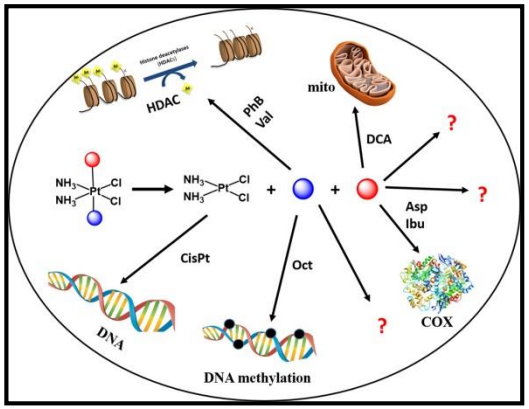
DISCOVERY OF NEW PLATINUM ANTITUMOR AGENTS THAT KILL CELLS BY A MULTIMODAL MECHANISM OF ACTION

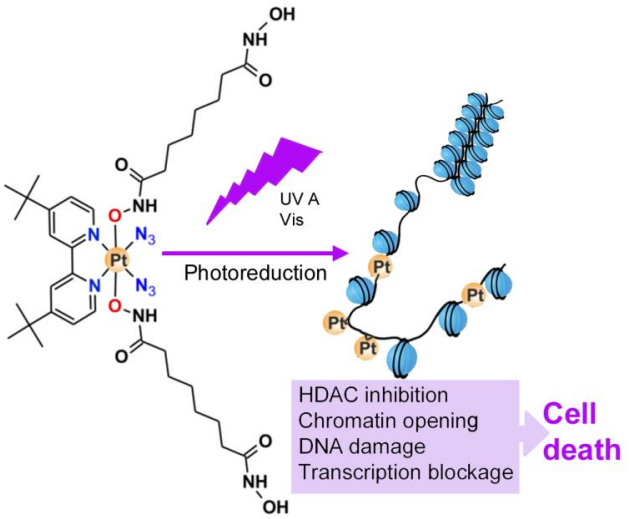
We show that the **Pt(IV) derivatives of cisplatin, oxaliplatin and other anticancer Pt(II) complexes with various biologically active axial ligands act by multimodal MoA**. This MoA results in the global biological effects, that is, the Pt(IV) derivatives **damage nuclear DNA, reduce the mitochondrial membrane potential, induce the epigenetic processes**, and last but not least, the data provide evidence that **changes in the organization of cytoskeleton networks** are functionally important for some Pt(IV) derivatives, in contrast to clinically used platinum cytostatics, to kill cancer cells.



Kostrhunova, H.; Zajac, J.; Novohradsky, V.; Kasparkova, J.; Malina, J.; Aldrich-Wright, J. R.; Petruzzella, E.; Sirota, R.; Gibson, D.; Brabec, V. A subset of new platinum antitumor agents kills cells by a multimodal mechanism of action also involving changes in the organization of the microtubule cytoskeleton. *J. Med. Chem.* 2019, 62, 5176-5190. **IF= 6.054**. Kostrhunova, H.; Petruzzella, E.; Gibson, D.; Kasparkova, J.; Brabec, V. A new anticancer Pt(IV) prodrug that acts by mechanisms involving DNA damage and different epigenetic effects. *Chem. Eur. J.* 2019, 25, 5235 – 5245. **IF=5.160**. Novohradsky, V.; Zanellato, I.; Marzano, C.; Pracharova, J.; Kasparkova, J.; Gibson, D.; Gandin, V.; Osella, D.; Brabec, V. Epigenetic and antitumor effects of platinum(IV)-octanoato conjugates. *Sci. Rep.* 2017, 7, 3751. **IF=4.011**. Raveendran, R.; Braude, J. P.; Wexselblatt, E.; Novohradsky, V.; Stuchlikova, O.; Brabec, V.; Gandin, V.; Gibson, D. Pt(IV) derivatives of cisplatin and oxaliplatin with phenylbutyrate axial ligands are potent cytotoxic agents that act by several mechanisms of action. *Chem. Sci.* 2016, 7, 2381-2391. **IF=9.556**.

A PHOTOACTIVATABLE PLATINUM(IV) COMPLEX TARGETING GENOMIC DNA AND HISTONE DEACETYLASES

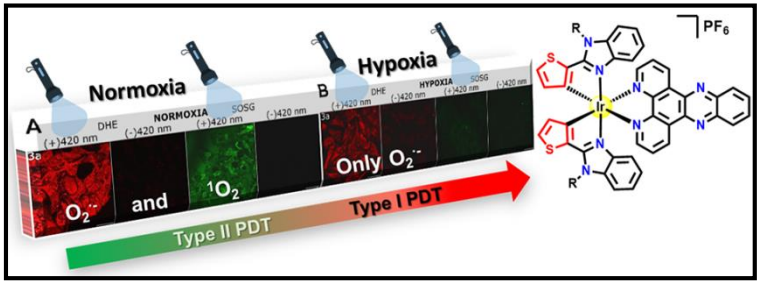
We reported toxic effects of **photoactivatable platinum(IV) complex** conjugated with **suberoyl-bis-hydroxamic acid** in tumor cells. The conjugate exerts, after photoactivation, the two functions: activity of both **platinum(II) anticancer drug and histone deacetylase (HDAC) inhibition** in cancer cells. The novelty of this approach resides in the use of a Pt(IV) pro-drug, acting by two independent mechanisms of biological action in a cooperative manner, which **can be selectively photoactivated to cytotoxic species in and around a tumor** thereby increasing selectivity towards cancer cells. The results suggest that this new strategy is a valuable route to design new platinum agents with higher efficacy for photodynamic anticancer chemotherapy. *Recent advances in laser and fiber-optic technologies make it possible to irradiate also internal organs with light of highly defined intensity and wavelength.*



Kasparkova, J.; Kostrhunova, H.; Novakova, O.; Křikavová, R.; Vančo, J.; Trávníček, Z.; Brabec, V. A photoactivatable platinum(IV) complex targeting genomic DNA and histone deacetylases. *Angew. Chem. Int. Ed.* 2015, 54, 14478-14482**. IF=12.257.**

THE ANTICANCER ACTIVITY OF THE NEW PHOSPHORESCENT IRIDIUM(III) COMPLEXES SUITABLE FOR PHOTODYNAMIC THERAPY ACTING AS PROTEOSYNTHESIS INHIBITORS

The **phototoxicity in cancer cells of three series of octahedral Ir(III) complexes** of general formula $[Ir(C^N)_2(N^N)][PF_6]$, where the N^N ligand is dipyrido[3,2-*a*:2',3'-*c*]phenazine (*dppz*) and the C^N ligands are deprotonated 2-phenyl-, 2-(naphthalen-2-yl)- or 2-(thiophen-2-yl)-benzimidazole derivatives (**series 1, 2** and **3**, respectively) with different substituents (H, methyl or 4-(trifluoromethyl)benzyl) on the imidazole units, has been studied. The compounds were found to be photoactive in model human cervical cancer HeLa cells (IC_{50} about 20 nM under irradiation conditions, λ_{exc} = 420 nm), inducing a substantial formation of apoptotic bodies as shown by flow cytometry. Some of these compounds showed the **high phototoxic indexes**. Notably, the antiproliferative activity of the photoactivated Ir(III) compounds was also significant under **hypoxic conditions** (2 % O_2). Further investigations on series **3** compounds have shown that molecular superoxide radical ($O_2^{-\bullet}$) generation is the main responsible for the oxidative stress induced by irradiation of the cells treated with the 2-(thiophen-2-yl)benzimidazole derivatives **3a**-**c**. The photopotentiation of compounds of series **3 also involves the formation of singlet oxygen ($^1O_2$)**. The results also showed that in tumor HeLa cells, the **generation of superoxide radicals** competed with singlet oxygen production in cells in normoxia, but became dominant under hypoxia.

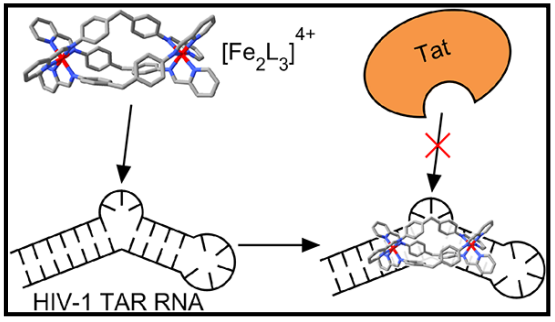


Novohradsky, V.; Vigueras, G.; Pracharova, J.; Cutillas, N.; Janiak, C.; Kostrhunova, H.; Brabec, V.; Ruiz, J.; Kasparkova, J. Molecular superoxide radical photogeneration in cancer cells by dipyridophenazine iridium(III) complexes. *Inorg. Chem. Front.* 2019, DOI: 10.1039/C9QI00811J.. **IF=5.934**.

IRON(II) SUPRAMOLECULAR HELICATES INTERFERE WITH THE HIV-1 Tat–TAR RNA INTERACTION CRITICAL FOR VIRAL REPLICATION

The binding of **the viral trans-activator protein (Tat) to the TAR RNA** is an essential step in the HIV-1 replication cycle. Therefore, **the blockage of the Tat-TAR interaction is a potential route for AIDS chemotherapy**. Compounds that bind to TAR RNA, and prevent binding by Tat, could disrupt processive transcription and thereby inhibit viral growth.

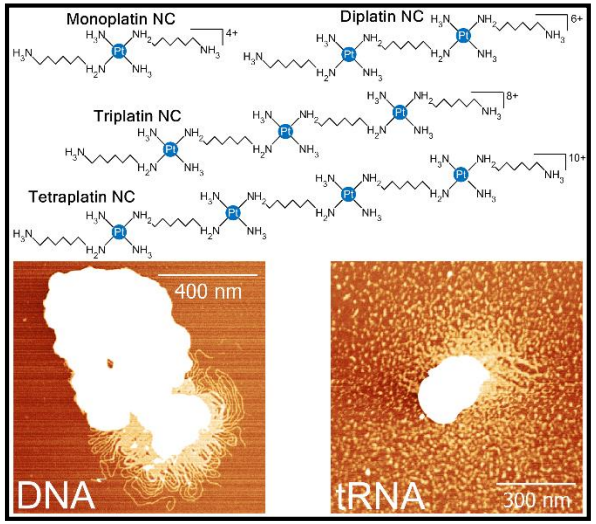
The interaction between the HIV-1 transactivator protein Tat and TAR (transactivation responsive region) RNA, plays a critical role in HIV-1 transcription. **Iron(II) supramolecular helicates were evaluated for their *in vitro* activity to inhibit Tat–TAR RNA interaction** using UV melting studies, electrophoretic mobility shift assay, and RNase A footprinting. The results demonstrate that **iron(II) supramolecular helicates inhibit Tat-TAR interaction at nanomolar concentrations by binding to TAR RNA with high affinity**. Thus, **iron(II) supramolecular helicates inhibit the HIV-1 Tat-TAR interaction at notably lower concentrations than many inhibitors of Tat-TAR binding so far tested**. These studies provide a new insight into the biological potential of metallosupramolecular helicates.



Malina, J.; Hannon, M. J.; Brabec, V. Iron(II) supramolecular helicates interfere with the HIV-1 Tat–TAR RNA interaction critical for viral replication. *Sci. Rep.* 2016, 6, 29674; doi: 10.1038/srep29674. **IF=4.011**.

SUBSTITUTION-INERT POLYNUCLEAR PLATINUM COMPLEXES ACT AS VERY POTENT INDUCERS OF CONDENSATION/AGGREGATION OF DNA AND RNA INCLUDING THEIR SHORT FRAGMENTS THAT MIGHT HAVE POTENTIAL IN GENE THERAPY, BIOTECHNOLOGY, AND BIONANOTECHNOLOGY

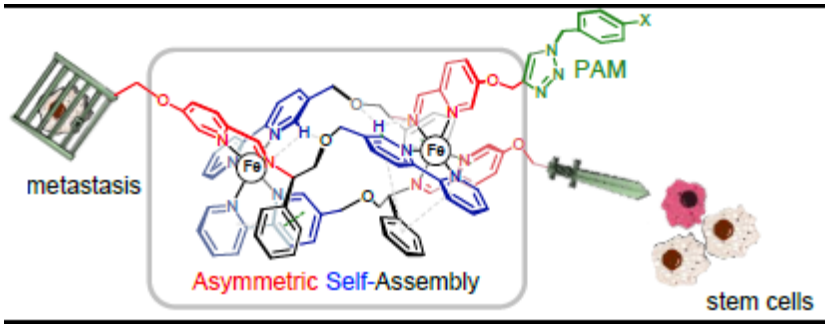
The **substitution-inert polynuclear platinum complexes (SI-PPCs) represent a unique group of platinum-based anticancer agents** that exhibit high affinity towards nucleic acids. We investigated the effects of SI-PPCs containing dangling amine groups in place of NH_3 as ligands to increase the length of the molecule and therefore overall charge and its distribution. The results obtained with the aid of **biophysical techniques, such as total intensity light scattering, gel electrophoresis and atomic force microscopy** show that addition of dangling amine groups considerably **augments the ability of SI-PPCs to condense/aggregate nucleic acids**. Moreover, this **enhanced capability of SI-PPCs correlates with their heightened efficiency to inhibit DNA-related enzymatic activities**, such as those connected with DNA transcription, catalysis of DNA relaxation by DNA topoisomerase I and DNA synthesis catalyzed by Taq DNA polymerase. Thus, the structures of SI-PPCs, which differ so markedly from the derivatives of cisplatin used in the clinic, appears to contribute to the overall biological activity of these molecules.



Malina, J.; Farrell, N. P.; Brabec, V. Substitution-inert polynuclear platinum complexes act as potent inducers of condensation/aggregation of short single- and double-stranded DNA and RNA oligonucleotides. *Chem. Eur. J.* 2019, 25, 2995–2999 **IF=5.160**; Malina, J.; Čechová, K.; Farrell, N. P.; Brabec, V. Substitution-inert polynuclear platinum complexes with dangling amines: Condensation/aggregation of nucleic acids and inhibition of DNA-related enzymatic activities. *Inorg. Chem.* 2019, 58, 6804-6810. **IF=4.850**.

DISCOVERY OF SELECTIVE, ANTI-METASTATIC AND ANTI-CANCER STEM CELL METALLOHELICES

Lehn envisaged in his original report that helicates – self-assembling multimetallic coordination compounds – may find uses in biochemistry. **Helicates** and related metallofoldamers, synthesised by dynamic self-assembly, represent an area of chemical space inaccessible by traditional organic synthesis, and yet with potential for discovery of new classes of drug. We reported that water-soluble, optically pure Fe(II)- and even Zn(II)-based triplex metallohelices are an excellent platform for post-assembly click reactions. By these means, **the *in vitro* anticancer activity and most importantly the selectivity of a triplex metallohelix Fe(II) system is dramatically improved**. For one compound, a remarkable array of mechanistic and pharmacological behaviours is discovered**: inhibition of Na^+/K^+ ATPase** with potency comparable to the drug ouabain, **antimetastatic properties** (including inhibition of cell migration, re-adhesion and invasion), **cancer stem cell targeting**, and finally **colonosphere inhibition** competitive with the drug salinomycin. This study was performed in collaboration with researchers of the University of Warwick in England.



Song, H.; Rogers, N. J.; Allison, S. S.; Brabec, V.; Bridgewater, H.; Kostrhunova, H.; Markova, L.; Phillips, R. M.; Pinder, E.; Shepherd, S.; Young, L.; Zajac, J.; Scott, P. Discovery of selective, antimetastatic and anti-cancer stem cell metallohelices via post-assembly modification. *Chem. Sci.* 2019, DOI: 10.1039/C9SC02651G. **IF=9.556**.