NATIONAL MARROW DONOR PROGRAM®

BE THE MATCH®

January 9, 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 N00014-17-1-2850 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 June 01, 2018 through December 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 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
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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.

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

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			Dennis L. Confer, MD – Chief Medical Office
U	U	U		8	**19b. TELEPONE NUMBER (*Include area code*)** 763-406-3425

Grant Award N00014-17-1-2850

DEVELOPMENT OF MEDICAL TECHNOLOGY FOR CONTINGENCY RESPONSE TO MARROW TOXIC AGENTS

INTERIM RESEARCH PERFORMANCE REPORT

SUBMITTED JANUARY 9, 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

N00014-17-1-2850

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. 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.

C. 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.

Project: Triage Guidelines for Cytokine Administration Following a Radiological Disaster

1. The workgroup developed a draft set of adult and pediatric guidelines.
2. These draft guidelines are in circulation for feedback from the RITN Executive Committee.
3. The next step will be to circulate for feedback to all of RITN and its partners.

Project: Hematologic Laboratory Surge Network Exercise and Plan Development

1. A draft concept of operations (CONOPS) was created and ready for review by stakeholders.
2. The project team has talked with DHHS-ASPR about collaborating to ensure that it is in alignment with government expectations and guidance.
3. Due to hurricane season and other public health emergencies DHHS-ASPR staff have not been available to proceed with these in depth discussions.
4. In expectation that this in-availability will continue the project team is talking to New York City emergency management and hospital staff to conduct an exercise to validate assumptions in the document.

Project: Local Public Health Radiological Preparedness Gap Review and Tool Development Identification

1. The National Association of County and City Health Officials (NACCHO) finalized the report in August.
2. The report was shared with all of RITN and its partners as well as posted on the RITN website as NACCHO/RITN Gap Analysis: Understanding the Shortfalls within Radiation Preparedness: https://ritn.net/WorkArea/DownloadAsset.aspx?id=2147484410

Project: Radiological Disaster Webinar Training Series for Inexperienced Public Health Staff

1. The Association of State and Territorial Health Officials (ASTHO) has hired a videographer to record the modules.
2. Scripts for the first two training courses are drafted and being circulated for finalization before recording the voiceovers.
3. The third and fourth training courses are being written.

B. 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.

Project: Evaluation and identification of whole genome donor-recipient pair variation and donor-specific DNA methylation patterns that affect HCT outcomes

1. DNA methylation sequencing and long insert whole genome sequencing was completed on the pilot cohort of 188 samples. Data was transferred from the sequencing center and is under preliminary analysis to evaluate associations between donor and recipient DNA methylation signatures and whole genome sequence variation on disease relapse following hematopoietic cell transplantation for Myelodysplastic syndromes (MDS).
2. A request for quotation was distributed to solicit bids for the next round of testing. A cohort of >1,000 MDS transplant donor/recipient pairs was selected and DNA preparation initiated to facilitate the testing. The sequencing is expected to commence in late February with completion in late May.
3. Weekly collaborative meetings were held between researchers from both Minneapolis and Milwaukee Center for International Blood and Marrow Transplant Research (CIBMTR) campuses to track the progress of the typing, develop the statistical analysis approach and review results.

C. Clinical Research in Transplantation

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

Project: Patient Report Outcomes (PRO). Incorporating patient reported quality of life (QOL) assessments into CIBMTR data collection

CIBMTR's Electronic Patient Reported Outcomes (ePRO) system integrates Qualtrics online surveys with PROMIS® (Patient-Reported Outcomes Measurement Information System) computer adapted test measures and Salesforce CRM (customer relationship management) to administer quality of life and other patient reported outcomes with follow-up support by Survey Research Group (SRG).

Previous accomplishments included deployment of ePRO system, including integration of Qualtrics, PROMIS API (application programming interface) and Salesforce, and security enhancements for compliance with HIPAA and NMDP security standards.

Accomplishments in this reporting period:

1. The pilot study was launched, and patients began enrolling in July 2018. Two of six sites have been activated. As of December 17 there are 27 completed surveys out of a target accrual of 218 completed surveys.
2. PRO data was started being stored and scores in the Integrated Data Warehouse (IDW) for the pilot study. Data mapping has been completed and processes are in place to pull data from Qualtrics into the IDW on-demand.
3. Reviewed and enhanced system-monitoring capabilities for when servers are down or there are other issues with the APIs or other system components. The business owner and IT support receive notification of errors in either Qualtrics or the API manager.

Remaining scope to be delivered:

1. Complete the pilot study.

Project: Development of a Regenerative Medicine Registry

The CIBMTR has developed a new infrastructure to capture information on recipients of cellular therapy outside the setting of a hematopoietic cell transplantation. The Cellular Therapy Outcomes Registry was launched in 2016 and has a broad scope to collect information on recipients of multiple types of cellular therapies for a wide range of indications. The goal of this project is to build on this existing infrastructure and expand the types of data collected on selected indications within the scope of regenerative medicine. This requires outreach to

different specialty groups to build disease-specific modules of pertinent data elements for assessment of the disease prior to treatment and the response thereafter. The ultimate goal is to have a functioning outcomes database of emerging cellular therapies for treatment of regenerative medicine indication and can be used for research.

Previous accomplishments include the release of the cellular therapy registry with capabilities to collect relevant information on regenerative therapy indications and outcomes related to cellular therapy, including toxicity. Outreach to multiple groups to demonstrate the capabilities of this infrastructure and to initiate a prioritization plan on what indications should be addressed first.

Accomplishments in this reporting period:

1. There was outreach to disease-specific groups to discuss a strategy for development of data collection instruments and studies to assist their implementation.
2. An in person meeting was held in September 2018 which established a roadmap based on the groups input which included the following topics to concentrate on for the CIBMTR data collection pilots: osteoarthritis of the knee, acute ischemic stroke, irradiation-induced tissue fibrosis and chronic heart failure. All these disease indications have existing groups which will facilitate the alignment with CIBMTR.

Remaining scope to be delivered:

1. Hire a dedicated regenerative medicine coordinator.
2. Develop and implement disease specific forms.
3. Activate and train new centers with active regenerative medicine programs.

Project: Enhancing Existing IRB software application(s) to streamline NMDP single IRB Processes

1. In October a 3-year agreement with an IRB software called “IRB Manager” was finalized.
2. In November the first meeting identifying the plan with IRB Manager was held.
3. In December the first implementation meeting was held.
4. Ongoing biweekly meetings have been scheduled for the next several month to build and implement the system.

Project: Support for developing HL7 Fast Healthcare Interoperability Resources (FHIR) tools to enhance interoperability of AGNIS® with Electronic Medical Records

The tremendous scientific value of CIBMTR research is threatened by reliance on manual data entry through web-based forms at most HCT centers. CIBMTR created A Growable Network Information System **(**AGNIS) to overcome this challenge. While powerful, adoption of AGNIS at a broader range of transplant centers has been limited because of burdens associated with data mapping and/or a lack of available resources with sufficient technical expertise. Because AGNIS replicates the FormsNet User Interface forms, any change to information being captured requires new form definitions, resulting in new mappings to local data elements. This process is inefficient. Beginning in the fall of 2017, we embarked on a project to incorporate a new data

transmission interface to AGNIS using healthcare informatics standards that embrace modern approaches to data exchange – HL7 FHIR.

Accomplishments in this reporting period:

1. The initial FHIR client interface application was demonstrated at a FHIR Connectathon, which is an international meeting where developers exchange data and test connections.
2. Demonstration of draft (client) application to senior leadership were provided.
3. NMDP architectural requirements for the development of a secure environment for future data exchange were defined.
4. A FHIR development server for the testing and implementation of necessary security and authentication tooling was introduced.

Remaining scope to be delivered:

1. Consult FHIR SMEs to ensure conformance with established FHIR standards.
2. Collaborate with partner transplant centers to identify necessary enhancements to the draft client application.
3. Introduction of security layers for FHIR server interaction.
4. Introduction of security layers for interactions with CIBMTR services.
5. Upload genomic resource to Epic FHIR sandbox for retrieval by our tool using alternate search criteria.
6. Enhancement of automated search scripts to allow additional FHIR Resources to be used in search criteria or retrieved from the Epic Sandbox.
7. Introduction of a mapping script to ease the burden of implementation for partner transplant centers.
8. Development of a draft Implementation Guide (a set of rules about how FHIR resources are used when exchanging data with CIBMTR).

V. Major Problems/Issues (if any)

No major problems encountered to date.

VI. Technology Transfer

No technology transfer to report.

VII. 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.

VIII. Productivity

1. Refereed Journal Articles – None to report
2. Non-Refereed Significant Publications – None to report
3. Books or Chapters – None to report
4. Technical Reports
    a. HL7 FHIR Clinical Genomics Working Group - HLA reporting FHIR Implementation Guide for Clinical Genomics Reporting
        i. May 2018 ballot - http://www.hl7.org/fhir/uv/genomics-reporting/2018May/index.html
        ii. Current Ballot - http://www.hl7.org/fhir/uv/genomics-reporting/2019Jan/index.html
5. Workshop and conference abstracts and presentations
    a. Data Standards Symposium and Hackathon - 25 July 2018, Minneapolis MN Oral Presentations
        i. Introduction to FHIR: HL7, Resources, Profiles, versions, and ballots - Bob Milius
        ii. Genomics Reporting Implementation Guide Reporting HLA genotyping using the Clinical Genomics IG - Bob Milius
        iii. Mapping HML to FHIR - Bob Milius
        iv. Tool for high throughput conversion of HML to FHIR- -Andrew Brown
        v. HLA Terminology Services - Joel Schneider
6. Patents – None to report
7. Awards/Honors – None to report

IX. Award Participants

Employee name	**Employee name**	**Employee name**
Andrew Brown	Jane Pollack	Matt Prestegaard
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