B-cell non-Hodgkin lymphoma is the 11th most common malignancy and cancer-related cause of death worldwide. 5-year survival rates range from very poor (20%) to over 90% and highly depend on the stage and subtype of B-cell lymphoma. Due to frequent relapse and toxic side-effects of current treatment regimens, there is a need for more specific treatments with fewer side effects. Cancers often present structural aberrations of the chromosomes. In B-cell lymphoma, the characteristic features are chromosomal translocations between the immunoglobulin heavy chain (IGH) locus and oncogenes such as *MYC, BCL2, BCL6, CCND1*. IGH locus contains three enhancers (Eμ, 3'RR1 and 3'RR2), which are DNA sequences that control transcription from the IGH locus, allowing expression of antibodies in B-cells. This is mediated by the so-called enhancer RNAs (eRNAs) – noncoding RNA transcripts produced from the enhancers. As a result of the translocation, the oncogenes are placed under the control of IGH enhancers and this leads to their high expression. Animal experiments demonstrated that mice bearing IGH translocations develop B-cell lymphomas. **However, the core IGH regulatory regions and eRNAs essential for driving oncogene expression and lymphomagenesis in human cancer cells have not been defined so far**. This question has been addressed by us using the state-of-the-art CRISPR/Cas9 technology. **We identified a region in the IGH enhancers that was essential for the growth of lymphoma cells**. We also confirmed that this region is transcribed into an enhancer RNA, and this transcript is in itself also crucial for lymphoma cells.

Given the fundamental role of IGH regulatory regions in lymphomagenesis, they appear as attractive targets for therapeutic approaches. So far, a few agents have been shown to affect activity of the IGH enhancers. However, their effect on lymphomas driven by IGH translocations has not been evaluated. Here, we propose a novel approach based on targeting eRNAs from the IGH region. RNA is not a linear molecule but folds into a variety of 3D structures. These structural elements can be specifically blocked by small molecules with drug-like properties. Recently, this approach has been successfully applied for a handful or RNA transcripts. Libraries of thousands of small molecules designed to target RNA are available and allow testing in a high-throughput manner. **The goal of this project is to develop a novel therapeutic approach for B-cell lymphoma based on inhibiting the IGH enhancer RNA.** To this end, we will conduct a high-throughput screening to identify small molecules binding to the eRNA transcribed from the essential IGH region. Next, hit molecules will be validated in lymphoma cells and normal cells. We will select molecules that inhibit growth of lymphoma cells but are not toxic for normal cells. Finally, efficacy and safety of selected molecules will be assessed *in vivo* in mouse models.

Results of our project will indicate novel therapeutic opportunities for treatment of B-cell lymphomas. **Our strategy will universally target IGH translocations, regardless of the oncogene involved.** This may be especially relevant for the group of so-called double hit B-cell lymphoma patients (with two oncogenes translocated to IGH), who in general respond poorly to current treatment regimens. **Results of this pre-clinical proof of concept study will provide novel B-cell lymphoma therapeutics with a direct translation to clinical studies.**