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REVIEW

# Biomimetic ZIF-8 Nanoparticles: A Novel Approach for Biomimetic Drug Delivery Systems

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**Abstract:** Metal-organic frameworks (MOFs) are porous materials resulting from the coordination of metal clusters or ions with organic ligands, merging macromolecular and coordination chemistry features. Among these, zeolitic imidazolate framework-8 (ZIF-8) stands out as a widely utilized MOF known for its robust stability in aqueous environments owing to the robust interaction between its constituent zinc ions ($Zn^{2+}$) and 2-methylimidazole (2-MIM). ZIF-8 readily decomposes under acidic conditions, serving as a promising candidate for pH-responsive drug delivery systems. Moreover, biomimetic materials typically possess good biocompatibility, reducing immune reactions. By mimicking natural structures or surface features within the body, they enhance the targeting of nanoparticles, prolong their circulation time, and increase their bioavailability in vivo. This review explores the latest advancements in biomimetic ZIF-8 nanoparticles for drug delivery, elucidating the primary obstacles and future prospects in utilizing ZIF-8 for drug delivery applications.

**Keywords:** MOF, ZIF-8, cell membrane, biomimetic drug delivery

## Introduction

In recent years, metal-organic frameworks (MOFs) have emerged as promising candidates for drug delivery systems in the field of pharmaceutical research.[1,2] The utilization of MOFs as carriers enables the chemical conjugation or physical encapsulation of drugs, which is facilitated by a diverse array of interactions such as hydrogen bonding, van der Waals forces, π-π stacking between aromatic rings, electrostatic interactions, ligand bonding, and covalent bonding. In contrast to conventional drug carriers such as liposomes, micelles, and polymeric nanoparticles, MOFs exhibit superior drug loading capacity owing to their extensive porosity and hydrophobic cavities.[3] Moreover, the controlled host-object interactions and biodegradability of MOFs, achieved through coordination methods, further contribute to their appeal in drug delivery applications.

Compared to conventional drug delivery systems, MOFs possess several distinctive advantages.[4] Firstly, MOFs can be easily synthesized at the nanoscale and can also be multi-functionalized through physical wrapping or surface modification, which enables more efficient drug loading. Secondly, the diverse structures, morphologies, compositions, sizes, and chemical properties of different MOFs make them functionally versatile, allowing for controlled drug release. Thirdly, the modification of MOFs does not significantly alter their desirable physical and chemical properties, as the functionalized MOF materials retain controlled size, shape, and high dispersibility. Lastly, the weak coordination bond between the metal and the ligand in MOFs ensures both stable conformation under physiological conditions and biodegradability of the MOFs.[5] Not only that, these unique properties of MOFs can also be used as a biosensor to detect hydrogen peroxide, metal ions, hydrogen sulfide and organic molecules in biological cells.[6]

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Among the MOFs, some Zn-MOFs can prevent the aggregation and self-destruction of photosensitisers (PSs) and reactive oxygen species (ROS), which allows them to effectively load PSs, and the chemical structure characteristics of Zn-MOFs allow them to be embedded into a wide range of biomolecules for therapeutic use through simple synthesis.[7] ZIFs, a type of MOF material, are coordination polymers formed by bridging transition metals, such as zinc, with imidazole (Imi) or imidazole derivatives through nitrogen atoms.[8] Zinc, the second most abundant transition metal in living organisms, is known to be beneficial for bone health and repair as it protects bone.[9] Imidazole moiety is a component of histidine, which further highlights the biological relevance of ZIFs. Among various ZIFs, ZIF-8 is the most commonly used and well-studied. ZIF-8 possesses a zeolitic structure and is known for its simplicity in preparation, slow-release properties, and biodegradability under acidic conditions. These attributes make ZIF-8 a representative and highly sought-after member of the ZIFs family. Various methods have been employed for the synthesis of ZIF-8, including the multiple emulsification-solvent evaporation method,[10] One-pot method,[11] Solvent evaporation seeding coupled with microwave-assisted heating method,[12] direct solvent-free synthesis,[13] and special methods.[14] As an exceptional subclass of MOFs materials, ZIF-8 has found extensive use as a drug carrier. However, it is crucial to thoroughly assess the toxicity and biocompatibility of ZIF-8. Furthermore, ZIF-8 has the potential to non-specifically adsorb biomolecules present in the bloodstream, leading to the formation of a protein corona on its surface. The presence of this protein corona may trigger recognition by the immune system and subsequent elimination.

In a recently published review on MOF, Luo et al reviewed the aspect of MOFs as apt luminescent probes for the detection of biochemical analytes, focusing on the advances in the study of MOFs as biosensors for the detection of hydrogen peroxide, metal ions, hydrogen sulphide and organic molecules in biological cells.[6] Meanwhile, Li et al explored the synthesis of Zn-MOF and its use in cancer chemotherapy, phototherapy, chemodynamic therapy, sonodynamic therapy, immunotherapy, gene therapy, starvation therapy, or a combination of two or more of the above therapies.[7] Unlike them, this review focuses on the application of biomimetic material-modified ZIF-8 as drug delivery systems in disease.

Surface functionalization is a well-established strategy for enhancing the biocompatibility of ZIF-8 nanoparticles. Biomimetic nano-drug delivery system (BNDDS) mainly consists of core particles with drug-loaded nanostructures and biomimetic outer membranes with biological activity.[15] In recent years, a novel approach utilizing biomimetic material coatings has revolutionized nanoparticle functionalization.[16] This innovative technique involves the transfer of plasma membranes from native cells onto synthetic nanoparticles. As a result, the resulting biomimetic material-coated ZIF-8 nanoparticles not only retain the intricate surface features inherited from the source cells, but also acquire remarkable cell-mimetic functions.[17,18] Thus far, numerous ZIF-8 formulations coated with different types of biomimetic materials have been meticulously developed and extensively studied for their potential applications in drug delivery systems.

## Synthesis of ZIF-8

### The Multiple Emulsification-Solvent Evaporation Method and Solvent Evaporation Seeding Coupled Microwave-Assisted Heating Method

A Teflon liner is necessary in the multiple emulsification-solvent evaporation method and the solvent evaporation seeding coupled microwave-assisted heating method. To start the process, 0.297 g of Zn $(NO_3)_2.6H_2O$ was dissolved in 20 mL of methanol. Simultaneously, a solution containing 0.164 g of 2-MeIm and 0.269 g of HCOONa dissolved in 20 mL of methanol was prepared. The metal solution was then added to the linker solution and transferred to a Teflon liner. After that, the liner was sealed inside a stainless-steel autoclave from Parr Instruments and incubated at 363 K for 48 hours. Following the incubation period, the crystals were centrifuged at 8500 rpm for 5 minutes and washed three times with fresh methanol. Lastly, the crystals were air-dried at 333 K and degassed overnight at 453 K under vacuum conditions.[10]

Whereas, different heating durations of 2 and 4 hours were required to prepare ZIF-8 seed supports using the solvent evaporation seeding method.[12] Initially, a seeding solution was prepared by dissolving 2.39 g of $ZnCl_2$, 2.23 g of Hmim, and 1.22 g of HCOONa in 180 mL of MeOH with continuous stirring. A tubular support was then inserted vertically into a Teflon vessel using a custom-made holder. A magnetic stirrer was placed at the bottom of the Teflon vessel. The seeding solution was carefully added to the vessel and placed in a water bath. To facilitate the evaporation of the solvent,

the vessel was covered with aluminum foil, and the temperature was maintained at 65°C for 2 and 4 hours, respectively. Under these conditions of high supersaturation, ZIF-8 seeds formed on the tubular porous support through heterogeneous nucleation and crystallization. Finally, the seeded support was dried overnight in a desiccator at room temperature.

## A Direct Solvent-Free Synthesis

Direct solvent-free synthesis also requires heating, in this approach, various combinations of 2-methylimidazolyl ester (mi), 2-methylbenzimidazolyl ester (mb), and 2-ethylimidazolyl ester (ei) were utilized, incorporating larger substituents at the 2 or 4–5 positions (Figure 1). To synthesize these materials, Cobaltocene (for ZIF-67-mix, 30 mg, 0.16 mmol) or ZnO (for ZIF-8-mix, 13 mg, 0.16 mmol) was combined with a mixture of 2-methylimidazole, 2-ethylimidazole, and/or 2-methylbenzimidazole (0.10–0.24 mmol per reactant). The reaction mixtures were sealed under vacuum in a layering tube with a diameter of 4 mm. Subsequently, the mixtures were heated at 150°C for 4 days, resulting in the formation of purple powder (ZIF-67-eimb, ZIF-67-mimb, ZIF-67-eimi) or white powder (ZIF-8-eimb, ZIF-8-mimb, ZIF-8-eimi). After cooling to room temperature, the layering tubes were opened to obtain the final products.[19] The results indicate that increasing the mb fraction leads to the rapid destabilization of the qtz topology. This destabilization occurs when the energy difference exceeds 1 eV and occurs at a concentration of 100% mb compared to pure-ei ZIF-8. The reason for this destabilization can be explained by the Introduction of bulkier mb ligands, which leads to significant steric hindrance within the relatively small qtz unit cell. As a result, the qtz unit cell expands by 45% when transitioning from pure-ei to pure-mb. In contrast, the substitution of ligands has minimal impact on the phase stability of the dia topology. For ei:mb ratios higher than 0.25, the dia topology is found to be more stable than the qtz topology (Figure 2).

It is noteworthy that the researchers successfully achieved precise control over the synthesis of ZIF-8 by manipulating the pH conditions. Conventionally, the synthesis of ZIF-8 requires highly alkaline conditions (pH 11.0) to deprotonate the N-pyrrole atom in the 2-MIM ligand. However, the researchers made a significant breakthrough by effectively encapsulating intact inactivated foot-and-mouth disease virus (known as 146S) into ZIF-8 through a pH reduction to 9.0 in the 2-MIM solution.[14] To further optimize the particle size and morphology of the 146S@ZIF-8 complex, the researchers either increased the concentration of $Zn^{2+}$ or introduced cetyltrimethylammonium bromide (CTAB). These modifications resulted in an approximate 5°C enhancement in the thermal stability of the 146S antigen (Figure 3). Ultimately, the successful synthesis of ZIF-8-encapsulated viral antigen demonstrates its potential for application in viral vaccines.

## One-Pot Method

One of the most commonly used and straightforward methods for synthesis is the one-pot method. In this approach, 0.1 mL of 0.30 M Zn $(NO_3)_2$, 5 µL of 1 mg/mL streptavidin (SA), and 5 µL of 1 mg/mL horseradish peroxidase (HRP) were combined with

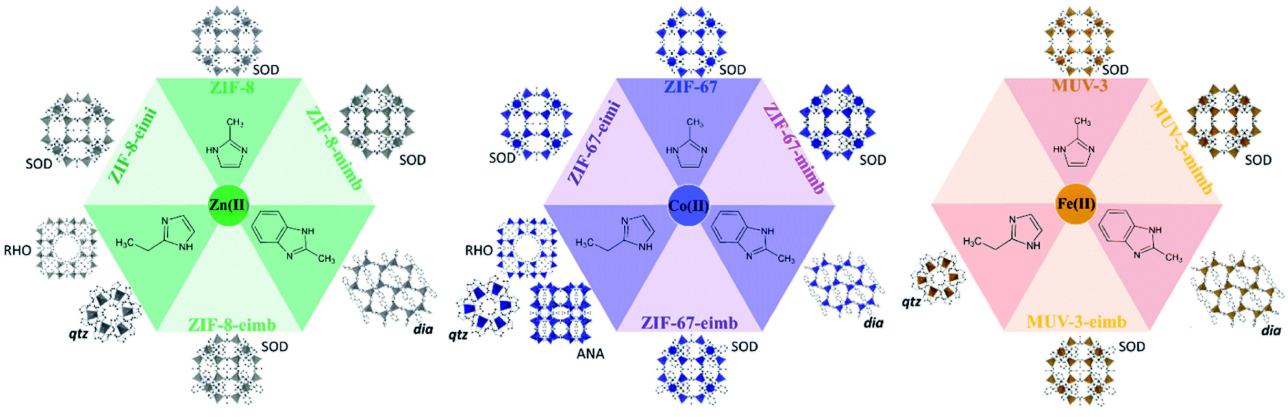


**Figure 1** Scheme of the different achievable crystal structures by solvent-free synthesis combining M(ii) and three imidazoles: 2-methylimidazole, 2-ethylimidazole and 2-methylbenzimidazole. Reprinted from López-Cabrelles J, Miguel-Casañ E, Esteve-Rochina M, et al. Multivariate sodalite zeolitic imidazolate frameworks: a direct solvent-free synthesis. *Chem Sci*. 2022;13(3):842–847. Creative Commons.[19]

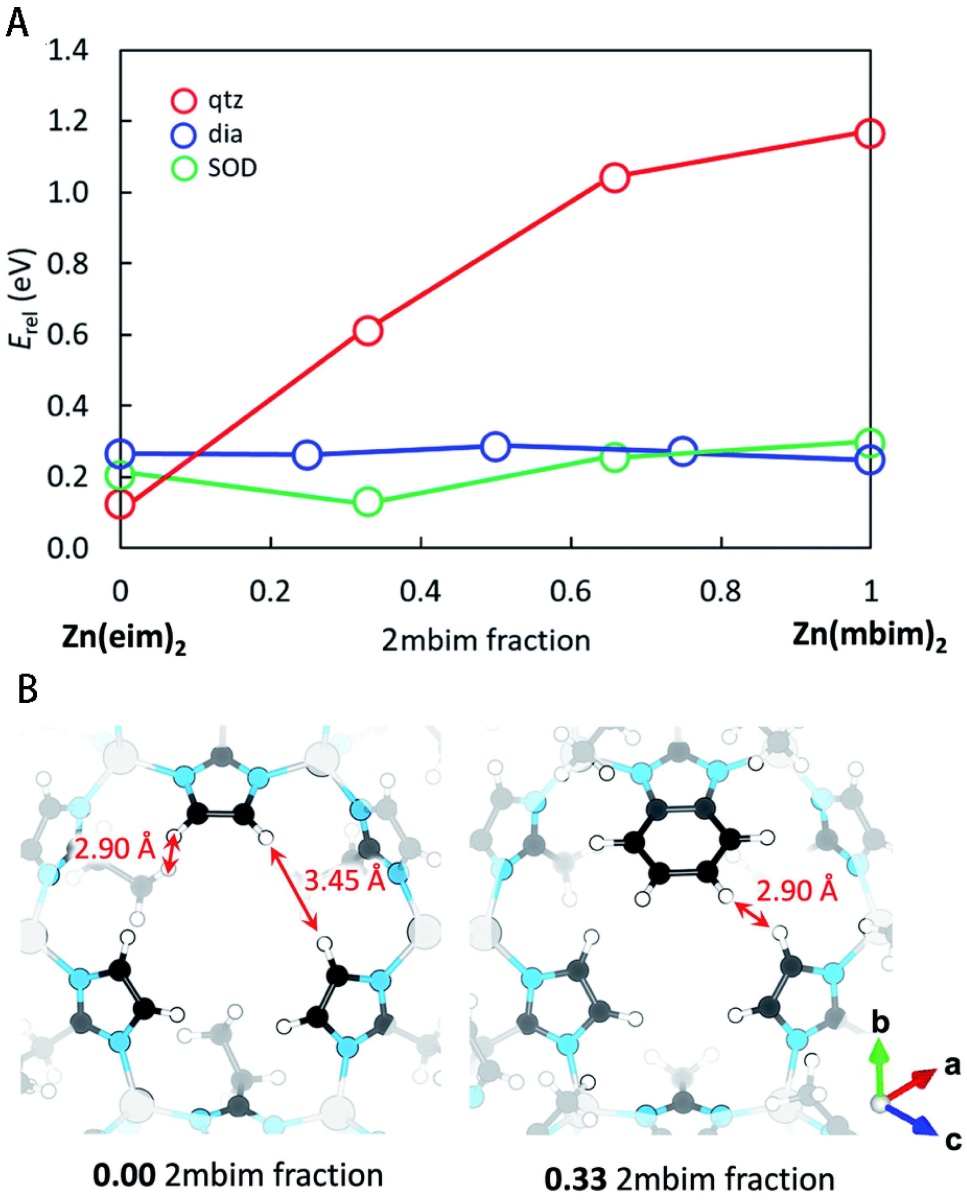


**Figure 2** (**A**) Phase stability diagram calculated at the PBEsol level for mixed eim:mbim Zn-based ZIF-8 with respect to the most stable pure-mim ZIF-8. (**B**) Crystal structure calculated for pure-eim ZIF-8 (left) and ZIF-8-eimb at a 2: 1 ei: mb composition (right). Relevant H···H distances are indicated. Reprinted from López-Cabrelles J, Miguel-Casañ E, Esteve-Rochina M, et al. Multivariate sodalite zeolitic imidazolate frameworks: a direct solvent-free synthesis. *Chem Sci*. 2022;13(3):842–847. Creative Commons.

1 mL of 1.2 M 2-methylimidazole at room temperature, and the mixture was stirred for 30 minutes. The resulting precipitate was then collected through centrifugation at 7000 rpm for 15 minutes, followed by three washes with deionised water (Figure 4).[11] Similarly, Lyu et al employed the one-pot method to synthesize cytochrome c (cyt c)/ZIF-8 nanocomposites, which exhibited 10-fold higher activity compared to free cytochrome c.[20] In another study, Fan et al developed ZIF-8 nanoparticles (NPs) loaded with gemcitabine (Gem) and D-1-methyltryptophan (D-1-MT) for combination chemotherapy and immunotherapy of osteosarcoma (OS).[21] The ZIF-8@Gem/D-1-MT nanoparticles were prepared using a similar one-pot method. In a recent study,[22] Zhong et al designed a simple one-pot DOX-donating iron nanocarrier using self-assembly of doxorubicin (DOX), 2-MIM and $FeSO_4$. Among them, the doping of iron ions promoted a synergistic effect of iron sagging and apoptosis, which demonstrated an effective anti-breast cancer effect.

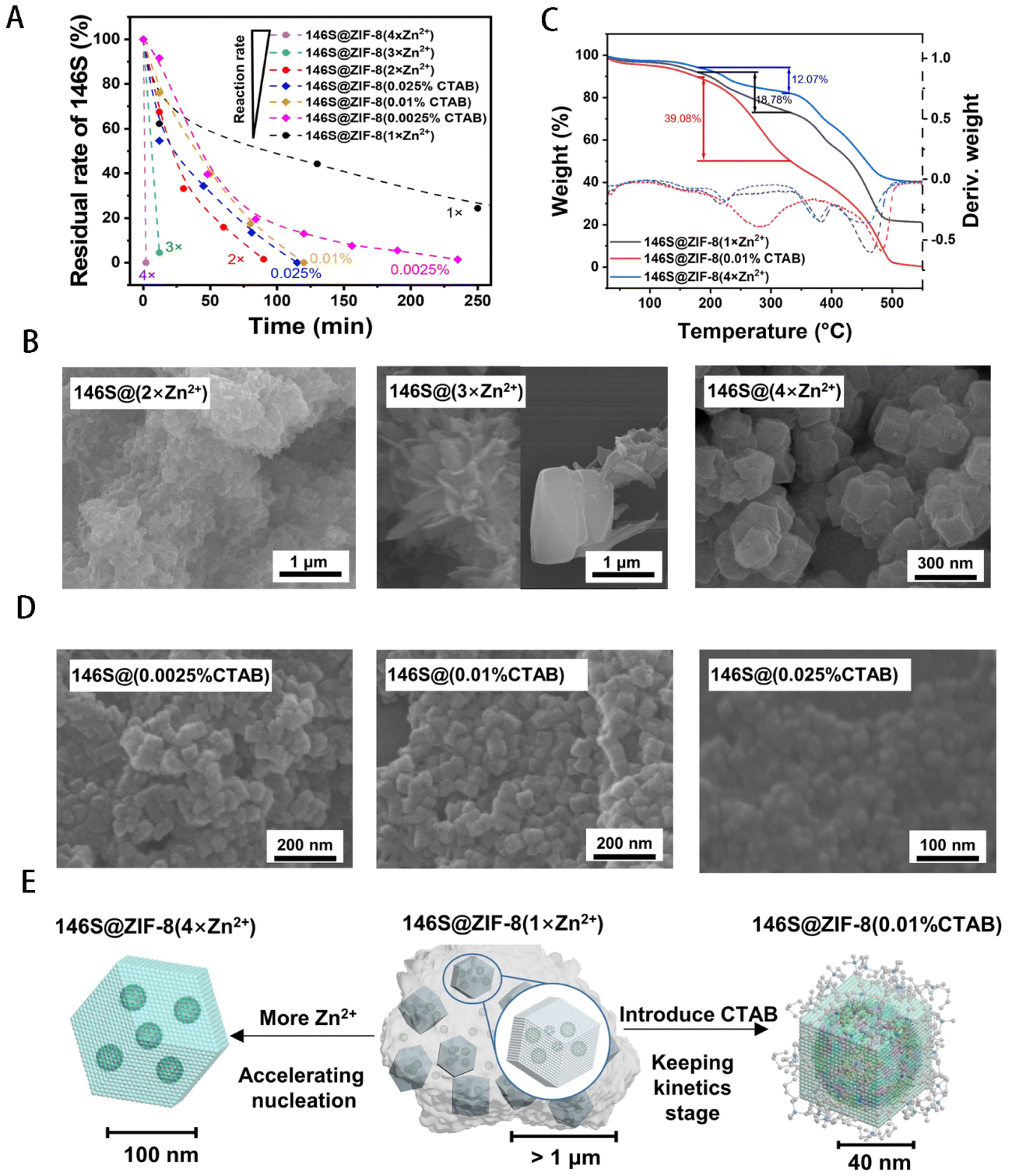


**Figure 3** Optimization of the morphology of 146S@ZIF-8. (**A**) Encapsulation rate of 146S during the preparation of each ZIF-8 under different conditions. The complete reaction curve of 146S@ZIF-8(1×$Zn^{2+}$), including the depletion process of 146S from 250 min to 10 hours (**B**) The SEM images of 146S@ZIF-8 synthesized by adjusting the $Zn^{2+}$/2-MIM molar ratios from initial 1:62 (1×$Zn^{2+}$) to 1:31 (2×$Zn^{2+}$), 1:21 (3×$Zn^{2+}$) and 1:16 (4×$Zn^{2+}$). (**C**) Identification of 146S@ZIF-8 synthesized under different conditions using TGA. (**D**) The SEM images of 146S@ZIF-8 were synthesized by adding 0.0025% (w/v), 0.01% (w/v) or 0.025% (w/v) CTAB. (**E**) Schematic illustration of the structure conjecture of 146S@ZIF-8 with different sizes and morphologies. Reprinted from Wang L, Lin X, Sheng Y, et al. Synthesis of a crystalline zeolitic imidazole framework-8 nano-coating on single environment-sensitive viral particles for enhanced immune responses. *Nanoscale Adv.* 2023;5(5):1433–1449. Creative Commons.[14]
**Abbreviations**: SEM, scanning electron microscopy; TGA, thermogravimetric analysis; CTAB, cetyltrimethylammonium bromide.

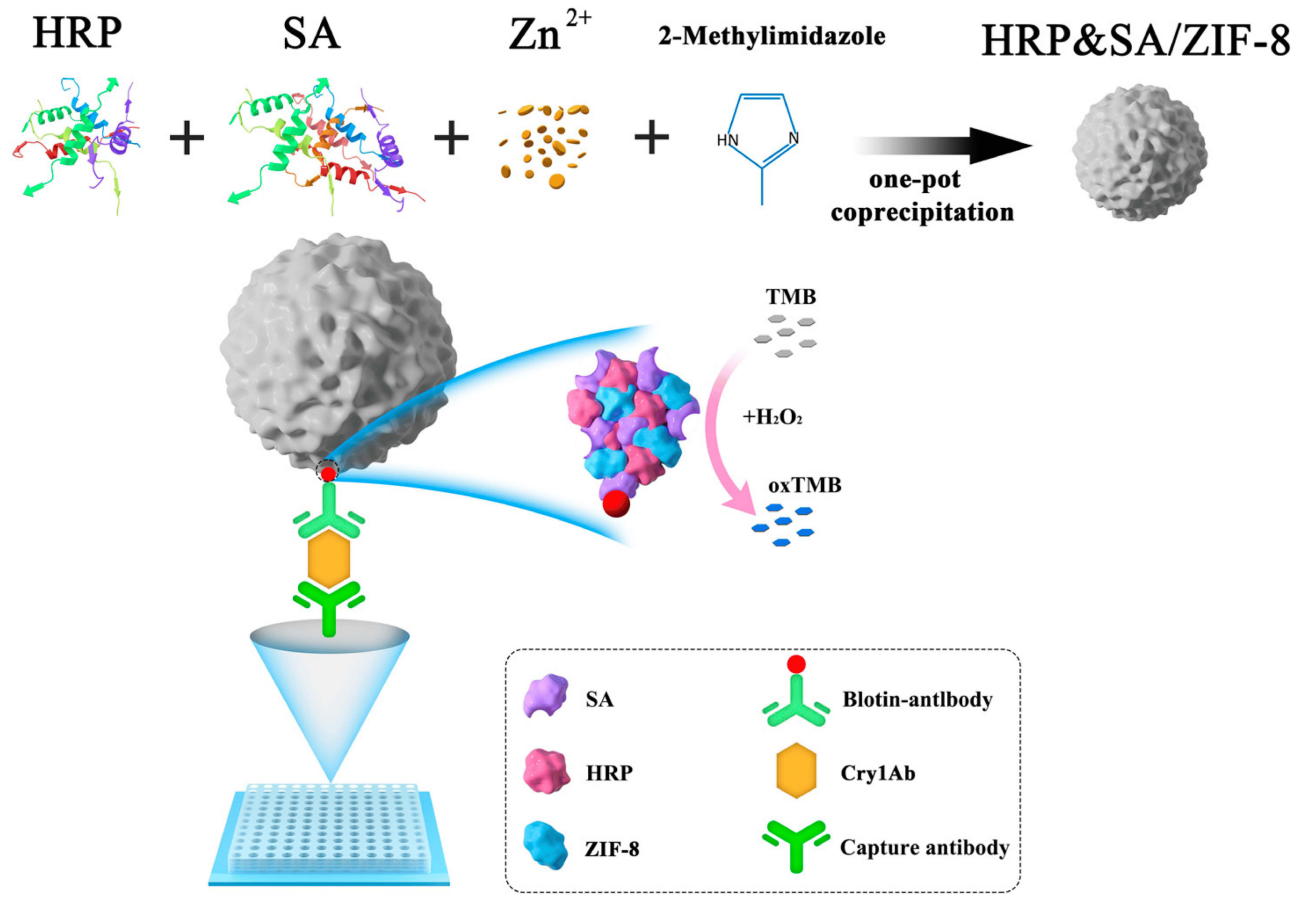


**Figure 4** Illustration of the preparation process for HRP&SA/ZIF-8 nanocomposite. Reprinted from Ye R, Chen H, Li H. One-pot synthesis of HRP&SA/ZIF-8 nanocomposite and its application in the detection of insecticidal crystalline protein Cry1Ab. *Nanomaterials*. 2022;12(15):2679. Creative Commons.[11]
**Abbreviations**: SA, streptavidin; HRP, horseradish peroxidase; TMB, 3,3′,5,5′-tetramethylbenzidine.

# Modification of ZIF-8

## Common Modifications

ZIF-8 exhibits promising potential as a drug delivery carrier. However, modifications are necessary to optimize its practical applications. These modifications serve to enhance the stability of ZIF-8, alleviate toxic side effects, and protect drugs during the delivery process. Additionally, they enable precise control over drug release, allowing for sustained and controlled release effects at specific sites or under certain conditions. The implementation of these modification strategies collectively enhances the effectiveness and feasibility of ZIF-8 as a drug delivery carrier, propelling its application potential in the field of drug delivery. For instance, surface modification of ZIF-8 nanoparticles typically involves the attachment of PEG or PEG with carboxyl groups ($PEG_{2000}$-COOH).[23] The incorporation of PEG introduces steric hindrance to the nanoparticles, thereby reducing their non-specific interactions with plasma proteins and effectively prolonging their circulation time. In addition to PEG, various other biopolymers, such as hyaluronic acid (HA), chitosan, and polyvinylpyrrolidone (PVP),[24,25] are commonly employed for surface functionalization. Furthermore, the integration of small molecules, such as folic acid, ligands, and antibodies, has emerged as a prevalent strategy to enhance the targeted delivery capability of MOF-NPs.[26,27] It is worth noting that the generation of antibodies by the immune system specifically targeting PEG, thereby compromising the clinical efficacy of pegylated drugs and potentially increasing adverse reactions.[28] Consequently, the current trend in biomimetic strategies involves the utilization of native cell membrane coating nanotechnology.

## Modification of Biological Membranes

Currently, there are limitations in the use of various organic or inorganic materials for exogenous modification. These materials can potentially accumulate in the body, leading to long-term toxicity and high clearance rates by the

reticuloendothelial system. In order to overcome these limitations, biomimetic strategies have been developed, such as the use of natural cell membranes or vesicles to encapsulate nanoparticles. This approach directly replicates highly complex functions and achieves a bio-interface on the surface, which offers a promising solution for the modification of ZIF-8.

The main objective of imparting a cell membrane to nanoparticles is to enhance their biocompatibility, stability, and functionality. The structure of the cell membrane closely resembles that of natural cells, which can reduce the immune response and toxicity of nanoparticles when interacting with biological tissues. This, in turn, allows for better interaction within the biological system. Furthermore, the presence of specific receptors or proteins on the surface of cell membranes enables nanoparticles to be targeted in drug delivery, and to evade clearance by the immune system, allowing for long-term stable circulation in the blood. The cell membrane serves as a protective barrier, thereby improving the stability of nanoparticles and endowing them with additional biological functions. Table 1 summarizes representative designs from recent research on the use of cell membrane-encapsulated ZIF-8 as a drug delivery system.

In Conclusion, the utilization of natural cell membranes or vesicles as a means of encapsulating nanoparticles offers a promising approach to overcome the limitations associated with conventional material modifications. This biomimetic strategy enhances the biocompatibility, stability, and functionality of nanoparticles, while also enabling targeted delivery and providing additional biological functions.

## Erythrocyte Membrane

The use of erythrocyte membrane (EM) as a protective "shell" nanoparticles offers several advantages.[43] EM is a natural lipid bilayer membrane with inherent biocompatibility, making it suitable for use in biomedical applications. This biointerface similarity allows the EM-modified nanoparticles to evade immune system clearance, leading to stable and long-term circulation in the blood. One example of EM-modified nanoparticles is a glucose-responsive nano-platform developed by He et al. CD47 (a transmembrane protein) is present on the EM, and when combined with signal-regulated protein α (SIRPα) expressed in macrophages, SIRPα transmits the so-called "do not-eat-me" inhibitory signal, which suppresses macrophage phagocytic activity. Meanwhile, insulin receptors and glucose transporters (GLUTs) present on the EM enable transmembrane transport of insulin and glucose, respectively. So in this study, insulin, glucose oxidase (GOx), and catalase (CAT) were co-encapsulated within ZIF-8 nanoparticles to form the "core". The surface of the "core" was then coated with EM as the "shell". Under hyperglycemic conditions, glucose can enter the nanoparticles through the GLUTs naturally present on the EM. MOFs have a rigid molecular structure that maintains the biological activity of the protein even under harsh conditions. Inside the nanoparticles, GOx oxidizes glucose, leading to the generation of gluconic acid. This acid rapidly lowers the local pH, triggering the collapse of ZIF-8 nanoparticles and subsequent release of insulin. As the glucose concentration decreases to normal blood sugar levels, less glucose is internalized, leading to an increase in pH and inhibiting insulin release.[31] The results demonstrated that the "core shell" GCI@ZIF-8@RM NPs could achieve long-term "smart" BGL-dependent insulin delivery with negligible risk of hypoglycemia when injected intravenously into type 1 diabetic mice.

Another example is the construction of a biomimetic nano-reactor by Liu et al. In this study, pH-responsive ZIF-8 nanoparticles were used as a stable carrier for encapsulating SOD-Fe and β-lapachone (LAPA). The nanoparticles were then camouflaged with tumor-targeting red blood cell membrane to protect the cargo enzymes from protease digestion and to prolong blood circulation time. The resulting biomimetic nano-reactor, SOD-Fe@Lapa-ZRF, exhibited specific targeting and killing of tumor cells. Under the catalysis of NAD(P)H:quinone oxidoreductase-1 (NQO1), LAPA produced $O^{2-}$•, which was 100 times more expressed in tumor cells compared to normal cells. The produced $O^{2-}$• was further converted into $H_2O_2$ through SOD-mediated catalytic reactions. The Fe nanoparticles in the nano-reactor rapidly ionized in the acidic tumor environment, releasing toxic hydroxyl radicals through a Fenton-like reaction, specifically killing tumor cells. Importantly, under neutral pH conditions, Fe nanoparticles were unable to catalyze $H_2O_2$, reducing oxidative damage to normal cells. In vivo experiments showed that SOD-Fe0@Lapa-ZRF could accurately play a catalytic cascade in the tumor microenvironment and specifically induce oxidative damage in 4T1 tumors.[33] Moreover, a groundbreaking approach was utilized to fabricate rOPH/ZIF-8 nanomaterials and subsequently encapsulate them within an innovative erythrocyte membrane-liposome hybrid membrane (E-Lipo) that had been modified with monosialic acid ganglioside

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**Table 1** Recent Research on the Use of Cell Membrane-Encapsulated ZIF-8 as a Drug Delivery System

| Biological Membrane | Nanocomposites | Loaded Drug | Disease Models/Cell Types | Functions |
|---|---|---|---|---|
| Cell Membrane | | | | |
| Red blood cell | CNP-NO@RBC | NO donor | Hemangioma | Photothermal/nitric oxide synergistic anti-tumor therapy[29] |
| | rOPH/ZIF-8@E-Lipo | Inner recombinant organophosphorus hydrolase | Organophosphorus poisoning | Significant protection against MP-induced AChE inactivation, oxidative stress, and cytotoxicity[30] |
| | GCI@ZIF-8@RM | Insulin, glucose oxidase (GOx), and catalase (CAT) | Type 1 diabetes mellitus | The nanoparticles stably maintain a long-term existence in blood circulation to achieve long-term insulin delivery[31] |
| | DOX@ZIF-8@eM-cRGD | Doxorubicin (DOX) | Cervical cancer | Prolong blood circulation, enhancing the tumor-specific accumulation[32] |
| | SOD-Fe@Lapa-ZRF | FeNP-embedded SOD (SOD-Fe), β-lapachone | Breast cancer | Killing tumor cells through multi-enzyme cascade[33] |
| 4T1 cell | ZDC@M | 2-dodecyl-6-methoxycyclohexa-2,5-diene-1,4-dione, sonosensitizer chlorin e6 | Breast cancer | Nanoparticle and sonodynamic co-therapy for cancer[34] |
| | mEHGZ | Epirubicin (EPI), Gox and hemin | Triple-negative breast cancer | Induces cascade-amplified ICD effect to promote dendritic cells (DCs) maturation and cytotoxic T lymphocytes (CTLs) infiltration into the tumor site[35] |
| | mCG@ZIF | Chloroquine (CQ, an autophagy inhibitor) and GOx | Triple-negative breast cancer | Inhibition of starvation-induced pro-survival autophagy and enhancement of starvation therapy[36] |
| | DIHPm | DOX and indocyanine green (ICG) | Triple-negative breast cancer | Synergistic photodynamic/photothermal/chemotherapy anticancer activity[37] |
| HepG2 | AQ4N/GOx@ZIF-8@CM | GOx and hypoxia activated prodrug banoxantrone (AQ4N) | Hepatocellular carcinoma | Starvation therapy and cascade amplificated chemotherapy[38] |
| | CDZs | Dihydroartemisinin (DHA) | Hepatocellular carcinoma | Homologous targeting ability and can accumulate in tumor tissues[39] |
| Stem cell | SCM/ZIF-8 | | Tissue repair | Increase MSCs' osteogenic potentials[40] |
| | DEX@ZIF-8-SCM | Dexamethasone (DEX) | Enhanced osteogenic differentiation and bone repair | Facilitates the specific uptake of mesenchymal stem cells (MSCs)[41] |
| MCF-7 | CC-ZIF | CRISPR/Cas9 gene | Breast cancer | Enhances the accumulation within the source cells and critically improves the targetability of any gene editing machinery[42] |

**Abbreviations**: CNP, carbon nanoparticle; rOPH, recombinant organophosphorus hydrolase; AChE, acetylcholinesterase; E-Lipo, enzyme immobilization and erythrocyte-liposome hybrid membrane; MP, methyl paraoxon; DOX, doxorubicin.

(GM1). The objective of this modification was to augment the capacity of the nanomaterials to traverse the highly impermeable blood-brain barrier (BBB), thereby facilitating their efficient penetration into the brain. The outcomes of the investigation evinced that the developed decontaminant evinced substantial preventive detoxification efficacy against methyl paraoxon (MP) poisoning and demonstrated the remarkable ability to successfully transgress the blood-brain barrier.[30] Furthermore, an additional study endeavored to enhance the therapeutic precision of cervical cancer treatment through the manipulation of the red blood cell membrane via cyclic RGD (cRGD) modification and the subsequent encapsulation of DOX within ZIF-8 nanoparticles.[32] This pioneering drug delivery system, boasting an impressive drug loading capacity of 49%, effectively harnessed the enhanced permeability and retention (EPR) effect to promote the preferential accumulation of nanoparticles within tumor tissues. In vivo studies confirmed that RGD-modified nanoparticles enhanced tumor-specific accumulation via integrin αvβ3 receptor-mediated pathway and were further evaluated in mice with human cervical cancer (HeLa) cells, with tumor inhibition up to 85.46%.

In summary, the use of erythrocyte membrane as a protective "shell" of ZIF-8 can enhance biocompatibility, stability and targeted drug delivery, which can stably maintain the drug a long-term existence in the blood circulation. It is a promising method for biomedical application.

## Cancer Cell Membrane

### HepG2 Cell Membrane

Taking into consideration the distinctive characteristics of tumor cell membranes, such as their ability to evade immune responses and exhibit homotypic targeting behavior,[44] as well as their capacity to retain antigens on the cell surface to stimulate immune responses and maintain homotypic cell adhesion for targeted drug delivery,[45] these membranes have been extensively explored for encapsulating nanoparticles in targeted tumor therapy. Specifically, cancer cell membranes offer the advantage of mimicking cancer cell behavior, thus avoiding phagocytosis by macrophage cells, possessing immune evasion abilities, prolonging circulation time, and facilitating targeted delivery in vivo.[46] In line with these advantages, recent research by Shao et al demonstrated the loading of GOx and the hypoxia-activated prodrug banoxantrone (AQ4N) into biodegradable ZIF-8 nanocarriers with large surface area, adjustable pores, and intrinsic pH induction, which were subsequently camouflaged with liver cancer cell (HepG2 cells) membranes. Upon accumulation at the tumor site, the biomimetic nano delivery system undergoes dissociation triggered by the acidic tumor microenvironment, leading to the release of GOx and AQ4N. GOx rapidly depletes endogenous glucose and oxygen, thereby cutting off the energy supply to tumor cells and inducing starvation therapy. Moreover, the intensified hypoxic environment within tumor cells activates the cytotoxicity of AQ4N for chemotherapy.[38] A tumor-bearing mouse model was established and the distribution of AQ4N/GOx@ZIF-8@CM was measured using an in vivo real-time fluorescence imaging system. The fluorescence intensity almost peaked at 12 h, which may be related to the EPR effect of the biomimetic nanoparticles. Thereafter, the fluorescence intensity gradually weakened after 24 hours. However, the fluorescence was still maintained for more than 48 hours, which may be due to the enhanced immune escape and specific targeting effects of the biomimetic CM. The therapeutic effect was greatly improved. Furthermore, an innovative approach has been developed that combines iron-doped ZIF-8 nanoparticles with dihydroartemisinin (DHA), based on the HepG2 tumor cell membrane. This methodology has been utilized to design a biomimetic nano-reactor that simulates the tumor cell membrane, which can be applied for low-toxicity and targeted treatments.[39]

### 4T1 Cell Membrane

The 4T1 tumor cell line serves as a widely utilized in vitro model system for investigating various aspects related to breast cancer, including its occurrence, development, and therapeutic interventions. Notably, this cell line has found extensive application in research endeavors pertaining to cancer biology and treatment strategies. By implanting the 4T1 tumor cells within ZIF materials, it becomes possible to simulate the complex microenvironment conducive to tumor growth. This sophisticated model system effectively assists researchers in elucidating the intricate mechanisms governing tumor initiation and progression, ultimately paving the way for the formulation of innovative therapeutic approaches targeting breast cancer. For example, Li et al developed a self-amplifying biomimetic nano-system called mEHGZ by encapsulating epirubicin (EPI), GOx, and chlorin e6 (Ce6) within ZIF-8 nanoparticles and coating them with tumor cell

membranes that overexpress calreticulin (CRT). This innovative approach aimed to enhance the response rate of immune checkpoint inhibitors, specifically anti-PD-L1 antibodies, in immunosuppressive tumors such as triple-negative breast cancer. The inclusion of EPI in the system facilitated the induction of immunogenic cell death (ICD), while GOx and Ce6 played crucial roles in mediating the generation of ROS, thereby enhancing the ICD effect. Furthermore, the tumor cell membrane enriched in CRT served as an "eat me" signal, promoting antigen presentation and release by dendritic cells (DCs) to initiate tumor immune surveillance. By utilizing this biomimetic delivery system, the researchers demonstrated amplified ICD effects through the oxidation of GOx, generation of hydroxyl radicals, and depletion of glutathione (GSH), ultimately enhancing the therapeutic efficacy of anti-PD-L1 antibodies.[35] In a similar vein, Ji et al designed a therapeutic system by incorporating apyrase and GOx into ZIF-8 nanoparticles, which were cleverly disguised as tumor cell membranes. Specifically, ZIF-8 was chosen as the carrier platform to maintain GOx and apyrase activity because ZIF-8 is stable under neutral physiological conditions, its small pore size prevents leakage of the enzyme and removes interference from external stimuli. More importantly, the nanoparticles encapsulated in the 4T1 tumor cell membrane have active tumor-specific targeting ability. This system effectively disrupted the energy supply of tumor cells by depleting ATP and glucose, leading to tumor cell death.[47]

It is evident that the integration of 4T1 tumor cells with ZIF materials holds great promise in the field of tumor research and treatment. This innovative approach not only enables the simulation of tumor growth environments but also facilitates the investigation of intricate tumor mechanisms. Harnessing the synergistic capabilities of 4T1 tumor cells and ZIF materials opens up new avenues for advancing our understanding of tumor biology and developing novel therapeutic strategies. Sun et al introduced PVP-stabilized ZIF-8 nanoparticles into a solution of dimethylformamide (DMF) containing $ZrCl_4$ and tetrakis (4-carboxyphenyl) porphyrin (TCPP), resulting in the formation of hollow porphyrin metal-organic frameworks (H-PMOF) with mesoporous shell structures. This system exhibited significantly enhanced photodynamic therapy (PDT) effects and served as an excellent drug carrier for co-loading the anticancer drugs DOX and Indocyanine Green (ICG). Remarkably, the H-PMOF system demonstrated a high drug loading capacity of 635%. Additionally, when disguised with 4T1 cell membranes, the system displayed prominent homologous tumor targeting. It effectively exerted anticancer and anti-metastatic effects at low dosages through synergistic PDT/photothermal therapy (PTT)/chemotherapy.[37] In another study, Cheng et al constructed a biomimetic cascaded nanocatalytic reactor (Mem@Gox@ZIF-8@BDOX) by assembling a hydrogen peroxide-sensitive camptothecin prodrug (BDOX) and GOX onto ZIF-8, and then used 4T1 cell membrane camouflage to confer immune escape and homologous targeting ability to nanoparticles. This system was utilized for tumor-targeted starvation therapy.[48]

Previous research has demonstrated that ZIF-8 nanoparticles can modulate the level of autophagy in cancer cells, resulting in either a survival-promoting or death-promoting effect depending on the specific cell line.[49,50] Autophagy induction often serves as a protective mechanism for cancer cells when exposed to starvation treatment reagents.[51] Li et al employed ZIF-8 as a nanocarrier for Chloroquine (CQ) and GOx, which were encapsulated within 4T1 cell membranes (mCG@ZIF). ZIF-8 sensitizes cancer cells to autophagy inhibitors by inducing pro-survival autophagy. Upon cellular uptake, GOx encapsulated within mCG@ZIF induces cell starvation by depleting endogenous glucose. This leads to an increase in ROS levels, which ultimately kill cancer cells. The dual autophagic responses of ZIF-8 and starvation-induced pro-survival autophagy allow for the release of CQ under acidic conditions. CQ exerts cytotoxic effects on cancer cells by inhibiting the autophagy process, thereby enhancing the therapeutic efficacy of GOx.[36]

## Neutrophil Membrane

Neutrophils, a pivotal component of the immune system, exhibit a diverse range of functions including antibacterial, anti-inflammatory, and antitumor activities. Recent investigations have shed light on the potential of neutrophil membranes for the encapsulation of nanomaterials, thereby amplifying their utility in the realm of biomedicine. Notably, when applied to ZIF nanoparticles, neutrophil membranes can be employed to enrobe and modify these particles, thereby bolstering their efficacy in drug delivery and therapeutic interventions. The researchers conducted a study in which they incorporated GOX and chloroperoxidase (CPO) into ZIF-8, resulting in the production of HClO via enzyme-catalysis. To specifically target inflammation, these enzyme-loaded ZIF-8 particles were subsequently enveloped in neutrophil membranes (NM), creating what was referred to as "super neutrophils" (denoted as GCZM).[52] Remarkably, both

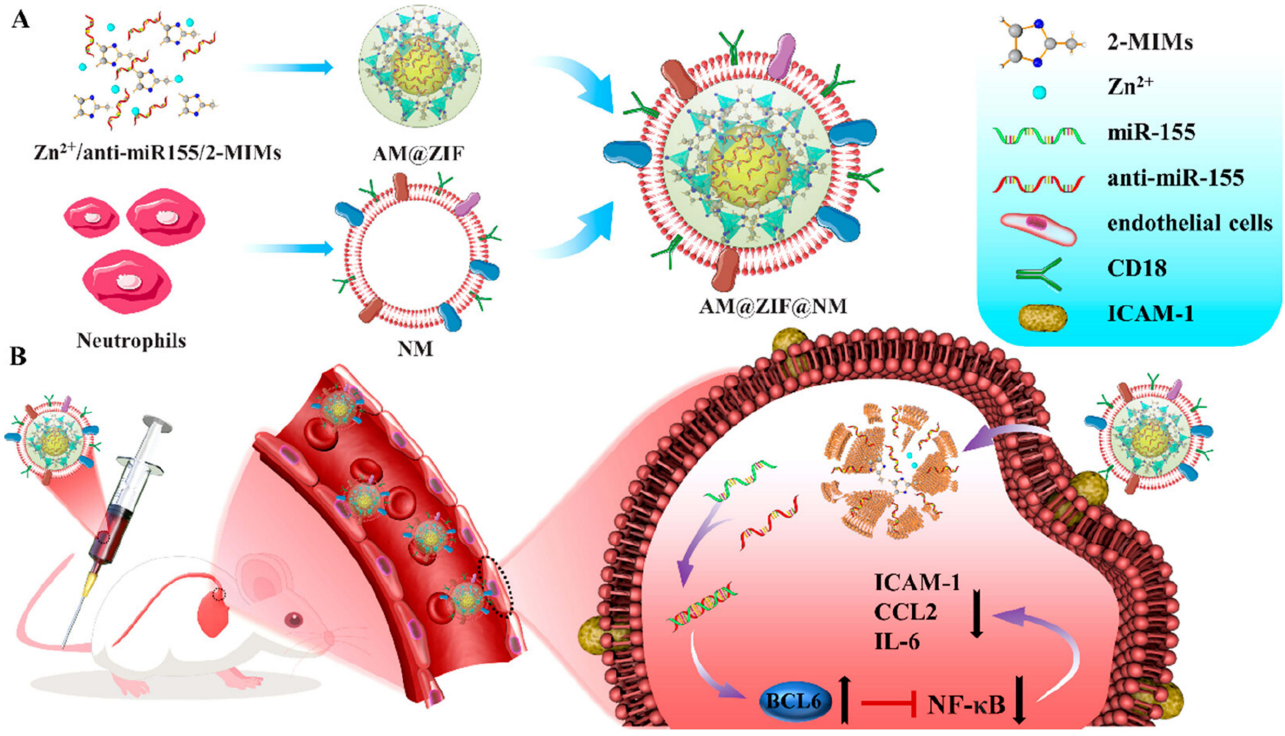


**Figure 5** Schematic illustration of the antiatherosclerosis targeted treatment by using neutrophil-membrane-coated anti-miR-155-loaded ZIF-8 nanoparticles (AM@ZIF@NM NPs). (**A**) Preparation of AM@ZIF@NM. (**B**) Sketch of targeted treatment of atherosclerosis with AM@ZIF@NM NPs by silencing miR-155 and inhibiting NF-κB activation. Reprinted with permission from Liu Y, He M, Yuan Y, et al. Neutrophil-membrane-coated biomineralized metal-organic framework nanoparticles for atherosclerosis treatment by targeting gene silencing. *ACS Nano*. 2023;17(8):7721–7732. Copyright © 2023 American Chemical Society.[53]
**Abbreviations**: AM, anti-miR-155; NM, neutrophil-membrane; NPs, nanoparticles; NF-κB, nuclear factor-Kb, ICAM-1, intracellular adhesion molecule-1.

in vitro and in vivo experiments demonstrated that these artificial "super neutrophils" exhibited HClO activity levels seven times higher than natural neutrophils. In vivo studies showed that the GCZM group exhibited fewer and smaller premetastatic niches than the other groups, indicating excellent antitumor ability of the "super neutrophils" GCZM. In addition, scientists introduced a novel nanodelivery platform termed AM@ZIF@NM (Figure 5A), which involves the encapsulation of neutrophil membranes.[53] This strategy capitalizes on the enhanced targeting capabilities provided by neutrophil membranes, which can specifically interact with intercellular adhesion molecule-1 (ICAM-1) on plaque endothelial cells via the CD18 protein present in the neutrophil membrane. Through this targeted approach, successful delivery of antisense oligonucleotides (ASOs) to sites of inflammatory atherosclerotic lesions was achieved. AM@ZIF@NM NPs effectively slowed the progression of atherosclerosis by inhibiting the activation of the NF-κB pathway, while the delivery of anti-miR-155 effectively reduced the expression of miR-155 and saved the expression of its target gene BCL6 (Figure 5B). This innovative technique holds great promise for precise and effective delivery of therapeutics to inflammatory sites. However, there remain several unresolved issues that necessitate attention, including the extraction of neutrophil membranes and the stability of nanomaterial encapsulation. Thus, future investigations should delve into the application of neutrophil membranes in ZIF and tackle the associated technical hurdles.

## Stem Cell Membranes

Stem cell membranes have attracted considerable attention in recent years due to their unique properties and potential applications in various fields, including biomedicine. One promising area of research is their utilization in ZIF nanoparticles. The incorporation of stem cell membranes into ZIF nanocarriers offers several advantages. Firstly, stem cell membranes possess a natural ability to target specific tissues or organs, making them ideal for targeted drug delivery. By coating ZIF nanoparticles with stem cell membranes, researchers can enhance the specificity and efficiency of drug delivery to diseased cells or tissues. Ren et al successfully employed stem cell membranes (SCMs) to encapsulate ZIF-8 nanoparticles, thereby mimicking natural molecules and improving biocompatibility as well as targeted delivery

capabilities towards mesenchymal stem cells (MSCs). The resultant SCM/ZIF-8 nanoparticles exhibited adjustable sustained release of zinc and facilitated specific internalization by MSCs. Notably, the internalized SCM/ZIF-8 nanoparticles demonstrated exceptional biocompatibility and significantly enhanced the osteogenic potential of MSCs.[40] Additionally, Liang et al developed a ZIF-8 nano-platform loaded with dexamethasone (DEX) and enveloped by SCMs, resulting in efficient delivery of DEX and promoting DEX-mediated bone repair. However, further research is required to optimize the extraction and purification of stem cell membranes and to understand their interactions with ZIF nanoparticles.

## Extracellular Vesicles (EVs)

There exists a strong connection between extracellular vesicles (EVs) and the cell membrane. EVs are small vesicular structures that originate within the cell and interact dynamically with the cell membrane. Various types of cells secrete extracellular vesicles, including exosomes (Exo) and microvesicles (MVs), which possess a lipid bilayer structure. These vesicles have the ability to fuse with cell membranes, providing a route for the transportation of vesicular contents between cells and evading phagocytosis by reticuloendothelial cells, thereby enabling their stability in circulation. In a particular study, proteins were successfully encapsulated in ZIF-8, a material known for its high drug loading capacity and encapsulation efficiency. Furthermore, these proteins were modified with EVs, resulting in an impressive efficiency of approximately 97%. In vitro and in vivo investigations have demonstrated that EV-mimicking nanoparticles not only safeguard proteins from enzymatic degradation and immune clearance, but also selectively target homotypic tumor sites, enhancing the uptake and autonomous release of proteins following internalization by tumor cells.[46]

In our previous research,[54] the anti-rheumatoid arthritis drug methotrexate (MTX) was loaded into ZIF-8 and then disguised with MVs secreted by macrophages (Figure 6), resulting in nanoparticles with high drug loading (70%) and encapsulation efficiency (82%). Negatively charged MVs can bind to the positively charged surface of ZIF-8 via electrostatic and hydrophilic interactions, while unsaturated zinc ions on the ZIF-8 nanoparticle surface can coordinate with the P–O bonds of the phospholipid molecules in MVs, stabilizing the nanoparticle. In vitro and in vivo experiments demonstrated that the nanoparticles achieve sufficient release at inflamed acidic sites in arthritis and exhibit prolonged retention in joint tissues of arthritic rats. Moreover, the hepatotoxicity of the nanoparticles was significantly lower than that of free MTX, while they also significantly downregulated pro-inflammatory cytokine levels in arthritic rats. These effects, along with significantly reduced histological scores and decreased cartilage degeneration and joint destruction,

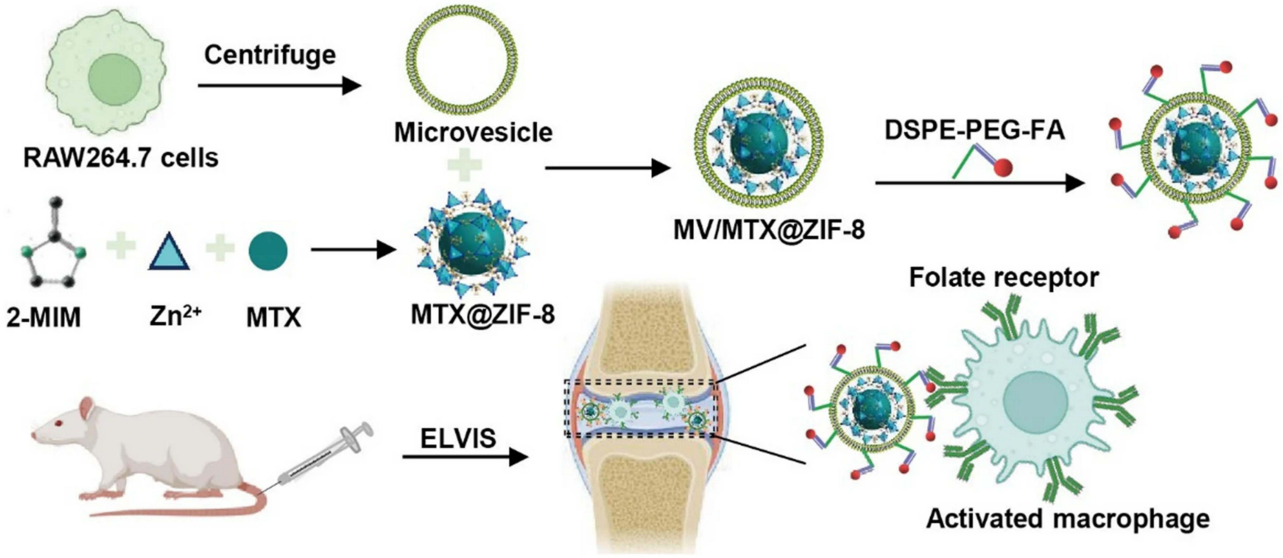


**Figure 6** Schematic illustration of the procedure of preparing biomimetic FPD/MV/MTX@ZIF-8 nanoparticles for targeting and intracellular delivery of drugs. Reprinted from Wang Y, Jia M, Zheng X, et al. Microvesicle-camouflaged biomimetic nanoparticles encapsulating a metal-organic framework for targeted rheumatoid arthritis therapy. *J Nanobiotechnology.* 2022;20(1):253. Creative Commons.[54]

**Abbreviations**: FPD, DSPE-PEG-FA; MV, microvesicle; MTX, methotrexate; ELVIS, extravasation through leaky vasculature and subsequent inflammatory cell-mediated sequestration.

indicate that our developed nano-delivery system has the potential to be a safe and effective drug delivery system for treating rheumatoid arthritis. Furthermore, we encapsulated Dex in ZIF-8 and camouflaged the nanoparticles with MVs. Experimental results have demonstrated that the camouflaged nanoparticles can prevent phagocytosis and prolong their circulation time.[55]

## Polysaccharide

HA is a naturally occurring Polysaccharide present in the extracellular matrix, renowned for its remarkable biocompatibility and safety.[56,57] Its unique polysaccharide structure grants it a high drug loading capacity and allows for targeted delivery and selective drug release by binding to specific receptors on cell surfaces. Additionally, HA extends the retention time of drugs in local tissues, thereby enhancing their therapeutic effectiveness. In a study, researchers employed a one-step self-assembly approach to efficiently encapsulate the anti-atherosclerosis (AS) drug simvastatin (SIM) within ZIF-8 (SIM/ZIF-8), which was subsequently coated with HA to form the SIM/ZIF-8@HA nanoplatform. This resultant nanoplatform demonstrates the ability to accumulate effectively in plaque areas through specific recognition between HA and CD44. Moreover, the nanoplatform exhibits favorable biocompatibility and does not induce any adverse effects during treatment.[58]

### The Treatment of Osteosarcoma

Presently, the treatment of osteosarcoma often relies on the administration of tumor-targeted drugs. However, these therapeutic strategies are constrained by the non-uniform distribution of drugs within the body as well as their deleterious effects on healthy cells. To surmount these limitations, investigations have commenced into the utilization of nanomaterials for site-specific drug delivery to attenuate harm inflicted upon normal cells. In this regard, a notable initiative encompasses the fabrication of a dual-targeting nanocarrier that combines ZIF with HA. A NF-κB inhibitor was loaded into ZIF-8, forming a composite called CZ. To enhance its specificity and efficacy, CZ was further coated with hyaluronic acid/alendronic acid (HA/ALN). The resulting nanocarrier, CZ@HA/ALN, was found to effectively inhibit the PD-1 immune checkpoint, leading to the differentiation of Raw 264.7 cells into anti-tumor macrophages instead of osteoclasts. As a result, CZ@HA/ALN demonstrated significant suppression of bone resorption and tumor progression, ultimately improving the bone microenvironment.[59] In another study conducted by Yang et al, a bone-targeted nanocarrier with detachable capability was designed using a combination of ZIF-8 and hyaluronic acid modified with a bone-targeted and MMP enzyme-sensitive peptide. The cargo used in this nanocarrier was bortezomib (BTZ), a drug commonly used for the treatment of bone metastases. By utilizing the bone-targeting properties of hyaluronic acid, which binds to CD44 receptors overexpressed on tumor cells, the endocytic uptake and cellular toxicity of the nanoparticles were significantly enhanced.[60]

### Chemodynamic Therapy

ZIF-8 nanoparticles exhibit a significantly large surface area and an intricate porous structure, facilitating the encapsulation of a substantial amount of pharmaceutical agents. Moreover, the structural characteristics of ZIF-8 nanoparticles can be precisely manipulated through specific conditions, such as variations in solvent composition or temperature, enabling meticulous regulation of drug release kinetics. This chemodynamic therapy (CDT) imparts enhanced bioavailability to therapeutic agents and achieves controlled and protracted drug delivery within designated circumstances, thereby augmenting treatment efficacy. Several studies have utilized biomimetic ZIF-8 nanoparticles for CDT. For instance, in a study conducted by Cui et al, biodegradable Cu/ZIF-8 shell-coated CaO nanoparticles loaded with the chemotherapeutic drug DOX were prepared.[61] These nanoparticles were further encapsulated with a HA shell to provide targeting functionality and improve cycling stability, resulting in the formation of CaO/DOX@Cu/ZIF-8@HA. DOX plays a role in chemotherapy and bioimaging, while CaO generates highly reactive hydroxyl radicals via the Cu-Fenton-like reaction, providing chemodynamic therapy. Another study by Zhou et al involved the development of pH-responsive ZIF-8 modified with HA and encapsulating the chemotherapeutic drug mitoxantrone (MIT) and the DNA demethylating agent hydralazine (HYD).[62] These components were encapsulated within ZIF-8 to obtain (M+H)@ZIF/HA nanoparticles, which exhibited a prolonged blood circulation time. This approach not only converts tumors into antigen depots,

stimulating potent immune responses, but also inhibits immune evasion, leading to significant tumor eradication and establishment of long-term immune memory against metastasis. Additionally, a study focused on bladder cancer (BCa) utilized hyaluronic acid-modified ZIF-8 nanoparticles co-encapsulating PdCuAu nanoparticles and glucose oxidase.[63] This formulation, termed ZIF-8/PdCuAu/GOx@HA (ZPG@H), acted as a cascade nanoreactor for starvation therapy and iron death in BCa. The HA modification allowed for specific targeting of BCa cells expressing the CD44 receptor. Furthermore, intracellular hyaluronidase (Hyase) decomposed the HA, which was then oxidized by $O_2$ to generate $H_2O_2$ for iron death therapy through the production of a large amount of ROS. There have also been studies of targeting nanoparticles to tumor sites via CD44 by encapsulating HA. Due to the excellent water solubility of low-molecular-weight HA was coated on the surface of ZIF-8-IR820-MnPc nanoparticles. Under 808 nm laser irradiation, HA acted as a "sponge" in this nanosystem, aiding in the generation of singlet oxygen species. Systemic energy depletion by synergising "zinc interference"-mediated inhibition of glycolysis with zinc-activated tumor-specific depletion of GLUT1 (glucose transporter 1).[64] In a recent study,[65] a CDT catalyst, a ferrocene-(phenylboronic acid pinacol ester) conjugate (Fc-BE), and a photosensitiser, IR825, were effectively encapsulated in ZIF-8. The cinnamaldehyde-modified hyaluronic acid (HA-CA), which up-regulates $H_2O_2$ capacity, was also encapsulated on the surface of ZIF-8 via metal-ligand interactions to form active-targeted nanoparticles (NPs@Fc-BE&IR825) (Figure 7). Combining chemodynamic therapy with photodynamic therapy, CDT/PDT enhancement was achieved through photothermal effects, $H_2O_2$ elevation and GSH depletion.

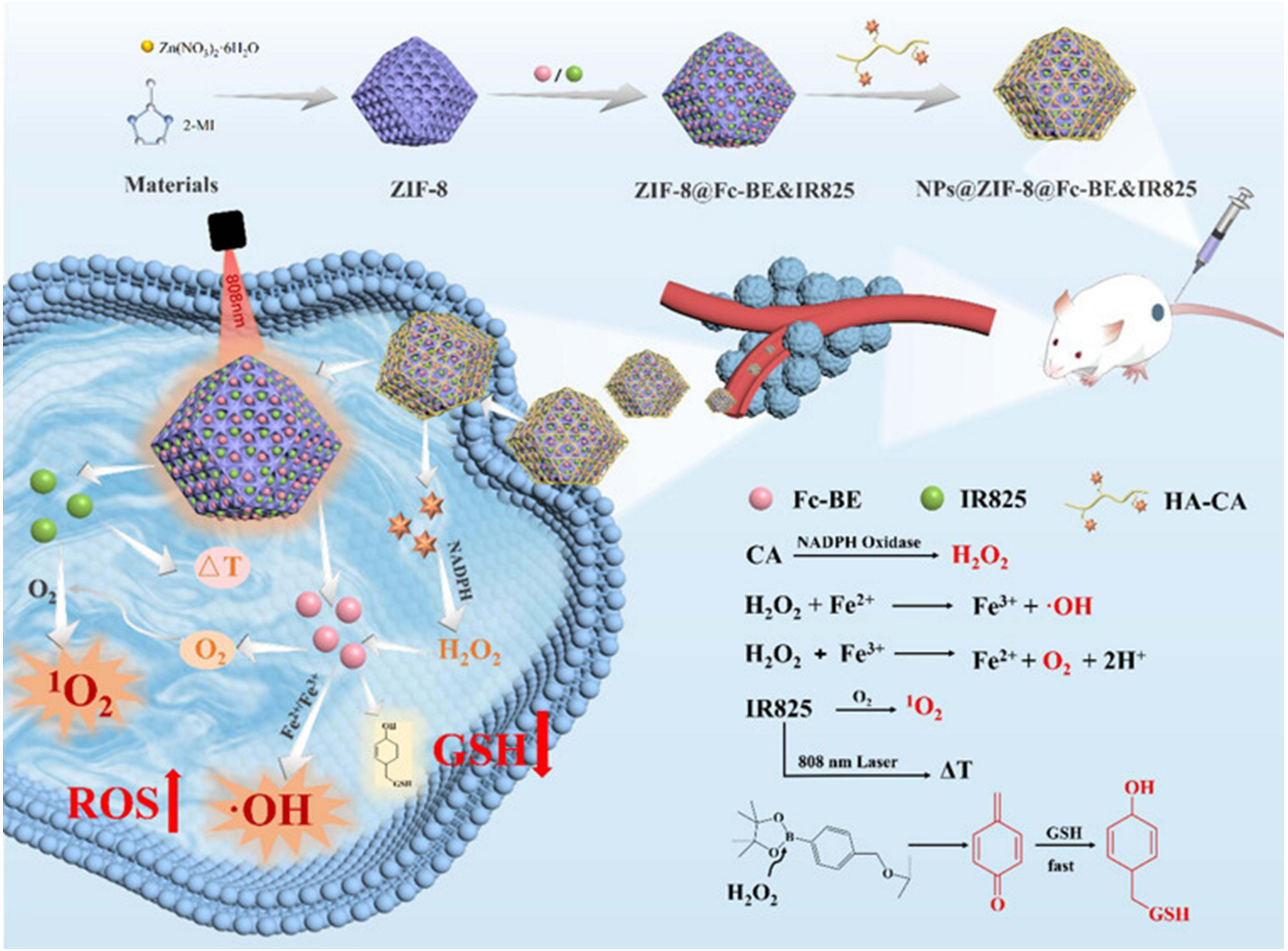


**Figure 7** $H_2O_2$-Elevation, and GSH-Consumption Triply Enhanced CDT/PDT through Accelerated and Boosting Oxidative Stress Amplification. Reprinted with permission from Bai Y, Liu M, Wang X, Liu K, Liu X, Duan X. Multifunctional nanoparticles for enhanced chemodynamic/photodynamic therapy through a photothermal, H(2)O(2)-elevation, and GSH-consumption strategy. *ACS Appl Mater Interfaces*. 2023;15(48):55379–55391. Copyright © 2023 American Chemical Society.[65]

**Abbreviations**: $H_2O_2$, hydrogen peroxide; GSH, glutathione; CDT, chemodynamic therapy; PDT, photodynamic therapy; Fc-BE, ferrocene-(phenylboronic acid pinacol ester) conjugate; HA-CA, cinnamaldehyde-modified hyaluronic acid; ROS, reactive oxygen species.

### Antimicrobial Therapy

ZIF-8 has demonstrated significant potential as an antimicrobial material in various applications. For instance, Yang et al developed a multifunctional therapeutic material by incorporating naringin into ZIF-8 and coating it with HA. This material exhibited excellent stability and drug loading capacity, enabling sustained release in vivo. The presence of surface-bound HA facilitated the penetration of active ingredients into cells, effectively exerting antibacterial properties.[66] In a similar study, Tan et al utilized HA modification on ZIF-8 loaded with silver nanoparticles (Ag NPs), resulting in nanoparticles that exhibited strong inhibition against the growth of Escherichia coli (99.1%) and Staphylococcus aureus (99.5%) while maintaining good biocompatibility and no impact on cell growth.[67] Additionally, Liang et al synthesized an antibacterial gel by incorporating dopamine-modified hyaluronic acid (HA-DA) and ZIF-8 loaded with dopamine-modified hematoporphyrin monomethyl ether (HMME).[68] This gel demonstrated rapid haemostasis through blood-induced shape recovery and enhanced coagulation, as well as anti-cancer effects through acoustic dynamics in a liver cancer model.

In addition to the aforementioned applications, HA-encapsulated ZIF nanoparticles have also found utility in the treatment of various other diseases. A nano-drug delivery system, HA-SS@CuS@ZIF-8@TPZ&TBMACN (HSCZTT), has been developed to overcome detoxification barriers and achieve precise drug release of tirapazamine (TPZ) by encapsulating it with HA.[69] Another study by Song et al involved the design and construction of a novel surface molecularly imprinted polymer, ZIF-8/DOX-HA@MIP, which utilized HA-modified ZIF-8 as a substrate for loading DOX and employed a responsive molecularly imprinted polymer membrane as the shell. This system demonstrated high drug loading efficiency (over 88%).[70] Additionally, Yu et al synthesized Curcumin@ZIF-8@HA nanoparticles by exploiting the pH-dependent solubility of curcumin and the electrostatic interaction between zinc ions and carboxyl groups of HA.[71] These nanoparticles exhibited promising therapeutic efficacy against breast cancer. However, it has been observed that ZIF-8 exhibits high toxicity at concentrations above 30 μg/mL, which limits its application in drug delivery systems (DDS). To address this issue, Khalilian et al proposed a new strategy to synthesize biocompatible ZIF-8 by synthesizing it in an aqueous medium at room temperature in the presence of gum arabic (GA) (Figure 8). GA, a heteropolysaccharide extracted from Acacia trees, offers advantages such as biocompatibility, non-toxicity, and good water solubility. The resulting ZIF-8-GA exhibited higher biocompatibility compared to ZIF-8, with a determined non-toxic concentration of 70 μg/mL, whereas the non-toxic concentration of ZIF-8 determined by MTT assay was 30 μg/mL.[72]

## Peptides

Peptides, as integral constituents of drug carriers, assume a pivotal role in attaining accurate delivery and targeted transportation of therapeutic agents. Furthermore, peptides confer assembly stability to drug carriers, thereby facilitating the formation of robust nanoparticles, microcapsules, or hydrogel structures that shield drugs from extraneous environmental factors.

### Bovine Serum Albumin

PDT is a novel therapeutic modality that primarily utilizes the irradiation of a specific wavelength of light onto a photosensitizer to generate a form of reactive oxygen species. This reactive oxygen species has the ability to kill cancer cells, viruses, and other pathogens. However, a major challenge of PDT lies in the effective delivery of the photosensitizer to target cells. The Multifunctional Bionic Nanomedicine Delivery System (MBNDS) holds potential in addressing this issue. This system mimics biological processes and mechanisms to enhance the efficiency and precision of drug delivery. For instance, Deng et al synthesized iridium oxide nanoparticles (IrO NPs) with peroxidase-like activity and PTT effect through hydrolysis. These particles were subsequently coated with a ZIF-8 shell to enhance the physical absorption of chlorin e6 (Ce6), and functionalized with bovine serum albumin-folic acid (BSA-FA) for tumor cell targeting. The resulting IrO@ZIF-8/BSA-FA nanocomposites demonstrated a photothermal conversion efficiency of 62.1% under laser irradiation. Furthermore, the incorporation of Ce6 endowed the nanoplatform with the capability to induce cell apoptosis via a ROS-mediated mechanism under near-infrared laser irradiation at 660 nm. This led to synergistic photothermal therapy-photodynamic therapy (PTT-PDT) effects in the treatment of osteosarcoma.[26] Similarly, Lv et al developed a multifunctional nanoplatform (BSArGO@ZIF-8 NSs) in their study, where ZIF-8 nanoparticles were coated onto the surface of graphene oxide (GO),

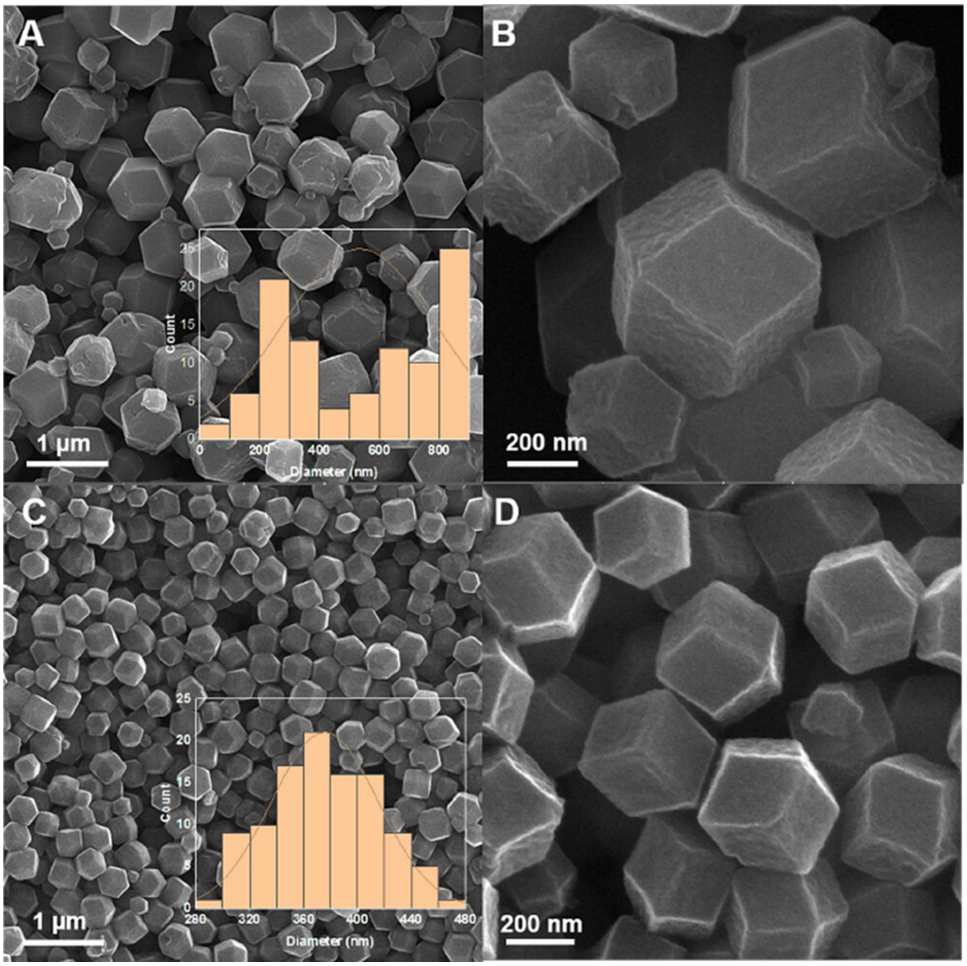


**Figure 8** FESEM images of (**A** and **B**) ZIF-8-CCM and (**C** and **D**) ZIF-8-GA CCM. Reprinted with permission from Khalilian SF, Tohidi M, Rastegari B. Synthesis of biocompatible nanoporous ZIF-8-gum arabic as a new carrier for the targeted delivery of curcumin. *ACS Omega*. 2023;8(3):3245–3257. Copyright © 2023 The Authors. Published by American Chemical Society. This publication is licensed under CC-BY-NC-ND 4.0.
**Abbreviations**: FESEM, field-emission scanning electron microscopy; GA, gum arabic; CCM, curcumin.

followed by reduction with ascorbic acid and modification with BSA.[73] This nanocomposite resulted in zinc overload within cells, resulting in increased ROS production and broad-spectrum cytotoxicity against various types of cancer cells. Overall, the combined effect of ion interference and photothermal therapy mediated by BSArGO@ZIF-8 NSs, along with the photothermal effect of reduced graphene oxide (rGO), led to effective apoptosis, inhibition of cell proliferation, and angiogenesis, thereby exhibiting significant tumor suppression effects.

## Other Peptides

The blood-brain barrier (BBB) poses a significant challenge in delivering drugs to the brain. One approach to overcome this obstacle is to utilize the rabies virus glycoprotein (RVG), which binds to the nicotinic acetylcholine receptor (nAChR) on brain endothelial and neuronal cells, facilitating viral entry and infection. Wu et al developed RVG 15 -PEG@DTX@ZIF-8 bionanoparticles by encapsulating DOX within ZIF-8 wrapped with the RVG 15 peptide. This biomimetic nanotherapeutic system demonstrated brain-targeting and penetration capabilities, enabling efficient elimination of glioblastomas.[74] The RVG 15 peptide specifically binds to nAChR on brain endothelial and neuronal cells, allowing the nanoparticles to cross the BBB and enter the brain. Once inside the tumor cells, the DTX payload is released in a precise pH-sensitive manner due to the pH-responsive degradation of the ZIF-8 carrier within the endosomes and/or lysosomes. In vivo experiments (Figure 9), Magnetic Resonance Imaging (MRI) and images of brain tissues showed a significant reduction in the average glioma area in mice treated with RVG 15-PEG@DTX@ZIF-8 (Figure 9B–D). There was no notable decrease in body weight, and survival time was prolonged (Figure 9E and F). Additionally, TUNEL assays revealed higher levels of apoptosis in tumor

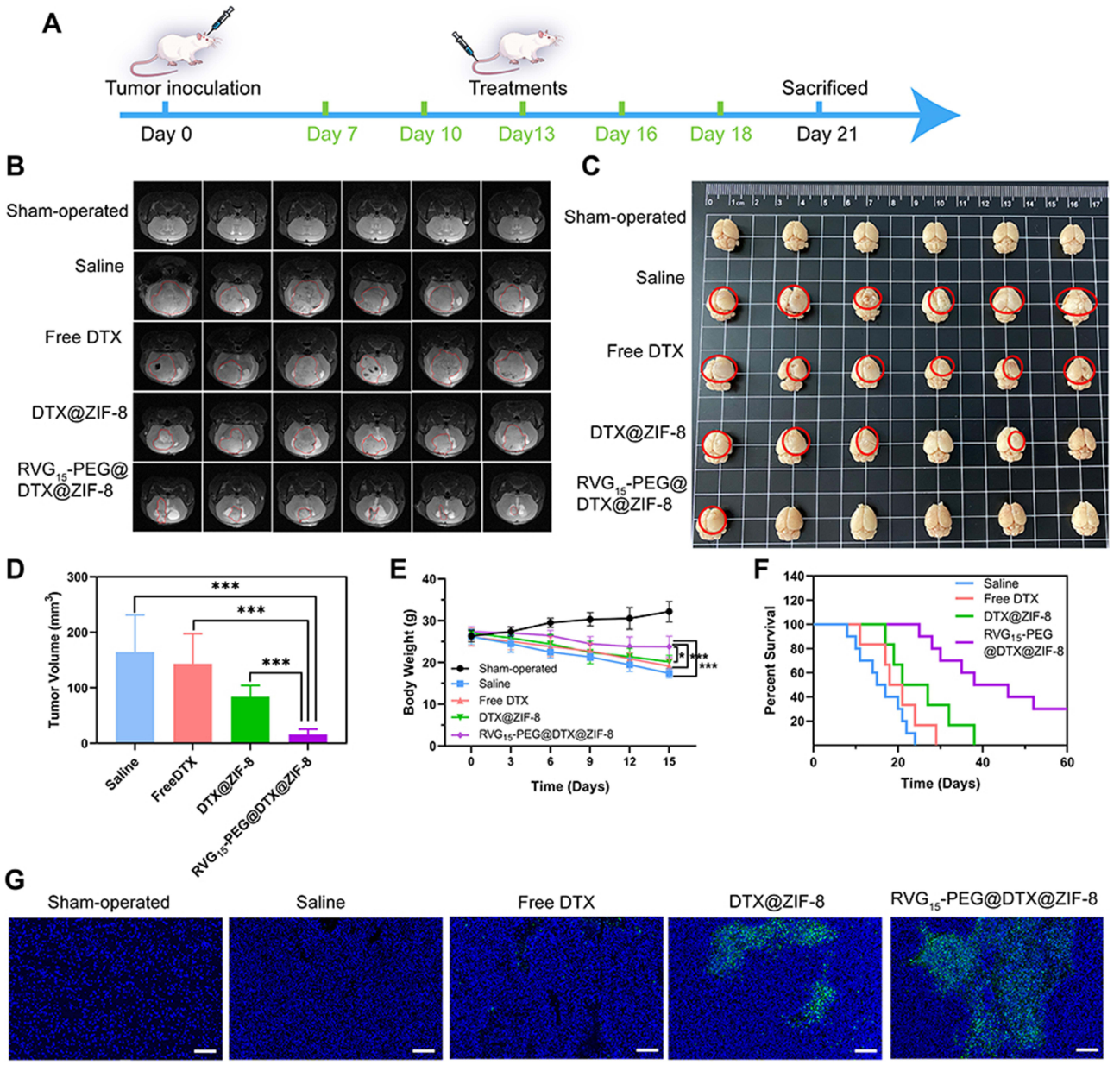


**Figure 9** In vivo anti-glioma efficacy. (**A**) Schematic diagram of in vivo anti-glioma effect study. (**B**) MRI of the brain in sham-operated group and brains from orthotopic glioma mice. (**C**) Images of brain tissues isolated from orthotopic glioma mice. (**D**) Quantitative tumor volume analysis of (**B**). (**E**) Body weight change of glioma tumor mice. (**F**) Kaplan–Meier survival curves of percentage survival of orthotopic glioma mice. (**G**) TUNEL assay of orthotopic glioma tumor tissues isolated from mice. Means ± SD, n = 6; *P < 0.05, ***P < 0.001. Reprinted with permission from Dove Medical Press. Wu H, Liu Y, Chen L, et al. Combined biomimetic MOF-RVG15 nanoformulation efficient over BBB for effective anti-glioblastoma in mice model. *Int J Nanomed*. 2022;17:6377–6398.[74]

**Abbreviations**: MRI, magnetic resonance imaging; DTX, docetaxel; $RVG_{15}$, glycoprotein 15.

tissues from treated mice (Figure 9G). In another study, a novel peptide named AREYGTRFSLIGGYR was discovered and used to modify ZIF-8 for targeted delivery to MCF-7 breast cancer cells.[75]

## Discussion and Prospect

In recent years, there has been a growing interest in the medical field regarding the use of MOFs due to their unique advantages, such as controllable pore size, ease of modification, cationic nature, and high drug storage capacity.[76] Among these MOFs, ZIF-8 has been extensively studied in the field of drug delivery due to its high porosity, ease of modification, and excellent biocompatibility. Zinc, an essential trace element in the human body, is a highly biocompatible metal ion, making it clinically safe.[77] The size of ZIF-8 nanoparticles can range from tens to hundreds of

nanometers, and particles within the range of 10 nm to 200 nm can passively target lesion tissues through the enhanced permeability and retention effect. Studies have shown that ZIF-8 nanoparticles can effectively target cancer cells, deliver chemotherapeutic agents with enhanced efficacy, and reduce systemic toxicity compared to conventional drug delivery methods. The pH-sensitive nature of ZIF-8 allows for controlled drug release in the acidic tumor microenvironment, improving therapeutic outcomes. Furthermore, the versatility of ZIF-8 in surface modification and functionalization provides opportunities for targeted drug delivery and combination therapy approaches. By incorporating targeting ligands or imaging agents onto ZIF-8 nanoparticles, researchers have been able to improve tumor specificity and monitoring of drug delivery.[78]

However, the utilization of ZIF-8 as a drug delivery carrier may lead to non-uniform drug release from its structure, resulting in an inadequate maintenance of the effective drug concentration at therapeutic levels, thus compromising drug efficacy. Additionally, fluctuations in pH levels and enzymatic activity can induce structural instability or degradation of ZIF-8, thereby influencing both drug release dynamics and overall stability.[79] In order to address these challenges, biomimetic mineralization or surface coating strategies have emerged as promising approaches. For example, the utilization of cancer cell membranes, red blood cell membranes, and platelet membranes has gained attention in recent years due to their ability to prolong circulation time through immune evasion. Recent studies have provided evidence of the potential of biomimetic material-encapsulated ZIF-8 to address a variety of challenges in drug delivery. These challenges include targeted delivery, enhanced therapeutic efficacy, and minimization of adverse effects. An important advantage of employing biomimetic material encapsulation is its ability to replicate the natural interaction between cells, thereby improving biocompatibility and reducing immune responses. The application of this system is primarily determined by two key factors. Firstly, it leverages the intrinsic targeting capabilities of biomimetic materials.[80,81] Secondly, the acid sensitivity of ZIF-8 plays a crucial role, as it undergoes hydrolysis at acidic lesion sites, facilitating the release of the corresponding drug.[82] Moreover, this approach allows for precise targeting of specific tissues or cells, resulting in increased drug accumulation at the desired site and improved therapeutic effects.

Despite the significant progress made in this field, several challenges need to be addressed before the full application of biomimetic MOF nanocarriers. To optimize therapeutic outcomes, it is essential to enhance the extraction of biomimetic materials, minimize potential losses following immobilization onto MOF-NPs, and improve the inner surface properties of MOF pores, such as surface charge or pH. Another issue is the problem of inhomogeneous encapsulation of biomimetic materials, which can lead to inconsistent drug release. In general, the process of obtaining cell membranes involves the separation of cells through multiple centrifugation-based methods. Subsequently, the cells are subjected to hypotonic cell lysis or repeated freeze-thaw treatments, and soluble proteins are removed by centrifugation to obtain purified cell membrane fragments. However, this approach is complicated and inefficient. In addition, under specific in vivo or in vitro conditions, cell membranes may be affected by biochemical effects, temperature changes, or mechanical stresses, resulting in loss of integrity or degradation. This can impact the stability and functionality of the drug delivery system. Additionally, cell membranes may trigger immune or toxic reactions upon contact with an organism. Certain components or structures within the membranes may induce cytotoxic or inflammatory responses, thereby limiting their safety and feasibility for clinical use.

Finally, the synthesis and functionalization of MOF-NPs involve intricate procedures, which may present challenges for large-scale manufacturing and efficient quality control. The synthesis of ZIFs typically involves precisely controlled synthetic conditions, including solvent selection, temperature, pH, among other factors. When transitioning ZIFs from the lab to clinical application, it is essential to ensure the reproducibility and scalability of the manufacturing process to meet the demands of large-scale production. Additionally, the formulation stability of ZIFs is crucial, as these materials may degrade or become ineffective due to environmental conditions, which can impact treatment efficacy. Although their safety and efficacy have been demonstrated through in vitro and in vivo, comprehensive long-term in vivo safety data and extensive preclinical research are still necessary. While ZIFs have shown potential anti-tumor activity in animal models of biomedical disease, their long-term safety and potential toxic side effects in the human body require in-depth research. Some ZIFs may trigger allergic reactions, cytotoxicity, or other adverse effects, so extensive toxicological assessments and safety testing must be conducted before clinical application. To overcome

these challenges, critical considerations include conducting thorough research on their long-term safety, optimizing synthesis processes for reproducibility and scalability, and developing stable formulations to ensure efficacy and stability during clinical use.

Overall, while ZIFs hold great potential in drug delivery, increased research efforts are necessary to address safety and technical challenges to achieve successful clinical application.

## Conclusion

In general, the use of biomimetic ZIF-8 nanoparticles in drug delivery systems has demonstrated significant potential in the field of disease treatment. By mimicking the characteristics of natural biomimetic materials, this biomimetic drug delivery system can achieve efficient drug carrier transport, targeted release, and biocompatibility, offering novel possibilities for medication therapy. Its unique structural design enables precise delivery of drugs to target sites, enhancing drug bioavailability and therapeutic effects, bringing about significant breakthroughs and advancements in clinical medicine.

## Acknowledgments

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## Disclosure

The authors have declared no conflicts of interest in this work.

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