Nanoscale

REVIEW

View Article Online
View Journal | View Issue

Cite this: *Nanoscale*, 2025, **17**, 27066

Nanomaterial-mediated ferroptosis as a promising strategy for cancer therapy

Yuqing Tang,†[a] Qingqing Zhou,†[b] Yiyang Fan,[c] Tzu-Ming Liu, *[b] Luying Zhu*[d] and Mingxian Liu *[e]

Received 27th August 2025,
Accepted 21st October 2025

DOI: 10.1039/d5nr03627e

rsc.li/nanoscale

Conventional cancer therapies, such as chemotherapy and radiotherapy, often face limitations due to drug resistance, systemic toxicity, and tumor heterogeneity, which significantly limit the therapeutic effect. Ferroptosis, an iron-dependent form of regulated cell death driven by lipid peroxidation and antioxidant defense collapse, has emerged as a promising approach, particularly for aggressive and therapy-resistant malignancies. However, the clinical application of molecular ferroptosis inducers is hindered by poor pharmacokinetics and off-target effects. Nanotechnology offers a promising solution by enabling targeted delivery and controlled ferroptosis induction. This review provides a critical summary of nanomaterial-mediated ferroptosis, with a focus on lysosome-targeted strategies as the pathological epicenter. First, a critical analysis of the current molecular mechanisms and regulatory networks of nanomaterial-mediated ferroptosis was conducted, which can promote targeted delivery and develop cancer treatment methods. Then, we classify and evaluate nanomaterials based on their primary mechanism of action, detailing the design principles, structure–activity relationships, and characteristics of both iron-based nanomaterials and non-iron-based nanomaterials. Finally, we summarize the applications of the multifunctional nanoplatform, which can combine ferroptosis induction with existing treatments to improve the therapeutic effect. This review highlights the potential of nanomaterial-mediated ferroptosis as a targeted, effective, and resistance-overcoming paradigm for next-generation cancer therapy.

1. Introduction

Cancer remains a leading cause of death worldwide, placing a heavy burden on healthcare systems worldwide.[1,2] Traditional therapies such as surgery, chemotherapy, and radiotherapy, while improving the outcome of patients, also face serious limitations, including severe systemic toxicity, the development of intrinsic or acquired multidrug resistance, and poor efficacy against metastatic or deep tumors.[3–6] Therefore, the development of novel therapeutic strategies that selectively target malignant cells while protecting healthy tissues and overcoming resistance mechanisms has become a focus of oncology research.[7,8] In recent years, ferroptosis has emerged as a distinct, iron-dependent form of regulated cell death (RCD), fundamentally different from apoptosis, necrosis, and autophagy.[9–12] It is characterized by the lethal accumulation of iron-catalyzed lipid peroxides, driven by the inactivation of the antioxidant glutathione peroxidase 4 (GPX4) system and depletion of glutathione (GSH).[13] Many cancer cells exhibit inherent vulnerabilities to ferroptosis due to their altered iron metabolism, high reactive oxygen species (ROS) levels, and dependence on specific antioxidant pathways.[14,15] This intrinsic susceptibility positions ferroptosis induction as a highly promising therapeutic avenue, particularly for eradicating aggressive, therapy-resistant, and metastatic cancers that evade conventional apoptosis-based treatments.[16–18]

However, the clinical translation of molecular ferroptosis inducers (*e.g.*, erastin, RSL3, and sorafenib) faces substantial pharmacological hurdles.[19–22] Their inherently poor aqueous solubility often necessitates the use of solubilizing agents, which can introduce additional toxicity and complicate formulation. This leads to limited oral bioavailability and rapid systemic clearance, resulting in sub-therapeutic drug concentrations at the tumor site and demanding frequent, high-dose administrations that exacerbate systemic toxicity. Furthermore,

[a]*Department of Biomedical Engineering, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, PR of China*
[b]*Institute of Translational Medicine, Faculty of Health Sciences & Ministry of Education Frontiers Science Center for Precision Oncology, University of Macau, Taipa, Macau 999078, PR of China. E-mail: tmliu@um.edu.mo*
[c]*Department of Chemical and Biological Engineering, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, PR of China*
[d]*Stomatological Hospital, School of Stomatology, Southern Medical University, Guangzhou 500515, PR of China. E-mail: zhu_luying05@163.com*
[e]*Department of Materials Science and Engineering, College of Chemistry and Materials Science, Jinan University, Guangzhou 511443, PR of China. E-mail: liumx@jnu.edu.cn*
†These authors contributed equally to this work.

their non-specific biodistribution causes unintended accumulation in healthy tissues, leading to dose-limiting off-target effects. For instance, systemically administered erastin can induce hepatotoxicity, while the multi-kinase inhibitor sorafenib, though clinically approved, exhibits a broad range of side effects due to its lack of tumor selectivity. Finally, these small molecules often demonstrate insufficient penetration and retention within the complex tumor microenvironment (TME), failing to reach therapeutic thresholds, particularly in poorly vascularized or metastatic lesions.[23,24] These collective challenges significantly limit the efficacy and safety of molecular ferroptosis inducers in clinical oncology.

Nanomaterials offer a revolutionary platform to overcome these barriers. Their unique physicochemical properties enable precise tumor targeting through enhanced permeability and retention (EPR) effects and active targeting ligands.[25–28] More importantly, nanomaterials themselves can be ingeniously designed not merely as passive carriers, but as active inducers of ferroptosis.[24,29,30] This can be achieved through diverse mechanisms, including intrinsic catalytic activity, GSH depletion, GPX4 inhibition, iron ion delivery, and disruption of intracellular redox homeostasis.[31,32] Therefore, the convergence of nanotechnology and ferroptosis represents a transformative strategy for cancer therapy.[33] However, existing summaries often provide broad overviews of materials or molecules but lack a systematic dissection of the precise structure–activity relationships (SARs) governing how nanomaterial composition, size, surface chemistry, and morphology dictate their ferroptosis-inducing efficacy. Furthermore, while the potential of combining ferroptosis induction with other therapies is frequently mentioned, comprehensive analyses of the synergistic mechanisms, optimal sequencing, and the specific design principles for nanomaterials in these multimodal regimens are still lacking. Therefore, a comprehensive and in-depth understanding of the role of nanomaterial-induced ferroptosis in cancer, addressing these specific gaps, is essential to effectively guide its application in cancer treatment.

In this review, we systematically examine recent advances in nanomaterial-augmented ferroptosis therapy for cancer. We illustrate how nanomaterials co-localize inducers at lysosomal checkpoints governing iron overload, PUFA peroxidation, and antioxidant defense collapse (Fig. 1). Next, we classify nanomaterials by material composition, highlighting iron-based and non-iron nanomaterials and their structure–activity relationships. We explore combination strategies that amplify ferroptosis, including chemo-/radio-therapy, photothermal/dynamic therapy (PTT/PDT), immunotherapy, and multimodal approaches. Finally, we discuss translational challenges and future directions, emphasizing clinical scalability and biocompatibility. By bridging mechanistic insights with nanomaterial innovations, this review aims to inspire next-generation ferroptosis therapies for intractable cancers.

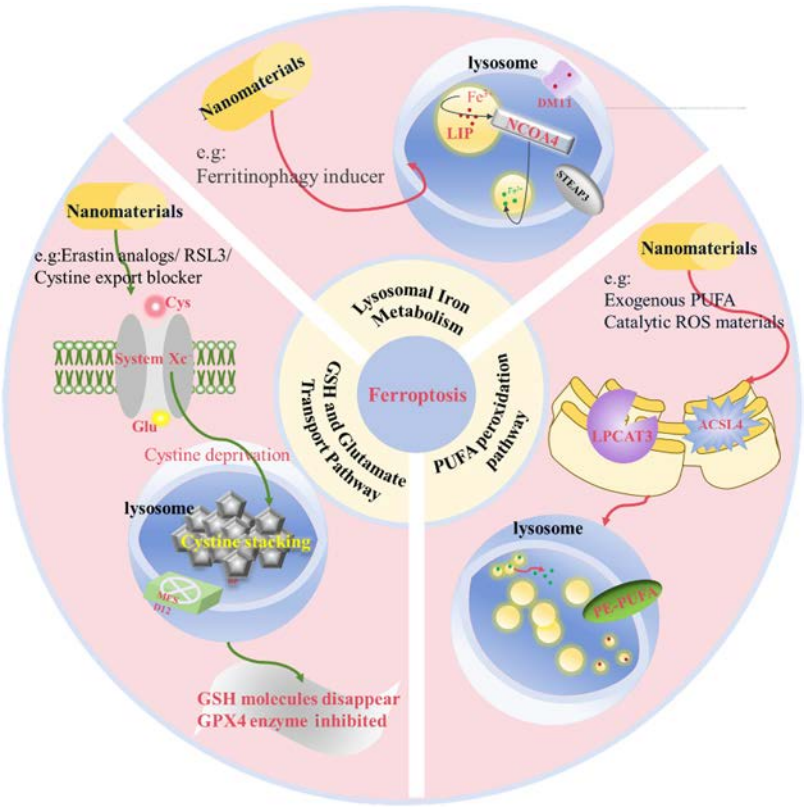

Fig. 1 Lysosome-targeted nanomaterials for ferroptosis induction *via* triple-pathway modulation.

2. Molecular mechanisms of ferroptosis

The therapeutic potency of ferroptosis fundamentally arises from the synergistic dysregulation of three core pathways: iron metabolism, polyunsaturated fatty acid (PUFA) peroxidation, and the glutathione (GSH)/GPX4 antioxidant axis. Critically, emerging evidence positions the lysosome as the master regulator and primary execution site for these processes, where spatial colocalization amplifies lethal lipid peroxidation (LPO). Nanomaterials designed to target and permeabilize lysosomal membranes offer a potent strategy to co-localize inducers at this pathological epicenter, driving irreversible ferroptotic death (Fig. 2).[34–39]

2.1 Lysosomal iron metabolism

Ferroptosis critically depends on iron overload within the lysosomal labile iron pool (LIP), where dysregulated iron handling pathways converge. Nanomaterials can leverage natural lysosomal trafficking to deliver iron or disrupt iron regulatory mechanisms specifically within this compartment. Enhanced iron uptake occurs through lysosomal reduction of endocytosed Fe^{3+}, often facilitated by enzymes like STEAP3, followed by DMT1-mediated import, concentrating Fe^{2+} within lysosomes.[10,40,41] Impaired iron storage further contributes, as NCOA4-mediated ferritinophagy degrades ferritin directly within lysosomes, releasing substantial Fe^{2+} into the lysosomal lumen.[42,43] Additionally, dysregulation of lysosomal Fe^{2+} export mechanisms, such as ferroportin, further elevates intralysosomal Fe^{2+} levels. This surge of Fe^{2+} confined within the lysosome fuels the Fenton reaction ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\bullet}OH + OH^-$), generating highly reactive hydroxyl radicals ($^{\bullet}OH$) that initiate membrane lipid peroxidation at the site.[44–47] Lysosome-targeted nanomaterials amplify this cascade by delivering iron donors or inducers of ferritinophagy directly to lysosomes, thereby ensuring high local concentrations of catalytic Fe^{2+} adjacent to vulnerable membranes.

2.2 Lysosomal vulnerability in PUFA peroxidation

PUFAs, esterified into phospholipids (*e.g.*, PE-PUFAs), are peroxidized on membranes, with the lysosomal membrane being critically vulnerable.[42,48,49] While ACSL4/LPCAT3 activity occurs cytosolically, the incorporation of PUFA-PLs into endolysosomal membranes during vesicle trafficking primes these compartments for oxidation. Nanomaterials induce ferroptosis by: (1) delivering exogenous PUFAs (*e.g.*, arachidonic acid) *via* endocytosis, concentrating them within endolysosomal membranes after degradation of the carrier; (2) modulating ACSL4/LPCAT3 to increase PUFA-PL incorporation generally, including into lysosomal membranes; and (3) generating ROS

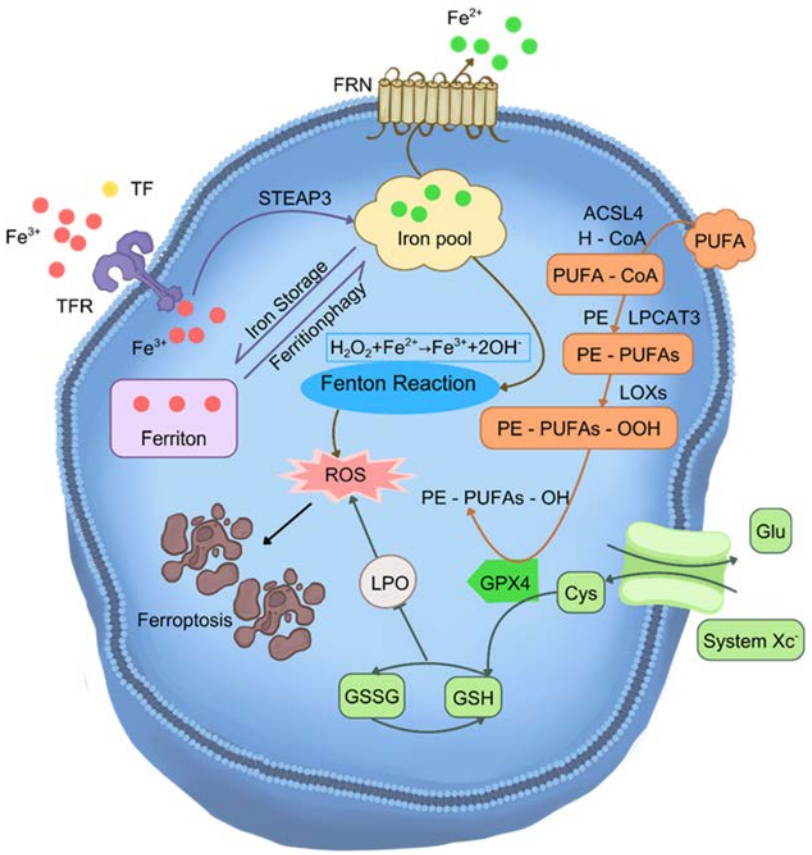

Fig. 2 Schematic diagram illustrating the core molecular mechanisms underlying ferroptosis.

(˙OH *via* the Fenton reaction) directly within lysosomes using catalytic nanomaterials or ROS-generating agents localized there. The proximity of high lysosomal Fe^{2+} and PUFA-rich membranes creates a spatially optimized environment for non-enzymatic peroxidation. Accumulating peroxidized lipids (PE-PUFAs-OOH) directly compromise lysosomal membrane integrity, leading to permeabilization (LMP), a key terminal event in ferroptosis.[50–57] Nanomaterials engineered for lysosomal delivery ensure PUFA substrates or ROS generators act precisely where Fe^{2+} catalysis occurs.

2.3 GSH and glutamate transport pathway

The GSH/GPX4 axis plays a crucial role in suppressing ferroptosis, with lysosomal compartmentalization being vital for defense mechanisms. System Xc^- facilitates the import of cystine into endosomes/lysosomes through endocytosis.[58–60] Once inside the lysosome, cystine is reduced to cysteine. However, cysteine needs specific lysosomal exporters such as MFSD12 to exit the lysosome and enter the cytosol for GSH synthesis. Importantly, lysosomes store cysteine and potentially GSH, acting as a local antioxidant reservoir to neutralize intra-lysosomal ROS and protect lysosomal membranes. Disruption of this pathway at the lysosomal level can have significant effects. Inhibiting system Xc^- leads to depletion of lysosomal cystine. Blocking lysosomal cysteine export traps cysteine within the lysosome, making it unavailable for cytosolic GSH synthesis and potentially saturating lysosomal storage capacity. Direct GPX4 inhibition or GSH depletion prevents the reduction of lipid hydroperoxides (L-OOH) on membranes, including lysosomal membranes. The loss of this lysosomal antioxidant capacity allows locally generated ˙OH from lysosomal Fe^{2+} to peroxidize PUFA-PLs in the lysosomal membrane unchecked.[61,62] Lysosome-targeted nanomaterials can deplete lysosomal cysteine/GSH by delivering cystine mimetics or exporter blockers to lysosomes, or directly deliver GPX4 inhibitors, thereby maximizing local antioxidant collapse and membrane damage within this organelle.

2.4 Rationale for lysosome-targeted nanomaterial design

The design and advancement of lysosome-targeted nanomaterials center on exact subcellular localization and microenvironment responsiveness to enhance therapeutic effectiveness and specificity. For instance, the NLTC nanoplatform developed by Liu's team, surfaced modified with protein targeting ligands and lysozyme targeting ligands, not only facilitates the degradation of specific extracellular/membrane proteins but also incorporates immune regulatory functions.[63] It can carry catalase to alleviate the tumor immune suppressive microenvironment and has pH-responsive modifications to boost tumor selectivity. The TAEN system, with modular design, enables nanocarriers to release drugs in the lysosome's acidic environment.[64] The drugs then passively diffuse to the mitochondria, inducing spatiotemporal-controlled tumor pyroptosis and increasing the killing efficiency 30–50 times. AcNPs restore the acidic pH of lysosomes in Parkinson's models, promoting α-synuclein autophagic clearance and mitochondrial function repair, underlining the therapeutic value of lysosome microenvironment regulation for neurodegenerative diseases.

In targeting design, passive targeting relies on the natural endocytic pathway of nanomaterials to enrich in lysosomes, while active targeting enhances specificity *via* ligand modification. Stimuli-responsive mechanisms ensure precise drug release within lysosomes. Notably, LAN innovatively uses tumor-overexpressed H_2O_2 to generate OH^- *via* cascade catalysis, alkalizing lysosomes and selectively suppressing tumor autophagy. Future design should integrate multi-target co-delivery and cross-organelle synergy to regulate ferroptosis and pyroptosis. The co-assembly platform developed by Wang *et al.* noncovalently connects scavenger receptor SR-A with target proteins, simplifying degrader design and expanding receptor adaptability, highlighting the potential of modular strategies.[65] The core of lysosome-targeted nanomaterials lies in integrating localization precision, environmental responsiveness, and biological mechanism synergy to overcome subcellular barriers in disease treatment.

Compared to other organelles such as mitochondria or the endoplasmic reticulum (ER), lysosomes serve as a uniquely vulnerable hub for ferroptosis execution due to their central role in iron storage, redox-active metal ion compartmentalization, and antioxidant precursor trafficking.[66] While mitochondria contribute to ROS generation and lipid peroxidation, and the ER is involved in lipid synthesis and stress signaling, the lysosome concentrates multiple ferroptotic triggers, which houses the LIP, facilitates ferritinophagy-mediated iron release, and serves as a site for cystine reduction and cysteine storage.[67] This spatial convergence of iron, polyunsaturated fatty acids (PUFAs), and antioxidant defenses within lysosomes creates a localized environment where nanomaterial-induced perturbations can efficiently initiate and amplify lipid peroxidation cascades. Moreover, lysosomal membrane permeabilization acts as a terminal event in ferroptosis, directly leading to the release of hydrolytic enzymes and cathepsins that exacerbate cellular damage.[61] Thus, targeting lysosomes enables a more integrated and potent disruption of the core ferroptotic pathways compared to organelle-specific strategies focused solely on mitochondrial ROS or ER stress.

3. Classification and characterization of nanomaterials

The effective therapeutic induction of ferroptosis using nanomaterials requires precise delivery to the lysosomal compartment, which serves as a pathological epicenter for this process. Furthermore, it necessitates targeted dysregulation of the core ferroptotic pathways, including iron metabolism, PUFA peroxidation, and the GSH/GPX4 axis. Consequently, effective nanomaterial design must achieve dual targeting objectives: (1) spatial targeting to ensure efficient accumulation within lysosomes and (2) pathway targeting to specifically disrupt one or more of the key ferroptotic mechanisms.

The following sections outline the critical design rules for achieving this and classify nanomaterials based on their primary mode of action in inducing ferroptosis.

3.1 Iron-based nanomaterials: amplifying catalytic Fe^{2+} within lysosomes

Iron-based nano-sensitizers can be broadly categorized into several types based on their chemical composition and iron release mechanisms, including iron oxides (*e.g.*, Fe_3O_4 and Fe_2O_3), iron-based metal–organic frameworks (Fe-MOFs), iron-doped carbon nanomaterials, ferrocene-containing polymers, and iron–sulfur composites (*e.g.*, FeS_2). Each type exhibits distinct ferroptosis-inducing properties through Fe^{2+} release, Fenton reactivity, or lysosomal targeting.

Iron-based nanomaterials have shown great potential in directly supplying or regulating redox-active iron (mainly Fe^{2+}) to boost the Fenton reaction within lysosomes, which is critical for triggering fatal lipid peroxidation (LPO).[68–70] The design of these nanomaterials centers on elevating the local concentration of catalytic Fe^{2+} specifically within lysosomes. As shown in Table 1, representative iron-based nanomaterials specifically enhance the catalytic Fe^{2+} concentration within lysosomes through various strategies, thereby efficiently driving the Fenton reaction and ferroptosis. Direct Fe^{2+} delivery is achieved using nanomaterials encapsulating or composed of Fe^{2+} sources, such as FeO, ferrocene (Fc), and Fe_3O_4, which release Fe^{2+} under lysosomal acidic conditions.[71]

Another approach is Fe^{3+} delivery and reduction, which leverages the high intratumoral GSH levels to reduce Fe^{3+} to active Fe^{2+}, creating a self-amplifying loop. Ferrocene (Fc) redox cycling utilizes Fc's stable Fe^{2+} state, which undergoes reversible oxidation, enabling sustained ROS generation by cycling with cellular oxidants or reductants.[71,72] Multimodal activation strategies, such as ultrasound, magnetic fields, and light/thermal integration, are also employed to enhance Fe^{2+} release or ROS generation. Iron-based nanomaterials offer advantages in biocompatibility and clearance due to iron being endogenous, and they are highly responsive to the acidic pH and high GSH levels of the tumor microenvironment, enabling targeted activation.[73] As shown in Table 1, iron-based nanomaterials are powerful tools for directly increasing lysosomal labile Fe^{2+} to drive the Fenton reaction, integrating lysosomal targeting with controlled Fe^{2+} release or generation within this compartment to maximize catalytic LPO initiation.[74]

The size of iron-based nanoparticles critically determines their biodistribution, cellular uptake, and therapeutic efficiency. For instance, Tian *et al.* synthesized Fe_3O_4 nanoparticles (Fe_3O_4-NPs) with sizes ranging from 2 to 100 nm and assessed their antitumor effects, as shown in Fig. 3.[90] Ultrasmall NPs (<5 nm) demonstrated rapid Fe^{2+} release and superior ROS generation due to their high surface-to-volume ratio, enabling nuclear accumulation and enhanced cytotoxicity *in vitro*.[91] However, *in vivo* studies revealed that 10 nm Fe_3O_4-NPs achieve optimal tumor accumulation and penetration, maximizing therapeutic outcomes. This discrepancy arises from the balance between tumor penetration and retention—ultra-small nanoparticles are rapidly metabolized, while larger nanoparticles exhibit poor intratumoral diffusion. Smaller nanoparticles dissolve faster under the acidic TME, releasing Fe^{2+} to catalyze Fenton reactions.[92] Ultra-small Fe_3O_4-NPs generated 11.99-fold more hydroxyl radicals than 100 nm nanoparticles *in vitro*, though excessive ROS may cause off-target toxicity, necessitating precise control over dissolution rates.

3.2 Non-iron-based nanomaterials: promoting PUFA peroxidation

Non-iron-based nano-sensitizers encompass a diverse range of materials that induce ferroptosis without relying on exogenous iron supplementation. These materials can be broadly classi-

Table 1 Representative iron-based nanomaterials for ferroptosis induction *via* Fe^{2+} amplification

Ferroptosis inducer	Iron existence form	Key action for Fe^{2+} increase	Cancer type	Ref.
pH@FeP	Fe^{2+}	Acid-triggered explosive release	4T1 tumor-bearing mice	73
FeCO-DOX@MCN	Fe^{0}	Acid-triggered decomposition	MCF-7 cell line	75
Lipo-PplX@ferumoxytol	Fe^{2+}	Release Fe^{2+}	4T1 tumor-bearing mice	71
GION@RGD	Fe_3O_4	Release Fe^{2+}	TNBC mouse model	76
Fe-CDs@Ce6	Fe^{2+}	Release Fe^{2+}	Mouse orthotopic melanoma model	77
DAR	Fe^{2+}	Release Fe^{2+}	4T1 cells	78
IR783-Fe@MnO_2-HA	Fe^{3+}	GSH reduces Fe^{3+}	Human normal lung epithelial cells	79
HCF@B-lap	Fe^{3+}	GSH reduces Fe^{3+}	Breast cancer cells	80
Pt-FMO	Fe^{2+}/Fe^{3+}	GSH reduces Fe^{3+}	Tumor-bearing BALB/c-nude mice	81
FelIPDA@LAP-PEG-cRGD	Fe^{3+}	GSH reduces Fe^{3+}	B16F10 tumor-bearing nude mice	82
Fe_3O_4-SAS@PLT	Fe^{3+}	GSH reduces Fe^{3+}	4T1 metastatic tumors	83
USPFLR NPs	K_2FeO_4	GSH reduces Fe^{3+}	Mice bearing 4T1 tumors	84
NLC/H (D + F + S) NPs	Fc	Sustained ROS *via* NADPH-driven Fc cycling	Breast cancer cell	85
HA/DOX@Fc-SS-ATRA NPs	Fc	Redox cycling	TNBC mouse model/4T1 cells	86
RSL3@CPT-SS-Fc-RGD	Fc	GSH reduces Fe^{3+}	TNBC mouse models	87
MP-FA@R-F NPs	Fe_3O_4	US reduction → Fe^{2+} release	4T1 tumor-bearing mice	88
SPCFe/siP	Fe_3O_4	Ultrasonic reduction of Fe_3O_4 → ROS → ferroptosis	Orthotopic glioma mouse model	89
SPNFep	Fe_3O_4, Fe^{2+}, and Fe^{3+}	Ultrasonic reduction of Fe_3O_4	CT26 mouse tumor model	72

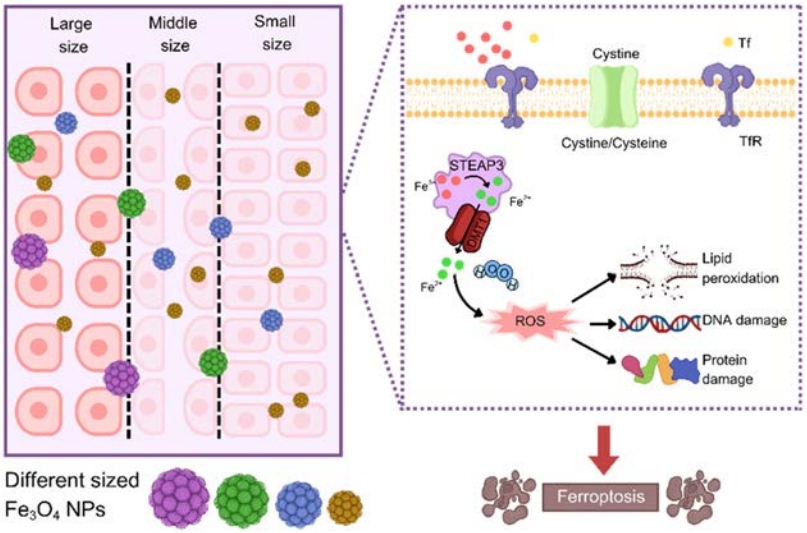

Fig. 3 Effect of particle size parameters of Fe_3O_4-NPs on cell ferroptosis.

Table 2 Representative non-iron-based nanomaterials for ferroptosis induction *via* PUFA peroxidation promotion

Ferroptosis inducer	Functional mechanism	Cancer type	Ref.
UCNP@LP(Aro-CA4)	Near-infrared photocatalysis → inhibition of microtubule kinetics + Fenton reaction → ferroptosis	MDA-MB-231 tumor-laden xenograft nude mouse model	100
Zr(Cu)-MOF@Au@DHA	Photocatalysis of H_2O_2 → free radical generation + DHA degradation of ferritin to release iron → synergistic ROS → ferroptosis	Cell-derived xenograft tumor model	97
Ca/DHA@Afn	Targeted degradation of ferritin releases iron + calcium signals and amplifies oxidative stress → inhibits GPX4 → ferroptosis	4T1 subcutaneous xenograft tumor models	98
Bi_2O_3 : S	Photoexcitation → massive ROS → lipid peroxidation → membrane damage → ferroptosis	4T1 tumor model	96

fied into several categories based on their composition and primary mechanism of action: metal-based nanomaterials (*e.g.*, MnO_2, Cu_2WS_4, and Bi_2O_3) that generate ROS or GSH *via* catalytic or redox reactions; selenium or tellurium-containing nanoparticles (*e.g.*, SeNPs and TeNPs) that inhibit GPX4 activity or mimic glutathione peroxidase function, thereby disrupting the cellular antioxidant system; polymer-based or lipid-based nanocarriers that deliver polyunsaturated fatty acids (PUFAs) or small-molecule ferroptosis inducers (*e.g.*, RSL3 and erastin) to enhance lipid peroxidation; and other inorganic or hybrid systems (*e.g.*, ZnO and mesoporous silica) that induce lysosomal membrane permeabilization or oxidative stress. These nanomaterials decouple ferroptosis induction from direct iron delivery, reducing the risk of systemic iron overload, and offer versatile mechanisms for spatiotemporally controlled therapy, particularly when designed for lysosomal targeting.

Non-iron-based nanomaterials primarily induce ferroptosis by increasing the peroxidation of PUFAs, especially those in phospholipids on vulnerable membranes like the lysosomal membrane.[93] As shown in Table 2, a variety of representative non-iron-based nanomaterials have been developed to induce ferroptosis by promoting the peroxidation of PUFAs. For example, some nanocarriers encapsulate and deliver PUFAs such as arachidonic acid and DHA. After endocytosis and lysosomal degradation of the carrier, PUFAs concentrate within endolysosomal membranes, providing abundant substrates for peroxidation. Other nanomaterials influence the activity of enzymes like ACSL4 and LPCAT3 to increase the incorporation of PUFAs into phospholipids, enriching cellular membranes with peroxidation-susceptible PUFA-PLs.[94,95]

Direct ROS generation for LPO initiation can be achieved through various methods. Photodynamic therapy (PDT) uses nanoparticles like Bi_2O_3 : S to generate massive ROS under light excitation, causing lipid peroxidation and membrane damage in tumor models.[96] Some non-iron materials also incorporate components that liberate endogenous iron *in situ* to synergize with their ROS-generating capability.[97,98] These nanomaterials offer advantages by decoupling ferroptosis induction from direct iron supplementation, reducing the risk of systemic iron overload. They provide versatile mechanisms, especially light control, for precise spatiotemporal activation and can be designed to be highly responsive to the tumor microenvironment.[99] The efficacy of these materials depends critically on lysosomal targeting to ensure the delivered PUFAs or generated ROS act in close proximity to the lysosomal LIP and the vulnerable lysosomal membrane, maximizing peroxidation efficiency and membrane damage.

Similar to iron-based systems, the size of non-iron-based nanomaterials significantly influences their tumor accumulation, cellular internalization, and lysosomal delivery efficiency. Optimal sizing (typically 10–100 nm) ensures effective EPR-mediated tumor targeting while facilitating endo-lysosomal trafficking, where these materials can exert their effects on PUFA peroxidation and membrane integrity.

3.3 Non-iron-based nanomaterials: disrupting the GSH/GPX4 antioxidant shield

Non-iron-based nanomaterials can induce ferroptosis by inhibiting the synthesis or function of glutathione GSH/GPX4. This undermines the cellular defense against lipid peroxidation, causing ROS and LPO to accumulate and drive cells to ferroptotic death.[101] This strategy often indirectly uses endogenous iron. These nanomaterials work in several ways. Some block the cystine/glutamate antiporter (system Xc^-), depleting intracellular cystine and cysteine, a key precursor for GSH synthesis.[102] Others disrupt lysosomal cysteine export, preventing cytosolic GSH synthesis. While specific examples for this are less common, it is a potential design strategy. Some directly consume or sequester GSH.[99,103] Others inhibit GPX4 activity, preventing the reduction of lipid hydroperoxides.[87,102,104] Many materials combine GSH depletion with other mechanisms like ROS generation or iron modulation. For instance, FP@SFN enhances oxidative stress and impacts redox balance in lung cancer.[105] This approach targets a critical vulnerability in ferroptosis defense and can be effective even in cells with lower iron availability. To maximize the disruption of the lysosomal antioxidant reservoir and protect the lysosomal membrane, nanomaterials must effectively deliver their inhibitory payload into or near lysosomes. This ensures the disruption occurs where defense against lysosomal Fe^{2+}-driven $^{\bullet}OH$ is most critical.[99,101,104,106]

As shown in Table 3, a variety of representative non-iron-based nanomaterials have been developed to induce ferroptosis through targeting the GSH/GPX4 pathway. These materials cover different mechanisms of action and have demonstrated the ability to induce ferroptosis in multiple cancer models. These examples specifically illustrate the diversity and effectiveness of using nanomaterials to interfere with the GSH/GPX4 antioxidant defense to trigger ferroptosis.

4. Nanomaterial-based combination therapies for cancer treatment

Although nanomaterial-induced ferroptosis alone exhibits significant antitumor potential, its efficacy may be limited by complex adaptive mechanisms of tumors, such as antioxidant compensation, metabolic plasticity, and immunosuppressive microenvironment remodeling. To overcome these barriers and expand treatment outcomes, the strategic integration of ferroptosis with conventional or emerging modalities (*e.g.* chemotherapy, radiotherapy, and immunotherapy) has emerged as a transformative paradigm. This synergistic effect utilizes nanomaterials as "multifunctional sensitizers", which not only directly triggers ferroptosis but also effectively enhances the sensitivity of cancer cells to co-delivery therapies. In this section, we systematically dissect six major combinatorial approaches (Fig. 4) in which nanoplatforms orchestrate spatiotemporally controlled interactions between ferroptosis inducers and adjuvant therapies, thereby: (1) overcoming drug resistance through parallel pathway inhibition, (2) targeting tumor types through physicochemical–biological dual activation expansion, and (3) minimizing off-target toxicity by limiting cytotoxic effects to the tumor site. The following subsections describe the design rationale, mechanical crosstalk, and preclinical validation of these combination strategies, providing a roadmap for the next generation of synergistic cancer therapies.

4.1 Chemo-ferroptosis combination therapy

Recent advances in nanomedicine have demonstrated the remarkable potential of combining ferroptosis induction with other therapeutic modalities to overcome drug resistance and enhance cancer treatment efficacy.[108–110] A key strategy involves exploiting the TME characteristics, such as GSH levels and acidic pH, to achieve targeted drug release and synergistic effects.[111] Several innovative nanosystems have been developed to co-deliver ferroptosis inducers with chemotherapeutic agents or differentiation therapy compounds, creating multi-pronged attacks on tumors.[112] The rationale behind these combination approaches stems from the need to address multiple resistance mechanisms simultaneously.[113] Wu *et al.* addressed the challenge of chemoresistance, particularly from

Table 3 Representative non-iron-based nanomaterials for ferroptosis induction *via* GSH/GPX4 disruption

Ferroptosis inducer	Functional mechanism	Cancer type	Ref.
Pt/Co-BNN@SAS	Blocking the system Xc^- → exhaustion of GSH → accumulation of lipid peroxidation (LPO) → ferroptosis	Bladder cancer cells	107
Nano-Dox	Down-regulation of GPX4/SLC7A11 expression → ferroptosis	Drug-resistant osteosarcoma cells	102
M(BAI/Pt)	Down-regulation of GPX4/SLC7A11 expression → ferroptosis	4T1 cells	104
RSL3@CPT-SS-Fc-RGD	Deliver GPX4 inhibitor (RSL3)	TNBC mouse models	87
Ca/DHA@AFn	Targeted degradation of ferritin releases iron + calcium signals and amplifies oxidative stress → inhibits GPX4 → ferroptosis	4T1 subcutaneous xenograft tumor models	98
PNPs@cGAMP	Inhibit GSH synthesis → weaken antioxidant capacity → oxidative stress → ferroptosis	Subcutaneous xenograft and distal B16F10 tumor models	103
CWP	Promote the participation of iron ions in the Fenton reaction → ferroptosis	BALB/c mouse bilateral tumor model	99
FP@SFN	Enhancing oxidative stress + activating autophagy pathways → ferroptosis	Subcutaneous lung cancer tumors	105

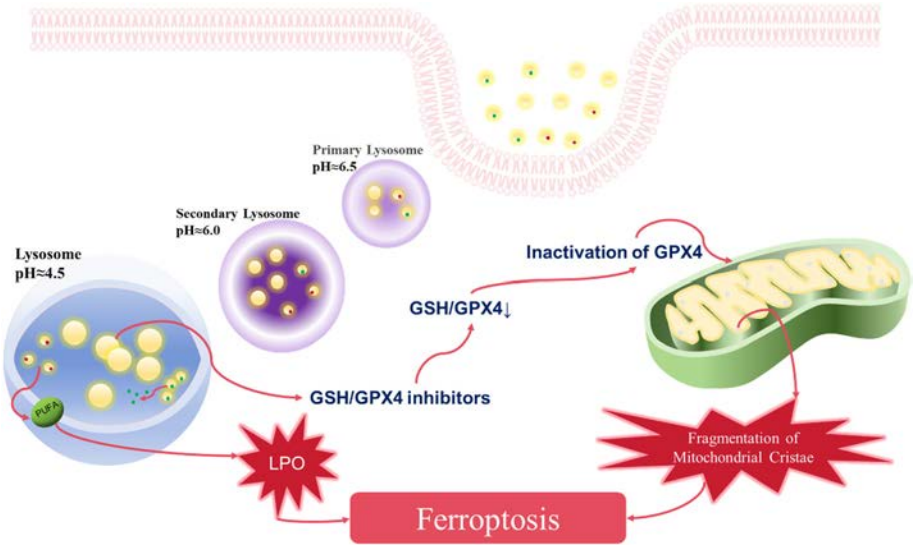

Fig. 4 Lysosome-targeted nanoplatform for ferroptosis amplification *via* triple mechanisms.

cancer stem cells (CSCs), by developing a self-assembled nano-prodrug, HA/DOX@Fc-SS-ATRA NPs.[86] This multifunctional system leverages hyaluronic acid (HA) for targeted tumor delivery, achieving strong and sustained accumulation specifically within tumor tissues.

Extending the strategy of redox homeostasis disruption, Zhao *et al.* developed the HCF@β-lap nanosystem to integrate ferroptosis induction with apoptosis.[80] The self-assembled HA/DOX@Fc-SS-ATRA nano-prodrug co-delivers the ferroptosis inducer Fc, differentiation agent ATRA, and chemotherapeutic DOX to TNBC for integrated ferroptosis–differentiation–chemotherapy (Fig. 5).

ALDH1 immunostaining (Fig. 6A) reveals a marked reduction of cancer stem cells in tumors treated with the complete nano-prodrug (G6) compared with all other groups. Robust intracellular $^{\bullet}OH$ generation in 4T1 cells is evidenced by green fluorescence (Fig. 6B). Time-course *in vivo* NIR imaging of ICG-loaded HA/DOX@Fc-SS-ATRA NPs (Fig. 6C) shows prolonged and enriched tumor accumulation, and quantified fluorescence intensities (Fig. 6E) demonstrate significantly higher and sustained retention for the HA-decorated formulation *versus* controls. Confocal images (Fig. 6D) display elevated green lipid-ROS and red oxidized C11-BODIPY signals that confirm ferroptotic cell death.

The combined treatment of nanomedicines and chemotherapy provides a powerful strategy to overcome traditional chemotherapy limitations through multimodal synergistic mechanisms.[114] These nanosystems enable precise co-delivery, target CSCs, activate ferroptosis and other death pathways, and overcome key resistance mechanisms, leading to significantly enhanced efficacy and reduced toxicity.[115] Future research should focus on optimizing nanocarrier targeting efficiency and stability, exploring their potential in regulating metastatic tumors and the immune microenvironment, and accelerating clinical translation to realize the full potential of these innovative therapies.

4.2 Radio-ferroptosis combination therapy

Radiotherapy (RT) remains a cornerstone cancer treatment but is frequently limited by tumor radioresistance.[116] Nanotechnology offers promising strategies to overcome this resistance by developing nanomaterials that enhance tumor cell sensitivity to radiation.[117] Recent advances focus on combining RT with nanoparticles designed to induce ferroptosis, a form of iron-dependent cell death driven by lipid peroxidation, creating synergistic anti-tumor effects through amplified oxidative damage and metabolic disruption.[118] Another critical approach involves targeting radioresistance genes to enhance ferroptosis sensitivity. Wang *et al.* developed Au/FeNDs to enhance cervical cancer radiotherapy.[119] This platform functions through generating ROS *via* the Fenton reaction for chemodynamic therapy (CDT), depositing more X-ray energy to increase DNA damage, and inducing G2/M phase cell cycle arrest to radiosensitize cells. Additionally, Au/FeNDs provide excellent CT imaging for precise tumor targeting. *In vivo*, Au/FeNDs combined with RT significantly suppressed tumor growth without obvious toxicity, demonstrating good biocompatibility and efficacy.[120]

The combination of ferroptosis induction and RT provides a powerful strategy to overcome radiation resistance by synergistically amplifying tumor cell oxidative damage and metabolic imbalance.[121,122] Preclinical evidence, as demonstrated by the nanoparticle studies above, indicates that this combined strategy can simultaneously inhibit primary tumor progression and metastasis. By integrating mechanisms like gene regulation, metabolic intervention, and oxidative stress amplification, this approach lays the foundation for developing a new generation of highly effective radiotherapy sensitization regimens.[123]

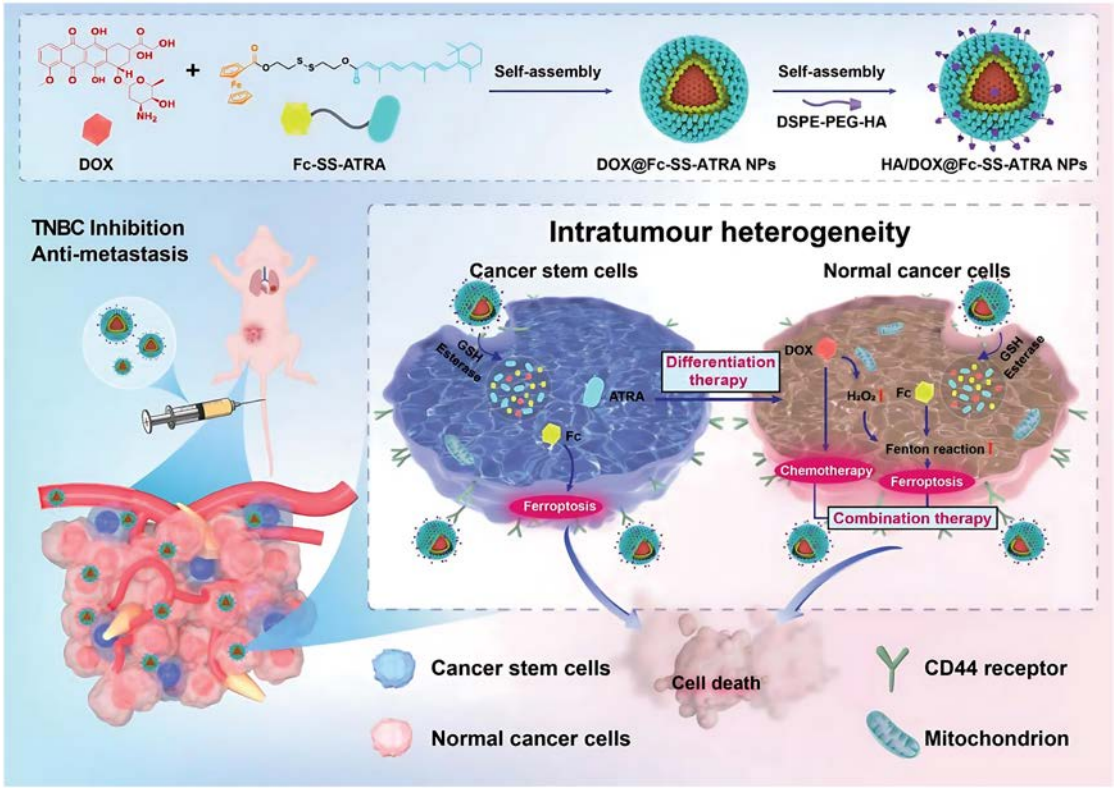

Fig. 5 Mechanism of HA/DOX@Fc-SS-ATRA NP-mediated ferroptosis–chemotherapy co-therapy in triple-negative breast cancer models (reproduced from ref. 86 with permission from Wiley, copyright (2023)).

4.3 Photothermal/photodynamic-ferroptosis combination therapy

Photothermal therapy (PTT) and photodynamic therapy (PDT) exert anti-tumor effects through localized heat generation and reactive oxygen species (ROS) production.[124,125] Recent advances integrate these modalities with ferroptosis—an iron-dependent cell death pathway driven by lipid peroxidation and glutathione peroxidase 4 (GPX4) failure.[126] Nanoplatforms enabling this synergy demonstrate enhanced efficacy through multiple mechanisms. A critical advantage is precise tumor targeting, minimizing off-target effects. This is exemplified by Cai *et al.*'s IR783-Fe@MnO_2-HA nanoplatform, where Fe^{3+} coordination enables tumor-specific ferroptosis induction.[79] The IR783-Fe@MnO_2-HA nanosystem integrates photothermal therapy (PTT) and ferroptosis to enhance anti-tumor efficacy. The schematic (Fig. 7A) illustrates how the nanosystem enhances photodynamic therapy (PDT) and ferroptosis through the generation of ROS and depletion of GSH. Confocal microscopy images (Fig. 7B) show ROS production in 4T1 cells treated with IR783-Fe@MnO_2-HA NPs, indicated by green fluorescence. Western blot analysis (Fig. 7C) reveals decreased GPX4 protein expression following treatment, indicating ferroptosis induction. Immunohistochemical staining of Ki-67, TUNEL, and GPX4 in 4T1 tumors shows significant changes across different treatment groups, with notable cell death and GPX4 downregulation in the IR783-Fe@MnO_2-HA group (Fig. 7D–F). Further integration of diagnostic capabilities is demonstrated in Wei *et al.*'s Janus Au-Fe_3O_4 nanoparticles (GION@RGD), which amplify tumor-specific Fenton reactions under NIR laser exposure.[76] To address limited tumor penetration, Ma *et al.* developed deep-penetrating MAR nano-photosensitizers that generate synergistic PTT/PDT effects under irradiation, inducing ROS production, arachidonic acid peroxidation, and ferroptosis.

Importantly, photosensitizer-induced massive ferroptotic death leverages a fundamental propagation mechanism, revealed in recent studies, whereby ferroptosis propagates *via* trigger waves.[127] While wave-like spread was previously observed, definitive confirmation required spatiotemporal quantification. Using retinal pigment epithelial (RPE) cells—known for light sensitivity and ferroptosis involvement in retinal degeneration—researchers established that ferroptotic waves maintain constant speed across millimeter distances, characteristic of trigger waves rather than diffusion-limited spread. Crucially, blue-light irradiation (432 nm) enabled precise spatiotemporal control of ferroptosis initiation in erastin-treated RPE cells by generating exogenous ROS, analogous to adding H_2O_2. This light-induced death was confirmed as ferroptosis-specific through inhibitor studies. This photosensitization strategy provides controlled, large-scale ferropto-

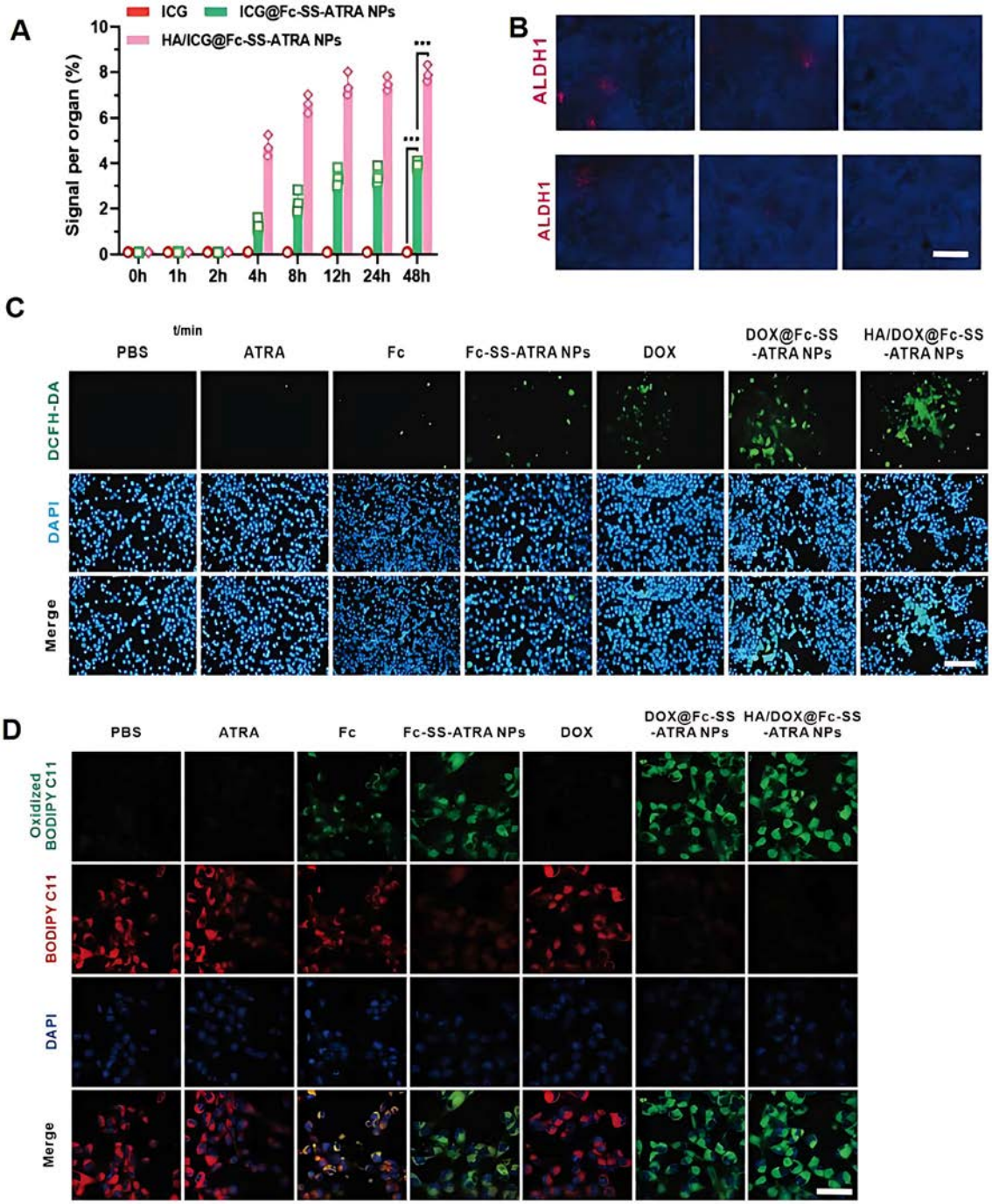

Fig. 6 Evaluation of the antitumor efficacy and mechanisms of HA/DOX@Fc-SS-ATRA NPs *in vitro* and *in vivo*. (A) Quantification of the average fluorescence intensity in tumors over time after intravenous injection of ICG-loaded formulations (n = 3). (B) ALDH1 staining of the tumor tissues from G1-6 groups after different treatments. Scale bar: 100 μm. (C) The ˙OH production of nano-prodrug with different formulations in 4T1 cells was measured by ROS Assay Kit (Green fluorescence: DCFH-DA, ROS indicator; Blue fluorescence: DAPI, nuclei). Scale bar: 200 μm. (D) CLSM images of 4T1 cells after treating with different formulations were co-stained with C11-BODIPY (Green: oxidized BOD-IPY C11; Red: lipid ROS) and DAPI (Blue: nuclei). Scale bar: 50 μm.

sis induction essential for therapeutic efficacy. These findings demonstrate that phototherapy not only initiates ferroptosis locally but also harnesses its self-propagating trigger wave nature, enabling amplified tumor eradication through precisely controlled photosensitizer activation.[128–130]

Photothermal (PTT) and photodynamic therapy (PDT) exert anti-tumor effects through localized heat generation and ROS production.[124,125] Recent advances integrate these modalities with ferroptosis, which is an iron-dependent cell death pathway driven by lipid peroxidation and antioxidant system

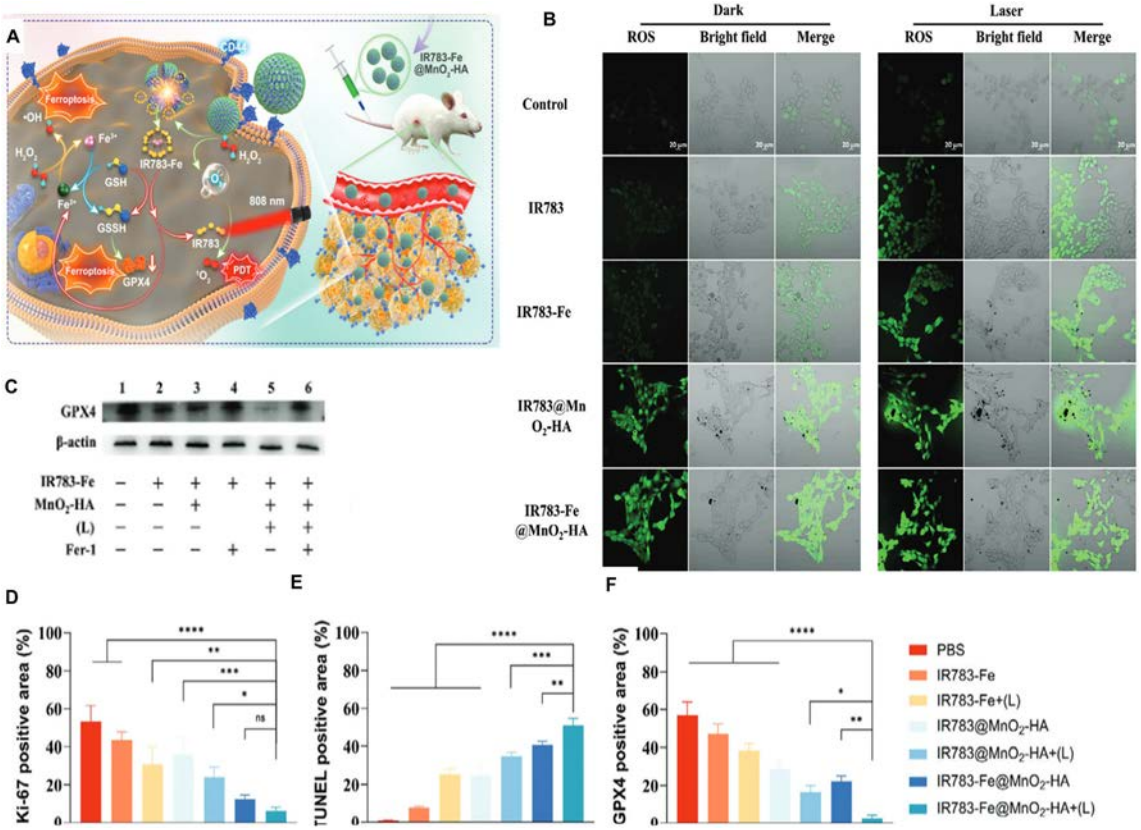

Fig. 7 IR783-Fe@MnO_2-HA nanosystems induce ferroptosis in combination with photothermal therapy to fight tumor. (A) Schematic illustration of the process of enhancing photodynamic therapy (PDT) and ferroptosis. (B) Ability of IR783-Fe@MnO_2-HA NPs to produce reactive oxygen species (ROS) in 4T1 cells. Scale bar: 20 μm. (C) Protein expression results of GPX4 after different treatments. (D–F) Positive area percentages of Ki-67, TUNEL, and GPX4 immunohistochemistry in 4T1 tumors across different treatment groups (n = 3, ****p < 0.0001, ***p < 0.001, **p < 0.01, and *p < 0.05) (reproduced from ref. 79 with permission from Wiley, copyright (2024)).

failure.[126] Nanoplatforms enabling this synergy demonstrate enhanced therapeutic efficacy through several mechanisms.

4.4 Immuno-ferroptosis combination therapy

Recent advancements focus on multifunctional nanoplatforms that combine ferroptosis induction with other therapies and immune activation.[131–133] Chen *et al.* introduced a novel nanoplatform demonstrating synergy between ferroptosis induction and various treatment modalities, including chemotherapy, gas therapy, sonodynamic therapy (SDT), photodynamic therapy (PDT), and photothermal therapy (PTT).[134] These platforms not only improve therapeutic efficacy but also amplify the anti-tumor immune response through immunogenic cell death (ICD).

A particularly promising application is in treating aggressive triple-negative breast cancer (TNBC), where conventional therapies often fail.[135] Shetake *et al.* developed a specific nano cell TNBC attack of T-LMD for three-negative breast cancer (TNBC).[108] Li *et al.*'s mechanistic study using PGNPs@Fe nanoparticles significantly advanced the understanding of ferroptosis–immune crosstalk,[103] revealing a self-reinforcing feedback loop between ferroptosis induction and immune activation. This reciprocal relationship initiates when PGNPs@Fe elevates intracellular ROS levels as the upstream trigger, driving massive lipid peroxidation (LPO) accumulation—core biochemical hallmarks of ferroptosis.

These studies indicate that multifunctional nano-delivery systems are transforming cancer immunotherapy.[136,137] At their heart is the accurate induction of ferroptosis. This process is marked by ROS accumulation, a surge in LPO, and damage to mitochondria.[138] Meanwhile, the activated immune pathways boost the ferroptosis effect. This self-reinforcing cycle greatly strengthens the cytotoxicity of tumor cells in multimodal therapy.[139] It curbs their proliferation, encourages apoptosis and necrosis, and cuts down on systemic toxicity. This offers a powerful way to get over resistance and achieve effective, low-toxicity anti-tumor treatment.[140]

4.5 Sonodynamic-ferroptosis combination therapy

The strategy of combining nanomaterials with sonodynamic therapy (SDT) to induce ferroptosis has demonstrated significant potential in cancer treatment, offering a novel approach for deep-seated tumors.[71,141,142] The molecular synergy between SDT and ferroptosis stems from their shared dependence on ROS generation and ability to disrupt cellular antioxidant systems. SDT provides the spatial control and tissue

penetration, while ferroptosis induction ensures sustained cytotoxic effects through iron-mediated lipid peroxidation cascades. This combination is particularly effective because ultrasound can simultaneously activate sonosensitizers and enhance iron-mediated Fenton reactions in the TME.[72] Zhou *et al.* developed a liposomal nano-DDS based on the sonosensitizer PpIX, co-encapsulating the clinically approved iron supplement ferumoxytol.[143] This system induced both ferroptosis and apoptosis *via* SDT-mediated oxidative ferrotherapy, achieving substantial tumor suppression. Furthermore, SDT modulates key ferroptosis checkpoints, enhancing tumor cell sensitivity and promoting synergistic anti-tumor effects.[144,145]

Wang *et al.* developed the dual-programmable semiconductor polymer nano-ProTAC (SPNFeP) using nano-precipitation.[72] This platform integrates semiconductor polymers, ferroptosis inducers, and novel PROTAC molecules to enable spatiotemporally controlled therapy. Under ultrasound activation, semiconductor polymers generate ROS while ferroptosis inducers simultaneously produce hydroxyl radicals *via* Fenton reactions. Their synergistic interaction amplifies ROS production, facilitating precise deep-tissue tumor targeting. Experimental evidence confirmed significantly enhanced ROS fluorescence in SPNFeP + US-treated cells, demonstrating cooperative ferroptosis–sonodynamic therapy (SDT) tumor killing. As GPX4 critically suppresses ferroptosis, its significant downregulation in the SPNFeP + US group (Fig. 8A) definitively established ferroptosis induction. This mechanistic synergy translated to potent *in vivo* efficacy, with SPNFeP + US treatment substantially reducing or eliminating both primary and distal tumors (Fig. 8B and C). Fluorescence imaging corroborated efficient ultrasound-triggered ROS generation (Fig. 8D), driving the ferroptosis–SDT synergy. Beyond direct cytotoxicity, enhanced calreticulin (CRT) exposure (Fig. 8E) and coordinated CRT/HMGB1 release (Fig. 8F and G) demonstrated immunogenic cell death (ICD) induction. These damage-

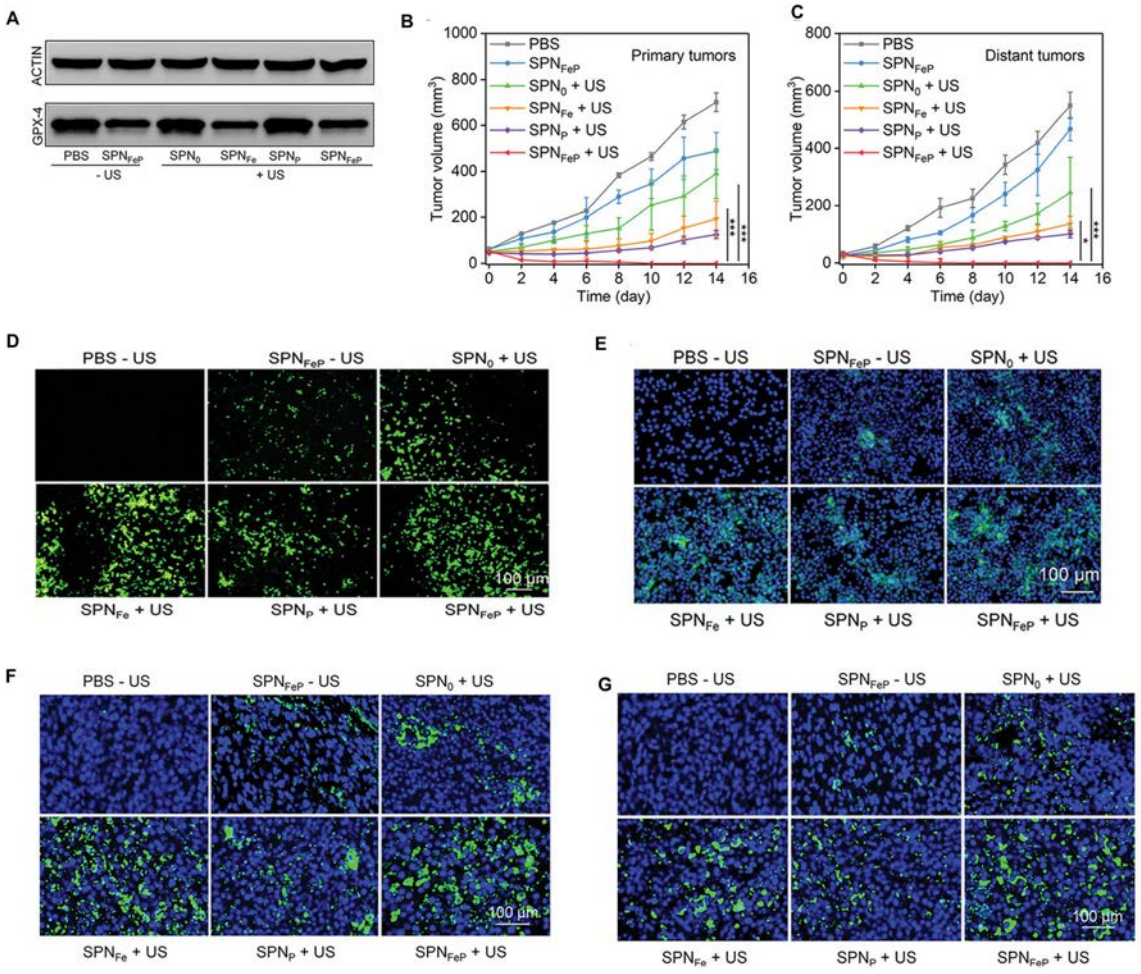

Fig. 8 Sonodynamic-ferroptosis combined with immunotherapy for deep tumors of SPNFeP. (A) The expression of GPX-4 in various treated CT26 cells. (B) Tumor volumes of primary tumors in mice (n = 5). (C) Tumor volumes of distant tumors in mice (n = 5). (D) ROS fluorescence images of SPN0-, SPNFe-, SPNP- and SPNFeP-treated cells in the presence of H_2O_2 (100 μM) without or with US irradiation. (E) CRT immunofluorescence staining images of various treated CT26 cells. (F) CRT fluorescence staining images for primary tumors. (G) HMGB1 fluorescence staining images for primary tumor (reproduced from ref. 72 with permission from Wiley, copyright (2024)).

associated molecular patterns collectively signify anti-tumor immune activation. SPNFeP therefore exemplifies a sonodynamic-ferroptosis strategy that achieves deep-tissue immunotherapy through dual-pathway eradication—direct tumor cytotoxicity converging with systemic immune engagement.

Collectively, the integration of ferroptosis induction with diverse therapeutic modalities within multifunctional nanoplatforms significantly amplifies anti-tumor efficacy.[146–148] Nanoparticles serve as ideal carriers that enable spatiotemporal control over ferroptosis inducers, enhance ROS generation through catalytic reactions, and precisely disrupt key ferroptosis defenses.[149] Critically, this combination approach transforms ferroptosis from a localized cell death mechanism into a potent immunomodulatory event.[76,150,151] By promoting immunogenic cell death (ICD) and releasing DAMPs, nanomaterial-mediated combination therapies reprogram the TME, enhancing antigen presentation and establishing a self-reinforcing cycle of ferroptotic cell death and systemic anti-tumor immunity.[87] This synergy not only overcomes the limitations of monotherapies but also provides a robust strategy for targeting resistant tumors and inhibiting metastasis.[152]

5. Conclusion and prospects

Nanomaterial-mediated ferroptosis has emerged as a highly promising strategy in cancer therapy. This review elucidates the molecular mechanisms of ferroptosis, including iron metabolism disorders, PUFA peroxidation, and the failure of the GPX4/GSH antioxidant system. It also categorizes and evaluates the design principles of iron-based and non-iron-based nanomaterials. Moreover, multifunctional nanoplatforms combining traditional therapies with ferroptosis show synergy.

Despite the promising advances, it is crucial to critically acknowledge the inherent limitations of current nanomaterial-based ferroptosis strategies before their successful clinical translation. Off-target effects remain a significant concern, as non-specific accumulation of nanomaterials in healthy tissues can induce ferroptosis in normal cells, leading to systemic toxicity. While targeting ligands and the EPR effect improve tumor selectivity, their efficiency varies greatly between individuals and tumor types. The immune responses triggered by nanomaterials also warrant careful consideration; while some nanomaterials can beneficially stimulate anti-tumor immunity, others may elicit unintended inflammatory reactions or complement activation, potentially leading to adverse effects and altered biodistribution. Furthermore, scalability and manufacturing present substantial hurdles, as the reproducible and cost-effective synthesis of complex, multi-functional nanoplatforms with stringent quality control for clinical use is notoriously challenging. Finally, the long-term toxicity and fate of these materials in the body are not yet fully understood. The potential for organ accumulation, particularly of non-biodegradable or slowly cleared components, raises concerns about chronic inflammation and fibrosis. A comprehensive evaluation of the pharmacokinetics, biodegradation pathways, and chronic safety profiles is therefore indispensable for the future development of clinically viable ferroptosis nanotherapeutics.

While significant progress has been made in the field of nanomaterial-mediated ferroptosis, several challenges remain to be addressed. Future research should focus on in-depth mechanistic studies, such as elucidating how the TME (*e.g.*, hypoxia and acidic pH) affects the efficiency of ferroptosis induction by nanomaterials, and investigating the crosstalk mechanisms between ferroptosis and other forms of cell death, including apoptosis and pyroptosis. In terms of material design, it is necessary to develop intelligent and responsive nanocarriers that can accurately control the release of inducers. Optimizing the metabolic pathways of these materials is crucial to balance effective ferroptosis with long-term biological safety and prevent systemic iron overload. To advance clinical translation, establishing standardized biomarker detection systems for ferroptosis and exploring patient stratification strategies to identify tumor subtypes with high sensitivity to ferroptosis are essential steps. Furthermore, conducting clinical trials to validate the efficacy of nanomaterial-induced ferroptosis against metastatic and drug-resistant tumors is necessary. In the context of combination therapies, efforts should be directed toward integrating ferroptosis with emerging immunotherapies like CAR-T and oncolytic viruses to establish a "ferroptosis-immunity positive feedback loop".

In conclusion, ferroptosis induced by nanomaterials represents a transformation to overcome the bottleneck of traditional treatment. Through cross-disciplinary innovation, this strategy has the potential to drive the development of the next generation of precise, effective and low-toxicity cancer treatment regimens into clinical practice.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

References

1 H. Yusuf and A. Kumar, The current state and future direction of childcare for cancer patients: a narrative review, *Support. Care Cancer*, 2025, **33**, 129.
2 S. J. Dixon, K. M. Lemberg, M. R. Lamprecht, R. Skouta, E. M. Zaitsev, C. E. Gleason, *et al.*, Ferroptosis: an iron-dependent form of nonapoptotic cell death, *Cell*, 2012, **149**, 1060–1072.
3 B. P. Streck, J. B. Vo, C. Brandt, W. M. P. Klein, P. Han, R. A. Ferrer, *et al.*, Understanding Cancer Treatment Decision Making Among Cancer Survivors: Weighing

Cancer Recurrence Versus Cardiotoxicity, *Psycho-Oncol.*, 2025, **34**, e70061.
4 W. G. Yun, Y. S. Chae, Y. Han, H. S. Jung, Y. J. Cho, H. C. Kang, *et al.*, Efficacy of Neoadjuvant Radiotherapy After Chemotherapy and the Optimal Interval from Radiotherapy to Surgery for Borderline Resectable and Resectable Pancreatic Cancer, *Ann. Surg. Oncol.*, 2025, **32**, 2819–2829.
5 M. Rast, A. Tehrani-Banihashemi, P. Fadavi, M. Nojomi, D. Hatami, K. Ansari, *et al.*, Delays in chemotherapy and radiotherapy of breast cancer during COVID-19 pandemic, *J. Infect. Public Health*, 2025, **18**, 102657.
6 V. Bhat, S. Pellizzari, A. L. Allan, E. Wong, M. Lock, M. Brackstone, *et al.*, Radiotherapy and radiosensitization in breast cancer: Molecular targets and clinical applications, *Crit. Rev. Oncol. Hematol.*, 2022, **169**, 103566.
7 N. Buaron, A. Mangraviti, Y. Wang, A. Liu, M. Pedone, E. Sankey, *et al.*, Ultrasound inhibits tumor growth and selectively eliminates malignant brain tumor in vivo, *Bioeng. Transl. Med.*, 2024, **9**, e10660.
8 X. Li, J. Dai, Y. Shi, J. Chen, F. Zhou, X. Qian, *et al.*, Bispecific Aptamer-Drug Conjugates Selectively Eliminate Malignant Hematologic Cells for Treating Acute Myeloid Leukemia, *Langmuir*, 2025, **41**, 2580–2590.
9 X. Li, W. Li, X. Xie, T. Fang, J. Yang, Y. Shen, *et al.*, ROS Regulate Rotenone-induced SH-SY5Y Dopamine Neuron Death Through Ferroptosis-mediated Autophagy and Apoptosis, *Mol. Neurobiol.*, 2025, **62**, 9271–9289.
10 B. Wang, Y. Wang, J. Zhang, C. Hu, J. Jiang, Y. Li, *et al.*, ROS-induced lipid peroxidation modulates cell death outcome: mechanisms behind apoptosis, autophagy, and ferroptosis, *Arch. Toxicol.*, 2023, **97**, 1439–1451.
11 Q. Yang, W. Zhang, S.-Y. Lu, X. Cai, C. Chen, Q. Zhang, *et al.*, Biodegradable doxorubicin-loaded ferric phosphate nanosheets for specific tumor elimination through autophagy inhibition-enhanced apoptosis/ferroptosis pathway, *Chem. Eng. J.*, 2023, **454**, 140455.
12 T. S. Anthonymuthu, Y. Y. Tyurina, W. Y. Sun, K. Mikulska-Ruminska, I. H. Shrivastava, V. A. Tyurin, *et al.*, Resolving the paradox of ferroptotic cell death: Ferrostatin-1 binds to 15LOX/PEBP1 complex, suppresses generation of peroxidized ETE-PE, and protects against ferroptosis, *Redox Biol.*, 2021, **38**, 101744.
13 L. Sun, M. Zou, L. Du, S. Wang, R. Ding, K. Lu, *et al.*, A mitochondria-targeted far-red AIE fluorescent probe for distinguishing between mitophagy and ferroptosis in cancer cells, *Chem. Commun.*, 2023, **59**, 12735–12738.
14 M. Pourhabib Mamaghani, S. N. Mousavikia and H. Azimian, Ferroptosis in cancer: Mechanisms, therapeutic strategies, and clinical implications, *Pathol., Res. Pract.*, 2025, **269**, 155907.
15 Y. Dai, J. Guo, B. Zhang, J. Chen, H. Ou, R. R. He, *et al.*, Lycium barbarum (Wolfberry) glycopeptide prevents stress-induced anxiety disorders by regulating oxidative stress and ferroptosis in the medial prefrontal cortex, *Phytomedicine*, 2023, **116**, 154864.
16 X. Jiang, Q. Peng, M. Peng, L. Oyang, H. Wang, Q. Liu, *et al.*, Cellular metabolism: A key player in cancer ferroptosis, *Cancer Commun.*, 2024, **44**, 185–204.
17 L. Zhao, X. Zhou, F. Xie, L. Zhang, H. Yan, J. Huang, *et al.*, Ferroptosis in cancer and cancer immunotherapy, *Cancer Commun.*, 2022, **42**, 88–116.
18 X. Luo, H. B. Gong, Z. C. Li, D. D. Li, Z. X. Li, J. Sun, *et al.*, Phospholipid peroxidation in macrophage confers tumor resistance by suppressing phagocytic capability towards ferroptotic cells, *Cell Death Differ.*, 2024, **31**, 1184–1201.
19 C. Liang, X. Zhang, M. Yang and X. Dong, Recent Progress in Ferroptosis Inducers for Cancer Therapy, *Adv. Mater.*, 2019, **31**, e1904197.
20 S. Farzipour, F. J. Zefrei, S. Bahadorikhalili, M. Alvandi, A. Salari and Z. Shaghaghi, Nanotechnology Utilizing Ferroptosis Inducers in Cancer Treatment, *Anticancer Agents Med. Chem.*, 2024, **24**, 571–589.
21 H. Kumada, M. Itoh and S. Tohda, Effect of Ferroptosis Inducers and Inhibitors on Cell Proliferation in Acute Leukemia, *Anticancer Res.*, 2024, **44**, 1003–1010.
22 X. Tang, Y. Niu, J. Jian, Y. Guo, Y. Wang, Y. Zhu, *et al.*, Potential applications of ferroptosis inducers and regulatory molecules in hematological malignancy therapy, *Crit. Rev. Oncol. Hematol.*, 2024, **193**, 104203.
23 S. Jin, H. Wang, Z. Zhang and M. Yan, Targeting Ferroptosis: Small-molecule Inducers as Novel Anticancer Agents, *Anticancer Agents Med. Chem.*, 2025, **25**, 517–532.
24 Y. Luo, X. Y. Bai, L. Zhang, Q. Q. Hu, N. Zhang, J. Z. Cheng, *et al.*, Ferroptosis in Cancer Therapy: Mechanisms, Small Molecule Inducers, and Novel Approaches, *Drug Des., Dev. Ther.*, 2024, **18**, 2485–2529.
25 N. Meher, A. P. Bidkar, A. Wadhwa, K. N. Bobba, S. Dhrona, C. Dasari, *et al.*, PET Imaging Using 89Zr-Labeled StarPEG Nanocarriers Reveals Heterogeneous Enhanced Permeability and Retention in Prostate Cancer, *Mol. Cancer Ther.*, 2025, **24**, 141–151.
26 S. Shekhar, M. Chauhan, Sonali, B. Yadav, R. Dutt, L. Hu, *et al.*, Enhanced permeability and retention effect-focused tumor-targeted nanomedicines: latest trends, obstacles and future perspective, *Nanomedicine*, 2022, **17**, 1213–1216.
27 Y. Kang and S. Li, Nanomaterials: Breaking through the bottleneck of tumor immunotherapy, *Int. J. Biol. Macromol.*, 2023, **230**, 123159.
28 M. Li, N. Li, H. Piao, S. Jin, H. Wei, Q. Liu, *et al.*, Nanomaterials for targeted drug delivery for immunotherapy of digestive tract tumors, *Front. Immunol.*, 2025, **16**, 1562766.
29 S. Zhang, J. Zhang, X. Fan, H. Liu, M. Zhu, M. Yang, *et al.*, Ionizing Radiation-Induced Ferroptosis Based on Nanomaterials, *Int. J. Nanomed.*, 2022, **17**, 3497–3507.
30 Q. Liu, Y. Zhao, H. Zhou and C. Chen, Ferroptosis: challenges and opportunities for nanomaterials in cancer therapy, *Regener. Biomater.*, 2023, **10**, rbad004.
31 N. Xiao, S. Xiong, Z. Zhou, M. Zhong, H. Bai, Q. Li, *et al.*, Recent progress in biomaterials-driven ferroptosis for cancer therapy, *Biomater. Sci.*, 2024, **12**, 288–307.

32 H. Zheng, J. Jiang, S. Xu, W. Liu, Q. Xie, X. Cai, *et al.*, Nanoparticle-induced ferroptosis: detection methods, mechanisms and applications, *Nanoscale*, 2021, **13**, 2266–2285.
33 H. Wang, Y. Cheng, C. Mao, S. Liu, D. Xiao, J. Huang, *et al.*, Emerging mechanisms and targeted therapy of ferroptosis in cancer, *Mol. Ther.*, 2021, **29**, 2185–2208.
34 X. Liu, Y. Zhang, X. Wu, F. Xu, H. Ma, M. Wu, *et al.*, Targeting Ferroptosis Pathway to Combat Therapy Resistance and Metastasis of Cancer, *Front. Pharmacol.*, 2022, **13**, 909821.
35 M. Liu, X. Y. Kong, Y. Yao, X. A. Wang, W. Yang, H. Wu, *et al.*, The critical role and molecular mechanisms of ferroptosis in antioxidant systems: a narrative review, *Ann. Transl. Med.*, 2022, **10**, 368.
36 L. Lai, M. Tan, M. Hu, X. Yue, L. Tao, Y. Zhai, *et al.*, Important molecular mechanisms in ferroptosis, *Mol. Cell. Biochem.*, 2025, **480**, 639–658.
37 J. Zhu, Y. Xiong, Y. Zhang, J. Wen, N. Cai, K. Cheng, *et al.*, The Molecular Mechanisms of Regulating Oxidative Stress-Induced Ferroptosis and Therapeutic Strategy in Tumors, *Oxid. Med. Cell. Longevity*, 2020, **2020**, 8810785.
38 Y. Wang, Z. Wei, K. Pan, J. Li and Q. Chen, The function and mechanism of ferroptosis in cancer, *Apoptosis*, 2020, **25**, 786–798.
39 F. Wang, J. He, R. Xing, T. Sha and B. Sun, Molecular mechanisms of ferroptosis and their role in inflammation, *Int. Rev. Immunol.*, 2023, **42**, 71–81.
40 Y. Saimoto, D. Kusakabe, K. Morimoto, Y. Matsuoka, E. Kozakura, N. Kato, *et al.*, Lysosomal lipid peroxidation contributes to ferroptosis induction via lysosomal membrane permeabilization, *Nat. Commun.*, 2025, **16**, 3554.
41 G. O. Latunde-Dada, Ferroptosis: Role of lipid peroxidation, iron and ferritinophagy, *Biochim. Biophys. Acta, Gen. Subj.*, 2017, **1861**, 1893–1900.
42 J. Feng, Z. X. Wang, J. L. Bin, Y. X. Chen, J. Ma, J. H. Deng, *et al.*, Pharmacological approaches for targeting lysosomes to induce ferroptotic cell death in cancer, *Cancer Lett.*, 2024, **587**, 216728.
43 X. Zhu, L. Wang, K. Wang, Y. Yao and F. Zhou, Erdafitinib promotes ferroptosis in human uveal melanoma by inducing ferritinophagy and lysosome biogenesis via modulating the FGFR1/mTORC1/TFEB signaling axis, *Free Radicals Biol. Med.*, 2024, **222**, 552–568.
44 L. Huang, J. Feng, J. Zhu, J. Yang, W. Xiong, X. Lu, *et al.*, A Strategy of Fenton Reaction Cycloacceleration for High-Performance Ferroptosis Therapy Initiated by Tumor Microenvironment Remodeling, *Adv. Healthc. Mater.*, 2023, **12**, e2203362.
45 Z. Shen, T. Liu, Y. Li, J. Lau, Z. Yang, W. Fan, *et al.*, Fenton-Reaction-Acceleratable Magnetic Nanoparticles for Ferroptosis Therapy of Orthotopic Brain Tumors, *ACS Nano*, 2018, **12**, 11355–11365.
46 Y. Chen, X. Guo, Y. Zeng, X. Mo, S. Hong, H. He, *et al.*, Oxidative stress induces mitochondrial iron overload and ferroptotic cell death, *Sci. Rep.*, 2023, **13**, 15515.
47 X. Yang, C. Gu, J. Cai, F. Li, X. He, L. Luo, *et al.*, Excessive SOX8 reprograms energy and iron metabolism to prime hepatocellular carcinoma for ferroptosis, *Redox Biol.*, 2024, **69**, 103002.
48 A. Suda, B. A. Umaru, Y. Yamamoto, H. Shima, Y. Saiki, Y. Pan, *et al.*, Polyunsaturated fatty acids-induced ferroptosis suppresses pancreatic cancer growth, *Sci. Rep.*, 2024, **14**, 4409.
49 F. Rizzollo, S. More, P. Vangheluwe and P. Agostinis, The lysosome as a master regulator of iron metabolism, *Trends Biochem. Sci.*, 2021, **46**, 960–975.
50 E. Dierge, E. Debock, C. Guilbaud, C. Corbet, E. Mignolet, L. Mignard, *et al.*, Peroxidation of n-3 and n-6 polyunsaturated fatty acids in the acidic tumor environment leads to ferroptosis-mediated anticancer effects, *Cell Metab.*, 2021, **33**, 1701–1715.
51 D. Yan, Y. Hou, X. Lei, H. Xiao, Z. Zeng, W. Xiong, *et al.*, The Impact of Polyunsaturated Fatty Acids in Cancer and Therapeutic Strategies, *Curr. Nutr. Rep.*, 2025, **14**, 46.
52 J. Y. Lee, M. Nam, H. Y. Son, K. Hyun, S. Y. Jang, J. W. Kim, *et al.*, Polyunsaturated fatty acid biosynthesis pathway determines ferroptosis sensitivity in gastric cancer, *Proc. Natl. Acad. Sci. U. S. A.*, 2020, **117**, 32433–32442.
53 C. Panaroni, K. Fulzele, R. Soucy, C. Huang, K. Mukaihara, S. Chattopadhyay, *et al.*, Polyunsaturated Fatty Acid (PUFA) Signaling Induces Ferroptosis-Mediated Cell-Death in Multiple Myeloma, *Blood*, 2019, **134**, 3108–3108.
54 W. S. Yang, K. J. Kim, M. M. Gaschler, M. Patel, M. S. Shchepinov and B. R. Stockwell, Peroxidation of polyunsaturated fatty acids by lipoxygenases drives ferroptosis, *Proc. Natl. Acad. Sci. U. S. A.*, 2016, **113**, E4966–E4975.
55 Y. A. Moon, Emerging roles of polyunsaturated fatty acid synthesis pathway in colorectal cancer, *Anim. Cells Syst.*, 2023, **27**, 61–71.
56 R. Turchi, F. Tortolici, M. Benvenuto, C. Punziano, A. De Luca, S. Rufini, *et al.*, Low Sulfur Amino Acid, High Polyunsaturated Fatty Acid Diet Inhibits Breast Cancer Growth, *Int. J. Mol. Sci.*, 2022, **24**, 249.
57 Y. Yang, T. Zhu, X. Wang, F. Xiong, Z. Hu, X. Qiao, *et al.*, ACSL3 and ACSL4, Distinct Roles in Ferroptosis and Cancers, *Cancers*, 2022, **14**, 5896.
58 T. Chen, R. Shi, Q. Suo, S. Wu, C. Liu, S. Huang, *et al.*, Progranulin released from microglial lysosomes reduces neuronal ferroptosis after cerebral ischemia in mice, *J. Cereb. Blood Flow Metab.*, 2023, **43**, 505–517.
59 Y. Liu, Y. Wan, Y. Jiang, L. Zhang and W. Cheng, GPX4: The hub of lipid oxidation, ferroptosis, disease and treatment, *Biochim. Biophys. Acta, Rev. Cancer*, 2023, **1878**, 188890.
60 J. Liu, G. Yang and H. Zhang, Glyphosate-triggered hepatocyte ferroptosis via suppressing Nrf2/GSH/GPX4 axis exacerbates hepatotoxicity, *Sci. Total Environ.*, 2023, **862**, 160839.
61 P. Wang, Y. Liu, L. Tao, D. Cheng, L. He and S. Li, Monitoring cysteine changes and assessing ferroptosis in

diabetic mice with a lysosome-targeted near-infrared fluorescence probe, *Sens. Actuators, B*, 2024, **421**, 136549.

62 B. Daher, M. Vucetic and J. Pouyssegur, Cysteine Depletion, a Key Action to Challenge Cancer Cells to Ferroptotic Cell Death, *Front. Oncol.*, 2020, **10**, 723.

63 Y. Xing, J. Li, L. Wang, Z. Zhu, J. Yan, Y. Liu, Q. Liu, *et al.*, A Bifunctional Lysosome-Targeting Chimera Nanoplatform for Tumor-Selective Protein Degradation and Enhanced Cancer Immunotherapy, *Adv. Mater.*, 2025, **37**, e2417942.

64 J. Liu, Y. Yan, Y. Zhang, X. Pan, H. Xia, J. Zhou, *et al.*, Lysosome-Mitochondria Cascade Targeting Nanoparticle Drives Robust Pyroptosis for Cancer Immunotherapy, *J. Am. Chem. Soc.*, 2024, **146**, 34568–34582.

65 Q. Wang, X. Yang, R. Yuan, A. Shen, P. Wang, H. Li, *et al.*, A co-assembly platform engaging macrophage scavenger receptor A for lysosome-targeting protein degradation, *Nat. Commun.*, 2024, **15**, 1663.

66 J. Li, R. Feng, W. Yang, P. Liang, T. Qiu, J. Zhang, *et al.*, Lysosomal iron accumulation and subsequent lysosomes-mitochondria iron transmission mediate PFOS-induced hepatocyte ferroptosis, *Ecotoxicol. Environ. Saf.*, 2024, **284**, 116890.

67 L. Zhong, D. Fu, J. Xu, L. Tan, H. Wu and M. Wang, Rational design of a lysosome-targeted fluorescent probe for monitoring the generation of hydroxyl radicals in ferroptosis pathways, *RSC Adv.*, 2024, **14**, 12864–12872.

68 B. I. Kharisov, H. V. Rasika Dias, O. V. Kharissova, V. M. Jiménez-Pérez, B. Olvera Pérez and B. Muñoz Flores, Iron-containing nanomaterials: synthesis, properties, and environmental applications, *RSC Adv.*, 2012, **2**, 9325.

69 R. Fu, Z. Ma, H. Zhao, H. Jin, Y. Tang, T. He, *et al.*, Research Progress in Iron-Based Nanozymes: Catalytic Mechanisms, Classification, and Biomedical Applications, *Anal. Chem.*, 2023, **95**, 10844–10858.

70 X. Wu and H. Zhang, Therapeutic strategies of iron-based nanomaterials for cancer therapy, *Biomed. Mater.*, 2021, **16**, 032003.

71 L. Zhou, C. Dong, L. Ding, W. Feng, L. Yu, X. Cui, *et al.*, Targeting ferroptosis synergistically sensitizes apoptotic sonodynamic anti-tumor nanotherapy, *Nano Today*, 2021, **39**, 101212.

72 F. Wang, G. Dong, M. Ding, N. Yu, C. Sheng and J. Li, Dual-Programmable Semiconducting Polymer NanoPROTACs for Deep-Tissue Sonodynamic-Ferroptosis Activatable Immunotherapy, *Small*, 2024, **20**, e2306378.

73 G. Chen, Y. Yang, Q. Xu, M. Ling, H. Lin, W. Ma, *et al.*, Self-Amplification of Tumor Oxidative Stress with Degradable Metallic Complexes for Synergistic Cascade Tumor Therapy, *Nano Lett.*, 2020, **20**, 8141–8150.

74 W. Xu, G. Guan, R. Yue, Z. Dong, L. Lei, H. Kang, *et al.*, Chemical Design of Magnetic Nanomaterials for Imaging and Ferroptosis-Based Cancer Therapy, *Chem. Rev.*, 2025, **125**, 1897–1961.

75 X. Yao, P. Yang, Z. Jin, Q. Jiang, R. Guo, R. Xie, *et al.*, Multifunctional nanoplatform for photoacoustic imaging-guided combined therapy enhanced by CO induced ferroptosis, *Biomaterials*, 2019, **197**, 268–283.

76 R. Wei, G. Fu, Z. Li, Y. Liu, L. Qi, K. Liu, *et al.*, Au-Fe(3)O(4) Janus nanoparticles for imaging-guided near infrared-enhanced ferroptosis therapy in triple negative breast cancer, *J. Colloid Interface Sci.*, 2024, **663**, 644–655.

77 H. Li, Y. Dou, H. Yang, H. Xing, C. Zhu, T. Wang, *et al.*, Ce6-modified Fe ions-doped carbon dots as multifunctional nanoplatform for ferroptosis and photodynamic synergistic therapy of melanoma, *J. Nanobiotechnol.*, 2024, **22**, 100.

78 H. Xiong, C. Wang, Z. Wang, H. Lu and J. Yao, Self-assembled nano-activator constructed ferroptosis-immunotherapy through hijacking endogenous iron to intracellular positive feedback loop, *J. Controlled Release*, 2021, **332**, 539–552.

79 X. Cai, W. Liu, J. Zhang, Z. Li, M. Liu, S. Hu, *et al.*, Study of Iron Complex Photosensitizer with Hollow Double-Shell Nano Structure Used to Enhance Ferroptosis and Photodynamic Therapy, *Small*, 2024, **20**, e2309086.

80 P. Zhao, L. Gong, L. Chang, H. Du, M. Geng, S. Meng, *et al.*, Multifunctional Fe-based coordination polymer nano-bomb modified with beta-lapachone and CaO(2) for targeted tumor dual chemodynamic therapy with enhanced ferroptosis and H(2)O(2) self-supply, *J. Nanobiotechnol.*, 2024, **22**, 3.

81 J. Cheng, Y. Zhu, X. Xing, J. Xiao, H. Chen, H. Zhang, *et al.*, Manganese-deposited iron oxide promotes tumor-responsive ferroptosis that synergizes the apoptosis of cisplatin, *Theranostics*, 2021, **11**, 5418–5429.

82 C. Xue, M. Li, C. Liu, Y. Li, Y. Fei, Y. Hu, *et al.*, NIR-Actuated Remote Activation of Ferroptosis in Target Tumor Cells through a Photothermally Responsive Iron-Chelated Biopolymer Nanoplatform, *Angew. Chem., Int. Ed.*, 2021, **60**, 8938–8947.

83 Q. Jiang, K. Wang, X. Zhang, B. Ouyang, H. Liu, Z. Pang, *et al.*, Platelet Membrane-Camouflaged Magnetic Nanoparticles for Ferroptosis-Enhanced Cancer Immunotherapy, *Small*, 2020, **16**, e2001704.

84 H. Chen, J. Song, Y. Wang, T. Wang, F. Zhang, Y. Lv, *et al.*, "Triple-Hop" nano-bomb combining CDT, PDT and immunetherapy for NIR-triggered cancer therapy, *Chem. Eng. J.*, 2024, **481**, 148268.

85 J. Zhang, J. Yang, T. Zuo, S. Ma, N. Xokrat, Z. Hu, *et al.*, Heparanase-driven sequential released nanoparticles for ferroptosis and tumor microenvironment modulations synergism in breast cancer therapy, *Biomaterials*, 2021, **266**, 120429.

86 C. Wu, F. Zhang, B. Li, Z. Li, X. Xie, Y. Huang, *et al.*, A Self-Assembly Nano-Prodrug for Combination Therapy in Triple-Negative Breast Cancer Stem Cells, *Small*, 2023, **19**, e2301600.

87 Y. Chen, Z. Yao, P. Liu, Q. Hu, Y. Huang, L. Ping, *et al.*, A self-assembly nano-prodrug for triple-negative breast cancer combined treatment by ferroptosis therapy and chemotherapy, *Acta Biomater.*, 2023, **159**, 275–288.

88 X. Zhu, L. Xie, J. Tian, Y. Jiang, E. Song and Y. Song, A multi-mode Rhein-based nano-platform synergizing ferrotherapy/chemotherapy-induced immunotherapy for enhanced tumor therapy, *Acta Biomater.*, 2024, **180**, 383–393.

89 M. Ding, A. Zhu, Y. Zhang, J. Liu, L. Lin, X. Wang, *et al.*, Neutrophil-based Trojan horse containing polymer nano-therapeutics for sono-activatable ferroptosis-immunotherapy of orthotopic glioma, *Nano Today*, 2024, **57**, 102398.

90 X. Tian, L. Ruan, S. Zhou, L. Wu, J. Cao, X. Qi, *et al.*, Appropriate Size of Fe(3)O(4) Nanoparticles for Cancer Therapy by Ferroptosis, *ACS Appl. Bio Mater.*, 2022, **5**, 1692–1699.

91 M. Goyal and B. R. K. Gupta, Study of shape, size and temperature-dependent elastic properties of nanomaterials, *Mod. Phys. Lett. B*, 2019, **33**, 1950310.

92 G. Guisbiers, S. Mejía-Rosales and F. L. Deepak, Nanomaterial Properties: Size and Shape Dependencies, *J. Nanomater.*, 2012, **2012**, 1–2.

93 O. Claudio-Ares, J. Luciano-Rodriguez, Y. L. Del Valle-Gonzalez, S. L. Schiavone-Chamorro, A. J. Pastor, J. O. Rivera-Reyes, *et al.*, Exploring the Use of Intracellular Chelation and Non-Iron Metals to Program Ferroptosis for Anticancer Application, *Inorganics*, 2024, **12**, 26.

94 R. Wei, G. Fu, Z. Li, Y. Liu and M. Xue, Engineering Iron-Based Nanomaterials for Breast Cancer Therapy Associated with Ferroptosis, *Nanomedicine*, 2024, **19**, 537–555.

95 D. Xie, L. Sun, M. Wu and Q. Li, From detection to elimination: iron-based nanomaterials driving tumor imaging and advanced therapies, *Front. Oncol.*, 2025, **15**, 1536779.

96 G. Chen, L. Gu, Y. Liu, J. Du, Q. Qi, Q. Miao, *et al.*, Topology-regulated nanocatalysts for ferroptosis-mediated cancer phototherapy, *J. Colloid Interface Sci.*, 2024, **656**, 320–331.

97 H. Zhao, H. Zhu, Y. Du, M. He, M. Ding and F. Cheng, Gold nanoparticles/Cu decorated metal-organic frameworks for synergistic photodynamic/ferroptosis cancer therapy, *Biomed. Mater.*, 2025, **20**, 025042.

98 S. Zhao, P. Liu and Y. Li, Biomineralized apoferritin nanoparticles delivering dihydroartemisinin and calcium for synergistic breast cancer therapy, *Sci. Rep.*, 2024, **14**, 29402.

99 S. Fu, Y. Li, L. Shen, Y. Chen, J. Lu, Y. Ran, *et al.*, Cu(2)WS(4)-PEG Nanozyme as Multifunctional Sensitizers for Enhancing Immuno-Radiotherapy by Inducing Ferroptosis, *Small*, 2024, **20**, e2309537.

100 J. Zhu, P. Dai, F. Liu, Y. Li, Y. Qin, Q. Yang, *et al.*, Upconverting Nanocarriers Enable Triggered Microtubule Inhibition and Concurrent Ferroptosis Induction for Selective Treatment of Triple-Negative Breast Cancer, *Nano Lett.*, 2020, **20**, 6235–6245.

101 Y. Wang, T. Sun and C. Jiang, Nanodrug delivery systems for ferroptosis-based cancer therapy, *J. Controlled Release*, 2022, **344**, 289–301.

102 X. Tian, Y. Zhang, M. Zhang, G. Liu, Y. Hao and W. Liu, Nanoparticles-encapsulated doxorubicin alleviates drug resistance of osteosarcoma via inducing ferroptosis, *Nanotoxicology*, 2024, **18**, 401–409.

103 Y. Li, X. Li, M. Zhang, X. Weng, J. Yi, Y. Cao, *et al.*, Spatiotemporal orchestration of a ferroptosis-immunotherapy "cycle" via a sequential drug delivery system for antitumor immunity, *Nano Today*, 2024, **59**, 102535.

104 Y. Zhao, T. Qiu, C. Zhuang, D. Li, Z. Wan, H. Zheng, *et al.*, HASc-responsive dual-drug nano-particles for co-delivery of Pt(II) and BAI for combination therapy of tumors, *React. Funct. Polym.*, 2025, **208**, 106165.

105 D. Guo, Q. Lin, N. Liu, Q. Jin, C. Liu, Y. Wang, *et al.*, Copper-based metal-organic framework co-loaded doxorubicin and curcumin for anti-cancer with synergistic apoptosis and ferroptosis therapy, *Int. J. Pharm.*, 2024, **666**, 124744.

106 S. Hong, J. Park, Y. Oh, H. Cho and K. Kim, Nanotechnology-Based Strategies for Safe and Effective Immunotherapy, *Molecules*, 2024, **29**, 5855.

107 X. Yan, Q. Li, S. Xiao, J. Chen and W. Song, Sulfasalazine-loaded nanoframes: A new frontier in bladder cancer therapy through ferroptosis induction, *Colloids Surf., B*, 2025, **246**, 114394.

108 N. G. Shetake, S. K. Das, A. Kumar and B. N. Pandey, Nano-inducer of ferroptosis for targeted chemotherapy of human triple negative breast carcinoma, *Biomater. Adv.*, 2024, **161**, 213868.

109 B. Niu, K. Liao, Y. Zhou, T. Wen, G. Quan, X. Pan, *et al.*, Application of glutathione depletion in cancer therapy: Enhanced ROS-based therapy, ferroptosis, and chemotherapy, *Biomaterials*, 2021, **277**, 121110.

110 H. Yu, H. Zhao, Y. Zhang, Y. Hou, R. Li, T. Liang, *et al.*, A biomimetic nanoreactor for combinational chemo/chemodynamic therapy of choriocarcinoma through synergistic apoptosis and ferroptosis strategy, *Chem. Eng. J.*, 2023, **472**, 144690.

111 J. Zhu, X. Wang, Y. Su, J. Shao, X. Song, W. Wang, *et al.*, Multifunctional nanolocks with GSH as the key for synergistic ferroptosis and anti-chemotherapeutic resistance, *Biomaterials*, 2022, **288**, 121704.

112 Y. Qin, N. Liu, F. Wang, Z. Gao, C. Luo, C. Tian, *et al.*, Self-amplifying ROS-responsive SN38 prodrug nanoparticles for combined chemotherapy and ferroptosis in cancer treatment, *Carbon*, 2025, **235**, 120099.

113 J. Li, Q. Zhang, H. Yang, W. Lu, Y. Fu, Y. Xiong, *et al.*, Sequential dual-locking strategy using photoactivated Pt(IV)-based metallo-nano prodrug for enhanced chemotherapy and photodynamic efficacy by triggering ferroptosis and macrophage polarization, *Acta Pharm. Sin. B*, 2024, **14**, 3251–3265.

114 C. Kapper, P. Oppelt, B. Arbeithuber, A. A. Gyunesh, I. Vilusic, P. Stelzl, *et al.*, Targeting ferroptosis in ovarian cancer: Novel strategies to overcome chemotherapy resistance, *Life Sci.*, 2024, **349**, 122720.

115 J. Zhang, K. Zhou, J. Lin, X. Yao, D. Ju, X. Zeng, *et al.*, Ferroptosis-enhanced chemotherapy for triple-negative breast cancer with magnetic composite nanoparticles, *Biomaterials*, 2023, **303**, 122395.
116 G. Lei, C. Mao, Y. Yan, L. Zhuang and B. Gan, Ferroptosis, radiotherapy, and combination therapeutic strategies, *Protein Cell*, 2021, **12**, 836–857.
117 J. Su, Q. Zhao, Z. Zheng, H. Wang, C. Bian, L. Meng, *et al.*, Prospective Application of Ferroptosis in Hypoxic Cells for Tumor Radiotherapy, *Antioxidants*, 2022, **11**, 921.
118 G. L. Beretta and N. Zaffaroni, Radiotherapy-induced ferroptosis for cancer treatment, *Front. Mol. Biosci.*, 2023, **10**, 1216733.
119 D. Wang, Z. Wang, X. Ren, Y. Li, Y. Zhang, H. Liang, *et al.*, A multifunctional bimetallic nanoplatform for enhancing radiotherapy via oxidative damage and ferroptosis of cervical cancer, *Sep. Purif. Technol.*, 2024, **338**, 126567.
120 Y. Lin, X. Chen, C. Yu, G. Xu, X. Nie, Y. Cheng, *et al.*, Radiotherapy-mediated redox homeostasis-controllable nanomedicine for enhanced ferroptosis sensitivity in tumor therapy, *Acta Biomater.*, 2023, **159**, 300–311.
121 Y. Xie, Y. Xiao, Y. Liu, X. Lu, Z. Wang, S. Sun, *et al.*, Construction of a novel radiosensitivity- and ferroptosis-associated gene signature for prognosis prediction in gliomas, *J. Cancer*, 2022, **13**, 2683–2693.
122 X. Tan, X. Huang, B. Niu, X. Guo, X. Lei and B. Qu, Targeting GSTP1-dependent ferroptosis in lung cancer radiotherapy: Existing evidence and future directions, *Front. Mol. Biosci.*, 2022, **9**, 1102158.
123 X. Lin, Q. Zhang, Q. Li, J. Deng, S. Shen, M. Tang, *et al.*, Upregulation of CoQ shifts ferroptosis dependence from GPX4 to FSP1 in acquired radioresistance, *Drug Resistance Updates*, 2024, **73**, 101032.
124 L. Chen, G. Chen, K. Hu, L. Chen, Z. Zeng, B. Li, *et al.*, Combined photothermal and photodynamic therapy enhances ferroptosis to prevent cancer recurrence after surgery using nanoparticle-hydrogel composite, *Chem. Eng. J.*, 2023, **468**, 143685.
125 G.-H. Chen, L. Gan, L.-Y. Tian, B.-X. Huang, Q. Xiao, Y.-J. Zhang, *et al.*, Mutually reinforced cancer treatment based on phototherapy combined with ferroptosis, *Chem. Eng. J.*, 2024, **493**, 152397.
126 M. Feng, S. Xiao, Z. Liu, M. Li, X. Zhang, X. Chen, *et al.*, Multifunctional platinum-doped porous FeS2 nanoparticles for photothermal-enhanced photodynamic ferroptosis combination therapy, *Mater. Today Nano*, 2023, **23**, 100371.
127 H. K. C. Co, C. C. Wu, Y. C. Lee and S. H. Chen, Emergence of large-scale cell death through ferroptotic trigger waves, *Nature*, 2024, **631**, 654–662.
128 D. Qi and M. Peng, Ferroptosis-mediated immune responses in cancer, *Front. Immunol.*, 2023, **14**, 1188365.
129 X. Yang, Y. Liu, Z. Wang, Y. Jin and W. Gu, Ferroptosis as a new tool for tumor suppression through lipid peroxidation, *Commun. Biol.*, 2024, **7**, 1475.
130 C. Qiao, H. Wang, Q. Guan, M. Wei and Z. Li, Ferroptosis-based nano delivery systems targeted therapy for colorectal cancer: Insights and future perspectives, *Asian J. Pharm. Sci.*, 2022, **17**, 613–629.
131 F. Yang, Y. Xiao, J. H. Ding, X. Jin, D. Ma, D. Q. Li, *et al.*, Ferroptosis heterogeneity in triple-negative breast cancer reveals an innovative immunotherapy combination strategy, *Cell Metab.*, 2023, **35**, 84–100.
132 X. Lang, M. D. Green, W. Wang, J. Yu, J. E. Choi, L. Jiang, *et al.*, Radiotherapy and Immunotherapy Promote Tumoral Lipid Oxidation and Ferroptosis via Synergistic Repression of SLC7A11, *Cancer Discovery*, 2019, **9**, 1673–1685.
133 X. Zhang, H. Ge, Y. Ma, L. Song, Y. Ma, G. Tian, *et al.*, Engineered anti-cancer nanomedicine for synergistic ferroptosis-immunotherapy, *Chem. Eng. J.*, 2023, **455**, 140688.
134 S. Chen, J. Shi, D. Yu and S. Dong, Advance on combination therapy strategies based on biomedical nanotechnology induced ferroptosis for cancer therapeutics, *Biomed. Pharmacother.*, 2024, **176**, 116904.
135 X. Zhai, Y. Lin, L. Zhu, Y. Wang, J. Zhang, J. Liu, *et al.*, Ferroptosis in cancer immunity and immunotherapy: Multifaceted interplay and clinical implications, *Cytokine Growth Factor Rev.*, 2024, **75**, 101–109.
136 S. Du, F. Zeng and G. Deng, Tumor neutrophils ferroptosis: a targetable immunosuppressive mechanism for cancer immunotherapy, *Signal Transduction Targeted Ther.*, 2023, **8**, 77.
137 Z. Zhou, B. Xu, N. Hu, Z. Guo, W. Bao, B. Shao, *et al.*, Targeting the Macrophage-Ferroptosis Crosstalk: A Novel Insight into Tumor Immunotherapy, *Front. Biosci.*, 2022, **27**, 203.
138 H. Cai, Y. Ren, S. Chen, Y. Wang and L. Chu, Ferroptosis and tumor immunotherapy: A promising combination therapy for tumors, *Front. Oncol.*, 2023, **13**, 1119369.
139 Z. Mao, Y. Hu, Y. Zhao, X. Zhang, L. Guo, X. Wang, *et al.*, The Mutual Regulatory Role of Ferroptosis and Immunotherapy in Anti-tumor Therapy, *Apoptosis*, 2024, **29**, 1291–1308.
140 H. Liang, X. Wu, G. Zhao, K. Feng, K. Ni and X. Sun, Renal Clearable Ultrasmall Single-Crystal Fe Nanoparticles for Highly Selective and Effective Ferroptosis Therapy and Immunotherapy, *J. Am. Chem. Soc.*, 2021, **143**, 15812–15823.
141 A. Zhou, T. Fang, K. Chen, Y. Xu, Z. Chen and X. Ning, Biomimetic Activator of Sonodynamic Ferroptosis Amplifies Inherent Peroxidation for Improving the Treatment of Breast Cancer, *Small*, 2022, **18**, e2106568.
142 W. Su, H. Wang, J. Pan and Q. Zhou, Advances in Sonodynamic Therapy: Focus on Ferroptosis, *J. Med. Chem.*, 2025, **68**, 5976–5992.
143 L. Q. Zhou, C. H. Dong, L. Ding, W. Feng, L. D. Yu, X. W. Cui, *et al.*, Targeting ferroptosis synergistically sensitizes apoptotic sonodynamic anti-tumor nanotherapy, *Nano Today*, 2021, **39**, 101212.
144 M. F. Wang, J. Guo, S. J. Yuan, K. Li, Q. Zhang, H. M. Lei, *et al.*, Targeted sonodynamic therapy induces tumor cell quasi-immunogenic ferroptosis and macrophage immunostimulatory autophagy in glioblastoma, *Biomaterials*, 2025, **315**, 122913.

145 C. You, X. Li, D. Wang, H. Chen, L. Liang, Y. Chen, *et al.*, Self-Assembled Aza-Boron-Dipyrromethene for Ferroptosis-Boosted Sonodynamic Therapy, *Angew. Chem., Int. Ed.*, 2022, **61**, e202210174.

146 C. Gong, Q. Ji, M. Wu, Z. Tu, K. Lei, M. Luo, *et al.*, Ferroptosis in tumor immunity and therapy, *J. Cell. Mol. Med.*, 2022, **26**, 5565–5579.

147 W. Bao, X. Liu, Y. Lv, G. H. Lu, F. Li, F. Zhang, *et al.*, Nanolongan with Multiple On-Demand Conversions for Ferroptosis-Apoptosis Combined Anticancer Therapy, *ACS Nano*, 2019, **13**, 260–273.

148 Y. Zheng, L. Sun, J. Guo and J. Ma, The crosstalk between ferroptosis and anti-tumor immunity in the tumor microenvironment: molecular mechanisms and therapeutic controversy, *Cancer Commun.*, 2023, **43**, 1071–1096.

149 M. Liu, B. Liu, Q. Liu, K. Du, Z. Wang and N. He, Nanomaterial-induced ferroptosis for cancer specific therapy, *Coord. Chem. Rev.*, 2019, **382**, 160–180.

150 X. Zhang, Y. Ma, J. Wan, J. Yuan, D. Wang, W. Wang, *et al.*, Biomimetic Nanomaterials Triggered Ferroptosis for Cancer Theranostics, *Front. Chem.*, 2021, **9**, 768248.

151 V. K. Yadav, N. Choudhary, A. Gacem, R. K. Verma, M. Abul Hasan, M. Tarique Imam, *et al.*, Deeper insight into ferroptosis: association with Alzheimer's, Parkinson's disease, and brain tumors and their possible treatment by nanomaterials induced ferroptosis, *Redox Rep.*, 2023, **28**, 2269331.

152 Q. Nie, Y. Hu, X. Yu, X. Li and X. Fang, Induction and application of ferroptosis in cancer therapy, *Cancer Cell Int.*, 2022, **22**, 12.

