Master 2 research internship in Integrated Structural & Cell Biology in Grenoble

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Host laboratory:
Lab : BGE

Host group/team:
MetaNucleomics

Title of the M2 research internship:
Structural impact of histone lactylation on nucleosome stability: a comparative approach using proteomics and native mass spectrometry.

Project summary:
Histone **lactylation** is an emerging post-translational modification identified in key physiological processes such as spermatogenesis, and in pathological contexts including neurodegenerative diseases. Unlike acetylation (charge neutralization, +42 Da), lactylation introduces a lactyl group (+72 Da) bearing an additional hydroxyl moiety, potentially **modifying electrostatic histone-DNA interactions and hydrogen bonding networks within the nucleosome**. While lactylation occurrence profiles are beginning to be mapped by proteomics, its structural consequences on nucleosome assembly and stability remain unexplored. This structure-function dimension is nevertheless essential to understand how lactylation regulates DNA accessibility and chromatin compaction. The primary objective of this internship will be to **determine whether histone lysine hyper-lactylation alters nucleosome structure compared to acetylation**. The intern will produce modified (lactylated and acetylated controls) recombinant nucleosomes using chemical as well as *in-vitro* lactylation (resp. acetylation). Unmodified nucleosomes will be used as negative control. He/she will then characterize the resulting samples using **LC-MS/MS based proteomics** on digested histones to determine modification sites, as well as **Native-Mass Spectrometry** and **Thermal Shift Assay** of intact nucleosomes to assess their integrity and stability. Comparative analysis of modified and unmodified nucleosomes will shed light on the structural effects of lactylation and pave the way for future analyses of polynucleosomes by Charge Detection Mass Spectrometry to assess longer range effects of this modification.

Keywords:
Histone Lactylation; Nucleosome structure; Proteomics; Native MS

Relevant publications of the team:
Manessier J., Hijazi H., Brugière S., Courçon M., Masselon C., de la Iglesia A., Cocquet J., Pflieger D. Both L-lactyl and D-lactyl enantiomers modify histones in mouse testis. bioRxiv : **2025**.10. 09.681385

El Kennani, S.; Crespo, M.; Govin, J.; Pflieger, D. Proteomic Analysis of Histone Variants and Their PTMs: Strategies and Pitfalls. *Proteomes* **2018**, *6*, 29.

Boeri Erba E., Signor L., Petosa C. Exploring the structure and dynamics of macromolecular complexes by native mass spectrometry *J. Proteomics*, **2020**, 103799