June 14, 2018

Lt. Cdr. Brian Andrews-Shigaki
Office Warfighter Performance S&T Dept
875 N. Randolph St.
Arlington, VA 22203-1995

Subject: Interim Technical Report with SF298 by the National Marrow Donor Program®

Reference: Grant N00014-18-1-2045 between the Office of Naval Research and the National Marrow Donor Program

Dear Lt. Cdr. Andrews-Shigaki,

In accordance with the requirements of the referenced Office of Naval Research Grant, the National Marrow Donor Program (NMDP) hereby submits the required Interim Technical Report for the period of January 01, 2018 through May 31, 2018.

Should you have any questions regarding the performance activity of under this Grant, you may contact our Chief Medical Officer – Dennis Confer, MD directly at 763-406-3425.

Please direct any contractual questions pertaining to the Grant to me at 763-406-3401 or to npoland@nmdp.org.

Sincerely,

Nancy R. Poland, M.A.
Contracts and Compliance Manager

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14. ABSTRACT
1. Contingency Prepardness: 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. Immunogenetic 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.

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Research in HLA Typing, Hematopoietic Stem Cell Transplantation and Clinical Studies to Improve Outcomes

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Grant Award N00014-17-1-2045

DEVELOPMENT OF MEDICAL TECHNOLOGY FOR CONTINGENCY RESPONSE TO MARROW TOXIC AGENTS

INTERIM RESEARCH PERFORMANCE REPORT

SUBMITTED JUNE 14, 2018

Office of Naval Research

And

The National Marrow Donor Program®

500 5th St N

Minneapolis, MN 55401

I. Heading

PI: Dennis L. Confer, M.D.

National Marrow Donor Program

N00014-17-2045

Development of Medical Technology for Contingency Response to Marrow Toxic Agents

II. Scientific and Technical Objectives

The main objective of this grant is to develop, test and mature the ability of the National Marrow Donor Program® (NMDP) to address contingency events wherein civilian or military personnel are exposed to marrow toxic agents, primarily ionizing radiation or chemical weapons containing nitrogen mustard. An accident, a military incident, or terrorist act in which a number of individuals are exposed to marrow toxic agents will result in injuries from mild to lethal. Casualties will be triaged by first responders, and those with major marrow injuries who may ultimately be candidates for hematopoietic cell transplantation (HCT) will need to be identified. HCT donor identification activities will be initiated for all potential HCT candidates. 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 process 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 to improve outcomes and quality of life for the patients.

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. Concise Accomplishments

a. Contingency Preparedness
   i. Planned table top, regional and functional exercises for execution during the project period.
   ii. Conducted training sessions and tracked training activities at RITN centers.
   iii. Tested the Operational Resiliency Plan at the coordinating center during the work disruption caused by Super Bowl LLII held in Minneapolis.

b. Development of Science and Technology for Rapid Identification of Matched Donors
   i. Recruited 81,935 minority race and 141,750 White donors for a total of 223,685 U.S. donors added to the registry. This grant provided HLA typing support for 78% of the recruited donors.
   ii. Held one Data Standards Hackathon in Utrecht, The Netherlands and planned another for this July in Minneapolis, MN.
   iii. Provided support for collection of 9 products for the National Institutes of Health transplant program.

c. Immunogenetic Studies in Transplantation
   i. Initiated full gene HLA and presence/absence KIR typing on a cohort of >3,500 unrelated and related adult donor/recipient transplant pairs.
   ii. Completed an analysis of non-antigen recognition domain sequence variation in a cohort of >4,600 donor/recipient transplant pairs.
   iii. Initiated an Integrative Genomics pilot project to identify putative minor histocompatibility mismatches.

d. Clinical Research in Transplantation
   i. Published 50 peer reviewed manuscripts.
   ii. Reviewed 207 new study proposals and accepted 80 for discussion at the February 2018 ASBMT/CIBMTR Transplant Tandem Meetings.
   iii. Presented 24 abstracts at the American Society of Hematology Annual Meeting meeting in December 2017.
   iv. Presented 15 abstracts at the ASBMT/CIBMTR BMT Tandem Meetings in February 2018.

V. Expanded Accomplishments

Contingency Preparedness

Recovery of casualties with significant myelosuppression following radiation or chemical exposure is optimal when care plans are designed and implemented by transplant physicians.

Hospitals are eligible to join RITN if they participate in both the NMDP Network of treatment centers and the NDMS. The NDMS is comprised of over 1,800 accredited hospitals across the nation that have agreed to receive trauma casualties following a disaster. The program is managed by the Department of Health and Human Services. RITN conducts targeted recruitment on an annual basis with a goal of expanding the network. RITN consists of 68 transplant centers, 5 donor centers, and 6 cord blood banks (Figure 1).

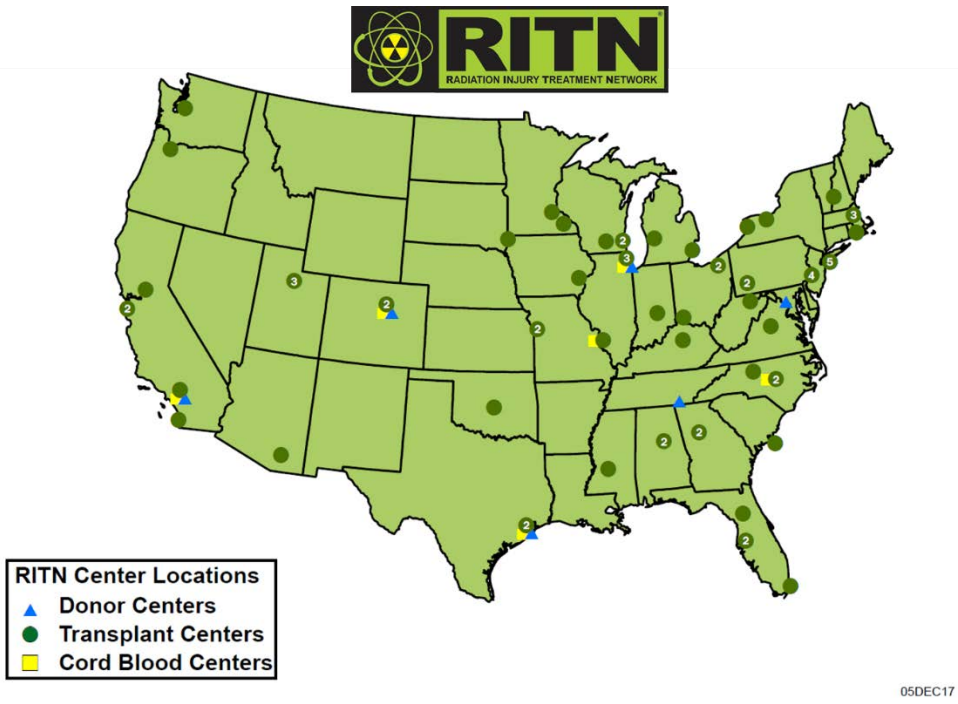


Figure 1. Location of RITN Centers

RITN Preparedness Activities

RITN centers were asked to continue to develop their level of preparedness during the grant period. Tasks included communications drills, updating of standard operating procedures, outreach to local public health and emergency management contacts, a tabletop exercise and training of staff.

Training tasks:

RITN centers were asked to conduct training with the intent to educate and increase the awareness of RITN and its efforts to the appropriate response community. Training options continue to be publicly accessible online at no cost to anyone who is interested. In addition, the in person training option has expanded to include an Advanced HAZMAT Life Support (AHLS) for Radiological Incidents course. As shown in Figure 6 the training options continue to grow, centers can now choose between conducting Basic Radiation Training, having a physician or Advanced Practitioner complete the REAC/TS training, hosting an AHLS course, conducting an Acute Radiation Syndrome Medical Grand rounds session, and having a site assessment conducted. In addition, centers can conduct community outreach and education using the RITN Overview Presentation. All of these materials, with the exception of the REAC/TS training, are available unrestricted, through the RITN website. The RITN web based training catalog includes:

1. Introduction to RITN
2. RITN Concept of Operations
3. GETS 101
4. Satellite telephone 101
5. Basic Radiation Training
6. Non-medical Radiation Awareness Training
7. Radiation Safety Communication Course

The online learning management system allows RITN center staff to complete the full course at their own pace and receive an electronic certificate of completion after meeting all the course objectives and knowledge assessments. Since 2006, RITN has had a hand in the disaster response training or education of approximately 15,000 medical personnel and staff affiliated with RITN hospitals.

The RITN continuously seeks to formalize and develop further partnerships with federal agencies and organizations. Memoranda of Understanding (MOU) have been established with the following groups to collaborate on preparedness efforts:

- ASBMT since 2006
- Department of Health and Human Services – Office of the Assistant Secretary for Preparedness and Response (HHS-ASPR) since 2007
- AABB-Disasters Task Force since 2008
- European Group for Blood and Marrow Transplantation - Nuclear Accident Committee (EBMT-NAC) since 2011

Additionally, the RITN maintains informal relationships to increase awareness about RITN worldwide through close interaction with:

- Biomedical Advanced Research and Development Authority (BARDA)
- Health Resources and Services Administration (HRSA)

- World Health Organization - Radiation Emergency Medical Preparedness and Assistance Network (WHO-REMPAN)
- Radiation Emergency Assistance Center and Training Site (REAC/TS)
- Armed Forces Radiobiology Research Institute (AFRRI)
- National Institute of Allergy and Infectious Diseases (NIAID)
- National Institutes of Health (NIH) - National Library of Medicine (NLM) - Radiation Emergency Medical Management (REMM)
- American Hospital Association (AHA)
- Association of State and Territorial Health Officials (ASTHO)
- National Association of City and County Health Officials (NACCHO)
- Veteran's Administration Health System
- Centers for Medical Countermeasures Against Radiation (CMCR)
- National Alliance for Radiation Readiness (NARR)

RITN uses Health Care Standard® (HCS®) software to consolidate participating hospitals Capability Reports and to communicate situation status updates to the network through a web based interface. Annual tests are conducted to ensure that users are familiar with the system and that it is capable of receiving and consolidating submitted data. This system allowed RITN to collect the bed availability and on-hand G-CSF quantities throughout the network during a prior grant period.

The Assistant Secretary for Preparedness and Response from the Department of Health and Human Services has been a partner since the foundation of RITN. This partnership is formalized through an MOU and is prominently displayed on the Department of Health and Human Services website for Public Health Emergencies on the Chemical, Biological, Radiological, Nuclear and Explosive Branch page, (http://www.PHE.gov/about/oem/cbrne, and Figure 2):

Figure 2. Chemical, Biological, Radiological, Nuclear and Explosive Branch webpage noting the partnership with RITN.

NMDP's critical functions must remain operational during contingency situations that directly affect the Coordinating Center.

During the grant period, the NMDP updated the Operational Resiliency Plan (ORP) and all supporting documentation. In addition, the ORP was evaluated in a real world test in response to a work disruption caused by Super Bowl LLII held in Minneapolis. During the week leading up to the Super Bowl over 70% of NMDP employees worked from an alternate location, validating the organizations ability to conduct operations from a location other than the Coordinating Center for a short duration (Figure 3). The Operational Resiliency Steering Committee reviewed changes and additions to the plan at the annual meeting. The committee is chaired by the Chief Medical Officer and seated by the Chief Information Officer; Chief Financial Officer; Chief Legal Officer; Chief Operating Officer; and Chief Human Resources Officer.

Strength 1: Virtual Private Network (VPN) capability was able to support over 700 employees working remotely.

Super Bowl Week

Date	Average	Max
Monday 1/29	649	738
Tuesday 1/30	678	750
Wednesday 1/31	676	744
Thursday 2/1	689	759
Friday 2/2	662	738

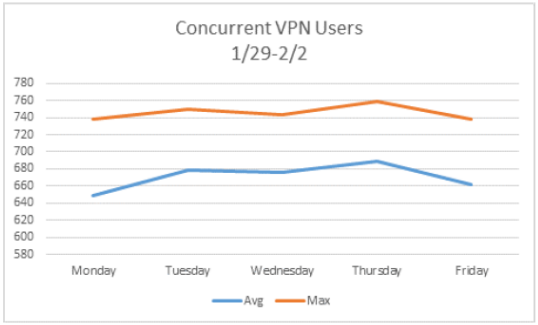


Figure 3. Daily network access by staff working remote during the Super Bowl work disruption.

Through the feedback of 97 people leaders who responded to a survey after the Super Bowl 94% reported that their teams were as or more productive as during a normal work week (Figure 4).

Question 12: Rate how productive you felt your team was during the week?

Answer Options	Response Percent	Response Count
A lot more productive	8.6%	7
Slightly more productive	21.0%	17
Same as a usual week	64.2%	52
Slightly less productive	6.2%	5
A lot less productive	0.0%	0

Figure 4. Survey response data from people leaders following the Super Bowl work disruption.

Development of Science and Technology for Rapid Identification of Matched Donors

Increasing the resolution and quality of the HLA testing of volunteers on the Registry will speed donor selection.

Increased diversity of newly recruited donors

During the NMDP's FY18 to date (Oct 1, 2017 to April 30, 2018), NMDP donor centers (including DoD) and recruitment groups recruited 81,935 minority race and 141,750 White donors for a total of 223,685 U.S. donors added to the registry. Navy funding supported the HLA typing of 175,131 donors (excluding DoD) of this culturally diverse group (37.8% minority). These numbers continue to accumulate with current funding and the summaries for the current fiscal year will be reported after October 2018.

Advancing technology improved performance and pricing

The NMDP typing strategy maximizes the use of funds by utilizing new typing methodologies that deliver a higher resolution of results at a lower cost than previous methods. The overall goal is to ensure that new donors are listed on the registry with the best possible resolution and number of loci tested. This is particularly critical during times of a contingency where well HLA-characterized adult donors must be readily matched to patients in need of HCT for ARS. Since January 2017, 100% of newly recruited donors are typed with this methodology at HLA-A, B, C, DRB1, DQB1, DPB1, exon-based for DRB3/4/5, ABO/RhD, and the CCR5 delta 32 mutation.

Enhancing Non-HLA data for selected donors

Transplant centers utilize donor CMV status and blood type (ABO/Rh) as non-HLA selection factors when multiple equally well-matched donors are available. Historically, the only process to obtain this information was to request the potential donor on behalf of the patient, obtain a fresh blood sample, and perform IDM tests that include the donor blood type and presence/absence of circulating antibodies to CMV. CMV antibodies are present in oral transudate fluid, in addition to blood serum. Over the course of several experiments, two different NMDP contract laboratories have been able to satisfactorily use a modified assay to test for the CMV virus when flocked swabs were used to collect oral specimens. The studies achieved both 100% positive predictive values and assay specificity, as well as >85% assay sensitivity and negative predictive values, when a small percent (<9%) of results were excluded as equivocal. Incorporation of this testing, in parallel with the HLA testing, of registry members at the time of recruitment, would provide a presumptive CMV serostatus to enhance the non-HLA information available and aid the transplant center with quicker optimal donor selection.

The first step to evaluate whether presumptive CMV testing will be valuable to transplant centers by assessing whether donors with this information are selected at higher rates. From January 2018 through March 2018, a select cohort of 3,500 newly recruited young male donors were CMV tested with this modified assay using flocked swabs. This cohort will be tracked over the next several months, alongside a control cohort of similar demographics, to compare activation rates for those with and without the presumptive CMV serostatus. A phase 2 of this utilization study will ensue over the next few months to continue to add CMV testing for additional donors at recruitment, and tracking for a longer period of time to monitor possibly increased activation rates on patient searches and potential for faster time to transplant.

ABO/Rh and CCR5Δ32 mutation at Recruitment by DNA-based testing

As of October 01, 2014, all recruitment samples receive DNA based ABO/RhD testing along with HLA testing as noted above. As of October 2016, all recruitment samples receive DNA based testing to detect the presence/absence of CCR5Δ32 mutation. Donors homozygous for the CCR5Δ32 deletion are of interest in HCT for patients infected by both HIV-1 and a hematologic

malignancy. The mutation confers natural HIV resistance to individuals carrying two copies (homozygotes), while heterozygous individuals show increased resistance and lower viral loads compared to wild type. The addition of this testing to the donor recruitment panel has allowed NMDP to characterize the CCR5Δ32 deletion frequency in the diverse unrelated donor populations listed on the registry.

Overall, 0.73% URDs were identified as CCR5Δ32 homozygous. The frequency of homozygotes found in unrelated registry donors self-identified as race group of White was similar (1.16%) to previously published data on European individuals (1%). The frequency of homozygotes in the remaining populations was low with 0.03% observed in Black, <0.01% in Asian/Pacific Islander, 0.20% in Hispanic and 0.90% in Native American. The frequency of self-identified White U.S. registry donors homozygous for the CCR5Δ3 deletion is consistent with previous studies on individuals of European descent. An abstract describing these data was submitted to the 2018 American Society of Histocompatibility and Immunogenetics Annual Meeting and was accepted as an oral presentation.

Quality of HLA typings improved

The NMDP's comprehensive quality control (QC) program has supported the successful increase in the quality of HLA typing received through the contract laboratory network. Blind QC samples are added to each weekly shipment of new donor recruitment samples. These QC samples comprise 2.5% of each shipment and are indistinguishable from the other samples. There are more than 1,000 QC Masters in active rotation, representing over 87% of common HLA alleles and 13% of well-documented HLA alleles. In order to maintain a robust and diverse inventory of QC Master samples into the long term future, a program to obtain samples from registry donors with desirable HLA types and other unique immunogenetic factors has been developed and implemented. A software application has been developed and released in the past year for business users to manage QC sample inventory and track incoming test results. This will allow staff to track sample age, document sample lineage, and detect patterns in reporting errors in real time.

Primary DNA typing data can be used within the registry to improve the quality and resolution of volunteer donor HLA assignments.

Data Standards Hackathons

Following six successful Data Standards Hackathons (DaSH) during past grant periods, two Hackathons were organized this grant period:

- DaSH 7, Utrecht, The Netherlands, November 2017

This meeting was co-hosted by GenDx. Forty coders and scientists attended, including 17 people from Europe

- DaSH Fast Healthcare Interoperability Resources (FHIR, pronounced "fire"), Minneapolis, July 2018
  The focus of this hackathon is on HL7-FHIR and its application to HLA reporting, cytogenetics and communication between transplant centers and registries.

The work has focused on two main areas.

- Data standards for HLA: specifying principles for annotation and testing out data formats, tools and services with producers and consumers working together to provide rapid assessment of prototypes. The goal is to develop a public “ecosystem” which is a set of tools and standards to create a shared facility for the storage, exchange and analysis of HLA and KIR data, project related data, and analytic results building on Minimal Information for Reporting Immunogenomic NGS Genotyping (MIRING), histoimmunogenetics mark-up language (HML) and (genotype list(GL)-services.
- HL7 FHIR: exploring the use of HL7 as a convenient platform for exchanging HLA typing data, particularly by providing the code to test messages, as well as trouble shooting any problems in the data message exchange. This also included work on Continuity of Care Record (CCR) and ABO/Rh reporting, and preparing a new HML schema to support nested specifications like FHIR.

Allele Calling Tool

A publicly available service for accurately annotating and assigning allele names to HLA and KIR consensus sequences has been developed, that is a valuable community resource. Gene feature enumeration (GFE) notation was developed as a way to retain and characterize sequence variation outside of the current nomenclature. GFE notation for every sequence in the IPD-IMGT/HLA and -KIR Databases has been generated, and loaded into a neo4j graph database (neo4j.b12x.org), which includes KIR, HLA, GFE and sequence feature nodes. An allele-calling tool (ACT) annotates sequences and converts those annotations to GFE notation. The ACT uses these GFE notations and the graph database to make allele calls by finding alleles that share similar features. A representational state transfer (RESTful) service web-interface makes the ACT easy to use and allows for cross-platform compatibility (act.b12x.org). 118,585 NMDP donors typed at high resolution with consensus sequences available for HLA-A, B, C, DRB3/4/5, DRB1, DQB1 and DPB1 were used to test the ACT. The allele calls generated by the ACT were compared to the lab-reported allele calls using the same IPD-IMGT/HLA release as the labs and IPD-IMGT/HLA release 3.31.0. To test the ACT with KIR, all the KIR sequences that were characterized in IPD-KIR release 2.7.0 and then made allele calls with the ACT using release 2.6.0. The allele calls made by the ACT matched the lab reported typing 100% of the time for class I and 99.5% of the time for class II when using the same IMGT release as the lab.

Accurate allele calls and sequence annotations are made when using the NMDP developed GFE-based ACT. The ACT can also be used to extend the nomenclature for allele assignments made with previous IPD-IMGT/HLA releases. This service will allow anyone to easily convert HLA and KIR consensus sequences into detailed sequence annotations and allele names.

The following resources have been developed for public use:

- GFE DB: a graph database representing IPD-IMGT/HLA data as Gene Feature Enumeration strings https://github.com/nmdp-bioinformatics/gfe-db live version: http://neo4j.b12x.org/browser/
- ACT: allele calling tool – converts consensus sequence to GFE and HLA nomenclature https://github.com/nmdp-bioinformatics/service-act live version: http://act.b12x.org/ui/
- pyGFE: Python package for creating GFE notation from annotated sequences https://github.com/nmdp-bioinformatics/pyGFE
- SeqAnn: A Python package for doing fast and accurate sequence annotation https://github.com/nmdp-bioinformatics/SeqAnn

HL7 (Health Level 7) Genomics

New and emerging technologies force the development of new and emerging standards. For example, the immunogenomics NGS community has recently developed a set of principles describing MIRING. However, these guidelines are not implementable using currently available data standard formats. The approach has been to go forward in developing a technical implementation of the MIRING guidelines by extending HML, and at the same time work with the larger genomics community standards being developed (Global Alliance for Genomics and Health, ClinGen) and healthcare interoperability standards communities HL7. By working with these communities, the development of new standards informed by MIRING principles and HML 1.0 specifications has been enabled. While HML 1.0 meets the current needs for reporting NGS based genotyping, it is not yet poised to interoperate seamlessly with clinical electronic medical record systems (EMRs). It is proposed to evolve HML so that the next major version (HML 2.0) will be based on HL7 FHIR and should more easily integrate with EMRs.

The primary activity towards this goal in the past year has been:

- Continued development of HL7 FHIR Profiles for HLA and KIR reporting through participation in the HL7 Clinical Genomics (CG) Work Group.

- Development of an HLA Terminology Service

    - A proof-of-concept HL7 FHIR terminology service has been developed [http://mac-and-fhir-prototype.us-east-1.elasticbeanstalk.com/doc/]

    - A static FHIR Bundle containing CodeSystem and ValueSet FHIR resources for

HLA nomenclature has been made available [https://s3.amazonaws.com/nmdp-fhir-terminology/who/fhir-imgt-hla-terminology-20170729.zip]

- Development of an open-source HML to FHIR converter application

  A series of libraries has been developed and made available for this effort

  - https://github.com/nmdp-bioinformatics/hml-to-fhir
  - https://github.com/nmdp-bioinformatics/service-hml-fhir-converter
  - https://github.com/nmdp-bioinformatics/hml-fhir-mongo
  - https://github.com/nmdp-bioinformatics/service-hml-fhir-converter-api
  - https://github.com/nmdp-bioinformatics/service-hml-fhir-converter-models

- Working with vendors to include HML 1.0 and newly developed HL7 FHIR resources into their products
  - **EPIC** –An EPIC App Orchard application for patient submission to CIBMTR has been developed (described in more detail in section IID.1.1).
  - **CareDx** – Representatives have joined the HL7 Clinical Genomics Work Group and are collaborating on the development of FHIR resources and profiles for reporting HLA.
  - **LabCorp** is committed to a pilot project to submit HL7-FHIR HLA typing reports.
  - **Blood Centers of Wisconsin** has drafted a pilot for sending full-HLA sequence data from the laboratory to their transplant centers for nomenclature-agnostic matching.
  - **Stanford** has agreed to participate in a pilot where they will work with their lab software vendor (**M'Tilda**) to testing submission of HLA lab reports using HL7-FHIR.

- Informing the larger genomics communities of the unique needs of HLA and KIR. This includes participation with the data modeling efforts of Global Alliance for Genomics and Health, and the ClinGen Allele Data Model.
  - We have continued participating in the HL7-FHIR Clinical Genomics Work Group, and have sent several participants to FHIR connectathons participating in the Clinical Genomics track.
  - Six people attended FHIR Dev Days in Nov 2017.
  - A new FHIR resource called BiologicallyDerivedProduct to describe transplant material (stem cells, organs, blood, etc) was proposed, which is now in the current build of FHIR and is in the R4 ballot. (http://hl7.org/fhir/2018May/biologicallyderivedproduct.html)

- A public development FHIR server using HAPI java libraries (hapifhir.io) was deployed. This is found on http://fhirtest.b12x.org/.
- A 1-day symposium on HL7-FHIR followed by a 2-day hackathon in Minneapolis scheduled for July 25-27, 2018 was organized.

Registry data on HLA allele and haplotype frequencies and on the nuances of HLA typing can be used to design computer algorithms to predict the best matched donor or cord blood unit.

Haplotype Frequency Curation

Implementation has begun on a Public Haplotype Frequency Curation Service (PHYCuS). The goal is to address several unmet needs in the field for applications that consume HLA Haplotype Frequency data:

- Standard input formats for genotypes and output formats for haplotypes
- Standard representations of ambiguity (multiple allele codes, genotype lists)
- Standardized version-specific validation of HLA
- Globally unique IDs to refer to "populations", "cohorts" and the one-to-many relationship between them
- Access control with appropriate licensing agreements
- Automated access (REST API not clickthrough pages)
- Quality metrics
- Standardized metadata

HLA Imputation

Imputation is a statistical filter applied to HLA typing data. The goal of imputation is to transform HLA typings that are ambiguous, un-phased or incomplete into complete phased HLA genotypes with associated probabilities. Imputation is at the heart of the HapLogic^{SM} matching algorithm and underlies many of the modeling and analytical efforts carried out under this section of the research grant.

During the past year a new graph-based implementation of imputation was produced and validated as being capable of reproducing consensus results of statistical matching. This new implementation provides flexibility in terms of:

- Population haplotype frequency used and loci used as input and output: beyond the 21 US populations and 5-loci and antigen-recognition-domain alleles
- Ability to provide high-quality estimates in the context of rare HLA haplotypes and alleles
- Ability to address multi-racial individuals or those whose race/ethnic self-identification is inaccurate
- Ability to access the imputation method programmatically via a web service interface
- Ability to impute large cohorts (full registry) efficiently and persist results in real-time
- Ability to use alternative reference data for mapping between serologic and DNA-based typing

- Flexibility in terms of HLA resolution for input and output from serology, to WHO nomenclature specified at anywhere from 1-4 fields, to multiple-allele-code and GL-strings and ultimately with full-gene HLA results "GFE alleles"

During the past year a system has been developed to generate HapLogic-based imputation results of every registry subject (donor or cord blood unit) and make this data available for analysis. Using cloud storage and elastic map-reduce, 719 million rows of imputation results on 24.5 million subjects can be analyzed efficiently.

Machine Learning for Optimizing Donor Selection

The success of unrelated donor HCT depends not only on finding genetically matched donors but also on donor availability. On average 50% of potential donors in the NMDP database are unavailable for a variety of reasons, after initially matching a patient, with significant variations in availability among subgroups (e.g., by race or age). Several studies have established univariate donor characteristics associated with availability. Individual consideration of each applicable characteristic is laborious. Extrapolating group averages to individual donor level tends to be highly inaccurate. In the current environment with enhanced donor data collection, better estimates of individual donor availability are possible. A machine learning based approach to predict availability of every registered donor was investigated. The main findings from the analysis were that machine learning approaches can provide individual level estimates of donor availability. This approach could simplify the donor selection process and reduce the time taken to successfully complete the transplant. The results of this analysis are submitted for publication.

Reducing the time and effort required to identify closely matched donors for patients in urgent need of HSC transplants will improve access to transplantation and patient survival in the context of a contingency response and routine patient care.

Selection, Typing and Transplant (STaT) project

Patients transplanted earlier in their disease cycle are associated with better outcomes and better chance at survival[18]. The median time from preliminary search to donor workup is over 100 days, potentially putting patients at higher risk for relapse and disease progression in addition to additional cost and morbidity due to exposure to further therapy (chemotherapy and/or radiation). Haploidentical transplant numbers continue to increase, potentially as a result of the perceived increased time and cost associated with unrelated donor transplant. Transplant centers may be using less desirable haploidentical donor (per treatment protocols) because of slow delivery of unrelated donors.

The STaT study was aimed to determine the feasibility of identifying a suitably matched unrelated donor in an expedited timeframe (14 days). The goal was to decrease the overall timeline to transplant for urgent patient cases and allow clinical decisions to be made with the full complement of stem cell product choices available for best treatment of the patient.

To date, 67 patients from 4 transplant centers have been enrolled. Nearly 90% of the patients with donors activated had at least one work-up ready donor delivered within 14 calendar days. Twenty-five of the patients proceeded to transplant within a median of 70 days (22-211 days). The majority of the patients did not reach the targeted transplant timeline due to patient related delays due to infections and the need for additional disease treatment.

NIH Search Support

The National Institutes of Health (NIH) has been accepted as an NMDP transplant center since 2007. Prior to that time, the NIH, representing our nation's premier medical research endeavor, was not applying their considerable problem-solving skills to issues surrounding unrelated donor transplantation. The NMDP, with ONR support, set out to remedy that deficiency by entering into collaboration with NIH. This collaboration has been extremely successful.

The NMDP is collaborating with intramural NIH transplant programs from the National Cancer Institute, the National Heart Lung and Blood Institute and the National Institute of Allergy and Infectious Diseases. These programs are investigating alternative approaches in unrelated donor transplantation to improve patient outcomes. The actual transplants and the investigational portions of each transplant (i.e., the research protocols) are supported entirely with NIH funds. Navy funding supplies support for donor identification, selection and collection. NMDP donors are not research subjects on these protocols because the donors are making standard donations for accepted transplant indications. The research component of these transplants is conducted entirely by NIH intramural program staff and funded entirely with NIH dollars. The NMDP provided support for the collection of 9 products (6 PBSC, 1 CBU and 2 marrow) under the current grant through May 2018.

Rapid identification of potential donors for newly diagnosed AML patients

The Southwest Oncology Group (SWOG) has identified the time from diagnosis of Acute Myelogenous Leukemia (AML) to transplant as critical for successful treatment of patients with cytogenetically defined high risk disease. Proceeding to transplant within four months of diagnosis for patients with high risk disease in first chronic remission could potentially improve the overall disease free survival rates. Currently, these patients are referred for transplant following cytogenetic screening and several lines of therapy. The initial diagnosis and treatment phase can take several months significantly delaying the initiation of an unrelated donor search and making transplant within four months highly unlikely. NMDP/CIBMTR up front involvement would permit the rapid identification and pre-search screening of potential donors, so patients will be well along in the search process when/if ultimately referred for HCT.

In April 2013 SWOG initiated the clinical trial entitled, *"S1203: A Randomized Phase III Study of Standard Cytarabine plus Daunorubicin (7+3) Therapy or Idarubicin with High Dose*

Cytarabine (IA) versus IA with Vorinostat (IA+V) in Younger Patients with Previously Untreated Acute Myeloid Leukemia (AML)". The trial was a randomized phase III trial of cytarabine and daunorubicin hydrochloride or idarubicin and cytarabine with or without vorinostat to see how well they work in treating younger patients (18-60 years old) with previously untreated acute myeloid leukemia. Drugs used in chemotherapy, such as cytarabine, daunorubicin hydrochloride, idarubicin, and vorinostat, work in different ways to stop the growth of cancer cells, either by killing the cells or stopping them from dividing. Giving more than one drug (combination chemotherapy) and giving the drugs in different doses and in different combinations may kill more cancer cells. It is not yet known which combination chemotherapy is more effective in treating acute myeloid leukemia. The study included a transplant arm for patients diagnosed with high risk cytogenetics following the initiation of induction therapy (see Figure 5 below). NMDP/CIBMTR supported the project using ONR grant funds to provide study-specific sample collection kits for all enrolled patients, processed samples, typed, HLA typing patients that were diagnosed as cytogenetic high-risk and generated preliminary search strategy reports to assist in the identification of donors and/or CBUs through the NMDP. The resulting search information was provided to the S1203 transplant arm principal investigator who shared the data with the referring physician.

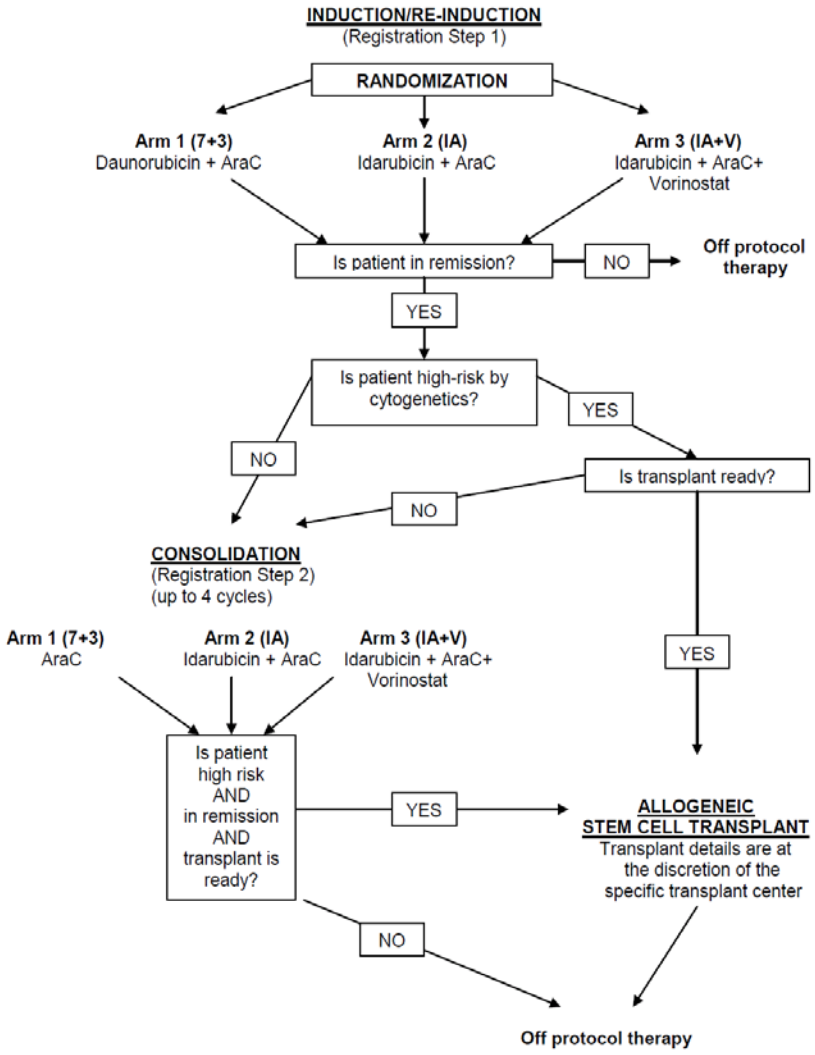


Figure 5. S1203 trial randomization and treatment schema.

The study opened in April 2013 and accrual was completed November 2015. The results of the transplant cohort were reported as an oral abstract at the 2016 ASH annual meeting and a draft manuscript was completed in June 2018. Of 738 eligible patients (median age, 49 years; range, 18-60), 159 (22%) had high-risk cytogenetics, of whom 60 (38%), 61 (38%), and 38 (24%) received induction with 7+3, IA, or IA+V, respectively. A total of 107 of the 159 high-risk patients achieved complete remission (CR1) (67%). HCT was performed in 317 of all 738 patients (43%) and 68 (64%) of the high-risk patients received a transplant in CR1 ($p<0.001$ compared to historical rate of 40%). Twenty-five (37%) had a matched related donor, 31 (45%) had a matched unrelated donor, 3 (4%) had a mismatched related donor, 8 (12%) had a mismatched unrelated donor, and 1 (1%) received an umbilical cord blood transplant. Median

time to HCT from CR1 was 76 days (range, 20-365). Fifty-seven patients (86%) received a myeloablative regimen and 9 (14%) reduced-intensity conditioning. Reasons for 39 high-risk CR1 patients not receiving a transplant in CR1 were: co-morbidities (n=1), death (n=6), no insurance (n=1), no donor (n=1), physician decision (n=3), patient decision (n=3), relapse (n=6), other (n=10), or unknown (n=8). The 2-year relapse-free (RFS) estimate in the entire high-risk cohort is 32%, significantly higher than the 22% historical rate (p=0.05). Median RFS in the high-risk CR1 cohort (n=107) was 10 months [range, 1-32* (censored) months]. RFS and overall survival (OS) were similar among HCT patients using matched related [1 year estimates: 40% (95% confidence interval (CI) 27%, 74%) and 56% (37%, 74%), respectively] and matched unrelated [1 year estimates: 52% (37%, 75%) and 56% (37%, 74%), respectively] donors in CR1. The HR (reference = unrelated) for RFS was 0.67 (0.32, 1.37) and for OS was 0.88 (0.41, 1.90). Median overall survival (OS) among all patients in the high-risk cohort (n=159) was 12 months [range, 1-33* (censored) months] and was 18 months [range 3-33* (censored) months] for those transplanted in CR1 (Figure 6). The study clearly demonstrated that in newly diagnosed adults with AML age 18-60, early cytogenetic testing with an organized effort to identify a suitable allogeneic HCT donor led to a CR1 transplant rate of 64% in the high-risk group, which in turn led to a significant improvement in RFS over historical controls. Better outcomes in poor prognosis AML patients may be achieved simply by rapidly finding unrelated donors and performing allogeneic HCT in CR1 as soon as possible.

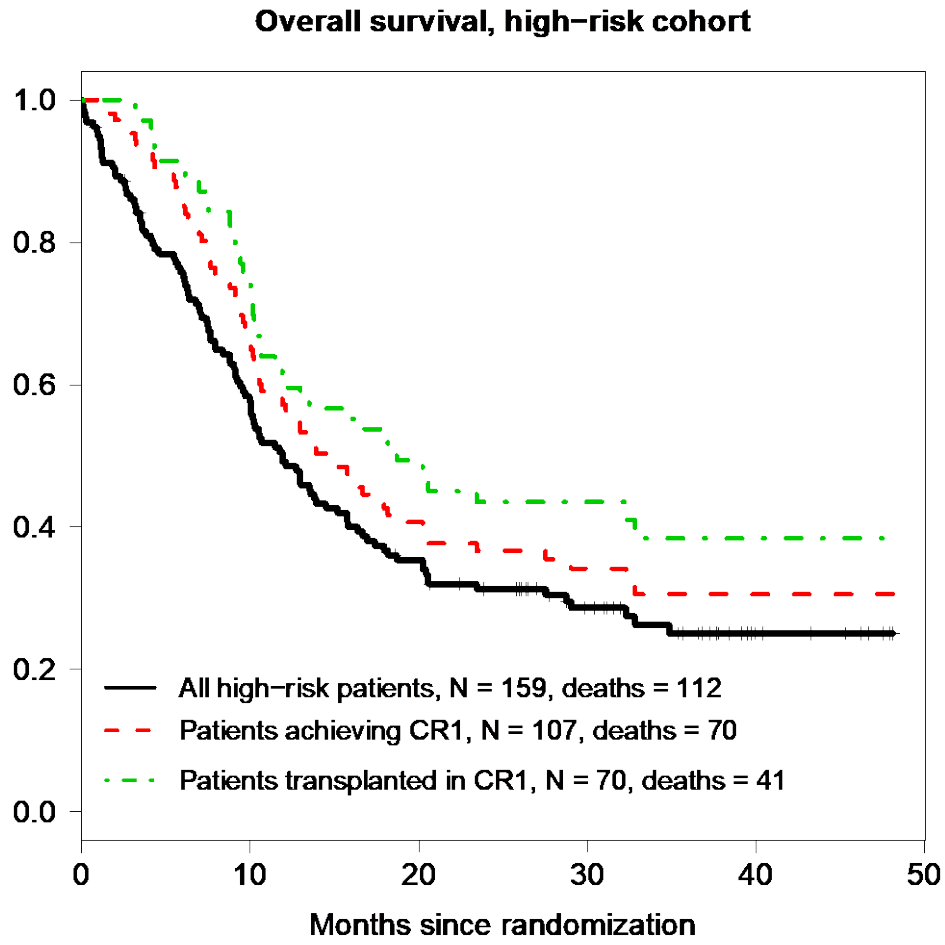


Figure 6. Overall survival of high risk cytogenetic AML patients enrolled in SWOG 1203.

Immunogenetic Studies in Transplantation

HLA mismatches may differ in their impact on transplant outcome, therefore, it is important to identify and quantify the influence of specific HLA mismatches. In contingency situations, it will not be possible to delay transplant until a perfectly matched donor can be found.

Donor/Recipient Pair Project

A retrospective Donor/Recipient Pair HLA typing project(DRPP) to characterize class I (HLA-A, B and C) and class II (HLA-DRB, DQB1, DQA1, DPA1 and DPB1) alleles of stored donor/recipient paired samples was initiated in 1994. To date, over 29,000 unrelated paired samples and more than 1,900 related paired samples from the CIBMTR research repository have been fully characterized and the resultant data are available for research use. The data are stored in an NMDP developed database and is available to any researcher with a CIBMTR-approved study wishing to analyze the impact of matching as either the focus of, or as a variable, in a research study. To date, 177 published research studies (not including abstracts) have used these data, including the seminal publication from Lee et al, published in Blood in 2007 describing the

importance of high resolution HLA matching in unrelated donor transplantation that formed the basis for NMDP's current guidelines for unrelated adult donor HCT HLA matching.

All samples are currently tested for whole gene at HLA-A, B and C, extended gene at DRB1, DQB1, and DPB1 and presence/absence for the 16 KIR loci. During the grant period, HLA and KIR typing was initiated on a cohort of >3,500 unrelated and related adult donor transplant pairs for the project. All samples were selected in collaboration with the CIBMTR statistical center to ensure the additional cases would benefit ongoing and future analyses. Transplantation practices are constantly evolving and the project will continue to enroll the most recent transplant pairs to ensure that changes in practice can be evaluated with fully quality controlled high resolution HLA data.

Full HLA Gene Typing Match Assessment

The impact of amino acid differences outside of the antigen recognition domain (ARD) have not been previously evaluated in a retrospective analysis. During a prior grant period, a collaborative project was launched with the research laboratory at the Georgetown University Medical Center to generate complete HLA gene sequencing at HLA-A, B, C, DRB1, DQB1 and DPB1 on a cohort of previously characterized ARD identical at HLA-A, B, C, DRB1 and DQB1 unrelated donor/recipient pairs from the CIBMTR research repository.

A pilot cohort of 360 pairs were analyzed to assess the frequency of sequence disparities outside of the ARD and facilitate a sample size calculation for the final study cohort. The majority of the population was self-identified Caucasian (80%). NGS was performed on the Illumina MiSeq platform and interpreted with Connexio Assign MPS. Class I gene sequences covered 5'UTR-3'UTR; DRB1, intron 1-intron 3; DQA1 5'UTR-exon 4; DQB1, intron 1-3'UTR. DQ noncoding regions were not evaluated. The majority (98.1%) of the pairs were matched for sequences outside the ARD exons: 0.5% differed in non-ARD exons, 1.9% differ in noncoding regions. A small number (0.2%) differed within ARD exons. Mismatches in non-ARD exons varied from 0.7% for HLA-C and DQA1 to 0% DQB1; noncoding variation ranges from 2.8% for HLA-C to 1.3%, HLA-B and DRB1. Within non-ARD exons, both nonsynonymous (16 allele pairs) and silent (2) variation were present. Intron variation was minor and usually impact only a single nucleotide. The results of the initial study were presented as an ASHI Scholar award winning oral abstract during the 2016 ASHI annual meeting and was published in HLA20.

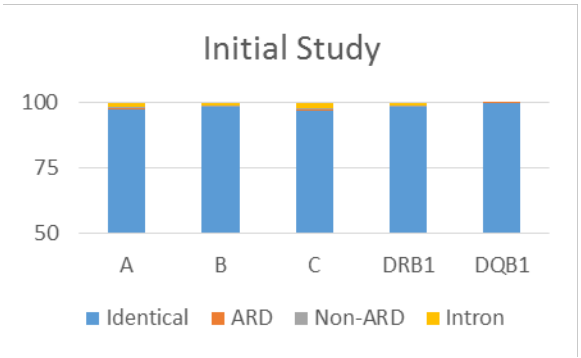
To extend these findings was continued the study in a larger cohort. Full-length HLA Class I allele sequences (HLA-A, -B, -C) and partial-length (partial intron 1 through partial intron 3) Class II allele sequences (HLA-DRB1, DQB1) were compared for 4,646 high-resolution 10/10 HLA-matched HCT donor-recipient pairs using a comprehensive HLA allele sequence comparison pipeline. The sequence analysis pipeline identifies and annotates the mismatched positions between two alleles by their functional region and their protein sequence differences using IMGT/HLA Database (v3.31.0).

In this larger cohort, we found that for HLA Class I alleles, 95.4% of the ARD matched alleles have identical sequences outside the ARD, including introns and non-ARD exons. 0.3% of the mismatches were synonymous variants from the ARD region while 0.2% and 0.1% of mismatches found from non-ARD exons were synonymous and nonsynonymous variants, respectively. The intronic variation accounted for 4.2% of the mismatches. Similarly, for HLA Class II alleles, 0.3% of mismatches were synonymous ARD variants, and the mismatches in the non-ARD exons were also very rare (synonymous: 0.3%; nonsynonymous: 0.2%). However, due to the high polymorphism in the intronic regions of the Class II genes, 26.5% of mismatches were intronic, and only 77.3% of allele pairs shared identical sequences. 0.2% and 4.6% of Class I and Class II allele pairs, respectively, showed both exonic and intronic mismatches (Figure 7).

This analysis confirmed that HCT donor/recipient pairs matched at high resolution for HLA-A, B, C, DRB1 and DQB1 have limited coding variation outside of the ARD. Intronic variation was observed at a higher rate, but these non-coding differences are unlikely to influence alloreactivity as they do not contribute to the final protein structure. The results of this analysis were submitted as an abstract to the 2018 ASHI annual meeting.

Assessment of non-ARD mismatches and impact on clinical outcome will require larger datasets due to the low frequency of coding variant mismatches. This study population will continue to be extended as data is generated through the DRPP.

A.



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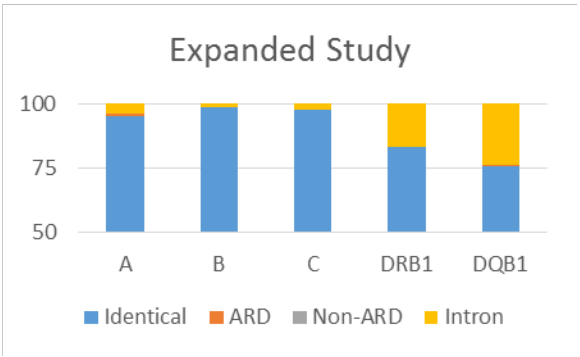

Figure 7. Summary of HLA matching between unrelated donor and recipient by locus. The four categories include: (1) donor and recipient carry identical alleles (exons and introns); (2) donor and recipient exhibit a difference in the exons encoding the ARD; (3) donor and recipient exhibit a difference in the non-ARD encoding exons; and (4) donor and recipient exhibit a difference in an intron. Chart A represents 720 allele comparisons while chart B represents 9,292 allele comparisons.

Non-Antigen Recognition Domain (ARD) Mismatch study

Analysis of four HLA Class I ARD mismatches; A*02:01 and 02:09, B*44:02 and 44:27, C*07:01, 07:06 and 07:18 have shown that the selected pairs do not travel on the same haplotypes. A manuscript describing these results is under review in the Journal of Human Immunology.

Imputation and match grade assignment

The CIBMTR HLA database includes unrelated donor and recipient transplant pair data collected over 30 years. The resolution of the typing varies significantly over this time frame. A prior study led by Dr. Daniel Weisdorf derived a clustering strategy to allow for any resolution of typing to be classified as well matched, partially matched and mismatched for retrospective analyses[21]. Improvements in the HLA imputation algorithms developed by the NMDP Bioinformatics Research team may allow for a more precise imputation of match that could improve upon the Weisdorf et al strategy.

Comparison of the predicted match grades (MG) vs. known MGs from the DRPP typed pool was used to validate the imputation method. The entire CIBMTR HLA database was then imputed to obtain a MG result for each pair. The imputed results were then compared against the Weisdorf et al assignment, to evaluate how the designations differed. Finally, we determined what MG corresponded best to the clinical outcomes. Upon analysis we determined that additional effort to define appropriate confidence thresholds as well as updates to the HapLogic^{SM} null allele haplotype processing is needed. The HLA imputation methodologies will continue to be refined to ensure consistent match grade calling based on the gold standard typing through the DRPP.

Even when patient and donor are HLA matched, GVHD occurs, therefore, other loci may play a role.

Integrative Genomics

The CIBMTR Bioinformatics Research Team has continued to develop analytical methods and tools to support analysis of genomic data. The submitted manuscript by Wang et al. entitled, “Genomic analysis of HLA-matched stem-cell transplant reveals chromosome X-Y mismatches that associate with acute graft-versus-host disease in male patients with female donors” describes the minor histocompatibility antigen (MiHA) pipeline that was developed to identify discordant SNPs between donors and recipients that result in variant peptides with predicted HLA-binding affinities. The MiHA pipeline integrated HLA typing, whole genome sequencing (WGS) and clinical outcomes (acute GVHD). The analysis identified statistical associations of MiHA associated peptides with relevant outcomes. However, additional

empirical validation would further support the clinical findings by providing evidence of peptide presentation in vivo.

In an attempt to pilot such a validation project, a collaboration was initiated with Dr. Everett Meyer and colleagues at Stanford, selecting 6 bone marrow transplant recipients and their related, HLA-matched donors for whole exome sequencing (WES) and post-transplant gut biopsy. The biopsy tissue was subjected to peptide-MHC immunoprecipitation and proteomic analysis, specifically liquid chromatography-mass spectrometry (Figure 8).

The next step is to analyze the cohort WES data using our previously developed bioinformatics pipeline to identify predicted MiHAs and corroborate these with patient-HLA-presented peptides. Preliminary results for a single patient are promising (Figure 9), suggesting that with strict specificity thresholds we can use proteomic data to validate MiHAs predicted from genomic sequence. In the next grant period, the team will continue the process of applying this analytical approach and validation to the full cohort (6 patients).

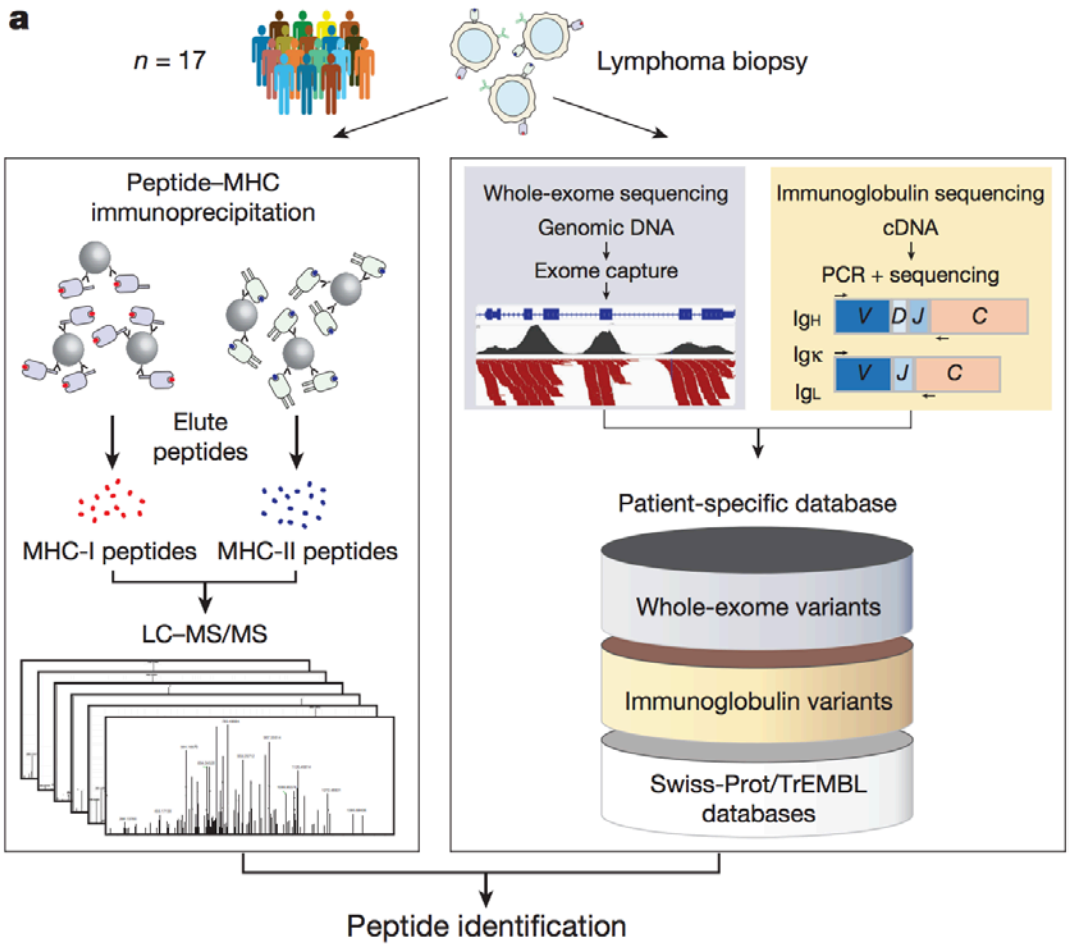

Figure 8: General approach for integrating whole exome sequencing (WES) and HLA-presented proteomic data for validation of predicted minor histocompatibility antigens (from Khodadoust et al, 2017)

Peptide (pMHC)	Uniprot Accession	Gene names	Donor.raw.area	Rec.raw.area	Donor.rank	Rec.rank	Donor.Scale	Rec.Scale
RIHTGEKPY	**Q8N2I2**	**ZNF619**	**113000**	**2270000**	**0.534**	**0.813**	**0.5**	**0.8**
YPAEITLTW	P13747	HLA-E HLA-6.2 HLAE	5280000	0	0.978	0	1	0
SAMPTVRSF	Q03518	TAP1 ABCB2 PSF1 RING4 Y3	833000	0	0.826	0	0.8	0
LLWAGPVNA	P46940	IQGAP1 KIAA0051	197000	0	0.615	0	0.6	0
ASGFTFSSY	**O14579**	**COPE**	**0**	**6250000**	**0**	**0.927**	**0**	**0.9**
GANQSGQVF	**Q99439**	**CNN2**	**0**	**308000**	**0**	**0.5**	**0**	**0.5**

Figure 9: Top validation hits for a single patient

KIR Genomics

In previous grant years, sequencing of complete genomic haplotypes the KIR region by combining a Fosmid cloning approach with Single Molecule, Real-Time (SMRT®) Sequencing was achieved. This method led to comprehensive sequencing and phasing of sixteen KIR haplotypes from eight individuals without imputation. The information revealed four novel haplotype structures ranging in size from 69kb to 269kb, a novel gene-fusion allele, novel and confirmed insertion/deletion events, a homozygous individual, and overall diversity for the structural haplotypes and their alleles.

Building on this approach and material (samples and data) a workflow is in development for library preparation, single-molecule sequencing, assembly, and interpretation of full KIR diploid haplotypes. The workflow combines targeted medium-length read sequencing and known structural haplotypes for scalable low-cost full haplotype interpretation.
https://www.pacb.com/wp-content/uploads/Procedure-Checklist-Multiplexed-Genomic-DNA-Target-Capture-Using-IDT-xGen-Lockdown-Probes.pdf

A design for a 200 probe capture plan was completed and is being manufactured and will be used to prepare a sequencing library for the same panel of 8 samples sequenced by Fosmid-based targeting of KIR. The results sequencing of this library using long-read technology will allow direct comparison to the Fosmid-based approach and will inform refinements in the capture and sequencing approach.

Immunobiology Project Results Database

As part of the support for whole genome sequencing (WGS) data, T-cell receptor (TCR) Sequencing, and other immunogenetic experiments, the repository system for the genetic typing results (Immunobiology Project Results (IPR)) must be updated to validate, manage, and store the expanded set of data. The architecture of IPR was upgraded to use RESTful services as appropriate in order to decouple validation functions from storage functions. This provides flexibility as these validation functions evolve due to our increasing knowledge of the full sequences.

Recent activity includes:

- Reaffirming the use of RESTful services for Genomic Reference Data. This work is being done to accommodate the development of new databases to store the HLA and KIR reference data
- Accessing and delivering WGS to a prototype Genomics Analysis Pipeline
- Upgraded data-loading and processing pipelines using new technologies and reducing redundancies which resulted in close to 50% improvement in efficiency in processing typings
- Successfully integrated with CIBMTR research repository / inventory management software

Table 1 lists currently active and completed NMDP/CIBMTR-supported studies that are conducted on NMDP samples. The CIBMTR/NMDP encourages such collaborative projects and closely monitor them. Such studies are instrumental to understanding the role of non-HLA loci in HCT. The data is obtained and generated via NMDP donor and recipient research samples, along with their outcomes and demographics. The researchers are required to submit the interpreted results of all assays performed on the samples. The data submission requirement ensures that all sample testing yields information that is readily available to the HCT research community for subsequent analysis and eliminates or reduces duplicative testing to preserve resources and sample inventory. These results are stored in the IPR and IIDB databases, and associated with their samples in the CIBMTR research repository database.

Non-HLA data is available for use in research studies in a fashion analogous to the Donor/Recipient Pair Project generated HLA data and is made available, when possible, via the NMDP Bioinformatics web site. Data origin will be noted for all information stored, along with relevant citations. Access to the detailed data will be subject to the existing NMDP/CIBMTR data request procedures.

Table 1. Immunobiology typing projects utilizing NMDP samples and contributing data to the IPR database

Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data submitted
NK Cells[22], Their Receptors and Unrelated Donor Transplant[23, 24]	J. Miller	2300 pairs	KIR	RT-PCR, FACS, SSO, MALDI-TOF	Yes
Survey of Diversity of Immune Response Genes in Unrelated Hematopoietic Stem Cell Transplantation	C. Hurley	40 Pairs	cytokine and KIR	SBT	Yes
Candidate Gene Study to Examine the Impact of Chemokine and Chemokine Receptor Gene Polymorphisms on the Incidence and Severity of Acute and Chronic GVHD[25]	R. Abdi	1300 pairs	CCL1, CCL2, CCR5, CCR2, CX3CR1	Taqman PCR	Yes
Functional Significance of Killer Ig-like Receptor (KIR) Genes in HLA Matched and Mismatched Unrelated HCT[26]	B. Dupont, K. Hsu	2000 pairs	KIR	SSP	Yes
Functional Significance of Cytokine Gene Polymorphism in Modulation Risk of Post-Transplant Complications[27]	E. Petersdorf	2500 pairs	>30 Immune response genes	Taqman PCR	Yes
Identification of Functional SNPs in Unrelated HCT[28,29]	E. Petersdorf	3500 pairs	Entire MHC region	Taqman PCR	In Process

Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data submitted
Use of Female Donors with Pre-existing Antibody to H-Y Antigen will Result in Robust Serologic Response to H-Y Antigens in Male HSC transplantation Recipients[30]	D. Miklos	288 pairs	H-Y Antigen	ELISA, protein array	Yes
Multiplexed Genotyping of Human Minor Histocompatibility Antigens (mHAg): Clinical Relevance of mHAg Disparity in Stem Cell Transplantation[31]	T. Ellis	730 pairs	mHAg	Allele-specific Primer Extension	Yes
Genetic Polymorphisms in the Genes Encoding Human Interleukin-7 Receptor-a: Prognostic significance in Allogeneic Stem Cell Transplantation[32]	K. Muller	851 pairs	IL-7	Taqman PCR	Yes
The Effect of Non-Inherited Maternal Antigens in Cord Blood Transplantation[33]	L. Baxter-Lowe	102 pairs	HLA	SBT	Yes
Detection of HLA Antibody in Single Antigen HLA-Mismatched Unrelated Donor Transplants	S. Arai, D. Miklos	200 pairs	Anti-body	ELISA, Protein array	Yes
Detection of Donor-Directed, HLA-Specific Alloantibodies in Recipients of Unrelated Stem Cell Transplantation and Their Relationship to Graft/Patient Outcome[34]	R. Bray	111 pairs	Anti-bodies	Flow cytometry	Yes
Genome-wide Association in Unrelated Donor Transplant Recipients and Donors: A Pilot Study[35]	R. Goyal	858 pairs	> 600,000 Genome wide SNPs	Human 610 - Quad V1 arrays	Yes

Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data submitted
SNPs in the p53 Pathway and Outcomes in URD HCT	B. DuPont	1500 pairs	p53, ATM, MDM2 and p21/Waf1	Taqman	In process
Association of Donor and Recipient Gene Polymorphisms of Drug and Innate Immune Response with Outcomes after URD HCT	V. Rocha	725 pairs	GSTP, GSTT, GSTM, UGT CD14, TIRAP, and NALPs	Taqman	Yes
To Develop and Test a Prognostic Index for Survival in CML URD HCT[27]	A. Dickinson	1100 pairs	TNF, IL-1RA and IL-10	Taqman	Yes
Evaluation of TGF-β1 Promoter and Signal Peptide Polymorphisms as Risk Factors for Renal Dysfunction in HCT Patients Treated with Cyclosporine A[36]	R. Shah	400 samples	TGF-β1	Taqman	Yes
Donor and Recipient Telomere Length [37, 38]as Predictors of Outcomes after Hematopoietic Stem Cell Transplant in Patients with Acquired Severe Aplastic Anemia[39]	S. Gadalla	650 samples	Telomere length and Telomerase Polymorphisms	Taqman	Yes
Development of a GVHD Prevention Biodiagnostic Test	R. Somogyi	450 samples	Gene Expression Array	Array	Yes
Genetic polymorphisms and HCT [40]related mortality Re: Pre-HCT conditioning in matched unrelated donor HCT[41]	T. Hahn	>4,000 pairs	GWAS	Array	In process
Impact of CTLA4 SNPs on outcome after URD transplant[42]	M. Jagasia	1,200 pairs	CTLA-4 SNPs	Taqman	Yes
KIR genotyping and immune function in MDS patients prior to unrelated donor transplantation[43]	E. E.Warlick and J. Miller	970 samples	KIR genotype, expression and cellular function	SSP, flow cytometry and cellular assays	In process

Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data submitted
Plasma YKL-40 and CHI3LI genotype to predict mortality after unrelated donor HCT[44]	B. Kornblit	800 pairs	YKL-40 plasma levels and CHI3LI SNPs	ELISA and Taqman	Yes
Natural killer cell genomics and outcomes after allogeneic transplantation for lymphoma[45]	V. Bachanova, J. Miller, D. Weisdorf and L. Burns	800 pairs	KIR genotype, expression and cellular function	SSP, flow cytometry and cellular assays	Yes
Effect of genetic ancestry matching on HCT outcomes[46]	A. Madbouly, M. Maiers and N. Majhail	2300 pairs	Ancestry Informative Markers	Taqman GWAS	Yes
Impact of MHC Class I chain related polymorphisms on HCT outcomes[47]	M. Askar and R. Sobecks	700 pairs	MICA genotypes	Taqman	Yes
Impact of donor signal-regulatory protein alpha polymorphism on HCT outcome	A. Gassas, J. Danska and S. Rajakumar	400 pairs	SIRP-α SNPs	Taqman	In process
Discrepancy analysis of microsatellite loci as a proxy measure for ancestral differentiation	J. Harvey, C. Steward and V. Rocha	800 pairs	Microsatellites and STR	Taqman	In process
Prognostic impact of somatic mutation[48] and the levels of CXC chemokine ligands in MDS	W. Saber, R.C. Lindsley and B. Ebert	1300 pairs	Chemokine levels Somatic mutations	ELISA Sequence capture	Yes
Mitochondrial DNA haplotypes and outcome	M. Verneris and J. Ross	4000 pairs	SNPs	Taqman	In process
Assessing T cell repertoire similarity in HLA mismatched HCT	E. Meyer	50 samples	TCR repertoire sequence	NGS	In process
Impact of SNPs in the Gamma Block of the MHC	M. Askar and R. Sobecks	700 pairs	SNPs	Taqman	In process
Clinical outcomes among HCT recipients as a function of socioeconomic status and transcriptome differences	J. Knight, J.D. Rizzo and S. Cole	252 samples	Gene expression array	Array	In process

Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data submitted
Natural killer cell genomics and outcomes after HCT for CLL	V. Bachanova, J. Miller, D. Weisdorf and S. Cooley	600 samples	KIR genotype	SSP	Yes
Donor telomere length and outcomes after HCT for acute leukemia[49]	S. Gadalla, S. Savage, D. Loftus and E. Hytopoulos	1145 samples	Leukocyte telomere length	qPCR	Yes
KIR gene content and pediatric acute leukemia HCT outcome	M. Verneris, J. Miller and S. Cooley	500 samples	KIR genotype	SSP	In process
Functional genetic variants of the ST2 gene in pairs of recipient and donors for risk stratification of GVHD and TRM outcomes.	S. Paczesny and S. Spellman	1000 pairs	sST2	Taqman	Yes
The role of HLA-E compatibility in the prognosis of acute leukemia patients undergoing 10/10 HLA matched HCT	C. Tsamadou, D. Furst and J. Mytilineos	3300 pairs	HLA-E	NGS	In process
Donor-Recipient NK cell determinants associated with survival in JMML after HCT	D. Lee, H. Rangarahan	465 pairs	KIR	NGS	In process
Identification of genomic markers of post-HCT outcomes in patients with myelofibrosis	W. Saber, S. Gadalla	393 samples	Somatic mutations	Taqman	In process
Impact of HLA Class I risk alleles associated with SAA immune pathogenesis	D. Babushok, T. Olson	50 samples	HLA LOH	NGS	In process
Impact of somatic mutations in CMML	M. Mei, R. Nakamura, R. Pillai	340 samples	Somatic mutations	NGS	In process

Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data submitted
Impact of donor clonal hematopoiesis of indeterminate potential on HCT	T. Druley	30 samples	Somatic mutations	NGS	In process

Clinical Research in Transplantation

IID.1 Objective 1

Clinical research in transplantation improves transplant outcomes and supports preparedness for a contingency response.

Clinical Outcomes Research

Clinical outcomes research using the CIBMTR research database is a core activity of the organization. These studies address a wide range of issues, focusing on questions that are difficult or impossible to address in single center studies or randomized trials because diseases treated with HCT are uncommon, single centers treat few patients with a given disorder, and not all important questions are amenable to a randomized research design. The majority of the clinical outcomes research is conducted through the CIBMTR WC structure, which incorporates many highly successful researchers in clinical transplantation. The WC perform retrospective studies to identify the most promising transplant approaches, and by identifying the patients most likely to benefit from this therapy. In addition, research in immunobiology was conducted to better understand how transplantation works including how to harness the power of the immune system to control cancer.

The CIBMTR collects data for approximately 24,000 new transplant recipients annually as well as a continually increasing volume of follow-up data on previously reported recipients and donors. Figure 10 shows cumulative accession of transplants since 1970 when the International Bone Marrow Transplant Registry began collecting these data. These data are the basis for the CIBMTR Clinical Outcomes Research program and are accessed by the WC to conduct studies.

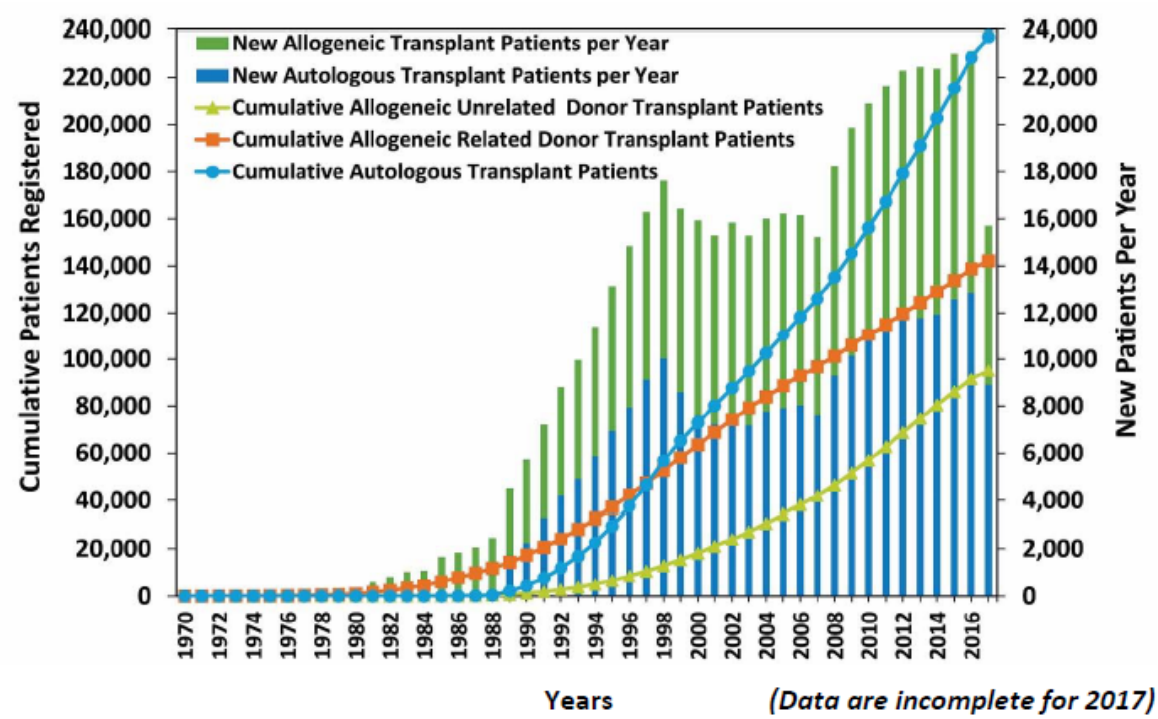

Figure 10. Accession of Transplant Recipients Registered with the CIBMTR

Currently, there are 15 WC within the CIBMTR with 175 active studies in progress (Table 2). The CIBMTR received 207 new study proposals and accepted 80 for discussion at the February 2018 ASBMT/CIBMTR Transplant Tandem Meetings (renamed the Transplant and Cellular Therapy Meeting for 2019). Proposals can be dropped for various reasons including; feasibility, low scientific impact, overlap with existing studies or combined with other proposals due to overlapping hypotheses.

Table 2. 2017 CIBMTR Working Committee portfolio and productivity

Working Committee	Studies in Progress	Publications	Presentations
Acute Leukemia	13	6	2 (1 oral / 1 poster)
Autoimmune Diseases and Cellular Therapies	5	1	0 (0 oral / 0 poster)
Chronic Leukemia	12	3	3 (2 oral / 1 poster)
Donor Health and Safety	13	2	1 (0 oral / 1 poster)
Graft Sources and Manipulation	7	3	1 (1 oral / 0 poster)
Graft-versus-Host Disease	13	3	2 (1 oral / 1 poster)
Health Services and International Studies	10	2	0 (0 oral / 0 poster)
Immunobiology	38	10	5 (1 oral / 4 poster)
Infection and Immune Reconstitution	7	0	1 (0 oral / 1 poster)
Late Effects and Quality of Life	13	6	4 (4 oral / 0 poster)
Lymphoma	10	6	3 (3 oral / 0 poster)
Pediatric Cancer	1	3	0 (0 oral / 0 poster)
Plasma Cell Disorders and Adult Solid Tumors	8	7	3 (1 oral / 2 poster)
Primary Immune Deficiencies, Inborn Errors of Metabolism, and Other Non-Malignant Marrow Disorders	13	4	1 (0 oral / 1 poster)
Regimen-Related Toxicity and Supportive Care	12	3	4 (3 oral / 1 poster)
TOTAL	175	59	30

Clinical Trials

In October 2010, RCI BMT activated a study referred to as the Long Term Donor Follow up study. The primary goal of this study is to evaluate the hypothesis that the incidence of targeted malignant, thrombotic and autoimmune disorders after unrelated hematopoietic stem cell donation are similar between unstimulated BM and filgrastim-mobilized PBSC donors. Once the donor has consented to participate, the donor is contacted and asked study specific questions every other year. This will continue until study completion which is estimated to be 2020. If the donor reports an incidence of interest, a request for their medical records is made. Cases of targeted disorders are reviewed by the medical monitors to confirm the veracity of the report.

In October 2015, accrual to this study was closed; however, follow-up assessments will continue until the end of 2020. Table 3 summarizes the accrual by cohort and product. The SRG team is responsible for the follow up assessments of just over 63% of the enrolled donors. To-date, the SRG has completed a total of 36,941 assessments of which 6,009 were during this past year.

Table 3. Long Term Donor Follow-up Study accrual summary

	Marrow	PBSC	BOTH	Total
Prospective	3009	8904	170	12083
Retrospective	3852	5478	381	9711
Totals	6861	14382	551	21794

Other Clinical Research activities

In 2014, we explored options for a) comprehensive system for management of activities and studies within the SRG and b) electronic data capture system (EDC) and CTMS to coordinate operational and administrative activities within RCI BMT. In March 2015 the SRG call tracking system built within SalesForce platform went into production. In June 2015, we initiated work on implementing Medidata RAVE for our EDC system and their CTMS solution for our internal trial management activities. In 2018, we explored options and began implementing a solution for an eTMF (electronic Trial Master File) system to efficiently store clinical regulatory documents in compliance with FDA regulations.

SRG solution

Fully implemented Medidata RAVE for electronic data capture system and a CTMS. During the past year all study management has been transitioned to the CTMS. Currently there are a total of 3 trials in RAVE with an additional 3 studies in process of design/build. In addition to multi-

center trials, CIBMTR is also utilizing RAVE to collect supplemental data for observational studies or for corporate projects when appropriate. One supplemental data project currently resides in RAVE with three supplemental data collection projects in discussion.

Patient Reported Outcomes (PRO) system within SRG:

Numerous studies now recognize the value of measuring PROs as the most accurate measure of the patient's experience with disease and treatment, primary and secondary outcomes in clinical trials, and 'biomarkers' of disease activities. Several studies in HCT show that pre-HCT PROs can predict survival and post-HCT health related quality of life (HRQoL). Collecting PRO data will allow CIBMTR to conduct research in HCT outcomes that are important to patients and their caregivers. Collecting PRO with an electronic system will allow for the most direct, cost effective and efficient way to collect this important data. In 2017, the team determined the requirements of a system and explored potential solutions, inclusive of use of Patient-Reported Outcomes Measurement Information System (PROMIS®) measures. PROMIS is a set of person-centered measures that evaluate and monitor physical, mental and social health in adults and in children. It is important for the selected system to also allow other measures to be incorporated into the surveys and be flexible and easy access for patients, donors and research subjects. A recommendation was presented to CIBMTR leadership and an initial proof of concept executed in 2017. The initial ePRO pilot study will launch in May/June 2018, utilizing the interaction among the PROMIS measures, Qualtrics (patient interface), Salesforce (CRM system) and IDW (CIBMTR's outcomes database). Following execution of the study, the system will be assessed for more broad utilization.

Explored Options for an Electronic Trial Master File (eTMF) System:

Recognizing the need for a paperless trial management system that complies with 21 CFR Part 11, CIBMTR has begun implementation of the Medidata Edge eTMF system. The system will go-live in 2018 and will be used as a platform for all new RCI BMT research studies going-forward.

Cord Blood Research Initiatives

During the project period, the Cord Blood Research Sub-advisory Group met semi-monthly to discuss study priorities and plan analyses for the following:

Colony Forming Unit – State of the Science

Cord blood banks (CBB) regard the colony forming unit (CFU) assay as an important way to measure the quality of a cord blood unit. The CBBs recognize that transplant centers generally have insufficient knowledge of the assay to incorporate the results appropriately into their selection practices. Therefore, the Cord Blood Advisory Group deemed that CBBs are responsible for educating their clinical colleagues. As a result, members of the Cord Blood Advisory Group began preparation of a CFU State of the Science manuscript with the intent of describing CBB practices and assay indications to help establish informed transplant center applications. The group also submitted an abstract on the topic to the AABB International Cord

Blood Symposium that received a best abstract award. The manuscript will be submitted during the current grant period.

NMDP Cord Blood Access (10-CBA) Protocol Clinical Results

Umbilical cord blood transplantation (UCBT) is an important option for patients, including those of diverse race/ethnicity, without a matched donor. The FDA began licensure of UCB units in 2011. Fewer than 5% of UCB units are licensed; therefore, the NMDP facilitated UCBT under IND: "A Multicenter Access and Distribution Protocol for Unlicensed Cryopreserved Cord Blood Units for Transplantation in Pediatric and Adult Patients with Hematologic Malignancies and Other Indications." The CIBMTR analyzed and presented outcomes of 1589 patients undergoing UCBT using unlicensed units. Engraftment and overall survival were excellent for the diverse patients receiving UCBT using these unlicensed units. Incidence of neutrophil engraftment (ANC > 500) at Day 42 was 88%, 89%, and 92% for adults, pediatric-malignant disease (PediM), and pediatric non-malignant disease (pediNM) respectively (Figure 11). Overall survival (OS) at 100 days/1 year was 82% and 55% for adults, 86% and 67% for pediM, and 92% and 79% for pediNM (Figure 12). The results were presented as a poster at the 2017 BMT Tandem Meetings and as an oral presentation at the 2017 NMDP Council Meeting. A manuscript describing the results is currently under review in BBMT.

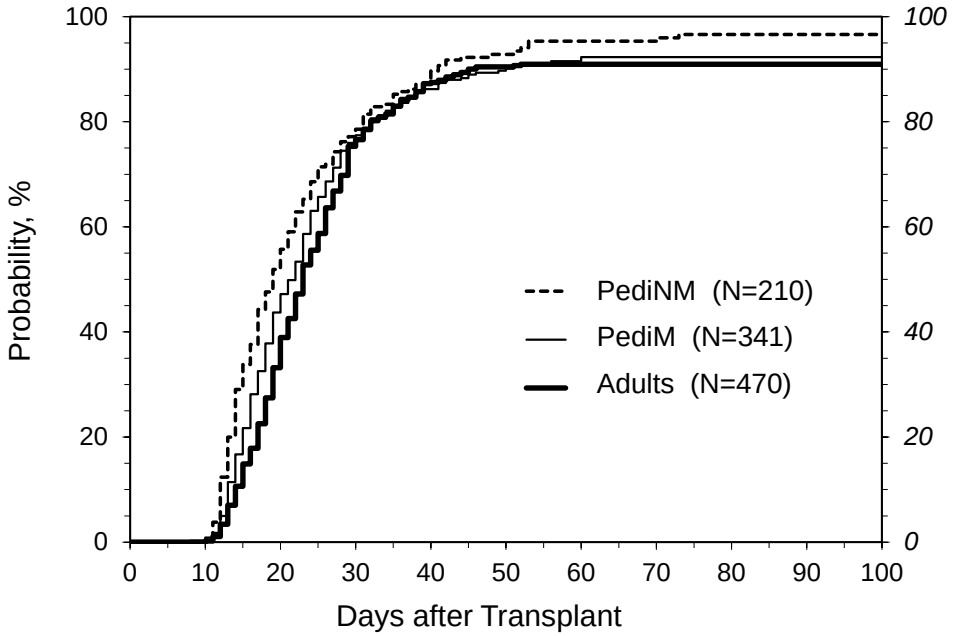

Figure 11. Neutrophil Engraftment after First Umbilical Cord Blood Transplantation (Myeloablative only)

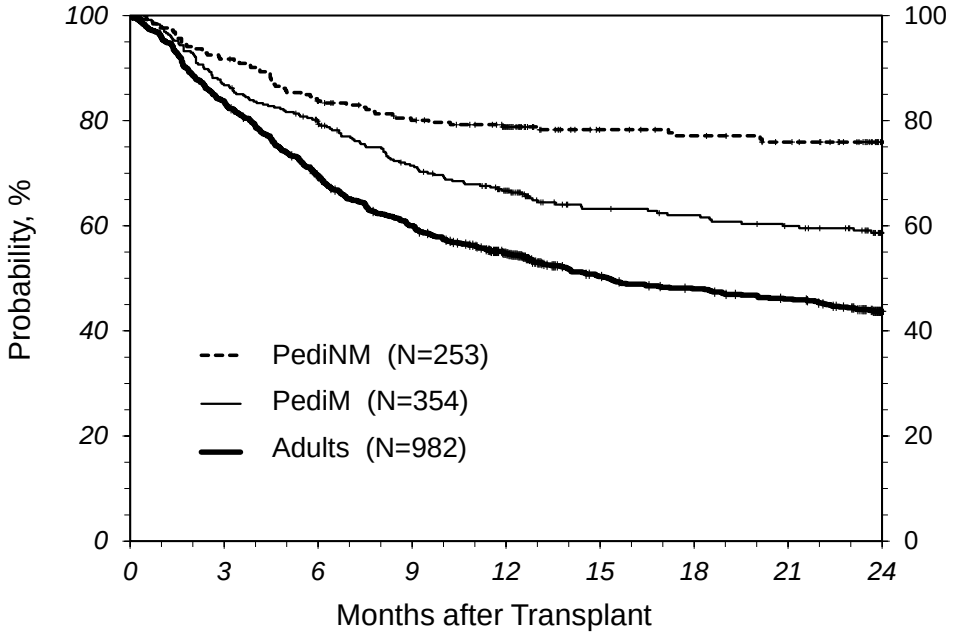

Figure 12. Overall Survival after First Umbilical Cord Blood Transplantation

Immunobiology Research

During a previous grant period, the NMDP developed the Immunobiology Research grant request and award procedures for use by the Immunobiology Working Committee (IBWC) and developed the IBWC Web site (http://www.cibmtr.org/COMMITTEES/Working_Committees/Immunobiology/index.html). The content was further refined and migrated to the CIBMTR.org Web site in 2010 and is refreshed annually.

During the past grant period, grant funds supported significant outreach efforts by the IBWC leadership to increase exposure for the IBWC to basic scientists. The IBWC leadership attended several scientific meetings including: American Society of Hematology, BMT Tandem, European Group for Blood and Marrow Transplant and American Society for Histocompatibility and Immunogenetics meetings. In addition, the assistant scientific director gave presentations on CIBMTR and IBWC research activities at the 3rd Annual Pujiang Symposium and the 2018 Data Management Professional meeting. Five new proposals were accepted by the IBWC during the 2018 BMT Tandem Meeting.

IBWC 2018 proposals:

1. Effect of HLA phenotypes on long term GVHD risk. PIs: C Story, M Riches and P Armistead)

2. The impact of HLA class I risk alleles associated with AA Immune pathogenesis on allogeneic transplant outcomes in patients with severe acquired aplastic anemia. PIs: D Babushok and T Olson

3. Evaluation of the impact of donor KIR genotype on outcome after unrelated donor transplantation in patients with myelodysplastic syndromes or secondary acute myeloid leukemia – Joint study with EBMT Chronic Leukemia Working Party. PIs: J Schetelig, N Kröger and M Robin

4. The Effect of HLA Class I Heterozygosity and HLA Supertypes on Outcomes Following Allogeneic Hematopoietic Cell Transplant For Myeloid and Lymphoid Malignancies. PIs: C Camacho-Bydume and K Hsu

5. Imputation of KIR in genome-wide association study and the association of KIR-HLA with outcomes following alloHCT In AML and MDS. PIs: C Camacho-Bydume, L Sucheston-Campbell, S Leslie and K Hsu)

CIBMTR Information Technology (CIT) Minneapolis Initiatives

The scope of the work performed by the CIT department in Minneapolis includes collecting and reporting outcomes data on all allogeneic transplantations performed in the U.S. (for the Stem

Cell Therapeutic Outcomes Database (SCTOD), as required by U.S. law). U.S. transplant centers also voluntarily submit autologous transplantation data, and transplant centers worldwide voluntarily submit both autologous and allogeneic transplantation data. As a result, and as reported in the CIBMTR 2017 Annual Report, the CIBMTR Research database now contains information on more than 475,000 patients. CIT strives to provide applications that will reduce center burden for government mandated forms and provide high quality data on demand.

CIBMTR Technology Platforms:

- FormsNet: Recipient – Donor
- AGNIS
- Medidata Rave / CTMS
- LabVantage
- Integrated Data Warehouse

FormsNet

FormsNet 3.0 is CIBMTR's currently operational, 21 CFR Part 11 compliant, secure Web-based application for collecting HCT outcomes data electronically. FormsNet supports data collection, auditing, and event reporting; donor clearance and follow-up; web services; and messaging. FormsNet offers real-time data validations; error messaging; and control of data entry flow, which includes enabling/disabling of questions and "smart navigation" between fields on a form. The system also collects information on non-HCT cellular therapies using a flexible design to accommodate therapies used independently, before or after HCT.

Since its original release in Dec 2007, the recipient module of the FormsNet application has been used at more than 527 centers to register 233,782 patients and collect over 1,865,640 forms with more than 10 million data elements. This program was developed for both local data entry from paper forms and web-based entry by clinical centers. More than 99% of data collected by the CIBMTR is submitted electronically via FormsNet. Two forms (2800 – log of appended documents and 2801 – transfer forms) can only be submitted on paper to ensure audit standards. The Form 2800 – log of appended documents, is in process of being decommissioned as a new feature has been added to FormsNet3 providing the ability to attach electronic documents directly to a form.

System Enhancements:

During the current grant period, FormsNet was upgraded quarterly to keep Recipient forms current with existing treatment practices. Recipient form updates included 5 pre/post disease insert revisions, 9 new study forms, 1 new form and 5 other revisions. Recipient tool migration was completed from FormsNet 2 for the 3 remaining tools requiring conversion.

- Check all that apply functionality was implemented into the Recipient module, which allows the user to utilize checkboxes to check all applicable answers instead of having to answer yes or no for each option.
- A project to update the business rules engine is underway. Upon completion, the new engine will enable release of forms on a monthly basis, and without requiring a software release.
- Implemented six cell therapy form revisions and 2 new forms needed to support a cellular therapies registry.
- Transitioned infectious disease marker results from FormsNet1 (FN1) to FormsNet3 (FN3) in order to correct regulatory deficiencies, improve operational efficiencies and allow for the import of electronic results.

- The sample tracking application was decommissioned as its functionality is no longer needed by the Prospective Research team.

- FormsNet is updated monthly to enhance the recipient, donor, and audit modules to apply enhancements and ensure optimal performance, flexibility and efficiency of applications.

In early 2016, the production rollout of the contact, baseline, and follow-up forms necessary to collect the required data points took place. The data collection forms were fully validated during a RITN tabletop exercise in 2016. The successful mock test of the workflow and data gathering capabilities involved testing the forms at a cross-section of centers.

A Growable Network Information System® (AGNIS)

AGNIS is a system for electronic messaging of standard common data elements (CDEs) between participating nodes. Messaging can occur between transplant centers, registries, investigators or any combination of entities willing to map relevant data elements and install the software/messaging system. The system relies on two key components, data standards in the form of common data elements (CDEs), and software for transferring the data, providing audit trails, conveying error messages, etc.

- CDE Development:
  CIBMTR has invested substantial effort defining CDEs for CIBMTR forms. All CDEs are defined in the Cancer Data Standards Repository (caDSR) of the NCI. This leverages a strong national system of standards regarding the definitions and related metadata. Additionally, a substantial portion of the CDEs have also been defined in the Biomedical Research Integrated Domain Group (BRIDG) model, which is compatible with HL7, the most prevalent ‘language’ used in biomedical informatics.

- caDSR:
    - Definitions have been created for nearly 2,500 CDEs associated with 14,000 data points on more than 90 forms.

      The following 13 recipient outcome forms have been released in the caDSR and are available for electronic data exchange via AGNIS: six mandated forms (Pre-TED and Pre-TED disease classification, Post-TED, HLA, IDM, and Infusion), three Comprehensive Forms (Baseline, Follow-Up, and Death), Unique ID Assignment, Indication for CRID Assignment, and two disease specific inserts (Pre- and Post-HSCT Hodgkin and Non-Hodgkins Lymphoma). 4 CIBMTR Recipient forms were retired in January of 2017 and their data is not collected on other AGNIS supported forms.

- System Users:

    - Independent Transplant Centers:
        - 5 centers actively submitting and retrieving data through AGNIS: H. Lee Moffitt, MD Anderson, Cleveland Clinic, Stanford and Maisonneuve-Rosemont Hospital (RedCap compatible solution)
        - 2 center actively retrieving through AGNIS: Seidman Cancer Center and MD Anderson Cancer Center

    - Transplant centers using Vendor solutions:
        - Eight vendor solutions supporting sixteen actively submitting centers and twenty-eight retrieving centers
        - Jagriti - BMT Plus: three centers submitting and retrieving data
        - Management Science Associates(MSA): Three centers submitting and retrieving data
        - Mediware: Two sites submitting data
        - OTTR: Six sites retrieving and submitting data
        - StemSoft: One site submitting and eight retrieving
        - Velos: Six sites retrieving data
        - TeleResults: One site retrieving data
        - StemTrek and Title21: authorized but not currently supporting centers

- System Enhancements:

  In the last year, the AGNIS team accomplished the following:

  - Provided ongoing support for EBMT-CIBMTR and CIBMTR-Eurocord AGNIS connections
  - Released the new revisions of the 2400r5 Pre-Transplant Essential Data Form, 2402r1 Pre-Transplant Essential Data: Disease Classification Form, 2450r4 Post TED Form, 2100r4 100 Day Post-HSCT Data Form, and the second revision of the 2402 Pre Transplant Essential Data: Disease Classification Form.

- Registry connections:

  - EBMT has been working with the CIBMTR to develop a pathway to share TED-level data from EBMT centers that also participate in the CIBMTR. Mapping has occurred for the Pre-TED, Post-TED at 100 days, Unique ID, and Infusion forms. Data submission, initially manually and now with automation for prospective data submitted for 42 participating centers so far and plans continue to grow users
    - 8 centers with authorization to randomization to TED or CRF
    - 34 TED only centers
  - Received >76,000 forms in complete status from EBMT through the AGNIS submission process since the beginning of this project and over 30,000 in 2016

- Electronic Medical Records (EMR) connections:

  - CIBMTR worked with EPIC to integrate 51 standard CDEs into the BMT registration form in EPIC (BMT smartform).
    - Consists of HCT physicians and IT staff who are working to standardize data collection in the EMR to facilitate ease of data collection, consistent with national data standards, and submission for use of research
    - Working with one EMR vendor (Epic) on development of data collection tools for the EMR that will use CIBMTR-defined data standards in the caDSR and Biomedical Research Integrated Domain Group (BRIDG); this project should serve to increase future interoperability of EMR systems with CIBMTR
    - Developed three tools so far: aGVHD documentation flow sheet, cGVHD documentation tool, and BMT SmartForm

Integrated Data Warehouse

The CIBMTR Information Management Strategy (IMS) project's main objective is to establish a comprehensive program for the management of data across the enterprise, turning the large

volumes of data into a strategic asset supporting high value, sophisticated analyses. The IDW is the primary deliverable for this project. At delivery, the IDW will contain high quality, validated data readily available to researchers for immunobiology, outcomes, and other types of analyses. It will be the single source of truth of data that supports the diverse administrative and scientific needs of internal and external stakeholders. The team is building a unified domain to house multiple sources and dimensions of data. CIBMTR operational teams will be able to dramatically reduce the amount of time they spend on data consolidation, preparation, and validation of datasets and instead focus on the analysis. As a result, analyses will be completed in a timely manner facilitating decision-making based on these data assets.

- This effort is aligned with NMDP enterprise architectural standards, and incorporates selective use of industry standards, including Biomedical Research Integrated Domain Group (BRIDG) and HL-7 FHIR (Fast Healthcare Interoperability Resources).The first deliverable implemented an Integrated Data Store (IDS) which serves as the foundation for the long-term data warehouse. Using the IDS as the unified data source, the first phase of the data warehouse was completed by integrating data used for immunobiology analyses into the data warehouse. The team completed the logical and physical design of a new unified data model to optimally support consolidation of data from various application sources
- Successful implementation of new data model structure using Transplant Center Specific Analysis (TCSA) data
- Initial architecture design to facilitate the extraction of data for future reporting and data analytic needs
- Expanding data model to incorporate cellular therapy data

Table 8 below shows the types of data stored in the Data Warehouse and their data sources, including data sources added since the original release of the IDS:

Table 9. Types of sources of data in CIBMTR Data Warehouse

Focus area	**Description**	**Source**
IDM	• Donor IDMs information for NMDP facilitated HCTs	Legacy (Formsnet1) & current FormsNet3
Infusion data	• 50 most Requested Variables for ad-hoc and center volumes reporting requests from FN3 • Clinical outcome data tied to each infusion event (future)	FormsNet, SIP

Focus area	Description	Source
Research Specimen Data	• Research Repository Specimen Inventory data on related and unrelated cords, donors, and recipient samples • Data on Research Repository Specimen submission and compliance	BIO Res (IPR/RR) **Lab Vantage vendor application**
NMDP Source Data	• Cord Blood Unit Data • Double Cord (Multi)	StarLink CordLink (SyBase) Emtrax through Reg ODS
HLA/KIR Match Data	• Transformed CIBMTR Legacy HLA data • HLA data for donor/recipient for NMDP facilitated HCTs, legacy and current (STAR/SIP) (form 2005) • HLA data transformation on new form 2005/non-NMDP Tx SCTOD data • Donor-Recipient Match Grade results (HLA Save) • KIR data • Re-Evaluate current data sources	• CIBMTR OBS DB • STAR • FormsNet3 • IPR • HLA Save
Donor & Recipient data	• Transformed Donor and Recipient data • Provides self-service environment for analysis through pre-defined joins (business view of the metadata), calculations and generating adhoc data sets • Capability for near real time(~ 5 minutes) data sharing and analytics across forms through combined and unified virtualization layer (views) • Faster turnaround on visibility to data quality fixes.	• FormsNet • NMDP Legacy
Metadata	• Provides data lineage, impact analysis and FormsNet metadata analysis	• FormsNet Metadata, BODI metadata, OBIEE metadata

Focus area	Description	Source
Center volumes	• Provides metrics around the number of infusions by center/donor type/product type/disease/age group/race variables • Replaces existing manual process	• FormsNet, NMDP
Research Repository Sample Data	• Integration with 3rd party vendor, Labvantage, to provide Research Sample data • Provides self-service environment for analysis through Business Intelligence tool. (OBIEE) • Provides end user defined reports utilized to complete HRSA reporting requirements.	• FormsNet, Labvantage
Clinical Trials **CT Rave**	• Integration with 3rd party vendor, Metadata Rave, to provide Clinical Trials data • Provides self-service environment for analysis through Business Intelligence tool. (OBIEE)	• Rave, NMDP, FormsNet

In addition to the referenced source data consolidated in the Data Warehouse, CIT has also implemented operational improvements to the warehouse, and developed, in the last 12 months, the following functionality:

- Business Intelligence Products
  - Developed new business intelligence environments to support internal audit and clinical trials teams
  - Developed new processes to transition operational reporting from legacy system to data warehouse business intelligence tool
  - Developed new business intelligence processes to provide Immunobiology users access to additional forms submitted data
- Cord Blood Quality Report
  - Produced additional data elements to support cord blood bank needs. Data additions include chimerism, adverse event, and product complaint information
- Center Volumes Data Report
  - Completed 2017 Center Volumes Data Reporting project. This data set is available on a HRSA website for external consumption

- Enhancing the Business Intelligence application suite which shares data back with centers
  - Enhanced Data Back to Centers (eDBtC), which enables visualization of center trends and descriptive statistics as well as ad hoc querying capabilities, was enhanced with additional capabilities within sub-disease, support for

GVHD prophylaxis and conditioning regimen agents, as well as an enhancement to data download capabilities.
- Center Performance Analytics (CPA), which enables a center to analyze center trends related to other centers in data set, create selective queries, and export filtered data for analysis, incorporated changes to support cytogenetics.
- Enhanced ASBMT for RFI (Request for Information) report, which Streamlines preparation of center's ASBMT Annual Request for Information – Outcomes Data Form, by providing additional support for CML.

VI. Work plan

a. Contingency Preparedness

- Grow the RITN by increasing the number of participating hospitals.
- Monitor RITN center completion of radiological preparedness tasks.
- Continue to build partnerships with government agencies.
- Plan and complete multiple Fullscale and/or Functional exercises at RITN centers.
- Offer educational opportunities to RITN staff through mobile REAC/TS training.

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 resolution HLA typing methodologies.
- Evaluate the factors of donor utilization and speed of search process after strategic upgrading of selected adult volunteer donors.
- Continue development of immunogenetic data sharing standards using HL7 FHIR.

c. Immunogenetic Studies in Transplantation

- Complete HLA and KIR typing on additional donor/recipient transplant pairs to support evaluation of clinical studies of HLA mismatched transplants in an attempt to define tolerable mismatching in the unrelated donor HCT setting.
- Continue the integrative genomics analysis
- Continue evaluation of full KIR gene typing techniques

d. Clinical Research in Transplantation

- Continue to conduct observational research studies through the 15 working committees of the CIBMTR. Efforts are focused on finalizing publications from the studies completed to date in FY17 and finalizing analyses for the submission to the 2018 ASH and 2019 TCT annual meetings.
- The Survey Research Group will continue to conduct donor follow-up assessments for the Long Term Donor Follow-up study.
- Develop and release FormsNet enhancements to improve system performance, user experience, data quality and forms development turnaround time.
- Continue development and execution of the CIBMTR Information Management Strategy project.

VII. Major Problems/Issues (if any)

No major problems encountered to date.

VIII. Technology Transfer

No technology transfer to report.

IX. Foreign Collaborations and Supported Foreign Nationals

NMDP has no sub awards with nor is it collaborating with any foreign entity or foreign national under this grant.

X. Productivity

a. Refereed Journal Articles

1. Heimall J, Logan BR, Cowan MJ, et al. Immune reconstitution and survival of 100 SCID patients post-hematopoietic cell transplant: A PIDTC natural history study. Blood. 2017 Dec 21; 130(25):2718-2727. doi:10.1182/blood-2017-05-781849. Epub 2017 Oct 11. PMC5746165.

2. Hill BT, Ahn KW, Hu Z-H, et al. Assessment of impact of HLA type on outcomes of allogeneic hematopoietic stem cell transplantation for chronic lymphocytic leukemia. Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation. 2018 Mar 1; 24(3):581-586. doi:10.1016/j.bbmt.2017.10.015. Epub 2017 Oct 12.

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4. Turcotte LM, DeFor TE, Newell LF, et al. Donor and recipient plasma follistatin levels are associated with acute GvHD in Blood and Marrow Transplant Clinical Trials Network 0402. Bone Marrow Transplantation. 2018 Jan 1; 53(1):64-68. doi:10.1038/bmt.2017.236. Epub 2017 Oct 23. PMC5752567.

5. Htut M, D'Souza A, Krishnan A, et al. Autologous/allogeneic Hematopoietic cell transplantation versus tandem autologous transplantation for multiple myeloma: Comparison of long-term postrelapse survival. Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation. 2018 Mar 1; 24(3):478-485. doi:10.1016/j.bbmt.2017.10.024. Epub 2017 Oct 24. PMC5826888.

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8. Louzon Y, Alter I, Gragert L, et al. Modeling coverage gaps in haplotype frequencies via Bayesian inference to improve stem cell donor selection. Immunogenetics. doi:10.1007/s00251-017-1040-4. Epub 2017 Nov 9. NA.

9. Myers RM, Hill BT, Shaw BE, et al. Long-term outcomes among 2-year survivors of autologous hematopoietic cell transplantation for Hodgkin and diffuse large b-cell lymphoma. Cancer. 2018 Feb 15; 124(4):816-825. doi:10.1002/cncr.31114. Epub 2017 Nov 10. PMCID5871233.

10. William BM, Wang T, Haagenson M, et al. Impact of human leukocyte antigen (HLA) alleles on outcomes of allogeneic transplantation for B-cell non-Hodgkin lymphomas: A Center for International Blood and Marrow Transplant Research analysis. Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation. doi:10.1016/j.bbmt.2017.11.003. Epub 2017 Nov 16.

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a. Non-Refereed Significant Publications – None to report
b. Books or Chapters – None to report
c. Technical Reports – None to report
d. Workshop and conference abstracts and presentations

1. Lazaryn A. Prognostic significance of cytogenetic abnormalities in patients with Philadelphia-negative ALL undergoing allogeneic hematopoietic stem cell transplantation in complete remission: A CIBMTR analysis. American Society of

Hematology Annual Meeting. Dec 2017.

2. Yeshurun M. Graft-vs-leukemia effect in acute lymphoblastic leukemia: mild acute Graft-vs-Host disease protects against relapse and improves survival after allogeneic transplantation: A CIBMTR analysis. American Society of Hematology Annual Meeting. Dec 2017.

3. Brown J. Prognostic score and cyteogenetic risk classification for chronic lymphocytic leukemia patients who underwent reduced intensity conditioning allogeneic HCT: A CIBMTR report. American Society of Hematology Annual Meeting. Dec 2017.

4. Chhabra S. Comparison of outcomes after myloablative versus reduced intensity conditioning allogeneic hematopoietic cell transplantation for chronic myeloid leukemia. American Society of Hematology Annual Meeting. Dec 2017.

5. Hu B. Optimal timing of allogeneic stem cell transplantation for chronic myeloid leukemia patients in the tyrosine kinase inhibitor era. American Society of Hematology Annual Meeting. Dec 2017.

6. Prokopishyn N. Bone marrow transplant product quality has decreased over time. A retrospective examination of NMDP collected bone marrow products from 1994-2016. American Society of Hematology Annual Meeting. Dec 2017.

7. Fuchs E. Selecting between HLA-matched siblings and HLA-haploidentical related donors for acute leukemia in the era of post-transplant cyclophosphamid: The CIBMTR and Acute Leukemia Aorking party of the EBMT. American Society of Hematology Annual Meeting. Dec 2017.

8. Mehta R. Graft-versus-Host disease free relapse free survival and chronic GVHD in alternative donor hematopoietic cell transplantation in pediatric patients. American Society of Hematology Annual Meeting. Dec 2017.

9. Mehta R. Graft-versus-Host disease free relapse free survival and chronic GVHD in alternative donor hematopoietic cell transplantation in adults. American Society of Hematology Annual Meeting. Dec 2017.

10. Shaw B. nalysis of 10,462 8/8 HLA-matched unrelated donor transplants could not identify a donor selection score, as younger age is the only significant donor characteristic associated with survival. American Society of Hematology Annual Meeting. Dec 2017.

11. Gadalla S. Chromosome 6 loss of heterozygosity in pre-transplant blood samples of patients with severe aplastic anemia is associated with lower risk of acute GVHD.

American Society of Hematology Annual Meeting. Dec 2017.

12. Gadalla S. Donor lymphocyte cell-specific telomere length and causes of death after unrelated hematopoietic cell transplant in patients with marrow failure. American Society of Hematology Annual Meeting. Dec 2017.

13. Norkin M. Late fetal infections remain higher than expected in adults receiving allogeneic stem cell transplant. American Society of Hematology Annual Meeting. Dec 2017.

14. Norkin M. Late fetal infections remains frequent cause of mortality in pediatric allogeneic stem cell transplant recipients. American Society of Hematology Annual Meeting. Dec 2017.

15. Kumar S. Revised-international staging system is independently predictive and prognostic for early relapse after upfront autologous hematopoietic cell transplantation for newly diagnosed multiple myeloma. American Society of Hematology Annual Meeting. Dec 2017.

16. Kumar S. A comparison between 3 staging systems in multiple myeloma using the center for international blood and marrow transplant research database. American Society of Hematology Annual Meeting. Dec 2017.

17. Eikema R. Allogeneic hematopoietic stem cell transplantation in older patients aged 50 or older with severe aplastic anaemia: results from the european society for blood and marrow transplant and the center for international blood and marrow transplant research. American Society of Hematology Annual Meeting. Dec 2017.

18. Brunstein C. The effect of conditioning regimen dose reduction in obese patients undergoing autologous transplantation. American Society of Hematology Annual Meeting. Dec 2017.

19. Majhail N. Individualized treatment summaries and survivorship care plans for hematopoietic cell transplant survivors reduces cancer treatment distress in a randomized multicenter study. American Society of Hematology Annual Meeting. Dec 2017.

20. Medac. Allogeneic hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndrome: effect of transplant conditioning regimen intensity on outcomes. American Society of Hematology Annual Meeting. Dec 2017.

21. Denzen E. Healthcare reimbursement and service utilization for one year of post-allogeneic hematopoietic cell transplantation care for medicare beneficiaries ages 65 and older with acute myeloid leukemia. American Society of Hematology Annual Meeting.

Dec 2017.

22. Murphy E. Individualized treatment summaries and survivorship care plans for hematopoietic cell transplant survivors reduces cancer treatment distress in a randomized multicenter study. American Society of Hematology Annual Meeting. Dec 2017.

23. El-Jawahri A. What do transplant physicians think about palliative care? A national survey study. American Society of Hematology Annual Meeting. Dec 2017.

24. Horowitz M. Nicord single unit expanded umbilical cod bblood transplantation: Final results of a multicenter Phase I/II trual. American Society of Hematology Annual Meeting. Dec 2017.

25. Chhabra S. Graft-Versus-Host Disease (GVHD) Prophylaxis in Reduced Intensity Conditioning (RIC) Allogeneic Hematopoietic Cell Transplantation (alloHCT): Comparing the Efficacy of mycophenolate mofetil (MMF) and methotrexate (MTX) in combination with calcineurin inhibitor (CNI). ASBMT/CIBMTR BMT Tandem Annual Meetings. Feb 2018.

26. Hamilton B. Cyclosporine (CSA) in combination with Mycophenolate Mofetil (MMF) Leads to Increased incidence of Graft-versus-Host Disease (GVHD) and Inferior Outcomes after Myeloablative Allogeneic Hematopoietic Cell Transplantation (HCT): a Center for International Blood and Marrow Transplant Research (CIBMTR) analysis. ASBMT/CIBMTR BMT Tandem Annual Meetings. Feb 2018.

27. Hahn T. Genome-wide significant donor genetic associations with disease death in AML and MDS patients in the first 1 year after BMT are not modified by Conditioning Intensity or TBI. ASBMT/CIBMTR BMT Tandem Annual Meetings. Feb 2018.

28. Hahn T. Genetic Associations with Day +100 Transplant Related Mortality (TRM) after HLA-Matched Unrelated Donor (MUD) Blood and Marrow Transplantation (DISCOVeRY-BMT Study). ASBMT/CIBMTR BMT Tandem Annual Meetings. Feb 2018.

29. Wang Y. Clonal alterations and survival after unrelated donor allogeneic hematopoietic stem cell transplant in patients with Fanconi anemia. ASBMT/CIBMTR BMT Tandem Annual Meetings. Feb 2018.

30. Askar M. Analysis of Single Nucleotide Polymorphisms (SNP) Donor/Recipient Mismatches in the Gamma Block of the Major Histocompatibility Complex (MHC) And Their Association With Hematopoietic Cell Transplantation (HCT) Outcomes: A CIBMTR Study. ASBMT/CIBMTR BMT Tandem Annual Meetings. Feb 2018.

31. Bachanova V. Graft-versus-leukemia responses in chronic lymphocytic leukemia (CLL) are not influenced by natural killer cell (NK) KIR immunogenetics: a CIBMTR analysis. ASBMT/CIBMTR BMT Tandem Annual Meetings. Feb 2018.

32. Naik S. Outcomes of Allogeneic Hematopoietic Cell Transplants with EBV Positive or EBV Negative Post-Transplant Lymphoproliferative Disorder (PTLD). ASBMT/CIBMTR BMT Tandem Annual Meetings. Feb 2018.

33. Bhatt N. Survivors of Childhood Allogeneic Hematopoietic Cell Transplant Have Higher Unemployment Rates Compared to the General US Population. ASBMT/CIBMTR BMT Tandem Annual Meetings. Feb 2018.

34. Shah N. Outcome of Patients 65 Years and Older with Non-Hodgkin Lymphoma (NHL) Receiving Reduced-Intensity Conditioning Allogeneic Hematopoietic Stem Cell Transplantation Compared to Patients 55-64 Years of Age: A Center for International Bone Marrow Transplant Research (CIBMTR) Analysis. ASBMT/CIBMTR BMT Tandem Annual Meetings. Feb 2018.

35. Brogile L. Evaluation of the Hematopoietic Cell Comorbidity Index (HCT-CI) in Recipients of Allogeneic Transplantation for Non-Malignant Diseases. ASBMT/CIBMTR BMT Tandem Annual Meetings. Feb 2018.

36. Parikg S. Survival Trends after Allogeneic Hematopoietic Cell Transplant (HCT) in Children less than one-year-old (infants). ASBMT/CIBMTR BMT Tandem Annual Meetings. Feb 2018.

37. Zinter M. Improved Mortality Prognostication for Critically Ill Pediatric Hematopoietic Cell Transplant Patients: Results from a Virtual Pediatric Systems (VPS) and Center for International Blood and Marrow Transplant Research (CIBMTR) Database Merger. ASBMT/CIBMTR BMT Tandem Annual Meetings. Feb 2018.

38. Vanness D. Estimating Propensity Scores for the Receipt of Allogeneic Hematopoietic Cell Transplantation (AlloHCT) in Outcomes Research using Claims Data: A Machine Learning Approach. ASBMT/CIBMTR BMT Tandem Annual Meetings. Feb 2018.

39. El-Jawahri A. A National Survey Study of Transplant Physicians' Attitudes about Palliative Care. ASBMT/CIBMTR BMT Tandem Annual Meetings. Feb 2018.

40. Maiers M. HLA and KIR: selection and admixture. HLA and KIR Population Dynamics Workshop. March 2018.

41. Louzoun Y, Litniski A, Madbouly A, et al. Single haplotype admixture models using large-scale HLA genotypes to reproduce human admixture. European Federation of

Immunogenetics Annual Meeting. May 2018.

42. Bishara A, Halagan M, Crautbar C, et al. High resolution HLA-A, -B, -C, -DRB1, and –DQB1 allele and haplotype frequencies for Arab donors in the Hadassah bone marrow registry. European Federation of Immunogenetics Annual Meeting. May 2018.

43. Louzoun Y, Gragert L, Maiers M, et al. HLA Class I haplotype diversity is consistent with selection for frequent existing haplotypes. European Federation of Immunogenetics Annual Meeting. May 2018.

e. Patents – None to report
f. Awards/Honors – None to report

51. Award Participants

Abeer Madbouly	Deb Turner	Michele Nych
Alex Gomez	Deborah Mattila	Mike Halagan
Andrew Westin	Eric Williams	Nathan Hood
Arnold Fritsch	Eric Zink	Pradeep Bashyal
Ashley Pull	Eva Chan	Ray Hornung
Ashley Spahn	Gretta Stritesky	Robinette Renner
Balu Samba	Jacob Smith	Rupesh Kumar
Bert Roers	Jane Kempenich	Sandra Sorensen
Beth Beduhn	Jane Pollack	Sean Stagg
Bill Burgess	Janelle Olson	Sharon Ewer
Billy Grose	Jason Brelsford	Shawn Freeman
Bob Milius	Jen Venero	Shengchun (Ann) Zheng
Bridget Wakaruk	Jennifer Novakovich	Stephanie Waldvogel
Caleb Kennedy	Jennifer Oakes	Stephen Spellman
Charles Jordahl	Joel Schneider	Tony Wirth
Chelsey Kornetzke	Katherine Gee	Vedavani Murukurthy
Chia Yang	Kelly Buck	Venu Yarra
Christine Kofstad-Johnson	Kelly Lazration	Wei Wang
Colleen Brady	Kim Wadsworth	Xiaoyun Zhang
Cullen Case	Kirt Schaper	Zubair Ahmed
Curt Mueller	Laura Clements	
Cynthia Vierra-Green	Lucas Nacusi	
Daniel Campbell	Maria Brown	
Dave Roe	Matt Prestegaard	
David McDonell	Michael Haagenson	

Development of Medical Technology for Contingency Response to Marrow Toxic Agents

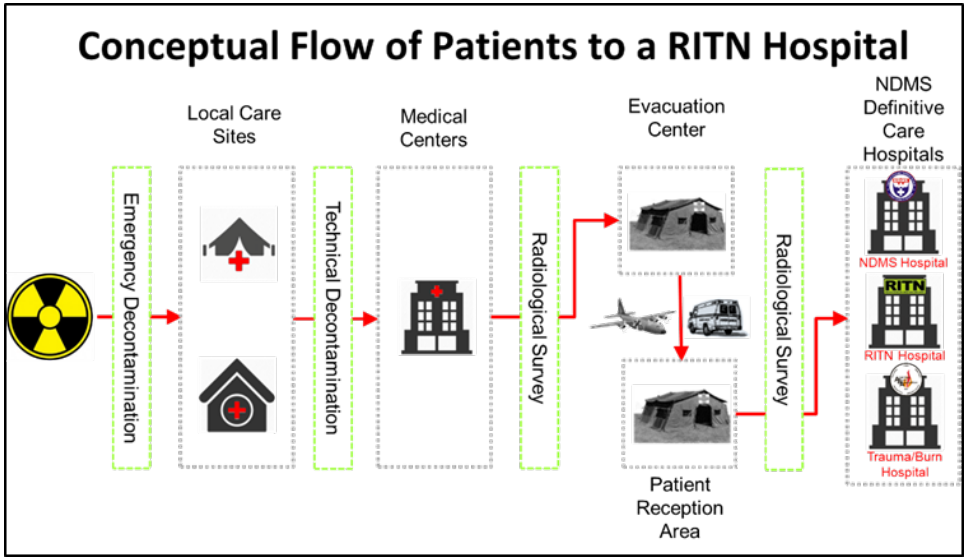
Dennis L. Confer, M.D., National Marrow Donor Program

Objective:

- Develop, test and mature the ability of the NMDP to address contingency events wherein civilian or military personnel are exposed to marrow toxic agents

Approach:

- Contingency preparedness through RITN
- Develop science and technology to facilitate the rapid identification of donors
- Conduct immunogenetic research in transplantation
- Perform observational and prospective clinical research in transplantation



Accomplishments:

- Planned table top, regional and functional exercises for execution during the project period.
- Tested the Operational Resiliency Plan at the coordinating center during work disruption due to Super Bowl LLII.
- Published 50 peer reviewed manuscripts and presented 43 abstracts at national/international meetings.
- Recruited 81,935 minority race and 141,750 White donors for a total of 223,685 U.S. donors added to the registry. This grant provided HLA typing support for 78% of the recruited donors.
- Held one Data Standards Hackathon in Utrecht, The Netherlands and planned another for July in Minneapolis, MN.
- Completed an analysis of non-antigen recognition domain sequence variation in a cohort of >4,600 donor/recipient transplant pairs.

Impact/Transitions:

- Published 50 peer reviewed manuscripts and presented 43 abstracts at national/international meetings.
- Recruited 81,935 minority race and 141,750 White donors for a total of 223,685 U.S. donors added to the registry.