Ruthenium Complexes for the Treatment of Protozoan Diseases

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Recently, some of us have shown that dinuclear thiolato-bridged arene ruthenium complexes of the type $[\eta^8-p$-cymene]$_2$Ru$_2$(μ$_2$-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, $[\eta^8-p$-cymene]$_2$Ru$_2$(μ$_2$-SC$_6$H$_4$p-Bu)$_3^+$, 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 \textit{Neospora caninum} and \textit{Toxoplasma gondii}. Two complexes, namely $[\eta^8-p$-cymene]$_2$Ru$_2$(μ$_2$-SC$_6$H$_4$p-CH$_3$)$_3^+$ and diruthenium-1, displayed IC$_{50}$ values on \textit{T. gondii} of 34 and 62 nM, respectively, with a high selectivity on \textit{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. \textit{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.


