suppression after non-ablative conditioning for haploidentical (3/6 and 4/6 MHC matched related donor) blood HCT. 17 patients with poor prognosis hematological malignancies received cyclophosphamide (1gm/m2 days -7 and -6) and fludarabine (25mg/m2 days -7 through -3) with sirolimus and tacrolimus, (both adjusted to 5-15ng/ml) and methotrexate (5mg/m2 days 1,3, 6) immunoprophyllaxis. Tacrolimus was tapered between days 40-100 in patients without acute GVHD. ATG 30mg/M was also given days -1,1,3, and 5. Median age was 61. 10 patients had acute leukemias, 6 had Non-hodgkins lymphoma and one Hodgkins disease. Only 6 patients were in remission (CR) at the time of transplant, all of the other 11 having multiply pretreated active malignancy at HCT. Donor cells engrafted stably in all patients (table below). 16/17 achieved >70% donor chimerism by day 30 and 11/13 >90% by day 100. 15/17 patients developed acute (<d100) GVHD, but this was >grade 2 in only 4/17. In 1 patient GVHD developed at day 121 only after discontinuation of both tacrolimus and sirolimus. To date 2 patients remain alive free of any progression of malignancy 1216 and 1543 days post HCT. Only one of these survivors was in CR at HCT, and this individual is now enjoying a second remission more than 3 years longer than his first. 6 deaths have resulted from GVHD/Infection, while progressive malignancy (PD) has been the cause of mortality in 8 patients. One patient died of an unrelated cerebrovascular accident while free of disease or GVHD at 689 days from transplant. We conclude that, while GVHD and transplant related mortality remain obstacles, sirolimus and non-ablative conditioning allow reliable engraftment of haplodentical donor HCT with some long term survivors. These findings were in elderly and infirm patients with advanced hematological malignancy.

*Engraftment of Haploidentical Cells**

	D0	D15	D30	D60	D100
Mean Chimerism	0	0.73	0.88	0.94	0.98
Standard Deviation	0	0.38	0.19	0.15	0.05

Whole Blood Chimerism*

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A CRITICAL ROLE OF CD100 IN ALLOGENEIC IMMUNE RESPONSES

Duran-Struuck, R.[1,2], Lowler, K.[1], Beth, W.[1], Luker, G.[3], Liu, C.[4], Kumanogoh, A.[5], Reddy, P.[1], Ferrara, J.L.M.[1] [1]University of Michigan Cancer Center, Ann Arbor, MI; [2]University of Michigan Unit for Laboratory Animal Medicine, Ann Arbor, MI; [3]University of Michigan Dept of Microbiology & Immunology, Ann Arbor, MI; [4]University of Florida College of Medicine, Gainesville, FL; [5]Osaka University, Osaka, Japan.

Sema4D (CD100) is a novel 150 kDa protein that belongs to the semaphorin family and has recently been shown to modulate autoimmunity. We tested the requirement of CD100 expression on T cells in regulating allo-immune responses. When allogeneic BALB/c stimulators were cultured with responder cells from either wild type(wt) B6 or CD100 deficient-/-B6, T cells from the CD100-/-animals showed a ten fold less expansion than the WT controls(10,800 +/- 1,230 vs. 1,600 +/- 258 cpm $p<0.01$). Consistent with the reduced proliferation, CD100-/- T cells produced less IFNγ (1890 pg/mL) compared to B6 wt Tcells (3478pg/mL) ($p<0.01$). Similar reduction in proliferation and IFN γ production was observed using anti-CD100 mAb's (data not shown). We next determined the *in vivo* relevance of CD100 expression on T cell allogeneic responses in a well characterized experimental model of GVHD. We utilized the B6($H2^b$) -->BALB/c ($H2^d$) model where the donor and recipient are mismatched at both major and minor histocompatibility antigens. Recipient BALB/c animals were irradiated with 8Gy and transplanted with 5.0×10^6 million bone marrow (BM) cells from wtB6 animals together with 0.5 million T cells from either wtB6 or CD100 -/- donors. Allogeneic recipients that were injected with CD100 -/- donor Tcells showed significantly reduced mortality, less clinical and GVHD specific target organ damage (see table). Similar benefit in the reduction of GVHD was observed with anti-CD100 mAb treatment into the recipients. When BALB/c recipient mice were challenged with the P815 ($H2^d$) murine mastocytoma cell line and received wt or CD100-/- B6 T cells, there was a significant improvement in the tumor free survival when compared to syngeneic recipients thus demonstrating preservation of graft-versus-leukemia (90% survival in allogeneic vs. 0% survival in syngeneic on day +12 post BMT $p<0.05$). We next tested the hypothesis that absence of CD100 expression on Tcells reduced the function of allogeneic APCs. When BALB/c DCs were treated with LPS and co-cultured with CD100-/- B6 T cells, they secreted less amounts of TNFa and IL12p70 compared to co-culture with wt B6 Tcells (table). Use of antiCD100 mAb's showed similar results. In conclusion, we demonstrate a novel role for CD100 in regulating *in vitro* and *in vivo* allogeneic responses using these two complementary approaches.

CD100-/- vs Wild Type Tcell in Vitro and in Vivo Outcomes

	wt T cells	CD100-/- T cells	p value
OUTCOMES			
GvHD Clinical Score (day + 60)	4.6+/-0.8	1.8+/-0.2	<0.02
Survival (day + 60)	55%	100%	<0.05
Liver Pathology (day + 60)	17.0+/-1.5	9.0+/-1.3	<0.01
Skin Pathology (day + 60)	1.5+/-0.2	0.8+/-0.2	0.02
Intestinal Pathology (day + 60)	7.8+/-0.8	4.8+/-1.0	0.03
CYTOKINES (pg/mL)			
IFNg serum d+14 post BMT	584+/-148	286+/-97	<0.06
IFNg in vitro	3477+/-254	1889+/-221	<0.01
DC IL-12p70 in vitro	107+/-7	68.5+/-2	<0.01
DC TNFa in vitro	5930+/-123	4252+/-233	<0.01

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CD34 DOSE AND CHRONIC GRAFT VERSUS HOST DISEASE (CGVHD) AFFECT SURVIVAL IN ALLOGENEIC PERIPHERAL BLOOD STEM CELL TRANSPLANTATION (ALLOPBSCT) FOLLOWING NON-MYELOABLATIVE (NM) CONDITIONING: THE VANDERBILT UNIVERSITY/NASHVILLE VA SCT PROGRAM EXPERIENCE

Ewing, G.[1,2], Giglia, J.[1,2], Vusirikala, M.[2], Ye, F.[1], Shyr, Y.[1], Chinratanalab, W.[1,2], Ruffner, K.[1,2], Kassim, A.[1], Jagasia, M.[1], Engelhardt, B.[1], Brandt, S.[1,2], Morgan, D.[1,2], Stein, R.[1], John, G.[1], Schuening, F.[1], Goodman, S.[1,2] [1]Vanderbilt University Medical Center, Nashville, TN; [2]Nashville Veterans Administration/Tennessee Valley Healthcare System, Nashville, TN.

AlloPBSCT utilizing NM conditioning is hypothesized to minimize the toxicity of myeloablative regimens while harnessing a potent graft vs malignancy effect. We sought to identify factors predicting survival in a retrospective analysis of 60 patients (pts) undergoing alloPBSCT from HLA-matched related donors between 8/00 and 8/05 at our program. All pts received 90 mg/m^2 fludarabine and 200 cGy TBI. GVHD prophylaxis consisted of CSA/MMF. The median age was 55 years (range 41-66). Male: female was 51:9. All transplants were performed for hematologic malignancies. The median number of treatments prior to transplant was 4 (range 0-8). The mean cell doses infused were 8.0 (range 3.5-16.3) x 10^6 CD34+/kg and 28.4 (range 0.9-65.9) x 10^7 CD3+/kg. Among 33 (55%) pts who became neutropenic, the median time to ANC > 500 was 21 days (range 14-49). Primary graft failure occurred in 2 patients.