Organometallic (Fe, Ru, Ir, Os) phospho-inducers of drug-resistant cancer cells' ferroptosis

Anticancer drugs used today are still too unselective and cause several various side effects, leading to general destruction of the body. Therefore, developing a system that will selectively destroy only cancer cells is still one of the most important challenges in chemistry and medicine. Despite many excellent medical achievements in the field of cancer therapies, ***resistance to chemotherapy as well as disease relapses remain a huge clinical challenge.*** One of the strategies in designing new anticancer therapeutics is the use of compounds based on metal ions surrounded by selected ligands (metal drugs). Different metal centers may exhibit different coordination geometries and ***redox capabilities***, while ligands may additionally exhibit different biological activities. Moreover, metal ions have a high affinity for biologically important intracellular thiols, which may significantly disturb the intracellular redox balance, lead to protein and enzyme dysfunction, and even to the accumulation of lipid peroxides inside the cell, which may result in cell death *via* the so-called ***ferroptosis (fig. 1)***.

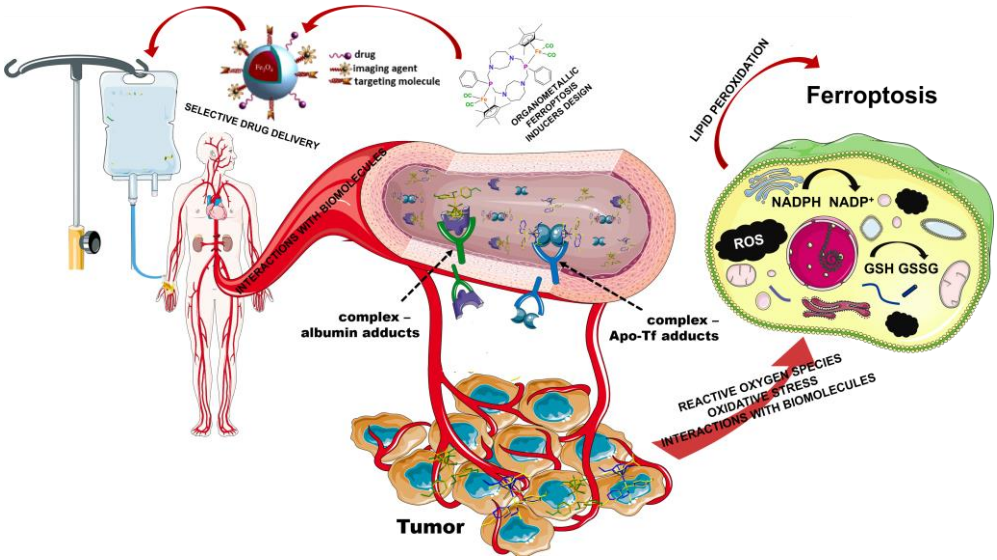

Figure 1. Schematic view of the proposed project.

The main objectives of the presented project are the design, synthesis, and characterization of Fe(II)/Fe(III), Ru(II), Ir(III), Os(II) **mononuclear** as well as **heteronuclear** Fe(II)/Fe(III)/M, Ru(II)/M, Ir(III)/M, Os(II)/M (M = Cu(II), Fe(II)/(III)) **complexes** leading to **ferroptosis of drug-resistant cancer cells**. Such metallic systems will consist of **mono- and di-phosphines** derived from biologically active amines, amino acids, and peptides **that can be selectively delivered** to the cancer cell surface. The aim is to better understand the stability and behavior of the proposed compounds in biological systems (cells, zebrafish model), detailed studies of their interaction with high and low molecular biomolecules (e.g., ctDNA, plasmid DNA, 9-ethylguanine, 9-methyladenin, human albumins, nicotinamide adenine dinucleotide. cysteine, glutathione, and ascorbic acid) mimicking natural, biological environment will be performed. In addition, to improve the efficiency and reliability of drug delivery to the tumor site, **nanoparticle systems for drug delivery** (e.g., liposome (pH-sensitive), micelle, magnetic micelle) will be developed (**fig. 1**).

In implementing this project, we are going to (*i*) develop an effective and efficient method for the synthesis of phosphines and complex-phosphine systems, (*ii*) determine the physicochemical properties of compounds, (*iii*) design and prepare the nanoparticles (e.g., magnetic nanoparticles, biomimetic nanoparticles), (*iv*) encapsulate the resulting complexes, (*v*) characterize the physicochemical properties of new multifunctional nanoparticles, (*vi*) examine their biological activity *in vitro* against various cancer and control cells and *in vivo* using zebrafish model, (*vii*) establish the mechanism of cancer cell death, (*viii*) examine the reactivity of complex-conjugates in various biological media, and in the presence of biomolecules.

The results of this project will be important for the development of several scientific fields: (i) contribution to the development of basic bioorganic and bioinorganic chemistry of phosphines and Fe, Ir, Ru, and Os complexes, (ii) an important step towards the use of amine/peptide/amino acid carriers as well as nanoparticles and magnetic nanoparticles in anticancer therapy, (iii) understanding the mechanisms of action will help in the future to create a therapeutic compound with anticancer properties.

Successfully obtained systems will be good candidates for the next stage of pre- and clinical research and in the future may be considered as medicines.