Objective of the project: According to the World Health Organisation study in primary care settings across the world, approximately one-fifth of all those patients suffer from persistent debilitating pain, and they are four times more likely to have co-morbid anxiety or depression than pain-free basic health care patients. The comorbidity of chronic pain and depression has been consistently associated with a poor prognosis and greater disability in patients as compared to those suffering from each illness alone. Also, the risk of suicide is significantly increased in chronic pain patients. Recent findings imply significant role of inflammation in the development of depression. Therefore, we would like to study the occurrence of depressive-like symptoms in animal model of OA with particular focus on accompanying neurotransmitter and neuroinflammatory changes.

Up to date, depression was perceived as isolated mental disorder, caused by a combination of genetic and environmental factors, where the depletion of serotonin, noradrenaline, and dopamine transmission was thought to be directly responsible for symptoms observed in depressive subjects. However, similarity of the symptoms to common cold and very high comorbidity between chronic illnesses and depression has led to suspicion that inflammatory factors may drive those changes. Indeed, scientists have discovered elevated levels of inflammatory proteins in the blood of patients with major depressive disorder (MDD). Furthermore, treatment with inflammatory cytokines (for example for chronic hepatitis) leads to onset of depression in around 30% of the patients. Further evidence comes from animal models of depression, in which we observe increase in inflammatory factors in both blood and the brain. Moreover, so-called "depressed" animals also develop the symptoms of chronic pain, namely hyperalgesia (excessive sensitivity to pain) and allodynia (pain sensation in response to stimuli which do not normally provoke pain). Hence, in the next step we are aiming at identifying relevant biomarkers in search for molecules associated with development of chronic pain and depression.

Description of the basic research to be carried out: In our project, we would like to tackle the question: how osteoarthritis is affecting inflammatory factors and neurotransmitters' levels in the brain and whether and how they are related to each other? In order to answer this question, we will assess the depressive-like behavior and anxiety in an animal model of osteoarthritis; subsequently we will measure the levels of neurotransmitters in the brain and inflammatory factors both in blood and in the brain. Moreover, we would like to counteract the symptoms of both pain and depression by targeting endocannabinoid system (ECS), which governs both immune and nervous system. We and other experts believe that maintaining homeostasis if the primary role of the ECS. ECS involves three core components: endocannabinoids, receptors, and enzymes. We'll focus on the last element. Using the latest discoveries of polypharmacology will not only target endocannabinoid degradation by stopping its hydrolysis (thus elevating the endogenously produced endocannabinoids) but we'll concomitantly dampen the action of pro-inflammatory prostaglandins with a single drug.

Just ten years ago, the idea that microorganisms in the human gut could influence the brain was often dismissed as wild. Not anymore. Current thinking in the field of neuropsychology and the study of mental health problems includes strong speculation that depression, and other psychological or neurological problems may also be associated with alternations in the microbiome. We'll try to unveil the link between gut microbiota composition and depression caused by chronic pain.

Reasons for choosing the research topic: The co morbidity of chronic pain and depression has been consistently associated with a poorer prognosis and greater disability in patients as compared to those suffering from each illness alone. The financial cost of these disorders is estimated in the billions, while the psychological and social effects are more difficult to quantify. This further has implications on significant financial costs to the patients and to our society. Although the field has evolved in the past decade, more efforts should now focus on understanding the biological underpinnings of this shared co morbidity, while shedding light on treatment implications for these two devastating conditions.

Impact of the results: A comprehensive research approach may provide information on OA markers and their usefulness in proposing of a new treatment regimen. We'll provide new evidence on the effectiveness of polypharmacology, which may lead to the development of a new therapy to treat pain and depression concurrently in comorbid.