^{1}H HR-MAS NMR based metabolomics of cells lines responding to treatment with the diruthenium trithiolato complex $[(p\text{-}MeC_6H_4{}^{i}Pr)_2Ru_2(SC_6H_4\text{-}p\text{-}Bu^{t})_3]^+$ (DiRu-1)

H. Primasova[1], L. E. Paul[1], M. Vermathen[1], G. Diserens[2], P. Vermathen[2], J. Furrer[1]*

[1]Departement für Chemie und Biochemie, Universität Bern, Freiestrasse 3, CH-3012 Bern, Switzerland, [2]Departement Klinische Forschung und Radiologie, Universität Bern, Erlachstr. 9a, CH-3012 Bern, Switzerland

The diruthenium trithiolato complex $[(p\text{-}MeC_6H_4iPr)_2Ru_2(SC_6H_4\text{-}p\text{-}Bu^{t})_3]^+$ (DiRu-1) is highly toxic against human ovarian cancer cells A2780 and the corresponding ciscisplatin resistant variant A2780cisR in vitro with IC_{50} value of 0.03 µM [1]. In vivo experiments showed that the survival rate of mice could be significantly prolonged using DiRu-1 compared to cisplatin, and proved presence of ruthenium in cancer cells. In vitro measurements revealed inhibition of mitochondrial respiration and decrease in glutathione levels [2], and showed that DiRu-1 causes increased levels of reactive oxygen species (ROS) in cells and induces caspase-driven apoptosis in estrogen-responsive breast adenocarcinoma (MCF-7) cells as well as necrosis, mitotic catastrophe, necrosis and autopaghy [3].

In order to gain more insight into its modes of action, ^{1}H high resolution magic angle spinning (HR-MAS) NMR spectroscopy was employed to analyze the metabolic profile of ovarian cancer cells A2780, A2780cisR, and Human embryonic kidney cells HEK-293, used as a model for healthy cells treated with 0.03 µM and 0.015 µM of DiRu-1, respectively, for 24 h. The data have been analyzed using a classical principal component analysis (PCA) and partial least squares discriminant analysis (PLS-DA) to evaluate the effects of the treatment by DiRu-1 on the metabolic profile and to provide a hint on metabolites or groups of metabolites correlated with the cellular response, as shown previously for a ruthenium hexacationic metallaprism [4].

[1] F. Giannini, J. Furrer, A. F. Ibao, G. Süss-Fink, B. Therrien, O. Zava, M. Baquie, P. J. Dyson, and P. Štěpnička, *J. Biol. Inorg. Chem.*, **2012**, 17, 951–960.
[2] P. Tomsik, D. Muthna, M. Rezacova, S. Micuda, J. Cmielova, M. Hroch, R. Endlicher, Z. Cervinkova, E. Rudolf, S. Hann, D. Stibal, B. Therrien, G. Süss-Fink, *J. Organomet. Chem.,* **2015**, 782, 42-51. and J. Furrer and G. Süss-Fink, *Coord. Chem. Rev.*, **2016**, 309, 36–50.
[3] A. Koceva-Chyła, K. Matczak, M.P. Hikisz, M.K. Durka, M.K. Kochel, G. Süss-Fink, J. Furrer, K. Kowalski, ChemMedChem, **2016**, 11, 2171-2187.
[4] M. Vermathen, L. E. H. Paul, G. Diserens, P. Vermathen, and J. Furrer, *PLoS One*, **2015**, 10, e0128478.