Universität Basel

# Research Project

# SINERGIA: Molecular and Cellular Modulation in Parkinson's Disease

**Third-party funded project**

**Project title** SINERGIA: Molecular and Cellular Modulation in Parkinson's Disease
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**Organisation / Research unit**
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Departement Biozentrum / Structural Biology (Stahlberg)
**Department**
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Parkinson's Disease (PD) is a prominent and severe neurodegenerative disease that affects about 2% of our population, particularly the elderly. It is considered to be one of the protein aggregation diseases, which also include Alzheimer's disease and Huntington's disease. In PD, dopaminergic neurons in the substantia nigra (SN) region of the brain are lost, yielding the typical disease symptoms of tremor or slowness of movement and rigidity. The pathological hallmarks of PD are large aggregates within the affected neurons, which are called Lewy bodies or Lewy neurites, and which are composed of lipids and the protein alpha-synuclein ($\alpha$-Syn). Familial PD is often related to mutants at the $\alpha$-Syn gene locus, while recent genome-wide association studies (GWAS) identified several other so called "PD risk genes". Despite several decades of intensive research on PD, the molecular mechanism behind neurodegeneration and the protein players involved are not known. Early diagnosis of the disease with positron-emission tomography (PET) is so far not possible, because a suitable protein target for a PET tracer has not been identified. So far, medical treatment of PD can only weaken the symptoms of the disease, it cannot prevent, slow-down or stop disease progression. No cell line or animal model is considered to be fully representative of the disease. In this 4-year Sinergia project, we will study PD from a structural perspective in situ, using human brain tissue and fluids from PD patients. We will translate this information to the cellular level and to animal models for detailed structural, dynamic and cell biological analysis, and compare these findings with those obtained from human samples. In parallel, we will analyze the structural and mechanistic consequences of "PD risk gene" proteins within model cells. This project will use systems-biology screens, GWAS PD risk gene analysis, and three complementary structural methods: Cryo-electron microscopy and tomography will be used to elucidate both protein conformations and tissue structure at high resolution, conformation-sensitive mass spectrometry based on limited proteolysis will be used to fingerprint the structures and alterations of structures of various proteins, comparing those present in healthy and PD tissue and model cells, and finally, in-cell nuclear magnetic resonance (NMR) will be used to determine the 3D structure and dynamics of the proteins, including the identification of transient interactors of $\alpha$-Syn and other proteins of interest, at near-atomic resolution within the cells. These three structural methods are able to study structures and structural alterations within the physiological milieu. This will be complemented with a systems biology approach at the cell level to elucidate the biological consequences of the structural alterations. The proteins encoded by the PD risk genes will be characterized for their structural and biochemical impact on the biology of the cell. And finally, the structure and function of specific, identified proteins of interest with relevancy in PD neurodegeneration will be determined. The unique combination of methods employed here, and their application to human PD brain tissue, and cell and animal models for PD will allow screens to be

made for novel proteins that may be so far unrecognized players in the development of PD. This research will provide a better mechanistic insight into the molecular processes underlying the progression of neurodegeneration in Parkinson's disease, and may identify novel PET tracers or even drug targets to help understand and treat this debilitating disease. Parkinson's Disease (PD) is a prominent and severe neurodegenerative disease that affects about 2% of our population, particularly the elderly. It is considered to be one of the protein aggregation diseases, which also include Alzheimer's disease and Huntington's disease.

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