Program & Abstract Book

Organoids
Microbiome
Modeling
Precision medicine
Networks
Imaging
Multi-omics

4th INTERDISCIPLINARY SIGNALING WORKSHOP

VISEGRAD, HUNGARY, 2025

https://2025.signalingworkshop.org/

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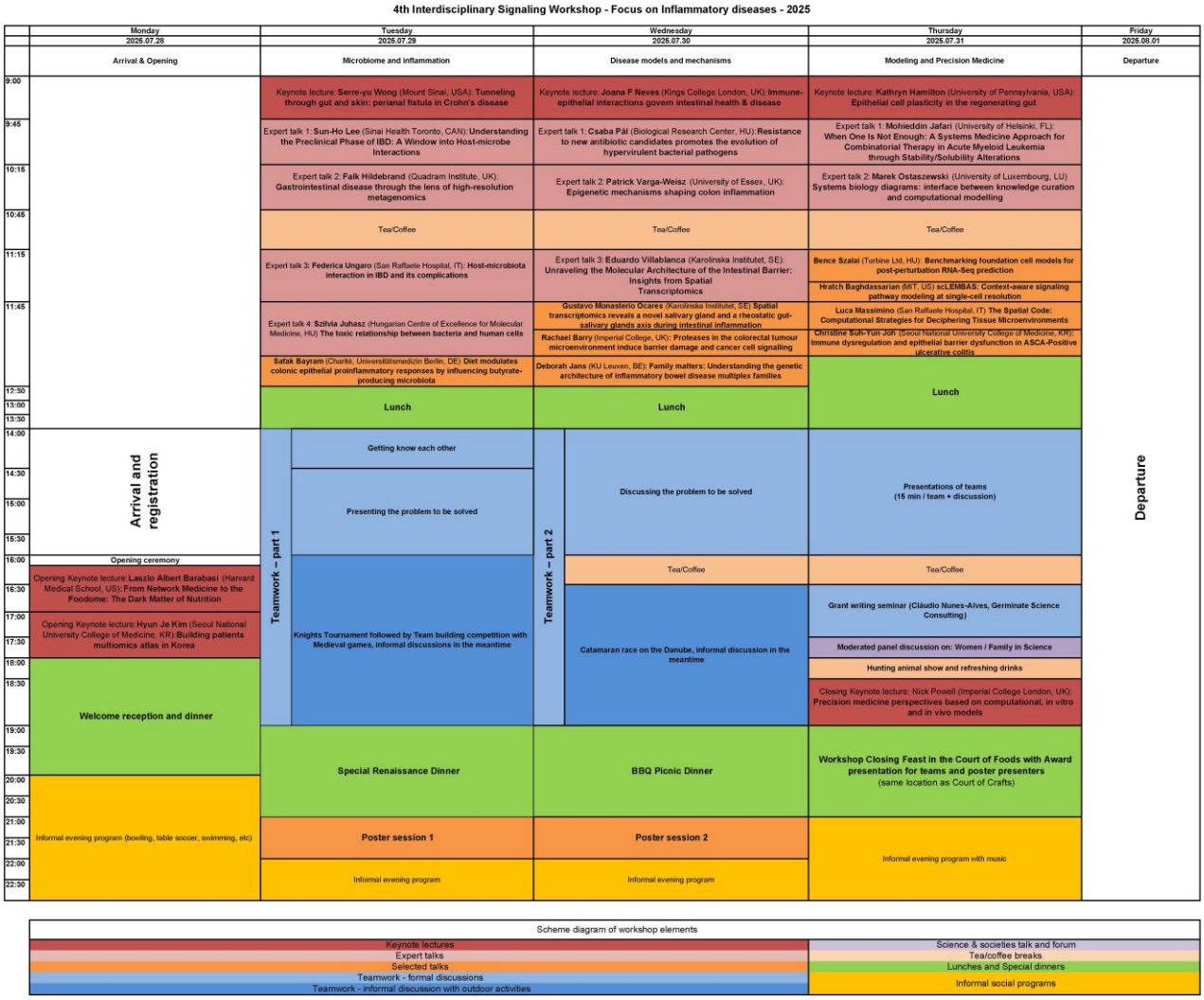
Timetable



Scientific program

Monday – 28 July 2025

14:00	**Arrival and registration**
16:00	**Opening ceremony** **Chair: Tamás Korcsmáros**
16:05	Opening Keynote lecture: **Albert-László Barabási (Harvard Medical School, USA):** From network medicine to the Foodome: The dark matter of nutrition
17:00	Opening Keynote lecture: **Hyun Je Kim (Seoul National University College of Medicine, KR):** Building patients multiomics atlas in Korea
18:00	**Welcome coctail and dinner**
20:00	**Informal evening program (bowling, table soccer, swimming, etc)**

Tuesday – 29 July 2025

	Microbiome and inflammation **Chair: Hajir Ibraheim**
9:00	Keynote lecture: **Serre-Yu Wong (Mount Sinai, USA):** Tunneling through gut and skin: Perianal fistula in Crohn's disease
9:45	Expert talk 1: **Sun-Ho Lee (Sinai Health Toronto, CAN):** Longitudinal effect of the microbiome on IBD development
10:15	Expert talk 2: **Falk Hildebrand (Quadram Institute, UK):** Gastrointestinal disease through the lens of high-resolution metagenomics
10:45	**Tea/Coffee**
	Microbiome and inflammation **Chair: John Thomas**
11:15	Expert talk 3: **Federica Ungaro (San Raffaele Hospital, IT):** Host-microbiota interaction in IBD and its complications
11:45	Expert talk 4: **Szilvia Juhász (Hungarian Centre of Excellence for Molecular Medicine, HU):** The toxic relationship between bacteria and human cells
12:15	**Safak Bayram (Charité, Universitätsmedizin Berlin, DE):** Diet modulates colonic epithelial proinflammatory responses by influencing butyrate-producing microbiota
12:30	**Lunch**
14:00	**Teamwork – part 1** Getting know each other
14:30	**Teamwork – part 1** Presenting the problem to be solved
16:00	**Teamwork – part 1** Medieval team building competition, informal discussions in the meantime
19:00	**Special renaissance dinner**
21:00	**Poster session 1**
22:00	**Informal evening program**

Wednesday – 30 July 2025

	Disease models and mechanisms **Chair: Rachael Barry**
9:00	Keynote lecture: **Joana F. Neves (Kings College London, UK):** Immune-epithelial interactions govern intestinal health & disease
9:45	Expert talk 1: **Csaba Pál (Biological Research Center, HU):** Evolution of resistance to antibiotics in development promotes the rise of hypervirulent bacteria
10:15	Expert talk 2: **Patrick Varga-Weisz (University of Essex, UK):** Epigenetic mechanisms shaping colon inflammation
10:45	**Tea/Coffee**
	Disease models and mechanisms **Chair: Marek Ostaszewski**
11:15	Expert talk 3: **Eduardo Villablanca (Karolinska Institutet, SE):** Unraveling the molecular architecture of the intestinal barrier: Insights from spatial transcriptomics
11:45	**Gustavo Monasterio Ocares (Karolinska Institutet, SE):** Spatial transcriptomics reveals a novel salivary gland and a rheostatic gut-salivary glands axis during intestinal inflammation
12:00	**Rachael Barry (Imperial College, UK):** Proteases in the colorectal tumour microenvironment induce barrier damage and cancer cell signalling
12:15	**Deborah Jans (KU Leuven, BE):** Family matters: Understanding the genetic architecture of inflammatory bowel disease multiplex families
12:30	**Lunch**
14:00	**Teamwork – part 2** Discussing the problem to be solved
16:00	**Tea/Coffee**
16:30	**Catamaran race on the Danube, informal discussion in the meantime**
19:00	**BBQ Picnic Dinner in the Garden of the Hotel Visegrád**
21:00	**Poster session 2**
22:00	**Informal evening program**

Thursday – 31 July 2025

	Modeling and precision medicine **Chair: Dezső Módos**
9:00	Keynote lecture: **Kathryn Hamilton (University of Pennsylvania, USA):** Epithelial cell plasticity in the regenerating gut
9:45	Expert talk 1: **Mohieddin Jafari (University of Helsinki, FL):** When one is not enough: A systems medicine approach for combinatorial therapy in acute *myeloid* leukemia through stability/solubility alterations
10:15	Expert talk 2: **Marek Ostaszewski (University of Luxembourg, LU):** Systems biology diagrams: Interface between knowledge curation and computational modellingmodels
10:45	**Tea/Coffee**
	Modeling and precision medicine **Chair: Dénes Türei**
11:15	**Bence Szalai (Turbine Ltd, HU):** Benchmarking foundation cell models for post-perturbation RNA-Seq prediction
11:30	**Hratch Baghdassarian (MIT, US):** scLEMBAS: Context-aware signaling pathway modeling at single-cell resolution
11:45	**Luca Massimino (San Raffaele Hospital, IT):** The spatial code: Computational strategies for deciphering tissue microenvironments
12:00	**Christine Suh-Yun Joh (Seoul National University College of Medicine, KR):** Immune dysregulation and epithelial barrier dysfunction in ASCA-Positive ulcerative colitis
12:15	**Lunch**
14:00	**Presentations of teams (15 min / team + discussion)**
16:00	**Tee/Coffee**
16:30	**Grant writing seminar (Cláudio Nunes-Alves, Germinate Science Consulting)**
17:30	**Moderated panel discussion on: Women / Family in Science**
18:00	**Hunting animal show and refreshing drinks**
	Closing I Chair: Joana F. Neves
18:30	Closing Keynote: **Nick Powell (Imperial College London, UK):** Precision medicine persepctives based on computatational, *in vitro* and *in vivo* models
19:00	**Workshop Closing Feast in the Court of Foods Foods with** **Award presentation for teams and poster presenters**
21:30	**Informal evening program with music**

Poster session 1 – 29 July 2025

In silico approaches - Chairs: Dénes Türei, Bence Szalai, Mohieddin Jafari

Matteo Riva	**P-01**	Harnessing Internet-of-Things and Temporal Fusion Transformer to decode environmental impacts and predict relapses in chronic inflammatory disorders
Wing Koon	**P-02**	Exploring machine learning approaches to improve inflammatory bowel disease prediction
Bence Hajdú	**P-03**	Investigating ferroptosis and autophagy interactions through integrated database analysis
Luca Farkas	**P-04**	AutophagyNet Reveals Functional Non-Coding SNPs in Autophagy Pathways Associated with Crohn's Disease Genetic Architecture
Yufan Liu	**P-05**	Patient-specific network modelling reveals functional impact of non-coding snps in ulcerative colitis
Balázs Bohár	**P-06**	Rewired upstream signaling in IBD: The regulatory impact of non-coding SNPs

Host-microbe interactions - Chairs: Serre-Yu Wong, Eduardo Villablanca, Martina Poletti

Tahila Andrighetti	**P-13**	Functional programming of neutrophils by microbiota-derived acetate
Ema Mocsonokyova	**P-14**	Deciphering the microbiome–host crosstalk
Lejla Potari-Gul	**P-15**	Decoding cell type-specific host signalling modulation by microbial proteins & metabolites
Lena Weidert	**P-16**	Combining organoid and organ-on-chip technology for personalised host-microbiome interaction studies
EunHye Yoon	**P-17**	Mesenchymal–T cell interactions drive persistent inflammation in C. difficile–positive inflammatory bowel disease

Poster session 2 – 30 July 2025

Omics Analysis - Chairs: Marek Ostaszewski, Luca Massimino, Matthew Madgwick

Dezsõ Módos	**P-07**	Network propagation from regulatory SNPs through protein and gene regulatory networks reveals distinct patient clusters in inflammatory bowel disease
Yong Jun Kim	**P-08**	Single-cell transcriptomic analysis reveals Clusterin-expressing enteric neurons as immune modulators in inflammatory bowel disease
Luke Hanna	**P-09**	Single-cell transcriptomic analysis reveals upadacitinib-mediated modulation of immune cell states in perianal fistula
Rohan Sundramoorthi	**P-10**	A targeted metabolite array for inflammatory bowel disease
John Thomas	**P-11**	Unravelling the molecular landscape of anti-TNF failure in Ulcerative Colitis identifies MEK/ERK inhibitors as putative therapeutic candidates
Dénes Türei	**P-12**	OmniPath: prior knowledge for multi-omics analysis from 180+ databases

In vitro approaches - Chairs: Joana F Neves, Kathryn Hamilton, Liz Stewart

Stefania Cagliani	**P-18**	Exploring the function of MFSD2A in colorectal cancer-associated inflammation
Edvishka Dias	**P-19**	Investigating the role of bile acids in inflammatory bowel disease
Sandra Koigi	**P-20**	Imperial IBD Organoid Biobank
Inez Roegiers	**P-21**	Development of a high-throughput inflammation assay
Sabrina Nicolo'	**P-22**	Roseomonas mucosa as a potential driver of intestinal fibrosis in Crohn's disease: A multi-omic approach

Microbiome - Chairs: Patrick Varga-Weisz, Sun Ho Lee, Szilvia Juhász

Klara Cerk	**P-23**	Spatial metagenomics of the inflamed human gastrointestinal mucosal niche resolved at strain resolution.
Lejla Daruka	**P-24**	The effect of food additives on the gut microbiome
Carmela Errico	**P-25**	Investigating Caudovirales-induced molecular mimicry in Crohn's disease pathogenesis
Toby Lawrence	**P-26**	Rewiring host cells through metabolite-host interactions

ABSTRACTS OF KEYNOTE PRESENTATIONS

From network medicine to the foodome: The dark matter of nutrition

Albert-László Barabási

Center of Complex Networks Research, Northeastern University, United States

A disease is rarely a consequence of an abnormality in a single gene but reflects perturbations to the complex intracellular network. Network medicine offer a platform to explore systematically not only the molecular complexity of a particular disease, leading to the identification of disease modules and pathways, but also the molecular relationships between apparently distinct (patho) phenotypes. As an application, I will explore how we use network medicine to uncover the role individual food molecules in our health. Indeed, our current understanding of how diet affects our health is limited to the role of 150 key nutritional components systematically tracked by the USDA and other national databases in all foods. Yet, these nutritional components represent only a tiny fraction of the over 135,000 distinct, definable biochemicals present in our food. While many of these biochemicals have documented effects on health, they remain unquantified in any systematic fashion across different individual foods. Their invisibility to experimental, clinical, and epidemiological studies defines them as the 'Dark Matter of Nutrition.' I will speak about our efforts to develop a high-resolution library of this nutritional dark matter, and efforts to understand the role of these molecules on health, opening novel avenues by which to understand, avoid, and control disease.

Building patients multiomics atlas in Korea

Christine Suh-Yun Joh[1], Yong-Jun Kim[1], Eun-Hye Yoon[1], Tamas Korcsmaros[2], Seong-Joon Koh[3,4], Jong-Il Kim[5], **Hyun Je Kim**[1,5]

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[2] *Department of Metabolism, Digestion and Reproduction, Imperial College London, London, United Kingdom*
[3] *Seoul National University Hospital, Seoul, Korea*
[4] *Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea*
[5] *Genome Medicine Institute, Seoul National University College of Medicine, Seoul, Korea*

Immune-mediated diseases (IMDs) display complex cellular heterogeneity and tissue-specific immune responses, hindering mechanistic understanding. Despite advances in single-cell technologies, large-scale, multi-omic datasets across diverse IMDs remain scarce, particularly in East Asian populations. To address this, we established a standardized pipeline encompassing tissue processing, data generation, and integrative analysis, leveraging a nationwide hospital consortium in Korea. Since 2022, our lab has collected clinical specimens from over 2,000 patients diagnosed with 50 major IMDs, spanning multiple organs including skin, gut, lung, brain, heart, kidney, and liver. To date, we have generated 3,253 high-resolution multi-omic datasets, including single-cell RNA-seq (scRNA-seq), CITE-seq, and CyTOF, profiling both tissue and PBMC-derived immune cells. Spatial transcriptomics (GeoMx, Xenium) and spatial proteomics (MACSima) were also applied for integrative spatial profiling.

As illustrative examples, for gut diseases (e.g., IBD), we collected 418 gut tissues and 150 PBMC samples, with scRNA-seq conducted on 88 gut tissues and 11 PBMCs. For skin diseases (e.g., atopic dermatitis, psoriasis, alopecia areata), we obtained 86 skin tissues and 403 PBMCs, with scRNA-seq performed on 77 tissues and 100 PBMCs. Similar efforts are ongoing for other organs with matched controls. Cross-modal integration enables in-depth mapping of immune cell states, tissue-specific niches, and disease-associated circuits.

We present the first population-scale, multi-organ, multi-omic single-cell atlas of IMDs in the Korean population. This resource provides a comprehensive platform for discovering immune biomarkers, delineating pathogenic pathways, and identifying therapeutic targets. Ultimately, it enables precision medicine tailored to East Asian populations and promotes international collaboration in immune disease research.

Immune-epithelial interactions govern intestinal health & disease

Joana F Neves

King's College London, United Kingdom

Intestinal homeostasis relies on intricate interactions between epithelial, immune, mesenchymal, neural, and microbial components. Disruption of these networks contributes to the pathogenesis of Inflammatory Bowel Disease (IBD). Using advanced murine and human intestinal organoid co-culture systems, we investigated how epithelial-immune crosstalk—particularly involving Innate Lymphoid Cells (ILCs)—regulates intestinal health and disease.

We demonstrate that epithelial cells support the maturation of all ILC subsets, including ILC1, ILC2, ILC3, and NK cells, even in the absence of microbial cues or cytokine supplementation. In addition, organoid identity alone was sufficient to recapitulate tissue-specific ILC imprints.

We show ILC1s can drive extracellular matrix remodeling via TGF-β production, implicating them in IBD-associated fibrosis and cancer progression.

Finally, focusing on ILC3s, we reveal that these RORγt+ cells not only produce TGF-β but also activate latent TGF-β through mechanical and proteolytic mechanisms. This activation promotes regulatory T cell (Treg) differentiation via FoxP3 induction and enhances regenerative transcriptional programs in intestinal epithelial cells (IECs). While this pathway is conserved across species, the mechanisms of TGF-β activation differ between mice and humans, underscoring the importance of human models. Despite ILC3 depletion in inflamed IBD tissues, residual ILC3s retain *TGFB* expression and activation potential, highlighting the potential for ILC3s targeted cellular therapies as a new therapeutic approach for the treatment of IBD to promote both epithelial repair and regulatory T cell responses.

Together, our findings offer unprecedented insight into epithelial-driven ILC maturation and function, revealing new mechanisms of immune-epithelial crosstalk relevant to intestinal health and IBD.

Epithelial cell plasticity in the regenerating gut

Kathryn (Kate) Hamilton

Associate Professor of Pediatrics, Division of Gastroenterology, Hepatology, and Nutrition, Co-Director, Gastrointestinal Epithelium Modeling Program, Children's Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, United States

One of the most significant questions in the intestinal stem cell field is whether chronic inflammatory disease alters epithelial stem cell function to promote pathogenesis. Recent studies begin to address this question, identifying stem and progenitor cells as origins of metaplasia in inflammatory bowel disease (IBD) and other chronic gastrointestinal diseases. While compelling, prior studies infer but do not evaluate the function of disease-associated cell types describes. Our lab uses single-cell transcriptomic and epigenomic approaches in matched patient tissues and organoids to investigate epithelial gene expression and function in healthy versus Crohn's patients. We identify an inflammatory secretory progenitor (ISP) cell state present almost exclusively in patients with Crohn's disease compared to healthy subjects. ISPs exhibit gene expression profiles consistent with normal secretory progenitor cells but concomitantly express a suite of distinguishing pro-inflammatory genes. Mechanistically, ISPs exhibit open chromatin at ISP gene loci including around key regulatory regions. While ISP-specific genes are not expressed in intestinal stem cells, their chromatin is accessible in Crohn's disease stem cells suggesting that ISP genes are epigenetically poised in stem cells and subsequently transcriptionally activated in ISPs in the presence of inflammatory stimuli. Consistently, Crohn's disease colonoids exhibit sustained ISP gene expression that can be elicited further with pro-inflammatory cytokines or via co-culture with pro-inflammatory macrophages. In summary, we identify a disease-driven cell state, denoted the inflammatory secretory progenitor state, possessing transcriptional and chromatin features consistent with epigenetic memory and pathologic gene expression. Epigenetic changes begin in stem and progenitor cells and are coupled to enhanced responsiveness to inflammatory challenge in vitro. Our findings support evaluating epigenetic modifiers as therapeutic targets to break the vicious cycle of barrier failure and inflammation in inflammatory bowel disease.

ABSTRACTS OF EXPERT TALK PRESENTATIONS

Longitudinal effect of the microbiome on IBD development

Sun-Ho Lee

Sinai Health Toronto, Canada

Inflammatory Bowel Disease (IBD), especially Crohn's disease (CD) often arises from a prolonged preclinical phase, offering an unique opportunity for early detection and prevention. Leveraging the GEM Project, a global prospective cohort of >5,000 healthy first-degree relatives (FDRs) of individuals with CD, we have identified key biological signatures that precede IBD onset, including impaired gut barrier function, elevated anti-microbial antibodies, and distinct gut microbiome features. Using machine learning, we developed the GEM Integrative Risk Score (GEM-IRS), which incorporates demographic, clinical, and microbiome-based data—including taxonomic composition and microbial functional pathways—to predict incident IBD with high predictive performance (C-index 0.80). Subclinical inflammation and microbiome-based clusters further stratify risk, independent of genetics or demographics. Studies in multiplex families and offspring exposed to IBD during the perinatal period suggest that early-life environmental exposures have lasting impacts on intestinal permeability, microbiome composition, and disease risk. Germ-free mouse experiments validate the pathogenic potential of pre-IBD microbiota. This integrative approach provides a roadmap for precise risk stratification and paves the way for targeted interventions—ranging from diet to immune modulation—to intercept disease before clinical onset.

Gastrointestinal disease through the lens of high-resolution metagenomics

Falk Hildebrand

Quadram Institute Bioscience, Norwich Research Park, Norwich, United Kingdom

The human gut microbiome is central to our well-being and healthy ageing. The taxonomic diversity of the human gut microbiome is – compared to other microbiomes – relatively well characterized. However, at strain resolution the genome content between two bacteria of the same species can differ by more than 50%.

I will present the research in my group, that proposes a "genome-centric" approach to understanding gut microbiomes. Increase taxonomic resolution can thereby enable understanding of ecoevolutionary dynamics within the gut microbiome, as exemplified for the dispersal of gut bacteria among families and even countries, on the probiotic biasing of gut microbiomes to help Parkinson's Disease patients, and to investigate strain dynamics in Inflammatory bowel disease (IBD) patients. For the latter, I want to propose a new mechanism how gut biodiversity is lost and why this cannot be just as easily replenished.

Host-microbiota interaction in IBD and its complications

Federica Ungaro

I.R.C.C.S. Ospedale San Raffaele, Milano, Italy

Inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), are chronic inflammatory disorders of the gastrointestinal tract with rising global prevalence. While both share features of mucosal immune dysregulation, they diverge in their long-term complications: colitis-associated cancer (CAC) in UC and intestinal fibrosis in CD. Understanding the distinct molecular mechanisms driving these outcomes is key to preventing irreversible damage.

In UC, the severity and chronicity of inflammation are the strongest predictors of CAC, a condition with 60% higher cancer risk than the general population and worse prognosis than sporadic colorectal cancer. Recent findings identified the Hepatitis B Virus protein X (HBx) in the intestinal mucosa of 40% of UC patients. HBx reprograms epithelial cells into a stem-like, mesenchymal state, impairs barrier function, and drives DNA damage, accelerating tumorigenesis in vitro and *in vivo*. Its enrichment in CAC tissues suggests a potential role as a biomarker for malignant transformation.

In CD, over 50% of patients develop intestinal fibrosis, leading to strictures and frequent surgical intervention. Despite progress in anti-inflammatory therapies, fibrotic complications remain an unmet need. Emerging data implicate the gut microbiota in fibrosis progression independently of inflammation. Microbial profiling revealed enrichment of *Roseomonas mucosa* across multiple cellular compartments in fibrotic CD tissue. Fibroblasts exposed to *R. mucosa* lysates showed upregulation of profibrotic genes, suggesting that this bacterium may alter host transcriptional programs and promote fibrogenesis.

Together, these findings highlight the distinct microbial and viral triggers that shape the pathological trajectories of IBD. HBx may contribute to carcinogenesis in UC, while *R. mucosa* may drive fibrosis in CD. Targeting these interactions offers new avenues for biomarker discovery and personalized therapeutic strategies to prevent IBD-associated complications.

Evolution of resistance to antibiotics in development promotes the rise of hypervirulent bacteria

Csaba Pál

HUN-REN Biological Research Center. Hungary

Although several new antibiotics are in development, it's uncertain whether selecting for resistance during treatment will result in more virulent strains. In this study, we examine the impact of resistance evolution on virulence in four Gram-negative bacterial pathogens, with a focus on 20 antibiotics that have not yet been commercialized. Using multiple infection models, we discovered that several antibiotics with different modes of action can induce the evolution of hypervirulent bacteria, raising concerns. These bacteria displayed an enhanced ability to invade human epithelial cells and evade the innate immune system simultaneously. The mutations underlying these changes are present in natural bacterial populations and often alter lipopolysaccharide production, causing structural changes in the bacterial cell envelope. Our work may guide the safe clinical use of new antibiotics.

Epigenetic mechanisms shaping colon inflammation

Nathália Araújo[1], Mariane Font Fernandes[1], Sajad A. Wani[2], Kashaf Javed[1], Vinícius Nirello[1], Amanda R. Wasylishen[2], Naiara Beraza[3], Marco Aurélio Ramirez Vinolo[1], **Patrick Varga-Weisz**[1,4]

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Inflammatory bowel diseases (IBDs) are on the rise both globally, implying life style changes driving this trend, such as changes in diet which in turn affect microbiome composition. It is plausible that epigenetic mechanism that affect long term gene regulation through chromatin remodelling are involved in this phenomenon. Indeed, genome-wide association studies (GWAS) and related analyses have linked mutations in chromatin factors to the aetiology of IBDs (reviewed in ref. 1). We and others have shown that the microbiota affect the chromatin of the intestinal epithelium (reviewed in ref.2). We use mouse models to reveal how epigenetic processes shape the host-microbiota interaction and the inflammatory response in the gut. Using this approach, we have shown that a chromatin remodelling factor, SMARCAD1, is critical for the inflammatory response to microbes in the gut (ref. 3): mice where this factor is specifically deleted in the intestinal epithelium show a strongly diminished pathology response in a model of ulcerative colitis (Dextran Sodium Sulfate -DSS-mediated colitis). DAXX is a histone variant H3.3 chaperone that in embryonic stem cells opposes the function of SMARCAD1 (ref. 4). We show that intestinal epithelium specific deletion of DAXX leads to exacerbated colitis response and this is linked to a complete rewiring of histone H3.3 occupancy genome-wide. Thus, our work highlights the role of histone variants and chromatin factors in regulating the inflammatory response in the gut.

(1) Pereira GV, Varga-Weisz P. Dig Med Res 2024
(2) Fellows R, P Varga-Weisz P. Molecular metabolism 2020
(3) Kazakevych J. et al. Genome Biology 2020
(4) Navarro C et al. Nat Commun. 2020

Unraveling the molecular architecture of the intestinal barrier: Insights from spatial transcriptomics

Eduardo Villablanca

Karolinska Institutet, Stockholm, Sweden

űThe intestinal barrier is composed of a dynamic and complex network of cells essential for maintaining gut health and preventing disease. In this talk, I will explore the spatiotemporal dynamics of intestinal inflammation and healing, highlighting how spatial transcriptomics (ST) enables a high-resolution view of tissue organization and molecular activity over time. Using ST, we uncovered a previously unrecognized upper GI organ, cell-cell interactions, and a functional molecular regionalization of the colon, which is profoundly altered during inflammation and mucosal repair. Our analysis revealed distinct, spatially coordinated transcriptional programs that orchestrate localized inflammatory and healing responses. I will also highlight the translational relevance of these findings by demonstrating how specific transcriptomic modules align with molecular signatures of human disease, offering new insights into potential therapeutic targets in conditions such as IBD and colorectal cancer.

When one is not enough: A systems medicine approach for combinatorial therapy in acute myeloid leukemia

Mohieddin Jafari

University of Helsinki, Helsinki, Finland

Acute myeloid leukemia (AML) is a genetically diverse and aggressive blood cancer that remains a major therapeutic challenge. Its poor response to monotherapy and high relapse rates underscore the need for effective combination treatments. Yet, identifying optimal drug pairs is difficult due to the vast number of possible combinations and limited consideration of efficacy and toxicity in current computational methods. In this talk, I present a systems-level framework integrating network biology and proteomics to rationally design and mechanistically evaluate AML drug combinations. We built a bipartite network linking patient-derived tumor samples with drugs based on response profiling. Projecting this network into drug space produced a drug similarity network, revealing clusters with shared mechanisms, confirmed through protein target enrichment analysis. From these clusters, we selected drugs with high efficacy and low toxicity, testing combinations in AML samples. Two pairs—ruxolitinib-ulixertinib and sapanisertib-LY3009120—showed strong synergy and minimal toxicity. To uncover the mechanistic basis of these synergies, we developed CoPISA (Combinatorial Proteome Integral Solubility/Stability Alteration Analysis), a high-throughput proteomics workflow that identifies drug–protein interactions unique to combinations. CoPISA uncovered a new mechanistic concept—conjunctional inhibition—where drug pairs trigger cellular responses not seen with either agent alone, akin to an AND-gate logic. These effects disrupt AML-critical pathways, including DNA damage response, mitochondrial metabolism, RNA splicing, and SUMOylation. CoPISA also revealed synthetic-lethal vulnerabilities and selective targeting of key AML mutations such as TP53, DNMT3A, and NPM1. This approach offers a precision framework for rational drug pairing in AML and potentially other heterogeneous cancers.

Systems biology diagrams: interface between knowledge curation and computational modelling

Marek Ostaszewski

University of Luxembourg, Luxemburg

Complexity of human diseases remains a challenge for clinical and translational research, despite great progress in our understanding of molecular pathways governing various tissues and cell types, fuelled by enormous amounts of data generated at rapidly increasing pace. Often, the main obstacle becomes the expertise gap between clinical and experimental researchers defining the problem, and bioinformaticians and computational biologists, modelling it and analysing related data.

Systems biology diagrams help to address this challenge by describing biomedical knowledge in a standardised format that is human- and machine-readable. Diagrammatic representation of molecular mechanisms is a powerful tool that can establish a bridge between the domain experts and bioinformaticians. This, however, requires an ecosystem involving users, tools and protocols of best practice.

I will describe our experience with construction of different disease maps – knowledge repositories based on systems biology diagrams. A small introduction to the approach will include curation, data integration and modelling aspects. This will be illustrated on an example of establishing the community working on COVID-19 Disease Map. The abovementioned ecosystem will be described in detail, involving standards, knowledge bases, data and tool interfaces used to build it. Finally, I'll summarise our experience and outcomes achieved by the community, including the gains from the communication loop between domain experts, diagram creators, and computational biologists, established computational workflows and different endpoints for use of systems biology diagrams – from complex data visualisation to modelling multi-cellular systems.

ABSTRACTS OF SELECTED TALK PRESENTATIONS

Diet modulates colonic epithelial proinflammatory responses by influencing butyrate-producing microbiota

Şafak Bayram[1,2], Kimberly Hartl[1,2], Hilmar Berger[1], Marie Florence Kiefer[3], Michael Schupp[3], Michael Sigal[1,2]

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[2] *Berlin Institute for Medical Systems Biology (BIMSB), Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC), Berlin, Germany*

[3] *Institute of Pharmacology, Max Rubner Center (MRC) for Cardiovascular Metabolic Renal Research, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin, Germany*

The increasing prevalence of obesity poses a significant challenge to modern medicine and is intricately linked to a multitude of diseases. Experimental and clinical data have revealed that dietary alterations that promote obesity are linked to alterations in the gut microbiota. Conversely these dysbiosis states are associated with chronic inflammation, which is known to be a key constituent not only of inflammatory, but also malignant diseases in the gut and elsewhere. Despite the growing understanding of the importance of the microbiota for health, the mechanistic link between diet, gut dysbiosis and inflammation has not been fully elucidated.

High-fat diet (HFD) has been shown to induce alterations in gut microbiota, potentially leading to dysbiosis and contributing to the pathophysiology of obesity-related ailments. The aim of this study is to analyze HFD-associated changes in the colonic microbiota and to mechanistically dissect their impact on colonic inflammatory responses.

HFD-fed mice exhibited a substantial weight gain of 67% over a 13-week period. 16S-sequence analysis of the microbiota of HFD-exposed mice revealed notable shifts in composition and diversity, particularly a significant reduction in butyrate-producing bacteria. Butyrate is a SCFA that serves as a nutrient to colonocytes and has been proposed to influence various physiological functions in the gut. Assessment of stool samples via gas chromatography coupled to mass spectrometry indeed revealed a significant reduction in butyrate levels in HFD-exposed mice.

Examination of colonic tissue via immunofluorescence indicated a significantly enhanced immune cell infiltration in mice exposed to HFD, which was particularly apparent for macrophages, corroborated by the marker Iba1. This was associated with alterations in epithelial crypt organization and an increased activation of Nf-kB signaling in the epithelium. Exposure of epithelial cells in organoids to Lipopolysaccharide (LPS) caused Nf-kB activation and a massive expression of proinflammatory chemokines such as Cxcl1 and Cxcl2, that are known Nf-kB targets. Pretreatment of epithelial cells with butyrate significantly attenuated the proinflammatory response when exposed to LPS, indicating its ability to suppress proinflammatory epithelial responses.

These findings underscore the potential role of butyrate in mediating tolerance to the gut microbiota and highlight how its depletion, induced by dietary intervention, can lead to

heightened proinflammatory responses in the gut epithelium. Subsequent investigations are underway to discern the precise impact of butyrate on mucosal immunity and human health.

Spatial transcriptomics reveals a novel salivary gland and a rheostatic gut–salivary glands axis during intestinal inflammation

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Salivary glands, beyond their digestive role, respond to systemic cues to maintain homeostasis. Here, using spatial transcriptomics in mouse models of intestinal inflammation, we identified a previously unrecognized mucous salivary gland resembling sublingual glands, which we term the retropharyngeal salivary gland (RPG). Colitis induces transcriptomic changes in this RPG and concurrently triggers a transient and severe atrophy of submandibular glands (SMGs) in both sexes across multiple models of acute and chronic intestinal perturbations, but not in pulmonary or oral mucosal injury. SMG atrophy is linked to a surge of plasma cells in the gland, although these immune cells are not required for tissue loss. Parabiosis and vagotomy experiments ruled out blood-borne or vagal signals as drivers of SMG atrophy. Instead, betareceptor pharmacological sympathetic stimulation prevented colitis-induced atrophy, implicating a sympathetic gut–salivary gland circuit. Mechanistically, early intestinal injury dampens local sympathetic (norepinephrine) release in SMGs, thereby downregulating salivary epidermal growth factor (EGF) secretion. This EGF deficit triggers gland atrophy and reduces EGF delivery to the gastrointestinal lumen, modulating mucosal inflammation and potentially lowering the risk of inflammation-associated tumorigenesis during intestinal repair. These findings reveal a previously unknown sympathetic gut–salivary gland axis that dynamically calibrates EGF levels in response to intestinal inflammation, uncovering an adaptive mechanism that regulates tissue homeostasis and disease progression.

Proteases in the colorectal tumour microenvironment induce barrier damage and cancer cell signalling

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Over 16,000 people in the United Kingdom died of colorectal cancer in 2017 (CRUK), and alarmingly, prevalence is increasing among younger adults. Effective prevention, early diagnosis and timely treatment are essential to reducing this burden. Proteins that compromise colon barrier integrity are ideal candidates as early markers of colorectal cancer and therapeutic targets. The colon is a physical barrier between our mucosal immune system and ~38 trillion microscopic organisms in the lumen. Disruption of this barrier results in an inflammatory response to the microbial products creating an environment conducive for tumorigenesis. Little is known about what compromises barrier integrity. Proteases are enzymes which cleave proteins and are important for maintaining colonic homeostasis, including digestion. However, excessive protease activity can damage the intestinal barrier and trigger inflammation. In the colon, serine proteases are released from human and microbial cells into the lumen and collected by passing faeces-like content. By analysing post-operative luminal contents from cancer patients, I have found that the tumour microenvironment has a specific protease activity and endogenous inhibitor profile compared to contents from neighbouring tissue. Moreover, using gut-culture models our data demonstrates that human luminal contents associated with colorectal tumours induces mucosal barrier dysfunction that is dependent on serine protease activity. We have identified specific serine proteases within the tumour microenvironment that contribute to barrier dysfunction and promote the activation of cancer-associated signalling pathways. Therefore, targeting serine proteases either through chemical or endogenous inhibitors offers novel strategies for prevention and treatment of colorectal cancer.

Family matters: Understanding the genetic architecture of inflammatory bowel disease multiplex families

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Crohn's disease (CD) and ulcerative colitis (UC), the main forms of inflammatory bowel disease (IBD), arise from an inappropriate immune response against the gut microbiome, leading to chronic intestinal inflammation. The genetic architecture of IBD is diverse, with some monogenic forms, but most patients exhibit polygenic susceptibility. Some families show clustering of IBD for unknown reasons. This study investigates the contribution of known common and rare IBD risk variants in multiplex families.

We analyzed 65 IBD multiplex families (146 CD, 33 UC, 111 unaffected first-degree relatives), each with at least three affected first-degree relatives. A sporadic dataset (1,198 CD, 842 UC and 598 unrelated controls) served as reference. Polygenic risk scores (PRS) and rare variant polygenic risk scores (rvPRS) were computed using summary statistics from de Lange et al. (2017) and Sazonovs et al. (2022), respectively. RvPRS analyses were restricted to families with CD cases (n=56).

Affected relatives had significantly higher PRS than unaffected relatives (OR[95%CI]=1.45[1.15-1.84], p.adj=0.01), while rvPRS did not differ between these groups. PRS and rvPRS showed substantial heterogeneity across families: 27 (42%) families had higher PRS than sporadic cases, and 10 (15%) families fell below the controls' mean. For rvPRS, 6 (11%) exceeded the sporadic cases' mean and 2 (4%) families fell below the controls' mean. No correlation was seen between PRS and rvPRS at the individual or family level.

These findings highlight genetic heterogeneity in multiplex families, with independent contributions of common and rare variants. About half the families showed elevated genetic risk through high common and/or rare variant burden, while others may harbor undiscovered pathogenic variants. This emphasizes the need for tailored research approaches to risk stratification and genetic screening in familial IBD, and suggests that families with low PRS and rvPRS are prime candidates for novel variant discovery through sequencing.

Benchmarking foundation cell models for post-perturbation RNA-seq prediction

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Accurately predicting cellular responses to perturbations is essential for understanding cell behaviour in both healthy and diseased states. While perturbation data is ideal for building such predictive models, its availability is considerably lower than baseline (non-perturbed) cellular data. To address this limitation, several foundation cell models have been developed using large-scale single-cell gene expression data. These models are fine-tuned after pre-training for specific tasks, such as predicting post-perturbation gene expression profiles, and are considered state-of-the-art for these problems. However, proper benchmarking of these models remains an unsolved challenge.

In this study, we benchmarked two recently published foundation models, scGPT and scFoundation, against baseline models. Surprisingly, we found that even the simplest baseline model - taking the mean of training examples - outperformed scGPT and scFoundation. Furthermore, basic machine learning models that incorporate biologically meaningful features outperformed scGPT by a large margin. Additionally, we identified that the current Perturb-Seq benchmark datasets exhibit low perturbation-specific variance, making them suboptimal for evaluating such models.

Our results highlight important limitations in current benchmarking approaches and provide insights into more effectively evaluating post-perturbation gene expression prediction models.

scLEMBAS: Context-aware signaling pathway modeling at single-cell resolution

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Signaling pathways sense and propagate information from the extracellular environment

to dictate a cell's response[1], governing essential functions such as cell growth, differentiation, metabolism, and apoptosis. By integrating multiple signals, the underlying network of interacting components can achieve context-specificity and multicellular coordination[2]. However, signaling pathway activity is difficult to decipher due to the vast combinatorial space of possible interactions[2], the nonlinearity of these interactions[3], and pathway crosstalk[4].

Aims: Here, we develop a computational approach to model this complexity. Specifically, we set out to develop a model that provides genome-scale, mechanistic signaling pathway simulations across multiple contexts and at single-cell resolution. To do so, we adapt LEMBAS[5], which predicts transcription factor (TF) activity from ligand concentration in bulk omics, for single-cell predictions (scLEMBAS). scLEMBAS generalizes to multiple contexts (e.g., cell types, disease states, etc) and captures the heterogeneity within cell subpopulations.

Results: We demonstrate that scLEMBAS can accurately predict transcription factor activity in immune cell subpopulations subjected to cytokine stimulation. We implement a number of perturbation metrics that demonstrate that predictions recapitulate global and local single-cell distributions in feature space and univariately (i.e., differentially expressed TFs). In the future, we aim to generalize this to larger perturbational datasets and integrate cell-cell communication.

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The spatial code: Computational strategies for deciphering tissue microenvironments

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Spatial transcriptomics technologies, particularly 10x Visium, enable high-resolution analysis of gene expression while preserving tissue architecture. This presentation outlines a comprehensive computational workflow for deciphering complex tissue microenvironments. The process begins with SpaceRanger for initial data processing from FASTQ reads and H&E images, generating .h5 files. Subsequent analysis utilizes Seurat for loading, normalization, and crucial harmonization steps to correct for batch effects. Unsupervised clustering identifies distinct cellular populations, which are then spatially mapped back to the tissue. Further characterization involves identifying cluster-specific markers and performing functional enrichment analysis to elucidate associated biological pathways. The workflow integrates deconvolution techniques to infer cell type proportions within each spatial spot by leveraging reference single-cell data. Finally, advanced analyses explore ligand-receptor interactions to infer spatially proximal cell-cell communication and discuss emerging strategies for spatial microbiome analysis. This integrated computational approach provides robust insights into cellular heterogeneity, functional states, and intercellular communication within their native tissue context.

Immune dysregulation and epithelial barrier dysfunction in ASCA-Positive ulcerative colitis

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Inflammatory bowel disease (IBD) is a chronic gastrointestinal disorder characterized by immune dysregulation targeting the gut microbiota, leading to epithelial dysfunction and persistent inflammation. Anti-*Saccharomyces cerevisiae* antibody (ASCA), an anti-microbial antibody against commensal fungi, has been identified as a marker of poor prognosis in IBD patients, yet its detailed mechanisms contributing the poor clinical outcome remain poorly understood.

We analyzed 71 biopsies (43 inflamed, 28 non-inflamed) from 35 ulcerative colitis (UC) patients stratified by ASCA status at Seoul National University Hospital by using single cell RNA sequencing.

In ASCA-positive patients, we observed a significant reduction in type 3 innate lymphoid cells (ILC3) in non-inflamed mucosa, accompanied by reduced expression of *IL23R*, *IL18*, and *IL22*, suggesting ILC3 dysfunction and impaired gut homeostasis. Epithelial cells in these patients exhibited downregulation of tight junction-associated genes such as *TJP1*, *CLDN3*, and *CLDN4*, indicating compromised barrier integrity. In inflamed regions, cytotoxic Th1 cells displayed follicle-associated markers but reduced cytotoxicity and tissue-residency signatures, reflecting a shift toward a dysfunctional or follicular-like phenotype. Additionally, we observed a loss of IgA plasma cells and an expansion of IgG plasma cells, which might suggest a transition from protective mucosal immunity to systemic inflammatory responses.

These findings suggest that *S. cerevisiae* infection drives immunologic reprogramming characterized by weakened barrier integrity, heightened responsiveness to commensal antigens, and dysregulated antibody production.

POSTER ABSTRACTS

P-01 | Harnessing internet-of-things and temporal fusion transformer to decode environmental impacts and predict relapses in chronic inflammatory disorders

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Changes in the gut barrier and intestinal dysbiosis have been widely recognized as results of environmental stressors, playing a role in the development of ulcerative colitis (UC) and type 1 diabetes (T1D). However, the full range of environmental exposures affecting patients, which may disrupt gut and microbiota balance, is still not fully understood. This research aims to identify environmental factors contributing to chronic inflammation in the intestines and peripheral organs by utilizing Internet-of-Things (IoT) technologies and artificial intelligence (AI) methodologies, which have demonstrated efficacy in diagnostic assistance and prognosis prediction across various medical fields, including gastroenterology. By collecting real-time data on various parameters, such as diet, smoking, physical activity, and weather, through wearables and a user-friendly WebApp, we propose to develop a Temporal Fusion Transformer (TFT), a novel and robust AI model for multi-horizon and multivariate time series forecasting applications. The substantial volume of data, combined with this model, will enable us to capture complex temporal patterns and predict which environmental factors most significantly influence patient conditions and the timing of potential relapses. Finally, this project aims to uncover new preventive and therapeutic approaches, improving existing protocols for managing and preventing these conditions, ultimately enhancing patient outcomes and quality of life.

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P-02 | Exploring machine learning approaches to improve IBD prediction

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Background: Inflammatory bowel disease (IBD) refers to a series of chronic diseases affecting the gastrointestinal tract, with many studies noting a strong shift in the gut microbiota of patients. Understanding the taxonomical and functional differences of a disease-associated microbiome could lead to novel methods of diagnosis. However, studies often apply 16S sequencing, limiting resolution to the genus level, and masking functional differences that are found at higher levels. This can be resolved using whole genome shotgun sequencing (WGS) instead. We hypothesize that strain-level information reflects characteristics of bacteria more adapted to a diseased environment, thus improving predictability for IBD when used within supervised machine learning (ML) algorithms.

Aims: This study investigates methods of predicting IBD that incorporate strain-resolved metagenomics.

Methods: Public WGS data from 13 cohorts were metagenomically assembled and strain resolved using MG-TK. Random Forest models were then trained on abundances at different taxonomic levels and assessed by 5-fold and leave-one-cohort-out (LOCO) cross validation (CV). Strain phylogenies were used to derive a distance-based metric to apply to models.

Results: As resolution increases, so does the performance of ML models, plateauing at genus and species level at ROC-AUC values >=0.9 using 5-fold CV, but lower at 0.8 when using the more conservative LOCO-CV. Comparing important features between different cohorts identified a heterogenous set of taxa important in the predictions. Strong confounding factors affect the predictability of disease, therefore, no generalizable signature was found, reflecting the heterogenous nature of IBD dysbiosis. Strain-resolved phylogenies show promise as a replacement of taxonomic abundance tables, yielding similar performances. With further development to fully utilise strain information, performances of ML models may improve and identify novel associations.

P-03 | Investigating ferroptosis and autophagy interactions through integrated database analysis

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Ferroptosis is an iron-dependent, regulated form of cell death characterized by lipid peroxidation, reactive oxygen species (ROS) accumulation, and loss of redox homeostasis. It is morphologically, biochemically, and genetically distinct from other cell death mechanisms. During ferroptosis, key observable phenomena include the accumulation of labile iron, peroxidation of polyunsaturated fatty acids (PUFAs), and excessive production of ROS that mediate further reactions causing chromatin condensation defects, increased membrane density, and outer cell membrane rupture.

Two pathways of ferroptosis have been identified: an extrinsic pathway characterized by increased iron uptake and decreased cysteine/glutamate uptake, and an intrinsic pathway involving the inhibition of glutathione peroxidase 4 (GPX4), a crucial antagonist of ferroptosis that maintains redox homeostasis. Ferroptosis has been implicated in several diseases, including neurodegeneration and inflammatory bowel disease (IBD).

Accumulating evidence suggests a complex interplay between ferroptosis and autophagy; however, the precise molecular interactions between these pathways remain unclear. To address this, we have integrated several existing ferroptosis-related databases into a standardized resource that allows direct comparison with the autophagy-specific interaction database, AutophagyNetDB. By analyzing the overlap between these datasets, we aim to identify key regulatory nodes linking ferroptosis and autophagy, providing new insights into their crosstalk and potential therapeutic implications.

P-04 | AutophagyNet reveals functional non-coding SNPs in autophagy pathways associated with Crohn's disease genetic architecture

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Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), is a complex inflammatory disorder with a strong genetic component, particularly implicating autophagy-related pathways. Autophagy is a critical cellular process for maintaining homeostasis and immune regulation, and its dysregulation has been closely linked to CD pathogenesis. During my PhD, I developed AutophagyNet, a comprehensive, multi-layered database dedicated to autophagy regulation, integrating over 600,000 experimentally validated interactions across 34 core autophagy proteins. The database includes regulatory information from 829 transcription factors, 609 miRNAs, and extensive protein–protein interaction networks, providing a valuable resource for systems-level investigations into autophagy in disease contexts.

Utilizing AutophagyNet, I conducted a focused analysis of single nucleotide polymorphisms (SNPs) within autophagy-associated genes to elucidate the contribution of non-coding variants to IBD susceptibility. Machine learning analysis of SNP profiles from a CD patient cohort identified five distinct genetic clusters, each enriched for specific biological pathways. Notably, Toll-like receptor (TLR) signaling and neuroimmune interaction pathways emerged prominently in certain clusters, underscoring heterogeneous mechanisms by which autophagy may influence CD pathophysiology. Among these, non-coding SNPs regulating ATG16L1 were found to modulate transcription factor binding and chromatin accessibility—mechanisms often overlooked in favor of coding variants in prior studies.

Integration of SNP-based regulatory data with transcriptomic profiles further revealed cell-type-specific effects, particularly in epithelial and immune cells, linking autophagy-related expression changes to gut barrier integrity and immune responses. These findings highlight the significance of non-coding genetic variation in autophagy regulation and its impact on disease heterogeneity. This work not only advances our understanding of autophagy in IBD but also lays the groundwork for functional validation of key SNPs, exploration of gene–environment interactions, and the development of personalized therapeutic strategies. AutophagyNet will continue to support these efforts, offering a foundational platform for research into autophagy-related disorders beyond IBD.

P-05 | Patient-specific network modelling reveals functional impact of non-coding SNPs in ulcerative colitis

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Genome-wide association studies (GWAS) have identified numerous non-coding single nucleotide polymorphisms (SNPs) associated with ulcerative colitis (UC), yet their functional consequences in disease incidence and progression remain largely unexplored. Here, we applied the integrated single nucleotide polymorphism network platform (iSNP) to investigate the downstream impact of non-coding SNPs on signalling and gene regulatory networks in UC. Using genotype data from 452 UC patients in the etrolizumab phase 3 clinical trial, we constructed patient-specific signalling and gene regulatory networks to identify functionally distinct network modules. These modules were enriched in key molecular processes relevant to UC, including NFkB signalling and cell cycle. Unsupervised clustering of patient-specific networks stratifies patients into distinct subgroups, which exhibit significant differences in gene expression and clinical outcomes, including disease severity and treatment response. Our approach enables the identification of patients subsets based on their disease-associated SNPs fingerprints and uncovers distinct disease subgroups by coalescing GWAS signals that perturb downstream signalling, providing a mechanistic framework for understanding UC heterogeneity and guiding precision medicine strategies. This study underscores the value of network-based methodologies in elucidating genotype-phenotype relationships in complex diseases.

P-06 | Rewired upstream signaling in IBD: The regulatory impact of non-coding SNPs

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Inflammatory bowel disease (IBD) is strongly associated with non-coding single nucleotide polymorphisms (SNPs), many of which disrupt transcription factor (TF) binding sites. These alterations can rewire regulatory networks by changing which upstream signaling pathways control gene expression. While the downstream consequences of IBD-associated SNPs are well studied, their impact on upstream signals remains poorly understood.

Aims: We aimed to investigate how IBD-associated non-coding SNPs alter the landscape of upstream signaling in a patient-specific manner. By focusing on the regulatory rewiring caused by disrupted TF binding, we investigated how genetic variation contributes to disease pathogenesis through altered incoming signals.

Results: Using a systems genomics pipeline we developed, and genotype data from 2,636 IBD patients, we predicted TF binding changes driven by disease-associated SNPs. Functional annotation of these TFs revealed widespread rewiring of upstream signals in IBD patients compared to healthy conditions. Despite genetic heterogeneity, we identified consistently altered pathways across patients, including pro-inflammatory signaling, epithelial barrier dysfunction, stress responses, and antiviral defenses. We observed 144 gained and 138 lost upstream signals in ulcerative colitis (UC) and Crohn's disease (CD) patients, respectively, with 95 shared between the two. These findings suggest that, regardless of individual SNP profiles, IBD patients converge on a common set of signaling disruptions.

P-07 | Network propagation from regulatory SNPs through protein and gene regulatory networks reveals distinct patient clusters in inflammatory bowel disease

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Inflammatory bowel disease (IBD) is a complex disease with poorly understood pathogenesis involving immune, genetic and microbial components. Network biology offers a framework to integrate these distinct layers of disease biology.

Recently, we developed the integrated single nucleotide polymorphism (SNP) network platform which predicts the effect of SNPs on gene regulatory elements. Applying this approach to genomic data from 1,695 Crohn's disease (CD) and 941 ulcerative colitis (UC) patients, we used heat diffusion-based network propagation to trace the effects of regulatory SNPs through protein-protein interaction (PPI) networks and into gene regulatory networks (GRNs).

This multi-layer propagation enabled the stratification of patients into distinct clusters, characterised by key transcription factors, including STAT3, NFKB1, and ETS2—clustering that was not possible using PPIs or SNPs alone. Leveraging a large single-cell RNA-seq dataset in CD, we showed that these regulatory network-defined clusters align with cell type-specific differentially expressed GENES distinguishing between colonic and ileal CD. Furthermore, using an independent bulk transcriptomic dataset in UC, we demonstrated how clusters correspond with response to anti-IL12/IL23 (ustekinumab) treatment .

Our results highlight the importance of incorporating gene regulatory networks—beyond PPIs—for patient stratification in IBD. This integrative approach offers a promising direction for network-based precision medicine.

P-08 | Single-cell transcriptomic analysis reveals Clusterin-expressing enteric neurons as immune modulators in inflammatory bowel disease

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The enteric nervous system (ENS) plays a critical role in regulating gut motility, secretion, and barrier function. Recent studies suggest that the ENS closely communicates with the intestinal epithelium, immune system, microbiota, and central nervous system, forming an interconnected network that helps maintain gut homeostasis. However, the contribution of enteric neurons to immune regulation remains poorly understood.

In this study, we aimed to investigate the role of enteric neurons in the inflamed intestinal environment based on the hypothesis that they contribute to immune cell regulation in human Inflammatory bowel disease (IBD). To achieve this, we conducted single-cell RNA sequencing (scRNA-seq) analysis using human intestinal biopsy samples obtained via endoscopy from 45 individuals.

We analyzed 91,549 cells after quality control and found that the *CLU* gene was predominantly expressed in an enteric neuron cluster. Based on this observation, we focused our downstream analyses on this population. We found that *IL32* and *CD74* were upregulated in inflamed tissues, and ligand–receptor analysis revealed increased *CCL2* expression under inflammatory conditions. These findings suggest that enteric neurons may contribute to chronic mucosal inflammation in IBD. They may promote the recruitment of pro-inflammatory immune cells, such as T helper 1 (Th1), T helper 17 (Th17), $CD8^+$ T cells, and $CCR2^+$ monocytes, through cytokine and chemokine signaling.

Our study suggests that *CLU*, which is highly expressed in enteric neurons, could be a canonical marker candidate in gut scRNA-seq data. In addition, these findings suggest that the nervous system may play a role in intestinal inflammation and that CLU-expressing neurons could be considered a therapeutic target.

P-09 | Single-cell transcriptomic analysis reveals upadacitinib-mediated modulation of immune cell states in perianal fistula

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Background:

Perianal fistulising Crohn's disease (pfCD) is a severe, treatment-resistant phenotype of inflammatory bowel disease (IBD), characterised by the formation of fistulae connecting the anorectal canal to the perianal skin. Management involves combined surgical and medical care, with anti-TNF agents currently considered the gold standard; however, fistula remission is achieved in only ~35–40% of patients at 1 year. Janus kinase (JAK) inhibitors, particularly the selective JAK1 inhibitor upadacitinib, have emerged as promising alternatives. We investigated the impact of upadacitinib on fistula-resident immune cells using single-cell RNA sequencing (scRNA-seq).

Methods:

Fistula curettage samples were collected from 12 pfCD patients and 7 non-Crohn's (idiopathic perianal fistula) controls. CD45+ immune cells were isolated via enzymatic digestion, density centrifugation, and magnetic separation. All samples were cultured in RPMI media for 12 hours prior to sequencing. In 5 pfCD donors, parallel cultures were treated with or without 1 μM upadacitinib during this incubation period to assess treatment effects. All samples subsequently underwent live-cell sorting and scRNA-seq. Cell type annotation was performed, and cytokine response signatures were inferred by integrating previously published gut organoid transcriptomic data (Pavlidis et al., Cell Rep, 2022). Pathway analysis was performed using PROGENy and gene set enrichment analysis (GSEA).

Results:

Twenty distinct immune cell populations were identified. Interferon-gamma response signatures were markedly enriched in pfCD compared to non-Crohn's samples, across T lymphocyte, B cell, and myeloid subsets. PROGENy analysis revealed heightened JAK-STAT signalling in pfCD immune cells. Treatment with upadacitinib significantly attenuated JAK-STAT pathway activity across multiple lineages. GSEA corroborated these findings, showing downregulation of interferon-alpha and -gamma associated gene sets following treatment.

Conclusion:

Our data support increased interferon-driven and JAK-STAT-mediated immune activation in pfCD. In vitro upadacitinib treatment led to consistent suppression of these inflammatory programs, providing single-cell evidence of its mechanistic impact. To our knowledge, this is the first single-cell transcriptomic study of upadacitinib in pfCD. These findings support further

clinical investigation of JAK1 inhibition as a second-line or potentially first-line therapy in pfCD, with the potential to improve outcomes in this difficult-to-treat IBD subset.

P-10 | A targeted metabolite array for inflammatory bowel disease

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Metabolites such as short chain fatty acids (SCFA), carboxylic acids, amines and amino acids have previously been identified as potential indicators of inflammatory bowel disease (IBD). We explored whether urine, serum and stool from ulcerative colitis and Crohn's disease patients can be differentiated from healthy controls using a concise panel of metabolites.

We quantitated 33 metabolites (SCFA, carboxylic acids, amines and amino acids) in three biofluids: serum, urine, and stool samples using ultra-high performance liquid chromatography tandem mass spectrometry. Univariate, multivariate, correlations and receiver operating characteristic curve (ROC) were performed to differentiate between UC and CD from healthy controls as well as to determine the best metabolomic predictors of the disease.

Sixty participants (20 ulcerative colitis, 20 Crohn's disease and 20 healthy controls) were recruited. Multivariate analysis of the targeted metabolome from urine, serum and stool samples provided a distinct separation between healthy controls and IBD patients (OPLS-DA: $R2X \geq 0.52$, $R2Y \geq 0.5$ and $Q2 \geq 0.4$, $p < 0.0001$) (ROC curves: $AUC \geq 0.85$, $p < 0.05$). However, differentiation between ulcerative colitis and Crohn's disease was not evident in any of the analysed biofluids. Univariate analysis showed that urine presented fourteen metabolites that significantly ($p < 0.05$) differentiated between ulcerative colitis from Crohn's disease patients compared to two in serum (betaine and kynurenine) and none in stool.

This targeted metabolite array provides a streamlined, focused method of distinguishing inflammatory bowel disease from healthy patients across multiple biofluids. This metabolite panel could be used to investigate metabolite pathways and the analysis of simultaneously obtained biosamples facilitates understanding of the functionality of metabolic changes in IBD.

P-11 | Unravelling the molecular landscape of anti-TNF failure in ulcerative colitis identifies MEK/ERK inhibitors as putative therapeutic candidates

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Background:

Anti-TNF agents are frequently positioned as first-line biologics in ulcerative colitis (UC), but up to 70% of patients fail to respond. Patient who have failed anti-TNF therapies exhibit reduced response rates to subsequent advanced therapies. However, the mechanistic basis of anti-TNF failure remains poorly understood. This study aimed to investigate the molecular landscape underpinning anti-TNF failure in UC patients.

Methods:

Pre-treatment mucosal microarray profiles of 275 anti-TNF failure and 262 anti-TNF naïve UC patients with moderate-to-severe disease from the UNIFI phase 3 trial were analysed. Differential gene expression, pathway enrichment, cellular deconvolution, gene regulatory network (GRN), upstream signalling and connectivity map analyses were performed.

Results:

Gene set enrichment analysis revealed upregulation of multiple extracellular matrix (ECM)- and stroma-related pathways in anti-TNF failed patients compared to anti-TNF naïve patients. PROGENy pathway perturbation analysis indicated increased activity of EGFR, MAPK, and PI3K pathways in anti-TNF failed patients. Cellular deconvolution analysis using xCell revealed increased stromal cell and reduced T cell abundance in the colonic mucosa following anti-TNF failure. GRN analysis suggested that transcriptional dysregulation may underlie these cellular and functional changes, with MAPK3 (ERK1) and CDK2 identified as key upregulated upstream signalling proteins. Connectivity map analysis using the iLINCS database revealed compounds targeting the MAPK pathway, particularly MEK/ERK inhibitors, as promising candidates to counteract the transcriptomic landscape associated with anti-TNF failure.

Conclusion:

Anti-TNF failure in UC patients is characterised by remodelling of the colonic stroma and ECM, which is underpinned by upstream signalling and transcriptional dysregulation. MEK/ERK inhibitors are appealing drug candidates for overcoming anti-TNF failure in UC.

P-12 | OmniPath: prior knowledge for multi-omics analysis from 180+ databases

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OmniPath is a molecular biology database combining more than 180 original resources. It covers a broad variety of data, including signalling, metabolic, gene regulatory and miRNA networks, along with rich annotations of protein and gene function, structure, localization. OmniPath is publicly available by a web API (omnipathdb.org), with convenient access from R and Python by dedicated packages. Thanks to its integration with the DecoupleR and AnnData packages, it seamlessly supports transcription factor and pathway activity inference from bulk or single cell transcriptomics. Its literature curated network of activatory and inhibitory molecular interactions is routinely applied for causal reasoning by the software CARNIVAL and COSMOS, deriving mechanistic insights from transcriptomics or multi-omics data. OmniPath also features comprehensive knowledge about intercellular signalling which, connected to the LIANA module, enables easy inference of cell-cell communication from single cell transcriptomics. These are only a few examples for the applications of OmniPath's diverse data. In the poster we also give an overview of our ongoing works, which include database development for metabolomics and microbiomics, major extensions of our web API, and interfaces for LLMs.

P-13 | A targeted metabolite array for inflammatory bowel diseaseFunctional programming of neutrophils by microbiota-derived acetate

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Neutrophils are essential components of innate immunity, involved in antimicrobial defense, inflammatory resolution, and tissue repair. They are produced in the bone marrow and released into the blood once mature. This process involves transcriptional and metabolic programming that define distinct neutrophil functional phenotypes. The gut microbiota plays a key role in shaping it through its metabolites, particularly, the short-chain fatty acids (SCFAs). Among them, acetate is the most abundant and acts through the G-protein coupled receptor FFAR2 (GPR43), which is expressed in myeloid progenitors and mature neutrophils.

Aims: This project aims to investigate how acetate–FFAR2 signaling influences neutrophil development and function. Our previous data indicate that acetate promotes the emergence of neutrophils with a regulatory and protective phenotype during intestinal inflammation, and that this effect is abolished in Ffar2-deficient mice. To explore the molecular mechanisms, we analyzed single-cell RNA sequencing data from bone marrow and blood neutrophils of wild-type and Ffar2 knockout mice treated with acetate.

Results: The dataset showed high quality, with over 4,000 cells per sample, broad gene coverage (~23,000 genes detected), and good transcript complexity (medians of ~1,400 genes per cell). After filtering and correction, informative content was preserved. Our preliminary findings show that we captured myeloid cells at different maturation stages in the bone marrow, from precursor cells (promyelocytes, G1), myelocytes (G2), band cells (G3) to mature neutrophils (G4). In blood, we mainly observed neutrophils in mature stages (G5a, G5b and G5c), matching the expected neutrophil cycle. We also detected differential gene expression between wild-type and knockout cells, with changes related to inflammation and maturation. Together, our preliminary findings suggest that Ffar2-signaling may impact neutrophil transcriptional activity and phenotype.

P-14 | Deciphering the microbiome-host crosstalk

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The human microbiome, often called the "hidden organ," comprises the collective genomes of microorganisms living in the gut, skin, lungs, and oral cavity. These microbes produce diverse metabolites that can modulate host physiology by interacting with human proteins, mimicking drug–receptor interactions. Cheminformatics approaches can help elucidate the biological activity of these gut-derived molecules by predicting their protein targets and physiological effects.

We applied Extended Connectivity Fingerprints (ECFP4) and Tanimoto similarity clustering to compare the chemical space of microbial metabolites, natural products, and approved drugs. Our results show that microbial metabolites partially overlap with drug-like chemical space, suggesting potential bioactivity.

To assess this further, we used Prediction IncluDinG INactivity (PIDGIN), a structure-based machine learning model trained on ChEMBL and PubChem bioactivity data, alongside XGBoost classifiers. This model uses molecular fingerprint to predict binary activity against human targets. One notable example is phenylacetylcarnitine, a microbiome derived metabolite elevated in individuals with cardiometabolic disease, which was predicted to bind the Muscarinic Acetylcholine Receptor M2R, a key cardiovascular target. Molecular docking supports its potential interaction with M2R.

This study highlights how computational tools can uncover novel microbiome–host interactions. While experimental validation remains essential to confirm predicted bioactivities, these predictions linking microbial metabolites to human receptors and disease pathways open new avenues for therapeutic discovery.

P-15 | Decoding cell type-specific host signalling modulation by microbial proteins & metabolites

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The molecular crosstalk between host and microbiota is mediated by microbial proteins and metabolites that modulate host cell signalling. Decoding how these signals rewire host pathways across different cell types is a major challenge in systems biology and essential for understanding immune regulation, tissue integrity, and inflammation.

We present an update on the MicrobioLink pipeline that integrates host-microbe protein-protein interactions with metabolite-receptor connections in a unified framework. This development addresses the lack of standardised metabolite–host interaction resources, enabling integration of diverse molecular signals into host signalling networks.

Building on structural biology advancements, we incorporated AIUPred, a deep learning-based tool, into MicrobioLink to predict binding interfaces and model domain–motif interactions in 3D, providing confidence-scored, mechanistically grounded hypotheses.

We applied the enhanced MicrobioLink to analyse microbial extracellular vesicles (EVs) and their impact on gut-associated host cells under inflammatory conditions. In Goblet cells, short-chain fatty acids activating FFAR2, together with EV-derived proteins, influence mucin secretion and modulate cytokine release, affecting the epithelial barrier. In myofibroblasts, butyrate-activated HCA2 and vitamin-related pathways converge with microbial proteins to reshape wound healing and ECM remodelling, central to fibrosis. In dendritic cells, kynurenic acid and other tryptophan-derived metabolites, together with bacterial effectors, modulate NF-κB signalling and antigen presentation, reshaping immune responses.

These findings show how microbial metabolites and proteins coordinate cell type-specific signalling and immune outcomes. MicrobioLink provides a scalable tool for mechanistic modelling of host-microbe interactions, supporting hypothesis generation, target discovery, and microbiota-based therapeutic development.

P-16 | Combining organoid and organ-on-chip technology for personalised host-microbiome interaction studies

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The gut microbiome is linked to numerous diseases, yet patient-specific host-microbiome interactions remain poorly studied due to a lack of personalised models. Conventional cell culture does not recapitulate individual-specific responses and fails to support coculture between human cells and anaerobic gut bacteria. Organoids and organ-onchips present a promising new in vitro approach, providing a simplified but accurate representation of human physiology, experimental controllability, and efficiency.

We present the integration of patient-derived intestinal cells into our gut-on-chip model, known as Human Microbial Crosstalk (HuMiX). Thanks to an oxygen-nitrogen gradient and continuous fluid flow, the HuMiX model supports the coculture of human intestinal epithelial cells (previously: cell lines) and gut bacteria. To mimic a patient's intestinal epithelium, we grew organoids derived from the healthy colonic tissue of a patient as differentiated 2D monolayers in the HuMiX. We characterised the monolayers in the absence of bacteria. The barrier formation was monitored with integrated TEER electrodes. Furthermore, we assessed the presence of the main intestinal epithelial cell types via immunostaining and gene expression analysis (qPCR). The results were compared to organoid monolayers grown in cell culture inserts. As a proof-of-concept, we performed a 24-h coculture with the probiotic strain, *Lacticaseibacillus rhamnosus* GG, and measured the effect of the probiotic on the epithelial barrier. In a next step, we will perform RNA-seq and metabolomics for an in-depth characterisation and benchmarking of our system.

The integration of patient-derived organoids into the HuMiX model enhances its physiological relevance and patient specificity, paving the way for a personalised platform to coculture human and bacterial cells of the gut under physiologically representative conditions.

P-17 | Mesenchymal-T cell interactions drive persistent inflammation in *C. difficile*-positive inflammatory bowel disease

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Clostridium difficile infection (CDI) represents a significant complication in patients with inflammatory bowel disease (IBD), often arising from prolonged use of systemic antibiotics. The presence of CDI is associated with worsened clinical outcomes in IBD. Despite its clinical significance, the mechanisms by which *C. difficile* drives IBD pathogenesis remain largely unknown, underscoring the need for immunologically targeted treatments beyond conventional vancomycin. In this study, we utilized single-cell RNA sequencing (scRNA-seq) to analyze intestine biopsy samples from 35 patients with ulcerative colitis (UC) or Crohn's disease (CD). Patients testing positive for *C. difficile* infection were identified by detecting C. difficile genes via polymerase chain reaction (PCR).

We hypothesized that the inflammatory environment induced by C. difficile plays a key role in sustaining chronic inflammation through interactions between mesenchymal cells and T cells. Our observations revealed that C. difficile-positive patients showed elevated IL-1 expression, which known to be correlated with increased recruitment of neutrophils, subsequently driving higher frequencies of inflammatory monocytes/macrophages and T follicular helper (Tfh) cells. In addition, signaling pathways involving IL-2 and CXCL12 were upregulated in C. difficile-positive samples, especially in mesenchymal cells between T cells, contributing to impaired wound healing process. These findings suggest that *C. difficile* infection contributes to the interaction between mesenchymal cells and T cells which persist inflammation is maintained in IBD patients.

P-18 | Exploring the function of MFSD2A in colorectal cancer-associated inflammation

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The intrinsic connection between inflammation and tumor promotion is well-established in colorectal cancer (CRC), where chronic inflammation, like ulcerative colitis (UC), plays a significant role in intestinal carcinogenesis. UC patients are at increased risk of developing CRC, reinforcing the connection between inflammation and cancer. Previous studies from our laboratory revealed that UC patients with active inflammation have impaired production of inflammation-resolving DHA-derived metabolites due to a defect in the endothelial Major Facilitator Superfamily Domain containing 2A (MFSD2A).

Given the MFSD2A's role in reducing colonic inflammation, we hypothesize it also counteracts colorectal cancer-associated inflammation.

Human Intestinal Microvascular Endothelial Cells (HIMEC) isolated from CRC and healthy samples were transduced with lentiviruses carrying GFP-tagged MFSD2A (MFSD2A-OE), GFP control, MFSD2A-targeting shRNAs (shMFSD2A), or scramble control (shCTRL), and analyzed using transcriptomics and lipidomics. CRC HIMEC exhibited a pro-resolving lipidomic profile linked to higher MFSD2A expression, but gene expression analysis revealed a pro-inflammatory profile, suggesting that MFSD2A alone is insufficient to fully induce a pro-resolving phenotype. Loss of function experiments confirmed MFSD2A's role in balancing pro-inflammatory and pro-resolving signals in CRC. Co-culturing Caco-2 cells with MFSD2A-OE CRC HIMEC reduced tumor cell proliferation, and an orthotopic CRC model showed that mice injected with Caco-2/MFSD2A-OE CRC HIMEC developed smaller, lighter tumors, with increased pro-resolving lipid release. Flow cytometry indicated enhanced M2 macrophage polarization, suggesting a shift toward a pro-resolving immune response.

These findings imply that MFSD2A may counteract colorectal cancer-associated inflammation by promoting a balanced pro-inflammatory and pro-resolving environment.

P-19 | Investigating the role of bile acids in inflammatory Bowel disease

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The delicate balance of intestinal homeostasis hinges on an intricate network of interactions between the gut microbiome, intestinal epithelial cells, and the host's immune system. Disruption of this balance impairs barrier function and immune regulation, contributing to chronic inflammation, a characteristic of inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC).

Recent studies have shown that IBD patients have an increased primary bile acid (PBA) and a reduced secondary bile acids (SBA) composition. However, the impact of this shift on intestinal homeostasis and disease pathogenesis remains unclear. In parallel, defective autophagy which is essential in maintaining epithelial integrity has also been linked to IBD. Impaired autophagy can lead to decreased pathogen clearance, heightened inflammation, and epithelial dysfunction. Yet, the mechanisms by which bile acids influence autophagy in the colonic epithelium, and their contribution to IBD-associated inflammation, is poorly understood.

To address these gaps, my project has two primary aims. First, I will investigate how bile acids regulate intestinal homeostasis using intestinal organoids by assessing the differential effects of PBAs and SBAs on epithelial barrier integrity, inflammatory responses, and mucus production. To achieve this, I successfully established intestinal organoid-derived monolayers on Transwell inserts and conducted preliminary experiments by exposing a PBA to the apical surface. Second, I will investigate how bile acids regulate autophagy during inflammation by monitoring autophagic flux with autophagy reporter expressing organoid lines.

Uncovering these mechanisms will provide critical insights into the interplay between bile acid signalling, autophagy, and intestinal inflammation in IBD, and may reveal insights into targeting the bile acid shift as a novel therapeutic target.

P-20 | Imperial IBD organoid biobank

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Inflammatory Bowel Disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract. The two most common forms of IBD are Crohn's disease (CD) and ulcerative colitis (UC). IBD is a highly heterogeneous disease, which can be observed in the patients' diverse responses to treatments. Thus, there is great demand for developing novel resources that allow the investigation of IBD's heterogeneity *in vitro*.

Organoids are stem cell-based 3D structures that are capable of self-renewal and differentiation resembling the organs of their origin. Patient-derived organoids keep key features of their donor. Thus, organoids have emerged as a potential new tool to model complex diseases such as IBD. However, access to patients, clinical data, adequate expertise and infrastructure in organoid technology have so far limited the development of large-scale IBD organoid models.

The Imperial Organoid Facility supported by the NIHR Imperial Biomedical Research Centre aimed to est

ablish a versatile IBD organoid biobank. This goal became a reality thanks to the collaborative effort of clinicians and researchers based at the Imperial College Healthcare Trust and Imperial College London, respectively.

Our goal was to create a collection of diverse IBD patient-derived organoids taken from different areas of the gastrointestinal tract. Currently, the Imperial IBD Organoid Biobank contains 74 organoid lines from 39% healthy, 46% UC, and 11% CD donors. Demographic analysis of the collection shows that 58% of the donors are male; 60% of the donors are younger than 45 years old; the largest ethnic group is 'white' with 42%.

Ongoing efforts aim to involve more participants from the underrepresented patient groups (especially ethnicity) to the Biobank. In summary we aim to further enhance the Biobank's ability to model IBD heterogeneity and facilitate IBD research.

P-21 | Development of a high-throughput inflammation assay

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Introduction: Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract affecting over 2 million people in Europe and 6-8 million people worldwide. The multifactorial nature of the disease and current experimental limitations make IBD challenging to study, delaying the development of new therapies. Innovative approaches are therefore needed to study this highly complex disease. Organoids emerged as novel in vitro, near-physiological 3D models of the intestinal epithelium that accurately recapitulate in vivo phenotypes, including inflamed phenotypes of IBD, and are therefore highly valuable model systems to model IBD.

Methods: We developed a high-throughput inflammation assay by including patient-derived organoids in a Gut-on-Chip system. We hypothesized that a gut-on-a-chip model combined with patient-derived organoids can recapitulate key features of IBD (e.g., loss of barrier function, increased levels of cytokines). To recapitulate these hallmarks in vitro, both IBD and healthy-derived organoids were seeded on the apical side of both a Transwell model and the Mimetas OrganoPlate model. After a differentiation period, the epithelium was then basally exposed to a mix of proinflammatory stimuli (TNF-α, IL-1β) for 24 and 48 h. To assess the model, we analyzed gene expression of inflammation-related genes with RT-qPCR, cytokine secretion, cell morphology, barrier function (permeability assays), serotonin secretion and cytotoxicity.

Results: We observed a significant increase in cytotoxicity towards the epithelium 48h after basal exposure to the pro-inflammatory cytokine mix, while no significant effect on epithelial barrier integrity was observed.

Discussion/Conclusion: In the future, the model complexity can be further increased by adding extra cell types and ultimately be used to further dissect mechanisms of clinically relevant gut metabolites on the intestinal epithelial layer in the context of IBD.

P-22 | *Roseomonas mucosa* as a potential driver of intestinal fibrosis in Crohn's Disease: A multi-omic approach

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In Crohn's disease (CD), over 50% of cases develop fibrosis, often resulting in strictures. Despite advances in anti-inflammatory therapies, these complications persist due to chronic inflammation, which causes tissue injury and disrupts mucosal functions. Recent studies highlight microbiota dysbiosis as a potential inflammation-independent driver of fibrosis in CD, but specific microbial signatures across fibrosis stages remain underexplored.

We employed the IBD TaMMA framework for a meta-analysis of RNA-seq data from fibrotic CD-associated and healthy tissues. Fibroblast, endothelial, and epithelial populations were isolated via FACS and analyzed at the transcriptomic level. Organoids were derived from epithelial layer. Co-culture experiments were performed to explore cellular-bacterial interactions in fibrosis progression, and fibrosis markers (α-SMA, vimentin and FAP) in fibroblasts were assessed via immunofluorescence (IF).

Gene ontology analysis revealed activation of antimicrobial immune processes, suggesting a targeted response to microbiota during fibrosis progression. Microbiota analysis showed an increased abundance of *Roseomonas mucosa* in CD patients compared to controls across multiple cell types (endothelial, epithelial, fibroblast, and immune cells). Moreover, fibroblast co-cultures with lysates of *R. mucosa* (10 μg/mL) displayed elevated fibrosis markers in IF compared to unstimulated controls.

Our findings suggest that *R. mucosa*, or its products, may modulate the transcriptional state of mucosal cells, including fibroblasts, thereby contributing to intestinal fibrosis. To further elucidate the role of bacterial proteins in the transition from healthy to fibrotic tissue, we are conducting spatial transcriptomics analysis on ileocecal resection tissues, followed by RNA-scope with bacteria-specific probes. This integrative approach aims to map the temporal progression of fibrosis in relation to microbiota, providing deeper insights into its development.

P-23 | Spatial metagenomics of the inflamed human gastrointestinal mucosal niche resolved at strain resolution.

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The gastrointestinal (GI) microbial ecosystem plays a critical role in nutrient absorption, immune function, and defence against pathogens. The mucosa represents an important interface between the gastrointestinal lumen, containing the microbes and food stream, and the gastrointestinal lining composed of host cells. In inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), inflammation may spread from localized areas to the entire GI tract, and is associated with a decrease in mucosal thickness and increased colonization of bacteria into the mucosa. This is likely leading to a distinct dysbiotic signature of the mucosal microbiome. Furthermore, differences between the distal and proximal GI in nutrient uptake, luminal bacterial composition and localized inflammation in IBD suggest, that the mucosal ecosystems change as we move from the terminal ileum to the rectum.

Aims: Through spatial mucosal sampling, we aim to identify distinct colonization patterns in specific (inflamed/non-inflamed) sites and characterize bacterial species linked to dysbiosis and other clinically relevant phenotypic data from participant's clinical records in IBD throughout the GI tract.

Results: We profiled 312 intestinal biopsies and 31 stool samples from 51 IBD participants, leveraging shotgun metagenomics, with proportion of participants with severe disease progression higher in CD group and more UC participants in the remission. Most studies that investigate the mucosa are limited to amplicon sequencing since the high ratio of human to microbial DNA makes direct shotgun metagenomic sequencing unfeasible. Newly developed protocols allowed us to reduce the host reads to an average 43.4% of metagenomic reads. This allowed us to reconstruct 1090 metagenome assembled genomes (MAGs) that were clustered into 358 metagenomic species (MGS) that were subsequently used for a closer examination of functional distinctions among bacteria in inflamed/non-inflamed tissue, both within the mucosa and the lumen, as well as across various sites within the GI tract.

In this study, we developed an approach to investigate colonization patterns of bacteria in the human mucosa and host–microbe interactions, while disentangling disease-, location- and inflammation-specific associations.

P-24 | The effect of food additives on the gut microbiom

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Diet directly impacts the human gut microbiome, which influences overall health, behavior, and mood. With the rising intake of ultra-processed foods, there is a growing concern over the effects of food additives on gut bacterial communities. Although many food additives have been individually studied, their cumulative or systematic effects on members of the gut microbiome remain poorly characterized.

In this study, we assess the impact of 112 commonly used food additives on two bacterial species: *Escherichia coli*, a commensal gut bacterium, and *Salmonella spp.*, an opportunistic foodborne pathogen. Our results show that in 37% of the cases, additives selectively promoted *Salmonella* growth over *E. coli*, suggesting that specific additives may lead to gut microbiome imbalances. These findings implicate food additives as potential contributors to dysbiosis and microbiome-mediated health risks.

As a next step, we aim to expand this screen to 40 representative gut bacterial species to better understand community-level responses. This study may inform dietary guidelines and microbiome-targeted disease prevention strategies.

P-25 | Investigating caudovirales-induced molecular mimicry in Crohn's disease pathogenesis

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Crohn's disease (CD) has been increasingly linked to imbalances in the gut microbiota, notably through dysregulation in the gut virome. Particularly, elevated levels of Caudovirales have been observed in CD patients. Among these, the Proteus virus Isfahan species is abundant in CD, suggesting it might trigger an autoimmune response through molecular mimicry. This study investigates whether Proteus virus Isfahan proteins share homology with human proteins, potentially initiating autoimmune mechanisms in CD.

Utilizing the IBD Transcriptome and Metatranscriptome Meta-Analysis (TaMMA) framework, we analyzed cell populations from intestinal biopsies of CD patients and healthy controls. Immune and non-immune cells were isolated using flow cytometry and underwent transcriptomic analysis. Additionally, we examined the homology of viral proteins to human proteins using NCBI BLAST and iPBA. In vitro experiments involved coculturing T cells with immune cells overexpressing Proteus virus Isfahan protein to explore immune responses.

Our results confirmed increased levels of Proteus virus Isfahan, in CD patients, especially in dendritic cells and macrophages. Gene ontology analysis indicated compromised immune responses in dendritic cells and enhanced viral-response pathways in CD macrophages. Notably, the viral protein gp82 showed structural homology with human dCMP deaminase, supporting the molecular mimicry hypothesis. These findings highlight Proteus virus Isfahan as a potential activator of autoreactive T cells, exacerbating CD's autoimmunity.

This evidence suggests that Proteus virus Isfahan may play a significant role in CD pathogenesis through molecular mimicry, where its protein's similarity to human proteins could trigger immune misrecognition, fostering autoimmunity and perpetuating inflammation in CD. Ongoing experiments aim to further elucidate these interactions, potentially identifying novel therapeutic targets.

P-26 | Rewiring host cells through metabolite-host interactions

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The relationship between the human microbiome and host cells regulates the metabolites that are secreted into the gut. In inflammatory diseases, such as inflammatory bowel disease (IBD), there is an alteration in the metabolites that are secreted by the microbiome or host cells. These metabolites can rewire host metabolism and cell signalling via metabolite-protein interactions resulting in changes in immune response and cellular behaviour.

To understand the effect that metabolites have on cellular signalling, there is a current gap in resources that contain a comprehensive collection of metabolite-protein interactions. Therefore, we are developing a metabolite-protein interaction database that is more comprehensive than previous resources and will be easy to access and use. This database will allow the integration of metabolites with other molecular biology prior knowledge to understand how metabolites affect host cell processes such as signalling pathways and gene regulation.

As a proof-of-concept case study, we analysed metabolite profiling of IBD patients versus controls revealing differentially abundant small molecules. Analysing their impact on metabolic pathways with ocEAn we revealed coordinated suppression of fatty-acid metabolism and rewiring of four hexose-processing pathways alongside tryptophan catabolism. Integrating single-cell transcriptomics from colonic biopsies modelled the cell-type specific enzyme activity changes. We found that the tryptophan-degrading enzyme IDO1 was selectively up-regulated in M cells.

Contextualisation with our emerging metabolite-protein interaction resource revealed the role of differentially abundant metabolites in cellular signalling. We linked 36 of the dysregulated metabolites to human protein targets, including the immunomodulatory GPR35 binding kynurenine, thereby connecting metabolic shifts to candidate signalling nodes.

Overall, the two methodologies provide mechanistic insights into the relationship between metabolites and host cells. This will offer a valuable tool for understanding how metabolites can influence diseases such as IBD and for identifying therapeutic targets.