**Reasons for choosing the research topic:**

B cell lymphoma and leukemia are malignant neoplasms derived from B lymphocytes. B lymphocytes, also known as B cells, are a type of white blood cells. Their unique feature is an ability to produce antibodies, so they are crucial components of the humoral immunity. However, before B cells are able to produce specific antibodies, they undergo a multi-step development process. B cell precursors originate in the bone marrow, undergo maturation and migrate to the lymph nodes. In the lymph nodes they encounter antigens, proliferate in so called germinal centers and differentiate to effector cells producing antibodies. B cell neoplasms may develop at various stages of B cell development. B cell non-Hodgkin lymphoma and B cell chronic lymphocytic leukemia derive from mature germinal or post-germinal center B cells. They are the most frequent hematological cancers in adults. These malignancies are mainly treated with chemotherapy combined with monoclonal antibodies. Although the response to therapy is relatively good, up to 30% of patients experiences relapse, which is usually resistant to therapy. Therefore, new therapeutic strategies to better treat resistant disease and decrease side effects of the existing aggressive treatment are urgently needed.

Malignant B cells due to increased metabolism and treatment with chemotherapy generate higher levels of reactive oxygen species as compared to their normal counterparts, which results in oxidative stress. This triggers upregulation of antioxidant enzymes, which, in stress conditions, support malignant cell growth and may confer treatment resistance. In our preliminary studies in cell line models of non-Hodgkin lymphoma and B cell chronic lymphocytic leukemia we have observed synergistic cytotoxic effects of a combination of two agents: an inhibitor of an antioxidant enzyme and a prooxidant compound. Noteworthy, the combination kills > 90% of malignant B cells in concentrations which are not toxic when applied as single agents. Importantly, the combination caused no toxicity to normal B cells.

**Objective of the project:**

The main goal of this project is to test the efficacy and selectivity of the combination treatment towards a broader range of B cell neoplasms in preclinical studies. Furthermore, we will investigate the mechanisms of the combination treatment and its effects on key signaling pathways in malignant B cells. Notably, both components of the combination are approved for clinical use in other diseases, so the pharmacokinetics and safety profile are well recognized. If the animal studies planned within this project confirm the effects observed in cultured cells, the combination could quickly enter into clinical trials. The results of our studies can be translated into novel, clinically applicable treatment of B cell derived malignancies.

**Research to be carried out:**

In this proposal we have planned three research tasks. In *Task 1* we will investigate the effects of the combination on proliferation and survival of malignant and normal B cells. We will use established cell lines, primary cells derived from leukemia and lymphoma patients, as well normal B cells isolated from human tonsils. In *Task 2* we will evaluate the effectiveness of the combination in murine models. We will assess how the combination affects localized and disseminated B cell neoplasms as well as how it affects metastasis. Animal models are a golden standard of preclinical studies and are a necessary step before trials in humans. In *Task 3* we will study the mechanisms of the combination. We would like to find out what triggers the synergistic cytotoxic effect and will try to delineate the basis for the selectivity of the combination towards B cell neoplasms.