Diffuse large B-cell lymphoma (DLBCL) is the tumor originating from lymph node-resident immune cells called B-lymphocytes. It the most common form of a B-cell malignancy in adults. Treatment of this disease involves multi-agent chemotherapy combined with antibodies. B-cell lymphomas are also susceptible to immunotherapies with modified T-cells. Our group has recently demonstrated that blocking the activity of proteins called PIM kinases induces lymphoma cell death, but simultaneously increases the susceptibility of the tumor to be attacked by the immune system.

During these previous studies, we characterized additional, potentially immunogenic consequences of PIM inhibition in lymphoma cells. PIM inhibition induced profound changes in the gene expression profile and caused DNA breaks. These observations were intriguing since the integrity of cellular DNA and fidelity of its replication is fundamental for cancer cell survival and induction of DNA damage is a central mechanism of activity of multiple cancer therapeutics. Second, recent studies indicate that DNA damage is not solely a prerequisite of cell death, but it can trigger and potentiate immune response, facilitating tumor elimination by the immune system.

We thus hypothesize that PIM inhibition might not only directly kill tumor cells (as we have previously demonstrated), but through DNA damage and generation of "danger signals", would engage immune system facilitating tumor elimination. For these reasons, we plan to characterize and understand in detail the mechanisms of PIM kinase inhibition-induced DNA damage. Fragmented tumor DNA leaked from the nucleus to the cytosol leads to activation of immune system. Generated inflammatory signals may reshape tumor microenvironment from "cold" (i.e. immune cell-depleted) to "hot", which helps the immune system to combat the tumor. This phenomenon, known as "immunogenic cell death" has recently been shown to facilitate tumor clearance in response to radiotherapy, certain chemotherapeutics, but also novel targeted drugs. In line with these findings, PIM-inhibitor treated lymphoma cells exhibited certain proinflammatory features. For these reasons, we will determine and characterize the immunogenic consequences of PIM inhibitor-induced DNA breaks using *in vitro* models and *in vivo* experiments. We will study additional features of immunogenic cell death and determine rational combinations of PIM kinase inhibitors with other drugs, boosting anti-tumor immune responses. Since pan PIM inhibitors are developed clinically and lymphoma trials are being planned, these features might be particularly important for lymphoma immunotherapies.