HGD/CRC-free >5 years later. The two patient groups are matched for age, gender, disease duration and LGD location.

Histological diagnosis was confirmed by two blinded pathologists. Shallow whole genome sequencing (0.1x) was performed using a standardised pipeline for epithelial cell enrichment, DNA extraction, library preparation, next generation sequencing and bioinformatic analysis.

Results A median 12% of the genome of LGDs from proctocolectomy specimens showed CNAs (IQR 4%–32%), compared to 23% in HGD/CRC (IQR 19%–42%, $p=0.003$). Similarly, the number of CNA events was greater in HGD/CRC compared to LGD ($p<0.001$). Multiple CNAs involving key driver genes were more frequent in HGD/CRC compared to LGD (adjusted p -values <0.05), including 8q gain (*MYC* loss, OR 17.2), 4q loss (OR 4.59) and 18q loss (*DCC/SMAD4* loss, OR 4.15).

Abstract OTU-004 Figure 1 Both the maximal total CNA burden and number of CNA events are greater in LGD of progressor than in LGD of non-progressors ($p<0.01$) as shown in the two violin plots.

Abstract OTU-004 Figure 2

The Kaplan-Meier plot demonstrates that patients in this cohort bearing LGD with the 25% greatest CNA burden are significantly more likely to develop future CRC/HGD than the remaining 75% of patients (HR 5.1, $p=0.001$).

Conclusions LGD lesions demonstrate a surprising diversity in CNA burden, with some LGD lesions bearing CNA profiles indistinguishable from HGD/CRC. Shallow whole-genome sequencing has potential translational utility, by stratifying patients with LGD lesions according to risk of progression to HGD/CRC.

OTU-005

TARGETING EXPANDED GUT HOMING EFFECTOR T CELL LINEAGES IN GI-GVHD: A NEW THERAPEUTIC PARADIGM

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Introduction Acute graft versus host disease may affect the gastrointestinal track (aGI-GvHD) in up to 60% of haematopoietic stem cell transplant (HSCT) recipients who develop GvHD resulting in significant morbidity. Half of these patients will develop steroid refractory disease which is associated with high mortality (up to 90%) due to lack of safe and efficacious therapies. Here we test the hypothesis that the integrin $\alpha 4\beta 7$ /Madcarn-1 pathway is clinically important in the pathogenesis of human aGI-GvHD.

Methods Prospective experimental study, recruiting HSCT recipients with aGI-GvHD ($n=10$) and controls [IBD ($n=36$) and non-IBD controls ($n=32$)]. Samples collected included peripheral blood and distal colonic biopsies. The $\beta 7$ +CD4 +compartment was phenotyped with a multiparametric flow cytometry panel. MADCAM-1 and S100A8 (the calprotectin subunit, biomarker of intestinal damage) expression in the gut were tested with RT-PCR. Clinical data on aGI-GvHD patients treated with vedolizumab were prospectively collected.

Results Within the effector memory population (CD3 +CD4 +CD45RA-CD45RO+CCR7-) there was significant enrichment of $\beta 7$ +effector memory cells in both inflammatory conditions (IBD: $24\% \pm 2.7$, aGI-GvHD: $29\% \pm 6.5$ vs. controls: $17\% \pm 1.1$, both $p<0.05$). Analysis of each individual subtype of the effector T cell lineages demonstrated that $\beta 7$ expression was especially enriched in Th1 (CXCR3 +CCR6-), Th17 (CCR6 +CXCR3-) and Th1/17 (CXCR3 +CCR6+) ($p=0.0034$). MADCAM-1 expression in aGI-GvHD is upregulated in comparison to non-IBD controls [fold change: 2 (0, 5), $p=0.006$] and at similar levels to patients with UC [2 (0, 9)]. Levels of MADCAM-1 expression correlated to the expression of the calprotectin subunit S100A8 [$r=0.90$, 95% CI(0.34, 0.99), $p=0.014$]. Six patients with steroid refractory aGI-GvHD patients were treated with vedolizumab, a monoclonal antibody targeting $\alpha 4\beta 7$. Five patients had a sustained clinical improvement (75% median reduction in clinical score, $p=0.03$) up to 6 months of follow up. These results compare favourably to other patients with steroid refractory aGI-GvHD treated at our centre with other second line treatments.

Conclusions For the first time, we show that aGI-GvHD is associated with significant expansion of gut homing effector lineages, most notably Th1 and Th17 cells. Interestingly the ligand for the $\alpha 4\beta 7$ integrin (Madcarn-1) is also highly expressed in gut tissue from aGI-GvHD patients, supporting further the therapeutic targeting of this gut homing pathway. Our promising clinical data on vedolizumab use have the potential to change the landscape of treatment in this condition.