



IK BioProMoTION Seminar

Thursday, October 20, 2011; 3.30 pm
Lecture hall 4, Waehringer Str. 42, 1090 Vienna

Organometallic anticancer drugs with novel modes of action

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This presentation will focus on our research on organometallic compounds based on the ruthenium(II)-arene unit that exhibit selective anticancer activity against highly invasive tumour types, and potentially overcome certain limitations of present metal-based anticancer drugs [1]. In particular, drug resistance to transition metal-based drugs such as cisplatin is a major problem and is known to be the consequence of a multitude of factors such as reduced drug uptake, increased efflux and drug inactivation by intracellular thiol-containing biomolecules. Based on our early promising results, that show our ruthenium(II)-arene compounds to selectively induce apoptosis in invasive cancer cells without damaging healthy cells, we have modified their structure to also overcome certain types of drug resistance mechanisms and therefore act in a targeted fashion.

Various resistance pathways will be discussed, but particular attention will be paid to drug inactivation involving glutathione-S-transferase enzymes (GST). GSTs are an important class of biotransformation enzymes present in the cytoplasm whose main function is the detoxification of alien compounds. By combining the organometallic ruthenium function with a potent GST inhibitor, ethacrynic acid, covalently tethered via the arene ring, a compound that is active in cancer cells expressing high levels of GSTs is obtained, and indeed activities are superior to other well established drugs. The characterization and activity of these complexes will be discussed and their mechanism of action highlighted [2, 3].

- [1] A. Bergamo, A. Masi, P. J. Dyson, G. Sava, *Int. J. Onco.*, **2008**, *33*, 1281.
- [2] W. H. Ang, L. J. Parker, A. De Luca, L. Juillerat-Jeanneret, C. J. Morton, M. Lo Bello, M. W. Parker, P. J. Dyson, *Angew. Chem. Int. Ed.*, **2009**, *48*, 3854.
- [3] S. Chatterjee, I. Biondi, P. J. Dyson, A. Bhattacharyya, *J. Biol. Inorg. Chem.*, **2011**, *16*, 715.