REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
04/14/2023	Interim Technical Report	January – March 2023

4. TITLE AND SUBTITLE
Development of Medical Technology for Contingency Response to Marrow Toxic Agents – Interim Technical Report with SF298 January 1, 2023 – March 31, 2023

5a. CONTRACT NUMBER
N/A

5b. GRANT NUMBER
N00014-23-1-2057

5c. PROGRAM ELEMENT NUMBER
N/A

6. AUTHOR(S)
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5d. PROJECT NUMBER
N/A

5e. TASK NUMBER
Project 1, 2, 3, 4

5f. WORK UNIT NUMBER
N/A

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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8. PERFORMING ORGANIZATION REPORT NUMBER
N/A

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

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Arlington VA 22203-1995

10. SPONSOR/MONITOR'S ACRONYM(S)
ONR

11. SPONSORING/MONITORING AGENCY REPORT NUMBER
N/A

12. DISTRIBUTION AVAILABILITY STATEMENT
Approved for public release; distribution is unlimited

13. SUPPLEMENTARY NOTES
N/A

14. ABSTRACT

1. Contingency Preparedness: Collect information from transplant centers, build awareness of the Transplant Center Contingency Planning Committee and educate the transplant community about the critical importance of establishing a nationwide contingency response plan.

2. Rapid Identification of Matched Donors: Increase operational efficiencies that accelerate the search process and increase patient access are key to preparedness in a contingency event.

3. Immunogenic Studies: Increase understanding of the immunologic factors important in HSC transplantation.

4. Clinical Research in Transplantation**:** Create a platform that facilitates multicenter collaboration and data management.

15. SUBJECT TERMS
Research in HLA Typing, Hematopoietic Stem Cell Transplantation and Clinical Studies to Improve Outcomes

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
				18	Jeffery Auletta, M.D. - Sr Vice President and Chief Scientific Director
a. REPORT U	**b. ABSTRACT** U	**c. THIS PAGE** U			**19b. TELEPONE NUMBER (*Include area code*)** 763-406-4730

Grant Award N00014-23-1-2057

DEVELOPMENT OF MEDICAL TECHNOLOGY

FOR CONTINGENCY RESPONSE TO MARROW TOXIC AGENTS

QUARTERLY RESEARCH PERFORMANCE REPORT

SUBMITTED April 14, 2023

Office of Naval Research

And

The National Marrow Donor Program®

500 5th St N

Minneapolis, MN 55401

I. Heading

PI: Jeffrey Auletta, M.D.
National Marrow Donor Program
N00014-23-1-2057
Development of Medical Technology for Contingency Response to Marrow Toxic Agents

II. Scientific and Technical Objectives

The main goal of all activities funded through this grant is to develop, test and mature the ability of the NMDP Coordinating Center and NMDP contracted network sites network sites to address contingency events wherein civilian or military personnel are exposed to marrow toxic agents, primarily ionizing radiation or chemical weapons containing nitrogen mustard. As a result of prior efforts in this regard a solid foundation has been established. The proposed new activities will continue to enhance and expand our capabilities in each of the four focus areas. Contingency preparedness activities will continue to integrate NMDP's role with federal, state and local agencies.

An accident, a military incident, or a terrorist act in which a number of individuals are exposed to marrow toxic agents will result in injuries from mild to lethal. But the extent of individual injuries and the likelihood of recovery in many cases will not be apparent until days or weeks after the event. Casualties will be triaged by first responders, and those with major marrow injuries who will need aggressive medical support and may be ultimately candidates for hematopoietic cell transplantation (HCT) will need to be identified. While these patients are being supported, HCT donor identification activities will be initiated because it will not be initially clear which ones may ultimately require HCT. NMDP-approved transplant centers will provide a uniform and consistent clinical foundation for receiving, evaluating and caring for casualties. NMDP Coordinating Center will orchestrate the selection and testing necessary to rapidly identify the best available donor or cord blood unit for each patient utilizing its state-of-the-art communication infrastructure, sample repository, laboratory network, and human leukocyte antigen (HLA) expertise. NMDP's on-going immunobiologic, bioinformatics and clinical research activities promote studies to advance the science and technology of HCT transplantation and directly translate research results to improve outcomes and quality of life for the patients.

Importantly, most individuals with near-lethal marrow toxic injuries will recover their own marrow function provided they receive intensive supportive care from the medical professionals that are part of the contingency response community.1 These professionals can save the lives of persons with severe marrow suppression using the knowledge and skills practiced every day to treat patients undergoing HCT coordinated through the NMDP.

III. Approach

A. Contingency Preparedness

HCT teams are uniquely positioned to care for the casualties with marrow toxic injuries, such as Acute Radiation Syndrome (ARS), from exposure to ionizing radiation or chemicals. The NMDP manages a network of hospitals that work in concert to facilitate unrelated HCT. The Radiation Injury Treatment Network (RITN), comprised of a subset of NMDP's network centers as well as non-NMDP network centers, is a national network of medical centers with expertise in the management of bone marrow failure and works with partners from other medical specialties to assist with managing ARS and its health-related consequences in response to marrow toxic mass casualty incidents.

B. Development of Science and Technology for Rapid Identification of Matched Donors
Rapid progression to successful transplantation following a marrow toxic exposure or disease diagnosis affects survival. Decreasing the time to identify the optimal donor is critical. Methods are under development to rapidly identify and provide the optimal donor for HCT.

C. Immunogenetic Studies in Transplantation
Improving strategies to avoid and manage complications due to graft alloreactivity is essential to improve the outcomes of HCT. Research efforts focus on strategies to maximize success of HCT while minimizing the toxicity related to alloreactivity between the donor graft and the recipient.

D. Clinical Research in Transplantation
Clinical research creates a platform that facilitates multi-center collaboration and data management to address issues important for managing radiation exposure casualties. Advancing the already robust research capabilities of the NMDP network will facilitate a coordinated and effective contingency response.

IV. Updates

A. Contingency Preparedness

Maintain the Radiation Injury Treatment Network (RITN) to prepare for the care of patients resulting from a hematopoietic toxic event

Radiation disaster and countermeasure research education

- Advanced HAZMAT Life Support (AHLS) for Radiological Incidents & Terrorism 4-hour course (1) Has a target audience of physicians, physician multipliers, nursing staff, administrators and coordinators from departments such as bone marrow transplant, hematology, oncology, radiation safety, nuclear medicine, and the emergency department, as well as emergency management, and first responders; and (2) Will include interactive lectures and tabletop exercises that trains healthcare professionals to evaluate and care for irradiated and radiologically contaminated patients.
    - Due to cancelation of REAC/TS sponsorships, four additional RITN hospitals will host two 4-hour sessions on radiological incidents and terrorism.
    - This is in addition to the one RITN hospital in the FY2023 budget (West Virginia University Hospital, Morgantown, WV).
    - Additional hospitals:
        - Corewell Health (Grand Rapids, MI)
        - University of Wisconsin (Madison, WI)
        - Orlando Health, (Orlando, FL)
        - Temple University (Philadelphia, PA)

Radiation disaster preparedness training

- No updates at this time.

Hospital radiation disaster preparedness

- Annual disaster readiness tabletop exercises (drills) will be scheduled for current RITN hospitals to participate for their annual task completion. Seven sessions will be offered between June and August 2023.
- Additional disaster readiness exercises (drills) have yet to be scheduled: one Full-scale exercise (TBD), five Functional exercises (Grand Rapids, MI, Atlanta, GA, Salt Lake City, UT, and one TBD), and two Regional Tabletop exercises (Maryland Healthcare Coalitions and Guam).

Hospital network growth

To ensure the appropriate growth in a direction that supports the vision and needs of the Department of Defense-Office of Naval Research as well as the Department of Health and Human Services Administration for Strategic Preparedness and Response plans for response to a radiological/nuclear disaster with-in the continental U.S.

- Targeted hospitals in the following cities:
    - Atlanta, GA
    - Nashville, TN
    - Los Angeles, CA
    - San Antonio, TX
    - Dublin, CA
    - Memphis, TN
    - Phoenix, AZ
    - New Orleans, LA
    - Albuquerque, NM
- Specific hospitals:
    - Children's Healthcare of Atlanta (CHOA) (Atlanta, GA)
    - Skyline Medical (Nashville, TN)
    - Children's Hospital Los Angeles (CHLA) (Los Angeles, CA)
    - Stanford (Dublin, CA)
    - Corewell East Beaumont Children's Hospital (Royal Oak, MI)
    - Cooper Health (Camden, NJ)
    - LCMC (New Orleans, LA)

Federal partnership development

- Association of Healthcare Preparedness Professionals (AHEPP)
    - RITN presented at AHEPP's annual meeting February 28, 2023.
    - AHEPP's mission is to provide healthcare and other preparedness professionals with opportunities for networking, resource sharing, continuing education, and scholarly exchange (ahepp.org).
- National Association of County and City Health Officials (NACCHO) Preparedness Summit
    - Recovering from a long pandemic response, there is a need to redefine not only the endemic phase of COVID-19, but reassess responses to natural disasters, emerging infectious diseases, terrorist threats, climate issues, and maintenance of all-hazards plans. "Recover. Renew: Reprioritizing All-Hazards Preparedness" is the theme and will give attendees the opportunity to reevaluate issues (old and new) in preparedness, share resources, build skills, and to network with others in the industry.

- RITN is a member of the Radiation Workshop Planning Committee which is conducting a 1-day radiation-specific planning workshop Sunday, April 23, 2023.

B. Development of Science and Technology for Rapid Identification of Matched Donors

Expand the genetic diversity of the registry through continued addition of adult donors and cord blood units, utilizing high volume HLA typing methodologies

During the past quarter, a total of 39,722 newly registered volunteer donors were HLA typed and added to the Be The Match Registry.

Modeling and analysis of registry coverage for the Warfighter

Population genetics-based registry models projected donor coverage for warfighters as potential patients approaches but does not reach 100% when considering HLA match levels down to 5 of 8 matching alleles. Our models seek to better understand the contribution of racially and ethnically diverse donors for matching in diverse groups. Current resources for validation of these results through simulations of donor registry searches with patient-donor HLA match criteria require more frequent and comprehensive data updates and greater flexibility in matching rules along with the ability to consider outcome probabilities in the presence of missing data. Previously, registry models were restricted in the number of mismatched HLA alleles that could be calculated.

Over the last quarter, we produced new Python code to improve the capabilities and efficiency of registry analysis. This new code allows another level of mismatch. Registry searches were conducted for the purposes of validating modeled results and evaluated for quality testing and assessment of model result accuracies. During this process, developers implemented new improvements for greater accuracy in the modeling results. This modeling aids in preparation for coverage of potential donor sources to Warfighters of diverse race and ethnic backgrounds in case of radiation emergencies.

Development of science and technology for rapid communication of HLA data

In the last quarter, a manuscript, titled "Assessment of HLA-DPB1 Genetic Variation with an HLA-DP Tool and Implications in Clinical Transplantation", was submitted with major revisions invited by the journal *Blood Advances*. This manuscript describes genetic variation in HLA-DPB1 exon 2 that defines permissive and non-permissive TCE groups, and exons 2 and 3 (in linkage with rs9277534) inform low- and high-expression allotypes with varying implications for transplant outcomes identified in previous studies. The complex relationship between TCE and expression models was explored, and the importance of exon 3 sequence data was uncovered through this analysis. Archived donor search lists for 2,545

patients who underwent transplantation from an HLA-11/12 unrelated donor mismatched for a single HLA-DPB1 allele were analyzed. Depending on the order in which TCE and expression criteria are considered, some patients have different TCE- and expression-favorable donors in terms of transplant outcome risk. In addition, many expression-favorable alternatives exist in the search lists were uncovered. A novel tool called ExPAT (Expression of HLA-DP Assessment Tool), consisting of a public web application, Python code package, and analysis pipeline (Figure 1) was developed and launched to facilitate exploration of HLA-DP genetics and impact on expression and improved matching of transplant donors and patients.

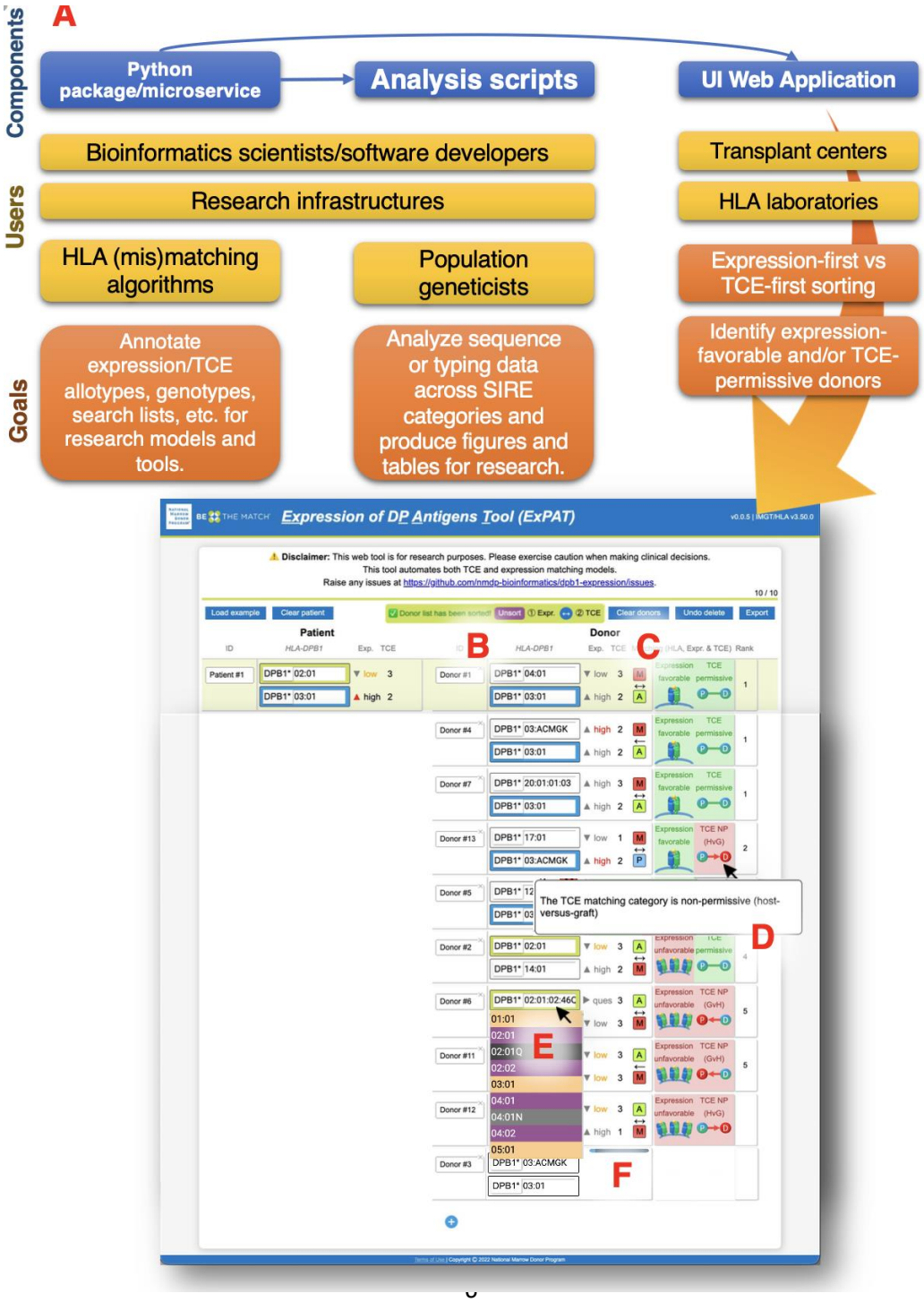

Figure 1: A diagram of ExPAT's utilities for several user types and a wide array of capabilities. (A) The user interface web application sports several functionalities via the immunogenic TCE model: (B) reversible expression and TCE donor sorting, (C) matching information (HapLogic grades and vector directionality), (D) allele expansion, (E) tooltips, (F) HLA typing autocompletion, and (G) real-time calculations.

Several prognostic scores and models for predicting the outcomes of allogeneic hematopoietic cell transplantation (allo-HCT) have demonstrated utility in stratifying patients into risk classes but struggle to make accurate individualized predictions. A machine-learning pipeline for predicting one-year overall survival after hematopoietic cell transplantation (HCT) was developed using a set of readily available clinical variables. Transplant records from the CIBMTR database restricted to the years 2014 - 2018 in the United States (N=36,538) were utilized. The dataset was split into training (85%) and test (15%) sets. Several machine learning models were built using the selected features, and their predictive performances were evaluated. XGB was identified as the best model and also performed better than standard logistic regression, C-index 0.76 vs. 0.63. The top-ranked predictors (features) identified by the XGB model include patient-related factors (recipient age and Karnofsky performance status), disease-related factors (disease type and status at time of HCT), and transplant-related factors (donor/recipient sex and CMV serostatus match, conditioning regimen, donor type, donor age group). Potential uses of this clinically based machine learning pipeline include (1) providing a personalized prognostic assessment, (2) informing clinical decisions regarding donor selection and conditioning regimen choices, (3) generation of testable hypotheses that could potentially guide future trials, and (4) establishing a baseline, upon which the added value of integrating more costly high dimensional data, such as omics data, can be evaluated. A manuscript summarizing this work entitled "Machine Learning Approach to Predicting Overall Survival After Allogeneic Hematopoietic Cell Transplantation" was submitted. In addition, an invited talk titled "Disease-Specific Overall Survival Prediction after Allogeneic Hematopoietic Cell Transplantation" was presented at the BMT Tandem Meetings.

Use of population genetics and machine learning to automate the donor selection process

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Apply BART NFT method to prediction of transplant outcomes

The paper "Nonparametric Failure Time: Time-to-event Machine Learning with Heteroskedastic Bayesian Additive Regression Trees and Low Information Omnibus Dirichlet Process Mixtures," was published in the journal Biometrics. (https://doi.org/10.1111/biom.13857). This method is an advance in the field of machine learning for time-to-event analysis such as survival after HCT. The method specifically expands upon previous methods that depend on proportional hazards by incorporating non-proportional hazards and it accommodates heteroskedasticity or heterogeneity of variance typical of transplantation survival data. Open software that implements the method is available publicly as described in the paper.

Apply population genetics to automate donor selection

A manuscript "Family based HLA imputation and optimization of haplo-identical transplants" was accepted in the journal HLA (https://doi.org/10.48550/arXiv.2208.05882). This is a new method to assign chromosomal phase based on HLA and family relationships. This method was applied to simulated family data and real datasets, and it was shown that the error rate in terms of phasing HLA is 15% with highest resolution typing and increases with lower resolution. Phasing HLA is important for stratifying comparisons between the outcomes of mismatched unrelated donor

transplants (that sometimes share a full haplotype) to related haploidentical transplants (that always share a full haplotype). This software to implement this method is available publicly with the paper as well as a public web tool.

C. Immunogenetic Studies in Transplantation

Evaluate HLA disparity and impact on HCT by adding selected pairs to the Donor/Recipient Pair project utilizing sample selection criteria that optimize the new data generated by the typing project

The Donor/Recipient Pair project continues to enroll the most recent related and unrelated transplant pairs to ensure that changes in practice can be evaluated using quality-controlled high resolution HLA data. Strategic selection of pairs for testing and optimization of practices associated with data storage and management ensure that investigators have timely access to robust, high-quality data to analyze the impact of matching as either the focus of or as a variable in CIBMTR-approved research studies. This period, development of a standard operating procedure for the process of selection for typing upgrades from donor-recipient pairs was initiated. A complete audit of typing results received in the last year was completed, including analysis of typing quality and coverage. Data from sample groups 72-74 was received and audited. Through collaboration across the immunobiology and bioinformatics research team, the data was analyzed to determine whether the anticipated resolution was achieved by the laboratory using the current vendor and typing strategy. These results inform selection and typing decisions for the following cycle.

Development of a national framework to standardize measurable residual disease evaluation in the clinical care of patients receiving allogeneic transplant for acute myeloid leukemia

While allogeneic HCT is a curative therapy for many patients with acute myeloid leukemia (AML), the risk of relapse even after achieving a cytomorphological complete remission (CR) is the most common form of treatment failure and death. Transplant-related morbidity and mortality is a major obstacle for the effective use of alloHCT, resulting in the potential under- or over-utilization of conditioning regimen intensity to prevent AML relapse. The presence of residual leukemic burden, known as measurable residual disease (MRD), prior to transplant is associated with worse outcomes after transplantation. AML MRD testing is not standardized, and no clear path to translate findings from research laboratories to clinical transplant settings currently exists.

A multicenter prospective observational study was launched in 2022 to address this issue by developing a coordinated national framework to 1) allow collection of leftover initial AML diagnosis material from patients who have received alloHCT in US centers, 2) prospectively collect samples from AML patients after alloHCT to determine optimal timing and method for post-alloHCT MRD monitoring and 3) implement findings from phases 1 and 2, together with a central reference laboratory, to allow local centers to perform standardized MRD testing pre or post alloHCT. This would allow both selection of conditioning intensity, but also inform post-transplant maintenance and allow patient selection for novel clinical trials.

During the past quarter the protocol team continued to meet regularly to manage the IRB approved and ClinicalTrials.gov registered study protocol entitled, "MEASURE: **M**olecular **E**valuation of **A**ML patients after **S**tem cell transplant to **U**nderstand **R**elapse **E**vents". To date, 18 centers have committed to participate in the study and combined plan to enroll >250 patients per year. Thirteen of 18 sites have received local IRB approval for the protocol. All sites have initiated submission of regulatory documents required for participation. Eight sites have fully opened the study and have enrolled 13 patients.

Determine the impact of peripheral blood stem cell graft composition on the outcome of hematopoietic cell transplantation

While allogeneic HCT offers potentially curative therapy to patients with a variety of benign and malignant diseases, both acute and chronic GVHD continue to plague the field and often limit the longevity and quality of life for patients. The composition of PBSC grafts has been evaluated in multiple studies to attempt to discern associations between various cellular subsets and outcomes. The BMT CTN 0201 randomized trial of bone marrow versus PBSC found that PBSC grafts were associated with a higher risk of cGVHD and worse quality of life following unrelated donor HCT compared to BM. A correlative study of graft immunophenotype failed to identify any associations between PBSC graft composition and outcomes. However, the PBSC cohort included only 147 evaluable products limiting the power to evaluate various cellular subsets. The association between PBSC graft immunophenotype and outcomes remains unclear.

The primary aim of this study is to evaluate PBSC graft stem cell and associated immune cell composition and to determine at 12-months of follow-up how either the comprehensive graft cellular composition profile or specific graft composition elements influences the primary outcomes of time to neutrophil engraftment and overall survival. Secondary outcomes of interest include, but not limited to, incidence of acute and chronic GVHD, primary disease relapse, TRM, and DFS. The study will evaluate approximately 2,100 PBSC products over a 3-year accrual period with 1,100 collected in the U.S. through the NMDP and an additional 1,000 collected in Germany for U.S. based patients through the DKMS. The U.S. testing will be supported through the ONR (prior grant years and the current) and DKMS will support testing of German collected products. Data will be merged with CIBMTR collected clinical outcomes for analysis and correlation with clinical outcomes.

During the past quarter accrual continued for U.S. based donors. A total of 365 product samples were received and tested through March 31, 2023, with 71 tested in the last quarter. Preliminary analyses focused on graft composition correlation with donor characteristics and the impact of cryopreservation are underway. Testing costs are covered under a subsequent grant while staff support is funded under this grant. Testing of German donors will be fully funded by DKMS.

Determine the impact of non-HLA genes and gene expression on allogeneic cell transplantation

A manuscript "Whole Genome Sequencing Identifies Novel Predictors for Hematopoietic Cell Transplant Outcomes for Patients with Myelodysplastic Syndrome: A CIBMTR Study" was accepted for publication by the *Journal of Hematology & Oncology* based on research performed under this grant. Here, we identified recurrent mutations in TP53, RAS pathway, and JAK2 genes and found them to be highly prognostic of allogeneic hematopoietic cell transplant (alloHCT) outcomes in myelodysplastic syndromes (MDS). In addition, since a significant proportion of MDS patients have no such mutations, we conducted whole genome sequencing (WGS) on whole blood samples from 494 patients with MDS to discover novel prognostic genetic alterations. We ran genome-wide association tests via gene-based,

sliding-window and cluster based multivariate proportional hazard models to identify candidate genomic variants that associated with transplant outcomes (Figure 2). We used a random survival forest (RSF) modeling with build-in cross-validation to develop a prognostic model from identified genomic candidates and subgroups, patient-, disease-, and HCT-related clinical factors. Twelve novel regions and three molecular signatures were identified with significant associations to overall survival, and mutations in two novel genes, *CHD1* and *DDX11*, demonstrated a negative impact on survival in AML/MDS and lymphoid cancer data from The Cancer Genome Atlas (TCGA). From unsupervised clustering of recurrent genomic alterations, genomic subgroup with *TP53*/del5q was characterized with ignificant association to inferior overall survival and replicated by an independent dataset. From supervised clustering of all genomic variants, additional molecular signatures related to myeloid malignancies are characterized from supervised clustering, including Fc-receptor *FCGRs*, catenin complex *CDHs*, and B-cell receptor regulators *MTUS2*/*RFTN1* were identified. The RSF model with genomic candidates, their subgroups and combined clinical variables achieved superior performance in outcomes prediction compared to models that included only clinical variables.

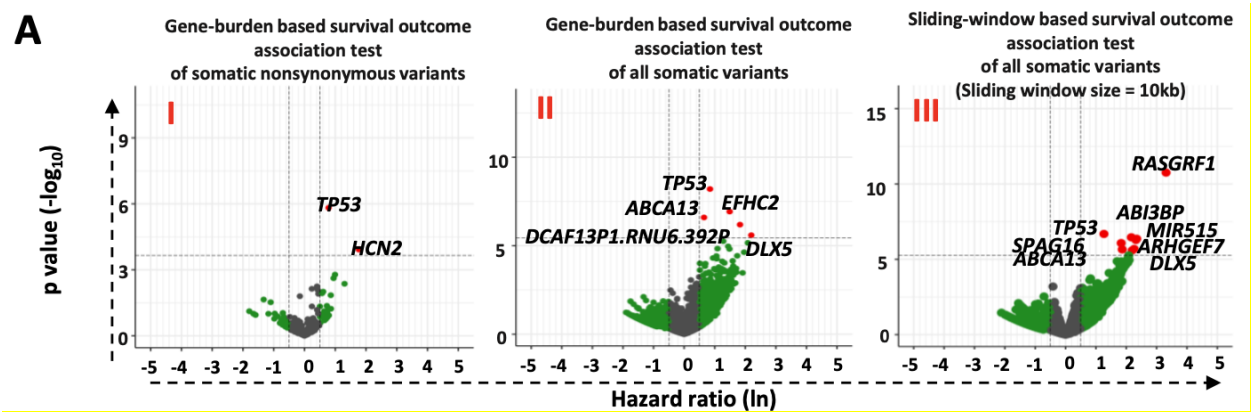

Figure 2. Genomic variants significantly associated with OS among the whole cohort. (**A**) Volcano plots for genome wide scanning of overall survival outcome association respectively for gene-based test of all nonsynonymous somatic coding variants (left), gene-based test of all somatic variants (middle) and sliding window test of all somatic variants (right).

D. Clinical Research in Transplantation

Conduct clinical outcomes research using the CIBMTR research database and repository.

Observational Research

- Published 14 manuscripts in peer-reviewed journals during the last quarter (see publications below).
- A total of 21 abstracts were presented at the 2023 BMT Tandem Meetings of the CIBMTR and American Society for Transplant and Cellular Therapy held February 15-19 in Orlando, FL. Presentation titles and type are detailed in table 1 below. Abstracts were published in a supplement to the Journal of Transplant and Cellular Therapy.

Table 1. CIBMTR presentations at 2023 BMT Tandem Meetings

Title	Status
Posttransplant Cyclophosphamide-Based Transplantation from Haploidentical Donors Has Similar Outcomes As Unrelated Donor Transplantation in Myelofibrosis: A Center for International BMT Research (CIBMTR) Study	Oral
Comparison of Allogeneic Hematopoietic Cell Transplantation Outcomes from Younger Matched Unrelated Donor Versus Older Sibling Donor for Acute Myeloid Leukemia	Oral
Younger Matched Unrelated Donors Confer a Decreased Relapse Risk As Compared to Older Sibling Donors for Adult B-Cell ALL Patients Undergoing Allogeneic Hematopoietic Cell Transplantation	Oral
Associations of Minor Histocompatibility Antigens with Clinical Outcomes Following Allogeneic Hematopoietic Cell Transplantation	Oral
Improved Relapse-Free Survival (RFS) for Pediatric and Young Adult Patients with Relapsed or Refractory (R/R) B-Cell Acute Lymphoblastic Leukemia (B-ALL) and Low or Intermediate Preinfusion Disease Burden Treated with Tisagenlecleucel: Results from the CIBMTR Registry	Oral
Shared Graft Versus Leukemia Minor Histocompatibility Antigens in Discovery-BMT	Oral
HLA Evolutionary Divergence Does Not Predict Relapse and Survival Following Allogeneic Hematopoietic Stem Cell Transplant for Myeloid and Lymphoid Malignancies	Poster
Access: A Multi-Center, Phase II Trial of HLA-Mismatched Unrelated Donor Hematopoietic Cell Transplantation with Post-Transplantation Cyclophosphamide for Patients with Hematologic Malignancies	Poster
Impact of Public Reporting of Center-Specific Analysis Scores on Hematopoietic Cell Transplant Center Volumes	Poster

Title	Status
An Exploration of Unrelated Donor Existence for Patients Who Received Haploidentical Hematopoietic Cell Transplants	Poster
Association between Patient-Reported Social Determinant of Health Outcomes and a Social Genomics Profile in Allogeneic Hematopoietic Cell Transplantation: A Center for International Blood and Marrow Transplant Research (CIBMTR) Analysis	Poster
Can You Spare 100 Days? The Allogeneic Hematopoietic Cell Transplant Caregiver Requirement	Poster
Can You Spare 100 Days? Allogeneic Hematopoietic Cell Transplant Caregiver Requirements from the Perspective of Recipients and Caregivers	Poster
Does Race/Ethnicity Impact Umbilical Cord Blood Transplant in a Contemporary Era?	Poster
Delayed CD4+ T Cell Recovery after Allogeneic Hematopoietic Cell Transplantation Is Associated with Decreased Overall Survival in Adult but Not Pediatric Recipients	Poster
Patient-Reported Outcomes in Long-Term Survivors of Autologous Hematopoietic Cell Transplantation (AHCT) for Hodgkin (HL) and Non-Hodgkin Lymphoma (NHL): Secondary Analysis from Two Multicenter Randomized Controlled Trials (RCT) of Hematopoietic Cell Transplant Survivorship Interventions	Poster
Ph-Positive ALL Patients Who Are Treated with Tyrosine Kinase Inhibitors Have Similar Post-Transplant Survival As Ph-Negative Patients	Poster
Ongoing Risk of Unrelated Donors Testing Positive for COVID-19 Following Medical Clearance and Impact on Operations: A Report from the National Marrow Donor Program	Poster
Trends in Utilization of Autologous and Allogeneic Hematopoietic Cell Transplantation in Racial/Ethnic Minorities	Poster
Disease-Specific Overall Survival Prediction after Allogeneic Hematopoietic Cell Transplantation	Poster
A Retrospective Analysis of Genotype Copy Number (GCN) in Unrelated Donor Transplants and Future Implications for Mismatched Transplants	Poster

Research data collection and systems enhancements
During the past quarter, CIBMTR has continued support for electronic data submission initiatives, production FormsNet Recipient, FormsNet Donor, and AGNIS customers, as well as Data Warehouse users. Progress has been made on the following critical projects to upgrade our technology supporting the program:

Simplify Data Acquisition
To acquire timely, high quality, data with less administrative burden to current and new partners/patients.

FormsNet (FN3)
Continued the quarterly releases of recipient form revisions to be current with existing treatment practices, as well as implemented revisions of forms to support the cellular therapies registry. Completed and in-process enhancements within Data Capture applications include:

- Added collection fields within FN3 and updated functionality for supporting the Data Transformation Initiative, with a planned April release

- Upstream CRID Assignment was introduced for a group of pilot centers on January 27th. A total of 20 centers are now using this functionality in production.
    - Formsnet3 was configured to capture patient demographic and infusion data already captured by the NMDP MatchSource application to assign a CRID at the time of infusion and to autocomplete and make applicable forms due
    - This project will reduce center data entry, improve CIBMTR reporting capabilities, improve data quality, and reduce the troubleshooting between CIBMTR and transplant centers to reconcile discrepancies.
    - Additional enhancements will be added in April 2023 and additional centers will be invited to participate.

- Enhancements to FN3 Transfer Tool to provide more options and more complete and accurate contact information to transplant centers
- Analysis and work started to have FN3 call a web service to validate cytogenetic karyotype data entered as an ISCN compatible string
- FormsNet3 Forms Definition Manager (FDM): Completed several proactive security vulnerability updates revealed by new scans
- Enhanced internal FDM editors for validation and events & actions rules
- FDM/AGNIS Tool Suite:
    - The Cancer Data Standards Registry and Repository upgraded to new software that required changes to their APIs, which is using the new standard of RESTful calls. The CIBMTR completed the migration in February 2023 in advance of the scheduled retirement of the legacy caDSR and old APIs in May 2023.
- Study updates were made to the FN3 Donor Form 3000
- Audit Migration to FN3:
    - Testing in progress for Audit Patient and Event Randomization (released month by month) that reduce manual work, increase data quality, reporting capabilities, and configurability for the future

- Developed and tested the following forms that were released in January 2023:

Form	Form Name	Category
3000r7	Protocol Deviation Form	Revised Donor Form
3004r1	Genetic Mutation Report Form	New Recipient Form

Electronic data submission/AGNIS

CIBMTR continued support for electronic data submission initiatives and production AGNIS customers. Effort focused on support for CIBMTR form revision updates to existing forms.

- Recent AGNIS and other electronic data submission accomplishments:
- The AGNIS team continues to release forms for centers to use in data submission to the CIBMTR as well as address questions or issues raised by centers and their vendors.
    - Three AGNIS forms were released to production:
        - 2400r9 Pre-Transplant Essential Data
        - 2450r6 Post-Transplant Essential Data
        - 2814r4 Indication for CRID Assignment
    - Four AGNIS form was released to external test and is awaiting external partner testing before it can move to production:

- 4000r9 Pre-Cellular Therapy Essential Data Form
- 4100r8 Cellular Therapy Essential Data Follow-Up
- 2100r8 Post-HSCT Data
- 2450r7 Post-Transplant Essential Data

Automated data exchange using electronic data collection systems that interface directly with source health and laboratory records

CIBMTR has continued to update its reporting application to exchange additional discrete electronic data records. Using the data extracted directly from data collection systems at partner centers, CIBMTR further expanded capabilities to populate additional laboratory data points on 26 forms at both pre-infusion and post-infusion time points. These expanded capabilities provide partner transplant centers with improved time savings and eliminate the potential of manual data entry errors. The underlying structures for data exchange and storage were updated based on current standards – these updates are the foundation upon which we will be able to expand the types of data that can be exchanged electronically.

Simplify Data Analysis

Collect & analyze more data more frequently without increasing the burden on centers.

Integrated Data Warehouse (IDW)

CIBMTR continued to increase the capabilities of the IDW, which is the Operational Data Warehouse utilized for delivery of key data to stakeholders. Accomplishments include:

- Incorporated ongoing forms revisions into the warehouse
- Continued enhancing processes to support CIBMTR's Domestic and International CPI Processes.
- Continued enhancing study information and visualizations to support our Prospective Research team.
- Continued development to enhance our Sample Inventory data processes with Labvantage
- Began development to produce dashboards pairing Sample Inventory data with data from other CIBMTR systems
- Provided ePRO data for use in Data Back to Centers (DBtC) dashboard.
- Updated Survivorship Plans for external partners use through the DBtC portal based on data consumer feedback
- Provided variable-specific audit instructions for Japanese Data Center Hematopoietic Cell Transplantation.

Unified Domain Model (UDM)

Continuing the process of building this single source of truth of data that will contain high quality, validated data readily available to researchers for immunobiology, outcomes, and other types of analyses.

- Continued transitioning HCT data from the Research Database to the Unified Domain Model (UDM) including delivery of 15 data extracts directly from UDM and continued development of a relapse-specific data domain.
- Continued delivery of monthly and quarterly CAR T-cell data sets to our Japan (JDCHCT) and pharmaceutical partners.
- Continued refinement and delivery of Periodic Safety Update Reports (PSUR) for CAR T-cell therapies.
- Provided quarterly Stem Cell Therapeutic Outcomes Data required for the HRSA SCTOD quarterly report.

Enhance Data Sharing and Visualization
Deliver data visualization and analytic tools that will enable stakeholders to more efficiently interact with data to identify relevant trends and patterns.

- Transplant Center Specific Analysis (TCSA) annual extracts generated and provided to the member centers for review.
- Business Intelligence Data Sharing- Continued expansion of business intelligence tool capabilities. Adding to the existing suite of external Business Intelligence data sharing applications including the introduction of more data, dimensions and measures, stakeholder groups, and continuing data quality initiatives.
- Implemented annual updates for the Data for RFI
- Kicked off a substantial project upgrading the hardware and software used to share data with the participating member centers. New enhanced portal is expected to go live in April.

Conduct clinical trials on the use of HLA mismatched graft sources to expand access to all patients in need of allogeneic cell transplantation

During the last quarter, work continued on the development of a new prospective clinical trial protocol designed to build upon the successful MMUD post-transplant cyclophosphamide platform. The study team continued to seek feedback on the trial design and primary endpoint from a scientific advisory board to refine and finalize the trial protocol. Funds from this grant will support protocol defined correlative studies to evaluate immune reconstitution and explore mechanisms of relapse post-transplant.

Publications

1. Cusatis R, Balza J, Uttke Z, et al. Patient-reported cognitive function among hematopoietic stem cell transplant and cellular therapy patients: A scoping review. Quality of Life Research. doi:10.1007/s11136-022-03258-0. Epub 2022 Oct 6. Impact Factor: 4.14

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3. Boyiadzis M, Zhang MJ, Chen K, et al. Impact of pre-transplant induction and consolidation cycles on AML allogeneic transplant outcomes: A CIBMTR analysis in 3113 AML patients. Leukemia. doi:10.1038/s41375-022-01738-3. Epub 2022 Oct 12. Impact Factor: 12.88

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