



Receptor-targeted metal-organic frameworks: Recent progress in synthesis, modifications, and applications in targeted drug delivery

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ABSTRACT

Metal-organic frameworks (MOFs) have emerged as pivotal materials in contemporary scientific research, offering vast potential for the development of portable and sophisticated systems. This has opened new avenues for exploration across various fields and enabled a broad spectrum of novel applications. Over the past decade, MOFs have rapidly evolved in drug delivery systems (DDS), showcasing significant advancements in the creation of novel targeted platforms. Notably, receptor-targeted MOFs have introduced innovative architectures with adaptable features, particularly in biologically relevant scaffolds, thereby suggesting alternatives for cancer therapy. This review delves into recent developments in receptor-targeted MOFs, focusing on their synthesis, chemical modification, and applications in targeted anticancer drug delivery, highlighting their potential to drive future innovations in biomedical fields.

1. Introduction

Cancer is still one of the most common causes of death worldwide. This requires the continuous development of advanced therapeutic strategies to improve treatment efficacy while minimizing side effects [1,2]. For centuries, conventional chemotherapy has often suffered from the lack of selectivity, systemic toxicity, and multidrug resistance despite its widespread use [3,4]. To overcome these challenges, various drug delivery systems (DDS), including those based on nanoparticles (NPs) [5], hydrogels [6] polymeric micelles [7], dendrimers [8], liposomes [9], and microcapsules [10], have been developed to improve drug loading capacity and controlled release.

However, despite their clear therapeutic benefits, these conventional approaches have notable limitations. A major concern is the difficulty of maintaining stable plasma drug levels, which are often affected by rapid drug metabolism and premature excretion from the body [11–13]. Consequently, this leads to fluctuating drug concentrations that may diminish treatment effectiveness and patient outcomes. In addition, the non-specific drug distribution in the body reduces the concentration at the target site, leading to side effects in healthy tissues and organs

[14,15].

To overcome these challenges, receptor-targeted DDS has emerged as a promising strategy to enhance the pharmacokinetic properties of therapeutics. These systems improve drug absorption and distribution while reducing side effects [16]. The development of nanotechnology has mainly led to significant advances in receptor-targeted DDSs. Triggers from inside the body (e.g., internal cues in the cancer microenvironment) and outside of the body (external stimuli) provide spatially and temporarily controlled properties for the release of drugs encapsulated in these systems [17,18]. The basic mechanisms of receptor-targeted DDSs can be described as follows: after injection, the receptor-targeted DDS (nanocarriers) accumulates at a disease site through active targeting (receptor-ligand affinity) [19,20]. When activated by specific triggers, the chemical composition or physical structure of these systems undergoes a predetermined transformation that induces drug release at the intended site in a controlled manner [21,22].

A wide range of nanomaterials, including polymers, metals, metal oxides, and carbon-based structures, have been explored for use in receptor-targeted DDSs [23–25]. Each of these materials offers unique advantages, such as physical stability, high drug-loading capacity,

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biodegradability, and biocompatibility, all of which are crucial for developing effective nanocarriers [26,27]. However, designing an ideal nanocarrier requires a balance between structural tunability, controlled release properties, and biological safety. One class of materials that meet these criteria well are metal-organic frameworks (MOFs) [28]. MOFs are a highly versatile platform with applications in biosensors [29], storage of biopharmaceuticals [30], tissue and bone repair scaffolds [31,32], biomedical [33], small molecule [34], biomacromolecule delivery [35], vaccine adjuvants [36], microwave absorption [37], and immunotherapeutic applications [38]. Due to their tunable structures, high porosity, and ability to be synthesized in various morphologies, sizes, and shapes, MOFs are also excellent candidates for drug delivery. Unlike conventional nanocarriers, MOFs offer an unprecedented level of structural customization, enabling precise modulation of their physicochemical properties for targeted therapeutic applications [39–41]. To illustrate the breadth of receptor-targeted DDS strategies involving MOFs, Table 1 provides a representative summary of current platforms and their therapeutic outcomes. Subsequent efforts should prioritize the thoughtful design of ligands with attention to their selectivity, the improvement of nanoscale MOFs (NMOFs) physicochemical properties, and the incorporation of stimuli-responsive release mechanisms to address ongoing limitations in biosafety and targeting.

Among the various receptor-targeted DDSs, MOF-based systems have recently attracted great interest in achieving active, targeted drug delivery [42,43] (Figure 1). As a new class of porous materials, MOFs have been extensively studied in DDSs lately as they have exciting features,

Table 1
Summary of receptor-targeted MOF systems applied in drug delivery

Limitation	Description	Potential Strategies to Overcome
Ligand limitations	High-affinity ligands (e.g., proteins, aptamers) can be unstable and expensive to produce	Explore cost-effective alternatives like small molecules and polysaccharides; develop engineered or synthetic ligands with enhanced stability
Poor stability and aggregation of MOFs	MOFs may degrade prematurely or aggregate in biological fluids, reducing efficacy	Surface modification with polymers, lipid coatings, or hydrophilic molecules to improve colloidal stability Use stimuli-responsive MOFs (e.g., pH-sensitive ZIF-8, MIL-series); apply capping agents, polymer coatings, or gatekeepers
Premature drug release/burst release	Some MOFs release their cargo too quickly, limiting therapeutic control	Improve ligand-receptor affinity, employ dual-targeting strategies, or design multimodal nanoplateforms combining imaging and targeting
Lack of targeting specificity	Some ligand-receptor interactions are not highly specific, leading to off-target effects	Optimize physicochemical parameters (e.g., nanoscale size, neutral-to-slightly negative charge, spherical shape) Conduct systematic toxicity studies, use scalable and reproducible synthesis methods, and engage in regulatory pathway planning
Suboptimal biodistribution and uptake	Size, shape, and surface charge affect how MOFs are distributed and taken up by cells	Adopt advanced models like 3D cell cultures, organoids, and co-cultures; implement more robust control experiments
Limited clinical translation	Most MOF-based DDSs are still in preclinical stages; very few have reached clinical trials	Use live-cell imaging, labeling techniques, and systems biology tools to track MOF-cell interactions
Insufficient biological testing	Basic in vitro models may not reflect in vivo behavior accurately	
Incomplete understanding of cellular uptake	Internalization and intracellular trafficking mechanisms are not fully understood	

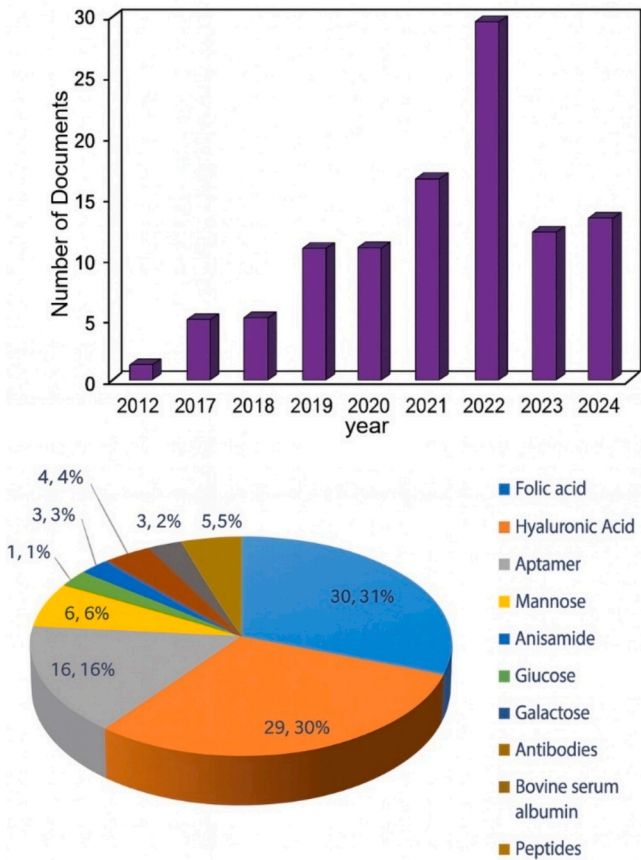


Fig. 1. Recently published documents in receptor-targeted MOFs in targeted drug delivery (top) and related receptor-targeted types (down).

including high drug-loading capacity, biodegradability, biocompatibility, and easy functionalization [44–46]. In biomedicine, MOFs can be modified with targeting molecules to facilitate active drug delivery or used as responsive drug carriers, making them appealing candidates for DDSs [47,48]. The ease of modulating the structure and properties of MOFs results in highly versatile platforms for drug delivery, demonstrating exceptional capabilities in enhancing therapeutic interventions. Integrating the unique features of nanomaterials and MOFs into DDSs will significantly improve the efficacy and safety of treatments while addressing some of the limitations of current drug delivery methodologies [49,50]. By fully realizing the potential of both smart DDSs and newly invented nanomaterials while considering the quality of life of a patient in health-related areas, researchers try to change the face of drug delivery accordingly [51,52].

This review provides a comprehensive analysis of receptor-functionalized MOFs in targeted cancer therapy, discussing their structural modifications, drug encapsulation efficiencies, and therapeutic outcomes. It introduces MOF-based receptor-targeted systems, including folic acid, anisamide, hyaluronic acid, glucose, galactose, aptamers, mannose, peptides, bovine serum albumin, and antibodies, which enable targeted drug delivery via receptor-mediated uptake. By systematically exploring different ligand-MOF conjugates and their interactions with specific cancer cell receptors, we highlight the potential of these hybrid platforms in advancing personalized medicine. Furthermore, we examine recent studies demonstrating the efficacy of these nanocarriers in in vitro and in vivo models, emphasizing their advantages in overcoming biological barriers and improving therapeutic efficacy.

2. Receptor-targeted MOFs

Despite recent advances in using MOFs for drug delivery, several critical challenges remain, including limited stability, aggregation in biological fluids, poor biodistribution, and insufficient tissue specificity [53]. To address these issues, surface modifications of MOFs have attracted increasing attention, particularly for enhancing colloidal stability, dispersibility, and biological performance [54].

In cancer treatment, targeting remains a major hurdle due to the difficulty in distinguishing malignant cells from healthy ones. Ineffective targeting strategies can lead to off-target toxicity and damage to normal tissues [55]. As a result, current strategies increasingly exploit the distinct cellular processes and surface biomarkers that differentiate cancer cells from healthy cells [56]. Functionalization of the MOF outer surface with targeting ligands, stealth coatings, or bioactive molecules can significantly influence cellular uptake pathways, enhance pharmacokinetic and pharmacodynamic profiles, and enable cell-specific targeting [57]. Compared to other NPs platforms, MOFs offer unique opportunities for surface modification owing to their unsaturated metal sites and reactive linker groups (e.g., carboxylic acids), which can undergo coordination or covalent conjugation with various functional moieties [58]. Surface functionalization can be achieved through post-synthetic modification (e.g., coordination of ligands to vacant metal sites or click chemistry on organic linkers) or by incorporating molecules during synthesis using modulators as capping agents. Table 2 summarizes selected receptor-targeted DDSs based on MOFs and their key findings. The following sections provide a detailed overview of recent advances in receptor-targeted MOFs for drug delivery applications.

2.1. Folic acid

The folate receptors (FR) is a glycosylphosphatidylinositol (GPI)-anchored cell surface protein that is overexpressed in many cancers of epithelial origin, including ovarian, breast, diabetes, cervical, lung, kidney, colon, and brain tumors. [152,153]. In healthy tissues, FR is expressed at relatively low levels and is typically restricted to regions not readily accessible to the bloodstream, such as the apical surfaces of polarized epithelial cells. This differential expression makes FR a compelling target for selective cancer therapy.

In this context, Considerable progress has been made in modifying the surface of MOFs with FA to provide FR mediated targeting. Xie and colleagues created a biocompatible FA-functionalized nanoscale MOF MIL-101(Fe)@FU@FA, which is intended for the delivery of 5-FU to cancer cells that overexpress FR. The covalent attachment of FA to MOF has significantly increased cellular uptake; in addition, the covalently bound FA increased inhibition of SMMC-7721 Hepatocellular Carcinoma (HCC) cell proliferation compared with both unmodified MIL-101(Fe)@FU and free 5-FU, decreasing invasion and migration while promoting apoptosis [59].

Building on this strategy, Mokhtarian et al. synthesized an FA-functionalized MOF, MIL-100(Fe)/FA, using an electrochemical approach (Figure 2A). Their study demonstrated that FA conjugation substantially improved selectivity: the uptake ratio between FR-positive MCF-7 breast cancer cells and healthy cells increased from 3.21 to 12.48. Using prodigiosin as a model drug, the system showed pH-responsive behavior, releasing 69–73% of the drug within 24 hours under acidic conditions that mimic the tumor microenvironment, highlighting the promise of FA-functionalized MOFs for targeted and stimuli-responsive cancer therapy [60].

While FA-functionalized MOFs have shown great promise in targeted drug delivery, their potential extends beyond conventional chemotherapy drugs like 5-FU and prodigiosin. Given the necessity of developing efficient nanocarriers for highly toxic drugs, researchers have explored FA-functionalized MOFs for delivering potent anticancer agents such as triptolide (TP). In this regard, Cai et al. investigated the therapeutic potential of FA-functionalized Fe-MIL-101 by incorporating

TP alongside a fluorescent tracking agent, 5-carboxylic acid fluorescein (5-FAM), to create a multifunctional nano-platform (5-FAM/FA/TP@Fe-MIL-101) (Figure 2B-D). The results from both in vitro and in vivo studies demonstrated enhanced cancer cell targeting with minimal systemic toxicity. Notably, in a liver cancer model using nude mice, this nanocarrier exhibited a significant tumor suppression rate, underscoring its potential for effective anticancer therapy. However, unlike other FA-functionalized MOFs designed for pH-sensitive drug release, this system lacked a pH-responsive profile, suggesting that further modifications might optimize its controlled release properties [154].

The versatility of FA-functionalized MOFs extends beyond conventional drug delivery, paving the way for innovative theranostic platforms that integrate imaging and therapy. In addition to their role in targeted chemotherapy, recent advancements have focused on designing multifunctional NMOFs capable of both cancer diagnosis and treatment [155]. One remarkable instance is the FA-functionalized Hf-Mn-NMOF (fHMNM), which is a combination of Hf clusters and Mn(III)-porphyrin ligands that improves both tumor targeting and therapy's efficacy. Functionalization with FA alone brought about the largest prize of preferential uptake by HeLa cancer cells in vitro assays. However, the in vivo studies tracing the progression of tumors in mice showed not only massive inhibition of tumor growth but also no adverse effect on the surrounding normal tissue, which implies both safety and clinical utility (Fig. 2E-H). Apart from being a therapeutic agent, the fHMNM platform was found to be remarkable in terms of imaging and could be used in combination with magnetic resonance imaging (MRI), chemotherapy and photoacoustic imaging (PAI). It is important to highlight that the fHMNM system caused the attenuation of X-rays by 1.7 times and the T1 relaxation rates were even 3–5 times higher than those of the clinical agents that are conventionally used, which confirms that it is an extremely efficient imaging contrast agent. The decomposition of H₂O₂ into O₂ due to the catalytic activity of Mn-porphyrin paved the way for the alleviation of tumor hypoxia which is a barrier in cancer treatment. The oxygenation effect from this activity also contributed to a significant increase in the effectiveness of photothermal therapy (PTT) and RT, thus more firmly establishing the multifunctionality of FA-functionalized NMOFs in precision oncology. The outcome of the aforementioned studies places fHMNM as a very promising theranostic platform with the ability to not only diagnose cancer accurately but also provide the beneficial effects of combined treatment strategies. The longer the research in improving the design of FA-functionalized MOFs, the clearer their potential for clinical implementation becomes [155].

Building upon the multifunctional potential of FA-functionalized MOFs, researchers have also explored their application in PDT, a treatment strategy that relies on generating reactive oxygen species (ROS) upon light activation to induce cancer cell death [156]. The researchers Chen et al. are demonstrating the use of FA-conjugated nanoscale porphyrin gadolinium MOFs as a novel multifunctional imaging and PDT platform for HCC using a mice model (Figures 3A-F). The new nanoparticles created by combining FA with gadolinium porphyrin MOFs exhibited high water solubility, good biocompatibility, and a preferential affinity towards FR-overexpressing tumour cells. In-vitro cell assays (HepG2) and zebrafish embryo studies showed minimal toxicity and excellent dual modality imaging capabilities via demonstration of bright red fluorescence as well as MRI contrast enhancement. Importantly, the substantial accumulation of FA-NPMOFs within tumours, along with the generation of ROS upon laser irradiation, resulted in selective destruction of HCC cells through photodynamic means. These data indicate that FA-NPMOFs will be a promising and advantageous theranostic modality for both accurate detection and PDT treatment of tumours. Their specificity for targeting FR-positive tumours, low toxicity profile and the ability to generate substantial ROS suggest that these nano-porous gadolinium-functionalised nanomaterials will enhance treatment efficacy in both HCC and other FR-positive cancers using PDT [156].

Besides the developments in PDT and targeted drug delivery, another

Table 2

Summarizing some recent receptor-targeted DDSs.

Type of receptor-targeted	Type of MOF	Drug	Properties	Date	Ref.
Folic acid	MIL-101(Fe)	5-fluorouracil (5-FU)	Enhanced 5-FU delivery; Improved cytotoxicity; Modulated apoptosis, migration, and invasion	2022	[59]
	MIL-100(Fe)	Prodigiosin	Enhanced targeted delivery to Folic acid (FA)-positive MCF-7 cells; SI increased from 3.21 to 12.48	2022	[60]
	ZIF-8	Drug	Improved cancer selectivity (3.95× for MCF-7); Enhanced survival in zebrafish embryos (80% increase); Minimal toxicity; Enhanced permeability for targeted therapy	2024	[61]
	MOF	Doxorubicin (DOX)	FA-functionalized NPs (~100 nm) enhance DOX delivery to MG63 cells via folate receptors (FR); Superior anticancer efficacy in vitro and in vivo vs free DOX or unmodified MOF/DOX	2020	[62]
	PCN-224	DOX	FA modification enhances MOF targeting to cancer cells	2022	[63]
	MOF-Zr-DTBA	Bufalin (BUF)	FA aided in boosting selective absorption by leveraging receptor-targeted endocytosis; Enhancing the permeability and retention effect	2021	[64]
	UiO-66	Sunitinib, ICG	Dual-functional UiO-66 MOF functionalized with FA, loaded with sunitinib (2.30%, 72.67% efficiency) and indocyanine green (2.87%, 90.28% efficiency); Showed significant cytotoxicity against HepG2 cells	2021	[65]
	UiO-66	DOX	Mono-ligated and dual-ligated nanoscale MOFs (NMOFs) exhibited enhanced cytotoxicity against HepG2 cells, indicating the effectiveness of the selected receptors	2021	[66]
	ZIF-8	DOX and Cyclophosphamide	Addition of FA specifically enhanced drug intake in MCF-7 and MDA-MB-231 breast cancer cells; Minimized uptake by healthy cells	2021	[67]
	NH ₂ -Fe-BDC	DOX	Folate moiety assisted selective targeting of over-expressed cancer cells, as shown by flow cytometry results	2021	[68]
	UiO-66	Drug	FA@UiO-66 nanocomposite-modified gold electrode exhibited good selectivity for FAR-rich cancer cells (HeLa, H1299) vs FAR-negative cells (HEK-293) within 1 × 10 ² to 1 × 10 ⁶ cells/mL	2019	[45]
	ZIF-8	DOX	hMIL-88B(Fe)@ZIF-8 developed using 2-methylimidazole increased DOX loading from 9.2% to 43.2%; MnOx and FA added for FI/MRI imaging; MOF degradation released Fe ³⁺ for Fenton reaction-based cancer therapy	2021	[69]
	ZIF-90	Cisplatin	FA-ZIF-90/DDP nanocarriers functionalized with FA enhance cisplatin delivery; Overcome drug resistance; Target ovarian cancer cells and mitochondria; Significantly inhibit tumor growth in vivo	2024	[70]
	RMOFs	DOX	FA and ferritin-functionalized reduced iron-based MOFs loaded with DOX (FADMOF) show high cytotoxicity in 4T1, HeLa, and MCF7 cells; Dual-targeting enhances drug delivery and efficacy	2024	[71]
	UiO-66	5-FU	UiO-66-NH ₂ -FA-5-FAM/5-FU modified with FA and 5-carboxyfluorescein targets HepG2 cells; Exhibits excellent fluorescence imaging in vitro and in vivo	2018	[46]
	Zn-NMOF	5-FU	In vitro and in vivo MRI studies showed negative signal enhancement in tumors; Suggesting potential use of the nanocarrier as a diagnostic agent	2019	[72]
	ZIF-8	Curcumin (CUR)	Enhanced targeted delivery of CUR using FA-targeted ZIF-8 nanocarriers; Improved anticancer efficacy against cervical cancer cells	2023	[73]
	bio-MOF-100	CUR	Functionalized N ₃ -bio-MOF-100 with FA via CuAAC click chemistry; γ-carboxylate site modification preserves FR recognition; Strategy enhances tumor cell targeting efficiency	2021	[74]
	MIL-88	DOX	Fe ₃ O ₄ @C@MIL-88-DOX-FC NPs for FA-targeted and pH-responsive DOX delivery; Enhanced antitumor activity; Induced apoptosis in MCF-7 breast cancer cells	2023	[75]
	ZIF-8	Methotrexate (MTX)	FA-conjugated BSA-stabilized selenium-ZIF-8 NPs (FA-BSA@MTX@Se@ZIF-8) enhanced MTX delivery in breast cancer; Reduced IC50 from 40.29 μg/mL to 12.27 μg/mL; Decreased tumor volume 2.8-fold in vivo; Improved hemocompatibility and minimal organ toxicity	2024	[76]
	ZIF-8	CUR	FA-conjugated ZIF-8 (FA-g-AZIF-8) for targeted and pH-responsive CUR delivery; Enhanced drug release and cytotoxicity in acidic tumor environments	2023	[77]
	ZIF-8	CUR	Enhanced targeted delivery of CUR using FA-target bioMOF-101 nanocarriers; Improved therapeutic efficacy against breast cancer cells; Maintained safety in normal cells	2023	[78]
	ZIF-8	Letrozole (LTZ)	pH-responsive ZIF-8@LTZ@CS-FA NPs for targeted breast cancer therapy; 92% drug loading; Enhanced cytotoxicity in MCF-7 cells; Effective drug release at acidic pH; Potential for controlled cancer treatment	2024	[79]
	MOF-808	Quercetin (QU)	FA-conjugated chitosan (CS-FA) on MOF-808 enhances QU delivery; Improves targeting and pH-dependent release; Increases cytotoxicity against FR-positive MCF7 cells	2024	[80]
	ZIF-8	DOX	FA-conjugated polyethylene glycol (FA-PEG) on ZIF-8 enhances targeted DOX delivery; Enables real-time monitoring of DOX release; Facilitates effective chemo-photothermal therapy (PTT)	2022	[81]
	UiO-66	DOX	Conjugating FA to UiO-66 enhances stability, biocompatibility, and targeted delivery of camptothecin (CPT), DOX, and rose bengal (RB); Enables combined chemotherapy and photodynamic therapy	2022	[63]
	ZIF	DOX	FA conjugation enhances targeted delivery and pH-responsive DOX and ICG release in zinc-based NPs; Improves combined chemotherapy and PTT efficacy; Reduces nanotoxicity in cancer cells	2022	[82]
	ZIF	Methyl gallate	FA-conjugated ZIF-L frameworks improve pH-responsive release of methyl gallate; Enhances cytotoxicity against A549 lung cancer cells; Provides anti-biofilm activity against MRSA and N7 strains	2022	[83]
	MIL-88B	5-FU	FeCo bimetallic bi-MIL-88B MOFs conjugated with FA enhance targeted delivery and pH-responsive release of 5-FU; Increases cytotoxicity against FR-positive cancer cells	2023	[84]
	Ni-MOF-Ta	DOX and CUR	FA-conjugated chitosan; pH-sensitive DOX and CUR release; Enhanced cytotoxicity and synergistic antitumor effects in FR-positive MCF-7 cells	2022	[85]

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Table 2 (continued)

Type of receptor-targeted	Type of MOF	Drug	Properties	Date	Ref.
Hyaluronic Acid	UiO-66	DOX	FA-conjugated pluronic F127; Targeted DOX delivery in UiO-66@SiO ₂ /F127-FA NPs; Specific uptake in FR-positive MCF-7 cells; Prolonged drug release	2022	[86]
	ZIF-8/ZIF-67	QU and 5FU	FA-targeted nanocomposite; Enhanced cytotoxicity against MDA-MB-231 breast cancer cells; QU and 5-FU as delivered drugs; Encapsulation in ZIF-8/ZIF-67 MOF	2022	[87]
	MOF	Artesunate (AS)	Hyaluronic Acid (HA)-functionalized MOF-AS NPs; Overexpression of HAase in cancer cells; Effective against breast, pancreatic, ovarian, and colorectal cancers; Efficient targeted delivery	2020	[88]
	ZIF-8	Cytochrome	HA-functionalized ZIF-8 NPs; Co-encapsulation of chlorin e6 and cytochrome c; Enhanced photodynamic therapy (PDT) efficacy; Cancer-targeting nanoplatform	2020	[89]
	MIL-101	DOX	Host-guest interaction between β -Cyclodextrin and adamantane; High affinity of phosphite for iron on NMOF surface; Improved nanoplatform stability; Robust nanoplatform design	2021	[90]
	MIL-100	DOX	Combination of MOF and HA; Increased targeting of cancer cells	2019	[91]
	MOF	MTX	MTX conjugated with tannic acid and coordinated with ferric ions; High drug loading (45%); Sustained drug release; Enhanced therapeutic efficacy and reduced side effects	2021	[92]
	MIL-125-Ti	DOX	HA self-assembled onto MIL-125-Ti; MIL-125-Ti-HA@DOX; Enhanced serum stability and in vivo circulation; Improved drug release	2020	[93]
	ZIF-8	DOX	HA-modified ZIF-8 encapsulating gallic acid-iron complexes, glucose oxidase (GOx), and DOX; Improved biocompatibility and tumor targeting; Enhanced internalization in cancer cells; Fenton reaction-mediated cytotoxicity	2022	[94]
	ZIF-8	Mitoxantrone	HA-functionalized ZIF NPs ((M+H)@ZIF/HA); Higher cellular internalization; Superior cytotoxicity compared to free MIT; Efficient targeted drug delivery	2021	[95]
	PCN-224	DOX	HA functionalization of PMDH; Enhanced accumulation in tumor sites; Improved cellular uptake by CD44-overexpressing tumor cells; Catalyzes H ₂ O ₂ to O ₂ conversion to alleviate tumor hypoxia	2020	[96]
	ZIF-8	DOX	HA-functionalization; Targeting CD44-overexpressing cells; Extensively expressed in 4T1 cells; Efficient cancer cell targeting	2022	[97]
	ZIF-8	DOX	HA-targeted ZIF-8/DOX-HA@MIP nanovesicles; Enhanced targeted delivery of DOX; Controlled drug release; Improved prostate cancer treatment with biodegradability	2023	[98]
	MIL-100 (Fe)	DOX	HA-targeted MIL-100 (Fe) NPs (DMTH NPs); Enhanced targeted cytotoxicity of DOX; Improved uptake and pH-dependent drug release	2022	[99]
	MSNs-MOF	DOX	HA-functionalized gold nanorods/mesoporous silica/iron-based MOF shells; Multifunctional nanoplatform for targeted chemo-PTT; High drug loading and laser-triggered drug release; Tri-modal imaging (MR/CT/PA) and effective tumor inhibition in vitro and in vivo	2020	[100]
	ZIF-8	Oxaliplatin (OXA)	HA-targeted oHA@ZIF-8@Oxa NPs; Enhanced targeted cytotoxicity of OXA; pH-responsive drug delivery with enhanced drug loading; Improved antitumor efficacy against colorectal cancer	2023	[101]
	ZIF-8	QU	HA-modified ZIF-8 NPs (ZIF-8/HA); Enhanced QU cytotoxicity against MCF-7 cells; Reduced toxicity to L929 normal cells; CD44-mediated targeting and improved bioavailability	2024	[102]
	ZIF-8	5-FU	pH-responsive ZIF-8 MOF nanoplatform with lactoferrin and HA-lenalidomide conjugate; Dual-drug delivery (5-FU and titanocene dichloride); Enhanced reactive oxygen species (ROS) generation and mitochondrial disruption; Superior tumor suppression in vitro with stability in biomimetic environments	2020	[103]
	ZIF-8	Indocyanine Green	HA-modified ZIF-8 NPs (ICG@ZIF-8/HA); Encapsulation of ICG; Potent PDT against MRSA; Low systemic toxicity	2024	[104]
	MOF	DOX	HA-MOF@DOX pH-responsive nanoplatform; chemodynamic therapy (CDT) via DOX-loaded Cu-MOFs with 3-AT ligands; Enhanced Fenton reaction and catalase inhibition; Efficient drug delivery and targeted therapy for HepG2 cells	2022	[105]
	MOF	SN-38	HA-coated iron-based MOF (SN-38@HA@MOF); High SN-38 loading efficiency; Potent cytotoxicity against SH-SY5Y and IMR 32 cells; Low toxicity to non-cancerous cells and good biocompatibility	2024	[106]
	ZIF-8	Ganciclovir	HA/GCV@ZIF-8 nanomedical delivery system; Improved targeted delivery and efficacy of ganciclovir (GCV); pH-responsive release with enhanced cellular uptake; Reduced toxicity and effective tumor suppression in vitro and in vivo	2025	[107]
	ZIF-8	Glucose oxidase (GOx)	HA-modified ZIF-8 nanoreactors (ZPG@H) incorporating PdCuAu NPs and GOx; Enhanced cytotoxicity via ferroptosis in bladder cancer; Increased ROS; Reduced mitochondrial depolarization	2022	[108]
	MIL-101(Fe)	5-FU	HA-conjugated lactoferrin-coated iron-based MOFs (MIL-101(Fe)); Enhanced targeted delivery of 5-FU; Biocompatibility and enhanced cellular uptake; Stable drug release, promising for cancer treatment	2022	[109]
	ZIF-67	Gemcitabine (GEM)	HA-modified ZIF-67 NPs (GEM@ZIF-67-HA); Targeted delivery of GEM; Reduced cytotoxicity to normal cells; Effective suppression of cholangiocarcinoma growth in vivo	2024	[110]
	ZIF-8	QU	HA-modified ZIF-8 NPs for targeted QU delivery; High QU loading capacity (439 mg/g) and pH-responsive release; Reduced toxicity to normal cells; Enhanced cytotoxicity to MCF-7 breast cancer cells	2024	[102]
	MOF	DOX	HA-modified γ -cyclodextrin MOFs (γ -CD-MOF-HA); Targeted delivery of DOX to HeLa cells; pH-responsive drug release; Biocompatibility	2022	[111]
	MIL-101 (Fe)	Platinum-CUR	HA-targeted NH ₂ -MIL-101 (Fe) NPs delivering platinum-CUR (Pt-CUR) prodrug; Enhanced cytotoxicity against MDA-MB-231 cells; Increased reactive oxygen species (ROS) production; pH-responsive drug release	2022	[112]
	MOF	DOX	HA-BP-MOF@DOX hydrogel; Enhanced tumor growth suppression; Controlled drug release; Promising for localized cancer treatment	2022	[113]

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Table 2 (continued)

Type of receptor-targeted	Type of MOF	Drug	Properties	Date	Ref.
Aptamer	MIL-100 (Fe)	OXA	HA-modified MIL-100 (Fe) NPs (OIMH NPs) delivering OXA and ICG; Enables photoacoustic imaging (PAI)-guided chemo-PTT; Synergistic tumor cell killing; Enhanced therapeutic efficacy	2022	[114]
	MIL-88(Fe)	5-Fu	Dual-targeted oral delivery system using mannose-functionalized HAP/MIL-88(Fe) MOF in HA hydrogel film; Enhanced drug bioavailability and efficacy; Minimized systemic side effects; Enhanced cytotoxicity against HT29 cancer cells	2024	[115]
	UiO-66	DOX	Nucleolin-targeted DDS (UiO-66@AgNCs@APT@DOX); Transport of drug into the nucleus; pH-responsive drug release in cancer cells; Potential for enhanced anticancer efficacy	2019	[116]
	NMOFs	DOX	DOX-loaded aptamer (APT)-AS1411-gated NMOFs; Targeted delivery via aptamer gating; Efficient penetration of stimuli-responsive NMOFs into cancer cells; Improved cytotoxicity against cancer cells	2017	[117]
	NMOFs	DOX	AS1411 aptamer linked to locking units; Targeting nucleolin biomarker in cancer cells	2017	[118]
	MIL-101	Tirapazamine (TPZ)	AS1411 aptamer-functionalized iron-based MOF (TPZ@Apt-MOF); Targeted delivery of hypoxia-activated prodrug TPZ; Increased production of toxic superoxide anions and enhanced therapeutic efficacy	2022	[119]
	NMOFs	Cancer drugs	VEGF aptamer and VEGF aptamer/AS1411 APT conjugate-caged NMOFs; Induced 55–70% apoptosis in MDA-MB-231 cells over three days; Minimal apoptosis (<10%) in normal MCF10A cells; Demonstrates selective cytotoxicity of aptamer-functionalized NMOFs	2018	[120]
	MOF	DOX	Multifunctional core-shell NPs (Au@Cu3(BTC)2 NPs) functionalized with aptamers; Enhanced drug delivery; PTT capability; Effective cancer cell targeting	2019	[121]
	UiO-66	DOX	Fe ₃ O ₄ @MOF-DOX-CDs-Apt nanocarriers; Effectively hindered cell proliferation; Induced selective apoptosis in MDA-MB-231 cells (>77% at 24 h); Demonstrates potent and targeted cytotoxicity	2020	[122]
	UiO-66	DOX	APT-modified tetrahedral NMOFs; DOX-loaded for chemotherapy; Heightened cytotoxicity toward malignant cells; Enhanced selectivity over normal cells	2021	[123]
	[CuL-[AlOH] ₂] _n (Cu MOF)	DOX	APT-RBC-MOF@DOX nanocarriers; Enhanced DOX transport and delivery efficiency; Increased cytotoxicity against 4T1 and MCF7 breast cancer cells; Compared to non-targeted RBC-MOF@DOX	2021	[124]
	UCMOFs	DOX	ATP-responsive UCMOFs; Simultaneous transport of Cyt c (protein therapeutics), DOX, and Zn ²⁺ ; Generation of ROS for oxidative stress; Targeted combinational therapy for cervical cancer	2022	[125]
	UiO-66	Drug	APT-targeted DDS; Potential for cancer treatment	2021	[126]
	PCN	DOX	APT-modified nanoplatfrom (DOX@PCN@Apt-M) using MUC1 aptamer; Combined chemo-PDT(DOX + PCN-224 for ¹ O ₂ production); Enhanced therapeutic effects under 808 nm laser irradiation; Reduced side effects	2023	[127]
	MOF	DOX	AS1411@PEGMA@GQD@γ-CD-MOF carrier; High DOX loading efficiency (89.1%); Outstanding targeting capability; Low cytotoxicity	2019	[128]
Mannose	MOF-199	DOX	DOX/CuS@MOF-199/Apt-M nanoplatfrom using MUC1 aptamer; Targeted delivery of DOX and CuS NPs; Enhanced Photothermal Therapy – Chemotherapy (PTT-CT) efficacy; Minimal systemic toxicity	2024	[129]
	MOF	DOX	AS1411 aptamer-functionalized porphyrinic MOF (porMOF); Targeted delivery of DOX; Synergistic PDT; Effective cancer cell killing under acidic conditions	2023	[130]
	MOF	TPZ	TPZ@Apt-MOF using AS1411 aptamer; Hypoxia-activated delivery of TPZ; Potential for enhanced tumor-specific therapy	2022	[119]
	MIL-88A(Fe)	Drug	Mannosylated MIL-88A(Fe); Highly increased cellular uptake; Enhanced number of cells involved in internalization; Potential for improved targeted drug delivery	2019	[131]
	MOF	DOX	Mannose-modified ferrocene MOFs; pH-responsive drug delivery of DOX and ferrocene; Enhanced cytotoxicity via CDT and chemotherapy; Synergistic dual-drug delivery	2022	[132]
	MOF-808	Carboplatin	Mannose-modified MOF-808 NPs; Loaded with floxuridine (FUDR) and carboplatin (CARB); Enhanced cytotoxicity against HepG2 cells; Synergistic chemotherapy effect	2022	[133]
	Fe-MOF	MTX and DOX	Mannose-functionalized MgAl-LDH/Fe-MOF NPs; Loaded with MTX and DOX; pH-responsive drug release; Enhanced cytotoxicity and potential as dual drug carriers	2022	[134]
	MIL-88(Fe)	MTX	Magnetic nanocomposite hydrogel beads (Fe ₃ O ₄ /MIL-88(Fe)-MTX) with mannose functionalization; Targeted oral anticancer delivery; Enhanced pH-sensitive drug release; Increased efficacy against colon cancer cells	2024	[135]
	ZIF	Saccharomyces Cerevisiae	SC@ZIF@ADH nanoplatfrom targeting CRC via mannose-mediated TAM mechanisms; Production of toxic acetaldehyde in hypoxic tumors; Induces apoptosis and TAM polarization; Significant tumor inhibition in vivo; potential non-surgical PEI alternative	2022	[136]
	nanoscale coordination polymers	MTX	Lipid-coated, anisamide-targeted NCPs; Enhanced in vitro efficacy; Compared to free drug; Targeted delivery for acute lymphoblastic leukemia cells	2012	[137]
Glucose	NMOF	DOX	Versatile NMOF-based theranostic platfrom with glucose coating; Targeted delivery to glucose-hungry cancer cells; Controlled drug release; Imaging capabilities via incorporated Gd ³⁺ or Yb ions	2018	[138]
	ZIF-8	5-FU	Fe-doped ZIF-8 MOFs modified with gallic acid (GA) and GOx; Enhanced pH-sensitive drug release; Significant anticancer efficacy; Potential for targeted breast cancer therapy	2023	[139]
	PCN-224	DOX	Galactose-modified MOF NPs; Targeted delivery of DOX; Acting as a photosensitizer for PDT; Enhanced tumor inhibition via combined PDT and chemotherapy	2020	[140]
Galactose	ZIF-8	Sorafenib	N-acetyl-galactosamine-modified MOF NPs; Combined targeted chemotherapy with sorafenib and glucose starvation therapy; Effective inhibition of hepatocellular carcinoma growth; Prevention of metastasis	2022	[141]
Antibodies	MIL-101 (Fe)	GEM	Iron-based MOF nanocages in a covalent organic framework modified with pancreatic cancer-specific antibody; Overcoming GEM resistance via autophagy-dependent	2023	[142]

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Table 2 (continued)

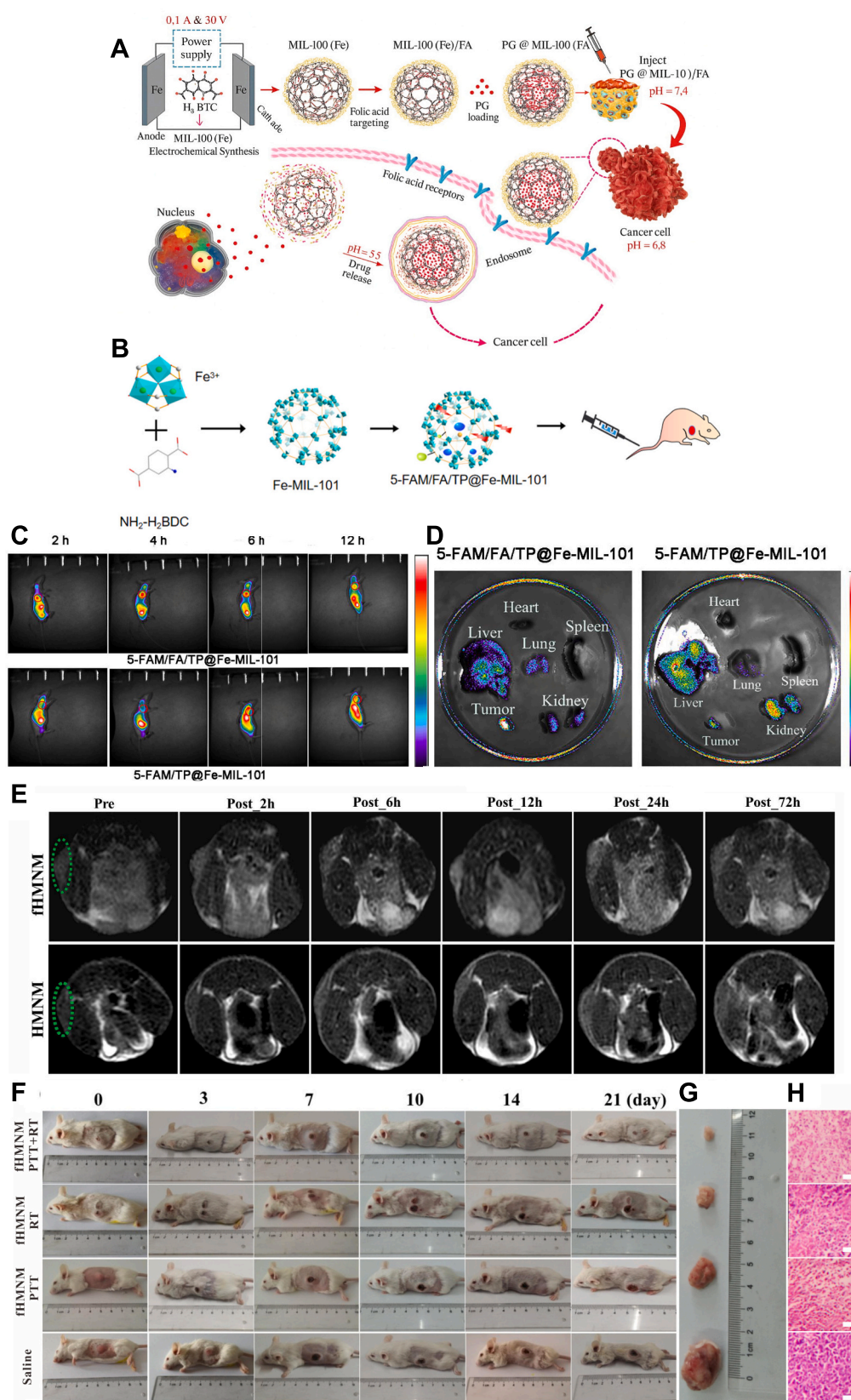
Type of receptor-targeted	Type of MOF	Drug	Properties	Date	Ref.
Bovine serum albumin	MIL-100	DOX	ferroptosis; ROS generation under ultrasound irradiation; Significant tumor volume reduction in vivo without harming healthy tissues	2020	[143]
	ZIF-8	DOX	Nanosized MOFs functionalized with antibodies; High drug loading and sustained release; Carboxymethyl-dextran coating preserves antibody specificity; Targeted delivery to HER2/neu-positive breast cancer cells with DOX or daunorubicin	2024	[144]
	bio-MOF	DOX	MOFs modified with antibody targets; Significant increase in cancer cell cytotoxicity (up to 80%); Improved selectivity and targeted DDS; Potential for more effective and safer cancer treatment	2021	[145]
	ZIF-8	DOX	Peptide-doped MOF (ZFH-DGR) for versatile drug encapsulation and targeted delivery; Selective cytotoxicity with pH-triggered drug release; DOX-loaded ZFH-DGR reduces tumor volume in HepG2-bearing mice; Potential for precise cancer treatment with minimal normal tissue toxicity	2018	[146]
	ZIF-8	GEM	Core@shell nanocomposite using biocompatible bovine serum albumin (BSA) and pH-sensitive ZIF-8; Targeted DOX delivery; Efficient pH-responsive drug release and enhanced cellular uptake; Improved efficacy against MCF-7 breast cancer cells	2022	[147]
	ZIF-8	DOX	MOFs with BSA and ZIF-8 as pH-sensitive nanocarriers; Effective targeting of MCF-7 breast cancer cells; Reduced toxicity to human umbilical vein endothelial cells; Delivery of anticancer drugs	2021	[148]
Peptides	ZIF-90	Oridonin and Survivin	Histidine polypeptide-hybridized nanoscale MOF (fH12/ZIF-8); pH-responsive drug release and enhanced cellular uptake; Theranostic platform for effective cancer therapy; Real-time monitoring capabilities	2023	[149]
	ZIF, UIO-66 and HKUST-1	DOX	PEG-CPP33@NPs using ZIF-90 for targeted co-delivery of oridonin (ORI) and survivin siRNA; High drug-loading capacity, pH-sensitive release, and enhanced stability; Improved bioavailability of siRNA and enhanced cellular uptake via PEG-conjugated cell-penetrating peptides; Synergistic anti-tumor effects in vitro and in vivo	2022	[150]
	ZIF-8	CPT	Enzyme-sensitive DDS using Cathepsin B-sensitive DOX-conjugated peptides; Stable NPs formed with ZIF, UIO-66, and HKUST-1 MOFs; Molecular dynamics simulations indicate optimal stability at lower prodrug concentrations; Microfluidics enhances drug delivery efficiency, especially with ZIF NPs	2019	[151]
			pH-sensitive ZIF-8 NPs loaded with CPT and grafted with RGD; pH-responsive drug release (75% at pH 5 vs. <5% at pH 7.4); Tumor targeting via receptor-mediated endocytosis; Intracellular ROS generation for enhanced cancer therapy		

strategy based on zirconium containing MOFs appears to be very promising. The research by Xie et al., demonstrated that zirconium-based MOF (PCN-224) is porphyrinic and can renounce a multifunctional nanocarrier Drug@PCN-224-FA, consisting of combined chemotherapy and PDT. This system merged camptothecin (CPT) and DOX as anti-cancer drugs which were both trapped within the framework and functionalized with FA to better targeting the FR overexpressing tumor cells. Drug@PCN-224-FA had a size of less than 200 nm and showed a high drug-loading efficiency, releasing 46.42% of CPT and 40.80% of DOX under acidic conditions. Moreover, when irradiated with a laser of 630 nm, the system produced ROS very effectively which induced the simultaneous chemotherapy and PDT treatment [157]. The FA modification ensured selective accumulation in tumor cells, significantly enhancing cellular uptake and therapeutic efficacy. In vitro, cytotoxicity assays on HepG2 cells confirmed its low toxicity and high therapeutic efficiency. These findings position Drug@PCN-224-FA as a promising dual-modality therapeutic platform, combining targeted drug delivery with the advantages of chemotherapy and PDT for effective cancer treatment.

Zeng et al. have designed a new DDS that takes advantage of the previous research, which emphasized the benefits of targeting tumor cells via FR. This system uses a pH-responsive and redox-sensitive MOF to maximize the therapeutic efficacy of bufalin (BUF), a bioactive compound from traditional Chinese medicine that is very good at killing cancer cells. The DDS called FA-MOF/BUF is designed especially for breast cancer treatment. It increases the targeted delivery and controlled release of BUF while also reducing the off-target effects. The construction of the FA-MOF/BUF system utilized ligand-bonded glutathione (GSH)-sensitivity in conjunction with $ZrCl_4$, enabling BUF to be trapped inside the MOF lattice. FA was then attached to the surface for the selective targeting of the cancer cells that overexpress FR. FA-MOF/BUG showed stability under neutral conditions but quickly dissolved in the acidic microenvironment of tumors (pH 6.5–7.1). Furthermore, this

degradation was enhanced by the intracellular GSH in the cancer cells, which acted to break the disulfide bonds in the MOF leading to the release of BUF in a controlled manner [158]. Compared to free BUF, FA-MOF/BUF exhibited improved water solubility, stability, and selective uptake through receptor-targeted endocytosis. In vitro experiments demonstrated stronger cytotoxicity against breast cancer cells, while in vivo studies showed enhanced drug accumulation in tumor tissues, leading to higher antitumor efficacy with fewer systemic side effects (Figure 3G-I). These findings suggest that FA-MOF/BUF represents a promising nanocarrier system for targeted and efficient breast cancer treatment, with reduced side effects [158].

As a part of the strategies for targeted drug delivery improvement, Singh et al. introduced a novel dual-drug nanocarrier system which consisted of GO-FA/ZIF-8 namely a hybrid system combining FA-functionalized ZIF-8 with GO. This nanocarrier had an ability to load DOX inside ZIF-8 and to fasten the other drug CUR on GO by the adhesive forces of hydrogen bonding and π - π interactions. The FA conjugation remarkably increased the selective cellular uptake in MCF-7 and MDA-MB-231 breast cancer cells keeping the normal cells out. The drug release was observed to be dependent on the pH level, with 76% and 80% of DOX and cyclophosphamide (CP), respectively, being released in the acidic environment which is characteristic of the tumor microenvironment [67]. In a similar approach, another nanocomposite was developed using a combination of two MOFs, IO/Z8-Z67/FA/QU, demonstrating 50% drug loading efficiency for QU [87]. The selective targeting of the system towards FA-targeted positive MDA-MB-231 cells has not only proven its potential as a theranostic platform for both cancer therapy and imaging, but has also given hope in the future of (Figure 4A). It is also a fact that MOF-based systems have been able to deliver drugs very efficiently and specifically to the tumors, which is a clear sign of their versatility and effectiveness in breast cancer therapy. Among the numerous achievements of CUR@FA-g-AZIF-8, its drug loading efficiency of 91.6% was the most prominent one, obtained along



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Fig. 2. Schematic illustration and in vivo evaluation of folic acid (FA)-targeted metal–organic framework (MOF)-based nanocarriers for tumor imaging and therapy. (A) Schematic procedure of PG@MIL-100(Fe)/FA-targeted delivery. Reproduced with permission from Ref. [60]. (B) Schematic procedure of 5-FAM/FA/TP@Fe-MIL-101. (C) Fluorescence imaging in mice at 2 h, 4 h, 6 h, and 12 h after injection of nanoparticles. (D) Fluorescence imaging of major organs and tumors in mice 12 h after nanoparticle injection. Permission from Ref. [154]. (E) In vivo MR experiments comparing two samples using tumor-bearing mice, with green dotted circles highlighting the tumor regions ($n = 3$ per group). (F, G) Photographs of tumor-bearing mice under different therapeutic conditions and corresponding excised tumors at the end of the study (21 days). (H) H&E-stained tumor slices collected from mice after various treatments ($n = 5$ per group). Scale bar: 100 μm . Permission from Ref. [155].

with excellent chemical stability. The drug release in vitro study conducted by Reshmi et al. at acidic pH (5) typical for the tumor microenvironment reiterated this point where the release was three times higher than at physiological pH (7.4) for CUR. Besides, the cytotoxicity testing of CUR@FA-g-AZIF-8 (MTT assay) against HeLa cells gave a cell death rate of 76.8% at a concentration of 25 $\mu\text{g/mL}$, while free CUR at only 1 $\mu\text{g/mL}$ resulted in a cell mortality rate of 71.2%. Thus, the results clearly strengthen the FA-g-AZIF-8's position as a highly effective tumor-targeting DDS that can not only deliver the drug in acidic environments but also cause significant cytotoxicity to the cancer cells. This work backs previous conclusions that the optimization of MOF-based nanocarriers is essential for attaining better targeting, drug release, and therapeutic efficacy in cancer treatment [77].

Chinnathambi et al. synthesized a novel pH-responsive DDS for docetaxel (DTX) based on a ZIF-8 modified with ethylene diamine (ED) and conjugated with FA. The fabricated nanocomposites (DTX/FA@ED-ZIF-8) showed high drug-loading efficiency (91.6%) and excellent chemical stability. In vitro drug release studies showed a three-fold increase in DTX release under acidic pH (5.0) compared to physiological pH (7.4), leveraging the tumor's acidic microenvironment for targeted delivery. Cytotoxicity studies via MTT assays on A549 and H1299 cells presented 76.8% cell death, further supported by analysis of cell morphology and nuclear staining studies. Apoptosis was confirmed through flow cytometric analysis with Annexin V-FITC and PI as the major mode of cell death. Selective binding and uptake of FA in cancer cells for tumor targeting are mediated by FR. The acid-sensitive bond between Zn and imidazolate in ZIF-8 ensures the collapse of the framework and controlled release of DTX in low-pH tumor microenvironments. This strategy addresses the functionalization challenge of MOFs for drug delivery by surface amination with the conjugation of FA and effective loading of DTX. These results show that FA@ED-ZIF-8 is a promising DDS for pH-responsive, site-specific delivery of DTX and thus has great potential for improving cancer therapy [159].

Expanding on the advancement of targeted DDS, another study further investigated the application of nanomaterials in cancer therapy. Mokri et al. designed a novel nano MOF based on zinc, functionalized with FA-functionalized chitosan, to deliver locked nucleic acid-antisense miR-224 to colon cancer cells. The system achieved an impressive drug loading efficiency of $72 \pm 5\%$, with 50% of the drug released within the first 6 hours. The resulting MCFL224 nano-complex showed remarkable anticancer activity, significantly reducing cell viability to just $14.22 \pm 0.3\%$ after 72 hours of treatment. This treatment also induced a notable increase in apoptosis and autophagy-related gene expression, including BECLIN1, BAX, mTORC1, and Caspase-9, demonstrating the therapeutic potential of this system. Furthermore, 19.53% of the cells were arrested in the sub-G1 phase, with a striking 67.7% of cells undergoing late apoptosis. These findings are consistent with the results of the previously discussed pH-responsive DDS for DTX, where the combination of targeting and controlled release led to high anticancer efficacy. Similarly, the MCFL224 nano-complex proves the effectiveness of targeted MOFs in enhancing drug delivery and improving cancer treatment outcomes. These advances further reinforce the growing promise of MOF-based DDS for both localized drug delivery and maximizing therapeutic impact [160].

Further innovations in MOF-based DDS have focused on integrating both therapeutic and diagnostic capabilities, leading to the development of multifunctional platforms for enhanced tumor targeting. In a study done by Nejadshafiee et al., they highlighted the versatility of MOF-

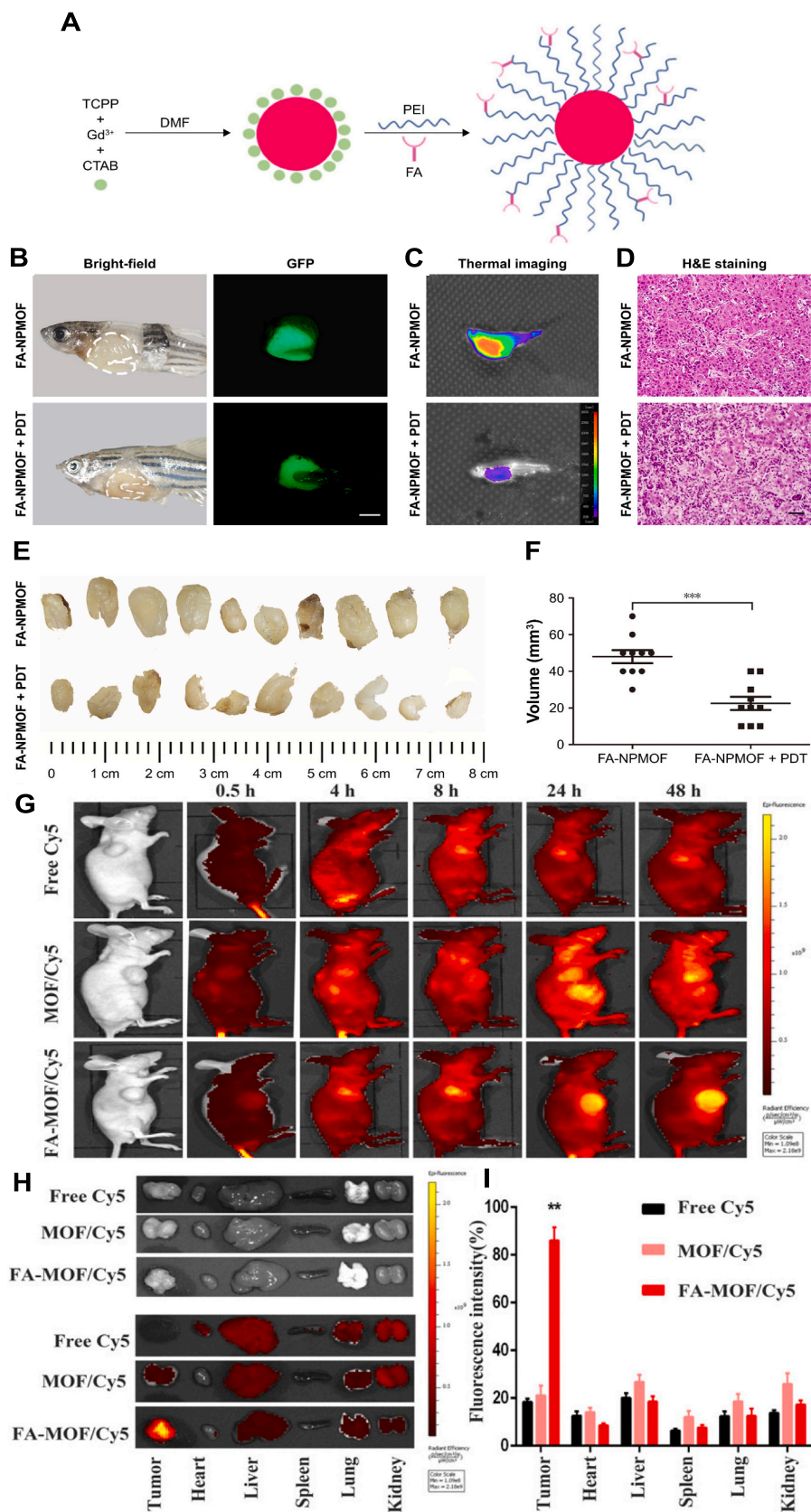
based DDS by introducing a magnetic Bio-MOF platform (Fe_3O_4 @Bio-MOF) tailored for effective tumor targeting. This approach incorporates a folic acid-chitosan (FC) combination for drug delivery, capable of encapsulating both CUR and 5-FU, two widely used anticancer drugs (Figure 4B–D). The Fe_3O_4 core endows the system with magnetic properties, enhancing its use in T2 MRI imaging. Additionally, the CUR-Zn MOF structure enables high drug loading, with controlled, sustained release in the acidic microenvironment typical of tumors. In vitro studies demonstrated the selective uptake of the system by FR-positive MDA-MB-231 breast cancer cells, with enhanced toxicity against cancer cells compared to normal ones. In vivo MRI studies further confirmed the diagnostic capabilities of the system, showing tumor-specific negative signal enhancement. This highlights the dual functionality of the DDS, combining both therapeutic and diagnostic applications, often referred to as theranostic platforms. The system also displayed excellent hemocompatibility, reinforcing its suitability for clinical applications. These findings align with earlier studies, such as the pH-responsive DTX system, in demonstrating the success of combining drug delivery with targeted cancer treatment, thereby paving the way for advanced theranostic strategies. In future studies, further investigations into in vivo biodistribution and tumor shrinkage could facilitate the clinical translation of this promising DDS for breast cancer therapy [72].

The previous advances in MOF-based DDS were further developed by Jalaladdiny et al. who, through FA-activated chitosan core-shell MOF, came up with a new strategy for the pH-sensitive, targeted drug delivery of DOX and CUR. The besides mentioned the FC- MOFs revealed a large increase in release of CUR and DOX at acidic pH 5 as compared to the uncoated MOFs thus indicating their use for release of drugs in acid environments like that of tumor sites, however, the release remained stable for 72 hrs. To check the efficiency and toxicity of the system, the FC-MOF (CUR + DOX) was tested on MCF-7 (FR-positive) and HepG2 (FR-negative) cells by means of MTT assay. The outcomes displayed that MCF-7 cells had much higher toxicity (86% cell death and 14% survival) than HepG2 cells (26% survival), thus confirming the receptor-targeted uptake through FR. Moreover, the FC-MOF (CUR + DOX) system showed a synergistic effect: at a low DOX concentration of 25 CUR + 0.5 DOX g/mL, it led to more than 60% cell death in MCF-7 cells, exceeding that of the MOF-CUR + DOX (45%) system, although slightly less than that of the maximum concentration of FC-MOF-DOX. To sum up, these results point out the capability of the FC-MOF as an efficient pH-responsive carrier for combination therapy, augmentation of the therapeutic efficacy as well as reduction of the toxicity to healthy cells, in addition to the benefits brought about by FA-mediated co-delivery in the targeted cancer therapy [85].

2.2. Hyaluronic acid

Transitioning from FA-mediated targeting strategies, another promising approach involves using HA, a naturally occurring linear mucopolysaccharide found in the extracellular matrix [161]. HA is praised for its remarkable biocompatibility and immune evasion abilities and thus has become one of the major focuses in nanomedicine for cancer treatment. Not only this, it also has a high affinity for the receptor CD44 which is an 85 kDa transmembrane glycoprotein involved in cell attachment, movement and tumor development. Since CD44 is overexpressed in many solid tumors as well as in cancer stem cells, it is a very good target for HA-coated drug delivery systems [162,163].

Consequently, HA has been widely employed to modify the outer



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Fig. 3. Schematic representation, in vivo imaging, and therapeutic evaluation of folic acid-functionalized metal-organic framework (FA-MOF) nanocarriers for photodynamic therapy (PDT) and tumor targeting. **(A)** Schematic illustration of FA-nanoscale gadolinium-porphyrin metal-organic framework (FA-NPMOF) synthesis. **(B–D)** Bright-field, fluorescence, thermal, and H&E staining images of HCC-bearing zebrafish before treatment (FA-NPMOF; left column) and after photodynamic therapy (FA-NPMOF + potent PDT; right column). **(E)** Representative images of tumors in the FA-NPMOF and NPMOF + PDT groups. **(F)** Statistical analysis of tumor volume between the two groups. Scale bars: **(B)** 500 μm , **(D)** 20 μm . *** $P < 0.001$. Reproduced with permission from Ref. [156]. **(G)** In vivo fluorescence imaging of tumor-bearing mice at 0.5, 4, 8, 24, and 48 h after intravenous injection, where fluorescence intensity decreases gradually as shown by the color bar from yellow to red. **(H)** Fluorescence images of main organs (heart, liver, spleen, lungs, kidneys) and tumors collected from mice 48 h post-injection. **(I)** Biodistribution of Cy5, MOF/Cy5, and FA-MOF/Cy5 in tumor tissues and various organs. ** $p < 0.01$. Reproduced with permission from Ref. [158].

surfaces of MOFs post-synthetically, enabling enhanced tumor-specific targeting while preserving the structural integrity of these carriers [164,165]. A comparison of findings from different studies reveals that researchers have leveraged HA-functionalized MOFs for targeted drug delivery by designing advanced systems that integrate biorecognition and controlled drug release mechanisms. One such example is the ZIF-8/DOX-HA@MIP system, where molecularly imprinted polymer (MIP) is applied to the surface of HA-modified ZIF-8 loaded with DOX, enhancing selective drug delivery. (Figure 5A–E). This dual-functional platform is a remarkable accomplishment that not only achieves over 88% during the loading of drugs but also improves the cancer cell-patient specificity through the combined effect of HA and molecular imprinting. Furthermore, this system manifests excellent biodegradability in conditions mimicking tumors. Tumor microenvironment is where the degradation of the system happens gradually; the release of DOX is then controlled by the lower pH levels, higher GSH concentrations and hyaluronidase activity that occurs in the tumor. The in vitro and in vivo experiments have confirmed the drug's great compatibility with the human body, strong tumor killing power, and selective uptake in prostate cancer (PCa) cells. Thus, it further supports the application of HA-modified MOFs in precision oncology [98].

Recent research has investigated the integration of HA into multifunctional nanoplateforms, aiming to improve both therapeutic efficacy and tumor selectivity in targeted DDS. One such innovation is Fe²⁺-doped ZIF-8 NPs (FZ NMs), designed for a combination of chemotherapy. To further optimize their performance, these NPs were coated with polydopamine (PDA) and HA, a strategic modification that improved both their stability and tumor-targeting capability. This dual-functional system operated through a synergistic mechanism.

The PDA coating played a crucial role in depleting GSH, weakening the tumor's natural defense system, while the Fe²⁺/Fe³⁺ transition catalyzed the Fenton reaction, generating hydroxyl radicals that inflicted oxidative damage on cancer cells. The HA modification, at the same time, allowed selective interaction with CD44 receptors, thus facilitating the targeted cellular uptake and increasing the efficiency of drug delivery (Figure 5F–J). The preclinical studies showed that this approach resulted in substantial tumor suppression in CT26 models with almost no toxicity to the surrounding healthy tissues. This strategy leveraging the combined actions of oxidative stress induction and receptor-targeted targeting, reveals the power of HA-modified MOFs in the precision oncology field [166].

In light of previous successes with HA for targeted delivery, Yuan et al. introduced an innovative self-synergistic nanoplateform, PAO@PCN@HA, designed for chemotherapy-sensitized PDT targeting hypoxic tumors. This platform combined phenylarsine oxide (PAO), a potent ROS inducer, encapsulated within PCN-224 and modified with HA for enhanced tumor specificity. The HA modification was crucial in improving the biocompatibility of the system while ensuring selective targeting of tumor cells through CD44 receptor interactions. In the case of this dual-purpose system, PAO played a double role by providing the production of ROS that killed cancer cells at the same time as getting rid of the oxygen deficiency and using the intracellular GSH (Figure 6A–H). The approach to hypoxic tumor microenvironments enhanced PDT's effectiveness greatly. The in vitro and in vivo studies results indicated the great potential of PAO@PCN@HA for being an effective tumor growth inhibitor with very low toxicity to the whole body, and it also showed its ability to deal with situations like chemoresistance and

hypoxia [167].

The development of this cancer cell-targeted nanoplateform builds upon the growing trend of combining multiple therapeutic approaches within nanomaterials to enhance the efficacy of cancer treatment. As demonstrated in previous studies, modifying the surface of NPs with biocompatible polymers, such as HA, has proven effective in improving the selectivity of drug delivery to tumor sites by targeting specific receptors like CD44. The HA coating, as demonstrated by Ding et al., worked synergistically with ZIF-8 NPs, facilitating both PDT and protein therapy for a dual therapeutic effect. In line with other multifunctional nanoplateforms, the incorporation of Ce6 and Cyt c within the ZIF-8 framework provided a unique combination of ROS generation and apoptosis induction, further enhanced by HA-mediated tumor targeting (Figure 6I–N). This enhanced targeting along with the platform's ability to respond to the acidic tumor microenvironment, highlights the importance of designing smart DDS capable of addressing complex challenges, such as hypoxia and chemoresistance in solid tumors. By combining the benefits of HA-targeting with a pH-sensitive release mechanism and the potent therapeutic properties of Ce6 and Cyt c, this approach exemplifies the potential for advanced, targeted cancer therapies with improved efficacy and minimal side effects [89].

This development marks a significant advancement in the design of targeted cancer therapies by combining multiple mechanisms within a single nanoplateform. Inspired by the concept of multifunctional nanocomposites, the combination of ZIF-90 NPs with a spermine-modified acetylated dextran (SAD) shell and HA targeting effectively addresses major drug delivery challenges, such as improving stability, preventing premature drug release, and enhancing tumor-specific targeting (Figure 7A–F). The pH-sensitive release behavior of the SAD shell allows for controlled drug delivery in the acidic environment typically found in tumors, which further enhances therapeutic outcomes. As with previous nanoplateforms that leverage the targeting capabilities of HA to enhance tumor-specific drug delivery, the HA modification here facilitates the targeting of CD44 receptors that are overexpressed on cancer cells. This system's dual delivery of hydrophilic DOX and hydrophobic IR780 exemplifies the potential of combining chemotherapy and PDT in a single nanoplateform. The impressive results from in vivo studies, which showed a significant improvement in IR780 loading efficiency and effective tumor suppression, highlight the promise of this strategy in advancing cancer treatment. By minimizing systemic toxicity while enhancing tumor-specific drug delivery, this nanocomposite demonstrates the potential for developing more effective and less harmful cancer therapy [168].

The comprehensive study of DOX&GGF@ZIF-8@HA NPs reported by Fu et al. demonstrates yet another instance of the application of nanotechnology in the area of targeted cancer therapy. The inventive encapsulation of DOX, GA/Fe nano complexes, and glucose oxidase (Gox) within ZIF-8, followed by the surface modification with HA, places the NPs in the right position to reach and treat tumors via the overexpressed CD44 receptors (Figure 7G–J). The tumoral heterogeneity that poses a problem in the delivery of the drug is thus tackled, and the treatment response is more pronounced. The particularity of the system is that it is based on two mechanisms, i.e. the fusion of chemotherapy and the induction of ferroptosis, which together constitute a strong therapeutic reaction cascade. The time at which the NPs dispense their payload in the acidic tumor microenvironment is when the NPs go on to use GOx to convert glucose into hydrogen peroxide (H₂O₂) which then

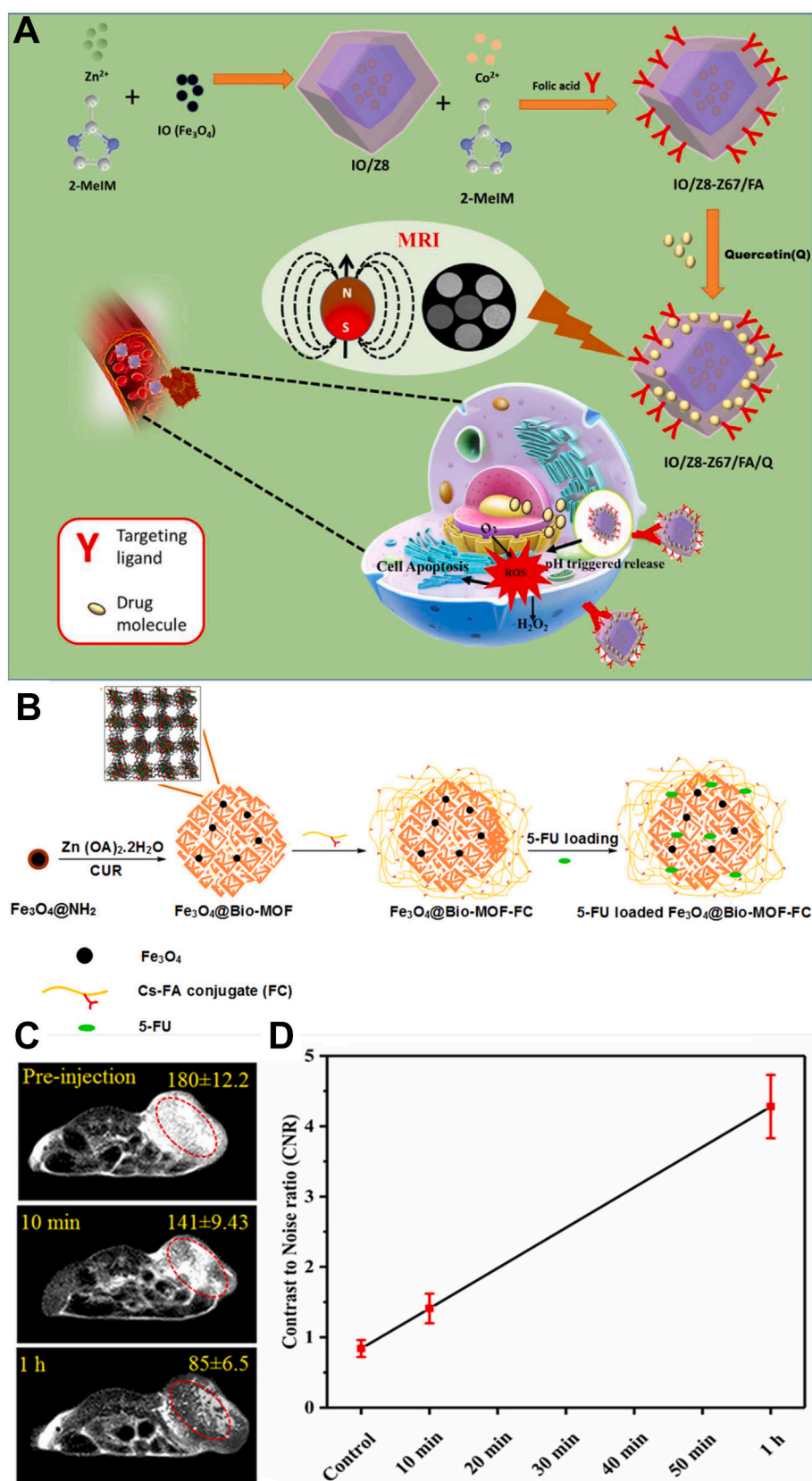
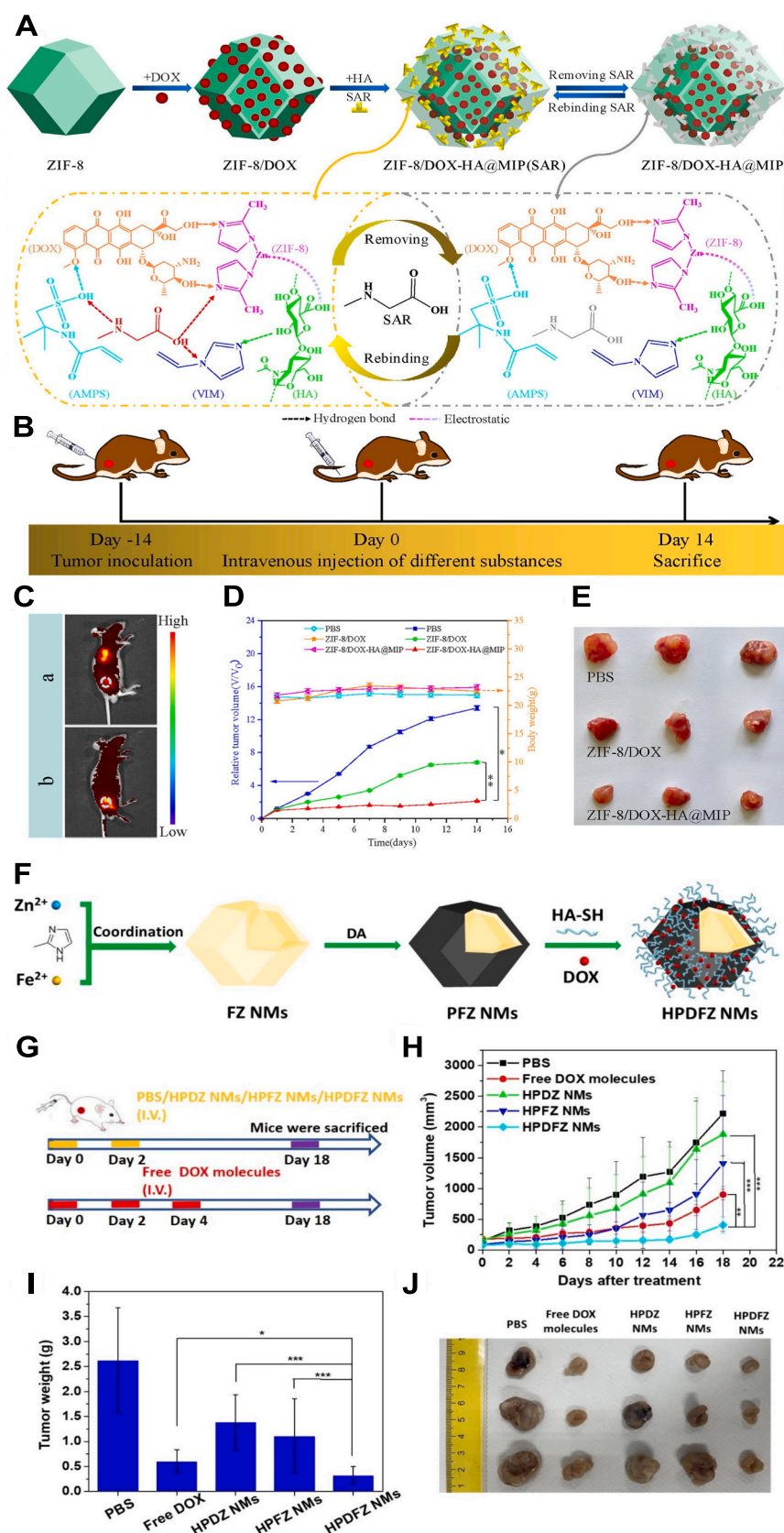


Fig. 4. Schematic design, synthesis, and in vivo imaging evaluation of multifunctional iron oxide (Fe_3O_4)-based MOF nanocomposites for cancer diagnosis and therapy. **(A)** Schematic representation of IO/Z8-67/FA/Q design and fabrication as an effective multifunctional cancer therapeutic agent. Reproduced with permission from Ref. [87]. **(B)** Sequential steps for the preparation of 5-FU-loaded Fe_3O_4 @Bio-MOF-FC nanocomposites. **(C)** In vivo T_2 -weighted MRI images of tumor-bearing BALB/c mice before injection and at 10 min or 1 h after injection of Fe_3O_4 @Bio-MOF-FC NCs (red circles indicate the tumor regions). **(D)** Contrast-to-noise ratio (CNR) profile calculated from the tumor signal intensity over time corresponding to panel (C). $p < 0.05$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.) Reproduced with permission from Ref. [72].



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Fig. 5. Schematic design, fabrication, and in vivo therapeutic evaluation of multifunctional ZIF-8-based nanomaterials for targeted drug delivery and tumor inhibition. **(A)** Schematic illustration of ZIF-8/DOX-HA@MIP system for specific recognition and treatment of SAR. **(B)** Schematic representation of DU 145 tumor establishment and treatment process. **(C)** Fluorescence imaging of tumor-bearing mice injected with **(a)** ZIF-8/DOX and **(b)** ZIF-8/DOX-HA@MIP (circles indicate tumor regions). **(D)** Changes in body weight and tumor volume of mice following PBS, ZIF-8/DOX, and ZIF-8/DOX-HA@MIP treatments ($n = 3$, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$). **(E)** Photographs of dissected tumors from DU 145 tumor-bearing mice after 14 days of therapy in each treatment group. Reproduced with permission from Ref. [98]. **(F)** Schematic illustration of HPDFZ NMs fabrication process. **(G)** Experimental flowchart outlining the in vivo tumor growth inhibition study. **(H)** Tumor growth inhibition profiles of CT26 tumor-bearing mice under various treatments. **(I, J)** Tumor weight and corresponding photographs of tumors harvested from euthanized mice on day 18 post-treatment. Reproduced with permission from Ref. [166].

brings the Fenton reaction going on to create the toxic hydroxyl radicals (OH) that cause cell death via ferroptosis. At the same time, the GA/Fe complexes strengthen the Fenton reaction by promoting the redox circulation of Fe(II), and DOX pushes apoptosis along. The in vivo results, which depict marked tumor inhibition and possible MRI enhancement, are a witness to the multifaceted nature of the strategy, thus highlighting its promise. Such developments in nanocomposites imply that a thorough delivery, cascading therapeutic reactions, and enhanced imaging capabilities can already be envisaged in the future as being the main features of the cancer-coping biomedicine, which in fact is a big gain in the field [97].

Long and coworkers not only made a significant leap in targeted cancer therapy but also came up with a nanoplatfrom made of halloysite nanotubes (HNTs) and ZIF-8 with HA that synergistically treated breast cancer with chemo/photothermal. The HNTs@ZIF-8@DOX@ICG@HA system was able to precisely reach and kill MDA-MB-231 cells via near-infrared (NIR) laser-induced drug discharge. This ground-breaking way proved the possibility of giving PTT milieu of chemotherapy, therefore, increasing the cure rate with less adverse effects that accompany conventional treatments [94]. In a similar approach, Zhou et al. designed a novel pH-responsive MOF system using HA-modified ZIF-8 for targeted drug delivery, incorporating mitoxantrone and hydralazine (HYD) to enhance tumor clearance and stimulate an immune response. This system's pH responsiveness allowed for controlled drug release in the acidic tumor microenvironment, improving the potency and efficacy of the treatment [95]. Meanwhile, Yao et al. focused on enhancing the stability and delivery efficiency of a β -cyclodextrin and HA-modified MIL-101-NH₂ (Fe) carrier. The high encapsulation and loading rates achieved in their study (41.20% and 48.84%, respectively) significantly boosted the stability of the nanoplatfrom, making it a promising candidate for cancer therapy [90]. Following the theme of HA-enhanced drug delivery, Xue et al. modified MIL-100 with HA for DOX loading, improving its targeting capability and dispersion (Figure 7K-Q). This modification led to improved cancer treatment efficiency by optimizing the delivery and bioavailability of the chemotherapy drug [91]. Collectively, these studies underscore the potential of HA-modified nanoplatforms in targeted cancer therapy, demonstrating how modifying MOFs and carriers with biocompatible molecules like HA can significantly improve drug delivery, targeting accuracy, and therapeutic outcomes.

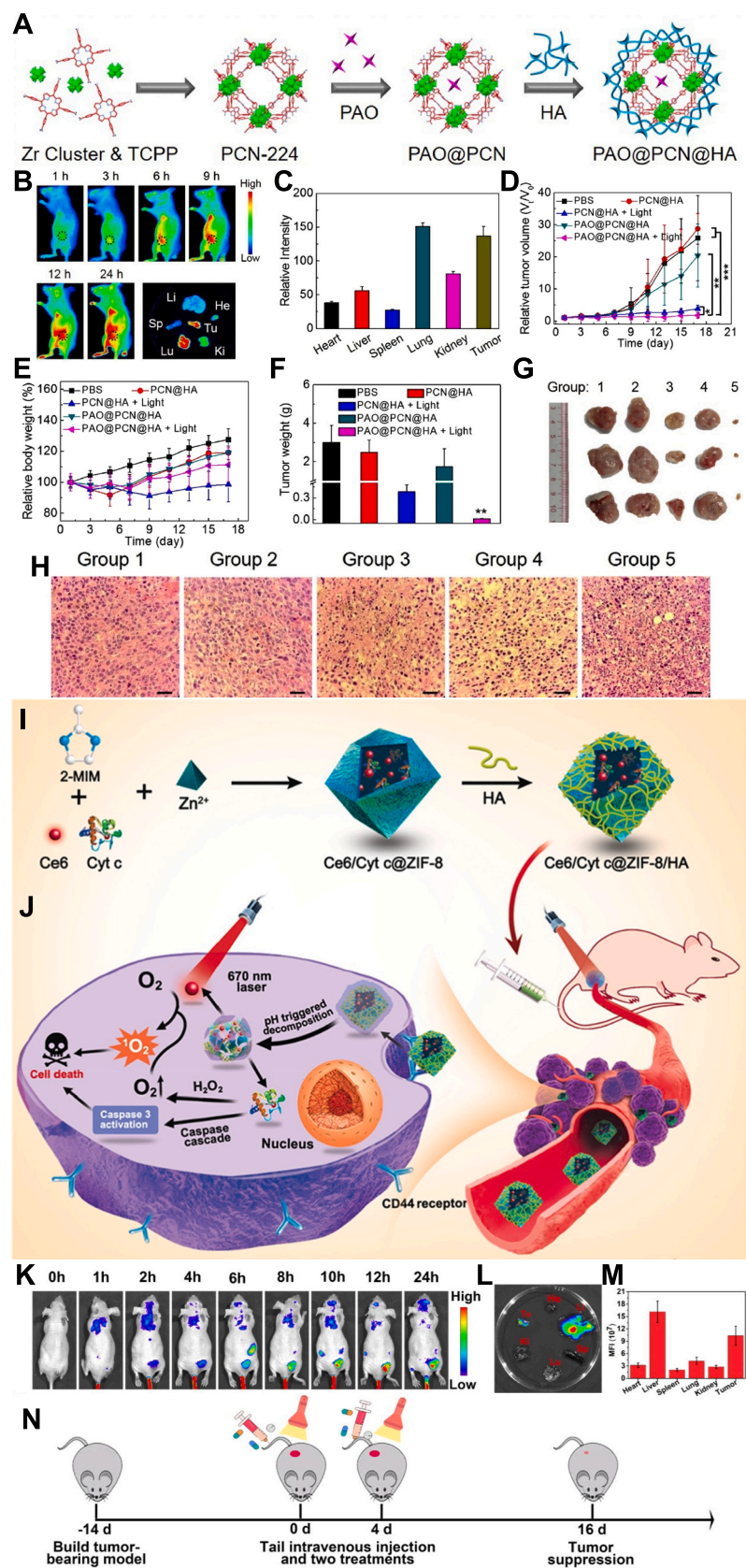
In their study, Song et al. explored the effect of changing HA ratios on MIL-125-Ti MOFs for targeted drug delivery and discovered that HA modification markedly improved serum stability, storage and in vivo drug release duration while still maintaining the MOFs crystallinity. They highlighted the power of HA as a stabilizer for MOFs which leads to more efficient and controlled DDS [93]. Moradi et al. taking advantage of the positive influence of HA on DDS, researched breast cancer therapy with He- and Ni-based drugs, and used NPs of NH₂-MIL-101(Fe) MOF that had been coated with HA to cover a platinum-CUR prodrug (Pt-CUR) (Figure 8A). The characteristics of HA-modified NPs were remarkable in their hydrodynamic size as well as their drug loading capacity and release in an acidic pH condition; the hydrodynamic size increased from 252 nm to 308 nm, the drug loading capacity was 30%-35%, and up to 80% of the drug could be released. In the cytotoxicity assays, the HA-coated system was found to be more potent in MDA-MB-231 cells than free Pt-CUR, leading to less toxicity in normal cells. This confirms the selectivity of the targeting through CD44 receptors. The

result indicates that HA-MOF-NPs composites represent a new and more effective method for targeted therapy in triple-negative breast cancer [112]. Together, these studies emphasize the growing importance of HA in enhancing the effectiveness and specificity of MOF-based DDS for cancer treatment. In the HA surface-modified DOX-loaded MIL-100 multifunctional NPs reported by Hu et al., DMTH NPs exhibited enhanced treatment efficacy against breast cancer via a synergistic approach of PAI-guided CDT, chemo, and photothermal therapies [99]. Inspired by the success of multifunctional NPs, Liu et al. introduced a novel approach for colorectal cancer treatment, utilizing HA-modified MIL-100(Fe) NPs loaded with OXA and indocyanine green. This dual approach combined chemotherapy with photothermal ablation, achieving remarkable antitumor effects (Figure 8B-F). The NPs exhibit high efficiency of drug loading, stability in the bloodstream, and targeted drug release in acidic tumor environments, all due to the enhanced permeability and retention (EPR) effect. In vivo results showed that there was a strong tumor inhibition effect mediated by Immunogenic cell death (ICD) induction and increased immune cell infiltration, sensitizing the tumors to the therapy with immune checkpoint blockade (aPD-L1). Significantly, the therapy elicited an increase in effector memory cells in the spleen to maintain long-lasting protection against relapse and metastasis of tumors. By using this methodology, imaging-guided interventions through PAI were accurately completed, and modulation of the tumor microenvironment was effectively finished [114].

With the latest improvements in MOF-based DDS, Ji et al. have come up with a new pH-responsive cancer treatment platform to be used for targeting cancer cells. The new system is a step further in the application of nanocarriers for the harness of anticancer agents, i.e., they will be more effective and at the same time, patients will suffer from fewer side effects. Having developed the drug delivery system based on the use of Calcium and hyaluronic acid, the researchers proceeded to name it HA@MOF-AS. The targeted drug delivery system promises accurate targeting of the tumor with the regulated drug release, as shown in the (Figure 8G-M). The high drug loading capacity along with good cellular uptake and high intracellular ROS production were the key features of the system. The in vivo experiments were done to determine the amounts of HA@MOF-AS in the tumor and to see the tumor growth suppression, which showed that this system has the potential for the use of Fe²⁺-dependent drugs to lessen the toxicity meanwhile increasing their efficacy. These results open up new possibilities for the development of cancer therapy in the future [88].

Poursadegh et al. developed a dual-targeted oral anticancer delivery system using mannose-functionalized HAP/MIL-88(Fe) (HM) incorporated into an HA hydrogel film (Figure 8N). The Mannose-HM (MHM) nanocomposite fabricated via Steglich esterification was drug-loaded with 5-Fu and surface-coated with HA to form the HA/5-Fu-MHM hydrogel film. It exhibited a pH-responsive drug release profile; more drugs were released under neutral conditions in the intestines than in acidic conditions. The in vitro cytotoxicity study against HT29 cancer cells demonstrated enhanced efficacy due to the synergistic dual-targeting effect of mannose and HA. Thus, HA/5-Fu-MHM hydrogel films are promising for oral cancer therapy by improving their bioavailability and reducing systemic side effects [115].

Guo et al. in a research paper, used HA-modified MOFs to target drug delivery through the conjugation of MTX with tannic acid and its coordination with ferric ions for increasing the drug delivery (Figure 8O).



(caption on next page)

Fig. 6. Schematic illustration, in vivo fluorescence imaging, and therapeutic evaluation of HA-functionalized MOF-based nanoplateforms for cancer targeting and treatment. (A) Schematic illustration of PAO@PCN@HA. (B) Fluorescence images of CT26 tumor-bearing mice at different time points post-injection and ex vivo tissue images at 24 h. (C) Mean fluorescence intensity of tissues after 24 h. (D) Tumor volume changes. (E) Body weight changes during treatment. (F) Mean tumor weight. (G) Representative tumor images. (H) H&E staining of tumor tissues after 17 days of treatment. Reproduced with permission from Ref. [167]. (I, J) Illustration for synthesizing Ce6/Cyt c@ZIF-8/HA NPs and their applications in cancer cell-targeted photodynamic and protein synergy therapy. (K) In vivo fluorescence imaging of a tumor-bearing mouse after intravenous injection of Ce6/Cyt c@ZIF-8/HA NPs. (L) Photographs of the major organs and tumor dissection. (M) Mean fluorescence intensity of the tumor and major organs (heart, liver, spleen, lung, and kidney) dissection. (N) Schematic illustration of the therapeutic study timeline. Reproduced with permission from Ref. [89].

The proposed system revealed an incredible drug-loading capacity, up to 45%, and a release profile that was very slow and thus long-lasting therapeutic effects. The combination of HA-modified MOFs in the delivery of MTX not only increased the anti-rheumatic activity but also decreased the toxicity in the system. The resulting dual-purpose strategy was a promising one for the treatment of cancer and the management of rheumatoid arthritis. Their results pointed out the multifaceted nature of HA-modified MOFs in drug bioavailability enhancement, controlled release, and therapeutic efficacy improvement over a wider range of diseases [92].

Incorporating this advancement, Li et al. introduced the design of intelligent nanoplateforms called PCN@MnO₂@DOX@HA (PMDH), which facilitate MR imaging guidance and enable O₂ self-sufficient chemo/photodynamic combination therapy (Figure 9A). The drug nanocarriers were constructed upon a porphyrinic MOF of PCN-224, employing a MnO₂ nanoshell coating for the loading of DOX, subsequently enhanced through functionalization with HA. The incorporation of HA promotes the localization of PMDH at tumor sites, thereby augmenting cellular uptake by CD44-overexpressing tumor cells and catalyzing the conversion of H₂O₂ into O₂, effectively alleviating tumor hypoxia. Furthermore, PMDH demonstrates favorable biocompatibility, minimal cardiotoxicity, and negligible systemic side effects. These findings further underscore the potential of HA-modified MOFs in targeted drug delivery and tumor microenvironment modulation, reinforcing their promise as a versatile strategy for synergistic tumor theragnostic application [169].

In order to tackle the issues of MOFs more thoroughly, like premature drug release and off-target effects, Zeng and colleagues proposed an injectable MOF-based hydrogel that was cross-linked by dynamic coordination bonds between the DOX-loaded MOF (MOF@DOX) and bisphosphonate-modified hyaluronic acid (HA-BP). The hydrogel was able to release the drug powerfully in response to pH or adenosine triphosphate (ATP), thereby killing the cancer cells in vitro and limiting the tumor growth in vivo to a larger extent than the case of using MOF@DOX alone (as shown in Figure 9B). Such a ground-breaking technique not merely confirms the use of HA-modified MOFs in drug delivery but also adds a new dimension to this application by overcoming the previously posed issues in the area of cancer therapy and further refining the treatment in terms of lowering the side effects on the whole body [113].

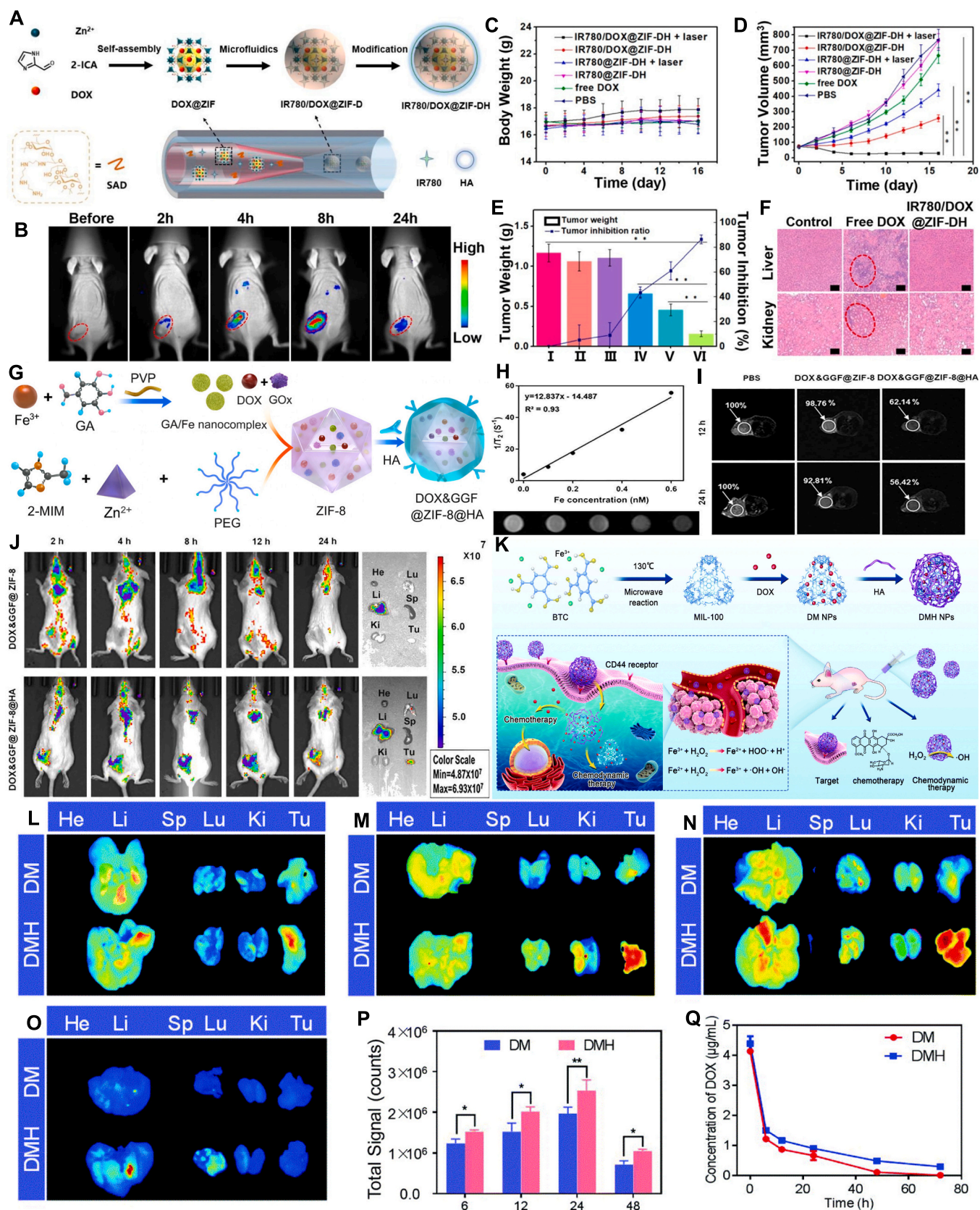
Advancing the development of DDS for cancer treatment, Zhou et al. encapsulated evodiamine (EVO) within ZIF-8 and modified the surface with HA, introducing EVO@ZIF-8/HA NPs. This modification not only enhanced the drug-loading efficiency but also facilitated the active targeting of CD44-overexpressing tumor cells, a feature also observed in earlier studies utilizing HA for tumor targeting. The HA modification promoted the internalization of the NPs into cancer cells, where the acidic environment triggered the release of EVO from the MOF matrix (Figure 9C-D). In both in vitro and in vivo experiments, these NPs demonstrated significantly better antitumor effects compared to free EVO, emphasizing their potential as an effective DDS for cancer treatment. Furthermore, HA serves as an excellent ligand for targeting and diagnosing cancer cells due to its strong affinity for CD44 receptors, thus enhancing the specificity of cancer therapies and opening new possibilities for diagnostic applications in targeting DDS [170].

2.3. Aptamers

Researchers have leveraged the advantages, such as enhanced target specificity and controlled drug release, to integrate aptamers with MOFs, aiming to develop highly selective and efficient DDS [171]. By leveraging the strong binding affinity of aptamers toward specific biomarkers, these hybrid nanosystems enable precise targeting of diseased cells while minimizing off-target effects [172,173]. Notably, aptamer-functionalized MOFs have demonstrated great potential in overcoming multidrug resistance, enhancing cellular uptake, and improving the stability of therapeutic agents [174]. Given these remarkable attributes, several studies have focused on optimizing aptamer-MOF conjugates for cancer therapy, utilizing different aptamer sequences to recognize and bind to overexpressed receptors on malignant cells selectively. In the following, we will delve into these studies and explore the various approaches and findings in this area. To illustrate the potential of aptamer-functionalized MOFs in targeted drug delivery, Chen et al. explored the application of nucleic acid-functionalized MOFs for cancer therapy. Their study demonstrated that ATP aptamer- and ATP-AS1411 aptamer-coated NMOFs effectively enhanced the selective delivery of DOX to MDA-MB-231 cancer cells, significantly increasing cytotoxicity while sparing normal cells [118]. Moreover, VEGF aptamer-modified NMOFs exhibited even higher apoptosis rates in cancer cells, reinforcing the role of aptamers in improving the specificity of MOF-based drug carriers. These findings not only highlight the potential of aptamer-functionalized MOFs in cancer therapy but also suggest broader applications in diseases characterized by VEGF overexpression, such as rheumatoid arthritis and bronchial asthma. This further establishes aptamers as highly promising ligands for the targeted recognition and treatment of malignant cells [120].

In order to make the most of the various applications of aptamer-functionalized MOFs in cancer treatment, Fang et al. made a multifunctional DDS called DOX/Au-Apt@ZIF-8 that combines chemotherapy, targeted therapy and photothermal treatment. The application of the AS1411 aptamer-modified gold nanorods for selective tumor targeting was the main feature of the platform, while ZIF-8 encapsulation contributed to the release of the drug in a pH-dependent manner (Figure 10A-E). The system was able to achieve a significant tumor growth inhibition effect through apoptosis and cell cycle arrest at the S phase, all due to the photothermal conversion efficiency of 53.5%. Both the in vitro and in vivo trials showed that there were increased therapeutic effects with almost no harm done to the surrounding healthy tissues. Such innovations bring the MOFs with aptamer grafts closer to being the most efficient and accurate cancer treatment methods in the future [175].

Researchers have also explored DNzyme/substrate complex-capped NMOFs as intelligent DDS, utilizing pH-responsive and metal-ion-dependent mechanisms for controlled drug release [117]. In one approach, Su et al. incorporated the AS1411 aptamer to selectively target nucleolin, a key biomarker in cancer cells, thereby enhancing specificity. Among the developed systems, UiO-66@AgNCs@Apt@DOX exhibited an impressive DOX loading efficiency of 98.0% and demonstrated effective drug delivery to cancer cells while minimizing cytotoxicity to normal MCF-7 cells across a broad concentration range (Figure 10F). The dual therapeutic action of DOX and AS1411 further amplified the anticancer effects, emphasizing the potential of aptamer-functionalized NMOFs as highly adaptable platforms for both targeted



(caption on next page)

Fig. 7. Schematic illustration, in vivo imaging, and therapeutic assessment of multifunctional ZIF-8-based nanoplateforms for targeted cancer therapy. **(A)** Schematic of IR780/DOX@ZIF-DH synthesis. **(B)** Fluorescence imaging of a mouse before and at different time points post-injection, highlighting the tumor site. **(C)** Average body weight changes across treatment groups. **(D)** Tumor volume measurements over time. **(E)** Comparison of excised tumor weights and inhibition ratios among different treatments. **(F)** H&E staining of liver and kidney tissues showing toxicity effects. Reproduced with permission from Ref. [168]. **(G)** Schematic representation of DOX&GGF@ZIF-8@HA NP synthesis via encapsulation of GA/Fe nanocomplexes, GOx, and DOX into ZIF-8 NPs using PEG as a mineralizer. **(H)** T₂-weighted MRI signal changes of DOX&GGF@ZIF-8@HA NPs at varying Fe concentrations. **(I)** T₂-weighted MR images of tumor-bearing mice injected with PBS, DOX&GGF@ZIF-8, and DOX&GGF@ZIF-8@HA NPs at different time points. **(J)** Biodistribution study of DOX&GGF@ZIF-8 and DOX&GGF@ZIF-8@HA NPs post-intravenous injection, including ex vivo imaging of major organs and tumors after 24 h. Reproduced with permission from Ref. [97]. **(K)** Schematic illustration of DMH NP preparation and application. **(L–O)** Biodistribution of DMH NPs in major organs and tumors at 6, 12, 24, and 48 h post-injection. **(P)** Quantified DOX fluorescence intensity in tumor regions using ROI analysis. **(Q)** DOX plasma concentration versus time curves of DM and DMH. Reproduced with permission from Ref. [91].

drug delivery and cancer diagnostics [116].

One of the main breakthroughs in cancer treatment is the use of multifunctional nanoplateforms to combine different treatment methods, which results in maximizing the efficaciousness of the cancer treatment and minimizing the side effects. The MOF@OXA-APT nanoplateform is such a case, which unifies the three main cancer therapy types, PDT, chemotherapy and immunotherapy, in a very effective way. The system is made of a porphyrinic Zr₆ MOF core (PCN-224) that is loaded with OXA and then attached with PD-L1 aptamers (aptPD-L1). This system is founded to activate all the therapeutic pathways through light irradiation (**Figure 10G–K**). MOF@OXA-APT performs PDT, supports ICD through chemotherapy, and boosts immunotherapy by blocking PD-L1 signaling. The PD-L1 inhibitor ensures the exact targeting of the tumor, and at the same time, the core of the nanomaterial acts as a photosensitizer that produces singlet oxygen (¹O₂) to awaken the immune system. In mouse studies, the tumor-death effect of MOF@OXA-APT was a lot more potent, but the systemic immunotoxicity was significantly less compared to conventional PD-L1 monoclonal antibody therapies. This method indicates the affirmation of new concepts like the use of aptamer-functionalized MOFs for the enhancement of the precision-targeted cancer immunotherapy, one that has better immune response with fewer side effects. Furthermore, the aptamer's selectivity towards the tumor cells not only makes it a great candidate for use in the diagnosis and treatment of cancers through targeted therapies but also moves it further as a powerful ligand in this area of research [176].

The aptamer-functionalized MOFs are capable of doing various things on account of their characteristics such as high drug-loading, targeting, and biocompatibility and thus, they are being used widely in cancer therapy. Dong et al. used poly(ethylene glycol) methacrylate (PEGMA) as an agent for improving biocompatibility, coating-granules of graphene as their photothermal and fluorescence properties- the graphene quantum dots (GQDs)- and gamma-cyclodextrin (γ-CD) as a solubility and bioavailability enhancers through a drug carrier to improve solubility and bioavailability. They put together these components and produced a multifunctional aptamer-functionalized MOF system including AS1411@PEGMA@GQDs@γ-CD-MOF that managed to realize a remarkable DOX loading efficiency of 89.1%. The nanoplateform was characterized by to a large extent photothermal conversion, to a high degree SERS performance, and to a great extent biocompatibility. Besides, it acted as a tumor-targeting probe that greatly reduced tumor growth in vivo by drug build-up at the tumor site with little to no systemic side effects. The study highlights the possibility of such nanoplateforms being used for combined cancer diagnosis and therapy [128]. Another encouraging case is the hybrid nanocarrier of Fe₃O₄@MOF-DOX-CDs-Apt that was made by Alijani et al. and it was able to demonstrate selective killing of MDA-MB-231 cancer cells with more than 77% apoptosis in 24 hours while normal human umbilical vein endothelial cells experienced less than 10% apoptosis. The system showed extraordinary stability in the presence of serum for a period of six days, which made it possible to deliver the drug to the cancer site without significantly harming the surrounding healthy tissues. Its high DOX loading efficiency coupled with pH-sensitive drug release is another reason for its great potential for targeted cancer therapy (**Figure 11A**). Together, these results convince us of the capability of the aptamer-functionalized MOFs to be the best drug delivery systems in

cancer treatment that not only improve therapeutic efficacy but also minimize off-target effects [122].

Liu et al. developed an innovative multifunctional nano DDS, Apt/(siRNA + GEF)@ZIF-8, to overcome drug resistance in non-small cell lung cancer (NSCLC). This system integrates an EGFR aptamer for targeted co-delivery of gefitinib (GEF), an EGFR tyrosine kinase inhibitor, and EGFR siRNA to silence the drug-resistant EGFR gene. ZIF-8 acts as a high-capacity delivery vehicle for both GEF and siRNA, releasing them in response to the acidic conditions of the tumor microenvironment. The combined action of GEF and siRNA results in enhanced inhibition of both the EGFR and MEK/ERK signaling pathways, inducing apoptosis in tumor cells and overcoming drug resistance. In vitro studies demonstrated that the dual approach of GEF and siRNA significantly improved the therapeutic effects on drug-resistant cancer cells. In vivo experiments showed a tumor inhibition rate of 40.6% after administering Apt/(siRNA + GEF)@ZIF-8, along with efficient tumor targeting, excellent biocompatibility, high drug delivery efficiency, and low toxicity (**Figure 11B–H**). This nano complex holds great promise for the treatment of drug-resistant NSCLC by integrating chemotherapy with gene therapy, providing a new approach to overcome resistance to tyrosine kinase inhibitors [177].

Furthermore, Zhang et al. investigated using UiO-66 MOF NPs (NMOFs) functionalized with DNA tetrahedrons and aptamers to enhance cancer therapy. These tetrahedral NMOFs, loaded with DOX, exhibited increased cytotoxicity and selectivity toward cancerous cells due to effective targeting facilitated by the specific aptamers. The unique tetrahedral structure of the NMOFs improved penetration and localization of the PDT agents, resulting in selective cytotoxicity toward cancer cells (**Figure 11I–J**). The aptamers not only enhance targeting specificity but also contribute to the development of self-sustaining nanostructures that show promise in treating a variety of diseases. This study underscores the potential of integrating aptamer-functionalized NMOFs with DNA nanostructures for more effective and targeted cancer treatment [123].

Falsafi et al. introduced an innovative strategy for cancer treatment using NMOFs that combine multiple therapeutic capabilities. In this study, a Cu-based MOF with a Cu(II) core was designed for PDT. This MOF was initially loaded with the chemotherapy drug DOX and then coated with red blood cell (RBC) membranes to enhance circulation time and reduce clearance from the body. However, this was just the beginning; to further improve targeting, specific aptamers that recognize MUC1, a tumor marker, were attached to the RBC-coated DOX-loaded MOF. This resulted in improved drug delivery and cytotoxicity against breast cancer cells (4T1 and MCF7) in vitro. In vivo, a single intravenous dose of Apt-RBC-MOF@DOX reduced tumor growth by 56%. This study not only showcased the potential of MOF-based systems for targeted cancer therapy but also highlighted the importance of combining various therapeutic modalities, including chemotherapy and PDT, to enhance the treatment's effectiveness [124]. Additionally, in another study Yang et al. explored the use of ATP-responsive transition MOFs, which were co-loaded with cytochrome c, DOX, and Zn²⁺ for targeted combination therapy against cervical cancer (**Figure 11K–L**). These MOFs were specifically designed to respond to ATP levels, making them ideal for targeted delivery using aptamers for precise recognition of tumor cells. The combination of these systems suggests that integrating

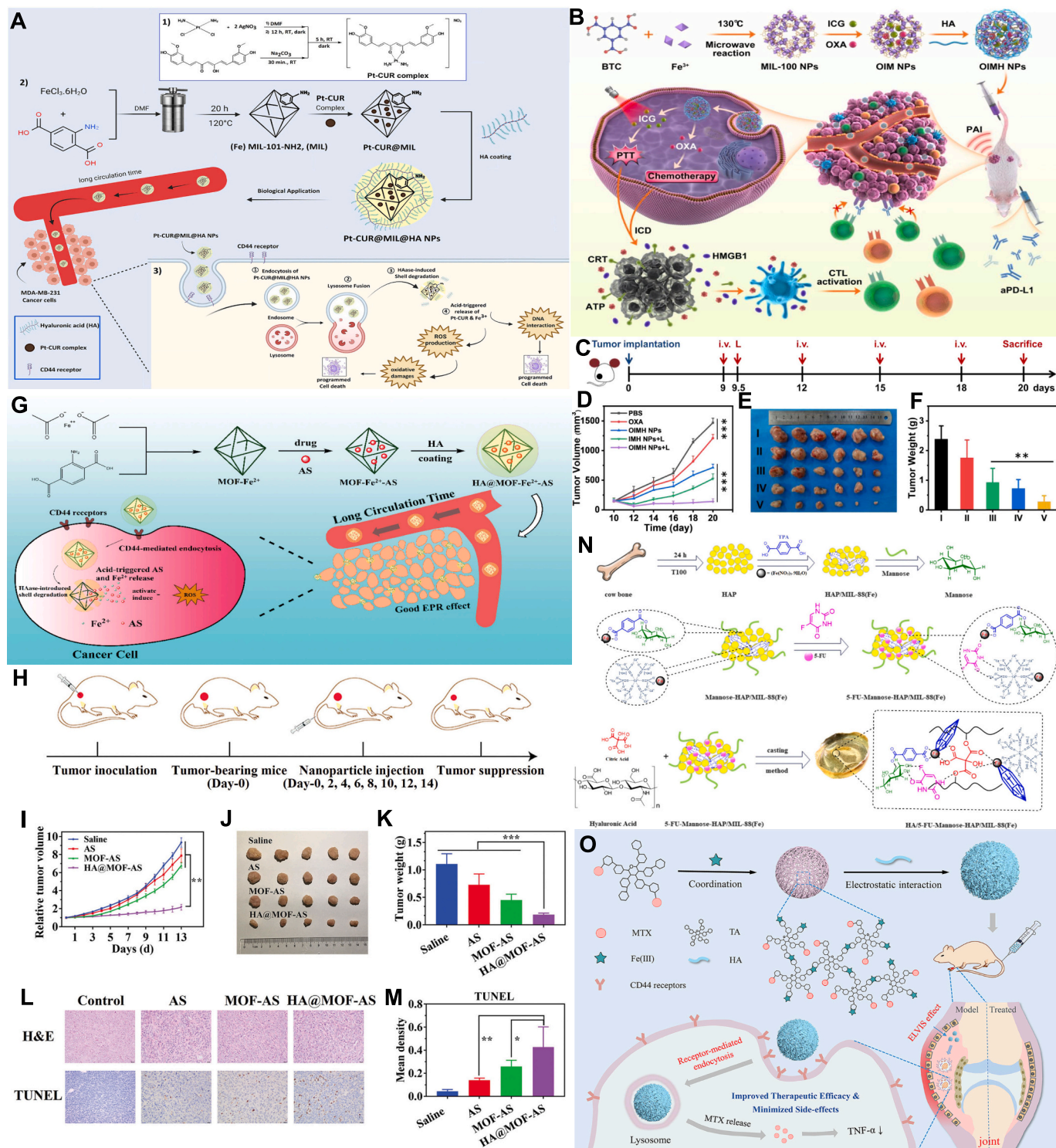


Fig. 8. Schematic design, synthesis, and in vivo evaluation of HA-functionalized MOF-based nanoplateforms for targeted drug delivery and therapeutic applications. (A) General steps of the study: (1) chemical synthesis of the Pt-CUR complex, (2) synthesis of MIL, Pt-CUR loading, and HA coating to obtain Pt-CUR@MIL@HA NPs, and (3) predicted biological pathway within cancer cells. Reproduced with permission from Ref. [112]. (B) Schematic illustration of OIMH NP-mediated PAI-guided chemo-photothermal therapy. (C) Therapeutic schedule for in vivo antitumor treatment. (D) Tumor volume changes across treatment groups. (E) Representative tumor images after different treatments. (F) Tumor weights of treated mice. Reproduced with permission from Ref. [114]. (G) Schematic representation of the synthesis, drug delivery process, and enhanced cancer treatment mechanism of HA@MOF-Fe²⁺-AS (HA@MOF-AS) NPs. (H) Experimental design scheme. (I) Relative tumor volume curves for different treatments (n = 5). (J) Tumor photographs from each group. (K) Tumor weight after 14 days of treatment (n = 5). (L) H&E and TUNEL staining images of tumor tissues (scale bar: 100 μm). (M) Quantification of the integrated optical density (IOD) of tumor sections from each group using TUNEL staining. Reproduced with permission from Ref. [88]. (N) Schematic illustration of the synthesis of HA/5-Fu-MHM hydrogel film. Reproduced with permission from Ref. [115]. (O) Schematic of MTX-TA/Fe³⁺-HA construction for targeted RA treatment, showing passive accumulation via the ELVIS effect and CD44 receptor-mediated endocytosis for MTX delivery. Reproduced with permission from Ref. [92].

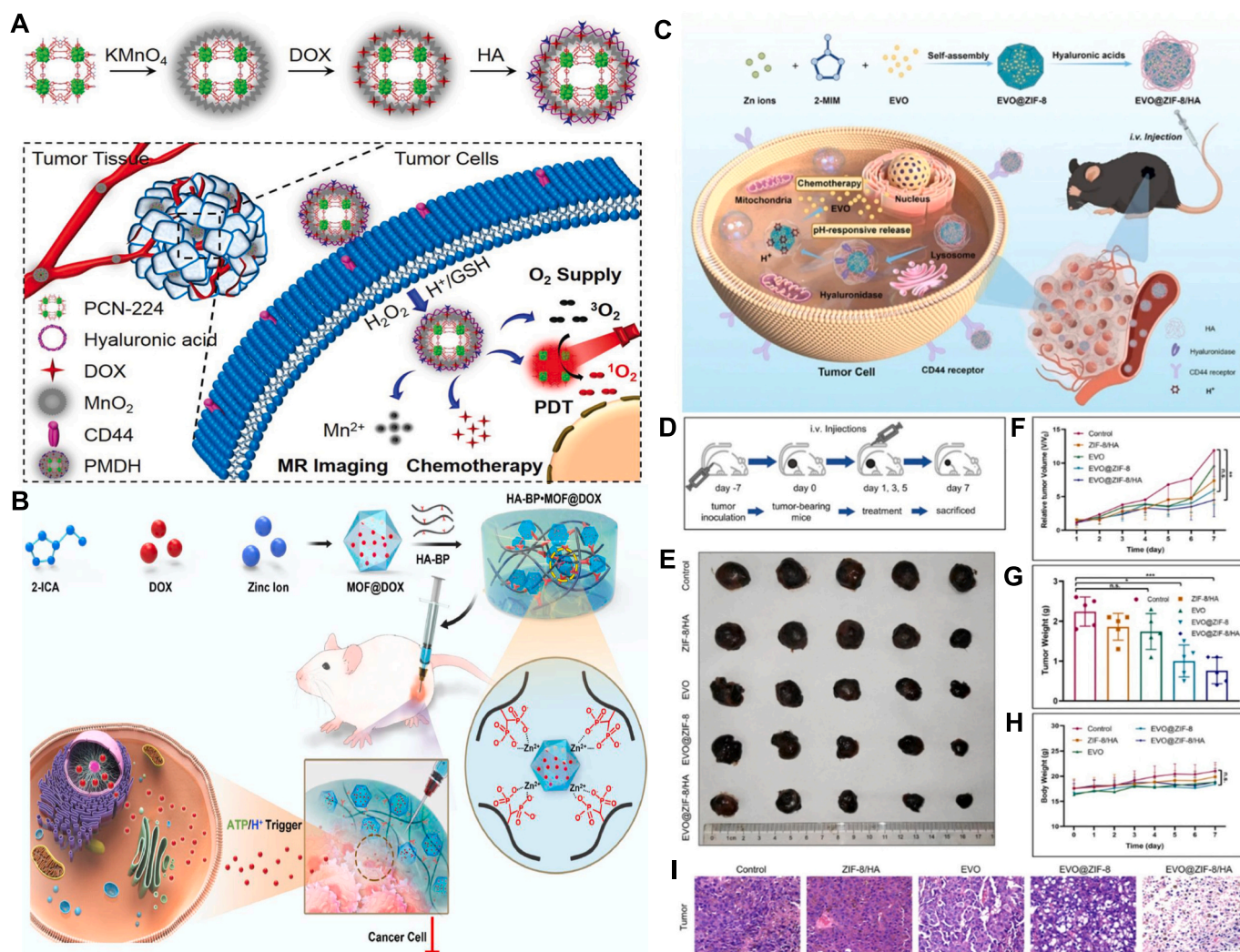


Fig. 9. Schematic illustration, synthesis process, and in vivo evaluation of multifunctional HA-modified MOF nanoplateforms for chemo/photodynamic cancer therapy. **(A)** Preparation process and proposed mechanism of the intelligent nanoplateform PCN@MnO₂@DOX@HA (PMDH) for MR imaging-guided chemo/photodynamic combination therapy. Reproduced with permission from Ref. [169]. **(B)** Schematic of the design and preparation of structurally dynamic HA-BP-MOF@DOX hydrogel as an injectable localized DDS for cancer treatment. Reproduced with permission from Ref. [113]. **(C)** Schematic illustration of EVO@ZIF-8/HA design for in vivo antitumor therapy. **(D)** Tumor-bearing mouse model and schematic diagram of the antitumor treatment. **(E)** Photographs of tumors from each treatment group. **(F)** Relative tumor growth curves of mice in different groups. **(G)** Tumor mass comparison among groups. **(H)** Body weight changes of B16-F10 tumor-bearing mice under various treatments. **(I)** H&E staining images of tumor tissues from different groups. Scale bars for all images: 50 μ m (n = 5). (Ns means no statistical significance, * is $p < 0.05$, ** is $p < 0.01$, *** is $p < 0.001$). Reproduced with permission from Ref. [170].

multiple treatment strategies—such as targeted drug delivery, PDT, and gene therapy could be a promising approach for improving cancer treatment outcomes and minimizing side effects [125].

In another study, significant progress was made in developing a microfluidic strategy for rapidly synthesizing aptamer-functionalized BioZIF-8 MOFs, aiming to enhance targeted drug delivery capabilities. The integrated microfluidic chip facilitates the one-step formation of ZIF-8 MOFs, which encapsulate various biomolecules such as BSA, small interfering RNA (siRNA), and DOX. These MOFs can then be post-functionalized with surface aptamers specifically targeting lymph nodes and tumors. This approach offers an efficient and versatile platform for precise drug delivery, significantly reducing synthesis time (~3 mg/10 min vs. 15 h of conventional techniques) and improving the encapsulation efficiency of biomolecules, with potential applications in cancer therapy and other disease treatments requiring targeted molecular interventions. The two-step procedure first encapsulates biomolecules, and then a secondary step functionalizes the surface with aptamers, e.g., anti-CCL21 DNA aptamers for targeting lymph nodes or A10 RNA aptamers for targeting PCa cells. The resulting BioZIF-8 MOFs

exhibit high targeting efficiency toward specific organs, such as lymph nodes and tumors, along with negligible toxicity. In the in vivo studies, aptamer-functionalized BSA@ZIF-8 MOFs were tested for their targeting efficiency toward lymph nodes and tumors in a mouse model (Figure 12A-F). FITC-labeled BSA was used for tracking the accumulation of the MOFs. Thus, the anti-CCL21 DNA aptamer-modified BSA@ZIF-8 MOFs could show significant accumulation in lymph nodes, evidenced by the increased fluorescence intensity in the excised inguinal and axillary lymph nodes. What's more, the zinc concentration in the lymph nodes was much higher for the anti-CCL21 DNA aptamer-BSA@ZIF-8 MOFs than that of the control. They concluded that the subcutaneous immunization route provided better efficiency of targeting than the footpad method, owing to factors including minimal reflux and reduced local inflammation, with the ability to spread materials in a larger area. This paper shows the prospects of microfluidic technology for preparing functionalized BioZIF-8 MOFs for efficient and target-specific delivery of biomolecules into disease treatment [178].

Building on these advances, Zhang et al. developed stimuli-responsive hybrid NPs based on drug-loaded UiO-66 NPs gated by pH-

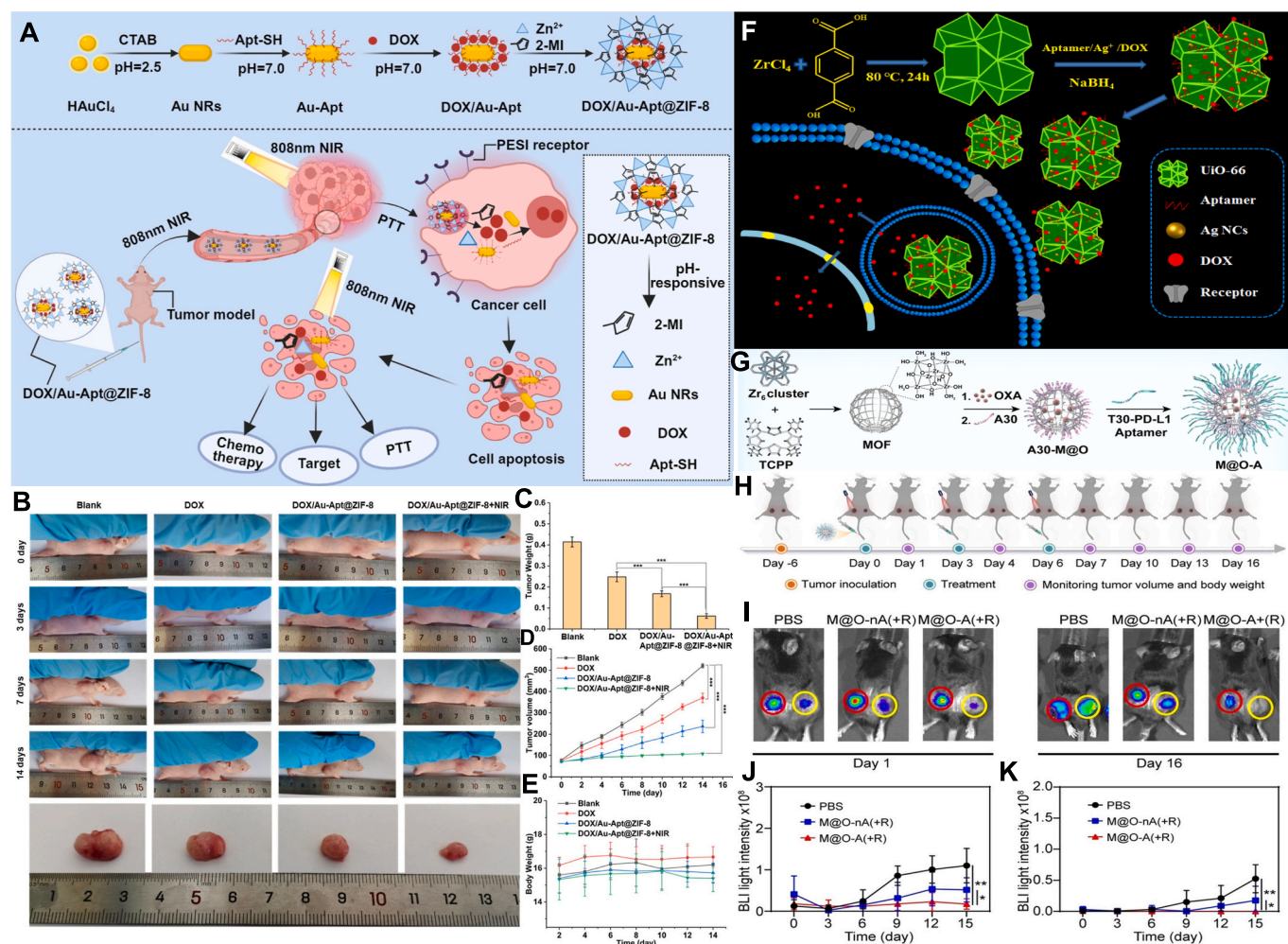


Fig. 10. Schematic design, synthesis, and in vivo therapeutic evaluation of multifunctional MOF-based nanoplateforms for targeted and photothermal-enhanced cancer therapy. (A) Schematic representation of the synthesis of DOX/Au-Apt@ZIF-8 NPs and their injection into mouse breast cancer models. (B) In vivo images showing the effects of DOX, DOX/Au-Apt@ZIF-8, and DOX/Au-Apt@ZIF-8 + NIR treatments on nude mice with breast cancer and the corresponding tumor diameter changes. (C) Relative tumor mass comparisons. (D) Tumor volume variations during treatment. (E) Body weight changes of mice across different groups. Reproduced with permission from Ref. [175]. (F) Schematic of a targeted antitumor DDS based on UiO-66 embedded with bioactive Ag nanoclusters (Ag NCs) using the AS1411 aptamer as a template (denoted as UiO-66@AgNCs@Apt@DOX). Reproduced with permission from Ref. [116]. (G) Schematic illustration of the design and synthesis of M@O-A NPs and their in vivo antitumor activity against bilateral tumors. (H) Schematic representation of the bilateral tumor therapeutic experiment ($n = 5$). (I) Bioluminescence imaging (BLI) of primary (red circle) and distant (yellow circle) tumor growth. (J, K) Mean light intensities of primary and distant tumors under different treatments. Reproduced with permission from Ref. [176].

or miRNA-responsive DNA tetrahedra. These NPs can also respond to specific stimuli by releasing drugs or dyes, enabling effective cell permeation and selective cytotoxicity against cancer cells [126]. In another study, Chen et al. designed a hybrid system, DOX/CuS@MOF-199/Apt-M, to improve Photothermal Therapy – Chemotherapy (PTT-CT) combined therapy. This approach aims to overcome the challenges associated with tumor complexity by integrating PTT with chemotherapy, with the added benefit of aptamer-mediated targeting for enhanced precision in drug delivery. The proposed platform, which is constructed via sulfating at the nanoscale of MOF-199 and aptamer MUC1 conjugation, exhibits a high DOX-loading capacity. CuS NPs give the platform the ability to absorb light energy and transfer it to thermal energy, increasing the efficiency of PTT under the irradiation of an NIR laser. In vivo, experiments showed the effectiveness of this platform in targeting neoplastic cells and, therefore, bringing about drug release in the acidic environment of the tumors, which resulted in better antitumor activity compared to monotherapy (Figure 12G–J). The combination of photothermal and chitosan resulted in the effective ablation of tumors with reduced systemic toxicity. Cytotoxicity analyses and tumor growth inhibition were significantly higher with this nanoplateform, indicating

great potential for multimodal cancer therapy with reduced adverse effects [129].

Recent trends in research show that earlier advancements, such as the work by Zhao et al., led to the creation of a DNA-functionalized porphyrinic (POR) MOF, designed to enhance the synergistic effects of PDT. The system utilizes a DNA layer attached to the POR MOF surface, achieved through strong coordination between the zirconium cluster of the MOF and the terminal phosphate group of the DNA, ensuring stable functionalization and efficient therapeutic performance. This modification enhances the loading capacity for the chemotherapy DOX drug, facilitated by the C/G-rich sequences in the DNA. The introduction of the AS1411 aptamer enables selective targeting of cancer cells by recognizing overexpressed nucleolin proteins. Upon reaching the acidic tumor environment, the C-rich DNA sequences form an i-motif structure, promoting rapid DOX release both from the DNA strands and the por-MOF pores. The combination of DOX delivery with PDT under 650 nm laser irradiation results in highly efficient cancer cell killing and tumor ablation, as demonstrated in both in vitro and in vivo tests (Figure 12K–N). The system exhibits excellent tumor suppression without significant side effects, highlighting its potential for effective and targeted cancer

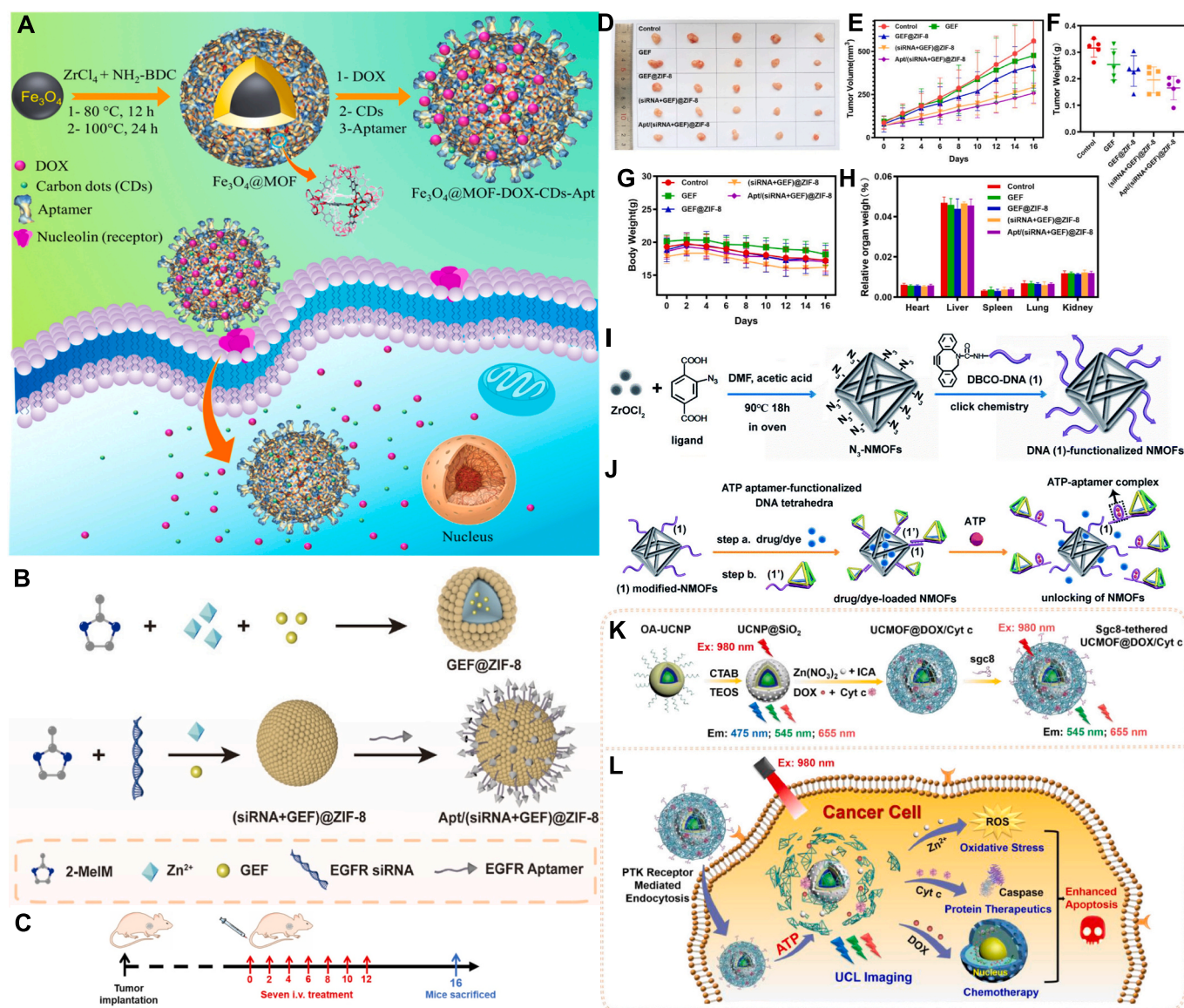


Fig. 11. Schematic illustration, synthesis, and in vivo evaluation of MOF-based nanocarriers for targeted and responsive drug delivery. (A) Schematic illustration of the synthetic procedure of the nanocarrier and its targeted drug delivery mechanism. Reproduced with permission from Ref. [122]. (B) Preparation process of MOF-based NPs. (C) Schematic illustration of the treatment process. (D) Photographs of dissected tumors following various treatments. (E) Tumor volume changes over the treatment period. (F) Mean tumor weights in each treatment group. (G) Body weight variations during therapy. (H) Relative organ weights of each group. Reproduced with permission from Ref. [177]. (I) Schematic synthesis of nucleic acid-tethered UiO-66 NMOFs. (J) Illustration of loading and gating of nucleic acid-modified UiO-66 NMOFs using ATP aptamer-functionalized DNA tetrahedra gates; ATP binding triggers gate unlocking and drug release. Reproduced with permission from Ref. [123]. (K, L) Schematics of ATP-responsive up conversion MOFs (UCMOFs) enabling in situ imaging and targeted combinational cancer therapy. Reproduced with permission from Ref. [125].

treatment [130].

2.4. Mannose

Mannose is one of the ligands that show great promise in the development of targeted therapy, especially through the lectin receptors, mainly the mannose receptor (CD206), which is heavily expressed on professional antigen-presenting cells (APCs) like dendritic cells and macrophages. Because of this overexpression, mannose is seen as a potential to be the target for those therapeutic strategies that intend to manipulate the immune response in the case of either cancer or infectious diseases. The immune cells targeted by mannose can be the ones that the mannose-functionalized systems rely on for their specificity and consequently, the off-target effects can be minimized [179–181].

Among the most promising platforms for this purpose are

mannosylated MOFs, which have been engineered to interact with mannose receptors on APCs, facilitating targeted drug delivery and improving immune engagement [182,183]. Mannose-coated, mannose-conjugated, and mannose-derived MOFs represent a growing class of targeted DDSs. For example, Vargas-Berenguer et al. developed MIL-100 (Fe) coated with β -cyclodextrin derivatives containing mannose and rhodamine, showing improved drug release control compared to monomeric coatings, thus demonstrating the advantages of polymeric surface engineering in DDS design [184]. Similarly, Reineke et al. synthesized mannose-coated MIL-88A(Fe) and MIL-100(Fe) that mimicked pathogen-like structures and enhanced uptake via macropinocytosis and phagocytosis, key pathways for internalization by APCs [131]. Further expanding on this concept, Zr-based MOF-808 functionalized with poly (acrylic acid-mannose acrylamide) enabled dual drug delivery of floxuridine and carboplatin, significantly improving both drug loading

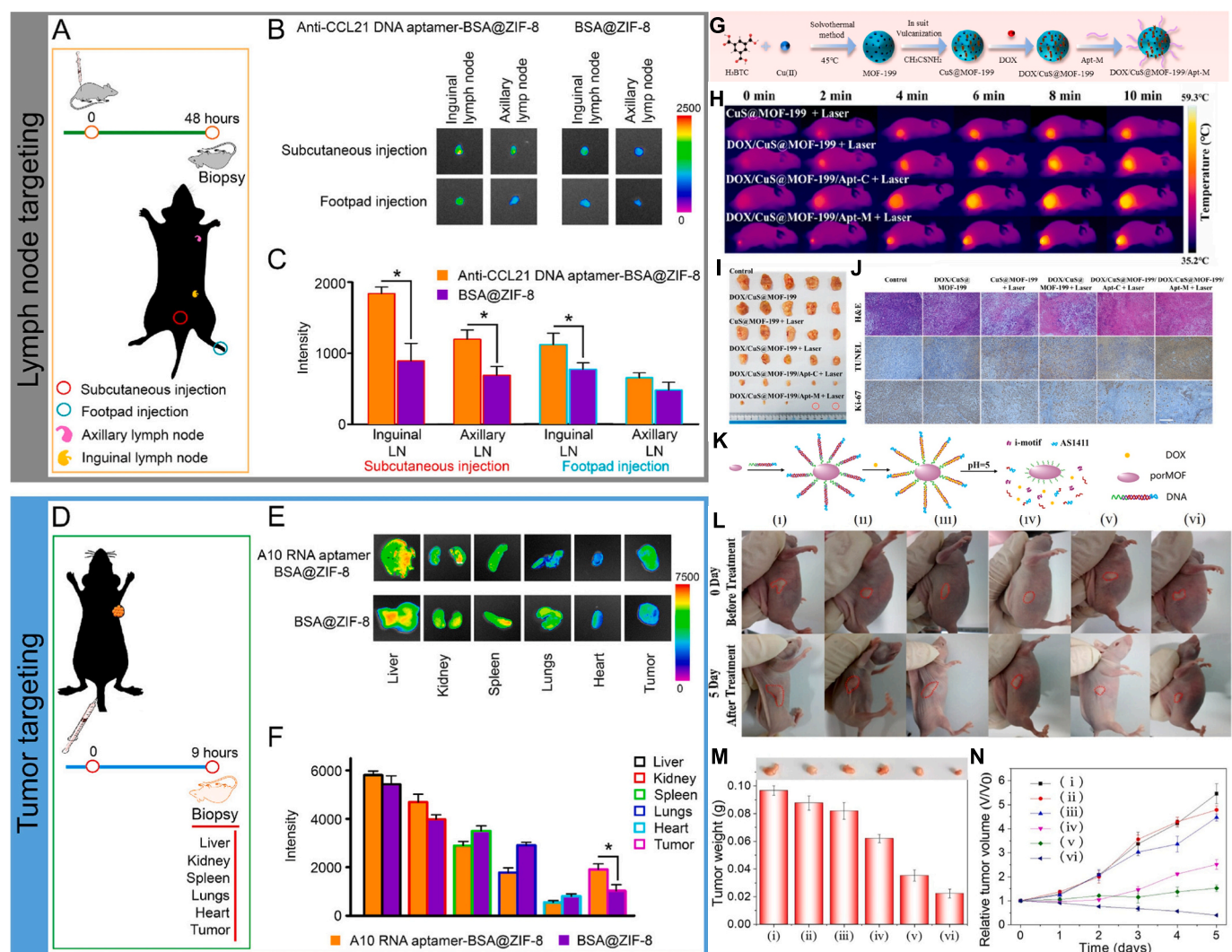


Fig. 12. Schematic illustrations and in vivo evaluations of aptamer-functionalized MOF-based nanoplateforms for targeted imaging and combinational cancer therapy. (A) Targeting efficiency of anti-CCL21 DNA aptamer-FITC-BSA@ZIF-8 in inguinal and axillary lymph nodes via subcutaneous and footpad administration routes. (B) Ex vivo fluorescence images of inguinal and axillary lymph nodes following MOF exposure. (C) Comparative fluorescence intensity showing enhanced accumulation with anti-CCL21 DNA aptamer-FITC-BSA@ZIF-8. (D) Illustration of targeting efficiency measurement of A10 RNA aptamer-BSA@ZIF-8 to tumors. (E) Ex vivo fluorescence images showing the biodistribution of A10 RNA aptamer-FITC-BSA@ZIF-8 in major organs and tumors after 9 h. (F) Fluorescence intensity of tumors in A10 RNA aptamer-FITC-BSA@ZIF-8-treated mice was significantly higher than in neat FITC-BSA@ZIF-8-treated mice. Reproduced with permission from Ref. [178]. (G) Schematic illustration of the synthetic route of DOX/CuS@MOF-199/Apt-M. (H) Photothermal imaging of in vivo PTT-CT combined tumor therapy. (I) Photographs of excised tumors post-treatment. (J) Histological evaluation of excised tumor tissues after different MOF treatments using H&E, TUNEL, and Ki-67 staining (scale bar: 300 μm). Reproduced with permission from Ref. [129]. (K) Schematic illustration of poor MOF@DNA-DOX nano system preparation and therapeutic application in HeLa tumor-bearing mice. (L) Photographs of mice before (0 days) and after (5 days) treatment with different modalities. (M) Tumor weights after 5 days of treatment, with the top image showing dissected tumors. (N) Tumor growth curves for each treatment group. Reproduced with permission from Ref. [130].

capacity and cytotoxicity, particularly in HepG2 liver cancer cells, while potentially reducing systemic side effects [133].

Building upon these developments, Jin et al. came up with a new mannose-modified MOF-based system M-FNM (Mannose-doped Fe₃O₄@NH₂-MIL-100) which was aimed at supporting tumor immunotherapy by the creation of pyroptosis, which is a pro-inflammatory type of programmed cell death. They made use of selective mannose receptor-mediated endocytosis to gain access into CAL27 cancer cells, which caused an increase in the generation of the intracellular ROS and consequently triggered endoplasmic reticulum (ER) stress. The stress-activated PERK-eIF2 α -ATF4-CHOP pathway, which in the end, resulted in pyroptosis through Caspase-1 activation and N-GSDMD formation. In animal tests, M-FNM was very effective and choked the tumor growth more than its unmodified form (FNM). The tumors in the BALB/c-nude mice with CAL27 were reduced by M-FNM to 355 mm³ after 12

days while the FNM group was still in the range of uncontrolled tumors. In the SCC-7 tumor model in C57BL/6J mice, M-FNM treatment caused a 441 mm³ reduction in tumor volume compared with controls, resulting in a final average of 242 mm³. Moreover, histopathological examination evidenced wide tumor necrosis, immunofluorescence staining further confirmed the increase in cleaved Caspase-1 expression (Figure 13A-F). Most importantly, M-FNM also improved T lymphocyte infiltration into the tumor microenvironment and showed excellent biocompatibility, as indicated by steady body weights. All in all, these observations point to the great potential of mannose-functionalized MOFs to be used as targeted DDSs for cancer immunotherapy, particularly through the use of pyroptosis mechanisms that alter the immune landscape and increase antitumor immunity [185].

Combinational therapies have long been used in cancer treatment, with research continually expanding to enhance their efficacy. The

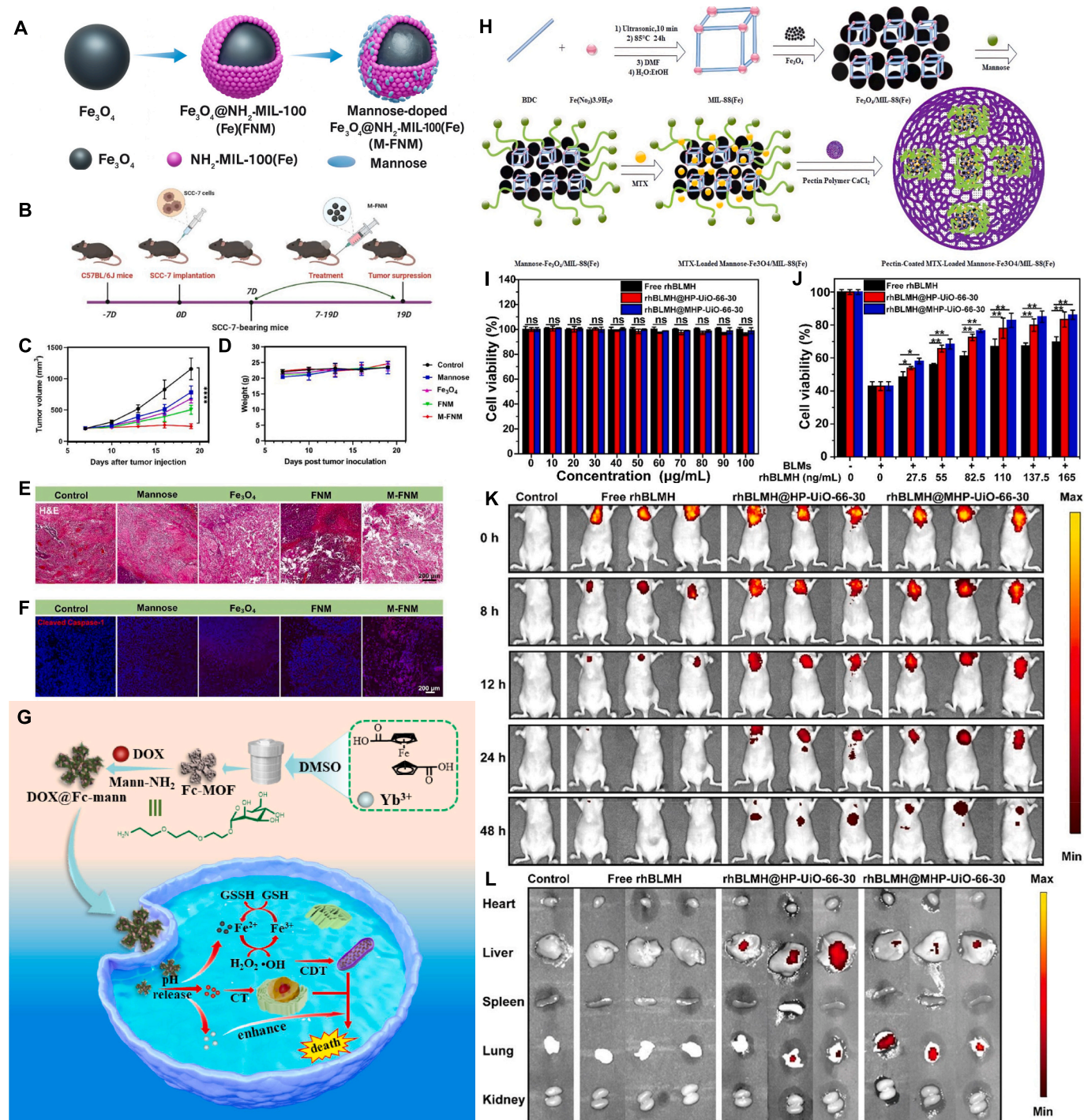


Fig. 13. Schematic illustrations, synthesis, and in vivo evaluations of mannose-functionalized MOF-based nanoplateforms for targeted drug delivery and tumor therapy. (A) Preparation and characterization of M-FNM and its antitumor activity against SCC-7 tumor xenografts in mice. (B) Treatment schedule for evaluating M-FNM in antitumor therapy. (C, D) Tumor volume and body-weight profiles of SCC-7-tumor-bearing mice subjected to different treatments (C57BL/6J, $n = 5$). Mice received PBS, mannose, Fe_3O_4 , FNM, or M-FNM injections (10 mg/kg). (E) Histological images of SCC-7 tumors after various treatments. (F) CLSM fluorescence images showing cleaved caspase-1 expression in tumors following treatment. Compared to control, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, and **** $P < 0.001$. Reproduced with permission from Ref. [185]. (G) Schematic illustration of the preparation of DOX@Fc-MOFs-Mann and their related biological applications. Reproduced with permission from Ref. [132]. (H) Schematic illustration of the synthesis of FM nanohybrids ($\text{Fe}_3\text{O}_4/\text{MIL-88(Fe)}$), mannose functionalization, MTX loading, and pectin coating. Reproduced with permission from Ref. [135]. (I, J) Biocompatibility and detoxification efficiency of free and encapsulated samples. (K) Near-infrared whole-body fluorescence imaging of mice after intratracheal instillation of free or encapsulated rhBLMH. (L) Ex vivo fluorescence images of organs from mice administered free rhBLMH, rhBLMH@HP-Uio-66-30, or rhBLMH@MHP-Uio-66-30 NPs. Reproduced with permission from Ref. [186].

integration of chemotherapy with chemoimmunotherapy has demonstrated promising results in improving treatment outcomes. MOFs have emerged as versatile drug-delivery vehicles in biomedicine due to their biocompatibility and ability to be functionalized with specific targeting ligands. In this context, biocompatible carbohydrates, such as mannose, serve as effective ligands for targeting overexpressed glycoprotein receptors on cancer cell membranes. For instance, pH-responsive ferrocene MOFs were synthesized by coordinating 1,1'-Ferrocenedicarboxylic acid with ytterbium chloride, resulting in the formation of DOX@Fc-MOFs-Mann NPs, which are designed to deliver the chemotherapy DOX drug specifically to cancer cells while taking advantage of the benefits of both CDT and chemotherapy (Figure 13G). These NPs are designed for targeting HepG2 cells via mannose receptors, degrading in the tumor's acidic environment and releasing ferrocene, DOX, and ytterbium ions. The Fe²⁺-activated ferrocene in NPs initiated Fenton reactions to produce ROS, which induced the apoptosis or necroptosis of cancer cells. In addition, Yb³⁺ also contributed to cytotoxicity and thus reached a synergistic effect of CDT and chemotherapy. This approach indicates the future of rare earth metals and mannose-modified MOFs for enhanced cancer therapy [132].

Building upon these findings, another approach involved modifying magnetic nanocomposite hydrogel beads, Fe₃O₄/MIL-88(Fe), with mannose and loading them with MTX (Figure 13H). These pH-sensitive pectin-coated beads effectively protected MTX and facilitated its controlled release within the intestine during digestion. Notably, this system exhibited approximately 20% enhanced anticancer efficacy against colon HT29 cells. This dual-functional approach further underscores the potential of mannose-functionalized nanostructures as promising vectors for targeted and efficient cancer therapy [135].

In light of these findings, Cutrone et al. highlighted the potential of mannose-functionalized MIL-100(Fe) NMOFs for cancer therapy, emphasizing their role in selectively targeting mannose receptors. At the same time, this functionalization reduced the likelihood of immune system recognition, enhancing the stability and effectiveness of the delivery system. A simple, organic solvent-free self-assembly method was used to functionalize the NMOFs with mannose, tetramethylene glycol (TEG), and polyethylene glycol (PEG) using phosphorylated β -cyclodextrins (PCDs) as coating agents. The mannose-coated NMOFs showed a significantly enhanced binding affinity toward mannose-specific receptors like Concanavalin A due to the multivalent presentation of mannose moieties. In vitro, such coatings reduced macrophage uptake, especially for TEG-modified NMOFs, which exhibited the highest "stealth" efficiency. The functionalization process could be successfully performed on DOX-loaded NMOFs without affecting the payload and improved properties related to biorecognition. These results underline the potential of mannose-coated NMOFs in targeted cancer therapy and clearly show the interest in further studying such systems toward optimization in biological media [187].

In order to open new avenues for the biomedical applications of mannose-modified MOFs, scientists made use of mannose-modified hierarchically porous UiO-66 (MHP-UiO-66) NPs to encapsulate recombinant human bleomycin hydrolase (rhBLMH). This method was aimed at pulmonary fibrosis (PF) therapy, a slowly progressive lung disease, which is characterized by excessive deposition of extracellular matrix and scarring, that is, the latter being caused by BLM as a side effect of chemotherapy, which is often the case with NPs. BLM's anticancer agents are extremely powerful; however, their application is restricted due to high levels of pulmonary toxicity. Encapsulating rhBLMH into MHP-UiO-66 not only disallowed the enzyme's extinction, but also allowed the enzyme's protection from proteolytic degradation, while at the same time. The results indicated that the combination of rhBLMH with MHP-UiO-66 NPs led to a great enhancement in the accumulation of the enzyme in pulmonary tissues, and, consequently, the decrease of BLM-induced pulmonary fibrosis without a decline in BLM's anti-tumor activity. In the mouse model, the rhBLMH encapsulated in MHP-UiO-66-30 NPs resulted in a reduction of PF in the treated BLM-based

chemotherapy mice, indicating the pulmonary protection along with therapeutic benefits. The NPs showed minimal cytotoxicity and excellent biodegradability, establishing their safety for use in biological systems. Further biodistribution studies using far-red fluorescent dye-labeled rhBLMH showed that the encapsulated rhBLMH persisted in the pulmonary tissues for as long as 48 hours, while free rhBLMH was cleared rapidly. Fluorescence of encapsulated rhBLMH in the liver did suggest a certain degree of mobilization of these NPs, although this was at lower levels than in previously published works. Notably, MHP-UiO-66-30 NPs showed improved retention in the lungs compared to other formulations, which may indicate that mannose-functionalized NPs could lead to longer therapeutic effects. These findings suggest that MHP-UiO-66 NPs are a promising modality for the pulmonary delivery of therapeutic proteins, such as rhBLMH, to counteract BLM-induced pulmonary toxicity related to chemotherapy (Figure 13I-L). On the other hand, this research also underlines the further investigation that needs to be performed on the biocompatibility of NPs and their optimization, in addition to practically applicable methods of their delivery to the lungs [186].

2.5. Anisamide

Expanding the scope of tumor-targeting ligands beyond mannose, anisamide a small-molecule ligand first proposed by Banerjee et al. [188] has gained attention for the functionalization of nanocarriers [189,190]. Anisamide selectively targets sigma receptors, which are overexpressed in a variety of cancer cell types, including those in lung, colon, prostate, and breast tumors, making it a valuable moiety for enhancing the precision and efficacy of DDS [191,192].

The rationale for anisamide-based targeting originated from earlier studies of radiolabeled iodobenzamides, which demonstrated strong tumor affinity and were evaluated as scintigraphic agents for non-invasive tumor imaging. Building on this foundation, recent research has incorporated anisamide into MOF-based systems for targeted cancer therapy. For example, Lin et al. developed nanoscale coordination polymers (NCPs) functionalized with anisamide for improved tumor targeting [137]. These anisamide-decorated MOFs were loaded with MTX, achieving a high drug loading of up to 79.1 wt%. The MTX-loaded NCPs were encapsulated within a functionalized lipid bilayer to improve biological stability and delivery efficiency. Additionally, a phosphorescent dye was included to enable optical imaging of cellular uptake. The anisamide-functionalized NCPs showed enhanced in vitro cytotoxicity against acute lymphoblastic leukemia cells compared to free MTX, demonstrating the potential of anisamide-mediated targeting for improving the delivery and efficacy of organic chemotherapeutics.

2.6. Glucose

One of the newer and more promising cancer-targeting methods to be researched is the use of glucose transport mechanisms, since glucose metabolism is so important to cancer development. Out of all the glucose transporters, GLUT1 is the one most commonly overexpressed in tumors of different kinds and is very much involved in the metabolic shift of cancer cells [173,193]. In the case of cancer, GLUT1 is not just the main transporter of glucose, but also one of the key elements in the progression of cancer because it leads to increased glucose utilization even under the less favourable conditions of normoxic lactate production [194].

To sustain this metabolic phenotype, tumor cells upregulate GLUT1 on their surfaces, enabling enhanced glucose uptake. This characteristic makes GLUT1 an attractive target for glucose-mediated DDS, where glucose-functionalized nanocarriers can exploit GLUT1 overexpression for selective uptake [195]. Moreover, aside from GLUTs, lectins that are carbohydrates-binding proteins expressed on the surface of some cancer cells may support the attachment and absorption of carbohydrate-based nanocarriers by increasing their binding, thus creating more options for

targeting. These changes in the metabolism of the tumor not only make it possible for the cancer cells to live longer and become more resistant to apoptosis but also make them able to migrate and thrive in different environments [139].

Researchers are actively developing carbohydrate-functionalized DDSs to disrupt the metabolic dependence of tumor cells and improve selective drug delivery. In a recent study, Fe-doped ZIF-8-based nanocarriers were engineered for improved chemotherapy targeting of triple-negative breast cancer (TNBC). These DDSs were modified with GA and loaded with 5-FU, while also incorporating GOx and gold NPs (Au) to enhance targeting efficiency and therapeutic effect (Figure 14A). Structural and morphological characterization confirmed the successful fabrication of these multifunctional nanocarriers [139].

Drug release studies performed in vitro showed a pH-responsive profile, with drug release being significantly higher under acidic conditions (pH 5.0) than at neutral (pH 7.4), which is in line with the tumor microenvironment's acidic characteristic. The formulation ZIF-8@GA@Fe@5-FU@GOx was the most effective among the different formulations tested and it induced apoptosis as well as morphological changes in MDA-MB-231 cells of triple-negative breast cancer type. Not only that, but it also surpassed its non-enzyme-containing equivalents in terms of cytotoxicity and apoptosis induction. In summary, the current research demonstrates the potential of glucose-targeted, enzyme-integrated MOF-based DDSs for upgraded precision therapy in aggressive tumors like TNBC [139].

Zhang et al. have demonstrated the use of glucose-modified MOFs as potential theranostic platforms for targeted chemotherapy. This study was conducted on glucose-coated MOFs for the delivery of DOX in

animal tumor models. The glucose coating resulted in better MOF solubility in the body fluids and also greatly increased their capacity to target tumors. This was made possible by the upregulation of glucose transporter proteins (GLUT1) on the surface of cancer cells which allowed the drug to be delivered selectively to the tumor site. This work opens up new avenues for glucose-functionalized MOFs in enhancing cancer therapy through targeted drug delivery. The data showed that the DOX@Gd-MOFs-Glu group had a very significant reduction in tumor growth compared to the control groups (Figure 14B-H). Furthermore, the neoplastic cell death in this group was about 85%, and no unacceptable damage to the main organs was seen which implies the high compatibility of the platform with the living body [138].

2.7. Galactose

Continuing the previous talk about different receptors, we are now directing our attention to the galactose receptor, an important factor in targeted drug delivery, mainly for liver cancer treatment. The galactose receptors, particularly the asialoglycoprotein receptor (ASGPR), are found in high amounts in liver cells and have been the subject of numerous studies regarding their role in making possible the selective delivery of drugs to cancer cells in liver cancer treatment. [196,197]. The ASGPR is abundant in hepatocytes and certain cancer cells, making it an attractive target for galactose-modified DDS. It has a strong binding affinity for galactose residues and facilitates the internalization of glycoproteins terminated with galactose [198].

In cancer therapy, this receptor-ligand interaction is exploited by attaching galactose components to nanocarriers, drugs, or imaging

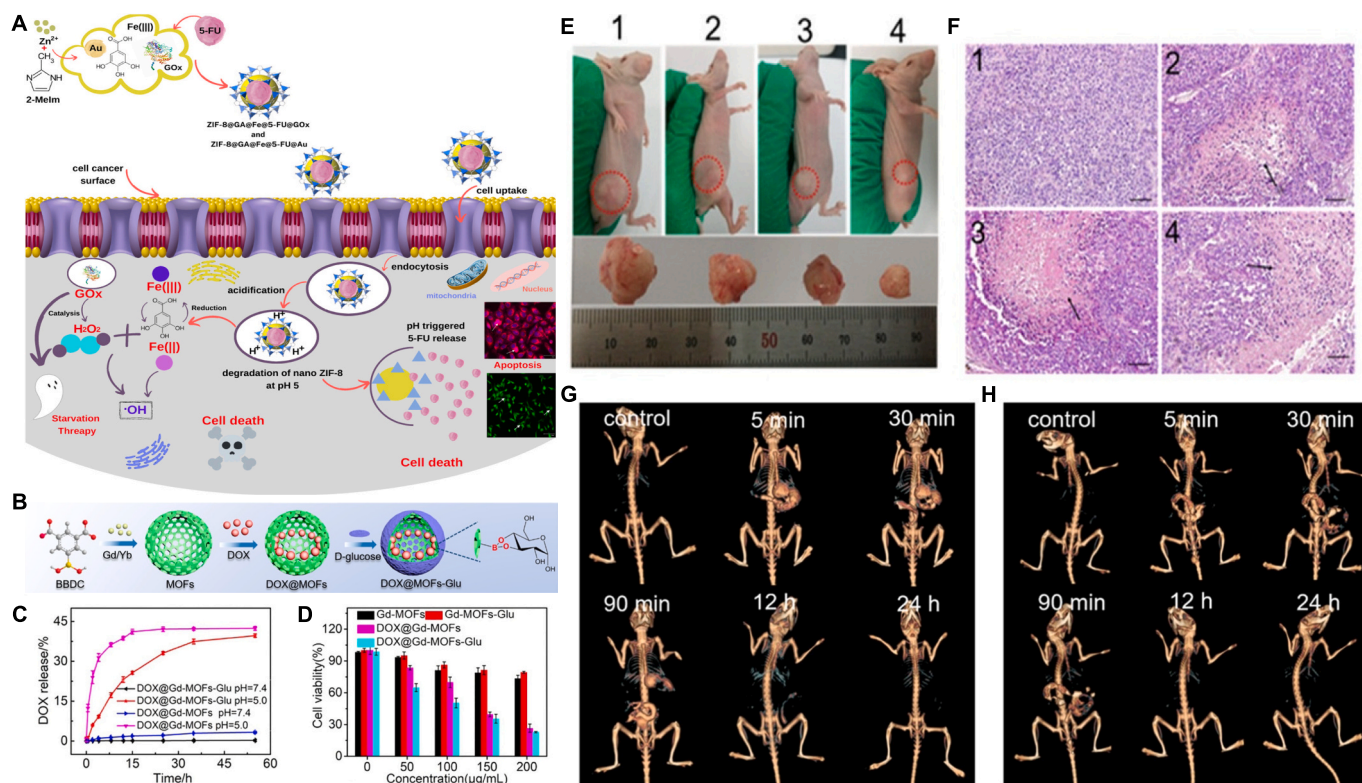


Fig. 14. Schematic illustration, synthesis, and in vivo evaluation of glucose- and metal-functionalized MOF nanoplatforms for pH-responsive and enzyme-assisted anticancer therapy. (A) Schematic depiction of ZIF-8@GA@Fe@5-FU@GOx and ZIF-8@GA@Fe@5-FU@Au synthesis, showing detailed intracellular processes and the proposed mechanism of anticancer activity. Reproduced with permission from Ref. [139]. (B) Schematic illustration of the synthesis of DOX@MOFs-glucose nanocarrier. (C) pH-responsive DOX release behavior at pH 5.0 and 7.4, demonstrating controlled drug release under acidic tumor microenvironments. (D) Cell viability analysis of various formulations at different concentrations, confirming cytotoxic efficacy. (E) Representative tumor photographs following treatment with different formulations. (F) Histological examination of tumor tissues from treated mice, indicating therapeutic outcomes. (G, H) In vivo chemotherapeutic imaging of the gastrointestinal tract before and after oral administration of Yb-MOFs-Glu, demonstrating biodistribution and targeting efficiency. Reproduced with permission from Ref. [138].

agents to improve their selectivity and cellular uptake in cancer cells overexpressing ASGPR [199]. Such interaction of galactose with ASGPR promotes targeted drug delivery and enables the construction of diagnostic devices and theranostic agents for both diagnosis and therapy of cancer [196,200]. However, it should be noted that although ASGPR is predominantly expressed in liver cells, several papers have also detected galactose receptors on many other types of tumor cells, further

expanding the scope for galactose-based targeting techniques in cancer treatment [200,201]. In recent studies, it has been demonstrated that MOFs can effectively conjugate with the galactose receptor, particularly the asialoglycoprotein receptor (ASGPR), to create highly targeted DDS.

Following the exploration of various receptor-targeted DDS, an innovative method was introduced by Wang et al. using the nitrile imine-mediated tetrazole-ene cycloaddition (NITEC) protocol, a photo-

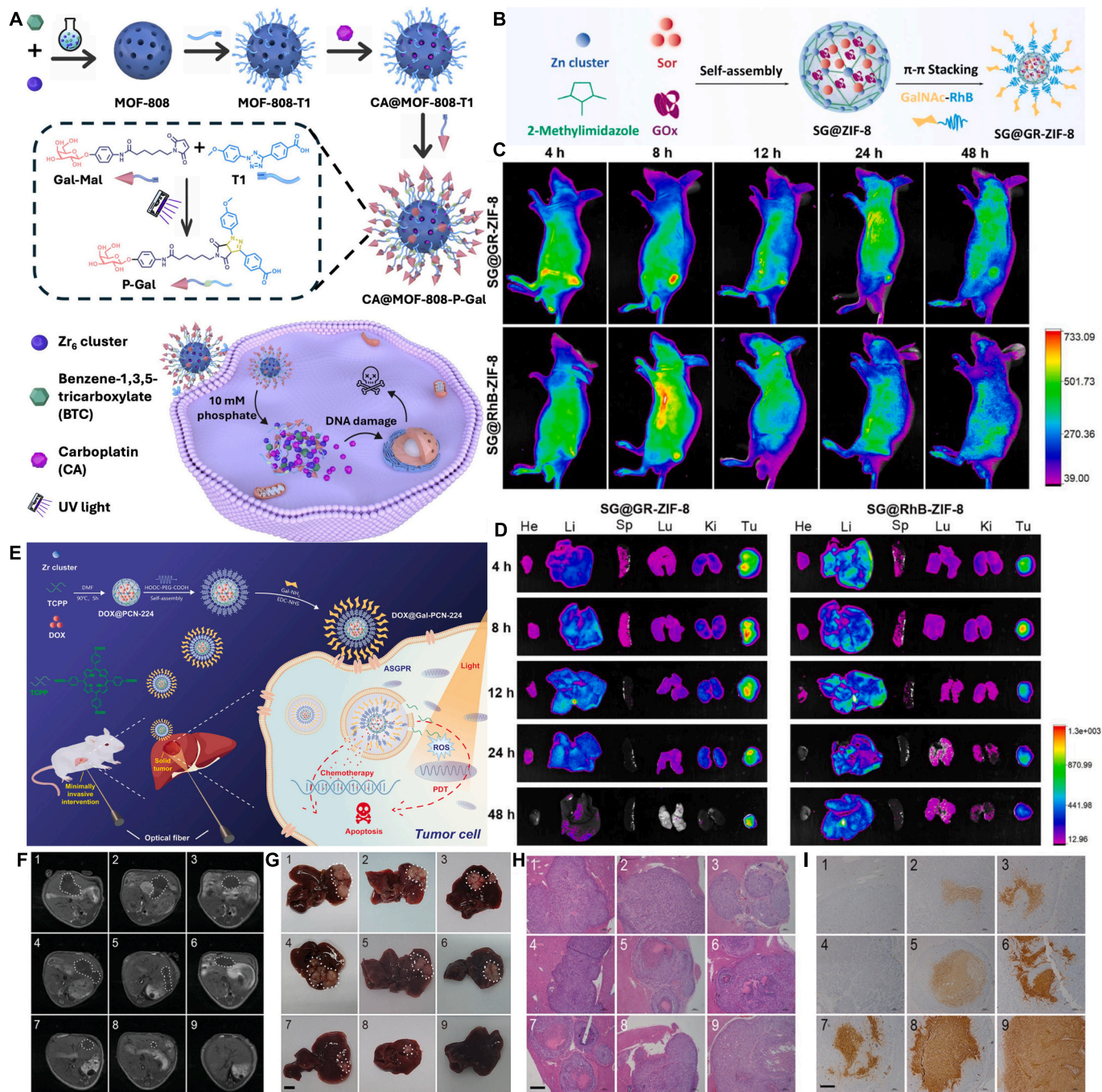


Fig. 15. Schematic illustrations, synthesis, and in vivo evaluation of galactose-functionalized MOF-based nanoplatforms for targeted and responsive cancer therapy. (A) Fabrication of CA@MOF-808-P-Gal and schematic representation of its phosphate-responsive drug release and galactose-mediated targeted chemotherapy via intracellular carboplatin release. Reproduced with permission from Ref. [202]. (B) Schematic illustration of the preparation of Glyco-MOFs SG@GR-ZIF-8 and their biodistribution in vivo. (C) In vivo fluorescence imaging of RhB at various time points after intravenous injection through the tail vein in the form of SG@GR-ZIF-8 and SG@RhB-ZIF-8. (D) Representative ex vivo fluorescence images of harvested organs (He: Heart; Li: Liver; Sp: Spleen; Lu: Lung; Ki: Kidney; Tu: Tumor) after different injection times. Reproduced with permission from Ref. [141]. (E) Schematic of the minimally invasive synergistic therapy and in vivo evaluation of DOX@Gal-PCN-224 for PDT/CT in an HCC-bearing mouse model. (F) T1-weighted MR images showing tumor sites across treatment groups. (G) Photographs of excised liver tissues from various groups, with tumor regions marked by white dotted circles. (H) H&E-stained tumor sections following treatment. (I) TUNEL-stained tumor sections highlighting apoptosis. Scale bars: 200 μ m (staining images) and 5 mm (photographs). Reproduced with permission from Ref. [140].

induced process for controllable surface modification of MOFs. This technique demonstrated great potential for developing materials capable of targeted drug delivery. Specifically, the NITEC photoclick reaction was utilized to functionalize MOF-808 with galactose residues, enabling targeted delivery to liver carcinoma cells (HepG2), which overexpress the ASGPR. This targeted approach enhances the precision and efficiency of drug delivery, particularly for liver cancer therapy (Figure 15A).

The carboplatin-loaded, galactose-modified MOF-808 (CA@MOF-808-P-Gal) showed increased endocytosis and cytotoxicity in 2D and 3D HepG2 cell cultures compared with non-targeted or unmodified systems, most notably in reducing IC50 values by several times in spheroid models. The advantages of the NITEC method include short reaction times, precise control over surface modification, and the avoidance of toxic catalysts, which are compatible with drug loading. Beyond its biomedical application, this methodology offers a flexible platform for tailoring MOF surfaces for specific interactions. The results underline the potential of carbohydrate targeting in nanomedicine for enabling selective cancer therapy with reduced effects on normal cells [202]. Further to these findings, the researchers have already shown more applications of MOFs in the field of liver cancer treatment. The galactosamine-modified ZIF-8-based platform, SG@GR-ZIF-8, is one of the main breakthroughs, which is intended for the combination of chemotherapy and starvation therapy targeting the metastatic HCC. This nanostructure carries the anti-angiogenesis drug sorafenib together with GOx, which is to induce metabolic stress in the tumor cells. The drug, through the N-acetyl-galactosamine (GalNAc) functionalization, achieves hepatic targeting via ASGPR-mediated method, thus the drug gets accumulated more at the tumor site and the therapeutic efficacy is increased. In vivo experiments in a subcutaneous C5WN1 tumor-bearing mouse model (Figure 15B-D) resulted in strong tumor inhibition (89%) and survival extension. Besides, in an orthotopic HCC model with spontaneous pulmonary metastases, SG@GR-ZIF-8 was able to stop the growth of the primary tumor and its metastasis without significantly diminishing the oxygen levels even though it was using its hypoxia-inducing mechanisms. The combination of sorafenib and GOx worked together to enhance therapeutic outcomes by withdrawing glucose from the tumor and provoking oxidative stress, which ultimately resulted in cancer cell death. This dual-function nanoplatform is a promising technology that can be used in treating advanced metastatic HCC and it may also be further improved in the future for better dealing with tumor heterogeneity [141]. This combined approach enhances treatment efficacy by leveraging the localized cytotoxic effects of PDT while simultaneously delivering chemotherapeutic agents to HCC cells. By integrating targeted DDS with ASGPR-specific ligands, such as galactose derivatives, researchers aim to maximize drug accumulation in liver tumors while minimizing off-target toxicity. In this approach, galactose-functionalized porphyrin-based MOFs serve as a multifunctional platform, enabling targeted delivery and enhanced synergistic efficacy in HCC treatment. The designed DOX@Gal-PCN-224 nanosystem, which integrates the chemotherapeutic drug DOX and a photosensitive porphyrin, exhibited galactose-mediated targeting to hepatocytes, thereby improving the drug delivery efficacy. In vivo studies in orthotopic HCC-bearing mouse models showed that the system provided a 98% tumor inhibition rate after only one 10-minute IPDT session. Histological examination confirmed the necrosis of tumors and apoptosis of cells. Side effects on normal tissues were minimal; there was no major organ damage. This bimodal strategy of IPDT combined with chemotherapy proved to be effective, with an impressive TGI rate of 98.2%, significantly outperforming single treatments (Figure 15E-I). These results suggest that DOX@Gal-PCN-224, with its targeting ability and synergistic effects, is laden with great promise for the clinical treatment of HCC [140].

2.8. Antibodies

Antibodies targeting cancer cell receptors have become a prominent strategy in cancer treatment due to their high specificity and effectiveness in attacking malignant cells. These therapeutic antibodies are engineered to attach to particular receptors that are overly present in cancer cells, such as the epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), and programmed death-ligand 1 (PD-L1) [203,204].

Through interaction with these receptors, the antibodies can successfully interfere with the vital cellular signaling pathways responsible for cancer cell division and survival, initiate the process of antibody-dependent cell-mediated cytotoxicity (ADCC), or prevent the action of immune checkpoint inhibitors, thereby strengthening the overall immune fight against tumor cells [142,205]. Some of the most well-known are trastuzumab, directed against the HER2 receptor in breast cancer; cetuximab, which targets EGFR in colorectal and head and neck cancer; and pembrolizumab, which aims at the PD-L1 in a range of tumors [206]. These therapies based on monoclonal antibodies have changed the practice of oncology, in a lot of cases delivering the same or even better efficacy along with fewer side effects when compared to standard chemotherapy. Moreover, researchers are constantly working on novel cancer-associate targets and antibody-based therapies comprising antibody-drug conjugates (ADCs) and bispecific antibodies to further enhance the potency and selectivity of the treatments [207].

These nanocomposites, composed of antibodies, chemotherapeutic drugs, and photosensitizing agents for PDT, achieved remarkable in vitro and in vivo efficiencies against liver (HepG2) and gastric (AGS) tumors (Figure 16A-F). It resulted in an improvement in tumor-suppressing effects under combination treatment with 473 nm³ and 100 mm³ reduced volumes of HepG2 and AGS tumors, respectively. Additionally, no observed pathological abnormalities of major organs were further recorded, which also proved biosafety. This will provide an appropriate and effective strategy for tumor targeting, multimodal imaging, and comprehensive cancer treatment by integrating chemotherapy, immunotherapy, and PDT into a single platform [208].

In continuation of the previous efforts to enhance MOF-based DDS, recent studies have explored further advancements in functionalizing these platforms with antibodies to improve specificity and efficacy. Antibody-covered MOF-808 particles counteract the protein corona phenomenon, thus showing an enhanced colloidal stability and stealth effect in biological media. Functionalization with specific antibodies, such as anti-EGFR, allowed for precise targeting of cancer cells and appeared to induce a high in vivo tumor accumulation. Such a system showed 75% suppression of tumor growth in a mouse model and exhibited high in vivo biocompatibility, without side effects (Figure 16G-M). Such an outcome illustrates the enormous potential of antibody-MOF platforms as stable and efficient DDS for cancer therapy [209].

Following the growing interest in antibody-mediated drug delivery, Chen et al. developed a novel targeted DDS, Trastuzumab@ZIF-8@DOX, leveraging trastuzumab, an anti-HER2 antibody, for precise cancer therapy. By functionalizing the surface of ZIF-8 with trastuzumab, this system was designed for targeted cancer therapy, specifically aimed at HER2-positive tumors. The pH-responsive nature of this system enables the controlled release of DOX in acidic tumor microenvironments, thus enhancing therapeutic efficiency. The excellent drug loading efficiency of 12.53% and favorable biocompatibility further highlight the potential of this approach for precise and effective cancer treatment. It could noticeably restrain the early leakage of DOX under neutral conditions, while acid pH triggered a competent release of the drug and, hence, succeeded in its controlled delivery. In addition, a cell internalization study demonstrated effective internalization via HER2-receptor-targeted endocytosis, and the viability of SK-BR-3 cancer cells was reduced to 47.75% at a DOX dose of 5 µg/mL, whereas healthy HaCaT cells showed better viability of 75.25%. Further in vivo investigation in

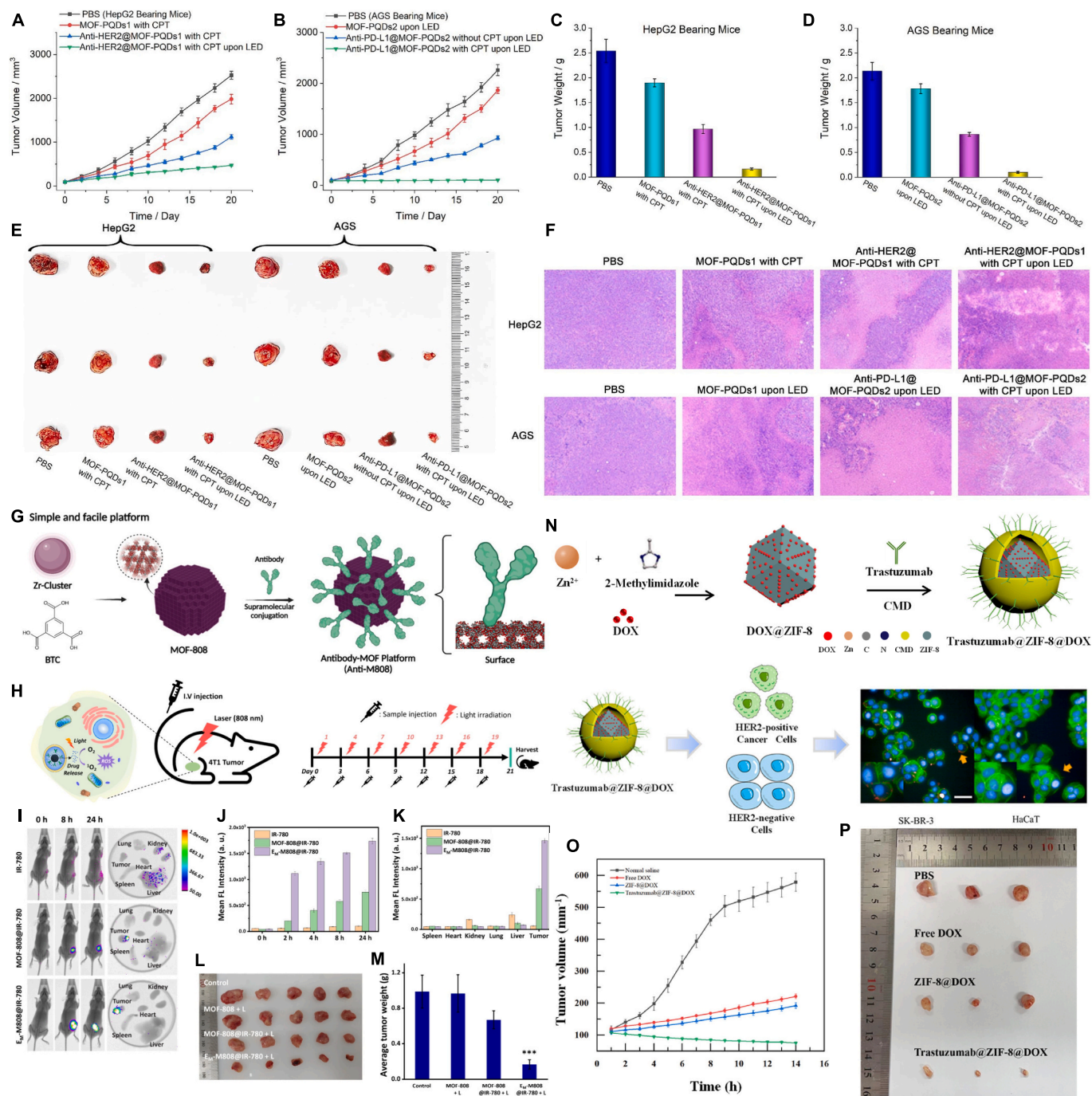


Fig. 16. In vivo therapeutic evaluation and antibody-functionalized MOF systems for targeted cancer treatment. (A, B) Tumor growth curves of liver (HepG2) and gastric (AGS) tumor-bearing mice subjected to different treatments over 20 days. (C, D) Tumor weights of the corresponding treatment groups after 20 days. (E) Representative photographs of tumors dissected from tumor-bearing mice at the therapeutic endpoint. (F) H&E staining results of tumor tissues from each treatment group. Reproduced with permission from Ref. [208]. (G) Schematic representation of an antibody-modified MOF design. (H) Illustration of the in vivo experiment using the antibody-MOF complex. (I) In vivo fluorescence imaging and biodistribution of IR-780 in tumor-bearing mice after injection. (J, K) Fluorescence intensity tracking in tumors and organs over 24 hours, showing accumulation and clearance patterns. (L) Tumor photographs on day 21 post-treatment and (M) corresponding tumor weights. Reproduced with permission from Ref. [209]. (N) Fabrication scheme of Trastuzumab@ZIF-8@DOX nanoparticles and their attachment to HER2-positive cancer cells. (O) Tumor volume progression following treatment with DOX, ZIF-8@DOX, Trastuzumab@ZIF-8@DOX, or PBS. (P) Photographs of excised tumors from each treatment group at the study endpoint. Reproduced with permission from Ref. [144].

BALB/c nude mice proved the improved tumor inhibition and safety profile of the system compared to free DOX or DOX@ZIF-8 (Figure 16N-P). From the above results, one may recognize such antibody-functionalized MOF, like Trastuzumab@ZIF-8@DOX, as a promising candidate for targeted and controlled cancer treatments [144].

The creation of antibody-coated NMOFs allowed cancer therapy to

use a more precise drug delivery method. Zhao and his coworkers worked on making nano-agents that consist of a magnetic core and a MOF shell, which are further wrapped with carboxymethyl-dextran, and are capable of loading drugs very efficiently with a loading capacity of 15.7 mg/g for daunorubicin or DOX. The system delivers drugs consistently; thus, it shows the potential of magnetic targeting combined with

MOFs to escalate chemotherapy delivery and cancer cell extermination. To new heights of specificity, the monoclonal antibodies against HER2 were bonded in a covalent way to the surface of MOF, thus the antibodies retained their property of discriminating between HER2-negative and -positive cells. The lab tests showed that only those particular cells were killed, whereas the others remained alive even when the concentration was as high as 300 mg/L. This technique reveals the ability of antibody-functionalized NMOFs to combine high drug-loading capacity with controlled release and precise targeting, thus, the area of personalized medicine, bioimaging, and theranostics is going to benefit from new advanced applications [142].

2.9. Bovine serum albumin

Carrying on from the previous discussions on receptor-targeted DDS, we now turn to BSA as a promising and adaptable carrier. BSA has been the subject of much research as a potential carrier of cancer drugs and not only because of its biocompatibility, prolonged blood circulation and the EPR effect-induced tumoral accumulation but also due to those features. BSA itself does not exhibit the property of being tumor-specific but its mechanisms of action allow interaction with proteins that are present in high quantities in the tumor microenvironment [210,211]. An illustration of this is the case of gp60 (also known as albumin), which is an albumin-binding protein and through its interaction with albumin enables the albumin to cross the endothelium, a process that is particularly pronounced in tumors [212]. Likewise, SPARC (secreted protein acidic and rich in cysteine), a matricellular protein that is often over-expressed in cancer has high binding affinity for albumin and thus can be involved in the accumulation of albumin in the tumor matrix [213,214]. These biological interactions between BSA and the tumor microenvironment have led to the conclusion that BSA passive accumulation in the tumor site can be achieved, while in the case of functionalized BSA with ligands like FA or mannose that bind to the corresponding cell receptors which are often upregulated in cancer, the active targeting can be accomplished. For instance, BSA NPs decorated

with folate have been shown to selectively bind and internalize into tumor cells overexpressing the FR. These passive and active targeting strategies together position BSA as a flexible and promising foundation for the development of targeted drug delivery platforms in cancer therapy [215].

In addition to these findings, several studies have investigated the versatility of BSA-functionalized systems. Deng et al. developed a novel multifunctional nanopatform, $\text{IrO}_2\text{@ZIF-8/BSA-FA}$ (Ce6), for cancer therapy by integrating PTT and PDT to improve therapeutic efficacy. This platform incorporates iridium dioxide (IrO_2) NPs within ZIF-8 shells to enhance drug loading capacity, while BSA is functionalized with FA and subsequently conjugated to the MOF surface to facilitate selective targeting of tumor cells. The system also shows a high photothermal conversion efficiency of 62.1% and can generate ROS effectively under near-infrared (NIR) irradiation. In acidic tumor microenvironments, IrO_2 also catalyzes endogenous hydrogen peroxide (H_2O_2) to oxygen, relieving hypoxia and enhancing the PDT effect. Both in vitro and in vivo experiments show greater tumor-specific accumulation and combined PTT-PDT efficacy, where the tumor volume was reduced to a much larger extent than all monotherapies (Figure 17A-F). The biocompatibility and EPR effect, enhanced by FA-mediated targeting, ensure precise tumor delivery. This study offers a robust platform for synergistic cancer treatment through intelligent nanocarrier design [216].

Continuing from previous advances in albumin-based nanocarriers, Salimi et al. introduced a pH-sensitive nanocarrier, MTX@ZIF-8@BSA , designed to enhance the antitumor and antimetastatic properties of MTX. The formulation demonstrated excellent stability and suitable particle size (68.5 ± 13.31 nm), alongside a high drug loading capacity of $28.77 \pm 2.54\%$ and an encapsulation efficiency of $96.3 \pm 0.67\%$, confirming its potential as a promising system for targeted cancer therapy. The system exhibited pH-responsive drug release, releasing 1.73-fold more MTX at pH 5.4 than at pH 7.4. In vitro, MTX@ZIF-8@BSA showed higher cytotoxicity against breast cancer cells with an IC_{50} value of 32.7 ± 7.3 $\mu\text{g/mL}$ compared with free MTX (IC_{50} : 53.3 ± 3.7 $\mu\text{g/mL}$). In vivo, MTX@ZIF-8@BSA significantly inhibited tumor growth

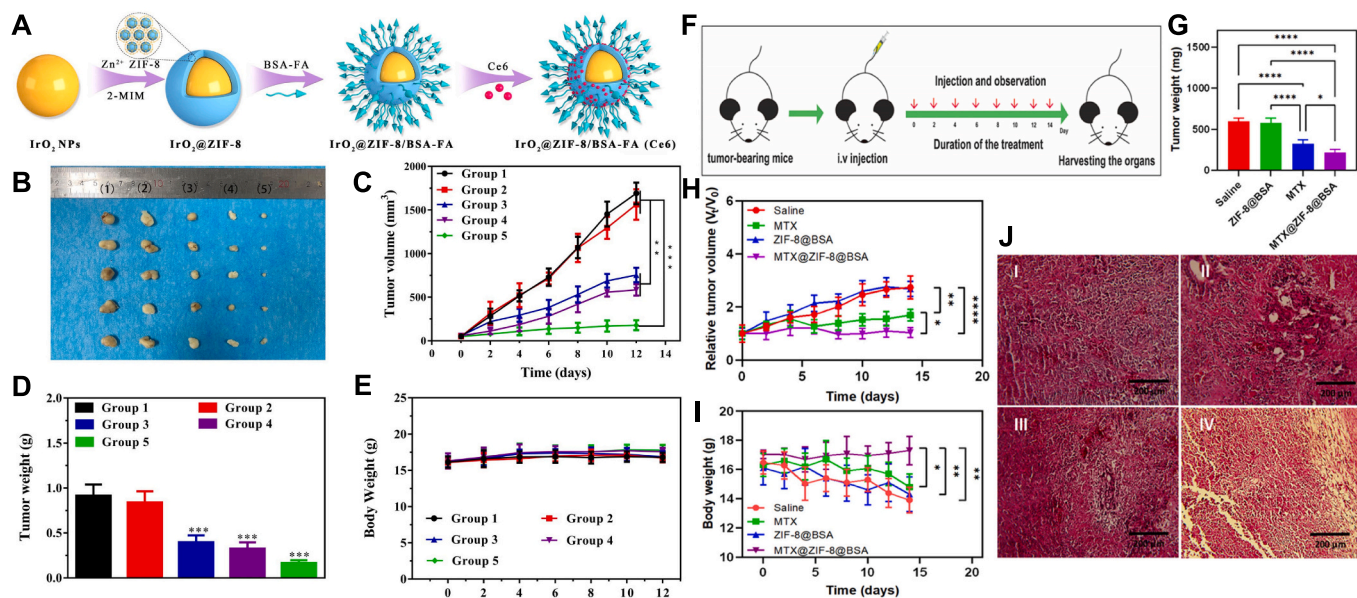


Fig. 17. Schematic illustrations and in vivo evaluations of multifunctional MOF-based nanopatforms for photothermal, photodynamic, and chemotherapeutic cancer treatments. (A) Schematic illustration of $\text{IrO}_2\text{@ZIF-8/BSA-FA}$ (Ce6) nanoparticle (NP) preparation and their in vivo evaluation for combined photothermal-photodynamic therapy. (B) Photographs of excised tumors from different treatment groups. (C) Tumor growth curves demonstrating volume progression across treatment groups. (D) Comparative tumor weights post-treatment. (E) Body weight variations of tumor-bearing mice during the treatment period. Reproduced with permission from Ref. [216]. (F) Illustration of the treatment timeline used for in vivo studies. (G) Tumor weight comparison between four experimental groups. (H) In vivo antitumor efficacy of each treatment group over time ($n = 4$). (I) Body weight changes following intravenous administration of saline, MTX, ZIF-8@BSA, and MTX@ZIF-8@BSA ($n = 4$). (J) Histological images of H&E-stained tumor tissue sections treated with (J-I) Saline, (J-II) MTX, (J-III) ZIF-8@BSA, and (J-IV) MTX@ZIF-8@BSA , showing therapeutic histopathological differences. Reproduced with permission from Ref. [217].

and reduced lung and liver metastasis, showing better biocompatibility than free MTX, which caused severe kidney and liver toxicity (Figure 17F–J). The stability of the system at physiological pH reduced systemic toxicity, while BSA coating enhanced biocompatibility, prolonged circulation time, and tumor-specific uptake by receptor-targeted endocytosis. Once in the acidic environment of tumor cell endocytosis, ZIF-8 degraded, MTX was efficiently released, zinc ions induced ROS production, and anticancer efficacy was enhanced. The results illustrate that MTX@ZIF-8@BSA holds great potential as a promising nanopatform for improving both the effectiveness and safety of chemotherapy against breast cancer [217].

Abd Al-Jabbar et al. explored an important aspect of BSA-based systems by developing pH-sensitive, multifunctional nanocomposites for targeted cancer therapy. In their study, BSA was combined with ZIF-8 to create nanocarriers capable of enhanced drug delivery. The anticancer drugs GEM and Amygdalin (Amy) were successfully encapsulated with BSA-based nanocarriers, namely BSA-Gem@ZIF-8 and BSA-Gem-Amy@ZIF-8, showcasing their potential for improved therapeutic efficacy. In addition, these nanocarriers were functionalized with PDA, gold (Au^{3+}), and GA to optimize their performance. Due to their pH sensitivity, these nanocomposites exhibited higher apoptosis rates in MCF-7 breast cancer cells while reducing toxicity compared to free Gem, highlighting their promise in drug delivery applications [147]. Building on previous research, the core shell structure of BSA/DOX@ZIF demonstrated improved cellular uptake and therapeutic efficacy. This was attributed to its pH-sensitive drug release, where it remained stable at physiological pH (7.4) but efficiently released DOX in the acidic tumor microenvironment (pH 5.0–6.0). These characteristics highlight the potential of BSA-ZIF-8-based nanocarriers as promising candidates for targeted and effective cancer therapy [146].

2.10. Peptides

At the previous conversation, we went over the fact that receptor targeting is an essential factor in DDS for chemotherapy, and peptide receptors are slowly but surely becoming the target of choice. Not only have peptide receptors demonstrated their significant role in cancer biology, but also, they have been the main focus of diagnostics and targeted therapy. Specific peptide receptors are overexpressed by many cancer cells on their membranes, thus rendering them as not only the targets for drug delivery but also for development of diagnostic imaging applications [218,219]. The most frequently and widely studied peptide receptors in cancer are somatostatin receptors, bombesin receptors, vasoactive intestinal peptide (VIP) receptors, and gastrin-releasing peptide receptors. Generally, these receptors are expressed at much higher levels in tumor cells than in adjacent normal tissues, which is why they are considered to be very good candidates for therapeutic interventions [220,221].

In order to exploit the mentioned targets, numerous peptide ligands have been designed that bind to peptide receptors with great affinity and specificity. These peptides can be utilized as carriers for the targeted drug delivery, imaging agents, or even radionuclides focused on the cancer cells. One of the typical cases is that somatostatin analogues have been frequently employed in the imaging and treatment of neuroendocrine tumors. New peptide ligands and peptide-drug conjugates specifically targeting tumor receptors are the subject of ongoing research, the goal of which is to enhance treatment effectiveness and at the same time lessen the negative consequences of cancer therapy [219,222].

The bio-MOFs composed of peptides is an inventive technique that causes the targeted strategies for cancer treatment to gain more strength and to be conquered, and this has been talked about in the previous sections. The incorporation of the tumor-targeting peptide Fmoc-HDGR into the ZFH-DGR framework enables the platform to zero in on the $\alpha\beta3$ integrin, which is present in large amounts in liver cancer cells. Just like the strategies with BSA, folate, and other receptors, this peptide-based approach is one that has drug delivery, and thus the specificity of

drug delivery is being enhanced, leading to off-target effects being reduced and therapeutic outcomes being improved. The capacity of ZFH-DGR to provide pH-responsive drug release and high biocompatibility are among the factors that give it the chance for being the next generation of targeted cancer therapies. The *in vivo* tests performed on Heps tumor-bearing mice demonstrated that ZFH-DGR loaded with DOX (ZFH-DGR/DOX) was able to considerably reduce tumor growth in comparison to free DOX at a dose of 5 mg/kg intravenous administration every two days. The tumor volumes were effectively regulated with minimized systemic toxicity (Figure 18A–F). Histological analysis revealed increased apoptosis in tumors but without significant harm to major organs. This bio-MOF system has been able to demonstrate its potential for accurate cancer treatment through the combination of targeted delivery, selective cytotoxicity, and reduced systemic side effects [145].

In addition, a report from Cai and colleagues introduces the PEG-CPP33@NPs nanopatform to carry both oridonin and survivin siRNA near the tumor in the cancer treatment process and makes use of MOFs like ZIF-90. The drug delivery's accuracy is improved by this method, thereby displaying the MOFs' flexibility in the therapeutic agents' merging for the more efficient cancer treatment (Figure 18G–J). The drug delivery system has very high capacity and is pH-sensitive, which means that the drug will remain stable for a longer time and the bioavailability of siRNA will be increased. The addition of PEG-conjugated cell-penetrating peptides brought about a change, as the uptake of the drug by the cells was greatly increased in both *in vitro* and *in vivo* studies. The combination of ORI and survivin siRNA was observed to have a synergistic effect on the anti-tumor activity with a significant decrease in tumor size and normal tissues suffering less damage. Thus, it could be a beneficial strategy to merge chemotherapy and gene therapy for future clinical applications [149].

Dahri et al. expanded on previous research in receptor-targeted targeting and drug delivery by introducing enzyme-sensitive DDSs with peptide-conjugated prodrugs. Incorporating peptides sensitive to Cathepsin B enhances the specificity and controlled release of drugs like DOX in tumor sites, aligning with the previous discussions on pH and receptor-targeted DDS. The interaction between MOFs such as ZIF, UiO-66, and HKUST-1 with these peptide-conjugated prodrugs not only improves the stability of the NPs but also showcases the advantage of tailoring the carrier system to respond to specific enzymes, further optimizing the targeting and release profiles for cancer therapy. The study highlights that lower prodrug concentrations result in more stable NPs, emphasizing the importance of fine-tuning the DDS for effective cancer treatment [150]. Another study done by Xu et al. reported the synthesis of histidine polypeptide-hybridized NMOF, fH12/ZIF-8 in water at room temperature without additives. This method aligns with the trend of using peptide-functionalized MOFs for targeted drug delivery, further supporting their potential in cancer therapy (Figure 18K).

Building on previous advancements in targeted drug delivery, a novel nanopatform, AR-ZS/ID-P NPs, was engineered by combining ZIF-8 with a tumor-targeting peptide, AREYGTRFSLIGGYR (AR), to enhance multimodal cancer therapy. This platform leverages the peptide's targeting capabilities to improve drug delivery specifically to tumor cells, thereby boosting the effectiveness of cancer treatments. This innovative platform demonstrates impressive encapsulation of indocyanine green (ICG) and DOX, achieving an encapsulation efficiency exceeding 95%. The AR-ZS/ID-P NPs exert synergistic chemotherapy PDT and PTT upon near-infrared (NIR) irradiation. The ZIF-8 framework is pH-sensitive to ensure controlled drug release under acidic tumor conditions, and AR peptide targets the breast cancer cells. *In vivo* studies demonstrated that AR-ZS/ID-P NPs could enhance tumor accumulation and inhibit tumor growth through the combined ICG-induced PDT and PTT and DOX chemotherapy, showing better results than other groups (Figure 18L–U). More importantly, the platform exhibited good biocompatibility with few side effects, thus it is a potential candidate for

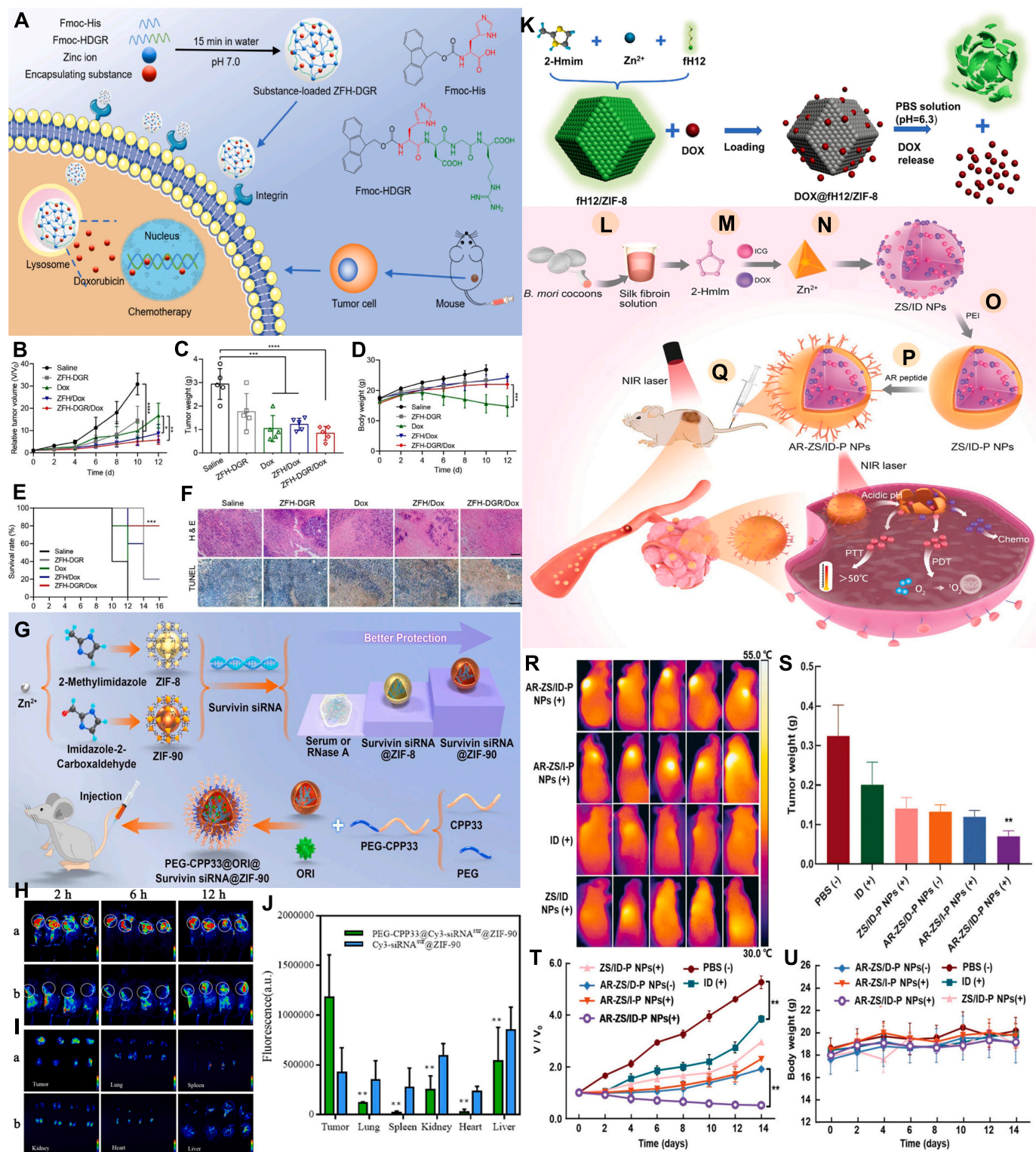


Fig. 18. Schematic illustrations and in vivo evaluation of multifunctional MOF-based nanoplateforms for targeted, gene-assisted, and photothermal cancer therapy. (A) One-pot preparation of ZFH-DGR/Cargos and their targeted tumor delivery for precise therapy. (B) Relative tumor volumes of Hep3B-bearing mice over 12 days of treatment. (C) Tumor weights on days 10 and 12 for different groups. (D) Average body-weight changes of tumor-bearing mice during treatment. (E) Survival curve of mice receiving various formulations. (F) H&E and TUNEL-stained tumor sections showing apoptosis in control and test groups at 10- and 12-days post-injection. Statistical significance: $P < 0.05$; $P < 0.01$; $P < 0.001$; $P < 0.0001$. Reproduced with permission from Ref. [145]. (G) Schematic illustration of siRNA protection by ZIF-8 and ZIF-90 and in vivo biodistribution of nanoformulations. (H) In vivo fluorescence imaging at 2, 6, and 12 h after injection of nanoparticles. (I) Fluorescence imaging of major organs and tumors 12 h post-injection. (J) Quantified fluorescence intensity of organs and tumors. Reproduced with permission from Ref. [149]. (K) Schematic of fh12/ZIF-8 nanoparticle synthesis for pH-triggered drug delivery. Reproduced with permission from Ref. [148]. (L–Q) Schematic synthesis of AR-ZS/ID-P NPs and their use in targeted breast-cancer therapy. (R) Thermal imaging showing laser-induced heating. (S) Tumor weight after 14 days. (T, U) Tumor-volume reduction and body-weight variation across treatments. Reproduced with permission from Ref. [223].

Table 3

Summary of Targeting Mechanisms, Receptor–Ligand Interactions, and In Vivo Biosafety Data of MOF-Based Nanoplatfroms

MOF Type / Modification	Animal Model	Targeting Mechanism	Parameters (Key Receptor-Ligand / Binding Data)	In Vivo Toxicity / Metabolism Findings (Long-term Biototoxicity, Metabolic Pathways, Organ Damage)	Reference
5-FAM/FA/TP@Fe-MIL-101	Balb/c nude mice, HepG2 xenograft	FA-mediated active targeting; EPR effect	Preferential uptake via FA receptor; higher tumor fluorescence	No systemic toxicity; liver/spleen normal; tumor growth inhibited	[154]
FA-Hf-Mn-NMOF	S180 tumor-bearing mice	FA-mediated; receptor-mediated endocytosis; EPR	Higher uptake in FA receptor-positive cells; confirmed by ICP-OES & imaging	Minimal toxicity; organs normal; effective PTT/RT	[155]
FA-functionalized MOF loaded with Buf (FA-MOF/Buf)	BALB/c nude mice, 4T1 breast cancer xenograft	FA-mediated; EPR; pH/redox release	Higher uptake in FA receptor-overexpressing tumor cells; confocal & flow cytometry	Minimal toxicity; organs normal; better tumor suppression vs free Buf	[158]
HPDFZ NMs (PDA/HA-coated Fe/Zn-based NMs with DOX)	CT26 tumor-bearing mice (BALB/c)	HA-mediated CD44; EPR; Fenton; GSH depletion	Enhanced ROS & ferroptosis; smallest tumor volumes & weights	No body weight changes; organs normal; effective at low DOX dose	[166]
PAO@PCN@HA	BALB/c mice; subcutaneous CT26 tumor model; IV injection; Light irradiation 12 h post-injection	HA-mediated CD44 targeting; chemo/PDT combination	CD44 receptor; HA ligand; Flow cytometry: 3-fold higher uptake in CT26 vs COS7; Pre-blocking with HA reduced uptake	High CT26 uptake; low COS7 uptake; Dark toxicity reduced; Light-activated cytotoxicity high; Hypoxia overcame via PAO; Tumor growth inhibited; Low systemic toxicity	[167]
DOX&GGF@ZIF-8@HA	BALB/c mice; subcutaneous 4T1 tumor model; IV injection; tumor monitoring 14 days	HA-mediated CD44 targeting; chemo/ferroptosis	CD44 receptor; HA ligand; Mean fluorescence intensity higher vs DOX&GGF@ZIF-8; Time- and concentration-dependent uptake	Higher MFI and Fe(II) content; Enhanced ROS/•OH production; Stronger cytotoxicity in vitro; Tumor accumulation improved; Tumor growth suppressed; Minimal organ toxicity	[97]
DMH NPs (DOX+MIL-100+HA)	BALB/c nude mice; subcutaneous MCF-7 tumor model; IV injection every 3 days; tumor monitoring 14 days	HA-mediated CD44 targeting; chemo/CDT	CD44 receptor; HA ligand; ROI analysis of tumor fluorescence; EPR effect	HA modification enhanced tumor accumulation; DMH NPs stronger cytotoxicity vs DM NPs or free DOX; Combined therapy effective; Reduced systemic toxicity; H&E showed larger necrosis area in tumors	[91]
OIMH NPs (OXA+ICG@MIL-100)	BALB/c mice; subcutaneous CT26 tumor model; IV injection every 3 days; 808 nm NIR laser irradiation 12 h post-injection	Chemo-photothermal therapy; ICD induction	DAMPs: CRT, HMGB1, ATP; tumor accumulation via EPR; enhanced CD4+/CD8+ T cells; abscopal effect with aPD-L1	Low systemic toxicity; liver/kidney function mostly normal; ICD triggered; photothermal effect enhanced tumor ablation	[114]
MTX-TA/Fe ³⁺ @HA MOFs	CIA mice; collagen-induced arthritis	HA-mediated CD44 targeting; anti-inflammatory	IC50 lower in activated macrophages vs normal; ELVIS effect; selective targeting of inflamed joints	No significant body weight change; nephrotoxicity (BUN/Cre) normal; ALT/AST elevated only in free MTX; H&E of major organs normal; improved RA symptoms	[92]
HA-BP-MOF@DOX	CT-26 tumor-bearing BALB/c mice (peritumoral injection)	Local peritumoral retention; tumor-responsive degradation via low pH & high ATP; hydrogel–MOF dual-stage release enhances intratumoral drug accumulation.	pH-triggered Zn ²⁺ –imidazole bond cleavage; ATP competitively binds Zn ²⁺ accelerating MOF collapse; stepwise hydrogel + MOF degradation enabling controlled DOX release (2.6% at pH 7.4; up to 26.9% with pH 5 + ATP).	Strong long-term tumor suppression (up to 35 days) after single injection; 100% survival in treatment group; minimal body-weight changes; no organ damage in H&E (heart, liver, spleen, lung, kidney); severe toxicity seen with free DOX but not with hydrogel.	[113]
EVO@ZIF-8/HA	C57BL/6 mice, B16F10 melanoma tumor-bearing	HA–CD44 active targeting; improved cellular uptake; pH-responsive MOF degradation and drug release in acidic tumor microenvironment.	HA–CD44 binding confirmed by competitive inhibition (reduced uptake after HA pre-incubation); HA-modified NPs showed 4.7× and 1.9× higher uptake at 1 h and 3 h vs non-HA NPs; pH-triggered release: 83.1% (EVO@ZIF-8) and 75.2% (EVO@ZIF-8/HA) at pH 5.0 in 72 h vs ~35% at pH 7.4; HA coating improved dispersion and reduced aggregation, enhancing targeting and in vivo delivery.	Strong tumor suppression with smallest tumor volume and weight; no significant body-weight loss; no histological damage in heart, liver, spleen, lung, kidney; <5% hemolysis at high doses; better safety and lower mortality vs EVO@ZIF-8; good biocompatibility and minimal systemic toxicity.	[170]
DOX/Au Apt@ZIF-8	BALB/c nude mice (MCF-7 breast cancer xenograft)	Aptamer-mediated active targeting; enhanced DOX accumulation in tumor cells; combined chemotherapy + photothermal therapy (NIR-triggered).	Specific aptamer–tumor cell binding; enhanced cellular uptake vs DOX/Au@ZIF-8; NIR irradiation activates Au nanorods for photothermal effect; concentration-dependent	Strongest tumor inhibition in DOX/Au-Apt@ZIF-8 + NIR group (smallest tumor volume/weight); no significant body-weight loss; no major organ damage in	[175]

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Table 3 (continued)

MOF Type / Modification	Animal Model	Targeting Mechanism	Parameters (Key Receptor-Ligand / Binding Data)	In Vivo Toxicity / Metabolism Findings (Long-term Biototoxicity, Metabolic Pathways, Organ Damage)	Reference
Apt/(siRNA+GEF) @ZIF-8	A549 xenograft NSCLC mice	EGFR aptamer-mediated targeting; enhanced uptake in EGFR ⁺ cells; pH-triggered siRNA/GEF release.	apoptosis and cytotoxicity improvement. Aptamer-EGFR binding; strong FAM-siRNA uptake; IC ₅₀ drop: PC-9 (1.817→0.831 µg/mL); A549 (58.475→8.341 µg/mL); EGFR/ERK downregulation.	histology; safe biosafety profile for Au-Apt@ZIF-8 in normal mice. No organ damage; normal serum biochemistry; strong tumor accumulation; tumor inhibition 40.6%; no systemic toxicity.	[177]
Aptamer-BSA@ZIF-8	Bal B/c mice (lymph node targeting) / Tumor-bearing nude mice (prostate tumor)	Anti-CCL21 DNA: lymph node targeting via CCL21; A10 RNA: tumor cell targeting via aptamer	Anti-CCL21: high accumulation in lymph nodes vs nonfunctionalized MOFs; A10 RNA: ~2× higher cellular/tumor uptake vs neat MOFs	Excellent biocompatibility; in vitro (HUVEC) and in vivo (mice) showed no significant toxicity, normal ALT/AST, CREA/BUN, and no histopathological changes in major organs	[178]
DOX/CuS@MOF-199/Apt-M	MCF-7 xenograft mouse model	Apt-M-mediated intelligent targeting to MCF-7 tumor cells; PTT-CT combined therapy	Enhanced cellular uptake via Apt-M; intracellular temperature increases under laser; ~78.1% apoptosis in vitro with laser; effective tumor accumulation in vivo	Excellent biosafety; no body weight fluctuation; no histopathological abnormalities in major organs; selective tumor ablation	[129]
porMOF@DNA-DOX (AS1411 aptamer-modified)	BALB/cu nude mice; HeLa cells in vitro	AS1411 aptamer-mediated nucleolin targeting; selective tumor recognition; synergistic PDT/chemotherapy	Enhanced cellular uptake in HeLa vs HL-7702; DOX fluorescence intensity increased over time; cell viability <20% under PDT+DOX; selective tumor accumulation in vivo; tumor ablation observed	Excellent biosafety; no significant body weight changes; no histopathological abnormalities in major organs; high tumor necrosis/apoptosis in synergistic therapy group	[130]
M-FNM (mannose-modified FNM)	CAL27 and SCC-7 tumor-bearing mice (BALB/c-nude, C57BL/6J); CAL27 cells in vitro	Mannose receptor (MR)-mediated endocytosis; selective tumor targeting; induces pyroptosis; boosts anti-tumor immunity	Enhanced cellular uptake vs FNM; IC ₅₀ ≈ 80 µg/mL; ROS ↑, LDH ↑, IL-1β ↑; cleaved Caspase-1 and N-GSDMD ↑; vacuolar death pattern; tumor accumulation observed via Cy5.5 labeling; Treg cells ↓; DCs and CD8 ⁺ /CD4 ⁺ T cells ↑	Excellent biosafety; no significant change in body weight; accumulation/metabolism mainly via kidney; histological analysis shows tumor cell damage without toxicity in major organs	[185]
rhBLMH@MHP-UiO-66-30	A549 cells (in vitro), BALB/c nude mice (in vivo)	Mannose-functionalized UiO-66 NPs; MR-mediated endocytosis in pulmonary cells; sustained pulmonary retention; enzyme protection against proteolysis	Enhanced cellular uptake in A549 cells, significant detoxification of bleomycin-induced pulmonary fibrosis, reduction in lung coefficient, lower Ashcroft score, decreased collagen I and α-SMA deposition. Antitumor effect of bleomycin was preserved	Good biocompatibility, no significant change in body weight, nanoparticles gradually degraded and cleared from lungs, minimal systemic distribution	[186]
DOX@Gd-MOFs-Glu and Yb-MOFs-Glu	HeLa cells (in vitro) and HeLa tumor-bearing mice (in vivo) for Gd-MOFs; GI tract imaging in mice for Yb-MOFs	Glucose-functionalized MOFs (Gd or Yb) providing active tumor targeting via GLUT1 receptor, pH-responsive drug release through boric ester bond cleavage; Yb-MOFs additionally act as CT contrast agent	Gd-MOFs-Glu: enhanced cellular uptake and nuclear delivery of DOX, higher cytotoxicity than free DOX or non-targeted MOFs, effective tumor growth inhibition in vivo (~85% necrosis), strong MR imaging signal (r1=8.27 mM ⁻¹ s ⁻¹); Yb-MOFs-Glu: efficient GI tract visualization by CT with high contrast (slope 5.02 HU mM ⁻¹), rapid excretion after 1 day	Low cytotoxicity of blank MOFs, no significant weight loss in mice, no organ damage, good long-term biocompatibility	[138]
SG@GR-ZIF-8	C5WN1, HepG2, Huh7 (ASGPR+), HEK293 (ASGPR-); subcutaneous and orthotopic tumor-bearing BALB/c nude mice	ASGPR-targeted delivery of Sor/GOx via GR-ZIF-8 nanoparticles, enabling synergistic chemo/starvation therapy; cytoplasmic release from endosomal compartments	In vitro: strong targeted uptake by ASGPR+ cells, SG@GR-ZIF-8 reduced cell viability to 6.7%, potent synergistic antitumor effect confirmed by live/dead staining; In vivo: enhanced tumor accumulation and retention (fluorescence imaging), tumor growth inhibition rate 89% in subcutaneous model, suppression of lung metastasis in orthotopic model, improved survival rate (60% at 60 days)	Low cytotoxicity of carrier (cell viability >80%), negligible hemolysis (<1%), no body weight loss or organ lesions in mice, indicating good systemic biocompatibility	[141]
DOX@Gal-PCN-224	HepG2, Huh7 (ASGPR+), HEK293, L02; subcutaneous and orthotopic Huh7 tumor-bearing mice	ASGPR-targeted delivery of DOX and TCPP via galactose-modified PCN-224 for synergistic PDT/Chemotherapy; cytoplasmic release from acidic organelles; minimally invasive percutaneous light delivery for PDT in orthotopic tumors	In vitro: specific uptake by ASGPR+ cells, 102 generation, cell viability reduced to 9% under 660 nm irradiation; In vivo: enhanced tumor accumulation, long circulation, subcutaneous tumor TGI 88.8% (DOX@Gal-PCN-224), orthotopic tumor TGI 98.2% with minimally invasive PDT;	Negligible cytotoxicity of carrier (>80% cell viability), very low hemolysis (<0.2%), no body weight loss or organ lesions in mice, indicating high systemic biocompatibility	[140]

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Table 3 (continued)

MOF Type / Modification	Animal Model	Targeting Mechanism	Parameters (Key Receptor-Ligand / Binding Data)	In Vivo Toxicity / Metabolism Findings (Long-term Biototoxicity, Metabolic Pathways, Organ Damage)	Reference
DVP-MOF-PQDs	HepG2 (HER2+), AGS (PD-L1+), nude BALB/c mice; subcutaneous and orthotopic tumor models	Anti-HER2 or anti-PD-L1 antibodies guide MOF-PQDs loaded with CPT for targeted chemotherapy and PDT; multimodal imaging (FL/PL, MRI) for precision diagnosis; intracellular ROS generation and apoptosis via LED irradiation	strong apoptosis and necrosis in tumor tissue In vitro: high uptake and cytotoxicity in antigen-positive cells (cell viability 5–8.9% at 300 µg/mL); enhanced ROS generation and apoptosis under LED irradiation; In vivo: subcutaneous and orthotopic tumor inhibition, HepG2 tumor volume reduced to 473 mm ³ with anti-HER2 + PDT, AGS tumor volume 100 mm ³ with anti-PD-L1 + PDT; improved imaging contrast in FL/PL and MRI; synergistic combination therapy In vitro: high cellular uptake and selective cytotoxicity in target cells (EM-M808@IR-780 IC50 0.97 µg/mL in 4T1, 0.62 µg/mL in MDA-MB-468); selective ROS-mediated apoptosis under 808 nm light; In vivo: 4T1 tumor-bearing mice showed ~75% tumor growth inhibition, tumor weight reduced to 0.16 g vs 0.98 g in control; significant tumor accumulation and ROS-mediated apoptosis confirmed by TUNEL In vitro: ZFH-DGR/Dox showed 7.3× higher uptake in HepG2 vs L02; IC50 in HepG2 = 1.79 µg/mL vs Dox = 4.76 µg/mL; in vivo: significant tumor growth suppression (RTV = 5.72 ± 1.88 vs 16.77 ± 5.57 for free Dox-HCl) after 12 days; highest survival (80%) In vitro: PEG-CPP33@NPs induced highest apoptosis (60.73%), synergistic effect vs single drugs; In vivo: PEG-CPP33@NPs showed strongest tumor inhibition (61.04%), significant tumor apoptosis via survivin, caspase-3, Bcl-2/Bax pathways; NPs showed additive effect of ORI + siRNA In vitro: AR-ZS/ID-P NPs + 808 nm laser showed ~50% cell death, highest ROS generation, enhanced uptake; In vivo: rapid tumor accumulation, highest fluorescence at tumor site, tumor temp >50°C upon laser irradiation, tumor weight ~25% of PBS, significant necrosis and apoptosis in tumor tissues	MOF and MOF-PQDs alone show high biosafety (>90% cell viability), low systemic toxicity in vivo, no organ abnormalities in H&E staining, negligible weight loss during treatment	[208]
M808 MOF Platform	MDA-MB-468 (EGFR+), SK-BR-3 (HER2+), HeLa (CD44+), 4T1 tumor-bearing mice	Antibody-conjugated MOF-808 (E-, H-, C-M808) loaded with IR-780 for targeted PDT; IgG layer for stealth effect; specific antibody enhances targeting to overexpressed receptors		MOF-808 alone shows negligible toxicity; IgG-M808 reduces protein corona; no body weight loss or organ abnormalities observed in H&E staining; good biosafety after 1-week repeated injection	[209]
ZFH-DGR/Dox	HepG2 cells, L02 cells, Heps tumor-bearing ICR mice	DGR peptide-mediated αβ3 integrin targeting; pH-responsive drug release		Excellent biosafety: normal organ histology (H&E, TUNEL), stable body weight, minimal systemic toxicity compared to Dox-HCl; pH-sensitive release reduces off-target effects	[145]
ORI & survivin siRNA@ZIF-90 / PEG-CPP33@NPs	A549 cells, A549 tumor-bearing nude mice	CPP33 peptide-mediated active targeting; siRNA + ORI combined therapy		Excellent biosafety: stable body weight, normal ALT/AST/ALB/BUN, routine blood tests normal; no histopathological changes in major organs (H&E)	[149]
AR-ZS/ID-P NPs	MCF-7 cells, MCF-7 tumor-bearing mice	AR peptide-mediated active targeting; DOX + ID for chemo + PDT/PTT		Excellent biosafety: stable body weight, no histological damage in major organs, normal liver and kidney function (ALT, AST, ALP, LDH, BUN)	[223]

efficient and targeted cancer treatment. The findings indicate that AR-ZS/ID-P NPs may provide a multifunctional strategy for clinical cancer therapy with less toxicity [223].

3. Evaluation of targeting specificity and biosafety of MOF-based nanoplatforms

It is necessary to assess the biosafety and specificity of MOF-based

nanoplatforms through thorough and accurate testing to ensure their safety and effectiveness as a novel therapeutic modality for cancer treatment. Table 3 provides an overview of the various ways MOFs have been validated as useful technological tools. Receptor-ligand interactions can enhance the selective uptake of functionalized MOFs by using methods such as receptor-blocking assays, competition binding studies, and intracellular localization studies. There has been increased emphasis on long-term biosafety through comprehensive in vivo studies,

including biodistribution, blood chemistry, and pathological evaluation of major organs. Properly designed MOF nanomaterials show excellent biocompatibility with very low systemic toxicity.

4. Conclusions, challenges, and prospects

Nanotechnology is one of the main reasons for the radical and fast changes in health and medicine. Besides, nanotech has changed the whole idea of conventional DDS and gave rise to the invention of nanocarriers. These can deliver drugs accurately and efficiently either by passive or active mechanisms, or even both at the same time. The focusing of drugs on cancer cells, for instance, is of utmost importance in the improvement of therapeutic efficacy together with the elimination of side effects on the healthy tissues. Among these, active targeting is one of the most powerful and efficient ways for drug delivery right to the very spot where it is most needed. This method hinges upon the attaching of the nanocarriers to the specific tumor cell receptors with the help of ligands. The ligands can be made from different biomolecules, such as proteins, peptides, aptamers, polysaccharides, and small molecules, and these are the ingredients that help to make nanocarriers interact better with the cell receptors. The scientific community is very active in research and training, particularly in the area of refining the targeting strategies, drug carrier performance, and finally the clinical translation issue.

The choice of appropriate targeting ligands is influenced by a number of considerations, such as the species of cell surface receptors, the availability of functional groups on the nanocarrier, the drug's physicochemical properties, and commercial viability. Despite the fact that ligands such as proteins and aptamers are good for their high specificity and strong binding affinity, the limited stability and high production costs are issues that confront them. However, these restrictions have resulted in the production of cheaper substitutes like small molecules and polysaccharides, which, at the same time, have lower receptor-ligand specificity.

The use of targeting ligands on NPs leads to increased drug concentration at the desired location. On the other hand, NPs' physicochemical properties like size, shape, and surface characteristics should be fine-tuned to facilitate cellular uptake. NMOFs have been among the various nanocarrier platforms that have caught attention as active targeting contender because of their high porosity, large internal surface area, well-defined structure, and versatile functionalization options.

The functional groups on the surface of MOFs facilitate the binding of ligands through chemical interactions and thus enable the targeted delivery of drugs. In addition, charge release in these MOFs can be regulated by both external and internal stimuli. However, certain pH-sensitive MOF scaffolds, such as ZIF-8 and MIL, are degraded in acidic environments, a property that has been exploited for drug release in the tumor microenvironment. Various strategies have been developed to minimize premature drug leakage and prevent uncontrolled release. Not only have these methods boosted the therapeutic efficacy of DDS, but they have also made their design and application considerably more complex. Out of all the research done, only a handful of nanocarriers have been approved for clinical use, with the majority of the systems in clinical use being based on liposomes and polymers. Hence, it is very important to carry out further studies to assess the toxicity of MOF-based nanocarriers and also to create nanoplatforms that would be therapeutically more effective, stable, and biocompatible for clinical use. The use of MOFs for receptor-targeted drug delivery has gained momentum in the last ten years and has expanded the horizon of drug delivery to cover even proteins and nucleic acids. The relentless progress in the synthesis and design of MOFs, especially with respect to their particle size, shape, and surface chemistry, has opened up avenues for their applications in the fields of sensing, theranostics, and cell-specific targeting. Nevertheless, together with these rapid developments in materials science, there is a need for very stringent biological testing to ensure that the materials will be accepted by the clinic.

In vitro studies are very much progressed but still a lot of work is needed to be done. Implementing appropriate controls to separate the targeted effects from non-targeted ones, choosing the most relevant cellular models, and testing MOFs in more biologically confirmative systems such as 3D cultures, organoids, and co-culture models are some of the necessary steps. The insight into the cellular uptake and transport of MOFs needs to be obtained by a vast and comprehensive manner which includes physicochemical properties, surface modifications, biological models, and the tests done on them. Furthermore, in vivo experiments using appropriate animal models are paramount to determine the pharmacokinetics, biodistribution, therapeutic efficacy, and long-term safety of MOF-based drug delivery systems. A targeted strategy will have to take ligand selection, NMOF surface modification, and stimulus-responsive features into an effective and coherent approach that will be the future. The use of advanced preclinical models, including 3D cultures, organoids, and in vivo models, is recommended for more precise evaluation of efficacy and safety.

To further enhance targeting specificity, future receptor-targeted MOFs should incorporate dual-ligand or multimodal designs, improved ligand-receptor affinity engineering, and biomimetic or stealth surface coatings to minimize off-target uptake. At the same time, biosafety must be strengthened through long-term metabolic tracking, standardized toxicity evaluation frameworks, and the development of degradable MOFs with predictable clearance pathways. From a translational perspective, scalable and reproducible synthesis, batch-to-batch manufacturing consistency, and alignment with regulatory expectations are essential steps for moving MOF-based DDS toward clinical testing. Together, these targeted strategies directly address the key limitations outlined in the Introduction such as target specificity and biosafety and provide a clear forward-looking roadmap for advancing MOF-based targeted drug delivery toward clinical application.

Importantly, even though receptor-targeted MOFs have exhibited outstanding effectiveness in vitro and animal studies, their passage into the clinic remains very restricted [224,225]. Issues of long-term biocompatibility, in vivo stability, large-scale reproducibility, and regulatory requirements must be solved. Pointing out these obstacles emphasizes more research is necessary to connect preclinical triumphs with clinical use. Such strategies will speed up the clinical translation of MOF-based DDS with the preserving of high therapeutic efficacy and low toxicity.

CRediT authorship contribution statement

Hossein Poursadegh: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Data curation, Conceptualization. **Siamak Javanbakht:** Writing – review & editing, Methodology, Investigation, Data curation. **Jeremiah J. Gassensmith:** Writing – review & editing, Validation, Investigation, Conceptualization. **Shengqian Ma:** Writing – review & editing, Validation, Supervision, Methodology. **Seyed Mohammad Davachi:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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