According to the definition of the International Society for the Study of Pain (IASP), neuropathic pain is pain initiated or caused by damage to the nervous system. In contrast to acute pain which is a defensive response of the body to tissue injury, neuropathic pain is considered as a disease that requires comprehensive treatment. Typically appearing in neuropathic pain sensory nerve hypersensitivity, manifested as allodynia (pain evoked by stimuli which under physiological conditions do not cause pain) and hyperalgesia (exaggerated response to a painful stimulus with a moderate potency), spontaneous pain episodes, as well as tendency for long-term persistence of pain which is often difficult to control by available analgesics are important problems of modern pharmacotherapy.

It is estimated that approximately 40% of patients suffering from neuropathic pain are resistant to available analgesics. Moreover, it has been estimated that about one-third of patients are likely to achieve 50% pain relief with monotherapy. Therefore, in order to optimize pharmacotherapy of neuropathic pain and improve the efficiency of treatment in drug-resistant patients the search for novel analgesic active compounds and exploration of new therapeutic/molecular targets for analgesic drugs are two mainstreams in this field. Despite significant progress in pain research, the challenges facing the development of novel therapeutics remain significant. However, the drug discovery process is a very high-risk endeavor, being a costly, time-consuming, and often ineffective procedure. Hence, as an alternative to this research direction, combination drug therapy with the use of two or more analgesics with well-defined mechanisms of action, proven analgesic efficacy and well-established adverse effects is applied. This approach often allows to achieve analgesia with the use of lower doses of combined drugs as compared to monotherapy. However, it should be strongly emphasized that combination drug therapy may be advantageous from a therapeutic point of view (enhanced effectiveness – drug synergism), but the other hand, it may also pose a risk of increased toxicity of one drug potentiated by the other one concomitantly used. In view of this, there is a strong need to develop optimization methods aiming to increase the effectiveness of combination drug therapy and investigate its safety in neuropathic pain, and this trend appears to be a priority in pharmacological studies.

The aim of this project is to examine the analgesic activity of approximately 30 dose combinations of drugs currently used in the treatment of neuropathic pain in combination with selected agents investigated in different phases of clinical trials. The results obtained in tests in mice will be used to develop a novel method for dose selection of analgesics used as a combination therapy for neuropathic pain, using mathematical models based on artificial intelligence methods. For selected combination of drugs the safety profile (the impact on some functions of the central nervous system) will be assessed.

The planned study will assess the analgesic activity of drug combinations in response to thermal and mechanical stimuli. Moreover, their impact on spontaneous pain intensity will be assessed in animals with oxaliplatin-induced neuropathy. Oxaliplatin is an anticancer drug which is used for the treatment of colon and rectal tumors. Its high antitumor efficacy is however frequently limited by its significant adverse effects, of which the most frequently mentioned is painful peripheral neuropathy, a complication that is frequently the cause of premature discontinuation of the drug use.

At the moment there are no simple methods for predicting efficacy and/or toxicity of drug combinations used in the treatment of neuropathic pain. This need strongly justifies tackling this research topic. Although such studies could be carried out exclusively in animal models, the use of artificial intelligence methods will significantly reduce time and costs of pharmacological studies. It should be noted that it is also extremely important in terms of ethical reasons as these methods reduce the number of animals used for research.

Taken together, the planned studies will increase knowledge about new drug combinations in neuropathic pain, which will enable to create a method for the optimization of combination drug therapy in neuropathic pain.