



CONVOCATORIA DE PRÁCTICAS INTERNACIONALES

CONVENIO UCLM/CERFA 2022

PROYECTO 3

Afiliación del supervisor y Enlace a afiliación / Supervisor affiliation and Affiliation link

University Hospital Schleswig-Holstein (UKSH) – Christian-Albrechts-University Kiel (CAU)

<https://www.ikmb.uni-kiel.de/>

Título del Proyecto/ Project Title

Intestinal epithelial cell stress modulates enteric fibroblastic and neuronal profiles in inflammatory bowel disease

Perfil preferencial del estudiante

BSc or MSc (Biotechnology, Biochemistry, Pharmacy)

Fechas orientativas/Available Dates

13/06/2022 to 23/09/2022

Programa/ Detailed program of the traineeship period (aprox. 100-200 palabras)

Intestinal epithelial cell (IEC) stress is a dominant pathomechanism in inflammatory bowel disease (IBD) that leads to intestinal barrier defects, and subsequently to inflammation. Failing autophagy (natural clearance of unnecessary or dysfunctional proteins, organelles or cells) by defective *ATG16L1* expression is associated with Crohn's disease, and endoplasmic reticulum (ER) stress (unfolded protein response mechanisms – led by *XBP1* and *ATF6*) is a major pathway downstream of dysfunctional *ATG16L1* in IECs. Thus, we propose that autophagy/ER stress, which has a pivotal influence on IEC regeneration, is crucial for IBD-associated complications such as fibrosis (by affecting the profile of fibroblasts), and intestinal motility impairments (by modification of the profile of enteric neurons).

To investigate how epithelial stress modifies the programs of enteric non-immune cells, wild-type, *ATG16L1*, and *XBP1* deleted small intestinal organoids will be used to recapitulate the main IEC lineages, including intestinal stem cells, absorptive enterocytes, secretory goblet cells, sensory/hormone-secretory enteroendocrine (EEC) cells, and stem-cell-protective Paneth cells. Enteric fibroblasts and neurons will be isolated from wild-type mice colon for co-culture with organoid-derived IECs in tubular disposition in organ-on-a-chip platforms that mimicry intestinal flow shear stress. Cell phenotype will be assessed by quantitative PCR (qPCR) and immunofluorescence (IF) using biomarkers for enteric fibroblasts and fibrosis (vimentin, α -SMA, collagen I, TGF- β , IL-11, IL-13, FN1, CTGF) and enteric neurons and motility (Tuj-1, NPY, ChAT, VACHT, neuronal NOS, calretinin, calbindin, serotonin, substance P, VIP), while cell viability will be assessed using a Live-Dead cell staining kit before and after the in vitro assays (Figure 1, objective 1). In parallel, we will perform neuronal cell counts and analyze the distribution of ganglia and fibrotic areas in tissue from *ATG16L1*, and *XBP1* knock-out mice using immunohistochemistry (IHC) or IF of the above mentioned markers (Figure 1, Objective 2) following published analyses (Nestor-Kalinowski A. et al, 2022 Cell Mol Gastroenterol Hepatol 13(1): 309-337). We will ultimately use RNA-sequencing (RNA-seq) to explore the transcriptional landscape of challenged enteric fibroblasts and neurons in an unbiased manner (Figure 1).

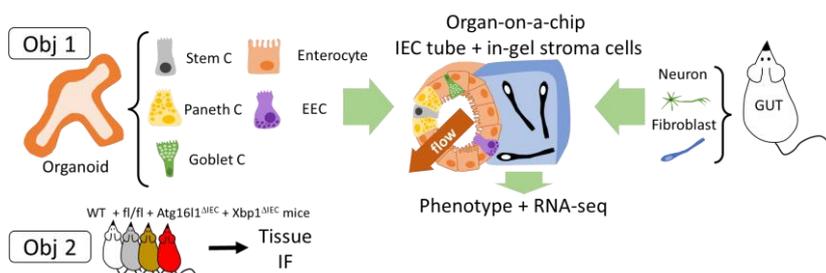


Figure 1: Schematic representation of the research plan.

Competencias a adquirir por parte del estudiante/ Knowledge, skills and competences to be acquired by the trainee at the end of the traineeship (expected Learning Outcomes) (aprox. 100 palabras)

Immunofluorescence (IF) of cells and tissue samples.

Microscopy and image analyses.

General knowledge on in vitro assays and RNA isolation.

Experimental design and analyses.

Seguimiento/ Monitoring Plan (aprox. 50 palabras)

Celia will directly train and supervise the student daily at the beginning. After a few weeks, the student should be able to work alone, and be independent to plan and perform IF staining and image analyses. Therefore, Celia's supervision will be adjusted to the level of independence and confidence shown, from daily, to every-other-day or weekly meetings, also according to the project requirements. The student will be invited to the weekly lab meetings and journal clubs with other lab members to get a better insight into the field and openly discuss science.

Evaluación/ Evaluation plan (aprox. 50 palabras)

The student's progress, including new abilities and independence, will be evaluated weekly by Celia. She will also provide with feedback that will promote the student's learning and evolution towards independent lab work and experimental design. At the end of each month, a formal evaluation meeting will be scheduled to assess the student's and the project's progress, make space for reflection and provide additional feedback. A closing evaluation meeting will take place in September to assess what aspects could be referred to again if a new traineeship relationship would start, and what both would do differently next time.

Conocimientos técnicos o experiencia requerida (si procede) / Technical knowledge or experience required (if applicable)

Language competence required: English B1, spanish optional

Previous experience in immunohistochemistry/immunofluorescence and microscopy will be positively evaluated. Experience working with animals is not required.

Especificaciones extra de la institución de acogida (si procede) / Additional specifications of the host institution (if applicable)

N/A

Disponibilidad para evaluar informes de convalidación de créditos (Si/No) / Availability to evaluate credit convalidation reports (Yes / No)

YES

Otra información relevante / Any additional important information

Además del soporte económico del Programa Erasmus+ Placement de la UCLM, los estudiantes recibirán el paquete de **Ayudas CERFA-Fundación Ramón Areces**. En la convocatoria 2022, éste se divide en dos conceptos:



- Ayuda económica en concepto de viaje: 400 euros
- Curso práctico destinado a ofrecer formación sobre gestión de carrera profesional

Toda la información aquí: <https://cerfa.de/ayudas-cerfa-fra/>