



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

Parcours : **Biologie et Développement Cellulaires 'BDC'**

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Fiche de Projet de Stage M2, Année 2021-2022

Unité INSERM ou CNRS ou Université : INSERM U1016, CNRS UMR 8104, Université de Paris	Responsable du Stage : Sandra GUILMEAU
Intitulé Equipe : Signalisation de l'insuline et du glucose et glucotoxicité	Contacts Adresse : Institut Cochin, 24 rue du Faubourg Saint Jacques, 75014 PARIS
ED d'appartenance : BioSPC	Email : sandra.guilmeau@inserm.fr
Responsables de l'Equipe : Catherine POSTIC et Tarik ISSAD	Tel : 06-61-59-73-78

Titre du projet : Epithelial insulin sensitivity as a gatekeeper of the gut barrier?

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

A common feature of metabolic diseases, including obesity, associated insulin resistance and subsequent type 2 diabetes, is their association with chronic inflammatory processes in various tissues, as well as higher risk of infection. In this context, an early increase of **intestinal permeability** and subsequent translocation of bacterial endotoxins into circulation have been suggested to pave the road to the **metaflammation** that accompanies the **diabesity cascade**. While a comprehensive mapping of the mechanisms that elicit or sustain such defective epithelial integrity remains poorly understood, microbial imbalance, food composition and hyperglycemia have been proposed to be at play.

However, our preliminary results reveal that **intestinal insulin sensitivity** is decreased upon obesity and controls (independently of hyperglycemia or adiposity) two essential components of the **epithelial gut barrier**: bactericidal and renewal capacities. Therefore, our proposal aims at investigating the role of intestinal epithelial insulin receptor as a gatekeeper of the gut barrier, by (i) evaluating the molecular and cellular mechanisms underlying functional defects of **anti-microbial defense** upon gut insulin resistance, and (ii) assessing whether insulin signaling represents an **intestinal stem cell** intrinsic mechanism for gut barrier integrity maintenance.

The success of this proposal relies on (i) the development, through genetic approaches, of **original mouse models of gut specific insulin action deficiency** that do not display parallel hyperglycemia or obesity, and (ii) the use of **mouse and human gut organoids** to pre-screen selective pharmacological targeting of insulin receptor downstream pathways and will help to translate our results into clinic. This will allow the specific exploration of the molecular and cellular mechanisms mediating gut barrier impairment upon local insulin signaling loss, which is central to the design of preventive and therapeutic strategies.

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

- Gut mucosa alterations and loss of segmented filamentous bacteria in type 1 diabetes are associated with inflammation rather than hyperglycaemia. Rouland M et al., Gut 2021. PMID: 33593807
- Deletion of intestinal epithelial AMP-activated protein kinase alters distal colon permeability but not glucose homeostasis. Olivier S et al., Molecular Metabolism 2021. PMID: 33548500
- Insulin activates hepatic Wnt/ β -catenin signaling through stearoyl-CoA desaturase 1 and Porcupine. Cabrae R et al., Scientific Report 2020. PMID: 32198362
- Interaction between hormone-sensitive lipase and ChREBP in fat cells controls insulin sensitivity. Morigny P et al., Nature Metabolism 2019. PMID: 32694809
- Growth factor receptor binding protein 14 inhibition triggers insulin-induced mouse hepatocyte proliferation and is associated with hepatocellular carcinoma. Morzyglod L et al., Hepatology 2017. PMID: 27981611