

Master's degree in Biology – Chemistry-Biology Department

## Master 2 internship project Year 2023-2024

Laboratory/Institute: Institute for Advanced Biosciences Address: Site Santé, allée des Alpes 38700 La Tronche Gre	Director: Pierre Hainaut noble
<b>Co-supervision with:</b> <b>Guillermo Orsi</b> , CRCN INSERM <b>Team:</b> Epigenetics of Regeneration and Cancer <b>Phone</b> : 06 85 11 72 45	HDR: yes ⊠ no □ Head of the team: Guillermo Orsi e-mail: guillermo.orsi@univ-grenoble-alpes.fr
Chantal Thibert, CRCN CNRSHDR: yes ∑ no □Group: Metabolic regulations by LKB1 & p53 in development and diseasesHead of the team: P. HainautPhone: 07 70 5 28 59e-mail: chantal.thibert@univ-grenoble-alpes.fr	
Program of the Master's degree in Biology:	
<ul> <li>Microbiology, Infectious Diseases and Immunology</li> <li>Structural Biology of Pathogens</li> <li>Physiology, Epigenetics, Differentiation, Cancer</li> <li>Neurosciences and Neurobiology</li> </ul>	
Title of the project: LKB1 signaling to connect metabolism and epigenetics	
during cell fate choices	

<u>Objectives:</u> The Master2 project aims at unravelling the molecular mechanisms by which the metabolic regulator and master kinase LKB1 bridges together metabolism, epigenomics and cell fate during neural crest stem cell (NCCs) formation.

<u>Abstract:</u> Cell fate choices, such as self-renewal or differentiation, rely on precisely defined gene expression programs, tightly controlled by chromatin remodeling complexes. Metabolic changes have recently been uncovered to drive chromatin dynamics and control gene expressions governing cell differentiation. However, the connection between signaling pathways and chromatinmodifying metabolites is still underexplored especially during stem cell fate choices.

The project relies on unique genetically engineered mouse models generated by C. Thibert's team to spatiotemporally inactivate *Lkb1* in NCCs, as well as a NCC line which can be cultivated as progenitors or differentiated into several neural crest derivatives. G. Orsi's lab is expert in chromatin dynamics using cutting-edge approaches in high-resolution epigenomic profiling (Cut&Run technology) and microscopy.

Using these models, the master student will characterize epigenomic and transcriptional profiles depending on LKB1 activity in progenitors or differentiated NCCs both *in vitro* and *ex vivo*.

This master project is part of a collaborative project between the two teams of IAB and the team of L. Le Cam (IRCM, Montpellier) with ongoing funding applications.



Fig1. Connecting metabolism to chromatin through signaling during neural crest cell fate

<u>Methods:</u> Handling of a neural crest stem cell line (cultures of progenitors, neurons and glial cells); NCCs sorting by FACS from embryos; Chromatin dynamics by Cut&Run-qPCR and Cut&Run-seq; Gene expression analysis by RT-qPCR and RNA-seq; Western blot; Immunofluorescence and confocal microscopy; Bioinformatic analyses of sequencing data.



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## Relevant publications of the teams:

\* Torres-Campana D, Horard B, Denaud S, Benoit G, Loppin B, Orsi GA. Three classes of epigenomic regulators converge to hyperactivate the essential maternal gene deadhead within a heterochromatin mini-domain. *PLoS Genet*. 2022;18(1):e1009615. \* Orsi GA, Kasinathan S, Hughes KT, Saminadin-Peter S, Henikoff S, Ahmad K. High-resolution mapping defines the cooperative architecture of Polycomb response elements. *Genome Res*. 2014;24(5):809-820.

\* Radu AG, Torch S, Fauvelle F, Pernet-Gallay K, Blervaque R, Lucas A, Delmas V, Schlattner U, Tricaud N, Lafenechère L, Hainaut P, Tricaud N, Pingault V, Bondurand N, Bardeesy N, Larue L, Thibert C and Billaud M. LKB1 specifies neural crest cell lineages through pyruvate-alanine cycling. *Science Advances* 2019, eaau5106.

\* Thibert C, Lucas A, Billaud M, Torch S, Mével-Aliset M, Allard J. Functions of LKB1 in neural crest development: the story unfolds. *Developmental Dynamics*. 2023 dvdy.581.

<u>Requested domains of expertise:</u> Chromatin dynamics, Cell signaling, Cell biology, Metabolism, Development.

The job offer is also available through the Euraxess website: https://euraxess.ec.europa.eu/jobs/110903