Single-cell proteomics to quantify α-synuclein using cell models of Parkinson's disease

MSc project available in the Galvagnion's group – Protein-membrane interactions in health and disease

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Parkinson's disease (PD) is the second most common neurodegenerative disease. It is characterized by the loss of dopaminergic neurons and the presence of protein deposits called Lewy bodies, mainly composed of α-synuclein. Mutations in the *GBA* gene, encoding for glucosylcerebrosidase (GCase), have been recently associated as a major genetic risk factor for PD. These mutations induce conformational changes in the protein that affect its activity, leading to an increase in α-synuclein levels and accumulation of GCase substrates such as glucosylceramide and glucosylsphingosine in the cell. The MSc project that we propose will aim to characterize α-synuclein solubility by quantifying its soluble and insoluble levels in healthy and disease neurons and to correlate these levels with those of GCase as well as enzymes involved in lipid metabolism using single-cell proteomics. We will use two types of neuronal cells: established neuroblastoma cells with *GBA* knock-down to set up the methods and dopaminergic neurons derived from induced pluripotent stem cells with specific *GBA* mutations and controls to confirm our results in patients' derived cells. The proteomics experiments will be carried out in collaboration with Assoc. Prof. Erwin Schoof at the Proteomics Core facility of the Department of Biotechnology and Biomedicine at the Technical University of Denmark, DTU. Recent breakthrough in technical achievements have now increased the sensitivity of proteomics workflows to single cells, and in this project, we will work towards achieving this sensitivity for the first time also for neuronal cells.

This study will help us to further understand not only the role that GCase and α-synuclein play in PD, but also the interaction between them.