DESCRIPTION FOR THE GENERAL PUBLIC

Over the last decade, the number of death due to cancer significantly increased, despite the rapid progress in the diagnosis of even small, early stage of cancerous transformations. Currently, surgery, next to external radiotherapy, and chemotherapy and immunotherapy are the most common therapy options. Due to the spread of small size tumors to the bones, metastases treatment is one of the most challenging aspects of the therapy process for these tumors. The clinical goals of bone metastases therapy are to relieve pain, reduce the incidence of bone fractures and prolongation of survival time. In recent years, radionuclide therapy has been one of the most effective treatments for bone metastases. For this purpose, α and β^- particle emitting radiopharmaceuticals have been applied. Very good results are obtained in the treatment of pain by β^- emitters labelled bisphosphonates as well as in the case of $^{223}RaCl_2$ (α-emitter) prolongation of survival time. However, in the case of β^- emitters, a significant limitation is the relatively long range of the emitted electrons, which may destroy the bone marrow. Serious complications can also arise with ^{223}Ra therapy because in the decay of ^{223}Ra, α emitters ^{211}Pb and ^{211}Bi are formed, which can accumulate in healthy tissues.

However, we believe that using Auger electron emitters can significantly improve the efficiency of radiopharmaceuticals, allowing for not only pain treatment but also survival time extension. The low-energetic Auger electrons are emitted by some radioisotopes. Typically, 5 to more than 35 Auger electrons are emitted per decaying atom. The toxicity of Auger electrons is similar to the toxicity of high-LET particles, like α particles and produces highly damaging effects in cells. Because the path length of Auger electrons is short, smaller than the size of a cell, they are minimally toxic to surrounding non-targeted cells. In the case of Auger electron therapy, the barrier to the wider application of this method is the necessity to transport the radioisotope inside the cell nucleus. This is a very difficult task because we need to construct a radiopharmaceutical that first finds cancer cells and then places the radioisotope in the cell nucleus near the DNA strand.

The inspiration for the present project is two papers published in last year on the first successful studies of Auger electrons emitter (^{195m}Pt) bisphosphonate complex for therapy of bone cancer metastases. The therapeutic effect was significantly higher than for ^{223}Ra. Unfortunately, the production of therapeutic activities of ^{195m}Pt is very difficult and expensive. However, the production of ^{103}Pd (an isotope of element very similar to platinum) is much more efficient and cheaper. We believe that the use of ^{103}Pd($t_{1/2}$ = 16.99 d) bisphosphonates will open new perspectives for Auger electron therapy of bone cancer metastases. Although^{103}Pd emits X ray radiation and a only small number of Auger electrons, but decays to a radionuclide ^{103m}Rh ($t_{1/2}$=56 min), one of the most promising candidates for Auger radiotherapy.

Our idea presented in the project is to obtain radioactive palladium complexes by their synthesis from ^{103}Pd radioisotope ($t_{1/2}$=16.99 d), which is mother radionuclide of ^{103m}Rh, very effective emitters of Auger electrons. In our approach, synthesized mixed complexes of ^{103}Pd with bisphosphonates and aromatic diamine will accumulate on bone cancer cells, pass through the cell and nuclear membranes and intercalate into DNA, just as non-radioactive analog complexes which have been previously studied. Subsequently, as a result of nuclear decay $^{103}Pd \xrightarrow{EC} {}^{103m}Rh$, the Auger electron emitter ^{103m}Rh will be partially released from the ^{103}Pd complex. In the chemical form of $^{103}Rh_{aq}^{3+}$ it will bind to the DNA, inducing cytotoxic effects by Auger electron emission.

The proposed project will be carried out at the Centre of Nuclear Chemistry and Radiochemistry of the Institute of Nuclear Chemistry and Technology (INCT) in Warsaw. Part of the proposed project related to the production of Auger electrons emitting ^{103}Pd will be realized in cooperation with the National Center for Nuclear Research (Świerk, Poland) and Institute Laue-Langevin in Grenoble.

Positive results from planned experiments in the project will allow us to proceed in the future to the next stage which will be *in-vivo* studies on animal models. We believe that the obtained results will allow for more effective and precise treatment of cancer bone metastases. It should also be noted that the toxicity of our drug to healthy tissues will be negligible in contrast to radio- and chemotherapy.