

Preferential DNA Double-Strand Cleavage under Anerobic Conditions using a Redox Active Ruthenium Polypyridyl Dimer: Potential towards Hypoxia Selective Cancer Chemotherapy

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One of the main challenges of cancer is the selective targeting of microscopic metastases, which due to their invasive nature often require systemic therapies. Traditional chemotherapy is typically a 'brute-force' method in which all rapidly dividing cells are affected. Efforts to specifically target tumor cells using, for example, antibody-conjugate drugs show potential but have not yet lived up to their promise as magic bullet drugs. Another potential way to target tumor cells is to take advantage of the hypoxic environment that is typical of many of the cells in rapidly developing metastasis, in that drugs which are only activated under such conditions would only damage cancerous tissue.

The cationic ruthenium dimer, $[(\text{phen})_2\text{Ru}(\text{tatpp})\text{Ru}(\text{phen})_2]^{4+}$ or (\mathbf{P}^{4+}) both tightly binds DNA via an intercalative mode ($K_b \sim 10^9 \text{ M}^{-1}$) and selectively induces DNA double-strand breaks under hypoxic or anerobic conditions. We have further established that \mathbf{P}^{4+} is a pro-drug and is reduced by glutathione (GSH) to the form the doubly reduced, doubly protonated complex $[(\text{phen})_2\text{Ru}(\text{H}_2\text{tatpp})\text{Ru}(\text{phen})_2]^{4+}$ ($\mathbf{H}_2\mathbf{P}^{4+}$) which is responsible for the ds-DNA damage. We postulate that the $p\text{O}_2$ regulates the appearance of $\mathbf{H}_2\mathbf{P}^{4+}$ and that only under hypoxic conditions will significant ds-DNA breaks occur. Possible mechanisms of DNA cleavage will be presented.

Preliminary cytotoxicity studies show \mathbf{P}^{4+} is efficient at killing non-small cell lung cancer (H358) cells *in vitro* ($\text{IC}_{50} = 8.25 \pm 0.5 \text{ } \mu\text{M}$) and injections in mice (0.2 mg $[\mathbf{P}]\text{Cl}_4$ in 200 μL buffer) were tolerated well. Importantly, preliminary studies in an orthotopic mouse melanoma model revealed i.p. treatment with \mathbf{P}^{4+} significantly delayed tumor-growth. These results taken in combination reveal that this complex and closely related derivatives have promise as a new class of selective chemotherapeutic drugs.

