B cell precursor acute lymphoblastic leukemia (B-ALL) is a genetically heterogeneous malignancy that affects mainly children but also adolescents and adults. In the past years, there have been made a significant progress in the treatment of this disease. Unfortunately, not all B-ALL genetic subtypes respond to classical treatment protocols. One of the subtypes which is characterized by extremely poor outcome is B-ALL with *MLL* gene rearrangements (MLLr B-ALL). This subtype of B-ALL affects mostly infants, rarely adolescents, but later the incidence increases with age. Considering poor response to the existing treatment, novel targeted therapies are needed to improve the MLLr B-ALL patients' outcome.

One of the novel targeted drugs which are tested in pre-clinical studies against MLLr B-ALL is venetoclax. This agent induces programmed cell death specifically in cancer cells. Venetoclax is already approved by Food and Drug Administration for the treatment of another B cell malignancy – chronic lymphocytic leukemia (CLL). The reason to use venetoclax in MLLr B-ALL is justified in many studies, however it is not fully effective as a single agent. The therapeutic regimens in B-ALL involve combination of many chemotherapeutics which may have synergistic effects. In this project we will investigate what mechanisms are involved in limiting venetoclax efficacy in MLLr B-ALL and will search for drugs to use in combination with venetoclax.

Another important issue in cancer treatment is the development of drug resistance. Acquired venetoclax resistance is commonly observed in many haematological cancers, including CLL, however the escape mechanisms are variable, specific for a particular cancer type. Thus far, the mechanisms of venetoclax resistance have not been described in MLLr B-ALL. For this reason, we will investigate the pathways involved in this process using the benefits of the new, high-throughput sequencing technologies. To achieve the goals of this study, we will perform *in vitro* and *in vivo* pre-clinical studies using MLLr B-ALL cell lines, as well as patients-derived primary malignant cells.

We believe that for the purpose of future clinical trials, our studies will help to identify the best drugs to use in combination with venetoclax. Looking further ahead, elucidation of the mechanisms involved in venetoclax resistance may contribute to the improvement in the therapy of MLLr B-ALL patients and thus their quality of life.