Cancer is still one of the leading causes of death and unfortunately, its incidence is still rising, which is a significant economic and social problem. Standard cancer treatment involves chemotherapy, radiotherapy and surgery. However, these therapeutic methods have severe side effects and are frequently only partially successful. Therefore, more effective and save therapeutic approaches are urgently needed. Due to basic research discoveries in the field of immunology and remarkable progress in genetic modification techniques, cancer immunotherapy has emerged as an alternative option for cancer treatment. In fact it is considered as the biggest breakthrough in cancer therapy in recent years.

Immunotherapy of cancer aims to mobilize the patient's own immune system to kill cancer. Immune system can protect us from foreign molecules – antigens, not only derived from infectious agents, but also from cancer cells. The crucial players in the development of immune response are antigen presenting cells, which engulf antigens, present them to T cells, and provide signals for effector T cells proliferation, which can subsequently kill cancer cells. However, the growing cancer often escapes from immune system control and blocks the development and function of the T cells. In the proposal we will identify the mechanisms how the tumor escapes from the control of the immune system, which in the future may improve cancer immunotherapy. Cancer immunotherapy is not equally effective in every type of cancer. One of the cancers, in which the effectiveness of immunotherapy is still limited, is chronic lymphocytic leukemia (CLL). It is one of the most prevalent hematological cancers in adults. CLL is a chronic, usually long-lasting disease but in many patients at some point it takes an aggressive form, resistant to treatment. For CLL patients with treatment-resistant disease the only treatment option is immunotherapy.

Unfortunately, the effectiveness of immunotherapy in CLL is limited. Presumably, one of the reasons is strong immunosuppression observed in CLL patients. Various immune system impairments have been observed in CLL including aberrant accumulation of regulatory T cells (Tregs). In mice models of solid tumors, it was revealed that depletion of Tregs triggers antitumor, effector T cell mediated immune response and results in tumor eradication. The role of regulatory T cells in hematological malignancies is poorly understood. In CLL patients, the increased frequency of Tregs is observed in peripheral blood, but no functional studies have been undertaken so far. Moreover, the elevated activity of indoleamine-2,3-dioxygenase (IDO), one of the key enzymes responsible for Tregs accumulation and activity, has been reported in CLL patients. However, current knowledge on the role of Tregs and the mechanisms of their induction and trafficking are insufficient to employ them for therapeutic targeting.

In this project, using the murine model of CLL that very well reflects the immune dysfunctions observed in CLL patients, we will investigate the role of Tregs and IDO in CLL. We want to answer the following questions: (1) do Tregs affect leukemia progression?, (2) how does Tregs depletion influence numbers and function of effector T cells and antigen presenting cells?, (3) what is the role of IDO in accumulation of Tregs during leukemia progression?, (4) does IDO affect leukemia progression?, (5) what are the consequences of IDO inhibition to other immune cell function?

We hope that the results of the project will greatly improve the knowledge on the immunoregulatory mechanisms affecting immune response in CLL. We believe that better understanding of the mechanism driving the immunosuppression in CLL will result in improvement of CLL therapy.