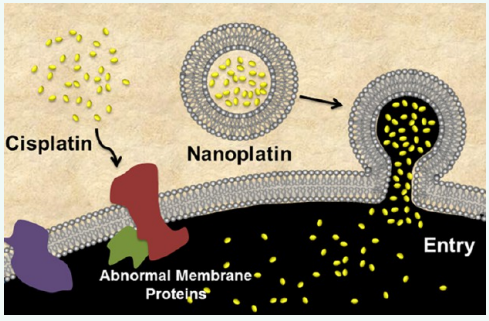
Nanoscale Drug Delivery Platforms Overcome Platinum-Based Resistance in Cancer Cells Due to Abnormal Membrane Protein Trafficking

Xue Xue,[†,‡] Matthew D. Hall,[§] Qiang Zhang,[‡] Paul C. Wang,[⊥] Michael M. Gottesman,[§,*] and Xing-Jie Liang[†,*]

[†]CAS Key Laboratory for Biomedical Effects of Nanomaterials and Nanosafety, National Center for Nanoscience and Technology of China, Beijing 100190, People's Republic of China, [‡]Department of Pharmaceutics, School of Pharmaceutical Science, Peking University, Beijing 100191, People's Republic of China, [§]Laboratory of Cell Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, United States, and [⊥]Molecular Imaging Laboratory, Department of Radiology, Howard University, Washington DC 20060, United States

ABSTRACT The development of cellular resistance to platinum-based chemotherapies is often associated with reduced intracellular platinum concentrations. In some models, this reduction is due to abnormal membrane protein trafficking, resulting in reduced uptake by transporters at the cell surface. Given the central role of platinum drugs in the clinic, it is critical to overcome cisplatin resistance by bypassing the plasma membrane barrier to significantly increase the intracellular cisplatin concentration enough to inhibit the proliferation of cisplatin-resistant cells. Therefore, rational design of appropriate nanoscale drug delivery platforms (nDDPs) loaded with cisplatin or other platinum analogues as payloads is a possible strategy to solve this problem. This review will focus on the known mechanism of membrane trafficking in cisplatin-resistant cells and the development and employment of nDDPs to improve cell uptake of cisplatin.



KEYWORDS: cancer · cisplatin · drug resistance · nanoscale drug delivery platforms · membrane trafficking · nanotechnology · chemotherapy · abnormal membrane proteins

Platinum (Pt)-based chemotherapeutic drugs, principally cisplatin (cis-[$PtCl_2(NH_3)_2$]) and carboplatin ([Pt(*O*,*O*′-cdbca)$(NH_3)_2$], cbdca = cyclobutane-1,1-dicarboxylate) are widely employed in the clinic to treat malignancies such as cancer of the testis, lung, ovary, breast, bladder, head and neck, colon, and rectum.[1−3] Clinically, the chemotherapeutic effect of platinum-based drugs presents a satisfactory response when tumors are first exposed to the drugs.[4] However, after repeated treatments, most malignancies sooner or later become resistant to even unrelated anticancer agents, in spite of different chemical structures or different mechanisms of intracellular activity.[5] The exception to this is testicular cancer, for which platinum therapy provides an approximately 99% cure rate. Thus, intrinsic and/or acquired resistance, as well as the formidable side effects of accumulating platinum in normal tissues, often hampers Pt-based treatment of cancer.[6,7] Movement of chemotherapeutic agents through the cellular lipid bilayer membrane was first thought to occur predominantly by passive diffusion.[8,9] However, emerging evidence in the literature indicates that active processes are more likely the major determinant of cellular uptake of cisplatin.[6,10] Evidence suggests that various membrane proteins collectively regulate the uptake and efflux of drugs. The reduction of platinum accumulation as a pivotal factor influencing the effectiveness of tumor chemotherapy is therefore mediated by down-regulation of these facilitative transporters and alteration in membrane protein trafficking.[11−13] Understanding the role of abnormal membrane proteins in the development of platinum drug resistance can serve as a basis for selecting drug targets and promoting drug development.

Many studies have been published concerning the role of active transport of platinum drugs across biological membranes.[14−16]

* Address correspondence to mgottesman@nih.gov, liangxj@nanoctr.cn.

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However, in order to achieve successful and effective drug delivery in cases of resistant cancer, new therapeutic strategies still need to be developed.[17−19] Newer, more targeted agents have not displaced shotgun therapeutics such as cisplatin. In recent years, nanotechnology, through an amalgamation of chemistry, engineering, biology, and medicine, has provided potential solutions to some of the daunting challenges associated with cancer therapy. Furthermore, although the feasibility and efficacy of reversing drug resistance have been studied in the clinic, ways to use nanotechnology to circumvent the resistant phenotype have not been clarified or fully explored. This review examines the reduced drug accumulation that occurs in resistant cancer cells caused by abnormal membrane transporter expression and unusual protein-related metabolic modulation and introduces nanotechnology formulations and current nanomedical approaches to address platinum-based resistance, with a specific focus on the effort to overcome abnormal membrane protein trafficking and increase cellular uptake of chemotherapeutic agents.

VOCABULARY: nDDPs - nanoscale drug delivery platforms; **Pt** - platinum; **ABC** - ATP-binding cassette; **SLCs** - solute carriers; **MRP** - multidrug resistance-associated protein; **BCRP** - breast cancer resistance protein; **RFC** - reduced folate carrier; **CNT** - concentrative nucleoside transporter; **ENT** - equilibrative nucleoside transporter; **CTR** - copper transporter; **DCA** - dichloroacetate; **CDKs** - cyclin-dependent kinases; **PDK** - pyruvate dehydrogenase; **MDR** - multidrug resistance; **EGFR** - epidermal growth factor receptor; **FDA** - Food and Drug Administration; **PE-Gylated** - poly(ethylene glycol)-conjugated; **P-gp** - P-glycoprotein; **SWNTs** - single-walled carbon nanotubes; **MWNTs** - multiwalled carbon nanotubes; **iNOS** - inducible nitric oxide synthase; **NSCLC** - non-small-cell lung cancer; **FR** - folate receptor;

ABNORMAL MEMBRANE PROTEINS PLAY PIVOTAL ROLES IN PLATINUM-BASED RESISTANCE

Modulation of Membrane Transporters in Resistant Cells. Membrane transporters are a group of integral membrane proteins that facilitate the movement of a variety of endogenous and exogenous substrates across cellular and organelle membranes, including the movement of ions, small molecules, and macromolecules. An increasing number of membrane transporters have been identified as contributing to cancer resistance. These transporters govern the movement of drugs and their secondary metabolites, thereby determining their pharmacodynamics and adverse drug reactions. Changes in several transporters, such as in the ATP-binding cassette (ABC) transporters, solute carriers (SLCs), and ATPase membrane protein superfamilies have been implicated as determinants of the pharmacology of cisplatin, oxaliplatin, carboplatin, and related investigational compounds.[11,20,21] Changes in membrane transporters affect the accumulation of platinum drugs in resistant cells or tissues by increasing drug efflux or decreasing drug uptake, by metabolic modifications or by detoxification.[22,23]

Of these transporter-related resistance mechanisms, overexpression of ABC transport molecules is generally considered the most frequent. ABC transporters are transmembrane proteins that use the energy of ATP hydrolysis to shuttle various substrates against the concentration gradient outward or into intracellular organelles. To date, there are 48 known human transporters in the ABC family, classified into seven subfamilies A through G. At least 13 of them have been recognized as drug transporters when drugs share physiochemical characteristics with certain endogenous substrates,[21,24,25] and three, ABCB1 (P-glycoprotein), ABCC1 (MRP, or multidrug resistance-associated protein), and ABCG2 (BCRP, or breast cancer resistance protein), are broad spectrum multidrug efflux pumps.[24]

The solute carrier (SLC) family of transporters is another superfamily of membrane proteins that mediates the cellular uptake of anticancer agents, including SLC19A1 (RFC1) and SLC1B1 (SLC21A6). SLC transporters play a critical role in multiple cellular physiological processes and traffic specific substrates such as amino acids, oligopeptides, sugars, monocarboxylic acids, organic cations, anions, phosphates, nucleosides, metals, and vitamins. SLCs also mediate drug absorption, distribution, metabolism, and elimination, particularly in the case of uptake of hydrophilic anticancer drugs that cannot rely solely on passive diffusion, including cisplatin, carboplatin, and oxaliplatin.[26,27] Structurally, members of the SLC19 family (the reduced folate carrier (RFC) family), SLC28 and 29 families (concentrative and equilibrative nucleoside transporter proteins (CNT and ENT, respectively)), SLC7A and 3A families (amino acid transporters), and SLC31A (the copper transporter family (CTR)) are associated with uptake of anticancer drugs.[10,20] CTR1 has been identified as a mediator that increases drug accumulation and cytotoxic properties.[28] For instance, CTR1-deficient mouse embryonic fibroblasts have been shown to demonstrate reduced influx of cisplatin, carboplatin, and oxaliplatin.[29] In addition, studies have indicated that platinum accumulation is partly mediated by different energy-dependent cellular proteins that use ATP hydrolysis as an energy source. In resistant cancer cells, ATP levels tend to be depleted, leading to metabolic dysfunction and decreased drug accumulation.[28]

Modulation of Membrane Content and Potential in Resistant Cells. The plasma membrane itself also plays a role in drug resistance, especially through abnormal membrane protein trafficking. A number of studies have pointed to abnormal membranes as contributing to

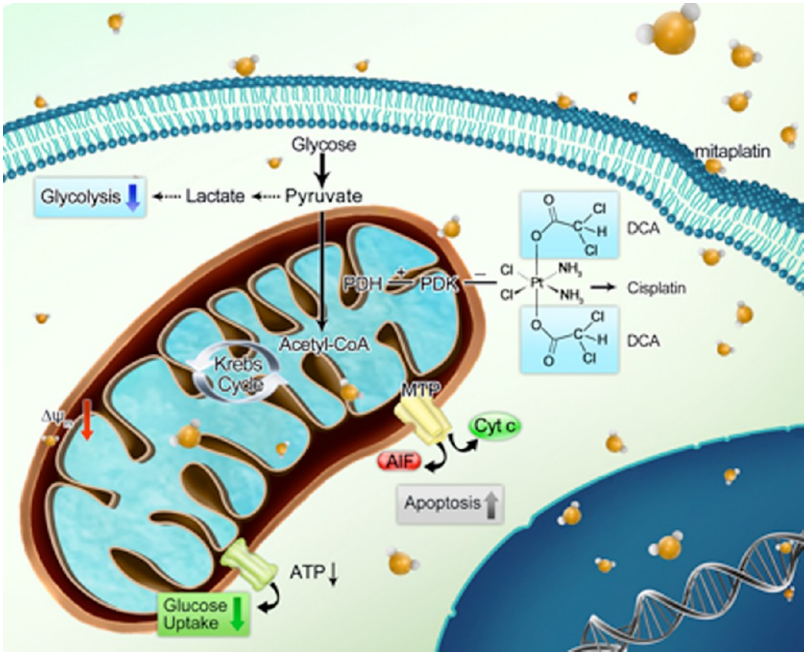

Figure 1. Mitaplatin circumvents cancer resistance to cisplatin by targeting mitochondria. In cancer cells, oxidative phosphorylation is inhibited, and cancer cells rely on cytoplasmic glycolysis to produce energy. This metabolic shift induces apoptosis resistance. After crossing the membrane, mitaplatin targets mitochondria, inhibits the activity of mitochondrial PDK, and leads to activation of PDH, which promotes the influx of acetyl-CoA into mitochondria and increases the Krebs cycle. With triggering hyperpolarized $\Delta\psi m$ in resistant cells, mitaplatin also results in reduced glucose utilization. Similar to cisplatin, mitaplatin also enters the nuclei and targets DNA to form 1,2-intrastrand d (GpG) cross-links. Adapted from Figure 7 of ref 31. Copyright 2012 American Chemical Society.

resistance in cancer cells. These abnormalities include higher membrane potentials, abnormal fluidity of the plasma membrane, and changes in competency. Altered membrane protein trafficking results in a lowered level of transporters at the cell surface, therefore reducing the potential capacity of cells to facilitate the uptake of drugs (and nutrients).

Previous studies by us found that the biophysical status of cellular membranes was associated with cisplatin resistance. Compared to sensitive cells, resistant cells had higher plasma membrane potentials[30] and mitochondrial membrane potentials,[31] which would be dependent on differences in the structure or function of fatty acid composition, resistance-related membrane protein expression, ion conductivity, or metabolic regulation.[32] One study indicated that the change of lipid content in cisplatin-resistant cells could mediate the modulation of membrane fluidity, which was determined by cholesterol, total lipids, and phospholipid content.[33] The study pointed out that, compared to sensitive cells, the cholesterol and cholesterol ether content was significantly higher, while diacylglycerol and triacylglycerol content was apparently lower in the resistant cells. These differences provide potential opportunities for drugs designed to selectively target resistant tumor cells. For instance, the orphan drug dichloroacetate (DCA) reverses the Warburg effect by inhibiting pyruvate dehydrogenase kinase (PDK), providing a mitochondrial target to influence the unique cellular metabolism of cancer cells and promote their apoptosis.[34,35] Mitaplatin, a platinum(IV) complex containing cisplatin and two DCA molecules bound as ligands that are released when the complex is reduced, alters the mitochondrial membrane potential and selectively kills cancer cells by targeting both nuclear DNA *via* cisplatin and mitochondria *via* DCA.[36] In cancer-sensitive cells, oxidative phosphorylation is inhibited to force cancer cells to rely on cytoplasmic glycolysis to produce energy. This metabolic shift induces apoptosis resistance. The enhanced lipophilicity of mitaplatin increases its ability to cross the plasma membrane and thus be further employed to overcome tumor resistance by modulating abnormal glycolysis and by rendering resistant cancer cells more vulnerable to hyperpolarized mitochondrial membrane potentials (Figure 1).[31] Subsequently, other platinum(II) and platinum(IV) complexes containing DCA incorporated as a ligand have been reported.[37]

Modulation of Intracellular pH in Resistant Cells. In addition, an acidic pH-activated mechanism to overcome efflux-dependent resistance has been explored.[38−41] This has been driven by observations that cells resistant to cisplatin have acidified intracellular compartments. Furthermore, the influence of pH on the cytotoxicity of cisplatin in mouse mammary tumor cells can be exploited, as tumor cells are more sensitive to cisplatin when cultured in pH 6.0 medium rather than physiologic pH.[42] Given this, the expectation is that an

acid-labile linker would release its payload at a greater rate inside the more acidic cisplatin-resistant cells. By way of example, Kievit *et al.* demonstrated that doxorubicin tethered to iron oxide NPs by an acid-labile hydrazone linkage was released to a greater extent at acidic pH.[39]

Modulation of Cell Cycle in Resistant Cells. The cell life cycle is the sequence of events that occur during DNA replication and cell division, which is divided into four successive phases: G_1, S (synthesis), G_2 (collectively known as interphase), and M (mitosis). During G_1, S, and G_2, cells accumulate nutrients needed for mitosis. After mitosis, cells enter a state of quiescence called the G_0 phase and stop dividing temporarily.[43,44] Cell cycle arrest is coordinated with the production of membrane phospholipids, the major cellular constituents required for the assembly of biological membranes. A doubling of membrane phospholipids is required for cell proliferation. Previous studies have demonstrated that phospholipids accumulate when cells enter S phase[45] and are synthesized in the G_2/M phase,[46] which are controlled by a series of cell cycle regulators.[47,48] The cell cycle can be disturbed or delayed by various molecular events, including the intertwined actions of cyclin-dependent kinases (CDKs)[49] and specific proteolytic mechanisms,[50] as well as chemotherapeutic agents.[51,52] Cisplatin is well-known to arrest cells at G_2,[53] a process mediated by checkpoint kinases[54] and the miRNAs that control them.[55] In cells that have acquired multidrug resistance, cell cycle distribution and cell cycle arrest is often altered as a result of this cycle-specific toxin. For example, cisplatin-resistant hepatocellular carcinoma cells have been shown to spend more time in the G_2/M and S phases (allowing them to spend greater time recognizing and repairing DNA damage).[56] Interfering with cell cycle arrest, by inhibiting or down-regulating checkpoint kinases, can resensitize cisplatin-resistant cells by forcing the cells to continue through the G_2 checkpoint into mitosis, enforcing apoptosis.[55,57] However, gene silencing technologies are limited in their efficiency, and small molecules face challenges associated with pharmacokinetics and unwanted side effects.

As such, NP-mediated interference with the cell cycle state has received attention. In fact, bare liposomes not loaded with drug have been shown to arrest cells in G_0/G_1 phase and induce apoptosis, though obviously the delivery of a drug by liposomes results in altered cellular responses.[58−60] Roa *et al.*[61] reported that glucose-capped gold nanoparticles accelerate cells through the G_0/G_1 phase and arrest them in G_2/M (much like cisplatin). Increasing evidence has been reported that metal-based nanomaterials such as iron NPs,[62] silver NPs,[63−65] albumin NPs,[66,67] ENREF 60 ZnO NPs,[68] and Au NPs[61,69] can affect the cell cycle in different phases. While modification of the cell cycle state of cells may alter cell fate by sensitizing chemotherapy, further study of the mechanisms of interaction between nanoparticles and phospholipid cell membranes is required, as drugs that arrest cells can inhibit each other's efficacy.[70]

SUCCESSFUL APPLICATIONS OF NANOTECHNOLOGY AS THERAPY FOR DRUG-RESISTANT CANCER

Nanoscale Drug Delivery Platforms That Target Membrane Transporters. Drugs are often internalized by diffusion across the cellular membrane or by transport-facilitated processes. The drug efflux pumps (such as P-glycoprotein (P-gp; ABCB1)) on the cell membrane can recognize free drug molecules, capture, and efflux them when they attempt to cross the membrane.

Nanoscale drug delivery platforms (nDDPs, not to be confused with the often-used acronym for cisplatin, DDP) based on biodegradable, biocompatible, and FDA-approved components are taken up by endocytosis, preventing the drugs from being recognized by efflux pumps. The drugs are covalently bound to the nDDP, which results in a higher intracellular accumulation unaffected by transport processes.[71−73] This increase is achieved partly because of circumvention of membrane-crossing events and partly because each nDDP nanoparticle can deliver many drug molecules (the analogy being that of a Trojan horse).

Because of the side effects of platinum-based chemotherapeutic drugs, efforts to design targeted and/or controlled-release drug delivery systems is ongoing, with various modifications and accommodations for multiple types of drug payloads. At a chemical level, controlled release is achieved by installing linkers between the nanoparticle and drug containing functional groups that are susceptible to either enzymatic (*e.g.*, esterase) or nonenzymatic (*e.g.*, hydrolysis) cleavage.

The main objective of nDDPs is to localize the therapeutic agent at its site of action for maximal effect without resulting in a toxic distribution of the agent at nontarget sites. After careful consideration of their size, toxicity, absorbance, distribution, and elimination, most nanostructure platforms derive their effectiveness from adequate delivery systems, including polymers, liposomes, micelles, dendrimers, nanoshells, and nanotubes, as well as magnetic or metal nanoparticles.[74−76] Some of them are promising applications or becoming realities in healthcare. For instance, it has been reported that poly(ethylene glycol)-conjugated (PEGylated) multiwalled carbon nanotubes (MWCNTs) act as drug efflux modulators. They accumulate in resistant cancer cells as well as in sensitive cancer cells without damaging the plasma membrane, indicating that they are efficient drug carriers able to overcome drug resistance.[77] This is likely achieved because the nanoparticle itself is either not recognized by, or is too large to be extruded by, multidrug resistance efflux pumps. Moreover, ligand-mediated

interaction between nanoparticles and the surface of resistant cancer cells is one of the most popular strategies. Properly designed nanoparticles can focus on active targets at specific targeting sites with therapeutic payloads, taking advantage of markers on the membranes of resistant cancer cells, reducing the dispersal of the drug and enhancing its therapeutic potential.[78,79]

Defective endocytosis causes less intracellular accumulation of drugs such as cisplatin. Metallofullerene nanoparticles have been successfully designed to repair receptor-mediated endocytosis in resistant cells, resulting in more efficient formation of cisplatin−DNA adducts to sensitize the resistant cells both *in vitro* and *in vivo*.[80] In addition, active nanocarrier endocytosis has been accomplished by other ligands such as transferrin,[80] epidermal growth factor receptor (EGFR), peptides,[81,82] and siRNA[83] *via* receptor-mediated endocytosis.

Other Modification Strategies Related to Abnormal Membrane Protein Trafficking. *nDDPs That Modify the Phospholipids of Resistant Cells.* Alterations in the composition of the cell membranes of resistant tumor cells have been observed.[84−86] For example, a study based on virtual screening found a novel phospholipid named phosphatidylinositol-(1,2-dioctanoyl) sodium salt, identified with transmembrane P-gp transportation inhibitory activity. Further tests showed that the phosphatidylinositol derivative increased the bioactivity of drugs in several tumor cell lines, due to P-gp inhibition.[87] Another study indicated that MCF-7 cisplatin-resistant cells accumulated more 3,3′-dioctadecyloxacarbocyanine perchlorate (DiO) dye from dye-loaded liposomes than sensitive cells.[88]

Among different kinds of drug carriers, such as polymeric micelles, niosomes, liposomes, microspheres, immunoglobulins, peptides, and small proteins, liposomes are considered as suitable lipophilic carriers due to their natural lipid components. Liposomes are nanosized artificial vesicles composed of one or more phospholipid-enriched bilayers containing mixed lipid chains that are employed to attach to unhealthy tissue.[89,90] Liposomes afford a unique opportunity to deliver drugs due to their attractive composition, including fluidity, permeability, stability, and structure, which makes them biocompatible and biodegradable. On the other hand, liposomes sometimes alter the pharmacokinetic parameters and dynamic interactions between tumor cells and encapsulated drugs: strongly lipophilic drugs are entrapped almost completely in the lipid bilayer; strongly hydrophilic drugs are located exclusively in the aqueous compartment, and drugs with intermediate log *P* partition between the lipid and aqueous phases, both in the bilayer and in the aqueous core. Futhermore, liposomes can easily be loaded with different drugs for combination chemotherapy. Ye *et al.* showed that cationic liposome-mediated inducible nitric oxide synthase (iNOS) gene therapy is effective with low dose cisplatin treatment in lung cancer. Systemic delivery of the liposome−pVAX-iNOS complex enhanced cisplatin-mediated suppression of tumors by inhibition of cell proliferation, invasion, migration, and promotion of cell apoptosis both *in vitro* and *in vivo*.[91] Because lipid-based nanoparticles have the advantage of minimum toxicity for *in vivo* applications, their potential success in the clinic has been apparent. Lipoplatin, a liposomal encapsulation of cisplatin into tumor-targeted 110 nm nanoparticles (Figure 2A), shown to be effective in non-small-cell lung cancer (NSCLC) both in phase II and III trials, combines a reduction in the toxicity associated with antitumor activity similar to the free drug.[92,93] Lipoplatin infusion in tumor cells exhibited 10−50 times higher activity than in the adjacent normal specimens, with less general toxicity and nephrotoxity, no significant weight gain reduction, and fewer renal and liver impairments than cisplatin administration.[93,94] The direct fusion of lipoplatin with the membrane allows for a therapeutic effect even after the development of cisplatin resistance (Figure 2B).[95]

nDDPs That Modify Cellular Metabolism. An alternative to traditional ways to treat cancer resistance is to decrease intracellular ATP levels by inhibiting mitochondrial function, which can significantly reduce the activity of drug efflux pumps. The pluronic block copolymer (P85) is an important and promising example of a modifying agent for P-gp, the best-known and most thoroughly studied multidrug resistance membrane transporter, which was discovered in 1986.[96,97] Membrane fluidization by P85 treatment inhibits the P-gp ATPase drug efflux system and interferes with metabolic processes. Therefore, both energy depletion and increased permeability and fluidization of a broad spectrum of drugs are critical factors contributing to the activity of the block copolymer for reversion of multidrug resistance (MDR).[98,99]

As an alternative approach to the use of biological nanoparticles, anticancer peptide therapy focuses on the development of therapeutic peptides to kill resistant cells. A novel peptide, CT20p, derived from a helical unit of the pro-apoptotic protein Bax, is an example of a peptide that is an effective killer both *in vitro* and in a murine breast cancer tumor model. Boohaker and colleagues found that CT20p is amphiphilic. It can be encapsulated in polymeric nanoparticles, modifying tumor metabolism by causing an increase in mitochondrial membrane potential.[82] Another group focused on the small ubiquitin-like modifier 1 (SUMO1) peptidase SENP1, which reduces hypoxia and enhances chemosensitivity as a potential therapeutic target for drug-resistant testicular germ cell tumors.[100] Garg *et al.* also reported that PEGylated liposomes modified with a fibronectin mimetic peptide to target metastatic colon cancer cells inhibited tumor

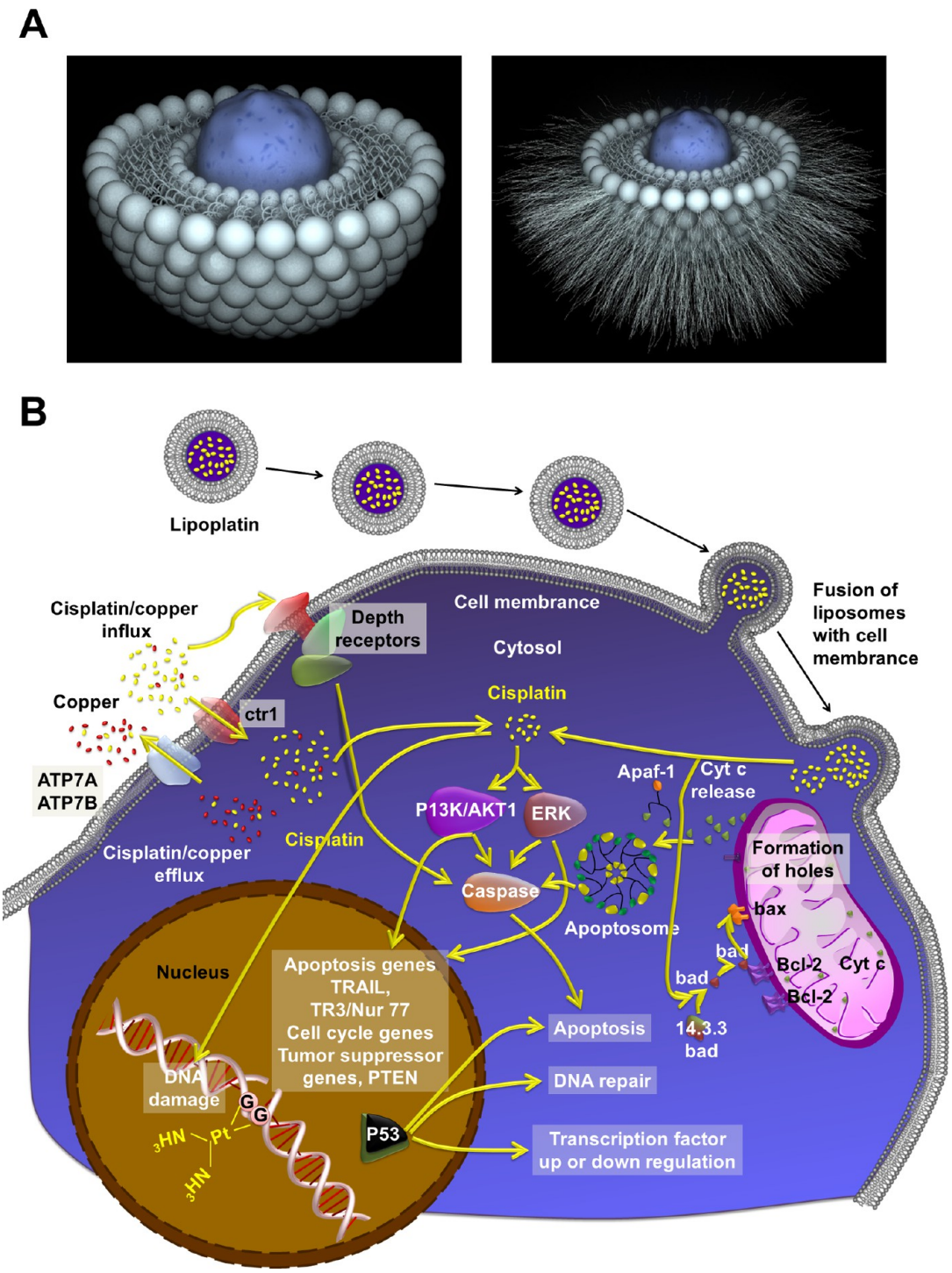

Figure 2. Depiction of a lipoplatin nanoparticle. (A) Cisplatin molecules are depicted as blue spheres surrounded by the lipid bilayer with hair-like PEGylated lipids protruding from the outer surface. These images were produced by François Caillaud, CNRS/SAGASCIENCE. (B) Penetration of lipoplatin nanoparticles through the cell membrane of tumor cells. Lipoplatin nanoparticles once inside the tumor cell mass can fuse with the cell membrane because of the presence of the fusogenic lipid DPPG in their lipid bilayer; an alternative mechanism proposed is that lipoplatin is taken up by endocytosis by tumor cells. These processes occurring at the cell membrane level are promoted by the lipid shell of the nanoparticles (disguised as nutrients).[142,143] Adapted from Boulikas, *et al.*, *Cancer Ther.* 2007, *5*, 551−376. Used with permission.[144]

growth, reduced tumor metastasis, and stimulated drug internalization.[101] By targeting metabolism in resistant tumor cells, nanotechnology exhibits significant antitumor efficacy by inducing apoptosis in both sensitive and resistant cancer cells.

nDDPs That Regulate Protein Trafficking and Degradation. Autophagy begins with the formation of double-membrane vesicles (autophagosomes), which then fuse with lysosomes, where the sequestered contents undergo degradation and recycling, eliminating

misfolded proteins and damaged organelles.[102,103] The critically important process of autophagy, which is a mechanism of cell survival in the presence of genomic injury, oxidant stress, nutrient deprivation, hypoxia, inflammation, and viral/bacterial infection, has been recently recognized as important for conferring resistance to cancer treatment. Moreover, it was found that autophagy protects tumors from drug-treated apoptosis and aids survival and recovery with chemotherapeutic drug treatment. Modulation of autophagy dysfunction was found to resensitize resistant cancer cells to anticancer therapy.[104−106] Unlike cisplatin, which mainly causes cell death by inducing apoptosis, other platinum compounds have been shown to kill cells *via* autophagy.[107]

Fullerene C_{60} (a spherical carbon structure) is a chemotherapeutic sensitizer that causes authentic autophagy at noncytotoxic concentrations.[108] These nanoparticles have been reported to induce autophagy and sensitize resistant cells to chemotherapy when combined with platinum drugs, killing both drug-sensitive and drug-resistant cancer cells, a novel therapeutic approach to circumvent drug resistance through modifying intracellular metabolism.[109]

RECENTLY DEVELOPED PT-TETHER NDDPS TO TREAT DRUG-RESISTANT CANCER WITH ABNORMAL MEMBRANE PROTEIN TRAFFICKING

A number of nanoparticles have recently been produced to conjugate with platinum. The process of designing Pt-tether nanoparticles includes tuning their shape and size in order to avoid disturbing the abnormal membrane protein in resistant cells. Surface modifications are also made, including various coatings and charges to increase hydrophilicity, which can alter the pharmacokinetics of platinum-based drugs. As it is difficult to entrap cisplatin in polymeric sustained-release nanoparticles (due to its small cross-section), Dhar *et al.* generated a platinum(IV) complex (*c*,*t*,*c*-[Pt-$(NH_3)_2(O_2CCH_2CH_2COOH)_2Cl_2$]) as a prodrug that can be intracellularly processed into cisplatin. This release of cisplatin is achieved by reduction of the platinum(IV) complex by endogenous reductants and loss of the axial ligands. The prodrug has increased hydrophobicity and offers a position (pendant carboxylic acids) on the axial ligands for conjugation to a nanocarrier for efficient delivery, for example, by reaction with terminal amines (Figure 3A).[110−113]

Based on this chemistry, a series of Pt(IV)-tethered nanoparticles has been produced including single-walled carbon nanotubes,[114] gold nanoparticles,[115] PLGA-PEG nanoparticles,[110,116] peptides,[117] and aptamers,[111] providing good examples of both active platinum(II) derivative development and nDDPs. These nanoparticles provide platinum-based drugs with true drug carriers (Figure 3A). These studies also shed light on the impact of the complex environment of platinum on drug efficacy. Additionally, various studies have reported that several kinds of Pt(IV)-based nanoparticles have shown very promising efficacy *in vivo*, with long blood circulation time and thereby high accumulation in tumors, with low systemic toxicity and better tolerance.[111,117−120]

Meanwhile, researchers are working to advance the ability of nDDPs to carry platinum drugs into resistant cells, especially with nanoparticle−Pt linkers. One popular strategy is to link a nanoparticle *via* a pH-sensitive coordination bond for endosomal release. Comenge *et al.*[121] used gold nanoparticles to tether cisplatin with pH-sensitive linkers, without affecting the therapeutic and imaging benefits. A novel rational engineering of cisplatin nanoparticles by polyethylene glycol (PEG)-functionalized poly(isobutylene maleic acid) (PEG−PIMA) copolymer can coordinate with a [*cis*-diammineplatinum(II)] moiety through the pendant carboxylate ligands in a similar fashion to the carboxylate ligands of oxaliplatin. In effect, the NP acts as a bidentate ligand (Figure 3B). This complex self-assembles into a nanoparticle, releasing cisplatin in a pH-dependent manner.

Another strategy often used is to incorporate cisplatin into the hollow interior of nanoparticles. Single-walled carbon nanotubes (SWNTs), a "long boat" delivery system, offer abundant volume to encapsulate cisplatin. It was reported that cisplatin-bearing SWNTs increased anticancer efficiency 4−6 times that of cisplatin alone, causing high concentrations locally in cells of tumor xenograft tissue.[122] An assessment of a series of platinum(IV) complexes based on cisplatin with increasing lipophilicity were assessed by Johnstone *et al.*, showing that the most lipophilic platinum complex displayed the highest level of encapsulation in PLGA-PEG-COOH nanoparticles.[123] Lian *et al.* used highly biocompatible hollow Prussian blue (HPB) nanoparticles with a hollow interior and a microporous framework to absorb cisplatin noncovalently, and these were demonstrated to exert cytotoxicity in cell culture.[124] Mesoporous materials containing pores with diameters between 2 and 50 nm have become popular due to their large surface area, high core volume, and tunable nanoscale pores. The matrix pore architecture makes them suitable for hosting a broad variety of compounds, and they achieve localized intracellular release of the platinum drugs to minimize the influence of abnormal membrane proteins.[83,125] For example, mesoporous silica materials loaded with cisplatin and transplatin demonstrated cellular internalization and synergistic cell killing (the nanoparticles themselves display cytotoxicity).[125] Mesoporous silica nanoparticles conjugated with folic acid have been shown to enter cells *via* folate receptor (FR)-mediated endocytosis.[126] When loaded with cisplatin, these targeted mesoporous silica nanoparticles only showed cytotoxicity toward cells expressing FR. While this targeting concept is attractive, relying on endocytic

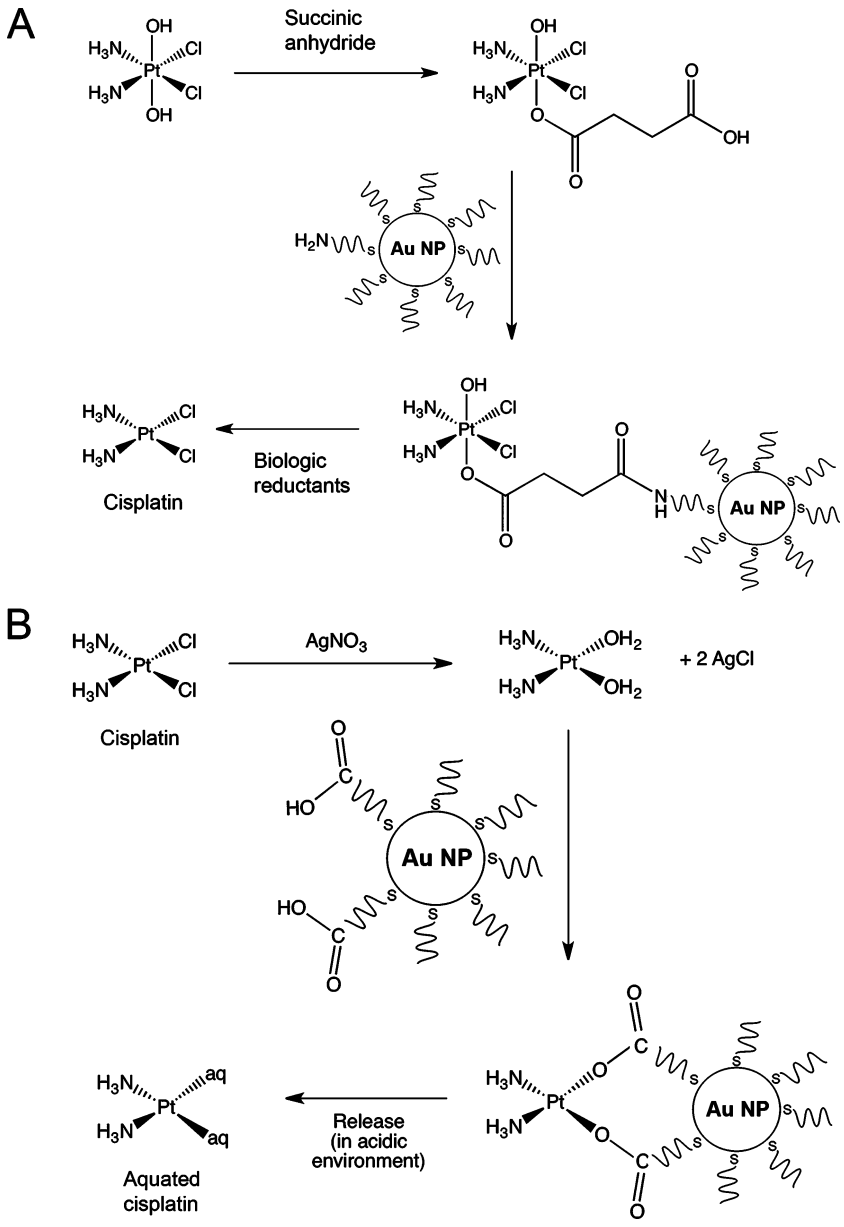

Figure 3. Examples of the chemical strategies used to tether cisplatin and cisplatin-like moieties to nanoparticle constructs. (A) Platinum(IV) complex *cis*,*trans*,*cis*-$[PtCl_2(OH)_2(NH_3)_2]$ contains cisplatin in the equatorial plane along with two hydroxido ligands in the axial positions. Reaction with succinic acid produces *cis*,*trans*,*cis*-$[PtCl_2(OH)(O_2CCH_2CH_2CO_2H)(NH_3)_2]$. The terminal carboxylic acid can then be conjugated to amine-functionalized nanoparticles (NPs) by amide coupling. In a biological environment, the tethered NP−platinum(IV) complex can be reduced by biological reductants such as glutathione or ascorbate. This results in the release of cisplatin, a platinum(II) complex, and the axial ligands (one of which is the NP). As such, provided that ligand exchange reactions at the platinum(IV) center do not take place, this conjugation method results in NPs that release cisplatin. (B) In this instance, cisplatin is tethered to the NP *via* its "leaving groups". To achieve this chemistry, cisplatin is reacted with silver nitrate. While silver nitrate is soluble, silver chloride is highly insoluble—as silver precipitates with chloride exchanged from cisplatin, a "diaqua" species is produced. Aqua ligands are relatively unstable, and this aquation step of cisplatin (by loss of chlorido ligands) in cells is considered to be a necessary intermediate reaction before cisplatin reacts with DNA. Once the "reactive" diaqua species is produced, it is reacted with carboxylic-acid-functionalized NPs. The NP carboylate groups coordinate with platinum(II) complex in place of the aqua ligands. In this sense, the NP acts as a very large bidentate ligand, analogous to the leaving groups of the platinum(II) drug carboplatin. Release of the platinum complex from the NP in a relatively acidic environment in theory releases the highly reactive diaqua form of cisplatin.

processing for targeting resistant cells may be limiting in cisplatin-resistant cells given their depressed endocytic rate.

Although novel chemotherapeutic nDDPs have been established every day, several problems still need careful investigation. Researchers expect nanomedicine to resolve the problem of how to get enough of the right drug to the right place without causing side effects (from either the drug or the NPs), immune responses, or inducing resistance. A micelle-encapsulated hydrophobic platinum(II) nanomedicine displayed excellent tumor to tissue ratios and 6 times higher cellular accumulation

compared with the free platinum compound, providing a good example of not only outstanding pharmacokinetics and tumor selectivity but also specifically high cytotoxicity against tumor cells.[127] Harnessing the immune system capacity in order to induce antitumor response remains an important challenge. How to utilize immune response in prognosis and therapy remains unknown despite its high prevalence. A 15 kDa variable domain of *camelid* heavy-chain-only antibodies, called Nanobodies, are being explored for their ability to potentiate cancer therapy.[128−130] In other cases, bionanoparticles, such as antibodies peptides, *etc.*, showed their ability to induce immune response and apoptosis.[131] In recent years, several nanoscale drug carriers have entered clinical trials.[132] Cisplatin treatment results in severe kidney toxicity, requiring patients to drink large amounts of water during treatment. However, that is not the case in NanoCarrier (Nanoplatin) trials, as the carrier's size allows it to move into and accumulate in the pancreatic tumor, instead of accumulating in the kidney.[133−135] A 30 nm polymer to transport chemotherapeutic drugs is currently undergoing phase II clinical trials with advanced or metastatic pancreatic cancer, doubling survival time from 5 months to more than 12.[132,134,136−138]

FURTHER CHALLENGES AND PROSPECTS FOR THERAPEUTIC STRATEGIES TO COMBAT DRUG-RESISTANT CANCER

Cisplatin resistance still remains a major challenge to successful treatment of cancer. Nanotechnology is a field that has developed rapidly and provides a promising approach to chemotherapy. In addition, the properties of nDDPs, including stable and strong fluorescence, *etc.*, also give promising opportunities to evaluate the sensitivity of imaging systems for chemotherapy.[80,139,140] For example, Xue *et al.* developed a self-indicating drug delivery system that visualized spatiotemporal drug release *via* tunable aggregation-induced emission by monitoring drug cargo fluorescence.[141] Although exciting approaches have been reported in the recent years, applications of nanotechnology to cancer treatment appear to overcome some of the limitations of traditional chemotherapy, giving hope that solutions to the problems of drug resistance can be found. To develop this approach, further study is needed in the following areas:

(1) Abnormal membrane proteins as potential drug targets
(2) The interaction and relationship between abnormal membrane proteins and tumor metabolism as well as the extracellular environment
(3) The pharmacokinetics (including absorbance, distribution, metabolism, and excretion) of nanoscale drug delivery systems, especially active delivery of functionalized nanocarriers
(4) Higher sensitivity imaging techniques with molecular specificity (as platinum-based drugs are difficult to trace)
(5) The safety and toxicity of nanoparticles, as well as immune response

To achieve tangible therapeutic benefits from the above information, the mechanisms that cause abnormal membrane protein trafficking to develop into cisplatin resistance need to be exploited. Based on research reported so far, it can be expected that nDDPs that target abnormal membrane proteins may represent a useful approach to improving the clinical outcomes of existing platinum-based anticancer drugs.

Conflict of Interest: The authors declare no competing financial interest.

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