Advisory Council on Blood Stem Cell Transplantation
Health Resources and Services Administration
September 25, 2020

Members Present

Voting Members
Manish Gandhi, MD
Staci Arnold, MD
Colleen Delaney, MD, MSc.
Sergio Giralt, MD, FACP
Mary Laughlin, MD
Amanda Salazar

Non-Voting/Ex-Officio Members
Frank Holloman, Health Resources and Services Administration (HRSA)
Nancy L. DiFronzo, Ph.D., National Institutes of Health (NIH)
Safa Karandish, Food and Drug Administration (FDA)

Not Present
Sridhar Basavaraju, M.D., Centers for Disease Control and Prevention (CDC)

Executive Secretary
Robert Walsh

General Counsel Staff
Laura Odwazny, JD

Welcome and Opening Remarks

Manish Gandhi, MD, Chair, ACBSCT
Robert Walsh, ACBSCT Executive Secretary

Mr. Robert Walsh opened the meeting at 12:04 pm EST. Dr. Manish Gandhi welcomed the participants and reviewed the principal purpose of the Advisory Council on Blood Stem Cell Transplantation (ACBSCT), which is to make blood cells from other donors and cord blood units available for patients who need a transplant to treat life-threatening conditions and who lack suitably matched related donors. Presentations will focus on issues related to utilization of cord blood, blood stem cells, and cellular therapies.

HRSA Division of Transplantation Blood Stem Cell Transplantation Program Update

Frank Holloman, Director, Division of Transplantation (DoT), HRSA

Mr. Frank Holloman reviewed the purpose of the HRSA Department of Transplantation, which is the primary federal entity responsible for oversight of organ and blood stem cell transplant systems, donations, and transplantation in the United States (U.S.). HRSA staff also serve as non-voting members of the Board of Directors of the National Marrow Donor Program (NMPD) and the Organ Procurement

Transplantation Network (OPTN) and participate in committees and working groups under NMPD, OPTN, and the Center for International Blood and Marrow Transplant Research (CIBMTR).

Mr. Holloman reviewed the statutory framework of the Stem Cell Therapeutic and Research Act of 2005 (reauthorized in 2015). The legislation authorizes the C.W. Bill Young Cell Transplantation Program (CWBYCTP), the National Cord Blood Inventory (NCBI), and the Secretary's Advisory Council on Blood Stem Cell Transplantation (ACBSCT). The goal of the CWBYCTP is to increase the number of bone marrow and cord blood transplants for recipients suitably matched to biologically unrelated donors. The NCBI is a contract with cord blood banks to meet the statutory goal of building a public inventory of 150,000 new, high-quality, genetically diverse cord blood units. This meeting focuses on the ACBSCT, which is responsible for advising, assisting, consulting with, and developing recommendations for the Secretary of Health and Human Services and the HRSA Administrator on the activities of the CWBYCTP and the NCBI programs.

The HRSA program provides oversight to five major functions: the Organ Transplant Program, the NCBI, and the three contracts under the CWBYCTP—the Office of Patient Advocacy, the Single Point of Access Coordinating Center, and the Stem Cell Therapeutic Outcomes Database. These three contracts provide support to patients who need unrelated bone marrow or umbilical cord blood transplants. NCBI distributes contractors around the nation, including five contracts issued in 2019: Bloodworks in Seattle, WA; Cleveland Cord Blood Center in Cleveland, OH; LifeSouth Community Blood Centers in Gainesville, FL; New York Blood Center in New York City, NY; and University of Texas, MD Anderson Cancer Center in Houston, TX. In 2020, under the same request for proposals, HRSA awarded a new NCBI contract to Carolina's Cord Blood Bank at Duke University in Durham, NC. Cumulatively since 2019, they have awarded $16 million across these contracts. Since the inception of the project in 2004, HRSA has awarded to 23 contracts to 13 different contractors, and the NCBI has reimbursed more than 107,000 cord blood units.

Mr. Holloman then reported fiscal year appropriations. Appropriations for the CWBYCTP increased from fiscal year 2019 to 2020, then remained steady to 2021. Appropriations for the NCBI remained steady from fiscal year 2019 to 2020 and decreased for 2021. As of fiscal year 2019, the CWBYCTP and NCBI registry held over 22 million adult donors, including more than 3.9 million adults of underrepresented racial or ethnic populations. HRSA cord blood banks delivered more than 100,000 cord blood units, representing 65% of the minimum statutory goal of 150,000 units. Over 60% of those contracted cord blood units were from underrepresented racial or ethnic populations. More than 240,000 cord blood units are now available through the CWBYCTP. The total number of transplants in fiscal year 2019 was 6,426, representing a 5% increase over 2018; this included 5,329 transplants for domestic individuals and 1,004 transplants for members of underrepresented racial or ethnic populations. The number of cord blood units released for transplantation in fiscal year 2019 was 848, representing an 11% decrease from 2018.

Mr. Holloman discussed federal collaborations, including the Hematopoietic Stem Cell Transplantation (HSCT) Work Group (WG) that HRSA chairs and is comprised of representatives from NIH, CDC, Centers for Medicare and Medicaid Services (CMS), FDA, Veterans Administration (VA), and the Department of Defense (DoD). The HSCT WG meets twice a year and has historically focused on the state of HRSA's contractual authority in unrelated blood stem cell transplantation, but has since broadened within the field of cellular activity. The Department of State also collaborates with HRSA to facilitate blood stem cell translations through the CWBYSTP, and the Department of Homeland Security (DHS) assists with the timely transport of blood stem cell products during public health emergencies.

Mr. Holloman concluded by reviewing special contract collaborations with CWBYCTP and NCBI to understand and respond to the impact of COVID -19 on the workforce. The COVID-19 pandemic has prompted special engagement with the CWBYCTP and NCBI to understand the impact of COVID-19 on meeting contractual obligations. HRSA has offered its contractors partial stop work orders and has worked with contractors and federal agencies (including the State Department, DoD, and the Office of Management and Budget) to provide support during this unprecedented crisis.

Blood Stem Cell Transplantation Trends: An Overview

Stephen Spellman, MBS Program

Mr. Stephen Spellman presented an overview of blood stem cell transplantation trends in the U.S. from 2008 to present, using data sourced from the National Marrow Donor Program (NMDP) and the Center for International Blood and Marrow Transplant Research (CIBMTR). He focused on trends in hematopoietic cell transplantation (HCT) by overall donor source, by recipient age group, by race/ethnicity of donors and recipients, and by race/ethnic group match status for cord blood HCT.

He began by discussing relative trends in allogeneic HCT recipients by donor type. HLA-matched unrelated donors HCT has nearly doubled since 2008, and the use of haploidentical related donors tripled from about 500 per year to about 1,500 per year between 2013 and 2018. Next, he reviewed recipient donor types by age group. Among pediatric patients, unrelated donors were the most common donor type, followed by HLA-identical siblings, unrelated donor cord blood transplants, and haploidentical transplants from other relatives. Trends are similar among adults, with the exception of haploidentical transplant as the most favored alternative donor over umbilical cord transplants. Among adults older than 60 years, sibling donor transplants are uncommon, reflecting the aging process and the reduced suitability of siblings among this older population.

Next, Mr. Spellman discussed distribution and trends by race/ethnicity. Among White non-Hispanic recipients, matched unrelated donor (MURD) use has remained steady at about 60% of donor sources, while cord blood and mismatched unrelated donor (MMURD) use have declined. Haploidentical related donor use increased from 4% to 20% during this time period. According to data collected by NMDP between 2010 and 2020, the most common cord blood race/ethnicity among White non-Hispanic recipients was White non-Hispanic cord blood (representing 59% of cord blood donors), followed by unknown race/ethnicity, White Hispanic, and multiple race.

Among White Hispanic recipients, MURD use has increased slightly. Cord blood and MMURD use both have declined from 40% to 10%, while haploidentical related donor use has increased substantially from 4% to 40%. NMDP data indicate that the most common cord blood race/ethnicity was White Hispanic (representing 49% of cord blood donors), followed by White non-Hispanic, unknown, and multiple race.

Trends among Black African American recipients are similar to those of the White Hispanic population. Black African American recipients have seen a dramatic increase (from 14% to 60%) in haploidentical related donors, while cord blood and MMURD use have also declined. MURD use remains steady and uncommon in this population, reflecting challenges in finding a suitable match on the registry. NMDP data show that the most common cord blood race/ethnicity was Black African American (representing 41% of cord blood donors), followed by White non-Hispanic, multiple race, White Hispanic, and unknown.

For Asian or Pacific Islander recipients, MURD use has increased from 30% to 40%, while cord blood and MMURD use have declined. Haploidentical related donor use has increased substantially from 10% to 36%. NMDP data indicate that the most common cord blood race/ethnicity among Asian or Pacific Islander recipients is Asian or Pacific Islander (representing 40% of cord blood donors), followed by White non-Hispanic, White Hispanic, and unknown.

For recipients of multiple race, the most common cord race/ethnicity was White Hispanic (36%), followed by White non-Hispanic, multiple race, Black African American, Asian or Pacific Islander, and unknown.

Among Hawaiian recipients, the most common cord race/ethnicity was White non-Hispanic (38%), followed by Asian or Pacific Islander, multiple race, unknown, and White Hispanic.

Among American Indian or Alaska Native recipients, the most common cord race/ethnicity was White non-Hispanic at 31% of cord blood donors, followed by White Hispanic (30%), unknown race, Asian or Pacific Islander, and multiple race.

Last, among recipients of unknown race, the most common cord blood race/ethnicity was White non-Hispanic (50%), followed by White Hispanic, multiple race, Black African American, and unknown.

Discussion session
Dr. Staci Arnold asked if Dr. Spellman has outcomes data by ethnic distributions. **Dr. Spellman** replied that he does not have those data for this presentation, but the CIBMTR outcome analysis published annually does apply some adjustments for race/ethnicity. There are some interactions across those distributions; for example, Black African Americans have slightly worse outcomes.

Dr. Mary Laughlin asked Dr. Spellman to elaborate on aspects of trends in graph selection based on recipient age. **Dr. Spellman** said that this is not necessarily a change over time in the age groups, but there has been a shift away from cord blood transplantation in adult recipients as haploidentical grafts. Overall, some GVHD prophylaxis strategies have enabled a slight increase in MMURDs.

Dr. Arthur Bracey asked Dr. Spellman to comment about unmet need versus availability. **Dr. Spellman** replied that there is an unmet need in the registry and availability of fully matched unrelated donors within ethnically diverse populations (for example, the likelihood of finding a donor is only 20% in the Black African American population compared to 70% of the White population). Some of these mixed strategies have been effective in filling gaps that exist fully matched transplant sources.

Dr. Colleen Delaney asked Dr. Spellman to comment further on accessibility. She asked if he thinks that alternative sources will overtake the MURD setting as these alternative sources show increasingly positive outcomes. **Dr. Spellman** said that this is possible, given graft manipulation or GVHD prophylaxis manipulation strategies that levels outcomes regardless of graft source or HLA match. This may also occur if a mismatched graft sources had some characteristics that are more favorable than a fully HLA-matched source. Today, a matched sibling donor or MURD remain the standard for graft selection. Additionally, allowing a disease to progress while waiting for an optimal donor may be more detrimental than finding an adequate match on a faster time scale.

Dr. Laughlin noted that NMDP distributes three of these grafts (MURD, MMURD, and cord blood) from various banks. She wondered if the cost of a MURD or MMURD is equivalent to that of a cord blood graft and if there are cost constraints associated with NMDP distributor fees to cord blood banks. **Dr. Spellman** said he is not an economist nor does he set pricing; therefore he will leave this question to the experts. **Dr. Arnold** added that these outcomes are unclear and are dependent on transplant population traits such as age or disease malignancy, while other cost analysis factors associated with acquiring, storing, and procuring the graft itself.

Haploidentical Transplantation: An Overview

Mary Eapen, MBBS, MS

Dr. Mary Eapen began by stating that in 2019 in the U.S., HLA-haploidentical siblings accounted for about 20% of allogeneic transplants in adults and children, primarily a mixture of hematologic, malignant, and non-malignant diseases (although predominantly malignant diseases in adults). In the past, the most common graft type was bone marrow, but now about 70% use peripheral blood, particularly for adults with hematological malignancy. Most of these haploidentical-related donor transplants use a GVHD prophylaxis method called post-transplant cyclophosphamide (PT-Cy), which helps to overcome the histocompatibility barrier. While initially built on the platform of reduced intensity conditioning regimens, practices have expanded to include the myeloablative regimen.

Donor selection varies between centers. Although some centers conventionally prioritize matched sibling donors and then search for MURDs, many centers now prioritize a haploidentical relative over a MURD. Centers are interested to know if these haploidentical relatives are comparable to MURDs, particularly the extent to which PT-Cy can overcome the HLA barrier.

A 2015 study compared survival between haploidentical versus MURD transplants for acute myeloid leukemia. The study found no difference in mortality between the two donor sources in either the myeloablative or reduced intensity regimens. However, Dr. Eapen pointed out that all of the haploidentical transplant patients received a calcium inhibitor containing GVHD prophylaxis and all patients in the haploidentical setting received PT-Cy. A similar study in 2019 used similar selection criteria and included a larger population of haploidentical patients, confirming that the original findings were not caused by small effect sizes.

A 2020 study of patients with acute myeloid leukemia examined differences in mortality between haploidentical transplantation and fully matched URD transplantation with PT-Cy. The study found no differences in the myeloablative setting. However, in the reduced intensity setting, fully matched URD transplant recipients were significantly more likely to survive than haploidentical transplant recipients. The researchers also found lower incidence of GVHD and lower non-relapse mortality among the MURD population.

Research comparing graft types finds that survival does not differ between bone marrow recipients and peripheral blood recipients, but peripheral blood grafts have a significantly higher risk of chronic GVHD, even with the use of PT-Cy.

Next, Dr. Eapen reviewed age-related effects on transplant outcomes. Younger MURD donors are associated with the best survival, and the hazard ratio for overall mortality increases by 5.5% for every 10-year increase in MURD donor age. A 2018 CIBMTR study of haploidentical HCT donors found a strong correlation between recipient age and donor relationship, a strong correlation between donor age and

donor relationship, but no correlation between patient age and donor age. The study also found significantly higher mortality for recipients aged 55 years and older, as well as higher mortality among recipients of transplants from donors aged 30 years and older. Grafts were more likely to fail when parents are donors, regardless of age.

These results suggest that, in the haploidentical donor setting, patient age is a more important predictor of survival than donor age or donor-recipient relationship. The data also indicate that parent donors have a higher risk of graft failure, which is particularly relevant for the pediatric population. Overall, haploidentical relatives are suitable alternatives to MURDs when matched siblings are unavailable and in unselected populations (which show a similar two-year survival to the MURD setting) and in selected population (in which fully matched URDs and HLA-matched siblings are preferred).

Dr. Eapen then discussed the use of alternative donors for non-malignant diseases, including sickle cell anemia and aplastic anemia. After sickle cell disease, fully matched sibling transplants show exceptional overall survival rates (exceeding 95%), while MURD transplants show only 82-85% overall survival rates. However, event-free survival is much lower among alternative transplants. After three years, event-free survival is only 69% in the MURD setting, compared to 89% in the matched sibling setting.

Graft failure rates increase with increasing HLA mismatch. The highest graft failure (38%) is seen after haploidentical transplants, compared to only 7% graft failure after matched sibling transplantation and 16% for MURD transplants. Importantly, most negative events after a matched occur within the first two years, while negative events persist after two years in the mismatched setting, demonstrating the need for longer-term follow-up.

Dr. Eapen summarized that event-free survival is highest in children younger than 13 years old and after matched sibling transplant HCT for sickle cell disease. Both mortality and graft failure are higher after alternative donor HCT, and, while the data do not favor one alternative donor over another, haploidentical and MMURD settings show more and longer-term graft failure and other morbidities.

To facilitate counseling for HCT for sickle cell disease, researchers developed and validated a simple risk score based on age at HCT and donor type. They classified patients by three risk groups (good, intermediate, and high). Patients who were under 12 years old at time of HCT and a had a matched sibling donor were classified as “good” risk. The “intermediate risk” included patients under 12 years who received MURD transplants and patients older than 13 years who received a matched sibling donor. “High” risk patients were those younger than 12 years who received mismatched donors and patients older than 13 years who received alternative donors. On average, three-year event-free survival was about 60%, mortality was about 10%, and graft failure was about 30%. As a result, patients and families choosing haploidentical HCT for sickle cell disease must be willing to accept 10% mortality relatively early after HCT and 30% chance of disease recurrence.

Last, Dr. Eapen reviewed data on aplastic anemia. A study of 90 patients with severe aplastic anemia found an overall survival rate of about 80% and a graft failure rate of about 30%, consistent with findings from patients with sickle cell disease. Data reported to transplant registries suggest that HLA-matched URDs are preferable to mismatched relatives, while data from single institutions suggest that survival is comparable to HCT in the MURD setting. To clarify these findings, data from an ongoing multi-center national Phase 2 clinical trial using haploidentical related donor transplantation will become available in 2022.

In general, haploidentical HCT for malignant and non-malignant hematologic diseases has extended the donor pool and increased transplant accessibility to eligible patients. This is particularly important for minority populations, who may be less likely to find an HLA-matched URD on the registry. For non-malignant hematologic diseases in particular, there is an urgent need to improve current transplant strategies to overcome high rates of graft failure after haploidentical donor HCT and GVHD after URD HCT.

Discussion session
Dr. Laughlin noted that no overall survival or event-free survival effects were seen among malignant diseases in the myeloablative setting, but lower event-free survival was identified between haploidentical and MURD sources in the reduced intensity setting. She asked Dr. Eapen to further elaborate on this and to comment on differences in relapse between marrow and peripheral blood. **Dr. Eapen** explained that when the GVHD prophylaxis regimen is a calcium inhibitor with methotrexate or mycophenolate, the GVHD rate is generally higher for MURD compared to haploidentical related donors. When PT-Cy is used instead, the difference between MURD and MMURD settings disappear, which translates to lower non-relapse mortality in the fully matched URD setting because GVHD was the biggest obstacle in prior comparisons. The lack of difference in the myeloablative setting may be explained by the smaller patient population size. Additionally, in a study undertaken by CIBMTR, peripheral blood showed a slightly lower relapse risk, but this was negated by a combination of GVHD and other negative events, therefore this small advantage did not translate into survival or leukemic pre-survival advantage for either bone marrow or peripheral blood. Among adults, the difference between URDs and fully matched siblings (which showed an advantage to bone marrow in overall survival) was only seen for chronic myeloid leukemia; these differences were not present in the acute myeloid leukemia setting. The predominant graft source (more than 90%) for MURD is peripheral blood, and therefore data are limited.

Dr. Mary Horowitz commented that there are two randomized trials in the BMT CTN addressing whether PT-Cy produces superior survival and event-free survival compared to calcineurin-based GVHD prophylaxis in the HLA-identical related donor and URD setting. One has accrued and the other is still accruing.

Mismatched Bone Marrow Transplantation: An Overview

Stephen Spellman, MBS

Dr. Spellman introduced the NMDP Donor-Recipient Pair Project, which was started in 1994 with funding from the U.S. Office of Naval Research. Their goals were to generate data to determine the impact of allele-level matching of HLA-A, B, and DRB1 of HCT outcomes; and to determine the contribution of matching at other loci (HLA-C, DPA1, DPB1, DQA1 and DQB1). Most of the patients in the following studies received calcineurin inhibitor-based CVHD prophylaxis.

The first major publication was Flomenberg et al. 2004, which studied the impact of high-resolution matching. Between 1988 and 1996, 1,874 patients with acute myeloid leukemia and other diseases received bone marrow grafts and myeloablative conditioning regimens. They found that matching at HLA-A, B, and C and DRB1 impacts overall survival. A single allele or antigen mismatch was associated with approximately 10% decrease in overall survival at five years post-transplant. A subsequent 2007 study of 3,860 patients who received transplants between 1988-2003 confirmed these findings, determining that HLA-A, B, and C and DRB1 impact overall survival at high-resolution levels. Again, a

single allele or antigen mismatch was associated with a 10% decrease in survival and more than one mismatch was associated with a 20% decrease in survival at five years. Importantly, HLA-DQ lacked had no impact, neither as a single mismatch alone nor as a second mismatch paired with HLA-A, B, or C or DRB1. Another 2014 study once again replicated these findings. As a result, 8/8 allele-level matching is the gold standard.

Not every patient can find a fully matched donor, so researchers are working to identify permissive mismatches at the classical loci. These include cross-reactive antigen (CREG) groups, histocheck algorithms, HLA matchmaking algorithms, supertype matching, and predicted indirectly recognizable HLA epitopes (PIRCHE). None of these studies have defined or demonstrated effective methods for permissive mismatches.

Dr. Spellman presented a 2019 center-specific outcome analysis of one-year mortality among all first allogeneic HCT performed in the U.S. These data find no significant difference in mortality between 8/8 MURD and HLA-matched sibling HCT. However, one-year mortality significantly increased in the MMURD, haploidentical related, and cord blood HCT settings.

The likelihood of finding a match for alternative graft sources (URDs) varies by race/ethnicity. CIBMTR provides data on the likelihood of finding a match, accounting not only for genotyping in the registry but for the readiness and availability of the donor to proceed with the transplant.

Likelihood of finding an 8/8 match varies from 20% among African American people to 70% among the European Caucasian population. The likelihood of finding a 7/8 match begins to fill this gap, and the likelihood increases as the match decreases. The likelihood of finding a <7/8 match is nearly 100%. However, despite best efforts to build a representative volunteer donor registry, disparities still exist among racial/ethnic groups.

New research has minimized the impact of HLA mismatches in the MMURD HCT setting. Promising methods include PT-Cy, sirolimus as GVHD prophylaxis, abatacept in the pediatric setting, and graft engineering. A multi-center, single-arm Phase 2 study recently assessed the safety and efficacy of MMURD (4/8 to 7/8 match) bone marrow transplantation using PT-Cy, sirolimus, and mycophenolate mofetil (MMF). Patients received a fresh bone marrow graft, followed by Pt-Cy on days three and four post-transplant, while sirolimus and MMF were initiated on day five post-transplant. The study enrolled 80 patients across 11 transplant centers, half of whom received full-intensity conditioning and half of whom received reduced-intensity conditioning. At one year, overall survival was 75%, surpassing the 65% benchmark established for the trial. GVHD occurred in 11.4% of patients, with a slight increase to 20.5% in the myeloablative conditioning regimen. Graft failure was only 3.8%. The researchers found that overall survival did not significantly differ by conditioning intensity nor by HLA match.

Dr. Spellman highlighted that the use of MMURD expands donor choice, reducing limitations such as family size and registry availability that are associated with the haploidentical and MURD settings. MMURD also enables selection of demographics such as younger age, matched sex, donor-specific antibodies, and other important factors. Younger age in particular has shown to yield better outcomes, as two-year survival linearly decreases by 4% per decade of donor age. Among the NMDP file, donors 18 to 29 years old account for 50-90% of 7/8 matched donors available to patients across all race/ethnicity groups.

He concluded that these new approaches have the potential to transplant across HLA barriers, to expand donor choice, and to expedite the donor selection process to avoid disease progression.

Discussion session
(Unidentified) asked what percentage of MMURD transplants use the PT-Cy platform and wondered if the platform is used universally. **Dr. Spellman** answered that the registry records a mix, although there has been a substantial increase. They are looking at proposals to evaluate this. Right now, 500-600 cases of MMURD PT-Cy have been reported for acute leukemia. **(Unidentified)** followed by asking about the learning curve of PT-Cy. They wondered if a center that is new to PT-Cy will have immediate good results. **Dr. Spellman** said that outcomes vary, but they generally see a difference in PT-Cy over time, which may reflect a learning curve and variation in approach.

Dr. Delaney pointed out that the numbers seem quite low on center-specific outcomes analysis looking at one-year mortality during a two-year period. **Dr. Spellman** said this was because they selected for the largest group. Within center-specific outcomes, they break out single, double, and match grade across all the cord sources. These data represented the double cord sources.

Dr. Horowitz pointed out the value of studying the superiority of a young MMURD vs. an older haploidentical donor. She said that it is important to spread the message that no patient who needs a transplant should be unable to receive one due to lack of donor.

A Multi-Center, Phase III, Randomized Trial of Reduced Intensity Conditioning and Transplantation of Double Unrelated Umbilical Cord Blood versus HLA-Haploidentical Related Bone Marrow for Patients with Hematologic Malignancies

Claudio Brunstein, MD, PhD

Dr. Claudio Brunstein presented a study on double umbilical cord blood (dUCB) versus HLA-haploidentical related bone marrow (haplo-BM) for patients with hematologic malignancies. His research team hypothesized that, compared to dUCB, haplo-BM patients would have a 15% higher two-year progression-free survival.

The study was a Phase 3 randomized trial in the reduced intensity setting. They enrolled patients with hematologic malignancies, namely acute myeloid leukemia or lymphoma, with a primary endpoint of progression-free survival at two years post-transplant. From 2012-2018, the study accrued 368 patients aged 18-70 years with acute leukemia or lymphoma who were required to have a dUCB or haplo-BM donor available prior to enrollment. Dr. Brunstein noted that, of those patients who eventually went to transplant, one patient in the dUCB arm ended up receiving haplo-BM, while 11 patients in the haplo-BM arm ended up receiving dUCB. The results by intention-to-treat from the time of randomization included progression-free survival, treatment-related mortality, relapse/progression, and overall survival. Other treatment arm-specific endpoints included neutrophil recovery, platelet recovery, and acute and chronic GVHD.

Progression-free survival at two years was similar between the two treatment arms, estimated at 35% for dUCB and 41% for haplo-BM. Multivariate analyses revealed that only disease status with lymphoma in partial remission and disease risk at time of transplant were independent predictors of higher risk of treatment failure. Cumulative incidence at two years was the same between the two treatment arms, while treatment-related mortality was slightly higher in the dUCB group (18%) than the haplo-BM group

(11%). Overall survival at two years was statistically significantly higher in the haplo-BM arm (57%) compared to the dUCB arm (46%). The primary causes of death were relapse and infection.

By treatment arm, neutrophil recovery was better in the haplo-BM group than the dUCB group, although the dUCB recovered neutrophils slightly faster. At 100 days after transplant, haplo-BM patients were more likely (84%) to have recovered more than 20,000 platelets compared to dUCB patients (78%). The dUCB group was more likely (35%) to have grade II-IV acute GVHD at 180 days after transplant than the haplo-BM group (28%). There were no significant differences in grade III-IV acute or chronic GVHD.

Dr. Brunstein concluded that there was no significant difference in two-year progression-free survival between dUCB and haplo-BM patients, with or without adjustment for transplant center. Neutrophil recovery was faster in dUCB patients, but haplo-BM patients showed better neutrophil recovery by day 60 post-transplant. Haplo-BM patients also showed lower treatment-related mortality and better overall survival. There were no significant differences in relapse, grade II-IV or III-IV acute GVHD, or chronic GVHD.

These results suggest that both double umbilical cord blood and haploidentical bone marrow extend access to transplantation. Although the trial did not find the expected 15% difference in progression-free survival, the lower treatment-related mortality and better overall survival favor haploidentical bone marrow.

Dr. Brunstein said an upcoming study will compare the results of this study with results from the community. Preliminary results find that the community has begun to favor peripheral cord blood with PT-Cy. Another exploratory study on center expertise and outcomes finds that centers with greater experience in dUCB transplants or haplo-BM transplants showed better outcomes in each, respectively. Meanwhile, centers with little experience in either showed better performance on haplo-BM procedures, suggesting that this platform is more exportable to centers with less expertise.

Discussion session
(Unidentified) asked how many centers were cord blood experts. **Dr. Brunstein** said that ten centers were experts.

Cord Blood Derived Versus Specific T Cells

Catherine Bollard, MD, MBChB

Dr. Catherine Bollard started by suggesting that antiviral drugs in the post-transplant setting are not always effective, and that antiviral T cell therapy after stem cell transplant may offer a viable alternative as a post-transplant therapy. When virus-specific T cell (VST) immunity post-transplant decreases, rates of viremia increase. The adoptive transfer of VST has proven efficacy in the seropositive setting, and improved technology has increased access to VST beyond boutique centers. A substantial number of patients have been treated with VST with high success rates and minimal risk of GVHD.

However, the incidence of viral infections after alternate donor transplant increases when the donor is seronegative for the virus of interest. This is particularly important in the cord blood setting because of the naivety of the donor cord blood. There is also a need to target multiple viruses in a single strategy.

Dr. Bollard's research team was interested in manufacturing cord blood-derived VSTs for clinical use, trying to take a portion of the cord blood unit to generate VSTs using dendritic cells as the antigen presenting cells, pulsed with peptides overlapping and spanning the regions of interest (in this case CMV, EBV, and adenovirus). The idea was that the 80% of the cord blood unit is used for the transplant, while 20% remainder is used to generate VSTs. They had better expansion when they used peptide pulsed antigen presenting cells instead of gene-engineered antigen presenting cells. No matter the production method, they were left with a product that looks very similar to products in the seropositive donor setting, with a mix of CD4s, CD8s, and components of CD62s, which are important for long-term persistence *in vivo.*

They found that the epitopes recognized by the cord blood-derived products were different than those recognized by seropositives, specifically in the CMV setting. They saw a restricted response in the seropositive setting compared to the seronegative setting, which had a broader response and recognized more atypical regions of the virus, which is important for avoiding immune escape *in vivo.* Blood cord-derived VSTs are also more genetically diverse than seropositive donor-derived T cells.

To determine efficacy, they studied cord blood-derived VSTs in a pediatric population. Some of the children received cell infusion for active viral disease, while some received T cells as prophylaxis to prevent viral activation. Only one patient in the prophylaxis setting showed evidence of viral activation, and all of the patients had excellent outcomes. The majority of patients treated for active viral infection also did well, and only two had a leukemia relapse (unrelated to VST treatment). Another team found that cord blood VSTs may have a small alloreactive component, but there is no clinical translation into acute GVHD.

Dr. Bollard reviewed persistence issues in cord blood VSTs. Her team conducted TCR sequencing of the products and of the peripheral blood samples pre- and post-infusion. They were able to track unique clones present in the products but not in pre-infusion sample out to at least 12 months post-VST infusion. In some cases, these clones expand exponentially; expansion increases in the presence of viral reactivation, but unique clones still persist even in the absence of viral reactivation. The TCR repertoire also correlates with CMV control: higher diversity at one-year post-transfusion is associated with longer-term protection against CMV.

She summarized that cord blood-derived VSTs in the donor-specific setting are safe, persistent, and protective *in vivo* (especially in the prophylaxis setting). Unfortunately, broadened applications may be limited by long manufacturing times, which can take up to 70 days. To address this, Dr. Bollard's team cut manufacturing time to 21 days by omitting the gene engineering strategy. They also expanded the virus targets to include BKV, which commonly occurs in this population. Their current product is cord blood-derived VSTs for BKV, CMV, EBV, and adenovirus.

They plan to explore this approach in the double cord setting and other areas, which may include the third-party VST approach. Currently, they are exploring cord blood VSTs in the HIV and Zika virus settings, with plans to expand to SARS-CoV-2. In the seropositive setting, they have found broad specificity to the structural proteins of SARS-CoV-2; seropositive COVID patients see a much broader response than seronegative COVID patients. To broaden to true naïve donors, they have used the cord blood platform and shown that they can generate SARS-CoV-2 specific T cells from cord blood.

Dr. Bollard concluded that they have had success in safely expanding VSTs from naïve cord blood in multiple targets in the donor-specific settings, and a study on the double cord setting is underway.

There is an opportunity to expand cord blood as a third-party donor source in the VST setting. In HIV and CMV, and perhaps SARS-CoV-2, these cord blood-derived TSVs recognize a much broader region of the viral antigen. This approach also offers an off-the-shelf platform for gene modification and gene engineering strategies.

Discussion session
Dr. Delaney asked Dr. Bollard to talk about her vision of how to move the third-party approach forward towards broad accessibility. She also wanted clarification on partnerships with public cord blood banks, as well as the team's COVID-19 approach. **Dr. Bollard** replied that cord blood as the ideal donor source for third-party products is appealing and demonstrates the increased ease of manufacturing VSTs. A private-public relationship would necessitate a bank with a lot more products, and a model for this may entail centralized manufacturing or a GMP-in-the-box model. Either way, cord blood will eventually be a readily available donor source. Cord blood banks have also been valuable during the current pandemic context because donors have been unaffected by viral infection. In some communities they treat, many children have been unable to clear SARS-CoV-2. Her team is looking at treating this patient population, which they hope will not have a messy or uncontrolled inflammatory response to the T cell therapy.

Dr. Laughlin asked if their group or others have data that would support or refute whether full or partial HLA match might impact persistence of these cells in the third-party off-the-shelf setting. **Dr. Bollard** replied that third-party T cells all get rejected within three months, which may be beneficial because third-party donor cells may be undesirable in the post-bone marrow transplant setting. This approach would be a bridge therapy to endogenous immune reconstitution, although repeat dosing is also an option. There are opportunities for the donor-specific setting if 20% of the cord is available. You have to know through which HLA allele you have your virus-specific activity, and as long as you have shed alleles at the location of the virus-specific activity, the chances of the third-party VST product eliciting a clinical response increase appreciably.

Cord Blood Derived CAR NK Cells

Katy Rezvani, MD, PhD

Dr. Katy Rezvani began by reviewing how the chimeric antigen receptor (CAR) brings together the antigen recognition site or domain of a monoclonal antibody and the signaling domain of a T cell or a natural killer (NK) cell. This chimeric molecule can be inserted into a T cell or an NK cell using viral methods or electroporation so that the immune cell can recognize a tumor that expresses the antigen against which the CAR is directed, much the way an antibody would.

There are a number of FDA-approved CAR T cells available (Kymriah, Yescarta, and Tecartus), all of which are autologous products. The process takes three to four weeks from the time the patient undergoes apheresis to the time the patient receives the product. The results have been unprecedented and have resulted in a paradigm shift in the field of cell therapy. Three early studies in pediatrics and young adults with acute lymphoblastic leukemia show that responses are 80% or higher. However, it is important to note that the therapy has a risk of toxicity in the form of cytokine release syndrome. Toxicity occurs in about 15-50% of patients, and 30-50% of those with toxicity require ICU management. Similarly, in non-Hodgkin lymphoma, overall response rates range from 50-70%, and one-year survival is about 30-40%.

In addition to the risk of toxicity, CAR T cell therapy carries significant financial burdens. All three of the FDA-approved CAR T cell products range from $373,000 to $475,000 each, attributed to the autologous nature of each product. Additionally, inpatient management can range from $400,000 to $1 million.

These problems led researchers to consider a different kind of CAR therapy. Researchers discovered that NK cells are an attractive alternative to T cells because they are part of the innate immune system, they carry low GVHD risk, and recognition occurs through a complex array of receptors. NK cells also enable creation of an off-the-shelf allogeneic product that allows one donor to treat multiple patients at low cost with negligible GVHD risk.

Yet there are limitations to NK cell immunotherapy for treatment of cancer. Unlike T cells, NK cells have a limited persistence with a half-life of two weeks, while full immunotherapy would require weeks-long persistence. And although NK cells are already poised to recognize cancer cells through germline-encoded receptors, not all cancers are susceptible to NK-mediated killing, and there may be a need to introduce antigen specificity with a CAR. Finally, there are logistical challenges to obtaining NK cells, which need to be collected on an individual-case basis from cord blood or a healthy haploidentical donor. Although NK cells can be collected from the patient, autologous products are less effective. Another potential advantage of using cord blood (as opposed to peripheral blood) as a source for NK cells is that cord blood NK cells are naïve and immature. Her team did transcriptome profiling to looke at gene expression profiles and found that cord blood-derived NK cells have higher expression of genes related to cell cycling, cell division, and DNA replication, suggesting that they are better at *in vivo* proliferation and persistence.

To overcome some of the limitations of NK cells, specifically *in vivo* persistence and antigen specificity, Dr. Rezvani's team collaborated with Dr. Pietro Dotti to test a retroviral vector. Another investigator then developed a protocol for *ex vivo* expansion and transduction of cord blood derived NK cells with this CAR, and then demonstrated that when these CAR NK cells are infused into immunodeficient mice, high frequencies of CAR NK cells were still present in the blood at 70 days post-infusion, nearly ten times as long as one would expect.

Next, they went to their GNP facility to develop the GMP program for expansion and transduction of CAR NK cells. Dr. Rezvani reviewed the 15-day production process, from collection of the frozen cord blood unit at the bank, ficolling, negative selection of NK cells, expansion and activation, transduction with retroviral supernatant, culture conditioning, and flow cytometry. The process mines a median of 40 billion cells from one cord blood unit, enabling production of more than 100 doses of CAR NK cells from a single cord blood unit.

With these data, they went to the FDA to start a first-in-human clinical trial, where the cord unit was initially picked as 4/6 HLA matching but later changed to off-the-shelf with no consideration for HLA match. The CAR NK cells were manufactured and patients received an infusion of CAR NK cells at different levels. The data from the stage 1 dose escalation study were recently published in the NEJM. None of the 11 study participants experienced cytokine release syndrome or neurotoxicity. Response was positive in 8 of 11 patients, 7 of whom experienced full remission—including patients who received completely mismatched cords.

Dr. Rezvani summarized by emphasizing that cord blood NK cells can be engineered to express a CAR to redirect their specificity and a cytokine to enhance their *in vivo* proliferation and persistence. A first-in-human clinical trial of CAR19/IL5 transduced cord blood NK cells resulted in responses in 8 of 11 patients

with no occurrence of cytokine release syndrome or GVHD. Cord blood CAR NK cells are under development for other types of cancer, including T cell lymphoma, acute myeloid leukemia, multiple myeloma, and glioblastoma.

Discussion session
There were no questions from the members of the Council.

Cord Blood in Regenerative Medicine

Joanne Kurtzberg, MD

Dr. Joanne Kurtzberg began by introducing cell and regenerative therapy as a rapidly changing and emerging field. There are hundreds of ongoing trials on cord blood and other derived cells for a wide array of diseases and routes of administration. The product that is furthest along uses bone marrow-derived third-party MSCs for treatment of acute refractory GVHD in children.

She reviewed ongoing work at Duke University to expand uses of cord blood and cells manufactured from cord blood tissues. They currently manufacture three types of therapeutic cells under GMP: cord blood, cord tissue MSCs, and DUOC (a microglial-like cell manufactured from monocytes in cord blood that can remyelinate the brain and other nerves). She talked about some of their key findings, beginning with cerebral palsy and hypoxic-ischemic injury (HIE). They have done preclinical work using mouse brain slices to find that human umbilical cord monocytes can rescue mouse brain cells from HIE. Importantly, this seems to be a property of cord blood monocytes, but not adult peripheral blood monocytes.

This work led Dr. Kurtzberg and her team to pursue an IND to determine if autologous cord blood infusions can restore motor function in children with spastic cerebral palsy. They conducted a study in which children were treated either with a cord blood infusion or with a placebo; after twelve months, the study conditions switched to ensure that all children eventually received an infusion. They found that the infusions were well tolerated and that children treated with cord blood doses exceeding 25m cells/kg showed a significant improvement in motor function as measured by the GMF-66 Scoring System at one year post-treatment.

Because they identified a dose effect in the first study, the team tested the dose with allogeneic cord blood, moving to 100m cells/kg of cord blood per infusion. Participants were 90 pediatric patients with cerebral palsy who were randomized to receive high-dose allogeneic unrelated cord blood, human cord tissue MSCs, or control setting. The children were evaluated at baseline and at six months and one year after treatment. They found that the allogeneic cord blood arm showed a statistically significant improvement in motor function, while the MSC arm did not.

The research team also studied these treatments in babies with HIE. Without any treatment, HIE has an 80% fatality rate; treated with head hypothermia, 50% of babies with HIE survive, but most have significant neurological impairment by one year. This study compared babies who were treated with head cooling to those who were treated with a cord blood infusion. At one year after treatment, babies who received cord blood were twice as likely to survive with normal function.

They went on to do a Phase 2 randomized study, which was powered for 160 babies across 12 centers. Unfortunately, enrollment stopped at 37 babies due to accrual difficulties. Of the 162 babies screened,

half were eligible but not enrolled because their own cord blood was not collected. Analysis of first 29 babies again showed that twice as many babies survived with normal function at one year after treatment.

Given these results, they aimed to develop an off-the-shelf allogeneic product for these babies with consideration for babies' high risk for GVHD. They treated babies with allogeneic umbilical cord tissue-derived MSCs. The babies were able to leave the hospital at 9-10 days old (very early for babies with HIE), and their day 9 MRIs were normal. None showed formation of anti-HLA antibodies, and all babies had normal developmental milestones at one-year follow-up.

Her team also studies autologous cord blood infusions in children with autism spectrum disorder (ASD). They treated 25 children with autism (aged 2-6 years) with previously banked autologous cord blood, finding the same dose binding effect of 25m cells/kg. Children with nonverbal IQ of 70+ (not intellectually impaired but below average) were responsible for most of the responses at 6 months, which were sustained at 12 months.

They used these data to move forward to a Phase 2 trial in 180 children ages 2-7 years. No significant safety adverse events were observed during the study, although infusion reactions occurred in 4 of 61 children in the placebo group, 2 of 56 children in the autologous cord blood group, and 3 of 63 children in the allogeneic cord group. None were serious and all resolved with additional treatment with Benadryl, albuterol, and/or a second dose of solumedrol. Many parents (about half in each setting) reported mild and transient anxiety or other psychiatric symptoms in their children in the weeks after infusion. Psychiatric effects likely are attributable to disruption in the children's daily routines.

Responses in the placebo group were higher than expected, even in higher functioning children (with nonverbal IQ higher than 70). When they broke out the group by children aged 4-7 years with higher nonverbal IQ, they did see effects. Scores on the Vineland Adaptive Behavior Scales (VABS-3) showed huge placebo effects in children with intellectual disability, while older children with higher cognitive function were less likely to respond to placebo and had more improvements in communication. On the Clinical Global Impression-Improvement (CGI-I), they did not see an effect in autologous cord blood, perhaps because the cell dose was lower. Eye tracking and EEG analyses found statistically significant effects in the cord blood group among children with IQ greater than 70.

Dr. Kurtzberg concluded that although they did not meet their primary endpoint, this may be attributable to study design flaws. In children without intellectual disability, they did find improvements in communication, attention, and alpha and beta EEG power. Children receiving allogeneic cord blood showed improvement on the CGI-I compared to placebo. Notably, the high number of participants with intellectual disability may have compromised the interpretation of the study results, especially the high expectancy effect in the placebo arm.

They also finished and published a descriptive trial of cord tissue MSCs over a four-month period in 12 children who received 27 doses, finding subjective improvement in two-thirds of the children. However, they did see formation of anti-HLA antibodies in about half of the children. They have opened a randomized Phase 2 study of HCT-MSCs in children with ASD, giving 6m cells/kg to children with ASD aged 4 to 11 years with IQ higher than 70. Their primary endpoint will be a composite score of the socialization and communication standard score.

Last, Dr. Kurtzberg discussed a cell called DUOC-01, a microglial-like macrophage-derived cell grown from cord blood with the capacity to remyelinate the brain. This therapy could be revolutionary for children with leukodystrophies. Functional outcomes vary, with best outcomes in babies transplanted in the first month of life. Regardless, they have determined that DUOC promotes myelination and can modulate inflammation, and replace enzymes.

Based on these results, they have moved towards a clinical trial treating children with leukodystrophies using standard transplant followed by an intrathecal infusion of DUOC cells, either manufactured from the same cord blood unit or a different cord blood unit a month after transplant. Thus far, they have treated 28 patients. Children who received transfusions from a second cord blood unit developed fever and hypertension on the day of transfusion and they added hydrocortisone to the formulation, which has been well tolerated since then. They are moving this study towards adults with progressive muscular dystrophy.

Dr. Kurtzberg concluded that both autologous and allogeneic cord blood shows excellent safety profiles and efficacy in Phase 1 and 2 clinical trials in children with brain injury. Well-designed phase 2 studies will be necessary to confirm efficacy and to obtain regulatory approvals. Additionally, CT-MSCs modulate neuroinflammation and are undergoing testing in children with ASD. These therapies have immense potential to treat diseases with unmet needs.

Discussion session
Dr. Nancy DiFronzo asked if they give conditioning regimens with these products. **Dr. Kurtzberg** said that they do not, because they are not performing transplants; rather, they use these cells like drugs as intravenous infusions (except DUOC, which was administered intrathecally).

Cord Blood Transplantation: Challenges and Opportunities

Juliet Barker, MBBS

Dr. Juliet Barker discussed the importance of cord blood as an alternative stem source. Her presentation emphasized three primary benefits of cord blood, including outstanding results in centers of expertise, increased access for racial/ethnic minority groups, and rapid availability of cord blood grafts.

First, she talked about outstanding results of cord blood transplantation in centers of expertise. Over the last decade, many investigators have attempted to perfect ex vivo expansion with cord blood. Investigators at Sloan-Kettering have worked to reduce mortality without cord blood expansion. They have focused on all the components of a successful cord blood transplant other than manipulating the graft, including efficient searches, expert management, and optimal unit selection. A recent cohort of 90 adult patients who received cord blood transplants (primarily for acute leukemia) at Sloan-Kettering had an overall survival rate of 82% and event-free survival rate of 76%. All but one patient engrafted, and the three-year relapse was only 9%.

Notably, there were no survival differences by European versus non-European ancestry nor by HLA match, indicating that cord blood transplants extend access to minority populations. Dr. Barker noted that these cord blood transplants can be performed as a routine procedure because they were achieved without graft engineering. Long-term advantages also include very low rates of chronic GVHD and relapse. These survival outcomes rival those of any adult donor stem cell source.

Dr. Barker emphasized that the non-myeloablative cord blood transplant approach was abandoned more than a decade ago. In retrospect, there has been insufficient attention to ensuring center expertise and implementation of best practices, such as optimal unit selection. The goal now should be to improve each transplantation approach.

Next, Dr. Barker pointed out that cord blood extends transplant access to racial/ethnic minorities. Recent data indicate that increasing the size of the URD registry does not appreciably improve 8/8 match access for minority patients. The increasing diversity of the U.S. population presents challenges to finding an adequate match, particularly because the population of young donors is more diverse and less closely related to any given recipient. Additionally, not all patients will find an MMURD, and MMURD workup can lengthen transplant delays. Many patients have haploidentical related donors, but these families may face socioeconomic limitations, and in many cases the donor either is too young or too old. In fact, a 2017 study found that fewer than half of patients of African ancestry had suitable haploidentical donors. On the other hand, one study found that more than half of patients who received cord blood transplants were of non-European ancestry, indicating that cord blood transplants extend access to a broader, more diverse group of patients.

Last, Dr. Barker talked about the rapid availability and flexibility of obtaining cord blood grafts. This is particularly important for overcoming supply chain disruption, which has occurred this year as a result of the COVID-19 pandemic. Consequently, cord blood transplant can proceed quite quickly, and the rate-limiting factor to moving the patient into transplant is rarely the graft; more often, it is logistical factors such as patient work-up, insurance, bed space, and OR scheduling. Cord blood procurement remains the fastest of any stem cell source.

Despite these strong arguments in favor of continuing cord blood transplants, recent trends indicate a major contraction in cord blood transplant activity. Dr. Barker emphasized the need to increase interest, ease, and expertise in cord blood transplantation. Ongoing efforts to highlight and public good outcomes have seen limited success; instead, Dr. Barker suggested a need to conduct efficient URD searches and haploidentical workups to stop the futile pursuit of adult donors. Unfortunately, nearly 80% of U.S. centers have little or no cord blood transplant expertise, which may further compromise cord blood activity and outcomes.

This year, Dr. Barker has worked with a group to write cord blood transplant guidelines on behalf of the American Society for Transplantation and Cellular Therapy (ASTCT) cord blood special interest group. Four of these are published, two are in submission, and two are in progress. Pediatric guidelines are in development.

Dr. Barker concluded that cord blood is a high-quality stem cell source for a majority of patients, regardless of race, and loss of cord blood transplants will discriminate against racial/ethnic minorities. Cord blood also represents a national resource that remains stable even during supply chain disruptions. Given these benefits, the U.S. cord blood inventory must be preserved, and the ability to perform cord blood transplants must be maintained and supported. She suggested developing a national initiative to optimize the use of cord blood, which would include a national network of centers of excellence in cord blood transplant.

Discussion session

Dr. Bracey pointed out that the virtual response to COVID-19 has revolutionized patient management, and he wondered if these technologies can bridge the expertise gap across centers. **Dr. Barker** expressed interested in this idea.

Dr. Sergio Giralt reiterated that outcomes for cord blood are equivalent to (if not better than) alternatives when performed in centers of excellence, but activity and expertise in cord blood is starting to disappear. He asked about ways to incentivize people to get trained in cord blood, such as training fellowships. He also wondered how many centers would be needed to form a national cord blood network of excellence**. Dr. Barker** replied that the cell therapy field is vulnerable to the influences of "fashionable" science; although cord blood has become much easier (especially with the introduction of letermovir), people have lost interest in favor of trendier options. She cautioned physicians to remain aware that even in dedicated cord blood centers, it is difficult to thrive in an academic center without dedicated funding for a given platform. As a result, there is an urgent need for funding. The number of centers would depend on the scope of enterprise and funding availability, but she would want at least six centers.

Dr. Milano added that there is a need to focus on the benefits of cord blood, with careful attention to the way data are presented. **Dr. Delaney** agreed with Sergio's comment and said it is very important to consider that increasing population diversity will complicate donor-patient availability, which will change trends moving forward. There is a need for collaborative studies that define the "right" donor for the "right patient," balancing ease of match with best practices. **Dr. Arnold** agreed that limiting alternative donors would create health care disparities and limiting chance for cure/treatment among minority individuals. Dr. Barker's and Dr. Milano's talks are particularly important for ensuring we provide opportunities to protect those options.

Cord Blood Transplantation: Challenges and Opportunities

Filippo Milano, MD

Dr. Filippo Milano continued Dr. Barker's discussion by reviewing real and perceived barriers to performing cord blood transplants.

The first barrier is delayed hematopoietic recovery. While the rate of graft failure has significantly decreased since the introduction of dUCB, studies still find a continued delay in time to hematopoietic response for cord blood transplants compared to other sources such as bone marrow and peripheral blood. This perceived delay in graft recovery has led many centers to expand stem cell therapies to accelerate engraftment, reducing the time to neutrophil recovery from 25 to 11 days. However, Dr. Milano suggested that these efforts may have been unnecessary. His team just finished a randomized study comparing patients receiving expanded cells versus a conventional single or double cord blood transplant. In the standard group, they found that median time of engraftment using myeloablative regimen was about 20 days, comparable to the timeline for bone marrow.

The second barrier is about viral infections. His team compared patients receiving cord blood to those receiving an HLA-matched or HLA-mismatched transplants. They found that those who received a mismatched transplant had a twofold-to-threefold higher risk of viral infection after transplantation. Prior to adoption of aggressive preventive strategies, nearly every patient experienced CMV reaction. After treatment with high-dose antiviral medications, the CMV reactivation rate dropped from 100% to 60%, and a new drug called letermovir may prevent CMV reactivation in all cases.

The third barrier is clinical outcomes and GVHD. Dr. Milano reviewed a study comparing cord blood from MURDs and MMURDs and found no difference in survival between the two donor sources. These good outcomes were primarily contributed to lower relapse rates. Some people do not believe these data, due in part to misunderstanding about the molecular mechanisms underlying relapse. One study identified HLA loss as one of these mechanisms, by which the disease escapes the graft's immunological surveillance. The study found that HLA loss was a common mechanism of relapse among haploidentical transplants (24%), MMURDs (11%), and MURDs (6%), while cord blood transplants showed 0% relapse due to HLA loss.

Dr. Milano also discussed chronic GVHD severity and functional status after alternative donor hematopoietic cell transplantation. His team conducted a study of 145 patients who received MMURD peripheral blood transplants, finding that the rate of chronic GVHD was significantly higher among patients receiving MMURD transplants compared to cord blood and haploidentical transplants. Patients receiving cord blood and haploidentical transplants also were better able to return to their daily activities and were more likely to cease immunosuppressive therapy.

He concluded that outcomes after myeloablative cord blood transplant have significantly improved over the last two decades, reaching outcomes comparable to MURD and haploidentical transplants. Cord blood transplants tend to have higher donor availability and diversity, lower relapse rates, less chronic GVHD, faster time to transplant, improved quality of life, and less risk of relapse. Additionally, engraftment and primary graft failure are no longer barriers to myeloablative cord blood transplants. Although higher risk for viral infections remain a concern, new drugs are promising for reducing post-transplant viral infections and CMV reactivation.

To defend this important stem cell source, there is a need to ensure that centers perform enough cord blood transplants, increasing the number of expert centers in the U.S. In terms of research, there is a need for more rigorous preclinical science to understand the unique biology of cord blood and to reinforce the importance of prospective and retrospective collaborative studies. Finally, a successful national initiative to protect cord blood transplantation may require data sharing among centers and the development of a common sample repository.

Discussion session
Dr. Laughlin said that it is premature to abandon cord blood in favor of haploidentical, based only on small datasets of short duration. She pointed out that much of the haploidentical data are based on bone marrow, but the community has gone to mobilize haploidentical peripheral blood as a graft source. She asked if this impacts quality of life and incidence of GVHD. **Dr. Milano** responded that they only do haploidentical peripheral blood transplants at this point; bone marrow is not used at his location. He said that GVHD is a concern, and he agreed that abandoning cord blood is premature and should not be entertained.

Dr. Bracey emphasized the importance of uniformity in the form of guidelines. He asked if the field of stem cell therapy is still maturing such that uniformity is not yet feasible. **Dr. Milano** replied that uniformity is challenging in the transplant field. Every center is different, and each prefers their own "magic recipe" for transplantation. Consequently, centers are averse to adopting standardized guidelines.

Dr. Laughlin pointed out that no one has discussed the business and financial enterprise of stem cell and bone marrow transplants. In the U.S., revenues from transplants often exceed those of interventional cardiology. Rapid uptake of haploidentical transplantation has been financially motivated. Even if an individual physician preferred to select a cord blood graft, this decision is not always supported within a given hospital system. This has contributed to a loss in physician expertise, particularly in cord blood transplantation. **Dr. Milano** said that they need to focus on the benefits and best practices of cord blood, rather than compare this source to others.

Consideration of Recommendation on Cord Blood

Council members discussed the draft recommendations on cord blood, which were shared with them for review in advance of this meeting. Their goal was to discuss the language of the draft, propose basic amendments if necessary, and vote on the recommendation.

Dr. Giralt began by reading through the high-level formal recommendation, which is that the ACBSCT recommends that HRSA "*continue to support collection of high-quality cord blood units through the NCBI to support the development of a demonstration project to optimize the utilization of cord blood for transplantation by providing guidance to transplant centers on uses of cord blood and coordinate and share best practices among entities involved in cord blood collection, selection, logistics, and transplant.*"

Dr. Bracey asked if the language of the recommendation was strong enough to yield the prior recommendation for six expert centers. **Dr. Gandhi** said that specifying exact numbers may not be advisable. The recommendation should be more general to guarantee long-term flexibility. **Dr. Giralt** recommended adding language to *"incentivize and promote creation of a network of cord blood centers of excellence"* rather than specifying an exact number. **Dr. Arnold** agreed with these additions and suggested adding a note for cord blood referral base or resource for providers of excellence.

Dr. Laughlin asked the Council to consider a shared protocol. She said that developing written best practices and providing web-based education is laudable, but as a clinician and transplant physician, they rely on protocols to carry best practices forward. **Dr. Gandhi** suggested changing Point 1 to *"develop and promote simplified CBU selection guidelines in conjunction with NMDP"* and changing Point 2 to "*work with transplant centers to develop sharable standard operating procedures for CBU selection and cord blood transplant activity*."

Dr. DiFronzo asked if they need to specify criteria for "centers of excellence." **Dr. Giralt** said that these criteria would eventually be defined by outcomes. **Dr. Gandhi** suggested changing Point 5 to *"incentivize the promotion of the creation and subsequent expansion of centers of excellence for cord blood transplantation"* **Dr. Barker** pointed out that the centers of excellence need immediate financial and administrative support. **Dr. Milano** suggested defining centers of excellence by number of procedures performed rather than outcomes, which may incentivize centers to begin performing cord blood transplants. **Dr. Horowitz** said this meeting is not the venue to establish criteria for defining centers of excellence, as this needs a much longer and more thoughtful consideration. The Council members strongly agreed with this point and proceeded without specifically defining "centers of excellence."

There was a motion to vote on the recommendation. All were in favor.

Car T Therapy: Current Status and Future Challenges

Sergio Giralt, MD

Dr. Giralt talked about current issues in commercial CAR T, with a focus on future challenges.

He briefly reviewed CAR T therapy, the name given to chimeric antigen receptor (CAR) genetically modified T cells that are designed to recognize specific antigens on tumor cells, resulting in their activation and proliferation, which eventually causes significant and durable destruction of malignant cells. CAR T cells are considered a "living drug" because they persist for long periods of time. They are generally created autologously, although technology is evolving to develop off-the-shelf allogeneic CAR T cells. The CAR is created by an antigen binding domain that can be modified to target specific antigens, most commonly CD19. The antigen of interest is only expressed in malignant cells, causing the CAR T cells to target those areas. The process is highly involved and may be time intensive, taking 10 to 28 days.

In general, what they have learned from commercial products is that there have been very few infusional toxicities. When toxicity does occur, it may be severe, including tumor lysis syndrome, cytokine release syndrome, neurological toxicity, and cytopenias. These cells need to be delivered in specialized centers, where experts can rapidly recognize and treat CAR-mediated treatment effects. Another challenge is that these toxicities (particularly cytokine release syndrome and neurologic toxicity) have late onset, therefore the patient needs to remain close to the expert center for at least four weeks after transplantation.

Currently, three FDA-approved products are commercially available: Kymriah, Yescarta, and Tecartus. Dr. Giralt reviewed some challenges related to these products. Products can only be infused in FACT-accredited programs, and patients require four weeks of stay post-transplantation, reducing access. Toxicities, when they occur, require hospitalization, and inpatient beds may be a limitation. There remain limited trained medical and non-medical personnel to staff CAR T therapy programs, and these programs require significant start-up investment to develop a suitable infrastructure and resource base.

Dr. Giralt then discussed the Cellular Immunotherapy Data Resource (CIDR) updates and governance, a genomics lab funded by the National Institutes of Health (NIH). The objectives of CIDR are to build the cell therapy registry for cancer as a resource for the medical community, to incentivize projects that will build the necessary infrastructure, to create systems and initiatives to maximize its use, and to leverage partnerships to sustain and expand programs. As of 2019, the registry comprised 1,603 patients.

Looking to the future, myeloma likely will be the next indication for cell therapy. A myeloma-targeted product from Bristol Myers Squibb is anticipated in 2021, as well as indications for adult ALL and CLL. At this time, off-the-shelf CAR T is not yet ready but is under development. A new off-the-shelf therapy called bispecific T cell engagers (BiTE) will soon become commercially available, which will directly compete with CAR T cell products. Access and resources remain a primary challenge as volume increases.

Dr. Giralt summarized that CAR T cells are a major therapeutic breakthrough for lymphoid malignancies. However, their use is associated with unique toxicities requiring specialized resources and personnel, and costs are likely to become problematic in the coming years. Access to these therapies will depend on support and development of specialized expert centers across the U.S.

Discussion session
Dr. Bracey commented on the need for revenue among blood donor centers, pointing out an opportunity to partner for increased access for selections. **Dr. Giralt** said they have discussed this with manufacturers, who are open to the idea of accrediting collection centers independent of the patient's treatment location. The transplant center apheresis resources can be freed once these commitments are made, which will remove apheresis as a limiting step.

CCR5 Genotype

Mary J. Laughlin, MD

Dr. Laughlin reviewed a protocol funded and supported by NHLBI through the R43 mechanism. The protocol is a Phase 1/2 prospective, open label, multisite, non-randomized study in which patients with HIV and hematological malignancies will be enrolled. These patients are uniformly excluded from the majority of clinical trials in allogeneic transplant. Their goal is to evaluate the safety of a single unit homozygous or heterozygous CCR5 Delta32 cord blood transplant, followed by a second non-matched off-the-shelf *ex vivo* expanded cryopreserved umbilical cord cell infusion.

Strong evidence suggests that allogeneic stem cell transplants have the potential to eliminate the HIV reservoir via the GvH mechanism. The rationale for cord blood as the graft source is the improbability (only .1-.4%) of finding a CCR5 Delta32 homozygous allogeneic marrow donor for HIV-infected hematology patients. HLA-mismatched umbilical cord blood expands the likelihood of finding CCR5 Delta32 homozygous donors, as the prevalence of CCR5 Delta32 homozygous units is estimated to be .8% with potentially over 5,000 units carrying the mutation.

Other investigators have taken the approach to type the entire inventory of a cord blood bank. Their approach was to tap into the 600,000 units that are searchable via the NMDP registry online, select from the best match for a particular patient, and then test those identified units to determine if they carry the CCR5 Delta 32 genotype.

HIV can enter a host cell via one of two mechanisms. Viruses that use the chemokine receptor CCR5 are termed "R5 HIV," those that use CXCR4 are termed "X4 HIV," and viruses that can use both co-receptors are called "R5X4 HIV." Although high levels of CXCR4 expression on circulating HIV target cells may be present at earlier timepoints, X4 or even R5X4 HIV rarely predominate until late in infection. This trial is directed towards the R5 HIV, which targets human CD4 cells by CCR5 binding.

They established proof-of-concept in a patient dubbed "the Berlin patient." The patient's physician searched his potential adult donors to identify a donor that carried the CCR5 Delta32 deletion. After transplantation, the patient showed stable engraftment of an HIV-resistant immune system, and the patient's antiretroviral therapy was discontinued successfully with no evidence of viral rebound over a period of 13 years.

The CCR5 Delta32 mutation is found only in European, West Asian, and North African populations. The allele frequency exhibits a north-south decline, with frequencies ranging from 16% in northern Europe to 6% in Italy and 4% in Greece. The broadest area of high frequency is located in northeastern Europe, particularly the Baltic region, Sweden, Finland, Belarus, Estonia, and Lithuania. The probability of finding an adequately HLA-matched unit is 85.6% for Caucasian pediatric patients and 82.1% for Caucasian adult patients, while the projected probabilities are lower for minority populations.

Dr. Laughlin reviewed the study design. Once an HIV-infected hematology patient requiring allogeneic stem cell therapy is identified, researchers use NMDP to conduct a preliminary search for potential adult donors. This is followed by screening blood spots of the ID's suitably HLA-matched UCB for CCR5D32 homo/heterozygous graft. The screening process involves CCR5 genotypic analysis using a nested PCR-based assay system on DNA preparations extracted from cord blood spots.

During the clinical trial, the patient receives an adequately HLA-matched CCR5 Delta32 homo- or heterozygous unmanipulated cord blood unit, given with an off-the-shelf, NOTCH-1 based *ex vivo* expanded second cord blood graft to support the patient during the first 90 days and to facilitate engraftment. Immune reconstitution is monitored post-transplant to determine optimal timing of planned antiretroviral therapy interruption, during which time viral load is closely monitored to determine any evidence of rebound. Accrual of 10 patients is expected across six centers, which were selected based on cord blood expertise and HIV expertise.

Discussion session
There were no questions from members of the Council.

COVID-19: Impact on Blood Stem Cell Transplantation

Kristin Naruko, CHTC
Ray Hornung, MBA

Ms. Kristin Naruko provided an update on NMPD volumes, both domestic and international, and the challenges presented by the COVID-19 pandemic. She highlighted specific examples of collaboration and partnership to achieve international success stories.

Over the last four weeks, there has been a small decline in formal patient searches. However, donor workups and cord blood order requests have not declined, and the number of donor collections and cord blood shipments has remained stable since 2019. Ms. Naruko also emphasized a massive uptick in cryopreservation, which increased from 8% in 2019 to about 80% in August and September 2020. NMDP asked centers to cryopreserve products in March to protect products during the pandemic. Cryopreservation requirements have been relaxed as of August, but this remains a safe and popular option. In terms of donor supply, the weekly median international products during FY2020 has remained steady from FY2019 at about 55 products per week from international donors.

Mr. Ray Hornung reviewed specific logistical challenges related to COVID-19. One of the primary barriers has been transportation, including delayed and cancelled flights, travel restrictions, low courier availability, reduced donor availability, and restrictions on final hand-offs. The NMDP emergency preparedness team has made substantial efforts to overcome these challenges. Cryopreservation guidance and support activities have included expanding the Mobilized Biobank capabilities to increase flexibility in collection scheduling and transport to ensure that patient treatment windows are met.

They have also leveraged multiple partnership to cross borders, including collaborations with Customs and Border Protection (CBP), the Transportation Security Administration (TSA), and more than 300 couriers and partner courier companies. The team has implemented donor and patient safety measures, such as remote donor testing and reduced donor travel to collection sites.

NMDP has successfully implemented a hub-and-spoke model to facilitate international product exchanges. Since the beginning of COVID-19, they have conducted more than 980 excursions. They have collaborated with partners in Europe to use European couriers who bring products to Germany, pack them in cooled containers, and fly them to Chicago where a team recovers the products for distribution to U.S.-based couriers. During the pandemic, they have completed 4,621 transportation legs and 2,842 total transports with 99.9% delivery success.

HRSA and Lockheed Martin have been invaluable partners for completing the most challenging excursions. Mr. Hornung highlighted ten cases in which few options were viable for delivery of life-saving therapy. Lockheed Martin facilitated these efforts by flying non-stop round-trip internationally to pick up and drop off products. A particularly extraordinary case required a flight into a small mountain town in Colombia to pick up a donor and transport her to the U.S.

Public Comment

Mr. Walsh introduced the one public commenter, Dr. Asawari Bapat. Dr. Bapat suggested that that physicians and patients in the Middle East and Asia have faced many similar challenges. She commented on the need to support patients across the world by developing guidelines to facilitate procedure logistics and reduce time to transplant, particularly for cord blood. She pointed out that COVID-19 has intensified this ongoing need.

Closing

Mr. Walsh and Dr. Gandhi thanked the members of the Council, and Mr. Walsh adjourned the meeting at 5:39 pm EST.