Laboratoire de Biologie Structurale de la Cellule (BIOC)
UMR 7654 - CNRS - Ecole Polytechnique
F-91128 Palaiseau Cedex

PhD research Project

Understanding the Role of a Human tRNA-Modifying Enzyme in the Cellular Response to Stress

Project Summary (English):

Most RNAs (tRNAs, mRNAs, and rRNAs) involved in protein synthesis are decorated by diverse chemical modifications, which contribute to an optimal mRNA translation process. Several RNA modification enzymes play critical roles in the cell cycle, and their defects are involved in human diseases. tRNAs are by far the most heavily modified RNAs. While the RNA modifications occurring in the anticodon stem loop are known to be important for correct mRNA decoding, the function of the modifications present in the tRNA body is far less understood. In this project, we will investigate the role of a human RNA modification enzyme targeting a specific position within the tRNA body. Preliminary data indicate that this enzyme is over-expressed under exposure of human cells to specific stress.

The goal of this project is to decipher the molecular mechanisms and cellular pathways involved in the up-regulation of this tRNA modification enzyme upon exposure of human cells to stress, as well as the importance of this enzyme for cell adaptation or survival under stress.

Complementary methodological approaches (molecular/cellular biology, protein/RNA biochemistry, RNA sequencing, quantitative proteomics, etc.) will be used. This ambitious project will unravel the mechanisms governed by an evolutionary conserved modification localized in a region of tRNAs, which has long been considered to have no major function beyond tRNA folding. This project will foster our knowledge of its role in mRNA translation and will likely uncover roles in the cellular stress response. Finally, it will enhance our knowledge of the role of RNA post-transcriptional modifications as a new layer of regulation of eukaryotic gene expression.

Keywords : Epitranscriptomics, cell biology, RNA modification enzymes, cellular stress response

Host laboratory:
Laboratoire de Biologie Structurale de la Cellule (BIOC); UMR7654; CNRS
Ecole polytechnique, Institut Polytechnique de Paris
91128 Palaiseau CEDEX
FRANCE
Host team: “RNA & Protein modifications” (https://bioc.ip-paris.fr/en/research/rna-and-protein-modifications)
Team leader / PhD supervisor: Dr. Marc GRAILLE (DR1 CNRS)

To apply : https://adum.fr/as/ed/voirproposition.pl?site=adumR&matricule_prop=70661
Application Deadline: 04/04/2026

Thesis Start Date: 01/10/2026

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Résumé du projet (Français):

Les ARN (ARNt, ARNm et ARNr) impliqués dans la synthèse des protéines sont modifiés par des groupements chimiques qui contribuent à une traduction optimale des ARNm. Plusieurs enzymes de modification des ARN jouent un rôle essentiel dans le cycle cellulaire et leurs anomalies sont associées à certaines maladies. Les ARNt sont largement modifiés. Si les modifications localisées dans la boucle anticodon des ARNt sont cruciales pour le décodage correct de l'ARNm, la fonction des modifications présentes dans le corps de l'ARNt est beaucoup moins bien comprise. Lors de ce projet, nous étudierons le rôle d'une enzyme de modification de l'ARN humain ciblant une position spécifique dans le corps de l'ARNt. Les données préliminaires indiquent que cette enzyme est sur-exprimée lorsque les cellules humaines sont exposées à un stress spécifique.
L'objectif de ce projet est donc de déchiffrer les mécanismes moléculaires et les voies cellulaires impliqués dans la sur-expression de cette enzyme de modification de l'ARNt lors de l'exposition des cellules humaines à un stress, ainsi que l'importance de cette enzyme pour l'adaptation ou la survie des cellules au stress.

Des approches méthodologiques complémentaires (biologie moléculaire/cellulaire, biochimie des protéines/ARN, séquençage des ARN à haut débit…) seront utilisées. Ce projet ambitieux permettra d'identifier les mécanismes régis par une modification localisée dans une région des ARNt, qui a longtemps été considérée comme peu importante. Ce projet permettra d'approfondir nos connaissances sur son rôle dans la traduction des ARNm et devrait révéler ses rôles dans la réponse cellulaire au stress.

Mots clés : Epitranscriptomique, biologie cellulaire, enzymes de modification des ARN, réponse cellulaire au stress

Laboratoire d'accueil :
Laboratoire de Biologie Structurale de la Cellule (BIOC); UMR7654; CNRS
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Equipe d'accueil: "RNA & Protein modifications" (https://bioc.ip-paris.fr/en/research/rna-and-protein-modifications)
Chef d'équipe / Encadrant de thèse: Dr. Marc GRAILLE (DR1 CNRS)

Pour candidater : https://adum.fr/as/ed/voirproposition.pl?site=adumR&matricule_prop=70661
Date limite de candidature: 04/04/2026

Début de thèse: 01/10/2026

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More details on the project and supervision

Theme:
This research project deals with the highly competitive and dynamic field of epitranscriptomics. More and more studies reveal that these RNA modifications play critical roles in several cellular processes, as demonstrated by their involvement in human pathologies such as neurodevelopmental disorders and cancers.

Field:
This project focuses on deciphering the cellular mechanisms involved in the cell response to adapt to stress exposures (drugs, pollutants…).

Objectives:
RNAs (tRNAs, mRNAs, rRNAs) undergo post-transcriptional chemical modifications that are essential for the efficiency and fidelity of mRNA translation. These modifications, catalyzed by specialized enzymes, play a key role in regulating the cell cycle. Their dysfunction is associated with various diseases. Among these RNAs, tRNAs are particularly rich in chemical modifications: while the functions of modifications located in the anticodon loop are well characterized for their role in the accurate decoding of mRNA, those of modifications present in the body of the tRNA remain largely unknown.
Our project focuses on a specific human enzyme responsible for modifying a specific position in the body of tRNA. Preliminary data reveal that this enzyme is significantly over-expressed in response to a particular cellular stress.
The objectives of this project are to:

- Decipher the molecular mechanisms and signaling pathways involved in this stress-induced over-expression.
- Use high-throughput RNA sequencing/ribosome profiling to analyze the cellular response at the transcriptional and translational levels.
- Evaluate the functional importance of this enzyme for cell adaptation and survival under stress conditions.

Context:
RNA modification enzymes are not only important for global protein synthesis but are now emerging as crucial in the cellular response to stress exposure. Consequently, this project will use complementary methodological approaches to unravel the mechanisms governed by an evolutionary conserved small chemical modification localized in a region of tRNAs, which has long been assumed to have no major function beyond a structural role for tRNA. This project will foster our knowledge of its role in mRNA translation and will likely uncover roles in the cellular stress response. Finally, it will enhance our knowledge of the emerging field of epitranscriptomics, which contributes a new layer of regulation of gene expression in eukaryotic organisms.

Method:
To achieve these objectives, we will combine complementary techniques:

- Molecular and cellular biology (genetic manipulation, phenotypic analyses).
- RNA sequencing and quantitative proteomics to analyze the cell response at the transcription and translation levels, respectively.
- Functional tests (cell viability, stress response, identification of cellular signaling pathways…).

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Expected Results:
This project aims to elucidate the role of a localized modification in a region of tRNAs, traditionally considered secondary, but whose importance in the cellular response to stress may be underestimated. The results obtained could open new perspectives for understanding how cells modulate their translational machinery in response to environmental stimuli, with potential implications in fundamental biology and medicine.

Bibliographic references from the team and related to the project:
•Wang, C.; Ulryck, N.; Herzel, L.; Pythoud, N.; Kleiber, N.; Guérineau, V.; Jactel, V.; Moritz, C.; Bohnsack, M.; Carapito, C.; Touboul, D.; Bohnsack, K.E.; Graille, M. (2023), *N2-methylguanosine modifications on human tRNAs and snRNA U6 are important for cell proliferation, protein translation and pre-mRNA splicing*. Nucleic Acids Res, 51(14), 7496-7519.
•Graille M. (2022), *Division of labor in epitranscriptomics: What have we learnt from the structures of eukaryotic and viral multimeric RNA methyltransferases?* WIREs RNA. 13 (1), e1673.
•Wang C.; van Tran, N.; Jactel V.; Guerineau V.; Graille M. (2020), *Structural and functional insights into Archaeoglobus fulgidus m2G10 tRNA methyltransferase Trm11 and its Trm112 activator.* Nucleic Acids Res, 48(19); 11068-11082.
•van Tran N.; Ernst, F.G.M.; Hawley, B.R.; Zorbas, C.; Ulryck, N.; Hackert, P.; Bohnsack, K.E.; Bohnsack M.T.; Jaffrey, S.R.; Graille M.; Lafontaine D.L.J. (2019), *The human 18S rRNA m6A methyltransferase METTL5 is stabilized by TRMT112*. Nucleic Acids Res, 47(15); 7719-7733.
•Leismann J.; Spagnuolo M.; Pradhan M.; Wacheul L.; Vu M.A.; Musheev M.; Mier P.; Andrade-Navarro M.A.; Graille M.; Niehrs C.; Lafontaine D.L.J.; Roignant J.Y. (2020), *The 18S ribosomal RNA m6A methyltransferase Mettl5 is required for normal walking behavior in Drosophila*. Embo reports, 21(7); e49443.

Supervision, Training, and Research Progress:
The PhD student will work under the supervision of Dr. Marc Graille in the Laboratory of Structural Biology of the Cell (BIOC) at École Polytechnique (Institut Polytechnique de Paris, Palaiseau, France). The student will discuss results face-to-face with Dr. Graille weekly but can ask him questions at any time, depending on his availability.
In the Graille lab, bi-weekly lab meetings in English are held, allowing each person to present their latest results to all team members and discuss recently published papers relevant to their research project.
The student will benefit from local infrastructure (biochemistry lab, cell culture room…) and will work closely with a CNRS technician/engineer to learn new approaches when necessary.

Material, Scientific, and Financial Conditions:
The host lab has in-house access to all the equipment required to perform this research project.
The student will be trained in the safety procedures specific to the lab.

International Collaboration:
Two collaborations are ongoing with biology labs in Belgium and Germany.

Planned Collaborations:
Established collaborations with two French groups (one in Gif/Yvette and one in Strasbourg) specializing in ribosome profiling/RNAseq analyses and quantitative proteomics, respectively.

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Research Valorization Objectives:
The results will be published in high-impact international journals and presented either orally or as a poster at international meetings by the student.

PhD Funding
Type of PhD Funding: Competition for a doctoral contract
Funding Start Date: 01/10/2026
Funding End Date: 30/09/2029

Source of Funding: Institut Polytechnique de Paris Doctoral Scholarship
Employer: École Polytechnique
Funding Status: Requested

Sought profile and Required Skills:
The applicant should hold a master's degree (or equivalent) in cell biology, molecular biology, biochemistry, or biotechnology.
The candidate should be motivated, well-organized, willing to learn.
They should have completed a long internship (at least 6 months) in a laboratory.
They should master at least one of the following techniques: human cell culture, microbiology, molecular biology.

Required French Level: None
Required English Level: B2/C1
Online Application: Yes https://adum.fr/as/ed/voirproposition.pl?site=adumR&matricule_prop=70661