REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
7-16-2019	Interim Technical Report	April - June, 2019

4. TITLE AND SUBTITLE
Development of Medical Technology for Contingency Response to Marrow Toxic Agents – Interim Technical Report with SF298 April 1, 2019 – June 30, 2019

5a. CONTRACT NUMBER
N/A

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

5c. PROGRAM ELEMENT NUMBER
N/A

6. AUTHOR(S)
Maiers, Martin

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)
National Marrow Donor Program
500 N. 5th St.
Minneapolis, MN 55401-1206

8. PERFORMING ORGANIZATION REPORT NUMBER
N/A

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

Office of Naval Research
875 N. Randolph Street, Suite 1425
Arlington VA 22203-1995

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			Dennis L. Confer, MD – Chief Medical Officer
U	U	U		10	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 JULY 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

Held review meeting on May 22-23, 2019 in Washington, DC to review the draft Cytokine Triage Guidelines and collect feedback on necessary components. This was conducted in coordination with the National Alliance for Radiation Readiness (NARR), operated by the Association of State and Territorial Health Officials (ASTHO), the workshop identified discrepancies in plans and determined updates for the distribution and administration of cytokines to casualties following the detonation of an improvised nuclear device in the United States. Outcomes, updated SOPs and the RITN Cytokine Triage Guidelines will be published in the late summer/early fall.

Project: Hematologic Laboratory Surge Network Exercise and Plan Development

Initiated coordination with three cities 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.

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

Complete.

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

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 three main areas with regard to preparation for outcomes analysis of donor-recipient pair whole genome variation and DNA methylation:

1. genomics/omics platform and tool development,
2. pilot data analysis,
3. sample preparation and shipment to laboratories.

A new serverless pipeline was developed in the Genomic Data Repository to automate processing of whole genome sequencing data input to alignment and annotation output (Figure 1) using Amazon Web Services in the cloud computing environment.

Tool	Input	Output
Isaac	2 FastQs(L1R1 and L1R2), Reference	bam, bam.bai, bam.md5
Strelka	bam, bam.bai, reference	vcf.gz
Samtools	bam, reference	bam.stats
SnpEff	vcf.gz, reference	anno.vcf

Figure 1: Serverless pipeline developed that transforms whole genome sequencing data input into annotated output with automated step functions and batch options.

Whole Genome Sequencing and Reduced Representation Bisulfite Sequencing data in .fastq data formats were received from the Genomic Sciences and Precision Medicine Center at the Medical College of Wisconsin for the pilot subset (188 samples) to enable quality control analysis and reprocessing with the latest genomic reference data. Statistics on quality scores and methylation coverage are shown in Figures 2 and 3.

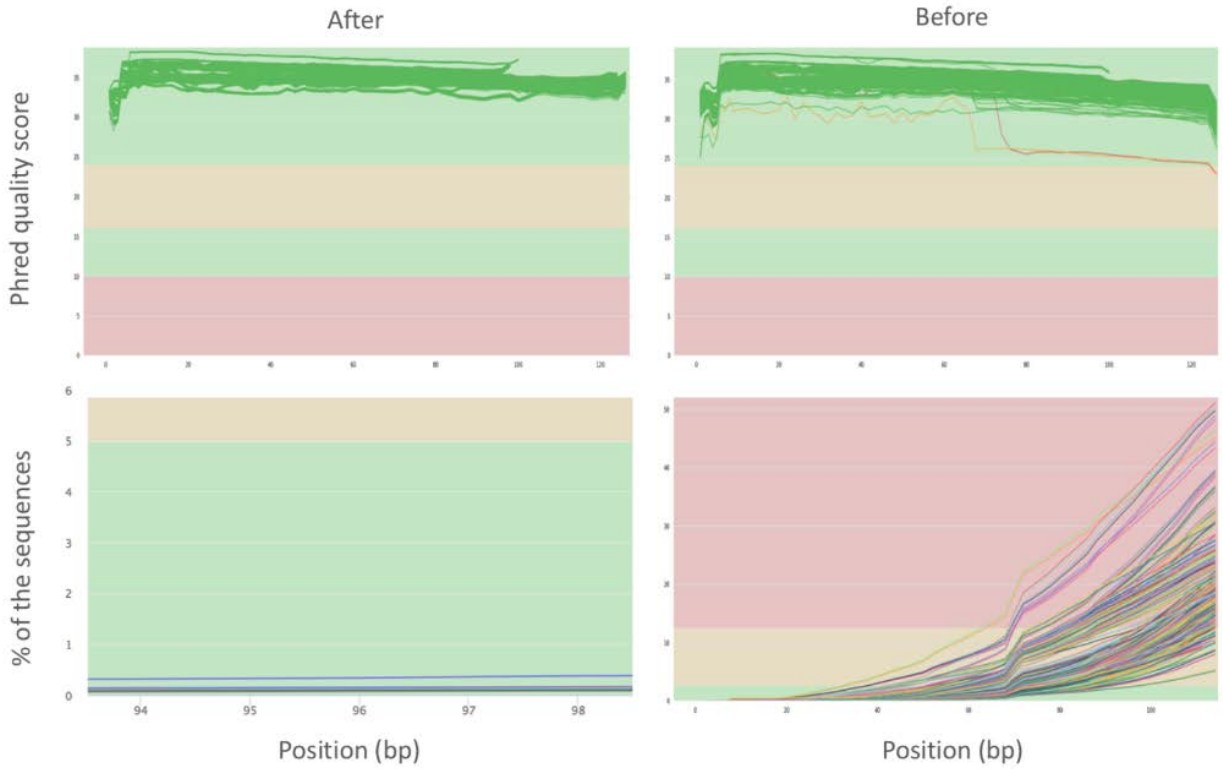


Figure 2: Quality control graphs before and after adapter trimming based on .fastq read files. Plots on the left show that all reads have high phred (a measure of the quality of the identification of the nucleobases generated by automated DNA sequencing) scores without adapter contamination.

DNA samples (500 patient samples and 500 donor samples) were prepared and shipped to the Broad institute for whole genome sequencing results. In addition, DNA for 1188 samples was shipped to the University of Minnesota for genome-wide methylation chip processing. Preparations for downstream processing of both anticipated datasets are underway.

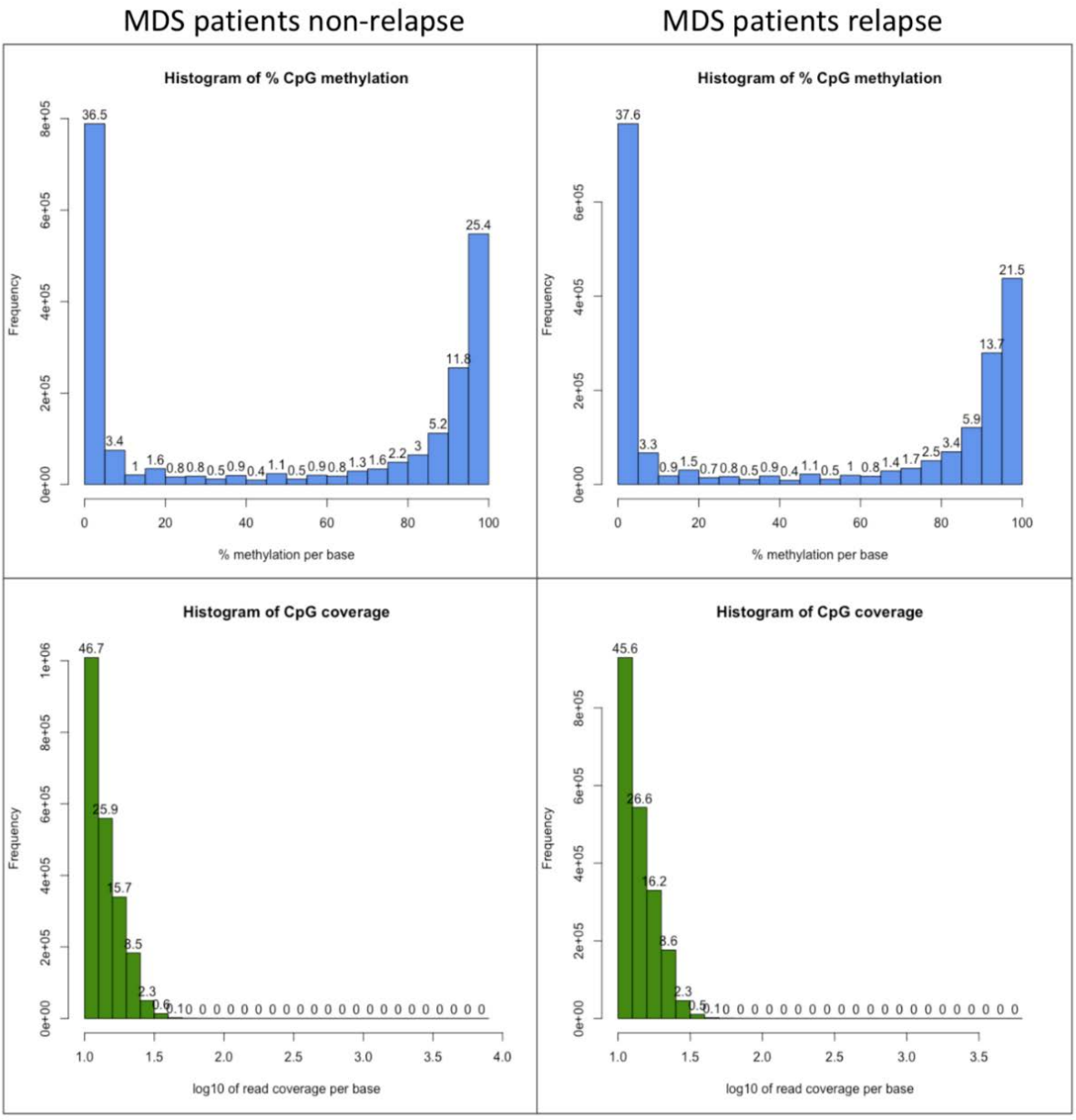


Figure 3: Overall statistics on frequency of different levels of % CpG methylation per base in Myelodysplastic syndrome patients without relapse of disease vs. patients with relapse.

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

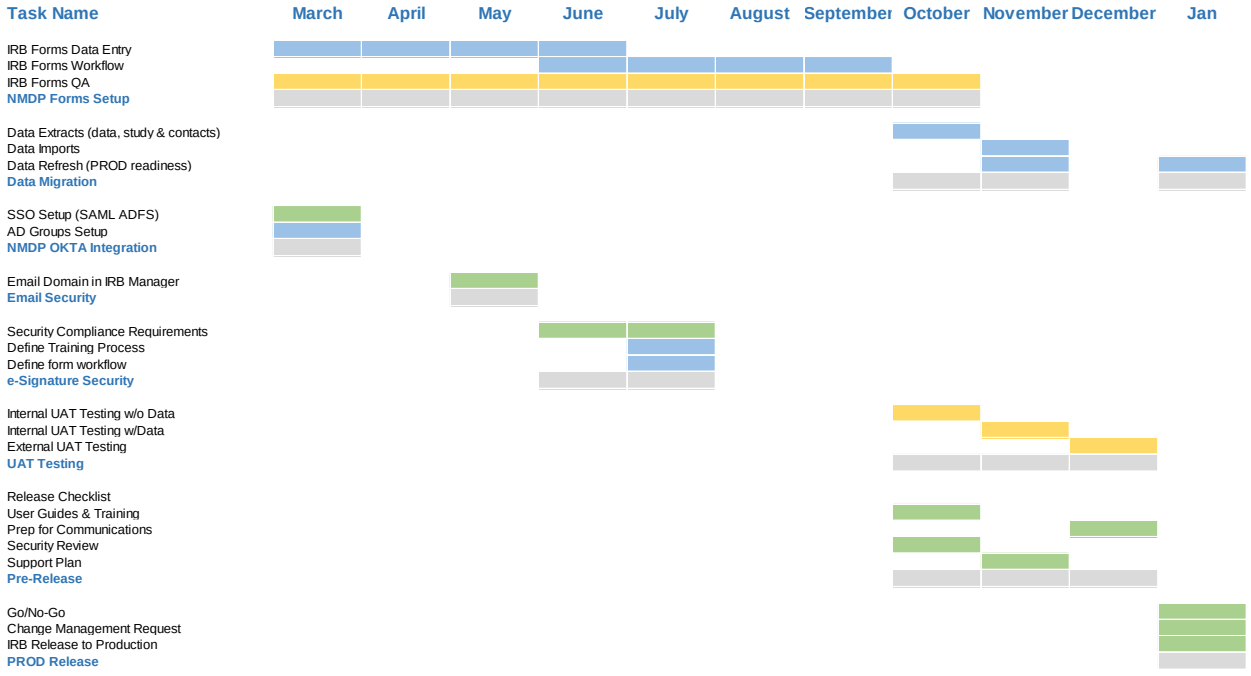
The pilot study is complete, finishing this project.

Project: Development of a Regenerative Medicine Registry

The Regenerative Medicine initiative continued to make progress with developing infrastructure for RM data collection during this period. Specifically work began on the first pilot project: use of umbilical cord blood units for neurological indications. UCB infusion for Stroke (cerebro-vascular accidents) was selected, but work on cerebral palsy and autism will begin in the next period. The RM coordinator is building a data dictionary based on the 'stroke' case-report forms and performing a cross walk with existing CIBMTR data dictionaries. She is analyzing data elements to determine the best methods for data capture and integration in the database. She and other members of staff will attend the Cord Blood Connect meeting in September 2019 to share findings and plan next steps.

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

In May 2019 the project plan for IRB Manager implementation was finalized. We will release the software to the users in January 2020. Work is continuing on IRB forms development, workflow management, and QA testing. So far, three IRB forms have been developed and tested.

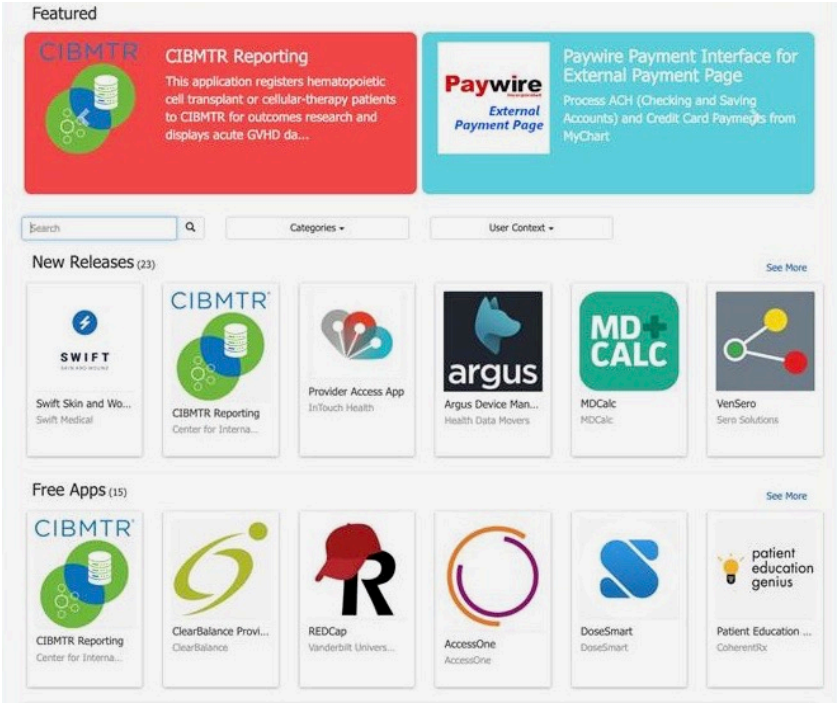


Project: Support for developing HL7 Fast Healthcare Interoperability Resources (FHIR) tools to enhance interoperability of AGNIS® with Electronic Medical Records

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. Implemented architectural requirements in the development of a secure Development Server, Quality Assurance Server and Testing Server for partner organizations.
2. Applied secure authorization and authentication layers.
3. Version 0.1 of the Client App was published in the Epic App Orchard and released for use. This version allows patient registration, assignment of a unique patient registration number, and the display of key outcome data (graft vs. host disease observations).



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 updated application to potential partner transplant centers.
6. Generation of validated FHIR bundles of HLA typing data.
7. Initial development of infrastructure to permit HLA data exchange.

Remaining scope to be delivered:

1. Consult FHIR SMEs to ensure conformance with established FHIR standards.
2. Collaborate with partner transplant centers to identify additional enhancements to the client application.
3. Development and release of Production server environment.
4. Refinement of security layers for FHIR server interaction.
5. Refinement of security layers for interactions with CIBMTR services.
6. Integration of client application into data ecosystem of partner transplant center for test-level data exchange.
7. Integration of client application into data ecosystem of partner transplant center or production-level data exchange.
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 – 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
Christina Jobe	Josh Mandel	Tom Wiegand
Christine Kofstad-Johnson	Julia Tkachenko	Wael Saber
Cullen Case	Julia Udell	Wei Wang
Curt Mueller	Kirt Schaper	Xiaoyun (Wendy) Zhang
Cynthia Vierra-Green	Lloyd McKenzie	Yung-Tsi Bolon
Deborah Mattila	Marcelo Pasquini	
Dawn Lyons	Martin Maiers	