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Novel *in silico*-designed anti-cancer compounds: From *in vitro* exploration to potential clinical considerations

A E Theron[1], L Lafanechère[2], M S Pepper[1], R Prudent[2], J Viallet[2], C Jackson[1], C du Rant[1] and **A M Joubert[1]**
[1]University of Pretoria, South Africa
[2]Université Joseph Fourier, France

The concept behind these novel *in silico*-designed anti-cancer compounds encompasses harnessing the well described anti-mitotic effects of 2-methoxyestradiol with modifications to increase bioavailability, as well as preferential tumour localization via carbonic anhydrase IX binding. Spectrophotometric dose analysis revealed that these novel compounds are cytotoxic at nanomolar concentrations in a number of neoplastic cell types, a property retained in a PgP-overexpressing multi-drug resistant cell line. Microscopy techniques including live imaging of tubulin dynamics confirmed the induction of apoptosis and autophagy due to alternation of spindle dynamics. Molecular pathways and intracellular responses were assessed via multiple techniques including Western blotting and flow cytometry. Chick chorioallantoic membrane assays revealed a significant reduction in primary tumour size and a decreased number of distant metastasis. *Ex vivo* effects on human blood, as well as potential platelet interference were examined both microscopically and via flow cytometry. In bridging the gap towards clinical applications, acute mouse toxicity and metabolism studies were performed. Potential effects on haematopoietic stem cells were investigated; the results of which indicated that the compounds are not toxic at the IC50 concentrations established for cancer cells. Additionally, after drug exposure, stem cells retained their differentiating capacity. Potential use of the compounds within a combined treatment regimen was investigated; both with established chemotherepeutic drugs in spectrophotometric matrices, and in radiosensitization studies. Further studies will encompass mouse tumour models, as well as to elucidated whether the conceptual preferential tumour localization is achieved *in vivo*.

Biography

A E Theron qualified as a medical doctor, and after a few years as a trauma and aviation doctor, and then returned to her first interest of molecular medical science. She joined the University of Pretoria in 2009 where she is currently a senior Lecturer in physiology. She is part of a research team involved in developing and investigating novel anti-cancer molecules.

Joji.Theron@up.ac.za