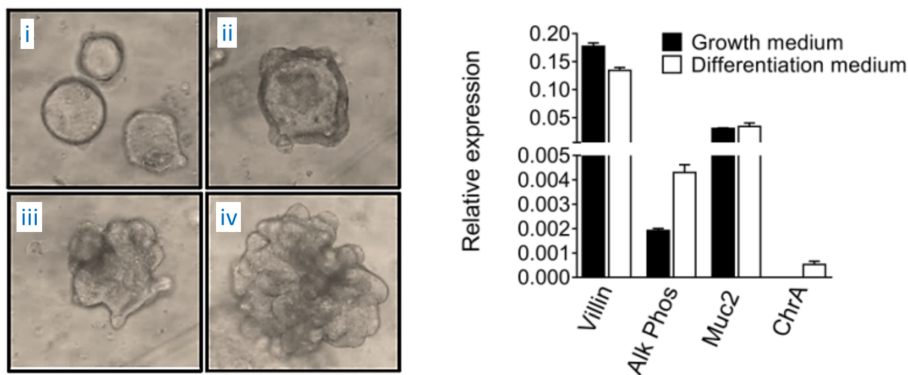
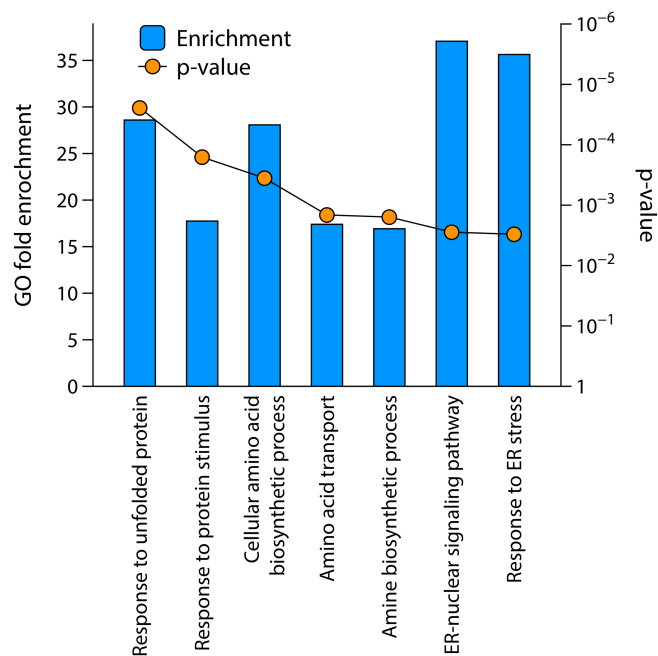


Supplementary Figure 1



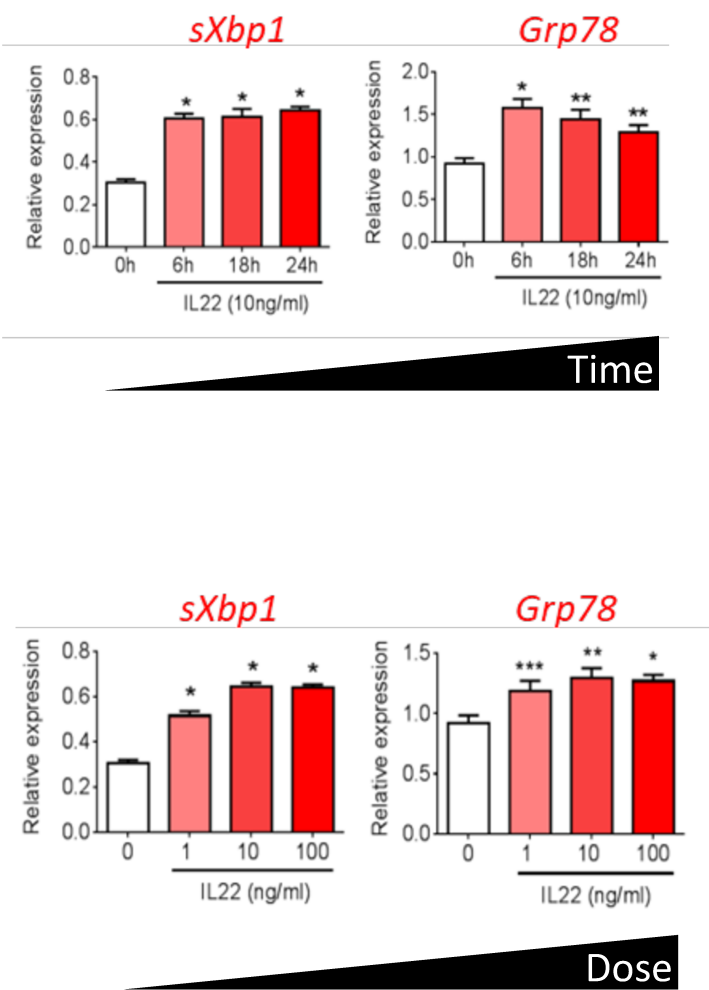
**Supplementary Figure 1: Generation of murine colonoids as a tool to interrogate immune-epithelial interactions.** *Left panel* shows 3D colonic epithelial “miniguts” were grown from isolated mouse colonic crypt units. Images depict development of organoids over time. **i**, 3 days, **ii**, 4 days, **iii**, 5 days **iv**, 6 days post isolation/passage. *Right panel* - Expression of epithelial markers Villin (all epithelial cells), Alkaline phosphatase (mature enterocytes), Mucin (goblet cells), and chromogranin A (endocrine cells) in colonoids cultured in growth and differentiation medium.

Supplementary Figure 2



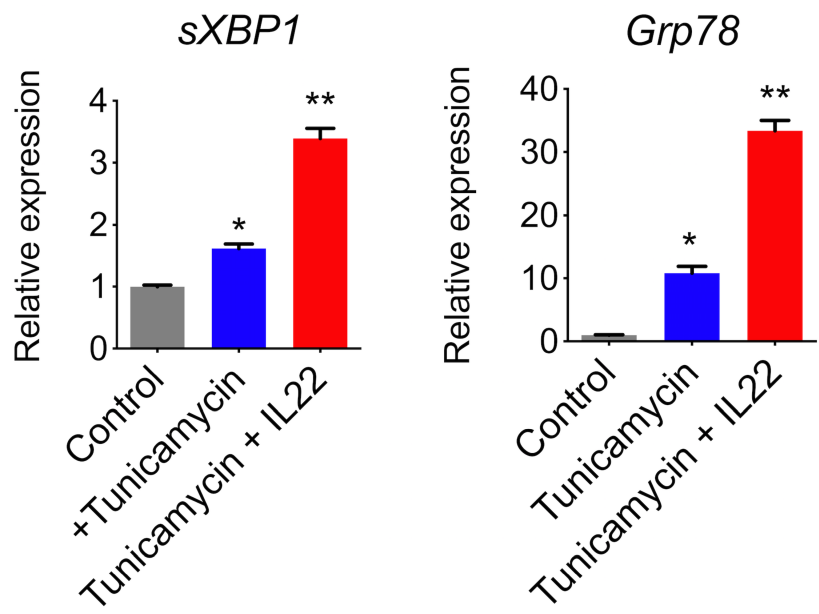
**Supplementary Figure 2: Tunicamycin induces an ER stress response transcriptional module in colonic epithelial cells.** Enrichment analysis for functional annotation groups (GO biological processes) of 163 genes that were significantly ( $P < 0.05$ ) differentially expressed ( $\pm 2$  fold change) by colonoids after treatment with tunicamycin ( $n = 3$ ) compared to vehicle treated colonoids ( $n = 3$ , Mouse Gene 2.0 ST array, Affymetrix).

Supplementary Figure 3



**Supplementary Figure 3: IL22 induces an ER stress response transcripts in a time and dose dependent manner.** Real time qPCR analysis of ER stress transcript expression in colonoids exposed to IL22 for varying amounts of time, and different doses of IL22 (f, n=6 for each dose or time point). Bars show mean expression and error bars depict SEM. \*P<0.005, \*\*P<0.02, \*\*\*P<0.05 (Mann Whitney U Test).

Supplementary Figure 4

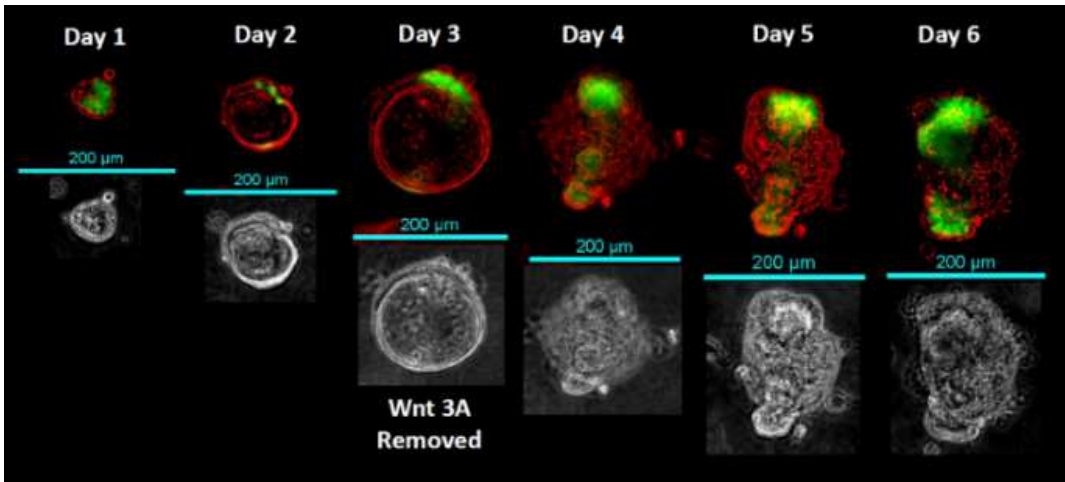


**Supplementary Figure 4: IL22 synergistically augments ER stress induced by tunicamycin in colonoids.** Real time qPCR analysis of ER stress transcript expression in colonoids exposed to tunicamycin in the presence or absence of IL22 (n=6 for condition). Bars show mean expression and error bars depict SEM. \*P<0.0025 (vs control), \*\*P<0.0025 (vs tunicamycin alone). Mann Whitney U Test.

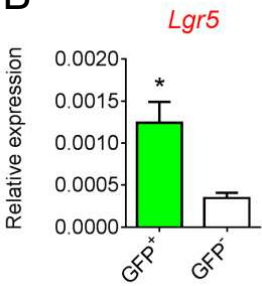


Supplementary Figure 5

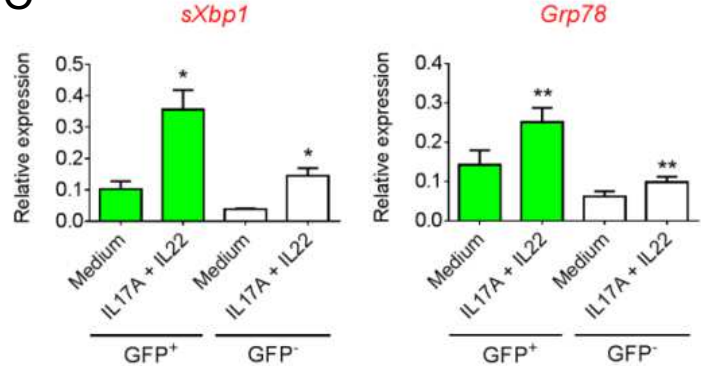
A



B

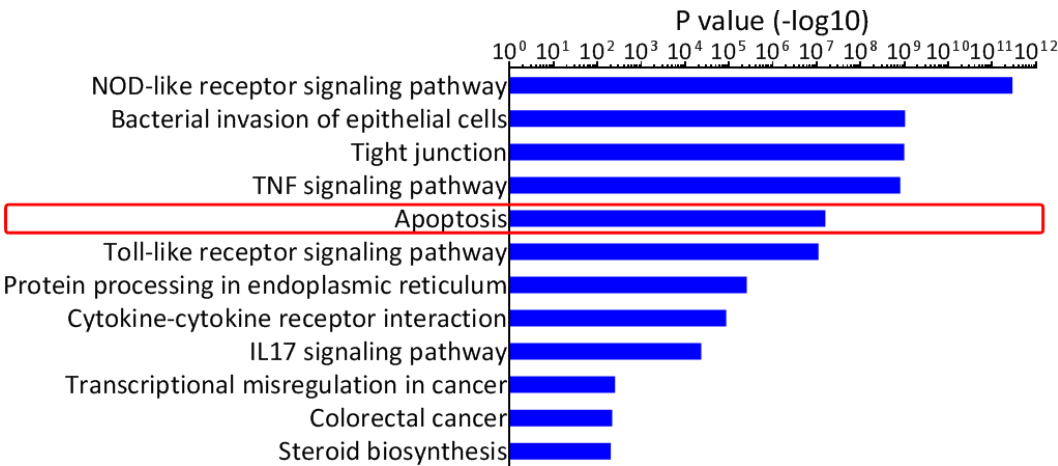


C

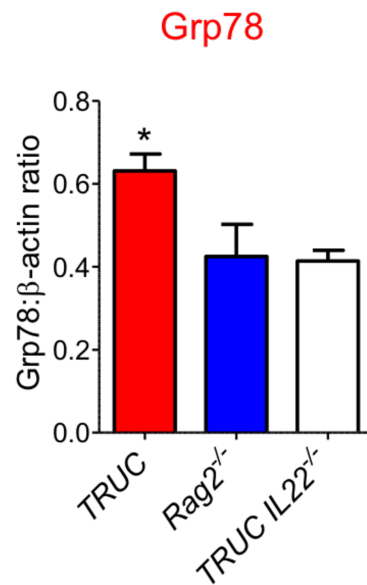


**Supplementary Figure 5: Generation of LGR5-eGFP colonoids.** (A) Microscopy of colonoids generated from *Lgr5* GFP mice at different days of development. (B) Real time PCR analysis of *Lgr5* mRNA expression in FACs sorted GFP<sup>+</sup> and GFP<sup>-</sup> EpCam<sup>+</sup> epithelial cells from colonoids (n=6) from *Lgr5*-GFP reporter mice. (C) Real time PCR analysis of *sXbp1* and *Grp78* mRNA expression in FACs sorted GFP<sup>+</sup> and GFP<sup>-</sup> EpCam<sup>+</sup> epithelial cells from colonoids (n=6) from *Lgr5*-GFP reporter mice. \*P<0.005, \*\*P<0.05.

Supplementary Figure 6

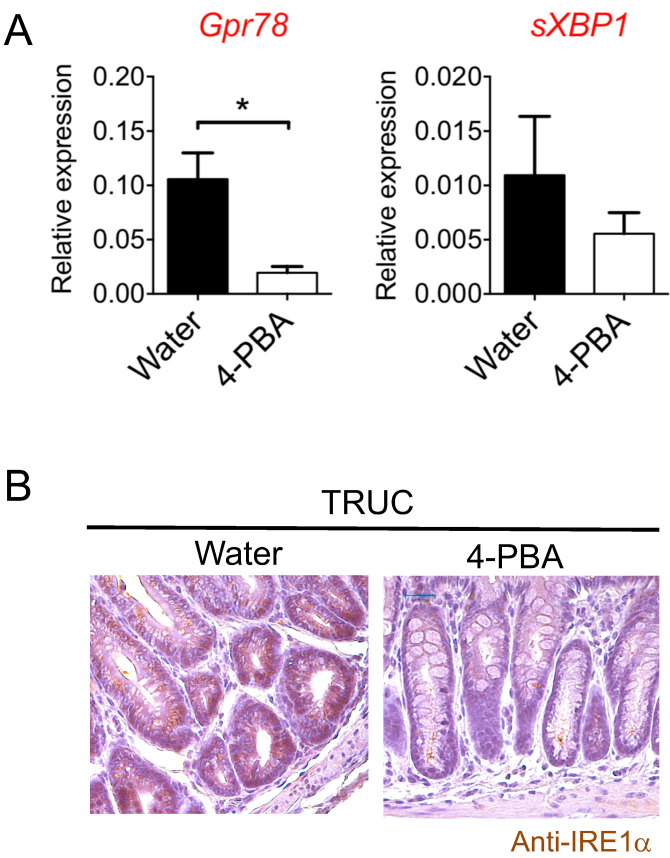


**Supplementary Figure 6:** KEGG pathway analysis of differentially expressed genes in defined signalling pathways in IL22 treated colonoids from ERR247358-ERR247389.

**Supplementary Figure 7**

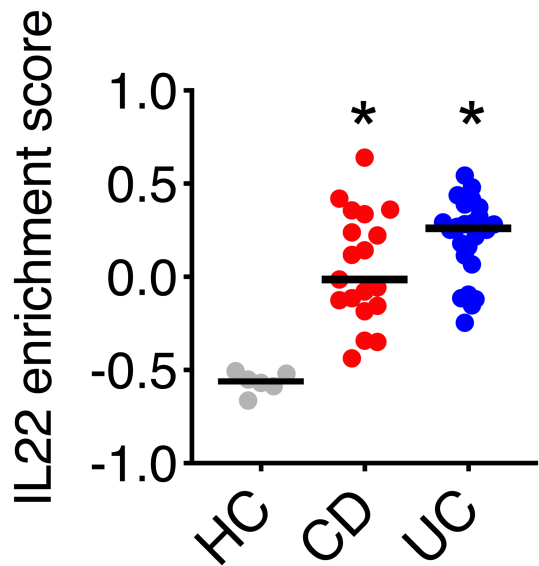
**Supplementary Figure 7: Densitometry plot of Grp78 protein expression in Western blot from colon of TRUC mice.** Western blots of Grp78 protein expression in the colon of TRUC (n=9) Rag2<sup>-/-</sup> (n=4) and TRUC IL22<sup>-/-</sup> mice (n=5). \*P<0.01 (vs Rag2<sup>-/-</sup> and TRUC IL22<sup>-/-</sup>).

Supplementary Figure 8



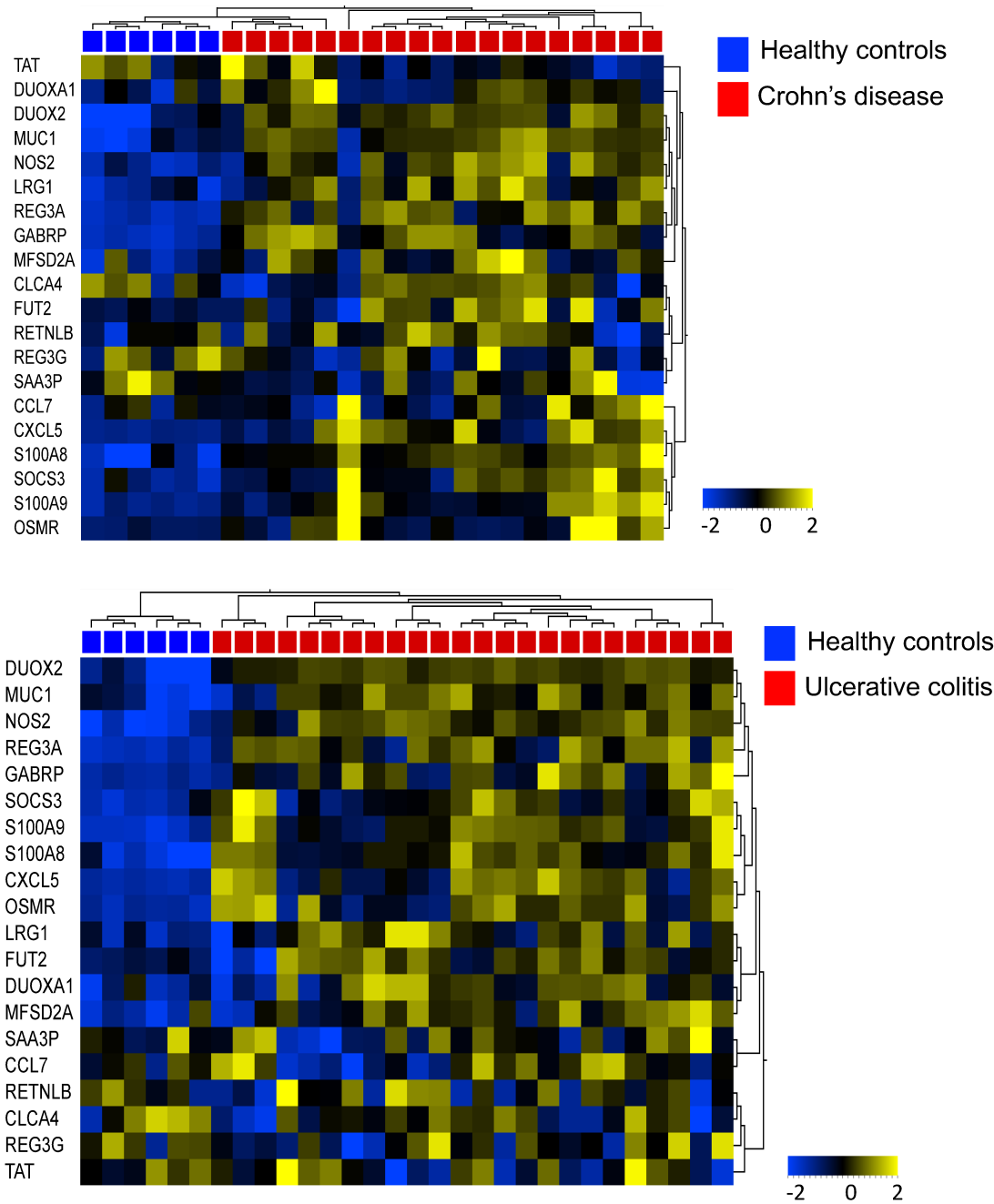
**Supplementary figure 8: 4-PBA reduces colonic ER stress in TRUC mice.** (A) Real time PCR analyses of ER stress transcript expression in the colon of the distal colon of TRUC mice treated with 4-PBA in drinking water (n=8) or water alone (n=8). \*P<0.025, and representative immunohistochemistry (IRE1 $\alpha$  immunoreactivity).

Supplementary Figure 9



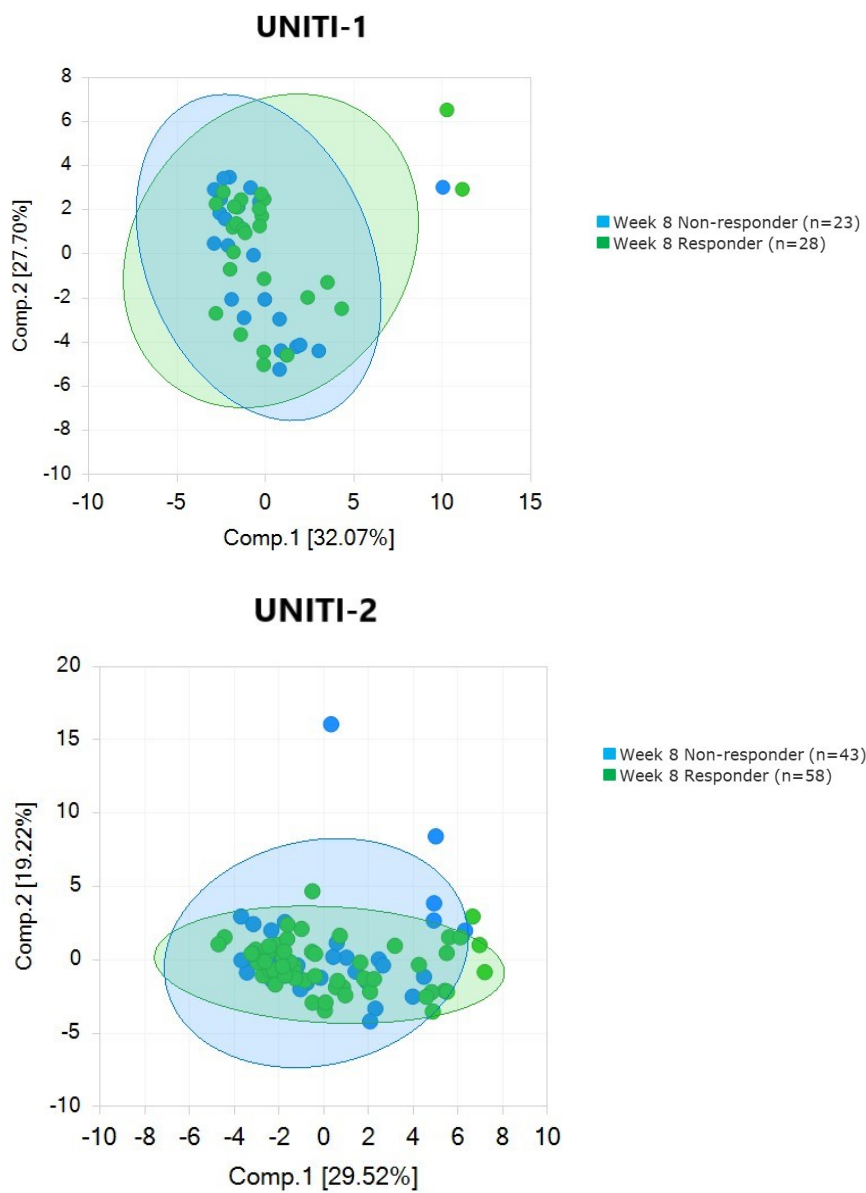
**Supplementary figure 9: IL22 responsive transcripts are enriched in colonic biopsies sampled from patients with colonic CD and UC.** Enrichment scores of IL22 responsive transcripts (GSVA) in healthy controls (n=6) and patients with colonic CD (n=19) and UC (n=24) from GSE16879. \*P<0.0001.

Supplementary Figure 10



**Supplementary Figure 10: Enrichment of IL22 responsive transcripts in the colon of IBD patients.** Unsupervised hierarchical clustering of IL22 responsive transcripts in patients with CD (upper panel), UC (lower panel) and non-inflammatory control subjects (GSE16879).

Supplementary Figure 11



**Supplementary Figure 11: IL22 responsive transcriptional signature does not predict response to ustekinumab in the UNITI trial program.** Clinical response was measured by CDAI change ( $\geq 100$  points) at week 8 (relative to baseline).