Reasons for undertaking the research topic: Diffuse large B-cell lymphoma (DLBCL) is the most common hematologic malignancy. It is an aggressive, but potentially curable malignancy. The use of the first-line therapy based on the combination of the monoclonal antibody rituximab (RTX) with chemotherapy leads to a cure in about 50% of patients. Unfortunately, in the remaining patients, mechanisms of resistance and tumor recurrence develop. This group of patients has a very poor prognosis, as only half of them survive for more than six months. Currently, the most promising therapeutic option for this group of patients is cellular immunotherapy. Natural killer (NK) cells are a unique population of lymphocytes capable of efficient killing of tumor cells. In the recent years there is a considerable interest in their application in the therapy of cancer, including lymphoma. However, the results of our preliminary results suggest that lymphoma cells that have been treated with RTX acquire a more aggressive phenotype characterized with resistance to cytotoxicity of NK cells.

Aim of the project: The aim of the project is to investigate the mechanisms leading to the ineffectiveness of NK cells in DLBCL cells resistant to rituximab. The knowledge gathered during the project will allow us to propose new effective strategies in patients with DLBCL resistant to the first line of treatment.

Research description: As part of the project, we plan to create new models of lymphoma cell lines resistant to monoclonal antibodies. We will characterize the changes in proteins on the surface of resistant cells. In cooperation with Prof. Watzl, a world-renowned expert in the field of cytotoxicity mechanisms of effector cells of the immune system, we will investigate which stages of NK activity are impaired in contact with resistant lymphoma cells. We will look for protein interactions between cancer cells and effector cells of the immune system, which are crucial for the effective process of eliminating cancer cells. We will validate our findings in primary material. Finally, based on the results generated throughout the project, we will design new, more effective against rituximab-resistant cells strategies of cellular immunotherapy, which we will test in cell line models and primary material.

Key expected outcomes: By better understanding of the mechanisms by which exposure to monoclonal antibodies inhibits the effectiveness of NK cells, we expect to develop a new therapeutic strategies for DLBCL patients. Although rituximab has been used in haemato-oncology for almost 30 years now, the mechanisms leading to the emergence of resistance to second-line therapies are still not elucidated. With our research, we want to contribute to filling this gap. The outcomes achieved through this project will establish a basis for a larger follow-up collaborative project. This forthcoming initiative will aim to create a CAR NK cell construct to be tested in lymphoma patients.