The increase in the average life expectancy is accompanied by an elevated prevalence of age-related diseases, including neurodegenerative diseases which currently affect over 30 million people worldwide. Efficient treatment of ageing-associated neurodegenerative diseases, like Alzheimer's disease and Parkinson's disease, is still unavailable. The rational design of neuroprotective drugs is a particularly difficult challenge due to the ambiguous etiology of a majority of neurodegenerative diseases and insufficient knowledge of molecular targets for potential drugs.

According to the latest concepts, long-term inflammation in the brain, associated with chronic activation of its main immunocompetent cells, i.e. microglia, production of toxic factors, pro-inflammatory cytokines and chemokines, and oxidative stress, creates the basis for the development of neurodegenerative diseases. Unexpectedly, recent research shows that also a deficit of hydrogen sulfide exaggerates the progression of neurodegenerative diseases and adversely impacts cell functions in the brain.

It was found that, in contrast to classical anti-inflammatory drugs, the use of endogenous substances promoting resolution of inflammation (RoI) (called *small pro-resolving mediators*, SPMs) can offer a promising strategy to halt the loss of nerve cells and to fend off aggravating neurological deficit occurring in the course of the above diseases. The SPMs are metabolites of fatty acids that restore homeostasis in the brain tissue affected by inflammation, reduce excessive activation of the immune cells and increase phagocytosis of apoptotic cells acting *via* the specific receptor – formyl peptide receptor 2, FPR2. Unfortunately, the therapeutic use of endogenous SPMs is significantly hindered by their unfavorable pharmacokinetic properties. Therefore, our many years of research conducted in cooperation with leading centres, including those from abroad, focus on the discovery of new ureidopropanamide-like compounds with agonistic FPR2 potential, which could be a useful tool for RoI (pharmacotherapy of resolution). Importantly, our 'biased' agonists stimulate FPR2 in a functionally selective manner – activating only selected signal transmission pathways and intracellular mechanisms, which could increase their therapeutic effectiveness and significantly reduce potential side effects, thus setting a new treatment direction for neurodegenerative diseases.

Based on our previous research, the aim of the project is to verify the hypothesis that hybrid FPR2 receptor agonists, newly designed by us to possess beneficial pharmacokinetic properties and high inflammation pro-resolving potential, both by anti-inflammatory receptor activation as well as increasing endogenous hydrogen sulfide levels, will efficiently suppress (or at least slow down) neurodegeneration and cognitive decline in a commonly accepted model of Alzheimer's disease in mice. Although recent data suggest that biophysical changes in the brain tissue may correlate with disease progression, still little is known about the biomechanical mechanisms of these changes in microglia cells during the resolution of inflammation. For this reason, apart from explaining the contribution of intracellular signaling pathways related to the mechanism of action of FPR2 and promoting hydrogen sulfide release, in our project cutting-edge research will be performed to determine the role of hybrid compounds in modulating the biomechanical properties of microglia in RoI processes. Our innovative research will be conducted *in vitro* (using primary microglia cultures) and then we will perform their multi-faceted *in vivo* verification using the tools of molecular biology, transcriptomics, proteomics and atomic forces microscopy in a recognized model of Alzheimer's disease.

We expect that the determination of pharmacokinetic characteristics of FPR2 agonists, elucidation of the molecular mechanism of their action and explanation of biomechanical changes induced by these substances that promote the anti-inflammatory phenotype of microglia can set a new direction in neuroprotective drug design. Moreover, we are convinced that the results of this project will enrich knowledge on the efficacy, immune-pharmacological properties and mechanism of action of this unique group of substances and that combining physical, chemical and pharmacological methodologies will significantly advance the translational value of the obtained results in the context of therapeutic strategies also for a wide spectrum of others neurodegenerative diseases (e.g. Parkinson's disease, multiple sclerosis).