Project Details	
Project Code	MRCNMH26Br Collinson
Title	Alternative mitochondrial destinations of PINK1 and its role in Parkinson's Disease
Research Theme	NMH
Project Type	It is both a wet and a dry project.
Summary	Mitochondria are vital for energy production, cell function and homeostasis, and thereby health. This project explores how the protein PINK1, key to mitochondrial quality-control, is imported into mitochondria and how its misdirection contributes to early-onset Parkinson's disease. We have discovered a new pathway for PINK1 import, and show that its structure influences its fate and function. Using advanced biochemical, biophysical, and computational tools, the project will investigate how PINK1 variants associated with Parkinson's affect mitochondrial function, and progression of disease. This interdisciplinary project offers exciting opportunities to uncover novel mechanisms of neuro-degeneration and gain hands-on experience with cutting-edge research techniques.
Description	**Background:** Mitochondria are essential organelles responsible for ATP production, metabolic regulation, and biosynthesis. Their function depends on the precise import of nuclear-encoded proteins via the TOM and TIM complexes, particularly the TIM23 pathway. This import is vital for mitochondrial biogenesis and maintenance. A key player in mitochondrial quality control is the kinase PINK1, which under normal conditions is imported, subject to cleavage by the rhomboid protease PARL. This then enables retro-translocation and degradation. However, in damaged mitochondria, PARL cleavage is prevented and PINK1 accumulates on the outer membrane, triggering mitophagy. Mutations in PINK1 disrupt this process and are linked to early-onset Parkinson's disease. Recent findings from our laboratories suggest an unexpected alternative import route for PINK1 into the mitochondrial matrix via the TIM23 pathway (see reference below). Structural modelling indicates that PINK1's trans-membrane domain (TMD) may adopt different conformations, influencing its import fate and function. This discovery opens new avenues for understanding of the regulation of mitochondrial structure, function and quality control, relevant to the progression of Parkinson's disease. **Key Research Question:** How does the structural flexibility of PINK1's TMD determine its mitochondrial import pathway and functional role, and how do disease-associated mutations disrupt this process to contribute to the progression Parkinson's associated neuro-degeneration? **Specific Objectives:** 1. Structural and dynamic modelling of PINK1 - Use computational modelling (e.g., AlphaFold, Molecular Dynamics) to predict different conformational states of the TMD, and determine how they can be stabilised. - Determine how variants of PINK affect the structure of its TMD. 2. Mechanistic Analysis of TIM23 Import and PARL Cleavage

	- Establish mitochondrial import assays of PINK1 and examine the effects of variants (identified above) affecting TMD conformation. - Establish cleavage assays of PINK1 by PARL, and examine the effects of variants (identified above) affecting TMD structure. 3. Consequences of TMD perturbation, and PINK1 fate, on mitochondrial structure and function - Generate cell lines producing variants of PINK with different TMD structures. - Assess consequences for mitochondrial function (respiration, membrane potential, reactive oxygen species (ROS)) using Seahorse assays and fluorescence microscopy. - Examine effects on mitochondrial structure by electron cryo-tomography. 4. Impact of Parkinson's-linked PINK1 variants - Introduce disease-associated mutations into PINK1 constructs. - Analyse effects on PINK1 import and cleavage (as above). - Monitor the effects on mitochondrial structure and function (as above) - Correlate molecular defects with disease mechanisms. Student Ownership and Development: The student will have the opportunity to: - Design and optimise experimental protocols. Lead computational modelling and structural validation. - Select and characterise disease-relevant PINK1 variants. - Interpret data and propose new hypotheses. - Contribute to publications and present findings at conferences. This interdisciplinary project combines computational biology, biochemistry, structural biology and cell biology, offering a rich training environment and the chance to make impactful discoveries in mitochondrial biology and neuro-degeneration. **Reference:** Lorriman, J. S., Grieve, A. G., Corey, R. A.* & Collinson, I.* Alternative Import-Channels And Destinations Of Mitochondrial PINK1 Controlled By Trans-Membrane-Domain Structural Plasticity. Under Review EMBO J. https://www.biorxiv.org/content/10.1101/2024.11.06.622366v1
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