Everyone experience pain, yet luckily not all would confront a type of pain that cannot be effectively handled. Still many, that is over 1/5th of the Polish population, so about 7.6 million people, would suffer from persistent pain the treatment of which is frequently inefficient.

Current approaches for pain treatment rely, in simplification, on four major classes of pharmaceuticals: *1) the anti-inflammatory drugs (i.e., ibuprofen), 2) these acting on central sensory terminals (i.e., pregabalin), 3) opioids with a broad spectrum of action on both central and peripheral nervous system (i.e., morphine), and 4) agents acting to restore the balance of monoamines in the central nervous system (i.e., duloxetine)*. The latter are also used in the treatment of affective disorders, like depression. Luckily, many of us would never experience effects of the latter three classes, given their use is mostly restricted for the treatment of pain in chronicity. Hence, for headaches or toothaches, one would likely reach for so called *'nsaids'* (NSAID – nonsteroidal anti-inflammatory drugs) like ibuprofen, that would successfully tackle acute, but transient ache. The situation gets complicated when pain persists and cannot be resolved by classic painkillers.

Chronic pain is linked particularly to cancer diseases, multiple sclerosis, diabetes, or severe neuronal inflammation or damage, and this type of pain requires a specialist approach. In chronicity, we often reach for stronger painkillers, though their long-term use frequently results in many side effects (from physical symptoms like chronic nausea or constipations leading to another pain, up to addiction). It might be perhaps surprising for some, but lots of currently used painkillers do not have well understood mechanism(s) of action. **A mission of my group is to search for innovative solutions aiming to resolve pain with the least side effects possible.** We approach it by a more complete understanding of the nervous system functioning. It is a long-term process that requires full understanding of the so-called pain axis physiology. Luckily today we are presented with more tools, which allow us to approach this topic in a very precise way, offering to explain transmission mechanisms of noxious impulses on the molecular level. In research conveyed by my group at Jagiellonian University and by our collaborators at King's College London, we focus on the understanding of our own bodily systems (that is endogenous systems) which regulate pain. An example of their action may be a Covid-19 vaccination, whereby a terrifying nurse would draw all your attention to the needle penetrating the arm – you would feel the piercing pain way stronger than if looked away. In another scenario, you would perceive stepping on the shredded glass in your dining room very differently than when chased by an angry dog. **In both situations, activated are so called 'descending pain modulatory pathways' – those that hamper and those that facilitate pain. These are investigated by my group, and these systems are most likely responsible for the action of the fourth class of painkillers – the antidepressants.**

Unfortunately, our understanding of how the brain can control pain is still less than ideal. In our research we can selectively, that is on the molecular level, activate the pathways that send inhibitory signals to the spinal cord. It is in the cord, where the first relay of the painful information from peripheral neurons (i.e., those innervating your foot) onto the projection neurons (those sending signals all the way up to the brain) occurs. After initial processing, the brain sends back a message to the cord saying: *'give more'* (i.e., the terrifying nurse from the example above) or *'stop it'* (i.e., we are escaping the dog). In our research, we use '*a Cinderella method'* (that is lentil by lentil) to activate individual brain centres, which project to the cord and observe the way they modulate noxious responses. **In this way we learn which system works best, therefore promising next therapeutic target, this time specific, without side-effects.**

In this project we aim to dissect noradrenergic pain inhibitory pathways that directly act on the central terminals of sensory fibres within the spinal cord. We know that the brain can directly modulate the peripheral nervous system via its molecular transmitter – noradrenaline. **This time, we will check how noradrenaline originated from different brain areas could influence the neuronal transmission from peripheral nervous system onto the projection neurons of the spinal cord.** We know that the nerves contain only one from nine existing receptors for noradrenaline – an Adra2c. In this project we will selectively remove this receptor, only on the peripheral neurons, and test how would that impact painful signals transmission. In the future we hope to fully understand each individual pathway the brain utilises to modulate activity of this *'first relay station'* located in the spinal cord, so that we could design new class of painkillers with selective action.