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Clinical translation of metal–organic frameworks

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This Comment discusses metal–organic frameworks and their progress towards translation in a health-care setting. We explore their prospects in clinical applications, why translation seems slow, and what opportunities and obstacles await as they move towards the clinic.

Engineered nanomaterials are emerging tools to diagnose, sense and treat diseases with high selectivity and sensitivity. In particular, interest in metal–organic frameworks (MOFs) as drug delivery and diagnostic materials has soared in the past decade, with exponential growth in publications jumping from 351 in 2012 to >3,500 in 2022 (PubMed July 2023). Over the course of their development, MOFs have carried increasingly sophisticated drugs, from ibuprofen to enzymes, viruses and mRNA, and shown that they can improve the stability of loaded cargo while enhancing delivery efficacy (Fig. 1). Despite the abundant literature, their translation into the clinic has been slow; only one clinical trial thus far has seen MOFs delivered to humans. This commentary discusses why research on translational potential is rare, what clinical opportunities we see and what research directions may address current obstacles.

Why research on translational potential is rare

MOFs are characterized by their unique structure — a porous matrix of metal ions or clusters connected by organic ligands through strong coordination bonds. Their unusual set of properties, including tunable host–guest interactions, easy surface functionalization, high drug loading capacity (sometimes exceeding 50% w/w) and good biodegradability, make them ideal candidates for drug carriers, imaging agents, radio-sensitizers, vaccine adjuvants or components in medical devices[1]. Despite being featured in many publications and having around 90,000 known structures[2], only one MOF has entered a phase I clinical trial. This slow progress raises questions as to why. The biocompatibility of the transition metals used in the framework is potentially a key issue, but it is important to note that MOFs have the unique ability to organize metals into micro-nano structures with high surface area, which is a highly translatable feature. Researchers — authors and reviewers — need to remember the ancient axiom "*dosis sola facit venenum*", or "the dose makes the poison", when considering the therapeutic application of MOFs.

Exploring translatability in MOFs can be challenging owing to the vast range of structures that can be created through reticular chemistry. The many complexities surrounding the toxicity of MOFs are comprehensively and clearly explained in a recent review[3]. For instance, the review highlights the structural diversity of the 'top 10 MOFs used in drug delivery'. This list of MOFs contains 9 different metals: Mg, Cr, Mn, Fe, Co, Ni, Cu, Zn and Zr. The review also discusses the complexities in determining the actual 'toxicity' of a MOF, given that size and physical shape are crucial factors often overlooked. Despite these complexities, the review attempts to order the relative toxicities of MOFs and their ligands, with Ca-, Bi- and Eu-based MOFs being the most biocompatible, followed closely by Ti- and Fe-based MOFs. Zn-based MOFs were slightly more cytotoxic, while Cu-based MOFs were identified as the most cytotoxic. However, if we order these metals' known oral median lethal dose (LD_{50}; see Supplementary Information), Fe is comparable to Cu in toxicity. This begs the question, why would metals suddenly become more toxic when incorporated into a MOF? Again, we come back to size, shape and application: MOF nanoparticles — unlike free metal salts — are easily endocytosed, which makes direct comparisons with the free metal impossible[3]. Consequently, it appears very hard to predict toxicity based on composition; within a given formulation, and within different sizes, different morphologies (anisotropic versus isotropic particles) must be assessed separately. Unfortunately, such data are not available to handpick a MOF for a specific clinical application.

Even then, it is important to remember that what is toxic in some applications is within a safe therapeutic window for others. ZIF-8 appears more toxic than most other MOFs in vitro[3]. However, when evaluated as a vaccine adjuvant, ZIF-8 is actually less toxic at concentrations above 50 μg ml^{-1} than aluminum hydroxide nanoparticles, which have been used as vaccine adjuvants for almost 80 years[4]. The method and mode of administration is also critical. ZIF-8 microparticles injected into the skin or lavaged into the lungs have little tissue-specific and systemic toxicity owing to their ability to form a large depot, while ZIF-8 nanoparticles administered directly into the tail vein of mice have a very narrow therapeutic window.

Translating MOFs is also complicated by their instability in many biological fluids like serum and blood. The metal centres in MOFs are kinetically labile and can easily be stripped out by endogenous proteins and biological anions. Albumin and phosphates are well known to compete for the metals in MOFs, particularly Zn and Zr, making MOFs containing either metal very unstable in the biological milieu. If these MOFs are used as drug carriers, they will prematurely release encapsulated drugs in the presence of phosphate or albumin, leading to structural degradation and reduced effectiveness. Thus, it is crucial to demonstrate the stability of MOF formulations in serum — not just cell media or buffered water — and under appropriate pH and enzymatic conditions. To address this issue, researchers are exploring surface modifications to enhance colloidal stability, water dispersity, blood circulation and targeting capabilities of MOFs[5]. Grafting polymers such as polyethylene glycol derivatives onto MOFs increases their colloidal stability in blood or tissue and improves their circulation time and therapeutic utility[5].

With this said, the kinetic lability of the metal is also a highly exploitable feature, and MOFs are gaining popularity as degradation-induced

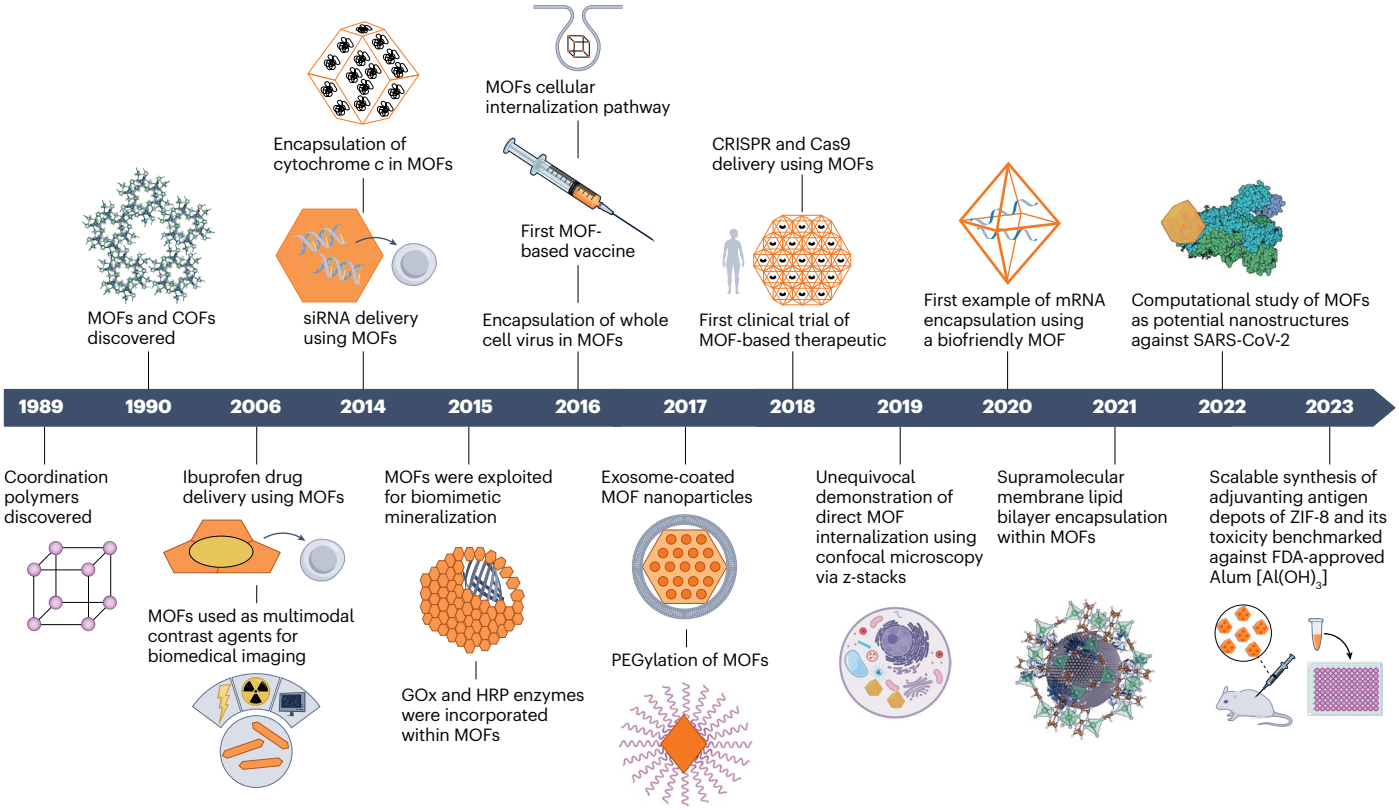

Fig. 1 | A rough timeline of important advancements in MOFs and their emerging applications in drug delivery and diagnosis. See Supplementary Fig. 1 for a more detailed timeline with references. COF, covalent organic framework; MOF, metal–organic framework; PEG, polyethylene glycol; siRNA, short interfering RNA.

slow-release materials. When locally administered within the skin, sinuses or tumour, MOFs form a depot that prolongs the release of drugs and biomacromolecules over extended periods, suggesting that this 'downside' in serum has exploitable benefits in other tissues.

What clinical opportunities we see

It should be clear why the first clinical trial involving a MOF administers directly into a tumour, depending on transient tissue residency, and focuses on the therapeutic aspects of the metal centre. Nanosized MOFs based on hafnium nodes and porphyrin linkers (RiMO) started phase I testing (NCT05838729 and NCT03444714) in April 2018 as a component of cancer radiotherapy treatment. Because the heavy Hf atoms have a high tendency to absorb X-rays and produce reactive oxygen species, this material enhances the effects of X-ray radiotherapy and thus reduces the amount of radiation required, resulting in fewer negative side effects. Additionally, the treatment may trigger a systemic response that can eliminate both treated and untreated tumours[6]. This trial is an exciting development: not only does the scientific community get to see for the first time how MOFs perform in humans, but if RiMO-301 moves to phase II trials, it may be able to be directly benchmarked against an analogous non-MOF hafnium oxide polymer composite nanoparticle formulation called NBTXR3, which has been undergoing human testing (NCT04505267) for the same application.

It is important to note that MOFs need not be drugs for them to be clinically translated. They have shown promise as components in new medical devices for years, given the intrinsic properties, including high surface area, redox activity of metal ions, guest-carrying capabilities and antimicrobial properties of associated metal centres. Zn- and Cu-based MOFs are examples of antibacterial materials used in this capacity[7], and the metal centres (including Zn, Cu, Se and In) of MOFs incorporated into NO-releasing substrates have been shown to enhance the scaffold's antimicrobial activity without notable biocidal agent leaching, reducing bacterial adhesion and viability[8]. Although obtaining FDA approval for medical devices can be challenging, it is generally less complicated than applying for approval for a new drug. Thus, it is somewhat surprising that the first clinical trial utilizing a MOF's metal chemistry is for a new drug candidate rather than a component for a medical device or clinical assay, considering the notable role that nanoparticle size, controlled chemistry and biocidal activity can play in these latter areas.

What research directions may address current obstacles

We are enthusiastic about MOFs integrated into devices or becoming active pharmaceutical ingredients. To move MOFs more towards translation, there are several things that researchers can do.

Embrace the metal. Research using the metal itself as a therapeutic or adjuvant or exploiting organometallic chemistry's unique properties is already gaining momentum. Many metals, including Al, Mn and Zn, are known to modulate our immune system. High-Z metals are ideal for X-ray contrast agents and radiosensitizers. Cu's biocidal and redox activity is useful outside of the body and for delivery in metabolic diseases (such as Menkes disease or copper deficiency). Many of these applications require only low doses to be effective.

Comprehensive preclinical toxicity evaluation in MOFs. Very few MOF toxicity studies have been conducted in preclinical animal models. So far, only murine models, rabbits and zebrafish have been utilized to assess the toxicity profile of MOFs in vivo, primarily focusing on changes in biocompatibility, systemic toxicity, organ function and histopathology following a single dose administration of MOFs. Comprehensive long-term multi-dose studies are crucial to grasp the potential cumulative effects of MOF exposure. Therefore, expanding the number and diversity of preclinical animal models, such as

non-human primates, would enhance our understanding of the risks to humans and aid in developing safe and effective clinical MOF-based therapeutics.

Local administration versus systemic administration and toxicity. Most in vivo research using MOFs has focused on intravenous delivery. An emerging direction is to explore local delivery of MOFs, including assessing their potential in tissue depots and for non-invasive administration routes, such as biolistic, oral or intra-nasal delivery. Understanding of these alternative routes is still in its infancy, and biocompatibility or biodistribution of MOFs delivered in these ways is an active work area. Biolistic delivery of MOFs shows potential for controlling drug biodistribution and release kinetics in vivo. This control is achieved by altering the carrier gas without modifying the formulation itself[9]. Only one paper has examined the toxicity and metabolic outcomes of intranasal administration[10]. Consequently, delving into alternative administration routes while carefully assessing their metabolic outcomes and toxicity will pave the way for a successful clinical translation of MOFs.

Finally, materials scientists and pharmaceutical and preclinical researchers will need to collaborate to fully explore the capabilities of MOFs for clinical translation. Funding these research efforts will also be vital to advancing the application of MOFs in the clinical setting.

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Competing interests

The authors declare no competing interests.

Additional information

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