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Metal–organic frameworks: a biomimetic odyssey in cancer theranostics

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This review comprehensively explores biomimetic metal–organic frameworks (MOFs) and their significant applications in cancer theranostics. Although MOFs have promising features such as adjustable porosity, improved surface area, and multifunctionality, they are limited by factors like low biocompatibility and specificity. Biomimetic strategies involving biological membranes and materials are proposed to address these challenges. The review begins by examining the unique characteristics and preparation methods of biomimetic carriers used in MOF-based nanoplatforms, with a comparative analysis of each method. It then delves into the various biomedical applications of biomimetic MOFs, including biosensing, bioimaging, immunotherapy, gene therapy, and multimodal therapies. The review also discusses the biointeraction of these nanoplatforms, including their immunogenicity and interactions with fluids and tissues. Toxicity perspectives are also critically assessed. Overall, the article emphasizes the need for continued research into biomimetic MOFs, highlighting their potential to overcome current obstacles and provide safe, effective, and targeted therapeutic options.

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1. Introduction

The extraordinary properties of metal–organic frameworks (MOFs) like their high porosity, crystallinity and customised structures,[1] have secured their position as one of the most intriguing material classes in science and engineering. These are a sub-class of porous coordination polymers,[2] and can further form nanoscale coordination polymers or nanoscale metal–organic framework (NMOF) particles.[3] Dimensionality-controlled MOF downsizing facilitates tailored usage of nano-MOFs for certain applications where dimensions such as shape and size are vital components.[3] Size-dependent internalisation kinetics, the half-life, and particle redistribution across a biological system are all important factors responsible for various biomedical applications.[4] Smaller particles, for example, have been demonstrated to have longer plasma retention periods and possess the ability to enter the lymphatic system.[5] Concerning shape, nonspherical or anisotropic geometries may be desirable in catalysis as well as optics, mainly because of the predominance of edges and corners holding the active sites or better-suited configurations of channel systems, whereas spherical shapes provide balanced and more uniform framework degradation and ultimately lead to drug release.[6] By leveraging their anisotropic forms and biomimetic properties, non-spherical MOFs provide unique benefits in cancer treatment. Unlike spherical MOFs, which primarily focus on uniform drug delivery and phototherapy, non-spherical MOFs shown to exhibit superior transport and trafficking capability compared to corresponding nanospheres. Their large surface areas and extremely porous architectures make them ideal for loading a variety of therapeutic agents like immunomodulatory agents, prodrugs, and photosensitizers. Coating these MOFs with biomimetic layers, like cancer cell membranes, enables them to target homotypic targets and avoid immune surveillance. The use of carriers with precisely controlled non-spherical geometries introduces new opportunities for optimized vascular targeting by facilitating navigation through physiological flow conditions, reducing clearance by the immune system, and promoting adhesion to damaged vascular tissues.[7] The anisotropic shape also improves tumor infiltration and packing efficiency in composite systems, which is especially advantageous for immunotherapy, photodynamic therapy (PDT), and chemodynamic therapy (CDT).[8,9] The precise morphology, size, and shape provide nano-MOFs with a wide range of tunable functionalities and reactivities, which are based primarily on step-by-step preparation techniques.[10] To mimic biological enzymes effectively, MOFs can be designed with diverse structures and porosity, incorporating various active catalytic sites that accommodate various sub-

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strates. The ability of these hybrid composites to integrate with metal centres relevant to physiological processes and organic linkers that are active biologically makes them highly appealing for biomedical applications. Additionally, their development and engineering at the crystallite level are straightforward, enhancing their practicality for such uses. MOFs offer distinct advantages that make them highly desirable for biomedical applications like drug delivery, imaging, and disease diagnosis. Their significant high surface area and porosity (ranging from 1000 to 10 000 $m^2\ g^{-1}$) enable efficient loading and encapsulation of chemotherapeutic agents. MOFs also feature tunable pore sizes, open architectures, and high crystallinity, all of which support molecular diffusion and host–guest interactions. Furthermore, their structural diversity, derived from a wide variety of metal ions and organic ligands, allows for the customization of physicochemical properties, while their biodegradability guarantees controlled drug release due to weak coordination bonds.[11–13]

Just like every coin has two sides, MOFs also have some drawbacks. These include poor dispersibility in solvents, low electrical conductivity, high concentrations of metal centres (such as zinc, silver, iron manganese, or aluminium) that exceed safe levels for humans, and low stability in different environments. Heavy metals like lead, arsenic, chromium, and cadmium, along with potentially toxic ligands like carboxylates, phosphonates, phenates, sulfonates, and amines, are sometimes incorporated into MOFs. Upon metabolic degradation in the body, these components may induce undesired biological effects. Since MOFs are mainly used as carrier systems in various treatment methods, it can be difficult to effectively deliver them to the targeted area and achieve consistent, regulated, and uniform distribution of the drug throughout the target area. Additionally, creating MOFs with pores large enough to hold enzymes or other large molecules remains extremely complicated and challenging at times.[14–16] Overall, the advantages outweigh the disadvantages; hence, MOFs are now widely scrutinised further for future applications, such as efficient drug carriers, coating materials for enzymes or cells, phototherapy, antibiotics, and detecting various biomarkers.

Biomimicry utilises nature-inspired concepts to develop innovative solutions for complex challenges in artificial systems, incorporating structural and functional advancements. The areas of energy, materials science, biology, and chemistry have all attracted considerable interest in biomimetic research.[17,18] To build enhanced functionality biomaterials, scientists combine biomimetic cell primitives, such as bacteria, phages, cells, and cell membranes, with synthetic materials, particularly nanoparticulate systems, and their distinct bioactive properties.[19] Drug delivery, biomimetic catalysis, biosensing, and other biological applications have directed the extensive design and fabrication of biomimetic materials that imitate specific functional and conformational or morphological properties of pharmacologically active substances, spanning various biological molecules to biological frameworks.[20] These materials include conventional inorganic substances such as mesoporous silica, metal nanoparticles, quantum dots, polymer micelles, and organic entities such as liposomes and dendrimers.[21] Enzyme immobilisation, the coating of biostructures as outside layers (*e.g.*, cell membranes), and the customisation of biomolecules to replace linkers inside MOFs are a few methods for creating biomimetic MOFs. When subjected to high temperatures, abnormal pH, organic solvents, *etc.*, enzymes such as glucose oxidase (GOx) typically lose their biological functions. Hence, using immobilised enzymes or biomarkers with MOFs as their exoskeletons is a viable technique for shielding enzyme structures from abrasive external environments to promote effective catalysis or biomarker sensing. To imitate their targeting properties, nanoscale MOFs can be stacked with constructs, including cell membranes that are usually derived from various cells, or they can serve as carriers in complex biological-based systems that are acceptable in terms of biocompatibility; here, biocompatible ligands and metal centres are essentially sought after.[22] Therefore, MOFs are perfect foundations for functionally or structurally replicating biologically active components that offer biochemical activities in a way that is bioinspired to MOFs.

This review presents a new approach by thoroughly examining biomimetic MOFs in terms of their synthesis, biomedical applications, and clinical potential. Unlike existing literature that mainly focuses on either the synthesis or individual applications of MOFs, this review uniquely integrates the synthesis strategies of biomimetic MOFs with their wide range of biomedical uses, such as in photothermal therapy, immunotherapy, gene therapy, and multimodal treatments. Additionally, the review provides insights into bio-interactions and perspectives on the toxicity of these innovative platforms. With the growing interest in biomimetic materials to overcome the limitations of conventional MOFs, this review is essential for guiding future research and development. It offers a comprehensive perspective on how biomimetic MOFs can revolutionize targeted therapies, drug delivery, and diagnostic tools in modern medicine, highlighting their potential for clinical success.

2. Categories of biomimetic cell membrane-coated MOF-based nanoplatforms in cancer treatment

Nanoformulations modified with biomimetic cellular coatings show significant potential for enhancing tumour therapy. Various biomimetic cell membranes have been explored to potentiate the cancer therapeutic activity of MOF-based nanoformulations (Table 1).

2.1. Erythrocyte cell membrane-coated MOFs

Erythrocytes have emerged as a promising source of biomimetic membranes in nanoparticle formulations because to their innate biocompatibility, long circulation lifespan in

Table 1 Various types, extraction and coating approaches of biomimetic MOFs in cancer therapy

Coated cell membrane	Advantages	Core MOF	Incorporated agents	Cell membrane extraction/ coating technique	Implementations	Cell type	Ref.
Erythrocyte membrane	• Improved targeting ability • Prolonged blood circulation	ZIF-8	TPZ, GOx	Hypotonic treatment or co-extrusion method	Chemotherapy and starvation therapy	Red blood cells	51
Cancer cell	• Enhanced PDT and O_2 self-sufficiency • NIR-mediated tumour killing	ZIF-8	Catalase, Al(III) phthalocyanine chloride tetrasulfonic acid (AlPcS4)	Hypotonic treatment or co-extrusion method	PDT	4T1 cells	52
Platelets	• Efficient siRNA delivery • Effective gene silencing	ZIF-8	siRNA	Freeze–thaw process or co-extrusion method	Gene silencing	Human platelet membrane	53
Cancer cells and dendritic cell	• Excellent antitumour activity *via* the regulation of immunoactivation pathways	PCN-224	—	Hypotonic treatment or co-extrusion method	Immunotherapy	4T1 and dendritic cells	54
Neutrophils	• Ion-based tumour therapy • Efficient PDT	PCN-224	AgNPs	Hypotonic treatment or co-extrusion method	PDT and Ag-based therapy	Neutrophils	55
Erythrocyte membrane and macrophage	• Efficient enzyme delivery • Usefulness in enzyme therapy	ZIF-8	(GOx) and chloroperoxidase	Hypotonic treatment or co-extrusion method	Enzyme therapy	RBCs and macrophage	56
Cancer cell	• Efficient cell homologous recognition • Precise recognition	MIL-100	GOx	Hypotonic treatment or co-extrusion method	Ferroptosis and starvation treatment	4T1 cells	57
Cancer cell	• Desired tumour ablation • Synergistic therapy	ZIF-90	ICG and GOx	Hypotonic treatment or co-extrusion method	Photothermal–starvation therapy	4T1 cells	58

bloodstream, enhanced tumour accumulation and immune-evasive characteristics.[23] Erythrocyte-coated nanoparticles can resist macrophage clearance by exploiting their natural structure and surface proteins, such as CD47, which interacts with SIRP-α to impede phagocytosis. This allows for prolonged systemic circulation *via* enhanced permeability and retention (EPR) effect, which is crucial for tumour targeting.[24] In addition, the RBC coated NPs are biocompatible in nature and degrade with no formation of toxic by-products.[25] For instance, Han *et al*. demonstrated that nanoerythrosomes nanoparticles derived from RBC membranes can deliver tumor antigens (TAs) to the spleen, thereby enhancing cancer immunotherapy.[26] The distinctive characteristics of erythrocyte membranes enhance the targeted delivery of therapeutic agents while reducing unintended effects and immune responses. These membranes serve as a flexible platform for surface modification, enabling the addition of targeting ligands or other functional elements. Consequently, erythrocyte-derived biomimetic membranes represent a promising advancement in nanoparticle-based delivery systems, particularly for applications in cancer therapy, vaccine development, and various biomedical fields.[27] While RBC membranes themselves do not inherently target specific diseases, their biomimetic nature enable immune system evasion and enhanced pharmacokinetics, which support improved drug accumulation at tumour region. Furthermore, the membrane functionalized nanocarriers allows the attachment of targeting ligands like peptides or antibodies, allowing for the active targeting of cancer cells.

In cancer therapy, researchers have designed biomimetic MOFs for targeted and precise delivery of a drug. In a recent work, pH-responsive Zeolitic Imidazolate Framework-8 (ZIF-8) has been employed as a nanocarrier to develop biomimetic

MOFs specifically for colon cancer treatment. The study focuses on the development of ZIF-8 nanoparticles loaded with GOx and tirapazamine (TPZ) encased in erythrocyte membranes, which improve biocompatibility and lengthen systemic circulation time, resulting in better targeting efficacy against cancer cells. This technique is distinguished by its starvation-activated mechanism, in which nanoparticles are tailored to release therapeutic medicines only in reaction to the nutrient-deprived microenvironment found in tumour tissues. This tailored administration improves therapeutic efficacy while minimizing harm to healthy cells. These erythrocyte membrane-cloaked MOF nanoparticles behave as biomimetic nanoreactors, allowing for controlled drug release and presenting a promising technique for improving colon cancer treatment outcomes.[28]

A nanoscale copper-based MOF (Cu MOF) with a core of copper(II) was created to serve as an active centre for photodynamic treatment. To improve its functionality, the Cu MOF was coated with erythrocyte membrane and loaded with doxorubicin (DOX), which extended circulation time and prevented fast clearance. Erythrocyte membranes (EM) were mixed with CuMOF@DOX at a 1 : 2 ratio in phosphate-buffered saline (PBS), stirred for 2 hours, then centrifuged to isolate EM–CuMOF@DOX. This coating technique takes use of the CD47 glycoprotein found in erythrocyte membranes, which prevents phagocytosis *via* the reticuloendothelial system (RES). The major goal was to increase the circulation duration and pharmacokinetic parameters of the coated nanomaterials, emphasizing their potential as biocompatible drug delivery systems with improved therapeutic activity.[29]

2.2. Platelet membrane-coated MOFs

Platelets, obtained from megakaryocytes, are anucleate cells with a lifetime of 7–11 days and lower immunogenicity compared to WBCs.[30] They play a critical role in targeting vascular damage caused by various factors, including infections, angiocardiography, malignancies, and tumour progression. Additionally, platelets contribute to promoting tumour growth, invasion, and metastasis.[31] Platelet membranes have attracted attention as biomimetic nanoparticle coatings due to their distinct biological features, such as their inherent ability to escape immune detection and their significance in vascular functions. They target and adhere to damaged areas of the vasculature, evade macrophage phagocytic uptake, and exhibit increased adherence to platelet-adhering pathogens.[32] This immune evasion is primarily attributed to the presence of CD47 on platelet surfaces, which acts as a "don't eat me" signal to macrophages, thereby preventing phagocytosis and enabling prolonged systemic circulation of platelet-coated nanoparticles.[33] Platelet membrane-coated nanoplatforms can imitate the natural activity of platelets by leveraging their surface proteins and receptors, such as CD47 and integrins, thereby increasing biocompatibility and prolonging systemic circulation. These membranes also allow for targeted administration, particularly to regions of vascular injury, inflammation, or malignancies, by binding to specific indicators such as P-selectin or exposed collagen. Furthermore, platelet-coated nanoparticles have the potential to combine therapeutic delivery with thrombus targeting and immune regulation. The positive aspects of this biomimetic strategy have demonstrated its applicability in phototherapeutic and diagnostic applications, as well as in the prevention and treatment of a number of diseases, including cancer, immunological disorders, and heart conditions.[34]

Zhuang *et al.* created a novel biomimetic technique for the targeted siRNA delivery using nanoparticles based on ZIF-8 MOFs. The human platelet membranes used to coat the ZIF-8 MOFs were obtained from platelet-rich plasma from O+ blood donors. After undergoing a freeze–thaw process, the platelet membranes were suspended in water. Equal amounts of MOF or MOF-siRNA nanoparticles were then added to the membrane solution and incubated for 0.5 h. The mixture was extruded sequentially to ensure uniform coating, and then centrifuged to isolate the coated nanoparticles, which were resuspended in water for further usage. Furthermore, platelet-derived cell membranes for coating applications were created by extruding platelet membranes through porous membranes.[35]

A new nanoplatform of magnetic MOF has been developed, coated with a platelet membrane, for the synergistic administration of oxymatrine along with astragaloside IV. This formulation works as a combination programmed cell death protein 1 (PD-1) inhibitor, specifically targeting hepatic cancer. Platelet membranes were extracted from C57BL/6 mouse blood using a kit in the presence of 1.5 g L^{-1} EDTA-2Na, then frozen and thawed repeatedly to obtain the platelet membrane. To create the PmMN@Om&As nanoparticles, the platelet membrane was combined with magnetic nanoparticles loaded with oxymatrine and astragaloside IV at a weight ratio of 1 : 2. The mixture was then sonicated on ice at 200 watts for 10 minutes and collected using a magnet. This novel nanoformulation illustrates a personalized strategy to the simultaneous delivery of therapeutic drugs, with substantial potential efficacy as a PD-1 inhibitor towards HCC.[36]

2.3. Immune cell membrane MOFs

An inventive approach in nanomedicine is immune cell membrane coating, which entails functionalizing nanoparticles with membranes from immune cells like macrophages, or dendritic cells. This biomimetic approach imparts nanocarriers with the native surface proteins and receptors of immune cells, enabling immune evasion, prolonged circulation, and enhanced targeting to diseased tissues. By replicating immune cell functions, these coatings improve interaction with the biological environment, supporting precise delivery and better therapeutic outcomes.

2.3.1. Macrophage membrane-coated MOFs. Macrophage membranes have emerged as a viable biomimetic coating for nanoparticles, with distinct advantages in drug delivery and immunotherapy. These membranes contain essential functional proteins and receptors, such as CD47 and pattern recognition receptors (PRRs), which enable immune evasion and

active targeting of inflammatory or sick areas. Membrane-coated nanoparticles can navigate the immune system without triggering phagocytosis, permitting them to circulate for prolonged duration. Because of their propensity for aberrant microenvironments and pathogen-associated molecular patterns, macrophage membranes can also target locations of inflammation, malignancies, and infections. The integration of macrophage membranes into nanoparticle formulations improves biocompatibility, decreases immunogenicity, and enables site-specific administration, making them a useful tool for cancer therapy, antimicrobial therapies, and immunological modulation.[37] In a recent study, macrophage-membrane-functionalized MOFs were employed as a therapeutic platform to treat triple-negative breast cancer. It combines atorvastatin and polydatin into the biomimetic MOF of ZIF-8, revealing the ability to modulate glucose metabolism. The synthesis procedure involves sonication for optimal mixing, resulting in a complex nanostructure with anticancer activity.[38] Ling and team fabricated a biomimetic nanoplatform of pH-responsive MOF of ZIF-8 for chemodynamic therapy of cancer based on Fenton reaction. ZIF-8 containing Fe^{2+} core shell was coated with macrophage membrane which imparted high stability under physiological microenvironment. The membrane ZIF-8 particles exhibited efficient cancer cell uptake and better antitumour activity on animal models.[39]

2.3.2. Dendritic cell membrane-coated MOFs. Dendritic cell (DCs) membranes have developed as a new biomimetic coating for nanoparticle formulations, taking advantage of their role as powerful antigen-presenting cells in the immune system. These membranes contain functional proteins, including as major histocompatibility complex (MHC) molecules and co-stimulatory signals, allowing them to interact with T cells and influence immunological responses. Dendritic cell membranes, when utilized to cover nanoparticles, improve biocompatibility, allow for immune evasion, and give tailored distribution to lymphoid tissues or immunological locations. Furthermore, these biomimetic membranes can be modified to display tumour-associated antigens, transforming nanoparticles into tailored cancer vaccines with improved immune recognition and anti-tumour action. This method shows promise for cancer immunotherapy, vaccine administration, and other applications that need precise immune system control.[40] Recent research introduced an innovative approach to the production of tumour vaccines. This approach makes use of physiologically modified membranes derived from a combination of DC and tumour cells. The method began with the addition of MOFs to a dispersion comprising fused cell membranes in comparable ratios. The nanoparticles were subsequently purified using centrifugation, which removed any unbound cell membranes. This groundbreaking strategy has showed tremendous promise in the realm of cancer immunotherapy, revealing a possible new pathway for vaccine production.[41]

2.3.3. Neutrophil membrane-coated MOFs. Neutrophil cell membranes are increasingly being used in nanoparticle formulations to generate biomimetic membranes with improved medication delivery and targeting capabilities. These neutrophil membrane-coated nanoparticles (NNPs) take advantage of neutrophils' inherent features, such as their capacity to transit the immune system and target inflamed tissues, thereby increasing the therapeutic efficacy of encapsulated medicines. The inclusion of neutrophil membranes improves cellular internalization and increases bloodstream circulation time, both of which are crucial for effective cancer and inflammatory disease treatments.[42] This technique improves nanoparticles' therapeutic potential in cancer therapy, anti-inflammatory therapies, and infectious disease management by increasing biocompatibility, prolonging circulation, and precisely targeting sick tissues.[43]

In a study aimed at targeted inflammation therapy, researchers generated hypochlorous acid (HClO) to combat tumours and infections by incorporating two enzymes such as GOx and chloroperoxidase (CPO), within a ZIF-8 framework. Following this, a biomimetic modification was performed by encapsulating a natural neutrophil membrane (NM) onto the surface of the GOx/CPO-incorporated ZIF-8, resulting in a composite referred to as GCZ. The neutrophil cell membrane was isolated by extracting its intracellular contents and was then combined with an equal amount of GCZ. This mixture underwent coextrusion, leading to the formation of structures that mimic neutrophils.[44]

2.4. Cancer cell membrane-functionalized MOFs

Cancer cell membrane-coated nanoparticles (CCM-NPs) are a new biomimetic approach that aims to improve the therapeutic and diagnostic capabilities of nanomedicines. By encasing nanoparticles in cancer cell membranes, these systems acquire the functional surface proteins and antigens of their parent cells, allowing for enhanced biomimicry. This coating aids immune evasion by mimicking host cells, increasing circulation time, and minimizing premature immune clearance. Furthermore, CCM-NPs have homologous targeting properties, which means they preferentially bind to cancer cells of the same type by utilizing natural cell–cell adhesion pathways. This homotypic targeting improves therapeutic delivery specificity, reduces off-target effects, and boosts therapeutic index. Additionally, CCM-NPs are adaptable platforms for combining chemotherapy, photothermal treatment, and immune regulation. As a result, they have shown promise in preclinical tests for treating a variety of malignancies, as well as imaging and diagnostic applications. Despite these benefits, obstacles persist, including as scalable production, batch-to-batch variability, and regulatory barriers to clinical translation.[45]

Yang *et al.* have prepared a novel biomimetic formulation that utilizes ZIF-8 functionalized with cell membranes of human bone marrow mesenchymal stem cells. This innovative design facilitates the targeted delivery of "biological bombs", specifically herpes simplex virus type I thymidine kinase-encoded plasmids and ganciclovir, aimed at treating lung tumour. The nanoparticles incorporated with these biological agents effectively destroy transfected tumour cells and adjacent tumour cells *via* a phenomenon known as the "bystander

effect", showcasing significant lung tumour destruction. Additionally, these biomimetic NPs are characterized by prolonged circulation times, improved tumour accumulation, and notable tumour inhibition. This research represents a straightforward and effective method for delivering biological bombs *via* biomimetic MOFs, marking the first instance of this approach being applied to lung cancer therapy.[46] In a similar study by Shi-Yang and team developed porphyrinic-based MOF of PCN-224 loaded with TPZ and functionalized with CCM for the targeted therapy of tumour management. Following injection, the nanoformulation showed precise localization and prolonged retention at cancer region because of immune evasion and homologous targeting provided by the CCM functionalization. NIR irradiation of the nanoformulation causes a PCN-mediated ROS production for PDT activity, which in turn led to the TPZ activation accompanied with local hypoxic environment and resulted in improved tumour ablation. The study found that using this bioinspired technique for cancer targeting PDT was far superior, providing new insights into precise and successful cancer therapy.[47] Although CCMs may retain oncogenic proteins and adhesion molecules, their accumulation is predominantly localized to tumor sites due to targeted delivery, minimizing off-target interactions in healthy organs. Additionally, functionalization strategies and controlled payload release further reduce the risk of unwanted signaling. However, the presence of tumor-associated antigens on the membrane surface may elicit *in vivo* immune responses. To address these concerns, it is critical to carefully select the source cells, and conduct detailed *in vivo* studies to assess the safety, immunogenicity, and biodistribution of these biomimetic nanocarriers.[48–50]

3. Synthesis of biomimetic MOFs: cell membrane isolation and coating of vesicles with MOFs

The synthesis of biomimetic MOFs involves a dual-step process: first, cell membrane-derived vesicles are isolated and prepared, and later, MOFs are coated with these membranes. Cellular membranes, which are crucial for cellular physiology and environmental interactions, possess an asymmetric arrangement of phospholipids and diverse functional surface proteins.[59] A specific methodological approach enables the extraction of membranes from various cellular entities, such as RBCs, platelets, and cancer cells. For neutrophils, a subtype of leukocyte, a more intricate procedure involving hypotonic solution treatment, extrusion, and discontinuous sucrose gradient centrifugation is needed to eliminate intracellular biomacromolecules and the nucleus, yielding a purified neutrophil membrane suitable for analytical investigations.[60] Immune cells have surface markers such as adhesion molecules, antigens, and receptors crucial for cancer immunity. These biomarkers facilitate immune system recognition and responsiveness to cancer cells.[61] Hence, precise separation and extraction methods are needed to maintain the intrinsic properties of the cell membrane constituents. Cancer immunotherapy's commonly used membrane architecture is derived from immune cells, especially dendritic cells, macrophages, and neutrophils. Despite diverse and well-established extraction and separation methods for these immune cell membranes, the intricate processes involved in membrane coating have distinct advantages and limitations.[62] Fig. 1 provides a schematic illustration of different biomimetic membranes employed and their extraction procedures.

3.1. Isolation and preparation of membrane-derived vesicles

The process of isolating membrane vesicles involves several key steps. First, the cells were harvested and lysed, followed by ultracentrifugation. Supplementary nutrients are introduced into culture plates for scarce cells like cancer cells and mesenchymal stem cells. To obtain membrane vesicles, intracellular contents are extracted by subjecting the sample to freeze–thaw cycles or hypotonic treatment. Subsequent ultracentrifugation yields pellets that undergo washing until a colourless supernatant is obtained. The concentrated membrane pellet is homogenised, producing nonuniformly sized vesicles (1–2 μm). To achieve monodispersed vesicles (200–400 nm), the homogenised mixture is extruded using a mini extruder utilising a nanoscale polycarbonate membrane.[63]

The extraction of membranes from immune cells is a tedious procedure than that from anucleated cells, such as RBCs and platelets, primarily because of nuclei. In the case of anucleated cell membranes, the conventional approach involves freeze–thawing or hypotonic treatment, followed by differential centrifugation. This method aims to achieve efficient membrane purification by eliminating soluble proteins.[64] Moreover, extracting immune cell membranes requires a wide range of procedures. These include various lysis methods, including hypotonic treatment, mechanical disruption techniques and repeated freeze–thawing. The immune cell membranes are subsequently purified *via* ultrafiltration, discontinuous sucrose gradient centrifugation, or high-speed differential centrifugation to attain a pure state.[62] Maintaining a low-temperature environment during membrane extraction is crucial for preserving the original protein activity. Additionally, incorporating protease inhibitors throughout the extraction process is standard practice.

3.2. Coating of cell membranes onto MOFs for advanced functionalization

Various techniques are employed in cell membrane coating, including physical extrusion, coating through sonication, impregnation coating, microfluidic electroporation, incubation[37] and polymerization templated by the cell membrane. However, the existing coating techniques employed for MOFs are restricted to physical extrusion, sonication, and impregnation.

3.2.1. Extrusion coating method. Coextrusion is a mechanical process that propels a blend of nanocore and cell membranes through various porous polycarbonate membranes iteratively. This method facilitates membrane-core coating, producing a regenerative nanocore.[17] The quantification of

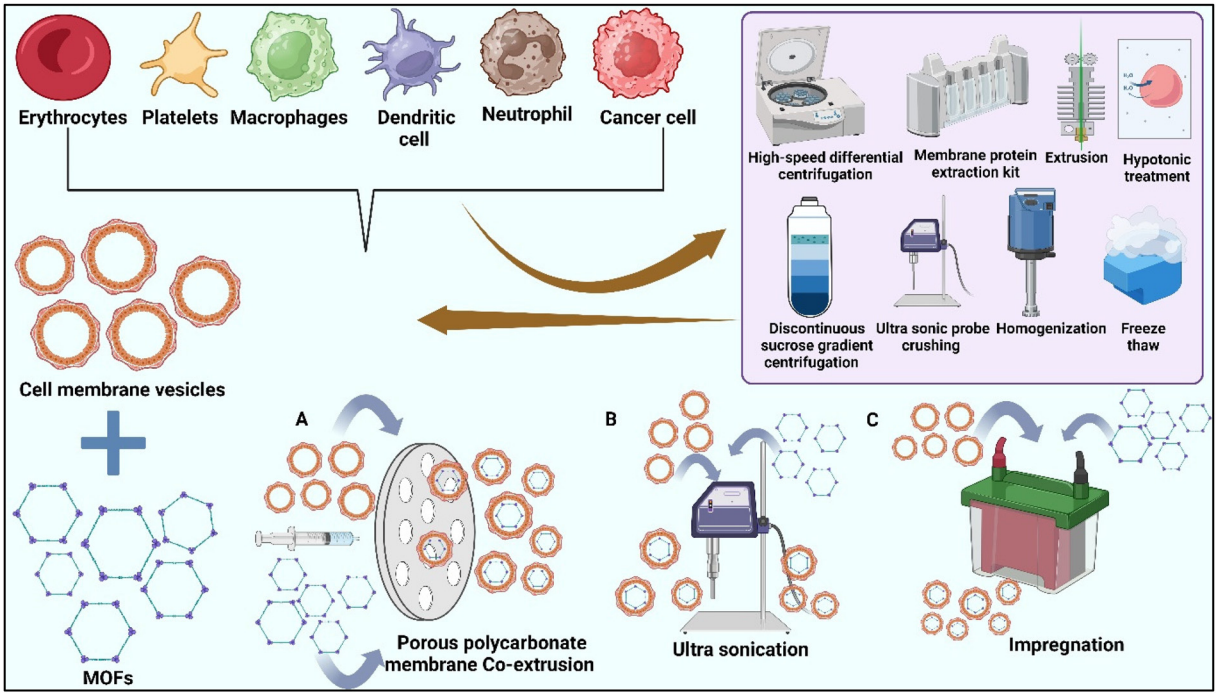

Fig. 1 Schematic illustration of different biomimetic membranes employed and their extraction procedures.

extracted cell membranes typically involves the utilisation of a bicinchoninic acid protein kit or applying freeze-drying and weighing methods. Following quantification, the cellular membrane and nanoscopic core are combined in predetermined proportions and subjected to multiple extrusions. Excess vesicles are separated through either centrifugation or ultrafiltration *via* membrane tubes for interception, resulting in a precipitate that serves as the final product. This innovative process holds promise for the controlled development of bionic nanocores, highlighting their potential applications in various scientific domains. The utilisation of rigorous quantification methods ensures accuracy in the composition of the final product, contributing to the reproducibility and reliability of the coextrusion technique.[65] The core principle of coextrusion revolves around the mechanical disruption of the membrane structure, which promotes interfacial contact between the membrane surface and the cell's core and leads to the formation of a core–shell structure.[66,67] Despite its practical utility, coextrusion presents inherent limitations, notably in time consumption, posing significant challenges for large-scale preparation. Additionally, the process mandates specialised extruder equipment, and there is a consequential loss of raw material during the extrusion procedure.

3.2.2. Sonication coating method. The incorporation of sound energy disrupts the nanocore of the cell membrane, ultimately causing the creation of a core–shell structure characterised by effective encapsulation.[68] Typically, two solutions are combined at a designated weight ratio of membrane-to-core and then subjected to sonication either in a bath or probe sonicator under ice-cold environments for a predetermined duration.[69] The selection of the sonication instrument, duration, and power is contingent upon the specific characteristics of the cell membrane and core. The optimisation of these parameters is essential for enhancing coating efficiency while minimising protein denaturation and drug leakage.[70] Ultrasonic coating yields effects similar to physical extrusion but with a diminished waste rate of raw materials. This approach enables the deposition of multiple layers of the cell membrane, consolidating functionalities from various cells into a singular core.[71]

3.2.3. Impregnation coating method. The membrane and nanocore coating process involves dispersing membranes and nanocores in ultrapure water or phosphate-buffered saline (PBS) at a specific mass ratio. The mixture will be subjected to agitation for a predetermined duration, facilitating the membrane's stepwise adsorption onto the nanomaterial's external surface. Upon reaching impregnation equilibrium, centrifugation is applied to eliminate the supernatant, creating biomimetic nanomaterials. This method is recognised for its operational simplicity, as it does not necessitate specialised equipment. Additionally, it involves gentle treatment of the cell membrane, thereby minimising the risk of protein denaturation or drug leakage.[72]

4. Biomedical applications

Biomimetic MOFs hold promising benefits in the field of cancer theranostics. This section details many of such applications against cancer. Fig. 2 gives an overview of the application of biomimetic MOFs.

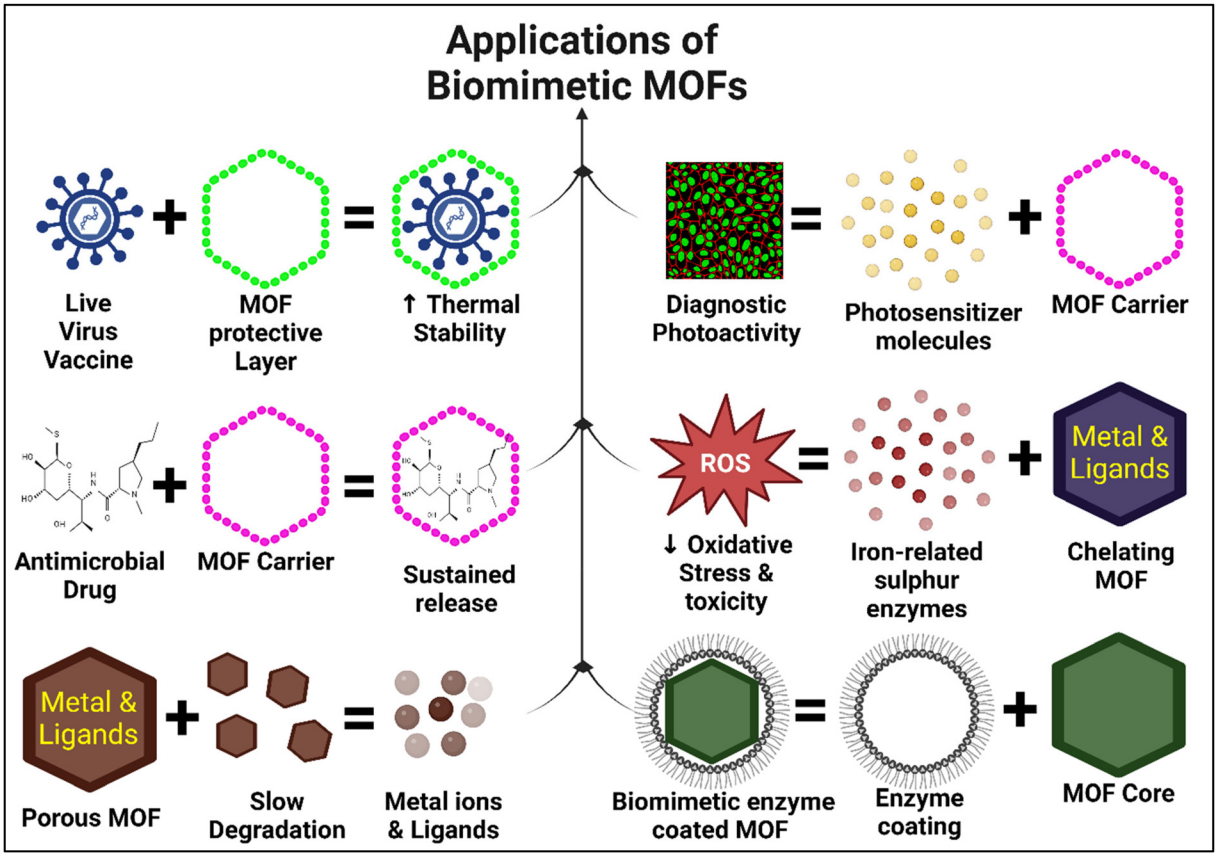

Fig. 2 Applications of biomimetic MOFs.

4.1. Phototherapy

Light has historically held great promise as an energy source across multiple disciplines and has recently garnered attention from researchers for its significant application in tumour therapy. MOFs are utilised in cancer phototherapy, which includes photothermal therapy (PTT) and photodynamic therapy (PDT). PTT aims to induce cell death by converting light into heat, whereas in PDT, light is converted into free radicals.[73,74] Numerous methodologies have been employed to fabricate photo-responsive MOFs suitable for phototherapy. Different techniques are utilised to develop photo-responsive MOFs, including microwave-assisted, solvothermal, electrochemical, sono-chemical, and mechanochemical synthesis. The operation of photo-responsive MOFs involves subjecting them to NIR light exposure at a definite wavelength. When electrons in MOFs receive photon energy, they are stimulated from the singlet to excited state. It then discharges energy to revert to its singlet state. This energy is either converted to heat due to its photothermal conversion efficiency (PCE) or discharged as fluorescent photons, which can be utilized in bioimaging processes.[75,76]

The role of biomimetic MOFs as both PTT and PDT platforms in cancer therapy has been explored in several studies. A few of those studies are discussed in this section. A study[77] presented a versatile erastin-loaded Fe–MOF coated with PDA and decorated with an osteosarcoma membrane against osteosarcoma. This study enabled the amalgamation of NIR-aided, programmed death, and osteosarcoma targeting. Fe results in an iron-rich milieu, whereas erastin is a ferroptosis inducing agent. The therapeutic effectiveness of the platform was proved in mice induced with osteosarcoma *via* allograft models. In another study,[78] a DOX-loaded Fe–MOF was developed. Graphene oxide (GO) was coated on the MOF *via* electrostatic interactions to enable GSH-responsive fluorescence imaging. Furthermore, it was coated with a folate-modified EM to create a biomimetic nanoplatform. FA–EM camouflaged the elimination of mononuclear phagocytes and enhanced target binding with tumour cells by overexpressing folate receptors. Additionally, the Fe ions of MOF exhibited horseradish peroxidase-mimicking activity, decomposing intracellular H_2O_2 to lessen tumour hypoxia and improve PDT activities while also serving as an MRI contrast agent for real-time monitoring throughout tumour treatment duration.

PDT creates ROS using photosensitiser and light, effectively eradicating cancer cells.[79] However, PDT has several limitations, including its limited ability to penetrate deep into tissues, insufficient specificity for targeting tumours, and dependence on oxygen.[80] Scientists are currently exploring its potential with chemotherapy, radiation treatment, immu-

notherapy, and other therapeutic approaches.[80] One such strategy to address the limitations of PDT is to modify the conditions in which the tumour grows to improve the effectiveness of treatment. Focusing on this solution, a research team[81] developed a porphyrinic MOF (PCN-224) that contained TPZ and was coated with a 4T1 cell membrane (TPZ@PCN@Mem). This nanoplatform targeted tumours specifically, facilitated PDT and enhanced bioreductive therapy through hypoxia. After injection, TPZ@PCN@Mem showed targeted binding and prolonged accumulation in tumour tissue due to the 4T1 coating. This coating allowed for immune evasion and precise binding. PCN-224 induced the generation of ROS when exposed to light, which was subsequently utilised for PDT. This mechanism also generates a specific area with low oxygen levels, known as a localised hypoxic microenvironment, which further enhances the activation of TPZ. This activation resulted in enhanced chemotherapy effectiveness in 4T1 orthotopic tumours. Generally, the 4T1 cell membrane coating facilitates homotypic targeting *via* membrane protein-mediated recognition, improving the nanoparticle accumulation in the tumour tissue.[82]

Glutathione (GSH) is an antioxidant enzyme that neutralises the ROS generated during PDT and, in addition, leads to a proangiogenic tumour response. To address this challenge, a research team[83] developed a PCN-224 MOF loaded with apatinib, coated it with MnO_2 and decorated it with a 4T1 membrane. The porphyrinic MOF served dual purposes, acting as a drug carrier and as a photosensitiser for PDT. Elevated levels of intratumoural GSH are associated with the scavenging ability of MnO_2 and apatinib, which endows the MOF with antiangiogenic properties. This combination successfully inhibited the new blood vessel formation following PDT treatment, and the nanosystem demonstrated remarkable tumour-targeting ability and therapeutic efficacy.

4.2. Chemotherapy

Chemotherapy is a crucial component of cancer treatment, as it employs potent therapeutic medications to target and eradicate cancer cells. Chemotherapy can be used as a main intervention to reduce the size of tumours before surgery, as an adjuvant treatment to eliminate any residual tumour cells followed by surgery.[84–86] However, chemotherapy has several limitations, including off-target effects that affect normal cells and tissues. By harnessing nanotechnology, scientists have greatly improved the efficacy of chemotherapy, leading to the approval of several nanodrugs, such as DOXIL and Abraxane.[87] Although nanodrugs have made progress in specifically targeting tumour tissue through the improved permeability and retention (EPR) outcome, they still face hurdles in delivering drugs effectively into solid tumours. The atypical extracellular matrix (ECM) around cancer cells impedes the intratumoural dispersion of nano drugs. To address this problem, a biomimetic nanoplatform was specifically engineered in a study[88] to control the activity of transforming growth factor-beta to restore the normal function of the ECM. ZIF-8–DOX–LY NPs were formed by effectively loading the chemotherapeutic medication DOX and the TGFBR1 inhibitor LY364947 (LY) into ZIF-8 *via in situ* encapsulation. To improve the ability of nanoparticles to target tumours and circulate effectively in the body, an RBC membrane coating was applied. ZIF-8–DOX–LY–RM could release LY within the tumour microenvironment, thereby efficiently disrupting the ECM (Fig. 3). These effects enhanced the infiltration of nanodrugs and reduced the resistance to chemotherapy caused by hypoxia. The efficacy of MOF-based formulation was demonstrated through *in vivo* investigations performed in 4T1 tumour models. This approach shows promise for enhancing the effectiveness of chemotherapy in solid tumours.

A biomimetic cascade nanoreactor was designed by another team[89] with precisely controlled drug release and activation to pursue precision tumour therapy. This nanoreactor, Mem@GOx@ZIF-8@BDOX, was specifically designed for tumour-targeted starvation therapy-amplified chemotherapy. The assembly process entailed combining a tumour cell membrane cloaked with glucose oxidase (GOx) on ZIF-8, which contains the prodrug H_2O_2-sensitive BDOX. The use of a biomimetic membrane enhanced the ability of the nanoreactor to evade the immune system and adhere to similar cells, resulting in a considerable increase in the accumulation and uptake of drugs in tumours for targeted administration. In summary, integrating biomimetic techniques into MOFs has significant potential in enhancing the efficacy of chemotherapy. Owing to its efficacy in *in vitro* and *in vivo* studies, this innovative methodology can revolutionize the field of tumour therapy by furnishing a more refined and efficient method for personalized chemotherapy.

4.3. Starvation therapy

Starvation therapy in cancer is an emerging approach aimed at depriving cancer cells of nutrients to suppress tumour growth and survival.[90] This method involves various strategies, such as blocking the blood supply, depleting critical nutrients, and inhibiting the metabolic processes of cancer cells. Research has focused on interventions targeting tumour angiogenesis, metabolic pathways, and nanomedicine to achieve synergistic effects with other cancer treatments. Studies have also highlighted the possibility of combining starvation therapy with other therapeutic approaches to maximise therapeutic efficiency.

As cancer cells undergo faster metabolism and proliferation than normal cells do, tumour cells are sensitive to differences in glucose concentration. GOx-based starvation therapy has gained widespread attention because of its unique ability to convert glucose to gluconic acid and H_2O_2 *via* reactions with oxygen. The formation of gluconic acid can decrease the pH of the tumour microenvironment to increase its acidity, increasing the release of pH-sensitive chemotherapeutics. The production of H_2O_2 enhances oxidative stress, which can lead to cellular apoptosis. All these advantages of starvation therapy are being combined and used by researchers in combating cancer therapy. Shao *et al.*[91] introduced the concept of a ZIF8-based biomimetic nanoreactor for synergistic starvation

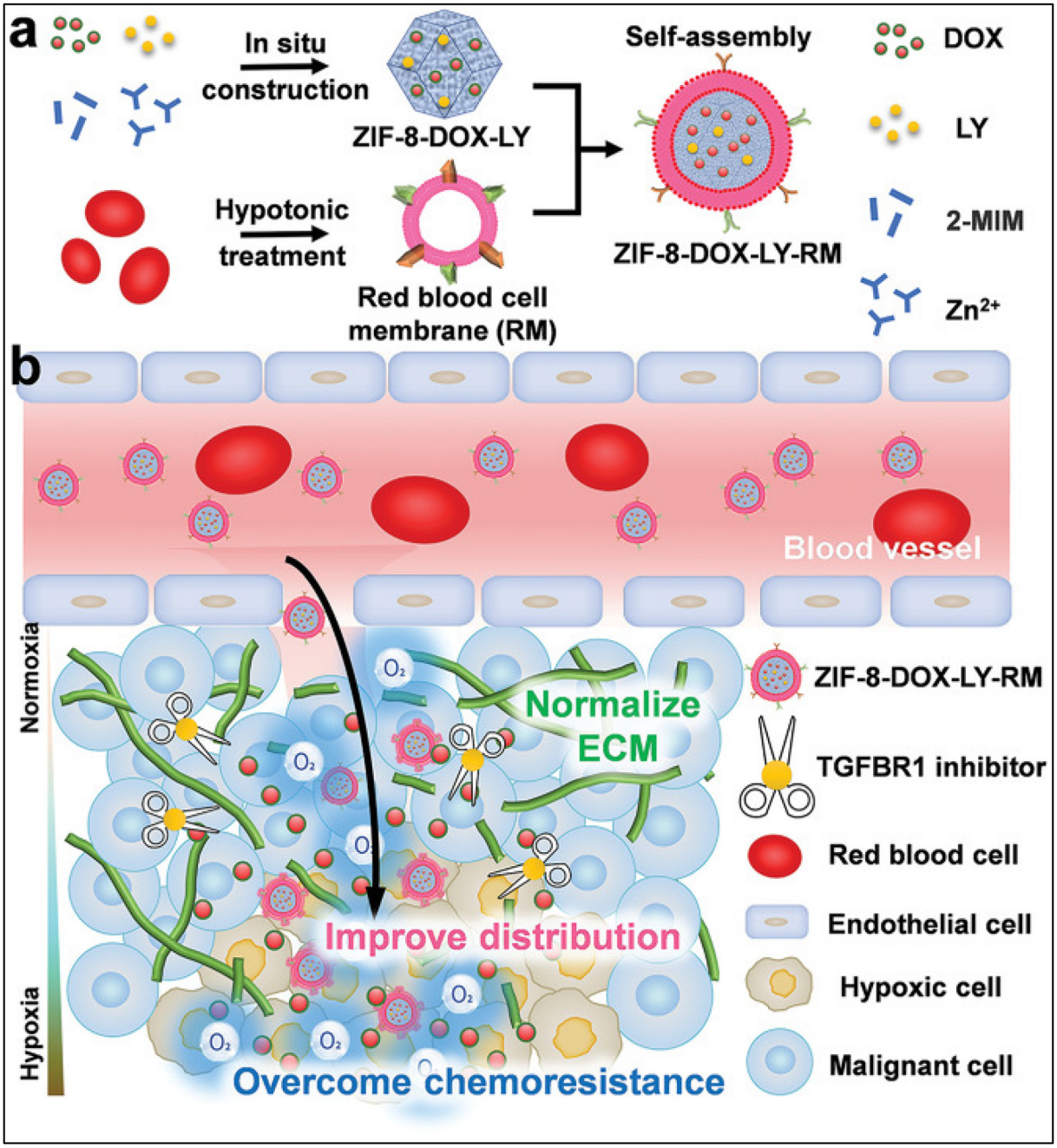

Fig. 3 Overcoming chemotherapeutic resistance using biomimetic MOFs. (a) Synthesis of ZIF-8–DOX–LY–RM NPs and (b) pictorial representation demonstrating the release and therapeutic efficacy of DOX by ZIF-8–DOX–LY–RM NPs. Reproduced with permission from ref. 88.

therapy of cancer. The ZIF-8 MOF was successfully loaded with the hypoxia-activated drug banoxantrone and camouflaged with a cancer cell membrane to produce a biomimetic nanocarrier (Fig. 4). Once the nanoreactor was attached to the tumour cells, ZIF-8 decomposed in the acidic microenvironment, releasing GOx and banoxantrone. Furthermore, the increased intracellular hypoxia within the tumour activated the cytotoxic effects of banoxantrone for cancer treatment. Combining starvation treatment with cascade-amplified hypoxia-activated chemotherapy substantially suppressed cancer development and enhanced therapeutic activity.

In a similar study by Zhang *et al.*,[92] erythrocyte-camouflaged ZIF-8-based biomimetic nanocarriers loaded with GOx and a prodrug, TPZ, were designed for starvation-induced colon tumour treatment. On the basis of the biomimetic attributes of EMs, the nanoreactor displays efficient accumulation within tumour tissues, immune-escaping capabilities and enhanced systemic circulation. GOx efficiently uses natural

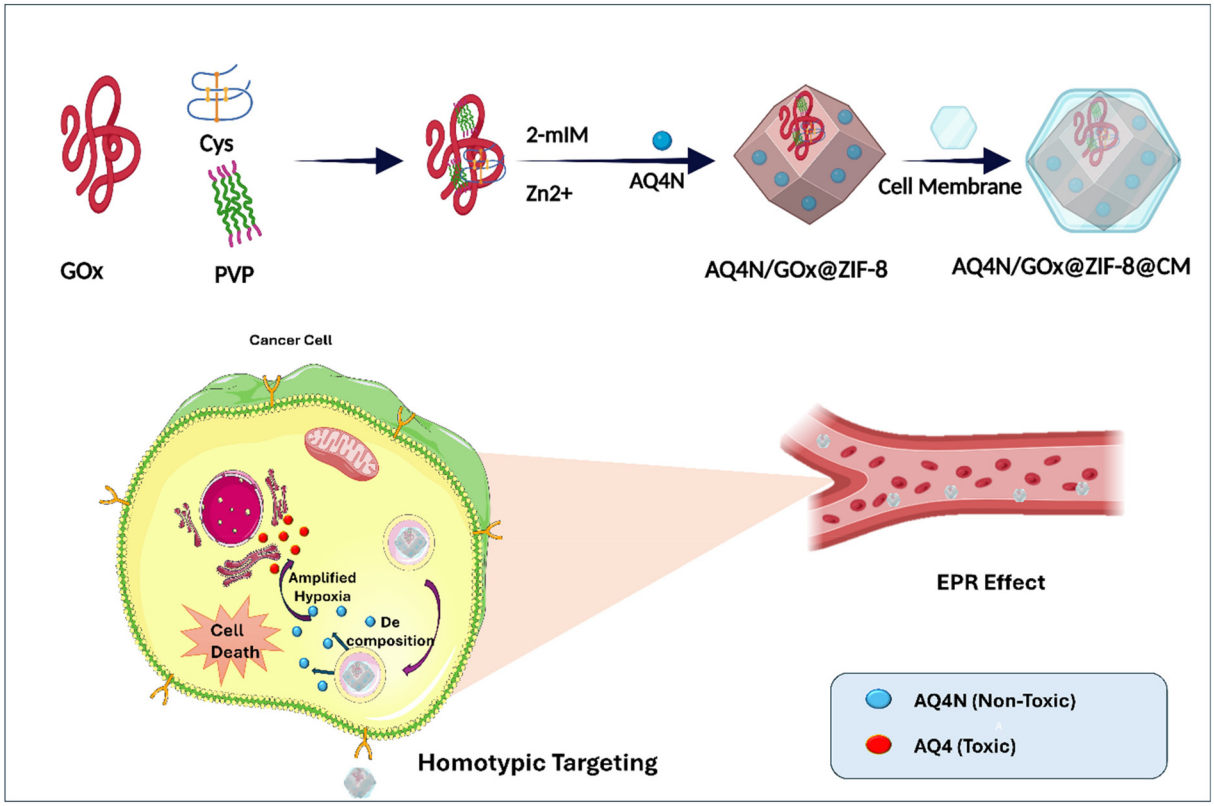

Fig. 4 Preparation of biomimetic MOF for starvation therapy.

glucose and O_2 to starve cancer cells. Moreover, the nanoreactor-induced enhancement of the hypoxic microenvironment within tumours aided in the transformation of the prodrug TPZ. When the drug is released in an acidic lyso-/endosome milieu, it is transformed into a highly cytotoxic radical, which further promotes cell death. *In vivo* evaluations of BALB/c mice revealed a tumour inhibition rate of 97.6% after intravenous administration, indicating the most satisfactory therapeutic activity. This approach had a strong synergistic outcome, which has beneficially influenced the overall effectiveness of the treatment. Liu and coworkers prepared a combination of tumour starvation/ROS-based/chemotherapy with GOx and camptothecin loaded onto a Fe-based MOF.[93] The tumour acidic microenvironment of tumours, aided by the produced gluconic acid, dissolves the MOF(Fe), releasing camptothecin for chemotherapy and Fe^{3+} and converting H_2O_2 into ROS, allowing ROS-facilitated cancer therapy. The *in vitro* and *in vivo* data indicate trimodal synergistic antitumour activity.

4.4. Immunotherapy

Since the latter part of the twentieth century, advances in chemotherapy and radiation therapy have been beneficial for the efficient treatment of a broad area of tumour types. These therapeutic strategies, however, have mostly achieved their full potential, necessitating the development of innovative and more efficient approaches to improve therapeutic results.[94] Recently, cancer immunotherapy has developed as an important approach for the successful management of a number of tumours.[95] The immune system is a complex network of components capable of identifying and reacting to invading infections, including lymphoid organs and cytokines. Nevertheless, the battle to combat cancer is complicated since tumour cells have been shown to use a variety of immune tolerance mechanisms. Tumours create an immuno-suppressive microenvironment by including T regulatory cells or suppressive myeloid cells, surpassing detection by the immune system.[96]

Epigenetic alteration-based antigenicity for lowering leukemic blasts is a major immune escape mechanism during T-cell-mediated immunotherapy. Song *et al.*[97] fabricated a Mn^{2+}/Fe^{3+}-based bimetallic MOF nanoformulation (AFMMB) containing a DNA hypomethylating agent, an azido-labelled stem cell membrane from leukaemia, and a Beclin-1 peptide. Cellular uptake studies demonstrated better uptake of the membrane-coated nanoformulation, indicating its precise ability to target leukemic blasts. The developed nanoformulation exhibited significant anticancer activity even at a low concentration of 50 μg mL^{-1}, achieving a tumor growth inhibition rate of 67.6%, which was notably higher than that observed with the free drug azacitidine (31.7%). Furthermore, administration of AFMMB at a dose of 100 μg mL^{-1} resulted in almost complete tumor elimination, with 100% of the treated mice surviving for 60 days post-injection, indicating robust *in vivo* efficacy in the animal model.

Ni and coworkers[98] developed biomimetic hafnium-based MOFs for bimodal radiotherapy and immunotherapy.

Conjugation of an immune checkpoint inhibitor called an anti-PD-L1 antibody allowed efficient tumour ablation and rejection of distant tumours *via* systemic antitumour immunity in an MC38 colorectal cancer model. In another study by Xu *et al.*,[99] a Mn MOF-based biomimetic nanoformulation was developed for efficient cancer immunotherapy. A polyphyllin I (PPI)-loaded Mn-based MOF was prepared *via* a facile single-step process followed by camouflaging with an RBC membrane. The combination of PPIs with the known STING agonist Mn^{2+} can address many issues, such as rapid metabolism, low biocompatibility, and reduced accumulation of Mn^{2+} and PPIs in the tumour *via* delivery systems. The nanosystem showed the desired biocompatibility, hydrophilicity, and biodegradability for improved cancer immunotherapy. Biomimetic nanoformulations, which are camouflaged as endogenous molecules, resist identification and clearance by the immune system after intravenous delivery to tumour-bearing animals. The nanoformulation assisted in the transformation of cold tumours to hot tumours by enhancing DC maturation and NK recruitment *via* the STING pathway.

Luo *et al.*[100] fabricated TPP-loaded porphyrin-conjugated Zr-based MOFs functionalized with a 4T1 cell membrane for mitochondrion-targeted R837 delivery for synergistic sonodynamic therapy and immunotherapy. This nanoplatform has the ability to overturn the immunosuppressive tumour microenvironment (TME), leading to improved antitumour activity. This efficiently suppressed the development of metastatic cancer and promoted the establishment of enduring antitumour memory responses. The blood–brain barrier (BBB) is a major hurdle to drug delivery into the brain. To address this, Wu *et al.*[101] developed a biomimetic MOF-based nanoformulation for the effective treatment of glioblastoma in a mouse model. They fabricated RVG_{15}-membrane-coated ZIF-8 MOF nanocarriers loaded with docetaxel. CLSM and flow cytometry were utilised to examine the BBB-penetrating characteristics of various NPs in C6 cells. The transport efficiency of the membrane-functionalized MOF was 3.16 times greater than that of the uncoated formulation. *In vitro* experiments revealed that this developed MOF-based nanoplatform system had great targeting effectiveness and biosafety in HBMECs and C6 cells, as well as improved potency in crossing the BBB. Moreover, the nanoformulations improved docetaxel brain accumulation, enabling deeper penetration into glioma tumour tissues. *In vivo* anticancer evaluation findings revealed that the nanoformulation effectively suppressed glioma tumour development and spread, increasing the survival of tumour-bearing mice.

4.5. Gene therapy

Gene therapy includes substituting an impaired gene with a functioning copy of the same gene and can be a more efficient cancer therapeutic option than chemotherapy, which sometimes lacks selectivity and can induce nonspecific side effects. Despite immense preclinical advances in terms of better targeting and cancer-specific expression, numerous barriers remain in terms of clinical success, including imprecise expression, delivery inefficiency, and biosafety concerns. Several new genetic approaches are being developed to recreate vectors/transgenes, making them safer and more effective.

Huang *et al.*[102] introduced a novel strategy that incorporates biomimetic concepts into the design of a nanoformulation for hepatocellular carcinoma therapy. Researchers created a delivery method inspired by natural biological processes that mimics the targeting mechanisms seen in nanoscale biological systems. The novel dual-targeting platform was fabricated by modifying MOF with a nuclear location sequence and coating it with an A54-loaded erythrocyte membrane. This biomimetic nano-delivery method was designed to enhance the distribution of medicinal drugs, such as cisplatin and NOR1 shRNA, to cancer cells and has the potential to increase therapeutic efficacy and lessen adverse effects (Fig. 5). These studies demonstrated the efficient internalization of the MOF-based biomimetic nanomedicine into tumour cells because of its ability to bind precisely to the A54 receptor present in hepatocellular cancer cells. While RBC membranes themselves do not inherently target specific diseases, the stealth nature of them allows the therapeutic payload to remain in circulation longer, and increasing the probability of passive tumor accumulation.[103]

Triple-negative breast cancer (TNBC) patients have an inadequate prognosis because of their limited response to chemotherapy, the absence of clinically approved targeted treatments, and rapid disease progression. Small interfering RNAs (siRNAs) can inhibit aerobic glycolysis, a reprogramming metabolic activity observed in tumour cells. The absence of suitable carriers to deliver susceptible siRNAs limits the therapeutic potential of glycolysis-mediated gene therapy for TNBC. In a recent research by Huang *et al.*,[104] a cancer-targeted biomimetic MnO_2-coated ZIF-8 MOF-based nanoplatform was developed for the delivery of siRNA to the siPKM2 enzyme for efficient inhibition of glycolysis in TNBC cells. RNase can degrade free siRNAs in tissues and bodily fluids. Genetic nanoplatforms play crucial roles in protecting against siRNA delivery. Research suggests that encapsulating fragile bioentities within ZIF-8 significantly increased their stability, preventing siPKM2 degradation by nucleases. The ZIF-8-based genetic nanoplatform effectively suppresses the glycolytic pathway and enhances intracellular hypoxia in TNBC cells, leading to O_2-mediated antitumour activity. These findings suggest that the MRI-visible ZIF-8 MOF-based nanoplatform can effectively cure TNBC by inhibiting glycolysis through RNA interference. In another investigation, Ma *et al.*[105] constructed a biomimetic pH-responsive MOF nanocarrier for the targeted delivery of a carbon nanodot-SOD nanozyme. In this complex system, carbon nanodots and the CD98 CRISPR/Cas9 plasmid were effectively integrated into the ZIF-8 MOF nanocarrier *via* a one-pot technique, followed by macrophage membrane camouflage. Notably, the C-dot nanozyme demonstrated high superoxide dismutase enzymatic activity, efficiently scavenging ROS. The biomimetic system displayed pH-responsive activity, immune evasion, and inflammatory targeting capabilities all at once. *In vitro* tests indicated substantial ROS removal, but CD98 expression was significantly decreased.

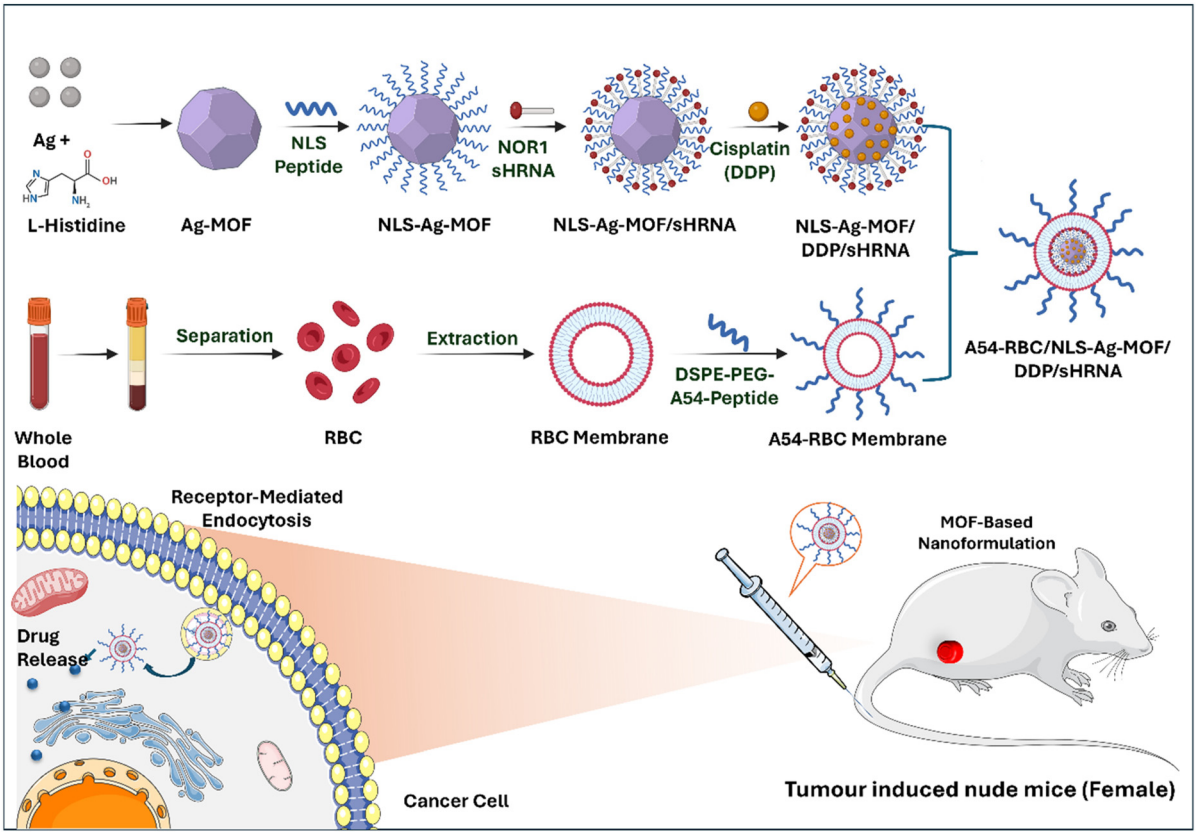

Fig. 5 Graphical illustration depicting the formulation of biomimetic MOF for immunotherapy of hepatocellular carcinoma.

4.6. Sonodynamic therapy

In last few years, sonodynamic therapy (SDT) has obtained substantial attention in cancer research as a promising noninvasive therapeutic approach because of its improved safety, accuracy, and non-invasiveness.[106] SDT combines oxygen, low-intensity ultrasound, and nontoxic sonosensitizers to produce ROS, which leads to tumour death through either apoptosis or pyroptosis.[107] When activated *via* sonoluminescence, the sonosensitive ligands in MOFs demonstrate a multitude of charge transfer mechanisms. However, their stability is compromised by ligand oxidation in an oxidizing environment. In addition, tumour hypoxia impedes the effectiveness of sonosensitizers. To maximize the applicability of MOFs as sonosensitizers, improving the efficacy of carrier separation and selecting them with superior potential are critical.[108] The research conducted by Yu *et al.*[109] focused on the subject in question. ZIF-8 was synthesized and used loaded with chlorin e6 (Ce6) and hydrophilic TPZ for combined treatment with sonodynamic chemotherapy. The therapeutic platform was also modified with the cytomembrane of gastric cancer (GC) cells, resulting in biomimetic features. Combining Ce6-mediated SDT with ultrasonic irradiation selectively induced the release of ROS, aggravated hypoxia and activated TPZ. The combination of these properties could trigger pyroptosis in GC cells, producing an antitumour effect. To evaluate the targeting ability, two different cytomembrane (AGS and 4T1 cell membrane)-coated nanosystems were compared. The cellular uptake was better in the nanosystem coated with AGS cells, which targeted the acidic tumour microenvironment to release chemotherapeutic drug. In addition, pharmacodynamic studies conducted on nude mice with AGS tumours revealed that the group treated with the AGS-modified nanosystem in combination with US irradiation not only suppressed tumour growth by achieving targeted delivery but also utilized TPZ to enhance the effect of SDT, thereby further improving the combination of chemotherapy and SDT. These findings could lead to a promising therapeutic approach for cancer treatment.

Recent research has revealed that parthenogenic anaerobic bacteria can selectively inhabit tumour tissues by exploiting their hypoxic microenvironment.[110] Similarly, bacterial outer membrane vesicles (OMVs) can target hypoxic environments *via* surface receptors, which provides a benefit over direct bacterial injection in that they prevent the development of bacteraemia.[111] Furthermore, the presence of pathogen-associated molecular patterns (OMVs) in bacterial OMVs has the potential to augment the immunogenic cell death (ICD) effect of SDT, thereby facilitating tumour immunotherapy. A method has been developed by Zhang *et al.*[112] to exploit these characteristics, whereby bacterial OMVs are modified with sonosensitizer-loaded MOFs. This research created a system for the targeted delivery of sonosensitizers to tumours *via* the use of

ZIF-8 NPs. First, Ce6 incorporated MOF (CMOF) was prepared and then surface modified with the OMVs of *E. coli* to develop OCMOF. The OCMOF nanoplatform demonstrated successful tumour targeting by integrating bacterial OMVs, thereby promoting immune responses inside the tumour microenvironment. The combination of SDT and immunotherapy shows great potential in triple-negative breast cancer therapy.

4.7. Ferroptosis

Ferroptosis, an emerging form of nontraditional programmed cell death (PCD), is caused by the lipid peroxidation products accumulation, which compromise the integrity and structure of the cell. Specific conventional chemotherapies, such as doxorubicin (DOX), are capable of inducing ICD.[113,114] A previous study[113] developed a DOX- and glucose oxidase (GOx)-loaded Fe-based MOF were rendered biomimetic by coating with a 4T1 cell membrane. By utilizing the interaction between Fe^{3+} and ligands containing disulfide, the nanosystem effectively eliminated glutathione (GSH) and suppressed the activity of glutathione peroxidase 4 (GPX4), ultimately triggering ferroptosis. GOx facilitates the conversion of glucose into H_2O_2, which in turn boosts the Fenton reaction and leads to an abundance of ROS within tumours. The surge of ROS simultaneously triggered ferroptosis while suppressing glycolysis. Through a synergistic effect of ferroptosis as well as DOX, the process of ICD is activated, leading to the release of tumour antigens and the initiation of a powerful antitumour immune response. This innovative nanoplatform thus combines tumour metabolism and immune regulation through the interplay of ROS, ferroptosis, and glycolysis, presenting a highly promising approach to combatting tumours.

In contrast to apoptosis, autophagy, and necroptosis, ferroptosis is an important therapeutic target for cancer treatment due to its dependence on intracellular ferrous iron and the activation of distinct pathways. Luo *et al.*[115] introduced a biomimetic Fe–MOF specifically engineered to treat non-small cell lung cancer. The study showed that A549 cell membrane-functionalized Fe–MOF ($mFe–MOF_{DOX}$) effectively stimulates the production of Fe^{2+} and the DOX release in the tumour acidic intracellular milieu. Through different *in vitro* and *in vivo* studies, it was found that these NPs substantially increased the generation of ROS, resulting in apoptosis induced by DOX and GPX4-mediated ferroptosis. Moreover, the A549 biomimetic coating enhanced the tumour-targeting ability in a xenograft mouse model. The concurrent implementation of chemotherapy-induced apoptosis and biomimetic nanoparticle-induced ferroptosis successfully impeded lung metastasis and tumour development. In another study,[116] the combination of a MOF (MIL-100), an anticancer molecule (methotrexate), a cancer cell membrane (JEG-3 cell membrane) and the concept of ferroptosis was used to overcome the challenges faced in the treatment of choriocarcinoma. The *in vitro* results in JEG-3 cells revealed that the nanoreactor could arrest the cell cycle at the G_0/G_1 stage and thus inhibit cell proliferation and migration. Additionally, the Fenton reaction induced by the Fe^{2+} ions led to the overproduction of hydroxyl radicals, resulting in chemodynamic therapy. Ferroptosis is triggered by lipid peroxidation, and redox dyshomeostasis is induced by GSH scavenging. Furthermore, the xenograft tumour model showed that the biomimetic nanoreactor could effectively target and accumulate at tumour sites, reducing and potentially inhibiting cancer.

4.8. Gas therapy

Owing to their environmentally friendly nature and minimal side effects, gas therapy, which utilizes gaseous molecules such as nitric oxide (NO), sulfur dioxide (SO_2), hydrogen sulfide (H_2S), carbon monoxide (CO), and carbon dioxide (CO_2), has emerged as a significant therapeutic approach for treating cancer, wounds, and inflammation.[117] NO is implicated in numerous physiological and pathological processes, particularly in cancer treatment, as a "star" signalling molecule. At concentrations exceeding 1 μM, NO induces the nitrosation of DNA and mitochondria and directly destroys cancerous cells.[118] Furthermore, NO enhances PDT and radiotherapy efficacy when used in conjunction. The potential of gas therapy was reported by a group of researchers,[119] by developing a biomimetic nanoplatform composed of a porphyrin MOF loaded with L-arginine (L-Arg; NO donor) and coated it with GOx with the aid of tannic acid (polyphenol). The biomimetic feature was rendered by decorating this nanosystem with a 4T1 cell membrane. The developed nanosystem initiated a cascade of reactions beginning with the oxidation of glucose triggered by GOx, followed by the generation of ROS from the MOF, ultimately leading to NO release (through the conversion of L-Arg to L-citrulline), which could efficiently inhibit cancer (Fig. 6). The synergistic therapy involves chemotherapy, gas therapy, and PDT. The authors demonstrated the potential of this nanosystem through different *in vitro* and *in vivo* studies in a 4T1-induced breast cancer model. A similar line of work was conducted by Jing *et al.*, who developed MOF nanosheets loaded with L-Arg and AuNPs. Similarly, the cascade reactions were expected. The only differentiating factor was that the AuNPs served as nanozymes to oxidize glucose into peroxide molecules. Although there are no biomimetic coatings to target cancer, the nanosheets accumulate in the tumour *via* an EPR effect, enhancing the therapeutic activity in a glioblastoma cancer model. Therefore, gas therapy can potentially be explored further by the scientific community for synergistic therapeutics against cancers.

4.9. Radiotherapy

Radiotherapy (RT) is a highly effective method for the treatment of tumours by irradiating tumour sites with high doses of ionizing rays, thereby destroying cancer cells and impeding tumour development.[120] Despite its ability to deeply penetrate and eliminate local cells, the therapeutic effectiveness of RT is limited in clinical settings because of its nonspecific lethality and requirement of high dose. Furthermore, the tumour microenvironment, which is characterized primarily by hypoxia, intensifies resistance to RT and contributes to resistance mechanisms. Using radiosensitizers that contain

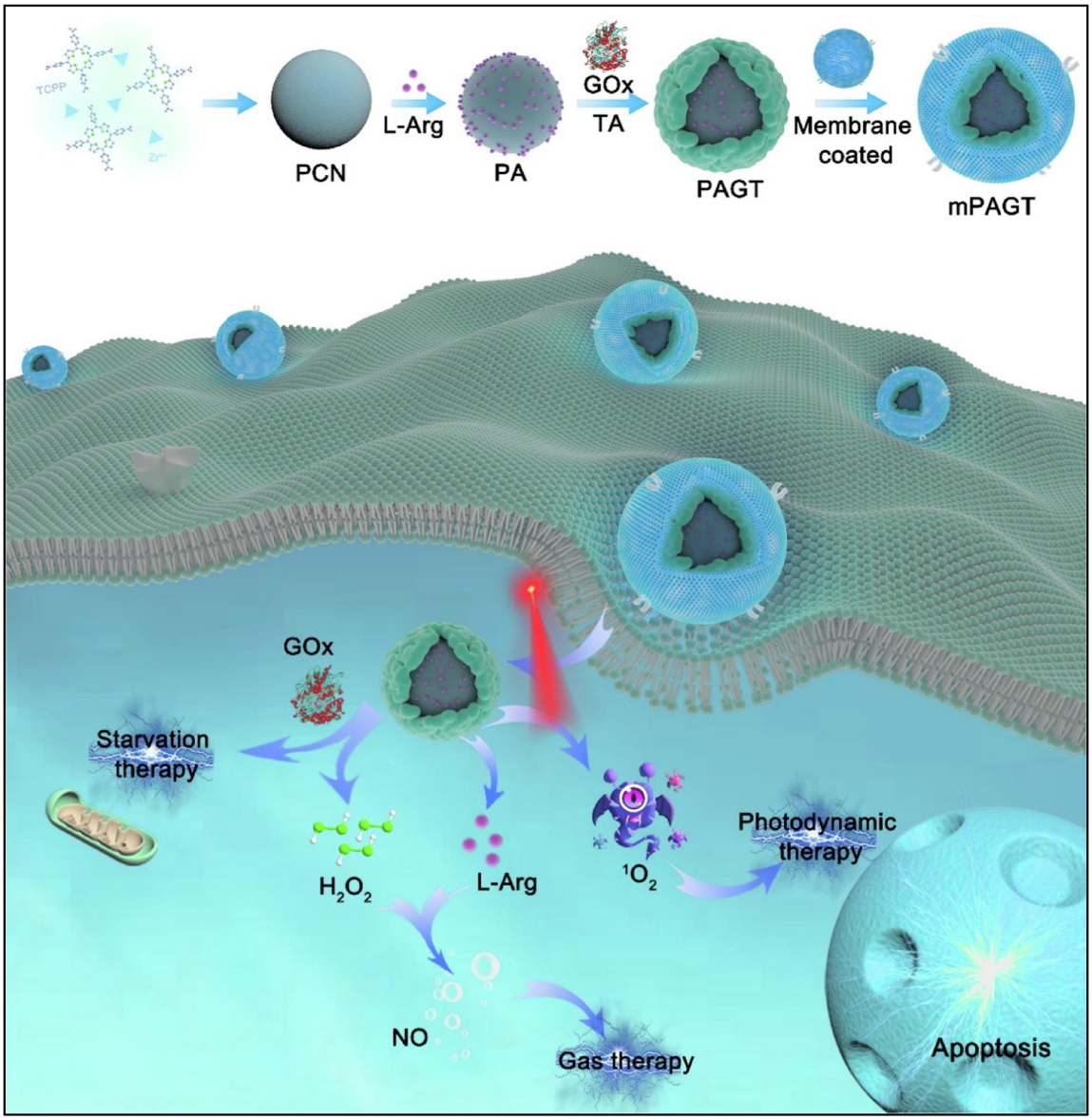

Fig. 6 Schematic illustration of the fabrication of a biomimetic MOF platform and its application in catalytic cascade-enhanced synergistic therapy. Reproduced with permission from ref. 119.

elements with high atomic numbers effectively increases the absorption of X-rays. This approach was reported[121] in a study in which UiO-66–NH_2 (Hf) was designed to be used as a radiosensitizer at RT. The NPs were sub 100 nm long and stable in a physiological environment. By enhancing X-ray absorption, the MOF could induce apoptosis in oesophageal cancer cells (KYSE 150) and a xenograft model without surface modifications. However, these studies did not explore the utilization of biomimetic approaches. In contrast, another study[122] introduced porphyrin–Fe bridging ligands as biomimetic oxygen generators into MOFs to address the issue of hypoxia and achieve extremely efficient RT. The porphyrin–Fe centers act as catalysts for peroxide breakdown, producing O_2 and hydroxyl radicals. The generated oxygen helps relieve hypoxia, enabling radiodynamic therapy when exposed to X-ray radiation, while the hydroxyl radicals cause direct harm to cancer cells, promoting CDT. Hf–DBP–Fe facilitates targeted therapy for hypoxic malignancies *via* low-dose X-ray radiation, resulting in the development of highly immunogenic tumour microenvironments. This combination of anti-PD-L1 immune checkpoint blockade not only eliminates the main tumours but also reduces the growth of tumours in other parts of the body by stimulating the body's immune response against the tumours. Thus, this study demonstrated progress in the use of a biomimetic MOF-based approach to effectively target hypoxic tumour microenvironments in cancer treatment by synergistically combining low-dose radiation and immune checkpoint inhibition.

4.10. Multimodal therapy

Biomimetic MOFs offer a promising platform for multimodal cancer therapy by integrating various treatment modalities within a single framework. These frameworks can encapsulate different therapeutic agents, such as chemotherapeutic drugs, photodynamic therapy agents, or immunomodulatory compounds, in a controlled and targeted manner.[123] The advantage lies in their ability to concurrently deliver multiple therapies, enhancing treatment efficacy while minimizing systemic toxicity. Their modular nature enables the combination of different therapies to combat drug resistance and achieve synergistic effects against tumours.[124,125]

The development of biomimetic MOFs has led to groundbreaking advancements in multimodal cancer therapy. A noteworthy nanoplatform, FA–EM@GO–MOF, has been ingeniously engineered by integrating graphene oxide (GO) and a MOF consisting of Fe–porphyrin.[126] Owing to its biomimetic nature, this nanoplatform, which is enveloped with a folate-functionalized EM (FA–EM), has remarkable potential for targeted cancer cell delivery while evading immune clearance and extending circulation. The incorporation of GO and paramagnetic Fe ions enables strong fluorescence imaging and T_2-weighted magnetic resonance imaging. Additionally, its porous architecture and large surface area make it an ideal choice for effective drug delivery in chemotherapy. FA–EM@GO–MOF, under 808 nm laser irradiation, remarkably enables both PTT and PDT, utilizing the MOF as a photosensitizer. Additionally, the GSH-responsive fluorescence imaging and O_2 generation capabilities of the biomimetic MOF within the tumour microenvironment alleviate hypoxia, while its ability to deliver drugs for chemotherapy, combined with the induced immune response, is a robust multimodal approach for effective cancer treatment. Another study introduces multifunctional biomimetic MOFs produced *via* microfluidics for advanced cancer therapy.[127] FeTPt@CCM, created by encapsulating Fe^{3+}, *meso*-tetra(4-carboxyphenyl) porphine, and an oxaliplatin prodrug, acts as a targeted drug delivery system resembling a "Trojan horse". FeTPt@CCM exhibited excellent catalytic activity, generating oxygen (O_2) from hydrogen peroxide (H_2O_2) for photodynamic therapy and GSH peroxidase-like activity, transforming Fe^{3+} to Fe^{2+} and Pt(IV) to Pt(II). When internalized by cancer cells, it triggers Fenton-like and redox reactions, producing hydroxyl radicals ($^{\bullet}OH$) and oxygen, inducing ferroptosis and enhancing PDT along with Pt–drug chemotherapy.

Yang and colleagues introduced a cancer cell membrane-coated nanoplatform (mPAGT), integrating porphyrin MOFs (PCNs), an endogenous NO donor (L-Arg), and GOx for targeted cancer therapy.[128] Both *in vitro* and *in vivo* experiments demonstrated an efficient generation of ROS and NO with minimal systemic toxicity. The study revealed noteworthy cancer cell growth inhibition *via* gas therapy, starvation therapy, and PDT with or without laser irradiation. The findings underscore the efficacy of the multifunctional nanoplatform in impeding cancer cell proliferation through diverse therapeutic modalities and inducing significant programmed cell death, confirming its potential for advanced cancer treatment strategies. Recent research has introduced cancer-specific biomimetic MOFs that selectively activate prodrugs and enhance chemodynamic therapy (CDT). The platform MIL-53@F–@M accumulates in cancer cells, enabling precise prodrug activation within the tumour microenvironment.[129] *In vivo* and *in vitro* evaluations demonstrated significant tumour growth inhibition without systemic toxicity. Recent studies have made breakthroughs in cancer treatment by creating a specialized nanoplatform using cancer cell membrane-functionalized nano MOFs (nMOFs) loaded with sonosensitizers and a Toll-like receptor agonist (R837). This nanotechnology effectively targeted mitochondria in tumour cells, inducing immunogenic cell death (ICD) upon ultrasound exposure. It also promotes dendritic cell maturation, which is crucial for activating immune responses. Combining this nanoplatform with anti-CTLA-4 immune checkpoint blockade reversed tumour immunosuppression, fostering robust antitumour immunity. This innovative strategy holds immense potential in revolutionizing cancer treatment by leveraging nanotechnology to enhance therapy and activate the immune system against cancer.[130]

4.11. Biosensing

In biosensing applications, biomimetic MOFs function as effective sensing platforms for detecting cancer biomarkers or other disease-related molecules. These frameworks can be designed with tailored pore sizes and functionalized with specific ligands or receptors to selectively capture and concentrate target molecules. This selective binding enables highly sensitive detection and quantification of biomarkers present in complex biological fluids, thereby facilitating early disease diagnosis, monitoring disease progression, and evaluating treatment responses. The improved surface area and tunable porosity of these materials contribute to their efficacy as biosensors.[131] The MOF itself can be transformed into a high-tech contrast agent for MRI or CT scans, providing further detailed maps of the cancerous regions. For enhanced effectiveness, the MOF can be configured to deliver multiple therapeutic agents simultaneously, tackling drug resistance and increasing overall treatment success. By mimicking the architecture and functionality of natural enzymes, it is possible to design MOFs with vastly improved enzyme-like activity. Furthermore, the integration of biological components such as peptides or antibodies unlocks an exciting realm of biorecognition, allowing the MOFs to recognize and bind specifically to cancer cells with laser-like precision.[132]

The boronic acid-modified MOF MIL-100(Fe)–BA has potential for cancer treatment because of its biomimetic properties. Primarily designed for biosensing, its dual oxidase/peroxidase activity enables sensitive detection of tumour markers, aiding early-stage cancer diagnosis. When conjugated with imaging agents, MIL-100(Fe)–BA becomes a targeted probe for noninvasive tumour visualization. In targeted therapy, the hierarchical pores facilitate the loading of anticancer drugs, allowing their controlled release directly to cancer cells. The multienzyme

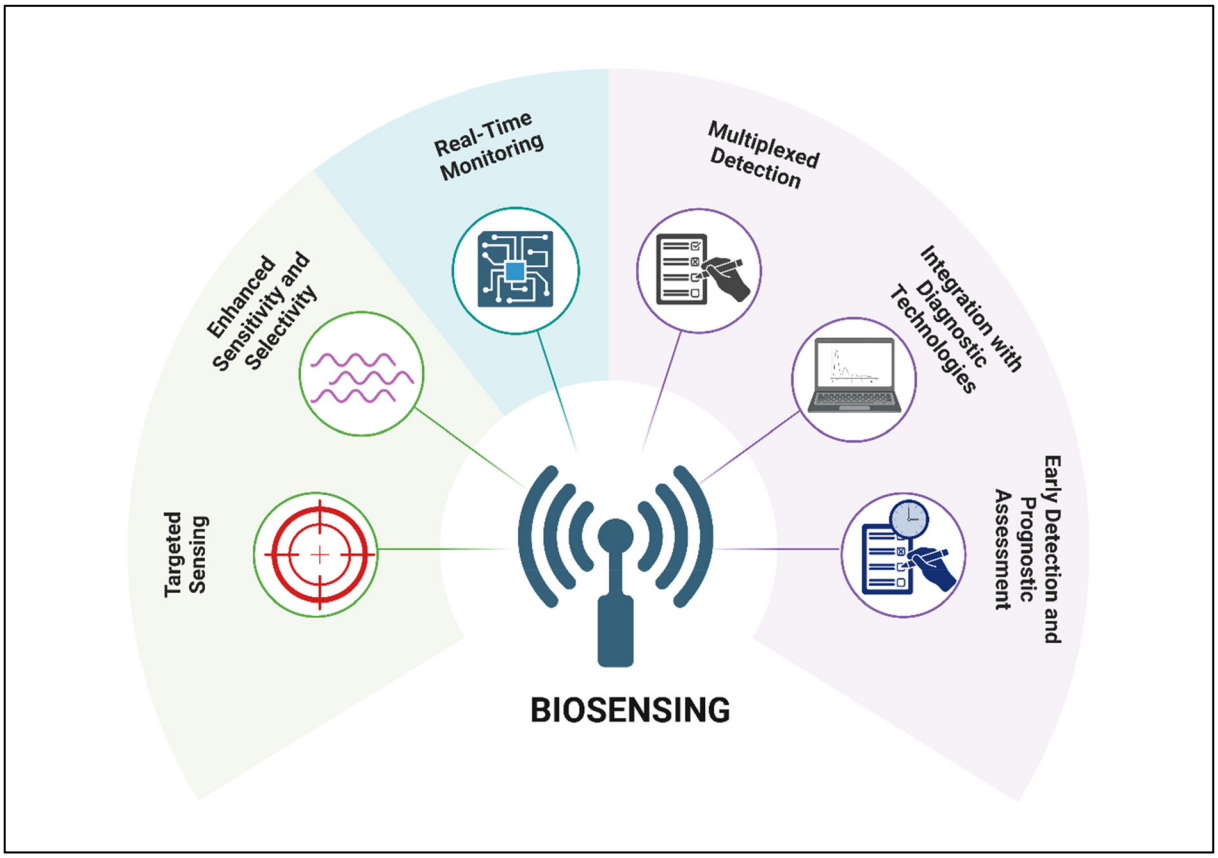

Fig. 7 Different biosensing applications of biomimetic MOFs.

cascade platform triggers specific therapeutic reactions within cancer cells for enhanced localized therapy. Biomimetic design possibilities include mimicking enzymes in cancer cell metabolism, integrating with tumour-targeting ligands, and expanding enzyme mimicry. While these are potential applications that need further research, MIL-100(Fe)–BA offers promise for advancing cancer diagnosis and therapy through its biomimetic capabilities. The future of cancer treatment may involve personalized, targeted approaches, with MOF-based platforms such as MIL-100(Fe)–BA paving the way for improved outcomes in cancer patients.[133] Biomimetic MOFs present immense potential in biosensing applications for cancer detection and monitoring. Their unique structural features, coupled with tailored functionalities, pave the way for highly sensitive, selective, and multiplexed detection strategies that contribute significantly to early diagnosis, treatment efficacy assessment, and personalized medicine in cancer care. Different biosensing applications of biomimetic MOFs are given in Fig. 7.

4.12. Bioimaging

In an effort to effectively lay the groundwork for the precise and highly selective detection, identification and diagnosis, MOFs have been instrumental in the establishment of various bioimaging platforms. Numerous MOF types have been adopted recently for various clinical analytic applications, notably computed tomography (CT) and magnetic resonance imaging (MRI). The fabrication technique, process alterations, and core or basic structure of the MOF determine its optimum efficiency in the bioimaging domain.[134] Li *et al.*, for instance, successfully fabricated a new MOF product that was intercalated with a DNA amplifier and utilized it to detect and image intracellular mRNA.[135] MOFs accumulate disproportionately in tumour areas due to the electron paramagnetic resonance (EPR) effect. When a specific type of magnetic field is present, species containing unpaired electrons, including radicals, radical cations and triplets, can be found *via* EPR, a subfield of magnetic resonance spectroscopy. The two primary types of contrast agents used in MRI are agents with T1 (positive contrast) that have the capacity to reduce the overall longitudinal relaxation period and T2 agents (negative contrast) that can minimize the transverse relaxation period.[136] Contrast agents made of iron, manganese, and gadolinium are often used in clinical research and evaluations.[137] In an investigation led by G. Boyes *et al.*, the CT imaging contrast may also be increased by the use of Gd–PAA (polyacrylic acid)–Au nanocomposites, even if the concentration of gold (Au) is only 1.66 mg mL^{-1}. The formation of AuNPs on the Gd–NMOFs necessitated PAA. To enhance the association with the Gd^{3+} ions, hydrophilic PAA can also act as a blueprint for the AuNPs and allow water

molecules to reach the surface of the Gd–NMOF. The results revealed excellent long-term relaxation for MRI and exceptional efficiency for CT imaging.[138] As another example for the objective of multimodal imaging, a core–shell PB@MIL-100 (Fe) dual MOF nanoparticle (d-NMOF) system was developed. Here, Wang *et al*. integrated chemotherapy with theranostic MIL-100(Fe) MOFs for pH-dependent release of the drug artemisinin with a photothermal effect. The effective contrast agents for T1–T2 dual-modal MRI were carried out by the dual-NMOFs. The exceptional combination and cumulative treatment impact achieved by incorporating photothermal chemotherapies, including the reduced toxic effects of artemisinin and dual-NMOFs, render therapeutic and diagnostic nanomedicines potential candidates for next-generation nomedicines, which could be used to treat cancer in a safe and efficient manner.[139] For breast cancer therapy, the produced AuNS@MOF–ZD2 nanoprobes can specifically target TNBC cells, indicating a promising future for theranostics of this disease. These nanocomposites exhibit excellent biocompatibility, stable photothermal alteration capacity and efficient T_1-weighted magnetic resonance (MR) relaxivity, further improving the MRI quality.[140,141] In research by Zhang *et al*., the results of *in vivo* CT imaging in a rat model indicated that UiO–PDT nanocrystals can predominantly collect in tumour sites rather than adjacent connective tissue. The optimal image was also obtained following a 24 hour intravenous injection.[142] For a range of biological applications, the functional 89Zr–UiO-66 offered excellent material and radiochemical stabilization. The results of *in vivo* PET imaging and cell-specific targeting demonstrates that the Py–PGA–PEG–F3/89Zr–UiO-66 is regarded as an effective nanoplatform that functions as an image-directable and tumour-selective cargo delivery system.[143] By using a microemulsion technique, Zhang *et al*. developed a biocompatible imaging-guided therapy system (IGTS) built on a nanoscale zirconium–porphyrin MOF (NPMOF). Effective fluorescence imaging and photodynamic treatment (PDT) are feasible with a high porphyrin concentration of 59.8%. The concentration of NPMOFs in cancer locations following laser irradiation and doxorubicin release confirms the fluorescence guidance of the chemotherapy-and-PDT dual system, while negligible toxicity is observed in normal tissues.[144]

4.13. Biomineralization

Biomineralization involves the deliberate deposit of inorganic elements on an organic substrate, involving the involvement of live body cells to produce hard tissue components. The most significant process involved in the formation and growth of the hard tissues found in living organisms, such as bones, teeth, and shells, is called biomineralization. Versatile nanoplatforms for a range of biomedical applications have been created on the basis of the mechanism of this natural biomineralization process. Compared with manufactured nanomaterials, these biosynthesized nanomaterials offer the benefits of Sufficient biocompatibility, a stable physiological state, improved biological activity, and Easy and affordable synthesis. As a result, a range of nano-bio minerals may be simply created and used in biomedical procedures through biomineralization, which has excellent potential for use in the loading, transfer, and controlled release of medications. Numerous minerals, including calcium phosphate, zinc sulfide, iron oxides, silica, and metalorganic frameworks, have been used in biomimetic mineralization.[145–147] ZIF-8 has remarkable biocompatibility and is easy to produce, making it a preferred choice for biomimetic mineralization. Yan *et al*. loaded chlorin e6, a photosensitive agent and chemotherapeutic agent, DOX, onto a ZIF-8 MOF coated with *E. coli* through a biomineralization approach.[148] The loading of chemotherapeutic agents and photosensitizers onto the ZIF-8 MOF had no remarkable influence on the precise tumour-targeting activity or viability of the *E. coli* coating. The fabricated nanoformulation demonstrated efficient therapeutic activity under mild NIR irradiation. Biomineralized MOF could successfully deliver chemotherapeutics and Ce6 to tumours, enabling synergistic cancer treatment. It showed greater tumour suppression efficacy. These results show that, compared with plain ZIF-8 particles, ZIF-8-biomineralized *E. coli* is a more effective way to deliver therapeutics. This research suggests that biomimetic mineralization of living organisms has potential for therapeutic applications and may provide new insights into biomineralization.

4.14. Other biomedical applications

Biomimetic MOFs have demonstrated tremendous potential in a variety of fields, not only in biomedical, biocatalytic, and biosensing activities but also in other biomedical applications like such as vaccine delivery, cell culture and tissue engineering, antimicrobial applications, *etc*. Singh *et al*. reported the use of the MOF biomimetic-mineralization technique to load or encapsulate live viral vaccines (LVVs), creating an optimized composite that substantially improves the shelf-life of vaccines. For this study, live viral vaccination against the Newcastle disease virus strain V4, which is commercially available, was utilized. Here, the process of biomimetic mineralization produces the ZIF-8@NDV, ZIF-8@WSN, and AlFum@WSN combinations, while the ZIF-8 MOF on the LVV strain NDV V4 combines with the ZIF-8 and aluminum fumarate MOFs on the influenza A WSN viral strain. The vaccination was considerably stabilized by ZIF-8 MOF encapsulation in ambient settings after four weeks and at all times, even at high temperatures of 37 °C.[149]

ZIF-8 has the capacity to crystallize on the surface of a live cell to form an exoskeleton that provides physical defense and permits the passage of vital nutrients, preserving the life of the cell. Cell division is inhibited by the MOF shell, creating synthetic pseudohibernation conditions. After the removal of MOF, the cellular functions of yeast and other microbes can be fully restored. Metal ions are drawn to yeast cell walls and may act as repositories for MOF crystal formation.[150] Through the use of functional groups such as amines or carboxylic acids, MOF coatings may be externally decorated with enzymes. This technique has been widely applied to graft streptavidin,[151]

hydrolase,[152] β-glucosidase,[153] and trypsin[154] onto MOFs.[153] Although attaching enzymes to the MOF surface is an effective technique, it does not provide a substantial level of protection against environmental media (for example, enzymes will breakdown when proteolytic agents are present). Eventually, it is possible to immobilize enzymes immediately on the cell surface, and then a cell–enzyme system can be established *via* biomimetic mineralization.

A MOF can exhibit antimicrobial activity through various mechanisms. First, it can serve as a reservoir for the progressively released antibacterial compounds confined by highly ordered forces inside the MOFs. Second, it can degrade bioactive MOFs that emit linkers and/or metal ions. Third, it can operate as a chelating agent. In addition, it can exhibit photoactivity due to the prevalence of photosensitizer molecules. Finally, it could further aid in physical disinfection. Sometimes, a combination of many pathways might have a cumulative antimicrobial impact, resulting in a significant antimicrobial effect.[155] MOF and enzyme hybrid nanoreactors (MIL@GOx–MIL NRs) with a self-activated sequence were created by Tong *et al*. GOx catalyzed the development of gluconic acid, which decreased the pH to approximately four. This resulted in MOF nanoparticles breaking down H_2O_2, generating hydroxyl radicals that further kill *Staphylococcus aureus* and prevent the development of biofilms.[156] Nasrabadi and colleagues reported that ciprofloxacin (CIP) has a high loading capacity of 84 w% in a Zr-based MOF called UiO-66, which serves as a nanoconder for the sustained or delayed release of the drug. Furthermore, CIP–UiO-66 has greater antibacterial activity than both UiO-66 and CIP individually.[157] Zhuang *et al*. conducted another investigation in which a cobalt-based MOF (Co–TDM) was synthesized using an octa-topic linker. The MOF-based composite demonstrated exceptional stability for over 4 weeks and was found to be 100% recyclable for bactericidal action.[158]

5. Bio-interaction

Understanding the interactions of biomimetic MOFs with biological systems is crucial for their biomedical applications. Researchers have focused on evaluating their biocompatibility, biodistribution, and potential immunogenicity. Studies have investigated how these frameworks interact with different tissues, organs, and biological fluids to ensure minimal toxicity and favourable biodistribution for effective therapy. Moreover, assessing the immune response elicited by MOFs aids in determining their safety profile and potential immune reactions, guiding their design for clinical applications. Although immune cell membranes typically maintain immune tolerance and are obtained from endogenous sources, some surface proteins may interact with immune components, potentially inducing immune stress, particularly in sensitive organs like liver and spleen. Thus, thorough *in vivo* studies are crucial to assess the immunogenicity and safety of immune cell membrane-coated MOFs prior to clinical use. Additionally, understanding the biodegradability and clearance of MOFs from the body is vital to ensure their safe use in biomedical settings. The promising future of biomimetic MOFs in cancer treatment centers lies in their exceptional functionality and interactions with different biological systems.

5.1. Blood circulation

Biocompatible MOFs are crucial for smooth navigation through the bloodstream, avoiding premature clearance by the immune system. Surface modifications with polyethylene glycol (PEG) or other stealth coatings can minimize opsonization and prolong the circulation time.

5.2. Tissue penetration

Reaching the tumour site requires traversing intricate tissue barriers. Engineered MOFs with specific sizes, shapes, and surface charges can overcome these hurdles and target tumours effectively.[159]

5.3. Endothelial targeting

Specific ligands on the MOF surface can interact with tumour endothelial cells, enabling the targeted transport of drugs to the tumour microenvironment.

5.4. Cellular uptake

Internalization by cancer cells is important for therapeutic efficacy. Fabricating MOFs with tumour-specific targeting ligands or responsive functionalities can trigger efficient cellular uptake.[160]

Designing MOFs that biodegrade after delivering their payload or are readily cleared by the body minimizes long-term toxicity and accumulation.[161]

6. Toxicity perspectives of biomimetic MOFs

Owing to the evolution of MOF synthesis approaches and the extensive use of MOF derivates, their unavoidable exposure might have negative impacts on the environment and humans, making it critical to assess the toxicity of biomimetic MOFs (Fig. 8). The latest discoveries in biomimetic MOFs are quite interesting because of their potential applications in the treatment and diagnosis of various diseases. Nonetheless, various challenges must be addressed before they can proceed with their clinical interpretation. One of the most significant barriers to using these composites for cancer therapy and tissue regeneration, is the lack of common guidelines for safety testing that all researchers must follow. Numerous cell lines, doses, and animal models have been used in various studies for safety. Furthermore, toxicity tests must be performed on both healthy and sick models. In addition, because distinct biomimetic MOFs are synthesized under various chemical circumstances and configurations, much study is needed to obtain a deeper understanding of the relationship between individual biomimetic particles and MOFs.

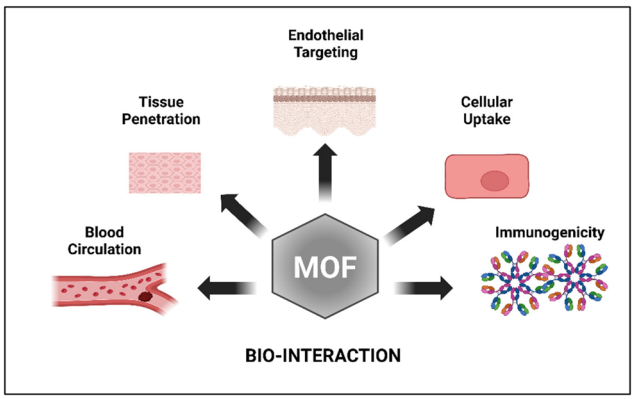

Fig. 8 Bio-interaction of Biomimetic MOFs.

The toxicity of biomimetic MOFs is still poorly known. The size of a substance significantly influences its toxicological qualities, affecting its cellular absorption, biodistribution, translocation, and excretion. As the size decreases, the surface-to-volume ratio increases, resulting in increased reactivity. Numerous studies have shown that the size of NPs significantly affects their cytotoxicity and translocation. As a result, it is critical to prioritize the assessment of the potential toxicity of biomimetic MOFs to organisms.[162] However, in regard to MOFs, their toxicity cannot be explained only by size. The composition of materials employed in synthesis is also an important consideration. Thus, complete toxicity studies should include assessments of all metals, organic ligands, biomimetic materials, linkers, and functionalized materials used in MOF production.

To be labelled "practically nontoxic", nanocomposites must also undergo a series of extensive biosafety tests on animal models to gain a better understanding of their acute and chronic effects on various organs. Furthermore, while the overall effects of biomimetic MOFs on cancer therapy, tissue repair, and infection therapy are well understood, the underlying molecular mechanisms are not well understood. The molecular pathways behind these interactions are similarly poorly understood, despite extensive research into the overall influence of biomimetic MOFs on cancer therapy, tissue repair, and infection therapy. The development of biomimetic MOFs is still in its earliest phases, and additional studies are needed to determine how to make biocompatible biomimetic MOFs and how to employ them for therapy and regeneration.

7. Conclusion and outlook

MOFs are employed in a wide range of sectors, including mechanical and chemical engineering, biomedical fields, and electronics, making them the most active area of research. We highlight some of the intriguing possibilities associated with ongoing biofriendly advancements in the biomedical applications of MOFs. An exhaustive literature focusing on this area and its relevance to cancer therapy is provided in detail. The diverse compositions, large surface areas, tailorable morphologies, tunable pore sizes, biocompatibility and ease of functionalization of these materials enable them to carry a wide range of bioactive molecules, thereby enhancing their therapeutic effects against cancer. The accumulation of therapeutic agents at tumour sites is facilitated by the active and passive targeting effects of MOF-based nanoplatforms. A special focus is on the use of biomimetic membranes and their cancer-targeting abilities. Recent developments in biomimetic MOF-based nanocomposites for effective tumour theranostics are described in this article, including individual and combination therapies such as photo-, chemo-, starvation-, gene-, immune-, radio-, sonodynamic-, ferroptosis- and gas therapy. The preparation and fabrication of biomimetic-MOFs delve into different strategies for extracting biomimetic membranes and decorating them with MOFs. The biointeraction of such surface-modified MOFs with biological tissues and systems explain the advantages and limitations of bio-MOFs. These applications, including conventional and new facets of the discipline, present opportunities and difficulties, demonstrating the growing interest in and promising future for biomimetic MOF applications. In addition, we expect that these advancements will encourage further research endeavors and provide fresh prospects in the biomedical application of biomimetic MOFs.

The challenges and future directions in the development of biomimetic MOFs for cancer treatment also include the need for reliable models to predict and optimize biological interactions with different tissues and fluids, minimize immunogenicity for long-term biocompatibility, and integrate multiple functionalities within a single MOF platform for targeting, drug delivery, and therapeutic action. Despite these challenges, the future outlook for biomimetic MOFs in cancer treatment is promising. Addressing biointeraction predictability and optimizing functionality can unlock the immense potential of these platforms for personalized, targeted, and effective cancer therapy. With ongoing research and development, biomimetic MOFs have the potential to redefine the landscape of cancer treatment, offering hope for improved patient outcomes.

Author contributions

Soji Soman & Sanjay Kulkarni: Writing – original draft, writing – review & editing, conceptualization, methodology, data curation. Jahnavi Kulkarni, Namdev Dhas, Amrita Arup Roy, Rahul Pokale, Anoushka Mukharya: Writing – original draft, methodology, data curation. Srinivas Mutalik: Investigation, conceptualization, project administration, resources, supervision, validation, writing – review & editing.

Data availability

This is a review paper and as such it does not include any primary datasets. All the data we discussed and analyzed

within this review are derived from the published studies and literature references in the manuscript.

Conflicts of interest

The authors declare no competing interests.

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