DESCRIPTION FOR THE GENERAL PUBLIC (IN ENGLISH)

The project is devoted to basic research towards the design of new medical materials (radiopharmaceuticals). The obtained preparations will potentially be new medical compounds for cancer diagnosis and/or therapy. Rapid progress of sciences auxiliary to medicine (biology, biochemistry, chemistry, biophysics) allows for a much earlier diagnosis and thus an earlier start of treatment in many types of cancer. while the progress of radiochemistry allows for proper selection of diagnostic or therapeutic radionuclide. The finding that the NK1 receptor (NK1R) are overexpressed on glial tumour (glioblastoma multiforme), thyroid cancer, lung cancer, pancreatic cancer and breast cancer resulted in the interest in using Substance P (endogenous agonist peptide having a high affinity for the NK1 receptor) as a vector leading the diagnostic or therapeutic radionuclide to the tumour cells.

The practical aim of the project is to develop new potential NK1 receptor radiopharmaceuticals, based on the NK1R antagonists, for diagnosis and therapy of glioblastoma multiforme. The aim of basic research, planned in the first step of the project, is to design and synthesize new mixed peptide/non-peptide NK1 receptor antagonists (vectors, biomolecules).Then we plan to design and optimize the conditions of a coupling reaction between the selected biomolecules and macrocyclic ligands able to form stable complexes with selected radionuclides. The coupling of the ligand and the biomolecule must not cause a significant decrease in the biomolecule affinity to the receptor. The biomolecules to be used are NK1R antagonists.. These will be: selected newly synthesized biomolecules, peptidic compounds – Spantide I(1-11) (the derivative of substance P(1-11) and its shorter analogue Spantide I(5-11) (derivative of Substance P(5-11), as well as a non-peptidic compound – the drug aprepitant. As macrocyclic ligands, we shall use DOTA, DOTAGA and NODAGA.. In the next step, the obtained bioconjugates will be labelled with selected radionuclides (*e.g.* diagnostic Ga-68, therapeutic Lu-177). Then, for the obtained radiobioconjutgates, physicochemical (stability, lipophilicity) and biological (parameters IC_{50}, B_{max}, K_D, K_i, biodistribution) properties (important from the point of view of their use as new materials in nuclear medicine) will be studied. The *in vitro* biological tests will be performed using selected cell line having overexpression of the NK-1 receptor, e.g. T98G or U373. Results obtained in the course of the project will enrich the radiopharmaceutical chemistry and the compound with the best parameters (the compound that meets the requirements for radiopharmaceuticals) will be handed over to oncologists that may proceed it performing further research needed before a direct application (formulation, establishing of dosage regimes *etc.*)

The interest in the planned research topics is in direct connection with the current needs of nuclear medicine in the field of treatment of a brain tumour glioblastoma multiforme. These tumours are characterized by rapid growth, intensive migration and rapid spread within the surrounding nerve tissue. Such type of glioma growth (infiltration along the nerve fibres, blood vessels, pia mater and around nerve cells) often impedes the effective surgical resection of tumour, which follows in rapid recurrence, usually before the expiration of 52 weeks since surgery. The preparation currently used in medical experiments (in the Department of Nuclear Medicine, Central Clinical Hospital in Warsaw) is a receptor therapeutic radiopharmaceutical ^{213}Bi-DOTA-[Thi^{8},Met(O_2)^{11}]-substance P administered locally to the cavity after surgical removal of the tumour. The disadvantage of this approach is, among others, its poor effective migration into walls of post-surgery cavity what makes difficult to reach the single tumour cells and destroy them.

One can expect that a new radiopharmaceutical based on non-peptidic NK1R antagonist, containing therapeutic radionuclide (e.g. α radiation emitter) will become a new, more effective receptor radiopharmaceutical for glioblastoma multiforme therapy in comparison with the radiopharmaceutical currently used. Due to a presumably smaller molecular weight and higher lipophilicity it should be able to migrate into post-surgery cavity walls in a more effective way and to reach and destroy single tumour cells (sometimes located up to 2 cm away from the main tumour mass), among them also stem cells. Obtaining the new medical material will become another milestone in glioblastoma multiforme treatment.