Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's and the most frequent synucleinopathy, affecting over 10 million people worldwide. The major molecular event underlying the pathophysiology of PD is the abnormal accumulation of α-synuclein (α-syn) within the dopaminergic neurons of the midbrain, that contributes to progressive neuronal loss. Among all forms of aggregated α-syn, oligomers are regarded as the most relevant as they may exert neurotoxicity in a variety of mechanisms, impair synaptic function, self-replicate and propagate from cell to cell in prion-like fashion. Multiple lines of evidence have suggested that endoplasmic reticulum (ER) stress triggered by oligomers is particularly implicated in the pathogenesis of PD. Accumulation of misfolded α-syn within the ER lumen induces ER stress conditions that leads to activation of the Unfolded Protein Response (UPR). According to the newest data, the main UPR sensor, PKR-like ER kinase (PERK), plays major role in α-syn-induced pathology, as it may activate pro-apoptotic pathways in dopaminergic neurons upon prolonged ER stress conditions.

The main aim of the present research project is to study the potential effect of the small-molecule inhibitors of protein aggregation and ER stress-mediated UPR signaling pathway against neurodegeneration in PD. Anle138b is a new, promising drug-candidate, currently being tested in phase I clinical trials, that specifically targets and disrupts α-syn oligomers. LDN-0060609 (LDN) is a highly specific PERK inhibitor, selected by our research group in the collaboration with the Medical University of South Carolina. Our hypothesis assumes that disruption of α-syn oligomers with the simultaneous amelioration of ER stress conditions could vastly enhance neuroprotection in the course of PD. If this is the case, either anle138b/LDN or other molecules of similar or even more specific activity, after extensive preclinical and clinical research, could eventually be implemented into clinical use. Such combination therapy specifically targeting the two molecular events essential to PD pathology may lead to development of the first disease-modifying therapeutic approach for this yet incurable disease.

In our research, we aim to utilize a newly-developed model of PD based on 3D human midbrain organoids generated from induced pluripotent stem cells, that is considered to reflect PD pathophysiology more accurately than widely used 2D cultures or animal models. We will assess cytotoxicity of each compound, determine the inhibitory effect of the compounds on α-syn accumulation and the level of apoptosis, evaluate how tested compounds affect the expression of specific proteins related to ER and autophagy-lysosomal system, as well as the accumulation of sphingolipids. We firmly believe that obtained results could expand current knowledge and significantly contribute to research in PD field.