A G E N D A
CIBMTR WORKING COMMITTEE FOR IMMUNOBIOLOGY
Orlando, FL
Friday, February 17, 2023, 12:00 p.m. – 02:00 p.m. (EST)

Co-Chair:	**Sophie Paczesny, MD, PhD; Medical University of South Carolina**
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Co-Chair:	**Steven Marsh, BSc, PhD, ARCS; Anthony Nolan Research Institute**
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Co-Chair:	**Shahinaz Gadalla, MD, PhD; National Cancer Institute**
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Co-Scientific Dir:	**Stephanie Lee, MD, MPH, Fred Hutchinson Cancer Center**
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Co-Scientific Dir:	**Yung-Tsi Bolon, PhD, Be The Match/NMDP, Minneapolis, MN**
	Telephone: 763-406-5742; E-mail: ybolon@nmdp.org
Statistical Director:	**Tao Wang, PhD, CIBMTR Statistical Center**
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Agenda Summary

- Introduction and overview of progress 12:00pm
- Presentation of new proposals 12:05-12:55pm
  - PROP2210-70
  - PROP2210-201
  - PROP2209-12; PROP2210-27
- Associated molecular genetic data resources update 12:55-1:10pm
- Presentation of updates for completed/ongoing studies 1:10-1:55pm
  - IB20-04
  - IB18-02
  - IB20-03
- Concluding remarks 1:55pm

Detailed Agenda

1. Introduction **Sophie Paczesny** 12:00pm

a. Minutes and Overview Plan of Immunobiology Working Committee from Tandem 2022 (***Attachment 1***)

2. Published and submitted papers (14) in the last year 12:05pm

a. **IB06-05e** HLA-DQ heterodimers in hematopoietic cell transplantation. Petersdorf EW, Bengtsson M, Horowitz MM, McKallor C, Spellman SR, Spierings E, Gooley TA, Stevenson PA. ***Blood. 2022 May 19; 139(20):3009-3017. doi:10.1182/blood.2022015860. Epub 2022 Mar 10. PMC9121842.***

b. **IB06-05f** Race and survival in unrelated hematopoietic cell transplantation. Morishima Y, Morishima S, Stevenson P, Kodera Y, Horowitz M, McKallor C, Malkki M, Spellman SR, Gooley T, Petersdorf EW. ***Transplantation and Cellular Therapy. 2022 Jul 1; 28(7):357.e1-357.e6. doi:10.1016/j.jtct.2022.03.026. Epub 2022 Apr 8. PMC9387555.***

c. **IB10-01m** Telomere length and epigenetic clocks as markers of cellular aging: A comparative study. Pearce EE, Alsaggaf R, Katta S, Dagnall C, Aubert G, Hicks BD, Spellman SR, Savage SA, Horvath S, Gadalla SM. ***GeroScience. 2022 Jun 1; 44(3):1861-1869. doi:10.1007/ s11357-022-00586-4. Epub 2022 May 18. PMC9213578.***

d. **IB19-01b** 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 SM, Paczesny S, Marsh SGE, Lee SJ, Spellman SR, Bolon Y, Fleischhauer K**. *Blood. 2022 Aug 11; 140(6):659-663. doi:10.1182/blood.2022015708. Epub 2022 May 24. PMC9373015.***

e. **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, Vina MAF, Wang T, Bolon YT, Lazaryan A, Beitinjaneh A, Bhatt VR, Castillo P, Marsh SGE, Hildebrandt GC, Assal A, Brown VI, Hsu J, Spellman S, de Lima M, Lee SJ. ***Transplantation and Cellular Therapy. 2022 Aug 1; 28(8):483.e1-483.e7. doi:10.1016/j.jtct.2022.05.034. Epub 2022 May 26. PMC9357149.***

f. **IB10-01n** Genetic testing in severe aplastic anemia is required for optimal hematopoietic cell transplant outcomes. McReynolds LJ, Rafati M, Wang Y, Ballew BJ, Kim J, Williams VV, Zhou W, Hendricks RM, Dagnall C, Freedman ND, Carter B, Strollo S, Hicks B, Zhu B, Jones K, Paczesny S, Marsh SGE, Spellman SR, He M, Wang T, Lee SJ, Savage SA, Gadalla SM. ***Blood. 2022 Aug 25; 140(8):909-921. doi:10.1182/blood.2022016508. Epub 2022 Jul 1. PMC9412004.***

g. **IB17-03a** Germline-somatic JAK2 interactions are associated with clonal expansion in myelofibrosis. Brown DW, Zhou W, Wang Y, Jones K, Luo W, Dagnall C, Teshome K, Klein A, Zhang T, Lin SH, Lee OW, Khan S, Vo JB, Hutchinson A, Liu J, Wang J, Zhu B, Hicks B, Martin AS, Spellman SR, Wang T, Deeg HJ, Gupta V, Lee SJ, Freedman ND, Yeager M, Chanock SJ, Savage SA, Saber W, Gadalla SM, Machiela MJ. ***Nature Communications. 13(1):5284. doi:10.1038/s41467-22-32986-7. Epub 2022 Sep 8. PMC9458655. Oral Presentation, ASH 2022.***

h. **IB18-02** Pathogenicity and impact of HLA class I alleles in aplastic anemia patients of different ethnicities. Olson TS, Frost BF, Duke JL, Dribus M, Xie HM, Prudowsky ZD, Furutani E, Gudera J, Shah YB, Ferriola D, Dinou A, Pagkrati I, Kim S, Xu Y, He M, Zheng S, Nijim S, Lin P, Xu C, Nakano TA, Oved JH, Carreno BM, Bolon YT, Gadalla SM, Marsh SGE, Paczesny S, Lee SJ, Monos DS,

Shimamura A, Bertuch AA, Gragert L, Spellman SR, Babushok DV. ***Journal of Clinical Investigation Insight. 2022 Nov 22; 7(22):e163040. doi:10.1172/jci.insight.163040. Epub 2022 Oct 11. PMC9746824. Dr. Daria Babushok will present at 1:25.***

i. **IB10-01o** Molecular landscape of immune pressure and escape in aplastic anemia. Pagliuca S, Gurnari C, Hercus C, Hergalant S, Nadarajah N, Wahida A, Terkawi L, Mori M, Zhou W, Visconte V, Spellman S, Gadalla SM, Zhu C, Zhu P, Haferlach T, Maciejewski JP. ***Leukemia. doi:10.1038/s41375-022-01723-w. Epub 2022 Oct 17.***

j. **IB20-04** Haploidentical versus matched unrelated donor transplants using post-transplant cyclophosphamide for lymphomas. Mussetti A, Kanate AS, Wang T, He M, Hamadani M, Sr HF, Boumendil A Sr, Glass B, Castagna L, Dominietto A, McGuirk J, Blaise D, Gülbas Z, Diez-Martin J, Marsh SGE, Paczesny S, Gadalla SM, Dreger P, Zhang MJ, Spellman SR, Lee SJ, Bolon Y-T, Sureda A. ***Transplantation and Cellular Therapy. doi:10.1016/j.jtct.2022.11.028. Epub 2022 Dec 25. Dr. Anna Sureda will present at 1:10.***

k. **IB20-01** Impact of High Immunopeptidome Divergence between Single Class I HLA-Mismatches on Survival after Unrelated Donor Transplantation. Pietro Crivello, Esteban Arrieta-Bolaños, Meilun He, Tao Wang, Stephanie Fingerson, Shahinaz Gadalla, Sophie Paczesny, Steven G. E. Marsh, Stephanie J. Lee, Stephen R. Spellman, Yung-Tsi Bolon, Katharina Fleischhauer. ***Journal of Clinical Oncology. In press.***

l. **IB17-04** Donor whole blood DNA methylation is not a strong predictor of acute graft versus host disease in unrelated donor allogeneic hematopoietic 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.***

m. **IB20-03** Donor socioeconomic status as a predictor of recipient mortality following hematopoietic cell transplantation for hematologic malignancy. Lucie M. Turcotte, Tao Wang, Kirsten M. Beyer, Steven W. Cole, Stephen R. Spellman, Mariam Allbee-Johnson, Eric Williams, Yuhong Zhou, Michael R. Verneris, J. Douglas Rizzo, Jennifer M. Knight. ***Submitted. Dr. Jennifer Knight will present at 1:40.***

n. **IB19-04** HLA Class I genotype is associated with relapse risk after allogeneic stem cell transplantation for NPM1-mutated AML**.** Rupa Narayan, Abhishek Niroula, Tao Wang, Michelle Kuxhausen, Meilun He, Everett Meyer, Yi-Bin Chen, Vijaya Raj Bhatt, Amer Beitinjaneh, Taiga Nishihori, Akshay Sharma, Valerie I. Brown, Malek Kamoun, Miguel A Diaz, Muhammad Bilal Abid, Medhat Askar, Christopher G. Kanakry, Loren Gragert, Yung-Tsi Bolon, Steven G.E. Marsh, Shahinaz M. Gadalla, Sophie Paczesny, Stephen Spellman, Stephanie J Lee. ***Submitted.***

3. Future/proposed studies and discussion **Shahinaz Gadalla** 12:05-12:55pm

a. Voting guidelines
b. **Proposal presentations (3)**

i. **PROP2210-70** Younger MMUD vs older haploidentical donor HCT (Rohtesh S. Mehta) ***(Attachment 2)*** ***Dr. Rohtesh Mehta will present.***

ii. **PROP2210-201** Immunopeptidome divergence between mismatched HLA and outcome of haploidentical HCT (Pietro Crivello, Katharina Fleischhauer) *(**Attachment 3**)* ***Dr. Pietro Crivello will present.***

iii. **PROP2209-12; PROP2210-27** Effect of donor KIR, recipient KIR ligand, and recipient B-leader genotype on transplant outcomes following PTCy-based Haplo-HSCT (Jun Zou; Stefan O. Ciurea; Scott R Solomon) *(**Attachment 4**)* ***Dr. Stefan Ciurea will present.***

c. **Dropped Proposals (5)**

i. **PROP2203-01** The Impact of Donor/Recipient Immunogenicity on Outcome of Bone Marrow Transplantation (Stanislaw Stepkowski) – *Provided with a dataset.*

ii. **PROP2206-01** HLA and Susceptibility to Type 1 Diabetes in Immunodeficiency, polyendocrinopathy and enteropathy X-linked (IPEX) Syndrome (Christina Roark; Louise Helander) – *Small sample size.*

iii. **PROP2210-113** Is there an antileukemic effect by allograft rejection following hematopoietic cell transplantation? (Olle Ringden; Behnam Safeghi) – *Lower scientific impact, lack of sufficient detail in forms.*

iv. **PROP2210-133** Understanding the role of directional permissive HLA-DP T-cell epitope matching for disease control in current unrelated donor-HCT practice. (Esteban Arrieta-Bolaños; Katharina Fleischhauer) – *Extension of current study/Publication.*

v. **PROP2210-254** Impact of the HLA locus and the number of allele mismatches on outcomes after unrelated donor transplant using post-transplant cyclophosphamide in hematologic malignancy patients (Ronald M. Sobecks; Medhat Askar) – *Small sample size.*

4. Research sample repository update with data accrual tables *(**Attachment 5**)*

5. Associated molecular genetic data resources update **Yung-Tsi Bolon** 12:55-1:10pm

a. **IB21-02** DISCOVeRY-BMT: Multi-ethnic high-throughput study to identify novel non-HLA genetic contributors to mortality after blood and marrow transplantation. ***Dr. Theresa Hahn will present.***

b. **IB10-01 and IB17-03** NCI-CIBMTR Collaborative Molecular Studies in HCT. ***Dr. Shahinaz Gadalla will present.***

6. 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) **Manuscript Preparation.**

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) **Manuscript Preparation.**

b. **IB21-01** Effect of HLA evolutionary divergence on survival and relapse following allogeneic hematopoietic cell transplant (Christine Camacho-Bydume/Diego Chowell/ Katharine C. Hsu) **Manuscript Preparation.** ***Poster Presentation, 2023 Tandem Meetings.***

c. **IB22-01** Impact of HLA-DPB1 matching on survival following unrelated donor transplantation with post-transplant cyclophosphamide for adults 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) **Protocol Development.**

Other Genes

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

b. **IB22-02** Effect of SIRPα mismatch on the outcome of allogeneic hematopoietic stem cell transplantation from an HLA matched related donor. (Jun Zou; Samer Srour) **Protocol Development.**

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. (Theresa Hahn/Alyssa Clay-Gilmour) **Ongoing.**

7. Study Presentations **Steven Marsh** 1:10-1:55pm

a. **IB20-04** Haploidentical versus matched unrelated donor transplants using post-transplant cyclophosphamide for lymphomas.
b. **IB18-02** Pathogenicity and impact of HLA class I alleles in aplastic anemia patients of different ethnicities.
c. **IB20-03** Donor socioeconomic status as a predictor of recipient mortality following hematopoietic cell transplantation for hematologic malignancy.

8. Closing Remarks **Stephanie Lee** 1:55pm

A G E N D A
CIBMTR IMMUNOBIOLOGY WORKING COMMITTEE
Salt Lake City, Utah
Sunday, April 24, 2022, 12:15 pm–13:45 pm MT

Co-Chair:	**Sophie Paczesny, MD, PhD; Medical University of South Carolina**
	Telephone: 317-278-5487; E-mail: paczesns@musc.edu
Co-Chair:	**Steven Marsh, BSc, PhD, ARCS; Anthony Nolan Research Institute**
	Telephone: +44 20 7284 8321; E-mail: steven.marsh@ucl.ac.uk
Co-Chair:	**Shahinaz Gadalla, MD, PhD; National Cancer Institute**
	Telephone: 240-276-7254; E-mail: shahinaz.gadalla@nih.gov
Co-Scientific Dir:	**Stephanie Lee, MD, MPH, Fred Hutchinson Cancer Center**
	Telephone: 206-667-6190; E-mail: sjlee@fredhutch.org
Co-Scientific Dir:	**Stephen Spellman, MBS, CIBMTR Immunobiology Research**
	Telephone: 763-406-8334; E-mail: sspellma@nmdp.org
Co-Scientific Dir:	**Yung-Tsi Bolon, PhD, CIBMTR Immunobiology Research**
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Statistical Director:	**Tao Wang, PhD, CIBMTR Statistical Center**
	Telephone: 414-955-4339; E-mail: taowang@mcw.edu
Statistician:	**Meilun He, MPH, CIBMTR Statistical Center**
	Telephone: 763-406-4435; E-mail: mhe@nmdp.org

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 and Overview Plan of Immunobiology Working Committee from TCT 2021 (Attachment 1)

The CIBMTR Immunobiology Working Committee (IBWC) was called to order at 12:15 pm on Sunday April 24th, 2022, by Dr. Steven Marsh. Dr. Marsh introduced the CIBMTR COI policy

along with working committee leadership. Dr. Marsh continued by reviewing the membership and goals of the working committee, areas of focus, and limitations of the IBWC. He gave a brief overview of the status of the current portfolio and number of proposals to be presented at the meeting and voting and prioritization guidelines.

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

Recently published or submitted papers from the committee were announced.

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 SM,

Paczesny S, Marsh SGE, Lee SJ, Spellman SR, 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) *(Attachment3)*

Dr. Zou presented this proposal. Signal Regulatory Protein α (SIRPα) polymorphism is a key regulator of the innate immune allorecognition response. SIRPα interacts with ubiquitously expressed ligand, CD47, that elicits inhibitory signal and suppresses macrophage phagocytic function. Ten human SIRPα variants have been identified, and the majority of the polymorphisms are located in the CD47-binding domain, which is likely associated with different binding affinities to CD47. Based on the polymorphism, SIRPα variants can be classified into two large groups. The investigators would like to study the frequency and possible clinical impact of SIRPα mismatching in the setting of HCT. One preliminary study with 350 patients with AML/MDS undergoing HLA-matched related HSCT found mismatched SIRPα was associated with increased risk of cGVHD and improved RFS. A recent study in lymphoid malignancies showed the SIRPα mismatch was associated with a significantly high risk of cGvHD, a lower rate of relapse, and improved RFS.

Dr. Zhou hypothesized that an innate immune response is elicited by the non-self signal from the mismatched SIRPα, which will further enhance adaptive immunity manifested as cGVHD and relapse protection. Consideration of SIRPα will assist in donor selection and may help explain the role of innate immunity in the context of HSCT. The CIBMTR identified 3045 patients who underwent first HSCT from MRD, 2010-2019 with AML, ALL, MDS. The following questions were answered during the Q&A:

a. What is the frequency of the SIRPα variants? Do you have enough for matched vs. mismatched? Answer: The V1, V2 comprised 80% of the population; the V1, V4, V5, V6, and V9 have the same binding motif with CD47, and we will focus on those binding motifs.

b. Is there any in-vitro evidence that CD47 has a different binding affinity to these variants? Is CD47 itself polymorphic? Answer: We did not see CD47 polymorphism. For the different binding question, there are several conflict reports. A JBC paper showed no difference. But probably there are some downstream signal differences that we will explore in future.

c. Should matched unrelated donors be included? Answer: We are doing some genotyping for MUD. The reason to study MRD is to minimize the impact of mismatched HLA and other differences, which allows us to focus on innate immunity.

d. For the 10 variants, how will you define matched vs. mismatched? Answer: First, consider at least one mismatched allele as mismatched and consider GVH and HVG directionality. Or mismatch could be the presence of a non-V2 SIRPα in the graft or host.

e. Any functional studies showing that mismatches can trigger T cell responses? Answer: not yet. We plan to do these studies, but they are difficult.

f. Comment: Need to pay attention on the GVHD prophylaxis selection, like TCD vs. PTCY. Dr. Zhou agreed with the comment.

g. Your previous studies showed increased cGVHD and protection from relapse. How will you use the results clinically? Answer: We don't know the answer yet. For example, for patients with high risk of relapse, they can use SIRPα mismatched donors to decrease the risk of relapse although there might be more cGVHD

h. Should you look at CD47 itself? Answer: CD47 is not polymorphic, and several previous studies showed conflicting results about whether binding affinity changed or not with SIRPα polymorphisms. Several studies are looking at CD47.

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) *(Attachment4)*

Dr. Fernandez-Vina presented this proposal. The hypotheses of this proposal are: 1) HLA mismatched alleles that differ only at AA residues that are not directly involved in peptide binding are not immunogeneic and could be classified as permissible (e.g. C*03:03/C*03:04) 2) HLA mismatches in DRB1 alleles that differ only at amino acid residue 86 (dimorphism 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. A mismatch in the opposite direction (86-G/V) may be immunogenic. The objective of this proposal is to determine the effect of a putative non-immunogenic HLA mismatches on the outcomes of UD-HSCT. Primary end points include OS, TRM, DFS, grade II-IV acute GVHD, grade III-IV aGvHD and relapse.

A preliminary study included 4417 BMT patient/donor pairs from MUD, CIBMTR data. There were three groups: Matched vs. Permissible+86V/G vs. Non-permissible+86G/V.

Significant differences in OS and DFS were seen between matched vs. non-permissible+86G/V, and Permissible+86V/G vs. Non-permissible+86G/V cohorts. Based on the preliminary study, Dr. Fernandez-Vina mentioned that if validated, these new classifications could be used in day-to-day donor prioritization based on match grades. The examination of peptide binding repertoire profiles imputed from structural differences between HLA mismatched alleles may become a new paradigm to evaluate mismatches, and their applications may change clinical practice for donor selection and prioritization. The CIBMTR identified 550 DRB1 MM patients, 3217 HLA-A, -B, or -C MM patients, and 20707 8/8 patients who underwent first HSCT from URD, 2012-2020 with AML, ALL, MDS and CML. The following questions were answered during the Q&A:

a. From your preliminary study, it seems the permissible mismatched pairs has better survival than matched pais. How do you explain this? Answer: Yes, but the number of permissible mismatches is small, only 95 patients, probably biasing the results.

b. Is there any linkage for 86V/G with HLA-DR51, -DR52, -DR53? William Hildebrand's study in peptides not only eluted the peptides from DRB1, but also from additional DRB groups. Answer: Yes, there are several pairs like HLA-DRB1*14:01/14:54, and DRB3*02:02/02:24. Eventually will use DRB3/4/5 as a scoring system, as well as DQ, DP mismatches, because we believe the linkage will cause more GVL effects. So it is important to control/adjust for these factors.

c. In terms of how HLA typing for the donor and recipient are input in the database, will there be any issues if P or G groups were used to determine mismatched vs. matched? Answer: No, we use the classic P matches.

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) *(Attachment5)*

Dr. Scott Solomon presented this proposal. The research questions are: 1) Should the presence of a high risk/non-permissive (npmm) HLA-DPB1 mismatch be considered for donor selection following matched unrelated donor (MUD) transplantation using post-transplant cyclophosphamide (PTCy)? 2) In the context of HLA-DPB1 npmm, is there a preference for PTCy- vs. non-PTCy-based GVHD prophylaxis strategy? Dr. Solomon introduced three models for predicting HLA-DPB1 permissive mismatches: T cell epitope (TCE) model, Expression model, and Predicted Indirectly Recognizable HLA Epitopes (PIRCHE). Previous studies using the TCE model indicated the HLA-DPB1 nmpp group has high risk of NRM, while the permissive group was similar to the matched group when

standard GVHD prophylaxis is given. The hypothesis is, in patients with an HLA-DPB1 npmm, survival following MUD transplantation will be improved with the use of PTCy-based GVHD prophylaxis (by negating the negative impact of using a DP non-permissively mismatched donor) compared to calcineurin inhibitor (CNI)-based GVHD prophylaxis.

The main variable is high-risk HLA-DPB1 mismatch vs. low-risk mm/DP match. "High risk" is defined by the three different models: TCE, Expression, and PIRCHE. The primary endpoint is OS (ptcy vs. non-ptcy cohort), and secondary endpoints are: DFS, NRM, relapse, GRFS, a/c GVHD. The CIBMTR identified 785 ptcy patients and 9023 CNI-based patients who underwent first HCT from 8/8 MUD, 2008-2018 with AML, ALL, MDS, and lymphoma. Based on prior studies, a 5-10% improvement in 1-year OS in patients with high-risk HLA-DPB1 mismatch received ptcy is expected. The following questions were answered during the Q&A:

a. Two questions: Should lymphoma patients be excluded since most of the patients have leukemia and MDS? Will you use infectious complications as a secondary endpoint? Since PTCY might increase infections, and HLA disparity can impact that, is it worth studying at least virus and fugus infection. Answer: 1) It is good to minimize heterogeneity, but we do not want to exclude the lymphoma patients. 2) We can potentially include the infectious data.

b. Comment: Lymphoma should be excluded. This is a small group that will not impact the power, so it is better to exclude them from this study.

c. Will there be a bias because more recent transplants are more likely to give PTCy, use younger donors, have more permissive DPB1 donors? Answer: We can try to control for the donor age, and the number of HLA mismatches could adversely impact the power calculations.

d. How homogeneous is the ptcy in this cohort? Are patients receiving the standard dose or reduced doses? Will different doses impact the degree of immunosuppression? Answer: We can check the dose data, but it would be very rare for patients to receive non-conventional doses.

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 *(Attachment6)*

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-Update to be presented 13:20**

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. (Theresa Hahn/Alyssa Clay-Gilmour) **Ongoing.**

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

a. **IB19-02**

Dr. Shannon R. McCurdy remotely provided an update on IB19-02. This study has been published in Blood in Mar 2022. Using a retrospective cohort of 1434 haplo donor transplants using Ptcy, the investigators found there is no association of number of HLA mismatches with TRM or GVHD, but fewer mismatches were associated with more relapses. MM at individual loci have different clinical effects. HLA-B leader MM has high risk in mortality and TRM. HLA-DPB1 non-permissive MM increased mortality, and HLA-DRB1 MM has low risk in relapse. HLA-C mismatch increased the risk of cGVHD. Effects of DRB1 MM and B-leader match are additive, with the best OS group in HLA-DRB1 GVH mismatch, B-leader match, and worst OS in DRB1 match, B-leader mismatch. A donor-selection calculator was developed that can predict the DFS after haploidentical transplant using different donors. Users can enter patient disease, disease stage, HCT-CI, age, CMV serostatus, each donor's HLA-B leader status, DRB1 and DQB1 match status, and DPB1 TCE status. The online calculator can show the predicted DFS if different donors are used. The following questions were answered during the Q&A:

a. Comment: The calculator helps translate one single study into a tool that everyone can use when selecting donors.

b. Did you see any differences between the allele level mismatches in DRB1 or only mismatch in antigen level? Answer: we only did the antigen level, and did not separate allele vs. antigen level mismatching. For our first study we used the antigen level mismatches, and saw the association of DRB1 MM with less relapse.

c. Have you applied the same algorithm for MUD? Answer: No. We submitted a proposal for MUD to look at the same criteria.

d. For HLA-C MM associated with cGVHD. Did you look at the KIR ligand mismatch aspect, or just the antigen level? Answer: We did not look at KIR in this analysis. There will be too many factors if KIR is taken into account.

b. **IB17-03**

Dr. Maryam Rafati provided an update on IB17-03. This study was submitted for publication. Eligible patients for this study underwent HCT for primary or secondary myelofibrosis, and had a pre-HCT blood sample available. Among the 973 patients, 85% are URD. The primary hypotheses are: Genetic changes present in pre-HCT samples are associated with post-HCT outcomes. Specifically, they hypothesize that chromosomal abnormalities, germline genetic variants in telomere biology genes and/or telomere length, and somatic mutations affect outcomes. Using GWAS they identified six significant loci, four of which replicate prior MPN susceptibility study findings (JAK2, TERT, IFT80, and TET2) and two novel loci on chromosomes 6 and 17. The most significant signals were intronic variants of TERT and JAK2. Work is ongoing to identify JAK2 alterations and their effects on HCT outcomes, including relapse, TRM, and OS. Currently they have the clinical data, mCAs, somatic variants data, germline variants, telomere length data. They aim to study all the information together to see how the different genomic alterations affect HCT outcomes. Also aim to define distinct genetic subgroups, which may lead to development of genetically inspired prognostic models. The following questions were answered during the Q&A:

a. Telomere length may correlate with the age of individuals. Did you look at the correlation of recipients' telomere length and age? Also, will be interesting to see the donor age. Answer: For this study, we adjusted for recipient age.

b. GWAS data showed an association for chromosomes 6 with HLA-DRB9. Did you look more deeper if it links with other DRB types? Answer: We haven't done yet but could.

c. **IB18-04b**

Dr. Johannes Schetelig provided an update on IB18-04b. Donor KIR genotype-based prediction of outcomes can be grouped in three different classifications, which are KIR-Ligand interactions, haplotype B motifs, and functional scores that have been tried before. The goal of this study is to validate previously published models to predict relapse, and to explore alternative classifications. The donor samples were genotyping at DKMS life science lab, and patient data were obtained from EBMT and CIBMTR. Total number of patients (N=5019) who received HCT from 2013 to 2018. The confirmatory testing of various models showed no statistically significant prediction of EFS, relapse, and NRM. Patients with Cen-B/B & Tel A/A donor motifs had better relapse-free survival. When the B motif was grouped into Cen-B01/B01 vs. Cen-B02/B02 motifs, B01/B01 had lower risks of relapse. Analysis of aGVHD has low number at risk and needs supplemental data from CIBMTR. The reasons for many studies to fail validation: 1) no good animal model; 2) NK alloreactivity poorly reproduced in vitro; 3) Too few data to factor in KIR-Ligand patterns. The following questions were answered during the Q&A:

a. Comment: Even after several failures to validate the models, the major hypothesis still should be tested. Probably the KIR genotype is not a good indicator for predicting the outcome in MUD HCT. But still worth exploring the role of KIR in relapse.

b. Two questions: 1) In table 1 you showed there was t-cell depletion. Have you considered providing detailed GVHD prophylaxis information, including ptcy, because they may have different effects on outcomes? Answer: We looked at the conditioning regimen, but not GVHD prophylaxis, and will consider adding it. 2) We learned a lot recently about ptcy and ATG immune reconstitution after transplant. Do we have data about immune reconstitution in these different KIR mismatches, independent of the outcomes? Just trying to see biology happening early after transplant. Answer: There was a haploidentical transplant study that did not give a clear answer on the role of KIR but explored the different type of KIRs expression on cells.

c. Comment: Since you have the collaboration with Biobank, might be a way to tackle the biology of KIR, that will be helpful to understand the mechanism of these KIR models.

7. Closing Remarks 13:40 PM

Working Committee Overview Plan for 2022-2023

Study number and title	Current status	Chairs priority
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.	Analysis	9
IB16-02 Use of HLA structure and function parameters to understand the relationship between HLA disparity and transplant outcomes.	Analysis	2
IB18-02 Impact of HLA class I risk alleles associated with AA immune pathogenesis on allo TX outcomes in patients with SAA.	Submitted	12
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.	Submitted	11
IB19-04 Impact of donor HLA on transplant outcomes in NPM1 mutated AML	Manuscript Preparation	9
IB17-03 Germline-somatic interactions drive JAK2-mediated clonal expansion in myelofibrosis.	Submitted	10
IB17-04 Donor whole blood DNA methylation is not a strong predictor of acute graft versus host disease in unrelated donor allogeneic hematopoietic cell transplantation.	Submitted	5
IB18-07 Donor and recipient genomic associations with acute GVHD	Analysis	1
IB20-03 Donor socioeconomic status as a predictor of altered immune function and treatment response following hematopoietic cell transplantation for hematologic malignancy	Submitted	1
IB20-04 Haploidentical versus matched unrelated donor transplants using post-transplant cyclophosphamide for lymphomas.	Submitted	2

IB21-01 Effect of HLA evolutionary divergence on survival and relapse following allogeneic hematopoietic cell transplant.	Analysis	2
IB22-01 Impact of HLA-DPB1 matching on survival following unrelated donor transplantation with post transplant cyclophosphamide for adults with hematologic malignancies.	Protocol Pending	1
IB22-02 Effect of SIRPα mismatch on the outcome of allogeneic hematopoietic stem cell transplantation from an HLA matched related donor.	Protocol Pending	2

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

Younger MMUD vs older haploidentical donor HCT

Q2. Key Words

mismatched unrelated donor; haploidentical donor; donor age; patient age

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Rohtesh S. Mehta, MD MPH MS
Email address:	rmehta1@mdanderson.org
Institution name:	MD Anderson Cancer Center
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?

- Yes

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	N/A
Email address:	N/A
Institution name:	N/A
Academic rank:	N/A

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:

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/p*

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

N/A

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:

Stephen Spellman

Q15. RESEARCH QUESTION:

Is a younger mismatched unrelated donor (MMUD) better than an older haploidentical donor for patients undergoing allogeneic HCT with PTCy-based GVHD prophylaxis?

Q16. RESEARCH HYPOTHESIS:

Among patients without HLA-matched donors, a younger mismatched unrelated donor (MMUD) would yield better outcomes with lower risk of GVHD, non-relapse mortality and improved survival than an older haploidentical donor, especially in older patients undergoing allogeneic HCT with PTCy-based GVHD prophylaxis

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

Suggested word limit of 200 words:

Primary: Compare GRFS in patients with a younger MMUD vs older haploidentical donor who received PTCy-based GVHD prophylaxis
Secondary: Compare the risks of acute and chronic GVHD, relapse, NRM, PFS and OS between the two groups.

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.

Among patients with no HLA-matched donors, haploidentical donor is usually preferred over an HLA-MMUD due to logistic issues, easy of finding a donor and graft procurement. Although donor age is recognized as one of the critical factors that determine HCT outcomes, the impact of donor age among patients with an alternated donor HCT has not been assessed, and may have prognostic implications. If our hypothesis is correct, it would support the use of a younger HLA-MMUD over an older haploidentical donor, which is not the current standard practice.

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.

In a recent single center study at our institution, we analyzed the outcomes of 661 patients who underwent haploidentical (n=275), HLA-matched unrelated donor (MUD; n=246), and HLA-matched sibling donor (MSD; n= 140) HCT with PTCy-based prophylaxis. HLA-mismatched donor group was excluded due to small numbers. In exploratory analysis, we noted that a subset of the haploidentical group that included older patients with an older donor (both 50 years or older) behaved poorly and was more susceptible to NRM than the others. Although no firm conclusions could be made from these exploratory analyses, the effect of older donors (>/=50 years) appeared to be detrimental solely in the haploidentical group, and not in any other group, and was further intensified in older patients (>/=50 years). The Classification and Regression Tree (CART) analysis in haploidentical patients revealed that the patients with older donors had the highest risk; older donor age (>/=50 years) was associated with significantly higher NRM only in the haploidentical (n=32; HR 2.5, 95% CI 1.5-4, p=0.001) but not in other groups (n=104). This adverse impact of donor age was further augmented in older patients, but more so in the haploidentical group than others. In cases where donor/recipient pairs where both were >/=50 years (n=119), NRM was 10% in other donors and 74% in the haploidentical; HR 9.4 (95% CI 3.9-22), p<0.001. On the other hand, when both donor and recipient were <50 years (n=233), NRM was 15% (95% CI 10-23) in the haploidentical versus 7% (95% CI 4-15) in other groups; HR 2.1 (95% CI 0.9-4.8), p=0.08. Accordingly, the 2-year OS in the young donor/recipient pairs was 64% (haploidentical) vs 72% (others); HR 1.3, 95% CI 0.8-2.1, p=0.3; while in the old donor/recipient pairs it was 13% (haploidentical) vs 70% (others); HR 5.7 (95% CI 2.8-11.4), p<0.001. [Transplant Cell Ther. 2022 Jul;28(7):395.e1-395.e11]
The adverse outcomes associated with older donors and/or patients have been reported in multiple studies [1-5], and may be related to an increased risk of clonal hematopoiesis in older donors [6-8], or due to epigenetic aging [9,10], but it remains unclear why the haploidentical group experienced the highest impact.
A recent CIBMTR study showed lower relapse and better survival with younger MUD than older MSD in patients with MDS [11]. As the outcomes of MMUD HCT, especially with BM graft, have improved drastically with the use of PTCy and are similar to that of haploidentical,[12] one may question whether a younger MMUD should be preferred over an older haploidentical donor. This question can only be addressed through registry studies such as the CIBMTR.

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

N/A

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

1. All patient age groups (adults and peds)
2. Any hematologic malignancy
3. Haploidentical or HLA-mismatched donor
4. PTCy-based GVHD prophylaxis
5. Include both RIC and MAC
6. Include both BM and PBPC graft
7. Exclude patients with ex-vivo T cell depletion
8. Must have donor age available

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.

Patient-related:
- Age at transplant
- Recipient gender
- Disease
- Disease status at HCT
- HCT-specific comorbidity index (HCT-CI)
- Revised disease risk index (DRI)
- Karnofsky performance score (KPS) HCT
- Recipient cytomegalovirus (CMV) status
- ABO typing

Donor/graft-related:
- Donor type (haplo or MMUD)
- Donor age
- Donor gender
- Donor relationship (if haplo)
- Donor cytomegalovirus (CMV) status
- Donor ABO typing
- Graft source (PB, BM)
- Total nucleated cell (TNC) dose
- CD34 dose
- CD3 dose

Transplant-related:
- Conditioning regimen intensity
- Conditioning regimen
- GVHD prophylaxis drugs used with PTCy
- Year of transplant

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

N/A

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

N/A

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.

N/A

Q26. REFERENCES:

1. Guru Murthy GS, Kim S, Hu ZH, Estrada-Merly N, Abid MB, Aljurf M, et al. Relapse and Disease-Free Survival in Patients With Myelodysplastic Syndrome Undergoing Allogeneic Hematopoietic Cell Transplantation Using Older Matched Sibling Donors vs Younger Matched Unrelated Donors. JAMA Oncol. 2022.
2. Shaw BE, Logan BR, Spellman SR, Marsh SGE, Robinson J, Pidala J, et al. Development of an Unrelated Donor Selection Score Predictive of Survival after HCT: Donor Age Matters Most. Biol Blood Marrow Transplant. 2018;24(5):1049-1056.
3. Kollman C, Spellman SR, Zhang MJ, Hassebroek A, Anasetti C, Antin JH, et al. The effect of donor characteristics on survival after unrelated donor transplantation for hematologic malignancy. Blood. 2016;127(2):260-267.
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10. Xhaard A, Cunha R, Busson M, Robin M, Dhedin N, Coman T, et al. Clinical profile, biological markers, and comorbidity index as predictors of transplant-related mortality after allo-HSCT. Blood Adv. 2017;1(18):1409-1413
11. Guru Murthy GS, Kim S, Hu ZH, Estrada-Merly N, Abid MB, Aljurf M, et al. Relapse and Disease-Free Survival in Patients With Myelodysplastic Syndrome Undergoing Allogeneic Hematopoietic Cell Transplantation Using Older Matched Sibling Donors vs Younger Matched Unrelated Donors. JAMA Oncol. 2022.
12. Shaw BE, Jimenez-Jimenez AM, Burns LJ, Logan BR, Khimani F, Shaffer BC, et al. National Marrow Donor Program-Sponsored Multicenter, Phase II Trial of HLA-Mismatched Unrelated Donor Bone Marrow Transplantation Using Post-Transplant Cyclophosphamide. J Clin Oncol. 2021;39(18):1971-1982

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

Table 1. Prop 2210-70 Haplo + MMUD patients received first HCT with PTCY, 2008-2020. By donor age.

Variable	Haplo **N (%)**	MMUD **N (%)**
Number of patients	4250	725
Number of centers	235	103
Disease at transplant		
AML	1833 (43)	321 (44)
ALL	755 (18)	110 (15)
Other leukemia	83 (2)	9 (1)
CML	125 (3)	35 (5)
MDS	711 (17)	127 (18)
Other acute leukemia	60 (1)	14 (2)
NHL	379 (9)	67 (9)
HD	152 (4)	17 (2)
MPN	152 (4)	25 (3)
Recipient age at transplant		
<10	129 (3)	2 (<1)
10-17	203 (5)	10 (1)
18-29	542 (13)	51 (7)
30-39	451 (11)	79 (11)
40-49	513 (12)	116 (16)
50-59	581 (14)	171 (24)
60-69	1286 (30)	236 (33)
>=70	545 (13)	60 (8)
Median (Range)	56 (1-88)	56 (2-79)
Recipient age at transplant		
<30	874 (21)	63 (9)
30-49	964 (23)	195 (27)
>=50	2412 (57)	467 (64)
Median (Range)	56 (1-88)	56 (2-79)
Recipient sex		
Male	2492 (59)	376 (52)
Female	1758 (41)	349 (48)
Graft type		
Bone marrow	1246 (29)	205 (28)
Peripheral blood	3004 (71)	520 (72)
Planned conditioning regimen		
MAC	1744 (41)	270 (37)
RIC/NMA	2369 (56)	439 (61)
TBD	137 (3)	16 (2)
Donor age at transplant		
18-35	0	725 (100)
36-49	2923 (69)	0

Variable	Haplo **N (%)**	MMUD **N (%)**
>=50	1327 (31)	0
Median (Range)	45 (35-80)	26 (18-35)
8/8 match degree		
1	1 (<1)	0
2	2 (<1)	0
3	14 (<1)	2 (<1)
4	2394 (75)	6 (1)
5	650 (20)	17 (2)
6	141 (4)	59 (8)
7	0	641 (88)
Unknown	1048 (N/A)	0 (N/A)
GvHD Prophylaxis		
Post-CY + other(s)	4229 (>99)	718 (99)
Post-CY alone	21 (<1)	7 (1)
In-vivo T-cell depletion		
No	4127 (97)	684 (94)
Yes	123 (3)	41 (6)
Donor/Recipient sex match		
M-M	1614 (38)	241 (33)
M-F	1004 (24)	179 (25)
F-M	878 (21)	135 (19)
F-F	754 (18)	169 (23)
Unknown	0 (N/A)	1 (N/A)
Year of transplant		
2008	26 (1)	0
2009	32 (1)	0
2010	12 (<1)	3 (<1)
2011	16 (<1)	6 (1)
2012	38 (1)	11 (2)
2013	101 (2)	9 (1)
2014	216 (5)	19 (3)
2015	370 (9)	35 (5)
2016	499 (12)	46 (6)
2017	648 (15)	99 (14)
2018	679 (16)	156 (22)
2019	762 (18)	167 (23)
2020	851 (20)	174 (24)

I. Study Title: Immunopeptidome divergence between mismatched HLA and outcome of haploidentical HCT

II. Key Words

Haploidentical HCT, post-transplant cyclophosphamide, immunopeptidome, peptide binding motifs

III. Principal Investigator Information

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Junior investigator status: yes
Current ongoing work with CIBMTR: PI in study IB20-01

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Junior investigator status: no
Current ongoing work with CIBMTR: co-PI in study IB20-01

IV. Proposed Working Committee

Immunobiology

V. Research Question

In study IB20-01, we showed that single mismatches in HLA class I involving alleles with different peptide-binding-motifs (PBM mismatches), in particular in the graft-versus-host (GvH) direction (uni-directional GvH or bi-directional), drive significant associations with inferior survival in 9/10 compared to 10/10 matched unrelated hematopoietic cell transplantation (HCT) [1]. We postulate that the PBM approach for defining non-permissive, poorly tolerated HLA mismatches might be extendable to HCT from haploidentical family donors (haplo-HCT) under graft-versus-host disease (GVHD) prophylaxis by post-transplant cyclophosphamide (PTCy), a setting in which the identification of high-risk HLA mismatch combinations is only at its beginnings.

VI. Research Hypothesis

We hypothesize that it might be possible to identify high risk, non-permissive HLA mismatches in haplo-HCT on the PTCy platform, by PBM classification of HLA-A, -B, -C, -DRB1 alleles on the unshared haplotype as a proxy for immunopeptidome divergence between patient and donor.

VII. Specific Objectives/Outcomes to be Investigated

The main objective of the present proposal is to understand whether the number and/or directionality of HLA-A, -B, -C, and -DRB1 PBM mismatches on the unshared haplotype can inform outcome after haplo-HCT under GVHD prophylaxis by PTCy. Primary endpoint will be Overall Survival (OS), secondary endpoints will include relapse-free survival (RFS), transplant-related mortality (TRM), acute and chronic GVHD, relapse and neutrophil/platelet recovery.

VIII. Scientific Impact

Haplo-HCT is increasingly being used to treat onco-hematologic patients lacking a fully HLA-matched sibling or unrelated donor, with 1,901 such transplants performed in the US in 2020 alone, exceeding for the first time the number of transplants from HLA-matched sibling donor [2]. Moreover, HCT from unrelated donors (UD) with multiple HLA mismatches has recently also entered clinical practice, with promising results [3]. These developments are particularly relevant for ethnic minorities, who receive HLA mismatched allogeneic transplants in up to almost 50% of cases [2]. The clinical success in overcoming the HLA barrier relates to the use of PTCy as GVHD prophylaxis, which dampens T-cell alloreactivity and hence the immunogenicity of HLA mismatches [4 5]. Concordantly, a recent study showed that non-permissive HLA-DPB1 T-cell epitope (TCE) mismatches, which are associated with adverse outcome after UD-HCT under calcineurin inhibitor (CNI)-based GvHD prophylaxis [6-8], reduced the risks of mortality in the PTCy-based haplo-HCT setting [9]. The same study identified HLA-B leader matches as well as directional GVH mismatches at HLA-DRB1 as positive prognostic factors for OS and/or RFS. Despite these encouraging results, the investigation of new models apt to identify high risk, non-permissive HLA mismatches in haplo-HCT is of great interest both scientifically and clinically. Recent findings by our group highlighted the relevance of HLA immunopeptidome divergence between mismatched HLA allotypes in patient and donor as a mechanistic driver of non-permissive mismatches at HLA-DPB1 [10] and, most recently within the IB20-01 study, at HLA-A, -B, -C [1]. The emerging picture is that the degree of overlap between the peptide repertoires (i.e. the immunopeptidomes) presented by mismatched HLA alleles, which in turn is decisively impacted by the respective peptide motifs, determines the number and diversity of reacting alloreactive T-cell clonotypes. As a clinical consequence, in CNI-based HCT, non-permissive mismatches associated with excessive alloreactivity and hence GHD-mediated toxicity, involves alleles across different HLA-DPB1 TCE groups [6-8], or across different HLA class I PBM groups [1]. The present study will elucidate if these mechanisms apply also to multiple HLA mismatches in PTCy-based haplo-HCT. The expected findings will have a direct impact both on our understanding of the mechanisms underlying clinically relevant T-cell alloreactivity, and on clinical patient care.

IX. Scientific Justification

122 HLA-A, -B, or –C allotypes occurring with a cumulative frequency of 89,3% in the European population, have been recently assigned by us to distinct PBM groups based on reported hierarchical clustering of HLA class I PBM [1,11]. This allowed us to classify 1,629/2,391 (68.1%) of 9/10 UD-HCT from the IB20-01 study as PBM-matched (when the mismatched HLA allele in patient and donor belongs to the same PBM group) or PBM-mismatched (when the mismatched HLA allele in patient and donor belongs to different PBM groups) (**Figure 1A**). In this cohort, transplanted under CNI-based GVHD prophylaxis, PBM-mismatches, in particular those in the GVH vector, were associated with worse survival compared to PBM-matches [1]. It is currently unclear if and how these associations are impacted by use of PTCy, and if there is an additive effect of PBM mismatches after transplants with multiple HLA disparities.

One caveat of the above-mentioned study was that not all HLA class I alleles occurring in the cohort were assigned to PBM groups based on the data in the literature [11], and that no PBM assignments were available for HLA-DRB1. To tackle this limitation, we retrieved immunopeptidomes for 102 informative (i.e. with at least 1,000 reported peptides) HLA-A, -B, and -C alleles from the Immune Epitope Database (IEDB) [12], including 80 alleles previously assigned to PBM groups, and 22 additional alleles. All 102 alleles were assigned to PBM groups based on hierarchical clustering of peptide motifs, validating most of the 80 previous PBM assignments, and adding assignment to one of the 20 previous PBM groups for the 22 additional alleles. Using the same approach, we also assigned 4 new PBM groups to 15 HLA-DRB1 alleles. As expected, the percentage of immunopeptidome overlap was significantly higher for alleles from the same PBM group than for alleles from different PBM groups (**Figure 1B**).

In total, our updated PBM classification covers 159 HLA-A,-B,-C,-DRB1 alleles (122 alleles from the previous classification [1] and 37 previously unassigned alleles). These occur with a cumulative frequency of at least 87,7% for HLA class I and 75,6% for HLA-DRB1 in Europeans, and at least 77,3% for HLA class I and 65,9% for HLA-DRB1 in other ethnic groups [13]. Based on this, we will determine the number and direction of PBM matches or mismatches at HLA-A, -B, -C, and -DRB1 in haploidentical pairs (**Figure 1A**). Matched alleles on the unshared haplotypes of patient and donor will be classified as PBM matches. HLA loci involving alleles with unknown PBM assignment will not be considered, and the number of informative loci for each patient will be included as co-variate in the multivariate analysis. We will then stratify the pairs according to the number of PBM mismatches (0-4) at HLA-A, -B, -C, -DRB1, considering also directionality. 8/8 matched unrelated donors (MUD) transplanted under PTCy GvHD-prophylaxis will be used as reference for the statistical analysis.

X. Participant Selection Criteria

The patients available for inclusion into this study according to the criteria outlined below, are summarized in **Table 1**.

Inclusion Criteria:

- Patients treated for ALL, AML, or MDS
- Adult and pediatric patients
- First allogeneic transplant
- Bone marrow or peripheral blood as stem cell source
- Haploidentical family donor or 8/8 matched unrelated donor (MUD; reference)
- GvHD prophylaxis by PTCy for both haplo-HCT and MUD
- 2nd field HLA-A,-B,-C-,DRB1 typing available
- Transplants performed 2010-2020
- RIC or MAC conditioning

Exclusion Criteria:

- *Ex-vivo* T-cell depletion (e.g. CD34 selection, CD3 selection)

XI. Data Requirements

Main effect:

- PBM matching status of unshared HLA-A, -B, -C, -DRB1 alleles in patient and donor

Patient-related:

- Age at transplant
- Sex
- Karnofsky score: <90 vs. 90-100%

Disease-related:

- Diagnosis (AML vs. MDS vs. ALL)
- Disease status at transplant (early vs. intermediate vs. advanced)
- Disease risk index or cytogenetic risk

Transplant-related:

- Donor age
- Donor parity
- Ethnicity match (matched vs. mismatched)
- ABO match (matched, major, minor and bi-directional)
- Year of transplant
- Conditioning regimen intensity (myeloablative or NMA/RIC)
- Use of TBI
- Donor-recipient sex match (M/M vs. M/F vs. F/M vs. F/F)
- Source of stem cells (bone marrow vs. peripheral blood)
- HCT-CI
- CMV match status (+/+ vs. +/- vs. -/+ vs. -/-)
- Relationship of patients and haploidentical family donors
- HLA-DPB1 matching status by TCE
- HLA-DQB1 matching status
- Number of HLA-A,-B,-C,-DRB1 mismatches without PBM assignment

XII. Patient-Reported Outcome (PRO) Requirements

Not required.

XIII. Sample Requirements (if the study will use biologic samples from the CIBMTR Repository)

Not applicable.

XIV. Non-CIBMTR Data Source, *if applicable*

Not applicable.

XV. References

1. Crivello P, Arrieta-Bolanos E, He, M, et al. Impact of High Immunopeptidome Divergence between Single Class I HLA-Mismatches on Survival after Unrelated Donor Transplantation. *J Clin Oncol.* 2022 in press.
2. Auletta JJK, J.; Chen, M.; Shaw, B.E. . Current use and outcome of hematopoietic stem cell transplantation: CIBMTR US summary slides, 2021.
3. Shaw BE, Jimenez-Jimenez AM, Burns LJ, et al. National Marrow Donor Program-Sponsored Multicenter, Phase II Trial of HLA-Mismatched Unrelated Donor Bone Marrow Transplantation Using Post-Transplant Cyclophosphamide. *J Clin Oncol*. 2021;39(18):1971-1982.
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10. Meurer T, Crivello P, Metzing M, et al. Permissive HLA-DPB1 mismatches in HCT depend on immunopeptidome divergence and editing by HLA-DM. *Blood*. 2021;137(7):923-928.
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13. Hurley CK, Kempenich J, Wadsworth K, et al. Common, intermediate and well-documented HLA alleles in world populations: CIWD version 3.0.0. *HLA*. 2020;95(6):516-531.

XVI. Conflicts of Interest

Nothing to declare.

A)

PBM group			Immunopeptidome	PBM Status	Direction
Shared	Donor	Patient			
PBM-x	PBM-x	PBM-x	Low divergence	Match	None
PBM-x	PBM-y	PBM-y			
PBM-x	PBM-z	PBM-z			
PBM-x	PBM-y	PBM-z	High divergence	Mismatch	Bi-directional
PBM-x	PBM-x	PBM-y			Uni-directional GvH
PBM-x	PBM-y	PBM-x			Uni-directional HvG

B)

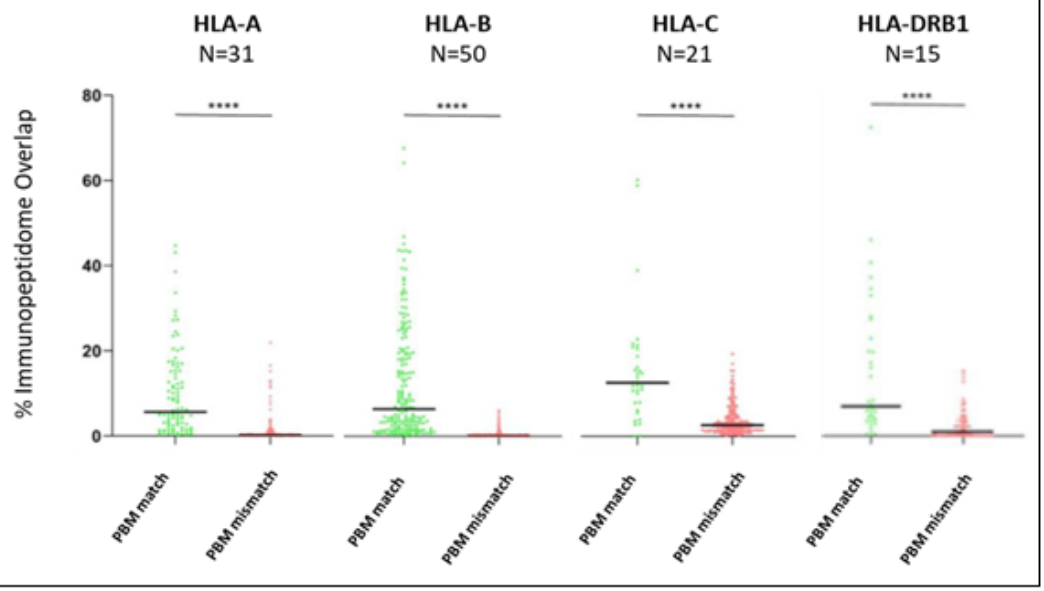

Figure 1. PBM assignment of HLA alleles and PBM matching of haploidentical donor-recipient pairs. A) PBM assignment of HLA mismatches on the unshared haplotype for haploidentical pairs, which by definition share one of the two HLA alleles at each locus. Shown is the assignment strategy for each individual HLA locus, as described in the IB20-01 study for 9/10 UD-HCT [1]. Matched HLA alleles on the unshared haplotype will be classified as PBM matched. HLA loci involving alleles with unknown PBM assignment will not be considered. B) Immunopeptidome overlaps between HLA alleles from the same or different PBM groups. Included are 117 HLA alleles with informative immunopeptide data in the IEDB [12]. The indicated number of HLA-A,-B,-C,-DRB1 alleles were divided into 7, 8, 5 and 4 different PBM groups based on hierarchical clustering of peptide motifs. The percentages of immunopeptidome overlap between alleles in the same PBM cluster („PBM match“) or in different PBM clusters („PBM mismatch“) were compared, the horizontal lines indicate the median. Statistical differences were determined by the Mann-Whitney-U test (**** P<0.0001).

Table 1. Prop 2210-201 Haplo + MUD patients with AML, ALL, MDS, received first allo HCT with PTCY, 2010-2020

Variable	Haplo N (%)	MUD N (%)
Number of patients	4748	2033
Number of centers	219	127
Disease at transplant		
AML	2570 (54)	1137 (56)
ALL	1146 (24)	313 (15)
MDS	1032 (22)	583 (29)
AML Disease status at transplant		
CR1	1702 (66)	819 (72)
CR2	414 (16)	148 (13)
CR3+	33 (1)	11 (1)
Advanced or active disease	408 (16)	153 (13)
Missing	13 (1)	6 (1)
ALL Disease status at transplant		
CR1	695 (61)	223 (71)
CR2	326 (28)	65 (21)
CR3+	57 (5)	13 (4)
Advanced or active disease	67 (6)	12 (4)
Missing	1 (<1)	0
MDS Disease status at transplant		
Early	146 (14)	98 (17)
Advanced	830 (80)	461 (79)
Missing	56 (5)	24 (4)
Recipient race group		
White	3203 (75)	1766 (95)
Black or African American	670 (16)	42 (2)
Asian	289 (7)	43 (2)
Native Hawaiian or other Pacific Islander	29 (1)	1 (<1)
American Indian or Alaska Native	22 (1)	5 (<1)
More than one race	47 (1)	7 (<1)
Unknown	488 (N/A)	169 (N/A)
Recipient ethnicity		
Hispanic or Latino	788 (17)	93 (5)
Non-Hispanic or non-Latino	3339 (73)	1708 (88)
Non-resident of the U.S.	457 (10)	139 (7)
Unknown	164 (N/A)	93 (N/A)
Recipient age at transplant		
<10	211 (4)	10 (<1)
10-17	209 (4)	19 (1)
18-29	574 (12)	144 (7)
30-39	409 (9)	178 (9)
40-49	595 (13)	238 (12)
50-59	953 (20)	386 (19)
60-69	1345 (28)	785 (39)

Variable	Haplo N (%)	MUD N (%)
70+	452 (10)	273 (13)
Median (Range)	55 (1-88)	61 (1-82)
Recipient sex		
Male	2824 (59)	1203 (59)
Female	1924 (41)	830 (41)
Graft type		
Bone marrow	1397 (29)	341 (17)
Peripheral blood	3351 (71)	1692 (83)
Donor age at transplant		
<18	229 (5)	0
18-29	1351 (28)	1276 (63)
30-39	1430 (30)	503 (25)
40-49	1020 (21)	180 (9)
50+	716 (15)	64 (3)
Missing	2 (N/A)	10 (N/A)
Median (Range)	36 (0-76)	28 (18-61)
8/8 match degree		
1	1 (<1)	0
2	2 (<1)	0
3	23 (<1)	0
4	3571 (75)	0
5	948 (20)	0
6	203 (4)	0
8	0	2033 (100)
GvHD Prophylaxis		
Post-CY + other(s)	4734 (>99)	1917 (94)
Post-CY alone	14 (<1)	116 (6)
Year of transplant		
2010	14 (<1)	28 (1)
2011	18 (<1)	28 (1)
2012	24 (1)	38 (2)
2013	85 (2)	40 (2)
2014	213 (4)	52 (3)
2015	397 (8)	77 (4)
2016	528 (11)	126 (6)
2017	684 (14)	183 (9)
2018	873 (18)	364 (18)
2019	947 (20)	496 (24)
2020	965 (20)	601 (30)

CIBMTR Study Combined Proposal (2209-12 and 2210-027)

STUDY TITLE:

Effect of donor KIR, recipient KIR ligand, and NKG2A/HLA-E interaction regulated by recipient's B-leader allotype on transplant outcomes following PTCy-based Haplo-HSCT

KEYWORDS:

Haploidentical HSCT; PTCy; Natural killer cell; Killer cell immunoglobulin-like receptors (KIRs), Alloreactivity; HLA-B leader

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RESEARCH QUESTION:

Assess the impact of count functional inhibitory killer cell immunoglobulin-like receptors (CF iKIR) score, recipient's HLA-C-group KIR ligand, and the interaction of NKG2A/HLA-E regulated by recipient's methionine/threonine (M/T) containing HLA-B-leader allotypes on clinical outcomes in patients who underwent haplo-HSCT with PTCy.

HYPOTHESIS:

We hypothesize that following PTCY-based haplo-HSCT: 1) NK cell alloreactivity assessed by CF iKIR is associated with the clinical outcomes of haplo-HSCT, and a predictive algorithm incorporating NK cell alloreactivity and donor characteristics can therefore assist haplo-HSCT donor selection; 2) Patients expressing both HLA-C group 1 and 2 ligands (C1C2) will have an increased cumulative incidence of relapse/progression (CIR) and inferior disease-free survival (DFS), and that this effect will be restricted to patients with myeloid malignancies (AML/MDS/CML), and 3) patients without a methionine (M)-containing HLA-B-leader allotypes (i.e. TT vs. MM/MT) will have an increased cumulative incidence of relapse/progression (CIR) and inferior disease-free survival (DFS), and that this effect will be restricted to patients with lymphoid malignancies (ALL, NHL, HL, CLL).

SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED:

Primary objectives:

To investigate the impact of NK alloreactivity predicted by CF iKIR, recipient HLA-C-group KIR ligand and NKG2A/HLA-E interaction regulated by recipient HLA-B-leader allotype on disease-free survival (DFS) of patients who received an allogeneic transplant from a haploidentical donor with PTCy.

Secondary objectives:

To study and validate the association of all available models of NK cell alloreactivity reported to date on outcomes in haplo-HSCT on the following clinical endpoints.

1. Overall survival (OS)
2. Cumulative incidence of grades II-IV and III-IV acute GVHD at Day 100 and overall
3. Cumulative incidence of relapse
4. Cumulative incidence of non-relapse mortality (NRM)

SCIENTIFIC IMPACT:

With an ever-increasing number of haploidentical transplants performed, selecting the best donor for transplantation becomes increasingly important. Unlike other forms of stem cell transplantation, the immune disparity exists in both HLA and KIR systems between donor and recipient in the setting of haplo-HSCT, which may provoke the corresponding innate and adaptive alloreactivities. While several donor/recipient characteristics have been studied and shown to influence the clinical outcomes in haplo-HSCT, the role of killer cell immunoglobulin-like receptors (KIRs) in alloreactivity remains inconclusive, highlighting the limits of the current understanding of NK cell-mediated alloresponse. Additionally, there remains an unmet need to improve the current modeling systems in the context of haplo-HSCT with PTCy, given all models were developed on different HSCT platforms. Therefore, a comprehensive registry study comparing the effect of different KIR alloreactive models on outcomes after haplo-HSCT with PTCy is necessary and the results could aid in donor selection and risk stratification.

SCIENTIFIC JUSTIFICATION:

The role of KIRs in stem cell transplantation is often debated, with conflicting results using different predictive algorithms. Previous studies in class-I HLA-mismatched HSCT demonstrated that alloreactivity from NK cells contributed to the GVL effect, suggesting a missing-self mechanism in which the alloreactivity is elicited when

the inhibitory KIRs on donor cells can no longer bind to their cognate ligands on the recipient cells [1,2]. Several models were successively created with improved sequencing technology and an understanding of the KIR expression and their corresponding ligands. The superior relapse protection was shown to be associated with the presence of activating KIR2DS1/HLA-C1C2 and/or reduced interaction between inhibitory KIR3DL1 and its HLA-Bw4 ligands [3,4], while several large studies including registry-based studies failed to validate the predictive value of these models [5,6]. Rather than focusing on the presence or absence of a particular receptor-ligand combination, Boelen et al developed a KIR scoring system that quantitively measures the functional engagement of inhibitory receptors, and demonstrated that an increased CF-iKIR score is significantly associated with enhanced $CD8^+$ T cell survival and response against viral infections [7]. Interestingly, CF-iKIR was also found to be correlated with improved event-free survival in HSCT from an unrelated donor [6].

Following haplo-HSCT, effective NK cell education and function require donor NK cell receptors to recognize HLA class I on the surface of host cells, via two structurally unrelated but complementary mechanisms: 1) iKIRs (e.g. 2DL1, 2DL2/3, 3DL1) recognize downregulation or absence of their ligands (C2, C1, Bw4, respectively), a process known as missing self, and 2) the CD94:NKG2A (inhibitory) and CD94:NKG2C (activating) receptors which recognize HLA-E, a non-classical HLA molecule. For proper surface expression, HLA-E binds peptides cleaved from the leader sequences (from −22 to −14 residues) of HLA-A, -B, or -C. Therefore, it has been generally considered as a sensor of the overall amount of HLA class I molecules expressed on the cell surface. More recently, the methionine/threonine (M/T) dimorphism at position −21 of the HLA-B-leader sequence (i.e., −21M and −21T) has been described to strongly impact the CD94:NKG2A/HLA-E interaction. Accordingly, individuals with M+ HLA-B-leader (either MM or MT allotype) show higher HLA-E expression and more efficient NKG2A+ NK cells [8].

Using a relatively homogenous group of patients treated with the same conditioning regimen and PTCy-based GVHD prophylaxis (n=354, with <1% missing data), the MD Anderson group recently investigated the impact of KIR alloreactivity by all major models described to date, along with all other donor variables known to impact survival post-transplant, and demonstrated for the first time that a higher CF-iKIR score was significantly associated with improved progression-free survival and overall survival (OS) in haploidentical transplants (Figure 1) [9]. Additionally, using exploratory classification and regression tree analysis (CART) of clinical predictors, It was found that a higher CF-iKIR score was associated with significantly improved OS (Figure 2).

At the Northside Hospital Cancer Institute, Solomon and his colleagues studied the relative effects of iKIR missing ligand (ML) and recipient HLA-B-leader allotype on relapse/progression and transplant outcome following HIDT-PTCy, in 315 patients with myeloid (AML/MDS/CML, n=177) and lymphoid (ALL/NHL/HL/CLL, n=138) malignancies [10]. In univariate analysis, both recipient HLA-B-leader allotype (M+ vs. M-) and HLA-C-group iKIR ML (C1C1 or C2C2 vs. C1C2) were associated with lower CIR and superior DFS following Haplo-HSCT with PTCy. However, the relative impact of each was dependent on the disease type (Figure 3 and 4). HLA-C-group iKIR ML improved relapse risk and DFS only in myeloid malignancies (25% vs. 45%, p=0.001 and 64% vs. 44%, p=0.001, respectively), whereas M+ recipient HLA-B-leader improved relapse risk and DFS only in lymphoid malignancies (16% vs. 42%, p=0.001 and 72% vs. 41%, p=0.001, respectively). In multivariate analysis, controlling for patient age/sex/race, DRI, donor age, and year of transplantation, both M+ HLA-B-leader (lymphoid) and HLA-C-group iKIR ML (myeloid) were independently associated with lower relapse/progression (HR 0.24, p<0.001 and HR 0.45, p=0.004) and improved DFS (HR 0.36, p<0.001 and HR 0.53, p=0.006).

In the setting of T cell replete (TCR) haplo-HSCT, the beneficial role of NK alloreactivity remains unclear with conflicting results [11-13]. PTCy administration that could significantly eliminate the alloreactive NK cells, adds

another layer of complexity [13-15]. Moreover, NK cells derived from stem cells are exposed and educated by HLA ligands on the host stromal cells during reconstitution, the competence of donor NK cells in allorecognizing and alloreactivity is, therefore, undecided [16]. The findings from these single institution studies represent definitive data that took into account all important transplant variables and suggest that NK alloreactivity appreciated by CF-iKIR and the presence of recipient's M+ HLA-B-leader may have a significant impact on the survival of patients receiving a haploidentical transplant, and if validated by the registry-based study, it will impact how donors are selected for haploidentical transplants.

Methodology

KIR haplotype assignment and KIR ligand– and KIR motif-based classification models

The models that will be included are: 1) Missing ligand (ML) model, the NK cell alloreactivity was predicted based on high-resolution HLA typing of the donor and recipient, as described previously [17]. Briefly, KIR ligand HLA-C and HLA-B molecules were grouped into three major categories (C1, C2, Bw4) based on the specific amino acid sequence that defines specific KIR ligand binding https://www.ebi.ac.uk/ipd/kir/ligand.html. NK cell alloreactivity in the graft-versus-host direction was assigned when the recipient lacked at least one of the HLA ligands that were present in the donor. 2) KIR2DS1/C1C2 epitope combination model, binding between the KIR2DS1 and C1C2 ligands was classified as described by Venstrom et al [4]. 3) donor centromeric motif and telomeric motif models, donor A or B haplotypes were assigned according to the definition described by Cooley et al, based on the presence or absence of KIR-B–specific genes [18,19]. 4)KIR B-content score model, donors were classified into three groups (neutral, better, best) using the B-content score and the presence of the Cen-B/B motif, as described previously [19]. 5) Inhibitory KIR score and CF-iKIR score models, as described by Schetelig et al [6] and Boelen et al [7], the inhibitory score was calculated based on the donor's KIR genotype and the recipient's HLA ligands, and KIR was considered functional only when the cognate ligands were exhibited by the recipient's HLA molecules. the CF-iKIR score was calculated based on the donor's KIR genotype and the recipient's HLA ligands: CF-iKIR score = 1 if functional KIR2DL1 + 1 if functional KIR2DL2 and/or functional KIR2DL3 + 1 if functional 3DL1[7]. 6) Recipient's M+ B leader status is inferred from the known HLA typing https://www.ebi.ac.uk/ipd/imgt/hla/matching/b_leader/.

HLA ligand models (recipient/donor HLA typing is needed)	**KIR haplotype motif-based models and additive models (recipient/donor HLA typing and donor KIR typing are required)**
Miss ligand (ML) model	KIR2DS1/C1C2 epitope combination model
Presence of recipient's M+ B leader allotype (regulating NKG2A/HLA-E interaction on NK cells)	Donor centromeric motif and telomeric motif models
	KIR B-content score model
	Inhibitory KIR score model
	CF-iKIR score model

PARTICIPANT SELECTION CRITERIA:

All adult patients (> 18 y.o.) with hematological malignancies (Myeloid including AML, MDS, CML; and Lymphoid including ALL, NHL, HL, and CLL), who underwent a first HSCT from a haploidentical donor from January 2015 to

December 2021 and reported to CIBMTR will be included in the study, both donor /patient HLA and donor KIR genotyping results are available or if the KIR typing has not been performed, donor DNA samples are available for KIR testing. The patients who did not receive PTCy as GVHD prophylaxis, or receive Ex vivo T cell manipulation or in vivo T cell depletion with ATG or alemtuzumab will be excluded from the study.

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/DataCollectionForms/. Outline any supplementary data required. Additional data collection is extremely difficult and will make you proposal less feasible.

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: <3 and ≥3

Race (white vs. black vs. other)

Disease-related:

- Diagnosis: Myeloid including AML, MDS, CML; and Lymphoid including ALL, NHL, HL, and CLL
- 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 HLA typing at high resolution
- Year of transplant: 2015-2021
- Condition regimen intensity: myeloablative vs. RIC/non-myeloablative
- Donor cytomegalovirus serostatus match: P/P, P/N, N/P, N/N (or N/N vs other)
- Donor-recipient gender match: M/M, M/F, F/M, F/F (or F to M vs other)
- Donor age- continuous
- Source of stem cells: (BM vs PBSC)

SAMPLE REQUIREMENTS: If the study requires biological 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.

Many patients/donors have been genotyped for HLA and KIR accredited to the recent NMDP or CIBMTR research activities. For the patients eligible for the study but lacking the KIR typing, we will need a DNA specimen (or whole blood for DNA extraction) to conduct KIR genotyping. KIR genotyping will be performed by KIR sequence-specific oligonucleotide probes and interpreted by Fusion software (Thermo Fisher Scientific Life Science,

Waltham, MA; and One Lambda, Canoga Park, CA). In short, we will need roughly 2 µl of DNA at 40 ng/µl for each recipient and donor. The PCR amplification and interpretation are straightforward.

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Table 1. Prop 2209-12 and 27. Adult haplo patients received first HCT with PTCY, AML, ALL, CLL, CML, MDS, NHL, and HD, 2015-2021, Donor sample available.

Variable	N (%)
Number of patients	1449
Number of centers	55
Disease at transplant	
AML	655 (45)
ALL	273 (19)
CLL	17 (1)
CML	58 (4)
MDS	260 (18)
NHL	142 (10)
HD	44 (3)
AML Disease status at transplant	
CR1	425 (65)
CR2	90 (14)
CR3+	11 (2)
Advanced or active disease	124 (19)
Missing	5 (1)
ALL Disease status at transplant	
CR1	175 (64)
CR2	66 (24)
CR3+	15 (5)
Advanced or active disease	17 (6)
MDS Disease status at transplant	
Early	43 (17)
Advanced	212 (82)
Missing	5 (2)
CML Disease status at transplant	
Chronic phase	46 (79)
Accelerated phase	5 (9)
Blast phase	1 (2)
Missing	6 (10)
CLL Disease status at transplant	
CR	4 (24)
PR	8 (47)
Advanced (PIF/Relapse)	4 (24)
Missing	1 (6)
NHL Disease status at transplant	
CR1	28 (20)
CR2	38 (27)
CR3+	11 (8)
PR	1 (1)
Advanced	63 (44)
Missing	1 (1)

HD Disease status at transplant	
CR1	8 (18)
CR2	4 (9)
CR3+	12 (27)
Advanced	20 (45)
Recipient age at transplant	
18-29	204 (14)
30-39	163 (11)
40-49	207 (14)
50-59	307 (21)
60-69	437 (30)
>=70	131 (9)
Median (Range)	56 (18-82)
Recipient sex	
Male	879 (61)
Female	570 (39)
Graft type	
Marrow	403 (28)
PBSC	1046 (72)
8/8 high resolution matched status	
1	1 (<1)
2	3 (<1)
3	6 (<1)
4	1098 (76)
5	291 (20)
6	50 (3)
GvHD Prophylaxis	
Post-CY + other(s)	1441 (99)
Post-CY alone	8 (1)
Sample available	
Samples Available for Recipient and Donor	1356 (94)
Samples Available for Donor Only	93 (6)
Related donor DNA sample available	
No	31 (2)
Yes	1418 (98)
Related donor whole blood sample available	
No	2 (<1)
Yes	1447 (>99)
Year of transplant	
2015	140 (10)
2016	190 (13)
2017	200 (14)
2018	226 (16)
2019	253 (17)
2020	207 (14)
2021	233 (16)

Figure 1

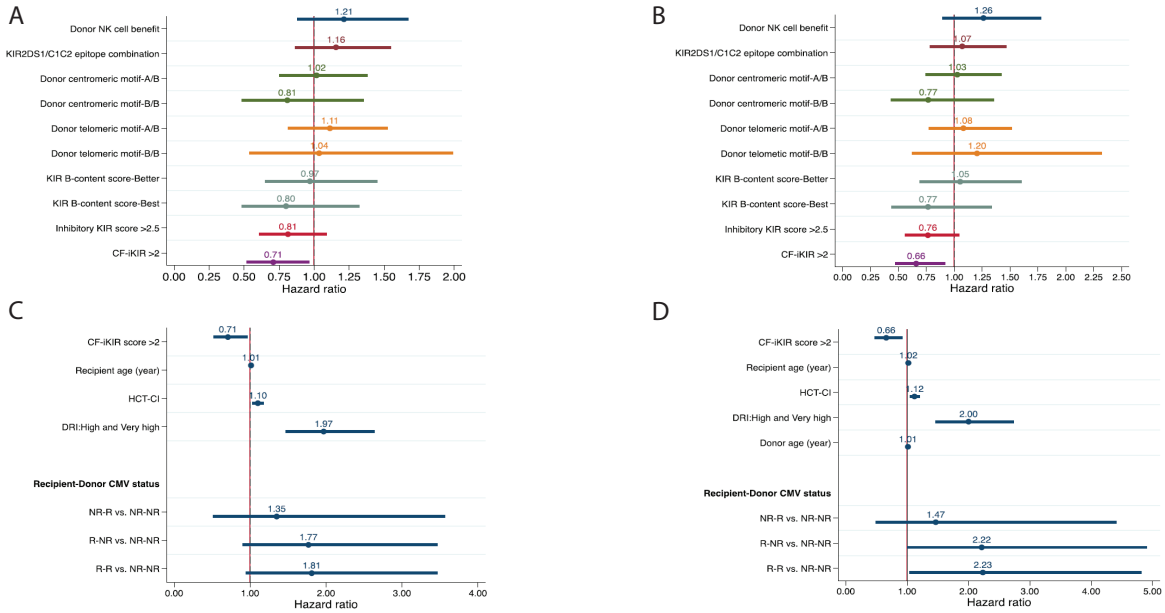
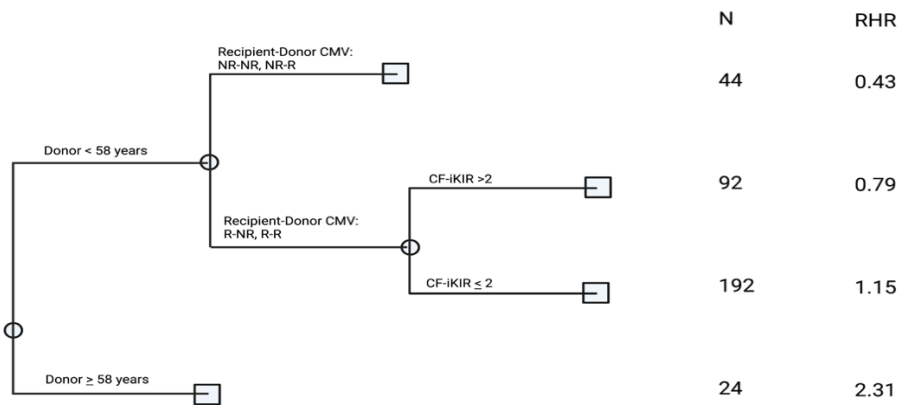


Figure 1. Effects of NK cell alloreactivity according to various models and patient and transplant-related factors on survival outcomes of patients who underwent haploidentical hematopoietic stem cell transplant (n = 354). Forest plots show effects of NK cell alloreactivity on progression-free survival (A) and overall survival (B) and effects of patient- and transplant-related factors on progression-free survival (C) and overall survival (D).

Figure 2



	Donor age	Recipient-Donor CMV status	CF-iKIR score	N	3-yr OS	HR (adjusted)	95%CI	P value
Group 1: Best	<58	NR-NR or NR-R	Any	44	73.9	Ref		
Group 2: Better	<58	R-NR or R-R	>2	92	54.1	1.84	1.12-3.69	0.044
Group 3: Poor	<58	R-NR or R-R	≤2	192	44.5	2.70	1.41-5.19	0.003
Group 4: Worst	≥58	Any	Any	24	18.5	5.44	2.54-11.64	<0.001

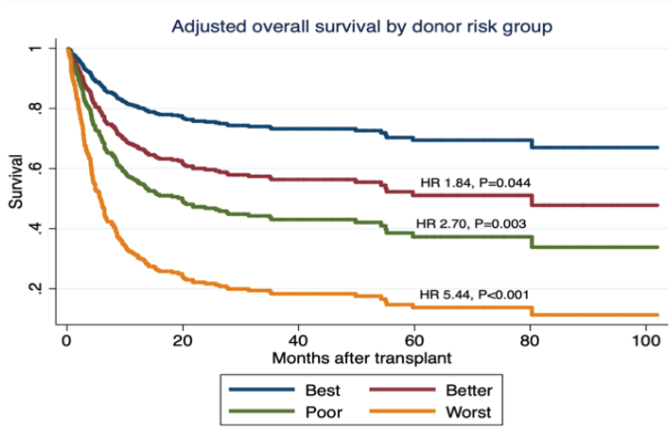


Figure 2. Algorithm for donor selection based on donor characteristics and natural killer cell alloreactivity predicted by CF-iKIR score.

Figure 1 and 2 are adopted from Zou et al... Frontiers in Immunology, 2022

Figure 3. Disease-specific impact of recipient HLA-B-leader genotype and HLA-C-group iKIR missing ligand on relapse incidence after PTCy-based haplo-HSCT

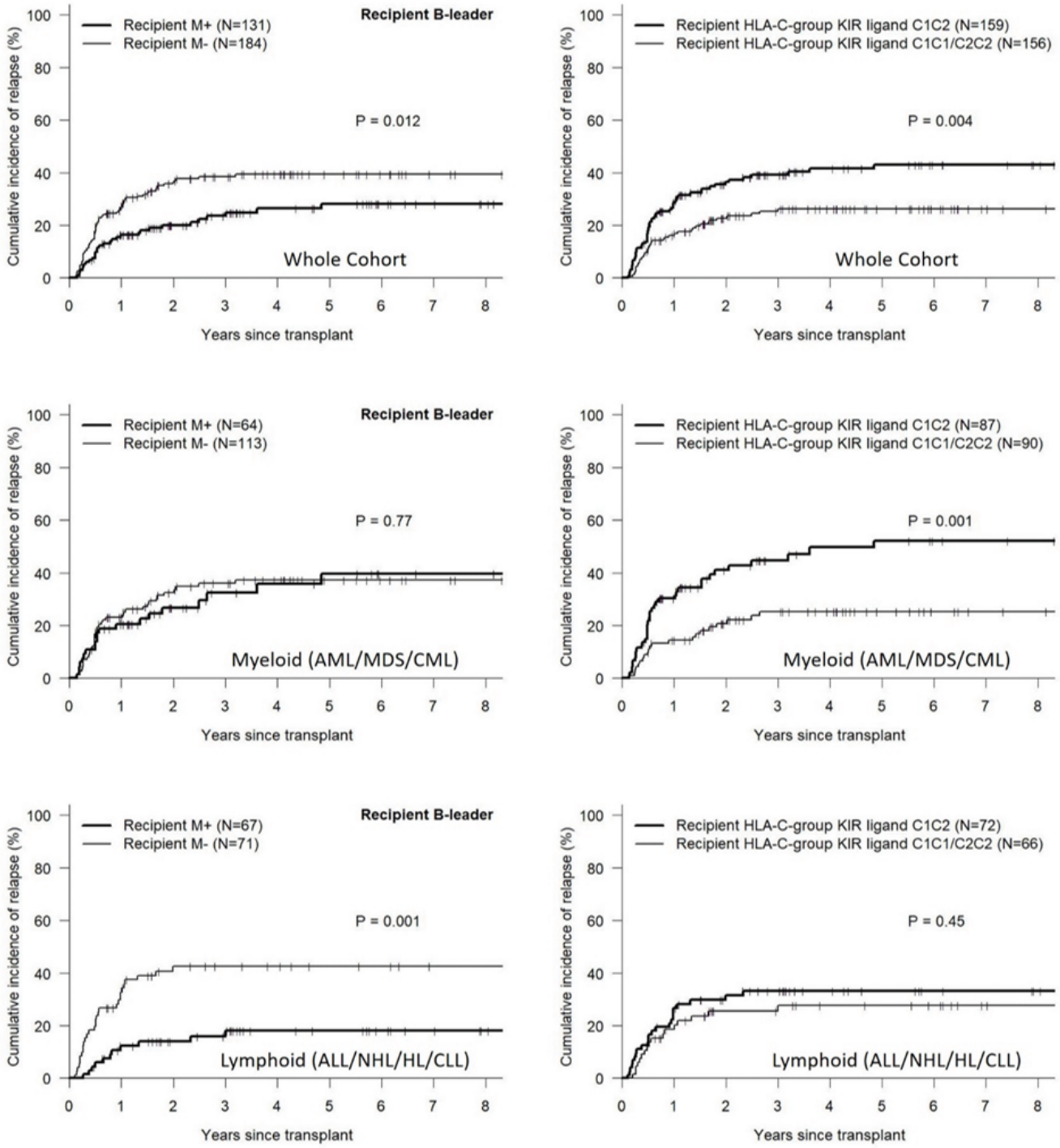
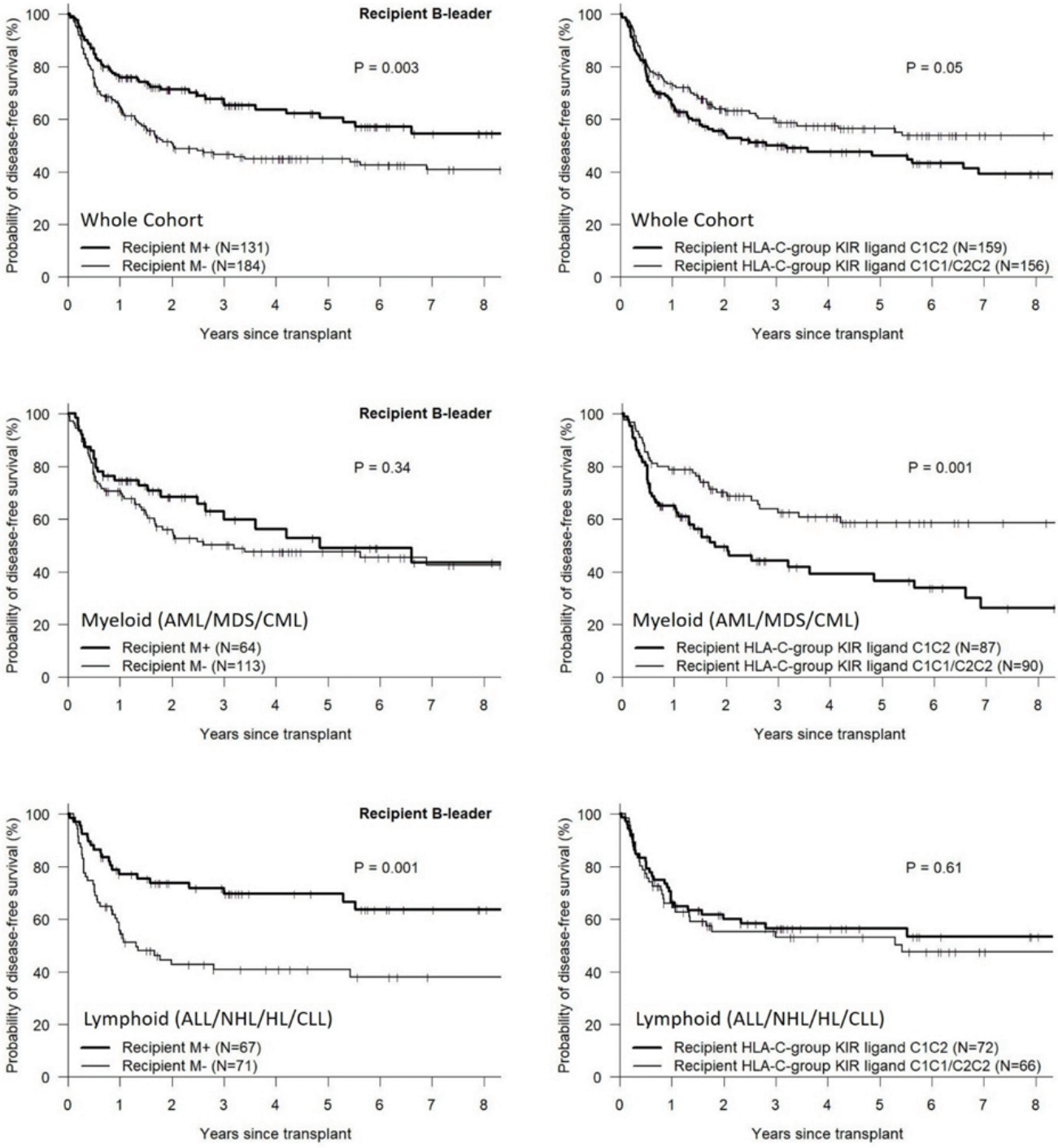


Figure 4. Disease-specific impact of recipient HLA-B-leader genotype and HLA-C-group iKIR missing ligand on disease-free survival after PTCy-based haplo-HSCT



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	47323	19111	12053
Source of data			
CRF	24443 (52)	7079 (37)	5666 (47)
TED	22880 (48)	12032 (63)	6387 (53)
Number of centers	264	241	378
Disease at transplant			
AML	16388 (35)	7160 (37)	3977 (33)
ALL	6871 (15)	2478 (13)	1928 (16)
Other leukemia	1469 (3)	423 (2)	310 (3)
CML	3528 (7)	1111 (6)	1028 (9)
MDS	6936 (15)	3307 (17)	1526 (13)
Other acute leukemia	501 (1)	230 (1)	142 (1)
NHL	4211 (9)	1361 (7)	904 (8)
Hodgkin Lymphoma	947 (2)	258 (1)	212 (2)
Plasma Cell Disorders, MM	940 (2)	292 (2)	206 (2)
Other malignancies	58 (<1)	14 (<1)	22 (<1)
Breast cancer	7 (<1)	3 (<1)	1 (<1)
SAA	1519 (3)	594 (3)	510 (4)
Inherited abnormalities erythrocyte diff fxn	728 (2)	255 (1)	231 (2)
Inherited bone marrow failure syndromes	26 (<1)	32 (<1)	20 (<1)
Hemoglobinopathies	22 (<1)	22 (<1)	15 (<1)
Paroxysmal nocturnal hemoglobinuria	4 (<1)	7 (<1)	2 (<1)
SCIDs	827 (2)	328 (2)	370 (3)
Inherited abnormalities of platelets	40 (<1)	16 (<1)	12 (<1)
Inherited disorders of metabolism	301 (1)	89 (<1)	143 (1)
Histiocytic disorders	387 (1)	125 (1)	129 (1)
Autoimmune disorders	27 (<1)	14 (<1)	11 (<1)
Other	53 (<1)	18 (<1)	25 (<1)
MPN	1507 (3)	947 (5)	297 (2)
Disease missing	26 (<1)	27 (<1)	32 (<1)
AML Disease status at transplant			
CR1	8855 (54)	4408 (62)	1974 (50)
CR2	3149 (19)	1237 (17)	782 (20)
CR3+	337 (2)	108 (2)	92 (2)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Advanced or active disease	3862 (24)	1364 (19)	984 (25)
Missing	185 (1)	43 (1)	145 (4)
ALL Disease status at transplant			
CR1	3403 (50)	1426 (58)	814 (42)
CR2	1956 (28)	631 (25)	557 (29)
CR3+	570 (8)	167 (7)	180 (9)
Advanced or active disease	860 (13)	230 (9)	257 (13)
Missing	82 (1)	24 (1)	120 (6)
MDS Disease status at transplant			
Early	1480 (21)	609 (18)	351 (23)
Advanced	4487 (65)	2464 (75)	836 (55)
Missing	969 (14)	234 (7)	339 (22)
NHL Disease status at transplant			
CR1	598 (14)	262 (19)	125 (14)
CR2	781 (19)	259 (19)	145 (16)
CR3+	365 (9)	114 (8)	80 (9)
PR	448 (11)	112 (8)	95 (11)
Advanced	1928 (46)	588 (43)	424 (47)
Missing	71 (2)	18 (1)	32 (4)
Recipient age at transplant			
0-9 years	3974 (8)	1246 (7)	1582 (13)
10-17 years	3152 (7)	969 (5)	1122 (9)
18-29 years	5720 (12)	1928 (10)	1607 (13)
30-39 years	5327 (11)	1851 (10)	1428 (12)
40-49 years	7110 (15)	2503 (13)	1748 (15)
50-59 years	9750 (21)	3711 (19)	2071 (17)
60-69 years	10023 (21)	5257 (28)	2052 (17)
70+ years	2267 (5)	1646 (9)	443 (4)
Median (Range)	48 (0-84)	53 (0-82)	42 (0-84)
Recipient race/ethnicity			
White	39105 (83)	15871 (83)	8419 (70)
Black or African American	2150 (5)	753 (4)	555 (5)
Asian	1167 (2)	602 (3)	520 (4)
Native Hawaiian or other Pacific Islander	59 (<1)	31 (<1)	32 (<1)
American Indian or Alaska Native	172 (<1)	73 (<1)	49 (<1)
Hispanic	2873 (6)	1076 (6)	718 (6)
Missing	1797 (4)	705 (4)	1760 (15)
Recipient sex			
Male	27519 (58)	11189 (59)	7161 (59)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Female	19804 (42)	7922 (41)	4892 (41)
Karnofsky score			
10-80	16419 (35)	7366 (39)	3802 (32)
90-100	29141 (62)	11142 (58)	7620 (63)
Missing	1763 (4)	603 (3)	631 (5)
HLA-A B DRB1 groups - low resolution			
<=3/6	31 (<1)	54 (<1)	5 (<1)
4/6	246 (1)	98 (1)	58 (1)
5/6	6320 (14)	1956 (12)	1680 (15)
6/6	39021 (86)	13671 (87)	9199 (84)
Unknown	1705 (N/A)	3332 (N/A)	1111 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	907 (2)	104 (1)	82 (1)
6/8	1783 (4)	159 (1)	224 (3)
7/8	8777 (20)	2047 (16)	1797 (23)
8/8	33290 (74)	10596 (82)	5866 (74)
Unknown	2566 (N/A)	6205 (N/A)	4084 (N/A)
HLA-DPB1 Match			
Double allele mismatch	11284 (29)	1543 (23)	914 (26)
Single allele mismatch	20903 (54)	3374 (51)	1832 (52)
Full allele matched	6608 (17)	1716 (26)	787 (22)
Unknown	8528 (N/A)	12478 (N/A)	8520 (N/A)
High resolution release score			
No	11606 (25)	19036 (>99)	11519 (96)
Yes	35717 (75)	75 (<1)	534 (4)
KIR typing available			
No	33478 (71)	19085 (>99)	11980 (99)
Yes	13845 (29)	26 (<1)	73 (1)
Graft type			
Marrow	16451 (35)	5091 (27)	4800 (40)
PBSC	30790 (65)	13824 (72)	7191 (60)
BM+PBSC	10 (<1)	6 (<1)	1 (<1)
PBSC+UCB	38 (<1)	170 (1)	10 (<1)
Others	34 (<1)	20 (<1)	51 (<1)
Conditioning regimen			
Myeloablative	28854 (61)	10141 (53)	7518 (62)
RIC/Nonmyeloablative	18244 (39)	8909 (47)	4372 (36)
TBD	225 (<1)	61 (<1)	163 (1)
Donor age at donation			

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
To Be Determined/NA	396 (1)	563 (3)	147 (1)
0-9 years	5 (<1)	37 (<1)	4 (<1)
10-17 years	2 (<1)	13 (<1)	1 (<1)
18-29 years	23149 (49)	9900 (52)	5152 (43)
30-39 years	13299 (28)	4964 (26)	3623 (30)
40-49 years	7988 (17)	2533 (13)	2357 (20)
50+ years	2484 (5)	1101 (6)	769 (6)
Median (Range)	30 (0-123)	29 (0-121)	32 (0-123)
Donor/Recipient CMV serostatus			
+/+	11583 (24)	4767 (25)	3042 (25)
+/-	5466 (12)	2181 (11)	1479 (12)
-/+	15215 (32)	5254 (27)	3593 (30)
-/-	13359 (28)	4498 (24)	3132 (26)
CB - recipient +	34 (<1)	136 (1)	9 (<1)
CB - recipient -	4 (<1)	42 (<1)	2 (<1)
CB - recipient CMV unknown	0	1 (<1)	0
Missing	1662 (4)	2232 (12)	796 (7)
GvHD Prophylaxis			
No GVHD prophylaxis	200 (<1)	94 (<1)	67 (1)
Ex vivo T-cell depletion	1160 (2)	319 (2)	408 (3)
CD34 selection	720 (2)	339 (2)	194 (2)
Post-CY + other(s)	3020 (6)	2569 (13)	743 (6)
Post-CY alone	228 (<1)	109 (1)	58 (<1)
Tacrolimus + MMF +- others	5383 (11)	1947 (10)	920 (8)
Tacrolimus + MTX +- others (except MMF)	20389 (43)	8407 (44)	3390 (28)
Tacrolimus + others (except MTX, MMF)	2432 (5)	1220 (6)	469 (4)
Tacrolimus alone	1182 (2)	484 (3)	216 (2)
CSA + MMF +- others (except Tacrolimus)	3083 (7)	909 (5)	1017 (8)
CSA + MTX +- others (except Tacrolimus, MMF)	6993 (15)	1899 (10)	3358 (28)
CSA + others (except Tacrolimus, MTX, MMF)	1089 (2)	335 (2)	452 (4)
CSA alone	482 (1)	136 (1)	402 (3)
Other GVHD prophylaxis	752 (2)	270 (1)	208 (2)
Missing	210 (<1)	74 (<1)	151 (1)
Donor/Recipient sex match			
Male-Male	19283 (41)	7409 (39)	4699 (39)
Male-Female	11786 (25)	4525 (24)	2668 (22)
Female-Male	8013 (17)	3384 (18)	2383 (20)
Female-Female	7842 (17)	3072 (16)	2157 (18)
CB - recipient M	18 (<1)	96 (1)	3 (<1)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
CB - recipient F	20 (<1)	83 (<1)	8 (<1)
Missing	361 (1)	542 (3)	135 (1)
Year of transplant			
1986-1990	350 (1)	46 (<1)	106 (1)
1991-1995	1839 (4)	439 (2)	748 (6)
1996-2000	3305 (7)	1185 (6)	1215 (10)
2001-2005	5345 (11)	1074 (6)	1880 (16)
2006-2010	9622 (20)	1923 (10)	1829 (15)
2011-2015	13414 (28)	3587 (19)	2563 (21)
2016-2020	10431 (22)	7184 (38)	2758 (23)
2021-2022	3017 (6)	3673 (19)	954 (8)
Follow-up among survivors, Months			
N Eval	20064	9350	5352
Median (Range)	60 (0-385)	24 (0-362)	40 (0-372)

Unrelated Cord Blood 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	6214	1700	2170
Source of data			
CRF	4494 (72)	1137 (67)	1068 (49)
TED	1720 (28)	563 (33)	1102 (51)
Number of centers	154	142	223
Disease at transplant			
AML	2354 (38)	580 (34)	706 (33)
ALL	1279 (21)	373 (22)	468 (22)
Other leukemia	98 (2)	30 (2)	37 (2)
CML	132 (2)	36 (2)	57 (3)
MDS	559 (9)	168 (10)	172 (8)
Other acute leukemia	96 (2)	24 (1)	44 (2)
NHL	403 (6)	98 (6)	134 (6)
Hodgkin Lymphoma	103 (2)	27 (2)	36 (2)
Plasma Cell Disorders, MM	38 (1)	12 (1)	13 (1)
Other malignancies	11 (<1)	1 (<1)	3 (<1)
SAA	97 (2)	32 (2)	49 (2)
Inherited abnormalities erythrocyte diff fxn	171 (3)	51 (3)	45 (2)
Inherited bone marrow failure syndromes	4 (<1)	3 (<1)	3 (<1)
Hemoglobinopathies	2 (<1)	1 (<1)	0
SCIDs	278 (4)	91 (5)	165 (8)
Inherited abnormalities of platelets	20 (<1)	5 (<1)	10 (<1)
Inherited disorders of metabolism	387 (6)	118 (7)	142 (7)
Histiocytic disorders	107 (2)	29 (2)	51 (2)
Autoimmune disorders	9 (<1)	0	6 (<1)
Other	10 (<1)	2 (<1)	9 (<1)
Disease missing	4 (<1)	3 (<1)	0
MPN	52 (1)	16 (1)	20 (1)
AML Disease status at transplant			
CR1	1222 (52)	324 (56)	350 (50)
CR2	636 (27)	149 (26)	188 (27)
CR3+	66 (3)	9 (2)	26 (4)
Advanced or active disease	422 (18)	96 (17)	138 (20)
Missing	8 (<1)	2 (<1)	4 (1)
ALL Disease status at transplant			

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
CR1	574 (45)	159 (43)	202 (43)
CR2	480 (38)	137 (37)	166 (35)
CR3+	148 (12)	54 (14)	61 (13)
Advanced or active disease	76 (6)	22 (6)	38 (8)
Missing	1 (<1)	1 (<1)	1 (<1)
MDS Disease status at transplant			
Early	173 (31)	41 (24)	72 (42)
Advanced	337 (60)	113 (67)	78 (45)
Missing	49 (9)	14 (8)	22 (13)
NHL Disease status at transplant			
CR1	63 (16)	9 (9)	25 (19)
CR2	75 (19)	22 (22)	35 (26)
CR3+	45 (11)	11 (11)	12 (9)
PR	68 (17)	12 (12)	16 (12)
Advanced	149 (37)	43 (44)	42 (32)
Missing	0	1 (1)	3 (2)
Recipient age at transplant			
0-9 years	1868 (30)	612 (36)	771 (36)
10-19 years	655 (11)	158 (9)	255 (12)
20-29 years	745 (12)	152 (9)	234 (11)
30-39 years	599 (10)	150 (9)	210 (10)
40-49 years	655 (11)	172 (10)	203 (9)
50-59 years	856 (14)	210 (12)	280 (13)
60-69 years	722 (12)	212 (12)	201 (9)
70+ years	114 (2)	34 (2)	16 (1)
Median (Range)	27 (0-83)	24 (0-78)	20 (0-78)
Recipient race/ethnicity			
White	3432 (55)	996 (59)	1090 (50)
Black or African American	893 (14)	221 (13)	263 (12)
Asian	366 (6)	120 (7)	163 (8)
Native Hawaiian or other Pacific Islander	32 (1)	3 (<1)	17 (1)
American Indian or Alaska Native	45 (1)	10 (1)	19 (1)
Hispanic	1108 (18)	253 (15)	297 (14)
Missing	338 (5)	97 (6)	321 (15)
Recipient sex			
Male	3439 (55)	968 (57)	1241 (57)
Female	2775 (45)	732 (43)	929 (43)
Karnofsky score			
10-80	1647 (27)	437 (26)	556 (26)
90-100	4361 (70)	1157 (68)	1433 (66)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Missing	206 (3)	106 (6)	181 (8)
HLA-A B DRB1 groups - low resolution			
<=3/6	101 (2)	57 (4)	32 (2)
4/6	2448 (41)	557 (40)	789 (40)
5/6	2664 (45)	596 (43)	854 (43)
6/6	750 (13)	184 (13)	294 (15)
Unknown	251 (N/A)	306 (N/A)	201 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	2891 (55)	569 (55)	881 (55)
6/8	1271 (24)	248 (24)	370 (23)
7/8	730 (14)	141 (14)	221 (14)
8/8	349 (7)	70 (7)	123 (8)
Unknown	973 (N/A)	672 (N/A)	575 (N/A)
HLA-DPB1 Match			
Double allele mismatch	859 (39)	99 (38)	164 (40)
Single allele mismatch	1117 (51)	136 (52)	209 (51)
Full allele matched	202 (9)	25 (10)	33 (8)
Unknown	4036 (N/A)	1440 (N/A)	1764 (N/A)
High resolution release score			
No	4674 (75)	1650 (97)	2145 (99)
Yes	1540 (25)	50 (3)	25 (1)
KIR typing available			
No	4941 (80)	1694 (>99)	2150 (99)
Yes	1273 (20)	6 (<1)	20 (1)
Graft type			
UCB	5836 (94)	1521 (89)	2034 (94)
BM+UCB	1 (<1)	0	0
PBSC+UCB	347 (6)	170 (10)	122 (6)
Others	30 (<1)	9 (1)	14 (1)
Number of cord units			
1	5200 (84)	0	1809 (83)
2	1012 (16)	0	360 (17)
3	1 (<1)	0	0
Unknown	1 (N/A)	1700 (N/A)	1 (N/A)
Conditioning regimen			
Myeloablative	4030 (65)	1076 (63)	1346 (62)
RIC/Nonmyeloablative	2168 (35)	619 (36)	807 (37)
TBD	16 (<1)	5 (<1)	17 (1)
Donor age at donation			
To Be Determined/NA	4858 (78)	646 (38)	1741 (80)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
0-9 years	1081 (17)	844 (50)	348 (16)
10-19 years	58 (1)	88 (5)	17 (1)
20-29 years	65 (1)	37 (2)	15 (1)
30-39 years	57 (1)	38 (2)	21 (1)
40-49 years	46 (1)	21 (1)	11 (1)
50+ years	49 (1)	26 (2)	17 (1)
Median (Range)	4 (0-112)	5 (0-73)	4 (0-119)
Donor/Recipient CMV serostatus			
+/+	0	0	1 (<1)
-/-	0	0	1 (<1)
CB - recipient +	3888 (63)	1027 (60)	1306 (60)
CB - recipient -	2227 (36)	613 (36)	790 (36)
CB - recipient CMV unknown	99 (2)	60 (4)	72 (3)
GvHD Prophylaxis			
No GVHD prophylaxis	23 (<1)	8 (<1)	14 (1)
Ex vivo T-cell depletion	25 (<1)	9 (1)	8 (<1)
CD34 selection	213 (3)	100 (6)	61 (3)
Post-CY + other(s)	12 (<1)	9 (1)	13 (1)
Post-CY alone	0	0	1 (<1)
Tacrolimus + MMF +- others	1857 (30)	539 (32)	446 (21)
Tacrolimus + MTX +- others (except MMF)	216 (3)	56 (3)	78 (4)
Tacrolimus + others (except MTX, MMF)	225 (4)	64 (4)	84 (4)
Tacrolimus alone	153 (2)	45 (3)	30 (1)
CSA + MMF +- others (except Tacrolimus)	2847 (46)	683 (40)	1039 (48)
CSA + MTX +- others (except Tacrolimus, MMF)	101 (2)	29 (2)	50 (2)
CSA + others (except Tacrolimus, MTX, MMF)	341 (5)	117 (7)	223 (10)
CSA alone	52 (1)	18 (1)	70 (3)
Other GVHD prophylaxis	137 (2)	20 (1)	42 (2)
Missing	12 (<1)	3 (<1)	11 (1)
Donor/Recipient sex match			
Male-Female	0	0	1 (<1)
Female-Male	0	0	1 (<1)
CB - recipient M	3439 (55)	968 (57)	1239 (57)
CB - recipient F	2775 (45)	732 (43)	928 (43)
CB - recipient sex unknown	0	0	1 (<1)
Year of transplant			
1996-2000	1 (<1)	2 (<1)	5 (<1)
2001-2005	112 (2)	86 (5)	34 (2)
2006-2010	1850 (30)	426 (25)	601 (28)
2011-2015	2682 (43)	510 (30)	839 (39)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
2016-2020	1341 (22)	528 (31)	547 (25)
2021-2022	228 (4)	148 (9)	144 (7)
Follow-up among survivors, Months			
N Eval	2964	887	1105
Median (Range)	64 (0-196)	49 (0-213)	43 (0-240)

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	11071	1859	851
Source of data			
CRF	3500 (32)	454 (24)	281 (33)
TED	7571 (68)	1405 (76)	570 (67)
Number of centers	93	78	63
Disease at transplant			
AML	3667 (33)	605 (33)	285 (33)
ALL	1843 (17)	362 (19)	163 (19)
Other leukemia	205 (2)	41 (2)	19 (2)
CML	337 (3)	45 (2)	24 (3)
MDS	1483 (13)	226 (12)	111 (13)
Other acute leukemia	164 (1)	33 (2)	11 (1)
NHL	936 (8)	168 (9)	76 (9)
Hodgkin Lymphoma	204 (2)	40 (2)	23 (3)
Plasma Cell Disorders, MM	257 (2)	39 (2)	23 (3)
Other malignancies	24 (<1)	0	1 (<1)
Breast cancer	1 (<1)	0	0
SAA	516 (5)	81 (4)	29 (3)
Inherited abnormalities erythrocyte diff fxn	494 (4)	72 (4)	20 (2)
Inherited bone marrow failure syndromes	16 (<1)	2 (<1)	4 (<1)
Hemoglobinopathies	111 (1)	22 (1)	8 (1)
Paroxysmal nocturnal hemoglobinuria	2 (<1)	0	0
SCIDs	228 (2)	36 (2)	16 (2)
Inherited abnormalities of platelets	10 (<1)	0	0
Inherited disorders of metabolism	16 (<1)	5 (<1)	2 (<1)
Histiocytic disorders	63 (1)	9 (<1)	5 (1)
Autoimmune disorders	11 (<1)	0	1 (<1)
Other	16 (<1)	0	0
Disease missing	10 (<1)	4 (<1)	1 (<1)
MPN	457 (4)	69 (4)	29 (3)
AML Disease status at transplant			
CR1	2403 (66)	411 (68)	186 (65)
CR2	562 (15)	86 (14)	36 (13)
CR3+	44 (1)	14 (2)	1 (<1)
Advanced or active disease	651 (18)	90 (15)	62 (22)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Missing	7 (<1)	4 (1)	0
ALL Disease status at transplant			
CR1	1119 (61)	226 (62)	103 (63)
CR2	522 (28)	91 (25)	40 (25)
CR3+	114 (6)	19 (5)	11 (7)
Advanced or active disease	86 (5)	26 (7)	9 (6)
Missing	2 (<1)	0	0
MDS Disease status at transplant			
Early	253 (17)	31 (14)	20 (18)
Advanced	1177 (79)	183 (81)	85 (77)
Missing	53 (4)	12 (5)	6 (5)
NHL Disease status at transplant			
CR1	174 (19)	39 (23)	16 (21)
CR2	176 (19)	34 (20)	10 (13)
CR3+	100 (11)	18 (11)	4 (5)
PR	68 (7)	13 (8)	7 (9)
Advanced	409 (44)	63 (38)	39 (51)
Missing	5 (1)	0	0
Recipient age at transplant			
0-9 years	1123 (10)	180 (10)	68 (8)
10-19 years	1071 (10)	139 (7)	63 (7)
20-29 years	1257 (11)	250 (13)	90 (11)
30-39 years	865 (8)	166 (9)	88 (10)
40-49 years	1356 (12)	218 (12)	99 (12)
50-59 years	2336 (21)	401 (22)	185 (22)
60-69 years	2583 (23)	431 (23)	226 (27)
70+ years	480 (4)	74 (4)	32 (4)
Median (Range)	49 (0-82)	49 (0-76)	51 (0-83)
Recipient race/ethnicity			
White	6869 (62)	977 (53)	514 (60)
Black or African American	1373 (12)	240 (13)	81 (10)
Asian	518 (5)	138 (7)	43 (5)
Native Hawaiian or other Pacific Islander	34 (<1)	5 (<1)	2 (<1)
American Indian or Alaska Native	47 (<1)	4 (<1)	4 (<1)
Hispanic	1677 (15)	357 (19)	151 (18)
Missing	553 (5)	138 (7)	56 (7)
Recipient sex			
Male	6513 (59)	1084 (58)	496 (58)
Female	4558 (41)	775 (42)	355 (42)
Karnofsky score			

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
10-80	3971 (36)	745 (40)	349 (41)
90-100	6760 (61)	1052 (57)	454 (53)
Missing	340 (3)	62 (3)	48 (6)
HLA-A B DRB1 groups - low resolution			
<=3/6	2161 (23)	346 (26)	166 (28)
4/6	636 (7)	112 (8)	65 (11)
5/6	204 (2)	37 (3)	21 (4)
6/6	6481 (68)	861 (63)	333 (57)
Unknown	1589 (N/A)	503 (N/A)	266 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	2647 (29)	416 (33)	200 (38)
6/8	118 (1)	26 (2)	14 (3)
7/8	143 (2)	26 (2)	15 (3)
8/8	6262 (68)	798 (63)	296 (56)
Unknown	1901 (N/A)	593 (N/A)	326 (N/A)
HLA-DPB1 Match			
Double allele mismatch	9 (<1)	0	0
Single allele mismatch	725 (26)	8 (18)	6 (25)
Full allele matched	2072 (74)	37 (82)	18 (75)
Unknown	8265 (N/A)	1814 (N/A)	827 (N/A)
High resolution release score			
No	4655 (42)	1830 (98)	835 (98)
Yes	6416 (58)	29 (2)	16 (2)
Graft type			
Marrow	3187 (29)	431 (23)	238 (28)
PBSC	7789 (70)	1395 (75)	599 (70)
UCB	2 (<1)	14 (1)	0
BM+PBSC	8 (<1)	4 (<1)	1 (<1)
BM+UCB	30 (<1)	9 (<1)	2 (<1)
PBSC+UCB	0	0	11 (1)
Others	55 (<1)	6 (<1)	0
Conditioning regimen			
Myeloablative	6168 (56)	1021 (55)	439 (52)
RIC/Nonmyeloablative	4849 (44)	825 (44)	395 (46)
TBD	54 (<1)	13 (1)	17 (2)
Donor age at donation			
To Be Determined/NA	15 (<1)	3 (<1)	8 (1)
0-9 years	761 (7)	119 (6)	32 (4)
10-19 years	843 (8)	139 (7)	52 (6)
20-29 years	1915 (17)	319 (17)	167 (20)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
30-39 years	1633 (15)	323 (17)	161 (19)
40-49 years	1796 (16)	300 (16)	115 (14)
50+ years	4108 (37)	656 (35)	316 (37)
Median (Range)	42 (0-122)	41 (0-118)	41 (0-121)
Donor/Recipient CMV serostatus			
+/+	4485 (41)	812 (44)	288 (34)
+/-	1187 (11)	151 (8)	72 (8)
-/+	2766 (25)	443 (24)	198 (23)
-/-	2371 (21)	381 (20)	162 (19)
CB - recipient +	24 (<1)	14 (1)	7 (1)
CB - recipient -	8 (<1)	9 (<1)	6 (1)
Missing	230 (2)	49 (3)	118 (14)
GvHD Prophylaxis			
No GVHD prophylaxis	156 (1)	35 (2)	16 (2)
Ex vivo T-cell depletion	114 (1)	31 (2)	11 (1)
CD34 selection	119 (1)	33 (2)	13 (2)
Post-CY + other(s)	3488 (32)	547 (29)	309 (36)
Post-CY alone	76 (1)	11 (1)	8 (1)
Tacrolimus + MMF +- others	794 (7)	93 (5)	26 (3)
Tacrolimus + MTX +- others (except MMF)	4050 (37)	606 (33)	309 (36)
Tacrolimus + others (except MTX, MMF)	815 (7)	292 (16)	67 (8)
Tacrolimus alone	108 (1)	22 (1)	7 (1)
CSA + MMF +- others (except Tacrolimus)	243 (2)	38 (2)	15 (2)
CSA + MTX +- others (except Tacrolimus, MMF)	719 (6)	95 (5)	43 (5)
CSA + others (except Tacrolimus, MTX, MMF)	81 (1)	11 (1)	3 (<1)
CSA alone	85 (1)	12 (1)	4 (<1)
Other GVHD prophylaxis	148 (1)	19 (1)	15 (2)
Missing	75 (1)	14 (1)	5 (1)
Donor/Recipient sex match			
Male-Male	3666 (33)	646 (35)	285 (33)
Male-Female	2322 (21)	388 (21)	182 (21)
Female-Male	2791 (25)	415 (22)	196 (23)
Female-Female	2200 (20)	374 (20)	164 (19)
CB - recipient M	21 (<1)	16 (1)	8 (1)
CB - recipient F	11 (<1)	7 (<1)	5 (1)
Missing	60 (1)	13 (1)	11 (1)
Year of transplant			
2006-2010	601 (5)	71 (4)	61 (7)
2011-2015	3701 (33)	503 (27)	203 (24)
2016-2020	5028 (45)	894 (48)	399 (47)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
2021-2022	1741 (16)	391 (21)	188 (22)
Follow-up among survivors, Months			
N Eval	6629	1113	510
Median (Range)	35 (0-150)	24 (0-124)	24 (0-148)

Haplo Donor with PtCy 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	2904	462	247
Source of data			
CRF	1082 (37)	136 (29)	98 (40)
TED	1822 (63)	326 (71)	149 (60)
Number of centers	71	53	42
Disease at transplant			
AML	1066 (37)	169 (37)	97 (39)
ALL	530 (18)	91 (20)	51 (21)
Other leukemia	42 (1)	7 (2)	5 (2)
CML	105 (4)	14 (3)	7 (3)
MDS	430 (15)	54 (12)	39 (16)
Other acute leukemia	45 (2)	9 (2)	3 (1)
NHL	214 (7)	49 (11)	16 (6)
Hodgkins Lymphoma	67 (2)	18 (4)	7 (3)
Plasma Cell Disorders, MM	42 (1)	3 (1)	3 (1)
Other malignancies	9 (<1)	0	0
SAA	101 (3)	15 (3)	4 (2)
Inherited abnormalities erythrocyte diff fxn	64 (2)	9 (2)	3 (1)
Inherited bone marrow failure syndromes	0	1 (<1)	1 (<1)
Hemoglobinopathies	24 (1)	3 (1)	1 (<1)
SCIDs	18 (1)	2 (<1)	1 (<1)
Inherited abnormalities of platelets	1 (<1)	0	0
Inherited disorders of metabolism	2 (<1)	0	0
Histiocytic disorders	14 (<1)	2 (<1)	1 (<1)
Autoimmune disorders	3 (<1)	0	0
Other	1 (<1)	0	0
Disease missing	2 (<1)	1 (<1)	0
MPN	124 (4)	15 (3)	8 (3)
AML Disease status at transplant			
CR1	670 (63)	110 (65)	59 (61)
CR2	187 (18)	28 (17)	12 (12)
CR3+	17 (2)	5 (3)	1 (1)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Advanced or active disease	191 (18)	25 (15)	25 (26)
Missing	1 (<1)	1 (1)	0
ALL Disease status at transplant			
CR1	303 (57)	57 (63)	31 (61)
CR2	160 (30)	25 (27)	15 (29)
CR3+	45 (8)	4 (4)	2 (4)
Advanced or active disease	22 (4)	5 (5)	3 (6)
MDS Disease status at transplant			
Early	66 (15)	8 (15)	5 (13)
Advanced	346 (80)	44 (81)	32 (82)
Missing	18 (4)	2 (4)	2 (5)
NHL Disease status at transplant			
CR1	53 (25)	12 (25)	4 (25)
CR2	52 (24)	11 (23)	2 (13)
CR3+	17 (8)	8 (17)	2 (13)
PR	4 (2)	0	0
Advanced	85 (40)	17 (35)	8 (50)
Missing	2 (1)	0	0
Recipient age at transplant			
0-9 years	184 (6)	21 (5)	12 (5)
10-17 years	230 (8)	19 (4)	9 (4)
18-29 years	405 (14)	71 (15)	27 (11)
30-39 years	248 (9)	42 (9)	33 (13)
40-49 years	355 (12)	63 (14)	21 (9)
50-59 years	541 (19)	95 (21)	50 (20)
60-69 years	720 (25)	125 (27)	79 (32)
70+ years	221 (8)	26 (6)	16 (6)
Median (Range)	51 (0-82)	52 (0-76)	55 (2-83)
Recipient race/ethnicity			
White, Non-Hispanic	1499 (52)	201 (44)	133 (54)
Black or African American, Non-Hispanic	550 (19)	97 (21)	35 (14)
Asian, Non-Hispanic	144 (5)	37 (8)	13 (5)
Native Hawaiian or Pacific Islander, Non-Hispanic	5 (<1)	1 (<1)	1 (<1)
American Indian or Alaska Native, Non-Hispanic	12 (<1)	0	2 (1)
Hispanic	506 (17)	94 (20)	45 (18)
Missing	188 (6)	32 (7)	18 (7)
Recipient sex			
Male	1719 (59)	288 (62)	147 (60)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Female	1185 (41)	174 (38)	100 (40)
Karnofsky score			
10-80	1255 (43)	216 (47)	124 (50)
90-100	1567 (54)	227 (49)	108 (44)
Missing	82 (3)	19 (4)	15 (6)
HLA-A B DRB1 groups - low resolution			
<=3/6	1884 (76)	290 (77)	156 (74)
4/6	558 (22)	85 (22)	51 (24)
5/6	41 (2)	4 (1)	4 (2)
Unknown	421 (N/A)	83 (N/A)	36 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	2312 (96)	344 (95)	179 (96)
6/8	85 (4)	17 (5)	8 (4)
Unknown	507 (N/A)	101 (N/A)	60 (N/A)
HLA-DPB1 Match			
Double allele mismatch	5 (1)	0	0
Single allele mismatch	570 (81)	8 (89)	3 (75)
Full allele matched	132 (19)	1 (11)	1 (25)
Unknown	2197 (N/A)	453 (N/A)	243 (N/A)
High resolution release score			
No	1488 (51)	460 (>99)	242 (98)
Yes	1416 (49)	2 (<1)	5 (2)
Graft type			
Marrow	1154 (40)	148 (32)	97 (39)
PBSC	1742 (60)	312 (68)	150 (61)
BM+PBSC	4 (<1)	1 (<1)	0
Others	4 (<1)	1 (<1)	0
Conditioning regimen			
Myeloablative	1299 (45)	201 (44)	96 (39)
RIC/Nonmyeloablative	1604 (55)	261 (56)	150 (61)
TBD	1 (<1)	0	1 (<1)
Donor age at donation			
To Be Determined/NA	1 (<1)	0	0
0-9 years	31 (1)	2 (<1)	2 (1)
10-17 years	144 (5)	30 (6)	10 (4)
18-29 years	859 (30)	147 (32)	73 (30)
30-39 years	812 (28)	136 (29)	77 (31)
40-49 years	619 (21)	92 (20)	46 (19)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
50+ years	438 (15)	55 (12)	39 (16)
Median (Range)	35 (2-77)	34 (1-70)	34 (7-74)
Donor/Recipient CMV serostatus			
+/+	1239 (43)	214 (46)	84 (34)
+/-	305 (11)	33 (7)	23 (9)
-/+	794 (27)	126 (27)	63 (26)
-/-	542 (19)	81 (18)	48 (19)
Missing	24 (1)	8 (2)	29 (12)
GvHD Prophylaxis			
Post-CY + other(s)	2889 (99)	459 (99)	246 (>99)
Post-CY alone	15 (1)	3 (1)	1 (<1)
Donor/Recipient sex match			
Male-Male	1105 (38)	203 (44)	90 (36)
Male-Female	635 (22)	103 (22)	48 (19)
Female-Male	614 (21)	85 (18)	57 (23)
Female-Female	550 (19)	71 (15)	52 (21)
Year of transplant			
2006-2010	15 (1)	1 (<1)	5 (2)
2011-2015	449 (15)	59 (13)	30 (12)
2016-2020	1742 (60)	258 (56)	150 (61)
2021-2022	698 (24)	144 (31)	62 (25)
Follow-up among survivors, Months			
N Eval	1740	265	154
Median (Range)	22 (0-133)	13 (2-82)	13 (0-114)

TO: Immunobiology Working Committee Members

FROM: Stephanie Lee, MD, MPH; 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. **Manuscript Preparation**

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. **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. **Manuscript Preparation**

IB22-01 Impact of HLA-DPB1 matching on survival following unrelated donor transplantation with post-transplant cyclophosphamide for adults 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). The goal of this study is to determine the overall survival (OS) of patients with high-risk HLA-DPB1 mismatches following unrelated donor (URD) transplantation utilizing PTCy when compared with: 1) patients with high-risk HLA-DPB1 mismatches who receive URD transplantation utilizing non-PTCy-based prophylaxis; and 2) patients without high risk HLA-DPB1 mismatches who receive PTCy. **Protocol Development**

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**

IB22-02 Effect of SIRPα mismatch on the outcome of allogeneic hematopoietic stem cell transplantation from an HLA matched related donor. (Jun Zou; Samer Srour). This study hypothesized that 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 chronic graft-versus-host disease (cGVHD) accompanied by a lower risk of relapse. **Protocol Development.**

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. (Theresa Hahn/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

IB06-05e HLA-DQ heterodimers in hematopoietic cell transplantation. Petersdorf EW, Bengtsson M, Horowitz MM, McKallor C, Spellman SR, Spierings E, Gooley TA, Stevenson PA. **Blood. 2022 May 19; 139(20):3009-3017. doi:10.1182/blood.2022015860. Epub 2022 Mar 10. PMC9121842**. Heterodimers were defined in 5164 HLA-matched and 520 HLA-DQ-mismatched patients and their transplant donors according to well-established crystallographic criteria. Group 1 (G1) heterodimers are any DQA1*02/03/04/05/06α paired with any DQB1*02/03/04β. Group 2 (G2) heterodimers are DQA1*01α paired with any DQB1*05/06β. Multivariable models identified significantly higher relapse risk in G1G2 and G2G2 compared with G1G1 HLA-matched patients with malignant disease; risk increased with an increasing number of G2 molecules. In HLA-DQ-mismatched transplantation for malignant diseases, matching or mismatching for G2 increased relapse risk. G2 lowered disease-free survival after both HLA-matched and HLA-DQ-mismatched transplantation.

IB06-05f Race and survival in unrelated hematopoietic cell transplantation. Morishima Y, Morishima S, Stevenson P, Kodera Y, Horowitz M, McKallor C, Malkki M, Spellman SR, Gooley T, Petersdorf EW. **Transplantation and Cellular Therapy. 2022 Jul 1; 28(7):357.e1-357.e6. doi:10.1016/j.jtct.2022.03.026. Epub 2022 Apr 8. PMC9387555.** The purpose of this study is to determine disparities in transplant survivorship among patients of diverse race while accounting for patient and donor HLA variation. After HLA adjustment, three mortality risk strata were identified: Japanese and U.S. Asian (low-risk); White and Hispanic (intermediate-risk), and Black patients (high-risk). Transplant survivorship disparities are influenced by HLA as a genetic construct of race.

IB10-01m Telomere length and epigenetic clocks as markers of cellular aging: A comparative study. Pearce EE, Alsaggaf R, Katta S, Dagnall C, Aubert G, Hicks BD, Spellman SR, Savage SA, Horvath S, Gadalla SM. **GeroScience. 2022 Jun 1; 44(3):1861-1869. doi:10.1007/s11357-022-00586-4. Epub 2022 May 18. PMC9213578.** This study used multivariable regression models to evaluate the relationships between leukocyte TL (LTL; measured by qPCR [n = 635] or flow FISH [n = 144]) and five epigenetic clocks (Hannum, DNAmAge pan-tissue, PhenoAge, SkinBlood, or GrimAge clocks), or their epigenetic age acceleration measures in healthy adults (age 19-61 years). LTL showed statistically significant negative correlations with all clocks (qPCR: r = - 0.26 to - 0.32; flow FISH: r = - 0.34 to - 0.49; $p < 0.001$ for all). Yet, models adjusted for age, sex, and race revealed significant associations between three of five clocks (PhenoAge, GrimAge, and Hannum clocks) and LTL by flow FISH ($p < 0.01$ for all) or qPCR ($p < 0.001$ for all). Significant associations between age acceleration measures for the same three clocks and qPCR or flow FISH TL were also found ($p < 0.01$ for all). Additionally, LTL (by qPCR or flow FISH) showed significant associations with extrinsic epigenetic age acceleration (EEAA: $p < 0.0001$ for both), but not intrinsic epigenetic age acceleration (IEAA; $p > 0.05$ for both).

IB19-01b 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 SM, Paczesny S, Marsh SGE, Lee SJ, Spellman SR, Bolon Y, Fleischhauer K. **Blood. 2022 Aug 11; 140(6):659-663. doi:10.1182/blood.2022015708. Epub 2022 May 24. PMC9373015.** This study hypothesized that a similarity measure reflecting the peptide-binding region of HLA-DPB1 alleles could constitute a proxy for immunopeptidome overlap and hence predict permissive mismatches in the clinical setting. In a CIBMTR cohort of 5140 10/10-matched patients transplanted for AML, ALL, or MDS from 2008-2017, the risks of aGVHD II-IV increased progressively from "core" TCE3 permissive (N=930; HR 1.12 [0.98-1.28]; p=0.1012) to "non-core" TCE3-permissive (N=1286; HR 1.24 [1.06-1.46]; p= 0.0082), and non-permissive mismatches (N=2023; HR 1.32 [1.16-1.50]; p<.0001) compared to allele-matched patients (N=785). "Core" TCE3-permissive pairs (HR 0.78 [0.68-0.88]; p=0.0002), but not "non-core" TCE3-permissive pairs (HR 0.95 [0.83-1.09]; p=0.4578) showed significantly lower risks of TRM when compared to non-permissive pairs. The results suggest that frequent mismatches between structurally similar "core" HLA-DPB1 alleles are the main drivers of permissiveness after HCT, and provide evidence for a role of immunopeptidome differences between mismatched HLA-DPB1 alleles in the clinical outcome of HCT.

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, Vina MAF, Wang T, Bolon YT, Lazaryan A, Beitinjaneh A, Bhatt VR, Castillo P, Marsh SGE, Hildebrandt GC, Assal A, Brown VI, Hsu J, Spellman S, de Lima M, Lee SJ. **Transplantation and Cellular Therapy. 2022 Aug 1; 28(8):483.e1-483.e7. doi:10.1016/j.jtct.2022.05.034. Epub 2022 May 26. PMC9357149.** In this study, 900 single CBT (sCBT), 954 double CBT (dCBT), and 671 Haplo HCT performed between 2008 and 2017 for acute leukemias and myelodysplastic syndrome were examined. Several models of KIR-L interactions were analyzed by multiple regression analyses for their association

with engraftment, overall survival (OS), and transplant-related mortality (TRM). In sCBT, there was no significant difference in neutrophil and platelet engraftment. In dCBT, no significant differences were seen in engraftment, OS and TRM. In the Haplo cohort there was faster platelet recovery in the GvH KIR-L-MM/KIR-L-M pairs versus HvG KIR-L-MM or bidirectional mismatch (HR 1.23, P= .0116). There was no significant association with OS, TRM, or neutrophil engraftment. In this large registry study, KIR-L mismatching did not significantly impact engraftment, TRM, or survival in CBT and Haplo HCT, although an association with platelet engraftment in Haplo HCT was demonstrated.

IB10-01n Genetic testing in severe aplastic anemia is required for optimal hematopoietic cell transplant outcomes. McReynolds LJ, Rafati M, Wang Y, Ballew BJ, Kim J, Williams VV, Zhou W, Hendricks RM, Dagnall C, Freedman ND, Carter B, Strollo S, Hicks B, Zhu B, Jones K, Paczesny S, Marsh SGE, Spellman SR, He M, Wang T, Lee SJ, Savage SA, Gadalla SM. **Blood. 2022 Aug 25; 140(8):909-921. doi:10.1182/blood.2022016508. Epub 2022 Jul 1. PMC9412004.** Patients with severe aplastic anemia (SAA) can have an unrecognized inherited bone marrow failure syndrome (IBMFS) because of phenotypic heterogeneity. This study revealed no survival difference between dVUS and acquired SAA was noted. Compared with acquired SAA (no P/LP variants), patients with unrecognized IBMFS, but not carriers, had worse survival after HCT (IBMFS hazard ratio [HR], 2.13; 95% confidence interval[CI], 1.40-3.24; P = .0004; carriers HR, 0.96; 95% CI, 0.62-1.50; P = .86). Results were similar in analyses restricted to patients receiving reduced-intensity conditioning (n = 448; HR IBMFS = 2.39; P = .01). The excess mortality risk in unrecognized IBMFS attributed to death from organ failure (HR = 4.88; P < .0001).

IB17-03a Germline-somatic JAK2 interactions are associated with clonal expansion in myelofibrosis. Brown DW, Zhou W, Wang Y, Jones K, Luo W, Dagnall C, Teshome K, Klein A, Zhang T, Lin SH, Lee OW, Khan S, Vo JB, Hutchinson A, Liu J, Wang J, Zhu B, Hicks B, Martin AS, Spellman SR, Wang T, Deeg HJ, Gupta V, Lee SJ, Freedman ND, Yeager M, Chanock SJ, Savage SA, Saber W, Gadalla SM, Machiela MJ. **Nature Communications. 13(1):5284. doi:10.1038/s41467-022-32986-7. Epub 2022 Sep 8. PMC9458655.** Myelofibrosis is a rare myeloproliferative neoplasm (MPN) with high risk for progression to acute myeloid leukemia. Our integrated genomic analysis of up to 933 myelofibrosis cases identifies 6 germline susceptibility loci, 4 of which overlap with previously identified MPN loci. Our results advance understanding of the germline-somatic interaction at JAK2 and implicate mCAs involving JAK2 as strong promoters of clonal expansion of those mutated clones.

IB18-02 Pathogenicity and impact of HLA class I alleles in aplastic anemia patients of different ethnicities. Olson TS, Frost BF, Duke JL, Dribus M, Xie HM, Prudowsky ZD, Furutani E, Gudera J, Shah YB, Ferriola D, Dinou A, Pagkrati I, Kim S, Xu Y, He M, Zheng S, Nijim S, Lin P, Xu C, Nakano TA, Oved JH, Carreno BM, Bolon YT, Gadalla SM, Marsh SGE, Paczesny S, Lee SJ, Monos DS, Shimamura A, Bertuch AA, Gragert L, Spellman SR, Babushok DV. **Journal of Clinical Investigation Insight. 2022 Nov 22; 7(22):e163040. doi:10.1172/jci.insight.163040. Epub 2022 Oct 11. PMC9746824.** This study demonstrates that HLA alleles confer different risks of developing AA, but once AA develops, specific alleles are not associated with response to immunosuppression or transplant outcomes. However, higher pathogenicity alleles, particularly HLA-B*14:02, are associated with higher rates of clonal evolution in adult patients with AA.

IB10-01o Molecular landscape of immune pressure and escape in aplastic anemia. Pagliuca S, Gurnari C, Hercus C, Hergalant S, Nadarajah N, Wahida A, Terkawi L, Mori M, Zhou W, Visconte V, Spellman S, Gadalla SM, Zhu C, Zhu P, Haferlach T, Maciejewski JP**. Leukemia. doi:10.1038/s41375-022-01723-w. Epub 2022 Oct 17.** This study hypothesized that in analogy with antitumor immunity, the pathophysiological cascade of immune escape in IAA is initiated by immunoediting pressures and

culminates with mechanisms of clonal evolution characterized by hits in immune recognition and response genes. Using a newly implemented bioinformatic framework we found that not only class I but also class II genes were often impaired by acquisition of genetic aberrations.

IB20-04 Haploidentical versus matched unrelated donor transplants using post-transplant cyclophosphamide for lymphomas. Mussetti A, Kanate AS, Wang T, He M, Hamadani M, Sr HF, Boumendil A Sr, Glass B, Castagna L, Dominietto A, McGuirk J, Blaise D, Gülbas Z, Diez-Martin J, Marsh SGE, Paczesny S, Gadalla SM, Dreger P, Zhang MJ, Spellman SR, Lee SJ, Bolon Y-T, Sureda A. **Transplantation and Cellular Therapy. doi:10.1016/j.jtct.2022.11.028. Epub 2022 Dec 25.** This study aimed to test if using a haploidentical donor has the same results of a MUD. The result revealed Haploidentical HCT has less favorable results versus MUD cohort in terms of overall mortality (HR=1.69, 95%CI=1.30-2.27, p<0.001), progression-free survival (HR=1.39, 95%CI=1.10 – 1.79, p=0.008), non-relapse mortality (HR=1.93, 95% CI=1.21 – 3.07, p=0.006), platelets engraftment (HR=0.69, 95%CI=0.59 – 0.80, p<0.001), acute grade 2-4 GVHD incidence (HR=1.65, 95%CI=1.28 – 2.14, p<0.001) and chronic GVHD (HR=1.79, 95%CI=1.30 – 2.48, p<0.001).

IB20-01 Impact of High Immunopeptidome Divergence between Single Class I HLA-Mismatches on Survival after Unrelated Donor Transplantation. Pietro Crivello, Esteban Arrieta-Bolaños, Meilun He, Tao Wang, Stephanie Fingerson, Shahinaz Gadalla, Sophie Paczesny, Steven G. E. Marsh, Stephanie J. Lee, Stephen R. Spellman, Yung-Tsi Bolon, 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. **Journal of Clinical Oncology. In press**.

IB17-04 Donor whole blood DNA methylation is not a strong predictor of acute graft versus host disease in unrelated donor allogeneic hematopoietic 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.**

IB20-03 Donor socioeconomic status as a predictor of recipient mortality following hematopoietic cell transplantation for hematologic malignancy. Lucie M. Turcotte, Tao Wang, Kirsten M. Beyer, Steven W. Cole, Stephen R. Spellman, Mariam Allbee-Johnson, Eric Williams, Yuhong Zhou, Michael R. Verneris, J. Douglas Rizzo, Jennifer M. 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. **Submitted.**

IB19-04 HLA Class I genotype is associated with relapse risk after allogeneic stem cell transplantation for NPM1-mutated AML. Rupa Narayan, Abhishek Niroula, Tao Wang, Michelle Kuxhausen, Meilun He, Everett Meyer, Yi-Bin Chen, Vijaya Raj Bhatt, Amer Beitinjaneh, Taiga Nishihori, Akshay Sharma, Valerie I. Brown, Malek Kamoun, Miguel A Diaz, Muhammad Bilal Abid, Medhat Askar, Christopher G. Kanakry, Loren Gragert, Yung-Tsi Bolon, Steven G.E. Marsh, Shahinaz M. Gadalla, Sophie Paczesny, Stephen Spellman, Stephanie J Lee. This study hypothesized that HLA genotype may impact allo-HCT outcomes in NPM1-mutated AML due to differences in antigen presentation. **Submitted.**