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

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

Unité INSERM ou CNRS ou Université : Institut Cochin, INSERM U1016, CNRS UMR 8104, Université Paris Cité **Intitulé Equipe :** Signalisation du glucose et de l'insuline, et glucotoxicité **ED d'appartenance :** ED 562 BioSpc **Responsable de l'Equipe :** Catherine Postic & Tarik Issad	**Responsable du Stage : Sandra Guilmeau** **Contacts** Adresse : Institut Cochin, Département Métabolisme & Endocrinologie, 24 rue du faubourg Saint Jacques, 75014 Paris Email : sandra.guilmeau@inserm.fr Tel : 06.61.59.73.78

Titre du projet: Identification of the molecular mechanisms underlying Paneth and intestinal stem cells defects upon loss of epithelial insulin action**.**

Résumé du Projet de Stage :

Gut leakiness is suggested to underlie the **chronic low-grade inflammation** that accompanies obesity and its complications. While the mechanistic basics of such gut dysfunction remain unclear, we recently showed that **insulin resistance** contributes to major epithelial defects of gut barrier functions (*Gueddouri et al, 2022*). Moreover, we unveiled the specific contribution of **intestinal insulin signaling** in the control of epithelial integrity, in $IR^{\Delta GUT}$ mice with an inducible deletion of insulin receptor (IR) in the intestinal epithelium. Further mechanistic investigations demonstrated that insulin controls two essential epithelial components of the gut barrier integrity: (i) the **antimicrobial defense by Paneth cells** and (ii) the **homeostasis of intestinal stem cells**.

While these results pinpoint defective insulin signaling as a prime candidate of gut leakiness, further explorations are needed to provide an extensive characterization of the cellular and molecular mechanisms underlying the contribution of intestinal insulin resistance to gut barrier dysfunctions, which is central to preventive and therapeutic strategies upon obesity and diabetic conditions.

The project will aim at either (i) identifying the **molecular and signaling defects in IR-deficient Paneth cells**, or (ii) characterizing the **reduced stemness capacity in IR-deficient intestinal stem cells**.

Various models and approaches will be used to address these issues:
- **mouse models** of IR deficiency specifically in Paneth cells or intestinal stem cells
- mouse **gut organoids** enriched in Paneth cells or intestinal stem cells
- **FACS-sorting** of Paneth cells or intestinal stem cells
- molecular analyses and pharmacological approaches targeting identified pathways

Publications de l'équipe relatives au projet de stage :

- Gueddouri D et al. Insulin resistance per se drives early and reversible dysbiosis-mediated gut barrier impairment and bactericidal dysfunction. ***Mol Metab. 2022***; 57:101438. PMID: 35007789.
- Rouland M et al. Gut mucosa alterations and loss of segmented filamentous bacteria in type 1 diabetes are associated with inflammation rather than hyperglycaemia. ***Gut. 2022***; 71(2):296-308. PMID: 33593807
- Olivier S et al. Deletion of intestinal epithelial AMP-activated protein kinase alters distal colon permeability but not glucose homeostasis. ***Mol Metab. 2021***; 47:101183. PMID: 33548500