Major depressive disorder (MDD) is a leading cause of global disease burden, potentially lethal, due to the high risk of suicide. Current therapies of depression are not optimal, therapies are long-lasting and often ineffective. These shortcomings are mostly due to insufficient knowledge of molecular mechanisms of the disease. To improve the situation, several global initiatives exist to resolve biological basics of distinct symptoms of depression at the cellular and molecular level. These joined efforts provided evidence that glial cells, significantly contribute to pathophysiology of depression.

In this project, we focus on one subtype of glia, namely astrocytes. These cells support neurons in several ways, e.g. they regulate levels of main excitatory neurotransmitter, glutamate, and they link this process to brain energy metabolism. Importantly, it has been reported that both, glutamate and energy homeostasis, are defective in the brain of patients suffering from depression, pointing to astrocytes as the possible cellular site of these disease. Strikingly, beneficial effects of recently developed antidepressant, ketamine, encompass restoration of glutamatergic synapse plasticity and normalization of glucose metabolism, suggesting that astrocytes may be a target of the drug. In this project, we aim to understand metabolic dysfunction of astrocytes in the context of depression to identify novel and more efficient therapeutic strategies.

One of the most common symptoms in patients with depression is glucocorticoid resistance. Glucocorticoids are hormones engaged in stress response, and they act as regulators of circadian metabolism across the body. A large body of evidence has shown the relationship between deficient glucocorticoid signaling and metabolic impairment in peripheral tissues, as this interaction occurs in several other disorders, for example diabetes. However, the impact of glucocorticoid resistance on the brain remains unknown.

We started to fill this knowledge gap by showing that astrocytes mediate many effects of glucocorticoids in the brain. Furthermore, we shown that chronic stress, a major risk factor in depression, has dramatic effect on gene expression profile in astrocytes. We therefore hypothesize that impaired glucocorticoid signaling accompanying depression negatively affects astrocytes metabolism. This view is supported by consistent downregulation of genes specifically in astrocytes, in the brain samples from MDD patients. In this project, my group will employ state-of-the-art genetic and imaging tools to explore this hypothesis.

We will focus on the protein FKBP5, a regulator of the transcriptional activity of glucocorticoid receptors. Interestingly, FKBP5 exists in several variants across the population studies shown that some of these variants are more frequent in the population of patients suffering from depression. To understand how these variants affect cell biology, a major effort was made to establish novel tools enabling functional studies of these variants. Hence, novel transgenic mice were generated which carry the human version of ‘high risk’ and ‘low risk’ variants. Moreover, new lines of pluripotent stem cells were established from healthy human or patients with treatment-resistant depression with specific variants of FKBP5. In this project, we will use these tools to examine the role of FKBP5 genetic variants in metabolism of two major brain cell types, neurons and astrocytes. By monitoring of metabolic processes in cells carrying the distinct variants, we will shed new light on the relationship between metabolic functions in a cellular model of MDD-relevant brain microcircuits. We believe that our approach will lead to deeper understanding of molecular mechanisms underlying depression, so much needed for accelerating the development of efficient therapeutic strategies.