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 (p<0.001). Multiple CNAs involving key driver genes were more frequent in HGD/CRC compared to LGD (p<0.001). Multiple CNAs involving key driver genes were more frequent in HGD/CRC compared to LGD (p<0.001). Multiple CNAs involving key driver genes were more frequent in HGD/CRC compared to LGD (p<0.001). Multiple CNAs involving key driver genes were more frequent in HGD/CRC compared to LGD (p<0.001).

**Conclusions** 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).

**Abstract OTU-005**

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


**Introduction** Acute graft versus host disease may affect the gastrointestinal tract (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 α4β7/ Madcam-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 β7 +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 β7 +effector memory cells in both inflammatory conditions (IBD: 24%±2.7, aGI-GvHD: 29%±6.5 vs. controls: 17%±1.1, both p<0.05). Analysis of each individual subtype of the effector T cell lineages demonstrated that β7 expression was especially enriched in Th1 (CXCR3 +CCR6-), Th17 (CXCR6 +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 α4β7. 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 α4β7 integrin (Madcam-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.