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Metal-based Drugs

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The discovery of the antitumour properties of cisplatin[1] by Barnett Rosenberg and his coworkers at Michigan State University, not only represented a turning point in cancer chemotherapy, but also a paradigm shift in the interests of inorganic chemists. Rosenberg's statement, 'I just thought, by intuition, I might try it',[2] ultimately led to a magic bullet for testicular cancer, without neglecting the fact that cisplatin is a highly versatile agent used to treat many other forms of cancer. A recent and very informative review provides the current situation regarding platinum drugs, their current clinical status, and also highlights compounds that have been discontinued.[3] One cannot overlook the fact that organometallic compounds based on main group metals were used in the clinic to treat other diseases[4] long before cisplatin received clinical approval; nevertheless it was cisplatin that captured the interests and imagination of coordination chemists, and the birth of medicinal inorganic chemistry as a well defined discipline.

Most chemists appreciate that organometallic compounds are essential reagents and catalysts facilitating the synthesis of most of organic drug molecules. However, about a decade after cisplatin entered the clinic, Hartmut Köpf and Petra Köpf-Maier described the direct antitumour effects of an organometallic compound – titanocene dichloride.[5] After spending many years in clinical trials, titanocene dichloride was finally abandoned due to a lack of advantage relative to drugs that were already in use.[6] These nascent studies, however, paved the way for further research on transition metal-based organometallic drugs,[7] with the field witnessing tremendous growth in the past 10 years.[8] Essentially every class of metal-carbon bond has been shown to have potential therapeutic applications, including metal-carbonyls,[9] metal-alkyls that are found in naturally occurring systems such as the vitamin B_{12} family,[10] metal-carbenes,[11] metal-arene π-bonded systems,[12] and organometallic compounds with metal-metal bonds.[13] Gérard Jaouen and his group in Paris brought rational drug design to the field with the development of the so-called ferrocifens that are based on oestrogen targeting organic compounds covalently linked to ferrocene – the classical organometallic motif.[14] Indeed, these studies inspired the development of an antimalarial compound known as ferroquine, a ferrocene-chloroquine hybrid, that is progressing through clinical trials and is particularly effective in regions where resistance to the existing range of antimalarial drugs is prevalent.[15]

The properties of organometallic compounds that makes them attractive as drug candidates compared with purely inorganic compounds or organic molecules is not easily defined. Nevertheless, from an analysis of the literature several generalizations can be made regarding the physiological role of the different types of metal-carbon compounds under evaluation. For example, organometallic compounds with weakly binding ligands may be useful in binding to biomolecules in the blood plasma, which could enhance the storage and distribution of the compound in the body – and even help target it to a diseased site. Biologically active (organic) molecules covalently linked to organometallic units often increases the potency of the compound – especially where drug resistance is a problem. Functional ligands that have well defined properties in organometallic chemistry and catalysis can be exploited in biological systems, e.g. influencing the redox properties at the metal ion and hence the biological properties of the compound in vivo. Finally, water soluble organometallics based on radioactive elements are important in medical diagnosis. It should be noted that these simple classifications do not do justice to the detailed biological and mechanistic studies associated with organometallic compounds and their implication in rational drug design. Indeed, very recently two papers describing new ways of tracing the fate of organometallic compounds inside cells were published and these techniques are likely to provide new insights into the mode of action on organometallic drugs.[16]

In this issue, all the contributions are concerned with organometallic compounds and these papers reflect the diversity of the types of compounds being studied. In the first article, Richard (Dick) Fish gives an overview of his research activities in the area of bioorganometallic chemistry. The journey commences with his discovery of the first metabolites of tributyltin compounds with P450 enzymes, progresses through

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his groundbreaking work on the interaction of organometallics with oligonucleotides, and finishes with a description of potential anticancer drugs rhodium-pentamethylcyclopentadienyl-tamoxifen derivatives. Matthias Tacke and coworkers describe new examples of substituted vanadocene dichlorides – descendants of titanocene dichloride mentioned above. Indeed, over the years his group has shown how modifications to early transition metallocenes using a rational approach can significantly enhance the pharmacological properties of these systems, and this paper provides further interesting examples. Considerable recent interest in the anticancer properties of ruthenium-arene complexes inspired the research presented in the paper by Christian Hartinger and coworkers. In particular, they explore the role of the arene ligand and in the systems studied find remarkably little influence on biological activity. The implications here are important and with the success of the Vienna group in translational medicine, with metal drugs not based on platinum entering clinical trials, it may not be too long before they have success with an organometallic system. Bruno Therrien and coworkers have recently applied the concepts of supramolecular organometallic chemistry to drug delivery and discovery. In their current contribution large, highly charged metalla-cubes incorporating porphyrin and metallo-porphyrin panels are described, and their in vitro antiproliferative properties evaluated.

Not every aspect of organometallic medicinal chemistry is covered in these papers, not every promising compound class included, or every technique used. However, I hope that readers find these papers interesting and with scientists from so many different backgrounds converging on this subject, I hope these papers motivate further research from those who may not have previously considered the potential application of organometallic compounds in medicine.

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