DC7: The impact of nutrient metabolism on mitochondrial DNA maintenance and expression in health and disease

Host institution: Biodonostia Health Research Institute, Neurosciences department, San Sebastián, Spain.

Supervisor: Dr. Ian Holt

Co-Supervisors: Dr. Antonella Spinazzola, University College London, Queen Square Institute of Neurology, London, United Kingdom (Academic); Dr. Thomas Frischmuth, baseclick GmbH, Neuried, Germany (Industrial).

Project description: It has long been known that mitochondria are reliant on their many small circles of DNA (mtDNA) for energy production from food, and that the mitochondria serve as metabolic hubs for the entire cell. However, only recently have we begun to appreciate that mtDNA dysfunction reprograms nutrient metabolism and, conversely, that nutrient availability regulates mtDNA metabolism. Accordingly, the molecular basis and key elements underlying these phenomena remain to be elucidated. To advance this field, the successful student will investigate the effect of nutrients on replication, transcription and translation in the mitochondria of human fibroblasts in normal and disease states. S/he will characterize the composition and distribution of the mitochondrial nucleo-protein complexes in these cells, as well as in tissues from a mouse model of mtDNA disease. To determine how nutrient availability affects the course of the disease, we will test several diets and assess their effect on disease progression at the macro and molecular level, the latter including analysis of mtDNA replication and expression via DNA, RNA and protein labeling. Targeted approaches will be coupled with unbiased approaches, including proteomic and metabolomic analyses. The new knowledge will be used to develop and refine methods of manipulating energy metabolism to mitigate mitochondrial diseases in cell and animal models in advance of experimental medicine studies.

Host laboratory: The host laboratory is based in the Basque country in the north of Spain, which invests twice the national average in research and boasts a high density of research institutes with complementary skills and technologies. The group is a global leader in the field of mitochondrial function and disease, and skilled and highly motivated doctoral students have driven many of the group's successes.

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. Thomas Frischmuth, baseclick GmbH, Neuried, Germany;
- Dr. Antonella Spinazzola, University College London, London, United Kingdom;
- Dr. Hans Spelbrink, Radboud Center of Mitochondrial Medicine, Nijmegen, The Netherlands.

Co-funded by the European Union

Engineering and Physical Sciences Research Council

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Eligibility conditions

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

Required Skills

- While experience in cell or molecular biology would be advantageous, the host laboratory has always prized intelligence, aptitude and drive over knowledge of specific skills, which can be taught.

Enquiries

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

For additional information on this project please contact Dr. Carlo Vascotto (ian.holt@biodonostia.org; i.holt@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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