Advances in Os(II)-catalysed intracellular asymmetric reduction: new targets, stability improvement and anticancer potency enhancement

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Metals are essential to life. Over half of all known proteins contain a metal, and since the discovery of the antineoplastic agent cisplatin, the use of metal complexes as chemotherapeutics has fascinated the bioinorganic research community. Inspired by nature's use of metalloproteins to facilitate otherwise inaccessible biochemical transformations, we have developed synthetic organometallic complexes, based on osmium, to carry out in-cell catalytic transformations in cancer cells. The successful development of a catalytic metallodrug could facilitate dose reduction, and a multi-targeting mechanism of action may circumvent drug resistance. Os catalysts provided the first example of asymmetric intracellular catalysis carried out by a synthetic catalyst, achieving the enantioselective reduction of pyruvate to either L-lactate or D-lactate (depending on the choice of catalyst) using a non-toxic concentration of sodium formate as a hydride source.[1] Alternative sources of hydride were explored, including the formate precursor *N*-formylmethionine, thus exploiting the increased expression of human peptide deformylase enzyme in certain cancer cells to improve selectivity. Additionally, co-administration of the Os catalyst with a monocarboxylate transporter (MCT) inhibitor appeared to further increase potency towards breast cancer cells.

Studies concerning the intracellular fate of the Os catalyst have identified deactivation pathways involving conjugation to low molecular weight thiols, while elemental mapping using x-ray fluorescence spectroscopy revealed loss of the *N*,*N*-bidentate diamine ligand.[2] To improve intracellular stability, we have recently prepared and characterized a tethered Os catalyst bearing a permanent carbon linker between diamine and arene ligands. Furthermore, synthetic organometallic catalysts are unlikely to demonstrate high specificity for one transformation and, in addition to pyruvate reduction, we have preliminary chemical and biological data which suggest that the mitochondrial electron transport chain may afford additional subcellular target(s).[3]

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[1] J. P. C. Coverdale, I. Romero-Canelon, C. Sanchez-Cano, G. J. Clarkson, A. Habtemariam, M. Wills, P. J. Sadler *Nature Chemistry*, **2018**, *10*, 347-354.

[2] E. M. Bolitho, J. P. C. Coverdale, H. E. Bridgewater, G. J. Clarkson, P. D. Quinn, C. Sanchez-Cano, P. J. Sadler *Angewandte Chemie Int. Ed. Eng.*, **2021**, *60*, 6462-6472.

[3] E. M. Bolitho, N. G. Worby, J. P. C. Coverdale, J. A. Wolny, V. Schunemann, P. J. Sadler, *Organometallics*, **2021**, *40*, 3012-3023