MINUTES AND OVERVIEW PLAN
CIBMTR IMMUNOBIOLOGY WORKING COMMITTEE
Orlando, Florida
Friday, Feb 17th, 2023, 12:00 pm–14:00 pm EST

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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