****

**PhD Project Commencing October 2024**

**(Closing date: 16 May 2024)**

**Principal Supervisor:** [**Julien Prudent**](https://www.mrc-mbu.cam.ac.uk/research-groups/prudent-group)(enquiries to: julien.prudent@mrc-mbu.cam.ac.uk)

**Second Supervisor:** [**Michal Minczuk**](https://www.mrc-mbu.cam.ac.uk/research-groups/minczuk-group)

**Investigating how mitochondrial dynamics control mtDNA homeostasis and engineering tools to visualise mtDNA molecules**

Mitochondria are dynamic organelles forming a specific network by membrane remodeling events according to cellular needs1. Mitochondria contain multiple copies of their own genome, mtDNA, a circular molecule that encodes essential proteins involved in cellular energy production. A reduced levels of mtDNA or pathogenic mutations in the mitochondrial genome have been associated with human diseases. These include inherited primary mitochondrial diseases, as well as age-related conditions like neurodegeneration and cancer. However, the precise mechanisms through which mitochondrial dynamics regulate both the levels and quality control of mtDNA remain not well understood.

The goals of this collaborative project is: (i) to elucidate how mitochondrial dynamics control the regulation of mtDNA copy number and/or its quality and (ii) to engineer tools to visualise different genetic mtDNA variants in living cells. Using recently developed methods of mitochondrial genome editing, we will generate cellular and mouse models of mitochondrial disorders that harbour mtDNA mutations2 and employ state-of-the-art microscopy, mitochondrial function and mtDNA analysis3, to investigate (1) how the manipulation of mitochondrial membrane remodelling events control mtDNA content, (2) how these pathways are involved in mtDNA quality control to reduce mutant mtDNA in cellular and in vivo models, (3) the molecular mechanism regulating these processes; and (4) the implication on mitochondrial function. In addition, we will engineer fluorescent probes to specifically label wild-type or mutant mtDNA in order to monitor their dynamics by live-cell imaging during different cellular stress conditions. Together, the successful candidate will monitor mtDNA dynamics and determine how the regulation of mtDNA quality control/levels, by targeting mitochondrial dynamics, could represent a future potential therapeutic target for pathogenic mtDNA mutations.

This multi-disciplinary project will allow the student to employ a range of experimental procedures including molecular and cellular biology, protein engineering, cutting-edge confocal and super-resolution microscopy to mtDNA and mitochondrial function analysis both in cellulo and in vivo. The student will also apply mtDNA editing technologies to develop novel cellular and mouse models in order to increase the physiological relevance of their findings.

**Keywords**

General: mitochondrial dynamics, mtDNA, heteroplasmy, microscopy

More specific: Membrane remodelling, mitochondrial disease

**References**

1: Tilokani L, Nagashima S, Paupe V, Prudent J. Mitochondrial dynamics: overview of molecular mechanisms. Essays in Biochem 2018 Jul 20;62(3):341-360. PMID: 30030364.

2: Silva-Pinheiro P, Mutti CD, Van Haute L, Powell CA, Nash PA, Turner K, Minczuk M. A library of base editors for the precise ablation of all protein-coding genes in the mouse mitochondrial genome. Nat Biomed Eng 2023 May;7(5):692-703. PMID: 36470976.

3: Zecchini V, Paupe V, Herranz-Montoya I, Young T, Janssen J, Wortel IMN, Morris JL, Ferguson A, Costa SAH, Tronci L, Nikitopoulou E, Yang M, Bihary D, Caicci F, Nagashima S, Speed A, Samarajiwah S, Prudent J#, Frezza C#. Fumarate induces mtDNA release via mitochondrial-derived vesicles and drives innate immunity. Nature. 2023 Mar;615(7952):499-506. #: corresponding author.PMID: 36890229.

**Subject areas**

Biochemistry, Cell Biology, Developmental Biology, Genetic Engineering, Molecular Biology, Molecular Genetics

**How to apply:** please visit the[MBU's Postgraduate Studies website](https://www.mrc-mbu.cam.ac.uk/postgraduate-studies)