The impairment of the regulation of immune response is involved in the pathogenesis of various diseases. Insufficient suppression of excessive or unnecessary immune response results in chronic inflammation that leads to, among others, tissue damage. On the other side, excessive suppression of immune cell activity impairs the efficient elimination of pathogens or cancer cells. For the last decades, it was well established that immune cells are both crucial effectors and regulators of the immune response. However, recent studies reveal a previously underappreciated role of non-immune cells in the regulation of immune response.

$CD71^+$ erythroid cells (CECs) are one of the recently identified "non-immune" regulators of the immune cells' activity and functions. CECs are progenitors and precursors of oxygen-transporting erythrocytes (red blood cells). In healthy humans, they reside in the bone marrow where they are responsible for the production of erythrocytes. However, in some conditions CECs expand and accumulate in various organs outside the bone marrow, where they regulate the immune response. CECs modulate neonatal immunity, contribute to the development and maintenance of feto-maternal tolerance, and suppress the immune response in patients with advanced cancer. Depending on the condition, their role may be beneficial (by inducing tolerance to harmless microbes and the developing fetus) or detrimental (by suppressing host immunity against pathogens and anti-tumor immune response). Thus, modulating CECs functions seems to be a promising therapeutic strategy.

CECs use a variety of mechanisms to regulate the immune response. Despite observed differences in the immunoregulatory potential of CECs in various conditions, factors potentiating or decreasing their immunoregulatory properties remain unknown. One of the common factors of conditions in which CECs were identified to be potent immune suppressors is hypoxia (insufficient oxygenation). Thus, the aim of our project is to determine whether hypoxia is responsible for the regulation of CECs immune functions. The results of our preliminary experiments confirm that hypoxia may be a regulator of CECs immunoregulatory properties. In this project, we will investigate the effects of hypoxia on the expression of immunomodulatory genes as well as on the immunoregulatory potential of CECs on immune cells. To verify our hypothesis, we will perform experiments in different concentrations of oxygen as well as with hypoxia-mimicking chemical compounds. To achieve the goals of this project, we will perform *in vitro* studies using murine CECs, human erythroid cell lines, and healthy donor-derived primary CECs. Moreover, we will take the benefits of a murine model of T-cell immune response to confirm our findings *in vivo.* Furthermore, we will identify the molecular mechanism of observed effects.

We believe that our findings 1) will identify the first mechanism of the regulation of immunoregulatory properties of CECs and 2) will uncover novel therapeutic targets for the regulation of CECs functions in different human diseases.