Overview and SWOT analysis of nano-ferroptosis therapy for cancers

Qian Chen[b], Junli Zhu[b], Junhuang Jiang[b]*, Zhengwei Huang[a,b]*

(a State Key Laboratory of Bioactive Molecules and Druggability Assessment, Department of Pharmacy, Jinan University, Guangzhou 511436, P. R. China

b Department of Pharmacy, College of Pharmacy, Jinan University, Guangzhou 511436, P. R. China)

*Corresponding authors.

Zhengwei Huang, Ph.D., Tel & Fax: 020-39943117, E-mail address: huangzhengw@jnu.edu.cn

E-mail addresses of the authors are listed below.

Qian Chen (Q. Chen, Q. C.): chenqian@stu2024.jnu.edu.cn

Junli Zhu (J. Zhu, J. Z.): zhujunli@stu2024.jnu.edu.cn

Junhuang Jiang (J. Jiang, J. J.): junhuangjiang@163.com

Zhengwei Huang (Z. Huang, Z. H.): huangzhengw@jnu.edu.cn

Recent progress in various cancers treatment

Currently, nano-ferroptosis therapy has demonstrated promising efficacy in the treating various cancers, including glioma, lung cancer, breast cancer, pancreatic cancer, colorectal cancer (CRC), melanoma, prostate cancer, and ovarian cancer. In the following sections, we will review studies detailing the use of nano-ferroptosis therapy in each of these cancer types.

Glioma therapy

Glioma is a highly aggressive and lethal primary brain tumor that accounts for 40-60% of all primary intracranial tumors, making it the most common type of tumor in the central nervous system [1]. Glioblastoma (GBM), a subtype of glioma, is characterized by high morbidity, recurrence, and mortality, with a 5-year survival rate of approximately 5% [2]. Emerging ferroptosis therapy have shown potential not only in shaping the acidic, hypoxic, and immunosuppressive glioma microenvironment but also in inhibiting glioma cell proliferation and aggressive growth [3]. For instance, ferroptosis inducer RSL3 has been found to induce glycolytic dysfunction and autophagy-dependent ferroptosis in glioma cells, thereby inhibiting glioma cell growth [4]. In addition, ferroptosis inducers that inhibit GPX4 expression can synergize with radiotherapy to kill glioma cells without exacerbating DNA damage [5]. These findings underscore ferroptosis as a promising therapeutic strategy for glioma treatment.

Researchers have recently reported an effective treatment for glioma using nanocomposites to induce ferroptosis. Liu *et al.* developed a new bionic brain-targeted nano-delivery system (Fe_3O_4-siPD-L1@M-BV2 type) for combined ferroptosis-immunization therapy of drug-resistant GBM. Fe_3O_4 nanoparticles alone were difficult to cross the blood-brain barrier (BBB), but the nanosystems coated with microglial cell membranes (M-BV2 type) mimic the natural penetration mechanism of microglia, and were successfully recruited into drug-resistant GBMs through the BBB. When uptake by GBM cells, the loaded siPD-L1 was released to inhibit the protein expression of programmed cell death ligand-1 (PD-L1) in GBM cells. This inhibition activated Effector T cells (Teff cells), which secreted interferon-γ (IFN-γ) to promote ferroptosis of GBM cells, and the process also promoted the maturation of DC cells (Figure S2) [6].

In another study, Zhu *et al.* prepared surface-modified polymer nanomedicine (HPNFcN) with neutrophil-targeting ligands. Due to the natural BBB crossing and tumor-infiltrating ability of neutrophils, HPNFcN could be delivered to the in situ glioma site via neutrophil-mediated hitchhiking across the BBB. The results suggested that HPNFcN achieved a synergistic ferroptosis immunotherapy cascade, with a potent inhibitory effect on the growth of *in situ* gliomas [7]. Similarly, Li et al. designed a ferroptosis therapeutic platform by coupling angiopep-2 peptide-modified engineered exosomes with magnetic nanoparticles (MNPs). Angiopep-2 triggered transcytosis, allowing particles to cross the BBB and target GBM cells by recognizing low-density lipoprotein receptor protein 1 (LRP-1) [8].

Lung cancer therapy

Lung cancer is one of the most prevalent cancers worldwide. Despite the many therapeutic options, the 5-year survival rate for lung cancer remains low, with drug resistance posing a significant challenge in treatment [9]. Literature suggests that the progression of lung cancer can be suppressed through the induction of ferroptosis in lung cancer cells, concurrently bypassing the issue of drug resistance in these cells [10]. Further studies revealed that curcumin, a biologically active natural compound, could induce the onset of ferroptosis by inhibiting the expression of GPX4 and FSP1 in lung cancer cells, thereby inhibiting the growth of lung cancer cells [11]. In addition, Feng et al. demonstrated that the combination of isoorientin (IO) and DDP induced ferroptosis and reversed drug resistance in lung cancer cells by modulating the SIRT6/Nrf2/GPX4 signaling pathway [12]. These findings illustrate the great potential of ferroptosis as a therapeutic strategy in lung cancer treatment.

Further evidence has demonstrated the effectiveness of ferroptosis for treating lung cancer. Tian *et al.* developed a nanomedicine for non-small cell lung cancer (NSCLC) treatment of by self-assembly of tetravalent platinum (Pt) encapsulated in human serum albumin (HSA@Pt(IV)). They investigated the *in vivo* distribution of cisplatin and HSA@Pt(IV) using the Lewis Lung Carcinoma (LLC) subcutaneous homograft mouse model. Fluorescence analysis showed that HSA@Pt(IV) had a stronger ability to accumulate at the tumor site compared to cisplatin, suggesting its

drug delivery capacity. The experimental results indicated that HSA@Pt (IV) could significantly deplete GSH in tumor cells, triggering ferroptosis (Figure S3) [13]. Similarly, Fu *et al.* developed an inhalable biomineralized liposome LDM co-loaded with DHA and calcium phosphate, administered via nebulization to achieve effective accumulation in the lungs and further enhanced ferroptosis therapy by an endoplasmic reticulum (ER) process centered on Ca^{2+} burst. The results demonstrated the sustained lung accumulation and remarkable anti-tumor capacity of LDM [14].

Breast cancer

Breast cancer remains the most common cancer globally, especially among females, accounting for about 30% of all cancers in women and posing a significant threat to human health. It is influenced by several factors, including economic development, family genetics, hormone therapy, and lifestyle [15]. While radiotherapy is commonly employed for local treatment, it is often associated with non-specific toxicity and drug resistance. Studies have shown that drug-resistant breast cancer cells are dependent on GPX4, suggesting that they may be sensitive to ferroptosis induced by downregulation of GPX4 expression. This indicates that ferroptosis could serve as a potential target to overcome drug resistance in breast cancer [16]. Ferroptosis inducers such as RSL3 [17] and SAS [18] have been shown to inhibit the peroxidase activity of GPX4 in breast cancer cells, thereby triggering ferroptosis. Hence, ferroptosis therapy holds promise as an alternative to traditional radiotherapy for the treatment of breast cancer, potentially offering a novel approach.

In this context, Liang *et al*. constructed novel tumor microenvironment-activated metal-organic frameworks (AuFCSP MOFs) to enhance anticancer therapy through a combination of radiotherapy and ferroptosis induction. These nanoparticles were enriched at the tumor site through the EPR effect and reduced by GSH within the tumor, releasing Au NPs and Fe/Cu ions, ultimately triggering ferroptosis [19]. Similarly, Wu *et al.* engineered a binary lipid nanoregulator (RO NA) using nano-assembly technology and molecular engineering. RO NA consists of a GPX4 inhibitor and lipid metabolism regulators designed to disrupt the ultimate lipid membrane defense against ferroptosis in cancer cells. Orlistat in nanosystem (sp-RO NAs) acted as a “dual enhancer”. On the

one hand, it acted as an inhibitor of the enzyme FASN to regulate lipid composition. On the other hand, non-cytotoxic orlistat in combination with RSL3 significantly enhanced the cytotoxicity of RSL3 on tumor cells as well as RSL3-induced GPX4 depletion, thereby promoting the ferroptosis of breast cancer cells, as shown in Figure S4. *In vivo* results demonstrated the anti-tumor efficacy of RO NA in 4T1-loaded mice [20].

Pancreatic cancer therapy

Despite ongoing advancements in oncology, the treatment of pancreatic cancer remains a major challenge to human health, generally recognized as "the king of cancers". The five-year survival rate for pancreatic cancer is still under 10%, largely due to the unique biology of pancreatic tumors, which hampers the treatment effects [21]. Studies have shown that linoleic acid (LA) and α-linolenic acid (αLA) in 18-carbon fatty acids increased lipid peroxidation in pancreatic cancer cells, exhibiting morphological changes in ferroptosis and inhibiting cancer cell growth [22]. In addition, Eling *et al.* found that ART specifically induced ferroptosis in pancreatic ductal adenocarcinoma (PDAC) cell lines and achieved the highest cytotoxicity in PDAC cell lines. After treatment with ferrostatin-1, a ferroptosis inhibitor, lipid peroxidation, and cell death were inhibited and cell survival increased in PDAC [23]. Overall, these findings indicate that ferroptosis activation offers a promising and novel approach for treating pancreatic cancer.

In a recent study, Huang *et al*. developed a novel iron-containing nanoparticle formulation loaded with the ferroptosis inducer erastin, termed PTFE. This nanoparticle system operates via a dual anti-tumor mechanism, providing an efficient treatment for pancreatic cancer. The nanoparticle consists of two parts: a nanocore made from erastin encapsulated within a PLGA and a MOF shell formed by liganding Fe^{3+} with tannic acid (TA). When entering the pancreatic cancer cells, the PTFE nanoparticles release both erastin and Fe^{3+}, which synergistically disrupted the redox balance at the tumor site, leading to ferroptosis of the cancer cells (Figure S5). Both *in vivo* and *in vitro* experiments demonstrated the efficacy of PTFE in treating pancreatic cancer, with good tolerability and biocompatibility *in vivo,* highlighting its potential as a therapeutic agent

[24]. In addition, Yu *et al.* developed a dual-gated nanodrug based on MXene that specifically targeted pancreatic cancer cells and induced ferroptosis, demonstrating potent anti-cancer effects [25].

CRC therapy

CRC is the most common and highly aggressive malignant tumor of the gastrointestinal system. The mainstay of clinical treatment includes chemotherapy, surgery, and radiotherapy. However, clinical resistance and the inflammatory tumor microenvironment (TME) lead to poor responses to current therapies, resulting in unsatisfactory treatment outcomes for patients [26]. Encouragingly, it has been reported that the level of ROS, a key component of ferroptosis, is typically higher in CRC cells than in normal cells, suggesting that CRC cells are particularly susceptible to ferroptosis [27]. Another study revealed that downregulation of the m^6A demethylase fat mass and obesity-associated protein (FTO) expression in CRC cells inhibited the effects of SLC7A11 or GPX4, enhancing the sensitivity of CRC cells to erastin and RSL3 treatment, thereby triggering ferroptosis and ultimately inhibiting CRC cell proliferation [28]. The above results further support the potential and feasibility of ferroptosis as a therapeutic approach to treat CRC.

In response, Deng *et al.* developed a multifunctional chemical-photothermal nanoplatform LCC NPs, consisting of camptothecin (CPT) and IR820. The Se-Se bond in the LCC NPs, upon rupture, triggered oxidative stress and depletion of GSH in cancer cells to counteract this effect, leading to excessive accumulation of LPO. Simultaneously, exogenous LA was oxidized under photothermal conditions, resulting in a significant increase in ROS, further promoting LPO accumulation and inducing ferroptosis in CRC cells (Figure S6) [29]. Recent studies have targeted hydrogen sulfide (H_2S), a known promoter of colorectal tumor growth. Pan *et al.* designed H_2S-responsive zinc oxide-coated virus-like silica nanoparticles (VZnO), in which zinc oxide (ZnO) was an efficient desulphurizing agent. When reaching the tumor site, VZnO reacted with H_2S in the tumor cells, significantly reducing the GSH level in the tumor cells and leading to a substantial accumulation of LPO in the tumor cells, which ultimately induced ferroptosis [30].

Other cancers therapy

In addition to the cancers mentioned above, other cancers such as melanoma [31], prostate cancer [32], and ovarian cancer [33] have also been widely treated with nano-ferroptosis therapy. For example, Wang *et al.* designed an EFP nanocapsule by self-assembling epigallocatechin gallate (EGCG) and ROS-producer phenethyl isothiocyanate (PEITC). This nanocapsule was then integrated into a microneedle patch, forming EFP@MNs, which showed enhanced therapeutic efficacy in melanoma treatment. The results indicated that EFP@MNs promoted the accumulation of LPO, thereby inducing ferroptosis in melanoma cells [34]. For prostate cancer, Wang *et al*. designed metal-free arsenic nanosheets PMANs loaded with DOX, targeting the prostate-specific membrane antigen (PSMA) for efficient treatment of prostate cancer. PMANs inhibited the expression of SLC7A11 and GPX4, leading to enhanced ROS production and LPO accumulation, which triggered ferroptosis. Moreover, PMANs increased the sensitivity of prostate cancer cells to DOX, thereby amplifying the tumor-killing effect of the synergistic treatment [35]. Similarly, Wang *et al.* developed Pt(IV)-loaded human serum albumin (HSA) nanoparticles, named Abplatin $^{(iv)}$, for the treatment of ovarian cancer. Abplatin $^{(iv)}$ demonstrated low systemic toxicity, induced ferroptosis in ovarian cancer cells, and significantly inhibited the growth of platinum-resistant ovarian cancer cells [36]. In conclusion, these studies underscore the promising future of nano-ferroptosis therapy across a wide range of cancers. As a potential alternative to conventional therapies, this innovative approach holds great promise for enhancing the efficacy and reducing the toxicity of cancer treatment.

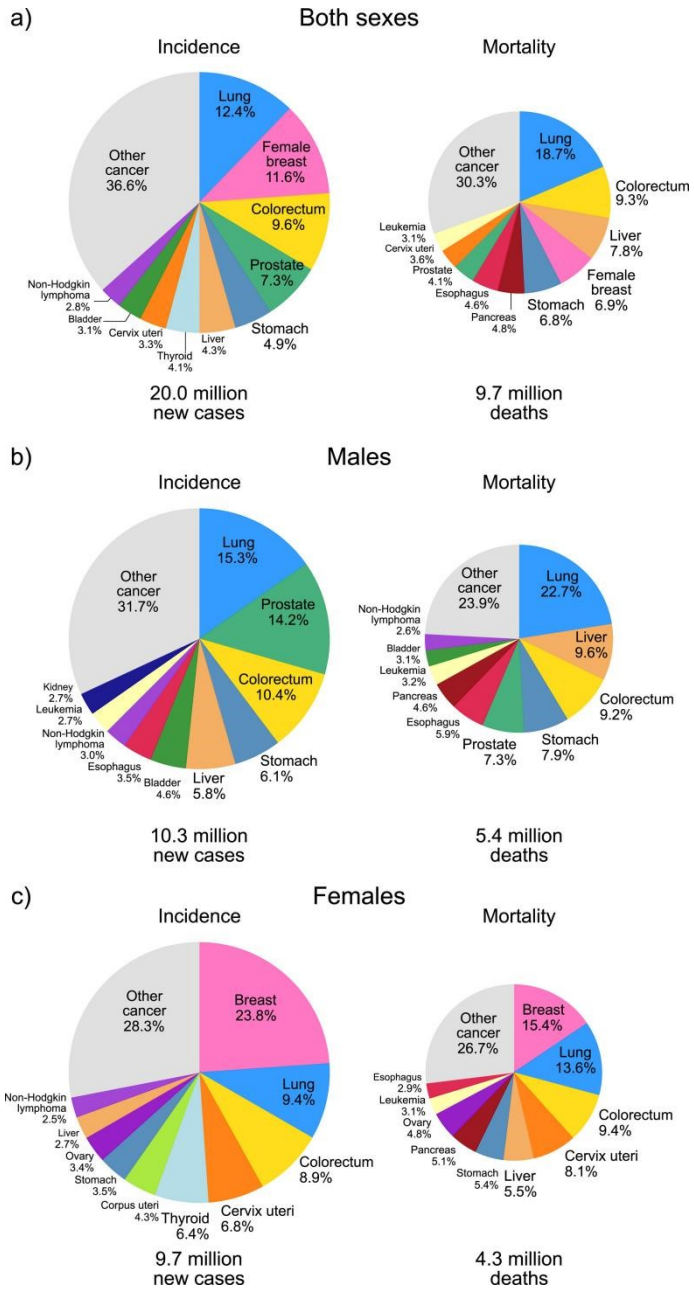

Figure S1. Incidence and mortality rates of various cancers in (a) both sexes, (b) men and (c) women, Reproduced from Bray et al. with permission from the CA: A Cancer Journal for Clinicians [37].

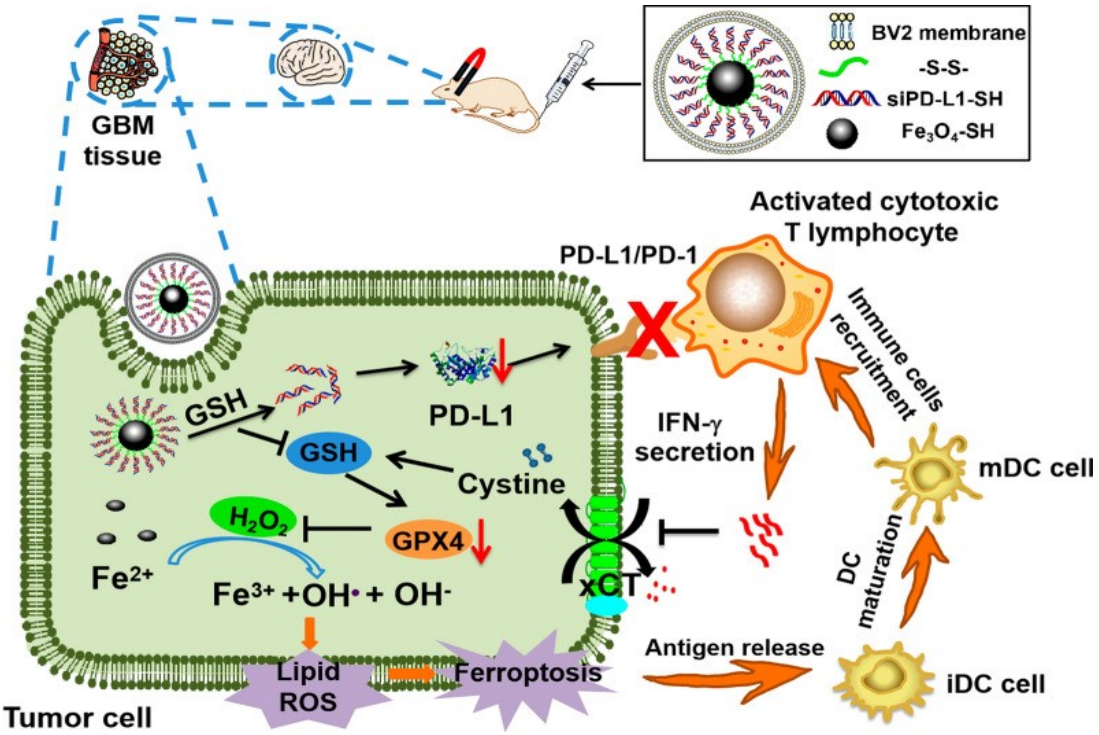

Figure S2. Reciprocal cascade amplification between ferroptosis and immunotherapy of Fe_3O_4-siPD-L1@M-BV2 for GBN treatment. Reproduced from Liu *et al.* with permission from the Journal of Nanobiotechnology [6]. Abbreviations: GBM: glioblastoma, IFN-γ: interferon-γ, PD-L1: programmed cell death ligand-1, GSH: glutathione, GPX4: glutathione peroxidase 4, H_2O_2: hydrogen peroxide, ROS: reactive oxygen species, DC: dendritic cell.

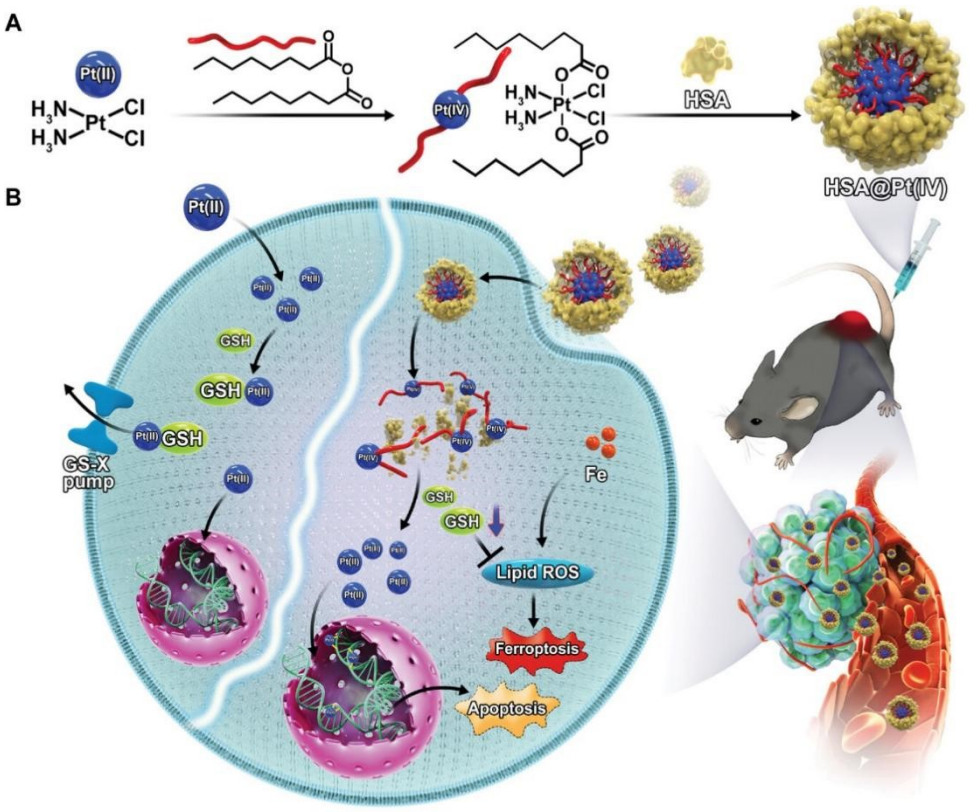

Figure S3. (A) Construction of HSA@Pt(IV) and (B) schematic illustration of NSCLC cell death induced by HSA@Pt(IV). Reproduced from Tian *et al.* with permission from the Small [13]. Abbreviations: Pt: platinum, HAS: human serum albumin, GSH: glutathione, ROS: reactive oxygen species.

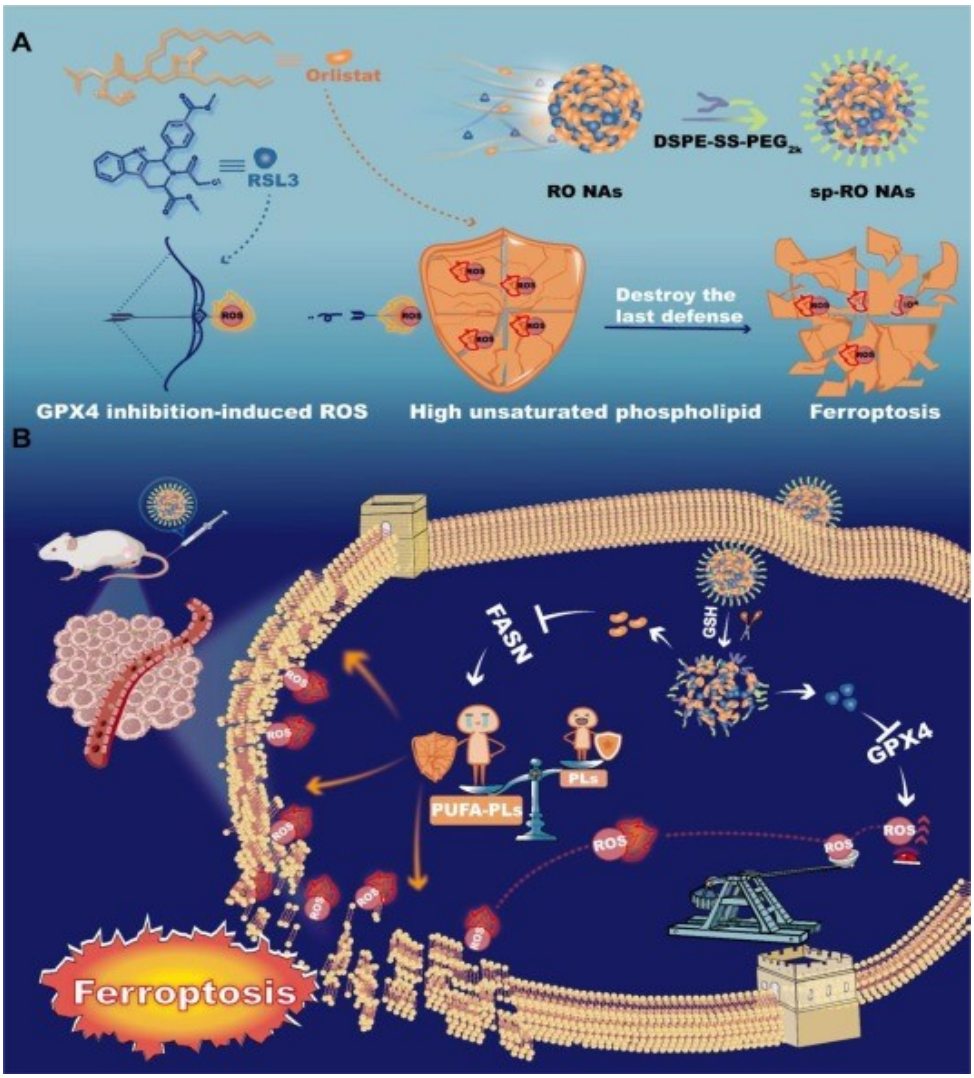

Figure S4. Schematic presentation of a self-engineered lipid nanoregulator for ferroptosis-driven breast cancer treatment. Reproduced from Wu *et al.* with permission from the Chemical Engineering Journal [20]. Abbreviations: DSPE: distearoylphosphatidylethanolamine, PEG: polyethylene glycol, GSH: glutathione, GPX4: glutathione peroxidase 4, PUFA: polyunsaturated fatty acid, ROS: reactive oxygen species, FASN: fatty acid synthase.

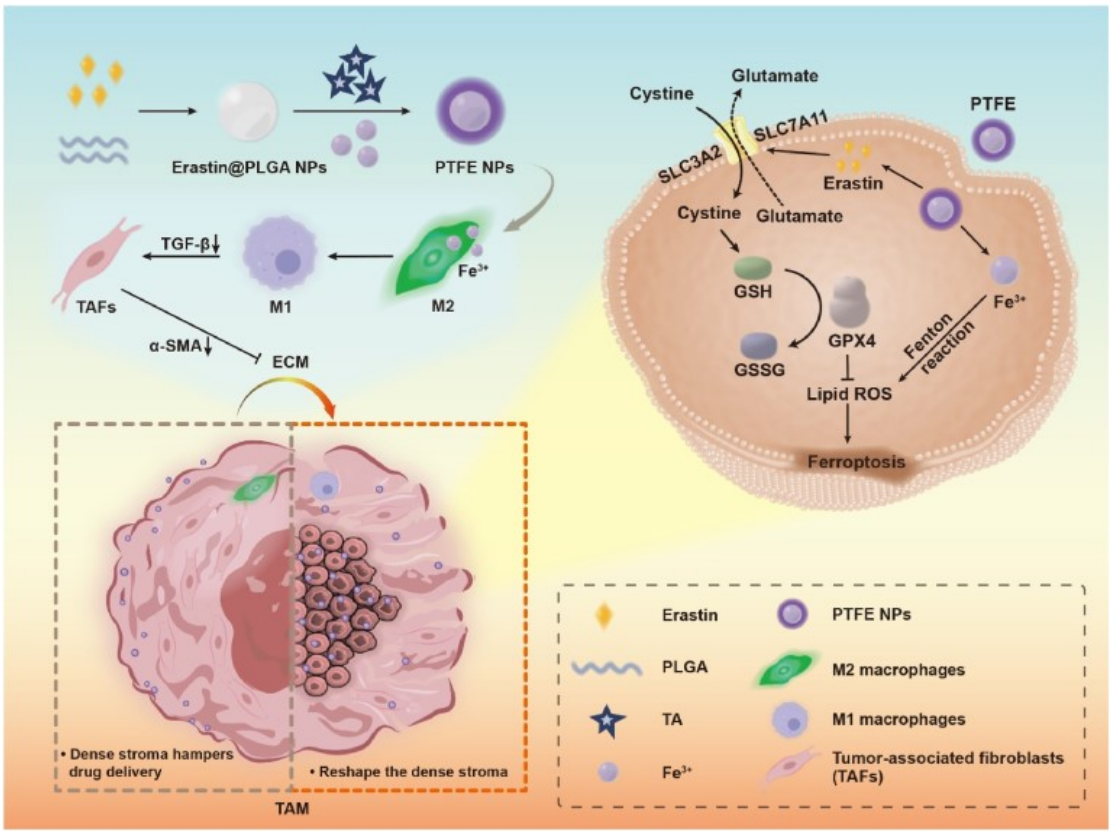

Figure S5. Schematic illustration of the preparation and mechanism of action for the PTFE for pancreatic cancer treatment. Reproduced from Huang *et al.* with permission from the Materials Today Bio [24]. Abbreviations: PLGA: poly(lactic-co-glycolic acid), TAM: tumor-associated macrophages, TAFs: tumor-associated fibroblasts, TGF-β: transforming growth factor-beta, ECM: extracellular matrix, GSH: glutathione, GPX4: glutathione peroxidase 4, GSSG: oxidized GSH, ROS: reactive oxygen species, TA: tannic acid.

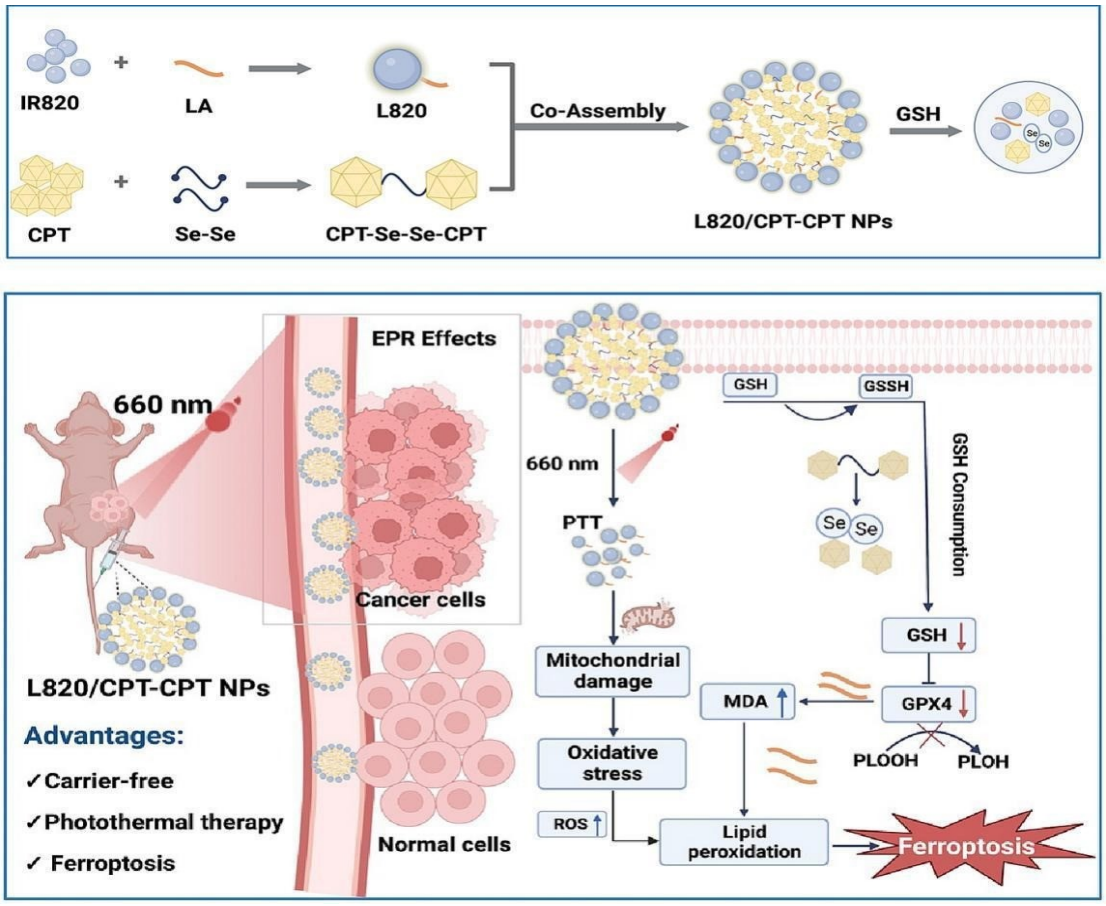

Figure S6. Schematic illustration of GSH-triggered NPs for anti-CRC treatment. Reproduced from Deng *et al.* with permission from the Journal of Controlled Release [29]. Abbreviations: CPT: camptothecin, LA: linoleic acid, MDA: malondialdehyde, PTT: photothermal therapy, EPR: enhanced permeability and retention, GSH: glutathione, GPX4: glutathione peroxidase 4, GSSH: glutathione disulfide, ROS: reactive oxygen species.

263 **Table S1.** Abbreviations and their full forms in the review.

Abbreviations	Full Forms
Aa	auriculoside acetate
ACSL4	Acyl-CoA synthetase long-chain family member 4
ADME	adsorption, distribution, metabolism, and excretion
AI	Artificial intelligence
AI-CSR	AI-based Complex Systems Response
AKI	acute kidney injury
AML	acute myeloid leukemia
AMPK	human phosphorylated adenylate-activated protein kinase
ANG	angiopep-2
APE1	apurinic/apyrimidinic endonuclease 1
ASO-MALAT1	adenocarcinoma transcript1
Arg	arginine
ART	artesunate
ATRA	all-trans retinoic acid
BBB	blood-brain barrier
BQR	brequinar
BTC	bile duct carcinoma
CA	cinnamaldehyde
CACN	co-activated catalytic nano
CF	cobalt ferrite
CHP	copper-doped hollow Prussian blue
CMC	carboxymethyl chitosan
COF	covalent organic framework
CoQ	coenzyme Q
CPT	camptothecin
CRC	colorectal cancer
CTL	cytotoxic T-lymphocyte

Table S1 *(continued)*

Abbreviations	Full Forms
Cu	copper
Cys	cysteine
DCs	dendritic cells
DHA	dihydroartemisinin
DHODH	dihydro nicotinic acid dehydrogenase
DL	deep learning
DMT1	divalent metal transporter protein 1
DNA-FON	DNA-functionalized iron oxide nanoparticles
DRF	disulfidoptosis-related ferroptosis
EPR	enhanced permeability and retention
ER	endoplasmic reticulum
Er	erastin
FAP	fibroblast activation protein-alpha
FCSP MOFs	ferroptosis-inducing metal-organic framework
FDFT1	farnesyl-diphosphate farnesyltransferase
FSP1	ferroptosis inhibitory protein 1
GBM	Glioblastoma
GCL	glutamate-cysteine ligase
Glu	glutamate
GOx	glucose oxidase
GPX4	Glutathione peroxidase 4
GPx-like	GSH peroxidase-like
GRAS	generally recognized as safe
GSEA	gene set enrichment analysis
GSH	glutathione
GSS	glutathione synthase
GSSG	oxidized GSH

Table S1 *(continued)*

Abbreviations	Full Forms
GT	green tea extract
HA	hyaluronic acid
HAP	hydroxyapatite
Hb	hemoglobin
HCC	hepatocellular carcinoma
HMSN	hollow mesoporous silica nanoparticle
4-HNE	4-hydroxy-2-nonenal
H_2O_2	hydrogen peroxide
HO-1	heme oxygenase 1
H_2S	hydrogen sulfide
HSA	human serum albumin
IARC	International Agency for Research on Cancer
IC50	half maximal inhibitory concentration
ICC	intrahepatic cholangiocarcinoma
ICD	immunogenic cell death
ICG	indocyanine green
IFN-γ	interferon-γ
IO	isoorientin
IONPs	iron oxide nanoparticles
LA	lactic acid
LA	linoleic acid
αLA	α-linolenic acid
LAE	lauryl arginine ethylester
LLC	Lewis Lung Carcinoma
L-OH	non-toxic fatty alcohols
LOX	lipoxygenase
LOV	lovastatin

Table S1 *(continued)*

Abbreviations	Full Forms
LPO	lipid peroxide
LRP-1	lipoprotein receptor-related-1 protein
LTB	lapatinib
MB	methylene blue
MCF	magnesium-cobalt ferrite
MDR	multidrug resistance
ML	machine learning
MMP	mitochondrial membrane potential
Mn	manganese
MOA	mode of action
MPDA	mediator pore polydopamine
MPNA	magnetoplasmonic nanoassembly
MRI	magnetic resonance imaging
MSNs	mesoporous silica nanoparticles
MTO	mitoxantrone
NC	nanocluster
NCOA4	nuclear receptor coactivator 4
NDA	new drug application
NDs	nanodroplets
NOX2	NAPDH oxidase 2
NPs	nanoparticles
NSCLC	non-small cell carcinoma
OMV	outer membrane vesicle
OXA	oxaliplatin
PAMAM	polyamidoamine
PBPK	pharmacokinetic
PCVs	polyelectrolyte complex nanovesicles

Table S1 *(continued)*

Abbreviations	Full Forms
PCa	prostate cancer
PDAC	pancreatic ductal adenocarcinoma
PD-L1	programmed cell death ligand-1
PDMS	polydimethylsiloxane
PE	polyethylene
PEG	polyethylene glycol
PEGDA	poly (ethylene glycol) diacrylate
PET	polyethylene terephthalate
PFH	perfluorohexane
PLC	Primary liver cancer
PMs	polymeric micelles
POD-like	Peroxidase-like
PP	polypropylene
PSMA	prostate-specific membrane antigen
Pt	platinum
PTPmu	protein tyrosine phosphatase mu
PTX	paclitaxel
PUFA	polyunsaturated fatty acids
PUFA-CoAs	acyl-coenzyme A derivatives
PVC	polyvinyl chloride
R&D	research and development
ROS	reactive oxygen species
SA	scutellaria barbadensis A
SAC	oligonucleotide conjugate
SAS	sulfasalazine
SCLC	small cell carcinoma
siGPX4	small interfering RNA of GPX4

Table S1 *(continued)*

Abbreviations	Full Forms
SLC7A11	solute transporter family 7A11
SRF	sorafenib
SS	sodium selenite
STAD	stomach adenocarcinoma
STEAP3	STEAP family member 3
SWOT	strengths, weaknesses, opportunities, and threats
TA	tannic acid
Teff cells	Effector T cells
TfR1	transferrin receptor 1
TGI	tumor growth inhibition
TME	tumor microenvironment
TNBC	triple-negative breast cancer
TPP	(4-carboxybutyl)triphenylphosphonium
TSPO	translocator protein
TXN	thioredoxin
UCNPs	upconversion nanoparticles
ZnO	zinc oxide

References

1. M. Weller, P. Y. Wen, S. M. Chang, L. Dirven, M. Lim, M. Monje and G. Reifenberger, Glioma, *Nature Reviews Disease Primers* 2024,**10**.

2. A. F. Tamimi and M. Juweid. Epidemiology and Outcome of Glioblastoma. In: S. De Vleeschouwer, editor. Glioblastoma. Brisbane (AU): Codon Publications Copyright: The Authors.; 2017.

3. Y. Luo, G. Tian, X. Fang, S. Bai, G. Yuan and Y. Pan, Ferroptosis and Its Potential Role in Glioma: From Molecular Mechanisms to Therapeutic Opportunities, *Antioxidants* 2022,**11**.

4. X. Wang, S. Lu, C. He, C. Wang, L. Wang, M. Piao, G. Chi, Y. Luo and P. Ge, RSL3 induced autophagic death in glioma cells via causing glycolysis dysfunction, *Biochem Biophys Res Commun* 2019,**518**,590.

5. L. F. Ye, K. R. Chaudhary, F. Zandkarimi, A. D. Harken, C. J. Kinslow, P. S. Upadhyayula, A. Dovas, D. M. Higgins, H. Tan, Y. Zhang, M. Buonanno, T. J. C. Wang, T. K. Hei, J. N. Bruce, P. D. Canoll, S. K. Cheng and B. R. Stockwell, Radiation-Induced Lipid Peroxidation Triggers Ferroptosis and Synergizes with Ferroptosis Inducers, *ACS Chem. Biol.* 2020,**15**,469.

6. B. Liu, Q. F. Ji, Y. Cheng, M. Liu, B. L. Zhang, Q. B. Mei, D. Z. Liu and S. Y. Zhou, Biomimetic GBM-targeted drug delivery system boosting ferroptosis for immunotherapy of orthotopic drug-resistant GBM, *Journal of Nanobiotechnology* 2022,**20**.

7. A. Zhu, W. Tu, M. Ding, Y. Zhang, J. Liu, X. Chen, L. Wang, Y. Liu and J. Li, X-ray-activatable hitchhiking polymer nanodrugs enable controllable ferroptosis and immunization for orthotopic glioma rejection, *Chem. Eng. J.* 2024,**497**.

8. B. Li, X. Chen, W. Qiu, R. Zhao, J. Duan, S. Zhang, Z. Pan, S. Zhao, Q. Guo, Y. Qi, W. Wang, L. Deng, S. Ni, Y. Sang, H. Xue, H. Liu and G. Li, Synchronous Disintegration of Ferroptosis Defense Axis via Engineered Exosome-Conjugated Magnetic Nanoparticles for Glioblastoma Therapy, *Advanced Science* 2022,**9**.

9. Y. Li, B. Yan and S. He, Advances and challenges in the treatment of lung cancer, *Biomed. Pharmacother.* 2023,**169**.

10. L. Zeng, X. Liu, C. Geng, X. Gao and L. Liu, Ferroptosis in cancer (Review), *Oncol. Lett.* 2024,**28**.

11. J. Zhou, L. Zhang, J. Yan, A. Hou, W. Sui and M. Sun, Curcumin Induces Ferroptosis in A549 CD133⁺ Cells through the GSH-GPX4 and FSP1-CoQ10-NAPH Pathways, *Discov. Med.* 2023,**35**,251.

12. S. Feng, Y. Li, H. Huang, H. Huang, Y. Duan, Z. Yuan, W. Zhu, Z. Mei, L. Luo and P. Yan, Isoorientin reverses lung cancer drug resistance by promoting ferroptosis via the SIRT6/Nrf2/GPX4 signaling pathway, *Eur J Pharmacol* 2023,**954**.

13. H.-X. Tian, J. Mei, L. Cao, J. Song, D. Rong, M. Fang, Z. Xu, J. Chen, J. Tang, H. Xiao, Z. Liu, P.-Y. Wang, J.-Y. Yin and X.-P. Li, Disruption of Iron Homeostasis to Induce Ferroptosis with Albumin-Encapsulated Pt(IV) Nanodrug for the Treatment of Non-Small Cell Lung Cancer, *Small* 2023,**19**.

14. F. Q. Fu, W. H. Wang, L. J. Wu, W. H. Wang, Z. W. Huang, Y. Huang, C. B. Wu and X. Pan, Inhalable Biomineralized Liposomes for Cyclic Ca2+-Burst-Centered Endoplasmic Reticulum Stress Enhanced Lung Cancer Ferroptosis Therapy, *Acs Nano* 2023,**17**,5486.

15. M. L. Wilson, K. A. Fleming, M. A. Kuti, L. M. Looi, N. Lago and K. Ru, Pathology and laboratory medicine in low-income and middle-income countries 1: Access to pathology and laboratory medicine services: a crucial gap, *Lancet* 2018,**391**,1927.

16. M. J. Hangauer, V. S. Viswanathan, M. J. Ryan, D. Bole, J. K. Eaton, A. Matov, J. Galeas, H. D. Dhruv, M. E. Berens, S. L. Schreiber, F. McCormick and M. T. McManus, Drug-tolerant persister cancer cells are vulnerable to GPX4 inhibition, *Natur* 2017,**551**,247.

17. W. S. Yang, R. SriRamaratnam, M. E. Welsch, K. Shimada, R. Skouta, V. S. Viswanathan, J. H. Cheah, P. A. Clemons, A. F. Shamji, C. B. Clish, L. M. Brown, A. W. Girotti, V. W. Cornish, S. L. Schreiber and B. R. Stockwell, Regulation of Ferroptotic Cancer Cell Death by GPX4, *Cell* 2014,**156**,317.

18. H. Yu, C. Yang, L. Jian, S. Guo, R. Chen, K. Li, F. Qu, K. Tao, Y. Fu, F. Luo and S. Liu, Sulfasalazine-induced ferroptosis in breast cancer cells is reduced by the

inhibitory effect of estrogen receptor on the transferrin receptor, *Oncol. Rep.* 2019,**42**,826.

19. Y. Liang, C. Peng, N. Su, Q. Y. Li, S. W. Chen, D. Wu, B. Wu, Y. Gao, Z. T. Xu, Q. Dan, S. Zheng, B. X. Zhao and Y. J. Li, Tumor microenvironments self-activated cascade catalytic nanoscale metal organic frameworks as ferroptosis inducer for radiosensitization, *Chem. Eng. J.* 2022,**437**.

20. J. Wu, X. Zhang, D. Sun, X. Shi, J. Sun, C. Luo, Z. He and S. Zhang, Molecularly engineering a lipid nanoregulator destroying the last defense of ferroptosis in breast cancer therapy, *Chem. Eng. J.* 2024,**495**.

21. M. Domagala-Haduch, A. Gorzelak-Magiera, L. Michalecki and I. Gisterek-Grocholska, Radiochemotherapy in Pancreatic Cancer, *Current Oncology* 2024,**31**,3291.

22. A. Suda, B. A. Umaru, Y. Yamamoto, H. Shima, Y. Saiki, Y. Pan, L. Jin, J. Sun, Y. L. C. Low, C. Suzuki, T. Abe, K. Igarashi, T. Furukawa, Y. Owada and Y. Kagawa, Polyunsaturated fatty acids-induced ferroptosis suppresses pancreatic cancer growth, *Sci. Rep.* 2024,**14**.

23. N. Eling, L. Reuter, J. Hazin, A. Hamacher-Brady and N. R. Brady, Identification of artesunate as a specific activator of ferroptosis in pancreatic cancer cells, *Oncoscience* 2015,**2**,517.

24. A. Huang, Q. Li, X. Shi, J. Gao, Y. Ma, J. Ding, S. Hua and W. Zhou, An iron-containing nanomedicine for inducing deep tumor penetration and synergistic ferroptosis in enhanced pancreatic cancer therapy, *Materials Today Bio* 2024,**27**.

25. X. Yu, H. Pan, Q. He, J. Yang, M. Xiao, J. Xu, W. Wang, X. Yu and S. Shi, MXene-based dual-gated multifunctional nanodrug induced ferroptosis and modulated tumor microenvironment to treat pancreatic cancer, *Chem. Eng. J.* 2024,**500**.

26. 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 Journal of Pharmaceutical Sciences* 2022,**17**,613.

27. S. Lin, Y. Li, A. A. Zamyatnin, Jr., J. Werner and A. V. Bazhin, Reactive oxygen species and colorectal cancer, *J Cell Physiol* 2018,**233**,5119.

28. Y. Y. Qiao, M. Su, H. F. Zhao, H. L. Liu, C. X. Wang, X. T. Dai, L. L. Liu, G. J. Liu, H. R. Sun, M. M. Sun, J. Y. Wang, Z. Li, J. Fan, Q. Zhang, C. S. Li, F. M. Situ, J. Xue, Z. H. Jia, C. Z. Zhang, S. Zhang and C. L. Shan, Targeting FTO induces colorectal cancer ferroptotic cell death by decreasing SLC7A11/GPX4 expression, *J. Exp. Clin. Cancer Res.* 2024,**43**.

29. K. Deng, H. Tian, T. Zhang, Y. Gao, E. C. Nice, C. Huang, N. Xie, G. Ye and Y. Zhou, Chemo-photothermal nanoplatform with diselenide as the key for ferroptosis in colorectal cancer, *J. Controlled Release* 2024,**366**,684.

30. X. Pan, Y. Qi, Z. Du, J. He, S. Yao, W. Lu, K. Ding and M. Zhou, Zinc oxide nanosphere for hydrogen sulfide scavenging and ferroptosis of colorectal cancer, *Journal of Nanobiotechnology* 2021,**19**.

31. K. Khorsandi, H. Esfahani, S. Keyvani-Ghamsari and P. Lakhshehei, Targeting ferroptosis in melanoma: cancer therapeutics, *Cell Communication and Signaling* 2023,**21**.

32. Y. Wang, Y. Ma and K. Jiang, The role of ferroptosis in prostate cancer: a novel therapeutic strategy, *Prostate Cancer Prostatic Dis.* 2023,**26**,25.

33. Y. Wang, M. Hu, J. Cao, F. Wang, J. R. Han, T. W. Wu, L. Li, J. Yu, Y. Fan, G. Xie, H. Lian, Y. Cao, N. Naowarojna, X. Wang and Y. Zou, ACSL4 and polyunsaturated lipids support metastatic extravasation and colonization, *Cell* 2024.

34. W. Wang, Z. Zhong, S. Peng, J. Fu, M. Chen, T. Lang, X. Yue, Y. Fu, J. He, Y. Jin, Y. Huang, C. Wu, Z. Huang and X. Pan, "All-in-one" metal polyphenol network nanocapsules integrated microneedle patches for lipophagy fueled ferroptosis-mediated multimodal therapy, *J. Controlled Release* 2024,**373**,599.

35. H. Wang, L. Zhang, Z. Miao, M. Zhang, H. Liu, Q. He, J. Meng, L. Wen, Z. Ke, Z. Zha, R. Lin and C. Liang, PSMA-targeted arsenic nanosheets: a platform for prostate cancer therapy via ferroptosis and ATM deficiency-triggered chemosensitization, *Materials Horizons* 2021,**8**,2216.

36. W. Wang, J. Cai, J. Wen, X. Li, Y. Yu, L. Zhang, Q. Han, Z. Wei, Y. Ma, F. Ying, X. Xu, W. Li, Q. Yang, S. Sun, X. He, L. Cai, H. Xiao and Z. Wang, Boosting ferroptosis via abplatin^(iv) for treatment of platinum-resistant

recurrent ovarian cancer, *Nano Today* 2022,**44**.

37. F. Bray, M. Laversanne, H. Sung, J. Ferlay, R. L. Siegel, I. Soerjomataram and A. Jemal, Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, *Ca-a Cancer Journal for Clinicians* 2024,**74**,229.