DOI: 10.1002/anie.201000048

BioMOFs

BioMOFs: Metal–Organic Frameworks for Biological and Medical Applications

Alistair C. McKinlay, Russell E. Morris, Patricia Horcajada, Gérard Férey, Ruxandra Gref, Patrick Couvreur, and Christian Serre**

drug delivery · metal–organic frameworks · nitric oxide · theranostics

The class of highly porous materials called metal–organic frameworks offer many opportunities for applications across biology and medicine. Their wide range of chemical composition makes toxicologically acceptable formulation possible, and their high level of functionality enables possible applications as imaging agents and as delivery vehicles for therapeutic agents. The challenges in the area encompass not only the development of new solids but also improvements in the formulation and processing of the materials, including tailoring the morphology and surface chemistry of the frameworks to fit the proposed applications.

1. Introduction

Metal–organic frameworks (MOFs) are among the most exciting, high-profile developments in nanotechnology in the last ten years.[1] Composed of metals (or metal clusters, chains, or layers) connected by organic linkers, they show some of the highest porosities known, with pore sizes between 0.4 and 6 nm, which is ideal for capture, storage, and/or delivery applications.[2] MOFs have been particularly highlighted for their excellent gas-storage and separation properties. In this Minireview, we will discuss the underlying concepts and future potential for biological applications of MOFs, an area that is only really beginning to be studied in any great detail.

[*] A. C. McKinlay, Prof. R. E. Morris
EaStChem School of Chemistry, University of St Andrews
Purdie Building, St Andrews, KY16 9ST (UK)
Fax: (+44) 1334-463-808
E-mail: rem1@st-and.ac.uk
Dr. P. Horcajada, Prof. G. Férey, Dr. C. Serre
Institut Lavoisier, UMR CNRS 8180
Universite de Versailles St Quentin en Yvelines
45 avenue des Etats-Unis, 78035 Versailles (France)
Fax: (+33) 1-3925-4452
E-mail: serre@chimie.uvsq.fr
Dr. R. Gref, Prof. P. Couvreur
Faculté de Pharmacie (CNRS 8612)
Université Paris-Sud, 92296 Châtenay-Malabry (France),
3CNRS 2301, 91190 Gif-sur-Yvette (France)
and CNRS8081, Université PARIS-Sud 91405 Orsay (France)

As one can imagine, the requirements for biological applications, particularly medical applications in vivo, are even stricter than those for other types of commercial activity. Regulatory approval for human and animal applications requires a great investment, but the early signs are that the sheer breadth of properties available in the MOF field offers great hope for the development of new therapeutic and diagnostic applications. Among the properties that must be developed and approved are the materials' toxicology and stability, efficacy, and their ease and reproducibility of manufacture.

2. Toxicology and Stability of MOFs in Biological Settings

With any new class of materials there are inevitable concerns regarding toxicology. As MOFs are now available with a wide range of chemical compositions, many may be toxicologically acceptable for use in healthcare applications (Figure 1). In vitro and in vivo toxicological studies carried out so far (e.g. on iron carboxylate materials) are extremely encouraging, and point to acceptable properties. Intravenous administration of very high doses to rats (up to 220 $mg\,kg^{-1}$) of three different iron carboxylate MOFs, with different structures and organic compositions (MIL-88A, MIL-88B_4CH_3, and MIL-100; for information on these designations see Ref. [3]) based on either endogenous or exogenous hydrophilic/hydrophobic aliphatic/aromatic linkers, indicates no toxicity, with no detrimental effects after acute or subacute exposure.[4] It should also be noted that compounds with the same chemical composition as MOFs have been approved for medical use as prescribed drugs. For instance, iron fumarate, which has the same chemical composition as MIL-88A, is an approved oral iron supplement.[5]

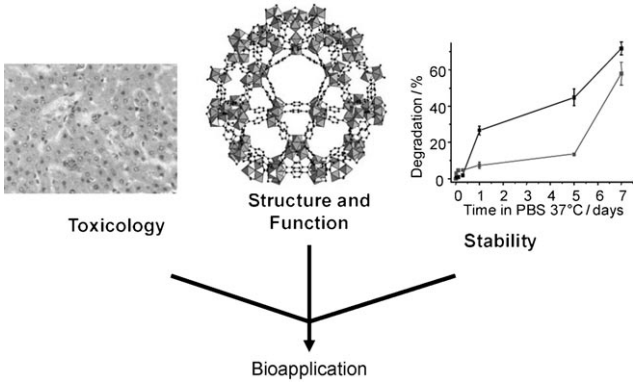

Figure 1. The structure and function of MOFs combined with acceptable toxicology and suitable biodegradation properties offer great promise for bioapplications.

Another recurring topic in discussions regarding the potential applications of MOFs is their stability. It is often stated that the lack of stability hampers their potential uses. This reputation was probably made worse by the relatively poor hydrolytic stability of some of the early and better known MOFs, such as MOF-5.[6] However, for medical applications, a certain amount of chemical instability in the material is a desirable property to avoid endogenous accumulation. As long as the MOF remains intact long enough to complete its function, it can then degrade in situ and the degradation products are dealt with by the body's own systems. Recent studies on the stability of frameworks such as M-CPO-27 or MIL-100 under simulated (e.g. phosphate-buffered saline, PBS, and bovine serum albumin, BSA) physiological conditions show that these solids do not simply dissolve, but may be persistent over days, weeks, or even longer in biological settings.[7] Depending on the crystalline structure, composition, particle size, and formulation, the degradation of MOFs can be modulated over some days to several weeks (up to three weeks) under simulated physiological conditions.[4,8] In addition, preliminary in vivo experiments indicate that iron carboxylate MOFs are biodegradable, with recycling of iron and relatively easy clearance of the linker. Given that some MOFs are likely to exhibit both suitable toxicology and acceptable stability, then what are the areas where MOFs could make a difference in biology and medicine?

3. MOFs as Nanoencapsulators

Given their striking appearance and highly porous structures, one potential biomedical application of MOFs is their use as nanoencapsulators and controlled-release agents. The delivery of therapeutic compounds often requires the use of carrier systems to ensure suitable drug levels at active sites, to increase efficiency and minimize toxicity, and also to increase their half-life, by protecting the drug from overly rapid biodegradation. Until now, polymeric and mixed systems are most commonly used for the controlled release of drugs.[9] Recently, alternative inorganic carriers such as mesoporous silicas and zeolites have been proposed.[10] However, both organic and inorganic routes suffer from important drawbacks, such as low drug-storage capacity and/or too rapid delivery (often referred to as the "burst effect"). Recently, the use of porous MOFs as new drug carriers has been proposed as a way to tackle both of these problems.[11] In tests using ibuprofen as a model drug, MOFs showed extremely high drug capacity (up to 1.4 gram of drug per gram of porous solid) and very long release times (up to three weeks in simulated body fluid). This approach has now been extended with the use of nanoparticles of MOFs (nanoMOFs) compatible with intravenous administration (Figure 2). These nanoMOFs, which are composed of nontoxic and biodegradable porous iron carboxylates, are suitable for the encapsulation and controlled delivery of a large number of therapeutic molecules, including several challenging antitumor and antiretroviral drugs such as busulfan, cidofovir, and azidothymidine triphosphate, as well as cosmetic agents. The exceptionally high drug capacities (up to 42 wt%), as well as the prolonged release (from 3 to 14 days), without any burst effects make the nanoMOFs attractive as new drug nanocarriers. For instance, the mesoporous iron(III) trimesate MIL-100 entraps between 5 and 60 times more busulfan than the best existing polymer or liposome nanosystems and 20 times more azidothymidine triphosphate than the best known carrier. Recently, other examples of MOF drug-delivery systems have been published. The adsorption and delivery of a cationic drug (procainamide; 22 wt%) has been demonstrated from the cationic zinc adeninate MOF and was released after three days under simulated biological conditions in PBS.[12] The cisplatin prodrug (ethoxysuccinato-cisplatin; 12.8 wt%, released over three days under physio-

Russell Morris studied chemistry at the University of Oxford before undertaking postdoctoral studies at the University of California, Santa Barbara. He returned to the UK in 1995 to the University of St Andrews, where he is now a Professor of Chemistry. His research interests include the synthesis, characterization, and application of porous solids. Highlights of his research include the invention of the ionothermal method of synthesis, the development of chiral induction in porous solids, and gas-storage applications of porous materials in medicine.

Christian Serre received an engineering degree from the Ecole Supérieure de Physique et de Chimie Industrielles de Paris. He obtained a PhD in Inorganic Chemistry in 1999. After a postdoctoral fellowship in the USA in 2000, he moved to a permanent CNRS research position in 2001 in the Porous Solids group in Versailles. He has been director of research since 2009. His research topics include the synthesis, structure determination, and applications of porous hybrid solids.

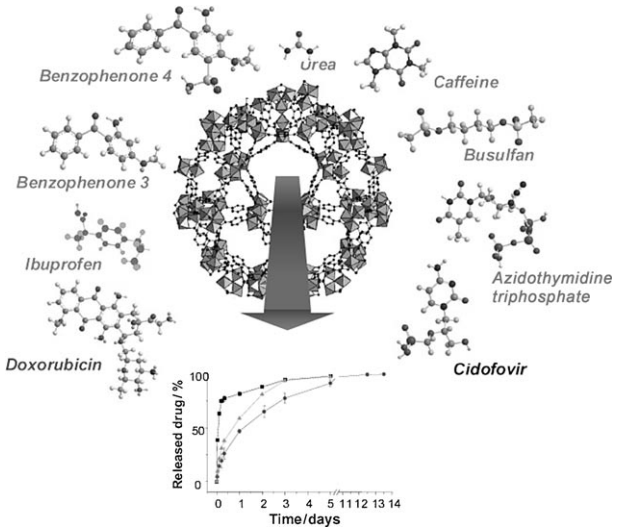

Figure 2. A range of drug molecules with different structures and sizes can be accomodated within MOFs, and then released slowly over several days. The plot shows the release profile for cidofovir (top), azidothymidine triphosphate (middle), and doxorubicin (bottom).

logical conditions in PBS) has been delivered from silica-covered iron terephthalate MIL-101.[13]

It is clear from these results that MOFs exhibit a high potential for drug-delivery applications with many interesting features suitable for the encapsulation and controlled release of drugs: 1) a large number of porous MOFs are available, built up from nontoxic metals (Fe, Zn, Ca, Mg, etc.) and low-toxicity carboxylic or phosphonic acids; 2) most MOFs are biodegradable, at least to some degree, upon exposure to aqueous medium; 3) their hydrophilic–hydrophobic internal microenvironment is adaptable to host a large variety of active molecules with different chemistry; 4) finally, MOFs are versatile: it should be possible to modulate drug delivery by tuning the host–guest interactions through the introduction of various polar or apolar functional groups within the organic part of the MOFs, and/or by changing the structure of the solid (interconnectivity, pore size, flexibility) to control diffusion through the porous structure.

MOFs have also been of great interest for the capture, storage, separation, and delivery of gases. This is also true for biologically and medically active gases. It is quite a paradox that several gases that we normally think of as extremely toxic (e.g. NO, CO) are in fact vital in mammalian biology (in the right amounts). Nitric oxide (NO) is the most well-known of these gases. The discovery of its activity in the cardiovascular system was recognized with the Nobel Prize in Medicine and led to an explosion of research in NO biology and chemistry.[14] NO is an extremely important biological signaling molecule, and its release from a storage material is attractive for many in vitro and in vivo antibacterial, antithrombotic, and wound-healing applications.[15–17] Owing to the physical and chemical characteristics of NO, its release from a material is a method of generating local (rather than systemic) effects, which also has the advantage of reducing undesired side effects. In recent times materials such as polymers,[18,19] functionalized silica nanoparticles,[20] and zeolites[21,22] have all been used to deliver vastly different amounts of NO for different functions. Unfortunately, many of these NO donors generate carcinogenic or pro-inflammatory side products, which may limit their applicability in certain circumstances.[23]

MOFs have attracted attention in this area primarily because of their high storage capacity and the degree to which the interaction between the gas and the framework can be controlled through changes in MOF chemical composition. For instance, M-CPO-27, a honeycomblike MOF, shows exceptional behavior over the entire adsorption–storage–delivery cycle as shown in Figure 3. This material delivers a significant amount of pure NO, something that is important if unwanted side effects are to be avoided. Such a flux of NO has been shown to be active in the vasodilation of porcine arteries (Figure 3c).[24] In contrast, the copper trimesate HKUST-1

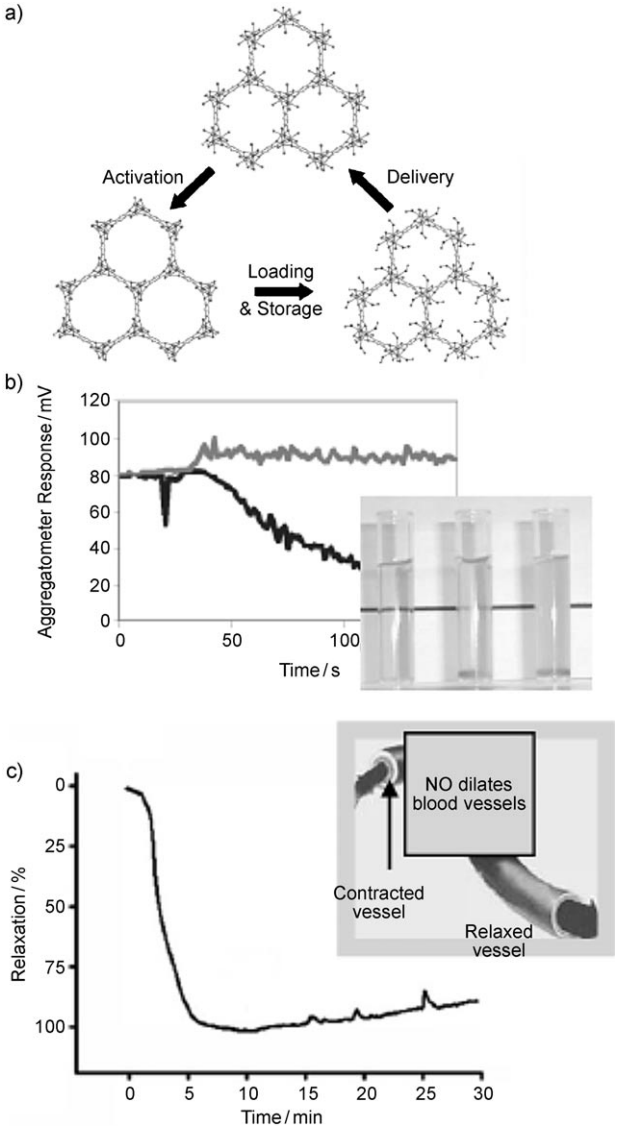

Figure 3. a) MOFs show exceptional gas-storage behavior for bioactive gases such as nitric oxide over the whole adsorption–storage–delivery cycle. NO delivered from MOFs shows bioactivity in antiplatelet experiments on human blood (b) and for the vasodilation of porcine arteries (c). Details can be found in the references.

releases almost 7000 times less NO over the same timescale and under the same conditions. This flux of NO is active for antiplatelet activities, and this MOF shows promise in antithrombosis applications (Figure 3b).[25,26] In between these two extremes other NO-delivering MOFs show a range of delivery capacity, giving tuneable NO delivery based on MOF systems, where the desired flux can be chosen, almost off the shelf, by selecting the right material. In more recent publications materials have been reported that adsorb only NO (and no other gases measured)[27] and others can be functionalized to improve their release properties.[28]

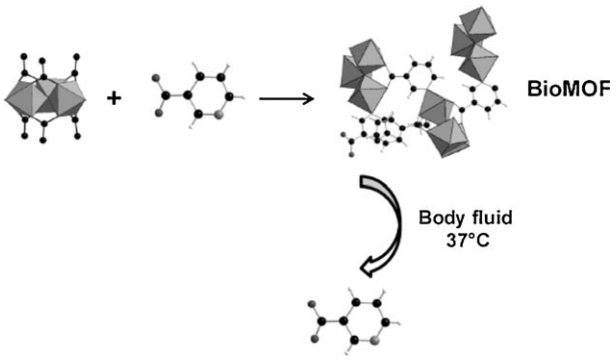

Figure 4. A BioMOF (Bio-MIL1) containing a bioactive linker delivers its bioactive linker, in this case nicotinic acid, into simulated body fluid over a few hours.

4. Bioactive MOFs

MOFs that nano-encapsulate therapeutic molecules clearly show great promise for several different applications. However, in these cases the MOF is a benign biological species. Some MOFs can be prepared from components that are endogenous, which may be more acceptable than a MOF derived from nonbiological material. This approach works particularly well for endogenous organic linkers, in particular those based on amino acids such as Zn-MOFs based on phenylalanine and tyrosine derivatives,[29] and exogenous polytopic ligands with therapeutic activity.

Taking this concept one stage further could lead to the development of a new class of biologically active materials. Up to now, drug delivery from porous solids has been achieved through the encapsulation of the drug by impregnation of the solid from a solution of the active molecule. This process strongly depends on the porosity and interactions. The efficiency of drug delivery to the physiological medium is related to the pore characteristics of the solid (volume and pore size), the nature of the host–guest interactions, and the degradation of the solid. As the MOF is likely to degrade inside the body, the linker is also released, which raises additional toxicity concerns. To prevent such unwanted effects, another approach consists of introducing the therapeutic molecule directly as an organic constitutive part of the MOF framework itself (Figure 4). No pores are required, and the release of the drug molecule is achieved only through the degradation of the solid, without any side effects arising from the release of a nonactive ligand. The small pores iron(II/III) nicotinate Bio-MIL1 and $Fe_2^{III}Fe_{1-x}^{III}Fe_x^{II}O_{1-y}(OH)_y[O_2C\text{-}C_5H_4N]_5[O_2CCH_3]$ ($x \approx 0.15$) illustrate this concept with a release of nicotinic acid and iron in less than a few hours in simulated body fluid (Figure 4).[30] As most drugs exhibit complexing groups such as carboxylates, phosphates, phosphates, amines, and/or heterocycles, this method has potential for the development of fully biocompatible drug-delivery systems.

An alternative to MOFs with biologically active organic linkers consists of MOFs with an active metal. Recently extensive research has been focused on the development of new magnetic resonance imaging (MRI) contrast agents. Firstly, a Gd^{III}-based nanoscale MOF was reported since Gd^{III} is highly paramagnetic (a requirement for useful MRI contrast agents).[31–33] This Gd^{III} nanoMOF showed large relaxivities several orders of magnitude higher than those of other Gd^{III}-based MRI contrast agents. However, the toxicity of the Gd^{III} nanoMOF would probably be too problematic for clinical use. Possibly more acceptable is a Mn^{II}-based nanoMOF (Mn^{II} is much less toxic than its Gd^{III} counterpart).[34] Although the relaxivities observed were modest, they proved that site-specific imaging would be possible if a silica-based coating is used on nanoMOFs to delay the leaching of metal ions until they reach the specific site.

Combining bioactivity with imaging in MOFs also leads to the exciting possibility of MOF-based theranostics—following drug delivery within the body through the imaging properties of the MOF. Nanoscale iron terephthalate MIL-101 can be surface-modified post-synthetically through the use of aminoterephthalate groups. An anticancer drug (12.8 wt%) and a fluorophore (5.6–11.6%) were then loaded onto the MOF in order to combine in vitro optical imaging and anticancer therapy. However, nanoparticles had to be covered with silica to increase the stability of the MOF and control the drug/fluorophore release, since the fluorophore agent is active when it is free as a result of the quenching effect of Fe^{III}.[13]

A better approach for theranostics applications is to use nanoparticles of nontoxic porous iron(III) carboxylates, which provide very interesting relaxivity times, exceptionally high loadings, and controlled delivery of various challenging cytotoxic drugs or cosmetics. These nanoparticles, which not only possess nontoxic paramagnetic iron trimers within the interconnected porous structure but also higher quantities of coordinated/free water molecules, have shown r2 relaxivities up to $50\ s^{-1}\,мм^{-1}$ (at 9.4 T), which is considered sufficient for in vivo use (Figure 5).[4] In all cases, whatever the composition of the Ln-, Mn-, or Fe-based carboxylate MOFs, the high relaxivity values are likely arise because water molecules bound to the acidic Lewis metal centers exchange their protons with those of the free water molecules present within the pores, a feature well known in many MOFs.

5. Manufacture and Formulation

One aspect that has not been studied much to date is the formulation of MOFs in a suitable form for biological

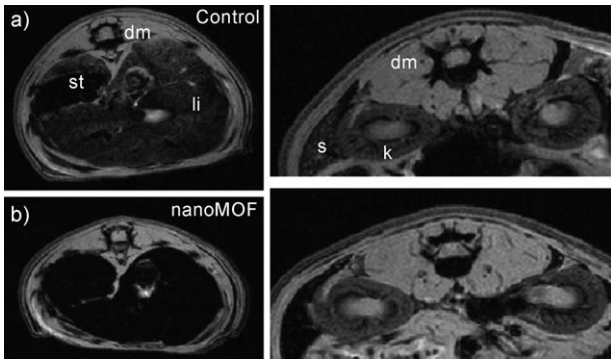

Figure 5. Magnetic resonance images after exposure of rats to iron-based MOFs, acquired with gradient echo sequence for a) control rats and b) rats injected with 220 mg kg^{-1} in liver (left) and spleen (right) regions (dm: dorsal muscle; k: kidney, li: liver; s: spleen; st: stomach). Results from Dr. B. Gillet and Dr. C. Sebries (Gif sur Yvette, France).

application. One can envisage different administration modes for MOFs (oral, intravenous, intranasal, cutaneous, and others), but each method requires its own particular formulation. Control of particle size is a key point, not only in administration routes that require small nanoparticles for avoiding tissue damage (intravenous, intraperitoneal, subcutaneous, intranasal, and intraocular) but also for producing stable and reproducible formulations (patches, pellets, tablets etc). In vivo administration of nanoMOFs sets particular requirements to avoid embolism, such as small and homogeneous particle size (<200 nm) and high stable suspensions in aqueous medium (without aggregation or precipitation). First studies have shown that the synthesis of nanoparticles of MOFs does not require specific and complex synthetic methods. Inverse emulsions[31,33,34] and microwave-assisted[4,35] solvothermal synthesis conditions have been implemented to obtain MOF nanoparticles of suitable size and with narrow particle size distribution (Figure 6).

Particle stability and/or aggregation in solution is, at this point, a critical factor to avoid the formation of large aggregates that would prevent embolism after in vivo injection. However, several examples of stable suspensions of MOF nanoparticles have been developed recently,[36–38] and even if much research is needed to better address this critical point, these results are very promising for the future of biomedical nanoapplications of MOFs.

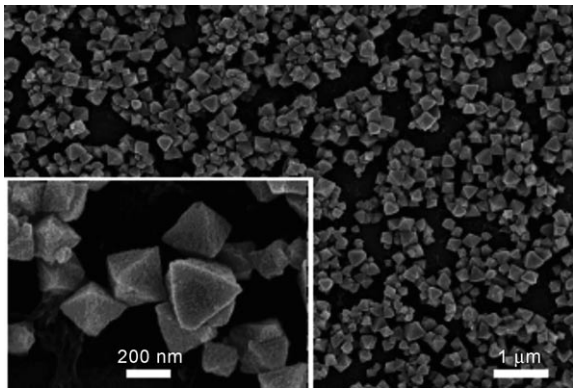

Figure 6. Nanoparticles of the mesoporous iron aminoterephthalate MIL-101 synthesised by the hydrothermal microwave-assisted method.

5.1. Surface Modification

Another interesting aspect, especially for nanoparticles, is the surface modification with different organic molecules. This could further stabilize the nanoMOF suspensions, provide attractive "stealth" properties, and also ensure that the nanoMOFs reach the active sites and/or bioadhesion.

For biological applications, the surface of iron carboxylate nanoMOFs can be engineered by coating with a hydrophilic polymer, poly(ethylene glycol) (PEG),[4] to control the interaction with biological media and to increase the blood circulation half-life from minutes up to several hours. PEG contents up to 17 wt % were obtained, which is higher than those described as sufficient to ensure "stealth" properties.[39] Similarly, the surface of the nanoparticles could be also functionalized, either during the synthesis or post-synthetically, with amphiphilic polysaccharides dextran-fluorescein-biotin or chitosan to aid in addressing, in vitro imaging, and/or bioadhesion.[4] By the same principle, silica-covered manganese terephthalate or trimesate can be modified with a fluorescence moiety (rhodamine) and the cyclic pentapeptide c(RGDfK) ($\alpha_v\beta_3$ integrin; overexpressed in many angiogenic cancers) for in vitro imaging and targeting, respectively.[34]

Finally, surface grafting is another means to introduce imaging properties. This was achieved, for instance, through the surface covering of either silica-covered nanoMOFs with a Tb complex and dipicolinic acid[32] or nanoparticles of iron terephthalate MIL-101 with silica. The particles were then both further surface-functionalized with an in vitro imaging agent (1,3,5,7-tetramethyl-4,4-difluoro-8-bromomethyl-4-bora-3*a*,4*a*-diaza-*s*-indacene) and a cisplatin prodrug (ethoxy-succinato-cisplatin), respectively.[13]

5.2. Composites

Composite materials, formed by mixing two immiscible materials, are also of interest. The formulation of MOFs for biomedical applications could thus be achieved by an appropriate mixture of the MOFs with different organic or inorganic materials, such as polymers or silica, either through dispersion of the MOF particles into the matrix itself or by the production of core–shell composites by covering the MOFs particles with one or several materials. Concerning the first approach, the copper trimesate MOF HKUST-1 was introduced into a monolithic macroporous hydrophilic polyHIPEs (porous polymers from high internal phase emulsions).[40] It is also possible to use a cream/ointment preparation, which has proved particularly successful for delivering gases onto human skin using zeolites. Depending on the nature of the cream, the delivery rate of the gas can be changed, highlighting the role that the formulation can play in determining the success of a drug-delivery material.[22] Another approach

deals with the covering of MOF nanoparticles with a polyvinylpyrrolidone polymer and a silica shell to avoid fast degradation and minimize the effects of toxic metals.[13,32,34]

6. Conclusion and Outlook

Given that there are already established inorganic, polymeric, and mixed materials for the delivery of therapeutic agents, what is it about MOFs that makes them so attractive for these applications? First of all, MOFs are a unique class of porous hybrid solids with a wide range of compositions, structures, tuneable pore sizes, and pore volumes. Their very high porosity means that very large loadings of biological molecules, including anticancer drugs or biogases, can be entrapped within the pores of the MOFs. The capacities significantly exceed those of the existing nanocarriers. Combining this with the highly available functionality in MOFs, in the form of either metal sites or functional groups on the linkers, leads to opportunities to control the interaction with guests rather more precisely than is possible in most other systems, so that not only the high capacity but the release into the environment can be tuned more effectively. In addition, the fact that MOFs are usually highly crystalline is a distinct advantage when one wants to characterize the material so that its properties can be understood better. This understanding undoubtedly aids in tailoring the properties of any material to a particular target application.

First studies have also shown that some MOFs are, at the preclinical level, nontoxic, while their degradability under in vitro physiological conditions have been assessed as suitable. A key advantage of MOFs is also the possibility of directly introducing a bioactive molecule as the linker or a bioactive metal as the inorganic part of the MOF; in some cases imaging properties pave the way for the use of bio-nanoMOFs for theranostics.

This field of research, which has emerged only very recently, has focused on the use of selected MOFs for a few given applications. Thus, considering the large number of existing MOFs and the wide range of possible bioapplications, there is still a lot to do in this domain. In addition, challenges are still numerous for the practical use of MOFs for bioapplications. First, the control of MOF particle size is critical for producing stable formulations amenable to different administration routes. Preventing the agglomeration of nanoparticles in solution is also a crucial issue that needs to be fully understood. Another main aspect concerns the particle surface engineering through the presence of reactive groups on surface (metals, counter anions, noncoordinating complexing functions, functional groups of the linker). In this way it may be possible to improve stabilities and incorporate additional and attractive properties such as furtivity (or stealth properties), addressing the active sites, detection, and/or bioadhesion. Third, for in vivo applications, we need to know how MOF nanoparticles cross natural barriers. Fourth, since first toxicity studies have shown the unharmful character of selected iron carboxylates, other MOF compositions should be examined and the in vivo degradation mechanisms determined. Fifth, the development of practical and stable formulations meeting the requirements of a given administration is required for real applications. One possibility would be to develop organic or inorganic composites of MOFs suitable, for example, for patches or creams. Finally, even if the development of MOFs for biomedical applications is still at an early stage, results show that MOFs have some significant advantages over existing bioorganic or inorganic systems. Considering the huge number of drug molecules that have been developed but are still not used in real applications owing to poor bioavailability, this clearly strengthens the interest in developing further the use of MOFs for bioapplications.

R.E.M. thanks the GEMI Fund and the E.P.S.R.C for funding. R.E.M is a Royal Society Wolfson Merit Award Holder. P.H and C.S. also thank the EU for the funding via the ERC-2007-209241-BioMOF, as well as scientists working on the project.

Received: January 5, 2010
Published online: July 22, 2010

[1] a) G. Férey, *Chem. Soc. Rev.* **2008**, *37*, 191 – 214; b) Themed issue: Metal-organic frameworks, *Chem. Soc. Rev.* **2009**, *38*, 1201.
[2] R. E. Morris, P. S. Wheatley, *Angew. Chem.* **2008**, *120*, 5044 – 5059; *Angew. Chem. Int. Ed.* **2008**, *47*, 4966 – 4981.
[3] Please note that the complex architectures of MOFs are designated by codes such as MIL-88, MIL-101, M-CPO-27, etc. These codes often originate from the first place of synthesis—for example, MIL stands for Material from Institut Lavoisier—and generally define the topological architecture of the materials. A different code indicates different shapes of pores and cavities, and often a different chemical composition. For the compounds mentioned in the text the organic linker molecules used are fumarate, tetramethylterephthlate, and benzene-1,3,5-tricarboxylate.
[4] P. Horcajada, T. Chalati, C. Serre, B. Gillet, C. Sebrie, T. Baati, J. F. Eubank, E. Heurtaux, P. Clayette, C. Kreuz, J.-S. Chang, Y. K. Hwang, V. Marsaud, P.-N. Bories, L. Cynober, S. Gil, G. Férey, P. Couvreur, R. Gref, *Nat. Mater.* **2010**, *9*, 172 – 178.
[5] Ferrous fumarate is sold as an iron supplement by Pharmics inc (http://www.pharmics.com/) under the trade name Ferrets.
[6] J. J. Low, A. I. Benin, P. Jakubczak, J. F. Abrahamian, S. A. Faheem, R. R. Willis, *J. Am. Chem. Soc.* **2009**, *131*, 15834 – 15842.
[7] N. J. Hinks, A. C. McKinlay, B. Xiao, P. S. Wheatley, R. E. Morris, *Microporous Mesoporous Mater.* **2010**, *129*, 330 – 334.
[8] P. Horcajada, C. Serre, G. Maurin, N. A. Ramsahye, F. Balas, M. Vallet-Regi, F. Taulelle, G. Férey, *J. Am. Chem. Soc.* **2008**, *130*, 6774 – 6780.
[9] D. Peer, J. M. Karp, S. Hong, O. C. Farokhzad, R. Margalit, R. Langer, *Nat. Nanotechnol.* **2007**, *2*, 751 – 760.
[10] M. Manzano, M. Colilla, M. Vallet-Regí, *Expert Opin. Drug Delivery* **2009**, *6*, 1383 – 1400.
[11] P. Horcajada, C. Serre, M. Vallet-Regi, M. Sebban, F. Taulelle, G. Férey *Angew. Chem.* **2006**, *118, 6120–6124; Angew. Chem. Int. Ed.* **2006**, 45, 5974 – 5978; *Angew. Chem. Int. Ed.* **2006**, *45*, 5974 – 5978.
[12] J. An, S. J. Geib, N. L. Rosi, *J. Am. Chem. Soc.* **2009**, *131*, 8376 – 8377.
[13] K. M. L. Taylor-Pashow, J. D. Rocca, Z. Xie, S. Tran, W. Lin, *J. Am. Chem. Soc.* **2009**, *131*, 14261 – 14263.
[14] S. Moncada, R. M. J. Palmer, E. A. Higgs, *Pharmacol. Rev.* **1991**, *43*, 109 – 142.

[15] S. Fox, T. S. Wilkinson, P. S. Wheatley, B. Xiao, R. E. Morris, A. Sutherland, A. J. Simpson, P. G. Barlow, A. R. Butler, I. L. Megson, A. G. Rossi, *Acta Biomater.* **2010**, *6*, 1515 – 1521.
[16] H. F. Zhu, B. Ka, F. Murad, *World J. Surg.* **2007**, *31*, 624 – 631.
[17] M. R. Miller, I. L. Megson, *Br. J. Pharmacol.* **2007**, *151*, 305 – 321.
[18] P. G. Parzuchowski, M. C. Frost, M. E. Meyerhoff, *J. Am. Chem. Soc.* **2002**, *124*, 12182 – 12191.
[19] F. DeRosa, M. R. Kibbe, S. F. Najjar, M. L. Citro, L. K. Keefer, J. A. Hrabie, *J. Am. Chem. Soc.* **2007**, *129*, 3786 – 3787.
[20] J. H. Shin, M. H. Schoenfisch, *Chem. Mater.* **2008**, *20*, 239 – 249.
[21] P. S. Wheatley, A. R. Butler, M. S. Crane, S. Fox, B. Xiao, A. G. Rossi, I. L. Megson, R. E. Morris, *J. Am. Chem. Soc.* **2006**, *128*, 502 – 509.
[22] M. Mowbray, X. J. Tan, P. S. Wheatley, R. E. Morris, R. B. Weller, *J. Invest. Dermatol.* **2008**, *128*, 352 – 360.
[23] K. D. Kröncke, C. V. Suschek, *J. Invest. Dermatol.* **2008**, *128*, 258 – 259.
[24] A. C. McKinlay, B. Xiao, D. S. Wragg, P. S. Wheatley, I. L. Megson, R. E. Morris, *J. Am. Chem. Soc.* **2008**, *130*, 10440 – 10444.
[25] B. Xiao, P. S. Wheatley, X. B. Zhao, A. J. Fletcher, S. Fox, A. G. Rossi, I. L. Megson, S. Bordiga, L. Regli, K. M. Thomas, R. E. Morris, *J. Am. Chem. Soc.* **2007**, *129*, 1203 – 1209.
[26] S. Bordiga, L. Regli, F. Bonino, E. Groppo, C. Lamberti, B. Xiao, P. S. Wheatley, R. E. Morris, A. Zecchina, *Phys. Chem. Chem. Phys.* **2007**, *9*, 2676 – 2685.
[27] B. Xiao, P. J. Byrne, P. S. Wheatley, D. S. Wragg, X. B. Zhao, A. J. Fletcher, K. M. Thomas, L. Peters, J. S. O. Evans, J. E. Warren, W. Z. Zhou, R. E. Morris, *Nat. Chem.* **2009**, *1*, 289 – 294.
[28] M. J. Ingleson, R. Heck, J. A. Gould, M. J. Rosseinsky, *Inorg. Chem.* **2009**, *48*, 9986 – 9988.
[29] Y. Xie, Z. Yu, X. Huang, Z. Wang, L. Niu, M. Teng, J. Li, *Chem. Eur. J.* **2007**, *13*, 9399 – 9405.
[30] S. R. Miller, D. Heurtaux, T. Baati, P. Horcajada, J.-M. Grenèche, C. Serre, *Chem. Commun.* **2010**, *46*, 4526 – 4528.
[31] W. J. Rieter, K. M. L. Taylor, H. An, W. Lin, W. Lin, *J. Am. Chem. Soc.* **2006**, *128*, 9024 – 9025.
[32] W. J. Rieter, K. M. L. Taylor, W. Lin, *J. Am. Chem. Soc.* **2007**, *129*, 9852 – 9853.
[33] K. M. L. Taylor, A. Jin, W. Lin, *Angew. Chem.* **2008**, *120*, 7836 – 7839; *Angew. Chem. Int. Ed.* **2008**, *47*, 7722 – 7725.
[34] K. M. L. Taylor, W. J. Rieter, W. Lin, *J. Am. Chem. Soc.* **2008**, *130*, 14358 – 14359.
[35] S. H. Jhung, J.-H. Lee, J. W. Yoon, C. Serre, G. Férey, J.-S. Chang, *Adv. Mater.* **2007**, *19*, 121 – 124.
[36] P. Horcajada, C. Serre, D. Grosso, C. Boissière, S. Perruchas, C. Sanchez, G. Férey, *Adv. Mater.* **2009**, *21*, 1931 – 1935.
[37] H. Bux, F. Liang, Y. Li, J. Cravillon, M. Wiebcke, J. Caro, *J. Am. Chem. Soc.* **2009**, *131*, 16000 – 16001.
[38] A. Demessence, P. Horcajada, C. Serre, C. Boissière, D. Grosso, C. Sanchez, G. Férey, *Chem. Commun.* **2009**, 7149 – 7151.
[39] R. Gref, A. Domb, P. Quellec, T. Blunk, R. H. Müller, J. M. Verbavatz, R. Langer, *Adv. Drug Delivery Rev.* **1995**, *16*, 215 – 233.
[40] M. G. Schwab, I. Senkovska, M. Rose, M. Koch, L. Pahnke, G. Jonschker, S. Kaskel, *Adv. Eng. Mater.* **2008**, *10*, 1151 – 1155.

