Progress in the medicine and social changes has led to an increase in the proportion of elderly people in society. With the increasing average life span of humans, the elevation in population of people affected by neurodegenerative disorders, e.g. Parkinson's disease (PD), is observed. PD is caused by the loss of dopaminergic cells in the substantia nigra as a result of oxidative stress or disturbance of energy production in neurons. A characteristic feature of PD is pathological accumulation of alpha-synuclein in Lewy bodies. The missfolded forms of this protein can be released into the extracellular space and penetrate neighboring neurons, thus initiating pathological processes. In addition, alpha-synuclein present in the extracellular space can directly interact with cellular membrane receptors, causing their deregulation and activation of cell death signaling. Among various receptors that interact with alpha-synuclein, purinergic P2X7 receptors for extracellular nucleotides deserve the special attention. Upon interaction with extracellular alpha-synuclein these receptors become overstimulated, leading to increased release of free radicals and damage to micro- and macromolecules, including mitochondria. Mitochondria are the main powerhouses of the cells through the production of ATP. However, these important organelles are extremely susceptible to the damage caused by free radicals, which can accumulate over time and play a significant role in the process of neurodegeneration. Dysfunctional mitochondria can be repaired in a process called mitochondrial unfolded protein response (mtUPR), which leads to the replacement of the individual defective protein components to the proper ones. When this process is overwhelmed, the removal of defective mitochondria via mitophagy occurs. However, in PD both of these processes are severely impacted, resulting in the gradual accumulation of damaged mitochondria in the cell. Mitochondrial deficiencies are also compensated by glycolysis that produces energy from glucose metabolism, but this process is significantly limited in neurons. Recent data indicate that the pathological effects of the P2X7 receptor include deregulation of glycolysis and mitophagy, however, this relevant interaction has not yet been studied within the pathogenesis of PD.

We therefore suggest that alterations in purinergic P2X7 receptor function play a key role in metabolic impairments associated with alpha-synuclein neurotoxicity in PD. We will particularly focus on verifying the role of the P2X7 receptor in alterations in glucose metabolism, cellular bioenergetics, oxidative stress, and mitochondria quality control induced by extracellular alpha-synuclein. Finally, we will determine whether P2X7 receptor inhibition prevents morphological damage and behavioral alterations. This hypothesis is addressed in model systems of α-Syn toxicity of increasing complexity, starting at the level of isolated organelles, and progressing to mouse cultures of neurons, in vivo measurement of metabolic and morphological changes in animal brains and finally to behavioral studies, that is a great advantage of this project.

The obtained results may thus not only lead to the verification of accepted views about PD pathomechanisms, but also extend previous findings to defining new molecular aspects of the disease, with P2X7R playing a key role. Moreover, the final outcome of this project is to verify whether P2X7R might be a compelling therapeutic target for PD. This is especially interesting since various P2X7 receptor antagonists are now undergoing clinical trials for the treatment of other neurodegenerative disorders.