

Development of Metal-Organic Frameworks for Biomedical Applications – A Review

Mostafa Yousefzadeh Borzehandani, Emilia Abdulmalek, Mohd Basyaruddin Abdul Rahman and Muhammad Alif Mohammad Latif
Integrated Chemical Biophysics Research,
Faculty of Science, Universiti Putra Malaysia, 43400 UPM, Serdang, Selangor, Malaysia

Muhammad Alif Mohammad Latif
Centre of Foundation Studies for Agricultural Science, Universiti Putra Malaysia, 43400 UPM, Serdang, Selangor, Malaysia

Email address: aliflatif@upm.edu.my

Abstract— Metal-organic frameworks (MOFs) are porous materials made from coordination bonding of organic linkers and metal nodes. Nowadays, MOFs have already achieved a considerable growth in many fields including in bio-related applications. In this review, we focus on the alternative, green route of MOFs synthesis as well as their toxicological properties. We also highlighted the potential of MOFs as therapeutic agents and nano-MOFs (NMOFs) for biomedical sensing. Water as an alternative media for MOF synthesis showed excellent results in term of particle size, stability and selectivity. Toxicological assessments revealed Fe (III) and MIL-100 as the most promising metal and MOF for medical applications. It was also shown that MOFs are sensitive towards physiological and pathological criteria such as pH, fluorescence and O₂. Although many attempts have been made in utilizing MOFs for bio applications, further improvements should be considered before MOFs can become effective therapeutics options.

Keywords— metal-organic framework; green synthesis; toxicity; biomedical; biosensing

I. INTRODUCTION

Metal Organic Frameworks (MOFs) are porous crystal structures that comprises of metal ions linked with organic molecules in a large framework. These metal-organic linkages create secondary building units (SBUs) which resulted to one-dimensional (1D), two-dimensional (2D), and three-dimensional (3D) structures. Repetition between fragments (unit cells), which expended in each direction lead to the formation of coordination structures [1]. Although a number of MOFs were synthesized early 1990s but the term of “Metal-Organic Frameworks” was firstly reported by Omar Yaghi’s group in 1995 [2] as subclass of coordination polymers and often is well-known their porosity (up to 90%) and internal surface area (beyond 6000 m²/g) [3–5]. Based on types of metal centre’s coordination and how organic linkers combined with, MOFs have introduced several

important topologies of ‘nets’ such as primitive cubic (pcu), queen of MOFs (qom), twisted boracite (tbo), northwestern topology (ntt) and extended biphenyl (etb) (Fig. 1) [6]. The pcu net is exemplified by MOF-1001 [7] in which linear organic linkers built a simple cubic unit cell. MOF-177 [7] is a case of qom net created by tritopic linker, while tbo net can be formed by using the same linker but expanding in different direction (different SBU) such as in MOF-199 [8]. Other nets such as ntt (Cu₃(TDPAT)) [9] and etb (IRMOF-74) [7] are constructed by hexatopic and tetratopic linkers respectively.

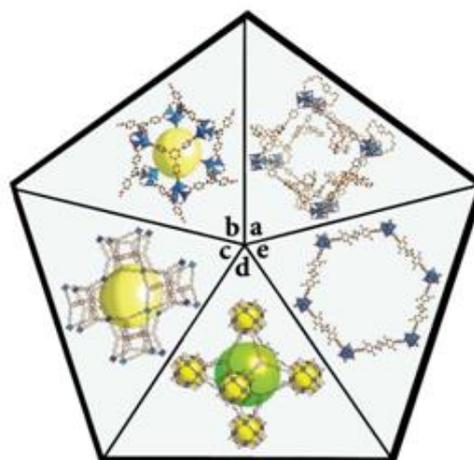


Fig. 1. Five types of net in MOFs structures. a) pcu b) qom c) tbo d) ntt e) etb.

The methods to synthesize MOFs are not so different from zeolites, in which both crystals are slowly grew by solvothermal reaction [10]. There is an approach called templating that utilizes the metal-binding solvent like water and *N,N*-diethylformamide where the metals were allowed to bind with hydrogen when the solvents were evacuated [11]. This method is beneficial for gas storage purposes, although, in terms of growing time and scaling up problems, microwave-assisted solvothermal technique is more preferable [12,13]. The chemical and thermal sensitivity as well as high reactivity of MOFs have

made direct synthesis challenging. To manage these problems and to expand new functionality, several new MOFs have been produced by post-synthesis modifications [14]. This is done by exchanging organic linker or metal during post-synthesis, where the initial structure is washed by solvent and then is soaked in solution containing new organic linkers or metals (with consideration of reaction conditions such as pH and temperature) [15–17].

Emerging different types of MOF based on functionality and topology lead to a wide range of applications such as in drug delivery [18], biosensing and bioimaging [19], catalysis [20], separation [21], and storage media [22]. Due to the highly tunable nature and potency of synthesis in nanoscale, MOFs are now touted as an alternative to drug delivery platform compared to conventional nanocarriers [23–26]. By having a specific functional site, higher molecular specificity can be achieved which is useful for biosensing and bioimaging [27–29]. This property allowed for better DNA/RNA sensing, small bimolecular sensing, enzyme activity sensing, computed tomography (CT) and magnetic resonance (MR) imaging. Although there are many similarities between MOFs and zeolites, MOFs have unique advantages in catalysis application. Firstly, organic linkers in MOFs can be synthesized from a different sort of chemicals. Secondly, thermal stability of MOFs is recognizable as compared to zeolites [30] and finally, many zeolites-like MOFs are persistent in terms of microporosity even when the solvent is evacuated [31–33].

In the past decade, MOFs have generated a great deal of attention; the number of review study related to MOFs has increased remarkably. Between the year of 2010 and 2012, three highlighted reviews for the importance and potentials of MOFs in biomedical applications were reported [34–36]. Considerable challenges encountered such as synthesis by nontoxic solvent, scarcely available *in vivo* and *in vitro* data, surface modification, sensing, and imaging have already been revealed and reviewed by literatures [37][38]. Although there have been several reviews on the potential ability of MOFs in several applications, we are focusing on MOFs which were cleanly synthesized with the least toxicity. For example, with the goal of green synthesis for biomedical applications and according to the view of eliminating the use of toxic solvents, the ability of MOFs to be produced through recycling method is shown. We select and emphasize the considerable potentials of MOFs in relevant fields based on unique attributes which would open a window for disease therapy and biomedical application in the future.

II. GREEN SYNTHESIS OF METAL-ORGANIC FRAMEWORKS

A. *Eliminating the use of toxic solvents*

Many different classes of organic solvents, including aliphatic hydrocarbons, aromatic hydrocarbons, amines, esters, ethers, ketones, and nitrated or chlorinated agents are well-known as biologically hazardous. For example, *N,N*-dimethylformamide (DMF) is identified as a toxic mutagen and thus a potential threat for the environment [39–41]. In addition, hydrofluoric acid (HF) is an extremely corrosive acid used for many purposes including mineral digestion, surface cleaning, etching, and biological staining, in which, based on exposure will lead to eye [42], skin [43], liver and kidney damage in the long-term [44]. To apply MOFs for medicinal purposes, it is required that these toxic solvents to be avoided [45].

Commonly, MOFs are synthesized by solvothermal batch reaction in Teflon-lined stainless steel bombs or glass pressure tubes using organic solvents such as 1-octanol [46], DMF [47], EtOH [48] and HF [49]. Finding a clean route to the synthesis of new Zn(II)-carboxylate MOF using water was considered by Martin Schröder and co-workers [50]. This was the first time that MOF was synthesized by applying near-critical water (300 °C) as solvent which produced an isolated narrow pore diameter $[Zn_2(L)(dmf)_2]$ without water bound to Zn(II) metal centers. Moreover, thermal gravimetric analysis (TGA) confirmed a high thermal stability (up to 425 °C) and a high adsorption enthalpy (11.0 KJ.mol⁻¹) for H₂ at zero coverage. Comparison between HF-dependent and HF-free synthesis of nano sized MIL-100 with regard to crystallinity, porosity, particle size, and yield was carried out in 2013 [51]. The possibility of obtaining higher yield (~1 g) clear-cut MIL-100 nano-MOFs by enhancement of the reaction mixture and using another form of iron without any toxic mineralizing agents was shown. Comparison between the two nanosystems on the loading capability and drug-release kinetic profile of anti-HIV (azidothymidine triphosphate, AZT-TP) drug was illustrated, also substantial loading capacity and low *in vitro* toxicity were observed. While MIL-100 nano-MOFs was synthesized by the solution of iron metal and trimesic acid in water and HF conventionally, HF-free route (called diluted HF-free here) was reported recently based on iron chloride hexahydrate as a procedure to avoid using the toxic HF [52–54]. According to Table 1, the size of MIL-100 nano-MOFs were 140 ± 25 (nm) and 225 ± 12 (nm) for diluted HF-free and HF-free, respectively, which were better than the ones with the presence of HF.

TABLE I. COMPARISON RESULTS BETWEEN HF AND HF-FREE SOLVENTS IN MIL-100 NANO MOFS SYNTHESIS [51]

Parameters	Synthetic procedure		
	HF dependant ^a	Diluted HF free ^b	HF free ^c
Fe source	Fe	FeCl ₃ .6H ₂ O	FeCl ₃ .6H ₂ O
[Fe source]: M	0.20	0.20	0.30
[BTC]:	0.13	0.13	0.2
HF	Yes	No	No
Temperature: °C	200	130	130
Time: min	30	6	6
Yield: %	~8	~80	~80
STY: kg/m ³ /d	112	8 x .10 ³	12 x .10 ³
Size: nm	235 ± 28	140 ± 25	225 ± 12
PDI	0.3	0.1	0.2
C/Fe (theo=6)	6.2	7.0	6.5
S _{BET} : m ² /g	1700 ± 180	1350 ± 230	1500 ± 150

(BTC: benzenetricarboxylic acid, HF: hydrofluoric acid, STY: space time yield, PDI: polydispersity index)

^a Data obtained from [52]

^b Data obtained from [54]

^c Data obtained from [51]

It is noteworthy that the yield increased ten folds for free-HF synthesis (~80%) compared to HF-dependent synthesis (~8%) which allowed for new approach to scale up industrially. Moreover, the space time yield (STY), which refers to the mass of product produced per unit volume per unit time for both HF-free conditions (8x10³ and 12x10³ kg/m³/d) were higher than HF-dependent (112 kg/m³/d). The replacement of organic solvent in continuous flow synthesis of MIL-53(Al) by using high-temperature water (HTW) was also reported [55]. Scaling up of MIL-53(Al) to 0.5 kg through continuous flow synthesis strategy has shown promising results. Although MIL-53(Al) is available commercially, it is not cost effective for applications. However, the STY value for MIL-53(Al) using the green approach was reported as 1300 Kg m⁻³ d⁻¹ significantly higher than 160 kg m⁻³ d⁻¹ at commercial level [56, 57]. It seems that water is developing as the favorite green solvent for the replacement of hazardous organic solvents. For example, the zirconium-based MOFs (Zr-MOFs) was synthesized by Dirk De Vos and colleagues [58] and they applied Zr(SO₄)₂ as reactant and water as the solvent, to reason water is soluble for Zr⁴⁺ sources efficiently. Among three new Zr-MOFs produced, bcu-framework compounds revealed reversible structural disarrangement which can be attributed to the high density of defects in the structures.

The green synthesis route for Ti-based MOF have produced excellent water stability and high selectivity as well as fast transport kinetics of CO₂ [59]. Hydrophilic and highly water stable MIL-91(Ti) was built in the aqueous environment by two synthesis methods, hydrothermal and reflux. In hydrothermal,

comparison of high adsorption enthalpy differences for CO₂ between experiment and modeling data revealed MIL-91(Ti) as an interesting selective adsorbate for CO₂ over CH₄ and N₂ ($\Delta(\Delta H(\text{CO}_2) - \Delta H(\text{CH}_4)) \sim -20.0$ (simulated: 19.4) kJ mol⁻¹ and $\Delta(\Delta H(\text{CO}_2) - \Delta H(\text{N}_2)) \sim -25$ (simulated: -24.4) kJ mol⁻¹). Furthermore, co-adsorption selectivity of ~90 at 1 bar and 303 K was determined for the mixture of CO₂/N₂ (10/90 molar composition) and it decreased to 60 for the case of CO₂/N₂ (15/85). Meanwhile in the same condition, MIL-91(Ti) indicated a selectivity of 18, which was validated by experiment data (reflux synthesis) and simulation.

In another report [60], synthesis of several hybrid nanocomposites, using green strategy and solvothermal method with the aim of removal organic pollutants, was carried out. In this regard, graphene oxide (GO), carbon nanotubes (CNTs) both were used as platforms to pack Cu-BTC MOF and Fe₃O₄ magnetic nanoparticles (MNPs). The nanocomposites were characterized and exhibited high crystallinity, nano-scale in size and remarkably porous surface area. Since methylene blue (MB) is well-known as organic pollutant and can cause health problems [61] such as mental confusion, nausea and eye damage, aforementioned synthesized nanocomposites were used as pollutant adsorption test. Generally, pollutants were adsorbed significantly more by nanocomposites compare to the parent materials. An improved formation and functionality of MOF through synthesis in presence of GO and CNT platforms were also identified.

B. Recycling Approach

Polyethylene terephthalate (PET) is produced when ethylene glycol (EG) reacts with terephthalic acid (TPA) or dimethyl terephthalate (DMT) [62]. Mass consumption of this material (such as in packaging, movie tapes, x-ray films and many others), poor biodegradability and chemical recovery under natural route is still a serious challenge in environmental pollution and waste management [63, 64]. Regarding this issue, MOFs have shown promising characteristics for PET recycling purposes (Fig 2).



Fig. 2. PET as a recyclable material to build MOF.

In 2013, the use of waste PET as organic linkers was successfully achieved in the synthesis of MIL-53(Al) and MIL-47(V) by one-pot single step in aqueous solvent [65]. Aluminium hydroxide $\text{Al}(\text{OH})_3$ and HCl were used to lower the pH in order to optimize the yield for MIL-53(Al). In addition, every step of the synthesis was carried out without purification of terephthalic acid (BDC) and dimethylformamide (DMF). According to Brunauer–Emmett–Teller (BET) analysis [66], the surface area was improved from $842 \text{ m}^2/\text{g}$ for MIL-53 sample calcined at $350 \text{ }^\circ\text{C}$ to $1481 \text{ m}^2/\text{g}$ at $400 \text{ }^\circ\text{C}$ by the elimination of impurities which is an emphasis on suitable activation. Recently, waste PET recycling approach was further developed in the preparation of five nanoporous MOFs (MIL-47, MIL-53(Cr), MIL-53(Al), MIL-53(Ga) and MIL-101(Cr)) [67]. After confirmation of nanoporous MOFs by PXRD, SEM and nitrogen gas sorption measurements, CO_2 and H_2 sorption tests revealed that MIL-53(Cr) and MIL-101(Cr) were best in terms of gas uptake among the products (Fig 3).

A similar work on the synthesis of Cr-MOF from waste PET as a source of BDC was reported which showed the comparison between sorption of synthesized and commercial BDC (prepared from Sigma-Aldrich) [68]. Importantly, Cr-MOF, PET-derived BDC observed better sorption profiles for N_2 and H_2 gases rather than commercial BDC. Furthermore, UiO-66(Zr) was synthesized successfully using PET-derived BDC and the N_2 and H_2 gas sorption was also compared with the ones using commercial BDC [69]. Spectroscopic observations revealed that commercial BDC reactants demonstrated better properties in terms of nano-size, density, BET surface area, pore volume, micropore volume and H_2 uptake. However, with regards to the N_2 sorption isotherms and economic strategy, PET derived BDC product was more preferred.

III. TOXICOLOGICAL CONSIDERATION

The study of nanoporous MOFs application in biomedical area is rapidly growing. MOFs is one of the most interesting recent advances in biomedical concerning toxicological aspects and treatment of disease. Since various types of MOFs are made by different metals, toxicity is a concern in biomedical applications. Most of the study in this area is focused on toxicological assessment before application to medicine. Of course, identification of non-toxic MOF (NMOF) as drug carrier should be a consideration for health benefits. In this part, we look at several *in vitro* and *in vivo* results which showed the lowest toxicity of NMOFs.

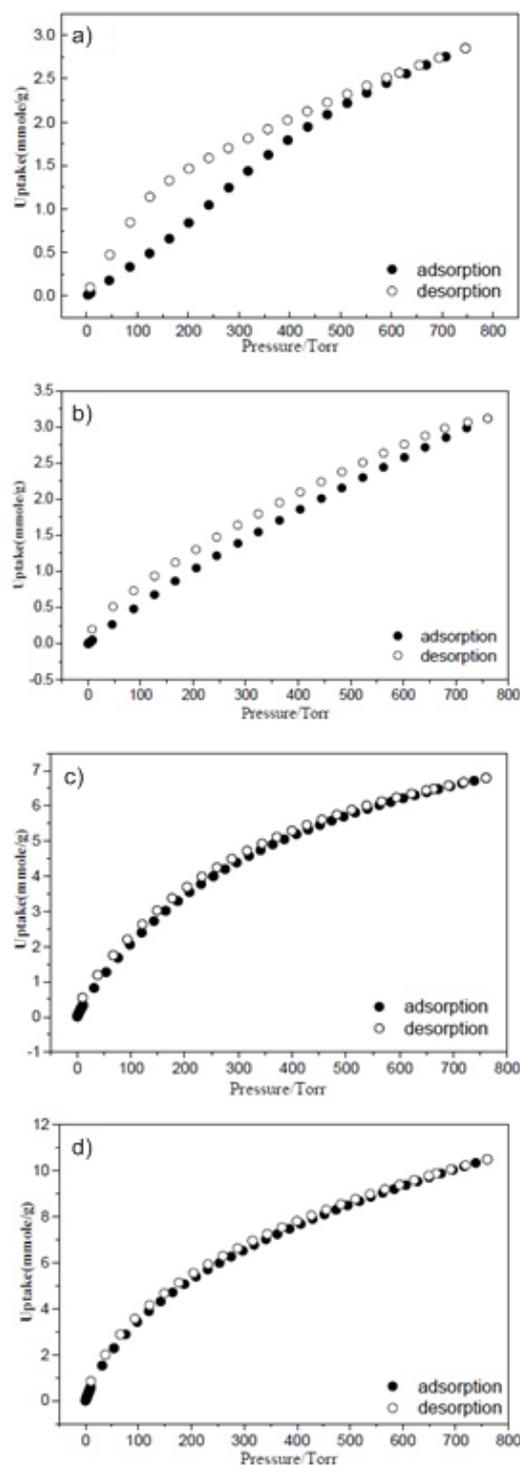


Fig. 3. The CO_2 gas sorption of isotherms of (a) MIL-53(Cr) at 293 K, (b) MIL-101(Cr) at 293 K and H_2 gas sorption isotherms of (c) MIL-53(Cr) and (d) MIL-101(Cr) at 77 K. Reproduced with permission of Royal Society of Chemistry, from [67]; permission conveyed through Copyright Clearance Center, Inc. Confirmation number: 11834610

A. *In Vitro* Study

After many years of synthesis and introduction of new MOFs, limited data for toxicity has encouraged researchers to report *in vitro* and *in vivo* for the produced MOFs [2, 52]. *In vitro* is associated with various biological processes that are made to occur outside the living cultured organism in media such as bacteria or mammalian cells for recognizing of potentially beneficial or hazardous chemicals. Starting from 2010, the toxicity of several Fe(III) carboxylate NMOFs (e.g., nanoMIL-53, nanoMIL-88, nanoMIL-100, and nanoMIL-101) were evaluated by Horcajada et al. [52]. By exposing various cell lines including the mouse macrophage J774.A1, human leukemia (CCRF-CEM), human multiple myeloma (RPMI-8226) and human cervical adenocarcinoma (HeLa) cells to NMOFs, they successfully observed that iron (III)-based MOFs were non-toxic nanocarriers.

Doxorubicin, a chemotherapy drug was well-incorporated into a ZIF-8 (DOXO-ZIF-8) and the cytotoxicity was measured by Junior et al. [70]. They concluded that the assayed DOXO-ZIF-8 by three types of cell lines (mucoepidermoid carcinoma of the lung [NCI-H292], colorectal adenocarcinoma [HT-29], and promyelocytic leukemia [HL-60]) exhibited lower cytotoxicity than pure doxorubicin. The results was explained by the slower release of the incorporated drug. Furthermore, XRD and molecular docking calculation suggested that after adsorption of doxorubicin, while lattice parameters of ZIF-8 were not changed, doxorubicin interacted mainly with the surface of ZIF-8. Successful synthesis of MOF at nanoscale (various type of MIL, UiO-66 and ZIF-8) and assessment of IC₅₀ for fourteen NMOFs were reported by Horcajada et al. [71]. Comparison of IC₅₀ data revealed that Fe (III) carboxylate and zinc (IV) imidazolate were the least and the most toxic, respectively. Moreover, application of two cell lines including human epithelial cells from fetal cervical carcinoma (HeLa) and murine macrophage cell line (J774) showed higher cytotoxicity in J774 which was due to faster internalization of nanoparticles in the macrophage line. Along with *in vitro* test by zebrafish embryos, *in vitro* study carried out on human hepatocyte (HepG2) and breast cancer (MCF7) cells by 16 uncoated MOF nanoparticles in 2014 [72]. Exposure of MOFs to organic ligands and metal units individually at doses ranging from 1 to 200 µm for 24 hours illustrated that organic ligands were considerably non-cytotoxic. For the case of metals, even at the highest dose, the cytotoxicity for Co(II), Ni(II), Zn(II), Zr(IV) and Mg(II) salts were insignificant, while Cu(II) and Mn(II) salts showed high cytotoxicity even at low doses and Fe(III) showed moderate cytotoxicity. Strong correlation was found between *in vitro* and *in vivo* test for Mg-MOF-74 which exhibited the least toxic in both assays. The most promising and potential drug nanocarrier MIL-100(Fe) encouraged Horcajada et al. to find more relevant mechanisms of three cations Fe(III), Al(III) and Cr(III) in the MIL-100 toxicity [73]. After evaluation of physicochemical

properties, four cell lines including Lung (A549 and Calu-3) and hepatic (HepG2 and Hep3B) were chosen to underwent cytotoxicity analysis by considering cell impedance, cell survival/death, reactive oxygen species (ROS) generation and the level of DNA damage. Eventually, MIL-100 (Fe, Al, Cr) NMOFs did not induce *in vitro* cytotoxicity, even at high doses in the p53 wild-type cell lines (A549 and calu-3 (lung) and HepG2 (liver)). Only toxic effect of MIL100-Fe was observed in the hepatocarcinoma cell line Hep3B, which is stress sensitive (because it does not express TP53 and guardian of the genome). However, both Fe(III) trimesate nanoparticles, MIL-100(Fe), and its coated form with heparin had shown that cell recognition and uptake declined at the early incubation stages due to their low toxicity [74]. *In vitro* analysis of rosuvastatin adsorption and release using high-performance liquid chromatography (HPLC) was performed after successful synthesis of three types of MOFs through mixture of copper serinate, copper proline, and copper threoninate with essential amino acids (serine, proline, and threonine) [75]. Up to 0.25 g/g of rosuvastatin was adsorbed within copper threoninate and the release of the drug took five days. Recently, zinc-based NMOFs functionalized with folate for the encapsulation of 5-fluorouracil and *in vivo* analysis for three cancer cell lines were performed. The results indicated stronger cytotoxicity for 5-fluorouracil-loaded NMOFs compared to the pure drug [76].

B. *In Vivo* Study

In 2013, based on three MOFs structure (MIL-88A, MIL-88B-4CH₃ and MIL-100), Fe(III) carboxylate NMOFs was studied in different aspects of toxicity such as animal behavior, water and food consumption, weight changes of body and organs, serum parameters, oxidative stress, oxidative metabolism, macro and microscopic histological observations with some insights on nano-particles biodistribution and elimination [77]. After intravenous administration, liver and spleen kept their function intact and showed no sign of constant toxicity and confirmed that Fe (III) carboxylate NMOFs as a non-toxic nanoparticle. According to the National Institute of Environmental Health Science (NIEHS, USA) and the Institute for Environment and Sustainability (IES, Europe), zebrafish is introduced as a well-chosen organism to explore the environmental toxicity effects. This approach to study the toxicity of MOFs was adopted by Maspoch and co-workers [72]. A diverse sets of nine MOFs among sixteen uncoated NMOFs were ranked for *in vivo* test in terms of the amount and severity of phenotypic changes in the treated zebrafish embryos. The method was established by Peterson et al. [78], [79] and modified by Nel et al. which then named scoring system [80]. They found that Mg-MOF-74 and HKUST-1 exhibited the least and the most toxicity, respectively. As this review [81] mentioned, a few *in vivo* data led to the difficulty in analysis of clinical issues, in addition, the authors concluded that more rigorous *in vivo* testing is needed

for the most promising NMOFs/NCPs to establish their therapeutic and imaging efficacy. Unlike many *in vivo* assessment that took from 1 up to 30 days, Horcajada and co-workers [82] already reported *in vivo* results in shorter time (less than 1 day). They believe that nanoparticles are significantly influenced by their early interaction with blood constituents after intravenous administration. Followed by consideration of pharmacokinetics (PK) and biodistribution (BD), MIL-100 (trimesate and iron) was used as nanocarrier to study blood circulating profile and accumulation of NMOFs in liver and spleen. PK profile of MIL-100 NPs indicates an increase in the BTC (1,3,5-benzenetricarboxylates) linker level during the first 30 min, suggesting that nanoparticles act as a depot in bloodstream. Moreover, accumulation analysis proved it occurs mainly in the liver and some extent of spleen (respectively 45% and 4% of administration after 30 min) without any biotransformation (28% at 24h). Rapid recognition of bared MIL-100 NPs by immune system was shown in the last study. Horcajada et al. [83] demonstrated MIL-100 as the most promising MOFs for biomedical application due to green synthesis (bio-friendly microwave), physicochemical stability, *in vivo* and *in vitro* toxicity, high loading capacities and good degradation/release profile.

IV. METAL-ORGANIC FRAMEWORKS AS NEW GENERATION OF THERAPEUTIC AGENTS

Nanotechnology has offered a wide range of nanomaterials for many applications, especially in medicine which also known as nanomedicine. Although there are not enough reports such as toxicological, hydrophilicity and drug releases, MOFs as a new generation of nanomaterials have provided good potential for drug delivery platform [84][85]. For this part, we are going to review some potential MOFs for therapy based on the type of disease.

A possible way for treatment of HIV, using MIL-100, was explored by Horcajada et al. in 2013 [86]. They identified low cellular uptake and efficiency of anti-HIV drug (azidothymidine triphosphate, AZT-TP). So that AZT-TP encapsulated by MIL-100 and resulted enhancement of high drug loading and release. Adsorption up to 24 wt% and maximal loading of 33 wt% by molecular sponges and further evidence from molecular modeling studies proved a strong agreement. More studies such as spectrophotometry, isothermal titration calorimetry, and solid-state NMR reveal that AZT-TP built strong coordination with unsaturated iron sites of nanoMIL-100. Furthermore comparing non phosphate AZT and AZT-TP interaction with MIL-100 was analyzed by Monte Carlo simulations and isothermal titration calorimetry (ITC). Both agreed that there is too weak interaction between AZT and pore wall of the MOF, in which led to poor loading and uncontrolled release.

The cytotoxic activity of 5-fluorouracil, a well-known drug for therapy of cancers, was evaluated by incorporation into Cu-BTC MOF [87]. Four cell lines including NCI-H292, MCF-7, HT29 and HL60 were

applied for 48 hours. The breast cancer (MCF-7) and promyelocytic leukemia (HL60) cell lines were extremely affected. 5-fluorouracil attached in Cu-BTC MOF exhibited slower release (82% drug in 48 hours). On the other hand, in rodents the number of leukocytes of the peritoneal cavity, level of cytokines and nitric oxide production fell down significantly. To overcome encapsulation of highly hydrophilic anticancer prodrugs such as phosphate gemcitabin (Gem-MP) due instability and inability during the transmission of cell membranes, MIL-100(Fe) was studied as a drug carrier [88] (Fig 4). This anticancer drug showed a maximal loading around 30 wt% due to the strong interaction between the drug and iron trimesate matrices. Also, *In vitro* test on the pancreatic cell line (PANC-1), for the assessment of MIL-100 effects, has illustrated that Gem-MP loaded was nine fold more efficient. Moreover, degradation and loss crystalline structure was not observed after loading the Gem-MP.

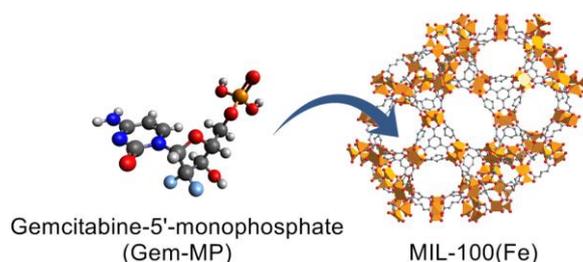


Fig. 4. Schematic representation of Gem-MP encapsulation in MIL-100(Fe) [88].

A recent report [89] claimed that chlorine-based MOF can be a new alternative to combat colon cancer. In this regard, a MOF based on 5,15-di(p-benzoato)chlorine (DBC-UiO) was studied with the aim of improving its crystallinity, nanoplate morphology, framework stability, porosity, high photosensitizer loading and enhanced intersystem crossing. Surprisingly it indicated 13 nm red shift and 11 fold enhance in the extinction coefficient of the lowest-energy Q band compared to 5,15-di(p-benzoato)porphyrin ligand based MOF (DBP-UiO). After that, exploration of two colon cancer cell lines revealed that DBC-UiO was three times as more effective as DBP-UiO in generating $^1\text{O}_2$ and much higher in photodynamic therapy (PDT) cytotoxicity. An indoleamine 2,3-dioxygenase (IDO) inhibitor was encapsulated in TBC-Hf MOF to induce the antitumor immunity system [90]. After activation of the immunity system, increased T cell infiltration in the tumors was founded. At the end highlighted immunological mechanisms, compensatory roles of neutrophils and B cells in tumor-associated antigens for T cells were identified (Fig 5).

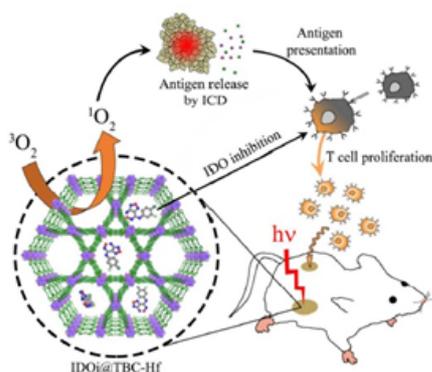


Fig. 5. The combined strategy of PDT and immunotherapy by IDOi@TBC-Hf. Adapted with permission from [90]. Copyright 2016. American Chemical Society.

Improvement of bioavailability and drug efficacy with the aim of treatment of lung metastasis was accomplished by Simon-Yarza and co-workers [91]. Smart mesoporous MIL-100(Fe) was chosen for specific pH-responsiveness and reversible aggregation behaviors in order to target tissue.

Along with toxicity analysis of MIL-89 and its formulated in polyethylene glycol (MIL-89 PEG), solving the Pulmonary Arterial Hypertension (PAH) problems by MOFs was investigated in 2016 [92]. By using previous preparation data [52] and spectroscopic characterizations [93], function of MOFs on endothelial cell inflammatory let to facilitated CXCL8 and ET-1 release from endothelial cells. Both MOFs represented non-toxic and anti-inflammatory properties as well as PAH drug carrier like sildenafil and bosentan.

V. METAL-ORGANIC FRAMEWORKS FOR BIOMEDICAL SENSING

Sensors play an ever more important role in medical technology with the aim of making medical devices even more effective and safer. Discovery of nanoscale structure with different shapes, size and composition has led to a well-developed nano-sensors [94]. A Copper-centered MOF was prepared by Jiping Chen et al. to detect Bisphenol A (BPA), an endocrine disruptor [95]. Large surface area and π - π stacking interaction between BPA and Cu-MOF were identified as the most important factors for enhancement of sensitivity in Cu-MOF. Using Tyrosinase (Tyr) as model enzyme, they revealed some important properties for BPA such as significant sensitivity of 0.2242 A M^{-1} , a low detection limit of 13 nmol L^{-1} , wide linear range $5.0 \times 10^{-8} - 3.0 \times 10^{-6} \text{ mol L}^{-1}$ and less than 11 s for response time. In 2015, during the expansion of new fluorescence investigation for thiol detection, UiO-MOFs-based was demonstrated as highly sensitive and selective for cysteine and glutathione with 10^{-11} M [96]. Two cases, Mi-Uio-66 and Mi-Uio-67, were used to detect physiologically relevant amino acids in water and displayed good linear relationship between the relative luminescent

intensities and concentration of RSH species in the range of 10^{-11} to 10^{-3} M (linear coefficient 0.9902 – 0.9923). Real-time sensing of pH changes inside living cells is important for the understanding of physiological, pathological process and also intracellular drug delivery issues. With the aim of real time measurement of pH in a living cell by MOFs, Wenbin Lin et al. combined covalently fluorescein isothiocyanate (FITC) as a pH sensitive component with the UiO NMOFs [97]. F-UiO showed desired structural stability, high FITC loading, efficient fluorescence, excellent ratiometric pH sensing properties and efficient cellular uptake.

Oxygen, O_2 plays a vital role in aerobic respiration and the amount of it is associated to various diseases. Monitoring and quantifying O_2 level in living cells are thus crucial for cancer diagnosis, tumor pathophysiology assessment, and the evaluation of the therapeutic effects in anticancer treatments [98]. Apart from a number of methods, ratiometric oxygen sensing in living cell using MOFs was reported in 2016 for the first time [99]. For the purpose of design and synthesis of the aforementioned agent, Pt-5, 15-di(*p*-benzoato)-porphyrin (DBP-Pt) was used as an O_2 -sensitive component while Rhodamine-B isothiocyanate (RITC) conjugated quaterphenyldicarboxylate (QPDC) was used as an O_2 -intensive ligand. They were employed to construct the R-UiO MOF. The produced structure indicated good crystallinity, high stability and excellent ratiometric luminescence response to O_2 partial pressure. Furthermore, the applicability of R-UiO towards intracellular O_2 biosensor was confirmed by *in vitro* experiments. Recently MIL-53(Fe) was identified as a sensor device for glucose. Huang and colleagues analyzed the chemiluminescence (CL) for MIL-53(Fe) and found that the attached MOF leads to increased CL luminal in H_2O_2 (around 20 times higher) [100]. When it combined with glucose oxidase, a meaningful correlation between CL intensity and glucose concentration from 0.1 to 10 μM range, at the end 0.05 μM (S/N=3) was determined. Later on, with the prospect of a new strategy for detection of glucose in human serum in mind, glycine functionalized MIL-53(Fe) demonstrated more efficient oxidative behavior than pure MIL-53(Fe) [101]. Beside peroxidase-like activity, glycine-MIL-53(Fe) has shown more stable under alkaline or acidic conditions as well as higher sensitivity for detection of glucose and H_2O_2 . A linear detection was observed for both glucose and H_2O_2 in range of 0.25-10 μM (0.13 μM detection limit) and 0.10-10 μM (49 nM detection limit), respectively.

VI. CONCLUSIONS

Given that MOFs are a rapidly-developed material, they attracted interest of biological and medical approaches. Eliminating the use of toxic solvents is an initial parameter be considered in order to obtain non-toxic MOFs for the development of biomedical application. Water as a favorite replacement showed excellent results in term of particle size, stability and selectivity of MOFs. Furthermore, recycled waste PET

as organic linker exhibited prospective results to synthesis MOFs compared to industrial products. Toxicological assessments reveal Fe (III) and MIL-100 are the most promising metal and MOF for medical applications. MOFs have shown it can be an emerging trend as carrier to enhance drug efficacy and bioavailability. Several works of combining drugs with MOFs have demonstrated a clear positive effect. MOFs were also shown to be sensitive towards physiological and pathological properties such as pH, fluorescence and O₂. MOFs should be considered for further studies on solving biomedical challenges as they can provide smart solutions, as suggested by current findings.

REFERENCES

- [1] H.-C. Zhou, J. R. Long, and O. M. Yaghi, "Introduction to metal-organic frameworks." ACS Publications, 2012.
- [2] O. M. Yaghi and H. Li, "Hydrothermal synthesis of a metal-organic framework containing large rectangular channels," *J. Am. Chem. Soc.*, vol. 117, no. 41, pp. 10401–10402, 1995.
- [3] S. Kitagawa, R. Kitaura, and S. Noro, "Functional porous coordination polymers," *Angew. Chemie Int. Ed.*, vol. 43, no. 18, pp. 2334–2375, 2004.
- [4] G. Férey, "Microporous solids: From organically templated inorganic skeletons to hybrid frameworks... ecumenism in chemistry," *Chem. Mater.*, vol. 13, no. 10, pp. 3084–3098, 2001.
- [5] J. L. C. Rowsell and O. M. Yaghi, "Metal-organic frameworks: a new class of porous materials," *Microporous Mesoporous Mater.*, vol. 73, no. 1–2, pp. 3–14, 2004.
- [6] H. Furukawa, K. E. Cordova, M. O'Keeffe, and O. M. Yaghi, "The chemistry and applications of metal-organic frameworks," *Science (80-.)*, vol. 341, no. 6149, p. 1230444, 2013.
- [7] N. L. Rosi, J. Kim, M. Eddaoudi, B. Chen, M. O'Keeffe, and O. M. Yaghi, "Rod packings and metal-organic frameworks constructed from rod-shaped secondary building units," *J. Am. Chem. Soc.*, vol. 127, no. 5, pp. 1504–1518, 2005.
- [8] M. Lanchas *et al.*, "Two appealing alternatives for MOFs synthesis: solvent-free oven heating vs. microwave heating," *RSC Adv.*, vol. 4, no. 104, pp. 60409–60412, 2014.
- [9] G. Xu, B. Li, H. Wu, W. Zhou, and B. Chen, "Construction of ntt-Type Metal-Organic Framework from C₂-Symmetry Hexacarboxylate Linker for Enhanced Methane Storage," *Cryst. Growth Des.*, vol. 17, no. 9, pp. 4795–4800, 2017.
- [10] A. K. Cheetham, G. Férey, and T. Loiseau, "Open- framework inorganic materials," *Angew. Chemie Int. Ed.*, vol. 38, no. 22, pp. 3268–3292, 1999.
- [11] M. Dincă and J. R. Long, "Hydrogen storage in microporous metal-organic frameworks with exposed metal sites," *Angew. Chemie Int. Ed.*, vol. 47, no. 36, pp. 6766–6779, 2008.
- [12] J.-S. Choi, W.-J. Son, J. Kim, and W.-S. Ahn, "Metal-organic framework MOF-5 prepared by microwave heating: Factors to be considered," *Microporous Mesoporous Mater.*, vol. 116, no. 1–3, pp. 727–731, 2008.
- [13] Z. Ni and R. I. Masel, "Rapid production of metal-organic frameworks via microwave-assisted solvothermal synthesis," *J. Am. Chem. Soc.*, vol. 128, no. 38, pp. 12394–12395, 2006.
- [14] P. Deria, J. E. Mondloch, O. Karagiari, W. Bury, J. T. Hupp, and O. K. Farha, "Beyond post-synthesis modification: evolution of metal-organic frameworks via building block replacement," *Chem. Soc. Rev.*, vol. 43, no. 16, pp. 5896–5912, 2014.
- [15] T. Li, M. T. Kozłowski, E. A. Doud, M. N. Blakely, and N. L. Rosi, "Stepwise ligand exchange for the preparation of a family of mesoporous MOFs," *J. Am. Chem. Soc.*, vol. 135, no. 32, pp. 11688–11691, 2013.
- [16] A. D. Burrows, C. G. Frost, M. F. Mahon, and C. Richardson, "Post- Synthetic Modification of Tagged Metal-Organic Frameworks," *Angew. Chemie Int. Ed.*, vol. 47, no. 44, pp. 8482–8486, 2008.
- [17] S. Das, H. Kim, and K. Kim, "Metathesis in single crystal: complete and reversible exchange of metal ions constituting the frameworks of Metal- Organic frameworks," *J. Am. Chem. Soc.*, vol. 131, no. 11, pp. 3814–3815, 2009.
- [18] J. Zhuang, C.-H. Kuo, L.-Y. Chou, D.-Y. Liu, E. Weerapana, and C.-K. Tsung, "Optimized metal-organic-framework nanospheres for drug delivery: evaluation of small-molecule encapsulation," *ACS Nano*, vol. 8, no. 3, pp. 2812–2819, 2014.
- [19] P. Falcaro *et al.*, "A new method to position and functionalize metal-organic framework crystals," *Nat. Commun.*, vol. 2, p. 237, 2011.
- [20] G. Lu *et al.*, "Imparting functionality to a metal-organic framework material by controlled nanoparticle encapsulation," *Nat. Chem.*, vol. 4, no. 4, p. 310, 2012.
- [21] A. Ahmed, M. Forster, R. Clowes, D. Bradshaw, P. Myers, and H. Zhang, "Silica SOS@ HKUST-1 composite microspheres as

- easily packed stationary phases for fast separation," *J. Mater. Chem. A*, vol. 1, no. 10, pp. 3276–3286, 2013.
- [22] D. Alezi *et al.*, "MOF crystal chemistry paving the way to gas storage needs: aluminum-based soc-MOF for CH₄, O₂, and CO₂ storage," *J. Am. Chem. Soc.*, vol. 137, no. 41, pp. 13308–13318, 2015.
- [23] P. Horcajada *et al.*, "Flexible porous metal-organic frameworks for a controlled drug delivery," *J. Am. Chem. Soc.*, vol. 130, no. 21, pp. 6774–6780, 2008.
- [24] K. M. L. Taylor-Pashow, J. Della Rocca, Z. Xie, S. Tran, and W. Lin, "Postsynthetic modifications of iron-carboxylate nanoscale metal-organic frameworks for imaging and drug delivery," *J. Am. Chem. Soc.*, vol. 131, no. 40, pp. 14261–14263, 2009.
- [25] D. Liu, R. C. Huxford, and W. Lin, "Phosphorescent nanoscale coordination polymers as contrast agents for optical imaging," *Angew. Chemie*, vol. 123, no. 16, pp. 3780–3784, 2011.
- [26] C. Orellana-Tavra *et al.*, "Amorphous metal-organic frameworks for drug delivery," *Chem. Commun.*, vol. 51, no. 73, pp. 13878–13881, 2015.
- [27] S. Furukawa, J. Reboul, S. Diring, K. Sumida, and S. Kitagawa, "Structuring of metal-organic frameworks at the mesoscopic/macroscopic scale," *Chem. Soc. Rev.*, vol. 43, no. 16, pp. 5700–5734, 2014.
- [28] M. L. Foo, R. Matsuda, and S. Kitagawa, "Functional hybrid porous coordination polymers," *Chem. Mater.*, vol. 26, no. 1, pp. 310–322, 2013.
- [29] H.-S. Wang, "Metal-organic frameworks for biosensing and bioimaging applications," *Coord. Chem. Rev.*, vol. 349, pp. 139–155, 2017.
- [30] J. Lee, O. K. Farha, J. Roberts, K. A. Scheidt, S. T. Nguyen, and J. T. Hupp, "Metal-organic framework materials as catalysts," *Chem. Soc. Rev.*, vol. 38, no. 5, pp. 1450–1459, 2009.
- [31] J. H. Cavka *et al.*, "A new zirconium inorganic building brick forming metal organic frameworks with exceptional stability," *J. Am. Chem. Soc.*, vol. 130, no. 42, pp. 13850–13851, 2008.
- [32] O. K. Farha, A. M. Spokoyny, K. L. Mulfort, M. F. Hawthorne, C. A. Mirkin, and J. T. Hupp, "Synthesis and hydrogen sorption properties of carborane based metal-organic framework materials," *J. Am. Chem. Soc.*, vol. 129, no. 42, pp. 12680–12681, 2007.
- [33] A. H. Chughtai, N. Ahmad, H. A. Younus, A. Laypkov, and F. Verpoort, "Metal-organic frameworks: versatile heterogeneous catalysts for efficient catalytic organic transformations," *Chem. Soc. Rev.*, vol. 44, no. 19, pp. 6804–6849, 2015.
- [34] A. C. McKinlay *et al.*, "BioMOFs: metal-organic frameworks for biological and medical applications," *Angew. Chemie Int. Ed.*, vol. 49, no. 36, pp. 6260–6266, 2010.
- [35] S. Keskin and S. Kızılel, "Biomedical applications of metal organic frameworks," *Ind. Eng. Chem. Res.*, vol. 50, no. 4, pp. 1799–1812, 2011.
- [36] C.-Y. Sun, C. Qin, X.-L. Wang, and Z.-M. Su, "Metal-organic frameworks as potential drug delivery systems," *Expert Opin. Drug Deliv.*, vol. 10, no. 1, pp. 89–101, 2013.
- [37] W. Cai, C. Chu, G. Liu, and Y. J. Wang, "Metal-organic framework-based nanomedicine platforms for drug delivery and molecular imaging," *Small*, vol. 11, no. 37, pp. 4806–4822, 2015.
- [38] M. Giménez-Marqués, T. Hidalgo, C. Serre, and P. Horcajada, "Nanostructured metal-organic frameworks and their bio-related applications," *Coord. Chem. Rev.*, vol. 307, pp. 342–360, 2016.
- [39] H. U. Käfferlein and J. Angerer, "N-methylcarbamoylated valine of hemoglobin in humans after exposure to N, N-dimethylformamide: evidence for the formation of methyl isocyanate?," *Chem. Res. Toxicol.*, vol. 14, no. 7, pp. 833–840, 2001.
- [40] T. H. Kim, Y. W. Kim, S. M. Shin, C. W. Kim, I. J. Yu, and S. G. Kim, "Synergistic hepatotoxicity of N, N-dimethylformamide with carbon tetrachloride in association with endoplasmic reticulum stress," *Chem. Biol. Interact.*, vol. 184, no. 3, pp. 492–501, 2010.
- [41] J. Fan *et al.*, "Bio-Engineered Graphene-Based Cage for Efficient Local Enrichment and Biodegradation of Aqueous Organic Wastes," *Sci. Rep.*, vol. 7, no. 1, p. 1271, 2017.
- [42] S. Altan and Z. Oğurtan, "Dimethyl sulfoxide but not indomethacin is efficient for healing in hydrofluoric acid eye burns," *burns*, vol. 43, no. 1, pp. 232–244, 2017.
- [43] K. Dennerlein *et al.*, "Dermal absorption and skin damage following hydrofluoric acid exposure in an ex vivo human skin model," *Toxicol. Lett.*, vol. 248, pp. 25–33, 2016.
- [44] X. Wang *et al.*, "A review of treatment strategies for hydrofluoric acid burns: current status and future prospects," *Burns*, vol. 40, no. 8, pp. 1447–1457, 2014.
- [45] X. Wu, C. Yang, and J. Ge, "Green synthesis

- of enzyme/metal-organic framework composites with high stability in protein denaturing solvents," *Bioresour. Bioprocess.*, vol. 4, no. 1, p. 24, 2017.
- [46] R. Ameloot, F. Vermoortele, W. Vanhove, M. B. J. Roeffaers, B. F. Sels, and D. E. De Vos, "Interfacial synthesis of hollow metal-organic framework capsules demonstrating selective permeability," *Nat. Chem.*, vol. 3, no. 5, p. 382, 2011.
- [47] M. Gimeno-Fabra *et al.*, "Instant MOFs: continuous synthesis of metal-organic frameworks by rapid solvent mixing," *Chem. Commun.*, vol. 48, no. 86, pp. 10642–10644, 2012.
- [48] K.-J. Kim *et al.*, "High-rate synthesis of Cu-BTC metal-organic frameworks," *Chem. Commun.*, vol. 49, no. 98, pp. 11518–11520, 2013.
- [49] L. H. Wee, F. Bonino, C. Lamberti, S. Bordiga, and J. A. Martens, "Cr-MIL-101 encapsulated Keggin phosphotungstic acid as active nanomaterial for catalysing the alcoholysis of styrene oxide," *Green Chem.*, vol. 16, no. 3, pp. 1351–1357, 2014.
- [50] I. A. Ibarra *et al.*, "Near-critical water, a cleaner solvent for the synthesis of a metal-organic framework," *Green Chem.*, vol. 14, no. 1, pp. 117–122, 2012.
- [51] V. Agostoni *et al.*, "Green fluorine-free mesoporous iron (III) trimesate nanoparticles for drug delivery," *Green Mater.*, vol. 1, no. 4, pp. 209–217, 2013.
- [52] P. Horcajada *et al.*, "Porous metal-organic-framework nanoscale carriers as a potential platform for drug delivery and imaging," *Nat. Mater.*, vol. 9, no. 2, p. 172, 2010.
- [53] A. García Márquez *et al.*, "Green Microwave Synthesis of MIL-100 (Al, Cr, Fe) Nanoparticles for Thin-Film Elaboration," *Eur. J. Inorg. Chem.*, vol. 2012, no. 32, pp. 5165–5174, 2012.
- [54] Y.-K. Seo *et al.*, "Large scale fluorine-free synthesis of hierarchically porous iron (III) trimesate MIL-100 (Fe) with a zeolite MTN topology," *Microporous Mesoporous Mater.*, vol. 157, pp. 137–145, 2012.
- [55] P. A. Bayliss *et al.*, "Synthesis of metal-organic frameworks by continuous flow," *Green Chem.*, vol. 16, no. 8, pp. 3796–3802, 2014.
- [56] A. U. Czaja, N. Trukhan, and U. Müller, "Industrial applications of metal-organic frameworks," *Chem. Soc. Rev.*, vol. 38, no. 5, pp. 1284–1293, 2009.
- [57] U. Mueller, M. Schubert, F. Teich, H. Puetter, K. Schierle-Arndt, and J. Pastre, "Metal-organic frameworks—prospective industrial applications," *J. Mater. Chem.*, vol. 16, no. 7, pp. 626–636, 2006.
- [58] H. Reinsch *et al.*, "Green synthesis of zirconium-MOFs," *CrystEngComm*, vol. 17, no. 22, pp. 4070–4074, 2015.
- [59] V. Benoit *et al.*, "MIL-91 (Ti), a small pore metal-organic framework which fulfils several criteria: an upscaled green synthesis, excellent water stability, high CO₂ selectivity and fast CO₂ transport," *J. Mater. Chem. A*, vol. 4, no. 4, pp. 1383–1389, 2016.
- [60] V. Jabbari, J. M. Veleta, M. Zarei-Chaleshtori, J. Gardea-Torresdey, and D. Villagrán, "Green synthesis of magnetic MOF@ GO and MOF@ CNT hybrid nanocomposites with high adsorption capacity towards organic pollutants," *Chem. Eng. J.*, vol. 304, pp. 774–783, 2016.
- [61] Y. Yao, F. Xu, M. Chen, Z. Xu, and Z. Zhu, "Adsorption behavior of methylene blue on carbon nanotubes," *Bioresour. Technol.*, vol. 101, no. 9, pp. 3040–3046, 2010.
- [62] F. Awaja and D. Pavel, "Recycling of PET," *Eur. Polym. J.*, vol. 41, no. 7, pp. 1453–1477, 2005.
- [63] S. Wang, C. Wang, H. Wang, X. Chen, and S. Wang, "Sodium titanium tris (glycolate) as a catalyst for the chemical recycling of poly (ethylene terephthalate) via glycolysis and repolycondensation," *Polym. Degrad. Stab.*, vol. 114, pp. 105–114, 2015.
- [64] R. K. Al-tamimi, M. N. Khalaf, M. Sabri, and L. Sabri, "Post consumer poly (ethylene terephthalate) depolymerization by waste of battery acid hydrolysis," *J. Mater. Environ. Sci.*, vol. 2, no. 2, pp. 88–93, 2011.
- [65] W. P. R. Deleu, I. Stassen, D. Jonckheere, R. Ameloot, and D. E. De Vos, "Waste PET (bottles) as a resource or substrate for MOF synthesis," *J. Mater. Chem. A*, vol. 4, no. 24, pp. 9519–9525, 2016.
- [66] P. L. Llewellyn, F. Rodriguez-Reinoso, J. Rouquerol, and N. Seaton, "Is the BET equation applicable to microporous adsorbents?," *Stud. Surf. Sci. Catal.*, vol. 160, p. 49, 2007.
- [67] S.-H. Lo, D. S. Raja, C.-W. Chen, Y.-H. Kang, J.-J. Chen, and C.-H. Lin, "Waste polyethylene terephthalate (PET) materials as sustainable precursors for the synthesis of nanoporous MOFs, MIL-47, MIL-53 (Cr, Al, Ga) and MIL-101 (Cr)," *Dalt. Trans.*, vol. 45, no. 23, pp. 9565–9573, 2016.
- [68] J. Ren *et al.*, "Green synthesis of chromium-based metal-organic framework (Cr-MOF) from waste polyethylene terephthalate (PET) bottles

- for hydrogen storage applications," *Int. J. Hydrogen Energy*, vol. 41, no. 40, pp. 18141–18146, 2016.
- [69] X. Dyosiba, J. Ren, N. M. Musyoka, H. W. Langmi, M. Mathe, and M. S. Onyango, "Preparation of value-added metal-organic frameworks (MOFs) using waste PET bottles as source of acid linker," *Sustain. Mater. Technol.*, vol. 10, pp. 10–13, 2016.
- [70] I. B. Vasconcelos *et al.*, "Cytotoxicity and slow release of the anti-cancer drug doxorubicin from ZIF-8," *RSC Adv.*, vol. 2, no. 25, pp. 9437–9442, 2012.
- [71] C. Tamames-Tabar *et al.*, "Cytotoxicity of nanoscaled metal-organic frameworks," *J. Mater. Chem. B*, vol. 2, no. 3, pp. 262–271, 2014.
- [72] À. Ruyra *et al.*, "Synthesis, culture medium stability, and in vitro and in vivo zebrafish embryo toxicity of metal-organic framework nanoparticles," *Chem. Eur. J.*, vol. 21, no. 6, pp. 2508–2518, 2015.
- [73] R. Grall, T. Hidalgo, J. Delic, A. Garcia-Marquez, S. Chevillard, and P. Horcajada, "In vitro biocompatibility of mesoporous metal (III; Fe, Al, Cr) trimesate MOF nanocarriers," *J. Mater. Chem. B*, vol. 3, no. 42, pp. 8279–8292, 2015.
- [74] E. Bellido *et al.*, "Heparin-Engineered Mesoporous Iron Metal-Organic Framework Nanoparticles: Toward Stealth Drug Nanocarriers," *Adv. Healthc. Mater.*, vol. 4, no. 8, pp. 1246–1257, 2015.
- [75] T. Sattar, M. Athar, and M. Najamul Haq, "Hydrothermal Synthesis, Characterization, and In Vitro Drug Adsorption Studies of Some Nano-BioMOFs," *J. Nanomater.*, vol. 2016, 2016.
- [76] B. Yang, M. Shen, J. Liu, and F. Ren, "Post-Synthetic Modification Nanoscale Metal-Organic Frameworks for Targeted Drug Delivery in Cancer Cells," *Pharm. Res.*, vol. 34, no. 11, pp. 2440–2450, 2017.
- [77] T. Baati *et al.*, "In depth analysis of the in vivo toxicity of nanoparticles of porous iron (III) metal-organic frameworks," *Chem. Sci.*, vol. 4, no. 4, pp. 1597–1607, 2013.
- [78] T. C. K. Heiden, E. Dengler, W. J. Kao, W. Heideman, and R. E. Peterson, "Developmental toxicity of low generation PAMAM dendrimers in zebrafish," *Toxicol. Appl. Pharmacol.*, vol. 225, no. 1, pp. 70–79, 2007.
- [79] O. Bar-Ilan, R. M. Albrecht, V. E. Fako, and D. Y. Furgeson, "Toxicity assessments of multisized gold and silver nanoparticles in zebrafish embryos," *Small*, vol. 5, no. 16, pp. 1897–1910, 2009.
- [80] S. George *et al.*, "Use of a high-throughput screening approach coupled with in vivo zebrafish embryo screening to develop hazard ranking for engineered nanomaterials," *ACS Nano*, vol. 5, no. 3, pp. 1805–1817, 2011.
- [81] C. He, D. Liu, and W. Lin, "Nanomedicine applications of hybrid nanomaterials built from metal-ligand coordination bonds: nanoscale metal-organic frameworks and nanoscale coordination polymers," *Chem. Rev.*, vol. 115, no. 19, pp. 11079–11108, 2015.
- [82] T. Simon-Yarza *et al.*, "In vivo behavior of MIL-100 nanoparticles at early times after intravenous administration," *Int. J. Pharm.*, vol. 511, no. 2, pp. 1042–1047, 2016.
- [83] P. Horcajada *et al.*, "Synthesis and catalytic properties of MIL-100 (Fe), an iron (III) carboxylate with large pores," *Chem. Commun.*, no. 27, pp. 2820–2822, 2007.
- [84] D. J. Levine *et al.*, "Olsalazine-based metal-organic frameworks as biocompatible platforms for H₂ adsorption and drug delivery," *J. Am. Chem. Soc.*, vol. 138, no. 32, pp. 10143–10150, 2016.
- [85] M. Kotzabasaki, I. Galdadas, E. Tylianakis, E. Klontzas, Z. Cournia, and G. E. Froudakis, "Multiscale simulations reveal IRMOF-74-III as a potent drug carrier for gemcitabine delivery," *J. Mater. Chem. B*, vol. 5, no. 18, pp. 3277–3282, 2017.
- [86] V. Agostoni *et al.*, "Towards an Improved anti-HIV Activity of NRTI via Metal-Organic Frameworks Nanoparticles," *Adv. Healthc. Mater.*, vol. 2, no. 12, pp. 1630–1637, 2013.
- [87] F. R. S. Lucena *et al.*, "Induction of cancer cell death by apoptosis and slow release of 5-fluoracil from metal-organic frameworks Cu-BTC," *Biomed. Pharmacother.*, vol. 67, no. 8, pp. 707–713, 2013.
- [88] V. Rodriguez-Ruiz *et al.*, "Efficient 'green' encapsulation of a highly hydrophilic anticancer drug in metal-organic framework nanoparticles," *J. Drug Target.*, vol. 23, no. 7–8, pp. 759–767, 2015.
- [89] K. Lu, C. He, and W. Lin, "A chlorin-based nanoscale metal-organic framework for photodynamic therapy of colon cancers," *J. Am. Chem. Soc.*, vol. 137, no. 24, pp. 7600–7603, 2015.
- [90] K. Lu *et al.*, "Chlorin-based nanoscale metal-organic framework systemically rejects colorectal cancers via synergistic photodynamic therapy and checkpoint blockade immunotherapy," *J. Am. Chem. Soc.*,

- vol. 138, no. 38, pp. 12502–12510, 2016.
- [91] T. Simon-Yarza *et al.*, “A Smart Metal–Organic Framework Nanomaterial for Lung Targeting,” *Angew. Chemie Int. Ed.*, vol. 56, no. 49, pp. 15565–15569, 2017.
- [92] N. A. Mohamed *et al.*, “Metal Organic Framework as a Potential Drug Carrier for Pulmonary Arterial Hypertension,” in *Qatar Foundation Annual Research Conference Proceedings*, 2016, vol. 2016, no. 1, p. HBSP2477.
- [93] D. M. Reed *et al.*, “Morphology and vasoactive hormone profiles from endothelial cells derived from stem cells of different sources,” *Biochem. Biophys. Res. Commun.*, vol. 455, no. 3, pp. 172–177, 2014.
- [94] A. El-Ansary and L. M. Faddah, “Nanoparticles as biochemical sensors,” *Nanotechnol. Sci. Appl.*, vol. 3, p. 65, 2010.
- [95] X. Wang, X. Lu, L. Wu, and J. Chen, “3D metal-organic framework as highly efficient biosensing platform for ultrasensitive and rapid detection of bisphenol A,” *Biosens. Bioelectron.*, vol. 65, pp. 295–301, 2015.
- [96] Y.-A. Li *et al.*, “Nanoscale UiO-MOF-based luminescent sensors for highly selective detection of cysteine and glutathione and their application in bioimaging,” *Chem. Commun.*, vol. 51, no. 100, pp. 17672–17675, 2015.
- [97] C. He, K. Lu, and W. Lin, “Nanoscale metal–organic frameworks for real-time intracellular pH sensing in live cells,” *J. Am. Chem. Soc.*, vol. 136, no. 35, pp. 12253–12256, 2014.
- [98] E. Ikeda, “Cellular response to tissue hypoxia and its involvement in disease progression,” *Pathol. Int.*, vol. 55, no. 10, pp. 603–610, 2005.
- [99] R. Xu *et al.*, “Nanoscale metal–organic frameworks for ratiometric oxygen sensing in live cells,” *J. Am. Chem. Soc.*, vol. 138, no. 7, pp. 2158–2161, 2016.
- [100] X. Yi, W. Dong, X. Zhang, J. Xie, and Y. Huang, “MIL-53 (Fe) MOF-mediated catalytic chemiluminescence for sensitive detection of glucose,” *Anal. Bioanal. Chem.*, vol. 408, no. 30, pp. 8805–8812, 2016.
- [101] W. Dong, L. Yang, and Y. Huang, “Glycine post-synthetic modification of MIL-53 (Fe) metal–organic framework with enhanced and stable peroxidase-like activity for sensitive glucose biosensing,” *Talanta*, vol. 167, pp. 359–366, 2017.