Ruthenium in Cancer Chemotherapy

A SELECTIVE REVIEW OF THE TRIESTE SYMPOSIUM

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Since many "soft" metal ions bind to the same DNA co-ordination sites as the widely used anti-cancer drug, cisplatin, it seems likely that some of these should also yield effective chemotherapeutic agents. New results in this area were presented at a symposium held in Trieste, Italy, on 30th June–1st July 1988 which focused on the design and modes of action of non-platinum metal ions in cancer chemotherapy.

Ruthenium appears to be a likely candidate, even though its chemistry differs substantially from that of platinum. The most significant differences are its octahedral geometry and greater propensity to undergo redox reactions. The hypoxic environments of many tumours may favour the reduction of Ru(III) compounds (which are relatively slow to bind to most biological substrates) to Ru(II) species, which bind rapidly. Once co-ordinated to a DNA target, the metal may interfere with DNA metabolism by a variety of mechanisms. Migration between sites can also occur in a manner which is controlled by redox potential and pH.

According to Dr. Jacqueline K. Barton of Columbia University, advantage can be taken of the two additional binding sites provided by octahedral geometries to design chiral compounds that are selective for the particular shapes of the various DNA conformers. Outer-sphere binding may occur electrostatically, hydrophobically or intercalatively. If open co-ordination sites are available on the metal ion, subsequent bond formation may ensue. Scission of the DNA induced by the metal ion may occur by photochemical or redox routes and can be highly selective.

An interdisciplinary group in northern Italy headed by Professors G. Mestroni in Trieste and F. Quadrifoglio in Udine has been investigating the solution chemistry and DNA interactions of a family of compounds involving cis and trans isomers of $X_2(DMSO)_4Ru$, where X=Cl or Br, and DMSO is dimethyl sulphoxide. While only mildly active, these compounds are fairly non-toxic and the trans isomer strongly inhibits metastases of Lewis lung carcinoma. In aqueous solution, the cis complex rapidly loses the O-bound DMSO ligand, while the trans isomer quickly aquates on losing two cis-DMSO ligands. The trans isomer binds to DNA much more rapidly and to a higher degree than the cis isomer. DNA co-ordination by the cis species almost ceases in chloride concentrations approximating that of plasma, and the site of binding of both is suggested to be on the N7 of guanine with a possible involvement by the phosphate.

Dr. Bernard K. Keppler from the University of Heidelberg, Germany, reported very promising results on a number of compounds with the general formulae: trans-$HB[RuB_2Cl_4]$ and $(HB)_2[RuBCl_5]$, where B=nitrogen heterocycle. These compounds are effective against colorectal tumours, which commonly occur and, once metastasised, are presently incurable. Keppler, in collaboration with M. E. Heim, also reported on the first stage of clinical trials of Budotitane, the titanium compound diethoxybis(1-phenylbutane-1,3-dionato)titanium(IV), which is also active against autochthonous colorectal carcinomas. This compound is well tolerated at a level of 150 mg/m^2, it exhibits liver toxicity but no myelosuppression or nephrotoxicity.

Dr. Petra Köpf-Maier of the Free University of Berlin presented results on three different types of metallocene complexes: a) neutral cis-diacido complexes, Cp_2MX_2, M=Ti(IV) or V(IV); b) cationic metallocenes, such as

ferrocinium, and c) decasubstituted neutral metallocenes, $(C_5R_5)_2M$, where R = phenyl or benzyl and M = Sn(II) or Ge(II). Examples of each type were active in markedly inhibiting tumour growth and induced severe cytological and histological changes in the tumours treated, which suggested that the complexes interfere with nucleic acid metabolism. Reaction of the titanium complex resulted in $[Cp_2Ti]^+$ co-ordinated to purine nucleosides through both monodentate N7 and N7-O6 chelation. The vanadocene moiety appears to bind in a labile outer-sphere fashion to phosphate groups. Doses of Cp_2TiCl_2 are limited by liver toxicity.

Ruthenium and platinum compounds may be used to direct radiosensitising molecules to DNA, according to Professor Nicholas Farrell of the University of Vermont. This approach is particularly useful in radiotherapy applied to hypoxic or anoxic areas of tumours, where radiation is less effective. Studies on the radiation killing of cells indicate that metal complexes ligated with nitroimidazoles are more active than either the metal or ligand precursor molecules alone and so point a way to the design of new agents.

The ruthenium isotope, ^{97}Ru, has excellent radiophysical properties for use in diagnostic imaging agents. Its γ-ray is easily collimated by existing radioscintigraphic cameras and its 3-day half-life provides adequate time for synthesis and quality control. Dr. Suresh Srivastava of Brookhaven National Laboratory presented the first clinical studies of a liver-imaging agent using a complex with diisopropyl carbamoylmethyl iminodiacetate, which proved very effective in imaging the livers of neonates suspected of liver dysfunction. Radiolabelling studies also showed that some Ru(III) complexes can be bound to transferrin and carried to receptor sites on tumours. The metal ion is fixed inside the cell, possibly by a redox mechanism, while the transferrin is released.

The symposium discussions concerning the various approaches to ruthenium-containing anti-cancer drugs reflected the versatility of this element in synthesis, electron transfer, and even photochemistry. These properties, coupled with the affinity of ruthenium's intermediate oxidation states for imine nitrogens, facilitate DNA targeting for both chemotherapeutic and radiosensitising agents. Finally, the existence of isotopes with desirable properties for diagnostic imaging indicates that exploration of the medical applications of ruthenium is likely to produce useful pharmaceuticals.

Lean-Burn Oxygen Sensor Material

PLATINUM CATALYST IMPROVES RESPONSE TIME

Oxygen sensors are widely used as automobile engine control devices in order to obtain an optimised balance of exhaust emissions, fuel economy and vehicle drivability, and generally this is achieved by controlling the air to fuel ratio at the stoichiometric mix of 14.7:1. Now there is increasing interest in controlling the air to fuel ratio away from the stoichiometric point, in the lean-burn region, with the aim of increasing engine efficiency and decreasing nitrogen oxides emissions.

Lean-burn oxygen sensors are generally classified as either semiconducting or electrochemical pumping. The former are small, simple, low cost devices which are based upon the resistivity changes that take place in oxide semiconductors as the partial pressure of oxygen in the surrounding atmosphere varies.

A recent paper by C. Yu, Y. Shimizu and H. Arai of Kyushu University, Fukuoka, Japan, reports on their investigation of several species of magnesium-doped $SrTiO_3$ in the exhaust gas resulting from air-propane combustion containing water vapour ("Mg-Doped $SrTiO_3$ as a Lean-Burn Oxygen Sensor", *Sens. Actuators*, 1988, **14**, (4), 309–318). At temperatures between 600 and 800°C, the highest sensitivity to oxygen in the lean-burn region and the lowest sensitivity in the rich-burn region was shown by $SrTi_{0.6}Mg_{0.4}O_{3-\delta}$, and therefore it was considered to be a suitable material for a lean-burn oxygen sensor. However the response time was about 1.5 seconds, which is too long for use in an automobile engine system. When 1 weight per cent platinum was added as a catalyst the response time was reduced significantly and in addition the sensitivity was increased in the lean-burn region.