loaded Pt-based drugs into nanoscale coordination polymers, constructed from Tb^{3+} ions and DSCP (c,c,t-(diamminedichlorodisuccinato)) $Tb_2(DSCP)_3(H_2O)_{12}$, stabilized with silica shell.[86]

More recently, Wuttke et al. reported a "core–shell"-like approach, where nanoMOFs were encapsulated into a lipid bilayer shell.[67] They demonstrated that MIL-100(Fe) and the chromium dicarboxylate MIL-101(Cr) NPs, coated with a lipid bilayer consisting of (1,2-dioleoyl-snglycero-3-phosphocholine), exhibited a better colloidal stability than the uncoated nanomaterial. Noteworthily, the integrity of the lipid bilayer was confirmed and led to a higher uptake by cancer cells (T24 bladder carcinoma cells), without cytotoxic effect of empty-coated NPs. The same team reported very recently the coating of MOF NPs with exosomes via lipid fusion (**Figure 3**).[87] This method ensured the preparation of an exosome delivery system with unprecedented loading efficiency. The resulting exosome-coated NPs showed no burst leakage with an efficient release of their cargo into the cells.

Another core–shell strategy for surface modification of MOFs was proposed by Li et al.[60] A biomimetic theranostic oxygen (O_2) meter (cancer cell membrane@Pt(II) porphyrinic-nanoMOF (mPPt)) was constructed for cancer targeting and phosphorescence image-guided photodynamic therapy (PDT). Pt(II) porphyrinic nanoMOF was formed by O_2-sensitive Pt(II) *meso*-tetra(4-carboxyphenyl)porphyrin and Zr_6 clusters. Cancer cell membrane (from 4T1 cells) was selected as a target for MOFs' surface modification, to increase cancer targeting due to homotypic targeting and immune escape abilities. Moreover, mPPt were loaded with photosensitizers. This led to an increase in particle size from 108.5 to 150.5 nm while the ζ potential decreased from 24.5 to –28.5 mV for the coated nanoparticles in comparison with the bare ones. Singlet oxygen ($^1O_2$) production ability, as the main cytotoxic species associated with PDT, was evaluated in vitro in 4T1 cells under various O_2 atmospheres.

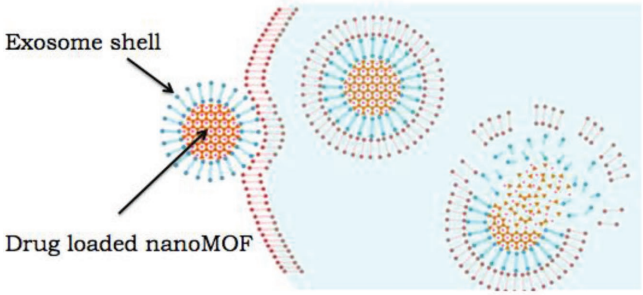

Figure 3. Schematic illustration of the cell uptake of exosome-coated nanoMOFs and release mechanism of the cargo. Reproduced with permission.[87] Copyright 2017, American Chemical Society.

An increase of O_2 levels was observed in cells with mPPt and the highest $^1O_2$ production in 21% O_2 atmosphere. The cell uptake was determined after incubation with 4T1 cells and heterogeneous COS7 normal cells, as the controls. mPPt were easily recognized by 4T1 cells, which was not the case with COS7 cells. On the other hand, the escape of mPPt from RAW264.7 murine macrophages was demonstrated, whereas uncoated NPs were captured by macrophages. In addition, in vitro PDT led to a significant cytotoxicity against 4T1 cells in 21% O_2, under O_2 sensor. Fast and accurate response of mPPt toward O_2 fluctuation was also observed by in vivo imaging, and an improved anticancer activity was noted after treatment with mPPt of BALB/c mice with subcutaneously injected 4T1 cells.[60]

Wang and colleagues also reported nanoscale polymer–MOF hybrids, where the Zr terepthalate UiO-66 was coated with polyaniline (PAN) (UiO-66@PAN) for phototermal therapy (PTT).[91] The photothermal performance of PAN-coated NPs was investigated and the temperature raised until 57.2 °C at a concentration of 100 µg mL^{-1} UiO-66@PAN upon laser irradiation, which was sufficient for the efficient killing of malignant cells. Regarding cellular assays, coated NPs did not induce any cytotoxicity in both murine colon cancer CT26 and human colon cancer HTC116 cell lines, but once irradiated, nearly 70% cells were dead. In vivo tests carried out with both UiO-66@PAN and NIR irradiation showed a complete tumor regression after 10 d, when compared to the controls (untreated or NPs alone), proving that UiO-66@PAN was a good candidate for PTT-based cancer therapy.[91]

3. Toxicity: From In Vitro to In Vivo Evaluation

There is to date an increasing number of publications demonstrating the lack of significant in vitro toxicity of nanoMOFs based on 2D cell studies using established cell lines. However, these in vitro tests are far from reproducing the in vivo situation. Thus, it is important to emphasize that the lack of in vitro cytotoxicity does not mean that the nanodevice is safe and biocompatible. In general, toxicity issues should be tackled down based on a more rational safe-by-design approach when considering nanoMOFs for biomedical applications. Most of the authors justify the choice of their nanoMOFs based on their constitutive parts, i.e., through the reported metal and ligand individual toxicity. This strategy can be useful mainly to discard the most toxic nanoMOFs, but it is far from being optimal. The data that we possess about metal toxicity refer mainly to medial oral lethal dose, that is the amount of a drug or other substance that, when orally administered to a group of experimental animals, will kill 50% of the group in a specified time (LD50), and to human exposure to metals present in the environment (water, air, soils, and food). Administration of nanoMOFs in the human being as part of a pharmacological treatment implies active penetration of the metal in the organism. In this case, exposure to metals is different than the previously studied ones and will be determined by the intensity (dose), frequency, and duration of the treatment, as well as by the administration route that determines how the metal is distributed, accumulated, metabolized, and eliminated. Certainly, LD50 value cannot be extrapolated to other administration routes for which biodistribution will be totally different. Furthermore, when one deals with in vivo human toxicity, there is even less data available for most of the constitutive MOF ligands, such as terephtalic acid in MIL-101 or UiO-66, whose toxicological properties after i.v. administration have not been thoroughly investigated.

As a consequence, to obtain more information about potential toxicity of the nanoMOFs after administration into humans, one shall focus more on reports dealing with in vitro or ex vivo models that specifically mimic an in vivo situation rather than relying on simple 2D in vitro toxicity tests using established cell lines (**Figure 4**).[94] In many cases the cytotoxicity is only performed in cancer cell lines to demonstrate a potential anticancer effect, and not in healthy cells to assess the toxicity of the carrier,[62,95,96] even if Tamames et al. already demonstrated that toxicity of numerous MOFs is higher for healthy cells than for tumor cells.[97] Besides, when healthy cells are used the choice of the cell type is rarely justified based on therapeutic applications.[98] Some efforts have already been made to design more pertinent cytotoxic in vitro studies by Wuttke et al. who explored the toxicity of various nanoMOFs using different primary healthy cell types depending on the proposed medical application.[99] For their use as drug delivery systems, toxicity and inflammatory response on vascular cells and lung cells were tested, whereas for their application as drug delivery implant

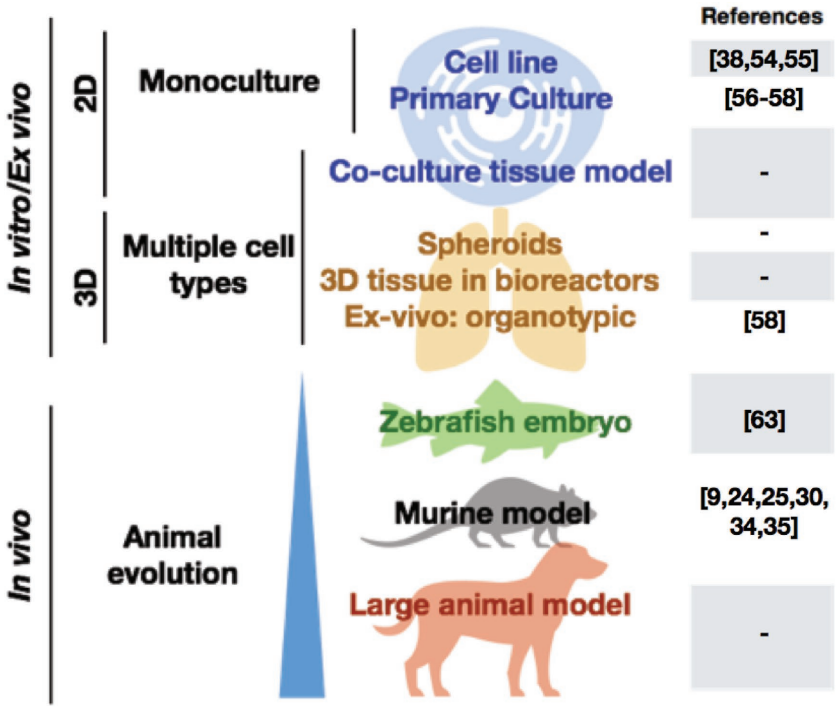

Figure 4. In vitro and in vivo models employed to assess nanoMOFs' toxicity.

coatings of dental or nerve guidance tubes, fibroblasts and neural cells were chosen, respectively. Furthermore, alternative models to screen toxicology, such as numerous 3D in vitro models, are currently being developed to better reproduce the in vivo conditions of a particular tissue, such as the tumor environment, the liver, or the skin.[100–103] These new models were also reported by Wuttke et al. where the biological response of sensory neurons to the nanoMOFs was monitored using rat neonatal organotypic dorsal root ganglion cultures.[99] It is expected that in a near future these 3D models will replace the monolayer cell cultures to better investigate eventual adverse effect of nanoMOFs.

Concerning the in vivo toxicity tests of nanoMOFs, a very few studies have been performed to date. The first study describing toxicological information in vivo of nanoMOFs was reported by some of us in 2010.[24] In this pioneering experiment, iron carboxylate NPs such as MIL-88A NPs with particle sizes of 150 or 500 nm, as well as MIL-88B_4CH_3 NPs with 50 or 140 nm, were intravenously administered into Wistar rats via the jugular vein. Animals were followed up to 3 months and several parameters were evaluated such as animal behavior, animal weight evolution, weight changes of different organs, cytochrome P-450 activity, ALT and AST transaminases levels, and interkeukine-6 serum concentration. The only significant effect was a slight transitory increase in the spleen and liver weights, attributed to the fast sequestration by the reticuloendothelial organs of the nanoMOFs that went back to normality 1–3 months after injection. The absence of immune or inflammatory reactions after NP administration supported their lack of toxicity. Moreover, the absence of activation of cytochrome P-450 suggested a direct excretion of the polyacids, in agreement with their high polarity.

In 2013, some of us investigated the in vivo toxicity and biodistribution of three different uncoated iron carboxylate-based nanoMOFs, namely, MIL-100, MIL-88A, and MIL-88B_4CH_3, using Wistar rats.[52] First, i.v. administration of increasing doses of these NPs was performed to assess lethal dose 10 (LD10). Animal behavior during 7 d was analyzed and then animals were sacrificed and organs harvested for histological examination. This early study led to very promising results. Indeed, the LD10 was never reached with the studied nanoMOFS, and any mortality was caused by nanoMOF administration or significant toxicity signs were observed. In fact, the highest practicable dose was established based on colloidal stability and not on toxicity issues. Only an expected increase in the oxidative stress was observed but it came back to the control level after 1 month.

In 2015, a third study systematically describing the in vivo toxicity of a series of nine different nanoMOFs was reported by Ruyra and colleagues.[104] The in vitro cytotoxic test using 2D cell culture was compared to results obtained using the zebrafish embryo in vivo model (Figure 4). On the whole, a strong correlation between the results using both methods was found except for MIL-101(Fe), which was more toxic in vivo in zebrafish than in vitro. Very interestingly, authors concluded that the toxicity of these materials was mainly governed by the release of metal ions during degradation, while they also highlighted the importance of the formation of other species upon degradation. This confirms that when assessing nanoMOF's toxicity more information about degradation mechanisms and degradation products under physiological conditions is required. For a while, it was generally assumed that nanoMOF in vivo degradation resulted in releasing the constitutive metal ion and the ligand. However, this is in contradiction with the findings of Ruyra et al. who have proven that a few nanoMOFs once in contact with cell culture medium became amorphous and underwent structural rearrangements and/or reactions that generated new inorganic species, responsible for adverse effects.[104] In a more recent study, this phenomenon has been described in detail for MIL-100(Fe) nano- or microparticles, confirming the progressive formation of dense phases (iron oxide and phosphate) associated with a degradation under physiological simulated conditions.[105]

Besides the above-mentioned studies, a few recent reports dealing with in vivo nanoMOFs' applications also disclosed brief results concerning in vivo toxicity,[59,68,106,107] but it is far from being enough to establish material biocompatibility.

As a conclusion, despite promises, there is still a great effort to be carried out to assess the toxicity profiles of nanoMOFs before eventual translation into the clinic. Until that, toxicity remains without any doubt one of the keystones to continue building the bridge to move from bench to bedside.

An important advantage of MOFs compared to other nanomaterials lies in the preparation of metal biomolecule frameworks (also known as bioMOFs for bioactive MOFs or bioMIL for bioactive MIL) by the incorporation of endogenous molecules or active ingredients as building blocks.[41] This allows reducing the amount of nonactive undesirable compounds to be administered at the benefit of an anticipated decrease of toxicity. Numerous active ligands have been proposed to date to produce bioMOFs: peptides (metal peptide frameworks),[108] nucleobases,[109,110] carbohydrates,[111–115] porphyrines,[48,116] as well as some active ingredients.[117–122] Unfortunately, most of these bioMOFs are still at their initial stages of development and a very few of them have undergone in vivo preclinical evaluation. In 2014, Lu et al. performed the in vivo administration of a porphyrine-based bioMOF.[48] Using a subcutaneous xenograft model in mice of human head and neck cancer cells SQ20B, this study was the first in vivo proof of concept of using nanoMOFs for photodynamic therapy purposes. Of note, MOFs were only locally administered at the tumor site and in vivo toxicity was not assessed since the authors only measured anticancer activity. Therefore, the in vivo toxicity associated with this bioMOF still needs to be determined.

In addition to the toxicity associated with the nanoMOF itself, toxicity issues can be intimately related to the synthesis process, especially to the solvents and reaction modulators employed to prepare the NPs. Indeed, the synthesis of most bioMOFs requires the use of toxic solvents such as dimethylformamide or pyridine.[120,121] Thus, to prepare suitable nanomaterials relevant for clinical applications, alternative "green" synthesis routes are urgently needed as it has already been done for other MOFs.[61,69,122]

4. Biodistribution, Targeting, and Pharmacological Efficacy

The major aim in using nanocarriers for drug delivery is related to the improvement of the pharmacokinetic profile and

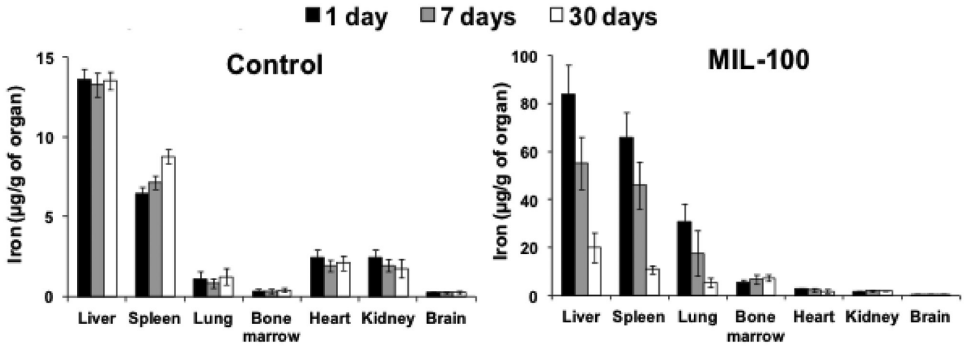

Figure 5. Iron level in different organs after 1, 7, and 30 d of i.v. administration of glucose solution of 220 mg kg^{-1} MIL-100(Fe) NPs in rats. Reproduced with permission.[52] Copyright 2013, Royal Society of Chemistry.

biodistribution to allow a better drug targeting toward diseased cells and tissues. Despite the great number of studies claiming that nanoMOFs are promising drug carriers, a very few of them focus on demonstrating the ability of these systems to modify and improve drug biodistribution.

The first investigation dealing with the pharmacokinetic and biodistribution of nanoMOFs was reported by Baati et al., in which the long-term biodistribution (from 1 to 30 d) of three different uncoated iron carboxylate nanoMOFs was examined in rats (**Figure 5**).[52] After i.v. administration of MIL-100, MIL-88A, and MIL-88B_4CH_3 NPs, both the iron and the organic linker concentrations were quantified in several complex biological media, including liver, spleen, and urine. Iron levels were quantified by atomic absorption spectroscopy, whereas the linker concentration was determined by specific extraction and high-performance liquid chromatography methods.[123]

An important reversible accumulation in the organs of the reticulo-endothelial system, liver and spleen, was observed for all the tested nanoMOFs (**Figure 6**). However, liver accumulation was higher for the MIL-88B_4CH_3 NPs, whose constitutive linker, i.e., tetramethyl benzendicarboxylic acid, exhibits a more pronounced hydrophobic character, which could also explain the slight accumulation of this nanoMOF in the brain that was not observed for any of the other materials. Besides, even if the observed normal breathing of the animals supported the lack of lung toxicity, upon histological examination of the pulmonary tissue of nanoMOF-treated rats, it was observed that a large amount of nanoMOFs was found to aggregate and to accumulate in the lungs. Taken together, these data demonstrated that nanoMOFs distributed in different tissues for a period of time, and as a consequence they could act as prolonged drug delivery systems. However, this first study was focused on the evaluation of nanoMOFs without any drug loaded inside their pores. Recently, we showed how the encapsulation of the anticancer drug Busulfan into MIL-100(Fe) NPs drastically modified the drug pharmacokinetics profile compared to the commercial formulation Busilvex.[124] Busulfan detected after MIL-100(Fe)-Busulfan administration was much lower than after Busilvex dosage with a mean area under the curve in a plot of drug concentration in blood plasma versus time of 2.6 and 25 mg mL^{-1} min^{-1}, respectively. Moreover, it was also demonstrated that the clearance of NPs from the blood was faster in the case of drug-loaded nanoMOFs, probably due to changes on the surface of the particles that became more hydrophobic, and therefore, more easily recognized by macrophages in the bloodstream. Increased levels of trimesic acid linker in urine after 24 h, i.e., two times higher than after empty NPs injection, were observed. All this indicates that the biodistribution/elimination data of the empty nanoMOFs cannot be extrapolated to drug-loaded nanoMOFs. In fact,

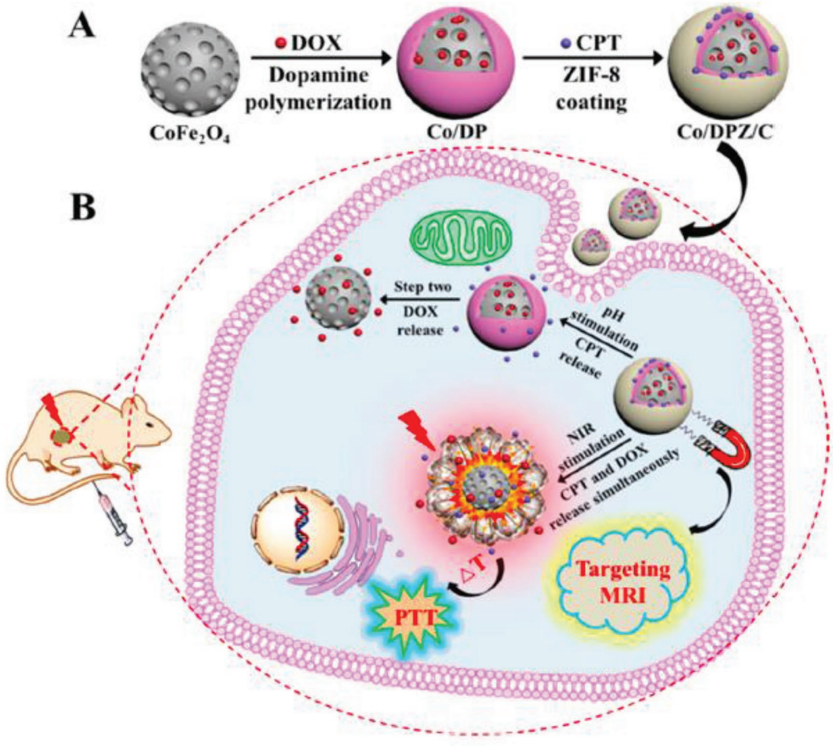

Figure 6. Biodistribution of iron nanoMOFs according to the iron concentration. Reproduced with permission.[9] Copyright 2012, American Chemical Society.

depending on the nature of the encapsulated molecule, the biological interaction of the drug delivery system might change. Early biodistribution of MIL-100(Fe) NPs in rats has also been investigated. Interestingly, a reversible accumulation of NPs in the lungs after i.v. administration was observed, which was mainly attributed to a pH-triggered decrease of NP colloidal stability in the blood upon i.v. administration. This unique property of MIL-100(Fe) NPs hold promise for specific lung targeting. Thus, MIL-100(Fe) NPs loaded with the anticancer drug gemcitabine monophosphate were found to increase the lung concentration of the drug, leading to the efficient treatment of an experimental model of lung metastasis.[125]

In other in vivo experiments, biodistribution of coated nanoMOFs was assessed. For example, bioMOF prepared from the therapeutic agent zoledronate and calcium (CaZol) was modified by incorporating the targeting molecule folate and chains of PEG (Fol-PEG-CaZol).[68] Folate is a molecule with a high affinity for the folic acid receptor, highly expressed in many human cancers. Folate–NP conjugates tightly bind the folate receptor and trigger cellular uptake by endocytosis.[126] The biodistribution after single i.v. tail injection was evaluated both in healthy mice and in a xenograft subcutaneous tumor model. Unfortunately, in the study with healthy mice only one group of animals was treated by surface-modified nanoMOFs and therefore authors could not compare the biodistribution results with uncoated nanoMOFs, making impossible to conclude about the benefits of PEGylation in this model, in which 60% and 20% of the administered dose were found in liver and kidney, respectively. In the experiment using the xenograft tumor animal model, three groups were included and were treated with PBS (control group), Ca-Zol, and Fol-PEG-CaZol. Authors observed important differences in the tumor uptake: 82% of the administrated Fol-PEG-CaZol nanoMOFs were accumulated in the tumor compared to only 52% after treatment with the nontargeted nanoMOFs. This was attributed to the active targeting mediated by the folate molecules at the surface of the nanoMOFs. Once again, a fair conclusion about the role of PEGylation versus folate decoration is difficult to draw since a control group treated with PEG-CaZol, without folate molecules, was not included in this study. Zhang et al. also incorporated PEG and folate to coat the zinc imidazolate ZIF-8 NPs to develop an antitumoral formulation.[127] Two different drugs were encapsulated, the *p*-glycoprotein inhibitor verapamil and the antitumoral Dox. After i.v. administration in a xenograft subcutaneous model of melanome, the best tumor inhibition was observed when ZIF-8 nanoMOFs encapsulating both drugs were PEG coated and folate decorated. The authors assumed that the superiority of the treatment was due to the enhanced permeability and retention effect (EPR) and folate-mediated active targeting.

A very few studies dealing with nanoMOFs' distribution and therapeutic effect after oral administration have been performed to date. Lucena et al. reported the anti-inflammatory effect of orally administered 5-FU encapsulated in Cu-BTC,[96] using a peritonitis mice model induced by carrageenan. Authors concluded that the cytotoxicity against tumor cells observed in vitro could be related to the route of leukocyte activation or suppression of the inflammatory process. Future experiments should include a more adequate animal model to evaluate the mechanisms behind 5-FU-loaded Cu-BTC antitumor activity. Another example was proposed by Hartlieb et al.[128] where ibuprofen was cocrystallized with γ-cyclodextrins (γ-CD), the carboxylic group of the drug being coordinated to alkali metal cations such as K+. The main target of this porous framework, built up from (γ-CD)6 cubes, was to reduce the time required for the maximum uptake of ibuprofen (C_{max}) and to increase the half-life of the drug within the body. The benefit in terms of drug bioavailability after oral administration was demonstrated, using a mice model, with a 100% longer half-life in blood samples.

5. Recent Advances in Theranostics

Many of the recent advances in the field of MOFs for drug delivery have already been discussed in the precedent sections. In the past few years, another target in the field was to develop more complex systems to integrate therapeutics and diagnostics in a unique theranostic tool.[45,66,129–131]

The potential of iron carboxylates as theranostic agents was first proposed by some of us in 2010, when MRI measurements were performed on Wistar rats after i.v. injection of a suspension of MIL-88A NPs.[24] In this report, it was shown that the iron-based core was responsible for favorable relaxivities and imaging properties.

The surface of the iron carboxylate MIL-100(Fe) NPs was recently decorated by Sene et al. with γ-Fe_2O_3-cit ultrasmall NPs of superparamagnetic of iron oxide (USPIO) leading to novel nanoobjects (MIL/USPIO-cit). The system demonstrated good stability in aqueous solution and physiological media. Moreover, the presence of maghemite NPs conferred to the nanoMOFs a very high r_2 relaxivity, comparable to the best commercial available systems and these imaging properties were further confirmed in vivo by T_2-weighted MRI. This potential theranostic tool improved imaging contrast properties of the nanoMOFs in vivo while conserving the high drug loading/release capacities.[130] Another theranostic approach based on ZIF-8 NPs was recently reported by Yang et al. in a sophisticated system to combine MRI, multidrug chemotherapy, and photothermal synergistic therapy (**Figure 7**).[129] Here the nanoMOFs were used as a shell within the "sandwich" nanocomposite made from a core of $CoFe_2O_4$ mesoporous NPs, a polydopamine layer and a shell of ZIF-8. The core acted as an MRI probe, as a photothermal agent, and as a loading platform for Dox. The polydopamine layer prevented from the leakage of Dox while the nanoMOFs' shell allowed encapsulation of the hydrophobic anticancer drug camptothecin and as the switch for the pH and NIR stimulation-responsive release of the two drugs. After in vivo i.v. administration in a xenograft tumor model in mice, an efficient photothermal integration was observed together with high drug concentration at the tumor site by quick release of encapsulated drugs, negligible toxicity, and a synergic antitumor effect of the hybrid nanocomposites.[129] A UiO-type Zr carboxylate MOF has also been proposed for photodynamic therapy by Zhang et al.[45] In this study, CT images demonstrated the accumulation of the nanoMOF into the tumor, after intravenous administration in rats bearing an hepatoma. One can nevertheless raise concerns about this study as part of a lack of control experiments in

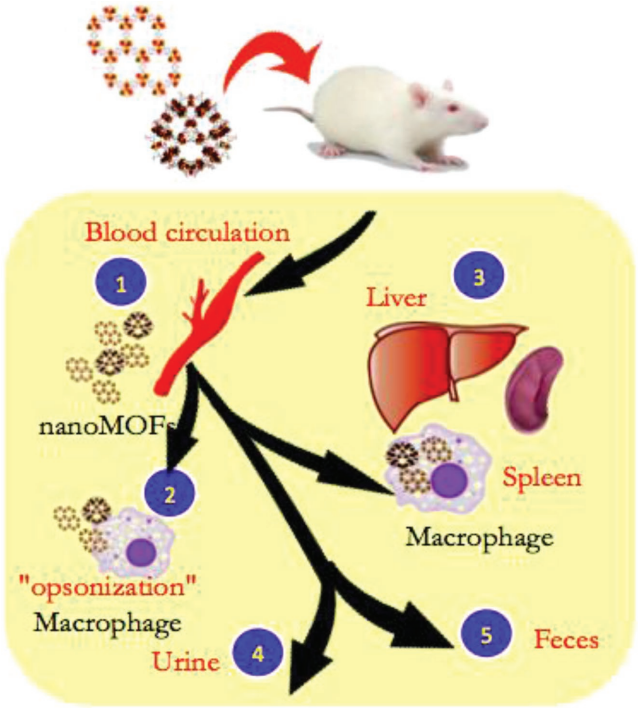

Figure 7. A) Synthesis of Co/DPZ/C nanocarrier and B) theranostic strategy for MR imaging-guided multidrug chemotherapy and photothermal synergistic therapy. Reproduced with permission.[129] Copyright 2017, American Chemical Society.

healthy rats. Indeed, as previously mentioned, nanoparticles tend to spontaneously accumulate into the liver healthy macrophages due to the opsonization process. It is therefore difficult to conclude if the tumor accumulation resulted from a specific targeting or corresponded only to unspecific capture by the Kupffer cells of the liver, common to most nanoparticles.

6. Conclusion and Perspectives

MOFs' materials have emerged initially due to their promises for numerous industrial applications such as gas separation/storage or catalysis, as a consequence of their tunable porosity and large chemical and structural diversity. In parallel, the field of biomaterials has been under continuous development with numerous natural and synthetic materials being considered for controlled drug delivery and theranostic applications. The temporal convergence of MOF discovery and biomaterials science expansion explains probably why these new hybrid materials, prepared by chemists far from the clinical environment, were soon identified as potential candidates in the search of new and more safe drug nanocarriers.[138,24,139] Since then, in the last decade, studies dealing with applications of MOFs in the pharmaceutical sciences have grown steadily (see **Figure 8**). Initial reports in this domain have focused on fundamentals that govern the drug loading and release of a large array of therapeutic and theranostic systems, while later reports incorporated basic in vitro characterization including first toxicity studies. Noteworthily, during the past 3–4 years,

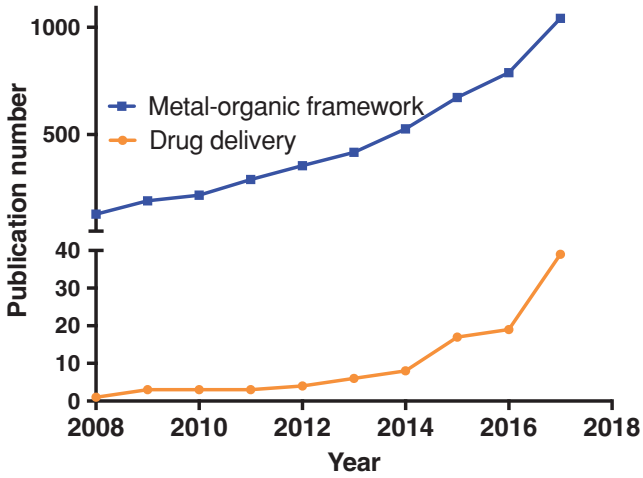

Figure 8. Representative evolution on the number of articles on metal-organic frameworks for drug delivery since 2008. In PubMed, the initial research topic of "metal-organic framework" was further refined using the research topic of "drug delivery."

an increasing number of studies have highlighted the first in vivo benefits of nanoMOFs to treat different diseases in animal models. One can thus expect in the upcoming years exciting new developments concerning the preclinical in vivo evaluation of MOFs.[59,107,125,127,129–131,133,128,140] A key condition of success will nevertheless require furthering strengthening the exchanges between chemists, pharmacists, and clinicians, for the creation of multidisciplinary projects dealing with the translation of nanoMOFs into more realistic biomedical solutions. When analyzing the evolution of the field in the last 5 years (Figure 8), one realizes that now is time to move from "simple" collaborations and teaming to integrate additional data, methodologies, perspectives, and concepts from the various disciplines implied, which would lead to important advances in fundamental understanding and to solve real biomedical problems. Individual researchers also need to acquire a deeper understanding in these disciplines and be fluent in their languages and methodologies. Numerous university programs already offer multidisciplinary training in biomaterials science, especially for postgraduate students and through Ph.D. programs. Some of these programs have already started to deliver researchers with the knowledge and skills to work at the interfaces of biomaterials disciplines that will hopefully make a precious contribution for the progression of MOFs' bioapplications.

The remaining challenges are, however, still numerous if one targets the use of nanoMOFs as third-generation drug delivery systems as summarized by Yun et al.[141] According to Park's group classification, third-generation formulations are modulated delivery systems that must be able to cross both physicochemical and biological barriers (**Table 3**).[141] A particular effort will be required to get a rational design approach covering all the development stages, from the choice of the nanoMOF composition, the development of safe synthesis, and the surface modification and formulation conditions, the best route of administration and dose, bearing in mind the current treatment for a specific disease

Table 3. Barriers to overcome by the third-generation drug delivery systems (adapted from ref. [141]).

Third-generation drug delivery systems: barriers to overcome	Formulation barriers (physicochemical)	Increasing drug solubility Control of drug release kinetics Control of drug loading Control of therapeutic period Control of particle size, shape, functionality and flexibility Surface modification with ligands Stimuli-sensitive delivery systems Self-regulated delivery systems
	Biological barriers	Lack of toxicity in vivo Colloidal stability in the blood In vitro–in vivo correlation Long-term delivery Noninvasive delivery Controlling biodistribution Navigating microenvironment of diseased tissues to reach target cells Crossing mucosal barriers

and the identification of the best animal model for the in vivo preclinical evaluation. **Table 4** attempts to summarize the main steps and some relevant considerations in MOF development, from physicochemical characterization to in vivo evaluation.

All this being said, one cannot obviate that the nanomedicine field itself currently faces a challenging phase in which several important questions about the medical service provided by nanotechnology are being discussed.[141,142] In particular, major critics are made about the models used for preclinical evaluation of nanomedicines. For instance, for the treatment of cancer diseases, the excessive reliance on the mice xenograft animal models is contested because the data obtained with those models are hardly reproduced in humans. The use of extremely high doses in mice, impossible to extrapolate to humans, and the labeling with fluorescence probes to demonstrate a stealth or targeting effect, when it is known that these markers do not provide quantitative results, are other examples of irrelevant methodologies.[142] Carefully looking at the most recent in vivo studies with MOFs, here reviewed, one could address the same comments for most of them. In the next years, MOFs' researchers should therefore i) innovate and for instance move toward more reliable animal models, such as orthotopic tumor models, syngeneic mouse tumor models, including genetically engineered mice or patient-derived xenograft, in the case of cancer disease,[143] or the use of 3D in vitro

Table 4. Summary of the different stages and relevant points to considered to develop MOFs for biomedical applications, from the physicochemical characterization to the in vivo tests.

	Material properties	Relevant considerations
Physicochemical	• Size • Shape • Surface charge • Behavior in physiological fluids • Degradation in physiological fluids • Identification of degradation products in physiological fluids	• The physiological fluids in contact with MOFs depend on the administration route and biodistribution • Composition of the physiological fluids varies within species
In vitro	• Nanoparticles cytotoxicity • Toxicity of degradation products • Cellular uptake • Intracellular trafficking • Intracellular delivery • Pharmacological activity in cell culture • Crossing biological barriers	• Different models can be used for toxicity evaluation: cell lines, primary cells, and 3D in vitro models. The choice should be justify • Besides toxicity tests based on metabolic activity and cell proliferation, other deleterious effects of MOFs may be identified, such as oxidative stress and proinflammatory cytokine induction • Identify the intracellular target of the drug and verify the ability of the MOF to assure the delivery of the active drug • Depending on the administration route the capacity to cross the biological barriers (i.e., gastrointestinal, endothelial, blood–brain barrier) should be proved
Ex vivo	• Nanoparticle toxicity • Degradation product toxicity • Hemocompatibility	
In vivo	• Nanoparticle and drug pharmacokinetics • Nanoparticle and drug biodistribution • Toxicity • Efficacy	• Identify the adequate administration route • Choose the adequate animal model and species • Distinguish between NP and the drug (i.e., pharmacokinetic and biodistribution) • When using a drug model justify the choice (hydrophobicity, molecule size, reactive groups, etc.). Idem when using a fluorescent probe • To describe toxicity consider different aspects such as animal behavior, hematological analysis, biochemistry, histological study • Distinguish between acute toxicity and chronic toxicity • Toxicity studies should mimic the therapeutic dosage schedule • Use the adequate control groups to prove efficacy (empty carrier, free drug). If they are missing give a scientific justification • When multiple parameters are evaluated within a unique delivery system (i.e., surface modification and drug release, co-delivery of drugs) add the corresponding controls (i.e., empty carriers with and without surface modification; free drugs separately and in combination, and loaded drugs separately and in combination).

models; ii) stop assuming effects, such as EPR or active targeting without performing the experiments that scientifically demonstrate these phenomena, by including the adequate control groups or using labeling strategies that ensure quantitative analysis of drug biodistribution; and, for instance, iii) avoid the use of model drugs or fluorescent probes that do not possess the same physicochemical properties as those of the real drug.

The risk also exists to limit the in vivo studies to the reproduction of those experiments already performed with other nanocarriers (i.e., liposomes, lipid/polymer NPs or polymer micelles), without showing any ground-breaking advantages for nanoMOFs. Moreover, until now, cancer treatment is almost the unique application of nanoMOFs when several other important biomedical applications may be considered, such as improved oral bioavailability for traditional drugs (see the work by Hartlieb et al.[128]), oral controlled release, nonviral gene delivery, vaccine adjuvant delivery systems, or delivery across the blood–brain barrier, among others.

Even if the number of works rapidly increases every year (Figure 8), MOFs as delivery systems are still at their infancy. Indeed, they have appeared more than 30 years after the first drug delivery systems, such as liposomes in the 1960s,[144] polymeric particles in the 1970s,[145] and polymeric micelles in the 1980s.[146] Thus, results with MOFs have not reached yet the maturity of other nanovectors in terms of pharmaceutical development, and it is difficult to make a rigorous comparison. However, MOFs present two important advantages that could help to overcome limitations to cross biological barriers, such as the gastrointestinal or the blood–brain barrier, in contrast to other materials used in drug delivery. First, the great flexibility of MOFs' chemistry offers unprecedented possibilities to easily modify the surface of the NPs to modulate biological interactions. Second, MOFs' drug loading is in many cases far superior to most of the other studied drug delivery systems, meaning that even with a limited passage, the pharmacological effects would be significantly improved; one shall also consider that despite biodegradation, the kinetics of release of the drug can be controlled through a careful tuning of the host–guest interactions. Finally, when developing new MOF-based delivery systems, one shall also pay attention to the ability to produce nanoMOFs under conditions compatible with the pharmaceutical industry from their scale-up to their integration into adapted pharmaceutical formulations.

In conclusion, MOFs are promising materials for biomedical applications but before to be able to reach the clinical arena, MOF scientists should take advantage of the knowledge acquired during decades by others and go further in solving the relevant limitations of other already developed nanomedicines.

Conflict of Interest

The authors declare no conflict of interest.

Keywords

drug delivery, in vivo evaluation, metal-organic frameworks, nanomedicine, surface modification

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