Funded PhD project in Integrated Structural & Cell Biology in Grenoble, France (2024-2027)

Title of the PhD project: Structure-function study of the nuclear cap-binding complex mediated RNA export

PhD supervisor: Jan Kadlec
Host laboratory: Institut de Biologie Structurale
Host team: Epigenetics and molecular pathways Group (EPIGEN), Kadlec team
Contact: jan.kadlec@ibs.fr

Project summary:
The research in RNA biology has recently resulted in quite unexpected ground-breaking technologies such as gene editing by CRISPR-Cas9 or the mRNA vaccines. These discoveries were largely possible thanks to the previous intense fundamental research on RNA biogenesis mechanisms. One of the outstanding questions in the RNA field is how is the fate of nascent transcripts determined. Indeed, eukaryotic transcription produces large amounts of RNAs, with some being useful, processed, and exported to the cytoplasm, while others are aberrant and eliminated in the nucleus. The nuclear cap-binding complex (CBC) plays a pivotal role in these processes. During early transcription, CBC forms the CBCA complex with ARS2, influencing the fate of transcripts. Various RNA factors, referred to as 'effectors,' compete for interactions with CBCA to direct transcripts towards processing, export, or degradation. However, the molecular details governing this competition remain unclear. We will use structural analysis combined with in vivo functional approaches to obtain detailed insights into this important CBC-mediated RNA sorting mechanism. We aim to provide better understanding of how the competition of the effector proteins with CBC-ARS2 complex eventually results in a specific RNA outcome. The proposed work that is based on solid preliminary results will thus enhance our understanding of this fundamental regulatory mechanism in eukaryotic gene expression.

Preferred skills: Biochemistry (bacterial and insect cell protein expression, recombinant protein purification), biophysical protein characterization (affinity, stoichiometry) and structural biology (cryo-electron microscopy)

Student role: The role of the student will be to reconstitute several complexes involved in RNA regulation. He/she will then characterize these complexes biochemically, biophysically and structurally (by cryo-EM). Using structure guided mutagenesis, the student will identify residues expected to be key for the function of these regulators. The importance of these critical residues in RNA biogenesis mechanisms will by studied in vivo together with collaborating cell biology laboratories.

Keywords: RNA biogenesis, RNA export, protein complexes, protein structure, cryo-EM

Relevant publications of the team:

1. Dubiez, E., Pellegrini, E., Finderup Brask M., Garland, W., Foucher, A.-E., Huard, K., Jensen, T.H, Cusack, S.* and **Kadlec, J.*** Structural basis for competitive binding of productive and degradative co-transcriptional effectors to the nuclear cap-binding complex. Cell Rep 43:113639 (2024)
2. Laroussi, H., Juarez-Martinez, A.B., Le Roy, A., Boeri Erba, E., Gabel, F., de Massy, B. and **Kadlec, J.** Characterization of the REC114-MEI4-IHO1 complex regulating meiotic DNA double-strand break formation. EMBO J. 42: e113866 (2023)
3. Foucher, A.-E., Touat-Todeschini, L., Juarez-Martinez, A.B., Rakitch, A., Laroussi, H., Karczewski, C., Acajjaoui, S., Soler-López, M., Cusack, S., Mackereth, C.D.*, Verdel, A.* and **Kadlec, J.*** Structural analysis of Red1 as a conserved scaffold of the RNA-targeting MTREC/PAXT complex. Nat. Commun. 13, 4969 (2022).
4. Nore, A., Juarez-Martinez, A.B., Clément, J., Brun, C., Diagouraga, B., Laroussi, H., Grey, C., Bourbon, H.M., **Kadlec, J.***, Robert, T*. and de Massy, B.* TOPOVIBL-REC114 interaction regulates meiotic DNA double-strand breaks. Nat. Commun. 13:7048 (2022)
5. Diagouraga, B., Clément, J.A.J., Duret, L., **Kadlec, J.**, de Massy, B. and Baudat, F. PRDM9 Methyltransferase Activity Is Essential for Meiotic DNA Double-Strand Break Formation at Its Binding Sites. Mol. Cell, 69:853-865 (2018)