Developments in Cisplatin Research

Cisplatin: Chemistry and Biochemistry of a Leading Anticancer Drug
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It is 30 years since Barnett Rosenberg and his colleagues published their seminal paper in *Nature* entitled "Platinum compounds: a new class of potent antitumour agents" (1). This initial paper marked the beginning of what was to become one of the most exciting uses of platinum, and initiated international research efforts in scientific fields as diverse as inorganic chemistry, cell and molecular biology, and oncology. The platinum drugs, cisplatin and carboplatin, are still at the forefront of anticancer therapy, and there are four major new compounds presently in clinical trials: JM216 being jointly developed by Johnson Matthey and Bristol Meyers Squibb, AnorMED's AMD473 being developed in collaboration with Zeneca, BBR3464 which is being developed by Roche-Boehringer Mannhein in collaboration with its inventor, N. P. Farrell of Virginia Commonwealth University, and Sanofi's oxaliplatin. Bernhard Lippert's excellent book reviews the achievement, progress, and new developments in cisplatin research over the last thirty years.

The book is divided into 6 Parts and contains 22 chapters, each written by current leaders in the field. The international aspect of the research is demonstrated by the choice of authors who come from Europe, the U.S.A. and Japan. The length of the book precludes a discussion of each individual chapter so selected highlights will be discussed. The choices are purely subjective and reflects the reviewer's own interests.

Discovery of Cisplatin

It is fitting that Part 1, "The Start", is a very personal account of the discovery of cisplatin by Barnett Rosenberg. The account is one of basic research and a physicist's fascination with the similarities between the physical appearance of chromosomes during cell division and the magnetic dipole field such as that seen with iron filings around a bar magnet. It was this unlikely coupling of ideas which gave rise to the experiments that ultimately led to the discovery of the anticancer activity of platinum compounds. Part 2, "Cisplatin - How Good is it?" by P. J. O'Dwyer, J. P. Stevenson and S. W. Johnson, reviews the clinical use of platinum drugs. What is apparent from reading this chapter is not only the efficacy of the platinum drugs, but the wide range of cancers in which they are a component of the therapeutic regimen. One disappointing aspect of this chapter is that it ends without a concluding section and therefore does not answer the question posed in the title.

Biochemical Mechanisms and Chemical Interactions

Part 3 consists of 4 chapters describing the efforts that have gone into understanding the biochemical mechanism of cisplatin. D. B. Zamble and S. J. Lippard describe the response of cellular proteins to cisplatin-damaged DNA. A group of proteins that recognise the cisplatin-DNA lesion, HMG proteins, appear to be associated with enhanced sensitivity to cisplatin. Another protein of great interest is the product of the p53 tumour suppressor gene. This is discussed both in this chapter and the subsequent chapter by A. Eastman. Eastman discusses the mechanism by which cisplatin-DNA binding leads to cell death by apoptosis (programmed cell death).

Part 4 and Part 5 examine the chemistry of platinum compounds relevant to their antitumour activity. R. B. Martin describes the relevance of the hydrolysis of platinum complexes to their mechanism of action; Y. Chen, Z. Guo and P. J. Sadler exploit NMR to examine the interactions of platinum complexes with biomolecules. J. Reedijk and J. M. Teuben review platinum-sulfur interactions relevant to the biochemical mechanism of cisplatin. The reactions

of platinum drugs with S-donor ligands are important for two reasons: [a] a mechanism of resistance to the platinum drugs is inactivation resulting from the reaction with S-containing biomolecules such as glutatione and methionine, and [b] thiol reagents can potentially act as "rescue agents" to prevent some of the toxicity of cisplatin.

The chapters in Part 5 illustrate how the discovery of the pharmacological properties of cisplatin have influenced the direction of co-ordination chemistry. Lippert takes a personal look at the "platinum blues", particularly those formed by the interaction of cisplatin and pyrimidine nucleobases. This theme is developed in the following chapters, written by L. Randaccio and E. Zangrando; G. Natile, F. P. Intini and C. Pacifico; and K. Matsumoto.

New Developments

The book ends with a description of new developments. The first two chapters of Part 6 focus on compounds in clinical trials. N. Farrell, Y. Qu, U. Bierbach, M. Valsecchi and E. Menta review the structure-activity relationships of di- and trinuclear platinum compounds undergoing Phase I clinical trials. L. R. Kelland reviews the development of orally active platinum drugs including JM216 and AMD473. The development of AMD473 takes up the theme of thiol reactivity as this compound was designed to have reduced reactivity with thiols, thereby overcoming this mechanism of resistance. K. E. Sandman and S. J. Lippard address the problem of new drug discovery in the light of the recent advances and application of combinatorial chemistry in drug discovery. They evaluate novel screening methodologies for testing libraries of platinum compounds.

One of the striking aspects of this book is the way in which personalities come through the description of the science. This is at its best in the dedication at the end of the chapter by Eastman in which he acknowledges the work of the late J. J. Roberts who was responsible for much of the early fundamental research on the biochemical mechanism of cisplatin. The discovery of cisplatin has inspired many scientists from diverse backgrounds and this is demonstrated throughout the many excellent reviews. Bernhard Lippert is to be congratulated on producing a book consisting not only of numerous scientific articles of high quality describing current research, but also a book that conveys the essence of scientific research. This book is recommended to all those with an interest in platinum chemistry, bioinorganic chemistry, biochemistry, and the clinical development of platinum anticancer drugs, and is a good illustration of their significance.

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Reference

1 B. Rosenberg, L. VanCamp, J. E. Trosko and V. H. Mansour, *Nature*, 1969, **222**, 385

Thin-Film Light-Emitting Ruthenium(II) Devices

Solid-state light-emitting devices, based on ruthenium(II) complexes and operating at low voltages, do not have the high brightness and efficiency of electrogenerated chemiluminescence cells, also based on Ru(II) complexes. This is due to a slow electrochemical "charging" mechanism, which redistributes the counterions to create redox states for charge transport and light emission, and delays the device response after an applied potential bias. If solid-state devices are to be used in flat-panel displays, clearly shorter "charging" times (to brightness) are required.

Now, a team from Massachusetts Institute of Technology has produced single-layer, spin-cast films of small-molecule $Ru(bpy)_3(PF_6)_2$ (1) complexes (bpy = 2,2′-bipyridine) with high-brightness at low voltage, and no need of "charging" or reactive cathode materials (E. S. Handy, A. J. Pal and M. F. Rubner, *J. Am. Chem. Soc.*, 1999, **121**, (14), 3525–3528).

Thin films (~ 1000 Å) of the Ru(II) complex were spin-cast onto an indium tin oxide (anode) patterned glass from pyridine solutions. An aluminium cathode completed the devices. All devices had luminance levels of 1000 cd m^{-2} at 5 V and 200 cd m^{-2} at 3 V and external quantum efficiencies of 1 per cent at low voltage. The emitted red light could be shifted to a more useful red with increased device stability on replacing ligands in (1) by esterified bpy ligands. Device response times can be shortened by using short, high-voltage pulses, and low voltage operation.