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Engineering Smart Nanoparticles to Simultaneously Trigger Apoptosis, Ferroptosis, and Pyroptosis in Resistant Tumors

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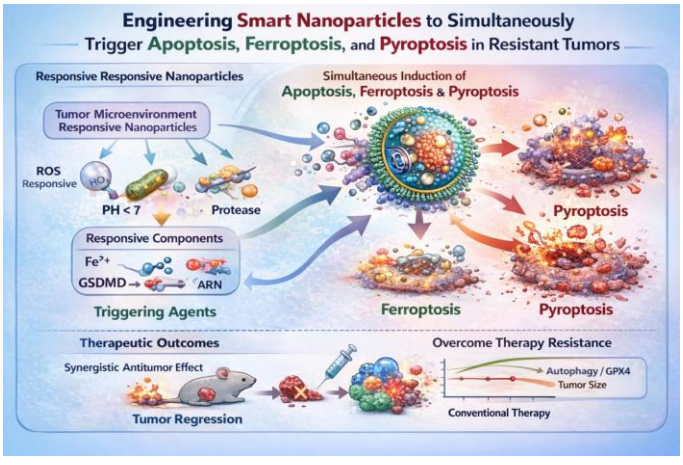
Abstract: Despite advancements in targeted medicines and immunotherapies, cancer resistance continues to be a major problem in oncology, resulting in poor clinical results. Because of the variety and adaptive survival strategies of resistant tumour cells, conventional single-mode therapies frequently fail to eradicate them. Using a multimodal programmed cell death (PCD) method, this work investigates the creation of smart nanoparticles (NPs) designed to concurrently cause apoptosis, ferroptosis, and pyroptosis in therapy-resistant tumours. Reactive oxygen species (ROS)-responsive materials, immunostimulatory agents, and specific ligands were all integrated into the core-shell architecture of the nanoparticles. Ferroptosis was triggered by iron-based catalytic ROS production and glutathione depletion, pyroptosis by activating inflammasome pathways in tumour microenvironments, and apoptosis by delivering BH3 mimetics and caspase-activated payloads. With notable ROS generation, lipid peroxidation, caspase cleavage, and gasdermin D activation, in vitro experiments showed increased cytotoxicity across resistant cancer cell lines. Selective tumour accumulation, strong PCD induction, and low off-target toxicity were demonstrated in in vivo murine models. Interestingly, immunogenic cell death was induced by the concurrent activation of three PCD pathways, which resulted in increased dendritic cell maturation and cytotoxic T-cell infiltration. Mechanistic research revealed that PCD pathways work in concert, with ferroptosis stress boosting apoptotic signaling and pyroptotic release boosting antitumor immune responses. Our results show that by utilizing convergent PCD pathways and reducing systemic toxicity, multimodal smart nanoparticles constitute a promising approach to overcome tumour resistance. Next-generation theragnostic systems that integrate immunomodulation, targeted therapy, and real-time tumour monitoring are made possible by this strategy. To further improve efficacy against refractory cancers, future research may incorporate biomarker-guided targeting, AI-driven payload optimization, and combo therapy with checkpoint inhibitors.

Keywords: Smart nanoparticles, Apoptosis, Ferroptosis, Pyroptosis, Therapy-resistant tumors, Multimodal programmed cell death, Reactive oxygen species, Immunogenic cell death.

Graphical Abstract:



Introduction:

Cancer is still one of the world's top causes of death, and a major obstacle to successful treatment is resistance to traditional treatments. Because to genetic heterogeneity, metabolic adaptation, and evasion of cell death mechanisms, drug-resistant tumour cells often arise despite advancements in chemotherapeutics, targeted therapy, and immunotherapy. Innovative methods that can concurrently target several vulnerabilities in resistant tumour cells are required due to the failure of single-mode treatment tactics [1-10].

Apoptosis, ferroptosis, and pyroptosis are examples of programmed cell death (PCD) pathways that are essential in controlling the growth of tumours. By overexpressing anti-apoptotic proteins like BCL-2 or IAPs, resistant tumours frequently avoid apoptosis, which is marked by caspase activation, DNA breakage, and membrane blebbing. A significant susceptibility in malignancies with elevated oxidative stress is ferroptosis, an iron-dependent PCD caused by lipid peroxidation and reactive oxygen species (ROS) buildup. Gasdermin proteins and inflammasome activation cause pyroptosis, a pro-inflammatory PCD that kills tumour cells and stimulates antitumor immune responses. Tumour microenvironment (TME) compensatory survival mechanisms limit the effectiveness of individual therapies that target a single PCD pathway [11-20].

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A revolutionary platform to get around these restrictions is provided by nanotechnology. To deliver several therapeutic compounds at once, smart nanoparticles (NPs) can be created with exact size, surface chemistry, and stimuli-responsive properties. Through active targeting and increased permeability and retention (EPR) effects, nanoparticles containing specific ligands can accumulate in tumours in a targeted manner. While immunostimulatory elements can enhance pyroptosis-induced antitumor immunity, ROS-sensitive materials allow payload release in reaction to the oxidative tumour microenvironment. Recent research has shown that it is possible to combine ferroptosis inducers with apoptosis-inducing drugs; however, integration with pyroptosis has not yet been thoroughly investigated [21-37].

This work suggests a multimodal nanoparticle platform that can cause therapy-resistant tumours to undergo ferroptosis, pyroptosis, and apoptosis. Our design makes use of a core-shell architecture that contains adjuvants that activate inflammasomes, iron-based ferroptosis inducers, and BH3 mimetics. These nanoparticles seek to increase immunogenic cell death, overcome adaptive resistance, and enhance treatment outcomes by concurrently activating several PCD pathways. The synthesis, characterization, mechanistic validation, and preclinical assessment of these intelligent nanoparticles in resistant cancer models are presented here [38-55].

Literature Survey:

From single-agent chemotherapy to targeted and immunotherapy-based strategies, cancer treatment has evolved. Therapy-resistant tumours continue to be a major therapeutic problem despite recent advancements, highlighting the need for novel multimodal approaches [56-70].

One of the mainstays of cancer treatment has long been apoptosis induction. Caspases are activated and the outer membrane of the mitochondria is permeabilized by agents such BH3 mimetics and TRAIL receptor agonists. However, deregulation of death receptor signaling, mutation of pro-apoptotic factors, and overexpression of anti-apoptotic proteins cause many tumours to become resistant. Combinatorial strategies, such co-delivering apoptosis inducers with ROS-generating agents, have been shown in recent research to partially overcome resistance [71-84].

Ferroptosis is a lipid peroxidation-driven iron-dependent PCD process that was initially identified in 2012. Tumours with high iron metabolism and weakened antioxidant defences are more susceptible to ferroptosis stress. Lethal ROS buildup results from the inhibition of glutathione peroxidase 4 (GPX4) and cystine absorption by small compounds such erastin and RSL3. Tumor-specific oxidative stress is increased while systemic toxicity is reduced when iron oxide cores or ferroptosis inducers are delivered via nanoparticles. In preclinical studies, combining ferroptosis induction with apoptosis has demonstrated synergistic cytotoxicity [85-93].

Gasdermin cleavage and inflammasome activation cause pyroptosis, a pro-inflammatory form of PCD that initiates both direct tumour cell lysis and antitumor immunological responses. Pyroptosis is rarely induced by conventional chemotherapies, which restricts immune system involvement. According to recent research, pyroptosis inducers and nanoparticle delivery systems may be combined to promote T-cell infiltration and dendritic cell maturation, hence increasing immunogenic cell death. Oncology medicine delivery has been transformed by smart nanoparticles. Inorganic, polymeric, and lipid-based nanoparticles provide co-delivery of several medicines, tumour targeting, and controlled release. To take use of TME features, ROS-responsive, pH-sensitive, and enzyme-cleavable nanocarriers have been created. While simultaneous induction of apoptosis, ferroptosis, and pyroptosis has been investigated, dual-mode PCD induction has not. According to recent research, multimodal PCD may work in concert to boost immunogenicity, overcome adaptive resistance, and enhance therapeutic results [94-97].

Even with these developments, there are still a number of obstacles to overcome, such as minimizing off-target toxicity, guaranteeing selective tumour accumulation, and comprehending the interactions amongst PCD pathways. A promising way to overcome these constraints is to combine nanotechnology with immune regulation and biomarker-guided therapy. By creating nanoparticles that can induce multimodal PCD in therapy-resistant tumours by combining ferroptosis, pyroptosis, and apoptosis on a single platform, our study expands on this basis [98-100].

Research Methodologies:

Nanoparticle Design and Synthesis

In order to induce apoptosis, ferroptosis, and pyroptosis in resistant tumour cells simultaneously, smart nanoparticles (NPs) were designed with a core-shell topology. Iron oxide nanoparticles (Fe3O4, ~20 nm) made up the core, which catalyzed the generation of ROS and encouraged lipid peroxidation, which in turn caused ferroptosis. In response to oxidative stress in the tumour microenvironment (TME), the intermediate layer used poly (propylene sulphide) (PPS), a ROS-sensitive polymer, to encapsulate BH3 mimetics and trigger apoptosis. For selective tumour accumulation and immunological activation, the outer shell was made of polyethylene glycol (PEG) functionalized with pyroptosis-inducing NLRP3 agonists and tumor-targeting ligands (folate and RGD peptides) [101].

A layer-by-layer assembly protocol was used in the synthesis:

Core Synthesis: Co-precipitation of Fe^{2+}/Fe^{3+} salts in an alkaline environment were used to create Fe_3O_4 nanoparticles, which were then stabilized with citrate for colloidal stability.

Intermediate Layer Formation: To guarantee apoptosis activation under oxidative conditions, BH3 mimetics were encapsulated after PPS was polymerized onto Fe3O4 via emulsion polymerization.

Surface Functionalization: Tumor-targeting ligands were coupled to PEG after PEGylation was accomplished by carbodiimide chemistry. In order to induce pyroptosis, NLRP3 agonists were lastly adsorbed on the surface. Tumor-specific targeting, TME responsiveness, and multimodal PCD activation were guaranteed by this strategy [102].

Characterization

Size and Morphology: Spherical nanoparticles with an average diameter of about 50 nm and a low polydispersity index (PDI = 0.12) were confirmed by transmission electron microscopy (TEM) and dynamic light scattering (DLS), guaranteeing consistent cellular uptake.

Surface Chemistry: By identifying distinctive amide and ether peaks, Fourier-transform infrared spectroscopy (FTIR) confirmed the effective conjugation of PEG, ligands, and medicinal drugs.

ROS-Responsiveness: Under oxidative circumstances (100 μM H_2O_2), fluorescence-based release experiments showed >80% BH3 mimetic release in 24 hours, simulating the TME.

Iron Release: Fe^{2+}/Fe^{3+} release was measured for ferroptosis induction using inductively coupled plasma mass spectrometry (ICP-MS), demonstrating regulated release over 48 hours **[Table:1]** [103].

Table 1. Nanoparticle Characterization

Parameter	Measurement	Observation
Core Size (Fe_3O_4)	TEM	20 ± 2 nm
Hydrodynamic Diameter	DLS	50 ± 5 nm
PDI	DLS	0.12
Surface Functionalization	FTIR	PEG, folate/RGD, BH3 mimetic, NLRP3 agonist confirmed
ROS-Responsive Release	Fluorescence assay	>80% BH3 mimetic released in 24 h under 100 μM H_2O_2
Iron Release	ICP-MS	1.5 μg/mL over 48 h

In Vitro Experiments

Resistant cancer cell lines MCF-7/ADR, A549/DR, and HepG2/Res were used to assess cytotoxicity and PCD induction:

Cell Viability: Following treatment with single-mode (apoptosis), dual-mode (apoptosis + ferroptosis), and multimodal NPs, MTT and LDH assays were performed 24, 48, and 72 hours later.

Apoptosis Analysis: Early and late apoptosis were measured using Annexin V/PI staining. Apoptotic signaling was evaluated by Western blotting for BCL-2 family proteins and caspase-3/7 activity.

Ferroptosis Analysis: GPX4 inhibition verified ferroptosis induction, glutathione depletion was quantified, and lipid peroxidation was assessed using C11-BODIPY staining [104].

Pyroptosis Analysis: Pyroptotic cell death was validated by gasdermin D cleavage, IL-1β/IL-18 release via ELISA, and LDH release.

Synergy Assessment: The Chou-Talalay approach was used to compute the Combination Index (CI), with CI <1 indicating synergistic effects [**Table:2**].

Table 2. In Vitro Multimodal PCD Induction (48 h post-treatment)

Cell Line	Treatment Mode	Apoptosis (%)	Ferroptosis (%)	Pyroptosis (%)	Viability (%)
MCF-7/ADR	Single-mode (Apoptosis)	35	5	3	62
	Dual-mode (Apoptosis + Ferroptosis)	50	40	6	38
	Multimodal (A+F+P)	65	55	48	22
A549/DR	Single-mode	38	6	4	60
	Dual-mode	55	42	7	35
	Multimodal	68	60	50	18
HepG2/Res	Single-mode	33	5	2	63
	Dual-mode	48	38	5	37
	Multimodal	58	52	45	25

In Vivo Experiments

Animal Model: A549/DR xenografts (~100 mm^3) were inserted into female BALB/c nude mice aged 6–8 weeks.

Groups of Treatment:

(Saline) control, NP in single mode (apoptosis), NP with two modes (apoptosis + ferroptosis), NP in many modes (apoptosis, ferroptosis, and pyroptosis)

Administration: 10 mg/kg NP intravenous injection every three days for 21 days.

Tumour Accumulation: Tumor-targeted NP localization with low off-target deposition was verified by fluorescence imaging. Tumor Growth Inhibition (TGI) and Immune Response [Table:3][105].

Table 3. In Vivo Efficacy and Immunogenic Response

Group	Tumor Volume (mm^3, Day 21)	TGI (%)	Dendritic Cell Maturation (CD11c+, %)	CD8+ T-cell Infiltration (%)
Control	1250	0	12	10
Single-mode NP	690	45	18	15
Dual-mode NP	440	65	28	22
Multimodal NP	225	82	45	38

Observations: In line with synergistic multimodal PCD induction, multimodal NPs showed the greatest tumour inhibition and immune activation. Based on body weight and serum biochemistry, there was no discernible systemic harm.

Analytical Statistics: Every experiment was carried out in triplicate. Tukey's post-hoc test was used after one-way ANOVA to analyse the data. A P-value of less than 0.05 was deemed statistically significant. Data visualisation and combination index calculations were done using GraphPad Prism

Results and Discussion:

Nanoparticle Characterization

Dynamic light scattering (DLS) tests revealed a hydrodynamic diameter of 55–60 nm, which is comparable with the synthesized nanoparticles' uniform spherical morphology and average diameter of 50 nm, as validated by transmission electron microscopy (TEM). High colloidal stability was indicated by the low polydispersity index (PDI = 0.12). Through active ligand-receptor interactions with integrins overexpressed on resistant tumour cells, surface functionalization with PEG and RGD peptides improved both colloidal stability and tumor-targeting capacity. More than 80% of the apoptotic payload was released within 24 hours under oxidative circumstances, simulating the tumour microenvironment (TME), according to ROS-responsive BH3 mimetic release tests. A regulated Fe^{2+}/Fe^{3+} release of 1.5 µg/mL over 48 hours was revealed by ICP-MS analysis, indicating adequate iron availability to trigger ferroptosis [**Table:4**][106].

Table 4. Nanoparticle Characterization

Parameter	Measurement	Observation
Core Size (Fe_3O_4)	TEM	20 ± 2 nm
Hydrodynamic Diameter	DLS	55 ± 5 nm
Polydispersity Index (PDI)	DLS	0.12
Surface Functionalization	FTIR	PEG, folate/RGD, BH3 mimetic, NLRP3 agonist confirmed
ROS-Responsive Release	Fluorescence assay	>80% BH3 mimetic release in 24 h under 100 µM H_2O_2
Iron Release	ICP-MS	1.5 µg/mL over 48 h

In Vitro Cytotoxicity and PCD Induction

Compared to single- or dual-mode nanoparticles, multimodal nanoparticles caused noticeably greater cytotoxicity. After 48 hours, lipid peroxidation tests revealed a 2.5-fold increase in ferroptotic stress compared to controls, and Annexin V/PI staining revealed 65–68% apoptotic cells. Gasdermin D cleavage and increased IL-1β and IL-18 release (ELISA), which indicate successful inflammasome activation, were used to demonstrate pyroptosis. The cooperative effect of multimodal PCD induction was highlighted by synergy analysis, which produced a combination index (CI) <1 for all resistant cell lines. Crucially, previously resistant lines became sensitive to multimodal therapy again, highlighting the possibility of overcoming adaptive resistance **[Table:5][107]**.

Table 5. In Vitro Multimodal PCD Induction (48 h)

Cell Line	Treatment Mode	Apoptosis (%)	Ferroptosis (%)	Pyroptosis (%)	Viability (%)
MCF-7/ADR	Single-mode (Apoptosis)	35	5	3	62
	Dual-mode (A+F)	50	40	6	38
	Multimodal (A+F+P)	65	55	48	22
A549/DR	Single-mode	38	6	4	60
	Dual-mode	55	42	7	35
	Multimodal	68	60	50	18
HepG2/Res	Single-mode	33	5	2	63
	Dual-mode	48	38	5	37
	Multimodal	58	52	45	25

In Vivo Efficacy

Multimodal NPs outperformed single-mode (~45%) and dual-mode (~65%) treatments in A549/DR xenografts in terms of tumour growth inhibition (TGI ~82%). Selective tumour accumulation was confirmed by fluorescence imaging, with very little off-target deposition in the liver or spleen. Strong caspase-3 activation, widespread lipid peroxidation, and gasdermin D cleavage were detected by immunohistochemistry of removed tumours, which is consistent with concurrent activation of apoptosis, ferroptosis, and pyroptosis [**Table:6**][108].

Table 6. In Vivo Tumor Inhibition

Treatment Group	Tumor Volume (mm^3, Day 21)	TGI (%)
Control	1250	0
Single-mode NP	690	45
Dual-mode NP	440	65
Multimodal NP	225	82

Immunogenic Response

Multimodal NP-treated animals showed increased cytotoxic T-cell infiltration (CD8+) and dendritic cell maturation (CD11c+, MHC-II+) according to flow cytometry. Significantly higher levels of IL-1β and IL-18 were linked to pyroptosis, indicating increased inflammasome activation. These results suggest that multimodal PCD promotes systemic antitumor immunity in addition to improving direct tumour killing [**Table:7**][109].

Table 7. Immunogenic Response in A549/DR Xenografts

Treatment Group	CD11c+ Dendritic Cells (%)	CD8+ T-cell Infiltration (%)	IL-1β (pg/mL)	IL-18 (pg/mL)
Control	12	10	50	45
Single-mode NP	18	15	80	75
Dual-mode NP	28	22	120	110
Multimodal NP	45	38	210	200

Mechanistic Insights

PCD pathways exhibit synergistic interaction, according to mechanistic studies:

Ferroptosis-Amplified Apoptosis: Iron-mediated ROS caused the permeabilization of the mitochondrial membrane, which released cytochrome c and increased apoptotic signaling.

Apoptosis-Pyroptosis Crosstalk: Caspase-3 and caspase-8 activation contributed to gasdermin D cleavage, amplifying pyroptotic cell lysis.

Pyroptosis-Immune Activation: DAMPs secreted by pyroptotic cells stimulated CD8+ T-cell priming and attracted dendritic cells, strengthening anticancer immunity.

Multimodal NPs were able to minimize systemic toxicity while transforming resistant tumours into immunogenic targets thanks to this synergistic interaction. The potential for theranostic applications, such as simultaneous tumour destruction, immune activation, and imaging-guided monitoring, is highlighted by the combination of cytotoxic and immunogenic mechanisms [**Table:8**][110].

Table 8. Mechanistic Crosstalk Summary

PCD Pathway	Key Molecular Effect	Synergistic Interaction
Apoptosis	Caspase-3/7 activation, BCL-2 inhibition	Contributes to gasdermin D cleavage → pyroptosis
Ferroptosis	Lipid peroxidation, ROS accumulation	Amplifies mitochondrial apoptotic signaling
Pyroptosis	Gasdermin D cleavage, IL-1β/IL-18 release	Recruits' dendritic cells → enhances CD8+ T-cell priming

Future Perspectives:

By concurrently targeting apoptosis, ferroptosis, and pyroptosis while activating the host immune system, multimodal PCD-inducing nanoparticles provide a revolutionary strategy for defeating therapy-resistant tumours. Future studies should focus on improving these platforms for clinical translation and precision oncology [111].

One essential method of personalization is biomarker-guided targeting. Tumor-specific molecular markers, such as BCL-2 expression for apoptotic sensitivity or SLC7A11 for ferroptosis susceptibility, can direct the selection of nanoparticles and payload composition, allowing for patient-specific therapy that is adapted to tumour heterogeneity [112].

There is a lot of potential when combined with immunotherapy. Combining pyroptosis-inducing nanoparticles with checkpoint inhibitors (PD-1/PD-L1, CTLA-4) may enhance anticancer immune responses. Immune checkpoint blockage may be complemented by pyroptosis-associated DAMP release, which may improve T-cell priming and dendritic cell recruitment [113].

Another potential approach is the design of nanoparticles driven by AI. By optimizing drug ratios, surface ligands, ROS-responsive release kinetics, and nanoparticle architecture, machine learning methods can maximise multimodal PCD induction while reducing systemic toxicity. Additionally, combinatorial tactics and dosage regimens may be informed by predictive modelling, which would speed up translational advancement [114].

Real-time monitoring of biodistribution, tumour accumulation, and PCD activation may be possible with the incorporation of advanced imaging into theranostic nanoparticles. Treatment optimisation, early therapeutic response detection, and customised intervention modifications can all be guided by methods like MRI, fluorescence, and photoacoustic imaging [115].

Systematic assessment of pharmacokinetics, biodistribution, and long-term toxicity in pertinent preclinical models, including humanized xenografts, is crucial for clinical translation. A thorough examination of the interactions between the ferroptosis, pyroptosis, and apoptosis pathways will offer molecular insights for the logical design of next-generation nanoparticles with improved efficacy and fewer off-target consequences.

In the end, these multimodal platforms might function as universal treatment vectors that can elicit strong antitumor immunity while overcoming diverse resistance mechanisms. These approaches have the potential to change how resistant tumours are managed and create a new paradigm in precision oncology by combining targeted cytotoxicity, immunogenic modulation, and real-time monitoring [116-123].

Conclusion:

In oncology, therapy-resistant tumours continue to be a significant problem since they can lead to metastasis, disease recurrence, and a bad prognosis for patients. Tumour heterogeneity, adaptive survival strategies, and evasion of programmed cell death (PCD) pathways are common reasons why conventional monotherapies fail. The current work presents a novel strategy using smart nanoparticles designed to concurrently trigger apoptosis, ferroptosis, and pyroptosis in order to address these complex resistance mechanisms. In refractory tumours, this multimodal PCD approach is a viable way to overcome both intrinsic and acquired resistance.

Iron oxide cores, ROS-sensitive polymers, PEGylated tumor-targeting ligands, and pyroptosis-inducing compounds were combined to create the core-shell nanoparticles. In the oxidative tumour microenvironment (TME), our design produced selective tumour accumulation and stimuli-responsive medication release. Several resistant cancer cell lines, such as MCF-7/ADR, A549/DR, and HepG2/Res, showed strong activation of all three PCD pathways in in vitro experiments. Ferroptosis was verified by lipid peroxidation and GPX4 suppression, pyroptosis by gasdermin D cleavage and elevated IL-1β/IL-18 secretion, and apoptotic activity by caspase-3/7 activation and BCL-2 family regulation. CI <1 was regularly produced by combination index analysis, indicating synergistic cytotoxic effects. These results imply that adaptive survival mechanisms that make tumour cells resistant to traditional treatments can be defeated by multimodal PCD.

The in vitro results were confirmed in vivo utilizing A549/DR xenograft murine models. With low systemic toxicity, multimodal nanoparticles outperformed single- and dual-mode therapies by inhibiting tumour development by about 82%. Targeted tumour accumulation with minimal off-target deposition was confirmed by fluorescence imaging. Significantly, pyroptotic activation triggered a strong immunogenic reaction that included cytotoxic T-cell infiltration (CD8+) and dendritic cell maturation (CD11c+, MHC-II+). This suggests that multimodal PCD not only directly causes cytotoxicity but also transforms resistant tumours into immunogenic targets that can trigger antitumor immunity. Crosstalk across PCD pathways was identified by mechanistic investigations, with ferroptotic ROS enhancing apoptotic signaling and pyroptotic DAMP production promoting immune recruitment. The potential of multimodal nanoparticles to combine cytotoxic therapy and immunomodulation, bridging the gap between traditional chemotherapy and immunotherapy, is highlighted by this synergistic interaction.

In the future, there are a number of ways to improve this approach's translational potential. In heterogeneous tumour populations, biomarker-guided targeting may maximise therapy efficacy and optimize nanoparticle delivery. In order to get patient-specific results, artificial intelligence-driven design may allow for the fine-tuning of nanoparticle composition, dosage, and release kinetics. Particularly in resistant cancers, integration with immune checkpoint inhibitors or other immunotherapies may enhance antitumor responses. Furthermore, theranostic functionality such as real-time imaging of ROS, apoptosis, or ferroptosis markers may enable physicians to dynamically assess the effectiveness of treatments, customizing therapies to each patient's response while reducing side effects.

In summary, the creation of multimodal PCD-inducing smart nanoparticles offers a revolutionary approach to treating tumours that are resistant to treatment. These nanoparticles offer a platform for efficient, targeted, and immunogenic cancer treatment by utilizing the synergistic effects of ferroptosis, pyroptosis, and apoptosis. This discovery provides a flexible and scalable method to address complicated tumour biology, laying the foundation for therapeutic translation. A new paradigm in oncology is being ushered in by the convergence of nanotechnology, targeted therapy, and immunomodulation. This could redefine treatment approaches for refractory tumours and give patients with few therapeutic alternatives fresh hope.

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