Neuropathic pain, which develops as a result of damage to peripheral nerves, diabetes, cancer or multiple sclerosis, remains a constant challenge for modern medicine. Neuropathic pain affects up to 7-10% of the general population, with the most frequent occurrence in patients over 50 years of age and in women (for reasons that are not completely understood). This type of pain has many negative consequences due to a wide range of accompanying symptoms, such as insomnia, anxiety, and even depression. Nevertheless, despite numerous basic and clinical studies, the current understanding does not allow for its effective alleviation. Pharmacotherapy of severe pain is based on opioid drugs such as morphine, buprenorphine and oxycodone. However, these drugs have many side effects and hence cannot be used over a prolonged periods. Therefore, attempts are being made to develop a more effective treatment based on the combined use of therapy with nonopioid substances that help alleviate pain symptoms while concurrently reducing the number of opioid doses. This project is the result of the author's many years of research on the neuroimmune basis of pain processes and will enable the continuation of experiments and exploration of these important issues. Currently, it is known that both neurons and nonneuronal cells (microglia, astroglia, neutrophils) are involved in the development of neuropathy. These cell populations "communicate" with each other by releasing numerous factors, including chemokines. Those that exhibit strong pronociceptive properties are attributed to the development of tactile and thermal hypersensitivity, as well as impair the effectiveness of opioid drugs in neuropathy. Importantly, some of the substances modulating microglial activity that we plan to investigate in this project are already used in the clinic (e.g., minocycline, maraviroc); however, none of them have up to now been applied to treat patients suffering from neuropathy. The aim of the project is to determine the neuroimmune events underlying neuropathic pain of various etiologies. To date, 50 chemokines and 20 of their receptors have been classified. Recent scientific results indicate that many chemokines exert pronociceptive effects, and some may also hamper the analgesic effects of morphine (e.g., CCL1/2/3/7/9 and CXCL10/11/13). Our long-term studies reveal that in addition to chemokine inactivation, the blockade of their receptors (e.g., CCR1/2/3/4/5; CXCR3) may bring therapeutic benefits. Therefore, this project is focused on the possibility of using chemokine system modulation to restore opioid efficacy and delay the development of tolerance after repeated administering of opioids. Experiments will be conducted on female and male mice/rats. All planned procedures were in accordance with the recommendations of the International Society for the Study of Pain. We plan to use two common and well-grounded animal models of neuropathic pain characterized by different pathomechanisms, one resulting from mechanical damage and the second from metabolic damage to the nervous system, as a model of diabetic neuropathy, a complication that develops in one of the most common 21st century diseases. We will modulate nociceptive transmission directly by using antibodies that neutralize pronociceptive chemokines and antagonists that block chemokine receptors. This modulation will make it possible to determine the degree of participation of individual elements of the chemokine system in the pathogenesis of neuropathic pain and the development of opioid tolerance. We also plan to modulate the pain-processing system indirectly by pharmacological inhibition of the activation of the mentioned cells, which are known to produce pronociceptive chemokines. Moreover, and most significantly, we plan to perform multiple and simultaneous administration of immunomodulators with opioid drugs. Recent studies have revealed that there exists an interaction between chemokines and opioid receptors at the cellular level and that its pharmacological modulation may be beneficial, giving hope for the effectiveness of combined therapy. We will evaluate the analgesic effects in behavioral tests, and then, thanks to the use of molecular biology methods, we will examine changes in the expression of selected genes and proteins to determine their role in the effects of tested substances demonstrating distinct analgesic potential. Furthermore, experiments on primary cultures of microglia, astroglia and neutrophils will help determine the direct influence of substances with analgesic properties on the activity of these cells. **In conclusion, the results obtained during this project will advance the understanding of the mechanisms underlying the development and maintenance of neuropathic pain, as well as the use of novel targets for effective polytherapy that could be implemented when multiple administrations of opioid drugs are required. We plan to publish the findings of the research proposed herein in renowned international journals and present them at conferences, and the results will form the basis of 2-3 PhD dissertations.**