Nanotechnology, Science and Applications

Dovepress
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REVIEW

Nanoparticle-Mediated Ferroptosis for Cancer Therapy: Mechanisms and Therapeutic Strategies

Marzena Szwed, Anastazja Poczta-Krawczyk, Karol Bukowski, Agnieszka Marczak

Department of Medical Biophysics, Institute of Biophysics, Faculty of Biology and Environmental Protection, University of Lodz, Lodz, 90-236, Poland

Correspondence: Marzena Szwed, University of Lodz, 141/143 Pomorska Street, Lodz, 90-236, Poland, Email marzena.szwed@biol.uni.lodz.pl

Abstract: Ferroptosis, an iron-dependent form of regulated cell death, is increasingly leveraged in nanomedicine to sensitise tumours and overcome drug resistance. Driven by the Fenton reaction, ferroptosis results in lipid peroxidation through elevated intracellular iron levels and excessive production of reactive oxygen species (ROS). In this review, we outline the molecular markers of ferroptosis and define the criteria necessary to attribute ferroptosis induction to nanoparticles (NPs). We emphasise the importance of distinguishing targeted ferroptosis from non-specific ROS-mediated nanotoxicity and other types of programmed cell death. This distinction requires the use of lipophilic radical-trapping antioxidants (eg, ferrostatin-1, liproxstatin-1), iron chelators, and evidence implicating glutathione peroxidase 4 (GPX4) or the system Xc^- antiporter. Morphology is considered supportive but non-diagnostic, requiring converging evidence from both biochemical and genetic sources. We then compare various nanosystems designed to induce ferroptosis, such as iron-based nanoparticles, lipid nanocarriers, light-triggered nanoparticles, and magnetically induced nanocarriers, highlighting mechanistic patterns, efficacy determinants, and common pitfalls that often occur during biological investigations. Finally, we discuss translational challenges, including tumour microenvironment heterogeneity, NP protein corona dynamics, clearance and off-target effects. We aim to provide a framework that links NP design to ferroptotic mechanisms and clinically relevant outcomes, offering clear criteria and priorities for future research.

Keywords: nanoparticles, regulated cell death, nanomedicine, iron ions, oxidative stress

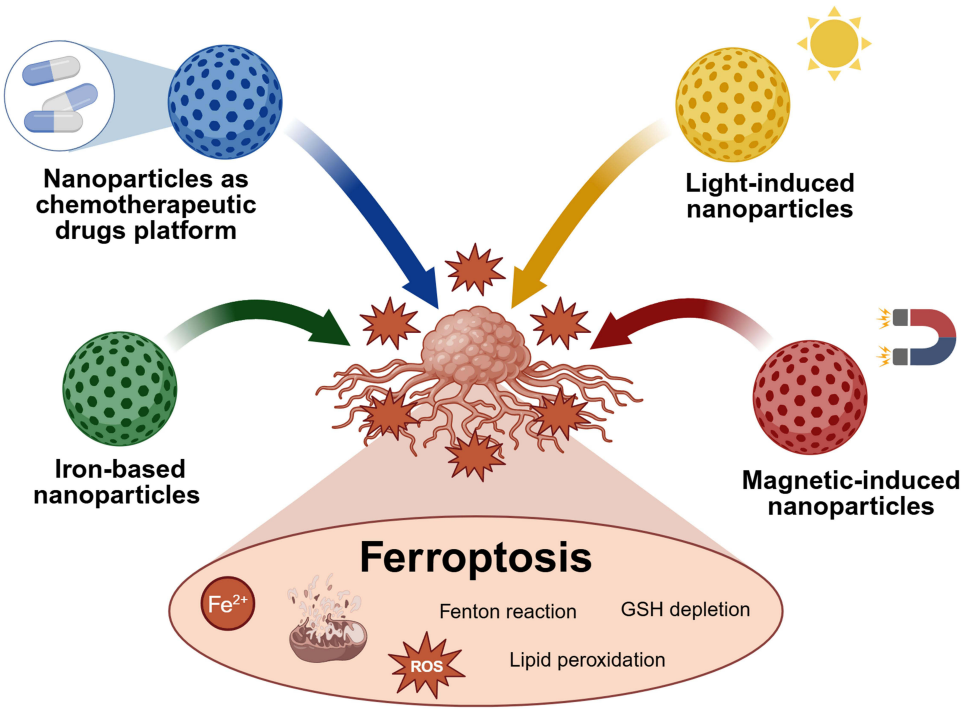
Ferroptosis: Introduction to the Non-Apoptotic Form of Regulated Cell Death

First identified and characterised in 2012, ferroptosis is a distinct, regulated form of non-apoptotic cell death marked by iron-dependent accumulation of reactive oxygen species (ROS), depletion of glutathione (GSH), inactivation of glutathione peroxidase 4 (GPX4), and uncontrolled lipid peroxidation.[1,2] Morphologically, ferroptotic cells lack the defining features of other cell death modalities; for instance, they do not exhibit the loss of plasma membrane integrity typical of necrosis, the formation of double-membrane autophagic vacuoles observed in autophagy, or the chromatin condensation characteristic of apoptosis[3]. Functionally, ferroptosis contrasts with apoptosis not only in its morphology but also in its immunological profile (Figure 1); while apoptosis is typically anti-inflammatory and immunologically silent, ferroptosis promotes inflammation through the release of damage-associated molecular patterns (DAMPs).[4]

Furthermore, necroptosis and pyroptosis are other necessary regulated forms of cell death (RCD) that are mechanistically distinct from ferroptosis. In necroptosis, caspase inhibition or death receptor/pattern-recognition receptors signalling activates the receptor-interacting serine/threonine-protein kinases 1 or 2 and mixed lineage kinase domain-like pseudokinase (RIPK1–RIPK3–MLKL) axis. Phosphorylated MLKL oligomerises at the plasma membrane to provoke rapid loss of membrane integrity and DAMP release, and the phenotype is suppressible by RIPK1/3 or MLKL inhibition. In pyroptosis, canonical (caspase-1) or non-canonical (caspase-4/5 in humans; caspase-11 in mice) inflammasomes cleave gasdermin D (GSDMD). The N-terminal fragments form membrane pores, driving cell swelling and interleukin-1 beta/interleukin-18 IL-1β/IL-18 secretion, with detection typically relying on GSDMD cleavage and dependence on the inflammasome/caspase. Ferroptosis, in contrast to both, is iron-dependent and centred on uncontrolled

Received: 1 July 2025
Accepted: 27 September 2025
Published: 25 October 2025

Graphical Abstract



lipid peroxidation with GPX4/system Xc^- vulnerability; assignment is best supported by rescue with radical-trapping antioxidants (eg, ferrostatin-1, liproxstatin-1) or iron chelation, rather than by caspase/inflammasome or MLKL modulation.[7–10]

Cuproptosis represents a metal-dependent RCD defined in 2022, in which intracellular copper binds to lipoylated tricarboxylic-acid (TCA) cycle enzymes, most notably dihydrolipoamide S-acetyltransferase (DLAT), driving protein oligomerisation/aggregation, loss of Fe–S-cluster proteins, and mitochondrial proteotoxic stress in cells reliant on oxidative phosphorylation. This form of cell death depends on ferredoxin 1 (FDX1) and the lipoic acid pathway, and is not driven by iron or lipid peroxidation. Accordingly, cuproptosis is typically mitigated by copper chelators or disruption of protein lipoylation, but not by ferroptosis inhibitors - underscoring that metal-associated death programmes are not interchangeable.[11–14]

Ferroptosis-inducing compounds have been shown to suppress tumour growth and progression,[15] while also enhancing the efficacy of chemotherapeutic agents such as cisplatin,[16] temozolomide,[17] cytarabine, and doxorubicin (DOX).[18,19] Remarkably, tumours with a high-mesenchymal/EMT-like phenotype, including sarcomas (of mesenchymal origin), claudin-low/mesenchymal-like triple-negative breast cancers (TNBC), mesenchymal subtype glioblastoma, and CMS4 (mesenchymal) colorectal cancers, are among the most drug-resistant malignancies.[20] These cells rely heavily on the lipid peroxidase pathway, particularly the GPX4 pathway, to evade ferroptotic cell death.[21,22] As a result, maintaining adequate levels of cystine, a precursor for GSH synthesis, is essential for the survival of ferroptosis-prone cells. However, oncogenic mutations increase cellular sensitivity to cystine deprivation,[23] making such cells highly susceptible to GSH depletion.[24]

In this review, we discuss the potential of using ferroptosis regulators as a target for chemotherapy, with particular emphasis on ultra-small nanoparticles (NPs) as ferroptosis inducers to overcome tumour drug resistance. Numerous reports have highlighted the role of nanomaterials (NMs) in modulating ferroptosis, and NM-induced ferroptosis has been identified as one of the underlying mechanisms of nanotoxicity.[25–27] Several recent reviews have surveyed

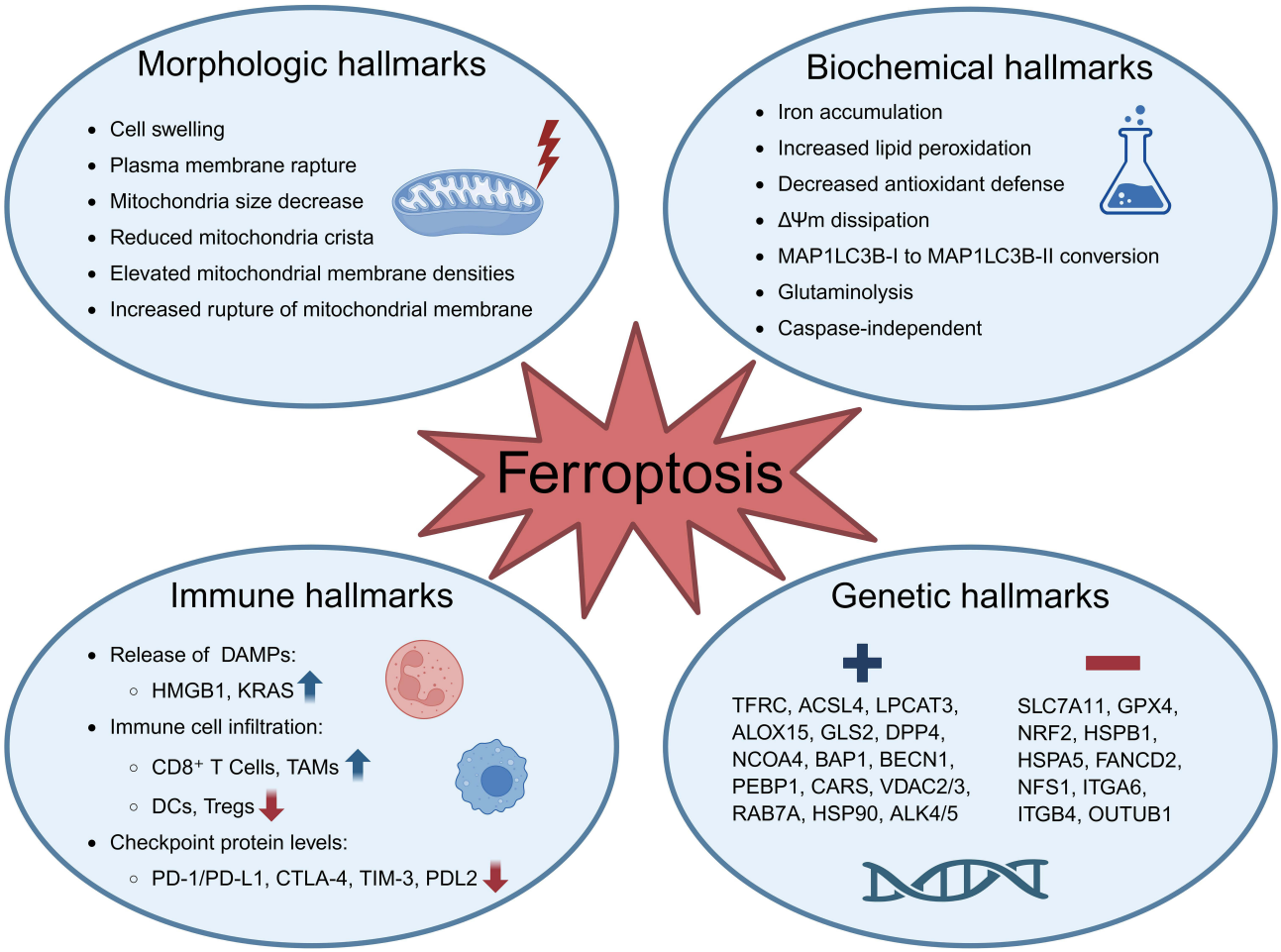


Figure 1 Hallmarks of ferroptosis across complementary evidence levels. Ferroptosis is an iron-dependent form of regulated cell death driven by glutathione depletion, iron-catalysed lipid peroxidation, and reactive oxygen species, rather than caspase-mediated apoptosis or necroptosis/pyroptosis. Morphological alterations are supportive but non-diagnostic and must be interpreted together with biochemical and pathway-level evidence. Therefore, a confident assignment requires multiple, converging lines of evidence. First, lipid peroxidation should be demonstrated (eg, a lipid peroxidation probe's shift - C11-BODIPY, 4-hydroxynonenal, malondialdehyde (4-HNE/MDA)). Furthermore, cell death and lipid peroxidation should be reversed by lipophilic radical-trapping antioxidants (ferrostatin-1, liproxstatin-1) and/or an iron chelator (deferoxamine), indicating a dependence on iron and lipid peroxidation. Additionally, the involvement of GPX4 or system Xc^- should be further evaluated. Immunogenic/DAMP-related responses may accompany ferroptosis but are not specific. Transcript- and post-transcript-level changes alone are insufficient and should be interpreted in conjunction with the above criteria. Created in BioRender. Marczak, A. (2025) https://BioRender.com/7iq116t.[5,6]

Abbreviations: ACSL4, Acyl-CoA Synthetase Long Chain Family Member 4; ALK4, Activin Receptor-Like Kinase 4; ALK5, Activin Receptor-Like Kinase 5; ALOX15, Arachidonate 15-Lipoxygenase; BAP1, BRCA1 Associated Protein 1; BECN1, Beclin 1; CARS, Cysteinyl-tRNA Synthetase; DAMPs, Damage-associated molecular patterns; DPP4, Dipeptidyl Peptidase 4; FANCD2, Fanconi Anemia Group D2 Protein; GLS2, Glutaminase 2; GPX4, Glutathione Peroxidase 4; GSH, glutathione; HSP90, Heat Shock Protein 90; HSPA5, Heat Shock Protein Family A Member 5; HSPB1, Heat Shock Protein Beta-1; ITGA6, Integrin Subunit Alpha 6; ITGB4, Integrin Subunit Beta 4; KRAS, Kirsten rat sarcoma virus; LPCAT3, Lysophosphatidylcholine Acyltransferase 3; MAP1LC3B, Microtubule-associated Protein 1 Light Chain 3 Beta; NCOA4, Nuclear Receptor Coactivator 4; NRF2, Nuclear Factor; Erythroid 2-Like 2; NFS1, NFS1 Cysteine Desulfurase; OTUB1, OTU Domain-Containing Ubiquitin Aldehyde-Binding Protein 1; PEBP1, Phosphatidylethanolamine Binding Protein 1; RAB7A, Member of the Rat Sarcoma Virus (RAS) Oncogene Family; ROS, Reactive oxygen species; SLC7A11, Solute Carrier Family 7 Member 11; TFRC, Transferrin Receptor; VDAC2, Voltage-Dependent Anion Channel 2; VDAC3, Voltage-Dependent Anion Channel 3; ΔΨm, Mitochondrial membrane potential.

nanoparticle-associated ferroptosis in oncology.[28–30] In contrast, our contribution is a mechanism-first, cross-platform synthesis that maps NP properties to ferroptosis checkpoints and formalises evidence standards to distinguish ferroptosis from generic ROS nanotoxicity.[7,31,32] A central challenge in vivo is that ROS accumulation is non-specific, so mechanistic assignment should combine lipid-peroxidation readouts with rescue controls and engagement of GPX4/system Xc^-. Equally important is non-invasive monitoring, for which robust biomarkers and imaging readouts of lipid peroxidation are still evolving.[33,34]

Translation is further constrained by protein-corona–driven biodistribution drift, EPR variability, and chemistry, manufacturing, and controls (CMC) demands (iron-content specification, batch-to-batch reproducibility). Together with patient selection by tumour iron/redox context, these factors determine whether NP designs yield reproducible ferroptotic

responses.[35–37] Rather than repeating catalogues of ferroptosis-inducing nanomaterials, we integrate platform-specific findings into a comparative synthesis that links NP properties to ferroptosis control points and highlights common preclinical pitfalls (eg, non-orthotopic models, supra-physiological dosing, insufficient rescue controls). Finally, we synthesise current insights into the therapeutic potential of NPs as controllable ferroptosis-inducing agents or ferroptosis-modulating drug carriers, outlining criteria and priorities for future research.[37–39]

Molecular Markers Indicating Ferroptosis

As ferroptotic cells excessively produce ROS that initiate lipid peroxidation via the Fenton reaction ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \bullet OH + OH^-$), the primary biochemical features of ferroptosis include elevated levels of lipid hydroperoxides (LOOH) and ferrous ions (Fe^{2+}).[40] Morphologically, ferroptotic cells, compared to those maintaining normal homeostasis, exhibit dysmorphic, small, shrunken mitochondria; reduced or absent mitochondrial cristae; and increased rupture of the mitochondrial membrane, including condensation of the inner membrane and damage to the outer mitochondrial membrane.[41]

Changes in the mitochondrial morphology accompanying disturbances in iron ions homeostasis suggest the active participation of these cell "powerhouses" in ferroptotic cell death. Indeed, ferroptosis involves the activation of voltage-dependent mitochondrial anion channels and mitogen-activated protein kinases, as well as being associated with increased endoplasmic reticulum protein expression and inhibition of the cystine/glutamate antiporter.[31] The most important biochemical hallmark of ferroptosis is the elevated level of LOOH, resulting from the oxidative degradation of lipids, particularly polyunsaturated fatty acids (PUFAs), which are highly susceptible to lipid peroxidation. The abundance and cellular localisation of PUFAs determine the extent of lipid peroxidation and, consequently, the severity of ferroptosis.[42] Hydroperoxides are generated by iron-dependent lipoxygenases (enzymatic events) or through non-enzymatic processes (Fenton reactions) via an iron-catalysed spontaneous peroxyl radical-mediated chain reaction. In normal cells under homeostatic conditions, the ferroptotic signal is suppressed by GPX4, a phospholipid hydroperoxidase that functions as a lipid repair enzyme using GSH as a cofactor.[43,44] GPX4 converts reduced GSH to oxidised glutathione (GSSG) while reducing LOOH to their corresponding alcohols or free hydrogen peroxide to water and thus protects the cell against the accumulation of peroxides.[45] The loss of GPX4 activity during ferroptosis occurs through two distinct mechanisms: direct and indirect. The direct mechanism involves the inhibition of GPX4 itself, leading to the accumulation of lipid ROS and ferroptotic cell death. This can result from the loss of GPX4 activity, as seen with (1S, 3R)-RAS-selective lethal 3 (RSL3), which irreversibly targets the selenocysteine residue in the active site of GPX4,[46] or through enhanced degradation, such as with FIN56, which reduces GPX4 abundance.[47] The indirect mechanism involves inhibition of system Xc^-, the cystine/glutamate antiporter, leading to decreased intracellular levels of cystine and, consequently, cysteine, a precursor of GSH.[48] GSH, the most abundant endogenous antioxidant, is synthesised in two steps. First, glutamate-cysteine ligase catalyses the formation of γ-glutamylcysteine from L-glutamate and cysteine (Figure 2). Second, glutathione synthetase catalyses the addition of glycine to the C-terminus of γ-glutamylcysteine.[49] Under homeostatic conditions, the rate of GSH synthesis is primarily determined by the availability of cysteine and the activity of glutamate–cysteine ligase. While cysteine readily autoxidises to cystine in the extracellular fluid, it is rapidly reduced to cysteine upon entering the cell.[50] Consequently, cystine import via system Xc^- is a crucial factor in regulating intracellular cysteine levels.[51] System Xc^- is a cystine/glutamate antiporter comprising the catalytic subunit Solute Carrier Family 7 Member 11 (SLC7A11) and the anchoring protein Solute Carrier Family 3 Member 2 (SLC3A2).[52] Inhibiting cystine import through system Xc^- induces ferroptosis, an iron-dependent, lipid peroxidation-mediated form of RCD, highlighting the importance of this antiporter in maintaining cellular GSH levels and redox balance[53] (Figure 2).

The transmembrane Xc^- system can be inhibited by endoplasmic reticulum proteins such as stress-induced cation transport regulator-like protein 1. In certain cancer cell lines, inhibition of cystine uptake from the extracellular environment via the Xc^- system alone is sufficient for ferroptosis.[54]

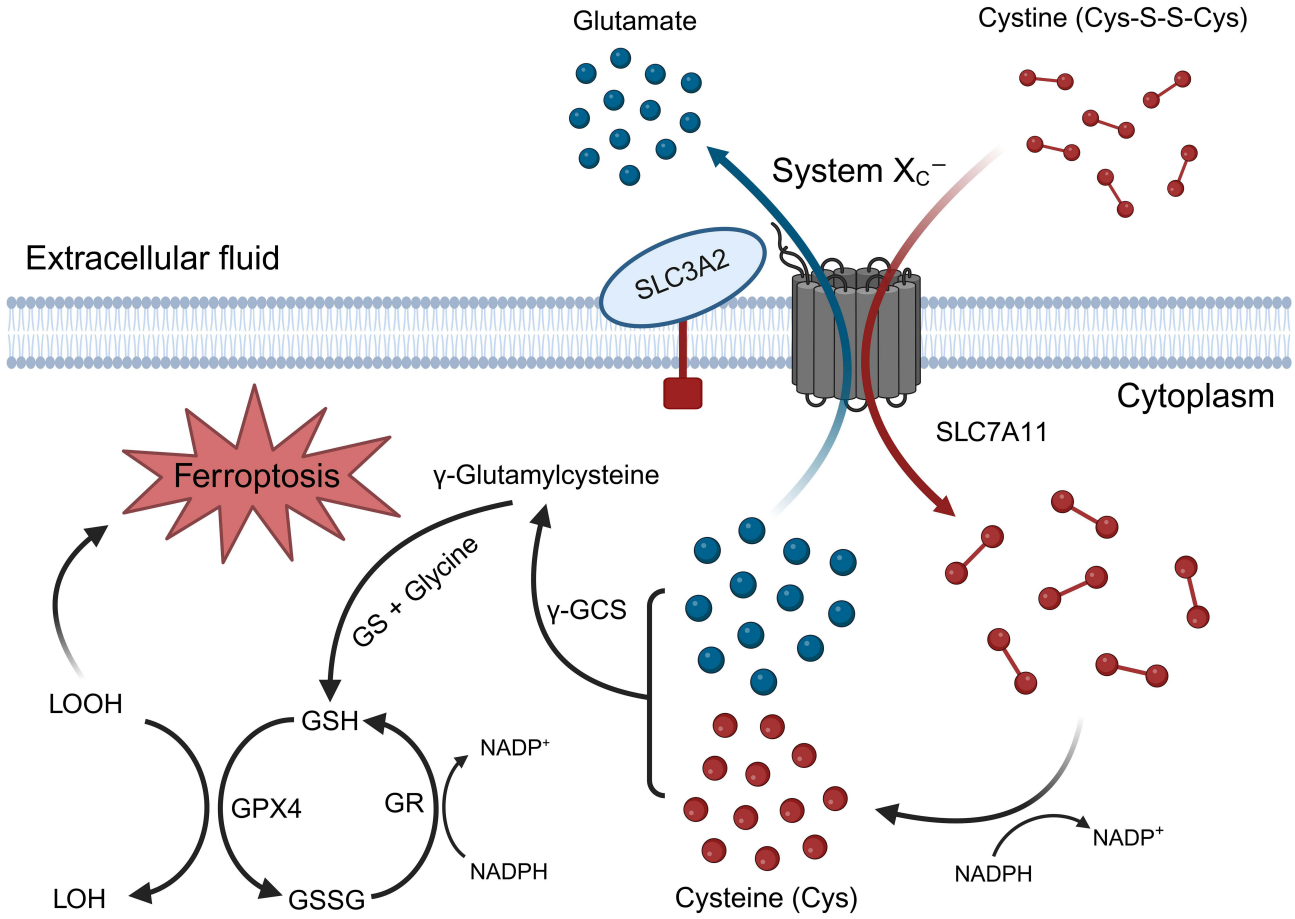


Figure 2 Structure and role of the cystine/glutamate antiporter (X_C^-) in GSH synthesis and maintaining the redox balance of the cell. GSH is a small-molecule antioxidant that is essential for maintaining the redox balance of cells. The precursor of GSH, cystine, is transported into cells via the cystine/glutamate antiporter system Xc^-. System Xc^- is a heterodimer consisting of the light-chain subunit solute carrier family 7 member 11 (SLC7A11) and the heavy-chain subunit SLC3A2. SLC7A11 mediates the antiporter activity of system Xc^-. Once inside the cell, cystine is reduced to cysteine via a NADPH-dependent reaction. The addition of glycine to γ-glutamylcysteine by glutathione synthetase results in the formation of GSH, which may be oxidised into GSSG. This oxidation reaction is catalysed by GPX4 and enables the cell to eliminate excess molecules such as LOOH. GSH can be regenerated from GSSG through reduction by glutathione reductase, also consuming NADPH. Created in BioRender. Marczak, A. (2025) https://BioRender.com/k2xhuo.

Abbreviations: Cys, Cysteine; Cys–S-S-Cys, Cystine; γ-GCS, γ-glutamylcysteine synthetase; GS, Glutathione synthetase; GPX4, Glutathione peroxidase 4; GR, Glutathione reductase; GSH, Glutathione; GSSG, Oxidised glutathione; LOOH, Lipid hydroperoxide; LOH, Lipid alcohol; NADPH, Nicotinamide adenine dinucleotide phosphate; SLC3A2, Solute Carrier Family 3 Member 2; SLC7A11, Solute Carrier Family 7 Member 11.

Free Radical Imbalance is Insufficient to Trigger Ferroptosis: The Substantial Role of Iron

It is well established that biological redox reactions facilitate both physiological processes and pathological signalling.[55] At low to moderate concentrations, ROS and reactive nitrogen species play essential roles in the signalling pathways and defence mechanisms that initiate homeostatic responses. Conversely, excessive generation of these reactive species exerts cytotoxic effects, causing protein, DNA, and lipid damage. Within the cellular defence system, enzymatic and non-enzymatic antioxidants, along with antioxidant signalling pathways, have evolved to scavenge surplus ROS.[56] Multiple ROS-sensing pathways converge on transcription factors such as Nuclear factor erythroid 2–related factor 2 (Nrf2),[57] activator protein-1,[58] and nuclear factor kappa B,[59] which regulate the expression of genes involved in ROS-dependent cellular homeostasis. The Nrf2–Keap1 (Kelch-like ECH-associated protein 1) pathway is a key regulator of cytoprotective responses to oxidative stress.[60] The half-life and transcriptional activity of Nrf2 are regulated by its interaction with Keap1 (Figure 3).

When Keap1 targets Nrf2, its ubiquitination and degradation via a Cullin-3-mediated complex are initiated.[64] Under normal conditions, Keap1 maintains a low Nrf2 level. However, when cells experience oxidative stress, Keap1 becomes inactivated through the oxidation of reactive cysteine residues, leading to stabilisation of Nrf2 and its subsequent

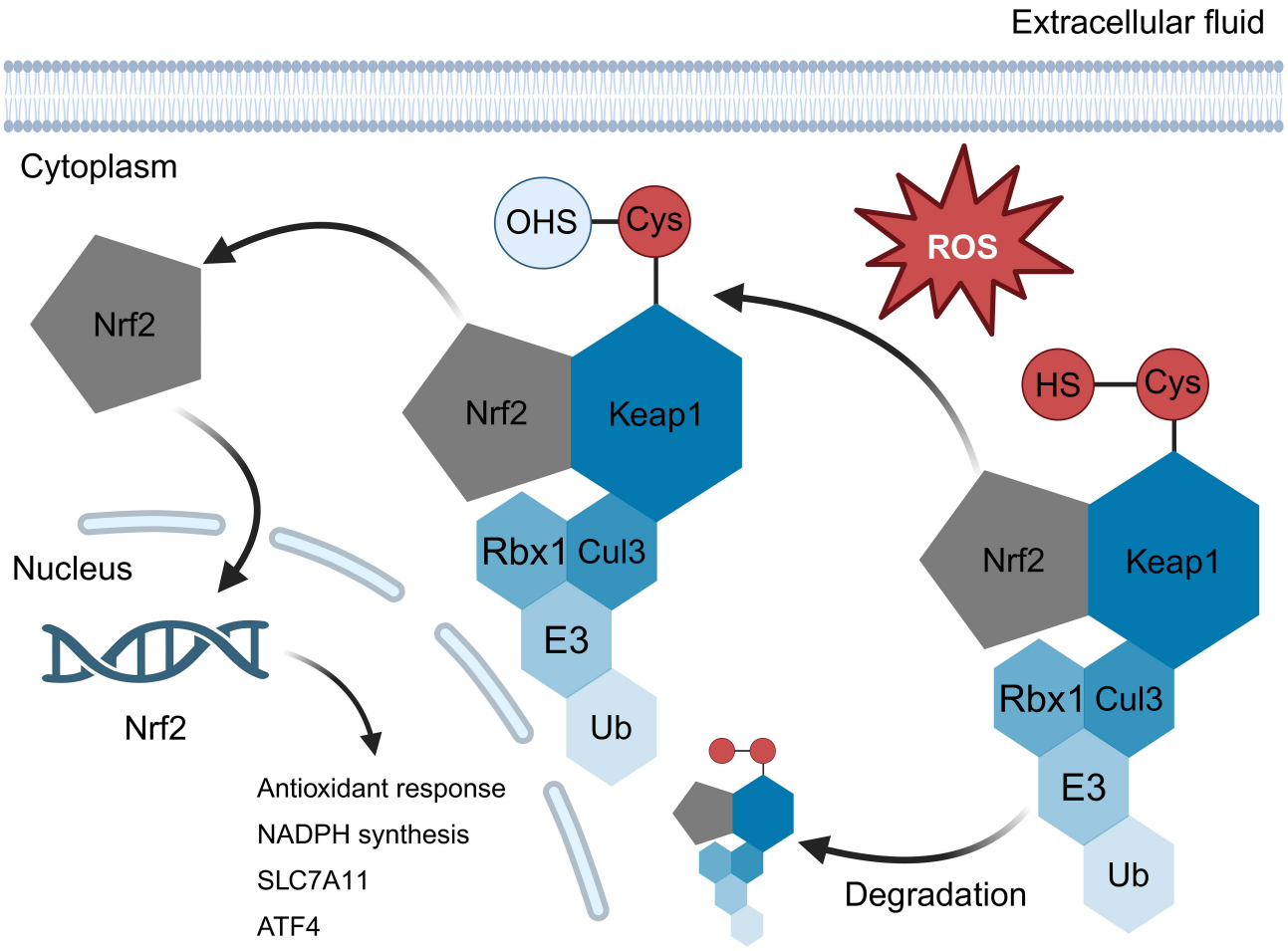


Figure 3 Nrf2–Keap1 pathway represents one of the major regulators of cytoprotective responses to oxidative stress. In the cytosol under normal conditions, Keap1 promotes Nrf2 ubiquitination and subsequent degradation by a Cullin-3-mediated ubiquitination complex. Exposure to excessive ROS leads to the oxidation of cysteine residues in the Keap1 complex, resulting in Nrf2 stabilisation, its translocation to the nucleus, and the upregulation of cytoprotective genes, such as SLC7A11 and enzymes involved in NADPH regeneration. ATF4 is activated in parallel and cooperates with NRF2 in SLC7A11 transactivation. Created in BioRender. Marczak, A. (2025) https://BioRender.com/k2xhuoj.[61–63]
Abbreviations: ATF4, Activating transcription factor 4; Cul 3, Cullin-3; Cys, Cysteine; E3, An E3-like enzyme; Keap 1, Kelch-like ECH-associated protein 1; NADPH, Nicotinamide adenine dinucleotide phosphate; Nrf2, Nuclear factor erythroid 2–related factor 2; Rbx1, RING box protein 1; ROS, Reactive oxygen species; SLC7A11, Solute Carrier Family 7 Member 11; Ub, Ubiquitin.

translocation to the nucleus.[65] Within the nucleus, Nrf2 forms heterodimers with members of the small Maf protein family and binds to a cis-acting antioxidant response element located in the promoter regions of numerous cytoprotective genes.[61] Nrf2 initiates the transcriptional upregulation of enzymes involved in GSH-dependent antioxidant responses (glutamate-cysteine ligase, glutathione S-transferases), system Xc^- functionality, NADPH regeneration, and proteins involved in lipid metabolism.[66]

ROS imbalance and oxidative stress are caused by Fenton or Fenton-like reactions.[67–69] Overloading the cell with labile iron (Fe^{2+}) can directly catalyse lipid peroxidation via Fenton reactions and ultimately lead to ferroptosis.[70] Thus, ferroptosis relies on the balance between iron accumulation-induced ROS production and the antioxidant system during lipid peroxidation.[29,71,72]

Iron is crucial for various biological processes, including iron–sulfur (Fe–S) cluster biogenesis; synthesis of haem, DNA, and RNA; ATP generation; oxygen transport; detoxification processes; cell cycle progression; the activity of numerous enzymes; immune function; and metabolism.[73–76] Furthermore, in the bone marrow, iron is required for red blood cells and haemoglobin synthesis. Macrophages recycle iron from senescent erythrocytes and export it back into circulation by ferroportin (FPN).[77] The liver stores unused iron and controls its systemic iron levels through hepcidin secretion. This peptide hormone is produced and released into circulation by the liver in response to elevated systemic

iron levels. Degradation of FPN by hepcidin decreases iron efflux from macrophages and enterocytes (intestinal absorptive epithelial cells responsible for dietary iron uptake and export via ferroportin) into the bloodstream, thereby normalising systemic iron levels.[78,79]

Decreased red blood cell count and anaemia, frequently observed in patients with cancer, are associated with dysregulation of systemic iron homeostasis. Cancer-induced anaemia of inflammation is correlated with erythropoiesis reduction and iron limitation.[80] The determinants responsible for cancer-induced anaemia include the presence of comorbidities and the location and extent of the disease.[81] A distinct form of therapy-induced anaemia is associated with impaired haematopoiesis caused by cytotoxic drugs and antitumour therapies. Treatment options for cancer- and therapy-induced anaemia include iron supplementation, erythropoiesis-stimulating agents, and blood transfusions.[82]

The exact role of iron in the promotion of ferroptotic cell death has not yet been fully elucidated. It has been speculated that the accumulation of ROS, leading to lipid peroxidation, is primarily responsible for ferroptosis. However, experiments using hydrogen peroxide treatment have shown that ROS induction alone is insufficient to trigger the ferroptotic cell death pathway.[48] Therefore, iron may play additional roles in activating ferroptosis. Regardless of the precise mechanism, increased intracellular iron levels promote the ferroptotic cell death pathway (Figure 4).[73]

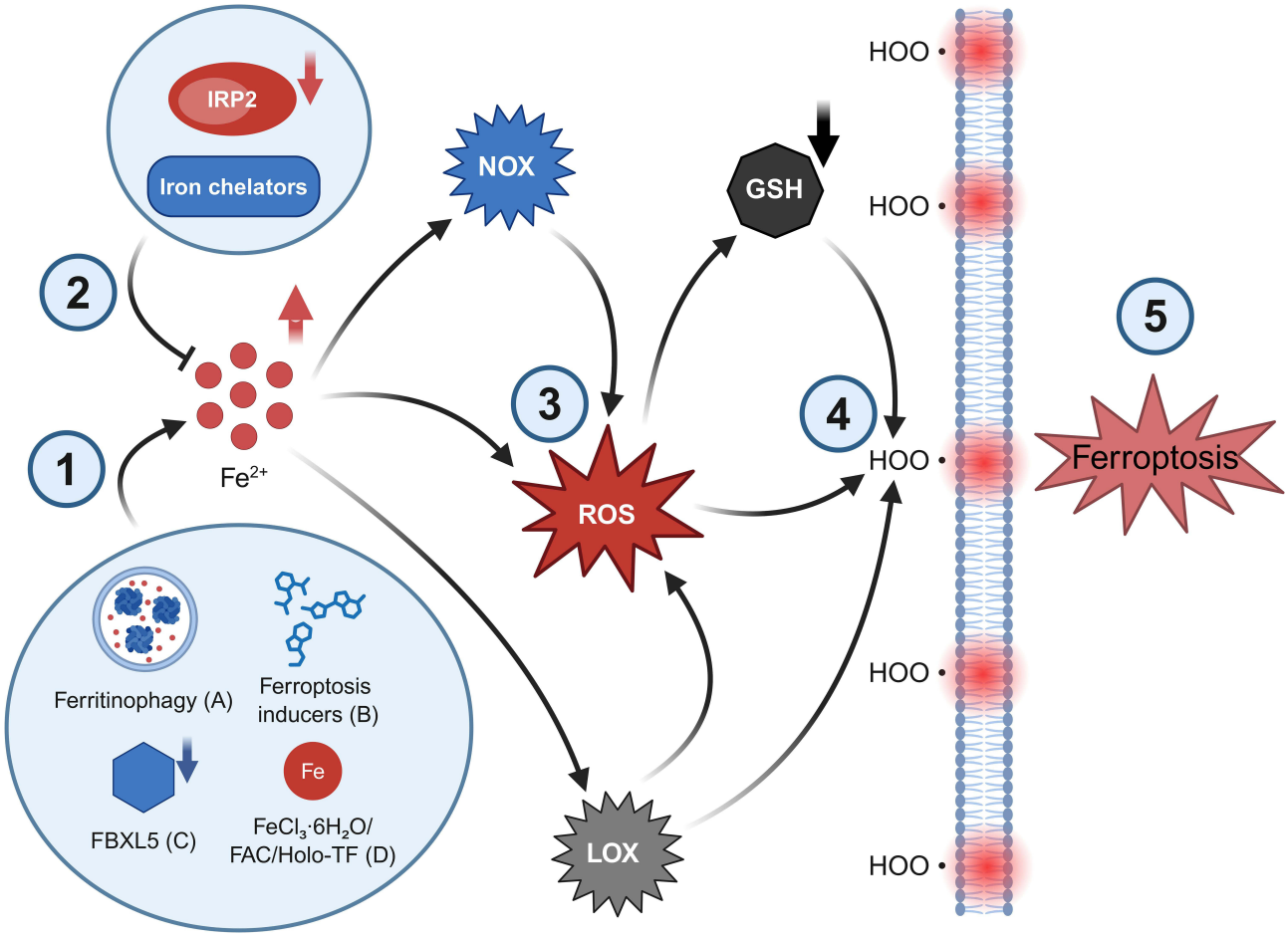


Figure 4 Role of iron in ferroptosis. Accumulation of intracellular iron induced by ferritinophagy (A), ferroptosis inducers such as erastin and RSL3 (B), knockdown of FBXL5 (a negative regulator of IRP2) (C), or treatment with $FeCl_3 \cdot 6H_2O$, FAC, or holo-TF (D), has been shown to promote ferroptosis (1). In contrast, treatment with iron chelators decreases intracellular iron levels, thereby suppressing ferroptosis (2). Elevated intracellular iron can initiate the Fenton reaction, generating ROS. Additionally, iron can enhance the activity of enzymes such as NOX and LOX, further contributing to ROS accumulation (3). ROS promotes lipid peroxidation both directly and indirectly via GSH depletion, whereas LOX contributes to lipid peroxidation through direct enzymatic activity (4), culminating in ferroptotic cell death (5). Created in BioRender. Marczak, A. (2025) https://BioRender.com/pobx0ey.

Abbreviations: FAC, Ferric ammonium citrate; FBXL5, F-box and leucine-rich repeat protein 5; $FeCl_3 \cdot 6H_2O$, Iron chloride hexahydrate; GSH, Glutathione; holo-TF, Holo-transferrin; IRP2, Iron-responsive element-binding protein 2; LOX, Lipoxygenases; NOX, NADPH, Nicotinamide adenine dinucleotide phosphate oxidases; ROS, Reactive oxygen species; RSL3, RAS-selective lethal 3.

https://doi.org/10.2147/NSA.S550828

Consequently, the tendency for intracellular iron accumulation may be exploited as a potential strategy in cancer therapy.[83] Indeed, as mentioned previously, the iron-seeking phenotype of neoplastic cells is associated with the crucial role of iron in various intracellular processes.[84–87] A deficiency in intracellular iron may impair the activity of the iron-dependent enzyme ribonucleotide reductase, which catalyses the synthesis of new deoxyribonucleotides and may be the rate-limiting factor of DNA synthesis.[88] Thus, intracellular iron accumulation in tumour cells represents a natural response to their constant proliferative demand. Notably, tumour growth can be inhibited by modifications to proteins involved in iron metabolism. Strategies such as iron depletion through iron chelators, knockout of iron regulatory proteins, upregulation of FPN expression (increasing iron export), or inhibition of transferrin (depleting iron import) all contribute to reduced cancer cell proliferation and tumour growth.[89–93] In addition, downregulation of Divalent Metal Transporter 1 decreases proliferation in colorectal cancer.[94] Iron-depleted conditions may also lead to G0/G1 cell cycle arrest and cell death, mediated by cyclins, cyclin-dependent kinases, and the induction of tumour suppressor p53.[90,95] Finally, ATP production through oxidative phosphorylation, the citric acid cycle, and mitochondrial oxygen consumption under iron-rich conditions may promote tumour growth.[96]

Small Molecular Compounds as Inducers of Ferroptosis

Given the critical role of amino acid transport systems necessary for GSH synthesis in ferroptosis, the use of exogenous low-molecular-weight inhibitors, such as erastin, sorafenib, and sulfasalazine (SSZ), which inhibit the Xc^- system by affecting the extracellular glutamate concentration, appears appropriate. These substances are often used in experiments as positive controls and in reference trials.[97]

Erastin induces ferroptosis primarily by inhibiting the system Xc^- antiporter (SLC7A11), depleting GSH, and secondarily inactivating GPX4. Furthermore, it can bind to mitochondrial VDAC2/3, further disturbing redox homeostasis and promoting ROS. Early observations linked erastin sensitivity to RAS pathway activity, but this is not its core mechanism of action.[98–100] Voltage-dependent anion channels (VDAC) in mitochondria represent another molecular target of erastin.[101] In addition, erastin directly binds to voltage-dependent anion channels 2 (VDAC2) in mitochondria and indirectly generates ROS by disrupting the respiratory chain.[102,103] Promising therapeutic effects of erastin have been demonstrated when combined with other chemotherapeutic agents, such as DOX, cisplatin, temozolomide, or cytarabine.[101,104] The Stockwell group[48] studied the potential application of ferroptosis inducers for chemotherapy-resistant cancer cells overexpressing the RAS family small GTPases. The results showed that, among the 117 tested cell lines, renal cell carcinoma and diffuse large B-cell lymphoma cells were much more sensitive to erastin than other cancer cells (eg, lung and ovarian cancer cells) with reduced RAS family small GTPases expression, as observed in normal cells. However, the poor water solubility and low in vivo stability of erastin significantly limit its broader biological application.[102] Therefore, it is essential to search for new and better erastin analogues. A promising candidate chemotherapeutic agent appears to be piperazine erastin, which has better water solubility and effectively limits the proliferation of HT-1080 cells.[105] In contrast, imidazole ketone erastin has shown promising results for treating lymphoma in a mouse xenograft model (SUDHL6).[106]

Recently, repurposing therapeutic substances already approved for clinical use has become popular. Among these efforts, SSZ, as a conventional synthetic disease-modifying antirheumatic drug approved for rheumatoid arthritis and used as an alternative or in combination regimens, has been approved for medical use by the FDA.[107,108] Like erastin, SSZ induces ferroptosis by inhibiting the Xc^- system; however, its effect is weaker, achieving the desired results only at very high drug concentrations. SSZ has been shown to induce ferroptosis in various cancer cell lines, including non-small cell lung cancer (Calu-1), osteosarcoma (143B), and fibrosarcoma (HT-1080).[48] Moreover, in clinical trials, as part of a combination therapy, SSZ with other chemotherapeutic agents showed promising results against glioma.[109]

Sorafenib is an FDA-approved inhibitor that can induce ferroptosis in preclinical models.[99,110] As a molecular inhibitor targeting multiple protein kinases, sorafenib has been approved for the treatment of advanced hepatocellular carcinoma and thyroid cancer.[111] An analysis of the activity of 87 sorafenib analogues showed that two main mechanisms could be responsible for its function as a ferroptosis inducer: (1) inhibition of a kinase necessary for Xc^- system activity; and (2) competition at the enzyme's active site with other substrates of kinases that mediate the

proper function of the SLC7A11 (xCT) transporter.[48] Unfortunately, many cancer cell lines exhibit resistance to sorafenib, and the mechanism underlying this phenomenon remains unclear, which makes its combination with erastin a promising approach.[112]

Application of Multifunctional NPs as Free Radical Inducers: A Direct Approach to Trigger Ferroptosis in Cancer Cells

Nanomedicine is an emerging field with substantial potential for advancing personalised medicine through novel NPs. Due to their effective interactions with biological systems, NPs have been extensively developed as drug delivery systems to enhance bioavailability and targeted drug delivery, thereby minimising side effects. The primary objective of a drug carrier is to optimise the pharmacokinetic and biodistribution profiles of the drug, enhancing its biological efficacy and reducing side effects through more efficient distribution at the target site.[113] This objective is achieved by exploiting the unique properties of NPs. Encapsulation within NPs can increase the solubility and stability of a drug, thereby extending its circulation time and improving bioavailability. NPs can also be engineered to enhance distribution specificity and overcome significant physiological barriers, facilitating greater accumulation at the target site and thus enabling dose reduction and limiting side effects.[114,115]

Due to their nanoscale size, NMs occupy a niche between bulk structures and atomic or molecular structures, allowing for unique applications.[116] One of their notable characteristics is the increased surface area to volume ratio, which modifies the material's mechanical, thermal, and catalytic properties compared to bulk properties. Despite significant advancements in the understanding of NPs as drug carriers, several challenges remain to be addressed before their effective implementation in clinical settings. When NPs interact with living cells, their modified properties, such as surface reactivity, can lead to unexpected and undesirable physiological effects.[117,118] Besides, the interface between NPs and biological systems involves several components, including the NP surface, the solid-liquid interface defined by the protein corona, and the contact zone with the biological substrate (interaction between NPs, biological identity, and cells).

Cell membranes are self-assembled lipid bilayers, where the shape of the lipid species and membrane curvature affect transmembrane structures, membrane permeability, and enzyme activation. NP–cell interactions can cause changes to membrane fluidity, microdomain composition, or membrane curvature, which can affect the activity of membrane proteins such as receptors, enzymes, ion channels, and nutrient transporters, possibly signalling membrane stress to the cell interior.[119,120] The nature and extent of these interactions influence processes such as NP wrapping at the cell surface, endocytosis, and intracellular biocatalytic properties and play a role in determining the biocompatibility of NPs.

A key attribute of NMs is their capacity to facilitate electron transfer, which can either promote oxidative damage or provide antioxidant protection. ROS are considered inevitable byproducts of aerobic metabolism and are continuously generated, transformed, and consumed by all living organisms. As such, ROS function as crucial physiological regulators that activate signalling pathways. However, when the balance between NM-induced ROS production and scavenging is disrupted, elevated ROS levels can induce oxidative stress, potentially damaging proteins, DNA, lipids, and triggering ferroptosis.[121,122]

The generation of free radicals and other reactive species, which disrupt the existing oxidative balance, is the primary cause of NM-induced cytotoxicity. The process of electron transfer at the nano–bio interface is complex, as the redox potentials and states of surface atoms vary with the structural characteristics of NMs, such as their size, shape, coating, and adsorbed proteins.[123,124] Furthermore, external factors (eg, solution pH) and possible external irradiation significantly influence the pro- or antioxidant capabilities of NMs. As the particle size decreases, a larger proportion of its atoms or molecules are exposed on the surface rather than within the interior of the material.[125,126] The smaller particle size may increase the number of structural defects, leading to altered electronic properties and the establishment of specific surface groups that function as reactive sites. Depending on the chemical composition of the NMs, these surface groups may exhibit passive or active properties, eg hydrophilic or hydrophobic, lipophilic or lipophobic, or catalytically active or passive.[127,128] When the energy levels of NPs are lower than the redox potential of reactive species in biological fluids, electrons can be transferred directly to the NPs, allowing them to function as ROS scavengers and mitigate oxidative stress. This phenomenon has been demonstrated in carbon-based NPs such as fullerenes, cerium oxide NPs, and

palladium nanocrystals.[129] In contrast, some NPs induce the formation of reactive species through surface sorbates acquired through interactions with biological components. Attached molecules can alter the surface energy properties of NPs, enabling surface atom dissolution or electron donation, thereby forming $O_2^{\bullet-}$ or $^{\bullet}OH$ by the reduction of H_2O, O_2, and H_2O_2.[130,131] Finally, metal ions released by metal oxide NPs promote ROS generation through redox cycling or catalysis via Fenton-like reactions. NPs such as silver and silicon dioxide can cause enzyme deactivation or disruption of the membrane structure, further facilitating ROS generation by affecting NADPH oxidase, disturbing cellular calcium homeostasis, and impairing mitochondrial respiration.[132,133]

However, ROS elevation alone is insufficient to conclude ferroptosis. By definition, ferroptosis is iron-dependent and requires lipid peroxidation together with standard assignment criteria (eg, rescue by ferrostatin-1/liproxstatin-1 or iron chelators, and GPX4/system Xc^- involvement). Non-iron platforms (eg, Au-coated hybrid nanosystems under NIR) may increase ROS and often engage photothermal/photodynamic or apoptotic mechanisms unless these ferroptosis criteria are met.[1,134–136] Thus, a correlation between NP properties and ferroptotic checkpoints regarding ROS imbalance and nanotoxicity should follow four property taxes: (I) iron handling (the intracellular content of labile iron), (ii) redox catalysis (peroxide decomposition and the engagement of lipid ROS), (III) antioxidant system modulation (GSH-dependent mechanisms), and (IV) interface of NPs with biological molecules (protein corona effect, surface charge and size disturbing uptake and organelle routing). For instance, iron-bearing nanostructures can raise the labile iron pool and catalyse Fenton chemistry, whereas polymeric carriers often co-deliver inducers (eg, RSL3) or deplete GSH. Protein corona formation modulates targeting and endolysosomal routing, frequently overriding intended ligands and thereby altering where and how ferroptotic chemistry unfolds.[137]

Since ROS elevation alone is non-diagnostic, the attribution of ferroptosis requires evidence of iron dependence and lipid peroxidation, supported by pathway-level engagement beyond morphology.[48,138] In nanoparticle systems, these outcomes are governed by design variables that control cellular routing and redox chemistry, including protein corona–driven bio-identity.[139] Figure 5 summarises the linkage between NP properties and ferroptosis checkpoints, together with the evidentiary criteria used to assign ferroptosis.

Despite strong preclinical signals, the clinical translation of NPs that induce ferroptosis faces numerous hurdles in nanomedicine, including variability in the enhanced permeability and retention (EPR) effect across patients and tumours, corona-driven biodistribution shifts, and limited non-invasive ferroptosis readouts. Regulatory agencies (for instance, the FDA) have issued cross-cutting guidance for products containing nanomaterials, emphasising the need to characterise critical quality attributes and how they relate to safety and performance.[140,141] These restrictions are categorised into government platform comparisons and propose study designs that better anticipate human variability.[140,142]

Overview of NPs That Stimulate Ferroptosis and Can Be Used in Translational Medicine

Nanoparticle-triggered ferroptosis, a regulated mechanism of cell death induced by NPs, is a promising tool in anticancer therapy for effective drug delivery or active tumour targeting.[146] Additionally, owing to their physicochemical properties, NPs can be loaded with anticancer drugs and/or functionalised with cancer-targeting molecules. Moreover, tumour regions exhibit an (EPR) effect, associated with the irregular structure of the extracellular matrix and large gaps in the capillary network (100–800 nm).[147] Thus, NPs can specifically accumulate at tumour sites, significantly increasing the likelihood of selective tumour targeting.[148] NPs may induce ferroptosis on their own or be used for targeted delivery of pro-ferroptotic anticancer drugs. Sufficient drug loading and targeted drug release are required for NPs to function effectively as drug nanocarriers. Furthermore, their physicochemical properties are key factors influencing NP performance, determining (I) how the ferroptosis inducer is loaded, (II) how the nanocarriers enter cancer cells, and (III) the efficiency of the biological response.[30,149] According to recent literature, numerous studies have yielded promising findings on the application of NPs as ferroptosis-inducing agents. In the following sections, we present an in-depth overview of the diversity of NPs and their potential to activate ferroptosis-dependent pathways.

As summarised in Table 1, iron-based platforms primarily modulate labile iron pools and chemodynamic Fenton activity.[29,30,150] In contrast, polymeric/lipid systems more often co-deliver ferroptosis enablers or sensitise antioxidant

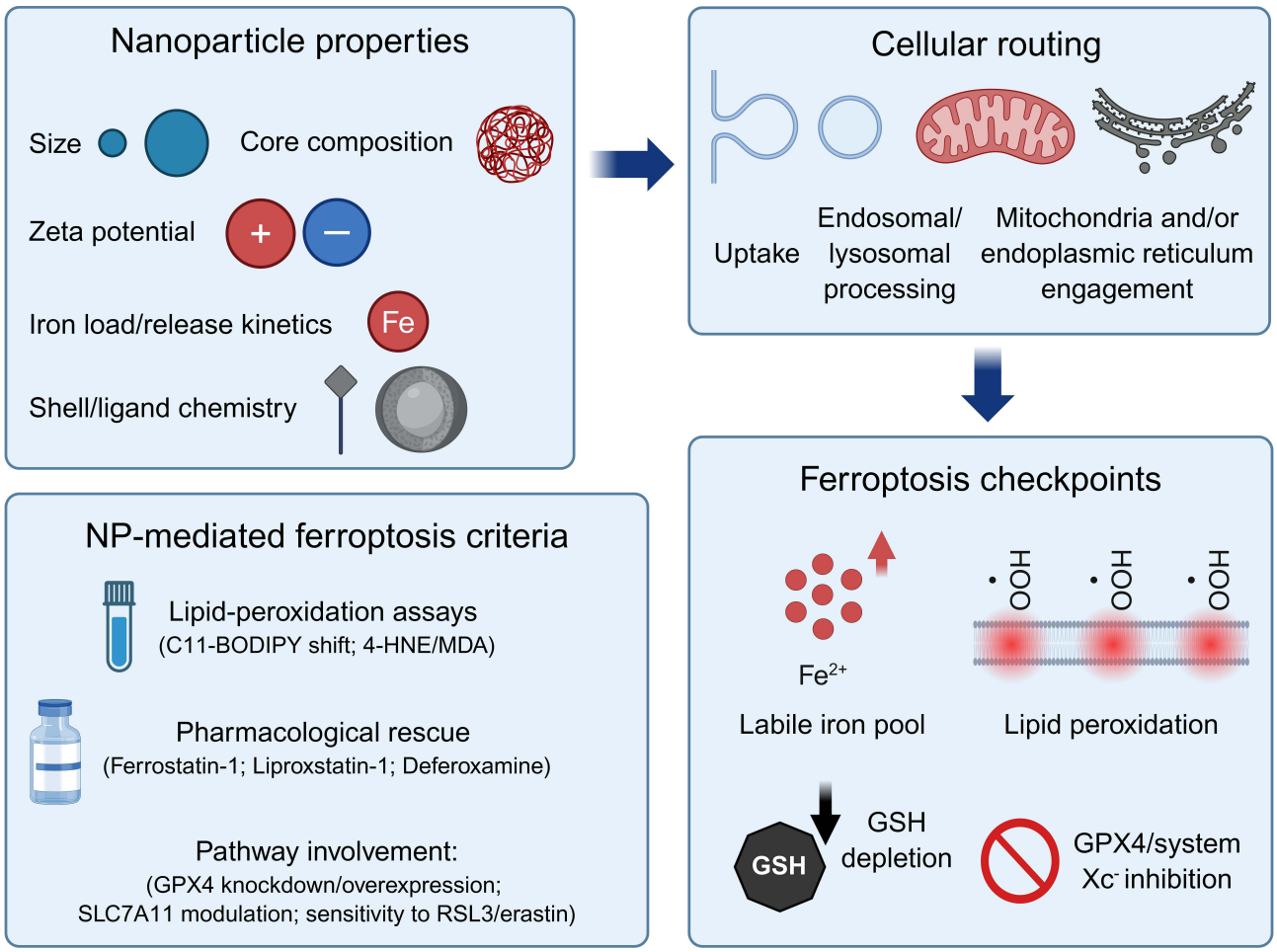


Figure 5 Mechanistic map linking nanoparticle properties to ferroptosis checkpoints. Key physicochemical parameters include size, zeta potential (surface charge), shell/ligand chemistry, iron load and release kinetics, and core composition (iron-based/iron oxides, metal–organic framework/inorganic, polymeric/organic, or lipid-based /liposomal). These parameters affect cellular routing, which includes uptake, endosomal/lysosomal processing, and possible engagement of mitochondria and/or the endoplasmic reticulum. This routing influences the activation of ferroptosis checkpoints, including the expansion of the labile iron pool, lipid peroxidation, GSH depletion, and inhibition of GPX4/system Xc^-. Attribution of NP-mediated ferroptosis relies on converging evidence, including biochemical lipid-peroxidation readouts (C11-BODIPY shift, 4-HNE/MDA), pharmacological rescue with ferrostatin-1/liproxstatin-1 and/or deferoxamine, and pathway-level dependency evidenced by GPX4 inactivation and/or system Xc^- inhibition (eg, by sensitivity to RSL3 or erastin, or by genetic perturbation). Together, these criteria distinguish targeted ferroptosis from non-specific ROS nanotoxicity. Morphology is supportive but non-diagnostic. Ferroptosis confirmation requires lipid peroxidation readouts plus rescue by ferrostatin-1/liproxstatin-1 or iron chelators, with GPX4/system Xc^- involvement. Created in BioRender. Marczak, A. (2025) https://BioRender.com/v55ezrn.[134,143–145]

checkpoints.[151–153] Targeting ligands and external triggers (magnetic, PTT/PDT) tune exposure and the locale of lipid peroxidation.[154–156] Notably, studies that met rescue criteria (ferrostatin-1/liproxstatin-1 or iron chelators) and demonstrated pathway involvement (eg, GPX4 or system Xc^-) provided stronger translational signals (orthotopic models, dose realism) than descriptive ROS readouts alone.[135,157,158]

Ferroptosis-Inducing NPs as a Chemotherapeutic Platform

To overcome the cellular evasion of RCD during chemotherapy, increasing attention has been paid to ferroptosis-inducing NPs in combination with chemotherapeutic drugs. One example is ferroptosis-inducing NPs designed by conjugating lactoferrin (LF) and the RGD_2 dimer with cisplatin-loaded hybrid Fe_3O_4/Gd_2O_3 NPs. FeGd-HN@Pt@LF/RGD_2 NPs are engineered to cross the blood-brain barrier (BBB) via LF receptor-mediated transcytosis and be internalised by cancer cells through integrin $\alpha v\beta_3$ (RGD_2 receptor) binding. Simultaneous increases in the local concentrations of Fe^{2+}, Fe^{3+}, and H_2O_2 lead to the death of orthotopic brain tumours. Due to their small size (6.6 nm) and LF receptor-mediated transcytosis, these NPs can effectively cross the BBB. The resulting iron species (Fe^{2+} and Fe^{3+}) directly participate in the Fenton reaction, whereas cisplatin indirectly promotes H_2O_2 production to accelerate this

Table 1 Representative NPs That Induce Ferroptosis in Cancer Models

NPs	Ferroptosis Inducer	Ferroptotic Mechanism	Application (in vitro and/or in vivo)	Ref
ZVI@CMC	ZVI	Mitochondrial lipid peroxidation; GPX reduction; ROS accumulation; SLC7A11, AKR1B1, AKR1C1, AKR1C2 and AKR1C3 downregulation	OC2, OC3, KOSC3, OEC-M1, SCC9, HSC3, and SAS cell lines; OSCC tumour-bearing mice.	[159]
ZVI@Ag			H1299, H460, A549 and LLC cell lines; lung tumour-bearing mice.	[160]
FeGd-HN@Pt@LF/RGD_2	Fe_3O_4	ROS accumulation	U-87 MG cell line and brain tumour-bearing mice	[161]
γ-Fe_2O_3	-	ROS accumulation; Inhibition of Xc^- system; Lipid peroxidation	4T1 cell line and breast tumour-bearing mice	[162]
RPDGs	Fe^{2+}	ROS accumulation; lipid peroxidation		[163]
SRF@Fe^{3+}TA	Fe^{2}+ SRF	ROS accumulation; Inhibition of system Xc^-; GSH depletion; GPX4 downregulation; lipid peroxidation	4T1, CT26, SCC-7, HepG2, HT-1080 cell lines; tumour-bearing mice	[164]
Ce6-erastin	Erastin Ce6	ROS accumulation; SLC7A11 downregulation	CAL-27 cell line; tumour-bearing mice.	[165]
PtH@FeP	Fe^{3+} cisplatinum	ROS accumulation; GPX4 suppression; NOX activation; lipid peroxidation	4T1 cell line; tumour-bearing mice	[166]
PFG MPNs	Fe^{3+}	ROS accumulation; SLC7A11, SLC3A2, cystine, GSH, and GPX4 downregulation; lipid peroxidation	B16F10 cell line; tumour-bearing mice	[167]
GBP@Fe_3O_4	Fe_3O_4	ROS accumulation; HMOX-1, GCLM, SLC7A11 downregulation; GSH depletion	PC3, C4-2, 786-O, and MDA-MB-231 cell lines; tumour-bearing mice	[168]
Brusatol/silica@MnO_2/Ce6@PEG-FA	Brusatol; MnO_2	ROS accumulation; Inhibition of the activation of the Nrf2 defence pathway; GPX4 and FTH inactivation	MIA PaCa-2 cell line; tumour-bearing mice	[169]
PEG-Fns	Ferrihydrite in ferritin	ROS accumulation, iron/ROS-related irreversible DNA fragmentation, GPX4 inhibition	SCC-7 cell line; tumour-bearing mice	[170]

Abbreviations: 4T1, Murine breast cancer cell line; 786-O, Human renal cell carcinoma cell line; A549, Human lung adenocarcinoma cell line; AKR1B1/AKR1C1/AKR1C2/AKR1C3, Aldo-keto reductases; B16F10, Murine melanoma cell line; brusatol/silica@MnO_2/Ce6@PEG-FA, Nanoparticle combining brusatol; MnO_2-coated silica; and chlorin e6; functionalised with PEG–folic acid for targeted cancer therapy; C4-2, Human prostate cancer cell line; CAL-27, Human oral tongue squamous cell carcinoma cell line; Ce6, Chlorin e6; CT26, Murine colon carcinoma cell line; FeGd-HN@Pt@LF/RGD_2, FeGd nanoparticle loaded with platinum and functionalised with lactoferrin and dimeric RGD (arginine–glycine–aspartic acid) peptide; FTH, Ferritin heavy chain; GBP, Glycyrrhizin; GPX, Glutathione peroxidase enzymes; H1299, Human non-small cell lung carcinoma cell line (p53-null); H460, Human large cell lung carcinoma cell line; HepG2, Human liver carcinoma cell line; HMOX-1, Heme oxygenase-1; HSC3/KOSC3/OC2/OC3/OEC-M1/SAS/SCC9, Human oral squamous cell carcinoma cell lines (OSCC); HT-1080, Human fibrosarcoma cell line; LLC, Lewis Lung Carcinoma; murine lung cancer cell line; MDA-MB-231, Human triple-negative breast cancer cell line; MIA PaCa-2, Human pancreatic adenocarcinoma cell line; MPNs, Phototheranostic metal–polyphenol networks; PC3, Human prostate cancer cell line; PEG-Fns, Polyethylene glycol (PEG)-coated ferrihydrite nanoparticles; PFG MPNs, Phototheranostic metal–polyphenol networks; RPDGs, Cyclised RGD peptide and platinum-conjugated graphene fluoride nanoparticles loaded with doxorubicin (cRGD/Pt + DOX@GFNPs); SCC-7, Murine squamous cell carcinoma cell line; SRF@Fe^{3+}TA, Nanoparticles composed of sorafenib (SRF) loaded into a metal–phenolic network formed by ferric ions (Fe^{3+}) and tannic acid (TA); U-87 MG, Human glioblastoma cell line; ZVI@Ag, Zero-valent iron nanoparticles coated with silver; ZVI@CMC, Zero-valent iron nanoparticles coated with carboxymethyl cellulose.

process,[171,172] ultimately generating ROS. Ferroptosis therapy using FeGd-HN@Pt_2@LF/RGD_2 has been shown to reduce tumour cell proliferation in an orthotopic model (U-87 MG, mice bearing U-87 MG tumours).[173] Additionally, FeGd-HN@Pt_2 and FeGd-HN@Pt_2@LF/RGD_2 showed no toxicity in mouse tissues, confirming the high biocompatibility of these NPs. The intrinsic magnetic resonance imaging (MRI) capability of the NPs was used to monitor the tumour response to ferroptosis (MRI self-monitoring).[161]

Other researchers have also shown that increasing the levels of ROS through lipid peroxidation of biological membranes is a promising strategy for inducing ferroptosis. Accordingly, liposomes embedded with PEG-coated ultrasmall (3 nm) iron oxide NPs (γ-Fe_2O_3) in the lipid bilayer (Lp-IO) were designed. Lp-IO was developed for the intralayer generation of hydroxyl radicals from hydrogen peroxide, and the permeability of the lipid membrane to these radicals was improved by integrating amphiphilic PEG moieties into the liposomal bilayer. This resulted in the effective

initiation of lipid peroxidation and induction of ferroptosis for breast cancer therapy in vitro (4T1 cell line) and in vivo (4T1 tumour-bearing BALB/c mice). In addition, the resulting NPs were identifiable by MRI. A synergistic anticancer effect of chemotherapy and ferroptosis, along with reduced toxicity, was achieved by administering DOX, which downregulates xCT and reduces GPX activity. This, together with Lp-IO, intensifies lipid peroxidation.[162]

NPs that potentially induce ferroptosis have shown promising results against glioblastoma (GBM), the most aggressive and difficult-to-treat form of brain cancer. Zhang et al[163] reported that gallic acid (GA) and Fe^{2+} NPs (GFNPs) form a drug platform in which DOX is loaded by electrostatic adsorption with DSPE-PEG-Pt(IV), and the targeting moiety DSPE-PEG(2000) is coated on the surface with cRGD. The resulting nanoformulation, cRGD/Pt + DOX@GFNPs (RPDGs), releases large amounts of Fe^{2+} in response to near-infrared (NIR) light stimulation. Excess Fe^{2+} and H_2O_2 trigger the Fenton reaction, while free GA further sustains it, generating abundant intracellular •OH radicals. These intracellular•OH radicals oxidise unsaturated fatty acids, leading to the accumulation of lipid peroxidation products and the induction of ferroptosis. RPDGs also exhibit strong photothermal responsiveness and MRI capabilities. This therapeutic system has demonstrated potent anti-GBM activity both in vitro (U-87 MG cell line) and in vivo (GBM-bearing xenograft mice), offering a new strategy for cancer treatment by inducing apoptosis and ferroptosis in combination with photodynamic therapy.[163] Platinum(IV) prodrugs exemplify this logic: abplatin(IV) potentiates ferroptotic lipid peroxidation and improves control of platinum-resistant tumours when delivered via nanocarriers.[174]

Given the crucial role of GSH as a key cellular antioxidant, ferroptosis induced by GSH depletion was achieved using arginine-rich manganese silicate nanosystems (AMSN) in liver cancer cells in vitro (Huh7) and in vivo (BALB/c nude mice). The AMSNs demonstrated a high capacity to deplete GSH, thereby inducing ferroptosis by inactivating GPX4, leading to tumour suppression. Furthermore, the degradation of AMSNs during GSH depletion contributed to enhanced MRI and the on-demand release of DOX in synergistic anticancer therapy. AMSNs exhibited sustained DOX release, which was accelerated under high GSH concentrations and low pH conditions, indicating their high drug-loading efficiency and tumour microenvironment-responsive release. Notably, the AMSN/DOX group exhibited significantly lower cytotoxicity than the free DOX group in normal liver cells.[175]

Iron-Based NPs as Effective Inducers of Ferroptosis

As previously mentioned, iron is critical for the induction of ferroptosis, and its accumulation sensitises tumours to this form of cell death. Therefore, NPs that cause a rapid and substantial increase in intracellular iron levels are promising candidates for oncological therapy.[176] Iron-based NPs can generate ROS via the Fenton reaction, which damages intracellular macromolecules. Additionally, the combination of iron oxide NPs with ROS generators or LOOH can enhance local Fenton reactions, thereby increasing the effectiveness of anticancer drugs.[177]

Zero-valent iron NPs (ZVI-NPs) have been widely studied due to their capacity to generate large amounts of ROS via the Fenton reaction and other chemical processes.[159,178] The efficacy of ZVI-based NPs (bare ZVI, carboxymethylcellulose-coated ZVI@CMC, gold-shelled ZVI@Au, and ZVI@Au@CMC NPs) was evaluated in oral squamous carcinoma cell lines, including OC2, OC3, KOSC3, OEC-M1, SCC9, HSC3, and SAS cells. CMC and Au coatings reduced the aggregation of bare ZVI NPs. The OEC-M1, OC3, and SCC9 cell lines were consistently sensitive to all four NP types, while HSC-3, SAS, KOSC-3, and OC2 were consistently resistant. ZVI@CMC NPs were found to be the most soluble and stable. It has been reported that after incubation with these designed NPs, tumour cells exhibited mitochondrial lipid peroxidation and reduced levels of GPX in subcellular organelles. ZVI@CMC also demonstrated a stronger mitochondrial respiration capacity, counteracting the loss of mitochondrial membrane potential induced by ZVI-NPs. ZVI-resistant cancer cells displayed a set of genes associated with increased NADPH supply, enhanced ROS detoxification capacity, and reduced sensitivity to ferroptosis inducers. Some of these genes sensitised resistant cells to become treatable without affecting healthy, non-cancerous cells. Importantly, ZVI-NPs were rapidly converted to iron ions preferentially within the lysosomes of cancer cells, owing to the more acidic environment of neoplastic lysosomes. The release of iron ions induced a rapid increase in ROS in tumour cells and damaged subcellular organelles, ultimately triggering ferroptosis.[159]

Hsieh et al[160] showed that silver- and carboxymethyl cellulose-coated zero-valent iron NPs (ZVI@Ag and ZVI@CMC NPs) synergistically induced ferroptosis and reprogrammed the immunosuppressive microenvironment in

human lung cancer cell cultures (H1299, H460, A549) and mouse Lewis lung carcinoma. Following treatment with dual-functional NPs, the expression levels of the Nrf2-targeting antioxidant gene *SLC7A11* and ROS detoxification genes eg Aldo-keto reductases (*AKR1B1, AKR1C1, AKR1C2*, and *AKR1C3)* were reduced, sensitising the cells to ferroptosis. Additionally, ZVI-NPs attenuated the cancer cells' self-renewal capacity and downregulated angiogenesis-related genes.[160]

Magnetic Delivery Systems of Drug-Filled NPs as Effective Ferroptosis Initiators

Magnetic delivery systems of drug-filled NPs to the tumour site have long been employed as a therapeutic strategy to enhance drug delivery to the target tissue.[179] However, this drug delivery approach requires the NPs to exhibit magnetic behaviour only when exposed to an external magnetic field and become inactive once the field is removed.[180] Superparamagnetism occurs in ferromagnetic and ferrimagnetic nanostructures. The size of these nanostructures ranges from a few nanometres to several tens of nanometres, depending on the type of materials used.[181] Magnetic NMs, such as superparamagnetic iron oxide NPs, can be steered by external magnetic fields and are increasingly being used in advanced biomedical applications. Iron oxide nanoparticles (IONPs) possess several unique properties, including high physicochemical stability and relatively low toxicity, which can be utilised for hyperthermia and mechanical damage to cancer cells via alternating magnetic fields.[182,183] Besides, IONPs can be classified based on different oxidation states and crystal structures, ie magnetite (Fe_3O_4), maghemite (γ-Fe_2O_3), and haematite (α-Fe_2O_3).[184]

Lin's group constructed an apigenin (API) delivery system for target A549 cells. API is a flavonoid with significant inhibitory effects on various cancer cell types. Magnetic heterogeneous Fe_2O_3/Fe_3O_4 NPs were coated with mesoporous SiO_2. API was then loaded into these nanocomposites, and the surfaces were modified with hyaluronic acid (HA) to obtain a magnetic drug delivery system for API: Fe_2O_3/Fe_3O_4@mSiO_2-HA. The surface modification of iron oxide NPs with mesoporous SiO_2 is an effective strategy for increasing the drug-loading capacity of magnetic NPs. The SiO_2 coating is characterised by superior biocompatibility and hydrophilicity, helping to stabilise the magnetic iron oxide NPs and minimise their agglomeration. HA, a major component of polysaccharides and the extracellular matrix, is highly biodegradable and biocompatible. In CD44-overexpressing cancer cells, it also functions as a broad-spectrum targeting ligand. Moreover, HA modification of NPs can effectively reduce plasma protein adhesion and prolong in vivo circulation time.[185] The magnetic nano-system (Fe_2O_3/Fe_3O_4@mSiO_2–HA) demonstrated effective magnetic and HA-mediated active targeting, supporting its suitability as a targeted delivery platform for various anticancer drugs. Fluorescence imaging, flow cytometry, Western blotting, and assays for ROS, superoxide dismutase, and malondialdehyde confirmed that the enhanced therapeutic effect was due to the induction of apoptosis, lipid peroxidation, and ferroptosis.[183]

Several ferroptosis inducers have recently been developed based on extensive research and growing recognition of the importance of ferroptosis in oncology and cancer therapy.[186] As mentioned previously, RSL3, a known ferroptosis inducer, strongly inhibits the GPX4 system, leading to the accumulation of lipid peroxides and thereby facilitating ferroptosis-induced cell death.[187] RSL3 does not always work alone but can be a component of magnetic delivery systems and actively kill cancer cells. To prevent clearance from the circulatory system, Fe_3O_4 NPs are surface functionalised with Polyethyleneimine (PEI). Additionally, the hydrophobic cavities of hyperbranched PEI allow for efficient encapsulation of metal ions and metal oxides, resulting in stable NPs. Magnetic NPs have been synthesised by modifying Fe_3O_4 with PEI and HA to form Fe_3O_4-PEI@HA. These Fe_3O_4 NPs (loaded with RSL3) were guided to cancer cells via an external magnetic field and activated the ferroptosis signalling pathway by inhibiting the expression of LF, fatty acid-CoA ligase 4 (FACL4), GPX4, and ferritin, while promoting ROS formation. This delivery approach enhanced ferroptosis activation in hepatocellular carcinoma models.[188]

Biological tissues are essentially transparent to magnetic fields, which has led to the development of various strategies aimed at enhancing the permeability and EPR effect of NPs for improved tumour penetration.[189,190] Magnetophoresis has been proposed as a method to increase the accumulation and potential penetration of NMs in tumours.[191] Magnetic PEGylated manganese zinc ferrite nanocrystals (PMZFNs) have emerged as a promising strategy for prostate cancer treatment. Micromagnets are implanted directly into the tumour tissue to guide and retain the intravenously administered PMZFNs at the target site. Manganese-based NMs, including arginine-rich manganese silicate NPs and Mn(III)-rich

manganese oxide NPs, have been shown to significantly disrupt redox balance through intracellular GSH depletion and GPX4 inhibition, ultimately inducing ferroptotic cancer cell death.[175] Guided by the internal magnetic field, PMZFNs accumulate efficiently in prostate cancer models both in vitro (mouse RM-1 and human PC3 prostate cancer cell lines) and in vivo (BALB/c nude mice), triggering potent ferroptosis and activating the cyclic GMP-AMP synthase–stimulator of interferon genes (cGAS-STING) pathway. In addition to directly suppressing tumour growth, ferroptosis initiates immunogenic cell death (ICD) by releasing tumour-associated antigens. The activation of the cGAS-STING pathway further enhances ICD through interferon-β production. The intratumourally implanted micromagnets confer a prolonged EPR effect on PMZFNs, resulting in synergistic anti-tumour activity with reduced systemic toxicity.[192]

Light-Induced NP-Based Theranostics Induce Effective Ferroptosis in Cancer Cells

The recently proposed nanotheranostic strategy, which targets membrane receptors frequently overexpressed in cancer cells, represents a tactical tool for combating malignant tumours.[189] For instance, FA is widely used in active targeting because of its high affinity for folate receptors on cell membranes, which are often overexpressed in cancer cells, making it an effective biomolecule for drug–NP conjugation.[193] Mansur et al[182] investigated a novel nanosystem composed of colloidal hybrid nanostructures designed to simultaneously target, image, and kill TNBC cells in vitro. This nanohybrid consisted of four components: (I) superparamagnetic iron oxide NPs, serving as bifunctional NMs for inducing ferroptosis via inorganic nanozyme-mediated catalysis and magnetotherapy through hyperthermia; (II) a carboxymethyl cellulose biopolymer; (III) FA; and (IV) the chemotherapeutic drug DOX. The approach effectively targeted and eliminated TNBC cells with high folate membrane receptor expression levels in vitro. The findings indicated that the following three interconnected mechanisms contributed to cancer cell death in vitro: (a) ferroptosis, induced by a Fenton-like reaction via magnetite NPs; (b) magneto-hyperthermia, producing heat under an alternating magnetic field; and (c) chemotherapy, causing DNA damage due to DOX release.[182]

Recent advances in nanomedicine have accelerated the development of light-induced theranostics based on adaptable nanomagnets with a variety of light-induced applications, such as the conversion of NIR to visible light, photodynamic therapy (PDT), and photothermal therapy (PTT).[194] PDT is a minimally invasive, multistep process that leverages the toxicity of singlet oxygen and other ROS produced through a reaction between a photosensitiser (PS), which accumulates in malignant cells, and light of a specific wavelength corresponding to the PS's absorbance band, resulting in its excitation and subsequent induction of cancer cell death.[195,196] The design of PSs is often directly linked to the activation of ferroptosis in cancer cells during PDT. To enhance cancer cell targeting, third-generation PSs are frequently integrated with NPs and additional therapeutic agents, including ferroptosis inducers. This formulation reduces cytotoxic side effects in healthy cells and improves PS pharmacokinetics. Recent studies have demonstrated that ferroptosis may be induced effectively and selectively using NP-based systems, either alone or co-loaded with both PS and a ferroptosis-inducing agent.[196] In one approach, an imidazole ligand was coordinated with zinc to form an all-active metal–organic framework nanocarrier in which the photosensitiser Ce6 was encapsulated. This system demonstrated high efficiency in combating 4T1 breast cancer cells in a xenograft mouse model through ferroptosis activation. Ce6-loaded NPs induced intracellular GSH depletion via a disulfide–thiol exchange reaction. GSH depletion led to GPX4 inactivation and increased cytotoxicity, which were reduced by ferroptosis inhibitors. The nanocarrier's enhanced anticancer effects were demonstrated by its ability to inhibit tumour growth and improve survival rates in vivo. Conversely, the co-administration of an iron chelator reduced ferroptosis, diminished anticancer efficacy, accelerated tumour growth, and restored GPX4 activity.[197]

Hypoxic tumour cells significantly limit the effectiveness of PDT in cancer therapy because of the reliance of photosensitizers on oxygen for ROS generation. Therefore, supplying sufficient oxygen is essential for enhancing the therapeutic impact of PDT. Haemoglobin, characterised by its high oxygen saturation capacity and iron content, can serve as both an oxygen carrier for PDT and as a source of iron for ferroptosis.[198] A nanoplatform combining haemoglobin with the photosensitiser Ce6 and the ferroptosis promoter sorafenib (SRF) (SRF@Hb-Ce6) has shown significant potential, revealing promising prospects for combined PDT and ferroptosis therapy in vitro and in vivo. SRF can directly inhibit the glutamate-cystine antiport system Xc^- and indirectly inactivate GPX4, triggering severe ferroptosis when

accompanied by an enriched iron source. PDT has also been shown to effectively downregulate the expression of SLC7A11 and SLC3A2, further enhancing ferroptosis in cancer cells.[199]

The combination of NMs and PTT has also emerged as a promising therapeutic option, as PTT uses a photothermal nanoagent to generate localised hyperthermia upon tumour exposure to light.[200] Hyperthermia is a cancer treatment method in which the tumour is heated to 40–45°C, initiating molecular events that render cells more susceptible to various forms of damage and cell death.[201] Heat can be generated using different methods, including laser light, thermal chambers, and ultrasound. Hyperthermia can be applied locally, regionally, or systemically, based on the tumour's type, size, and location.[202] Although normal cells are not inherently more sensitive to heat than cancer cells, the low pH and hypoxic microenvironment in tumours make cancer cells more vulnerable to thermal stress.[203] The effects of hyperthermia depend on several factors, including the NP size and shape, excitation wavelength, and tissue properties. In response to hyperthermal stimulation, tumour cells tend to overexpress heat shock proteins to protect against thermal damage, which can hinder complete ablation of deep-seated tumours.[204] Numerous studies have indicated that iron-containing NPs can be effectively used as photothermal agents to generate localised hyperthermia.[205] Notably, NIR-II mild hyperthermia can serve as a precise exogenous trigger; a cisplatin–artemisinin nanoparticle system leverages NIR-II to amplify chemo/chemodynamic therapy and synergise with immunotherapy in vivo.[206] More broadly, nano-drug delivery systems can be engineered to enhance T-cell-based immunotherapy - optimising trafficking, antigen delivery and co-stimulation - thereby providing a rational interface with ferroptosis-linked immunogenicity.[207] For instance, GBP@Fe_3O_4, synthesised by encapsulating Fe_3O_4 NPs and liquid 1H-perfluoropentane (1H-PFP) within poly(lactide-co-glycolide)-b-poly(ethylene glycol) (PLGA-PEG) and modified with a heterodimeric polypeptide, has been designed to target prostate cancer and initiate a heat-dependent, tumour-specific ferroptosis strategy. Laser irradiation raises the tumour temperature to 45°C, triggering a liquid-to-gas phase transition of 1H-PFP and the rapid release of Fe_3O_4 NPs, which generate substantial ROS levels in the tumour microenvironment. Simultaneously, heat stress suppresses the tumour's antioxidant response by downregulating the expression of key antioxidant genes, including *HMOX1, GCLM*, and *SLC7A11*, ultimately inhibiting GSH synthesis. Additionally, Xie et al[168] identified the acyl-CoA synthetase ACSBG1 as a crucial pro-ferroptotic factor, knockout of which caused cancer cells to undergo non-ferroptotic rather than ferroptotic cell death.[168]

Cross-Platform Trends in NPs-Mediated Ferroptosis

Identification of ferroptosis-inducing NPs represents a promising avenue for enhancing therapeutic efficacy, either as drug delivery vehicles that sensitise target cells or as standalone treatment modalities.[146,173] NPs engineered for cancer therapy with ferroptosis-inducing capabilities are typically categorised into iron-based, polymeric, and lipid-based platforms. These systems exhibit considerable versatility in terms of composition, functional properties, and mechanisms of action.[30,117,118] Besides, their diversity facilitates the optimisation of biological effects, delivery strategies, and safety profiles.

There are many controversies in nanoparticle-induced ferroptosis regarding the unrealistic dosing and exposure conditions. For instance, iron oxide nanoparticles (IONPs) are often administered at doses exceeding 100 μg/mL in vitro, which may not be achievable or safe in vivo.[208] Such dosing can artificially amplify oxidative stress and ferroptotic markers, leading to overestimation of therapeutic efficacy or toxicity. Moreover, the lack of pharmacokinetic modelling and biodistribution data further complicates the extrapolation of these results to human systems. Many studies rely on subcutaneous xenografts or monocultures of cancer cells to evaluate the induction of ferroptosis. For instance, animal models fail to recapitulate the tumour microenvironment, including immune cell interactions, vascularisation, and metabolic gradients that critically influence ferroptosis sensitivity.[209] The absence of orthotopic or genetically engineered mouse models (GEMMs) limits the ability to assess context-dependent ferroptotic responses and may obscure tissue-specific toxicities or therapeutic windows.

Although the induction of ferroptosis by NPs has emerged as a promising strategy in cancer therapy, numerous studies have asserted a connection between particles' physicochemical properties, such as size, surface charge, composition, and degradability. Surface coatings, such as citrate or PEG, modulate NP stability and cellular uptake; however, their role in ferroptosis remains speculative, primarily due to the limited number of studies that have investigated how surface

functionalization alters iron release kinetics or ROS generation.[210] For instance, iron-based NPs are characterised by cores enriched with iron, a critical element for catalysing Fenton reactions and promoting lipid peroxidation.[70,176] In contrast, polymeric carriers composed of synthetic or natural polymers such as PLGA or PEG enable controlled delivery of ferroptosis inducers (eg, erastin, RSL3, siRNA targeting GPX4 or plasmids encoding shGPX4) into the tumour microenvironment.[52,164,165,188] Lipid-based NPs, which mimic biological membranes, are particularly effective in modulating lipid metabolism. They can enhance lipid peroxidation either by delivering polyunsaturated fatty acids (PUFAs) or by increasing PUFA-phosphatidylethanolamine pools in an ACSL4-dependent manner.[44,187] Furthermore, emerging evidence suggests that surface functionalization of NPs can influence GPX4 interaction through multiple pathways, including enhanced binding, altered cellular trafficking, and microenvironment-responsive assembly.[211] Across nanoplatforms, these physicochemical levers map onto ferroptosis checkpoints in a predictable manner. Composition/degradability governs Fe mobilisation and Fenton reactivity. At the same time, size/shape biases uptake and endo-lysosomal routing (hence where GPX4/system Xc^- can be engaged), and surface chemistry/protein corona modulate cystine/GSH availability and GPX4 vulnerability (Figure 5).

A growing body of evidence suggests that NP size is a critical determinant of iron release kinetics, which in turn modulates the efficiency of Fenton chemistry. In a spectromicroscopy study of iron NPs ranging from 80 nm to 6 nm, smaller particles demonstrated a marked increase in the initial rate of oxidation, attributed to their higher surface-to-volume ratio and enhanced surface reactivity.[208,212] This accelerated redox cycling facilitates the release of Fe(II), the catalytically active species in Fenton reactions. Despite similar intrinsic chemical properties per active site, the total redox flux is significantly elevated in smaller NPs, amplifying their oxidative potential.[212] Upon cellular internalisation, iron oxide NPs are trafficked to lysosomes, where the acidic environment promotes size-dependent dissolution. Smaller NPs dissolve more rapidly, releasing Fe(II) ions that catalyse the conversion of hydrogen peroxide (H_2O_2) into hydroxyl radicals (•OH) via the Fenton reaction.[208] These size-programmed redox and dissolution kinetics are directly relevant to Fe(II) availability required for Fenton chemistry at the membrane.[208,212]

Even though iron oxide NPs can directly generate ROS by themselves, this effect can be further amplified by external magnetic fields.[162,182,205] While these platforms often demonstrate robust in vitro activity, their in vivo efficacy remains variable due to intratumoural heterogeneity and dynamic remodelling of the protein corona.[117,190] Consequently, clinical application of iron-based NPs may necessitate imaging-guided planning (eg, MRI-visible constructs) and careful iron handling/quantification to mitigate off-target accumulation in the liver and spleen and to assess anaemia risk.[73,80,113,161] To prevent the misassignment of generic ROS nanotoxicity as ferroptosis, we recommend including iron-salt comparators (equimolar Fe), reporting trafficking/lysosomal dwell time versus cytosolic access, and using autophagy inhibitors/rescues alongside ferroptosis-specific controls where appropriate.[208,212]

Polymeric systems offer more favourable and tunable pharmacokinetics, allowing for higher drug payloads and facile surface functionalisation with targeting ligands; however, their safety profile is contingent upon drug accumulation and payload characteristics and may be compromised by variability in the EPR effect. Key limitations of polymeric NPs include potential immunogenicity and premature drug release.[113,114,118,147] Lipid-based NPs, while often less immunogenic, require stringent control over lipid composition and stability during manufacturing and storage; batch-to-batch consistency is critical to ensure reproducibility and therapeutic reliability.[116,117]

Polymeric carriers that deliver GPX4 or system Xc^- modulators (eg, RSL3, si/shGPX4) must escape endosomes to reach their cytosolic targets.[57,169,170,213] In contrast, iron-donating NPs often perform better the longer they dwell in lysosomes, where processing liberates Fe(II) via acidic dissolution and ferritinophagy.[212,214] Identifying the dominant trafficking route for a given NP formulation enables deliberate design choices. For GPX4/system Xc^- modulators, designs should prioritise endosomal escape, while for iron-donating constructs, prolonged lysosomal residence and Fe(II) mobilisation.

Despite encouraging preclinical evidence, no nanoparticle-based ferroptosis therapy has yet progressed to routine clinical use; only early clinical exploration has been initiated, underscoring a translational gap.[189] This gap reflects an incomplete understanding of nano–structure–activity relationships (nano-SARs) and the dynamic in vivo transformation of NPs (eg, protein corona remodelling), compounded by tumour-microenvironment heterogeneity.[30,117,149] To advance nano-SAR, we advocate integrating lipidomics/proteomics with computational modelling and high-throughput screening

of systematically varied NP libraries, all under a standardised evidence framework (rescue genetics/chemistry, attribution controls, and platform-specific comparators) to maximise on-target ferroptosis while minimising off-target toxicity.[149,176]

Conclusions and Outlook

Given the differences between the tumour microenvironment and normal physiological conditions, along with the faster proliferation rate of tumour cells, employing NPs for selective drug delivery appears promising. With a growing understanding of ferroptosis mechanisms from biological and medical perspectives, it has recently been recognised that ferroptosis may play a significant role in tumour therapy. Although ferroptosis-based nanotherapies are advancing, several challenges remain. For instance, the interactions between NPs and cellular ferroptosis pathways are complex and depend on the physicochemical properties of the NPs, including their size, load distribution, concentration, type, and cell model characteristics. In addition, the inevitable toxic side effects of NPs or drug-loaded nanosystems have contributed to the failure of some clinical trials.

The same chemistry that drives tumour cell killing can oxidise lipids in ferroptosis-sensitive normal tissues such as the kidney and liver, so exposure and tissue selectivity must be tightly controlled.[1,209] Systemic iron handling adds further complexity: perturbations of the labile iron pool risk iron overload and inflammatory sequelae.[215] A central methodological bottleneck is mechanistic attribution in vivo, as ROS accumulation is non-specific. Therefore, the robust assignment of ferroptosis should involve coupling of lipid-peroxidation readouts with rescue by lipophilic radical-trapping antioxidants or iron chelators and evidence of GPX4/system Xc^- contribution.[7,32,157] These signals are likely to vary across and within tumours, given heterogeneity in iron and redox metabolism, which complicates patient selection and response monitoring.[1,209] In addition, non-invasive monitoring of on-target lipid peroxidation or ferroptosis pathway engagement remains underdeveloped and should be incorporated into early-phase trials to enable pharmacodynamic decision-making.[34,216–218] Thus, the effect of ferroptosis on the function of normal tissues requires further exploration. This suggests that the drug should be targeted more precisely to the focal tissue, which remains a challenge for the research community and industry.

Consequently, the synthesis and development of new NMs capable of effectively modulating the ferroptosis pathway are crucial for the development of future therapeutic strategies and the establishment of novel clinical trials. Despite compelling preclinical data, several translational constraints remain. First, delivery efficiency and tumour heterogeneity limit reproducible target engagement as meta-analyses estimate that a median of ~0.7% of the injected nanoparticle dose reaches solid tumours after systemic administration, with wide variability across tumour types and models.[38,219] This variability reflects patient-specific vascular permeability, perfusion, and interstitial pressure, which challenge EPR-dependent designs and patient selection strategies.[147] Furthermore, nano–bio interactions reprogram nano-formulations in vivo. Protein corona formation reshapes colloidal identity, opsonisation, and biodistribution, often steering particles to the mononuclear phagocyte system (liver/spleen) and away from tumours; pre-formed and evolving coronas further complicate scale-up and lot-to-lot reproducibility.[142,220,221]

In terms of reported clinical data on the subject, only one clinical trial has sought to investigate ferroptosis induction by the intratumorally injection of carbon nanoparticle-loaded iron [CNSI-Fe(II)] (clinical trial NCT 06048367). Phase I of this study, conducted at West China Hospital, Sichuan University, is enrolling patients with advanced solid tumours. Particular focus is given to those with KRAS mutations, including colorectal, pancreatic, breast, gastric, cervical, lung, head and neck, and prostate cancers. The emphasis on KRAS-mutant tumours reflects preclinical observations that KRAS-driven cancers (eg, pancreatic ductal adenocarcinoma) exhibit cystine/cysteine addiction and are susceptible to cystine/cysteine deprivation–induced ferroptosis. At the same time, genetic or pharmacologic inhibition of system Xc^- augments this vulnerability. Although KRAS mutation is not universally required for ferroptosis, these tumours present a compelling ferroptosis-sensitised context that may benefit from iron-augmented strategies.[222–224] This clinical trial has two main objectives. First, to assess the safety and tolerability of intratumoural injection of CNSI-Fe(II) in patients with advanced solid tumours, and second, to evaluate the pharmacokinetics of CNSI-Fe(II) and its preliminary ability to limit tumour growth. The trial is recruiting male and female patients aged 18–75 years. The study was expected to be completed in February 2024, but data are still being collected. As relevant precedents, iron-oxide nanoparticle magnetic

hyperthermia (NanoTherm®) is being explored in recurrent glioblastoma (NCT06271421), and clinically approved ferumoxytol delineates the safety envelope and immunological caveats of parenteral iron-oxide nanoparticles in humans.

Complement activation and anti-PEG responses can trigger acute infusion reactions and shorten nanoparticle circulation upon repeat dosing (CARPA, ABC). Screening for pre-existing anti-PEG antibodies, slow-infusion strategies, and PEG-alternatives or shielding approaches may mitigate risk.[225–227] Systemically delivered ferroptosis-oriented nanomaterials typically accumulate in the liver/spleen; sub-6–8 nm constructs favour renal elimination but limit loading, whereas larger constructs risk prolonged retention in the reticuloendothelial system and off-target oxidative injury.[228,229] Iron-rich nano-formulations and Fenton-activatable cargos may amplify lipid peroxidation in non-tumour tissues (eg, liver/kidney). Clinically used iron-oxide nanoparticles (eg, ferumoxytol) demonstrate that formulation and dosing critically modify their immunomodulatory and catalytic behaviour, underscoring the need for hemocompatibility and complement testing in GLP packages.[230,231]

Translation depends on disciplined product engineering, including scalable synthesis, tight control of iron content/valence, impurity profiles (eg, endotoxin), corona-sensitive attributes, and robust in vitro–in vivo correlations, to ensure predictable pharmacology. Regulators increasingly expect comprehensive physicochemical characterisation and explicit immunotoxicology (complement activation and anti-PEG assessments) within a quality-by-design CMC framework.[209,232] Furthermore, when nanoparticles co-deliver drugs or are paired with external energy triggers, regulatory classification as a combination product may apply. Therefore, planning for device–drug interactions and human-factors considerations should be made explicit at the trial design stage.[233–236]

The above-mentioned clinical trial demonstrates that nanotherapeutics-based ferroptosis modulation has promise as a novel cancer treatment strategy. Although the clinical application of nanotherapeutics targeting ferroptosis remains limited, this approach is expected to offer an alternative pathway to enhance therapeutic outcomes in patients with cancer. Continued rigorous research is essential to bridge the gap between the therapeutic potential of ferroptosis-inducing NPs and current biomedical requirements.

Disclosure

The authors report no conflicts of interest in this work.

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