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**PhD Project Commencing October 2023**

**(Closing date: 5 January 2023)**

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**Investigating mechanisms of mitochondrial quality control in**

***Drosophila* models of neurodegeneration**

*PINK1* and *Parkin* (*PRKN*), two genes linked to Parkinson's disease, have been strongly linked to the selective degradation of mitochondria (mitophagy). However, much of our current understanding comes from *in vitro* studies, and we still have a poor understanding of this process in a physiological context *in vivo* [1]. PINK1 phosphorylates ubiquitin (pS65-Ub) on mitochondria to trigger mitophagy. We have recently developed protocols to detect PINK1 activity and monitor mitophagy under physiological conditions *in vivo* in *Drosophila* [2]. With these quantitative mass spectrometry and immunodetection methods, we can now deeply analyse the spatiotemporal activation of the pathway *in vivo* by monitoring the level and localisation of pS65-Ub.

This project will investigate the mechanisms of Pink1 activation in *Drosophila*, in particular analysing the tissue specific distribution of pS65-Ub and mechanisms of degradation. Using state-of-the-art super-resolution microscopy, the project will also probe the sub-cellular distribution of pS65-Ub, addressing whether it may associate with sub-mitochondrial compartments *in vivo*. Importantly, we will also investigate the physiological mechanisms of stimuli. We are also interested in understanding the role that mitochondrial calcium plays in quality control processes [3], and this project would provide an opportunity to collaborate on these investigations. This project will shed new light on important mechanisms of mitochondrial quality control and potentially identify new targets for therapeutic interventions.

**Keywords**

General:

Mitochondria, Neurodegeneration, Mitophagy

More specific:

PINK1, quality control, mass spectrometry, super-resolution microscopy, calcium, Drosophila

**References**

[1] [PINK1/Parkin mitophagy and neurodegeneration-what do we really know in vivo?](https://pubmed.ncbi.nlm.nih.gov/28213158/)

Whitworth AJ, Pallanck LJ.Curr Opin Genet Dev. 2017 Jun;44:47-53. doi: 10.1016/j.gde.2017.01.016. PMID: 28213158

[2] https://doi.org/10.1101/2021.06.10.447841

[3] [Comprehensive Genetic Characterization of Mitochondrial Ca2+ Uniporter Components Reveals Their Different Physiological Requirements In Vivo.](https://pubmed.ncbi.nlm.nih.gov/31042479/)

Tufi R, Gleeson TP, von Stockum S, Hewitt VL, Lee JJ, Terriente-Felix A, Sanchez-Martinez A, Ziviani E, Whitworth AJ.Cell Rep. 2019 Apr 30;27(5):1541-1550.e5. doi: 10.1016/j.celrep.2019.04.033. PMID: 31042479

**Subject areas**

Cell Biology, Genetics, Molecular Biology, Molecular Genetics, Neuroscience

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