Internship Proposition
(one page max)
Master 2 GP Immunology & ImmunoIntervention (I^3)
2024-2025

Lab: Mehandru Lab, Icahn School of Medicine at Mount Sinai

Team: Pablo Canales-Herrerias, PhD, Divya Jha, PhD

Name and position of the PI:
Saurabh Mehandru,
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Candidate (if internship filled):
TBD

Title of the internship:
Examining mucosal lymphoid aggregates in patients with Ulcerative Colitis

Summary of the internship proposal:
Ulcerative colitis (UC) is a sub-type of inflammatory bowel disease (IBD) that affects the large intestine, with a global prevalence of approximately 5 million. The pathogenesis of UC is multi-factorial, involving aberrant immune responses in genetically predisposed individuals. Induction of intestinal immune responses occurs in specialized compartments called gut-associated lymphoid tissues (GALT), which include Peyer's patches, isolated lymphoid follicles (ILF) and tertiary lymphoid structures (TLS). The inflamed colon of UC patients is enriched in GALT size, frequency and cellularity, including an increase in GALT-associated endothelial cells, naïve B cells and naïve T cells. Moreover, a profound dysregulation of the B cell response, including autoantibody production, is seen in UC (*Uzzan et al, Nature Medicine, 2022*). Considering its association with intestinal inflammation, a careful characterization of GALT in UC could provide new tools to predict response to immunotherapy and guide decision-making during therapeutic course. We recently described that therapeutic response to the frontline immunotherapy vedolizumab, which blocks the gut-homing integrin α4β7, is associated with attenuation of GALT in UC patients (*Canales-Herrerias et al. Science Immunology, 2024*). Specific to treatment-responders we observed a loss of size and cellularity of GALT, which was associated with an attenuation of the IgG^+ response and FcγR signaling in the intestine. These findings demonstrate that the GALT plays a pathogenic role in patients with UC, and that targeting GALT could represent a novel paradigm in UC therapeutics.

The overarching hypothesis that will be explored in the proposed research is that GALT plays an important role in the immune dysregulation in UC. Consequently, studying the GALT in patients with UC will lead to better patient characterization and the development of predictive therapeutic tools. To examine this hypothesis, the following Aims are proposed:

AIM 1. To spatially characterize the composition and transcriptional profile of GALT in patients with UC
Approach: formalin-fixed paraffin-embedded (FFPE) intestinal tissues from untreated UC patients (n=10) and healthy controls (n=5) will be interrogated using in-situ single-cell spatial transcriptomics (Visium-HD, 10X genomics). In collaboration with the Human Immune Monitoring Center (HIMC) at Mount Sinai, we will use this novel platform to profile whole-

transcriptome spatial gene expression in intestinal samples, which enables single-cell resolution. Colorectal specimens will be obtained from a carefully curated cohort of patients form the Mount Sinai IBD Biobank, where we have identified tissues taken before and after immunotherapy, and where GALT structures are present.

AIM 2. To identify determinants of treatment response to immunotherapy in UC.
Approach: using the newly generated dataset from AIM 1, we will compare patients that went on to respond to vedolizumab therapy (n=5) with those who did not (n=5), to identify cell composition and transcriptional signatures associated with response and non-response. In order to test for the predictive value of the identified transcriptional signatures, we will evaluate the expression of the signatures in a larger dataset derived from the seminal GEMINI-I/LTS clinical trials of vedolizumab, where longitudinal transcriptomic data from intestinal biopsies is available for a subset of UC patients (Arijs et al. 2018).

Scientific Environment: The research project proposed below will be conducted within the Henry D. Janowitz Division of Gastroenterology and Department of Immunology at the Icahn School of Medicine at Mount Sinai. Notably, the student will join an environment with a well-established tradition of research, and a long history of excellence in clinical care and scientific discovery. Faculty members who will supervise the student are funded by the NIH (including NCI and NIDDK). The scientific environment will enhance the probability of success of this project. Indeed, Dr. Mehandru and members of their laboratory will continue to interact with a number of immunologists working in research areas closely correlated to this project, including Dr. Miriam Merad. Thus, the scientific environment is highly collaborative and truly excellent.

Option(s) linked to the project:

☐ Experimental Biology Profile