Institute for Research on Cancer and Aging, Nice

Equipe Véronique PAQUIS

3-year postdoctoral position at IRCAN, CNRS UMR7284 / INSERM U1081, team « Genetics of mitochondrial diseases »

A **three-year postdoctoral position**, starting July 1st 2021, funded by the Fondation pour la Recherche Médicale (FRM) is available in the team of Véronique Paquis-Flucklinger at IRCAN Institute in Nice, south of France.

Title: Understand how mitochondrial defect triggers motor neuron disease

We showed that motor neuron disease (MND) can be triggered by mitochondrial dysfunction. We uncovered the genetic basis of this disease in patients from a large family with a mitochondrial myopathy associated with MND. Soon after, we and others reported *CHCHD10* mutations in amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD) and other neurodegenerative diseases. We generated knock-in (KI) mice, carrying the p.Ser59Leu mutation, that mimic the mitochondrial myopathy displayed by the patients from our original family. KI mice are born healthy but develop a fatal mitochondrial cardiomyopathy by 14 months of age, which is associated with enhanced mitophagy. Neurological features include neuromuscular junction (NMJ) degeneration with motor neuron loss in lumbar spinal cord and TDP- 43 cytoplasmic aggregates in spinal neurons. Longitudinal analyses revealed that skeletal muscle dysfunction precedes NMJ dysfunction and motor neuron death. Using patient-derived motor neurons, we showed that the p.Ser59Leu mutation increases caspase activation and cell death in response to apoptotic stimuli. Together, our results confirm that mitochondrial dysfunction caused by *CHCHD10* mutations can be at the origin of MND.

The proposed project seeks to understand the molecular bases of MND caused by *CHCHD10* mutations. We will explore the hypothesis that respiratory chain deficiency, loss of cristae junctions and destabilization of internal membrane structure within mitochondria causes dysfunction of the neuromuscular system and motor neuron death. By leveraging cell and animal models that we have generated, this project aims to (i) understand the role of CHCHD10 and molecular pathways leading to MND, (ii) define tissue and genetic crosstalk leading to MN death and (iii) to screen for genetic modifiers of *CHCHD10* in different patient-derived cell models.

Candidate profile:
The candidate should hold a PhD in cell biology or related disciplines and have previous expertise in induced pluripotent stem cells (IPS) generation/characterization or she/he should be skilled in cell culture as well as in molecular biology techniques. Practice or knowledge of primary motor neuron culture and analysis would be appreciated. Experience in the analysis of mitochondrial functions would be an added advantage.

How to apply?
Candidates should send a *curriculum vitae* with publication list, a short summary of research achievements, and the names and email addresses of at least two references to paquis@unice.fr

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