Role of histone H3 serine 10 (H3S10) kinases in deregulation of transcription in diffuse large B- cell lymphoma.

Diffuse large B-cell lymphomas are aggressive tumors, originating from the immune system cells and localizing primarily to the lymph nodes. These malignancies are very heterogenous clinically – with the currently available standard treatment options, only about half of the patients are cured, whereas remaining patients succumb to their disease. Recent years brought many important discoveries elucidating the molecular background of this clinical heterogeneity – lymphomas are also very heterogenous genetically.

DNA mutations result in altered cell functions and malignant transformation through production of altered proteins. Production of a DNA- encoded protein in the cell involves two steps: first, called transcription, produces messenger RNA (mRNA), which later serves as a template for protein synthesis. Transcription, a process of copying the genetic information from DNA to mRNA is thus crucial for a mutated gene to operate and to give rise mutated protein. Importantly, mutations of the transcriptional machinery do not occur in lymphomas, indicating that the process of transcription is fundamental for cancer cell division and survival.

Functioning of the transcriptional machinery involves very complex interactions between many specialized proteins that regulate the accessibility of DNA, recognize appropriate genes, and initiate and sustain transcription. Some of these proteins mark specific genes to be transcribed, whereas others recognize these marks and assemble the transcriptional complexes. The aim of the proposed project is to investigate how one of these marks, (phosphorylation of histone H3 serine 10) contributes to deregulated transcription in lymphomas. We will study the role of the enzymes that write this mark. Since this modification localizes to transcriptionally active genes, we hypothesize that pharmacological inhibition of these „writers" would interfere with deregulated transcription and might be a universal therapeutic option, independent of the underlying genetic lesions.