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 2021-2022

Unité INSERM ou CNRS ou Université : Inserm U1163 – Institut Imagine **Intitulé Equipe :** Laboratory of Inherited Kidney Diseases **ED d'appartenance :** BioSPC **Responsable de l'Equipe :** Sophie SAUNIER	**Responsable du Stage :** Amandine VIAU **Contacts** Adresse : 24 Boulevard du Montparnasse 75015 Paris Email : amandine.viau@inserm.fr Tel : +33 1 42 75 43 41

Titre du projet : Molecular mechanisms involved in inflammation-driven renal damage in the context of renal ciliopathies : a particular look to Hippo pathway.

Résumé du Projet de Stage (en 300 mots maximum, mots clés en gras)

Ciliopathies are genetic diseases caused by mutations in genes encoding proteins localizing to primary cilia. In the kidney, the primary cilium projects into the tubule lumen acting as a sensor for chemical and mechanical cues delivered by urine flow. **Nephronophthisis** (NPH), the most common renal ciliopathy in children, is an autosomal recessive disorder characterized by interstitial renal fibrosis and formation of tubular cysts. 22 causative genes (*NPHP*) are mutated in NPH, most of them assemble in functional modules controlling cilia morphology and gating.

Recently, we established **renal inflammation** as a prominent feature of NPH and identified a specific **cytokine signature**. We further observed in distinct models of NPH, a precocious activation of the transcription co-activator YAP in renal tubular cells. **YAP** integrates mechanical and chemical cues to regulate cell fate. Surprisingly, we observed that reducing YAP gene dosage in tubular cells in a murine model of NPH led to a proportional increase in the expression of cilia regulated cytokines, immune cell recruitment and renal scarring. These data strongly support that cilia signaling and YAP jointly repress an inflammatory transcriptional program in tubular cells.

This project seeks to determine how cilia signaling intersects with YAP to regulate renal inflammation and to investigate the role of this inflammatory pathway in kidney damage using NPH models. To this aim, we will combine cutting edge technologies (ChIP seq) with robust *in vivo* (conditional allele inactivation) and *in vitro* (inducible knock-down of YAP and/or NPHP) approaches. Our goals are (1) to characterize the transcriptional program jointly regulated by Nphp and Yap, (2) to identify YAP transcriptional targets in the context of kidney damage and (3) to investigate the impact of YAP and/or NPHP inactivation on the major inflammatory signaling pathways.

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

1/ Quatredeniers M *et al*. The renal inflammatory network of nephronophthisis. ***bioRxiv***. **2021**. https://doi.org/10.1101/2021.01.07.425719.

2/ Viau A *et al*. Cilia-localized LKB1 regulates chemokine signaling, macrophage recruitment, and tissue homeostasis in the kidney. **EMBO J**. **2018**. PMID: 29925518.

3/ Grampa V *et al*. Novel NEK8 Mutations Cause Severe Syndromic Renal Cystic Dysplasia through YAP Dysregulation. **Plos Genet**. **2016**. doi: 10.1371/journal.pgen.1005894.