**Master 2 internship project**

**Year 2023-2024**

**Laboratory/Institute:** INFINITy (Institut Toulousain des Maladies Infectieuses et Inflammatoires)

**Director:** Dr. Nicolas Fazilleau

**Team:** Inflammatory diseases of the central nervous system: mechanisms and therapies

**Head of the team:** Pr. Roland LIBLAU /Dr. Abdelhadi SAOUDI

**Name and status of the scientist in charge of the project:**

Dr. Marion SZELECHOWSKI, CRCN CNRS **HDR: yes  no ☐**

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**Program of the Master’s degree in Biology:**

**** Microbiology, Infectious Diseases and Immunology **☐** Structural Biology of Pathogens

**☐** Physiology, Epigenetics, Differentiation, Cancer **** Neurosciences and Neurobiology

**Title of the project:**

**Transcriptionnal adaptation of CNS cells during neurodegeneration**

# Objectives (up to 3 lines):

By combining ex-vivo (primary cell cultures and co-cultures, organotypic cultures) and in-vivo (mouse models) studies using genetically modified mouse strains, the goal of this project will be to address how oxidative stress and metabolic constrains modulate the crosstalk between CNS cells during Parkinsonism, in the brain and the retina.

# Abstract (up to 10 lines):

Parkinson's disease (PD) is a neurodegenerative disease caused by the progressive loss of dopaminergic neurons. However, neurodegeneration occurs in an inflammatory context that triggers a strong metabolic scarcity in the CNS. Together with oxidative stress, the metabolic adaptation of CNS cells rely on their ability to initiate phenotypic changes, involving transcriptomic remodeling.

Recently, we observed that a transcription factor, Foxo3, is activated upon neurodegeneration in dopaminergic neurons, in models of Parkinson’s disease (PD). However, Foxo3 KO mice display opposite outcomes in 2 different models of PD, without this being attributable to its functions in neurons. Hence, we turned to cells mediating inflammation, CNS resident or not, and established a landscape of inflammation in the course of disease development. In particular, we observed strong modulations of microglial phenotype. We now want to address how those changes directly affect neuronal outcome, in presence or absence of Foxo3.

# Methods:

Mouse manipulation (contention, intraperitoneal, intracerebral (stereotaxic), intravitreal injections…), histochemistry, cell isolation, flow cytometry (FACS), biochemistry, oxygraphy, RNA sequencing.

# Up to 3 relevant publications of the team:

• Mortalin/Hspa9 involvement and therapeutic perspective in Parkinson's disease. Texier B, Prime M, Atamena D, Belenguer P, Szelechowski M. Neural Regen Res. 2023 Feb;18(2):293-298. doi: 10.4103/1673-5374.346487.

• HSPA9/Mortalin mediates axo-protection and modulates mitochondrial dynamics in neurons. Ferré CA, Thouard A, Bétourné A, Le Dorze AL, Belenguer P, Miquel MC, Peyrin JM, Gonzalez-Dunia D, Szelechowski M. Sci Rep. 2021 Sep 6;11(1):17705. doi: 10.1038/s41598-021-97162-1.

• A viral peptide that targets mitochondria protects against neuronal degeneration in models of Parkinson's disease. Szelechowski M, Bétourné A, Monnet Y, Ferré CA, Thouard A, Foret C, Peyrin JM, Hunot S, Gonzalez-Dunia D. Nat Commun. 2014 Oct 21;5:5181. doi: 10.1038/ncomms6181. PMID: 25333748

# Requested domains of expertise (up to 5 keywords):

**Either neurosciences** (neurobiology, physiology, specific technics such as stereotaxy, brain dissection, IHC…) **or immunology** (inflammatory cells, flow cytometry, activation markers etc)