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B cell acute lymphoblastic leukemia is a malignant neoplasm of white blood cells. It is characterized by abnormal numbers of immature B cells, so called lymphoblasts, in the bone marrow. This type of leukemia occurs most frequently in children. It is treated mainly with chemotherapy. Although the response to therapy is relatively good, up to 20% of patients experiences relapse, which is usually resistant to chemotherapy. Despite effective treatment protocols, this type of leukemia is the second, after accidents, cause of death in children due to high incidence. Therefore, new therapeutic strategies to better treat relapsed or chemotherapy-resistant leukemia patients are urgently needed.

The cause of leukemia relapse is not entirely understood. Adaptation of leukemic cells to oxidative stress may be one of the reasons. Lymphoblasts divide rapidly in uncontrolled manner, which requires accelerated oxygen metabolism. The increased metabolism, together with chemotherapy, result in overproduction of reactive oxygen species and oxidative stress. This triggers upregulation of antioxidant enzymes, which, in stress conditions, support leukemia cell growth. Moreover, these enzymes may confer chemoresistance. Our preliminary studies suggest that one group of antioxidant enzymes, which belong to thioredoxin family, contributes to lymphoblasts survival. As the main goal of this proposal, we would like to validate this group of antioxidant enzymes as therapeutic targets in acute lymphoblastic leukemia. We will study how inhibition of these enzymes affects proliferation and survival of leukemia cells. Furthermore, we will investigate the efficacy of antioxidant enzymes inhibitors in combination with chemotherapeutics used to treat leukemia patients.

In our studies we will use cell line models, primary material (serum and bone marrow cells) derived from pediatric and adult leukemia patients, as well as murine model of human leukemia. We will use advanced lentiviral vector-based genetic modification techniques, high-throughput genetic methods, and bioinformatics analyses. To achieve our goals, we will establish an interdisciplinary team comprising cell biologists, biochemists, geneticists, experimental oncologists, clinicians, and bioinformatics analyst. Better understanding of leukemia biology, in particular the role of antioxidant enzymes, can lead to the development of novel therapeutic approaches, more effective drug combinations or reduce the side effects of the existing therapy.