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Nanoparticle formulations of cisplatin for cancer therapy

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Abstract

The genotoxic agent cisplatin, used alone or in combination with radiation and/or other chemotherapeutic agents, is an important first-line chemotherapy for a broad range of cancers. The clinical utility of cisplatin is limited both by intrinsic and acquired resistance and dose-limiting normal tissue toxicity. That cisplatin shows little selectivity for tumor versus normal tissue may be a critical factor limiting its value. To overcome the low therapeutic ratio of the free drug, macromolecular, liposomal and nanoparticle drug delivery systems have been explored toward leveraging the enhanced permeability and retention (EPR) effect and promoting delivery of cisplatin to tumors. Here, we survey recent advances in nanoparticle formulations of cisplatin, focusing on agents that show promise in preclinical or clinical settings.

INTRODUCTION

Cisplatin (cis-diamminedichloroplatinum(II), CDDP) is a platinum coordination complex that displays significant genotoxicity, mediated by covalent modification of DNA to form intrastrand crosslinks and other adducts. Cisplatin was proposed as a candidate chemotherapy agent by Rosenberg et al. in 1969,[1] and gained FDA approval for treating testicular and ovarian cancers in 1978. Today, cisplatin remains one of the most widely used and effective anticancer agents for the treatment of a variety of solid tumors, including breast, liver, lung, ovarian, testicular, bladder, head and neck, small-cell and non-small-cell lung cancers, owing to its wide spectrum of anti-tumor activity.[2,3] However, non-selective distribution of the drug between normal and tumor tissue likely increases the impact of dose-limiting side effects including acute nephrotoxicity, myelosuppression, and chronic neurotoxicity.[4,5] The therapeutic ratio is further compressed by tumors that display intrinsic cisplatin resistance or acquire resistance over the course of treatment.[6,7] Toward overcoming these limitations, a wide range of nanoparticle (NP) drug carriers have been explored as drug delivery systems (DDSs) for cisplatin in order to promote preferential accumulation in cancer cells and thereby reduce adverse side effects.

Nanoparticle DDSs are designed to take advantage of the enhanced permeability and retention (EPR) effect, which results from the leaky neovasculature and the lack of

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functional lymphatic drainage in tumor tissue. For particles to take advantage of the EPR effect, they must first evade the mononuclear phagocytic system (MPS) and avoid renal clearance. Prolonged blood circulation provides the particles with the opportunity to exit the leaky neovasculature and accumulate in tumors.[8] A variety of carriers, including organic (polymeric NPs,[9,10] polymeric micelles,[11,12] polymeric conjugates,[13,14] dendrimers,[15] liposomes,[16,17] polymer-coated liposomes[18] and nanocapsules[19,20]), inorganic (carbon nanotubes,[21] iron oxide NPs,[22] gold NPs,[22] and mesoporous silica NPs[24]) and hybrid NPs (nanoscale coordination polymers[25] and polysilsesquioxane NPs[26]), have been adapted to facilitate delivery of platinum-based drugs (Figure 1). Some of these NP DDSs have demonstrated promising preclinical results, and a few have entered clinical trials (Table 1). This review summarizes recent advances, focusing on NP formulations of cisplatin that show the greatest promise for translation to the clinic.

ORGANIC NANOPARTICLES

Polymeric NPs

Polymeric NPs have frequently been used as drug delivery vehicles due to their favorable properties including simple encapsulation, high capacity, controlled release, and low toxicity. Encapsulation into polymeric NPs increases drug efficacy, specificity, and tolerability, enhancing the therapeutic index.[27] Recent advances in polymeric NP drug delivery systems have yielded promising results in preclinical cancer models.

Poly (lactic-co-glycolic acid) (PLGA) is widely used as a biodegradable polymer for drug delivery. Cisplatin-loaded PLGA NPs have been developed and demonstrated to reduce side effects without compromising drug efficacy in tumor-bearing mice.[28,29] Long-circulating NPs formed from poly(lactic-co-glycolic acid)-β-poly(ethylene glycol) (PLGA-PEG) offer enhanced tumor accumulation and improved anticancer activity.[30,31] However, PLGA encapsulation of cisplatin results in low drug loading and undesirable burst release, reflecting cisplatin's combination of low water solubility and low lipophilicity.[32] Dhar et al. exploited the hydrophobicity of an inactive cisplatin prodrug to improve loading in PLGA-PEG NPs, achieving a Pt content of 10 wt.%.[9,10] The Pt(IV) prodrug could be reduced to active cisplatin after release from the NPs inside the cells, showing sufficient cancer cell killing (Figure 2). Dhar and coworkers then constructed a hydrophobic mitochondria-targeted cisplatin prodrug, Platin-M, which they efficiently loaded into mitochondria-targeted PLGA-PEG NPs to overcome drug resistance, as mitochondrial DNAs lack nucleotide excision repair machinery, one of cisplatin resistance mechanisms. The targeted Platin-M NPs (T-Platin-M-NPs) allowed for delivery of Platin-M inside the mitochondria of neuroblastoma cells, resulting in ~17 times higher activity than cisplatin.[33] T-Platin-M-NPs showed high levels of Pt accumulation in the brain with no observed neurotoxicity in beagles.[34] Recently, Cheng et al. conjugated a novel Pt(IV) prodrug of cisplatin, asplatin, to cholesterol to increase the hydrophobicity and facilitate the incorporation into PLGA-PEG NPs. The cholesterol–asplatin-incorporated nanoparticles (SCANs) exhibited high gastrointestinal stability, sustained drug release, and enhanced cell uptake. SCANs showed 4.32-fold higher oral bioavailability than that of free Pt(IV) prodrug and efficaciously inhibited tumor growth with negligible toxicity after oral administration.[35] Miller et al.

demonstrated that Pt(IV) prodrug-loaded PLGA-PEG NPs accumulated at high levels within tumor-associated macrophages (TAMs) after intravenous (i.v.) injection, and that TAMs served as a local drug depot, gradually releasing the Pt payload into neighboring tumor cells. Depletion of macrophages significantly decreased intratumoral Pt accumulation and correspondingly increased tumor growth.[36] Furthermore, co-delivery of cisplatin prodrug with siRNA[37], other anticancer drugs[38] or anti-inflammatory drugs[39] using PLGA-PEG as a delivery carrier revealed a synergistic effect and was more effective than platinum monotherapy. Recently, protein NPs based on albumin, gelatin, and silk protein have drawn interest as DDSs because they are biocompatible, biodegradable, and non-antigenic. Casein NPs loaded with cisplatin and cross-linked by transglutaminase were capable of penetrating cell membranes and targeting tumor tissue, inhibiting tumor growth with 1.5-fold higher efficacy than free cisplatin.[40] In cisplatin-loaded gelatin-poly(acrylic acid) NPs, the formation of a polymer-metal complex by cisplatin binding carboxylic groups allowed a drug loading of nearly 40%. Intraperitoneal (i.p.) administration of the gelatin-poly(acrylic acid) NPs provided high activity in mice against tumors formed from the transplantable H22 murine hepatic cancer cell line.[41]

Natural polysaccharides such as chitosan, a chemically deacetylated form of chitin (N-acetylglucosamine polymer), and the extracellular matrix polysaccharide hyaluronic acid (HA) have been modified to yield amphiphilic polymers, which self-assemble into nanoparticles and encapsulate cisplatin simultaneously. After modification with hydrophobic cholanic acid, glycol chitosan self-assembled into 420 nm diameter nanoparticles with cisplatin encapsulated in the hydrophobic core, with a drug loading of approximately 9 wt. %. These NPs accumulated in tumor tissues after i.v. administration, displaying higher antitumor efficacy and lower toxicity compared to free cisplatin.[42] Alternatively, NPs formed by electrostatic interactions between chitosan or N-trimethyl chitosan (substitution degree of 85%) with anionic cisplatin-alginate complex could also be used to deliver cisplatin.[43] Similarly, ionic interactions between HA and cisplatin were used to form NPs that were well tolerated by mice.[44] The HA-cisplatin NPs showed high lymphatic deposition and efficacy against a lymphatically metastatic breast tumor model.[45,46] HA NPs can also be used to co-deliver siRNA and cisplatin to CD44 hyaluronan receptor-overexpressing, cisplatin-resistant tumors.[47,48]

A number of pH-responsive NPs have been used to specifically deliver cisplatin to tumors.[49–51] A common design goal of these NPs is to remain stable during circulation in blood, where the pH is approximately 7.4, but allow rapid intracellular drug release once the NPs enter the more acidic tumor environment (pH 6.5–7.2) and/or are endocytosed by tumor cells and delivered to endosomes (pH 4.5–6.5). For example, pH-responsive poly(L-glutamic acid-co-L-lysine) [P(Glu-co-Lys)] NPs remain negatively charged in circulation, but protonation of ε amino groups on the L-lysine in acidic tumor environments releases cisplatin to inhibit cell proliferation.[52]

Polymeric micelles

Polymeric micelles are formed by self-assembly of amphiphilic block or graft copolymers, typically resulting in a 10 to 100 nm diameter core-shell structure. The hydrophobic core

provides a loading space for therapeutic agents, while the hydrophilic shell stabilizes the micelles in aqueous solution. To prolong circulation time, the surface of micelles can be modified to decrease interactions with serum proteins, particle opsonization, and clearance by the MPS.

Kataoka and coworkers designed a series of PEG-b-poly(amino acid)-based micelles loaded with cisplatin for passive drug targeting into tumors.[53,54] The carboxylic groups in the poly(amino acid) can complex with cisplatin, oxaliplatin, or other organometallic compounds via coordination.[55] The free drug is regenerated in the presence of chloride ions (Figure 3). Compared to the free drug, the micelles delivered greater amounts of cisplatin to solid tumors but also were avidly taken up in the liver and spleen. Overall, they provided comparable antitumor activity to free cisplatin and reduced nephrotoxicity.[56] Further work to improve the stability and drug release profile of the cisplatin-loaded PEG-P(Glu) micelles led to Nanoplatin™ (NC-6004). Preclinical data suggested prolonged blood circulation, increased accumulation in solid tumors, and effective inhibition of tumor growth.[11,12] NC-6004 is currently being evaluated for pancreatic cancer in a phase III trial in Asia and head and neck cancer in a phase I trial in Japan. Phase II trials for non-small cell lung cancer, bladder cancer, and bile duct cancer are ongoing in the US.[57]

Cisplatin is commonly used as a component of combination therapy along with other genotoxic agents. This has prompted efforts to load cisplatin along with other drugs in a single nanocarrier. Xiao et al. sought to co-deliver hydrophobic paclitaxel and hydrophilic cisplatin using a biodegradable amphiphilic copolymer by conjugating paclitaxel and Pt(IV) prodrug to the copolymer and then co-assembling them together. The composite micelles efficiently released cisplatin upon cellular reduction and paclitaxel via acid hydrolysis once the micelles entered cancer cells, leading to synergistic effects and enhanced antitumor efficacy with reduced systematic toxicity in vivo.[58] Likewise, a novel poly(ethylene glycol)-b-poly(L-glutamic acid)-b-poly(L-phenylalanine) (PEG-P(Glu)-P(Phe)) triblock copolymer was prepared and explored as a micelle carrier for the co-delivery of paclitaxel and cisplatin. Paclitaxel and cisplatin were loaded inside the hydrophobic P(Phe) inner core and chelated to the anionic P(Glu) shell, respectively, while PEG provided an outer corona for prolonged circulation. The paclitaxel and cisplatin-loaded micelles were highly effective against A549 human lung cancer cells in vitro and in xenograft tumors.[59]

The difficulty of maintaining the delicate balance of extracellular stability and intracellular drug release remains a challenge for the in vivo application of polymeric micelles. Conventional un-crosslinked micelles may disintegrate upon dilution in plasma, leading to premature release of drug and low delivery efficiency due to loss of the EPR effect.[60] Several studies of reversible crosslinking of either the core or the shell can increase the stability of drug-loaded micelles in circulation without compromising payload release after cellular uptake. The Jing group used a Pt(IV) complex containing two axial succinic moieties as a crosslinker to prepare crosslinked micelles, which demonstrated improved stability but could be dissociated by acid hydrolysis or mild reducing agents.[61,62] Huynh et al. prepared cisplatin-loaded micelles crosslinked with acid-degradable ketal diamino crosslinkers. These micelles displayed high cellular uptake like stably crosslinked micelles but offered faster intracellular drug release.[63] Cisplatin carriers based on core-surface-

crosslinked micelles based on poly(ε-caprolactone)-PEG (PCL-PEG) or PCL-poly[2-(N,N-dimethylamino)ethyl methacrylate] (PCL-PDMA) have also been evaluated, displaying superior cell uptake and cytotoxicity compared to free cisplatin.[64]

Polymeric conjugates

The reversible tethering of low molecular weight drugs to water-soluble polymers has long been explored to increase the selectivity of drug action. Cisplatin lends itself to complex formation with polycarboxylic polymers because one or more of the chlorides can be displaced, allowing reversible coordination with the polymer. Among the many macromolecular carriers available, N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer is of particular interest because of its low immunogenicity and low toxicity. In an initial study by Gianasi and colleagues, cisplatin was covalently linked to the HPMA copolymer via a tetrapeptide glycyl-phenylalanyl-leucyl-glycine (GFLG) linker coupled to an ethylenediamine chelating group.[65] GFLG is subject to proteolytic cleavage by the lysosomal cysteine proteinase cathepsin B, providing a means for intracellular delivery. In further development, the ethylenediamine chelating group was replaced by an amidomalonate group,[66] and cisplatin by carboplatin (CBDCA) to yield the investigational polymer platinate AP5280, which displayed an improved therapeutic index in preclinical models, though reduced potency compared to free carboplatin (Figure 4).[13] AP5280 was also well-tolerated in a Phase I clinical trial.[67]

Poly(γ, L-glutamic acid) (γ-PGA) is a water soluble, biodegradable, and nontoxic biopolymer, in which a carboxyl group in each repeating unit provides functionality for drug attachment. Ye et al. successfully synthesized a γ-PGA-cisplatin conjugate, which released cisplatin in a sustained manner. Although less potent than free cisplatin in vitro, it displayed encouraging antitumor activity with low toxicity in vivo.[68,69] However, further development was stymied by its low drug-loading capacity and slow drug release. Toward overcoming these drawbacks, Xiong et al. synthesized γ-glutamyl citrate (γ-PGA-CA) as an alternative cisplatin carrier. The additional carboxyl groups presented by the citrate-modified γ-PGA along with its less compact structure increased cisplatin binding capacity. γ-PGA-CA-cisplatin displayed favorable properties in in vitro and in vivo studies, displaying higher antitumor activity compared to γ-PGA-cisplatin and lower toxicity compared to unconjugated cisplatin.[14]

Dendrimers

Dendrimers are branched synthetic polymers with a number of characteristics that make them useful in biological systems, especially in the field of drug delivery. Dendrimers can be functionalized so that drugs can be physically entrapped, encapsulated, or conjugated by covalent bonds, hydrogen bonds, or ionic interactions.[70]

Poly(amidoamine) (PAMAM) dendrimers consist of polyamide branches stemming from a central amine or diaminoalkane core. Full generation PAMAM dendrimers have terminal primary amine groups that display multiple cationic charges in water, which makes them ideal delivery vehicles for anionic drugs. Half generation dendrimers have carboxylic acid/carboxylate terminal groups that display multiple anionic charges, which are ideal for

cationic drugs or for reversible coordination to platinum complexes.[15] In some cases when dendrimers have been used to deliver platinum drugs, the agents were tethered through coordination to amine groups. More commonly, platinum agents have been attached either by electrostatic attraction or reversible but direct coordination of the platinum atom to the terminal carboxylate groups. Dendrimers have been found to enhance the targeting and delivery of cisplatin to tumor cells and slowly release cisplatin.[71,72] The dendrimer-cisplatin complexes displayed selective accumulation in solid tumor tissues and less toxicity than free cisplatin, supporting further investigation as antitumor agents.[73]

Liposomes

Because of their simple formulation and high solubility, liposomes offer an attractive means of encapsulating and delivering cisplatin. Despite a wide range of liposomal preparations of cisplatin studied to date,[16,17,74] there remain no FDA-approved formulations.

Several PEGylated liposomal platinum agents have progressed to clinical trials, including SPI-077, Lipoplatin, LiPlaCis, and L-NDDP. SPI-077 was the first liposomal cisplatin to enter clinical trials. Preclinical studies showed that SPI-077 exhibited improved stability, prolonged circulation time, increased antitumor effect, and reduced side effects compared with the free drug.[75,76] Multiple clinical trials confirmed the low toxicity of SPI-077, but most failed to demonstrate efficacy.[77,78] One possible explanation for the discrepancy between the high tumor exposure and low antitumor effect could be incomplete release of cisplatin from liposomes localized within the tumor.[79] Another limitation is the low drug loading, reflecting the poor water solubility and low lipophilicity of cisplatin.[80] In Lipoplatin, electrostatic interactions promote loading of positively charged platinum into negatively charged 1,2-dipalmitoyl-sn-glycero-3-phosphoglycerol sodium salt (DPPG)-containing liposomes to achieve a drug loading of 9 wt.%.[81] Lipoplatin has been evaluated in a number of Phase II and Phase III clinical trials in combination with other chemotherapeutics such as gemcitabine, 5-fluorouracil, and vinorelbine.[82] Lipoplatin enhanced cisplatin retention in tumor tissue and substantially reduced renal toxicity, peripheral neuropathy, ototoxicity, and myelotoxicity.[83] Nonetheless, no improvement in its therapeutic efficacy compared to cisplatin was observed in multiple cancers.[84,85] LiPlaCis is a recent liposomal formulation with a phospholipase-based drug release mechanism. Unfortunately, LiPlaCis led to significant renal toxicities and infusion reactions in a recent phase I clinical trial, leading to abrupt cessation of clinical investigation.[86] In L-NDDP, a highly water soluble precursor of cisplatin, cis-diamminedinitratoplatinum, is encapsulated into liposomes in the absence of chloride ions. Treating the liposomes with chloride converts L-NDDP to cisplatin, resulting in a significantly improved loading efficiency of cisplatin.[87] In a Phase I trial, the maximum tolerated dose (MTD) of L-NDDP was 312.5 mg/m^2 with myelosuppression as the dose-limiting toxicity.[88] While the ultimate value of L-NDDP remains to be determined, a Phase II study of L-NDDP in patients with malignant pleural mesothelioma or advanced colorectal cancer demonstrated significant but manageable toxicity at the effective dose.[89,90]

Drug release from liposomes appears to be a critical parameter. pH-sensitivity is most commonly used for the triggered release of drugs from liposomes in cells.[91] Liposomes can

be taken up by cells via endocytosis and delivered to endosomes where the acid pH (5.5–6.5) promotes the fusion of pH-sensitive liposomes with the endosomal membrane, delivering the encapsulated contents to the cytoplasm. For example, cholesteryl hemisuccinate (CHEMS) is negatively charged at a neutral pH, stabilizing the bilayer envelope of liposomes by electrostatic repulsion. Protonation of CHEMS can thus destabilize liposomes to release aqueous content.[92]

Nanocapsules

While the poor solubility of cisplatin in either aqueous or organic solutions has remained a major obstacle for most formulation strategies, the Huang group synthesized cisplatin-loaded nanocapsules with a controllable size (12–75 nm in diameter) and high drug loading capacity by taking advantage of the poor solubility.[93,94] Two reverse microemulsions containing KCl and a highly soluble precursor of cisplatin, cis-diamine-di(aqua)platinum (II), were mixed. Cisplatin NPs were then precipitated in the presence of 1, 2-dioleoylsn-glycero-3-phosphate (DOPA), as a result of ligand exchange and decreased water solubility. The drug loading of the pure cisplatin NPs is as high as 81 wt.%. After purification, additional lipids were added to stabilize the NPs for dispersion in an aqueous solution (Figure 5).[19] Encapsulation in nanocapsules dramatically improved cell uptake and in vitro cytotoxicity. In addition, the cisplatin nanocapsules achieved potent antitumor efficacy both in vitro and in vivo.[20]

INORGANIC NANOPARTICLES

Ferromagnetic NPs

Based on their simple chemistry and ferromagnetic properties, iron oxide particles and other superparamagnetic NPs (MNPs) have a long history of use as model agents for therapy and/or imaging. MNPs also possess unique advantages for cisplatin delivery. One feature is the potential for active targeting via magnetic fields, potentially allowing circulating MNPs to be trapped and concentrated as they perfuse tumors and thereby promoting local delivery of tethered drugs. In turn, high frequency magnetic fields enable induction heating with MNPs. Not only can this be leveraged to promote drug release, but the heating of local tissue may further augment therapeutic effects. Thus, MNPS can take advantage of the well-known benefits of hyperthermia on chemotherapy. The synergy has been ascribed to effects of hyperthermia on the microvasculature, stroma and/or tumor cells, leading to enhanced accumulation, uptake, and effects of multiple cytotoxic agents, including cisplatin.[95]

The magnetic properties of MNPs constrain their materials, size, and shape, all of which negatively influence their potential drug loading capacity. The simple strategy of direct absorption of cisplatin to the surface of iron oxide NPs results in early drug release during circulation.[95,96] Overcoating MNPs with a polymer shell decreased leaching and enhanced delivery.[22] Cisplatin binding to MNPs was increased by modifying the surface with carboxylic functionalities that chelate the platinum in place of the chloro ligands in cisplatin. Here, drug release was dependent on chloride concentration, pH, and temperature, making it ideal for applications involving chemotherapy and hyperthermia. These conjugates displayed increased toxicity compared to free cisplatin.[97,98]

Gold NPs

Much like iron oxide NPs, colloidal gold and other gold NPs (AuNPs) such as nanorods have multiple potential applications as drug carriers. The size and shape of AuNPs can be controlled and their surfaces readily modified for passivation with PEG or other polymers and/or to tether drugs. Given their special properties and simple chemistry, AuNPs also enable photo-thermal drug release, glutathione-mediated release, radiosensitization, and other strategies. As with MNPs, direct adsorption of cisplatin to colloidal gold led to early release.[99,100] Chemical conjugation of cisplatin to AuNPs achieved a high loading of the drug with improved stability.[101] Similarly, conjugation with cisplatin prodrugs or other platinum compounds can provide enhanced delivery.[23,102] For example, the cellular uptake of platinum drugs was enhanced by conjugating to PEGylated gold nanorods (PEG-AuNRs). On entering cells, the Pt(IV) prodrug can be reduced by cellular reductants (e.g., glutathione) to the active divalent platinum, exhibiting superior cytotoxicity compared to free cisplatin against different types of cancer cells.[103] Moreover, the conjugation of cisplatin prodrug with PEG-AuNRs facilitated drug uptake in cisplatin-resistant cells through endocytosis, and the Pt(IV) prodrug was made less susceptible to deactivation by the detoxification protein. Consequently, the Pt-PEG-AuNR conjugates could overcome cisplatin-resistance, showing high cytotoxicity to cisplatin-resistant tumor cells.[102] In addition to increasing cellular uptake and enhancing cytotoxicity, the linkage of cisplatin to AuNPs has important effects on pharmacokinetics and biodistribution, thereby reducing cisplatin-induced toxicity without affecting the therapeutic benefits in mice models.[104]

Mesoporous silica NPs

Mesoporous silica NPs (MSNs) have several important structural and functional features that make them excellent drug delivery carriers. The high surface area and large pore volume endow MSNs with exceptional capacity for drug storage. The tunable and sustained release of drug molecules from the ordered mesoporous structures is beneficial for reducing overall dosage and enhancing local drug concentration. Meanwhile, the size and morphology of the MSNs can be easily tuned to maximize cellular uptake.[105]

MSNs have been exploited as local and controlled delivery vehicles for cisplatin.[24] However, for pure silica MSNs, the low affinity between the pore wall and cisplatin molecules limits loading and promotes burst release. Surface functionalization within the pore channels can create favorable surface-drug interactions.[106] Grafting carboxylic groups onto the pore channels to coordinate with platinum increased drug loading efficiency while facilitating cytosolic release.[107] The cisplatin-loaded MSNs exhibited a higher antitumor activity than free drug.[108] Additionally, the functionalization with carboxylic groups on the surface of MSNs can also reduce the aggregation and increase the stability of the MSNs in aqueous solution, as a result of the electrostatic repulsion. This improved dispersibility can facilitate distribution and cellular uptake of MSNs.

HYBRID NANOPARTICLES

Carbon nanotubes

Carbon nanotubes (CNTs) are cylindrical graphene sheets with unique chemical and physical properties that can be exploited to enhance drug delivery. The high aspect ratio of CNTs may enhance cell penetration and nuclear accumulation.

Drug molecules can be adsorbed to the surface or tethered by covalent chemistries. Bhirde et al. demonstrated that cisplatin conjugated to PEGylated single-walled CNTs (PEG-SWCNTs) was effective against head and neck tumor xenografts in mice.[109] Similarly, a Pt(IV) cisplatin prodrug was conjugated by a peptide linkage to terminal amino groups displayed on phospholipid-PEG-modified single-walled CNTs (PL-PEG-SWCNT).[21] These complexes were taken up by tumor via endocytosis, leading to intracellular drug release.

Alternatively, drugs can be encapsulated inside CNTs and hence sequestered during transport to target sites.[110] This offers high drug loading, but the open ends of CNTs leave encapsulated drugs exposed to plasma, promoting premature release during circulation. Toward stabilizing CNTs as drug carriers, the open ends have been capped by functionalized gold NPs[111] and pluronic-F108 surfactant[112].

As an alternative geometry to cylindrical CNTs, cone-shaped hole-opened single-wall nanohorns (SWNHox) have been examined as carriers for cisplatin. Cisplatin-loaded SWNHox was taken up by cancer cells in vitro and accumulated in tumors in vivo, achieving a high local concentration leading to higher efficacy in vitro and in vivo.[113]

Nanoscale coordination polymers

Coordination polymers (CPs) and metal-organic frameworks (MOFs) are an emerging class of hybrid materials constructed by linking organic bridging ligands with metal-connecting points. CPs/MOFs possess a number of interesting properties including porosity, high surface area, compositional tunability, and versatile functionalities. Nanoscale CPs (NCPs) or nanoscale MOFs (NMOFs) not only retain the beneficial properties of their bulk counterparts but also possess additional functions that are unique to nanomaterials.[114]

The Lin group has developed a series of NCP or NMOF platforms to deliver cisplatin or cisplatin prodrugs. For example, an NCP was assembled from the cisplatin prodrug disuccinatocisplatin (DSCP) and Tb(III) ions and coated with a thin layer of silica and a targeting peptide.[25] Tb-DSCP decomposed in physiological media, slowly releasing the DSCP by diffusing out of the silica shell, and showed cytotoxicity against human colorectal and breast cancer cell lines. NMOFs built from DSCP and Zr(IV) or La(III) and capped with lipid, further modified with PEG, and targeted with anisamide exhibited enhanced cellular uptake and cytotoxicity in human lung cancer cells compared to non-targeted cisplatin NMOFs.[115] When an NMOF was used to co-deliver cisplatin along with small interfering RNA (siRNA), it displayed increased effects on drug resistant ovarian cancer cells (Figure 6a).[116] In an alternative method, cisplatin prodrug was encapsulated by loading into the channels of NMOFs and siRNA was attached to their surface via coordination bonds. Co-

delivery of the cisplatin and siRNA led to an order of magnitude enhancement in chemotherapeutic efficacy *in vitro*.

Lin et al. also developed a lipid-coated NCP-based nanomedicine platform for platinum drug delivery. The solid core is constructed from platinum drugs and zinc bisphosphonate, and the shell is an asymmetric lipid layer containing high amount of PEG (Figure 6b). The highly modular nature of NCP synthesis allows the co-delivery of multiple therapies within one NCP vehicle. The original NCP platform carries high amount of cisplatin and showed minimal uptake by the MPS and prolonged blood circulation, with a half-life of >16 hours after i.v. injection in mice. NCP carrying cisplatin alone exhibited superior potency and efficacy at very low drug dose compared with free cisplatin in multiple subcutaneous tumor mouse models including colorectal and lung cancer.[117] The Lin group also developed NCP-based nanoparticles carrying high payloads of cisplatin and the photosensitizer pyrolipid for combined chemotherapy and PDT.[118] This NCP releases cisplatin and pyrolipid in a triggered manner at the site of action and synergistically kill cancer cells. In a subcutaneous xenograft mouse model of resistant head and neck cancer, NCP effectively led to tumor regression (83% reduction in tumor volume) at low drug doses. NCP technology can also be applied to the co-delivery of cisplatin and siRNAs. NCPs loaded with cisplatin and pooled siRNAs targeting multidrug resistance genes decreased cisplatin IC_{50} values in vitro by two-orders of magnitude compared to free cisplatin and induced ~60% reduction in tumor volume after local injection in a mouse model of cisplatin-resistant ovarian cancer.[119]

Polysilsesquioxane (PSQ) NPs

PSQ nanoparticles are a class of hybrid nanomaterials formed by condensation of silanol-based monomers. While PSQs inherit the biocompatibility of silica-based materials, they allow much higher drug loadings than conventional silica-based materials that only have grafted drugs on their surfaces.[26,120] Lin, Wang, and coworkers reported a PSQ nanoparticle loaded with a cisplatin prodrug at 42 wt.% and PEGylated for prolonged circulation demonstrated enhanced efficacy in combination with radiotherapy in a subcutaneous xenograft mouse model of human lung cancer.[121]

CONCLUSIONS

Nanoparticle formulations designed to leverage the EPR effect to improve drug delivery have the potential to enhance the selective accumulation of cisplatin in tumor cells without increasing off-target effects and toxicities. Several formulations, including the long-circulating polymeric micelle NC-6004, the polymeric conjugate AP5280, and three long-circulating liposomes, L-NDDP, SPI-077 and Lipoplatin, that had demonstrated promising results in preclinical studies have entered clinical trials. While safety criteria have been met, the hoped-for improvement in efficacy over free cisplatin or other standard-of-care has not been observed to date, possibly because nanoparticle formulations cannot completely overcome off-target effects and tumor resistance to the current cisplatin formulation. Further efforts are needed on clinical development of cisplatin nanoparticles designed to not only reach tumor cells but also release their payloads locally to achieve maximum beneficial effects. Another opportunity is to go beyond delivering cisplatin alone. Simply increasing

local drug concentration may not be sufficient. Much like conventional chemotherapy agents, which are typically used in combination with radiation or other chemotherapy drugs, ongoing clinical trials are evaluating the feasibility of combining nanomedicines with other therapeutics to overcome drug resistance and provide synergistic effects. Recent progress has suggested even greater benefits might be achieved by co-delivery of multiple agents via nanoparticles. Formulations that enable enhanced delivery and controlled release of multiple synergistic therapeutics may achieve the promise of nanomedicine as a route to greater efficacy and decreased adverse effects.

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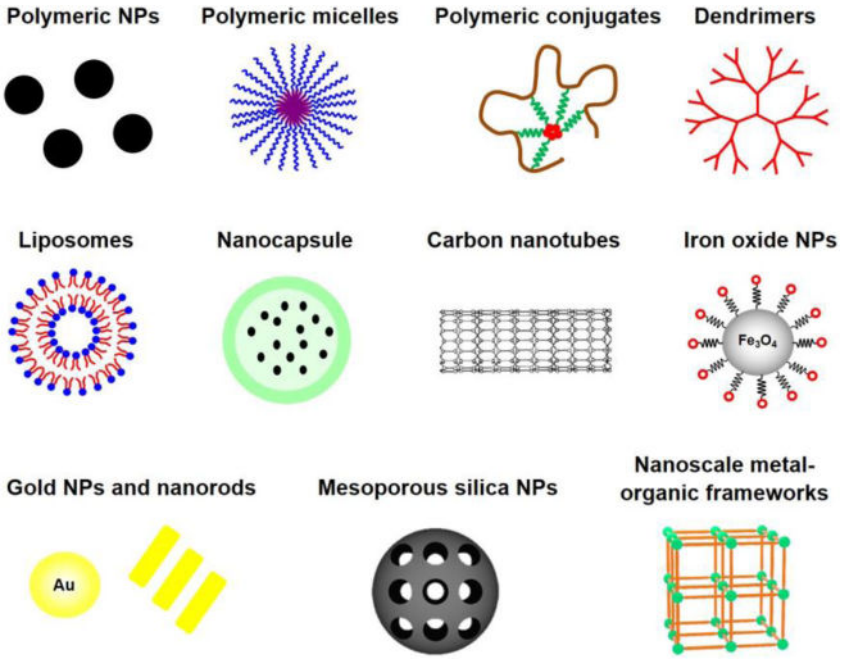

FIGURE 1.
Nanoparticle formulations used for cisplatin delivery.

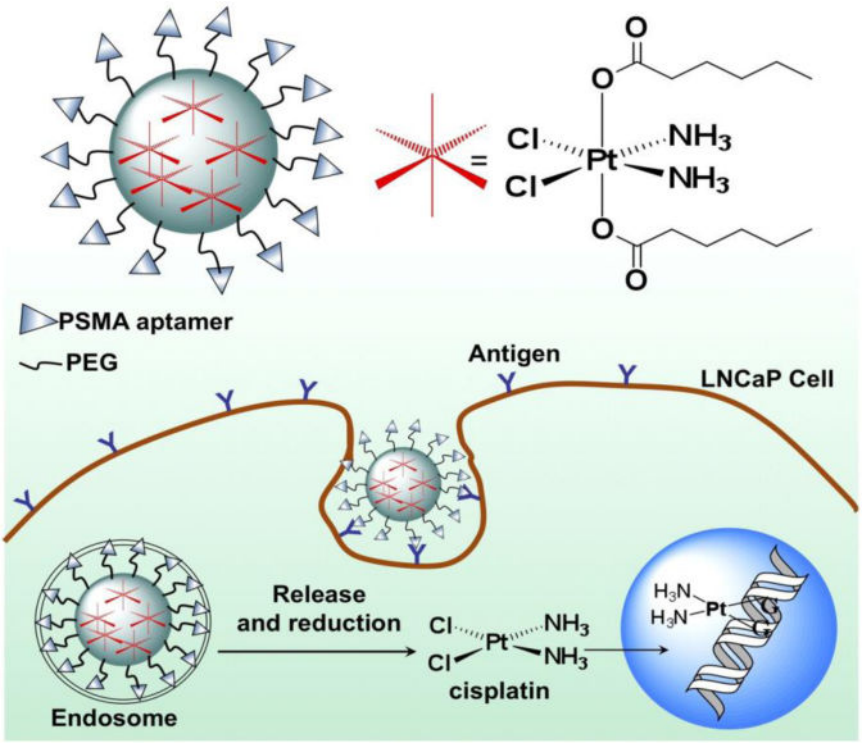

FIGURE 2.

Schematic representation of the cisplatin-loaded PLGA-PEG NPs, and intracellular reduction of Pt(IV) prodrug for the release of active cisplatin in PSMA expressing human prostate cancer LNCaP cells after receptor mediated endocytosis.[10]

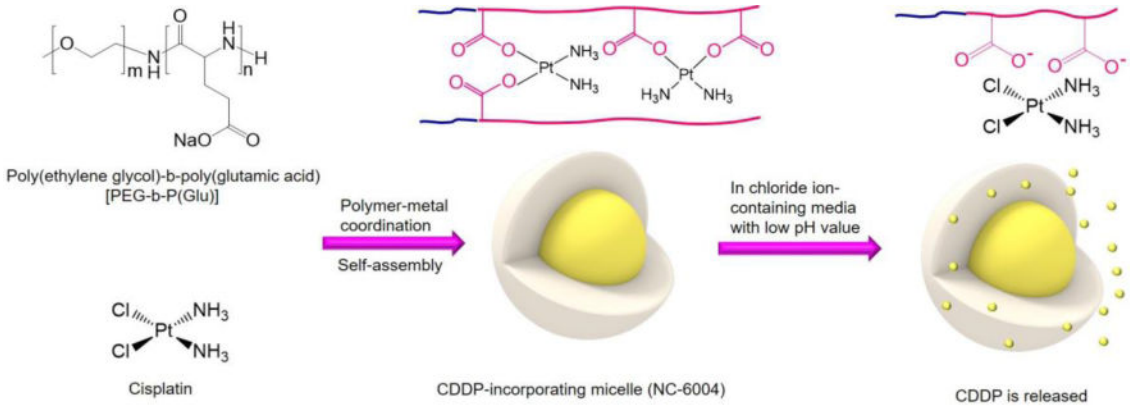

FIGURE 3.

Chemical structures of cisplatin and PEG-P(Glu) copolymer, and the formation and dissociation of cisplatin-incorporating polymeric micelles (NC-6004).

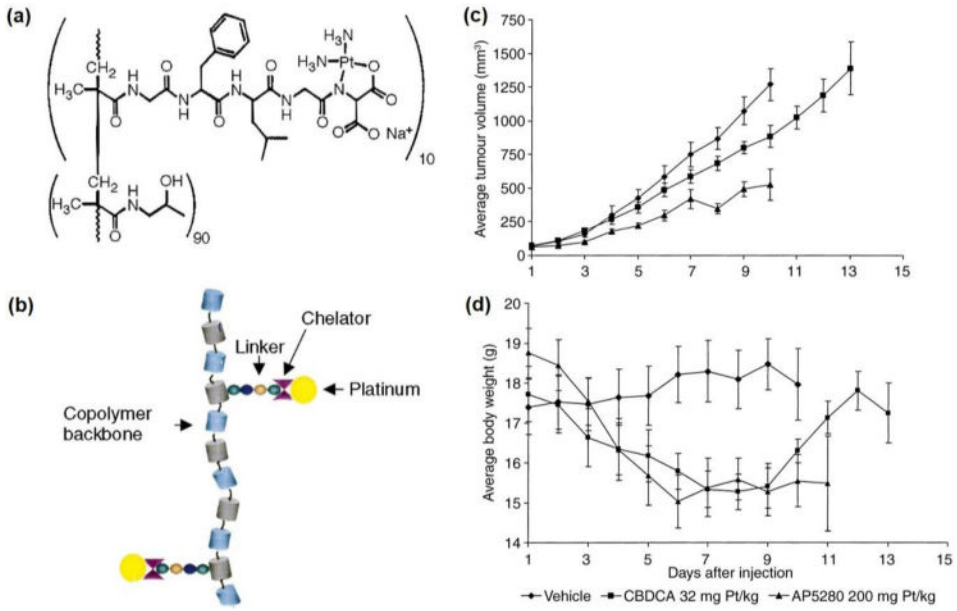

FIGURE 4.

(a) Chemical structure of AP5280. (b) Schematic diagram of structural components showing the HMPA copolymer carrier, the tetrapeptide linker, and the N,O-chelated platinum(II) diammine complex. Activity of AP5280 in the murine B16F10 tumor model: (c) Tumor volume and (d) animal weight as a function of time. (◆) vehicle; (■) CBDCA 32 mg Pt/kg; (▲) AP5280 200 mg Pt/kg. (Reprinted with permission from Ref 13. Copyright 2004 Elsevier)

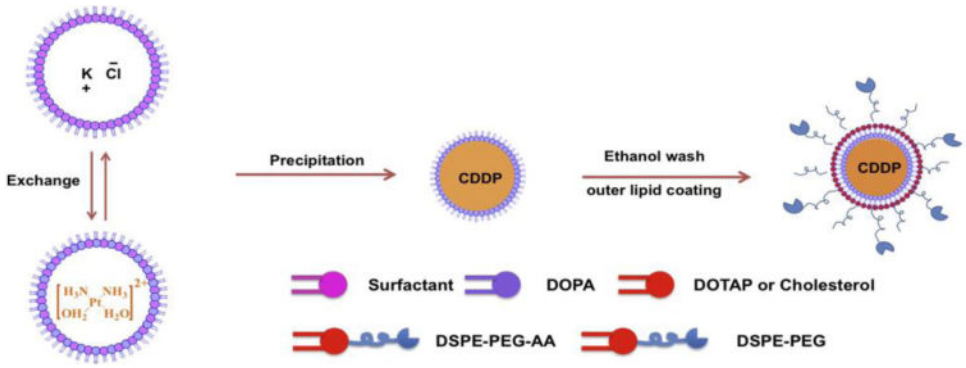

FIGURE 5.

Synthesis of lipid bilayer-coated cisplatin NPs using a reverse microemulsion method. (Reprinted with permission from Ref 19. Copyright 2014 Elsevier)

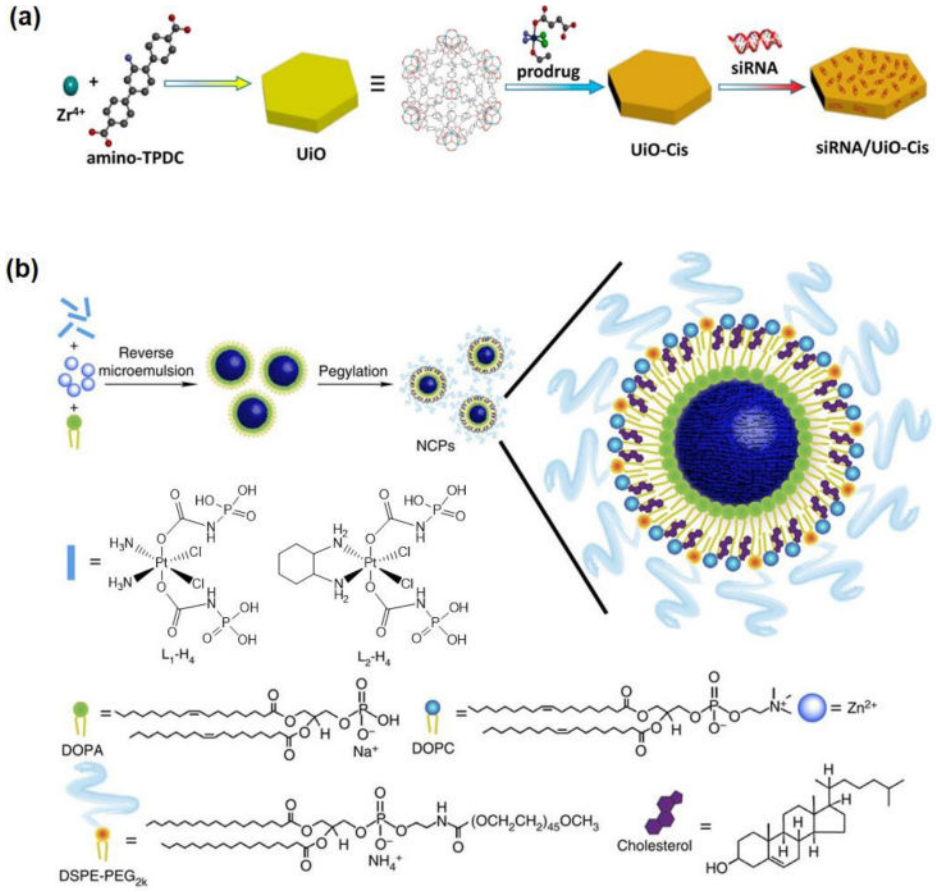

FIGURE 6.

(a) Cisplatin prodrug was attached onto the framework after synthesis. (Reprinted with permission from Ref 116. Copyright 2014 American Chemical Society) (b) Cisplatin prodrug was incorporated within NCPs through use of the prodrug as the building block. (Reprinted with permission from Ref 117. Copyright 2014 Nature Publishing Group)

TABLE 1

Cisplatin nanoparticle formulations undergoing clinical investigation.

	Formulation	Company	Indication	Clinical trail
NC-6004 (Nanoplatin™)	Polymeric micelles (PEG-P(Glu)) formulation of cisplatin	NanoCarrier Co.	Various cancers	Phase I / II / III
AP5280	Polymer (HPMA) conjugate of cisplatin	Access Pharmaceuticals, Inc.	Various cancers	Phase II
L-NDDP (Aroplatin™)	Liposomal cisplatin analog	New York University School of Medicine	malignant pleural mesothelioma	Phase II
SPI-077	Peglyated liposomal cisplatin	Alza Corporation	Head and neck cancer, lung cancer	Phase II
LiPlaCis	Peglyated liposomal cisplatin	LiPlasome Pharma	Advanced or Refractory Tumours	Phase I
Lipoplatin	Peglyated liposomal cisplatin	Regulon Inc.	Various cancers	Phase III