NATIONAL MARROW DONOR PROGRAM®

Entrusted to operate the C.W. Bill Young Cell Transplantation Program,
including Be The Match Registry®

July 29, 2011

CDR Sheri Parker
Office of Naval Research (ONR 342)
875 N. Randolph St.
Arlington, VA 22203-1995

Subject: **Quarterly Performance/Technical Report of the National Marrow Donor Program®**

Reference: Grant Award #N00014-10-1-0204 between the Office of Naval Research and the National Marrow Donor Program

Dear Cdr. Parker:

Enclosed is subject document which provides the performance activity for each statement of work task item of the above reference for the period of April 1, 2011 to June 31, 2011.

Should you have any questions as to the scientific content of the tasks and the performance activity of this progress report, you may contact our Chief Medical Officer – Dennis L Confer, MD directly at 612-362-3425.

With this submittal of the quarterly progress report, the National Marrow Donor Program has satisfied the reporting requirements of the above reference for quarterly documentation. Other such quarterly documentation has been previously submitted under separate cover.

Please direct any questions pertaining to the cooperative agreement to my attention at 612-362-3403 or at cabler@nmdp.org.

Sincerely,

Carla Abler-Erickson

Carla Abler-Erickson, MA
Sr. Contracts Representative

Enclosure: Quarterly Report with SF298

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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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NATIONAL MARROW DONOR PROGRAM®

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Grant Award N00014-10-1-0204

QUARTERLY
PERFORMANCE / TECHNICAL REPORT
FOR
APRIL 01, 2011 to JUNE 30, 2011
PERIOD 5

Office of Naval Research

And

The National Marrow Donor Program
3001 Broadway Street N.E.
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QUARTER PROGRESS REPORT

Development of Medical Technology for Contingency Response to Marrow Toxic Agents

April 01, 2011 through June 30, 2011

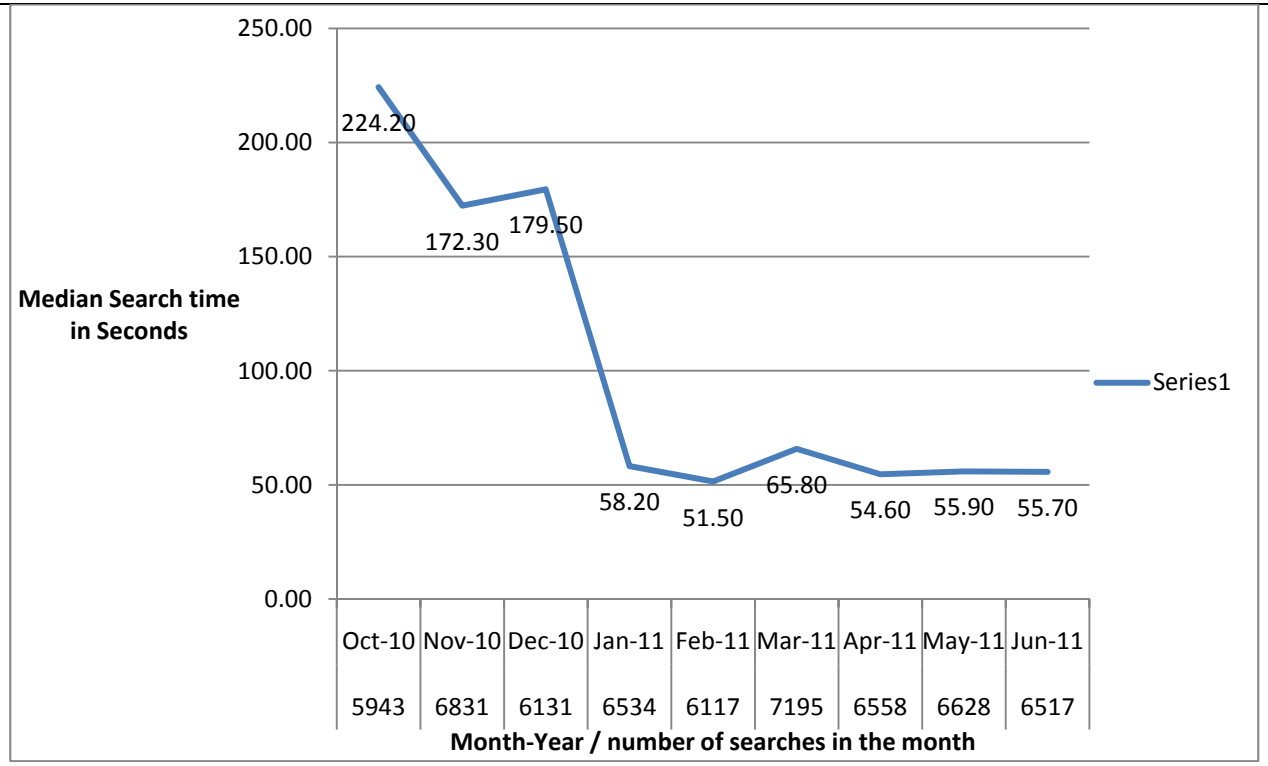
TABLE OF CONTENTS

IIA. Contingency Preparedness – Objective 1: Recovery of casualties with significant myelosuppression following radiation or chemical exposure is optimal when care plans are designed and implemented by transplant physicians	
IIA.1 Task 1: Secure Interest of Transplant Physicians	**Period 5 Activity:** • No activity this quarter.
IIA.1 Task 2: GCSF in Radiation Exposure	**Period 5 Activity:** • No activity this quarter.
IIA.1 Task 3: Patient Assessment Guidelines and System Enhancements	**Period 5 Activity:** • No activity this quarter.
IIA 1 Task 4: National Data Collection Model – This task is closed.	
IIA. Contingency Preparedness – Objective 2: Coordination of the care of casualties who will require hematopoietic support will be essential in a contingency situation.	
IIA.2 Task 1: Contingency Response Network	**Period 5 Activity:** • Learning Management System (LMS) web based education system implementation project: o LMS system requirements were identified with key stakeholders of the organization. o Research on LMS vendors was conducted. o RFQs were issued. o Three were selected for demonstration - Taleo Learn, Saba and SumTotal - all three have been moved on in the process to Proof of Concept and System Integration demonstration that began in mid-July. • REAC/TS o Coordinated the training of 24 RITN center staff on Advanced Medical Radiation Response to be held at the Radiation Emergency Assistance Center and Training Site in Oakridge, TN.

	Eight of these attendees are physicians.
IIA.2.2 Task 2: Sibling Typing Standard Operating Procedures	**Period 5 Activity:** • No activity this quarter.
IIA. Contingency Preparedness – Objective 3: NMDP's critical information technology infrastructure must remain operational during contingency situations that directly affect the Coordinating Center.	
IIA.3 Task 1: I.S. Disaster Recovery	**Period 5 Activity:** • No activity this quarter.
IIA.3 Task 2: Critical Facility and Staff Related Functions	**Period 5 Activity:** • Received critical business continuity equipment to ensure key staff can access NMDP systems from up to ten remote non-NMDP locations. The equipment will be secured at the NMDP Data Center.
IIB. Rapid Identification of Matched Donors – Objective 1: Increasing the resolution and quality of the HLA testing of volunteers on the registry will speed donor selection.	
IIB.1 Task 1: Increase Registry Diversity	**Period 5 Activity:** • During this quarter NMDP staff continued to manage the HLA Typing of Registry Donors program, worked on registry file maintenance and analysis, and continued work on HLA discrepancy resolution.
IIB.1 Task 2: Evaluate HLA-DRB1 High Res typing – This task is closed.	
IIB.1 Task 3: Evaluate HLA-C Typing of Donors – This task is closed.	
IIB.1 Task 4: Evaluate Buccal Swabs	**Period 5 Activity:** • No activity during this quarter.

<table>
<tr><td>IIB 1 Task 5:
Enhancing HLA Data for Selected Donors</td><td>Period 5 Activity:
AB only donor DRB1 typing Project
A project which adds DRB1 typing to donors with AB only registry typing was initiated this quarter.
Goals for this study include:
1) Determining if the selection practice of AB only donor testing for searching patients who have no 6/6 donor matches at the time of initial search is a good allocation of resources.
2) Whether testing donors from the AB only pool reveals further genetic diversity to the overall registry, allowing new potential donor options for current and future patients with difficult searches.
Methods:
• 2,247 AB only donors were selected for DRB1 typing from 8 weeks of daily queries that identified all NMDP preliminary patient searches meeting these criteria:
o No 6/6 matched donors available
o NMDP AB only donor(s) with repository sample(s) available
• 2,200 AB only samples have been shipped to an NMDP contracted DRB1 recruitment typing lab for testing with a standard 14 day turnaround time. Final shipment will be July 12, 2011.
Results to date on 1,800 tested AB only samples:
• One DRB1 matched project donor with case patient
• Four project donors selected for HR testing (after DRB1 typed) for three non-project patients
HLA testing will continue next period.</td></tr>
<tr><td colspan="2">IIB 1 Task 6: Maintain a Quality Control Program – This task is closed.</td></tr>
</table>

IIB. Rapid Identification of Matched Donors – Objective 2: Primary DNA typing data can be used within the registry to improve the quality and resolution of volunteer donor HLA assignments.	
IIB 2 Task 1: Collection of Primary Data	**Period 5 Activity:** • No activity this quarter.
IIB 2 Task 2: Validation of Logic of Primary Data – This task is closed.	
IIB 2 Task 3: Reinterpretation of Primary Data – This task is closed.	
IIB 2 Task 4: Genotype Lists & Matching Algorithm	**Period 5 Activity:** • This phase of the task is complete with the operationalizing of code to interpret incoming SBT typings on March 30th, 2011.
IIB. Rapid Identification of Matched Donors – Objective 3: Registry data on HLA allele and haplotype frequencies and on the nuances of HLA typing can be used to design computer algorithms to predict the best matched donor.	
IIB.3 Task 1: Phase I of EM Haplotype Logic	**Period 5 Activity:** Prior to First Quarter (Oct. – Dec.) returns on search results were running well over 200 seconds. We have made significant performance improvements. • By implementing foundational platform changes to the matching algorithm, we have increased performance during this reporting period by over 50% since First Quarter. The following chart represents the improved performance.



The completion of the design and development of a haplotype frequency tool allows us to display potential HLA haplotypes (A-C-B-DRB1-DRBX-DQB1) and HLA haplotype pairs based on entered HLA typing. The information is used to determine which haplotypes and alleles are the most likely in each of 26 different race groups. This information is then used to determine which race may have the best chance of matching the patient.

Additionally, current algorithm baselines can now be defined to support subsequent analysis and improvement to the HapLogic III algorithm.

IIB 3 Task 2: Enhancement of EM Algorithm	**Period 5 Activity:** • Completed draft of DPA1-DPB1 haplotype frequencies manuscript
IIB 3 Task 3: Optimal Registry Size Analysis	**Period 5 Activity:** • Submitted Math Model manuscript to the journal BBMT.
IIB 3 Task 4: Target Under- Repre-sented Phenotypes	**Period 5 Activity:** • Completed building a comprehensive database to hold Imputation Experimentation data. Began implementing full-scale imputation algorithm in order to obtain a full load of the data for this database.
IIB 3 Task 5: Bioinformatics Web Site – This task is closed.	
IIB 3 Task 6: Consultants to Improve Algorithm – This task is closed.	
IIB 3 Task 7: Population Genetics – This task is closed.	
IIB 3 Task 8: Haplotype Matching – This task is closed.	
IIB 3 Task 9: Global Haplotype/Benchmark – This task is closed.	
IIB. Rapid Identification of Matched Donors – Objective 4: Reducing the time and effort required to identify closely matched donors for patients in urgent need of HSC transplants will improve access to transplantation and patient survival in the context of a contingency response and routine patient care.	
IIB.4 Task 1: Expand Network Communications	**Period 5 Activity:** • No activity this quarter.
IIB.4 Task 2: Central Contingency Management	**Period 5 Activity:** • Buccal swab kits have been sent to about 148 donors that had no repository sample stored in order to further complete the donor typing for this project. About 26 kits have been returned and of these, 19 donors have had HLA typing completed. In addition, study data looking at the effectiveness of the strategic donor selection portion of the study was submitted and accepted for poster presentation at the

	annual EFI 2011 meeting in May 2011.
IIB.4 Task 3: Benchmarking Analysis – This task is closed.	
IIB.4 Task 4: Expand Capabilities of Collection and Apheresis Centers – This task is closed.	
IIC. Immunogenetic Studies – Objective 1: 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.	
IIC.1 Task 1: Donor Recipient Pair Project	**Period 5 Activity:** Current HLA matching guidelines for unrelated HCT recommend avoidance of mismatches only within the Antigen Binding Domain (ABD). This recommendation is based on the hypothesis that amino acid differences outside the ABD are not immunogenic. The ABD allo-reactivity assessment project will give insight into the allowable percent tolerance of matching needed outside of the ABD. • Initiated investigation of the first class II non-ABD mismatch (DRB1*140101/1454) where both alleles have been seen in the same genotype. Specific queries of the Be The Match Registry allowed for selection of ninety-nine potential donors to be typed at high resolution. • 72 donors were invited to participate in the study. 21 study participants consented and submitted blood samples. • Eleven samples of four different haplotype pairs were shipped to be tested. The testing period of performance is from May 9, 2011 to August 31, 2011.
IIC. Immunogenetic Studies – Objective 2: Even when patient and donor are HLA matched, GVHD occurs so other loci may play a role.	
IIC 2 Task 1: Analysis of non-HLA loci	**Period 5 Activity:** The Immunobiology Project Results (IPR) database and its applications will allow for storage and analysis of all immunogenetic data collected on NMDP research samples. This database has replaced the existing HLA donor/recipient pair's database and facilitates storage and analysis of data from other immunogenetic loci (KIR, microsatellites, single nucleotide polymorphisms, etc).

	• 15 bugs/minor enhancements were completed. These mainly relate to 'look and feel' issues. • Development was completed for a report that lists the 'study' date in a horizontal fashion. • Development was competed for an 'ID Pairs' report. In 2005 a pilot study to perform high resolution KIR gene typing was launched. The primary objectives of the study were to move technology forward from the current practice of locus level typing to high resolution typing, disseminate information and protocols in an open source mechanism and develop reference lines for use in individual laboratories. • 46 novel alleles were fully characterized, submitted and names received. Publication of the new IPD database containing these alleles is expected within the next year. • Preparation continued on the KIR Typing Project manuscript. • Two abstracts were presented at the 2011 KIR workshop in Tammsvik Sweden and one has been accepted for poster presentation at the American Society of Human Genetics.
IIC 2 Task 2: Related Pairs Research Repository – This task is closed.	
IIC 2 Task 3: CIBMTR Integration – This task is closed.	
IID. Clinical Research in Transplantation – Objective 1: Clinical research in transplantation improves transplant outcomes and supports preparedness for a contingency response.	
IID.1 Task 1: Observational Research, Clinical Trials and NIH Transplant Center	**Period 5 Activity:** **Observational Research** • Staff continued work on various observational studies within the area of Immunobiology, GVHD and Graft Sources Working Committees. **Prospective Studies; RCI BMT** • Site monitoring took place during this report period for sites participating on the double cord clinical trial. Monitors completed 2 visits and monitored records of accrued recipients.
IID.1 Task 2: Research with NMDP Donors – This task is closed.	

IID.1 Task 3: Expand Immuno-biology Research	**Period 5 Activity:** The CIBMTR IBWC met monthly during the quarter to discuss progress on ongoing research studies • The scientific director attended the International Cord Blood Symposium and met with investigators to plan upcoming analyses. • Work continued on several draft manuscripts and analyses to be submitted as abstracts in the next quarter. • The CIBMTR Immunobiology Research group held a strategic planning session with senior CIBMTR leadership in late April. The session focused on defining the mission for the group and outlining actionable goals for the coming year. • One abstract was presented: o Katharina Fleischhauer, et al., *No apparent contribution of HLA-DPA1 to the significantly increased risk for non-relapse mortality associated with non-permissive donor-recipient HLA-DPB1 T cell epitope disparities in unrelated stem cell transplant facilitated through the National Marrow Donor Program.* Poster presentation 2011 EFI meeting.

ACRONYM LIST

AABB	American Association of Blood Banks	HR	High Resolution
AFA	African American	HRSA	Health Resources and Services Administration
AGNIS	A Growable Network Information System	HSC	Hematopoietic Stem Cell
AML	Acute Myelogenous Leukemia	IBWC	Immunobiology Working Committee
ABD	Antigen Binding Domain	IDM	Infectious Disease Markers
API	Asian Pacific Islander	IHWG	International Histocompatibility Working Group
ARS	Acute Radiation Syndrome (also known as Acute Radiation Sickness)	IPR	Immunobiology Project Results
ASBMT	American Society for Blood and Marrow Transplantation	ICRHER	International Consortium for Research on Health Effects of Radiation
ASHI	American Society for Histocompatibility and Immunogenetics	IND	Investigational New Drug
B-LCLs	B-Lymphoblastoid Cell Lines	IS	Information Services
BARDA	Biomedical Advanced Research and Development Authority	IT	Information Technology
BBMT	Biology of Blood and Marrow Transplant	IRB	Institutional Review Board
BCP	Business Continuity Plan	JCAHO	Joint Commission on Accreditation of Healthcare Organizations
BCPeX	Business Continuity Plan Exercise	KIR	Killer Immunoglobulin-like Receptor
BMCC	Bone Marrow Coordinating Center	MDACC	MD Anderson Cancer Center
BMDW	Bone Marrow Donors Worldwide	MDS	Myelodysplastic Syndrome
BMT	Bone Marrow Transplantation	MHC	Major Histocompatibility Complex
BMT CTN	Blood and Marrow Transplant - Clinical Trials Network	MICA	MHC Class I-Like Molecule, Chain A
BODI	Business Objects Data Integrator	MICB	MHC Class I-Like Molecule, Chain B
BRT	Basic Radiation Training	MKE	Milwaukee
C&A	Certification and Accreditation	MRD	Minimal Residual Disease
CAU	Caucasian	MSKCC	Memorial Sloan-Kettering Cancer Center
CBMTG	Canadian Blood and Marrow Transplant Group	MSP	Minneapolis
CBB	Cord Blood Bank	MUD	Matched Unrelated Donor

CBC	Congressional Black Caucus	NAC	Nuclear Accident Committee
CBS	Canadian Blood Service	NCBM	National Conference of Black Mayors
CBU	Cord Blood Unit	NCI	National Cancer Institute
CHTC	Certified Hematopoeitic Transplant Coordinator	NEMO	N-locus Expectation-Maximization using Oligonucleotide typing data
CIBMTR	Center for International Blood & Marrow Transplant Research	NHLBI	National Heart Lung and Blood Institute
CIT	CIBMTR Information Technology	NIH	National Institutes of Health
CLIA	Clinical Laboratory Improvement Amendment	NIMS	National Incident Management System
CME	Continuing Medical Education	NK	Natural Killer
CMF	Community Matching Funds	NLE	National Level Exercise
COG	Children's Oncology Group	NMDP	National Marrow Donor Program
CREG	Cross Reactive Groups	NRP	National Response Plan
CSS	Center Support Services	NST	Non-myeloablative Allogeneic Stem Cell Transplantation
CT	Confirmatory Testing	OCR/ICR	Optical Character Recognition/Intelligent Character Recognition
CTA	Clinical Trial Application	OIT	Office of Information Technology
DC	Donor Center	OMB	Office of Management and Budget
DHHS-ASPR	Department of Health and Human Service – Assistant Secretary Preparedness and Response	ONR	Office of Naval Research
DIY	Do it yourself	P2P	Peer-to-Peer
DKMS	Deutsche Knochenmarkspenderdatei	PBMC	Peripheral Blood Mononuclear Cells
DMSO	Dimethylsulphoxide	PBSC	Peripheral Blood Stem Cell
DoD	Department of Defense	PCR	Polymerase Chain Reaction
DHHS-ASPR	Department of Health and Human Services – Assistant Secretary for Preparedness and Response	PSA	Public Service Announcement
DNA	Deoxyribonucleic Acid	QC	Quality control
DR	Disaster Recovery	RCC	Renal Cell Carcinoma
D/R	Donor/Recipient	RCI BMT	Resource for Clinical Investigations in Blood and

			Marrow Transplantation
EBMT	European Group for Blood and Marrow Transplantation	REAC/TS	Radiation Emergency Assistance Center/Training Site
EDC	Electronic Data Capture	RFP	Request for Proposal
EFI	European Federation of Immunogenetics	RFQ	Request for Quotation
EM	Expectation Maximization	RG	Recruitment Group
EMDIS	European Marrow Donor Information System	RITN	Radiation Injury Treatment Network
ENS	Emergency Notification System	SBT	Sequence Based Typing
ERSI	Environment Remote Sensing Institute	SCTOD	Stem Cell Therapeutics Outcome Database
FBI	Federal Bureau of Investigation	SG	Sample Group
FDA	Food and Drug Administration	SLW	STAR Link® Web
FDR	Fund Drive Request	SSA	Search Strategy Advice
FLOCK	Flow Cytometry Analysis Component	SSO	Sequence Specific Oligonucleotides
Fst	Fixation Index	SSP	Sequence Specific Primers
GETS	Government Emergency Telecommunications Service	SSOP	Sequence Specific Oligonucleotide Probes
GCSF	Granulocyte-Colony Stimulating Factor (also known as filgrastim)	STAR®	Search, Tracking and Registry
GIS	Geographic Information System	TC	Transplant Center
GvHD	Graft vs Host Disease	TED	Transplant Essential Data
HCS	HealthCare Standard	TNC	Total Nucleated Cell
HCT	Hematopoietic Cell Transplantation	TSA	Transportation Security Agency
HEPP	Hospital Emergency Preparedness Program	UI	User Interface
HHQ	Health History Questionnaire	UML	Unified Modeling Language
HHS	Health and Human Services	URD	Unrelated Donor
HIPAA	Health Insurance Portability and Accountability Act	WGA	Whole Genome Amplification
HIS	Hispanic	WMDA	World Marrow Donor Association
HLA	Human Leukocyte Antigen	WU	Work-up
HML	Histoimmunogenetics Mark-up Language		