COLLEGE DOCTORAL PAYS DE LA LOIRE — ED BIOLOGIE SANTE

Année 2023/2024

FICHE SUJET DE THESE

Sujet N° (à remplir par l'ED) :	FINANCEMENT : ☒ Demandé ☐ Acquis	Origine du financement :
Titre de la thèse : **Role of the Enteric Nervous System in the intestinal translocation of the opportunistic bacteria *Streptococcus agalactiae***		3 mots-clés : opportunistic bacteria, enteric neurons, intestinal epithelium
Unité/équipe encadrante : TENS- **INSERM U1235**		
Directeur de thèse : **Laetitia AYMERIC**		N° de tél : 06 84 20 53 86 Mail : laetitia.aymeric@univ-nantes.fr

Contexte socioéconomique et scientifique (env. 10 lignes) :

***Streptococcus agalactiae*, known as group B Streptococcus (GBS)**, is a commensal bacteria present in the gut microbiota of 30% of the population. GBS causes severe systemic infection in vulnerable individuals (neonates, elderly), representing the first cause of neonatal meningitidis in the world. Antibiotic prophylaxis is the only preventive strategy currently available. Despite the suspected role of the gut as being one of the main reservoir for GBS, the **specific conditions and mechanisms leading to GBS intestinal translocation remain poorly characterized.**

Enteric neurons and glia, which belongs to the enteric nervous system, have recently emerged as novel modulators of host/bacteria interaction and of the infectious risk in the gut. More specifically, the **neuroepithelial unit (NEU),** which is characterized by the closely apposition of enteric neurons and intestinal epithelial cells, is an important modulator of epithelial barrier function. Depending on the inflammatory context, the NEU positively or negatively modulates epithelial anti-microbial functions. Although **the NEU can play a protective role against some infections, its potential deleterious role in favoring barrier disruption and pathogens translocation has never been addressed**.

Hypothèses et questions posées (env. 8 lignes) :

Our hypothesis, which is based on strong preliminary data, is that GBS crosses the intestinal epithelium by modulating the neuro-epithelial unit.

During this PhD project, **we expect to reach the 2 following objectives** :

a) To identify the inflammatory mediators released upon GBS / epithelium interaction, leading to enteric neurons activation.

b) To decipher the cellular and molecular mechanisms underlying the impact of neuromediators on GBS epithelial translocation.

Grandes étapes de la thèse (env. 12 lignes) :

The first objective is to identify the inflammatory mediators released by epithelial cells, upon GBS/epithelium interaction, leading to enteric neurons activation. To reach this objective, we will first identify GBS virulence factors involved in neurons activation, using isogenic mutants, and quantify a panel of inflammatory mediators upon GBS infection. Their role in neuron activation will be studied using antagonists and genetic tools (shRNA).

The second objective is to understand the cellular and molecular mechanisms underlying the role of neuromediators in epithelial barrier disruption leading to GBS translocation. In this part, we will use imaging technics using fluorescent bacteria and traditional bacterial adhesion/invasion assay. We will study the route of GBS translocation (para- trans-cellular) and the role of key pathways (regulation of tight junction proteins, endocytosis, apoptosis).

This project will be done using *in vitro, ex vivo* and *in vivo* infection models, including the use of human derived enteroids.

The student will be mentored on a daily basis by the thesis director. In addition, meetings with the external collaborators will be organized twice a year.

Compétences scientifiques et techniques requises par le candidat (2 lignes) :

The PhD candidate should have knowledge and/or experimental skills in one or several of the following fields : cellular biology, host/pathogen interaction, microbiology, neurobiology. Communication : french or english

3 publications de l'équipe d'accueil relatives au domaine (5 dernières années) :

Blin, J.; Gautier, C.; Aubert, P.; Durand, T.; Oullier, T.; Aymeric, L.; Naveilhan, P.; Masson, D.; Neunlist, M.; Bach-Ngohou, K. **Psychological Stress Induces an Increase in Cholinergic Enteric Neuromuscular Pathways Mediated by Glucocorticoid Receptors**. *Front Neurosci* **2023**, *17*, 1100473. https://doi.org/10.3389/fnins.2023.1100473.

Herbreteau, A.; Aubert, P.; Croyal, M.; Naveilhan, P.; Billon-Crossouard, S.; Neunlist, M.; Delneste, Y.; Couez, D.*; Aymeric, L*. **Late-Stage Glioma Is Associated with Deleterious Alteration of Gut Bacterial Metabolites in Mice.** Metabolites **2022**, 12 (4). https://doi.org/10.3390/metabo12040290.

Aymeric, L.; Donnadieu, F.; Mulet, C.; du Merle, L.; Nigro, G.; Saffarian, A.; Bérard, M.; Poyart, C.; Robine, S.; Regnault, B.; Trieu-Cuot, P.; Sansonetti, P. J.; Dramsi, S. **Colorectal Cancer Specific Conditions Promote Streptococcus Gallolyticus Gut Colonization**. Proc Natl Acad Sci U S A **2018**, 115 (2), E283–E291. https://doi.org/10.1073/pnas.1715112115.

Collaborations nationales et internationales :

-Dr Asmaa TAZI (MCU-PH), Pr Claire POYART (PU-PH) ; National Reference Center on Streptococci ; Institut Cochin, Paris (expert in GBS infection)

-Dr Shaynoor DRAMSI (Research Director), Institut Pasteur, Paris (expert in Streptococci biology and genetics)

-Dr Andrea PUHAR (Group Leader), Umea University, Sweden (expert in pathogen-induced inflammation in the gut)