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POSTER SESSION 2: HISTOCOMPATIBILITY/ALTERNATIVE STEM CELL SOURCES

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A Novel State Funded Program to Increase Cord Blood Collections for Public Banking

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The Umbilical Cord Blood Collection Program (UCBCP), administered by UC Davis Health System, is a new statewide public program designed to capture the genetic diversity of Californians through collection of cord blood units (CBUs) for unrelated transplantation. This program is funded with revenue from California state birth certificate fees. The vision for the implementation of the mission by UCBCP is to expand access to cord blood stem cells by targeting current inventory deficiencies to provide greater probabilities that people of any race or ethnicity will find an appropriately matched CBU in the National Cord Blood Inventory (NCBI). In support of these goals, the UCBCP plans to promote targeted education programs for health professionals and to utilize best practices for cord blood collections. Through this process UCBCP will facilitate the provision of high quality CBUs for transplantation, as well as promote research and development of effective treatments utilizing cord blood stem cells by making the CBUs collected that do not meet the criteria for banking available to researchers.

Much progress has been made toward developing a sustainable cord blood collection program for the state over the first year. The UCBCP leadership team has been developed and we have identified cord blood banks through an RFP bidding process that will be partnered with hospitals in various parts of the state. The UCBCP is in varying stages of contract negotiations with three of the public banks who responded to the RFP. To date negotiations are in place for California collections in Southern California to occur at five Scripps hospitals, funded in part by the UCBCP; and by collections set to begin at 13 Kaiser Hospitals, also with support from the UCBCP. In the Central Valley, a collection site is being developed in Fresno, at the Community Regional Medical Center. In the Bay area the UCBCP is in negotiations with several hospitals, including California Pacific Medical Center and Alta Bates. In the Sacramento area, the UCBCP has commitments from 2 hospitals and are seeking the same from two additional birthing centers. At UCDHS, we have received IRB approval for the program, and have now initiated cord blood collections for purposes of collector training and process validation.

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Immunophenotypic, Proteomic and Genomic Characterization of Human Cord Blood (CB) vs Peripheral Blood (PB) CD56^{+dim} NK Cells: A More Pro NK Phenotype in CB

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CB is a viable alternative source of allogeneic HSC for the treatment of malignant and non-malignant disease (Cairo et al *BBMT* 2008, Szabolcs/Cairo et al *Sem in Hem* 2010). NK cells play a role in innate and adaptive immunity and are characterized as CD56^{+} cell population. Cytotoxic CD56^{+dim} cells make up 90% of PB NK populations (Shereck/Cairo *PBC* 2007). We previously ex-vivo expanded CB MNC into various phenotypes of CD56$^{+dim\ and\ +bright}$ NK cells (Ayello/Cairo *BBMT* 2006; *Exp. Hematology* 2009). NK cell anti-leukemic and anti-rejection activities may be essential to the interplay between GVT effects and GVHD after haploidentical HSCT (Dunbar et al, *Haematologica*, 2008).

Objective: To determine differential expression, immunophenotype and genomic and proteomic signatures in CB vs PB CD56^{+dim}NK cells.

Methods: CB NK CD56 cells (94% enrichment) isolated using a standard kit (Miltenyi Biotec) and sorted into CD3^{-}/CD56^{bright} and CD3^{-}/CD56^{dim} subsets. NKR expression was measured by flow-cytometry. Isolated RNA from CB and PB CD56^{+dim}cells underwent microarray studies (Affymetrix, U133A_2). (Agilent GeneSpring and Ingenuity pathway analyses, IPA). Proteomic performed by LC MS/MS with iTRAQ labeling and analyzed with SEQUEST, ProteinProphet, and INTERACT.

Results: There was no difference in NKR expression of CD16, KIR2DL1, KIR2DS1, KIR2DL2, CD161, NKG2C, NKp44, and NKp46 in CB vs. PB CD56^{dim}. There was a significant difference in CB vs PB CD56^{+dim} NK cells in gene expression including: pro-apoptotic genes: CASP10 (3.1F), TNFSF11 (4.7F), CDC2 (3.0F), BCL2L1 (4.3F), NOTCH2 (1.5F); and cell development: PBX1 (7.6F), IL1RN (5.1F), CD24 (5.3F), CD34 (3.5F), CD55 (2.1F), CCL13 (2.2F). Further, there was a significant change in protein expression, CB vs PB CD56^{+dim}cells over 35 proteins, including CELSR1 (25.0F), BLM (25.0F), BDNF (20.0F), PKD1 (16.7F), NOTCH2 (16.7F), BIRC2 (12.5F), AIFM1 (12.5F), EP400 (5.3F), PBX1 (3.9F), SIRT2 (2.9F), LETM1 (2.9F), and ESR2 (2.4F). qRT-PCR and Western blot analysis validated the genomic and proteomic results, respectively.

Conclusion: These results suggest that CB vs PB CD56^{+dim} NK cells are more prone to undergo programmed cell death (apoptosis), over expression of numerous pro-apoptotic genes, and may be earlier in development (pro-NK) with significant over expression of CD34.

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Double-Unit Cord Blood Transplantation (DCBT) for Acute Leukemia: High Disease-Free Survival in Adults and Children with Comparable Survival in European and Minority Patients

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Background: Given DCBT may improve engraftment & protect against relapse, we have adopted DCBT for both children & adults with acute leukemia, myelodysplasia (MDS), & myeloproliferative diseases (MPD). However, determinants of disease-free survival (DFS) after DCBT have yet to be established.

Methods: We analyzed the DFS of 92 DCBT recipients with acute leukemia in morphologic remission or aplasia (n = 83), & MDS/MPD with ≤ 5% blasts at work-up (n = 9) transplanted from 10/2005-5/2012. Nearly all patients had high-risk disease.

Results: Children [n = 27, median age 7 years (range 0.9-15), median weight 30 kg (range 8-72)] were 33% European & 26% CMV sero-positive with diagnoses of AML (or biphenotypic) in 44%, ALL in 52%, MDS/MPD in 4%, & all received high-dose conditioning. Their grafts had a median infused TNC x 10^7/kg of 4.4 (larger unit) & 2.9 (smaller unit), & 4% of units were 6/6 HLA-A,-B antigen,-DRB1 allele matched, 61% 5/6, & 35% 4/6. Adults [n = 65, median age 47 years (range 16-69), median weight 69 kg (range 45-105)] were 48% European & 68% CMV sero-positive. Diagnoses in adult patients were AML (or biphenotypic) in 62%, ALL in 26%, & MDS/MPD in 12%. Forty-two percent of adults received high-dose & 58% reduced intensity conditioning. Their units had a median infused TNC/kg of 2.7 & 2.0, respectively, & 3% were 6/6 HLA-matched, 44% 5/6, & 53% 4/6. All patients received calcineurin-inhibitor/mycophenolate mofetil immunosuppression. Sustained donor neutrophil engraftment was seen in 93% of children (median neutrophil recovery at 20 days) & 97% of adults (median 25 days). Platelet engraftment was seen in 85% of children (median recovery at 50 days) & 83% of adults (median 48 days). The incidence of day 180 grade II-IV acute GVHD was 41% in children & 60% in adults. Day 100 TRM was 7% in children & 15% in adults. The 2-year relapse incidence was 17% in children & 7% in adults. With a median 33 month (range 3-84) follow-up of survivors, the 2-year DFS is 72% in children & 65% in adults. Univariate analysis of variables potentially influencing 2-year DFS (Table 1) demonstrated there were no differences according to patient age, ancestry, remission status, conditioning intensity, engrafting unit-recipient HLA-match, or engrafting unit infused TNC dose/kg. However, patients who were CMV seronegative had a higher 2-year DFS (81% vs 53%, $P = .01$). Multivariate analysis revealed recipient CMV serostatus was a predictor of DFS independent of patient age, & its effect was mediated by an influence on TRM.

Table 1

Comparison		2-Year DFS	*P* value
Age	0-15 years (n = 27)	72%	0.29
	>16 years (n = 65)	65%	
Ancestry	Europeans (n = 40)	69%	0.90
	Non-Europeans (n = 52)	66%	
Remission Status	CR1 (n = 49)	65%	0.92
	All others (n = 43)	69%	
Conditioning Intensity	High-dose (n = 54)	70%	0.50
	Reduced intensity (n = 38)	62%	
Recipient CMV Sero-status	CMV+ (n = 51)	53%	0.01
	CMV- (n = 41)	81%	
Engrafting Unit - Recipient HLA-match	4/6 (n = 36)	74%	0.96
	5-6/6 (n = 51)	69%	
	2-6/10 (n = 50)	69%	0.87
	7-9/10 (n = 37)	72%	
Engrafting Unit Infused TNC dose	< 3.0 × 10^7/kg (n = 62)	72%	0.90
	≥ 3.0 x 10^7/kg (n = 25)	68%	

Conclusions: DCBT can achieve high & comparable DFS in both European & non-European patients with acute leukemia with a low rate of relapse. While the mechanism of the mortality risk associated with CMV seropositivity requires further investigation, our findings support DCBT as an immediate alternative therapy for high-risk acute leukemia in patients without suitable unrelated volunteer donors.

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HLA-DP Matching is Not Clinically Relevant in 10/10 HLA Matched Transplants: A Single Center Study

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The association between HLA-DP and hematopoietic stem cell transplantation (HCT) outcomes is still questionable. In the present study, we examined 80 patients who underwent first allogeneic HCT between the years of 2005-2008 and were followed up for at least 2 years post transplant. These patients were 10/10 matched for HLA-A, -B, -C, -DR and -DQ at high resolution using Sequence Specific Priming (SSP) and/or Sequence Based Typing (SBT). We analyzed the impact of donor/recipient (D/R) mismatches at HLA-DPA1 and HLA-DPB1 on different HCT outcomes including aGVHD, cGVHD, and risk of disease relapse in a single center study. Additionally, we classified HLA-DPB1 mismatches as permissive or non-permissive according to a previously described TCE4 algorithm and attempted to confirm its efficacy. Each categorical testing variable were compared with the different clinical end points by 2-tailed Fischer's exact test. The magnitude of effect was estimated by risk ratios and their 95% confidence intervals. "p" value ≤0.05 (two-sided) was considered significant. A total of 160 alleles were observed at HLA-DPA1 and 159 alleles were observed at HLA-DPB1 locus. HLA-DPA1 and DPB1 allelic frequencies in the study population were not significantly different from those previously observed in other Caucasian populations. At DPA1 locus, D/R mismatching was observed in 15% of D/R pairs, however almost all of them were mismatched at the level of single allele. Since only one patient was mismatched for both DPA1 alleles, the effect of DPA1 mismatches were not analyzed for single or double mismatches. At the DPB1 locus, 44% D/R pairs were found mismatched, including 24% for single allele and 20% for both alleles. No variables analyzed (allelic or non-permissive mismatches) were significantly associated with any transplant outcomes evaluated in this patient cohort. Our study did not confirm the association between HLA-DP mismatches and HCT outcomes. The TCE4 algorithm also did not yield significant advantageous results. Our results are in accord with a recent French study but discordant with various studies conducted elsewhere, including the United States and the United Kingdom. Further molecular study of HLA-DP in the clinical setting is warranted to further elucidate the role of this gene and its mismatching on HCT outcome.