SNPs. An inverse correlation was present between free anti-TNF-α and IL-26 serum levels (r=–0.36; p=0.01).

Conclusions: IL-26 SNPs may compromise translocated bactDNA clearance in CD patients, facilitating an upheld proinflammatory environment. This may contribute to an increased anti-TNF-α consumption in CD patients with bactDNA.

P077
Histological remission in ulcerative colitis: an analysis of two independent cohorts

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Background: The relationship of histological and clinical or endoscopic measures of ulcerative colitis (UC) is not well-described. Based on prior analysis[1], we proposed a definition of Histological remission (HR) using selected features of the Geboes score (neutrophils in <5% of the crypts, no crypt destruction, ulceration, or erosion). Here we validate the definition in two additional independent UC cohorts.

Methods: Biopsies were collected during endoscopies at screening and post-treatment in two phase 2 clinical trials targeting patients (pts) with moderate to severe UC defined as a Mayo score of 6–12 inclusive, including endoscopy score ≥2 (Table 1). All endoscopies were videoed and centrally read using Mayo endoscopy subscore. A Mayo endoscopic score ≤1 defined endoscopic healing (EH). A single, blinded histopathologist assessed 453 biopsies from 219 pts in 54781532UCO2001 and 526 biopsies from 103 pts in PROgECT. Association of dichotomous endpoints was assessed by Fisher's exact test. Clinical differences between histological remitters and non-remitters were evaluated by t-test. P-values <0.05 were considered significant.

Results: Performance of the histological endpoint was highly reproducible in 54781532UCO2001 and PROgECT. Histological remission was significantly associated with endoscopic healing in both studies across all the time points. 92% and 90% of pts who achieved endoscopic healing at wk 8 in 54781532UCO2001 and wk 30 in PROgECT, respectively, also achieved histological remission. Furthermore, pts with histological remission had significantly lower disease activity including lower stool frequency and rectal bleeding scores compared to histological non-remitters (e.g. mean Mayo=3.78 vs. 7.52 at wk 8 in 54781532UCO2001). Early (wk 4) HR was also a strong indicator of wk 8 HR, EH, and clinical response/remission in 54781532UCO2001 (all p<0.005). In PROgECT, 73% of wk 6 HR achieved long-term (wk 30) HR (p=0.0013).

Conclusions: Histological remission defined as minimal residual microscopic disease and absence of epithelial damage is highly reproducible in multiple UC cohorts. Histological remitters are more likely to achieve endoscopic and clinical response/remission.

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P078
Gut microbiome profiling of MMP-9 deficient mice and their wild-type littermates in a model of acute DSS-induced colitis

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Background: Commensal microbiota help to educate the immune system in the periphery and a number of involved immune cells have recently been characterized. However, specific molecular determinants in these processes are not known and, reciprocally, little information exists about single host determinants that alter the microbiome. Matrix metalloproteinase (MMP)-9 deficiency has previously been linked to alterations in gut microbiota composition in a model of infectious colitis [1].

Methods: Acute colitis was induced in MMP-9 knockout (KO) mice (n=10) and their wild-type (WT) littermates (n=10) via oral administration of 3% dextran sodium sulphate (DSS) for 7 days followed by 2 days of regular drinking water. Control mice (10 WT and 10 MMP-9 KO) received normal drinking water throughout the experiment. Both genotypes were raised under identical environmental conditions for more than 15 years and were co-housed during the experiment according to phenotype (control vs DSS). Faecal samples were collected at time of sacrifice and immediately frozen at –80°C. Illumina MiSeq sequencer was used for 16S rDNA paired-end sequencing targeting the V4 hypervariable region. Sequencing depth was downsized to 10000 reads/sample. Taxonomic annotation was performed with Ribosomal Database Project. PICRUSt was used for metagenome prediction and analysed with STAMP software (version 2.1.3). R software was used for statistical analysis with multiple testing correction (Bonferroni).

Results: No significant differences in clinical or histopathological parameters were found between both genotypes (WT and MMP-9 KO) after induction of acute colitis. Observed microbial richness (genus level, t-test) and microbiota composition (Bray-Curtis dissimilarities, adonis) were not significantly influenced by genotype. In contrast, weight loss, disease activity index, cage and phenotype (control vs DSS) did significantly influence the intestinal microbiota composition (envfit, r2>0.7, p=0.001). The genera *Bacteroides* and *Alistipes* explained most of the variability in microbiota composition between genotype in the control group, whereas this was the case for the genera *Bacteroides* and *Allobaculum* in the DSS group (Constrained Principal Coordinate Analyses, capscale). After multivariate analysis (MaAsLin, p<0.05), however, cage was identified as the sole driver of microbiota composition variability. Functional profiling indicated

Abstract P077 – Table 1. Trial characteristics of 54781532UCO2001 and PROgECT

	54781532UCO2001	PROgECT
Study	Placebo-controlled	Open-label
Study agent	Peficitinib, a Janus kinase inhibitor	Golimumab, an anti-TNFa therapy
Dosing regimen	Wks 0–8: placebo, JNJ-54781532 25 mg once daily (QD), 75 mg QD, 150 mg QD, or 75 mg twice daily by 1:1:1:1:1 randomization ratio	Wk 0: 200 mg SC Wk 2: 100 mg SC Wks 6–50: 100 mg per 4 wks or country approved maintenance dose
Endoscopy with biopsies	Wks 0, 4 (optional) & 8	Wks 0, 6 & 30

that both genotype and phenotype influenced the metagenome (PICRUSt). However, after multiple testing correction, only phenotype remained significantly associated with changes in metagenomic profile.

Conclusions: Changes in gut microbiota composition were mainly driven by DSS and were not significantly altered by MMP-9 gene knockout.

References:

[1] Rodrigues DM, (2012), Matrix metalloproteinase 9 contributes to gut microbe homeostasis in a model of infectious colitis, BMC Microbiol, 105, 12

P079
Association of gut microbiota with mucosal inflammation in ulcerative colitis

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Background: Disturbance in gut microbiota (dysbiosis) is a characteristic feature of ulcerative colitis (UC). However it remains unclear whether this dysbiosis contributes to disease pathogenesis by driving immune dysregulation or is merely secondary to mucosal inflammation and/or a result of host immune response. We aimed to determine whether microbiota dysbiosis varied between areas of inflamed and non-inflamed colon in patients with UC and whether this was associated with a humoral immune response.

Methods: We collected colonic biopsies from histologically confirmed areas of inflamed and non-inflamed colon from 15 patients with active left sided ulcerative colitis or proctosigmoiditis. DNA was extracted using the FASTSpin Kit and gut microbiota was characterized using 16s rRNA based analysis of the V3–V4 region (Illumina MiSeq). Quality control and operational taxonomic unit classification of sequences was executed using QIIME. As a marker of mucosal humoral immune responses, inflamed and non-inflamed colonic biopsy samples were cultured in media (RPMI + 10% FCS) for 1 to 3 days prior to measurement of immunoglobulin production (IgA, IgG and IgM) by ELISA.

Results: Consistent with previous observations patients with UC demonstrated reduced bacterial diversity with an increase in *Proteobacteria*, *Bacteroides* and *Clostridiales* species along with a decrease in *Firmicutes* to *Bacteroides* ratio. No differences were found in the microbial diversity nor phylae and genera in mucosally adherent gut microbiota between inflamed and non-inflamed colonic segments in patients with active UC. This observation was also seen when patients were subdivided based on disease activity as defined by Mayo scoring. Total immunoglobulin production did not differ between inflamed (n=6, mean 4966 ± sd 3670 ng/ml) and non-inflamed tissue (n=11; mean 5756 ± sd 8989 ng/ml; $p>0.05$) suggesting that equal numbers of antibody-producing B cells are present regardless of inflammation.

Conclusions: We have demonstrated that the dysbiosis observed in patients with UC is consistent and is not influenced by mucosal inflammation or disease activity. Mucosal immunoglobulin production was not upregulated at sites of inflammation possibly suggestive of a uniform humoral response across the colon; although future work may uncover differences in antibody specificity to UC-associated dysbiosis. The mechanism for the complex interplay between the host immune system and gut microbiota in contributing to mucosal inflammation remains to be understood.

P080
IL-10 induction properties of the TLR-9 agonist cobitolimod – a candidate for treatment of active ulcerative colitis in late stage of clinical development

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Background: Cobitolimod (DIMS0150, Kappaproct®) is an oligonucleotide that acts as a Toll-Like Receptor 9 (TLR-9) agonist and is able to induce clinical remission in patients with active ulcerative colitis (UC) after topical administration. To gain further insights into the mechanism of action of cobitolimod we studied the stimulatory properties of cobitolimod in induction of IL-10 *in vitro*.

Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from buffy coats of healthy blood donors and were cultured with increasing concentrations of cobitolimod (0.1–100 μM). In control experiments a CpG reverted form of cobitolimod (IDX0526) was tested. The IL-10 levels were analyzed by ELISpot and ELISA assays. Furthermore, PBMCs isolated from whole blood of patients with UC were exposed to cobitolimod.

Results: PBMCs from different healthy donors all showed a dose dependent IL-10 induction as analyzed by ELISpot in response to cobitolimod. In agreement with the results obtained by ELISpot data, cobitolimod resulted in a dose dependent increase of IL-10 levels in the supernatant using the ELISA measure. Cobitolimod gave rise to the highest IL-10 response at 100 μM and was not effective at lower concentrations (0.1 μM to 1 μM), In PBMCs derived from patients with UC cobitolimod induced IL-10 expression levels in a dose dependent manner and to a similar extent as observed in healthy individuals.

Conclusions: The data illustrate that cobitolimod induces IL-10 expression in PBMCs derived from healthy individuals and ulcerative colitis patients and that this induction was dose-dependent. The *in vitro* dose response relationship provides further support for the upcoming clinical phase IIb study named CONDUCT in which different doses of cobitolimod will be administered at different frequencies to patients with moderate to severe, treatment refractory, active UC.

P081
10 years of the UK Inflammatory Bowel Disease (IBD) Audit and the journey is just beginning

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