may be independent of whether the phenotype of the donor immune cells is malignant and that GvHD and GvL may be more a quantitative than qualitative effect.

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Ocular Gvhd: Epidemiology, Risk Factors and Impact on Quality of Life-a Chronic Gvhd Consortium Study

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Background: Ocular GVHD (o-GVHD) is a known manifestation of chronic GVHD (cGVHD). There are no prospective studies of factors associated with o-GVHD or its impact on quality of life (QOL). We analyzed the above endpoints using the cGVHD consortium database; a prospective multi-center longitudinal observational study.

Methods: The study included patients with cGVHD requiring systemic treatment and enrolled within 3 months of diagnosis. O-GVHD was defined as NIH eye score > 0 and patient reported symptoms (> 1 on 0-10 eye related symptoms or >20 on Lee symptom eye score). Variables associated with o-GVHD at enrollment and subsequent new onset o-GVHD, and the associations with QOL were studied.

Results: The cumulative incidence of o-GVHD at 2 y after cGVHD diagnosis was 58%. Of the 290 patients with o-GVHD, 117 (40%) had it within 3 months of cGVHD diagnosis ("early o-GVHD"). Chronic GVHD characteristics associated with early o-GVHD included: more severe global cGVHD (P<0.001), and greater severity of mouth (P=0.001), esophagus (P=0.002), and liver (P<0.001) involvement. In a multivariable analysis, female sex (OR 2.0, P=0.01) and higher prednisone dose at enrollment (P=0.04) were associated with o-GVHD. Early o-GVHD was not associated with subsequent non-relapse mortality (HR 1.2, P=0.53) or survival (HR 1.1, P=0.85).

Late o-GVHD (new onset > 3 months after cGVHD diagnosis) occurred in 68 patients. The cumulative incidence of late o-GVHD at 2-y post enrollment was 39%. In multivariable modeling, presence of prior grade I-IV aGVHD (HR 1.8, P=0.03) was associated with shorter time to late o-GVHD, while female donor into male recipient (HR 0.5, P=0.05) was associated with longer time to late o-GVHD onset.

The Table shows the association of o-GVHD with QOL metrics, using all available visit data adjusted for center effect, months since enrollment, platelet count, NIH severity, bilirubin, prior aGVHD, and overlap vs. classic cGVHD.

QOL Metric	O-GVHD	Estimate	P	NIH Eye score	Estimate	P
FACT-G	No	0*	0.006	0	0*	0.05-
	Yes	-2.1		1	-0.7	0.40
				2 or 3	-2.5	0.01
FACT-TOI	No	0*	<0.001	0	0*	0.03-
	Yes	-2.6		1	-1.5	0.04
				2 or 3	-2.4	0.01
FACT-BMT	No	0*	0.002	0	0*	0.08-
	Yes	-3.0		1	-1.3	0.19
				2 or 3	-3	0.03
Lee Score**	No	0*	<0.001	0	0*	0.01-
	Yes	2.8		1	1.7	0.01
				2 or 3	2.1	0.02

-overall P value; *Estimate 0-reference category; **Lee symptom score-eye component excluded

Conclusion: This large multicenter, prospective study shows that o-GVHD affects 58% of patients at 2 y after a diagnosis of cGVHD and is statistically associated with worse QOL and more cGVHD symptoms compared to patients with cGVHD without ocular involvement. Since o-GVHD may be due to permanent destruction of lacrimal glands, prophylactic or pre-emptive clinical trial strategies prior to onset of irreversible dry eye syndrome are needed. Women, patients on higher doses of prednisone, and those with a history of acute GVHD seem to be at higher risk for o-GVHD.

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In Silico Derivation of HLA-Specific Alloreactivity Potential from Whole Exome Sequencing of Stem Cell Transplant Donor-Recipient Pairs

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Graft vs. host (GVH) effect mediated by donor T cells are responsible for a significant measure of therapeutic benefit as well as toxicity observed following stem cell transplantation (SCT) between HLA-identical donors and recipients. Donor T cell-mediated GVH effects may be influenced by the aggregate alloreactivity to minor histocompatibility antigens (mHA) presented by the HLA in each donor-recipient pair (DRP). The cumulative mHA variation in each DRP may thus be regarded as the alloreactivity potential (AP) of that pair. To estimate AP in DRP, whole exome sequencing (WES) of 4 matched-related (MRD) and 5 unrelated (URD) pairs was performed and revealed extensive coding variation between them. To quantify the contribution of exome sequence variation to AP, data from each DRP was filtered to isolate non-synonymous single nucleotide polymorphisms (SNP) in the GVH direction (polymorphisms present in recipient and absent in donor). Logically, the SNP involved in encoding peptides presented on the HLA in each DRP will contribute to the AP in that pair. To identify these peptides, the nucleotide sequence flanking all of the several thousand SNP in each DRP was obtained with the ANNOVAR software package. All possible resulting nonameric-peptides were interrogated in-silico for their likelihood to be presented by each of the 6 HLA class I molecules in individual DRP, using the Immune-Epitope Database (IEDB) SMM algorithm. The IEDB-SMM algorithm predicted between 1,043,514 and 366,426 peptides/DRP (~ 18 peptides/SNP). Peptide-HLA binding affinity estimate was reported as an IC50 value, which when <500 nM, predicts that peptides

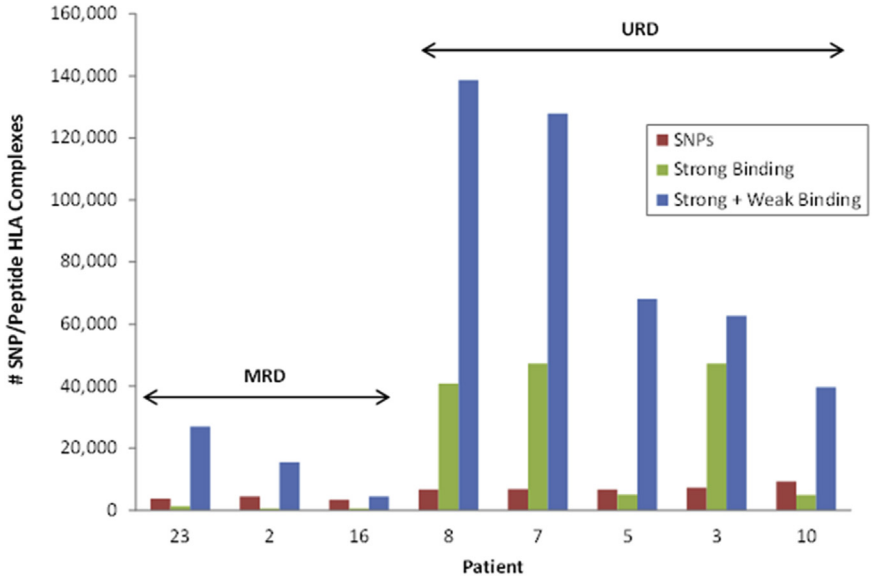

Figure 1. Comparison of total number of SNP (WES) in each DRP, *in silico* derived nona-peptides with strong binding (IC50 <50 nm) and strong-week binding (IC50 <500 nM).

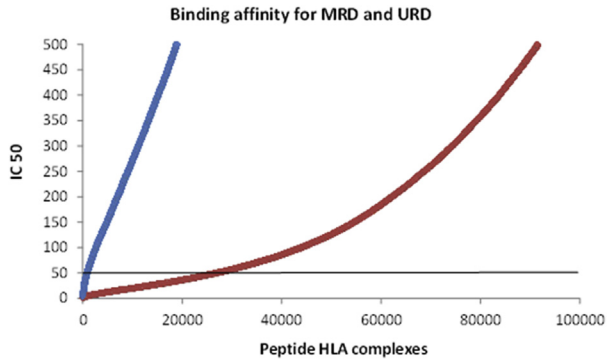

Figure 2. IC50 values of peptide-HLA complexes for MRD (red) URD (blue) for IC50 < 500nm. Data for a single allele presented. Peptides below the black line are strong binding (IC50 <50 nm).

may be presented by the HLA. Using this cutoff, from 18.9-1.2% of all the above peptides were categorized as presented by the HLA class I molecules in the DRP examined, with a smaller fraction of these peptides being strong binders (IC50 <50nM). (Fig 1) In our small cohort, MRD presented a median 3% (range 1-10) of all the predicted peptides, compared with 13.5% (4-20) for the URD. Further, plotting the IC50 values of the presented-peptides in each DRP, demonstrated a continuum of binding affinities (Fig 2) as opposed to discrete sets of values taken on by different peptides, implying a certain degree of plasticity in this system. Computing the area under the curve for these data to account for both number of and binding affinity of peptide-HLA complexes, demonstrated a marked difference between MRD (1x10-6 nM.Peptide-HLA) and URD (8x10-6). Our data demonstrates that a marked difference is evident between URD and MRD when WES is used to predict potential protein-coding differences - estimating an HLA-specific AP in unique DRP. This represents a paradigm shift away from looking for unique mHA to predict likelihood of developing GVH phenomenon in a population-based manner, and may eventually better define GVHD risk in HLA matched DRP.

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CD8-Predominant T Cell Meningitis Accompanies Gvhd in Primates and Is Prevented with Immunoprophylaxis

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Graft versus host disease (GvHD) is an often fatal complication of allogeneic tissue transplantation. While typical targets of GvHD include the skin, lung, liver and GI tract, a myriad of other organ systems are being identified as targets of this disease. Although the neurologic complications that occur during hematopoietic stem cell transplant (HCT) have been extensively described (Siegal et al., BBMT, 2007), little information is available about the incidence and biology of GvHD in the central nervous system (CNS). Case reports have shown that the CNS can be a target of GvHD and show high mortality rates when involved (Saad et al., JCO, 2009). A recent study found both pathologic and behavioral consequences of CNS-GVHD in a mouse model (Hartrampf et al., Blood, 2013). Further study of CNS-GvHD is needed to better understand this entity that is often difficult to access clinically.

Non-human primates have been shown to closely model humans during and after HCT. To investigate the prevalence of CNS manifestations of acute GvHD such a model, we conducted a HCT study with the following Transplant/GvHD prophylaxis regimens: 1) Autologous/None 2) Allogeneic/