PhD position (3 years ANR-funded) in cellular biochemistry in the field of proteostasis, phase separation, and protein modifications.

Integrative analysis of the impact of lysine acetylation on nuclear proteostasis and biocondensates.

Keywords: Protein quality control, phase separation, protein modification, protein aggregates, neurodegenerative disorders

Team: Protein Maturation, Cell fate and Therapeutics; Institute for Integrative Biology of the Cell (I2BC); CNRS UMR9198, Bâtiment 21; 1 avenue de la Terrasse; F-91198 Gif-sur-Yvette cedex, France
https://www.i2bc.paris-saclay.fr/equipe-protein-maturation-cell-fate-therapeutics/

Background: Proteostasis (or protein homeostasis) is essential and its collapse is associated with numerous diseases. The generation of misfolded proteins and aggregates is the hallmark of many neurodegenerative disorders, cancers, and aging. Thus, cells have evolved a protein quality control network of components that act to maintain and restore proteostasis. The nucleus is a target of pathological aggregation but pathways that handle nuclear misfolded proteins are not well understood. It was recently discovered that an integral part of the cellular management of nuclear misfolded proteins is their reversible sequestration into the nucleolus upon proteotoxic stress. Therefore, the nucleolus prevents irreversible and toxic protein aggregation highlighting a novel chaperone-like function. The nucleolus is a paradigm example of liquid-like phase separated compartment that is formed through multivalent interactions of its constituents. The liquid-like nature of the organelle ensures its protein quality control function. How this is regulated is largely elusive as well as the factors required for nucleolar translocation of misfolded proteins.

Aim of the project: To discover new players involved in the regulation of the nucleolar protein quality control pathway. In particular, the project aims to decipher the impact of protein modifications, such as lysine acetylation, on nuclear protein quality control and biocondensate properties.

To this end, the student will take advantage of the excellent scientific environment of the I2BC and CNRS campus. This integrative study will make use of cellular biochemistry, quantitative proteomics, fixed and live-cell imaging, optogenetic tools, and cell-free systems. The student will have access (within the building) to the imaging facility and mass spectrometry facility that are running state-of-the-art instruments. The student will benefit from the recognized expertise of the team in in vitro analysis, microscopy, and mass spectrometry with privileged access to these equipment.

We invite highly motivated PhD candidates for an application who want to work in a stimulating interdisciplinary field that allows to obtain a multiplicity of expertise. Candidates should have a strong background in cell biology and biochemistry. Experience with cell culture, protein purification, mass spectrometry, and imaging is advantageous but not mandatory.
Applications including CV, cover letter, and names with contact details of 2 referees should be sent to **Dr. Frédéric Frottin** (frederic.frottin@i2bc.paris-saclay.fr).

Start date: Between March and October 2023

Selected references:

1. Frottin, F. *et al.* The nucleolus functions as a phase-separated protein quality control compartment. *Science (80-.).* **365**, 342–347 (2019).
2. Lafontaine, D. L. J., Riback, J. A., Bascetin, R. & Brangwynne, C. P. The nucleolus as a multiphase liquid condensate. *Nature Reviews Molecular Cell Biology* vol. 22 165–182 (2021).
3. Azkanaz, M. *et al.* Protein quality control in the nucleolus safeguards recovery of epigenetic regulators after heat shock. *Elife* **8**, (2019).
4. Frottin, F., Pérez-Berlanga, M., Hartl, F. U. & Hipp, M. S. Multiple pathways of toxicity induced by c9orf72 dipeptide repeat aggregates and g4c2 rna in a cellular model. *Elife* (2021) doi:10.7554/eLife.62718.