Centre de Recherche de Biologie cellulaire de Montpellier
CRBM / CNRS – Université de Montpellier
1919 Route de Mende, 34293 Montpellier Cedex 05

2027 Internship Offer

Master 1: YES – Duration: 6 months **Master 2**: YES– Duration: 6 months

Team, Contact	Dimitris Xirodimas dimitris.xirodimas@crbm.cnrs.fr
Title	TARGETTING PROTEIN AGGREGATION IN NEURODEGENERATION
Research Themes and questions	Protein aggregation—when proteins stick together in abnormal ways—is a major cause of many neurodegenerative diseases. In Amyotrophic Lateral Sclerosis (ALS), a disease that affects motor neurons, mutations in certain proteins lead to the formation of harmful aggregates inside the cell's cytoplasm. These aggregates often form within structures called stress granules (SGs), which normally help cells cope with proteotoxic stress by temporarily pausing protein production. Under healthy conditions, SGs dissolve once the stress is removed, allowing normal protein synthesis to resume. In ALS, however, the abnormal aggregates fail to clear and instead persist in the cytoplasm. Their continued presence disrupts protein synthesis and contributes to the death of motor neurons. Finding ways to remove these aggregates is therefore a key focus of current research and may open new therapeutic opportunities for ALS, a disease that currently has no cure and typically leads to death within 2–5 years after diagnosis. Cells naturally use post-translational modifications—especially tagging proteins with ubiquitin and ubiquitin-like molecules (Ubls) such as SUMO and NEDD8—to clear misfolded proteins and prevent harmful aggregation. This project builds on recent discoveries from the host laboratory and aims to understand how ubiquitin and Ubls help eliminate the abnormal aggregates found in ALS. The student will investigate how abnormal aggregates contribute to ALS-related symptoms—such as impaired movement—and whether promoting aggregate clearance can improve these disease phenotypes.
Methods and experimental approaches	The student involved in this project will work at the intersection of biochemistry, molecular biology, advanced microscopy, live-cell imaging, and quantitative proteomics using human cell lines, mouse-derived neurons, and fibroblasts from ALS patients. These in vitro studies will be combined with genetic experiments in C. elegans, a widely used model organism for ALS.

Illustration	
2-3 Publications	1. I. Meszka, J. Polanowska, D. P. Xirodimas, Mixed in chains: NEDD8 polymers in the Protein Quality Control system. *Seminars in Cell & Developmental Biology*, S1084952122000131 (2022). 2. T. Kassouf, R. Shrivastava, I. Meszka, A. Bailly, J. Polanowska, H. Trauchessec, J. Mandrioli, S. Carra, D. P. Xirodimas, Targeting the NEDP1 enzyme to ameliorate ALS phenotypes through stress granule disassembly. *Sci. Adv.* 9, eabq7585 (2023). 3. Brunello L, Polanowska J, Le Tareau L, Maghames C, Georget V, Guette C, Chaoui K, Balor S, O'Donohue MF, Bousquet MP, Gleizes PE, Xirodimas DP (2025). A nuclear protein quality control system for elimination of nucleolus-related inclusions. *EMBO J.* doi: 10.1038/s44318-024-00333-9