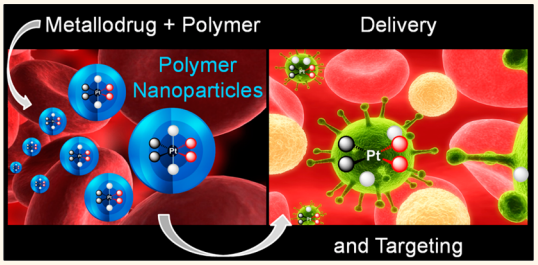
Challenges for Metals in Medicine: How Nanotechnology May Help To Shape the Future

Nicolas P. E. Barry* **and Peter J. Sadler***

Department of Chemistry, University of Warwick, Coventry CV4 7AL, U.K.

ABSTRACT Encapsulation of the platinum(IV) prodrug mitaplatin in block copolymer nanoparticles increases drug circulation time in the blood and reduces accumulation in the kidneys, as reported by Lippard and colleagues in this issue of *ACS Nano*. Importantly, controlled drug release from the nanoparticles produces long-term anticancer efficacy, with the prospect of reduced side effects. We highlight the potential that such a strategy holds for the future development of metallodrugs. Metal coordination complexes offer the prospect of novel mechanisms of activity on account of their unique architectures, as well as potential activation mechanisms, including ligand substitution and metal- and ligand-centered redox properties. Nanoparticles offer exciting prospects for improving delivery, cell uptake, and targeting of metallodrugs, especially anticancer drugs, to make them more effective and safer.



Inorganic medicinal chemistry is in the early days of its development, although there are now a significant number of clinical trials involving metal compounds or other agents that interfere with metabolic pathways for metals, both for therapy and for diagnosis.[1] There is an urgent need for the discovery of drugs with novel mechanisms of action, particularly because some diseases and conditions develop resistances to current drugs. Metal coordination complexes offer biological and chemical diversity that is distinct from that of organic drugs. This diversity arises not only from the choice of the metal itself and its oxidation state, but also from the types and numbers of coordinated ligands and the coordination geometry of the complex.

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Interest in metallodrugs has been stimulated by the recent success of platinum anticancer drugs (used as a component of nearly 50% of all cancer treatments). To date, three platinum(II) compounds, cisplatin, carboplatin, and oxaliplatin, have been approved by the FDA (FDA approvals in 1978, 1989, and 2002, respectively, Chart 1). Nonetheless, side effects associated with these complexes and the development of tumor resistance have led to the search for new generations of platinum-based anticancer agents.[2]

Octahedral low-spin $5d^6$ Pt^{IV} complexes are known to be relatively inert toward ligand substitution but can be activated chemically by reduction. Hence, they have potential advantages as anticancer prodrugs. They often have higher aqueous solubility than square-planar Pt^{II} complexes, a feature exploited long ago by Tobe *et al.* who synthesized iproplatin (CHIP, JM9, *cis*, *trans*,*cis*-$[PtCl_2(OH)_2(isopropylamine)_2]$, Chart 1).[3] Iproplatin entered phase I and II clinical trials, and even phase III, but ultimately was found to be less active than cisplatin and so was not registered for clinical use.[4] Platinum(IV)-based drugs can release active Pt^{II} species as well as bioactive ligands on chemical reduction in the environment of cancerous cells, for example by ascorbate or by a thiol such as glutathione. An interesting example of such a Pt^{IV} prodrug

* Address correspondence to N.Barry@warwick.ac.uk, P.J.sadler@warwick.ac.uk.

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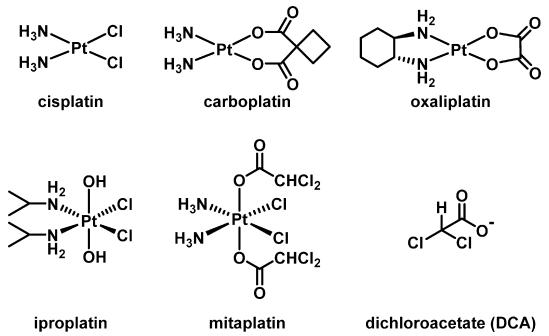


Chart 1. Molecular structures of three square-planar Pt^{II} anticancer drugs, two octahedral Pt^{IV} anticancer compounds, and the enzyme inhibitor dichloroacetate (a ligand in mitaplatin).

is mitaplatin, developed by Dhar and Lippard (Chart 1).[5] Mitaplatin releases two equivalents of dichloroacetate (DCA, Chart 1), an inhibitor of the enzyme pyruvate dehydrogenase kinase, and one equivalent of cisplatin upon reduction in cancer cells. Dichloroacetate is an FDA orphan drug currently in clinical phase II trials for head and neck carcinoma treatment.

Nanotechnology, which has been defined as the engineering and manufacturing of materials at the atomic and molecular scale,[6] offers unique tools for developing safer and more effective medicines (nanomedicines), and provides several potential advantages for drug formulation and delivery.

(i) Control of drug solubility. This might involve either increasing the aqueous solubility of highly lipophilic complexes or decreasing the solubility of complexes that might otherwise be rapidly excreted: a "slow-release" strategy that may engender less toxicity and improve the therapeutic response compared to a burst release.

(ii) Modulation of drug distribution. The uptake of drugs encapsulated in nanoparticles is likely to depend on the shape, size, and surface recognition of the nanoparticles by cells rather than on the characteristics of the drug. For example, cells can take up particles by endocytosis as well as by passive diffusion across the membrane.

(iii) Targeting. The nanoparticle might be designed so that it has vectors on its surface that can target specific cell receptors as well as have the capacity to encapsulate the drug, thus reducing side effects and limiting attack to target cells or organelles only.

(iv) Multidrug delivery and theranostics. More than one drug might be encapsulated for combination therapy. Diagnostic aids (*e.g.*, imaging tags) and multiple therapeutic drugs might also be incorporated into a single nanoparticle.

Nanoparticles made of polymers (NPs) are of particular interest as drug delivery systems because of their synthetic versatility as well as their tunable properties (*e.g.*, thermosensitivity and pH-response). As early as 1994, it was demonstrated that nanospheres, synthesized from amphiphilic copolymers composed of two biocompatible blocks (including a polyethylene glycol(PEG)-block, Chart 2), exhibit dramatically increased blood circulation times and low liver accumulation in mice.[7] This discovery was followed by numerous reports of PEGylated NPs with various architectures,[8] and eventually led to PEG being listed as "Generally Recognized as Safe" (GRAS) by the FDA, and to the clinical translation of a number of NPs.[9] Among them, the biodegradable poly(ethylene glycol)-poly(D,L-lactide) copolymer self-assembled into micellar NPs (see Chart 2 for molecular structure of poly(D,L-lactide)), which can entrap paclitaxel, an organic drug used for the treatment of various cancers, including lung, ovarian, and breast. This micellar paclitaxel formulation, named Genexol-PM (Chart 2), has been approved by the FDA for use in patients with breast cancer. The copolymer increases the water solubility of paclitaxel and allows delivery of higher doses than those achievable with paclitaxel alone while avoiding the use of adjuvants, which might have side effects. Another paclitaxel formulation, NK105, consisting of PEG and modified polyaspartate (50% of the carboxylic groups of the polyaspartate block are esterified with 4-phenyl-1-butanol, Chart 2) is currently undergoing phase II clinical trials for treatment of advanced stomach cancer.[10] Metallodrugs have also been encapsulated into NPs. For instance, cisplatin has been formulated in micelles composed of PEG and poly(γ-benzyl-L-glutamate) (PEG-PGlu, Chart 2), a formulation named NC-6004 or Nanoplatin, which is under phase I/II clinical evaluation for the treatment of pancreatic cancer. Other examples include micellar metal-based magnetic resonance imaging (MRI) contrast or single-photon emission computed tomography/X-ray computed tomography imaging agents.[11,12]

Drug loading into NPs can be achieved by three techniques: (i) covalent attachment to the polymer backbone, (ii) adsorption to the polymer surface, or (iii) entrapment in the polymer matrix during preparation of the NPs.[9] In most cases (Table 1), metallodrug–polymer systems have been formulated by covalent attachment of the metal-based drug to the polymer backbone (formulations usually termed "polymer–metal complex" or "polymer–drug conjugates"). Although attractive because it offers facile and reproducible drug–polymer conjugates with high metallodrug loading percentages, this

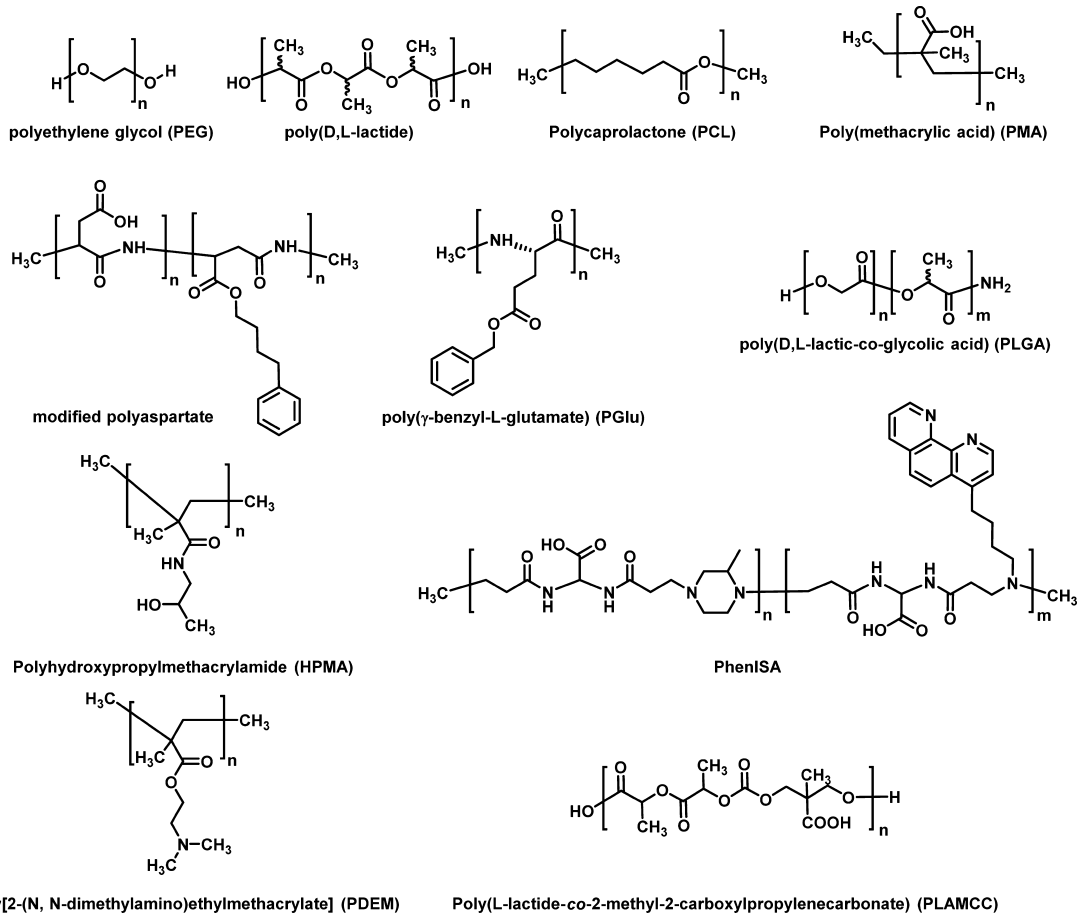
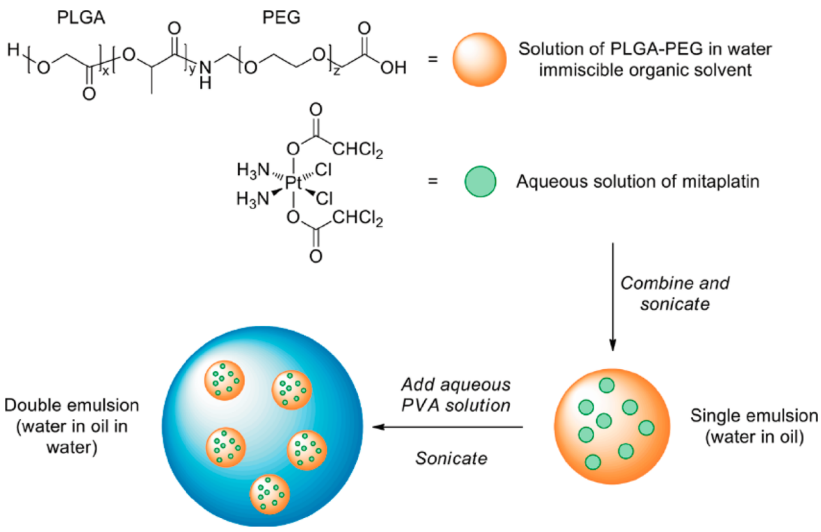


Chart 2. Molecular structures of some of the polymers discussed.

TABLE 1. Examples of Platinum and Ruthenium Anticancer Complexes Encapsulated into Polymer Nanoparticles (NPs)[a]

block copolymer	metal complex	formulation	outcome	ref
PEG-PGlu	cisplatin	nanoplatin: complex entrapped in NPs	pancreatic cancer: phase I/II clinical trials (sponsor Nanocarrier Co., Ltd.)	13
PEG-PDEM, PEG-PCL, PCL-PDEM		complex entrapped in NPs	*in vivo*: better activity than cisplatin	14
PEG-PAsp	$\{(NH_3)_2\text{-}Pt\}^{2+}$	polymer—metal conjugation (dicarboxylated polymer$(COO)_2$Pt chelation)	*in vivo*: minimal nephrotoxicity, higher accumulation in tumors than cisplatin, similar activity	15
PLGA-PEG	mitaplatin	complex entrapped in NPs	*in vivo:* slow-release of mitaplatin, longer circulation time, similar tumor growth inhibition and less accumulation in kidneys than mitaplatin	16
PEG-PLAMCC	dinuclear Pt(II) complex $\{di\text{-}DACH\text{-}Pt_2\}^{4+}$	polymer—metal conjugation (carboxylated polymerCOOPt)	*in vivo:* longer blood circulation time and higher antitumor efficacy than oxaliplatin	17
PEG-PGlu	$\{DACH\text{-}Pt\}^{2+}$	polymer—metal conjugation (dicarboxylated polymer$(COO)_2$Pt chelation)	*in vivo*: longer plasma half-life than oxaliplatin in micelles; high specificity for tumor tissue; strong antitumor activity in mice	18
amidomalonato chelator-HPMA		ProLindac (AP5346): polymer—metal conjugation (amidomalonato chelation)	head and neck cancer: randomized, pilot clinical trials (sponsor University of California, San Diego)	19
PhenISA	$\{Ru(phen)_2\}^{2+}$	polymer—metal conjugation (phenanthroline chelation)	*in vitro*: cellular uptake by endocytic pathway	20

[a] Acronyms: PCL, polycaprolactone; PAsp, poly(aspartic acid); PMA, poly(methacrylicacid); PDEM, poly[2-(*N*,*N*-dimethylamino)ethyl methacrylate]; PLAMCC, poly(L-lactide-*co*-2-methyl-2-carboxylpropylenecarbonate); PGLA, poly(D,L-lactic-*co*-glycolic acid); HPMA, hydroxypropylmethacrylamide; phen, 1,10-phenanthroline. See Chart 2 for molecular structures. DACH = diaminocyclohexane.



Scheme 1. Diagrammatic representation of the double emulsion method for encapsulating mitaplatin in PLGA-PEG nanoparticles. PVA = poly(vinyl alcohol). Reproduced from ref 16. Copyright 2013 American Chemical Society.

method presents the drug as a prodrug which must then be released, with inherent disadvantages: the drug is structurally modified, which can impact its biological activity; the release of the drug from the polymer backbone needs to be achievable under physiological conditions; upon cleavage, the drug must retain its therapeutic properties; poisoning and contamination by catalysts or other reagents must be avoided during the drug–polymer-conjugation synthesis, which also underlies the difficulties surrounding the characterization of covalently modified NPs. Such systems will not be described in detail in this Perspective; instead, we focus on the entrapment of intact metallodrugs through noncovalent hydrophobic or polar interactions, that is, without grafting of the metal-based drug onto the polymer chains. This method allows the retention of the structural integrity of the loaded drug (ligands, geometry, metal oxidation state, and stereochemistry), which is of the utmost importance for metal-based drug candidates.

In this issue of *ACS Nano*, Lippard and colleagues report the encapsulation of the octahedral platinum(IV) compound mitaplatin in a poly(D,L-lactic-*co*-glycolic acid)-block-poly(ethylene glycol) (PLGA-PEG) NP (see Chart 2 for molecular structure of PLGA).[16] Because the presence of axial dichloroacetate ligands is a key structural feature of mitaplatin, an unusual synthetic strategy was employed for its encapsulation in the NPs. Instead of classical drug loading methods, such as nanoprecipitation or conjugation, a water/oil/water double emulsion pathway was employed (Scheme 1). The encapsulation process was optimized to increase platinum loading and to minimize particle diameter. Both mitaplatin-loaded and mitaplatin-free NPs were synthesized.

In vivo studies on these NPs showed that the encapsulation of mitaplatin prolongs retention of platinum in the bloodstream as compared to administration of mitaplatin alone, which correlates with *in vitro* release studies. The tumor burden of mice carrying MDA-MB-468 triple-negative breast cancer xenografts was also reduced by both mitaplatin alone and mitaplatin-loaded-NPs (no effect for mitaplatin-free-NPs), and the biodistribution of the nanodelivery platinum is significantly shifted from accumulation in the kidneys to the liver. Increasing the circulation time of platinum in the bloodstream, reducing accumulation in the kidneys, and the controlled release of the drug over time, are all key potential advantages of this approach using nanoparticle treatment.

Future Challenges. We now highlight three future challenges for medicinal inorganic chemists that might be overcome using polymer NPs.

Targeting Specific Classes of Cells or Specific Cell Components. To date, both clinically validated therapeutic and imaging NPs usually target cancer cells in a passive way. Such a passive drug targeting and delivery strategy is achieved by taking advantage of the enhanced permeability and retention (EPR) effect in tumor tissues.[21] Tumor vasculature is highly disorganized as compared to the vasculature in normal tissues, and the vascular endothelium in tumors proliferates rapidly and discontinuously. This results in a higher number of fenestrations and open junctions (from 200 nm to 1.2 μm) than in normal vessels. Therefore, particles with a typical size of a few hundred nanometers can passively cross the tumor endothelial barrier through fenestrations, and accumulate at particular sites through blood hemodynamic forces and diffusion mechanisms.[22] This leads to the passive targeting of cancer cells. The EPR effect may be used to enhance the uptake of specific drugs into cancer cells with high selectivity as compared to normal cells. Nevertheless,

the delivery of the active pharmaceutical ingredient (API) into specific intracellular sites in cancer cells requires active targeting. Actively targeted NPs may be internalized through clathrin-dependent endocytosis pathways, caveolin-assistance, cell-adhesion-molecule directed, or lipid-raft-associated mechanisms, leading to endosome formation, which ultimately leads to lysosomes.[23]

Control of the API release from NPs depends on the hydrophilicity of the API. Hydrophobic small molecules may be released within the endosome, resulting in permeation within the intracellular components, while release of bioactive macromolecules such as nucleic acids (DNA, siRNA, miRNA) or charged hydrophilic small molecules requires first the escape of the NPs from the endosome, and then fusing with lysosomes in order to reach the desired subcellular organelle. Numerous reports comparing targeted and nontargeted NPs have confirmed that the primary role of the targeting ligand is to enhance cellular uptake into target cells. The encapsulation of metallodrugs in nanoparticles thus provides a degree of protection to the metal-based drug from reductants and nucleophiles by physically preventing interaction between these agents and the encapsulated metal complex.

Reducing the Side Effects of Drugs. Nanotechnology tools also open up new prospects for the control of the biodistribution of metallodrugs. One of the achievements reported in the article by Lippard and colleagues[16] is the demonstration that NP encapsulation can reduce unwanted accumulation of platinum from the platinum(IV) prodrug mitaplatin in the kidneys. Unencapsulated mitaplatin displays a greater acute effect, but the long-term tumor growth inhibition realized by both treatments is the same. Other reports in the recent literature also show that metallodrugs loaded in NPs do not cause as much damage as the drugs on their own.[24] This advantageous nanoparticle formulation strategy for inorganic drugs is worthy of further exploration and exploitation in the near future.

One of the achievements reported in the article by Lippard and colleagues is the demonstration that NP encapsulation can reduce unwanted accumulation of platinum from the platinum(IV) prodrug mitaplatin in the kidneys.

Speciation of Metal Complexes in Cells. Understanding the mechanism of the action of metallodrugs, not only to optimize activity but also to reduce side effects, requires knowledge of the speciation of metal-based drugs, both en route to the tumor cells and in cells. This is a difficult task—metal complexes in general are susceptible to ligand exchange reactions on a wide ranging time scale (years to nanoseconds, or even less if photoexcitation is used), and to metal- and ligand-centered redox reactions. The choice made by Lippard and colleagues[16] of a platinum(IV) complex instead of a platinum(II) is based on the fact that Pt^{IV} complexes with their low-spin $5d^6$ outer shell electronic configuration are more inert to substitution reactions than square-planar Pt^{II} complexes. Hence, they are likely to undergo fewer side reactions en route to the tumor, although once they arrive they need to undergo reduction to Pt^{II} (*e.g.,* by intracellular glutathione) to be active. In this case, there is dual activity arising from the release of the axial dichloroacetate ligands (which can stimulate mitochondrial function) and from attack on DNA by the Pt^{II} product. Delivery of intact metal complexes directly into cells by nanoparticles (as distinct from metal−polymer conjugates) provides a means of avoiding changes to the speciation of metal complexes before they enter cells, while preventing nonspecific binding of NP surfaces to blood components and avoiding clearance by the mononuclear phagocyte system (MPS), or by the reticuloendothelial system (RES), as distinct from the behavior of liposomes.

At the subcellular level, there is currently a lack of techniques powerful enough for studying the speciation of metal complexes directly in cells. Nanotechnology tools, if applied for specifically delivering intact metallodrugs to subcellular organelles, might help to simplify this problem. Indeed, advances in metal analysis and especially speciation techniques are expected within a few years, and the restriction of localization of metal complexes in specific organelles would help such speciation analysis. This work, spanning chemistry, biology, and physics, might also be fruitfully applied to the identification of target sites and understanding of metabolic pathways.

In conclusion, this Perspective is based on results reported in this issue of *ACS Nano* by Lippard and colleagues, highlighting the role that polymer nanoparticles can play in the slow release of platinum compounds into cancer cells, shift of biodistribution of platinum from kidneys to liver, increase of circulation time in blood, and retention of the anticancer activity of the intact encapsulated metal complex.[16] It is, however, clear that inorganic compounds offer different mechanisms of drug action depending on the metal(s) used, their structures, and their redox properties. Thus, they can be utilized for the design of novel drugs in the treatment of a broad range of diseases.[1] For instance, lithium salts, used clinically for stabilization of bipolar disorders, might take advantage of slow release by entrapment in polymer particles. The shift of biodistribution

away from kidneys might be of interest for a variety of gold complexes used for the treatment of rheumatoid arthritis. The safety enhancement obtainable by passive and active targeting of metallodrugs encapsulated into NPs is of potential interest for a range of metal-based drug candidates, while a high metal-complex loading might be an advantage for the delivery of gadolinium MRI contrast agents.

Furthermore, bioinspired, bioengineered, and biomimetic NPs with shapes other than spherical micelles[25] as well as the understanding of release mechanisms and metabolism are now beginning to be explored. Such understanding should enable the design of new NPs with optimized blood circulation times, able to target specific cells and organelles. The diversity and versatility of metallodrugs along with the technological progress made in the design of polymer nanocarriers may provide opportunities for tackling medical challenges in the near future.

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

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