**Internship offer**
**M2 Musculo-Skeletal system, Locomotion, Exercise (MuSkLE)**

**Title of the Internship**:

## Deciphering the role of SMN in oxidative DNA damage repair and neuromuscular stress responses

**Laboratory** Institut NeuroMyoGène – Pathophysiology and Genetics of Neuron and Muscle (INMG-PGNM), Université Claude Bernard Lyon 1 / CNRS / INSERM, Lyon, France.
Website: https://pgnm.inmg.fr/

**Research team** : Team Giglia-Mari – Nucleolar Dynamics and Genome Stability.

Website: https://pgnm.inmg.fr/en/giglia-mari/

https://www.teammari.com/

**Supervisor to contact** : Dr Ambra Giglia-Mari, ambra.giglia-mari@univ-lyon1.fr

**Project description including a short introduction, aim/objectives and methods/approach to be used**

**Context:**

Spinal muscular atrophy (SMA) is a severe neuromuscular disease caused by reduced levels of the Survival Motor Neuron (SMN) protein. Although SMN is classically known for its role in snRNP biogenesis and RNA metabolism, increasing evidence indicates that SMN deficiency also affects genome stability, nucleolar homeostasis and cellular responses to stress. These mechanisms are particularly relevant in post-mitotic and metabolically active tissues such as motor neurons and skeletal muscle, where oxidative stress and transcriptional stress may contribute to disease progression.

Recent work from the host team has shown that SMN participates in nucleolar reorganization after genotoxic stress and is required for the recovery of nucleolar architecture after DNA repair. Preliminary data further suggest that SMN interacts with components of the oxidative DNA damage response, including the 8-oxoG repair pathway. This M2 project will investigate how SMN contributes to the detection and/or repair of oxidative DNA damage and whether this pathway can be pharmacologically modulated in SMA-relevant cellular models.

**Internship Objective:**

- Determine whether SMN deficiency alters the accumulation and repair kinetics of oxidative DNA lesions, with a focus on 8-oxoG.
- Assess the recruitment and/or chromatin association of oxidative DNA repair factors such as OGG1 and XRCC1 in control and SMN-deficient cells.
- Investigate the impact of oxidative stress on nucleolar organization and transcription-associated nuclear compartments in SMA-relevant models.
- Test whether selected antioxidant or pro-repair treatments can reduce oxidative DNA damage markers and improve cellular resilience.

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**Methodologies Used:**

- Cell culture models: control and SMN-deficient fibroblasts or muscle-relevant cellular models; optional validation in SMA patient-derived or differentiated cellular systems depending on availability.
- Induction of oxidative DNA damage using calibrated oxidative stress conditions, followed by time-course recovery experiments.
- Immunofluorescence detection of oxidative lesions and DNA repair markers, including 8-oxoG, OGG1, XRCC1 and DNA damage response markers.
- Confocal microscopy and, when relevant, super-resolution imaging to analyse nuclear/nucleolar organization and protein relocalization after stress.
- Chromatin fractionation and/or proximity ligation assay to assess recruitment or interaction of SMN with oxidative DNA repair factors.
- Quantitative image analysis using Fiji/ImageJ and statistical analysis of lesion load, nuclear distribution and repair kinetics.
- Pilot treatment assays with antioxidant combinations or candidate modulators to evaluate partial rescue of oxidative stress sensitivity.

**References:**


- Musawi S. et al. Nucleolar reorganization after cellular stress is orchestrated by the survival motor neuron protein SMN. Nature Communications, 2023.


**Skills required:**

The project is suitable for a motivated M2 student interested in cell biology, genome stability and neuromuscular disease mechanisms. Previous experience in mammalian cell culture, immunofluorescence, microscopy or quantitative image analysis would be appreciated but is not mandatory. The student should be rigorous, organized, comfortable with quantitative analysis, and willing to work at the interface between molecular mechanisms and disease-oriented research.

**Supervision and Environment:**

The student will be supervised by Dr Ambra Giglia-Mari within the INMG-PGNM environment in Lyon. The host team has strong expertise in DNA repair, transcription recovery, nucleolar dynamics and advanced microscopy. The project will benefit from access to the imaging and cellular biology facilities available at the Rockefeller/INMG site, including confocal and super-resolution microscopy, as well as interactions with researchers working on neuromuscular disease, SMA models and stress-response mechanisms. The internship will provide training in experimental design, quantitative microscopy, data interpretation and scientific communication.