Chronic pain is a major health issue in the global population that clearly impacts the individuals' health status and quality of life and represents a major clinical, social, and economic problem. In the European Union, €300 billion per year was spent on the treatment of chronic pain. The studies affirmed that pain and pain-related diseases are the leading cause of disability globally. Neuropathic pain is a pathological disorder caused by lesions or diseases of the somatosensory nervous system, where pain loses its protective and adaptative function and paradoxically leads to increased pain sensitivity. To date, no drug has shown long-term efficacy, and this type of pain is recognized to be particularly difficult to treat. Epidemiological data revealed that neuropathic pain is prevalent in 6.9-10% of the general population, affecting more women (8%) than men (5.7%). Despite greatly improving our understanding of this pathology, 40% of patients did not achieve satisfactory pain relief. Therefore, pharmacological therapies are considered to constitute an unmet medical need.

Despite advancements in understanding neuropathic pain mechanisms, effective long-term therapies remain elusive, with opioids continuing to dominate despite severe side effects, among which are opioid-induced hyperalgesia (OIH), tolerance, respiratory depression, hyperlocomotion, central sleep apnea, which are of major importance. OIH is a state of enhanced nociception observed upon opioid administration, which is a troublesome clinical issue with a still unknown mechanism. The poorly controlled chronic pain results in the escalation of opioids used. Data from recent years highlights the increased risk of overdose death associated with opioid-based pain therapy. However, the situation is even more alarming during the time of pandemic COVID-19, when the increase in opioid overdose was attributed to reduced access to the healthcare system. Moreover, with potentially fatal consequences, opioid-related side effects may limit the use of opioid analgesia, resulting in inadequate pain treatment. Therefore, development in this area is crucial for understanding the mechanism of the opioid switch from analgesic medication to hyperalgesic "medication" with harmful side effects.

Our recent studies indicate that histamine 3 receptor (H_3R) is a promising target for research into new analgesic drugs in neuropathic pain therapy. We revealed that H_3R antagonists have a strong analgesic effect, and interestingly, the blockade of H_3R produced prolonged pain relief in neuropathic females. Moreover, our pharmacological studies demonstrated that H_3R antagonist potentiated morphine analgesia. Our data strongly suggest that drugs acting at different molecular targets and by different mechanisms may help to reduce opioid doses and, in consequence, limit opioid dose escalation. This pharmacological approach, when lower doses of drugs are used, results in fewer side effects and provides a promising further pharmacological intervention in neuropathic pain and OIH. Our preliminary data have shown that the clinically used drug pitolisant produced strong analgesic effects in neuropathic mice and reduced morphine-induced hyperlocomotion. Pitolisant (Wakix®, Ozawade®) is the first marketed H_3R antagonist, use in human therapy for adults suffering from narcolepsy and Obstructive Sleep Apnoea. In 2023, pitolisant received its first approval in adolescents and children to treat Excessive Daytime Sleepiness in the EU. Pitolisant is a substance of great therapeutic potential but is currently very understudied in the context of chronic pain and opioid analgesia. Unlike previous strategies, our approach leverages to combine pitolisant, which is already in a clinic with a favorable safety profile, with morphine, a gold-standard opioid analgesic. Therefore, our project has a translational character and might have a great chance of being included in human therapy. Using a comprehensive approach, combining behavioral tests with electrophysiological studies and novel molecular techniques (such as Imaging Mass Cytometry and data-independent acquisition (DIA) quantitative proteomic analysis), we will bridge the gap in the H_3R molecular mechanism of action in neuropathic pain and OIH development. Another novel approach to our project is to investigate the sex-related differences in H_3R antagonists actions in the course of opioid analgesia and hyperalgesia, which remained a fully unexplored issue. We believe that obtaining unique results will enrich our knowledge and establish a basis for a new approach to enhancing the utility of opioids in treating chronic pain.