EPIGENETICS
CHRONIC DISEASES
CANCER

Institute for Advanced Biosciences

CENTRE DE RECHERCHE UGA - INSERM U 1209 - CNRS UMR 5309

PhD OFFER

Title: **Study of the molecular basis of "decision-making" in signaling downstream the SRC-family kinases through the coupling between optotgenetic control, proximity labelling and phosphoproteomics.**
Starting date: July 2023,
Funding: ANR grant

Scientific context:
The **main function of cell signaling is to integrate the complexity of the extracellular environment** (extracellular matrix, cell-cell-contact, physical parameters, soluble factors…) **to induce specific and diverse decision-making events,** generating adapted cellular responses.
The new challenge in cell signaling is to understand the high pleiotropy of a signaling relay that can both be activated by highly diverse receptors and generate very disctint cellular responses. This suppposes that each signaling relay can generate different and adapted decision-making events of signaling leading to adapted cellular answers. Even though the central role of pleiotropy is well acknowledged, **the molecular mechanisms of underlying decision-making events are still poorly understood**.
As a canonical example of pleiotrope signaling relay, we proposed to focus on the *Src Family Kinase* (*SFK*). This family of tyrosine kinases is composed of eight members; *Src*, *Fyn*, *Yes* which are ubiquitous, and *Hck*, *Lyn*, *Fgr*, *Blk* and *Lck* which are tissue specific. c-SRC, its prototypal member, is highly pleiotropic since implicated in multiple, even antagonistic, decision-making events related to migration and invasion. Genetic mouse models supported the idea that there is a high level of functional redundancy between the SFK members. To counteract this apparent redundancy, we will benefit from our **optogenetic probes to induce different SFK-dependent decision-making events** leading to distinct cellular responses **by light**. Indeed, we will determine the molecular consequences of the different decision-making events by identifying the specific **biochemical complexes** associated with each optoSFK and their specific **phosphorylation substrates**. Through **multidimensional analysis of biological networks**, we will then model how the formed biochemical complexes lead to different decision-making events through protein-protein interaction networks (ppin). This will allow us to investigate the **propagation of a controlled SFK signal into downstream signaling networks**.

Objectives and experimental approaches:
The goal of this PhD work will be to combine optogenetic activation of our optoSFKs with both proximity labelling approach (Apex, biOID) and phosphoproteomic.
Our lab is expert in optogenetic control of cell signaling and has developed numerous optogenetic probes to control each members of the SFK.
Proximity labelling approach (Apex, biOID) is a rapidly developing technique. It allows to identify directly in the living cell the proximate molecular environment of a protein of interest thanks to its labeling by biotinylation. The tagged proteins are then extracted and analyzed by mass spectrometry.

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We will couple our optoprobes with both proximity labeling analysis and also phosphoproteomic. Thus, we will be able to activate specifically a signaling event (downstream the activation of a specific optokinase) and then map both the molecular environment associated with the optoprobe and its transfer of information through identification of downstream phosphorylated proteins. The obtained data will be then analyzed through dedicated network pipe-line of interactomic networks developed jointly with Dr C. Brun from TAGC-Marseille. To our knowledge, such an experimental setup has never been published and will be a new way to redefine signaling pathways *without a priori.*

Keywords:
Signaling, SRC kinases, invasion, optogenetics, proximity labelling approach (Apex, biOID), proteomic and phosphoproteomic analyses, interactomic and network biology

Laboratories:
This PhD will be performed in IAB, Grenoble in the group led by Olivier DESTAING in DYSAD team. This work will lie in the context of a national collaboration with Dr C. Brun from TAGC-Marseille, Dr. D. Bourgeois from IBS-Grenoble and prof. Fourcade from Liphy-GRenoble, and will be open to international collaborations (USA and Canada). The student will benefit from our collaboration with the EDyP proteomic facility in CEA Grenoble and from the microscopy facility at IAB (MicroCell).

Requested knowledge and skills:
The project requires that the candidate has very good knowledge in biochemistry and cell biology, and network analysis. Some skills acquired through internships in either of these domains will be appreciated.The successful applicant must also have the willingness and enthusiasm to work independently while being integrate in a strong collective and able to communicate with the various scientists involved in this project whether they are biologists, engineers, or computer science peoples. The ideal candidate should be curious, and should enjoy solving problems and developing new tools from synthetic biology with personal creativity and innovation.

Publications from the lab:
-*Integrin-based adhesion compartmentalizes ALK3 of the BMPRII to control cell adhesion and migration.* Guevara-Garcia A, Fourel L, Bourrin-Reynard I, Sales A, Oddou C, Pezet M, Rossier O, Machillot P, Chaar L, Bouin AP, Giannone G, **Destaing O***, Picart C*, Albiges-Rizo C*. J Cell Biol. 2022 Dec 5;221(12):e202107110. * co-last-authors
-*Control of SRC molecular dynamics encodes distinct cytoskeletal responses by specifying its signaling pathway usage.* Kerjouan A, Boyault C, Oddou C, Hiriart-Bryant E, Pezet M, Balland M, Faurobert E, Bonnet I, Coute Y, Fourcade B, Albiges-Rizo C, **Destaing O**. J Cell Sci. 2021 Jan 25;134(2):jcs254599.
- *Cross-talk between the calcium channel TRPV4 and reactive oxygen species interlocks adhesive and degradative functions of invadosomes.* Vellino S, Oddou C, Rivier P, Boyault C, Hiriart-Bryant E, Kraut A, Martin R, Coute Y, Knölker HJ, Valverde AM, Albiges-Rizo C, **Destaing O**. J Cell Biol. 2021 Feb 1;220(2):e201910079.

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