Homo- and heterometallic phosphine ruthenium and iridium complexes - design, synthesis, bioactivity and magnetic-nanoformulation as a potential platform for dual-targeted drug delivery.

Approximately 7 million people die from cancer-related cases per year, and it is estimated that there will be more than 22 million new cancer cases every year by 2030. Chemotherapy is one of the major approaches to treat cancer by delivery of a cytotoxic agent to cancer cells. Disadvantage of conventional chemotherapy is the inability to deliver the correct amount of drugs directly to cancer cells without affecting normal ones. Today, anticancer medications are not very selective. In addition, most of cancer treatments are delivered intravenously and accumulated in tumours containing the plenty of leaking blood vessels. Unfortunately, this affects healthy tissue and causes numerous side effects, ranging from bone marrow suppression to acute nephrotoxicity and, ultimately, the emergence of intrinsic and extrinsic platinum resistant cancers. All this makes that it is so important to understand the mechanism of cytotoxic action of therapeutics and thus develop a system that will selectively destroy only cancer cells.

Selective transport studies of chemotherapeutic agents are based on specific tumor cells properties such as the overexpression of various receptors. They can bind drug carriers e.g. peptides, proteins or antibiotics e.g. fluoroquinolones. Molecularly targeted drugs, for example antibody-based drugs, are known to bind to specific molecules in tissues. However, once they are administered, their target can no longer be changed. In contrast, magnetically based systems may have the advantage that delivery can be guided with magnet, even after drug administration, simply by applying a magnetic field. In addition, compared to traditional drug delivery systems, nanocarriers have shown greater potential in improving drug bioavailability, prolonging drug circulation time and controlling drug release. Nanotechnology plays an increasing role in molecular diagnostics, *in vivo* imaging, and improved treatment of disease.

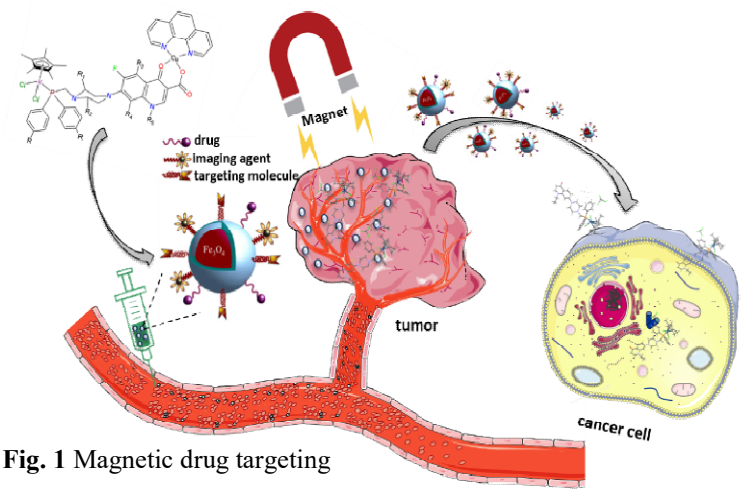

Fig. 1 Magnetic drug targeting

In this project we propose a novel approach – connecting the phosphine (derived from biologically active fluoroquinolone) with **homo (Ru^{II}; Ir^{III}) - and heteronuclear (Ru^{II}/Cu^{II}, and Ir^{III}/Cu^{II})** ***complexes encapsulated in multifunctional nanoparticles (especially magnetic ones) (fig. 1). In the literature there are no such systems reported so far.*** It is worth to note that the complexes with transition metal give wide possibilities in the design of new therapeutics, unavailable for organic chemistry. In addition, when we incorporate two different cytotoxic metals into the same molecule may improve their activity as antitumor agents because of the interaction of the different metals with multiple biological targets.

In implementing this project, we are going to:

(a) develop effective and efficient method for the synthesis of phosphine-fluoroquinolone conjugates and complex-fluoroquinolone systems,
(b) determine the physicochemical properties of the synthesized conjugates, mononuclear complexes of Ir^{III} and Ru^{II}, and heteronuclear complexes of Ru^{II}/Cu^{II} and Ir^{III}/Cu^{II} with phosphine derived from fluoroquinolones,
(c) design and prepare the structured magnetic nanoparticles,
(d) encapsulation of the resulting homo- and heteronuclear complexes,
(e) precise characterization of the physicochemical properties, including magnetism of new multifunctional magnetic nanoparticlesloaded with potential chemotherapeutics,
(f) examine their biological activity *in vitro* against several tumor and normal cell lines,
(g) establish the mechanism of cancer cell death induced by the tested compounds, and
(h) examine the reactivity of complex-fluoroquinolone systems with potential cellular targets and different biomolecules (DNA, albumin, lipid membranes).

The ultimate goal of this project is to develop complex-fluoroquinolone systems with high therapeutic index. In addition, design and prepare the structured magnetic nanoparticles, which will have potential application in magnetic targeting therapy with new bioactive molecules. Successfully obtained complexes will be good candidates to the next stage of in vivo research and in future may be considered as medicines