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Review

Potential of nanotheranostic zeolitic imidazolate frameworks in cancer management

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Abstract

Cancer is a major threat to human health, and it is still the leading cause of death from disease. Due to how quickly nanomedicine is developing, it is thought that nanoscale metal–organic frameworks (MOF) could be used in the treatment and biomedical imaging of many types of cancer. More and more researchers are interested in zeolite imidazole framework (ZIF)−8 because it has a high porosity, a large specific surface area, and reacts to changes in pH. Understanding the properties of nanomaterials and how tumour works requires a complex and thorough look at how ZIF-8 nanoparticles (NPs) are made, how they can be changed, and how drugs are loaded into them. We mostly looked at the research that came out in the last three years, summed up how their use in imaging and treating tumour has changed, and talked about the pros and cons of using ZIF-8 NPs for cancer theranostic now and in the future. As a MOF material with a lot of potentials, ZIF-8 is likely to be used in more therapeutic systems in the future and to continue to help with all parts of tumour therapy and diagnosis.

Keywords: nanotechnology, metal-organic framework, zeolite imidazole framework, combination therapy, theranostic
Classification numbers: 2.05, 5.08

1. Introduction

Researchers have been working hard to find a cure for cancer for a long time [1]. In recent years, cutting-edge strategies like targeted therapy and immunotherapy increased the survival rate of cancer patients. Research on advanced nanomaterials could help biomedical imaging and develop novel cancer therapy methods to treat cancer [2–4]. ZIF is a type of MOF. 2-Methylimidazole and zinc ions are the most typical ZIF-8 because they have a large surface area and are stable at high temperatures [5]. ZIF-8 is a crystallised coordination compound with the shape of a cage with a regular rhombic dodecahedron. The sodalite cages had holes that were 11.6 Å wide and 3.4 Å tall [6]. Some of the synthesis methods are the solution reaction

at room temperature, solvothermal, electrodeposition-solvothermal, microfluidic, etc [7]. Drug-loaded ZIF-8 is typically manufactured using the one-pot method to encapsulate medicines larger than ZIF-8 pores and boost drug-loading capacity. ZIF-8-based NPs could be employed in biomedical imaging, such as MRI, CT, and photoacoustic imaging, and cancer therapy, including immunotherapy, starvation therapy, phototherapy, chemotherapy, and gene therapy. When used in cancer therapy, it has the following properties: it has more porosity and a high specific surface area, is relatively safe to use, breaks down in acidic solutions, which makes it easier to control how the drugs are released, releases reactive oxygen species (ROS) through Fenton-like reactions from its breakdown product Zn^{2+}, and triggers cellular autophagy (figure 1) [8–10].

ZIF-8 is used as a template for self-sacrifice and as a part of a nano-reactor to stop drugs from leaking. ZIF-8 is prone to polymerisation and does not spread well in water [11]. So, the surface of ZIF-8 is often changed by adding hyaluronic acid and polyethylene glycol [12]. Focusing on ZIF-8 surface ligand modification enabled the active transport of ligands to tumour cells. Hyaluronic acid, lactobionic acid, folic acid, and RGD peptide are common ligands. Bionic mineralisation on the ZIF-8 surface can be coated with cancer cells or erythrocyte membranes to maintain blood flow and escape the immune system [13, 14]. ZIF-8's features, specifically the processes that determine tumour growth and long-term toxicity *in vivo*, were neglected in previous investigations. Before clinic application, the ZIF-8 medication delivery system needs more *in vitro* and *in vivo* testing. In this review project, recent research on nanoplatforms based on ZIF-8 for cancer theranostic was summed up. We also talked about the chances and problems they might face in the future.

2. Bio-imaging with ZIF-8

Photothermal agents (PTAs) such as metal ions can be used to make ZIF-8 nanostructures which are used for cancer bioimaging (table 1). These well-thought-out nanoplatforms can do simple single-mode imaging as well as multi-mode imaging, which improves the accuracy of diagnostics [20, 27]. Also, changing nano-complexes in a way that is specific to tumours or releasing them in a way that is specific to tumours can raise their relative concentration in tumour tissues, making them stand out more on an image compared to healthy tissues. As a flexible and theranostic platform in oncology field, a small number of these nano-complexes can also hold therapeutic drugs at the same time so that the effects of the drugs can be tracked in real-time.

2.1. Computer tomography

Studies showed that ZIF-8 nanocomposites that had parted with a high x-ray attenuation coefficient could make clear computer tomography (CT) pictures. For example, it was common to use the gold (Au)-based NPs as contrast agents in CT. Zhang *et al* created LA-AuNR/ZIF-8 NPs for cancer bioimaging. *In vitro* experiments demonstrated that in comparison with MCF-7 cells (without LA receptors), designed NPs have more uptake of LA-targeted HepG-2 cells. 24 h after injecting in animal model, the CT showed clear pictures [15]. In addition, the doxorubicin-loaded Pt-tipped Au@ZIF-8 NPs were made in a similar way by Xu *et al* It has better photothermal and CT imaging abilities because used atomic elements (Pt and Au) have excellent absorbing light and block x-rays [16].

2.2. Magnetic resonance imaging (MRI)

Strong paramagnetic ions like Fe^{3+}, Cu^{2+}, Mn^{2+}, and Gd^{3+} are used as T_1/T_2 contrast agents to improve contrast and relaxation [19, 23]. Pan *et al* made Mn-ZIF-8/5-Fu nanostructures to use in T_1-weighted imaging and to treat tumours [17]. After 12 h of injection of the Mn-ZIF-8/5-Fu intravenously into the cancerous animal's model, the signal strength peaked, and the increased signal was much more substantial. Notably, the major organs had a high rate of Mn^{2+} clearance, and almost all of it was gone after 7 days. This stopped the NPs from doing any long-term damage [17]. Chen *et al* developed the Mn-Zn-ZIF-PEG NPs for imaging with both MRI and fluorescence imaging (FI) [28]. This paper was the first to talk about the fluorescence imaging abilities of ZIF-8, which may have something to do with 2-methylimidazole. The nanostructures gave off Mn^{2+} that stood out more in the acidic tumour microenvironment. The PEG change made the nanostructure safer for living things while also making it more water-repellent and improving its MRI effects [28].

2.3. Photoacoustic imaging

A new biomedical imaging method called photoacoustic imaging (PAI) is non-invasive, does not use ionising radiation, has better resolution, and goes deeper. Most PTAs are good for PAI, in which laser irradiation changes light energy into heat energy, which causes local tissue to expand and create photoacoustic signals [25]. Guo *et al* changed ZIF-8 by adding Mn^{2+}, PEG, and a DOX-wrapped polydopamine (PDA) shell. Due to the high rate of photon-to-thermal conversion, PDA is often used for PTT and photoacoustic imaging. In the other hand, Mn^{2+} is usually thought of as an MRI contrast agent. Both an MRI and a PAI of mice with tumours showed that there was a lot of enhancement [21]. With the use of ZIF-8, Deng *et al* designed DOX-loaded Au@MOF NPs. When the nanostructure was exposed to laser light in the near-infrared (IR), the gold NPs showed excellent photon-to-thermal conversation properties [29]. This result shows which designed nanostructure can be used for both PAI and thermal imaging. *In vivo* result in the cancerous animal models shows that the PA signal is much stronger. More importantly, it has low cytotoxicity and is very safe for living things.

3. ZIF-8 in cancer therapy

3.1. Monotherapy

3.1.1. Immunotherapy. Checkpoint inhibitors, therapeutic antibodies, and immunomodulatory agents are

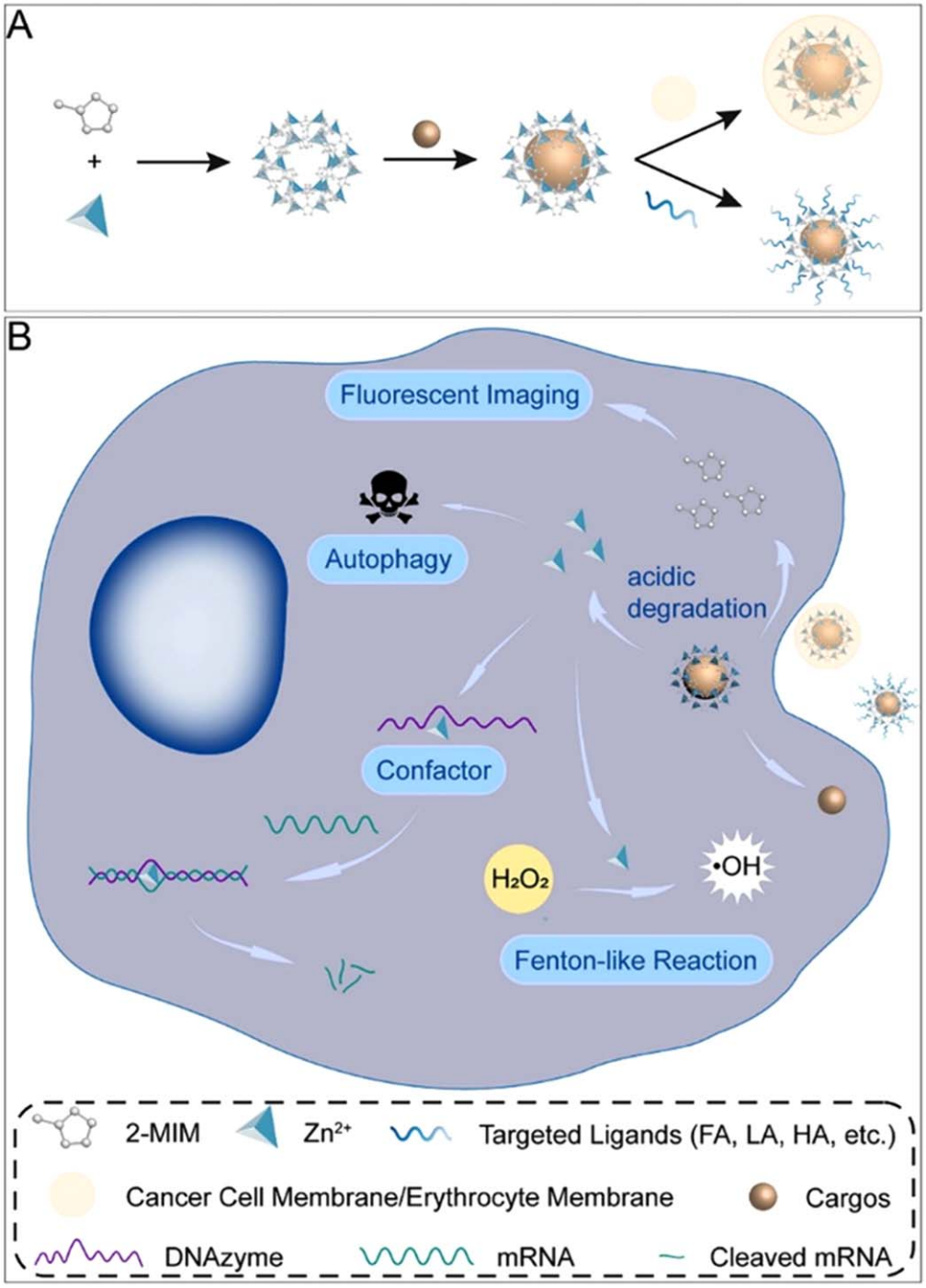

Figure 1. Cancer cell ZIF–8 nanocomposites synthesis and breakdown. (A) ZIF–8 nanocomposite synthesis schematic. (B) Cancer cell ZIF–8 nanoformulations.

immunotherapeutic agents which have lower side effects than radiation and chemotherapy. ZIF-8 has been studied a lot and is used more and more in cancer immunotherapy as a way to deliver immunological adjuvants agents or cancer vaccines [30] (table 2). The use of immunological adjuvant agents is an excellent candidate for cancer immunotherapy because they have a long circulation time and good biocompatibility [1, 44]. Alsaiari *et al* designed nivolumab-loaded ZIF-8 (NV-ZIF) NPs that release NV slowly and continuously so that the drug can be delivered effectively [31]. When compared to NV, the steady release of NV-ZIF may be a better way to get T cells to work. In one study, KN046, PD-L1/CTLA-4 single-domain antibody-Fc that can block both PD-L1 and CTLA-4, was loaded in fluorine-filled ZIF-8 [32]. In the acidic conditions of the tumour microenvironment, where KN046@^{19}F-ZIF-8 broke down, KN046 antibodies are released. When ZIF-8 is broken, the MRI signal of ^{19}F could be used to image tumours. In the tumour model,

Table 1. Some of the ZIF–8–based nanostructures that are used for the targeted imaging.

Nanostructures	Applications	Properties	Referefnces
LA-Au@ZIF-8	CT	Enhanced x-ray absorbing	[15]
DOX-Pt-AU@ZIF-8	CT	Improved photothermal conversion and x-ray absorption	[16]
Mn-ZIF-8/5-Fu	MRI	Improve the relaxation	[17]
BSA-MnO_2/Ce6@ZIF-8	MRI	Improve the relaxation	[18]
Fe_3O_4-ZIF-8	MRI	Responsive T2-T1 switching MRI contrast agent	[19]
Mn_3o_4@PAA@ZIF-8	MRI	Enhanced relaxation	[20]
ZIF-8/DMPP	PAI-MRI	Improve the relaxation and high NIR absorption	[21]
ZIF-8/DOX-PD-FA	FI-MRI	Improve the relaxation and FI ability	[22]
Gd/Tm-PB@ZIF-8/PDA	FI-MRI	Improve the relaxation and FI ability	[23]
Fe_3O_4@PAA/Au/ZIF-8	MRI-FI-CT	Improve the relaxation and FI ability and enhanced x-ray absorbing	[24]
Au@ZIF-8	PAI	High NIR absorption	[25]
PDAs-ZIF-8	PAI-IR	Improved photothermal conversion	[26]

KN046@^{19}F-ZIF-8 decreased tumour growth [32] (figure 2(A)).

Zhang *et al* placed immune checkpoint inhibitors inside Toll-like receptor 9 agonist cytosine-phosphate-guanine (CpG) oligodeoxynucleotides (ODNs) on ZIF-8 to form a complex that activates innate immunity and promotes cytokine production [45]. Electrostatic interaction between negatively charged CpG ODNs and the electronegative cell membrane slowed their uptake. CpG ODN absorption can be sped up by combining it with ZIF-8, which also makes pH-sensitive endolysosomal release possible [45]. In addition, nanocarriers can be used for synthesising the cancer vaccines, which work to prevent cancer by activating the body's immune system with antigens from tumour cells [46]. Zhong *et al* first described ZANPs, aluminum-integrated nanoscale MOFs with ovalbumin (OVA) packed in ZIF-8 (figure 2(B)). CpG/ZANPs are CpG-coated ZANPs. After injecting OVA into a mouse's footpad, near-IR fluorescence imaging *in vivo* indicated that ZANPs persisted in lymph nodes for at least 24 h longer than OVA. The CpG/ZAPs group has the most $CD8^+$ T cells. The researchers also inoculated C57BL/6 mice three times a week using EG7-OVA cells. CpG/ZANPs reduced tumour size and survival [33].

3.1.2. Starvation therapy. Starvation therapy (ST) kills cancer cells by restricting their growth in hard conditions. For example, glucose oxidase (GOx) is often used to get rid of glucose. Even though GOx has a short half-life *in vivo* and is quickly turned off, taking glucose from healthy tissues raises oxidative stress levels, which has a number of bad effects [47]. The flaws were fixed by a device made of GOx coated with ZIF-8. This made it possible for GOx to be released in the tumour when the pH changed [48]. ZIF-8 can host several substances with nano-enzymes that can be used to improve and fine-tune ST (table 2). In one study, Bai *et al* encapsulated the horseradish peroxidase (HRP) and GOx into ZIF-8. After seven days, there was no obvious clumping, which means that the dispersion was stable [34]. When HRP is present, the H_2O_2 made by GOx turns into hydroxyl radicals that kill tumour cells (figure 3(A)). In another study, Yu *et al* [35] made the -cyano-4-hydroxycinnamate (CHC)/GOx@ZIF-8 NPs by combining GOx and CHC, which blocks lactate transporter monocarboxylate transporter 1 (MCT1). In addition to blocking one of the ways cancer cells get energy, CHC stopped lactate from coming in and slowed down lactate metabolism to treat low oxygen levels at tumour sites [35] (figure 3(B)).

3.1.3. Phototherapy. Tumour phototherapy, which includes photodynamic therapy (PDT) and photothermal therapy (PTT), has got a lot of attention because it is non-invasive and has low toxicity [49, 50]. Phototherapy can act as an immunological agent by initiating immunological responses, resulting in stimulation of the innate immune system. It also destroys established tumour cells by selective photochemical and photothermal interactions, releases tumour antigens, and creates an *in situ* cancer vaccine. Traditional photosensitisers, which are also called PTAs, are not very stable, tend to stick together, and are hard for cells to take in. So, photosensitisers, or PTAs, were used to make nanosystems (table 2). ZIF-8 can be used to help make nanosystems because it is very porous, releases chemicals in response to pH, and is safe for living things [51].

Photosensitisers used in PDT could be less dangerous in the dark and less likely to fade when exposed to light if ZIF-8 was added [36]. Fu *et al* made ZIF-8@chlorin e6 (Ce6)-HA, which has an average size of 150 nm and caused the tumour to store more of the photosensitiser Ce6 [52]. Xu and coworkers made zinc phthalocyanine (ZnPc)@ZIF-8 with the photosensitiser ZnPc [37]. They optimised the volume of ZnPc so that it would not stick together in the ZIF-8 pores. A single loading of photosensitiser can block hydrophobic photosensitiser from building up and letting cells absorb more, but it cannot cure tumour hypoxia, making PDT less effective [37]. Ma *et al* wrapped Ce6 and put AuNPs on the surface of ZIF-8 as catalase [53]. In another study, Sun *et al* synthesised a BSA-MnO2/Ce6@ZIF-8 NPs which was active as a catalase. Besides the Ce6, phycocyanin (PC, extracted from spirulina) is a photosensitiser with a high QY, good biocompatibility, and the ability to absorb light. But because it is a protein photosensitiser, it can be broken down by enzymes, and because cell membranes have a negative

Table 2. ZIF–8–based nanostructures for cancer monotherapy.

Application	Nanostructure	Tumour or cell line	Function	References
	NV–ZIFMCF	Xenograft 4T1 tumour, HeLa and MCF–7 cells	Activate the T cells and excellent targeted delivery to tumour	[31]
Immunotherapy	KN046@ ^{19}F-ZIF-8	Xenograft B16F10 tumour, B16F10 cells	Improve the immune system response	[32]
	CpG/ZANPs	Xenograft EG7-OVA tumour	Induce of humoral immune system and motivate the T lymphocyte responses	[33]
	ZIF–8@GOx/HRP	Xenograft U14 tumour, HeLa cell	Decrease the glucose-based energy and the toxic effect of ROS	[34]
ST	CHC/Gox@ZIF-8	Xenograft SiHa, MCF-7 cell	Blocking the lactate and glucose-based energy sources	[35]
	BSA-MnO_2/Ce6@ZIF-8	Xenograft U14 /HeLa cell	Decreasing tumour hypoxia and increasing the efficiency of PDT	[36]
PDT	ZnPc@ZIF–8	HepG2 cell	Enhancing the PDT efficiency	[37]
	PMs	Xenograft of patient–derived bladder, bladder derived cancer cell	Reducing intra-tumour O_2 consumption and increasing PDT efficiency	[38]
	GBZ	Xenograft Huh-7, Huh-7 and MCF-7 cells	Low temperature for PTT	[39]
PTT	Cy5.5&ICG@ZIF–8–Dextran	Xenograft A549, A549 cells	Increasing PTT efficiency and targeted delivery	[40]
	RAPA@ZIF–8	Xenograft MCF-7/ADR, MCF-7 cells	Promoting the autophagy	[8]
Chemotherapy	Camptothecin@ZIF 8@RGD	HeLa cells	Enhancing the tumour therapy	[41]
GT	RNase A@ZIF–8	A549 cells	Blocking the cells proliferation	[42]
	C3–ZIF	Xenograft MCF-7, HeLa and MCF-7 cells	Improving the selectivity in genome editing	[43]

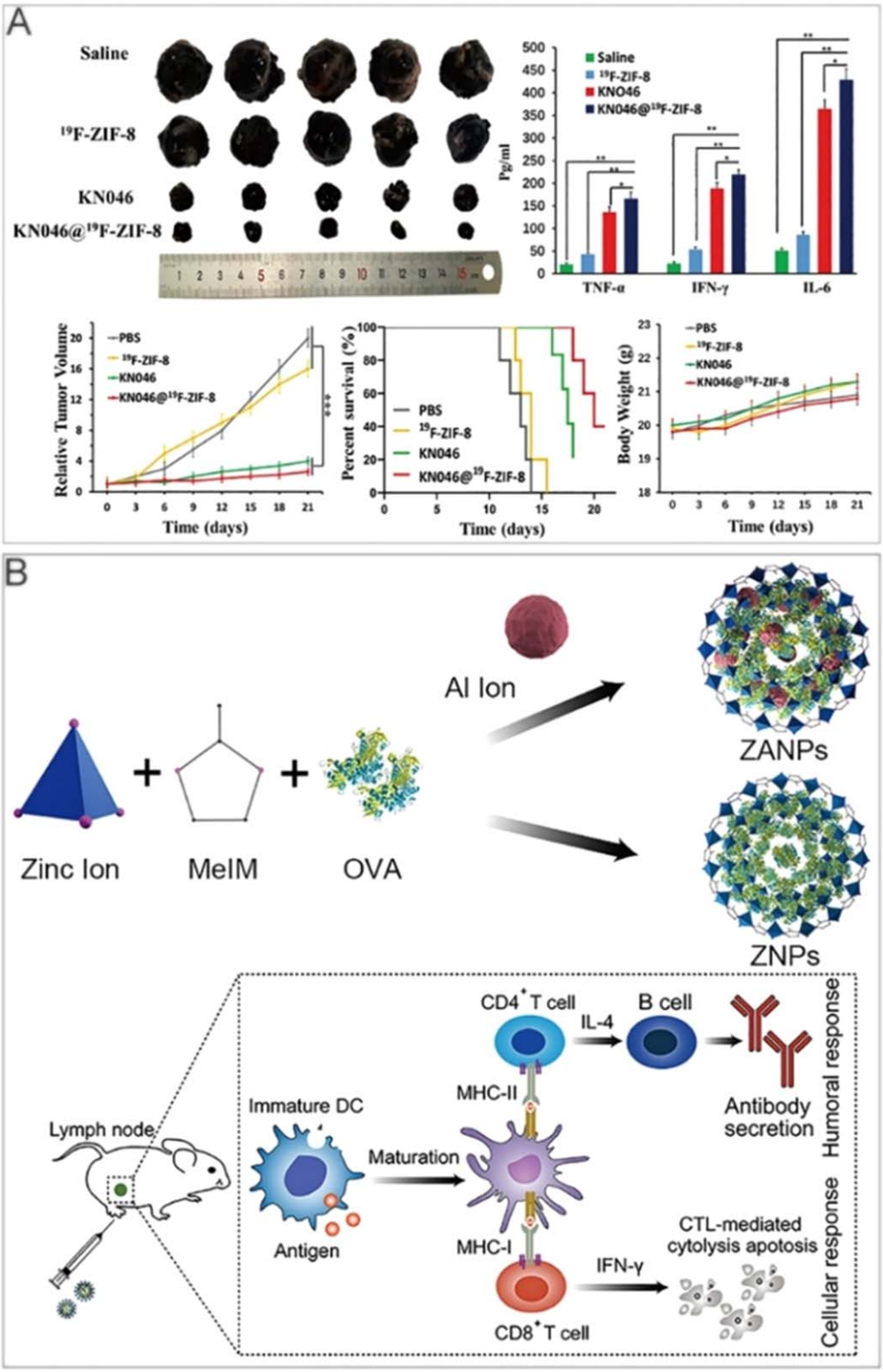

Figure 2. Immunotherapy nanoplatforms ZIF–8. (A) KN046@19F–ZIF–8 prevents mouse tumours. From [32] Copyright 2021 Advanced Science, Wiley–VCH GmbH; Reproduced from [32]. CC BY 4.0. (B) Mice immunised with vaccine-delivering ZANPs develop anticancer immunity.

charge, tumour cells cannot take it up [18]. Chen and coworkers made a PEG-ZIF/PC nano-complex in which PEG was decorated on its surface by coordinating the COOH group with zinc ions [38]. Papaverine, a mitochondrial complex I inhibitor, decreased the amount of oxygen used by the tumour and the production of adenosine triphosphate. This can protect the photosensitiser and allow it to be released at a specific site in the tumour. Cai *et al* made UCNPs/MB@ZIF-8@ nanocomposites out of methylene blue and upconversion NPs. The catalase can catalyse H_2O_2 to treat

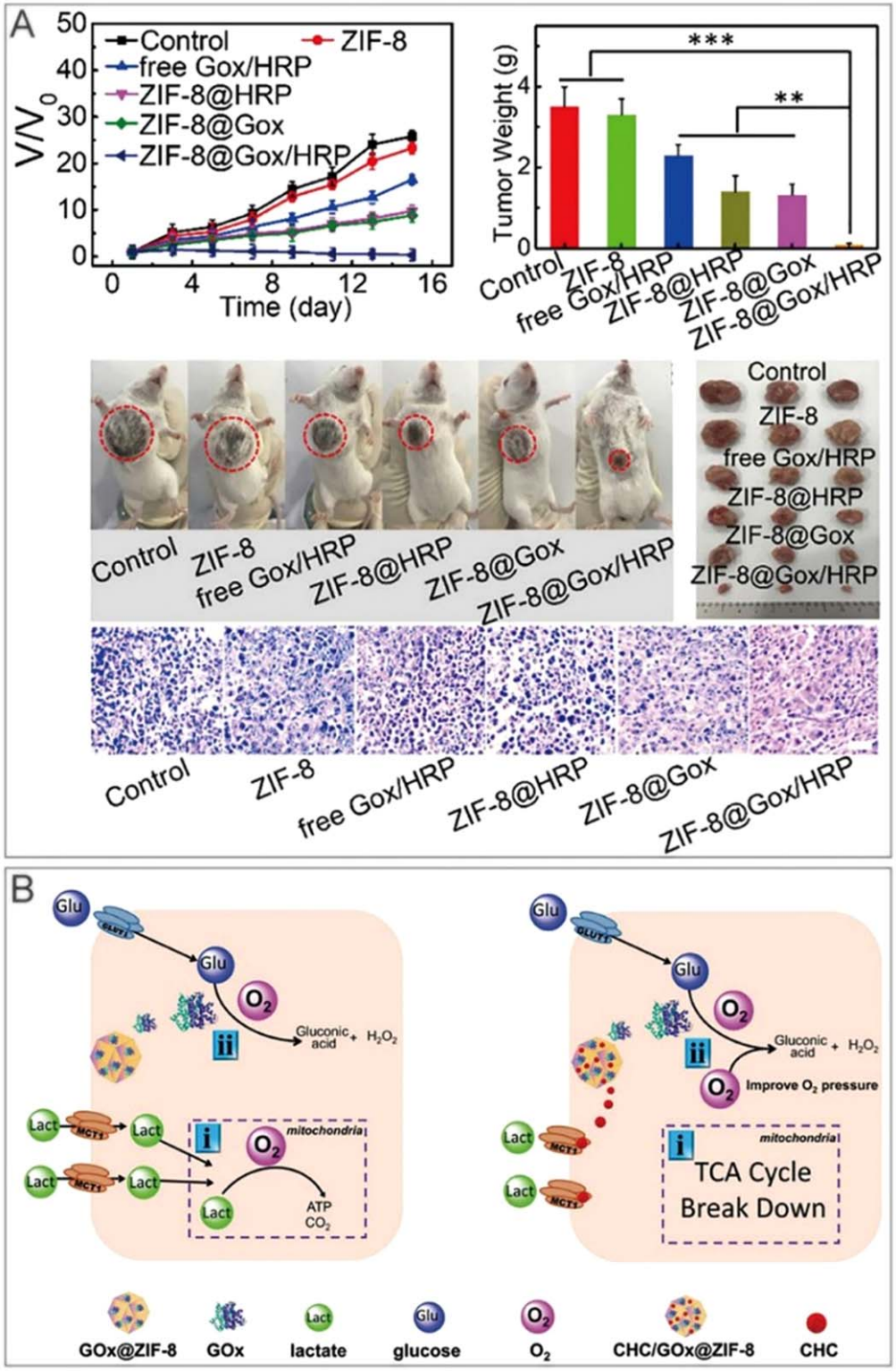

Figure 3. ST-specific ZIF–8 nanoplatforms. ZIF–8@Gox/HRP suppresses mouse tumour development. From [34]. Copyright 2020 Advanced Healthcare, Wiley–VCH GmbH.; Reproduced from [34]. CC BY 4.0. (B) CHC/GOx@ZIF–8 doubles cancer cell nutrition blockage. From [35] Copyright 2021 Advanced Science, Wiley–VCH GmbH. Reproduced from [35]. CC BY 4.0.

tumour hypoxia. This nanocomposite made it easier for oxygen molecules to stick to its surface, and it also sealed the photosensitiser well [54].

ZIF-8 might be able to help PTT with problems like the fact that organic dyes are hard to dissolve, unstable, and break down quickly [40]. Li and coworkers made cyanine-@ZIF-8 NPs by adding the organic dye cyanine. These NPs were used for PTT and tumour fluorescence imaging [55]. Wang *et al* came up with the idea of ICG@ZIF-8 NPs that work well for near-IR imaging and heat up when exposed to laser light [56].

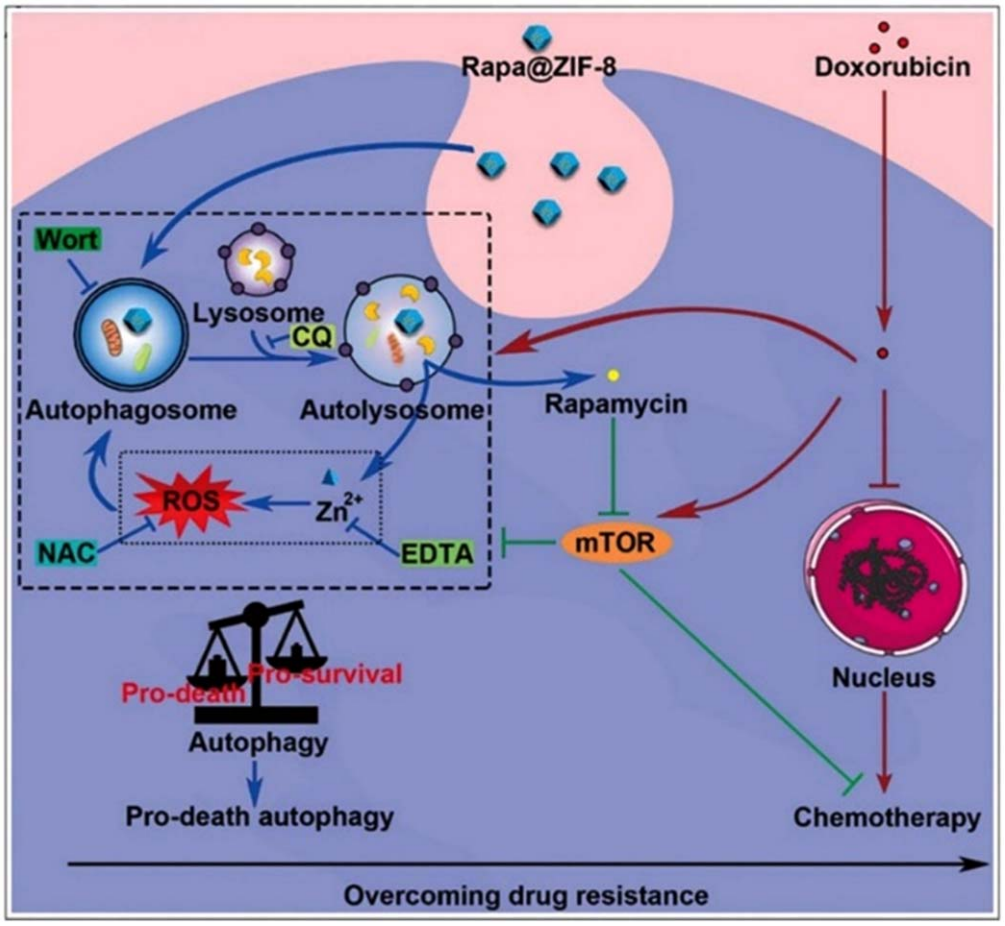

Figure 4. Individual chemotherapeutic nanoplatforms ZIF–8. RAPA@ZIF–8 overcomes drug resistance.

Also, when targeted cells were exposed to high temperatures, the levels of heat shock proteins (HSPs) increased. This made the body more resistant to heat. So, higher HSP levels in tumour cells would make PTT less effective as a treatment [57]. Li *et al* solved this problem by putting garcinia cambogia acid, which blocks HSP90 on ZIF-8 NPs with bismuth. By stopping cancer cells from making HSP90, apoptosis could happen at below 43 °C [39].

3.1.4. Chemotherapy. One of the most common ways to treat cancer is to use ZIF-8 to deliver and release the chemotherapeutic drugs at the tumour sites [58, 59] (table 2). Interestingly, Xu and coworkers found that ZIF-8 caused autophagy (by promoting PI3K-regulate death) [8]. This is surprising because other nanostructures have also been shown to cause pro-autophagy [88]. After 24 h, autophagy inhibitors brought back the decreased cell viability that ZIF-8 had caused. By making autophagy break down ZIF-8 faster, cytotoxic Zn^{2+} and ROS were made, which in turn made autophagy work better. Mammalian target of rapamycin (mTOR) activation, on the other hand, was important for cell survival [24, 26], which led to DOX resistance and resistance to other chemotherapeutic drugs [60]. To do this, rapamycin (RAPA) and ZIF-8 were put into a nanoparticle and used to stop mTOR function (figure 4). Indeed, ZIF-8 was found to turn on pro-survival autophagy, which may be due to different cells, different amounts of ZIF-8, or longer culture times [9].

3.1.5. Gene therapy. The gene regulators including nucleases, non-coding RNAs, DNAzyme, RNase A, miRNAs, and siRNA could achieve therapeutic goals by turning off certain genes and applied as gene therapy (table 2). But their uses are limited because they do not get into cells very well and they break down easily. They can be sent to cancer cells by ZIF-8, and released zinc ions can be used as a co-factor for enzyme-based cleavage, thus making it easier to control gene expression. Jia and co-workers put RNase A inside ZIF-8 to use as an individual gene therapy agent. Confocal microscopy imaging and MTT assay showed that ZIF-8 helps cells to uptake the RNase A Alyami *et al* also introduced and used ZIF-based nanoplatforms for transferring CRISPR/Cas9 gene-editing elements to the surface of cancer cell membranes. After incubating with the cell, the nanoplatform was absorbed by targeted cells, and the inhibition of EGFP in cells transfected with nanoplatforms was three times greater than in non-transfected cells [43]. These results showed that gene editing can work better when the nanoplatform was covered with the cell membrane. Using nanomaterials like ZIF-8 to carry CRISPR/Cas9 could be safer than using virus-based vectors, which can change genes

that are not meant to be changed. There will likely be more research and applications.

3.2. Dual therapy of cancer

3.2.1. PTT/ immunotherapy. Immunogenic cell death (ICD) is the change from non-immunogenicity to immunogenicity that sets off the immune system's anticancer responses [61]. ICD happens when tumour cells die in response to outside stimuli. Immune effector cells can be made by irradiation [62], PDT [63], PTT [64], and some chemotherapy agents [65]. With ICD, the number of immune effector cells was seen to increase. Recently, ZIF-8 nanocomposites loaded with both immunological reagents and photothermal agents were studied for combinatorial therapy of immunotherapy and PTT (table 3).

Yu *et al* developed HA/ZIF-8@ICG@IMQ (immune adjuvant imiquimod) NPs that can be used to treat tumours. When the IMQ was mixed with the photothermal drug ICG, it improved antitumor immunity and made the immune memory response last longer [67]. Zhang *et al* made two ZIF NPs: mannan (MAN)/(R837+1MT)@ZIF-8 and HA/IR820@ZIF-8 [66]. The ICG was the photothermal part of HA/IR820@ZIF-8 NPs. Through receptor-mediated endocytosis, HA modification made it possible to send the drug directly to tumour cells and made it easier for the cells to take in the drug. Laser irradiation stopped the growth of the tumour where it was, and the release of danger-associated molecular patterns (DAMPs) and tumour-associated antigens (TAAs) started the immune response against the tumour. After B16F10 cells were treated with NPs and then exposed to laser light, the amount of ICD markers like HSP70, calreticulin, and high mobility group box protein 1 went up. This shows that NPs stimulate antitumor immunity.

The IMQ is an agonist of the TLR-7, while 1-Methyl-D-tryptophan was an inhibitor of indoleamine 2,3-dioxygenase, which was said to stop the growth of T cells by turning tryptophan into the immunosuppressive amino acid kynurenine [75]. Because there were a lot of receptors for the NPs on the surface of the dendritic cells, mannan was used to change them. When NPs were added to bone marrow-derived dendritic cells, they became more mature. This was shown by more CD80 and CD86 expression and more necrosis factor and IL-6 being released. When the two NPs were used together, the ICD made by PTT caused more TAA to be released. This made dendritic cells more mature. There were also the fewest immune-suppressing Tregs. *In vitro*, these two nanodrugs considerably slowed the growth of both primary and distant cancers and were able to create immunological memory. After the cancer cells were injected into the body, the immunological memory cells fought back.

3.2.2. Immunotherapy/gas therapy. ICD is also caused by gas therapy, which is a new way to treat tumours. Carbon monoxide (CO) and other common gases can bind to hemoglobin in tumour sites and stop O_2 from getting to the mitochondria and stopping them from breathing. Gas therapy is a low-toxicity and high-efficacy therapy strategy that can sensitise cells to chemotherapeutic drugs, thus effectively killing cancer cells and realising the combination between gas therapy and traditional therapy. Xiao and coworkers made a CO nano-generator called CO_2-g-C_3N_4-Au@ZIF-8@F127 (CCAZF). It is broken down in the acidic tumour microenvironment and releases CO_2-g-C_3N_4-Au (CA). When laser light irritated, CO_2 was turned into CO, allowing CO to be released under light control [68]. This made CO less harmful to normal cells and led to ROS growth and mitochondria destruction in the tumour cells, which led to ICD in the end. Co-treatment of CCAZF and anti-PD-L1 antibody significantly reduced tumour growth in the mouse model [68].

3.2.3. Immunotherapy/chemotherapy. Pyroptosis is a type of planned cell death that is caused by the gasdermin protein and followed by sever inflammatory responses. Recent research showed that chemotherapy drugs cause pyroptosis in cancer cells that express gasdermin E. This, in turn, boosts the immune system's ability to fight tumours [76]. So, Zhou *et al* put the drugs hydralazine (HYD) for DNA demethylation and mitoxantrone (MIT) for chemotherapy in the same ZIF-8 capsule (table 3). While MIT turned on caspase-3, which killed the cell, HYD made gasdermin E go up. HYD can also stop the metabolic markers of myeloid-derived stopper cells, which are involved in the immune paralysis of $CD8^+$ T cells [69]. By putting HYD and MIT on ZIF-8 nanoparticles at the same time, immune escape was stopped and the immune system's ability to fight cancer was boosted.

3.2.4. Gene/chemo therapy. The cytoplasmic miRNAs bind and form inducing silencing complex in the 3′-UTR region of mRNAs-encoding proteins, breaking down the mRNAs as well as inhibition of translation [77, 78]. Considering the low stability of miRNAs *in vivo*, Zhao and his colleagues used ZIF-8 as a nanocarrier to get miRNAs into the target cells. ZIF-8 stopped ribonucleases from cutting bare miRNAs in the bloodstream (table 3). When cells took in miR-34a-m@ZIF-8, it released Zn^{2+} and miR into the acidic lysosome. Through a Fenton-like reaction, zinc ions then made ROS. This caused the lysosomes to break, which in turn caused more Zn^{2+} to be released (figure 5) [70]. RT-PCR and immunoblotting results showed that miR-34a-m@ZIF-8 reduced the level of Bcl-2 mRNA and protein l, which indicated the improvement of miRNA-mediating gene silencing.

Considering the combination of gene and chemotherapy, Wang and coworkers put DNAzyme targeted EGR-1 into MOF-based NPs to avoid the side effects of traditional chemotherapy and stop spreading tumour cells upon therapy. In the acidic conditions of the lysosome, the NPs broke apart and let out Cu^{2+}, Zn^{2+}, and DNAzyme. Cu^{2+} was turned into Cu^+ by sodium ascorbate. This Cu-catalysed reaction made resveratrol derivatives that can kill tumour cells [71]. Also, Zn^{2+} worked with DNAzyme to cut EGR-1 mRNA, which stopped cancer cells from multiplying and moving. Making drugs inside cells made sure that they were safe for living things.

Table 3. ZIF-8-based nanostructures for combination therapy of cancer.

Application	Nanostructure	Cancer type/cell type	Function	References
	MAN/(R837+1MT)@ZIF–8	Xenograft B16F10 tumour/ B16F10 cell	Prevented immune evasion	[66]
Immunotherapy/PTT	HA/ZIF–8@ICG@IMQ	Xenograft CT26 tumour/CT26 cell	Creating a long-term immune memory to suppress and controlling tumour recurrence	[67]
Immunotherapy/Gas therapy	CCAZF	Xenograft 4T1 tumour/4T1 cell	Regression of tumour	[68]
Immunotherapy/Chemotherapy	(M+H) @ZIF/HA	Xenograft 4T1 tumour/4T1 cell	Suppressing immune escape/Creating a long-term immune memory against metastasis	[69]
GT/CDT	miR–34a–m@ZIF–8	Xenograft MDA-MB-231 tumour /MDA-MB-231 cell	Enhanced apoptosis and suppressed the tumour growth	[70]
GT/Chemotherapy	DNAzyme@Cu/ZIF–8	Xenograft MCF tumour/MCF-7 cell	Intracellular synthesis of therapeutic agents/Cleaving of the oncogene agents	[71]
ST/CDT/PDT GT/PDT/Chemotherapy	CGZPM	Xenograft 4T1 tumours/4T1 cells	Improve the therapeutic results and accelerate the cascade reactions	[72]
	CDHNs	Xenograft MCF-7 tumour/MCF-7 cell	Decreasing the drug resistance and suppression of metastasis	[73]
Immunotherapy/PTT/ST	CuCo(O)/GOx@PCNs	Xenograft 4T1 tumour/4T1 cell	Improve the photothermal conversion and regression of primary tumour	[64]
ST/CDT/PTT/Immunotherapy	Fe3O4@ZIF–8/GOx@MnO2	Xenograft 4T1 tumour/4T1 cell	Amplification of therapeutic cascade efficacy/killing the tumour cells and inhibiting the metastasis	[74]

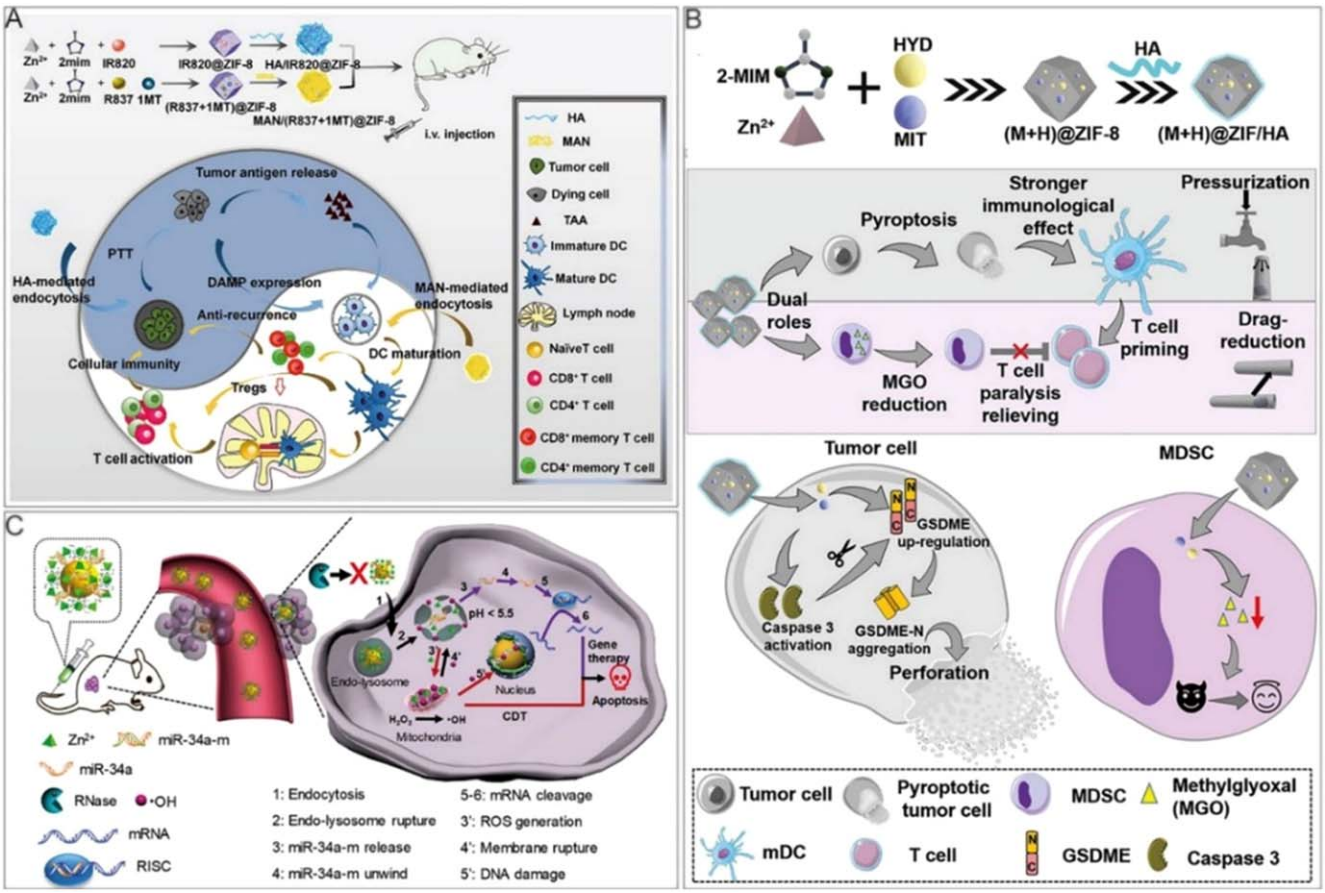

Figure 5. Dual cancer treatment nanoplatforms ZIF–8. Immunotherapy/PTT ZIF–8 nanoplatforms. Immunotherapy/chemotherapy ZIF–8 NPs. GT/CDT ZIF–8 nanoplatforms. Reprinted with permission from [70]. Copyright 2023 Advanced Science, Wiley–VCH GmbH. Reproduced from [70]. CC BY 4.0.

3.2.5. Chemodynamic therapy. Chemodynamic therapy (CDT) differs from many other proof-in-concept ROS-related cancer therapy approaches, such as conventional chemotherapy, radiotherapy, PDT, and SDT, in which it uses chemodynamic therapeutic agents to convert internal hydrogen peroxide (H_2O_2) into toxic hydroxyl radicals (OH) for killing the cancer cells [79, 80]. This may be due to several factors, including its lack of medication resistance, device restrictions, and external stimulation, more specific responsiveness to H_2O_2, lack of external field penetration depth restriction, fewer adverse effects on healthy tissues, and more desirable ROS production ability [81]. As a result, CDT has promise for the future of clinical transformation and other useful uses. Throughout CDT, the effectiveness of the treatment is heavily influenced by Fenton/Fenton-like reactions. In general, lowering the reaction potential of Fenton/Fenton-like reactions could maximise CDT's performance in TME. From this perspective, two approaches should be properly taken into account to optimise CDT in TME performance. On the one hand, it is important to rationally design and build chemodynamic agents (Fenton agents) with more active sites to catalyse the conversion of more H_2O_2 into OH. On the other hand, the TME, which has a low H_2O_2 content, a high pH, and an overexpressed reduced material, might be modified to offer better reaction conditions for Fenton/Fenton-like reactions [82].

3.3. Triple therapy of cancer

3.3.1. PTT/ST/immunotherapy. Wang and coworkers made CuCo(O)/GOx@PCNs in addition to immunotherapy and PTT. These unique nanoformulations showed that immunotherapy/PTT/ST triple therapy could work (table 3). Before pyrolysing ZIF in nitrogen to make porous carbon nanocomposites (CuCo(O)@PCNs), they grew ZIF-67 on top of the Cu/ZIF-8 that was made. The next step was calcination in air. After GOx was put into porous carbon, CuCo(O)/GOx@PCNs, as a nano-enzyme, was made. When the designed nano-enzyme was working in the tumours, CuCo(O) reacted with H_2O_2 to make oxygen, while GOx ate glucose to make H_2O_2 with the help of oxygen, which made ST work better. Photothermal conversion can work well enough for porous nanocarbon to get up to 40.04% [64]. When exposed to laser light, it does the following: i) it kills the primary tumour; (ii) it simulates the GOx efficacy; (iii) it encourages the production of TAAs; and (iv) it speeds up the maturation of DCs, which attracts and activates T lymphocytes. Stimulation of cytotoxic T cells can decrease the tumour growth and spread. In contrast to immune/

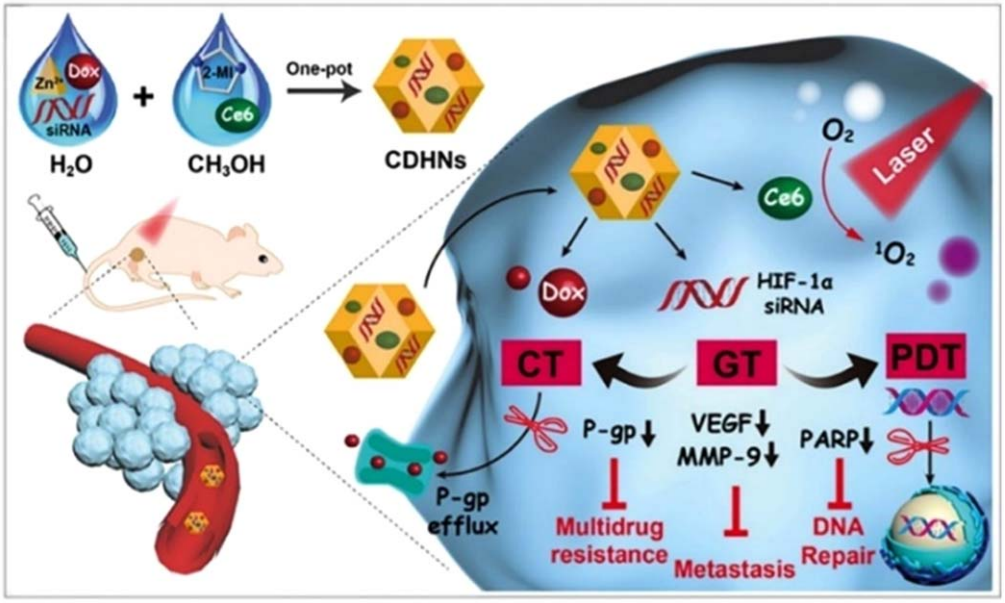

Figure 6. Triple cancer treatment nanoplatforms ZIF–8. GT/PDT/Chemotherapy nanoplatforms ZIF–8.

photothermal therapy, giving GOx not only cut off the tumour cells' main source of food, but photothermal conversion also made glycolysis in the tumour cells work better.

3.3.2. ST/CDT/PDT. Glycolysis makes the tumour environment more acidic, which makes the Fenton reaction more likely to make free radicals. Also, the heating effects of PTT increase the rate at which GOx and CDT work. Since tumour microenvironments often have low oxygen levels and too much glutathione (GSH) production, Zhang and coworkers designed a Ce6/GOx@ZIF-8/PDA@MnO_2 nano-reactor (table 3). When MnO_2 reacted with H_2O_2 and got rid of GSH, it made Mn^{2+} and O_2. Ce6 was used as a photosensitiser, and Mn^{2+} was used as a reagent similar to Fenton's [72]. The production of O_2 decreased the lack of oxygen in the tumour, which made PDT work better and sped up glycolysis. The PDA coating on its surface made it more stable, and it ate MnO_2 and GSH. In a mouse model of colorectal cancer, laser radiation stopped the growth of tumours best when designed NP was present (figure 6).

3.3.3. GT/PDT/chemotherapy. The lack of oxygen in the tumour sites and hypoxia are linked to metastasis and treatment resistance [83]. Wang *et al* made multifunctional ZIF-8 nanoparticles that were filled with Ce6, DOX, and HIF-1 siRNA so that Ce6, DOX, and HIF-1 siRNA could be delivered into the cells (CDHNs, figure 6(B)). By stopping the production of matrix metallopeptidase 9, PARP, and VEGF, HIF-1 siRNA stopped tumour spread and multidrug resistance, and repaired the DNA damage [73]. In *in vitro* studies, the GT was shown to improve the efficacy of chemo/PD therapy. Also, it can increase therapeutic efficacy by inhibiting P-gp-based drug resistance and PARP-based DNA repair, respectively. In mice with tumours, CDHNs were shown to be safe and to stop micro-metastatic lesions from happening. Chemotherapy was less harmful when drug release was controlled by light. GT-sensitised photo-chemotherapy works better because it uses a nanosystem that is more flexible [73].

3.4. Quadruple therapy of cancer

3.4.1. Immunotherapy/ST/CDT/PTT. When several cancer therapy methods are used together, there can be a cascade amplification effect on the therapy [84] (table 3) . Zhang and coworkers made a nano-complex called Fe_3O_4@ZIF-8/GOx@MnO_2 (FZGM) and used it for immunotherapy/ST/CDT/PTT. The magnetic targeting of Fe_3O_4 can send the FZGM NPs to the tumour site. The Fe^{2+} that was released by Fe_3O_4 during the Fenton reaction speeds up both the Fenton reaction and the rate at which the nano-enzyme eats glucose [74]. This helps shrink the tumour. The production of gluconic acid helped to speed up the breakdown of ZIF-8 in cancer cells. Also, when ST, CDT, and PDT were used together, they caused ICD, releasing the TAAs, and changing M2 macrophages into M1 macrophages. It is possible by improving the immune systems in the tumour site, to make immune checkpoint inhibitors work better. When laser light and a magnetic field were used on the mouse model, FZGM stopped the primary tumour from growing significantly. But when FZGM and PD-1 antibodies were used together, distant tumours were stopped as much as possible [74].

4. Challenges

ZIF-8 is pretty safe for living things, but when the concentration was higher than the critical level, it did a lot of damage to DNA [85]. Because of this, its concentration needs to be carefully examined and more research needs to be done on animals. Researchers also found that ZIF-8 caused cellular autophagy, but it was not clear yet whether this autophagy

helped cells live or killed them. It is possible that different cell types or different ways of setting up the experiments led to different results. But these differences change the results of experiments when ZIF-8 is made into a nanocarrier. More research needs to be done so that information can be used as a guide for making nanoplatforms in the future. Also, more researches are needed to find out the production and storage methods of the different ZIF-8 drug-loaded nanoplatforms and consider the factors that affect the consistency and stability of these platforms. This is because the use of nanoplatforms in clinical settings depends on how safe and stable they are. Putting multiple payloads on ZIF-8 at the same time makes the synthesis process more complicated, even though these increasingly complicated designs of nanomedicine have led to good results. Also, a more thorough and organised evaluation may be needed to figure out how the different cargoes interact with each other and whether they can be unloaded in an orderly way.

Also, ZIF-8 nanoparticles can be anywhere from 10 to 100 nanometers in size. Due to increased permeability and retention, NPs can be passively targeted to tumour site. However, most NPs loaded with multiple therapeutic agents tend to be bigger than nanometers, and this caused their uptakes to be harder. For these particles, a surface coating or biomimetic mineralisation can be a good choice. Cancer cells, erythrocytes, and platelet membranes are all examples of membranes that can trick the immune system and make circulation last longer. All these membranes have got a lot of attention recently. Changes to the surface of the FA, HA, and RGD peptides, which can find matching receptors on the cell membranes of tumour cells, cause tumour tissues to take in more nanoparticles. Coatings made of PEG and polyvinylpyrrolidone can stop reticuloendothelial systems from getting rid of nanoparticles while still keeping their physicochemical properties and functions.

Even though *in vitro* and *in vivo* studies have shown that ZIF-8-based delivery systems are safe and work well, there is no evidence for long-term safety of *in vivo* and preclinical studies. To find out if and how much differences in tumour types and tumour microenvironments affect the effectiveness of NPs therapy, more studies are needed on a wider range of tumour types, including xenograft models made from tumours taken from patients. The synthesis process also needs to be optimised and standardised so that the yield goes up and costs go down.

5. Prospects and conclusions

In the last decades, ZIF-8 has been thought to have a lot of potential as a platform for the delivery of cargo because it has a lot of pores. Unlike the FAD-approved therapeutic agents, the ZIF-8 can be modified by targeting agents and combined with imaging probes to make more specific images. Also, ZIF-8's high porosity makes it possible to load it with drugs while it acts as a contrast agent, so it can be used for theranostic applications. Zinc is a biocompatible metal ion that is used in clinical translation. It is also one of the trace elements that the body needs. *In vivo* toxicity tests also showed their good safety profile [86]. But the lack of long-term toxicity data is one of the biggest reasons why potential ZIF-8 NPs cannot be used in the clinic. Most ZIF-8 nanoparticles can be made quickly and with a lot of cargo on them through electrostatic contact, coordination reactions, etc Because it is sensitive to pH, the payload can be released in a controlled way. For other types of nanoparticles, like porous silicon, nanotubes, or super porous hydrogels, different gatekeepers are often made so that drugs can be released in a controlled way. But ZIF-8's natural ability to respond to pH makes this process possible without any changes and keeps drugs from leaking out too soon. Also, it has been shown that ZIF-8 is more toxic to cancer cells than to normal cells [87]. This may be because, first, cancer cells take in more zinc ions as they are more permeable. Most of ZIF-8's toxicity comes from the zinc ions it lets out. Second, it has been seen that zinc ions react with H_2O_2, which is found in large amounts in cancer cells, in a way that is similar to a Fenton reaction. This makes more ROS and makes it easier to kill cancer cells.

Most of the research on ZIF-8's use in cancer treatments still looks at how well it works with phototherapy, but there is growing interest in how it could be used in immunotherapy and GT. Even though it does not carry cargo, ZIF-8 can improve the immune state of the tumour microenvironment in some ways. Future research should focus more on ZIF-8 because it has the potential to be a platform for both immunotherapy and the delivery of gene editing components. In modern times, ZIF-8 is often used to make nanosystems. Changes made to the nanoparticles and taking into account the drugs they carry make it possible for them to fight cancer from many different systemic angles. A smart nanostructure that combines diagnosis, release, and therapy can help patients. ZIF-8 has a lot of potentials and is likely to be used in more therapeutic systems and has good potential to help in cancer therapy and diagnosis in the future.

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