THE ROLE OF SIMULTANEOUS AND INDIVIDUAL MODULATION OF μ-OPIOID, SIGMA-1 AND HISTAMINE H_3 RECEPTORS AS A NEW THERAPEUTIC APPROACH IN THE TREATMENT OF NOCICEPTIVE AND NEUROPATHIC PAIN

Drug discovery in the 21st century has the disadvantage that it is very difficult to get new compounds into the clinic. The diseases where cures or at least treatments are sought are complex ones involving many potential defects in the structure, function, or regulation of the cells involved. Traditionally, drugs have been designed with the aim of targeting a single biological entity, usually a protein (the so-called "on-target"), with high selectivity to avoid any unwanted effects arising from mis-targeting other biological targets ("off-targets"). On this basis, the concept of drugs interacting with multiple targets has long been flagged as undesirable, as it was inherently associated with adverse side effects. However, the complexity of the current incurable pathologies has clearly demonstrated that such single-target drugs are inadequate to achieve a therapeutic effect. In parallel, we have learned that molecules hitting more than one target may possess in principle a safer profile compared to single-targeted ones. Indeed, in the years, the concept of creating multi-target molecules has triggered the interest of the drug discovery community both in academia and pharmaceutical companies to such a point that a plethora of multi-target drugs are already available on the market.

Neuropathic pain is an expensive and debilitating condition that affects 7-10% of the general population, with the prevalence increasing with age. First-line treatments for this disorder include anticonvulsants, tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitor antidepressants. In addition, opioids provide second-line treatment. Unfortunately, these drugs are limited in their efficacy and have side effects, in particular with chronic use. Thus, there is a strong need to explore novel analgesic mechanisms that improve the efficacy of existing therapies while reducing their adverse effects. On the other hand, several studies have suggested a potential therapeutic use of selective sigma-1 receptor (σ_1R) antagonists for the treatment of pain conditions including neuropathic, inflammatory and visceral pain, also as adjuvants to opioid therapy. Moreover, being localized in many central nervous system regions involved in nociception, histamine H_3 receptors (H_3R) are also associated with pain being involved in central sensitization of pain. Due to the fact that dual-targeting drugs could promise several improvements when compared to selective drugs, the latest studies have shown promising analgesic properties of dual μ-opioid/σ_1 receptor ligands as well as the histamine H_3/σ_1 receptor targeting compounds (**Figure 1**). This brings up the question whether dual-acting compounds are more effective at lower doses when compared to selective ligands? The combination of which two biological targets could have a higher therapeutic efficacy in the treatment of neuropathic pain? Is it possible to obtain dual μ-opioid/H_3R ligands or compounds that would interact simultaneously with these three receptors? Which strategy could be the the most effective and safe?

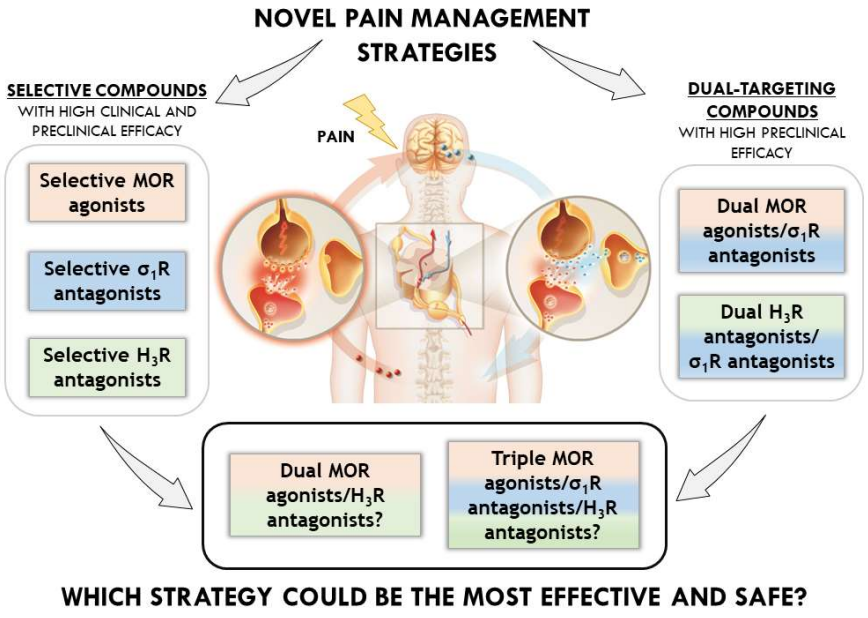

Figure 1. Current treatment strategies for nociceptive and neuropathic pain (MOR: μ-opioid receptor).

As the result of this Project, we will identify new pharmacological tools with unique biological properties – high affinity at histamine H_3, σ_1 and μ-opioid receptors, that can improve existing therapies for the neuropathic pain. Secondly, we will determine whether such triple-acting ligands are more effective in the treatment of neuropathic pain compared to selective and dual-targeting ones. Moreover, the comparison of the efficacy and safety profile between the dual μ-opioid/σ_1R and H_3/σ_1R ligands also seems to be crucial for the further development of these studies. This Project also aims at finding necessary structural requirements of obtained compounds, responsible for their biological activity, that might play a role in their overall efficacy and facilitate the design of further compounds with this activity profile.