Not for publication or presentation

A G E N D A
CIBMTR WORKING COMMITTEE FOR IMMUNOBIOLOGY
Orlando, FL
Thursday, February 20, 2020, 12:15 pm–3:00 pm

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1. Introduction 12:15pm

a. Minutes and Overview Plan of Immunobiology Working Committee from TCT 2019 *(Attachment 1)*

b. Newly appointed chair: Shahinaz Gadalla, MD, PhD; National Cancer Institute
Telephone: 240-276-7254; E-mail: shahinaz.gadalla@nih.gov

2. Published and submitted papers 12:25pm

a. **IB06-05b** Role of HLA-B exon 1 in graft-versus-host disease after unrelated haemopoietic cell transplantation: A retrospective cohort study. Petersdorf EW, Carrington M, O'hUigin C, Bengtsson M, De Santis D, Dubois V, Gooley T, Horowitz M, Hsu K, Madrigal JA, Maiers MJ, Malkki M, McKallor C, Morishima Y, Oudshoorn M, Spellman SR, Villard J, Stevenson P. ***Lancet Haematology*. doi:10.1016/S2352-3026(19)30208-X. Epub 2019 Oct 25.**

b. **IB09-06s** Tang H, Hahn T, Karaesmen E, Rizvi AA, Wang J, Paczesny S, Wang T, Preus L, Zhu Q, Wang Y, Haiman CA, Stram D, Pooler L, Sheng X, Van Den Berg D, Brock G, Webb A, Pasquini MC, McCarthy PL, Spellman SR, Sucheston-Campbell LE. Validation of genetic associations with acute GVHD and non-relapse mortality in DISCOVeRY-BMT. ***Blood Advances.* 2019 Aug 13; 3(15):2337-2341. doi:10.1182/bloodadvances.2019000052. Epub 2019 Aug 7. PMC6693017.**

c. **IB10-01h** Pre-transplant short telomeres are associated with high mortality risk after unrelated donor haematopoietic cell transplant for severe aplastic anaemia. Wang Y, McReynolds LJ, Dagnall C, Katki HA, Spellman SR, Wang T, Hicks B, Freedman ND, Jones

K, Lee SJ, Savage SA, Gadalla SM. ***British Journal of Haematology.*** **doi:10.1111/ bjh.16153. Epub 2019 Aug 19**

d. **IB15-04** Molecular correlates of socioeconomic status and clinical outcomes following hematopoietic cell transplantation for leukemia. Knight JM, Rizzo JD, Wang T, He N, Logan BR, Spellman SR, Lee SJ, Verneris MR, Arevalo JMG, Cole SW. ***JNCI Cancer Spectrum.*** **2019 Dec 1; 3(4):pkz073. doi:10.1093/jncics/pkz073. Epub 2019 Sep 12. PMC6859844.**

e. **IB15-07** Multiple functional variants in the IL1RL1 region are pretransplant markers for risk of GVHD and infection deaths. Karaesmen E, Hahn T, Dile AJ, Rizvi AA, Wang J, Wang T, Haagenson MD, Preus L, Zhu Q, Liu Q, Yan L, Liu S, Haiman CA, Stram D, Pooler L, Sheng X, Van Den Berg D, Brock G, Webb A, McCarthy PL, Pasquini MC, Spellman SR, Lee SJ, Paczesny S, Sucheston-Campbell LE. ***Blood Advances.*** **2019 Aug 27; 3(16):2512-2524. doi:10.1182/bloodadvances.2019000075. Epub 2019 Aug 27. PMC6712530.**

f. **IB16-01** Donor HLA-E status associates with disease free survival and transplant related mortality after non in vivo T-cell depleted HSCT for acute leukemia. Tsamadou C, Fürst D, Wang T, He N, Lee SJ, Spellman SR, Fleischhauer K, Hsu KC, Paczesny S, Verneris MR, Schrezenmeier H, Mytilineos J. ***Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation.*** **doi:10.1016/j.bbmt.2019.08.007. Epub 2019 Aug 16.**

g. **IB10-01c** Telomere length telomerase polymorphism in Severe Aplastic Anemia - Exome Analysis and Mosaicism. (S Gadalla/S Savage) **In press. British Journal of Haematology**

h. **IB10-01i** Genome-wide association study identified HLA-DPB1 as significant risk factor for severe aplastic anemia (S Savage/S Gadalla) **In press. Biology of Blood and Marrow Transplantation**

i. **R02-40/R03-63d** KIR B donors improve the outcome for AML patients given reduced intensity conditioning and unrelated donor transplant (J Miller) **In press. Blood Advances**

j. **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) **In press. Biology of Blood and Marrow Transplantation**

k. **IB09-06b/RT09-04b** Genetic susceptibility to transplant-related mortality after unrelated donor stem cell transplant (T Hahn/L Sucheston-Campbell) **Submitted.**

l. **IB09-06m** DISCOVeRY-BMT: Compare unrelated donor to Welcome Trust Case Control Consortium controls (K Onel/A Clay-Gilmour/E Karaesmen) **Submitted.**

m. **IB09-06p** DISCOVeRY-BMT: Genetics and epidemiology of Myeloid Malignancies genome-wide association (A Clay-Gilmour/K Onel/T Hahn) **Submitted.**

n. **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) **Submitted.**

o. **IB15-03** Killer Immunoglobulin Receptor (KIR) gene content and pediatric acute leukemia transplant outcomes (MR Verneris/J Miller/S Cooley) **Submitted.**

p. **IB16-03** Role of recipient and donor genetic polymorphisms in interferon lambda 4 (INFL4) on outcomes after unrelated allogeneic cell transplant (S Gadalla) **Submitted.**

q. **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) **Submitted.**

3. Research repository update and accrual tables *(Attachment 2)* 12:25pm

4. Future/proposed studies and discussion 12:35pm

a. Voting guidelines

HLA GENES – presented

b. **PROP1908-01** Evaluation of the impact of HLA molecular mismatch on clinical outcomes in patients who underwent haploidentical hematopoietic stem cell transplantation (J Zou/S Ciurea) – *(Attachment 3)*

c. **PROP1911-135** Association of immunopeptidome divergence between mismatched HLA class I alleles and outcome of 9/10 matched unrelated HCT (P Crivello/E Arrieta-Bolaños/ K Fleischhauer) – *(Attachment 4)*

d. **PROP1911-15** HLA-Mismatches in the Setting of Post-Transplant Cyclophosphamide and Lymphomas: Are Matched Unrelated or Haploidentical Donors Still an Issue? (A Mussetti/A Sureda/A Kanate) – *(Attachment 5)*

SENSITIZATION AND TOLERANCE – presented

e. **PROP1911-182** Role of Recipients' Specific anti-HLA Antibodies (RSA) in hematopoietic stem cell transplantation with Human Leukocyte antigen (HLA) mismatched donors (J Zou/K Cao/S Ciurea) – *(Attachment 6)*

OTHER-FUNDED PROPOSALS AND EXTENSIONS OF EXISITING STUDIES – not presented

f. **PROP1911-133** IB12-02D: Refinement of the T cell epitope algorithm for the definition of permissive HLA-DPB1 mismatches in allogeneic hematopoietic cell transplantation: stratification of TCE group 3 mismatches (E Arrieta-Bolaños/P Crivello/K Fleischhauer)

g. **PROP1911-172** Evaluation of Killer Cell Immunoglobulin-like Receptor - HLA class I Ligand models for donor selection- Joint Study of the Cellular Therapy and Immunobiology Working Party (CTIWP) of EBMT and the Immunobiology Working Committee (IBWC) of CIBMTR (J Schetelig/K Fleischhauer/C Chabannon)

h. **PROP1911-268** Genetic epidemiology of Adolescent, Young adult, and Adult Acute Lymphoblastic Leukemia (A Clay-Gilmour/L Sucheston-Campbell/T Hahn/E Cull)

i. **PROP1912-02** Clinical outcomes among hematopoietic stem cell transplant recipients as a function of socioeconomic status and related transcriptome differences (J Knight/J Rizzo/S Cole/K Rentscher)

DROPPED PROPOSALS – not presented

j. **PROP1904-01** The effect of HLA mismatch on the outcomes of haploidentical transplantation for hematological non-malignant disorders – *Feasibility*

k. **PROP1919-18** The impact of HLA mismatches on haploidentical hematopoietic stem cell transplant recipient outcome – *Overlap with IB19-02*

l. **PROP1911-02** Clonal hematopoiesis and hematologic ageing in long-term allo-SCT survivors- *Feasibility*

m. **PROP1911-108** An association study of Non-Hodgkin Lymphoma (NHL) subtypes and Histocompatibility Leukocyte Antigen (HLA) alleles, haplotypes, and zygosity – *Feasibility*

n. **PROP1911-140** Impact of HLA Antigen Mismatch in Haploidentical Donor Transplantation Using Post-Transplant Cyclophosphamide – *Overlap with IB19-02*

5. Studies in progress *(Attachment 7)* 1:40 pm

NK/KIR

a. **IB17-02** Donor-recipient NK cell determinants associated with survival in JMML after hematopoietic stem cell transplantation (D Lee/H Rangarahan) **Data file preparation**
b. **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**
c. **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 (F Otegebeye/M Fernandez-Viña/M de Lima) **Protocol development**
d. **R04-74d** Functional significance of killer cell immunoglobulin-like receptor genes in HLA-matched and mismatched unrelated HCT (K Hsu) **Ongoing – UPDATE PRESENTED**

HLA GENES – CLASSICAL MATCHING

a. **IB06-05** Use of high-resolution HLA data from the NMDP for the International Histocompatibility Working Group in HCT (E Petersdorf) **Ongoing**
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. **IB16-02** Use of HLA structure and function parameters to understand the relationship between HLA disparity and transplant outcomes (LA Baxter-Lowe) **Manuscript preparation – UPDATE PRESENTED**
d. **IB18-01** Effect of HLA phenotypes on long term GVHD risk (C Story/M Riches/P Armisted) **Manuscript preparation – UPDATE PRESENTED**
e. **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) **Sample typing**
f. **IB19-01** The impact of ultra-high resolution HLA matching on the outcome of unrelated donor hematopoietic cell transplantation (N Mayor/S Spellman/S Marsh) **Data file preparation**
g. **IB19-02** Effect of class II HLA mismatching on the outcome of HLA-haploidentical hematopoietic cell transplantation with high dose, post-transplantation cyclophosphamide: a combined CIBMTR/EBMT analysis (S McCurdy/S Solomon/Y Kasamon/A Bashey/E Fuchs) **Data file preparation**

CYTOKINE/CHEMOKINE

a. **IB14-03c** Effect of telomere length in MDS patients without TP53/RASTK/JAK2 mutations (RC Lindsley/W Saber) **Manuscript preparation – UPDATE PRESENTED**

OTHER GENES

a. **IB09-06/RT09-04b** Genetic susceptibility to transplant-related mortality after unrelated donor stem cell transplant (T Hahn/L Sucheston-Campbell) **Submitted – UPDATE PRESENTED**
b. **IB10-01f** Epigenetic clock: Can this guide donor selection in HCT (S Gadalla/S Savage) **Manuscript preparation – UPDATE PRESENTED**
c. **IB14-05** mtDNA haplotypes and unrelated donor transplant outcomes (M Verneris/J Ross) **Manuscript preparation**
d. **IB17-03** Identification of genomic markers of post hematopoietic cell transplantation (HCT) outcomes in patients with myelofibrosis: A pilot study (W Saber/S Gadalla) **Data file preparation**
e. **IB17-04** Epigenetic profiling of unrelated donor-recipient pairs to improve donor selection during HCT transplants (S Beck/K Peggs/V Rakyan/A Webster) **Analysis**

f. **IB18-06** Clonal mosaicism and HCT outcomes in patients with acute leukemia and myelodysplastic syndromes (S Gadalla/T Hahn/L Sucheston-Campbell) **Manuscript preparation – UPDATE PRESENTED**

g. **IB18-07** Donor and recipient genomic associations with acute GVHD (V Afshar-Khargan) **Sample typing**

SENSITIZATION AND TOLERANCE

a. **IB19-04** Impact of donor HLA on transplant outcomes in NPM1 mutated AML (R Narayan/E Meyer/Y Chen) **Protocol development**

ONGOING AND OTHER-FUNDED STUDIES

a. **R02-40/R03-63** Acquisition of natural killer cell receptors in recipients of unrelated transplant (J Miller/E Trachtenberg) **Ongoing**

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

c. **IB09-01** Clinical importance of minor histocompatibility complex haplotypes in umbilical cord blood transplantation (E Petersdorf) **Ongoing**

d. **IB09-03** Clinical relevance of cytokine/immune response gene polymorphisms in umbilical cord blood transplantation (E Petersdorf) **Ongoing**

e. **IB09-05** Identification of functional single nucleotide polymorphisms in umbilical cord blood transplantation (E Petersdorf) **Ongoing**

f. **IB09-07** Clinical significance of genome-wide variation in unrelated HCT (E Petersdorf) **Ongoing**

g. **RT09-04/IB09-06i** DISCOVeRY-BMT: Recip, Donor Genome-wide association study Interaction with Conditioning Intensity (Myeloablative/Reduced intensity conditioning), Total body irradiation, Disease status (E Karaesemen/L Sucheston-Campbell/T Hahn) **Manuscript preparation**

h. **IB09-06j** DISCOVeRY-BMT: Additional analysis of major histocompatibility complex single nucleotide polymorphisms (S Spellman/L Sucheston-Campbell) **Manuscript preparation**

i. **IB09-06m** DISCOVeRY-BMT: Analysis of X chromosome single nucleotide polymorphisms (S Spellman/L Sucheston-Campbell) **Manuscript preparation**

j. **IB09-06o** DISCOVeRY-BMT: Genetics and Epidemiology of Myeloid Malignancies candidate gene (L Suchestion-Campbell/E Karaesmen/A Clay-Gilmour/T Hahn) **Manuscript Preparation**

DROPPED STUDIES

a. **IB18-05** Imputation of KIR in genome-wide association study and the association of KIR-HLA with outcomes following alloHCT In AML and MDS (C Camacho-Bydume/L Sucheston-Campbell/S Leslie/K Hsu) – *Lack of progress*

b. **IB19-05** Impact of donor signal-regulatory protein alpha polymorphism on outcomes of allogeneic hematopoietic stem cell transplantation (J Danska/F Lakkis) – *Lack of funding*

6. Closing Remarks 3:00 pm

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;**
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Co-Chair:	**Katharine Hsu, MD, PhD; Memorial Sloan-Kettering Cancer Center;**
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Co-Chair:	**Sophie Paczesny, MD, PhD; Indiana University Hospital;**
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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. ***PLOS1* 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.***

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, Haagenson 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-C^{245} is associated with lower relapse compared to KIR2DL1-R^{245}. 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 Rangarahan) **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

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 Rakyan/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

(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.

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**

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**

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**

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

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

Accrual Summaries for Immunobiology Working Committee

Comprehensive Report Form (CRF) data

Variable	CIBMTR HLA-identical sibling N (%)	CIBMTR Alternative related N (%)	CIBMTR Unrelated (non-US) N (%)	CIBMTR Unrelated (US) N (%)
Number of patients	48281	10593	9788	46665
Number of centers	524	454	230	214
Recipient age at transplant				
0-9 years	6602 (14)	2477 (23)	2257 (23)	7402 (16)
10-19 years	7840 (16)	1610 (15)	1586 (16)	5260 (11)
20-29 years	8125 (17)	1439 (14)	1451 (15)	5131 (11)
30-39 years	8767 (18)	1260 (12)	1605 (16)	5695 (12)
40-49 years	8199 (17)	1260 (12)	1409 (14)	6990 (15)
50-59 years	8740 (18)	2544 (24)	1479 (15)	16186 (35)
Unknown	8 (N/A)	3 (N/A)	1 (N/A)	1 (N/A)
Median (Range)	32 (-30-82)	28 (0-88)	27 (0-76)	40 (-0-83)
Recipient race/ethnicity				
Caucasian, non-Hispanic	36541 (79)	7047 (72)	7382 (79)	35953 (79)
African-American, non-Hispanic	2256 (5)	983 (10)	89 (1)	3514 (8)
Asian, non-Hispanic	4522 (10)	945 (10)	1400 (15)	1628 (4)
Pacific islander, non-Hispanic	77 (<1)	31 (<1)	52 (1)	94 (<1)
Native American, non-Hispanic	99 (<1)	47 (<1)	43 (<1)	177 (<1)
Hispanic, Caucasian	1158 (2)	505 (5)	298 (3)	3071 (7)
Hispanic, African-American	69 (<1)	27 (<1)	15 (<1)	119 (<1)
Hispanic, Asian	12 (<1)	3 (<1)	3 (<1)	20 (<1)
Hispanic, Pacific islander	4 (<1)	0	0	12 (<1)
Hispanic, Native American	22 (<1)	5 (<1)	3 (<1)	41 (<1)
Hispanic, race unknown	144 (<1)	27 (<1)	21 (<1)	741 (2)
Other	1424 (3)	224 (2)	83 (1)	106 (<1)
Unknown	1953 (N/A)	749 (N/A)	399 (N/A)	1189 (N/A)
Recipient sex				
Male	28269 (59)	6405 (60)	5816 (59)	27328 (59)
Female	20012 (41)	4188 (40)	3972 (41)	19337 (41)
Karnofsky score				
10-80	13153 (27)	3507 (33)	2601 (27)	14064 (30)
90-100	33477 (69)	6505 (61)	6809 (70)	30140 (65)
Missing	1651 (3)	581 (5)	378 (4)	2461 (5)
HLA-A B DRB1 groups - low resolution				
<=3/6	0	1918 (56)	26 (1)	287 (1)
4/6	0	671 (20)	235 (9)	4339 (10)
5/6	0	293 (9)	697 (25)	9246 (22)
6/6	48281 (100)	519 (15)	1804 (65)	29132 (68)
Unknown	0 (N/A)	7192 (N/A)	7026 (N/A)	3661 (N/A)

Variable	CIBMTR HLA-identical sibling N (%)	CIBMTR Alternative related N (%)	CIBMTR Unrelated (non-US) N (%)	CIBMTR Unrelated (US) N (%)
High-resolution HLA matches available out of 8				
<=5/8	36 (1)	2102 (76)	254 (14)	5431 (15)
6/8	8 (<1)	145 (5)	198 (11)	3413 (9)
7/8	36 (1)	179 (6)	484 (26)	7114 (20)
8/8	3785 (98)	357 (13)	900 (49)	20210 (56)
Unknown	44416 (N/A)	7810 (N/A)	7952 (N/A)	10497 (N/A)
High-resolution HLA typed and audited				
N	0	2 (<1)	23 (4)	1039 (4)
Y	1194 (100)	543 (>99)	533 (96)	22463 (96)
Unknown	47087 (N/A)	10048 (N/A)	9232 (N/A)	23163 (N/A)
Graft type				
Marrow	32088 (66)	6239 (59)	5399 (55)	17540 (38)
PBSC	15581 (32)	4181 (39)	2525 (26)	18052 (39)
UCB	206 (<1)	40 (<1)	1825 (19)	10680 (23)
BM+PBSC	241 (<1)	79 (1)	5 (<1)	10 (<1)
BM+UCB	110 (<1)	13 (<1)	2 (<1)	0
PBSC+UCB	5 (<1)	3 (<1)	7 (<1)	277 (1)
Others	50 (<1)	38 (<1)	25 (<1)	106 (<1)
Conditioning regimen				
Myeloablative	39209 (81)	7382 (70)	7230 (74)	29679 (64)
RIC	3680 (8)	948 (9)	1219 (12)	9032 (19)
Nonmyeloablative	3228 (7)	1585 (15)	710 (7)	5043 (11)
Other	2164 (4)	678 (6)	629 (6)	2911 (6)
Donor age at donation				
To Be Determined/NA	1534 (3)	369 (3)	1367 (14)	1713 (4)
0-9 years	5756 (12)	543 (5)	1443 (15)	9758 (21)
10-19 years	7754 (16)	1085 (10)	155 (2)	1198 (3)
20-29 years	8374 (17)	2094 (20)	2039 (21)	13146 (28)
30-39 years	8665 (18)	2682 (25)	2575 (26)	11279 (24)
40-49 years	7917 (16)	2021 (19)	1763 (18)	7465 (16)
50+ years	8281 (17)	1799 (17)	446 (5)	2106 (5)
Median (Range)	31 (-7-85)	35 (-11-81)	32 (0-80)	29 (0-69)
Disease at transplant				
AML	12518 (26)	2792 (26)	2414 (25)	14529 (31)
ALL	7317 (15)	1748 (17)	2011 (21)	7279 (16)
Other leukemia	871 (2)	147 (1)	168 (2)	1333 (3)
CML	7895 (16)	1056 (10)	1798 (18)	4503 (10)
MDS	4417 (9)	1157 (11)	1044 (11)	8008 (17)
Other acute leukemia	371 (1)	124 (1)	127 (1)	463 (1)
NHL	3256 (7)	709 (7)	352 (4)	3457 (7)
Hodgkins Lymphoma	469 (1)	190 (2)	68 (1)	854 (2)
Plasma Cell Disorders, MM	1527 (3)	263 (2)	98 (1)	678 (1)

Variable	CIBMTR HLA-identical sibling N (%)	CIBMTR Alternative related N (%)	CIBMTR Unrelated (non-US) N (%)	CIBMTR Unrelated (US) N (%)
Other malignancies	348 (1)	75 (1)	33 (<1)	100 (<1)
Breast cancer	82 (<1)	26 (<1)	2 (<1)	10 (<1)
SAA	4579 (9)	679 (6)	531 (5)	1539 (3)
Inherited abnormalities erythrocyte diff fxn	3466 (7)	549 (5)	352 (4)	1021 (2)
SCIDs	707 (1)	807 (8)	379 (4)	1273 (3)
Inherited abnormalities of platelets	26 (<1)	10 (<1)	14 (<1)	66 (<1)
Inherited disorders of metabolism	271 (1)	172 (2)	258 (3)	1001 (2)
Histiocytic disorders	121 (<1)	75 (1)	124 (1)	465 (1)
Autoimmune disorders	20 (<1)	5 (<1)	5 (<1)	24 (<1)
Other	20 (<1)	9 (<1)	10 (<1)	61 (<1)
Unknown	0 (N/A)	0 (N/A)	0 (N/A)	1 (N/A)
Disease status at transplant				
Early	12109 (25)	2191 (21)	1990 (20)	11846 (25)
Intermediate	11905 (25)	2159 (20)	2943 (30)	8032 (17)
Advanced	5979 (12)	1714 (16)	1323 (14)	8525 (18)
Other	18288 (38)	4529 (43)	3532 (36)	18262 (39)
Donor/Recipient CMV serostatus				
Negative/Negative	10752 (22)	2198 (21)	2150 (22)	9246 (20)
Negative/Positive	7441 (15)	1657 (16)	1947 (20)	9854 (21)
Positive/Negative	4440 (9)	1210 (11)	1089 (11)	3819 (8)
Positive/Positive	18227 (38)	3838 (36)	2242 (23)	6645 (14)
Unknown	7421 (15)	1690 (16)	2360 (24)	17101 (37)
GvHD Prophylaxis				
Ex vivo T-cell depletion	3419 (7)	2000 (19)	688 (7)	3487 (7)
CD34 selection	529 (1)	406 (4)	93 (1)	1045 (2)
Tacrolimus + MMF +- others	1280 (3)	396 (4)	160 (2)	6639 (14)
Tacrolimus + MTX +- others (except MMF)	4795 (10)	418 (4)	595 (6)	12462 (27)
Tacrolimus + others (except MTX, MMF)	689 (1)	49 (<1)	68 (1)	1939 (4)
Tacrolimus alone	340 (1)	72 (1)	31 (<1)	945 (2)
CSA + MMF +- others (except Tacrolimus)	1669 (3)	163 (2)	1031 (11)	6043 (13)
CSA + MTX +- others (except Tacrolimus, MMF)	21500 (45)	2159 (20)	5041 (52)	7889 (17)
CSA + others (except Tacrolimus, MTX, MMF)	3701 (8)	290 (3)	1040 (11)	2052 (4)
CSA alone	5114 (11)	463 (4)	453 (5)	420 (1)
Other GVHD prophylaxis	3130 (6)	328 (3)	69 (1)	567 (1)
Missing	2115 (4)	3849 (36)	519 (5)	3177 (7)
Donor/Recipient sex match				
Male/Male	8722 (33)	2477 (37)	2832 (38)	13246 (38)
Male/Female	5780 (22)	1250 (19)	1674 (23)	8274 (24)
Female/Male	7002 (26)	1615 (24)	1564 (21)	7292 (21)
Female/Female	5281 (20)	1398 (21)	1339 (18)	6353 (18)
Unknown	21496 (N/A)	3853 (N/A)	2379 (N/A)	11500 (N/A)
Year of transplant				

Variable	CIBMTR HLA-identical sibling N (%)	CIBMTR Alternative related N (%)	CIBMTR Unrelated (non-US) N (%)	CIBMTR Unrelated (US) N (%)
1964-1985	4815 (10)	889 (8)	42 (<1)	12 (<1)
1986	1375 (3)	260 (2)	14 (<1)	18 (<1)
1987	1466 (3)	249 (2)	32 (<1)	34 (<1)
1988	1622 (3)	245 (2)	55 (1)	96 (<1)
1989	1852 (4)	258 (2)	101 (1)	188 (<1)
1990	1953 (4)	321 (3)	142 (1)	303 (1)
1991	1900 (4)	255 (2)	179 (2)	430 (1)
1992	1995 (4)	281 (3)	237 (2)	502 (1)
1993	2006 (4)	288 (3)	242 (2)	607 (1)
1994	1862 (4)	274 (3)	260 (3)	753 (2)
1995	1938 (4)	344 (3)	347 (4)	906 (2)
1996	1995 (4)	340 (3)	436 (4)	1050 (2)
1997	1688 (3)	312 (3)	415 (4)	1137 (2)
1998	1548 (3)	229 (2)	477 (5)	1172 (3)
1999	1393 (3)	218 (2)	471 (5)	1225 (3)
2000	1511 (3)	217 (2)	523 (5)	1294 (3)
2001	1497 (3)	241 (2)	523 (5)	1391 (3)
2002	1445 (3)	203 (2)	485 (5)	1592 (3)
2003	1232 (3)	175 (2)	517 (5)	1770 (4)
2004	1471 (3)	150 (1)	628 (6)	1982 (4)
2005	1504 (3)	184 (2)	602 (6)	2171 (5)
2006	1261 (3)	151 (1)	503 (5)	2507 (5)
2007	749 (2)	94 (1)	359 (4)	2855 (6)
2008	1080 (2)	245 (2)	325 (3)	2492 (5)
2009	892 (2)	163 (2)	274 (3)	2628 (6)
2010	510 (1)	61 (1)	156 (2)	1906 (4)
2011	322 (1)	67 (1)	114 (1)	1505 (3)
2012	343 (1)	88 (1)	181 (2)	1431 (3)
2013	694 (1)	353 (3)	224 (2)	2207 (5)
2014	1041 (2)	466 (4)	245 (3)	2531 (5)
2015	961 (2)	580 (5)	222 (2)	2393 (5)
2016	892 (2)	731 (7)	204 (2)	2069 (4)
2017	796 (2)	830 (8)	149 (2)	1869 (4)
2018	672 (1)	831 (8)	104 (1)	1639 (4)
Follow-up among survivors, Months				
N Eval	23166	4737	4388	17546
Median (Range)	95 (0-513)	39 (0-570)	61 (0-360)	72 (0-394)

Unrelated Donor HCT Research Sample Inventory - Summary for First Allogeneic Transplants in CRF and TED with biospecimens available through the CIBMTR Repository stratified by availability of paired samples, recipient only samples and donor only samples, Biospecimens include: whole blood, serum/plasma and limited quantities of viable cells and cell lines (collected prior to 2006), Specific inventory queries available upon request through the CIBMTR Immunobiology Research Program

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	39798	12259	7464
Source of data			
CRF	22542 (57)	6191 (51)	4354 (58)
TED	17256 (43)	6068 (49)	3110 (42)
Number of centers	251	224	338
Disease at transplant			
AML	13566 (34)	4431 (36)	2418 (32)
ALL	5866 (15)	1674 (14)	1232 (17)
Other leukemia	1340 (3)	349 (3)	235 (3)
CML	3283 (8)	894 (7)	747 (10)
MDS	6574 (17)	2328 (19)	1031 (14)
Other acute leukemia	408 (1)	138 (1)	80 (1)
NHL	3703 (9)	1012 (8)	606 (8)
Hodgkins Lymphoma	823 (2)	179 (1)	128 (2)
Plasma Cell Disorders, MM	793 (2)	235 (2)	128 (2)
Other malignancies	55 (<1)	13 (<1)	17 (<1)
Breast cancer	7 (<1)	3 (<1)	1 (<1)
SAA	1267 (3)	358 (3)	304 (4)
Inherited abnormalities erythrocyte diff fxn	697 (2)	222 (2)	136 (2)
SCIDs	694 (2)	223 (2)	204 (3)
Inherited abnormalities of platelets	38 (<1)	11 (<1)	10 (<1)
Inherited disorders of metabolism	270 (1)	72 (1)	84 (1)
Histiocytic disorders	354 (1)	93 (1)	78 (1)
Autoimmune disorders	16 (<1)	9 (<1)	5 (<1)
Other	44 (<1)	15 (<1)	20 (<1)
AML Disease status at transplant			
CR1	6997 (52)	2391 (54)	1108 (46)
CR2	2700 (20)	841 (19)	499 (21)
CR3+	259 (2)	73 (2)	53 (2)
Advanced or active disease	3459 (26)	1085 (24)	707 (29)
Missing	147 (1)	41 (1)	47 (2)
ALL Disease status at transplant			
CR1	2842 (48)	871 (52)	516 (42)
CR2	1699 (29)	456 (27)	358 (29)
CR3+	482 (8)	127 (8)	118 (10)
Advanced or active disease	798 (14)	206 (12)	206 (17)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Missing	45 (1)	14 (1)	33 (3)
MDS Disease status at transplant			
Early	1299 (20)	383 (17)	236 (23)
Advanced	4769 (73)	1811 (78)	644 (63)
Missing	465 (7)	121 (5)	140 (14)
NHL Disease status at transplant			
CR1	483 (13)	173 (17)	69 (11)
CR2	684 (19)	177 (18)	101 (17)
CR3+	316 (9)	86 (9)	51 (8)
PR	431 (12)	108 (11)	78 (13)
Advanced	1711 (47)	451 (45)	294 (49)
Missing	46 (1)	8 (1)	10 (2)
Recipient age at transplant			
0-9 years	3515 (9)	937 (8)	943 (13)
10-19 years	3639 (9)	969 (8)	867 (12)
20-29 years	4192 (11)	1199 (10)	907 (12)
30-39 years	4637 (12)	1282 (10)	950 (13)
40-49 years	6197 (16)	1806 (15)	1185 (16)
50-59 years	8253 (21)	2481 (20)	1335 (18)
60-69 years	7889 (20)	2914 (24)	1114 (15)
70+ years	1476 (4)	671 (5)	163 (2)
Median (Range)	47 (0-84)	50 (0-79)	41 (0-79)
Recipient race/ethnicity			
Caucasian, non-Hispanic	33122 (86)	10232 (86)	5529 (85)
African-American, non-Hispanic	1831 (5)	516 (4)	319 (5)
Asian, non-Hispanic	883 (2)	399 (3)	267 (4)
Pacific islander, non-Hispanic	53 (<1)	19 (<1)	16 (<1)
Native American, non-Hispanic	147 (<1)	54 (<1)	26 (<1)
Hispanic	2375 (6)	631 (5)	339 (5)
Other	44 (<1)	26 (<1)	21 (<1)
Unknown	1343 (N/A)	382 (N/A)	947 (N/A)
Recipient sex			
Male	23241 (58)	7205 (59)	4411 (59)
Female	16557 (42)	5054 (41)	3053 (41)
Karnofsky score			
10-80	13300 (33)	4420 (36)	2281 (31)
90-100	24957 (63)	7241 (59)	4624 (62)
Missing	1541 (4)	598 (5)	559 (7)
HLA-A B DRB1 groups - low resolution			
<=3/6	22 (<1)	32 (<1)	1 (<1)
4/6	216 (1)	83 (1)	35 (1)
5/6	5551 (14)	1458 (14)	1056 (15)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
6/6	33446 (85)	9188 (85)	5845 (84)
Unknown	563 (N/A)	1498 (N/A)	527 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	845 (2)	81 (1)	32 (1)
6/8	1667 (4)	115 (1)	125 (3)
7/8	7742 (20)	1454 (18)	1030 (22)
8/8	28076 (73)	6626 (80)	3395 (74)
Unknown	1468 (N/A)	3983 (N/A)	2882 (N/A)
HLA-DPB1 Match			
Double allele mismatch	9305 (30)	759 (24)	381 (28)
Single allele mismatch	16827 (54)	1585 (51)	711 (52)
Full allele matched	5008 (16)	779 (25)	273 (20)
Unknown	8658 (N/A)	9136 (N/A)	6099 (N/A)
High resolution release score			
No	11077 (28)	12118 (99)	7291 (98)
Yes	28721 (72)	141 (1)	173 (2)
KIR typing available			
No	26106 (66)	12174 (99)	7425 (99)
Yes	13692 (34)	85 (1)	39 (1)
Graft type			
Marrow	14829 (37)	4153 (34)	3357 (45)
PBSC	24923 (63)	7973 (65)	4081 (55)
BM+PBSC	11 (<1)	6 (<1)	2 (<1)
PBSC+UCB	19 (<1)	117 (1)	2 (<1)
Others	16 (<1)	10 (<1)	22 (<1)
Conditioning regimen			
Myeloablative	25417 (64)	7348 (60)	4974 (67)
RIC/Nonmyeloablative	14204 (36)	4868 (40)	2389 (32)
TBD	177 (<1)	43 (<1)	101 (1)
Donor age at donation			
To Be Determined/NA	235 (1)	1392 (11)	77 (1)
0-9 years	6 (<1)	29 (<1)	1 (<1)
10-19 years	1105 (3)	397 (3)	157 (2)
20-29 years	17569 (44)	5031 (41)	2819 (38)
30-39 years	11434 (29)	3099 (25)	2318 (31)
40-49 years	7230 (18)	1763 (14)	1581 (21)
50+ years	2219 (6)	548 (4)	511 (7)
Median (Range)	31 (0-69)	30 (0-109)	33 (7-67)
Donor/Recipient CMV serostatus			
+/+	9790 (25)	3362 (28)	1809 (25)
+/-	4731 (12)	1591 (13)	939 (13)
-/+	13067 (33)	3680 (31)	2305 (32)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
-/-	11653 (30)	3208 (27)	2043 (29)
CB - recipient +	1 (<1)	11 (<1)	0
CB - recipient -	1 (<1)	4 (<1)	0
CB - recipient CMV unknown	0	1 (<1)	0
Unknown	555 (N/A)	402 (N/A)	368 (N/A)
GvHD Prophylaxis			
Ex vivo T-cell depletion	1114 (3)	288 (2)	309 (4)
CD34 selection	723 (2)	313 (3)	127 (2)
Post-CY + other(s)	1071 (3)	643 (5)	171 (2)
Post-CY alone	72 (<1)	31 (<1)	19 (<1)
Tacrolimus + MMF +- others	4732 (12)	1276 (10)	619 (8)
Tacrolimus + MTX +- others (except MMF)	17262 (43)	5492 (45)	2083 (28)
Tacrolimus + others (except MTX, MMF)	2077 (5)	794 (6)	297 (4)
Tacrolimus alone	962 (2)	327 (3)	120 (2)
CSA + MMF +- others (except Tacrolimus)	2654 (7)	637 (5)	613 (8)
CSA + MTX +- others (except Tacrolimus, MMF)	6541 (16)	1701 (14)	2276 (30)
CSA + others (except Tacrolimus, MTX, MMF)	996 (3)	303 (2)	286 (4)
CSA alone	466 (1)	115 (1)	293 (4)
Other GVHD prophylaxis	702 (2)	218 (2)	123 (2)
Missing	426 (1)	121 (1)	128 (2)
Donor/Recipient sex match			
Male-Male	16408 (41)	4862 (40)	2936 (40)
Male-Female	10010 (25)	2981 (25)	1703 (23)
Female-Male	6681 (17)	2171 (18)	1421 (19)
Female-Female	6450 (16)	1941 (16)	1307 (18)
CB - recipient M	10 (<1)	68 (1)	0
CB - recipient F	12 (<1)	57 (<1)	2 (<1)
Unknown	227 (N/A)	179 (N/A)	95 (N/A)
Year of transplant			
1986-1990	349 (1)	45 (<1)	85 (1)
1991-1995	1795 (5)	448 (4)	619 (8)
1996-2000	3149 (8)	1111 (9)	902 (12)
2001-2005	5001 (13)	988 (8)	1437 (19)
2006-2010	9204 (23)	1853 (15)	1418 (19)
2011-2015	12925 (32)	3555 (29)	1805 (24)
2016-2019	7375 (19)	4259 (35)	1198 (16)
Follow-up among survivors, Months			
N Eval	17027	5940	3016
Median (Range)	60 (0-365)	36 (0-336)	49 (1-350)

Unrelated Cord Blood Transplant Research Sample Inventory - Summary for First Allogeneic Transplants in CRF and TED with biospecimens available through the CIBMTR Repository stratified by availability of paired, recipient only and cord blood only samples, Biospecimens include: whole blood, serum/plasma and limited quantities of viable cells and cell lines (collected prior to 2006-recipient only), Specific inventory queries available upon request through the CIBMTR Immunobiology Research Program

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	5444	1351	1276
Source of data			
CRF	4129 (76)	1025 (76)	858 (67)
TED	1315 (24)	326 (24)	418 (33)
Number of centers	146	132	195
Disease at transplant			
AML	2044 (38)	451 (33)	409 (32)
ALL	1121 (21)	287 (21)	289 (23)
Other leukemia	91 (2)	26 (2)	24 (2)
CML	117 (2)	33 (2)	31 (2)
MDS	520 (10)	143 (11)	106 (8)
Other acute leukemia	85 (2)	18 (1)	22 (2)
NHL	378 (7)	83 (6)	85 (7)
Hodgkins Lymphoma	92 (2)	25 (2)	22 (2)
Plasma Cell Disorders, MM	35 (1)	10 (1)	7 (1)
Other malignancies	10 (<1)	0	1 (<1)
SAA	89 (2)	31 (2)	24 (2)
Inherited abnormalities erythrocyte diff fxn	157 (3)	48 (4)	31 (2)
SCIDs	236 (4)	71 (5)	97 (8)
Inherited abnormalities of platelets	17 (<1)	4 (<1)	5 (<1)
Inherited disorders of metabolism	332 (6)	93 (7)	84 (7)
Histiocytic disorders	100 (2)	26 (2)	33 (3)
Autoimmune disorders	9 (<1)	0	1 (<1)
Other	11 (<1)	2 (<1)	5 (<1)
AML Disease status at transplant			
CR1	1048 (51)	242 (54)	199 (49)
CR2	569 (28)	114 (25)	116 (28)
CR3+	50 (2)	6 (1)	12 (3)
Advanced or active disease	370 (18)	86 (19)	80 (20)
Missing	7 (<1)	2 (<1)	2 (<1)
ALL Disease status at transplant			
CR1	507 (45)	122 (43)	130 (45)
CR2	421 (38)	108 (38)	103 (36)
CR3+	120 (11)	39 (14)	31 (11)
Advanced or active disease	72 (6)	18 (6)	25 (9)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Missing	1 (<1)	0	0
MDS Disease status at transplant			
Early	163 (31)	36 (26)	48 (46)
Advanced	323 (62)	99 (70)	46 (44)
Missing	33 (6)	6 (4)	11 (10)
NHL Disease status at transplant			
CR1	59 (16)	5 (6)	16 (19)
CR2	71 (19)	18 (22)	24 (29)
CR3+	42 (11)	10 (12)	9 (11)
PR	65 (17)	12 (14)	11 (13)
Advanced	138 (37)	37 (45)	23 (27)
Missing	0	1 (1)	1 (1)
Recipient age at transplant			
0-9 years	1635 (30)	499 (37)	474 (37)
10-19 years	705 (13)	145 (11)	175 (14)
20-29 years	515 (9)	96 (7)	104 (8)
30-39 years	526 (10)	119 (9)	123 (10)
40-49 years	578 (11)	132 (10)	116 (9)
50-59 years	763 (14)	163 (12)	150 (12)
60-69 years	629 (12)	170 (13)	125 (10)
70+ years	93 (2)	27 (2)	9 (1)
Median (Range)	27 (0-83)	23 (0-77)	19 (0-78)
Recipient race/ethnicity			
Caucasian, non-Hispanic	3033 (59)	802 (62)	704 (62)
African-American, non-Hispanic	783 (15)	181 (14)	147 (13)
Asian, non-Hispanic	315 (6)	85 (7)	81 (7)
Pacific islander, non-Hispanic	27 (1)	3 (<1)	14 (1)
Native American, non-Hispanic	36 (1)	6 (<1)	13 (1)
Hispanic	981 (19)	208 (16)	174 (15)
Other	0	1 (<1)	1 (<1)
Unknown	269 (N/A)	65 (N/A)	142 (N/A)
Recipient sex			
Male	3007 (55)	783 (58)	736 (58)
Female	2437 (45)	568 (42)	540 (42)
Karnofsky score			
10-80	1408 (26)	332 (25)	311 (24)
90-100	3885 (71)	928 (69)	886 (69)
Missing	151 (3)	91 (7)	79 (6)
HLA-A B DRB1 groups - low resolution			
<=3/6	73 (1)	33 (3)	8 (1)
4/6	2139 (41)	433 (41)	444 (37)
5/6	2324 (45)	430 (41)	566 (48)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
6/6	666 (13)	150 (14)	168 (14)
Unknown	242 (N/A)	305 (N/A)	90 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	2560 (56)	440 (57)	510 (54)
6/8	1104 (24)	172 (22)	237 (25)
7/8	621 (14)	101 (13)	134 (14)
8/8	304 (7)	53 (7)	70 (7)
Unknown	855 (N/A)	585 (N/A)	325 (N/A)
HLA-DPB1 Match			
Double allele mismatch	725 (40)	55 (41)	55 (37)
Single allele mismatch	924 (51)	67 (50)	76 (52)
Full allele matched	169 (9)	12 (9)	16 (11)
Unknown	3626 (N/A)	1217 (N/A)	1129 (N/A)
High resolution release score			
No	3954 (73)	1301 (96)	1262 (99)
Yes	1490 (27)	50 (4)	14 (1)
KIR typing available			
No	4194 (77)	1345 (>99)	1264 (99)
Yes	1250 (23)	6 (<1)	12 (1)
Graft type			
UCB	5135 (94)	1234 (91)	1213 (95)
BM+UCB	1 (<1)	0	0
PBSC+UCB	279 (5)	117 (9)	54 (4)
Others	29 (1)	0	9 (1)
Number of cord units			
1	4572 (84)	0	1066 (84)
2	870 (16)	0	210 (16)
3	2 (<1)	0	0
Unknown	0 (N/A)	1351 (N/A)	0 (N/A)
Conditioning regimen			
Myeloablative	3579 (66)	870 (64)	828 (65)
RIC/Nonmyeloablative	1855 (34)	476 (35)	444 (35)
TBD	10 (<1)	5 (<1)	4 (<1)
Donor age at donation			
To Be Determined/NA	173 (3)	86 (6)	72 (6)
0-9 years	4843 (89)	1055 (78)	1117 (88)
10-19 years	254 (5)	116 (9)	51 (4)
20-29 years	50 (1)	30 (2)	6 (<1)
30-39 years	50 (1)	29 (2)	13 (1)
40-49 years	33 (1)	16 (1)	5 (<1)
50+ years	41 (1)	19 (1)	12 (1)
Median (Range)	3 (0-72)	5 (0-73)	3 (0-72)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Donor/Recipient CMV serostatus			
+/+	1259 (23)	273 (20)	260 (20)
+/-	543 (10)	129 (10)	116 (9)
-/+	1011 (19)	249 (18)	238 (19)
-/-	681 (13)	165 (12)	173 (14)
CB - recipient +	1112 (20)	285 (21)	246 (19)
CB - recipient -	755 (14)	201 (15)	198 (16)
CB - recipient CMV unknown	83 (2)	49 (4)	45 (4)
GvHD Prophylaxis			
Ex vivo T-cell depletion	28 (1)	9 (1)	4 (<1)
CD34 selection	219 (4)	93 (7)	45 (4)
Post-CY + other(s)	7 (<1)	6 (<1)	2 (<1)
Tacrolimus + MMF +- others	1476 (27)	357 (26)	210 (16)
Tacrolimus + MTX +- others (except MMF)	202 (4)	53 (4)	57 (4)
Tacrolimus + others (except MTX, MMF)	213 (4)	55 (4)	48 (4)
Tacrolimus alone	135 (2)	43 (3)	23 (2)
CSA + MMF +- others (except Tacrolimus)	2549 (47)	557 (41)	636 (50)
CSA + MTX +- others (except Tacrolimus, MMF)	93 (2)	27 (2)	38 (3)
CSA + others (except Tacrolimus, MTX, MMF)	313 (6)	109 (8)	138 (11)
CSA alone	56 (1)	16 (1)	44 (3)
Other GVHD prophylaxis	127 (2)	16 (1)	19 (1)
Missing	26 (<1)	10 (1)	12 (1)
Donor/Recipient sex match			
CB - recipient M	3007 (55)	783 (58)	734 (58)
CB - recipient F	2437 (45)	568 (42)	540 (42)
CB - recipient sex unknown	0	0	2 (<1)
Year of transplant			
1996-2000	0	2 (<1)	4 (<1)
2001-2005	105 (2)	82 (6)	30 (2)
2006-2010	1757 (32)	406 (30)	438 (34)
2011-2015	2574 (47)	494 (37)	575 (45)
2016-2019	1008 (19)	367 (27)	229 (18)
Follow-up among survivors, Months			
N Eval	2649	729	653
Median (Range)	60 (1-168)	47 (3-192)	51 (1-217)

Related Donor HCT Research Sample Inventory - Summary for First Allogeneic Transplants in CRF and TED with biospecimens available through the CIBMTR Repository stratified by availability of paired, recipient only and donor only samples, Biospecimens include: whole blood, serum/plasma and limited quantities of viable cells and cell lines (collected prior to 2006), Specific inventory queries available upon request through the CIBMTR Immunobiology Research Program

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	7714	1121	483
Source of data			
CRF	2971 (39)	349 (31)	219 (45)
TED	4743 (61)	772 (69)	264 (55)
Number of centers	86	68	52
Disease at transplant			
AML	2519 (33)	367 (33)	140 (29)
ALL	1219 (16)	215 (19)	83 (17)
Other leukemia	170 (2)	30 (3)	18 (4)
CML	256 (3)	26 (2)	11 (2)
MDS	1294 (17)	182 (16)	85 (18)
Other acute leukemia	102 (1)	16 (1)	3 (1)
NHL	747 (10)	102 (9)	65 (13)
Hodgkins Lymphoma	161 (2)	24 (2)	18 (4)
Plasma Cell Disorders, MM	230 (3)	33 (3)	18 (4)
Other malignancies	21 (<1)	0	0
Breast cancer	1 (<1)	0	0
SAA	346 (4)	40 (4)	13 (3)
Inherited abnormalities erythrocyte diff fxn	413 (5)	51 (5)	18 (4)
SCIDs	160 (2)	28 (2)	7 (1)
Inherited abnormalities of platelets	9 (<1)	0	0
Inherited disorders of metabolism	12 (<1)	2 (<1)	1 (<1)
Histiocytic disorders	38 (<1)	5 (<1)	2 (<1)
Autoimmune disorders	7 (<1)	0	1 (<1)
Other	9 (<1)	0	0
AML Disease status at transplant			
CR1	1570 (62)	243 (66)	86 (61)
CR2	391 (16)	42 (11)	15 (11)
CR3+	28 (1)	6 (2)	1 (1)
Advanced or active disease	520 (21)	73 (20)	36 (26)
Missing	10 (<1)	3 (1)	2 (1)
ALL Disease status at transplant			
CR1	765 (63)	136 (63)	56 (67)
CR2	326 (27)	49 (23)	16 (19)
CR3+	62 (5)	9 (4)	6 (7)
Advanced or active disease	66 (5)	20 (9)	5 (6)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Missing	0	1 (<1)	0
MDS Disease status at transplant			
Early	203 (16)	21 (12)	16 (19)
Advanced	1051 (81)	151 (83)	67 (79)
Missing	40 (3)	10 (5)	2 (2)
NHL Disease status at transplant			
CR1	126 (17)	19 (19)	11 (17)
CR2	141 (19)	20 (20)	11 (17)
CR3+	84 (11)	9 (9)	2 (3)
PR	65 (9)	13 (13)	7 (11)
Advanced	324 (44)	40 (40)	34 (52)
Missing	2 (<1)	0	0
Recipient age at transplant			
0-9 years	754 (10)	91 (8)	27 (6)
10-19 years	866 (11)	90 (8)	39 (8)
20-29 years	632 (8)	123 (11)	41 (8)
30-39 years	589 (8)	98 (9)	43 (9)
40-49 years	1006 (13)	150 (13)	66 (14)
50-59 years	1785 (23)	253 (23)	115 (24)
60-69 years	1817 (24)	278 (25)	139 (29)
70+ years	265 (3)	38 (3)	13 (3)
Median (Range)	50 (0-78)	50 (0-76)	53 (0-77)
Recipient race/ethnicity			
Caucasian, non-Hispanic	4973 (67)	622 (59)	323 (70)
African-American, non-Hispanic	906 (12)	118 (11)	45 (10)
Asian, non-Hispanic	342 (5)	90 (9)	20 (4)
Pacific islander, non-Hispanic	26 (<1)	3 (<1)	1 (<1)
Native American, non-Hispanic	29 (<1)	2 (<1)	1 (<1)
Hispanic	1119 (15)	214 (20)	71 (15)
Unknown	319 (N/A)	72 (N/A)	22 (N/A)
Recipient sex			
Male	4528 (59)	665 (59)	285 (59)
Female	3186 (41)	456 (41)	198 (41)
Karnofsky score			
10-80	2680 (35)	462 (41)	194 (40)
90-100	4846 (63)	628 (56)	266 (55)
Missing	188 (2)	31 (3)	23 (5)
Graft type			
Marrow	2221 (29)	259 (23)	137 (28)
PBSC	5443 (71)	841 (75)	336 (70)
BM+PBSC	6 (<1)	4 (<1)	0
BM+UCB	26 (<1)	7 (1)	1 (<1)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
PBSC+UCB	0	0	8 (2)
Others	18 (<1)	10 (1)	0
Conditioning regimen			
Myeloablative	4418 (57)	649 (58)	257 (53)
RIC/Nonmyeloablative	3256 (42)	464 (41)	220 (46)
TBD	40 (1)	8 (1)	6 (1)
Donor age at donation			
To Be Determined/NA	18 (<1)	4 (<1)	3 (1)
0-9 years	535 (7)	60 (5)	21 (4)
10-19 years	770 (10)	95 (8)	38 (8)
20-29 years	980 (13)	151 (13)	60 (12)
30-39 years	1004 (13)	178 (16)	79 (16)
40-49 years	1247 (16)	185 (17)	69 (14)
50+ years	3160 (41)	448 (40)	213 (44)
Median (Range)	45 (0-81)	44 (0-79)	46 (0-76)
Donor/Recipient CMV serostatus			
+/+	3114 (41)	509 (46)	201 (43)
+/-	872 (11)	87 (8)	48 (10)
-/+	1890 (25)	264 (24)	110 (24)
-/-	1719 (23)	239 (22)	104 (22)
Unknown	119 (N/A)	22 (N/A)	20 (N/A)
GvHD Prophylaxis			
Ex vivo T-cell depletion	93 (1)	28 (2)	8 (2)
CD34 selection	123 (2)	32 (3)	9 (2)
Post-CY + other(s)	1568 (20)	215 (19)	107 (22)
Post-CY alone	34 (<1)	8 (1)	3 (1)
Tacrolimus + MMF +- others	793 (10)	70 (6)	27 (6)
Tacrolimus + MTX +- others (except MMF)	3165 (41)	392 (35)	217 (45)
Tacrolimus + others (except MTX, MMF)	619 (8)	224 (20)	49 (10)
Tacrolimus alone	64 (1)	6 (1)	2 (<1)
CSA + MMF +- others (except Tacrolimus)	206 (3)	27 (2)	7 (1)
CSA + MTX +- others (except Tacrolimus, MMF)	623 (8)	76 (7)	31 (6)
CSA + others (except Tacrolimus, MTX, MMF)	80 (1)	9 (1)	2 (<1)
CSA alone	68 (1)	9 (1)	1 (<1)
Other GVHD prophylaxis	118 (2)	12 (1)	8 (2)
Missing	160 (2)	13 (1)	12 (2)
Donor/Recipient sex match			
Male-Male	2525 (33)	399 (36)	159 (33)
Male-Female	1662 (22)	219 (20)	97 (20)
Female-Male	1978 (26)	253 (23)	120 (25)
Female-Female	1516 (20)	233 (21)	97 (20)
CB - recipient M	20 (<1)	12 (1)	6 (1)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
CB - recipient F	8 (<1)	4 (<1)	4 (1)
Unknown	5 (N/A)	1 (N/A)	0 (N/A)
Year of transplant			
2006-2010	570 (7)	66 (6)	49 (10)
2011-2015	3617 (47)	469 (42)	194 (40)
2016-2019	3527 (46)	586 (52)	240 (50)
Follow-up among survivors, Months			
N Eval	4876	688	306
Median (Range)	33 (1-131)	24 (2-124)	26 (2-124)

Proposal: 1908-01

Title:
Evaluation of the impact of HLA molecular mismatch on clinical outcomes in patients who underwent haploidentical hematopoietic stem cell transplantation

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Hypothesis:
HLA (Human Leukocyte Antigen) molecular disparity quantified by mismatched eplets is associated with the clinical outcomes of haploidentical hematopoietic stem cell transplantation (haplo-HSCT) performed with post transplantation cyclophosphamide (PTCy), tacrolimus and mycophenolate mofetil (MMF) for GVHD prevention.

Primary objectives:
To investigate the impact of structural/molecular mismatch in HLA molecules (measured by the number of mismatched eplets on each HLA locus) on overall survival (OS) and disease free survival (DFS) of patients who received an allogeneic transplant from a haploidentical donor with PTCy.

Secondary objectives:
Study the impact of mismatched eplets (ME) of each HLA locus (HLA-A, B, C, DRB1, DRB345, DQB1 and DPB1) on:

- Cumulative incidence of neutrophil and platelet engraftment
- Cumulative incidence of grades II-IV and III-IV acute GVHD at Day 100 and overall
- Cumulative incidence of limited and extensive chronic graft-versus-host disease (cGVHD) at 1 year
- Cumulative incidence of relapse
- Cumulative incidence of non-relapse mortality (NRM)

Scientific justification:
Allogeneic hematopoietic stem cell transplantation is the only curative therapy for many advanced hematologic malignancies and nonmalignant hematologic disorders. With the success in prophylaxis of GVHD and graft rejection (1,2), haploidentical related donors, who share one haplotype with recipients, have become well accepted stem cell sources in clinical practice with comparable clinical outcomes (3-5). This alternative approach significantly expanded the likelihood of finding a source of hematopoietic stem cells, especially in certain ethnic minority groups (6-8). It has been well accepted that a greater HLA disparity is associated with worse clinical outcome and higher risk of GVHD in HSCT with mismatched related or unrelated donor transplants (9,10). However, the immune system seems to respond differently in the setting of haplo-HSCT with PTCy for GVHD prophylaxis. Raiola et al. recently studied a relatively large haplo-HSCT cohort and concluded that there is no correlation between the number of mismatched HLA antigens and clinical outcomes (11). However, although the immediate hyperacute reactions may be attenuated, higher disparities at particular HLA loci could perpetuate different alloreactive immune responses. The European Society for Blood and Marrow Transplantation (EBMT) reported recently that there is no influence of cumulative number of mismatched HLA antigens on clinical outcomes in their haplo-HSCT cohort, yet an association between mismatched HLA-DRB1 and a higher risk of grade II-IV GVHD was observed (12). As haplo-HSCT is commonly used for patients requiring transplantation, it is essential to understand the immunogenicity to alloantigens on the mismatched graft from haploidentical donors. With the rapid progress in molecular typing and protein modelling, the degree of HLA mismatch has recently been assessed at molecular level in solid organ transplantation to precisely determine HLA alloimmune risk(13,14). Different algorithms of molecular mismatching in predicting immunogenicity have been developed with different focuses, such as the number of mismatched amino acids or physiochemical properties of the

amino acid substitution (15). HLAMatchmaker is a molecular matching algorithm that reflects the structural similarity and considers the mismatched eplets, which are distinct configuration of amino acid polymorphisms composing functional component of epitopes exposed on HLA molecules. HLAMatchmaker program is used to quantitatively determine the degree of mismatch by comparing the eplets repertories of donor and recipients (16,17). Eplet matching improves outcome in renal transplantation (18) and reduces humoral sensitization(19). Additionally, compatibility assessment by HLA matchmaker was shown to be predictive of platelet transfusion outcome in platelets refractoriness patients (20).

We recently investigated the impact of HLA disparity quantified by mismatched eplets (ME) load of each HLA locus on the clinical outcome of 279 haploidentical donor transplants (manuscript submitted for publication). We demonstrated that HLA disparity quantified at molecular mismatch level, and not by cumulative number of mismatched antigens, is relevant to clinical outcome of patients receiving haplo-HSCT. Moreover, we have found that ME load at different loci has different impact on the clinical outcomes of haplo-HSCT. Specially, ME load at HLA-A locus in HVG direction, divided by quartiles, was associated with a better survival in a ME load-dependent manner (HR, 0.51; 95% CI, 0.31- 0.84; P = .008 for 4th quartile) (Figure 1A). For the transplants with no ME ab at HLA-A locus (1st quartile), 2-year OS rate was only 40.5%, significantly lower compared with 59.5% seen in transplants with higher number of A-ME ab (4th quartile). The risk of relapse was significantly reduced while the number of A-ME ab was increased (HR, 0.41; 95% CI, 0.20-0.84; P = .02 for 4th quartile) (Figure 1B). The two-year cumulative incidence of relapse was 23.7% in higher A-ME ab group (4th quartile) compared to 38.3% seen in no A-ME ab group (1st quartile). In contrast, the ME load at HLA-B locus in GVH direction was correlated with higher risk of developing grade III/IV acute GVHD.

Our study analyzed a relatively small number of patients, which may result in the lower statistical power to detect the subtle impact from HLA disparities, especially the effect of disparity across various ME at different HLA loci. Additionally, because each eplet does not contribute to immunogenicity equally, further studies exploring the impact of certain specific eplet would shed light on minimizing risks and maximizing benefit of alloreactive reactions in HLA-haploidentical transplantation.

The objectives of this study are to comprehensively assess the risks or benefits associated with HLA molecular disparity in haplo-HSCT reported to Center for International Blood and Marrow Transplant registry (CIBMTR) between years 2008 and 2016.

Methodology:

Patients who underwent TCR haplo-HSCT with myeloablative, RIC and non-myeloablative conditioning as previously defined (21) who received post-transplant cyclophosphamide, tacrolimus and MMF for GVHD prophylaxis from January 2008 to December 2016 and reported to CIBMTR will be included in the study. High resolution HLA typing on both donor and recipient will be collected at the HLA-A, -B, -C, DRB1, -DQB1 and DPB1 (if possible) loci. In the situation that only intermediate level resolution typing is available, the most likely high-resolution (two field) typing will be inferred using the haplostast online tool (www. halplostats.org) (22). Alleles reported with NMDP codes will be deduced to the most common allele in the coded string. ME at each HLA locus and total ME load of class I and class II loci will be quantified by using HLAMatchmaker module incorporated in HLA Fusion software. The analysis will be performed in both GVH and HVG directions. The software identifies antibody-verified eplets (ME ab) and theoretically predicted eplets (ME) based on the crystalized HLA molecule models.(17) Eplet repertoires are listed in HLA Epitope Registry http://www.epitopes.net/downloads.html.

Overall survival (OS) is defined as time from SCT to last follow-up. Similarly, non-relapse mortality (NRM) will be computed from time of SCT to last known vital sign. Time-to-progression is defined time of stem cell transplant and date of disease progression. Patients who are alive and did not experience progression of disease at the last follow-up date will be censored. The Kaplan-Meier method will be used to estimate OS and DFS and the log-rank test was used to assess differences between specific groups (23). NRM and relapse incidence will be determined by the cumulative incidence function using the competing risks method. The cumulative incidence of grade II-IV acute GVHD and cGVHD (limited and extensive) will also be determined using the competing risks method

(24). The competing risks include disease progression and death, while those patients who do not experience GVHD or progression of disease and alive at the last follow-up will be censored. All statistical analyses will be performed using SAS software.

Endpoints:

The primary endpoints of these analyses are:

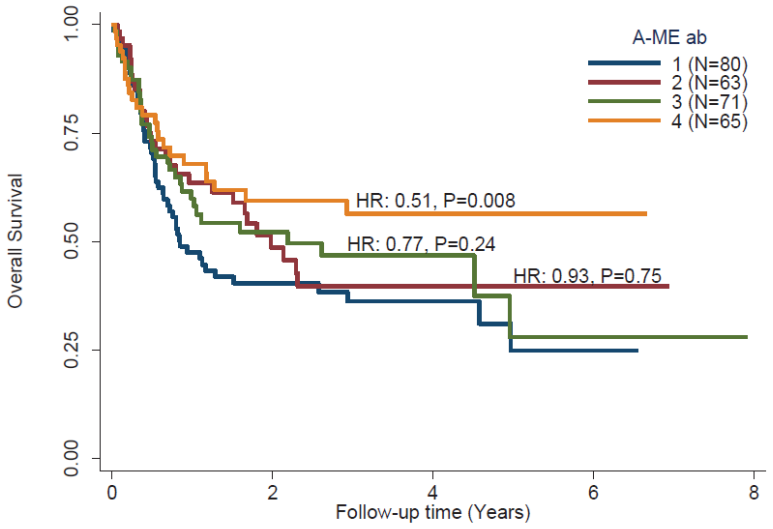
- Hematopoietic recovery:
  - Time to neutrophil engraftment - ANC > 0.5 x 10^9/L for three consecutive days will be the primary measure for comparisons of hematopoietic recovery without transfusion support.
  - Time to platelet engraftment - platelet count $\geq$ 20 x 10^9/L without transfusion support.
  - Time to platelet count $\geq$ 100 x 10^9/L.
- Graft Failure:
  - Primary graft failure – defined as no evidence of transplanted marrow function after day 28 post-transplant
  - Secondary graft failure - Development of inadequate marrow function (fall of granulocytes to <0.5/mcl for 3 or more consecutive days) any time after initial engraftment has been achieved.
  - Death and progressive disease within 28 days are competing risks.
- Incidence of acute and chronic GVHD: grade II-IV acute GVHD and limited and extensive chronic GVHD.
- Relapse incidence: time to onset of disease relapse. Patients will be censored at death in continuous CR or, for patients surviving in continuous complete remission, at the last contact.
- Disease free survival: time to treatment failure (death or relapse). Patients are censored at time of last follow-up.
- Overall survival: time to death. Patients are censored at time of last follow-up.
- Non-relapse mortality: time to death without evidence of disease recurrence/relapse. Death from any cause without prior progression are events
- Variables to be analyzed:
  - A-Continuous variables
  - B-Categorical variables
- Patient related:
  - Age at transplant (<50 y vs $\geq$ 50 y), (B)
  - Gender (female vs male) (B)
  - Karnofsky performance score at transplant (<90% vs $\geq$ 90%), when available (B)
  - Hematopoietic Cell Transplant-Comorbidity Index (HCT-CI), (0 vs 1-2 vs $\geq$ 3), when available (B)
- Disease-related (at initial diagnosis):
  - Disease risk (good/intermediate vs. poor prognosis) (B)
  - Philadelphia chromosome positive (yes/no) (B)
  - Extramedullary disease (yes/no) (B)
  - CNS disease? (yes/no) (B)
- Disease-related (at the time of transplant):
  - Disease status transplant (B)
  - Time from diagnosis to transplant (A)
  - Ever achieved a first remission? (yes/no) (B)
  - Time to achieve complete remission (A)
  - Duration of complete remission (B)
  - Number of cycles of induction therapy to achieve first complete remission (1 vs >1) for patients with acute leukemia (B)
- Treatment-related:

- Donor age (A)
- Donor-recipient gender match (F-M vs other) (B)
- Donor type (child/parent/sibling/other) (B)
- Donor-recipient HLA molecular mismatch (# of mismatched eplets at each HLA loci) (A)
- Donor-recipient CMV status: (-/- vs others) (B)
- Conditioning regimen (MA vs. RIC vs. NMA) (B)
- Conditioning regimen type (A)
- Infused number of nucleated and CD34+ cells: n/kg recipient weight (A)
- Infused number of CD3+ cells: n/kg recipient weight (A)
- Source of stem cells: (BM vs PBSC vs both) (B)

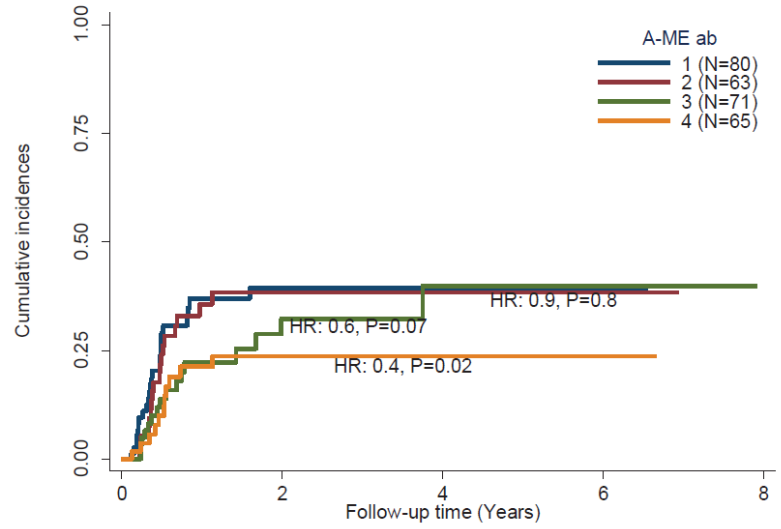
Significance:
Although the adverse role of MEs in solid organ transplantation has been recently identified, to date no large study has evaluated the impact of ME in the setting of haplo-HSCT. This study would have significant clinical implications in donor selection, and could change practice with regard to assessment of mismatched eplets between recipient and potential donors in HLA-haploidentical transplantation.

Figure 1.

A.


A-ME ab
1 (N=80)
2 (N=63)
3 (N=71)
4 (N=65)
HR: 0.51, P=0.008
HR: 0.77, P=0.24
HR: 0.93, P=0.75
Overall Survival
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
Follow-up time (Years)

B.


A-ME ab
1 (N=80)
2 (N=63)
3 (N=71)
4 (N=65)
HR: 0.9, P=0.8
HR: 0.6, P=0.07
HR: 0.4, P=0.02
Cumulative incidences
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
Follow-up time (Years)

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Prop 1908-01 - Recipients with AML,ALL,MDS receiving PT-Cy for mismatched related first allo HCT, 2008-2017

Variable	N (%)
Number of recipients	1484
Disease	
AML	852 (57)
ALL	349 (24)
MDS	283 (19)
AML Disease stage	
CR	666 (78)
Advanced - PIF, relapse	186 (22)
ALL Disease stage	
Intermediate, CR1	201 (58)
High, CR1 or CR2	105 (30)
Very high, advanced - PIF, relapse, NR/PD	23 (7)
Missing, CR unknown, >=3rd CR, or untreated	20 (6)
MDS Disease stage	
Early	41 (14)
Advanced	235 (83)
Missing	7 (2)
Race/Ethnicity	
Caucasian, non-Hispanic	840 (60)
African-American, non-Hispanic	245 (17)
Asian, non-Hispanic	91 (6)
Pacific islander, non-Hispanic	6 (<1)
Native American, non-Hispanic	6 (<1)
Hispanic, Caucasian	216 (15)
Hispanic, African-American	7 (<1)
Unknown	73 N/A
Recipient age at transplant	
0-10 years	49 (3)
10-17 years	73 (5)
18-29 years	170 (11)
30-39 years	144 (10)
40-49 years	205 (14)
50-59 years	322 (22)
60 years and older	521 (35)
Median (Range)	54 (1-78)
Sex	
Male	886 (60)
Female	598 (40)
Graft type	

Variable	N (%)
Marrow	617 (42)
PBSC	867 (58)
Donor relationship to recipient	
Sibling	341 (23)
Parent	151 (10)
Child	513 (35)
Other relative	14 (1)
NA - No form 2006	462 (31)
Missing	3 (<1)
Conditioning regimen	
TBI/Cy	59 (4)
TBI/Cy/Flu	687 (46)
TBI/Cy/TT	1 (<1)
TBI/Mel	63 (4)
TBI/Flu	251 (17)
TBI/other(s)	6 (<1)
Bu/Cy	158 (11)
Bu/Mel	4 (<1)
Flu/Bu/TT	41 (3)
Flu/Bu	78 (5)
Flu/Mel/TT	71 (5)
Flu/Mel	57 (4)
Cy/Flu	5 (<1)
Cy alone	2 (<1)
Other(s)	1 (<1)
Conditioning regimen intensity	
Myeloablative	672 (45)
Non-myeloablative/RIC	812 (55)
GVHD prophylaxis in addition to PTCy	
Tac based	1399 (94)
CSA based	39 (3)
Other	46 (3)
Recipient CMV Serostatus	
Negative	425 (29)
Positive	1049 (71)
Not tested	8 (1)
Unknown	2 N/A
HCT-CI score	
0	306 (21)
1	216 (15)
2	219 (15)

Variable	N (%)
3+	742 (50)
TBD, review needed for history of malignancies	1 (<1)
DRI-R	
Low	55 (4)
Intermediate	778 (52)
Intermediate - TED AML case <2013 missing cytogenetics	3 (<1)
High	355 (24)
Very high	46 (3)
TBD cytogenetics	73 (5)
Missing cyto, disease status, or disease risk	21 (1)
N/A - no DRI for patient characteristics	153 (10)
Donor-recipient ABO compatibility	
Matched	465 (31)
Minor mismatch	116 (8)
Major mismatch	111 (7)
Bi-directional	19 (1)
NA - No form 2000	767 (52)
Missing	6 (<1)
Karnofsky performance score	
10-80	624 (43)
90-100	817 (57)
Unknown	43 N/A
Number of high resolution matches out of 10	
5	964 (65)
6	330 (22)
7	141 (10)
8	49 (3)
DPB1 Match	
Mismatched	385 (82)
Matched	85 (18)
Unknown	1014 N/A
Retrospective high resolution typing	
Yes	477 (100)
Unknown	1007 N/A
Year of transplant	
2008	12 (1)
2009	2 (<1)
2010	9 (1)
2011	10 (1)
2012	19 (1)
2013	48 (3)

Variable	N (%)
2014	184 (12)
2015	317 (21)
2016	426 (29)
2017	457 (31)
Follow-up among survivors, Months	
N Eval	912
Median (Range)	13 (2-119)

Proposal: 1911-135

Title:
Association of immunopeptidome divergence between mismatched HLA class I alleles and outcome of 9/10 matched unrelated HCT

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Research hypothesis:
Mismatched HLA class I molecules in 9/10 matched unrelated donor Hematopoietic Cell Transplantation (HCT) present more or less divergent peptide repertoires, called immunopeptidomes. We hypothesize that the degree of peptide repertoire divergence of these HLA disparities determines the vigor of the alloreactive donor T cell response and hence influences the clinical outcome of HCT.

Specific aim:
To investigate whether the immunopeptidome divergence between mismatched HLA class I alleles, assessed by the clustering of HLA peptide binding motifs (PBM) based on naturally presented peptides, is associated with the outcome of 9/10 HLA matched unrelated donor HCT for the treatment of onco-hematological disorders.

Scientific impact:
HLA disparities in HCT are major targets of alloreactivity post-transplantation leading both to detrimental Graft versus Host Disease (GvHD) and to beneficial Graft versus Leukemia (GvL) effects in the treatment of onco-hematological disorders. Strategies to harness post-transplant alloreactivity and improve the balance between GvHD and GvL are pivotal for the improvement of this type of treatment. We previously established algorithms for permissive or non-permissive HLA-DPB1 mismatches associated with HCT outcomes from 10/10 HLA matched unrelated donors[1-4]. In the 9/10 unrelated HCT setting, specific patient/donor disparities associated with clinical outcome of HCT have previously been identified by others[5-7]. A new approach to risk prediction by single HLA class I mismatches was taken in a recent CIBMTR study by analyzing HLA supertypes. These supertypes are based on the peptide binding affinity at pocket B and F of HLA-A and B molecules proposed by Sidney et al in 2008[8], and the hypothesis was tested that HLA mismatches within the same supertype group would be less deleterious than those across different supertype groups in 9/10 HCT[9]. The results showed an association of HLA-B supertype mismatches with the incidence of acute GvHD[9]. A limitation of this study was that it was based on peptide binding assays rather than on direct analysis of the presented peptidomes for HLA-A and B, and on the serological dimorphism Ser77Asn for HLA-C with no documented implication for peptide presentation. Since then, huge advances have been made in the analysis of HLA peptidome data, which are now available for 122 different HLA-A,B,C antigens[10], making a revised classification based on actual immunopeptidome data feasible for all 3 class I loci. Moreover, our own recent unpublished observations suggest that the degree of peptide divergence between mismatched HLA-DP antigens determines their association with clinical HCT outcomes in the permissive/non-permissive setting. This led us to hypothesize that similar mechanisms might be relevant also for HLA class I mismatches in 9/10 unrelated HCT.

Scientific justification:

The amino acid polymorphism in the peptide binding domain of HLA molecules is directly responsible for the ability of these antigens to present heterogeneous peptide repertoires to potentially reactive T cells. The impact of this polymorphism on naturally presented immunopeptidomes has been until 2012 very difficult to investigate due to the limited amount of peptide data from Mass Spectrometry (MS) experiments, while most of the information was derived from *in-vitro* peptide binding assays[10, 11]. This changed in the last decade with the introduction of new technical and bioinformatics advances. New MS datasets are now available for 122 HLA class I alleles (41 HLA-A, 63 HLA-B and 18 HLA-C)[10]. Based on the published peptide binding motifs (PBM), we identified 21 different clusters (7 HLA-A, 9 HLA-B and 5 HLA-C; Table 1). According to our hypothesis, HLA mismatches within the same cluster (PBM matched), involving alleles with less divergent peptide repertoires, might be associated with better outcome after HCT than mismatches with highly divergent HLA alleles from different clusters (PBM mismatched). The directionality of the PBM mismatches will be also influenced by the second HLA allele shared between patient and donor (Table 2).

We received the typings of the mismatched HLA only for a CIBMTR cohort of 2367 9/10 HLA matched unrelated patient/donor pairs. In this cohort, 863 (23.8%) pairs could not be analyzed because they carried HLA class I mismatches for which no PBM data are available. For the remaining 1804 (76.2%) pairs, 521 (28.8%) and 1283 (71.1%) were PBM matched or mismatched, respectively. Distribution of PBM matched vs mismatched pairs per each locus was the following: 135 vs 666 (16.8%) for HLA-A, 178 vs 187 (48.7%) for HLA-B and 208 vs 430 (32.6%) for HLA-C. Directionality of these mismatches could not be ascertained since we did not have the information on the second allele shared between patient and donor. With respect to the previous supertype model, 20% (N=360/1804) of the overall pairs are discordantly scored, these differences are more frequent for HLA-C (N=215/638, 33.7%) than for HLA-A and HLA-B (N=106/801, 13.2% and N=39/365, 10.7%, respectively).

Patient eligibility population:

Inclusion criteria:

- Patients receiving allogeneic HCT from 9/10 HLA matched unrelated donors with a single mismatch at the loci HLA-A, B or C. Transplantation from 10/10 matched unrelated donors will serve as control group.
- Indications will include: acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome.
- Transplants performed between 2000 and 2019.

Data requirements:

Patient data:

- Demographics: age, gender, race and parity
- High resolution typing for HLA-A, B, C, DRB1, DQB1. HLA-DPB1 typing will be included if available.
- Karnofsky performance score prior HCT

Disease-related data:

- Diagnosis of hematological malignancy: date and disease type
- Disease status prior starting preparative regimens for HCT
- Induction / consolidation therapy
- Blood and bone marrow laboratory assessment at time of transplant: WBC, Blast %
- Disease risk group

Treatment-related data:

- Date of transplant
- Donor high resolution typing for HLA-A, B, C, DRB1, DQB1. HLA-DPB1 typing will be included if available.
- Patient/donor CMV serostatus
- Stem cell source: peripheral blood, bone marrow
- Preparative regimen and preparative regimen intensity
- GVHD prophylaxis

Post-Transplant Assessment Data:

- Acute GVHD: date, grade and treatment
- Chronic GvHD: date, grade and treatment
- Disease relapse: date and treatment
- Current disease status and Date assessed
- Death: date and cause

Study design:

The entire patient cohort will be retrospectively analyzed for the following clinical outcomes: overall survival (OS) as primary clinical endpoint, and disease-free survival (DFS), non-relapse mortality (NRM), relapse incidence (RI), acute GVHD and chronic GVHD as secondary clinical endpoints. Patients will be stratified into 3 major groups: fully matched 10/10 vs 9/10 PBM matched vs 9/10 PBM mismatched. PBM matches and mismatches will be considered both in the cohort overall and separately for HLA-A,B and C. Directionality of PBM mismatches, taking into account also the PBM category of the second, matched allele in the patient and in the donor, will also be investigated. Clinical associations in patients stratified according to PBM clusters will be compared with those observed in the same cohort stratified according to the previously reported HLA supertypes[9].

Statistical analysis:

Median OS and DFS, incidence of GvHD and time to engraftment between the patient groups described above will be compared using Kaplan-Meier analysis and log rank test. Competing risk analysis and Gray's test will be used for comparison of RI and NRM. Finally, multivariable model analysis will be performed using Cox regression with time-dependent covariates after adjusting for confounding factors.

Non-CIBMTR data source:

None

Conflicts of interest:

None

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Table 1: Classification of 122 HLA class I alleles into different peptide binding motif (PBM) clusters.

PBM cluster	Locus	Alleles
PBM1	HLA-A	*02:01, *02:02, *02:03, *02:04, *02:07, *02:11, *02:12, *02:16, *02:17, *02:19, *02:20, *02:50, *69:01
PBM2	HLA-A	*02:05, *02:06, *68:02
PBM3	HLA-A	*23:01, *24:02, *24:03, *24:06, *24:13
PBM4	HLA-A	*03:01, *11:01, *30:01, *31:01, *33:01, *66:01, *68:01
PBM5	HLA-A	*03:19, *32:01, *32:07, *32:15, *68:23
PBM6	HLA-A	*01:01, *26:02, *26:03, *29:02, *30:02, *80:01
PBM7	HLA-A	*25:01, *26:01
PBM8	HLA-B	*18:01, *18:03, *40:01, *40:02, *41:03, *44:02, *44:03, *44:27, *44:28, *45:01, *49:01, *50:01
PBM9	HLA-B	*14:01, *14:02, *27:01, *27:02, *27:03, *27:04, *27:05, *27:06, *27:07, *27:08, *27:09, *39:24, *73:01
PBM10	HLA-B	*07:02, *35:01, *35:02, *35:03, *35:08, *39:06, *51:01, *51:08, *53:01, *54:01, *56:01
PBM11	HLA-B	*13:01, *13:02, *44:08, *52:01
PBM12	HLA-B	*15:17, *57:01, *58:01
PBM13	HLA-B	*15:01, *15:02, *15:03, *15:11, *46:01
PBM14	HLA-B	*15:09, *15:10, *15:18, *38:01, *39:01
PBM15	HLA-B	*15:42, *27:20, *40:13, *45:06, *48:01, *83:01
PBM16	HLA-B	*08:01, *08:02, *37:01
PBM17	HLA-C	*02:02, *12:02, *12:03, *12:04, *16:01
PBM18	HLA-C	*01:02, *03:04, *03:03, *17:01
PBM19	HLA-C	*14:02, *15:02, *15:05
PBM20	HLA-C	*04:01, *05:01, *08:02
PBM21	HLA-C	*06:02, *07:01, *07:02

Table 2: Exemplary classification of 9/10 matched donor recipient pairs as PBM matched or mismatched. In this example, we consider 3 hypothetical PBM clusters (PBM1, 2 and3).

	Donor		Patient	
	Matched	Mismatched	Mismatched	PBM matching status
Case #1	PBM1	PBM2	PBM2	PBM matched
Case #2	PBM1	PBM2	PBM3	PBM mismatched
Case #3	PBM1	PBM1	PBM2	PBM mismatched - GvH
Case #4	PBM1	PBM2	PBM1	PBM mismatched - HvG

Prop 1911-135 - Recipients with AML,ALL,MDS receiving 9/10 and 10/10 unrelated first allo HCT, 2000-2018

	9/10	**10/10**
Variable	N (%)	N (%)
Number of recipients	4361	21575
Disease		
AML	2329 (53)	11510 (53)
ALL	1029 (24)	4119 (19)
MDS	1003 (23)	5946 (28)
AML-Disease status at transplant		
CR1	1089 (47)	6546 (57)
CR2	549 (24)	2088 (18)
CR3+	45 (2)	171 (1)
Advanced or active disease	627 (27)	2618 (23)
Missing	19 (1)	87 (1)
ALL-Disease status at transplant		
CR1	484 (47)	2390 (58)
CR2	318 (31)	1071 (26)
CR3+	93 (9)	243 (6)
Advanced or active disease	130 (13)	410 (10)
Missing	4 (<1)	5 (<1)
MDS-Disease status at transplant		
Early	250 (25)	1170 (20)
Advanced	706 (71)	4532 (76)
Missing	47 (4)	244 (4)
Race/ethnicity		
Caucasian, non-Hispanic	3031 (70)	18516 (86)
African-American, non-Hispanic	317 (7)	403 (2)
Asian, non-Hispanic	166 (4)	461 (2)
Pacific islander, non-Hispanic	9 (<1)	38 (<1)
Native American, non-Hispanic	18 (<1)	65 (<1)
Hispanic	451 (10)	1068 (5)
Other race	7 (<1)	4 (<1)
Unknown	362 (8)	1020 (5)
Recipient age at transplant		
0-10 years	286 (7)	949 (4)
10-17 years	436 (10)	1214 (6)
18-29 years	483 (11)	1897 (9)
30-39 years	471 (11)	1978 (9)
40-49 years	726 (17)	2945 (14)

Variable	9/10 N (%)	10/10 N (%)
50-59 years	951 (22)	4862 (23)
60 years and older	1008 (23)	7730 (36)
Median (Range)	47 (0-78)	54 (0-84)
Sex		
Male	2429 (56)	12191 (57)
Female	1932 (44)	9384 (43)
Karnofsky performance score		
10-80	1476 (34)	8065 (37)
90-100	2695 (62)	12778 (59)
Unknown	190 (4)	732 (3)
Donor age		
To Be Determined/NA	53 (1)	209 (1)
0-9 years	0	5 (<1)
10-19 years	84 (2)	843 (4)
20-29 years	1665 (38)	11203 (52)
30-39 years	1298 (30)	5485 (25)
40-49 years	914 (21)	2909 (13)
50+ years	347 (8)	921 (4)
Median (Range)	33 (18-61)	29 (0-64)
Graft type		
Marrow	1241 (28)	4791 (22)
PBSC	3120 (72)	16784 (78)
Conditioning regimen intensity		
Myeloablative	2755 (63)	12643 (59)
Non-myeloablative/RIC	1285 (29)	8081 (37)
Unknown	321 (7)	851 (4)
GVHD prophylaxis		
TAC + MMF +- other(s) (except post-CY)	561 (13)	2806 (13)
TAC + MTX +- other(s) (except MMF, post-CY)	2114 (48)	11750 (54)
TAC + other(s) (except MMF, MTX, post-CY)	221 (5)	1542 (7)
TAC alone	110 (3)	561 (3)
CSA + MMF +- other(s) (except post-CY)	352 (8)	1420 (7)
CSA + MTX +- other(s) (except MMF, post-CY)	778 (18)	2600 (12)
CSA + other(s) (except MMF, MTX, post-CY)	53 (1)	150 (1)
CSA alone	65 (1)	198 (1)
Other(s)	64 (1)	285 (1)
Missing	43 (1)	263 (1)
9/10 mismatch		

Variable	9/10 N (%)	10/10 N (%)
Mismatch at A	1994 (46)	0
Mismatch at B	995 (23)	0
Mismatch at C	1372 (31)	0
Unknown	0 (N/A)	21575 (N/A)
Year of transplant		
2000	75 (2)	193 (1)
2001	108 (2)	206 (1)
2002	91 (2)	225 (1)
2003	122 (3)	274 (1)
2004	160 (4)	437 (2)
2005	197 (5)	560 (3)
2006	203 (5)	683 (3)
2007	226 (5)	770 (4)
2008	276 (6)	967 (4)
2009	299 (7)	1098 (5)
2010	287 (7)	1215 (6)
2011	278 (6)	1341 (6)
2012	312 (7)	1482 (7)
2013	356 (8)	1791 (8)
2014	342 (8)	1994 (9)
2015	335 (8)	2058 (10)
2016	303 (7)	2085 (10)
2017	209 (5)	2043 (9)
2018	182 (4)	2153 (10)

Proposal: 1911-15

Title:
HLA-Mismatches In The Setting Of Post-Transplant Cyclophosphamide And Lymphomas:
Are A Matched Unrelated Or Haploidentical Donors Still An Issue?

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Hypothesis and scientific justification:
Post-transplant Cyclophosphamide (PT-Cy) has recently emerged as an effective graft-versus-host disease (GVHD) prophylaxis. Its first clinical use was tested in the setting of haploidentical allogeneic hematopoietic cell transplantation (alloHCT). First studies by the Baltimore group showed an impressive reduction of cGVHD incidence when using PT-Cy plus tacrolimus/MMF.[1] Extensive chronic GVHD ranging from 5% to 10% in the haploidentical setting was so promising that it led to the widespread application of this very feasible GVHD prophylaxis. After the confirmation of these results on larger cohorts of patients,[2,3] haploidentical alloHCT with PT-Cy was compared to alloHCT from matched unrelated donor (MUD) and standard GVHD prophylaxis in retrospective analysis in both myeloid and lymphoid malignancies.[4,5] Surprisingly, haploidentical alloHCT groups had less cGVHD than alloHCT using MUD with standard GVHD prophylaxis (tacrolimus/cyclosporine + methotrexate ± ATG). Despite recent reports regarding outcome differences based upon graft source[6] or conditioning regimen intensity,[7] there are still several areas of uncertainty in the PT-Cy setting. In particular, there is a current interest in defining the influence of donor characteristics and graft cell composition on survival outcomes.
A pivotal study by Kasamon et al. showed that HLA-mismatch degree does not influence clinical outcomes in haploidentical alloHCT. We recently reported that donor characteristics (sex, age, donor-recipient relationship) do not have a strong influence in this setting.[8] More recent retrospective studies, showed that haploidentical alloHCT with PT-Cy results in similar survival outcomes even when compared to matched-related donor (MRD) alloHCT with standard GVHD prophylaxis but with less chronic GVHD.[9,10] Thus, current studies suggest that PT-Cy GVHD prophylaxis could neutralize differences in terms of type of donor and HLA-mismatches.
A formal comparison between MUD vs haploidentical donor when using a PT-Cy based anti-GVHD prophylaxis has never been performed. Moreover, most studies have compared reduced-intensity conditioning regimens and marrow-derived grafts for the PT-Cy groups. Also, there is an ongoing discussion regarding a supposed anti-relapse effect of PT-Cy, especially for Hodgkin lymphoma patients. Our study could address for the first time if the type of donor (MUD vs haploidentical) is still a matter when a PT-Cy based strategy is used.
Our hypothesis is that a PT-Cy based strategy could neutralize differences between donors. If this will be confirmed, prospective studies addressing the same question could be made in order to possibly reduce or obviate the need for a MUD. This could potentially dramatically reduce the cost and time required to find a donor without a negative impact on transplant clinical outcomes.
If our hypothesis won't be confirmed, the study will be the first comparison between MUD and haploidentical donor using a PT-Cy based anti GVHD strategy for lymphoma patients.

Objectives:

Primary:

- OS: events are death from any cause. Surviving patients are censored at time of last contact

Secondary:

- Hematopoietic recovery: time to neutrophil (ANC) recovery $\geq 0.5 \times 10^9$/l; time to platelet recovery $\geq 20 \times 10^9$/L
- PFS: survival without progression. Patients are censored at time of last contact
- aGVHD: maximum overall grade of grade II-IV acute GVHD, we do not collect date of onset of acute GVHD
- Relapse incidence (RI): Time of relapse of the original malignancy post allo-HCT
- Non-relapse mortality (NRM): time to death without disease relapse
- GVHD: maximum extent of chronic GVHD, and time to cGVHD
- CGFRS: survival without moderate-severe chronic GVHD. Patients are censored at time of last contact
- Primary cause of death: according to Copelan algorithm, descriptive only

Study population:

This study will include adult patients of 18-70 years who received first allo-HCT between 01/2010 and 12/2018 for lymphomas using a MUD or haploidentical donor. GVHD prophylaxis will be limited to PT-Cy based strategies. Two groups will be compared: MUD vs haploidentical donors.

Inclusion criteria for haploidentical cohort:

- First allo-HCT between 2010 and 2018 (in order to have a sufficient follow-up)
- Age 18-70 years old
- >/= 2 HLA mismatched related donor
- Graft manipulation with PT-Cy based strategy only as GVHD prophylaxis. Addition of tacrolimus or cyclosporine to MMF will be included.
- Hodgkin disease, Diffuse large B cell lymphoma, Mantle cell lymphoma, Peripheral T cell lymphomas, Follicular lymphoma

Inclusion criteria for MUD cohort:

- first allo-HCT between 2010 and 2018 (in order to have a sufficient follow-up)
- Age 18-70 years old
- MUD
- 8/8 HLA matches defined at HLA compatibility at loci A, B, C and DRB1
- Graft manipulation with PT-Cy based strategy only as antiGVHD prophylaxis. Addition of tacrolimus or cyclosporine to MMF will be included.
- Hodgkin disease, Diffuse large B cell lymphoma, Mantel cell lymphoma, Peripheral T cell lymphomas, Follicular lymphoma

Both myeloablative and reduced intensity conditioning regimen will be included. Use of peripheral blood stem cells or bone marrow stem cells as a graft will be considered for the study. Recipients of prior allografts, non-malignant disease, leukemia in morphologic relapse or refractory disease will be excluded.

Outcomes:

- Hematopoietic recovery: The primary measures for hematopoietic recovery will be:
  - Time to neutrophils (ANC) > 0.5 x10^9/L sustained for three consecutive days. This endpoint will be evaluated at 28-day and 100-day after HCT.
  - Time to achieve a platelet count of (a) >20 x 10^9/L independent of platelet transfusions for 3 consecutive days, and (b) >50 x 10^9/L independent of platelet transfusions for 3 consecutive days within 28 and 100 days post-transplant.This endpoint will be evaluated at 28-day and 100-day after HCT.
- NRM: Cumulative incidence of TRM at day +100 and 2 years. NRM is defined as death without preceding disease relapse/progression. Relapse/progression are competing events.
- RI/POD: Cumulative incidence of disease relapse/progression at 2 years with TRM as competing event.
- PFS: survival without relapse/progression or death at 2 years. Relapse or progression of disease and death are events. Those who survive without recurrence or progression are censored at last contact.
- OS: time to death at 2 years. Death from any cause will be considered an event. Surviving patients will be censored at time of last follow-up.
- Acute GVHD: Cumulative incidence of grade II-IV acute GVHD per consensus criteria at day +100 and 2 years, with death as competing risk.
- Chronic GVHD: Cumulative incidence of limited and extensive chronic GVHD at 2 years, with death as competing risk.
- CGFRS: time to death or to moderate-severe chronic GVHD at 2 years. Death from any cause will be considered an event. Surviving patients will be censored at time of last follow-up.

Data requirements:
Data form #2400, post-transplant essential data form #2450, selective post-transplant selective data form #2455 and 100 day post-HCT data form #2100, Six Months to Two Years Post-HCT Data #2200. The parameters to be assessed are outlined in **table 1** below.

Table 1 Data Requirements:

Type of data	Data point	Specific data
Patient Specific	Patient specific characteristics	• Age at transplant (Date of birth) • Gender • Race • Significant comorbidities • Weight • Infectious serologies (CMV, EBV) • Primary disease type (NHLs, HL) • Disease risk (high risk or standard) • Prior autologous transplant • Remission status (CR1, CR2, etc)
Transplant Specific	Transplant date	• Transplant date
	Transplant information	• MUD/haploidentical donor
	Preparative regimen used	• Myeloablative • Reduced Intensity/ non-myeloablative
	GVHD prophylaxis	• PT-Cy based ± other (e.g. tacrolimus/MMF; CSA/MMF)
	Graft characteristic	• PBSC, BM

Outcome Measures	Engraftment	• Time to absolute neutrophil count ≥500 cells/mm^3 for 3 consecutive laboratory readings • Time to unsupported platelets ≥20 x 10^9 cells/L and ≥50 x 10^9 cells/L • Donor-recipient chimerism • Graft failure (primary and secondary)
	GVHD	• Acute GVHD (aGVHD) o Incidence of grade II-IV acute GVHD (aGVHD) (subset evaluating grade III-IV aGVHD) o Time to aGVHD • GVHD after day 100 o Incidence of chronic GVHD (cGVHD) o Severity of GVHD after day 100
	Mortality	• Time to mortality • Day 100, 6 months and 2 years mortality • Treatment related mortality at 6 months and 2 years • Cause of mortality
	Disease relapse	• Incidence of disease relapse • Time to disease relapse

Variables to be analyzed:

Patient-related:

- Age: continuous to find the appropriate cut point for the survival model
- Gender: male vs female
- Karnofsky performance score: <90% vs >=90%
- Comorbidity index: 0 vs 1-2 vs 3
- CMV serostatus: recipient positive vs recipient negative vs unknown

Disease related:

- Disease status at time of transplant: chemosensitive versus chemorefractory
- Previous auto-HSCT
- HL vs NHLs

Transplant related:

- Main effect: MUD vs haploidentical donor
- Conditioning regimen: myeloablative vs reduced intensity
- Bone marrow graft versus PBSC

Study design:

A retrospective multicenter study will be conducted utilizing CIBMTR data. Patients will be eligible if they satisfied the criteria detailed in the "Patient eligibility population" section. Patients will then be stratified according to MUD or haplo-PTCy. The objective of this analysis is to compare these two approaches and their effects on allo-HCT outcomes.

Chi-square or the Wilcoxon statistic will be used to compare patient, disease and transplantation characteristics between the 3 groups for categorical or continuous variables respectively. The

probabilities of neutrophils and platelets recovery, aGVHD, cGVHD, NRM, RI will be calculated using the cumulative incidence estimator. PFS, OS and CFRS will be calculated using the Kaplan-Meier estimator. For neutrophils and platelets recovery, aGVHD and cGVHD death without the event will be the competing event. For TRM relapse will be the competing event. For RI, NRM will be the competing event. Data on patients without an event will be censored at last follow up.
For univariate analysis, Gray test and log-rank test will be used to identify factors influencing cumulative incidence and survival respectively.
The association between treatment groups and outcomes will be studied with multivariate Cox regression models. P values are 2 sided and values < 0.05 will be considered significant.
The treatment group will be included in all steps of model building regardless of level of significance. The other variables tested will be retained in the final multivariate model if the variable will attain the level of significance set for these analyses.
Results will be expressed as hazard ratio (HR) with 95% confidence intervals (CI).
Possible interactions within the treatment groups and other variables will be tested.
All models will be tested regarding proportional hazard of assumptions (PHA). If the assumption will be violated, time dependent covariates will be constructed.

Potential pitfalls:
Even if the number of the patients using PT-Cy outside the haploidentical setting is steadily increasing during the last years, it is possible that the number of this population is too low to perform a statistical analysis. In this case, the study could be proposed to include EBMT patients as well.

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Prop 1911-15 - Recipients with lymphoma receiving PT-Cy for first allo HCT, 2010-2018

Variable	Haplo N (%)	8/8 MUD N (%)
Number of recipients	611	114
Disease		
NHL	438 (72)	96 (84)
Hodgkins Lymphoma	173 (28)	18 (16)
Subdisease		
CLL Chronic lymphocytic leukemia, NOS	5 (1)	0
NHL follicular,predominantly small cleaved cell	5 (1)	4 (4)
NHL follicular,mixed,small cleaved and large cell	14 (2)	3 (3)
NHL diffuse, large B-cell	127 (21)	26 (23)
Burkitt lym/Burkitt cell leukemia	5 (1)	1 (1)
NHL mantle cell	54 (9)	17 (15)
Primary CNS lymphoma	1 (<1)	0
T-cell / histiocytic rich large B-cell lymphoma	3 (<1)	0
Extranodal marginal zone B-cell of MALT	2 (<1)	2 (2)
Nodal marginal zone B-cell	1 (<1)	0
Splenic marginal zone B-cell	1 (<1)	1 (1)
Primary mediastinal large B-cell (095CORE)	6 (1)	1 (1)
Large granular lymphocytic leukemia	1 (<1)	0
Other B-cell, spec	9 (1)	2 (2)
Peripheral T-cell lymphoma, NOS	37 (6)	9 (8)
Angioimmunoblastic T-cell lymphoma	17 (3)	4 (4)
Enteropathy-type T-cell lymphoma	2 (<1)	0
Adult T-cell lymphoma/leukemia	16 (3)	0
Extranodal NK-T-cell	6 (1)	1 (1)
Other T/NK-cell lymphoma, specify	9 (1)	0
B-cell unclass. between DLBCL and Burkitt	7 (1)	1 (1)
Mycosis fungoides	14 (2)	2 (2)
Sezary syndrome	6 (1)	0
Anaplastic large-cell lymphoma (ALCL), ALK positive	7 (1)	1 (1)
Anaplastic large-cell lymphoma (ALCL), ALK negative	12 (2)	1 (1)
Hepatosplenic gamma-delta T-cell	8 (1)	1 (1)
Subcutaneous panniculitis T-cell	5 (1)	0
Anaplas LC,T/N cell, cutaneous	5 (1)	4 (4)
Anaplas LC,T/N cell, systemic	0	1 (1)
B-cell unclass. between DLBCL and hodgkin	3 (<1)	0
HD, NOS	25 (4)	5 (4)
HD lymphocyte-rich	2 (<1)	0
HD nodular sclerosis	123 (20)	9 (8)
HD mixed cellularity	17 (3)	3 (3)
Nodular lymphocyte predominant Hodgkin lymphoma	3 (<1)	0
Follicular, predominantly large cell Grade IIIA (2400v4)	13 (2)	4 (4)

Variable	Haplo N (%)	8/8 MUD N (%)
Follicular, predominantly large cell Grade IIIB (2400v4)	3 (<1)	0
Follicular unknown grade	13 (2)	1 (1)
Waldenstrom macroglobulinemia	2 (<1)	0
DLBCL- Germinal Center B-cell type	6 (1)	3 (3)
DLBCL- Activated B-cell type	5 (1)	3 (3)
EBV+ DLBCL, NOS	3 (<1)	1 (1)
High-grade B-cell lymphoma, NOS	1 (<1)	0
NHL with MYC and BCL2 and/or BCL6 rearrangements	2 (<1)	1 (1)
Primary cutaneous gamma-delta T-cell lymphoma	1 (<1)	1 (1)
Primary cutaneous CD4+ small/med T-cell LPD	1 (<1)	0
Classical Hodgkin lymphoma PTLD	3 (<1)	1 (1)
Race/ethnicity		
Caucasian, non-Hispanic	365 (60)	100 (88)
African-American, non-Hispanic	129 (21)	5 (4)
Asian, non-Hispanic	25 (4)	0
Pacific islander, non-Hispanic	3 (<1)	0
Native American, non-Hispanic	0	1 (1)
Hispanic	51 (8)	3 (3)
Unknown	38 (6)	5 (4)
Recipient age at transplant		
10-17 years	8 (1)	0
18-29 years	97 (16)	5 (4)
30-39 years	98 (16)	17 (15)
40-49 years	84 (14)	19 (17)
50-59 years	169 (28)	28 (25)
60 years and older	155 (25)	45 (39)
Median (Range)	52 (18-71)	55 (21-71)
Sex		
Male	381 (62)	78 (68)
Female	230 (38)	36 (32)
Karnofsky performance score		
10-80	224 (37)	43 (38)
90-100	373 (61)	69 (61)
Unknown	14 (2)	2 (2)
Graft type		
Marrow	242 (40)	19 (17)
PBSC	369 (60)	95 (83)
Conditioning regimen intensity		
Myeloablative	117 (19)	26 (23)
Non-myeloablative/RIC	493 (81)	87 (76)
Unknown	1 (<1)	1 (1)
GVHD prophylaxis		
CD34 selection	1 (<1)	0

Variable	Haplo N (%)	8/8 MUD N (%)
Post-CY + other(s)	567 (93)	90 (79)
Post-CY alone	5 (1)	3 (3)
TAC + MMF +- other(s) (except post-CY)	34 (6)	10 (9)
TAC alone	2 (<1)	0
CSA + MMF +- other(s) (except post-CY)	1 (<1)	0
Other(s)	0	10 (9)
Missing	1 (<1)	1 (1)
Year of transplant		
2010	12 (2)	0
2011	2 (<1)	4 (4)
2012	4 (1)	2 (2)
2013	18 (3)	7 (6)
2014	71 (12)	13 (11)
2015	86 (14)	15 (13)
2016	117 (19)	14 (12)
2017	162 (27)	26 (23)
2018	139 (23)	33 (29)

Proposal: 1911-182

Title:
Role of Recipients' Specific anti-HLA Antibodies (RSA) in hematopoietic stem cell transplantation with Human Leukocyte antigen (HLA) mismatched donors
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Hypothesis:
We hypothesize that a detrimental effect on transplant outcomes occurs when donor has HLA antibodies against recipients HLA antigens (recipient-specific anti-HLA antibodies, RSA)

Specific aims:
- To evaluate incidence of RSA in HLA mismatched transplants
- To correlate RSA with transplant outcomes
- To evaluate relationship between DSA and RSA in patients with HLA mismatched donor transplants, further assess the clinical relevance of different levels of DSA/RSA.

Scientific justification:
Utilization of hematopoietic stem cells from haploidentical donors who share half of the HLA with the patient, substantially expand the availability of stem cell resources and therefore can reform the entire field of hematopoietic stem cell transplantation (HSCT) (1). This alternative approach has opened the door for rapid identification of a source of hematopoietic stem cells from most of family members. With fairly successful regulation of T-lymphocyte mediated acute rejection and GVHD in haploidentical HSCT, the detrimental role of antibodies against donor HLA antigens (anti-HLA) produced by B-lymphocyte is now being acknowledged, and the role of anti-HLA antibodies in haploidentical HSCT has drawn increasing attention. The reported prevalence of donor-specific anti-HLA antibodies (DSA) in HSCT recipients is between 20-40% in different study cohorts (2,3).
Alloimmunization by pregnancies, blood transfusion or previous transplantation may lead to the generation of DSA (4). On the other hand, the presence of HLA antibodies in healthy donors against the recipient's HLA antigens, especially in parous female donors, is not uncommon. In women platelet donors, a history of pregnancy was significantly associated with HLA alloimmunization (ref). Presence of HLA antibodies was observed in approximately 20% of unselected apheresis donors who have ever been pregnant. Power et al. reported that the prevalence of HLA antibodies rises with increasing parity (5). Using a cutoff of 2.4-fold NBG (normalized background) value, which is commonly used for transplant donor screening, 41% of women platelet donors tested were sensitized after two pregnancies, while only 6.5% of nulliparous women donors tested positive.
Compared to traditional HSCT, the incidence of donor-specific or recipient specific HLA antibodies are much higher in the haploidentical HSCT setting as one haplotype between donor and recipient is mismatched. The presence of DSA in the recipients is associated with significant increasing risk of graft failure in haploidentical HSCT perhaps because the recipients' antibody recognizes the cognate HLA antigens expressed on the hematopoietic progenitor cells from the donor (6,7). On the other hand, to the best of our knowledge, the role of donor derived antibodies that are against recipients' HLA antigens in allogeneic HSCT setting has never been studied. Several lines of studies suggested that passive transferred donor antibodies capable of attacking recipient antigen molecules. Maternal antibodies are transferred across the placenta to protect the fetus from infection (8). However, it has been shown the transferred antibodies directed toward paternal MHC class I antigens to the developing fetus and accumulated at

most fetal organs except brain and cartilage (9). Recent studies have studied possible functional consequences of anti-fetal HLA antibodies on the development of fetus. Detection of anti-HLA antibodies in maternal blood in the second trimester is associated with risk of antibody-mediated anti-fetal rejection. The sensitivity of using positive HLA panel reactive antibody (PRA) test to detect spontaneous preterm delivery was 34.5% (10). Even in early gestation stage (before 16 weeks), the correlation has been demonstrated between the presence of maternal HLA antibodies and chronic chorioamnionitis, which is a feature of anti-fetal rejection (11).

The presence of RSA may or may not cause a direct injury as observed in the acute rejection events in solid organ transplant, yet it might initiate or augment harmful cascades which may lead to morbidity and/or mortality. Bacigalupo et al. analyzed a cohort of 174 patients receiving HLA identical allogeneic HSCT for factors associated with acute GVHD. Comparing to ABO matched or major mismatched group, a significant higher risk of severe acute GVHD is associated with minor ABO mismatch, in which the donor antibody is against recipient ABO antigen (12). A similar study observed that the incidence of liver GVHD was higher in minor ABO mismatched HSCT. This group hypothesized that donor derived anti-ABO antibodies attack the antigen expressed on the epithelial cells of the large bile tract and therefore enhance the incidence and severity of liver GVHD (13).

It is possible that anti-recipient antibodies are present transiently and will be absorbed quickly by recipient antigens post transplantation. However, it has been shown that transferred memory B cells from the donor is capable of production of antibodies with identical affinity upon further exposure to allogeneic antigen post HSCT (14). Passive donor to recipient transfer of autoimmune diseases post HSCT was reported (15-17). Ritchie et al. descripted that a HSCT recipient with no history of antiphospholipid syndrome (APLS) and no autoantibody prior to SCT developed symptomatic APLS with cerebral thrombosis post-transplant. The recipient acquired high titer anticardiolipin and anti-ds-DNA antibodies, which are identical to the donor antibody profile. Along with other studies, it was suggested that the passive transferred donor memory B cells are reactivated by exposure to autoantigens (15,16).

Here we aim to investigate the frequency of presence RSA and the impact of recipient-specific anti HLA antibodies (RSA) in donor serum on the outcome of HSCT with HLA mismatched donors.

If the recipient pre-transplant serum is also available, we would like to also evaluate the impact of DSA on transplant outcomes as well as the correlations between DSA and recipient-specific anti HLA antibodies (RSA) in patients receiving HLA mismatched transplants as described below.

It is now well accepted that the presence of DSAs is associated with delayed engraftment (18) or graft failure (19) in HSCT with HLA mismatched donors (refs). However, the high sensitivity of the Luminex assay in identifying HLA antibodies could potentially be problematic, given the cutoff (MFI) of positivity has not been standardized and differs significantly among studies and institutions. Two similar studies in HSCT using double-unit cord blood as the graft source made completely different conclusions (3,20). Cutler et al. have demonstrated that the presence of DSAs has a significant negative impact on engraftment, whereas Brunstein et al. have shown that the presence of DSAs is negligible with decent engraftment rate (83%). The cutoff value they used in their study is quite different (1000 MFI in Cutler's study versus 500 MFI in Brunstein's study), despite the similar percentage of DSA positive patients among their study population. There is certainly a caveat in establishing the clinical relevant threshold of DSA levels, as the low levels of DSAs are perhaps not associated with the risk of rejection or *vice versa*.

In solid organ transplant, the cutoff value is usually defined by comparison the levels of DSAs with the cytotoxic crossmatch reactivity (21). Individual cutoff on each HLA locus can be remarkably different. For instance, anti-HLA-A antibody with MFI around 3000-4000 is likely associated with a positive crossmatch whereas only anti-DQ antibodies with MFI>12,000 is capable of predicting positive crossmatch result (21). No correlation could be done in HSCT setting as there is no such crossmatch performed. A large cohort of patients would enable us to retrospectively study the clinical outcome over a wide spectrum of

antibody strengths. Predictive cutoff value of subgroup DSAs can be identified using Receiver operating characteristic (ROC) analysis.
Complement binding DSAs has been associated with the high risk of kidney allograft rejection (22). Studies suggested the correlation between C1q binding DSAs and graft failure in the haploidentical HSCT perhaps due to the activation of the classic complement cascade (18,19). These studies are limited by the small number of cases and varied desensitization treatment regimens. The assessment of the complement-binding capability of DSAs by C1q test is not routinely performed in identifying high risk of engraft failure in most institutions. It is unclear whether this C1q test has an improved ability to detect clinically significant DSAs as one may argue that MFI value of single antigen test is presumably a good predictor of positive C1q test and additional C1q test is not necessary considering a substantial cost of the test (23). A large cohort of recipients with pre-transplant serum sample would allow us to identify the C1q positive or negative DSAs with similar MFI value and therefore further study the role of complement binding HLA antibody in HSCT with HLA mismatched donors.
We do not anticipate a large number of HSCT with coexisting DSA and RSA, however, the bidirectional immune reactivity present simultaneously might be associated with inferior clinical consequences. The study on the synergistical relationship between DSA and RSA in patients with HLA mismatched donor transplants would direct future management strategies for HSCT.

Patient eligibility population:
Inclusion:
- Patients or any age (children and adults) with HLA mismatched donor transplants including haploidentical, cord blood, mismatched unrelated donor transplants, matched unrelated donor transplant (8/8) mismatched at least at one HLA locus
- Serum samples available for donor and/or recipient
- High resolution HLA typing is known for both donor and recipient

Exclusion:
- HLA matched related and HLA matched unrelated donor transplants matched at all HLA- loci (HLA-A, B, C, DRB1, DRB345, DQB1 and DPB1)
- Serum samples that have been tested negative for HLA antibody

Data requirements:
Transplant outcomes (engraftment, GVHD, non-relapse mortality, relapse, survival) for patients eligible for this study are needed. To be more specific:
The primary endpoints of these analyses are:
Hematopoietic recovery:
- Time to neutrophil engraftment - ANC > 0.5 x 10^9/L for three consecutive days will be the primary measure for comparisons of hematopoietic recovery without transfusion support.
- Time to platelet engraftment - platelet count $\geq$ 20 x 10^9/L without transfusion support.
- Time to platelet count $\geq$ 100 x 10^9/L.

Graft Failure:
- Primary graft failure – defined as no evidence of transplanted marrow function after day 28 post-transplant
- Secondary graft failure - Development of inadequate marrow function (fall of granulocytes to <0.5/mcl for 3 or more consecutive days) any time after initial engraftment has been achieved.
- Death and progressive disease within 28 days are competing risks.

Incidence of acute and chronic GVHD: grade II-IV acute GVHD and limited and extensive chronic GVHD.

Relapse incidence: time to onset of disease relapse. Patients will be censored at death in continuous CR or, for patients surviving in continuous complete remission, at the last contact.

Disease free survival: time to treatment failure (death or relapse). Patients are censored at time of last follow-up.

Overall survival: time to death. Patients are censored at time of last follow-up.

Non-relapse mortality: time to death without evidence of disease recurrence/relapse. Death from any cause without prior progression are events

Variables to be analyzed:
- A-Continuous variables
- B-Categorical variables

Patient related:
- Age at transplant (<50 y vs $\geq$ 50 y), (B)
- Gender (female vs male) (B)
- Karnofsky performance score at transplant (<90% vs $\geq$ 90%), when available (B)
- Hematopoietic Cell Transplant-Comorbidity Index (HCT-CI), (0 vs 1-2 vs $\geq$ 3), when available (B)

Disease-related (at initial diagnosis):
- Disease risk (good/intermediate vs. poor prognosis) (B)
- Philadelphia chromosome positive (yes/no) (B)
- Extramedullary disease (yes/no) (B)
- CNS disease? (yes/no) (B)

Disease-related (at the time of transplant):
- Disease status transplant (B)
- Time from diagnosis to transplant (A)
- Ever achieved a first remission? (yes/no) (B)
- Time to achieve complete remission (A)
- Duration of complete remission (B)
- Number of cycles of induction therapy to achieve first complete remission (1 vs >1) for patients with acute leukemia (B)

Treatment-related:
- Donor age (A)
- Donor-recipient gender match (F-M vs other) (B)
- Donor type (child/parent/sibling/other) (B)
- Donor-recipient HLA mismatch (A)
- Donor-recipient CMV status: (-/- vs others) (B)
- Conditioning regimen (MA vs. RIC vs. NMA) (B)
- Conditioning regimen type (A)

- Infused number of nucleated and CD34+ cells: n/kg recipient weight (if available) (A)
- Infused number of CD3+ cells: n/kg recipient weight (if available) (A)
- Source of stem cells: (BM vs PBSC vs both) (B)

Sample requirements:
Donor and recipient serum samples available in the database will be needed for the further anti-HLA antibody testing.

Significance:
The role of RSA in the HSCT with mismatched HLA antigens has not been studied and defined. This study would arrest this clinical question by comparing the outcomes between the transplants with or without RSA, while adjusting for the patient and disease related factors. Extended studies on the clinical relevance of DSA with different MFI levels and different complement binding capabilities as well as the association with RSA are also novel and clinically critical. The information gained from this study will certainly further assist in donor selection and clinical management in HSCT.

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Table 1. RSA Analysis - Patients receiving first allo HCT with donor serum samples available, *Restricted to female donors ≥ 18 to increase the rate of HLA sensitivity*

	Haplo	**7/8**	**8/8**
Variable	N (%)	N (%)	N (%)
Number of recipients	207	683	1831
Disease			
AML	112 (54)	341 (50)	880 (48)
ALL	55 (27)	134 (20)	321 (18)
MDS	40 (19)	208 (30)	630 (34)
Race/ethnicity			
Caucasian, non-Hispanic	109 (53)	450 (66)	1540 (84)
African-American, non-Hispanic	50 (24)	64 (9)	64 (3)
Asian, non-Hispanic	12 (6)	32 (5)	49 (3)
Pacific islander, non-Hispanic	1 (<1)	4 (1)	5 (<1)
Native American, non-Hispanic	1 (<1)	6 (1)	6 (<1)
Hispanic	25 (12)	89 (13)	113 (6)
Unknown	9 (4)	38 (6)	54 (3)
Recipient age at transplant			
0-9 years	6 (3)	30 (4)	88 (5)
10-19 years	16 (8)	53 (8)	83 (5)
20-29 years	24 (12)	65 (10)	149 (8)
30-39 years	16 (8)	75 (11)	166 (9)
40-49 years	30 (14)	108 (16)	231 (13)
50-59 years	55 (27)	152 (22)	404 (22)
60-69 years	60 (29)	200 (29)	710 (39)
Median (Range)	53 (1-76)	51 (0-78)	55 (1-81)
Recipient Sex			
Male	116 (56)	339 (50)	873 (48)
Female	91 (44)	344 (50)	958 (52)
Donor age at transplant			
18-19 years	12 (6)	16 (2)	81 (4)
20-29 years	46 (22)	302 (44)	931 (51)
30-39 years	51 (25)	170 (25)	424 (23)
40-49 years	52 (25)	124 (18)	281 (15)
50+ years	46 (22)	71 (10)	114 (6)
Median (Range)	39 (18-71)	31 (18-61)	28 (18-62)
Donor Sex			
Female	207 (100)	683 (100)	1831 (100)
Karnofsky performance score			
10-80	99 (49)	231 (34)	696 (38)
90-100	104 (51)	444 (66)	1116 (62)
Unknown	4 (N/A)	8 (N/A)	19 (N/A)
Graft type			
Marrow	92 (44)	138 (20)	353 (19)
PBSC	115 (56)	545 (80)	1478 (81)

Variable	**Haplo** N (%)	**7/8** N (%)	**8/8** N (%)
Conditioning regimen intensity			
Myeloablative	109 (53)	450 (66)	1076 (59)
Non-myeloablative/RIC	98 (47)	230 (34)	746 (41)
Unknown	0	3 (<1)	9 (<1)
GVHD prophylaxis			
Ex-vivo T-cell depletion	0	10 (1)	8 (<1)
CD34 selection	0	13 (2)	27 (1)
Post-CY alone	181 (87)	19 (3)	50 (3)
TAC + MMF +- other(s) (except post-CY)	26 (13)	86 (13)	244 (13)
TAC + MTX +- other(s) (except MMF, post-CY)	0	385 (56)	1019 (56)
TAC + other(s) (except MMF, MTX, post-CY)	0	42 (6)	130 (7)
TAC alone	0	14 (2)	47 (3)
CSA + MMF +- other(s) (except post-CY)	0	38 (6)	134 (7)
CSA + MTX +- other(s) (except MMF, post-CY)	0	50 (7)	101 (6)
CSA + other(s) (except MMF, MTX, post-CY)	0	3 (<1)	8 (<1)
CSA alone	0	6 (1)	8 (<1)
Other(s)	0	12 (2)	30 (2)
Missing	0	5 (1)	25 (1)
DP or DQ mismatch			
Mismatch at DQB1 only	0	0	12 (1)
Mismatch at DPB1 only	0	0	1660 (91)
Mismatch at DQB1 and DPB1	0	0	159 (9)
Unknown	207 (N/A)	683 (N/A)	0 (N/A)
Year of transplant			
2010	1 (<1)	105 (15)	192 (10)
2011	3 (1)	88 (13)	218 (12)
2012	7 (3)	99 (14)	219 (12)
2013	13 (6)	105 (15)	286 (16)
2014	28 (14)	108 (16)	314 (17)
2015	50 (24)	114 (17)	337 (18)
2016	74 (36)	47 (7)	222 (12)
2017	31 (15)	17 (2)	43 (2)

Table 2. DSA Analysis - Patients receiving first allo HCT with recipient serum samples available, *Restricted to female recipients ≥ 18 to increase the rate of HLA sensitivity*

	Haplo	**7/8**	**8/8**
Variable	N (%)	N (%)	N (%)
Number of recipients	184	614	2542
Disease			
AML	106 (58)	336 (55)	1383 (54)
ALL	42 (23)	111 (18)	366 (14)
MDS	36 (20)	167 (27)	793 (31)
Race/ethnicity			
Caucasian, non-Hispanic	100 (54)	429 (70)	2254 (89)
African-American, non-Hispanic	42 (23)	64 (10)	64 (3)
Asian, non-Hispanic	10 (5)	24 (4)	58 (2)
Pacific islander, non-Hispanic	1 (1)	4 (1)	6 (<1)
Native American, non-Hispanic	0	3 (<1)	7 (<1)
Hispanic	21 (11)	60 (10)	103 (4)
Unknown	10 (5)	30 (5)	50 (2)
Recipient age at transplant			
18-19 years	5 (3)	15 (2)	24 (1)
20-29 years	25 (14)	65 (11)	196 (8)
30-39 years	19 (10)	89 (14)	284 (11)
40-49 years	25 (14)	118 (19)	405 (16)
50-59 years	55 (30)	159 (26)	648 (25)
60-69 years	55 (30)	168 (27)	985 (39)
Median (Range)	53 (19-76)	52 (18-75)	56 (18-84)
Recipient Sex			
Female	184 (100)	614 (100)	2542 (100)
Donor age at transplant			
0-9 years	1 (1)	0	0
10-19 years	10 (5)	15 (2)	113 (4)
20-29 years	53 (29)	244 (40)	1430 (56)
30-39 years	34 (18)	179 (29)	569 (22)
40-49 years	46 (25)	113 (18)	325 (13)
50+ years	40 (22)	63 (10)	105 (4)
Median (Range)	38 (9-71)	32 (18-61)	28 (18-61)
Donor Sex			
Male	103 (56)	304 (50)	1659 (65)
Female	81 (44)	310 (50)	883 (35)
Karnofsky performance score			
10-80	92 (52)	239 (39)	1083 (43)
90-100	85 (48)	367 (61)	1431 (57)
Unknown	7 (N/A)	8 (N/A)	28 (N/A)
Graft type			
Marrow	86 (47)	111 (18)	396 (16)
PBSC	98 (53)	503 (82)	2146 (84)

Variable	**Haplo** N (%)	**7/8** N (%)	**8/8** N (%)
Conditioning regimen intensity			
Myeloablative	92 (50)	402 (65)	1506 (59)
Non-myeloablative/RIC	92 (50)	206 (34)	1027 (40)
Unknown	0	6 (1)	9 (<1)
GVHD prophylaxis			
Ex-vivo T-cell depletion	0	3 (<1)	6 (<1)
CD34 selection	0	10 (2)	32 (1)
Post-CY alone	156 (85)	29 (5)	77 (3)
TAC + MMF +- other(s) (except post-CY)	27 (15)	89 (14)	318 (13)
TAC + MTX +- other(s) (except MMF, post-CY)	1 (1)	348 (57)	1554 (61)
TAC + other(s) (except MMF, MTX, post-CY)	0	49 (8)	190 (7)
TAC alone	0	16 (3)	63 (2)
CSA + MMF +- other(s) (except post-CY)	0	24 (4)	143 (6)
CSA + MTX +- other(s) (except MMF, post-CY)	0	32 (5)	95 (4)
CSA + other(s) (except MMF, MTX, post-CY)	0	1 (<1)	7 (<1)
CSA alone	0	3 (<1)	7 (<1)
Other(s)	0	7 (1)	25 (1)
Missing	0	3 (<1)	25 (1)
DP or DQ mismatch			
Mismatch at DQB1 only	0	0	19 (1)
Mismatch at DPB1 only	0	0	2384 (94)
Mismatch at DQB1 and DPB1	0	0	139 (5)
Unknown	184 (N/A)	614 (N/A)	0 (N/A)
Year of transplant			
2010	2 (1)	91 (15)	239 (9)
2011	5 (3)	76 (12)	294 (12)
2012	4 (2)	91 (15)	304 (12)
2013	11 (6)	92 (15)	351 (14)
2014	31 (17)	93 (15)	479 (19)
2015	46 (25)	99 (16)	494 (19)
2016	59 (32)	58 (9)	308 (12)
2017	26 (14)	14 (2)	73 (3)

TO: Immunobiology Working Committee Members

FROM: Stephanie Lee, MD, MPH; Co-Scientific Director for the Immunobiology WC
Stephen Spellman, MBS; Co-Scientific Director for the Immunobiology WC

RE: Studies in Progress and Publication Summary

Studies in Progress Summary

NK/KIR

R02-40/R03-63: Choosing donors with favorable KIR B genotypes for unrelated hematopoietic cell transplantation (HCT) results in superior relapse protection and better relapse-free survival for patients with acute myeloid leukemia (AML) (J Miller) This is an ongoing study in support of Dr. Miller's NK Biology program project grant. Ongoing.

R04-74d Functional significance of killer cell immunoglobulin-like receptor genes in HLA-matched and mismatched unrelated HCT (K Hsu) This is an ongoing study in support of the IHWG KIR component led by Dr. Hsu. Ongoing.

IB15-03: Effect of Killer immunoglobulin like receptors on allogeneic HCT for pediatric acute leukemia (M Verneris/J Miller/S Cooley) The primary aim of the study is to examine the association of donor KIR genotype (A/A vs B/x) on relapse and disease free survival (DFS) in children undergoing allogeneic transplantation (allo-HCT) with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). The analysis did not show any association between KIR and relapse, DFS or the secondary endpoints in this population. This manuscript has been submitted.

IB17-02 Donor-recipient NK cell determinants associated with survival in JMML after hematopoietic stem cell transplantation (D Lee/H Rangarajan) This study will test whether determinants of NK cell function are associated with relapse and survival in patients transplanted for JMML. Data file preparation is in progress.

IB18-04 Impact of donor KIR genotype on outcome after URD TX in patients with MDS or sAML (J Schetelig/N Kröger/M Robin) This study is evaluating the role of donor KIR genotype on transplant outcome in a cohort of European patients. Donor samples were collected by the DKMS biorepository and KIR typing performed at the DKMS Life Sciences Laboratory. This is a joint analysis with the EBMT Acute Leukemia Working Party, CIBMTR and DKMS. Manuscript preparation is underway.

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 (F Otegebeye/M Fernandez-Viña/M

de Lima) The goal of this study is to determine the relationship between direction of KIR ligand mismatch and engraftment in umbilical cord and haploidentical stem cell transplant patients. Protocol development is underway.

HLA GENES

IB06-05 Use of high-resolution HLA data from the NMDP for the International Histocompatibility Working Group in HCT (E Petersdorf) This study proposes to identify novel major histocompatibility complex resident SNPs of clinical importance. This is a collaborative study with the International Histocompatibility Working Group – HCT component (IHWG). Ongoing.

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) This study was a validation analysis of the PIRCHES algorithm for identification of less immunogenic HLA mismatches in unrelated donor HCT. Manuscript preparation is underway.

IB16-02: Use of HLA structure and function parameters to understand the relationship between HLA disparity and transplant outcomes (LA Baxter-Lowe) The main objective of the study is to determine the relationship between HLA disparities ranked by their impact on T cell receptor docking, peptide binding and the combination of docking and binding. Manuscript preparation is underway.

IB18-01 Effect of HLA phenotypes on long term GVHD risk (C Story/M Riches/P Armisted) The goal of this study is to test whether the frequency of peptide binding by class I and II alleles is associated with acute GVHD or relapse. This analysis was conducted in HLA-matched related and unrelated donor pairs. Manuscript preparation is underway.

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) The goal of this study is to identify all common HLA Class I alleles that are targeted by clonal somatic loss in hematopoietic cells of SAA patients, and determine the impact of these risk alleles on clinical outcomes following HCT. Sample typing is underway.

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) The goal of this study is to examine the impact of HLA heterozygosity on survival and other clinical outcomes in patients with myeloid and lymphoid malignancies. Data analysis is in progress. Results thus far show no association with heterozygosity or expression of Bw4/HLA-C. Two associations of unclear clinical significance were seen with HLA-B supertype B62 and B27. This manuscript has been submitted.

IB19-01 The impact of ultra-high resolution HLA matching on the outcome of unrelated donor hematopoietic cell transplantation (N Mayor/S Spellman/S Marsh) This study aims to validate a UK study that demonstrated that HLA matching at an Ultra-High Resolution (UHR) for the six classical HLA loci (HLA-A, -B, -C, -DRB1, -DQB1 and -DPB1) resulted in significant survival advantages for patients undergoing predominantly T-cell depleted unrelated donor hematopoietic cell transplantation for a hematological malignancy. Data file preparation is underway.

IB19-02 Effect of class II HLA mismatching on the outcome of HLA-haploidentical hematopoietic cell transplantation with high dose, post-transplantation cyclophosphamide: a combined CIBMTR/EBMT analysis (S McCurdy/S Solomon/Y Kasamon/A Bashey/E Fuchs) The aim of this study is to examine whether mismatches in individual loci at HLA-A, -B, -C, -DRB1, -DQB1, and –DPB1 antigens or combined

class II mismatching in both HLA-DRB1 and HLA-DPB1, but not HLA-DQB1, impact clinical outcomes after HLA-haploidentical blood or marrow transplantation utilizing post-transplantation cyclophosphamide. Data file preparation is underway.

CYTOKINE/CHEMOKINE

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) The primary objective of the study is to evaluate the plasma CXCL4 and CXCL7 chemokine levels in patients undergoing transplantation for MDS in comparison to those with other conditions. Although levels of CXCL4 and CXCL7 were lower in MDS compared to normal donors, results did not show an association of CXC chemokine-related variables and transplant outcomes. This manuscript has been submitted.

IB14-03c Effect of telomere length in MDS patients without TP53/RASTK/JAK2 mutations (RC Lindsley/W Saber) The goal of this study is to evaluate the impact of recipient telomere length on clinical outcomes based on treatment intensity in patients with MDS receiving HCT. Manuscript preparation is underway.

OTHER GENES

IB09-05 Identification of functional single nucleotide polymorphisms (SNPs) in umbilical cord blood transplant (E Petersdorf) The primary hypothesis of the study is that umbilical cord blood units and recipients differ for genome-wide single nucleotide polymorphism and gene copy number variation and that these differences may define putative transplant outcome determinants. This is a collaborative study with IHWG. Ongoing.

IB09-06/RT09-04: Genetic susceptibility to transplant-related mortality after matched unrelated stem cell transplant (T Hahn) This is a joint study with the Regimen Related Toxicity working committee and is supported by an R01 grant to Drs. Hahn and Sucheston-Campbell. This study will test for a genetic association with transplant-related and overall mortality in recipients of myeloablative and reduced intensity conditioning matched unrelated donor HCT. Multiple manuscripts are in progress. Ongoing.

IB09-07: Clinical significance of genome-wide variation in unrelated donor hematopoietic stem cell transplantation (HCT) (E Petersdorf) This study is designed to assess the impact of genome-wide variation between donors and recepients in HLA matched unrelated donor HCT. This is a collaborative study with the IHWG. Ongoing.

IB10-01c Telomere length telomerase polymorphism in Severe Aplastic Anemia - Exome Analysis and Mosaicism (S Gadalla/S Savage) Two SNPs in the HMC region were associated with increased incidence of SAA. This manuscript was accepted by the British Journal of Haematology.

IB10-01f Epigenetic clock: Can this guide donor selection in HCT (S Gadalla/S Savage) The goal of this study is to evaluate the association between pre-HCT donor methylation age and post-transplant outcomes in patients receiving unrelated donor HCT for SAA. Manuscript preparation is underway.

IB10-01i Genome-wide association study identified HLA-DPB1 as significant risk factor for severe aplastic anemia (S Savage/S Gadalla) The aim of this GWAS study was to evaluate the contribution of germline SNPs to the etiology of severe aplastic anemia. Overall, SNPs in the HLA class II gene *HLA-DPB1* and

possibly class I (*HLA-B*) are associated with SAA. This manuscript has been accepted by Biology of Blood and Marrow Transplantation.

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) The goal of this study is to measure T cell alloreactivity following hematopoietic stem cell transplantation by examining cases where transplant recipients have the same HLA single, double or multiple HLA mismatch, to see if they develop similar alloreactivity. Control transplant recipients with the same HLA type who did not receive an HLA-mismatched transplant will be also analyzed. The number of samples was very limited and results were not conclusive. This manuscript has been accepted by Biology of Blood and Marrow Transplantation.

IB14-05: mtDNA haplotypes and unrelated donor transplant outcomes (M Verneris/L Spector) The goal of this study is to test whether patient or donor mitochondrial haplotypes predict outcomes of unrelated donor transplantation, particularly GVHD, relapse and survival. The study is supported by an R01 grant to Drs. Verneris and Spector. Manuscript preparation is underway.

IB16-03: Role of recipient and donor genetic polymorphisms in interferon lambda 4 (INFL4) on outcomes after unrelated allogeneic cell transplant (S Gadalla/L Prokunina-Olsson) 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 dG homozygous and heterozygous patients had higher TRM than the homozygous TT patients. Grade II-IV and III-IV acute GVHD were not different. Results are being compared with a cohort from Fred Hutchinson and DISCOVeRY-BMT. This manuscript has been submitted.

IB17-03 Identification of genomic markers of post hematopoietic cell transplantation (HCT) outcomes in patients with myelofibrosis: A pilot study (W Saber/ S Gadalla) The goal of this study is to describe mutations associated with MF, and to correlate these abnormalities with clinical outcomes. Samples have been analyzed and data file preparation is underway.

IB17-04 Epigenetic profiling of unrelated donor-recipient pairs to improve donor selection during HCT transplants (S Beck/K Peggs/V Rakyan/A Webster) The goal of this study is to determine whether donor specific epigenetic patterns associate with risk of acute GVHD III-IV and, if so, develop an epigenetic profile based donor selection algorithm. Sample analysis is underway. A preliminary signature has been identified and a replication cohort is being analyzed.

IB18-06 Clonal mosaicism and HCT outcomes in patients with acute leukemia and myelodysplastic syndromes (S Gadalla/T Hahn/L Sucheston-Campbell) This study aimed to use a high-resolution genome-wide single-nucleotide polymorphism (SNP) array to identify and determine the impact of large clonal chromosomal aberrations in pre-hematopoietic cell transplant (HCT) peripheral blood samples of patients with *de novo* or therapy-related AML and MDS. Manuscript preparation is underway.

IB18-07 Donor and recipient genomic associations with acute GVHD (V Afshar-Khargan) The goal of this R01-funded study is to determine the genetic risk factors of GVHD. The preliminary cohort has been identified and sample typing is underway.

SENSITATION AND TOLERANCE

IB19-04 Impact of donor HLA on transplant outcomes in NPM1 mutated AML (R Narayan/E Meyer/Y Chen) The aim of this study is to evaluate the impact of donor HLA haplotype on disease outcomes including relapse free survival and overall survival in patients with NPM1 mutated AML undergoing matched related or matched unrelated allogeneic transplantation. Protocol development is underway.

Publication Summary – Published manuscripts

IB06-05b Role of HLA-B exon 1 in graft-versus-host disease after unrelated haemopoietic cell transplantation: A retrospective cohort study. Petersdorf EW, Carrington M, O'hUigin C, Bengtsson M, De Santis D, Dubois V, Gooley T, Horowitz M, Hsu K, Madrigal JA, Maiers MJ, Malkki M, McKallor C, Morishima Y, Oudshoorn M, Spellman SR, Villard J, Stevenson P. ***Lancet Haematology*. doi:10.1016/S2352-3026(19)30208-X. Epub 2019 Oct 25.** A sequence dimorphism in exon 1 of HLA-B gives rise to leader peptides containing methionine or threonine, which differentially influence natural killer and T-cell alloresponses. The main aim of this study was to evaluate the role of the leader dimorphism in GVHD after HLA-B mismatched unrelated HCT. The results show the HLA-B leader informs GVHD risk after HLA-B mismatched unrelated HCT and differentiates high-risk HLA-B mismatches from those with lower risk.

IB09-06s Tang H, Hahn T, Karaesmen E, Rizvi AA, Wang J, Paczesny S, Wang T, Preus L, Zhu Q, Wang Y, Haiman CA, Stram D, Pooler L, Sheng X, Van Den Berg D, Brock G, Webb A, Pasquini MC, McCarthy PL, Spellman SR, Sucheston-Campbell LE. Validation of genetic associations with acute GVHD and non-relapse mortality in DISCOVeRY-BMT. ***Blood Advances.* 2019 Aug 13; 3(15):2337-2341. doi:10.1182/bloodadvances.2019000052. Epub 2019 Aug 7. PMC6693017.** This study attempted to validate previously reported SNP associations with acute GVHD and non-relapse mortality using the DISCOVeRY-BMT cohort. Results showed the 25 SNPs were not associated with either acute GVHD or non-relapse mortality for the unrelated donor-recipient pairs. It was suggested that the inability to validate the univariate associations or find SNPs predictive of either acute GVHD or non-relapse mortality may have been driven by the differences in transplantation type, distribution of disease, genomic ancestry, and/or event rates between the two cohorts.

IB10-01h Pre-transplant short telomeres are associated with high mortality risk after unrelated donor haematopoietic cell transplant for severe aplastic anaemia. Wang Y, McReynolds LJ, Dagnall C, Katki HA, Spellman SR, Wang T, Hicks B, Freedman ND, Jones K, Lee SJ, Savage SA, Gadalla SM. ***British Journal of Haematology.* doi:10.1111/ bjh.16153. Epub 2019 Aug 19. T**elomeres are essential for chromosomal stability and markers of biological age. This study evaluated the effect of pre-transplant short (<10th percentile-for-age) or very short (<5th or <1st percentile-for-age) leucocyte telomere length on survival after unrelated donor haematopoietic cell transplantation (HCT) for acquired severe aplastic anaemia . Results show relative telomere length <10th percentile-for-age was associated with higher risk of post-HCT mortality. Time dependent effects for post-HCT mortality were only observed in relation to very short relative telomere length. This study suggests a potential role for telomere length in risk stratification of SAA patients in regard to their HCT survival.

IB15-04 Molecular correlates of socioeconomic status and clinical outcomes following hematopoietic cell transplantation for leukemia. Knight JM, Rizzo JD, Wang T, He N, Logan BR, Spellman SR, Lee SJ, Verneris MR, Arevalo JMG, Cole SW. ***JNCI Cancer Spectrum.* 2019 Dec 1; 3(4):pkz073.**

doi:10.1093/jncics/pkz073. Epub 2019 Sep 12. PMC6859844. The primary hypothesis of the study is that increased expression of the conserved transcriptional response to adversity (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.

IB15-07 Multiple functional variants in the IL1RL1 region are pretransplant markers for risk of GVHD and infection deaths. Karaesmen E, Hahn T, Dile AJ, Rizvi AA, Wang J, Wang T, Haagenson MD, Preus L, Zhu Q, Liu Q, Yan L, Liu S, Haiman CA, Stram D, Pooler L, Sheng X, Van Den Berg D, Brock G, Webb A, McCarthy PL, Pasquini MC, Spellman SR, Lee SJ, Paczesny S, Sucheston-Campbell LE. ***Blood Advances.*** **2019 Aug 27; 3(16):2512-2524. doi:10.1182/bloodadvances.2019000075. Epub 2019 Aug 27. PMC6712530.** The serum biomarker sST2 is associated with an increased risk for therapy-resistant GVHD and death. The primary hypothesis is that similar to the heritability of sST2 in the Framingham Offspring Cohort explaining sST2 as a predictor of cardiovascular risk, the 16 SNPs most associated with sST2 will determine which donor /recipient pair is at risk of developing acute graft-versus-host disease (aGVHD) and transplant-related mortality (TRM) following allogeneic hematopoietic cell transplantation in a well-controlled cohort. The study used the GWAS typing results and dataset from the DISCOVERY-BMT (IB09-06/RT09-04) cohort to evaluate the association of 16 sST2 SNPs. Results showed that ST2 SNPs correlated with sST2 levels but ST2 SNPs did not strongly correlate with GVHD.

IB16-01 Donor HLA-E status associates with disease free survival and transplant related mortality after non in vivo T-cell depleted HSCT for acute leukemia. Tsamadou C, Fürst D, Wang T, He N, Lee SJ, Spellman SR, Fleischhauer K, Hsu KC, Paczesny S, Verneris MR, Schrezenmeier H, Mytilineos J. ***Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation.*** **doi:10.1016/j.bbmt.2019.08.007. Epub 2019 Aug 16.** Previous studies have suggested that HLA-E may have a significant role in the outcome of matched unrelated hematopoietic stem cell transplantation (HSCT), especially for patients with acute leukemia. We used samples of 1840 adult patients with acute leukemia and their 10/10 HLA-matched unrelated donors to investigate the impact of HLA-E matching status as well as of donor/recipient (D/R) HLA-E genotype on post-HSCT outcome. D/R HLA-E genotype analysis revealed a significant association of donor HLA-E*01:03/01:03 genotype with improvement of disease-free survival and transplant related mortality in patients who received T cell replete transplants.

Publication Summary – Submitted and in press manuscripts – see above for description of results

IB10-01c Telomere length telomerase polymorphism in Severe Aplastic Anemia - Exome Analysis and Mosaicism. (S Gadalla/S Savage) **In press. British Journal of Haematology**

IB10-01i Genome-wide association study identified HLA-DPB1 as significant risk factor for severe aplastic anemia (S Savage/S Gadalla) **In press. Biology of Blood and Marrow Transplantation**

R02-40/R03-63d KIR B donors improve the outcome for AML patients given reduced intensity conditioning and unrelated donor transplant (J Miller) **In press. Blood Advances**

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) **In press. Biology of Blood and Marrow Transplantation**

IB09-06b/RT09-04b Genetic susceptibility to transplant-related mortality after unrelated donor stem cell transplant (T Hahn/L Sucheston-Campbell) **Submitted**

IB09-06m DISCOVeRY-BMT: Compare unrelated donor to Welcome Trust Case Control Consortium controls (K Onel/A Clay-Gilmour/E Karaesmen) **Submitted.**

IB09-06p DISCOVeRY-BMT: Genetics and epidemiology of Myeloid Malignancies genome-wide association (A Clay-Gilmour/K Onel/T Hahn) **Submitted.**

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) **Submitted.**

IB15-03 Killer Immunoglobulin Receptor (KIR) gene content and pediatric acute leukemia transplant outcomes (MR Verneris/J Miller/S Cooley) **Submitted.**

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

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) **Submitted.**