Not for publication or presentation

A G E N D A
CIBMTR WORKING COMMITTEE FOR IMMUNOBIOLOGY
San Antonio, TX
Thursday, Feb 22nd, 2024, 1:00 pm–3:00 pm CST

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Co-Chair:	**Shahinaz Gadalla, MD, PhD; National Cancer Institute, Rockville, MD; Telephone: 240-276-7254; E-mail: shahinaz.gadalla@nih.gov**
Co-Chair:	**Brian Betts, MD; Roswell Park Cancer Institute, Buffalo, NY; Telephone: 716-845-2300; E-mail: brian.betts@roswellpark.org**
Co-Chair:	**Cara Benjamin, PhD; University of Miami, Miami, FL; Telephone: 305-243-5534; E-mail: c.benjamin3@miami.edu**
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Agenda Summary

- **Introduction and overview of progress** 1:00pm
- **Presentation of new proposals** 1:05-2:10pm
  - PROP2310-92: Impact of different HLA alleles on GVHD and GVL after sex mismatched allo-HCT
  - PROP2310-84: Impact of molecular disparity of HY antigens on cGVHD and relapse risks in male recipients receiving allogeneic HSCT from a female HLA-matched related donor
  - PROP2310-164: 6-locus HLA immunopeptidome divergence and outcome of mismatched unrelated HCT
  - PROP2308-05: Effect of donor KIR and donor KIR ligand on CD8+ T cell-mediated alloreactivity in unrelated HSCT for AML, ALL and MDS
- **Presentation of updates for completed/ongoing studies** 2:10-2:55pm
  - IB22-01: Impact of HLA-DPB1 matching on survival following unrelated donor transplantation with post-transplant cyclophosphamide for adults with hematologic malignancies.

- IB22-03: HLA matched sibling versus well-matched unrelated donor: Update including HLA-DPB1 match status in recipients of allogeneic hematopoietic cell transplantation.
- IB23-01: Immunopeptidome divergence between mismatched HLA and outcome of haploidentical HCT.

- **Concluding remarks** 2:55pm

Detailed Agenda

1. Introduction **Shahinaz Gadalla** 1:00pm

a. Minutes and Overview Plan of Immunobiology Working Committee from Tandem 2023 (Attachment 1)

2. Published and submitted papers (9) in the last year 1:05pm

a. **IB20-01** Impact of the HLA immunopeptidome on survival of leukemia patients after unrelated donor transplantation. Journal of Clinical Oncology. Crivello P, Arrieta-Bolaños E, He M, Wang T, Fingerson S, Gadalla SM, Paczesny S, Marsh SGE, Lee SJ, Spellman SR, Bolon YT, Fleischhauer K. ***Journal of Clinical Oncology. 2023 May 1; 41(13):2416-2427. doi:10.1200/JCO.22.01229. Epub 2023 Jan 20. PMC10150892.***

b. **IB06-05g** Role of NKG2D ligands and receptor in haploidentical related donor hematopoietic cell transplantation. Petersdorf EW, McKallor C, Malkki M, He M, Spellman SR, Hsu KC, Strong RK, Gooley T, Stevenson P. ***Blood Advances. 2023 Jun 27; 7(12):2888-2896. doi:10.1182/bloodadvances.2022008922. Epub 2023 Feb 10. PMC10300293.***

c. **IB19-04** HLA class I genotype is associated with relapse risk after allogeneic stem cell transplantation for NPM1-mutated acute myeloid leukemia**.** Narayan R, Niroula A, Wang T, Kuxhausen M, He M, Meyer E, Chen YB, Bhatt VR, Beitinjaneh A, Nishihori T, Sharma A, Brown VI, Kamoun M, Diaz MA, Abid MB, Askar M, Kanakry CG, Gragert L, Bolon YT, Marsh SGE, Gadalla SM, Paczesny S, Spellman S, Lee SJ. ***Transplantation and Cellular Therapy. 2023 Jul 1; 29(7):452.e1-452.e11. doi:10.1016/j.jtct.2023.03.027. Epub 2023 Mar 29. PMC10330307.***

d. **IB09-06u** Associations of minor histocompatibility antigens with outcomes following allogeneic hematopoietic cell transplantation. Jadi O, Tang H, Olsen K, Vensko S, Zhu Q, Wang Y, Haiman CA, Pooler L, Sheng X, Brock G, Webb A, Pasquini MC, McCarthy PL, Spellman SR, Hahn T, Vincent B, Armistead P, Sucheston-Campbell LE. ***American Journal of Hematology. 2023 Jun 1; 98(6):940-950. doi:10.1002/ajh.26925. Epub 2023 Apr 13. PMC10368187.***

e. **IB17-03b** JAK2 V617F mutation and associated chromosomal alterations in primary and secondary myelofibrosis and post-HCT outcomes. Rafati M, Brown DW, Zhou W, Jones K, Luo W, St Martin A, Wang Y, He M, Spellman SR, Wang T, Deeg HJ, Gupta V, Lee SJ, Bolon YT, Chanock SJ, Machiela MJ, Saber W, Gadalla SM. ***Blood Advances. 2023 Dec 26; 7(24):7506-7515. doi:10.1182/bloodadvances.2023010882. Epub 2023 Oct 27.***

f. **IB06-05h** HLA haplotypes and relapse after hematopoietic cell transplantation. Petersdorf EW, McKallor C, Malkki M, He M, Spellman SR, Gooley T, Stevenson P. ***Journal of Clinical Oncology. doi:10.1200/JCO.23.01264. Epub 2023 Dec 5.***

g. **SC19-06** Systematic evaluation of donor-KIR/recipient-HLA interactions in HLA-matched hematopoietic cell transplantation for AML. Fein JA, Shouval R, Krieger E, Spellman SR, Wang T, Baldauf H, Fleischhauer K, Kröger N, Horowitz MM, Maiers M, Miller JS, Mohty M, Nagler A, Weisdorf DJ, Malmberg KJ, Toor AA, Schetelig J, Romee R, Koreth J. ***Blood Advances. doi:10.1182/bloodadvances.2023011622. Epub 2023 Dec 5.***

h. **IB18-04b** Donor KIR genotype based outcome prediction after allogeneic stem cell transplantation: No Land in Sight! Schetelig J, Baldauf H, Heidenreich Falk, Hoogenboom JD, Spellman S, Kulagin A, Schroeder T, Sengeloev H, Dreger P, Forcade E, Vydra J, Wagner-Drouet E, Choi G, Paneesha S, Miranda N, Tanase A, De Wreede L, Lange V, Schmidt AH, Sauter J, Fein JA, Bolon YT, He M, Marsh SGE, Gadalla S, Paczesny S, Ruggeri A, Chabannon C, Fleischhauer K. ***Submitted.***

i. **IB20-03** Donor socioeconomic status as a predictor of recipient mortality following hematopoietic cell transplantation for hematologic malignancy. Turcotte LM, Wang T, Beyer KM, Cole SW, Spellman SR, Allbee-Johnson M, Williams E, Zhou Y, Verneris MR, Rizzo JD, Knight JM. ***Submitted.***

3. Future/proposed studies and discussion **Brian Betts & Cara Benjamin** 1:05pm-2:10pm

a. Voting guidelines

b. **Proposal presentations (4)**

i. **PROP2310-92** Impact of different HLA alleles on GVHD and GVL after sex mismatched allo-HCT (Alaa Ali, Scott Rowley) *(*Attachment 2*)* ***Dr. Alaa Ali will present.***

ii. **PROP2310-84** Impact of molecular disparity of HY antigens on cGVHD and relapse risks in male recipients receiving allogeneic HSCT from a female HLA-matched related donor (Jun Zou, Samer Srour) *(*Attachment 3*)* ***Dr. Jun Zou will present.***

iii. **PROP2310-164** 6-locus HLA immunopeptidome divergence and outcome of mismatched unrelated HCT (Esteban Arrieta-Bolaños, Katharina Fleischhauer) *(*Attachment 4*)* ***Dr. Katharina Fleischhauer will present.***

iv. **PROP2308-05** Effect of donor KIR and donor KIR ligand on CD8+ T cell-mediated alloreactivity in unrelated HSCT for AML, ALL and MDS (Becca Asquith) ***(***Attachment 5*)* ***Dr. Becca Asquith will present***

c. **Dropped Proposals (5)**

i. **PROP2308-03** Machine Learning-Based Tool: A New Approach to Improving Stem Cell Transplant Outcomes (Shatha Farhan, Adrian Mosquera Orgeira, Samer Al-Homsi) – *Overlap with current study.*

ii. **PROP2310-83** Effect of natural killer cell alloreactivity predicted by novel count functional inhibitory KIR (CF iKIR) score on clinical outcomes of patients who underwent haploidentical hematopoietic stem cell transplantation (haplo-HSCT) with post-transplant cyclophosphamide (PTCy) (Jun Zou, Stefan O. Ciurea) – *Small sample size.*

iii. **PROP2310-113** Association of Class I HLA Alleles and Outcomes of Anti-CD19 CAR T-Cell Therapy (Jiasheng Wang, Leland Metheny) – *Small sample size and overlap with current study.*

iv. **PROP2310-194** Younger "Lesser Matched" Donors Versus Older "Better Matched" Donors in Patients Undergoing HCT with PTCy prophylaxis. (Rohtesh S Mehta, Annalisa Ruggeri) – *Overlap with current study.*

v. **PROP2310-236** A Deep Learning approach to post-transplant mortality risk prediction of Hematopoietic Stem Cell Transplant recipients. (Regina Barzilay, Lindsley Robert Coleman) – *Small sample size and overlap with current study.*

4. Research sample repository update with data accrual tables *(*Attachment 6*)*

5. Studies in Progress *(*Attachment 7*)*

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. **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 SJ, Spellman SR, Wang T, Rakyan V, Peggs K, Beck S. **Manuscript Preparation.**

c. **IB21-01** HLA-DRB1 Hed Is Associated with Improved Survival and Decreased Relapse in Patients with Hematologic Malignancies Following Allogeneic Hematopoietic Stem Cell Transplant. (Christine Camacho-Bydume/Diego Chowell/ Katharine C. Hsu) **Manuscript Preparation.** ***Poster Presentation, 2023 ASH abstract presentation.***

d. **IB22-03** HLA matched sibling versus well-matched unrelated donor: Update including HLA-DPB1 match status in recipients of allogeneic hematopoietic cell transplantation (Karthik Nath/ Brian Shaffer/ Hannah Choe) **Analysis.**

e. **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) **Manuscript Preparation.**

f. **IB23-01** Immunopeptidome divergence between mismatched HLA and outcome of haploidentical HCT. (Pietro Crivello, Katharina Fleischhauer) **Analysis.**

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

h. **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) **Data File Preparation.**

i. **IB23-03** Impact of adherence to cord blood guidelines (Leland Metheny/ Filippo Milano) **Protocol Development.**

j. **IB10-01x** Monoallelic Germline Pathogenic Variants in DNA Damage Repair Genes and Their Impact on Post-Hematopoietic Cell Transplantation Outcomes in Severe Aplastic Anemia (Maryam Rafati, Shahinaz Gadalla). **Ongoing.** ***Oral Presentation, 2024 Tandem Meeting.***

k. **IB10-01y** Monoallelic Pathogenic Variants in Hemophagocytic Lymphohistiocytosis Genes are Uncommon and Not Associated with Hematopoietic Cell Transplantation Outcomes in Severe Aplastic Anemia. (Maryam Rafati, Shahinaz Gadalla). **Ongoing.** ***Poster Presentation, 2023 ASH Annual Meeting and Exposition.***

l. **IB23-02** Younger MMUD vs older haploidentical donor HCT (Rohtesh Mehta**) Data File Preparation.**

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. **IB09-06o** Genetics and epidemiology of myeloid malignancies candidate gene paper. (Lara Sucheston-Cambell/ Ezgi Karaesmen/ Alyssa Clay-Gilmour/ Theresa Hahn) **Manuscript Preparation.**

c. **IB09-06p** Genetics and epidemiology of myeloid malignancies genome-wide association study. (Alyssa Clay-Gilmour/ Kenan Onel/ Theresa Hahn) **Manuscript Preparation.**

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.**

e. **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. (Effie Petersdorf) **Ongoing.**

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

6. Study Presentations **Steven Marsh & Jennifer Saultz** 2:10pm-2:55pm

a. **IB22-01** Impact of HLA-DPB1 matching on survival following unrelated donor transplantation with post-transplant cyclophosphamide for adults with hematologic malignancies.

b. **IB22-03** HLA matched sibling versus well-matched unrelated donor: Update including HLA-DPB1 match status in recipients of allogeneic hematopoietic cell transplantation.

c. **IB23-01** Immunopeptidome divergence between mismatched HLA and outcome of haploidentical HCT.

7. Closing Remarks **Stephanie Lee** 2:55pm

A G E N D A
CIBMTR IMMUNOBIOLOGY WORKING COMMITTEE
Orlando, Florida
Friday, Feb 17th, 2023, 12:00 pm–14:00 pm EST

Co-Chair:	**Sophie Paczesny, MD, PhD; Medical University of South Carolina**
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	Telephone: +44 20 7284 8321; E-mail: steven.marsh@ucl.ac.uk
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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 12:55-13:10pm
- Presentation of updates for completed/ongoing studies 13:10-13:55pm
  - IB20-04
  - IB18-02
  - IB20-03
- Concluding remarks 13:55pm

Detailed Agenda

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

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

The CIBMTR Immunobiology Working Committee (IBWC) was called to order at 12:00 pm on Friday February 17th, 2023, by Dr. Sophie Paczesny. Dr. Paczesny introduced the IBWC

leadership and the outgoing chair (herself) and incoming chair Dr. Brian Betts. Dr. Paczesny discussed the following topics: CIBMTR COI policy, committee membership, goals of the working committee, areas of focus, and limitations of the IBWC, introduction of rules of authorship, publicly available research datasets, and sources of CIBMTR HCT dataset. She concluded with an overview of the status of the current portfolio and number of ongoing studies to be presented during the meeting.

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/s41467-022-32986-7. Epub 2022 Sep 8. PMC9458655.** ***Oral Presentation, 64th ASH Annual Meeting and Exposition***

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 13:25.***

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 13:10***

k. **IB20-01** Impact of High Immunopeptidome Divergence between Single Class I HLA-Mismatches on Survival after Unrelated Donor Transplantation. Crivello P, Arrieta-Bolaños E, He M, Wang T, Fingerson S, Gadalla S, Paczesny S, Marsh SGE, Lee SJ, Spellman SR, Bolon YT, Fleischhauer K. **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 SJ, Spellman SR, 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. Turcotte LM, Wang T, Beyer KM, Cole SW, Spellman SR, Allbee-Johnson M, Williams E, Zhou Y, Verneris MR, Rizzo JD, Knight JM. **Submitted.** ***Dr. Jennifer Knight will present at 13:40***

n. **IB19-04** HLA Class I genotype is associated with relapse risk after allogeneic stem cell transplantation for NPM1-mutated AML**.** Narayan R, Niroula A, Wang T, Kuxhausen M, He M, Meyer E, Chen Y-B, Bhatt VR, Beitinjaneh A, Nishihori T, Sharma A, Brown VI, Kamoun M, Diaz MA, Abid MB, Askar M, Kanakry CG, Gragert L, Bolon YT, Marsh SGE, Gadalla SM, Paczesny S,

Spellman SR, Lee SJ. **Submitted.**

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

Dr. Shahinaz Gadalla reviewed the voting and prioritization guidelines.

Proposal presentations (3)

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

Dr. Rohtesh Mehta presented this proposal. The hypothesis is that among patients without HLA-matched donors, a younger mismatched unrelated donor (MMUD) would yield better outcomes with improved survival and lower risk of GVHD and non-relapse mortality than an older haploidentical donor, especially in older patients undergoing allogeneic HCT with PTCy-based GVHD prophylaxis. If the hypothesis is confirmed, a young MMUD could be preferentially selected over an older Haplo donor.

Previous CIBMTR studies showed the probability of aGVHD3-4 increased significantly with increasing of donor age. Donor age is the only donor-related factor that predicted outcomes. Increasing of donor age is associated with worse OS, higher risk of aGVHD2-4, aGVHD3-4, and NRM, in both Haplo and MMUD settings.

Multiple studies showed survival benefit with donor age < 30-35 years old compared to older donors, and the latest NMDP prospective trial in MMUD HCT showed age above 35 years has worse outcomes. Therefore, a cut-off age of 35 years old was chosen. We categorized the donor age group as older (>35 years old), and younger (<=35 years old).

The CIBMTR identified 4250 patients who underwent first HSCT with PTCy-based GVHD prophylaxis from older Haplo donor and 725 younger MMUD donor, from 2008-2020. The following questions were answered during the Q&A:

Q: For this proposal, should we look at four survival curves (older Haplo vs. older MMUD vs. younger Haplo vs. younger MMUD), not only two?
A: The reason to specifically study younger MMUD vs. older haplo is because this is the usual choice for older patients. The interest in comparing similarly aged haplo vs mismatched donor was less but could be addressed in the proposal.

Q: Some of the studies suggested age 35 as a cut-off, but not all data says that, suggested including all age range. Studies suggest haplo transplantation isn't any faster than matched unrelated transplant. This is an opportunity to explore

the donor age question with more granularity than using age 35 split and restricting to younger MMUD and older haplo
A. The protocol can specify that we will first do an analysis to determine the appropriate age cutoff, in case it is different than age 35.

Q: There is a non-monotonic increasing of aGHVD with age, encourage to do biological assessment by access repository samples to see if age might contribute to the increasing of aGVHD. Not every old person is the same, some of older people stay young for a long time.
A: Dr. Gadalla and the team looked at the biological rationale that increasing the donor age associated with the outcomes in aplastic anemia. Agree not fully understood outside of aplastic anemia.

Q: In the real world, using a haplo donor is cheaper than using an unrelated donor. Consider costs of transplant, since the search for UD is quite costly.
A: Great question, the cost question is different and outside the scope of this current proposal.

Q: A Hopkins paper found that recipient age might change the effect of donor age. Also, I had a similar proposal in GVHD, which looking at sibling donor, haplo, and MUD. Wondering on resource utilization would it make sense to put together with our study to make more efficient?
A: The proposed study is limited to the question of a younger MMUD vs. older haplo.

Q: What is the degree of mismatch in MMUD group?
A: The majority of the patients are 6/8 or more, and if we have enough patients to adjust for individual level of mismatches, especially B leader and class II mismatches, those adjustments should definitely be considered.

Q: Donor age in a haplo setting has the factor of relationship. For example, the sibling vs. offspring vs. parents, how would you account for this?
A: We have the donor-recipient relationship for some patients and can do a subset analysis in the group where relationship is known.

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

Dr. Katharina Fleischhauer presented this proposal. Haploidentical donors with PTCy-based GVHD prophylaxis is increasingly being used to treat hematologic patients, and had similar 3-year survival with MUD transplant. Recent studies showed there is no association with number or locus of mismatched HLA in the haplo setting. The recent CIBMTR study published on Blood also showed the B-

Leader match and non-permissive DPB1 mismatch in haplo donor group had better OS.

A previous study explored the role of DPB1 mismatches and showed that non-permissive mismatches had higher immunopeptidome divergence. Due to different peptide binding groups leading to different peptide binding motifs, many immunopeptidome differences are recognized by alloreactive T-cell receptors. In the permissive setting, peptide grooves are similar, leading to low divergence of immunopeptidomes a little recognition. The recent IB20-01 study showed that this concept can be utilized for single HLA class I 9/10 mismatches. HvG directional mismatches and PBM matched group had better outcomes than the non-permissive mismatches and GvH direction mismatches in the URD group with CNI-based GVHD prophylaxis.

The hypothesis is: Survival after Haplo-HCT with PTCy GvHD prophylaxis is predicted by the number and directionality of PBM mismatches on the unshared haplotype. We will determine the number and direction of PBM matches or mismatches at HLA-A, -B, -C, and -DRB1 in haploidentical pairs. Matched alleles on the unshared haplotypes of patient and donor will be classified as PBM matches. We also consider the non-permissive mismatches in directionality based on PBM groups.

The CIBMTR identified 4,748 patients who underwent first HSCT with PTCy-based GVHD prophylaxis Haplo patients with AML, ALL, MDS and 2,034 8/8 MUD patients as reference. The following questions were answered during the Q&A:

Q: In your paper, there are a number of unassigned immunopeptidomes, but a lot of alleles belong to the P groups, and you can make assumptions that they have the same immunopeptidomes that could help to score and be informative. Regarding the DQB1 adjustment, wonder if you should consider Effie's presentation on DQ groups, if indeed there will be lower and higher affinity, like DQ alpha that contributed to mismatches? Otherwise will you consider DR4 or DR11 as much as DQB1?
A: I agree with P groups you can do that, and we did that in the IB20-01 study, considered them as not non-informative. On the DQ question, I agree, we could use Effie's models. And we will have the DR-3, -4, -5 data.

Q: Do you have idea how many mismatches in the haplo setting will be PBM matched? Also, could look at GVL effects.
A: We will have a range from zero to many PBM matches since there are more loci, but we will look at the number of PBM mismatches to see if it plays a role.

Q: Wondering if mismatches on surface residues could induce tolerance? Do you think location might modulate effect of immunopeptidome?
A: Hard to study and we don't know. We will build on our other studies in which immunopeptidome mismatches drive strong alloreactivity. Clinical data have not been obtained in the PTCy setting.

ii. **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 presented this proposal.

This combined proposal will evaluate: 1) Impact of functional inhibitory killer cell immunoglobulin-like receptors (CF iKIR) score on haploidentical transplant outcomes. 2) Evaluate the role of missing recipient's KIR ligand (HLA-C-group), and the presence of recipient's B-leader allotype regulating the interaction of NKG2A/HLA-E on clinical outcomes in patients who underwent haplo-HSCT with PTCy.

The CIBMTR identified 1,449 patients who underwent first haplo HSCT with PTCy-based GVHD prophylaxis from 2015-2021, and the donor DNA or blood samples are available for KIR typing. The following questions were answered during the Q&A:

Q: Since half of patients are AML, and regarding the Measurable residual disease (MRD) reporting, there is a lot of heterogeneity. Are you going to consider MRD in the analysis?
A: It is possible that patients who are MRD positive with high CF-iKIR may have lower relapse. Our proposal included other malignant diseases, e.g. lymphomas and others. We can include MRD status in the analysis if data are available.

Q: In mice and humans you can relicense or re-educated NK cells if you put them in a new MHC environment. Haplo transplants take NK cells uneducated based on the HLA and KIR genotyping from donors and places them into recipients with educating ligands. In that situation you will have now increase relicensing. You may see effects against the tumor targets low in class I, against the AML, and not so much in other diseases. In your single center haplo study, did you see effects across all diseases? Also, wonder if PTCy is changing the equation.

A: We did not look into disease type. AML is the majority and can driven the result. In the unrelated donor CIBMTR/EBMT cohort, all are MDS and secondary AML patients. For our study, we can extend to MDS and myelodysplastic

malignancies. We may look separately because Solomon's project aims to look at lymphoid and myeloid malignancies separately.

Q: Other comment on M/T dimorphism. There is an association with homozygosity for HLA C2, curious about how to study B -leader mismatch in haplos as well as the ligands when there is a skewed distribution.
A: The recent finding on B-leader has shown better outcomes if matched, believe it should be included in the multivariate analysis along with CF-iKIR. And maybe will do another CART analysis to see which one is more important in donor selection.

b. **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)***

Dr. Yung-Tsi Bolon gave a brief update on the status of the resources and data available via the CIBMTR Research Repository. The sample inventory included related and unrelated donor and recipients pairs available from 1988 to 2021.

5. Associated molecular genetic data resources update **Yung-Tsi Bolon** 12:55pm-13:10PM

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 provided an update on DISCOVeRY-BMT Study.

Phase I included two cohorts of >2,500 8/8 HLA matched unrelated donor and recipient pairs (>5,000 samples) for AML, ALL, MDS, which funded by an R01 grant from NHLBI. We also had an R03 funding to do a nested case-control GWAS study of inherited susceptibility to AML/MDS/ALL. We were able to run exome chip with ~2% coverage.

The second phase is ongoing. There are over 5,500 8/8 HLA matched related and unrelated donor and recipient pairs (>11,000 samples) included. This is funded by an R01 from NCI. We are able to do whole exome sequencing (WES, ~99% exome coverage) and meta-GWAS including data from phase 1 plus additional CIBMTR D-R pairs. All the sequencing will be done via CIDR (Center for Inherited Disease Research) X01 mechanism (X01 HG011126). Data will be available in dbGaP or contact Dr. Hahn or Steve Spellman for data reuse.

We also have several primary papers, collaboration papers and abstracts by using the cohorts mentioned above.

b. **IB10-01 and IB17-03** NCI-CIBMTR Collaborative Molecular Studies in HCT.

Dr. Shahinaz Gadalla provided an update on the NCI-CIBMTR Collaborative Molecular Studies in HCT. She introduced the IB10-01 series studies, focused on exploring transplant outcomes in aplastic anemia (TOAA), which started with ~350 recipient-donor pairs. The hypothesis is the telomere abnormalities in recipients and/or donors may play a role in HCT outcomes in patients with severe aplastic anemia (SAA). Now this study is one of the world's largest SAA cohorts, including 800 recipient-donor pairs. We received the clinical data from the CIBMTR, and we generated/arrayed the genomic data, including qPCR telomere length for the 800 recipient-donor pairs, Flow FISH Telomere Length for a subset of 197 donors, MethylationEpic array for donors and post-HCT, Illumina OmniExpress genotyping array and whole exome sequencing for all 800 recipients.

We published several papers and verified some key findings in different aspects through the past years, including biomarkers of cellular aging that predict outcomes after HCT independent of age, Germline Genetic Analysis Provide Insights in Patient Care, and Genotyping Array & other studies.

Another example is the IB17-03 series studies that focus on myelofibrosis etiology and HCT outcomes. This study including 937 patients, and we completed the illumina global screening array, PacBio sequencing for JAK2, and measured telomere length (qPCR), and now the samples are under exome sequencing. This study has been presented in ASH, that showed the JAK2 mutation/allele burden did not affect the OS, NRM or relapse, no matter whether primary myelofibrosis or Post Polycythemia Vera MF. But for the Post Essential Thrombocythemia MF, >=60% mutation/allele burden JAK2 was association with the increased risk of NRM.

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 | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR.***

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** 13:10PM-13:55PM

Dr. Steven Marsh noted there are 10 studies in progress this year.

a. **IB20-04** Haploidentical versus matched unrelated donor transplants using post-transplant cyclophosphamide for lymphomas.

Dr. Yung-Tsi Bolon provided an update on IB20-04. This study was published in the JTCT in Dec 2022. This study is a joint study between CIBMTR and EBMT, looking for Haploidentical vs. matched unrelated donor transplants using post-transplant cyclophosphamide for lymphomas. The hypothesis of this study is post-transplant cyclophosphamide (PTCy)-based GVHD prophylaxis strategy could neutralize differences between HLA haploidentical related donors and matched unrelated donors in allogeneic hematopoietic transplant outcomes for lymphomas. This is based on a previous study that showed haplo with PTCy has the same OS as MUD HCT with standard GVHD prophylaxis. The cohort included adult patients with HD/NHL, undergoing 1st allo HCT using PTCy only, either 8/8 allele matched URDs or haplo donors, from 2010-2019. There were 1843 Haplo patients and 313 8/8 MUD patients identified. The conclusions are: 1) PTCy was not able to neutralize differences between MUD and Haplo donors. 2) When using PTCy, MUD 8/8 has better outcomes in terms of OS, PFS, NRM, aGVHD grade 2-4, aGVHD grade 3-4, cGVHD, neutrophil and platelet recovery. 3) Whenever available in a timely manner, a MUD 8/8 should still be preferred over Haplo donor when using PTCy. The following questions were answered during the Q&A:
Q: Did the MUD also receive PTCy?
A: Yes, they all received PTCy.

b. **IB18-02** Pathogenicity and impact of HLA class I alleles in aplastic anemia patients of different ethnicities.

c.

Dr. Daria Babushok provided an update on IB18-02. Acquired aplastic anemia (AA) is an autoimmune bone marrow failure disorder caused by T lymphocyte–mediated attack on hematopoietic stem and progenitor cells (HSPCs). Antigenic target(s) of the autoimmune attack remain unknown, and triggers and specific mechanisms of autoimmunity in AA remain poorly understood. Somatic inactivation of HLA alleles without any other mutations was sufficient for clonal expansion in AA, indicating that it was the loss of targeted alleles that created the survival advantage of HLA allele–lacking hematopoietic cells. The targeted alleles have been presumed to be responsible for AA autoantigen presentation in the affected patients; henceforth these will

be referred to as “risk alleles”. This study analyzed HLA mutations in >500 patients performed in collaboration with CIBMTR and NAPAAC to identify the risk alleles.

The conclusions are: 1) HLA class I alleles are a key predisposition factor for AA. 2) Knowledge of HLA risk alleles opens the door to uncovering antigenic targets and molecular mechanisms of AA. 3) HLA risk alleles are the first connection between immunogenetics and malignant evolution in autoimmune disease. 4) HLA alleles likely underlie some of the differences in AA patient outcomes in different ethnic groups. The following questions were answered during the Q&A:

Q: Not very familiar with HLA mutations, what is the racial/ethnicity makeup of the cohort?
A: We have multiple patient populations in the analysis. For the mutation analysis (separate from association analysis) we tried to enrich individuals where we accrue, chosen to be as diverse as possible and enriched in other alleles. For association analysis, we matched racial and ethnic group and geographic distribution as able.

Q: Did you have a chance to look at T cell receptors of bone marrow graft patients? And would it be an approach to do a mismatched transplantation where we removed risk alleles to reduce AA?
A: Regarding the T cell receptors question, we are actively doing this study. If there were a public T-cell receptor that recognized this autoantigen would expect aplastic anemia to be much more common. There is no public clonal type that easily found, but perhaps there are some new approaches with convergence and we can find a signature.
Second question regarding the mismatch for HLA. We looked at it, and the haplo as exploratory analysis. There are very few patients, so we did not see any differences within limited cohorts.

Q: Did you look at DR15 in these patients?
A: DR15 is one of the Class II alleles, and we only focused on class I in this study. Previously we had a single center cohort, and we did nwhole exome sequencing. In that setting we did not see any DR15, even targeted sequencing still did not see it. Maybe because of the cohort patients, or because of the mechanism or could be an antigen presenting cell is absent.

Q: HLA-B*14:02 is most common in middle eastern ancestry and in Mexico, and high frequency for people do not know they have Jewish ancestry. Do you have a chance to see the high incidence of this among the populations?
A: We looked at the analysis by race/ethnicity, and we did see the HLA-B*14:02 absent in Asians which was one of key alleles strongly driving AA. We saw the association within the Native American, the African American, the Hispanic population. We only used the CIBMTR dataset, wasn't really looking at the National registries. We did see the HLA-B*14:02 across the race/ethnicity, except Asian.

d. **IB20-03** Donor socioeconomic status as a predictor of recipient mortality following hematopoietic cell transplantation for hematologic malignancy.

Dr. Jennifer Knight provided an update on IB20-03. The hypothesis is the SES and SES-related pro-inflammatory gene expression patterning (CTRA) in donors would be associated with inferior recipient HCT outcomes . Donor-recipient pairs identified with AML, ALL, MDS received HCT from 2000-2013 with unrelated 8/8 HLA-matched PBSCs, had Valid U.S. residential address (at least ZIP code) for recipient and donor geocoding from the time of stem cell donation or transplantation. The aims are: 1) Explore 2,005 Donor-recipient pairs for SES-clinical outcomes; 2) Subset 263 donor-recipient biospecimen pairs (whole blood) for CTRA-clinical outcomes. The results showed the higher SES composite score (more disadvantage) was associated with lower OS and increased risk of TRM. No significant association between donor standardized SES composite score and DFS, relapse, acute GVHD (grade 2-4 or 3-5) or chronic GVHD. Recipient standardized SES composite score was not significantly associated with any HCT Outcomes (OS, DFS, TRM, relapse, acute GVHD or chronic GVHD). Greater CTRA expression in donor blood samples was associated with reduced OS (HR=1.94/CTRA SD, 95% CI [1.01, 3.71], p=0.046). CTRA (53-gene profile) not associated with donor SES, but other CTRA biology components were, and the recipient CTRA was not associated with clinical outcomes. In conclusion, this is the first study to demonstrate an association between donor socioeconomic disadvantage and SES-related biology and adverse recipient HCT outcomes. These findings are independent of recipient SES. Donor socioeconomic disadvantage may be more impactful than that of the recipient. This study suggests biologic impact of SES on hematopoietic cells that is transferrable from HCT donor to recipient. The following questions were answered during the Q&A:

Q: Do you know if any data that CTRA correlates SES with thymic function?
A: I can't cite offhand, but it is interesting looking at SES because it reflects chronic cumulative stress. There are very few physiologic functions that seem don’t affect particularly immune-related.

Comments: It is important to see how we implement/respond to this data. Because this data showed the SES significantly impacts on NRM, maybe similar to what donor age impacts on outcomes. It has significant social implications on how we chose the donors, so need to be cautious about how we apply this information to policy changes.

Q: What is the correlation between SES and CTRA levels in the population?
A: We typically see it is not a linear correlation. When we divided by quartiles, we found the lower quartile is most different than others. When we do the analysis for TRM, we compared the 5%tile vs 95%tile treatment difference in CTRA expression here not two group comparison.

Q: What is the likely dominant component driving the TRM? Infections or organ dysfunction?
A: Don't entirely know, need to look at cause of death.

8. Closing Remarks **Stephanie Lee** 13:55PM

Dr. Stephanie Lee adjourned the meeting and thanked members for attending.

Working Committee Overview Plan for 2023-2024

Study number and title	Current status	Chairs priority
IB16-02 Use of HLA structure and function parameters to understand the relationship between HLA disparity and transplant outcomes.	Manuscript Preparation	4
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.	Manuscript Preparation	3
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	4
IB18-07 Donor and recipient genomic associations with acute GVHD	Analysis	2
IB20-03 Donor socioeconomic status as a predictor of altered immune function and treatment response following hematopoietic cell transplantation for hematologic malignancy	Submitted	2
IB21-01 Effect of HLA evolutionary divergence on survival and relapse following allogeneic hematopoietic cell transplant.	Manuscript Preparation	4
IB22-01 Impact of HLA-DPB1 matching on survival following unrelated donor transplantation with post transplant cyclophosphamide for adults with hematologic malignancies.	Protocol Development	3
IB22-02 Effect of SIRPα mismatch on the outcome of allogeneic hematopoietic stem cell transplantation from an HLA matched related donor.	Data File Preparation	1
IB23-01 Immunopeptidome divergence between mismatched HLA and outcome of haploidentical HCT.	Protocol Pending	3
IB23-02 Younger MMUD vs older haploidentical donor HCT.	Protocol Pending	1

Field	Response
Proposal Number	2310-92-ALI
Proposal Title	Impact of different HLA alleles on GVHD and GVL after sex mismatched allo-HCT
Key Words	Sex mismatch, HLA, graft-vs-host-disease, relapse, post-transplant cyclophosphamide, abatacept, matched donors
Principal Investigator #1: - First and last name, degree(s)	Alaa Ali, MD
Principal Investigator #1: - Email address	alaa.ali@gunet.georgetown.edu
Principal Investigator #1: - Institution name	Georgetown Lombardi Comprehensive Cancer Center
Principal Investigator #1: - Academic rank	Assistant Professor
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	No
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Scott Rowley, MD
Principal Investigator #2 (If applicable): - Email address:)	scott.rowley@hmhn.org
Principal Investigator #2 (If applicable): - Institution name:	Georgetown Lombardi Comprehensive Cancer Center
Principal Investigator #2 (If applicable): - Academic rank:	Professor
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No
If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:	Yes, I am a junior investigator and would like assistance identifying a senior mentor for my project
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	Outcomes of CD19 CAR-T in patients who received lymphodepleting chemotherapy using fludarabine-containing versus other regimens. co-PI
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Immunobiology
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No
RESEARCH QUESTION:	Is GVHD risk or GVL effect in HLA matched but sex mismatched transplants dependent on specific HLA alleles? Is there a specific organ predilection for acute or chronic GVHD in sex mismatched transplants?
RESEARCH HYPOTHESIS:	The increased risk of chronic GVHD (and possibly acute GVHD) after sex mismatched transplants is dependent on specific HLA alleles and has different organ predilection compared to cGVHD in sex matched transplants.

Field	Response
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	Primary: Compare the cumulative incidence rate and severity of acute and chronic GVHD after HLA matched but sex mismatched (male to female: M-to-F, female to male: F-to-M) transplants based on different HLA-A, -B, -C, -DR, DQ, DP alleles in patients with AML or MDS undergoing allo HCT Secondary: -Evaluate the risk of relapse in sex mismatched transplants based on different HLA alleles. - Determine the organ predilection of chronic GVHD in sex mismatched transplants. - Evaluate the impact of post-transplant cyclophosphamide on GVHD and relapse after sex mismatched transplants compared to other GVHD prevention strategies, such as calcineurin inhibitors/methotrexate.
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	If the aim of the project is completed, it will provide treating clinicians with evidence on the interplay between specific HLA alleles and the risk of GVHD (particularly chronic) following HLA matched but sex mismatched transplants. This can be helpful in donor selection when multiple HLA matched but sex mismatched donors are available. This will confirm recent research findings using large registry data and expand our mechanistic understanding of GVHD. Defining the impact of emerging GVHD prevention strategies such as PTCy on the risk of GVHD in sex mismatched transplants will also have clinical implications for donor selection in the modern transplant era.

Field	Response
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.	Sex mismatch, particularly female to male, has been long identified as a risk factor for chronic GVHD.[1-3] Alloimmunity to minor histocompatibility antigens, such as H-Y antigens encoded on the male-specific region of the Y-chromosome, has been implicated in the complex pathogenesis of cGVHD in these transplants.[4] The detection of alloantibodies directed against H-Y antigens after F-to-M patients has been shown to predict cGVHD and disease remission durability.[1, 2] Nevertheless, the exact mechanism by which H-Y antigens serve as a target for alloimmunity has remained unclear. Most recently, it has been shown that specific HLA class II alleles might influence the development of cGVHD in F-to-M transplants using the Japanese national database.[5] HLA/H-Y antigen complexes were detected on dermal vascular endothelial cells in patients with cGVHD as well as on some leukemic cells,[5] providing some insights into the potential mechanisms of cGVHD and GVL effect. Using data from larger and more ethnically diverse registries to confirm these findings and identify other HLA alleles will have clinical implications for donor selection and research implications for future mechanistic studies. PTCy is being increasingly used for non-haploidentical transplants, including transplants from HLA matched unrelated donors.[6] Most of the studies that associated sex mismatch with chronic GVHD examined patients who received traditional GVHD prevention strategies such as calcineurin inhibitor/methotrexate combination. Whether PTCy can mitigate the risk of cGVHD while maintaining the GVL effect in HLA matched but sex mismatched transplants is unknown and can be clinically relevant. Finally, H-Y antigens have tissue-specific expression.[7, 8] This may lead to different organ predilection of cGVHD following transplants from sex mismatched donors compared to other cGVHD. Corroborating the presence or absence of such an organ predilection in sex mismatched transplants will provide new insights for future mechanistic cGVHD studies.
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Inclusion criteria: - Age 18 or older - Patients who underwent allo HCT from a HLA matched (related or unrelated) but sex mismatched donor. - Any underlying disease, conditioning, GVHD prophylaxis regimen Exclusion criteria: - Patients who underwent allo HCT from mismatched donors, haploidentical or umbilical cord blood - Younger than 18
Does this study include pediatric patients?	No

Field	Response
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	Form 2005 (Confirmation of HLA Typing) - Recipient and donor HLA type - HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DQ, HLA-DP antigens Form 2400 (pre-transplant essential data) - Recipient information: Sex, ethnicity, race, age - Donor: only HLA matched, related or unrelated. - Donor information: sex - Product type (bone marrow, PBSC) - Preparative regimen (myeloablative, non-myeloablative, reduced intensity) - GVHD prophylaxis regimen Form 2402 (pre-TED Disease Classification) - Primary disease for HCT Form 2450 (post-transplant essential data), Form 2100 (post-HSCT data), Form 2900 (recipient death data) • aGVHD occurrence, persistence, grade and organ stage at diagnosis, maximum grade and stage, organ involvement at time of maximum grade • cGVHD occurrence, persistence, maximum grade, steroids treatment, other immunosuppressants, organ involvement at time of maximum grade • Relapse or progression post infusion • Survival status • Primary cause of death

Field	Response
REFERENCES:	1. Miklos DB, Kim HT, Miller KH, Guo L, Zorn E, Lee SJ, Hochberg EP, Wu CJ, Alyea EP, Cutler C et al: Antibody responses to H-Y minor histocompatibility antigens correlate with chronic graft-versus-host disease and disease remission. Blood 2005, 105(7):2973-2978. 2. Nakasone H, Tian L, Sahaf B, Kawase T, Schoenrock K, Perloff S, Ryan CE, Paul J, Popli R, Wu F et al: Allogeneic HY antibodies detected 3 months after female-to-male HCT predict chronic GVHD and nonrelapse mortality in humans. Blood 2015, 125(20):3193-3201. 3. Paul J, Nakasone H, Sahaf B, Wu F, Wang K, Ho V, Wu J, Kim H, Blazar B, Ritz J et al: A confirmation of chronic graft-versus-host disease prediction using allogeneic HY antibodies following sex-mismatched hematopoietic cell transplantation. Haematologica 2019, 104(7):e314-e317. 4. Popli R, Sahaf B, Nakasone H, Lee JY, Miklos DB: Clinical impact of H-Y alloimmunity. Immunol Res 2014, 58(2-3):249-258. 5. Umino K, Morita K, Ikeda T, Kawaguchi SI, Nagayama T, Ito S, Minakata D, Ashizawa M, Yamamoto C, Hatano K et al: Antibody-mediated pathogenesis of chronic GVHD through DBY/HLA class II complexes and induction of a GVL effect. Blood 2023, 142(11):1008-1021. 6. Bolaños-Meade J, Hamadani M, Wu J, Al Malki MM, Martens MJ, Runaas L, Elmariah H, Rezvani AR, Gooptu M, Larkin KT et al: Post-Transplantation Cyclophosphamide-Based Graft-versus-Host Disease Prophylaxis. N Engl J Med 2023, 388(25):2338-2348. 7. Godfrey AK, Naqvi S, Chmátal L, Chick JM, Mitchell RN, Gygi SP, Skaletsky H, Page DC: Quantitative analysis of Y-Chromosome gene expression across 36 human tissues. Genome Res 2020, 30(6):860-873. 8. Ditton HJ, Zimmer J, Kamp C, Rajpert-De Meyts E, Vogt PH: The AZFa gene DBY (DDX3Y) is widely transcribed but the protein is limited to the male germ cells by translation control. Hum Mol Genet 2004, 13(19):2333-2341.
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Selection Criteria:

- First allo HCT with AML, MDS from 2015-2021
- Adults only
- PBSC or BM
- 12/12 matched unrelated or related donors
- Donor and recipient sex mismatched.

Selection Criteria*	**Included**
First allogeneic transplant from 2015 to 2021 for AML, MDS	N = 40,130
Adults only	N = 37,178
Marrow or PBSC	N = 35,453
12/12 matched unrelated or related donors	N = 5,730
Consent and non-embargoed centers	N = 5253
Donor and recipient sex mismatched	**N = 2,380**

Prop 2310-92 Table 1 Adult patients with AML, MDS received 1st allo 12/12 Mathced HCT from 2015-2021, donor and recipient sex mismatch.

	Male-Female	**Female-Male**
Variable	**N (%)**	**N (%)**
Number of patients	1341	1039
Number of centers	156	134
Disease at transplant		
AML	968 (72)	717 (69)
MDS	373 (28)	322 (31)
AML Disease status at transplant		
CR1	718 (74)	527 (74)
CR2	122 (13)	88 (12)
CR3+	2 (<1)	3 (<1)
Advanced or active disease	126 (13)	99 (14)
MDS Disease status at transplant		
Early	59 (16)	46 (14)
Advanced	309 (83)	272 (84)
Missing	5 (1)	4 (1)
Recipient race group		
White	1154 (86)	871 (84)
Black or African American	37 (3)	42 (4)
Asian	57 (4)	47 (5)
Native Hawaiian or other Pacific Islander	5 (<1)	5 (<1)
American Indian or Alaska Native	4 (<1)	4 (<1)
More than one race	7 (1)	4 (<1)
Missing	77 (6)	66 (6)
Recipient ethnicity		
Hispanic or Latino	81 (6)	88 (8)
Non Hispanic or non-Latino	1139 (85)	874 (84)
Non-resident of the U.S.	87 (6)	59 (6)

Variable	Male-Female N (%)	Female-Male N (%)
Missing	34 (3)	18 (2)
Recipient age at transplant		
18-29 years	100 (7)	70 (7)
30-39 years	115 (9)	79 (8)
40-49 years	171 (13)	105 (10)
50-59 years	320 (24)	236 (23)
60-69 years	493 (37)	428 (41)
70+ years	142 (11)	121 (12)
Median (Range)	59 (18-79)	61 (18-78)
Recipient sex		
Male	0	1039 (100)
Female	1341 (100)	0
Graft type		
Marrow	151 (11)	70 (7)
PBSC	1190 (89)	969 (93)
HCT-CI		
0	243 (18)	208 (20)
1	182 (14)	147 (14)
2	186 (14)	160 (15)
3+	715 (53)	513 (49)
Missing	15 (1)	11 (1)
Donor group		
HLA-identical sibling	524 (39)	657 (63)
Other related	25 (2)	19 (2)
Well-matched unrelated	792 (59)	363 (35)
Conditioning regimen		
MAC	652 (49)	503 (48)
RIC/NMA	685 (51)	536 (52)
Missing	4 (<1)	0
donor age at transplant		
<18 years	7 (1)	8 (1)
18-29 years	592 (44)	289 (28)
30-39 years	232 (17)	130 (13)
40-49 years	137 (10)	111 (11)
50+ years	373 (28)	501 (48)
Missing	32 (12-79)	48 (14-78)
12/12 match degree		
12	1341 (100)	1039 (100)
GvHD Prophylaxis		
None	11 (1)	2 (<1)
Ex-vivo T-cell depletion	9 (1)	5 (<1)
CD34 selection	7 (1)	9 (1)
PtCy + other(s)	187 (14)	147 (14)
PtCy alone	12 (1)	9 (1)

Variable	Male-Female N (%)	Female-Male N (%)
FK506 + MMF +- others	145 (11)	76 (7)
FK506 + MTX +- others(not MMF)	628 (47)	531 (51)
FK506 +- others(not MMF,MTX)	130 (10)	105 (10)
FK506 alone	44 (3)	25 (2)
CSA + MMF +- others(not FK506)	59 (4)	47 (5)
CSA + MTX +- others(not MMF,FK506)	87 (6)	70 (7)
CSA +- others(not FK506,MMF,MTX)	1 (<1)	0
CSA alone	8 (1)	3 (<1)
Other(s)	13 (1)	10 (1)
Donor/Recipient CMV serostatus		
+/+	487 (36)	400 (38)
+/-	81 (6)	150 (14)
-/+	469 (35)	245 (24)
-/-	302 (23)	237 (23)
Missing	2 (<1)	7 (1)
Year of transplant		
2015	144 (11)	120 (12)
2016	185 (14)	119 (11)
2017	185 (14)	136 (13)
2018	205 (15)	168 (16)
2019	213 (16)	153 (15)
2020	207 (15)	161 (15)
2021	202 (15)	182 (18)
Follow-up among survivors, Months		
N Eval	754	545
Median (Range)	39 (0-101)	38 (0-99)

Field	Response
Proposal Number	2310-84-ZOU
Proposal Title	Impact of molecular disparity of HY antigens on cGVHD and relapse risks in male recipients receiving allogeneic HSCT from a female HLA-matched related donor
Key Words	HY molecular mismatch and cGVHD, relapse
Principal Investigator #1: - First and last name, degree(s)	Jun Zou, MD. PhD
Principal Investigator #1: - Email address	jzou@mdanderson.org
Principal Investigator #1: - Institution name	The University of Texas MD Anderson Cancer Center, Houston, TX
Principal Investigator #1: - Academic rank	Associate Professor
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Samer Srour, MD
Principal Investigator #2 (If applicable): - Email address:)	SSrour@mdanderson.org
Principal Investigator #2 (If applicable): - Institution name:	The University of Texas MD Anderson Cancer Center, Houston, TX
Principal Investigator #2 (If applicable): - Academic rank:	Assistant Professor
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	IB22-01: Impact of HLA-DPB1 Mismatching on Clinical Outcomes of Unrelated Donor Blood or Marrow Transplantation with and without Post-Transplant Cyclophosphamide for Hematologic Malignancies. Role: Co-PI IB22-02 Effect of SIRPα mismatch on the outcomes of allogeneic hematopoietic stem cell transplantation (HSCT) from an HLA-matched related donor (MRD). Role: Co-PI
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Immunobiology
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No
RESEARCH QUESTION:	Whether the Predicted Indirectly Recognizable HY Epitope (PIRCHyE) scores (PS) can predict clinical outcomes of HLA-matched related hematopoietic stem cell transplantation (HSCT) from gender-mismatched donors.

Field	Response
RESEARCH HYPOTHESIS:	With the advancements in molecular typing and protein modeling, we can now assess alloreactivity at the molecular level, focusing on specific allogeneic targets. In the context of allogeneic HSCT involving a female donor and a male recipient (FtoM), we hypothesize the following: 1. T-cell-mediated alloreactivity originating from Y chromosome-encoded antigens, quantified by PS, is predictive for transplant clinical outcomes. 2. A high PS-II score, indicating CD4+ T-cell alloreactivity, is associated with an increased risk of chronic graft-versus-host disease (cGVHD) and a reduced risk of relapse. 3. A significant correlation exists between higher PS-II/PS-I ratio and the risk of cGVHD, relapse, and progression-free survival. It's important to note that these associations are expected to be absent in the other 2 allogenic HSCT control groups, the MtoF gender-mismatched group, and the gender-matched group.
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	Primary objectives: To investigate the impact of HY alloreactivity predicted by PS on the risk of cGVHD in male patients who received an allogeneic HSCT from a female HLA-matched related donor. Secondary objectives: To study and validate the association of PS and clinical outcomes in allo-HSCT. We will assess the following clinical endpoints. 1. Cumulative incidence of relapse 2. Cumulative incidence of grades II-IV and III-IV acute GVHD at Day 100 and overall 3. Progression-free survival (PFS) 4. Cumulative incidence of non-relapse mortality (NRM) 5. Overall survival (OS)

Field	Response
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	HY antigens, unique minor histocompatibility antigens encoded by the Y chromosome, are potential immunological targets in FtoM allo-HSCT, which has been reportedly associated with a higher risk of cGVHD along with reduced risk of relapse. Yet, the mechanism behind T-cell responses elicited by HY antigens remains unclear. Our single institution study on patients transplanted from an HLA-matched donors revealed that the influence of HY antigen in FtoM HSCT is dependent on the recipient/donor HLA molecules' capacity to present HY allo-peptides to donor T cells (Saliba et al, manuscript submitted). The molecular mismatch algorithm, PIRCHyE allows for high-throughput screening of HY-derived immunogenic peptides specific to recipient/donor HLA molecules, providing a quantitative assessment of immunogenicity and predictive insights into clinical impacts. A comprehensive registry study validating the algorithm in allo-HSCT with gender-mismatched donors is essential, as the results could assist in donor selection and risk stratification.

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.	Several studies showed that allo-HSCT from a female donor to a male recipient is generally associated with an increased risk of GVHD and NRM. As a result, the European Group for Blood and Marrow Transplantation has integrated female-to-male (FtoM) transplants into its risk score calculations (1,2), and the prevalence of FtoM transplants has decreased in their registry (3). In the United States, many allo-HSCT programs aim to minimize the use of female donors when possible (4). In our recent study (Saliba et al, manuscript submitted), however, we found that the risk associated with the HY antigen in FtoM allo-HSCT may vary depending on the capacity of the individual HLA molecules presenting HY antigens to the donor T cells. HY antigens, which are minor histocompatibility antigens originating from specific regions of the Y chromosome, serve as immunogenic targets in FtoM allo-HSCT. T-cell clones that recognize the HY-specific antigens or peptides were identified to be associated with increased cGVHD but a protective effect on relapse (5). Additionally, Miklos et al. detected allogeneic HY antibodies and HY antigen-binding B cells in FtoM allo-HSCT recipients and demonstrated a coordinated B-cell and T-cell response against HY antigens during the development of cGVHD (6-8). However, the exact mechanism by which HY-derived allo-peptides stimulate T-cell responses and the subsequent cascade of events remains poorly understood. The diverse peptide-binding specificities of HLA molecules and the extensive HLA polymorphism can result in a variety of alloimmune responses which could impact transplant outcomes among patients exposed to HY antigens. Nevertheless, the use of traditional cytotoxic function assays can identify only a limited number of HLA-restricted HY antigens, which would be insufficient to perform a thorough analysis of the inter-individual alloimmune responses to HY antigens in FtoM allo-HSCT. Recent advancements have significantly improved our understanding of how HLA molecules bind to peptides. These breakthroughs have led to the development of several molecular mismatch methods that enable us to quantitatively evaluate the immunogenicity resulting from mismatched HLA molecules in transplantation (9-13). In our recent study (Saliba et al, manuscript submitted), we introduced a molecular mismatch approach named PIRCHyE to assess alloreactivity based on HY-derived peptides presented by specific HLA molecules in each allo-HSCT pair. In theory, the PIRCHyE-I score (PS-I) calculates the HLA class I binders, reflecting indirect alloreactivity from CD8+ T cells. Conversely, the PIRCHE-II score (PS-II) estimates the immunopeptides bound to HLA class II molecules, which are related to

Field	Response
	levels of indirect CD4+ T-cell response after allo-HSCT. In a retrospective cohort of patients who underwent FtoM allo-HSCT from HLA-matched related donors, we investigated the clinical implications of PIRCHyE score in 712 patients undergoing allo-HSCT from an HLA-matched related donor, including 336 gender-mismatched HSCT. Higher PS-II, is correlated with a reduced disease progression (HR=0.4; P=0.04) and an increased chronic GVHD risk (HR=1.9; P=0.03) in the FtoM group (N=194) but not in MtoF group (n=142) (Figure 1A-B). To further explore the interplay between CD4 T-helper cell responses (PS-II) and CD8 cytotoxic effects (PS-I), we assessed the impact of the PS-II/PS-I ratio and found that a higher ratio was associated with the increased risk of cGVHD (HR 2.2; P =0.003) and the protective effect on relapse (HR 0.2; P=0.02), which translated into an improved PFS (HR 0.4; P=0.02) in multivariate analysis (Figure 2A-D). These findings indicate that molecular assessment of HY antigens may enable quantitative prediction of HY alloreactivity (Figure 3A). Additionally, it is also suggested that the alloresponse may depend on achieving a balanced equilibrium between CD4+ and CD8+ responses. In simpler terms, the significant clinical aGVHD occurs when an intermediate ratio is achieved, indicating a substantial presence of both class II and class I epitopes. Conversely, the collective immune response leading to aGVHD weakens when there is an insufficient number of either CD4 class II epitopes or CD8 class I epitopes. However, in cases where the number of CD4 class II epitopes remains high while the number of class I epitopes is low, the clinical response appears to align with effects that require only a CD4 T-cell response, which subsequently leads to cGVHD and the activation of humoral immunity (Figure 3B). This algorithm holds promise for simplifying donor selection and reducing the complications associated with allo-HSCT. Hence, a comprehensive registry-based study is essential to confirm our findings from the single-institution study.
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Id	F_3hirs3g3R8qEOcl
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Name	Figures.jpg
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Size	4874397
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Type	image/jpeg

Field	Response
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	All patients with hematological malignancies (AML/MDS/ALL) who underwent a first HSCT from an HLA matched related donor from January 2010 to December 2021 and reported to CIBMTR will be included. The patients who received post-transplant cyclophosphamide (PTCy) as GVHD prophylaxis will be excluded from the study.
Does this study include pediatric patients?	Yes
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	PRIMARY ENDPOINTS: - Chronic graft-versus-host disease (cGVHD) SECONDARY ENDPOINTS: - Acute GVHD at day 100 (II-IV) - Relapse - Overall survival (OS) - Disease-free survival (DFS) - Non-relapse mortality (NRM) - Cumulative incidence of neutrophil and platelet engraftment VARIABLES TO BE ANALYZED Patient-related: − Age: continuous and <18 vs. 18-29 vs. 30-39 vs. 40-49 vs. 50-59 vs. ≥ 60 − Gender: male vs. female − Karnofsky score: <90 vs. 90-100% − Hematopoietic Cell Transplantation- Comorbidity Index (HCT-CI) Score: 0, 1, 2 and ≥3 Disease-related: − Diagnosis: AML vs. MDS vs. ALL − Disease status at transplant: early vs. advanced; (complete remission vs. minimal residual disease or active disease) − Disease Risk Index: Low or intermediate vs. High or very high risk Transplant-related: − Donor and recipient HLA typing − Year of transplant: 2010-2021 − Conditioning regimen: myeloablative vs. reduced intensity and TBI vs non-TBI-based − GVHD prophylaxis (tacrolimus/methotrexate; tacrolimus /MMF; others) − Donor-recipient cytomegalovirus serostatus match: P/P, P/N, N/P, N/N − Donor-recipient gender match: M/M, M/F, F/M, F/F − Donor age- continuous − Source of stem cells: (BM vs PBSC)
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 desc	NA
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	NA

Field	Response
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 o	NA
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.	NA

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Field	Response
	P. E., Goldberg, A., Karpinski, M., Shaw, J., Rush, D. N., and Nickerson, P. W. (2019) HLA-DR/DQ molecular mismatch: A prognostic biomarker for primary alloimmunity. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 19, 1708-1719 12. Wiebe, C., Rush, D. N., Nevins, T. E., Birk, P. E., Blydt-Hansen, T., Gibson, I. W., Goldberg, A., Ho, J., Karpinski, M., Pochinco, D., Sharma, A., Storsley, L., Matas, A. J., and Nickerson, P. W. (2017) Class II Eplet Mismatch Modulates Tacrolimus Trough Levels Required to Prevent Donor-Specific Antibody Development. J Am Soc Nephrol 28, 3353-3362 13. Ayuk, F., Bornhauser, M., Stelljes, M., Zabelina, T., Wagner, E. M., Schmid, C., Christopeit, M., Guellstorf, M., Kroger, N., and Bethge, W. (2019) Predicted Indirectly ReCognizable HLA Epitopes (PIRCHE) Are Associated with Poorer Outcome after Single Mismatch Unrelated Donor Stem Cell Transplantation: A Study of the Cooperative Transplant Study Group (KTS) of the German Group for Bone Marrow and Stem Cell Transplantation (DAG-KBT). Transfus Med Hemother 46, 370-375
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Selection Criteria:

- First allo HCT with AML, ALL, MDS from 2010-2021
- PBSC or BM
- Matched related donors (HLA-identical siblings and other related donors)
- CNI based GVHD prophylaxis.

Selection Criteria*	**Included**
First allogeneic transplant from 2015 to 2021 for AML, ALL, MDS	N = 87,643
Marrow or PBSC	N = 81,081
Matched related donors	N = 7,944
CNI based GVHD prophylaxis	N = 7,018
Consent and non-embargoed centers	N = 6,434

Prop2310-84 Table 1 Patients with AML, ALL, MDS received 1st allo MRD HCT using CNI based from 2010-2021.

Variable	**N (%)**
Number of patients	6434
Number of centers	233
Disease at transplant	
AML	3379 (53)
ALL	1605 (25)
MDS	1450 (23)
AML Disease status at transplant	
CR1	2288 (68)
CR2	479 (14)
CR3+	23 (1)
Advanced or active disease	582 (17)
Missing	7 (<1)
ALL Disease status at transplant	
CR1	1052 (66)
CR2	398 (25)
CR3+	63 (4)
Advanced or active disease	92 (6)
MDS Disease status at transplant	
Early	253 (17)
Advanced	1176 (81)
Missing	21 (1)
Recipient race group	
White	5160 (80)
Black or African American	345 (5)
Asian	443 (7)
Native Hawaiian or other Pacific Islander	31 (<1)
American Indian or Alaska Native	30 (<1)
More than one race	46 (1)
Missing	379 (6)

Variable	N (%)
Recipient ethnicity	
Hispanic or Latino	1039 (16)
Non Hispanic or non-Latino	4943 (77)
Non-resident of the U.S.	333 (5)
Missing	119 (2)
Recipient age at transplant	
0-9 years	351 (5)
10-17 years	392 (6)
18-29 years	650 (10)
30-39 years	590 (9)
40-49 years	854 (13)
50-59 years	1577 (25)
60-69 years	1733 (27)
70+ years	287 (4)
Median (Range)	53 (0-79)
Recipient sex	
Male	3663 (57)
Female	2771 (43)
Graft type	
Marrow	1014 (16)
PBSC	5420 (84)
HCT-CI	
0	1730 (27)
1	989 (15)
2	924 (14)
3+	2744 (43)
Missing	47 (1)
Donor group	
HLA-identical sibling	6151 (96)
Other related	283 (4)
Conditioning regimen	
MAC	4157 (65)
RIC/NMA	1868 (29)
Missing	409 (6)
Donor age at transplant	
<18 years	653 (10)
18-29 years	683 (11)
30-39 years	651 (10)
40-49 years	932 (14)
50+ years	3404 (53)
Missing	111 (2)
Median (Range)	52 (1-79)
8/8 match degree	
8	6434 (100)
GvHD Prophylaxis	

Variable	N (%)
FK506 + MMF +- others	629 (10)
FK506 + MTX +- others(not MMF)	3749 (58)
FK506 +- others(not MMF,MTX)	810 (13)
FK506 alone	136 (2)
CSA + MMF +- others(not FK506)	256 (4)
CSA + MTX +- others(not MMF,FK506)	782 (12)
CSA +- others(not FK506,MMF,MTX)	4 (<1)
CSA alone	68 (1)
Donor/Recipient CMV serostatus	
+/+	2743 (43)
+/-	619 (10)
-/+	1663 (26)
-/-	1332 (21)
Missing	77 (1)
Donor/Recipient sex match	
Male-Male	1976 (31)
Male-Female	1401 (22)
Female-Male	1687 (26)
Female-Female	1370 (21)
Year of transplant	
2010	275 (4)
2011	313 (5)
2012	400 (6)
2013	527 (8)
2014	727 (11)
2015	724 (11)
2016	744 (12)
2017	634 (10)
2018	662 (10)
2019	568 (9)
2020	417 (6)
2021	443 (7)
Follow-up among survivors, Months	
N Eval	3306
Median (Range)	60 (0-161)

Field	Response
Proposal Number	2310-164-ARRIETA-BOLAŃOS
Proposal Title	6-locus HLA immunopeptidome divergence and outcome of mismatched unrelated HCT
Key Words	mismatched unrelated HCT, immunopeptidome, permissive mismatches, peptide-binding motif groups, HLA-DPB1 T-cell epitope groups
Principal Investigator #1: - First and last name, degree(s)	Esteban Arrieta-Bolaños
Principal Investigator #1: - Email address	esteban.arrieta-bolanos@uk-essen.de
Principal Investigator #1: - Institution name	Institute for Experimental Cellular Therapy, University Hospital Essen
Principal Investigator #1: - Academic rank	PhD
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	No
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Katharina Fleischhauer
Principal Investigator #2 (If applicable): - Email address:)	katharina.fleischhauer@uk-essen.de
Principal Investigator #2 (If applicable): - Institution name:	Institute for Experimental Cellular Therapy, University Hospital Essen
Principal Investigator #2 (If applicable): - Academic rank:	Professor
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No
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:	Esteban Arrieta-Bolaños
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	IB19-01c: PI (EAB) and Co-PI (KF)
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Immunobiology
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No

Field	Response
RESEARCH QUESTION:	Over the last years, the HLA immunopeptidome, i.e. the repertoire of peptides displayed in the antigen recognition domain (ARD) of HLA molecules, has been identified as a key player for the clinical outcome of allogeneic hematopoietic cell transplantation (HCT) 1 2. The emerging picture suggests that the degree of immunopeptidome overlap between mismatched HLA molecules, which can be approximated by structurally and functionally defined T cell epitope (TCE) groups for HLA-DPB1, or peptide binding motif (PBM) groups for HLA-A,B,C, determines the strength of clinically relevant T-cell alloreactivity. For HLA-DPB1, this is at the basis of the established concept of permissive vs non-permissive mismatches after HLA-matched unrelated donor (MUD) HCT 3 4 5. For HLA class I, the CIBMTR study IB20-01 showed that PBM mismatches in the graft-versus-host (GvH) vector are associated with significantly worse overall survival (OS) compared to PBM-GvH matches in patients receiving HCT from unrelated donors with a single disparity at HLA-A, -B or -C 2. In the ongoing study IB23-01, this concept has been extended to include also HLA-DRB1, and is being explored in the context of haploidentical HCT under GvHD prophylaxis with post-transplant cyclophosphamide (PTCy). However, HCT from unrelated donors with multiple HLA mismatches (MMUD) are increasingly being used in clinical practice, on the basis of promising results from prospective clinical trials 6 7 8 9. In this setting, the relevance of the immunopeptidome divergence for transplant outcome has not been explored yet. Moreover, the previous (IB20-01) and ongoing (IB23-01) CIBMTR studies treated HLA class I PBM mismatches separately from HLA-DPB1 TCE mismatches, and did not include analysis of HLA-DQB1. Here, we propose to perform a comprehensive investigation of the role of immunopeptidome divergence for mismatches over all 6 HLA loci in the outcome of MMUD.
RESEARCH HYPOTHESIS:	We hypothesize that the number and/or directionality of HLA mismatches with high immunopeptidome divergence, i.e., PBM mismatches for HLA-A, -B, -C, -DRB1, -DQB1 and TCE non-permissive mismatches for HLA-DPB1, is associated with higher risks for patients treated for hematopoietic malignancies by MMUD.

Field	Response
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	The main objective of the present proposal is to investigate the association between the number and/or directionality of HLA mismatches with high immunopeptidome divergence, i.e., PBM mismatches for HLA-A, -B, -C, -DRB1, -DQB1 and TCE mismatches for HLA-DPB1 with clinical outcome of MMUD. Primary endpoint will be overall survival (OS); secondary endpoints will include relapse-free survival (RFS), transplant-related mortality (TRM), acute and chronic GVHD, and relapse.
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	MMUD-HCT is increasingly being used to facilitate access to transplant for patients with HLA types underrepresented in donor registries and higher genetic diversity, with promising results 6 7. Of note, accepting the use of MMUD essentially eliminates the matching likelihood gap between ethnic groups 10. In this setting, PTCy is nowadays often preferred as GvHD prophylaxis over conventional calcineurin inhibitor (CNI)-based regimens on account of the reduced risks when using PTCy. Hence, it is expected that MMUD HCT will grow in the near future. However, it is currently not known if selection of specific, better tolerated permissive mismatches could further improve outcome in these patients. Permissive mismatches in MMUD have been proposed to consist in allele pairs with identical ARD 11 or certain combinations statistically associated with outcome 12. For HLA-DPB1, conflicting results were obtained regarding the role of permissive TCE mismatches, with significant outcome associations in 7/8 matched unrelated HCT observed in one 3 but not another 4 study. Recently, PBM-GvH mismatches were associated with mortality risks after single HLA class I mismatched unrelated HCT und GvHD prophylaxis by CNI 2. These data suggest that immunopeptidome divergence of mismatched HLA, observed as driver of permissiveness for HLA-DPB1 TCE groups 1, is a mechanism relevant also for other HLA loci. However, its role in MMUD with multiple mismatches across all 6 HLA loci, has not been defined, nor have associations been comparatively assessed in transplants performed under PTCy or CNI GvHD prophylaxis. The present study will address these gaps, with findings that are expected to have a direct impact both on our understanding of the mechanisms underlying clinically relevant T-cell alloreactivity, and on clinical patient care, especially in diverse populations likely to benefit from MMUD HCT.

Field	Response
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.	For studies IB20-01 and IB23-01, we generated PBM classifications for 186 HLA-A,-B,-C, and -DRB1 alleles, occurring 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, based on publicly available immunopeptidome data 13 14 15. These data include also immunopeptidomes from 10 HLA-DQB1 dimerized with different DQA1 allotypes, which will allow us to generate a comprehensive panel of PBM groups also for HLA-DQ. For HLA-DPB1, we will utilize the previously described TCE classification 16, including the latest refinements to TCE group 3 obtained in study IB19-01b 5. Based on this, we will determine the number and direction of mismatches with high immunopeptidome divergence at the 6 HLA loci in MMUD-HCT. Since study IB20-01 included MMUD with a single disparity at HLA-A, -B, or -C, but did not consider immunopeptidome divergence for HLA-DP, we will include all transplants with at least two disparities at HLA-A, -B, -C, -DRB1, -DQB1 or -DPB1 (excluding however MUD with 2 HLA-DPB1 disparities). The number of mismatched HLA alleles will be included as a co-variate in multivariate analysis. HLA loci involving alleles with unknown PBM group assignment will not be considered, and the number of informative loci for each patient will also be included as co-variate in the multivariate analysis. We will then stratify the pairs according to the number of mismatches with high immunopeptidome divergence, considering also directionality and locus specificity (HLA class II only mismatches vs others). The group of MMUD with the lowest number of high immunopeptidome mismatches will be used as reference. as well as potentially 8/8 MUD in post-hoc analysis. If possible, subgroup analyses will be performed for MMUD with conventional GvHD prophylaxis or with PTCy. If the number of informative pairs is not sufficient, we will include the type of GvHD prophylaxis as additional co-variate in the multivariate analysis and/or test interactions.

Field	Response
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Patients will be included according to the following criteria: • Patients treated for ALL, AML, or MDS • Adult and pediatric patients • First allogeneic transplant • Bone marrow or peripheral blood as stem cell source • MMUD with at least 2 HLA disparities for HLA-A, -B, -C, -DRB1, -DQB1 or -DPB1 • HLA-A,-B,-C-,DRB1, -DQB1, -DPB1 typing available at 2nd field • Transplants performed 2010-2020 • RIC or MAC conditioning • GvHD prophylaxis PTCy, CNI or other Exclusion Criteria: • Ex-vivo T-cell depletion (e.g. CD34 selection, CD3 depletion)
Does this study include pediatric patients?	Yes
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	Main effect: • Immunopeptidome overlap between mismatched HLA-A, -B, -C, -DRB1, -DQB1 (PBM groups) and HLA-DPB1 (TCE groups) alleles in patient and donor (based on 2nd field HLA typing, scoring to be performed by PI) 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 • 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. -/-) • Number of mismatched HLA alleles • Number of HLA-A,-B,-C,-DRB1-DQB1 mismatches without PBM assignment • GvHD prophylaxis PTCy vs other (if no separate subgroup analysis)
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 desc	Not required.
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	Not required.

Field	Response
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 o	Not applicable.
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.	Not applicable.

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Field	Response
	associated with decreased risk of relapse: implications for the molecular mechanism. Blood. 2009;113(12):2851-2858. 13. Gfeller D, Bassani-Sternberg M. Predicting Antigen Presentation-What Could We Learn From a Million Peptides? Front Immunol. 2018;9:1716. 14. Racle J, Guillaume P, Schmidt J, et al. Machine learning predictions of MHC-II specificities reveal alternative binding mode of class II epitopes. Immunity. 2023. 15. Gfeller D, Schmidt J, Croce G, et al. Improved predictions of antigen presentation and TCR recognition with MixMHCpred2.2 and PRIME2.0 reveal potent SARS-CoV-2 CD8(+) T-cell epitopes. Cell Syst. 2023;14(1):72-83 e75. 16. Crivello P, Zito L, Sizzano F, et al. The impact of amino acid variability on alloreactivity defines a functional distance predictive of permissive HLA-DPB1 mismatches in hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2015;21(2):233-241.
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Selection Criteria:

- First allo HCT with AML, ALL, MDS from 2010-2020
- PBSC or BM
- <=10/12 MMUD
- CNI based or PTCy as GVHD prophylaxis

Selection Criteria*	**Included**
First allogeneic transplant from 2010 to 2020 for AML, ALL, MDS	N = 80,115
Marrow or PBSC	N = 74,888
<=10/12 MMUD	N = 8,907
CNI based or PTCy as GVHD prophylaxis	N = 8,531
Consent and non-embargoed centers	N = 7,903
6-locus HLA typing available	N = 7,258

Prop2310-164 Table 1 Patients with AML, ALL, MDS received <= 10/12 MMUD 1st allo from 2010-2020.

Variable	**N (%)**
Number of patients	7258
Number of centers	225
Disease at transplant	
AML	4027 (55)
ALL	1522 (21)
MDS	1709 (24)
AML Disease status at transplant	
CR1	2541 (63)
CR2	696 (17)
CR3+	36 (1)
Advanced or active disease	732 (18)
Missing	22 (1)
ALL Disease status at transplant	
CR1	958 (63)
CR2	376 (25)
CR3+	85 (6)
Advanced or active disease	102 (7)
Missing	1 (<1)
MDS Disease status at transplant	
Early	314 (18)
Advanced	1356 (79)
Missing	39 (2)
Recipient race group	
White	6178 (85)
Black or African American	391 (5)
Asian	220 (3)
Native Hawaiian or other Pacific Islander	17 (<1)
American Indian or Alaska Native	26 (<1)
More than one race	48 (1)
Missing	378 (5)
Recipient ethnicity	
Hispanic or Latino	670 (9)
Non Hispanic or non-Latino	6041 (83)
Non-resident of the U.S.	411 (6)
Missing	136 (2)

Variable	N (%)
Recipient age at transplant	
0-9 years	314 (4)
10-17 years	375 (5)
18-29 years	715 (10)
30-39 years	707 (10)
40-49 years	904 (12)
50-59 years	1538 (21)
60-69 years	2122 (29)
70+ years	583 (8)
Median (Range)	55 (0-83)
Recipient sex	
Male	4091 (56)
Female	3167 (44)
Graft type	
Marrow	1630 (22)
PBSC	5628 (78)
HCT-CI	
0	1749 (24)
1	1038 (14)
2	1119 (15)
3+	3312 (46)
Missing	40 (1)
Donor group	
Well-matched unrelated (8/8)	4724 (65)
Partially-matched unrelated (7/8)	2423 (33)
Mis-matched unrelated (<= 6/8)	111 (2)
Conditioning regimen	
MAC	4301 (59)
RIC/NMA	2182 (30)
Missing	775 (11)
Donor age at transplant	
<18 years	1 (<1)
18-29 years	4093 (56)
30-39 years	1811 (25)
40-49 years	989 (14)
50+ years	357 (5)
Missing	7 (<1)
Median (Range)	29 (18-61)
12/12 match degree	
5	1 (<1)
6	3 (<1)
7	13 (<1)
8	143 (2)
9	1210 (17)
10	5888 (81)
GvHD Prophylaxis	
PtCy + other(s)	832 (11)
PtCy alone	44 (1)
FK506 + MMF +- others	923 (13)
FK506 + MTX +- others(not MMF)	3800 (52)
FK506 +- others(not MMF,MTX)	450 (6)
FK506 alone	173 (2)
CSA + MMF +- others(not FK506)	360 (5)

Variable	N (%)
CSA + MTX +- others(not MMF,FK506)	622 (9)
CSA +- others(not FK506,MMF,MTX)	11 (<1)
CSA alone	43 (1)
Donor/Recipient CMV serostatus	
+/+	2196 (30)
+/-	820 (11)
-/+	2466 (34)
-/-	1729 (24)
Missing	47 (1)
Donor/Recipient sex match	
Male-Male	2820 (39)
Male-Female	1890 (26)
Female-Male	1271 (18)
Female-Female	1277 (18)
Year of transplant	
2010	512 (7)
2011	579 (8)
2012	607 (8)
2013	701 (10)
2014	722 (10)
2015	720 (10)
2016	653 (9)
2017	667 (9)
2018	704 (10)
2019	739 (10)
2020	654 (9)
Follow-up among survivors, Months	
N Eval	3268
Median (Range)	61 (0-152)

Field	Response
Proposal Number	2308-05-ASQUITH
Proposal Title	Effect of donor KIR and donor KIR ligand on CD8+ T cell-mediated alloreactivity in unrelated HSCT for AML, ALL and MDS
Key Words	CD8+ T cells, inhibitory killer-cell immunoglobulin like receptor (iKIR)
Principal Investigator #1: - First and last name, degree(s)	Becca Asquith BSc, MSc, PhD
Principal Investigator #1: - Email address	b.asquith@imperial.ac.uk
Principal Investigator #1: - Institution name	Imperial College London
Principal Investigator #1: - Academic rank	Professor
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	Yes
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	none
PROPOSED WORKING COMMITTEE:	Immunobiology
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	Yes
If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:	Martin Maiers, Steve Spellman and Yung-Tsi Bolon
RESEARCH QUESTION:	Does donor iKIR-donor ligand genotype, specifically the count of donor iKIR-ligand gene pairs, determine CD8+ T cell-mediated risk of GVHD and risk of relapse in unrelated HSCT.
RESEARCH HYPOTHESIS:	We have recently shown that an individual's iKIR-ligand genotype (specifically the count of iKIR-ligand gene pairs) is a highly significant determinant of memory CD8+ T cell lifespan in vivo [1]. We have also shown that this same metric determines CD8+ T cell-mediated control of 3 unrelated chronic virus infections (HIV-1, HCV and HTLV-1) as well as determining the risk of type I diabetes [2, 3]. We hypothesise that, in the context of unrelated HSCT, donors with a high count of iKIR-ligand pairs will have T cells with a survival advantage leading to better CD8+ T cell reconstitution in recipients. We hypothesise this will increase the risk of GVHD but decrease the risk of relapse of malignancy.
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	1: Does count of donor iKIR-ligand gene pairs determine risk of acute GVHD? 2: Does count of donor iKIR-ligand gene pairs determine risk of chronic GVHD? 3: Does count of donor iKIR-ligand gene pairs determine risk of relapse? 4: Does count of donor iKIR-ligand gene pairs determine the rate of CD8+ T cell reconstitution?

Field	Response
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	If we find that donor iKIR-ligand genotype is a significant determinant of the risk of GVHD and the risk of relapse then this will provide a rationale for donor selection. For example, in the case of aggressive leukemia with high risk of relapse, a donor with high count of iKIR-ligand gene pairs could be selected. The study of KIR in HSCT has been very frustrating with hints of effects that are then not reproduced even in well-powered studies. We believe that this may be due to looking at the right data in the wrong way. We hope that, by shifting the focus to CD8+ T cells, rather than NK cells, we will bring clarity and consistency. More generally, this study will contribute to our understanding of the role of iKIR in determining T cell reconstitution post-transplant and the efficacy of the CD8+ T cell mediated response.

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.	There have been a very large number of studies investigating the impact of KIR on outcome in allo-HSCT. All of these studies have focussed on NK alloreactivity and thus have considered either donor KIR genotype alone e.g. donor KIR B content in the neutral/better/best models [4, 5] or have considered donor-recipient ligand mismatches either with [6] or without [7-9] KIR typing. Furthermore, as the working hypothesis in these existing studies is that these are NK-mediated effects the primary outcome is usually relapse (rather than GVHD and T cell reconstitution) and protocols impacting T cells are not incorporated as interaction effects. Our rationale is completely different: we are interested in the impact of iKIR on the donor CD8+ T cell response. We have a specific hypothesis, motivated by our functional work in humans in vivo including work showing that iKIR-ligand genotype determines CD8+ T cell lifespan [1]; determines clinical outcome in the context of HIV-1, HCV and HTLV-1 infections [2, 3] and also influences the risk of type 1 diabetes (in prep). Our metric (count of iKIR-ligand pairs) is positively correlated with donor KIR B content (we have investigated this correlation in a healthy cohort we hold and find P=0.006, N=423) and so donors with a high count of iKIR-ligand gene pairs will tend to fall into the existing “better” or “best” category. This is interesting since it may explain why the neutral/better/best and KIRB content models are sometimes, but not always, predictive – we suggest neutral/better/best is an imperfect marker of the true determinant: the count of iKIR-ligand gene pairs. More recently, studies have widened the number of iKIR metrics considered, and in some cases have come close to the metric we are proposing. However, since these studies are all based on the assumption of NK cell alloreactivity there are always differences to the metric and/or methodology we propose. For example, Kreiger et al [10] uses a metric that is related to ours nevertheless there are significant differences e.g. we include C2 as a ligand for KIR2DL2 and we don’t include KIR3DL2 as an iKIR as there is considerable information that it behaves differently to KIR2DL1, KIR2DL2/L3 and KIR3DL1. We also include Bw4 motifs on A alleles and C1 motifs on B alleles. Finally, we use donor HLA not recipient HLA in the ligand count, conceptually this latter point is a major difference, though numerically it is unlikely to be important given the high degree of donor-recipient HLA matching. All these differences are reflected in the distribution of the number of iKIR-ligand gene pairs across the population in the Kreiger study which is different to what we see in our cohorts.

	Nevertheless, their calculation of their metric and ours are likely to be correlated (but certainly not identical). It is interesting then that their metric is associated with reduced risk of relapse (P=0.01) and a trend for an increased risk of GVHD (P=0.07); both are in the direction which we would predict mechanistically (donors with higher count of iKIR-ligand genes have longer lived T cells so we would predict higher risk of GVHD but reduced risk of relapse). Another study that explores a similar metric to ours comes from Schleteig et al. [11] Again, as for all existing studies (to our knowledge) they are assuming NK alloreactivity and as such they do not consider GVHD as an outcome nor do they consider interactions with GVHD prophylaxis (which would be expected to be considerable). However, Schleteig et al do find significance for an impact on relapse, again in the direction which we would predict. Interestingly, in their discussion they note that they cannot understand the association since it is in the opposite direction to what they would predict given their assumption of an NK cell-mediated response (why should more inhibition lead to better protective immunity) and they further note that since HLA tends not to be downregulated in MDS it is unclear why NK cells play a role. Both these questions are readily addressed under our interpretation of a CD8+ T cell-mediated effect. Finally, a very recent paper aims to perform a comprehensive analysis of "NK alloreactivity prediction models" [12]. Again, their starting point is an NK-mediated effect, and this affects their metric calculations and methodology. Though perhaps the greatest limitation of this work is cohort size (N=78), which is poorly powered for testing their 27 different models. We hypothesise that repeating these studies with a methodology assuming a CD8+ T cell mediated rather than an NK cell-mediated effect and using the exact metric we have shown determines CD8+ T cell lifespan would strengthen these associations and (with a properly powered design) make them reproducible across cohorts. It would also provide a mechanistic underpinning to the associations which is currently lacking. POWER CALCULATIONS: Outcome=relapse. We use the formula for estimating sample size for Cox Regression from Schoenfeld 1983 [13]. Using a prior estimate of the hazard ratio from Schetelig et al [11] of HR=0.74 then for 80% power at alpha=0.05 (two-sided) we need 541.6 events, assuming a 2 year relapse rate of 29% we need a cohort of N=1868. Based on a table of characteristics of unrelated transplants with KIR data (Martin Maiers 2023) there are three disease groups with a sufficient number of individuals: AML, ALL and MDS. Outcome=cGVHD. The prior data that best matches our study design and metric definition is from

Field	Response
	Kreiger et al [10]. They use count of iKIR-ligand pairs as a continuous variable (in contrast to Schetelig et al who classify people into high or low count). We therefore use the method of Hsieh and Lavori [14] for the sample size calculation. Using the prior estimate of the hazard ratio from Kreiger et al [10] of HR=1.09 and a rate of cGVHD of 0.3 [5] then for 80% power at alpha=0.05 (two-sided) we need a cohort size of 3728. Risk of cGVHD, unlike risk of relapse, is unlikely to depend on disease group (of course we will check this assumption) and so disease group will be included as a covariate and individuals with AML, ALL and MDS pooled giving a cohort size of N=10,662. If we find that risk of cGVHD does depend on disease group then we will stratify by group, calculate the individual p values and then combine them using the methods of Stouffer or Fisher (the AML cohort would also be of sufficient size in a stand alone study, N=6454). Our approach benefits from being driven by an underlying mechanistic hypothesis we will therefore only be testing one metric increasing the power of our study. TEAM: We are a mathematical modelling group with expertise in both KIR and in the human CD8+ T cell response. Due to our background in maths and statistics we will not require any statistical or data analysis support from CIMBTR. HSCT is a new area for us, we are therefore collaborating with Arthi Anand (Consultant Clinical Scientist and Laboratory Director in Histocompatability and Immunogenetics Imperial College Healthcare NHS Trust) and Eduardo Olavvaria (BMT clinical lead Hammersmith Hospital). Drs Anand and Olavarria have considerable practical knowledge of histocompatibility and transplantation as well as extensive links throughout the UK and international H&I community. Their input will help inform study design and will be invaluable in results interpretation. SUMMARY: In summary this is a low cost, low risk, high reward project. We only require existing data and we do not need any statistical support. If our hypothesis is correct, there is the potential that a new way of looking at the same data will help resolve the inconsistency and reproducibility issues that have marked KIR studies in HSCT for over a decade.

Field	Response
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Unrelated donor-recipient pair Donor has been KIR typed (presence/absence is sufficient) Disease: AML, ALL or MDS Graft type: bone marrow or peripheral blood Note: study includes pediatric patients (according to data breakdown provided by Martin Maiers there are 503 recipients under10 years and 735 recipients aged 10-19 years that meet our selection criteria. It would be ideal to include these data if possible to increase sample size but if paediatric data is problematic then we can forgo these data).
Does this study include pediatric patients?	Yes
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	no supplementary data required.
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 desc	no PRO data required.
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	No. A strength of our study is that it is driven by an underlying mechanistic hypothesis. We will therefore only be testing one metric thus eliminating the problem of multiple comparisons and overfitting and increasing the power of our study.
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 o	no biological samples required (only existing data).
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.	not applicable.

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Field	Response
	cell transplantation. Front Immunol, 2023. 14: p. 1028162. 13. Schoenfeld, D.A., Sample-size formula for the proportional-hazards regression model. Biometrics, 1983. 39(2): p. 499-503. 14. Hsieh, F.Y. and P.W. Lavori, Sample-size calculations for the Cox proportional hazards regression model with nonbinary covariates. Control Clin Trials, 2000. 21(6): p. 552-60.
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Criteria:

- First allo HCT with AML, ALL, MDS
- PBSC or BM
- Unrelated donors
- Donor-recipient paired; donors KIR typed.

Selection Criteria*	**Included**
First allogeneic transplant from 2008 to 2021 for AML, ALL, MDS	N = 99,315
Marrow or PBSC	N = 91,520
Unrelated donors and HLA typing available	N = 37,761
Consent and non-embargoed centers	N = 34,051
Paired KIR typing available	**N = 9,102**

Prop2308-05 Table 1 Patients with AML, ALL, MDS received 1st allo URD HCT, KIR typing available.

Variable	**N (%)**
Number of patients	9102
Number of centers	159
Disease at transplant	
AML	5139 (56)
ALL	1898 (21)
MDS	2065 (23)
AML Disease status at transplant	
CR1	2961 (58)
CR2	955 (19)
CR3+	69 (1)
Advanced or active disease	1124 (22)
Missing	30 (1)
ALL Disease status at transplant	
CR1	1140 (60)
CR2	481 (25)
CR3+	113 (6)
Advanced or active disease	164 (9)
MDS Disease status at transplant	
Early	374 (18)
Advanced	1658 (80)
Missing	33 (2)
Recipient race group	
White	8249 (91)
Black or African American	318 (3)
Asian	228 (3)
Native Hawaiian or other Pacific Islander	23 (<1)
American Indian or Alaska Native	39 (<1)
More than one race	56 (1)
Missing	189 (2)
Recipient ethnicity	
Hispanic or Latino	687 (8)
Non Hispanic or non-Latino	8226 (90)
Non-resident of the U.S.	64 (1)
Missing	125 (1)
Recipient age at transplant	
0-9 years	367 (4)

Variable	N (%)
10-17 years	430 (5)
18-29 years	933 (10)
30-39 years	849 (9)
40-49 years	1245 (14)
50-59 years	1993 (22)
60-69 years	2656 (29)
70+ years	629 (7)
Median (Range)	54 (0-84)
Recipient sex	
Male	5138 (56)
Female	3964 (44)
Graft type	
Marrow	1960 (22)
PBSC	7142 (78)
HCT-CI	
0	2410 (26)
1	1318 (14)
2	1345 (15)
3+	3956 (43)
Missing	73 (1)
Donor group	
Well-matched unrelated (8/8)	7462 (82)
Partially matched unrelated (7/8)	1565 (17)
Mismatched unrelated (<= 6/8)	75 (1)
Conditioning regimen	
MAC	5755 (63)
RIC/NMA	3290 (36)
Missing	57 (1)
donor age at transplant	
18-29 years	5126 (56)
30-39 years	2213 (24)
40-49 years	1309 (14)
50+ years	454 (5)
Median (Range)	29 (18-61)
8/8 match degree	
5	3 (<1)
6	72 (1)
7	1565 (17)
8	7462 (82)
GvHD Prophylaxis	
None	16 (<1)
Ex-vivo T-cell depletion	62 (1)
CD34 selection	61 (1)
PtCy + other(s)	284 (3)
PtCy alone	72 (1)
FK506 + MMF +- others	1413 (16)
FK506 + MTX +- others(not MMF)	5081 (56)
FK506 +- others(not MMF,MTX)	608 (7)
FK506 alone	247 (3)
CSA + MMF +- others(not FK506)	503 (6)
CSA + MTX +- others(not MMF,FK506)	581 (6)
CSA +- others(not FK506,MMF,MTX)	21 (<1)
CSA alone	55 (1)

Variable	N (%)
Other(s)	94 (1)
Missing	4 (<1)
Donor/Recipient CMV serostatus	
+/+	2502 (27)
+/-	891 (10)
-/+	3230 (35)
-/-	2397 (26)
Missing	82 (1)
Donor/Recipient sex match	
Male-Male	3830 (42)
Male-Female	2500 (27)
Female-Male	1308 (14)
Female-Female	1464 (16)
Year of transplant	
2008	759 (8)
2009	804 (9)
2010	747 (8)
2011	821 (9)
2012	846 (9)
2013	823 (9)
2014	1178 (13)
2015	1583 (17)
2016	984 (11)
2017	459 (5)
2018	98 (1)
Follow-up among survivors, Months	
N Eval	3547
Median (Range)	93 (0-183)

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	48612	21726	12745
Source of data			
CRF	25221 (52)	8369 (39)	5985 (47)
TED	23391 (48)	13357 (61)	6760 (53)
Number of centers	264	244	382
Disease at transplant			
AML	16913 (35)	8236 (38)	4255 (33)
ALL	7024 (14)	2775 (13)	2038 (16)
Other leukemia	1487 (3)	456 (2)	317 (2)
CML	3553 (7)	1171 (5)	1049 (8)
MDS	7232 (15)	3914 (18)	1638 (13)
Other acute leukemia	535 (1)	263 (1)	146 (1)
NHL	4284 (9)	1493 (7)	940 (7)
Hodgkin Lymphoma	962 (2)	277 (1)	216 (2)
Plasma Cell Disorders, MM	945 (2)	298 (1)	209 (2)
Other malignancies	60 (<1)	14 (<1)	22 (<1)
Breast cancer	7 (<1)	3 (<1)	1 (<1)
SAA	1557 (3)	671 (3)	561 (4)
Inherited abnormalities erythrocyte diff fxn	718 (1)	255 (1)	241 (2)
Inherited bone marrow failure syndromes	36 (<1)	51 (<1)	30 (<1)
Hemoglobinopathies	31 (<1)	31 (<1)	20 (<1)
Paroxysmal nocturnal hemoglobinuria	4 (<1)	10 (<1)	3 (<1)
SCIDs	842 (2)	367 (2)	401 (3)
Inherited abnormalities of platelets	42 (<1)	16 (<1)	12 (<1)
Inherited disorders of metabolism	306 (1)	93 (<1)	153 (1)
Histiocytic disorders	391 (1)	135 (1)	133 (1)
Autoimmune disorders	28 (<1)	19 (<1)	13 (<1)
MPN	1603 (3)	1160 (5)	323 (3)
Others	52 (<1)	18 (<1)	24 (<1)
AML Disease status at transplant			
CR1	9303 (55)	5250 (64)	2139 (50)
CR2	3208 (19)	1365 (17)	838 (20)
CR3+	341 (2)	116 (1)	98 (2)
Advanced or active disease	3877 (23)	1467 (18)	1033 (24)

Refresh date: Dec 2023

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Missing	184 (1)	38 (<1)	147 (3)
ALL Disease status at transplant			
CR1	3513 (50)	1625 (59)	870 (43)
CR2	1996 (28)	707 (25)	587 (29)
CR3+	581 (8)	180 (6)	191 (9)
Advanced or active disease	852 (12)	238 (9)	270 (13)
Missing	82 (1)	25 (1)	120 (6)
MDS Disease status at transplant			
Early	1535 (21)	712 (18)	370 (23)
Advanced	4722 (65)	2956 (76)	921 (56)
Missing	975 (13)	246 (6)	347 (21)
NHL Disease status at transplant			
CR1	613 (14)	290 (20)	133 (14)
CR2	800 (19)	296 (20)	153 (16)
CR3+	371 (9)	131 (9)	86 (9)
PR	449 (11)	111 (7)	94 (10)
Advanced	1959 (46)	637 (43)	440 (47)
Missing	72 (2)	20 (1)	31 (3)
Recipient age at transplant			
0-9 years	3999 (8)	1337 (6)	1694 (13)
10-17 years	3169 (7)	1049 (5)	1203 (9)
18-29 years	5825 (12)	2080 (10)	1687 (13)
30-39 years	5443 (11)	2021 (9)	1476 (12)
40-49 years	7259 (15)	2733 (13)	1823 (14)
50-59 years	9972 (21)	4217 (19)	2181 (17)
60-69 years	10440 (21)	6168 (28)	2185 (17)
70+ years	2505 (5)	2121 (10)	496 (4)
Median (Range)	48 (0-84)	55 (0-82)	42 (0-84)
Recipient race			
White	42622 (91)	19046 (91)	9527 (88)
Black or African American	2298 (5)	894 (4)	609 (6)
Asian	1235 (3)	664 (3)	553 (5)
Native Hawaiian or other Pacific Islander	70 (<1)	33 (<1)	40 (<1)
American Indian or Alaska Native	193 (<1)	96 (<1)	64 (1)
Other	49 (<1)	27 (<1)	28 (<1)
More than one race	285 (1)	129 (1)	62 (1)
Unknown	1860 (N/A)	837 (N/A)	1862 (N/A)
Recipient ethnicity			
Hispanic or Latino	4078 (10)	1642 (8)	1175 (11)
Non Hispanic or non-Latino	36772 (88)	17419 (90)	6776 (64)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Non-resident of the U.S.	882 (2)	297 (2)	2570 (24)
Unknown	6880 (N/A)	2368 (N/A)	2224 (N/A)
Recipient sex			
Male	28201 (58)	12741 (59)	7579 (59)
Female	20411 (42)	8985 (41)	5166 (41)
Karnofsky score			
10-80	17009 (35)	8589 (40)	4027 (32)
90-100	29824 (61)	12491 (57)	8060 (63)
Missing	1779 (4)	646 (3)	658 (5)
HLA-A B DRB1 groups - low resolution			
<=3/6	29 (<1)	97 (<1)	7 (<1)
4/6	265 (1)	112 (1)	60 (1)
5/6	6582 (14)	2447 (12)	1794 (15)
6/6	40711 (86)	17245 (87)	10049 (84)
Unknown	1025 (N/A)	1825 (N/A)	835 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	901 (2)	156 (1)	83 (1)
6/8	1833 (4)	194 (1)	262 (3)
7/8	9074 (19)	2726 (16)	1995 (22)
8/8	35275 (75)	14215 (82)	6922 (75)
Unknown	1529 (N/A)	4435 (N/A)	3483 (N/A)
HLA-DPB1 Match			
Double allele mismatch	11999 (29)	2830 (23)	1168 (25)
Single allele mismatch	22536 (54)	6397 (52)	2444 (52)
Full allele matched	7414 (18)	3115 (25)	1079 (23)
Unknown	6663 (N/A)	9384 (N/A)	8054 (N/A)
High resolution release score			
No	13343 (27)	21647 (>99)	12126 (95)
Yes	35269 (73)	79 (<1)	619 (5)
KIR typing available			
No	34811 (72)	21699 (>99)	12629 (99)
Yes	13801 (28)	27 (<1)	116 (1)
Graft type			
Marrow	16553 (34)	5318 (24)	4980 (39)
PBSC	31958 (66)	16179 (74)	7697 (60)
BM+PBSC	16 (<1)	20 (<1)	5 (<1)
PBSC+UCB	40 (<1)	186 (1)	10 (<1)
Others	45 (<1)	23 (<1)	53 (<1)
Conditioning regimen			
Myeloablative	29377 (60)	11114 (51)	7910 (62)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
RIC/Nonmyeloablative	19007 (39)	10541 (49)	4668 (37)
TBD	228 (<1)	71 (<1)	167 (1)
Donor age at donation			
To Be Determined/NA	788 (2)	1002 (5)	302 (2)
0-9 years	4 (<1)	33 (<1)	1 (<1)
10-17 years	1 (<1)	14 (<1)	1 (<1)
18-29 years	23838 (49)	11625 (54)	5477 (43)
30-39 years	13560 (28)	5555 (26)	3778 (30)
40-49 years	7985 (16)	2666 (12)	2414 (19)
50+ years	2436 (5)	831 (4)	772 (6)
Median (Range)	30 (0-69)	29 (0-89)	32 (4-77)
Donor/Recipient CMV serostatus			
+/+	12113 (25)	6051 (28)	3314 (26)
+/-	5690 (12)	2775 (13)	1552 (12)
-/+	15778 (32)	6481 (30)	3842 (30)
-/-	13788 (28)	5611 (26)	3360 (26)
CB - recipient +	36 (<1)	150 (1)	9 (<1)
CB - recipient -	4 (<1)	44 (<1)	2 (<1)
CB - recipient CMV unknown	0	1 (<1)	0
Missing	1203 (2)	613 (3)	666 (5)
GvHD Prophylaxis			
No GvHD Prophylaxis	176 (<1)	93 (<1)	54 (<1)
TDEPLETION alone	123 (<1)	49 (<1)	64 (1)
TDEPLETION +- other	1101 (2)	304 (1)	392 (3)
CD34 select alone	290 (1)	159 (1)	103 (1)
CD34 select +- other	514 (1)	276 (1)	141 (1)
Cyclophosphamide alone	234 (<1)	88 (<1)	59 (<1)
Cyclophosphamide +- others	3834 (8)	3975 (18)	925 (7)
FK506 + MMF +- others	5440 (11)	2132 (10)	975 (8)
FK506 + MTX +- others(not MMF)	20699 (43)	9116 (42)	3590 (28)
FK506 +- others(not MMF,MTX)	2475 (5)	1310 (6)	486 (4)
FK506 alone	1186 (2)	509 (2)	227 (2)
CSA + MMF +- others(not FK506)	3093 (6)	966 (4)	1044 (8)
CSA + MTX +- others(not MMF,FK506)	6961 (14)	1934 (9)	3484 (27)
CSA +- others(not FK506,MMF,MTX)	1087 (2)	334 (2)	462 (4)
CSA alone	461 (1)	133 (1)	388 (3)
Other GVHD Prophylaxis	758 (2)	292 (1)	216 (2)
Missing	180 (<1)	56 (<1)	135 (1)
Donor/Recipient sex match			
Male-Male	19692 (41)	8442 (39)	4919 (39)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Male-Female	12055 (25)	5123 (24)	2796 (22)
Female-Male	8277 (17)	3895 (18)	2548 (20)
Female-Female	8162 (17)	3546 (16)	2282 (18)
CB - recipient M	18 (<1)	105 (<1)	3 (<1)
CB - recipient F	22 (<1)	90 (<1)	8 (<1)
Missing	386 (1)	525 (2)	189 (1)
Year of transplant			
1986-1990	346 (1)	48 (<1)	103 (1)
1991-1995	1838 (4)	439 (2)	745 (6)
1996-2000	3298 (7)	1184 (5)	1220 (10)
2001-2005	5304 (11)	1084 (5)	1907 (15)
2006-2010	9564 (20)	1926 (9)	1884 (15)
2011-2015	13304 (27)	3591 (17)	2668 (21)
2016-2020	10386 (21)	7188 (33)	2800 (22)
2021-2023	4572 (9)	6266 (29)	1418 (11)
Follow-up among survivors, Months			
N Eval	21810	12456	6004
Median (Range)	55 (0-384)	14 (0-362)	36 (0-385)

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	6329	1790	2251
Source of data			
CRF	4553 (72)	1166 (65)	1090 (48)
TED	1776 (28)	624 (35)	1161 (52)
Number of centers	155	143	227
Disease at transplant			
AML	2405 (38)	618 (35)	733 (33)
ALL	1301 (21)	392 (22)	491 (22)
Other leukemia	98 (2)	30 (2)	37 (2)
CML	136 (2)	37 (2)	58 (3)
MDS	569 (9)	177 (10)	178 (8)
Other acute leukemia	100 (2)	24 (1)	48 (2)
NHL	410 (6)	107 (6)	134 (6)
Hodgkin Lymphoma	103 (2)	27 (2)	36 (2)
Plasma Cell Disorders, MM	38 (1)	12 (1)	13 (1)
Other malignancies	12 (<1)	1 (<1)	3 (<1)
SAA	95 (2)	33 (2)	51 (2)
Inherited abnormalities erythrocyte diff fxn	171 (3)	49 (3)	45 (2)
Inherited bone marrow failure syndromes	6 (<1)	5 (<1)	4 (<1)
Hemoglobinopathies	2 (<1)	1 (<1)	1 (<1)
SCIDs	284 (4)	92 (5)	174 (8)
Inherited abnormalities of platelets	21 (<1)	6 (<1)	10 (<1)
Inherited disorders of metabolism	398 (6)	130 (7)	145 (6)
Histiocytic disorders	108 (2)	30 (2)	53 (2)
Autoimmune disorders	9 (<1)	0	7 (<1)
MPN	53 (1)	16 (1)	20 (1)
Others	10 (<1)	3 (<1)	10 (<1)
AML Disease status at transplant			
CR1	1262 (52)	348 (56)	371 (51)
CR2	642 (27)	158 (26)	192 (26)
CR3+	66 (3)	11 (2)	26 (4)
Advanced or active disease	427 (18)	99 (16)	140 (19)
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	584 (45)	166 (42)	212 (43)
CR2	490 (38)	149 (38)	177 (36)
CR3+	149 (11)	54 (14)	63 (13)
Advanced or active disease	77 (6)	22 (6)	38 (8)
Missing	1 (<1)	1 (<1)	1 (<1)
MDS Disease status at transplant			
Early	175 (31)	42 (24)	72 (40)
Advanced	341 (60)	120 (68)	84 (47)
Missing	53 (9)	15 (8)	22 (12)
NHL Disease status at transplant			
CR1	65 (16)	13 (12)	25 (19)
CR2	76 (19)	24 (22)	35 (26)
CR3+	45 (11)	11 (10)	12 (9)
PR	68 (17)	12 (11)	16 (12)
Advanced	153 (38)	45 (42)	42 (32)
Missing	0	2 (2)	3 (2)
Recipient age at transplant			
0-9 years	1903 (30)	642 (36)	803 (36)
10-17 years	667 (11)	162 (9)	265 (12)
18-29 years	757 (12)	161 (9)	242 (11)
30-39 years	609 (10)	162 (9)	217 (10)
40-49 years	673 (11)	174 (10)	214 (10)
50-59 years	868 (14)	221 (12)	287 (13)
60-69 years	733 (12)	230 (13)	207 (9)
70+ years	119 (2)	38 (2)	16 (1)
Median (Range)	27 (0-85)	24 (0-78)	20 (0-78)
Recipient race			
White	4442 (74)	1250 (74)	1372 (72)
Black or African American	937 (16)	249 (15)	281 (15)
Asian	381 (6)	128 (8)	173 (9)
Native Hawaiian or other Pacific Islander	36 (1)	4 (<1)	19 (1)
American Indian or Alaska Native	59 (1)	17 (1)	23 (1)
Other	1 (<1)	1 (<1)	1 (<1)
More than one race	130 (2)	39 (2)	38 (2)
Unknown	343 (N/A)	102 (N/A)	344 (N/A)
Recipient ethnicity			
Hispanic or Latino	1336 (22)	328 (19)	377 (17)
Non Hispanic or non-Latino	4793 (78)	1367 (80)	1347 (61)
Non-resident of the U.S.	53 (1)	24 (1)	469 (21)
Unknown	147 (N/A)	71 (N/A)	58 (N/A)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Recipient sex			
Male	3511 (55)	1018 (57)	1282 (57)
Female	2818 (45)	772 (43)	969 (43)
Karnofsky score			
10-80	1682 (27)	461 (26)	576 (26)
90-100	4431 (70)	1212 (68)	1479 (66)
Missing	216 (3)	117 (7)	196 (9)
HLA-A B DRB1 groups - low resolution			
<=3/6	167 (3)	93 (7)	63 (3)
4/6	2375 (41)	572 (40)	792 (39)
5/6	2549 (44)	564 (40)	840 (42)
6/6	757 (13)	196 (14)	313 (16)
Unknown	481 (N/A)	365 (N/A)	243 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	2990 (55)	651 (55)	929 (54)
6/8	1301 (24)	276 (23)	413 (24)
7/8	785 (14)	168 (14)	249 (14)
8/8	380 (7)	92 (8)	145 (8)
Unknown	873 (N/A)	603 (N/A)	515 (N/A)
HLA-DPB1 Match			
Double allele mismatch	872 (37)	140 (34)	199 (38)
Single allele mismatch	1244 (53)	231 (56)	278 (52)
Full allele matched	228 (10)	44 (11)	53 (10)
Unknown	3985 (N/A)	1375 (N/A)	1721 (N/A)
High resolution release score			
No	4853 (77)	1740 (97)	2226 (99)
Yes	1476 (23)	50 (3)	25 (1)
KIR typing available			
No	5056 (80)	1784 (>99)	2231 (99)
Yes	1273 (20)	6 (<1)	20 (1)
Graft type			
UCB	5940 (94)	1595 (89)	2112 (94)
BM+UCB	1 (<1)	0	0
PBSC+UCB	357 (6)	186 (10)	125 (6)
Others	31 (<1)	9 (1)	14 (1)
Number of cord units			
1	5293 (84)	0	1880 (84)
2	1034 (16)	0	370 (16)
3	1 (<1)	0	0
Unknown	1 (N/A)	1790 (N/A)	1 (N/A)

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Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Conditioning regimen			
Myeloablative	4111 (65)	1137 (64)	1404 (62)
RIC/Nonmyeloablative	2201 (35)	646 (36)	827 (37)
TBD	17 (<1)	7 (<1)	20 (1)
Donor/Recipient CMV serostatus			
+/+	0	0	1 (<1)
+/-	1 (<1)	0	0
-/-	0	0	1 (<1)
CB - recipient +	3967 (63)	1088 (61)	1365 (61)
CB - recipient -	2259 (36)	638 (36)	812 (36)
CB - recipient CMV unknown	102 (2)	64 (4)	72 (3)
GvHD Prophylaxis			
No GvHD Prophylaxis	24 (<1)	9 (1)	15 (1)
TDEPLETION alone	1 (<1)	0	0
TDEPLETION +- other	27 (<1)	9 (1)	9 (<1)
CD34 select alone	0	2 (<1)	1 (<1)
CD34 select +- other	274 (4)	140 (8)	78 (3)
Cyclophosphamide alone	0	0	1 (<1)
Cyclophosphamide +- others	14 (<1)	10 (1)	12 (1)
FK506 + MMF +- others	1870 (30)	561 (31)	455 (20)
FK506 + MTX +- others(not MMF)	216 (3)	56 (3)	78 (3)
FK506 +- others(not MMF,MTX)	232 (4)	68 (4)	90 (4)
FK506 alone	145 (2)	44 (2)	27 (1)
CSA + MMF +- others(not FK506)	2883 (46)	704 (39)	1083 (48)
CSA + MTX +- others(not MMF,FK506)	101 (2)	29 (2)	52 (2)
CSA +- others(not FK506,MMF,MTX)	342 (5)	116 (6)	228 (10)
CSA alone	51 (1)	18 (1)	68 (3)
Other GVHD Prophylaxis	137 (2)	21 (1)	43 (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	3511 (55)	1018 (57)	1280 (57)
CB - recipient F	2817 (45)	772 (43)	968 (43)
CB - recipient sex unknown	0	0	1 (<1)
Missing	1 (<1)	0	0
Year of transplant			
1996-2000	1 (<1)	2 (<1)	5 (<1)
2001-2005	112 (2)	85 (5)	34 (2)
2006-2010	1849 (29)	428 (24)	603 (27)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
2011-2015	2682 (42)	510 (28)	841 (37)
2016-2020	1340 (21)	528 (29)	551 (24)
2021-2023	345 (5)	237 (13)	217 (10)
Follow-up among survivors, Months			
N Eval	3122	998	1185
Median (Range)	61 (0-196)	43 (0-213)	37 (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	11911	2051	1001
Source of data			
CRF	3933 (33)	566 (28)	332 (33)
TED	7978 (67)	1485 (72)	669 (67)
Number of centers	93	81	68
Disease at transplant			
AML	3939 (33)	666 (32)	340 (34)
ALL	1968 (17)	405 (20)	191 (19)
Other leukemia	224 (2)	42 (2)	19 (2)
CML	359 (3)	50 (2)	26 (3)
MDS	1600 (13)	249 (12)	130 (13)
Other acute leukemia	180 (2)	37 (2)	10 (1)
NHL	994 (8)	177 (9)	84 (8)
Hodgkin Lymphoma	214 (2)	41 (2)	27 (3)
Plasma Cell Disorders, MM	262 (2)	40 (2)	22 (2)
Other malignancies	24 (<1)	1 (<1)	1 (<1)
Breast cancer	1 (<1)	0	0
SAA	565 (5)	89 (4)	41 (4)
Inherited abnormalities erythrocyte diff fxn	488 (4)	72 (4)	22 (2)
Inherited bone marrow failure syndromes	26 (<1)	4 (<1)	4 (<1)
Hemoglobinopathies	185 (2)	36 (2)	18 (2)
Paroxysmal nocturnal hemoglobinuria	1 (<1)	1 (<1)	0
SCIDs	252 (2)	42 (2)	24 (2)
Inherited abnormalities of platelets	11 (<1)	0	0
Inherited disorders of metabolism	23 (<1)	6 (<1)	2 (<1)
Histiocytic disorders	67 (1)	10 (<1)	5 (<1)
Autoimmune disorders	11 (<1)	0	1 (<1)
MPN	498 (4)	82 (4)	34 (3)
Others	19 (<1)	1 (<1)	0
AML Disease status at transplant			
CR1	2615 (66)	463 (70)	219 (64)
CR2	600 (15)	89 (13)	42 (12)
CR3+	47 (1)	12 (2)	2 (1)
Advanced or active disease	669 (17)	97 (15)	77 (23)
Missing	8 (<1)	5 (1)	0

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Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
ALL Disease status at transplant			
CR1	1179 (60)	244 (60)	122 (64)
CR2	576 (29)	109 (27)	47 (25)
CR3+	124 (6)	26 (6)	10 (5)
Advanced or active disease	89 (5)	26 (6)	12 (6)
MDS Disease status at transplant			
Early	278 (17)	33 (13)	23 (18)
Advanced	1270 (79)	203 (82)	101 (78)
Missing	52 (3)	13 (5)	6 (5)
NHL Disease status at transplant			
CR1	197 (20)	41 (23)	18 (21)
CR2	188 (19)	35 (20)	11 (13)
CR3+	104 (11)	21 (12)	6 (7)
PR	69 (7)	13 (7)	6 (7)
Advanced	427 (43)	66 (38)	43 (51)
Missing	5 (1)	0	0
Recipient age at transplant			
0-9 years	1245 (10)	194 (9)	94 (9)
10-17 years	1177 (10)	168 (8)	79 (8)
18-29 years	1376 (12)	274 (13)	106 (11)
30-39 years	922 (8)	177 (9)	104 (10)
40-49 years	1424 (12)	249 (12)	112 (11)
50-59 years	2464 (21)	430 (21)	210 (21)
60-69 years	2761 (23)	472 (23)	252 (25)
70+ years	542 (5)	87 (4)	44 (4)
Median (Range)	49 (0-82)	49 (0-77)	51 (0-83)
Recipient race			
White	8882 (79)	1421 (75)	753 (80)
Black or African American	1569 (14)	277 (15)	112 (12)
Asian	566 (5)	155 (8)	55 (6)
Native Hawaiian or other Pacific Islander	45 (<1)	8 (<1)	2 (<1)
American Indian or Alaska Native	81 (1)	9 (<1)	5 (1)
More than one race	139 (1)	16 (1)	11 (1)
Unknown	629 (N/A)	165 (N/A)	63 (N/A)
Recipient ethnicity			
Hispanic or Latino	2227 (19)	481 (24)	215 (22)
Non Hispanic or non-Latino	9345 (80)	1492 (75)	751 (76)
Non-resident of the U.S.	124 (1)	26 (1)	17 (2)
Unknown	215 (N/A)	52 (N/A)	18 (N/A)
Recipient sex			

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Male	6979 (59)	1202 (59)	585 (58)
Female	4932 (41)	849 (41)	416 (42)
Karnofsky score			
10-80	4292 (36)	833 (41)	423 (42)
90-100	7224 (61)	1155 (56)	527 (53)
Missing	395 (3)	63 (3)	51 (5)
HLA-A B DRB1 groups - low resolution			
<=3/6	2609 (24)	431 (24)	225 (29)
4/6	775 (7)	143 (8)	81 (10)
5/6	227 (2)	45 (3)	24 (3)
6/6	7279 (67)	1166 (65)	444 (57)
Unknown	1021 (N/A)	266 (N/A)	227 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	3245 (31)	533 (31)	269 (38)
6/8	145 (1)	33 (2)	13 (2)
7/8	164 (2)	29 (2)	18 (3)
8/8	7028 (66)	1098 (65)	405 (57)
Unknown	1329 (N/A)	358 (N/A)	296 (N/A)
HLA-DPB1 Match			
Double allele mismatch	11 (<1)	0	1 (<1)
Single allele mismatch	2722 (29)	315 (30)	173 (39)
Full allele matched	6752 (71)	741 (70)	265 (60)
Unknown	2426 (N/A)	995 (N/A)	562 (N/A)
High resolution release score			
No	5794 (49)	2025 (99)	975 (97)
Yes	6117 (51)	26 (1)	26 (3)
Graft type			
Marrow	3434 (29)	469 (23)	281 (28)
PBSC	8370 (70)	1546 (75)	713 (71)
UCB (related)	2 (<1)	15 (1)	0
BM+PBSC	18 (<1)	4 (<1)	1 (<1)
BM+UCB	45 (<1)	12 (1)	2 (<1)
PBSC+UCB	1 (<1)	1 (<1)	4 (<1)
Others	41 (<1)	4 (<1)	0
Conditioning regimen			
Myeloablative	6607 (55)	1121 (55)	518 (52)
RIC/Nonmyeloablative	5242 (44)	915 (45)	464 (46)
TBD	62 (1)	15 (1)	19 (2)
Donor age at donation			
To Be Determined/NA	16 (<1)	5 (<1)	3 (<1)

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Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
0-9 years	828 (7)	129 (6)	47 (5)
10-17 years	928 (8)	148 (7)	66 (7)
18-29 years	2130 (18)	375 (18)	202 (20)
30-39 years	1812 (15)	356 (17)	185 (18)
40-49 years	1911 (16)	335 (16)	148 (15)
50+ years	4286 (36)	703 (34)	350 (35)
Median (Range)	41 (0-82)	40 (0-79)	40 (0-80)
Donor/Recipient CMV serostatus			
+/+	4848 (41)	906 (44)	394 (39)
+/-	1275 (11)	174 (8)	104 (10)
-/+	2998 (25)	494 (24)	260 (26)
-/-	2575 (22)	418 (20)	209 (21)
CB - recipient +	31 (<1)	16 (1)	5 (<1)
CB - recipient -	17 (<1)	12 (1)	1 (<1)
Missing	167 (1)	31 (2)	28 (3)
GvHD Prophylaxis			
No GvHD Prophylaxis	173 (1)	24 (1)	14 (1)
TDEPLETION alone	95 (1)	28 (1)	15 (1)
TDEPLETION +- other	99 (1)	23 (1)	7 (1)
CD34 select alone	83 (1)	23 (1)	11 (1)
CD34 select +- other	91 (1)	28 (1)	9 (1)
Cyclophosphamide alone	76 (1)	11 (1)	8 (1)
Cyclophosphamide +- others	4003 (34)	660 (32)	380 (38)
FK506 + MMF +- others	824 (7)	100 (5)	35 (3)
FK506 + MTX +- others(not MMF)	4204 (35)	641 (31)	344 (34)
FK506 +- others(not MMF,MTX)	839 (7)	306 (15)	72 (7)
FK506 alone	109 (1)	17 (1)	6 (1)
CSA + MMF +- others(not FK506)	241 (2)	43 (2)	19 (2)
CSA + MTX +- others(not MMF,FK506)	731 (6)	95 (5)	53 (5)
CSA +- others(not FK506,MMF,MTX)	82 (1)	10 (<1)	3 (<1)
CSA alone	82 (1)	13 (1)	4 (<1)
Other GVHD Prophylaxis	166 (1)	21 (1)	21 (2)
Missing	13 (<1)	8 (<1)	0
Donor/Recipient sex match			
Male-Male	3957 (33)	728 (35)	338 (34)
Male-Female	2522 (21)	417 (20)	218 (22)
Female-Male	2987 (25)	456 (22)	244 (24)
Female-Female	2393 (20)	421 (21)	195 (19)
CB - recipient M	31 (<1)	17 (1)	3 (<1)
CB - recipient F	17 (<1)	11 (1)	3 (<1)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Missing	4 (<1)	1 (<1)	0
Year of transplant			
2006-2010	600 (5)	71 (3)	62 (6)
2011-2015	3668 (31)	508 (25)	229 (23)
2016-2020	5010 (42)	903 (44)	408 (41)
2021-2023	2633 (22)	569 (28)	302 (30)
Follow-up among survivors, Months			
N Eval	7728	1356	657
Median (Range)	25 (0-150)	24 (0-147)	17 (0-148)

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

IBWC supported studies

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 HLA-DRB1 Hed Is Associated with Improved Survival and Decreased Relapse in Patients with Hematologic Malignancies Following Allogeneic Hematopoietic Stem 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**

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. **Manuscript Preparation**

IB22-03 HLA matched sibling versus well-matched unrelated donor: Update including HLA-DPB1 match status in recipients of allogeneic hematopoietic cell transplantation (Karthik Nath/ Brian Shaffer/ Hannah Choe). The study hypothesized that overall survival (OS) is better with young matched unrelated and alternative donors compared to older aged, matched sibling donors (MSD) in transplant recipients aged ≥ 50-years. Furthermore, the study hypothesized that HLA 8/8 URDs, ≤7/8 mismatched URDs and haploidentical donors that are HLA-DPB1-matched or T-cell epitope functional-distance (TCE-FD) permissive further improves OS versus HLA-DPB1 TCE non-permissive recipients. **Analysis.**

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. **Manuscript Preparation.**

IB23-01 Immunopeptidome divergence between mismatched HLA and outcome of haploidentical HCT. (Pietro Crivello, Katharina Fleischhauer) The main objective of this study 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. **Analysis.**

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. **Data File Preparation.**

IB23-03 Impact of adherence to cord blood guidelines (Leland Metheny/ Filippo Milano) The study hypothesized that adherence to published cord blood guidelines in cord blood transplant (TNC dose, CD34 dose, HLA matching, avoiding anti-thymocyte globulin (ATG), criteria for conditioning intensities) improves clinical outcomes, including disease free survival, non-relapse mortality, relapse free survival, and overall survival when compared to non-adherence to cord blood guidelines.**Protocol Development.**

IB10-01x Monoallelic Germline Pathogenic Variants in DNA Damage Repair Genes and Their Impact on Post-Hematopoietic Cell Transplantation Outcomes in Severe Aplastic Anemia (Maryam Rafati, Shahinaz Gadalla). The study indicated: 1) Pathogenic germline variants in DNA damage response or repair (DDRR) genes may influence the post-HCT outcomes in Severe aplastic anemia patients, as they face substantial stressors that can increase their susceptibility to DNA damage. 2) Patients with pathogenic variants in genes involved in the base excision repair pathway had inferior 1-year overall survival (adjusted HR=2.03, p=0.002), and those carrying variants in ERCC3, FANCD2, or MUTYH, identified as high-risk genes, experienced even worse outcomes (HR=2.74). 3) Germline testing prior to HCT is important to identify patients with pathogenic variants in high-risk DDRR genes, helping determine those who may require tailored conditioning regimens. **Ongoing.**

IB23-02 Younger MMUD vs older haploidentical donor HCT (Rohtesh Mehta) The primary aim of this study is to determine if donor age and type matters when an HLA-mismatched donor is used. This study will focus on two GRFS comparisons: (a) younger MMUD vs older haploidentical donor, and (b) younger haploidentical vs older MMUD groups. Secondary endpoints include acute (II-IV and III-IV) and chronic (overall and systemic therapy-requiring) GVHD, relapse, NRM, PFS, OS and causes of death. **Data File Preparation**.

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**

IB09-06o Genetics and epidemiology of myeloid malignancies candidate gene paper. (Lara Sucheston-Cambell/ Ezgi Karaesmen/ Alyssa Clay-Gilmour/ Theresa Hahn) **Manuscript Preparation**

IB09-06p Genetics and epidemiology of myeloid malignancies genome-wide association study. (Alyssa Clay-Gilmour/ Kenan Onel/ Theresa Hahn) **Manuscript Preparation**

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**

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**.

Publication Summary – Published and submitted manuscripts

IB20-01 Impact of the HLA immunopeptidome on survival of leukemia patients after unrelated donor transplantation. Journal of Clinical Oncology. Crivello P, Arrieta-Bolaños E, He M, Wang T, Fingerson S, Gadalla SM, Paczesny S, Marsh SGE, Lee SJ, Spellman SR, Bolon YT, Fleischhauer K. **Journal of Clinical Oncology. 2023 May 1; 41(13):2416-2427. doi:10.1200/JCO.22.01229. Epub 2023 Jan 20. PMC10150892.** 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.

IB06-05g Role of NKG2D ligands and receptor in haploidentical related donor hematopoietic cell transplantation. Petersdorf EW, McKallor C, Malkki M, He M, Spellman SR, Hsu KC, Strong RK, Gooley T, Stevenson P. **Blood Advances. 2023 Jun 27; 7(12):2888-2896. doi:10.1182/bloodadvances.2022008922. Epub 2023 Feb 10. PMC10300293.** This study tested the hypothesis that gene variation of the NKG2D receptor and its ligands MICA and MICB affect relapse and survival in 1629 patients who received a haploidentical HCT for the treatment of a malignant blood disorder. Patients and donors were characterized for MICA residue 129, the exon 5 short tandem repeat (STR), and MICB residues 52, 57, 98, and 189. Consideration of NKG2D ligand/receptor pairings may improve survival for future patients.

IB19-04 HLA class I genotype is associated with relapse risk after allogeneic stem cell transplantation for NPM1-mutated acute myeloid leukemia. Narayan R, Niroula A, Wang T, Kuxhausen M, He M, Meyer E, Chen YB, Bhatt VR, Beitinjaneh A, Nishihori T, Sharma A, Brown VI, Kamoun M, Diaz MA, Abid MB, Askar M, Kanakry CG, Gragert L, Bolon YT, Marsh SGE, Gadalla SM, Paczesny S, Spellman S, Lee SJ. **Transplantation and Cellular Therapy. 2023 Jul 1; 29(7):452.e1-452.e11. doi:10.1016/j.jtct.2023.03.027. Epub 2023 Mar 29. PMC10330307.** This study hypothesized that HLA genotype may impact allo-HCT outcomes in NPM1-mutated AML due to differences in antigen presentation.

IB09-06u Associations of minor histocompatibility antigens with outcomes following allogeneic hematopoietic cell transplantation. Jadi O, Tang H, Olsen K, Vensko S, Zhu Q, Wang Y, Haiman CA, Pooler L, Sheng X, Brock G, Webb A, Pasquini MC, McCarthy PL, Spellman SR, Hahn T, Vincent B, Armistead P, Sucheston-Campbell LE. **American Journal of Hematology. 2023 Jun 1; 98(6):940-950. doi:10.1002/ajh.26925. Epub 2023 Apr 13. PMC10368187.** This study showed that patients with a class I mHA count greater than the population median had an increased hazard of GvHD mortality (HR=1.39, 95%CI 1.01, 1.77, P=0.046). Competing risk analyses identified the class I mHAs DLRCKYISL (gene GSTP), WEHGPTSLL (CRISPLD2) and STSPTTNVL (SERPINF2) were associated with increased GVHD mortality (HR=2.84, 95%CI 1.52, 5.31, P=0.01), decreased leukemia-free survival (LFS) (HR=1.94,95%CI 1.27, 2.95, P=0.044), and increased disease-related mortality (DRM) (HR=2.32, 95%CI 1.5, 3.6, P=0.008), respectively. One class II mHA YQEIAAIPSAGRERQ (TACC2) was associated with increased risk of treatment-related mortality (TRM) (HR=3.05, 95%CI 1.75, 5.31, P=0.02). WEHGPTSLL and STSPTTNVL were both present within HLA haplotype B*40:01-C*03:04 and showed a positive dose-response relationship with increased all-cause mortality and DRM and decreased LFS, indicating these two mHAs contribute to risk of mortality in an additive manner.

IB17-03b JAK2 V617F mutation and associated chromosomal alterations in primary and secondary myelofibrosis and post-HCT outcomes. Rafati M, Brown DW, Zhou W, Jones K, Luo W, St Martin A, Wang Y, He M, Spellman SR, Wang T, Deeg HJ, Gupta V, Lee SJ, Bolon YT, Chanock SJ, Machiela MJ, Saber W, Gadalla SM. **Blood Advances. 2023 Dec 26; 7(24):7506-7515. doi:10.1182/bloodadvances.2023010882. Epub 2023 Oct 27.** Genomic testing was complete for 924 patients with MF (634 primary MF [PMF], 135 postpolycythemia vera [PPV-MF], and 155 postessential thrombocytopenia [PET-MF]). JAK2V617F affected 562 patients (57.6% of PMF, 97% of PPV-MF, and 42.6% of PET-MF). Almost all patients with mCAs involving the JAK2 region (97.9%) were JAK2V617-positive. In PMF, JAK2V617F mutation status, allele burden, or identified mCAs were not associated with disease progression/relapse, nonrelapse mortality (NRM), or overall survival. Almost all PPV-MF were JAK2V617F-positive (97%), with no association between HCT outcomes and mutation allele burden or mCAs. In PET-MF, JAK2V617F high mutation allele burden (≥60%) was associated with excess risk of NRM, restricted to transplants received in the era of JAK inhibitors (2013-2016; hazard ratio = 7.65; 95% confidence interval = 2.10-27.82; P = .002). However, allele burden was not associated with post-HCT disease progression/relapse or survival. Our findings support the concept that HCT can mitigate the known negative effect of JAK2V617F in patients with MF, particularly for PMF and PPV-MF.

IB06-05h HLA haplotypes and relapse after hematopoietic cell transplantation. Petersdorf EW, McKallor C, Malkki M, He M, Spellman SR, Gooley T, Stevenson P. **Journal of Clinical Oncology. doi:10.1200/JCO.23.01264. Epub 2023 Dec 5.** The result showed the risks of relapse were lower for DRβ-86 GlyGly patients when the donor was GlyVal (hazard ratio [HR], 0.46 [95% CI, 0.30 to 0.68]; P < .001); GlyVal patients benefited from HLA-DRB1-matched donors, whereas no donor was superior to another for ValVal patients. G1G2 patients with G1G2-mismatched donors had lower relapse.

Transplantation from donors with DMα residue 184 ArgHis was associated with higher risk of relapse (HR, 1.60 [95% CI, 1.09 to 2.36]; P = .02) relative to ArgArg. Relapse and mortality risks differed across HLA-DR-DQ-DM haplotypes.

SC19-06 Systematic evaluation of donor-KIR/recipient-HLA interactions in HLA-matched hematopoietic cell transplantation for AML. Fein JA, Shouval R, Krieger E, Spellman SR, Wang T, Baldauf H, Fleischhauer K, Kröger N, Horowitz MM, Maiers M, Miller JS, Mohty M, Nagler A, Weisdorf DJ, Malmberg KJ, Toor AA, Schetelig J, Romee R, Koreth J. **Blood Advances. doi:10.1182/bloodadvances.2023011622. Epub 2023 Dec 5.** The project systematically studied outcomes of individual donor-KIR/recipient-HLA interactions for HCT outcomes and empirically evaluated prevalent KIR genotypes for clinical benefit. Adult AML patients (n=2025) transplanted in complete remission who received MUD grafts reported to the Center for International Blood and Marrow Transplantation were evaluated. Only the donor-2DL2present/recipient-HLA-C1present pair was associated with reduced relapse (hazard ratio 0.79 [95% confidence interval: 0.67, 0.93], p = 0.006) compared with donor-2DL2absent/recipient-HLA-C1present. However, no association were found when comparing HLA-C groups among KIR-2DL2present-graft recipients.

IB18-04b Donor KIR genotype based outcome prediction after allogeneic stem cell transplantation: No Land in Sight! Schetelig J, Baldauf H, Heidenreich Falk, Hoogenboom JD, Spellman S, Kulagin A, Schroeder T, Sengeloev H, Dreger P, Forcade E, Vydra J, Wagner-Drouet E, Choi G, Paneesha S, Miranda N, Tanase A, De Wreede L, Lange V, Schmidt AH, Sauter J, Fein JA, Bolon YT, He M, Marsh SGE, Gadalla S, Paczesny S, Ruggeri A, Chabannon C, Fleischhauer K. 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. **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.**