ASTROMICS.

Major depressive disorder (MDD) is one of the leading causes of illness-induced disability worldwide. Despite this overwhelming burden, currently used antidepressive treatments are suboptimal: they are prescribed largely on a trial-and error basis, therapies are long-lasting, and only half of the patients respond to the first line of treatments. To alter the status quo, it is imperative to enhance the understanding the neurobiological basis of psychiatric disorders.

It is now accepted that depressive phenotypes stem from the interaction of genetic risk and environmental factors, particularly stress. We have previously shown that glucocorticoid receptor (GR) dependent signaling mediates many effects of chronic stress. These include alterations of glucose metabolism, mitochondrial performance and autophagy in multiple tissues and cell types. We also identified FKBP51 as a key modulator of GR-dependent signaling, which is particularly important in astrocytes. These cells are located at the interface of blood vessels and the brain parenchyma, which renders them ideally positioned to mediate the communication between systemic signals, such as hormones, and functioning of synapses. Moreover, astrocytes play a key role in controlling neurotransmitters levels and, crucially, govern brain energy metabolism. We therefore hypothesize that chronic stress affects the metabolic performance of astrocytes through deregulation of glucocorticoid-dependent pathways, leading to dysfunction of neural circuits controlling behavior. This connection may be especially important in females, which suffer from depression twice as frequent as males, and more commonly display metabolic phenotypes in disease.

In this project, the Astrocytes Biology group from Łukasiewicz-PORT in Wrocław (Dr M. Ślęzak), Neurohomeostasis group from the Uniklinik in Bonn (Dr. N. Gassen) and the Neurobiology of Stress Resilience group from the Max Planck Institute of Psychiatry in Munich (Dr. M. Schmidt) join their expertise to investigate the contribution of astrocyte-specific metabolic pathways to depressive-like phenotypes. Using advanced techniques of genetic manipulation, we will perturb the expression of three genes which, based on our joined data, may play a critical role in stress-induced metabolic dysfunction of astrocytes. We will manipulate those genes in the ‘brain stress center’ - prefrontal cortex - and examine how this intervention affects social behavior of females. In parallel, we will test the impact of our intervention on the local metabolites profile, parameters of mitochondrial function, autophagy and mitophagy, and fluctuations of main neurotransmitters, glutamate and GABA. Finally, we will test whether reversing stress-induced impairment of selected pathways can rescue molecular and behavioral effects of stress. Overall, this synergistic effort will reveal novel pathways for therapeutic intervention and is expected to improve treatment options for stress-related disorders.