



**MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR IMMUNOBIOLOGY
Houston, TX
Thursday, February 21, 2019, 12:15 pm– 4:45 pm**

Co-Chair: Katharina Fleischhauer, MD; Essen University Hospital;
Telephone: +49-201-723-4582; E-mail: Katharina.Fleischhauer@uk-essen.de

Co-Chair: Katharine Hsu, MD, PhD; Memorial Sloan-Kettering Cancer Center;
Telephone: 646-888-2667; E-mail: hsuk@mskcc.org

Co-Chair: Sophie Paczesny, MD, PhD; Indiana University Hospital;
Telephone: 317-278-5487; E-mail: sophpacz@iu.edu

Co-Scientific Dir: Stephanie Lee, MD, MPH, Fred Hutchinson Cancer Research Center
Telephone: 206-667-6190; E-mail: sjlee@fredhutch.org

Co-Scientific Dir: Stephen Spellman, MBS, CIBMTR Immunobiology Research
Telephone: 763-406-8334; E-mail: sspellma@nmdp.org

Statistical Director: Tao Wang, PhD, CIBMTR Statistical Center
Telephone: 414-955-4339; E-mail: taowang@mcw.edu

Statisticians: Michelle Kuxhausen, MS, CIBMTR Statistical Center
Telephone: 763-406-8727; E-mail: mformane@nmdp.org

1. Introduction

The CIBMTR Immunobiology Working Committee (IBWC) was called to order at 12:15 pm on Thursday February 21st, 2019 by Dr. Katharina Fleischhauer. Dr. Fleischhauer introduced the IBWC leadership and the outgoing (herself) and incoming chair Dr. Steven Marsh. Dr. Fleischhauer continued by reviewing the goals of the working committee, areas of focus, and limitations of the IBWC. She gave a brief overview of the status of the current portfolio, number of proposals to be presented at the meeting, and voting and prioritization guidelines.

2. Published or submitted papers

Due to the full agenda, the 2018 papers published or submitted were mentioned, but not presented. Thirteen papers were published and three papers were submitted in the last year.

- a. **IB06-05** Patient HLA germline variation and transplant survivorship. Petersdorf EW, Stevenson P, Malkki M, Strong RK, Spellman SR, Haagenson MD, Horowitz MM, Gooley T, Wang T. *J Clin Oncol.* 2018 Aug 20; 36(24):2524-2531. doi:10.1200/JCO.2017.77.6534. Epub 2018 Jun 14. PMC6097831.
- b. **IB09-06/RT09-04c** Exome chip Analyses Identify Genes affecting mortality after HLA-Matched Unrelated Donor Blood and Marrow Transplantation Qian Liu, Qiang Hu, Leah Preus, Alyssa I. Clay, Ken Onel, Daniel O. Stram, Loreall Pooler, Xin Sheng, Christopher A. Haiman, Xiaochun Zhu, Stephen R. Spellman, Marcelo Pasquini, Philip L. McCarthy, Song Liu, Theresa Hahn, Lara E. Sucheston-Campbell. *Blood.* 2018 May 31; 131(22):2490-2499. doi:10.1182/blood-2017-11-817973. Epub 2018 Apr 2. PMC5981168.

- c. **IB10-01d** Flow Cytometry using FISH techniques in a Severe Aplastic Anemia population. Gadalla S, Aubert G, Wang T, Haagenson M, Spellman SR, Wang L, Katki HA, Savage S, Lee SJ. *Mol Genet Genomic Med.* 2016 Jul 1; 4(4):475-479. doi:10.1002/mgg3.220. Epub 2016 Mar 20. PMC4947866.
- d. **IB10-01e** Chromosomal aberrations and survival after unrelated donor hematopoietic stem cell transplant in patients with Fanconi anemia. Wang Y, Zhou W, Alter BP, Wang T, Spellman SR, Haagenson M, Yeager M, Lee SJ, Chanock SJ, Savage SA, Gadalla SM. *Biol Blood Marrow Transplant.* 2018 Oct 1; 24(10):2003-2008. doi:10.1016/j.bbmt.2018.05.027. Epub 2018 Jun 4. PMC6239962.
- e. **IB10-01g** Telomere length calibration from qPCR measurement: Limitations of current method. Wang Y, Savage SA, Alsaggaf R, Aubert G, Dagnall CL, Spellman SR, Lee SJ, Hicks B, Jones K, Katki HA, Gadalla SM. *Cells.* 7(11):183. doi:10.3390/cells7110183. Epub 2018 Oct 24. PMC6262465.
- f. **IB11-01a** The effect of NIMA matching in adult unrelated mismatched hematopoietic stem cell transplantation - a joint study of the Acute Leukemia Working Party of the EBMT and the CIBMTR. Pingel J, Wang T, Hagenlocher Y, Hernández-Frederick CJ, Nagler A, Haagenson MD, Fleischhauer K, Hsu KC, Verneris MR, Lee SJ, Mohty M, Polge E, Spellman SR, Schmidt AH, van Rood JJ. *Bone Marrow Transplant.* doi:10.1038/s41409-018-0345-8. Epub 2018 Oct 2.
- g. **IB12-02c** In silico prediction of nonpermissive HLA-DPB1 mismatches in unrelated HCT by functional distance. Arrieta-Bolaños E, Crivello P, Shaw BE, Ahn KW, Wang H-L, Verneris MR, Hsu KC, Pidala J, Lee SJ, Fleischhauer K, Spellman SR. *Blood Advances.* 2018 Jul 24; 2(14):1773-1783. doi:10.1182/bloodadvances.2018019620. Epub 2018 Jul 24. PMC6058232.
- h. **IB13-08** Prediction of Acute Graft-Versus-Host Disease Following Hematopoietic Cell Transplantation. Lee C, Haneuse S, Wang H, Rose S, Spellman SR, Verneris M, Hsu K, Fleischhauer K, Lee SJ, Abdi R. *PLOS 1* 13(1):e0190610. doi:10.1371/journal.pone.0190610. Epub 2018 Jan 18. PMC5773230.
- i. **IB14-06** Donor-specific anti-HLA antibodies in unrelated hematopoietic cell transplantation for non-malignant disorders. Woolfrey A, Wang T, Lee SJ, Haagenson MD, Chen G, Fleischhauer K, Horan J, Hsu K, Tyan D, Verneris M, Spellman SR, Fernandez-Vina M. *Bone Marrow Transplantation.* doi:10.1038/s41409-018-0334-y. Epub 2018 Sep 19.
- j. **IB14-08** Development and validation of a clinical unrelated donor selection score. Shaw BE, Logan BR, Spellman SR, Marsh SGE, Robinson J, Pidala J, Hurley C, Barker J, Maiers M, Dehn J, Wang H, Haagenson M, Porter D, Petersdorf EW, Woolfrey A, Horowitz MM, Verneris M, Hsu KC, Fleischhauer K, Lee SJ. *Biol Blood Marrow Transplant.* 2018 May 1; 24(5):1049-1056. doi:10.1016/j.bbmt.2018.02.006. Epub 2018 Feb 14. PMC5953795.
- k. **IB15-01** Analysis of single nucleotide polymorphisms in the gamma block of the major histocompatibility complex in association with clinical outcomes of hematopoietic cell transplantation: A CIBMTR study. Askar M, Sayer D, Wang T, Haagenson M, Spellman SR, Lee SJ, Madbouly A, Fleischhauer K, Hsu KC, Verneris MR, Thomas D, Zhang A, Sobecks R, Majhail NS. *Biol Blood Marrow Transplant.* doi:10.1016/j.bbmt.2018.12.008. Epub 2018 Dec 18.
- l. **IB15-02** Donor killer-cell immunoglobulin-like receptor (KIR) genotype does not improve graft-versus-leukemia responses in chronic lymphocytic leukemia (CLL) after unrelated donor transplant: a CIBMTR analysis. Bachanova V, Weisdorf DJ, Wang T, Marsh SGE, Cereb N, Haagenson MD, Spellman SR, Lee SJ, Guethlein LA, Parham P, Miller JS, Cooley S. *Biol Blood Marrow Transplant.* doi:10.1016/j.bbmt.2018.12.763. Epub 2018 Dec 27.

Not for publication or presentation

- m. **IB15-06b** Evaluation of a Machine Learning-Based Prognostic Model for Unrelated Hematopoietic Cell Transplantation Donor Selection. Buturovic L, Shelton J, Spellman SR, Wang T, Friedman L, Loftus D, Hesterberg L, Woodring T, Fleischhauer K, Hsu KC, Verneris MR, Haagensohn M, Lee SJ. *Biol Blood Marrow Transplant* 2018 Jun 1; 24(6):1299-1306. doi:10.1016/j.bbmt.2018.01.038. Epub 2018 Feb 1. PMC5993610.
- n. **IB10-01c** Telomere length telomerase polymorphism in Severe Aplastic Anemia - Exome Analysis and Mosaicism. Gadalla S, Savage S. **Submitted. Journal of Clinical Investigation**
- o. **IB15-04** Clinical outcomes among hematopoietic stem cell transplant recipients as a function of socioeconomic status and related transcriptome differences. Knight J, Rizzo JD, Cole S. **Submitted. JNCI Cancer Spectrum**
- p. **IB15-07** Functional genetic variants of the ST2 gene in pairs of recipient and donors for risk stratification of GVHD and TRM outcomes. Paczesny S. **Submitted. Blood Advances**

3. Research repository update and accrual tables (Attachment 2)

Steve Spellman gave a brief update on the current status of the resources and data available via the CIBMTR Research Repository. There are samples on approximately 55,000 related and unrelated donor pairs available.

4. Future/proposed studies and discussion

Dr. Fleischhauer introduced all proposal presenters.

NK/KIR

- a. **PROP1811-12** Impact of the direction of NK cell alloreactivity predicted by KIR ligand mismatch on engraftment in umbilical cord blood and haploidentical stem cell transplantation (F Otegbeye) – (Attachment 3)

Dr. Otegbeye presented this proposal. The hypothesis is that the direction of KIR-ligand mismatch, as a surrogate for NK cell alloreactivity, predicts the risk of engraftment failure in HLA-mismatched transplants. More specifically, that KIR-ligand mismatch with alloreactivity in the host-vs-graft direction increases the risk of graft failure or delayed engraftment. It is also hypothesized that the dominant graft in a double cord blood transplant may be predicted by KIR-ligand mismatch interactions between the units and the recipient.

During the discussion, one attendee brought up the potential for confounding due to T-cell alloreactivity. He expressed how it may be difficult to untangle the T-cell alloreactivity from the NK alloreactivity, although did state that it is possible and important to plan and control for this in the design and analysis. Another attendee questioned how they plan to adjust for the presence or absence of alloreactivity. The study team is still considering the best way to incorporate this into the analysis, but it will be included. Another attendee mentioned a previous study in which chimerism data was analyzed for RIC transplants and questioned whether or not chimerism data would be available. Dr. Otegbeye responded that they do plan to look at mixed chimerism data, where available, for a subset of the data. Dr. Hsu asked questions to clarify how scoring would be carried out for alloreactivity in both directions.

- b. **PROP1811-97** A Novel KIR-HLA Interaction Scoring System and its Effect on Transplantation Outcomes after HLA Matched Allogeneic Hematopoietic Stem Cell Transplantation (E Krieger/A Toor/R Romee) – (*Attachment 4*)

Dr. Krieger presented this proposal. The hypothesis is that the cumulative effect of donor NK cell KIR and HLA, or KIR ligand interactions influence clinical outcomes following transplant. The study proposes to calculate and validate a KIR-HLA interaction score and estimate the effect of the scores on transplant outcomes.

During the discussion, Dr. Hsu noted that this algorithm builds on well-known inhibitory licensing models in which the biology is well understood. She stated that this is an interesting question, but some of the biology within this new algorithm is not so well elucidated and she would be interested to see more of a biological basis to support the algorithm.

An attendee suggested the study team might consider spitting the population into a discovery and validation set given the large amount of data that fits the inclusion/exclusion criteria. This would allow for a more robust test of the proposed algorithm.

HLA GENES

- c. **PROP1811-03/PROP1811-57/PROP1811-144/PROP1811-186** Effect of Class II HLA mismatching on the outcome of HLA-haploidentical hematopoietic cell transplantation (haploHCT) with high dose, post-transplantation cyclophosphamide (PTCy): a combined CIBMTR/EBMT analysis (S McCurdy/S Solomon/Y Kasamon/A Bashey/E Fuchs) – (*Attachment 5*)

Dr. McCurdy presented this proposal. The hypotheses were as follows: 1) Recipients of grafts from donors mismatched for one HLA-DRB1 antigen in the graft-versus-host direction will have improved progression-free survival (PFS) and overall survival (OS) when compared to recipients of grafts from donors without a mismatch at HLA-DRB1; 2) Recipients of grafts from donors with one non-permissive mismatch in HLA-DPB1 will have improved PFS and OS when compared to recipients of grafts from donors with a permissive mismatch or without a mismatch at HLA-DPB1.; 3) Mismatches in class I loci (HLA-A, B, and C) will not influence outcomes after haploidentical transplant with PTCy.

Dr. Fleischhauer asked for clarification on scoring for both donors and recipients that are heterozygous. She then questioned if DPB1 would be analyzed separately or in conjunction with DRB1. Dr. McCurdy stated that they would be analyzed separately and then further analyzed together in those patients that have data available for both.

One attendee suggested using high resolution typing data whenever possible. Dr. McCurdy replied that her only concern with that is not having enough observations to appropriately power the study.

- d. **PROP1811-68** Impact of ultra-high resolution HLA matching on the outcome of unrelated donor hematopoietic cell transplantation (N Mayor/S Spellman/S Marsh) – (*Attachment 6*)

Dr. Mayor presented this proposal. The hypothesis is that any degree of genetic variation at the classical HLA loci included when matching patients with unrelated donors for HCT will result in increased risks of post-transplant complications and mortality. This study aims to 1) validate ultra high-resolution (UHR) HLA matching findings from a UK study in a T-cell deplete cohort; 2) evaluate the impact of UHR HLA matching in a T-cell replete cohort; and 3) determine the impact of HLA-DPB1 TCE permissive mismatching in both cohorts.

During the discussion, an attendee questioned whether ultra high-resolution typing was going to be performed. Dr. Mayor confirmed that the typing had already been completed. Another attendee wondered whether the study team might consider a separate analysis to look at T-cell replete cohort and compare. Dr. Mayor stated that the idea of this proposal is a two-step process; to validate the initial findings in the T-cell replete cohort and then evaluate the findings in a T-cell replete cohort.

- e. **PROP1811-95** Evaluation of the impact of HLA Class I and II mismatches potentially non-immunogenic mismatches (A Bertaina/M Fernandez-Viña) – (*Attachment 7*)

Dr. Bertaina presented this proposal. This study hypothesizes that 1) HLA mismatches that only present amino acid differences at residues that do not determine peptide binding do not result in adverse outcomes; and 2) transplants with mismatches that include DRB1 alleles differing only at residue 86 in which the patient carries Valine and the donor carries Glycine may result in significantly better outcomes than transplants with other mismatches. The main outcomes to be examined are overall survival, acute GvHD, disease-free survival, and transplant-related mortality.

During the discussion, an attendee pointed out that the first part of this proposal had some potential overlap with a current study that is in the analysis stage. Mr. Spellman clarified that an evaluation for overlap was done, and it was determined that these were different scoring methodologies that both have unique components.

An attendee wanted further information on the rationale for looking at the particular combination of DRB1 in the donor and recipient. Dr. Fernandez-Vina provided a detailed description of the rationale citing several studies in the literature in which data had not been extrapolated to the particular combination of interest.

- f. **PROP1811-115** Effect of HLA-A Expression and HLA-B -21 M/T Dimorphism on Outcomes Following Allogeneic Hematopoietic Cell Transplant (C Camacho-Bydume/J Mytilineos/K Hsu) – (*Attachment 8*)

This proposal was withdrawn prior to the meeting.

- g. **PROP1811-157** Clinical correlation of DPB1 histocompatibility in BMT clinical outcome (P Cano/J Pidala/C Anasetti) – (*Attachment 9*)

Dr. Cano presented this proposal. The hypothesis is that matching for the main functional DP groups (DP1, DP2, DP3, and DP4) improves outcomes following bone

marrow transplantation. The specific aims of this study are to 1) study the correlation between DPB1 histocompatibility in the graft-versus-host direction based on DP functional epitopes and aGvHD; 2) assess the effect of functional epitope histocompatibility on outcome after adjusting for 3'UTR-SNP histocompatibility; 3) assess the effect of functional epitope histocompatibility on outcomes after adjusting for T-cell epitope histocompatibility; and 4) evaluate the role of other functional epitopes on aGvHD.

During the discussion, an attendee asked for clarification on the functional model. It was unclear how, or if, they planned to combine the mismatches looking at the specific positions. Dr. Cano stated that they planned to look at each mismatched epitope position individually.

h. **PROP1811-165** Impact of Donor HLA on Transplant Outcomes in NPM1 Mutated AML (R Narayan) – (*Attachment 10*)

Dr. Narayan presented this proposal. The hypothesis is that donor HLA genotype impacts outcomes of patients with NPM1 mutated AML undergoing allogeneic transplant. This study proposes to evaluate donor HLA versus outcomes in two ways: 1) group HLA that are predicted binders vs. non-binders to mutated NPM1 peptides and 2) group HLA that are predicted binders to both mutated and unmutated NPM1 peptides, as cytoplasmic translocation of the mutated NPM1 protein may impact HLA presentation of the whole protein.

During the discussion, an attendee asked how the study team would take into account the fact that more recent cases have more complete molecular data and some of the older cases may have had mutations that were not accounted for simply because they weren't tested. Dr. Narayan stated that they chose to assess and include FLT3 in this study as it was one of the earlier mutations that was tested for and the data is more complete. Another attendee noted that the performance of NetMHC is highly dependent by allele on the training set and asked if they planned to restrict their analysis to a restricted set of alleles where NetMHC performs well or if they're using it broadly. The study teams plans to use it broadly but is restricting to matched donors to account for some of that heterogeneity.

i. **PROP1811-185** The impact of single nucleotide gene polymorphisms in the gamma block of the major histocompatibility complex on unrelated donor hematopoietic cell transplants for hematological malignancies Part II: Extension of IB15-01 (M Askar/D Sayer/R Sobecks/N Majhail) – (*Attachment 11*)

Dr. Askar presented this proposal. This study is an extension of IB15-01 that aims to investigate the impact of GBSP donor and recipient genotypes on clinical outcomes. An attendee noted that their prior analysis and publication on variation in the MHC included an assessment of any variants in the gamma block and found no associations with outcomes. There were no further questions or comments.

OTHER GENES

- j. **PROP1812-05** Using whole-exome sequencing to identify novel non-HLA genetic contributors to mortality after blood and marrow transplantation (Q Zhu/L Sucheston-Campbell/T Hahn) – (*Attachment 12*)

Dr. Sucheston-Campbell presented this proposal. This study hypothesizes that functional coding genetic variants in non-HLA loci significantly affect patient survival after HLA-matched unrelated donor following blood and marrow transplant. This study aims to 1) whole-exome sequence HLA-matched unrelated recipient-donor pairs and carry out both variant-level and gene-level association tests to identify new non-HLA loci affecting mortality after BMT and 2) perform a meta-analysis of outcomes on HLA-matched unrelated recipient-donor pairs by integrating the new WES data and their existing genotype data.

During the discussion, an attendee asked if they have looked at this question in a matched-related population. Dr. Sucheston-Campbell said it is of interest but may not be feasible due to the sample size available through the CIBMTR.

Dropped proposals

- a. **PROP1801-01** Recipient HLA heterozygosity and the risk of AML/MDS relapse after reduced-intensity HLA-matched unrelated donor allograft – *Overlap with IB18-03*
- b. **PROP1811-39** HLA-disparity influence in the setting of matched-unrelated donor and PT-CY based anti-GVHD prophylaxis - *Feasibility*
- c. **PROP1811-184** The impact of HLA-A level of expression on clinical outcomes of HCT: extension of IB17-01 - *Feasibility*

BREAK – 20 minutes at 2:15

5. Studies in progress (*Attachment 13*)

NK/KIR

Dr. Katharine Hsu introduced speakers providing updates for NK/KIR studies.

- a. **R02-40/R03-63** Acquisition of natural killer cell receptors in recipients of unrelated transplant (J Miller/E Trachtenberg) **Ongoing**
- b. **R04-74d** Functional significance of killer cell immunoglobulin-like receptor genes in HLA-matched and mismatched unrelated HCT (K Hsu) **Manuscript preparation – Update**

Dr. Katharine Hsu provided an update for this study. Previous retrospective studies showed different combinations of KIR/HLA to be important. They didn't find any statistical significance in the original cenB studies, but it was suggestive. It was also concluded that 1.) cenB is a collective of partial KIR haplotypes, with defined LD between KIR alleles and 2.) donor KIR2DL1-C²⁴⁵ is associated with lower relapse compared to KIR2DL1-R²⁴⁵. There are an additional 1217 AML 10/10 samples that have been sent for KIR allele typing for use in a larger cohort.

- c. **IB15-03** Killer Immunoglobulin Receptor (KIR) gene content and pediatric acute leukemia transplant outcomes (MR Verneris/J Miller/S Cooley) **Manuscript preparation**
- e. **IB17-02** Donor-recipient NK cell determinants associated with survival in JMML after hematopoietic stem cell transplantation (D Lee/H Rangarajan) **Data file preparation**

- f. **IB18-04** Impact of donor KIR genotype on outcome after URD TX in patients with MDS or sAML (J Schetelig/N Kröger/M Robin) **Manuscript preparation – Update** (*Attachment 14*)

Dr. Shetelig provided an update for this study. This collaborative EBMT and CIBMTR study aimed to validate the role of donor KIR genotype on transplant outcome. Relapse incidence and overall survival after unrelated donor allogeneic transplant was not associated with KIR genotype in this cohort using the two previously defined models. This points to the possibility of interactions between NK-cell mediated alloreactivity and variations in transplant procedure.

- g. **IB18-05** Imputation of KIR in GWAS and association of KIR-HLA with outcomes following alloHCT In AML and MDS (C Camacho-Bydume/L Sucheston-Campbell/S Leslie/K Hsu)

Analysis

HLA GENES – CLASSICAL MATCHING

Dr. Katharina Fleischhauer introduced speakers providing updates for HLA Genes studies.

- a. **IB06-05** Use of high-resolution HLA data from the NMDP for the International Histocompatibility Working Group in HCT (E Petersdorf) **Ongoing – Update**

Dr. Effie Petersdorf provided updates on several ongoing studies within the International Histocompatibility Working Group-HCT component: 1.) Fine-mapping of MHC SNPs in 7,244 HLA mismatched unrelated donor transplants; 2) impact of HLA mismatching on clinical outcomes in 33,982 IHWG transplants; 3) significance of ethnicity in outcome after HLA mismatched unrelated transplant; and 4) role of HLA class I and class II expression.

- b. **IB14-07** Indirectly recognizable HLA epitopes (PIRCHES): a retrospective validation study on the role of indirect recognition of mismatched HLA in hematopoietic stem cell transplantation outcome (E Spierings) **Manuscript preparation**

- c. **IB16-01** The role of HLA-E compatibility in the prognosis of acute leukemia patients undergoing 10/10 HLA matched unrelated HSCT (C Tsamadou/D Fürst/J Mytilineos) **Manuscript preparation** (*Attachment 15*)

- d. **IB16-02** Use of HLA structure and function parameters to understand the relationship between HLA disparity and transplant outcomes (LA Baxter-Lowe) **Analysis**

- e. **IB18-01** Effect of HLA phenotypes on long term GVHD risk (C Story/M Riches/P Armisted) **Protocol development**

- f. **IB18-02** Impact of HLA class I risk alleles associated with AA Immune pathogenesis on allo TX outcomes in patients with SAA (D Babushok/T Olson) **Protocol development**

- g. **IB18-03** Effect of HLA Class I Heterozygosity and HLA Supertypes on Outcomes Following Allogeneic HCT for Myeloid and Lymphoid Malignancies (C Camacho-Bydume/K Hsu) **Analysis – Update** (*Attachment 16*)

Dr. Christine Camacho-Bydume provided an update for this study. The results indicate that zygosity of HLA class I loci was not associated with outcomes following allogeneic transplant for myeloid and lymphoid malignancies. The B62 supertype was found to be associated with decreased transplant related mortality. This data was presented as a poster at the 2019 TCT meetings.

CYTOKINE/CHEMOKINE

Not for publication or presentation

- a. **IB14-03a:** The prognostic impact of somatic mutations and levels of CXC chemokine ligands on post hematopoietic cell transplantation (HCT) outcomes in patients with myelodysplastic syndromes (MDS) (W Saber/B Dhakal) **Manuscript preparation**
- b. **IB14-03c** Effect of telomere length in MDS patients without TP53/RASTK/JAK2 mutations (RC Lindsley/W Saber) **Manuscript preparation** (*Attachment 17*)

OTHER GENES

Dr. Sophie Paczesny introduced speakers providing updates for Other Genes studies.

- a. **IB09-06/RT09-04b** Genetic susceptibility to transplant-related mortality after unrelated donor stem cell transplant (T Hahn/L Sucheston-Campbell) **Ongoing**
- b. **IB10-01f** Epigenetic clock: Can this guide donor selection in HCT (S Gadalla/S Savage) **Sample typing**
- c. **IB14-04** Assessing the similarity of the T cell receptor repertoire in allogeneic hematopoietic stem cell recipients with the same single human leukocyte mismatches (EH Meyer) **Manuscript preparation**
- d. **IB14-05** mtDNA haplotypes and unrelated donor transplant outcomes (M Verneris/J Ross) **Analysis**
- e. **IB16-03** Role of recipient and donor genetic polymorphisms in interferon lambda 4 (INFL4) on outcomes after unrelated allogeneic cell transplant (S Gadalla) **Manuscript preparation – Update** (*Attachment 18*)

Dr. Shahinaz Gadalla provided an update for this study. The primary goal of the study is to evaluate the effect of recipient and donor genetic polymorphisms in the type-III interferon, interferon lambda 4 (INFL4) on outcomes following unrelated donor HCT for SAA and acute leukemia. The study concluded that donor IFNL4 genotype is associated with the risk of transplant-related mortality in patients with acute leukemia. The data suggest that avoiding donors with dG/dG genotype will improve outcomes without limiting the potential donor pool. A validation study is currently underway focusing on TRM and one-year cause specific mortality using the DISCOVERy-BMT cohort.

- f. **IB17-03** Identification of genomic markers of post hematopoietic cell transplantation (HCT) outcomes in patients with myelofibrosis: A pilot study (W Saber/S Gadalla) **Sample typing**
- g. **IB17-04** Epigenetic profiling of unrelated donor-recipient pairs to improve donor selection during HCT transplants (S Beck/K Peggs/V Rakyen/A Webster) **Analysis**
- h. **IB18-06** Clonal mosaicism and HCT outcomes in patients with acute leukemia and myelodysplastic syndromes (S Gadalla/T Hahn/L Sucheston-Campbell) **Protocol development**
- i. **IB18-07** Donor and recipient genomic associations with acute GVHD (V Afshar-Khargan) **Protocol pending**
- j. **IB15-04** Clinical outcomes among hematopoietic stem cell transplant recipients as a function of socioeconomic status and related transcriptome differences (J Knight/JD Rizzo/S Cole) **Submitted to JNCI Cancer Spectrum**

Dr. Jennifer Knight provided an update for this study. The primary hypothesis of the study is that increased expression of the conserved transcriptional response to adversity

Not for publication or presentation

(CTRA) gene profile will be associated with lower socioeconomic status (SES) and worse clinical outcomes among a group of unrelated donor (URD) myeloablative (MA) acute myelogenous leukemia (AML) recipients in CR1. Results showed that very high or very low CTRA inflammatory gene profiles were associated with relapse and disease-free survival.

7. Deferred studies pending accrual/funding

- a. **IB17-01** The impact of HLA-DPB1 level of expression on clinical outcomes of transplantation (M Askar/M Fernandez-Vina) **Pending funding**

8. Dropped studies

- a. **IB09-04** D/R gene polymorphisms of drug metabolisms and innate immune response post allele matched MUD HSCT (V Rocha) – *Lack of progress*
- b. **IB11-01b** IPA effect on outcome in URD PBSC/BM HCT (G Ehninger) – *Lack of progress*
- c. **IB13-09** Machine learning classifiers to define the alloreactivity of HLA mismatches in URD HCT (Y Louzoun) – *Lack of progress*
- d. **IB15-05** Secondary Findings in Exome Sequencing Data (S Savage) – *Lack of progress*

9. Closing remarks

Dr. Fleischhauer adjourned the meeting and thanked members for attending.

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Working Committee Overview Plan for 2019-2020

Study number and title	Current status	Goal with date	Total hours to complete	Total hours to goal	Hours allocated to 6/30/2019	Hours allocated 7/1/2019-6/30/2020	Total Hours allocated
HLA GENES							
IB16-01 HLA-E compatibility in acute leukemia for 10/10 HLA matched URD HCT	Submitted	Published – August 2019	0	0	0	0	0
IB16-02 HLA structure and function parameters in the relationship between HLA disparity and HCT outcomes	Manuscript Preparation	Published – June 2020	70	70	70	10	70
IB18-01 Effect of HLA phenotypes on long term GVHD risk	Data file preparation	Manuscript Preparation – April 2020	200	130	50	80	130
IB18-02 Impact of HLA class I risk alleles associated with AA Immune pathogenesis on allo TX outcomes in patients with SAA	Protocol Development	Manuscript Preparation – June 2020	260	190	10	180	190
IB18-03 Effect of HLA Class I Heterozygosity and HLA Supertypes on Outcomes Following Allogeneic HCT for Myeloid and Lymphoid Malignancies	Manuscript Preparation	Submitted – December 2019	70	70	0	70	70
IB19-01 Impact of ultra-high resolution HLA matching on outcome of URD HCT	Protocol Pending	Analysis – June 2020	330	200	0	200	200

Not for publication or presentation

IB19-02 Effect of HLA Class II mismatching on outcome of HaploHCT with high dose PTCy	Protocol Pending	Analysis – June 2020	330	200	0	200	200
CYTOKINE/CHEMOKINE							
IB14-03a CXC chemokine ligands on MDS HCT outcomes	Manuscript Preparation	Published – September 2019	10	10	10	10	10
IB14-03c Effect of telomere length in MDS patients without TP53/RASTK/JAK2 mutations	Manuscript Preparation	Published – December 2019	70	70	70	10	70
NK/KIR							
IB15-03 Effect of KIR on AlloHCT for Pediatric acute leukemia	Manuscript Preparation	Submitted – December 2019	70	70	0	70	70
IB17-02 Donor-recipient NK cell determinants associated with survival in JMML after HSCT	Sample Typing	Manuscript Preparation – June 2020	150	40	40	40	40
IB18-04 Impact of donor KIR genotype on outcome after URD TX in patients with MDS or sAML	Manuscript Preparation	Submitted – January 2020	70	70	0	70	70
IB18-05 Imputation of KIR in GWAS and association of KIR-HLA with outcomes following alloHCT In AML and MDS	Analysis	Manuscript Preparation – June 2020	110	40	0	40	40

Not for publication or presentation

IB19-03 KIR ligand mismatch in UCB and haplo	Protocol Pending	Data File Preparation – June 2020	330	100	0	100	100
OTHER GENES							
IB10-01c Telomere length telomerase polymorphism in SAA-Exome Analysis and Mosaicism	Submitted	Published – October 2019	0	0	0	0	0
IB10-01f Epigenetic clock and outcome	Sample Typing	Manuscript Preparation – June 2020	250	180	10	170	180
IB14-04 T cell receptor repertoire in AlloHCT with the same single human leukocyte mismatches	Submitted	Published – June 2019	10	10	10	0	10
IB14-05 mtDNA haplotypes and unrelated donor transplant outcomes	Manuscript Preparation	Submitted – May 2020	70	70	0	70	70
IB15-04 Association of CTRA and socioeconomic status in URD HCT	Submitted	Published – July 2019	0	0	0	0	0
IB15-07 Functional genetic variants of the ST2 gene in pairs of recipient and donor	Submitted	Published – July 2019	10	10	10	0	10
IB16-03 Role of genetic polymorphisms in INFL4 after URD HCT	Submitted	Published – August 2019	10	10	10	0	10

Not for publication or presentation

IB17-03 Identification of genomic markers of post-HCT outcomes in patients with myelofibrosis	Sample Typing	Manuscript Preparation – June 2020	260	190	110	80	190
IB17-04 Improve donor selection during HCT using epigenetic signatures	Analysis	Manuscript Preparation – December 2019	90	20	10	10	20
IB18-06 Clonal mosaicism in acute leukemia	Analysis	Manuscript Preparation – February 2020	80	30	20	10	30
IB18-07 Donor and recipient genomic associations with acute GVHD	Protocol Development	Analysis – June 2020	320	170	70	100	170
SENSITIZATION AND TOLERANCE							
IB19-04 Impact of donor HLA on transplant outcomes in NPM1 mutated AML	Protocol Pending	Analysis – June 2020	330	200	0	200	200

Oversight Assignments for Working Committee Leadership

Sophie Paczesny

IB14-05 mtDNA haplotypes and unrelated donor transplant outcomes

IB15-04 Clinical outcomes among hematopoietic stem cell transplant recipients as a function of socioeconomic status and related transcriptome differences

IB15-07 Functional genetic variants of the ST2 gene in pairs of recipient and donors for risk stratification of GVHD and TRM outcomes

IB16-03: Role of recipient and donor genetic polymorphisms in interferon lambda 4 (INFL4) on outcomes after unrelated allogeneic cell transplant

IB17-03 Identification of genomic markers of post hematopoietic cell transplantation (HCT) outcomes in patients with myelofibrosis (MF): A pilot study

IB18-04 Evaluation of the impact of donor KIR genotype on outcome after unrelated donor transplantation in patients with myelodysplastic syndromes or secondary acute myeloid leukemia

IB18-06 Clonal mosaicism and HCT outcomes in patients with acute leukemia and myelodysplastic syndromes

IB18-07 Donor and recipient genomic associations with acute GVHD

Katharine Hsu

IB14-03a The levels of CXC chemokine ligands on post hematopoietic cell transplantation outcomes in patients with myelodysplastic syndromes

IB14-03c Impact of telomere length and telomerase gene mutations on allogeneic stem cell transplantation outcomes in myelodysplastic syndrome

IB14-04 Assessing the similarity of the T cell receptor repertoire in allogeneic hematopoietic stem cell recipients with the same single human leukocyte mismatches

IB15-03 Killer Immunoglobulin Receptor (KIR) gene content and pediatric acute leukemia transplant outcomes

IB16-01 The role of HLA-E compatibility in the prognosis of acute leukemia patients undergoing 10/10 HLA matched unrelated HSCT

IB17-02 Donor-recipient NK cell determinants associated with survival in JMML after hematopoietic stem cell transplantation

IB18-05 Imputation of KIR in genome-wide association study and the association of KIR-HLA with outcomes following alloHCT In AML and MDS

IB19-03 Impact of the direction of NK cell alloreactivity predicted by KIR ligand mismatch on engraftment in umbilical cord blood and haploidentical stem cell transplantation

Steven Marsh

IB19-04 Impact of donor HLA on transplant outcomes in NPM1 mutated AML

IB10-01c Telomere length telomerase polymorphism in Severe Aplastic Anemia - Exome Analysis and Mosaicism

IB10-01f Epigenetic clock: Can this guide donor selection in HCT

IB16-02 Use of HLA structure and function parameters to understand the relationship between HLA disparity and transplant outcomes

IB17-04 Epigenetic profiling of unrelated donor-recipient pairs to improve donor selection during HCT transplants

IB18-01 Effect of HLA phenotypes on long term GVHD risk

IB18-02 The impact of HLA class I risk alleles associated with AA Immune pathogenesis on allogeneic transplant outcomes in patients with severe acquired aplastic anemia

IB18-03 The Effect of HLA Class I Heterozygosity and HLA Supertypes on Outcomes Following Allogeneic Hematopoietic Cell Transplant for Myeloid and Lymphoid Malignancies

IB19-01 The impact of ultra-high resolution HLA matching on the outcome of unrelated donor hematopoietic cell transplantation

IB19-02 Effect of class II HLA mismatching on the outcome of HLA-haploidentical hematopoietic cell transplantation with high dose, post-transplantation cyclophosphamide