In PBMC from patients with the CT genotype, basal mRNA expression of those genes was already elevated, and their mRNA expression level following IFNγ treatment was clearly higher than those observed in PTPN2 wild-type cells. Activation of PTPN2 by spermidine clearly ameliorated IFN-γ-induced up-regulation of ICAM1, IFNG and NOD2 mRNA expression in all patients (p < 0.05). Of particular interest and despite elevated IFN-γ responses, spermidine treatment was more effective in patients with the CT genotype (p < 0.05).

Conclusions: Our results demonstrate that spermidine treatment is effective in reducing inflammatory signalling in PBMC from IBD patients. The presence of the C allele in PTPN2 SNP rs1893217 promotes inflammatory responses, but concurrently renders the cells more susceptible to the anti-inflammatory effects of spermidine. This indicates that spermidine treatment might be a promising novel therapeutic approach in IBD patients and that the C allele might serve as a good predictor for treatment response. This might be a step towards personalised medicine in the management of IBD.

**DOP014**

**Impact of genetic variation on gene and protein expression in Crohn’s disease**

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**Background:** Understanding the genetic landscape of Crohn’s disease (CD) may help shed light on disease aetiology to inform disease
understanding and aid biomarker identification. Towards this end, we evaluated the association of genetic polymorphisms with baseline intestinal and blood gene and protein expression in the phase 3 UNITI program.

Methods: The UNITI studies assessed the efficacy of ustekinumab induction and maintenance therapies in patients with moderate-to-severe CD who had previously failed TNF-antagonist therapy (UNITI-1) or conventional therapies (UNITI-2). Gene expression was profiled using RNA extracted from intestinal biopsies and whole blood using Affymetrix HG U133 Plus 2 arrays and 11 protein analytes were measured in serum. Additionally, subjects were genotyped on the Illumina Infinium Omni5Exome platform. Gene expression quantitative trait loci (eQTL) mapping was performed separately in rectum (n = 161), ileum (n = 142), and whole blood (n = 132). Protein quantitative trait loci (pQTL) mapping was performed in 864 serum samples.

Results: At a false discovery rate of 5%, we identified local cis-eQTLs for 1308 genes in rectum, 806 in ileum, and 1499 in whole blood. We observed highly significant overlap of the cis-eQTL gene sets between biopsy regions and between blood and biopsy. Furthermore, we found significant enrichment of genome-wide association study (GWAS) associated single-nucleotide polymorphisms (SNPs) within all eQTL sets, particularly from SNPs associated with inflammatory bowel disease and other immune-mediated diseases. In the limited set of proteins we tested for association with genetic variants, we identified four highly significant pQTLs: two independent cis-pQTLs for MMP1, one cis-pQTL for MMP3, and one cis-pQTL for IL17F. These serum analytes were significantly elevated in CD compared with healthy subjects, and these pQTLs explained a portion of the variance in their serum levels: 13% for MMP1, 6% for MMP3, and 8% for IL17F. There was a trend for association between the MMP1 pQTL SNPs with MMP1 gene expression in blood, but no association of the MMP3 and IL17F pQTL SNPs with gene expression.

Conclusions: We integrated genetic information, gene and protein expression, and existing data from GWAS to provide insights into the molecular mechanisms underlying CD. From these analyses, we found eQTLs in both biopsy and blood that are enriched for disease-associated genetic variants and also identified highly significant associations between genetic variants and protein biomarkers of CD disease activity.

DOP015
Disregulation of cell-type-specific long ncRNA in the ileum of treatment naive early onset Crohn disease

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Background: Long non-coding RNAs (IncRNA) are key regulators of gene transcription and many show tissue-specific expression. We previously defined a novel inflammatory and metabolic ileal gene signature in treatment naive paediatric Crohn disease (CD). We now extend our analyses to include potential regulatory IncRNA.

Methods: Using RNAseq of the Crohn’s & Colitis Foundation (CCF)-sponsored RISK study, we systematically profiled IncRNAs and protein-coding genes expression in 177 ileal biopsies. Co-expression analysis was used to identify functions and tissue-specific expression. RNA in situ hybridisation was used to validate expression. RT-PCR was used to test IncRNAs regulation by IL-1β in Caco-2 enterocytes.

Results: We characterise widespread dysregulation of 459 IncRNA in the ileum of CD patients. Using only the IncRNA in discovery and independent validation cohorts showed as accurate patients’ classification as the protein-coding genes, linking IncRNA to CD pathogenesis. Co-expression and functional annotation enrichment analyses across several tissues and cell types showed that the up-regulated LINC01272 is associated with a myeloid pro-inflammatory signature, while the down-regulated HNF4A-AS1 exhibits association with an epithelial metabolic signature. We confirmed tissue-specific expression in biopsies using in situ hybridisation, and validated regulation of prioritised IncRNA upon IL-1β exposure in differentiated Caco-2 cells. Finally, we identified significant correlations between LINC01272 and HNF4A-AS1 expression and more severe mucosal injury.

Conclusions: We systematically define differentially expressed IncRNA in the ileum of newly diagnosed paediatric CD. We show IncRNA utility to correctly classify disease or healthy states and demonstrate their regulation in response to an inflammatory signal. These IncRNA, after mechanistic exploration, may serve as potential new tissue-specific targets for RNA-based interventions.

DOP016
Metagenomic analysis of intestinal mucosa revealed an IBD-specific shift in the eukaryotic gut virome composition at early stages of gut inflammation

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Background: Intestinal dysbiosis is one of the causes underlying the pathogenesis of inflammatory bowel disease (IBD), encompassing ulcerative colitis (UC) and Crohn’s disease (CD). Besides bacteria, microbiota comprises both prokaryotic and eukaryotic viruses (gut virome). Although many works defined the gut virome of stools, the viral community of intestinal mucosa from IBD patients is under-studied. We profiled the entire eukaryotic viral populations of gut mucosal samples from early-diagnosed patients with IBD to uncover viral species associated with disease onset.

Methods: Publicly available RNA-seq data were retrieved from NCBI GEO (GSE57945). FASTQ reads of gut mucosa from young (2–17 years) naïve patients, early-diagnosed for CD (n = 243) and UC (n = 73), and from healthy subjects (n = 43, Ctrl) were adaptor trimmed, quality controlled, and mapped to the hg38 human reference genome with TopHat for splicing specific alignment. Unaligned reads were used for metagenomic analysis. Viral reads were visualised with Integrative Genomics Viewer (IGV; Broad Institute). Functional enrichment for Gene Ontology (GO) biological processes was performed with the Gene Set Enrichment Analysis (GSEA) software. Specific viral transcript abundance was confirmed in a validation cohort of patients by qRT-PCR. Statistical analysis was performed with IBM SPSS and Graph Pad 7-Prism.

Results: By GSEA analysis, GO data sets related to virus response were enriched in IBD patients compared with controls. Such enrichment was associated with specific eukaryotic viral infections of mucosal