Green Light-Induced Cancer Cells Death With Ruthenium Prodrugs

Sylvestre Bonnet,[1] Vincent H.S. van Rixel,[1] Bianka Siewert,[1] Sven H.C. Askes,[1] Maxime A. Siegler[2]

[1] *Leiden Institute of Chemistry, Leiden University, Leiden, The Netherlands*

[2] *John Hopkins University, Baltimore, USA*

E-mail: bonnet@chem.leidenuniv.nl

Like PhotoDynamic Therapy (PDT), Photo-Activated Chemotherapy (PACT) aims at activating anticancer prodrugs with visible light to circumvent the toxicity of the compound to the tumour tissue. Unlike PDT however, PACT agents are activated in an oxygen-independent manner, which may allow for treating hypoxic tumours. In this presentation two PACT compounds based on ruthenium will be presented. In these prodrugs a tetrapyridyl ligand coordinates the basal plane of the metal center, leaving two trans coordination sites for the binding of monodentate ligand(s). Due to the distortion of the molecule one of these monodentate ligands can be photosubstituted by water upon visible light irradiation in aqueous solution. In vitro cytotoxicity data on A431 and A549 human cancer cell lines shows a 20-fold increased cytotoxicity after green light irradiation (520 nm, 75 J.cm^{-2}), compared to the dark control. Optical microscopy cell imaging and fluorescence-activated-cell-sorting indicate that the cancer cells die via apoptosis, while low to very low singlet oxygen quantum yields (1.3-2.3%) conclude that light-induced cell death is not caused by singlet oxygen generation. We will discuss the mechanism of action of this new class of oxygen-independent compounds, and discuss the link between the light activation *in vitro* and the photosubstitution reactions occurring at the metal center.

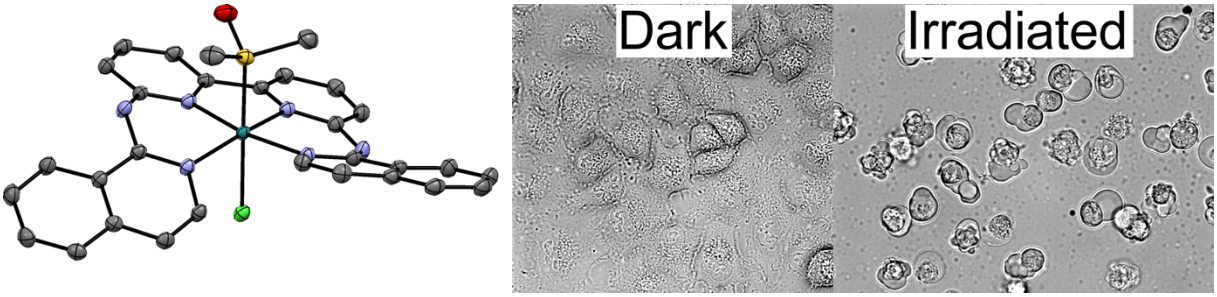

Figure 1. Left: X-ray structure of compound [1]Cl. Middle and right: Bright field microscopic images of A549 lung cancer cells treated with [1]Cl (1.5 μM) for 7 h in the dark (middle), or for 6 h in the dark followed by 1 h green light irradiation (right). Irradiation conditions: 520 nm, 75 J.cm^{-2}.

Funding: European Research Council, NWO-CW, Leiden University

References:

[1] R. E. Goldbach, I. Rodriguez-Garcia, J. H. van Lenthe, M. A. Siegler, S. Bonnet *Chemistry a European Journal,* **2011***,* 17*,* 9924

[2] V. H. S. van Rixel, B. Siewert, S. H. C. Askes, M. A. Siegler, S. Bonnet, *Chemical Science* **2016**, **7***,* 4922

[3] S. L. Hopkins, B. Siewert, S. H. C. Askes, P. Veldhuizen, R. Zwier, M. Heger, S. Bonnet, *Photochemical and Photobiological Sciences* **2016**, 15*,* 644