REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
1/15/2021	Interim Technical Report	August - December 2020

4. TITLE AND SUBTITLE
Development of Medical Technology for Contingency Response to Marrow Toxic Agents – Interim Technical Report with SF298 August 26, 2020 – December 31, 2020

5a. CONTRACT NUMBER
N/A

5b. GRANT NUMBER
N00014-20-1-2832

5c. PROGRAM ELEMENT NUMBER
N/A

6. AUTHOR(S)
Spellman, Stephen

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)
National Marrow Donor Program
500 N. 5th St.
Minneapolis, MN 55401-1206

8. PERFORMING ORGANIZATION REPORT NUMBER
N/A

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

Office of Naval Research
875 N. Randolph Street, Suite 1425
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
a. REPORT	b. ABSTRACT	c. THIS PAGE			Steven Devine, MD – Chief Medical Office
U	U	U		20	19b. TELEPONE NUMBER (*Include area code)* 763-406-8239

Grant Award N00014-20-1-2832

DEVELOPMENT OF MEDICAL TECHNOLOGY

FOR CONTINGENCY RESPONSE TO MARROW TOXIC AGENTS

QUARTERLY RESEARCH PERFORMANCE REPORT

SUBMITTED January 15th, 2021

Office of Naval Research

And

The National Marrow Donor Program®

500 5th St N

Minneapolis, MN 55401

I. Heading

PI: Steven Devine, M.D.

National Marrow Donor Program

N00014-20-1-2832

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 and clinical research activities promote studies to advance the science and technology of HCT transplantation to improve outcome 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 of marrow toxic injuries. The NMDP manages a network of centers that work in concert to facilitate unrelated HCT. The Radiation Injury Treatment Network (RITN), comprised of a subset of NMDP's network centers, is dedicated to radiological disaster preparedness activities and develops procedures for response to marrow toxic mass casualty incidents.

B. Development of Science and Technology for Rapid Identification of Matched Donors
Disease stage at the time of transplantation is a significant predictor of survival, decreasing the time to identify the best matched donor is critical. Methods are under development to rapidly provide the best matched 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 are focused on strategies to maximize disease control while minimizing the toxicity related to alloreactivity in HCT.

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.

During this quarter RITN continued to develop the preparedness of its network of hospitals through the following activities:

- Reviewed the best use of RITN hospitals' time and efforts during the SARS CoV-2 pandemic; resulting in a minimally reduced task list for the year to balance between over straining hospitals during this crisis and maintaining their readiness and engagement to radiological preparedness.
- Continued to collaborate with the Department of Defense through the Uniformed Services University with the American Burn Association to co-host a virtual panel workgroup meeting in late January 2021 to identify best practices for identifying and treating warfighters with combined injuries (burns or trauma and acute radiation syndrome).
- Initiated a workgroup to develop a modular acute radiation syndrome treatment just-in-time training course for healthcare providers.
- Initiated the development of virtual quarterly educational training sessions for RITN hospitals and partners; in lieu of the semi-annual RITN Workshop that would typically be held in summer 2021.

- Continued collaboration with the American Burn Association to develop advanced practice guidelines for the combined care of patients by RITN and burn centers.
- Supported Gryphon Scientific's Center for Disease Control (CDC) funded project to assess United States laboratory capabilities for ionizing radiation related testing.
- Continued to develop the Hospital Radiation Morbidity Toolkit as part of the CDC grant awarded to RITN; submitted the final form for CDC review and comment

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.

No activity to report this quarter.

Modeling and analysis of registry coverage for the Warfighter

Forward deployed Warfighters are a higher risk of exposure to marrow toxic injuries due to ionizing radiation or marrow toxic chemical agents. As such, it is important to model and determine the likelihood that Warfighters will have a suitably matched unrelated donor (defined as 8/8 or 7/8 matched for HLA-A, B, C and DRB1) on the NMDP/Be The Match Registry to support lifesaving HCT or cellular therapy. Our prior results indicated that most warfighters will have suitable adult donors though there is not an optimal match for many warfighters.

Adult-donor Match Likelihood for 21 populations

Table 1 lists the 8/8 and 7/8 match rates for 21 populations. The highest and lowest match rates were found for European Caucasian and African, respectively.

Table 1. Match rates of 21 populations

Race code	8/8 Match (%)	7/8 Match (%)
AAFA	22	74
AFB	18	71
AINDI	37	87
AISC	52	88

ALANAM	57	89
AMIND	62	95
CARB	21	74
CARHIS	50	91
CARIBI	41	85
FILII	48	89
HAWI	37	81
JAPI	44	89
KORI	43	88
MENAFC	52	92
MSWHIS	49	90
NAMER (EURCAU)	79	99
NCHI	45	88
SCAHIS	40	85
SCAMB	40	81
SCSEAI	32	80
VIET	48	86
AAFA	22	74

Previously, we identified the likelihood of finding an unrelated donor on the Be The Match registry to provide an estimate for providing HCT or cellular therapy to warfighters in the event of radiation or marrow toxic chemical exposure. We also identified gaps in warfighter population coverage that will assist in targeted future recruitment efforts to address deficiencies.

To model and analyze registry coverage, however, we assumed 100% adult donor availability. Availability is the percentage of donors that will agree to donate if they are a match. Sometimes donors refuse or are unable to donate despite being a match, and this availability rate varies by population. To regenerate match rates while taking into account the actual percentage of donor availability, we are reviewing models for prediction of donor availability. Currently, we do not have actual HLA data and age-specific population distributions for the warfighter. However, we can refresh this calculation upon obtaining any new HLA frequencies and actual population distributions for warfighters.

To address the gaps in warfighter population coverage, we are also in the planning stages to redefine and re-estimate match rates. Here, we will consider the increasing body of evidence for advances in post-HCT immune modulation that allow for safe and effective HCT despite a greater number of HLA mismatches between the donor and potential patient. Future modeling efforts will evaluate less stringent HLA matching criteria (<7/8 matched) that will expand access and allow for rapid identification of suitable donors for HCT and cellular therapy.

Development of science and technology for rapid communication of HLA data

Py-ARD HLA annotation and conversion tool development

Development and improvement of tools continues for handling HLA data toward the rapid communication, identification, and evaluation of matched donors in transplantation. Updates to Py-ARD, a Python-based HLA annotation and conversion tool, were implemented. These updates allow for input of alleles based on protein and genotype groupings and for sorting of HLA nomenclature in the fourth field, loading of references to multiple allele codes in a more efficient manner and support for serological typing in genotype-list strings.

Additional improvements were made for serology mapping and expansion fixes for multiple allele codes, nomenclature version handling and genotype-list strings. These improvements facilitate the communication, integration, and handling of HLA data in general across platforms. Immediate benefits to these improvements also include application of corrected HLA handling in the HLA frequency generation pipeline.

HL7 FHIR Genomics Reporting

NMDP participated in a pilot project to further develop support within the HL7 FHIR Genomics Reporting Implementation Guide (IG) for complex transplant genomic data, and to use that IG to develop tooling to convert vendor specific HLA reports to FHIR.

A report was published summarizing the results of this pilot as part of Sync for Genes Phase 3 (https://www.healthit.gov/sites/default/files/page/2021-01/Sync-for-Genes-Phase-3-Engaging-Laboratories.pdf). Launched in 2019, Sync for Genes Phase 3 explored the use of the HL7 FHIR Genomics Reporting IG (STU1) to report genomic data generated by testing labs. The goal was to identify challenges that testing labs experience when adopting health IT standards. Solutions were also identified to facilitate broad adoption of standards by generators of genomic data. Lessons learned from the demonstration project sites informed needs for the further development of the HL7 FHIR Genomics Reporting IG (STU1).

Development of HLA Reporting FHIR Implementation Guide: The NMDP previously led the development of an HLA-specific section of the FHIR Genomics Reporting IG (http://hl7.org/fhir/uv/genomics-reporting/histocompatibility.html). While this described best practices for reporting HLA using that IG, it did not have the capability of validating FHIR resources to specifically follow those practices. In this year we constrained HL7 FHIR Genomics Reporting IG (published Nov 2019) create a full IG specifically for HLA reporting. The HLA Reporting IG includes local extensions that were necessary to support the requirements of the highly specialized HLA use case and genomic data, and it incorporates specialized business rules that were unique to the HLA domain. These FHIR profiles include

- HLA Summary Report
- HLA Genotype Observation

- HLA Allele Observation
- HLA Molecular Sequence

Code systems, value-sets, extensions, and examples for HLA reporting were also developed and included in this FHIR IG. The use of these artifacts allows for computational validation of FHIR resources for reporting HLA. The first draft of this IG can be found in http://fhir.nmdp.org/ig/hla-reporting.

TARR2FHIR: In addition to developing the HLA Reporting IG described above, the NMDP collaborated with Versiti, a laboratory that provides 11% of all clinical HLA typing reports in the U.S., to implement and test tooling that would enable HLA test results to be reported in FHIR format. This tooling enables the production and exchange of FHIR-formatted HLA genotyping reports that contained molecular sequences, a requirement that was not supported by the FHIR Genomics IG. The availability of such tooling eliminated the need to exchange HLA data using HML as an intermediate format. Versiti uses software from GenDx to for HLA sequence analysis and genotype assignment. This software can export results into their XML format called TARR. For this activity, we developed a translator tool to convert this file into a FHIR bundle that conforms to the HLA Reporting FHIR IG described above. The converter is publicly available at https://github.com/nmdp-bioinformatics/tarr2fhir.

One of the key barriers that this project addressed was the difficultly for a genetic testing lab to invest the resources required to upgrade existing software to support the FHIR standard, especially when that standard is still under active development. To overcome that challenge, the development of the translator tool allowed the lab to explore the standard and evaluate its ability to render test reports without requiring a large investment of resources or a reconfiguration of software systems. This approach could help encourage early adopters to implement FHIR because it requires developing only a translator that converts existing output to FHIR format, enabling them to test the specification and provide feedback to the FHIR development teams without significant cost to or disruption of a production pipeline.

This project also demonstrated an increase in efficiency and more accurate data representation by translating results directly into FHIR format rather than performing the multiple, sequential translations that would be necessary if existing formats were utilized. The use of intermediate formats, such as HML, would result in the loss of data and/or the introduction of ambiguities that would require the recipient of the message to make assumptions when interpreting the data. The HLA Reporting IG that was created during this pilot activity captures the test results more robustly and it eliminates the need for multiple translation steps between formats.

This pilot project identified several opportunities for further development of the FHIR specification. For example, additional support is needed to capture information about organizations that act on behalf of other organizations, which is common in transplantation scenarios where one organization reports a result on behalf of another. In addition, it is necessary to develop methods that better capture novel genomic results and parameters that support organization-specific workflows. Other parameters include identifying the typing it done for recipients or donors or cord blood units (information not captured in the TARR file), as well as the relationship between donor and recipient (unrelated, mother, sibling, etc).

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

Donor Readiness Score

Data input and model preparation is under way for exploration of a new Donor Readiness score to facilitate automation of the donor selection process. Existing inputs were recorded and mapped for system of record and new input possibilities and sources are under evaluation. Existing modeling scripts were evaluated and are prepared for transition and further research and validation planned in future quarters.

Machine Learning-based prediction of overall surival

Progress was made evaluating the use of various machine learning methods applied to the US allogeneic hematopoietic cell transplantation dataset from 2014 to 2018 to improve prediction of one-year post transplantation Overall Survival. Table 1 summarizes the results of the performance of these machine learning models. Although the MLPClassifier performed well in training, it did not perform well in testing due to issues in overfitting. The XGB extreme gradient boosting model performed the best overall and was selected for use in modeling of overall survival prediction going forward.

Table 1: Machine learning performance summaries for models applied to 1-yr post hematopoietic cell transplantation overall survival prediction.

Model	Performance			
	Training		Testing	
	Accuracy	AUC	Accuracy	AUC
Logistic regression	0.65	0.71	0.64	0.70
AdaBoost	0.76	0.72	0.77	0.72
XGB	0.79	0.81	0.77	0.73
LightGBM	0.78	0.78	0.76	0.72
SVM	0.75	0.70	0.75	0.69
KNN	0.38	0.69	0.37	0.66
MLPClassifier	0.97	0.99	0.71	0.62
GaussianNB	0.47	0.63	0.47	0.62
BernoulliNB	0.65	0.64	0.65	0.63
DecisionTreeClassifier	0.80	0.79	0.71	0.61

Machine learning models to predict Event Free Survival

A dataset was prepared for the development of machine learning models to predict the 4 outcomes that constitute Event Free Survival (EFS): death, relapse, rejection and moderate to severe chronic Graft vs Host Disease. This dataset includes 9527 matched unrelated transplants from 2016-2018 and was augmented imputation of partial genetic information. Two academic collaborators: one at the Medical College of Wisconsin, and one at Bar Ilan University in Israel, have started working on prediction models using a variety of machine learning methods including:

- Bayesian Additive Regression Trees (BART)
- Boosted Trees (XGBoost)
- K-nearest neighbors (KNN)
- Random-Forest
- Fully connected neural network (FCNN)

Preliminary will be evaluated in the next quarter and additional datasets will be prepared to extend the modeling from the matched unrelated adult donor setting to:

- Mismatched unrelated adult donor transplants
- Cord blood transplants
- Matched and mismatched related transplants

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.

Donor Recipient Pair Project

- The study team continued to audit typing results generated in the prior grant year. To date, 8,200 of 8,600 pairs have been audited and released for use in research studies. Efforts are underway to identify pairs for testing in the current grant year.

Full HLA Gene Matching Analysis

Submitted the manuscript for the study IB19-01: Impact of ultra-high resolution (UHR) HLA matching on the outcome of unrelated donor hematopoietic cell transplantation..

Develop and mature typing characterization of immunogenetic regions from underserved populations to improve matching and transplant outcomes for more diverse patients

A manuscript “Efficient Sequencing, Assembly, and Annotation of Human KIR Haplotypes” went to press in Frontiers in Immunology Oct 9, 2020. This study was supported under this grant and is a collaboration with industry partners to deliver a new typing protocol for the highly polymorphic KIR.

During the past quarter the method was scaled to apply it to a panel of 48 samples. Data analysis of the results is underway.

A paper "A Detailed View of KIR Haplotype Structures and Gene Families as Provided by a New Motif-Based Multiple Sequence Alignment" (https://doi.org/10.3389/fimmu.2020.58573) was published in Frontiers in Immunology on Nov 18, 2020. This paper presents data from an NMDP cohort of African American bone marrow donors and a new tool for analysis and comparison of the gene arrangements and sequencing of the KIR region. Some of the relevant finding in this study are:

- KIR haplotypes cluster by structure, not population.
- KIR haplotypes from Africans or African Americans now constitute 47% of the KIR alternate references in the human genome project
- The human genome project contains more than three times as many alternative references for KIR than any part of the genome

Determine the frequency and risks associated with donor clonal hematopoiesis of indeterminate potential in HCT.

Evaluating the impact of donor clonal hematopoiesis of indeterminate potential (CHIP) on HCT outcomes

Completed the analysis for the study entitled "GV19-01: Exploring the link between donor engrafted clonal hematopoiesis and adverse outcomes in allogeneic HCT: Pilot study. The study found no associations between donor CHIP and any outcomes. The lack of an association between CHIP and outcomes resulted in a reevaluation of this line of inquiry under this grant. Funds allocated for this effort have been reassigned to address the more pressing topics noted below.

Evaluation of Unrelated Donor Peripheral Blood Stem Cell (PBSC) Graft Composition and Impact on Allogeneic HCT Outcomes

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.

Analyses include:

- Stem cell subset composition (not just number) influences time to engraftment and immune reconstitution

- Both conventional and novel unconventional T cell subsets within the graft influence GVHD, relapse, infection and immune reconstitution after transplant
- Natural killer cells have a role in transplant biology and number and phenotype in the donor graft influence GVHD, relapse, infection and immune reconstitution after transplant.
- The myeloid/antigen presenting cell compartment of the graft influences infection risk and immune reconstitution, thus play a role in long term patient outcome

The secondary aims of this study are:

- Explore potential associations of favorable PBSC graft composition features that may be predicted by analysis of peripheral blood samples at time of unrelated donor work-up such that these biomarkers could be incorporated into donor selection algorithms.

- Evaluate graft composition association with >12-month outcomes for overall survival, primary disease relapse, DFS and the incidence of late transplant effects including, but not limited to, chronic GVHD, diseases of the cardiovascular, pulmonary, and endocrine systems, dysfunction of the thyroid gland, bone diseases and the development of secondary primary malignancies.

- Establish a cohort of pre-transplant recipient and pre-donation adult unrelated donor biologic samples (whole blood, plasma, viable PBMC and viable donor PBSC graft mononuclear cells) collected prospectively from donors and patients enrolled on this study, This important biospecimen resource will be critical for the support of additional protocol team defined allogeneic HCT related correlative studies that will extend the knowledge gained from the primary study.

The study protocol is currently under development with finalization and implementation expected in the next quarter.

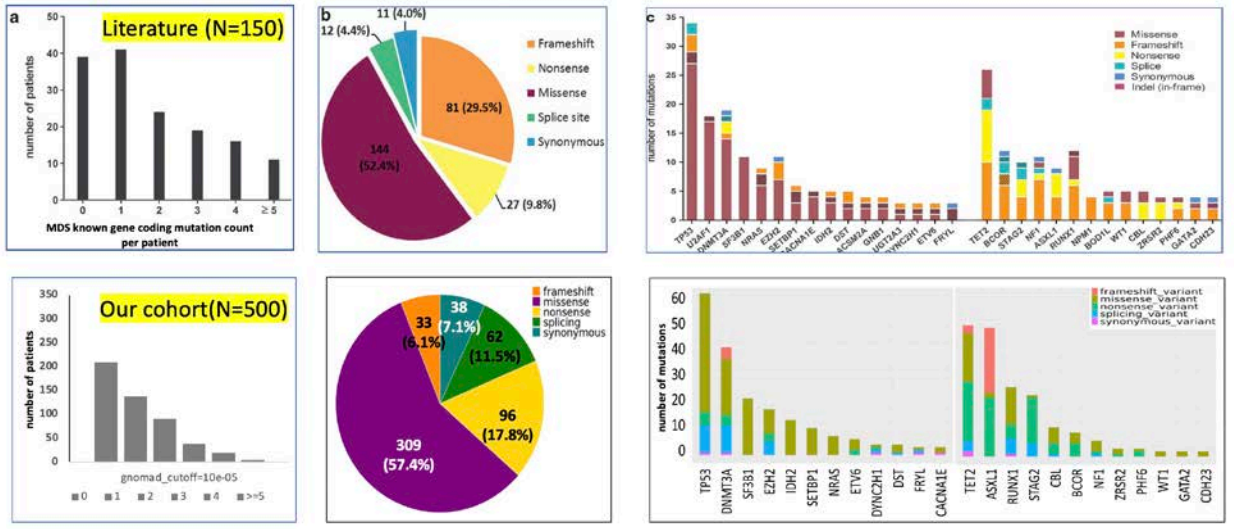
Even when patient and donor are HLA matched, post-transplant complications occur, therefore, other loci may play a role

Evaluation and identification of whole genome donor-recipient pair variation and omics patterns that affect HCT outcomes

While matching donors and transplant recipients on HLA and other well-studied loci is known to improve transplant outcomes, much remains to be explored with regards to whole genome factors and effects of mutations and other variation. We recently completed a multi-omics pilot study on a cohort of transplant recipients with Myelodysplastic Syndromes (MDS). Since then, we have followed up with the whole genome sequencing of an additional 500 pairs of donors and transplant recipients with MDS with funding from a prior Navy grant.

Quality control for sequencing results was performed, and variant allele frequency was assessed against reference data and results from prior studies. Figure 1 shows the correlation of somatic genomic variants detected in these transplant recipients compared to MDS genomic variants detected in prior studies.

Figure 1: Detection of MDS-associated genomic variants.



Future quarterly reports will detail outcomes of interest selected and tested for clinical covariates ahead of results from preliminary genomic variation association testing with outcomes.

D. Clinical Research in Transplantation

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

Observational Research

- Published 18 manuscripts in peer-reviewed journals during the last quarter.
- CIBMTR and BMTCTN presented 24 abstracts to the 2020 American Society of Hematology (ASH) annual meeting. All were accepted with 9 assigned to oral presentations and 15 as poster presentations. The study titles, presentation type and presenting author are noted below.
- CIBMTR submitted 8 abstracts to the 2021 Transplant and Cellular Therapy (TCT) annual meeting. All were accepted with 5 assigned to oral presentations and 3 as poster presentations. The study titles, presentation type and presenting author are noted below.

Presentations at the 2020 ASH annual meeting

Study Title	*Presentation type*	*Presenting author*
A Multi-Center Biologic Assignment Trial Comparing Reduced Intensity Allogeneic Hematopoietic Cell Transplantation to Hypomethylating Therapy or Best Supportive Care in Patients Aged 50-75 with Advanced Myelodysplastic Syndrome: Blood and Marrow Transplant Clinical Trials Network Study 1102	**Oral**	Corey Cutler
Comparison of Outcomes after Haploidentical Relative and HLA Matched Unrelated Donor Transplantation with Post-Transplant Cyclophosphamide Containing Gvhd Prophylaxis Regimens	**Oral**	Mahasweta Gooptu
Impact of Cryopreservation of Donor Grafts on Outcomes of Allogeneic Hematopoietic Cell Transplant (HCT)	**Oral**	Jack Hsu
Bridging the Gap in Access to Transplant for Underserved Minority Patients Using Mismatched Unrelated Donors and Post-Transplant Cyclophosphamide: A National Marrow Donor Program/be the Match (NMDP/BTM) Initiative	**Oral**	Bronwen Shaw
Comparison of Haploidentical Donor Hematopoietic Cell Transplantation Using Post-Transplant Cyclophosphamide to Matched-Sibling, Matched-Unrelated, Mismatched-Unrelated, and Umbilical Cord Blood Donor Transplantation in Adults with Acute Lymphoblastic Leukemia: A CIBMTR Study	**Oral**	Matthew Wieduwilt
Chromosomal Aberrations in Pre-HCT Blood Samples and Outcomes after Transplantation in Patients with Myelofibrosis (Received an ASH Abstract Achievement Award)	**Oral**	Youjin Wang

Expanded Comorbidity Definitions Improve Application of the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) for Children and Young Adults with Non-Malignant Diseases Receiving Allogeneic Hematopoietic Cell Transplantation	**Oral**	Larisa Broglie
Superiority of Thiotepa-Containing Conditioning Regimens in Patients with Primary Diffuse Large B-Cell Lymphoma (DLBCL) of the Central Nervous System (CNS) Undergoing Autologous Hematopoietic Cell Transplantation (autoHCT)	**Oral**	Trent Wang
Population Distribution of GvL and GvH Minor Histocompatibility Antigens	**Oral**	Kelly Olsen
Allogeneic Hematopoietic Cell Transplantation (allo-HCT) in T-Cell Prolymphocytic Leukemia (T-PLL): An Analysis from the CIBMTR	**Poster**	Hemant Murthy
Impact of Age on the Outcomes of HCT for AML in CR1: Promising Therapy for Older Adults	**Poster**	Joseph Maakaron
Improving Donor Selection for Haploidentical Stem Cell Transplantation with Post-Transplant Cyclophosphamide through Selective HLA-Mis/Matching	**Poster**	Ephraim Fuchs
Conditioning Regimens and Outcomes after Allogeneic Hematopoietic Cell Transplant for Hyperinflammatory Inborn Errors of Immunity	**Poster**	Rebecca Marsh
Outcomes of Pediatric Patients with JMML Following Unrelated Donor Transplant: The Impact of Donor KIR Gene Content and KIR Ligand Matching	**Poster**	Hemalatha Rangarajan
Geographic Disparities of Hematopoietic Cell Transplantation in Acute Myeloid Leukemia Patients in Virginia	**Poster**	Joseph Mock
Prognostic Impact of a Modified European LeukemiaNet (ELN) Genetic Risk Stratification in Predicting Outcomes for Adults with Acute Myeloid Leukemia (AML) Undergoing Allogeneic Hematopoietic Stem Cell Transplantation (HCT). a Center for International Blood and Marrow Transplant Research (CIBMTR) Analysis for the CIBMTR Acute Leukemia Writing Committee	**Poster**	Antonio Jimenez
Expanded Comorbidity Definitions Improve Applicability of the Hematopoietic Stem Cell Transplantation-Comorbidity Index for Children, Adolescents, and Young Adults with Hematologic Malignancies Undergoing Allogeneic Stem Cell Transplantation	**Poster**	Brian Friend
Meta-Analysis of Genome-Wide Association Studies of Acute Myeloid Leukemia (AML) Patients Identifies Variants Associated with Risk of 11q23/*KMT2A*-Translocated and Core-Binding Factor (CBF) AML and Suggests a Role for Transcription Elongation in Leukemogenesis	**Poster**	Lara Sucheston-Campbell
BMT CTN 1803: Haploidentical Natural Killer Cells (K-NK002) to Prevent Post-Transplant Relapse in AML and MDS (NK-REALM)	**Poster**	Sumithira Vasu
Associations of Clinical Outcomes after Allogeneic Hematopoietic Cell Transplantation with Number of Predicted Class II Restricted mHA	**Poster**	Othmane Jadi

Pre-Transplant Clonal Mosaicism Is Associated with Increased Relapse and Lower Survival in Acute Lymphoblastic Leukemia Patients Undergoing Allogeneic Hematopoietic Cell Transplant	**Poster**	Yiwen Wang
Non-Infectious Pulmonary Toxicity after Allogeneic Hematopoietic Cell Transplantation (HCT): A Center for International Blood and Marrow Transplant Research (CIBMTR) Study	**Poster**	Sagar Patel
Maintenance Use Is More Important Than the Choice of Bortezomib-Based Triplet Induction in Newly Diagnosed Multiple Myeloma Patients Undergoing Upfront Autologous Stem Cell Transplantation	**Poster**	Surbhi Sidana
Younger HLA-Matched Unrelated Donor Allogeneic Hematopoietic Cell Transplantation (allo-HCT) for Myelodysplastic Syndromes (MDS) Is Associated with Superior Disease-Free Survival Compared to Older HLA-Identical Sibling Donors: CIBMTR Analysis	**Poster**	Guru Murthy

Abstracts accepted for presentation at the 2021 TCT annual meeting

Study Title	***Presentation Type***	***Presenting Author***
Chronic Graft-Versus-Host Disease (cGVHD), Non-Relapse Mortality (NRM) and Disease Relapse in Older Vs. Younger Adult Recipients of Matched Sibling or Unrelated Donor Allogeneic Peripheral Blood Hematopoietic Cell Transplant (alloHCT): A CIBMTR Analysis	**Poster**	Vijaya Bhatt
Hematopoietic Cell Transplant Outcomes among Medicaid and Privately Insured Patients with Sickle Cell Disease	**Poster**	Tatenda Mupfudze
Effect of Obesity on Outcomes after Alternative Donor Allogeneic Hematopoietic Stem Cell Transplant (alloHCT)	**Poster**	Mouhamed Yazan Abou-Ismail
First Late Effect in Pediatric Survivors with Chronic Graft-Versus-Host Disease Following Hematopoietic Cell Transplantation for Hematologic Malignancy	**Oral**	Catherine Lee
Impact of Chronic Graft-Versus-Host Disease on First Late Effect Among Adult Survivors of Hematopoietic Cell Transplantation: A Center for International Blood and Marrow Transplant Research (CIBMTR) Analysis	**Oral**	Catherine Lee
Utilization and Outcomes of Autologous Hematopoietic Cell Transplant in Elderly Multiple Myeloma Patients Aged 75 Years and Older in the US.	**Oral**	Pashna Munshi
HLA Class I Genotypes with Predicted Strong Binding Affinity to Mutated NPM1 Are Associated with Lower Relapse Risk in Matched Related or Unrelated Transplant for NPM1 Mutated Acute Myeloid Leukemia	**Oral**	Rupa Narayan
COVID-19 in Hematopoietic Cell Transplant Recipients: A CIBMTR Study	**Oral**	Akshay Sharma

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.

FormsNet

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:

- The Japanese multi-language support, allowing FormsNet system and forms to display in a language other than English, was updated in October 2020 to reflect two Cellular Therapy form revisions.
- Enhancements to form capabilities to support data capture for COVID-19.
- Continued monthly security monitoring and incorporating fixes to security vulnerabilities within the month. Two vulnerabilities were fixed.
- Updated normalized mapping for the FDM Mapping Tool to automate major portions of the AGNIS metadata mapping to decrease manual errors and the time to map FormsNet form revisions to AGNIS.
- Deployed the Infections Disease Marker (IDM) Automation project which reduces the time it takes to clear a donor by automating the reporting of IDM results and improving error handling.
- Developed a new tool to capture consent, so that baseline data for patient reported outcomes can be collected earlier.
- Removed NMDP Donor ID (DID) from FormsNet 3 to meet Global Registration Identifier for Donors (GRID) requirements. Also updated non-NMDP Donor ID to Registry Donor ID for clarity.
- Disabled DID for Donor Forms and IDM Upload Tool to support the last phase of GRID requirements (including Registry Donor ID field name change).
- Creation and configuration of a second Enterprise Service Bus (ESB) message to communicate typing results received by CORE system for customized typing orders, so that FN3 recipient module can inform users of the status of the order and the scanned form (supports impending KeyLink retirement).
- Developed and released the following data collection forms in October 2020.

Form	Form Name	Category
2000R6	Recipient Baseline Data	Revised recipient form
2018R6	Hodgkin and Non-Hodgkin Lymphoma (LYM) Pre-Infusion Data	Revised recipient form
2028R3	Aplastic Anemia Pre-Infusion Data	Revised recipient form

2100R6	Post-HCT Follow-Up Data	Revised recipient form
2128R3	Aplastic Anemia Post-Infusion Data	Revised recipient form
2402R6	Disease Classification	Revised recipient form

Electronic data submission/AGNIS

CIBMTR continued support for electronic data submission initiatives and production AGNIS customers. Effort focused on development of new AGNIS instances of CIBMTR disease specific forms, and support for CIBMTR form revision updates to existing forms. The team is in process of completing communication, educational and technical project implementations to lower AGNIS submission burden and increase the client-base including but not limited to:

- Increasing the reuse of existing AGNIS modules when supporting form revisions and other Forms Builder reports enhancements
- Investigations and pilots into the acquisition of discrete / structured data elements outside of the forms context; such as acquisition of structured laboratory data from source systems.
- Additional AGNIS reports and enhancements to the AGNIS test environments to help support external users when they are testing new AGNIS forms.

Recent AGNIS and other electronic data submission accomplishments:

- Successfully connected Oregon Health & Science University (OHSU) environment using the CIBMTR Reporting App and began exchanging:
    - Patient demographics
    - CRID assignment
- Forms 4000r6, 4006r4, and 4100r5 have been released in Production for AGNIS users.
- AGNIS Auto-Population QA Testing and Development issue resolution in progress. Testing and release efforts for AGNIS maintenance release updates include:
    - 2400 - Study ID Value Added
    - 2450r5 - Updated to ensure Q50-51 can be submitted as a “multiple”
    - 2804r6 - Common validations updates
    - 2006 - Updates to ensure Non-NMDP CBU ID submissions do not automatically populate Non-NMDP unrelated donor ID values in the database
- Development of the 2815r1 for an AGNIS implementation of the Consent Tool

Integrated Data Warehouse (IDW) and Unified Data Model (UDM)

CIBMTR continued to increase the capabilities of the IDW and UDM. Accomplishments include:

Integrated Data Warehouse (IDW) – Operational Data Warehouse utilized for delivery of key data to stakeholders.

- Incorporated ongoing forms revisions into the warehouse.
- Added additional checks to CIBMTR’s Critical Systems Dashboard to track the status of CIBMTR systems and reports.

- Implemented new processes to support CIBMTR's International CPI Processes.
- Added additional reporting capabilities to our business intelligence suite to support CIBMTR Prospective Research team needs.
- Completed pathway to capture and store survey data from CIBMTR's ePRO system.
- Enhanced Cord Blood Data Quality Report to include a newly developed Change Report, highlighting month to month data changes.
- Completed Transplant Center data review for the 2020 Center Volumes Data Reporting project.
- Business Intelligence Data Sharing- Continue 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. Recent accomplishments include:
    - Introduced more data and visualizations related to Chimeric Antigen Receptor T-cells (CAR-T), Enabling users to visualize CAR-T and HCT information within the same application.
    - Improvements to the user interface to maximize screen space and usability
    - Introduction of Risk Evaluation and Mitigation Strategy (REMS) reports significantly simplifying the relationship between the centers and the CAR-T therapy vendors

  Center Performance Analytics Dashboard
    - Executed the annual update of the data set used for this application. The update includes updated data and new data points and accompanying graphs

  Data Operations Dashboard
    - Published the annual Transplant Center Specific Analysis (univariant) reports for 2020 for each center.
    - Published the annual Specific Survival Report for all centers

- Unified Domain Model- in 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 delivery of monthly and quarterly CAR T-cell data sets to our Japan and pharmaceutical partners,
    - Began work on a proof of concept to bring hematopoietic cell transplant data into the Unified Domain Model and make it available for research purposes.

Support for the Clinical Transplant-Related Long-term Outcomes of Alternative Donor Allogeneic Transplantation (CTRL-ALT-D) trial

---

BMT CTN 1702: Clinical Transplant-Related Long-term Outcomes of Alternative Donor Allogeneic Transplantation (CTRL-ALT-D) trial has accrued 765 subjects through December 2020. A total of 195 patients were accrued in the past quarter.

Publications

1. Bejanyan N, Zhang M, Bo-Subait K, et al. Myeloablative conditioning for allogeneic transplantation results in superior disease-free survival for acute myeloid leukemia and myelodysplastic syndromes with low/intermediate, but not high disease risk index: A CIBMTR study: Superior DFS with MAC compared to RIC HCT in AML/MDS with low/intermediate risk DRI. Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation. doi:10.1016/j.bbmt.2020.09.026. Epub 2020 Oct 1. Impact factor: 3.9

2. Gadalla SM, Wang Y, Wang T, et al. Association of donor IFNL4 genotype and non-relapse mortality after unrelated donor myeloablative haematopoietic stem-cell transplantation for acute leukaemia: A retrospective cohort study. The Lancet Haematology. 7(10):e715-e723. doi:10.1016/S2352-3026(20)30294-5. Epub 2020 Oct 1. PMC7735535. Impact factor: 10.4

3. Gupta V, Kim S, Hu Z-H, et al. Comparison of outcomes of HCT in blast phase of BCR-ABL1-MPN with de novo AML and with AML following MDS. Blood Advances. 2020 Oct 13; 4(19):4748-4757. doi:10.1182/bloodadvances.2020002621. Epub 2020 Oct 2. PMC7556156. Impact factor: 4.6

4. Kim S, Logan B, Riches M, et al. Tatistical methods for time-dependent variables in hematopoietic cell transplantation studies. Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation. doi:10.1016/j.bbmt.2020.09.034. Epub 2020 Oct 2. Impact factor: 4.7

5. Fahadfar N, Burns LJ, Mupfudze T, et al. Hematopoietic Cell Transplantation Predictions for the Year 2023 Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation. doi:10.1016/j.bbmt.2020.10.006. Epub 2020 Oct 9. PMC7546661. Impact factor: 3.9

6. Roe D, Williams J, Ivery K, et al. Efficient sequencing, assembly, and annotation of human KIR haplotypes. Frontiers in Immunology. 11:582927. doi:10.3389/fimmu.2020.582927. Epub 2020 Oct 9. PMC7581912. Impact factor: 6.4

7. Dehn J, Chitphakdithai P, Shaw BE, et al. Likelihood of proceeding to allogeneic hematopoietic cell transplantation in the United States after search activation in the National Registry: Impact of patient age, disease and search prognosis. Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation. doi:10.1016/j.bbmt.2020.10.004. Epub 2020 Oct 10. Impact factor: 3.9

8. Camacho-Bydume C, Wang T, Sees JA, et al. Specific class I HLA supertypes but not HLA zygosity or expression are associated with outcomes following HLA-matched allogeneic hematopoietic cell transplant: HLA supertypes impact allogeneic HCT outcomes. Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation. doi:10.1016/j.bbmt.2020.10.010. Epub 2020 Oct 11. Impact factor: 4.7

9. Hong S, Brazauskas R, Hebert KM, et al. Community health status and outcomes after allogeneic hematopoietic cell transplantation in the United States. Cancer. doi:10.1002/cncr.33232. Epub 2020 Oct 21. Impact factor: 5.7

10. Dhakal B, D'Souza A, Callander N, et al. Novel prognostic scoring system for autologous hematopoietic cell transplantation in multiple myeloma. British Journal of Haematology. 2020 Nov 20; 191(3):442-452. doi:10.1111/bjh.16987. Epub 2020 Oct 23. Impact factor: 5.5

11. Bona K, Brazauskas R, He N, et al. Neighborhood-poverty and pediatric allogeneic hematopoietic cell transplantation outcomes: A CIBMTR analysis. Blood. doi:10.1182/blood.2020006252. Epub 2020 Oct 26. Impact factor: 17.5

12. Shah NN, Ahn KW, Litovich C, et al. Is autologous transplant in relapsed DLBCL patients achieving only a PET+ PR appropriate in the CAR-T cell era? Blood. doi:10.1182/blood.2020007939. Epub 2020 Oct 29. Impact factor: 17.5

13. Pasquini MC, Hu Z-H, Curran K, et al. Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma. Blood Advances. 2020 Nov 10; 4(21):5414-5424. doi:10.1182/bloodadvances.2020003092. Epub 2020 Nov 4. PMC7656920. Impact factor: 4.6

14. Single RM, Meyer D, Nunes K, et al. Demographic history and selection at HLA loci in Native Americans. PLoS One. 15(11):e0241282. doi:10.1371/journal.pone.0241282. Epub 2020 Nov 4. PMC7641399. Impact factor: 2.7

15. Qayed M, Ahn KW, Kitko CL, et al. A validated pediatric disease risk index for allogeneic hematopoietic cell transplantation. Blood. doi:10.1182/blood.2020009342. Epub 2020 Nov 18. Impact factor: 17.5

16. Martens, MJ, Logan, B. A unified approach to sample size and power determination for testing parameters in generalized linear and time-to-event regression models. Statistics in Medicine. doi:10.1002/sim.8823. Epub 2020 Nov 18. Impact factor: 1.8

17. Roe D, Vierra-Green C, Pyo C-W, et al. A detailed view of KIR haplotype structures and gene families as provided by a new motif-based multiple sequence alignment. Frontiers in Immunology. 11:585731. doi:10.3389/fimmu.2020.585731. Epub 2020 Nov 18. PMC7708349. Impact factor: 6.4

18. Gupta V, Kennedy JA, Capo-Chichi J-M, et al. enetic factors rather than blast reduction determine outcomes of allogeneic HCT in BCR-ABL?negative MPN in blast phase. Blood Advances. 2020 Nov 20; 4(21):5562-5573. doi:10.1182/bloodadvances.2020002727. Epub 2020 Nov 20. PMC7656913. Impact factor: 4.6