Multimodal gold nanoparticles as potential radiopharmaceuticals for targeted radionuclide therapy

Currently, besides the cardiovascular diseases, cancer is one of the leading causes of premature deaths in the world. Based on statistics, in the nearest future the overall number of deaths due to malignant cancers will grow systematically and become the main cause of death of people under 65 years old. In Europe, the most common types of cancer, which are responsible for half of all deaths are: lung, colon, breast, prostate, and gastric tumors. Unfortunately, the development of effective diagnostics does not follow efficient and non-toxic therapies. Chemotherapy and radiotherapy are the most often used conventional methods of cancer treatment besides surgery. Unfortunately, in many patients, especially in advanced stages or in recurrence, these methods appear to be ineffective and cause undesirable side effects. One of the reasons of the failure of standard antitumor therapies is the drug and radiation resistance of cancer cells.

Nowadays, ongoing studies on novel antitumor treatments are mostly focused on targeted therapies, including the so-called "targeted radionuclide therapy". This method is based on the use of radioactive isotopes, which are attached to biologically active molecules (exhibiting affinity to receptor on cancer cells) and selectively accumulate in cancer cells, destroying them without damaging the healthy tissues of the body. The choice of appropriate radionuclide is a critical factor for cancer treatment and depends on the tumor size and location. Among the low energy emitters of corpuscular radiation used for the treatment of small tumors in early stages or in metastasis, the ^{198}Au radionuclide shows very attractive nuclear properties ($t_{1/2}$ = 2.7 d, β_{max} = 0.96 MeV). Unfortunately, gold cations do not form stable complexes, therefore they cannot be bound to biomolecules in a conventional way. One of the promising approaches to attach ^{198}Au to a biomolecule is the application of gold nanoparticles using ^{198}Au radionuclide for their synthesis. The main advantage of this proposed method is that each nanoparticle contains a large number of radioactive atoms, whereas in the case of conventional radiopharmaceuticals the biomolecule is labeled with only one or few atoms of radionuclide.

The aim of this project is to synthesize radioactive gold nanoparticles (^{198}AuNPs) and attach them to the commonly used chemotherapeutic in oncology - doxorubicin and the guiding vector - octreotide (somatostatin analog). The project will consist of several steps: i) synthesis and characterization of radioactive gold nanoparticles; ii) synthesis of DOX-PEG and octreotide-PEG conjugates and their attachment to ^{198}AuNPs; iii) *in vitro* studies of the obtained multimodal radiobioconjugate; iv) biodistribution studies in mice. The crucial part of this project will be the synthesis of the smallest ^{198}AuNPs, due to their biodistribution in the body. Unfortunately, larger-size nanoparticles accumulate unspecifically in critical organs such as the liver, spleen and lungs. In addition, to improve the pharmacokinetic, the surface of nanoparticles will be modified by hydrophilic polymer - polyethylene glycol (PEG).

We expect that the use of cytostatic and radionuclide in one multimodal drug will enhance the therapeutic effect (synergistic effect) in comparison to compounds used separately. In addition, conjugation of octreotide, will enable to target neuroendocrine cancer cell overexpressing somatostatin receptors - SSTR2. We assume that combining both therapies will allow for application of lower doses of chemotherapeutics and ionizing radiation, significantly reducing the risk of side effects of the treatment. Proposing multimodal radiobioconjugate as a potential drug will enable a much more effective therapy of patients suffering from severe diseases, such as cancer.