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REVIEW

Key Nano-Strategies for Cisplatin Resistance in Advancing Anti-Cancer Therapy

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Abstract: Cisplatin (CDDP) and other platinum-based agents remain cornerstones of cancer therapy. However, drug resistance severely impairs their clinical efficacy and therapeutic potential. Extensive research has identified diverse CDDP resistance mechanisms, broadly categorized as pre-target, on-target, off-target, and post-target resistance. These mechanisms exhibit substantial heterogeneity across patients and tumor types, highlighting the complexity of resistance development. Notably, resistance to other platinum drugs shares similarities with CDDP, presenting a common therapeutic challenge. Leveraging insights into CDDP resistance, personalized therapeutic strategies offer promise to enhance anti-tumor efficacy and overcome platinum resistance. The integration of nanotechnology and precision medicine has emerged as a pivotal frontier in oncology, where nanotechnology-based drug delivery systems (NDDSs) serve as multifunctional vectors for co-delivering CDDP and resistance-modulating agents. These intelligent platforms enable precise targeting and active circumvention of resistance mechanisms. This review comprehensively explores innovative NDDS strategies to overcome CDDP resistance, focusing on pre-target, on-target, off-target, and post-target mechanisms within a precision medicine framework. By synthesizing these advancements, we aim to provide a forward-looking perspective on NDDSs development and their potential to address the persistent challenge of platinum resistance in anti-cancer therapy.

Keywords: cisplatin, nanotechnology, drug resistance, platinum-based drugs, cancer

Introduction

Cis-diamminedichloroplatinum(II) (cisplatin, CDDP, or CDDPum) was first described by the Italian chemist Michele Peyrone in 1845.[1] More than one hundred years later, Barnett Rosenberg discovered the anti-tumor effect of CDDP.[2] In 1978, the Food and Drug Administration (FDA) approved CDDP as a chemotherapy drug for testicular cancer, advanced ovarian cancer and bladder cancer.[3] After that, CDDP-based chemotherapy was extended to head and neck tumors, lung cancer, digestive tract tumors, etc. Unfortunately, many tumors initially responsive to platinum-based therapy rapidly acquire secondary resistance. Furthermore, certain tumors exhibit intrinsic primary resistance to CDDP. These situations limit the widespread application of CDDP in most solid tumors. Therefore, scholars have devoted their research to synthesizing new CDDP-derived chemotherapy drugs. However, it has been increasingly recognized that most CDDP-resistant tumors exhibit cross-resistance to other platinum-based agents.[4] To date, solid tumors, the main tumor type resistant to platinum-based drugs, have a high incidence globally, accounting for 90% of all cancer diagnoses and posing a significant public health burden.[5] For example, 60%–80% of ovarian cancer patients are initially sensitive to first-line platinum-based chemotherapy. Still, over 70% of patients relapse and develop drug resistance after initial treatment, which has become the main cause of poor prognosis.[6] People have gradually discovered that CDDP and other platinum drugs share a common drug-resistance mechanism. Fundamentally addressing platinum resistance challenges thus requires elucidating the mechanisms underlying both CDDP's anti-tumor efficacy and tumor chemoresistance to CDDP.

CDDP undergoes intracellular aquation (water-mediated chloride displacement) due to low chloride concentration, forming cytotoxic hydrated species that preferentially form covalent adducts at guanine-N7 residues in nuclear DNA.[7]

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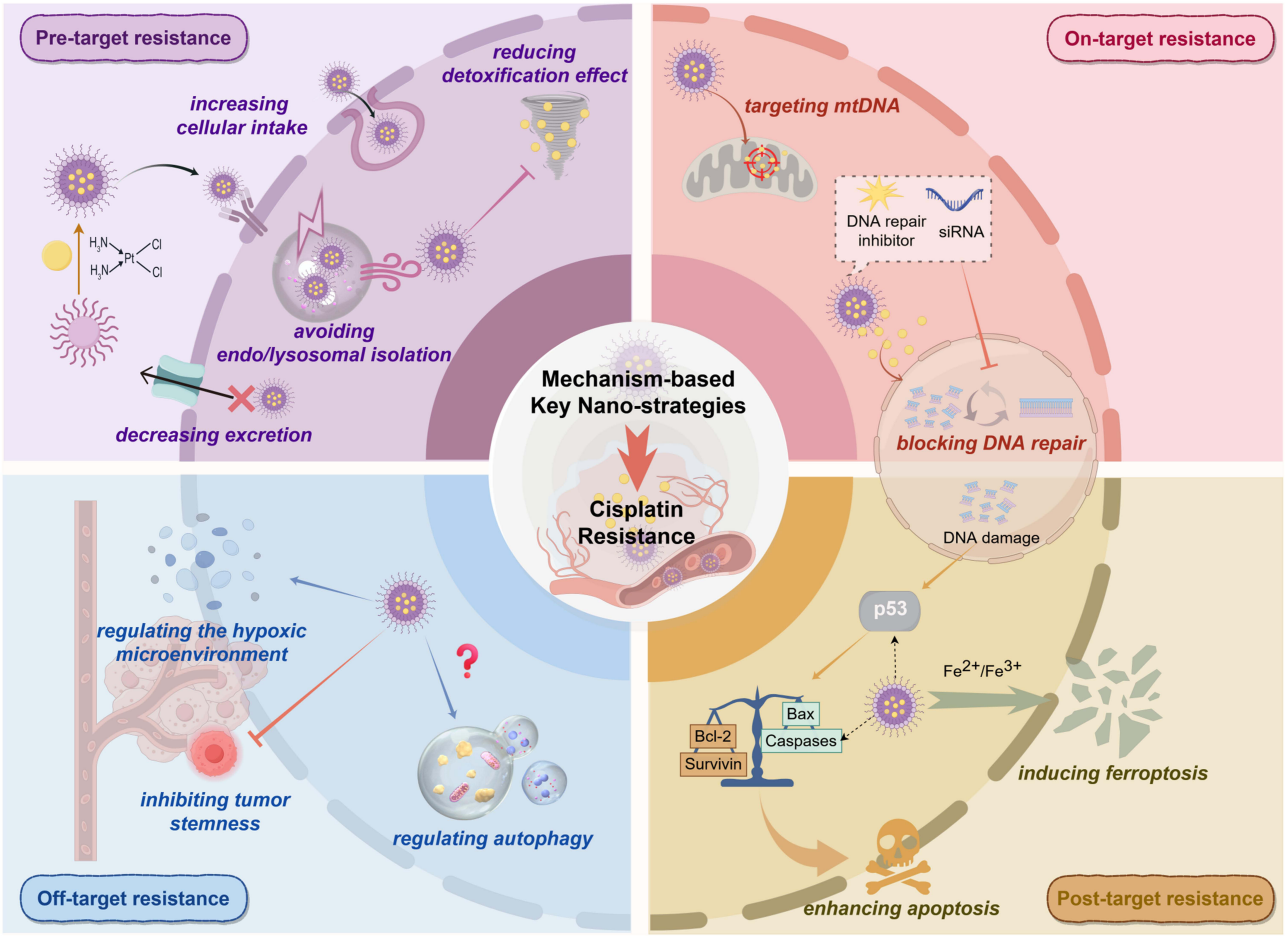
Graphical Abstract



However, studies have found that nuclear DNA is not the single target of CDDP. Intracellular oxidative stress induced by CDDP and its interactions with mitochondria, endosomes/lysosomes and other organelles are all related to cytotoxicity.[8] During malignant progression, tumors acquire increasingly diverse resistance mechanisms to CDDP, driven by dynamic genomic instability and phenotypic plasticity: (1) pre-target resistance: steps preceding CDDP working on the target; (2) on-target resistance: steps directly related to CDDP working on the target; (3) post-target resistance: concerning the death-related signaling pathways induced by CDDP; and (4) off-target resistance: affecting molecular circuitries that deliver compensatory pro-survival signals which CDDP does not directly activate.[9,10] Consequently, targeting these resistance pathways to reverse CDDP refractoriness represents an urgent therapeutic imperative and a frontier in oncology drug development.

CDDP-based chemotherapy is increasingly integrating multimodal regimens (eg, gene silencers, pathway modulators, redox regulators) to counteract intratumoral heterogeneity and dynamic resistance. Conventional combinatorial approaches lack multiplex targeting capability, whereas nanotechnology-based delivery systems (NDDSs) enable spatiotemporally controlled co-delivery of CDDP with gene therapeutics and adjuvants, ensuring pharmacokinetic-pharmacodynamic congruence.[11] This aligns with oncology's shift toward precision medicine, where clonal evolution and spatial metabolic reprogramming necessitate mechanism-driven NDDS personalization to overcome multidimensional resistance. This review classifies key NDDSs with anticancer potential based on the four major CDDP resistance mechanisms. Each section systematically outlines the core pathological processes and therapeutic targets associated with

a specific mechanism, followed by a critical analysis of nano-strategies to circumvent the corresponding resistance pathway.

Pre-Target Resistance Mechanism-Based Strategies to Reverse CDDP Resistance

CDDP cytotoxicity hinges on its accumulation at intracellular targets (eg, nuclear DNA/mitochondrial DNA [mtDNA]), governed by three key determinants: (1) Cellular uptake via passive diffusion or carrier-mediated transport (copper transporter 1 [CTR1], organic cation transporters [OCTs], and organic carnitine and zwitterion transporters [OCTNs]), where transporter downregulation drives tumor resistance;[3] (2) Pre-target sequestration through covalent conjugation by glutathione (GSH), GSH synthase, glutathione-S-transferase, and metallothionein, reducing drug bioavailability and nuclear deliver;[12] (3) Active efflux mediated by membrane transporters (multidrug resistance-associated proteins [MRPs], P-gp, ATP7A/7B/11), conferring classical multidrug resistance.[13,14] Current NDDSs targeting pre-target resistance mechanisms effectively enhance intracellular CDDP accumulation and synergistically potentiate tumor cell killing.

Nanomedicines Increasing the Intake of Platinum Drugs

Nanomedicines Benefiting from Endocytosis

While CDDP internalization was initially attributed primarily to passive membrane diffusion, subsequent studies established the critical involvement of carrier-mediated transport mechanisms.[3] Tumor cells inefficiently accumulate free CDDP due to intrinsic uptake limitations and acquired resistance via downregulation of influx transporters (eg, CTR1). By contrast, nanoparticles (NPs) leverage the enhanced permeability and retention (EPR) effect for superior tumor accumulation, while cellular internalization primarily occurs through endocytic pathways—effectively bypassing transporter-dependent uptake mechanisms.[15]

Min et al engineered poly(ethylene glycol)ylated (PEGylated) gold nanorods (PEG-GNRs) conjugate with Pt(IV) prodrug.[16] CDDP-resistant lung cancer cells A549R with low expression of CTR1 (IC_{50} value of CDDP = 24.1μM) and lung cancer cells A549 with high expression of CTR1 (IC_{50} = 3.4μM) were used to detect the cytotoxicity of free CDDP and the Pt-PEG-GNRs conjugate. After 3h treatment, CDDP accumulation in A549R cells was ~50% lower than in A549 cells, whereas Pt-PEG-GNRs uptake by A549R exceeded free CDDP by 4.7-fold, with transmission electron microscope confirming endocytic internalization. Moreover, the Pt(IV) prodrug component effectively suppressed detoxification mechanisms mediated by metallothionein and GSH, resulting in a marked reduction of CDDP's IC_{50} value to 0.24μM in A549R cells. Notably, Pt-PEG-GNRs restored drug sensitivity in resistant cells, independent of CTR1 expression levels. To further validate NPs endocytosis, Han et al utilized synthetic copolymer Pt(IV)-loaded PEG-b-PBEMA micelles (PtBE-micelle) composed of PEG and polymerized phenylboronic ester-containing methacrylate (PBEMA) for hydrophobic CDDP prodrug delivery.[17] PtBE-micelle achieved 6.1-fold higher cellular accumulation than free CDDP in A549R cells, reducing the IC_{50} value of CDDP to 0.20μM. Critically, inductively coupled plasma mass spectrometry (ICP-MS) quantification demonstrated that PtBE-micelle internalization was suppressed under chlorpromazine (endocytosis inhibitor), NaN_3 (energy-depleting agent), and low temperature (4 °C), with cellular Pt content significantly reduced after 4h treatment—conclusively establishing energy-dependent endocytosis as the dominant entry mechanism. Similarly, Du et al reported significantly reduced platinum-loaded NPs accumulation in the human ovarian cancer adenocarcinoma cell line SKOV-3 after adding NaN_3 and setting a low temperature.[18] Song et al engineered octadecylcarbamoylacrylic acid-CDDP nanocomplexes encapsulated in liposomes (OCP-L) that entered A549R cells partially via endocytosis, achieving superior cytotoxicity versus CDDP monotherapy.[19] Mechanistically, OCP-L restored OCT2 transporter expression—unexpectedly enhancing CDDP uptake—thereby reversing transporter-mediated resistance.

Despite inherent tumor accumulation via endocytosis and EPR effects, passive targeting efficiency of nanodrugs is constrained by critical physicochemical determinants (size/charge/shape—necessitating significant resources for NDDS optimization.[20] Moreover, dysregulated endocytosis-related proteins in tumor cells can disrupt cytokinesis, hindering chemotherapy efficacy even when passive targeting succeeds.[21]

Nanomedicines Targeting Tumor Cell Surface Receptors

Tumor cells exhibit characteristic overexpression of surface receptors to sustain proliferative, invasive, and pro-survival signaling—a vulnerability exploited by active-targeting NDDSs. Such strategies enhance tumor-specific affinity and receptor-mediated endocytosis while minimizing off-target accumulation, thereby elevating intratumoral platinum concentrations.[22] Among these receptors, CD44 and EGFR emerge as pivotal regulators of apoptosis evasion, metastasis, and angiogenesis, with established overexpression in multiple cancers.[23,24] Given their extensive mechanistic characterization, we focus here on CD44/EGFR-targeted approaches; other receptors are summarized in Table 1.

Hyaluronic acid (HA)—the primary ligand for CD44—or CD44-specific antibodies are commonly employed to target CD44-overexpressing tumor cells.[23] Ganesh et al synthesized CDDP-loaded HA-1,8-diaminooctane NPs to treat A549R xenografts.[40] ICP-MS quantification revealed higher CDDP accumulation in tumors treated with HA-based NPs versus free CDDP, demonstrating enhanced tumor-specific delivery. Wen et al prepared HA-coated iron-based metal-organic framework NPs for CDDP delivery. In two lung cancer cell lines (A549 and Lewis), HA-coated NPs exhibited high cellular uptake, consequently showing enhanced cytotoxicity.[41] Bai et al prepared CDDP-loaded NPs functionalized with CD44 antibodies.[42] The increased uptake of NPs by tumor cells with high expression of CD44 was verified by a laser confocal microscope. The above studies provide preliminary evidence of the feasibility of coupling CD44 antibodies or HA in NDDSs to target CD44 for platinum drug delivery. Cai et al found that HA-CDDP NPs internalization was blocked by both endocytosis inhibitors chlorpromazine and CD44 antibodies, confirming CD44 receptor-mediated endocytosis as the dominant entry pathway.[43] Zhang et al synthesized HA/CDDP/rhodamine B (HA/Cis/Rb) NPs by a simple one-pot strategy.[44] In breast cancer cell lines MDA-MB-231 (high expression of CD44) and MCF-7 (low expression of CD44), they demonstrated specific HA/Cis/Rb NPs accumulation in endosomes/lysosomes of MDA-MB-231, where hyaluronidase-catalyzed HA degradation enabled sustained rhodamine B release. However, free HA could competitively inhibit the uptake of HA/Cis/Rb NPs, thereby conclusively confirming CD44 receptor-mediated endocytosis as the cellular entry mechanism (Figure 1). CDDP-loaded CD44-targeting NPs consistently demonstrate therapeutic efficacy with low systemic toxicity across studies. Leveraging (-)-epigallocatechin-3-O-gallate (EGCG)—a chemosensitizer that enhances tumor-selective CDDP cytotoxicity while sparing normal tissues—Bae et al fabricated micellar nanocomplexes (MNCs) from HA-EGCG conjugates and CDDP.[45] These MNCs selectively entered ovarian cancer cells via CD44-mediated endocytosis, achieving significant tumor accumulation in murine xenografts. MNCs outperformed both free CDDP and HA-EGCG in suppressing primary tumor growth, and uniquely inhibited peritoneal metastasis in ovarian cancer models where CDDP monotherapy failed. Notably, MNCs contributed to preventing CDDP-induced hepatotoxicity in vivo. Cancer stem cells (CSCs)—a minor subpopulation within tumors endowed with self-renewal and differentiation capacity—drive chemoresistance by surviving conventional therapies, subsequently undergoing proliferative resurgence to fuel tumor recurrence and therapeutic failure.[46] It is worth noting that CD44 serves as a master CSC surface marker; thus, CD44-targeted strategies simultaneously eradicate CSCs and potentiate CDDP efficacy, as detailed in subsequent sections.

EGFR-targeted NDDSs conjugated to single-chain variable fragments (ScFvEGFR) represent an emerging strategy to enhance platinum drug delivery. Compared to full-length anti-EGFR antibodies, ScFvEGFR offers critical advantages of low molecular weight, small volume, and less accumulation in bone marrow.[47] Based on the synthesis of highly biocompatible, non-anticoagulant active heparin-CDDP (HDDP) NPs, Peng et al developed ScFvEGFR-heparin-CDDP (EHDDP) NPs by chemically conjugating ScFvEGFR to the surface of HDDP NPs.[48] To validate EGFR-mediated internalization of EHDDP NP, competitive inhibition assays with free ScFvEGFR blocked cellular entry of EHDDP NPs in lung cancer cells H292. Consistently, siRNA silencing of EGFR failed to enhance platinum accumulation, whereas targeted EHDDP NPs significantly increased intracellular Pt content and Pt-DNA adduct formation versus non-targeted HDDP NPs and free CDDP (Figure 2). To prepare excellent drug carriers with high stability, non-toxicity, and biodegradability, Geng et al integrated aspartate PGA (PGA-Asp), Maleimide-functionalized polymers (Mal), EGFR targeting peptide (TP13), and CDDP to synthesize TP13-Mal-PGA-Asp3-Pt polymer.[49] This polymer demonstrated sustained CDDP release kinetics and selective targeting efficacy against human hepatoma cell line SMMC7721

Table 1 Detailed Description of CDDP/CDDP Prodrug-Loaded NDDSs to Target Different Cell Surface Receptors

Cell Surface Receptor	Target Cancer	NDDSs	Particle Size (nm)	Zeta Potential (MV)	Drug Entrapment Efficiency (DEE%)/Drug Loading Efficiency (DLE%)	Drug Release (%) (Time, Stimuli)	Reference
Thyroid-stimulating hormone (TSH) receptor	Thyroid cancer	CDDP-loaded TSH-conjugated polymer–lipid hybrid NPs	185.8	−19.2	>95	50 (24h, pH 7.4)	[25]
CXC chemokine receptor 1 (CXCR1)	Osteosarcoma	CDDP-loaded CXCR1 targeting peptide-conjugated Fe_3O_4 NPs	129.4 ± 5.2	/	/	80 (8h, pH 5.0)	[26]
Connexin 43 (Cx43) and brain-specific anion transporter 1 (BSAT1)	Glioma	CDDP-loaded mAbCx43- and BSAT1-conjugated nanogels	/	−15 ± 5	~45	16.5 ± 2.1 (24h)	[27]
Luteinizing hormone-releasing hormone (LHRH) receptor	Breast cancer	CDDP-loaded, LHRH-modified dextran NPs	50	−16.8 ± 4.5	85.5	60 (120h, pH 7.4)	[28]
Fibroblast growth factor-2 (FGF2) receptors	Breast cancer	CDDP-loaded, heparin-conjugated gelatin NPs	189 ± 3.4	–26.87 ± 1.1	70.8 ± 1.4	31.96 ± 2.34 (48h, pH 7.4)	[29]
Human epithelial growth factor receptor 2 (HER2)	Breast cancer	CDDP/doxorubicin-loaded, HER2 antibody-decorated NPs	162	–28	81.71	57.68 (24h, pH 5.5)	[30]
Platelet-derived growth factor (PDGF) receptor	Cervical cancer	CDDP-loaded, poly-acrylic acid-modified mesoporous silica NPs	60–100	–26.4	/	<20 (50h, pH 7.4)	[31]
Transferrin receptor (TFR)	Cervical cancer	CDDP-loaded, TFR-targeted peptide(maleimide) Asp-γ-PGA complex	89 ± 18	/	37 ± 6	/	[32]
Ephrin transmembrane receptors A2 (EphA2)	Lung cancer	CDDP and radiation sensitizer NU7441-loaded, EphA2 antibody-conjugated NPs	323 ± 21	/	56	90 (72h, GSH and radiation)	[33]
Mannose receptor	Lung cancer	CDDP-loaded, con-A-decorated gelatin NPs	214.8 ± 2.5	7.4 ± 0.8	73.81 ± 4.62	52 (24h, MMP-2 enzyme)	[34]
Integrin $\alpha_v\beta_3$	Lung cancer	CDDP-loaded, RDG peptide-modified PLGA-Chitosan NPs	/	/	44	80 (100h, pH 7.2)	[35]
	Urinary bladder cancer	CDDP-loaded, tetraiodothyroacetic acid-bonded PLGA NPs	187	–6.32	70–75	/	[36]
Folate (FA) receptors	Cervical cancer	CDDP-loaded, FA-modified nanostructured lipid carriers	143.2 ± 5.3	25.7 ± 2.3	87.5 ± 3.2	>90 (48h, pH 7.4)	[37]
	Cervical cancer	CDDP prodrug-loaded, FA-modified mesoporous silica NPs	216.1	–11.0	/	/	[38]
	Ovarian cancer	CDDP/paclitaxel-loaded, FA-modified NPs	95 ± 3	−5.5 ± 1.0	/	80 (24h, pH 7.4)	[39]

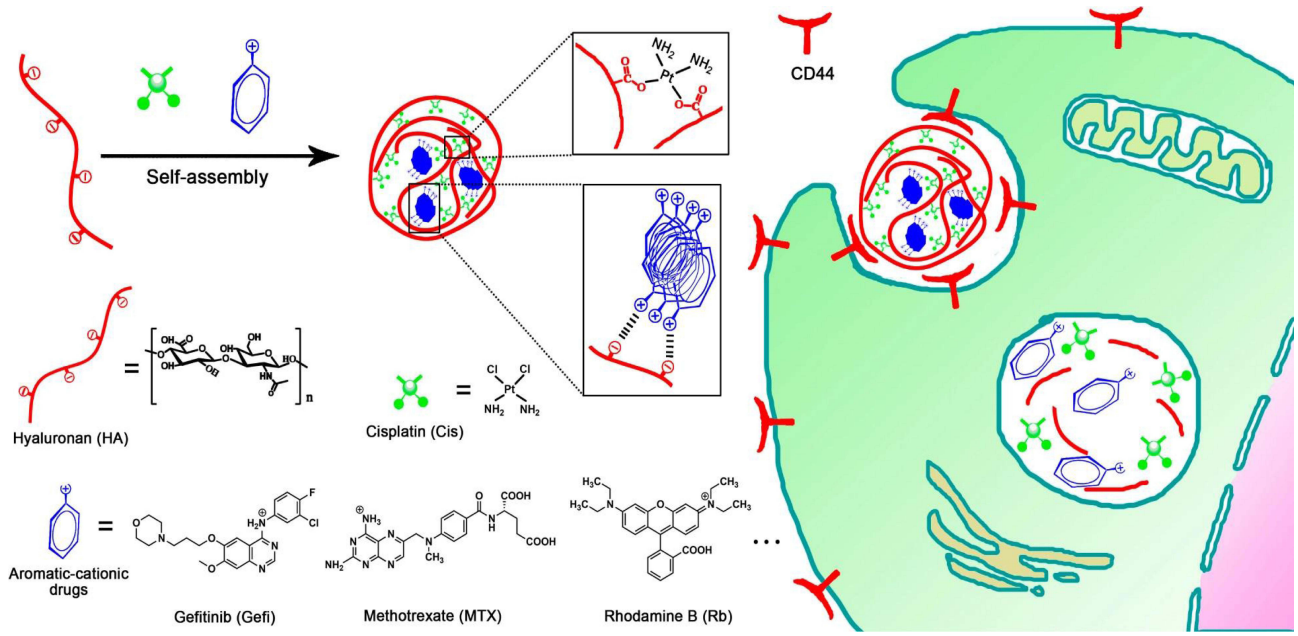


Figure 1 Design and synthesis of HA/Cis/Rb NPs, and the mechanism of their targeting tumor cell surface receptors CD44 to increase intracellular uptake through endocytosis. Reproduced from Zhang W, Tung C-H. Cisplatin cross-linked multifunctional nanodrugplexes for combination therapy. *ACS Applied Materials & Interfaces*. 2017;9:8547–8555. © 2017 American Chemical Society.[44]
Abbreviations: HA, hyaluronic acid; Cis, cisplatin; Rb, rhodamine.

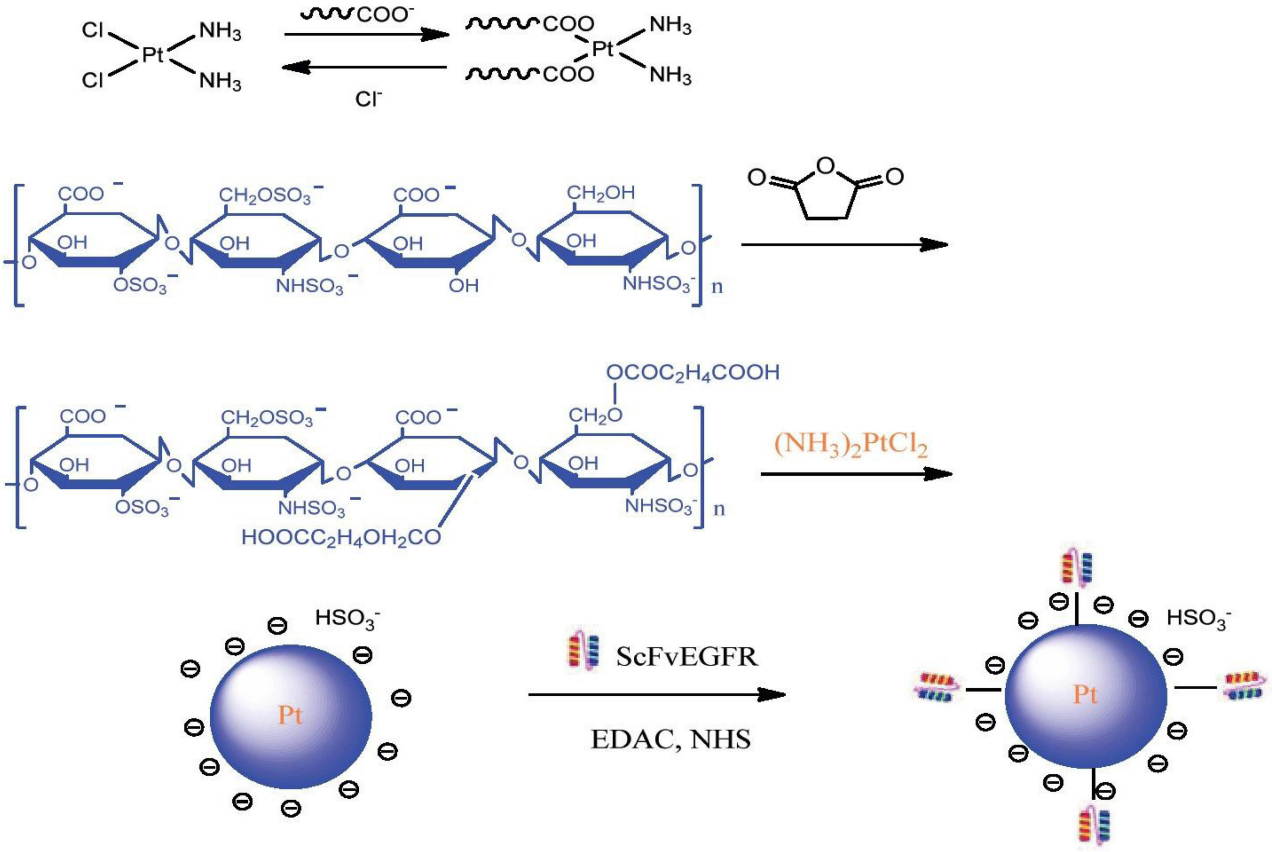


Figure 2 Design and synthesis of ScFvEGFR-heparin-cisplatin NPs for targeting EGFR-positive tumor cells. Reproduced from Peng XH, Wang Y, Huang D et al. Targeted delivery of cisplatin to lung cancer using ScFvEGFR-heparin-cisplatin nanoparticles. *ACS Nano*. 2011;5:9480–93. © 2011 American Chemical Society.[48]
Abbreviation: ScFvEGFR, single-chain antibody against EGFR.

in vitro; however, in vivo validation of cellular uptake dynamics and systemic toxicity profiles remains outstanding, representing a critical gap for clinical translation potential. The degradation kinetics of gelatin nanoparticles (GP) can be precisely tailored by tuning the cross-linking density, thereby enabling controlled modulation of drug release profiles and sustained release over an extended timeframe, which collectively contributes to enhanced anti-tumor efficacy.[50] Tseng et al synthesized the GP complex with CDDP (GP-Pt) surface-modified with NeutrAvidin ^{FITC}-biotinylated epidermal growth factor (bEGF), named GP-Pt-bEGF.[51] GP-Pt-bEGF significantly enhanced platinum accumulation in A549 cells versus free CDDP, reducing CDDP's IC_{50} by 50% after 48h treatment. Nan et al creatively prepared EGFR-targeted lipid polymerized NPs (LPNs) loaded with CDDP and azithromycin.[52] By actively targeting tumor cells, the synergistic effect of the two drugs was exploited to improve the efficacy of lung cancer.

Developing effective active targeting strategies mandates tumor biopsy analysis to identify overexpressed receptors. However, ligand conjugation to NDDSs often compromises targeting activity due to structural denaturation or steric hindrance from carrier matrices—particularly when surface-bound ligands are masked by outer-layer macromolecules. These limitations necessitate rigorous preclinical validation through ligand-activity assays and competitive binding studies. Consequently, employing minimal protein fragments as targeting moieties offers distinct advantages: reduced steric bulk mitigates immunogenicity and shielding effects, while lower production costs enhance translational feasibility.

Others

Fe_3O_4 NPs are magnetic nanomaterials approved by the FDA and have been widely studied in biomedical research.[53] Li et al demonstrated that CDDP-loaded magnetic Fe_3O_4 NPs (Fe_3O_4-MNPs) achieved nearly 3-fold higher CDDP accumulation in A549R cells versus free CDDP after 48h treatment, as quantified by ICP-MS.[54] Complementing this, Cheng et al engineered porous hollow Fe_3O_4 NPs with deliberately widened inter-crystalline gaps in the shell architecture.[55] This unique design enhanced CDDP diffusion into internal cavities, boosting drug loading efficiency and enabling pH-responsive release kinetics in acidic tumor microenvironments (TME), thereby maximizing tumor-specific CDDP accumulation. Beyond biological targeting (eg, antigen-antibody or receptor-ligand bindings), Fe_3O_4 NPs enable spatiotemporally controlled CDDP accumulation via physicochemical targeting—particularly magnetic guidance. Medříková et al exemplify this by engineering carboxymethylcellulose-coated magnetic NPs (cMNPs) co-loaded with CDDP and surface-conjugated folic acid (cMNPs-cisPt-FA).[56] This dual-targeting system achieved ~30-fold higher cytotoxicity against CDDP-resistant ovarian cancer cells A2780R versus free CDDP. More importantly, external magnetic field application induced directional cMNPs-cisPt-FA migration to targeted regions, triggering localized tumor cell apoptosis and demonstrating magnetic field-enhanced regional CDDP accumulation. Moreover, magnetic nanomaterials serve as highly effective delivery carriers for CDDP and bioactive molecules, while functioning as intrinsic contrast agents for MRI—enabling non-invasive evaluation of therapeutic efficacy through drug distribution monitoring.[57,58] By complexing with fluorescent markers, the established imaging technique enables real-time in vivo imaging for tracking drug fate in tumors.[59] In particular, Fe_3O_4 NPs can release metal ions, Fe^{2+}/Fe^{3+}, in tumor cells to catalyze hydrogen peroxide to produce hydroxyl radical (OH) (Fenton reaction) and a large amount of reactive oxygen species (ROS).[60] This further induces ferroptosis and has a synergistic therapeutic effect with CDDP. Fe_3O_4 NPs usually require surface modification to improve dispersion and stability. Despite surface modifications improving dispersion and stability, challenges persist: rapid agglomeration, chemical reactivity, high surface energy, and oxidation.[61] Their high specific surface area and penetration capacity raise biosafety concerns, as even modified Fe_3O_4 NPs disrupt cytoskeletons and accumulate in the spleen during prolonged circulation.[62] Classical toxicology methods are inadequate for clinical translation; novel analytical approaches for quantitative biodistribution and structural characterization must be developed to ensure safety.[63]

Human serum albumin has emerged as an exceptional CDDP nanocarrier, leveraging its status as the most abundant human plasma protein to enhance passive tumor targeting via the EPR effect. Besides, serum albumin-based NDDSs achieve active targeting by binding to the secreted protein acidic and rich in cysteine (SPARC, an albumin-binding protein highly expressed in tumor cells), thus increasing the accumulation of CDDP and reducing systemic toxicity, particularly nephrotoxicity.[64,65]

Nanomedicines Increasing the Effective Concentration of Platinum Drugs

Nanomedicines Reducing the Intracellular GSH Detoxification Effect

Cytoplasmic thiol-containing molecules function as intracellular antidotes by reacting with CDDP to form adducts, thereby compromising chemotherapy efficacy. As the most abundant human thiol, GSH accumulates aberrantly in tumor cells, promoting progression and metastasis through dual mechanisms: (1) detoxifying exogenous toxins/drugs via adduct formation; (2) scavenging ROS to sustain redox homeostasis.[66] CDDP reacts with GSH to generate $[Pt(NH_3)_2Cl_2(GSH+H)]^+$ complexes, shielding DNA from platinum-induced damage and driving chemoresistance.[67] Consequently, depleting intracellular GSH or inhibiting GSH-CDDP binding sensitizes tumor cells to platinum therapy.

Hydrophobic nanomaterials like polycaprolactone (PCL)-based skeletons serve as isolation barriers within core-shell NPs, physically shielding CDDP from cytoplasmic GSH-mediated detoxification. Surnar et al synthesized GSH-resistant polymer-CDDP core-shell NPs based on biodegradable carboxylic functional PCL-block-poly (ethylene glycol) diblock copolymers.[68] In vitro release studies revealed that while free CDDP reacted with GSH to form Pt-S adducts (detected by new absorbance peaks), NPs showed no increase in Pt-S absorbance—confirming successful detoxification blockade. Consequently, these NPs induced 100% cell death in MCF-7 cells, doubling the efficacy of free CDDP. Moreover, Niu et al prepared mesoporous organosilica NPs (MONs) loaded with CDDP that consumed cytoplasmic GSH in A549R cells, boosting nuclear Pt-DNA adducts >4-fold versus free CDDP.[69] Lv et al adapted MONs with mitochondrial-targeting ligands, selectively depleting mitochondrial GSH and amplifying ROS—synergizing with CDDP to induce catastrophic mitochondrial damage in A2780R cells.[70] He et al pioneered lipid-coated CaO_2/CDDP NPs (LipoCaO_2/DDP), demonstrating GSH depletion capacity in vitro and ~2-fold higher cytotoxicity than CDDP-only LipoDDP NPs in hepatocellular carcinoma.[71] Complementary studies confirm GSH-consuming capabilities in Copper (II) bis (diethyldithiocarbamate) nanocomposites,[72] MnO_2-doped nanosheet,[73] and Zinc oxide NPs.[74]

Nano-strategies incorporating active molecules to regulate GSH detoxification offer a more direct approach than previous methods. For instance, phenylboronic ester-functionalized polymers release quinone methide upon intracellular H_2O_2 triggering, where quinone methide consumes GSH via nucleophilic addition.[75] Han et al demonstrated this with PtBE-micelles carrying hydrophobic CDDP prodrugs, reducing GSH levels significantly in A549R cells and tumor-bearing BALB/c nude mice—quantified via biochemical kits and fluorescent probes.[17] Critically, these micelles suppressed tumor growth in vivo without apparent toxicity. Zhu et al constructed Probe 1/ CDDP-loaded lipid-polymer hybrid NPs, as a powerful NDDS that cleverly combines the advantages of NPs and liposomes.[76] Probe 1 competitively sequesters GSH, blocking CDDP-GSH conjugation and disrupting detoxification, thereby amplifying CDDP's cytotoxicity against malignant cells.

However, achieving sustained chemosensitization requires targeting GSH biosynthesis pathways alongside transient depletion strategies. Following temporary GSH consumption, compensatory metabolic recycling and de novo synthesis rapidly regenerate GSH pools—enabling tumor cells to maintain CDDP detoxification capacity and intrinsic chemoresistance.[77] These potential processes that make GSH "resurgence" should be considered. Besides, off-target GSH depletion may interfere with redox homeostasis in healthy tissues and lead to serious side effects. And excessive depletion of tumor cell GSH may lead to immune dysregulation and affect T cell function.[78] Hence, more efforts are needed to develop NDDSs that specifically deplete GSH from tumor tissues and to monitor GSH reduction for quantitative assessment of anti-tumor effects accurately.[79]

Nanomedicines Avoiding CDDP Endosomal/Lysosomal Isolation

Studies confirm that free CDDP accumulates highly in endosomes/lysosomes of various tumor cells. This phenomenon, termed endosomal/lysosomal isolation or capture, significantly reduces CDDP's effective concentration and cytotoxicity at target sites, emerging as a critical mechanism underlying CDDP resistance.[80–82] Through photochemical internalization (membrane disruption) or the proton sponge effect (osmotic pressure elevation), NDDSs induce endosomal/lysosomal swelling and rupture, enabling drug escape into the cytoplasm for therapeutic action.[83] This critical endosomal/lysosomal escape capability drives the application of NDDSs in reversing CDDP resistance.

Photochemical internalization is a novel technique derived from photodynamic therapy principles. Upon light-triggered activation, the endosomal/lysosomal-trapped photosensitizer generates ROS, inducing membrane peroxidation

and rupture for spatiotemporally controlled drug liberation.[84] Huang et al engineered a multifunctional NDDS integrating a solar-activatable ROS generator—biscyclometalated iridium(III) (Ir(III), a photocytotoxic metallodrug) and aggregation-induced emission fluorogen (AIEgen)—with a diselenide dynamic linker enabling ROS-responsive CDDP release (Figure 3).[85] Within 1 min of irradiation, AIEgen-generated ROS triggered two critical events: 1) increased endosomal/lysosomal membrane permeability via lipid peroxidation;[86] 2) cleavage of diselenide bonds, facilitating cytosolic escape of CDDP and Ir(III). Remarkably, prolonged irradiation induced nuclear membrane destabilization, enabling nuclear co-localization of both agents to synergistically amplify chemo-photodynamic therapy efficacy. Similarly, Li et al prepared light-triggered micelles loaded with Pt(IV) prodrug and near-infrared cyanine dyes Cypate, synergistically integrating photohyperthermia with chemotherapy.[87] Under laser irradiation, these micelles generated singlet oxygen—even at minimal Cypate concentrations—inducing endosomal/lysosomal membrane disruption to facilitate cytoplasmic release of both agents. In A549R tumor-bearing mice, intravenous micelle administration achieved 2.9-fold higher Pt(IV) accumulation versus free Pt(IV)/Cypate treatment.

The proton sponge effect describes nanomaterial-mediated endosomal/lysosomal disruption through sequential ion imbalance: cationic polymers buffer proton, inducing proton pump hyperactivity; chloride ions influx to maintain charge neutrality; osmotic water influx causes endosomal/lysosomal swelling and rupture, releasing therapeutic payloads into the cytosol.[88] As a pH response, dimethylmaleic acid reverses its surface charge and increases drug uptake in the weak acidic environment outside tumor cells, and the proton sponge effect is induced.[89] Chen et al designed tumor extracellular pH-sensitive Pt (IV) prodrug-loaded NPs, whose shells were modified by dimethylmaleic acid.[90] In A549 cells, the uptake of NPs was significantly enhanced under TME-mimicking conditions (pH 6.8) compared to blood circulation-mimicking conditions (pH 7.4). Notably, following

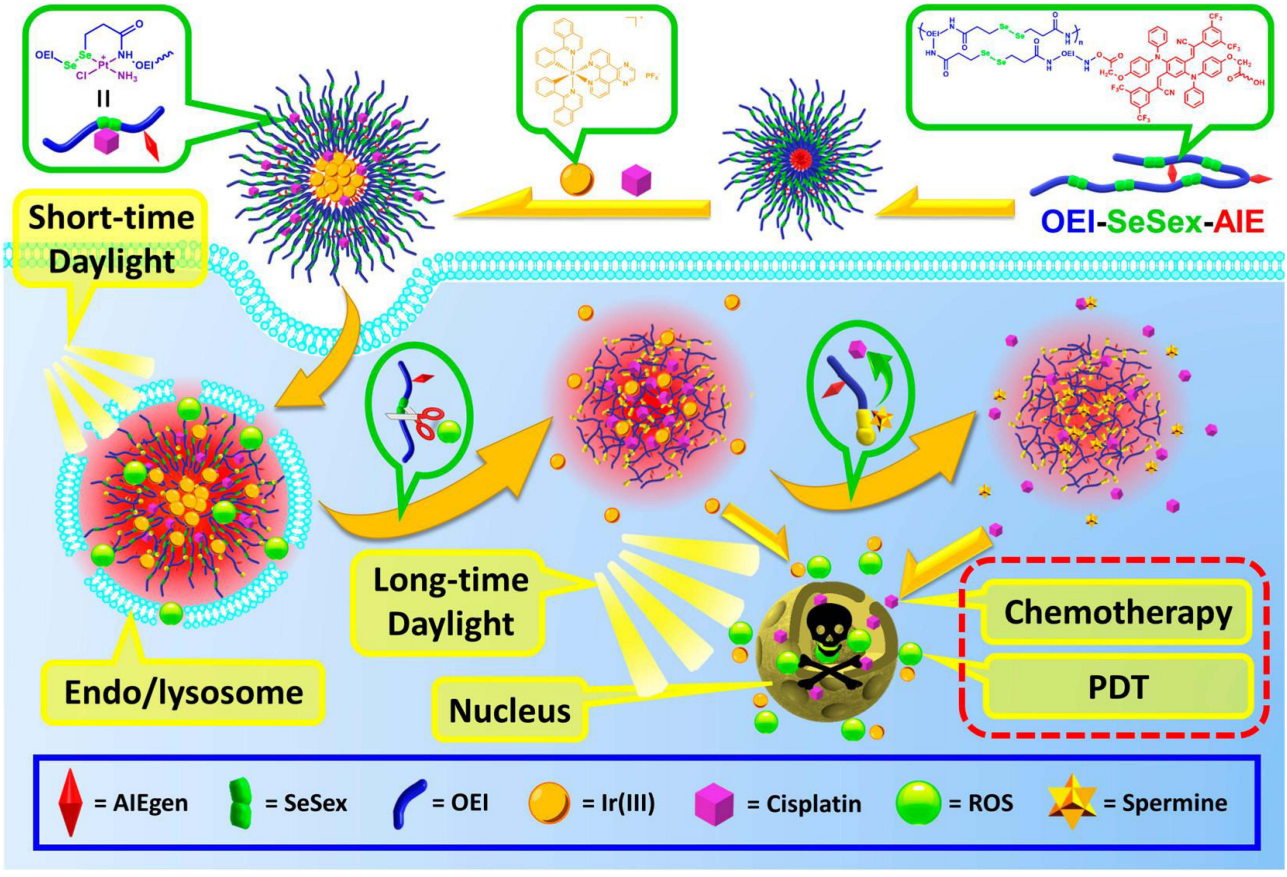


Figure 3 Schematic illustration of ROS self-sufficient Pt&Ir@P NPs and their mechanism for the treatment of breast cancer by promoting endosomal/lysosomal escape and achieving a synergistic effect of chemotherapy and photodynamic therapy. Reproduced from Huang Y, Liu DE, An J et al. Reactive oxygen species self-sufficient multifunctional nanoplatform for synergistic chemo-photodynamic therapy with red/near-infrared dual-imaging. *ACS Appl Bio Mater.* 2020;3:9135–9144. © 2020 American Chemical Society.[85]
Abbreviation: ROS, reactive oxygen species.

https://doi.org/10.2147/IJN.S551752

reductive activation of Pt(IV), both the release rate and cumulative amount of CDDP increased 6-fold, accompanied by a marked improvement in cell inhibition efficiency. These performance metrics surpassed those observed in the free CDDP and non-pH-responsive NP groups. Zheng et al prepared CDDP-loaded selenium NPs modified with amine-terminated G5 polyamidoamine (PAMAM) dendrimer.[91] Confocal microscopy and flow cytometry revealed that after 12h incubation in A549R cells, NPs initially co-localized with endosomes/lysosomes but subsequently achieved efficient cytoplasmic escape—releasing CDDP via PAMAM's proton sponge effect.[92] This cationic polymer enhanced NP stability and cellular uptake while improving tumor-targeting capability.

Unlike small-molecule lysosomotropic agents, NDDSs can be engineered for selective endosomal/lysosomal membrane permeabilization—bypassing CDDP sequestration. However, achieving tumor-selective disruption while overcoming protective mechanisms (eg, HSP70-mediated stabilization of endosomal/lysosomal membranes) remains a translational barrier.[93] Furthermore, the precise mechanisms governing NDDS-mediated escape are inadequately characterized, partly due to limitations in quantifying subcellular trafficking dynamics with current techniques.[94] Advanced methods for real-time, single-vesicle analysis of endosomal/lysosomal rupture are critically needed to deconvolve these escape pathways.

Nanomedicines Inhibiting the Excretion of Platinum Drugs

The ATP-binding cassette (ABC) superfamily constitutes a major class of membrane transporters that drive multidrug resistance by mediating drug efflux.[95] ABC superfamily transporter genes like P-gp and MRPs (especially MRP-1/2) are up-regulated in diverse tumors, directly contributing to CDDP resistance. The NDDSs can circumvent this efflux-mediated resistance through selective/non-selective ABC transporter inhibition, thereby maintaining therapeutic CDDP concentrations.

NO downregulates P-gp expression and inhibits drug efflux, thereby sensitizing tumors to chemotherapy.[96] Moreover, NO donors could react with GSH through redox reactions, simultaneously releasing NO and depleting intracellular GSH reserves. Chu et al developed cocktail polyprodrug NPs (CPNs) copolymerization of three functional monomers: CDDP prodrug crosslinker (PtMA), NO prodrug monomer (StNO), and hydrophilic monomer *N, N*-dimethylacrylamide (DMA).[97] In A549R cells, CPNs treatment markedly attenuated P-gp immunofluorescence—reaching levels comparable to native CDDP-sensitive A549 cells—while significantly reducing cell viability versus free CDDP, confirming reversal of efflux-mediated resistance. Additionally, CDDP in the form of Pt (II) activates intracellular NOXs to produce superoxide in a variety of ways, and participates in the synthesis of peroxynitrite with NO to achieve higher cytotoxicity. D-α-tocopheryl polyethylene glycol succinate (TPGS) can interfere with ATP production and has been proven to inhibit efflux pumps expression (eg, MRP-2, P-gp).[98] He et al designed TPGS-CDDP hybrid micelles that enhanced intracellular platinum accumulation in A549R cells while reducing efflux rates to 13.9% in multicellular spheroids—5-fold lower than CDDP-only micelles.[99] Selenium NPs containing multidrug resistance-1 gene siRNA created by Zheng et al suppressed P-gp expression below free CDDP or naked siRNA levels, achieving 46.2% apoptosis (9-fold increase versus CDDP) with potent tumor growth inhibition and minimal toxicity in xenografts.[91] Similarly, mesoporous silica NPs (MSN) constructed by Taratula et al were equipped with both anti-cancer drugs (CDDP and doxorubicin) and two types of siRNA (MRP-1 siRNA and Bcl-2 siRNA) and modified by luteinizing hormone-releasing hormone (LHRH) peptide on the surface for the target portion.[100] They found that this MSN could reverse pump and non-pump cellular resistance in vitro and improve anti-cancer efficiency. In nude mice bearing orthotopic human lung cancer by nebulized inhalation, the MSN could accumulate in the lungs in large quantities (the cumulative amount was 14.6-fold that of intravenous injection), reducing the toxic side effects on other organs. This study is of great significance for the precise treatment of lung cancer with platinum-based drugs.

Novel nanocomposites have been found to inhibit the expression of drug resistance-related proteins. Prylutskyy et al constructed a CDDP-C_{60} fullerene nanocomposite (FC60).[101] Molecular docking studies revealed FC60 binding to key efflux transporters—P-gp, MRP-1/2—demonstrating the possible mechanism for overcoming CDDP resistance through efflux pump inhibition. Guo et al developed a light-activatable hyperbranched polyprodrug (polyPPM) by copolymerizing Pt(IV) prodrug monomers (PPM) with 2-methacryloyloxyethyl phosphorylcholine (MPC).[102] Under light irradiation, polyPPM abolished MRP-1 expression in A549R cells and downregulated anti-apoptotic Bcl-2 while upregulating pro-

apoptotic Caspase-3. This suggested that polyPPM had the dual advantages of down-regulating the expression of MRP-1 and inducing apoptosis to mediate the reversal of CDDP resistance. Two-dimensional MnO_2 nanoscale exhibits high photothermal conversion efficiency, enabling hyperthermia-mediated suppression of drug resistance proteins, enhanced cellular metabolism, and increased membrane permeability to potentiate therapeutic efficacy.[103,104] Gao et al synthesized MnO_2 nanosheets via H_2O_2-assisted oxidation of $MnCl_2$, followed by ultrasonication.[105] These nanosheets were coated with soybean phospholipid encapsulating CDDP prodrug, yielding the novel MnO_2@Pt-SP nanosystem. Under laser irradiation, MnO_2@Pt-SP significantly downregulated MRP-1 expression in A549R cells and elevated apoptosis rates from 25% to 57%, demonstrating dual-action resistance reversal through MRP-1 suppression and photothermally enhanced tumor cell death.

On-Target Resistance Mechanism-Based Strategies to Reverse CDDP Resistance

Nuclear DNA and mtDNA constitute the primary molecular targets of CDDP. While nuclear DNA damage activates sophisticated repair mechanisms—predominantly nucleotide excision repair (NER)—tumor cells exploit augmented DNA repair capacity to develop CDDP resistance. Emerging evidence implicates mitochondria as pivotal regulators of resistance, with CDDP-induced mtDNA damage triggering distinct survival pathways that complement nuclear repair mechanisms. Tumor cells typically reprogram metabolism toward glycolysis (Warburg effect), yet under chemotherapeutic pressure, heightened energy demands dysregulate canonical metabolic pathways while activating compensatory adaptations to maintain viability.[106,107] Mitochondria confer biological energy plasticity upon tumor cells, enabling them to evade death pathways under chemotherapeutic stress. To overcome this resistance, mechanism-based strategies focus on reversing CDDP resistance by inhibiting key DNA repair processes and directly targeting tumor cell mitochondria.

Nanomedicines Carrying DNA Repair Inhibitors

Multiple genes and signaling pathways orchestrate the regulation of DNA repair, with over 30 proteins specifically implicated in the NER pathway.[14] CDDP forms N^7-d(GpG) and N^7-d(ApG) DNA adducts that activate NER-mediated repair, enabling tumor survival. Critically, therapeutic efficacy hinges on the equilibrium between DNA damage induction and repair capacity—a balance exploitable through co-delivery of CDDP and DNA repair inhibitors via nanocarriers. Only by simple physical superposition of CDDP and a DNA repair inhibitor, outstanding anti-cancer efficiency has been observed in vitro and in vivo.[108] Combining nanomaterials with CDDP and DNA repair inhibitors improves the stability of free drugs, increases drug intake, and reduces toxic side effects.[109,110]

Wortmannin (Wtmn), an inhibitor of inositol phosphate 3-kinase (PI3K), can reverse the chemoradiotherapy sensitivity by inhibiting DNA-dependent protein kinase and further blocking the downstream DNA repair pathway.[111] Zhang et al prepared Wtmn and CDDP prodrug co-loaded NPs via nano-precipitation.[112] In A2780R cells, this formulation markedly elevated γ-H2AX levels—a biomarker of DNA double-strand breaks and repair inhibition—and achieved a 21-fold lower IC_{50} compared to single CDDP prodrug-loaded NPs. In the NER pathway, ERCC1 plays a major role in the cutting of damaged DNA 5′ site, and thymine phosphorylase (TP) is a key enzyme in the pyrimidine remediation pathway.[9] Lin et al previously found that the cytotoxicity enhancement mediated by the combination of Demethoxycurcumin (DMC) and CDDP was achieved by downregulating the expression of TP and ERCC1 by the PI3K-Akt-Snail pathway.[113] However, free DMC suffers from poor aqueous solubility, low bioavailability, and rapid metabolic clearance, limiting its clinical utility. To overcome these limitations, a core-shell hydrogel NPs was engineered, comprising a DMC-polyvinylpyrrolidone core encapsulated within a carbomethyl-hexanoyl chitosan (CHC) shell.[114] The CDDP-loaded nanomedicine potently inhibits ERCC1 and TP via PI3K-Akt signaling. Separately, PEG-b-PLGA nanomicelles co-encapsulating a DMC derivative and CDDP prodrug specifically inhibited protein phosphatase 2A (PP2A)—a regulator of DNA replication and cell cycle progression—thereby suppressing DNA repair and enhancing CDDP cytotoxicity.[115] Xin et al constructed a multidrug nanocomposite co-delivering CDDP and arsenic trioxide (ATO), demonstrating that ATO inhibits poly(ADP-ribose) polymerase-1 (PARP-1, a critical DNA repair enzyme), while RNA sequencing revealed concurrent downregulation of DNA damage repair genes, synergistically enhancing CDDP's

cytotoxic efficacy.[116] This mechanistic elucidation underscores the necessity of decoding resistance-reversal pathways to accelerate clinical translation of nanocarrier therapeutics.

While NDDSs serve as promising platforms for DNA repair inhibitor delivery,[117] clinical considerations must address inhibitor-associated risks: platinum-PARP inhibitor combinations may induce myelodysplastic syndrome,[118] chronic inhibitor use can trigger secondary resistance via efflux pump upregulation (eg, P-gp),[119] and genomic instability may accelerate metastatic evolution. Implementing companion diagnostics—through genomic/functional DNA repair pathway profiling—to identify predictive biomarkers is thus essential for precision oncology paradigms that maximize therapeutic efficacy while mitigating resistance development.

Nanomedicines Carrying Therapeutic siRNA

siRNA offers a promising alternative for targeting DNA repair pathways to overcome CDDP resistance; however, unmodified siRNA faces formidable barriers: rapid degradation by plasma RNases, poor cellular uptake, and swift renal clearance—collectively resulting in dismal pharmacokinetics that undermine therapeutic potential.[120] These challenges are significantly mitigated by rationally selecting nano-carrier architectures and engineering NDDS surface properties to evade phagocytic clearance, thereby extending systemic circulation and enhancing tumor accumulation.[121]

Li et al developed self-assembled lipid NPs encapsulating CDDP prodrug and xeroderma pigmentosum group F (XPF)-targeted siRNA (Figure 4A).[122] In A549R cells, the NDDS had high gene knockout efficiency and could effectively downregulate XPF mRNA and protein expression levels. The overall platinum level of genomic DNA was prominently increased. Moreover, the level of p-P53 and cleaved-Caspase-3 increased by 3.5-fold and 4.0-fold, respectively, indicating a robust apoptotic response. Polyethylenimine is one of the most extensively studied non-viral vectors for siRNA delivery. Feldmann et al prepared a kind of triblock copolymer polyethylenimine-polycaprolactone-polyethylene glycol (PEI-PCL-PEG) NPs, encapsulated with excision repair cross-complementary 1 (ERCC1)-XPF siRNA assembled via microfluidic and exhibited high biocompatibility.[123] After PEG modification, the NPs showed

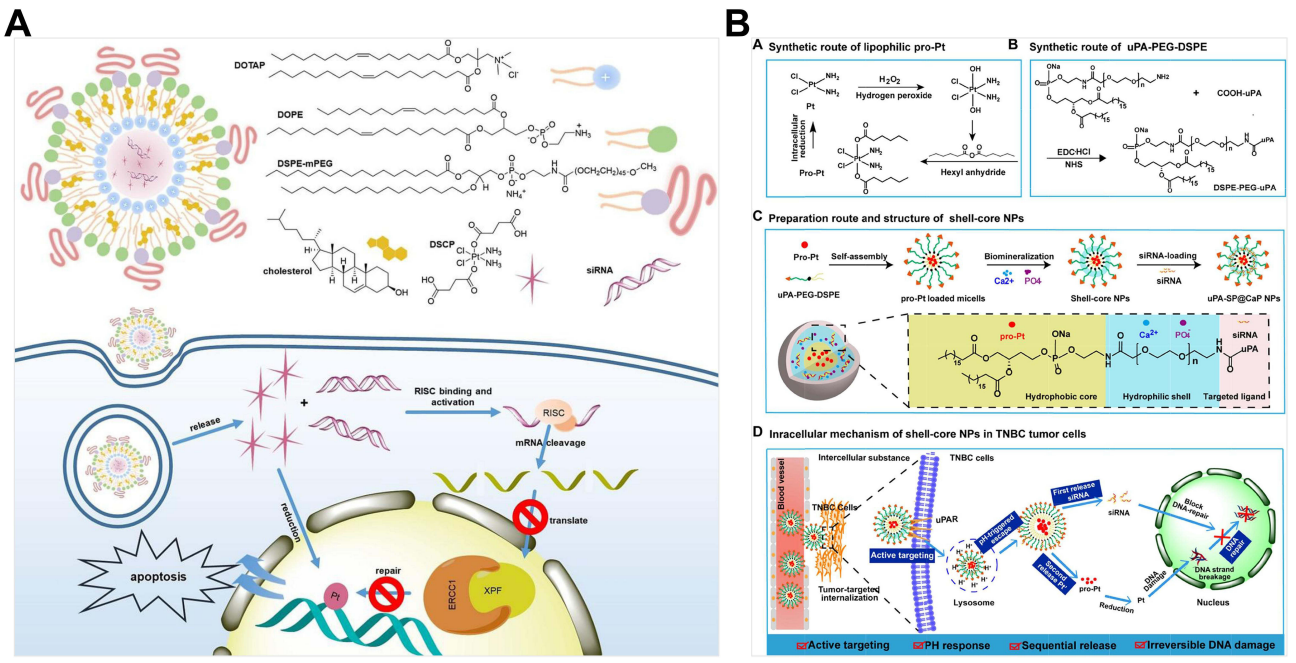


Figure 4 Therapeutic application of two cisplatin prodrug/therapeutic siRNA-loaded NDDSs to reverse the on-targetcisplatin resistance mechanism. (**A**) Schematic illustration of co-delivering the cisplatin prodrug and XPF-targeted siRNA self-assembled lipid NPs and their mechanism for the treatment of lung cancer by specifically downregulating XPF levels to promote apoptosis induced by cisplatin. Reproduced from Li C, Li T, Huang L et al. Self-assembled lipid nanoparticles for ratiometric codelivery of cisplatin and siRNA targeting XPF to combat drug resistance in lung cancer. *Chem Asian J*. 2019;14:1570–1576. © 2019 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.[122]. (**B**) Design and synthesis of uPA-SP@CaP NPs and their mechanism for the treatment of triple negative breast cancer by co-deliverying of Pt prodrug to induce DNA damage and BRCA1 siRNA to disable DNA repair pathways. Reproduced from Dong Y, Liao H, Fu Het al pH-sensitive shell-core platform block DNA repair pathway to amplify irreversible DNA damage of triple negative breast cancer. *ACS Appl Mater Interfaces*. 2019;11:38,417–38,428. © 2019 American Chemical Society.[125]
Abbreviations: XPF, xeroderma pigmentosum group F; uPA, urokinase plasminogen activator.

reduced toxicity and improved circulation profile, while PCL effectively drove micelle formation. Western blot analysis found that the A549 cells treated with the NPs reached > 90% knockdown of ERCC1 and XPF. Clonogenic assay results showed a 1.6-fold change in the IC_{50} value to CDDP. The BRCA1 gene functions not only as a tumor suppressor but also plays a critical role in DNA repair processes. Exploiting the synthetic lethality paradigm wherein BRCA1-deficient triple-negative breast cancer exhibits heightened CDDP sensitivity,[124] Dong et al prepared urokinase plasminogen activator (uPA)-functionalized NPs co-encapsulating CDDP prodrug and BRCA1 siRNA to selectively target uPA-overexpressing tumor cells (Figure 4B).[125] This platform achieved tumor-specific accumulation, enhanced cellular internalization, and potent DNA repair blockade.

In addition to the NER pathway, the DNA repair mechanisms include the translesion DNA synthesis (TLS) pathway, base excision repair, mismatch repair, and homology-directed repair.[126] To our knowledge, there are only a few studies on reversing CDDP resistance by interfering with these repair mechanisms. In the TLS pathway, the process of DNA replication is based on damaged nucleotides as a template, which is very error-prone and most likely will cause DNA mutations. These newly occurring mutations enhance DNA repair or damage tolerance, leading to acquired chemoresistance.[127] The Rev1/Rev3L/Rev7-dependent error-prone play an essential role in the TLS pathway-related CDDP-induced DNA mutation. Xu et al prepared a novel type of polymer/lipid hybrid NPs containing biodegradable PLGA-PEG block copolymers and G0-C14 compounds by double emulsion solvent evaporation, carrying REV1/REV3L-specific siRNAs (siREV1, siREV3L) and CDDP prodrug.[128] The cationic head group of the cationic lipid molecule G0-C14 can effectively bind to siRNA by electrostatic interaction, and its flexible hydrophobic tail can self-assemble with PLGA-PEG to form complete NPs. The study of human lymph node carcinoma of the prostate (LNCaP) xenograft mouse model of prostate cancer in vivo and LNCaP cells in vitro showed that the NPs containing siRNA could successfully reduce the level of the target gene. Compared with the control group, the EC_{50} of this NPs treatment was notably lower in vivo, and it was more sensitive to platinum induction chemotherapy.

Although co-delivering siRNA via CDDP-loaded NDDSs synergistically and effectively inhibits DNA repair, the risks of siRNA as a gene therapy agent—such as off-target effects and immune reactions—must be considered. Additionally, most diseases (including cancer) involve polygenic dysregulation, and manipulating a single gene type may offer limited benefits to patients. There is still a long way to go to explore the long-term effects of siRNA therapy in humans.[129]

Nanomedicines Targeting mtDNA

CDDP has a high affinity with mtDNA and can produce cytotoxicity through interaction with mitochondria.[130] It has been confirmed that mtDNA damage is a crucial factor triggering multiple cell death pathways.[131] Unlike the complex repair mechanism of nuclear DNA mentioned earlier, mtDNA damage repair is relatively simple and scarce because of the lack of an effective repair system.[132] These findings suggest that mtDNA damage induced by highly targeted anti-cancer drugs directed to the mitochondrial matrix may circumvent drug resistance associated with the "precise" repair mechanisms of nuclear DNA damage. Mitochondrially targeted NDDSs exploit the unique electrochemical gradient of mitochondrial membranes to selectively deliver CDDP and attack mtDNA, effectively reversing on-target CDDP resistance through chemiosensitization.

Triphenylphosphonium (TPP) has been widely used in NDDSs targeting the mitochondrial matrix (Table 2). Tumor cells exhibit significantly elevated mitochondrial membrane potential $\Delta\Psi m$ compared to normal cells.[133] TPP, as a lipophilic cation, can mediate the effective uptake of nanodrugs by mitochondria driven by high membrane potential. Marrache et al constructed a nano-system, PLGA-b-PEG-TPP NPs, based on biodegradable poly (lactic-co-glycolic acid) (PLGA)-block (b)-polyethyleneglycol (PEG) functionalized with a terminal TPP cation to carry CDDP prodrug Platin-M.[134] On the one hand, the small size and high lipophilic surface of these NPs contributed to their distribution and accumulation in mitochondrial-rich brain endothelial cells. On the other hand, TPP cations passed through the mitochondrial inner membrane with the help of negative $\Delta\Psi m$, so any Platin-M released from NPs could target mitochondria through TPP cations before reaching mitochondria. They found that Platin-M was transported into mitochondria of the neuroblastoma cell line SH-SY5Y, and its anti-tumor activity was ~17-fold higher than that of free CDDP, confirming that the dual-targeted NDDS has prominent mitochondrial targeting activity. Wei et al prepared novel micelles co-loaded

Table 2 Detailed Description of CDDP/CDDP Prodrug-Loaded NDDSs to Target mtDNA

Mitochondria-Targeting Component	Target Cancer	NDDSs	Particle Size (nm)	Zeta Potential (MV)	Drug Entrapment Efficiency (DEE %)/Drug Loading Efficiency (DLE%)	Drug Release (%) (Time, Stimuli)	Reference
Triphenylphosphonium (TPP)	Ovarian cancer	CDDP-loaded, TPP-modified mesoporous organic silica nanoplatform	/	27.5	/	30 (24h, GSH)	[70]
	Breast cancer	CDDP/collagenase-loaded, TPP-modified, biocompatible chondroitin sulfate coated NPs	91.1 ± 5.5	−15.6 ± 3.5	/	90.1 (28h, pH 6.8)	[137]
	Cervical cancer	CDDP-loaded, TPP-modified NPs	186.3	/	/	45.9 ± 14.1 (72h, pH 5.5)	[138]
	Ovarian cancer	CDDP prodrug-loaded, TPP-modified NPs	/	/	20–40	50 (96h, pH 7.4)	[139]
A cholesterol–TPP conjugate	Lung cancer, cervical cancer, breast cancer	CDDP/camptothecin/tigecycline-loaded, cholesterol-TPP-modified NPs	187	+19	19	49 (72h, pH 8.0)	[140]
TPP–Celastrol conjugate	Breast cancer	CDDP-loaded, TPP-Celastrol-modified NPs	99.65	−49.97	4.7	>99 (72h, NIR)	[141]
α-tocopheryl succinate (α-TOS)	Lung cancer	CDDP-loaded, α-TOS-modified NPs	/	−25	/	/	[142]
Rhodamine-110 (Rho-110)	Breast cancer, ovarian cancer	CDDP prodrug/3-bromopyruvate-loaded, Rho-110-modified multi-walled carbon nanotubes	/	/	35.4	/	[143]
IR780	Lung cancer	CDDP prodrug-loaded IR780-modified NPs	45	/	/	60 (48h, GSH)	[144]

with TPP, HA, CDDP prodrug and photosensitizer Ce6.[135] Upon binding CD44 receptors and cellular internalization, light-triggered ROS generation enhanced mitochondrial membrane permeability, driving TPP-directed CDDP accumulation that triggered cytochrome C (Cyt C) release and apoptosis—evidenced by collapsed ΔΨm, elevated Cyt C, and 83% apoptosis in irradiated B16F10 cells, while achieving 84.4% tumor suppression and 85.7% 45-day survival in melanoma-bearing mice, validating synergistic chemo-photodynamic efficacy. Similarly, dequalinium-conjugated mesoporous silica NPs loaded with CDDP demonstrated enhanced mitochondrial targeting in HeLa and SH-SY5Y cells, exhibiting 50% higher FITC fluorescence intensity in mitochondria versus non-dequalinium controls alongside significantly increased cytotoxicity.[136]

Certain mitochondrial-targeting agents exhibit dual functionality, serving as both auxiliary imaging tools and synergistic therapeutic agents. For instance, Rhodamine-110 (Rho-110), a fluorescent dye with lipophilic and cationic properties, can target mitochondria through positively charged fragments. Through a confocal microscope, Yoong et al observed that multi-walled carbon nanotubes (MWCNTs) functionalized by Rho-110 co-localized up to about 80% in mitochondria of MCF-7 cells.[143] Then, they used MWCNT-Rho complex to encapsulate CDDP prodrug (PtBz) and chemical enhancer 3-bromo-opyruvate (BP) to prepare MWCNT-Rho (PtBz + BP) nano-polymer. The toxicity test of A2780 cells showed that the synergistic effect of PtBz and BP co-treatment was amplified, which enhanced the cytotoxicity of PtBz. To ascertain mitochondrial involvement in the enhanced therapeutic efficacy of MWCNT-Rho (PtBz + BP), flow cytometry revealed a 2-fold increase in MCF-7 cells exhibiting mitochondrial membrane depolarization—directly implicating the nanocarrier in potentiating mitochondrial damage beyond platinum-induced cytotoxicity. IR780, a clinically established near-infrared fluorophore (NIR) and photothermal sensitizer, overcomes CDDP resistance through chemo-photothermal synergy: under NIR irradiation, its photothermal conversion depletes intracellular GSH while generating localized hyperthermia—potentiating CDDP efficacy by simultaneously disrupting redox homeostasis and inducing thermal tumor ablation.[145] Moreover, IR780 has been found to target mitochondria actively.[146] Yang et al constructed precisely self-assembled Pt(IV)-NPs via 1:1 molecular coordination of biotinylated CDDP prodrug Pt(IV) and IR780.[144] In A549R cells, mitochondrial CDDP accumulation consistently exceeded cytoplasmic/nuclear levels by 4-fold across timepoints, with sustained mitochondrial colocalization of both agents at 24h—enabling tumor-targeted chemo-phototherapy. Under NIR irradiation, Pt(IV)-NPs increased apoptosis to 84.2% (±2.7%), a 16% absolute increase over dark conditions. This platform delayed tumor growth, extended the circulation half-life 3.2-fold, and reduced CDDP-induced hepatorenal toxicity in a murine model, validating mitochondrial precision for resistance reversal (Figure 5).

To maximize the therapeutic potential of mitochondrial-targeted agents, refined NDDS strategies must be developed to specifically modulate mitochondrial function in tumor cells, necessitating extensive preclinical and clinical validation to achieve this objective. Recently, Tong et al revealed a novel pathway of cAMP response element-binding CREB5/TOP1MT/mitochondria mediating CDDP resistance.[147] A study innovatively constructed a CDDP-loaded multichannel Ca^{2+} nano-modulator capable of achieving mitochondrial Ca^{2+} overload and mtDNA damage, leading to multilevel mitochondrial damage.[148] The role of mitochondria in tumor drug resistance is extremely complex, and the mechanisms involved are yet to be elucidated.

Post-Target Resistance Mechanism-Based Strategies to Reverse CDDP Resistance

CDDP induces apoptosis primarily through DNA damage and cellular homeostasis disruption. This process is mainly regulated by a balance between anti-apoptotic proteins (Bcl-2, Bcl-xl, Bcl-w, Mcl-1) and pro-apoptotic proteins (Bax, Bak, and BH3-only protein), initiator caspases (Caspase-8, Caspase-9, and Caspase-10), and effector caspases (Caspase-3, Caspase-6, and Caspase-7).[149] Tumors resist CDDP-induced apoptosis through three key mechanisms: (1) inactivation of p53 (primary DNA damage sensor), (2) upregulation of anti-apoptotic family proteins, and (3) suppression of caspase activity. Currently, post-target resistance mechanism-based strategies mainly aim to overcome CDDP resistance by regulating apoptosis-related proteins and activating apoptosis.

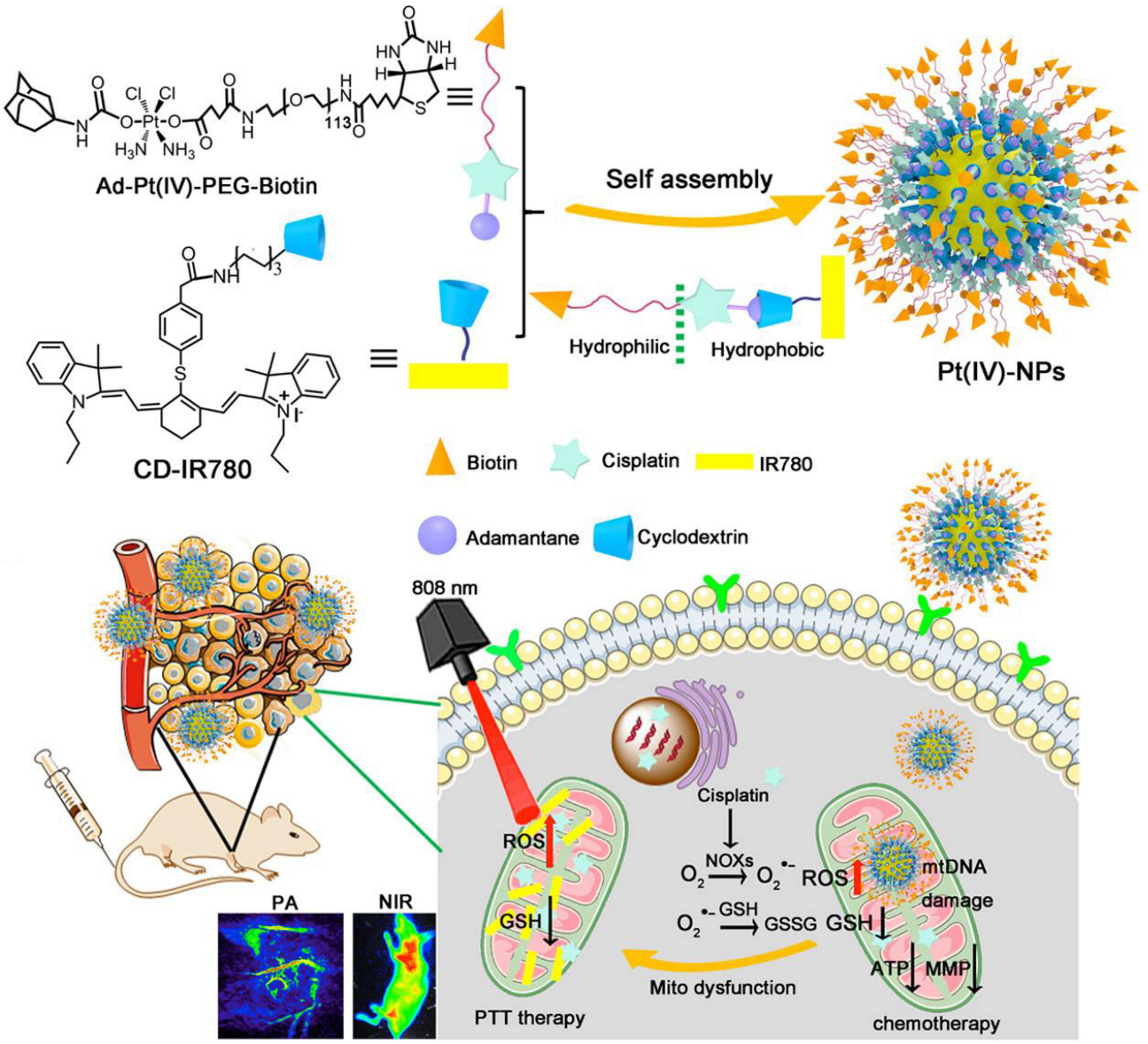


Figure 5 Schematic illustration of Pt(IV)-NPs and their mechanism for the treatment of lung cancer via targeting mitochondria and imaging-guided chemo-photothermal therapy. Reproduced from Yang GG, Pan ZY, Zhang DY et al. Precisely assembled nanoparticles against cisplatin resistance via cancer-specific targeting of mitochondria and imaging-guided chemo-photothermal therapy. *ACS Appl Mater Interfaces*. 2020;12:43,444–43,455. © 2020 American Chemical Society.[144]

Nanomedicines Upregulating p53 Protein Expression

The TP53 gene, mutated in ~50% of human cancers, encodes the tumor suppressor p53 that maintains genomic stability and inhibits tumor growth.[150] CDDP induces apoptosis by activating p53, which transactivates pro-apoptotic genes (Bax, TP53 apoptosis effector PERP, and BH3-only family [such as Noxa, Puma]) to initiate apoptosis.[151] Additionally, p53 reverses CDDP resistance by inhibiting GSH synthesis and downregulating MRP expression. Thus, NDDSs designed to restore p53 function enhance CDDP-induced cytotoxicity through dual apoptosis potentiation and resistance pathway suppression.

Oleanolic acid (3β-hydroxyolean-12-en-28-oic acid, OA), a ubiquitously distributed pentacyclic triterpenoid in medicinal plants, exerts multifaceted anticancer effects—notably by potentiating p53 transcriptional activity to amplify the mitochondrial apoptosis pathway.[152] Khan et al constructed lipid-coated calcium carbonate nanoparticles (CDDP/OA-LCC NPs) encapsulating a synergistic CDDP/OA combination (2:35 ratio).[153] In HepG2 cells, CDDP/OA-LCC NPs achieved 41% apoptosis (early + late) versus 34% (CDDP-LCC NPs) and 24% (OA-LCC NPs), with significantly

upregulated p53 expression—indicating OA amplifies CDDP efficacy via p53 potentiation. Separately, layered double hydroxide NPs co-loaded with CDDP prodrug and p53-activating chalcones demonstrated enhanced antitumor effects through dual-drug synergy.[154] However, drugs or small molecules that promote the functional recovery of p53 are difficult to explore in practical applications.[155] microRNA (miR)-based strategies offer promising alternatives for post-transcriptional regulation. miR34a, both a direct p53 transcriptional target and a modulator of p53 signaling pathways, forms an auto-amplification loop that potentiates p53-mediated tumor suppression.[156] Gu et al engineered NPs co-loaded with CDDP, miR34a, and KRAS-targeting siRNA to simultaneously reactivate p53 and silence oncogenic KRAS.[157] In TP53-deficient/KRAS-activated lung adenocarcinoma cells, NP delivery elevated miR34a expression by 60% within 72h and reduced CDDP IC_{50} by 5-fold versus scrambled RNA controls. This triple-targeting strategy significantly suppressed tumor growth and extended survival in murine models, demonstrating clinical potential for overcoming CDDP resistance.

Tumor-overexpressed proteins COX-2 and DJ-1 suppress p53-mediated apoptosis, conferring CDDP resistance. Inhibiting these proteins reverses resistance, as demonstrated by Yang et al's lipid-PLGA NPs encapsulating Tolfplatin—a prodrug synthesized from Tolfenamic acid (COX-2 inhibitor) and CDDP hydrate.[158] In 4T1 cells, Tolfplatin downregulated Bcl-2 (anti-apoptotic) while modulating Bax (pro-apoptotic) via p53 upregulation, accelerated the process of cell apoptosis, and synergistically enhanced CDDP efficacy (Figure 6). Schumann et al constructed a CDDP/DJ-1 siRNA co-loaded NDDS using polypropylene imide (PPI) dendrimers for siRNA transport, with PEG modification enhancing biocompatibility and LHRH peptide conjugation enabling ovarian cancer-specific targeting.[159] In vitro, this NDDS significantly upregulated p53 expression while suppressing proliferation and viability across CDDP-resistant ovarian cancer cell lines (A2780 > ES2 > IGROV-1, ranked by resistance severity), with maximal efficacy in A2780R cells—demonstrating DJ-1 inhibition activates p53-mediated Bax-caspase apoptosis pathways and restores cell cycle arrest. In vivo, three cycles of low-dose intraperitoneal DJ-1 siRNA/CDDP nanotherapy achieved complete tumor eradication and 35-week recurrence-free survival in metastatic ovarian cancer models.[160]

While the aforementioned strategies show promise for p53-defective cancers, their clinical translation necessitates rigorous consideration of tumor heterogeneity and oncogenic context. Paradoxically, while wild-type p53 tumors often exhibit heightened drug sensitivity, substantial evidence indicates p53-deficient malignancies may similarly display enhanced susceptibility to targeted therapies. p53 homeostasis governs tumorigenic progression—sustained p53 activation in hepatocytes promotes hepatocarcinogenesis,[161] whereas p53 deletion or dysregulated activation induces metabolism-related pathologies,[162] underscoring that therapeutic interventions must balance precision against paradoxical oncogenic risks.

Nanomedicines Regulating Apoptosis Signaling Pathway-Related Genes

Generally, most CDDP-resistant tumor cells avoid drug-induced apoptosis through three main ways: (1) overexpressing anti-apoptotic family proteins, such as Bcl-2, (2) reducing caspase family proteins production, and (3) inhibiting the activity of caspase family proteins, such as reducing the production of cytochrome enzymes or activating the inhibitor of apoptosis protein surviving, to play an inhibitory role.[163] The CDDP-loaded NDDSs—particularly when combined with multi-drug regimens—can rebalance apoptosis-regulating gene expression to reverse post-target resistance mechanisms.

Camphor, a traditional phytochemical from camphor laurel with documented anticancer activity, was engineered by Qi et al into the prodrug camplatin via fusion of camphoric anhydride with CDDP.[164] Covalently conjugated to MPEG-b-PCL-bPLL copolymer, camplatin self-assembled into micelles that reduced Bcl-2/Bax ratio from 5.5 to 1.2 in A2780R cells—reversing CDDP resistance without altering Bax expression. Contrastingly, Morovati et al's chitosan-modified iron oxide NPs upregulated Bax in MDA-MB-231 cells, elevating apoptosis to 50.48% versus 4.26% for free CDDP, highlighting divergent Bax-regulation mechanisms in resistance reversal strategies.[165] Qiu et al created folic acid-modified nanocomplexes from Auricularia auriculajudae polysaccharide (APP, a natural carrier with antitumor/anticoagulant properties) to deliver CDDP.[166] In HeLa tumor-bearing mice, this NDDS demonstrated exceptional biosafety (confirmed by multi-organ histopathology and hematological indices), while immunohistochemistry revealed: minimal Bcl-2 expression, maximal Bax upregulation, and robust Caspase-3 activation versus free CDDP or APP-CDDP controls. Additionally, it induced intrinsic apoptosis via Cyt C activation. Similarly, CDDP-loaded multiwall carbon nanotubes

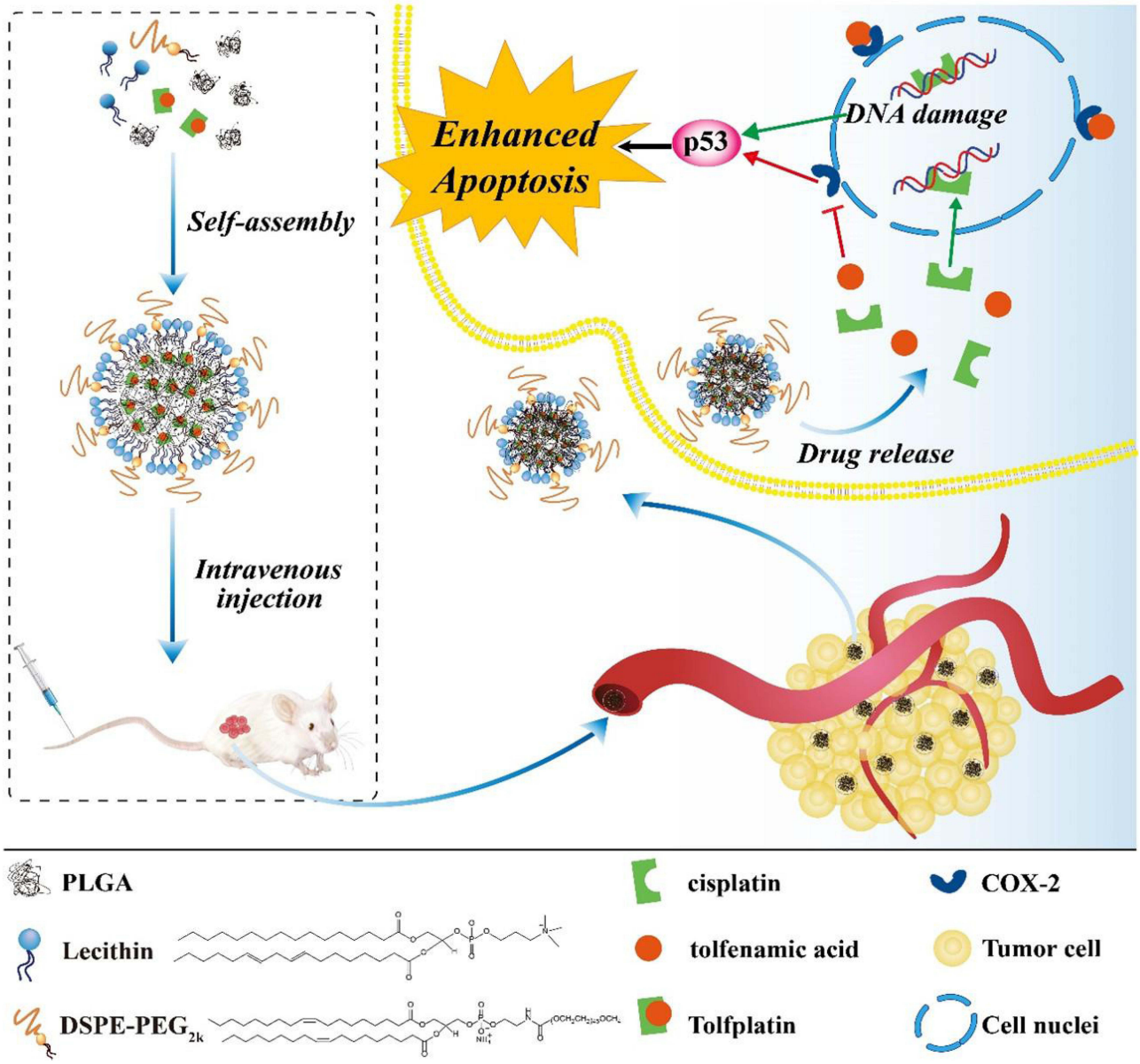


Figure 6 Schematic illustration of lipid-PLGA@Tolfplatin NPs and their mechanism for the treatment of breast cancer by synergistically promoting apoptosis through the delivery of COX-2 inhibitor tolfenamic acid and cisplatin. Reproduced from Yang CX, Xing L, Chang X et al. Synergistic platinum(II) prodrug nanoparticles for enhanced breast cancer therapy. *Mol Pharm*. 2020;17:1300–1309. © 2020 American Chemical Society.[158]
Abbreviation: Tolfplatin, tolfenamic acid and cisplatin.

prepared by Zhou et al led to downregulated Bcl-2 and upregulated Bax/Caspase-3/9 in A549R cells, achieving 2-fold higher apoptosis than free CDDP.[167]

To directly target apoptosis-related genes, Ma et al developed PGA-coated protamine/HA nanocarriers co-delivering CDDP prodrug Pt(IV) and survivin siRNA (NP-siRNA/Pt(IV)), achieving sequential electrostatic siRNA release followed by Pt(IV) reduction in A549R cells—effectively downregulating survivin while enhancing DNA binding and cytotoxicity, thereby reducing drug efflux and promoting apoptosis.[168] This system demonstrated 82.46% tumor suppression in A549R murine models with extensive tumor necrosis. Complementarily, He et al's self-assembled core-shell nanoscale coordination polymers (NCPs) co-loaded with CDDP and survivin/Bcl-2 dual siRNA eradicated tumors in 5/6 SKOV-3 subcutaneous xenografts and achieved 100% 90-day survival in A2780R intraperitoneal models.[169] Further optimization yielded NCP-1/siRNA particles linking Pt(IV)-Zn^{2+} cores to cationic lipid-coated siRNAs targeting

survivin, Bcl-2, and P-gp—restoring CDDP sensitivity in four resistant ovarian lines (ES-2/OVCAR-3/SKOV-3/A2780R) and reducing SKOV-3 viability to 25.2% versus 94.8% in controls, confirming potent apoptosis induction.[170]

A critical limitation persists in CDDP-loaded NDDS co-delivery studies: most merely report apoptosis-related gene expression changes without interrogating underlying mechanisms driving tumor apoptosis or resistance reversal. Promoting apoptosis does not mean that drug resistance has been successfully overcome, as compensatory proliferative responses may be triggered post-treatment—fueling resistance recurrence.[171] Thus, durable efficacy requires combinatorial regimens targeting multiple apoptotic pathways or integrating synergistic modalities like radiotherapy/thermotherapy to preempt compensatory adaptation.

Nanomedicines Inducing Ferroptosis

Ferroptosis—an iron-dependent, non-apoptotic cell death pathway—is morphologically defined by mitochondrial atrophy and iron-accumulated lipid peroxidation, distinct from classical apoptosis.[172] Current therapeutic strategies leverage iron-based nanocarriers to induce tumor ferroptosis: Fe^{2+} released in endosomes/lysosomes catalyzes Fenton reactions, generating ·OH and elevated ROS levels.[173] CDDP co-delivery synergistically amplifies this process by both initiating apoptosis and providing endogenous H_2O_2 as a Fenton substrate.[174]

Gao et al prepared peptide carriers co-encapsulating CDDP prodrugs and Fe_3O_4 NPs to generate high ROS levels, enabling chemotherapy-ferroptosis synergy.[57] However, free Fe^{2+} oxidizes rapidly to Fe^{3+}, halting Fenton reactions. Gallic acids (GA) counteracts this by reducing Fe^{3+} to Fe^{2+} via phenolic groups, sustaining ferroptosis.[175] Han et al's pH-responsive $CaCO_3$ NPs delivering GA/Fe^{2+}/CDDP prodrugs induced partial cell death reversal by apoptosis inhibitors in vitro—confirming ferroptosis contribution—while Fer-1 inhibition blocked lipid peroxidation in vivo.[176] Inhibition of glutathione peroxidase 4 (GPX4), a pivotal ferroptosis regulator, triggers lethal lipid peroxidation and commits cells to ferroptosis. Zhang et al designed folate-modified porous iron oxide NPs (FA/Pt-si-GPX4@IONPs) loaded with CDDP and GPX4 siRNA, wrapped in DSPE-PEG2K-FA lipofectamine.[177] After FA/Pt+si-GPX4@IONPs treatment in U87MG and P3#GBM cells, GPX4 levels decreased to 30.9% and 36.4% of the original levels, and Fe^{2+} concentrations increased 7.25-fold and 7.9-fold, respectively (Figure 7). Besides, the mortality rate of U87MG cells reached 33.3%, and the level of MDA (the product of intracellular lipid peroxidation) was 4-fold higher than that of the control group, suggesting a high iron mortality rate. In addition to Fe^{2+}, Mn^{2+} can also induce the Fenton-like reaction.[178] Cheng et al innovatively incorporated Mn^{2+} into iron-based NPs, co-releasing Fe^{2+}/Fe^{3+}/Mn^{2+} with CDDP prodrugs to promote ferroptosis.[179] These NPs exerted potent antitumor effects in tumor-bearing BALB/c-nude mice at merely 8.89% the platinum dose of free CDDP.

Despite the great promise of ferroptosis in tumor therapy, increasing attention is being directed toward its immunological effects. Research has revealed that ferroptosis inhibits the impact of killing dendritic cells and T cells in the immune microenvironment, thus promoting the immune escape of tumor cells and accelerating tumor progression.[180,181] Furthermore, ferroptosis heterogeneity in triple-negative breast cancer has been revealed.[182] These findings provide new directions for clinical precision treatment by inducing ferroptosis.

Off-Target Resistance Mechanism-Based Strategies to Reverse CDDP Resistance

Beyond apoptosis regulation, compensatory survival pathways—notably PI3K/AKT/mTOR-mediated control of tumor cell survival and autophagic flux—drive CDDP resistance by suppressing chemotherapeutic efficacy.[183] Tumor microenvironmental hypoxia and cellular heterogeneity (eg, cancer stem cells, CSCs) further modulate CDDP sensitivity. Consequently, NDDS-based integration of medical, chemical, and genetic engineering therapies has emerged as the cornerstone strategy to overcome off-target resistance mechanisms through multi-pathway disruption.

Nanomedicines Regulating the Hypoxic Microenvironment

The rapid tumor cell proliferation outpacing vascular supply induces pervasive hypoxia, driving adaptation toward aggressive, treatment-resistant phenotypes that fundamentally underlie clinical drug resistance.[184] This hypoxic

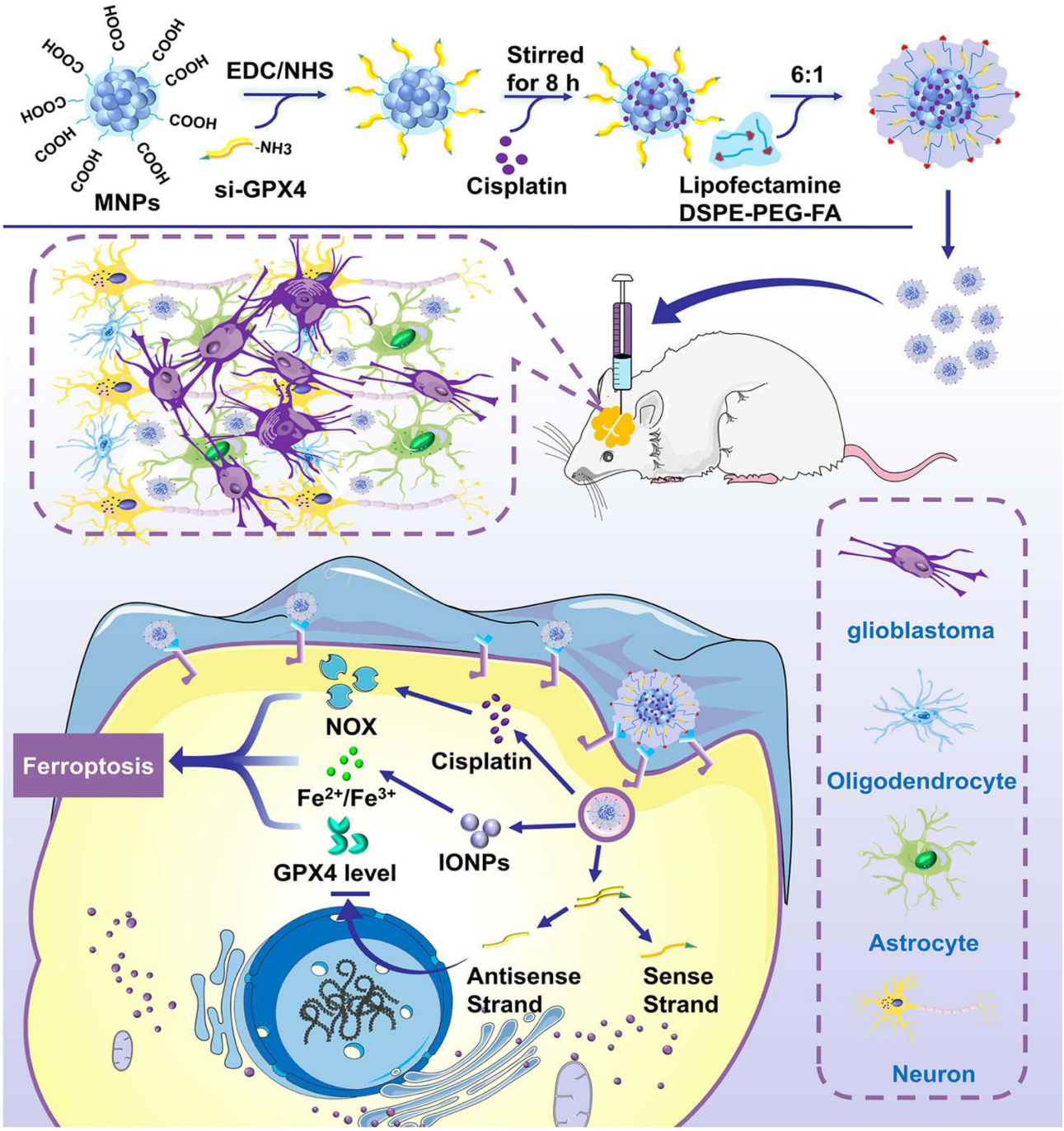


Figure 7 Schematic illustration of folate-modified cisplatin/GXP4 siRNA-loaded iron oxide NPs (FA/Pt + si-GPX4@IONPs) and their mechanism for the treatment of orthotopic glioblastoma by inducing ferroptosis. Reproduced from Zhang Y, Fu X, Jia J et al. Glioblastoma therapy using codelivery of cisplatin and glutathione peroxidase targeting siRNA from iron oxide nanoparticles. *ACS Appl Mater Interfaces*. 2020;12:43,408–43,421. © 2020 American Chemical Society.[177]
Abbreviations: FA, folate; GPX4, glutathione peroxidase 4; ONPs, porous iron oxide nanoparticles.

microenvironment concurrently acidifies via lactic acid accumulation, promoting MDR through impaired apoptosis, drug ion trapping (reducing intracellular concentrations), and ABC transporter upregulation.[185] For a long time, hypoxia-inducible factor-1α (HIF-1α) has been most extensively studied in the mechanisms related to hypoxia-mediated drug resistance. Hypoxia has been found to mediate the development of multiple CDDP resistance mechanisms, such as pre-target (promoting drug efflux protein expression), on-target (promoting DNA repair), post-target (down-regulating p53), and off-target (increasing tumor cell stemness) through up-regulation of HIF-1α expression.[186,187] Given conventional

therapies poorly correct hypoxia, NDDS-enabled combinatorial regimens—integrating CDDP with oxygen therapy, radiotherapy, or HIF-1α-targeted gene therapy—hold significant clinical-translational potential for overcoming hypoxia-driven resistance.

Nanomedicines Increasing Intracellular Oxygen Levels

Tumor-accumulated H_2O_2 serves as a natural substrate for oxygen generation,[188] exploited by catalase-mimetic MnO_2 nanostructures to alleviate hypoxia. Zhou et al engineered CDDP-loaded hollow mesoporous MnO_2-PEG nanoshells (H-MnO_2-PEG) for hypoxia relief and imaging-guided radiotherapy.[189] Superiorly, NDDS-mediated catalase (CAT) delivery enables H_2O_2-responsive oxygen generation: Chen et al's PLGA NPs co-loaded with CAT and CDDP utilized tumor H_2O_2 to produce O_2 bubbles that ruptured the nanocarriers, triggering localized CDDP release and reversing hypoxia-induced resistance.[190] Similarly, Zhang et al's CAT@Pt(IV)-liposome NPs reduced hypoxic areas in 4T1 tumors from 85.5% (control) to 11.45%, and when combined with X-ray irradiation, achieved superior tumor growth inhibition by synergistically decomposing endogenous H_2O_2 into O_2 during chemoradiotherapy.[191]

The oxygen production from endogenous H_2O_2 in tumor cells is limited. To solve this problem, He et al prepared biocompatible lipid-coated CaO_2/CDDP NPs, which could not only increase the intracellular oxygen content by continuous active oxygen generation, but also generate $Ca(OH)_2$ to increase the local pH and oxidize GSH to fully regulate the TME.[71] Innovatively, Song et al applied thermally mediated emulsification to prepare perfluorooctyl bromide (PFOB) nanoemulsion, which had high solubilizing oxygen capacities and a 2.5-fold increase in dissolved oxygen content compared to saline.[192] In A549 tumor-bearing mice, PFOB nanoemulsion was able to maintain tumor oxygenation for up to 6h under hyperoxic (95% O_2) conditions, and the rate of apoptosis induced by combined CDDP treatment was twice that of CDDP alone, as confirmed by the real-time in vivo Image-iT^{TM} hypoxia probe. Repeatedly high doses of chemotherapeutic agents increased tumor cell resistance, but due to PFOB nanoemulsion maintaining high oxygenation in tumor cells, a small dose of CDDP (1 mg/kg) was applied to effectively inhibit tumor growth.

Tumor hypoxia exhibits profound interspecies and intratumoral spatial heterogeneity,[193] complicating precise microenvironmental modulation. Advancing hypoxia detection technologies, developing versatile NDDSs, and expanding clinical trials are thus critical priorities. Simultaneously, remodeling the TME requires addressing both hypoxic niches and multifaceted resistance mediators, including cellular components (immune/mesenchymal cells) and non-cellular factors (extracellular matrix, cytokines), to unlock next-generation antitumor strategies.

Nanomedicines Targeting the HIF-1α

In the oxygen-rich environment, HIF-1α is hydroxylated and modified by proline hydroxylase, undergoes polyubiquitination, and is ultimately degraded by the E3 ubiquitin ligase von Hippel-Lindau protein (pVHL) complex proteasome.[194] However, in hypoxia, stabilized HIF-1α translocates to the nucleus and transactivates CDDP resistance genes (eg, VEGF induction, p53 downregulation).[194] NDDSs enable co-delivery of HIF-1α modulators and CDDP to tumor cells, representing a promising strategy to reverse drug resistance.

cyclo-CLFVY, a cyclic peptide, can bind to HIF-1α, prevent HIF-1α/β dimerization, and act as a potent HIF-1 inhibitor.[195] Soleymani Abyaneh et al developed an EGFR-target peptide modified polymeric micellar complexes of CDDP.[196] They found that the micelles only enhanced the uptake of CDDP, but did not affect its cytotoxicity in the breast cancer cell line MDA-MB-231. However, treatment with cyclo-CLFVY significantly increased the killing effect and overcame the HIF-1α-mediated CDDP resistance. Acriflavin has the exact mechanism of action as cyclo-CLFVY.[197] Zhang et al synthesized CDDP-loaded microporous organosilicon NPs (PMONA) via reverse-phase microemulsion, electrostatically adsorbing Acriflavine.[198] In A549 cells, PMONA induced 41% apoptosis (early + late) versus 8% for free CDDP, with significant S-phase cell cycle arrest. In vitro/vivo, PMONA markedly downregulated HIF-1α, resistance proteins (MRP-2/P-gp), and metastasis factor VEGF. Beyond direct HIF-1α inhibition, chitosan-coated selenium/CDDP NPs enhance bioadhesion, molecular stability, and anti-cancer efficacy relative to unmodified counterparts.[199] Selenium's antioxidant activity also scavenges excessive ROS, indirectly downregulating HIF-1 via ROS-dependent pathways to reverse CDDP resistance.[200] Chen et al prepared sialic acid receptor-targeted chitosan oligosaccharide micelles co-

delivering CDDP and NO, which downregulated HIF-1α, GSH, and MRP-2—directly or indirectly—inhibiting epithelial-mesenchymal transition (EMT) to reverse drug resistance and suppress metastasis (Figure 8).[201]

Studies investigating RNAi-engineered NPs combined with CDDP have increasingly shown that such formulations enhance tumor cell sensitivity to CDDP, providing indirect evidence for the effectiveness of HIF-1α-targeted nanostrategies. For instance, Lian et al's chitosan-modified TPGS-b-(PCL-ran-PGA) NPs delivering HIF-1α siRNA reduced HIF-1α protein expression by 12% and suppressed HIF-1α-mediated MDR1/P-gp in CNE-2 cells, slashing hypoxic cell viability to 38.23% versus 97.12% with free CDDP.[202] Moreover, Tu et al's magnetic iron oxide NPs delivered HIF-1α shRNA recombinant plasmid vectors to A549R cells, downregulating HIF-1α/MRP-1/ lung drug resistance-associated protein (LRP) expression and achieving 82% CDDP resistance reversal—outperforming liposomal vectors in transfection efficiency, HIF-1α inhibition, and tumor suppression in murine models through synergistic CDDP potentiation.[203]

Nanomedicines Carrying Hypoxia-Activated Prodrugs

Hypoxia-activated prodrugs (HAPs) are a new class of bioreductive drugs consisting of three main components: (1) a trigger, which determines hypoxia selectivity and activation of drug precursors, (2) an effector, which kills cells in a hypoxic microenvironment, and (3) a linker, which inactivates the effector.[204] These drugs are highly selective for hypoxic solid tumor cells. In a hypoxic environment, the non-toxic precursors are reduced to cytotoxic drugs by enzymatic catalysis. While in an oxygen-rich environment, the cytotoxic drugs are oxidized to form non-toxic precursors. Among them, Tirapazamine (TPZ) is one of the most studied HAPs with topoisomerase II toxicity.[205] Chen et al proposed a novel "downstream" nano-chemotherapy strategy by encapsulating TPZ and glucose oxidase (Gox) in liposomes containing CDDP prodrugs.[206] Gox amplifies tumor hypoxia by catalyzing glucose oxidation and oxygen consumption, fully activating TPZ while synergizing with CDDP to eradicate drug-resistant cells. In CDDP-resistant BEL7404 cells, patient-derived organoids (in vitro), and both cell-line-derived/patient-derived xenografts (in vivo), this

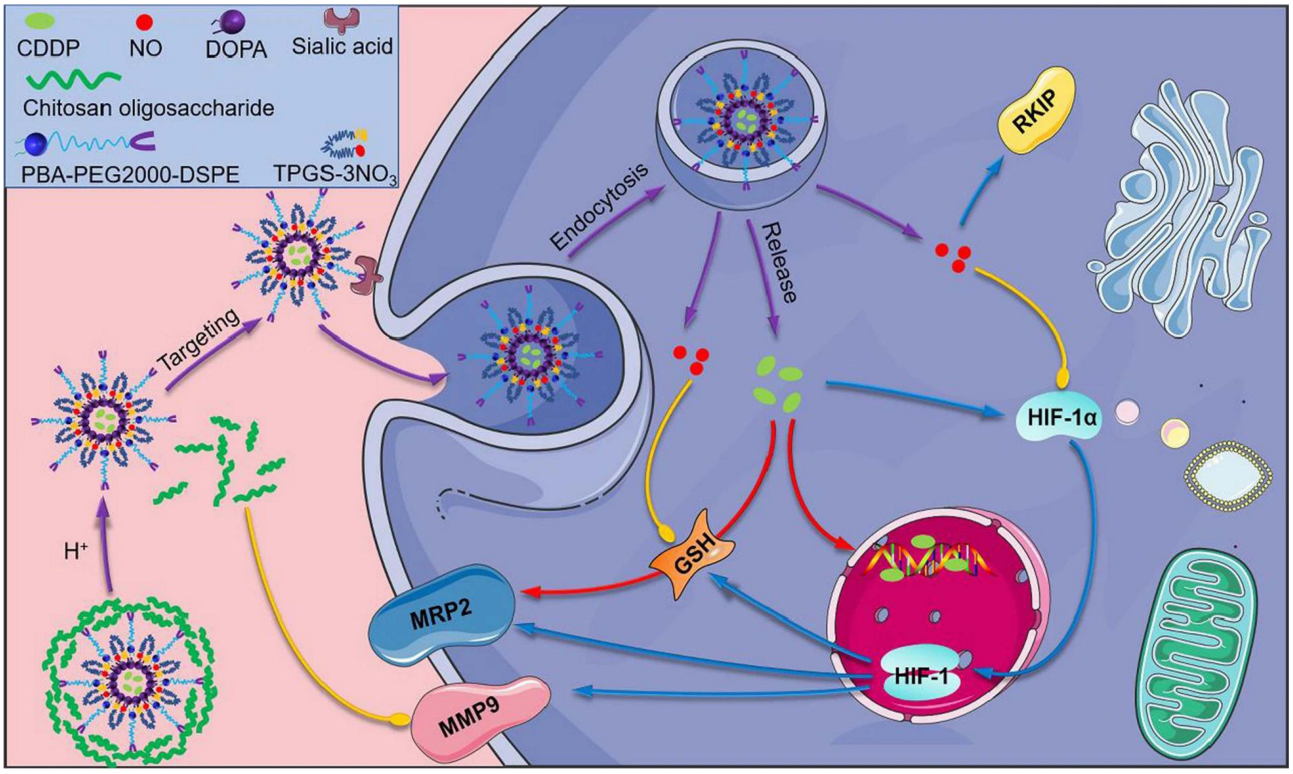


Figure 8 Schematic illustration of chitosan oligosaccharide-coated and sialic acid receptor-targeted nano-micelles and their mechanism for the treatment of breast cancer by reducing CDDP efflux and inhibiting drug resistance-related factors expression (HIF-1α, GSH, MRP2 and MMP9). Reproduced from Chen Y, Fang L, Zhou W et al. Nitric oxide-releasing micelles with intelligent targeting for enhanced anti-tumor effect of cisplatin in hypoxia. *J Nanobiotechnology*. 2021;19:246–246. © 2021 The Author(s).[201]
Abbreviations: CDDP, cisplatin; HIF-1α, hypoxia-inducible factor-1α; GSH, glutathione; MRP2, multidrug resistance-associated protein 2; MMP9, matrix metalloproteinase 9.

nano-strategy potently inhibited tumor growth/metastasis and demonstrated significant advantages in reversing CDDP resistance through hypoxia-amplified TPZ activation. Based on the hypoxia vulnerability of drug-resistant cancer cells, Liu et al engineered T/C@HN NPs, a nanomedicine constructed by TPZ and encapsulating Ce6 into 2-nitroimidazole modified HA using polymer assembly technology.[207] This innovative design leverages the hypoxic TME to dual-activate Ce6-based photodynamic therapy and amplify TPZ cytotoxicity, thereby offering a promising therapeutic strategy to combat CDDP-resistant tumors.

Nanomedicines Inhibiting CSCs and Tumor Stemness

CSCs, a rare subpopulation (0.01–2% of tumor cells) exhibiting self-renewal and multilineage differentiation, drive tumor heterogeneity and therapeutic resistance.[208] Under chemotherapy-induced chronic inflammation, CSCs activate stemness pathways (Wnt/Notch/Shh signaling pathways) to evade DNA damage, maintain genomic stability, and ultimately cause MDR.[209] Chemotherapeutic drugs, including CDDP, may eliminate bulk tumor cells but spare intrinsically resistant CSCs, which rapidly proliferate and differentiate, constituting the primary mechanism of chemoresistance and relapse.[210] CSC-targeting NDDSs represent a promising strategy to durably reverse CDDP resistance.

Recent studies on CSCs have identified specific surface biomarkers critically associated with tumor chemoresistance. For example, CD133 activates the PI3K/AKT/mTOR signaling pathway to induce autophagy and CDDP resistance in gastric cancer cell line KATO-III.[211,212] Consequently, quantifying these biomarkers provides a viable method for assessing CSC activity and therapeutic efficacy.[213] Wang et al observed persistent CD44v-positive cells (a key CSC marker in epithelial cancers) in CDDP-treated squamous carcinoma xenografts, where tumor growth was only transiently suppressed with eventual recurrence.[214] They demonstrated that CDDP-encapsulated polymeric micelles (CDDP/m) selectively accumulated in CD44v-positive regions, effectively eliminating CSCs and reversing chemoresistance. Complementary studies by Zhu et al revealed 1.3-fold enrichment of CD133-positive A549/H460 lung CSCs post-CDDP treatment versus PBS controls.[215] Micellar NPs self-assembled from CDDP-PEG-b-PCL not only reduced CD133-positive cell counts at equivalent platinum doses but also suppressed the tumorsphere formation capacity of CSCs. These findings collectively underscore the advantages of NDDSs in targeting CSC mechanisms, though further investigation is warranted to elucidate nanomaterial-CSC interactions.

These overexpressed biomarkers serve as critical targeting moieties for nanocarriers—exemplified by HA, which functions dually as a biodegradable protective layer and a selective ligand for CD44-positive CSCs. Leveraging this dual functionality, CDDP-loaded HA nanopolymers have been engineered to specifically eradicate CD44-positive CSCs, significantly enhancing tumor cell sensitivity to CDDP (Table 3). Targeting key proliferation/differentiation regulators offers an effective strategy for eradicating CSCs, exemplified in hepatocellular carcinoma by hepatocyte nuclear factor 4α (HNF-4α)—a transcriptional maintainer of hepatocyte differentiation that suppresses CSC generation and the EMT process while ameliorating inflammatory microenvironments and fibrosis, with its frequent downregulation correlating to poor prognosis.[216] Tsai et al constructed PEI-modified mesoporous silica NPs (PMSNs) for delivering HNF4α-encoding plasmids and CDDP.[217] In vitro, CD133 mRNA and protein were remarkably downregulated after PMSN-HNF4α transduction into CD133-positive Huh7 cells. Further treatment of the hepatoma cell line Huh7 revealed that the proportion of CD133-positive Huh7 cells was only about 1/2 of that in the PMSN-treated group by flow cytometry. Simultaneous delivery of plasmid and CDDP, ie, PMSN-HNF4α-cis treatment, greatly induced Huh7 cells apoptosis and increased the proportion of cells with S-phase cell cycle blockage, and in vivo tumor growth inhibition was more substantial than that of PMSN-HNF4α and PMSN-cis treatment groups (Figure 9). This indicated that the PMSN-HNF4α -cis nano-strategy could reduce the proportion of CSCs, downregulate stemness-related genes, and cure hepatocellular carcinoma. The Notch signaling pathway, which regulates self-renewal and proliferation of stem and early progenitor cells, is highly expressed in various CSCs and serves as a vital pathway for maintaining tumor cell stemness.[218] Shen et al developed micellar NPs carrying both CDDP prodrug and Notch1 siRNA to treat liver cancer.[219] In vitro, 14.7% of hepatocellular carcinoma SMMC7721 cells underwent apoptosis after CDDP treatment, and the proportion of CD133-positive cells increased 3–4 fold. While the micellar NPs -treated group (both with a platinum concentration of 12.5μM in the CDDP group) caused an apoptosis rate of 36.1%, and the proportion of CD133-positive cells was almost identical to that of the blank control group. Other stemness-related genes (Sox2, Oct4, and Nanog), highly expressed in CSCs, were

Table 3 Detailed Description of CDDP/CDDP Prodrug-Loaded NDDSs to Target CSCs Different Biomarkers

Biomarkers	Target Cancer	NDDSs	Particle Size (nm)	Zeta Potential (MV)	Drug Entrapment Efficiency (DEE%)/Drug Loading Efficiency (DLE%)	Drug Release (%) (Time, Stimuli)	Reference
Integrin α6	Nasopharyngeal carcinoma	CDDP prodrug-loaded, integrin α6 targeted peptide-conjugated NPs	110 ± 1.3	0.21 ± 0.04	/	85 (25h, pH 7.4)	[221]
Integrin $\alpha_v\beta_5$	Head and neck squamous cell carcinoma	CDDP-loaded, cRGD peptide- installed micelles	30	/	/	51 (48h)	[222]
CD24	Ovarian carcinoma	CDDP-loaded, CD24 monoclonal antibody-modified liposomal NPs	158	/	/	/	[223]
CD133	Lung cancer	CDDP/demethoxycurcumin-loaded, CD133 antibody-dressed NPs	190 ± 17	−3 ±1.0	60	30 (48h, pH 5.5)	[224]
CD44	Head and neck squamous cell carcinoma	CDDP-hyaluronan conjugates NPs	/	/	/	/	[225]
	Prostate cancer		153.4	/	87.4	70 (40h, pH 7.4)	[226]
	Lung cancer		/	/	/	/	[227]
	Lung cancer		/	/	/	59.77 (48h)	[228]
	Breast cancer	CDDP/azithromycin-loaded, hyaluronan-based nanocarrier	100	/	/	80 (72, pH 5.5)	[229]

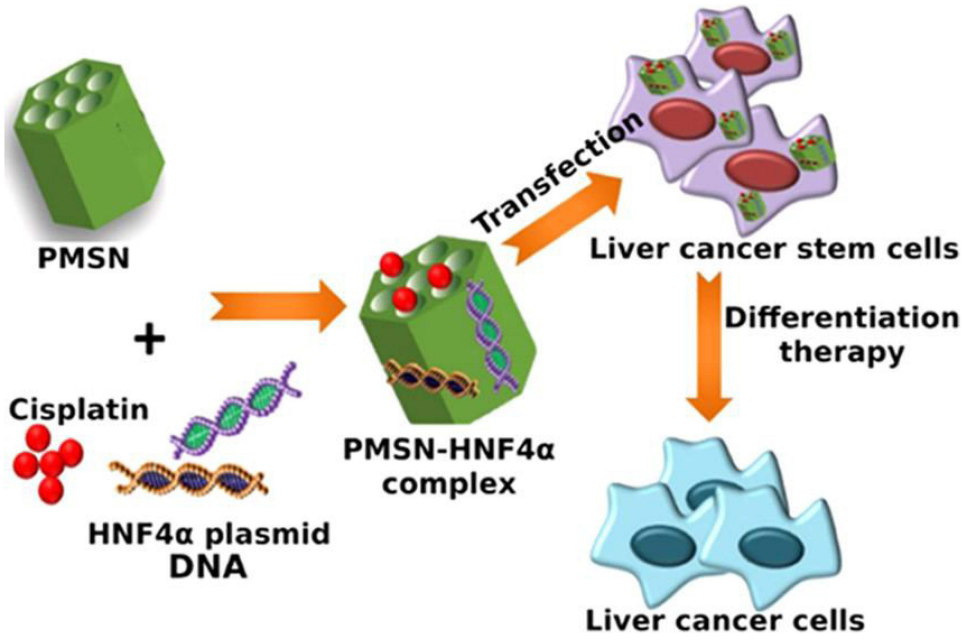


Figure 9 Schematic illustration of the PEI-modified mesoporous silica NPs (PMSNs) and their mechanism for the treatment of liver cancer by inhibiting CSCs and tumor stemness via HNF4α-encoding plasmids and cisplatin. Reproduced from Tsai PH, Wang ML, Chang JH et al. Dual delivery of HNF4α and cisplatin by mesoporous silica nanoparticles inhibits cancer pluripotency and tumorigenicity in hepatoma-derived CD133-expressing stem cells. *ACS Appl Mater Interfaces*. 2019;11:19,808–19,818. © 2019 American Chemical Society.[217]
Abbreviations: PEI, polyethylenimine; CSCs, cancer stem cells; HNF-4α, hepatocyte nuclear factor 4α.

also maintained at low expression levels. Similarly, Yang et al developed CDDP-loaded lipid-coated NPs delivering siRNA against Bmi1, a key regulator of hepatocellular carcinoma proliferation, which markedly inhibited growth in CDDP-resistant HepG2 cells while significantly reducing CSC markers CD133 and EpCAM at protein levels versus free CDDP-treated murine models.[220]

Nanotherapeutics targeting CSC markers and dysregulated signaling pathways enable sustained eradication of CSCs and resistant cells, preventing recurrence. However, critical limitations persist: (1) CSC plasticity allows dynamic interconversion with non-CSCs via shared signaling pathways, demanding clarification on pathway exclusivity and precise targeting strategies;[230,231] (2) CSC inhibition remains scientifically contentious, with most evidence derived from cellular/animal models that inadequately replicate human TME heterogeneity.[232] Rigorous multicenter clinical trials are thus imperative to validate therapeutic efficacy and safety.

Nanomedicines Regulating Autophagy

Autophagy, a process of cellular self-degradation, exerts paradoxical roles in oncology: cytostatic autophagy inhibits tumor growth by clearing oncogenic metabolites, degrading aberrant proteins, and suppressing inflammation, whereas cytoprotective autophagy mediates chemoresistance by eliminating chemotherapy-damaged organelles and biomolecules.[233] The above explains the "paradoxical" role of autophagy in the mechanism of tumor development and chemotherapeutic resistance. In summary, dysregulated autophagy constitutes a hallmark of malignant tumor progression, while autophagy-mediated chemoresistance emerges as a pivotal mechanism driving CDDP off-target resistance through cytoprotective organelle/biomolecule salvage.

Currently, one of the views indicates autophagy positively correlates with chemoresistance, where suppressing cytoprotective autophagy can effectively reverse CDDP resistance. Beclin1 is the first identified autophagic effector that initiates autophagy by interacting with PtdIns(3) kinase (Vps34).[234] Lin et al synthesized the siBec1@PPN, consisting of the tetravalent CDDP complex Pt(IV)-peptide-bis(pyrene) and Beclin1 siRNA.[235] In A549R cells, siBec1@PPN treatment activated apoptosis pathways and substantially reduced BECN1 and LC3-II (autophagic flux marker) expression. In vivo, siBec1@PPN achieved 82.98% tumor growth inhibition in A549R xenografts, with BECN1/

LC3-II downregulation confirming potent autophagy suppression. Li et al prepared CDDP/autophagy inhibitor chloroquine (CQ)-loaded poly lactic acid NPs (CDDP/CQ-PLA NPs).[236] Compared with CDDP-only PLA NPs, the CDDP/CQ-PLA NPs significantly suppressed autophagy while concurrently enhancing apoptosis induction, elevating ROS generation to promote lethal oxidative stress, and potently inhibiting oral squamous carcinoma proliferation. Notably, emerging evidence links excessive autophagy to tumor immune evasion, positioning autophagy modulation as a critical frontier in cancer immunotherapy.[237] Yang et al prepared a multifunctional nano-ultrasonic contrast agent co-loading CDDP prodrug, CQ, perfluorohexane (PFH), and PD-L1-targeting peptides to better target tumor cells expressing PD-L1 on the surface (Figure 10).[238] This NDDS not only effectively inhibited CDDP-induced protective autophagy, blocked tumor cell cycle at G0/G1, increased intracellular ROS production and thus promoted tumor cell apoptosis, but also enhanced immune response by inducing macrophages to M1-type polarization and activating cytokine release (eg IL-12, TNF-α) in vitro and in vivo. Overall, the nano-ultrasonic contrast agent notably outperformed free Pt/CQ in CDDP efficacy and immune activation, with ultrasonication amplifying therapeutic outcomes by accelerating drug uptake/release and bioavailability. Critically, PFH-enabled real-time imaging permitted in vivo localization and biodistribution tracking, demonstrating profound translational implications for clinical chemoimmunotherapy.

The context-dependent regulation of autophagy in tumor cell survival necessitates precision modulation to optimal therapeutic levels, a challenge unmet by prior studies. Predarska et al pioneered a paradigm-shifting strategy achieving graded autophagy regulation.[239] The team initially found that in CDDP-resistant MDA-MB-231 breast cancer cells (COX-overexpressing), COX inhibitors complexed with CDDP exhibited higher cytotoxicity than CDDP alone, mediated through non-COX-dependent pathways.[240] To mitigate free-drug toxicity and amplify efficacy, mesoporous silica NPs (SBA-15) were engineered to deliver three Pt(IV)-conjugated CDDP-COX inhibitors (naproxen/ibuprofen/flurbiprofen).[239] These SBA-15 NPs induced significantly elevated autophagic flux (24%, 18%, 12% vs 16% for CDDP) and enhanced ROS/NO production, while demonstrating superior cytotoxicity and anti-proliferative activity against four breast cancer cell lines—including triple-negative MDA-MB-468—with sub-micromolar IC_{50} values surpassing CDDP. Moderate endoplasmic reticulum (ER) stress is well-established to promote autophagy.[241] Pandey et al prepared the graphene oxide (GO) NPs equipped with CDDP and azithromycin, whose surface was modified by the dansyl group for ER targeting.[242] In HeLa cells, these GO NPs triggered pronounced ER events alongside marked upregulation of autophagy markers LC3B and Beclin, confirming autophagy induction. Notably, combinatorial treatment with autophagy inhibitor CQ exerted potent cytotoxic effects across diverse malignancies—including breast cancer cells MCF-7, lung cancer cells A549, and drug-resistant triple-negative breast cancer cells MDA-MB-231—suggesting pharmacological potentiation through autophagy modulation may broaden the therapeutic window for refractory tumors.

Prolonged exposure to CDDP or prodrug-loaded nanocomplexes often triggers excessive autophagy that may undermine therapeutic efficacy; paradoxically, studies confirm such hyperactivation can induce autophagic cell death (type II programmed death)—a distinct pathway from apoptosis that may reverse CDDP resistance when pharmacologically harnessed.[243] While cuprous oxide NPs,[244] reduced graphene oxide-silver nanocomposites,[245] and other nanomaterials combined with CDDP induce autophagy, current NDDS research predominantly reports autophagic flux alterations or apoptosis/necrosis outcomes, seldom elucidating autophagic death's role in resistance reversal. Notably, Wang et al designed on-demand autophagy cascade-amplifying NPs co-delivering autophagy inducer STF-62247 and oxaliplatin, which induced autophagic death and enhanced anti-tumor immunity.[246] Therefore, nanotechnology-enabled co-delivery of CDDP with autophagy inducers (eg, BH3 mimetics, metformin, rapamycin, natural compounds) may serve as a promising resistance-reversal strategy.[247] Although autophagic death, apoptosis and necrosis are different death pathways, the three involve interconnected signaling cascades. Hence, molecular mechanisms governing autophagy regulation require deeper elucidation to mitigate potential adverse effects from tumor autophagy activation.

Clinical Translation of CDDP Co-Delivery Nanoplatforms

Numerous CDDP co-delivery nanoplatforms have advanced to clinical trials, with liposomal delivery systems representing the subject of the most intensive investigation. Owing to their exceptional biocompatibility, high drug-loading capacity, and favorable pharmacokinetic profiles, liposomal carriers are recognized as highly promising nano-vehicles for CDDP delivery.[248] Consequently, CDDP-based liposomes, including L-NDDP, SPI-077, Lipoplatin, and LiPlaCis, have been advanced to clinical evaluation across diverse tumor types (Table 4). A meta-analysis of 523 patients demonstrated

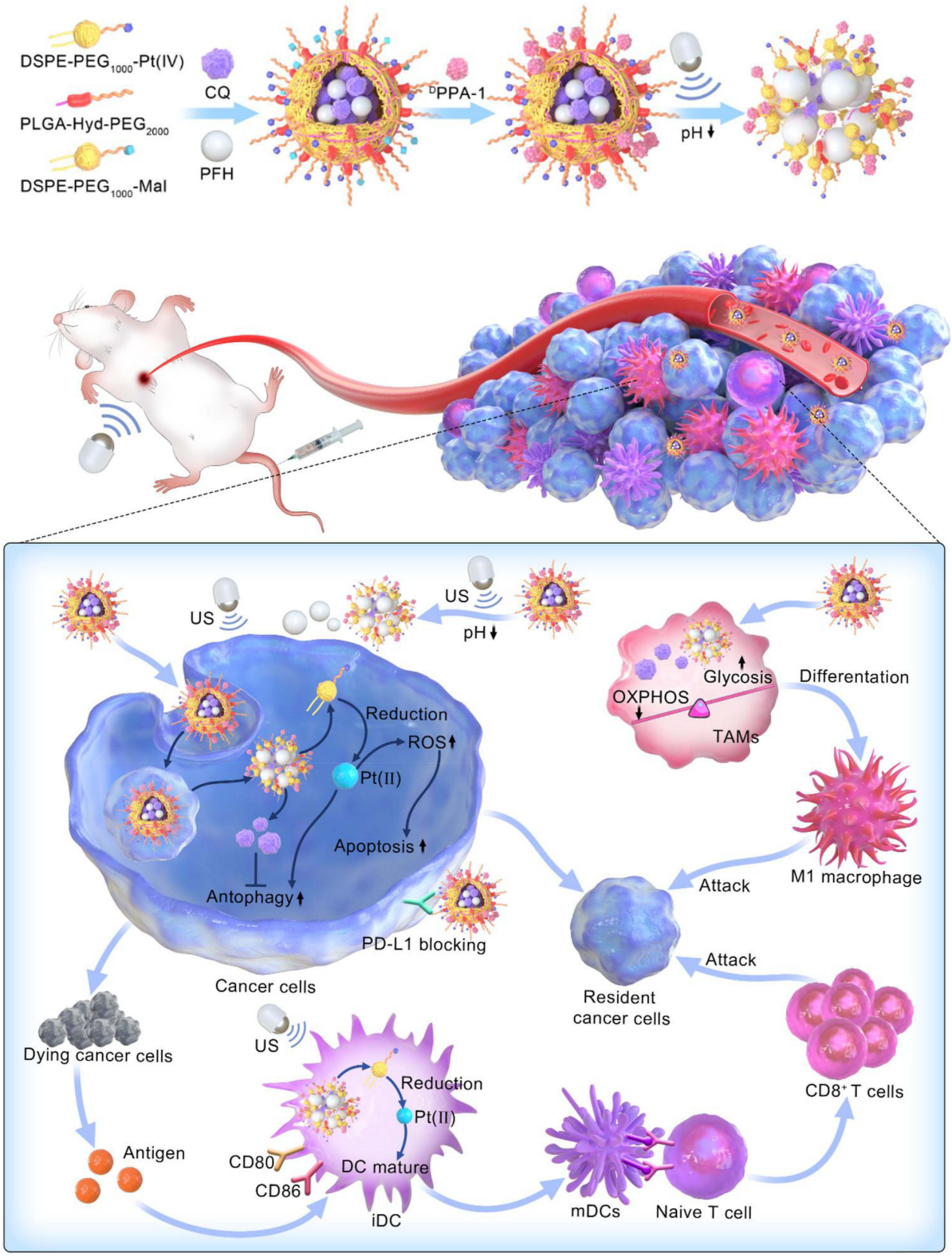


Figure 10 Schematic illustration of the tumor microenvironment-responsive nano-ultrasonic contrast agent Pt(IV)/CQ/PFH NPs-^{D}PPA-1 and their mechanism for the treatment of breast cancer by suppressing tumor cell autophagy and reprogramming immunocyte metabolism. Reproduced from Yang X, Zhao M, Wu Z et al. Nano-ultrasonic contrast agent for chemoimmunotherapy of breast cancer by immune metabolism reprogramming and tumor autophagy. *ACS Nano.* 2022;16:3417–3431. © 2022 American Chemical Society.[238]

Abbreviations: CQ, chloroquine; PFH, perfluorohexane; ^{D}PPA-1, anti-PD-L1 peptide.

https://doi.org/10.2147/IJN.S551752

Table 4 Summary of Different CDDP-Liposome Systems

Types	Characteristics	Limitations	Treated Tumors	Overall Evaluation
L-NDDP	• Favorable biocompatibility	• Susceptible to degradation • Suboptimal CDDP release kinetics • Off-target pulmonary accumulation	• Therapy-refractory advanced colorectal cancer	• Suboptimal therapeutic efficacy paired with significant systemic toxicity burden
SPI-077	• Prolonged circulation half-life • Enhanced tumor retention	• Suboptimal CDDP release kinetics	• Malignancies not amenable to other treatment • Ovarian cancer	• Favorable tolerability profile but suboptimal therapeutic efficacy
Lipoplatin	• Facilitated transmembrane transport via anionic lipid • Prolonged circulation half-life • Minimal systemic toxicity	• Pending additional evidence for clinical endpoints	• Metastatic non-small-cell lung cancer • Locally advanced gastric cancer • Advanced pancreatic cancer	• The first CDDP liposomal injection completing Phase III clinical evaluation, demonstrating substantial clinical translation potential
LiPlaCis	• Tumor site-specific drug release capability	• Significant dose-limiting nephrotoxicity • Notable infusion-related reactions	• Solid tumors without standard therapeutic options	• Suboptimal overall safety profile limiting broader clinical utility
SLIT	• Inhalable delivery platform • Respiratory tract/lung-focused accumulation	• Suboptimal pulmonary deposition reported • Adverse events: nausea/vomiting and reduced forced expiratory volume	• Lung carcinoma	• Theoretical potential for enhanced pulmonary CDDP accumulation, pending clinical validation
ILC	• Inhalable delivery platform • Lung-compatible phospholipid excipients	• Early developmental phase with limited preclinical/clinical evidence	• Recurrent osteosarcoma • Non-small-cell lung cancer	• Phase III trial initiation underway with high translational potential

that liposomal CDDP significantly improves progression-free survival and reduces treatment-related toxicities compared to conventional CDDP in non-small cell lung cancer and head/neck squamous cell carcinoma populations.[249] However, most formulations were discontinued due to dose-limiting toxicities, suboptimal drug release kinetics, and inadequate therapeutic efficacy. Currently, only Lipoplatin and ILC demonstrate sustained clinical translation potential. Lipoplatin leverages its PEG-rich composition to enhance tumor accumulation, while the anionic lipid component enables membrane fusion-mediated cellular uptake—bypassing CTR1-mediated transport and overcoming pre-target resistance mechanisms.[250] A clinical study reported 10- to 50-fold higher CDDP concentrations in tumor versus normal tissues post-Lipoplatin treatment, with colon cancer tissues exhibiting up to 200-fold accumulation.[251] Advanced to Phase III trials, Lipoplatin is now being evaluated in synergistic regimens combining chemotherapeutics (eg, 5-fluorouracil, gemcitabine) and radiotherapy.[252] Concurrently, ILC—an inhalable CDDP liposome formulation—has entered Phase III trials for metastatic lung tumors and non-small-cell lung cancer, aiming to localize drug deposition in the respiratory tract and lung tissues to maximize therapeutic efficacy.

Furthermore, the CDDP-encapsulated polymeric micelle NC-6004 demonstrated enhanced therapeutic potential in a Phase Ib/II trial for advanced solid tumors. When co-administered with gemcitabine, it achieved a maximum tolerated dose of 135 mg/m² without inducing significant neurotoxicity or nephrotoxicity.[253] The Phase III clinical trial (NCT02043288) evaluating NC-6004 in combination with gemcitabine for patients with locally advanced or metastatic pancreatic cancer in Asian countries has been completed, though results remain undisclosed. The nanoengineered CDDP patch PRV111 enables localized delivery of CDDP-loaded chitosan particles, demonstrating enhanced penetration into tumor tissues and lymphatic channels while minimizing systemic toxicity. In a Phase I/II trial (NCT03502148) for oral squamous cell carcinoma, PRV111 achieved 69% tumor volume reduction within 7 days and >87% efficacy, with no local recurrence observed during 6-month follow-up. This platform represents a novel paradigm for precision nanomedicine in localized oncology therapy.[254] Despite rapid clinical advancement of CDDP co-delivery nanoplatforms, few formulations have progressed to Phase III trials, necessitating accelerated translational development.

The Future Perspective

Tumor cell heterogeneity dictates variable responsiveness to platinum-based agents, necessitating precision medicine approaches for distinct malignancies. Tailored NDDSs offer a viable strategy to overcome CDDP resistance, yet three fundamental challenges persist:

1) Translational limitations of basic research. While most investigations remain predominantly in preclinical research, current strategies to enhance therapeutic efficacy increasingly employ synthetic derivatives or ligand-modified formulations. This trend toward structural complexity in NDDSs necessitates rigorous evaluation of in vivo pharmacokinetics and toxicological profiles. Crucially, optimizing tumor-targeted delivery efficiency and enhancing drug accumulation at tumor sites remain critical challenges requiring innovative solutions.[255]
2) Precision medicine implementation barriers. The clinical translation of individualized resistance profiling persists under significant temporal and financial constraints. To overcome these barriers, healthcare systems must accelerate the integration of multi-omics technologies (genomics/proteomics/metabolomics) with clinically validated platforms such as NGS-based diagnostics (eg, Guardant360 CDx) and AI-driven decision support systems.[256] This integration represents a critical imperative for optimizing resource allocation in oncology practice, particularly in resource-limited settings.
3) Mechanistic understanding gaps. Although NDDSs facilitate clinical applications for overcoming platinum resistance through targeted molecular interventions, the fundamental mechanisms underlying tumor resistance to platinum-based chemotherapeutics require comprehensive elucidation. Systematic investigation into CDDP resistance pathways will be essential for identifying novel predictive biomarkers and developing next-generation therapeutic targets. This research imperative bridges basic science and clinical translation in platinum-based cancer therapeutics.

This review primarily synthesizes perspectives from existing literature, potentially omitting cutting-edge research and nuanced details of emerging resistance mechanisms. While the four-category classification of resistance mechanisms establishes a coherent analytical framework, insufficient depth in examining certain sub-mechanisms undermines the precision of proposed nano-delivery strategies. Moreover, our prioritization of pathogenesis over nanomaterial taxonomy advances translational intervention frameworks—strengthening mechanistic insights at the cost of NDDS efficiency metrics. This deliberate focus catalyzes mechanism-driven therapeutics but necessitates companion studies quantifying nano-delivery performance.

Abbreviations

ABC, ATP-binding cassette; CAT, Catalase; CDDP, Cisplatin; CPNs, Cocktail polyprodrug nanoparticles; CSCs, Cancer stem cells; CTR1, Copper transporter 1; EGCG, (-)-epigallocatechin-3-O-gallate; EMT, Epithelial-mesenchymal transition; EPR, Enhanced permeability and retention effect; ER, Endoplasmic reticulum; FDA, Food and Drug Administration; GP, Gelatin nanoparticles; GSH, Glutathione; HA, Hyaluronic acid; HIF-1α, Hypoxia-inducible factor-1α; ICP-MS, Coupled plasma mass spectrometry; LHRH, Luteinizing hormone-releasing hormone; LPNs, Lipid polymerized nanoparticles; MNCs, Micellar nanocomplexes; MNPs, Magnetic nanoparticles; MONs, Mesoporous organosilica nanoparticles; MRP-1/2, Multidrug resistance-associated protein 1/2; MSN, Mesoporous silica nanoparticles; mtDNA, Mitochondrial DNA; MWCNTs, Multi-walled carbon nanotubes; NDDSs, Nanotechnology-based drug delivery systems; NPs, Nanoparticles; PCL, Polycaprolactone; PEG, Poly(ethylene glycol); PEG-b-PLGA, Poly(ethylene glycol)-b-poly(d, l-lactide-co-glycolide); PEG-GNRs, PEGylated gold nanorods; P-gp, P-glycoprotein; PLA, Poly lactic acid; PMSNs, PEI-modified mesoporous silica nanoparticles; ScFvEGFR, Single-chain antibody against EGFR; TME, Tumor microenvironment.

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Author Contributions

Shuang-Yin Lei: Writing – review & editing, Writing – original draft, Software, Methodology, Conceptualization. Hanjiao Qin: Writing – review & editing, Supervision, Resources, Investigation, Funding acquisition. Shui Liu: Writing – review & editing, Supervision. Jiyao Sheng: Writing – review & editing, Writing – original draft, Supervision, Investigation, Funding acquisition, Conceptualization.

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Disclosure

The authors report no conflicts of interest in this work.

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