Sciences de la Vie et de la Santé
Master BMC, Universités Paris Cité

Parcours : **Biologie et Développement Cellulaires 'BDC'**
http://www.master2bdc.fr/
Fiche de Projet de Stage M2, Année 2024-2025

Unité INSERM ou CNRS ou Université : INSERM U1163 –Institut Imagine **Intitulé Equipe :** Laboratoires des Maladies rénales héréditaires : cils et ciliopathies. **ED d'appartenance :** BioSPC **Responsable de l'Equipe :** Sophie Saunier	**Responsable du Stage :** Alexandre Benmerah **Contacts** Adresse : 24 Bd Montparnasse, 75015 Paris Email : alexandre.benmerah@inserm.fr Tel :

Titre du projet: Characterization of new therapeutic approaches for Nephronophthisis, a renal ciliopathy

Résumé du Projet de Stage
Ciliopathies are highly heterogeneous **genetic diseases** caused by mutations in genes encoding proteins playing key functions at the **primary cilium**, a ubiquitous organelle controlling numerous signaling pathways during development and tissues homeostasis. **Nephronophthisis** (NPH) is one of the most frequent manifestations in ciliopathies and represents the morbidity factor for the patients for which the kidney graft is the only therapeutic issue. The lab was involved in the identification of more than half of the 22 NPHP genes (Stokman M, 2021). We recently developed high throughput screening strategies which led to the identification of molecules able to rescue ciliary phenotypes in model cell lines invalidated for NPHP1, the main NPH gene (50% of the cases). This **screen** allowed the identification of an interesting prostaglandin-related **molecule** which was able to **rescue ciliopathy-associated phenotype**s in vitro and in vivo. The goal of this project is to further characterize the efficiency of this molecule family in the context of other NPHP genes as well as to identify shared dysregulated signaling pathways in various NPHP conditions which could be targeted by a similar small molecule-based approach. This project will rely on the use of model murine kidney cell lines and patients-derived urinary renal epithelial cells (URECs) to characterize the mechanisms of action of the candidate molecules (ciliogenesis, polarity, extracellular matrix). We also aim to use in vivo models for NPH (zebrafish or mouse) and iPSC-derived **kidney organoïds** to identify shared dysregulated pathway in NPH (RNAseq) and to validate the use of this drug as a potential new therapeutic approach for NPH.

Publications de l'équipe, relatives au stage proposé : Former PhD students are underlined

- Reilly ML, Ain NU, Muurinen M, Tata A, …, Cormier-Daire V*, **Benmerah A***, Makitie O*. Biallelic KIF24 Variants Are Responsible for a Spectrum of Skeletal Disorders Ranging From Lethal Skeletal Ciliopathy to Severe Acromesomelic Dysplasia. J Bone Miner Res. 2022 Sep;37(9):1642-1652. *contributed equally. https://onlinelibrary.wiley.com/doi/10.1002/jbmr.4639
- Hugo Garcia*, Alice Serafin*, Flora Silbermann*, …, **Alexandre Benmerah°**, Marion Delous°, Luis Briseño-Roa°, Sophie Saunier°. Agonists of prostaglandin E2 receptors as potential first in class treatment for Nephronophthisis and related ciliopathies. PNAS 2022 May 3; 119(18): e2115960119. https://doi.org/10.1073/pnas.2115960119 . *contributed equally °contributed equally
- Stokman M, Saunier S and **Benmerah A**. Renal Ciliopathies: Sorting Out Therapeutic Approaches for Nephronophthisis. Front. Cell Dev. Biol., 13 May 2021 | https://doi.org/10.3389/fcell.2021.653138
- Reilly ML, Stokman MF, [...] **Benmerah A**. Loss-of-function mutations in KIF14 cause severe microcephaly and kidney development defects in humans and zebrafish. Hum Mol Genet, 28(5):778-795, 01 Mar 2019 https://doi.org/10.1093%2Fhmg%2Fddy381
- Macia MS…, Saunier S*, Hildebrandt F*, **Benmerah A***. Mutations in MAPKBP1 Cause Juvenile or Late-Onset Cilia-Independent Nephronophthisis. Am J Hum Genet. 2017 Feb 2;100(2):323-333. * equal contributions. https://doi.org/10.1016/j.ajhg.2016.12.011