Narrative Review Article

Challenges In the Clinical Translation of Metal Organic Frameworks: A Review

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ABSTRACT

Metal Organic Frameworks (MOFs) are a novel class of materials that have great promise in the biomedical field owing to their preclinical success. Despite 15 years of demonstrated success in preclinical trials, only two hafnium-based MOFs (RiMO-301 and RiMO-401) have entered clinical testing. This paper aims to examine this bench-to-bedside gap in MOFs with the question: What are the key factors that contribute to the success of MOFs in preclinical studies but hinder their translation into the clinic? Through a comparative analysis of 19 MOFs, including well studied MOF groups such as Zeolitic imidazolate framework MOFs (ZIF) and Material Institute of Lavoisier MOFs (MIL), this literature review will identify the advantages over conventional nanocarriers established from preclinical testing, and the multifaceted barriers hindering clinical translation. Furthermore, it discusses systematic strategic approaches to guide MOF research into clinical transition. By synthesizing these insights, the paper aims to provide a roadmap for overcoming transitional bottlenecks.

Keywords: MOFs (Metal-organic frameworks); Clinical translation; Nanoparticles; Drug delivery; Biomedicine

INTRODUCTION

Since the start of the 21st century, harnessing the abilities of nanotechnology is arguably one of the most ambitious goals which will transform material science. Particles with dimensions of 1×10^{-9}m, Nanoparticles (NPs), have gained significant attention in the past few decades due to their unique physiochemical properties, enhanced surfaces, and exceptional surface area to volume ratio (1, 2), allowing NPs to become embedded in several scientific fields. Among these NPs, Metal Organic Frameworks (MOFs) have emerged as one of the most promising materials, offering structural and chemical tunability far beyond conventional NPs documented in literature.

MOFs are crystalline porous materials consisting of an inorganic metal cluster coordinated to multidentate organic ligands forming a framework with nanoporous cavities, classifying them as a sub class of coordination polymers that can be 1D, 2D, and 3D (2, 3). In 1995, Omar M. Yaghi and colleagues published one of the earliest demonstrations of a thermally stable MOF, constructed by stacking cobalt–carboxylate layers separated by pyridine ligands, forming ordered channels capable of selectively binding aromatic guest molecules (3). This work introduced a modular design principle that would evolve into the widely adopted Secondary Building Unit (SBU) concept (4, 5) – predictable, recurring

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metal–ligand clusters that serve as the foundation of framework construction. In 1998, Yaghi's team further advanced the field by synthesizing Zn(BDC)·(DMF)(H_2O), a MOF built from Zn–carboxylate SBUs and 1,4-benzenedicarboxylate linkers (6). This structure not only preserved its crystallinity upon guest removal but also exhibited reversible nitrogen and carbon dioxide sorption and remained thermally stable up to 300°C (4), providing the first demonstration of permanent microporosity in MOFs. This breakthrough established MOFs as tunable, robust analogues to zeolites, creating applications in gas storage, drug adsorption, catalysis, and molecular recognition (7, 8). The profound impact of this foundational work was later recognized when the pioneers of MOFs, including Susumu Kitagawa of Kyoto University, Richard Robson of the University of Melbourne, and Yaghi himself, were awarded the 2025 Nobel Prize in Chemistry for establishing the design principles that created these versatile materials.

MOF modularity enables theoretically unlimited metal node and organic linker combinations via computational simulation (9, 10). This versatility has led to the creation of over 100,000 unique MOFs to date (11), each with tunable pore sizes, topologies, and chemical functionalities tailored to specific applications. In 2010, Miller et al. conducted the first study on bio-MOF based drug delivery, demonstrating the potential biomedical application of MOFs. His team showed how their high porosity and modularity could be leveraged to encapsulate and release pharmaceutical agents in a controlled and protective manner (12). Since then, MOFs have been investigated extensively for biomedical applications including drug delivery (13–15), biosensing (14, 16), photodynamic therapy (PDT) (17), and imaging (14). Their remarkable surface area, chemical tunability, and biodegradability under physiological conditions have enabled researchers to engineer structures that respond to certain biological triggers such as pH, redox gradients, or enzymatic environments (14).

Preclinical studies suggest that MOF advancement has achieved a level where scientists are able to fine tune and optimize the size, surface, and porosity for specific applications. Among these parameters, surface functionalization has emerged as a critical in enhancing the biological performance of MOFs. The process often involves the application of surface coatings such as silica, proteins, lipids, synthetic polymers like PEG, or targeting ligands which can improve colloidal stability, solubility, and enhance localization at specific sites (14, 16). In the context of drug delivery, MOFs are synthesized at around 50~200 nm (15) to exploit the Enhanced Permeability and Retention (EPR) effect in cancer tissue (15), facilitate cellular uptake via endocytosis, and prolong systemic circulation (18). Observed preclinical success also highlights the role of tunable porosity in the context of drug loading. The intrinsic porosity of MOFs has yielded loading capacities up to 81 wt% (NU-1000 MOF) (14). Put into perspective, this significantly surpasses preceding drug carriers like liposomes (0.4 wt%) (13) and PLGA (33.7%) (19) by up to 200 times. This drastically increases therapeutic payload efficacy, reducing the actual dosage required for the drug to reach target tissues (15). Most importantly, MOFs would not have any biomedical value if they are not biocompatible with organisms. Transition metals used in MOF structures may be an issue when it comes to biocompatibility, however, *in vitro* viability assays suggest that Ca, Mg, Zn, Fe, Ti, and Zr are appropriate metal centers for the construction of MOFs (18, 20). However, the MOF dosage still needs to be considered according to appropriate LD50 values–understanding *dosis sola facit venenum,* even water is poisonous when too much is consumed.

Despite such pre-clinical success observed in laboratories, only two hafnium (Hf) based "RiMO" MOFs for enhanced radiotherapy have entered clinical trials. The contrast between preclinical success and clinical translation over the 30 years of MOF studies has not been majorly discussed. However, it is clear that MOFs work in controlled environments but something prevents them from advancing to human applications at scale. Most papers fail to address the challenges of MOF clinical translation at a larger scale, often only including family specific challenges. Through a comparative analysis of representative MOFs with varying structures, applications, and biological interfaces, this review examines the challenges present in MOF studies for biomedical applications ranging from high levels of unpredictability to regulatory bottlenecks. In doing so, it hopes to provide a clearer picture of current limitations and offer strategic directions for future research to bridge the gap between bench and bedside.

SUCCESS OF MOFS IN PRECLINICAL STUDIES

The coordination between metal nodes and organic linkers are essential in the preclinical success of MOF structures. Metals provide stability to the structure owing to their rigidity (4,21), meanwhile the organic

components provide the structure with flexibility, and therefore functionality (13,18,22). Hence, the combination of stability, flexibility, and functionality, makes MOFs valuable in several applications, but especially, both *in vitro* and *in vivo* studies consistently showed that MOF based nanocarriers have significant advantages over conventional nanocarriers in drug delivery (18, 21). Some MOFs, e.g. ZIF-8, MIL-100, and PCN-224, possess great drug-loading capacities, (13,14) efficient cellular internalization (14, 15, 18), as well as release characteristics with acidic or redox-sensitive triggers (13, 14), thus achieving enhanced cytotoxicity (18, 23) to various cell lines of cancer (24) as well as superior delivery of sensitive biomolecules, for example, siRNA and proteins (21). Such findings are also shown in *in vivo* studies, where MOFs displayed extended circulatory time (16, 18), tumor-targeted distribution due to a superior EPR effect (16, 23, 25), as well as lower systemic toxicity in murine models (23, 25). Additionally, MOFs have aided successful implementation of synergetic therapies such as chemo-photodynamic therapy and immunotherapy (25), results showing superior efficacy and decreased off-target toxic effects. Notably, two MOFs possessing hafnium ions approached first human trials due to favorable pharmacokinetic profiles and imaging modality (26). Overall, these preclinical advancements reveal MOF's strong potential for clinical translation, a significant proportion of which depends on four main parameters: particle size and morphology, surface chemistry, porosity and tunability, and biocompatibility.

Size And Morphology

Control of particle dimensions and form is essential for optimizing biological interaction and biodistribution of MOFs. Small MOFs (~50–200 nm) are optimum to exploit the EPR effect at tumor locations while achieving rapid clearance (16, 27). Nanocarrier dimensions of ~100 nm is sufficiently large to escape renal filtration (<5–6 nm (18)) but still narrow (<~200 nm (18)) enough to penetrate permeable tumor vasculature while minimizing incorporation by the mononuclear phagocyte system (18). Researchers have designed synthetic modulating methods (e.g., modulator additions, acid additions, solvent selections, etc.) (15) to change MOF crystal dimensions and form upon preparation. For example, by using trifluoroacetic acid as a modulator, nanoscale rods of a Zr–porphyrin MOF (PCN-222) were prepared with an average length ~118 nm (28). By modulating modulator concentration, PCN-222 crystals could be grown between 50 nm up to ~ 200 nm (28), demonstrating nanoscale-specific MOF dimensions engineering.

Importantly, MOF morphology (particularly their form and shape) can significantly impact cellular incorporation as well as drug release kinetics. Kim et al. investigated two morphologies of an Fe-containing MOF, NH_2-MIL-88B(Fe), prepared as nanorods vs. nano-octahedra (same composition and 100 nm). They found octahedral MOFs were rapidly internalized by cells, while rod-shaped MOFs were internalized gradually with a more sustained incorporation pattern (29). The rapid incorporation of octahedra resulted from its multiple sharp vertices that can activate curvature-inducing endocytosis via many contact sites (24). In contrast, rod-like particles (fewer curvature initiatory sites) were slowly incorporated, which can be ideal for slow pharmaceutical release (24). Thus, by controlling MOF particle shape (e.g., spheres, cubes, rods, sheets), it is possible to influence the cellular internalization rate and subsequent payload. Other studies of gold and silica nanoparticles also exhibit shape-dependent biodistribution and cellular interaction such that spherical particles are apt to endure higher total uptake within tumors compared to rod-shaped or planar ones (15). Rational MOF size and morphology design for specific applications, is thus a chief factor to the preclinical success of MOFs.

In practice, most viable nanoscale MOFs suitable for drug application fall within 50–150 nm diameters and are monomorphic in shape (30). For instance, ZIF-8, a Zn–imidazolate MOF, is always synthesized as ~80–100 nm polyhedral nanoparticles for biomedicine application (30). Ahmad et al. synthesized ZIF-8 (~95 nm) with satisfactory plasma half-life (~9.5 h circulation) upon intravenous injection of mice (31) – a diameter-related improvement compared to rapidly cleared meso-scaled particles. Similarly, Fe-containing MIL-100 and MIL-89 nano-MOFs were obtained within 50–100 nm range while being highly crystalline and well-ordered (32). MIL-89(Fe), an iron carboxylate MOF, produced ovoid nanoparticles ~82 × 31 nm (measured via SEM) which verified original ~50–100 nm reported by Horcajada et al (33). Such nanoMIL-89 particles were readily incorporated via endocytosis and suitable for loading vasodilatory pharmaceuticals under a pulmonary hypertension model (22). Generally, nano-MOF make-up capacity to convert MOFs to nanoscale as well as monodisperse form has been core to MOF preclinical success. Optimized sizing enhances tumor targeting as well as cellular ingression while morphology control makes it easier to modulate uptake kinetics as well as distribution, enhancing overall therapeutic performance.

Surface Properties

MOF surface chemistry strongly influences MOF nanoparticles' colloidal stability, biodistribution, and biorecognition. High surface charges or hydrophobic properties of unmodified ("bare") MOFs result in MOF aggregation within biological media or rapid clearance *in vivo* (34). In response to this challenge, researchers modified MOF surfaces to further advance their performance (35). Polymer coating is one common method, utilizing biocompatible polymers like polyethylene glycol (PEG). PEGylation creates a steric and hydrophilic shield around MOF particles to attenuate protein adsorption and aggregation, prolonging circulation time creating a "stealth" effect (36). For example, from Horcajada's work of coordinating mPEG chains to Fe-MIL-88A nanoMOFs, subsequent groups PEGylated MOFs to stabilize MOFs within the bloodstream and attenuate initial "burst" release of cargo (28). Additionally, PEG-phosphate coated Zr–MOF nanoparticles resisted aggregation and could easily redisperse into water with minimal alteration of ~120 nm diameter and drug loading upon storage (37). *In vitro*, PEGylated MOFs exhibited lower cytotoxicity and sustained release of drugs compared to uncoated MOFs (37), highlighting the protective role of the polymer shell. Moreover, at physiological pH, PEG coatings stabilized MOFs to rapid degradation by coordinating entities (like phosphate contained within serum) and attenuated premature cargo leakage (37).

Besides polymers, surface functionalization of MOFs using ligands has been most significant with regards to providing targeting ability and immunity. Different targeting moieties – folic acid (FA), hyaluronic acid (HA), Arg-Gly-Asp peptides (RGD), antibodies, aptamers – were incorporated into MOFs to introduce active targeting of carcinoma cells or other diseased cells (16, 38). UiO-66@SiO_2–FA, for instance, a core–shell MOF nanocomposite where stable silica and FA-functionalized pluronic polymer were grafted to UiO-66(Zr) MOFs, targeted folate receptor-positive cancers and carcinoma cells that overexpress folate receptors by DOX-loaded MOF nanocomposites were designed to prompt selective internalization by such cells while inhibiting internalization by off-target cells (e.g. RAW 264.7 cells) (39). Similarly, Abubakar et al. post-synthesis surface functionalized ZIF-90 nanoparticles with an RGD peptide (a tumor-homing peptide) to home lung carcinoma cells. RGD-functionalized ZIF-90(Cisplatin) showed very significantly higher antiproliferative activity against A549 carcinoma cells (65% dead cells at 6.25 μg/mL) as compared to non-functionalized ZIF-90(Cisplatin) (22% dead cells), and spared healthy cells to a larger extent (40). The latter shows how surface functionalization gives MOFs a targeting ability to ensure enhanced therapeutic effect as well as reduced adverse effect.

Another intuitive approach is biomimetic coatings by using natural cell membranes (e.g., cancer cells or red blood cells) to wrap around MOFs to hide them from the immune system and prolong circulation time (41). For one, cloaking ZIF-8 nanoparticles with cancer cell membranes provided them with a "self" identity to seek immunity and homotypic targeting to tumor sites (42). Other MOFs have also been similarly encapsulated with platelet membranes or exosome membranes to serve similar purposes in preclinical trials. The biomimetic MOFs carried significantly enhanced blood half-lives and enhanced tumor accumulation compared to bare MOFs (41). Importantly, MOF surface chemistry can also be engineered inherently by linker functional groups. For instance, incorporation of hydrophilic –NH_2 or –COOH groups to linkers, as seen with NH_2-UiO-66 or ZIF-90, improves water dispersibility with sites for later bioconjugation (16). In summary, MOF surface characteristics via PEGylation, functional ligand attachments, or bio-membrane coatings, has been shown to play an innovative role to sustain successful performance of MOFs with enhanced performance in animal disease models upon modification to include enhanced colloidal stability within bloodstream circulation, prolonged circulation and tumor accumulation, with improved targeted delivery.

Porosity and Tunability

The trademark attribute of MOFs is that they are highly porous and tunable. This leads to improved drug loading capacities and adjustable release profiles under preclinical conditions (37). MOFs typically consist of many nanoscale channels and pore systems that can accommodate voluminous amounts of guest molecules via either adsorption or encapsulation (21). Compared to classic drug carriers like liposomes and polymer particles that normally carry less than 5 wt% of drug load, MOFs often accomplish drug loadings of 10–30 wt% or higher (15, 43). That is a very significant advantage: higher drug loading decreases the number of carrier particles required to deliver a therapeutic dose, thus reducing carrier-caused toxicity. An example is the iron-containing MIL-100 MOF that has very spacious mesopores (~25–29 Å). MIL-100(Fe) has been shown to

encapsulate 25 wt% of busulfan, an anticancer prodrug, compared to around 5 wt% that are entrapped by the most efficient polymer nanoparticles and around 0.4wt% by liposomes (33). Similarly, nanoMIL-100, when packed with nucleoside analogues like AZT triphosphate and cidofovir or with doxorubicin, accumulated between 16–29 wt% of payload (thermodynamic drug loading) (33). Another more striking example is NU-1000, which has demonstrated very high loading capacities of up to 81wt% (14). Such very high payloads are basically without equal compared to other nanocarriers and reflect how MOF porosity lets them act like molecular sponges. For MIL-100, it is also notable that there were no observable burst release phenomena to be seen but rather, it slowly released its contained drugs with an insubstantial initial burst that could be ascribed to the bulk of the drugs being mostly encapsulated within internal pores rather than via mere surface adsorptions (33, 44). Such slow release spanning various days is very beneficial within keeping therapeutic drug levels up and has been confirmed with various cargos within MIL-100 (33).

Another powerful aspect of MOFs is the chemical tunability of their framework, which allows researchers to design stimulus-responsive delivery systems. As mentioned previously, by judicious choice of metal–linker chemistry, MOFs can be made sensitive to specific triggers such as pH, redox environment, or enzymes (45). Acidic pH-triggered drug release is a common strategy in cancer therapy since tumors (and endo/lysosomal compartments) have lower pH (~5–6) than blood (pH 7.4). MOFs like ZIF-8 are inherently pH-sensitive: ZIF-8's Zn–imidazole bonds remain intact at neutral pH but rapidly hydrolyze under mildly acidic conditions (46). Exploiting this, researchers have encapsulated chemotherapeutics in ZIF-8 to create smart nanocarriers that are stable in circulation but disintegrate in the acidic tumor microenvironment to release the drug (13). ZIF-8/Doxorubicin is a prime example: at pH 7.4 it retains >75% of DOX over 32 h, but at pH 5.5 it releases the drug much faster (complete release within a day) (45). Zhang et al. demonstrated an injectable hydrogel containing DOX-loaded ZIF-8 that remained largely inert under physiological pH, yet once in an acidic tumor site, the ZIF-8 degraded and dumped its DOX payload to kill residual cancer cells (45). Crucially, ZIF-8 also buffers pH and generates pores that facilitate endosomal escape of drugs, further enhancing delivery to the cytosol (45).

In addition to pH-triggering, MOFs can be tuned to respond to many other stimuli. Certain functional groups that vary in organic linkers respond to certain redox conditions (e.g. disulfide bonds cleavable by glutathione in cancer cells) or enzymes (peptide linkers cleaved by proteases). While enzyme responsive MOFs are still emerging, one example is CRISPR/Cas9 payload specifically in the presence of a cancer-specific enzyme, greatly improving gene editing specificity in cells (47). In addition, MOF structures can be doped or hybridized by active subunits like porphyrinic MOFs, such as PCN-224 and MOF-525, naturally integrate a photosensitizer (porphyrin) into their linkers, enabling in situ photodynamic therapy upon light exposure (48). In one instance, a hafnium–porphyrin MOF, built from hafnium clusters and TCPP porphyrin linkers, was used to generate singlet oxygen to induce tumor killing upon irradiation; simultaneously, the heavy hafnium atoms served as X-ray radiosensitizers, yielding dual modality therapy triggered by external stimuli (light or radiation) (26, 49). The native modularity of MOFs, defined by the ability to mix and swap metals, change linkers, or form core–shell composites, thus offers essentially unlimited design freedom for the pursuit of on-demand release of drugs along with multi-functional behavior (therapeutic and diagnostic). This adjustability has been validated with the application of preclinical models; for example, a hafnium-based MOF RiMO-301 was designed to enhance radiotherapy by releasing photo-induced radicals and was given in combination with checkpoint blockade therapy, leading to better control of tumors in murine models without systemic toxicity (26). This specific MOF is one of the two to reach clinical trials (Phase I) because of its outstanding efficacy (26).

Finally, the drug-carrying porosity of MOFs also hosts other medically important cargos such as gases (e.g. NO for vasodilation or CO for anti-inflammation) and macromolecules (enzymes, siRNA, vaccine antigens) (37). The application of Fe-MOFs as oxygen carriers to treat tumor hypoxia and copper MOFs with attached nitric oxide donors for efficient antibacterial activity by sustained NO release are some such examples (50). MOFs can also act as protective shells for proteins/genes – e.g. ZIF-8 can load enzymes or DNA (51), protecting them until delivery to cells where the MOF degrades to release an active biomolecule. Such multiplicity in loading multiple therapeutics mimics the tunability of MOFs. Overall, the high tunability and porosity of MOFs are the highlights of their preclinical success: these features enable excellent drug loading and customized release mechanisms, allowing MOFs to achieve specific therapeutic requirements (whether it is long-term

controlled release, targeted activation in the disease microenvironment, or multi-functional therapy).

Biocompatibility

The most important consideration for any biomedical nanomaterial is the biocompatibility. One of the biggest reasons why MOFs are credited as highly potential novel materials are because of their biodegradability and good tolerance, especially when composed of metals and linkers with low intrinsic toxicity (52). Early toxicity issues for MOFs based on metal content have been significantly alleviated by reports that the effect is dosage and design dependent: with proper formulation, MOFs can be administered at therapeutically relevant dosages with considerably minimal side effects (20). For instance, the lack of cytotoxicity within the context of empty MIL-100(Fe) nanoparticles in a range of human cell lines, even following exposure to high concentrations (22). *In vivo*, iron carboxylate nanoMOFs (MIL-88A and MIL-100) were found to be tolerable in murine models at doses up to 220 mg/kg, with no relevant discrepancies in animal behavior, serum chemistry, or organ histology in comparison to control animals (22). Transient elevation of liver and spleen weight was observed, due to MOF uptake by the reticuloendothelial system; however, this effect reversed within a time course of 1–3 months, with no indication of chronic inflammation or immune activation (22). These observations provided early assurance that MOFs, especially those constructed from iron, are compatible at dosages significantly in excess of typical drug loads, since their metabolites of degradation (iron ions and benign organic linkers) can be metabolized safely by the body (22).

Biocompatibility does, however, depend on MOF composition. A recent review by Tyagi et al. reported that of common MOF components, Ca^{2+}, Mg^{2+}, Fe^{3+}, Zr^{4+} will give the most biocompatible MOFs, while Cu^{2+} and certain heavy metals give more cytotoxic scaffolds. For instance, Ca- or Bi-based MOFs were extremely well tolerated (these metals are extensively used in medicinal applications), followed by Ti and Fe MOFs. Zn-based MOFs (e.g., ZIF-8) showed slightly higher cytotoxicity *in vitro*, and Cu-based MOFs (e.g., HKUST-1) were most cytotoxic in cell culture (20). This trend also corresponds to the way the MOF particles interact with cells (size, shape, dissolution rate). For instance, ZIF-8 can be more toxic than other MOFs in certain cell assays because of rapid dissolution releasing Zn^{2+} and imidazole – but when injected intramuscularly *in vivo* as a vaccine adjuvant, ZIF-8 was less toxic than conventional alum adjuvant at equipotent doses (45). In that case, ZIF-8 microparticles created an innocuous depot in tissue with minimal inflammation, whereas soluble alum caused more inflammation (45). This demonstrates that route of delivery and particle size (microparticle vs. nanoparticle) dramatically control biocompatibility. ZIF-8 delivered intravenously as <100 nm nanoparticles has a low dose window (because of rapid systemic release of Zn), but the same material as a localized or larger-particle form can be extremely safe (45).

Many MOFs are designed with endogenous (already found in the body) or low-toxicity building blocks that facilitate their biocompatibility (18). Iron carboxylate MOFs like MIL-88 and MIL-100 degrade to Fe^{3+} ions, which can be metabolized to the iron reservoir of the body along with harmless dicarboxylate linkers that typically get metabolized or excreted (53). Zirconium-based MOFs of the UiO-66 family degrade with release of Zr(IV) ions; although zirconium is unknown to have any biological activity, zirconium salts have been used safely in medicine, i.e., dental implants (54). Besides, studies reveal that zirconium-based MOFs provide exceptional stability until they become excreted or slowly dissolve without inducing acute toxicity (7, 55). Interestingly, the observation that MOF nanoparticles typically become sequestered well by the mononuclear phagocyte system, i.e., in the liver and spleen, poses a challenge: while reducing systemic exposure and toxicity, it can also compromise target-site delivery (22). Surface modifications, e.g., PEGylation, allow phagocyte avoidance by MOFs, which reduces accumulation in clearance organs, which indirectly improves biocompatibility by avoiding overload in any single organ. For a study, PEG-coated MIL-100(Fe) displayed near-neutral zeta potential and did not induce any complement activation or acute immune response, whereas the uncoated MIL-100 displayed weakly negative charge and was more opsonizable (16). The PEGylated MOF displayed extended circulation times and reduced splenic uptake, indicating increased *in vivo* compatibility.

This MOF toxicology is intricate and an active research field. There are issues of long-term fate (56): do MOFs break down and get excreted entirely, or do they remain? Data available indicate many nanoMOFs do break down *in vivo* (particularly the more soluble Zn or Mg species, and those prone to phosphate attack such as Zr MOFs). For instance, one report demonstrated a Mn-doped ZIF-8 completely cleared from the major organs in 7 days in mice, the Zn/Mn ions removed, and

no chronic toxicity detected (28). Alternatively, very stable MOFs may linger unless they are small enough to be filtered out by kidneys or slowly biodegrade (15) – this is an area of interest to avoid the potential for any long-term residues. Immuno-compatibility is also being investigated by researchers: reassuringly, most MOFs explored (iron, Zr, Zn) induce little immunogenicity or inflammation *in vivo* (18, 21). Some MOFs even possess anti-inflammatory or antioxidative activity e.g., cerium-doped ZIF-8 eliminating Reactive Oxygen Species (ROS) in wound models (24). Overall, although each MOF must be screened individually, the preclinical record is that well-defined MOFs can be biocompatible carriers, with toxicity mainly controlled by composition (preference for biofriendly metals/linkers), dosage, and careful surface engineering. This biocompatibility, demonstrated in many cell viability assays and animal experiments, is a foundation of MOFs' preclinical success and a prerequisite for their translation to the clinic.

CHALLENGES TO CLINICAL TRANSLATION

Despite the tremendous promise in preclinical success, their translation to clinical use has been relatively slower compared to other MOF applications. As discussed in the previous sections, researchers have demonstrated MOFs as carriers for diverse cargos with enhanced properties in laboratory models. But at present, only two hafnium-based MOF have entered human clinical trials – RIMO-401 in Phase I (NCT06182579) and RIMO-301 in Phase II (NCT05838729) undergoing clinical evaluation (26, 67) (Table 1). Both share similar applications and properties, used as radio enhancers for cancer therapy and are the lone pioneers in a field with thousands of publications. This translational gap will be analyzed through four major challenges impeding the clinical translation: biological interface uncertainty, toxicity and immune response, manufacturing and scalability, and regulatory/clinical challenges.

Biological Interface Uncertainty

One of the major challenges is the unpredictability at the bio-interface, specifically with respect to the behavior of MOFs nanoparticles in the complex milieu of bodily fluids and tissues. Upon exposure to a biological fluid-like blood or serum, a MOF is immediately surrounded by a protein corona, where a layer of adsorbed proteins form on the molecule which confers the particle's biological identity (44). The particular composition of this corona can strongly affect a MOF's functionalities, such as its cellular uptake, biodistribution, and bioreactivity. Importantly, the corona composition is difficult to predict; it depends on various factors, such as the surface chemistry, size of the MOF, and protein environment of the host (44). In a recent research, Tang et al. described the proteomic corona on three commonly-used MOFs (ZIF-8, MIL-53(Fe), and UiO-66) and found that each contained a distinctive set of serum proteins, illustrating the variability inherent to the bio-interface (68). Similarly, Jafari et al. showed that a copper-based MOF formed a corona rich in fibrinogen when exposed to human plasma, finding that the presence of this protein coating significantly reduced the MOF's *in vitro* cytotoxicity (69). These studies show how protein corona can hide reactive surface sites and lower toxicity, yet it can also enable the opsonization of nanoparticles for immune removal or lead to a loss of targeting capability. As a result, the overall biological effect remains difficult to predict and can vary between individuals or different biological settings, thus introducing uncertainty about the *in vivo* performance of a MOF.

In addition to protein adsorption, chemical instability in body fluids is another concern. The majority of MOFs are synthesized under highly controlled conditions, but within the body they are exposed to extreme conditions (buffers, salts, proteins) that drive the framework to destabilize. For example, Zn (II) and Zr (IV)-based MOFs, like widely used nanoscale frameworks ZIF-8 and UiO-66, are susceptible to degradation when they are exposed to serum proteins and phosphate ions (22). A recent review stated that albumin and phosphate in blood easily compete with the metal nodes, effectively stripping them away from the coordination network of the MOF (20). As a result, MOFs stable in water solution or buffers, can degrade in real biological fluids, thereby releasing their metal ions and cargo prematurely (28). Such instability not only potentially undermines the intended therapeutic effect (by releasing the drug payload prematurely than expected) but also creates safety concerns (like the sudden release of metal ions or linker molecules). A good example is ZIF-8, which is relatively stable at neutral pH in pure buffer; however, in phosphate-buffered saline, it hydrolyzes very rapidly, leading to the release of zinc ions and its porous structure collapse (70). Such behavior is making the dosing and efficacy prediction *in vivo* complicated. Overall, the behavior of MOFs in the biological environment, protein coronas formation, degradation rates, and cellular interface interactions, is complex. Each new MOF may have its own unique set of behaviors at the bio-interface, and small changes in

Table 1. Key MOF Systems for Biomedical Applications: Preclinical and Clinical Status

MOF	Metal Center	Organic Linker (Type)	Size (nm, method)	Surface Modification	Toxicity / Biocompatibility	Preclinical Model (Cell / Animal)	Clinical Status	Ref.
RiMO-301	Hf(IV) cluster	Ru-derived dicarboxylate (porphyrinic)	No data	None (intratumoral injection)	No systemic toxicity in rats/ dogs; high-Z Hf generates ROS to enhance radiotherapy	Mice (tumor xenografts with radiotherapy); no adverse effects	Phase II (First MOF in human trials; intratumoral, with radiotherapy + PD-1 inhibitor)	(25, 26)
RiMO-401	Hf(IV) cluster	Proprietary carboxylate linker	No data	None (intratumoral injection)	Well-tolerated in preclinical models; designed similarly to RiMO-301 for radiosensitization	Mice (advanced tumors + radiotherapy)	Phase I (Intratumoral MOF radio-enhancer, NCT06182579)	(26)
ZIF-90	Zn(II)	Imidazole2carboxyaldehyde (aldehyde-type)	~100-500nm (SEM)	Schiffbase & pH/ATP-responsive potential	Good biocompatibility noted; intelligent delivery potential	Not specified (in vitro potential)	Preclinical (in vitro only)	(57)
ZIF-8	Zn(II)	2-Methylimidazolate (imidazole)	~80 (SEM, synthesized with TEA and NaOH additives)	None, PVP, Abs	Degrades at pH <6 into benign Zn^{2+} and imidazole; "residue-free" drug release with minimal carrier toxicity	In vitro: e.g. camptothecin-loaded ZIF-8 showed enhanced cancer cell kill at pH6; In vivo: generally dissolves in acidic tumors (no long-term residue)	Not in clinical use (preclinical research only)	(58)
MIL-100(Fe)	Fe(III) cluster	1,3,5-Benzenetricarboxylate (trimesate)	~200 nm (TEM, sonication)	None, PEGylation, PVP, HA	Low toxicity: no significant abnormalities in rats at high dose; no immune/ inflammatory reaction after injection	MCF-7 cancer cells (high drug loading ~25 wt% ibuprofen); Acute and subacute toxicity tested in rats (no organ damage)	Not in clinical use (successful preclinical safety)	(13, 33)

Continued Table 1. Key MOF Systems for Biomedical Applications: Preclinical and Clinical Status

MOF	Metal Center	Organic Linker (Type)	Size (nm, method)	Surface Modification	Toxicity / Biocompatibility	Preclinical Model (Cell / Animal)	Clinical Status	Ref.
MIL-53(Fe)	Fe(III)	1,4-Benzenedicarboxylate (terephthalate)	~350 nm (Bimodal distribution of sizes, with micrometric particles)	None	Good biocompatibility; biodegrades under acidic conditions (Fe and terephthalate are biotolerable)	HepG2 liver cancer cells (loaded oridonin 56% w/w, pH-sensitive release); Tumor growth inhibition in mice with no major toxicity reported (subacute tests)	Not in clinical use (preclinical stage)	(33)
MIL-101-NH_2(Fe)	Fe(III)	2-Aminoterephthalate (BDC-NH_2)	~120 nm (TEM)	Targeted peptide & Terminal phosphate functionalized DNA	Well-tolerated; addition of biocompatible coatings (peptides) reduces any Fe-leaching toxicity	MDA-MB-231 breast cancer (Au@MIL-101-NH_2 with ZD2 peptide for tumor targeting; effective photothermal ablation); MRI-visible due to Fe core	Not in clinical use (advanced in vivo studies)	(33)
UiO-66@SiO_2-FA	Zr(IV) cluster	1,4-Benzenedicarboxylate (terephthalate)	~180 nm core–shell (DLS)	Silica shell + Folate (F127-FA)	Excellent biocompatibility; silica coating improves stability, negligible toxicity to normal cells	MCF-7 (folate-receptor+ breast cancer cells): enhanced DOX uptake and cytotoxicity; RAW 264.7 macrophages: biocompatible uptake	Not in clinical use (in vitro and mouse xenograft models)	(59)
UiO-66-NH_2-FA/Cisplatin	Zr(IV) cluster	2-Aminoterephthalate (BDC-NH_2)	236 ± 7 nm (DLS, with FA)	Folic acid (covalently conjugated), DCBO DNA	MOF alone showed >90% viability in normal cells; MOF-FA-Cisplatin killed cancer cells more effectively than free drug	MDA-MB-231 breast & A2780 ovarian cancer cells: enhanced apoptosis and antiproliferative effect vs free cisplatin; Minimal toxicity to healthy fibroblasts (HFF)	Not in clinical use (in vitro studies)	(59)

Continued Table 1. Key MOF Systems for Biomedical Applications: Preclinical and Clinical Status

MOF	Metal Center	Organic Linker (Type)	Size (nm, method)	Surface Modification	Toxicity / Biocompatibility	Preclinical Model (Cell / Animal)	Clinical Status	Ref.
PCN-222	Zr(IV)	Porphyrinic (TCPP-type)	~117.9 ± 22.0 nm (SEM), ~130 nm (DLS after PEGylation)	PEGylation (mPEG–PO_3)	PEG improves dispersity; good biocompatibility and classified as "safe"	4 Peripheral Blood Mononuclear Cell (PBMC): no observed evidence of toxicity	Not in clinical use (in vivo screening)	(60)
PCN-224 (HA-PCN-224)	Zr(IV) cluster	TCPP (meso-tetra(4-carboxyphenyl)porphyrin)	~100 nm (nanocrystals, DLS/TEM)	Hyaluronic acid (HA) coating	Biodegradable; HA targeting enables CD44-mediated uptake, minimizing off-target effects	MCF-7/MDR breast cancer cells: HA-PCN-224/DOX achieves enhanced chemo-photodynamic therapy (PDT) with higher tumor cell kill vs free DOX; In vivo: improved tumor targeting and inhibition in mice (PDT+chemo)	Not in clinical use (preclinical research)	(61)
NU-1000 (isoreticular to NU-901	Zr(IV) cluster	TBAPy (1,3,6,8-tetrakis(p-benzoic acid)pyrene)	~100–200 nm (solvent-controlled, TEM)	None (uncoated)	Good biocompatibility; high drug loading (~35% DOX) with sustained release over 2 weeks	MCF-7 breast cancer xenografts in mice: DOX@NU-1000 showed superior tumor growth inhibition vs free DOX, with no obvious systemic toxicity	Not in clinical use (in vivo efficacy demonstrated)	(62)
HKUST-1 (Cu-BTC)	Cu(II) paddlewheel	1,3,5-Benzenetricarboxylate (BTC)	~100 nm (nanoparticles, SEM)	Polydopamine coating (PDA) in some studies	Moderately biodegradable; releases Cu^{2+} ions that induce Fenton-like reactions – effective against cancer cells but need dose control (excess Cu can be toxic)	CT26 colon cancer cells: forms CuS in tumors, achieving synergistic photothermal & chemodynamic therapy; Enhanced tumor ablation in mice with minimal off-target damage (with PDA coating)	Not in clinical use (preclinical stage)	(63)

Continued Table 1. Key MOF Systems for Biomedical Applications: Preclinical and Clinical Status

MOF	Metal Center	Organic Linker (Type)	Size (nm, method)	Surface Modification	Toxicity / Biocompatibility	Preclinical Model (Cell / Animal)	Clinical Status	Ref.
Cyclodextrin MOF (CD-MOF)	K(I) ions	γ-Cyclodextrin (natural sugar ligand)	~50–100 nm (microscopy)	None (edible components)	Excellent safety profile – composed of food-grade ingredients; no organ damage observed in mice (fully biodegradable)	4T1 lung cancer model in mice: DOX-loaded CD-MOF showed effective tumor inhibition with no toxicity to heart, liver, kidneys, spleen	Not in clinical use (proof-of-concept in vivo)	(13)
IRMOF-3 (Zn-MOF-5–NH_2)	$Zn(II)_4O$ cluster	2-Aminoterephthalate (BDC-NH_2)	~80 nm (nanocrystals, TEM)	Folic acid (targeting ligand)	Low inherent toxicity; MOF carrier improves curcumin delivery – induces ROS in cancer cells while sparing normal cells	MDA-MB-468 breast & 4T1 murine breast cancer: FA-IRMOF-3 loaded with curcumin causes ROS-mediated DNA damage and mitochondrial dysfunction in cancer cells	Not in clinical use (preclinical research)	(63)
Zr-Fc MOF Nanosheet	Zr(IV) cluster	Ferrocenedicarboxylate (Fc, metallocene linker)	~90 nm (thin sheet, TEM)	None (intrinsic 2D morphology)	Good biocompatibility; releases ferrocene-iron in acidic tumor for Fenton reaction (CDT) and photothermal heating under NIR	4T1 breast tumor model in mice: Zr-Fc MOF nanosheets achieved dual photothermal therapy (PTT) and chemodynamic therapy, significantly suppressing tumor growth	Not in clinical use (preclinical in vivo demonstrated)	(63)
Pd–Porphyrin MOF	Pd(II) ions	TPyP or similar porphyrin (Pd-coordinated)	~93 nm (DLS)	None (inherent theranostic)	Porphyrin ligand affords phototherapy; Pd(II) provides high X-ray/ PA contrast. Biocompatibility demonstrated by good tolerability in mice	4T1 breast cancer in vivo (mouse): Pd–porphyrin MOF generated ROS for "hydrogenothermal" chemo-therapy (oxygen-independent) and enabled photoacoustic tumor imaging	Not in clinical use (animal studies ongoing)	(64)

Continued Table 1. Key MOF Systems for Biomedical Applications: Preclinical and Clinical Status

MOF	Metal Center	Organic Linker (Type)	Size (nm, method)	Surface Modification	Toxicity / Biocompatibility	Preclinical Model (Cell / Animal)	Clinical Status	Ref.
Single-Fe Porphyrin MOF	Fe(III) (single atoms)	Custom porphyrin analogue ($Fe–N_4$ centers)	~300-500 nm (SEM)	None (DOX loaded internally)	High efficacy with combined modalities; minimal added toxicity. Single-atom Fe active sites catalyze ROS for PDT and heat for PTT	MCF-7 breast cancer cells: DOX-loaded Fe–porphyrin MOF induced synergistic photodynamic + photothermal therapy, with enhanced cell ablation and photoacoustic imaging capability	Not in clinical use (in vitro proof-of-concept)	(63, 65)
Bio-MOF-100 (N3-bio-MOF-100)	Zn(II)	Adenine & other biomolecular linkers	No data	Folic acid (FA) on surface	Composed of bio-friendly building blocks; exhibits low toxicity. FA targeting improves cancer selectivity, pH-sensitive drug release avoids off-target effects	4T1 breast cancer model: Curcumin-loaded Bio-MOF-100-FA showed enhanced tumor cell apoptosis in vitro and inhibited tumor growth in mice (pH-responsive release)	Not in clinical use (preclinical research)	(66)

Note. There are many ways to synthesize MOFs and adjust their size, morphology, surfaces, and other physicochemical properties. The information with the representative MOFs listed in Table 1 include the physicochemical properties of which has been studied. All surface modifications were reviewed in "Advances in surface functionalization of next-generation metal-organic frameworks for biomedical applications: Design, strategies, and prospects" (16).

particle synthesis or surface modification may have a large impact on protein binding or dissolution rate (71). Such uncertainty at the biological interface is a strong translational barrier: regulators and clinicians need to be certain that a MOF will behave consistently and safely in the human body; however, our current models and assays usually fail to fully account for the complexity of the *in vivo* environment.

Toxicity and Immune Response

Toxicity and immunogenicity concerns are another major barrier for MOF clinical translation. At the heart of concern is that MOFs typically contain metal ions (e.g. Cu, Zn, Zr, etc.) and organic linkers as components and that, when released or in some forms, these can be toxic (20). But measuring MOF toxicity is nuanced and can't be extrapolated from free metal or ligand toxicity. The nanoscale properties of the framework (size, shape, surface charge, stability) have a dramatic impact on biocompatibility (15). Ettlinger et al. highlighted that a MOF's composition and physicochemical properties (particle size, crystallinity, surface chemistry, etc.) collectively determine its hazard profile (72). Importantly, they highlighted that *in vitro* cytotoxicity rankings of MOFs don't always follow classical predictions from bulk material toxicity, e.g. though free copper ions are only slightly more toxic than iron ions, Cu-based MOF nanoparticles were typically the most cytotoxic in cell studies, while Fe-based MOFs were among the more biocompatible (72). That is because nanoparticle-specific factors (easily being endocytosed, inducing oxidative stress, etc.) can enhance or attenuate the intrinsic constituent metal toxicity (73). The result is that generalizations (e.g. "iron MOFs are safe") cannot be accepted without empirical data and each MOF has to be assessed in its own right, and small tweaks (particle size, morphology, functionalization) can move the toxicity profile. Furthermore, MOF toxicity is highly context-dependent. A good example is the case of ZIF-8 (a Zn (II)- imidazolate framework). In typical cell culture assays, ZIF-8 typically exhibits remarkable cytotoxicity (more than many other MOFs). But when the same material was applied as a vaccine adjuvant *in vivo*, it was less toxic at high doses than aluminum hydroxide (alum, the conventional vaccine adjuvant in humans) (20,31). Ehrman et al. found that mice tolerated doses of ZIF-8 formulated with antigen concentrations over 50 μg/mL with little adverse effects, whereas alum caused more inflammation at similar doses (74). The explanation for the difference is the route and location of delivery of the MOF. ZIF-8 microparticles delivered to the dermis or the lung were a depot, localized and slowly releasing their contents, causing little systemic toxicity (74). By contrast, intravenous delivery of nanoscale ZIF-8 resulted in rapid distribution and acute severe toxicity with a much-reduced therapeutic window (74). This highlights how toxicity and immune responses can vary enormously with administration route and particle characteristics. MOFs inflammatory or cytotoxic in one situation can be inert in another. Such unpredictability makes clinical application difficult: regulatory authorities will demand extensive safety data for all the relevant situations, and developers will need to take great care adapting their approach to also consider immune triggers.

Indeed, immune response to MOFs is still a topic under active exploration. The above protein corona usually contains opsonins, i.e., complement proteins and immunoglobulins, which can be utilized to label nanoparticles for subsequent phagocytic elimination (22). Hidalgo et al. referred to this phenomenon as the "immune fingerprint" of MOFs, which reflects the distinctive immune recognition pattern provoked by each MOF (75). They contend that the awareness of this fingerprint is crucial to prevent unwanted immune reactions. For example, if an MOF is a potent activator of the complement cascade, it could cause infusion reactions or be rapidly sequestered by the mononuclear phagocyte system, particularly in the liver and spleen, thus reducing efficacy and causing inflammation (75). Conversely, certain MOFs are designed to modulate immune responses beneficially and act as vaccine adjuvants or immunotherapy boosters, as long as their interactions are well defined (74). The main stumbling block is that our knowledge of MOF immunology is still in its infancy, small changes in surface functional groups may inhibit complement activation or alter cytokine responses; but the latter has to be empirically quantified for each MOF (15). In short, a main translational barrier is the lack of comprehensive in vivo toxicology and immunogenicity information for MOFs. So far, most research has been based on acute toxicity using rodent models, and often the single mouse dose was used (20). Long-term implications, chronic exposure effects, and pharmacokinetics such as distribution, metabolism, and excretion were poorly defined for the majority of MOF candidates (20). Without these data, researchers will find it difficult to convince regulators about safety, particularly for systemic delivery. A lack of insight regarding the fate of the MOFs in the biological system, i.e., their sequestration in organs, their degradation and

elimination route, or ability to cause subtle immune perturbations, is a powerful barrier to clinical progress (20).

Manufacturing and Scalability

Scaling a MOF from bench to clinical-grade product is a significant manufacturing and scalability problems. In contrast to well-defined small-molecule drugs with reproducible synthesis routes, MOFs are long crystalline chains that can be highly sensitive to synthesis conditions (76). Reproducibility is essential: a therapeutic MOF must be synthesized reliably with the same particle size, phase purity, surface chemistry, and porosity batch-to-batch (67). It is notoriously hard to accomplish. As Forgan notes, the "capricious nature of MOF crystallization" is likely to yield variations or even a completely different framework phases when reactions are conducted in different labs (67). A striking example was an inter-lab experiment on two zirconium porphyrin MOFs (PCN-222 and PCN-224). Ten independent labs tried to synthesize these MOFs from a published recipe but only 1 out of 10 succeeded in producing the target PCN-222 (phase-pure), and the other nine produced an impure sample of PCN-224 even with the same recipe (77). This finding concludes that even small, unnoticed differences in reagents, temperature profiles, or mixing can tip the balance and produce a different crystal structure (37). Polymorphism and phase variation in pharmaceutical drugs can have different bioavailability or stability, and their presence can derail development if not managed (78). Likewise, a MOF that unpredictably switches between crystalline phases (or contains undetectable amorphous impurities) is not acceptable for clinical use. For example, the widely studied MOF UiO-66 (Zr-based) has at least four known polymorphic or closely related phases that can form under only marginally different conditions (67). Researchers have reported cases where material labeled "UiO-66" in the literature was later found, upon careful diffractogram examination, to be of a different phase or as a mixture (67). Therefore, phase purity and batch-to-batch reproducibility of MOFs is a serious challenge that needs to be overcome in order to meet good manufacturing practice (GMP) regulations.

Scaling up MOF production adds more complexity to this challenge. Most MOFs are synthesized through solvothermal or hydrothermal techniques in small amounts (autoclaves or vials) with solvents such as N,N--dimethylformamide (DMF) and slow controlled crystallization (37). It is not easy to scale up these laboratory-scale processes to industrial scale (hundreds of liters). Yields are mostly low, and productivity is not necessarily linear. There is also the problem of solvent removal and purification – excess solvent (e.g. toxic DMF) or unused organic linkers need to be thoroughly washed out of a MOF to be injected into humans (67). This creates additional processing steps (large-scale washing, solvent exchange) that add variability or compromise the product's properties. Forgan stresses the value of exhaustive characterization of every batch including surface area measurement, particle size distribution, crystallinity, composition, etc. to catch any deviations. Close analytical scrutiny needed for these processes is time- and resource-intensive, but without it, one can't guarantee that a "nominally same" MOF from two batches will perform the same *in vivo* (67). Scalability of synthesis protocols is another challenge. However, some of the latest innovations seek to make MOF synthesis more scalable and reproducible. Examples of investigated technologies include continuous flow reactors, spray-drying or microfluidic methods, and mechanochemical synthesis (grinding reactants in the absence of bulk solvents) to produce larger amounts with tighter control (79,80). Yet no MOF has yet been synthesized to date at the multi-kilogram scale under full GMP compliance for a therapeutic use (with the exception of those confidential efforts on the two clinical trial contenders). Until firm means to produce MOFs with pharmaceutical-grade consistency are established, scale-up issues will continue to hold back clinical translation. This problem also comes back to scientific reproducibility: if academic research groups can't reproduce each other's MOF preparations reliably, scaling that chemistry to a commercial process will be even more difficult.

Regulatory and Clinical Challenges

MOF based therapeutics are without a doubt a novel modality that regulators such as the Food and Drug Administration (FDA) and European Medicines Agency (EMA) have limited experience with, making the classification of these compounds as well as the supporting data to get approval unclear. The fundamental question is whether MOFs be regulated as drugs, medical devices, or a combination of both. Generally, MOFs can be seen as drug delivery systems (non-biological complex drug), as MOFs are highly applied in active payload encapsulation: this would demand the full Phase (I-III) pharmaceutical trials and toxicology evaluations (20). Alternatively, intrinsically therapeutic MOFs that aren't metabolized (i.e. X-ray therapy enhancing MOF) may be viewed more as a device or radiation

therapy enhancer (20). This is significant because there are several regulatory routes MOFs can take based on their applications, and note that regulatory pathways for medical devices may be less onerous (shorter trials, equivalence-based approvals) than drugs.

Furthermore, regulatory authorities will examine MOF products along various axes: purity, identity, and stability must be maintained by Chemistry, Manufacturing, and Controls (CMC) data (81); pharmacokinetic and ADME (absorption, distribution, metabolism and excretion) studies must detail the MOF's fate *in vivo*; and toxicology studies must cover not only acute effects, but chronic exposure, immunotoxicity, and developmental toxicity where applicable (81). In the case of traditional small-molecule drugs, highly developed protocols and guidelines for these studies already exist (82) – in contrast, for MOFs, their creators may need to develop new assays (e.g., to quantify trace metal release into tissue or to show the framework's structural integrity upon circulation). The lack of a standard template means that regulatory approval can be conservative and lengthy. In fact, the clinical progress of MOFs to date has been reasonably modest: the first MOF-based therapy (RiMO-301, a hafnium MOF loaded with a photosensitizer) began a Phase I trial in 2018, delivering the MOF directly into a tumor bed during radiation therapy (25). The reasoning behind this approach was that by targeting the MOF to the tumor site, systemic exposure would be low, which would limit safety concerns (20, 25). Early results from that trial were promising enough that it advanced to Phase II. But it's noteworthy that intramural injection was pursued because it likely mitigated regulatory issues (the MOF is not widely circulating in the body) and focused on a short duration of use (single dose during cancer treatment)(20). In effect, the creators cleverly wedged the MOF into a familiar clinical paradigm (radiation therapy) to enable an easy regulatory leap. For more systemic applications (e.g., IV drug delivery, chronic dosing), the challenges would be even greater. This is compounded by the fact that even for conventional oncology agents, preclinical toxicology studies in animals often fail to translate accurately into human outcomes: a large-scale study of 108 oncology drugs demonstrated that preclinical toxicities in rodents and non-rodents poorly predicted Phase I clinical toxicities, with only modest predictive values (median PPV 0.65; NPV 0.50), and with many categories such as neurologic, cutaneous, and cardiovascular toxicities showing little concordance between species (83).These findings underscore why regulators remain cautious with first-in-human studies of new modalities such as MOFs, where no historical benchmarks exist. Moreover, the high cost and risk of first-in-human trials for this new class of material may discourage investment by industry players. Compared to more mature nanocarriers, MOFs do not have any precedents that have been approved, and companies therefore must provide persuasive rationales to investors and regulators in terms of risk based on strong preclinical data packages. Greater interdisciplinary collaboration, along with targeted funding, will be necessary to overcome these regulatory and clinical trial challenges. Without collective efforts directed at answering regulatory questions early on, such as soliciting interactions with regulatory agencies through Pre-Investigational New Drug (Pre-IND) meetings or performing toxicity studies based on established guidelines, even the most effective MOF therapies may be delayed before reaching patient populations.

CONCLUSION

Despite MOFs tunable size, porosity, and biocompatibility enabling various biomedical applications such as drug delivery, and multimodal therapies, their clinical translation is impeded by several bottlenecks. Uncertainty in the biological interface with protein corona, toxicity and immune response, manufacturing reproducibility and scalability, and unclear regulatory pathways, continue to hinder the translation into the clinic. Currently, there are only two MOFs (RIMO-301 and RIMO-401), both hafnium based, that have entered clinical trials. Comparing this to the thousands of preclinical study publications and known MOFs, there is a clear translational gap that persists in the field.

To bridge this gap, it is important to implement systematic strategies that addresses these challenges directly. Table 2 gives a brief overview of the translational bottlenecks discussed in the previous section alongside proposed strategies. By implementing systematic strategies in a field where there is still ambiguity, there should be a more focused and clearer objective for MOF researchers.

As discussed in the "success of preclinical studies" section, rationalizing the construction of MOF surfaces to functionalize them for specific applications can greatly help tackle translational issues. For example, if a MOF is to be designed for longer circulation time, PEGylation of that MOF may help improve colloidal stability and reduce immunogenic recognition. Researchers also must learn to accept the inherent toxicity of metals in MOFs and

Table 2. Translational bottlenecks and proposed strategies to overcome them.

Translational Bottleneck	Strategies to Overcome
Bio interface uncertainty – Unpredictable protein adsorption (corona formation) and MOF instability in biological fluids obscure the *in vivo* identity of the material.	*Surface functionalization:* Modify MOF surfaces with coatings (e.g. PEGylation) to reduce protein fouling and stabilize the particles. *In vitro models:* Perform stability tests of serum and examine the protein-corona features of every metal-organic framework (MOF) to predict their *in-vivo* activity. *Adaptive design:* Design labile or cleavable linkers with predictable reactivity to the biological environment (e.g., consistent breakdown under a certain defined pH or enzymatic conditions), thus controlling MOF disassembling.
Toxicity & immune response – Potential release of toxic components, unpredictable immunogenicity, and lack of pharmacokinetic (ADME) data raise safety concerns.	*"Safe-by-design" MOFs:* Choose biocompatible metals (Ca^{2+}, Fe^{3+}, etc.) and FDA-approved or endogenous organic linkers to build MOFs. Focus research and design into MOFs for full biodegradability into nontoxic byproducts. *Comprehensive toxicology:* Perform thorough *in vivo* toxicity studies early, including multiple species and long-term exposure, to build an ADME and toxicology profile. Use these data to refine MOF design (e.g. eliminate problematic moieties). *Immune modulation strategies:* Use insights from immunology to engineer MOFs that avoid excessive immune activation – for example, cloaking MOFs in biomimetic coatings to reduce immune recognition, or deliberately loading immunosuppressive agents when a temporary dampening of immune response is needed.
Manufacturing and scalability – Difficulties in reproducible synthesis, batch-to-batch variability (phase changes, polymorphism), low yields, and challenges in scaling to GMP production.	*Standardization & protocol optimization:* Develop community standards for MOF synthesis and characterization (e.g. particle size, phase purity checks). Adopt modulated synthesis techniques shown to improve batch reproducibility. *Scale-up innovation:* Invest in and research scale-up methods like continuous flow reactors, spray drying, or mechanochemical synthesis to produce MOFs in bulk. Emphasize sustainable solvent-free methods where possible to meet industrial safety and environmental standards. *Quality by design (QbD):* Implement QbD principles by identifying critical process parameters that affect MOF quality (e.g. temperature, mixing rate) and controlling them tightly. Use extensive characterization of each batch (X-ray diffraction, surface area, composition by ICP-MS, etc.) to ensure consistency before any clinical use.
Regulatory and clinical trial hurdles – Unclear classification (drug vs device), extensive data requirements, lack of precedent, and funding gaps for translation.	*Regulatory engagement:* Communicate early with regulatory bodies to define the classification and required studies. For instance, if a MOF can be positioned as a device or implant coating, pursue that pathway to leverage a possibly simpler approval route. *Strategic application design:* Target applications that play to MOFs' strengths while mitigating risk, e.g. local therapies (tumor-localized treatments, implants) where systemic exposure is limited. Success in a niche (like MOF-based radiotherapy enhancers) can pave the way for broader uses. *Collaborative translation efforts:* Form interdisciplinary teams (chemists, pharmacologists, clinicians, industry partners) to share expertise. Secure translational research grants or partnerships to fund the costly IND-enabling studies. Publishing comprehensive translational data (toxicology, manufacturing process, etc.) for initial MOF candidates will also guide the field. Notably, comparing MOF formulations head-to-head with non-MOF nanomedicines (e.g. benchmarking *RiMO-301* against hafnium oxide nanoparticles) can highlight unique benefits and reassure regulators.

select more biocompatible metal ions (e.g., Ca, Bi, Eu, Ti, Fe) and (endogenous tend to be safer than exogenous (18)) linkers. Using FDA approved linkers may also be beneficial when facing regulatory procedures. Additionally, cloaking MOFs with biomimetic coatings to dampen immune response can greatly help the design of more biocompatible MOFs. As a community, it is also essential to create an industry standard for MOF synthesis and characterization for more inter-laboratory or interdisciplinary comparisons with same-field and among biologists, engineers, chemists. More studies into scale-up innovations such as continuous flow reactors, mechanochemical synthesis, etc. should also be conducted as there are very limited publications on those potential areas. To address the problem of MOFs regulation pathway, early conversations with an agency

like the FDA and/or EMA prior to finalizing the protocol may help ensure a MOF will be navigated as a drug, or a device, or a combination product, which will likely help with eventual commercialization, particularly for applications like implant coatings or localized therapeutic platforms. Likewise, carefully designing application areas around tumor-localized therapies, implantable devices, or radiotherapy enhancers, which have inherently limited systemic exposure, will take advantage of inherent benefits of MOFs while limiting regulatory and safety barriers. Finally, a collaborative translation process that incorporates a team approach by chemists, pharmacologists, clinicians, and industry representatives using early translational funding and high-quality data to support an IND (e.g., toxicology data, reproducibility of batch), will strengthen any case for MOFs. Establishing credible comparisons against canonical non-MOF nanomedicine products, such as comparing RiMO-301 with available hafnium oxide nanoparticles, is also likely to strengthen credibility with regulators. Considering the factors analyzed in this paper, MOFs are still in their early transitional stage, yet the increasing sophistication of its production and evaluation suggest that its clinical realization is no longer a question of if, but when–much like in other applications, their promise in biomedicine represents the next frontier.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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