PHD Molecular and Cellular Biology on Neurodegeneration

IGBMC - Strasbourg

A fully 3-years funded PhD position starting in January 2020 is available in the group of Dr. Charlet (http://www.igbmc.fr/research/department/4/team/42/) at the Institute of Genetics and Biology Molecular and Cellular (IGBMC, Strasbourg) on neuronal dysfunctions in cell and mouse models.

IGBMC (http://www.igbmc.fr/) is a large public research laboratory comprising ~800 persons involved in 50 research groups and 12 technological platforms, including all core services essential to the present project (AAV production, mouse models creation and phenotyping, proteomic and transcriptomic, confocal and super resolution microscopy, antibodies production services, etc.).

Work in the team investigate how repeat (microsatellite) expansions lead to human genetic diseases. We are notably interested in Myotonic Dystrophy (DM) caused by expanded CTG repeats, Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS) due to expanded CGG repeats and Amyotrophic Lateral Sclerosis (ALS) due to a GGGGCC expansion. Publications of the group during the past years include Fugier et al., Nature Medicine 2011; Rau et al., Nature Structural Molecular Biology 2011; Freyermuth et al., Nature Communication 2016; Sellier et al., Neuron 2017; Sellier et al., Nature Communication 2018; Boivin et al., EMBO Journal 2019.

The proposed PhD project aims at understanding how expanded CGG or GGGGCC repeats leads to neurodegenerative diseases, including Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS) and Amyotrophic Lateral Sclerosis (ALS).

FXTAS is a rare neurodegenerative disease characterized by cerebellar ataxia, dementia and tremor. FXTAS is caused by 55 to 200 CGG repeats located within the 5'UTR of the FMR1 gene. Our work show that these repeats are translated into a toxic polyGlycine-containing protein, which pathological mode of action remains to be defined.

ALS is the third most common neurodegenerative disease in the western world, affecting 1 individual in 50,000 people. This devastating disease is characterized by degeneration of motor neurons leading to muscle wasting and weakness, ultimately resulting in death of the patients. The most common genetic cause of ALS is an expansion of GGGGCC repeats located within the first intron of the C9ORF72 gene. This mutation leads to expression of toxic DPR proteins and decreased expression of the C9ORF72 protein. Our recent results indicate that C9ORF72 regulates autophagy, a catabolic process necessary to eliminate protein aggregates and altered organelles.

We developed novel cell and mouse models for FXTAS and ALS. The candidate will investigate how the CGG and the GGGGCC repeats are toxic using a wide range of molecular and cellular approaches (RT-PCR, immunoblot, immunoprecipitation, immunofluorescence, transfection and cell transduction, etc.). Furthermore, the candidate will study the phenotypes of mice expressing the CGG mutation. This study will comprise animal behavior and motor performances followed by molecular and histological analyses.

Overall, this proposal will help to better understand the cause of neuronal degeneration in ALS and/ or FXTAS, in order to define therapeutic strategies for these devastating diseases.

We seek a very motivated candidate with solid technical skill in molecular and cellular biology. Experience with animal models will be a plus.

CV, Motivation and Recommendation letters, Master 1 & 2 grades and E-mails of the candidate internship supervisors should be sent by E-mail to ncharlet@igbmc.fr