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REVIEW

Application of Metal-Organic Frameworks Nanoparticles in the Diagnosis and Treatment of Breast Cancer

Xin-Ran Jiang[1,*], Jiahao Mi[1,*], Yiling Wang[1], Mengqi Yin[1], Yuna Tong[2], Yuxuan Zhu[1]

[1]Department of Pharmacy, Personalized Drug Therapy Key Laboratory of Sichuan Province, Sichuan Academy of Medical Science & Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, 610072, People's Republic of China; [2]Department of Nephrology, The Third People's Hospital of Chengdu, Chengdu, 610031, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yuna Tong; Yuxuan Zhu, Email tongyuna1985@163.com; zhuyuxuan6688@163.com

Abstract: Breast cancer remains the most prevalent malignancy among women and the second leading cause of cancer-related mortality worldwide, primarily attributable to delayed diagnosis and limited therapeutic efficacy. Recent nanotechnology advances exhibit transformative potential in breast cancer management. Metal-organic frameworks (MOFs) have emerged as promising nanoplatforms for biomedical applications due to their exceptional adsorption capacity, high surface area, tunable porosity, structural stability, and facile surface functionalization-properties enabling advanced drug delivery systems (DDSs). This review systematically summarizes MOFs for DDSs and their applications in breast cancer. Classification by metal-ligand composition precedes critical analysis of synthesis methodologies, including comparative advantages and limitations alongside key factors influencing biomedical performance. A dedicated sections highlights normal and stimuli-responsive MOFs activated by endogenous or exogenous triggers. Furthermore, the application of multifunctional MOFs has been comprehensively explored, including chemotherapy, photothermal therapy, photodynamic therapy, immunotherapy, and diagnostic-therapeutic integration in breast cancer. Finally, challenges and possible solutions for MOFs in drug delivery are discussed.

Keywords: metal-organic frameworks, drug delivery systems, breast cancer

Introduction

According to the latest global cancer information provided by the International Agency for Research on Cancer (IARC), globally there are estimated to be nearly 20 million new cancer cases and 9.7 million cancer deaths in 2022, of which female breast cancer is second only to lung cancer (2.48 million, or 12.4%), with about 2.3 million new cases (11.6%), and death rates for female breast cancer in transitioning countries were higher compared with those in transitioned countries.[1] It follows that cancer, especially breast cancer, has contributed to a tremendous health hazard to human.

Conventional breast cancer therapies-surgery, radiotherapy and chemotherapy-remain first-line interventions yet face persistent limitations in metastasis suppression and tissue toxicity.[2] Surgery achieves curative outcomes in early-stage breast cancer but risks postoperative recurrence and fails in advanced cancers.[3] Radiotherapy targeting the hypothalamic-pituitary axis frequently induces growth hormone deficiency (GHD), causing developmental and metabolic sequelae in pediatric survivors.[4] Chemotherapy, though essential for advanced and metastatic disease, triggers near-ubiquitous myelosuppression through cytotoxicity against rapidly dividing tissues (eg, hematopoietic system),[5] compounded by drug resistance and poor aqueous solubility.[6] These constraints accelerate demand for precision therapeutics. Emerging delivery systems (liposomes, inclusion complexes, polymeric carriers; Figure 1) can enhance drug bioavailability and biocompatibility through structural modifications exploiting tumor permeability.[7–10] Nevertheless, the critical limitations of liposomes suffer from low drug-loading capacity[11] and blood instability,[12] while undefined pore architectures and

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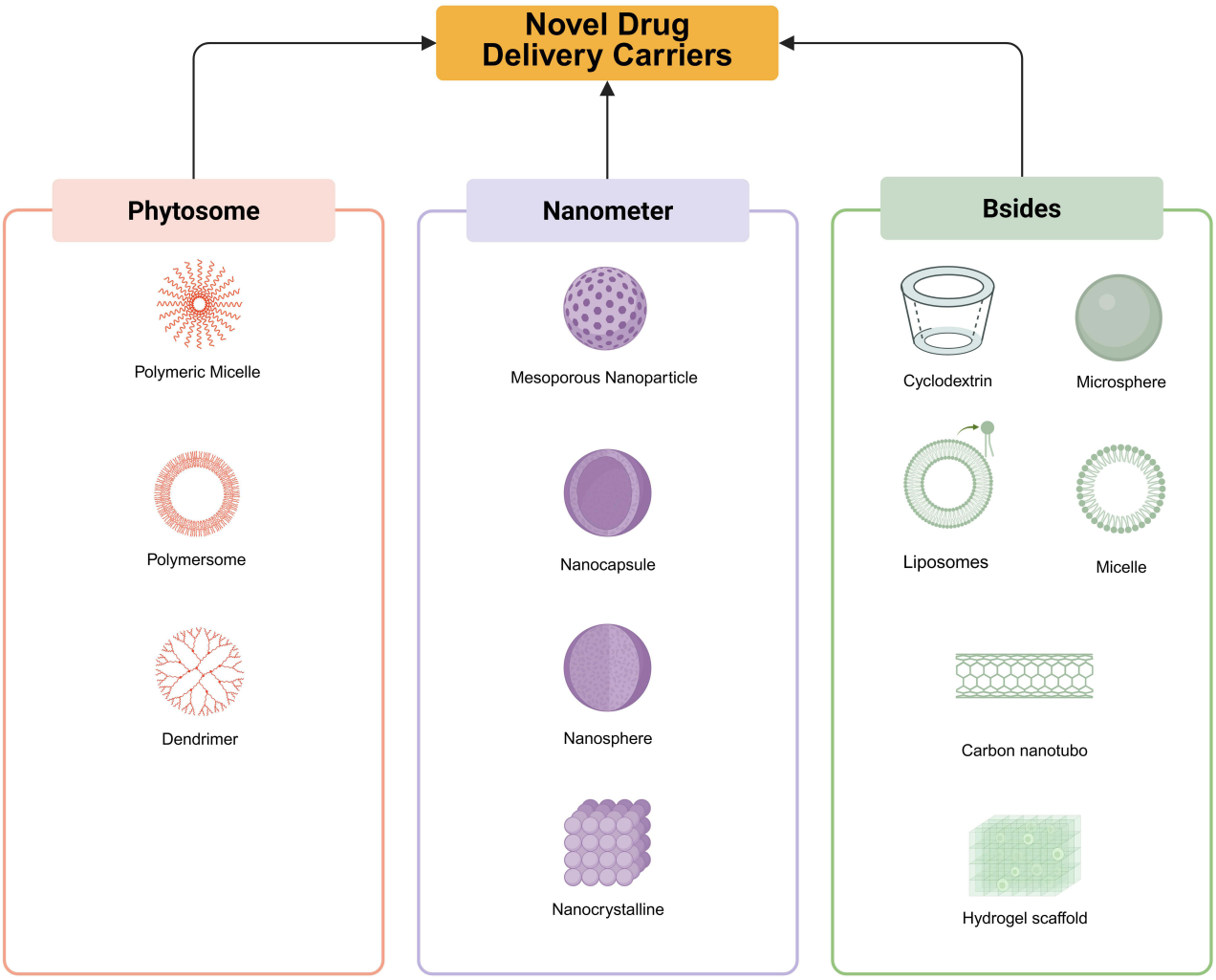

Figure 1 Novel drug delivery carriers.

weak drug-carrier interactions precipitate uncontrolled release.[13] These unresolved challenges underscore the imperative for innovative targeted breast cancer therapies.

Metal-organic framework materials (MOFs) are a class of compounds consisting of metal ions or metal clusters coordinated with organic ligands to form one-, two-, or three-dimensional structures where the organic ligands contain potential voids. Metal-organic frameworks have excellent properties such as high adsorption capacity, high surface area (for easy loading of goods), high porosity (for the encapsulation of various drugs and other functional reagents), thermal and chemical stability (for easy post-synthesis functionalization). It has been reported that Metal-Organic Frameworks (MOFs) achieve significantly higher drug loading capacities than liposomes, due to their tunable pore geometries, although they experience greater batch-to-batch variability. Moreover, the rigid framework of MOFs substantially enhances tumor penetration efficiency, especially within the dense breast cancer stroma, with active targeting strategies significantly improving tumor accumulation compared to conventional carriers. It is such properties that enable them to be used in a wide range of industries and technologies such as photocatalysis,[14] electrochemistry,[15] gas storage and separation,[16] energy,[17] imaging,[18] sensing[19] and biomedicine.[20]

Despite the ligand bonds in MOFs causing structural instability in biological environments, these nanomaterials paradoxically demonstrate exceptional potential as theragnostic carriers in breast cancer.[21] The controlled drug release kinetics, biocompatibility, and biodegradability of MOFs facilitate precise chemotherapeutic agent delivery through dual targeting mechanisms: (1) passive targeting via enhanced permeability and retention (EPR) effect;[22] and (2) active

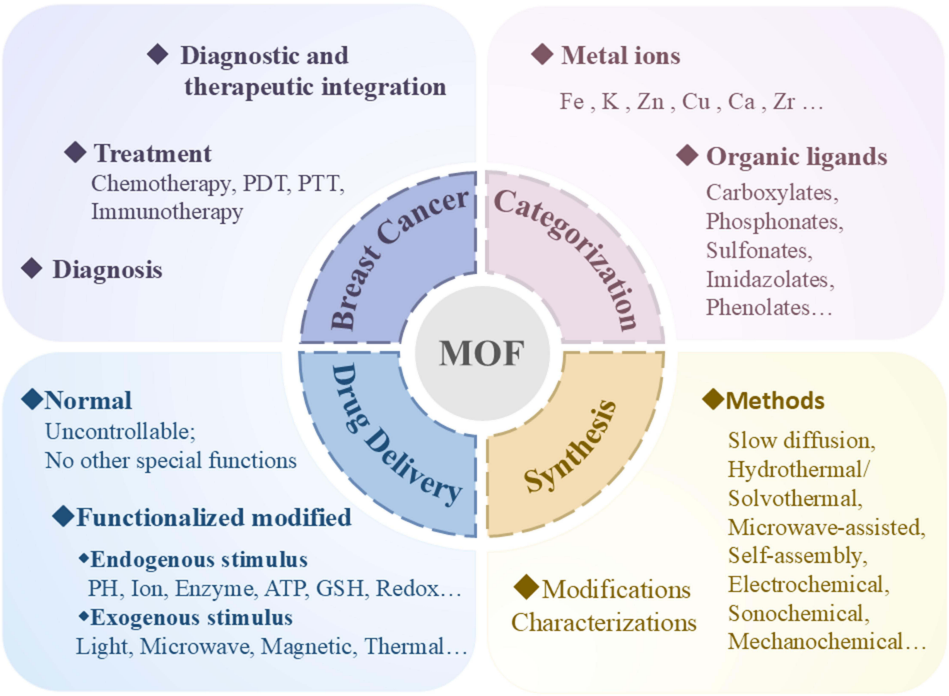

Figure 2 Classification, synthesis, and applications of MOFs in drug delivery and breast cancer.

targeting mediated by surface-conjugated ligands, aptamers, or antibodies.[23] This multimodal approach increases tumor accumulation while minimizing off-target toxicity, thus addressing key limitations of traditional chemotherapy.[24]

This review focuses on MOF-based on delivery systems and their application in breast cancer. Primary classification by metal-ligand coordination architectures establishes fundamental topological taxonomies. Critical analysis of prevalent synthesis strategies highlights their physicochemical determinants in biological performance. The functionalization strategies for drug delivery have been comparatively analyzed, which include passive targeting and active targeting via surface modification of ligands. Synergistically integrated diagnostic and therapeutic applications have also been systemized, proposing novel paradigms for precision breast cancer treatment. Finally, a possible solution to the problem of MOFs based drug delivery system is proposed (Figure 2).

Categorization of MOFs

MOFs are crystalline coordination networks formed by metal ions/clusters and multitopic organic linkers, possessing intrinsic porosity for hosting guest species (eg, therapeutic molecules, counterions).[25] Contemporary research has diversified MOF architectures through systematic variations of metallic nodes and organic ligands, enabling applications spanning DDSs, catalysis, sensing, and energy technologies. This review specifically focuses on MOF-based DDSs, classifying candidate materials by central metal ions (Table 1) and ligand functionalities.

Classification by Metal Ions

Biosafety profiling-encompassing biocompatibility, biodegradation kinetics, and inherent cytotoxicity-constitutes a primary design criterion for MOFs in drug delivery systems (DDSs). Most metallic constituents exhibit concentration-dependent toxicity, notably constraining usable varieties to endogenous physioregulatory ions, eg, iron (Fe), potassium (K), zinc (Zn), copper (Cu), and calcium (Ca). Despite favorable biocompatibility profiles, these cations necessitate comprehensive evaluation of administration routes, exposure duration, speciation dynamics, and bioaccumulation/elimination kinetics.[43] Additionally, exogenous elements applied for specific medical purposes are included, such as platinum (Pt) for anti-tumor,[44] gadolinium (Gd) and zirconium (Zr) for medical diagnostics.[45]

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Table 1 Classification of MOFs by Metal Ions for Drug Loading

Category	Naming	Organic Ligand	Drug Loading	Ref.
Fe-MOFs	MIL-88(Fe)	1,4-Benzenedicarboxylic acid	Tetracycline	[26]
		Terephthalic acid	Doxorubicin	[27]
	MIL-100(Fe)	1,3,5-Benzenetricarboxylic acid	Isoniazid, Oxaliplatin, Cyclophosphamide	[28–30]
	MIL-101(Fe)	Terephthalic acid	Procaine	[31]
K-MOFs	CD-MOF	Cyclodextrins	5-Fluorouracil, Carmofur, Salicylic acid	[32,33]
Zn-MOFs	Bio-MOF	2-Methoxy-4-methylphenol	Vancomycin	[34]
	$Zn_2(EBNB)_2(BPY)_2$ $2H_2$	(E)-Bis(p-3-nitrobenzoic acid) ethylene, 4,4′-Bipyridine	Methadone	[35]
Cu-MOFs	Cu-MOF	Terephthalic acid	Ibuprofen	[36]
	Cu-MOFs@Keratin	2-Aminoterephthalic acid	Doxorubicin	[37]
	Cu-BTC	Trimesic acid	Diethyl dithiocarbamate	[38]
Ca-MOFs	Ca-Sr-MOF	1,3,5-Benzenetricarboxylic acid	Tetracycline	[39]
	Ca-MOF	Chelidonic acid	Zoliflodacin	[40]
Zr-MOFs	UiO-67-CDC-$(CH_3)_2$	9H-Carbazole-2,7-dicarboxylic acid	5-Fluorouracil, Carmofur	[41]
	ZJU-800	(2*E*,2*E*′)-3,3′-(2-Fluoro-1,4-phenylene)diacrylic acid	Diclofenac sodium	[42]

Fe-MOFs

Iron cations (Fe), essential trace elements regulating hematopoiesis and immune function, demonstrate well-characterized biosafety profiles. These attributes establish iron-based MOFs as prime candidates for biomedical synthesis. It has been found that iron-based MOFs for biomedical applications should follow important specifications: precise particle size control, simple synthesis route, biocompatibility and non-toxicity, chemical stability and controlled degradation.[46] And iron-based MILs (Material of the Lavoisier Institute) have advantages over other subclasses of MOFs in biodegradability and cytotoxicity.[47] For example, Current studies utilizing MTT/CCK8 assays have demonstrated favorable biocompatibility of MIL-88, MIL-100, and MIL-101 with human or animal cells.[26–31,48] Recent advancements in iron-based MOFs include a novel litchi-like porous composite, Fe_3O_4@Fe-MOF@Hap, developed by Yang.[49] This composite exhibits a drug-loading capacity of 75.38 mg/g, saturation magnetization of 34 emu/g for magnetic targeting, along with pH-responsive drug release and excellent biocompatibility.

K-MOFs

Potassium-based MOFs (K-MOFs) demonstrate dual-functionality: their porous architectures facilitate energy-relevant processes (eg, selective ion transport, catalytic reactions, and gas adsorption), while exhibiting minimal cytotoxicity and environmental compatibility advantageous for drug delivery. Cyclodextrins (CDs), cyclic oligosaccharides, serve as biocompatible linkers for synthesizing CD-MOFs. Three variants (K-α-CD-MOF, K-β-CD-MOF, K-γ-CD-MOF) enhance drug solubility, bioavailability, structural integrity, and biosafety profiles.[32,33,50] Kristi et al[51] achieved 9–30 wt% active pharmaceutical ingredient (API) loading in K-γ-CD-MOF via crystallization optimization, with demonstrated cytoprotective effects in mammalian cell lines and *Danio rerio* models.

Zn-MOFs

Zinc ions (Zn^{2+}) exert bacteriostatic effects via binding anionic bacterial components, disrupting enzymatic activity and protein synthesis. This broad-spectrum antimicrobial activity synergizes with conventional antibiotics. Kai et al[34] engineered a bio-MOF utilizing Zn^{2+} nodes, immobilizing curcumin through electrostatic interactions. The resulting cationic MOF (QCSMOF-Van) demonstrated rapid bactericidal activity through bacterial adhesion and lysis, achieving a 33.47% drug loading efficiency 6.42% higher than the parent MOF. Beyond their antimicrobial advantages, Zn-MOFs exhibit excellent biocompatibility and notable sustained-release efficacy. Deng et al[35] pioneered $Zn_2(EBNB)_2(BPY)_2 \cdot 2H_2O$ as a 3D porous carrier, attaining 0.256 payload capacity. In vitro cytotoxicity assays revealed dose-dependent

responses, with >100% cell viability relative to controls at <20 μg/mL concentrations. Sustained release profiles showed 79.85% cumulative delivery within 30 hours.

Cu-MOFs

Although less extensively studied than Fe-MOFs, copper MOFs (Cu-MOFs) exhibit significant drug delivery potential owing to the catalytic activity of Cu^{2+} in pharmacologically relevant reactions.[36,37] Li et al[38] synthesized nanoscale Cu-BTC loaded with diethyldithiocarbamate (DDTC), a metabolite of the alcohol-aversion drug disulfiram. The Cu-DDTC complex (formed via Cu^{2+}-DDTC coordination) demonstrated high antitumor activity as a proteasome inhibitor, though exhibiting instability in vivo. The Cu-BTC@DDTC nanoformulation achieved 89%±0.4% tumor cell inhibition at 4 μg/mL within 48 h, indicating anticancer potential. Mechanistic studies revealed ferroptosis induction through SLC7A11/GPX4 signaling pathway inhibition. Notably, Cu-BTC@DDTC (10 mg/kg) synergized with low-dose cisplatin (1 mg/kg), showing enhanced antitumor efficacy and biosafety.

Ca-MOFs

Calcium ions (Ca^{2+}) regulate critical physiological processes including neuromuscular coordination, coagulation cascades, and osteogenesis. This biofunctional synergy enables calcium-based MOFs in orthopedic scaffolds to concurrently promote osteoblast proliferation and potentiate antimicrobial efficacy post-surgery. Vadivelmurugan et al[39] synthesized Ca-Sr-MOF via co-precipitation and coated it with aminomalononitrile (AMN) through electrostatic interactions. The antibiotic-loaded Ca-Sr-MOF and Ca-Sr-AMN-MOF exhibited loading capacities of 63% and 57%, respectively, with cumulative release rates of 55.15% versus 9.1% over 72 h. Both systems demonstrated potentiated antimicrobial efficacy (>90% bacterial inhibition) and osteoblast biocompatibility (viability >95%). Notably, a red blood cell membrane-derived nano-system (γ3-RCMZ) was engineered for sepsis treatment.[40] Calcium chloride donors exert dual anti-inflammatory actions through Caspase-1/NF-κB pathway suppression and oxidative stress mitigation, attenuating endothelial damage. The γ3-RCMZ platform further demonstrated target-specific bactericidal activity with uncompromised biocompatibility.

Zr-MOFs

Zr-MOFs are extensively studied for their high coordination versatility and chemical stability.[52] Sun et al[41] synthesized a carbazolyl-functionalized UiO-67-CDC via solvothermal method, followed by methylation modification to prepare UiO-67-CDC-$(CH_3)_2$, achieving a 56.5 wt% anticancer drug loading. The electron-deficient Zr-MOFs exhibit fluorescence sensing with high sensitivity through charge transfer mechanisms. Separately, Jiang et al[42] developed a Zr-cluster-based ZJU-800, demonstrating 58.8 wt% drug loading capacity and low cytotoxicity (cell viability >90% via MTT assay).

Classification by Organic Ligands

Theoretically feasible MOF combinations exceed thousands through systematic variation of metal nodes and organic linkers. Experimentally validated systems predominantly utilize carboxylate, phosphonate, sulfonate, imidazolate, and phenolate ligands, with dicarboxylic/polycarboxylic acids serving as the primary rigid backbone scaffolds.[53] Interestingly, Ligand functionalization enables precise modulation of MOF physicochemical properties,[54] creating highly active sites for multifunctional therapeutics. For instance, porphyrin-phthalocyanine MOFs incorporating phosphonate/azolate linkers exhibit water solubility and high stability.[55]

In DDSs, linker selection must balance physicochemical properties, biocompatibility, and degradation kinetics. For example, Abánades Lázaro et al[56] demonstrated that fumarate-ligated Zr-MOFs exhibit superior stability versus UiO-66 analogs due to lower ligand pK_a values, intensifying phosphate-carboxylate coordination competition. Ligand chemistry further governs drug loading/release profiles. Semirigid 5-(4′-carboxyphenoxy) nicotinic acid (H_2cpon) -derived Zn-cpon -1, synthesized via ClO_4^--templated assembly, displays significant DDS potential. And the loading of Zn-cpon-1 for 5-FU was significantly higher than that for 6-mercaptopurine (6-MP), 44.75 and 4.79 wt%, respectively.[57]

Bio-metal-organic frameworks (bio-MOFs), integrating biomolecules (eg, nucleobases, cyclodextrins, enzymes, peptides, porphyrins, sugars, and amino acids) as linker, combine structural tunability of MOFs with biocompatible

and biodegradable profiles.[58] The bio-MOF constructed from the small molecules of curcumin and Zn has now been successfully synthesized, exhibiting permanent porosity and a surface area of up to 3002 m^2/g.[59] There are now more researches on the preparation and application of bio-MOFs, such as anticancer drug-targeted delivery systems,[60] adsorbents,[61,62] and sensors.[63,64] Despite advances, key challenges persist: (1) complex synthesis routes with poor controllability and high cost; (2) limited stability under physiological conditions.[65]

Synthesis and Modification Strategies of MOFs

As discussed above, the synthesis of MOFs requires careful consideration of metal ions, organic linkers, and the loaded drug and/or solvent. Furthermore, the chosen synthesis method and experimental conditions significantly influence the crystallinity of MOFs, thereby determining their structure, properties, and functionality. Commonly reported synthesis strategies include slow diffusion, hydrothermal/solvothermal reactions, microwave-assisted synthesis, self-assembly, and electrochemical, sonochemical, or mechanochemical approaches. All methods depend on three key parameters: (1) reaction conditions (time, temperature, pressure, pH), (2) raw material properties (types and concentration ratios of metal salts, ligands, solvents, and modifiers), and (3) post-synthesis chemical modifications.[66–68] Understanding these variables is crucial for optimizing MOFs synthesis. A comparative analysis of the advantages and disadvantages of these methods is provided in Table 2.[69–77]

In biomedical applications, the safety of metal-organic frameworks (MOFs) necessitates particular consideration. Given that MOFs are synthesized using solvents, it is imperative to prioritize non-toxic and biodegradable solvents to minimize potential cytotoxic effects. For drug delivery systems, the selection of synthesis methods must take into account critical parameters such as biostability, pore size, particle size, drug loading capacity, and controlled release profiles,

Table 2 Synthesis Methods of MOFs

Method	Advantage	Disadvantage	Ref.
Slow evaporation synthesis	Under the constant low; temperature and atmospheric	Sluggish solvent evaporation; Unsuitable for large-scale production	
Hydrothermal or solvothermal synthesis	The effective growth of well-dispersed single crystals; Controlled temperature range for crystal growth	Long reaction time; High energy consumption	[69]
Microwave-assisted synthesis	High nucleation rate; Energy-efficient; Suitable for industrial scale-up	Unfavourable recycling; secondary pollution; Expensive reagent; Difficulty in analysing the single-crystal structure; Threat to health and safety from microwave reactors	[70,71]
Self-assembly synthesis	Synthesis of special structures that cannot be achieved by other methods	Long reaction time; Unsuitable for large-scale production; Unclear and unspecific mechanisms	[72]
Electrochemical synthesis	Gentle and controllable conditions; High flexibility and fast synthesis; Environmentally friendly; Suitable for industrial production	High requirements for equipment; Low output; Easy to generate impurities	[73]
Sonochemical synthesis	High efficiency; Ease of operation; Good dispersion; Environmental friendliness	Low yield; Unsuitable for scale-up; Crystals easily damaged by sonication; Inconsistent purity due to multiple structures	[74–76]
Mechanochemical synthesis	Environmental friendliness; High efficiency; Easy operation; Better thermal and water stability	Difficulty in obtaining the single-crystal structure	[77]

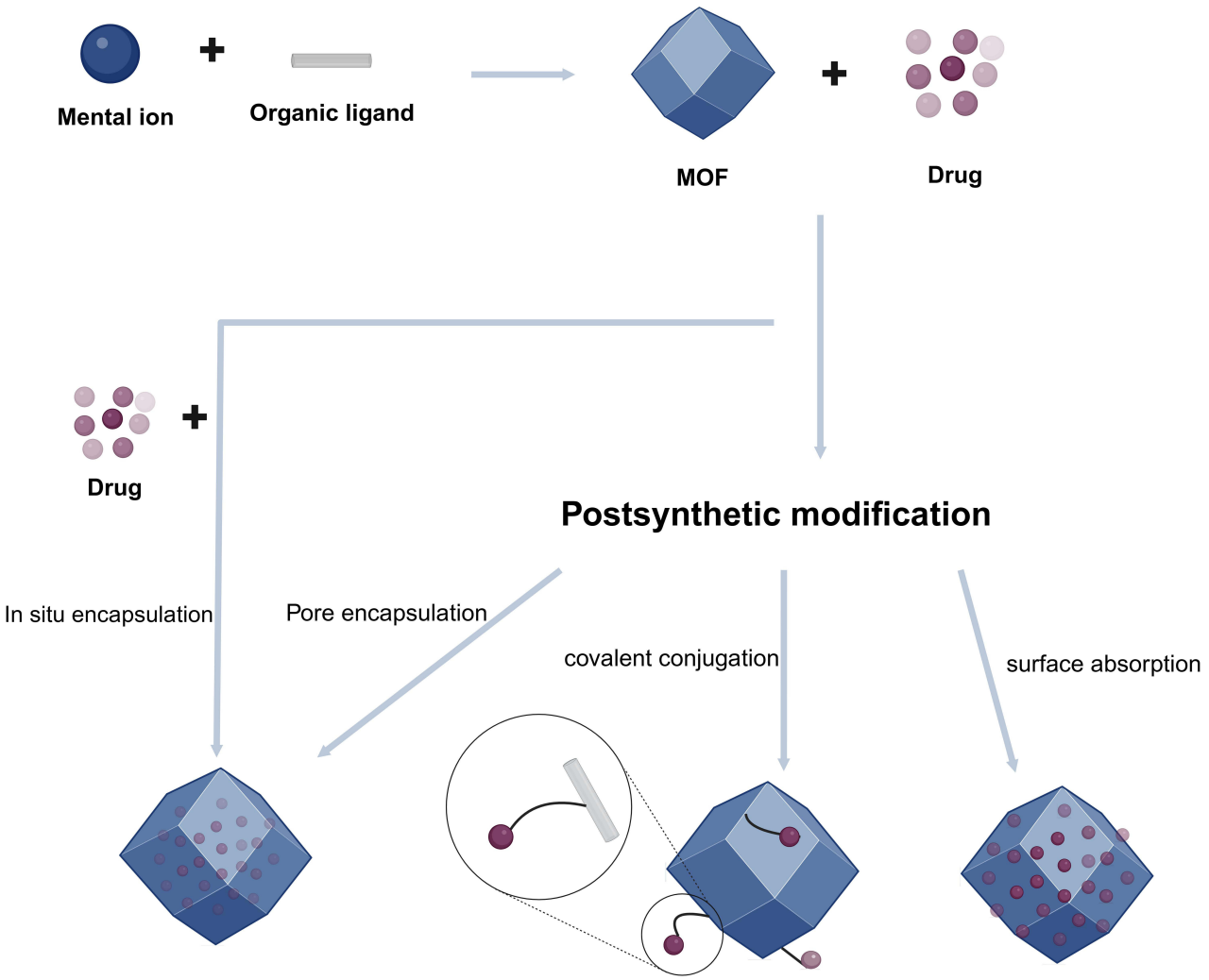

Figure 3 Schematic representation of the strategies to load drugs into MOFs.

ensuring compatibility with physiological environments. Representative drug loading strategies, including encapsulation, covalent conjugation and surface adsorption, are systematically compared (Figure 3).

Following initial synthesis, MOFs can be functionalized to enhance their framework properties and confer application-specific functionalities, particularly for targeted drug delivery. Two primary strategies are employedin-situ functionalization during synthesis (eg, ligand substitution) and post-synthetic modification (eg, surface grafting).[78,79] Subsequently, synthesized MOFs require systematic physicochemical characterization to: (i) confirm structural integrity via powder X-ray diffraction (PXRD) and electron microscopy (TEM, SEM); (ii) analyze chemical composition using nuclear magnetic resonance (NMR) and elemental analysis (EA); (iii) evaluate thermal stability through thermogravimetric analysis (TGA); and (iv) assess drug-loading efficiency and controlled release profiles via UV-vis and fluorescence spectroscopy.[80] These data collectively validate the material's suitability for biomedical applications, ensuring optimal performance while addressing toxicity concerns.

MOFs-Based Drug Delivery Systems

The excellent properties of MOFs can be well applied in DDSs: (i) high surface area and porosity enable superior drug loading capacity; (ii) tunable metal-ligand coordination allows precise customization for diverse drug physicochemical properties; (iii) post-synthetic functionalization (eg, PEGylation or antibody conjugation) enhances targeting specificity

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and controlled release kinetics; (iv) weak coordination bonds impart biodegradability while maintaining biocompatibility. Consequently, recent research efforts prioritize the development of three MOF-based DDS categories, including conventional, stimuli-responsive and targeted MOFs. This section reviews these systems, with emphasis on their encapsulation efficiency (EE) and loading efficiency (LE)-two critical metrics calculated as follows:

$$\text{Encapsulation efficiency}(\%) = \frac{\text{Mass of loaded drug}}{\text{Mass of total drug}} \times 100\%$$

$$\text{Loading efficiency}(\%) = \frac{\text{Mass of loaded drug}}{\text{Mass of drug} - \text{loaded MOF}} \times 100\%$$

Conventional MOFs-Based DDSs

Conventional MOF-based DDSs are synthesized using the methods detailed above. Drug loading is achieved via two primary strategies: (1) in-situ encapsulation during framework assembly, or (2) post-synthetic diffusion into porous architectures.[81] Non-functionalized systems rely exclusively on intrinsic MOF-drug physicochemical interactions for payload retention, thereby lacking targeting specificity or stimulus-responsive behavior. Consequently, drug release follows passive diffusion kinetics dictated by concentration gradients.

Xie et al[82] engineered sub-200 nm Ti-MOFs via tetraethyl orthosilicate (TEOS)-assisted synthesis, reducing particle size by 42.78% (698.6±22 nm → 399.7 nm) while maintaining crystallinity. The system demonstrated > 90% cell viability and pH-responsive IBU release: 55.3–72.1% within 5 h, reaching 99.4% cumulative release at 24 h, outperforming conventional carriers by 18.6%. Complementarily, Suresh et al[83] developed MOF-5-based carriers for amorphous drug stabilization, enhancing aqueous solubility and physical stability. Encapsulation of hydrophobic therapeutics-curcumin (CUR), sulindac (SUL), and tranexamic acid (TAT)-yielded stable composites (>120-day amorphous state retention) via host-guest interactions. Loading capacities spanned 7.7–34.0 wt%, correlating with drug hydrophobicity.

Expanding MOF-based solubility enhancement strategies, He et al[84] pioneered nanoscale cyclodextrin metal-organic frameworks (CD-MOFs) for azilsartan (AZL) encapsulation, employing a methanol-mediated crystallization protocol with PEG_{20000} as a crystallizing agent. This methodology yielded high-purity CD-MOFs enabling efficient AZL loading (17.2 ± 0.8 wt%), synergistically enhancing aqueous solubility by 340-fold and oral bioavailability by 9.7-fold versus free AZL-significantly surpassing conventional MOF-5 carriers in both metrics (Figure 4). Synchrotron Fourier-transform infrared spectroscopy (SR-FTIR) and small-angle X-ray scattering (SAXS) analyses revealed stabilization via dual supramolecular interactions: (1) γ-cyclodextrin cavity inclusion and (2) MOF pore confinement. This dual-host mechanism simultaneously prevented drug recrystallization and enabled pH-responsive release in intestinal fluid (pH 6.8 ± 0.2; cumulative release >92%), resolving critical limitations of single-mechanism systems.

Functionalized Modified MOFs-Based DDSs

The functionalization of MOFs has expanded their biomedical applications, particularly in stimuli-responsive drug delivery, cancer targeting, and antimicrobial therapies. As a specialized subclass of metal-organic frameworks, stimuli-responsive MOFs exhibit dynamic structural or functional adaptations when exposed to specific biological or external triggers. These triggers are primarily divided into two types. Endogenous stimuli arise naturally within biological systems, such as ions, pH, ATP, GSH, nucleic acids, enzymes, and redox. Exogenous stimuli involve externally applied physical factors like light, heat, electricity, and magnetism. Researchers now strategically integrate these triggers to design multi-stimuli-responsive systems capable of precise therapeutic control in complex physiological environments.

Endogenous Stimulus Response

Endogenous stimulus-responsive MOFs are engineered via biomimetic or natural component integration, enabling spatiotemporally precise drug release through activation by biological triggers. These systems undergo programmable morphological/chemical adaptations in response to pathological cues, enhancing therapeutic precision and diagnostic accuracy.[85]

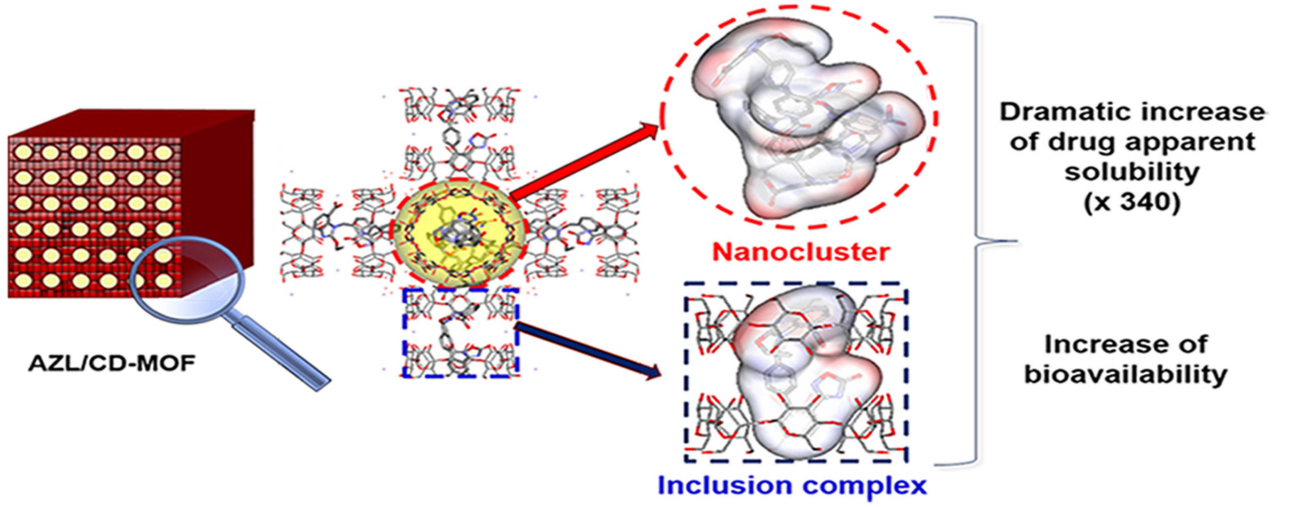

Figure 4 Dual molecular mechanism of complexation and nanoclustering in CD-MOF significantly enhanced bioavailability and solubility of insoluble drugs. Reproduced from He Y, Zhang W, Guo T, Zhang G et al. Drug Nanoclusters Formed in Confined Nano-Cages of CD-MOF: Dramatic Enhancement of Solubility and Bioavailability of Azilsartan. *Acta Pharmaceutica Sinica B* 2019, *9* (1), 97–106. *© 2018 Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences. Production and hosting by Elsevier B.V.*.[84] under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND 4.0).

Researchers optimize particle characteristics including size, shape, and mechanical stiffness to simultaneously evade immune surveillance and achieve organ-specific targeting.[86] A prominent application lies in cancer therapy, where these MOFs function as molecular gatekeepers that selectively release drugs upon encountering the tumor microenvironment (TME). Distinctive TME features-such as hypoxic conditions, lactate-induced acidosis with pH levels ranging from 5.0 to 6.5, elevated redox potential, overexpression of specific enzymes like matrix metalloproteinases, and aberrant vascular permeability-create unique biochemical signatures exploitable for targeted drug activation.[87,88]

Despite their targeting precision, excessive responsiveness to endogenous stimuli can compromise structural stability, leading to premature drug release prior to reaching diseased sites. Current strategies address this limitation by surface-functionalizing MOFs with polyethylene glycol (PEG) biopolymers.[89]

pH-Responsive

Recent advances in pH-responsive MOFs have demonstrated their potential for tumor-targeted therapy, particularly TME. The pH values in this environment range from 6.5 to 6.9, and after endocytosis and fusion with lysosomes, the pH decreases to 4.5.[90,91] pH-responsive MOFs make use of acid-labile bonds, which include amides, carboxylates, esters, imides, oximes, acetals, and ketals and which remain stable at physiological pH 7.4 but undergo selective hydrolysis when the pH is below 6.5. This pH-triggered bond cleavage induces structural degradation of the MOF framework, enabling targeted drug release specifically within acidic TME regions while maintaining stability during systemic circulation.[92] Some common pH-responsive compounds (carboxymethyl cellulose,[93,94] chitosan,[95,96] gelatin,[36,97] calcium phosphate[98]) are also based on this principle.

Amino-functionalized Mn-MOFs exhibit pH-responsive degradation, enabling rapid drug release in the acidic TME. Zhao et al[99] developed a core-shell DUCNP@Mn-MOF encapsulating 3-F-10-OH-evodiamine (FOE), leveraging small particle size for enhanced permeability and retention (EPR)-mediated tumor accumulation and pH-triggered FOE release. The system demonstrated pH-dependent burst release (83% at pH 5.6; 75% at pH 6.5 within 5 min) and high biocompatibility (> 80% cell viability at 250 μg/mL). DUCNP@Mn-MOF/FOE induced 39.4% tumor cell apoptosis without significant organ toxicity, showcasing its therapeutic precision.

Zhang et al[100] developed pH-responsive MIL-101-NH_2 (Figure 5) for dual loading of curcumin and anti-HIF-2α siRNA via covalent conjugation, achieving 69.5% drug loading efficiency. The framework demonstrated pH-dependent cumulative release (59.7% ± 1.8% at pH 5.0–7.0) while maintaining structural stability in osteoarthritic conditions. At 400 μg/mL, the system preserved >80% chondrocyte viability with no significant cytotoxicity. Mechanistically, MIL-101-

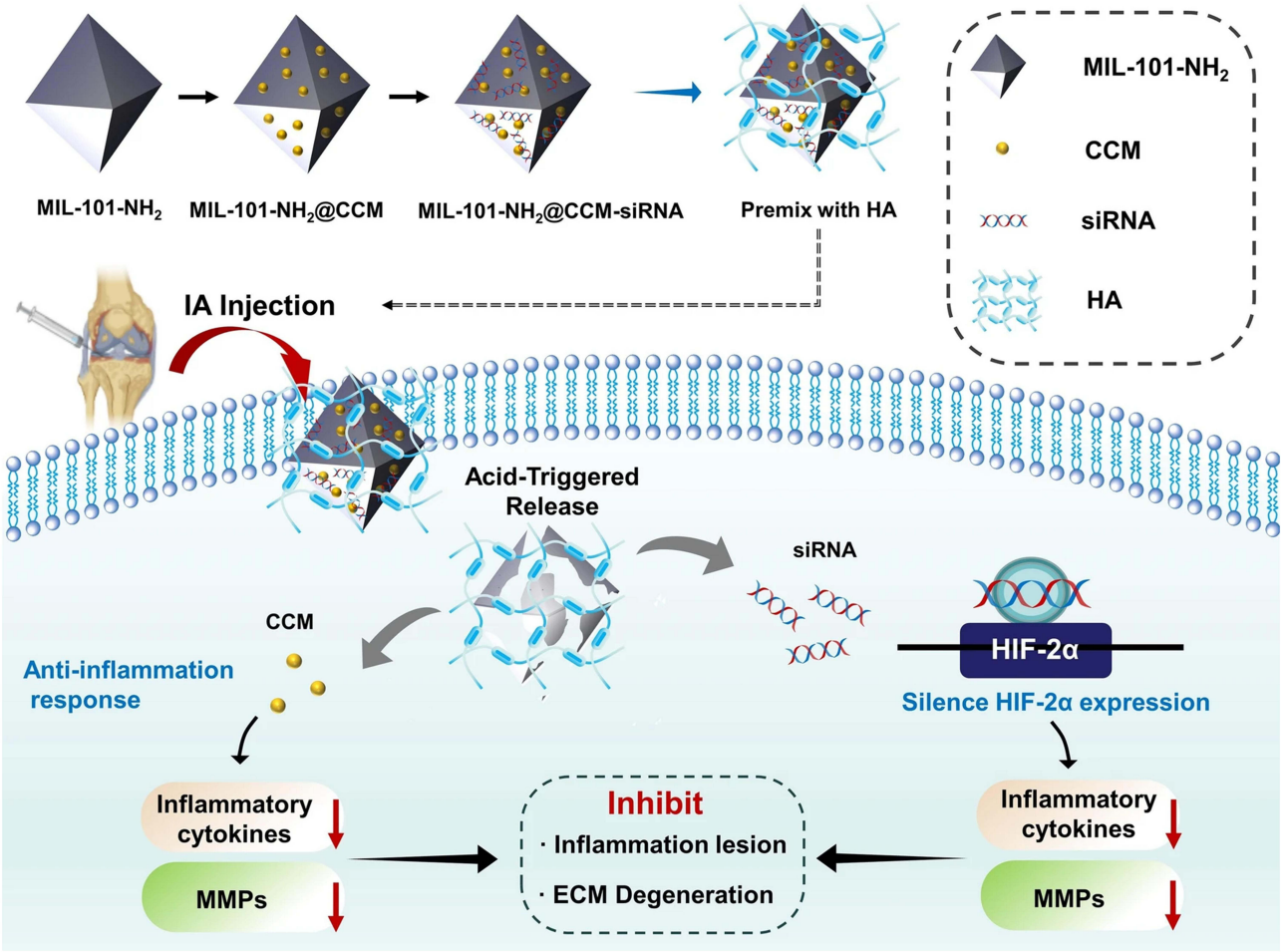

Figure 5 Preparation and schematic illustration of MIL-101-NH2@CCM-siRNA nanoparticles for OA therapy. Reproduced from Zhang, ZJ, Hou, YK, Chen, MW et al. A pH-responsive metal-organic framework for the co-delivery of HIF-2α siRNA and curcumin for enhanced therapy of osteoarthritis. *J Nanobiotechnol* 21, 18 (2023).[100] under the terms of the Creative Commons Attribution International License (CC BY 4.0).

NH_2 facilitated lysosomal escape of siHIF-2α, synergistically alleviating osteoarthritis through downregulation of disease-associated metabolites and upregulation of cartilage-specific markers.

Ion-Responsive

Ion-responsive MOFs employ metal ions (Ca^{2+}, Na^{+}, Pb^{2+}, Zn^{2+}, Mg^{2+}, K^{+}) or anions (PO_4^{3-}, H_2PO^{4-}) to regulate drug release through three primary mechanisms: anion exchange, competitive binding and metal ion/nucleic acid complex formation. Anion exchange represents the predominant mechanism, wherein incoming anions displace framework components by preferentially coordinating with metal nodes, thereby destabilizing the MOF architecture. Conversely, cations can degrade negatively charged MOFs through electrostatic interactions.[101] A representative study by Tan et al[102] demonstrated this principle using UiO-66-NH_2 functionalized with quaternary ammonium groups and capped with carboxylated pillar[5]arene (CP5). The resulting electronegative pseudorotaxanes exhibited Zn^{2+}-responsive 5-FU release, achieving a 115 μmol/g 5-FU loading capacity, which was 2.7-fold higher than that of non-conjugated CP5 systems. Zn^{2+}-triggered release demonstrated concentration-responsive kinetics, accelerating from 0.08 to 0.23 h^{-1} with payload increasing from 38% to 92% across Zn^{2+}, mechanistically confirming the CP5-mediated gating effect.

Enzyme-Responsive

Enzyme-responsive MOFs leverage enzymatic activity and programmable porosity to construct bioresponsive drug carriers. Targeted release is achieved through specific interactions between MOF pore channels and enzyme moieties.

A core design strategy employs enzymatic cleavage of peptide bonds integrated within the framework.[85] Recent advances demonstrate enzymes acting as molecular gatekeepers for MOF delivery systems. Upon exposure to target enzymes, the catalytic activity of these MOFs increases significantly, enabling spatiotemporally controlled drug release. Carrillo-Carrión et al[103] exemplified this concept by developing an ALP-responsive MOF that selectively releases drugs in tumor tissues overexpressing ALP (a validated tumor-associated biomarker), achieving 89% targeted drug accumulation versus 12% in normal tissues.

ATP-Responsive

ATP-responsive metal-organic frameworks (MOFs) dynamically respond to adenosine triphosphate (ATP) concentration fluctuations through three interconnected mechanisms: (i) ATP binds to MOF metal nodes or ligands via hydrogen bonding or electrostatic interactions, inducing structural transformations that regulate pore opening/closing. (ii) ATP-MOF binding triggers adaptive structural reconfiguration, modulating drug release kinetics and optoelectronic properties. (iii) integrated fluorescent probes amplify ATP detection signals, achieving nanomolar-level sensitivity. For instance, Chen et al[104] developed a near-infrared fluorescent nanoprobe that detects ATP concentrations within 0.25–10 mM while synchronously releasing anticancer drugs to induce tumor cell apoptosis. Inheriting the biocompatibility of endogenous stimuli-responsive systems, ATP-MOFs further enable ATP concentration-dependent drug release control, demonstrating significant potential for precision medicine.

GSH-Responsive

Glutathione, a thiol-rich tripeptide ubiquitous in eukaryotic systems, functions as both a metabolic regulator and antioxidant by neutralizing free radicals and detoxifying carcinogens. Critically, tumor cells exhibit dysregulated GSH homeostasis with intracellular concentrations reaching 10-fold higher than in normal cells, a pathological feature directly correlated with accelerated proliferation and chemoresistance.[105] This pathological overexpression has driven the development of GSH-responsive MOFs exploiting two distinct activation mechanisms: coordination-induced structural reconfiguration or redox-triggered bond cleavage. Du et al[106] demonstrated this by engineering a BMS-986205-conjugated MOF (BMS-SNAP-MOF) that degrades in GSH-rich tumor microenvironments, synchronously releasing the IDO inhibitor BMS-986205 and generating nitric oxide (NO) to potentiate immunotherapy. Similarly, Zhang et al[107] designed an iron-porphyrin MOF co-loaded with glucose oxidase(Gox) and iridium (Ir) nanoparticles. GSH-triggered decomposition releases porphyrin photosensitizer, inducing a cytotoxic ROS burst that enhances photodynamic and chemodynamic therapy efficacy.

Redox-Responsive

Tumor progression results from disrupted redox homeostasis, where elevated reactive oxygen species (ROS) serve as critical mediators. While physiological ROS levels maintain procancerigenic signaling through oxidative stress-activated pathways, supraphysiological ROS induce oxidative damage and trigger programmed cell death.[108] In TME, sustained ROS overproduction damages mitochondrial respiration, depolarizes membrane potentials, and propagates ROS over-production. Concurrently, ROS activate redox-sensitive pathways (eg, NF-κB, AP-1) in both cancer cells and tumor-associated macrophages, driving inflammatory factor release.[109] These dynamics underpin the design of redox-responsive MOFs for tumor-targeted therapy. Zhang et al[110] engineered a hyaluronic acid-functionalized MOF crosslinked via disulfide bonds (-S-S-), enabling glutathione-triggered drug release specifically in TME. Capitalizing on ROS-mediated cytotoxicity, He et al[111] developed a Fe/Cu-SS MOF (PFP@Fe/Cu-SS) that generates hydroxyl radicals (•OH) through Fenton-like reactions. The resulting lipid peroxides (LPO) induce ferroptosis, a ROS-dependent cell death mechanism, demonstrating potent antitumor efficacy.

Exogenous Stimulus Response

Endogenous stimulus-responsive MOFs adapt their structure and function to intracellular physiological conditions, enabling localized drug release that enhances therapeutic efficacy while minimizing systemic toxicity. In contrast, exogenous stimulus-responsive systems utilize externally applied triggers, offering artificial controllability unconstrained

by biological variability. Light-responsive MOFs exemplify this approach through wavelength-specific activation. Cornell et al[112] demonstrated this with UiO-AZB-F, a MOF activated by green light to achieve on-demand 5-fluorouracil (5-FU) release. Separately, microwave-responsive MOFs leverage deep tissue penetration for targeted therapy, as evidenced by Cui et al[113] who developed gadolinium-based MOFs (Gd-MOFs) that generate microwave-induced hyperthermia while releasing PD-1 inhibitors, synergistically enhancing antitumor immunity.

Magneto-responsive MOFs are typically engineered through two primary strategies: encapsulation of magnetic nanoparticles within MOF architectures, or hybridization with magnetic polymers. These systems enable multifunctional capabilities including magnetic targeting, controlled drug release, magnetic resonance imaging (MRI) contrast enhancement, and magnetothermal therapy through external magnetic guidance. Guo et al[114] applied magnetic fields to navigate Hm@TSA/As-MOFs through ascites fluid, negating extracellular matrix barriers to deliver Tanshinone IIA and Astragaloside IV precisely to hepatocellular carcinoma sites. Similarly, Wang et al[112] designed lactose-modified paramagnetic Lac-FcMOFs that amplify mild magnetothermal therapy (MMHT) efficacy by disrupting redox homeostasis (RDH), thereby enhancing tumor suppression.

Dual/Multiple Responsiveness

Dual/multi-stimuli-responsive MOF nanoplatforms integrate responses to endogenous physiological and exogenous environmental triggers, enabling spatiotemporally controlled drug release. Emerging research highlights their potential to overcome limitations of single-stimulus systems through synergistic therapeutic effects, enhanced environmental adaptability, and compatibility with combinatorial therapies. Representative designs include ATP and pH,[115] ions and pH,[116] pH, GSH and light[117] co-responsive MOFs, which achieve precise spatiotemporal targeting, improved signal transduction fidelity, and robust stability under dynamic biological conditions. These systems exemplify the convergence of stimuli-responsive adaptability with multi-modal therapeutic precision.

MOFs in Breast Cancer

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer deaths among women globally in 112 countries.[1] Major molecular subtypes include hormone receptor-positive (HR+, ~70%), human epidermal growth factor receptor 2-positive (HER2+, 15–20%), and triple-negative breast cancer (TNBC, 10–15%).[118–120] A comprehensive review identified 24 FDA-approved breast cancer therapeutics from 1991 to 2021, comprising 18 small molecules, 3 monoclonal antibodies, and 3 antibody-drug conjugates (ADCs).[121] Currently, MOFs significantly contribute to targeted therapy, early diagnosis and comprehensive treatment strategies for breast cancer, as evidenced in Table 3.[122,123–141]

For Breast Cancer Treatment

Chemotherapy

MOFs exhibit exceptional specific surface areas, tunable porosity, and biocompatibility, establishing them as optimal platforms for targeted drug delivery and controlled release systems. Taheri-Ledari et al has developed magnetic Bio-MOF -13 for doxorubicin DOX delivery, which greatly validated the therapeutic efficacy of engineered MOFs.[142] The Bio-MOF-13 system enables dual pH/magnetic field-responsive targeting in breast cancer cells, demonstrating low systemic toxicity suitable for intravenous administration. Furthermore, surface-functionalized MOFs synergize high drug loading capacity with pH-responsive behavior, positioning them as promising candidates for breast cancer therapy.[143,144]

Multivariate modulation (MTV) strategies represent a paradigm shift in optimizing MOFs for biomedicine. By incorporating multiple functional ligands into single frameworks, MTV enables co-delivery of therapeutic cargos. Demonstrating this approach, Abánades Lázaro et al[145] engineered defect-engineered UiO-66 MOFs through modulator diversification, successfully co-loading dichloroacetic acid and 5-fluorouracil (5-FU). This multi-drug-loaded system exhibited enhanced cytotoxicity against MCF-7 breast cancer cells compared to single-drug formulations.

Ferroptosis, a regulated cell death pathway characterized by iron-dependent lipid peroxidation, offers a novel therapeutic strategy against chemotherapy-resistant tumors. Li et al[146] engineered a copper-porphyrin MOF (Cu-TCPP (Fe)) to disrupt antiferroptotic defense mechanisms in TNBC. This nanoplatform integrates glucose-depleting gold

Table 3 MOFs in Breast Cancer Diagnosis and Treatments

	Type	MOFs	Application	Ref.
Treatment	Chemotherapy	UIO-66-Let/Epi@NH	Drug delivery	[122]
	Chemotherapy	La-MOFs	Drug delivery; Targeted therapy	[123]
	Microwave thermo-chemotherapy	AP@ZC-HSC@PEG@PCM-DEX	Drug delivery	[124]
	Chemotherapy	DOX@ZIF-8/GO-FA/CP	Drug delivery; Targeted therapy	[125]
	CDT	Apt-RBC-MOF@DOX	Drug delivery; Targeted therapy	[126]
	PDT	MA-HfMOF-PFP-Ni-Zn; MA-HfMOF-PFC-Ni-Zn	PDT agent for tumor therapy	[127]
	PDT	Zn(II)-PPIX@UiO-66-NH_2 NMOFs	Cell imaging	[128]
	PDT-SDT	Chl-MOF	PDT agent for tumor therapy	[129]
	SDT	PL-PEG-PCN	SDT agent for tumor therapy	[130]
	PTT	CV@Bi-TCA	PTT agent for tumor therapy	[131]
	chemo-photothermal-photodynamic therapy	UiO-DOX-ICG@PDA-TF	Drug delivery; Targeted therapy	[132]
	Immunotherapy	MOF@siDDR2+siITGAV	Drug delivery	[133]
	Immunotherapy	LYS-NP	Drug delivery	[134]
	Microwave thermo- immunotherapy	AIEu-MOF	MW thermotherapy-responsive pyroptosis inducers	[135]
	Photodynamic- immunotherapy	BMS@P/HP	Drug delivery	[136]
Diagnosis	Electrochemical biosensor	PEI@CQD@Ni-MOF	The breast cancer marker HER2 detector	[137]
	Surface plasmon resonance (SPR)	Au/UiO-66-NH_2	The breast cancer marker HER2 detector	[138]
	Fluorometric biosensor	2D Zn-TCPP MOF	The breast cancer marker HER2 detector	[139]
	Electrochemical biosensor	MIL-156 MOF@COF	The breast cancer marker CA15-3 detector	[140]
	Fluorescent biosensor	La (III) -MOF and Ag NPs	The breast cancer marker miRNA-155 detector	[141]

nanoparticles and the ferroptosis inducer RSL3 (inhibits glutathione biosynthesis). The peroxidase-mimetic activity amplified ferroptotic vulnerability in triple-negative breast cancer, disrupting antioxidant defenses for synergistic therapy.

Du et al[147] engineered core-shell PCP-MOF@G@B nanostructures for dual-starvation therapy. A pH/ROS-responsive PEG-CDM-PEI copolymer shell enabled tumor-triggered size/charge switching, enhancing penetration. Endogenous H_2O_2 generation accelerated MOF degradation, achieving 75–94% cumulative release. In MDA-MB-231 xenografts, PCP-MOF@G@B induced 42% apoptosis-mediated cell death, suppressing tumor volume by 89% while improving survival rates in murine models.

Photodynamic Therapy (PDT)

Photodynamic therapy (PDT) utilizes photosensitizers activated by specific wavelengths to generate ROS, primarily singlet oxygen ($^1O_2$), inducing tumor cell apoptosis. MOF-based carriers effectively encapsulate photosensitizers within their porous structures, enabling localized ROS generation upon light irradiation.[148] This process rapidly triggers immunogenic cell death (ICD), concurrently releasing tumor-associated antigens that stimulate acute inflammation and enhance antigen immunogenicity, thereby amplifying antitumor immunity.[149]

However, tumor hypoxia severely constrains PDT efficacy in deep tissues. To overcome this limitation, Xu et al[150] innovatively engineered a BODIPY-functionalized Zr-MOF (69-L2) via post-synthetic ligand exchange, hybridized with perfluorocarbon polymers to create an oxygen-elevating nanoplatform (Figure 6A). Under LED irradiation, this system demonstrated sustained oxygen-carrying capacity and potent $^1O_2$ generation (Figure 6B), achieving 50–70% cytotoxicity against MDA-MB-231 triple-negative breast cancer cells at 25–100 μg/mL. Subsequent integration into hydrogel scaffolds reduced tumor volumes by 80–85% in murine mammary carcinoma models after 80-day implantation.

Beyond single PDT, synergistic integration with complementary modalities addresses monotherapy constraints. Liang et al[136] engineered a hyaluronic acid-polyethylene glycol (HA-PEG) grafted PCN-224 MOFs co-loaded with the PD-L1 inhibitor BMS-202. In 4T1 tumor-bearing mice, combined PDT and PD-L1 blockade potentiated primary tumor ablation

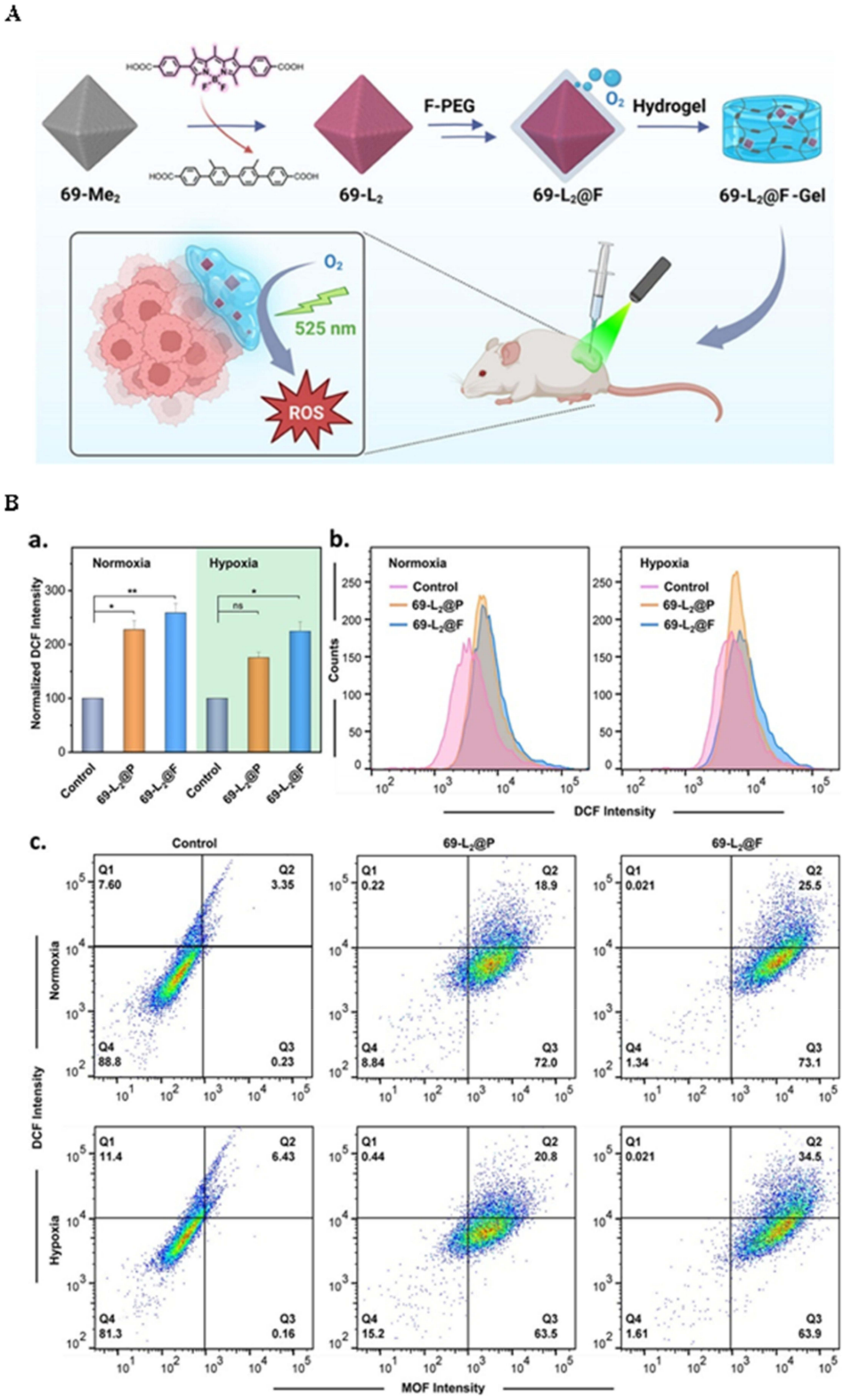

Figure 6 (**A**) Preparation and schematic illustration of 69-L_2@F. (**B**) ROS generation for 69-L2@P and 69-L2@F. (a) Normalized DCF fluorescent intensity. (n = 5; *p < 0.05, **p < 0.01, two-way ANOVA followed by a Sidak's test for multiple comparisons). (b) Overlapped histograms of DCF intensity for normoxic and hypoxic cells. (c) Flow cytometry analysis of cells with MOF intensity vs DCF intensity. Reproduced from Chen X, Mendes BB, Zhuang Y et al. A Fluorinated BODIPY-Based Zirconium Metal–Organic Framework for In Vivo Enhanced Photodynamic Therapy. *J Am Chem Soc* 2024, *146* (2), 1644–1656. Copyright © 2024 The Authors. Published by American Chemical Society.[150] under the terms of the Creative Commons Attribution International License (CC BY 4.0).

while inducing systemic antitumor immunity, suppressing metastatic growth by 73% through enhanced dendritic cell maturation and cytotoxic T-lymphocyte activation.

Photothermal Therapy (PTT)

Photothermal therapy (PTT) employs photothermal agents that convert near-infrared (NIR) radiation into localized hyperthermia through non-radiative relaxation, effectively ablating tumor cells.[151] Recognized for its non-invasiveness, precision, and capacity to induce antitumor immunity under specific conditions,[152] PTT commonly utilizes noble metal nanoparticles (eg, Au, Pd, Pt) that exhibit strong NIR absorption and photothermal conversion efficiency.[153] Current research focuses increasingly on synergistic PTT integration with complementary modalities for breast cancer treatment.

For synergistic photothermal-chemodynamic therapy (PTT/CDT) targeting malignant breast cancer bone metastases, Zou et al[154] developed a $Cu_{2-x}Se$@ZIF-8 nanocomposite against metastatic breast cancer. Encapsulating $Cu_{2-x}Se$ within ZIF-8 minimizes systemic toxicity while enabling efficient photothermal conversion and Cu^{+}/Cu^{2+}-mediated •OH generation via Fenton-like reactions. For the same synergistic therapy, Yang et al[155] engineered Fe^{3+}-loaded mesoporous organosilica frameworks for TNBC treatment. The platform simultaneously facilitates Fe^{3+}-mediated Fenton reactions and mild PTT, generating cytotoxic •OH and promoting immunogenic cell death, which demonstrates potent adaptive immune activation.

Immunotherapy

Tumor immunotherapy utilizes the host immune system to induce tumor-specific adaptive immunity, either through active immune activation or passive immunotherapy using therapeutic antibodies, thereby reducing off-target toxicity that is inherent in conventional therapies. Unlike chemotherapy or radiotherapy, immunotherapy primarily enhances endogenous antitumor responses by activating tumor-infiltrating lymphocytes (TILs) and antigen-presenting cells (APCs), rather than through direct tumor ablation. Advances in cancer immunology have established immunotherapy as a transformative modality with the potential for durable remission.

Several studies suggest that the high surface area of MOFs facilitates the efficient encapsulation of immunomodulators, such as PD-1 inhibitors and TLR agonists. Furthermore, surface engineering strategies, including the functionalization with hyaluronic acid, enhance tumor-specific targeting. MOFs are gaining momentum as precision nanocarriers for immunotherapeutic agents in breast cancer. Immunostimulatory MOF (ISAMn-MOF) based on Mn^{2+} utilizing a green synthesis method was developed by Zheng et al.[156] In murine models of breast cancer lung metastasis, ISAMn-MOF combined with anti-PD-1 antibodies reduced pulmonary metastatic nodules by 88% (10.4 vs 88.6 in PBS controls) and improved survival rate, demonstrating potent systemic antitumor immunity.

Defect-engineered MOFs strategically overcome therapy resistance through tunable redox activity. Peng et al[157] designed a ferric ion-based defect-engineered MOF biomimetic system that depletes glutathione (GSH) while downregulating glutathione peroxidase 4 (GPX4), inducing lethal lipid peroxidation. Concurrently, Fe^{3+} activates NADPH oxidase 4 (NOX4) to generate H_2O_2, which undergoes Fenton reactions to produce cytotoxic hydroxyl radical. This dual-action mechanism induced ferroptosis, achieving 87% tumor suppression in chemoresistant breast cancer models (Figure 7). Complementarily, Zn/Gd-bimetallic MOF-5 nanoparticles act as nano-immunomodulators,[158] directly inducing immunogenic cell death while synergizing with PD-L1 blockade to inhibit primary tumors growth and metastasis.

For Breast Cancer Diagnosis

Noteworthy, MOFs have demonstrated significant potential in tumor diagnostics, particularly for HER2-positive breast cancer detection through specific protein recognition and signal amplification.[159–162] Liang et al[163] engineered tetrahedral DNA-guided Zr-MOF superstructures integrating catalytic activity with molecular recognition, quantifying HER2 at molecular (LOD: 12 pg/mL) and cellular (LOD: 10 cells) levels. Zhang et al[73] developed a ZIF-8/Co-MOF hybrid electrochemical aptasensor for simultaneous detection of human epidermal growth factor receptor 2 (HER2) and estrogen receptor (ER) within 60 min, achieving linear ranges of 0–15 pg/mL with ultra-low detection limits (HER2: 3.8 fg/mL; ER: 6.8 fg/mL).

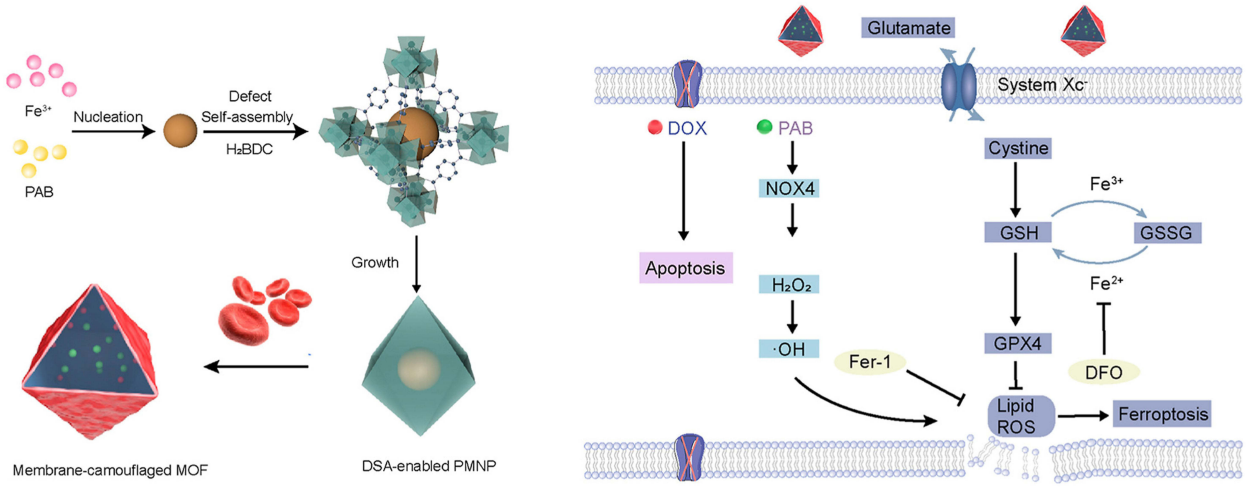

Figure 7 Synthesis procedure of defective self-assembled MOF and schematic illustration of this multidrug delivery nanoplatform triggering iron death to overcome drug resistance. Reproduced from Peng H, Zhang X, Yang P et al. Defect Self-Assembly of Metal-Organic Framework Triggers Ferroptosis to Overcome Resistance. *Bioactive Materials* 2023, *19*, 1–11. 10.1016/j.bioactmat.2021.12.018. © *2021 The Authors. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd.*[157] under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND 4.0).

In addition, a clinically feasible electrochemical biosensor enable multiplexed quantification of breast cancer biomarkers including ER, PR, HER2 and Ki67. The bio-platform can selectively detect HER2, ER, Ki67 and PR in the range of 0–1500 pg/mL with detection limits of 0.01420, 0.03201, 0.01430 and 0.01229 pg/mL, respectively, to achieve a wider and more comprehensive breast cancer diagnosis.[164] Beyond molecular diagnostics, MOFs facilitate tumor imaging through intrinsic or engineered contrast properties. These imaging capabilities are often integrated with therapeutic functions, such as photodynamic therapy or drug delivery, to achieve real-time theranostics. The following section reviews MOF-based platforms for integrated breast cancer diagnosis and treatment.

Therapy-Diagnostics Integration

Theranostics integrates diagnostic and therapeutic functions within a unified platform, offering significant advantages over isolated diagnostic or therapeutic approaches. In breast cancer management, MOFs enable simultaneous tumor detection and targeted intervention, enhancing early diagnosis accuracy while providing real-time treatment guidance. MOF-based theranostic systems improve therapeutic precision through stimuli-responsive drug release and multimodal imaging capabilities, advancing personalized oncology paradigms.

Zhang et al[165] exemplify this with core-shell AuNS@MOF-ZD2 nanocomposites, where ZD2 peptides confer selective targeting of triple-negative breast cancer (TNBC) cells. The MOF shell provides T_1-weighted magnetic resonance imaging (MRI) contrast, while the gold nanosphere (AuNS) core enables photothermal therapy (PTT) with 40.5% NIR photothermal conversion efficiency. This integrated platform facilitates concurrent tumor monitoring and precision hyperthermia ablation.

Beyond single-modality theranostics, synergistic integration of multiple therapeutic strategies significantly enhances treatment efficacy while minimizing systemic toxicity. Chen et al[166] engineered a pH/NIR dual-responsive platform (PCN-DOX@PDA) combining chemotherapy, photothermal therapy (PTT), and photodynamic therapy (PDT). The system achieved 78% doxorubicin (DOX) loading capacity, with pH 5.4-triggered release reaching 80% post 808-nm NIR irradiation. Concurrently, the PCN-600 carrier generated single-linear oxygen under 634-nm laser irradiation for potent tumor cell elimination, while polydopamine (PDA) enhanced photothermal conversion efficiency. The Fe^{3+}-centered MOF additionally served as a T2-weighted MRI contrast agent, enabling real-time therapeutic monitoring.

Recent studies further demonstrate MOFs as versatile platforms for multimodal imaging and combination therapies in breast cancer.[110,167,168] These systems integrate stimuli-responsive drug release with photodynamic/chemodynamic activities, often coupled with magnetic resonance or computed tomography imaging to guide precision treatment.

Conclusions and Outlook

Metal-organic frameworks (MOFs) establish a transformative paradigm for precision breast cancer theranostics through three core advancements: (1) Engineered stimuli-responsiveness enabling tumor-targeted drug release with minimized off-target effects; (2) Intrinsic multifunctionality supporting simultaneous diagnostic imaging and combinatorial therapy; (3) Synergistic modulation of tumor microenvironments to overcome therapeutic resistance. By integrating real-time monitoring capabilities with dynamically controlled treatment modalities, MOF-based platforms significantly enhance therapeutic precision while reducing systemic toxicity. These advances collectively position MOFs as next-generation nanoplatforms advancing personalized oncology frameworks.

Despite progress, challenges persist in clinical translation, such as toxicity, biostability, aggregation and premature clearance problems during circulation, and unclear metabolic pathways.[169] These limitations can be mitigated through structural and formulation optimizations, including biomimetic ligand design (eg, nucleotides, peptides), selection of biocompatible metal nodes (iron, calcium), surface engineering via polymer coatings or supramolecular assemblies, as well as targeted modulation of enzymatic degradation pathways and efflux transporters.

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Disclosure

The authors declare no competing interests.

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