Depressive disorder (DD, depression) is a severe psychiatric illness and one of the most frequently-diagnosed mental diseases. It affects more than 260 million people, which is more than 5% of the world's population, while the proportion is higher in developed countries and can reach as much as 10%. Due to the constantly increasing number of patients, depression is estimated to be leading, next to cancer and heart disease, economic and social problem. Wide spectrum of the disease symptoms such as persistent lack of pleasure (anhedonia) and interest, sense of fatigue and anxiety, often turn into chronic or recurrent, and without appropriate antidepressant treatment, may lead to suicide. Despite the fact that antidepressant drugs have been in use for over past few decades, more than one-third of the patients do not respond to traditional pharmacological medications. Therefore, failure to respond to conventional antidepressant treatment and incomplete knowledge about etiology of this disease, imply necessity for the investigation of DD. Nevertheless, growing body of evidence suggest role of that related biochemical pathways such neuroinflammation and neuroplasticity in depression. It is indicated that the disease is characterized by activation of microglia, i.e. immune cells resident within the central nervous system (CNS). This could contribute to neuroinflammation and nervous system disruptions, since activated microglia express pro-inflammatory molecules, such as chemokines, which act as neuromodulators, and thus play a role in brain functioning. Since, chemokines can interact with neurons and vice versa, it could be beneficial to understand cross-talk between inflammatory hypothesis and neuronal plasticity hypothesis. A key role in the etiology of this disorder may also play brain-derived neurotrophic factor (BDNF), a bridge between inflammation and neuroplasticity. Interplay between particular factors of each of mentioned pathways, and different pattern of their activity, may be responsible for various response or lack of response to antidepressant therapies, through interfering with their acting mechanism. However the use of many types of drugs, including selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SRNIs), has led to significant improvements in treatment outcomes, they have some restrictions, resulting in ineffective treatment. Therefore, it imply necessity for an investigation, which result in establishing a new, personalized approach to the patient and their treatment based on knowledge of the pathogenesis of depression. Comprehensive studies focused on determining the role of mentioned pathways in depressive disorder and in mechanism of antidepressant drugs acting in preclinical and clinical *in vitro* and *in vivo* studies at the genetic, epigenetic and functional level, may help in understanding of the molecular complexity of DD, and facilitate successful, targeted treatment. All experiments planned for this project will be conducted on material derived from peripheral blood from healthy controls and DD patients before and after antidepressant drug treatment (escitalopram, venlafaxine), as well as from peripheral blood and brain cells of rats (animal model of depression) before and after same drugs treatment.

The study will employ widely used animal model of depression, chronic mild stress (CMS), to induce depression-like behavior in rats. This procedure involves a long-term (several weeks) subjecting of the animals with variety of mild stress stimuli. This causes the gradual emergence of complex changes in stressed rats, behavioral, physiological and biochemical, showing a strong resemblance to the symptoms observed in patients with depression. The main symptom – anhedonia, which is the inability to experience pleasure will be determined by giving the animals access to a sweet drink and measuring how much they consume. Stressed animals usually drink less of the sucrose solution. CMS also makes them more anxious and bad at solving problems. However, daily treatment with antidepressant, their behavior returns to normal; they recover.

In this research, we will examine brain areas that are known to be important in depression, the hippocampus, prefrontal cortex and the rest of the brain areas. Use of these models may be helpful in complex understanding of the role and cross-talk between biochemical pathways in depression and mechanism of antidepressant drugs acting in peripheral circuit and central nervous system.

It is expected that all experiments, will bring us one step closer to understanding the molecular and biochemical processes underlying the pathogenesis of depressive disorders, and may facilitate early identification of disruptions causing depression, better prognosis for remission, and the development of targeted, personalized, successful therapy of this disorder.