

Project 2. Counteracting mitochondrial dysfunctions in neurodegenerative diseases (Group leader Jean-Charles Liévens)

Energy defects and increased oxidative stress resulting from **mitochondrial dysfunction** are key determinants in many neurodegenerative diseases. Our main objective is to find therapeutic targets to correct them. We are more particularly interested in two motor pathologies: ALS and **type 7 spastic paraplegia (SPG7)**.

1- ALS is due to the loss of motor neurons leading to the progressive paralysis of patients. Using genetic tools in *Drosophila*, we provided the first in vivo demonstration that the S1R could be a relevant target for preventing energy deficits and oxidative stress in ALS (Couly *et al.*, *Hum Mol Genet* 2020; Lee, Liévens, Wang *et al.*, *Nat Commun* 2020). A second therapeutic strategy that emerges from our work is to increase glucose metabolism (Besson *et al.*, *PLoS One* 2015; Manzo *et al.*, *ELife* 2019). Now we want to validate these targets and dissect their mechanism of action on vertebrate models of ALS in zebrafish or mice.

2- SPG7 is characterized by the presence of spasticity, cerebellar ataxia and chronic external ophthalmoplegia. It is due to the degeneration of the cortico-spinal pathway and cerebellum. SPG7 is an inherited disease caused by mutations in the *spg7* gene encoding the mitochondrial protease, Paraplegin. However, while this disease is considered recessive, some clinical observations also argue for a detrimental impact of *spg7* mutation at the heterozygous state. Our aim is to understand if the presence of a single mutated copy of *spg7* acts as a predisposing risk factor for the development of neurological symptoms. The study focuses on fibroblasts obtained from skin biopsies of symptomatic patients with the *spg7* mutation in the simple heterozygous state or homozygous/double heterozygous state and control individuals. In parallel, an analysis is also carried out in vivo on a model organism, *Drosophila*. The use of this genetic model allows the identification of genes and targets modifying the SPG7 pathology. In the longer term, they will be validated on zebrafish models.

Project staff:

Researchers/Clinicians: Jean-Charles Liévens, Cecilia Marelli, Mireille Rossel, Benjamin Delprat, Tanguy Maurice
Master students: Apolline Delauney, Amandine Peyrel, Thomas Reguero, Gabriel Vazquez

Collaborations:

Christelle Lasbleiz (groupe 1, MMDN)
Alexandra Durr (ICM, Paris)
Alex Whitworth (MRC, Cambridge UK); Daniela Zarnescu (Univ Arizona, USA); Tsung-Ping Su (NIDA, Baltimore USA)

Current funding:

Association Strümpell-Lorraine HSP France, EPHE, Key Initiatives MUSE.