Can Platinum(IV) Anti-Cancer Agents be Selectively Activated in Tumours?

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Almost all drugs used in the treatment of cancer cause serious side effects because they lack selectivity for tumours. However, the rapidly increasing knowledge and understanding of the differences between the chemistry and biochemistry of tumours and normal tissues means that it is now possible to envisage drugs that act selectively on tumours. Tumour hypoxia, the lower than normal oxygen levels present in solid tumours, is the result of the rapid growth and poor vascularisation of tumours. It is a property that is both common in and unique to solid tumours and is therefore an ideal basis for tumour-selective activation. For a prodrug to be activated in a hypoxic environment it must have an inactivated higher oxidation state and an activated lower oxidation state. Platinum(IV) complexes meet these criteria if the platinum(II) product is anticancer active, but their potential for selective activation in hypoxic environments has not been tested. To date it has not been possible to tune the properties of the compounds to achieve optimal activation in the most hypoxic regions. It is therefore a primary goal of our work to develop new technologies that enable the in situ determination of the oxidation state in different regions of tumours and in models of hypoxic tumours. Simultaneously, this work is providing information on the relationship between reduction potential and the extent of activation in hypoxic environments that will be of use to others developing future generations of hypoxia activated drugs. We will report our results showing that it is possible using XANES spectroscopy to monitor the oxidation state of platinum in tumour cells and to follow the reduction of these complexes. We will report on work aimed at determining the location and oxidation state of platinum in solid tumours and spheroid cancer cell clusters as models of solid tumours. The use of SRIXE mapping to determine the location of the platinum in cells, solid tumours and spheroids will be described. We will also report on tomographic mapping of the Pt distribution in spheroids (see Figure).