Parkinson's disease (PD) is a widespread neurodegenerative disorder characterized by progressive loss of dopaminergic neurons and deposition of α-synuclein (α-syn) protein in the brain. Mechanism-based therapies are still unavailable despite years of intense research and identification of many important aspects of PD pathogenesis. α-Syn–induced cellular stress, accumulation of mitochondrial damage, and deregulated neuroinflammatory responses are crucial for the disease progression and may constitute plausible targets of novel interventions. It is postulated that instead of one specific cause, the interaction of these factors is critical for the slow death of dopaminergic neurons. However, the mechanisms linking these phenomena are largely unknown.

Thus, the applicants from Poland and Germany joined their complementary expertise to investigate fundamental mechanisms contributing to the progressive degeneration of dopaminergic neurons. Our recent collaborative studies revealed that α-syn caused depletion of parkin protein, directly leading to the impairment of mitophagy (a parkin–dependent mitochondrial quality assurance mechanism), likely amplifying the neurotoxic effects of α-syn. α-Syn–caused mitochondrial impairments in human dopaminergic neurons could deregulate their energy metabolism and generate proinflammatory signals (which are activated by molecules released from damaged mitochondria). We also observed that α-syn caused immune activation of cultured mouse microglia, which switched their energy metabolism in a manner characteristic for inflammatory processes. All these observations suggest how α-syn might drive neuroinflammation and the resulting neurodegeneration. **We hypothesize that parkin dysfunction contributes to α-syn–induced mitochondrial impairment that leads to neuroinflammation and neurodegeneration in PD.** This hypothesis will be addressed in model systems of α-syn toxicity in increasing complexity at the level of isolated organelles, in (co-)cultures of human neurons and glial cells, in murine organotypic brain slice cultures, and *in vivo* (in genetically manipulated mice lacking parkin, or producing its increased quantities, treated with α-syn oligomres injected into brain striatum). We will analyze molecular/biochemical aspects of mitochondrial damage, ultrastructural changes, free radical stress, the production of cellular signaling molecules and inflammatory signals as well as investigate aspects of immune regulation of brain glia. We also plan to test pharmacological compounds capable of modulating immune activation and the energetic metabolism of immune cells, and to verify their influence on neuron survival, brain ultrastructural disturbances, and mouse behavioral abnormalities. Our studies will provide novel insights into parkin regulation and function, and might suggest targets for the much needed specific therapies of PD.