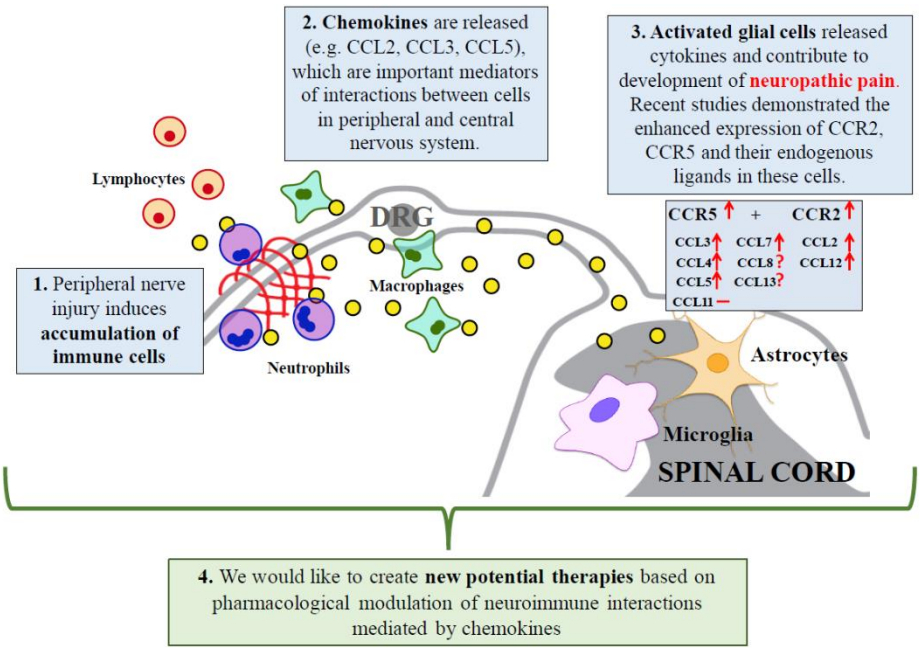
The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience connected with actual or potential tissue injury. We can talk about chronicity of pain when it lasts or recurs over the period longer than 3 months. It is estimated that currently it affects approximately 20% of adult Europeans, creating a serious clinical problem. When chronic pain results from a lesion or disease of the nervous system, we can talk about neuropathic pain characterized by allodynia, pain appearing due to a stimulus which normally does not induce pain and hyperalgesia, hypersensitivity to a nociceptive stimulus. Because of the wide range of accompanying symptoms such as sleeplessness, anxiety, or even depression, neuropathic pain has a negative influence on all aspects of patients' life, significantly lowering its quality. However, the therapy of neuropathic pain, despite numerous basic and clinical studies, remains extremely difficult, mainly due to the complex and still insufficiently understood mechanism underlying its development. Recent studies indicate that interactions occurring between neurons, glia and immune cells may be crucial for the generation and maintenance of neuropathic pain. It has been suggested that this processes are largely mediated by chemokines. In our current project we are intending to analyse the changes in the level of numerous intracellular factors and cytokines, especially interleukins and chemokines, involved in a pathological pain transmission after peripheral nerves injury. We would like to focus on two important chemokine receptors, by which these endogenous nociceptive factors may act, namely CCR2 and CCR5. The latest data indicates that their expression is changed under neuropathic pain, especially on neurons and glial cells. It is known that activated glia is an important source of pronociceptive mediators and inhibiting their activation brings beneficial effects in pain therapy. We are planning to determine whether the blocking of these two receptors can inhibit the secretion of pronociceptive factors involved in the formation of neuropathic pain and promote the release of antinociceptive factors contributing to the attenuation of painful symptoms. Moreover, we are planning to compare if these potential beneficial effects are enhanced in case of a simultaneous blocking of these two chemokine receptors. We would like to check if a direct inhibition of nociceptive chemokines, such as CCL2, CCL7 and CCL8, may have even more beneficial impact under neuropathic pain. The other reason for the lack of an effective neuropathic pain therapy is the fact that commonly used opioids lose their effectiveness in painful neuropathy. Thus, current studies are beginning to search for a successful combination drug therapy, which would allow for obtaining stronger analgesia without dangerous adverse effects. Previous reports suggest that some chemokines influence opioid-induced analgesia, and blocking their action by selective chemokine receptors antagonists can serve as applicable co-analgesics effective in a neuropathic pain therapy. In the light of such promising results, we would like to examine if a dual antagonist of CCR2 and CCR5, cenicriviroc, or an inhibitor of the CCL2, CCL7, and CCL8 release, bindarit, may enhance the analgesic potency of opioids used in clinic (e.g. morphine, buprenorphine, tramadol and/or oxycodone). We wish to compare if the eventual effects extend the effects of selective antagonists, such as maraviroc (CCR5 antagonist) or RS504393 (CCR2 antagonist). What is interesting, some of the substances used in our project have already been applied in clinic (e.g. maraviroc) or included in the advanced phases of clinical trials (e.g. cenicriviroc, bindarit). However, none of them is used in patients suffering from neuropathic pain. Furthermore, we believe that the translational character of basic studies is very important, thus we find it interesting to study the effects of the examined drugs in different routes of administration. In this way, we would be able to choose the most beneficial application for patients. We are planning to publish the results obtained in this project in high impact journals and present them at conferences. Moreover, all results will become the foundation for a PhD dissertation prepared by the project coordinator.



Hopefully, the results obtained in this project will allow us to expand our knowledge about the processes underlying neuropathic pain development and propose new pharmacological targets for innovative and effective therapies of neuropathic pain.