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

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

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

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

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

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DEVELOPMENT OF MEDICAL TECHNOLOGY FOR CONTINGENCY RESPONSE TO MARROW TOXIC AGENTS

FINAL RESEARCH PERFORMANCE REPORT

SUBMITTED JULY 15th, 2019

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

N00014-19-1-2888

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. Updates

A. Contingency Preparedness

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

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

RITN activities

- Continued planning for the semi-annual 2019 RITN Workshop: *Crisis in context: Minding the gaps in medical preparedness for a Rad/Nuke Incident*; to be held July 30-31, 2019 in Crystal City, VA.
    a. 47 speakers are confirmed for the workshop
    b. 93 people have currently registered to attend
- Assisted the BioBank project team with:
    a. The content and editing of the BioBank BARDA RFI proposal.
    b. Introductions to key subject matter experts in the field of radiation disaster response.
- Met with Methodist Hospital in San Antonio to confirm their interest in joining RITN.
- In March 2019 RITN presented at the National Academies of Science, Engineering and Math workshop titled "Challenges in Initiating and Conducting Long-Term Health Monitoring of Populations Following Nuclear and Radiological Emergencies in the United States" about the web based data collection systems and forms RITN has established to collect patient care data following a radiological disaster.
- In April 2019, RITN presented at the 38th US Military and Israeli Defense Forces Medical Conference in Tel Aviv ("The Shoresh" Conference) on the US medical preparedness efforts to handle the surge in Acute Radiation Syndrome patients following a radiological disaster.
- Continued to assessment of the radiation disaster response competence of RITN medical staff. Working with Professor Tener Veenema from John's Hopkins and Dr. Ziad Kazzi from Emory University; and culminate with a written report of the status of the RITN network's knowledge and suggestions for future initiatives.
- Completed the National Quality Forum project to develop a healthcare systems readiness standard for US hospitals nationwide.

Project: Resiliency

1. Completed rewrite of the NMDP/BTM IT-Disaster Recovery SOP.
2. Completed employee critical staff awareness survey and published results to participants to increase awareness of low level of knowledge of roles.
3. Conducted cross departmental assessment of the maturity of the organization's business continuity program against the ISO 22301 standard.
4. Conducted business continuity functional exercise with critical staff.
5. Initiated business impact analysis update.

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

Operational Continuity Planning

- Initiated a collaborative effort with the IT-Disaster Recovery team to assist in rewriting their SOP.
- Began the assessment and creation of a vendor continuity process for Infectious Disease Marker (IDM) laboratories that work with the NMDP. This is in response to the extended service outage in summer 2018 from the NMDPs primary IDM lab provider.
- Initiated an employee critical staff awareness survey to assess the knowledge of employee roles during a business disruption; surveyed employees are designated as critical by their managers and should be aware of their role.
- Began the cross functional assessment of the organizations readiness via the business continuity maturity model which follows the ISO 22301 standard.
- Rolled out to all employees and volunteer couriers the WorldAware software service which provides situational awareness information to NMDP travelers via a smartphone app; during a business disruption the NMDP emergency response team can utilize this software to graphically view the location of all current travelers.
- Implemented a critical event notification banner on the NMDP intranet to notify all employees of the status of business disruptions and provide additional details to everyone.

B. 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.

Donor Recruitment HLA Typing

Year to date, completed HLA typing of 180,279 newly recruited U.S. donors (30% minority).

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.

Machine Learning Strategies for Optimizing Donor Selection

During the past quarter, analysis occurred on a patient cohort which was prepared for this project (N=3,751) with the clinical outcomes from an 8/8 allele match transplant and the corresponding list of equally well-matched donors and a series of attributes involved in donor selection. Early results on led to a refinement of the donor attributes and the addition of new patient attributes.

Methods development to the determine the additivity of the parameters in the model has detected interactions (such as donor age and patient disease severity) which means this model may need include patient characteristics not typically collected at the time of search to be effective.

At the end of this grant period we plan to have advanced the method and to have evaluated it against a large retrospective cohort which will be critical for determining the suitability to apply this approach prospectively for informing donor selection in the future.

HLA Imputation

During the past quarter significant improvements have been made to the method to impute HLA, published at https://www.ncbi.nlm.nih.gov/pubmed/30689784.
This method has been extended to address multi-race populations, validation has occurred against both a simulated and a clinical cohort. The new method uses a Bayesian approach to assigning population origins for each haplotype and outputs the genotype probability distribution and the probability distribution of the population source of the subject's HLA. The weights of the priors are being tuned by applying a gradient descent method on donor low/high resolution data to optimize for its informativeness in predicting the high-resolution data from the low-resolution.

We expect that this method will provide a substantial improvement over the performance of previous algorithms for donor selection, in particular when applied to individuals with mixed ethnic background or from populations that are under-presented in the global donor registries.

Haplotype Frequency Curation

A data standards hackathon (DaSH) event was held in Denver at the Anschutz Medical Campus. A new user interface for the haplotype frequency curation system was demonstrated and several developers contributed enhancements and modifications to the software repository for this project. 12 developers have contributed to this project and are currently working through an issues list of 16 items. This system

is intended to be a source for high-quality HLA frequency information to drive matching applications in global populations.

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.

No activity to report this quarter.

C. 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 and Whole Genome Genotyping

- The contract laboratory completed whole genome genotyping (WGG) on 2000 samples using the Illumina Infinium Global Screening Array-24 v2.0 chip. Data interpretation and transfer for analysis is in process and will be completed next quarter.
- Approximately 700 of the 1000 WGG pairs were previously HLA typed by the Donor Recipient Pairs Project (DRPP), the remaining 300 pairs will be included in the DRPP 2019 project for completion next quarter.
- A cohort of 475 pairs transplanted for acute lymphocytic leukemia, acute myelogenous leukemia and myelodysplastic syndromes were selected for inclusion in the 2019 DRPP with typing expected to be completed next quarter.
- Additional sequence analysis and submission of new alleles to IMGT for name assignment has allowed for 84 more pairs to be audited for use in studies. Allele name assignment is still pending on approximately 100 pairs and will be completed by the end of the next quarter.

Full HLA Gene Matching Analysis

- The Donor-Recipient Pair Project has employed ultra-high resolution (UHR) HLA typing techniques for several years. Recent studies by the Anthony Nolan Research Institute and MCW/BCofWI have described potential benefits of matching at UHR resolution. A validation study using the CIBMTR database is needed to offer further guidance to the field on donor selection and support decisions regarding resolution for Registry typing.

- UHR HLA matching and clinical data are being compiled and the analysis will begin next quarter.

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

KIR Region Genomics

- During the past quarter we presented our results of a preliminary analysis of the results of fosmid-based sequencing of the KIR genomic region for an African American cohort at the European Federation for Immunogenetics conference. 23 haplotypes in 12 individuals were sequenced and new structural haplotypes were discovered. For the first time, we have documented haplotypes containing *KIR3DL1* without *KIR2DS4* and *KIR3DL2*, and a haplotype containing *KIR2DL2* without *KIR2DS2*. This work will affect the analysis of KIR genotyping on African American populations in light of these newly discovered structures.

- A second KIR genomics project has led to the development of a new method for the efficient Sequencing and Assembly of Diploid KIR Haplotypes. This work was presented at the European Federation for Immunogenetics conference This approach was demonstrated to be concordant with gold-standard fosmid cloning based results at 99.9% but at significantly lower cost (2 orders of magnitude).

D. Clinical Research in Transplantation

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

Observational Research

- Activated 39 observational studies for the 2019-2020 academic year.
- Completed analyses on greater than 20 studies for submission to the American Society of Hematology Annual Meeting. Abstract submission will be completed prior to the August 1, 2019 deadline for consideration.
- Published 21 peer-reviewed manuscripts in the last quarter.

Research data collection and systems enhancements

During the grant year, CIBMTR has continued support for electronic data submission initiatives, production FormsNet Recipient, FormsNet Donor, and AGNIS customers, as well as Data Warehouse users.

FormsNet

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

- A concerted effort to enhance performance and monitoring for the FormsNet application, as our user base continues to grow and evolve. In this reporting period, FormsNet 3 code efficiencies were identified, developed, and deployed, significantly increasing FormsNet 3 performance despite a significant increase in the utilization of the FormsNet database by a variety of newer tools and queries. We will continue to utilize feedback from the user perspective surveys to inform future performance enhancements.
- Investigations towards more modular (domain-based) data capture, to decrease form size and increase re-use of modules.
- Created and updated tools to enhance efficiencies. Continued work on multi-center reporting to accommodate cellular therapies. Developed proposal for this work including concurrent reporting and patient data portability.
- Added multi-language support to allow FormsNet system and forms to display in a language other than English. Cellular therapy forms translated into Japanese. This functionality will be released into FormsNet in October, 2019.
- Developed and released the following data collection forms:
    - Recipient Contact Form 2820,
    - Indication form 2814,
    - Enrollment form 2532,
    - Donor Testing form 2533,
    - 2534 Evaluation forms for the BMT CTN 1702 Study,
    - 2540 Tepadena Study form.
- Retirement of FormsNet 2 neared completion as the last remaining business rules were converted to the current FormsNet 3 business rules engine, which provides upgraded technology, consistency, quality, and flexibility for form revisions and maintenance of rules. Deployments in April and July of 2019 will close out this effort and coincide with FormsNet 2's retirement in August or September 2019. April's deployment, like the three before it, demonstrated that new donor and recipient form updates using the new business rules engine have been much quicker to update, more consistent, and significantly easier to test and troubleshoot.
- Completed monthly releases of the Data Integration Mapping Application (DIMA) tool in FormsNet 3's Forms Definition Manager. Recent releases included the ability to associate internal reference data with external reference data, and cross-form data dictionary code lookup. The DIMA tool supports efficient, consistent data mapping for new form revisions and NMDP data studies/sources through functionalities like mass pre-population of form mappings, data validations checks, cross-form metadata lookups, cross-form editing, as well as the ability to link CIBMTR data to external sources to support data interoperability for future expansion of reporting and data sharing.

Electronic data submission/AGNIS

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

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

Recent AGNIS and other electronic data submission accomplishments:

- First iteration of the Epic App for patient data exchange was approved by the Epic App Orchard team. Continuing to work on installation of the CIBMTR Reporting App at the pilot centers and developing the next iteration of the HLA / GVHD pilot App.
- All four Cellular Therapy forms have been tested by at least one AGNIS center and are on track for release in early August.

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

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

- Added infusion data for Cellular Therapy infusions. This newly integrated data will be available in select extracts.
- Refining our ability to make Cellular Therapy data available to external audiences in support of business development opportunities, including expansion of a new data domain to include Cellular Therapy data, initial development of an automated process for data extraction and data dashboards for external audiences.
- Incorporating ongoing forms revisions into the warehouse

- Business Intelligence Data Sharing- Continue expansion of business intelligence tool capabilities. Adding to the existing suite of external Business Intelligence data sharing applications including the introduction of more data, dimensions and measures, stakeholder groups, and continuing data quality initiatives. Recent accomplishments include:
    - Completed the annual ASBMT for RFI update, finalizing incorporation of CT data into the eDBtC data download, and began development of visualizations for CT data in eDBtC.
    - Began work on the annual refresh of the Center Volumes Data Report published on https://bloodcell.transplant.hrsa.gov.
- UDM

- Loaded cellular therapy data into the data warehouse, designed and began validation of the extract.
- Began mapping of transplant essential data to the physical data model.
- Designed infrastructure for enabling data extracts from the unified database.