A G E N D A
CIBMTR IMMUNOBIOLOGY WORKING COMMITTEE
Salt Lake City, Utah
Sunday, April 24, 2022, 12:15 pm – 1:45 pm

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Agenda Summary

- Introduction and overview of progress 12:15
- Presentation of new proposals 12:20-13:10
  - PROP2110-141
  - PROP2110-149
  - PROP2108-03; 2110-178; 2110-207; 2110-222; 2110-48; 2110-92
- Presentation of updates for completed/ongoing studies 13:10-13:40
  - IB19-02, IB18-04b, IB17-03
- Concluding remarks 13:40

Detailed Agenda

1. Introduction 12:15pm

a. Minutes from February 2021 TCT Working Committee Session (Attachment 1)

2. Published and submitted papers (21) in the last year 12:20pm

a. **IB09-06p** Genome-wide association analyses identify variants in IRF4 associated with acute myeloid leukemia and myelodysplastic syndrome susceptibility. Wang J, Clay-Gilmour AI, Karaesmen E, Rizvi A, Zhu Q, Yan L, Preus L, Liu S, Wang Y, Griffiths E, Stram DO, Pooler L, Sheng X, Haiman C, Van Den Berg D, Webb A, Brock G, Spellman S, Pasquini M, McCarthy P, Allan J, Stölzel F, Onel K, Hahn T, Sucheston-Campbell LE. ***Frontiers in Genetics. 12:554948. doi:10.3389/fgene.2021.554948. Epub 2021 Jun 17. PMC8248805.***

b. **IB09-06t** Novel genetic variants associated with mortality after unrelated donor allogeneic hematopoietic cell transplantation. Hahn T, Wang J, Preus LM, Karaesmen E, Rizvi A, Clay-Gilmour AI, Zhu Q, Wang Y, Yan L, Liu S, Stram DO, Pooler L, Sheng X, Haiman CA, Berg DVD, Webb A, Brock G, Spellman SR, Onel K, McCarthy PL, Pasquini MC, Sucheston-Campbell LE. ***EClinicalMedicine. 40:101093. doi:10.1016/j.eclinm.2021.101093. Epub 2021 Aug 24. PMC8548922.***

c. **IB10-01f** Epigenetic aging and hematopoietic cell transplantation in patients with severe aplastic anemia. Alsaggaf R, Katta S, Wang T, Hicks BD, Zhu B, Spellman SR, Lee SJ, Horvath S, Gadalla SM. ***Transplantation and Cellular Therapy. 2021 Apr 1; 27(4):313.e1-313.e8. doi:10.1016/j.jtct.2021.01.013. Epub 2021 Jan 16. PMC8036238.***

d. **IB10-01k** DNA-methylation-based telomere length estimator: Comparisons with measurements from flow FISH and qPCR. Pearce EE, Horvath S, Katta S, Dagnall C, Aubert G, Hicks BD, Spellman SR, Katki H, Savage SA, Alsaggaf R, Gadalla SM. ***Aging (Albany NY). 13(11):14675-14686. doi:10.18632/aging.203126. Epub 2021 Jun 3. PMC8221337.***

e. **IB14-03d** The clinical and functional effects of TERT variants in myelodysplastic syndrome. Reilly CR, Myllymäki M, Redd R, Padmanaban S, Karunakaran D, Tesmer V, Tsai FD, Gibson CJ, Rana HQ, Zhong L, Saber W, Spellman SR, Hu ZH, Orr EH, Chen MM, De Vivo I, DeAngelo DJ, Cutler C, Antin JH, Neuberg D, Garber JE, Nandakumar J, Agarwal S, Lindsley RC. ***Blood. 2021 Sep 9; 138(10):898-911. doi:10.1182/blood.2021011075. Epub 2021 May 21. PMC8432045.***

f. **IB14-05** Neither donor nor recipient mitochondrial haplotypes are associated with unrelated donor transplant outcomes: A validation study from the CIBMTR. Spector LG, Spellman SR, Thyagarajan B, Beckman KB, Hoffmann C, Garbe J, Hahn T, Sucheston-Campbell L, Richardson M, De For TE, Tolar J, Verneris MR. ***Transplantation and Cellular Therapy. 2021 Oct 1; 27(10):836.e1-836.e7. doi:10.1016/j.jtct.2021.06.019. Epub 2021 Jun 23. PMC8478819.***

g. **IB17-02** Donor killer immunoglobulin receptor gene content and ligand matching and outcomes of pediatric patients with juvenile myelomonocytic leukemia following unrelated donor transplantation. Rangarajan HG, Pereira MSF, Brazauskas R, St Martin A, Kussman A, Elmas E, Verneris MR, Gadalla SM, Marsh SGE, Paczesny S, Spellman SR, Lee SJ, Lee DA. ***Transplantation and Cellular Therapy. 2021 Nov 1; 27(11):926.e1-926.e10. doi:10.1016/j.jtct.2021.08.009. Epub 2021 Aug 15. PMC8574163.***

h. **IB18-01** Genetics of HLA peptide presentation and impact on outcomes in HLA-matched allogeneic hematopoietic cell transplantation. Story CM, Wang T, Bhatt VR, Battiwalla M, Badawy SM, Kamoun M, Gragert L, Brown V, Baxter-Lowe LA, Marsh SGE, Gadalla SM, Schetelig J, Mytilineos J, Miklos D, Waller EK, Kuxhausen M, Spellman S, Lee S, Paczesny S, Lansford JL, Vincent BG, Riches ML, Armistead PM. ***Transplantation and Cellular Therapy. 2021 Jul 1; 27(7):591-599. doi:10.1016/j.jtct.2021.04.003. Epub 2021 Apr 18. PMC8343993.***

i. **IB18-04a** Haplotype motif-based models for KIR-genotype informed selection of hematopoietic cell donors fail to predict outcome of patients with myelodysplastic syndromes or secondary acute myeloid leukemia. Schetelig J, Baldauf H, Koster L, Kuxhausen M, Heidenreich F, de Wreede LC, Spellman S, van Gelder M, Bruno B, Onida F, Lange V, Massalski C, Potter V, Ljungman P, Schaap N, Hayden P, Lee SJ, Kröger N, Hsu K, Schmidt AH, Yakoub-Agha I, Robin M. ***Frontiers in Immunology. 11:584520. doi:10.3389/fimmu.2020.584520. Epub 2021 Dec 21. PMC7851088.***

j. **IB18-06a** Pre-HCT mosaicism increases relapse risk and lowers survival in acute lymphoblastic leukemia patients post-unrelated HCT. Wang Y, Zhou W, Wang J, Karaesmen E, Tang H, McCarthy PL, Pasquini MC, Wang Y, McReynolds LJ, Katki HA, Machiela MJ, Yeager M, Pooler L, Sheng X, Haiman CA, Van Den Berg D, Spellman SR, Wang T, Kuxhausen M, Chanock SJ, Lee SJ, Clay-Gilmour AI, Hahn TE, Gadalla SM, Sucheston-Campbell LE. ***Blood Advances. 2021 Jan 12; 5(1):66-70. doi:10.1182/bloodadvances.2020003366. Epub 2021 Jan 5. PMC7805319.***

k. **IB18-06b** Prognostic impact of pre-transplant chromosomal aberrations in peripheral blood of patients undergoing unrelated donor hematopoietic cell transplant for acute myeloid leukemia. Wang Y, Zhou W, McReynolds LJ, Katki HA, Griffiths EA, Thota S, Machiela MJ, Yeager M, McCarthy P, Pasquini M, Wang J, Karaesmen E, Rizvi A, Preus L, Tang H, Wang Y, Pooler L, Sheng X, Haiman CA, Van Den Berg D, Spellman SR, Wang T, Kuxhausen M, Chanock SJ, Lee SJ, Hahn TE, Sucheston-Campbell LE, Gadalla SM. ***Scientific Reports. 11(1):15004. doi:10.1038/s41598-021-94539-0. Epub 2021 Jul 22. PMC8298542.***

l. **IB19-01a** Impact of previously unrecognized HLA mismatches using ultrahigh resolution typing in unrelated donor hematopoietic cell transplantation. Mayor NP, Wang T, Lee SJ, Kuxhausen M, Vierra-Green C, Barker DJ, Auletta J, Bhatt VR, Gadalla SM, Gragert L, Inamoto Y, Morris GP, Paczesny S, Reshef R, Ringdén O, Shaw BE, Shaw P, Spellman SR, Marsh SGE**. *Journal of Clinical Oncology. 2021 Jul 20; 39(21):2397-2409. doi:10.1200/JCO.20.03643. Epub 2021 Apr 9. PMC8280068.***

m. **IB19-02** HLA informs risk predictions after haploidentical stem cell transplantation with post-transplantation cyclophosphamide. Fuchs EJ, McCurdy SR, Solomon SR, Wang T, Herr MM, Modi D, Grunwald MR, Nishihori T, Kuxhausen M, Fingerson S, McKallor C, Bashey A, Kasamon YL, Bolon Y-T, Saad A, McGuirk JP, Paczesny S, Gadalla SM, Marsh SG, Shaw BE, Spellman SR, Lee SJ, Petersdorf EW. ***Blood. doi:10.1182/blood.2021013443. Epub 2021 Nov 1. update to be presented at 13:10 pm***

n. **IB20-02** Number of HLA mismatched eplets is not associated with major outcomes in haploidentical transplantation with post-transplantation cyclophosphamide: A Center for International Blood and Marrow Transplant Research Study. Zou J, Wang T, He M, Bolon YT, Gadalla SM, Marsh SGE, Kuxhausen M, Gale RP, Sharma A, Assal A, Prestidge T, Aljurf M, Cerny J, Paczesny S, Spellman SR, Lee SJ, Ciurea SO. ***Transplantation and Cellular Therapy. doi:10.1016/j.jtct.2021.11.001. Epub 2021 Nov 11.***

o. **R02-40/R03-63i** Following transplantation for acute myelogenous leukemia, donor KIR Cen B02 better protects against relapse than KIR Cen B01. Guethlein LA, Beyzaie N, Nemat-Gorgani N, Wang T, Ramesh V, Marin WM, Hollenbach JA, Schetelig J, Spellman SR, Marsh SGE, Cooley S, Weisdorf D, Norman PJ, Miller JS, Parham P. ***Journal of Immunology. 2021 Jun 15; 206(12):3064-3072. doi:10.4049/jimmunol.2100119. Epub 2021 Jun 11. PMC8664929.***

p. **IB19-03** Natural killer cell alloreactivity predicted by killer cell immunoglobulin-like receptor ligand mismatch does not impact engraftment in umbilical cord blood and haploidentical stem cell transplantation. Otegbeye F, Fernandez-Viña A, Wang T, Bolon Y, Lazaryan A, Beitinjaneh A, Bhatt V, Castillo P, Marsh S, Hildebrandt G, Assal A, Brown V, Hsu J, Spellman S, de Lima M, Lee S. ***Submitted.***

q. **IB17-03** Germline-somatic interactions drive JAK2-mediated clonal expansion in myelofibrosis. Brown D, Zhou W, Wang Y, Jones K, Lou W, Dagnall C, Teshome K, Klein A, Zhang T, Lin, S, Lee O, Khan S, Vo J, Hutchinson A, Liu J, Zhu B, Hicks B, St. Martin A, Spellman S, Wang T, Deeg T, Lee S, Freedman N, Yeager M, Chanock S, Savage S, Saber W, Gadalla S, Machiela M. ***Submitted.*** ***update to be presented at 13:30 pm***

r. **IB10-01x** Unrecognized Inherited Disorders Have Inferior Survival after Hematopoietic Cell Transplant for Aplastic Anemia. McReynolds L, Rafati M, Wang Y, Ballew B, Kim J, Williams V, Dagnall C, Freedman N, Carter B, Strollo S, Hicks B, Zhu B, Jones K, Paczesny S, Marsh S, Spellman S, He M, Wang T, Lee S, Savage S, Gadalla S. ***Submitted.***

s. **IB17-04** Donor whole blood DNA methylation is not a strong predictor of acute graft versus host disease in unrelated donor allogeneic haematopoietic cell transplantation. Webster A, Ecker S, Moghul I, Dhami P, Marzi S, Paul D, Feber A, Kuxhausen M, Lee S, Spellman S, Wang T, Rakyan V, Peggs K, Beck S. ***Submitted.***

t. **IB 19-01b** A core group of structurally similar HLA-DPB1 alleles drives permissiveness after hematopoietic cell transplantation. Arrieta-Bolaños E, Crivello P, He M, Wang T, Gadalla S, Paczesny S, Marsh S, Lee S, Spellman S, Bolon Y, Fleischhauer K. ***Submitted.***

u. **IB20-04** Haploidentical versus matched unrelated donor transplants using post-transplant cyclophosphamide for lymphomas. Mussetti A, Kanate A, Wang T, He M, Hamadani M, FINEL H, Boumendil A, Glass B, Castagna L, Dominietto A, McGuirk J, Blaise D, Gülbas Z, Diez-Martin J, Marsh S, Paczesny S, Gadalla S, Dreger P, Zhang M, Spellman S, Lee S, Bolon Y, Sureda A. ***Submitted.***

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

4. Future/proposed studies and discussion 12:20pm-13:10

a. Voting guidelines

b. **Proposal presentations (3)**

i. **PROP2110-141** Effect of SIRPα mismatch on the outcome of allogeneic hematopoietic stem cell transplantation (HSCT) from an HLA matched related donor (MRD). (Jun Zou; Samer Srour) (Attachment 3)

ii. **PROP2110-149** Characterization of Permissible HLA Allele Mismatches and their impact in Hematopoietic Stem Cell Transplantation with Unrelated Donors (Alice Bertaina; Marcelo Fernandez Vina) (Attachment 4)

iii. **PROP2108-03; 2110-178; 2110-207; 2110-222; 2110-48; 2110-92** Impact of HLA-DPB1 matching on clinical outcomes following unrelated donor transplantation using post-transplant cyclophosphamide as graft-versus-host disease prophylaxis for patients with hematologic malignancies. (Blouin, Amanda; Fuchs, Ephraim; Ibrahim, Uroosa; Keyzner, Alla; McCurdy, Shannon R; Nakhle, Saba;

Perales, Miguel-Angel; Petersdorf, Effie W; Safah, Hana; Shaffer, Brian C; Socola, Francisco A; Solomon, Scott R; Zou, Jun) (Attachment 5)

c. **Dropped Proposals (9)**

i. **PROP2101-01** Donor-Recipient Human Leukocyte Antigen Evolutionary Divergence After HLA Mismatched Unrelated or Related Donor Allogeneic Hematopoietic Cell Transplantation (Brian C Shaffer; Christine Camacho-Bydume; Katharine C. Hsu) – *Await results of ongoing study first*

ii. **PROP2103-02** Clinical relevance of alloreactive antigens and their HLA restriction post allogenic stem cell transplant (allo-SCT) for Acute Myeloid Leukaemia (AML) (Paresh Vyas; Charles Craddock) – *Move to corporate program*

iii. **PROP2107-01** Impact of donor-recipient HLA evolutionary divergence on outcomes of bone marrow transplant from unrelated donors in patients with idiopathic aplastic anemia (Simona Pagliuca; Shahinaz Gadalla; Nelli Bejanyan; Jaroslaw Maciejeweski) – *Will be done by NIH group using already collected data*

iv. **PROP2109-20** Effect of Recipient HLA-C-group KIR Ligand and HLA-B-leader Allotype on Relapse Risk and Disease-Free Survival Following Haploidentical Donor Transplantation (HIDT) with Post Transplant Cyclophosphamide (PTCy) for Adults with Hematologic Malignancies. (Scott Solomon) – *Overlap with current study/Publication*

v. **PROP2110-08** The impact of inherited and non-inherited maternal (IMA/NIMA) and paternal (IPA/NIPA) antigens on outcomes after haploidentical hematopoietic cell transplantation (HCT) with post-transplantation cyclophosphamide (PTCy)-based graft-versus-host-disease (GVHD) prophylaxis. (Rohtesh S. Mehta; Daniel Weisdorf) – *Supplemental data needed*

vi. **PROP2110-139** The dynamics of NLRP3 inflammasome activation following conditioning for allogeneic hematopoietic stem cell transplant: a predictor of risk for acute graft versus host disease. (Jignesh Dalal; Maria Pereda) - *Small sample size*

vii. **PROP2110-254** Optimal Selection of Unrelated Donor for Hematopoietic Cell Transplantation: HLA-A, B, C, DRB1 allele match or donor age (Eric Tam; George Yaghmour) – *Overlap with current study/Publication*

viii. **PROP2110-328** Impact of Previously Unrecognized HLA Mismatches Using Ultrahigh Resolution Typing and Bioinformatic Approaches for Determining The Association Between Individual SNPs and Clinical Outcomes Of Unrelated Donor Hematopoietic Cell Transplantation (Medhat Askar; Dimitrios Monos) – *Overlap with current study/Publication*

ix. **PROP2110-89** Donor-Recipient HLA matching: Factors that contribute to outcomes in unrelated donor stem cell transplantation (Christine Ho; Megan Herr) – *Lower scientific priority*

5. Studies in Progress (Attachment 6)

NK/KIR

a. **IB18-04b** Evaluation of the impact of donor killer immunoglobulin receptor genotype on outcome after unrelated donor transplantation in patients with myelodysplastic syndromes or acute myeloid leukemia. (J Schetelig/N Kröger/M Robin) **Analysis-<u>Update to be presented 13:20</u>**

HLA GENES – CLASSICAL MATCHING

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

b. **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) **Manuscript Preparation**

c. **IB20-01** Association of immunopeptidome divergence between mismatched human leukocyte antigen class I alleles and outcome of 9/10 matched unrelated hematopoietic stem cell transplant. (Pietro Crivello/Esteban Arrieta-Bolanos/Katharina Fleischhauer) **Manuscript Preparation.**

d. **IB21-01** Effect of HLA evolutionary divergence on survival and relapse following allogeneic hematopoietic cell transplant (Christine Camacho-Bydume/Diego Chowell/ Katharine C. Hsu) **Data File Preparation**

SENSITIZATION AND TOLERANCE

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

Other Genes

a. **IB18-07** Donor and recipient genomic associations with acute GVHD (V Afshar-Khargan) **Analysis.**

b. **IB20-03** Donor socioeconomic status as a predictor of altered immune function and treatment response following hematopoietic cell transplantation for hematologic malignancy (Jennifer Knight) **Analysis.**

ONGOING AND OTHER-FUNDED STUDIES

a. **R04-74d** Functional significance of killer cell immunoglobulin-like receptor genes in human leukocyte antigen matched and mismatched unrelated hematopoietic stem cell transplantation. (K Hsu) **Ongoing.**

b. **IB06-05** Use of high-resolution human leukocyte antigen data from the National Marrow Donor Program for the international histocompatibility working group in hematopoietic stem cell transplantation. (E Petersdorf) **Ongoing.**

c. **IB09-01/IB09-03/IB09-05/IB09-07** Clinical importance of minor histocompatibility complex haplotypes in umbilical cord blood transplantation. (E Petersdorf) **Ongoing.**

d. **IB21-02** DISCOVeRY-BMT: Multi-ethnic high-throughput study to identify novel non-HLA genetic contributors to mortality after blood and marrow transplantation. (There/Alyssa Clay-Gilmour) **Ongoing.**

6. Study Presentations 13:10-13:40 PM

a. **IB19-02**
b. **IB18-04b**
c. **IB17-03**

7. Closing Remarks 13:40 PM

MINUTES
CIBMTR WORKING COMMITTEE SESSION
Thursday, February 11, 2021, 1:00 - 4:00 pm
Co-Chair: Bronwen Shaw, MD, PhD; CIBMTR Statistical Center, Milwaukee, WI; E-mail: beshaw@mcw.edu
Co-Chair: John Wingard, MD; University of Florida, Gainesville, FL; E-mail: wingajr@ufl.edu

INTRODUCTION:

Dr. Wingard opened the virtual meeting at 1:00 pm by welcoming the working committee members and the presenters. He discussed the proposal selection and voting process. Though the pandemic amended the process for proposal selection, 368 working committee proposals were submitted and evaluated altogether by CIBMTR Working Committee Chairs and Scientific Directors. About 61% were screened out, 30% had less-relative scientific merit, and 3% were combined with overlapping proposals with relevant nature. 21 proposals (about 6%), were considered for advancing of further pro-development. The proposals were pre-recorded 5-minutes presentations of the 15 semi-finalists, which were presented by the principal investigators. Each presentation was followed by a 5-minute question and answer session, in which audience was invited to submit questions via live chat. For those not able to attend the live session, a link was posted with the session recording and voting was closed on Monday, February 15, 2021. Audience was also instructed on where to locate the scoring and voting links for the presentations. It was mentioned that over 1,000 Working Committee members voted on the first screening of these proposals. Dr. Shaw led the second part of the meeting starting with presentation #9.

GENERAL REMINDERS:

The following reminders were mentioned and posted via the chat option:

a. Thank you for participating in the CIBMTR Working Committee Session! Please cast your score here: https://mcwisc.co1.qualtrics.com/jfe/form/SV_7QwO1ZvzfPZV1NY to vote on the proposals that were presented during the session.
b. Several presenters provided their email addresses for any future communication.

PRESENTATIONS:

1. **Risk of subsequent neoplasms in patients with post-transplant cyclophosphamide use for graft-versus-host disease prophylaxis.** This proposal was presented by Dr. Ana Alarcon Tomas. The primary objective of this proposal is to describe the incidence rate, risk factors, characteristics, and outcomes of subsequent neoplasms in patients receiving post-transplant cyclophosphamide (PTCy) and compare it with calcineurin inhibitors-based graft-versus-host disease prophylaxis and the general population. The CIBMTR identified 64,935 patients ≥18 years of age who underwent a first allogeneic for a malignant disease between 2008-2017. 5,771 (9%) of these patients developed a subsequent neoplasm. Currently, there are no published studies on the incidence of subsequent neoplasms in patients who received post-transplant cyclophosphamide. The following questions were answered during the Q&A:
    a. How are we going to prove that these secondary neoplasms are related to post-transplant cyclophosphamide or cyclophosphamide in conditioning and not due to "by chance" itself- as in general population? This is a case-controlled study. For example, for each patient received with a post-transplant cyclophosphamide will be matched with at least three patients who didn't receive post-transplant cyclophosphamide. Characteristics including primary disease, HLA complexity, survival, follow up time etc. would be used for matching and reviewing survival will also allow us to see that this is because of PTCy and not by coincidence.

b. What is the median follow up time from transplant and subsequent malignancy in post-transplant cyclophosphamide group? I assume it is much shorter than other cohort? Information is not available for each median follow up time cohort. What is available is the median follow up for all patients and some numbers related to the type of diseases for each group. Dr. Rachel Phelan included in the chat that the median follow-up for the PT-Cy group is 38.2 months, and for the proposed control population is 60.3 months.
c. How is this in comparison with matched unrelated donor and cord transplants? Cord transplants will be excluded from the analysis because we don't think we can match those patients.
d. Do we have adequate follow up to answer this important question? We have follow-up for mantle hematological diseases but less time for solid tumors. However, when we saw the numbers that we have (around 5,000 - 5,700) subsequent neoplasms, the majority of cases occurred after the 1st - 5th year of post- transplant and have a 5-year median follow up. We think we have enough numbers to address this question now and we should not wait because it hasn't been published before. This is a noble study and if we wait for a longer median follow up, we might lose that opportunity to have it published first.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix A.

2. **Outcomes of chimeric antigen receptor-T cell therapy for patients with antecedent chronic lymphocytic leukemia (Richter's Syndrome)**. This proposal was presented by Dr. Farrukh Awan. The objective of this proposal is to assess outcomes in adult patients with chronic lymphocytic leukemia undergoing transformation to diffuse large B-cell lymphoma (Richter's Syndrome) and undergoing CAR-T therapy. The CIBMTR identified 36 patients underwent CAR-T for Richter's Syndrome from 2015-2019. The following questions were answered during the Q&A:
   a. I know that in the Ohio State paper have many patients that used concurrent Bruton Tyrosine Kinase (BTK) inhibitors. Will you be able to collect data on concurrent BTK inhibitors for these patients? Yes, this information is available through the CIBMTR dataset.
   b. Are you looking at diffuse large B-cell lymphoma derived Richter's Syndrome or chronic lymphocytic leukemia derived Richter's Syndrome? Yes, but it is difficult to determine a clonality between related and unrelated Richter's syndrome. Any studies that show similarities versus dissimilarities in the clone would be very helpful but unfortunately, previous studies have shown that this has been consistently difficult.
   c. You mentioned the opportunity of comparing to other treatment groups. Can you talk about that a little more? We can compare to patients with de novo diffuse large B-cell lymphoma. There are multiple approved and ongoing studies within CIBMTR of diffuse large B-cell lymphoma patients, who do undergo CAR-T therapy and look at toxicity outcomes and infectious outcomes, for example. There are efforts in place to look at outcomes of transplantation for patients with Richter's Syndrome, which can improve the impact of this project and be a competitor to those other ongoing studies.
   d. How many pts do we have? 36 patients
   e. How do you plan to deal with the very low patient numbers (n=36) to make meaningful conclusion? I agree that it is a small number, but it is substantial. Despite the small numbers, if the right competitors are used, such as those mentioned previously, this study can still provide an impactful dataset.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix B.

3. **Impact of graft versus host disease following allogeneic hematopoietic cell transplantation on leukemia free survival in hematologic malignancies**. This proposal was presented by Dr. Andrea Bauchat. The objectives of this proposal is to determine the impact of development of grade I-II acute graft versus host disease on relapse and leukemia-free survival, to assess the impact of development of grade III-IV acute graft versus host disease on relapse and leukemia-free survival, and to determine whether the impact of graft versus host disease on

relapse and leukemia-free survival is influenced by disease risk prior to HCT. The CIBMTR identified 1,345 children <18 years who received first HCT for acute lymphoblastic leukemia and acute myeloid leukemia receiving first allogeneic transplantation between 2008 - 2017. The following questions were answered during the Q&A:

a. What is the sample size of each sub-group: disease-risk index (DRI)-low, -intermediate, -high? Exact sample size not available but the high-risk group was less in comparison to others.
b. How will you factor in occurrence of chronic graft versus host disease in your analysis? Our main focus is on acute graft versus host disease because it will have more impact on our clinical practice. However, we will collect the data for the interactions of chronic graft versus host disease alone, and if the patient had a history of acute.
c. What is the biological basis for focusing this study on a pediatric population? The interest from our perspective is looking at the pediatric population compared to the adults. The literature on pediatric is severely lacking in comparison to adults and we need to expand on that for the patient population that we care for.
d. Are you going to separate acute myeloid leukemia and acute lymphoblastic leukemia numbers at DRI level? Yes, they are already divided from DRI protocol. Our acute lymphoblastic leukemia patients are about 1,300 and the acute myeloid leukemia are about 1,200.
e. Is the analysis going to be time dependent or landmark? Landmark
f. Do you have the date of this max acute graft versus host disease grade to take into account the time to event aspect of the effect? No
g. Do you have a plan to include/account for the various GVHD prophylaxis regimen "strengths?" We are taking into consideration of what GVHD prophylaxis regimen the patient uses. This data, which is already categorized, will show us the differences between trends.
h. What is the clinical benefit besides prognostic? This will help define a better foundation of which patients will benefit more from a little bit of graft versus host disease. If we can come up with a patient category that we see is beneficial to have exposure to a little bit of graft versus host disease, it can go forward with clinical trials and GVHD prophylaxis adjustment or manipulation to improve their Leukemia-free survival.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix C.

4. **Effect of HLA evolutionary divergence on survival and relapse following allogeneic hematopoietic cell transplant**. This proposal was presented by Dr. Christine Camacho-Bydume. The primary objective of this proposal is to determine if HLA evolutionary divergence (HED) of HLA class I alleles of HLA-A, -B, -C and HLA class II alleles of HLA-DR is associated with overall survival and relapse. The objective is to also evaluate association of HED with acute and chronic GVHD and treatment-related mortality (TRM). The CIBMTR identified pediatric and adult patients with acute myeloid leukemia, myelodysplastic syndromes, acute lymphoblastic leukemia, chronic myeloid leukemia, or lymphoma (non-Hodgkin or Hodgkin's lymphoma), who have received initial allogeneic 8/8 HLA-matched (HLA-A, -B, -C, -DR) transplant between 2008 - 2018. The following questions were answered during the Q&A:

   a. Could HLA diversity simply be a surrogate for race? How would you account for race in the study? Great question given there are particular HLA alleles that are more common in certain ethnic groups. We do think that evaluation of HED lows and highs within these different ethnicities can help to tease this out more, with potential to adjust for race more in this analysis. We think some of these differences in peptide binding grooves can help us to understand better the different peptides and how antigens are presented to T-cells.
   b. Extrapolating HLA data from solid tumors and checkpoint inhibitors and their antigen presentation is slightly challenging in context of allo donor T-cell interaction with antigen presented for bone marrow origin cancers. Yes, have to consider there could be some differences. Was a small previous study that

looked at this question, saw some signals there, larger population and different types of cancers, may be able to explore that more.

c. Leukemia (both lymphoblastic and myeloid) have low mutational burden as compared to melanoma and lung. Will the HED algorithm still work? Yes, we do expect to see differences in mutational burdens, and we do plan to look at the cohort at large to look at the disease subgroups to see more or less of this phenomenon in these groups. Do you have preliminary data in leukemias? There was a small study in Germany that looked at AML, to my knowledge only one that looked at leukemias. Mutational burden did see some differences, so we do expect it and also, besides the overall cohort, also plan to look at disease subgroups.
d. Given HED implications for infection surveillance, are you going to look at infectious sequelae differences? No, at the moment we have initially requested information in terms of tumor control, relapse, overall survival, graft versus host disease, and TRM. Not sure of availability of the other information but would be interesting to look at if available.
e. Would you please discuss the confounding effects of HLA mismatching for HLA-DRB3, 4, 5, DQ, and DP? Not known off the top of my head the percentages of mismatching differences in this cohort. For DR at least they will be matched, 8/8 matched, in terms of DP, don't have that info but if available it is something that can be looked at.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix D.

5. **Impact of IDH1 and IDH2 mutations on outcomes of acute myeloid leukemia patients undergoing allogeneic hematopoietic cell transplantation**. This proposal was presented by Dr. Evan C. Chen. The primary objective of this proposal is to identify differences in survival outcomes between mutIDH1/2 and wtIDH1/2 acute myeloid leukemia patients and to assess the prognostic significance of disease features in mutIDH1/2 and wtIDH1/2 acute myeloid leukemia patients. The CIBMTR identified patients ≥ 18 years old with a diagnosis of normal karyotype acute myeloid leukemia, receiving first allogeneic HCT during CR1 in 2013 - 2019. The following questions were answered during the Q&A:
   a. Is there any concern that patients with IDH1/2 mutated acute myeloid leukemia would have received more intensive conditioning / therapy than IDH1/2 wild-type? Yes, and it's important to look at how conditioning intensity can be an important covariant, which is a variable captured in CIBMTR.
   b. Will you have registry information on the type and duration of use of IDH inhibitors before/after HCT? It's currently not available with CIBMTR.
   c. IDH mutations are usually seen in older subjects. How will you a priori adjust for this known association? Age will certainly be a covariant in our multi-variant analysis.
   d. How reliable are the wild-type patients as some may just not be tested for IDH mutations? It is double checked. There is a datapoint in the forms that indicate whether or not testing has been done, versus if testing was done and IDH was found to be absent.
   e. Do you have information what the numbers will be like when you divide your patient groups with concomitant mutations such FLT3 or p53 that may have an impact on outcomes? Yes, the numbers are about 20-40 for co-mutated for ITD and NPM1 patients. p53 not provided.
   f. Is there data in CIBMTR forms that collect use of IDH inhibitors pre transplant? Will you be able to study their impact on the transplant? I'm not aware of this data point being available in the forms but it is something that we should follow up on.
   g. How do you analyze its (or ITS?) with multiple mutations? With regards to double-mutated patients, IDH1, and IDH2 patients, which are generally rarely reported, we would look at the CIBMTR forms to ensure accurate data entry. In regard to analyzing IDH with other co-mutations, we would include co-mutations as a co-variant in a multi-variant analysis, should the sample size permit.

h. What about other mutations in Wild type IDH? We focus on NPM1 and FLT3-ITD because they are prevalent in the cytogenetic risk population. We will look at the other mutations to see if they have any relevance at all.
i. Do the data forms reliably collect information on use of IDH inhibitors pretransplant? Data point is not available.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix E.

6. **Characteristics and outcomes of adolescent and young adults with multiple myeloma treated with autologous hematopoietic cell transplant**. This proposal was presented by Dr. Christin B. DeStefano. The primary objective of this proposal is to describe patient and disease related characteristics of adolescent and young adults (AYAs) with multiple myeloma treated with early high dose melphalan and AutoHCT and to characterize response to AutoHCT, survival outcomes, SPMs, and infections of AYA multiple myeloma patients and AutoHCT. The CIBMTR identified 1,142 AYA multiple myeloma patients who underwent autologous hematopoietic cell transplant) between 2008 -2018. The following questions were answered during the Q&A:
   a. What will differentiate this study from MM18-03 "To compare the outcomes in young patients with multiple myeloma at diagnosis undergoing upfront autologous hematopoietic stem cell transplant with older patients in the US: progression-free and overall survival"? There appears to be substantial population overlap. The Scientific Director clarified via the chat function that MM18-03 included the years 2013-2017 and excluded patients less than 40 years from the outcome analysis owing to small numbers.
   b. How do you plan to control for differences between your AYA group and older control group which would be attributable to age? In total, there are about 1,700 TED and CRF cases. We can adjust the critical variables of these cases, such as stage, treatment rendered, and cytogenetics, for example, to control for differences.
   c. Will results be stratified according to different induction regimens? Yes, we will adjust those critical variables amongst the CRF cases where this information is available.
   d. A cohort going back to 1995 seems too outdated. What was the N for a more recent group (since 2010)? There were 1,142 AYA cases between 2008-2018.
   e. This is a long cohort 1995-2019 with lots of changes in induction treatment, novel agents and time to bone marrow transplant. How will this be controlled for? We are going to study induction regimens, post-transplant treatment, use of tandem transplants in our analysis.
   f. Will you be also studying the effect of post-transplant maintenance therapy? Also, any effect of extramedullary plasmacytomas in this AYA group? We will for cases where this information is available. Extramedullary plasmacytomas are a good focus, as AYA patients may have a more aggressive presentation of myeloma.
   g. Are plasma cell leukemias included in this analysis? No

   Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix F.

7. **Impact of measurable residual disease status on outcomes of AML in patients 18-65 years old in CR1 undergoing Allo-HCT**. This proposal was presented by Dr. Firas El Chaer. The objectives of this proposal is to determine if acute myeloid leukemia measurable residual disease (MRD) analysis as currently performed has prognostic value when measured prior to AlloHCT, to explore factors that may modify the risk associated with detectable acute myeloid leukemia MRD pre-AlloHCT, and identification, using MRD combined with other clinical factors, of patients most at risk of post-AlloHCT relapse. The CIBMTR identified 753 MRD positive and 1986 MRD negative adult patients receiving first AlloHCT for de-novo AML in CR1 in 2007-2018. The following questions were answered during the Q&A:

a. What kind of MRD data is collected? Depending on the individual participating centers, the methodology uses molecular or immunotherapy? MRD
b. What is the rate of missing MRD status and are those patients different from those with MRD data available? The answer is not included in this study.
c. Are you going to also study the effect of post-transplant maintenance in AML FLT3, IHD mutations on relapse and overall survival? One of the aims of this study is to have future studies look at post-transplant maintenance from this study.
d. What do you mean by most "recent" pre-conditioning MRD assessment? Would testing need to be completed within a specific time frame before conditioning? All patients who will be receiving a stem cell transplant are required to get a bone marrow biopsy and peripheral blood aspiration before transplantation. Within a month before the transplant, we would look at data point.
e. What is your working definition of MRD? A combination of molecular testing as well as immunotherapy by NFC.
f. Are all mutations equivalent when thinking about MRD? Absolutely not.
g. How sure are you that the MRD patients are really MRD negative? We can never be absolutely sure.
h. How are you going to account for the different sensitivity of methods used to determine MRD? Are ELN risk available at CIBMTR, since when? The way that CIBMTR reports the acute myeloid leukemia data is by reporting their cytogenetics and mutation analysis so we can calculate the data for this population. The point of this study is to look at the commercial availability of these tests and we can rely on it or if we should standardize one testing at all centers.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix G.

8. **Racial, ethnicity and socioeconomic disparity in outcome of patients with chronic graft versus host disease.** This proposal was presented by Dr. Nosha Farhadfar. The objectives of this proposal are to determine whether clinical manifestations and severity of chronic GVHD differ based on racial/ethnic and socioeconomical status (SES) differences, to determine whether treatment patterns of chronic GVHD differ based on racial/ethnic and SES differences, and to evaluate whether chronic GVHD treatment outcomes differ based on racial/ethnic and SES differences. The CIBMTR identified 17,665 patients, age 18 years or older, who have received first allogeneic transplant for hematologic malignancy (acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome) between 2008 - 2019. The following questions were answered during the Q&A:
   a. I like the idea for looking at outcomes based on race/ethnicity/SES but not sure if incidence should be a primary outcome because it will be dependent on donor type which is very different amongst the groups. The primary outcome of this study is to look at the outcome of patients who develop chronic graft versus host disease. We need to look at the whole cohort, report the incidence, and then focus on chronic graft versus host disease cohort as the primary endpoint of this study.
   b. How will you correct for the impact of race on HLA mismatch between recipients and donors due to the lower chance of identifying a fully matched donor in non-Hispanic white patients? For the same reason, should cord blood recipients be excluded? We are going to include both the donor type, graft source and degree of HLA matching as covariables in a multi-variable analysis. Cord blood recipients should not be excluded, as there was near 14% of Non-Hispanic black, 14% Hispanic, and 15% Asian who received cord transplant. Approximately 7-8% of cord transplants were received by Non-Hispanic whites. We do have the number to look into cords but if a statistician reviews and determines we don't have the power, then we can eliminate the cords.
   c. Is it possible to access constitutional DNA to look at ancestry information markers in this population? This information is not available for the population. The analysis will focus on self-reported race/ethnicity.
   d. All patients in your cohort from 2008 were not reported with NIH consensus criteria for chronic GVHD. Since you have large numbers, should you limit this to more recent time period? We do have all of the

information on graft versus host disease and whether it was limited or extensive. There is information on whether graft versus host disease is progressive, de-novo or interrupted. We have organ involvement and maximum grade of chronic graft versus host disease. NIH scoring is available for at least the past 4 years and maybe we can look at that group separately. Within the past 4 years, the population limited to NIH grading only in about 1,500 non-Hispanic white, 270 non-Hispanic black, and 200 Hispanic, who have developed chronic graft versus host disease.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix H.

9. **Time from diagnosis to transplant as an important contributor for post allogeneic stem cell transplant infections, immune reconstitution and its associated mortality/morbidity**. This proposal was presented by Dr. Lohith Gowda. The objectives of this proposal are to identify density and types of early and late infections (bacterial, viral and fungal) in patients that went to transplant a) <6 months b) between 6- 12 months and c) > 12 months from diagnosis; to identify T cell lymphocyte absolute numbers at days 100 and 180 and CD4/CD8 ratio for the timeline cohorts examining individual donor types; to evaluate the impact of bacterial, viral or fungal infections by day 100 and day 180 on 1-year post-transplant outcomes (relapse, non-relapse mortality, disease free survival, acute and chronic graft versus host disease); and to evaluate quantitative immunoglobulin levels at D+ 100 and + 180 if available. The CIBMTR identified 6,877 ≥ 18 years old patients who underwent first allogeneic transplants for AML in CR1, ALL in CR1 or MDS in the United States from 2012 to 2019. The following questions were answered during the Q&A:
    a. How many patients in the registry have the immune parameters you wish to assess? >2100
    b. How will you account for the type of treatment used prior to transplant? For example, treatments such as hypomethylating agents may require months of treatment before transplant versus induction chemo that works more quickly. We do have some variables that are available, such as types of therapy, and we can analyze levels of intensity of therapy (low to high) and post-transplantation outcomes. The exact number of how many patients who have had different intensities of therapies is not available.

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix I.

10. **Efficacy and safety of CD19 directed CAR T-cell therapy for non-Hodgkin B-cell lymphomas with secondary central nervous system involvement**. This proposal was presented by Dr. Hamza Hashmi. The primary objective of this proposal. The CIBMTR identified 55 adult patients (age ≥ 18) who received CD19 CAR T-cell therapy for B-cell NHL with secondary central nervous system (CNS) involvement. The following questions were answered during the Q&A:
    a. How will you differentiate between immune effector cell-associated neurotoxicity syndrome (ICANS) and CNS relapse? ICANS will be documented as a neurotoxicity and CNS relapse will be when the form is filled out.
    b. Is this active CNS disease or previously treated CNS disease? The data received from CIBMTR looks at CNS disease at the time of diagnosis and the CNS disease that is present at the time of cellular therapy.
    c. Do you have any registry information on concomitant CNS therapy (chemo/radiation) pre, peri and post transplantation? Answer was not available at this time.
    d. How many patients are in your study? How will you define whether the patients have cleared their CNS involvement? There are currently 60 patients in the history of this data. Of the 60, 40 had this disease at the time of diagnosis and 20 had this disease at the time of cellular therapy. Whether the patients have cleared their CNS involvement, this information is not available at the time.
    e. Since this is your primary endpoint, how will you account for the differences of frequency of CRS and ICANS across different products (e.g. high in Yescarta, lower in Kymriah, low in Breyanzi)? If you look at the toxicity profile of CD19 therapy, they seem to be relatively similar.

f. Could you please include other agents such as anakinra, siltuximab, and other agents? Dasatinib for this populations for ICANS? Also, was CNS disease under control at CAR-T therapy? As for Anakinra, siltuximab, and other agents, I'm not sure if CIBMTR is capturing this data. As for dasatinib, I'm not sure if this information is available as well. Per Dr. Pasquini of CIBMTR in the live chat, he commented "we capture treatment of ICANS, like siltuximab, dasatinib has been reported as other treatment."
g. Will you have detail on the nature and extender features of secondary CNS involvement to associate with the toxicity and outcome? I only have the essential data with me but am hopeful that this comprehensive research will have further detail.
h. Will all the patients included have active CNS disease at the time of CAR-T or, are treated CNS disease are also included? They are both included, and we are able to tell who has had active disease with a prior history at the time they got the CAR-T therapy.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix J.

11. **Haploidentical donor versus matched donor allogeneic hematopoietic cell transplantation in patients with myelofibrosis**. This proposal was presented by Dr. Tania Jain. The primary objective of this proposal is to explore the impact of donor type on overall survival of patients undergoing HCT for myelofibrosis. The CIBMTR identified 1,640 patients ≥18 years old diagnosed with primary, post-ET or post-PV myelofibrosis and undergoing first HCT between 2013 and 2019. The following questions were answered during the Q&A:
    a. Are you also going to compare the effect of pretransplant Ruxo in haplo vs MUD/MRD? Also, are you going to look for graft failures as well in these patient populations? Yes, this will be included. We also do look at graft failures in these populations.
    b. Is there a difference in time from diagnosis to HCT across the groups? The median time from diagnosis to transplant for haploidentical patients was 38 months, while for HLA- identical sibling and URD 8/8 was 21 and 24 months, respectively.
    c. Are you including all conditioning regimens types: MAC, RIC and NMA? Yes, and they will be looked at for comparison in the univariable and may be taken to the multivariable analysis as well.
    d. For the graft failure or rejection analysis are you going to include spleen size? Ideally it should be included but the spleen size measurement has many variables and it may not be a clean assessment. We don't collect precise spleen size in our forms, but it can be analyzed as spleen size as splenomegaly, no splenomegaly or splenectomy.
    e. Can you comment on the bone marrow vs peripheral blood in the three groups? Peripheral blood is more common in the donor source (about 80%).

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix K.

12. **Assessing utilization and clinical outcome differences by sex and race in CAR-T for relapsed/refractory NHL**. This proposal was presented by Dr. Arushi Khurana. The objective of this proposal is to enhance our understanding of sex- and race-based differences in utilization of CAR-T vs AutoHCT and outcomes after CAR-T. The CIBMTR identified 1,133 patients to compare sex and race/ethnicity rates for first cellular infusion (AutoHCT vs. CAR-T) for relapsed/refractory non-hodgkins lymphoma patients from 2017 – 2019 (aim 1a). The CIBMTR identified 619 non-hodgkins lymphoma patients who relapse after first AutoHCT to describe subsequent treatment patterns (e.g. CAR-T, second AutoHCT, AlloHCT, other treatment, no treatment) by sex and race/ethnicity (aim 1b). The CIBMTR identified 1,253 patients to identify sex-and race-based differences in response to CD19 CAR-T in aggressive lymphomas (aim 2). The following questions were answered during the Q&A:
    a. Is there gender and race-based difference in SEER data with or without treatment for diffuse large B-cell lymphoma even before CAR T? Yes, that data does exist.

b. Can this be stratified by center/geography (private/public, large urban/rural)? Yes, it will be shown based on zip code (of patient and of recorded center), which will allow us to differentiate from urban/rural as well.
c. We saw almost no neurotoxicity in women so would you be plotting CRS and ICANS based on gender and race? Yes, and we believe CIBMTR is the best resource for this because of the larger numbers
d. How do you differentiate between larger trial centers vs less resourced centers? The information is reported based on the center type. Basing on academic or zip code, or city versus rural center, that will also be a way to differentiate the centers.
e. Would disease response status prior to cellular therapy be taken into account for analysis? Yes, that is one of the co-variants that will be included.
f. How reliable is the data you will get to study "access", as there are many factors, depending on patient specific factors (education, resource, finances, mobility, support, performance, etc.), center specific (criteria), and also access depends on the hematologist/oncologist who sees these patients in the community? Access to a center is not one of the main issues in this study. It is more about why some of these minorities receiving other treatments when they should be receiving cellular therapy at the time of indication.
g. Is there any way to take into account insurance issues? We do look at the insurance statuses as one of the co-variants.
h. Would it be possible to look at differences in access based on commercial CAR T vs. clinical trials? The majority of the patients from the forms received are from commercial CAR T.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix L.

13. **Optimal GVHD prevention strategy in older, robust patients with acute leukemias and myeloid malignancies undergoing myeloablative, matched donor hematopoietic cell transplantation**. This proposal was presented by Dr. Richard J. Lin. The primary objective of this proposal is to compare CRFS among patients ≥ 60 years old undergoing myeloablative conditioned, allogeneic hematopoietic cell transplantation with following graft versus host disease prophylaxis in 2 matched-pair analysis and to compare other transplant outcomes in the above 2 matched-pair analysis. The CIBMTR identified 1,301 patients at ≥ 60 years old at the time of first allo-HCT between 2010 and 2019, with any myeloablative conditioning defined by CIBMTR, 8/8 matched related or unrelated donor only, graft versus host disease prophylaxis (ex-vivo TCD/CD34+ selection versus PTCy-based versus Tac/MTX). The following questions were answered during the Q&A:
    a. What do you mean by "robust?" Is it based on KPS, HCT-CI, or just the fact that someone got MA. regimen? We use the definition of a patient getting a myelo-conditioning as a way of saying that they are robust by their transplant centers.
    b. Are patients with In-vivo T cell depletion (Campath or ATG) excluded from this analysis? T cell depletion and CD34 selection does include ATG and does not include Campath.
    c. Why do you pool post-CY and ex vivoCD34+ selection? Can we still consider ex vivoCD34 selection to be a promising transplant modality in 2021? We wanted to compare a 2-match pair analysis and not a direct comparison between CD34 selection and post-CY. We do know which will be better for an older patient.
    d. Why exclude TBI? For older patients, we don't consider TBI to be a conditioning regimen.
    e. How many patients with Tac/methotrexate prophylaxis had ATG? Answer was not available at the time of Q&A.
    f. Do we know GFR (creatinine) coming into allo in these groups? In this study, we didn't include the GFR (creatinine) as a variable but we have some evidence in older patients that does play a major role. I can discuss with our statistician on whether we can include this as a variable.

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix M.

14. **Outcomes of elderly patients receiving CD-19 directed CAR-T therapy for B-cell lymphomas**. This proposal was presented by Dr. Sayeef Mirza. The primary objectives of this proposal to evaluate cumulative incidence grades, duration and median time to onset of CRS and CRES/ICANS in patients > 65 years of age receiving CD-19 directed CAR-T therapy, describe post CAR-T clinical outcomes and resource utilization in elderly, and identify disease biology, comorbidities and other clinical predictive markers of toxicity, response, and survival in elderly patients. The CIBMTR identified 1,036 patients (<65y,n=612; 65-74y, n=348; >75y, n=76) with the diagnosis of any B-cell lymphoid malignancy (indolent or aggressive lymphoma) receiving CAR-T cell product (CD19 target). The following questions were answered during the Q&A:
    a. Would you please also look at Incidence of pancytopenia, hypogammaglobulinemia and HLH in elderly versus younger in 3 cohorts <60, 60-75 ,>75? I think it's very important to look at this as the data becomes available to us. We are primarily looking at different age groups. We have 81 patients over the age of 75 and five patients over the age of 85. Overall, there are 435 (40 %) of the group are over 65 years old.
    b. How does this defer from the data presented by Dr. Pasquini last year in older patients? This data will be more helpful in including both CAR-T products.
    c. In case of CAR T was used for post-alloHCT relapse, would the donor age of the CART source be analyzed? This is something that we should include in our analysis.
    d. Are data on baseline geriatric scores or HCT-CI available for all? The answer was not available at the time of the Q&A.
    e. Do we have registry information on whether CAR-T production succeeded or not, when attempted? The answer was not available at the time of the Q&A but the moderator did state that on behalf of CIBMTR, this information is not captured.

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix N.

15. **Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation**. This proposal was presented by Dr. Joseph Pidala. The primary objective of this proposal is to validate prediction models for immune suppression discontinuation (ISD) and ISD failure developed in prior DISCIS-defined population, explore ISD and ISD failure in a new population inclusive of full range of diversity in current HCT practices, construct and validate dynamic prediction models of ISD and ISD failure in the expanded population. The CIBMTR identified 20,031 patients with a hematologic malignancy who received an allogeneic HCT from matched sibling donor, matched or mismatched unrelated donor, umbilical cord blood or haploidentical donor between 2009-2018. The following questions were answered during the Q&A:
    a. Can you explain how the ISD data information was made feasible? We used CIBMTR follow up data in the previous analysis that led to the development of the prediction model for ISD that we intend to validate in this study.
    b. Can you provide more granularity on how the time of discontinuation of immune suppression will be defined? In the CIBMTR data, there is a hard stop date for a complete discontinuation of immune suppression. That granular data is available, and it was the data we used for the prior project. We used that hard stop of all systemic immune suppression because that's an unambiguous measure of success.
    c. Many with PTCY may be discontinuing by days 100 or 60- likely based on center practice rather than patient response, how will this be addressed? Our prior project was successfully addressed this issue, specifically within that study population. The first step in this project is to validate those findings. We will definitely be studying how immune suppression was performed and what are the subsequent outcomes.
    d. Do you plan to use age as one of the variables regarding likelihood to discontinue IST, or will you have a separate pediatric specific model? Yes, we will consider age as a variable and evaluate the need for a pediatric specific model.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix O.

CLOSING:

Dr. Shaw, on behalf of herself and co-chair, Dr. John Wingard, did thank presenters, conference organizers, and the CIBMTR staff for having coordinated this virtual session. She did mention that this session was recorded and encouraged attendees to take survey, as access would be available until Monday, February 15, 2021.

APPENDICES:

A. Risk of subsequent neoplasms in patients with post-transplant cyclophosphamide use for graft-versus-host disease prophylaxis.

1. How will authorship work for these studies? The same as usual, there are fewer studies being accepted but the process otherwise is the same
2. What if a higher risk of cancer is related to the almost uniform use of 2GyTBI in these patients rather than PTCY?
3. What is the breakdown of haploidentical versus matched sib/MUD in the post-transplant cyclophosphamide group?
4. How can we r/o genetic predisposition on samples and variables of TBI based conditioning therapies?
5. What is your sample size and follow-up period?
6. How long post BMT you will follow up? From where will you receive the SN data?
7. Will you be adjusting for chronic GVHD when looking at your outcome of SN?
8. Is this study statistically powered to detect a difference between PTCY and above a certain threshold? What is the threshold?
9. Will analysis be conducted separately for TBI/non-TBI and MAC/RIC conditioning? Are you evaluating all malignancies?
10. Since the total CY exposure is likely not that different in PTCY vs. BU/CY or CY/TBI, is your hypothesis that the timing of exposure to CY may lead to a difference in risk? And if so, why?
11. Information on skin cancers - ssc, bcc available?
12. Matching for HLA matching could be a limitation because the PTCY patients are more likely to receive haploidentical grafts.

B. Outcomes of chimeric antigen receptor-T cell (CAR-T) therapy for patients with antecedent chronic lymphocytic leukemia (Richter's Syndrome).

1. If patients had failed an auto or allo, how do you plan to compare to the results of auto? Isn't it a different group?
2. Can you please provide your thoughts if the small n will be able to generate meaningful results at this time?
3. Would you include both transformed lymphoma from other low-grade lymphoma and Richter's transformation?
4. Are there concerns about underreporting Richter's?
5. Since the numbers are small, can we go back to centers to establish clonality?

C. Impact of graft versus host disease following allogeneic hematopoietic cell transplantation on leukemia free survival in hematologic malignancies. *No additional questions*

D. Effect of HLA evolutionary divergence on survival and relapse following allogeneic hematopoietic cell transplant.

1. Does the HED algorithm take into account variations outside the peptide binding groove?

2. What is the size of the cohort you are looking at?

E. Impact of IDH1 and IDH2 mutations on outcomes of acute myeloid leukemia patients undergoing allogeneic hematopoietic cell transplantation. *No additional questions*

F. Characteristics and outcomes of adolescent and young adults with multiple myeloma treated with autologous hematopoietic cell transplant.

1. How do you plan to control for differences between your AYA group and older control group?

G. Impact of MRD status on outcomes of AML in patients 18-65 years old in CR1 undergoing Allo-HCT.

1. How are you going to account for the different sensitivity of methods used to determine MRD? Are ELN risk available at CIBMTR, since when?
2. Hi Firas, How are defining the MRD?
3. The methods for MRD assessment may be quite heterogeneous, including the threshold of detection. How will you deal with the high likelihood of false MRD negative assessments from using inadequately sensitive quantification?
4. MRD test is different from different centers. How can you control for this?
5. How do you account for different MRD- cut-offs?
6. To clarify, if AML-MRD is to become a "precision medicine tool", does that mean is will be used to guide treatment decisions in addition to being prognostic?
7. How will control for the various methods for detecting MRD as different techniques have different sensitivities/accuracy?
8. if both multiparameter flow and NGS are available and are discordant on the same patient, how will that be analyzed?
9. is the MRD before alloSCT is the one to be analyzed?
10. Will this require more data from centers to answer some of the questions above?

H. Racial, ethnicity and socioeconomic disparity in outcome of patients with chronic graft versus host disease.

1. Is age significantly different in your Hispanic cohort? How do you adjust for it?
2. Was the MMUD recipient cohort limited to single antigen mismatch? Or all mismatches (understanding most MMUD will likely be single antigen MM)?
3. Do you have information on health insurance? Why not to study this question in a more homogeneous patient population to avoid the complexity and interactions in different factors?
4. Are there any other sociodemographic variables available that could be used to adjust for socioeconomic status, or is median income in the patient's ZIP code the only one?
5. Baker et al 2009 demonstrated no impact of household income on GVHD (acute or chronic) and only minimal impact of race on Grade III-IV aGVHD (none of cGVHD). Why do you think this null relationship should be pursued again?
6. Is there a plan to study as per continent distribution?
7. Is there a better index to gauge SES or poverty level?
8. Are Native American/Hawaiian/Pacific islanders being grouped elsewhere?

I. Time from diagnosis to transplant as an important contributor for post allogeneic stem cell transplant infections, immune reconstitution and its associated mortality/morbidity.

1. Do you plan to address the confounding influence of different factors leading to delay in transplant timing?
2. How are you going to account for number of cycles of chemotherapy versus no

chemotherapy as a confounder in the time delay?

J. Efficacy and safety of CD19 directed CAR T-cell therapy for non-Hodgkin B-cell lymphomas with secondary central nervous system involvement.

1. Is site-specific response (CNS vs. other lesions) and pattern of relapse/progression (CNS vs. systemic) available?
2. Why not to consider a comparative group?
3. Will you stratify patients according if they received IT chemo vs radiation therapy?

K. Haploidentical donor versus matched donor allogeneic hematopoietic cell transplantation in patients with myelofibrosis.

1. Availability of somatic mutations?
2. Is pretransplant Splenectomy data available? Are you going to factor this in the outcomes?
3. At least look at splenectomies?
4. What risk stratification is being used? DIPSS or DIPSS+?

L. Assessing utilization and clinical outcome differences by sex and race in CAR-T for relapsed/refractory NHL. *No additional questions*

M. Optimal GVHD prevention strategy in older, robust patients with acute leukemias and myeloid malignancies undergoing myeloablative, matched donor hematopoietic cell transplantation. *No additional questions*

N. Outcomes of elderly patients receiving CD-19 directed CAR-T therapy for B-cell lymphomas. *No additional questions*

O. Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation.

1. How is immune suppression stop defined in the CIBMTR database?
2. How long after HCT do you expect data regarding ongoing IST usage to be reliable since many patients leave the transplant center and are managed elsewhere long-term?
3. How long will you deal with restart IST?

Accrual Summaries for Immunobiology Working Committee

Transplant Essential Data (TED)data

Variable	HLA-identical Sibling N (%)	Haplo Donor N (%)	Matched Unrelated Donor N (%)	Mismatched Unrelated Donor N (%)
Number of recipients	40136	10271	36056	8658
Number of centers	389	285	318	280
Data Source				
TED	31101 (77)	5938 (58)	23932 (66)	5723 (66)
CRF	9035 (23)	4333 (42)	12124 (34)	2935 (34)
Recipient age at transplant				
<10	4054 (10)	1097 (11)	2453 (7)	936 (11)
10-17	3175 (8)	810 (8)	1814 (5)	776 (9)
18-29	4853 (12)	1448 (14)	3533 (10)	1019 (12)
30-39	4106 (10)	987 (10)	3181 (9)	841 (10)
40-49	6257 (16)	1223 (12)	4628 (13)	1211 (14)
50-59	9860 (25)	1945 (19)	7969 (22)	1779 (21)
60-69	7184 (18)	2209 (22)	10100 (28)	1803 (21)
>=70	647 (2)	552 (5)	2378 (7)	293 (3)
Median (Range)	47 (0-80)	47 (0-88)	54 (0-84)	47 (0-81)
Sex				
Male	23358 (58)	6183 (60)	21145 (59)	4989 (58)
Female	16778 (42)	4088 (40)	14911 (41)	3669 (42)
Recipient Race				
White	25091 (63)	6088 (59)	31311 (87)	6246 (72)
Black or African-American	2316 (6)	1718 (17)	997 (3)	861 (10)
Asian	3623 (9)	995 (10)	997 (3)	437 (5)
Native Hawaiian or other Pacific Islander	187 (<1)	61 (1)	93 (<1)	25 (<1)
American Indian or Alaska Native	225 (1)	69 (1)	133 (<1)	55 (1)
Other	1 (<1)	0	0	0
More than one race	185 (<1)	80 (1)	155 (<1)	89 (1)
Missing	8508 (21)	1260 (12)	2370 (7)	945 (11)
Recipient ethnicity				
Hispanic or Latino	4432 (11)	1407 (14)	2208 (6)	1225 (14)
Non-Hispanic or non-Latino	24954 (62)	6906 (67)	29860 (83)	6227 (72)
Non-resident of the U.S.	10321 (26)	1748 (17)	3394 (9)	1073 (12)
Missing	429 (1)	210 (2)	594 (2)	133 (2)
Karnofsky performance score				
<=80	11972 (30)	3728 (36)	13347 (37)	2975 (34)
90-100	27115 (68)	6282 (61)	21925 (61)	5491 (63)
Missing	1049 (3)	261 (3)	784 (2)	192 (2)
Graft type				
Bone marrow	10266 (26)	3561 (35)	8247 (23)	2427 (28)
Peripheral blood	29652 (74)	6543 (64)	27790 (77)	6224 (72)

Variable	HLA-identical Sibling N (%)	Haplo Donor N (%)	Matched Unrelated Donor N (%)	Mismatched Unrelated Donor N (%)
BM + PB	127 (<1)	27 (<1)	9 (<1)	3 (<1)
Other, specify	1 (<1)	0	0	0
BM + OTH	9 (<1)	0	0	2 (<1)
PB + OTH	76 (<1)	140 (1)	10 (<1)	2 (<1)
BM + PB + OTH	1 (<1)	0	0	0
Others	4 (<1)	0	0	0
HCT-CI				
0	16822 (42)	3404 (33)	10531 (29)	3025 (35)
1	5050 (13)	1512 (15)	4970 (14)	1147 (13)
2	4157 (10)	1262 (12)	4918 (14)	1109 (13)
3+	14107 (35)	4093 (40)	15637 (43)	3377 (39)
Reported planned conditioning intensity				
RIC/NMA	14942 (37)	5717 (56)	16538 (46)	3622 (42)
MAC	24619 (61)	4472 (44)	19369 (54)	4984 (58)
Missing	575 (1)	82 (1)	149 (<1)	52 (1)
GVHD prophylaxis				
No GvHD Prophylaxis	292 (1)	116 (1)	140 (<1)	43 (<1)
TDEPLETION alone	45 (<1)	168 (2)	64 (<1)	37 (<1)
TDEPLETION +- other	151 (<1)	290 (3)	212 (1)	130 (2)
CD34 select alone	224 (1)	177 (2)	334 (1)	150 (2)
CD34 select +- other	217 (1)	314 (3)	171 (<1)	96 (1)
Cyclophosphamide alone	367 (1)	37 (<1)	258 (1)	18 (<1)
Cyclophosphamide +- others	1318 (3)	8165 (79)	1771 (5)	928 (11)
FK506 + MMF +- others	3103 (8)	266 (3)	4134 (11)	852 (10)
FK506 + MTX +- others(not MMF)	12152 (30)	167 (2)	17754 (49)	3400 (39)
FK506 +- others(not MMF,MTX)	2004 (5)	17 (<1)	2446 (7)	436 (5)
FK506 alone	638 (2)	22 (<1)	791 (2)	175 (2)
CSA + MMF +- others(not FK506)	3662 (9)	101 (1)	2579 (7)	725 (8)
CSA + MTX +- others(not MMF,FK506)	12114 (30)	251 (2)	4158 (12)	1245 (14)
CSA +- others(not FK506,MMF,MTX)	535 (1)	4 (<1)	397 (1)	182 (2)
CSA alone	2252 (6)	44 (<1)	326 (1)	108 (1)
Other GVHD Prophylaxis	945 (2)	100 (1)	467 (1)	120 (1)
Missing	117 (<1)	32 (<1)	54 (<1)	13 (<1)
High-resolution HLA typed and audited				
N	50 (1)	33 (2)	184 (1)	57 (1)
Y	3828 (99)	1558 (98)	17247 (99)	3776 (99)
Unknown	36258 (N/A)	8680 (N/A)	18625 (N/A)	4825 (N/A)
High-resolution HLA matches available out of 8				
<=5/8	9 (<1)	6398 (96)	0	58 (1)
6/8	3 (<1)	285 (4)	0	367 (5)
7/8	41 (<1)	0	0	7438 (95)
8/8	8948 (99)	0	34858 (100)	0
Unknown	31135 (N/A)	3588 (N/A)	1198 (N/A)	795 (N/A)
High-resolution HLA matches available out of 10				

Variable	HLA-identical Sibling N (%)	Haplo Donor N (%)	Matched Unrelated Donor N (%)	Mismatched Unrelated Donor N (%)
<=5/10	2 (<1)	4201 (67)	0	10 (<1)
6/10	2 (<1)	1394 (22)	0	20 (<1)
7/10	2 (<1)	563 (9)	0	105 (1)
8/10	1 (<1)	87 (1)	36 (<1)	1008 (13)
9/10	32 (<1)	0	1818 (5)	6443 (85)
10/10	7870 (>99)	0	31925 (95)	0
Unknown	32227 (N/A)	4026 (N/A)	2277 (N/A)	1072 (N/A)
High-resolution HLA matches available out of 12				
<=5/12	0	6 (1)	0	4 (<1)
6/12	1 (<1)	419 (55)	0	5 (<1)
7/12	0	235 (31)	0	30 (1)
8/12	0	75 (10)	9 (<1)	262 (6)
9/12	1 (<1)	19 (3)	389 (2)	1562 (34)
10/12	2 (<1)	1 (<1)	6407 (28)	2188 (47)
11/12	48 (3)	0	11713 (51)	574 (12)
12/12	1770 (97)	0	4455 (19)	0
Unknown	38314 (N/A)	9516 (N/A)	13083 (N/A)	4033 (N/A)
Donor age				
Missing	15947 (40)	1467 (14)	1607 (4)	558 (6)
Less than 20 years	4756 (12)	772 (8)	1426 (4)	216 (2)
20-29 years	2388 (6)	2182 (21)	18928 (52)	3446 (40)
30-39 years	2446 (6)	2618 (25)	8369 (23)	2335 (27)
40-49 years	3815 (10)	1810 (18)	4310 (12)	1529 (18)
50+ years	10784 (27)	1422 (14)	1416 (4)	574 (7)
Median (Range)	47 (-1-85)	35 (-3-80)	28 (-1-71)	31 (-1-72)
Primary Disease				
AML	13203 (33)	3679 (36)	13528 (38)	3106 (36)
ALL	6257 (16)	1609 (16)	4679 (13)	1316 (15)
Other leukemia	1112 (3)	208 (2)	1098 (3)	250 (3)
CML	1343 (3)	281 (3)	1168 (3)	314 (4)
MDS	4443 (11)	1276 (12)	5955 (17)	1173 (14)
Other acute leukemia	470 (1)	129 (1)	406 (1)	116 (1)
NHL	3724 (9)	929 (9)	3222 (9)	747 (9)
Hodgkins Lymphoma	759 (2)	365 (4)	621 (2)	178 (2)
Plasma Cell Disorders, MM	1193 (3)	172 (2)	683 (2)	144 (2)
Other malignancies	44 (<1)	53 (1)	15 (<1)	9 (<1)
Breast cancer	1 (<1)	0	2 (<1)	0
SAA	2497 (6)	366 (4)	1192 (3)	325 (4)
Inherited abnormalities erythrocyte diff fxn	2633 (7)	433 (4)	663 (2)	251 (3)
SCIDs	730 (2)	338 (3)	749 (2)	226 (3)
Inherited abnormalities of platelets	32 (<1)	3 (<1)	32 (<1)	11 (<1)
Inherited disorders of metabolism	131 (<1)	57 (1)	128 (<1)	53 (1)
Histiocytic disorders	204 (1)	82 (1)	270 (1)	128 (1)
Autoimmune disorders	25 (<1)	7 (<1)	26 (<1)	11 (<1)

Variable	HLA-identical Sibling N (%)	Haplo Donor N (%)	Matched Unrelated Donor N (%)	Mismatched Unrelated Donor N (%)
Other	37 (<1)	16 (<1)	40 (<1)	17 (<1)
MPN	1298 (3)	268 (3)	1579 (4)	283 (3)
Donor/recipient sex match				
Male/Male	12707 (32)	3725 (36)	15685 (44)	3169 (37)
Male/Female	8680 (22)	2252 (22)	9623 (27)	2003 (23)
Female/Male	10636 (26)	2458 (24)	5392 (15)	1808 (21)
Female/Female	8087 (20)	1836 (18)	5234 (15)	1658 (19)
Missing	26 (<1)	0	122 (<1)	20 (<1)
Donor/recipient CMV match status				
+/+	18614 (46)	4729 (46)	9962 (28)	2968 (34)
+/-	3783 (9)	1051 (10)	3936 (11)	1126 (13)
-/+	7632 (19)	2111 (21)	11676 (32)	2613 (30)
-/-	8408 (21)	2178 (21)	10203 (28)	1883 (22)
Missing	1699 (4)	202 (2)	279 (1)	68 (1)
Year of transplant				
2008	3283 (8)	171 (2)	1801 (5)	690 (8)
2009	3649 (9)	287 (3)	2015 (6)	726 (8)
2010	3893 (10)	295 (3)	2256 (6)	696 (8)
2011	3725 (9)	357 (3)	2502 (7)	708 (8)
2012	3694 (9)	428 (4)	2693 (7)	722 (8)
2013	3476 (9)	503 (5)	3085 (9)	831 (10)
2014	3404 (8)	616 (6)	3295 (9)	783 (9)
2015	3127 (8)	951 (9)	3289 (9)	739 (9)
2016	3122 (8)	1273 (12)	3399 (9)	697 (8)
2017	3100 (8)	1620 (16)	3607 (10)	693 (8)
2018	2959 (7)	1798 (18)	3985 (11)	717 (8)
2019	2704 (7)	1972 (19)	4129 (11)	656 (8)
Follow-up among survivors, Months				
N Eval	21850	5625	18773	3850
Median (Range)	47 (0-159)	28 (0-151)	48 (0-154)	51 (0-156)

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	49388	12021	10062	49474
Number of centers	537	467	233	219
Recipient age at transplant				
0-9 years	6802 (14)	2698 (22)	2314 (23)	7711 (16)
10-19 years	8010 (16)	1773 (15)	1627 (16)	5435 (11)
20-29 years	8263 (17)	1599 (13)	1483 (15)	5370 (11)
30-39 years	8878 (18)	1375 (11)	1628 (16)	5904 (12)
40-49 years	8296 (17)	1387 (12)	1437 (14)	7251 (15)
50-59 years	9131 (18)	3186 (27)	1572 (16)	17802 (36)
Unknown	8 (N/A)	3 (N/A)	1 (N/A)	1 (N/A)
Median (Range)	32 (-30-82)	30 (0-88)	27 (0-76)	41 (-0-83)
Recipient race/ethnicity				
Caucasian, non-Hispanic	37068 (78)	7733 (70)	7517 (78)	38026 (79)
African-American, non-Hispanic	2376 (5)	1221 (11)	104 (1)	3768 (8)
Asian, non-Hispanic	4710 (10)	1054 (10)	1431 (15)	1786 (4)
Pacific islander, non-Hispanic	88 (<1)	46 (<1)	56 (1)	103 (<1)
Native American, non-Hispanic	103 (<1)	61 (1)	50 (1)	192 (<1)
Hispanic, Caucasian	1231 (3)	645 (6)	306 (3)	3258 (7)
Hispanic, African-American	76 (<1)	41 (<1)	15 (<1)	129 (<1)
Hispanic, Asian	12 (<1)	4 (<1)	3 (<1)	24 (<1)
Hispanic, Pacific islander	4 (<1)	1 (<1)	0	13 (<1)
Hispanic, Native American	23 (<1)	9 (<1)	3 (<1)	44 (<1)
Hispanic, race unknown	144 (<1)	27 (<1)	21 (<1)	741 (2)
Other	1424 (3)	224 (2)	83 (1)	106 (<1)
Unknown	2129 (N/A)	955 (N/A)	473 (N/A)	1284 (N/A)
Recipient sex				
Male	28900 (59)	7285 (61)	5981 (59)	28969 (59)
Female	20488 (41)	4736 (39)	4081 (41)	20505 (41)
Karnofsky score				
10-80	13486 (27)	4057 (34)	2672 (27)	15252 (31)
90-100	34235 (69)	7343 (61)	7001 (70)	31670 (64)
Missing	1667 (3)	621 (5)	389 (4)	2552 (5)
HLA-A B DRB1 groups - low resolution				
<=3/6	0	2855 (58)	32 (1)	411 (1)
4/6	0	957 (19)	262 (8)	4648 (10)
5/6	0	377 (8)	765 (24)	9729 (21)
6/6	49388 (100)	728 (15)	2081 (66)	31144 (68)
Unknown	0 (N/A)	7104 (N/A)	6922 (N/A)	3542 (N/A)
High-resolution HLA matches available out of 8				
<=5/8	47 (1)	3171 (78)	271 (12)	5791 (15)

Variable	CIBMTR HLA-identical sibling N (%)	CIBMTR Alternative related N (%)	CIBMTR Unrelated (non-US) N (%)	CIBMTR Unrelated (US) N (%)
6/8	8 (<1)	181 (4)	207 (10)	3542 (9)
7/8	37 (1)	228 (6)	541 (25)	7500 (19)
8/8	4804 (98)	511 (12)	1151 (53)	22086 (57)
Unknown	44492 (N/A)	7930 (N/A)	7892 (N/A)	10555 (N/A)
High-resolution HLA typed and audited				
N	14 (1)	23 (2)	23 (4)	961 (4)
Y	1509 (99)	921 (98)	534 (96)	23766 (96)
Unknown	47865 (N/A)	11077 (N/A)	9505 (N/A)	24747 (N/A)
Graft type				
Marrow	32479 (66)	6693 (56)	5461 (54)	18042 (36)
PBSC	16272 (33)	5133 (43)	2678 (27)	19797 (40)
UCB	210 (<1)	39 (<1)	1886 (19)	11165 (23)
BM+PBSC	250 (1)	85 (1)	5 (<1)	10 (<1)
BM+UCB	122 (<1)	13 (<1)	2 (<1)	0
PBSC+UCB	3 (<1)	4 (<1)	6 (<1)	346 (1)
Others	52 (<1)	54 (<1)	24 (<1)	114 (<1)
Conditioning regimen				
Myeloablative	39639 (80)	7980 (66)	7337 (73)	30719 (62)
RIC	4078 (8)	1258 (10)	1300 (13)	10168 (21)
Nonmyeloablative	3406 (7)	2002 (17)	761 (8)	5408 (11)
Other	2265 (5)	781 (6)	664 (7)	3179 (6)
Donor age at donation				
To Be Determined/NA	1784 (4)	676 (6)	1350 (13)	1657 (3)
0-9 years	5910 (12)	559 (5)	1508 (15)	10177 (21)
10-19 years	7881 (16)	1167 (10)	169 (2)	1333 (3)
20-29 years	8485 (17)	2357 (20)	2133 (21)	14490 (29)
30-39 years	8760 (18)	3039 (25)	2643 (26)	11834 (24)
40-49 years	8009 (16)	2250 (19)	1800 (18)	7720 (16)
50+ years	8559 (17)	1973 (16)	459 (5)	2263 (5)
Median (Range)	31 (-7-85)	35 (-11-81)	32 (0-80)	29 (0-72)
Disease at transplant				
AML	12645 (26)	3162 (26)	2474 (25)	15241 (31)
ALL	7402 (15)	1935 (16)	2043 (20)	7593 (15)
Other leukemia	875 (2)	161 (1)	176 (2)	1352 (3)
CML	7910 (16)	1076 (9)	1801 (18)	4548 (9)
MDS	4062 (8)	1197 (10)	956 (10)	7401 (15)
Other acute leukemia	376 (1)	136 (1)	129 (1)	491 (1)
NHL	3336 (7)	799 (7)	365 (4)	3615 (7)
Hodgkins Lymphoma	515 (1)	263 (2)	82 (1)	935 (2)
Plasma Cell Disorders, MM	1557 (3)	278 (2)	104 (1)	708 (1)
Other malignancies	348 (1)	77 (1)	33 (<1)	100 (<1)
Breast cancer	82 (<1)	26 (<1)	2 (<1)	10 (<1)
SAA	4719 (10)	787 (7)	568 (6)	1730 (3)
Inherited abnormalities erythrocyte diff fxn	3765 (8)	701 (6)	368 (4)	1109 (2)

Variable	CIBMTR HLA-identical sibling N (%)	CIBMTR Alternative related N (%)	CIBMTR Unrelated (non-US) N (%)	CIBMTR Unrelated (US) N (%)
SCIDs	740 (1)	873 (7)	400 (4)	1369 (3)
Inherited abnormalities of platelets	26 (<1)	11 (<1)	14 (<1)	70 (<1)
Inherited disorders of metabolism	272 (1)	179 (1)	266 (3)	1032 (2)
Histiocytic disorders	121 (<1)	85 (1)	128 (1)	488 (1)
Autoimmune disorders	22 (<1)	6 (<1)	5 (<1)	25 (<1)
Other	20 (<1)	7 (<1)	7 (<1)	63 (<1)
MPN	595 (1)	262 (2)	141 (1)	1594 (3)
Disease status at transplant				
Early	12203 (25)	2568 (21)	2030 (20)	12379 (25)
Intermediate	11961 (24)	2295 (19)	2963 (29)	8211 (17)
Advanced	6043 (12)	1882 (16)	1345 (13)	8823 (18)
Other	19181 (39)	5276 (44)	3724 (37)	20061 (41)
Donor/Recipient CMV serostatus				
Negative/Negative	10897 (22)	2397 (20)	2175 (22)	9337 (19)
Negative/Positive	7578 (15)	1882 (16)	1985 (20)	9952 (20)
Positive/Negative	4513 (9)	1311 (11)	1101 (11)	3864 (8)
Positive/Positive	18661 (38)	4386 (36)	2309 (23)	6758 (14)
Unknown	7739 (16)	2045 (17)	2492 (25)	19563 (40)
GvHD Prophylaxis				
Ex vivo T-cell depletion	3420 (7)	2045 (17)	688 (7)	3508 (7)
CD34 selection	538 (1)	436 (4)	94 (1)	1148 (2)
Tacrolimus + MMF +- others	1349 (3)	429 (4)	166 (2)	7078 (14)
Tacrolimus + MTX +- others (except MMF)	5148 (10)	453 (4)	615 (6)	13441 (27)
Tacrolimus + others (except MTX, MMF)	728 (1)	50 (<1)	70 (1)	2071 (4)
Tacrolimus alone	351 (1)	82 (1)	33 (<1)	1001 (2)
CSA + MMF +- others (except Tacrolimus)	1724 (3)	176 (1)	1084 (11)	6355 (13)
CSA + MTX +- others (except Tacrolimus, MMF)	21762 (44)	2195 (18)	5147 (51)	7982 (16)
CSA + others (except Tacrolimus, MTX, MMF)	3705 (8)	293 (2)	1050 (10)	2088 (4)
CSA alone	5142 (10)	476 (4)	465 (5)	424 (1)
Other GVHD prophylaxis	3231 (7)	356 (3)	71 (1)	587 (1)
Missing	2290 (5)	5030 (42)	579 (6)	3791 (8)
Donor/Recipient sex match				
Male/Male	9061 (32)	3036 (37)	2930 (38)	13448 (38)
Male/Female	6027 (22)	1551 (19)	1737 (23)	8408 (24)
Female/Male	7295 (26)	1936 (24)	1604 (21)	7418 (21)
Female/Female	5510 (20)	1642 (20)	1363 (18)	6470 (18)
Unknown	21495 (N/A)	3856 (N/A)	2428 (N/A)	13730 (N/A)
Year of transplant				
1964-1985	4815 (10)	889 (7)	42 (<1)	12 (<1)
1986	1375 (3)	263 (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)

Variable	CIBMTR HLA-identical sibling N (%)	CIBMTR Alternative related N (%)	CIBMTR Unrelated (non-US) N (%)	CIBMTR Unrelated (US) N (%)
1991	1900 (4)	255 (2)	179 (2)	430 (1)
1992	1995 (4)	281 (2)	237 (2)	502 (1)
1993	2006 (4)	288 (2)	242 (2)	607 (1)
1994	1862 (4)	274 (2)	260 (3)	753 (2)
1995	1938 (4)	344 (3)	347 (3)	907 (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)	1173 (2)
1999	1393 (3)	218 (2)	471 (5)	1225 (2)
2000	1511 (3)	217 (2)	523 (5)	1298 (3)
2001	1497 (3)	241 (2)	523 (5)	1392 (3)
2002	1444 (3)	204 (2)	486 (5)	1593 (3)
2003	1232 (2)	175 (1)	517 (5)	1773 (4)
2004	1471 (3)	150 (1)	629 (6)	1986 (4)
2005	1503 (3)	184 (2)	602 (6)	2175 (4)
2006	1260 (3)	151 (1)	503 (5)	2510 (5)
2007	751 (2)	94 (1)	359 (4)	2863 (6)
2008	1077 (2)	247 (2)	326 (3)	2500 (5)
2009	895 (2)	163 (1)	277 (3)	2638 (5)
2010	511 (1)	61 (1)	161 (2)	1949 (4)
2011	320 (1)	70 (1)	121 (1)	1526 (3)
2012	357 (1)	92 (1)	193 (2)	1477 (3)
2013	717 (1)	364 (3)	232 (2)	2276 (5)
2014	1043 (2)	484 (4)	258 (3)	2601 (5)
2015	969 (2)	590 (5)	226 (2)	2439 (5)
2016	912 (2)	742 (6)	216 (2)	2117 (4)
2017	820 (2)	842 (7)	170 (2)	1910 (4)
2018	768 (2)	909 (8)	142 (1)	1764 (4)
2019	674 (1)	983 (8)	121 (1)	1504 (3)
2020	248 (1)	292 (2)	27 (<1)	748 (2)
Follow-up among survivors, Months				
N Eval	23608	5466	4518	18417
Median (Range)	94 (0-513)	43 (0-594)	62 (0-384)	73 (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	44543	15903	8657
Source of data			
CRF	24072 (54)	6924 (44)	4451 (51)
TED	20471 (46)	8979 (56)	4206 (49)
Number of centers	258	232	351
Disease at transplant			
AML	15294 (34)	5896 (37)	2918 (34)
ALL	6535 (15)	2123 (13)	1370 (16)
Other leukemia	1408 (3)	385 (2)	249 (3)
CML	3509 (8)	1045 (7)	695 (8)
MDS	6346 (14)	2568 (16)	1072 (12)
Other acute leukemia	462 (1)	185 (1)	106 (1)
NHL	4032 (9)	1194 (8)	710 (8)
Hodgkin Lymphoma	917 (2)	220 (1)	160 (2)
Plasma Cell Disorders, MM	892 (2)	270 (2)	159 (2)
Other malignancies	59 (<1)	13 (<1)	18 (<1)
Breast cancer	7 (<1)	3 (<1)	1 (<1)
SAA	1428 (3)	485 (3)	344 (4)
Inherited abnormalities erythrocyte diff fxn	727 (2)	251 (2)	157 (2)
Inherited bone marrow failure syndromes	9 (<1)	9 (<1)	11 (<1)
Hemoglobinopathies	8 (<1)	6 (<1)	4 (<1)
Paroxysmal nocturnal hemoglobinuria	1 (<1)	4 (<1)	0
SCIDs	780 (2)	280 (2)	253 (3)
Inherited abnormalities of platelets	40 (<1)	14 (<1)	11 (<1)
Inherited disorders of metabolism	292 (1)	79 (<1)	95 (1)
Histiocytic disorders	376 (1)	107 (1)	94 (1)
Autoimmune disorders	22 (<1)	12 (<1)	5 (<1)
Other	51 (<1)	21 (<1)	19 (<1)
MPN	1347 (3)	733 (5)	204 (2)
Disease missing	1 (N/A)	0 (N/A)	2 (N/A)
AML Disease status at transplant			
CR1	8061 (53)	3434 (58)	1439 (49)
CR2	2975 (19)	1072 (18)	590 (20)
CR3+	330 (2)	95 (2)	67 (2)
Advanced or active disease	3783 (25)	1262 (21)	767 (26)
Missing	145 (1)	33 (1)	55 (2)
ALL Disease status at transplant			
CR1	3206 (49)	1180 (56)	585 (43)
CR2	1873 (29)	548 (26)	393 (29)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
CR3+	558 (9)	157 (7)	139 (10)
Advanced or active disease	852 (13)	222 (10)	217 (16)
Missing	46 (1)	16 (1)	36 (3)
MDS Disease status at transplant			
Early	1380 (22)	488 (19)	256 (24)
Advanced	4003 (63)	1854 (72)	592 (55)
Missing	963 (15)	226 (9)	224 (21)
NHL Disease status at transplant			
CR1	556 (14)	205 (17)	90 (13)
CR2	741 (18)	223 (19)	117 (17)
CR3+	345 (9)	102 (9)	66 (9)
PR	439 (11)	110 (9)	76 (11)
Advanced	1866 (47)	531 (45)	346 (49)
Missing	65 (2)	15 (1)	12 (2)
Recipient age at transplant			
0-9 years	3829 (9)	1110 (7)	1068 (12)
10-19 years	3937 (9)	1138 (7)	978 (11)
20-29 years	4617 (10)	1454 (9)	981 (11)
30-39 years	5099 (11)	1604 (10)	1015 (12)
40-49 years	6813 (15)	2184 (14)	1294 (15)
50-59 years	9175 (21)	3138 (20)	1573 (18)
60-69 years	9168 (21)	4145 (26)	1465 (17)
70+ years	1905 (4)	1130 (7)	283 (3)
Median (Range)	47 (0-84)	52 (0-82)	43 (0-81)
Recipient race/ethnicity			
Caucasian, non-Hispanic	36965 (83)	13172 (83)	6184 (71)
African-American, non-Hispanic	2018 (5)	651 (4)	388 (4)
Asian, non-Hispanic	1027 (2)	498 (3)	331 (4)
Pacific islander, non-Hispanic	55 (<1)	25 (<1)	23 (<1)
Native American, non-Hispanic	168 (<1)	66 (<1)	33 (<1)
Hispanic	2662 (6)	861 (5)	468 (5)
Missing	1648 (4)	630 (4)	1230 (14)
Recipient sex			
Male	25968 (58)	9313 (59)	5132 (59)
Female	18575 (42)	6590 (41)	3525 (41)
Karnofsky score			
10-80	15260 (34)	5968 (38)	2755 (32)
90-100	27634 (62)	9412 (59)	5408 (62)
Missing	1649 (4)	523 (3)	494 (6)
HLA-A B DRB1 groups - low resolution			
<=3/6	28 (<1)	37 (<1)	3 (<1)
4/6	235 (1)	102 (1)	45 (1)
5/6	6059 (14)	1819 (13)	1217 (15)
6/6	37443 (86)	12508 (86)	6817 (84)
Unknown	778 (N/A)	1437 (N/A)	575 (N/A)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
High-resolution HLA matches available out of 8			
<=5/8	884 (2)	102 (1)	45 (1)
6/8	1724 (4)	139 (1)	152 (3)
7/8	8420 (20)	1863 (16)	1254 (22)
8/8	31783 (74)	9524 (82)	4335 (75)
Unknown	1732 (N/A)	4275 (N/A)	2871 (N/A)
HLA-DPB1 Match			
Double allele mismatch	10933 (29)	1275 (23)	590 (26)
Single allele mismatch	20128 (54)	2834 (51)	1199 (52)
Full allele matched	6179 (17)	1427 (26)	512 (22)
Unknown	7303 (N/A)	10367 (N/A)	6356 (N/A)
High resolution release score			
No	9149 (21)	15838 (>99)	8450 (98)
Yes	35394 (79)	65 (<1)	207 (2)
KIR typing available			
No	30764 (69)	15880 (>99)	8609 (99)
Yes	13779 (31)	23 (<1)	48 (1)
Graft type			
Marrow	16082 (36)	4740 (30)	3436 (40)
PBSC	28404 (64)	11007 (69)	5187 (60)
BM+PBSC	11 (<1)	7 (<1)	3 (<1)
PBSC+UCB	27 (<1)	137 (1)	5 (<1)
Others	19 (<1)	12 (<1)	26 (<1)
Conditioning regimen			
Myeloablative	27651 (62)	8835 (56)	5389 (62)
RIC/Nonmyeloablative	16685 (37)	7019 (44)	3146 (36)
TBD	207 (<1)	49 (<1)	122 (1)
Donor age at donation			
To Be Determined/NA	410 (1)	1434 (9)	126 (1)
0-9 years	8 (<1)	36 (<1)	3 (<1)
10-19 years	1223 (3)	550 (3)	184 (2)
20-29 years	20165 (45)	7124 (45)	3529 (41)
30-39 years	12640 (28)	3985 (25)	2591 (30)
40-49 years	7729 (17)	2111 (13)	1682 (19)
50+ years	2368 (5)	663 (4)	542 (6)
Median (Range)	30 (0-69)	29 (0-109)	32 (0-67)
Donor/Recipient CMV serostatus			
+/+	11076 (25)	4431 (28)	2157 (25)
+/-	5279 (12)	2016 (13)	1101 (13)
-/+	14617 (33)	4780 (30)	2679 (31)
-/-	12957 (29)	4204 (26)	2327 (27)
CB - recipient +	3 (<1)	17 (<1)	0
CB - recipient -	1 (<1)	8 (<1)	0
CB - recipient CMV unknown	0	1 (<1)	0
Missing	610 (1)	446 (3)	393 (5)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
GvHD Prophylaxis			
No GvHD Prophylaxis	146 (<1)	65 (<1)	45 (1)
TDEPLETION alone	100 (<1)	31 (<1)	31 (<1)
TDEPLETION +- other	1068 (2)	278 (2)	261 (3)
CD34 select alone	272 (1)	129 (1)	62 (1)
CD34 select +- other	881 (2)	628 (4)	194 (2)
Cyclophosphamide alone	785 (2)	676 (4)	226 (3)
Cyclophosphamide +- others	2016 (5)	1404 (9)	426 (5)
FK506 + MMF +- others	4990 (11)	1515 (10)	694 (8)
FK506 + MTX +- others(not MMF)	18673 (42)	6475 (41)	2380 (27)
FK506 +- others(not MMF,MTX)	2264 (5)	958 (6)	320 (4)
FK506 alone	1019 (2)	361 (2)	147 (2)
CSA + MMF +- others(not FK506)	2904 (7)	746 (5)	700 (8)
CSA + MTX +- others(not MMF,FK506)	6888 (15)	1819 (11)	2318 (27)
CSA +- others(not FK506,MMF,MTX)	1112 (2)	333 (2)	299 (3)
CSA alone	448 (1)	121 (1)	292 (3)
Other GVHD Prophylaxis	735 (2)	250 (2)	145 (2)
Missing	242 (1)	114 (1)	117 (1)
Donor/Recipient sex match			
Male-Male	18261 (41)	6197 (39)	3395 (39)
Male-Female	11147 (25)	3783 (24)	1963 (23)
Female-Male	7474 (17)	2729 (17)	1655 (19)
Female-Female	7249 (16)	2505 (16)	1506 (17)
CB - recipient M	13 (<1)	78 (<1)	0
CB - recipient F	14 (<1)	67 (<1)	6 (<1)
Missing	385 (1)	544 (3)	132 (2)
Year of transplant			
1986-1990	383 (1)	49 (<1)	53 (1)
1991-1995	1959 (4)	460 (3)	503 (6)
1996-2000	3363 (8)	1200 (8)	823 (10)
2001-2005	5238 (12)	1036 (7)	1553 (18)
2006-2010	9426 (21)	1872 (12)	1486 (17)
2011-2015	13159 (30)	3524 (22)	1900 (22)
2016-2020	10087 (23)	6869 (43)	2066 (24)
2021	928 (2)	893 (6)	273 (3)
Follow-up among survivors, Months			
N Eval	18378	7541	3603
Median (Range)	63 (0-385)	36 (0-362)	47 (0-365)

Unrelated Cord 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	5894	1566	1557
Source of data			
CRF	4361 (74)	1124 (72)	947 (61)
TED	1533 (26)	442 (28)	610 (39)
Number of centers	152	138	201
Disease at transplant			
AML	2221 (38)	529 (34)	505 (32)
ALL	1222 (21)	344 (22)	347 (22)
Other leukemia	93 (2)	30 (2)	27 (2)
CML	128 (2)	35 (2)	38 (2)
MDS	523 (9)	151 (10)	119 (8)
Other acute leukemia	93 (2)	26 (2)	28 (2)
NHL	394 (7)	89 (6)	100 (6)
Hodgkin Lymphoma	97 (2)	27 (2)	27 (2)
Plasma Cell Disorders, MM	37 (1)	12 (1)	11 (1)
Other malignancies	11 (<1)	1 (<1)	1 (<1)
SAA	93 (2)	31 (2)	27 (2)
Inherited abnormalities erythrocyte diff fxn	165 (3)	50 (3)	33 (2)
Inherited bone marrow failure syndromes	2 (<1)	2 (<1)	1 (<1)
Hemoglobinopathies	1 (<1)	0	0
SCIDs	262 (4)	87 (6)	122 (8)
Inherited abnormalities of platelets	20 (<1)	5 (<1)	7 (<1)
Inherited disorders of metabolism	361 (6)	105 (7)	105 (7)
Histiocytic disorders	105 (2)	27 (2)	38 (2)
Autoimmune disorders	9 (<1)	0	2 (<1)
Other	11 (<1)	2 (<1)	5 (<1)
MPN	46 (1)	13 (1)	14 (1)
AML Disease status at transplant			
CR1	1147 (52)	287 (54)	241 (48)
CR2	608 (27)	139 (26)	139 (28)
CR3+	62 (3)	8 (2)	22 (4)
Advanced or active disease	398 (18)	93 (18)	101 (20)
Missing	6 (<1)	2 (<1)	2 (<1)
ALL Disease status at transplant			
CR1	550 (45)	146 (42)	146 (42)
CR2	451 (37)	124 (36)	125 (36)
CR3+	143 (12)	51 (15)	48 (14)
Advanced or active disease	77 (6)	21 (6)	28 (8)
Missing	1 (<1)	2 (1)	0

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
MDS Disease status at transplant			
Early	163 (31)	41 (27)	52 (44)
Advanced	315 (60)	95 (63)	48 (40)
Missing	45 (9)	15 (10)	19 (16)
NHL Disease status at transplant			
CR1	60 (15)	6 (7)	18 (18)
CR2	74 (19)	20 (22)	31 (31)
CR3+	44 (11)	10 (11)	9 (9)
PR	67 (17)	12 (13)	11 (11)
Advanced	146 (37)	40 (45)	28 (28)
Missing	0	1 (1)	2 (2)
Recipient age at transplant			
0-9 years	1776 (30)	580 (37)	578 (37)
10-19 years	776 (13)	175 (11)	211 (14)
20-29 years	556 (9)	110 (7)	131 (8)
30-39 years	569 (10)	141 (9)	153 (10)
40-49 years	623 (11)	154 (10)	144 (9)
50-59 years	803 (14)	190 (12)	184 (12)
60-69 years	683 (12)	188 (12)	145 (9)
70+ years	108 (2)	28 (2)	11 (1)
Median (Range)	27 (0-83)	22 (0-76)	19 (0-78)
Recipient race/ethnicity			
Caucasian, non-Hispanic	3254 (55)	917 (59)	834 (54)
African-American, non-Hispanic	841 (14)	204 (13)	176 (11)
Asian, non-Hispanic	340 (6)	107 (7)	105 (7)
Pacific islander, non-Hispanic	30 (1)	3 (<1)	16 (1)
Native American, non-Hispanic	42 (1)	9 (1)	18 (1)
Hispanic	1054 (18)	229 (15)	209 (13)
Missing	333 (6)	97 (6)	199 (13)
Recipient sex			
Male	3249 (55)	892 (57)	879 (56)
Female	2645 (45)	674 (43)	678 (44)
Karnofsky score			
10-80	1563 (27)	400 (26)	391 (25)
90-100	4149 (70)	1075 (69)	1056 (68)
Missing	182 (3)	91 (6)	110 (7)
HLA-A B DRB1 groups - low resolution			
<=3/6	97 (2)	38 (3)	12 (1)
4/6	2341 (41)	537 (40)	555 (39)
5/6	2550 (45)	566 (42)	647 (46)
6/6	718 (13)	191 (14)	202 (14)
Unknown	188 (N/A)	234 (N/A)	141 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	2777 (55)	537 (56)	609 (54)
6/8	1193 (24)	228 (24)	279 (25)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
7/8	701 (14)	129 (13)	166 (15)
8/8	333 (7)	70 (7)	79 (7)
Unknown	890 (N/A)	602 (N/A)	424 (N/A)
HLA-DPB1 Match			
Double allele mismatch	815 (39)	97 (43)	109 (39)
Single allele mismatch	1065 (51)	108 (48)	145 (51)
Full allele matched	199 (10)	21 (9)	28 (10)
Unknown	3815 (N/A)	1340 (N/A)	1275 (N/A)
High resolution release score			
No	4378 (74)	1500 (96)	1539 (99)
Yes	1516 (26)	66 (4)	18 (1)
KIR typing available			
No	4634 (79)	1560 (>99)	1545 (99)
Yes	1260 (21)	6 (<1)	12 (1)
Graft type			
UCB	5557 (94)	1429 (91)	1472 (95)
BM+UCB	1 (<1)	0	0
PBSC+UCB	307 (5)	137 (9)	78 (5)
Others	29 (<1)	0	7 (<1)
Number of cord units			
1	4944 (84)	0	1310 (84)
2	946 (16)	0	247 (16)
3	2 (<1)	0	0
Unknown	2 (N/A)	1566 (N/A)	0 (N/A)
Conditioning regimen			
Myeloablative	3852 (65)	1008 (64)	978 (63)
RIC/Nonmyeloablative	2029 (34)	554 (35)	570 (37)
TBD	13 (<1)	4 (<1)	9 (1)
Donor age at donation			
To Be Determined/NA	209 (4)	113 (7)	120 (8)
0-9 years	5183 (88)	1205 (77)	1316 (85)
10-19 years	296 (5)	141 (9)	70 (4)
20-29 years	65 (1)	35 (2)	11 (1)
30-39 years	56 (1)	34 (2)	18 (1)
40-49 years	39 (1)	17 (1)	8 (1)
50+ years	46 (1)	21 (1)	14 (1)
Median (Range)	3 (0-72)	5 (0-73)	3 (0-69)
Donor/Recipient CMV serostatus			
+/+	1338 (23)	309 (20)	307 (20)
+/-	573 (10)	148 (9)	145 (9)
-/+	1084 (18)	283 (18)	267 (17)
-/-	724 (12)	195 (12)	201 (13)
CB - recipient +	1253 (21)	336 (21)	339 (22)
CB - recipient -	828 (14)	238 (15)	238 (15)
CB - recipient CMV unknown	94 (2)	57 (4)	60 (4)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
GvHD Prophylaxis			
No GvHD Prophylaxis	21 (<1)	8 (1)	9 (1)
TDEPLETION alone	1 (<1)	0	0
TDEPLETION +- other	27 (<1)	9 (1)	5 (<1)
CD34 select alone	0	2 (<1)	2 (<1)
CD34 select +- other	287 (5)	136 (9)	84 (5)
Cyclophosphamide alone	0	0	2 (<1)
Cyclophosphamide +- others	47 (1)	27 (2)	53 (3)
FK506 + MMF +- others	1622 (28)	415 (27)	260 (17)
FK506 + MTX +- others(not MMF)	214 (4)	56 (4)	71 (5)
FK506 +- others(not MMF,MTX)	221 (4)	63 (4)	65 (4)
FK506 alone	139 (2)	43 (3)	23 (1)
CSA + MMF +- others(not FK506)	2689 (46)	610 (39)	707 (45)
CSA + MTX +- others(not MMF,FK506)	99 (2)	33 (2)	41 (3)
CSA +- others(not FK506,MMF,MTX)	333 (6)	124 (8)	151 (10)
CSA alone	50 (1)	18 (1)	50 (3)
Other GVHD Prophylaxis	132 (2)	19 (1)	25 (2)
Missing	12 (<1)	3 (<1)	9 (1)
Donor/Recipient sex match			
CB - recipient M	3249 (55)	892 (57)	878 (56)
CB - recipient F	2645 (45)	674 (43)	678 (43)
CB - recipient sex unknown	0	0	1 (<1)
Year of transplant			
1996-2000	1 (<1)	2 (<1)	5 (<1)
2001-2005	115 (2)	108 (7)	27 (2)
2006-2010	1811 (31)	413 (26)	492 (32)
2011-2015	2613 (44)	501 (32)	608 (39)
2016-2020	1300 (22)	506 (32)	389 (25)
2021	54 (1)	36 (2)	36 (2)
Follow-up among survivors, Months			
N Eval	2805	808	788
Median (Range)	66 (1-196)	56 (3-213)	52 (1-240)

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 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	9695	1555	646
Source of data			
CRF	3455 (36)	446 (29)	245 (38)
TED	6240 (64)	1109 (71)	401 (62)
Number of centers	90	72	59
Disease at transplant			
AML	3214 (33)	506 (33)	206 (32)
ALL	1578 (16)	299 (19)	124 (19)
Other leukemia	189 (2)	35 (2)	14 (2)
CML	314 (3)	36 (2)	20 (3)
MDS	1277 (13)	191 (12)	92 (14)
Other acute leukemia	133 (1)	29 (2)	7 (1)
NHL	856 (9)	141 (9)	61 (9)
Hodgkin Lymphoma	188 (2)	37 (2)	17 (3)
Plasma Cell Disorders, MM	254 (3)	40 (3)	18 (3)
Other malignancies	24 (<1)	0	0
Breast cancer	1 (<1)	0	0
SAA	442 (5)	62 (4)	20 (3)
Inherited abnormalities erythrocyte diff fxn	484 (5)	69 (4)	20 (3)
Inherited bone marrow failure syndromes	7 (<1)	1 (<1)	0
Hemoglobinopathies	35 (<1)	7 (<1)	2 (<1)
Paroxysmal nocturnal hemoglobinuria	2 (<1)	0	0
SCIDs	201 (2)	33 (2)	11 (2)
Inherited abnormalities of platelets	10 (<1)	0	0
Inherited disorders of metabolism	14 (<1)	3 (<1)	2 (<1)
Histiocytic disorders	57 (1)	6 (<1)	3 (<1)
Autoimmune disorders	11 (<1)	0	1 (<1)
Other	11 (<1)	3 (<1)	1 (<1)
MPN	393 (4)	57 (4)	27 (4)
AML Disease status at transplant			
CR1	2063 (64)	340 (67)	134 (65)
CR2	486 (15)	66 (13)	26 (13)
CR3+	38 (1)	13 (3)	1 (<1)
Advanced or active disease	619 (19)	83 (16)	45 (22)
Missing	8 (<1)	4 (1)	0
ALL Disease status at transplant			
CR1	974 (62)	195 (65)	76 (61)
CR2	437 (28)	69 (23)	31 (25)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
CR3+	88 (6)	13 (4)	10 (8)
Advanced or active disease	78 (5)	22 (7)	7 (6)
Missing	1 (<1)	0	0
MDS Disease status at transplant			
Early	209 (16)	26 (14)	18 (20)
Advanced	1026 (80)	154 (81)	69 (75)
Missing	42 (3)	11 (6)	5 (5)
NHL Disease status at transplant			
CR1	154 (18)	32 (23)	11 (18)
CR2	162 (19)	31 (22)	8 (13)
CR3+	93 (11)	15 (11)	2 (3)
PR	67 (8)	13 (9)	5 (8)
Advanced	371 (44)	49 (35)	34 (56)
Missing	5 (1)	0	1 (2)
Recipient age at transplant			
0-9 years	961 (10)	137 (9)	48 (7)
10-19 years	1139 (12)	139 (9)	56 (9)
20-29 years	829 (9)	169 (11)	51 (8)
30-39 years	763 (8)	137 (9)	66 (10)
40-49 years	1226 (13)	196 (13)	77 (12)
50-59 years	2129 (22)	350 (23)	133 (21)
60-69 years	2254 (23)	369 (24)	190 (29)
70+ years	394 (4)	58 (4)	25 (4)
Median (Range)	50 (0-82)	50 (0-76)	52 (0-83)
Recipient race/ethnicity			
Caucasian, non-Hispanic	6077 (63)	825 (53)	421 (65)
African-American, non-Hispanic	1174 (12)	188 (12)	55 (9)
Asian, non-Hispanic	438 (5)	116 (7)	31 (5)
Pacific islander, non-Hispanic	30 (<1)	3 (<1)	1 (<1)
Native American, non-Hispanic	37 (<1)	4 (<1)	2 (<1)
Hispanic	1434 (15)	298 (19)	102 (16)
Missing	505 (5)	121 (8)	34 (5)
Recipient sex			
Male	5676 (59)	917 (59)	380 (59)
Female	4019 (41)	638 (41)	266 (41)
Karnofsky score			
10-80	3458 (36)	625 (40)	284 (44)
90-100	5979 (62)	887 (57)	338 (52)
Missing	258 (3)	43 (3)	24 (4)
Graft type			
Marrow	2780 (29)	348 (22)	168 (26)
PBSC	6834 (70)	1181 (76)	464 (72)
UCB (related)	2 (<1)	10 (1)	0
BM+PBSC	8 (<1)	4 (<1)	1 (<1)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
BM+UCB	38 (<1)	11 (1)	2 (<1)
PBSC+UCB	0	0	11 (2)
Others	33 (<1)	1 (<1)	0
Conditioning regimen			
Myeloablative	5411 (56)	862 (55)	327 (51)
RIC/Nonmyeloablative	4233 (44)	683 (44)	307 (48)
TBD	51 (1)	10 (1)	12 (2)
Donor age at donation			
To Be Determined/NA	16 (<1)	10 (1)	1 (<1)
0-9 years	659 (7)	89 (6)	28 (4)
10-19 years	983 (10)	140 (9)	56 (9)
20-29 years	1354 (14)	231 (15)	97 (15)
30-39 years	1382 (14)	246 (16)	121 (19)
40-49 years	1574 (16)	258 (17)	88 (14)
50+ years	3727 (38)	581 (37)	255 (39)
Median (Range)	43 (0-82)	43 (0-79)	43 (1-76)
Donor/Recipient CMV serostatus			
+/+	3949 (41)	706 (45)	248 (38)
+/-	1079 (11)	127 (8)	60 (9)
-/+	2411 (25)	368 (24)	163 (25)
-/-	2115 (22)	325 (21)	151 (23)
CB - recipient +	0	3 (<1)	0
CB - recipient -	0	0	3 (<1)
Missing	141 (1)	26 (2)	21 (3)
GvHD Prophylaxis			
No GvHD Prophylaxis	103 (1)	14 (1)	6 (1)
TDEPLETION alone	40 (<1)	17 (1)	4 (1)
TDEPLETION +- other	63 (1)	19 (1)	7 (1)
CD34 select alone	77 (1)	20 (1)	6 (1)
CD34 select +- other	371 (4)	86 (6)	47 (7)
Cyclophosphamide alone	261 (3)	50 (3)	24 (4)
Cyclophosphamide +- others	2500 (26)	360 (23)	176 (27)
FK506 + MMF +- others	690 (7)	73 (5)	19 (3)
FK506 + MTX +- others(not MMF)	3524 (36)	478 (31)	233 (36)
FK506 +- others(not MMF,MTX)	713 (7)	253 (16)	49 (8)
FK506 alone	67 (1)	9 (1)	3 (<1)
CSA + MMF +- others(not FK506)	223 (2)	33 (2)	12 (2)
CSA + MTX +- others(not MMF,FK506)	666 (7)	83 (5)	33 (5)
CSA +- others(not FK506,MMF,MTX)	80 (1)	10 (1)	1 (<1)
CSA alone	76 (1)	9 (1)	3 (<1)
Other GVHD Prophylaxis	136 (1)	16 (1)	12 (2)
Missing	105 (1)	25 (2)	11 (2)
Donor/Recipient sex match			
Male-Male	3212 (33)	546 (35)	222 (34)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Male-Female	2068 (21)	313 (20)	136 (21)
Female-Male	2436 (25)	350 (23)	150 (23)
Female-Female	1934 (20)	317 (20)	125 (19)
CB - recipient M	24 (<1)	15 (1)	8 (1)
CB - recipient F	16 (<1)	6 (<1)	5 (1)
Missing	5 (<1)	8 (1)	0
Year of transplant			
2006-2010	604 (6)	72 (5)	38 (6)
2011-2015	3665 (38)	491 (32)	181 (28)
2016-2020	4930 (51)	874 (56)	361 (56)
2021	496 (5)	118 (8)	66 (10)
Follow-up among survivors, Months			
N Eval	5758	893	368
Median (Range)	37 (1-150)	29 (0-124)	27 (2-143)

Response Summary:

This form is intended to be completed by a physician/researcher for the purpose of proposing a study. Content should not include Personal Identifiable Information (PII) or Protected Health Information (PHI). If you are a patient, do not complete this form. <u>Patients:</u> Contact your healthcare provider immediately for reports of problems with your treatment or problems with products received for your treatment. The CIBMTR uses de-identified data and is unable to associate reported treatment problems, adverse events, or corrections of information with a center, clinical trial, or healthcare provider.

Q1. Study Title

Effect of SIRPα mismatch on the outcome of allogeneic hematopoietic stem cell transplantation (HSCT) from an HLA matched related donor (MRD)

Q2. Key Words

SIRPα mismatch, Innate allorecognition, Matched related donor

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Jun Zou, MD., Ph.D.
Email address:	jzou@mdanderson.org
Institution name:	The University of Texas MD Anderson Cancer Center
Academic rank:	Assistant Professor

Q4. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- **No**

Q5. Do you identify as an underrepresented/minority?

- **No**

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Samer Srour, MD, MS
Email address:	SSrour@mdanderson.org
Institution name:	University of Texas MD Anderson Cancer Center
Academic rank:	Assistant Professor

Q7. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

N/A

Q8. Do you identify as an underrepresented/minority?

N/A

Q9. We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below:

N/A

Q10. If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:

N/A

LETTER OF COMMITMENT:

Please note: A letter of commitment will be signed by Lead and Last authors as it describes the expectations for filling that role. By signing the letter of commitment, the authors accept their responsibilities and will be held accountable for timely completion of all steps in the project. More details regarding author responsibilities can be found here:

https://www.cibmtr.org/Studies/Observational/StudyManagement/

Q12. CURRENT ONGOING WORK WITH CIBMTR: Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.

IB20-02: Evaluation of the impact of HLA molecular mismatch on clinical outcomes in patients who underwent haploidentical hematopoietic stem cell transplantation
Role: Corresponding PI
Status: Manuscript is under revision

Q13. PROPOSED WORKING COMMITTEE:

- **Immunobiology**

Q14. Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.

- **No**

Q15. RESEARCH QUESTION:

Whether the effect of mismatch in SIRPα, a regulatory protein in innate immunity, is associated with a higher risk of chronic graft-versus-host disease (cGVHD) in the HSCT from a matched related donor.

Q16. RESEARCH HYPOTHESIS:

SIRPα variant mismatch in HSCT may elicit a non-self recognition caused by a different binding between SIRPα-CD47. The enhanced innate immunity may further promote alloimmunity through specific effector cells and subsequentially lead to a higher risk of cGVHD accompanied by a lower risk of relapse.

Q17. SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.)

Suggested word limit of 200 words:

1. Retrospective analysis of SIRPα mismatch in HSCT from MRD to minimize the confounding alloreactivity caused by HLA mismatch. The SIRPα genotyping will be examined and the prevalence of SIRPα mismatch in allo-HSCT from MRD will be studied.
2. The clinical significance of SIRPα mismatch will be investigated; including the correlation between the mismatch and relapse, acute and chronic GVHD, overall and event-free survival, non-relapse mortality. This will determine the clinical role of SIRPα mismatch in the setting of HSCT.

Q18. SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.

Recent compelling evidence from experimental models demonstrated that the innate immune system could recognize the non-self signals and subsequentially prime the immunity against allogeneic grafts (1). Unlike allorecognition medicated by T cells, allorecognition by innate system seems to be independent of MHC mismatch and is possibly initiated by the mismatching signal from non-MHC genomic loci (2). Yet, whether the effect observed in the murine model still holds in the clinic, especially in the HSCT setting remained largely unknown.

The signal regulatory protein α (SIRPα) is an Ig superfamily receptor exclusively expressed on innate cells, whereas its ligand CD47 is expressed ubiquitously. The interaction of SIRPα/CD47 elicits an inhibitory signal and suppresses macrophage phagocytic function (3). It has been shown that SIRPα is polymorphic which could result in the non-self signaling upon binding to the CD47 with different affinity when mismatched SIRPα is introduced with allograft (4, 5). Our preliminary study in acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) patients (n=350) who underwent HSCT from MRD demonstrated for the first time that SIRPα is mismatched on both or one allele in 39% of transplants, and the presence of the mismatch is associated with a higher risk of cGVHD and a lower risk of relapse compared with matched SIRPα transplants (6). While the specific variations in human SIRPα have been identified (5) and the mismatches are frequently identified, the clinical impact of the mismatch of SIRPα on HSCT needs to been studied thoroughly. The optimal donor could be selected based on the finding of the study to mitigate the risk of GVHD and relapse.

Q19. SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary.

Regardless of the recent improvement in prophylaxis and the management of GVHD, GVHD remains a major complication of HSCT with significant morbidity and mortality (https://bloodcell.transplant.hrsa.gov). it has been demonstrated that donor T lymphocytes and recipient antigen-presenting cells (APCs) play crucial roles in the pathogenesis of GVHD and the beneficial Graft-versus-Leukemia (GVL) effect. As the most common long-term complication after HSCT, between 35% to 80% of patients develop chronic cGVHD with a wide spectrum of clinical symptoms (7) and a 5-year mortality rate of 30-50% (8). Given the high incidence and the risk of death and disability resulted from cGVHD, understanding the pathogenesis and the contributors of cGVHD would be critical.

In contrast to the cells from the adaptive immune system that express rearranging receptors upon recognizing non-self antigens, it was conventionally believed that cells from the innate immune system, suchas macrophages and monocytes that do not express rearranging receptors, are not involved in the allorecognition process. Instead, innate immunity is induced by non-specific “danger” molecules released from dying graft cells after transplant. Nevertheless, recent studies using immunodeficient mice showed that the innate immune system could specifically differentiate the non-self graft and subsequently prime the adaptive immune system. In a mouse model that lacks adaptive immune effector cells including T and B lymphocytes and NK cells, allogeneic but not syngeneic grafts induced persistent maturation of dendritic cells (DC) derived from host monocytes, which successively produced cytokines and stimulated T cell proliferation in vitro (1). Whether the innate immune system could sense the allograft and further promote the development of T-cell mediated GVHD has never been studied in humans. Moreover, an emerging body of evidence revealed that innate immune activation is crucial for the initiation and persistence of cGVHD, and innate responses were upregulated in the patient with cGVHD (9).

A study using a murine model with marrow plug transplantation showed the mismatches of SIRPα between donor and recipients is associated with the enhanced allorecognition response in transplant, further evidence suggested that the mismatched SIRPα molecule introduced by allograft may be recognized as non-self due to unbalance signals through different SIRPα-CD47 binding, which could subsequently result in an enhanced monocytes activation and DCs transformation (4). For the first time, we recently demonstrated that the mismatch of SIRPα, the regulatory protein exclusively expressed on the innate cells, is associated with a higher risk of cGVHD and relapse protection in a cohort of AML patients underwent HSCT transplantation (6). To minimize the confounding alloreactivity caused by HLA-mismatch, we set off and studied a cohort of patients who had undergone allo-HSCT from MRD for treatment of AML/MDL. Remarkably, we found that SIRPα mismatch was commonly detected in 39% of transplant donor/recipient pairs, and the presence of the mismatch was associated with a significant increase of cGvHD (hazard ratio [HR], 1.5; P = .03) and a lower trend of early relapse (HR, 0.6; P = .05) (6). It is worth noting that the association of SIRPα mismatch was significant for de novo cGVHD (HR, 2.0; P = .01) but not for +100 day incidence of aGVHD grade 2-4 (P = .8) (Figure 1), suggesting the pathogenesis of cGVHD associated with SIRPα mismatch is not simply a progression from overlaying aGVHD and might involve unique effect cells and pathways (Figure 2).

More recently, we further studied the impact of SIRPα mismatch in recipients of allo-HSCT for the treatment of lymphoid malignancies. The patients received their first allo-HSCT from an HLA matched-related donor at our institution between January 2008 and December 2018 for the treatment of lymphoid malignancies. Only engrafted patients who received tacrolimus/methotrexate for GvHD prophylaxis and a peripheral stem cell graft were included in the study. Among 310 eligible patients, 42% (N=130) of donor/recipient pairs were SIRPα mismatched. The majority of 310 patients were treated for acute lymphoblastic leukemia (N=115, 37%) or non-Hodgkin’s lymphoma (NHL) (N=114, 37%), followed by chronic lymphoblastic leukemia (N=59, 19%), and Hodgkin’s lymphoma (N=22, 7%). The vast majority (N=259, 84%) of patients had the chemo-sensitive disease. Outcomes were evaluated accounting for competing risks. Remarkably, Multivariate analysis showed that SIRPα mismatch was associated with a significantly higher rate of cGvHD (HR, 1.9; P = .005) requiring systemic immunosuppressive therapy, and a lower rate of disease progression (HR, 0.5; P = .004). There was no significant impact of SIRPα mismatch on grade 2-4 acute GVHD (HR, 1.2; P = .3) or NRM (HR, 0.7; P = .3) (Figure 3). We additionally evaluated the impact of mismatch directionality and found both GVH or HVG mismatches impacted outcomes in the same direction.

The validation of a genetic biomarker of cGVHD is rather complex and requires multiple steps (10), an independent series of well-controlled HSCT studies are warranted to verify our findings. Our initial study analyzed a relatively small number of patients, which may result in a lower statistical power to detect the subtle impact of SIRPα mismatch. While no significant outcome difference was notified between the GVH mismatch group and HVG mismatch group in our study, the positive findings could be overlooked due to limited statistical power. Moreover, other confounding factors such as underlying disease, stem cell source, conditioning intensity, and GVHD prophylactic regimens, could be instrumental in modulating both innate and adaptive immune response and remain to be investigated.

Q19a. SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF)

[Click here]

Q20. PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.

All patients with hematological malignancies (AML/MDS/ALL) who underwent a first HSCT from an HLA matched related donor from January 2010 to December 2019 and reported to CIBMTR, and donor /patient DNA samples are available for SIRPα testing, will be included in the study. The patients who received post-transplant cyclophosphamide (PTCy) as GVHD prophylaxis will be excluded from the study.

Q21. Does this study include pediatric patients?

- **Yes**

Q22. DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion-variables to be considered in the multivariate analyses. Data collection forms available at: http://www.cibmtr.org/DataManagement/DataCollection Outline any supplementary data required. Additional data collection is extremely difficult and will make your proposal less feasible.

ENDPOINTS:
PRIMARY ENDPOINTS:
- Chronic graft-versus-host disease (cGVHD)

SECONDARY ENDPOINTS:
- Acute GVHD at day 100 (II-IV)
- Relapse
- Overall survival (OS)
- Disease-free survival (DFS)
- Non-relapse mortality (NRM)
- Cumulative incidence of neutrophil and platelet engraftment

VARIABLES TO BE ANALYZED
Patient-related:
− Age: continuous and 18-29 vs. 30-39 vs. 40-49 vs. 50-59 vs. ≥ 60
− Gender: male vs. female
− Karnofsky score: <90 vs. 90-100%
− Hematopoietic Cell Transplantation- Comorbidity Index (HCT-CI) Score: 0, 1, 2 and ≥3
− Cytomegalovirus serostatus

Disease-related:
− Diagnosis: AML vs. MDS vs. ALL
− Disease status at transplant: early vs. advanced; (complete remission vs. minimal residual disease or active disease)
− Disease Risk Index: Low or intermediate vs. High or very high risk

Transplant-related:
− Donor and recipient SIRPα typing
− SIRPα matching status based on the genotyping result (Matched vs Mismatched)
− Year of transplant: 2010-2019
− Condition regimen intensity: myeloablative vs. non-myeloablative
− GVHD prophylaxis (tacrolimus/methotrexate; tacrolimus /MMF; others; etc.)
− Donor cytomegalovirus serostatus match: P/P, P/N, N/P, N/N
− Donor-recipient gender match: M/M, M/F, F/M, F/F
− Donor age- continuous
− Source of stem cells: (BM vs PBSC)

Q23. PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis specific to PROS.

For additional information on what PRO measures have been collected and timepoints of collection, please reach out to the Late Effects and Quality of Life or Health Services Working Committee leadership: https://www.cibmtr.org/About/WhoWeAre/Com

NA

Q24. SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal shouldalso include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous experience with the proposed assay systems. PIs should be encouraged to review the inventory details, sample types collected and reach out to research_repos@nmdp.org with any questions.

More information can be found at: https://www.cibmtr.org/Samples/Inventory/Pages/index

SIRPα typing was performed with two sets of SIRPα-specific targeting primers. Primer recognition sites were described previously. Each 20-μl PCR reaction included 2 μl of tested DNA at 20 ng/μl, 4 μl of primer mix, 13.9 μl of Labtype primer set Dmix (LTPDMX-B, One lambda), and 0.1 μl of Tag polymerase. PCR was conducted at 96 °C for 2 minutes, at 10× (96 °C for 10 seconds, 63 °C for 1 minute) and 20× (96 °C for 10 seconds, 59 °C for 50 seconds, 72 °C for 30 seconds). A total of 20 μl of the product was run on a 2% agarose gel by electrophoresis, along with controls. Typing was determined by the presence or absence of specific amplicons. SIRPα variants were identified and separated into two categories with different CD47 binding interfaces. In short, we will need roughly 5 μl of tested DNA at 20 ng/μl for each recipient and donor.

The PCR amplification and the interpretation are straightforward. We have successfully handled and tested over 2,000 DNA samples from donors or recipients, evidenced by one publication (Blood advances, 2021) and two accepted abstracts (ASH 2021/TCT 2022). Very rarely (<0.5%), the application failed due to the degradation or poor quality of tested DNA.

Q25. NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required, i.e., neither database contains all the data required to answer the study question.

NA

Q26. REFERENCES:

REFERENCES

1. Oberbarnscheidt MH, Zeng Q, Li Q, Dai H, Williams AL, Shlomchik WD, Rothstein DM, Lakkis FG. Non-self recognition by monocytes initiates allograft rejection. J Clin Invest. 2014 Aug;124(8):3579-89. Epub 2014/07/02. doi:10.1172/JCI74370. Cited in: Pubmed; PMID 24983319.
2. Zecher D, van Rooijen N, Rothstein DM, Shlomchik WD, Lakkis FG. An innate response toallogeneic nonself mediated by monocytes. J Immunol. 2009 Dec 15;183(12):7810-6. Epub 2009/11/20. doi:10.4049/jimmunol.0902194. Cited in: Pubmed; PMID 19923456.
3. Veillette A, Chen J. SIRPalpha-CD47 Immune Checkpoint Blockade in Anticancer Therapy. Trends Immunol. 2018 Mar;39(3):173-184. Epub 2018/01/18. doi:10.1016/j.it.2017.12.005. Cited in: Pubmed; PMID 29336991.
4. Dai H, Friday AJ, Abou-Daya KI, Williams AL, Mortin-Toth S, Nicotra ML, Rothstein DM, Shlomchik WD, Matozaki T, Isenberg JS, Oberbarnscheidt MH, Danska JS, Lakkis FG. Donor SIRPalpha polymorphism modulates the innate immune response to allogeneic grafts. Sci Immunol. 2017 Jun 23;2(12). Epub 2017/08/08. doi:10.1126/sciimmunol.aam6202. Cited in: Pubmed; PMID 28783664.
5. Takenaka K, Prasolava TK, Wang JC, Mortin-Toth SM, Khalouei S, Gan OI, Dick JE, Danska JS. Polymorphism in Sirpa modulates engraftment of human hematopoietic stem cells. Nat Immunol. 2007 Dec;8(12):1313-23. Epub 2007/11/06. doi:10.1038/ni1527. Cited in: Pubmed; PMID 17982459.
6. Saliba RM, Greenbaum U, Ma Q, Srour SA, Carmazzi Y, Li L, Oran B, Moller M, Wood J, Ciurea SO, Kongtim P, Rondon G, Partlow D, Li D, Rezvani K, Shpall EJ, Cao K, Champlin RE, Zou J. Mismatch in SIRPalpha, a regulatory protein in innate immunity, is associated with chronic GVHD in hematopoietic stem cell transplantation. Blood Adv. 2021 Sep 14;5(17):3407-3417. Epub 2021/09/09. doi:10.1182/bloodadvances.2021004307. Cited in: Pubmed; PMID 34495313.
7. Mawardi H, Hashmi SK, Elad S, Aljurf M, Treister N. Chronic graft-versus-host disease: Current management paradigm and future perspectives. Oral Dis. 2019 May;25(4):931-948. Epub 2018/07/10. doi:10.1111/odi.12936. Cited in: Pubmed; PMID 29984442.
8. Blazar BR, Murphy WJ, Abedi M. Advances in graft-versus-host disease biology and therapy. Nature reviews Immunology. 2012 May 11;12(6):443-58. Epub 2012/05/12. doi:10.1038/nri3212. Cited in: Pubmed; PMID 22576252.
9. Hakim FT, Memon S, Jin P, Imanguli MM, Wang H, Rehman N, Yan XY, Rose J, Mays JW, Dhamala S, Kapoor V, Telford W, Dickinson J, Davis S, Halverson D, Naik HB, Baird K, Fowler D, Stroncek D, Cowen EW, Pavletic SZ, Gress RE. Upregulation of IFN-Inducible and Damage-Response Pathways in Chronic Graft-versus-Host Disease. J Immunol. 2016 Nov 1;197(9):3490-3503. Epub 2016/10/04. doi:10.4049/jimmunol.1601054. Cited in: Pubmed; PMID 27694491.
10. Paczesny S, Hakim FT, Pidala J, Cooke KR, Lathrop J, Griffith LM, Hansen J, Jagasia M, Miklos D, Pavletic S, Parkman R, Russek-Cohen E, Flowers ME, Lee S, Martin P, Vogelsang G, Walton M, Schultz KR. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: III. The 2014 Biomarker Working Group Report. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2015 May;21(5):780-92. Epub 2015/02/04. doi:10.1016/j.bbmt.2015.01.003. Cited in: Pubmed; PMID 25644957.
11. Crivello P, Zito L, Sizzano F, Zino E, Maiers M, Mulder A, Toffalori C, Naldini L, Ciceri F, Vago L, Fleischhauer K. The impact of amino acid variability on alloreactivity defines a functional distance predictive of permissive HLA-DPB1 mismatches in hematopoietic stem cell transplantation. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2015 Feb;21(2):233-41. doi:10.1016/j.bbmt.2014.10.017. Cited in: Pubmed; PMID 25445022.
12. Oran B, Saliba RM, Carmazzi Y, de Lima M, Rondon G, Ahmed S, Alousi A, Andersson BS, Anderlini P, Alvarez M, Bashir Q, Ciurea S, Fernandez-Vina M, Hosing C, Kebriaei P, Korbling M, Cano P, Khouri I, Marin D, Nieto Y, Olson A, Popat U, Rezvani K, Qazilbash M, Shpall EJ, Champlin RE, Cao K. Effect of nonpermissive HLA-DPB1 mismatches after unrelated allogeneic transplantation with in vivo T-cell depletion. Blood. 2018 Mar 15;131(11):1248-1257. Epub 2018/02/02. doi:10.1182/blood-2017-07-798751. Cited in: Pubmed; PMID 29386198.
13. Duquesnoy RJ. Reflections on HLA Epitope-Based Matching for Transplantation. Front Immunol. 2016;7:469. Epub 2016/12/15. doi:10.3389/fimmu.2016.00469. Cited in: Pubmed; PMID 27965660.
14. Cox. D. Regression models and life tables (with Discussion) Journal of the Royal Statistical Society. 1972; (34):187-200.
15. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association. 1999 1999/06/01;94(446):496-509. doi:10.1080/01621459.1999.10474144.

Q27. CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:

1. Employment (such as an independent contractor, consultant or providing expert testimony)?
2. Relationships (such as executive and advisory committee positions, medical consultant, speaker's bureau)?
3. Ownership (such as equity, ownership or financial interests)?
4. Transactions (such as honoraria, patents, royalties and licenses)?
5. Legal (such as pending or current arbitration or legal proceedings)?

- No, I do not have any conflicts of interest pertinent to this proposal

Q27a. If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually.

N/A

BEFORE FINAL SUBMISSION, please review the PI checklist to ensure that you have completed all necessary steps. This will increase the likelihood of submitting a feasible and successful proposal.

Embedded Data:

N/A

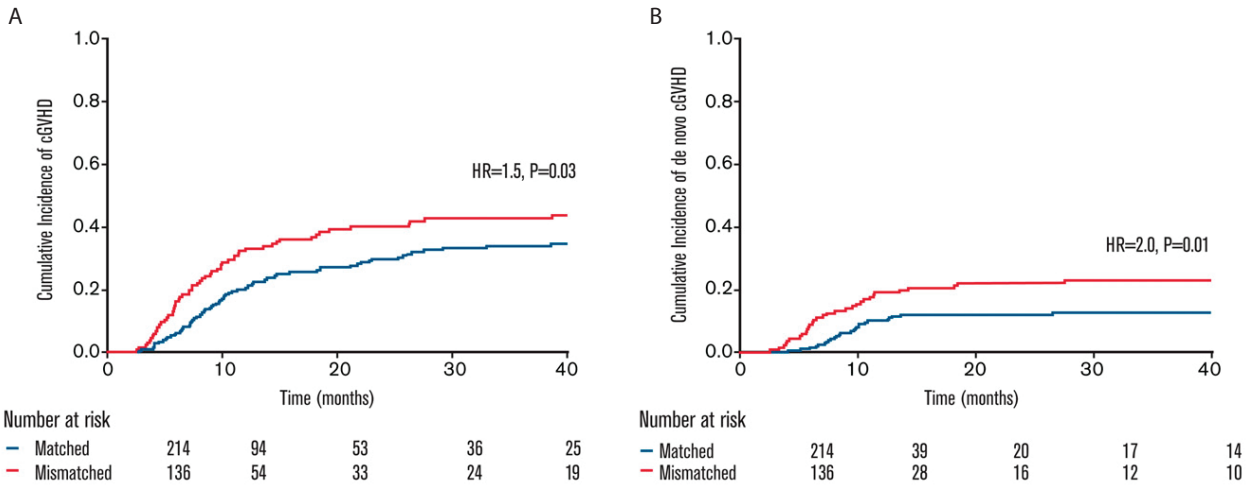

Figure 1. Impact of SIRPa mismatch on cGVHD in AML/MDS cohort. Cumulative incidence of overall cGVHD (A), de novo cGVHD (B).

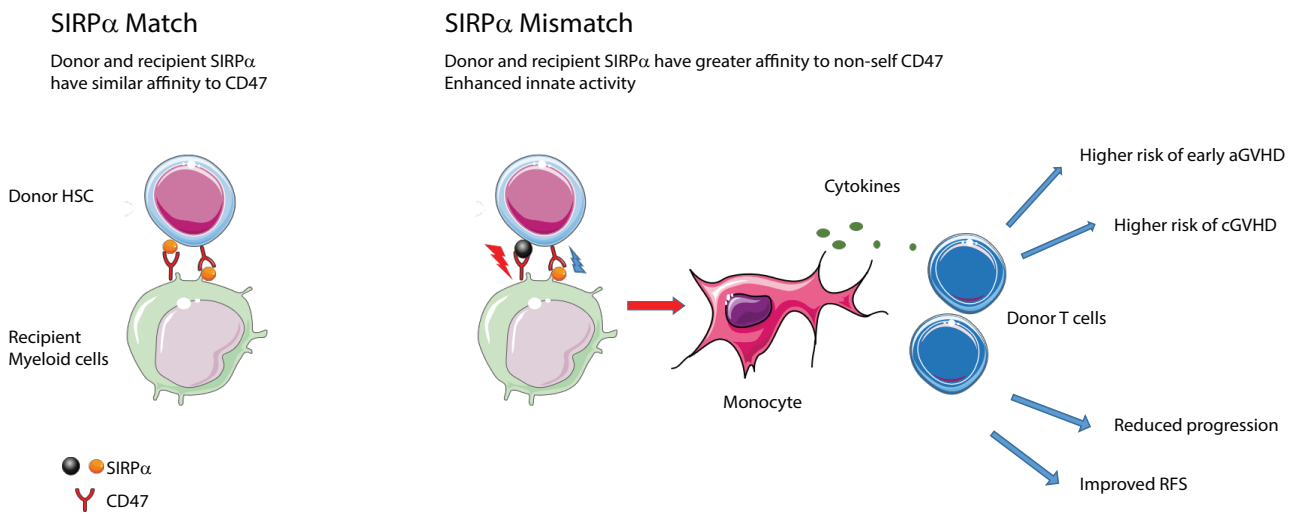

Figure 2. Hypothetical role of SIRPa variant mismatch in HSCT with an HLA-matched donor (Left) or a mistmatched donor (Right).

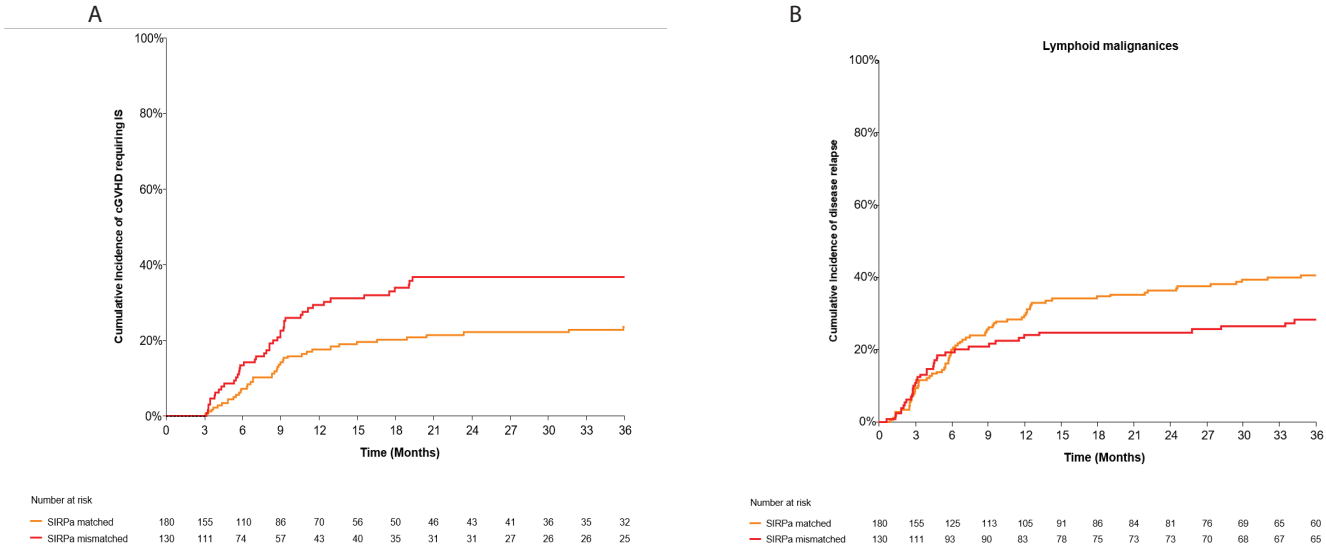

Figure 3. Impact of SIRPa mismatch on cGVHD in lymphoid malignancy cohort. Cumulative incidence of cGVHD requiring immunosuppressive therapy (A), disease relapse (B).

* Figure 1 and 2 were adopted from Saliba...Zou et al., Blood Advances. 2021 Sep14.

Selection Criteria:

- AML/MDS/ALL
- First allo
- HLA matched related donor
- 2010-2019
- Sample available
- Exclude PtCy

Proposal 2110-141 Recipients with AML, ALL, MDS received 8/8 related first allo HCT with sample available, 2010-2019

Variable	N (%)
Number of recipients	3045
Number of centers	76
Data Source	
TED	2065 (68)
CRF	980 (32)
Primary Disease	
AML	1632 (54)
ALL	788 (26)
MDS	625 (21)
AML-Disease status at transplant	
CR1	1080 (66)
CR2	232 (14)
CR3+	16 (1)
Advanced or active disease	301 (18)
Missing	3 (<1)
ALL-Disease status at transplant	
CR1	512 (65)
CR2	200 (25)
CR3+	30 (4)
Advanced or active disease	46 (6)
MDS-Disease status at transplant	
Early	112 (18)
Advanced	504 (81)
Missing	9 (1)
Recipient age at transplant	
<10	166 (5)
10-17	210 (7)
18-29	300 (10)
30-39	267 (9)
40-49	406 (13)
50-59	759 (25)

Variable	N (%)
60-69	820 (27)
>=70	117 (4)
Median (Range)	53 (1-77)
Sex	
Male	1752 (58)
Female	1293 (42)
Recipient Race	
White	2594 (85)
Black or African-American	150 (5)
Asian	119 (4)
Native Hawaiian or other Pacific Islander	14 (<1)
American Indian or Alaska Native	13 (<1)
More than one race	25 (1)
Missing	130 (4)
Recipient ethnicity	
Hispanic or Latino	508 (17)
Non-Hispanic or non-Latino	2454 (81)
Non-resident of the U.S.	31 (1)
Missing	52 (2)
Karnofsky performance score	
<=80	1132 (37)
90-100	1862 (61)
Missing	51 (2)
Graft type	
Bone marrow	504 (17)
Peripheral blood	2541 (83)
HCT-CI	
0	762 (25)
1	457 (15)
2	441 (14)
3+	1385 (45)
Reported planned conditioning intensity	
RIC/NMA	948 (31)
MAC	2087 (69)
Unknown	10 (N/A)
GVHD prophylaxis	
No GvHD Prophylaxis	6 (<1)
TDEPLETION alone	2 (<1)
TDEPLETION +- other	6 (<1)
CD34 select alone	26 (1)
CD34 select +- other	12 (<1)
FK506 + MMF +- others	274 (9)
FK506 + MTX +- others(not MMF)	1818 (60)
FK506 +- others(not MMF,MTX)	431 (14)

Variable	N (%)
FK506 alone	21 (1)
CSA + MMF +- others(not FK506)	74 (2)
CSA + MTX +- others(not MMF,FK506)	296 (10)
CSA +- others(not FK506,MMF,MTX)	1 (<1)
CSA alone	32 (1)
Other GVHD Prophylaxis	32 (1)
Identical twin donor	12 (<1)
Unknown	1 (N/A)
Donor Group	
HLA-identical sibling	2938 (96)
Twin	16 (1)
Other related	91 (3)
Recipient donor high resolution matching	
8	3045 (100)
Recipient donor high resolution matching	
10	3021 (100)
Unknown	24 (N/A)
Donor age	
<10	159 (5)
10-17	183 (6)
18-29	351 (12)
30-39	272 (9)
40-49	451 (15)
50-59	822 (27)
60-69	704 (23)
>=70	98 (3)
Missing	5 (N/A)
Median (Range)	51 (0-80)
Donor/recipient sex match	
M-M	940 (31)
M-F	670 (22)
F-M	811 (27)
F-F	623 (20)
Missing	1 (<1)
Donor/recipient CMV match status	
+/+	1220 (40)
+/-	318 (10)
-/+	827 (27)
-/-	635 (21)
Missing	45 (1)
Related donor DNA available	
No	340 (11)
Yes	2705 (89)
Related donor plasma available	

Variable	N (%)
No	119 (4)
Yes	2926 (96)
Related donor whole blood available	
No	96 (3)
Yes	2949 (97)
Related donor serum available	
No	2711 (89)
Yes	334 (11)
Related donor filter paper available	
No	9 (<1)
Yes	3036 (>99)
Related recipient DNA available	
No	269 (9)
Yes	2776 (91)
Related recipient plasma available	
No	86 (3)
Yes	2959 (97)
Related recipient whole blood available	
No	78 (3)
Yes	2967 (97)
Related recipient filter paper available	
No	4 (<1)
Yes	3041 (>99)
Year of transplant	
2010	118 (4)
2011	166 (5)
2012	239 (8)
2013	313 (10)
2014	406 (13)
2015	411 (13)
2016	386 (13)
2017	372 (12)
2018	351 (12)
2019	283 (9)
Follow-up among survivors, Months	
N Eval	1637
Median (Range)	48 (3-125)

Response Summary:

This form is intended to be completed by a physician/researcher for the purpose of proposing a study. Content should not include Personal Identifiable Information (PII) or Protected Health Information (PHI). If you are a patient, do not complete this form. Patients: Contact your healthcare provider immediately for reports of problems with your treatment or problems with products received for your treatment. The CIBMTR uses de-identified data and is unable to associate reported treatment problems, adverse events, or corrections of information with a center, clinical trial, or healthcare provider.

Q1. Study Title

Characterization of Permissible HLA Allele Mismatches and their impact in Hematopoietic Stem Cell Transplantion with Unrelated Donors

Q2. Key Words

Permissible
Peptide Binding Contact
Peptide Repertoire
Unidirectional Mismatch

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Alice Bertaina, MD
Email address:	aliceb1@stanford.edu
Institution name:	Stanford University School of Medicine, Pediatrics
Academic rank:	Associate Professor

Q4. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- No

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Marcelo Fernandez Vina, Ph.D.
Email address:	marcelof@stanford.edu
Institution name:	Stanford University School of Medicine, Pathology
Academic rank:	Professor

Q7. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- No

Q8. Do you identify as an underrepresented/minority?

- Yes

Q9. We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below:

Marcelo Anibal Fernandez Vina

Q10. If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:

N/A

LETTER OF COMMITMENT:

Please note: *A letter of commitment will be signed by Lead and Last authors as it describes the expectations for filling that role. By signing the letter of commitment, the authors accept their responsibilities and will be held accountable for timely completion of all steps in the project. More details regarding author responsibilities can be found here:* *https://www.cibmtr.org/Studies/Observational/StudyManagement/p*

Q12. CURRENT ONGOING WORK WITH CIBMTR: Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.

We are analyzing the outcomes in cohorts of 4417 BMT recipient/donor pairs from CIBMTR kindly provided by Steven Spellman (dataset: SC1319_data_7dec2020.xlsx) ; this dataset included transplants performed before 2012 and contained clinical outcomes and HLA genotypes for HLA-A, -B, -C, -DRB1, -DQB1 and -DPB1 loci; among the 4417 cases, 1128 matched in 7/8 alleles. The analysis that we are conducting are foundational for the study that we are proposing. The extended analyses of outcomes in this cohort will be presented and discussed.

Q13. PROPOSED WORKING COMMITTEE:

- Immunobiology

Q14. Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.

- Yes

Q14a. If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:

Yung-Tsi Bolon; Previously Steven Spellman

Q15. RESEARCH QUESTION:

Among HLA-mismatched transplant pairs can one identify specific mismatches assessed on the basis of structural features that are better tolerated than the average single HLA mismatch?

Q16. RESEARCH HYPOTHESIS:

Hypothesis #1 : HLA mismatches alleles that differ only at amino acid residues that are NOT DIRECTLY involved in PEPTIDE BINDING are NOT IMMUNOGENIC and could be be classified as PERMISSIBLE (e.g. C*03:03/C*03:04)
Hypothesis #2 : The HLA mismatch in DRB1 alleles that differ only at amino acid residue 86 (dimorhism V/G) in which the patient carries an allele with Valine at this position (86-V/G), in the GvH vector could be classified as PERMISSIBLE. The mismatch in the opposite direction (86-G/V) may be IMMUNOGENIC. DIRECTIONAL 86-V/G MM

Q17. SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.)

Suggested word limit of 200 words:

1.1 To determine the effect of a putative non-immunogenic HLA mismatches on the outcomes of UD-HSCT. Primary end points include O.S, TRM, DFS, Grade II-IV and Grade III-IV aGvHD and Relapse.
1.2 To compare the impact of the single mismatch in alleles presenting only amino acid differences in residues that do not determine peptide binding with other single antigen and/or allele level mismatches on the outcome of UD-HSCT.
1.3 To compare the impact of the single mismatch in DRB1 alleles in that differ only by one amino acid substitution at residue 86 in which the patient's DRB1 allele carries Valine and the donor carries Glycine with transplants in which the patient's DRB1 mismatched allele carries single mismatch in DRB alleles carries Glycine and the donor carries Valine.
1.4 To compare the impact of the single mismatch in DRB alleles that differ only by one amino acid substitution at residue 86 in which the patient's DRB1 allele carries Valine and the donor carries Glycine with other single antigen and/or allele level mismatches on the outcome of UD-HSCT.
1.5 To compare the impact of the single mismatch in alleles presenting only amino acid differences in residues that do not determine peptide binding with the outcome of transplants in which the patient and the UD are fully matched in HLA-A, B, C or DRB1 loci.
1.6 To compare the impact of the single mismatch in DRB alleles in that differ only by one amino acid substitution at residue 86 in which the patient's DRB1 allele carries Valine and the donor carries Glycine with the outcome of transplants in which the patient and the unrelated donors are fully matched in HLA-A, B, C or DRB1 loci.

Q18. SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.

If the proposed study proves that the Permissible Mismatches included in this proposal result in equivalent outcomes to those observed form HLA-matched transplants, the criteria described here will result in a significant number of patients transplanted with optimal donors. The software developed can be made accessible to donor registries and transplant centers for ready identification of better donors on the basis of the type of HLA mismatch.

Q19. SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary.

The two criteria for classification of mismatches presented in this proposal are original; the rationale for defining these mismatches is based on the function of HLA antigens in peptide presentation suggesting that T-cell allo-reactivity causing GvHD most likely results from differences or identity in peptide repertoires presented by mismatched alleles. The attached proposal includes existing data supporting both hypotheses. Dr Fernandez Vina has conducted reaser in CIBMTR cohorts and has been the first investigator to identify a fully PERMISSIBLE HLA mismatch (identical outcome as matched transplants).

Q19a. SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF)

[Click here]

Q20. PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.

Patients, with hematologic malignancies including: AML, ALL, CML, MDS

Q21. Does this study include pediatric patients?

- Yes

Q22. DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion-variables to be considered in the multivariate analyses. Data collection forms available at: http://www.cibmtr.org/DataManagement/DataCollectior Outline any supplementary data required. Additional data collection is extremely difficult and will make your proposal less feasible.

4.0 OUTCOMES TO BE STUDIED
4.1 Overall survival (OS)
4.2 Acute GVHD (grade II-IV and grade III-IV)
4.3 Chronic GVHD
4.4 Relapse (REL)
4.5 Disease-free Survival (DFS)
4.6 Transplant-related mortality (TRM)
5.0 VARIABLES TO BE ANALYZED
Main Effect to be tested:
- the impact of the single mismatch in alleles presenting only amino acid differences in residues that do not determine peptide binding with other single antigen and/or allele level mismatches;
- the impact of the single mismatch in DRB alleles that differ only by one amino acid substitution at residue 86 in which the patient's DRB1 allele carries Valine and the donor carries Glycine vs transplants in which the patient's DRB1 mismatched allele carries single mismatch in DRB alleles carries Glycine and the donor carries Valine.
Patient-related (at time of transplant):
- Age: in decades (0-9, 10-19, 20-29, 30-39, 40-49, 50 and older).
- Gender: female vs. male
- Lansky/Karnofsky score at transplant: < 90 vs. 90-100
Disease-Related:
- Disease at transplant
o Subanalysis by each disease: ALL, AML, CML and MDS
- Disease status prior to transplant: early (CR1) vs. intermediate (CR2) vs. advanced (>CR3) vs. others
o Subanalysis by disease stage: early (CR1), intermediate (CR2) and advanced (>CR3)
Transplant-Related:
- Source of stem cells: marrow (BM) vs. peripheral blood stem cells (PB)
- Donor age: in decades (18-29, 30-39, 40-49, 50 and older)
- Year of transplant: (1988-2015)
- Gender match: M-M vs. M-F vs. F-M vs. F-F
- Donor/recipient CMV status: -/- vs. -/+ vs. +/- vs. +/+ vs. Unknown
- Conditioning regimen: Traditional Myeloablative vs. reduced intensity
- GvHD prophylaxis: Tacrolimus +/-others vs. CSA +/-others vs. others

Q23. **PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis specific to PROS.**

For additional information on what PRO measures have been collected and timepoints of collection, please reach out to the Late Effects and Quality of Life or Health Services Working Committee leadership: https://www.cibmtr.org/About/WhoWeAre/Com

See above

Q24. **SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous experience with the proposed assay systems. PIs should be encouraged to review the inventory details, sample types collected and reach out to research_repos@nmdp.org with any questions.**

More information can be found at: https://www.cibmtr.org/Samples/Inventory/Pages/index

No samples requested. If possible statistical support

Q25. NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required, i.e., neither database contains all the data required to answer the study question.

Not Applicable

Q26. REFERENCES:

1- Oudshoorn M, Doxiadis II, van den Berg-Loonen PM, Voorter CE, Verduyn W, Claas FH. Functional versus structural matching: can the CTLp test be replaced by HLA allele typing? Hum Immunol. 2002 Mar;63(3):176-84.
2- Fernandez-Viña MA, Wang T, Lee SJ, Haagenson M, Aljurf M, Askar M, Battiwalla M, Baxter-Lowe LA, Gajewski J, Jakubowski AA, Marino S, Oudshoorn M, Marsh SG, Petersdorf EW, Schultz K, Turner EV, Waller EK, Woolfrey A, Umejiego J, Spellman SR, Setterholm M. Identification of a permissible HLA mismatch in hematopoietic stem cell transplantation. Blood. 2014 Feb 20;123(8):1270-8. doi: 10.1182/blood-2013-10-532671. Epub 2014 Jan 9. PubMed PMID: 24408320; PubMed Central PMCID: PMC3931192.
3- Pidala J, Lee SJ, Ahn KW, Spellman S, Wang HL, Aljurf M, Askar M, Dehn J, Fernandez Viña M, Gratwohl A, Gupta V, Hanna R, Horowitz MM, Hurley CK, Inamoto Y, Kassim AA, Nishihori T, Mueller C, Oudshoorn M, Petersdorf EW, Prasad V, Robinson J, Saber W, Schultz KR, Shaw B, Storek J, Wood WA, Woolfrey AE, Anasetti C. Nonpermissive HLA-DPB1 mismatch increases mortality after myeloablative unrelated allogeneic hematopoietic cell transplantation. Blood. 2014 Oct 16;124(16):2596-606. doi: 10.1182/blood-2014-05-576041. Epub 2014 Aug 26. PubMed PMID: 25161269; PubMed Central PMCID: PMC4199961.
4- Ayuk F, Beelen DW, Bornhäuser M, Stelljes M, Zabelina T, Finke J, Kobbe G, Wolff D, Wagner EM, Christopeit M, Schmid C, Ottinger H, Groth C, Faul C, Bertz H, Rachlis E, Wolschke C, Schetelig J, Horn PA, Mytilineos J, Guellstorf M, Kelsch R, Fleischhauer K, Kröger N, Bethge W. Relative Impact of HLA Matching and Non-HLA Donor Characteristics on Outcomes of Allogeneic Stem Cell Transplantation for Acute Myeloid Leukemia and Myelodysplastic Syndrome. Biol Blood Marrow Transplant. 2018 Jul 24. pii: S1083-8791(18)30365-3. doi: 10.1016/j.bbmt.2018.06.026. PubMed PMID: 29966760.
5- Verreck FA, Termijtelen A, Koning F. HLA-DR beta chain residue 86 controls DR alpha beta dimer stability. Eur J Immunol. 1993 Jun;23(6):1346-50. PubMed PMID: 8500529.
6- Demotz S, Barbey C, Corradin G, Amoroso A, Lanzavecchia A. The set of naturally processed peptides displayed by DR molecules is tuned by polymorphism of residue 86. Eur J Immunol. 1993 Feb;23(2):425-32. PubMed PMID: 7679644.
7- Freydell AC, Gebuhrer L, Betuel H, Farre A, Labonne MP, Lambert J. HLA-DRw11, DQw7 has four cellular subtypes revealed by homozygous typing cells and undetected by restriction fragment length polymorphism. Hum Immunol. 1991 Mar;30(3):183-9. PubMed PMID: 1676026.
8- Elsner HA, Blasczyk R. Sequence similarity matching: proposal of a structure-based rating system for bone marrow transplantation. Eur J Immunogenet 2002; 29: 229-236.

Q27. **CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:**

1. Employment (such as an independent contractor, consultant or providing expert testimony)?
2. Relationships (such as executive and advisory committee positions, medical consultant, speaker's bureau)?
3. Ownership (such as equity, ownership or financial interests)?
4. Transactions (such as honoraria, patents, royalties and licenses)?
5. Legal (such as pending or current arbitration or legal proceedings)?

- No, I do not have any conflicts of interest pertinent to this proposal

Q27a. **If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually.**

N/A

BEFORE FINAL SUBMISSION, please review the PI checklist to ensure that you have completed all necessary steps. This will increase the likelihood of submitting a feasible and successful proposal.

Embedded Data:

N/A

Selection criteria:

- **AML, ALL, MDS, CML**
- **7/8 mismatch at HLA-A, B, C, DRB1, 8/8 matched**
- **First allo**
- **2012-2020**

Proposal 2110-149 Recipients with AML, ALL, MDS, CML received 7/8 and 8/8 Unrelated first allo HCT, 2012-2020

Variable	7/8 mismatched at HLA-DRB1 N (%)	8/8 N (%)
Number of recipients	550	20707
Number of centers	135	279
Data Source		
TED	405 (74)	14905 (72)
CRF	145 (26)	5802 (28)
Primary Disease		
AML	278 (51)	11100 (54)
ALL	153 (28)	3819 (18)
CML	22 (4)	863 (4)
MDS	97 (18)	4925 (24)
AML-Disease status at transplant		
CR1	167 (60)	7340 (66)
CR2	53 (19)	1703 (15)
CR3+	2 (1)	92 (1)
Advanced or active disease	54 (19)	1922 (17)
Missing	2 (1)	43 (<1)
ALL-Disease status at transplant		
CR1	88 (58)	2522 (66)
CR2	45 (29)	879 (23)
CR3+	14 (9)	181 (5)
Advanced or active disease	5 (3)	231 (6)
Missing	1 (1)	6 (<1)
MDS-Disease status at transplant		
Early	21 (22)	766 (16)
Advanced	69 (71)	4054 (82)
Missing	7 (7)	105 (2)
CML-Disease status at transplant		
Chronic phase	15 (68)	692 (80)
Accelerated phase	4 (18)	94 (11)
Blast phase	2 (9)	46 (5)
Missing	1 (5)	31 (4)
Recipient age at transplant		

Variable	7/8 mismatched at HLA-DRB1 N (%)	8/8 N (%)
<10	44 (8)	745 (4)
10-17	47 (9)	840 (4)
18-29	60 (11)	1840 (9)
30-39	64 (12)	1821 (9)
40-49	63 (11)	2522 (12)
50-59	110 (20)	4235 (20)
60-69	132 (24)	6666 (32)
>=70	30 (5)	2038 (10)
Median (Range)	50 (1-81)	57 (0-84)
Sex		
Male	293 (53)	11813 (57)
Female	257 (47)	8894 (43)
Recipient Race		
White	385 (70)	17938 (87)
Black or African-American	65 (12)	422 (2)
Asian	21 (4)	573 (3)
Native Hawaiian or other Pacific Islander	0	56 (<1)
American Indian or Alaska Native	2 (<1)	73 (<1)
More than one race	7 (1)	79 (<1)
Missing	70 (13)	1566 (8)
Recipient ethnicity		
Hispanic or Latino	109 (20)	1268 (6)
Non-Hispanic or non-Latino	376 (68)	16712 (81)
Non-resident of the U.S.	58 (11)	2273 (11)
Missing	7 (1)	454 (2)
Karnofsky performance score		
<=80	215 (39)	8314 (40)
90-100	327 (59)	12070 (58)
Missing	8 (1)	323 (2)
Graft type		
Bone marrow	152 (28)	3926 (19)
Peripheral blood	398 (72)	16781 (81)
HCT-CI		
0	153 (28)	4789 (23)
1	84 (15)	2916 (14)
2	70 (13)	3016 (15)
3+	243 (44)	9986 (48)
Reported planned conditioning intensity		
RIC/NMA	220 (40)	8956 (43)
MAC	328 (60)	11714 (57)
Missing	2 (<1)	37 (<1)
GVHD prophylaxis		

Variable	7/8 mismatched at HLA-DRB1 N (%)	8/8 N (%)
No GvHD Prophylaxis	3 (1)	82 (<1)
TDEPLETION alone	0	42 (<1)
TDEPLETION +- other	2 (<1)	82 (<1)
CD34 select alone	7 (1)	183 (1)
CD34 select +- other	6 (1)	74 (<1)
Cyclophosphamide alone	3 (1)	126 (1)
Cyclophosphamide +- others	117 (21)	1624 (8)
FK506 + MMF +- others	48 (9)	2079 (10)
FK506 + MTX +- others(not MMF)	209 (38)	10728 (52)
FK506 +- others(not MMF,MTX)	20 (4)	1468 (7)
FK506 alone	9 (2)	428 (2)
CSA + MMF +- others(not FK506)	34 (6)	1130 (5)
CSA + MTX +- others(not MMF,FK506)	71 (13)	2199 (11)
CSA +- others(not FK506,MMF,MTX)	4 (1)	62 (<1)
CSA alone	5 (1)	126 (1)
Other GVHD Prophylaxis	9 (2)	222 (1)
Missing	1 (<1)	34 (<1)
Unknown	2 (N/A)	18 (N/A)
Recipient donor allele level matching at HLA-A		
Full allele matched	550 (100)	20707 (100)
Recipient donor allele level matching at HLA-B		
Full allele matched	550 (100)	20707 (100)
Recipient donor allele level matching at HLA-C		
Full allele matched	550 (100)	20707 (100)
Recipient donor allele level matching at HLA-DRB1		
Single allele mismatch	550 (100)	0
Full allele matched	0	20707 (100)
Donor age		
18-29	258 (47)	12810 (62)
30-39	155 (28)	4809 (23)
40-49	96 (17)	2124 (10)
50+	32 (6)	735 (4)
Missing	9 (2)	229 (1)
Median (Range)	31 (18-72)	28 (0-78)
Donor/recipient sex match		
M-M	195 (35)	8844 (43)
M-F	143 (26)	5715 (28)
F-M	98 (18)	2917 (14)
F-F	113 (21)	3135 (15)
Missing	1 (<1)	96 (<1)
Donor/recipient CMV match status		
+/+	217 (39)	6028 (29)

Variable	7/8 mismatched at HLA-DRB1 N (%)	8/8 N (%)
+/-	69 (13)	2175 (11)
-/+	175 (32)	6949 (34)
-/-	87 (16)	5434 (26)
Missing	2 (<1)	121 (1)
Year of transplant		
2012	52 (9)	1717 (8)
2013	60 (11)	2046 (10)
2014	63 (11)	2246 (11)
2015	76 (14)	2276 (11)
2016	57 (10)	2417 (12)
2017	66 (12)	2526 (12)
2018	57 (10)	2840 (14)
2019	72 (13)	2989 (14)
2020	47 (9)	1650 (8)
Follow-up among survivors, Months		
N Eval	288	11397
Median (Range)	36 (3-99)	36 (0-106)

Proposal 2110-149 Recipients with AML, ALL, MDS, CML received 7/8 Unrelated first allo HCT, 2012-2020

Variable	One locus mismatched at HLA-A, B, or C N (%)	One locus mismatched at HLA-DRB1 N (%)
Number of recipients	3217	550
Number of centers	233	135
Data Source		
TED	2342 (73)	405 (74)
CRF	875 (27)	145 (26)
Primary Disease		
AML	1668 (52)	278 (51)
ALL	737 (23)	153 (28)
CML	154 (5)	22 (4)
MDS	658 (20)	97 (18)
AML-Disease status at transplant		
CR1	1004 (60)	167 (60)
CR2	329 (20)	53 (19)
CR3+	21 (1)	2 (1)
Advanced or active disease	309 (19)	54 (19)
Missing	5 (<1)	2 (1)
ALL-Disease status at transplant		
CR1	416 (56)	88 (58)
CR2	221 (30)	45 (29)
CR3+	54 (7)	14 (9)
Advanced or active disease	46 (6)	5 (3)
Missing	0	1 (1)
MDS-Disease status at transplant		
Early	118 (18)	21 (22)
Advanced	528 (80)	69 (71)
Missing	12 (2)	7 (7)
CML-Disease status at transplant		
Chronic phase	123 (80)	15 (68)
Accelerated phase	13 (8)	4 (18)
Blast phase	13 (8)	2 (9)
Missing	5 (3)	1 (5)
Recipient age at transplant		
<10	198 (6)	44 (8)
10-17	261 (8)	47 (9)
18-29	369 (11)	60 (11)
30-39	323 (10)	64 (12)
40-49	420 (13)	63 (11)
50-59	671 (21)	110 (20)
60-69	797 (25)	132 (24)

Variable	One locus mismatched at HLA-A, B, or C N (%)	One locus mismatched at HLA-DRB1 N (%)
>=70	178 (6)	30 (5)
Median (Range)	51 (1-79)	50 (1-81)
Sex		
Male	1778 (55)	293 (53)
Female	1439 (45)	257 (47)
Recipient Race		
White	2316 (72)	385 (70)
Black or African-American	269 (8)	65 (12)
Asian	177 (6)	21 (4)
Native Hawaiian or other Pacific Islander	11 (<1)	0
American Indian or Alaska Native	19 (1)	2 (<1)
More than one race	22 (1)	7 (1)
Missing	403 (13)	70 (13)
Recipient ethnicity		
Hispanic or Latino	471 (15)	109 (20)
Non-Hispanic or non-Latino	2190 (68)	376 (68)
Non-resident of the U.S.	482 (15)	58 (11)
Missing	74 (2)	7 (1)
Karnofsky performance score		
<=80	1187 (37)	215 (39)
90-100	1977 (61)	327 (59)
Missing	53 (2)	8 (1)
Graft type		
Bone marrow	773 (24)	152 (28)
Peripheral blood	2444 (76)	398 (72)
HCT-CI		
0	938 (29)	153 (28)
1	420 (13)	84 (15)
2	447 (14)	70 (13)
3+	1412 (44)	243 (44)
Reported planned conditioning intensity		
RIC/NMA	1215 (38)	220 (40)
MAC	1987 (62)	328 (60)
Missing	15 (<1)	2 (<1)
GVHD prophylaxis		
No GvHD Prophylaxis	17 (1)	3 (1)
TDEPLETION alone	18 (1)	0
TDEPLETION +- other	20 (1)	2 (<1)
CD34 select alone	34 (1)	7 (1)
CD34 select +- other	20 (1)	6 (1)
Cyclophosphamide alone	5 (<1)	3 (1)
Cyclophosphamide +- others	543 (17)	117 (21)

Variable	One locus mismatched at HLA-A, B, or C N (%)	One locus mismatched at HLA-DRB1 N (%)
FK506 + MMF +- others	236 (7)	48 (9)
FK506 + MTX +- others(not MMF)	1364 (43)	209 (38)
FK506 +- others(not MMF,MTX)	157 (5)	20 (4)
FK506 alone	56 (2)	9 (2)
CSA + MMF +- others(not FK506)	231 (7)	34 (6)
CSA + MTX +- others(not MMF,FK506)	430 (13)	71 (13)
CSA +- others(not FK506,MMF,MTX)	18 (1)	4 (1)
CSA alone	29 (1)	5 (1)
Other GVHD Prophylaxis	26 (1)	9 (2)
Missing	13 (N/A)	3 (N/A)
Recipient donor high resolution matching		
7/8	3217 (100)	550 (100)
High Match At HLA-A		
Single allele mismatch	1726 (54)	0
Full allele matched	1491 (46)	550 (100)
High Match At HLA-B		
Single allele mismatch	847 (26)	0
Full allele matched	2370 (74)	550 (100)
High Match At HLA-C		
Single allele mismatch	644 (20)	0
Full allele matched	2573 (80)	550 (100)
High Match At HLA-DRB1		
Single allele mismatch	0	550 (100)
Full allele matched	3217 (100)	0
Donor age		
18-29	1590 (49)	258 (47)
30-39	882 (27)	155 (28)
40-49	510 (16)	96 (17)
50+	194 (6)	32 (6)
Missing	41 (1)	9 (2)
Median (Range)	30 (17-66)	31 (18-72)
Donor/recipient sex match		
M-M	1146 (36)	195 (35)
M-F	780 (24)	143 (26)
F-M	629 (20)	98 (18)
F-F	656 (20)	113 (21)
Missing	6 (<1)	1 (<1)
Donor/recipient CMV match status		
+/+	1220 (38)	217 (39)
+/-	375 (12)	69 (13)
-/+	964 (30)	175 (32)
-/-	637 (20)	87 (16)

Variable	One locus mismatched at HLA-A, B, or C N (%)	One locus mismatched at HLA-DRB1 N (%)
Missing	21 (1)	2 (<1)
Year of transplant		
2012	373 (12)	52 (9)
2013	427 (13)	60 (11)
2014	410 (13)	63 (11)
2015	414 (13)	76 (14)
2016	375 (12)	57 (10)
2017	347 (11)	66 (12)
2018	359 (11)	57 (10)
2019	320 (10)	72 (13)
2020	192 (6)	47 (9)
Follow-up among survivors, Months		
N Eval	1521	288
Median (Range)	37 (0-110)	36 (3-99)

CIBMTR Study Proposal

Study Title:

Impact of HLA-DPB1 matching on clinical outcomes following unrelated donor transplantation using post-transplant cyclophosphamide as graft-*versus*-host disease prophylaxis for patients with hematologic malignancies.

PI Information (in alphabetical order):

Blouin, Amanda; Fuchs, Ephraim; Ibrahim, Uroosa; Keyzner, Alla; McCurdy, Shannon R; Nakhle, Saba; Perales, Miguel-Angel; Petersdorf, Effie W; Safah, Hana; Shaffer, Brian C; Socola, Francisco A; Solomon, Scott R; Zou, Jun

Research Hypotheses:

Survival after transplantation from unrelated donors (URDs) with a high-risk HLA-DPB1 disparity is improved with the use of post-transplant cyclophosphamide (PTCy)-based graft-*versus*-host disease (GVHD) prophylaxis compared to non-PTCy-based approaches. The improved clinical outcome with PTCy is observed when the high-risk HLA-DPB1 mismatch is defined by the T-cell epitope (TCE), expression, and/or Predicted Indirectly ReCognizable HLA Epitopes [PIRCHE]) models. The improved survival is accompanied by lower incidence of chronic GVHD and relapse.

Specific Aims:

Primary objective: To compare overall survival in patients with high-risk HLA-DPB1 mismatches following URD transplantation utilizing PTCy versus URD transplantation utilizing non-PTCy-based prophylaxis. High-risk HLA-DPB1 mismatches are defined by three models: T-cell epitope, expression and PIRCHES.

Secondary objectives:

To compare the rates of moderate and severe chronic GVHD, cumulative incidence of relapse, rates of grades II-IV acute GVHD, relapse-free survival (RFS), GVHD-free/relapse-free survival (GRFS), and treatment-related mortality in the above cohorts.

Scientific Impact:

The current standard of care for GVHD prophylaxis after HLA-matched related or unrelated allogeneic hematopoietic cell transplantation (allo HCT) is a calcineurin inhibitor-based approach, typically in combination with methotrexate. A recent phase II study demonstrated that PTCy, in combination with tacrolimus and mycophenolate mofetil, resulted in superior GVHD-free, relapse-free survival when compared to a non-randomized, concurrent control arm receiving tacrolimus and methotrexate after an HLA-matched allo HCT [1].

High-risk HLA-DPB1 mismatches may be defined by T-cell epitope functional distance (TCE-FD), expression, and indirect recognition of HLA epitopes [2–9]. While encouraging data now support the use

of PTCy in both matched and mismatched URDs [6], the role of PTCy following transplantation from unrelated donors with high-risk HLA-DPB1 mismatches is less well understood.

Several large-scale studies demonstrate that approximately 10-20% of otherwise HLA-matched URD/recipient pairs are non-permissively mismatched at HLA-DPB1 [10-12]. Data that support the use of PTCy based GVHD prophylaxis regimens in this population would have significant effect on this large group of transplant recipients. These data are also relevant in assessing the impact of outcomes in the ongoing BMT-CTN 1703/PROGRESS-3 study [13] and future trial design evaluating PTCy in HLA-mismatched URD/recipient pairs.

Scientific Justification:

Allogeneic hematopoietic cell transplantation is a curative therapy for many patients with high risk neoplasia; however, the associated transplant related morbidity and mortality via graft-versus-host disease (GVHD) limits its application. Matching of the canonical class I human leukocyte antigens (HLA) HLA-A, -B, -C, as well as the class II HLA DRB1 between donor and recipient reduces the likelihood of transplant related mortality via reduction in severe GVHD [14]. The current standard of care is to use an HLA matched donor at HLA-A, -B, -C, and DRB1, and match for DQB1 if available.

HLA-DP loci encode class II major histocompatibility complex (MHC) proteins that comprise two polymorphic heterodimers: HLA-DPA1 and HLA-DPB1. HLA-DPB1 is more complex with >900 known alleles [14]. Among individuals undergoing 8/8 (HLA-A, -B, -C, -DRB1) matched unrelated donor allo HCT analyzed in a recent Center for International Blood & Marrow Research (CIBMTR) study, only 10% were matched at both HLA-DPB1 alleles [10]. Lee and colleagues reported that high resolution HLA-DPB1 matched donors did not have different outcomes from HLA-DPB1 mismatched unrelated donors [15]. More recently, development of the T-cell epitope grouping method (TCE) allowed for biologically driven grouping of HLA-DBP1 mismatches into so-called “permissive” mismatches, with low immunogenic potential, and non-permissive mismatches, with presumably higher immunogenicity and thus the potential to incite either HVG or GVH, depending on the direction of the mismatch [6-9]. The TCE methodology was further refined using prediction based on *in silico* determination of functional distance between HLA-DPB1 and the T-cell receptor (TCE-FD), then confirmed in a large registry-based analysis [6]. These results indicate that the TCE-FD defines a group of donor/recipient pairs that are “permissively” mismatched and have similar outcomes to HLA-DPB1 matched donor recipients, whereas “non-permissive” mismatches are immunogenic, lead to greater acute GVHD, and increase the risk for treatment-related mortality in recipients of HLA well-matched URD allo HCT. A recent large-scale analysis of patients undergoing allo HCT using *in vivo* T-cell depletion conducted by Oran and colleagues suggests that the TCE model is also prognostically relevant in determining transplant outcomes despite the use of T-cell depleting methodology [11]. In summary, 1) Among otherwise 8/8 matched donor donors, roughly 10-20% will be non-permissively mismatched at HLA-DPB1 in the GVH direction, 2) Non-permissive HLA-DPB1 mismatched donors confer an increased risk of GVHD and TRM when a calcineurin inhibitor based prophylaxis program is used.

The level of HLA-DP expression correlates with acute GVHD risk and mortality and is used to prospectively select URDs when the patient encodes one high-expression allotype [3-5; 16]. The PIRCHES model tests indirection allorecognition of HLA [2].

Post-transplant cyclophosphamide (PTCy) is an established regimen associated with enhanced protection from GVHD after HLA-mismatched related or unrelated donor allo HCT [17, 18], leading many to believe

that PTCy nullifies the detrimental effects of HLA-mismatch. In fact, in patients with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and myelodysplastic syndrome (MDS), it was found that in HLA-mismatched related donor HCT, non-permissive GVH mismatching at HLA-DPB1 was also associated with improved DFS (HR 0.72 [95% CI, 0.55-0.94], p=.015) and OS (HR 0.59 [95% CI, 0.43-0.82], p=.002), with a tendency towards lower relapse (HR 0.75 [95% CI, 0.54-1.05], p=.09), but with no effect on G2-4 aGVHD, cGVHD, or NRM. With this data, a tool to improve haplo donor selection was developed [19, 20]. Given that PTCy-based GvHD prophylaxis has also proven efficacious in HLA-matched URD allo HCT [1, 21] where HLA-DPB1 mismatching often occurs, we seek to examine the effects of PTCy on outcomes in the presence of this mismatch.

In the context of the current study, we propose to determine whether the use of PTCy can overcome the negative prognostic implications of high-risk HLA-DPB1 mismatches between donor and recipient, and would suggest that PTCy should be preferentially used in recipients where HLA-DPB1 matched or permissively mismatched URDs are unavailable. These outcomes data are immediately relevant to a large population of transplant recipients globally. Due to the sample size requirements of this study, the CIBMTR is uniquely positioned to support this research.

Patient Eligibility Population:

Inclusion Criteria:

1. Diagnosis of AML, ALL, MDS, lymphoma
2. Unrelated donor with 7/8 or higher degree of HLA-match
3. Available HLA-DPB1 typing
4. Undergoing a first PTCy-based UDT (experimental arm); a covariate matched cohort of patients treated with a calcineurin inhibitor-based prophylaxis approach will be included
5. Either BM or PBSC as stem cell source
6. No restriction on year of transplant, disease stage, recipient age or conditioning intensity

Exclusion Criteria:

1. Ex vivo T cell manipulation
2. In vivo T cell depletion with ATG or alemtuzumab
3. Prior allogeneic transplant

Data Requirements:

1. Clinical data:
    a. The study does not require collection of additional data beyond that contained in existing CIBMTR forms.
    b. The clinical data points required for this study are summarized in the below table.
2. HLA-DPB1 typing
    a. Donor/recipient pairs with existing HLA-DPB1 typing are included without need for further biospecimen analysis.

Patient specific	**Form**
Age	Baseline (2000)
HCT-CI	
Revised disease risk index	
Gender	
ABO	
Disease histology	Disease specific forms
CMV serostatus	Infectious disease markers (2004)
Remission status (CR1 or CR2)	
Transplant specific	
Donor HLA class I, HLA-DRB1 typing	HLA (2005)
Recipient HLA class I, HLA-DRB1 typing	
Donor/recipient HLA-DPB1 typing if available	
Donor age	HCT (2006)
Donor gender	
Donor ABO	
Year of transplant	
Stem cell source (BM or PBSC)	
Conditioning regimen	
GVHD prophylaxis	

3. Outcomes: Overall survival, cGVHD rate, relapse rate, aGVHD rate, RFS, GRFS, TRM

   We may use the following forms: Recipient Baseline Data, Hematopoietic Stem Cell transplant (HCT) infusion, Acute Myelogenous Leukemia Pre-HCT data, and post-HSCT data

Sample Requirements:
We will not collect any patient sample for this information.

Study Design:

This would be a retrospective cohort study using the CIBMTR database. The primary predictor outcome is HLA-DPB1 donor-recipient matching. The cohort will be defined according to three different models: TCE, expression and PIRCHES as previously described. Based on previous large-scale studies we anticipate that approximately 20% of the population will be HLA-DPB1 matched, 60% will be HLA-DPB1 permissively mismatched in the GVH direction and the remaining 20% will be non-permissively mismatched. The experimental hypothesis is that the use of PT-Cy will result in significant improvement in overall survival compared to the use of a calcineurin inhibitor-based approach in HLA-DPB1 non-permissive donor/recipient pairs, high-expression mismatches, and high-risk PIRCHES mismatches. The null hypothesis is that overall survival will be similar between the two GVHD prophylaxis approaches.

The secondary endpoints of the study will be to determine the hazard for grade II-IV acute GVHD, moderate/severe chronic GvHD using a competing risk adjustment framework according to Fine and Gray. The table below shows the pairs of groups being compared for the primary and secondary endpoints. We will adjust for significant covariates that are determined on univariate analysis. Secondary endpoints will be determined with a Cox proportional hazards model again adjusting for competing risks. Cumulative incidence functions will be determined for the primary and secondary endpoints. Descriptive statistics will be used to assess characteristics of the cohort.

Comparison	**PTCy-based GVHD prophylaxis**	**Calcineurin inhibitor-based GVHD prophylaxis**
1 (primary)	Non-permissive mismatch	Non-permissive mismatch
2	All mismatch	All mismatch
3	All patients	All patients

Power consideration: Based on previous large-scale studies, we anticipate that the improved clinical outcome of 5~10% at 1 years after transplant with PTCy versus the non-Pty patients (70~80% survival probability) for patients who had the high-risk HLA-DPB1 mismatches. Assume that the ratio of group sizes for patients using post-transplant cyclophosphamide (PTCy)-based versus non-PTCy-based graft-*versus*-host disease (GVHD) prophylaxis is 1:10. Based on log-rank test, the required total sample size to achieve 80% power for detecting a 5% difference in survival probability at the nominal significance level 0.05 is shown below.

Table 1. (OS) At the significance level of 0.05, the required sample size to achieve 80% power.

Non- PTCy	PTCt patients	Total sample size (patients with high-risk HLA-DPB1 mismatches)	Total sample size (all patients)*
70%	75%	7,986	22,818
75%	80%	7,128	20,366
80%	85%	6,072	17,349

65%	75%	2,222	6,349
70%	80%	2,046	5,846
75%	85%	1,815	5,215

Table 2. (aGVHD2-4) At the significance level of 0.05, the required sample size to achieve 80% power.

Non- PTCy	PTCt patients	Total sample size (patients with high-risk HLA-DPB1 mismatches)	Total sample size (all patients)*
35%	30%	7,084	20,240
40%	35%	7,755	22,158
45%	40%	8,228	23,509
50%	45%	8,503	24,295
40%	30%	1,793	5,123
45%	35%	1,925	5,500
50%	40%	2,013	5,752

* Based on previous large-scale studies, we anticipate that approximately 35% of the patient population will be the high-risk HLA-DPB1 mismatches.

Non-CIBMTR Data Source:
None.

References:

1. Bolaños-Meade J, Reshef R, Fraser R, Fei M, Abhyankar S, Al-Kadhimi Z, et al. Three prophylaxis regimens (tacrolimus, mycophenolate mofetil, and cyclophosphamide; tacrolimus, methotrexate, and bortezomib; or tacrolimus, methotrexate, and maraviroc) versus tacrolimus and methotrexate for prevention of graft-versus-host disease with haemopoietic cell transplantation with reduced-intensity conditioning: a randomised phase 2 trial with a non-randomised contemporaneous control group (BMT CTN 1203). Lancet Haematol. 2019 Mar;6(3):e132–43.

2. Thus KA, Ruizendaal MT, de Hoop TA, et al. Refinement of the definition of permissible HLA-DPB1 mismatches with predicted indirectly recognizable HLA-DPB1 epitopes. Biol Blood Marrow Transplant 2014;20:1705-10.
3. Petersdorf EW, Malkki M, O'hUigin C, Carrington M, Gooley T, Haagenson MD, Horowitz MM, Spellman SR, Wang T, Stevenson P. High HLA-DP expression and graft-versus-host disease. N Engl J Med 373:599-609, 2015.
4. Petersdorf EW, Bengtsson M, De Santis D, Dubois V, Fleischhauer K, Gooley T, Horowitz M, Madrigal JA, Malkki M, Mc Kallor C, Morishima Y, Oudshoorn M, Spellman SR, Villard J, Stevenson P, Carrington M. Role of HLA-DP expression in graft-versus-host disease after unrelated donor transplantation. J Clin Oncol 2020;38:2712-18.
5. Buhler S, Baldomero H, Ferrari-Lacraz S, et al. Analysis of biological models to predict outcomes based on HLA-DPB1 disparities in unrelated transplantation. Blood Adv 2021;5:3377-3386.
6. Arrieta-Bolaños E, Crivello P, Shaw BE, Ahn KW, Wang H-L, Verneris MR, et al. In silico prediction of nonpermissive HLA-DPB1 mismatches in unrelated HCT by functional distance. Blood Adv. 2018 24;2(14):1773–83.
7. Crivello P, Zito L, Sizzano F, Zino E, Maiers M, Mulder A, et al. The impact of amino acid variability on alloreactivity defines a functional distance predictive of permissive HLA-DPB1 mismatches in hematopoietic stem cell transplantation. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2015 Feb;21(2):233–41.
8. Crivello P, Heinold A, Rebmann V, Ottinger HD, Horn PA, Beelen DW, et al. Functional distance between recipient and donor HLA-DPB1 determines nonpermissive mismatches in unrelated HCT. Blood. 2016 07;128(1):120–9.
9. Fleischhauer K, Shaw BE, Gooley T, Malkki M, Bardy P, Bignon J-D, et al. Effect of T-cell-epitope matching at HLA-DPB1 in recipients of unrelated-donor haemopoietic-cell transplantation: a retrospective study. Lancet Oncol. 2012 Apr;13(4):366–74.
10. Pidala J, Lee SJ, Ahn KW, Spellman S, Wang H-L, Aljurf M, et al. Nonpermissive HLA-DPB1 mismatch increases mortality after myeloablative unrelated allogeneic hematopoietic cell transplantation. Blood. 2014 Oct 16;124(16):2596–606.
11. Oran B, Saliba RM, Carmazzi Y, de Lima M, Rondon G, Ahmed S, et al. Effect of nonpermissive HLA-DPB1 mismatches after unrelated allogeneic transplantation with in vivo T-cell depletion. Blood. 2018 Mar 15;131(11):1248–57.
12. Saber W, Opie S, Rizzo JD, Zhang M-J, Horowitz MM, Schriber J. Outcomes after matched unrelated donor versus identical sibling hematopoietic cell transplantation in adults with acute myelogenous leukemia. Blood. 2012 Apr 26;119(17):3908–16.
13. https://web.emmes.com/study/bmt2/protocol/1703-1801_protocol/1703-1801_protocol.html Accessed December 17, 2021.
14. Robinson J, Halliwell JA, Hayhurst JD, Flicek P, Parham P, Marsh SGE. The IPD and IMGT/HLA database: allele variant databases. Nucleic Acids Res. 2015 Jan 28;43(Database issue):D423–31.
15. Lee SJ, Klein J, Haagenson M, Baxter-Lowe LA, Confer DL, Eapen M, et al. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. Blood. 2007 Dec 15;110(13):4576–83.
16. Balgansuren G, Regen L, Sprague M, Shelton N, Petersdorf E, Hansen JA. Identification of the rs9277534 HLA-DP expression marker by next generation sequencing for the selection of

unrelated donors for hematopoietic cell transplantation. Hum Immunol. 2019 Oct;80(10):828-833. doi: 10.1016/j.humimm.2019.05.010. Epub 2019 Jun 5. PMID: 31176504.

17. Kasamon YL, Ambinder RF, Fuchs EJ, Zahurak M, Rosner GL, Bolaños-Meade J, et al. Prospective study of nonmyeloablative, HLA-mismatched unrelated BMT with high-dose posttransplantation cyclophosphamide. Blood Adv. 2017 Jan 10;1(4):288–92.
18. Ciurea SO, Zhang M-J, Bacigalupo AA, Bashey A, Appelbaum FR, Aljitawi OS, et al. Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia. Blood. 2015 Aug 20;126(8):1033–40.
19. Fuchs EJ, McCurdy SR, Solomon SR, Wang T, Herr MM, Modi D, Grunwald MR, et al; HLA Informs Risk Predictions after Haploidentical Stem Cell Transplantation with Post-transplantation Cyclophosphamide. Blood 2021; blood.2021013443
20. http://haplodonorselector.b12x.org/v1.0/ Accessed December 16, 2021
21. Kanakry CG, O'Donnell PV, Furlong T, de Lima MJ, Wei W, Medeot M, et al. Multi-institutional study of post-transplantation cyclophosphamide as single-agent graft-versus-host disease prophylaxis after allogeneic bone marrow transplantation using myeloablative busulfan and fludarabine conditioning. J Clin Oncol Off J Am Soc Clin Oncol. 2014 Nov 1;32(31):3497–505.

Conflicts of Interest:

Do you have any conflicts of interest pertinent to this proposal concerning:

- Employment (such as an independent contractor, consultant or providing expert testimony)?
- Relationships (such as executive and advisory committee positions, medical consultant, speaker's bureau)?
- Ownership (such as equity, ownership or financial interests)?
- Transactions (such as honoraria, patents, royalties and licenses)?
- Legal (such as pending or current arbitration or legal proceedings)?

□ Yes.

⊟ No.

Selection criteria:

- AML/ALL/MDS/NHL/HD
- Unrelated 8/8
- Available HLA-DPB1 typing
- PtCy based vs. Calcineurin inhibitor-based prophylaxis
- BM+PBSC
- 2008-2018
- Exclude: Ex-vivo and in-vivo T cell depletion

Proposal 2108-01 etc. Recipients with AML, ALL, MDS, Lymphoma received 7/8 and 8/8 Unrelated first allo HCT, 2008-2018

	Calcineurin inhibitor-based	**PTCy-based**
Variable	N (%)	N (%)
Number of recipients	9023	785
Number of centers	169	72
Data Source		
TED	5617 (62)	509 (65)
CRF	3406 (38)	276 (35)
Primary Disease		
AML	4744 (53)	410 (52)
ALL	1728 (19)	125 (16)
MDS	1853 (21)	181 (23)
NHL	607 (7)	56 (7)
HD	91 (1)	13 (2)
Recipient age at transplant		
<10	255 (3)	4 (1)
10-17	273 (3)	7 (1)
18-29	883 (10)	69 (9)
30-39	894 (10)	76 (10)
40-49	1291 (14)	103 (13)
50-59	2010 (22)	164 (21)
60-69	2714 (30)	283 (36)
>=70	703 (8)	79 (10)
Median (Range)	55 (1-81)	59 (1-82)
Sex		
Male	5051 (56)	462 (59)
Female	3972 (44)	323 (41)
Recipient Race		
White	8328 (92)	722 (92)
Black or African-American	171 (2)	18 (2)
Asian	222 (2)	15 (2)
Native Hawaiian or other Pacific Islander	19 (<1)	0
American Indian or Alaska Native	36 (<1)	4 (1)
More than one race	38 (<1)	3 (<1)
Missing	209 (2)	23 (3)

Variable	Calcineurin inhibitor-based N (%)	PTCy-based N (%)
Recipient ethnicity		
Hispanic or Latino	561 (6)	38 (5)
Non-Hispanic or non-Latino	8218 (91)	708 (90)
Non-resident of the U.S.	86 (1)	4 (1)
Missing	158 (2)	35 (4)
Karnofsky performance score		
<=80	3626 (40)	310 (39)
90-100	5302 (59)	451 (57)
Missing	95 (1)	24 (3)
Graft type		
Bone marrow	1792 (20)	210 (27)
Peripheral blood	7231 (80)	575 (73)
HCT-CI		
0	2088 (23)	145 (18)
1	1221 (14)	105 (13)
2	1343 (15)	139 (18)
3+	4371 (48)	396 (50)
GVHD prophylaxis		
Cyclophosphamide alone	0	137 (17)
Cyclophosphamide +- others	0	648 (83)
FK506 + MMF +- others	979 (11)	0
FK506 + MTX +- others(not MMF)	5585 (62)	0
FK506 +- others(not MMF,MTX)	1222 (14)	0
FK506 alone	50 (1)	0
CSA + MMF +- others(not FK506)	549 (6)	0
CSA + MTX +- others(not MMF,FK506)	609 (7)	0
CSA +- others(not FK506,MMF,MTX)	17 (<1)	0
CSA alone	12 (<1)	0
Conditioning intensity		
RIC/NMA	3565 (40)	394 (51)
MAC	5413 (60)	386 (49)
Missing	45 (N/A)	5 (N/A)
Time from diagnosis to HCT		
N Eval	9006	783
Median (Range)	6 (0-339)	6 (1-231)
Number of 10/10 match		
8	4 (<1)	1 (<1)
9	439 (5)	24 (3)
10	8580 (95)	760 (97)
Number of 12/12 match		
8	2 (<1)	1 (<1)
9	151 (2)	7 (1)
10	2567 (28)	205 (26)
11	4617 (51)	419 (53)

Variable	Calcineurin inhibitor-based N (%)	PTCy-based N (%)
12	1686 (19)	153 (19)
Recipient / 1st donor allele level matching at HLA-DPB1		
Double allele mismatch	2480 (27)	203 (26)
Single allele mismatch	4805 (53)	422 (54)
Full allele matched	1738 (19)	160 (20)
Donor age		
18-29	5455 (60)	483 (62)
30-39	2103 (23)	200 (26)
40-49	1089 (12)	77 (10)
50+	367 (4)	22 (3)
Missing	9 (<1)	3 (<1)
Median (Range)	28 (3-64)	28 (19-61)
Donor/recipient sex match		
M-M	3860 (43)	352 (45)
M-F	2528 (28)	209 (27)
F-M	1189 (13)	109 (14)
F-F	1441 (16)	113 (14)
Missing	5 (<1)	2 (<1)
Donor/recipient CMV match status		
+/+	2288 (25)	210 (27)
+/-	945 (10)	75 (10)
-/+	3142 (35)	268 (34)
-/-	2586 (29)	230 (29)
Missing	62 (1)	2 (<1)
Year of transplant		
2008	485 (5)	16 (2)
2009	573 (6)	5 (1)
2010	609 (7)	20 (3)
2011	692 (8)	22 (3)
2012	784 (9)	31 (4)
2013	922 (10)	34 (4)
2014	931 (10)	39 (5)
2015	970 (11)	72 (9)
2016	888 (10)	93 (12)
2017	1082 (12)	167 (21)
2018	1087 (12)	286 (36)
Follow-up among survivors, Months		
N Eval	4129	458
Median (Range)	60 (0-154)	36 (2-147)

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CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

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
Yung-Tsi Bolon, PhD; Co-Scientific Director for the Immunobiology WC

RE: Studies in Progress and Publication Summary

Studies in Progress Summary

NK/KIR

IB18-04b Evaluation of the impact of donor killer immunoglobulin receptor genotype on outcome after unrelated donor transplantation in patients with myelodysplastic syndromes or acute myeloid leukemia. (J Schetelig/N Kröger/M Robin) This study is evaluating the role of donor KIR genotype on transplant outcome in patients. Donor samples were collected by the DKMS biorepository and KIR typing performed at the DKMS Life Sciences Laboratory. **Analysis**

HLA GENES

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. **Analysis**

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. **Manuscript Preparation**

IB20-01 Association of immunopeptidome divergence between mismatched human leukocyte antigen class I alleles and outcome of 9/10 matched unrelated hematopoietic stem cell transplant. (Pietro Crivello/Esteban Arrieta-Bolanos/Katharina Fleischhauer). The goal of this study is 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. **Manuscript Preparation**

IB21-01 Effect of HLA evolutionary divergence on survival and relapse following allogeneic hematopoietic cell transplant (Christine Camacho-Bydume/Diego Chowell/ Katharine C. Hsu) The goal of this study is to determine if HED of HLA class I alleles of HLA-A, -B, and -C and class II HLA-DRB1 is associated with OS and relapse in patients with AML, MDS, ALL, CML, and lymphoma following allogeneic 8/8-HLA matched unrelated HCT. **Data File Preparation**

SENSITIZATION 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. **Manuscript Preparation**

Other Genes

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. **Analysis**

IB20-03 Donor socioeconomic status as a predictor of altered immune function and treatment response following hematopoietic cell transplantation for hematologic malignancy (Jennifer Knight). The hypothesis is that SES-related pro-inflammatory gene expression patterns in donors will be associated with inferior recipient HCT outcomes, and that this effect will be additive or interactive with recipient gene expression patterns in influencing recipient outcomes. **Analysis**

ONGOING AND OTHER-FUNDED STUDIES

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

IB06-05 Use of high-resolution human leukocyte antigen data from the National Marrow Donor Program for the international histocompatibility working group in hematopoietic stem cell transplantation. (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**

IB09-01/IB09-03/IB09-05/IB09-07 Clinical importance of minor histocompatibility complex haplotypes in umbilical cord blood transplantation. (E Petersdorf) **Ongoing**

IB21-02 DISCOVeRY-BMT: Multi-ethnic high-throughput study to identify novel non-HLA genetic contributors to mortality after blood and marrow transplantation. (There/Alyssa Clay-Gilmour) The goal of this study is two-fold: to deepen understanding of non-HLA genetic contributors to BMT mortality, and to build prognostic models to translate our results to clinical practice. **Ongoing**

Publication Summary – Published and submitted manuscripts

IB09-06p Genome-wide association analyses identify variants in IRF4 associated with acute myeloid leukemia and myelodysplastic syndrome susceptibility. Wang J, Clay-Gilmour AI, Karaesmen E, Rizvi A, Zhu Q, Yan L, Preus L, Liu S, Wang Y, Griffiths E, Stram DO, Pooler L, Sheng X, Haiman C, Van Den Berg D, Webb A, Brock G, Spellman S, Pasquini M, McCarthy P, Allan J, Stölzel F, Onel K, Hahn T, Sucheston-Campbell LE. **Frontiers in Genetics. 12:554948. doi:10.3389/fgene.2021.554948. Epub 2021 Jun 17. PMC8248805.** They performed AML and MDS genome-wide association studies (GWAS) in the DISCOVeRY-BMT cohorts (2,309 cases and 2,814 controls). ASSET identified an increased risk for de novo AML and MDS (OR = 1.38, 95% CI, 1.26-1.51, Pmeta = 2.8 × 10–12) in patients carrying the T allele at s12203592 in Interferon Regulatory Factor 4 (IRF4), a transcription factor which regulates myeloid and lymphoid hematopoietic differentiation. Transcriptome-wide association study (TWAS) analyses showed increased IRF4 gene expression is associated with increased risk of de novo AML and MDS (OR = 3.90, 95% CI, 2.36-6.44, Pmeta = 1.0 × 10–7). The identification of IRF4 by both GWAS and TWAS contributes valuable insight on the role of genetic variation in AML and MDS susceptibility.

IB09-06t Novel genetic variants associated with mortality after unrelated donor allogeneic hematopoietic cell transplantation. Hahn T, Wang J, Preus LM, Karaesmen E, Rizvi A, Clay-Gilmour AI, Zhu Q, Wang Y, Yan L, Liu S, Stram DO, Pooler L, Sheng X, Haiman CA, Berg DVD, Webb A, Brock G, Spellman SR, Onel K, McCarthy PL, Pasquini MC, Sucheston-Campbell LE. **EClinicalMedicine. 40:101093. doi:10.1016/j.eclinm.2021.101093. Epub 2021 Aug 24. PMC8548922**. They performed a genome-wide association study (GWAS) in 2,887 acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and acute lymphoblastic leukemia (ALL) patients and their ≥8/8 HLA-matched URDs comprising two independent cohorts treated from 2000–2011. These data provide the first evidence that non-HLA common genetic variation at novel loci with biochemical function significantly impacts 1-year URD-BMT survival.

IB10-01f Epigenetic aging and hematopoietic cell transplantation in patients with severe aplastic anemia. Alsaggaf R, Katta S, Wang T, Hicks BD, Zhu B, Spellman SR, Lee SJ, Horvath S, Gadalla SM. **Transplantation and Cellular Therapy. 2021 Apr 1; 27(4):313.e1-313.e8. doi:10.1016/j.jtct.2021.01.013. Epub 2021 Jan 16. PMC8036238**. We used Cox proportional hazards models to assess the possible associations of donor pre-HCT DNAm age, and its post-HCT changes, using the recently published lifespan-associated epigenetic clock known as "DNAm-GrimAge," with outcomes among patients with severe aplastic anemia (SAA). In multivariable analyses, we found similar associations for donor chronological age and pre-HCT DNAm-GrimAge with post-HCT survival. In donors with 10+ years of GrimAge acceleration, elevated risks of chronic graft versus host disease (HR = 2.4; 95% CI, 1.21-4.65; P = .01) and possibly post-HCT mortality (HR = 1.79; 95% CI, 0.96-3.33; P = .07) were observed. In the subset with post-HCT samples, we observed a significant increase in DNAm-GrimAge in the first 100 days after HCT (median change 12.5 years, range 1.4 to 26.4). Higher DNAm-GrimAge after HCT was associated with inferior survival (HR per year = 1.11; 95% CI, 1.02-1.21; P = .01), predominantly within the first year after HCT. This study highlights the possible role cellular aging may play in HCT outcomes.

IB10-01k DNA-methylation-based telomere length estimator: Comparisons with measurements from flow FISH and qPCR. Pearce EE, Horvath S, Katta S, Dagnall C, Aubert G, Hicks BD, Spellman SR, Katki H, Savage SA, Alsaggaf R, Gadalla SM. **Aging (Albany NY). 13(11):14675-14686. doi:10.18632/aging.203126. Epub 2021 Jun 3. PMC8221337.** Telomere length (TL) is a marker of

biological aging associated with several health outcomes. We compared the novel DNA methylation-based estimator (DNAmTL) with the high-throughput qPCR and the highly accurate flow cytometry with fluorescent in situ hybridization methods using blood samples from healthy adults. Shorter DNAmTL was associated with older age, male sex, white race, and cytomegalovirus seropositivity ($p<0.01$ for all). DNAmTL was moderately correlated with qPCR TL ($N=635$, $r=0.41$, $p < 0.0001$) and flow FISH total lymphocyte TL ($N=144$, $r=0.56$, $p < 0.0001$). The agreements between flow FISH TL and DNAmTL or qPCR were acceptable but with wide limits of agreement. DNAmTL correctly classified >70% of TL categorized above or below the median, but the accuracy dropped with increasing TL categories. The ability of DNAmTL to detect associations with age and other TL-related factors in the absence of strong correlation with measured TL may indicate its capture of aspects of telomere maintenance mechanisms and not necessarily TL. The inaccuracy of DNAmTL prediction should be considered during data interpretation and across-study comparisons.

IB14-03d The clinical and functional effects of TERT variants in myelodysplastic syndrome. Reilly CR, Myllymäki M, Redd R, Padmanaban S, Karunakaran D, Tesmer V, Tsai FD, Gibson CJ, Rana HQ, Zhong L, Saber W, Spellman SR, Hu ZH, Orr EH, Chen MM, De Vivo I, DeAngelo DJ, Cutler C, Antin JH, Neuberg D, Garber JE, Nandakumar J, Agarwal S, Lindsley RC. **Blood. 2021 Sep 9; 138(10):898-911. doi:10.1182/blood.2021011075. Epub 2021 May 21. PMC8432045.** We identified patients with a TERT rare variant had shorter telomere length ($P < .001$) and younger age at MDS diagnosis (52 vs 59 years, $P = .03$) than patients without a TERT rare variant. In multivariable models, TERT rare variants were associated with inferior overall survival ($P = .034$) driven by an increased incidence of non relapse mortality (NRM; $P = .015$). We found that 90% of TERT rare variants had severe or intermediate impairment in their capacity to elongate telomeres. Results indicate that the contribution of TERT rare variants to MDS pathogenesis and NRM risk is underrecognized. Routine screening for TERT rare variants in MDS patients regardless of age or clinical suspicion may identify clinically inapparent telomere biology disorders and improve transplant outcomes through risk-adapted approaches.

IB14-05 Neither donor nor recipient mitochondrial haplotypes are associated with unrelated donor transplant outcomes: A validation study from the CIBMTR. Spector LG, Spellman SR, Thyagarajan B, Beckman KB, Hoffmann C, Garbe J, Hahn T, Sucheston-Campbell L, Richardson M, De For TE, Tolar J, Verneris MR. **Transplantation and Cellular Therapy. 2021 Oct 1; 27(10):836.e1-836.e7. doi:10.1016/j.jtct.2021.06.019. Epub 2021 Jun 23. PMC8478819.** This pilot study identified uncommon mtDNA haplotypes potentially associated with inferior outcomes. We used multiple regression analysis to examine the independent association of mtDNA haplotype with overall survival and grade III-IV acute GVHD (aGVHD) adjusting for known risk factors for poor transplant outcome. Neither recipient nor donor mtDNA haplotype reached groupwise significance for overall survival or grade III-IV aGVHD. Adjustment for genomically determined ancestry in the subset of donor-recipient pairs for which this was available did not materially change results.

IB17-02 Donor killer immunoglobulin receptor gene content and ligand matching and outcomes of pediatric patients with juvenile myelomonocytic leukemia following unrelated donor transplantation. Rangarajan HG, Pereira MSF, Brazauskas R, St Martin A, Kussman A, Elmas E, Verneris MR, Gadalla SM, Marsh SGE, Paczesny S, Spellman SR, Lee SJ, Lee DA. **Transplantation and Cellular Therapy. 2021 Nov 1; 27(11):926.e1-926.e10. doi:10.1016/j.jtct.2021.08.009. Epub 2021 Aug 15. PMC8574163.** We

investigated NK cell-related donor and recipient immunogenetics as determinants of HCT outcomes in patients with JMML. The cumulative incidence of grade II-IV aGVHD at 100 days was 36% (95% CI, 27% to 44%), and that of cGVHD at 1 year was 23% (95% CI, 17% to 30%). There were no differences between AA donors and Bx donors for any recipient survival outcomes. The risk of grade II-IV aGVHD was lower in patients with donors with a B content score of ≥2, an activating KIR content score of >, centromeric A/B score, and telomeric A/B score. To our knowledge, this is the first study analyzing the association of NK cell determinants and outcomes in JMML HCT recipients. This study identifies potential benefits of donor KIR-B genotypes in reducing aGVHD. Our findings warrant further study of the role of NK cells in enhancing the graft-versus-leukemia effect via recognition of JMML blasts.

IB18-01 Genetics of HLA peptide presentation and impact on outcomes in HLA-matched allogeneic hematopoietic cell transplantation. Story CM, Wang T, Bhatt VR, Battiwalla M, Badawy SM, Kamoun M, Gragert L, Brown V, Baxter-Lowe LA, Marsh SGE, Gadalla SM, Schetelig J, Mytilineos J, Miklos D, Waller EK, Kuxhausen M, Spellman S, Lee S, Paczesny S, Lansford JL, Vincent BG, Riches ML, Armistead PM. **Transplantation and Cellular Therapy. 2021 Jul 1; 27(7):591-599. doi:10.1016/j.jtct.2021.04.003. Epub 2021 Apr 18. PMC8343993.** The purpose of this study was to test whether cumulative peptide-binding efficiency is associated with the risk of acute GVHD (aGVHD) or relapse. Multivariable analysis did not identify any impact of peptide-binding efficiency on aGVHD or relapse in MUD or MRD transplant recipients. Whereas GVHD is mediated by minor antigen mismatches in the context of HLA-matched allo-HCT, peptide-binding efficiency, which was used as a surrogate measurement for predicted number of binding antigens, did not provide additional clinical information for GVHD risk assessment. The negative result may be due to the limitations of this surrogate marker, or it is possible that GVHD is driven by a subset of immunogenic mHAs.

IB18-04a Haplotype motif-based models for KIR-genotype informed selection of hematopoietic cell donors fail to predict outcome of patients with myelodysplastic syndromes or secondary acute myeloid leukemia. Schetelig J, Baldauf H, Koster L, Kuxhausen M, Heidenreich F, de Wreede LC, Spellman S, van Gelder M, Bruno B, Onida F, Lange V, Massalski C, Potter V, Ljungman P, Schaap N, Hayden P, Lee SJ, Kröger N, Hsu K, Schmidt AH, Yakoub-Agha I, Robin M. **Frontiers in Immunology. 11:584520. doi:10.3389/fimmu.2020.584520. Epub 2021 Jan 19. PMC7851088.** This study aimed to validate different models for unrelated donor selection for patients with Myelodysplatic Syndromes (MDS) or secondary Acute Myeloid Leukemia (sAML). Our results do not support the hypothesis that optimizing NK-mediated alloreactivity is possible by KIR-genotype informed selection of HLA-matched unrelated donors.

IB18-06a Pre-HCT mosaicism increases relapse risk and lowers survival in acute lymphoblastic leukemia patients post-unrelated HCT. Wang Y, Zhou W, Wang J, Karaesmen E, Tang H, McCarthy PL, Pasquini MC, Wang Y, McReynolds LJ, Katki HA, Machiela MJ, Yeager M, Pooler L, Sheng X, Haiman CA, Van Den Berg D, Spellman SR, Wang T, Kuxhausen M, Chanock SJ, Lee SJ, Clay-Gilmour AI, Hahn TE, Gadalla SM, Sucheston-Campbell LE. **Blood Advances. 2021 Jan 12; 5(1):66-70. doi:10.1182/bloodadvances.2020003366. Epub 2021 Jan 5. PMC7805319.** Results showed Pre-HCT mosaicism is related to increased relapse risk and lower survival after unrelated HCT, independent of cytogenetics at diagnosis. Pre-HCT mosaicism could be a useful clinical tool to guide risk stratification in acute lymphoblastic leukemia patients.

IB18-06b Prognostic impact of pre-transplant chromosomal aberrations in peripheral blood of patients undergoing unrelated donor hematopoietic cell transplant for acute myeloid leukemia. Wang Y, Zhou W, McReynolds LJ, Katki HA, Griffiths EA, Thota S, Machiela MJ, Yeager M, McCarthy P, Pasquini M, Wang J, Karaesmen E, Rizvi A, Preus L, Tang H, Wang Y, Pooler L, Sheng X, Haiman CA, Van Den Berg D, Spellman SR, Wang T, Kuxhausen M, Chanock SJ, Lee SJ, Hahn TE, Sucheston-Campbell LE, Gadalla SM. **Scientific Reports. 11(1):15004. doi:10.1038/s41598-021-94539-0. Epub 2021 Jul 22. PMC8298542.** 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 AML.

IB19-01a Impact of previously unrecognized HLA mismatches using ultrahigh resolution typing in unrelated donor hematopoietic cell transplantation. Mayor NP, Wang T, Lee SJ, Kuxhausen M, Vierra-Green C, Barker DJ, Auletta J, Bhatt VR, Gadalla SM, Gragert L, Inamoto Y, Morris GP, Paczesny S, Reshef R, Ringdén O, Shaw BE, Shaw P, Spellman SR, Marsh SGE**. Journal of Clinical Oncology. 2021 Jul 20; 39(21):2397-2409. doi:10.1200/JCO.20.03643. Epub 2021 Apr 9. PMC8280068.** 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. This study did not confirm that UHR 12 out of 12 HLA matching increases the probability of overall survival but does demonstrate that aGVHD risk, and in certain settings TRM, is lowest in UHR HLA-matched pairs and thus warrants consideration when multiple 10 out of 10 HLA-matched donors of equivalent age are available.

IB19-02 HLA informs risk predictions after haploidentical stem cell transplantation with post-transplantation cyclophosphamide. Fuchs EJ, McCurdy SR, Solomon SR, Wang T, Herr MM, Modi D, Grunwald MR, Nishihori T, Kuxhausen M, Fingerson S, McKallor C, Bashey A, Kasamon YL, Bolon Y-T, Saad A, McGuirk JP, Paczesny S, Gadalla SM, Marsh SG, Shaw BE, Spellman SR, Lee SJ, Petersdorf EW. **Blood. doi:10.1182/blood.2021013443. Epub 2021 Nov 1.** The aim of this study is to examine whether mismatches in individual loci at HLA-A, -B, -C, -DRB1, -DQB1, and The HLA-B leader, and HLA-DPB1 T-cell epitope (TCE) impact clinical outcomes after HLA-haploidentical blood or marrow transplantation utilizing post-transplantation cyclophosphamide. HLA-DRB1 mismatches were associated with lower risk of disease recurrence. HLA-DRB1-mismatching with HLA-DQB1-matching correlated with improved disease-free survival. HLA-B leader matching and HLA-DPB1 TCE-non-permissive mismatching were each associated with improved overall survival. HLA-C matching lowered chronic GVHD risk, and the level of HLA-C expression correlated with transplant-related mortality. Matching status at the HLA-B leader and HLA-DRB1, -DQB1 and -DPB1 predicted disease-free survival, as did patient and donor CMV serostatus, patient age and co-morbidity index.

IB20-02 Number of HLA mismatched eplets is not associated with major outcomes in haploidentical transplantation with post-transplantation cyclophosphamide: A Center for International Blood and Marrow Transplant Research Study. Zou J, Wang T, He M, Bolon YT, Gadalla SM, Marsh SGE, Kuxhausen M, Gale RP, Sharma A, Assal A, Prestidge T, Aljurf M, Cerny J, Paczesny S, Spellman SR, Lee SJ, Ciurea SO.

Transplantation and Cellular Therapy. doi:10.1016/j.jtct.2021.11.001. Epub 2021 Nov 11. The goal of this study is to investigate whether ME load in HVG or GVH direction from total class I and class II loci, and ME from individual loci at HLA-A, -B, -C, -DRB1, -DQB1, and –DPB1 are associated with the clinical outcomes of haploidentical hematopoietic stem cell transplantation (haplo-HSCT) performed with post transplantation cyclophosphamide (PTCy), +/-others for GVHD prevention. The results showed an unexpected strong association was identified between total class II ME load in the GVH direction and slower neutrophil engraftment. This study failed to demonstrate the predictive value of ME from HLA molecules for major clinical outcomes.

R02-40/R03-63i Following transplantation for acute myelogenous leukemia, donor KIR Cen B02 better protects against relapse than KIR Cen B01. Guethlein LA, Beyzaie N, Nemat-Gorgani N, Wang T, Ramesh V, Marin WM, Hollenbach JA, Schetelig J, Spellman SR, Marsh SGE, Cooley S, Weisdorf D, Norman PJ, Miller JS, Parham P. **Journal of Immunology. 2021 Jun 15; 206(12):3064-3072. doi:10.4049/jimmunol.2100119. Epub 2021 Jun 11. PMC8664929** In this study, we developed high-resolution KIR sequence-based typing that defines all the KIR alleles and distinguishes the expressed alleles from those that are not expressed. This study showed 1) KIR Cen B is associated with protection from relapse following HCT; 2) KIR Cen B02 provides stronger protection against relapse; 3) Protection from relapse associates with presence of less inhibitory KIR.

IB19-03 Natural killer cell alloreactivity predicted by killer cell immunoglobulin-like receptor ligand mismatch does not impact engraftment in umbilical cord blood and haploidentical stem cell transplantation. Otegbeye F, Fernandez-Viña A, Wang T, Bolon Y, Lazaryan A, Beitinjaneh A, Bhatt V, Castillo P, Marsh S, Hildebrandt G, Assal A, Brown V, Hsu J, Spellman S, de Lima M, Lee S. 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. **Submitted.**

IB17-03 Germline-somatic interactions drive JAK2-mediated clonal expansion in myelofibrosis. Brown D, Zhou W, Wang Y, Jones K, Lou W, Dagnall C, Teshome K, Klein A, Zhang T, Lin, S, Lee O, Khan S, Vo J, Hutchinson A, Liu J, Zhu B, Hicks B, St. Martin A, Spellman S, Wang T, Deeg T, Lee S, Freedman N, Yeager M, Chanock S, Savage S, Saber W, Gadalla S, Machiela M. The goal of this study is to describe mutations associated with MF, and to correlate these abnormalities with clinical outcomes. **Submitted**

IB10-01x Unrecognized Inherited Disorders Have Inferior Survival after Hematopoietic Cell Transplant for Aplastic Anemia. McReynolds L, Rafati M, Wang Y, Ballew B, Kim J, Williams V, Dagnall C, Freedman N, Carter B, Strollo S, Hicks B, Zhu B, Jones K, Paczesny S, Marsh S, Spellman S, He M, Wang T, Lee S, Savage S, Gadalla S. **Submitted**

IB17-04 Donor whole blood DNA methylation is not a strong predictor of acute graft versus host disease in unrelated donor allogeneic haematopoietic cell transplantation. Webster A, Ecker S, Moghul I, Dhami P, Marzi S, Paul D, Feber A, Kuxhausen M, Lee S, Spellman S, Wang T, Rakyan V, Peggs K, Beck S.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. **Submitted**

IB 19-01b A core group of structurally similar HLA-DPB1 alleles drives permissiveness after hematopoietic cell transplantation. Arrieta-Bolaños E, Crivello P, He M, Wang T, Gadalla S, Paczesny S,

Marsh S, Lee S, Spellman S, Bolon Y, Fleischhauer K. The goal of this study is to determine whether some mismatches within TCE group 3 behave clinically as less permissive mismatches than others and impact HCT outcome accordingly. **Submitted**

IB20-04 Haploidentical versus matched unrelated donor transplants using post-transplant cyclophosphamide for lymphomas. Mussetti A, Kanate A, Wang T, He M, Hamadani M, FINEL H, Boumendil A, Glass B, Castagna L, Dominietto A, McGuirk J, Blaise D, Gülbas Z, Diez-Martin J, Marsh S, Paczesny S, Gadalla S, Dreger P, Zhang M, Spellman S, Lee S, Bolon Y, Sureda A. The goal of this study is to investigate if the use of a PTCy-based anti-GVHD strategy results in similar overall survival for patients with lymphomas receiving transplants from HLA-mismatched haploidentical donors vs. 8/8 HLA-matched unrelated donors. **Submitted**