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 N00014-17-1-2850 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 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,

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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.

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

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a. REPORT	b. ABSTRACT	c. THIS PAGE			Dennis L. Confer, MD – Chief Medical Officer
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Grant Award N00014-17-1-2850

DEVELOPMENT OF MEDICAL TECHNOLOGY FOR CONTINGENCY RESPONSE TO MARROW TOXIC AGENTS

INTERIM RESEARCH PERFORMANCE REPORT

SUBMITTED APRIL 15, 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 finalized the set of adult and pediatric guidelines.
2. These were circulated with all RITN hospitals and RITN partners for comment; comment period closed 3/29/19.
3. The Association of State and Territorial Health Officials-National Alliance for Radiation Readiness through funding from the CDC has developed a whitepaper on the distribution of Cytokines following a radiological disaster that will be presented at a meeting on May 22-23, 2019 in DC. As many of the same attendees for their meeting overlap with those to comment on the RITN Cytokine Triage Guidelines; we have partnered with ASTHO to support the meeting to gather final public comment on the guidelines created.

Project: Hematologic Laboratory Surge Network Exercise and Plan Development

1. Due to inability to secure federal comment on the draft concept of operations this project has been slightly modified to continue to move forward.
2. Multiple cities are being coordinated with to conduct a tabletop exercise to review patient triage and movement away from the disaster area and include in this exercise the lab surge that would result in the local community.
3. These exercises will be facilitated by RITN, feedback on the lab surge concept of operations will be used to update the document. Then it, along with the exercise after action reviews, will be published as whitepaper suggested best practices.

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

1. Complete

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

1. The Association of State and Territorial Health Officials (ASTHO) continues to develop the training courses.

B. Immunogenetic Studies in Transplantation

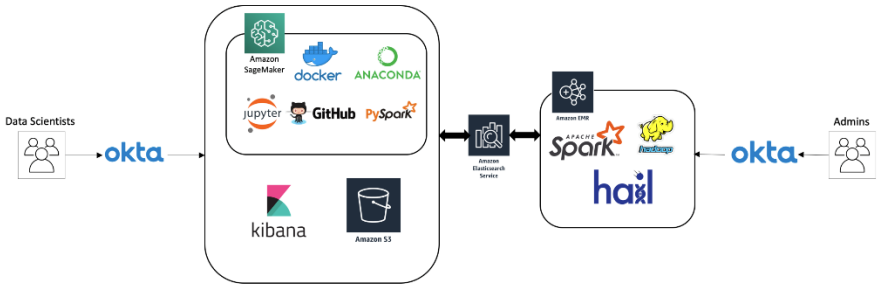
HLA mismatches may differ in their impact on transplant outcome, therefore, it is important to identify and quantify the influence of specific HLA mismatches. In contingency situations, it will not be possible to delay transplant until a perfectly matched donor can be found.

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

Over this quarter, progress was made in five areas with regard to preparation for outcomes analysis of donor-recipient pair whole genome variation and DNA methylation:

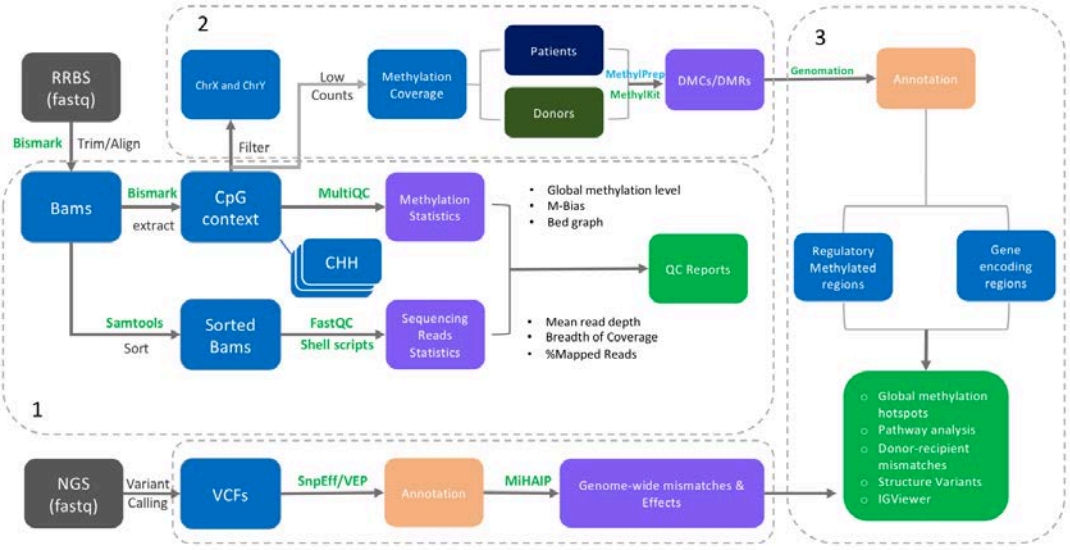
1. Genomics/omics platform development: The Genomic Data Repository was secured for user identity management using single sign-on. Beyond data storage, the Genomic Data Repository also moved in a new direction for platform development (Figure 1) to connect to data science capabilities with Amazon Web Services Sagemaker while releasing dependencies on Cloudera and Metistream services.

   Figure 1: High-level design of the Genomic Data Repository components.



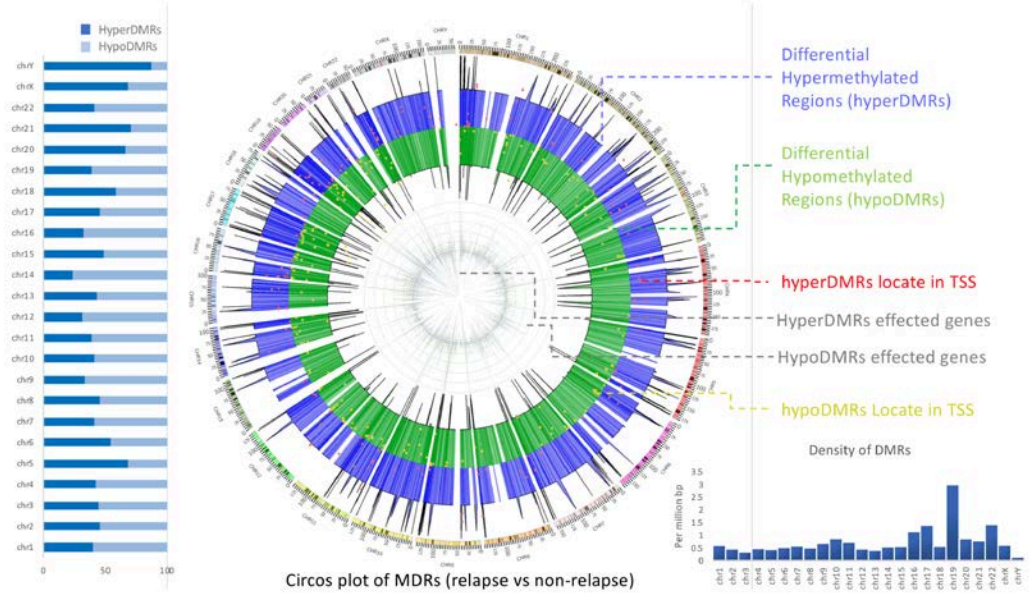
2. Pilot data acquisition: Whole Genome Sequencing data continued to be received from the Genomic Sciences and Precision Medicine Center at the Medical College of Wisconsin for the pilot subset (188 samples).
3. Pilot data analysis: Additional analysis of Reduced Representation Bisulfite Sequencing data from the pilot subset was performed (Figure 2).

Figure 2: Design of foundational workflow for genomic and epigenetic analysis.



4. Analysis plan development: From this preliminary dataset, differentially methylated regions were identified under various cases to evaluate potential patterns related to patient disease relapse or non-relapse after transplantation (Figure 3). Additional cases and conditions were identified for further evaluation and future comparison.

Figure 3: Plot of Differentially Methylated Regions in relapse vs. non-relapse cases.



5. New data acquisition contracts: Samples to round out cohorts were selected, and contracts were signed with two additional laboratories to acquire the genomics and epigenetic data for the larger study. One contract for Whole Genome Sequencing with the Broad institute was signed for 60x genome coverage of 500 patient samples and 30x genome coverage of 500 donor samples. Using a methylation chip platform with >850,000 CpG sites, a contract was signed with the University of Minnesota to obtain this genome-wide methylation data on 1188 samples. Preparations for storage and processing of this anticipated dataset is underway.

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:

Although PRO spend from the ONR 3-year funds (FY18 – FY20) has concluded, CIBMTR has accomplished the following in use and expansion of the ePRO system during this reporting period with existing CIBMTR resources.

1. Continue data collection in pilot study. Five of six sites have been activated. As of March 29, there are 44 completed surveys out of a target accrual of 218 completed surveys.
2. Developed efficiencies in the Salesforce CRM and Qualtrics integration.
3. Designed and started build on a process for gathering patient contact information from transplant centers and feeding that into ePRO system for more efficient and automated PRO data collection.

4. Conducted review of ePRO system to ensure compliance with 21 CFR Part 11 requirements regarding audit trails.

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.

Accomplishments in this reporting period:

1. Hired a dedicated regenerative medicine coordinator.
2. Developed a set of guidelines to assess potential new regenerative medicine initiatives:
    a. Does the therapy have the potential to improve event-free survival in patients for whom HCT is considered a curative therapy, i.e., hematologic malignancies, non-malignant marrow disorders and inherited or acquired disorders of the immune system?
        i. Examples are gene-modified cells for sickle cell disease, mesenchymal or other cells for graft-versus-host disease or other HCT complications.
    b. Does the therapy use cells derived from the bone marrow (obtained either by marrow harvest or leukapheresis) or umbilical cord blood, sources in which we have a long interest, even if for a non-traditional indication?
        i. Examples are umbilical cord blood for stroke or for autism.
    c. Does the initiative come with sufficient additional resources so that resources will not be diverted from other CIBMTR initiatives and operations?
        i. Examples include contracts with manufacturers and grants from the NIH and others.
3. Planned a second in-person meeting for September 2019 to review progress with stakeholders.

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

1. Ongoing biweekly meetings have been held to build and implement the system. Some forms are already in draft form, Figure 4.

Figure 4: Draft version of IRB Manager software

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.

<u>Accomplishments in this reporting period:</u>

1. Defined architectural requirements for the development of a secure environment for future data exchange.
2. Initial infrastructure established with the development of the needed hardware (servers) for initial Proof of Concept testing.
3. A draft (client) application was created to communicate with Epic's Electronic Health Records sandbox (testing) server.
4. An initial proof of concept data exchange with the Epic testing server using HL7 FHIR's Patient Resource (structured data set pertaining to patients) was developed; patient resource data exchanged.

5. Provided demonstration of draft (client) application to potential partner transplant centers.
6. Generation of validated FHIR bundles of HLA typing data.
7. Launch of FHIR Server meeting corporate infrastructure requirements.
8. Client enhancements to properly display and exchange Patient demographic data.

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. Refinement of security layers for FHIR server interaction.
4. Refinement of security layers for interactions with CIBMTR services.
5. Integration of client application into data ecosystem of partner transplant center or DEV-level data exchange
6. Integration of client application into data ecosystem of partner transplant center or production-level data exchange
7. 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 = None to report

5. Workshop and conference abstracts and presentations
    a. Mattila, D. (2019). Building a novel and flexible electronic patient-reported outcome collection system for cellular therapy research. Presentation, Health Measures User Conference, Chicago, IL.
    b. Mattila, D. (2019). QOL Data Collection: New ePRO System & Practices. Presentation, BMTCTN Coordinators Meeting, Transplant and Cellular Therapies Conference, Houston, TX.
    c. Lee, S. (2019). Electronic Patient Reported Outcomes (ePRO) and Survey Research Group. BMT CTN Steering Committee, Washington D.C.
    d. AGNIS on FHIR Client App Demonstration- 29 January 2019, Oral Presentation for Johns Hopkins
        i. Demonstration of Client App development to date
        ii. Forum discussion regarding user interface, analysis of use case scenarios, technical implementation considerations
    e. AGNIS on FHIR Client App Demonstration- 5 February 2019, Oral Presentation for Dana Farber Cancer Institute
        i. Demonstration of Client App development to date
        ii. Forum discussion regarding user interface, analysis of use case scenarios, technical implementation considerations
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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Ann Jakubowski	Jason Brelsford	Michelle Formanek
Bill Burgess	Jason Dehn	Peter Tonellato
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Caleb Kennedy	Joel Schneider	Robinette Renner
Christina Jobe	Josh Mandel	Stephen Spellman
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Cullen Case	Julia Udell	Wael Saber
Curt Mueller	Kirt Schaper	Wei Wang
Cynthia Vierra-Green	Lloyd McKenzie	Xiaoyun (Wendy) Zhang
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Hu Huang	Martin Maiers	