PhD program 2020 call for proposals:

LabEx co-direction fellowships

Title of the subject:

Study of mitochondrial dysfunctions in amyotrophic lateral sclerosis

Research Unit 1

Name: IGBMC

Director of the unit: Alain Beretz

Code : CNRS UMR 7104 - Inserm U 1258

Address: 1 Rue Laurent Fries, 67404 Illkirch

Research Unit 2

Name: GMGM

Director of the unit: Ivan Tarassov

Code: Strasbourg University - CNRS UMR 7156

Address: 4, allée K. Roentgen, 67000 Strasbourg

Research teams and team leaders

Team 1: RNA disease

http://www.igbmc.fr/research/department/4/team/42/

Team leader 1: Nicolas Charlet

Email: ncharlet@igbmc.fr

Phone number: +33 (0) 388 653 309

Team 1 members: 6 : 2 researchers, 2 PHD, 1 Engineer, 1 Master2

Number of PhDs in progress: 2, starting dates : Sept 2017 and January 2020.

3 relevant publications:

- Boivin et al. C9ORF72 haploinsufficiency synergizes DPR proteins toxicity, a double hit mechanism that can be prevented by drugs activating autophagy. **EMBO J**. 2019

- Sellier et al., rbFOX1/MBNL1 competition for CCUG RNA repeats binding contributes to myotonic dystrophy type 1/ 2 differences. **Nature Communications**. 2018; 9(1):2009.

- Sellier et al., Translation of Expanded CGG Repeats into FMRpolyG Is Pathogenic and May Contribute to Fragile X Tremor Ataxia Syndrome. **Neuron**. 2017; 93(2):331-347.

Team 2: Intracellular traffic of RNA and mitochondrial diseases

http://gmgm.unistra.fr/index.php?id=3662&L=2

Team leader 2: Nina Entelis & Ivan Tarassov

Email: n.entelis@unistra.fr / i.tarassov@unistra.fr

Phone number: +33 (0) 368 851 481

Team 2 members: 8 : 3 DR CNRS, 1 CRCN CNRS, 1 IE CNRS, 2 PhD (co-supervised), 1 postdoc

Number of PhDs in progress: 2, co-supervised, starting date Nov 2017 and Oct 2019.

3 relevant publications:

- D. Jeandard, A. Smirnova, I. Tarassov, E. Barrey, A. Smirnov, N. Entelis. Import of non-coding RNAs into human mitochondria: a critical review and emerging approaches. **Cells** 2019, 8, 286;

- R Loutre, AM Heckel, A Smirnova, N Entelis, I Tarassov. Can mitochondrial DNA be CRISPRized: pro and contra. **IUBMB Life**, 2018, Dec;70(12):1233-1239.

- I. Dovydenko, I. Tarassov, A. Venyaminova, N. Entelis. Method of carrier-free delivery of therapeutic RNA importable into human mitochondria: lipophilic conjugates with cleavable bonds. **Biomaterials**. 2016 Jan;76:408-17.

Phd supervisors

PhD director: Nicolas Charlet

Email: ncharlet@igbmc.fr

Phone number: +33 (0) 388 653 309

PhD co-director: Ivan Tarassov

Email: i.tarassov@unistra.fr

Phone number: +33 (0) 368 851 481

Website Team 1: http://igbmc.fr/research/department/4/team/42

Website Team 2: http://gmgm.unistra.fr/index.php?id=3662&L=2

Phd subject

Title: Study of mitochondrial dysfunctions in amyotrophic lateral sclerosis

Description:

Amyotrophic Lateral Sclerosis (ALS) is the third most common neurodegenerative disease. This devastating disease is characterized by degeneration of motor neurons leading to muscle wasting, ultimately resulting in paralysis and death of patients. Importantly, disruption of mitochondrial functions and alteration of their morphology has been extensively reported in ALS.

Recently, the most common genetic cause of ALS was identified as an expansion of CGGGGC repeats located within the *C9ORF72* gene. This mutation leads to decreased expression of the C9ORF72 protein. Recent results of team 1 indicate that C9ORF72 is involved in regulation of autophagy, a catabolic process necessary to eliminate protein aggregates and dysfunctional organelles (Sellier et al., 2016; Boivin et al., 2019). Team 2 is expert in various methodologies aimed to characterize isolated mitochondria and to study their integrity,, functions and morphology in cultured cells or . Thus, the objective of this PhD project will be to characterize whether C9ORF72 regulates autophagy of altered mitochondria (mitophagy). The candidate will investigate at the molecular and cellular level the effect of C9orf72 mutations on the mitochondrial functions and the mitophagy pathway using cell cultures and classic molecular, cellular and biochemical approaches (CRISPR-Cas9, immunoblotting and

immunofluorescence, immunoprecipitation, transfection, cell culture, mitochondria purification and characterization, NGS-related techniques, etc.).

Overall, this proposal will contribute to better understanding of the mechanisms of neuronal degeneration in ALS patients, in order to define therapeutic strategies for this devastating disease.

Key words: Genetic diseases, Neurodegeneration, Mitochondria, Autophagy