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

Parcours : **Biologie et Développement Cellulaires 'BDC'**
https://master2bdc.ijm.fr/
Fiche de Projet de Stage de M2, 2026-2027

Unité INSERM ou CNRS ou Université : **Intitulé Equipe : Epigenetics and development** **ED d'appartenance : ED562** **Responsable de l'Equipe : Marco Pontoglio**	**Responsable du Stage : Marco Pontoglio** **Contacts** Adresse : Institut Necker Enfants Malades Faculté Médecine Necker 160 Rue Vaugirard - 75015 Paris Email : marco.pontoglio@inserm.fr Tel : 01 40 61 53 75

Titre du projet : Breaking the loop: characterising the post-translational silencing of HNF1B in chronic kidney disease

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

Chronic kidney disease (CKD) leads to progressive, largely irreversible renal tubular damage regardless of the initial insult. The transcription factor **HNF1B** is a master regulator of renal tubular epithelial identity, establishing and maintaining the transcriptional program that defines differentiated, functional tubule cells. The loss of HNF1B leads to CKD, and, conversely, the onset of CKD drives a drastic loss of HNF1B transcriptional activity. This bidirectional relationship forms a vicious circle: injury signals repress HNF1B, the resulting loss of HNF1B activity further destabilises tubular identity, and this destabilisation in turn aggravates the injury, locking tubular cells into a **self-sustaining pathological loop** that perpetuates CKD independently of the original insult. Strikingly, this repression appears to be post-transcriptional: HNF1B mRNA and protein levels remain largely stable early after injury, while **its transcriptional activity rapidly collapses**, indicating that stress signals silence HNF1B by altering the protein activity itself rather than by shutting down its gene expression.
The project will combine in vitro and in vivo approaches to study how CKD-triggering factors induce this repression. We aim to capture the earliest molecular events involved in disease onset and to identify the modifications and modifying enzymes responsible for the functional silencing of HNF1B activity. In particular, we hypothesise that injury-associated kinases and stress pathways (e.g. **TGF-beta, inflammatory signalling**) drive specific phosphorylation, ubiquitination, SUMOylation or acetylation events on HNF1B that impair its DNA binding, dimerisation, or interaction with co-activators. These modifications will be characterised, and we will identify the molecular actors responsible for inducing them and for sustaining this functional silencing. The project should lead to an improved understanding of the molecular mechanisms of CKD and may open novel therapeutic perspectives for the treatment of the disease.

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

Verdeguer F, et al. A mitotic transcriptional switch in polycystic kidney disease. ***Nat M***ed 2010, 16: 106-110.

Lerner J, et al. Human mutations affect the epigenetic/bookmarking function of HNF1B. ***Nucleic Acids Res*** 2016 44:8097-111.

Fiorentino A, et al. Developmental Renal Glomerular Defects at the Origin of Glomerulocystic Disease. **Cell Rep 2020,** 33:108304.

Bagattin A, et al. HNF1β bookmarking involves Topoisomerase 1 activation and DNA topology relaxation in mitotic chromatin. ***Cell Rep*** 2024 43(10):114805

Isnard P, et al. HNF1B integrates signals in a feed-forward loop driving kidney disease progression. ***Science*** 2026, 392:6795.