

EuReCa International PhD Program
PhD thesis project
2021 Call for application

Control of gut development and physiology by cytokine signaling

General information

Call	2021
Reference	2021-07-HERNANDEZ
Keyword(s)	Gut epithelium; Development and Physiology; Immune Cytokines; Zebrafish; Microscopy and transcriptomics

Director(s) and team

Thesis director(s)	Pedro Hernandez
Research team	Development and Homeostasis of Mucosal Tissues
Research department	U 934 - Genetics and Developmental Biology

Description of the PhD thesis project

In our group we work at the intersection of immunology and developmental biology.

Our primary goal is to understand how environmental cues interact with host genetic networks to regulate organ development and physiology. We focus particularly on the intestine, which initially forms without major influence of extrinsic factors but later develops in interaction with several commensal microorganisms and dietary nutrients.

We study how the crosstalk between the immune system and environmental signals regulates gut development and epithelial function. To study these questions, we exploit the advantages of the zebrafish model such as ex utero and rapid development, transparency, large progeny, and simple genetic and environmental manipulation. We combine live imaging, flow cytometry, and bulk and single-cell transcriptomics with models that induce mucosal stress, including pathogenic challenges.

Project abstract: cytokines are small secreted proteins originally characterized as leukocyte-derived modulators of defense responses.

We have recently found that gut epithelial cells of the zebrafish larva express several cytokines before cytokine-expressing lymphocytes develop and populate this organ. These cytokines were thought to be produced only by leukocytes and we found that disruption of their signaling results in a profound impairment of gut development. We hypothesize that the orchestrated action of cytokines in the gut is essential for its development and the establishment of a functional epithelial layer.

We propose a research project aiming to uncover how cytokine signaling controls intestinal development and homeostasis. Also, we aim to determine the relationship between the microbiota and cytokine function in the control of intestinal development and physiology.

This project will provide fundamental insights into how intercellular communication mediated by immune signals controls organogenesis and maintains tissue homeostasis.

International, interdisciplinary & intersectoral aspects of the project

We will exploit and strengthen our ongoing local and international collaborations: Jean-Pierre Levrud, Institute of Neuroscience, Paris-Saclay, France (zebrafish immunity); Jean-Marc Ghigo, Institut Pasteur, Paris, France (gut microbiota); Carmen Feijoo, Andres Bello University, Santiago, Chile (diet-induced gut inflammation in zebrafish); Eduardo Villablanca, Karolinska Institutet, Sweden (mouse and zebrafish gut immunology).

The student will have the opportunity to do research stays in these laboratories. Also, the fish lines that will be generated will be used for high-throughput screening of molecules modulating gut inflammation (with E. Villablanca).

Finally, this project combines conceptual and technical approaches used in developmental biology, immunology, and bioinformatics.

Recent publications

1. Coronado M, Solis CJ, **HERNANDEZ PP*** and Feijoo CG. Soybean Meal-Induced Intestinal Inflammation in Zebrafish Is T Cell-Dependent and Has a Th17 Cytokine Profile. *Front Immunol.* 2019 Apr 2; 10:610. doi: 10.3389/fimmu.2019.00610. PMID: 31001250; PMCID: PMC6454071. (*) Corresponding author

2. Gronke K*, **HERNANDEZ PP***, Zimmermann J, Klose C, Kofoed-Branzk M, Guendel-Rojas F, Witkowski M, Tizian C, Amann L, Schumacher F, Glatt H, Triantafyllopoulou A, and Diefenbach A. Interleukin-22 protects intestinal stem cells against genotoxic stress. *Nature.* 2019 Feb; 566(7743):249-253. doi: 10.1038/s41586-019-0899-7. Epub 2019 Jan 30. PMID: 30700914; PMCID: PMC6420091. (*) Equal contribution.

3. **HERNANDEZ PP***, Strzelecka P, Athanasiadis E, Hall D, Robalo AF, Collins AM, Boudinot P, Levrud* JP, Cvejic* A. Single-cell transcriptional analysis reveals ILC-like cells in zebrafish. *Sci Immunol.* 2018 Nov 16; 3(29):eaau5265. doi: 10.1126/sciimmunol.aau5265. PMID: 30446505; PMCID: PMC6258902 (*) Corresponding author.

4. **HERNANDEZ PP**, Mahlakoiv T, Nguyen N, Guendel F, Ryffel B, Hoelscher C, Dumoutier L, Renauld JC, Staeheli P and Diefenbach A. Interferon- λ and interleukin 22 act synergistically for the induction of interferon-stimulated genes and control of rotavirus infection. *Nat Immunol.* 2015 Jul; 16(7):698-707. doi: 10.1038/ni.3180. Epub 2015 May 25. PMID: 26006013; PMCID: PMC4589158. Featured Paper of the Month of July, 2015 by the Society for Mucosal Immunology. Research highlight in *Nature Reviews Immunology*, 15, 402–403 (2015)

5. Mahlakoiv T*, **HERNANDEZ PP***, Diefenbach A and Staeheli P. Leukocyte-derived IFN- α /b and epithelial IFN- λ constitute a compartmentalized mucosal defense system that restricts enteric virus infections. *PLoS Pathog.* 2015 Apr 7; 11(4):e1004782. doi: 10.1371/journal.ppat.1004782. PMID: 25849543; PMCID: PMC4388470.. (*) Equal contribution. Recommended in The F1000Prime Faculty

Expected profile of the candidate

Applicants should be strongly motivated to study biological phenomena in an in vivo context, and should show a solid capacity for independent and creative thinking as well as for team work. Background and strong interest in developmental biology and/or immunology is strongly recommended. Interest in comparative biology using different animal models, as well as translational applications to humans are desired. Knowledge in bioinformatic analysis is a plus but not compulsory. Experience in molecular biology, RT-qPCR, microscopy and flow cytometry are also a plus.