Recurrent depression disorder (rDD, depression) is severe psychiatric illness, which at its worst can lead to suicidal death. It is also the world's most expensive illness in terms of working time lost to disability. Antidepressant drugs have been in use for over past few decades, but a high proportion of patients fail to respond to them. This condition is known as treatment-resistant depression (TRD). Although, pathogenesis of the disease has not be elucidated, growing body of evidence suggest a role of that related biochemical pathways such neuroinflammation, oxidative and nitrosative stress, trypthofan catabolites pathway (TRYCAT). A key role in the etiology of this disorder may also play an oxidative DNA damage (including elevated level of 8-oxoguanine - 8-oxoG) arising as a result of deregulation of these biochemical processes or altered protective antioxidative system, and finally, as our research group suggest, impaired DNA base excision repair (BER) - the main system removing oxidative DNA damage. Interactions between particular factors of each of mentioned biochemical pathways, and different pattern of their activity, variant in each rDD patient, may be responsible for lack of response to antidepressant therapies, through interfering with their acting mechanism. However the use of many types of antidepressant drugs, including selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SRNIs), has led to significant improvements in treatment outcomes, they have certain limitations, resulting in ineffective treatment and depression-related morbidity of rDD patients, thereby determining the need for establishing a new therapeutic methods 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 at the genetic, epigenetic and functional level, may help in understanding of the molecular complexity of rDD, and facilitate successful, targeted treatment.

All experiments will be done on material derived from peripheral blood (PB) from healthy controls and rDD patients before and after antidepressant drug treatment (escitalopram, venlafaxine, agomelatine), as well as from PB and brain cells of rats (animal model of depression) before and after same drugs treatment.

The study will employ a very widely used animal model of depression, chronic mild stress (CMS), to produce depression-like behaviours in rats. In the CMS model, the animal is bombarded with a variety of mild stressors – things like putting it together with another unknown rat, or leaving the lights on overnight. After a few weeks, the animal starts to show behavioural changes that are very similar to symptoms of depression: in particular, it becomes less responsive to rewards, which is thought to model the main symptom of depression, anhedonia (loss of pleasure). This is usually measured by giving the animals access to a sweet drink and measuring how much they consume. Stressed animals typically drink less of the sweet solution, but if they are then treated daily, for a few weeks, with an antidepressant drug, their behaviour returns to normal: that is, they recover. CMS also makes them more anxious and bad at solving problems (for example, recognizing that something in their environment has changed), and again, these behaviours also recover with antidepressant treatment.

We will examine two brain areas that are known from both laboratory and clinical studies to be important in depression and recovery, the hippocampus and the prefrontal cortex, as well as, additional areas of brain which may take a part in depression occurrence (amygdala, nucleus accumbens septi, striatum, hypothalamus, midbrain). Use of these models may be helpful in understanding the role of mentioned biochemical pathways in depression and mechanism of antidepressant drugs acting in peripheral circuit and central nervous system, as well.

It is expected that this study, will bring an understanding the pathophysiology of rDD at the molecular level and may facilitate early identification of changes causing depression, better prognosis of rDD, and the development targeted, successful therapy of this disorder, as well.