Demyelinating diseases represent a serious clinical problem worldwide, affecting not only patients' quality of life but also their social and professional functioning. The most common and best-studied demyelinating disease is multiple sclerosis, which affects approximately 2.8 million people globally. The incidence of multiple sclerosis is significantly higher in women, they are two to three times more likely to develop the disease than men. The market for multiple sclerosis medications reached a value of $23.5 billion in 2023, and forecasts indicate continued growth. These conditions are characterized by inflammatory and degenerative processes that lead to damage of the myelin sheath, which is essential for the proper conduction of nerve impulses. This results in a range of neurological symptoms, including vision disturbances, limb muscle weakness, difficulties with motor coordination, and in advanced stages paralysis. The process of demyelination is also associated with the death of oligodendrocytes, cells responsible for producing myelin, as well as their precursors.

One of the causes of demyelination is chronic inflammation triggered by an overactive immune system. For this reason, the primary therapeutic strategy remains immunosuppression, suppressing the immune system to limit further damage. Currently available immunosuppressive drugs show variable effectiveness and are associated with significant risks of side effects, ranging from mild symptoms such as rashes or flu-like complaints to severe complications, including increased susceptibility to infections, the development of autoimmune diseases, and liver damage.

Currently, there is no approved pharmacotherapy that enables effective restoration of damaged neural structures. Although spontaneous remyelination can occur in some cases, especially in the early stages of the disease and after symptoms subside, this process weakens over time. Each subsequent disease relapse reduces the nervous system’s regenerative capacity, leading to progressive neurological disability. Additionally, studies have shown impaired neurogenesis, the process of generating new nerve cells from neural stem cells, in patients suffering chronically from demyelinating diseases. These patients often exhibit symptoms of cognitive impairment, including memory problems, reduced concentration, and slowed information processing.

As a result, the search for new substances that could stimulate cell regeneration has become a significant direction in the development of new pharmacological therapies for the treatment of demyelinating diseases. Increasing attention is being devoted to strategies based on two main approaches: neuroprotection, protecting oligodendrocytes, their precursors, and myelin sheaths from further damage, and stimulation of remyelination by activating cells to differentiate into mature oligodendrocytes and neurons, thus supporting repair processes in damaged areas. Research into these approaches includes both the search for of new drugs and cell-based therapies.

Recent studies indicate the histamine H3 receptor (H_3R) as a new therapeutic target for central nervous system disorders. So far, only few studies have examined the effect of H_3R ligands on oligodendrocyte precursor cells, mature oligodendrocytes and neural stem cells. Pitolisant (Wakix® and Ozawade®) is the first H_3R antagonist/inverse agonist approved for sale. It is currently used to treat adults with narcolepsy and sleep apnea. In our preliminary studies, we have shown for the first time that pitolisant increases neural stem cells differentiation toward oligodendrocytes *in vitro*.

Our project involves using a cuprizone-induced demyelination model to investigate the effect of pitolisant on oligodendrogenesis and neurogenesis *in vivo* in male and female mice. In addition, we plan *in vitro* studies on primary cultures of neuronal stem cells, oligodendrocyte precursors and mature oligodendrocytes, which will allow for a more precise explanation of the mechanisms of pitolisant action in the inflammation-induced demyelination model.

We hope that the results of our studies will contribute to the development of new strategies for the treatment of demyelinating diseases based on simultaneous protection of cells from degeneration and stimulation of their differentiation in order to regenerate damaged areas.