Project Details	
Project Code	NMH27Br Collinson
Title	Alternative fates of PINK1 and its role in mitochondrial quality control, energy production and Parkinson's Disease
Research Theme	Neuroscience & Mental Health
Project Type	Wet lab
Summary	Mitochondria are vital for energy production, cellular homeostasis, and health. This project explores how 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, suggesting its structural plasticity influences its fate and function. Using advanced biochemical and computational tools, the project will investigate how PINK1 variants associated with Parkinson's affect mitochondrial function, and progression of disease — exploring also how this can be corrected. This interdisciplinary project offers exciting opportunities to uncover novel mechanisms of neuro-degeneration and training in cutting-edge research techniques.
Description	BACKGROUND: Mitochondria are organelles of eukaryotic cells critical for energy production (ATP), metabolic regulation and biosynthesis. They are complex, dynamic structures composed of a double outer and inner-membrane, encapsulating an inter-membrane space (IMS) and the interior matrix. The importance of mitochondria for cell function and homeostasis requires well-regulated maintenance involving biogenesis and degradation. Most of the mitochondrial proteome is nuclear-encoded, so biogenesis requires protein import from the cytosol. This occurs through translocases of the outer-membrane (TOM) and inner-membrane (TIM). The major route for precursor protein import into and across the inner-membrane occurs via the TIM23-pathway driven by the membrane-potential ($\Delta\psi$) and the turnover of ATP. Problems arising in this process restrict the cell's ability to maintain mitochondrial function. The quality-control process also requires the degradation of mitochondria that have become damaged beyond repair. This process is controlled by the precursor protein PINK1, which in functional mitochondrial is incorporated into the inner-membrane, via the TIM23-pathway, and cleaved by the rhomboid protease PARL. Cleavage results in retro-translocation, back to the outer-membrane and proteasomal degradation, and no further action is taken. In compromised mitochondria this process fails and PINK1 is activated at the outer-membrane, which initiates mitophagy. Failure of this quality control process, e.g. caused by the mutations in pink1, can bring about neurodegenerative disease, including early-onset Parkinson's disease. Our recent analysis of PINK1 import within intact cells reveals an unexpected alternative destination—by way of the TIM23-pathway—into the matrix [1]. Structural modelling predicts that PINK1's trans-membrane domain (TMD) forms either an α-helix or α/β-hybrid. We propose this structural plasticity underlies PINK1's destiny, respectively for matrix import or cleavage/retro-translocation. The results reveal new insights of PINK1's role in mitochondrial quality control and function. The analysis also predicts that some of the PINK1 variants linked to early-

onset Parkinson's disease will disturb the balance of its distribution to either the matrix or outer-membrane. With this, we believe we have uncovered a hitherto unknown aspect of the accelerated progression of neurodegeneration. Thus, this discovery opens new avenues for the understanding of (and correction of) the regulation of mitochondrial structure, function and quality control, relevant to the progression of Parkinson's disease.

The new findings have led to new QUESTIONS, to be addressed by this proposed PhD project. What controls the PINK1 switch? And what are the consequences of the different fates—principally, what is PINK1 regulating in the matrix? Finally, how does the fate of PINK1 contribute to health and disease? Therefore, we seek to empower a PhD student in an arsenal of cutting-edge technologies, developed in the supervisory team's laboratories, to address these questions.

The OBJECTIVES will be:

(1) To conduct biochemical, biophysical and computational analyses of the conformational switch within the TMD of PINK1 and the consequential interactions with PARL and the TIM23 protein import machinery.

(2) The role of PINK1 in the matrix has not been widely studied, so we will examine its effect on mitochondrial function. This will be achieved through the biochemical and cellular analysis of cells subject to matrix exposure or depletion of PINK1.

(3) Attempt to control the destiny of PINK1 for cleavage or for matrix import. This will be achieved through the design/ selection of small molecule and protein reagents to block/ enhance PINK1's interaction with the respective cleavage/ import complexes. Our objective will be to devise strategies to correct the misdirection of PINK1 responsible for the early progression of Parkinson's.

The project is interdisciplinary, combining computational methods with experimental empiricism of biochemical, biophysical and cell biology techniques. This multi-scale and innovative approach will provide the student with outstanding opportunities for training and discovery.

REFERENCES

[1] J.S. Lorriman, R.J. Hughes, A.G. Grieve, R.A. Corey, I. Collinson, Transmembrane domain switching controls PINK1 import and fate in mitochondria, EMBO J. (2026) 1–22. https://doi.org/10.1038/s44318-026-00789-x.

STUDENT OWNERSHIP AND DEVELOPMENT:

The student will have the opportunity to:

— Design and optimise experimental protocols. Lead computational modelling, simulations and design.

— 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, cell biology and design/ engineering biology — offering a rich training environment and the chance to make impactful discoveries in mitochondrial biology, neuro-degeneration and potentially also towards new therapeutic interventions.

Can be completed part time?	Yes
Supervisory Team	
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