Project goal:

One of the significant breakthroughs in the treatment of cancer patients has recently been made by using immune cells genetically modified to express so-called **chimeric antigen receptors, CAR**) in order to selectively fight the cancer cells in the body. Despite the success of this strategy in hematological malignancies, there is much to be done to benefit the patients suffering from solid tumors, such a s breast cancer, both in the efficacy and safety areas. The principal goal of the current project is elaborating a new strategy for genetic modifications of a specialized type of immune effector cells (called **natural killer cells, NK**) in order to make the CAR-NK therapy highly precise against the tumor and safer for the patient.

Description of research:

In the current project, we have plan to use a natural system of trafficking of the immune cells to various locations in the body. This system involves factors called chemokines, that are being produces in the tissues and attract the immune cells via acting on chemokine receptors on their surface. Hereby, we plan to study the set of chemokines produced by malignant cells and tumor microenvironment and to utilize the strategy of armoring the CAR-NK cells with the respective chemokine receptors binding the tumor-produced chemokine. The **novelty of our project** relies on the fact that in addition to trafficking the CAR-NK cells via chemokines and chemokine receptors, we will make the **appearance of CAR on the surface of the NK cells dependent on activation of the particular chemokine receptor**. That would allow using CAR against ubiquitous proteins, such as PD-L1 molecule described in the current project, as using the regular CAR-based approach against such molecules raises a significant danger of severe adverse effects.

The reasons for attempting the research topic:

Despite progress in the areas of cancer prevention and treatment, malignant tumors are still a significant and growing problem in the modern world. There is a vital need for new, efficient and safe therapies of this deadly disease. In the recent years, a strategy called an **adoptive immunotherapy** has been introduced to the oncology. This therapy uses the immune effector cells derived from the patient, such as T lymphocytes or natural killer (NK) cells. The real progress has been achieved by generating the new systems of genetic modifications involving the **CAR-based technology**. CARs allow the immune cells to specifically recognize surface proteins on cancer cells and to almost immediately kill the target, making the CAR-T or CAR-NK cells a highly precise molecularly-driven “knives” capable of physical elimination of cancer cells from the body. However, in real life **CAR-based technologies need a significant improvement**, especially in solid cancers, to be satisfactorily efficient and at the same time relatively precise and safe for the patients. It is therefore necessary to develop new therapeutic strategies in this regard, as proposed in the current project.

Substantial results expected:

In the current project, we use modern CAR technology to provide evidence for the experimental effectiveness and safety of eliminating such cancer cells that express a model protein also found on healthy tissues. In addition, the project will provide key information on the impact of signaling through chemokine receptors on gene expression profiles in NK cells, which will increase general knowledge about how the immune system works. In summary, the results of this project can have a direct impact on improving the effectiveness and safety of immunotherapeutic strategies used in modern oncology.