PhD program 2020 call for proposals: LabEx co-direction fellowships

Exploring the functional and structural diversity of NYN domain ribonucleases

☐ **LabEx MitoCross**

☐ **Research Unit 1**

Name : Institut de Biologie Moléculaire des Plantes

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☐ **LabEx NetRNA**

☐ **Research Unit 2**

Name : Architecture et Réactivité de l'ARN (IBMC)

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☐ **Research teams and team leaders**

Team 1: Functions of PPR proteins

Team leader 1: Philippe Giegé

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Phone number: 0367155363

Team members 1: Géraldine Bonnard, Anthony Gobert, Mathilde Arrivé, Mathieu Bruggeman, Nicolas Corre, Pierre Quan.

3 relevant publications:

-Waltz, F., Nguyen, T., Arrivé, M., Bochler, A., Chicher, J., Hammann, P., Kuhn, L., Quadrado, M., Mireau, H., Hashem, Y. and **Giegé, P.** (2019) Small is big in Arabidopsis mitochondrial ribosome. ***Nature plants*** 5, 106-117.

-Pinker, F, Schelcher C, Fernandez-Millan, P. Gobert, A., Birck, C, Thureau, A., Roblin, P., ***Giegé, P.** and ***Sauter C.** (2017) Biophysical analysis of Arabidopsis protein-only RNase P alone

and in complex with tRNA provides a refined model of tRNA binding. (*co-corresponding authors) ***J. Biol. Chem.*** 292, 13904-13913. (cover)
-Gobert, A., Pinker, F. Fuchsbauer, O. Gutmann, B., Boutin, R., Roblin, P., **Sauter, C.** and **Giegé, P.** (2013) Structural insights into protein-only RNase P complexed with tRNA. ***Nature comm.*** 4, 1353.

Number of PhDs in progress: (starting date)

Mathieu Bruggeman (October 1st 2017)

Nicolas Corre (December 1st 2018)

Team 2: Biology of tRNA and pathogenicity

Team leader 2: Magali Frugier

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Team members 2: Claude Sauter, Bernard Lorber, Anne Théobald-Dietrich, Joëlle Rudinger-Thirion, Philippe Bénas, José Jaramillo, Caroline Paulus, Kévin Rollet

3 relevant publications:

-Small but large enough: structural properties of armless mitochondrial tRNAs from the nematode *Romanomermis culicivorax*. Jühling T., Duchardt-Ferner E., Bonin S., Wöhnert J., Pütz J., Florentz C., Betat H., **Sauter C.**, Mörl M. ***Nucleic Acids Res.*** (2018), 46: 9170-9180.
-Pinker, F, Schelcher C, Fernandez-Millan, P. Gobert, A., Birck, C, Thureau, A., Roblin, P., ***Giegé, P.** and ***Sauter C.** (2017) Biophysical analysis of Arabidopsis protein-only RNase P alone and in complex with tRNA provides a refined model of tRNA binding. (*co-corresponding authors) ***J. Biol. Chem.*** 292, 13904-13913. (cover)
-Neurodegenerative disease-associated mutants of a human mitochondrial aminoacyl-tRNA synthetase present individual molecular signatures. **Sauter C.***, Lorber B., Gaudry A., Karim L., Schwenzer H., Wien F., Roblin P., Florentz C., Sissler M.* ***Scientific Reports*** (2015), 5: 17332.

Number of PhDs in progress:

Kévin Rollet (October 1st 2018) co-tutelle: Claude Sauter, Mario Mörl (Uni Lepzig)

José Jaramillo (October 1st 2016) direction: Magali Frugier

PhD supervisors

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☐ PhD subject

Title: **Exploring the functional and structural diversity of NYN domain ribonucleases**

Description: about 600 words (background, objectives, workplan, expected results)

Background: RNA is a transient support of information, it is part of the translational machinery, has regulatory and maturation functions and can catalyze enzymatic reactions. For their biogenesis and the control of their turnover, RNA molecules are processed by a variety of essential ribonucleases in the different compartments of the cell. Among them, a **novel family of nucleases with NYN domains** (which are PIN-like domains) was discovered by bioinformatics analyses. The eukaryotic Nedd4-binding protein 1 and the bacterial YacP nucleases typify the NYN domain. While NYN proteins are found in all domains of life, they have undergone a substantial expansion in modern plants as compared to animals.

The **first subgroup called "PRORP"** (PPR-NYN) was investigated in depth in Teams 1 and 2 at the functional and structural levels. This subgroup contains enzymes combining a NYN catalytic domain with a "PPR" RNA binding domain. PRORP was first characterized as a member of the RNase P complex in human mitochondria (RNase P activity removes the 5' leader of tRNA precursor) and PRORP enzymes were later found to be responsible for RNase P activities in plant nucleus, mitochondria and plastids.

The **second subgroup called "YacP"** comprises orthologs of BsRAE1, a novel nuclease characterized in bacteria but of unknown function in eukaryotes.

The **last subgroup, called "NYN.1"**, includes numerous eukaryotic nucleases, such as "MNU2" a mitochondrial nuclease found to interact with PRORP. This subgroup is particularly expanded in land plants.

These eukaryotes, in particular the model organism Arabidopsis, are therefore the ideal system to get insights into the functional diversity of these enzymes and to comprehend the neo-functionalization of this family of proteins in eukaryotes.

Objective and workplan: Based on strong preliminary results, the objective of the PhD project is to explore the diversity of functions and mode of action of selected NYN domain enzymes, which can be associated with various additional domains that bind RNA (PPR, OST-HTH, Zinc finger) or bind proteins (eLotus, WW domains). NYN domain proteins appear to be at the center of an intricate network of cellular partnerships and pivotal gene expression functions and regulations.

Complementary approaches including genetics, biochemistry and biophysics will reveal the specificities of the respective NYN domain proteins. A first task will be to characterize the complex formed by PRORP and tRNA at the atomic level by X-ray crystallography. Then, the diversity of PRORP enzymes among eukaryotes will be explored. PRORP proteins have been studied in plants, mammals and Trypanosomes, but not yet in important groups of eukaryotes such as apicomplexa, one major interest of Team 2. For example, PRORP is found in the malaria parasite Plasmodium and this part of the project

might serve in the longer term to design novel antimalarial drugs. Other representative NYN proteins of the second and third groups will also be characterized, in particular, Arabidopsis YacP and MNU2.

Expected results (and candidate's profile):

The combination of biochemistry, molecular and structural biology will bring insights into the architectural and functional diversity of this NYN family, as well as on variety, nature and specificity of substrates.

Altogether, functional and structural specificities identified on NYN enzymes during the project will be useful for **applications ranging from human health to agronomy**.

This multidisciplinary project is meant for a motivated master student, eager to learn new technics (and hard working), with a strong theoretical background, particularly in one or more of these topics: RNA binding proteins, structural biology, deep sequencing and RNA seq data analysis. In the 3-year PhD period, the candidate will have access to a large panel of genetic, molecular, biochemical and biophysical methods. Beyond the technical training, he/she will be extensively involved in experimental design and result analysis (and will acquire writing and presentation skills). This research project will provide a stimulating multidisciplinary and international environment to develop one's creativity and become an autonomous scientist.