# REPORT DOCUMENTATION PAGE

*Form Approved*
**OMB No. 0704-0188**



| 1. REPORT DATE *(DD-MM-YYYY)* | 2. REPORT TYPE | 3. DATES COVERED *(From - To)* |
|---|---|---|
| 07-13-2020 | Interim Technical Report | April - June, 2020 |

**4. TITLE AND SUBTITLE**
Development of Medical Technology for Contingency Response to Marrow Toxic Agents – Interim Technical Report with SF298 April 1, 2020 – June 30, 2020

**5a. CONTRACT NUMBER**
N/A

**5b. GRANT NUMBER**
N00014-17-1-2850

**5c. PROGRAM ELEMENT NUMBER**
N/A

**6. AUTHOR(S)**
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**5d. PROJECT NUMBER**
N/A

**5e. TASK NUMBER**
Project 1, 2, 3, 4

**5f. WORK UNIT NUMBER**
N/A

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**
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N/A

**9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)**
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**10. SPONSOR/MONITOR'S ACRONYM(S)**
ONR

**11. SPONSORING/MONITORING AGENCY REPORT NUMBER**
N/A

**12. DISTRIBUTION AVAILABILITY STATEMENT**
Approved for public release; distribution is unlimited

**13. SUPPLEMENTARY NOTES**
N/A

**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 |
| U | U | U | | 8 | 19b. TELEPONE NUMBER (*Include area code*) 763-406-8239 |

# Grant Award N00014-17-1-2850

# DEVELOPMENT OF MEDICAL TECHNOLOGY FOR CONTINGENCY RESPONSE TO MARROW TOXIC AGENTS

## INTERIM RESEARCH PERFORMANCE REPORT

## SUBMITTED JULY 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**

Worked with NMDP Marketing Team to take drafted guidelines and format in a more professional (polished) manner. Finalization of the product is delayed due to organizational focus on SARS CoV-2 virus response.

**Project: Hematologic Laboratory Surge Network Exercise and Plan Development**

Finalized the after action report summarizing the results of the Medical Response Workshop with the Chicago Hospital Coalition held on February 28, 2020. Finalization of this was delayed due to organizational focus on SARS CoV-2 virus response.

**Projects: Local Public Health Radiological Preparedness Gap Review and Tool Development Identification & Radiological Disaster Webinar Training Series for Inexperienced Public Health Staff**

Complete.

### 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.**

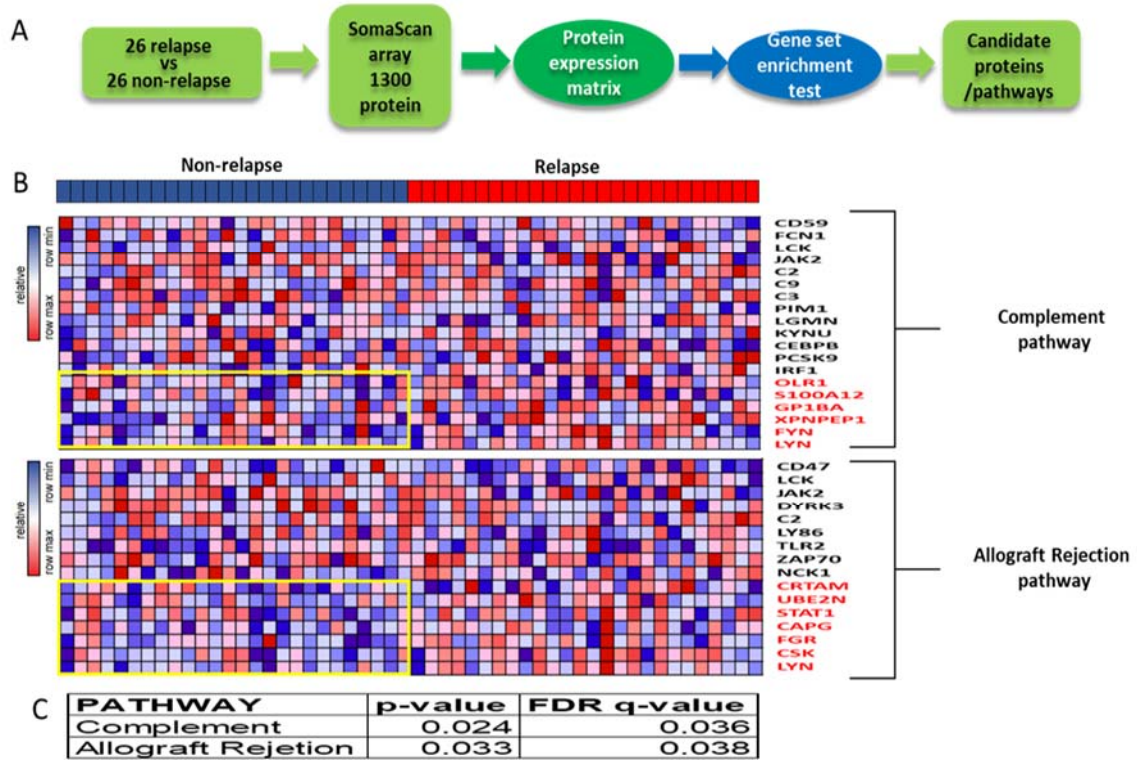
**Project: Evaluation and identification of whole genome donor-recipient pair variation and donor-specific DNA methylation patterns that affect HCT outcomes**

*Results from proteomics study on Pilot cohort*

In the proteomic analysis, no single protein was identified as a statistically significant candidate marker for patient outcome of disease relapse vs. non-relapse after transplant. However, with gene set enrichment analysis (GSEA), the "HALLMARK COMPLEMENT" and "HALLMARK

ALLOGRAFT_REJECTION" pathways were statistically enriched for associations in the patient group (p value<0.05, FDR<0.05) (Figure 1).

**Figure 1.** Candidate pathways from proteomics enrichment analysis on MDS outcome association tests. A. The workflow of proteomics analysis. B. Protein expression heatmap for two representative pathways: complement pathway and allograft rejection pathway; Differentially expressed proteins between non-relapse and relapse groups are highlighted by red color. C. The normal p value and FDR q value for complement pathway and allograft rejection pathway.




C

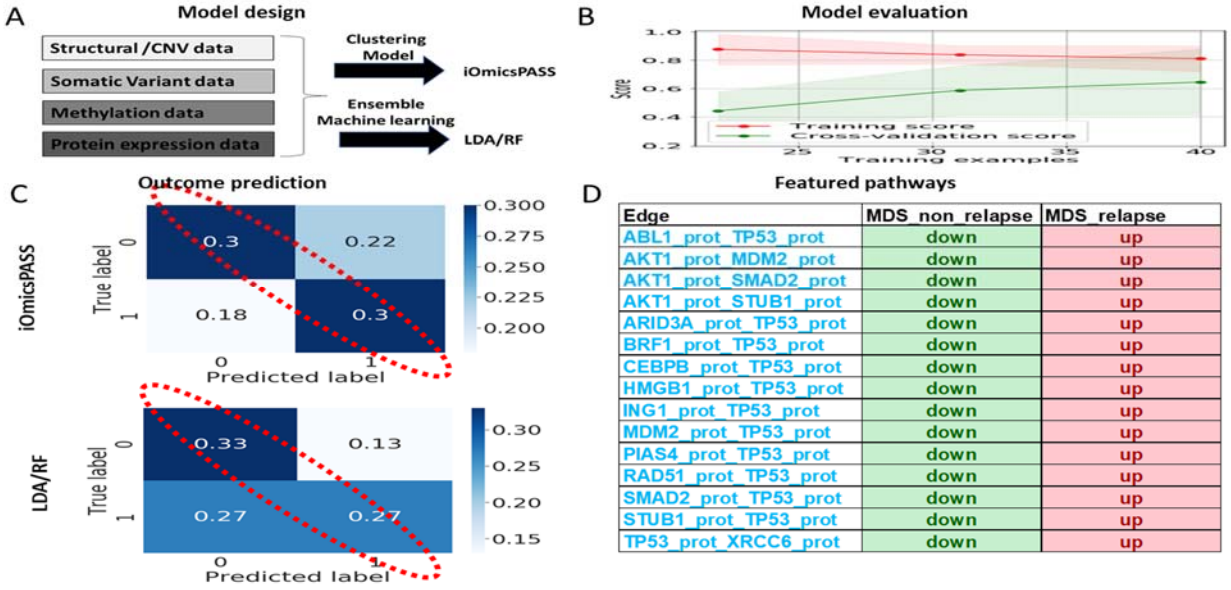
| PATHWAY | p-value | FDR q-value |
|---|---|---|
| Complement | 0.024 | 0.036 |
| Allograft Rejetion | 0.033 | 0.038 |

*Integrative analysis results on Pilot cohort*

In the iOmicsPASS analysis, multiple subnetwork edges from TP53 and AKT pathways were enriched in MDS relapse groups, consistent with our findings from genomics enrichment tests. However, the overall accuracy of MDS outcome prediction in the iOmicsPASS model was relatively low at 60% with 5-fold cross-validation (Figure 1). One likely reason is due to sample size limitation of our MDS study and the heterogenicity of MDS disease. It is noteworthy that the majority of enrichment signals were derived from the proteomics data.

In Ensemble machine learning analysis, the AUC of MDS outcome prediction from LDA/RF were around 65% with 5-fold cross-validation and slightly better than iOmicsPASS (Figure 2). There were minimal performance differences among various machine learning algorithms. Interestingly, recursive feature elimination indicated that the most important features come from the proteomics data. Note that the learning curve plot shows a converging trend between training and testing data when sample size increases (Figure 2).

**Figure 2.** Comparable accuracies from different modeling approaches using multi-Omics data on MDS outcome prediction. A. The workflow of MDS multi-omics data integrating and modeling analysis. B. Learning curve evaluation of MDS predictive model from Ensemble machine learning. C. The performance comparison between iOmicsPASS and Ensemble machine learning by confusion matrix. D. Important subnetwork features in TP53 / AKT signal pathways from iOmicsPASS analysis.




| Edge | MDS_non_relapse | MDS_relapse |
|---|---|---|
| ABL1_prot_TP53_prot | down | up |
| AKT1_prot_MDM2_prot | down | up |
| AKT1_prot_SMAD2_prot | down | up |
| AKT1_prot_STUB1_prot | down | up |
| ARID3A_prot_TP53_prot | down | up |
| BRF1_prot_TP53_prot | down | up |
| CEBPB_prot_TP53_prot | down | up |
| HMGB1_prot_TP53_prot | down | up |
| ING1_prot_TP53_prot | down | up |
| MDM2_prot_TP53_prot | down | up |
| PIAS4_prot_TP53_prot | down | up |
| RAD51_prot_TP53_prot | down | up |
| SMAD2_prot_TP53_prot | down | up |
| STUB1_prot_TP53_prot | down | up |
| TP53_prot_XRCC6_prot | down | up |

In summary, the results indicate that our MDS predictive analysis on the pilot cohort is consistent between different platforms but significantly underpowered. Application of this methodology to the larger cohort appears promising and potential additional proteomics data acquisition and analysis may be beneficial.

## 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 completed

design and build of a core PRO instrument for adult transplant and CAR-T patients and have automated data transmission between FormsNet and the ePRO system to automate identification of eligible patients. In the final quarter of this grant, we anticipate completing the following activities:

- 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.
- Launch core PRO collection with adult patients at four pilot centers.

**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.

**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>

- Production environment updated with industry-standard security and authentication.
- Ongoing use of CIBMTR Reporting App by Ohio State University within their production environment
    - All new patient registrations occur via the App
        - Electronic data exchange has allowed data managers to identify and correct historic manual data entry issues
    - Ongoing exchange of acute graft versus host disease observations

- Successfully processed production recipient HLA typing from Moffitt Cancer Center via the HML2FHIR Converter; data was consumed into the CIBMTR FormsNet database.
- Collaboration ongoing with CIBMTR FN3 Team to move 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 we 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 |
| Ann Jakubowski | Janelle Olson | Michelle Formanek |
| Paul Auer | Jason Brelsford | Peter Tonellato |
| Bill Burgess | Jason Dehn | Robert Milius |
| Bronwen Shaw | Jen Venero | Robinette Renner |
| Caleb Kennedy | Joel Schneider | Stephen Spellman |
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| Christine Kofstad-Johnson | Julia Tkachenko | Wael Saber |
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| Curt Mueller | Kirt Schaper | Xiaoyun (Wendy) Zhang |
| Cynthia Vierra-Green | Lloyd McKenzie | Yung-Tsi Bolon |
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| Dawn Lyons | Martin Maiers | |