In “Expression, regulation and function of super-enhancer non-coding RNAs [seRNAs] in Diffuse Large B-Cell Lymphoma (DLBCL)”, I plan to investigate the roles of seRNAs in lymphoma carcinogenesis, the role of PIM proteins in seRNA production, and the disruption of seRNAs expression as a potential way to kill cancer cells.

The study will be performed in Diffuse Large B-Cell Lymphoma (DLBCL), the most common B-cell lymphoma in adults. DLBCL is an aggressive disease that with modern therapy can be cured in 50-55% of cases. The remaining patients succumb to their disease, which underscores the need for better therapies. One of the difficulties in the invention of a successful, universal treatment is the fact that although their clinical manifestation is similar, DLBCL cases significantly differ on the molecular level. Therefore, cells from different patients are vulnerable in different aspects. There are, however, a few similarities between DLBCL specimens that can be potentially targeted by a therapy. One of them is dependence of tumour cells on maintaining extremely high level of oncogenes.

Although cells within one organism usually have identical genetic material, diverse cell types exhibit different properties, such as function, shape, or metabolism, among many others. That phenomenon is possible through cell-type-specific regulation of gene expression, e.g. thanks to enhancers, which boost the transcription of selected, indispensable genes, depending on cell type. Every healthy cell, but also, importantly, pathogenic cancer cells heavily relies on these “bookmarks,” called super-enhancers (SE). In fact, cancer cells acquire SEs near oncogenes, which may start or reinforce carcinogenesis. SEs themselves have several regulators of their activity. One of them are non-coding RNAs, the formerly unrecognised “junk RNAs,” and it seems that depriving cancer cells of ncRNA production attenuates the cells (which makes it easier to destroy tumour with other agents), or even kill them. Fortunately for us, we might have such a ncRNA-disrupting drug that works in DLBCL, namely, an inhibitor of PIM proteins.

Although SEs are present in all cells, the presence of PIM proteins is inherent in blood and bone marrow cells (in low levels), while large amounts of this proteins is characteristic for cancer cells. PIMs play a role in many important cellular processes. Recently, our group began the investigation of yet new, non-canonical functions of PIMs in epigenetic gene expression regulation. The preliminary evidence shows that PIMs might be involved in the production of seRNA. Therefore, inhibition of PIMs is a virtually specific way to target and kill blood cancer cells, by disruption of the most crucial cellular functions – which possibly includes seRNA deregulation.

In order to comprehensively characterise PIMs’ role in the expression of ncRNAs related to SEs, I will conduct a 4-stage project, which combines laboratory work and in-depth computational analyses. Firstly, I will identify SE-related ncRNAs with the use of so-called new generation sequencing (NGS). Next, also with NGS, I will find ncRNAs dependent on PIM kinases. Then, I will select the overlapping ncRNAs from these two groups, that is seRNAs regulated by PIMs. In the third stage, I will look for a correlation of PIM-dependent seRNAs and protein-coding gene expression (usually, proteins are effectors of cellular activity). This way I will investigate whether the deprivation of certain ncRNAs can explain the diminished level of important proteins important for DLBCL that we have observed after PIM inhibition in our previous studies. Finally, I will verify the computationally predicted correlation between ncRNA and protein levels by performing laboratory experiments.

The proposed project will be the first to provide comprehensive information about the role of PIMs in the expression of ncRNAs. It will complete the ongoing research of SEs in DLBCL – the topic which is still not comprehensively characterised, but therapeutically potent. That knowledge will be useful in better understanding oncogenic mechanisms in DLBCL, as well as DLBCL treatment with PIM inhibitors as single agents, or in possible synergies.