Nantes Université

Offre de stage M2 Cursus Master/Doctorat
Ecole Universitaire de Recherche Sciences et Technologies de la Santé
et Master 2 Biologie et Médicaments
UE XMS2BU100&101 – (2 pages max.)

FORMATION CONCERNEE

☐GP Immunologie et Immuno-Intervention (I^3)
☐GP Oncologie, Hématologie et Médecine Nucléaire (OHNU)
☒**GP Microbiote, Intestin, Cerveau, Alimentation, Santé (MICAS)**
☐GP Innovation for CArdiovascular, metabolic and REspiratory diseases (InnoCARE)
☐GP Médecine 4R, Réparer, Remplacer, Régénérer, Reprogrammer (M4R)

TITRE DU STAGE :

The INFIGHTER, or how to strengthen gut homeostasis by using the enteric glia

LABORATOIRE D'ACCUEIL :

Inserm UMR1235 TENS

EQUIPE D'ACCUEIL :

Gut Neuroinflammation

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TITRES ET TRAVAUX DE L'EQUIPE D'ACCUEIL (5 PUBLICATIONS LES PLUS SIGNIFICATIVES) :

Role of ICAM-1 in the Adhesion of T Cells to Enteric Glia: Perspectives in the Formation of Plexitis in Crohn's Disease.
Pabois J, Durand T, Le Berre C, Filippone RT, Noël T, Durieu E, Bossard C, Bruneau S, Rolli-Derkinderen M, Nurgali K, Neunlist M, Bourreille A, Neveu I, Naveilhan P. Cell Mol Gastroenterol Hepatol. 2024 Feb 29;18(1):133-153. doi: 10.1016/j.jcmgh.2024.02.016. Online ahead of print. PMID: 38428588 Free PMC article.

Enteric glia at center stage of inflammatory bowel disease.
Le Berre C, Naveilhan P, Rolli-Derkinderen M. Neurosci Lett. 2023 Jul 13;809:137315. doi: 10.1016/j.neulet.2023.137315. Epub 2023 May 29. PMID: 37257681 Free article.

Crosstalk between omega-6 oxylipins and the enteric nervous system: Implications for gut disorders?
Mantel M, Derkinderen P, Bach-Ngohou K, Neunlist M, Rolli-Derkinderen M. Front Med (Lausanne). 2023 Mar 28;10:1083351. doi: 10.3389/fmed.2023.1083351. eCollection 2023. PMID: 37056732 Free PMC article. Review.

PGI_2 Inhibits Intestinal Epithelial Permeability and Apoptosis to Alleviate Colitis.
Pochard C, Gonzales J, Bessard A, Mahe MM, Bourreille A, Cenac N, Jarry A, Coron E, Podevin J, Meurette G, Neunlist M, Rolli-Derkinderen M. Cell Mol Gastroenterol Hepatol. 2021;12(3):1037-1060. doi: 10.1016/j.jcmgh.2021.05.001. Epub 2021 May 7. PMID: 33971327 Free PMC article.

Defects in 15-HETE Production and Control of Epithelial Permeability by Human Enteric Glial Cells From Patients With Crohn's Disease.
Pochard C, Coquenlorge S, Jaulin J, Cenac N, Vergnolle N, Meurette G, Freyssinet M, Neunlist M, Rolli-Derkinderen M. Gastroenterology. 2016 Jan;150(1):168-80. doi: 10.1053/j.gastro.2015.09.038. Epub 2015 Nov 11. PMID: 26433161

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RESUME DU PROJET PROPOSE ET TECHNIQUES ENVISAGEES (MAXIMUM 1 PAGE) :

Enteric glial cells (EGCs) have emerged as a signaling hub capable of responding to environmental and tissue changes by regulating intestinal immunity, tissue repair and gastrointestinal barrier function. These effects are primarily mediated through the production of gliomediators, which modulate the behavior of neighboring cells such as immune or intestinal epithelial cells. Among such glia-derived mediators, lipids and more precisely oxylipins have received increased attention. We have recently shown that the oxylipin PGI_2, which is reduced in Crohn's Disease (CD) gut, alleviated DSS-induced colitis in mice and partly reversed the intestinal barrier abnormalities observed in gastrointestinal (GI) samples from CD subjects. In sharp contrast to CD, the amount of both PGI_2 and glial marker GFAP are markedly increased in EGCs in response to inflammatory challenge. These observations lead us to postulate that EGCs in CD display a loss of response to inflammation resulting in less PGI_2 production and dysregulation of the surrounding cells. To test this hypothesis the INFIGHTER project has three aims (i) to fully define EGC reaction to inflammation and if this reaction is lost with disease evolution, (ii) to demonstrate that CD-like EGC defect contribute to intestinal failure and (iii) to measure whether CD EGC correction can rescue EGC-IEB homeostasis.

First, EGCs and EGC neighboring cells from controls and CD patients at two different disease stages (at time of diagnosis *vs* first surgery) will be in-depth characterized using multi-omic analyses (bioinformatic integration of single cell sequencing and lipidomic, coupled to microbiomic, functional explorations and clinical data). This will allow to identify EGC dysfunctions and determine the cellular and molecular switch observed between the two CD groups. A second part of the project will study the effects of the absence of our first glial candidate, the PGI_2 production, on its microenvironment through cutting edge system biology approaches (*in vivo* murine models, inducible and tissue-specific gliomediator deletion and human organoids). As a result, the third part of the project will evaluate strategies to correct CD-EGC defaults by restoring PGI_2 levels via viral targeting of EGC and by maintaining PGI_2 levels through innovative bioactive lipids-probiotics cocktails. To successfully carry out this project, our assets are our human biocollections (biopsies and postoperative GI samples), our unique human EGC culture and functional explorations upon IEB using human organoids as well as different in vivo ileitis and colitis murine models.

The INFIGHTER project addresses, in an original way the question of CD pathophysiology and loss of inflammation resolution through enteric nervous system dysfunctions. It will additionally study therapeutic strategies to strengthen the digestive homeostasis through the control of the bioavailability of bioactive lipids to foster inflammation resolution.

TECHNIQUES ENVISAGEES :

ORGANOID CULTURE

GLIAL CELL TRANSFECTION

WESTERN BLOT

IMMUNOHISTOCHEMISTRY