NATIONAL MARROW DONOR PROGRAM®

BE THE MATCH®

April 15, 2019

Lt. Cdr. Joshua Swift
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 N00014-18-1-2888 between the Office of Naval Research and the National Marrow Donor Program

Dear Lt. Cdr. Swift,

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 1, 2019 through March 31, 2019.

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

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

Sincerely,

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

c: Patricia Woodhouse – ONR-Chicago
DTIC
NRL (Code 5596)
Dennis Confer, MD – NMDP
Steven Spellman – NMDP
Robert Hartzman, M.D.
Jennifer Ng, Ph.D.

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500 N. 5th St.
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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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Grant Award N00014-18-1-2888

DEVELOPMENT OF MEDICAL TECHNOLOGY FOR CONTINGENCY RESPONSE TO MARROW TOXIC AGENTS

FINAL RESEARCH PERFORMANCE REPORT

SUBMITTED APRIL 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

N00014-18-1-2888

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

- Finalized a manuscript of the proceedings of the NIAID-RITN workshop *Growth Factors and Other Cytokines for Treatment of Injuries During a Radiation Public Health Emergency* held on August 30, 2018 entitled, "COMMENTARY Use of Growth Factors and Cytokines to Treat Injuries Resulting from a Radiation Public Health Emergency" for submission to Radiation Research Journal.
- 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.
- Assisted the project team with the content and editing of the NMDP BioBank proposal and informational presentation given to DHHS-BARDA.
- Developed a RITN 5yr strategic plan to align the growth of RITN to match the needs expressed by the DOD and DHHS-ASPR based on these organizations planning for repatriation of warfighters, dependents, DOD Civilians and US expatriates following an OCONUS rad/nuke incident.
- Provided informational presentations to hospitals in San Antonio and Georgetown to educate the senior leadership at these institutions of the mission and expectations of participating RITN hospitals.

- Initiated a project to assess the competence of RITN medical staff. This will involve a short survey that incorporates questions and an assessment into one survey tool which will gauge the personal perception of radiological disaster knowledge and compare that against the accuracy of response to the assessment questions. The results will be reviewed by 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 educational initiatives.
- Participated in the National Quality Forum development of healthcare systems readiness standard for US hospitals nationwide.
- Presented on the RITN data collection system at the National Academies of Science, Engineering and Medicine workshop *Challenges in Initiating and Conducting Long-Term Health Monitoring of Populations Following Nuclear and Radiological Emergencies in the United States.*
- Invited by the Uniformed Services University of the Health Sciences to present at the Israeli Defense Forces meeting on rad/nuke response.
- Collaborated with the National Alliance for Radiation Readiness a CDC funded program managed by the Association of State and Territorial Health Officials to jointly hold a meeting to review their Cytokine distribution guidelines and to present the RITN Cytokine Triage Guidelines to stakeholders for comment.
- Partnered with the National Alliance for Radiation Readiness to co-host a Radiation Track at the National Association of City and County Health Officials Preparedness Summit.
- Assisted Anthony Nolan Hospital with the development and execution of a tabletop exercise.
- Assisted RITN hospitals awarded a FY19 exercise grant with the development of their functional and full-scale exercises.
- Developed the RITN annual tabletop exercise.
- Coordinated with the Radiation Emergency Assistance Center and Training Site (REAC/TS) and Advanced Hazmat Life Support (AHLS) to conduct advanced radiation mobile training.

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

Supported the 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

A patient cohort has been prepared for this project (N=3751) with the clinical outcomes from an 8/8 allele match transplant and the corresponding list of equally well-matched donors (1173 on average) and a series of attributes involved in donor selection. Evaluation of this cohort is underway which allow these searches to be evaluated relative to the optimal selection according to the model.

Methods development is underway to apply this machine learning method to censored survival data and also the determine the additivity of the parameters in the model and whether simpler models (e.g. using only DP and Age) are a better fit to the outcomes data.

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

HLA Imputation

The core method for graph-based imputation and matching was published during the previous quarter. (https://www.ncbi.nlm.nih.gov/pubmed/30689784))
This method has been extended to address multi-race populations and is being validated against both a simulated and a clinical validation cohort.

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
Development has occurred on the system for public haplotype frequency curation (PHYCuS) during the past quarter. https://github.com/nmdp-bioinformatics/phycus The plan for a graphical user interface and a user-management sub-system were developed at a data standards hackathon held in Leiden Mar 23-24, 2019.

C. Immunogenetic Studies in Transplantation

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.

- Supplied the NIH Transplant Program with 7 products (4 PBSC and 3 bone marrow)
- Supported development of the BMTCTN1702 Ctrl-Alt-D trial protocol

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

- Selected cases for full gene HLA class I and exon 2 and 3 with intron 2 for HLA class II of an additional 1364 unrelated and 354 related pairs.
- The Whole Genome Genotyping (WGG) pilot will use the Illumina GSA standard panel chip and full gene HLA class I and exon 2 and 3 with intron 2 for HLA class II. GSA chip typing will be performed on 1000 ethnically diverse related pairs (937 haplo-identical and 63 HLA matched pairs).
- The abstract, Genomic QC pipeline for biorepository research samples, was selected for a poster at the EFI meeting 2019.

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 performed preliminary analysis of the results of fosmid-based sequencing of the KIR genomic region for an African American cohort. 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. This work was accepted for oral abstract presentation at the European Federation for Immunogenetics conference.

A second KIR genomics projects has led to the development of a new method for the efficient Sequencing and Assembly of Diploid KIR Haplotypes. This method uses two probe capture strategies to target the KIR region for sequencing of 2-8kb genomic fragments on two different long-read NGS platforms (PacBio RSII and Sequel). This approach was demonstrated to be concordant with gold-standard fosmid cloning based results with 99.9% but at significantly lower cost (2 orders of magnitude). This probe capture and sequencing approach is the first of its kind to fully sequence and phase all human KIR haplotypes at a cost-efficient that will allow population-scale studies and clinical translation of this system. This work was accepted for oral abstract presentation at the European Federation for Immunogenetics conference.

D. Clinical Research in Transplantation

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

Observational Research

- Received 220 new study proposals, peer-reviewed 99 at the February 2019 ASBMT/CIBMTR Transplant and Cellular Therapy Meeting and accepted 39 for activation.
- Published 50 peer-reviewed manuscripts and presented 36 abstracts at national/international meetings.

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. We will utilize feedback from the user perspective surveys to inform 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, and investigating multi-center reporting to accommodate cellular therapies.
- Added multi-language support to allow FormsNet system and forms to display in a language other than English. Cellular therapy forms translated into Japanese.
- Business Rules Editor: the new business rules engine will include the business rules editor, which will allow more flexibility for form revision, easier maintenance of the rules and put us another step closer to have the ability to release forms outside of a quarterly release.
- Developed and released the following data collection forms:
    - Adverse Event Forms 3001 & 3010 (Global Registration Identifier for Donors (GRID) only)
    - Cellular Therapy Follow up Form 4100
    - Cellular Therapy Pregnancy Form 3501
    - Cellular Therapy Product Form 4003 r2 (Adding GRID only)
    - Recipient Death Form 2900
    - Lymphoma Form 2018
- 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. Quarterly batches of updated forms were successfully converted on January 25, 2019 and deployments in April and July of 2019 will close out this effort and coincide with FormsNet 2's retirement in July 2019.
- Completed monthly releases of the Data Integration Mapping Application (DIMA) tool in FormsNet 3's Forms Definition Manager. 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 supporting submission from EBMT for research, 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:

- Successful patient data exchange pilot demo with three potential transplant center partners. Teams continued to work on additional HLA and GVHD pilots.
- All four Cellular Therapy forms are now available for AGNIS users to test.
- Released error override functionality via AGNIS and a report to support testing AGNIS forms in lower environments that resets form submissions back to Due status.

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

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

- Expanding integration of research sample data with FormsNet based clinical data by adding additional FormsNet clinical data and automating manual processes
- Initial enhancement of the IDW Infusion mart to accommodate multi- product / multi infusion cases was completed. In process of adding infusion data for Cellular Therapy infusions.
- Refining our ability to make Cellular Therapy data available to external audiences in support of business development opportunities
- Incorporating ongoing forms revisions into the warehouse

- 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.
- Expansion of business intelligence tool capabilities. This includes on demand download capabilities for external partners.
- Business Intelligence Data Sharing
    - Creation of a Business Intelligence dashboard used by CIBMTR staff to track productivity metrics.
    - Creation of a proof of concept dashboard piloting the inclusion of Cellular Therapy within a customer-facing dashboard containing HCT data.
    - Creation of a customer facing dashboard focusing on Cellular Therapy accruals and demographic data.
    - Annual refresh of Center Performance Analytics dashboard including all data from the TCSA report (generated from the IDW).
    - 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.