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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			Steven Devine, M.D. – 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 13, 2020

Office of Naval Research

And

The National Marrow Donor Program®

500 5th St N

Minneapolis, MN 55401

I. Heading

PI: Steve Devine, 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

1. 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.

2. 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.

3. 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

Updated the RITN Cytokine Triage Guidelines circulated and received additional feedback for incorporation. Incorporation of feedback is delayed due to organizational focus on COVID-19 response.

Project: Hematologic Laboratory Surge Network Exercise and Plan Development

Held Medical Response Workshop with the Chicago Hospital Coalition on February 28, 2020. Attendance and participation was excellent, after action report is being developed however is delayed due to organizational and workshop participant focus on COVID-19 response.

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

Complete.

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

Complete.

Link to videos: www.RITN.net/training and https://www.radiationready.org/posted-tools/national-alliance-for-radiation-readiness-radiation-training-modules-for-public-health/

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, the team developed protocols for the following:

- Variant and enrichment analysis of genomic data.
- Association testing and cluster analysis of chip-based methylation data with outcomes.
- Integration of genome, methylome, and proteome data for preliminary prediction modeling.

Data on samples from 1,188 transplant donors and MDS recipients were processed, and candidates from the case-control pilot cohort were analyzed against known clinical outcomes. Genes in Immune regulatory/TP53/AKT associated biomarker pathways were enriched in recipients with MDS relapse after transplant. Multiple differentially methylated probe patterns were found to be associated with transplant outcome. Global methylation profiles from relapsed patients were lower than non-relapsed patients overall. Preliminary candidates from pilot analyses were identified for consideration as prognostic determinants of relapse in patients. Further investigation is required to validate pilot candidates in the remaining 500 donor-recipient pair cohort. Currently, new workflows for systems integration of genome, methylome, and proteome data are being utilized on data subsets, and prediction modeling approaches are being developed and tested initially on the pilot data.

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

The pilot study is complete. Additional functionality is being added to the CIBMTR electronic Patient Reported Outcomes (ePRO) system to allow the CIBMTR to collect routine PRO data on a long-term basis for all consenting transplant patients. Over this quarter we have continued development in the following areas

- Design and build core PRO instrument for adult transplant patients.
- Identify and establish metadata standards for core PRO instrument.
- Automate data transmission from ePRO system to CIBMTR outcomes database.
- Establish standard internal and external reporting mechanisms to track acquisition of PRO data.

Project: Development of a Regenerative Medicine Registry

Work on this deliverable continues according to plan. Funds are used for reimbursement of data forms provided to the registry for regenerative medicine and for the program manager who supports the development, collection and integration of regenerative medicine data into the registry.

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

This project is now complete, with all the tasks set out in the proposal finished. The application went live on February 3, 2020 with Initial Application forms for Biomedical and Social Behavioral studies as well as the Human Subjects Determination form released to the users. Request for Amendment form and Study Closure form were completed and tested in March and are available for users. The next forms to be released are Reportable Event form and Major Protocol Exceptions forms.

The forms are planned to continue to be released monthly until all are released and available for users within the IRBManager by the end of the fiscal year. This will be supported by internal NMDP funding.

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:

- Production environment established with industry-standard security and authentication.
- Promotion of CIBMTR Reporting App to the production environment at Ohio State University
    - All new patient registrations occur via the App
    - Initial data exchange of acute graft versus host disease observations has commenced
- Introduced enhancements to improve patient matching during registration.
- Using the HML2FHIR Converter, ongoing production-ready HLA data file submissions from Moffitt Cancer Center HLA Laboratory were received by CIBMTR for processing and validation; transition to production environment anticipated by early summer 2020.
- Further enhancements to the processing code were introduced to address edge case scenarios for HLA typing submissions.
- Collaboration ongoing with FN3 Team to move HLA typing FHIR Resources and aGVHD observations to the FormsNet database.
- Collaboration continues with partner transplant centers to install the CIBMTR Reporting App within their local Epic EHR application.

V. Major Problems/Issues (if any)

No major problems encountered to date. Due to COVID-19 there may be delays in any input from government agencies for the RITN project. We also anticipate that there will be no new workshop and conference abstracts and presentations in the remainder of the project.

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 – None to report
6. Patents – None to report
7. Awards/Honors – None to report

IX. Award Participants

Employee name	**Employee name**	**Employee name**
Andrew Brown	Hu Huang	Matt Prestegaard
Angela Kummerow	Jane Pollack	Michael Heuer
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