Every single day, cells of our immune system protect us from bacterial or viral infections by recognizing and destroying intruders. Some of the cells such as lymphocytes T are capable of “remembering” the pathogens, which is the basis of so-called immune memory. Interestingly, T cells are also able to recognize and destroy cancerous cells. This spectacular ability lead to attempts of using T cells in a new modality of cancer treatment – immunotherapy. To date, T cell-based immunotherapy was shown to have great potential in tumor eradication and induction of durable response. The success of CAR-T cell therapy in the treatment of B-cell malignancies lead to the recent approval of this therapy by the U.S. Food and Drug Administration (FDA). Nevertheless, the effectiveness of T cell therapy appeared to be limited in the case of solid tumors, due to the immunosuppressive tumor microenvironment (TME). One of the factors that has a negative impact on T cells, is a low oxygen level called hypoxia. Hypoxia in many leads to oxidative stress, which is an imbalance between free radicals and antioxidants in our body. Free radicals are associated with the aging process, the development of inflammation, and many diseases, such as diabetes, cardiovascular diseases, and cancer. Hypoxia and oxidative stress were shown to negatively influence T cell activation, cytotoxicity, or metabolism. But how do T cells know they are in a hypoxic environment? T lymphocytes, like other cells, receive stimuli from the environment with the help of appropriate receptors. The information that is received is then used by the cell to change its physiology to adapt better to changing external conditions. The group of receptors involved in receiving stimuli by the cells from the environment are, inter alia, the TRP ion channels. The most famous member of the TRP ion channels family is TRPV1, known as a capsaicin receptor. The discovery of the TRPV1 was awarded the Nobel Prize in Physiology and Medicine in 2021. Interestingly, TRP ion channels are also receptors of many natural compounds with immunomodulatory properties such as thymol, cinnamaldehyde or menthol. Among TRP channels, two of them, namely TRPA1 and TRPM2 deserve special attention regarding hypoxia and oxidative stress. TRPA1, known as a “wasabi receptor” is responsible for the detection of noxious stimuli from the external environment. TRPA1 was also shown to be activated by hypoxia and oxidative stress. Similarly, TRPM2 is described as an oxidative stress receptor. This means that TRPM2 is able to "sense" oxidative stress in the microenvironment, and its activation sends this information to the cell to turn on or off certain genes and subsequently respond to the external environment.

In the current project, we intend to investigate whether TRPA1 and TRPM2 play a role in regulating the immune response of T cells in relation to hypoxia. We will test whether the expression of TRPA1 and TRPM2 is influenced by hypoxia. We also intend to investigate how inhibition of the -A1 and -M2 channels influence T cell physiology. Hypoxia and free radicals were documented to influence immune cell metabolism. Recent studies show that modulation of T cell metabolism might be considered as a checkpoint, responsible for proper T cell functioning. For this reason, the presented project also aims to investigate whether inhibition of TRPA1 and -M2 influence T cell metabolism. We suspect that hypoxic signaling is at least partially received and transmitted by ion channels and thus both TRPA1 and -M2 might influence T cells physiology. Understanding the molecular aspects of T cell function may allow for the development of new treatments and might help to improve immunotherapy. In addition, research on the role of TRP ion channels in the immune system is still a relatively new and not fully understood area of knowledge, which is worth studying.