ECCO Research Grant

Inhibition of the gut sulfidogenic bacteria targeting the production of toxic and inflammatory sulfide

Awardee: Andreia Pimenta
Instituto de Tecnologia Química e Biológica António Xavier (ITQB NOVA), Universidade NOVA de Lisboa, Av. da República, 2780-157 Oeiras, Portugal

AIM OF THE RESEARCH

This project aims to develop novel strategies to modulate the human gut microbiota by inhibiting a key respiratory complex in sulfidogenic bacteria, thereby reducing the production of pathogenic sulfide associated with Inflammatory Bowel Disease.

METHODOLOGY THAT WAS USED IN THE RESEARCH

For this project, we combined genetic, microbiological and biochemical approaches to perform studies targeting the sulfur respiration complex DsrMKJOP in *Bilophila wadsworthia*. We successfully purified the native DsrMKJOP complex and recombinant DsrC, its physiological partner. However, despite extensive optimisation, we were unable to produce DsrAB, the enzyme required to activate DsrC, preventing the evaluation of inhibitor activity through in vitro enzymatic assays. We also assessed the efficacy and toxicity of seven candidate compounds by determining their antimicrobial activity against *B. wadsworthia* and nine representative gut bacterial species, as well as their cytotoxicity in human colonic cells and toxicity in a non-vertebrate animal model.

MAIN FINDINGS/RESULTS OF THE RESEARCH

Among the seven compounds tested, one emerged as a promising candidate. It inhibited the growth of *B. wadsworthia* while exhibiting minimal cytotoxicity toward Caco-2 and HT29-MTX human cell lines. In the *Galleria mellonella* model, the compound showed no detectable toxicity, even at high concentrations. Furthermore, it had limited inhibitory activity against other representative gut bacterial species, suggesting a relatively high specificity for sulfidogenic bacteria.

CONCLUSIONS AND PERCEIVED IMPACT OF THE FINDINGS

This study identified a promising commercially available compound that selectively inhibits sulfidogenic bacteria while sparing most members of the human gut microbiota, reducing the production of toxic, inflammatory sulfide. Future work will use computational approaches to identify improved analogues, which will be evaluated in a microbiota–gut-on-chip model to assess their efficacy and pharmacological potential in a physiologically relevant setting.

PLAN OF PUBLICATION

We plan to submit a publication to the JCC next year.

ECCO Research Grant

Caudovirales as a Trigger of Molecular Mimicry in Crohn's Disease

Awardee: Carmela Errico
Division of Immunology, Transplantation and Infectious Disease, IRCCS Hospital San Raffaele, Milan, Italy

AIM OF THE RESEARCH

This project aimed to elucidate the contribution of the gut virome to Crohn's Disease (CD) pathogenesis, focusing on bacteriophage-driven molecular mimicry as a mechanism of immune dysregulation. We specifically investigated whether virome-derived antigens can alter dendritic cell (DC) function and promote loss of immune tolerance.

METHODOLOGY THAT WAS USED IN THE RESEARCH

To define the cellular distribution of the gut virome, we performed integrated transcriptomic and metatranscriptomic profiling of intestinal biopsies from CD patients and healthy controls, analysing both immune and non-immune compartments. Computational approaches were applied to identify viral sequences enriched in specific cell populations and to assess sequence and structural homology between viral and human proteins. Among candidate antigens, the *Proteus virus Isfahan* protein gp82 was prioritised based on its homology to human dCMP deaminase. Functional validation was performed by ectopic expression of gp82 in monocyte-derived DCs using lentiviral systems. We characterised DC maturation, activation state and cytokine profiles and assessed their capacity to prime T cells. To model downstream effects on tissue homeostasis, co-culture systems with peripheral blood mononuclear cells and intestinal epithelial cells were established to evaluate immune-mediated epithelial damage. The experimental workflow closely followed the original proposal, with no substantial methodological deviations.

MAIN FINDINGS/RESULTS OF THE RESEARCH

We identified a significant expansion of *Caudovirales* bacteriophages in CD, with selective enrichment of *Proteus virus Isfahan* within DCs and macrophages. CD-derived DCs displayed dysregulated antiviral transcriptional programmes and impaired tolerogenic features, suggesting defective immune adaptation to virome signals. Expression of the gp82 viral protein induced a marked reprogramming of DCs towards a pro-inflammatory phenotype, characterised by increased activation markers. Functionally, gp82-expressing DCs enhanced T-cell priming and promoted the expansion of effector $CD4^+$ and $CD8^+$ T-cell subsets. In co-culture systems, this immune activation translated into epithelial cell stress and damage, supporting a mechanistic link between virome sensing and mucosal injury.

CONCLUSIONS AND PERCEIVED IMPACT OF THE FINDINGS

These findings support a model in which bacteriophage-derived antigens act as triggers of molecular mimicry, linking virome dysbiosis to sustained immune activation in CD. By identifying dendritic cells as central mediators of this process, this work provides a conceptual framework for understanding immune–virome interactions and highlights novel therapeutic opportunities targeting this axis in Inflammatory Bowel Disease.

PLAN OF PUBLICATION

The results are being prepared for submission to a peer-reviewed journal, with preference for Journal of Crohn's and Colitis or JCC Plus. Results are also being disseminated through international conferences, with further studies ongoing to extend these findings in in vivo models.

ECCO Research Grant

Targeting hypoxia-induced signaling via HIF-2 inhibition, a promising treatment strategy for intestinal fibrosis?

Awardee: Sophie Van Welden
Ghent University, Belgium

AIM OF THE RESEARCH

1. Elucidate the molecular mechanism(s) underlying intestinal fibrosis following fibroblast-specific *Phd2*-deletion in *Phd2*$^{f/f}$Col1a2ERT2:cre mice.
2. Determine whether HIF-2 inhibition suppresses experimental intestinal fibrosis.
3. Assess whether HIF-2 inhibition attenuates the profibrotic phenotype of fibrostenotic fibroblasts from CD patients.

METHODOLOGY THAT WAS USED IN THE RESEARCH

Colonic fibroblasts from *Phd2*$^{f/f}$Col1a2ERT2:cre mice and their wild-type littermate controls were analysed by RNA sequencing and gene set enrichment analysis, followed by qPCR validation of enriched genes. Fibroblast proliferation was monitored using Incucyte live-cell imaging. As no clear evidence for selective HIF-2 signaling was identified, the originally planned HIF-2 inhibitor belzutifan was replaced by the non-specific HIF inhibitor acriflavine to assess the contribution of HIF signaling to fibroblast behaviour and fibrogenesis. The effects of acriflavine were evaluated in vitro on fibroblasts collected from stenotic and non-stenotic ileal CD tissue.

MAIN FINDINGS/RESULTS OF THE RESEARCH

Fibroblasts from *Phd2*$^{f/f}$Col1a2ERT2:cre mice exhibited enhanced HIF signaling. *Phd2*-deletion increased fibroblast proliferation and was, at least in part, HIF dependent. Under baseline conditions, acriflavine significantly reduced HIF-driven erythropoiesis in *Phd2*$^{f/f}$Col1a2ERT2:cre mice and was associated with decreased intestinal collagen deposition. During chronic colitis, acriflavine treatment reduced collagen type III expression in colonic fibroblasts, but only a modest reduction in overall collagen deposition was observed. In human fibroblasts, acriflavine significantly decreased collagen type I and III mRNA expression.

CONCLUSIONS AND PERCEIVED IMPACT OF THE FINDINGS

These findings identify the PHD2–HIF axis as an important regulator of intestinal fibroblast activation and collagen production. While pharmacological HIF inhibition reduced profibrotic gene expression in both murine and human fibroblasts, it was insufficient to fully reverse established intestinal fibrosis. HIF-targeting may represent a promising strategy for limiting fibrosis, although optimisation of treatment timing and regimen may be required. A prophylactic treatment approach is currently being analysed.

PLAN OF PUBLICATION

Following completion of the remaining analyses, results will be submitted to JCC (anticipated by mid 2027).

ECCO Research Grant

Investigating the role of gut eukaryotic virome in contributing to colorectal cancer carcinogenesis

Awardee: Amanda Facoetti
Università Vita-Salute San Raffaele, Milano, Italy

AIM OF THE RESEARCH

Recently our group identified hepatitis B protein X (HBx), a gut virome-associated Orthohepadnaviridae protein, as a factor implicated in the pathogenesis of Ulcerative Colitis. HBx promotes intestinal inflammation in mice by disrupting the epithelial barrier and altering the gut mucosal immune environment. Additionally, it activates Wnt-related processes, which are involved in colitis-associated colorectal cancer (CAC). Based on this evidence, we aimed to investigate whether HBx-mediated alterations drive neoplastic transformation in intestinal epithelial cells, contributing to the onset and progression of CAC.

METHODOLOGY THAT WAS USED IN THE RESEARCH

Establishing a monolayer with HBx-transfected organoid-derived cells is challenging and requires additional optimisation, which is currently ongoing. Meanwhile, we proceeded with the co-culture experiment using Caco-2 cells transfected with lentiviral particles carrying either the HBx or GFP encoding sequence as a control, along with peripheral blood mononuclear cells (PBMCs) from healthy donors.
C57BL/6 mice were treated with intrarectal injections of liposomes conjugated with HBx or GFP plasmid as control every 3 days for 60 days.
CD1 nude mice received a single orthotopic injection of HBx- or GFP-transfected Caco-2 cells and were sacrificed after 21 days.

MAIN FINDINGS/RESULTS OF THE RESEARCH

HBx increases the oncogenic potential of Caco-2 cells by promoting DNA damage, driving proliferation and inducing epithelial-to-mesenchymal transition (EMT).
In co-culture with HBx-Caco-2 cells, PBMCs exhibited a reduction in pro-inflammatory M1 macrophages and CD4 naive T cells, along with an increase in exhausted neutrophils, regulatory T cells and CD8 naive T cells compared to the GFP condition.
Mice treated with HBx-liposome exhibited significant intestinal inflammation and colitis symptoms compared with the GFP group. However, no neoplastic changes were observed.
In the orthotopic model, treatment with HBx-Caco-2 cells resulted in higher tumour prevalence and a more aggressive tumour phenotype, with altered transcription factor expression linked to EMT, compared with GFP-injected mice.

CONCLUSIONS AND PERCEIVED IMPACT OF THE FINDINGS

HBx alone is not sufficient to induce neoplastic transformation in vivo. However, its overexpression in Caco-2 cells significantly enhances their oncogenic potential by promoting EMT and developing a more aggressive tumour phenotype. These findings could pave the way for further investigation into HBx's role in CAC progression and support the development of personalised treatments.

ECCO Research Grant

Immune-epithelial crosstalk boosting intestinal repair in ulcerative colitis

Awardee: Annika Hausmann
reNEW – NNF Center for Stem Cell Medicine, University of Copenhagen

AIM OF THE RESEARCH

A total of 1.3 million people in Europe suffer from Inflammatory Bowel Disease (IBD). Its most prevalent subtype is Ulcerative Colitis (UC), a chronic colon inflammation of unknown aetiology.
The breakdown of intestinal epithelial barrier integrity is a key event initiating intestinal inflammation in UC, and remission requires epithelial repair. Repair is modulated by inflammatory signals which exert anti- but also pro-proliferative effects. It is unknown how the epithelium integrates inflammatory signals to fine-tune repair, limiting current therapeutic strategies in UC to symptomatic suppression of inflammation with potential detrimental effects on repair. With this project, we aimed to gain a molecular understanding of immune cell–epithelial crosstalk in UC to inform targeted therapies that suppress detrimental inflammation and boost epithelial repair.

METHODOLOGY THAT WAS USED IN THE RESEARCH

To this end, we made use of a novel, interdisciplinary approach combining microscopy and deep visual proteomics of repairing epithelial cells in vivo and in vitro image-based screening setups using cytokine-exposed organoids to decipher immune cell–epithelium crosstalk driving epithelial repair in UC.

MAIN FINDINGS/RESULTS OF THE RESEARCH

Employing these methods, we found that early colitis is characterised by disappearance of Lgr5+ epithelial stem cells, with potential implications for epithelial maintenance. This phenotype can be recapitulated in vitro by exposure to specific cytokines, and we are currently running validation experiments to dissect this loss, as well as its impact on epithelial maintenance, mechanistically.
We anticipate that our findings will enable a refinement of treatment strategies for patients with UC in order to maintain epithelial maintenance and prevent epithelial barrier loss during colitis. This will improve patient quality of life and reduce treatment costs.

ECCO Research Grant

Dissecting the role of S1PR1 modulator in the mucosal regeneration of Ulcerative Colitis

Awardee: Giulia Rizzo
Laboratory of Gastrointestinal Immunopathology, Department of Gastroenterology, IRCCS Humanitas, Research Hospital, Rozzano, Milan, Italy

AIM OF THE RESEARCH

This study aimed to investigate the role of epithelial S1PR1 signalling during intestinal mucosal repair and evaluate the therapeutic effects of Ozanimod (OZN) in the recovery phase of experimental ulcerative colitis (UC).

METHODOLOGY THAT WAS USED IN THE RESEARCH

Chronic DSS-induced colitis was established in C57BL/6N mice (WT) and in a conditional epithelial-specific S1PR1 knockout model (S1PVillinCre+; S1PVillinCre-, control). During the recovery phase, mice were treated with OZN (3mg/kg, daily). Intestinal permeability (CD14 detection) and inflammatory profiles were assessed in blood. Further, injured iPSC-derived intestinal organoids (iHOs) were exposed to pro-inflammatory cytokines (IFN-γ, TNF-α, IL-1β; 20ng/mL) and treated with OZN (100ng/mL, different time points) to define phase-dependent responses.

MAIN FINDINGS/RESULTS OF THE RESEARCH

OZN promoted recovery in DSS-induced colitis in WT mice, as evidenced by improved body-weight, reduced DAI, and decreased systemic inflammatory mediators (KC, RANTES, G-CSF), and CD14 compared with vehicle-treated controls. In both S1PVillinCre+ and control mice, OZN enhanced recovery relative to vehicle, with ameliorated body-weight loss. However, vehicle-treated S1PVillinCre+ mice already showed improved recovery with respect to vehicle-treated control mice.
OZN treatment during recovery in S1PVillinCre+ mice increased IL-13, IL-2, IL-10, and IL-17, whereas vehicle-treated S1PVillinCre+ mice exhibited higher Eotaxin and IL-12(p40).
In iHOs, OZN exerted anti-inflammatory effects only under remission-like conditions, while showing no benefit in subacute inflammation and a pro-inflammatory shift under acute inflammation, highlighting a phase-dependent activity.

CONCLUSIONS AND PERCEIVED IMPACT OF THE FINDINGS

Our results demonstrated that OZN promotes recovery in chronic DSS-induced colitis, partly independently of epithelial S1PR1 signalling. Epithelial S1PR1 deletion alone appears to confer a protective effect, suggesting a role in sustaining inflammation and delaying tissue repair.
Overall, OZN activity is phase-dependent, promoting resolution during inflammation recovery rather than preventing disease onset. These findings support a key role for S1PR1 in epithelial-driven mucosal healing and highlight a therapeutic window for S1PR modulation in UC.

PLAN OF PUBLICATION

A manuscript will be submitted to peer-reviewed journals in the IBD field by end 2026.

ECCO Research Grant

Investigating regenerative pathways in salivary glands to mitigate oral manifestations of inflammatory bowel diseases

Awardee: Gustavo Monasterio
Department of Medicine, Solna, Karolinska Institute, Sweden

SUMMARY OF THE RESEARCH

In this project, I set out to understand why so many IBD patients experience oral complications, from dry mouth and taste changes to ulcers and periodontitis, and whether intestinal inflammation might be disrupting salivary gland function through a previously unrecognised gut–salivary axis. To explore this, we developed an innovative tissue-mounting technique, ORES rolls, enabling unbiased spatial analysis of the entire GI tract. Using this approach, alongside spatial transcriptomics and RNA sequencing of submandibular and sublingual glands, we found that intestinal inflammation alters submandibular gland activity via sympathetic neural signalling, pointing to these glands as distal responders to gut inflammation. We also showed that activation of the liver X receptor (LXR) promotes partial regeneration of irradiated salivary glands, and, through a serendipitous finding, identified a possible new, previously undescribed salivary organ. These results reveal a gut–salivary gland axis with potential therapeutic relevance for the oral manifestations of IBD. This work has already contributed to two published papers, with two further manuscripts currently in preparation.

ECCO Research Grant

Analysis of the tolerogenic role of the liver in controlling intestinal inflammation

Awardee: Jan Michael Kempski
reNEW – I. Department of Medicine, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany

AIM OF THE RESEARCH

Primary sclerosing cholangitis (PSC) is associated with Inflammatory Bowel Disease (IBD), but PSC-IBD often presents with milder colitis. We aimed to decipher the underlying mechanisms, hypothesising that (1) PSC-driven microbiota changes promote Foxp3+ regulatory T cells and (2) that an altered bile acid composition in PSC contributes to this effect.

METHODOLOGY THAT WAS USED IN THE RESEARCH

Faecal microbiota transfer (FMT) from Mdr2-/- mice and PSC-IBD patients into germ-free mice was followed by colitis induction. T cell composition and disease severity were assessed by flow cytometry and endoscopy. To identify mechanistic mediators, bile acid and SCFA levels in the stool were quantified by targeted metabolomics. Individual bile acids and faecal conditioned media (FCM) were then tested on T cell polarisation.

MAIN FINDINGS/RESULTS OF THE RESEARCH

FMT from Mdr2-/- mice and PSC-IBD patients into germ-free mice attenuated colitis severity by promoting Foxp3+ Treg cells. Bile acid profiling revealed an altered faecal bile acid pool in PSC-IBD patients and in Mdr2-/- mice, with an elevation in taurine-conjugated bile acids in IBD compared to PSC-IBD patients. FCM from the faecal content of Mdr2-/- mice influenced CD4+ T cell differentiation in vitro but did not affect Treg differentiation. Similarly, complete Mdr2-/- bile fluid did not influence Foxp3+ Treg polarisation, suggesting that the altered bile acids observed in IBD-PSC are not sufficient for promoting Foxp3+ Treg differentiation.

CONCLUSIONS AND PERCEIVED IMPACT OF THE FINDINGS

PSC has a protective effect on murine colitis models through a microbiota–Foxp3+ Treg axis. Differences in bile acid profiles between PSC-IBD and IBD patients suggest that these metabolites modulate the intestinal immune system. However, our data indicate that the alteration of bile acids in PSC does not directly influence Treg differentiation, suggesting involvement of a possible indirect mechanism in shaping the intestinal T cell repertoire.

PLAN OF PUBLICATION

A manuscript on the effects of PSC-IBD-associated bile acid changes on the intestinal microbiota and T cell responses is in preparation, and submission is planned in Q1/2027.

ECCO Research Grant

Risk of cardiovascular disease in patients with inflammatory bowel disease (IBD)

Awardee: Jiangwei Sun
Karolinska Institutet, Sweden

AIM OF THE RESEARCH

The aims of this project were: (1) to investigate the long-term risk (both absolute and relative) of cardiovascular disease (CVD) in patients with IBD, and (2) to assess CVD risks for patients in different phases of histological and clinical periods of IBD.

METHODOLOGY THAT WAS USED IN THE RESEARCH

We applied epidemiological and statistical methods to tackle the proposed research questions through use of data from a comprehensive linkage of a nationwide histopathology cohort, one quality register for IBD and several nationwide registers in Sweden.

MAIN FINDINGS/RESULTS OF THE RESEARCH

Aim 1: We conducted several nationwide cohort studies to investigate the long-term risk of CVD in patients with IBD, compared with general populations and their IBD-free full siblings. We observed that patients with IBD were at higher risk of developing heart failure (published), myocarditis (published), arrhythmias (published), stroke (published), acute coronary syndrome (published) and venous thromboembolism (published). Although family members of patients with IBD to some degree share genetic or environmental factors with IBD patients, our study did not support extra vigilance for CVD in family members of IBD patients (published).
Aim 2: We conducted one nationwide cohort study in Sweden to investigate how histological and clinical activity of IBD affects the risk of major adverse cardiovascular events (MACE, published). We found an increased MACE risk following histological inflammation compared to remission (aHR=1.16 [1.04–1.30]). This excess risk was evident in Crohn's Disease (aHR=1.30 [1.03–1.64]) and Ulcerative Colitis (aHR=1.13 [1.01–1.27]). Histological inflammation was associated with an increased risk of ischaemic heart disease, myocardial infarction, ischaemic stroke and heart failure, but not with haemorrhagic stroke. Compared to clinically quiescent IBD, active IBD was associated with an increased MACE risk (aHR=1.54 [1.46–1.63]). In patients with clinically quiescent IBD, histological inflammation remained linked to myocardial infarction (aHR=1.29 [1.06–1.58]) and heart failure (aHR=1.19 [1.00–1.43]). Similarly, we conducted another cohort study to investigate how histological and clinical activity of IBD affects the risk of arrhythmias (Accepted). We found that histological inflammation was associated with an increased risk of arrhythmias compared to histological remission (aHR=1.35 [1.18–1.54]).

CONCLUSIONS AND PERCEIVED IMPACT OF THE FINDINGS

Our findings indicate a need for awareness of the excess risk of CVD in IBD patients and suggest that improved disease control may reduce this excess risk.

PLAN OF PUBLICATION

Some publications supported by this grant:

Aim 1:

1. Geng J… Sun J. Association of inflammatory bowel disease with cardiovascular disease, and the mediating role of inflammation: a matched-cohort study. Therap Adv Gastroenterol. 2026;19:17562848261424145. doi:10.1177/17562848261424145
2. Sun J et al. Risk of heart failure in inflammatory bowel disease: a Swedish population-based study. European Heart Journal. 2024. doi.org/10.1093/eurheartj/ehae338
3. Sun J et al. Familial coaggregation of inflammatory bowel disease with cardiovascular disease: a nationwide multigenerational cohort study. Gut. 2024. DOI: 10.1136/gutjnl-2023-331632
4. Sun J et al. Long-term risk of myocarditis in patients with inflammatory bowel disease: a nationwide cohort study in Sweden. American Journal of Gastroenterology. 2024. DOI: 10.14309/ajg.0000000000002701
5. Sun J et al. Long-term risk of arrhythmias in patients with inflammatory bowel disease: A population-based, sibling-controlled cohort study. PLOS Medicine. 2023; 20(10): e1004305.
6. Sun J et al. Long-term risk of stroke in patients with inflammatory bowel disease: A population-based, sibling-controlled cohort study 1969-2019. Neurology. 2023;101(6):e653-e64.

Aim 2:

7. Sun J et al. Association of histologic and clinical activity with major adverse cardiovascular events in patients with inflammatory bowel disease: A cohort study. Journal of Internal Medicine. 2025. DOI: 10.1111/joim.70035.
8. Sun J et al. (2025). Association of histologic and clinical activity with arrhythmias in patients with inflammatory bowel disease: A cohort study. World Journal of Gastroenterology. Accepted.

ECCO Research Grant

Untangling the gut phageome dynamics of the relapse/remission cycle in ulcerative colitis

Awardee: Maria Kulecka
Medical Centre of Postgraduate Education, Poland

AIM OF THE RESEARCH

Most microbiome studies on Ulcerative Colitis (UC) focus on the gut bacteriome. However, recent discoveries suggest that phage-mediated bacterial cell lysis may contribute to sustained gut inflammation.
This study aimed to explore the gut phageome in UC patients with frequent relapses and to assess associations between gut viral composition and disease state.

METHODOLOGY THAT WAS USED IN THE RESEARCH

A total of 243 stool samples were collected monthly from 21 patients. Intestinal inflammation and symptom severity were assessed using faecal calprotectin (FCal) and the Simple Colitis Activity Index (SCAI), respectively. Viral-like particles (VLPs) were isolated using 0.45-µm filters. DNA isolation was paired with reverse transcription to capture RNA viruses. Shotgun sequencing was used to determine viral composition, and VLP identification/quantification was performed using BAQLaVa.

MAIN FINDINGS/RESULTS OF THE RESEARCH

Phages were detected in 238 samples from all 21 patients. Five of the ten most abundant viral genome bins (VGBs) belonged to the class Caudoviricetes. Viral richness (Chao1 index) was positively correlated with FCal levels (repeated measures correlation, $r=0.18$, $p<0.01$). After deconfounding, 13 VGBs were significantly associated with FCal, with 11 showing positive correlations. Among all tested metavariables, FCal had the strongest influence on gut viral composition, explaining 1.4% of variance. In contrast, FCal ranked 15th in importance for bacteriome composition, explaining only 0.7% of variance.

CONCLUSIONS AND PERCEIVED IMPACT OF THE FINDINGS

Gut phage load is positively associated with calprotectin levels in adults with UC. This association appears stronger than that observed for the bacteriome, positioning the virome as a promising omic layer for identifying novel biomarkers of UC activity.

PLAN OF PUBLICATION

Findings will be presented as a flash talk at FEMS Micro 2025 and as a poster at ECCO 2026. A peer-reviewed publication incorporating these and other omic data from the cohort is planned for 2026.

ECCO Research Grant

Serotonin gets into your genes: The Role of Histone Serotonylation in Inflammatory Response and Visceral Hypersensitivity in Crohn's Disease

Awardee: Mohammed Ghiboub
Tytgat Institute for Liver and Intestinal Research; Emma Children's Hospital, Department of Pediatric Surgery, Amsterdam UMC, the Netherlands

AIM OF THE RESEARCH

This project aimed to determine whether increased serotonin availability drives histone H3 glutamine-5 serotonylation (H3Q5ser) in immune cells and enteric neurons in Crohn's Disease (CD), and to evaluate its impact on inflammatory signalling and visceral hypersensitivity.

METHODOLOGY THAT WAS USED IN THE RESEARCH

We combined patient-derived samples [biopsies, peripheral blood mononuclear cells (PBMCs)] with immunofluorescence, Western blot, flow cytometry and ELISA. Flow cytometry identified CD14+ monocytes as the major H3Q5ser-positive population, so mechanistic work focused on purified monocytes from buffy coats cultured with serotonin and lipopolysaccharide alongside inhibition of TGM2, the enzyme that catalyses serotonin binding to histones. H3Q5ser chromatin profiling used CUT&Tag instead of the originally proposed ChIP-seq, offering higher sensitivity with limited primary-cell material. ATAC-seq, RNA-seq and H3Q5ser CUT&Tag were also generated from PBMCs of active and quiescent CD patients; bioinformatic integration is ongoing. The enteric neuron package was adapted from cell-line mutagenesis to a neurosphere model.

MAIN FINDINGS/RESULTS OF THE RESEARCH

Serotonin and H3Q5ser were increased in inflamed CD mucosa, with elevated TGM2 expression and H3Q5ser enrichment in $CD45^+$ immune cells. H3Q5ser was also higher in circulating PBMCs, with $CD14^+$ monocytes the principal H3Q5ser-positive population. Serotonin dose-dependently induced H3Q5ser in PBMCs; inhibition of SERT, the transporter that mediates intracellular serotonin uptake, blocked this induction and reduced serotonin-potentiated LPS-driven IL-6, IL-8 and IL-1β production, while TGM2 inhibition independently blocked H3Q5ser formation. ATAC-seq, RNA-seq and H3Q5ser CUT&Tag datasets were successfully generated from PBMCs of active and quiescent CD patients, providing a genome-wide resource to investigate serotonin-responsive chromatin regulation. Preliminary ATAC-seq analysis already demonstrates clear chromatin accessibility differences between disease states, while integration with RNA-seq and CUT&Tag is ongoing. Enteric neurospheres, three-dimensional cultures of enteric neural progenitor cells that differentiate into neurons and glia, model the enteric nervous system; H3Q5ser was detected in these cultures, increased upon serotonin stimulation and blocked by TGM2 inhibition, providing the first proof-of-concept that H3Q5ser is dynamically regulated in enteric neurons.

CONCLUSIONS AND PERCEIVED IMPACT OF THE FINDINGS

Together, these findings establish H3Q5ser as a serotonin-responsive epigenetic modification in CD and identify CD14+ monocytes as a major cellular target of serotonin-mediated chromatin regulation. The project generated a valuable multi-omics resource integrating chromatin accessibility, transcriptional profiling and H3Q5ser chromatin occupancy, and provides the first proof-of-concept that enteric neuronal H3Q5ser is

serotonin responsive, establishing a strong foundation for future studies of inflammation and visceral hypersensitivity.

PLAN OF PUBLICATION

This work was presented as a poster at ECCO’25 and accepted for UEGW 2026, with a manuscript on the immune cell findings in preparation. The work was also presented at ECCO’26 and further manuscripts are planned following completion of the multi-omics and enteric neuron analyses.

ECCO Research Grant

Looking for a needle in a haystack: Identification of the gut microbial strains contributing to chronic inflammation in human and mice

Awardee: Bahtiyar Yilmaz
University of Bern, Switzerland

AIM OF THE RESEARCH

This project aimed to identify gut microbial strains contributing to chronic intestinal inflammation through oxidative stress-associated mechanisms and to determine how microbial ecosystem structure shapes resilience to inflammation. The work focused on characterising intestinal bacteria isolated from human samples for their oxidative stress capacity, understanding how microbial community composition differs under inflammatory conditions and testing whether selected beneficial taxa can mitigate inflammation in vivo. A secondary objective was to investigate whether D-lactate-free gut commensal supplementation could act as a microbiota-supportive intervention in colitis and whether baseline microbial composition determines therapeutic responsiveness.

METHODOLOGY THAT WAS USED IN THE RESEARCH

The project combined human microbiota isolation, microbial phenotyping and mouse experimentation. Human intestinal bacterial strains were isolated from IBD and non-IBD subjects using multiple culture conditions designed to recover stress-resistant taxa from intestinal niches. Isolates were characterised using growth assays, oxidative stress exposure experiments, antioxidant profiling and sequencing-based taxonomic identification.

In parallel, murine dextran sulfate sodium (DSS)-induced colitis models were established using mice with distinct baseline gut microbiota ecosystems. D-lactate-free bacterial consortia containing *Lactobacillus* and *Bifidobacterium* species were administered preventively or therapeutically during chronic DSS cycles. Disease severity was assessed through body weight monitoring, histopathology, inflammatory cytokine measurements, colon gene expression profiling and microbiota sequencing.

Additional bioinformatic analyses included microbial co-occurrence network analysis, predictive functional profiling and machine-learning approaches to identify microbial signatures associated with oxidative stress resilience and probiotic responsiveness. Compared with the original proposal, the project evolved toward a stronger systems-level integration of microbial ecology, oxidative stress biology and microbiota-dependent treatment response.

MAIN FINDINGS/RESULTS OF THE RESEARCH

The project generated an expanded library of human intestinal isolates, including bacteria originating from inflammatory and non-inflammatory intestinal environments (Figure 1). Functional testing revealed strong variability between strains in oxidative stress resistance, antioxidant capacity and growth under inflammatory-like conditions (Figure 2).

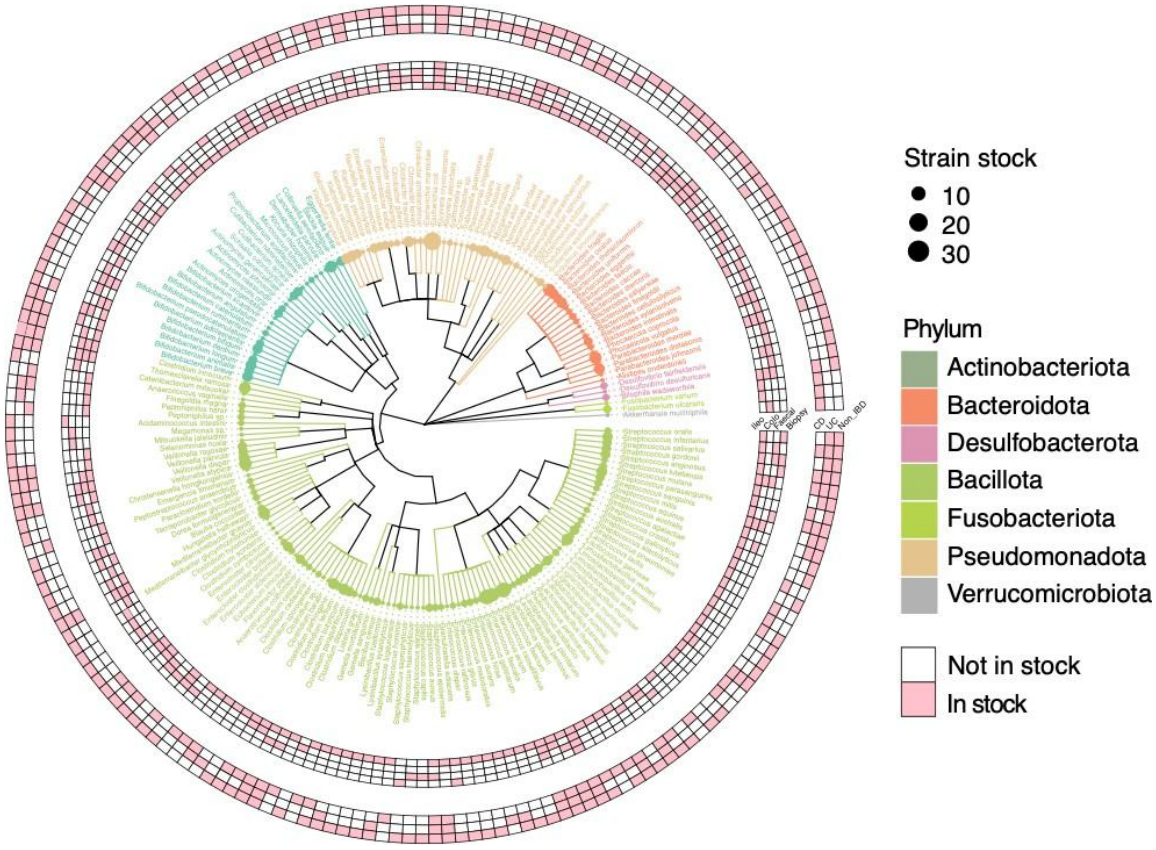


Figure 1. Phylogenetic tree of gut bacteria isolates showing taxonomic diversity, source origins and clinical associations in CD, UC and non-IBD individuals.

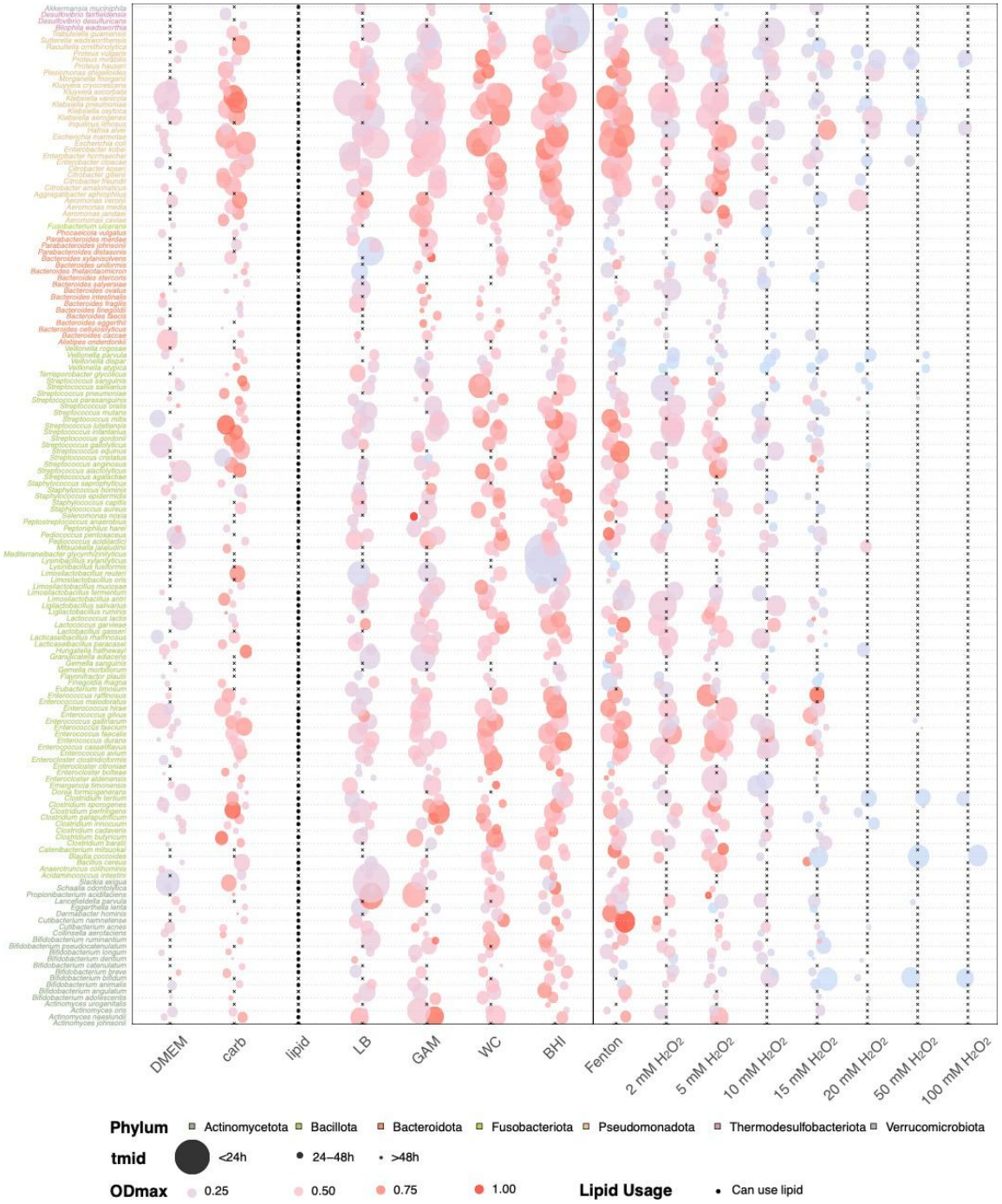


Figure 2. Growth characteristics and oxidative stress tolerance of gut bacterial isolates across different media and stress conditions. Growth capacity and growth rate across media and under different oxidative stress challenges. Growth capacity is defined by the absorbance value at 600 nm after 72 hours when bacterial cultures have reached their stationary phase, indicated by the bubble colour. Growth rate is defined by the time it takes for bacterial growth to reach the mid-log phase, depicted by bubble size (larger bubbles correspond to faster growth rates). Media types and oxidative stress conditions are listed along the x-axis. Species are clustered along the y-axis according to their phylum, with distinct colours used to visually differentiate each phylum.

Microbiota analyses demonstrated that inflammatory states were associated with enrichment of oxidative stress-tolerant taxa and depletion of metabolically beneficial bacteria linked to intestinal homeostasis (Figure 3).

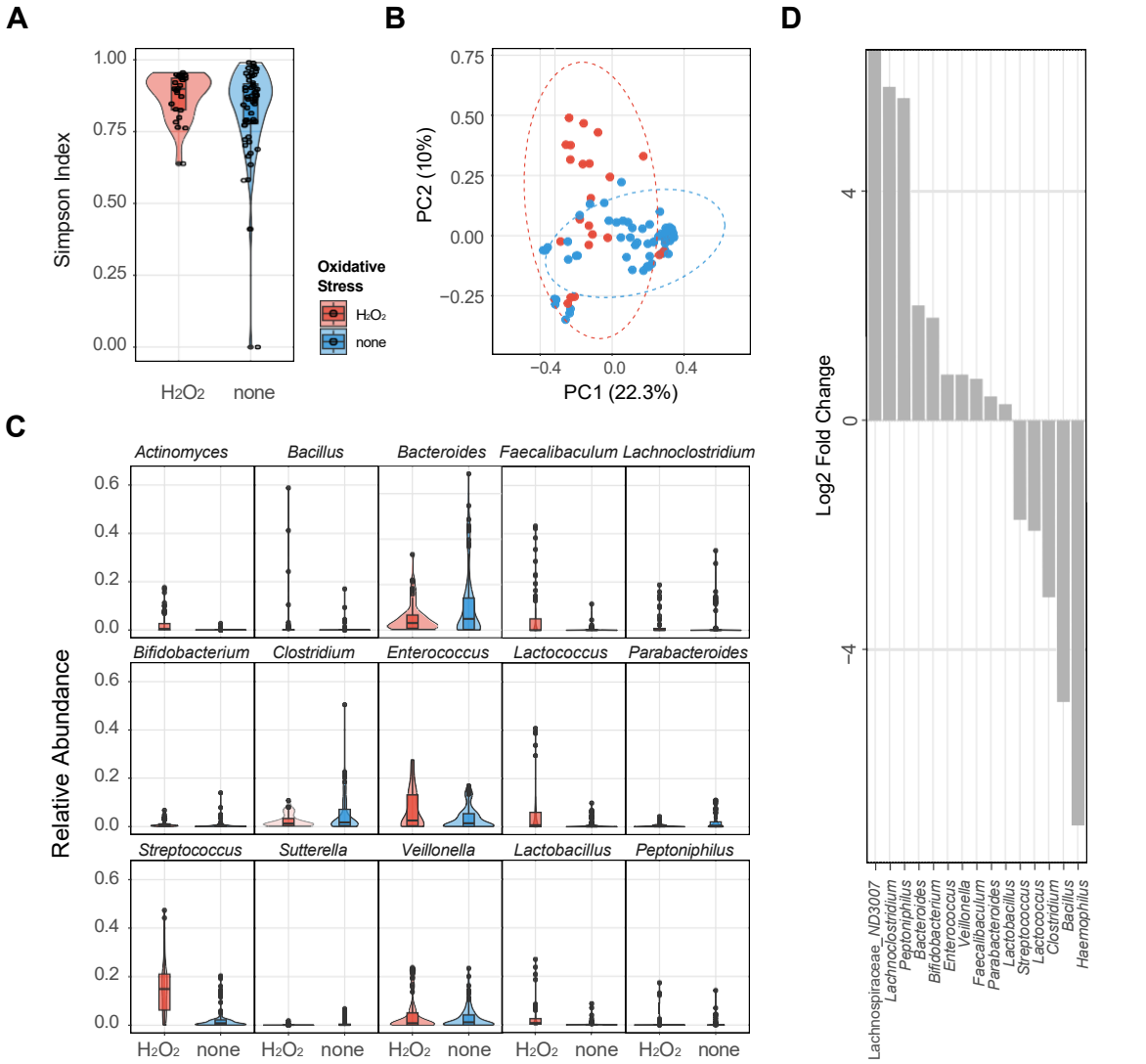


Figure 3. Chronic oxidative stress significantly changed the microbial structure in an in vitro culture. (A) Box plots with violin overlays show the Simpson diversity index for control (none) and H_2O_2-treated samples. Statistical significance was determined using Wilcoxon rank-sum tests. (B) Beta diversity analysis of microbial communities under oxidative stress without supplementary treatment. PCoA based on Bray-Curtis dissimilarity matrices shows the clustering of microbial communities. The first two principal coordinates (PC1 and PC2) are shown with their respective explained variance percentages. Each point represents a sample, the colour indicating oxidative stress conditions. Ellipses represent 95% confidence intervals. (C) Differential abundance analysis of the top 15 most abundant genera between oxidative stress conditions. Violin plots with embedded box plots show the relative abundance of each genus under control (none) and H_2O_2 treatment conditions. Statistical significance was determined using Wilcoxon rank-sum tests. Box plots show the median and interquartile ranges, while violin plots represent the data distribution. (D) The log2 fold change in relative abundance for the top 15 genera exhibited alterations from untreated samples, with positive values indicating an increase and negative values indicating a decrease in abundance from day 0 to day 3. None of the observed changes were statistically significant.

In DSS-induced colitis models, D-lactate-free bacterial supplementation improved disease outcomes, particularly when administered before severe inflammation developed. Reduced disease severity was associated with preservation of microbial diversity, improved ecological stability and lower inflammatory burden (Figure 4 and manuscript in revision).

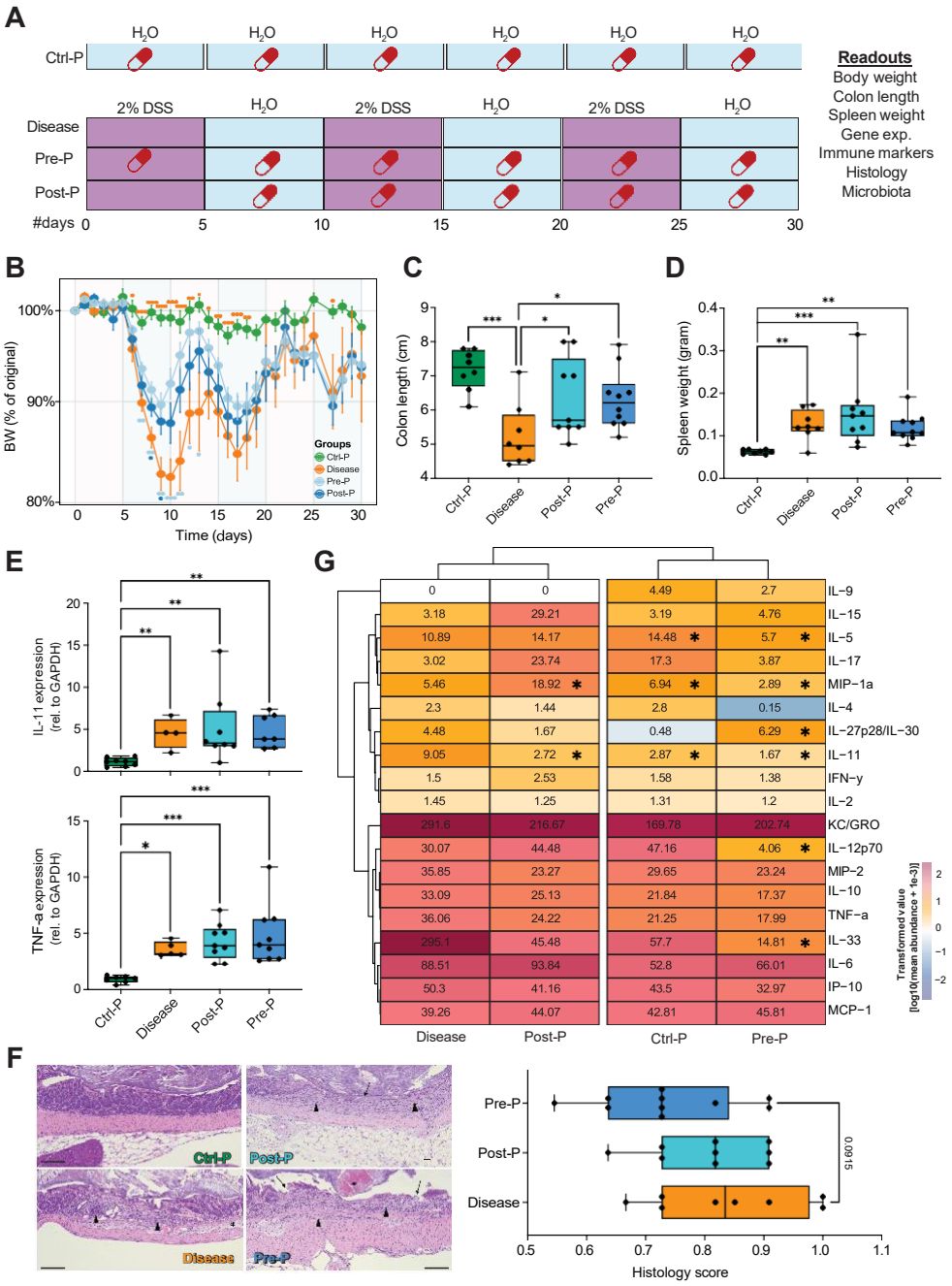


Figure 4. D-lactate-free probiotics alleviate colitis in the first cycle of chronic disease by reducing inflammation and improving clinical outcomes. (A) Mice were exposed to three cycles of 2% DSS for 5 days, each followed by a 5-day recovery with water. Probiotics were administered either preventively from the start of the experiment (Pre-P) or therapeutically following the first DSS cycle (Post-P). Control groups included probiotic-treated mice (Ctrl-P) and DSS-treated mice without probiotics (Disease). (B) Changes in body weight over 30 days expressed as a percentage of the original weight. (C) Measurements of colon length measurements at the end of the experiment. (D) Spleen

weight as a marker of systemic inflammation. (E) Gene expression analysis of the pro-inflammatory cytokines TNF-α and IL-1β in colonic tissue. Relative expression levels normalised to GAPDH are shown. (F) Serum cytokine profiles were assessed on day 30 for pro-inflammatory markers (e.g. IL-1β, TNF-α, MIP-1α) and immune-regulatory cytokines (e.g. IL-27p28/IL-30) using MesoScale (MSD). The figure summarises two independent experiments with 8–10 mice per group. (G) H&E staining of colon tissue (100×) showing the epithelial damage, crypt loss and inflammatory infiltration in different groups. Calculated histological scoring of colonic tissues was shown. * shows on heatmap in (F) $p<0.05$

Importantly, probiotic responsiveness varied substantially across microbiota backgrounds. Mice enriched in short-chain fatty acid-producing and anti-inflammatory taxa showed stronger responses than animals carrying inflammation-associated microbial communities. Machine-learning analyses identified baseline microbial diversity and specific taxa as predictors of therapeutic response.

CONCLUSIONS AND PERCEIVED IMPACT OF THE FINDINGS

This project demonstrates that oxidative stress is not only a consequence of intestinal inflammation but also an ecological driver that shapes gut microbial structure and function. Across human-derived isolates, inflammatory microbiota profiles and murine colitis models, microbial members displayed marked differences in their ability to tolerate, generate or counteract oxidative stress. These findings suggest that microbial resilience to inflammatory environments represents an important determinant of host–microbiota stability.

The work further supports the concept that intestinal inflammation is associated with selective enrichment of oxidative stress-adapted microbes, while metabolically beneficial taxa linked to barrier maintenance and short-chain fatty acid production are depleted. At the strain level, microbial functional heterogeneity emerged as a key feature, indicating that closely related taxa may differ substantially in their inflammatory potential and ecological behaviour.

In vivo experiments demonstrated that microbiota-targeted interventions can reduce inflammatory burden, but therapeutic benefit depends strongly on baseline microbial ecosystem composition. Rather than acting as universally effective interventions, beneficial bacterial supplementation appears to function within an ecological framework in which host response is shaped by existing microbial networks and community resilience.

Collectively, these findings contribute to a mechanistic understanding of how oxidative stress influences gut microbial ecology and inflammatory disease progression. The project provides an integrated framework linking human-derived microbial characterisation with experimental validation in vivo, supporting the development of precision microbiota-based therapies for IBD.

PLAN OF PUBLICATION

The results contribute to an ongoing PhD thesis focused on oxidative stress resilience of gut microbial strains under healthy and inflammatory conditions, as well as a manuscript currently in revision describing microbiota-dependent responses to D-lactate-free supplementation in chronic colitis models. Additional manuscripts focused on strain-level oxidative stress profiling and microbial ecosystem resilience are in preparation.

Findings are planned for presentation at future ECCO meetings and will be considered for submission to gastroenterology and microbiome-focused journals, including the Journal of Crohn’s and Colitis or JCC Plus.

ECCO Research Grant

Delineating an uptake-independent function of SR-BI in Paneth cells in metabolic gut inflammation diseases

Awardee: Felix Grabherr
Medical University Innsbruck, Austria

AIM OF THE RESEARCH

Dietary lipids pose a risk for the development of inflammatory Bowel Disease (IBD). Activity of glutathione peroxidase 4 (GPX4), an anti-oxidative selenoenzyme, is impaired in intestinal epithelial cells (IECs) from patients with ileal Crohn's Disease (CD). GPX4 controls intestinal inflammation triggered by dietary polyunsaturated fatty acids (PUFA) and dietary PUFA uptake is associated with CD flares. SR-BI (encoded by Scarb1) is a membrane-bound receptor, mainly reported to be involved in the uptake of cholesterol, and cholesterol uptake has been described to play a role in ferroptosis induction, a cell death pathway which is regulated by GPX4. Paneth cells (PCs), specialised IECs within the small intestine, have been described to be the origin of intestinal inflammation. Preliminary data indicate that PCs sense and translate dietary PUFA stress into intestinal inflammation.

METHODOLOGY THAT WAS USED IN THE RESEARCH

We are working with genetically modified cells, lacking SR-B1 or GPX4, and mice lacking both proteins specifically in PCs to decipher how SR-B1 regulates metabolic-induced intestinal inflammation.

MAIN FINDINGS/RESULTS OF THE RESEARCH

Co-silencing of SR-B1 in GPX4-deficient IECs ameliorates CXCL-1 production, as does co-silencing of PDZK1, which protects SR-B1 from degradation. This phenotype was dependent upon neither LPO scavenging nor arachidonic acid uptake. Reduced phosphorylation of cJUN in SR-B1 and GPX4 co-silenced cells compared to GPX4 single silenced cells indicates a regulatory role of SR-B1 in GPX4-dependent intestinal inflammation. Mice lacking GPX4 solely in PCs develop an enteritis phenotype, which resembles human CD, after being fed a PUFA-containing western diet. An additional knockout of SR-B1 in PCs seems to ameliorate this phenotype, though the final mouse experiment for validation is currently ongoing.

PLAN OF PUBLICATION

A manuscript containing data arising from this grant is currently under review and at least one further manuscript will be prepared when all final data are available from the ongoing experiments.

Results arising from this grant were presented at the ECCO Congresses 2023 (P068), 2024 (P050, P147) and 2025 (P0143).

ECCO Research Grant

iNKT cells immunomodulation and mucosal healing by microbiota-derived lactate (OCELOT)

Awardee: Francesco Strati
Past Affiliation: University of Milano-Bicocca, Milano, Italy
Current Affiliation: Lithuanian University of Health Sciences, Kaunas, Lithuania

AIM OF THE RESEARCH

Invariant natural killer T (iNKT) cells are unconventional T cells involved in mucosal immune homeostasis and Inflammatory Bowel Disease (IBD). OCELOT hypothesised that iNKT cells act as key immune sensors of microbiota-derived metabolites promoting the resolution of intestinal inflammation. In particular, the project investigated whether microbiota-derived lactate induces immunoregulatory iNKT cell (iNKT-reg) functions that promote mucosal healing.

METHODOLOGY THAT WAS USED IN THE RESEARCH

We performed multiparametric flow cytometry analysis of iNKT cells from surgical specimens of Crohn's Disease (CD) patients and correlated iNKT-reg responses with intra-colonic lactate levels. Transcriptomic and epigenetic analyses were used to investigate the molecular pathways underlying the iNKT-reg phenotype in lactate-enriched conditions. The role of microbiota-derived lactate was further validated in vivo using experimental colitis models.

MAIN FINDINGS/RESULTS OF THE RESEARCH

Microbiota-derived lactate promoted an iNKT-reg phenotype protecting against intestinal inflammation. Therapeutic faecal microbiota transplantation enriched in lactate-producing *Lactobacillus* species controlled colitis and promoted the expansion of IL-10-producing iNKT cells. iNKT-reg frequencies also correlated with *Lactobacillus* abundance and tissue lactate levels in CD patients. In vitro, sodium lactate or supernatants from lactate-producing *Lactobacillus plantarum* induced IL-10 production and increased expression of immunoregulatory markers, including TIGIT, TIM-3 and PD-1. These effects were absent with lactate-deficient bacterial strains. In vivo administration of lactate or lactate-producing *L. plantarum* expanded colonic iNKT-reg cells and protected wild-type, but not iNKT-deficient, mice from DSS-induced colitis. Transcriptomic analyses showed that lactate induces regulatory transcriptional programs associated with epigenetic regulation, possibly through histone lysine-lactylation. ChIP-seq analyses are ongoing due to technical challenges.

CONCLUSIONS AND PERCEIVED IMPACT OF THE FINDINGS

This project redefined the role of iNKT cells in intestinal homeostasis by demonstrating that microbiota-derived lactate promotes immunoregulatory iNKT cell responses that

protect against chronic intestinal inflammation. OCELOT opens new avenues of research suggesting that iNKT-reg cells may actively promote epithelial regeneration and barrier restoration through metabolic reprogramming of the intestinal epithelium, supporting a framework in which immune cells directly drive tissue repair.

PLAN OF PUBLICATION

Publication is expected in 2027.

ECCO Research Grant

Establishment of a multi-organ-on-chip model to advance gut-brain communication research and development

Awardee: Laure Maes
Ghent University, Belgium

AIM OF THE RESEARCH

Persistent fatigue severely affects the quality of life of IBD patients and reduces their ability to work. Although IBD patients, even when in clinical remission, report fatigue as one of the most disabling symptoms of their chronic disease, disease management is often focused only on attenuating gastrointestinal symptoms. In order to develop effective therapeutic interventions, a better understanding of what is causing IBD-associated fatigue is required. Therefore, the goal of this project was to develop a human gut–blood–brain in vitro model to explore the impact of extinguished gut inflammation on brain and brain barrier function.

METHODOLOGY THAT WAS USED IN THE RESEARCH

In this project, a human multi-organ-on-chip platform was established mimicking gut–brain communication via the systemic circulation (Figure 1). Extinguished intestinal inflammation was modelled by allowing an intestinal compartment to recover from a mix of pro-inflammatory cytokines. During the recovery, the compartment was fluidically connected to a blood–cerebrospinal fluid (CSF) barrier and a brain compartment. The effect of flow was assessed on each tissue compartment and the compartments were benchmarked against gold standard in vitro models with transepithelial electrical resistance (TEER), paracellular permeability assays, immunofluorescence and gene expression analysis via qPCR. To investigate the effect of extinguished inflammation, we are now performing mRNA sequencing on the distinct compartments and analysing the secreted cytokines/chemokines and extracellular vesicles in the surrogate blood and CSF circulation.

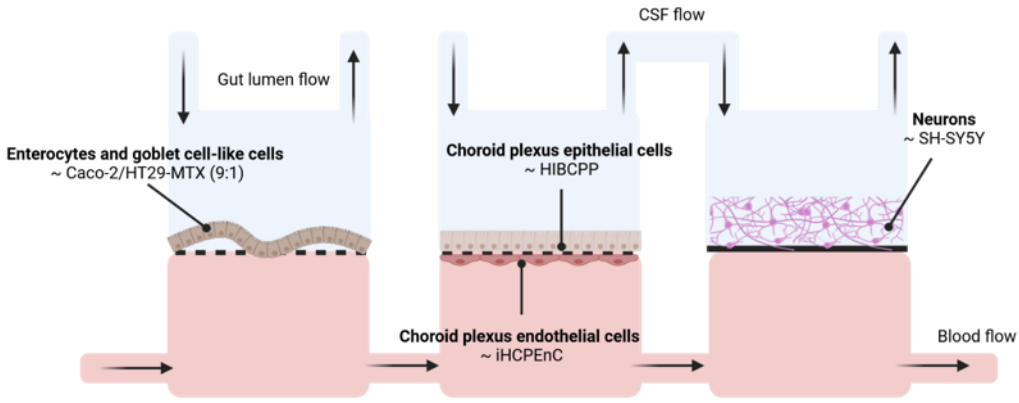


Figure 1. Schematic representation of the gut–brain organ-on-chip model

MAIN FINDINGS/RESULTS OF THE RESEARCH

Integrating a gut lumen, blood and CSF flow in the model has significantly improved the physiological relevance of the different compartments compared to their static counterparts. The intestinal compartment under flow exhibited increased expression of differentiation marker genes compared to static culture, such as LYZ, LGR5, ALPI and CYP3A4, indicating an improvement in cell differentiation. Moreover, flow induced the formation of 3D villi-like structures, mucus production and the reduction of barrier strength towards more physiological relevant levels. The barrier properties of the blood–CSF barrier under flow were not significantly different from a static setup, but less variance among biological replicates was observed in TEER. Neurons differentiated with BDNF and retinoic acid in our model displayed long projections and expressed mature neuronal marker genes including SYP, SNAP25 and TUBB3. Elevated cytokine release in the surrogate blood circulation indicated the responsiveness of the intestinal compartment towards the pro-inflammatory mix. We are now investigating whether resolution of this intestinal inflammation has induced alterations in gene and protein expression at the blood–CSF barrier and brain compartment.

CONCLUSIONS AND PERCEIVED IMPACT OF THE FINDINGS

We have successfully developed an in vitro model that outperforms the traditional 2D static cell cultures in accurately mimicking tissue physiology. Using this model, we aim to identify novel signalling pathways that may advance our understanding of the pathophysiology underlying IBD-associated fatigue.

PLAN OF PUBLICATION

The last results are now being analysed and we are currently writing the findings down in a manuscript. We plan to publish our manuscript by the end of the year.

ECCO Research Grant

Ascertaining the role of the appendix in inflammatory bowel disease in a population-based cohort

Awardee: Manasi Agrawal
Center for Molecular Prediction of IBD (PREDICT), Copenhagen, Denmark

AIM OF THE RESEARCH

Aim 1: To determine the impact of appendicitis and appendectomy on IBD risk.
Aim 2: To determine the impact of appendectomy on IBD outcomes.

METHODOLOGY THAT WAS USED IN THE RESEARCH

Using cross-linked Danish registers, we conducted two matched cohort studies during the study period from January 1996 to December 2024. First, we followed individuals with no IBD diagnosis who underwent appendectomy and matched controls for outcomes Crohn's Disease (CD) and Ulcerative Colitis (UC). Next, we identified individuals who underwent appendectomy following IBD diagnosis and matched them with individuals with IBD and no appendectomy. These were followed for IBD-related outcomes. Statistical analyses included adjusted Cox proportional hazards regression.

MAIN FINDINGS/RESULTS OF THE RESEARCH

To our knowledge, this is the first nationwide study reporting on the impact of appendectomy on IBD risk and outcomes, stratified by relevant clinical variables. We found that appendectomy in childhood and when the appendix was inflamed lowered UC risk, whereas appendectomy in adulthood and in the absence of appendiceal inflammation increased CD risk. Appendectomy after IBD diagnosis was not associated with IBD-related hospitalisation, surgery, systemic corticosteroid use or colorectal cancer on long-term follow-up irrespective of appendiceal inflammation status and IBD subtype.

CONCLUSIONS AND PERCEIVED IMPACT OF THE FINDINGS

These data emphasise the role of the appendix in modulating IBD risk, with effect modification by age at appendectomy, appendiceal inflammation status and IBD subtype. We also report on lack of improvement in IBD-related outcomes with appendectomy following IBD diagnosis.

PLAN OF PUBLICATION

Research presented at (1) ECCO 2025 (Aim 1, poster), (2) ECCO 2026 (Aim 2, poster), (3) DDW 2026 (oral, Aim 2). Manuscript completed and submitted for consideration for publication.

ECCO Research Grant

Identifying Biomarkers Prior to IBD Diagnosis from the Prospective Urban Rural Epidemiology Study (PURE-IBD)

Awardee: Neeraj Narula
McMaster University, Hamilton, Canada

AIM OF THE RESEARCH

The primary aim of this study was to identify novel serum biomarkers preceding IBD onset that may mediate IBD risk in the Prospective Urban Rural Epidemiology (PURE) study and to validate findings in a separate subset of the cohort.

METHODOLOGY THAT WAS USED IN THE RESEARCH

This was a prospective case-cohort study of approximately 12,000 participants in PURE (of whom 127 developed IBD) with serum samples and biomarker data available at baseline. Biomarkers were compared between the IBD and non-IBD cohorts. A 1:1 ratio of cases to controls was selected using propensity-score matching based on age, sex, smoking status, location, education and BMI. The Target 95 immuno-oncology Olink panel was used to assess the concentration of biomarkers. Logistic regression was used to analyse the association between biomarker concentrations and the likelihood of developing IBD. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of these associations, with adjustments made for potential confounders.

MAIN FINDINGS/RESULTS OF THE RESEARCH

A total of 92 biomarkers were assessed. After adjustment for age, sex, region and smoking status, MMP10 was significantly associated with an IBD diagnosis compared to controls [adjusted OR (aOR) 2.46; 95% CI 2.62–4.58, $p<0.001$], with similar findings among Crohn's Disease (aOR 1.63; 95% CI 1.25–2.14, $p<0.001$) and Ulcerative Colitis (aOR 2.67; 95% CI 2.06–3.47, $p<0.001$) individually. No other biomarker assessed was statistically significant.

CONCLUSIONS AND PERCEIVED IMPACT OF THE FINDINGS

We previously identified MMP10 as a biomarker of significance in epidemiologic analyses using the PURE cohort, and this was validated in the present analysis. Given its biologic plausibility and fit with current models of IBD pathogenesis, future studies are warranted to validate our findings.

PLAN OF PUBLICATION

The publication will be submitted for consideration in peer-reviewed journals such as Gastroenterology and Clinical Gastroenterology and Hepatology.

ECCO Research Grant

Deciphering of composition and characteristics of intra- and peritumoral immune cells in human IBD-associated dysplasia and cancer using novel spatial profiling techniques

Awardee: Sofie Frigerio
Tytgat Insitute for Liver and Intestinal Research, Amsterdam UMC

AIM OF THE RESEARCH

We aimed to spatially characterise immune-related adaptations to chronic inflammation in IBD versus non-IBD patients at the transcriptomic and single cell level.

METHODOLOGY THAT WAS USED IN THE RESEARCH

We used paraffin-embedded tissue blocks from IBD and non-IBD patients with dysplasia and/or cancer. Three regions of interest (normal, dysplasia and cancer) were defined and placed together on a single slide. We characterised immune-related adaptations in epithelium and immune cells by digital spatial profiling (DSP) and studied the spatial immune cell composition by imaging mass cytometry (IMC).

MAIN FINDINGS/RESULTS OF THE RESEARCH

Analysis of the epithelial compartment by DSP showed remarkable differences in transcriptome in the normal mucosa in IBD vs non-IBD. Transcriptional pathways related to T cell immune responses were downregulated in IBD. We observed decreased intraepithelial T lymphocyte (IEL) abundance in IBD, confirmed by immunohistochemistry. Moreover, IELs from IBD patients expressed less Granzyme B than IELs from non-IBD patients. In the immune compartment, most transcriptional differences were observed in dysplastic tissue, with the "T cells" pathway being the most differentially expressed in IBD vs non-IBD. Accordingly, preliminary IMC data revealed an increased proportion of T cells in dysplastic lesions compared to non-IBD patients. Moreover, CD4+ T cells from IBD patients showed increased expression of the checkpoint molecules PD-1 and Lag3.

CONCLUSIONS AND PERCEIVED IMPACT OF THE FINDINGS

We demonstrated altered immune-related adaptations to chronic inflammation in IBD patients that may compromise immunosurveillance against colorectal cancer. This study may add a novel concept of how chronic inflammation-induced cell adaptations may favour dysplasia development and progression to cancer.

PLAN OF PUBLICATION

We will publish our findings in two research articles focused on the DSP and IMC data, respectively. For the paper focused on the DSP experiment, we are currently at the manuscript preparation stage. We foresee submission of the first version by October 2024. Regarding the IMC article, we are currently at the stage of analysis and discussion of preliminary data.

ECCO Research Grant

Early prediction of treatment response in children with Inflammatory Bowel Disease with Intestinal Ultrasound

Awardee: E.A. van Wassenaer
Department of pediatric gastroenterology and nutrition, Emma Children's hospital, Amsterdam UMC, Amsterdam, the Netherlands

AIM OF THE RESEARCH

To assess the value of intestinal ultrasound (IUS) in the early prediction of therapeutic response in children with IBD.

METHODOLOGY THAT WAS USED IN THE RESEARCH

This was a prospective longitudinal cohort study in children with Crohn's Disease and Ulcerative Colitis who were starting remission induction therapy. IUS was performed at baseline, week 2, week 6 and week 13. The most affected bowel segment, defined by the highest bowel wall thickness (BWT) at baseline, was selected for longitudinal follow-up. At each time point, clinical assessment and laboratory markers were collected. Treatment response at week 13 was defined on the basis of faecal calprotectin level, with or without improvement in clinical disease activity scores.

MAIN FINDINGS/RESULTS OF THE RESEARCH

In total, 101 children starting different remission induction therapies were included, of whom 52 received anti-TNF therapy. Other therapies included EEN/CDED (n=16), prednisone (n=14), 5-ASA (n=16), vedolizumab (n=2) and ustekinumab (n=1).
In the anti-TNF cohort, the percentage decrease in BWT compared to baseline was higher in responders that in non-responders at 2 and 6 weeks (week 2: -10% [96% CI -23.7% to -2.1%] vs -1% [96% CI -10.4% to 14.1%], p=0.01, and week 6: -34.7% [95% CI -43.6% to -9.6%] vs -5.5% [95% CI -18% to 14%], p<0.001). The corresponding AUROCs were 0.72 and 0.85 at weeks 2 and 6, respectively. Analyses of the predictive value of IUS combined with calprotectin are due.

CONCLUSIONS AND PERCEIVED IMPACT OF THE FINDINGS

This study demonstrates that early IUS assessment at 6 weeks can predict anti-TNF treatment response at week 13 in children with IBD. These findings support the role of IUS as an early, non-invasive monitoring tool to facilitate timely treatment optimisation.

PLAN OF PUBLICATION

A manuscript on the anti-TNF cohort is in preparation for Journal of Crohn's and Colitis. Analyses of IUS dynamics in the other treatment cohorts are ongoing.

ECCO Research Grant

Comparative accuracy of TransPerineal UltraSound (TPUS) versus Magnetic Resonance Imaging (MRI) for the assessment of perianal fistulae in patients with Crohn's disease: a prospective observational longitudinal cohort study

Awardee: Ferdinando D'Amico
IRCCS San Raffaele Hospital, Gastroenterology and Endoscopy, Milan, Italy

AIM OF THE RESEARCH

Magnetic resonance imaging (MRI) is the first-line imaging modality for monitoring of perianal disease in patients with Crohn's Disease (CD). However, its use depends on local availability, costs and expertise. Few studies are available on the role of transperineal ultrasound (TPUS). Performing MRI alone would result in substantial expense for the health service and would be a limitation for the many patients who cannot tolerate the procedure (e.g. due to claustrophobia). For this reason, we urgently need a painless non-invasive, cost-effective and widely available modality to assess perianal disease and to predict disease outcomes. In this observational prospective study, we investigated the accuracy of TPUS versus pelvic MRI for diagnosis and monitoring of the medical and surgical therapy of perianal fistulas in CD patients.

METHODOLOGY THAT WAS USED IN THE RESEARCH

Adult patients with a confirmed CD diagnosis and perianal fistulas were enrolled by the Gastroenterology Department of the San Raffaele Hospital. Subjects underwent both TPUS and pelvic MRI at baseline. After radiological and ultrasound evaluation, subjects were treated according to international ECCO Guidelines. Finally, patients underwent both TPUS and pelvic MRI after 12 months. The primary endpoints of the study were the incidence of perianal fistulas at baseline and the rate of fistula closure at 12 months as assessed by both TPUS and MRI.

MAIN FINDINGS/RESULTS OF THE RESEARCH

As of 29 April 2025, 47 patients had been included (40.4% male with a mean age of 46±16 years). Definitive data on the comparative accuracy of MRI and TPUS are not yet available as not all patients have completed the follow-up.

CONCLUSIONS AND PERCEIVED IMPACT OF THE FINDINGS

TPUS and MRI are both recommended by international guidelines. Ultrasound is preferred as it is faster, less expensive and better tolerated by patients. We expect TPUS to have comparable accuracy to MRI. TPUS could become the reference tool for evaluating CD patients with perianal disease, significantly reducing healthcare costs.

PLAN OF PUBLICATION

We intend to submit an abstract to the ECCO Congress 2026 and to submit the full paper for publication by the second quarter of 2026.

ECCO Grant

The PTPN2 loss-of-function variant as predictor of therapeutic response to JAK-Inhibitor therapy in IBD

Awardee: Marianne R. Spalinger
Department of Gastroenterology and Hepatology, University Hospital Zürich

AIM OF THE RESEARCH

JAK inhibition has emerged as a novel, promising therapeutic strategy in IBD. Protein tyrosine phosphatase non-receptor type 2 (PTPN2) is a natural inhibitor of the JAK-STAT signalling pathway and carriers of loss-of-function variants in PTPN2 are more susceptible to develop IBD. The aim of this project was to define whether PTPN2 dysfunction can predict effective JAK-inhibitor therapy.

METHODOLOGY THAT WAS USED IN THE RESEARCH

Colitis was induced in mice with tissue-specific PTPN2 deletion in macrophages. The pan-JAK inhibitor tofacitinib or the JAK1 inhibitors filgotinib and upadacitinib were used as treatment. To translate our findings from the preclinical mouse model to the clinical setting, we used peripheral blood mononuclear cells (PBMCs) from PTPN2-genotyped IBD patients and intestinal samples from patients treated with upadacitinib.

MAIN FINDINGS/RESULTS OF THE RESEARCH

All three JAK inhibitors ameliorated colitis in mice with a PTPN2 deletion in macrophages, while the JAK1 inhibitors were more potent in suppressing colitis in wild-type mice, which was attributed to an inhibition of the NLRP3 inflammasome/IL-1β production. JAK1 inhibitors inhibit inflammasome activation in human cells independently of their PTPN2 genotype. Single cell sequencing showed that upadacitinib also suppressed IL-1β in UC patients, which was positively associated with treatment response. Thus, while all three JAK inhibitors suppressed colitis susceptibility mediated by hyperactive JAK/STAT signalling, only upadacitinib and filgotinib suppressed IL-1β production.

CONCLUSIONS AND PERCEIVED IMPACT OF THE FINDINGS

In addition to inhibiting JAK/STAT signalling, upadacitinib and filgotinib have the capacity to inhibit NLRP3/IL-1β, an effect contributing to their high efficacy in recent clinical trials. Overall, our findings suggest that tofacitinib might be most effective in patients with hyperactive JAK/STAT signalling, such as PTPN2 variant carriers, while upadacitinib and filgotinib might be especially useful in patients who show elevated IL-1β/inflammasome activation.

PLAN OF PUBLICATION

The work conducted with the support of this grant has been published in Nature Communications (doi: https://doi.org/10.1038/s41467-026-71808-y).

ECCO Research Grant

Decoding the neuroimmune crosstalk in inflammatory bowel diseases

Awardee: Silvia Cerantola
Department of Pharmaceutical and Pharmacological Sciences, University of Padova, Italy

AIM OF THE RESEARCH

This research aimed to decode the neuroimmune interactions between the catecholaminergic system and the innate immune sensor TLR4 in dinitrobenzene sulfonic acid (DNBS)-induced ileitis.

METHODOLOGY THAT WAS USED IN THE RESEARCH

Male c57bl6 wild type (wt) mice or Toll-like receptor 4 knockout (tlr4 ko) mice were subjected to peripheral cathecolamine depletion using 6-hydroxidopamine (6-ohda). In both wt and tlr4ko mice ileitis was induced by 2,4-dinitrosulfonic benzenic acid (dnbs). Changes in ileal muscle tension, alterations in gastrointestinal transit (GIT) time and integrity of the myenteric plexus were analysed. Neuroimmune biomarkers have been identified to disclose potential correlations between functional data and protein expression levels in order to possibly define an algorithm of IBD severity.

MAIN FINDINGS/RESULTS OF THE RESEARCH

In WT mice, peripheral sympathectomy resulted in a marked decrease in carbachol-mediated contraction together with a significant increase in NANC-mediated relaxation, mainly mediated by nNOS-derived NO. In TLR4KO mice, 6-OHDA treatment did not affect cholinergic or nitrergic responses. 6-OHDA treatment caused a significant increase in S100β, GFAP and PLP-1 immunoreactivity in WT mice and a reduction in HuC/D+ neurons in WT and TLR4KO mice, suggesting the development of enteric neuronal dysfunction. GIT time was affected only in WT 6-OHDA mice. In the presence of DNBS, 6-OHDA treatment did not alter cholinergic and nitrergic responses in WT mice, whereas it increased NO-mediated relaxation in TLR4KO mice. Sympathectomy, in the presence of inflammation, increased GIT time only in WT mice.

CONCLUSIONS AND PERCEIVED IMPACT OF THE FINDINGS

In WT mice, peripheral sympathetic innervation elicits an enhanced GIT time, marked glia activation and impaired cholinergic-mediated neuromuscular response due to higher NO-mediated relaxation. TLR4 signalling is involved in maintaining ENS integrity in the presence of sympathectomy and inflammation, confirming an important role of catecholamine–TLR4 crosstalk in ensuring the integrity of gut.

PLAN OF PUBLICATION

- 1 Poster presentation at IBS Days on the 21/06/2022, Bologna, Italy
- 1 Paper is under final preparation and will be submitted to the Journal of Crohn's and Colitis

ECCO Research Grant

Deciphering the role of plasmacytoid dendritic cells in gut-associated lymphoid tissues during homeostasis and Crohn's disease

Awardee: Urs Michael Mörbe
Formerly: Technical University of Denmark (DTU), Denmark
Currently: University of Copenhagen (UCPH), Denmark

AIM OF THE RESEARCH

T cells are key drivers of Crohn's Disease (CD); however, the molecular mechanisms underlying their activation and the roles of other immune cells remain incompletely understood. Myeloid cells, particularly dendritic cells (DCs), modulate immune responses, including the activation of T cells in gut-associated lymphoid tissues (GALT), which are specialised immune priming sites. Recent research has focused on classical DCs, but plasmacytoid DCs (pDCs), which are enriched in the mucosa of IBD patients, remain poorly characterised. This study aimed to elucidate the distribution of DCs and their functions in relation to intestinal immune responses during CD and homeostasis.

METHODOLOGY THAT WAS USED IN THE RESEARCH

We analysed clinical resections from patients with CD and non-inflamed controls. Using a protocol to isolate human GALT from the surrounding lamina propria, we characterised cells via flow cytometry, histology and single-cell RNA sequencing (scRNA-seq).

MAIN FINDINGS/RESULTS OF THE RESEARCH

Our scRNA-seq analysis mapped intestinal myeloid cells during CD. We described the differentiation trajectories of DCs and alterations in disease. Notably, we identified a CCR7-expressing classical DC cluster that was selectively enriched in the inflamed lamina propria and exhibited enhanced NF-κB signaling, cytokine production and transcriptional programs regulating lymphocyte proliferation.
We found that pDCs localised almost exclusively to the GALT T cell zones rather than to the lamina propria. Unlike their blood counterparts, intestinal pDCs displayed an immunosuppressive expression profile.

CONCLUSIONS AND PERCEIVED IMPACT OF THE FINDINGS

We offer novel insights into intestinal myeloid cell biology during CD and homeostasis. Our findings reveal substantial heterogeneity among myeloid cells and provide a valuable resource for future research into the contributions of these cells to IBD.

PLAN OF PUBLICATION

Findings on DC differentiation have been published in Science Immunology. scRNA-seq data generated during this project contributed to a study published in the Journal of Experimental Medicine. Our findings on pDCs remain unpublished. We plan to publish these results after elucidating the molecular mechanisms that render intestinal pDCs more immunosuppressive than their blood counterparts.