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**PhD Project Commencing October 2024**

**(Closing date: 4 January 2024)**

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**Genetic engineering of the human mitochondrial genome**

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 animal models and effective treatments for these disorders (Ref 1). We will improve and employ the recently developed genome editing technologies (such as TALE-DdCBE, ZF-DdCBEs and TALED – Ref 1 & 2) to develop and characterise cellular and animal models recapitulating common features of mtDNA disease. These models will be then subjected to a variety of pre-clinical interventions to, for example, induce specific reduction/correction of mutant mtDNA (Ref 3) or therapeutic increase of mtDNA copy-number (Ref 4). We will follow a reversion of mitochondrial dysfunction phenotypes using state-of the art approaches dedicated to assess mitochondrial function (Ref 2 & 3). The results obtained within this project will constitute proof of principle that targeting mtDNA 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**

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2. Silva-Pinheiro et al. (2023) A library of base editors for the precise ablation of all protein-coding genes in the mouse mitochondrial genome. **Nature Biomed Eng**. 7:692-703. doi:10.1038/s41551-022-00968-1
3. 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
4. Filograna et al. (2019) Modulation of mtDNA copy number ameliorates the pathological consequences of a heteroplasmic mtDNA mutation in the mouse. **Science Adv**. 5:eaav9824. doi: 10.1126/sciadv.aav9

**Subject areas**

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

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