Serendipity, Persistance, and Innovative Clinicians: Comments on the Discovery, Development and Approval of Carboplatin

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The potent anticancer activity of certain platinum ammine complexes, discovered by **Rosenberg et al** at **Michigan State University (MSU)** in the late 1960's, naturally initiated interest in seeking second generation compounds with a different/enhanced activity profile. One of the earliest studies was conducted here at MSU in Dr. Rosenberg's laboratory by **Dr. Jim Hoeschele** (one of the conferences organizers) and myself. The first comprehensive review of structure-activity studies on generic cis -[PtA2X2] molecules – where A2 represents a wide variety of mono- and bi – dentate organic amines and X2 comprises a large number of mono and bidentate anionic ligands- was published in 1973 **(M.J. Cleare and J.D. Hoeschele, Bioinorganic Chemistry (1973), Vol 2, Issue 3, Pgs. 187-210**. During the 1970's and 1980's many other laboratories joined in the search for new platinum based drugs but this presentation will focus on the initial work at MSU and the follow up studies by **Johnson Matthey PLC** (JM - my employers from 1966-99) and their collaborators -most notably the **UK Institute of Cancer Research (ICR)** and the **Royal Marsden Hospital, London).**

Literally hundreds of active cis -[PtA2X2] type molecules were identified against a variety of mouse tumor models but this talk will focus on **"carboplatin" (paraplatin)** also known as CBDCA due to the X2 being 1,1-cyclobutane dicarboxylate. The research at MSU had identified that replacing the two chloride groups in cisplatin with a bidentate dicarboxylate ligand gave rise to compounds with good activity and low toxicity, and carboplatin was the pick of these. This was confirmed by extensive chemical and biological studies at JM and the ICR during the 1970's. Indeed Carboplatin emerged as the preferred candidate in a "shoot out" conducted by **Dr. Ken Harrap** at the ICR against a selection of promising candidates. This took place in 1978/9 when Dr. Harrap declared that the **need for a more selective and less nephrotoxic analogue of cisplatin had been unequivocally established** (**see K.R. Harrap, Cancer Treatment Reviews (1985) 12 (Supplement A), 21-33).** It should be noted that as with cisplatin, **Research Corporation** on behalf of MSU had earlier licensed the patent covering carboplatin – USP 4140707A – to **Bristol Myers Squibb (BMS)**

The first clinical trial for carboplatin was carried out by **Dr. Hilary Calvert** at the Royal Marsden Hospital in London. Hilary will give a review of his clinical work in a later paper at this conference. Suffice it to say here that he did a wonderful job shepherding the drug through Phases I-III under a "Clinician Exemption Approval."
This was only the beginning of extensive chemical studies at JM. We worked on a comprehensive "Regulatory Approval Chemistry Package" covering all possible impurities and degradation products including the development of precise analytical procedures. JM became the exclusive supplier of carboplatin to BMS and set up a production facility in our UK Research Centre's pilot plant, operating under full GMP compliance.
Carboplatin was approved in the UK in 1986. It **got FDA approval in 1989** - some 18 years after I first filtered it out of solution in a laboratory at MSU!