



August 01, 2013

LCDR Christopher Steele
Office of Naval Research
Code 34 – Warfighter Performance
875 N. Randolph St.
Arlington, VA 22203-1995

Subject: Final Report of the National Marrow Donor Program®
Reference: Grant #N00014-08-1-1207 between the Office of Naval Research and the National Marrow Donor Program

Dear LCDR Steele:

In accordance with the requirements of the Referenced Cooperative Agreement, the enclosed subject document is provided as the Final Report for each statement of work task item of the Grant for the period of September 01, 2008 through September 30, 2010.

With this submittal of the Final Report, the National Marrow Donor Program has satisfied the all reporting requirements of the above referenced Grant.

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 Confer, MD directly at 612-362-3425.

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

Sincerely,

Carla Abler-Erickson, M.A.
Contracts Manager

Enclosure: One (1) copy of subject document

C: J. Kabisch – ACO (ONR-Chicago)
Jennifer Ng, PhD – C.W. Bill Young Marrow Donor Recruitment and Research Program
J. Rike - DTIC (Ste 0944)
NRL (Code 5227)
Dr. Robert J. Hartzman, CAPT, MC, USN (Ret)
Dennis Confer, MD – NMDP
Stephen Spellman – NMDP

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National Marrow Donor Program[®] N00014-08-1-1207

**Development of Medical Technology for
Contingency Response
To Marrow Toxic Agents**

FINAL REPORT

September 01, 2008 - September 30, 2010



National Marrow Donor Program® N00014-08-1-1207
HLA Typing for Bone Marrow Transplantation
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ACRONYM LIST

AABB	American Association of Blood Banks
AAFA	African American (NMDP race code)
AAR/IP	After Action Review/Improvement Plan
ABD	Antigen Binding Domain
ABMTR	Autologous Blood and Marrow Transplant Registry
AC	Apheresis Center
ACOG	American College of Obstetricians
AFA	African American
AFB	African
AFRRI	Armed Forces Radiobiology Research Institute
AGNIS®	A Growable Network Information System
AIM	Ancestry Informative Markers
AINDI	South Asian
AISC	American Indian South or Central
ALANAM	Alaska Native or Aleut
ALDH	Aldehyde Dehydrogenase
ALDHbr	Aldehyde Dehydrogenase bright
AMIND	North American Indian
AML	Acute Myelogenous Leukemia
API	Asian Pacific Islander
ARC GIS	ArcGIS is a brand name: GIS = Geographical Information System
ARS	Acute Radiation Syndrome (also known as Acute Radiation Sickness)
ARS	Antigen Recognition Site
ASBMT	American Society for Blood and Marrow Transplantation
ASEATTA	Australian and South East Asian Tissue Typing Association
ASH	American Society of Hematology
ASHG	American Society of Human Genetics
ASHI	American Society for Histocompatibility and Immunogenetics
ASPR	Assistant Secretary for Preparedness and Response
B2B	Business to Business
BAA	Broad Agency Announcement
BARDA	Biomedical Advanced Research and Development Authority
BBMT	Biology of Blood and Marrow Transplantation
BISC	Bioinformatics Integration Support Contract
B-LCLs	B-Lymphocytic Cell Lines
BMCC	Bone Marrow Coordinating Center
BMDW	Bone Marrow Donors Worldwide
BMT	Bone Marrow Transplant/Transplantation
BMT CTN	Blood and Marrow Transplant - Clinical Trials Network
BODI	Business Objects Data Integrator
BRIDG	Biomedical Research Integrated Domain Group

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BRT	Basic Radiation Training
caBIG	NIH/NCI Cancer Biomedical Informatics Grid
caDSR	Cancer Data Standards Repository
C&A	Certification and Accreditation
CARB	Black Caribbean
CARHIS	Caribbean Hispanic
CARIBI	Caribbean Indian
CATI	Computer Assisted Telephone Interviewing
CAU	Caucasian
C&A	Certification and Accreditation
CB	Cord Blood
CBITT	Center for Biomedical Informatics and Information Technology
CBMTG	Canadian Blood and Marrow Transplant Group
CBB	Cord Blood Bank
CBC	Congressional Black Caucus
CBS	Canadian Blood Service
CBT	Cord Blood Transplantation
CBU	Cord Blood Unit
CC	Collection Center
CDC	Centers for Disease Control
CDISC	Clinical Data Interchange Standards Consortium
CEM	Certified Emergency Manager
CEO	Chief Executive Officer
CFO	Chief Financial Officer
CFU	Colony Forming Unit
cGy	CentiGrey
CHTC	Certified Hematopoietic Transplant Coordinator
CHS	Certified Histocompatibility Specialist
CIBMTR®	Center for International Blood & Marrow Transplant Research
CIO	Chief Information Officer
CIT	CIBMTR Information Technology
CLIA	Clinical Laboratory Improvement Amendment
CME	Continuing Medical Education
CMF	Community Matching Funds
CML	Chronic Myelogenous Leukemia
CMO	Chief Medical Officer
CMS	Center for Medicare and Medicaid Services
CTMS	Clinical Trial Management System
COG	Children's Oncology Group
CPI	Continuous Process Improvement
CREG	Cross Reactive Groups
CRID	Unique ID

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CRIS	Computerized Repository Inventory System
CRO	Chief Recruitment Officer
CSF	Colony Stimulating Factors
CSO	Chief Strategy Officer
CSS	Center Support Services
CSS	Custom Search Support
CT	Confirmatory Testing
CTA	Clinical Trial Application
CTAC	Clinical Trials Advisory Committee
CWD	Common Well Documented
DAIT	Division of Allergy, Immunology, and Transplantation
DC	Donor Center
DCAA	Defense Contract Audit Agency
DHHS	Department of Health and Human Services
DIY	Do it yourself
DKMS	Deutsche Knochenmarkspenderdatei
DMSO	Dimethylsulphoxide
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DOE	Department of Energy
D/R	Donor/Recipient
DR	Disaster Recovery
DHHS	Department of Health and Human Services
DQ	Data Quality
DNA	Deoxyribonucleic Acid
DR	Disaster Recovery
D/R	Donor/Recipient
DSA	Donor specific anti-HLA antibody
DSMB	Data Safety Monitoring Board
DVD	Digital Video Disc
EBMT	European Group for Blood and Marrow Transplantation
EC	Ethics Committee
EDC	Electronic Data Capture
EFI	European Federation for Immunogenetics
ELISA	Enzyme-linked Immunosorbant Assay
EM	Expectation Maximization
EMDIS	European Marrow Donor Information System
ENS	Emergency Notification System
ERSI	Environment Remote Sensing Institute
ESRI	Environmental Systems Research Institute
FACS	Fluorescent Activated Cell Sorting
FBI	Federal Bureau of Investigation

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FDA	Food and Drug Administration
FDR	Fund Drive Request
FGM	France Greffe de Moelle
FHCRC	Fred Hutchinson Cancer Research Center
FILII	Filipino
FLOCK	Flow Cytometry Analysis Component
FN2	FormsNet2
Fst	Fixation Index
FWA	Federal-wide Assurance
FY	Fiscal Year
GETS	Government Emergency Telecommunications Service
GCSF	Granulocyte-Colony Stimulating Factor (also known as filgrastim)
GIS	Geographic Information System
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
GVHD	Graft vs. Host Disease
GWAS	Genome Wide Association Studies
Gy	Gray-measure of dose of irradiation
HARPs	HLA Ambiguity Resolution Primers
HAWI	Hawaiian or other Pacific Islander Unspecified
HBCU	Historical Black Colleges and University
HC	Hematopoietic Cell
HCS®	Health Care Standard
HCT	Hematopoietic Cell Transplantation
HEPP	Hospital Emergency Preparedness Program
HHQ	Health History Questionnaire
HHS	Health and Human Services
HIEDFS	HLA Information Exchange Data Format Standards
HIPAA	Health Insurance Portability and Accountability Act
HIS	Hispanic
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HML	Histoimmunogenetics Mark-up Language
HR	High Resolution
HRSA	Health Resources and Services Administration
HSC	Hematopoietic Stem Cell
HSCT	Hematopoietic Stem Cell Transplant
HWE	Hardy-Weinberg Equilibrium
IBMDR	Italian Bone Marrow Donor Registry
IBMTR	International Bone Marrow Transplant Registry
IBWC	Immunobiology Working Committee
ICRHER	International Consortium for Research on Health Effects of Radiation
IDAWG	Immunogenetics Data Analysis Working Group

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IDM	Infectious Disease Markers
Ig	Immunoglobulin
IHIWS	International Histocompatibility Work Shop
IHWG	International Histocompatibility Working Group
IIDB	Immunobiology Integration Database
IIMMS	International Immunomics Society
IMGT	ImMunoGeneTics
ImmPort	Immunology Database and Analysis Portal
IND	Investigational New Drug
IND	Improvised Nuclear Device
IPD	Immuno Polymorphism Database
IPR	Immunobiology Project Results
IRB	Institutional Review Board
IS	Information Services
IT	Information Technology
JAPI	Japanese
JCHO	Joint Commission of Healthcare Organizations
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
KIR	Killer Immunoglobulin-like Receptor
KORI	Korean
LD	Linkage Disequilibrium
LSSG	Life Sciences Strategy Group
LTA	Lymphotoxin Alpha
MALDI-TOF	Matrix-Assisted Laser Desorption/Ionization – Time Of Flight
MBS	Masters of Biological Science
MCW	Medical College of Wisconsin
MD	Medical Doctor
MDACC	MD Anderson Cancer Center
MDS	Myelodysplastic Syndrome
MENAFCA	MidEast/North Coast of Africa
MHC	Major Histocompatibility Complex
MICA	MHC Class I-Like Molecule, Chain A
MICB	MHC Class I-Like Molecule, Chain B
mHAg	Minor Histocompatibility Antigen
MKE	Milwaukee
MOU	Memorandum of Understanding
MRD	Minimal Residual Disease
MSKCC	Memorial Sloan-Kettering Cancer Center
MSP	Minneapolis
MSWHIS	Mexican or Chicano
MUD	Matched Unrelated Donor
NAC	Nuclear Accident Committee

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NAM	Native American
NAMER	North American
NCBI	National Center for Biotechnology Information
NCBM	National Conference of Black Mayors
NCHI	Chinese
NCI	National Cancer Institute
NECEP	New England Center for Emergency Preparedness
NEMO	N-locus Expectation-Maximization using Oligonucleotide typing data
NHLBI	National Heart Lung and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIMA	Non-inherited maternal antigen
NIMS	National Incident Management System
NK	Natural Killer
NL	Netherlands
NLE	National Level Exercise
NLM	National Library of Medicine
NMDP®	National Marrow Donor Program
NNSA	National Nuclear Security Administration
NRP	National Response Plan
NST	Non-myeloablative Allogeneic Stem Cell Transplantation
OB	Obstetrician
OB/GYN	Obstetrics & Gynecology
OCP	Operational Continuity Planning
OCR/ICR	Optical Character Recognition/Intelligent Character Recognition
OHRP	Office of Human Research Protections
OIT	Office of Information Technology
OMB	Office of Management and Budget
ONR	Office of Naval Research
OPA	Office of Patient Advocacy
PA	Physicians Assistant
P2P	Peer-to-Peer
PBMC	Peripheral Blood Mononuclear Cells
PBSC	Peripheral Blood Stem Cell
PCR	Polymerase Chain Reaction
PI	Principle Investigator
POI	Procedures of Interaction
PSA	Public Service Announcement
PT	Proficiency Testing
QAMS	Quality Assurance Membership Services
QARM	Quality Assurance and Risk Management
QC	Quality control

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RadCCore	Radiation Countermeasures Center of Research Excellence
RCC	Renal Cell Carcinoma
RCI	Resource for Clinical Investigations
RCI BMT	Resource for Clinical Investigations in Blood and Marrow Transplantation
RD Safe	Related Donor Safety
REAC/TS	Radiation Emergency Assistance Center/Training Site
REDMO	Spanish Bone Marrow Donor Registry
REMM	Radiation Event Medical Management
RFA	Request for Application
RFP	Request for Proposal
RFQ	Request for Quotation
RG	Recruitment Group
RITN	Radiation Injury Treatment Network
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
SAA	Severe Aplastic Anemia
SBT	Sequence Based Typing
SCAHIS	South/Central American Hispanic
SCAMB	Black South or Central America
SCSEAI	Southeast Asian
SCT	Stem Cell Transplantation
SCTOD	Stem Cell Therapeutics Outcome Database
SG	Sample Group
SLW	STAR Link® Web
SNP	Single Nucleotide Polymorphism
SNS	Strategic National Stockpile
SOA	Service Oriented Architecture
SOP	Standard Operating Procedure
SRB	Survey Research Group
SSA	Search Strategy Advice
SSO	Sequence Specific Oligonucleotides
SSP	Sequence Specific Primers
SSOP	Sequence Specific Oligonucleotide Probes
SSRS	Sample Storage Research Study
STAR®	Search, Tracking and Registry
SWOG	Southwest Oncology Group
TBI	Total Body Irradiation
TC	Transplant Center
TED	Transplant Essential Data
TNC	Total Nucleated Cell
TSA	Transportation Security Agency
TTY	Text Telephone
UCB	Umbilical Cord Blood

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UCBT	Umbilical Cord Blood Transplant
UI	User Interface
UML	Unified Modeling Language
URD	Unrelated Donor
US	United States
USB	Universal Serial Bus
VP	Vice President
VIET	Vietnamese
WebEOC®	Web-based Emergency Operations Center
WGA	Whole Genome Amplification
WHO	World Health Organization
WHO-REMPAN	World Health Organization, Radiation Emergency Medical Preparedness and Assistance Network
WMDA	World Marrow Donor Association
WU	Work-up
XML	Extensible Markup Language
ZKRD	Zentrales Knochenmarkspender – Register für die Bundesrepublik Deutschland

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Executive Summary

In 1986, Congress appropriated funds to begin development of the National Bone Marrow Donor Registry. Today, 24 years later, the National Marrow Donor Program (NMDP), as the contractor for the Registry, has built a racially diverse donor registry of 9 million donors, facilitated more than 43,000 hematopoietic stem cell transplants, developed comprehensive research programs to improve post-transplant outcomes and established a network of transplant centers (TCs) capable of treating casualties resulting from military or terrorist actions, as well as patients suffering from leukemia, aplastic anemia and other life-threatening diseases.

Contingency Preparedness Planning

During this funding period, multiple projects were accomplished to further expand and develop the Radiation Injury Treatment Network® (RITN). Physician and Network staff education opportunities were provided through an educational conference and multiple training sessions. RITN centers were identified as a tertiary care response asset in the federal publication “Planning Guidance for Response to a Nuclear Detonation,” published by a National Security Staff subcommittee. Existing relationships were fortified and new relationships were forged with federal agencies as well as private organizations for contingency response.

The NMDP’s Operational Continuity Plan was tested to ensure continuation of essential operations during a catastrophic disaster affecting the headquarters. Essential communication assets necessary for the NMDP’s emergency operations were updated and periodically tested to ensure ongoing availability when needed.

A Donor Management application was developed and beta tested, focusing on prioritized enhancements for the Navy Contingency project. This project promotes electronic contact with donors via email and allows them to update their contact information and complete an online Health History Questionnaire (HHQ) from the Do It Yourself Donor (DIY) online platform. Information provided by the donor is securely transferred to the donor’s record in the tool to manage Donor Activity, facilitating reporting, storage and review of this information in established donor management systems. The results of this initial implementation proved to be a resounding success and have saved thousands of man-hours.

Rapid Identification of Matched Donors

Published research data have clearly defined the relationship between Human Leukocyte Antigen (HLA) matching and optimal patient outcomes following unrelated adult donor transplantation. Continually working to increase the genetic diversity of the Registry helps to ensure that more patients will be able to locate a suitably matched stem cell product for a transplant. During this time period, NMDP donor centers, including Department of Defense (DoD) and recruitment

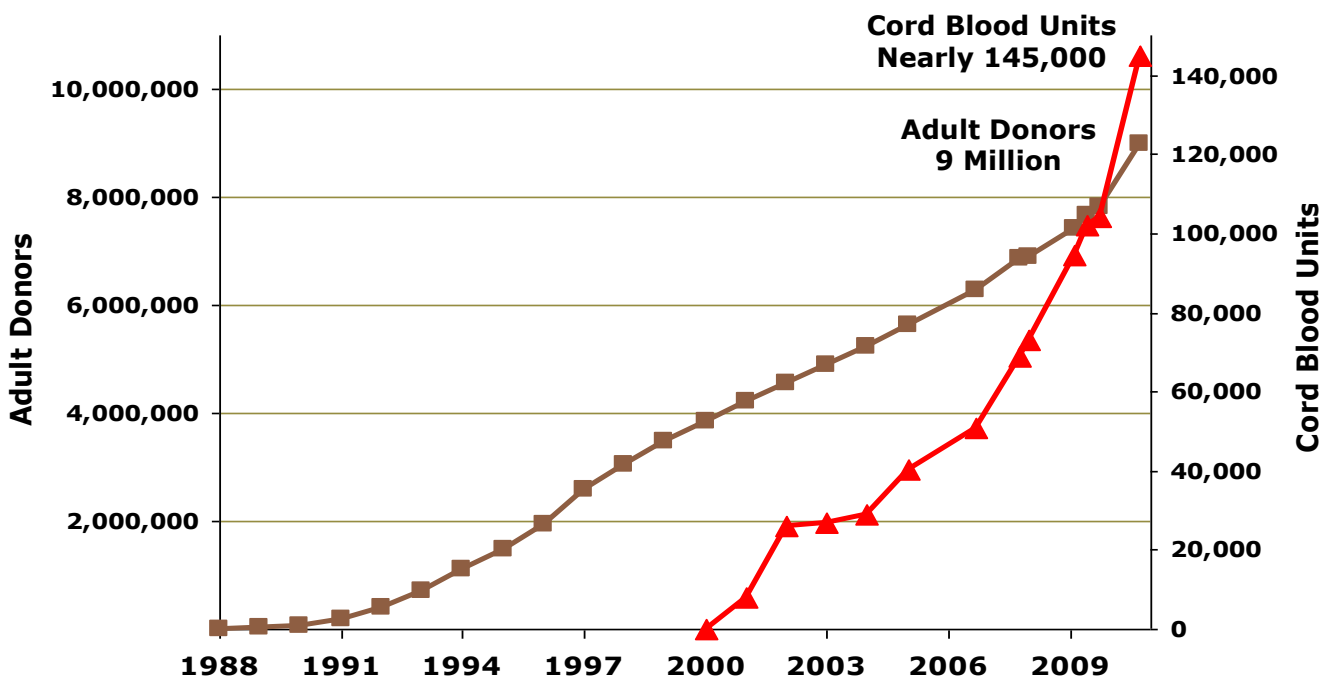
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groups, recruited 228,580 minority race and 252,509 Caucasian donors, for a total of 481,089 U.S. donors added to the Registry. Navy funding contributed to the addition of 113,228 new, culturally diverse donors, with 40,963 of these donors being minorities. All donors were typed for HLA-A, B and DRB1.

Advances in laboratory methods and technology continue to have a positive impact on lab performance and pricing. As of September 2010:

- 84% of new donors received higher than intermediate HLA-A, B typing
- 100% of new donors received higher than intermediate HLA-DRB1 typing
- 45% of new donors received intermediate HLA-C typing
- Blind quality control testing error rate was 0.1%, exceeding the project requirement of $\leq 2.0\%$.
- On-time testing completion rate was 98%, meeting the project requirement of a minimum of 90% of typing results reported within 14 days of shipment of samples.
- The cost of HLA typing continues to decrease as technology improves; during the period September 2008 through September 2010 the average price per sample was approximately \$40.00 compared to \$134.75 in 1997, which represents a decrease of over 70%.

Registry Growth: Adult Donors and Cord Blood Units



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Immunogenetic Research

The high resolution HLA typing of paired donor and recipient samples continued to provide substantive data to increase the understanding of the impact of HLA matching on patient outcome. The project data were also used to assess genetic diversity within the NMDP transplant population and Registry, and fed into the HapLogic matching algorithm. Testing was completed on an additional 837 donor/recipient pairs during the project period, bringing the total enrolled to over 14,800. Work also continued on the development of the Immunobiology Project Results (IPR) database, an application that supports the capture and validation of results generated on the research samples. Data generated through the project are utilized in all unrelated donor research studies conducted through the Center for International Blood and Marrow Transplant Research (CIBMTR). The project has developed the largest, fully validated pool of unrelated stem cell transplant donor-recipient HLA data in the world and is an unparalleled resource for transplant research. The data generated through the project have had a major impact on the evolution of the NMDP HLA matching requirements.

Current HLA matching guidelines for unrelated Hematopoietic Cell Transplantation (HCT) recommend avoidance of mismatches only within the antigen recognition site, i.e. exons 2 and 3 for HLA class I and exon 2 for HLA class II. This recommendation is based on the hypothesis that amino acid differences outside the antigen recognition site are not immunogenic. The Antigen Recognition Site Allo-reactivity Assessment Project will give insight into the allowable tolerance of matching needed outside of this binding region. Work was initiated to identify specific mismatches for evaluation in the project.

Clinical Research in Transplantation

Improving strategies to avoid and manage graft-versus-host disease (GVHD) is an essential step in improving the outcomes of transplantation and, consequently, the ability to incorporate transplantation as an effective therapy into a variety of settings, including contingency situations. The goal of the research activities funded through this grant has been to increase the understanding of the immunologic factors important in HCT.

During this grant, activities within the Resource for Clinical Investigations in Blood and Marrow Transplantation (RCI BMT) continued. The goal of this program is to provide an avenue for investigators to obtain statistical and data management support for Phase I and II prospective trials focusing on addressing various transplant issues. The following key elements were completed:

- The Clinical Trials Advisory Committee (CTAC) met twice for their annual in person meeting and one conference call meeting during this grant period. The in person meetings occurred at the 2009 and 2010 Tandem meetings. This committee has been charged with providing scientific review and recommendations on clinical trial proposals.

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The committee reviewed a total of 4 proposals of which two were approved to move forward to protocol developments and two denied. One of the approved proposals did not move to protocol development due to lack of funding and PI decision to not move forward with the study at this time.

- Managed all elements of the Adult Double Cord in patients with hematologic malignancies trial. Staff managed accrual, data management and performed site monitoring. At the end of this grant year, a total of thirty eight patients were accrued on this trial giving us a 69% completion rate.
- Staff continued to provide support to the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) PBSC vs Marrow Phase III trial. This support included managing the donor component of the study, and also assisting the BMT CTN in the area of accrual initiatives on the recipient portion of the study. Activities included were:
 - Completion of accrual for a total of 551 donor/recipient pairs
 - Performance of monitoring activities at the donor centers
- During this grant period, the Lenalidomide after allogeneic HCT for Myeloma trial utilized the EMMES data capture system for data management. During this time, defects were identified and staff worked with the trial management system vendor to resolve and make revisions.
- Support included the development and implementation of a protocol for long-term donor follow-up. This work included identifying and streamlining the operational processes needed to implement the protocol October 2010.
- Established internal structure to provide a mechanism to support studies that include a need for survey research functionality. This included hiring of an experienced supervisor with research call center experience and research interview staff. Staff developed processes and procedures to support studies requiring their expertise.

Support of the Observational Research program included statistical hours for managing studies within the Immunobiology, GVHD, and Graft Sources Working Committees. During this grant period, staff performed proposal review, protocol development, data preparation, data analysis, and manuscript preparations. Details regarding the Immunobiology activities can be found in IID1.3 below. The GVHD and Graft Sources Working Committees published 8 manuscripts. During the grant period staff supported progress on over 20 other studies.

Research was conducted with OB/GYN physicians to assess awareness of the option to donate umbilical cord blood to a public cord blood bank, and to understand barriers and motivations to supporting donation. The results will be used to develop educational resources to correct misperceptions that were discovered in the research and to increase OB/GYN physicians' commitment to supporting donation.

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To successfully serve all patients in need of cellular transplantation, the NMDP General Public Engagement team continued to focus on developing and executing strategies and tactics that increase awareness, education and engagement among target audiences to help add diverse and committed members to Be The Match Registry®.

In an effort to improve knowledge of physicians who refer patients for transplantation, an online educational program was developed and promoted. The 4-part educational series on Acute Myelogenous Leukemia (AML) and Myelodysplastic Syndrome (MDS) was accessed by more than 2,000 clinicians, and was intended to help these physicians understand when to recommend and refer their patients for transplantation. Based on the results, a new educational series is in development.

During the grant period, the NMDP Cord Blood Research Subcommittee met monthly via conference call to discuss study priorities and plan analyses and activities. The subcommittee oversaw a Duke and MD Anderson laboratory effort to validate assay methodologies in order to ensure consistent results were generated at both testing sites for a study investigating biomarkers associated with cord blood engraftment. The subcommittee developed educational sessions for the NMDP Council meeting highlighting the increased use of cord blood transplantation in adults and discussing strategies for improving outcomes. The group prepared a white paper detailing recommendations/guidelines for the assessment of new assays (potency or other assays) relevant to cord blood banking and/or transplantation. The subcommittee also finalized a CIBMTR research proposal to evaluate the impact of matching for non-inherited maternal antigens (NIMA) on cord blood transplantation outcomes.

To further stimulate completion of immunobiology studies within the CIBMTR, grant funds were used to provide support to investigators that required supplemental funding to cover research sample access costs. One grant was awarded during the grant period. Grant funds also supported Immunobiology Working Committee (IBWC) leadership outreach activities to promote the activities and resources of the committee to the scientific community. In addition, the IBWC continued work on the >40 active studies in the committee, accepted 6 new proposals, presented 4 abstracts and published/submitted 10 studies.

END – EXECUTIVE SUMMARY

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II.A. Contingency Preparedness – Hypothesis 1:

Recovery of casualties with significant myelosuppression following radiation or chemical exposure will be optimal when care plans are designed and implemented by transplant physicians

Aim A.1.1: Secure Interest of Transplant Physicians

In working to accomplish this Aim, the NMDP focused on the education of transplant physicians and their staff and the inclusion of a subset of physicians in the development of the Radiation Injury Treatment Network® (RITN).

Education of RITN center medical staff has grown into a progressive training program; beginning with the self directed Basic Radiation Training (BRT), then a Medical Grand Rounds on acute radiation syndrome and culminating with Advanced Medical Training on Radiation Emergency Medicine at the Radiation Emergency Assistance Center and Training Site (REAC/TS) in Oak Ridge, Tennessee.

This progression provides additional options for education of staff and allows staff to increase their knowledge about the treatment of radiation injuries as the number of RITN center staff available to perform the Basic Radiation Training continues to decrease due to more and more staff successfully completing this training.

During the performance period, RITN centers were still encouraged to train staff using the NMDP BRT course, which provided physicians and their staff the opportunity to gain a basic understanding of ionizing radiation and its adverse medical affects. The BRT course contains four sections and a 29 question exam that is submitted via the Internet. At the conclusion of this performance period, a total of 2,036 people had successfully completed this training, reflecting a passing rate of 96%; 320 people completed the training during the 2009 calendar year.

During this period of performance, two groups of RITN center staff traveled to Oak Ridge, Tennessee to attend the two-day Advanced Medical Training on Radiation Emergency Medicine course provided at the Radiation Emergency Assistance Center and Training Site facility. This course covers a comprehensive set of topics including:

- Basic Health Physics & Radiation Protection: Part I
- A History of Serious Radiological Incidents: The Real Risk
- Health Physics & Contamination Control: Part II
- Radiation Detection, Monitoring & Protection Laboratory Exercise & Quiz
- Diagnosis & Management of the Acute Radiation Syndrome (ARS)
- Diagnosis & Management of Internal Contamination
- Diagnosis & Management of Acute Local Radiation Injury & Case Review: Yanango Peru

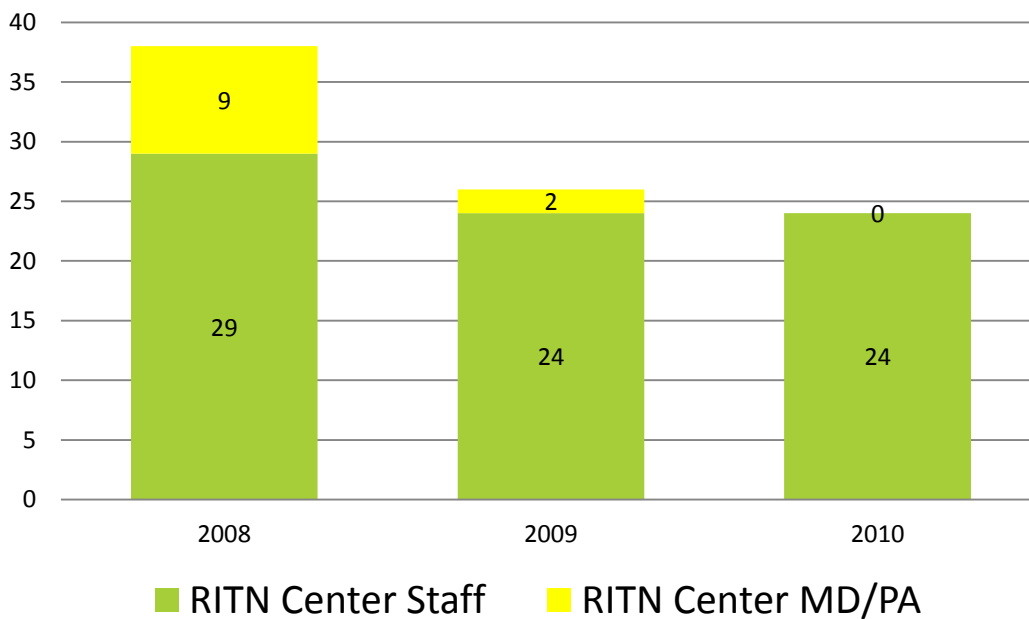
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- Radiation Sources & Radiological Terrorism
- Radiation Emergency Area Protocol Demonstration
- Radiation Emergency Medical Management Drill
- Radiation Dose Estimations – Problem Solving Session

Attendees earn 14 American Medical Association (AMA) PR Award Category 1 CME Credits for attending this course. However, due to the location and course hours, attendees typically must arrive the day prior to the course and depart the day following the completion; this increasingly has made the involvement of physicians difficult, as taking up to four days out of their schedule for training is a significant burden.

Figure 1. REAC/TS Training Attendance

RITN Center Staff Attendance of REAC/TS Advanced Medical Response Training



During this performance period, a RITN educational conference was held in Bethesda, Maryland, on May 18, 2009. This seminar, titled “Nuclear Terrorism: Hematology/Oncology Center Preparedness” drew 92 attendees. Attendees were solicited through the membership lists of American Society for Blood and Marrow Transplantation (ASBMT), American Society of

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Hematology (ASH), Health Physics Society (HPS), as well as physicians from the NMDP Network. Physicians could earn seven CME credits through the Medical College of Wisconsin.

The final seminar agenda consisted of an opening keynote address by RADM Ann Knebel (Deputy Director for Preparedness Planning in the Office of the Assistant Secretary for Preparedness and Response, United States Department of Health and Human Services)

- Morning group sessions included:
 - Threat Scenario Overview
 - National Disaster Medical System
 - Medical Response Expectations 10, 100, 1,000 Miles from Epicenter
 - Altered Standards of Medical Care Overview
 - NMDP Planning and data collection
- Afternoon interactive breakout workgroups included (each session was held three times so attendees could attend all sessions):
 - Altered Standards of Care
 - Logistical issues – bed mgmt, use of non-hospital locations, & staffing issues
 - Provision of medical care – early and late care
 - The conference culminated with a report of findings by the afternoon session moderators

The summary of findings presented many questions that need to be answered by all attendees once back at their institution:

- Altered Standards of Care findings:
 - Are we connected to institutions in our region for supplies, standards, policy and other obligations?
 - Who determines what the standards of care are?
 - Where are the gaps in care? Outpatient-inpatient connections, laboratory, and blood bank.
 - How can RITN become a regional resource?
- Logistical Issues findings:
 - Need to involve hospital administration to affect change.
 - Need to connect with burn centers.
 - Need formal connection to Strategic National Stockpile (SNS) for medications.
 - What is the licensure and liability of retired medical staff “activated” to help?
 - Can the NMDP help with related typing?
- Provision of Medical Care findings:
 - How do you surge to respond for: drugs, blood, beds, and staff?
 - Need to establish SOPs for outpatient care.
 - Do we need standards? What is worth delaying? Do we need a slightly larger inventory to bridge the gap of just in time inventory and what is needed for mass casualty?
 - How is this institutionalized into the hospital management plan, incident response plan, and with regional response plans?

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- How do you make local response agencies activate to respond to a national disaster?

Aim A.1.2: GCSF in Radiation Exposure

This Aim focused on non-transplant treatment guidelines and patient assessment related to the use of Granulocyte-Colony Stimulating Factor (GCSF) for patient treatment as a result of a marrow toxic mass casualty incident such as exposure to ionizing radiation.

No funding was requested under this Aim for the 1207 budget cycle.

Aim A.1.3: Patient Assessment Guidelines and System Enhancements

Donor Management tool application efforts were focused on required features and enhancements for the Navy Contingency project.

The tool provides the ability to electronically contact the donors via email and allows them to:

- Update their contact information
- Complete an online Health History Questionnaire (HHQ) from the Do It Yourself (DIY) donor online platform.

Information provided by the donor is securely transferred to the donor's record in the tool used to manage Donor Activity, facilitating reporting, storage and review of this information in established donor management systems.

Project Outcomes, related to the new versions of the tools used to manage Donor Activity, continue to show favorable results and strong user feedback:

- Donors continue to be responsive to online tools. New Online HHQ functionality resulted in (between 10/1/09 – 6/30/10):
 - 4948 “Completed” HHQs
 - 239 “In Process” HHQs
- Overall time Savings:
 - 1,113 hours saved for completed HHQs
 - 50% reduction in processing time per Online HHQ
- Approximately 40% of donors have given feedback through the email survey process:
 - 94% of donors were able to complete the health questionnaire online
 - Donors rated the following as ‘excellent’
 - Easy to Understand = 94%
 - Convenient = 91%
 - Visual Appeal Appearance = 82%

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During this period of performance, a new version of STAR Link was released to support the Navy Contingency project.

- Sample Tracking – Repository sample storage information is now sent to STAR Link Web. This information will be used to track receipt of returned donor recruitment sample kits. In addition, services have been deployed to send reminder emails back to the donors when they have not returned their kits. This functionality can be extended for contingency donors who have been requested to supply additional samples.

DIY application efforts were focused on project enhancements and preparation for the Navy Contingency project including:

- Kit Requests – System automatically sends sample kit requests after DIY donors register on-line.
- HHQ enhancements:
 - Void Form feature
 - DIY Form Language changes

Navy Contingency Project Pilot

The Event Portal Workflow Management Application is used to manage contingency events. The following features provide the ability to:

- Track preliminary event donors in a central screen, for purposes of donor management.
- Import the preliminary event donors, as identified through the preliminary event daily report.
- Export the preliminary event donors for purpose of supporting address validations, manual mail merges or automated letter merges.

Four donor centers have participated in the pilot. Key statistics gathered to date include

- 426 email requests sent to donors requesting a completed preliminary search HHQ
- 620 HHQs completed
- 211 preliminary search donors activated
- 6 day average close date on an HHQ

The General Release of Event Portal was completed July 2010, and is available to all domestic NMDP Network donor centers, excluding the DoD, DKMS Americas, Gift of Life Registry and Caitlyn Raymond Registry.

During this period of performance, the following project initiation and analysis deliverables to support future releases on the Navy Contingency Project were completed:

- Draft Quality Assurance Plan

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- Draft requirements/use case for iteration 3 (Voids)
- Iteration 4 requirements/use case (Accurint)
- Define/Tag Affected donor requirements/use case
- DIY extension requirements/use case
- Communicate to donors requirements/use case
- Began documenting requirements for manage affected donor requirements/use case

Aim A.1.4: National Data Collection Model

The focus of this AIM was to define and develop a national data collection and management model to collect data resulting from a mass radiological exposure event.

No funding was requested under this Aim for the 1207 budget cycle.

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II.A. Contingency Preparedness – Hypothesis 2:

Coordination of the care of casualties who will require hematopoietic support will be essential in a contingency situation.

Aim A.2.1: Contingency Response Network

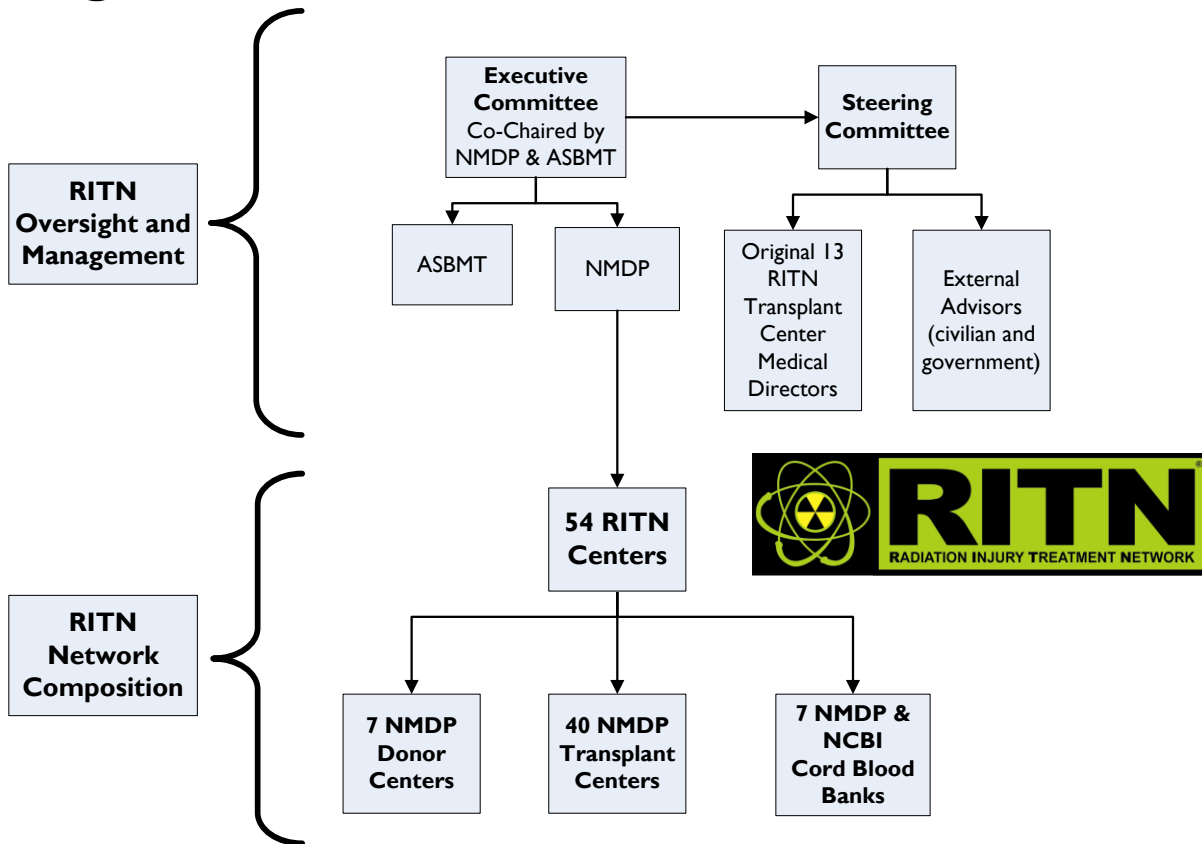
The RITN and its efforts were the focus of this Aim. The RITN was organized to provide comprehensive evaluation and treatment for victims of radiation exposure or other marrow toxic injuries. The RITN develops treatment guidelines, educates health care professionals, works to expand the network, and coordinates situation response. The RITN is a cooperative effort of the NMDP and ASBMT.

RITN centers include transplant centers, donor centers, and cord blood banks. Partner organizations with clinical experts participate through the RITN Steering Committee (see Figure 2 next page) with the medical directors (or their delegate) from the original 13 transplant centers. The RITN Steering Committee typically meets twice a year to discuss the further development of the RITN, its treatment procedures, training materials and other related products. An Executive Committee (comprised of NMDP, ASBMT representatives and technical advisors) meets periodically throughout the year by conference call.

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Figure 2. Organization of RITN

Organization of RITN



The RITN Steering Committee consists of RITN Center transplant physicians, RITN Center staff, experts in the field of transplantation, government and non-governmental partners. During the period of performance multiple opportunities for Committee members to gather were afforded:

- November 2008 – NMDP Annual Council Meeting (Minneapolis, MN)
- February 2009 – ASBMT/CIBMTR Tandem Meetings (Tampa, FL)
- May 2009 – 2009 RITN Educational Conference (Bethesda, MD)
- February 2010 – ASBMT/CIBMTR Tandem Meetings (Orlando, FL)

Outcomes of these meetings included:

- Review of accomplishments since the last RITN Committee Meeting
- Review of activities to be accomplished

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- Overview presentation about the Office of the Biomedical Advance Research and Development Authority (BARDA) from the Department of Health and Human Services Assistant Secretary for Preparedness and Response (DHHS-ASPR)
- Overview presentation about the Joint Task Force – Civil Support by U.S. Northern Command staff
- Determination to explore establishment of connections between RITN and burn centers
- Determination to expand efforts to connect RITN Centers with local or regional emergency preparedness staff

The RITN Executive Committee provides direction for the RITN and accomplishes the bulk of work in preparing products developed in RITN's name pending input from the Steering Committee. The RITN Executive Committee is chaired by a representative from the NMDP and from the ASBMT. During this period of performance an RITN Medical Advisor position was adopted to provide guidance to the Program Manager on medical issues as well as to represent the RITN at conferences, workshops or meetings where RITNs input is desired. There are also other members and technical advisors that support the activities of this committee; as of September 30, 2010 committee composition consisted of:

- Committee Chairs:
 - Co-Chair: Dennis Confer, MD
 - Co-Chair: Nelson Chao, MD
- RITN Medical Advisor:
 - David Weinstock, MD
- Committee Members:
 - ASBMT Representative: Julie Wilhauk, ARNP, AOCNP
 - Transplant Physician: Daniel Weisdorf, MD
 - Transplant Physician: John Chute, MD
 - ASBMT Alternate Representative: Robert Krawisz, MBA
 - RITN Program Manager: Cullen Case Jr., CEM

During this performance period the Executive Committee met by conference call periodically to review and further develop ongoing projects. Some of the notable outcomes of these meetings include:

- Identification of possible bone marrow transplant programs to be invited to join RITN in FY10
- Development of the agenda, content and speakers for the 2009 RITN Conference “Nuclear Terrorism: Hematology/Oncology Center Preparedness”
- Creation of role description for a RITN Medical Advisor
- Development of agendas for Steering Committee meetings
- Coordination of presentations by external subject matter experts at the Steering Committee meetings

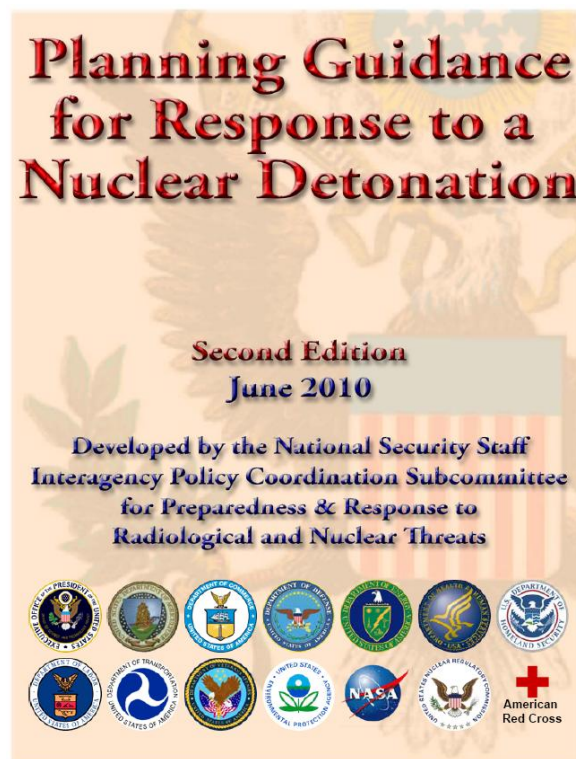
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- Coordination of partnerships with radiation emergency response organizations; including World Health Organization – Radiation Emergency Medical Preparedness and Assistance Network, The European Group for Blood & Marrow Transplantation, AABB, Radiation Emergency Assistance Center and Training Site and the Department of Health and Human Services Assistant Secretary for Preparedness and Response

One key relationship, which is solidified through a Memorandum of Understanding, is the relationship with the DHHS-ASPR. RITN continues to work to meet the needs of a National response guided by input from DHHS-ASPR. The strength of this relationship was evident by the inclusion of RITN in the document “Planning Guidance for Response to a Nuclear Detonation, Second edition, 6/2010” (National Security Staff, Interagency Policy Coordination Subcommittee for Preparedness & Response to Radiological and Nuclear Threats:

<http://www.remm.nlm.gov/PlanningGuidanceNuclearDetonation.pdf>)

This document lays out the concept of operations of how the nation’s response assets will respond to the detonation of a nuclear device on US soil.



Participating RITN centers work to establish and test a documented process to provide intensive supportive care for the treatment of victims from a mass casualty radiological incident with in marrow toxic injuries. To prepare for such an incident RITN centers accomplish tasks to support their preparedness efforts to better respond. Tasks for this grant included; the development or

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improvement of standard operating procedures, training of staff, and participation in an NMDP directed tabletop exercise.

Centers update and improve their standard operating procedures to incorporate organizational or procedural changes and to account for improvements often identified during the tabletop exercise. Each center is provided with two options for training and education of their staff, they can choose whichever fits their organizational structure or staff needs. “Basic Radiation Training” is a self-paced course that staff can complete and submit their answers to the skills assessment online. The other option is to perform a medical grand rounds education session, if selected centers are provided with a standardized course to present to their medical staff. Finally, the tabletop exercise is provided by the NMDP to RITN centers. This exercise presents a scenario for key staff to discuss then each center must submit responses to questions for review.

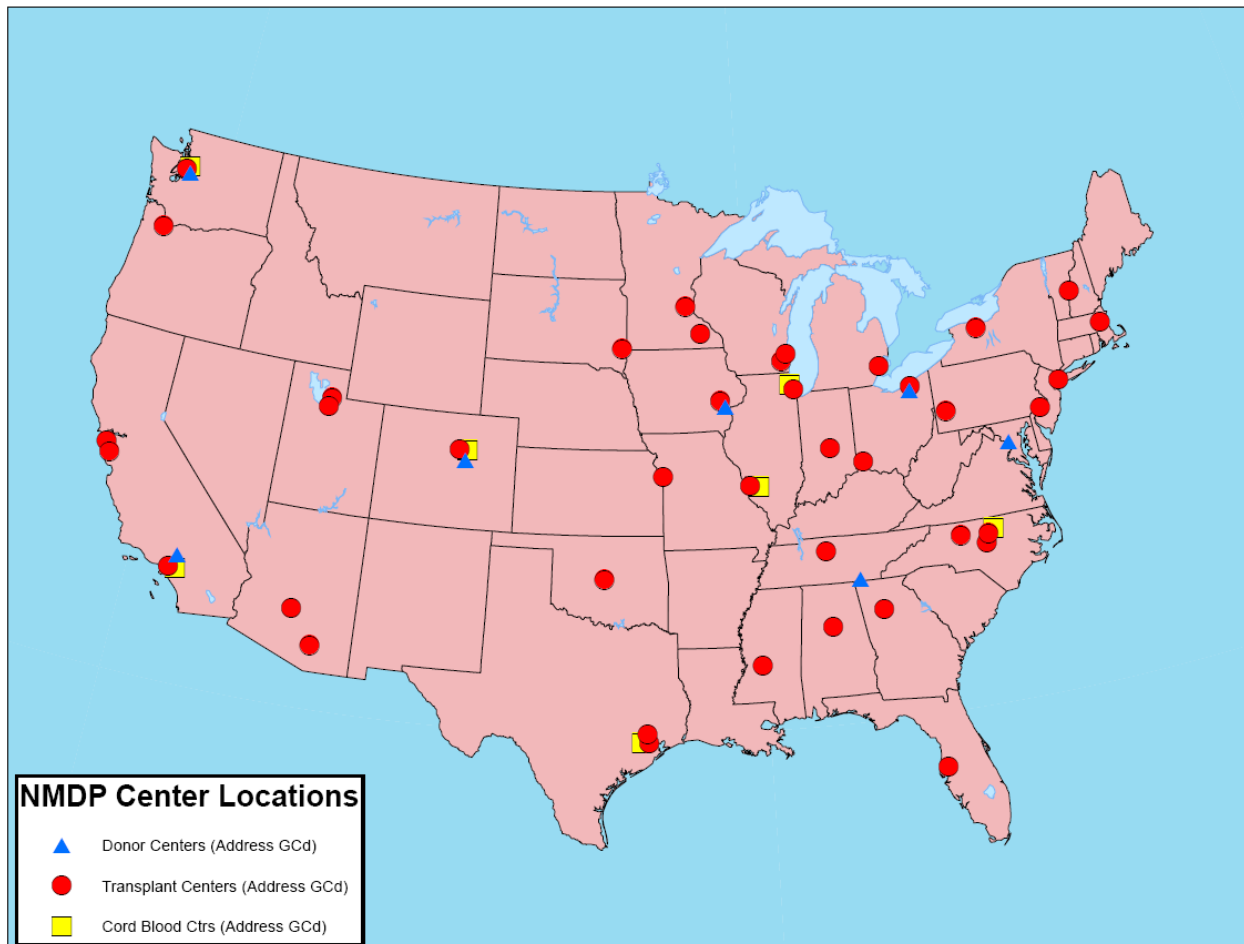
During this grant period, 98% of the RITN centers completed all of their tasks, a slight improvement over the previous grant period.

RITN centers also have incorporated, to the extent practical, the RITN Acute Radiation Syndrome Treatment Guidelines, donor selection criteria, data collection plan, and other related documents developed and updated by the RITN Executive and Steering Committees.

In developing the RITN, the NMDP began in 2005 with 13 transplant centers. These centers have grown to include 54 total participating centers distributed across the United States: 40 transplant centers, seven donor centers, and seven cord blood banks (Figure 3 below depicts the distribution across the United States).

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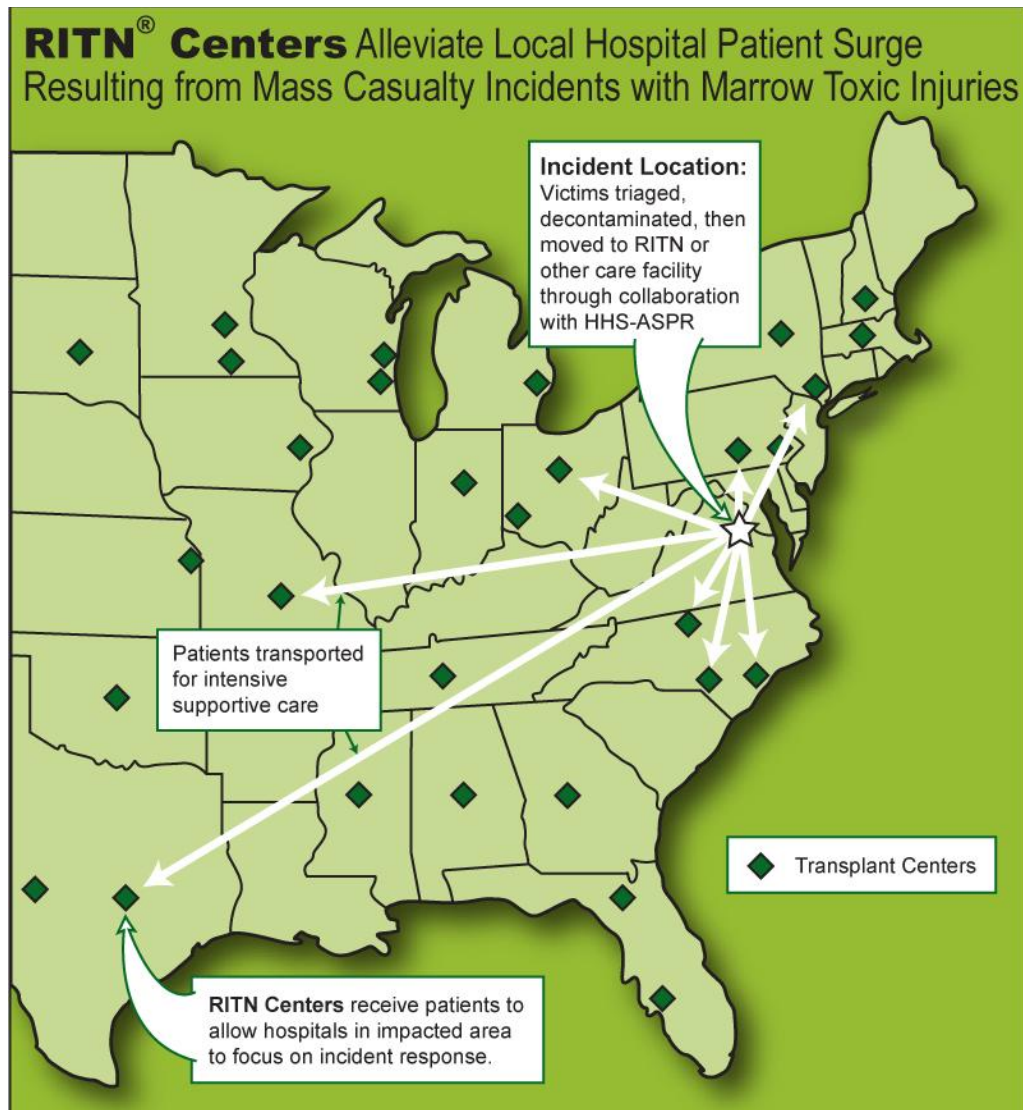
Figure 3. RITN Center Distribution by Type (as of December 2010)



It is very important to keep in mind that the RITN is not a first responder organization. All participating centers voluntarily prepare to respond to an incident that occurs in another city or distant location from their area. The NMDP anticipates that the RITN will receive patients from another part of the country to alleviate their medical load and to provide the best care possible for the victims of a mass casualty incident resulting in marrow toxic injuries (see Figure 4 below).

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Figure 4. RITN Centers



The RITN would not be able to successfully respond to a mass casualty incident without the support of partner organizations. The NMDP has worked diligently to develop and maintain these relationships so that when an event occurs we have established relationships with these key response organizations.

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Two types of partnerships have been developed, formal and informal. Formal relationships are documented through a Memorandum of Understanding (MOU). The NMDP has established formal relationships through an MOU with:

- Office of the Assistant Secretary for Preparedness and Response, DHHS-ASPR
- ASBMT
- American Association of Blood Banks (AABB), through the AABB Inter-organizational Task Force for Disasters and Acts of Terrorism

Organizations that the NMDP has developed informal partnerships with include:

- Radiation Countermeasures Center of Research Excellence (RadCCore) at Duke University
- National Institute of Health-National Institute of Allergy and Infectious Diseases-Division of Allergy, Immunology, and Transplantation (NIH-NAIAD-DAIT)
- National Institutes of Health-National Library of Medicine- Radiation Event Medical Management (NIH-NLM-REMM)
- National Cancer Institute (NCI)
- BARDA
- European Group for Blood and Marrow Transplantation (EBMT), Nuclear Accident Committee
- World Health Organization, Radiation Emergency Medical Preparedness and Assistance Network (WHO-REMPAN)
- REAC/TS

To increase the visibility of RITN and make new connections with additional organizations and agencies, overview presentations were given to various professional groups and government agencies. The groups receiving RITN presentations during this period of performance include:

- 18th Nuclear Medical Defense Conference in Munich Germany (Cullen Case, CEM)
- Advisory Council on Blood Stem Cell Transplantation in Washington, D.C. (Nelson Chao, M.D.)
- RITN poster was presented at the DHHS Integrated Medical, Public Health, Preparedness and Response Training Summit in Dallas, TX
- RITN poster was presented at the 55th Annual Health Physics Society Meeting in Minneapolis, MN

During the 2009 calendar year, 225 RITN presentations were conducted, and over 250 people were informed.

Aim A.2.2: Develop and test standard operating procedures, in conjunction with core transplant centers, to manage the activities required to HLA type siblings of casualties to evaluate their potential as HSC donors for their affected family member.

The focus of this Aim was to develop and test standard operating procedures that would manage the activities required to HLA type and evaluate transplant suitability of related donors (siblings) of casualties.

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In the event of a mass casualty incident resulting in marrow toxic injuries, such as an improvised nuclear device, there could be thousands of victims that will have suppressed immune function exhibited through the hematopoietic system. Some of these victims may require a transplant; those that fall into this category will want to have related donors HLA typed quickly. Since the country will likely be in turmoil it may not be easy to bring these related donors to the transplant center for typing or collection. The NMDPs existing processes and laboratory contracts are ideal for providing a means to fill this need.

During this period of performance the NMDP initiated the development of a project scope for automating a related donor typing process that would be integrated into NMDP systems. Additionally, a manual process was drafted that could be implemented in lieu of a fully automated system to allow for related donors to be typed in the absence of an automated process. This manual process is being reviewed and refined.

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II.A. Contingency Preparedness – Hypothesis 3:

NMDP's critical information technology infrastructure must remain operational during contingency situations that directly affect the Coordinating Center.

Aim A.3.1: Disaster Recovery

Ensure NMDP's ability to access and utilize its information management and communication infrastructure in a contingency situation in which its Minneapolis Coordinating Center is damaged or destroyed.

- Completed assessment to “true up” existing or missing infrastructure and software to build DR infrastructure to support changes to external and internal production applications
- Purchased and implemented NetApps Storage devices (i.e., NetApps 6080 clustered storage and 2040 storage devices) to support Snap Shots between our Production and Disaster Recovery sites. This work improved our site-to-site recovery processes and facilitated with Disaster Recovery Testing.

Aim A.3.2: Operational Continuity Planning:

The focus of this Aim is to improve organizational resiliency to severe operational disruptions through Operational Continuity Planning. In the event that the Coordinating Center is not available for an extended period of time, critical tasks will have to be conducted at an alternate location. To meet these needs the NMDP has a Operations Continuity Plan including a Critical Task List to prioritize the response.

The cohesive and efficient operation of the NMDP Network is dependent upon the availability of staff and systems at the Coordinating Center, as well as their resiliency to incidents that negatively impact operations. To help ensure that NMDP operations are able to continue despite operational interruptions, a Operational Continuity Plan is formally established to mitigate impact from catastrophic incidents. This plan ensures that critical operations continue, or are resumed as quickly as possible, in the event of operations interruptions.

The NMDP's formal Operational Continuity Plan is maintained by the Operational Continuity Planner. The Operational Continuity Planner ensures the proper focus is placed on this important area of operations resiliency and recovery. The Operational Continuity Planner works with each operational unit to determine priorities of work and recovery to accomplish their critical tasks, he then works with the Information Technology Disaster Recovery team to incorporate these operational unit needs into the disaster recovery plans where feasible. Appendices to this plan include the Critical Task List (a prioritized list of essential tasks to

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continue operations) and the Critical Document Register (a list of essential electronic documents provided by each department and the corresponding location on the network).

During this period of performance the revamp of the organizations Operational Continuity Plan was finalized and approved by the CEO in September 2009; shortly after its approval the first NMDP Operational Continuity Exercise was conducted. The purpose of the exercise was to validate the ability of selected department staff to execute identified departmental critical tasks from a remote location; in this case the remote location was a Ramada hotel conference room. This test was limited to two core operational units: Donor Resources and Search and Transplant. The exercise successfully validated the ability to establish remote data center connectivity and Unified communications at an ad hoc Critical Staff Recovery Site, successfully assessed the capability of Search and Transplant coordinators and Donor Resources liaisons to complete identified critical operational tasks, and captured shortcomings for corrective action.

The operational continuity exercise objectives were met during this test:

1. Establish operational staff recovery site within 48 hours: Successful < 48 hours
 - a. Start: 29 September 2009 8:00am
 - b. End: 30 September 2009 4:00pm
2. Complete 90% of assigned critical tasks: Successful 91.6% of tasks completed
 - a. 36 tasks assigned, 33 successfully accomplished

Key lessons learned from this exercise include:

1. Limit the number of workstations to no more than 12 for locations with limited Internet bandwidth; the hotel used had a T1 line which was insufficient for our needs.
2. The new NMDP Internet based telecommunications system required special hardware needs to operate from a non-standard site.
3. Inventory and periodically test stored equipment planned for use during operational interruptions.
4. Outdated desktop computers stored at the Repository would not be feasible alternatives to purchasing new computers for a recovery site.

To provide essential leadership direction for the prioritization of tasks the Critical Task Review Committee meets annually, to review updates and additions to the Critical Task List. The committee is chaired by Ray Hornung (Operational Continuity Planner) and consists of Dennis Confer, M.D. (CMO), Mike Boo (COO), Brian Lindberg (General Counsel), Karen Dodson (Senior VP, Operations), and Cullen Case (Senior Manager, Emergency Preparedness).

The Operational Continuity Planner provided operational unit representation and operational continuity expertise as a member of the Steering Committee for the two-phase IT Disaster Recovery test conducted in April and May 2009. This allowed IT staff to interface with one person for all operational unit prioritization needs for recovery of software systems and data.

Effective communications are essential when responding to any disaster, emergency or operational interruption. The NMDP is authorized to distribute through support of the National

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Communications System 155 Governmental Emergency Telecommunications Service (GETS) emergency calling cards. These emergency calling cards allow users to place phone calls during times of significant telephone network congestion. Quarterly user tests were conducted to ensure GETS card accountability and the users' ability to successfully place calls.

Satellite telephones are part of the emergency communications program as a means of last resort to ensure communications during a disaster that impacts landline telecommunications equipment in the United States. Most of these portable satellite telephones were issued to RITN members, and the remaining phones are maintained at the Coordinating Center or the Filter Paper Repository for use during a disaster. A fixed, "always on" satellite telephone antenna is also installed on the roof of the Coordinating Center to allow incoming and outgoing calls anytime. A similar fixed satellite telephone antenna was also installed at Memorial Sloan-Kettering Cancer Center (a RITN center in New York City) because of limited connectivity due to skyscrapers in their vicinity.

The Hazard Assessment of the Filter Paper Repository located in New Brighton, MN identified a number of vulnerabilities that could be easily mitigated. One of these was the vulnerability of the storefront glass windows to the effects of tornados or severe weather straight line winds. These windows could easily be damaged allowing the samples stored within to be susceptible to contamination by water, debris or merely the increased humidity. To mitigate this vulnerability high tinsel strength window film was installed to resist the affects of such severe weather.

NMDP operated donor centers are remote sites that report to the NMDP Coordinating Center. To assist these locations with their resiliency to disasters, small and large, an Operational Continuity Action Guide was created. The guide is a tool to assist managers of these facilities with responding to crisis situations. Sections of the guide include:

- Reporting what and when and to whom
- Local hazards
- How to prepare
- Hurricane
- Flooding
- Earthquake
- Tornado
- Winter storm
- Power outage
- Chemical spills
- Extreme heat
- Important contacts

The Operational Continuity Planner also conducted site visits to multiple NMDP operated donor centers to review the Operational Continuity Action Guide with each site manager to ensure proper implementation and improved preparedness.

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II.B. Rapid Identification of Matched Donors – Hypothesis 1:

Increasing the resolution and quality of the HLA testing of volunteers on the registry will speed donor selection.

Advances in laboratory methods and technology continued to positively impact the level of quality and typing resolution for newly recruited volunteer donors, while at the same time maintaining or even lowering the overall cost, allowing for an increase in the number of donors receiving HLA-C typing at recruitment. As of June 28, 2010, two laboratories now report HLA-C results in addition to HLA-A, B, and DRB1, increasing the percentage of newly recruited donors typed at HLA-C from 34% to 45%. Furthermore, two laboratories now use Sequenced Based Typing (SBT) to type our newly recruited donors, which has enhanced overall donor typing resolution by increasing the percentage of donors typed by this methodology from 11% to 41%. In an effort to maximize these resources and ensure the optimal use of typing funds, the NMDP has implemented a plan that allows selective typing based on donor characteristics; it involves directing samples from donors with particular demographics to specific laboratories, with the goal of ensuring that the most desirable donors are listed on the registry with the best typing possible.

Over the past 13 years, the NMDP successfully reduced the cost of HLA typing by over 70% while increasing the resolution and quality (See Table 1 below). The vision and efforts of the Navy to continually press the HLA community in this direction and to lead the advancement and testing of these technologies has been instrumental in achieving these accomplishments.

Table 1. Cost Decreases for HLA-ABDR Typing

Year	Price (Dollars)	Percent Price Decreases
1997	\$134.75	-
1998	\$73.50	45.5%
2000	\$62.20	15.4%
2002	\$56.02	10.0%
2003	\$53.80	4.0%
2004	\$53.29	1.0%
2006	\$45.78	14.1%
2007	\$45.52	0.6%
2008	\$40.04	12.1%
2009	\$40.00	0.1%
2010	\$40.00	0.0%
TOTAL DECREASE	\$94.75	70.3%

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Aim B.1.1: Increase Registry Diversity

Newly recruited donors increased diversity

During this time period, NMDP donor centers (including DoD) and recruitment groups recruited 228,580 minority race and 252,509 Caucasian donors, for a total of 481,089 U.S. donors added to the Registry. Navy funding contributed to the addition of 113,228 of this culturally diverse group of new donors, with 40,963 of these donors being minorities. All donors were typed for HLA-A, B, and DRB1.

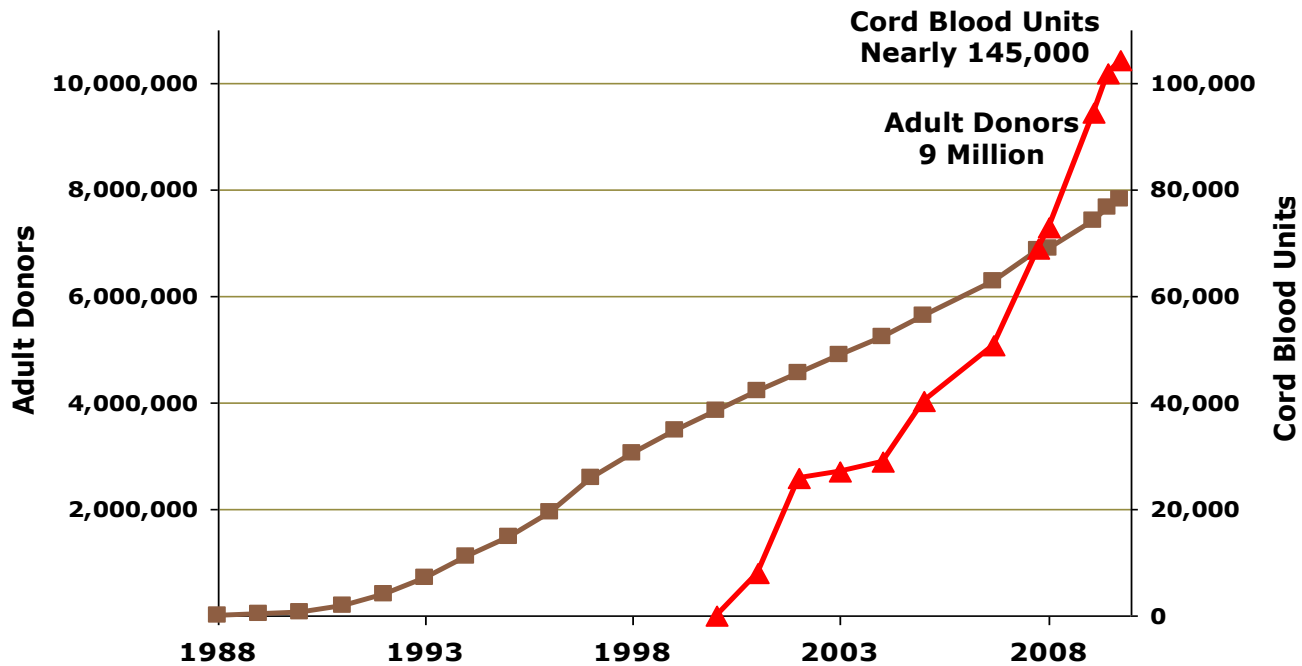
Advancing technology improved performance and pricing

Advances in laboratory methods and technology continue to have a positive impact on lab performance and pricing. As of September 2010:

- 84% of new donors received higher than intermediate HLA-A, B typing
- 100% of new donors received higher than intermediate HLA-DRB1 typing
- 45% of new donors received intermediate HLA-C typing
- Blind quality control testing error rate was 0.10%, exceeding the project requirement of $\leq 2.0\%$.
- On-time testing completion rate was 98%, meeting the project requirement of a minimum of 90% of typing results reported within 14 days of shipment of samples.
- The cost of HLA typing continues to decrease as technology improves; during the period September 2008 through September 2010 the average price per sample was approximately \$40.00, compared to \$134.75 in 1997, which represents a decrease of over 70%.

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Figure 5. Registry Growth: Adult Donors and Cord Blood Units



Quality of HLA Typing Improved

The NMDP maintains lists of rare alleles as a service to the American Society for Histocompatibility & Immunogenetics (ASHI). These lists are derived from HLA allele level typings of patients, adult volunteers, and cord blood units in the NMDP Registry. Careful review of the rare alleles reported to the NMDP on adult volunteer samples raised suspicion that some of these typings may have been incorrectly assigned. Some of the indications that raised the concerns included:

- Rare allele was typed more than 4 years ago and the allele has not been reported since
- Presence of two rare alleles in a donor typing
- Primary data interpretation doesn't match the rare allele reported
- Rare allele was typed on the same day in more than one sample reported from a lab
- Typing methodologies used to report the rare allele were problematic resulting in a correction of some of the rare allele results

Laboratories currently under contract with the NMDP were asked to review their typing for rare alleles that were reported within 5 years. In addition, TC reported results were examined for clerical errors. There were many questionable results that had type dates older than 5 years or where contact with the laboratory was not possible. 532 samples were sent to a contract

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laboratory for high resolution typing at A, B, or DRB1. In total, 819 typings were evaluated and 584 results (71%) changed from the previously reported rare allele. A poster detailing this project was presented at the ASHI annual meeting in September, 2010.¹ To date, three adult volunteers, who had typing corrected through this project, have been requested for additional testing on behalf of searching patients.

An example of a mistyped rare allele evaluated in the project is DRB1*16:08. DRB1*16:08 was described in 1996 but has not been reported on an adult volunteer sample in the Be The Match registry since 2001. 197 donors with DRB1*16:08 reported and with a stored sample at the Be The Match repository were retyped at intermediate resolution DRB1 to determine if these samples truly carried DRB1*16:08. 100% of the samples came back as DRB1*15:01, DRB1*15:02, DRB1*15:03, or DRB1*16:01. Of the 197 adult volunteers in this retyping group, one was requested for additional typing on behalf of a searching patient.

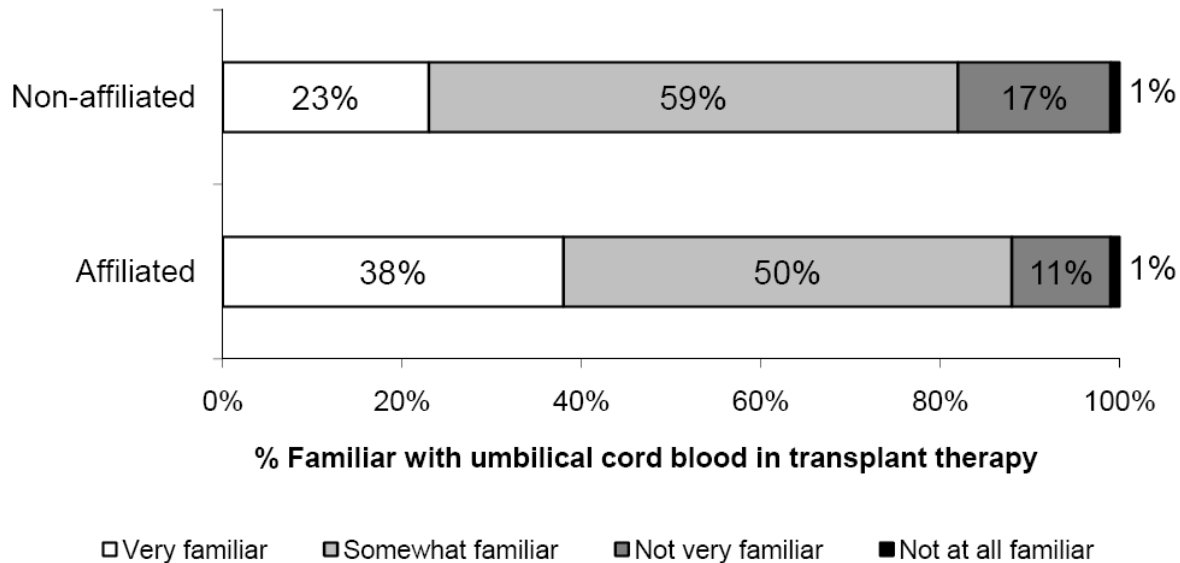
Conducted research with OB/GYN physicians to increase support for public cord blood donation

A research project was undertaken with U.S. OB/GYN physicians to gain a better understanding of awareness of the need for public cord blood donation, and to assess barriers and motivations to supporting donation. The research was conducted with two parallel groups. Group one included physicians who were currently affiliated with an NMDP Network cord blood bank and group two was with physicians who were not currently affiliated, but were in metropolitan areas that included a public cord blood bank, and who may be able to collect donations in the future. Of 2,041 surveys mailed, 295 were returned; 139 from obstetricians with privileges at hospitals affiliated with a public cord blood bank (affiliated) and 156 from obstetricians without such privileges (non-affiliated). Cross-tabulation analyses were conducted to compare responses between these two groups.

As shown in Figure 6 (next page), a high percentage of both affiliated and non-affiliated obstetricians reported that they were familiar or very familiar with the use of umbilical cord blood in transplant therapy: 88% vs. 82%, respectively; ($p=n.s.$). A significantly higher number of affiliated obstetricians said they were very familiar with the use of cord blood in transplantation than non-affiliated obstetricians: 38% v. 23%, respectively ($p<0.05$).

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Figure 6. Familiarity of obstetricians with the use of umbilical cord blood in transplant therapy



Eighty percent of affiliated obstetricians feel confident discussing cord blood options with their patients, and 51% believe they have enough information to answer patients' questions about donating cord blood, leaving 49% who indicate they do not currently have sufficient information.

The results also indicated that there are significant barriers in place that will likely affect the ability of achieving this goal. More than one-third of affiliated and non-affiliated obstetricians also strongly agreed or agreed that lack of compensation for doctors is a barrier to collection: 36% vs. 35%, respectively; $p=n.s.$ This finding suggests that public cord blood banks should carefully examine whether the cost of compensation would be worth the value of the increase in the number of Cord Blood Units (CBUs) collected.

A significantly higher percentage of affiliated obstetricians knew that there is no cost to women who donate their baby's cord blood to a public bank (86%, affiliated vs. 69%, non-affiliated; $p<0.05$). Although it is gratifying to know that a majority of obstetricians correctly know that public cord blood banks do not charge for donations, expectant mothers would be better served if all obstetricians caring for them could consistently convey this information.

Finally, the survey revealed that a majority of obstetricians believe that Cord Blood Transplantation (CBT) with a person's own cord blood is almost always preferable to using cord blood donated from someone else. As indicated in the American College of Obstetricians (ACOG) committee opinion, autologous transplantation using privately stored CBUs cannot be used treat genetic diseases such as inborn errors of metabolism as the cord blood cells would

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have the same genetic mutation. Autologous transplantation to treat a childhood leukemia or lymphoma would also be contraindicated due to the likelihood of reintroducing malignant cells to the recipient.

Work is underway to apply the research findings; a manuscript of the results will be prepared and submitted to a leading OB/GYN publication.

To address the needs of those who indicated they did not have enough information to properly educate their patients, an educational tool is under development that OB/GYNs can use to talk with their patients. The tool will provide the correct information for those misperceptions that were discovered in the research, so that expectant parents receive accurate information about cord blood donation.

Adult Donor Education and Recruitment

- A comprehensive marketing strategy was developed to support the launch of the “Say it Loud... Save Lives and Be Proud” program. This program engages Historically Black College and University (HBCU) students and their community in our mission. A key component of this program was the launch of a Be The Match® site on the HBCU Connect platform. This platform is the premiere interactive channel for HBCU students and alumni. The site serves as a key way to engage and educate this important community about the need for more African Americans to join the registry and to donate marrow when called. It features stories about HBCU students who are hosting registry drive events on campuses, stories about searching patients and stories about committed African American donors who stepped up to save lives.
- Outreach to the Hispanic/Latino community was strengthened by launching key Spanish-language materials and tools designed to enhance this community’s understanding of our mission, the drive experience and what it means to be a committed member on the registry.
- New or reprinted key educational materials, used by NMDP operated and contract recruiters to engage the public in our mission, were introduced. Included among them were the New Registry Member Exit Card, which reinforces key messages regarding the commitment one makes when they join the registry; Myths and Facts sell page, which dispels long-held myths about the donation process; and Take the First Step brochure, the primary educational tool that presents an overview of our life-saving mission, spotlights donors and recipients and provides key information about joining Be The Match Registry, contributing to Be The Match Foundation® and volunteering time to help save lives.

STAR II

The STAR II transaction broker was released in May of 2009. Of note was a change to make the Histoimmunogenetics Markup Language (HML) processor highly configurable with regard to the database versioning for lab typing kits. This will allow the NMDP to more quickly support new and different typing kits on a lab specific basis, and provides much more flexibility in

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accepting HLA information from labs for recipients and donors. In addition, this change provides flexibility for both operational (patient directed) and research based lab results.

Aim B.1.2: Evaluate HLA-DRB1 High Res Typing

No funding was requested under this Aim for the 1207 budget cycle.

Aim B.1.3: Evaluate HLA-C Typing of Donors

No funding was requested under this Aim for the 1207 budget cycle.

Aim B.1.4: Evaluate Suitability of Buccal Swabs

Sample Storage Research Study

The 5-year Sample Storage Research Study began in September 2007. Samples from 30 fully HLA characterized volunteer quality control donors were collected, processed and stored at the NMDP Repository. The samples, which consisted of fresh blood, blood spotted onto Whatman® 903 filter paper and buccal swabs for each donor, were sent to two laboratories in September 2007 to initiate the study (Time Point Zero). One laboratory was contracted to perform high resolution typing for HLA-A, B, C, DRB1, and DQB1. The second laboratory was contracted to perform intermediate resolution typing for HLA-A, B, C, and DRB1 and also to evaluate the quantity and quality of DNA within each sample type. Complete results were received from each of the two laboratories. All typing results were 100% accurate, and the evaluation of the DNA was complete and thorough. The results obtained at Time Point Zero are used as the baseline for comparison and evaluation of the stability and usefulness of the DNA stored in each sample type for the next 5 years. Results from this study will provide key quality parameters for NMDP operational decisions concerning sample storage and may also contribute sample storage guidelines for other registries.

During this grant period, the results for Time Point 3 Year were evaluated. In September 2010, 30 donor samples (frozen blood, blood spotted onto filter paper, and 2 buccal swabs for each donor) were sent to the two participating laboratories for the 3 year time point of this study.

Review of the data shows:

- 100% accuracy in HLA typing
- DNA extracted from the buccal swabs appears overall to be slightly degraded - 1 sample required the use of the second buccal swab
- All sample types contained DNA of sufficient quality and quantity to accurately obtain HLA results at all loci tested

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Alternate Sample Collection Methods Study

In an effort to evaluate the suitability of alternate sample collection methods, a limited feasibility study was initiated to gain a broader understanding of alternate sample collection and storage methods currently in the market, including possibilities for storage formats that offer increased sample lifetime, more compact storage, and greater downstream sample utility for further detailed typing. The potential to store DNA in a stable form at room temperature is an attractive possibility for the long-term storage of a resource that would be renewable and in an intact state for typing after decades of storage, when needed for patient or contingency needs.

During this grant period:

- Sample sets were collected from 15 volunteer donors for evaluation. Each donor collected samples using:
 - Oragene DNA saliva sample collection kit from DNA Genotek
 - CEP Swab, an ejectable-tip buccal swab from Fitzco, Inc., composed of cotton-based fibrous material in a matrix format
 - Standard NMDP cotton-tipped buccal swab on polystyrene shaft
- Samples were sent to 3 laboratories for analysis of the following attributes:
 - Quality and quantity of DNA
 - High resolution typing at HLA-A, B, C, DRB1, DQB1, and DPB1
 - Extraction and processing of DNA for dry storage in GenTegra tubes from GenVault
 - Report on the positives and negatives of each sample type and storage method, from a laboratory perspective
- Results were received from each of the labs. Initial results showed that all 3 sample types provide DNA of sufficient quality and quantity to obtain accurate high resolution HLA typing results at all loci tested. Results also showed variations in quantity, purity and ease of use, and these results are under further analysis.

Extracted DNA from each of the sample collection methods is now stored in a dry, room temperature stable state and ready for further evaluation. A future phase of this study is needed to:

- Evaluate the suitability of the stored DNA for a) whole genome amplification and b) reconstitution for high resolution HLA typing.
- Evaluate duplicate samples of each method after prolonged storage before HLA typing.

Aim B.1.5: Enhancing HLA Data for Selected Donors

This aim consists of registry-based typing projects, which have the potential to strategically identify and improve the HLA typing and availability of donors most likely to match searching patients from domestic TCs. All strategies being evaluated are extensions of the previous Replacement Donor and Optimal Donor typing projects.

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Back-up Donor Strategy to Support Donor Availability

While the primary study was completed in December 2007, the NMDP staff continued to monitor the patient-directed utilization of the 206 donors prospectively typed in this project. In this study, 1515 domestic patient searches and associated workup requests were reviewed. 81% (1230) of the searches already had one or more potentially available back-up donors identified by the TCs. Additional back-up donors were identified for another 4.8% (72) of the patients as a result of continued TC-directed Confirmatory Typing (CT) requests. NMDP TCs were found to be very efficient at identifying potential back-up donors.

NMDP prospectively typed 206 donors, and a suitable back-up donor was identified for an additional 2.6% (40) of the study patients. Follow-up of these prospectively typed donors during this reporting period revealed the activation of 16 donors for CT requests, followed by 6 workup requests and 3 stem cell donations. The back-up donor efforts evaluated in this study did provide the desired outcome, but the magnitude of the contribution was smaller than expected. With the HLA consultation, custom search support, and urgent customized typing services that the NMDP already provides, the benefit from a continuing effort may be of only minimal significance. An abstract reporting the results of this study was accepted for a poster presentation at the 2009 ASHI annual meeting.²

Prospective HLA Typing of HLA-A, B-Only Typed Donors-Formal Searches

While the project was officially completed in 2008, NMDP staff continued to monitor the patient-directed utilization of the 462 donors prospectively typed in this project. 58,840 unique patient and 318,024 unique donor phenotype categories were identified. Potentially matched donors were available for 56,649 (96.3%) of the unique patient phenotype categories. 10,902 of these categories were comprised of 3 or more patients. 3,070 patient searches from this category were evaluated, and prospective HLA typing performed on 462 confirmed available donors. Follow-up of these donors revealed the activation of 20 donors for CT requests, followed by 2 hold-for-workup requests, 2 workup requests and 1 stem cell donation. An abstract reporting the results of this study was accepted for oral presentation at the 2009 ASHI annual meeting.³

This systematic strategy of identifying and prospectively upgrading the HLA typing of donors likely to match future searching patients appeared promising. Therefore, the NMDP performed an additional 566 donor selections for prospective HLA typing using our donor selection algorithm now for patient phenotype categories with only 1-2 potentially allele-matching donors. Follow-up of these donors during this reporting period revealed the cumulative activation of 14 donors for CT requests on behalf of 9 different patients. Two of these donors were subsequently activated for workup. The donors activated for CT had been on the registry from 0.7 - 10.2 years prior to selection for HLA typing upgrade through the project. The donors were activated for new patients within an average of 210 days from the date upgraded HLA typing was made available. 13 of the 566 prospectively typed donors were requested within the first 315 days. During the reporting period, the NMDP Registry contained approximately 743,000 HLA-A, B only typed donors. Generally, less than 0.4% of these donors are activated by transplant centers

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for HLA-DRB1 typing in a given year. The donor utilization rate observed in this study (13/566; 2.3%) represents more than 5 fold increases over random donor CT selection rates.

This prospective donor selection strategy was extended to the patients having zero potential 6/6 donor matches in NMDP hosted registry or Bone Marrow Donors Worldwide (BMDW). This effort focused on a subset of 2,225 patient searches, comprised of 2,191 unique phenotypes, which did not have a broad serologic-level match within the HLA-A, B, DRB1 typed donor pool. From a pool of 30,924 donors carrying less common HLA-A, B phenotypes, 4,931 donors were identified who potentially matched the study patients. 1,359 donors with repository samples were selected for prospective typing. The AB only typed donors selected were found to be associated with unique phenotypes not seen in the fully typed donor population or phenotype categories with few (2-10) available donors. Follow-up of these donors revealed the activation of 10 donors for CT requests on behalf of 9 different patients, followed by a stem cell donation for a patient who had searched for almost two years. These donors had been on the registry from 8-14.7 years prior to prospective typing, but were then activated for new patients within an average of 228 days. An abstract reporting the results of this study was accepted for poster presentation at the 2009 Annual ASHI meeting.⁴

Evaluation of HLA-AB only typed donors potentially matching patients with formal searches

Patient searches with active work-up requests were evaluated and searches identified for which there are relatively few 6/6 matched donors. 691 donors were selected from the HLA-AB only typed pool and tested for HLA-DRB1. Prospective typing was completed in April 2009.

Follow-up of prospectively typed donors revealed the selection of 12 donors for CT requests on behalf of 11 different patients. The activated donors had been on the registry from 9 -12.7 years prior to selection for HLA typing upgrade through the project. The donors were activated for new patients within an average of 215 days from the date upgraded HLA typing results were available to searching patients. Two of the twelve donors went on to donate a stem cell product for a patient. One donor was a 10/10 allele match with the patient, and the second was a 9/10 allele match (HLA-C allele mismatch) with the patient.

During the reporting period, the NMDP Registry contained approximately 743,000 HLA-A, B only typed donors. Generally, less than 0.4% of these donors are activated by transplant centers for HLA-DRB1 typing in a given year. And only 0.1% of this small subset moves forward to donate a stem cell product. The donor utilization rate observed in this study (12/691; 1.74%) represents more than 4 fold increases over random donor CT selection rates further demonstrating the ability to strategically identify donors most likely to be needed for future searching patients.

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Aim B.1.6: Maintain a Quality Control Program

The NMDP's comprehensive Quality Control (QC) program has supported the successful increase in the quality of HLA typing received through the contract laboratory network. Blind QC samples are added to each weekly shipment of new donor recruitment samples; they comprise 2.5% of each shipment and are indistinguishable from the donor samples. This method of inserting blind quality control samples into each laboratory's shipment of volunteer donor samples has provided more than 12 years of data, tracking the accuracy of high volume HLA typing. Errors that have been investigated and corrected due to our quality control program include clerical, false negative and positive probe scores, software, sample switches, contamination and training issues. Over this time, the accuracy rates have continued to improve, as documented by decreased monthly error rates and decreased discrepancies as the donors are selected for patients and retyped by other laboratories. The effectiveness of this program and the efforts of the NMDP's high-volume HLA typing laboratory network to ensure the highest level of quality have resulted in a combined HLA class I and class II QC accuracy rate during this period of 99.97%.

The Research Sample Repository contains frozen cells from thousands of fully HLA-characterized donors and recipients. QC swabs are created by the Repository staff from expanded B-LCL vials chosen from this resource. Funding from this grant was used to carry out the following activities:

- In 2009, 121 new unique B-Lymphocytic Cell Lines (B-LCLs) were added to the QC Master inventory. 19 of these cell lines were selected due to rare alleles contained in their haplotypes.
- In 2010, 47 Research Repository samples with potential rare alleles were selected for possible inclusion in the quality control program. 18 (38%) failed to expand. Confirmatory high resolution confirmed the presence of a rare allele in 26 out of 41 samples (63%); rare typings were updated to more common alleles in 14 (34%) samples. 4 samples were sent to ImMunoGeneTics (IMGT) to provide the confirmatory sequences for previously unconfirmed alleles.

As a result of the above efforts, 150 new B-LCL QC Masters were added to the inventory, 33 of which contain 31 unique rare alleles.

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II.B. Rapid Identification of Matched Donors – Hypothesis 2:

Primary DNA typing data can be used within the registry to improve the quality and resolution of volunteer donor HLA assignments.

Aim B.2.1: Collection of Primary Data

During this grant period a program was optimized, validated, and run to “validate and push” probe results making them available to systems using HapLogic. Donors in the registry prior to February 2007 had already been pushed and have been used for searches; with this effort approximately 1.1 million donors from 2007 through November 2008 have validated primary data used in searches.

Aim B.2.2: Validation of Logic of Primary Data

No funding was requested under this Aim for the 1207 budget cycle.

Aim B.2.3: Reinterpretation of Primary Data

Reinterpretation of primary data to improve the level of resolution of previously reported donor typings

No funding was requested under this Aim for the 1207 budget cycle.

Aim B.2.4: Genotype Lists & Matching Algorithm

The theory underlying this Aim proposes that the interpretation of the primary data into genotype lists and the subsequent utilization of those lists (instead of search determinants) could provide a more rapid and more specific matching logic. The genotype list database developed as a result of this Aim has been used as the foundation for a new matching algorithm, HapLogic. HapLogic directly applies DNA typings of any complexity into the up-front search. This year re-interpretation of 9.8 million locus-level probe results was completed, upgrading it to the HLADB 2.24.0 (January 2009) allele list.

Additionally under this aim, work was done to update SBT interpretation. Laboratories use a variety of DNA-based methods to determine the HLA tissue type of an individual. These methods have evolved over the years as new technologies are discovered. One of the more recent technologies to be used by high-throughput HLA testing laboratories is SBT, which provides very high resolution results, and is now very competitive in price for registry typing. During this grant period, new SBT interpretation code was developed and tested on two HML files from a contract lab, one with class I data and one with class II data. We were able to interpret all the

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samples from this laboratory. We also tested SBT interpretation code on HML files from another contract lab that had 22 haploid samples, which required different processing from diploid samples. All samples from that laboratory were successfully interpreted as well.

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II.B. Rapid Identification of Matched Donors – Hypothesis 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.

Aim B.3.1: Phase I of Expectation Maximization (EM) Haplotype Logic

HapLogic Algorithm

The idea for HapLogic III, which includes x of 10 matching (HLA-A, -B, -C, -DRB1, -DQB1) and sorting, and significant upgrades to multi-race matching, was presented to the NMDP Histocompatibility Advisory Group on July 9, 2009. Feedback was received and utilized to confirm the scope of work for HapLogic III. Based on this feedback a project charter and technical documentation were created and a rough prototype was built to test the ability of the project to be done. After proving that the project could be done, a business systems analyst was hired and wrote detailed requirements for the HapLogic Phase III algorithm.

Aim B.3.2: Enhancement of EM Algorithm

A series of items were completed this year in order to enhance the EM Algorithm:

- An extract of primary DNA data for A, C, B, DRB1, and DQB1 loci were reinterpreted to the HLADB 2.24 allele list. This dataset includes 3.89 million donors typed using DNA methods at recruitment from the 147 detailed race and ethnic combinations that exist in the NMDP donor file.
- Tools for reducing the genotype lists (which can be on the order of trillions per donor) were developed. The techniques involve reduction to Antigen Recognition Site (ARS), a greedy algorithm to restrict allele lists to only alleles required to interpret all genotype lists, and genotype list bootstrapping. The resulting performance improvements were required for practical application of the EM algorithm to generate haplotype frequencies from highly ambiguous typing data.
- A greedy algorithm to create a reduced allele list and EM bootstrapping was implemented for multiple allele code data to reduce HLA ambiguity and make possible haplotype frequency computation using mixed resolution data for BMDW.
- Haplotype frequencies for all BMDW registries with typing by DNA methods have been completed and will be incorporated into a global matching benchmark and maps of worldwide HLA diversity.
- Frequency study of donors typed to distinguish some HLA alleles that differ only outside the ARS was completed.

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- Based on genetic distance, the size of the donor cohorts, and data integrity, the 147 detailed race and ethnic combinations were combined and pruned to 21 operationally useful categories which will be used for HapLogic III and registry modeling.
- High-resolution haplotype frequencies were generated using all DNA-typed donors in the 21 population categories for the A-B-DRB1, C-B, DRB1-DQB1, A-C-B-DRB1, and A-C-B-DRB1-DQB1 loci.
- Haplotype frequencies for 21 US populations were completed in September 2009 and have begun to be used for registry modeling analysis (discussed in more detail in IIB3.3).
- 2 abstracts were submitted to the European Federation of Immunogenetics (EFI) 2010 meeting detailing the haplotype frequency dataset and its application in showing population differentiation.

Aim B.3.3: Optimal Registry Size Analysis

This year, new methods for registry modeling were implemented that allow the generation of adult donor match rates at the allele-level for HLA-A, -B, -C & -DRB1. Methods for analyzing cord match rates, incorporating cell dose limitations have been combined with donor match models to develop a platform for comprehensive analysis of match rates in the context of specific product/stringency search strategies by ethnicity and under several models of registry growth, and adult donor availability.

A preliminary report was issued on September 30th, 2009 listing the current probabilities of 8/8 and 7/8 match at A,C,B,DRB1 for adult donors and 4/6, 5/6, and 6/6 match at A,B, and DRB1 using criteria for cord blood matching in the 21 population categories. The final report titled “Modeling effective patient-donor matching hematopoietic transplantation in United States populations” was completed on January 15th, 2010. Additionally, basic modeling for cost-benefit analysis comparing adult donor versus cord recruitment has begun. More complex and race-specific cost-benefit models are in development.

A simulation study of cord inventory depletion was undertaken showing that after depletion the remaining large cords in inventory will show enrichment for rare HLA types.

A manuscript entitled “Genetic Differentiation of Jewish Population” was published in Tissue Antigens.⁵

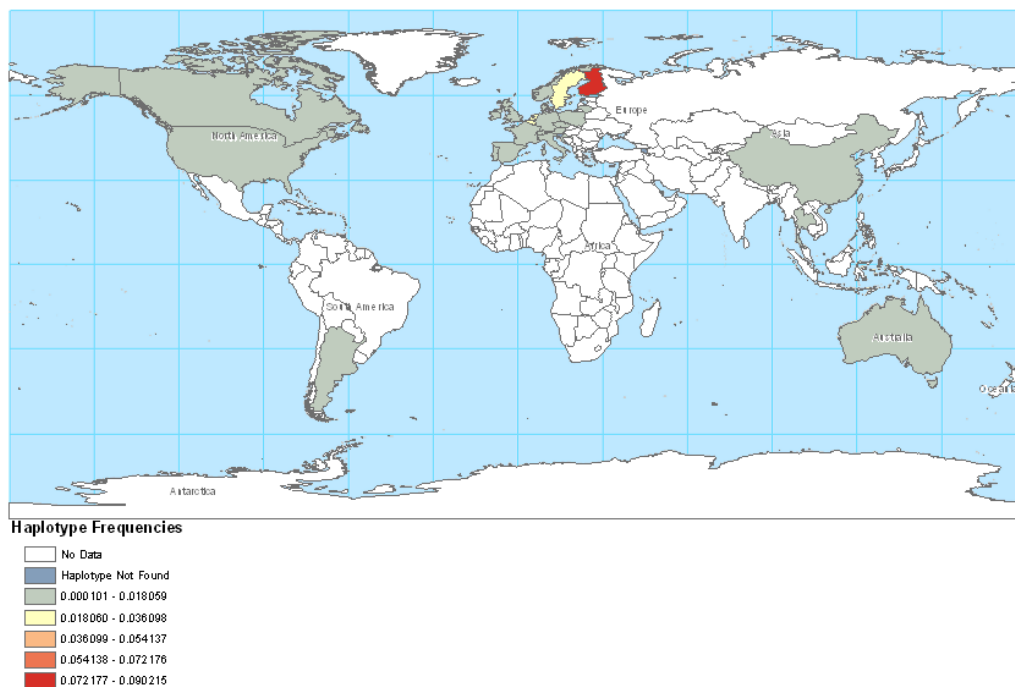
Aim B.3.4: Target Under-represented Phenotypes

The objective of this project was to link donor zip code information to HLA variables (alleles and haplotype assignments) and then integrate them into standard Geographic Information Systems (GIS) software for visualization.

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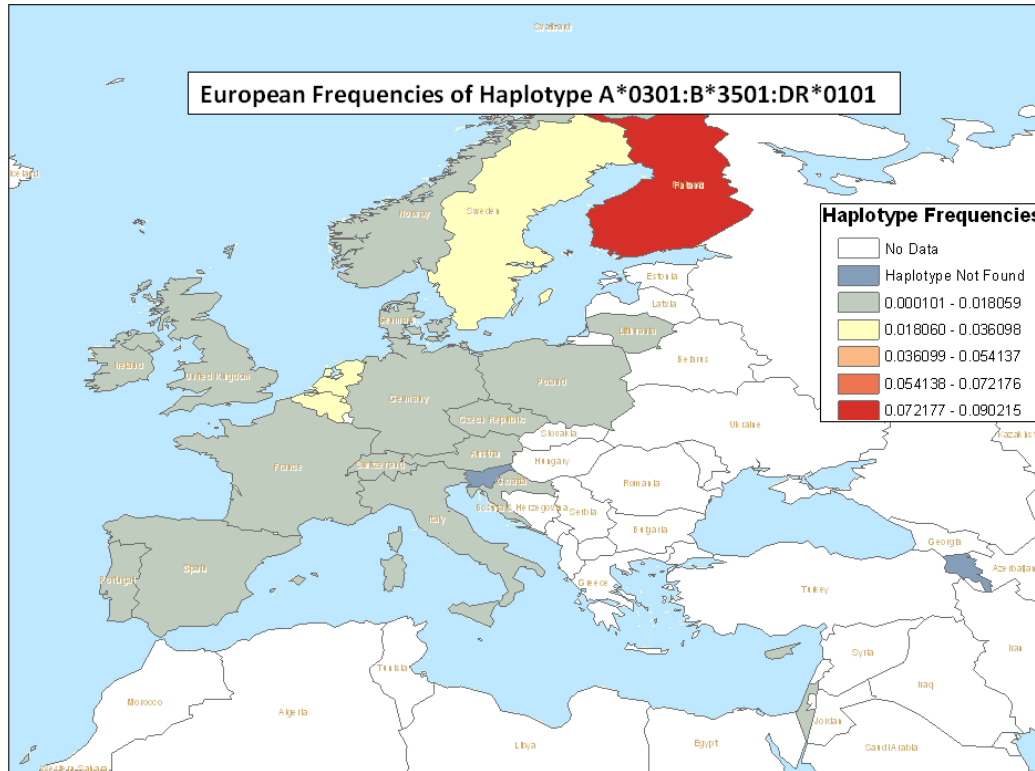
In order to accomplish that, Environmental Systems Research Institute (ESRI) ArcGIS Geographical Analysis software was used to build a concordance map prototype, normalized over population and recruitment rate. A database design was created for the underlying database for this aim, using a 2-digit 01:08:03 (common) map and a 02:44:04 (lower frequency) map. Feedback was received on the prototype and, from that, the following updates were made: better data representation, finding representative frequencies in low population areas, geospatial correlation of 2 variables tools, and how to evaluate data integrity in outliers. Using the EM algorithm, haplotype frequencies were determined from individual registries in the BMDW database. Data from the top 200 haplotypes, by frequency, are being consolidated on a country basis and then globally mapped. Maps give an indication of where donors or patients with specific haplotypes are most likely to be found on a world-wide basis. Below are examples maps of haplotype A*0301:B*3501:DRB1*0101, a haplotype with an apparent geographical center of origin in or near Finland.

Figure 7. Global Frequencies of Haplotype A*0301:B*3501:DR*0101 By Country



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Figure 8. European Frequencies of Haplotype A*0301:B*3501:DR*0101



- A comprehensive database to hold all research data in this task (as well as ensuring proper backups) was begun. During this period the table structures and ETL code to conform to NMDP Standards were laid out. Additionally the ETL processes were created and unit tested.
- ESRI was consulted about the process of automating map production for large numbers of HLA files. Progress was made on determining the best technology options to pursue and finding an ESRI program consultant to engage.

Aim B.3.5: Bioinformatics Web Site

No funding was requested under this Aim for the 1207 budget cycle.

Aim B.3.6: Maximize software using consultant data

No funding was requested under this Aim for the 1207 budget cycle.

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Aim B.3.7: Population Genetics

During this period, we worked on building relationships with external collaborators for the development of enhancements to the registry matching models.

Aim B.3.8: Haplotype Matching

No funding was requested under this Aim for the 1207 budget cycle.

Aim B.3.9: Global Haplotype/Benchmark

No funding was requested under this Aim for the 1207 budget cycle.

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II.B. Rapid Identification of Matched Donors – Hypothesis 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.

Aim B.4.1: Expand Network Communications

Business to Business (B2B) Gateway and Business Services Detailed design and implementation in order to support:

- HLA typing results from NMDP contract laboratories (incorporating HLA nomenclature changes)
- Inventory integration from affiliated business entities (i.e. European Marrow Donor Information System, EMDIS)
- Implementation of HLA Override as a business service intended to validate and audit HLA results received from contract laboratories.
- Formalization of pathways through which data are transmitted to NMDP from affiliates.
- Development of the underlying capabilities to support the Version 3 WHO nomenclature requirements.

Subsequently, work was performed to extend the B2B Services to support the new alleles and allele combinations expressed as allele codes:

- Limited Support for WHO approved P codes
- Full support of World Marrow Donor Association (WMDA) approved codes – XXXX, NNNN, UUUU, NEW.
- Support in external tools for user queries of allele code information
- Preparation for expansion of allele code information
- Support for new nomenclature vendor DNA typing kits

In addition, NMDP has initiated development on a B2B implementation of a Cord Blood Unit inventory exchange model. The following advancements have been completed:

- Development of modifications to B2B database schema to support inventory sharing
- Development of new B2B Gateway database schema to support transaction sharing
- Preliminary development of the components required to share NMDP cord blood unit inventory with strategic partners, and maintain updates.
- Exchanged test cord blood inventory messages with several partners.

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- Documented semantics describing the messages and process flow to exchange inventory.
- Documented fields that each will be sending in the inventory exchange.
- Shared house rules for searching based on CBU status, no differences or concerns.

It was agreed that ownership of data resides with the source registry. Consequently, the mirroring registry will only update a CBU's search antigens when a CBU change is received from the source registry; the search antigens will not be updated by the non-owner when lab results are received.

Aim B.4.2: Central Contingency Management

A research project was developed to estimate the 8/8 HLA high resolution donor match rate for the four largest NMDP patient populations: Caucasian (CAU), African American (AFA), Hispanic (HIS), and Asian-Pacific Islander (API) patients. The goal of the study was to also validate previous registry benchmark analyses and supply valuable information regarding donor selection in the event of a contingency.

During the project period:

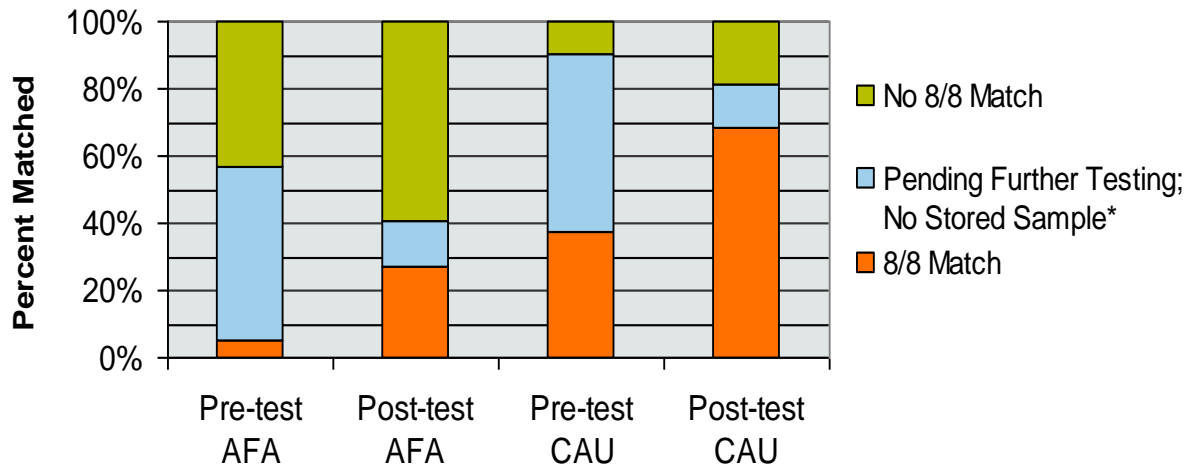
- Scientific Services search strategy staff completed donor selections on behalf of the study 'pseudo-patients' (PP) for 4 cohorts.
- A contract was established with an HLA testing lab.
- Donors with repository samples were tested to identify the 8/8 HLA high resolution match rate for 'pseudo-patients' in the four major race categories- CAU, AFA, HIS, and API.
- Established collaborative participation from international and domestic NMDP member donor registries.
- A total of 4069 donors and 6181 loci were typed during this project period. Additional donors were tested by participating international donor registries.
- Analysis of the donor typing results was performed to determine the match rate for 'patients' in the four cohorts
- An abstract was submitted to ASHI, accepted as a poster, and presented at the ASHI 2010 Annual Meeting in September 2010⁶
- A presentation on the results of the study to date was presented at the 2010 NMDP Annual Council Meeting in October 2010.
- An abstract was submitted to ASBMT and accepted as an oral presentation which will take place at the ASBMT Tandem Meetings in February 2011.

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Results (in-progress) for the project period are shown below:

Figure 9 below shows the match rate of cases, by race, at the time of initial review (pre-test) and after donor testing (post-test). Upon initial review of donor results, 37% of CAU and 5% of AFA cases had an existing 8/8 HR matched donor on the registry. Of note, many of the AFA patient cases had haplotypes common in multiple races and 52% of these donor matches were CAU.

Figure 9. 8/8 High Resolution Match Grade



The table below shows the 8/8 HR match rate of cases to be 68% for CAU, 42% for HIS, 45% for API, and 27% for AFA. Careful review of the cases “Pending further testing; no stored sample” suggests that few additional cases would yield 8/8 HR matches.

	CAU PP	HIS PP	API PP	AFA PP
8/8 HR Matched	258 (68%)	128 (42%)	122 (45%)	105 (27%)
Pending Further Testing; No Stored Sample	48 (13%)	65 (21%)	57 (21%)	54 (14%)
No 8/8 HR Match	71 (19%)	114 (37%)	91 (34%)	231 (59%)
TOTAL	377	307	270	390

This study is in the end stages and is currently obtaining DNA samples from registry donors who did not have sample stored. These donors will be tested and a manuscript will be written and submitted to a peer-reviewed journal.

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Developed Medical Education for Referring Physicians

To improve appropriate patient selection and application of transplantation for AML and MDS, an online education series was developed. The goal of the program was to increase understanding of the utility of transplantation, and also the appropriate timing for referral. The 4-part series was adapted from a live symposium, and then developed into an online program and promoted in partnership with Clinical Care Options, an educational provider, as a pilot to increase the number of physicians attending, versus previous programs delivered through NMDP alone. *Navigating the Therapeutic Pathways for AML and MDS* was live in Period 6, and remained active for CME credits (physician continuing medical education) for one year. The program was reinforced with a Clinical Fact Sheet of the key points, which was mailed to more than 8,000 U.S. hematologists/oncologists and is online at www.marrow.org/md-clinicalfacts.

Results of the program include:

- More than 2,000 clinicians accessed the program (vs. approximately 350 when NMDP promoted alone)
- 55% were hematology/oncology physicians. Additional attendees were allied health professionals in hem/onc, or physicians in other specialties.
- More than 6,000 slide modules were downloaded for later viewing
- Of those completing evaluations, 93% rated the program as good/excellent, and 96% indicated the education was evidence-based. Additionally, 67% indicated they learned information they could apply to their practice.

The results of the program indicate that:

- Partnering with an educational provider expands participation to the program
- Clinicians continue to need and seek education on the role and timing of transplantation
- Education is a valuable mechanism to improve decision-making in transplantation.

Based on this pilot:

- Future live programs should be made available online, and promoted through an education partner. New partners will be explored to attempt to increase participation by U.S. hematology/oncology physicians, and to improve the percentage who are able to apply the information learned.

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Aim B.4.3 Conduct a transplant center benchmarking analysis to identify center-specific factors (e.g., quality management techniques and processes) that contribute meaningfully to superior survival outcomes. Share processes that contribute to superior outcomes with the entire TC network as best practices.

No funding was requested under this Aim for the 1207 budget cycle.

Aim B.4.4 Identify plans to expand capabilities of collection center and apheresis center network to meet increasing number of donor product requests on both a short-term and long-term basis.

No funding was requested under this Aim for the 1207 budget cycle.

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II.C. Immunogenetic Studies – Hypothesis 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.

Aim C.1.1: Donor Recipient Pair Project

A retrospective Donor/Recipient (D/R) Pair HLA typing project to perform high resolution class I (HLA-A, B, and C) and class II (HLA-DRB and DQB1) typing of paired samples from NMDP's Repository, was initiated in 1994. The primary objectives of the Donor/Recipient Pair Project are to:

- Determine the impact of DNA-based HLA matching on unrelated donor transplant outcome
- Develop strategies for optimal HLA matching
- Evaluate the impact of matching at alternative HLA loci on transplant outcome
- Promote the development of DNA-based high resolution HLA typing methodologies

Transplant pairs were chosen from stored samples at the NMDP Research Sample Repository and distributed to participating laboratories for high resolution HLA typing. All paired samples are selected in collaboration with the CIBMTR Statistical Center to ensure the additional cases would benefit ongoing and future analyses. The cohorts tested during the project period consisted mainly of transplants that utilized peripheral blood stem cells as the cell source, reduced intensity or non-myeloablative preparative regimens, rare diseases and older patients reflecting the expanding indications for unrelated donor Hematopoietic Stem Cell Transplant (HSCT). In addition, the project has added cord blood transplant pair samples to facilitate studies of HLA matching in this high growth field.

Testing was completed on an additional 837 donor/recipient pairs during the project period, bringing the total enrolled to over 14,800. Typing results were reported electronically to the NMDP and compared with previous transplant center results as a measure of quality control. Presence/absence Killer Immunoglobulin-like Receptor (KIR) genotyping on 2DL1-5, 2DS1-5, 3DL1-3 and 3DS1 was performed on all 837 paired samples.

In order to continuously upgrade the Donor/Recipient Pairs Project, a group of 64 samples were sent out for resolution of new alleles. Resolution will allow for auditing of those pairs and inclusion into research studies.

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Current HLA matching guidelines for unrelated HCT recommend avoidance of mismatches only within the antigen recognition site, i.e. exons 2 and 3 for HLA class I and exon 2 for HLA class II. This recommendation is based on the hypothesis that amino acid differences outside the antigen recognition site are not immunogenic. There is little functional data available to prove this hypothesis and clinical analysis would require an unattainable data set to reach significance as previously reported. In brief, an investigation of DRB1*140101 and *1454 mismatches was performed. From a pool of 4222 8/8 matched European American donor/recipient transplant pairs in the NMDP database, only 102 pairs were identified that carried the unresolved DRB1*1401/DRB1*1454 with matching at class I loci. The DRB3 linkage was used to identify 12 pairs likely to be mismatched for DRB1*140101/DRB1*1454, but was determined an insufficient sample size to assess the impact of the mismatch on transplant outcome.

The Antigen Recognition Site Allo-reactivity Assessment Project will give insight into the allowable tolerance of matching needed outside of this binding region. Specific queries of the Be The Match Registry allowed for selection of ninety-nine potential donors from 4 of the 12 haplotypes identified to be typed at high resolution HLA-A, B, C, DRB1/3/4/5, DQA/B1 and DPB. 72 donors representing the 7/8 mismatch haplotypes have been selected to participate in the Antigen Recognition Site Allo-reactivity Assessment Project. Samples will be drawn, processed, and shipped for inclusion in in-vitro functional cellular assays.

The high resolution HLA data generated through the project are routinely incorporated into all outcomes analyses performed by the NMDP/CIBMTR to provide the best HLA typing and matching information possible. The project has developed the largest fully validated pool of unrelated stem cell transplant donor-recipient HLA data in the world and is an unparalleled resource for transplant research. The data generated through the project have had a major impact on the evolution of the NMDP HLA matching requirements.

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II.C. Immunogenetic Studies – Hypothesis 2:

Even when patient and donor are HLA matched, GVHD occurs so other loci may play a role.

Aim C.2.1: Analysis of non-HLA loci

Recent research has heightened interest in additional genetic polymorphisms which may modify the outcomes of transplantation. HLA genes other than the major histocompatibility complex (MHC) found on chromosome 6 and non-HLA genetic factors may all influence the suitability and success of allogeneic stem cell transplants. The largest body of data with clear correlation to unrelated stem cell transplant outcome was surrounding the role of Natural Killer (NK) cells. These cells express inhibitory receptors (KIR) that specifically interact with MHC class I molecules. Genes encoding for these Ig-like ligands are found on chromosome 19. The regulatory mechanism mediated by these receptors is thought to protect normal cells from autologous NK attack, while rendering cells for which class I expression is compromised (e.g. by tumor transformation or viral infection) or incompatible (e.g. by stem cell transplant) susceptible to NK-mediated killing. This has been shown to be responsible for anti-leukemic effects and protection against GVHD following allogeneic HSC transplantation.

Based on this information, the NMDP developed a pilot study to perform KIR ligand typing utilizing selected donor and recipient pair samples. The project was launched in early 2005 with ongoing support provided through the project period. The NMDP selected three laboratories to participate in the project through a competitive bid process. 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
- Develop reference lines for use in individual laboratories. Additionally, the project will provide more fully characterized and highly quality controlled transplant pairs for use in research studies connecting these factors to clinical outcome data

Final resolution of the 46 novel alleles found in the KIR Typing Pilot Project was completed and will be included in the Immuno Polymorphism Database (IPD) KIR database release 2.3. With the addition of the presence/absence genotyping of the KIR loci into the retrospective Donor/Recipient (D/R) Pair HLA typing project, over 1800 pairs have now been typed.

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The 435 high resolution donor samples from the KIR Typing Pilot Project represent the largest cohort of fully allele-level KIR typed samples to date and are a data rich reference resource for the KIR testing community. Cell lines of common haplotypes and novel haplotypes, i.e. containing novel alleles that represent 80% of the known KIR alleles as of KIR IPD database 2.1 have been produced. These cell lines have been made available through the NMDP Research Repository for the research community. Two cell line sets have been ordered so far.

Approximately 5% of the haplotypes in the KIR Typing Pilot Project were novel or otherwise prevented computational interpretation. Therefore, a new phase was initiated to unambiguously type those samples and physically link the alleles when the genomic structure was novel or unpredictable. This will be implemented in the following year.

NK cells have also been implicated in unrelated hematopoietic stem cell (HSC) transplant outcome through suppression of graft versus host disease, promotion of HSC engraftment, and mediation of graft versus leukemia effects. NK-HLA interaction through inhibitory KIR has been a major focus of investigations regarding the role of NK in HSC Transplantation.

During this grant period, we continued development of the IPR (Immunobiology Project Results) database and applications. This database and its applications will allow for storage and analysis of a variety of immunogenetic data collected on NMDP research samples. This database has replaced the previous HLA donor/recipient pair's database and will facilitate storage and analysis of data from other immunogenetic loci (KIR, microsatellites, single nucleotide polymorphisms, etc). Accomplishments include: an application that accepts, validates, and stores incoming HLA and KIR typing data via HML, an application that automates the processing flow of the data from loading to data analysis to comparison between the labs and the transplant centers to auditing to selection for study; reports to track and audit typing requests and their results; an application that allows users to monitor and resolve typing discrepancies.

Immunobiological test results generated through NMDP/CIBMTR approved studies and reported to the NMDP are summarized in Table 3. These data will be used for testing, validation and population of the IPR database.

Table 3. Immunobiology typing projects utilizing NMDP samples and contributing data to the IPR database

Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data Submitted
NK Cells, Their Receptors and Unrelated Donor Transplant	J. Miller	2300 pairs	KIR	RT-PCR, FACS, SSO, MALDI-TOF	Yes

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Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data Submitted
Survey of Diversity of Immune Response Genes in Unrelated Hematopoietic Stem Cell Transplantation	C. Hurley	40 Pairs	cytokine and KIR	SBT	Yes
Candidate Gene Study to Examine the Impact of Chemokine and Chemokine Receptor Gene Polymorphisms on the Incidence and Severity of Acute and Chronic GVHD	R. Abdi	1300 pairs	CCL1, CCL2, CCR5, CCR2, CX3CR1	Taqman PCR	Yes
Functional Significance of Killer Ig-like Receptor (KIR) Genes in HLA Matched and Mismatched Unrelated HCT	B. Dupont, K. Hsu	2000 pairs	KIR	SSP	Yes
Functional Significance of Cytokine Gene Polymorphism in Modulation Risk of Post-Transplant Complications	E. Petersdorf	2500 pairs	>30 Immune response genes	Taqman PCR	Yes
Identification of Functional SNPs in Unrelated HCT	E. Petersdorf	3500 pairs	Entire MHC region	Taqman PCR	In Process
Use of Female Donors with Pre-existing Antibody to H-Y Antigen will Result in Robust Serologic Response to H-Y Antigens in Male HSC transplantation Recipients	D. Miklos	288 pairs	H-Y Antigen	ELISA, protein array	Yes

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Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data Submitted
Multiplexed Genotyping of Human Minor Histocompatibility Antigens (mHAg): Clinical Relevance of mHAg Disparity in Stem Cell Transplantation	T. Ellis	730 pairs	mHAg	Allele-specific Primer Extension	Yes
Genetic Polymorphisms in the Genes Encoding Human Interleukin-7 Receptor- α : Prognostic significance in Allogeneic Stem Cell Transplantation	K. Muller	851 pairs	IL-7	Taqman PCR	Yes
The Effect of Non-Inherited Maternal Antigens in Cord Blood Transplantation	L. Baxter-Lowe	102 pairs	HLA	SBT	Yes
Detection of HLA Antibody in Single Antigen HLA-Mismatched Unrelated Donor Transplants	S. Arai, D. Miklos	200 pairs	Anti-body	ELISA, Protein array	Yes
Detection of Donor-Directed, HLA-Specific Alloantibodies in Recipients of Unrelated Stem Cell Transplantation and Their Relationship to Graft/Patient Outcome	R. Bray	111 pairs	Anti-bodies	Flow cytometry	Yes

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Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data Submitted
Genome-wide Association in Unrelated Donor Transplant Recipients and Donors: A Pilot Study	R. Goyal	858 pairs	> 600,000 Genome wide SNPs	Human 610 - Quad V1 arrays	In process
SNPs in the p53 Pathway and Outcomes in URD HCT	B. DuPont	1500 pairs	p53, ATM, MDM2 and p21/Waf1	Taqman	In process
Association of Donor and Recipient Gene Polymorphisms of Drug and Innate Immune Response with Outcomes after URD HCT	V. Rocha	725 pairs	GSTP, GSTT, GSTM, UGT CD14, TIRAP, and NALPs	Taqman	In process
To Develop and Test a Prognostic Index for Survival in CML URD HCT	A. Dickinson	1100 pairs	TNF, IL-1RA and IL-10	Taqman	Yes
Evaluation of Lymphotoxin Alpha (LTA) Alleles in Relation to Relapse in AML	P. Posch	~600 samples	LTA	Taqman	In process
Evaluation of TGF- β 1 Promoter and Signal Peptide Polymorphisms as Risk Factors for Renal Dysfunction in HCT Patients Treated with Cyclosporine A	R. Shah	400 samples	TGF- β 1	Taqman	Yes

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Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data Submitted
Donor and Recipient Telomere Length as Predictors of Outcomes after Hematopoietic Stem Cell Transplant in Patients with Acquired Severe Aplastic Anemia	S. Gadalla	650 samples	Telomere length and Telomerase Polymorphisms	Taqman	In process
Development of a GVHD Prevention Biodiagnostic Test	R. Somogyi	450 samples	Gene Expression Array	Array	In process
Genetic polymorphisms and HCT related mortality Re: Pre-HCT conditioning in matched unrelated donor HCT	T. Hahn	>4,000 pairs	GWAS	Array	Pending funding

Aim C.2.2: Related Pairs Research Repository

The whole genome amplification (WGA) project demonstrated the effectiveness of WGA using frozen DNA samples in July 2008 and cord blood samples in March of 2009. WGA is a promising alternative to Epstein Barr virus-induced B-LCL transformation to provide a renewable source of DNA for low volume samples in the Repository and is suitable for use on Peripheral Blood Mononuclear Cells (PBMC), granulocytes, whole blood, B-LCL, previously extracted DNA and non-degraded filter paper. In 2009, the Histocompatibility Advisory Group approved the transition from B-LCL to WGA. The procedure is particularly valuable for the expansion of cord blood research samples due to the minute input requirements and will ensure that these extremely low volume precious samples are available for multiple studies.

Aim C.2.3 CIBMTR Integration

During this period of performance, a task statement of work document was drafted, which builds a plan to integrate immunobiology data across disparate data sources (such as Infectious Disease Markers, IDM, and Research Specimens).

- Work was begun integrating infusion data from both FormsNet and SIP into one table, as well as infuse source and HLA, match grades. and research inventory into one table.

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- During this period the subject areas for Match Grades, Match Grade Variables, and Infectious Disease Markers were added to the Immunobiology Integrated Database in order to continue joining NMDP and CIBMTR data.

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II.D. Clinical Research in Transplantation – Hypothesis 1:

Clinical research in transplantation improves transplant outcomes and supports preparedness for a contingency response.

Aim D.1.1: Observational Research, Clinical Trials and NIH Transplant Center

Cord Blood Research Activity

During the project period, the Cord Blood Research sub-Committee met monthly to discuss study priorities and plan analyses for the following:

- Because the challenge grant application to the National Heart Lung and Blood Institute (NHLBI) to support a study to investigate biomarkers associated with cord blood engraftment was not awarded, the study protocol was re-evaluated and revised to allow the study to proceed with Office of Naval Research (ONR) support.
 - The Duke and MD Anderson laboratory staff continued work on validating the assay methodologies to ensure consistent results were generated at both testing sites for the study investigating biomarkers associated with cord blood engraftment. The study will proceed upon statistical verification of the validation testing results.
- Work continued on the observational study of single versus double cord blood transplants in adults. Further analyses were requested and completed. The principal investigator, EJ Shpall, MD, presented the results to the Graft Sources Working Committee at the 2010 Tandem Meeting. Suggestions from the committee will be incorporated into the analysis and a manuscript prepared.
- An updated analysis plan and study design to evaluate the impact of non-inherited maternal antigen (NIMA) mismatching in CBT was presented to the IBWC at the 2010 Tandem Meeting. Maternal samples were collected from participating Cord Blood Banks (CBBs) and tested.
- The cord blood race matching analysis was refreshed and the population size increased to 4,065 consecutive NMDP distributed CBUs for race and X/6 HLA match. The results were presented at the National Center for Biotechnology Information (NCBI) meeting in March and accepted for poster presentation at the 2010 Cord Blood Symposium.

NMDP staff prepared materials and provided an update on the research sub-Committee activities at the November 2009 Cord Committee Meeting.

- The full committee recommended initiation of a study to validate the findings in a recent publication by Jon van Rood and the New York Blood Center on the impact of NIMA matching in cord blood transplantation.

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- A survey was distributed to the network cord blood banks to determine the availability of maternal HLA typing data and/or samples for testing.
- The IBWC will conduct the validation analysis in cooperation with the research sub-Committee and the CIBMTR Graft Sources Working Committee.

NMDP staff organized and prepared materials for two cord blood workshops that were presented at the 2009 NMDP Council Meeting.

- **Cord Blood Transplants in Adults: A Growing Therapy: Session objectives** were to review history of cord blood transplantation in adult patients, to discuss current practices in adult cord blood transplants, and to describe the role of cord blood in the future of adult stem cell transplantation.
- **Strategies for Improving Outcomes in Cord Blood Transplant: Research and Practice: Session objectives** were to review historical outcome data for cord blood transplant, to discuss the limitations of cord blood transplants, and to discuss innovation techniques that focus on improving cord blood transplant.

Work continued on the development of a white paper detailing recommendations/guidelines for the assessment of new assays (potency or other assays) relevant to cord blood banking and/or transplantation. The final draft of the paper was completed for review at the June 2010 Cord Blood Committee meeting.

NIH Search Support

The National Institutes of Health (NIH) has been accepted as an NMDP transplant center since 2007. Prior to that time, the NIH, representing our Nation's premier medical research endeavor, was not applying their considerable problem-solving skills to issues surrounding unrelated donor transplantation. The NMDP, with ONR support, set out to remedy that deficiency by entering into collaboration with NIH. This collaboration has been extremely successful.

The NMDP is collaborating with intramural NIH transplant programs from the National Cancer Institute, the National Heart Lung and Blood Institute and the National Institute of Allergy and Infectious Diseases. These programs are investigating alternative approaches in unrelated donor transplantation to improve patient outcomes. The actual transplants and the investigational portions of each transplant (i.e., the research protocols) are supported entirely with NIH funds. Navy funding supplies support for donor identification, selection and collection. NMDP donors are not research subjects on these protocols because the donors are making standard donations for accepted transplant indications. The research component of these transplants is conducted entirely by NIH intramural program staff and funded entirely with NIH dollars. The NMDP provided support for the collection of 34 products (26 PBSC and 8 CBU) under the grant.

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Prospective Research

During this grant, activities within the Resource for Clinical Investigations in Blood and Marrow Transplantation (RCI BMT) continued. The goal of this program is to provide an avenue for investigators to obtain statistical and data management support for Phase I and II prospective trials focusing on addressing various transplant issues. The following key elements were completed:

- Clinical Trials Advisory Committee (CTAC) met twice for their annual in person meeting and one conference call meeting during this grant period. The in person meetings occurred at the 2009 and 2010 Tandem meetings. This committee has been charged with providing scientific review and recommendations on clinical trial proposals. The committee reviewed a total of 4 proposals of which two were approved to move forward to protocol developments and two denied. One of the approved proposals did not move to protocol development due to lack of funding and PI decision to not move forward with the study at this time.
- Managed all elements of the Adult Double Cord in patients with hematologic malignancies trial. Staff managed accrual, data management and performed site monitoring. At the end of this grant year, a total of thirty eight patients were accrued on this trial giving us a 69% completion rate.
- Staff continued to provide support to the BMT CTN PBSC vs Marrow Phase III trial. This support included managing the donor component of the study but also assisting the BMT CTN in the area of accrual initiatives on the recipient portion of the study. Activities included were:
 - Completion of accrual for a total of 551 donor/recipient pairs
 - Performed monitoring activities at the donor centers
- During this grant period, the Lenalidomide after allogeneic HCT for Myeloma trial utilized the EMMES data capture system for data management. During this time, defects were identified and staff worked with the trial management system vendor to resolve and make revisions.
- Support included the development and implementation of a protocol for long-term donor follow-up. This work included identifying and streamlining the operational processes needed to implement the protocol October 2010.
- Established internal structure to provide a mechanism to support studies that include a need for survey research functionality. This included hiring of an experienced supervisor with research call center experience and research interview staff. Staff developed processes and procedures to support studies requiring their expertise.

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CIBMTR Observational Research

Support of the Observational Research program included statistical hours for managing studies within the Immunobiology (see section IID1.3 below), GVHD, and Graft Sources Working Committees. During this grant period staff performed proposal review, protocol development, data preparation, data analysis, and manuscript preparations. Details regarding the Immunobiology activities can be found in IID1.3 below. The GVHD and Graft Sources Working Committees published 8 manuscripts.⁷⁻¹⁴ During the grant period staff performed various other functions on over 20 other studies.

FormsNet Development

- FormsNet v2.9, 2.9.1, 2.10, and 2.11 were released during the grant period, providing bug fixes and enhancements including Donor Forms and Functionality, Clinical Trials functionality, Recipient/Donor enhancements and 26 form revisions.
- A Growable Network Information System (AGNIS) v2.0 was released. An approach to allow re-publish of previously completed forms was implemented. All previously completed Transplant Essential Data (TED), pre-TED, and Death forms into the AGNIS 2.0 repository were re-published. Processes to authorize transplant center retrieval of completed forms through AGNIS 2.0 were established. Form 2005 (HLA) revision 1 to external development for submission by transplant centers was released. Curation of revision 2 of mandated forms (TED, Pre-TED, HLA, IDM, and Infusion) was completed.

Funding from the ONR provided the NIH the necessary resources to build a successful unrelated transplant program. NMDP provided support for donor identification, selection and collection for the NIH intramural unrelated donor transplant program. Activity during the period of performance was as follows:

- 46 formal searches
- 150 donor confirmatory typing blood sample and IDM testing requests
- 16 cord blood unit confirmatory typing requests
- 25 PBSC collections
- 8 cord blood shipments

Aim D.1.2: Research with NMDP Donors

During this grant period staff continued activities in support of donor studies proposed by investigators outside the NMDP.

- Dr. Galen Switzer's study to examine the impact race and culture has on a donor's decision to proceed through the confirmatory testing and donation process continued.

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Dr. Switzer has a five year NIH grant through the University of Pittsburgh to conduct the study.

- Staff continued to collaborate on a (Children's Oncology Group) COG KIR study. Activities included working with the donor center to ensure consent obtained, facilitating the collection of a donor blood sample, and shipment to the study lab. During the grant period a total of 119 donor samples were facilitated.

Aim D.1.3: Expand Immunobiology Research

During the grant period, the CIBMTR IBWC met monthly to discuss progress on ongoing research studies.

During the grant period, funds were used to contract with an Immunogenetic Biostatistician at the Medical College of Wisconsin to provide support to NMDP Scientific Services and the CIBMTR IBWC. The biostatistician helped to conduct and direct research within the IBWC and assisted the Scientific Services department to advance models for registry composition analyses, haplotype frequencies, predictive algorithm, and automated donor selection algorithms.

The grant funds also supported significant outreach efforts by the IBWC leadership to increase exposure for the IBWC to basic scientists and other investigators. The IBWC leadership updated the committee brochure and informational materials for distribution at basic science meetings and had a presence at the annual ASH, BMT Tandem, EBMT, EFI, and ASHI meetings. The IBWC sponsored an information booth promoting the activities and resources of the committee at the ASHI annual meeting. The scientific director and Ph.D. statistician also participated in the CIBMTR External Scientific Agenda review.

To further stimulate completion of immunobiology studies within the CIBMTR, grant funds were used to provide monetary support to investigators whose studies require modest supplemental funding for completion. The IBWC awarded the following Immunobiology Research grant during the grant period:

- Research funds were awarded to support DNA extraction and preparation of 408 samples for a study evaluating genome wide genetic diversity and the impact on acute graft versus host disease.

In addition, the IBWC continued work on the >40 active studies in the committee, accepted 6 new proposals for analysis, presented 4 abstracts and published/submitted 10 manuscripts. The IBWC also provided support for submission of several research grants providing study population determinations for the use of research specimens and letters of support.

The CIBMTR IBWC met monthly during the quarter to discuss progress on ongoing research studies. During this period of performance:

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- Eight manuscripts were published¹⁵⁻²² and two submitted for publication:
 - Lujia Dong, et al., The outcomes of family haploidentical hematopoietic stem cell transplantation in hematological malignancies are not associated with patient age. Rejected by Blood. Submitted to Biology of Blood and Marrow Transplantation.
 - Susana Marino, et al. Mismatched Unrelated Donor Stem Cell Transplantation: Identification of HLA Class I Amino Acid Substitutions Associated with Survival at Day 100. Submitted to Blood.

- Two abstracts were submitted and accepted for presentation at the 2009 ASH annual meeting,^{23,24} one abstract was submitted and accepted for presentation at the 2010 Tandem BMT annual meeting,²⁵ and one abstract was submitted to the 2010 ASH annual meeting:
 - Bronwen Shaw, et al., Permissive HLA-DPB1 mismatching compared to a non-permissive mismatching significantly improves overall survival following allogeneic transplantation in patients with both 10/10 and 9/10 matched unrelated donors. ASH Annual Meeting 2010.

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Attachment B – Published Manuscripts and Abstracts
Associated with this Grant

Manuscripts and Book Chapters

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