The study of alpha-synuclein pathology and related neuroinflammation in a human brain-like context: a human neurospheroid approach

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Synucleinopathies, including Parkinson's disease, are neurodegenerative disorders characterized by the formation of alpha-synuclein (αSyn) aggregates that propagate prion-like between nervous system cells. The exact role of αSyn pathology in disease progression remains unclear. Moreover, how microglia precisely affect αSyn pathology remains to be elucidated. Current in vitro models are limited in their ability to faithfully replicate human responses to pathological αSyn.

In my research, I will use human neurospheroids (NSPHs) to enhance our understanding of αSyn pathology, more specifically the pathophysiological pathways associated with αSyn accumulation. By using NSPHs with and without microglia, I aim to clarify the role of microglia and neuroinflammation in general in αSyn accumulation and downstream cellular responses. Hereto, pre-formed αSyn fibrils will be added to NSPHs and αSyn accumulation will be monitored over time by staining NSPHs for pathological αSyn. Next, pathways elicited with αSyn accumulation will be determined at the transcriptome and proteome level and further characterized at the cellular and functional level, by means of immunocytochemistry and functional assays (e.g. calcium imaging), respectively.

In summary, this research project will help to identify pathophysiological mechanisms associated with αSyn pathology possibly leading to neuronal dysfunction or loss, and clarify the role of microglia, in a human brain-like context.