



MINUTES AND OVERVIEW PLAN

CIBMTR WORKING COMMITTEE FOR IMMUNOBIOLOGY

San Antonio, TX

Thursday, Feb 22nd, 2024, 1:00 –3:00 PM CT

- Co-Chair:** Steven Marsh, BSc, PhD, ARCS; Anthony Nolan Research Institute, London, UK;
Telephone: +44 20 7284 8321; E-mail: steven.marsh@ucl.ac.uk
- 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
- Assistant - Chair:** Jennifer Saultz, D.O.; Oregon Health & Science University, Portland, OR;
Telephone: 503-494-7999; E-mail: saultzje@ohsu.edu
- Scientific Director:** Stephanie Lee, MD, MPH; Fred Hutchinson Cancer Center, Seattle, WA;
Telephone: 206-667-6190; E-mail: sjlee@fredhutch.org
- Scientific Director:** Yung-Tsi Bolon, PhD; CIBMTR[®] (Center for International Blood and Marrow Transplant Research), NMDP, Minneapolis, MN; Telephone: 763-406-5742;
E-mail: ybolon@nmdp.org
- Statistical Director:** Tao Wang, PhD; CIBMTR[®] (Center for International Blood and Marrow Transplant Research), Medical College of Wisconsin, Milwaukee, WI;
Telephone: 414-955-4339; E-mail: taowang@mcw.edu
- Statistician:** Meilun He, MPH; CIBMTR[®] (Center for International Blood and Marrow Transplant Research), NMDP, Minneapolis, MN; Telephone: 763-406-4435;
E-mail: mhe@nmdp.org
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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

Not for publication or presentation

- **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: Immunoepitome divergence between mismatched HLA and outcome of haploidentical HCT.
 - **Concluding remarks** 2:55pm
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Detailed Agenda

1. **Introduction** **Shahinaz Gadalla** 1:00pm
 - a. Minutes and Overview Plan of Immunobiology Working Committee from Tandem 2023

The CIBMTR Immunobiology Working Committee (IBWC) was called to order at 12:00 pm on Thursday, Feb 22nd, 2024, by Dr. Shahinaz Gadalla. Dr. Gadalla introduced the IBWC leadership, the outgoing chair Dr. Steven Marsh, incoming chair Dr. Esteban Arrieta-Bolanos, and WCTL program participant Dr. Jennifer Saultz. Dr. Gadalla 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, sources of CIBMTR HCT dataset, and new CIBMTR opportunity for early career investigators (ECIs). 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 (9) in the last year** 1:05pm
 - a. **IB20-01** Impact of the HLA immunoepitome 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.**

Not for publication or presentation

- 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

Dr. Brian Betts reviewed the proposals and introduced the voting and prioritization guidelines.

a. Proposal presentations (4)

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

Not for publication or presentation

Dr. Alaa Ali presented this proposal which tests the hypothesis that sex mismatch is a risk factor for cGVHD, due to the emergence of alloantibodies that are directed against the HY Antigens.

A recent study using the Japanese national database, evaluating female to male donors reported that certain HLA-DR alleles were associated with higher and others with lower chronic GVHD. The study also demonstrated the presence of HLA H-Y antigen complexes were detected on dermal vascular endothelial cells and on leukemic cells, provided possible explanation why cGVHD is associated with a GVL effect. However, the association between specific HLA allele and cGVHD in sex mismatch HCT has not been widely studied using a larger and more ethnically diverse database, or M-F HCT, or from URDs.

The hypothesis is cGVHD risk after HLA matched but sex mismatched HCT is dependent on specific HLA alleles. Primary endpoint is the cumulative incidence rate and severity of cGVHD after HLA matched but sex mismatched HCT based on different HLA-A, -B, -C, -DR, -DQ, -DP alleles in AML/MDS patients. Secondary outcomes including relapse based on different HLA alleles, impact of PTCy vs. other GVHD prophylaxis on cGVHD after sex mismatched transplants, and other predilection of cGVHD in sex mismatched HCT.

The CIBMTR identified 1341 M-F patients and 1039 F-M adult patients who underwent first HSCT with AML/MDS from 12/12 MRD or 12/12 MUD, from 2015-2021. The audience questioned: why would you see an effect in M-F transplants, will you focus on specific HLA alleles like the most common, will you compare URD to MRD, how will PTCy affect results?

- 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) Dr. Jun Zou will present.**

Dr. Zou presented this proposal. He reviewed that F-M HCT has a higher risk of GVHD, and the presence of H-Y antibodies is associated with cGVHD and relapse protection.

*A recent study showed the DRB1-15*02 is associated with a higher risk of cGVHD. The complex of HY/HLA DR was detected on the cell surfaces and vascular endothelial. They did a single center analysis of 700 patients who received MRD, including 194 F-M HCT, revealing that a high CD4 T cell alloreactivity presentation score was associated with higher risk of cGVHD and relapse protection but only in the F-M and not the M-F.*

The CIBMTR identified 6434 patients with AML, ALL, MDS receiving HCT from MRD, 2010-2021, while 26% (1700) are F-M patients. PtCy will be excluded from this study. Primary endpoint is cGVHD, and secondary endpoints included aGVHD, relapse, NRM, PFS, and OS. The following points came up in discussion: Why exclude PTCy (low rates of cGVHD, may affect alloreactivity derived from MiHA), why use cGVHD and not aGVHD as the primary endpoint, can you look at B cell phenotype, does disease matter?

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

Not for publication or presentation

Dr. Katharina Fleischhauer presented this proposal which looks at the immunopeptidome in multiply mismatched URD. The hypothesis is: the number and/or directionality of ≥ 2 mismatches with high immunopeptidome divergence at HLA-A, -B, -C, -DRB1, -DQB1, -DPB1 is associated with survival after UD-HCT. One precondition is to have PBM or TCE classification for the 6 loci.

The CIBMTR identified patients who underwent first HSCT using CNI- or PTCy-based GVHD prophylaxis with AML, ALL, and MDS, 6-locus 4-digit HLA typing available, and $\leq 10/12$ UD-HCT from 2010-2020. There are 3211 MMUD, while 4047 MUD (2 DPB1mM) patients in the cohort. Will evaluate the risk for the different endpoints, by increasing the number of immunopeptidome mismatches and directionality of IP mM. The endpoints included: OS, DFS, NRM, RI, a/c GVHD, GRFS. Questions from the audience included: why not extend the years to get more mismatched URDs?

- 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)

Dr. Becca Asquith will present.

Dr. Becca Asquith presented this proposal. The hypothesis is the donors with a high count of iKIR-ligand gene pairs will have long-lived T-cells leading to better T-cell reconstitution in recipients, which will increase the risk of GVHD, decrease the risk of relapse, and decrease the risk of virus reactivation. The difference from other KIR study is our hypothesis focus on CD8+ T cell alloreactivity, while other studies focus on NK cell response. Endpoints include acute GvHD, Chronic GvHD, and risk of relapse. Will include AML, ALL, MDS URD with donor has been KIR typed. Questions raised during discussion included: why only count inhibitory KIRs and not activating, wouldn't an association have come out in previous NK studies, range of binding pairs (depends on ethnicity of the population but goes up to 4 ligand pairs. So max KIR ligand pairs a person can carry is 4), does the metric include KIR ligand affinity (no, correlates with number of KIR ligand pairs), can this study be done with EBMT (no, they don't have the data), do you need to look at transcription to see if genes are suppressed or silenced (no, KIRs are constitutively expressed on NK cells and driving the interaction, rather than KIR expressed on the T cells themselves)?

b. 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

5. Studies in Progress

- 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, Dhimi P, Marzi S, Paul D, Feber A, Kuxhausen M, Lee SJ, Spellman SR, Wang T, Rakyen V, Peggs K, Beck S. **Manuscript Preparation.**
- c. **IB21-01** HLA-DRB1 Haplotype 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.**

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- h. **IB22-02** Effect of SIRP α 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.

Dr. Shannon McCurdy provided an update on IB22-01. Aim for this study is to 1) examine the effects of PTCy on OS of HLA-DPB1 non-permissive mismatched URD when compared to methotrexate and tacrolimus; 2) compare the outcomes of HLA-DPB1 NP MM URD vs. 12/12 URD, both using PTCy. The cohort analysis of 1290 HLA-DPB1 MM with PTCy and 2894 recipients of HLA-DPB1 NP MM with methotrexate/tacrolimus. Outcomes included OS, GRFS, TRM, relapse, and GVHD. The conclusions are: 1) In HLA-DPB1 NP MM unrelated donor HCT, PTCy based GVHD prophylaxis is associated with improved GRFS when compared to methotrexate and tacrolimus-based prophylaxis due to decreased TRM and all types of GVHD; 2) While relapse rate was higher in the PTCy group, this did not negatively affect OS or GRFS. 3) Outcomes are similar between HLA-DPB1 non-permissive mismatched, HLA-DPB1 permissive mismatched, and 12/12 HLA-matched unrelated donor transplantation with PTCy. 4) PTCy should be the preferred GVHD-prophylaxis strategy for HLA-DPB1 NP MM unrelated donor HCT. Questions during the discussion included: do you think reducing the dose of PTCy will decrease the relapse rate (yes), rates of infection (not evaluated)

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

Dr. Brian Shaffer provided an update on IB22-03. The hypothesis of this study is that using younger alternative donors results in improved outcomes compared to older-aged, matched sibling donors. Alternative donors were defined as MUD, MMUD, or haplo. The older-aged patients were defined as ≥ 50 years old, while older donors are defined as ≥ 50 years and younger donors were defined as ≤ 35 years. The primary analysis only focused on recipients who using PTCy, and the second analysis was siblings vs. URD in CNI-based recipients. The conclusions are: 1) Use of an older matched-sibling donor results in a small but significant decrement in DFS due to increased incidence of relapse; 2) Phenomenon observed across different GVHD prophylaxis regimens supporting biological phenomenon and not a product of patient selection or transplant procedures. Questions during the discussion: Do you have the correct definition of "younger", did you compare older siblings to older MUD (no), is CMV status included (yes)?

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

Dr. Pietro Crivello provided an update on IB22-03 testing the immunopeptidome model in the haplo setting, where up to 4 different single HLA class I and -DRB1 alleles are mismatched, and PTCy is used as GVHD prophylaxis. The hypothesis was the cumulatively number and direction of PBM mismatches in the cohort will associate with clinical outcomes. The cohort included patients underwent 1st Haplo HCT with AML, ALL, MDS using PTCy from 2010-2020, and 2198/3429 informative for PBM groups at all 4 HLA-A, -B, -C, -DRB1 loci were identified. Using 8/8 MUD

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under PTCy as a reference group. The results showed all haplo groups have worse OS than the MUD group. The group with only 1 PBM mismatch had the worst OS. And the 1 PBM mismatch in GVH direction has worse DFS, and relapse. One potential explanation is that single PBM-GvH mismatch is less efficient in inducing GvL than multiple PBM-GvH mismatches. Therefore, the next steps are: 1) including GRFS as a new outcome; 2) focus on additional analysis only on HLA Class I mismatches. Discussion questions included: what happens if you pool all PBM mismatches, e.g., 1+, is there a threshold effect or linear?

A: From previous analysis, single PBM analysis impacted while the others compensate and become similar, so better at this stage look at different groups and how they behave before putting them together. Isn't a 0 PBM mismatch a "matched cohort" (yes, but low frequency), why isn't -DQ included (don't have PBM info so the analysis is adjusted for DQ matching), should linkage disequilibrium and race/ethnicity be considered?

7. Closing Remarks

Stephanie Lee 2:55PM

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

Working Committee Overview Plan for 2024 - 2025		
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
IB18-07 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.	Manuscript Preparation	3
IB22-02 Effect of SIRP α mismatch on the outcome of allogeneic hematopoietic stem cell transplantation from an HLA matched related donor.	Data File Preparation	1
IB22-03 HLA matched sibling versus well-matched unrelated donor: Update including HLA-DPB1 match status in recipients of allogeneic hematopoietic cell transplantation.	Manuscript Preparation	1
IB23-01 Immunopeptidome divergence between mismatched HLA and outcome of haploidentical HCT.	Manuscript Preparation	3
IB23-02 Younger MMUD vs older haploidentical donor HCT.	Data File Preparation	1
IB23-03 Impact of adherence to cord blood guidelines.	Protocol Development	2
IB24-01 6-locus HLA immunopeptidome divergence and outcome of mismatched unrelated HCT.	Protocol Pending	3
IB24-02 Effect of donor KIR and donor KIR ligand on CD8+ T cell-mediated alloreactivity in unrelated HSCT for AML, ALL and MDS.	Protocol Pending	3