**THESIS TOPIC**

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<tr>
<th>Subject N° (to be completed by the ED):</th>
<th>FUNDING:</th>
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<th>Funding origin: Université Rennes 1 (selected for NuMeCan)</th>
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<td>3 keywords: Energy metabolism, Diet, Ulcerative colitis</td>
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**Thesis title:**
Mitochondrial function and mucosal healing in Inflammatory Bowel Diseases

**Unit / team:** NuMeCan - INSERM- U1241, Université Rennes 1, INRAE ; EXPRES Team

**Supervisor’s name:** Guillaume Bouguen

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**Email address:** guillaume.bouguen@chu-rennes.fr

**Socio-economic and scientific context (approximately 10 lines):**
To date, there is no cure for Ulcerative Colitis (UC, an Inflammatory Bowel Disease). Therapeutic strategies are based on the use of pharmacological agents that decrease non-specifically inflammation and immune responses. However, such management still remains insufficient for a majority of patients to control disease progression and disease complication that lead to the need for surgery. This finding led to consider mucosal healing (assessed by endoscopy) as the main target because of its association with sustained clinical remission, a decrease of the need for hospitalization and surgery.2,3 The cellular and molecular mechanisms involved in intestinal epithelial repair and its regulation remain poorly described. In particular, the involvement of the mitochondria, a major site of cellular energy production, is little known although alterations induced by inflammation have been reported.2,4 Tissue repair in response to intestinal inflammation presumably requires higher energy supplies and increased nutritional requirements for the restoration of barrier function and intestinal physiological functions. However, although the diet is one of the major environmental factors incriminated in the induction but also presumably in the perpetuation of IB (probably due to changes in the luminal intestinal environment), the specific role and the level of macro- and micro-nutrient intake in mucosal healing process has been barely studied, which makes it difficult to develop appropriate dietary recommendations.


**Working hypothesis and aims (approximately 8 lines):**

**What are the metabolic changes that contribute to the return to intestinal homeostasis in response to inflammatory stress?**

2. Mitochondrial function is probably a central actor of epithelial repair. Are there distinct patterns of mitochondrial activity related to mucosal healing achievement (validation / non validation of mucosal healing by endoscopic examination) in UC patients?

3. Diet would play a key role in the progression of the disease. What are the macro- and / or micro-nutrients that could influence the mucosal healing process?

**Main milestones of the thesis (approximately 12 lines):**

**Step 1 (6 months):** State-of-the-art: Finalization of analyses targeting mitochondrial function on a murine model with chemo-induced colitis. Handling of the human colon organoid model.

**Step 2 (15 months):**
- study of energy metabolism on intestinal epithelial cells in human colon organoid model in response to several factors involved in UC pathogenesis (inflammatory stress, deleterious bacterial metabolites, hypoxia)
- development and follow up of the clinical study: non-interventional monocentric study on a UC patient cohort at 3-month interval (inflammation vs healing), each individual being his own control according to the UC phase: colon biopsies and food frequency questionnaires (FFQ)

**Step 3 (12 months):**
- analysis of transcriptional signatures in colon biopsies by transcriptomics and bioinformatics (Ingenuity Pathway Analysis, Connectivity Map)
- analysis of mucosa adherent microbiota composition and activity
- statistical analyses of FFQ data and correlation study of clinical and biological data

**Step 4 (3 months):** thesis finalisation

**Scientific and technical skills required by the candidate (2 lines):**

**3 publications from the team related to the topic (last 5 years):**

Lan A, Blais A, Coelho D, Capron J, Maarouf M, Benamouzig R, Lancha AH Jr, Walker F, Tomé D, Blachier F. Dual effects of a high-protein diet...


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<th>National and international collaborations:</th>
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<td>Analyses on human samples collected at the Service des Maladies de l'Appareil Digestif (SMAD, CHU Pontchaillou, Rennes) will be conducted at NuMeCan Institute under the supervision of Annaïg Lan. She has recently developed the colon organoid model and is currently studying the inflammation and healing impacts on mitochondrial function in a mouse model of chemo-induced colitis. Statistical analyses of food consumption data and related correlations will be carried out in close collaboration with scientists of the UMR Physiology of Nutrition and Food Behavior at AgroParisTech. This project will also benefit from mitochondrial energy metabolism expertise from scientists of this UMR. Hybridization of DNA microarrays will be carried out at the Genotoul transcriptomics platform (Get-trix platform, Toulouse) and adherent microbiota analysis will be performed in collaboration with the bacteriology laboratory of the University Hospital of Rennes.</td>
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