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The design and synthesis of stabilised classical and non-classsical Platinum(IV) pro-drugs for targeted drug delivery

Platinum(II) based anti-cancer drugs are the most successful class of chemotherapy drugs in clinical use and are used to treat half of all patients undergoing chemotherapy. Despite their success they are often associated with dose limited toxicities, severe side effects and drug resistance.[1-3]
Platinum(IV) complexes are a promising class of pro-drugs which may bypass the problems associated with their platinum(II) counterparts. However, any pharmacokinetic advantages conferred by the platinum(IV) oxidation state is often lost due to the rapid reduction of these complexes en route to the tumour site.[4]
Recently, Zhang et al. reported that platinum(IV) complexes containing cis-diamminetetracarboxylato coordination sphere exhibited unusual stability to reduction by L-ascorbate that did not correlate with their electrochemical reduction potential.[5]
In this study, we further investigate the influence and relationship of structure, coordination and geometry on reduction stability, mechanism and metabolism of classical and non-classical platinum(IV) complexes in a range of endogenous and biological reductants and biological environments, using various spectroscopic and biological techniques such as XANES, SXFM, XRF μCT, 1D and 2D NMR and GF-AAS. Recently, we have reported reduction stability exhibited by cis diamminetetracarboxylato platinum(IV) complexes, using 1H NMR and XANES spectroscopy. Interestingly, this class of platinum(IV) complex appears to be usually stable to reduction in the presence of excess endogenous reductants but are rapidly reduced within DLD-1 human colon cancer cells.[6] Finally, we report several design and synthetic strategies for the development of targeted drug delivery for classical and non-classical platinum(IV) pro-drugs.
These preliminary results potentially provide insights into the development of new design strategies for platinum(IV) based chemotherapeutic therapies that have enhanced reduction stabilities in the extracellular environment; such as the blood stream, but are easily and selectively activated at the tumour site.

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Yes

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No

What is your gender?

Female

Primary author(s) : CHEN, Catherine (The University of Sydney)

Co-author(s) : Prof. HAMBLEY, Trevor (The University of Sydney)

Presenter(s) : CHEN, Catherine (The University of Sydney)

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