expansion of remaining families of Firmicutes (Table). Upon HSCT, these mice developed fulminant GVHD compared to their counterparts who did not receive ampicillin ($p < .01$). Interestingly, oral gavage with Lactobacillaceae following ampicillin appears to prevent exacerbation of GVHD.

Altogether, our results suggest that during GVHD, an increase of Lactobacillaceae in the gut may be a compensatory mechanism to reduce GVHD severity. Moreover, antibiotics prior to HSCT could predispose to GVHD, while the administration of Lactobacillaceae can be explored as GVHD prophylaxis.

Table 1. Bacterial family representation in ileal contents

	% Lactobacillaceae	% other Firmicutes
Normal B6 mice	42±3	26±1
HSCT mice without GVHD	54±2	27±2
HSCT mice with GVHD	95±2	2±0.5
B6 mice after ampicillin and recovery	0±0.1	98±1

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SINGLE NUCLEOTIDE POLYMORPHISM (SNP)-BASED PREDICTIVE MODELS FOR GRAFT-VERSUS-HOST DISEASE (GVHD) IDENTIFY HIGH RISK PATIENTS FOR OVERALL AND ORGAN SPECIFIC GVHD FOLLOWING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Introduction: The present study attempted to identify potential predictive SNP marker associating with the risk of acute (aGVHD) or chronic GVHD (cGVHD) and organ specific GVHDs. In addition, SNP markers predicting transplant outcomes such as overall survival (OS), relapse free survival (RFS) or non relapse mortality (NRM) were also analyzed with 259 SNPs in 54 genes which are potentially involved in the pathogenesis of GVHD.

Materials and Methods: 394 pairs of donors and recipients were included and their germline DNA samples were genotype for 259 SNPs in 54 genes using MALDI-TOF based platform. The Risk of aGVHD/cGVHD and organ specific GVHD were evaluated as well as RFS, NRM and OS in patients receiving related donor transplantation (n = 303). After multivariate analyses, the predictive model generated by combination of clinical and genetic SNP markers were attmpted to stratify patients into low (< Q1), moderate (Q2,3) and high risk groups (Q4), which were to be validated in 84 pairs receiving MUD transplantation. Finally, we performed C-statistic analysis for each transplant outcome in a pooled population (n = 394).

Results: Several SNP markers in the cytokine, apoptosis, TGF-β or PDGF mediated pathways were identified as potential predictive of aGVHD/cGVHD. Of interest, *NOS2* (nitric oxide 2) was associated with the risk of cutaneous or aGVHD. PDGF-mediated pathway was involved in the pathogenesis of cutaneous GVHD. These predictive models generated with both clinical and genetic factors were statistically significant ($P < 0.001$) except for overall cGVHD ($p = 0.07$). The genetic predictive models have been replicated in validation cohort in terms of skin cGVHD ($p < 0.0001$), skin aGVHD ($p = 0.0219$), aGVHD ($p = 0.0274$), and RFS ($p = 0.0166$). The C-statistics have been increased by median of 0.0745 (range 0.023-0.18, mean 0.0788) when adopted the predictive model generated combined with clinical and genetic factors compared to that generated only by clinical factors.

Conclusions: The present study suggested that 1) the predictive models improved stratification of the patients according to their transplant outcomes and the risk of GVHD (esp. organ specific GVHD) using donor-/recipient-SNP markers, and 2) the predictive models incorporating clinical and genetic factors were suggested to enhance stratification power predicting the prognosis of transplant patients and the risk of GVHD.

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UNIVERSAL ROLE FOR HLA-C AND KIR2DL LIGAND MISMATCH IN SEVERE ACUTE GRAFT-VERSUS-HOST DISEASE AFTER UNRELATED DONOR HEMATOPOIETIC STEM CELL TRANSPLANTATION (U-HSCT) IN JAPANESE AND CAUCASIAN TRANSPLANT RECIPIENTS: AN ANALYSIS ON BEHALF OF INTERNATIONAL HISTOCOMPATIBILITY WORKING GROUP IN HEMATOPOIETIC CELL TRANSPLANTATION

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Donor HLA mismatching is a known risk factor for morbidity and mortality after unrelated hematopoietic cell transplantation (HCT). The frequency of donor and recipient HLA phenotypes differs between ethnically diverse populations, as does the incidence of acute graft-versus-host disease (GVHD). Certain high-risk HLA mismatches are responsible for acute GVHD risk in the Japanese experience (Kawase et al Blood 2007). We tested the hypothesis that clinical outcome after HLA-C mismatched unrelated HCT depends on the specific mismatch combinations, and that risks are different depending on the HLA phenotypes of the transplant population. The International Histocompatibility Working Group dataset enables us to compare clinical outcome between Caucasian and Japanese populations to test these hypotheses. High resolution HLA typing was available for the Japanese (n = 5986) and Caucasian pairs (n = 9379). Multivariable Cox regression models adjusted for HLA matching status other than HLA-C and non-HLA factors known to influence GVHD risk. In both Japanese and Caucasian recipients, the presence of an HLA-C mismatch/KIR ligand match was associated with increased risk of grades III-IV acute GVHD compared to an HLA-C match (HR 1.69 [$p < 0.001$] and 1.23 [$p < 0.001$], respectively). KIR2DL ligand mismatching had an even stronger effect among the Japanese than the Caucasian recipients (HRs for HLA-C allele mismatch and KIR mismatch in GVH direction were 2.51 ($p < 0.001$) and 1.21 ($p = 0.017$), respectively). Since it is known that certain mismatches that occur in the Japanese population occur very infrequently (if at all) in the Caucasian population, and vice verse, we conducted the same analyses but limited to subjects who have HLA-C mismatch combinations occurring in more than 10 subjects in both populations. Compared to HLA-C matches, HLA-C mismatch/KIR ligand match and HLA-C mismatch/KIR ligand mismatch were associated with a statistically significantly increased risk of GVHD in Japanese (HR 1.39 [$p = 0.003$] and HR 3.13 [$p < 0.001$], respectively) but not in Caucasian recipients (HR 1.18 [$p = 0.128$] and HR 0.91 [$p = 0.588$]). These results suggest that the magnitude of risks associated with HLA-C disparity after unrelated HCT may be different in recipients of Japanese compared to Caucasian background, particularly in the presence of a KIR ligand mismatch. Risks may also depend on the specific HLA-C allele mismatch combinations.

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A PROSPECTIVE PHASE I/II TRIAL OF BORTEZOMIB-BASED GRAFT-VERSUS-HOST-DISEASE PROPHYLAXIS IN HLA-MISMATCHED UNRELATED DONOR REDUCED-INTENSITY CONDITIONING HEMATOPOIETIC STEM CELL TRANSPLANTATION: ENCOURAGING SAFETY, EFFICACY, AND SURVIVAL

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Introduction: The challenge in RIC HSCT is to prevent GVHD but maintain GVL and immunologic reconstitution. Bortezomib is an excellent candidate immunomodulator. In addition to antitumor activity via NF-κB and other pathways, it inhibits APC by attenuating TLR-4 mediated activation and cytokine production. In mouse models, bortezomib preferentially and specifically depletes alloreactive T cells, and prevents GVHD without impairing engraftment or