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REVIEW

Key Tumor Responsive ZIF-8 Nanocarriers for Effective Anti-Cancer Therapeutics

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Abstract: The intricate pathological features of the tumor microenvironment (TME) collectively contribute to therapeutic resistance, thereby substantially constraining the antitumor efficacy of conventional treatments. Zeolitic imidazolate framework-8 (ZIF-8), a pH-responsive metal-organic framework material, serves not only as an efficient drug delivery system but also actively participates in TME remodeling through the release of Zn^{2+} upon its degradation. This dual function as both a "carrier" and an "effector" offers a synergistic mechanism to mitigate therapeutic resistance. The article reviews recent research on ZIF-8, focusing on its role in targeted drug delivery and its transformation from a passive carrier to an active modulator of cellular environments. It examines how ZIF-8's synthetic pathways and surface modifications aid in delivering various drugs and analyzes the molecular mechanisms by which released Zn^{2+} triggers stress responses and immune reactions. The article also discusses ZIF-8's integration into theranostic platforms, its use in combination therapies, and the clinical translation challenges, including biosafety, reproducibility, and scalable production. This review aims to systematically synthesize existing knowledge across the aforementioned fields to establish a theoretical foundation for the design of next-generation ZIF-8 nanotheranostic systems and facilitate their progression toward clinical translation.

Keywords: tumor microenvironment, TME, pH-responsive, drug delivery, zinc ion interference

Introduction

Cancer ranks among the foremost causes of mortality globally, characterized by the uncontrolled proliferation of malignant cells, which exhibit significant invasiveness and metastatic capabilities, thereby posing a substantial threat to human health.[1] The TME constitutes a complex ecosystem that supports tumor cell survival and development, with its pathological characteristics closely linked to tumor progression and therapeutic resistance.[2] Consequently, a systematic analysis of the biological features of the TME, alongside the development of targeted intervention strategies, is essential for the advancement of precision cancer therapy.

The primary pathological alterations within the TME can be categorized into two principal domains: the aberrant metabolic microenvironment and the formation of biological barriers. Metabolically, the Warburg effect-induced aerobic glycolysis, coupled with excessively active glutamine metabolism, results in significant lactate and H^+ accumulation, thereby creating an acidic milieu with a pH range of 5.6 to 7.0.[3–5] This acidic environment not only facilitates genomic instability and local invasion but also diminishes the efficacy of weakly alkaline chemotherapeutic agents by modifying the transmembrane pH gradient.[6–8] Concurrently, hypoxia, a consequence of abnormal tumor vasculature, further stimulates angiogenesis, epithelial-mesenchymal transition, and immunosuppressive networks.[9,10] Regarding biological barriers, the intracellular concentration of glutathione (GSH) in tumor cells can be up to four times higher than in normal cells,[11,12] conferring resistance to oxidative stress by neutralizing reactive oxygen species (ROS) generated by chemotherapy and radiotherapy. Additionally, elevated interstitial fluid pressure (IFP) significantly hinders the penetration of therapeutic agents into deeper tumor regions.[13,14] Furthermore, M2-type tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs) contribute to the suppression of $CD8^+$ T cell and

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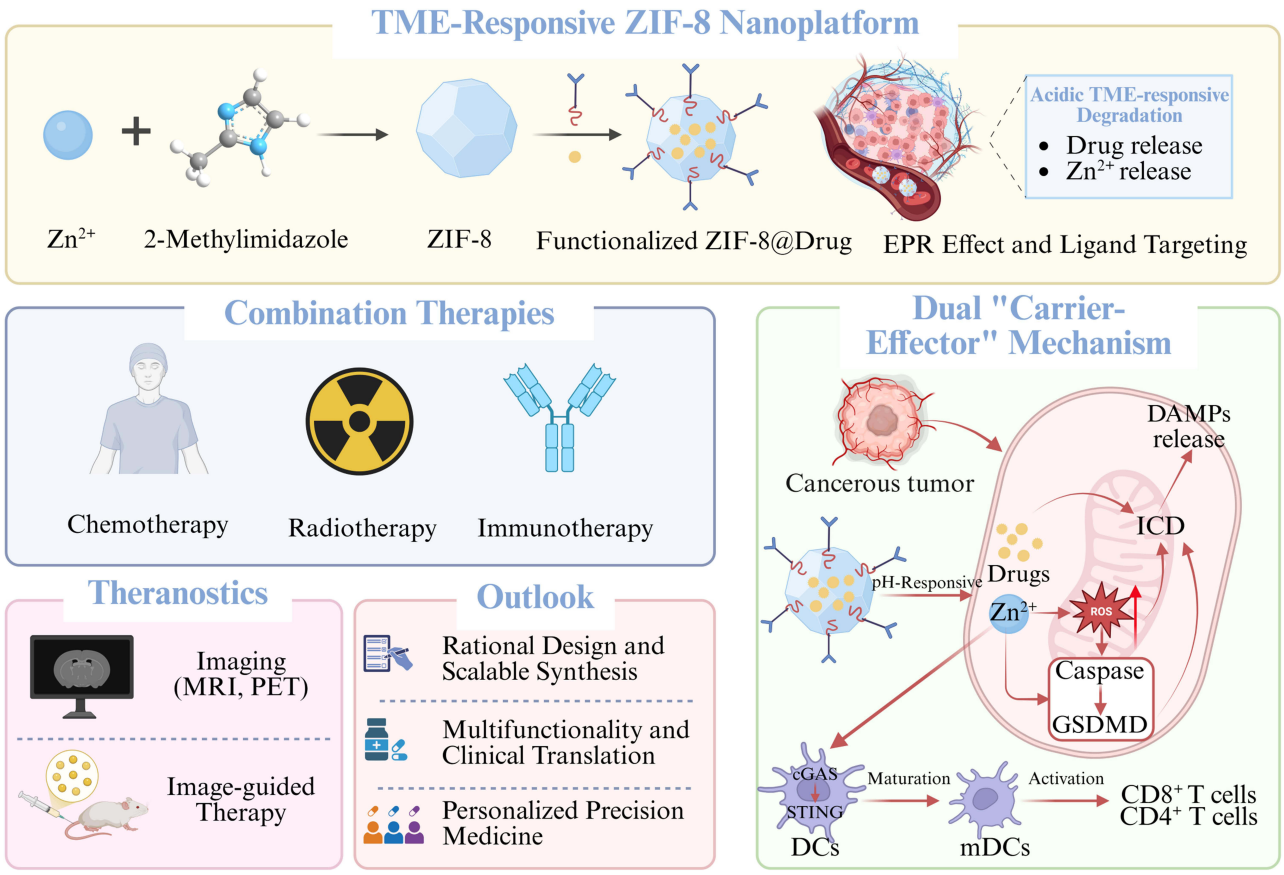
Graphical Abstract



natural killer (NK) cell activity by secreting immunosuppressive factors and expressing programmed death ligand-1 (PD-L1). This process facilitates immune evasion and reduces the effectiveness of immune checkpoint inhibitors.[15–17] These characteristics collectively form the pathological foundation of therapeutic resistance, thereby directing researchers' attention toward strategies for remodeling the TME. Figure 1 illustrates the fundamental characteristics of TME in relation to malignant progression and therapeutic resistance.

As our understanding of tumor biology has deepened, the design principles of nanoparticle drug delivery systems (NDDS) have undergone significant evolution. Initial approaches primarily depended on the enhanced permeability and retention (EPR) effect of solid tumors to achieve passive targeting.[18,19] However, the EPR effect displays considerable variability across different tumor types and individuals and is inadequate in overcoming the intrinsic drug penetration barriers presented by the TME. In recent years, active response strategies leveraging TME-specific signal levels, such as pH,[20,21] enzymes,[22,23] and ROS,[24,25] alongside external stimuli like light,[26,27] temperature,[28,29] and magnetic fields,[30,31] have facilitated precise activation of carrier structural transformation and drug release. These strategies actively engage with the TME to surmount delivery barriers and counteract immunosuppression.[32]

However, conventional nanocarriers exhibit limitations in drug loading capacity, biocompatibility, and multi-stimuli synergistic responsiveness, underscoring the need for the development of novel smart materials to fulfill clinical translation requirements. Metal-organic frameworks, which are coordination polymers formed from inorganic metal ions and organic ligands, present innovative opportunities for intelligent nanocarrier design due to their exceptionally high specific surface area, adjustable pore structures, and numerous unsaturated metal sites.[33–35] Among these, ZIF-8 has emerged as a focal point of research in oncology, attributed to its distinctive physicochemical and biological properties.

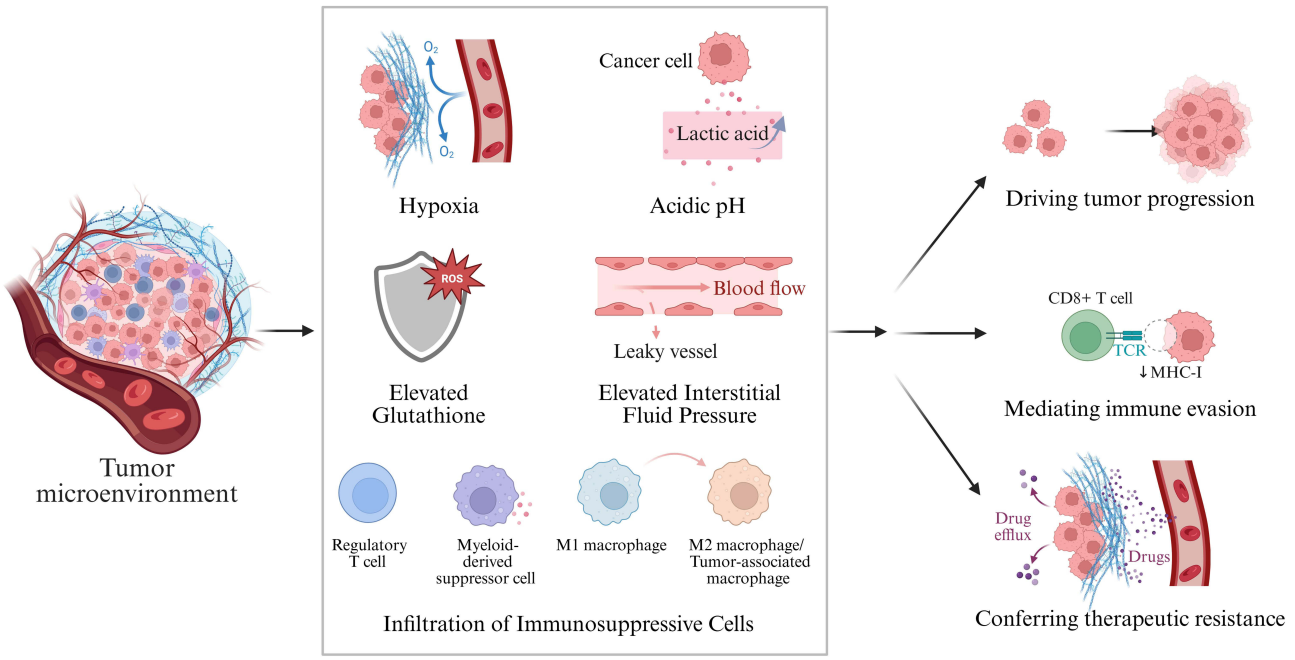


Figure 1 A schematic representation of the defining characteristics of the tumor microenvironment in malignant progression and therapeutic resistance (*Created in BioRender.he, W. (2026) https://BioRender.com/pjqtxof*).

ZIF-8, which is composed of Zn^{2+} ions and 2-methylimidazole (2-MIM), offers several advantages, including ease of synthesis, high porosity, excellent drug-loading capacity, and favorable biosafety profiles.[36–38] Notably, ZIF-8 undergoes rapid degradation under the mildly acidic conditions characteristic of the TME, facilitating the release of encapsulated drugs while simultaneously generating Zn^{2+} ions.[39] These released Zn^{2+} ions are not merely metabolic byproducts; they possess the capacity to directly induce cytotoxic effects on tumor cells by disrupting energy metabolism, inducing oxidative stress, and activating innate immune responses, thereby exhibiting a distinctive "carrier-effector" dual functionality.[40–42]

Although several existing reviews have explored the application of ZIF-8 in cancer therapy, focusing on aspects such as synthesis methods, drug loading, and surface modification, the majority of these studies predominantly emphasize the technical performance of ZIF-8 as a "drug carrier." Consequently, there is a relative paucity of detailed examination regarding the biological mechanisms through which the Zn^{2+} ions released from ZIF-8 degradation actively contribute to TME reprogramming. A comprehensive synthesis of the "carrier-effector" synergistic model is notably absent in the current literature. This review aims to address this gap by focusing on the dual functionality of ZIF-8, specifically its role in precise drug delivery and Zn^{2+}-mediated active TME remodeling. The review systematically explores the synthesis strategies of ZIF-8, its delivery performance, the biological effects of Zn^{2+}, and its immunomodulatory mechanisms. Additionally, it discusses the potential applications of ZIF-8 in combination therapy and identifies the challenges associated with its clinical translation.

What Do We Understand About ZIF-8 Nanocarriers?

Synthesis Strategies and Structural Tunability of ZIF-8

The synthetic strategies for ZIF-8 are varied, encompassing straightforward solution-based methods at ambient conditions as well as more sophisticated techniques such as solvothermal, microfluidic, and mechanochemical routes. This diversity offers extensive opportunities for material customization to suit different application scenarios. Based on reaction conditions and operational principles, the primary synthesis methods include room-temperature solution-based synthesis, the solvothermal method, microfluidic synthesis, mechanochemical synthesis, electrochemical synthesis, the xerogel method, and sonochemical synthesis, among others. By adjusting the synthetic pathway and key parameters,

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precise control over the particle size, morphology, and crystallinity of ZIF-8 nanoparticles can be achieved, alongside imparting excellent thermal stability. Table 1 provides a summary of the synthetic strategies for ZIF-8, detailing their characteristics and the applicable scenarios for each method.

The room-temperature solution-based method is recognized for its operational simplicity, typically necessitating only stirring at ambient temperature. Kulkarni et al[43] utilized a room-temperature aqueous synthesis approach, wherein zinc nitrate hexahydrate ($Zn(NO_3)_2{\cdot}6H_2O$) and 2-MIM were dissolved in 1 mL and 10 mL of water, respectively. Upon mixing and stirring, a milky white precipitate formed almost immediately, indicating the rapid formation of ZIF-8. Following centrifugal separation and water washing, characterization using a Malvern Zeta potential analyzer revealed a particle size of 98.4 nm with a notably low polydispersity index (PDI) of 0.06. The resultant product exhibited a regular rhombic dodecahedral morphology with an average particle size of approximately 100 nm. In contrast, Mittal et al[44] employed methanol as the solvent, dissolving $Zn(NO_3)_2{\cdot}6H_2O$ and 2-MIM separately in methanol. Stirring at room temperature for a mere 5 minutes resulted in the formation of a milky suspension. Dynamic light scattering (DLS) measurements indicated a hydrodynamic diameter of 211.9 nm and an exceptionally low PDI of 0.025, suggesting excellent uniformity. Notably, the duration of the reaction significantly influenced the resulting morphology.

The solvothermal method facilitates crystal growth under conditions of elevated temperature and pressure, thereby enabling the production of highly crystalline materials. Gao et al[45] separately dissolved $Zn(NO_3)_2{\cdot}6H_2O$ and 2-MIM in methanol, subjected the mixture to ultrasonication for 15 minutes, and subsequently transferred it to a stainless steel autoclave equipped with a polytetrafluoroethylene liner for thermal treatment at 120°C over a period of 2 hours. The resulting hollow ZIF-8 demonstrated well-defined crystallinity, with an average diameter of 408 nm (PDI = 0.044) and a uniform morphology.

Microfluidic synthesis has gained prominence as a pivotal approach for scalable production due to its continuous and potentially scalable characteristics. Hu et al[46] employed a peristaltic pump-driven microfluidic reactor, which facilitated

Table 1 Synthetic Strategies for ZIF-8 and Comparison of Methods

Method	Key Characteristics	Advantages	Disadvantages	Suitable Application Scenarios	Refs.
RT Aqueous Synthesis	Water as solvent, stirring at room temperature	Simple and convenient operation, low cost, environmentally friendly, small particle size (~100 nm), low PDI (0.06)	Limited morphology control, relatively low crystallinity, products mostly solid structures	Rapid laboratory-scale preparation, green chemistry requirements	[43]
RT Methanol Synthesis	Methanol as solvent, rapid precipitation upon stirring at room temperature	Excellent uniformity, controllable morphology via reaction time (spherical at short times, rhombic dodecahedral at longer times)	Use of organic solvent, methanol toxicity, safety hazards for scaled-up production	Morphology-controlled synthesis, mechanism studies	[44]
Solvothermal Method	High temperature and pressure, sealed autoclave	High crystallinity, capable of producing hollow structures, well-defined morphology, good thermal stability	High energy consumption, demanding equipment requirements, long reaction times	Applications requiring high crystallinity, hollow structures for drug loading, high-temperature stability	[45]
Microfluidic Synthesis	Continuous flow in microchannels, rapid mixing, precise temperature control	Continuous and scalable process, excellent product uniformity, small particle size with narrow distribution, good batch-to-batch reproducibility	Complex equipment, susceptibility to channel clogging, output limited by flow rates	Large-scale production, preparation of high-quality standard materials	[46]
Electrodeposition	Electrochemically driven, rapid deposition at room temperature	Mild conditions, fast reaction (seconds), precise control over film thickness (230 nm–1.8 μm), suitable for direct growth on substrates	Limited to film/coating fabrication, requires conductive substrates, specialized equipment	Thin-film devices, sensors, surface coatings, in situ growth applications	[47]
Mechanochemical Synthesis	Solid-state grinding, solvent-free or minimal solvent	Green and solvent-free, rapid and efficient, suitable for large-scale preparation (up to kilogram scale), high thermal stability	Limited morphology control, equipment wear	Industrial-scale mass production, green chemistry	[48]
Dry-Gel Conversion Method	Minimal solvent and ligand usage, high atom economy	Environmentally friendly, simple process, good product stability, enhances selectivity in H_2 sensing	Requires strict control of humidity, challenging for large-scale preparation	Green synthesis, preparation of sensing materials demanding high atom economy	[49]

the rapid mixing and reaction of $Zn(NO_3)_2{\cdot}6H_2O$ and 2-MIM solutions within microchannels (Figure 2A). The Py@ZS, DOX@ZS, and RB@ZS nanospheres synthesized via this method exhibited average particle sizes of 64.4±18.8 nm, 67.7 ±22.1 nm, and 93.8±17.3 nm, respectively. These nanospheres demonstrated notable sphericity and exceptional dispersity, thereby offering significant advantages over traditional batch synthesis methods.

The electrochemical approach provides mild conditions and rapid reaction kinetics, rendering it suitable for thin film fabrication. Guo et al[47] pioneered the synthesis of a ZIF-8 membrane through electrodeposition. Utilizing a zinc plate as the anode and a platinum-sputtered silicon wafer as the cathode in an aqueous solution containing 2-MIM and ammonium hydroxide, a constant current density of 0.5 $mA{\cdot}cm^{-2}$ was applied at room temperature. This facilitated the ultrafast deposition of a ZIF-8 film within 10 to 100 seconds (Figure 2C). By adjusting the deposition parameters, the film thickness could be precisely controlled, ranging from 230 nm to 1.8 μm. The resulting crystals, approximately 200 nm in size, exhibited a rhombic dodecahedral structure. Following heating at 150°C under vacuum for 12 hours, the film demonstrated no cracking or delamination, indicating excellent thermal stability. Martinez et al[50] successfully

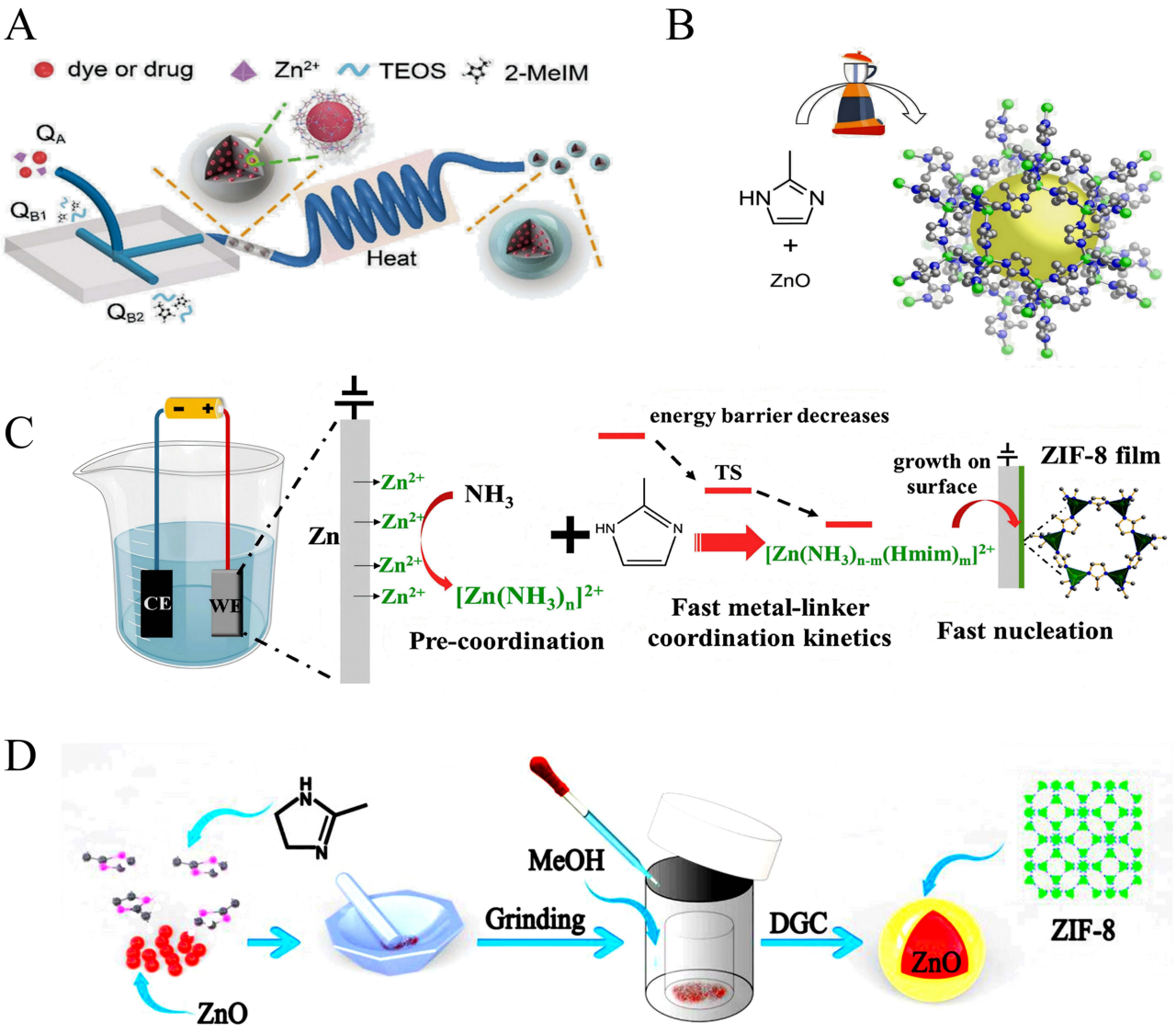

Figure 2 Presents various schematic representations of synthesis methods for ZIF-8 composites: (**A**) A schematic diagram illustrating the microfluidic system-assisted synthesis of ZIF-8@SiO_2. Reproduced from Hu et al, *J Mater Chem B*, 2018;6(47):7936–7942 with permission.[46] (**B**) A schematic depiction of the mechanochemical synthesis of ZIF-8-KG. Reproduced from Samal et al, *CrystEngComm*, 2018;20(18):2486–2490 with permission.[48] (**C**) A schematic illustration of the anodic deposition of ZIF-8 using ammonium hydroxide. Reproduced from Guo et al, *ACS Nano*, 2025;19(29):26,612–26623 with permission.[47] (**D**) A schematic diagram of the synthesis of ZnO@ZIF-8 via the xerogel method. Reproduced from Ji et al, *J Mater Chem C*, 2020;8(8):2927–2936 with permission.[49]

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synthesized ZIF-8 through an anodic oxidation-dissolution electrochemical strategy, characterized by mild reaction conditions, reduced processing time, and the facile production of nanoscale particles.

Mechanochemical synthesis emerges as an environmentally sustainable and efficient method, well-suited for large-scale production (Figure 2B). Samal et al[48] demonstrated the mechanochemical synthesis of ZIF-8 on a multi-gram scale (approximately 20 g) using a kitchen grinder. Thermogravimetric analysis confirmed the material's thermal stability up to 600°C. Scanning electron microscopy (SEM) and transmission electron microscopy analyses revealed a distinctive rhombic dodecahedral morphology, with crystal sizes ranging from 100 to 200 nm.

Furthermore, Ji et al[49] employed a dry-gel conversion technique to synthesize ZnO@ZIF-8 core-shell heterostructures. In this process, ZnO and 2-MIM powders were weighed, meticulously ground, and subjected to crystallization at 393 K for 24 hours within a vapor atmosphere produced by a methanol droplet under dry conditions. The desired product was subsequently obtained through filtration, washing, and drying (Figure 2D). This method effectively facilitated the formation of a ZIF-8 shell on the surface of ZnO crystals via an in situ growth mechanism, characterized by minimal solvent and ligand consumption and exceptional atom economy. The resulting core-shell structures exploit the precise molecular sieving capabilities of the ZIF-8 shell layer, providing substantial benefits for gas-sensing applications.

The selection of a ZIF-8 synthesis method necessitates a careful consideration of operational simplicity, product quality, and scalability. Room-temperature solution-based and solvothermal methods are particularly advantageous for laboratory-scale investigations focused on structural modifications. Conversely, microfluidic synthesis and mechanochemical techniques present feasible options for continuous production at an industrial scale. Electrochemical synthesis provides unique advantages for the fabrication of thin-film devices. By meticulously controlling synthetic parameters, it is feasible to tailor the properties of ZIF-8, including particle size (ranging from tens of nanometers to several micrometers), morphology (such as spherical, rhombic dodecahedral, or hollow), crystallinity, and thermal stability. This level of tunability enables ZIF-8 to meet a diverse array of application requirements in areas such as adsorption and separation, drug delivery, and catalytic conversion.

What Does Functionalization Enable ZIF-8 to Achieve?

Nonetheless, unmodified ZIF-8 exhibits inherent limitations as a drug delivery vehicle, including inadequate targeting capabilities, suboptimal biocompatibility, poor colloidal stability, and rapid clearance by the reticuloendothelial system (RES). These limitations significantly restrict its efficiency in in vivo delivery. Therefore, the clinical application of ZIF-8 as a drug delivery system is heavily reliant on surface engineering to concurrently enhance active targeting, biocompatibility, circulatory stability, and theranostic functionality. Owing to the ease of chemical modification afforded by its imidazole-based framework, the development of multifunctional ZIF-8-based composite drug delivery systems has emerged as a prominent area of research. Specifically, functionalization strategies primarily encompass: (1) targeted modification to confer active tumor recognition capabilities to the carrier; (2) stealth modification to extend systemic circulation time and evade immune clearance; (3) biomimetic membrane modification to achieve immune evasion and homologous targeting through biomimetic camouflage; and (4) multifunctional synergistic modification to integrate theranostics and immunomodulation.

Targeted Modification

The targeted modification process entails the precise integration of tumor-specific recognition units into the ZIF-8 framework through methodologies such as surface engineering. This confers upon the nanocarrier the capability to actively target tumor cells and respond to localized pathological characteristics, thereby facilitating the efficient accumulation and controlled release of therapeutic agents or imaging compounds at the site of the lesion.

The folate receptor (FR), a protein that binds folic acid (FA), is located on the cell membrane and has been recognized as a tumor-associated antigen. Folic acid presents several advantages, including low immunogenicity, high affinity, ease of modification, good stability, low cost, and wide availability. FR is abundantly expressed on the surface of various malignant tumor cells, while being nearly absent in normal tissue cells, rendering it an ideal target for active tumor-targeted drug delivery.[51] Adibifar et al[52] developed FA-conjugated FA-BSA@MTX@Se@ZIF-8 nanoparticles. Following FA modification, the half-maximal inhibitory concentration (IC_{50}) against 4T1 cells was reduced to

12.27 μg/mL, demonstrating significantly enhanced antitumor efficacy. Additionally, coating these nanoparticles with erythrocyte membranes (EMs) and further modifying them with FA facilitated targeted delivery to tumor tissues and effectively evaded clearance by the mononuclear phagocyte system, thereby promoting efficient uptake by tumor cells.[53]

The RGD peptide targeting strategy leverages the high-affinity interaction between the arginine-glycine-aspartate (RGD) sequence and the integrin αvβ3 receptor, which is overexpressed on tumor endothelial cells and certain tumor cell surfaces, to facilitate specific docking and drug delivery.[54,55] To advance this strategy, Lin et al[56] developed a DDS by coating nanoparticles with erythrocyte membranes modified with RGD peptides. This modification endowed the nanoparticles with tumor-targeting capabilities mediated by the integrin αvβ3 receptor, thereby significantly enhancing drug accumulation at the tumor site and inhibiting tumor growth. Furthermore, compared to linear RGD, the cyclic iRGD peptide, which contains a 9-amino acid sequence including the RGD motif, demonstrates a higher affinity for integrins αvβ3 and αvβ5 as well as neuropilin-1, and exhibits superior tumor-penetrating ability.[57] Zhou et al[58] utilized iRGD-functionalized liposomes to encapsulate black phosphorus nanosheet-doped ZIF-8 (BPN@ZIF-8), resulting in a marked enhancement of tumor accumulation, deep penetration, and cellular uptake. This approach improved antitumor efficacy while minimizing side effects.

Aptamer targeting exploits the high affinity and specific binding capacity of oligonucleotide sequences to target molecules, facilitating precise recognition. By integrating aptamers with ZIF-8, targeting specificity is not only enhanced, but the aptamers are also protected from nuclease degradation and rapid renal clearance, thereby prolonging their circulation time and reducing immunotoxicity.[59,60] Dong et al[61] incorporated the aptamer AS1411 into a ZIF-8 delivery system. In this context, AS1411 specifically binds to the nucleolin receptor, which is overexpressed on the surface of cancer cells, thereby significantly increasing drug accumulation at tumor sites while reducing nonspecific uptake by normal tissues. In a similar vein, Liu et al[62] utilized an aptamer modification strategy, demonstrating that nanoparticles functionalized with aptamers preferentially accumulated at tumor sites. This approach effectively circumvented cancer cell drug resistance and resulted in a significant reduction in tumor volume.

These findings have been corroborated through in vitro cellular experiments and in vivo animal models. Consequently, the practical application of these findings necessitates a rational selection or combinatorial optimization strategy, tailored to the specific tumor type and therapeutic objectives. FA, as a small-molecule targeting ligand, presents several advantages over aptamers and peptides, including rapid tissue penetration, high stability, reduced toxicity, and immunogenicity, as well as ease of conjugation to drugs or nanocarriers. Nonetheless, FA targeting is limited by the heterogeneous expression of FR across different tumor types and individuals, and its presence in some normal tissues, which may result in off-target effects.[63] In contrast, RGD/iRGD peptides demonstrate robust tissue penetration but are vulnerable to proteolytic degradation. Similarly, although aptamers exhibit high specificity, they encounter challenges related to complex synthesis and limited stability.

Stealth Modification

Stealth modification constitutes a fundamental strategy to realize the full potential of targeted modifications. By engineering a hydrophilic and biocompatible "protective shell" on the ZIF-8 surface, this method effectively circumvents nonspecific uptake by the RES, reduces plasma protein adsorption and immune recognition, and extends the circulatory half-life. This approach effectively addresses critical challenges, including rapid in vivo carrier clearance and limited targeting efficiency.

Polyethylene glycol (PEG) ylation represents a quintessential stealth modification technique that imparts immune-evasive "stealth" characteristics to nanoparticles through the covalent attachment of PEG to their surfaces.[64] This modification is applicable to a wide range of drug delivery systems and is particularly effective in enhancing drug accumulation within cancer cells by exploiting the hyperpermeable nature of tumor vasculature.[65] The hydrophilic nature of PEG serves to shield the nanoparticle surface, thereby reducing interparticle interactions and diminishing the likelihood of recognition and phagocytosis by opsonins and related proteins. This results in prolonged systemic circulation time and improved drug delivery efficiency to target cells.[66] Furthermore, PEGylation enhances the hydrophilicity of nanoparticles by reinforcing interactions with water molecules, reduces particle size, and improves dispersion stability.[67,68] In a study, an Fe_3O_4@SiO_2@HAp@ZIF-8-PEG delivery system was developed, wherein the surface PEG

effectively prevented premature leakage of doxorubicin (DOX), facilitating slower and more controlled drug release, maintaining stable dosage, and significantly improving biocompatibility.[69]

Building upon this foundational work, researchers have advanced the field by integrating PEG modification with additional functional ligands to develop composite modification systems that offer both stealth and targeting capabilities. A notable example is hyaluronic acid (HA), a naturally occurring, negatively charged hydrophilic polysaccharide, which possesses several advantageous properties such as biocompatibility, biodegradability, and non-immunogenicity. HA functions as an intelligent "switch" and a polymeric tumor-targeting "navigator," effectively extending blood circulation time. Furthermore, due to its high affinity for cell-specific surface markers like CD44, HA enhances the targeted accumulation of drug delivery systems at tumor sites via CD44-mediated pathways. Empirical studies have demonstrated that HA-modified ZIF-8 exhibits improved storage stability, slower drug release rates under both neutral and acidic conditions, enhanced biocompatibility, improved targeted delivery, and significantly stronger tumor suppression effects.[70,71] Supporting this, Zeng et al[72] prepared ID@ZIF-8@HPG through PEG-PLG and HA surface modification, illustrating the potential of these advanced systems. This system not only prolonged the circulatory half-life but also, through the incorporation of HA, acquired CD44-mediated active targeting capabilities. The ID@ZIF-8@HPG complex exhibited enhanced tumor retention, sustaining a robust fluorescent signal for up to 12 hours following injection, thereby achieving a synergistic dual functionality of "stealth-targeting."

Biomimetic Membrane Modification

Clinical investigations have revealed that PEG can stimulate the production of host-specific antibodies, leading to the accelerated blood clearance phenomenon and eliciting severe allergic reactions in certain patients. These antibodies significantly diminish the therapeutic efficacy of PEGylated drugs and increase the likelihood of adverse events.[73,74] To overcome challenges such as PEG's immunogenicity, the innovative approach of natural cell membrane coating has emerged as a prominent area of research. This technique involves creating a highly biomimetic biointerface on nanoparticle surfaces by directly replicating the complex functionalities of cell surfaces.[75] The structure of the cell membrane closely resembles that of natural cells, which can mitigate immune responses and toxicity during interactions between nanoparticles and biological tissues, thereby facilitating improved integration within biological systems. Moreover, specific receptors or proteins present on the cell membrane can enhance the targeting capabilities of nanoparticles and enable them to evade immune clearance, thus achieving prolonged and stable circulation in the bloodstream. In recent years, the utilization of biomimetic membranes, such as EMs and cancer cell membranes (CCMs), has garnered considerable attention due to their capacity to extend circulation time by evading the immune system.[76,77]

EMs, as naturally derived lipid bilayer structures, benefit from the intrinsic prolonged blood circulation properties and biocompatibility associated with red blood cells. Consequently, they are employed as protective "shells" to shield encapsulated nanoparticles from immune clearance. CD47, a transmembrane protein, is consistently and abundantly expressed on the surface of red blood cells, functioning primarily as a self-protection mechanism to facilitate immune evasion. The ligand for CD47 is signal regulatory protein alpha (SIRPα), predominantly expressed on the surfaces of macrophages. Upon binding to CD47, SIRPα transmits an inhibitory signal, commonly referred to as the "don't eat me" signal, which suppresses macrophage phagocytic activity.[78,79] For instance, Qiao et al[80] developed an EM-coated ZIF-8-DOX-LY-EM nanodrug through the in situ encapsulation of DOX and LY364947, a type I transforming growth factor-β receptor (TGFBR1) inhibitor. By exploiting the biomimetic characteristics of EMs, this nanodrug circumvents immune clearance, extends its circulation time in the bloodstream, and effectively accumulates within tumor tissues. The subsequent release of LY364947 leads to a reduction in type I collagen, resulting in the loosening of the extracellular matrix, which facilitates enhanced drug penetration, improves tumor oxygenation, and mitigates hypoxia-induced resistance to DOX. With improved oxygen supply, DOX demonstrates increased cellular uptake efficiency and ROS generation, thereby augmenting its chemotherapeutic efficacy. In vivo experiments demonstrated that this nanodrug achieved a tumor inhibition rate of 63% in mice bearing 4T1 tumors, extended the median survival time to 28 days, and exhibited favorable biosafety profiles.

The modification of CCM exploits the inherent properties of the homotypic cell membrane to facilitate immune evasion and homologous binding, thereby effectively addressing the challenges of immune clearance and non-specific binding in vivo. In a study by Xiao et al,[81] ferrous ion-doped ZIF-8@DHA nanoparticles were coated with CCM (CDZs) When co-cultured with U937 leukocytes, these CDZs exhibited a significantly reduced phagocytosis rate compared to uncoated ZIF-8, as evidenced by the weakest intracellular fluorescence signal and the lowest detected iron content. This finding substantiates the superior immune evasion properties imparted by the CCM coating on the nanoparticles. Similarly, Zhao et al[82] coated the cell membranes of 4T1 cells onto ZIF-8@DMDD/Ce6 (ZDC) nanodrugs to produce ZDC@M. Confocal laser scanning microscopy revealed the distribution of Chlorin e6 (Ce6) following uptake by 4T1 cells. The red fluorescence intensity of Ce6 was markedly higher in 4T1 cells incubated with ZDC@M compared to those incubated with ZDC at the same pH level, confirming that the application of the 4T1 cell membrane coating enhanced the nanodrug's recognition capability, thereby augmenting its targeting efficacy. Biomimetic membrane modification represents a strategic advancement from the use of "synthetic material camouflage" to "natural biomimicry." This approach circumvents the immunogenicity associated with PEG while achieving enhanced biocompatibility and offering greater potential for multifunctional integration. However, the clinical translation of this technology encounters several challenges, including issues related to production and quality control. The extraction and purification of cell membranes are difficult to standardize, and membrane proteins are susceptible to denaturation, which leads to significant batch-to-batch variations and results in unstable targeting efficiency. Furthermore, the long-term degradation and metabolic pathways of allogeneic cell membranes remain poorly understood, raising potential biosafety concerns.[83] These critical issues warrant further investigation and resolution in subsequent research endeavors.

Multifunctional Modification

The development of nanotheranostic platforms, guided by advanced imaging technologies, is essential for the advancement of personalized and efficient cancer therapies. For instance, the incorporation of SiGd nanoparticles into the ZIF-8 framework has facilitated the creation of a dual-modal imaging platform that utilizes both fluorescence and magnetic resonance imaging. This approach has demonstrated targeting selectivity, resulting in significant fluorescence signals and enhanced MRI contrast at the tumor site.[84] Furthermore, Liu et al[85] designed an intelligent system that responds to elevated GSH concentrations within the TME by modifying MnO_2 nanodots on the surface of ZIF-8. The reduction of MnO_2 to Mn^{2+} not only activated the magnetic resonance imaging signal but also restored quenched fluorescence, thereby enabling dual-modal fluorescence and MRI imaging. Additionally, the ROS generated during this reduction process may synergistically enhance the efficacy of photodynamic therapy. These strategies underscore the distinct advantages of ZIF-8 in the convergence of diagnostic and therapeutic functionalities. Its adaptable interface and adjustable release properties facilitate the systematic incorporation of imaging agents, therapeutic agents, and microenvironment-responsive components. This integration culminates in a synergistic closed-loop system of imaging-guided therapy and therapy-informed imaging.

In the context of multifunctional modification strategies for ZIF-8, recent research has increasingly focused on utilizing ZIF-8 as a delivery vehicle for immune agonists, beyond the conjugation of previously mentioned theranostic components. Encapsulation of these immunomodulatory molecules within the ZIF-8 framework significantly enhances their accumulation and controlled release within the tumor microenvironment, thereby activating systemic antitumor immune responses and substantially improving therapeutic efficacy. Zhang et al[86] synthesized a ZIF-8/CpG ODNs complex, demonstrating that, compared to free CpG oligodeoxynucleotides (CpG ODNs), the porous structure of ZIF-8 enhances loading efficiency and structural stability, facilitates internalization by immune cells, activates the Toll-like receptor 9 (TLR9) signaling pathway, and upregulates the secretion of pro-inflammatory cytokines. In vivo experiments have confirmed that systemic administration of this complex can effectively activate antitumor immunity and inhibit tumor growth.

The strategies for functionalizing ZIF-8 are experiencing a paradigm shift from a focus on "single-function optimization" to an emphasis on "multifunctional intelligent synergy." Targeted modifications address the issue of "directionality," stealth modifications focus on "prolonged survival," biomimetic membrane modifications facilitate "biomimetic camouflage and homotypic targeting," and multifunctional synergistic modifications endow the material

with advanced capabilities such as theranostics and immunomodulation. Readers are directed to Table 2 for detailed information on the chemical structures and respective applications of all functionalization agents discussed in this section.

pH-Responsive Degradation and Drug Release Mechanism

The structural dissociation characteristics of ZIF-8 under weakly acidic conditions make it an ideal carrier for pH-responsive drug delivery systems. Drug-loaded systems designed around this property can respond to the acidity gradient between the TME and normal tissues, enabling intelligent drug release and targeted accumulation at the lesion site, thereby improving therapeutic efficacy and reducing systemic toxicity. The pH-responsive degradation of ZIF-8 is primarily driven by the protonation of the imidazole ligand at acidic pH, which destabilizes the Zn-N coordination bonds. In the acidic microenvironment, protons (H^+) bind to and protonate the nitrogen atoms of imidazole ligands. This protonation process significantly alters the electron cloud distribution and charge state of the nitrogen atoms, thereby weakening the binding stability of the Zn-N coordination bonds and leading to their cleavage (Figure 3C). As a large number of Zn-N bonds break, the ZIF-8 crystal framework loses structural integrity, ultimately leading to its collapse.[112,113] Following this structural disintegration, the pore structure of ZIF-8 opens up, allowing the release of the encapsulated drug and thereby achieving pH-responsive controlled release.

Numerous experimental studies have provided direct evidence for the aforementioned degradation mechanism. For example, Gao et al[112] incubated BSA@ZIF-8 nanoparticles in phosphate-buffered saline (PBS) at pH 5.0 and 7.4 for 24 hours, comparing X-ray diffraction patterns, Fourier-transform infrared spectra, and SEM images before and after incubation. The results showed that in the pH 5.0 acidic environment, the crystal structure of BSA@ZIF-8 completely collapsed, characteristic absorption peaks in the FTIR spectra disappeared, and significant morphological changes were observed via SEM. In contrast, in the neutral pH 7.4 environment, the samples maintained good crystallinity and largely retained their initial morphology, with only the crystal surfaces becoming rougher and more porous. This confirms the slow degradation characteristics of ZIF-8 under physiological conditions (Figure 3A and B). The correlation between the pH-responsive degradation of ZIF-8 and its drug release efficiency was further confirmed by in vitro release experiments. ZIF-8@Dox exhibited a significant sustained-release profile under neutral pH 7.4 conditions, with a cumulative release of only 24.7% after 100 hours. Conversely, under acidic pH 4.0 conditions, a rapid release of 37.6% occurred within the first hour, reaching a cumulative release of 84.7% by 30 hours, demonstrating excellent pH-responsive drug release performance.[114] However, ZIF-8 is prone to acid degradation, which limits oral and long-term application. Surface coating and framework modification can improve its acid stability and broaden delivery applications.[115–118]

Recent Progress in ZIF-8-Based Platforms for Precision Delivery of Diverse Therapeutics

Delivery of Chemotherapeutic Drugs

Small-molecule chemotherapeutic agents, including DOX, cisplatin (DDP), and gemcitabine (Gem), are extensively utilized in the clinical management of various malignancies.[119–121] However, these agents are characterized by non-selective distribution, which results in significant dose-dependent toxic side effects. Additionally, oral administration of these drugs is constrained by gastrointestinal physiological barriers, leading to low bioavailability and limiting the expansion of the therapeutic window.[122,123] To overcome these challenges, researchers have encapsulated these drugs within nanocarriers possessing TME-responsive properties to facilitate site-specific drug release at the target lesion, thereby reducing systemic toxicity and enhancing therapeutic efficacy. Among these nanocarriers, ZIF-8 has emerged as a promising platform for the development of nanodrug delivery systems due to its pH sensitivity, high drug-loading capacity, and excellent biocompatibility.[124]

Research on DOX-loaded ZIF-8 has confirmed the viability of this drug delivery approach. The core-shell magnetic Fe_3O_4@ZIF-8 composite (DFZ) demonstrates high-efficiency DOX encapsulation and facilitates tumor-targeted accumulation under magnetic guidance. In vivo studies indicate that this nanocarrier exhibits superior anti-tumor efficacy compared to free DOX, minimizes toxicity to major organs such as the liver, and enhances biosafety.[125] To address

Table 2 Applications of ZIF-8-Based Nanoplatforms in Cancer Therapy

Nanocomposite	Loaded Drugs	Modified Ligands	Therapeutic Mechanisms	Animal Model	Therapeutic Outcome	Refs.
FA-BSA@MTX@Se@ZIF-8	MTX	FA-BSA	Chemotherapy	BALB/c mice bearing 4T1 cells	The IC_{50} of the nanoplateform was significantly lower than that of free MTX	[52]
FM@IQ/PST&ZIF-8/DOX	DOX, IQ	FM, PST	PTT, Chemotherapy, IT	BALB/c mice bearing 4T1 cells	Effectively compensated for the deficiencies of individual therapies, significantly enhancing the antitumor efficacy	[53]
Apt/(siRNA + GEF)@ZIF-8	GEF, siRNA	Aptamer	Chemotherapy, GT	BALB/c mice bearing A549 cells	The inhibition efficiency against acquired resistance was as high as 40.6%	[62]
PEG/ZIF-8@HF	HF	PEG-2000	Chemotherapy	BALB/c mice bearing B16F10 cells	Exhibited antitumor efficacy against melanoma	[68]
ID@ZIF-8@HPG	DSF, ICG	HPG	Chemotherapy,PDT, PTT	BALB/c mice bearing 4T1 cells	Effectively killed tumor cells	[72]
ZIF-8-DOX-LY-EM	TGFBR1 inhibitor, DOX	EM	Chemotherapy	BALB/c mice bearing 4T1 cells	Demonstrated excellent performance in tumor chemotherapy	[80]
ZIF-8@ DMDD/Ce6 @cytomembrane	DMDD, Ce6	CCM	Chemotherapy, SDT	Nude mice bearing 4T1 cells	The combined therapy enhanced antitumor efficacy	[82]
DDP-ADL@ZIF-8@PDA	DDP, ADL	PDA	Chemotherapy, PTT, Anti-inflammatory therapy	BALB/c mice bearing HeLa cells	Significantly inhibited the growth of distant tumors	[87]
CDDP@Fe/ZIF-8	DDP, Fe^{3+}	N/A	Chemotherapy, RT	C57BL/6 mice bearing LLC cells	Effectively inhibited tumor growth	[88]
HA/ZIF-8@Gem/D-1-MT	Gem, D-1-MT	HA	Chemotherapy, IT	BALB/c mice bearing K7M2 cells	Re-activated the anti-tumor immune response, reversing the development of OS	[89]
HTC@ZIF-8	TC, Hemin	N/A	Chemotherapy, Ferroptosis, PDT	BALB/c mice bearing EMT6 cells	Significant inhibition of tumor growth with low toxicity to normal tissues	[90]
Apt-PEG-siRNA@ZIF-8	siRNA	PEG, Aptamer (SLY3C)	GT	C57BL/6 mice bearing PC-3 cells	Enhanced apoptosis and significantly reduced tumor size	[91]
siRNA PD-L1@HA-ZIF-8	siRNA PD-L1	HA	ICB therapy, Pyroptosis	BALB/c mice bearing 4T1 cells	Alleviated the immunosuppressive TME, enhanced antitumor efficacy	[92]
OMV@ZIF-8@miR-34	miRNA	OMVs	GT, IT	BALB/c mice bearing 4T1 cells	Effectively inhibited target protein and tumor growth	[93]
pDNA@Mn/Zn-ZIF-8@HA	pDNA	HA	GT	BALB/c mice bearing 4T1 cells	Promoted systemic immune response, effectively inhibited tumor recurrence and metastasis	[94]
BAY/duRNPs@ZIF-8	duRNPs, BAY-876	N/A	GT, Cancer starvation therapy	NCG mice bearing Siha cells	Significant anti-proliferative effect on cancer cells	[95]
L-Arg@ZIF-8@CaP@HA/PDA	L-Arg	CaP coating, HA, PDA	Ferroptosis/Pyroptosis	BALB/c mice bearing CT26 cells	TME-specific oxidative imbalance significantly enhanced selective tumor killing	[96]

(*Continued*)

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Table 2 (Continued).

Nanocomposite	Loaded Drugs	Modified Ligands	Therapeutic Mechanisms	Animal Model	Therapeutic Outcome	Refs.
BC@Z-M	BN-O molecular probe, vascular disrupting agent CA4P	M1 macrophage membrane	PDT, PTT, IT	BALB/c mice bearing 4T1 cells	Blocked primary tumor (81% inhibition rate) and distant tumor progression (72% inhibition rate)	[97]
(M+H) @ZIF/HA	MIT, HYD	HA	Chemotherapy, IT	BALB/c mice bearing 4T1 cells	Remarkable tumor clearance capability and anti-metastatic effect	[98]
Au-Cu_{2-x}Se@ZIF-8@P18	P18	N/A	PDT, IT, Pyroptosis	C57BL/6 mice bearing B16 cells	Potently inhibited tumor growth	[99]
mEHGZ	EPI, GOx, Hemin	CCM	Chemotherapy, IT, Cancer starvation therapy	Tumor-bearing mice bearing 4T1 cells	Effectively suppressed tumor growth and limited lung metastasis	[100]
MIT@ZIF-8	MIT	N/A	Chemotherapy, IT	BALB/c mice bearing CT26 cells	Potent antitumor efficacy with good systemic safety	[101]
CDHNs	Ce6, DOX, HIF-1αsiRNA	N/A	Chemotherapy, PDT, GT	BALB/c mice bearing MDR/MCF-7 cells	Eradicated rapidly proliferating cancer cells and tumors	[102]
AR-ZS/ID-P	ICG, DOX	AR peptide, PEI	Chemotherapy, PDT, PTT	BALB/c mice bearing MCF-7 cells	Superior antitumor efficacy with reduced photo-associated side effects	[103]
CPZT	tranilast	CCM, PEG-2000	IT	BALB/c mice bearing 4T1 cells	Disrupted the key stromal barrier limiting immunotherapy efficacy	[104]
MAN/(R837+1-MT)@ZIF-8	R837, 1 -MT	MAN	IT	C57BL/6 mice bearing B16F10 cells	Tumor inhibition rate of 58.5%	[105]
HA/IR820@ZIF-8	Photothermal agent IR820	HA	PTT	C57BL/6 mice bearing B16F10 cells	Tumor inhibition rate of 87.0%	[105]
CMCS-(DOX+1-MT)/CpG@ZIF-8	DOX, 1-MT, CpG ODNs	CMCS	Chemotherapy, IT	BALB/c mice bearing 4T1 cells	Tumor inhibition rate of 85.6%	[106]
FA-Mn_3O_4@ZIF-8	Mn_3O_4	FA	RT	BALB/c mice bearing SiHa cells	Significantly enhanced the antitumor effect of radiotherapy	[107]
ZIF-8@MnCO@DOX	DOX, MnCO	N/A	Chemotherapy, RT, IT	C57BL/6 mice bearing hepa1-6 cells	Significantly promoted tumor regression and reduced metastasis	[108]
EGCG-ZIF-8@PDA-PEG	EGCG	PDA, PEG	IT	C57BL/6 mice bearing B16F10 cells	Favorable tumor inhibition and improved survival rate	[109]
[Dbait-ADM@ZIF-8] OPM	Radiosensitizer Dbait, ADM	OPM	Chemotherapy, RT	BALB/c mice bearing SaOS-2 cells	Exhibited excellent antitumor efficacy	[110]
RVG15-PEG@DTX@ZIF-8	DTX	RVG15, PEG	Chemotherapy	ICR mice bearing C6 cells	Significantly inhibited glioma growth and metastasis	[111]

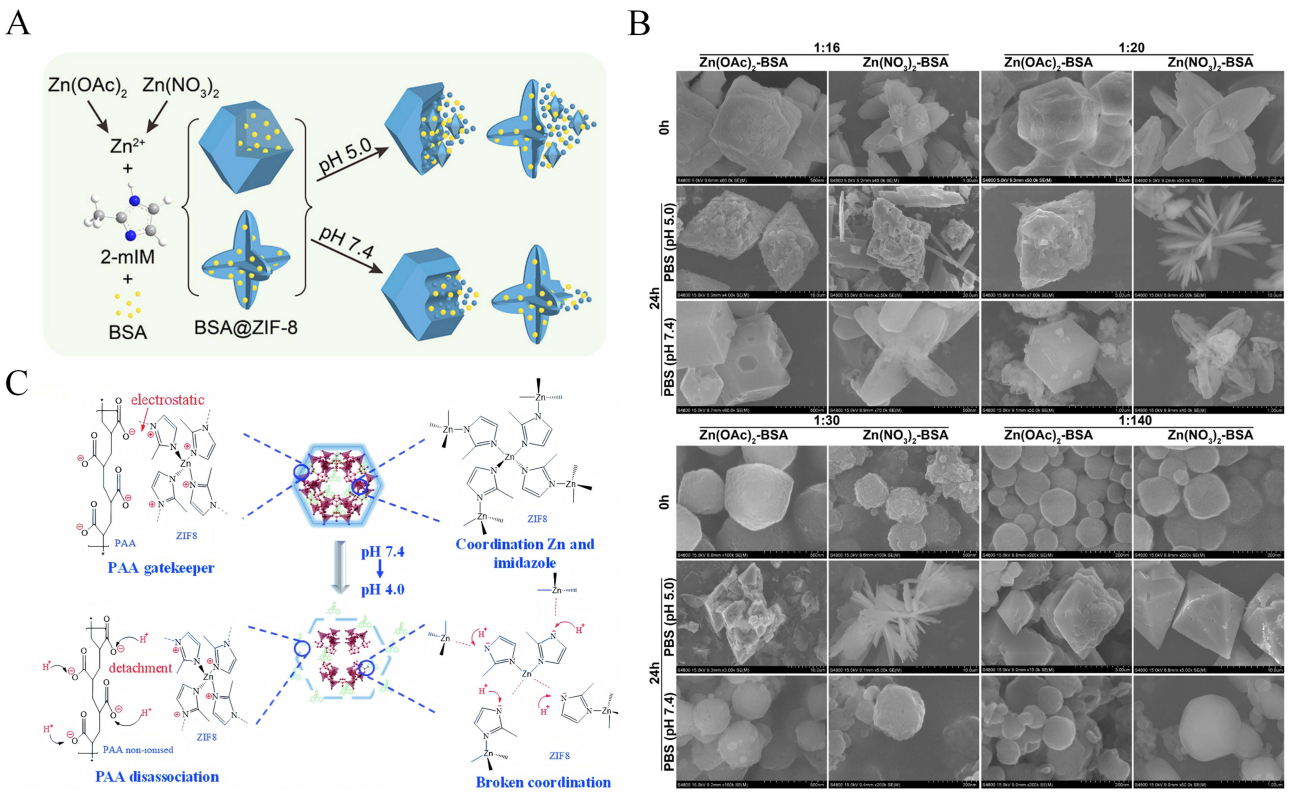

Figure 3 Presents the following: (**A**) A schematic representation of the release behavior under varying pH conditions. (**B**) SEM images of BSA@ZIF-8 nanoparticles before and after a 24-hour incubation period in PBS solutions at pH 5.0 and 7.4. Reproduced from Gao et al, *ACS Omega*, 2023;8(47):44601–44610 with permission.[112] (**C**) The mechanism of Dox release from ZIF-8-Dox@PAA as the pH decreases from 7.4 to 4.0 in PBS solution. Reproduced from Tran et al, *RSC Adv*, 2021;11(16):9222–9234 with permission.[114]

residual tumor cells and mitigate oxidative stress within the tumor microenvironment, researchers developed an injectable ZC-DOX@GEL hydrogel system. This dual-functional platform combines anti-tumor and antioxidant properties, effectively exerting cytotoxic effects on tumor cells while maintaining low toxicity to normal tissues. In vivo results validate its ability to inhibit tumor proliferation, reduce pathological damage, and prevent tumor recurrence.[119]

For the widely used platinum-based drug DDP, ZIF-8 carriers offer distinct advantages. Nanoparticles composed of polydopamine (PDA)-coated DDP@ZIF-8@PDA facilitate a synergistic photothermal-chemotherapy effect under near-infrared light irradiation, demonstrating significantly enhanced cytotoxicity against cancer cells compared to free cisplatin. This combination therapy achieves an apoptosis rate of 98.58% without causing damage to major organs in mice.[87] Targeting non-small cell lung cancer, iron-doped ZIF-8 loaded with DDP (CFZ) in conjunction with radiotherapy effectively inhibits cell proliferation, induces G_2/M phase arrest, and promotes ROS generation and DNA damage. In vivo studies confirm that this approach safely enhances the efficacy of radiotherapy while mitigating leukopenia and renal injury associated with premature cisplatin leakage.[88] Figure 4A depicts the synthesis process of CDDP@Fe/ZIF-8 nanoparticles.

As a first-line therapeutic agent for solid tumors, including pancreatic cancer, Gem encounters clinical challenges due to its limited half-life and systemic toxicity.[127] HA-modified ZIF-8 nanoparticles, co-loaded with Gem and the indoleamine 2,3-dioxygenase (IDO) inhibitor D-1-MT (HA/ZIF-8@Gem/D-1-MT), facilitate combined chemo-immunotherapy through CD44-mediated active targeting and pH-responsive drug release. This nanoparticle formulation exhibited a significantly enhanced inhibitory effect on osteosarcoma cells compared to free Gem, while maintaining low toxicity towards normal osteoblasts. Histopathological evaluations revealed no significant damage to major organs, representing a notable improvement over the free drug group.[89] Similarly, two pH-responsive nanocarriers developed by

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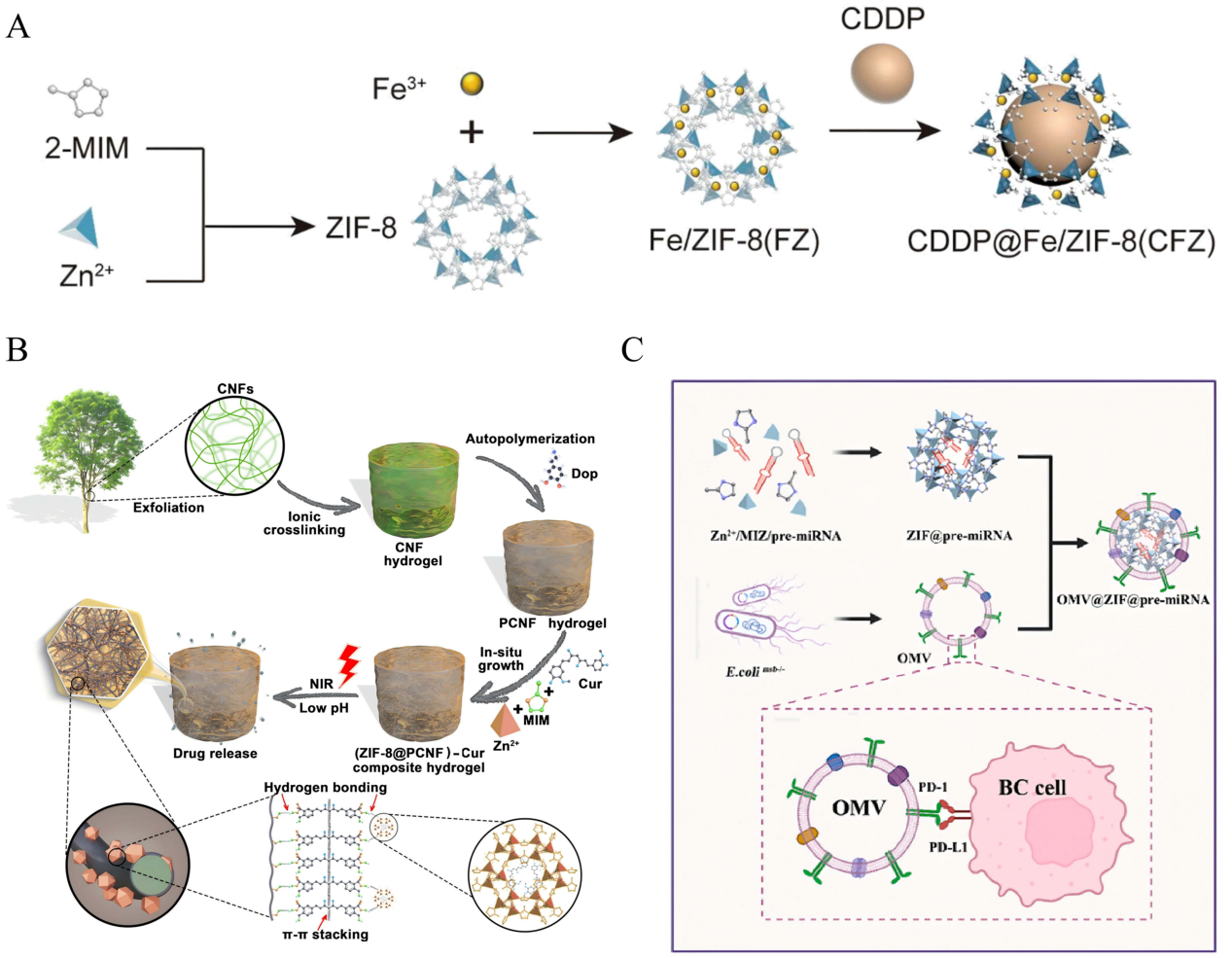

Figure 4 Illustrates the following processes: (**A**) The synthesis procedure for FZ and CFZ nanoparticles. Reproduced from Yang et al, *Sci Rep*, 2025;15(1):42758 with permission.[88] (**B**) A schematic representation of the preparation of the ZIF-8@PCNF composite hydrogel, including its drug release mechanism in response to pH changes and near-infrared (NIR) light irradiation. Reproduced from Liu et al, *Cellulose*, 2021;29(1):379–393 with permission.[126] (**C**) The preparation process of OMV-PD1@ZIF-8@miRNA. Reproduced from Cui et al, *Int J Biol Macromol*, 2023;247:125692 with permission.[93]

Abd et al[128] demonstrated superior inhibitory effects against breast cancer cells (MCF-7) relative to free Gem, along with reduced toxicity to normal cells and more efficient induction of apoptosis in MCF-7 cells.

Delivery of Natural Products

Natural compounds, including triptolide (TP),[129] curcumin (CUR),[130] artemisinin,[131] and their derivatives, frequently encounter obstacles such as limited water solubility, low bioavailability, and non-specific distribution. These issues undermine therapeutic efficacy and can potentially result in toxic side effects. Consequently, there is an urgent necessity to develop advanced DDS that facilitate efficient drug delivery and selective targeting of cancer cells. ZIF-8, with its distinctive physicochemical properties, offers a comprehensive solution to these challenges and has emerged as a focal point of research for the effective delivery of hydrophobic natural products.

ZIF-8 offers significant benefits for loading hydrophobic natural products. Firstly, it achieves ultra-high drug loading efficiency due to its large specific surface area (~1600 m^2/g) and adjustable pore structure, which accommodate hydrophobic molecules effectively.[44,132] The π-π stacking and hydrophobic interactions between imidazole rings and drugs enable near-complete encapsulation, as demonstrated with liquiritigenin, achieving 98.7% encapsulation efficiency and 32.1% drug loading capacity, surpassing traditional carriers. Secondly, ZIF-8 enhances solubility and dispersibility by stabilizing hydrophobic drugs as molecular dispersions or nanocrystals within its pores. Its hydrophilic surface

improves aqueous dispersion, allowing nearly insoluble drugs like CUR to form stable colloidal suspensions suitable for intravenous injection.[133,134] Third, microenvironment-responsive release: ZIF-8's pH sensitivity preserves its structure in neutral environments, preventing early drug leakage, and dissolves in acidic conditions for targeted release.[135] Fourth, controllable release kinetics: Composite systems like ZIF-8@PCNFs-CUR hydrogel extend CUR release to 107 hours, with accelerated release possible via near-infrared light or acidic conditions, offering sustained and responsive release.[126] Figure 4B depicts the synthesis process of the ZIF-8@PCNF composite hydrogel and examines its drug release behavior in response to pH and near-infrared stimuli. Fifth, expanded therapeutic window and reduced toxicity: TP's therapeutic dose is near its toxic dose, risking multi-organ side effects in clinical use.[136] ZIF-8 encapsulation enhances its pharmacokinetic profile. Fang et al found that the TP@ZIF-8 nanosystem preserved antitumor activity while minimizing toxicity to normal tissues.[90] Sixth, ZIF-8 allows for easy surface functionalization with targeting ligands like HA and FA through simple coordination or electrostatic interactions. This enables active targeting via CD44- or FA receptor-mediated endocytosis, boosting drug concentration in tumors or inflamed tissues.[137,138]

Delivery of Nucleic Acid Drugs

As a prototypical example of metal–organic frameworks, ZIF-8 demonstrates considerable promise for gene therapy applications, attributable to its structural adaptability and functional versatility. Its high specific surface area and nanoscale adjustable pores afford substantial capacity for the encapsulation of nucleic acid molecules. Furthermore, its diminutive particle size (approximately 77.8 nm) and surface positive charge enhance its ability to penetrate cell membranes effectively. The "proton sponge effect" associated with its imidazole rings facilitates endosomal escape, thereby enabling the gene cargo to more efficiently reach the nucleus and exert its intended function. In conjunction with its advantageous biocompatibility, responsiveness to the TME, and ease of surface functionalization, ZIF-8 presents significant benefits over conventional viral vectors and liposomal systems, particularly in terms of safety, drug loading efficiency, and targeting controllability. These attributes collectively pave the way for innovative technological advancements in gene therapy.[139,140]

Small interfering RNA (siRNA) holds significant promise for cancer therapy by targeting and silencing critical tumor-associated genes.[141] The positively charged surface of ZIF-8 facilitates the efficient loading of siRNA via electrostatic interactions, while its structural framework offers protection against nuclease-mediated degradation. Furthermore, ZIF-8 undergoes pH-responsive disassembly within the acidic tumor microenvironment, thereby enabling targeted drug release.[142] Saeinasab et al[91] developed a nanodelivery system comprising ZIF-8, PEG modification, and an epithelial cell adhesion molecule (EpCAM)-targeting aptamer. This system demonstrated the capacity for responsive loading and release of siRNA to silence the oncogene SNHG15, providing experimental support for targeted prostate cancer therapy. Similarly, Gong et al[92] engineered a hyaluronic acid-modified ZIF-8 vector for the co-delivery of PD-L1 siRNA. This system successfully achieved PD-L1 silencing through pH-responsive release, while the release of Zn^{2+} ions from ZIF-8 degradation induced tumor cell pyroptosis, highlighting a synergistic antitumor effect through the combination of gene silencing and immunogenic cell death.

MicroRNAs (miRNAs) play a critical role in maintaining cellular homeostasis through the regulation of target gene expression. Their dysregulation is intricately linked to the onset and progression of various cancers. Consequently, the modulation of specific miRNA expression has gained attention as a promising approach for cancer therapy.[143] In comparison to siRNA, miRNAs possess a smaller molecular weight and exhibit relatively greater structural stability. However, they require enhanced detection sensitivity and precise release control within delivery systems.[144] In a study by Li et al,[145] a folate-targeted ZIF-8 composite delivery system was developed, encapsulating ganciclovir within the core and adsorbing miR-34a-5p on the surface through electrostatic interactions The system was further coated with PEI-FA to improve cellular uptake and miRNA stability. This delivery system demonstrated partial success in achieving the synergistic release of drugs and nucleic acids within specific microenvironments, facilitated by the acid-responsive degradation of ZIF-8 and the proton sponge effect of PEI. These findings indicate the potential of ZIF-8 for the co-delivery of small molecules and nucleic acids. With the progression of research, the role of ZIF-8 has progressively evolved towards theranostic integration. Zhang et al[146] conceptualized ZIF-8 not only as a passive drug carrier but also as a reservoir for cofactors. By incorporating catalytic hairpin assembly signal amplification technology alongside

DNAzyme-mediated gene silencing, they developed an advanced theranostic platform responsive to miR-21. This platform facilitated the integration of ultrasensitive miRNA detection with gene silencing, thereby offering empirical evidence for the transformation of ZIF-8 from a mere delivery vehicle into a multifunctional theranostic system. In recent years, the integration of biohybrid materials has emerged as a significant trend in the field. Cui et al[93] utilized genetically engineered bacterial outer membrane vesicles (OMVs) displaying programmed death-1 (PD-1) on their surfaces to encapsulate the ZIF-8/miR-34a complex. In studies involving small animal models, this system demonstrated enhanced tumor-targeting capabilities. Furthermore, miR-34a exhibited a synergistic therapeutic effect in conjunction with OMVs-mediated immune activation and immune checkpoint inhibition, while maintaining favorable biosafety profiles. Figure 4C depicts the methodology employed in the preparation of OMV-PD1@ZIF-8@miRNA.

CRISPR/Cas9, recognized as a highly efficient gene-editing tool, has demonstrated the capability to suppress tumors by precisely targeting and either knocking out or repairing oncogene mutations.[147] However, the commonly employed CRISPR ribonucleoproteins (RNPs) encounter challenges related to low delivery efficiency and potential cytotoxicity in vivo.[148] The pore confinement effect of ZIF-8 has been shown to protect RNP integrity, while its pH-responsive release mechanism ensures the activation of the editing machinery within target cells.[149] Recent advancements in research suggest that delivery strategies utilizing ZIF-8 are transitioning from simple gene editing to encompass synergistic therapy and immunomodulation. Early investigations, such as the study conducted by Poddar et al,[150] preliminarily validated the feasibility of employing ZIF-8 to load CRISPR plasmids for gene therapy targeting prostate cancer The application of a surface coating with epigallocatechin gallate (EGCG) significantly improved cellular uptake efficiency and gene-editing outcomes, although the underlying mechanism primarily focused on direct gene knockout. Subsequent research has increasingly emphasized multi-dimensional synergy. Huang et al[94] developed a hyaluronic acid-modified bimetallic ZIF-8 nanoplatform that facilitated precise downregulation of the key immunometabolic gene SLC43A2 through the CRISPR system. Additionally, the Mn^{2+}/Zn^{2+} ions released from the framework were utilized to activate the cGAS-STING innate immune pathway. This dual approach, combining gene editing with immune activation, significantly enhanced the anti-tumor immune response. In a related study, Yu et al[95] advanced the scope of synergistic strategies by co-delivering a dual-cleaving CRISPR system and the glucose transporter inhibitor BAY-876 via ZIF-8. This approach effectively blocked lactate influx and glucose uptake in tumor cells, thereby inhibiting tumor growth from an energy-metabolism perspective. This represents an innovative synergistic therapeutic strategy termed "gene editing-metabolic intervention". A summary of the design and efficacy of ZIF-8-based nanoplatforms in cancer therapy is provided in Table 2.

It is important to highlight that the aforementioned studies are confined to in vitro and small animal models, and have yet to be validated in immunocompetent large animal models or clinical settings. Consequently, further research is necessary to substantiate the potential clinical translational value of their synergistic therapeutic effects.

ZIF-8/Zn^{2+}-Mediated Tumor Microenvironment Remodeling and Antitumor Mechanisms

Dual Biological Functions and Antitumor Applications of Zn^{2+}

Zn^{2+} are vital trace elements in the human body, playing a crucial role in cellular growth, metabolic regulation, and immune function.[151,152] Nevertheless, an excessive accumulation of Zn^{2+} can compromise mitochondrial function and induce oxidative stress, potentially resulting in cellular damage or apoptosis.[153] This dual functionality-facilitating growth while also having the potential to induce cell death-positions Zn^{2+} as a promising target for cancer therapy. Under homeostatic conditions, physiological concentrations of Zn^{2+} function as secondary messengers, activating the ERK and Akt signaling pathways.[154] These pathways are integral to cell proliferation, differentiation, and survival, forming a central regulatory network essential for maintaining tissue homeostasis. Zn^{2+} facilitates DNA synthesis and protein translation, acts as a critical signaling molecule for cell cycle progression, and serves as a pivotal metabolic switch. Conversely, elevated concentrations of Zn^{2+} can rapidly exert cytotoxic effects.[155,156] At concentrations as low as 10 nmol/L, Zn^{2+} can induce mitochondrial swelling and the opening of the mitochondrial permeability transition pore, leading to the release of pro-apoptotic factors and neuronal cell death.[157] In glial cells, Zn^{2+} promotes the production of

ROS, which subsequently activates the TRPM2 channel. This activation leads to Ca^{2+} overload and a positive feedback loop that ultimately disrupts ionic homeostasis and induces cell death.[158] Building upon the dose-dependent toxicity of Zn^{2+}, researchers have devised a range of zinc-overload antitumor strategies. Wu et al[159] introduced a zinc-ion-interference-based tumor starvation therapy. This approach synergistically combines "Zn^{2+} interference"-mediated glycolysis inhibition with Zn^{2+}-activated tumor-specific GLUT1 depletion, thereby achieving energy deprivation in tumor cells and addressing the limitations of conventional starvation therapies, such as high nonspecificity and incomplete energy blockade. In a related development, Zhao et al[160] engineered BaSO4@ZIF-8/TRF nano-macrophages (NMΦs) to serve as alternative carriers for immunologically active macrophages. This system exploits the tumor microenvironment-specific degradation of ZIF-8 to release Zn^{2+}, which functions as an "artificial cytokine." This dual-action mechanism not only reverses the immunosuppressive tumor microenvironment but also induces anoikis in tumor cells, offering a novel strategy for tumor immunotherapy.

Induction of Oxidative Stress and Endoplasmic Reticulum Stress

The degradation of ZIF-8 within the TME results in the release of Zn^{2+}, which induces tumor cell death through various mechanisms. A central pathological effect is the synergistic activation of oxidative stress and endoplasmic reticulum stress. Tumor cells, in comparison to normal cells, exhibit elevated basal levels of ROS, increased metabolic activity, and a relatively compromised antioxidant defense system. This redox vulnerability makes tumor cells particularly susceptible to apoptosis induced by Zn^{2+} overload, which precipitates a surge in ROS and protein misfolding. Consequently, this approach has emerged as a significant strategy in tumor metabolic intervention in recent years.[96,161]

Zn^{2+} induces ROS production in tumor cells through three interconnected pathways. The primary mechanism involves the inhibition of the mitochondrial electron transport chain. Excess Zn^{2+} specifically targets and disrupts the function of mitochondrial complexes I and III, impeding electron transfer and resulting in electron leakage. This leakage facilitates the reaction with oxygen molecules, thereby generating substantial quantities of superoxide anions.[162,163] Concurrently, Zn^{2+} compromises mitochondrial membrane stability, causing fragmentation of the mitochondrial network and enhancing ROS release into the cytosol.[164] The second pathway entails the activation of NADPH oxidase 1 (NOX1). Zn^{2+} directly activates NOX1, which catalyzes the oxidation of NADPH to produce ROS.[165] This process exerts a signal-amplifying effect, wherein mitochondrial ROS activate the NF-κB transcription factor, subsequently upregulating NOX1 expression. This creates a "ROS-NF-κB-NOX1-ROS" positive feedback loop, resulting in a marked increase in intracellular ROS levels.[166] The third mechanism involves the suppression of the antioxidant system, wherein Zn^{2+} inhibits the activity of glutathione peroxidase 4 (GPX4), a critical enzyme responsible for the detoxification of lipid peroxides. The functional inactivation of GPX4 results in the accumulation of lipid peroxidation products, thereby exacerbating oxidative damage.[167] Tumor cells' antioxidant systems are already operating under a compensatory high load. When subjected to multi-targeting by Zn^{2+}, the imbalance between ROS production and clearance becomes irreversible, ultimately initiating oxidative stress-mediated cell death pathways. The process of Zn^{2+}-induced severe oxidative stress is depicted in Figure 5.

The endoplasmic reticulum (ER), a pivotal organelle for protein folding and Ca^{2+} storage, operates with strict dependence on ionic homeostasis and redox balance. An excess of Zn^{2+} disrupts Ca^{2+} homeostasis by competitively inhibiting the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA), significantly impairing Ca^{2+} uptake capacity and resulting in the depletion of ER calcium stores.[168,169] This depletion of Ca^{2+}, an essential cofactor for chaperones such as calnexin and calreticulin, adversely affects the proper folding of nascent polypeptide chains, leading to the accumulation of misfolded proteins.[170,171] Additionally, Zn^{2+} overload directly interferes with the protein folding process by binding to non-physiological ligands, thereby trapping proteins in a misfolded state and preventing their transition to the native conformation.[172] More critically, the ROS burst induced by Zn^{2+} and protein misfolding creates a detrimental feedback loop. ROS disrupts precise redox regulation during disulfide bond formation, resulting in disulfide bond mismatches and further exacerbating aberrant protein conformations.[173,174] The accumulation of misfolded proteins within the ER lumen triggers the unfolded protein response (UPR).[175,176] Initially, adaptive mechanisms, including translational attenuation and the upregulation of chaperone expression, are activated to restore cellular homeostasis. However, the stress intensity induced by Zn^{2+} surpasses the regulatory capacity of tumor cells, thereby shifting the UPR from a protective mechanism

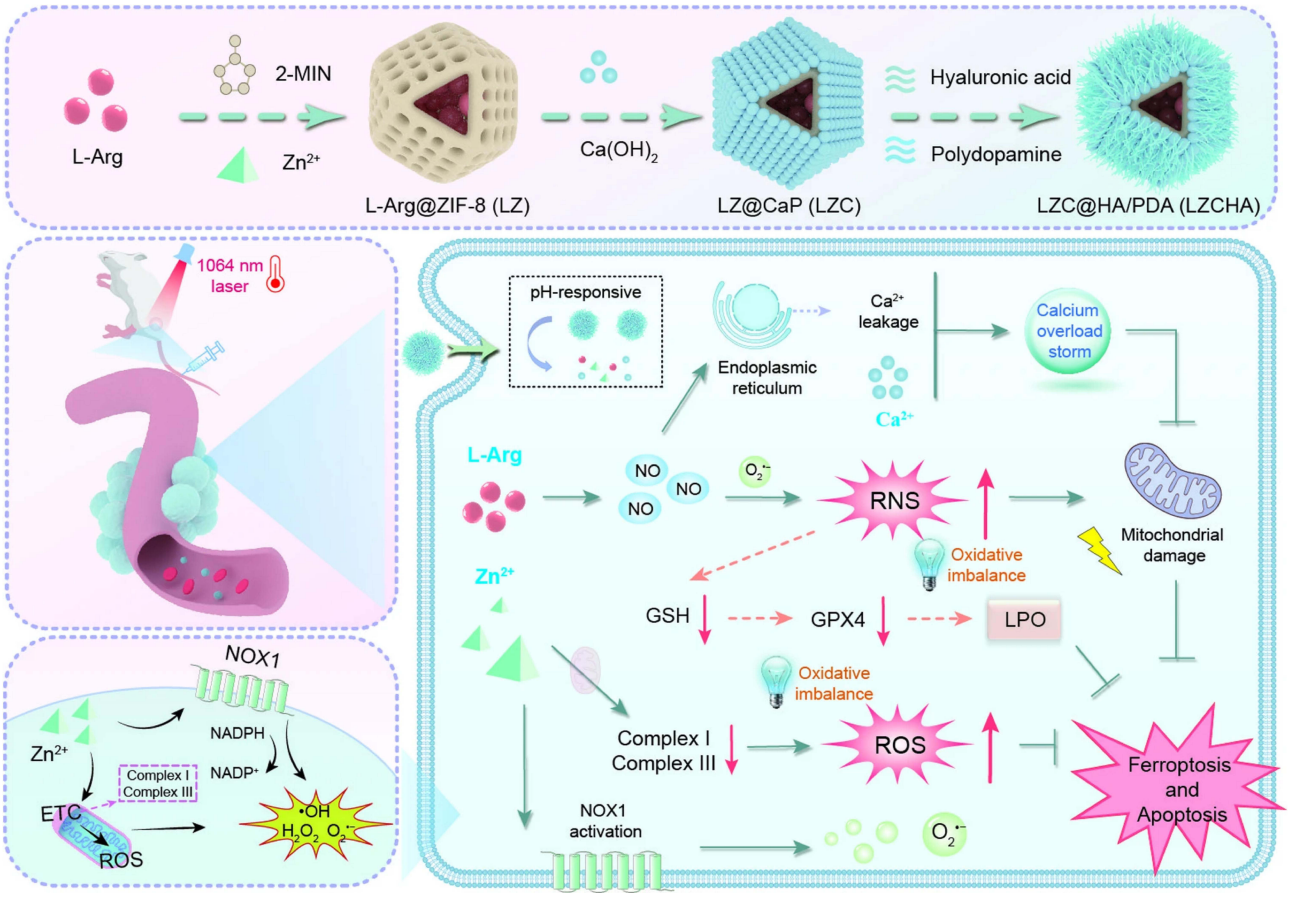

Figure 5 Illustrates the synthesis of LZCHA and its role in triggering ferroptosis/apoptosis for cancer treatment. LZCHA, a multifunctional nanoparticle, is created using ZIF-8 to encapsulate L-arginine, followed by CaP coating and HA/PDA modification. In the tumor microenvironment, Zn^{2+} from ZIF-8 degradation disrupts mitochondrial function and activates NOX1, increasing ROS levels and oxidative stress, selectively killing tumor cells. Reproduced from Zhou et al, *J Nanobiotechnology*, 2025;23(1):713 with permission.[96]

to a pro-apoptotic pathway. This transition is mediated through the activation of signaling pathways such as CHOP, JNK, and caspase-12, ultimately leading to apoptosis.[177–179]

The oxidative stress and ER stress induced by Zn^{2+} are not discrete occurrences; rather, they are interconnected through multiple pathways, constituting a positive feedback network. ROS can oxidize the thiol groups of ER-resident proteins, thereby impairing their protein-folding functions. Additionally, the leakage of Ca2+ from the ER into mitochondria further exacerbates mitochondrial ROS production. Furthermore, the UPR-activated transcription factor CHOP can upregulate the expression of oxidases such as NADPH oxidase 2, thereby creating a mutual amplification between oxidative stress and ER stress. This synergistic effect imposes "multiple hits" on tumor cells.

Activation of the cGAS/STING Signaling Pathway

Zn^{2+} facilitate the liberation of cytoplasmic DNA fragments and mitochondrial DNA (mtDNA) by disrupting DNA stability and inducing mitochondrial dysfunction, thereby effectively activating the pivotal innate immune signaling pathway, cGAS-STING. Specifically, Zn^{2+} increases intracellular ROS levels in tumor cells, resulting in mitochondrial damage and the subsequent release of mtDNA into the cytosol, which serves as an essential ligand for cGAS. Moreover, Zn^{2+} enhances the production of cyclic GMP-AMP and improves its binding affinity to STING, thereby augmenting the activity of the STING pathway.[97] Concurrently, Zn^{2+} can directly induce liquid-liquid phase separation of cGAS, a transition that significantly boosts its enzymatic activity and sensitivity to DNA, culminating in a robust anti-tumor immune response.[180,181] However, the activation of this pathway within the TME is often limited by intrinsic inhibitory factors, such as certain accumulated mutant p53 proteins, which have been shown to suppress cGAS-STING signaling.

Zn^{2+} has been shown to facilitate the degradation of inhibitory p53 mutants, thereby effectively removing a regulatory "brake" on the signaling cascade. By alleviating this negative regulation, Zn^{2+} ensures that the immunostimulatory signals generated in the preceding steps are adequately amplified and consistently transmitted downstream.[182] While studies have shown how Zn^{2+} activates the cGAS-STING pathway, its effectiveness in triggering immune responses in tumors is hindered by immunosuppressive elements. Most evidence comes from in vitro studies or single animal models, and there is a lack of thorough assessment of the risks of immune tolerance from Zn^{2+}-induced STING activation in diverse tumors and with prolonged use.

How Do ZIF-8 and Zn^{2+} Reverse Tumor Immunosuppression?

Reprogramming Tumor-Associated Macrophages

TAMs represent the most prevalent immune cell infiltrates within the tumor microenvironment, with their functional phenotypes being intricately linked to tumor progression and responses to immunotherapy.[183,184] TAMs are classified into the anti-tumor M1 phenotype and the pro-tumor M2 phenotype.[185–187] In the context of solid tumors, TAMs predominantly exhibit polarization towards the M2 phenotype, a condition correlated with unfavorable patient prognosis and resistance to immunotherapy.[188] However, TAMs possess significant phenotypic plasticity, allowing them to be repolarized to the M1 phenotype in response to specific microenvironmental stimuli, thus presenting a viable target for therapeutic intervention in tumor immunotherapy.[189,190] ZIF-8-based nanodelivery systems have the capability to locally release therapeutic agents and Zn^{2+} ions at tumor sites, facilitating the repolarization of M2-type TAMs to the M1 phenotype. This process contributes to the remodeling of the immunosuppressive microenvironment and enhances endogenous anti-tumor immune responses.[191,192]

Se@ZIF-8 core-satellite nanoassemblies facilitate the concurrent delivery of Zn^{2+} and selenium. In the acidic conditions characteristic of the tumor microenvironment, this nanosystem undergoes progressive degradation, leading to the simultaneous release of selenium nanoparticles and Zn^{2+} ions. These ions work synergistically to induce substantial intracellular ROS production, which subsequently activates the NF-κB signaling pathway. This activation effectively promotes the repolarization of TAMs from the protumorigenic M2 phenotype to the antitumorigenic M1 phenotype, thereby reinstating their immune surveillance capabilities.[193] The PZ@M-T platform facilitates coordinated immunomodulatory effects through the integration of Zn^{2+} with endogenous danger signals. Upon tumor-specific activation, mitochondrial DNA released from damaged cells synergizes with Zn^{2+} to activate the cGAS-STING pathway. Zn^{2+} directly stimulates the cGAS-STING cascade in macrophages, enhancing the secretion of proinflammatory cytokines via the TBK1/IRF3 signaling axis and inducing the phenotypic transition of TAMs from the M2 to the M1 phenotype. This process contributes to the remodeling of the immunosuppressive tumor microenvironment. However, the mechanistic evidence for Zn^{2+}-mediated activation of the cGAS-STING pathway and TAM repolarization presented in this study is primarily extrapolated from prior literature rather than being directly validated through experimental methods. Consequently, its true efficacy and reliability in specific tumor models necessitate systematic verification via comprehensive in vitro and in vivo investigations.[194] A novel integrated in situ tumor vaccine platform, designated as SOM-ZIF-8@Mn/ARV, has been recently developed to deliver the specific immunogenic cell death (ICD) inducer ARV-825. In vitro studies have demonstrated that ARV-825 effectively facilitates the repolarization of M2-type RAW264 macrophages towards the proinflammatory and tumoricidal M1 phenotype. This effect is likely linked to the upregulation of intracellular ROS through the degradation of the BRD4 protein. Nonetheless, the precise roles and underlying interactions of Mn^{2+} and Zn^{2+} in the regulation of macrophage polarization remain to be elucidated.[195] Notably, ROS signaling plays a dual regulatory role in the phenotypic plasticity of TAMs: it acts as a crucial mediator for M1 activation and is also involved in the differentiation and maintenance of the M2 phenotype.[196] However, the precise molecular mechanisms underlying Zn^{2+}-mediated activation of the cGAS-STING pathway and the consequent phenotypic switching of TAMs remain to be thoroughly elucidated.

Regulation of Myeloid-Derived Suppressor Cells

MDSCs represent a pivotal immunosuppressive cellular population within the TME, contributing to tumor cell proliferation and metastatic progression.[197] Beyond their immunosuppressive roles, MDSCs also enhance tumor growth and the

establishment of pre-metastatic niches via non-immunological pathways.[198] The expansion and infiltration of MDSCs are strongly correlated with adverse prognostic outcomes across a range of malignancies. Therefore, strategies aimed at depleting or functionally inhibiting MDSCs have emerged as essential approaches for modulating the anti-tumor immune microenvironment.

Research has shown that zinc supplementation, particularly with compounds like zinc-L-carnosine, can decrease the prevalence of immunosuppressive cells-including MDSCs, Tregs, and M2-type macrophages—in colorectal cancer models. Concurrently, it enhances the infiltration and cytotoxic activity of $CD8^+$ T cells.[199,200] The direct intratumoral administration of zinc ions can trigger pyroptosis in tumor cells, thereby reducing the infiltration of immunosuppressive cells such as MDSCs.[201] ZIF-8 nanocarriers offer an effective platform for the controlled co-delivery of therapeutic agents and Zn^{2+} to tumor sites; the release of drugs and Zn^{2+} during their degradation modulates MDSC function through various mechanisms. Zhou et al[98] developed a ZIF-8 nanodelivery system co-loaded with mitoxantrone (MIT) and the DNA demethylating agent hydralazine (HYD). This system decreases the concentration of methylglyoxal (MGO)—a specific metabolite in MDSCs-via HYD, thus mitigating the metabolic suppression exerted by MDSCs on the cytotoxic function of T cells. Tan et al[202] developed Ph-Zn, a nanostructure composed of Zn^{2+}-chelated L-phenylalanine, and integrated it with short-term starvation and anti-PD-1 antibody therapy. The findings demonstrated a notable reduction in MDSCs, effectively reversing the immunosuppressive tumor microenvironment. In vivo experiments further substantiated that its antitumor efficacy surpassed that of the control nanomaterials Ph-Mg and Ph-Fe, which incorporate Mg^{2+} or Fe^{2+}. This study confirmed that Zn^{2+} offers distinct advantages over other divalent metal ions in modulating MDSCs. Nevertheless, the study established only an indirect correlation and did not directly validate the regulatory effect of Zn^{2+} on MDSCs. Moreover, it remains challenging to delineate the individual contributions of zinc ions, the nanostructural framework, and phenylalanine, and the underlying molecular regulatory mechanisms require further elucidation. In summary, the role of Zn^{2+} in regulating MDSCs and tumor progression is not fully understood. However, evidence suggests that Zn^{2+} inhibits MDSCs expansion and function, indicating a protective role in tumors. Further research should explore the controlled release of Zn^{2+} using ZIF-8 nanocarriers, establish dose-effect models, and utilize single-cell sequencing and metabolomics to understand Zn^{2+}'s impact on MDSCs subsets. Additionally, its potential synergy with immune checkpoint inhibitors and metabolic regulators should be investigated to support ion-interference tumor immunotherapy.

Enhancing T Cell Function

T cells serve as the principal effector cells in anti-tumor immunity, with their activation, proliferation, and functionality reliant on the precise modulation of T cell receptor (TCR) signaling. Zn^{2+}, as a critical cofactor in TCR signal transduction, regulate T cell functions through various mechanisms, thereby providing a theoretical basis for ZIF-8-mediated tumor immunotherapy.[203,204] Zn^{2+} can form a "zinc clasp" structure by coordinately binding to CD4/CD8α and Lck kinase, which promotes the phosphorylation of the immunoreceptor tyrosine-based activation motifs within the TCR complex. This process amplifies activation signals and enhances the activation of downstream NF-κB, MAPK, and NFAT pathways, thereby driving T cell proliferation and cytokine production.[205] Additionally, Zn^{2+} inhibits the negative regulatory factor SHP-1, thereby sustaining T cell activation and mitigating T cell exhaustion.[206,207] Conversely, Zn^{2+} deficiency disrupts the Th1/Th2 balance and impairs cytotoxic T cell responses.[208] In a mouse model of hepatocellular carcinoma, zinc deficiency induces $CD8^+$ T cell exhaustion, whereas exogenous zinc supplementation (180 mg/kg) can reverse this phenotype and restore T cell function.[209]

ZIF-8 nanocarriers facilitate the targeted delivery of therapeutic agents and Zn^{2+} ions to tumor tissues, offering a controllable platform for the enhancement of T cell functionality. In contrast to the systemic effects associated with generalized zinc supplementation, localized Zn^{2+} accumulation establishes a high-zinc microenvironment at tumor sites, thereby optimizing the functional state of tumor-infiltrating T cells and mitigating the systemic toxicity associated with high-dose zinc. Yan et al[99] developed a pH-responsive dual-pathway immunostimulatory nanoreactor, designated as Au-$Cu_{2-x}Se$@ZIF-8@P18. Within the acidic tumor microenvironment, ZIF-8 undergoes degradation, releasing Zn^{2+} ions that disrupt intracellular zinc homeostasis and induce DNA damage and mitochondrial dysfunction. Upon exposure to laser irradiation, Au-$Cu_{2-x}Se$ initiates Fenton-like reactions through the valence state transition of copper ions, which

synergizes with P18-based photodynamic therapy to generate substantial levels of ROS. The synergistic interaction between Zn^{2+} and ROS activates the caspase-1/GSDMD pathway, thereby inducing tumor cell pyroptosis and ICD. This mechanism facilitates the release of damage-associated molecular patterns (DAMPs) and tumor-associated antigens, enhances dendritic cell maturation and antigen presentation, and ultimately stimulates the activation and recruitment of $CD4^+$ and $CD8^+$ T cells. Flow cytometry analyses demonstrated significantly increased levels of $CD4^+$ and $CD8^+$ T cells in the ACS-Z-P plus laser treatment group, indicative of a robust generation of helper and effector T cells, which is a critical indicator of nanomaterial-induced systemic antitumor immunity. However, it is important to note that the conclusions drawn from this study are currently validated only in subcutaneous xenograft tumor models. The therapeutic efficacy and immune activation effects have not been confirmed in orthotopic liver cancer models, which bear higher clinical relevance. Additionally, there is a lack of long-term safety assessments, leaving the potential for chronic organ toxicity and cumulative risk unaddressed.

Induction of Immunogenic Cell Death

ICD represents a distinct modality of cell death, characterized by the release of DAMPs from dying cells. These DAMPs activate antigen-presenting cells, thereby initiating adaptive anti-tumor immune responses.[210,211] Unlike immunologically silent forms of cell death, such as apoptosis, ICD converts tumors into in situ autologous vaccines through a sequential process involving cell death, antigen release, and immune activation. This process offers a vital strategy for overcoming tumor immune tolerance. The primary DAMPs involved in this process include calreticulin (CRT), adenosine triphosphate, high mobility group box 1, type I interferons, and annexin A1. Through the synergistic action of these molecules, ICD facilitates the maturation of dendritic cells (DCs), the cross-presentation of antigens, and the activation of cytotoxic T lymphocytes.[212–217]

As a co-delivery vector for chemotherapeutic agents and natural products, ZIF-8 facilitates the synergistic integration of chemotherapy, ICD induction, and immune microenvironment remodeling. Its primary advantage is its degradation in response to the acidic tumor microenvironment, which concurrently releases encapsulated drugs and Zn^{2+} ions. The released drugs directly target and kill tumor cells, while Zn^{2+} ions enhance ICD through the aforementioned mechanisms, collectively transforming immunologically "cold" tumors into "hot" tumors.[218] The mEHGZ nanosystem co-delivers epirubicin (EPI), glucose oxidase (GOx), and hemin within the ZIF-8 core, and is further camouflaged with tumor cell membranes overexpressing CRT. EPI functions as a classical ICD inducer, while the cascade catalysis by GOx and hemin enhances ROS generation, thereby amplifying ICD effects. Additionally, the outer membrane enriched with exogenous CRT provides supplementary "eat me" signals, promoting dendritic cell antigen presentation and cytotoxic T lymphocyte infiltration, ultimately reversing the immunosuppressive tumor microenvironment.[100] In the MIT@ZIF-8 system, mitoxantrone (MIT) induces apoptosis and ICD in tumor cells. Concurrently, the release of Zn^{2+} from ZIF-8 enhances ROS production and activates caspase-1/GSDMD-dependent pyroptosis, thereby augmenting MIT-mediated ICD. This study demonstrates that ZIF-8 functions not only as an effective nanocarrier, facilitating increased tumor cellular uptake of MIT and enhancing its cytotoxic effects, but also as a catalyst for pyroptosis, thereby amplifying MIT-induced ICD and remodeling the anti-tumor immune microenvironment. Furthermore, although blank ZIF-8 exhibits significant cytotoxicity against tumor cells in vitro, it shows negligible anti-tumor efficacy in vivo. This suggests that Zn^{2+}-mediated immune activation alone is insufficient to achieve substantial tumor suppression (Figure 6).[101] Recent research has demonstrated that ZIF-8, at a concentration of 100 μg/mL, can selectively induce apoptosis in oral squamous cell carcinoma cells by upregulating apoptotic markers such as Bax and caspase-3/6/10, while sparing normal mesenchymal stem cells. This finding highlights the intrinsic selective anti-cancer properties of ZIF-8 against oral cancer. However, these conclusions are currently supported only by in vitro data obtained at a single time point. The fundamental mechanisms, including the release of Zn^{2+} ions and the accumulation of ROS, remain inadequately elucidated. Furthermore, there is a lack of in vivo evidence regarding therapeutic efficacy, biosafety, and pharmacokinetics, necessitating further comprehensive investigation.[219]

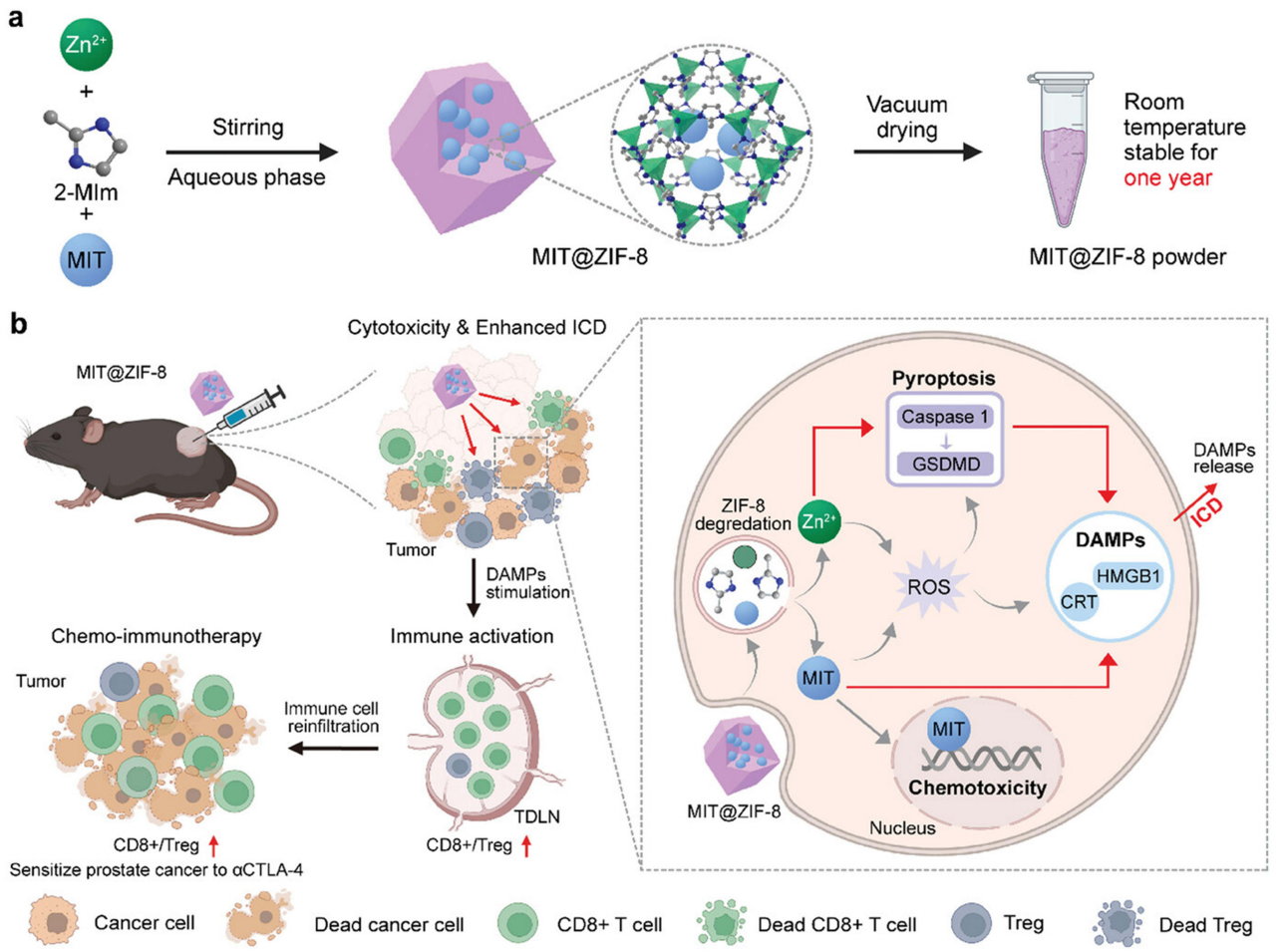

Figure 6 (**a**) Design and synthesis of MIT@ZIF-8 nanoparticles for improved chemo-immunotherapy. (**b**) MIT@ZIF-8 enhances ICD by boosting tumor uptake of MIT and inducing pyroptosis via Zn2+ ions, improving treatment for both "hot" and "cold" cancers and making prostate cancer more responsive to anti-CTLA-4 therapy. Reproduced from Li et al, *Adv Sci* (Weinh), 2025;12(14):e2501542 with permission.[101]

Inhibition of Tumor Metastasis

Tumor metastasis represents the primary cause of mortality associated with cancer, characterized by a complex, multi-step process that encompasses the detachment of tumor cells from the primary site, invasion through the basement membrane, entry into the circulatory system, and subsequent colonization at distant organs.[220] Critical pathological mechanisms facilitating metastasis include epithelial-mesenchymal transition (EMT), degradation of the extracellular matrix (ECM), and remodeling of the TME.

EMT is a critical process that initiates tumor metastasis by conferring migratory and invasive capabilities, stemness, and drug resistance to tumor cells.[221–223] This process is accompanied by the remodeling of characteristic markers and the cytoskeleton.[224–226] Residual tumors following local therapy are particularly susceptible to EMT activation and accelerated metastasis, underscoring the urgent need for effective interventions.[227] Consequently, targeting EMT has emerged as a pivotal strategy in combating tumor metastasis. ZIF-8 nanosystems have demonstrated the ability to inhibit metastasis through multiple mechanisms, including drug delivery and Zn^{2+} release. Arsenic trioxide (ATO), a well-established EMT inhibitor, promotes tumor cell differentiation and apoptosis; however, its clinical application is constrained by systemic toxicity and inadequate tumor accumulation.[228] In response to these limitations, Chen et al[229] developed As@ZIF-8 nanoparticles. In vitro experiments revealed that As@ZIF-8 nanoparticles exhibited superior efficacy compared to free ATO in inhibiting sublethal heat-induced cell proliferation, inducing apoptosis, and reversing

EMT. Furthermore, in vivo studies confirmed that this nanosystem significantly suppressed the growth and metastasis of residual tumors.

Tumor cells that have acquired migratory capabilities must degrade the ECM to facilitate invasion and distant dissemination. Matrix metalloproteinases (MMPs), a family of Zn^{2+}/Ca^{2+}-dependent proteolytic enzymes, play a crucial role in this process. By degrading ECM components such as collagen and laminin, as well as the basement membrane, MMPs create pathways for tumor cell invasion and serve as key mediators of tumor metastasis.[230–232] Hinokiflavone (HF) exhibits anti-metastatic properties primarily through the downregulation of MMPs, forming the molecular basis for its inhibitory effects on tumor metastasis.[233] However, HF's poor water solubility results in low bioavailability and necessitates high oral dosages, significantly limiting its clinical application. To address this, Peng et al[68] encapsulated HF within ZIF-8 and conjugated it with PEG to develop a PEG/ZIF-8@HF drug delivery system. This system is designed to degrade in the acidic tumor microenvironment, thereby efficiently releasing HF and enhancing its pharmacological efficacy. Animal experiments have demonstrated that PEG/ZIF-8@HF exhibits significant anti-tumor effects, primarily through the upregulation of pro-apoptotic proteins caspase-3 and caspase-8, and the downregulation of MMP-9, which is known to facilitate cell migration and invasion.

Rapid tumor proliferation results in local hypoxia, a pivotal microenvironmental factor that facilitates the activation of EMT, upregulation of MMPs, and aberrant angiogenesis. Hypoxia-inducible factor-1α (HIF-1α), as the central transcription factor in the hypoxic response, can synergistically activate prometastatic gene networks, including vascular endothelial growth factor (VEGF) and MMPs, thereby initiating a malignant cascade encompassing hypoxia, EMT, invasion, and angiogenesis.[234,235] Consequently, inhibiting HIF-1α signaling represents a critical intervention point to disrupt this cascade. The ZIF-8-based co-delivery system (CDHNs) engineered by Wang et al[102] simultaneously encapsulates HIF-1α siRNA, the photosensitizer Ce6, and the chemotherapeutic agent DOX, thereby facilitating a tri-modal therapeutic approach comprising photodynamic therapy, chemotherapy, and gene silencing. The intrinsic pH-responsive degradation characteristic of ZIF-8 permits spatiotemporally controlled drug release within the acidic tumor microenvironment, thereby enhancing therapeutic selectivity while mitigating systemic toxicity. HIF-1α siRNA effectively downregulates the target gene, suppresses the expression of VEGF and MMP-9, and inhibits angiogenesis as well as extracellular matrix degradation. Ce6-mediated photodynamic therapy induces the production of ROS, exacerbating oxidative damage, while DOX directly induces cytotoxicity in tumor cells. This multi-component synergistic strategy markedly inhibits the formation of micrometastases and diminishes the invasion of distant organs in animal models.

Recent research has developed an antibody-functionalized core-shell ZIF-8 nanosystem capable of targeting and accumulating in tumor cells with high EpCAM expression. Upon intracellular degradation, this nanosystem releases Zn^{2+} ions. This mechanism can partially inhibit tumor cell migration and invasion by modulating actin cytoskeleton assembly and altering cell-surface EpCAM expression. Consequently, this study offers a novel avenue for targeted interventions in tumor metastasis.[236]

ZIF-8-Based Strategies for Cancer Theranostics

ZIF-8 is characterized by its high surface area, customizable pore structure, and biocompatibility, rendering it an optimal nanoplatform for the integration of diagnostic and therapeutic functionalities. The compound's distinctive optical properties, attributed to the coordination between Zn^{2+} ions and imidazole ligands, facilitate fluorescence quenching and recovery in response to acid-induced Zn^{2+} release. This mechanism enables the real-time monitoring of drug release.[237] ZIF-8 is capable of encapsulating a variety of imaging agents and, through targeted surface modifications, can achieve selective tumor accumulation and enhanced imaging contrast. Additionally, it can co-encapsulate therapeutic agents, thereby establishing a theranostic platform that supports precision oncology by integrating diagnosis, treatment, and monitoring. Figure 7 provides a summary of representative strategies for tumor theranostics and combination therapy utilizing ZIF-8 nanoplatforms.

Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is a fundamental technique for clinical tumor diagnosis and evaluation of therapeutic efficacy due to its advantages, including non-ionizing radiation, high soft-tissue contrast, and deep tissue

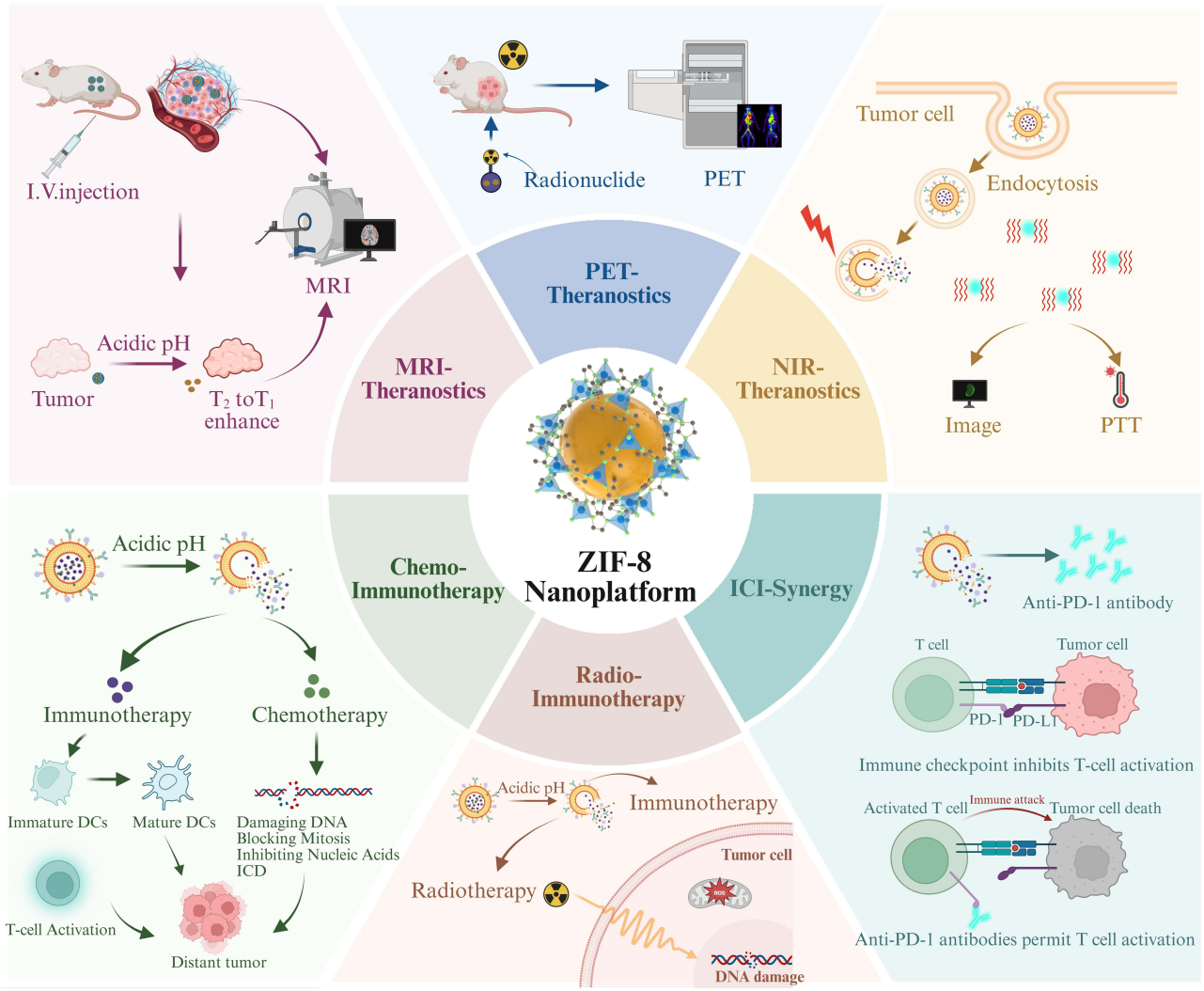

Figure 7 Presents a schematic representation of tumor theranostic strategies utilizing a ZIF-8 nanoplatform. This platform facilitates multimodal imaging—comprising MRI, PET, and NIR modalities—to guide combination therapies such as chemotherapy, photothermal therapy, radiotherapy, and immunotherapy (*Created in BioRender.he, W. (2026) https://BioRender.com/xlszftw*).

penetration.[238,239] Paramagnetic metal ions, such as Fe^{3+}, Mn^{2+}, and Gd^{3+}, are capable of reducing the relaxation time of adjacent water protons, thereby functioning as T_1/T_2-weighted contrast agents to improve signal contrast.[240] The pore confinement effect of ZIF-8 enhances the local concentration of these contrast agents, while its pH-responsive release mechanism allows for tumor-specific activation. Zhou et al[241] encapsulated Gd-DTPA within the pores of ZIF-8 to develop a T_1-weighted contrast agent, Gd-DTPA@ZIF-8. This system demonstrated a longitudinal relaxivity (r1) value of 29.60 $mM^{-1}\cdot s^{-1}$ at 0.5 Tesla, which is approximately six times greater than that of free Gd-DTPA. This enhancement is attributed to the ZIF-8 framework's ability to enrich Gd^{3+} ions and induce a slow tumbling effect. In vivo MRI studies revealed significantly improved signal intensity at the tumor site, corroborating the amplification effect of the ZIF-8 carrier on contrast performance. Pan et al[242] utilized Mn^{2+} as an endogenous contrast agent and developed Mn-ZIF-8 along with a drug-loaded system, Mn-ZIF-8/5-Fu. Within the acidic tumor microenvironment, Mn^{2+} is responsively released, concurrently producing T_1-weighted MRI contrast enhancement and facilitating the synchronized delivery of 5-Fluorouracil. The theranostic advantage of this design is underscored by the capability of real-time MRI signal alterations to indicate carrier degradation and drug release kinetics, thereby providing a foundation for optimizing individualized dosing regimens. Importantly, Mn-ZIF-8 is capable of being cleared from the body relatively swiftly, thereby mitigating the potential toxicity risk associated with prolonged retention.

Biological Optical Imaging

Biological optical imaging facilitates the visualization of in vivo structural or functional information through the detection of optical signals, including fluorescence and phosphorescence, emitted by biological tissues or exogenous probes. This technique is characterized by its straightforward operation, high sensitivity, and exceptional spatial and temporal resolution, attributes that are particularly advantageous for intraoperative tumor navigation and treatment monitoring.[243,244] However, conventional fluorescent probes encounter challenges such as limited in vivo half-lives, significant background interference, and inadequate tumor selectivity. ZIF-8, with its low near-infrared fluorescence background and minimal light absorption, serves as a "fluorescence silencing" carrier that effectively encapsulates fluorescent dyes. The fluorescence signal is restored only upon release triggered by the TME, thereby enhancing the imaging signal-to-noise ratio and targeting specificity.[245] Strategies such as targeted enrichment and multimodal synergy are crucial for addressing the limitations associated with free probes. Consider the clinically approved near-infrared dye, indocyanine green (ICG), which in its unbound form is subject to rapid in vivo clearance and limited uptake by tumor cells, thereby significantly diminishing its efficacy for both imaging and therapeutic applications. In response to these limitations, Chen et al[103] utilized silk fibroin-templated ZIF-8 to encapsulate ICG and DOX, thus developing the AR-ZS/ID-P nanosystem. The incorporation of silk fibroin serves to modulate the morphology and pore structure of ZIF-8, thereby enhancing the stability of ICG loading. Additionally, surface modification with tumor-targeting peptides (AR peptides) augments the accumulation of the nanosystem at tumor sites. Upon laser excitation, ICG induces photothermal effects and generates ROS, facilitating concurrent thermal and fluorescence imaging as well as photodynamic therapy. This process also triggers the release of the chemotherapeutic agent DOX. Consequently, this innovative design offers dynamic navigation for precise therapeutic intervention, effectively overcoming the limitations associated with single-modality imaging or treatment approaches.

Positron Emission Tomography

Positron emission tomography (PET) relies on the metabolic distribution of radionuclide-labeled tracers, enabling the quantitative assessment of the functional state and molecular-level alterations in tissues with high sensitivity and ease of quantitative analysis.[246,247] The metal-organic framework ZIF-8 is capable of stably encapsulating positron-emitting radionuclides while concurrently loading therapeutic agents, thus facilitating the development of a "theranostic" platform.

Traditionally, the assessment of the efficacy of immune checkpoint inhibitors, such as anti-PD-L1 antibodies, has predominantly depended on morphological imaging techniques like computed tomography. These methods inherently exhibit delays and are inadequate in capturing the functional molecular changes induced by therapy. PET imaging, however, offers a non-invasive approach to visualize critical immune and stromal markers in vivo. In a study by Feng et al,[104] a CPZT biomimetic nanoplatform was developed by co-functionalizing ZIF-8 with the anti-fibrotic agent tranilast and homologous cancer cell membranes The pH-responsive nature of ZIF-8 facilitates drug release triggered by the TME, while the homologous cancer cell membrane imparts tumor-targeting capabilities to the nanoparticles. Additionally, three PET tracers—[^{68}Ga]Ga-FAPI-04, [^{68}Ga]Ga-GZP, and [^{68}Ga]Ga-LLP2A—were incorporated to target fibroblast activation protein, granzyme B, and very late antigen-4 on γδ T cells, respectively. The imaging signals from these tracers do not interfere with each other, allowing for real-time, quantitative monitoring of tumor stromal remodeling, cytotoxic T cell activation, and γδ T cell infiltration levels. Through the integration of in vitro and in vivo experiments, this approach effectively facilitated the visualization of anti-fibrotic therapy-induced reprogramming of the TME and allowed for the dynamic monitoring of the efficacy of combination regimens involving PD-1 blockade or γδ T cell therapy. By advancing the assessment of immunotherapy efficacy from traditional morphological measurements to molecular-level functional imaging and enabling the concurrent monitoring of multi-dimensional biomarkers, this strategy offers a precise tool for the early prediction of responses in tumors associated with fibrosis and resistant to immunotherapy.

ZIF-8-Mediated Combination Therapy Strategies

Combination therapy, by means of synergistic intervention targeting multiple pathways, has the potential to lower individual drug dosages, surmount therapeutic resistance, and prevent tumor recurrence, thereby offering substantial advantages over monotherapy.[248,249]

Chemo-Immunotherapy

Chemo-immunotherapy, which synergistically combines the direct cytotoxic effects of chemotherapy with the systemic anti-tumor efficacy of immunotherapy, has emerged as a promising paradigm in cancer treatment. This approach leverages the benefits of both traditional chemotherapy and immunotherapy, wherein chemotherapeutic agents not only precisely target and eliminate cancer cells but also activate the host immune system's anti-tumor response, thereby substantially enhancing therapeutic outcomes. A multitude of studies have demonstrated that this regimen has achieved promising efficacy in the treatment of various malignancies, including melanoma and lung cancer.[250–252]

Toll-like receptor agonists activate innate immunity and connect it to the adaptive immune response, but their clinical use is hindered by systemic toxicity and quick degradation.[253] CpG ODNs, as TLR9 agonists, can stimulate Th1-type immune responses to boost anti-tumor activity.[254,255] Due to its pH-responsive characteristics and positively charged surface, ZIF-8 facilitates the protective delivery and targeted release of CpG ODNs. Furthermore, research has demonstrated that ZIF-8 nanoparticles function as immunostimulatory carriers, with the 2-MIM released upon their degradation selectively activating TLR signaling.[256] Zhang et al[86] developed a ZIF-8/CpG complex that effectively protected CpG from nuclease degradation through the ZIF-8 framework, facilitating a responsive release in the acidic endolysosomal environment. This approach significantly enhanced the secretion of immune cytokines both in vitro and in vivo. However, the effectiveness of utilizing a single immune agonist remains suboptimal. To address this, Zhang et al[105] advanced their strategy by co-encapsulating the TLR7 agonist imiquimod (R837) and the IDO inhibitor 1-methyltryptophan (1-MT) within ZIF-8, further functionalizing it with mannan (MAN) to target dendritic cells. This innovative system concurrently activated TLR7 signaling and mitigated immune suppression mediated by tryptophan metabolism, thereby amplifying the immune response by specifically targeting dendritic cells and overcoming the limitations associated with single agonist efficacy. Qi et al[106] engineered two distinct platforms: CMCS-(DOX+1-MT)@ZIF-8 and CpG@ZIF-8, which encapsulate the chemotherapeutic agent DOX, the IDO inhibitor 1-MT, and the TLR9 agonist CpG, respectively. These platforms were subsequently combined in a specific ratio to synthesize the composite system CMCS-(DOX+1-MT)/CpG@ZIF-8. DOX induced ICD, facilitating the release of DAMPs. Concurrently, 1-MT inhibited the IDO pathway, thereby reversing the immunosuppressive tumor microenvironment. CpG oligodeoxynucleotides activated TLR9, enhancing antigen presentation and the function of effector T-cells. Surface modification with carboxymethyl chitosan (CMCS) improved both the stability of circulation and the targeting of tumors. This integrated approach, characterized by a "chemotherapeutic killing-microenvironment regulation-immune response" closed-loop design, demonstrated significant therapeutic efficacy in the 4T1 breast cancer model, providing a proof of concept that suggests potential for clinical translation.

Radio-Immunotherapy

Radiotherapy kills tumor cells by causing DNA damage and altering the TME to boost immunogenicity, but its effectiveness is limited by tumor radiation resistance and an immunosuppressive TME.[257,258] Immunotherapy uses T cell responses for systemic tumor clearance, but its success is hindered by issues in tumor antigen presentation and immune checkpoint inhibition.[259] Radio-immunotherapy combines the strengths of both, with radiotherapy inducing ICD and releasing tumor antigens, while immunotherapy enhances the immune response, allowing for effective control of tumors. The X-ray responsive properties, high drug-loading capacity, and biocompatibility of ZIF-8 provide a robust foundation for developing an integrated platform aimed at enhancing radiotherapy sensitization and immune activation.[107,260,261]

Tumor hypoxia and elevated intracellular GSH levels are fundamental mechanisms contributing to tumor radioresistance. Hypoxia diminishes the oxygen fixation effect required for DNA damage, while GSH neutralizes ROS produced during radiotherapy. Pan et al[107] developed a folic acid-modified FA-Mn_3O_4@ZIF-8 nanosystem for targeted

tumor delivery. The Mn_3O_4 component mitigates tumor hypoxia and reduces excess GSH, while the ZIF-8 framework is utilized to load radiosensitizers. This nanoplatform leverages a triad of mechanisms: targeted tumor enrichment, modulation of the tumor microenvironment, and controlled release of sensitizers. In vivo experiments have demonstrated its superior antitumor efficacy compared to single-component materials, significantly enhancing the inhibitory effects of radiotherapy on tumor cell viability and proliferation. Radiotherapy-induced ICD has the potential to initiate antitumor immune responses; however, this immune activation is typically inadequate to overcome tumor-induced immunosuppression. In a study by Hu et al,[262] a novel dissolvable microneedle (MN) system was developed, incorporating Mn-ZIF-8 for the purpose of transdermal radioimmunotherapy targeting cutaneous melanoma Upon application, the microneedles rapidly dissolve, releasing Mn-ZIF-8 nanoparticles that function as radiosensitizers, facilitating DNA damage and inducing immunogenic cell death. The sustained release of Mn^{2+} following irradiation activates the cGAS-STING signaling pathway, thereby enhancing the secretion of type I interferons and promoting the maturation of DCs. Experiments conducted in relevant mouse models demonstrated that this combined treatment strategy could increase dendritic cell infiltration in tumor tissues by threefold and significantly reduce distant unirradiated tumor lesions. Advanced tumors frequently necessitate multimodal combined therapies to address heterogeneous therapeutic resistance. In this context, Hu et al[108] developed a ZIF-8@MnCO@DOX (ZMD) nanoplatform designed to degrade within the tumor microenvironment, thereby releasing Zn^{2+}, Mn^{2+}, and DOX. The liberated Zn^{2+} and Mn^{2+} ions facilitate Fenton-like reactions that generate reactive oxygen species, thereby enhancing tumor radiosensitivity, while DOX contributes to DNA damage and induces apoptosis in tumor cells. Furthermore, these metal ions work synergistically with damaged cell-derived double-stranded DNA to activate the cGAS-STING pathway, thereby eliciting robust systemic antitumor immune responses. This innovative therapeutic approach not only achieves regression of primary tumors but also suppresses distant metastases in B16 melanoma models, presenting a straightforward and safe integrated nanotherapeutic platform for the comprehensive treatment of advanced malignancies.

Combination with Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICIs) enhance T cell anti-tumor activity by blocking PD-1/PD-L1 signals, showing effectiveness in various solid tumors.[263,264] However, challenges like resistance, the TME hindering drug and cell infiltration, and off-target toxicity limit their use.[265] The TME promotes immune escape through abnormal angiogenesis, recruitment of suppressive cells, and increased PD-L1, driving ICI resistance.[266] ZIF-8, a pH-responsive carrier, targets tumors for controlled ICI release, boosting intratumoral drug levels.

The integration of natural products with ICIs constitutes a novel approach aimed at mitigating toxicity and enhancing therapeutic tolerance. EGCG, a polyphenolic compound sourced from green tea, demonstrates inhibitory activity against PD-L1; however, its application is hindered by poor bioavailability and rapid metabolic clearance in vivo. In a study by Jannatun et al,[109] an innovative nanosystem, EGCG-ZIF-8@PDA-PEG (EZP), was developed This system employs ZIF-8 as a core to encapsulate EGCG with a loading efficiency of 85%, and is further co-modified with PDA and PEG to enhance its stability and targeting capabilities. EGCG functions by directly obstructing the PD-L1/PD-1 axis, thereby alleviating T cell inhibition, while the released Zn^{2+} ions modulate the inflammatory TME and facilitate the infiltration of effector T cells. Both in vitro and in vivo experiments have demonstrated that EZP significantly reduces PD-L1 expression, decreases the secretion of inflammatory factors, and extends the survival of tumor-bearing mice. Fang et al[267] developed a biomimetic nanoplatform, designated as mPDZM, which is based on a tumor cell membrane-coated ZIF-8@MnOx system co-loaded with DOX and piperlongumine. This formulation, when used in conjunction with anti-PD-L1 ICIs, demonstrates significant efficacy in inhibiting tumor growth, inducing the abscopal effect, remodeling the tumor immune microenvironment, and extending host survival in murine models of hepatocellular carcinoma. The strategy leverages the pH-responsive drug-loading capability of ZIF-8, along with MnOx-mediated redox regulation, senescent cell clearance, and activation of the cGAS-STING pathway, thereby offering a novel approach to augmenting the anti-tumor efficacy of ICIs. However, it is important to note that current investigations are confined to animal models, and further research is required to assess the clinical translation potential and biosafety of this approach.

The Advances Of ZIF-8 As Anti-Cancer Therapeutics

Biosafety Modulation and Clinical Translation Strategies

Zinc is a crucial trace element for human health, with its in vivo homeostasis being meticulously regulated.[268] At physiological concentrations, Zn^{2+} is involved in numerous essential biological processes; however, excessive exposure to zinc can lead to DNA damage, mitochondrial dysfunction, oxidative stress, and even organ injury. The nervous system is particularly susceptible to zinc, as an excess of Zn^{2+} can induce neuronal apoptosis and elevate the risk of neurodegenerative diseases.[269–274] Consequently, it is imperative to precisely control the dosage and spatiotemporal distribution of Zn^{2+} released from ZIF-8 systems to ensure a balance between therapeutic efficacy and biosafety. Optimization of dosage and dynamic monitoring are crucial for achieving an optimal therapeutic safety window. The anti-tumor efficacy and toxic side effects of Zn^{2+} exhibit significant dose-dependent characteristics. In models of non-small cell lung cancer, Zn^{2+} concentrations below 25 μmol/L do not demonstrate a significant tumor-inhibitory effect; however, concentrations ranging from 50 to 100 μmol/L facilitate tumor apoptosis and enhance chemotherapeutic sensitivity, while concentrations exceeding 200 μmol/L result in damage to normal cells.[275] Monitoring serum zinc levels and implementing individualized administration protocols can facilitate treatment with high efficacy and low toxicity. Furthermore, strategies such as pH-responsive release and surface modification can effectively mitigate systemic toxicity. ZIF-8 enables targeted degradation and drug release within the acidic tumor microenvironment. When combined with targeting ligands such as FA and HA, it allows for selective tumor accumulation and minimizes zinc ion deposition in normal tissues.[276] Furthermore, biomimetic camouflage strategies utilizing erythrocyte membranes, platelet membranes, tumor cell membranes, and other biological membranes can significantly enhance the biocompatibility and targeting capabilities of ZIF-8. These strategies also prolong its circulation time in vivo and mitigate systemic adverse reactions.[110,277–280] This approach offers novel insights for the clinical and safe translation of ZIF-8-based nanotherapeutics.

Industrial Challenges and Green Synthesis Strategies for Scalable Production

The clinical translation and industrial application of ZIF-8 encounter significant challenges in large-scale production, necessitating adherence to dual criteria of quality control and environmental sustainability. The synthesis process comprises three main stages: nucleation, growth, and stabilization. Minor fluctuations in temperature and pressure within the reactor can result in batch-to-batch variations in crystal grain size and framework integrity, consequently compromising the stability of its adsorption, catalytic, and drug-loading properties.[281] Traditional solvothermal methods are plagued by issues such as high energy consumption and significant pollution. These methods utilize organic solvents in quantities far exceeding those of the reaction precursors, leading to prohibitive recovery costs. Additionally, the discharge of wastewater and solid waste contradicts the principles of green chemistry and circular economy, while the risks associated with solvent volatilization and leakage pose threats to production safety. Although aqueous-phase synthesis reduces dependence on organic solvents, the challenge of treating residual metal ions and organic ligands in wastewater persists.[282] Consequently, the advancement of continuous, standardized, and environmentally sustainable production processes is essential for facilitating the transition from laboratory research to industrial applications.

Continuous-flow synthesis, coupled with precise regulation, forms the technical foundation for enhancing batch stability. The thermally-assisted microfluidic system, which integrates a T-type mixer and a helical reaction tube, facilitates rapid and homogeneous mixing of precursors. When combined with a thermally-assisted reaction at 50 °C, this system allows for precise control over flow rate and residence time, thereby eliminating thermal history discrepancies associated with conventional batch reactions. This methodology produces ZIF-8 nanoparticles with uniform morphology and controllable size, demonstrating significant potential for industrial scale-up.[46] Mechanochemical synthesis, such as twin-screw or single-screw extrusion, enables nearly solvent-free continuous production, achieving a maximum ZIF-8 output of 4 kg/h. This approach fundamentally addresses batch fluctuations and solvent dependency, while substantially reducing the carbon footprint and energy consumption.[283] Furthermore, process analytical technology provides an effective tool for precise regulation. Quan et al[281] utilized a reaction calorimeter in conjunction with in-situ infrared spectroscopy to monitor reaction parameters in real time. They correlated crystallization kinetics using the Avrami model

and promptly adjusted process parameters to compensate for fluctuations, thereby establishing a theoretical foundation for defining standardized ranges of reaction parameters.

However, the complete translation of laboratory-scale protocols to industrial-scale production continues to face significant challenges. Beyond the substitution of toxic reagents with environmentally friendly solvent systems and the systematic optimization of key reaction parameters and morphology control strategies, several critical issues require urgent attention: the regulation of crystallinity and porosity in mechanochemically synthesized products, the validation of their long-term stability, and the benchmarking of their performance against products prepared through conventional solvothermal methods.[284,285]

Precision Therapy and Dynamic Adaptation Strategies Based on TME Heterogeneity

The heterogeneity of the TME, characterized by interindividual variations in acidic pH, FR expression levels, and redox status, serves as a pathological foundation for the personalized design of nanomedicines. The structural tunability and facile surface modifiability of ZIF-8 facilitate its tailored engineering to address such heterogeneity, thereby transitioning therapeutic strategies from a one-size-fits-all paradigm to a patient-tumor matched model. In response to the biochemical heterogeneity of the TME, a precise diagnostic stratification-design matching strategy can be developed. By utilizing individualized TME parameters obtained through imaging or biopsy, the degradation threshold of the carrier can be optimized by modifying substituents of imidazole ligands within the ZIF-8 framework or by incorporating pH-sensitive linkages. This ensures precise drug release within the tumor interstitial pH range specific to individual patients. Targeting density can be strategically designed in a hierarchical manner based on FR expression levels. For tumors with high FR expression, high-density folic acid modification is employed to enhance targeting efficacy. Conversely, for tumors with low FR expression, a combination of folic acid and cell-penetrating peptides is utilized to optimize the balance between targeting efficiency and intracellular uptake. Given the spatiotemporal heterogeneity inherent in tumor progression, relying solely on a single endogenous stimulus-response mechanism is insufficient for achieving precise control. Therefore, it is imperative to develop composite platforms that integrate endogenous signals—such as pH, redox potential, and enzyme activity—with exogenous physical fields, including light, magnetic fields, and ultrasound. This integration, coupled with logic-gated design, enhances the precision of drug release. For instance, carriers that are dual-responsive to pH and reactive oxygen species are activated exclusively in the tumor core region, characterized by an acidic microenvironment with high oxidative stress, thereby minimizing off-target effects in normal tissues. To address delivery challenges in specific anatomical regions, targeted penetration strategies are essential. The therapeutic effectiveness against central nervous system tumors is significantly hindered by the impediments to drug entry into the brain, primarily due to the blood-brain barrier and the blood-brain tumor barrier. This challenge can be effectively addressed through the optimization of particle size and the application of biomimetic surface modifications. For example, the RVG15-PEG@DTX@ZIF-8 system employs RVG15, a peptide derived from rabies virus glycoprotein, to facilitate transcytosis and enhance penetration of the BBB. Additionally, the polyethylene glycol coating extends the circulation time in the bloodstream, while the ZIF-8 core is utilized for loading chemotherapeutic agents. This system achieves targeted accumulation in brain lesions through a hierarchical strategy involving particle size optimization, surface camouflage, and active targeting.[111] The incorporation of minimally invasive TME detection technologies, such as liquid biopsy and microdialysis, alongside artificial intelligence-assisted design algorithms and automated synthesis platforms, facilitates real-time monitoring of TME evolution and drug response. This integration enables the iterative optimization of the physicochemical properties and functional modules of ZIF-8 carriers, as well as the adaptive modification of therapeutic strategies to address disease progression. Consequently, this approach achieves comprehensive personalized management of tumors throughout the entire course of treatment.

Challenges in the Clinical Translation Process

Despite the significant potential of nanomedicine, the efficiency of translating laboratory research into clinical applications remains considerably below expectations. By 2025, only 50 to 80 nanomedicines have been approved for clinical use worldwide, highlighting a stark contrast to the extensive volume of preclinical studies. The primary cause of this translational gap is the limited manifestation of the robust EPR effect observed in animal models within human tumors.

In humans, vascular heterogeneity and elevated interstitial fluid pressure lead to unpredictable drug distribution. Additionally, the transition from laboratory-scale preparation to current Good Manufacturing Practice-compliant production of nanomedicines is hindered by the absence of standardized characterization protocols and process control standards. Inconsistent criteria for ensuring batch-to-batch consistency, assessing long-term toxicity, and detecting immunological responses have emerged as significant obstacles to regulatory approval.[286,287] ZIF-8 exhibits significant potential for application in drug delivery; however, its clinical translation is hindered by several challenges: (1) the absence of long-term biosafety data; (2) inadequate batch-to-batch reproducibility and the lack of standardized quality control guidelines; (3) issues related to quality and environmental sustainability in large-scale production; and (4) the absence of a validated pathway for personalized adaptation and regulatory-endorsed standards for biomarker-efficacy correlations. Addressing these critical bottlenecks in a systematic manner is essential for the advancement of ZIF-8-based nanoplatforms from proof-of-concept laboratory studies to standardized clinical cancer therapies. Consequently, while ZIF-8 nanoplatforms demonstrate the innovative potential of "carrier-effector" synergy, it is important to recognize that the current evidence is primarily derived from preclinical models, and their clinical translational value necessitates validation through rigorously designed Phase I/II clinical trials.

Outlook

The research on ZIF-8-based nanoplatforms is undergoing a paradigm shift, transitioning from passive delivery systems to active modulators of the tumor microenvironment. This evolution indicates that nanomaterials are no longer merely inert carriers for chemotherapeutic agents; instead, they actively participate in the metabolic reprogramming and immune remodeling of the tumor microenvironment through the controlled release of Zn^{2+} ions. This dual functionality, referred to as "carrier as effector," represents a significant advancement. Nonetheless, the clinical translation of this innovative approach faces several critical challenges, including the necessity to balance biosafety with dosage control, ensure batch-to-batch consistency, and establish scalable manufacturing processes. To facilitate clinical translation, future research should focus on addressing these challenges by conducting rigorous long-term safety evaluations, establishing standardized preparation and quality control systems, overcoming bottlenecks in large-scale production, and developing dedicated regulatory guidelines. The primary aim of ZIF-8 nanoplatforms transcends the mere enhancement of individual drug delivery efficiency; it seeks to fundamentally revolutionize the paradigm of cancer therapy. This transformation is realized through interdisciplinary collaboration among materials science, immunology, and informatics, shifting from a drug-centric cytotoxic methodology to a microenvironment-focused systemic regulation model.

Abbreviations

TME, tumor microenvironment; ZIF-8, zeolitic imidazolate framework-8; GSH, glutathione; TAMs, tumor-associated macrophages; MDSCs, myeloid-derived suppressor cells; Tregs, regulatory T cells; PD-L1, programmed death ligand-1; NDDS, nanoparticle drug delivery systems; EPR, enhanced permeability and retention; ROS, reactive oxygen species; 2-MIM, 2-methylimidazole; PDI, polydispersity index; SEM, scanning electron microscopy; RES, reticuloendothelial system; FR, folate receptor; FA, folic acid; IC_{50}, half-maximal inhibitory concentration; EMs, erythrocyte membranes; RGD, arginine-glycine-aspartate; PEG, polyethylene glycol; DOX, doxorubicin; HA, hyaluronic acid; CCMs, cancer cell membranes; SIRPα, signal regulatory protein alpha; TGFBR1, transforming growth factor-β receptor; Ce6, chlorin e6; CpG ODNs, CpG oligodeoxynucleotides; TLR9, Toll-like receptor 9; H^+, protons; PBS, phosphate-buffered saline; DDP, cisplatin; Gem, gemcitabine; PDA, polydopamine; IDO, indoleamine 2,3-dioxygenase; TP, triptolide; CUR, curcumin; siRNA, small interfering RNA; EpCAM, epithelial cell adhesion molecule; miRNAs, microRNAs; OMVs, outer membrane vesicles; PD-1, programmed death-1; RNPs, ribonucleoproteins; EGCG, epigallocatechin gallate; NOX1, NADPH oxidase 1; GPX4, glutathione peroxidase 4; ER, endoplasmic reticulum; UPR, unfolded protein response; mtDNA, mitochondrial DNA; ICD, immunogenic cell death; HYD, hydralazine; TCR, T cell receptor; DAMPs, damage-associated molecular patterns; DCs, dendritic cells; EPI, epirubicin; GOx, glucose oxidase; MIT, mitoxantrone; EMT, epithelial-mesenchymal transition; ECM, extracellular matrix; ATO, arsenic trioxide; MMPs, matrix metalloproteinases; HF, hinokiflavone; HIF-1α, hypoxia-inducible factor-1α; VEGF, vascular endothelial growth factor; MRI, magnetic resonance imaging; ICG, indocyanine green; PET, positron emission tomography; 1-MT, 1-methyltryptophan; MAN, mannan; CMCS, carboxymethyl chitosan; ICIs,

immune checkpoint inhibitors; MTX, Methotrexate; FA-BSA, Folic acid-conjugated bovine serum albumin; IQ, Imiquimod; FM, Folic acid-modified erythrocyte membrane; PST, Polyserotonin; PTT, Photothermal therapy; IT, Immunotherapy; GEF, Gefitinib; GT, Gene therapy; DSF, Dithiocarbamate; HPG,Hyaluronic acid/polyethylene glycol-grafted polyglutamic aci; PDT, Photodynamic Therapy; DMDD, 2-dodecyl-6-methoxycyclohexa-2,5-diene-1,4-dione; SDT, Sonodynamic therapy; ADL, Aspirin-DL-lysine; RT, Radiotherapy; D-1-MT, D-1-methyltryptophan; OS, osteosarcoma; TC, Pt^{4+}-triptolide derivative; ICB, immune checkpoint blockade; pDNA, CRISPR/CAS9 plasmid; duRNPs, dual Cas9 ribonucleoproteins; L-Arg, L-arginine; CaP coating, calcium phosphate coating; P18, Photosensitizer purpurin 18; AR peptide, MCF-7 breast cancer-targeting peptide AREYGTRFSLIGGYR; PEI, Polyethylenimine; ADM, Adriamycin; RVG15, Rabies virus glycoprotein 15.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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