Pain is a common phenomenon that accompanied human being throughout life. Under physiological conditions, the experience of pain stimuli protects our organisms from harmful effects of certain behaviors. Such situation changes when physiological sensation of pain stimuli becomes pathology developed as a consequence of various diseases, illnesses or injuries. Neuropathic pain developing at that time leads to the deterioration of both physical and mental health. Pharmacological treatment of neuropathic pain is challenging and often does not bring desired effects. The reason for this difficulty is the complexity of pathological changes that lead to such pain and its coexistence with other diseases. Typical pharmacotherapy of pain bases on the administration of opioids such as morphine or buprenorphine. These substances, however, cause numerous adverse effects what impedes their long-term application. Researchers are therefore focusing their attention on creating more effective pain relief scheme based in a therapy combined with other non-opioid substances alleviating pain symptoms (more often now used pentoxifylline or minocycline) with a concurrent decrease in opioid dosage. Knowledge of the mechanisms lying behind the development of neuropathy is still limited. It is known, however, that this process applies to both nerve cells and associated glial cells (microglia and astroglia). These cell populations "*communicate"* with each other through the release of a number of factors including immunological ones. The microglia cell activation causes increased synthesis and release of pro-inflammatory factors such as interleukin (IL)-1beta, IL-6 or chemokine CCL3 or XCL1. Neurons which release for instance chemokine CCL2 or CCL5 also have impact on glial cells by means of receptors located on their surface. It is considered that one of the causes for neuropathy is disorders of cytokine release, including chemokines – molecules with strong pro-nociceptive properties.

The purpose of our project is to determine the role of selected chemokines in the processes of the development of neuropathy. These small signaling molecules play a highly significant role in immunological processes. It seems, though, that their role in pathomechanism leading to pain is of equal importance. Currently, there are 20 chemokine receptors classified as well as 50 of their natural endogenous ligands. The participation of certain chemokines (e.g. CX3CL1 or CCL2) in pain pathogenesis has been already verified. However, what does require further research is the role of all other chemokines as well as the involvement of chemokine receptors in nociceptive transmission. Due to this fact we are planning to use two animal models with different pathomechanism and this will provide us with the opportunity to analyze the contribution of the three subfamilies of chemokines (C, CC and CXC) in the pathogenesis of neuropathic pain. The role of chemokines in the development of pain induced by mechanical nerve injury will be investigated by means of animal model of neuropathy (chronic constriction injury to the sciatic nerve). By the aid of streptozotocin diabetic neuropathy model we are planning to investigate the involvement of the abovementioned chemokines in pathomechanism of pain typical for diabetes - one of the most common diseases of the 21st century. We will be able to determine the extent of the involvement of chemokines in the pathogenesis of neuropathic pain by using a therapy scheme based on the immunomodulation of these chemokines changed in the course of neuropathy (application of neutralizing antibodies) as well as by antagonizing their receptors. Moreover, the study aims to address the issue of the effects of the activation of G protein-coupled chemokine receptors. In other words, the project aims at dealing with the modulation of intracellular pathways of signal transmission. Both approaches will be combined with a typical opioid therapy what will allow us to determine the substances which increase the effectiveness of applied opioids. Furthermore, the changes of chosen immunological factors important for nociception will be determined in astroglial and microglial cell cultures. Afterwards, they will be correlated with neuropathic changes which can be observed at the level of spinal cord and dorsal root ganglia.

Obtained results will allow us to propose a new therapeutic approach where the modulation of immunological factors (chemokines) will enable to attenuate pain symptoms. On the top of this, the aim of our studies constitutes the search for substances that, when applied alongside opioid drugs in clinic, will reduce dosages of these opioids with a simultaneous increase of their effectiveness. All experiments on animals are in accordance with the recommendations of the International Association for the Study of Pain (IASP). The project has obtained the consent of the Local Ethical Committee (LKE).