

Dalton Discussion 10: Applications of Metals in Medicine and Healthcare

APPLICATIONS OF PLATINUM GROUP METALS IN CANCER AND HIV TREATMENT

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Dalton Discussion 10 on the topic “Applications of Metals in Medicine and Healthcare” was held at the University of Durham, U.K., from 3rd to 5th September 2007 (1). Dalton Discussions represent a conference concept quite different from the norm with a clear focus, as the name implies, on the discussion. Therefore the majority of the presentations were short five minute talks on papers submitted for a *Dalton Transactions* special issue (2), distributed in advance to all the participants, followed by a discussion of about twenty-five minutes. Additionally, five Keynote lectures, given by experts in the field, and approximately sixty poster presentations were included. The conference was perfectly suited to initiate collaborations, develop ideas or simply discuss. The follow-up meeting “Dalton Discussion 11: The Renaissance of Main Group Chemistry” was announced by Professor Robin Perutz, the President of the Dalton Division Council of the Royal Society of Chemistry, and will take place in 2008 at the University of California, Berkeley, U.S.A. (3).

About 100 participants from both academia and industry, including chemists, biologists and clinicians, discussed recent results obtained for metal-based therapeutics and diagnostics. Currently, metal compounds are not the drugs of first choice in clinical application or for companies to develop. As several experts pointed out, there is a need to initiate long-term discussion and interdisciplinary research, and to convince both clinicians and society of the benefit of metal-based drugs. The example of the vanadium compound bis(maltolato)oxovanadium(IV) (BMOV), which has insulin mimetic properties (developed by Chris

Orvig and colleagues), which re-entered clinical trials in 2007 after several years with a lack of interest from drug development companies, was used to underline the fact that patience is required, and that nobody in the field can expect to develop drugs overnight. This is a long term process with an average duration of about ten years, there are many failures and costs are high.

Antitumour and Anti-HIV Applications of PGMs

With regard to platinum group metals (pgms), an overwhelming number of presentations at Dalton Discussion 10 focused on their application as antineoplastic agents. Platinum complexes are applied in half of all chemotherapeutic schemes against a wide range of tumours, although they are effective against only a handful of tumourigenic diseases. Keynote presenter Chi-Ming Che (University of Hong Kong, China) *et al.* reported on their recent developments of platinum(II), ruthenium(II), ruthenium(III) and ruthenium(IV) complexes alongside non-pgm compounds (gold, iron and vanadium) as anticancer and anti-HIV agents (4). Che presented Pt complexes which bind non-covalently to biomolecules, and are capable of binding in an electrostatic or hydrophobic manner as well as *via* intercalation. Some of the complexes were found to be up to 100 times more potent *in vitro* than cisplatin. Furthermore, amino-alcohol-platinum complexes were proposed as protein-staining reagents in sodium dodecyl sulfate (SDS)-polyacrylamide gels, due to their high binding affinities to proteins, and protein interaction is also accompanied by an enhancement of the emission. In addition, Ru complexes with quinone-

diimine as auxiliary ligands were shown to intercalate into DNA, but were found to exhibit mild cytotoxicities of about 200 μM against epidermal KB-3-1 and KB-V-1 carcinoma cell lines. A ruthenium-oxo oxalato cluster was presented which exhibited promising anti-HIV properties, being about ten times more active than the common HIV-1 RT inhibitor 3'-azido-3'-deoxythymidine-5'-phosphate.

Nicholas P. Farrell (Virginia Commonwealth University, U.S.A.) and coworkers, who developed the trinuclear Pt compound BBR3464 up to clinical trials, reported on BBR3464 analogues which are not capable of binding covalently to biomolecules (5). They observed by mass spectrometry, circular dichroism and fluorescence studies the pre-association of these compounds with human serum albumin (HSA) at an initial stage. It is thought that non-covalent interaction of these Pt complexes with HSA might circumvent the deactivation of Pt drugs by binding to serum proteins, and this suggests a new mode of action for this compound class.

The contribution from Peter J. Sadler's group, presented by Abraha Habtemariam (University of Warwick, U.K.), was the ^{106}Ru -radiolabelled putative antitumour organometallic compound $[(\eta^6\text{-fluorene})\text{RuCl}(\text{en})]\text{PF}_6$ (6). Synthesised with the purpose of following and locating the Ru species *in vivo*, the compound was administered to a non-tumour bearing male albino rat. The compound was found to be distributed over the whole animal, with the highest level in liver and kidneys, which illustrates the difficulty in finding drugs that do not accumulate in these organs.

The Keynote talk of Simon P. Fricker (AnorMED Inc., Canada), entitled 'Metal based drugs: from serendipity to design', was focused on established Pt anticancer agents but also reported on new developments in the field, including compounds such as picoplatin, iproplatin and the orally administrable satraplatin, as well as non-Pt complexes (7). The advantages of second and third generation compounds in comparison to cisplatin were highlighted: carboplatin has lower toxicity, satraplatin is orally bioavailable and picoplatin overcomes resistance. Notably, an interesting road-map

from the presenter's point of view was given (Figure 1).

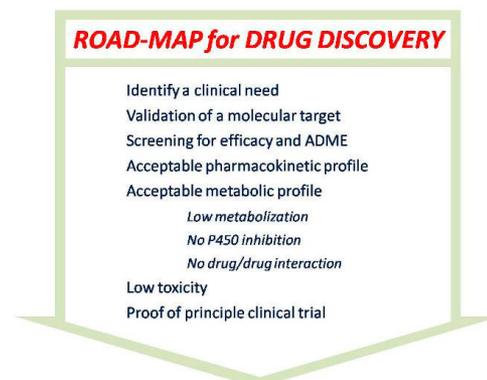


Fig. 1 A road-map for the development of drugs (ADME = adsorption, distribution, metabolism and excretion)

Fricker pointed out that the advantages of metal-based drugs are thought to derive from a precise 3D configuration, leading to precise target/drug interaction; a capacity to coordinate to biomolecules, which is also tuneable by modification of the ligand sphere; and capacities to participate in biological redox processes and to undergo ligand exchange reactions. The speaker reviewed progress in the field of non-Pt anticancer drug candidates, notably Ru anticancer agents including the two Ru compounds in clinical trials, indazolium *trans*-[tetrachlorobis(1*H*-indazole)ruthenate(III)] (KP1019) and imidazolium *trans*-[tetrachloro(imidazole)(dimethyl sulfoxide)-ruthenate(III)] (NAMI-A) (8).

In his Keynote lecture, Trevor W. Hambley (University of Sydney, Australia) described recent developments in metal-based pharmaceuticals (9) and classified metallodrugs into seven classes (see Figure 2). Several pgm compounds are represented in classes (i) and (iii). In particular, the Ru-based glycogen synthase kinase 3β (GSK3 β) inhibitor DW1/2, developed in Eric Meggers's group (Philipps-Universität Marburg, Germany) (10), was mentioned as an example of a class (i) metallodrug. Since most of the known anticancer Pt complexes are believed to exhibit their activity in other than their administered forms, cisplatin and carboplatin as well as Ru(III), Ru-arene and other Pt(II) and Pt(IV) complexes can be considered as representatives of class (iii).

CLASSES of METALLODRUGS

- (i) Inert metal complexes
e.g. the *GSK3 β* inhibitor *DW1/2*
- (ii) Reactive metal complexes
e.g. *superoxide dismutase mimics*
- (iii) Metal complex fragments
e.g. *cisplatin*
- (iv) Complexes that deliver an active metal
e.g. *insulin potentiating vanadium complexes*
- (v) Radiation sensitizing complexes
e.g. *Motexafin Gadolinium (Xcytrin™)*
- (vi) Radiotherapeutic complexes
e.g. the β emitters ^{67}Cu , ^{188}Re , ^{90}Y
- (vii) Complexes that deliver an active ligand
e.g. *CO releasing molecules*

Fig. 2 Classification of metallodrugs

Janice R. Aldrich-Wright (University of Western Sydney, Australia) *et al.* reported on a targeted approach exploiting molecular hosts as drug delivery vehicles (11). Notably, some Pt complexes containing the (1*S*,2*S*)-cyclohexane-diamine (chxn) moiety were found to be more active *in vitro* than oxaliplatin analogues with the (1*R*,2*R*)-chxn ligand. Loading such Pt(II) complexes onto cucurbit[*n*]urils resulted in only small modifications of the cytotoxicity of the complexes, indicating only minor influence of the drug delivery system on the activity of the complexes. However, the application of these compounds is limited by their low solubility, therefore other molecular hosts such as cyclodextrins, calix[*n*]arenes and dendrimers are being evaluated.

Finally, the contribution from Paul J. Dyson's (École Polytechnique Fédérale de Lausanne (EPFL), Switzerland) group dealt with the design of Ru organometallics, the tuning of lipophilicity, which influences the cellular uptake, and altering the compounds' reactivity towards DNA models and proteins (12). All these efforts were undertaken with a view to improving the efficacy of Ru compounds. Based on these studies, it was concluded that modifications which lead to increased interactions of a drug with DNA at the expense of protein binding are more toxic towards healthy cells, and therefore are likely to exhibit more unwanted side effects in patients.

Other Metals

Besides the talks mentioned above, there were numerous fascinating presentations and posters on applications of other metal compounds for medicinal purposes. These include gold, titanium, rhenium and iron complexes for cancer chemotherapy, CO-releasing molecules, radio-metallodrugs for diagnosis and therapy (for example, copper complexes for positron emission tomography (PET) imaging and technetium binding to peptides), gadolinium complex-based contrast agents, zinc and copper complexes as probes for *in vitro* fluorescence imaging and α -emitters such as ^{213}Bi bismuth, ^{211}At astatine and ^{225}Ac actinium as therapeutics.

Concluding Remarks

In summary, a broad variety of applications in metals in medicine and healthcare was presented, with Pt, Ru and other metal-based drugs demonstrating the potential to become the major treatments for some common diseases. Dalton Discussion 10 was a very interesting conference at a pleasant venue in the old city of Durham, and had an appropriate size to benefit from the special conference mode with its focus on discussion. All the contributions can be read in the special issue of *Dalton Transactions*, published in autumn 2007 (2).

References

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The Reviewer



Christian G. Hartinger received his M.S. and Ph.D. in Chemistry in 1999 and 2001, respectively, from the University of Vienna, Austria, under the supervision of Bernhard K. Keppler. Up to 2006, he worked as a research assistant at the same department. He has recently joined the working group of Paul Dyson at the EPFL in Switzerland as a Schrödinger Fellow. His research interests include the development of mono- and multinuclear platinum group metal complexes as anticancer agents, and the elucidation of the transport mechanism and mode of action for such compounds using modern separation and mass spectrometric techniques.