Cancer is the second, after cardiovascular diseases, leading cause of morbidity and mortality in the world and its incidence has been steadily increasing. Surgery, chemotherapy and external beam radiation are the mainstays of human cancer treatment; however, they have their own limitations. Some tumors are inoperable as they are too big or located in sensitive parts of the body, e.g. brain. Chemotherapy targets all cells that grow and divide quickly; therefore, it cannot differentiate between cancer and healthy cells, hence causes some adverse side effects. In turn, the external beam radiotherapy is limited to well-defined solid tumor and is less effective once it has disseminated. Incremental success have been achieved with more selective therapies targeting biomarkers typical for a cancer cell or its environment. However, some cells exhibit inherited or acquired drug resistance against conventional therapies, resulting in relapse and progression of disease, especially in the case of breast, ovarian and gastric cancers overexpressing *Human Epidermal Growth Factor Receptor* type 2 (HER2). Increased amount of HER2 receptors is associated with a more aggressive phenotype of cancer characterized by fast tumor growth, lymph nodes invasion and rapid metastasis, resulting in poor prognosis, higher recurrence rate and a shorter time to relapse.

Targeted Radionuclide Therapy (TRT), also known as radioimmunotherapy (RIT), uses radionuclides which are emitters of corpuscular radiation (particles) and are attached to the appropriate biomolecule specifically binding to cancer cells, accumulating in them and delivering cytotoxic ionizing radiation. This kind of therapy is able to treat not only the primary diagnosed tumor but also undetected micrometastases, single cancerous cells (hematologic malignancies) or residual tumor margins after surgical resection. Monoclonal antibodies (mAbs), with high affinity to receptors on cancer cells, are so far the most widely used targeting biomolecules. However, they are not ideal for TRT due to their high molecular weight (150 kDa), resulting in suboptimal pharmacokinetics, poor tumor penetration, slow blood and normal tissue clearance that lowers therapeutic efficiency, while increases risk of healthy organs toxicity. Therefore, as an alternative we propose to use as tumor-targeting moiety, innovative small nanobodies (nbs; VHHs; sdAbs) molecules which are single-domain antigen binding fragments isolated from camelid heavy-chain-only antibodies. Due to their high specificity and binding affinity to receptors on cancer cells, as wells as low immunogenicity, they are attractive probes for imaging and radionuclide therapy. Their small size, 10 to 15-times lower compare to monoclonal antibodies, facilitates faster tumor accumulation and penetration, rapid elimination from blood and excretion from the body. Because nanobodies have simpler structure than intact antibodies, they can be produced easier in bacterial or yeast expression systems on a larger scale, faster and less costly.

In our studies, we are going to use novel internalizing (entering inside the cell) nanobodies specifically binding with HER2 receptor and radiolabel them with α- and β^--particle emitting radionuclides (e.g. ^{90}Y, ^{131}I, ^{177}Lu, ^{212}Pb, ^{225}Ac or ^{227}Th). Those nanobodies labeled with radionuclides decaying with the emission of α-particles, having short range in tissue corresponding to only few cells diameter, might be ideal for treatment residual, metastatic and disseminated cancers. While labeled with radionuclides emitting β^--particles, having longer range in tissue up to 12 mm, would be suitable for therapy of large, solid and heterogeneous tumors. Thus obtained radiopharmaceuticals, after intravenous injection, will spread throughout the body along with the blood, reach cancer cells and specifically accumulate in the tumor. This feature enables local radiotherapy from "inside" the tumor, without affecting healthy tissues, in contrary to the commonly used "external" beam radiotherapy. We hypothesize that internalizing properties of newly obtained radiobioconjugates will influence on their higher accumulation in cancer cells and by this enhance their therapeutic efficacy while simultaneously reduce risk of normal cells toxicity. Moreover, we are going to use also bivalent formats of internalizing nanobodies, in which two molecules of the same or different nanobody are combined through a short peptide-based linker. Those bivalent formats should express even better binding and internalizing properties than single molecules. As reference materials we are going to use mediocre- or low/non-internalizing anti-HER2 nanobodies or even those do not binding to HER2 receptor. We are planning to perform extensive *in vitro* studies on HER2-positive and HER2-negative human breast, ovarian and gastric cancer cells that would allow us to differentiate toxicity caused due to the internalization process. The obtained results will help us to find an answer to the following question: which combination of a radionuclide (α- or β^--particle emitting) *vs* type of an anti-HER2 nanobody (internalizing, mediocre- or low/non-internalizing) is the best match to achieve the highest therapeutic efficacy in the treatment of very aggressive and metastatic types of breast, ovarian and gastric cancers with HER2 receptor overexpression. Furthermore, we believe to obtain radiobioconjugates with potential use as new radiopharmaceuticals that in the future can become a standard therapy in targeted radionuclide therapy of HER2-positive cancers.