



PhD program 2021 call for proposals: LabEx co-direction fellowships

Molecular basis of adenosine-to-inosine modification and its dysregulation in intellectual disorders

Research Unit 1

Name : IGBMC

Director of the unit: Frédéric Dardel

Code: UMR 7104

Address: 1 rue Laurent Fries, B.P. 10142, 67404 Illkirch Cedex, France

Research Unit 2

Name : IBMP

Director of the unit: Laurence Drouard

Code: UPR 2357

Address: 12 Rue du Général Zimmer, 67084 Strasbourg, France

Research teams and team leaders

Team 1: Molecular basis of chromatin and transcription regulation

Team leader 1: Christophe Romier

Email: romier@igbmc.fr

Phone number: +33 3 69 48 52 94

Team 1 members: Pierre Antony, Marie-Laure Durand, Pauline Landwerlin, Elizabeth Ramos Morales, Christophe Romier, Edouard Troesch, Marina Vitoria Gomes

3 relevant publications:

- Marek, M. et al. (2018) Characterization of histone deacetylase 8 (HDAC8) selective inhibition reveals specific active site structural and functional determinants. J. Med. Chem., 61, 10000-10016.



- Latrick, C.M. et al. (2016) Molecular basis and specificity of H2A.Z–H2B recognition and deposition by the histone chaperone YL1. *Nat. Struct. Mol. Biol.*, 23, 309-316.
- Obri, A. et al. (2014) ANP32E is a histone chaperone that removes H2A.Z from chromatin. *Nature*, 505, 648-653.

Number of PhDs in progress: Elizabeth Ramos Morales (start 2017), Marina Vitoria Gomes (start 2017), Pauline Landwerlin (start 2018)

Team 2: Metabolism and trafficking of RNA within the plant cell

Team leader 2: Laurence Drouard and Anne-Marie Duchêne

Email: laurence.drouard@ibmp-cnrs.unistra.fr; Anne-marie.duchêne@unistra.fr

Phone number: +33 3 67 15 53 98 / +33 3 67 15 53 69

Team 2 members: Marjory Cherry, Laurence Drouard, Anne-Marie Duchêne, Mickaele Hemono, Herrade Meichel, Patryk Ngondo, Thalia Salinas-Giegé, Elodie Ubrig

3 relevant publications:

- Hummel, A. et al. (2020) Epigenetic silencing of clustered tDNAs in Arabidopsis. *Nucleic Acids Res*, 48, 10297-10312.
- Lalande S, et al. (2020) Arabidopsis tRNA-derived fragments as potential modulators of translation. *RNA Biol*, 1-12
- Megel C, et al. (2019). Plant RNases T2, but not Dicer-like proteins are major players of tRNA-derived fragments biogenesis. *Nucleic Acids Res*, 47:941-952.

Number of PhDs in progress: Mickaele Hemono (start 2017), Marjorie Cherry (start 2018), Herrade Meichel (start 2019)

Phd supervisors

PhD director: Christophe Romier

Email: romier@igbmc.fr

Phone number: +33 3 69 48 52 94

Website: www.igbmc.fr/research/department/3/team/123/

PhD co-director: Laurence Drouard

Email: laurence.drouard@ibmp-cnrs.unistra.fr

Phone number: +33 3 67 15 53 98

Website: www.ibmp-cnrs.fr/teams/metabolism-and-trafficking-of-rna-within-the-plant-cell



Phd subject

Title: Molecular basis of adenosine-to-inosine modification and its dysregulation in intellectual disorders

Description:

Posttranscriptional RNA modifications expand the functions of RNAs and are often linked with the etiology of human diseases. The adenosine to inosine modification (A-to-I) plays crucial roles in RNAs. In tRNAs, wobble A-to-I is catalyzed by the essential ADAT complex that, when mutated, causes wobble inosine decrease and leads to human neurodevelopmental disorders, including intellectual disability, microcephaly, strabismus and epilepsy. The supervising teams have revealed how the mammalian ADAT complex assembles and can perform its deamination activity (manuscript in revision). However, the molecular and functional bases for ADAT dysregulation in disease remain elusive. The proposed project will make use of a biology integrated strategy to investigate tRNA recognition by ADAT and how disease mutations perturb ADAT mode of action. Notably, the project will combine biochemical, biophysical, structural and in cellulo analyzes to decipher how (i) ADAT recognizes its different cognate tRNAs, (ii) ADAT performs its catalytic mechanism, and (iii) how the wobble inosine effects on tRNA stability and function. The candidate will further collaborate with the team of Juliette Godin at IGBMC to study the consequences of the wobble inosine decrease on brain development and intellectual disorders.

Key words: RNA modification, inosine, ADAT complex, tRNA binding, brain development, intellectual disorders