Oral communications: Drug Design Theme (Wednesday).

Ruthenium Complexes for the Treatment of Protozoan Diseases

Afonso P. Basto[a], Joachim Müller[a], Riccardo Rubbiani[b], Federico Giannini[c], David Stibal[d], Georg Süss-Fink[d], Vreni Balmer[a], Andrew Hemphill[a], Gilles Gasser[e], Julien Furrer[c]

a Institute of Parasitology, Vetsuisse Faculty, University of Bern, Länggassstrasse 122, CH-3012 Berne, Switzerland.
b Department of Chemistry, University of Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland.
c Department for Chemistry and Biochemistry, Freiestrasse 3 CH-3012 Bern, Switzerland.
d Institut de Chimie, Université de Neuchâtel, Avenue de Bellevaux 51, CH-2000 Neuchâtel, Switzerland.
e Chimie ParisTech, PSL Research University, Laboratory for Inorganic Chemical Biology, F-14 75005 Paris, France.

E-mail: julien.furrer@dcb.unibe.ch

Recently, some of us have shown that dinuclear thiolato-bridged arene ruthenium complexes of the type $[(\eta^6\text{-}p\text{-cymene})_2Ru_2(\mu_2\text{-SR})_3]^+$ were among the most cytotoxic ruthenium complexes reported so far, with nanomolar IC_{50} values against both A2780 human ovarian cancer cells and their cisplatin-resistant mutant variant A2780cisR.[1] Interestingly, *in vivo* studies of *diruthenium-1*, $[(\eta^6\text{-}p\text{-cymene})_2Ru_2(\mu_2\text{-}SC_6H_4\text{-}p\text{-}Bu^t)_3]^+$, demonstrated a significant increase in survival of the treated mouse group.[2-3]

Motivated by the impressive results obtained in cancer therapy, we decided to test some of those compounds against *Neospora caninum* and *Toxoplasma gondii*. Two complexes, namely $[(\eta^6\text{-}p\text{-cymene})_2Ru_2(\mu_2\text{-}SC_6H_4\text{-}p\text{-}CH_3)_3]^+$ and *diruthenium-1*, displayed IC_{50} values on *T. gondii* of 34 and 62 nM, respectively, with a high selectivity on *T. gondii* over human foreskin fibroblasts (HFF) as expressed by a selectivity index of around 20'000. Transmission electron microscopy (TEM) showed that treatment with these compounds has a dramatic impact on the parasite mitochondrion [4]. Moreover, upon treatment of human ovarian carcinoma A2780 cells with these drugs, between 71 and 97% of the ruthenium was found to accumulate in the mitochondria. This strongly suggests that these compounds are targeting the mitochondria in both parasites and cancer cells. *Giardia lamblia* that is devoid of functional mitochondria is not affected by treatments with these complexes up to a concentration of 5 µM, thus further supporting this statement.

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