

DC8: Mitochondrial genomic instability and disease

Host institution: University College London, Queen Square Institute of Neurology, London, United Kingdom.

Supervisor: Dr. Antonella Spinazzola

Co-Supervisors: Dr. Roman Szczesny, Institute of Biochemistry and Biophysics, Polish Academy of Science, Warsaw, Poland (Academic); Dr. Noa Sher, Minovia Therapeutics LTD, Haifa, Israel.

Project description: Mitochondrial DNA (mtDNA) integrity is fundamental for health: defects in the molecule cause a variety of devastating genetic neuro-metabolic diseases, and mtDNA abnormalities have been linked to neurodegeneration and to the decline of tissue and organ function, as we age. A crucial factor contributing to mtDNA maintenance is the supply of precursors for DNA synthesis: either an excess or deficiency of deoxynucleotides (dNTPs) can result in the mtDNA loss or damaged molecules that accumulate in solid tissues; and to these we recently added aberrant incorporation of ribonucleotides in the mitochondrial genome; all of which lead to mitochondrial dysfunction and pathologies. Importantly, nucleotide supplementation can increase the level of mtDNA *in vitro* models of diseases, and likely *in vivo*. Hence, this strategy holds great promise as a treatment for an important group of mitochondrial diseases.

Here, we will study a mouse model of nucleotide insufficiency that **a)** recapitulates several aspects of the mtDNA maintenance disorders including tissue-specific differences in mtDNA abnormalities; and **b)** manifests multi-organ pathology characteristic of common neuro-metabolic disorders. Therefore, the model is ideal to determine **i)** the tissue-specific molecular determinants that give rise to the different abnormalities and organ-pathology; **ii)** the effect nucleotide perturbation on nucleic acid structure and dynamics; and develop **iii)** an effective *in vivo* therapeutic regime as the basis of a protocol for treating patients with mtDNA maintenance defects. Moreover, **iv)** the study will provide critical information to rigorously assess the role of mitochondrial dysfunction in common neuro-muscular and metabolic disorders. To achieve these goals the student will employ a wide range of molecular biology techniques and will analyse and integrate 'omics' data, coupled with *in vivo* treatments of mtDNA disease models.

Host laboratory: Professor Spinazzola's group is internationally renowned for its contribution to mitochondrial biology and medicine. The group offers excellent training in research for clinical and non-clinical students wishing to obtain higher degrees. We have well-funded and modern multidisciplinary facilities for studying cellular and animal disease models and the group has numerous collaborative research links across the Institute of Neurology, UCL and nationally and Internationally.

Secondments: This project is carried out in strong collaboration with the following groups, and visits to their laboratories are expected during the project. A willingness to travel and spend time abroad is therefore essential:

- Dr. Roman Szczesny, Institute of Biochemistry and Biophysics, Polish Academy of Science, Warsaw, Poland;
- Dr. Noa Sher, Minovia Therapeutics LTD, Haifa, Israel.

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Eligibility conditions

- Candidates must have a degree from a recognized University or equivalent institution of higher education, including a medical degree.

Required Skills

- Research experience in cellular and molecular biology techniques are required (through Master thesis work or research internships). Experience in mitochondrial biology and/or RNA biology will be a strong advantage.
- Proficiency in the English language is required, as well as good communication skills, both oral and written. Successful candidates will need to provide an English test (e.g. IELTS, TOEFL, Cambridge English) unless you are a national of a majority native-English speaking country.
- Commitment, enthusiasm, speculative mind and eager to learn are essential.

Enquiries

For general information about the MITGEST Doctoral Network visit the project website (www.mitgest.eu) or send an email to (info@mitgest.eu).

For additional information on this project please contact **Professor Antonella Spinazzola** (a.spinazzola@ucl.ac.uk).

How to apply

To complete your online application, visit the MITGEST recruitment web page (<https://www.mitgest.eu/open-positions/>).

Application deadline

The closing date for applications is **November 15th 2022**.



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