The reasons for choosing the research topic:

Cancer is the major challenge to modern medicine. Despite the advances in the field of diagnosis, prevention and treatment of malignancies, the results of therapeutic approaches are still far from satisfactory. In recent years, immunotherapy has emerged as a potent weapon against cancer. In particular, a great breakthrough has been made in use of so-called adoptive cell transfer that takes advantage of the patient's own genetically modified T lymphocytes or NK cells that express chimeric antigen receptors (CARs). CAR receptors enable immune effector cells specific recognition of proteins present on the surface of tumor cells. This recognition triggers their cytotoxic response that consequently lead to cancer cell elimination. However, despite the spectacular success of CAR-based therapy in treatment of blood cancers (such as leukemia or lymphoma), still it has only limited efficacy in the treatment of solid tumors. One of the main reasons for that outcome is a hostile, immunosuppressive microenvironment surrounding tumor cells that inhibits effector functions of T cells and NK cells. Importantly, the essential hallmark exhibited by the tumor milieu is an increased inflammatory activity that among others is associated with production of a large number of reactive oxygen species (ROS) followed by the generation of oxidative stress that impair antitumor response. Recent studies show that CAR receptors do not only serve as a guide that allow precise recognition of tumor cells but also introduce distinct changes in the biology and response of CAR-modified cells. Our initial results have not only shown the profound differences in response to redox stress among individual subsets of lymphocytes but also that, depending on the type of CAR modification used in a study we could observe improved or decreased viability of CAR-modified cells in presence of oxidative stress. Therefore, in this proposal we will focus on developing more effective therapeutic strategies that can shield CAR modified effector cells against oxidative stress.

The aim of the project:

The aim of the project is to elucidate the mechanisms regulating the functions of the CAR-modified cytotoxic cells under oxidative stress and to identify new strategies to improve the efficacy adoptive cell therapy with CAR-redirected immune cells with the increased resistance to oxidative stress.

Implementation of the project:

In the current project, we have planned the implementation of four Research Tasks. In Task 1, we will characterize the sensitivity of the distinct lymphocyte subsets towards tumor microenvironment-induced oxidative stress. In Task 2, we will examine the redox status and oxidative stress generated by inflammatory malignant cell lines. Next, in Task 3, we will test what type of CAR construct is the most efficient in increasing the efficacy of the CAR-modified cytotoxic cells ability to eliminate cancer cell lines characterized by high oxidative stress. Finally, in Task 4, we will evaluate of the efficacy of oxidant-resistant CAR-modified cytotoxic cells in vivo.

Expected results:

In the current project, we will identify key mechanisms for antioxidant defense systems of CAR-modified cytotoxic cells. We believe that by improving the efficacy of CAR-armored cytotoxic cells, we will achieve better results for their efficacy in a hostile oxidative tumor microenvironment. The results of this project can impose a direct impact on improving the effectiveness of the immunotherapeutic strategies used in modern oncology.