Nanomedicine: the future for platinum drugs or a research red herring?

Platinum drugs continue to be one of the most effective and prescribed families of agents used in the treatment of human cancers [1]. While there is a continued interest in improving the use of approved drugs for different cancer types and in different drug combinations, the development of new, small molecule platinum drugs is out of favor with drug companies. This feeling is not isolated to platinum, but to all cytotoxics, and the long development times of satraplatin and picoplatin (Pionard, WA, USA) and the failure of BBR3464 have only made this worse. There is now a clear focus internationally on the development of targeted therapeutics for cancer, based on the rapidly increasing knowledge of cancer biology and the identification of targetable and drugable cancer proteins [2]. As such, I believe if there is to be a future for platinum drug development then one potential lies in improving the delivery and effectiveness of the already approved platinum drugs: cisplatin, oxaliplatin, heptaplatin and lobaplatin. The focus of this editorial is on the nanoparticle-based delivery of platinum drugs, and whilst this seems the logical next step in platinum development, their commercialization may not be as straightforward as it would be for small molecule platinum drugs, and potentially more risky.

Types of nanoparticles
A number of different nanoparticle-based platinums have been examined in the past, all with unique advantages over normal small-molecule platinum drugs. Liposomes and micelles have been examined in the past, all with potentially more risky.

Platinum drugs continue to be one of the most effective and prescribed families of agents used in the treatment of human cancers [1]. While there is a continued interest in improving the use of approved drugs for different cancer types and in different drug combinations, the development of new, small molecule platinum drugs is out of favor with drug companies. This feeling is not isolated to platinum, but to all cytotoxics, and the long development times of satraplatin and picoplatin (Pionard, WA, USA) and the failure of BBR3464 have only made this worse. There is now a clear focus internationally on the development of targeted therapeutics for cancer, based on the rapidly increasing knowledge of cancer biology and the identification of targetable and drugable cancer proteins [2]. As such, I believe if there is to be a future for platinum drug development then one potential lies in improving the delivery and effectiveness of the already approved platinum drugs: cisplatin, oxaliplatin, heptaplatin and lobaplatin. The focus of this editorial is on the nanoparticle-based delivery of platinum drugs, and whilst this seems the logical next step in platinum development, their commercialization may not be as straightforward as it would be for small molecule platinum drugs, and potentially more risky.

Benefits of nanoparticles to platinum drugs
Nanoparticles are used to improve the delivery of platinum drugs principally through passive targeting of solid tumors via the enhanced permeability and retention (EPR) effect [12]. The passive targeting of tumors occurs because the vasculature surrounding tumors is highly porous, whereas the vasculature of normal tissue tends to be smooth and well aligned. As such, nanoparticles can get trapped in the tumor vasculature, thus leading to a greater concentration of drug in these areas. There is no perfect size for nanoparticles to take advantage of the EPR effect, although the consensus seems to be that a particle size smaller than 100 nm is more ideal.

Using nanoparticles for platinum drug delivery also has several other benefits. The large surface areas of nanoparticles facilitate the attachment of a large number of drug molecules. Recent research has shown that up to 70,000 cisplatin-like drug molecules can be attached to the surface of a single gold nanoparticle [13]. Second, while platinum drugs are usually taken up by cells via passive diffusion, copper transporters or organic cation transporters, the use of nanoparticles can facilitate uptake via endocytosis. The large surface area of nanoparticles also allows the...
simultaneous attachment of a large number of tumor-targeting groups to the drugs (e.g., aptamers [14], antibodies [15] and substrates like folate [16]), thus further improving tumor selectivity and improving cellular uptake through receptor-mediated endocytosis. Third, nanoparticles can be used to facilitate controlled platinum drug release. For example, platinum drugs can be tethered to nanoparticles through carboxylate functional groups. In the bloodstream where the pH is near 7, the platinum drugs remain attached. Upon uptake into the acidic environment of a cancer cell (pH 5–6), the carboxylate groups become protonated, thus releasing the drug. Alternatively, the platinum drugs can be in the platinum (IV) oxidation state and when reduced in vivo, yield the corresponding platinum (II) complex, free of the nanoparticle [17].

**Problems with nanoparticles**

Of all the benefits that nanoparticles can provide in improving the delivery of platinum anticancer drugs, they are not without their problems, most of which are not an issue for small-molecule drugs. Some of these problems may be enough to dissuade interest from companies to undertake their development, the problems may not have solutions, or may have solutions that are not acceptable for drug approval authorities and society.

The first issue has to do with accurate drug dosing. A drug is only effective when a predictable, and correct, dose is delivered to patients. There are two factors that can affect accurate drug dosing of nanoparticle-based platinum drugs. Whilst nanoparticles can be tethered with large numbers of drug molecules, the batch-to-batch variability can be as high as 30% and the variability increases with the increasing number of attached drug molecules. This may stem from the reproducibility and variability in nanoparticle size from batch to batch, as is observed for metallic spheres and carbon nanotubes. Further to this, those nanoparticle systems that are polymer- or dendrimer-based may contain amine groups to which platinum drugs can irreversibly bind (i.e., polyamidoamine dendrimers) [10]. The extent of the irreversible binding can be time dependent, and unpredictable, affecting both the delivered dose and making storage more difficult.

Second, some nanoparticles can only be synthesized at very low concentrations. For example, gold nanoparticles made using either the Turkelich–Frens or the Brust–Schiffrin methods are only stable at nanomolar concentrations. Scale up at higher concentrations can lead to nanoparticle agglomeration and precipitation. This is less of an issue for dendrimers that are stable at millimolar concentrations. Metallic nanoparticles may also change size/shape during manufacture and in storage [13].

Third, the safety of nanoparticles in general is not well understood. Whilst gold nanoparticles are generally regarded as safe, mineral nanoparticles and carbon nanotubes are thought to cause diseases such as mesothelioma and protein citrullination (a major cause of arthritis) [18,19].

"**Of all the benefits that nanoparticles can provide in improving the delivery of platinum anticancer drugs, they are not without their problems, most of which are not an issue for small-molecule drugs.**"

Finally, the screening and selection of a lead nanoparticle-based drug appears to be more complex than for small molecule testing. Because nanoparticles are used to target solid tumors, replicating the EPR in vitro is very difficult and in normal growth inhibition assays, no difference in cytotoxicity may be observed between the nanoparticle-based drug and control drugs. As such, a greater number and earlier in vivo experiments may be required, thus greatly adding to the cost of the research, both financially and in terms of the expertise required by research team members. In addition, there is a conscientious push to reduce the number of animals used in drug testing, and thus, the development of nanoparticle-based drugs may have further ethical and wider societal issues.

**Future of nanoparticle-based platinum drugs**

There are obvious benefits to the development of nanoparticle-based platinum drugs, including better selectivity and less severe side effects, but these new systems will need to provide significantly improved effectiveness to overcome the current reluctance by most pharmaceutical companies to develop cytotoxics. I feel that the litmus test will be the success or failure of Lipoplatin and ProLindac, and only once these have gained market approval will companies become less risk averse to platinums. The opportunity cost that arises from a global focus on pursuing nanoparticle-based platinums will be at the expense of other avenues for research, such as platinum drugs that derive their activity not through DNA binding, but as ‘molecularly targeted drugs’ for cancer-specific proteins and
enlargement, similar to the small molecule organic and antibody-based drugs currently being investigated.

Financial & competing interests disclosure
NJ Wheate is a co-inventor on an international patent for the use of metallic nanoparticles for platinum anticancer drug delivery, WO 2010/139942. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References