Master Biologie Moléculaire et Cellulaire 'BMC',
Université de Paris - *UFR Sciences du Vivant*

Parcours : **Biologie et Développement Cellulaires 'BDC'**
http://www.master2bdc.fr/
Fiche de Projet de Stage M2, Année 2023-2024

Unité INSERM ou CNRS ou Université :	**Responsable du Stage :**
Inserm U1151/CNRS UMR 8253, Institute Necker Enfants Malades (INEM) **Intitulé Equipe :** Team17: Laboratory of Nutrient Sensing Mechanisms; www.panasyuklab.fr **ED d'appartenance :** BIOSPC (ED 562) **Responsable de l'Equipe :** Dr. Ganna PANASYUK	Dr. Ganna PANASYUK **Contacts** Adresse :156-160 Rue Vaugirard,Paris 75015, France Email : ganna.panasyuk@inserm.fr Tel : 0033 1 40 61 53 44

Titre du projet: Nuclear class 3 PI3K in transcriptional control of metabolism

Résumé du Projet de Stage

In the Panasyuk Lab we want to know: **How do cells sense the lack of nutrients in their environment?** This is fundamental to better understand how **cellular metabolic activities** are coordinated, how **gene transcription** is orchestrated, and how their defects are implicated in **human diseases** (www.panasyuklab.fr).

To address these questions, we focus on phosphatidylinositol 3-kinase (PI3K) signaling, that emerged in evolution as a central signaling hub for effective use of metabolic fuel. Class 3 PI3K is the only member of the PI3K family active in all eukaryotes to generate PI3P, a membrane-born messenger critical at multiple steps for vesicular trafficking. These include essential cellular processes such as lysosomal degradation by autophagy, endocytosis, and ER-Golgi sorting. We discovered that class 3 PI3K, the least studied in mammals, is essential for life and is indispensable to maintain whole-body metabolic homeostasis (**1,2**). We also demonstrated that class 3 PI3K controls mitochondrial biogenesis and lipid catabolism in fasting (**3,4**). In our most recent work, we made a surprising discovery that both subunits of class 3 PI3K interact with RNA Pol2, co-localize with active transcription sites and can co-activate the circadian clock transcription factor complex of Bmal1-Clock. We also found that class 3 PI3K in liver is essential for metabolic rhythmicity and it specifically controls rhythmic *de novo* purine synthesis (**5**). **Our unpublished findings** show that class 3 PI3K is recruited upon fasting to promoters of selective genes involved in specific metabolic pathways, suggesting its wider roles in transcription and rewiring of the metabolic activities in hepatocytes in response to fasting. Building on these and other preliminary findings within the framework of an on-going ERC Consolidator grant in our laboratory, **the successful M2 candidate will contribute to an exciting project aiming to explore the novel roles of class 3 PI3K in transcription in control of cellular metabolism. To build the foundation for the future PhD project**, the M2 work will be constructed to answer following **two questions,** employing cutting edge methodology in cell models that will be interrogated in physiology and under metabolic stress conditions relevant to human disease:

(1) What is the extent of the cistrome controlled by nuclear class 3 PI3K?

(2) How does nuclear class 3 PI3K signaling operate?

Environment: We are looking for an enthusiastic, highly motivated, ready-to-learn, and scientifically driven trainee with a strong interest in signal transduction mechanisms with ambition to learn cutting edge molecular approaches (NGS analyses, dCas14, metabolomics). Our international laboratory (www.panasyuklab.fr) belongs to the Institute Necker Enfants Malades which is located at the heart of the world-renowned Necker Hospital research campus in a central Paris. You will be trained in a highly dynamic and scientifically stimulating French/English working environment. You will benefit from weekly seminars (in English) and interactions with scientists coming from all over the world.

Publications de l'équipe relatives au projet de stage (max 5)

1. Nemazanyy I, et al., Class III PI3K controls hepatic insulin receptor function on whole body glucose homeostasis by a retrograde signalling mechanism. **Nat. Comm.** 2015; 6:8283

2. Nemazanyy I, et al., Defects of Vps15 in skeletal muscles lead to autophagic vacuolar myopathy and lysosomal disease. **EMBO Mol Med**. 2013; 5(6):870-90

3. Shibayama Y, et al. Class 3 phosphoinositide 3-kinase promotes hepatic glucocorticoid receptor stability and transcriptional activity. **Acta Physiol (Oxf)** 2022;e13793. doi: 10.1111/apha.13793.

4: Iershov A, et al. The class 3 PI3K coordinates autophagy and mitochondrial lipid catabolism by controlling nuclear receptor PPARα. **Nat Commun.** 2019, Apr 5;10(1):1566.

5. Alkhoury, C., Henneman, N.F., et al. Class 3 PI3K coactivates the circadian clock to promote rhythmic de novo purine synthesis. **Nat Cell Biol** 25, 975–988 (2023). https://doi.org/10.1038/s41556-023-01171-3