



Master project 2024-2025

Personal Information

Supervisor	Júlia Perera-Bel & Giuliana Magri
Email	jperera@researchmar.net
Institution	Hospital del Mar Research Institute (HMRIB)
Website	http://grib.imim.es/
Group	Bioinformatics Unit, Research Programme on Biomedical Informatics (GRIB)

Project

Computational genomics

Project Title:

Deciphering Host-Microbiota Interaction in Crohn's Disease via Integrative Multi-omics

Keywords:

single-cell RNA sequencing, microbiota/metagenomics, mucosal immunity, antibodies, Crohn's disease

Summary:

Crohn's disease (CD) is a chronic and relapsing inflammatory condition of the gastrointestinal tract that manifests with a highly heterogeneous phenotype in terms of disease behavior and response to medical treatment. Alterations in the bacterial and fungal microbiota are recognized as pivotal hallmarks in its disease dynamics, driving dysregulated immune responses in genetically susceptible individuals. Although the gut microbiota has been recognized as one of the main factors in CD etiology, it remains unknown whether differences in gut microbiome composition could contribute to CD heterogeneity by eliciting different innate and adaptive responses in the intestinal mucosa. It is also unclear how the presence of specific microbiome profiles is associated with unique mucosal antibody repertoires. Our compelling preliminary data of human samples using single cell omics technologies led us to hypothesize that different gut microbiome profiles may associate with distinct inflammatory modules in CD and may trigger specific mucosal antibody responses. The general objective of this project is therefore to build a comprehensive map detailing the microbiome-associated inflammatory and humoral responses that evolve in the gut of CD patients using cutting-edge bioinformatic methods, single-cell immunology and transcriptomic technologies and unique human samples. Building upon this comprehensive characterization, our project aims to develop high affinity monoclonal antibodies targeting specific pathogenic microbial strains, which hold promising potential as therapeutic or diagnostic tools. To achieve this general objective, the student will pursue the following specific aims: 1) Characterize the mucus-embedded bacterial and fungal microbiota in CD via metagenomics or 16s rRNA sequencing. 2) Map microbiome-associated mucosal inflammatory and humoral responses in CD using single-cell RNA and single-cell V(D)J antibody sequencing. 3) Characterize the mucosal antibody reactivity to the gut microbiota in CD through phage-display immunoprecipitation sequencing (Phip-seq). The MICROHN project is expected to deliver unprecedented insights into the dynamics of host-microbiota interaction in the human intestine, offering key information to understand the role of the microbiota in CD immunopathology and disease heterogeneity. If successful, this study will pave the way to identify new personalized microbial-targeted therapies, that could ultimately improve treatment outcomes.

References:

Roda G et al. Crohn's disease. *Nat Rev Dis Primers*. 2020 Apr 2;6(1):22. Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. *Lancet*. 2017 Apr 29;389,1741-1755. Ni J, Wu GD, Albenberg L, Tomov VT. Gut microbiota and IBD: causation or correlation? *Nat Rev Gastroenterol Hepatol*. 2017 Oct;14(10):573-584. de Souza HS, Fiocchi C. Immunopathogenesis of IBD: current state of the art. *Nat Rev Gastroenterol Hepatol*. 2016 Jan;13(1):13-27. Franzosa EA et al. Gut microbiome structure and metabolic activity in inflammatory bowel disease. *Nat Microbiol*. 2019 Feb;4(2):293-305. Pascal V et al. A microbial signature for Crohn's disease. *Gut*. 2017 May;66(5):813-822. Martin JC et al. Single-Cell Analysis of Crohn's Disease Lesions Identifies a Pathogenic Cellular Module Associated with Resistance to Anti-TNF Therapy. *Cell*. 2019 Sep 5;178(6):1493-1508.e20. Smillie CS et al. Intra- and Inter-cellular Rewiring of the Human Colon during Ulcerative Colitis. *Cell*. 2019 Jul 25;178(3):714-730.e22. Uzzan M et al. Ulcerative colitis is characterized by a plasmablast-skewed humoral response associated with disease activity. *Nat Med*. 2022 Apr;28(4):766-779. Scheid JF et al. Remodeling of colon plasma cell repertoire within ulcerative colitis patients. *J Exp Med*. 2023 Apr

3;220(4):e20220538 Garrido-Trigo A et al. Macrophage and neutrophil heterogeneity at single-cell spatial resolution in human inflammatory bowel disease. *Nat Commun.* 2023 Jul 26;14(1):4506 Arumugam M et al. Enterotypes of the human gut microbiome. *Nature.* 2011 May 12;473(7346):174-80 Chen K, Magri G, Grasset EK, Cerutti A. Rethinking mucosal antibody responses: IgM, IgG and IgD join IgA. *Nat Rev Immunol.* 2020 Jul;20(7):427-441 Gutzeit C, Magri G, Cerutti A. Intestinal IgA production and its role in host-microbe interaction. *Immunol Rev.* 2014 Jul;260(1):76-85

Expected skills:

UNIX-like operating systems and shell scripting; R and Python programming language, Single cell RNASeq; NGS data analysis; Advanced statistics

Possibility of funding:

No

Possible continuity with PhD:

To be discussed

Comments:

The student will be co-supervised by Giuliana Magri (UB) and Júlia Perera (Hospital del Mar Research Institute - HMRIB). The student will join the Bioinformatics Unit at the Research Programme on Biomedical Informatics (GRIB, HMRIB), at the PRBB building. The PRBB offers a fantastic scientific community, with a highly innovative and enriching training environment for basic and translational research.