

Depression is one of the most common mental disorders and its prevalence is increasing worldwide. Despite many years of intensive research, the pathomechanism of depressive disorders remains unclear. It is commonly believed that this condition is a multifactorial disease caused by the interaction of biological, psychological and social aspects. Our many years of research in collaboration with the world's leading scientists in the field of psychoneuroimmunology clearly show that depression is accompanied by the activation of the immune system. Moreover, the currently used antidepressant drugs reduce the proinflammatory activity of the immune system, which indicates that it is feasible to look for new therapies based on changes in the immune parameters.

This project aims to investigate the role of the main regulators of the immune system, i.e. the immune checkpoints (ICP), namely the programmed death receptor 1 (PD-1) and its programmed death-ligand 1 (PD-L1), in the development and course of depressive disorders.

The immune system inhibition by the interaction of the PD-1 receptor on the immune cells with PD-L1 expressed on the surface of cancer cells is considered one of the key mechanisms allowing cancer cells to avoid/escape the immune response thereby facilitating tumor growth through immune tolerance. This discovery revolutionized oncology, which was confirmed by the 2018 Nobel Prize awarded to the scientists Tasuku Honjo and James P. Allison for this research. Accumulating evidence points to the important role of the immune checkpoints in the central nervous system. So far, changes in checkpoint regulation have been observed in diseases such as brain tumors, Alzheimer's disease, ischemic stroke, spinal cord injury, multiple sclerosis and pain. However, to date, there are no scientific reports on the ICP role in the development of depression.

Our preliminary studies (conducted in animals) on the mechanism of depression showed significant changes in the regulation of immune checkpoints in the brains of the tested animals, indicating a previously unknown mechanism related to the development of depression. Accordingly, we hypothesize that the interaction of the immune and nervous systems occurs at the level of checkpoints. In our project, we will use animal models of depression, based on the paradigm of chronic stress and bacterial infection, to investigate whether a harmful environment affects the expression of immune checkpoints in the central nervous system. We will also investigate whether blocking the immune checkpoints will be able to directly influence the factors disturbed in depression. We postulate that understanding the mechanisms of regulatory immune checkpoints may contribute to finding new therapeutic targets in the future.

It should be emphasized that the immune checkpoint signaling in the brain has not been described so far in depressive disorders. Therefore, understanding the link between the immune and nervous systems engaged in the expression of the immune checkpoint may revolutionize psychiatry, just as it once revolutionized oncology.