Internship project Master 2
Year 2017-2018

Laboratory/Institute: Institut de Biologie Structurale (IBS)

Director: Winfried Weissenhorn

Team: Epigenetic regulators **Head of the team:** Jan Kadlec

Name and status of the scientist in charge of the project:
Jan KADLEC, team leader **HDR: yes** ☒ **no** ☐
Address: 71 avenue des Martyrs, CS 10090, 38044 Grenoble Cedex 9

Phone: 0457428776 **e-mail:** jan.kadlec@ibs.fr

Program the Master's degree in Biology:

☐ Neurosciences and Neurobiology ☐ Immunology, Microbiology, Infectious Diseases
☒ Integrative Structural Biology ☐ Physiology, Epigenetics, Development, Differentiation

Title of the project: Structural analysis of a chromatin modifying complex

Objectives (up to 3 lines):

To biochemically and biophysically characterize a sub-complex of the Non-Specific Lethal complex (NSL). This stable sub-complex consists of three subunits (KANSL3, MCRS1 and KANSL2).
To optimize the existing purification protocol of the complex and initiate its structural analysis.

Abstract (up to 10 lines):

The Non-Specific Lethal (NSL) complex is chromatin modifying assembly, that acetylates histone H4 resulting in chromatin decompaction. It is a global transcription regulator involved in embryonic stem cell pluripotency and DNA repair control. Its misregulation results in cancer, intellectual disability and developmental disorders. The molecular architecture of the NSL complex and the mechanism by which it regulates transcription remains unknown. The aim of our project is to structurally characterise the NSL complex. We have recently identified a stable sub-complex consisting of three subunits that is suitable for structural analysis. The Master student will work together with a postdoctoral fellow to biochemically, biophysically and structurally characterize this sub-complex. To understand the function of these three subunits, the hypotheses based upon this structural work will then be tested using transgenic animal models.

Methods (up to 3 lines):

Molecular cloning, protein production (bacteria, insect cells) and purification, biophysical analysis of protein complexes (ITC, MALLS, AUC), X-ray crystallography

Up to 3 relevant publications of the team:

1) Dias, J., Nguyen, N., Georgiev, P., Gaub, A., Brettschneider, J., Cusack, S., **Kadlec, J.**[*] and Akhtar, A.[*] Structural analysis of the KANSL1/WDR5/KANSL2 complex reveals that WDR5 is required for efficient assembly and chromatin targeting of the NSL complex. **Genes Dev.** 28: 929-942 (2014)

2) Wu, H., Mathioudakis, N., Diagouraga, B., Dong A., Dombrovski, L., Baudat. F., Cusack, S., de Massy, B.[*] and **Kadlec, J.**[*] Molecular basis for the regulation of the H3K4 methyltransferase activity of PRDM9. **Cell Rep.** 5:13-20 (2013)

3) Hallacli, E., Lipp, M., Georgiev, P., Spielman, C., Cusack, S., Akhtar, A.[*] and **Kadlec, J**.[*] MSL1-mediated dimerization of the dosage compensation complex is essential for male X-chromosome regulation in Drosophila. **Mol. Cell** 48:587-600 (2012)

Requested domains of expertise (up to 5 keywords):

chromatin, epigenetics, cancer, protein complex, X-ray crystallography