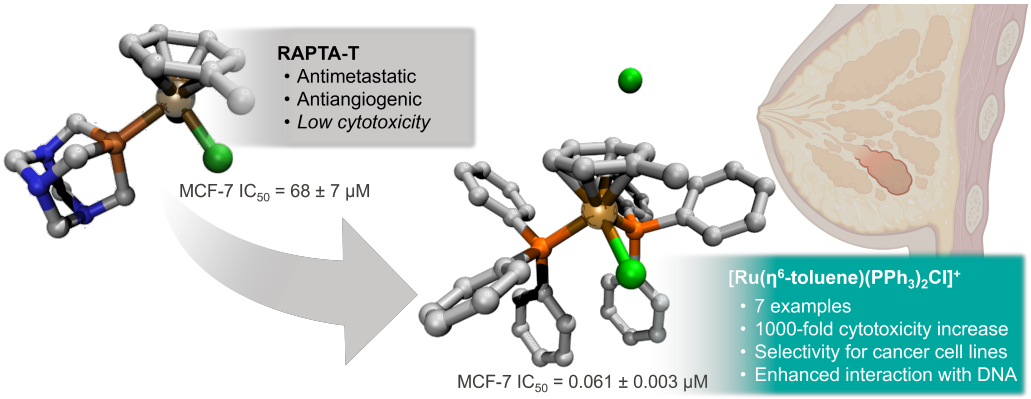
Fine-tuning the cytotoxicity of ruthenium(II) arene compounds to enhance selectivity against breast cancers

J. Romano-deGea[1], S. A. Pereira[1,2], M. M. Saraiva[2]*, P. J. Dyson[1]*

[1]Institut des Sciences et Ingénierie Chimiques, École Polytechnique Fédérale de Lausanne (EPFL), Lausanne (CH), [2]LAQV, REQUIMTE, Departamento de Ciências Químicas, Faculdade de Farmácia, Universidade do Porto (PT)

Ru(η^6-arene)(PTA)Cl_2 (PTA = 1,3,5-triaza-7-phosphaadamantane), or RAPTA, complexes have arisen (together with other ruthenium compounds) as alternatives to platinum-based drugs in cancer therapy [1]. RAPTA compounds exhibit reduced general toxicity [2] and have demonstrated efficacy against breast cancer by suppressing metastasis [3], tumorigenicity [4], and inhibiting the replication of the human tumour suppressor gene BRCA1 [5]. However, their limited cytotoxicity, and therefore comparatively high dosing, has hindered their translation to the clinic.

We synthesised and explored the activity of a series of RAPTA-like ruthenium(II) arene compounds against two breast cancer cell lines and identified [Ru(η^6-toluene)(PPh_3)$_2$Cl]Cl as a potential therapeutical candidate with nearly a 1000-fold increase in cytotoxicity compared to RAPTA-T. The compound was further studied, revealing its remarkable stability and enhanced interaction with the minor and major grooves of DNA.



[1] Benjamin S. Murray, Maria V. Babak, Christian G. Hartinger, Paul J. Dyson,*Coord. Chem. Rev.*, **2016**, 306, 86–114.
[2] Claudine Scolaro, Alberta Bergamo, Laura Brescacin, Riccarda Delfino, Moreno Cocchietto, Gábor Laurenczy, Tilmann J. Geldbach, Gianni Sava, Paul J. Dyson, *J. Med.* Chem., **2005**, 48(12), 4161–4171.
[3] Alberta Bergamo, Alessia Masi, Paul J. Dyson, Gianni Sava, *Int. J. Oncol.,* **2008**, 33(8),1281–1289.
[4] Patrycja Nowak-Sliwinska, Judy R. van Beijnum, Angela Casini, Alexey A. Nazarov, Georges Wagnières, Hubert van den Bergh, Paul J. Dyson, Arjan W. Griffioen, *J. Med. Chem.,* **2011**, 54(11), 3895–3902.
[5] Tidarat Nhukeaw, Khwanjira Hongthong, Paul J. Dyson, Adisorn Ratanaphan, *Apoptosis,* **2019**, 22(7–8), 612–622