

<b>Principal Investigator</b>	<b>FACCIOTTI FEDERICA</b>
<b>Institute of Affiliation</b>	Università degli Studi di Milano - Bicocca
<b>Title of the proposed project:</b>	Spatial Multi-Omics Mapping of the Intestinal Microenvironment in Colitis-Associated Cancer
<b>Short description of the project</b>	<p>Background and Rationale Patients with longstanding Inflammatory Bowel Disease (IBD) face a two-fold increased risk of developing colitis-associated colorectal cancer (CAC) compared to the general population. Despite advances in endoscopic surveillance, the cellular and molecular events driving the transition from chronic inflammation to malignant transformation remain poorly understood. Interleukin-22 (IL-22), produced by tissue-resident immune cells including conventional T and unconventional T cells, plays a dual role: sustaining mucosal healing in IBD while potentially promoting epithelial proliferation and tumorigenesis. The gut microbiome produces AhR ligands capable of polarizing T cells towards an IL-22-secreting phenotype. However, the spatial architecture of this microbiome-immune-epithelium circuit in pre-cancerous and cancerous intestinal tissues has never been systematically characterized. Overall Aim This PhD project aims to spatially resolve the IL-22-dependent cellular and molecular programs mediating CAC development by integrating state-of-the-art spatial multi-omics technologies at the single-cell level.</p> <p>Experimental Plan The project will unfold across four years. In Year 1, spatial transcriptomics (10X Genomics Xenium, 5,000-gene panel) will be performed on FFPE tissue sections from CAC, pre-CAC, IBD, and sporadic CRC patients (n≥55), mapping IL-22-producing cell populations and their transcriptional neighborhoods. In Year 2, spatial proteomics via multiplex iterative immunofluorescence (MACSIMA Miltenyi, up to 50 markers/slide) will phenotypically and functionally characterize immune, epithelial, and stromal compartments, including conventional and unconventional T cell subsets. In Year 3, MALDI-Mass Spectrometry Imaging will spatially localize microbial-derived metabolites and (iNK)T-stimulatory lipids within the same tissue specimens. In Year 4, multi-modal data integration using cloud-based bioinformatic pipelines (Squidpy, Scanpy, Seurat, Novae) will reconstruct cellular niches and temporal dynamics of IL-22-mediated microenvironment remodeling across disease stages. Expected Outcomes This project will generate the first spatially resolved, multi-omic atlas of the CAC microenvironment, identifying actionable cellular and molecular targets for CAC prevention in IBD patients.</p>
<b>Main research area for the project</b>	Immunology
<b>5 key words for the project</b>	NK and/or NKT cells, Cytokines/Interleukins, Mouse models, Colorectal and/or Intestinal ca., Microbiome

LAB INFO	
<b>Main topic/s of the lab</b>	My research group specifically focuses on understanding and functionally manipulating for therapeutic purposes the interactions between the mucosal immune system and the intestinal microenvironment.
<b>Short description of the lab activity</b>	The intestinal compartment is a complex biological system composed by different type of cells (immune cells, epithelial cells, gut microbiota) involved in functional crosstalks aimed at maintaining a balance between tolerance and immunity. These interactions may give rise to different functional outcomes. In healthy conditions immune cells contribute to intestinal homeostasis maintenance, while in genetically predisposed individuals hyperactivation of immune cells may lead to in chronic autoimmune intestinal inflammation. In the context of intestinal tumours, defective activation of immune cells may contribute to decreased immunosurveillance and tumour development. Specifically, our projects focus at: Deciphering the role of conventional and unconventional intestinal CD4+T helper cells in contributing to tissue homeostasis and in participating to inflammatory immune responses; Understanding the functions of intestinal T lymphocytes in the control of epithelial neoplastic transformations; Dissecting the functional interactions between T cells , the gut microbiota and the intestinal microenvironment during intestinal neoplastic transformation and inflammation Manipulating the function of immune cells for therapeutic purposes. To do so, we take advantage of a translational approach involving in vitro systems, murine models of colorectal cancer and intestinal inflammation, and patients'-derived surgical specimens. More recently we implemented spatial omics techniques to map the biogeography of immune cells, the microbiome and epithelial cells at different stages of disease.
<b>Recent bibliography</b>	<ul style="list-style-type: none"> <li>- Antibiotic-associated dysbiosis affects the ability of the gut microbiota to control intestinal inflammation upon fecal microbiota transplantation in experimental colitis models. MICROBIOME 2021 Feb; 9: 39</li> <li>- Human intestinal and circulating invariant natural killer T cells are cytotoxic against colorectal cancer cells via the perforin-granzyme pathway. MOL ONCOL 2021 Dec; 15: 3385</li> <li>- Porphyromonas gingivalis fuels colorectal cancer through CHI3L1-mediated iNKT cell-driven immune evasion. GUT MICROBES 2024; 16: 2388801</li> <li>- Estrogen-related differences in antitumor immunity and gut microbiome contribute to sexual dimorphism of colorectal cancer. ONCOIMMUNOLOGY 2024 Dec; 13: 2425125</li> <li>- iNKT cell-neutrophil crosstalk promotes colorectal cancer pathogenesis. Mucosal Immunol 2023 Jun; 16: 326</li> </ul>

<b>Group composition</b>	1 senior scientist (immunologist, expert in ex-vivo human cells manipulation and in vivo murine experiments, experti in advanced multidimensional imaging techniques) 2 Postdoc (1 computational biologist, 1 molecular biologist/spatial omics' expert) 1 PhD student (immunologist, expert in ex-vivo human cells manipulation and in vivo murine experiments) 2 fellows (1 computational biologist, 1 microbiologist expert in microbiome modulation) 2 master thesis students (1 computational, 1 immunologist)
<b>Institutional page link</b>	<a href="https://www.unimib.it/federica-facciotti">https://www.unimib.it/federica-facciotti</a>