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**PhD Project Commencing October 2023**

**(Closing date: 16 May 2023)**

**Principal Supervisor:** [**Michal Minczuk**](https://www.mrc-mbu.cam.ac.uk/research-groups/minczuk-group)(enquiries to: mam@mrc-mbu.cam.ac.uk)

**Second Supervisor:** [**Patrick**](https://www.mrc-mbu.cam.ac.uk/research-groups/chinnery-group) **Chinnery**

**Genome editing in mitochondria for *in vivo* correction of pathogenic mtDNA mutations**

Mammalian mitochondria contain several copies of their own genome (mtDNA) which encodes 13 essential subunits of the oxidative phosphorylation (OXPHOS) system. Pathogenic variants in the mitochondrial genome can result in mitochondrial diseases, which are a major group of inherited conditions affecting ~1 in 8,000 humans. These disorders are currently incurable and effectively untreatable, with heterogeneous penetrance, presentation and prognosis. This project aims at addressing the lack of effective treatment for these disorders. We will exploit a recently developed mouse models that recapitulate common molecular features of mtDNA disease [1, 2]. These models will be treated with programmable nuclease (mtZFNs and mitoTALENs) and mitochondrial base editors (DdCBE and TALED) [3] to induce specific reduction of mutant mtDNA in germline. We will follow a reversion of mitochondrial dysfunction phenotypes using single-cell genomics, proteomics and dedicated methods assessing mitochondrial function [2]. The results obtained within this project will constitute proof of principle that mtDNA mutation correction using genome modification tools could provide a therapeutic route for mitochondrial diseases of diverse genetic origin.

**Keywords**

General:

mitochondrial disease, genome editing, gene therapy

More specific:

base editing, programmable nucleases, mitochondrial genome

**References**

1. Gammage et al. (2018) Genome editing in mitochondria corrects a pathogenic mtDNA mutation *in vivo*. **Nat Med** 24, 1691-1695. doi: 10.1038/s41591-018-0165-9.
2. Burr et al. (2023) Cell lineage-specific mitochondrial resilience during mammalian organogenesis. **Cell**. doi.org/10.1016/j.cell.2023.01.034
3. Silva-Pinheiro & Minczuk (2021) The potential of mitochondrial genome engineering **Nat Rev Genet**, 23, 199-214. doi: 10.1038/s41576-021-00432-x

**Subject areas**

Bioinformatics, Biotechnology, Development Biology, Genetic Engineering, Genetics, Genomics, Human Genetics, Molecular Biology, Molecular Genetics, Neuroscience

**Eligibility:** UK/Irish citizens or UK permanent residents

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