Not for publication or presentation

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR IMMUNOBIOLOGY
Salt Lake City, UT
Sunday, April 24, 2022, 12:15 pm–1:45 pm MDT

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Agenda Summary

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

Detailed Agenda

1. **Introduction** (12:15pm) Minutes and Overview Plan of Immunobiology Working Committee from TCT 2021 (Attachment 1)
   The CIBMTR Immunobiology Working Committee (IBWC) was called to order at 12:15 pm on Sunday April 24th, 2022, by Dr. Steven Marsh. Dr. Marsh introduced the CIBMTR COI policy along with working committee leadership. Dr. Marsh continued by reviewing the membership and

goals of the working committee, areas of focus, and limitations of the IBWC. He gave a brief overview of the status of the current portfolio and number of proposals to be presented at the meeting and voting and prioritization guidelines.

2. Published and submitted papers (21) in the last year (12:20pm) *Recently published or submitted papers from the committee were announced.*

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

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

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

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

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

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

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

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

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

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

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

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

Epub 2021 Apr 9. PMC8280068.

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

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

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

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

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

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

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

T, Rakyan V, Peggs K, Beck S. ***Submitted.***

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

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

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

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

a. Voting guidelines

b. Proposal presentations (3)

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

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

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

a. What is the frequency of the SIRPα variants? Do you have enough for matched vs. mismatched? Answer: The V1, V2 comprised 80% of the population; the V1, V4, V5, V6,

and V9 have the same binding motif with CD47, and we will focus on those binding motifs.

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

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

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

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

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

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

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

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

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

A preliminary study included 4417 BMT patient/donor pairs from MUD, CIBMTR data. There were three groups: Matched vs. Permissible+86V/G vs. Non-permissible+86G/V. Significant differences in OS and DFS were seen between matched vs. non-permissible+86G/V, and Permissible+86V/G vs. Non-permissible+86G/V cohorts. Based on the preliminary study, Dr. Fernandez-Vina mentioned that if validated, these new classifications could be used in day-to-day donor prioritization based on match grades. The examination of peptide binding repertoire profiles imputed from structural differences between HLA mismatched alleles may become a new paradigm to evaluate mismatches, and their applications may change clinical practice for donor selection and prioritization. The CIBMTR identified 550 DRB1 MM patients, 3217 HLA-A, -B, or -C MM patients, and 20707 8/8 patients who underwent first HSCT from URD, 2012-2020 with AML, ALL, MDS and CML. The following questions were answered during the Q&A:

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

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

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

iii. **PROP2108-03; 2110-178; 2110-207; 2110-222; 2110-48; 2110-92:** Impact of HLA-DPB1 matching on clinical outcomes following unrelated donor transplantation using post-transplant cyclophosphamide as graft-versus-host disease prophylaxis for patients with hematologic malignancies. (Blouin, Amanda; Fuchs, Ephraim; Ibrahim, Uroosa; Keyzner, Alla; McCurdy, Shannon R; Nakhle, Saba; Perales, Miguel-Angel; Petersdorf, Effie W; Safah, Hana; Shaffer, Brian C; Socola, Francisco A; Solomon, Scott R; Zou, Jun) *(Attachment 5)*

Dr. Scott Solomon presented this proposal. The research questions are: 1) Should the presence of a high risk/non-permissive (npmm) HLA-DPB1 mismatch be considered for donor selection following matched unrelated donor (MUD) transplantation using post-transplant cyclophosphamide (PTCy)? 2) In the context of HLA-DPB1 npmm, is there a preference for PTCy- vs. non-PTCy-based GVHD prophylaxis strategy? Dr. Solomon introduced three models for predicting HLA-DPB1 permissive mismatches: T cell epitope

(TCE) model, Expression model, and Predicted Indirectly Recognizable HLA Epitopes (PIRCHE). Previous studies using the TCE model indicated the HLA-DPB1 nmpp group has high risk of NRM, while the permissive group was similar to the matched group when standard GVHD prophylaxis is given. The hypothesis is, in patients with an HLA-DPB1 npmm, survival following MUD transplantation will be improved with the use of PTCy-based GVHD prophylaxis (by negating the negative impact of using a DP non-permissively mismatched donor) compared to calcineurin inhibitor (CNI)-based GVHD prophylaxis.

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

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

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

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

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

c. Dropped Proposals (9)

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

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

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

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

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

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

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

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

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

Not for publication or presentation

5. Studies in Progress *(Attachment6)*

NK/KIR

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

HLA GENES – CLASSICAL MATCHING

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

b**. IB18-02:** Impact of HLA class I risk alleles associated with AA Immune pathogenesis on allo TX outcomes in patients with SAA (D Babushok/T Olson) ***Manuscript Preparation*.**

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

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

SENSITIZATION AND TOLERANCE

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

Other Genes

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

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

ONGOING AND OTHER-FUNDED STUDIES

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

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

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

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

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

a. **IB19-02**

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

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

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

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

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

b. **IB17-03**

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

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

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

c. **IB18-04b**

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

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

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

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

7. Closing Remarks (13:40 PM)

Not for publication or presentation

Working Committee Overview Plan for 2022-2023		
Study Number and Title	**Current Status**	**Chairs Priority**
IB18-04b: Evaluation of the impact of donor killer immunoglobulin receptor genotype on outcome after unrelated donor transplantation in patients with myelodysplastic syndromes or acute myeloid leukemia.	Analysis	9
IB16-02: Use of HLA structure and function parameters to understand the relationship between HLA disparity and transplant outcomes.	Analysis	2
IB18-02: Impact of HLA class I risk alleles associated with AA immune pathogenesis on allo TX outcomes in patients with SAA.	Submitted	12
IB20-01: Association of immunopeptidome divergence between mismatched human leukocyte antigen class I alleles and outcome of 9/10 matched unrelated hematopoietic stem cell transplant.	Submitted	11
IB19-04: Impact of donor HLA on transplant outcomes in NPM1 mutated AML	Manuscript Preparation	9
IB17-03: Germline-somatic interactions drive JAK2-mediated clonal expansion in myelofibrosis.	Submitted	10
IB17-04: Donor whole blood DNA methylation is not a strong predictor of acute graft versus host disease in unrelated donor allogeneic hematopoietic cell transplantation.	Submitted	5
IB18-07: Donor and recipient genomic associations with acute GVHD	Analysis	1
IB20-03: Donor socioeconomic status as a predictor of altered immune function and treatment response following hematopoietic cell transplantation for hematologic malignancy	Submitted	1
IB20-04: Haploidentical versus matched unrelated donor transplants using post-transplant cyclophosphamide for lymphomas.	Submitted	2
IB21-01: Effect of HLA evolutionary divergence on survival and relapse following allogeneic hematopoietic cell transplant.	Analysis	2
IB22-01: Impact of HLA-DPB1 matching on survival following unrelated donor transplantation with post transplant cyclophosphamide for adults with hematologic malignancies.	Protocol Pending	1
IB22-02: Effect of SIRPα mismatch on the outcome of allogeneic hematopoietic stem cell transplantation from an HLA matched related donor.	Protocol Pending	2