ACCOUNTS of chemical research

Article

pubs.acs.org/accounts

Functionalization of Platinum Complexes for Biomedical Applications

Published as part of the Accounts of Chemical Research special issue "Synthesis in Biological Inorganic Chemistry".

Xiaoyong Wang,*[,†,∥] Xiaohui Wang,[‡,§] and Zijian Guo*[,‡,∥]

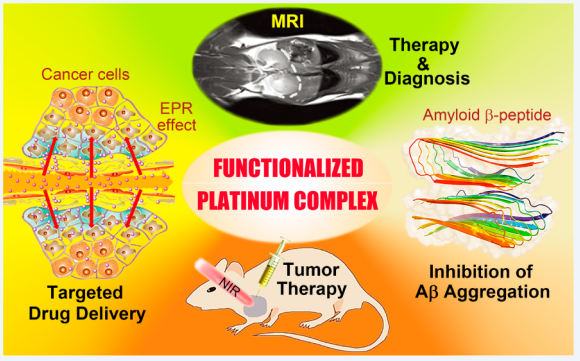
[†]State Key Laboratory of Pharmaceutical Biotechnology, School of Life Sciences, State Key Laboratory of Analytical Chemistry for Life Science, Nanjing University, Nanjing 210023, P. R. China

[‡]State Key Laboratory of Coordination Chemistry, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, P. R. China

[§]College of Chemistry and Molecular Engineering, Nanjing Tech University, Nanjing 211816, P. R. China

[∥]Collaborative Innovation Center of Chemistry for Life Sciences, Nanjing University, Nanjing 210093, P. R. China

CONSPECTUS: Platinum-based anticancer drugs are the mainstay of chemotherapy regimens in clinic. Nevertheless, the efficacy of platinum drugs is badly affected by serious systemic toxicities and drug resistance, and the pharmacokinetics of most platinum drugs is largely unknown. In recent years, a keen interest in functionalizing platinum complexes with bioactive molecules, targeting groups, photosensitizers, fluorophores, or nanomaterials has been sparked among chemical and biomedical researchers. The motivation for functionalization comes from some of the following demands: to improve the tumor selectivity or minimize the systemic toxicity of the drugs, to enhance the cellular accumulation of the drugs, to overcome the tumor resistance to the drugs, to visualize the drug molecules *in vitro* or *in vivo*, to achieve a synergistic anticancer effect between different therapeutic modalities, or to add extra functionality to the drugs.



In this Account, we present different strategies being used for functionalizing platinum complexes, including conjugation with bisphosphonates, peptides, receptor-specific ligands, polymers, nanoparticles, magnetic resonance imaging contrast agents, metal chelators, or photosensitizers. Among them, bisphosphonates, peptides, and receptor-specific ligands are used for actively targeted drug delivery, polymers and nanoparticles are for passively targeted drug delivery, magnetic resonance imaging contrast agents are for theranostic purposes, metal chelators are for the treatment or prevention of Alzheimer's disease (AD), and photosensitizers are for photodynamic therapy of cancers. The rationales behind these designs are explained and justified at the molecular or cellular level, associating with the requirements for diagnosis, therapy, and visualization of biological processes. To illustrate the wide range of opportunities and challenges that are emerging in this realm, representative examples of targeted drug delivery systems, anticancer conjugates, anticancer theranostic agents, and anti-AD compounds relevant to functionalized platinum complexes are provided. All the examples exhibit new potential of platinum complexes for future applications in biomedical areas. The emphases of this Account are placed on the functionalization for targeted drug delivery and theranostic agents. In the end, a general assessment of various strategies has been made according to their major shortcomings and defects. The original information in this Account comes entirely from literature appearing since 2010.

1. INTRODUCTION

Over the past few years, functionalization of platinum complexes has attracted much attention in the chemical and medicinal world. Here we define "functionalization" as a particular action of conjugating common platinum complexes with bioactive molecules, nanoparticles (NPs), or fluorophores in order to obtain smart compounds or composites that can perform different functions through the same construct for biomedical applications.

Platinum complexes are well-known for their antitumor activities. Up to now, thousands of platinum complexes have been prepared and tested as potential anticancer agents. Among them, cisplatin, carboplatin, and oxaliplatin have entered clinical application globally (Figure 1), and nedaplatin, lobaplatin, and heptaplatin have evolved into clinical drugs regionally.[1,2] Ideally, platinum drugs should kill cancerous cells exclusively without harming the normal ones. Practically, however, the tumor selectivity of platinum drugs is quite poor. Thus, systemic toxicity and drug resistance become the major defects of platinum drugs.[3,4] On the other hand, the distribution, accumulation, and metabolism of most platinum drugs in the

Received: April 15, 2015
Published: August 6, 2015

DOI: 10.1021/acs.accounts.5b00203
Acc. Chem. Res. 2015, 48, 2622−2631

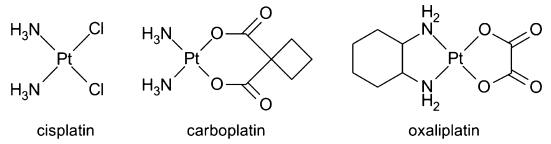


Figure 1. Platinum anticancer drugs being used worldwide in clinic: cisplatin, carboplatin, and oxaliplatin.

body are poorly understood. Although the cellular accumulation of platinum drugs can be readily determined, to monitor the cellular distribution and traveling pathway of the drugs is a more challenging problem. Thus, strategies for real-time monitoring of the drug location and therapeutic responses during treatment are highly desired.

In recent years, increasing numbers of researchers have been devoted to tethering platinum complexes to a wide range of functional molecules or NPs with or without targeting groups.[5−7] At least three benefits can be expected from the functionalization of canonical platinum complexes: (i) enhanced drug accumulation at the tumor site, (ii) enriched bioactivity with both diagnostic and therapeutic potentials, and (iii) unified pharmacokinetics of different functional molecules. Therefore, functionalization of platinum complexes is a promising approach to reduce the drawbacks of platinum drugs, to improve the effect of imaging agents, and to achieve clearer and more detailed diagnosis.

Besides therapeutic effect, considerable evidence has shown that functionalized platinum complexes can play an important role in the diagnostic process of cancers as fluorescent probes or magnetic resonance imaging (MRI) contrast agents. However, common platinum complexes and imaging agents are not tumor-selective. To actualize early detection, accurate localization, and precise characterization of malignancies, the uptake of fluorescent probes or imaging agents in tumors must be enhanced. This further motivates researchers to actively pursue different methods for functionalizing platinum complexes.

Furthermore, quite a few studies demonstrate that some functionalized platinum complexes can be used to fight against other illnesses such as Alzheimer's disease.[8] Multiple bioactive molecules or imaging agents can be accommodated in a single construct, thereby increasing their safety, efficacy, or functionality by means of synergy between the individual components. Hence, the functionalization of platinum complexes is likely to bring unexpected discoveries of new drugs and multimodal imaging agents. In this Account, we will outline the major strategies being used for the conjugation of platinum complexes with different functional molecules or NPs. The materials of this Account are exclusively sourced from papers published since 2010.

2. FUNCTIONALIZATION FOR DRUG DELIVERY

Platinum anticancer drugs are vital for chemotherapy of various cancers. However, indiscriminate body distribution or poor tumor selectivity of these drugs has resulted in some severe side effects and drug resistance. Therefore, enhancing the tumor selectivity has become a major challenge in the development of platinum drugs.[9] Over the years, various drug targeting and delivery systems have been developed in an attempt to obtain tumor-selective platinum drugs that can be administered at lower doses with fewer side effects and higher efficacy. Targeted delivery rests on either an active strategy or a passive strategy or sometimes on both.

Active targeting is based on the specific interactions between drug molecules and cellular or tissular elements. It is fit for tumors containing biochemical entities whose quantity or functionality differs from those of normal tissues. In a typical active targeting system, the platinum pharmacophore is connected to the targeting group via a linker, and the targeting group would bring the drug to the tumor tissue by the specific binding affinity. Bioactive substances, such as bisphosphonates, peptides, hormones, and sugars, are often used to fulfill the targeting function.[10]

Passive targeting is achieved by taking advantage of the enhanced permeability and retention (EPR) effect in tumor tissues. Ideally, EPR effect is supposed to be applicable for any biocompatible macromolecules above 40 kDa. Owing to EPR effect, the drug concentration in tumor tissues can be 10−30 times higher than that in the blood; moreover, EPR effect can prolong the drug retention for several weeks or longer.[11] Thus, macromolecules and NPs within the size of a few hundred nanometers are frequently used to functionalize platinum complexes for tumor-targeted delivery. Nevertheless, the efficiency and universality of the EPR effect are controversial; especially in some types of cancers the EPR effect is not commonly observed, and small metastases (<100 mm^3) are poorly vascularized and do not evoke EPR.[12]

2.1. Functionalization with Bone-Targeting Bisphosphonate

Bisphosphonates (BPs) possess a high affinity for bone and other calcified tissues because of their ability to chelate calcium ions. Preclinical studies found that BPs could be absorbed onto bone surfaces and inhibit the osteoclastic resorption or tumor growth; hence they are potential bone-targeting carriers for platinum drugs. In our attempt to seek more specific platinum drugs, analogues of picoplatin (ZD0473), a developing drug candidate at phase III stage, were linked to a BP tetraethyl ester targeting carrier. The resultant complexes **1** and **3** demonstrate much higher cytotoxicity than **2** and **4** against human osteosarcoma MG-63 and ovarian cancer COC1 cell lines possibly due to the more appropriate length of the linker between Pt^{II} center and BP ester (Figure 2). Apoptotic assays revealed that the cell death mode induced by the most cytotoxic

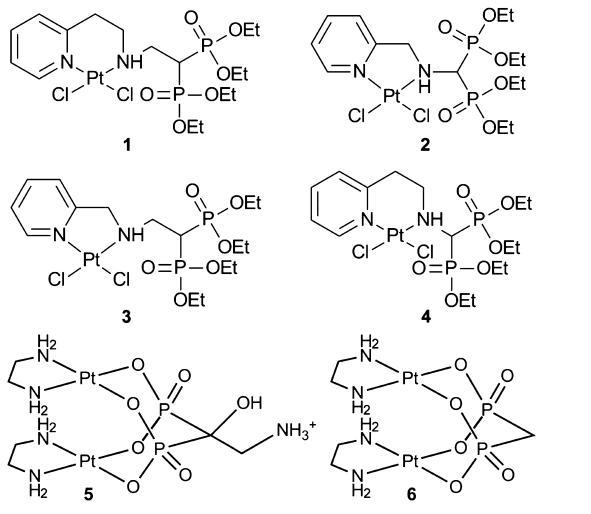


Figure 2. Bone-targeting platinum complexes **1**−**6**.

DOI: 10.1021/acs.accounts.5b00203
Acc. Chem. Res. 2015, 48, 2622−2631

3 is different from that induced by cisplatin. Complexes **1**−**4** hardly bind to DNA, which again differs from cisplatin. These complexes represent a new type of bone-targeting anticancer agents.[13] On the same idea, complexes **5** and **6** (Figure 2) were synthesized by Iafisco et al. They demonstrated that platinum drugs could be functionalized to yield a bone-filling delivery system, acting both as a bone substitute and as a drug releasing agent.[14]

2.2. Functionalization with Receptor-Specific Ligand

Peripheral benzodiazepine receptors (PBRs) or translocator protein (TSPO) lie primarily on the outer mitochondrial membrane and are involved in the control of apoptosis. TSPO-binding ligands may stimulate the opening of mitochondrial permeability transition pores and trigger the cascade of events leading to apoptosis. Interestingly, TSPOs are overexpressed in many tumor types, such as brain, liver, breast, and ovary cancers, with its overexpression grade correlating with the malignancy of the tumor. Thus, TSPO-binding ligands have been widely explored as carriers for receptor-mediated drug delivery. For example, the inert ligand of complexes **7** and **8** has a nanomolar specific affinity for TSPO (Figure 3). *In vitro*

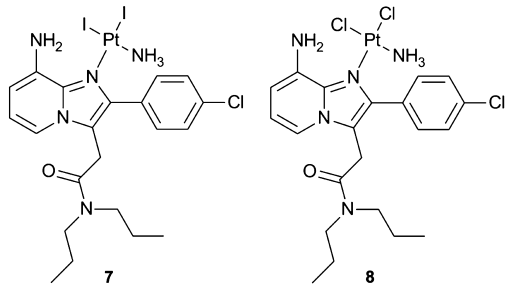


Figure 3. Structure of TSPO-specific platinum complexes **7** and **8**.

studies show that **7** and **8** maintain high affinity and selectivity for TSPO and are as cytotoxic as cisplatin against human and rat glioma cells. Moreover, they appear to be equally active against cisplatin-sensitive and -resistant A2780 cells. Similar to cisplatin, these complexes also induce apoptosis but show a 10−100-fold enhanced accumulation in glioma cells.[15]

2.3. Functionalization with Tumor-Targeting Peptide

Tumor-targeting peptides (TTPs) that are specific for tumor-related surface markers, such as membrane receptors, can be used to modify platinum complexes for tumor-targeted delivery. Peptides with RGD (Arg-Gly-Asp) or NGR (Asn-Gly-Arg) motifs are typical TTPs. RGD recognizes $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins, which are overexpressed in angiogenic blood vessels; NGR recognizes and binds to aminopeptidase N, which is overexpressed by endothelial cells of many tumors.[16]

Platinum(IV) complexes have two axial ligands, which provide the possibility of tethering other bioactive molecules or targeting groups to increase their functionality.[17] A recent report described the synthesis and biological evaluation of a Pt^{IV} prodrug whose two axial positions are functionalized with a cyclic RGD tripeptide and an apoptosis sensor, which is composed of tetraphenylsilole (TPS) fluorophore with aggregation-induced emission characteristics and an Asp-Glu-Val-Asp (DEVD) peptide specific to caspase-3 enzyme (Figure 4). The targeted Pt^{IV} prodrug can selectively bind to $\alpha_v\beta_3$ integrin overexpressing cancer cells to facilitate cellular uptake. Moreover, the conjugate can be reduced in cells to release the

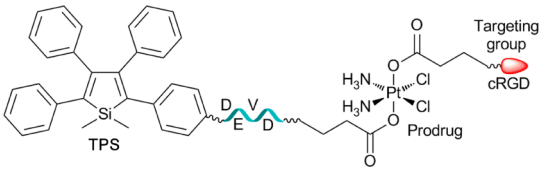


Figure 4. Structural motif of the $\alpha_v\beta_3$-targeted theranostic platinum(IV) prodrug with a built-in aggregation-induced emission light-up apoptosis sensor.

active Pt^{II} drug, that is, cisplatin, and the apoptosis sensor TPS-DEVD simultaneously. Cisplatin induces cell apoptosis and activates caspase-3 enzyme to cleave the DEVD peptide, generating the hydrophobic TPS residue. The TPS residue tends to aggregate, resulting in restriction of intramolecular rotations of the phenyl rings and ultimately leading to fluorescence enhancement.[18] Apparently, this design enables an early evaluation of the therapeutic responses to the drug.

More recently, a photoactivatable Pt^{IV} prodrug was conjugated to a cyclic RGD-containing peptide (Figure 5).

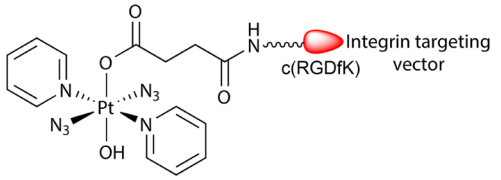


Figure 5. Schematic representation of the Pt−c(RGDfK) conjugate.

The Pt−c(RGDfK) conjugate can preferentially be internalized by SK-MEL-28 melanoma cancer cells overexpressing $\alpha_v\beta_3$ integrin. Upon visible light irradiation, higher phototoxicity was induced in SK-MEL-28 cells compared with control prostate carcinoma cells. An enhanced cell accumulation of the conjugate was also observed in MBA-MD-468 breast adenocarcinoma cells that highly express $\alpha_v\beta_5$ integrin. The novelty of this design resides in the use of a photoactivatable Pt^{IV} prodrug since irradiation with visible light directly in the tumor can trigger the release of cytotoxic Pt^{II} species from the internalized conjugate, thus achieving a dual control over the selectivity.[19]

Another example is chlorotoxin (CTX), which is a 36-residue peptide derived from the venom of the Israeli desert scorpion. CTX binds specifically to a chloride channel protein (CLC-3), which is highly expressed in gliomas, and also to annexin 2A, which is present on the surfaces of many cancer cell types.[20] Thus, CTX can be used to functionalize platinum complexes for cancer-targeted delivery (Figure 6). The cytotoxicity of complex **9** is greater than that of its Pt^{IV} precursor and CTX in several cancer cell lines. The greatest cytotoxicity appears in HeLa cells because they express both CLC-3 and annexin 2A on their surface.[21] Similarly, analogues of neurotensin (a

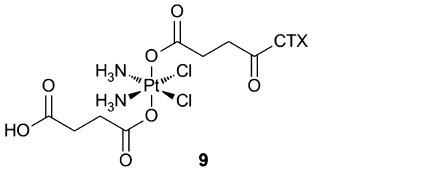


Figure 6. Peptide sequence of CTX and the structure of complex **9**.

DOI: 10.1021/acs.accounts.5b00203
Acc. Chem. Res. 2015, 48, 2622−2631

tridecapeptide) and somatostatin (a cyclic tetradecapeptide) have been conjugated to a platinum(IV) complex similar to the core of **9** for tumor-targeted delivery, because receptors of these two peptides are overexpressed in several human cancers.[22]

It should be noted that the targeting groups attached to platinum for receptor-mediated drug delivery must be extraordinarily sensitive because concentrations of biomolecules abnormally expressed in tumor tissues are very low. In addition, not all tumor cell types overexpress the same unique receptors, and the overexpressed receptors may also be present on normal tissues. Therefore, absolute targeting for cancer cells seems unattainable. In fact, many "tumor specific" target molecules such as receptors for folate and integrins also exist in normal cells, which may pose the risk of off-target binding and undesired side effects.

2.4. Functionalization with Polymer

Polymeric micelles are expected to enhance the accumulation of platinum drugs in tumor tissues by the EPR effect; they could protect platinum drugs from degradation, achieve controlled release in the delivery, and substantially improve the efficacy and reduce the side effects. Conjugate **10** is an acid-responsive drug delivery vehicle for cisplatin (Figure 7). It is

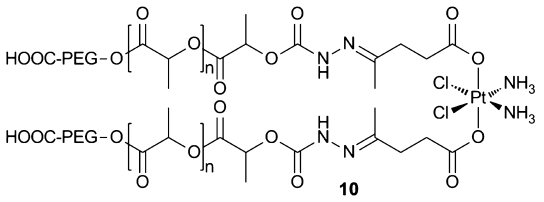


Figure 7. Structure of bi(PEG−PLA)−Pt(IV) conjugate **10**.

constructed by conjugating a Pt^{IV} prodrug with the hydrophobic segment of two biocompatible diblock copolymer chains through a pH-sensitive hydrazone bond. The conjugate readily precipitates to form sub-100 nm NPs in aqueous solution. The uniqueness of **10** lies in its different release profiles in different environments. During circulation, the nearly neutral pH (7.4) of the blood prevents any release of the drug. Upon entering cancer cells by endocytosis, the acidic endosomal pH (5−6) stimulates a rapid release of the drug in high doses, which could suppress the chemoresistance of cancer cells and thereby improve the therapeutic efficacy of the drug. This conjugate shows an enhanced *in vitro* cytotoxicity compared with cisplatin.[23] A similar drug delivery system for cisplatin is constructed by conjugating a Pt^{II} moiety with glucosamine-functionalized polyisobutylene−maleic acid. The conjugate self-assembles into a NP, which releases cisplatin in a pH-dependent manner. The NPs are rapidly internalized into the endolysosomal compartment of cancer cells (pH 5.5) and exhibit significantly improved antitumor efficacy in terms of tumor growth delay in breast and lung cancers and tumor regression in an ovarian cancer model. Furthermore, the systemic and nephrotoxicity is decreased.[24]

2.5. Functionalization with Nanoparticles

NPs can reach solid tumors via the EPR effect and hence change the pharmacokinetics of the loaded drugs, which would significantly improve their specificity for tumor tissues. The release kinetics of drug molecules from NPs can be controlled by internal and external stimuli. NP-based delivery possesses many advantages, such as enhanced drug accumulation and sustained drug release in tumor tissues. Besides, NPs can carry large payloads of platinum drugs and protect them from degradation and thereby prolong the blood circulation time and shield the body from systemic toxicity. Surface-functionalized NPs by bioactive molecules can further increase the specificity of platinum drugs for cancer cells.[25] The different processes by which NPs enter cancer cells offer the possibility of bypassing standard multidrug resistance mechanisms.[26,27] Therefore, functionalizing platinum complexes with NPs is a promising approach to develop more efficient and selective anticancer drugs for overcoming the intrinsic limitations.[28]

In recent years, gold nanoparticles (AuNPs) have attracted much attention for their use in medicine because they are inert, biocompatible, and easily prepared and functionalized.[29] Poly(ethylene glycol) (PEG)-modified AuNPs have been used to functionalize cisplatin[30] or oxaliplatin. For example, the active component of oxaliplatin has been tethered to AuNPs that are functionalized with a thiolated PEG monolayer capped with a carboxylate group (Figure 8). The platinum-

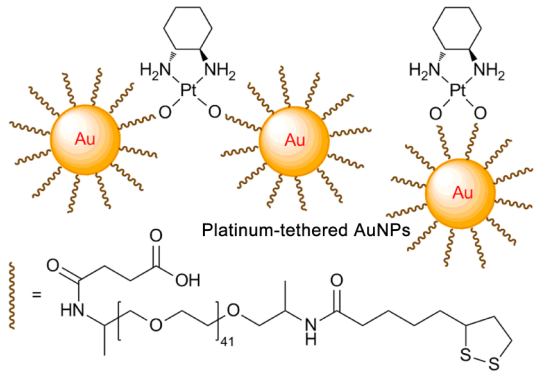


Figure 8. Binding mode of thiolate−PEG−Au NPs with the oxaliplatin fragment.

tethered NPs demonstrate comparable or significantly higher cytotoxicity than oxaliplatin against the A549 lung epithelial cancer and several colon cancer cell lines. Particularly, they show an unusual ability to penetrate the nucleus in the lung cancer cells.[31]

Carboplatin has also been conjugated onto AuNPs containing an FDA approved antiepidermal growth factor receptor (EGFR) antibody, cetuximab, for the treatment of EGFR overexpressing cancers, such as colorectal, lung, pancreatic, and ovarian cancers. The nanoconjugate shows an enhanced therapeutic efficacy toward both $EGFR^+$ A549 lung and OVCAR5 ovarian cancer cell lines compared with its nontargeted counterpart.[32]

Increased cellular uptake of folic acid (FA) and overexpression of folate receptor (FR) are biochemical characters of many tumor types. Therefore, FR has become an important target for anticancer agents. A AuNP-based drug delivery system consisting of FA, mercapto-PEG (PSH), and cisplatin (CP) has been prepared for potential application in ovarian cancer therapy. Au−PSH−CP−FA not only retains the cytotoxic effect of cisplatin on the tumor cells but also protects the normal cells from the cytotoxic insult.[33]

Gold nanorods (AuNRs) are even more attractive vehicles than AuNPs due to their longer circulation time compared with spherical NPs. Hence Pt^{IV} prodrug *c,c,t*-$[Pt(NH_3)_2Cl_2(O_2CCH_2CH_2CO_2H)_2]$ has been anchored to PEGylated AuNRs bearing surface amine groups. Compared with cisplatin, the conjugate shows an enhanced cellular

DOI: 10.1021/acs.accounts.5b00203
Acc. Chem. Res. 2015, 48, 2622−2631

accumulation and superior cytotoxicity (10−65-fold) against HeLa, A549, and MCF-7 cancer cell lines.[34] More interestingly, the conjugate is able to overcome the drug resistance in cisplatin-resistant A549R cells because it gets into cells through endocytosis and low expression of copper transport protein in A549R cells does not affect its uptake.[35]

A major limitation for nanodrugs is their rapid clearance by the reticuloendothelial system (RES), which can increase their toxicity to the off-target organs and reduce their efficacy. In fact, the total accumulation of nanodrugs in tumor tissues only represents a small fraction of total injected dose (1−10%); the majority (40−80%) of the injected nanodrugs ends up in the liver and spleen.[36] The size of NPs strongly affects their biodistribution. For different NPs, a 50 nm diameter is optimal to maximize the rate of uptake and intracellular concentration in certain mammalian cells.[37]

3. FUNCTIONALIZATION FOR CONCURRENT THERAPY AND DIAGNOSIS

3.1. Functionalization with Magnetic Iron Oxide Nanoparticles

Magnetic NPs are promising drug targeting carriers because they could guide drugs preferentially to the biological target through external magnets and hence diminish the damage to normal tissues. Superparamagnetic iron oxide NPs (SPIONs) are especially attractive because of their biocompatibility, biodegradability, aqueous dispersibility, and magnetizability. In addition, SPIONs can provide a strong negative contrast effect in T_2-weighted magnetic resonance imaging (MRI). After modification with biocompatible materials, functional ligands, or therapeutic units, they may form theranostic agents for simultaneous therapy and diagnosis.[38,39]

Four years ago, we fabricated the carboxymethylcellulose-modified superparamagnetic magnetite nanocrystal clusters (CMC-SPMNCs) as nanocarriers for platinum drugs.[40] Later on, we tethered *cis*-$[Pt(NH_3)_2Cl]^+$ (dechlorinated cisplatin, CMDP) to maghemite NPs modified with 4-oxo-4-(3-(triethoxysilyl)propylamino)butanoic acid (OTPBA-SPION) through the surface carboxylate groups (Figure 9). The DNA binding ability of CMDP−OTPBA-SPION is prominent in acidic medium (pH 5.2) but is insignificant under normal physiological conditions (pH 7.4), suggesting that the acidic cancerous milieu is favorable for the release of the platinum pharmacophore from the composite. The cytotoxicity of the composite toward MCF-7 and HeLa cancer cells displays slow and time-dependent characteristics, reaching a level comparable to that of cisplatin at 72 h. The diagnostic capability and tumor-specific accumulation of the composite are verified by the time-dependent T_2-weighted MRI using MCF-7 cells and tumor-bearing mice (Figure 9), respectively. CMDP−OTPBA-SPION shows the potential for simultaneous therapy and MRI under an external magnetic field.[41]

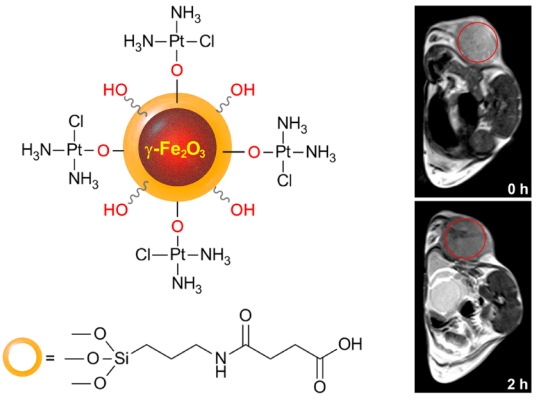


Figure 9. Schematic illustration of CMDP−OTPBA-SPION and the T_2-weighted MRI of RM1 murine prostate cancer (red circles) implanted in C57BL/6J mice in the presence of CMDP−OTPBA-SPION (5.0 mg kg^{-1}) and an external magnetic field. Adapted from ref 41.

Furthermore, we developed a fluorescent nanoconstruct for the specific therapy and tracing of platinum drugs. The composite is comprised of SPION (γ-Fe_2O_3), rhodamine 6G (R6G), silica, OTPBA, and CMDP (Figure 10). CMDP−OTPBA−R6G−SPION is more cytotoxic than cisplatin toward cisplatin-resistant A549R cells and thus demonstrates great potential for overcoming the drug resistance to cisplatin. The high cytotoxicity may result from the enhanced cellular accumulation. Moreover, the cellular distribution and accumulation of the drug entity can be monitored by confocal fluorescence imaging *in vitro* and *in vivo*. This multifunctional nanocomposite offers an alternative approach to the "see and treat" strategy for cancer treatment.[42] Regrettably, although silica is a common choice to encompass the NPs due to perceived biocompatibility and facile manipulation,[43,44] some studies noted that it can be toxic.[45] In addition, long-term exclusion of silica from human body remains unknown.

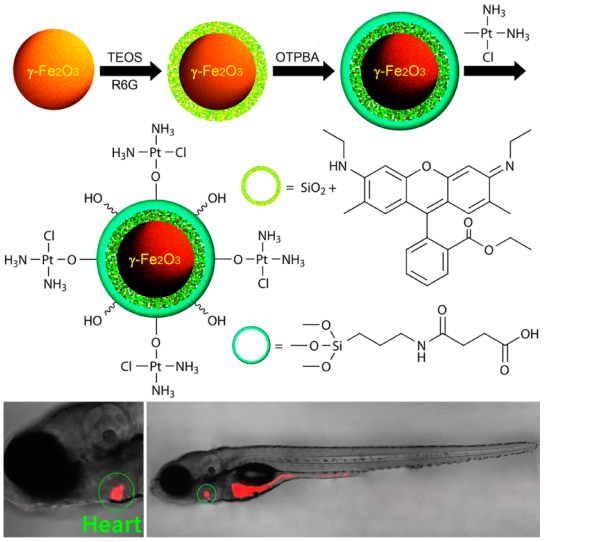


Figure 10. Synthesis of CMDP−OTPBA−R6G−SPION and the confocal fluorescence images of a 5-day-old zebrafish larva after incubation in distilled water containing CMDP−OTPBA−R6G−SPION (24 $\mu g\ mL^{-1}$) for 10 h. Adapted from ref 42.

3.2. Functionalization with Upconversion Nanoparticles

Upconversion nanoparticles (UCNPs) have been used for various bioimaging and biodetection.[46] Due to their excellent optical and chemical properties, platinum(IV) complexes have been attached to UCNPs to achieve tumor-specific therapy and diagnosis. For example, a nanocomposite that combines upconversion luminescence (UCL)/magnetic resonance (MR)/computer tomography (CT) trimodality imaging and near-infrared (NIR)-activated platinum prodrug delivery was described recently (Figure 11). The core−shell structured UCNPs were used for drug delivery and for both *in vitro* and *in*

DOI: 10.1021/acs.accounts.5b00203
Acc. Chem. Res. 2015, 48, 2622−2631

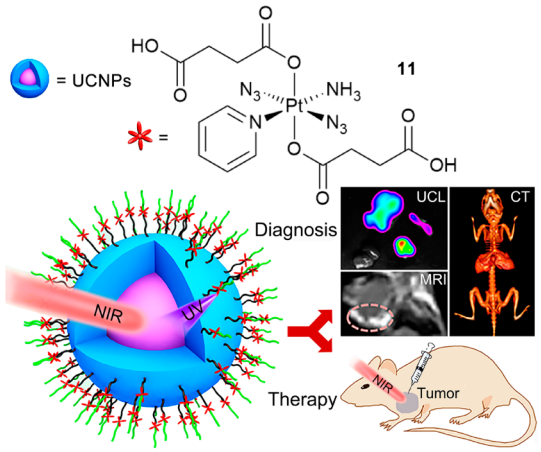


Figure 11. Structure of complex **11** and a schematic illustration showing the diagnostic and therapeutic effects of UCNP−**11**−PEG on animal models. Adapted from ref 47.

vivo NIR-to-NIR UCL, T_1-weighted MR, and CT imaging. The Pt^{IV} prodrug **11** was conjugated with the free amine of polyethylenimine on the surface of UCNPs as the anticancer pharmacophore. And UCNP−**11** was then coated with a monolayer of PEG to reduce the immunogenicity and antigenicity from the host's immune system. The prodrug can be activated to highly toxic Pt^{II} complexes via the NIR-to-UV strategy. The mice treated with UCNP−**11**−PEG under NIR irradiation demonstrated better inhibition of tumor growth than that under direct UV irradiation. This nanocomposite could be used as a multimodality imaging contrast agent and as an anticancer agent by converting NIR light into UV emission to release the drug activity in cancer therapy.[47] Coincidentally, a similar NIR light-activated nanocomposite composed of a Pt^{IV} prodrug, a peptide probe, and UCNPs was designed later for the remote control of prodrug activation and real-time imaging of apoptosis.[48]

3.3. Functionalization with Gadolinium-Based Contrast Agent

Among all the imaging modalities, MRI is especially useful for imaging tumors. We noted in section 3.1 that SPIONs have been adopted as T_2-weighted MRI contrast agents for tracing the distribution of platinum drugs. The following example shows that paramagnetic gadolinium(III) complexes as T_1-weighted MRI contrast agents have also been incorporated into platinum complexes for simultaneous imaging and therapy. Recently, we attached cationic Pt^{II} complex *cis*-$[Pt(NH_3)_2(py)Cl]^+$ (py is a pyridyl ligand) to the derivatives of gadolinium−diethylenetriaminepentaacetic acid (Gd-DTPA), a clinical T_1-weighted MRI contrast agent, obtaining multifunctional Pt−Gd complexes **12** and **13** for theranostic purposes (Figure 12). These complexes partially dissociate in cancer cells to provide cytostatic Pt moieties, while the residual Gd component and the untouched complexes perform the imaging function. The Pt units interact with DNA and significantly promote the cellular uptake of Gd complexes. The cytotoxicity of **12** and **13** is comparable to that of cisplatin at imaging concentrations (≥0.1 mM), and their proton relaxivity is higher than that of Gd−DTPA. MRI on mice demonstrates that these complexes can reveal the accumulation of platinum drugs *in vivo*. Furthermore, they display excellent biocompatibility. The relatively low cytotoxicity enables them to satisfy the tumor-imaging and inhibition requirements at the same dose. Therefore, they are

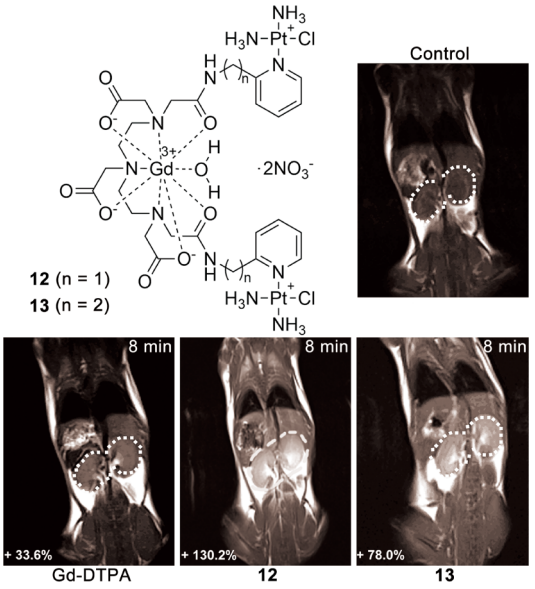


Figure 12. Chemical structure of Pt−Gd complexes and the T_1-weighted MR images of B6 mice at 8 min after the injection of Gd−DTPA, **12**, and **13** at a dose of 0.1 mmol Gd^{III}/kg of body weight. The circles indicate the area of the kidneys. Adapted from ref 49.

potential theranostic agents for simultaneous drug tracing and cancer inhibition.[49]

Integration of imaging functionality into a nanoscale drug carrier offers a promising theranostic platform for more effective cancer chemotherapy.[50] For instance, a fragment of oxaliplatin and Gd-DTPA were incorporated into the core of the micelles formed by poly(ethylene glycol)-*b*-poly(glutamic acid) through reversible complexation. The polymeric micellar system not only improves the efficacy and safety of the incorporated drugs but also assists in the real-time monitoring of the drug distribution and accumulation in the body.[51] A similar strategy was also used to functionalize platinum(IV) complexes.[52]

4. FUNCTIONALIZATION FOR OTHER PURPOSES

Aside from antitumor activity, platinum complexes also possess other biological activities, such as enzymatic activity,[53] antibacterial activity,[54] antimycobacterial activity,[55] and anti-amyloid activity.[56] The most interesting property might be their inhibitory activity against the aggregation of amyloid-β peptide (Aβ), which may lead to new drugs for the treatment or prevention of Alzheimer's disease (AD). Aβ has a high affinity for metal ions such as Zn^{2+} and Cu^{2+}, which basically accounts for the Aβ aggregation in the brain and related neurotoxicity. Chelators are potential therapeutic agents for AD because they could sequester metal ions from the Aβ aggregates and reverse the aggregation. Thus, we developed two macrocyclic platiniferous chelators, **14** and **15**, as inhibitors of the metal-induced Aβ aggregation, with cyclen being the metal-chelating unit and Pt(bipyridine)Cl_2 being the Aβ-binding unit (Figure 13). The platinum center can coordinate with histidine residues of Aβ, which would prevent them from reaction with Zn^{2+} and Cu^{2+} ions. The inhibition of **14** and **15** against Aβ aggregation induced by Zn^{2+} and Cu^{2+} is significant and more effective than that exerted by cyclen. By contrast, cisplatin exhibits no inhibition against Aβ aggregation. The chelators also suppress the Cu−Aβ mediated generation of reactive oxygen species and

DOI: 10.1021/acs.accounts.5b00203
Acc. Chem. Res. 2015, 48, 2622−2631

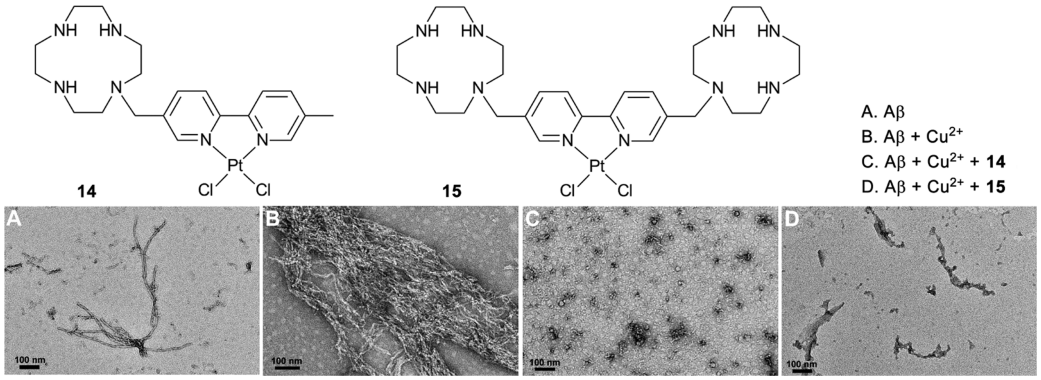


Figure 13. Structure of platiniferous chelators and TEM images of Aβ40 and Cu^{2+}-treated Aβ40 samples in the absence and presence of **14** or **15** after incubation for 24 h. Adapted from ref 57.

their neurotoxicity in cortical neuronal cells of mice and reduce the extent of Aβ aggregation in the brain homogenates of transgenic mice. These cyclen-functionalized platinum complexes may work through a dual mechanism involving metal chelation and peptide modification to interfere with Aβ aggregation.[57]

In some cases, other therapeutic modalities are incorporated into Pt-based chemotherapy in order to obtain synergistic effects. For example, photodynamic therapy (PDT) eradicates cancer cells mainly by singlet oxygen ($^1O_2$) generated through the combined action of photosensitizer, light, and molecular oxygen.[58] Recently, supramolecular self-assembled NPs that can overcome cisplatin resistance were constructed (Figure 14).

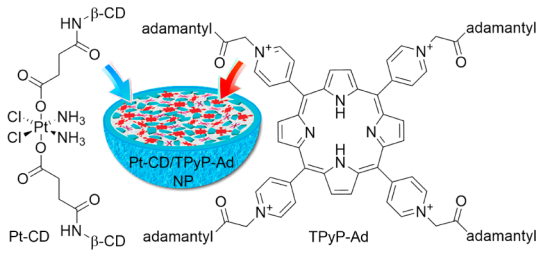


Figure 14. Schematic representation of the supramolecular self-assembled NP by Pt−CD and TPyP−Ad. Adapted from ref 59.

The host molecule Pt−CD is a Pt^{IV} prodrug bridged β-cyclodextrin (β-CD) dimer, and the guest molecule TPyP−Ad is an adamantyl-modified photosensitizer porphyrin. Pt−CD and TPyP−Ad not only serve as the building blocks but also as the cargos of the drug delivery system. The Pt cellular uptake of the Pt−CD/TPyP−Ad NPs is much higher than that of cisplatin, and visible light irradiation can induce the rise of cellular reactive oxygen species (ROS). The cytotoxicity of Pt−CD is quite low with or without light irradiation. TPyP−Ad only shows moderate cytotoxicity after light irradiation due to the PDT effect, whereas Pt−CD/TPyP−Ad NPs exhibit strong cytotoxicity toward A549R cells after light irradiation. Thus, a synergistic antiproliferative effect of Pt−CD and TPyP−Ad against cisplatin-resistant A549R cells is achieved by this strategy.[59] Conjugates of photosensitizers zinc(II) phthalocyanine and porphyrin with platinum complexes are designed on the same mechanism.[60,61] And the newly reported immunochemotherapeutic Pt-based agent is a combination of chemotherapy with immunotherapy.[62] In these multimodal anticancer systems, platinum drugs are more likely to avoid standard resistance mechanisms.

Last but not least, in the past few years many researchers,[63−65] including us,[66] have designed various luminescent platinum complexes for bioimaging applications. Readers who are interested in this aspect are advised to read more special reviews.[67,68]

5. CONCLUSIONS

Platinum complexes are versatile and adaptable compounds. Besides their established roles as anticancer drugs, some new possibilities have been explored and developed in recent years by functionalizing with bioactive molecules or nanomaterials. Such functionalization has given birth to many multifunctional platinum complexes, such as targeted anticancer drugs and detectable theranostic agents. This account summarized the representative achievements accomplished in this area in the past 5 years. We briefly depicted diverse strategies that can be used to highlight or complement the properties of platinum complexes for targeted drug delivery, for real-time imaging, for anticancer or anti-AD therapy, etc. From these examples, we conclude that functionalization of platinum complexes could create many opportunities to obtain innovative platinum agents for biomedical applications. Nevertheless, we have to note that after more than 40 years development, platinum anticancer drugs are still beset by systemic toxicities and drug resistance. Without doubt, the lack of tumor specificity is at the root of the problem. Nowadays, although various tumor-targeted delivery systems for platinum drugs have been proposed based on NPs, delivery of these nanoconstructs *in vivo* to the target site is still suboptimal due to RES clearance. Therefore, in the coming years improving tumor selectivity continues to be a major challenge for platinum complexes. For the development of platinum-based theranostic agents, a few fundamental challenges need to be taken into account. The first is the pharmacokinetics. In many cases when a multimodality imaging agent is imaged by one modality, its pharmacokinetics does not allow imaging by another modality, because the optimal time window and concentration for different imaging modalities differ from each other. The second is the dosage for imaging is usually inconsistent with that for therapy. The right ratio of the diagnostic component to the platinum therapeutic component may not always be realized in a composite suitable for the practical application. The third is the general toxicity of the theranostic composites or multimodality NPs, which remains poorly understood up to now. From the current trends, we can

DOI: 10.1021/acs.accounts.5b00203
Acc. Chem. Res. 2015, 48, 2622−2631

envision that platinum-loaded nanoconstructs will become smarter and more sophisticated by releasing the payloads in a more controlled manner in time and location, and the dream of devising ultrafunctional platinum complexes with all the desired functions hiding in one system will become true in the future. Nevertheless, adding new functionality would elevate the complexity of preparation, purification, and characterization, and the cost and regulatory barriers would rise. Therefore, as we set out to functionalize a simple platinum complex into a multifunctional entity, we had better make a reasonable balance between the ideal and reality.

AUTHOR INFORMATION

Corresponding Authors

*Fax: 86 25 83314502. Tel: 86 25 83594549. E-mail: boxwxy@nju.edu.cn.

*Fax: 86 25 83314502. Tel: 86 25 83594549. E-mail: zguo@nju.edu.cn.

Funding

We acknowledge the financial support from the National Natural Science Foundation of China (Grant Nos. 21271101, 21131003, 21301090, 91213305, 91413116, and 21361140352), the National Basic Research Program of China (Grant Nos. 2015CB856300 and 2011CB935800), and the Natural Science Foundation of Jiangsu Province (Grant No. BK20130923).

Notes

The authors declare no competing financial interest.

Biographies

Xiaoyong Wang is a professor of biochemistry at the State Key Laboratory of Pharmaceutical Biotechnology, School of Life Sciences, Nanjing University. He received his B.Sc. degree in chemistry in 1986 at Northwest Normal University, M.M.Sc. degree in medicinal chemistry in 1994 at Shandong University, and Ph.D. degree in 2003 at Nanjing University, where he completed postdoctoral research in 2005. His research interests mainly lie in the domain of inorganic medicinal chemistry and chemical biology, particularly in the design and mechanism of metal-based anticancer drugs.

Xiaohui Wang is an assistant professor at the College of Chemistry and Molecular Engineering, Nanjing Tech University. He received his Ph.D. degree from Nanjing University under the supervision of Professor Zijian Guo in 2012, majoring in bioinorganic chemistry and inorganic medicinal chemistry. His current research is focused on developing small functional molecules as imaging, therapeutic, and theranostic agents for cancers and Alzheimer's disease and as luminescent probes for biomolecules.

Zijian Guo is a professor of chemistry at the State Key Laboratory of Coordination Chemistry, School of Chemistry and Chemical Engineering, Nanjing University. He received his Ph.D. degree from the University of Padua in 1994 and engaged in postdoctoral research at the University of London, the University of British Columbia, and the University of Edinburgh from 1994 to 1999. His research covers several subjects in the field of bioinorganic chemistry and chemical biology, including metal-based anticancer complexes, fluorescent probes, and mechanism of action of metallodrugs.

REFERENCES

(1) Kaluđerović, G. N.; Paschke, R. Anticancer metallotherapeutics in preclinical development. *Curr. Med. Chem.* **2011**, *18*, 4738−4752.

(2) Wheate, N. J.; Walker, S.; Craig, G. E.; Oun, R. The status of platinum anticancer drugs in the clinic and in clinical trials. *Dalton Trans.* **2010**, *39*, 8113−8127.

(3) Wang, X. Y.; Guo, Z. J. New trends and future developments of Pt-based antitumor drugs. In *Bioinorganic Medicinal Chemistry*; Alessio, E., Ed.; WILEY-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2011; pp 97−149.

(4) Burger, H.; Loos, W. J.; Eechoute, K.; Verweij, J.; Mathijssen, R. H. J.; Wiemer, E. A. C. Drug transporters of platinum-based anticancer agents and their clinical significance. *Drug Resist. Updates* **2011**, *14*, 22−34.

(5) Harper, B. W.; Krause-Heuer, A. M.; Grant, M. P.; Manohar, M.; Garbutcheon-Singh, K. B.; Aldrich-Wright, J. R. Advances in platinum chemotherapeutics. *Chem. - Eur. J.* **2010**, *16*, 7064−7077.

(6) Xue, X.; You, S.; Zhang, Q.; Wu, Y.; Zou, G.-Z.; Wang, P. C.; Zhao, Y.-L.; Xu, Y.; Jia, L.; Zhang, X. N.; Liang, X.-J. Mitaplatin increases sensitivity of tumor cells to cisplatin by inducing mitochondrial dysfunction. *Mol. Pharmaceutics* **2012**, *9*, 634−644.

(7) Yang, J.; Sun, X. R.; Mao, W. W.; Sui, M. H.; Tang, J. B.; Shen, Y. Q. Conjugate of Pt(IV)−histone deacetylase inhibitor as a prodrug for cancer chemotherapy. *Mol. Pharmaceutics* **2012**, *9*, 2793−2800.

(8) Kenche, V. B.; Hung, L. W.; Perez, K.; Volitakes, I.; Ciccotosto, G.; Kwok, J.; Critch, N.; Sherratt, N.; Cortes, M.; Lal, V.; Masters, C. L.; Murakami, K.; Cappai, R.; Adlard, P. A.; Barnham, K. J. Development of a platinum complex as an anti-amyloid agent for the therapy of Alzheimer's disease. *Angew. Chem., Int. Ed.* **2013**, *52*, 3374−3378.

(9) Wang, X. Y. Fresh platinum complexes with promising antitumor activity. *Anticancer Agents Med. Chem.* **2010**, *10*, 396−411.

(10) Wang, X. Y.; Guo, Z. J. Targeting and delivery of Pt-based anticancer drugs. *Chem. Soc. Rev.* **2013**, *42*, 202−224.

(11) Fang, J.; Nakamura, H.; Maeda, H. The EPR effect: Unique features of tumor blood vessels for drug delivery, factors involved, and limitations and augmentation of the effect. *Adv. Drug Delivery Rev.* **2011**, *63*, 136−151.

(12) Adiseshaiah, P. P.; Hall, J. B.; McNeil, S. E. Nanomaterial standards for efficacy and toxicity assessment. *Wiley Interdiscip. Rev. −Nanomed. Nanobiotechnol.* **2010**, *2*, 99−112.

(13) Xue, Z. Q.; Lin, M. X.; Zhu, J. H.; Zhang, J. F.; Li, Y. Z.; Guo, Z. J. Platinum(II) compounds bearing bone-targeting group: synthesis, crystal structure and antitumor activity. *Chem. Commun.* **2010**, *46*, 1212−1214.

(14) Iafisco, M.; Palazzo, B.; Martra, G.; Margiotta, N.; Piccinonna, S.; Natile, G.; Gandin, V.; Marzano, C.; Roveri, N. Nanocrystalline carbonate-apatites: role of Ca/P ratio on the upload and release of anticancer platinum bisphosphonates. *Nanoscale* **2012**, *4*, 206−217.

(15) Margiotta, N.; Denora, N.; Ostuni, R.; Laquintana, V.; Anderson, A.; Johnson, S. W.; Trapani, G.; Natile, G. Platinum(II) complexes with bioactive carrier ligands having high affinity for the translocator protein. *J. Med. Chem.* **2010**, *53*, 5144−5154.

(16) Boohaker, R. J.; Lee, M. W.; Vishnubhotla, P.; Perez, J. M.; Khaled, A. R. The use of therapeutic peptides to target and to kill cancer cells. *Curr. Med. Chem.* **2012**, *19*, 3794−3804.

(17) Chin, C. F.; Wong, D. Y. Q.; Jothibasu, R.; Ang, W. H. Anticancer platinum(IV) prodrugs with novel modes of activity. *Curr. Top. Med. Chem.* **2011**, *11*, 2602−2612.

(18) Yuan, Y.; Kwok, R. T. K.; Tang, B. Z.; Liu, B. Targeted theranostic platinum(IV) prodrug with a built-in aggregation-induced emission light-up apoptosis sensor for noninvasive early evaluation of its therapeutic responses in situ. *J. Am. Chem. Soc.* **2014**, *136*, 2546−2554.

(19) Gandioso, A.; Shaili, E.; Massaguer, A.; Artigas, G.; González-Cantó, A.; Woods, J. A.; Sadler, P. J.; Marchán, V. An integrin-targeted photoactivatable Pt(IV) complex as a selective anticancer pro-drug: synthesis and photoactivation studies. *Chem. Commun.* **2015**, *51*, 9169−9172.

(20) Kesavan, K.; Ratliff, J.; Johnson, E. W.; Dahlberg, W.; Asara, J. M.; Misra, P.; Frangioni, J. V.; Jacoby, D. B. Annexin A2 is a molecular

DOI: 10.1021/acs.accounts.5b00203
Acc. Chem. Res. 2015, 48, 2622−2631

target for TM601, a peptide with tumor-targeting and anti-angiogenic effects. *J. Biol. Chem.* **2010**, *285*, 4366−4374.
(21) Graf, N.; Mokhtari, T. E.; Papayannopoulos, I. A.; Lippard, S. J. Platinum(IV)-chlorotoxin (CTX) conjugates for targeting cancer cells. *J. Inorg. Biochem.* **2012**, *110*, 58−63.
(22) Gaviglio, L.; Gross, A.; Metzler-Nolte, N.; Ravera, M. Synthesis and *in vitro* cytotoxicity of *cis,cis,trans*-diamminedichloridodisuccinatoplatinum(IV)−peptide bioconjugates. *Metallomics* **2012**, *4*, 260−266.
(23) Aryal, S.; Hu, C. -M. J.; Zhang, L. F. Polymer−cisplatin conjugate nanoparticles for acid-responsive drug delivery. *ACS Nano* **2010**, *4*, 251−258.
(24) Paraskar, A. S.; Soni, S.; Chin, K. T.; Chaudhuri, P.; Muto, K. W.; Berkowitz, J.; Handlogten, M. W.; Alves, N. J.; Bilgicer, B.; Dinulescu, D. M.; Mashelkar, R. A.; Sengupta, S. Harnessing structure-activity relationship to engineer a cisplatin nanoparticle for enhanced antitumor efficacy. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 12435−12440.
(25) Peng, X.-H.; Wang, Y. Q.; Huang, D. H.; Wang, Y. X.; Shin, H. J.; Chen, Z. J.; Spewak, M. B.; Mao, H.; Wang, X.; Wang, Y.; Chen, Z.; Nie, S. M.; Shin, D. M. Targeted delivery of cisplatin to lung cancer using ScFvEGFR-heparin-cisplatin nanoparticles. *ACS Nano* **2011**, *5*, 9480−9493.
(26) Verma, A.; Stellacci, F. Effect of surface properties on nanoparticle−cell interactions. *Small* **2010**, *6*, 12−21.
(27) Xue, X.; Hall, M. D.; Zhang, Q.; Wang, P. C.; Gottesman, M. M.; Liang, X.-J. Nanoscale drug delivery platforms overcome platinum-based resistance in cancer cells due to abnormal membrane protein trafficking. *ACS Nano* **2013**, *7*, 10452−10464.
(28) Oberoi, H. S.; Nukolova, N. V.; Kabanov, A. V.; Bronich, T. K. Nanocarriers for delivery of platinum anticancer drugs. *Adv. Drug Delivery Rev.* **2013**, *65*, 1667−1685.
(29) Giljohann, D. A.; Seferos, D. S.; Daniel, W. L.; Massich, M. D.; Patel, P. C.; Mirkin, C. A. Gold nanoparticles for biology and medicine. *Angew. Chem., Int. Ed.* **2010**, *49*, 3280−3294.
(30) Craig, G. E.; Brown, S. D.; Lamprou, D. A.; Graham, D.; Wheate, N. J. Cisplatin-tethered gold nanoparticles that exhibit enhanced reproducibility, drug loading, and stability: a step closer to pharmaceutical approval? *Inorg. Chem.* **2012**, *51*, 3490−3497.
(31) Brown, S. D.; Nativo, P.; Smith, J.-A.; Stirling, D.; Edwards, P. R.; Venugopal, B.; Flint, D. J.; Plumb, J. A.; Graham, D.; Wheate, N. J. Gold nanoparticles for the improved anticancer drug delivery of the active component of oxaliplatin. *J. Am. Chem. Soc.* **2010**, *132*, 4678−4684.
(32) Bhattacharyya, S.; Gonzalez, M.; Robertson, J. D.; Bhattacharya, R.; Mukherjee, P. A simple synthesis of a targeted drug delivery system with enhanced cytotoxicity. *Chem. Commun.* **2011**, *47*, 8530−8532.
(33) Patra, C. R.; Bhattacharya, R.; Mukherjee, P. Fabrication and functional characterization of goldnanoconjugates for potential application in ovarian cancer. *J. Mater. Chem.* **2010**, *20*, 547−554.
(34) Min, Y. Z.; Mao, C. Q.; Xu, D. C.; Wang, J.; Liu, Y. Z. Gold nanorods for platinum based prodrug delivery. *Chem. Commun.* **2010**, *46*, 8424−8426.
(35) Min, Y. Z.; Mao, C.-Q.; Chen, S. M.; Ma, G. L.; Wang, J.; Liu, Y. Z. Combating the drug resistance of cisplatin using a platinum prodrug based delivery system. *Angew. Chem., Int. Ed.* **2012**, *51*, 6742−6747.
(36) Liu, L.; Ye, Q.; Lu, M.; Lo, Y.-C.; Hsu, Y.-H.; Wei, M.-C.; Chen, Y.-H.; Lo, S.-C.; Wang, S.-J.; Bain, D. J.; Ho, C. A new approach to reduce toxicities and to improve bioavailabilities of platinum-containing anti-cancer nanodrugs. *Sci. Rep.* **2015**, *5*, 10881.
(37) Albanese, A.; Tang, P. S.; Chan, W. C. W. The effect of nanoparticle size, shape, and surface chemistry on biological systems. *Annu. Rev. Biomed. Eng.* **2012**, *14*, 1−16.
(38) Hao, R.; Xing, R. J.; Xu, Z. C.; Hou, Y. L.; Gao, S.; Sun, S. H. Synthesis, functionalization, and biomedical applications of multifunctional magnetic nanoparticles. *Adv. Mater.* **2010**, *22*, 2729−2742.
(39) Cho, H.-S.; Dong, Z.; Pauletti, G. M.; Zhang, J.; Xu, H.; Gu, H.; Wang, L.; Ewing, R. C.; Huth, C.; Wang, F.; Shi, D. Fluorescent, superparamagnetic nanospheres for drug storage, targeting, and imaging: A multifunctional nanocarrier system for cancer diagnosis and treatment. *ACS Nano* **2010**, *4*, 5398−5404.
(40) Xing, R. M.; Wang, X. Y.; Zhang, C. L.; Wang, J. Z.; Zhang, Y. M.; Song, Y.; Guo, Z. J. Superparamagnetic magnetite nanocrystal clusters as potential magnetic carriers for the delivery of platinum anticancer drugs. *J. Mater. Chem.* **2011**, *21*, 11142−11149.
(41) Wang, J. Z.; Wang, X. Y.; Song, Y. J.; Wang, J.; Zhang, C. L.; Chang, C. J.; Yan, J.; Qiu, L.; Wu, M. M.; Guo, Z. J. A platinum anticancer theranostic agent with magnetic targeting potential derived from maghemite nanoparticles. *Chem. Sci.* **2013**, *4*, 2605−2612.
(42) Wang, J. Z.; Wang, X. Y.; Song, Y. J.; Zhu, C. C.; Wang, J.; Wang, K.; Guo, Z. J. Detecting and delivering platinum anticancer drugs using fluorescent maghemite nanoparticles. *Chem. Commun.* **2013**, *49*, 2786−2788.
(43) Vivero-Escoto, J. L.; Huxford-Phillips, R. C.; Lin, W. Silica-based nanoprobes for biomedical imaging and theranostic applications. *Chem. Soc. Rev.* **2012**, *41*, 2673−2685.
(44) Peng, F.; Su, Y. Y.; Zhong, Y. L.; Fan, C. H.; Lee, S.-T.; He, Y. Silicon nanomaterials platform for bioimaging, biosensing, and cancer therapy. *Acc. Chem. Res.* **2014**, *47*, 612−623.
(45) Zhu, X. M.; Wang, Y. X. J.; Leung, K. C. F.; Lee, S. F.; Zhao, F.; Wang, D. W.; Lai, J. M. Y.; Wan, C.; Cheng, C. H. K.; Ahuja, A. T. Enhanced cellular uptake of aminosilane-coated superparamagnetic iron oxide nanoparticles in mammalian cell lines. *Int. J. Nanomed.* **2012**, *7*, 953−964.
(46) Sun, L.-D.; Wang, Y.-F.; Yan, C.-H. Paradigms and challenges for bioapplication of rare earth upconversion luminescent nanoparticles: Small size and tunable emission/excitation spectra. *Acc. Chem. Res.* **2014**, *47*, 1001−1009.
(47) Dai, Y. L.; Xiao, H. H.; Liu, J. H.; Yuan, Q. H.; Ma, P. A.; Yang, D. M.; Li, C. X.; Cheng, Z. Y.; Hou, Z. Y.; Yang, P. P.; Lin, J. In vivo multimodality imaging and cancer therapy by near-infrared light-triggered *trans*-platinum pro-drug-conjugated upconverison nanoparticles. *J. Am. Chem. Soc.* **2013**, *135*, 18920−18929.
(48) Min, Y. Z.; Li, J. M.; Liu, F.; Yeow, E. K. L.; Xing, B. G. Near-infrared light-mediated photoactivation of a platinum antitumor prodrug and simultaneous cellular apoptosis imaging by upconversion-luminescent nanoparticles. *Angew. Chem., Int. Ed.* **2014**, *53*, 1012−1016.
(49) Zhu, Z. Z.; Wang, X. Y.; Li, T. J.; Aime, S.; Sadler, P. J.; Guo, Z. J. Platinum(II)−gadolinium(III) complexes as potential single-molecular theranostic agents for cancer treatment. *Angew. Chem., Int. Ed.* **2014**, *53*, 13225−13228.
(50) Maldonado, C. R.; Salassa, L.; Gomez-Blanco, N.; Mareque-Rivas, J. C. Nano-functionalization of metal complexes for molecular imaging and anticancer therapy. *Coord. Chem. Rev.* **2013**, *257*, 2668−2688.
(51) Kaida, S.; Cabral, H.; Kumagai, M.; Kishimura, A.; Terada, Y.; Sekino, M.; Aoki, I.; Nishiyama, N.; Tani, T.; Kataoka, K. Visible drug delivery by supramolecular nanocarriers directing to single-platformed diagnosis and therapy of pancreatic tumor model. *Cancer Res.* **2010**, *70*, 7031−7041.
(52) Mi, P.; Cabral, H.; Kokuryo, D.; Rafi, M.; Terada, Y.; Aoki, I.; Saga, T.; Takehiko, I.; Nishiyama, N.; Kataoka, K. Gd-DTPA-loaded polymeremetal complex micelles with high relaxivity for MR cancer imaging. *Biomaterials* **2013**, *34*, 492−500.
(53) Dong, X. D.; Wang, X. Y.; Lin, M. X.; Sun, H.; Yang, X. L.; Guo, Z. J. Promotive effect of the platinum moiety on the DNA cleavage activity of copper-based artificial nucleases. *Inorg. Chem.* **2010**, *49*, 2541−2549.
(54) Johnstone, T. C.; Alexander, S. M.; Lin, W.; Lippard, S. J. Effects of monofunctional platinum agents on bacterial growth: A retrospective study. *J. Am. Chem. Soc.* **2014**, *136*, 116−118.
(55) Zhang, L. Y.; Zheng, Y. C.; Callahan, B.; Belfort, M.; Liu, Y. Z. Cisplatin inhibits protein splicing, suggesting inteins as therapeutic targets in mycobacteria. *J. Biol. Chem.* **2011**, *286*, 1277−1282.
(56) Valensin, D.; Gabbiani, C.; Messori, L. Metal compounds as inhibitors of β-amyloid aggregation. Perspectives for an innovative

DOI: 10.1021/acs.accounts.5b00203
Acc. Chem. Res. 2015, 48, 2622−2631

metallotherapeutics on Alzheimer's disease. *Coord. Chem. Rev.* **2012**, *256*, 2357−2366.
(57) Wang, X. H.; Wang, X. Y.; Zhang, C. L.; Jiao, Y.; Guo, Z. J. Inhibitory action of macrocyclic platiniferous chelators on metal-induced Aβ aggregation. *Chem. Sci.* **2012**, *3*, 1304−1312.
(58) Celli, J. P.; Spring, B. Q.; Rizvi, I.; Evans, C. L.; Samkoe, K. S.; Verma, S.; Pogue, B. W.; Hasan, T. Imaging and photodynamic therapy: mechanisms, monitoring, and optimization. *Chem. Rev.* **2010**, *110*, 2795−2838.
(59) Zhang, W.; Li, Y.; Sun, J.-H.; Tan, C.-P.; Ji, L.-N.; Mao, Z.-W. Supramolecular self-assembled nanoparticles for chemo-photodynamic dual therapy against cisplatin resistant cancer cells. *Chem. Commun.* **2015**, *51*, 1807−1810.
(60) Lau, J. T. F.; Lo, P.-C.; Fong, W.-P.; Ng, D. K. P. A zinc(II) phthalocyanine conjugated with an oxaliplatin derivative for dual chemo- and photodynamic therapy. *J. Med. Chem.* **2012**, *55*, 5446−5454.
(61) Naik, A.; Rubbiani, R.; Gasser, G.; Spingler, B. Visible-light-induced annihilation of tumor cells with platinum−porphyrin conjugates. *Angew. Chem., Int. Ed.* **2014**, *53*, 6938−6941.
(62) Wong, D. Y. Q.; Yeo, C. H. F.; Ang, W. H. Immuno-chemotherapeutic platinum(IV) prodrugs of cisplatin as multimodal anticancer agents. *Angew. Chem., Int. Ed.* **2014**, *53*, 6752−6756.
(63) Song, Y.; Suntharalingam, K.; Yeung, J. S.; Royzen, M.; Lippard, S. J. Synthesis and characterization of Pt(IV) fluorescein conjugates to investigate Pt(IV) intracellular transformations. *Bioconjugate Chem.* **2013**, *24*, 1733−1740.
(64) Guo, Z. Q.; Tong, W.-L.; Chan, M. C. W. Luminescent oligo(ethylene glycol)-functionalized cyclometalated platinum(II) complexes: Cellular characterization and mitochondria-specific localization. *Chem. Commun.* **2014**, *50*, 1711−1714.
(65) Koo, C.-K.; So, L. K. -Y.; Wong, K.-L.; Ho, Y.-M.; Lam, Y.-W.; Lam, M. H. -W.; Cheah, K.-W.; Cheng, C. C. -W.; Kwok, W.-M. A triphenylphosphonium-functionalised cyclometalated platinum(II) complex as a nucleolus-specific two-photon molecular dye. *Chem. - Eur. J.* **2010**, *16*, 3942−3950.
(66) Wu, S. D.; Wang, X. Y.; Zhu, C. C.; Song, Y. J.; Wang, J.; Li, Y. Z.; Guo, Z. J. Monofunctional platinum complexes containing a 4-nitrobenzo-2-oxa-1,3-diazole fluorophore: Distribution in tumour cells. *Dalton Trans.* **2011**, *40*, 10376−10382.
(67) Mauro, M.; Aliprandi, A.; Septiadi, D.; Kehr, N. S.; De Cola, L. When self-assembly meets biology: luminescent platinum complexes for imaging applications. *Chem. Soc. Rev.* **2014**, *43*, 4144−4166.
(68) Ma, D.-L.; He, H.-Z.; Leung, K.-H.; Chan, D. S. -H.; Leung, C.-H. Bioactive luminescent transition-metal complexes for biomedical applications. *Angew. Chem., Int. Ed.* **2013**, *52*, 7666−7682.

DOI: 10.1021/acs.accounts.5b00203
Acc. Chem. Res. 2015, 48, 2622−2631