PhD fellowship in human genetics and in cellular neurobiology

UMR1253, iBrain, Inserm, University of Tours, France

We are seeking a highly motivated candidate (M/F) for a PhD fellowship funded by the Région Centre Val de Loire (3 years contract – starting from Oct. 2023) on the following project:

Characterization of the role played by *PURA* in the neurodevelopmental phenotype associated with 5q31 duplications.

Purine rich element binding protein A (Pura) encoded by the *PURA* gene is an important transcriptional regulator which binds DNA and RNA and plays a crucial role in neuronal development and differentiation. Haploinsufficiency of this gene has been reported to cause a severe neurodevelopmental syndrome with a wide range of symptoms including neurodevelopmental delay, intellectual disability, profound hypotonia, feeding difficulties, abnormal breathing pattern and seizures. In the literature, only one large duplication involving this gene has been described but the consequences of PURA overexpression on neurocognitive development have never been studied.

Through a national collaboration and thanks to the DECIPHER database, we collected seven 5q31 duplications involving *PURA* and occurring mainly *de novo* in patients with a neurodevelopmental disorder. To understand the impact of these duplications on neuronal development, *in vitro* functional studies will be conducted in patients' cells or in cellular neuronal models, such as mouse primary hippocampal neurons in order to mimic gene dosage effect. Furthermore, induced pluripotent stem cells (iPSCs) carrying *PURA* duplication will be generated using CRISPR-Cas9 technology on a reference iPSC line available in the lab. These iPSCs will be differentiated into neurons (i.e. iPSC-derived human neurons). Cellular and multi-omics analyses will be performed in these cells to identify key dysregulated pathways associated with *PURA* duplication. Finally, these *in vitro* experiments will allow us to decipher the neuropathological mechanisms associated with 5q31 duplications and to determine if the duplication of *PURA* alter neurodevelopmental trajectory.

The PhD candidate will apply methodological and analytical cellular and molecular approaches perform research studies on *PURA* duplication associated with a neurodevelopmental disorder. He/She will work closely with other team members to investigate the pathophysiological mechanisms using primary neuronal cultures from mouse embryonic brains and from iPSC-derived neurons overexpressing the *PURA* gene. He/She will study the neuronal developmental processes altered by the *PURA* gene duplication, interpret the biological results, communicate his/her research findings to the scientific community. This PhD fellowship will benefit from practical and theoretical training organized by the INSERM and by the University of Tours.

This work will be carried out in Team "Neurogenomics and neuronal pathophysiology" at the Imaging and Brain (iBrain – UMR1253) research lab in Tours, France (https://ibrain.univ-tours.fr). The iBrain lab (Inserm, University of Tours) is a structure at the forefront of translational research on neuropsychiatric disorders, from neurodevelopmental to neurodegenerative ones, using interdisciplinary in vitro and in vivo approaches from patients to pathophysiological models, leading to a highly relevant research environment and dedicated infrastructure directly connected to clinical recruitment and diagnosis. The Team "Neurogenomics and neuronal pathophysiology" (Leader: Dr. Frédéric Laumonnier) is running translational research programs to identify genetic and pathophysiological defects associated with neurodevelopmental disorders and Amyotrophic Lateral Sclerosis (ALS) from clinical recruitment, the genetic analyses, to the study of neuronal cellular and/or animal models. The laboratory provides a highly interactive environment with collaborative opportunities, particularly within the recently created GenoMedS FHU network involving university

hospitals and research Labs from the Ouest part of France. The laboratory supports teamwork as well as individual career development.

The candidate shall have:
. Scientific and university background in genetics, cellular biology, neuroscience
. Demonstrated level of practice in neuronal cellular culture
. Experience in cellular neurobiology

The candidate must be under 30 years-old at the beginning of the PhD contract (1st Oct 23)

Applicants must send a CV and a cover letter, and reference letters from previous supervisors to:

Dr Frédéric LAUMONNIER ; email: frederic.laumonnier@inserm.fr
and
Dr Marie-Laure VUILLAUME-WINTER ; email: m.winter@chu-tours.fr

Deadline for application: 30 March 2023