Do copper(I) complexes with conjugates of phosphine-peptide carriers can cause selective cancer cells death? Synthesis, physicochemical and biological properties.

Mortality from cancer is about to surpass that from cardiovascular diseases in near future. Approximately 7 million people die from cancer-related cases per year, and it is estimated that there will be more than 16 million new cancer cases every year by 2020. 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 drug directly to cancer cells without affecting normal cells. Today, anticancer medications are not very selective. They inhibit the breakdown not only pathological tumor cells, but also affects the normal, physiologically proliferating cells in the body. The side effects of chemotherapy concern mainly organs in which cells divide intensively inter alia: mucosa of the digestive system, ulcers and diarrhea; bone marrow, decrease in white blood cells and platelets; folliculitis. The chemotherapeutic agents may act also damaging the cells of heart, kidney, bladder, lung, nervous system, and many others. 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 such as carbohydrates, proteins or peptides. Cancer cells have the ability to generate their own growth receptor.Currently, there are many known peptide sequences that selectively bind to the molecular targets (receptors, proteins). Unfortunately their mechanism of action is still not clear.

Examples of such peptides carriers are RGD (Arg-Gly-Asp) motif and other NGR peptide (Asn-Gly-Arg) selectively recognize mentioned integrins - proteins responsible for the growth, division, adhesion and migration of cancer cells (peptides that have entered clinical trials). It is worth noting that mentioned motifs combined with doxorubicin, paclitaxel and fluorouracil cause significant decrease of *in vivo* toxicity of these drugs.

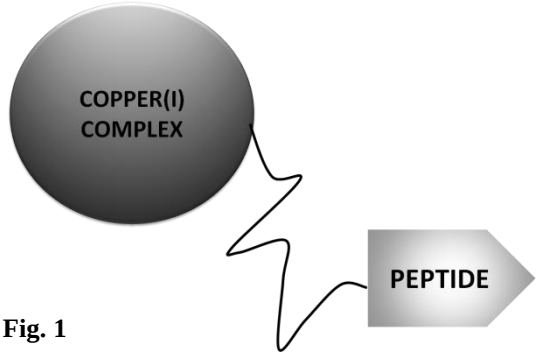

Fig. 1

In this project we propose a novel approach – connecting the peptide carrier with copper(I) complexes. In the literature there are no such systems reported so far (Fig. 1). It is worth to note that the complexes with transition metal give wide possibilities in the design of new therapeutics, available for organic chemistry. In addition, many transition metal complexes are intensively investigated as an alternative to imperfect platinum-based chemotherapeutic agents (for example well-known anticancer drug). An interesting example of complexes like this are phosphine-diimine copper(I) complexes characterized by durability and anticancer, antibacterials, antiviral, antifungal and inflammatory properties which makes them very good candidates as therapeutics.

In implementing this project, we are going to:

(**a**) develop effective and efficient method for the synthesis of phosphine-peptide conjugates and complex-peptide systems, (**b**) determine the physicochemical properties of the synthesized conjugates and their copper(I) complexes, (**c**) examine their biological activity *in vitro* against several tumor and normal cell lines, (**d**) establish the mechanism of cancer cell death induced by the tested compounds, and (**e**) examine the reactivity of complex-peptide systems with potential cellular targets and different biomolecules (DNA, albumin, lipid membranes).

The ultimate goal of this project is to develop stable complex-peptide systems with high therapeutic index. Successfully obtained complexes will be good candidates to the next stage of in vivo research and in future may be considered as medicines.