

Two funded post-doctoral positions are available in the laboratory of H el ene Puccio at the IGBMC in Strasbourg.

Our group focuses on hereditary ataxias, rare neurodegenerative disorders that affect the cerebellum and/or the spinal cord. One focus is on Friedreich's ataxia (FA), the most common hereditary autosomal recessive ataxia, due reduced levels of the frataxin protein (FXN). The consequence of FXN deficiency is a primary decrease in Fe-S cluster biogenesis. Fe-S cluster biogenesis is an essential process present in all living organisms and required for the function of a myriad of proteins involved in key cellular processes such as respiration, central metabolism and DNA maintenance. Our group is interested in unraveling the pathophysiological mechanisms implicated in FA and understanding the function of the proteins involved in the Fe-S biosynthesis pathway. Furthermore, we aim at developing therapeutic approaches to cure this devastating disease. We address these fundamental and medical questions by combining human genetics, mouse genetics, biochemistry, molecular and cell biology, and AAV-based gene therapy.

More information on the team can be found on the IGBMC Web site:
<http://www-igbmc.u-strasbg.fr/research/departement/4/team/49/>

Projects description:

1. The main objective of the ANR funded collaborative "FRACOL" project is to use synthetic biology to approach FA and the key step in early Fe-S biosynthesis involving FXN. The underlying hypothesis is that by modifying the Fe-S cluster components, it will be possible to ensure Fe-S biogenesis in the absence of FXN. Two main strategies are planned. One aims at validating variants of the scaffold and the cysteine desulfurase (identified by our partners in engineered *E. coli* strains) able to function in the absence of FXN. This will be accomplished by CRISP/Cas gene editing of FXN deficient cell lines. A first proof of concept has already been obtained. An extensively characterization at the biochemical and physiological level of the newly generated lines will be performed. The second aims at identifying drugs through a medium-scale chemical libraries screen enabling to bypass frataxin deficiency using novel humanized cell lines that present the biochemical characteristics of FA This will be performed in close collaboration with the high-throughput screening platform of the IGBMC. The most promising variants and/or drugs will then be tested on adequate FA mouse models.
2. The overall objective of the FARA-funded collaborative project is to investigate the pathogenic role of metabolic changes in FA neuropathology, and to identify and validate related biomarkers to be used as candidate surrogate outcomes in clinical trials. Transcriptomic and proteomic analyses on human induced-pluripotent stem cell-derived neurons from FA patients and on affected neural tissues from two mouse models will be performed to identify the pathophysiological pathways. Candidate pathways will then be validated by different biochemical and molecular biology methods. In parallel, based on preliminary data obtained both in mouse models and iPSC-neurons, targeted analysis of amino acids and neuroinflammation as potential biomarkers will be performed on plasma and cerebrospinal fluid (CSF) of FA patients. Finally, novel potential biomarkers identified by our partner through a proteomic analysis of FA serum and CSF will be cross-validated in the mouse models.

Candidates must be highly motivated and have a PhD in biological science. Strong working knowledge of molecular and cellular biology is required. Hands-on experience with molecular and cellular biology techniques is required. Prior experience with animal work, CRISP/Cas gene editing, high-throughput screening, bioinformatics or biomarkers identification would be an asset but is not required. French speaking is NOT a requirement. Ability to work independently and within a team environment, computer literacy and good communication skills are required. Applications are invited for a 2-3 years position. Please send your application including a statement of research interests, a complete curriculum vitae and at least two references (including email) to **H el ene Puccio** (hpuccio@igbmc.fr)

About us

The Puccio group is provided with a fully equipped molecular and biochemistry laboratory, and is embedded in a highly collaborative and multidisciplinary environment. The candidate will benefit from an excellent work environment, including various state-of-the-art research facilities at IGBMC (http://www.igbmc.fr/index_uk.html) and at the Mouse clinical Institute (www.mci-ics.fr) and international collaborations. Located in Illkirch near Strasbourg, France, the IGBMC is one of the leading European centers of biomedical research.