National Marrow Donor Program®

Entrusted to operate the
C.W. Bill Young
Cell Transplantation Program

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May 11, 2009

Cdr. Elizabeth Montcalm-Smith
Office of Naval Research (ONR 342)
875 N. Randolph St.
Arlington, VA 22203-1995

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

Reference: Grant Award #N00014-06-1-0058 between the Office of Naval Research and the National Marrow Donor Program

Dear Cdr. Montcalm-Smith:

Enclosed is subject document which provides the performance activity for each statement of work task item of the above reference for the period of January 1, 2009 to March 31, 2009.

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

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

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

Sincerely,

Carla Abler-Erickson

Carla Abler-Erickson, MA
Sr. Contracts Representative

Enclosure: Quarterly Report with SF298

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14. ABSTRACT

1. Contingency Prepardness: Collect information from transplant centers, build awareness of the Transplant Center Contingency Planning Committee and educate the transplant community about the critical importance of establishing a nationwide contingency response plan.

2. Rapid Identification of Matched Donors : Increase operational efficiencies that accelerate the search process and increase patient access are key to preparedness in a contingency event.

3. Immunogenetic Studies: Increase understanding of the immunologic factors important in HSC transplantation.

4. Clinical Research in Transplantation**:** Create a platform that facilitates multicenter collaboration and data management.

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Research in HLA Typing, Hematopoietic Stem Cell Transplantation and Clinical Studies to Improve Outcomes

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NATIONAL MARROW DONOR PROGRAM®

Creating Connections. Saving Lives.™

Grant Award N00014-08-1-0058

QUARTERLY
PERFORMANCE / TECHNICAL REPORT
FOR
JANUARY 01, 2008 to MARCH 31, 2008

Office of Naval Research

And

The National Marrow Donor Program
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IIA. Contingency Preparedness – Hypothesis 1: Recovery of casualties with significant myelosuppression following radiation or chemical exposure is optimal when care plans are designed and implemented by transplant physicians	
IIA.1.1 Aim 1: Secure Interest of Transplant Physicians	**Period 5 Activity:** • In 2009 a total of 67 RITN center staff successfully completed the Basic Radiation Training (BRT). Since its creation in 2006 a total of 1,836 RITN center staff have successfully completed BRT; this is a passing rate of 96%. • 26 RITN center staff members attended Advanced Radiation Medical Emergency training course conducted in Oakridge, TN at the Radiation Emergency Assistance Center/Training Site (REAC/TS) on March 26 & 27, 2009. Course lessons included: o Basic Health Physics & Radiation Protection: Part I o A History of Serious Radiological Incidents: The Real Risk o Health Physics & Contamination Control: Part II o Radiation Detection, Monitoring & Protection Laboratory Exercise & Quiz o Diagnosis & Management of the Acute Radiation Syndrome (ARS) o Diagnosis & Management of Internal Contamination o Diagnosis & Management of Acute Local Radiation Injury & Case Review: Yanango Peru o Radiation Sources & Radiological Terrorism o Radiation Emergency Area Protocol Demonstration o Radiation Emergency Medical Management Drill o Radiation Dose Estimations – Problem Solving Session • During this period we continued to plan for the 2009 RITN conference "Nuclear Terrorism: Hematology/Oncology Center Preparedness" to be held in Bethesda, MD on May 18th (additional details of this conference are listed under AIM II A 2.1).

IIA.1.2 Aim 2: GCSF in Radiation Exposure	**Period 5 Activity:** • No activity this period.
IIA.1 3 Aim 3: Patient Assessment Guidelines and System Enhancements	**Period 5 Activity:** • Participated in the Donor Contingency Portal project to improve response processes for emergencies that impact the NMDP and its' donors.
IIA 1.4 Aim 4: National Data Collection Model	**Period 5 Activity:** • FormsNet v2.7.1 was released on 2009-02-18. This version included a series of modifications to the patient forms. • FormsNet v.2.7.2 was released on 2009-03-18. This version included many changes for forms tracking and a number of modifications to prepare FormsNet for the pending AGNIS 1.2.0 release. • Development and Analysis is underway for FormsNet v2.9 (Donor Forms), v2.10 (Recipient Forms updates/modifications) and v2.11 (Clinical Trials and Audit) • AGNIS v1.2.0 was released 2009-03-27. Data elements curation is now complete on the mandated SCTOD core forms. The application is ready for processing data from Transplant Centers on 5 of the 6 core forms: 1. 2004 - Infectious Disease Markers 2. 2005 - Confirmation of HLA typing 3. 2400 - Pre-Transplant Essential Data (TED) 4. 2450 - Post-Transplant Essential Data (TED): 5. 2900 - Recipient Death Data These forms represent 46% of the total number of forms (153,000) processed since the launch of FormsNet Dec 3, 2007. The first production form was sent on the day of the release by the team at MD Anderson. The website (agnis.net) saw a flurry of activity and an additional 10 centers joined the pilot group.

IIA. Contingency Preparedness – Hypothesis 2: Coordination of the care of casualties who will require hematopoietic support will be essential in a contingency situation.	
IIA.2.1 Aim 1: Contingency Response Network	**Period 5 Activity:** • Completed the development of the 2009 RITN Tabletop Exercise and distributed it to all RITN centers to complete prior to the end of July 2009. • During this period we continued to plan for the 2009 RITN conference "Nuclear Terrorism: Hematology/Oncology Center Preparedness" to be held in Bethesda, MD on May 18, 2009. o Based on current registrations we will have approximately 100 attendees o During this period we finalized a keynote opening address on RADM by W. Craig Vanderwagen (Assistant Secretary for Preparedness and Response) o This conference will have a group session in the morning to provide a common operating picture then have three (3) interactive breakout workshops held three (3) times in the afternoon so that all attendees have the opportunity to participate. o Morning sessions include: ▪ 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 o Afternoon interactive breakout workgroups include: ▪ Altered Standards of Care ▪ Logistical issues – bed mgmt, use of non-hospital loc, & staffing issues ▪ Provision of medical care – early and late care

- The conference will culminate with a report of findings by the afternoon session moderators, with the intent of publishing these findings later in the year.

- **Meetings**:
  - A RITN poster was present at the U.S. Department of Health and Human Services 2009 Integrated Medical, Public Health, Preparedness and Response Training Summit conference.
  - Conducted three (3) monthly conference calls with RITN centers to assist in completion of required tasks and to improve integration into the network.
  - 26 Committee members attended the RITN Steering Committee meeting at the 2009 ASBMT/CIBMTR Tandem meetings on February 11, 2009, the meeting agenda consisted of:
    - RITN accomplishments in 2008
    - 2009 expansion of RITN
    - 2009 RITN tasks and educational activities
    - New developments
    - RITN Tabletop Exercises Lessons Learned from 2006-2008 and a 2009 Tabletop Exercise Overview
    - Maintaining RITN's Momentum
  - Continued to plan for a RITN Steering Committee meeting to be held on May 19, 2009 following the RITN educational conference, tentative meeting agenda includes:
    - 2009 conference review
    - 2010 or 2011 conference planning
    - Update on tabletop Lessons Learned project
    - Coordination with HHS on triage of incident victims

	▪ Update on RITN-VA mapping project ▪ Update on JCAHO interaction ▪ BARDA Presentation ▪ Tour of HHS Secretaries Emergency Operations Center o Distributed three (3) "Rad in the News" open source news summary reports to RITN centers and partner organizations with the intent to maintain awareness of international activities related to radioactive materials. o Presented "Hematologists/Oncologists Preparing for a Radiological Disaster" to the Mass Casualty Conference hosted by the Bundeswehr in Munich, Germany o Attended the 18th Medical Defense Conference on the behalf of RITN, hosted by the Bundeswher in Munich, Germany
IIA.2.2 Aim 2: Sibling Typing Standard Operating Procedures	**Period 5 Activity:** • No activity this period.
IIA. Contingency Preparedness – Hypothesis 3: NMDP's critical information technology infrastructure must remain operational during contingency situations that directly affect the Coordinating Center.	
IIA.3.1 Aim 1: I.S. Disaster Recovery	**Period 5 Activity:** • Additional hardware and software was purchased, installed and configured to support disaster recovery testing. Additional network segments were also added to support disaster recovery environment all for completing the upcoming test. • Completed the disaster recovery smoke test for all Tier 1 applications in preparation for the disaster recovery exercise in April 2009. Also, preparations have begun for disaster recovery testing for Tier 2 through 5 applications which will be completed early summer, 2009.

IIA.3.2 Aim 2: Critical Facility and Staff Related Functions	**Period 5 Activity:**
	• **Business Continuity Planning:**
	  • Emergency communications:
	  o In response to ongoing satellite telephone connectivity issues we completed the recall of 51 issued GlobalStar satellite telephones and issued 55 replacement Iridium satellite telephones to all RITN centers.
	  o Completed the installation of a fixed satellite telephone at MSKCC in New York City; a fixed system was necessary due to skyscrapers preventing sufficient signal strength with the satellites.
	  o Conducted a communications test with the NMDP Network via email notification, tested notifying NMDP staff and key partners via the telephonic Emergency Notification System, tested the Coordinating Center public announcement system and the GETS cards.
	  • Continued to develop a business continuity plan to improve the resiliency of the organization immediately following a catastrophic incident impacting the NMDP Coordinating Center.
	  • Initiated a Critical Document Registry to identify critical documents to sustained operations immediately following a disaster. This involved identifying the documents as well as their location, be it physical or electronic.
	  • Provided business unit representation and business continuity expertise on the Steering Committee for the IT Disaster Recovery test scheduled for April and May 2009.
	  • Continued to plan with IT staff to conduct a staff business continuity exercise where staff will perform key work duties from a remote work environment.

IIB. 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.	
IIB.1.1 Aim 1: Increase Registry Diversity	**Period 5 Activity:** Five contracted HLA testing laboratories performed HLA-A, B, DRB1 typing, one laboratory performed HLA-A, B, C, DRB1 typing, on a total of 36,849 newly recruited donors o Blind quality control testing error rate was 0.17%, meeting the project requirement of ≤ 2.0%. o On-time testing completion rate was 97%, meeting the project requirement of a minimum of 90% of typing results reported within 14 days of shipment of samples. During this period several HLA typing projects were developed to refine allele frequency data and reagents.. These studies were designed to increase the resolution and quality of HLA typing on the registry to potentially speed donor selection and correctly characterize the match for searching patients, especially from diverse donor populations. Specific alleles planned for retesting include: • The allele DRB1*0811 was described in March 1994 and is relatively common in Native American (NAM) populations. Until reagents were added to type for DRB1*0811, samples would have been reported as DRB1*0802 or with codes that contain the DRB1*0802 allele. It is postulated that NAM samples, typed before reagents for DRB1*0811 were added, may have been incorrectly reported. This project will test DRB1 on 92 NAM samples originally typed as DRB1*0802. Samples with serologic typing at A and B will also be retyped by DNA methods to upgrade the typing. • The allele DRB1*1506 was described in June 1996 and is seen in Asian populations. Until reagents were added to type for DRB1*1506, samples would have been reported as DRB1*1501 or with codes that contain DRB1*1501. It is postulated that Asian samples typed before January, 1997 may actually carry DRB1*1506. This cohort contained a relatively large number of samples. Rather than type all these samples, HapLogic was used to analyze the cohort and selectively remove samples with a low probability of carrying DRB1*1506. Samples with potential to type as DRB1*1506 and those where one or both haplotypes could not be predicted were retained for further typing (N=221). Samples with serologic typing at A and B will also be retyped by DNA methods to upgrade the

	typing. • A*3010 was described in Jan 2001. Samples with A*3010 typed prior to 2001 were reported as A*3002. In the NMDP database, samples with A*3010 are nearly always seen with B*4101/DRB1*0405 and it is hypothesized that this allele occurs on a well conserved haplotype. Retyping of samples (N=117) reported prior to 2002 as A*3002 with B*41 and DRB1*04 typing that includes DRB1*0405 will be completed to test the conserved haplotype hypothesis. • A*2423 was described in April 1999. Samples with A*2423 typed before 1999 were reported as A*2403. In a prospective typing project of minority donors, 22 NAM samples were reported with A*2423 (two initially were reported as having A*2403) and only one carried A*2403. This suggests that NAM samples typed as A*2403 prior to 2000 actually carry A*2423. NAM samples (N=20) reported prior to September 2000 as A*2403 will be retyped to test this hypothesis. <u>Adult Donor Registry:</u> To successfully serve all patients in need of cellular transplantation, the Marketing and Communications Department continues to focus on developing and executing strategies and tactics that increase awareness, education and engagement among target audiences. During the January – March, 2009 time-frame, we developed and implemented a program entitled "Get In The Game. Save a Life." The program is designed to educate college football athletes at 26 colleges and universities, their school community and their social network about the need for unrelated marrow donors and add 5,000 committed new members to the registry during the spring camp season. Additionally, the program has garnered significant press, helping to educate the general public about the need and how they can help save patients lives.
IIB.1.2 Aim 2: Evaluate HLA-DRB1 High Res typing	**Period 5 Activity:** • This task is closed.
IIB.1.3 Aim 3: Evaluate HLA-C Typing of Donors	**Period 5 Activity:** • This task is closed.

IIB.1.4 Aim 4: Evaluate Buccal Swabs	**Period 5 Activity:** • No activity this period.
IIB 1.5 Aim 5: Enhancing HLA Data for Selected Donors	**Period 5 Activity:** This aim consists of two prospective, 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. The primary goal of the Replacement Donor Pilot Study was to identify an HLA-A, B, DRB1 identical replacement donor for every donor selected for workup by a TC. • While the primary study was completed in December 2007, NMDP staff continued to monitor the patient-directed utilization of donors typed in this project. The primary objective of the Optimum Donor Pilot Study was to develop a systematic strategy to classify adult donors into phenotype categories based upon the likelihood to appear on a patient's search. Adult donors with high potential to match searching patients were selected and proactively contacted to verify availability, upgrade HLA, in an effort to increase their utilization and to help reduce the search times for patients. • NMDP staff continued to monitor the patient-directed utilization of all donors typed through the project. Further analysis of patient phenotype categories was completed, and will set the stage for the selection and prospective typing of additional donors in the next reporting period. Donor selection strategies were extended to include pilot strategies for the identification of AB only donors associated with current patient searches for which there are relatively few 6/6 matched donors. • 428 donors were selected and samples shipped for prospective HLA typing during this reporting period. NMDP staff continues to monitor the patient-directed utilization of all donors typed through the project.

IIB 1.6 Aim 6: Maintain a Quality Control Program	**Period 5 Activity:** New Quality Control (QC) master HLA types were added to the inventory of QC samples available for inclusion in recruitment and customized typing shipments. • 66 new volunteer donors were recruited to add HLA diversity to the QC program. A portion of the blood samples were spotted onto filter paper and the remainder aliquoted and frozen for future use. High resolution HLA-A, B, C, DRB1, DQB1, and DPB1 typing was performed on a sample from each volunteer. For volunteers that are also on the registry, these results will be used to update their registry typings. • 100 new and unique B-Lymphocytic Cell Line (B-LCL) samples were expanded to provide cells for the creation of B-LCL QC swabs.
IIB. 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.	
IIB 2.1 Aim 1: Collection of Primary Data	**Period 5 Activity:** The Primary Data Project included a previous summary on the utility of gentotype lists for newly recruited donors, a data refresh was performed that included August 2008 and January 2009. These new data will be evaluated for the overall usefulness of primary data and will be included in any future summary. • A new version of the KIR SSO kit was implemented. A basic "presence/absence" interpretation algorithm was implemented to allow the KIR SSO data to be validated. • Seven SSO probe kits were registered during the past quarter including two versions of the OLI high-definition bead system. A 2nd recruitment lab is now beta testing the SBT message format in HML.
IIB 2.2 Aim 2: Validation of Logic of Primary Data	**Period 5 Activity:** • This task is closed.

IIB 2.3 Aim 3: Reinterpretation of Primary Data	**Period 5 Activity:** • This task is closed.
IIB 2.4 Aim 4: Genotype Lists & Matching Algorithm	**Period 5 Activity:** • A re-interpretation of 9.8M locus-level probe results is underway to get all data to the HLADB 2.24.0 (Jan 2009) allele list.
IIB. 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.	
IIB.3.1 Aim 1: Phase I of EM Haplotype Logic	**Period 5 Activity:** The objective of the project was to complete extended high resolution DNA typing on 837 self-described Caucasian donor samples for HLA-A, B, C, DRB1/3/4/5 and DQB1 to provide additional haplotype frequency information and linkage data to enhance the HapLogic algorithm. The laboratories were required to resolve ambiguities outside of exons 2 and 3 for class I and outside of exon 2 for class II if an allele was considered 'common in the US' per the manuscript "Common and well-documented HLA alleles: report of the ad-hoc committee of the American Society for Histocompatibility and Immunogenetics," Hum Immunol 2007; 68 (5): 392-417. • The donors included in the project were 'Recently' contacted Caucasian race under age 31 with a stored repository sample and no activity from the 800K cohort. The typing was initiated in September 2008, and completed in December. The laboratory is investigating potential new alleles on 5 donor samples for an overall potential new allele rate is 0.57%. Discrepancy resolution was initiated on 9 samples and was completed in January 2009. The overall discrepancy rate was 1.0%. • Data are being evaluated for haplotype frequencies and linkages for use in the HapLogic algorithm. • A prototype of a new 8/8 and 10/10 prediction system within HapLogic was implemented. Further development and validation is planned.

IIB 3.2 Aim 2: Enhancement of EM Algorithm	**Period 5 Activity:** • Two manuscripts were submitted for publication during the past quarter: ▪ The Mexican Americans: HLA characteristics of a uniquely derived ethnic group ▪ The HLA genetics of Jewish populations o Both have received reviewer comments and are being prepared for re-submission
IIB 3.3 Aim 3: Optimal Registry Size Analysis	**Period 5 Activity:** • The full-registry haplotype frequency analysis project called NEMO, which is being implemented to generate high-resolution haplotype data for registry size analysis, made progress. • The re-interpretation of 9.8M locus-level probe results has been running for several weeks. Two factors are affecting the performance of this analysis: 1. The massive increase in alleles 2. The massive amount of primary data to re-interpret • A new developer was added to the project to focus on performance optimizations
IIB 3.4 Aim 4: Target Under-represented Phenotypes	**Period 5 Activity:** • More progress is being made with new ESRI-ARC GIS Geographical Analysis software. A preliminary analysis generated the following list of applications of HLA maps: o Maps would show areas where HLA types are congregated. This would allow targeted recruiting for rare HLA alleles, phenotypes or haplotypes. o Maps could be used for patients with rare alleles or haplotypes to identify areas where there may be a related HLA population. o Concordant maps could be overlaid for patients with one or two rare haplotypes. Overlap would identify geographic areas where there may be potential donors not yet recruited. o Maps would be offered to donors as a way to identify areas where relatives or ancestors may be located or originated, for those interested in such information.

	○ Maps would be used to identify trends in HLA population substructure, migration patterns and HLA phylogenetic evolution. ○ The underlying database for this project would provide information from which other important geographic studies of HLA could be conducted.
IIB 3.5 Aim 5: Bioinformatics Web Site	**Period 5 Activity:** • This task is closed.
IIB 3.6 Aim 6: Consultants to Improve Algorithm	**Period 5 Activity:** Funding on this aim provides support for the Search Strategy Advice (SSA) program provided to TCs to meet their need for HLA expertise for unrelated stem cell donor selection. The program includes external and internal HLA experts who review each patient search and write a report summarizing a search strategy to assist the TC in rapidly identifying the best potential stem cell source for their patient. The HLA experts provided valuable feedback for algorithm and IT enhancements throughout the quarter. The SSA program completed 417 patient reports for 85 TCs during this quarter. The average turnaround time for all reviews was 3.9 business days which met the program requirement of 5 business days. Both internal and external experts participate in a rigorous QC program and all met the requirements during the past quarter.
IIB. 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.	
IIB.4.1 Aim 1: Expand Network Communications	**Period 5 Activity:** In the last quarter, the effort for has been focused on the analysis and realization of request/fulfillment messaging and storage. This foundation (data model & integration) is a prerequisite for implementing improved electronic communication and parallel search stages. • Analysis and vetting of request/fulfillment messaging structure through peer-to-peer (P2P) message realization. • Analysis and vetting of request/fulfillment storage model.

	Do It Yourself (DIY) application project work efforts delivered the following functionality to allow Donor Centers and Recruitment Groups to use DIY as a recruitment tool: • Automation of Drive request by DC/RG's – formerly, Recruiters filled out a drive request in SLW, and then faxed in the request. Staff would manually approve these drives. • Ability to create single use promotional codes and create estimates for a drive. • Ability to set up multiple funding sources in a single drive. Example: CMF donor paid in which donor pays $25.00, or CMF sponsor paid, in which a sponsor is billed and the donor responsibility is $0. • Prioritization and automation of funding sources which allows recruiters to choose which funding type should be charged first. • Added functionality including Stage Drive, Cancel Drive, Estimate Status and Date, and View of actual against estimates via the Drive Estimates Grid. • Setting Drive types: This allowed for automation of "Live" drives as well. • Drive estimates automatically updating in FDR. • Automated status of donors including staged, newly entered, or duplicate. • Create unique "single use codes" - ability to have SLW automatically generate X number of unique codes for a single drive, with the added functionality to export these promotional codes to a spreadsheet for mail merge. • Drive max for Caucasian and overall drive totals. • Automatic invoicing of newly entered donors. • Automation of emails for kit returned, no kit received, and pending deletion due to incomplete registration in 45 and 60 days. • User Interface (UI) changes for Pending Donor and Pending Drive including new functionality of screens for additional edits. **DIY 2 - Updated Functionality and User Interface** • Automation of triggers to send emails to donor, email sent after 5, 10, and 15 days. • Interface changes such as "Verisign" logo. Reports that will allow tracking of donor recruitment and the supporting activities: • Drive Activity Reports • CSS Activity Reports

	• Drive Detail Report **FDR** • FDR will get new pushes of data from STAR Link via transactions. This new interaction will eliminate the need to send a Drive Detail report via email to the FDR user and will replace the "keying" of drive estimates. • Changing the invoicing frequency due to length of drive. Drives longer than 12 days will invoice only monthly compared to the standard weekly.
IIB.4.2 Aim 2: Central Contingency Management	**Period 5 Activity:** • During the past quarter provided physician education for Custom Search Support (CSS) program at the Tandem (ASBMT/CIBMTR) meeting. Transplant center (TC) medical directors were contacted to arrange meetings with CSS staff. The targeted centers were those TCs that had; 1) expressed interest in the program, 2) staff turnover, 3) increased transplant activity, or, 4) TC coordinators who were struggling with work volume. Five scheduled physician information meetings were held to assess interest. Four requested follow-up activity. • The CSS program was one of the NMDP services promoted in the NMDP booth at the Tandem meeting. CSS promotional materials were distributed and CSS staff were available to discuss the services. • The CSS program had an increase in activity this quarter. Two TCs received trial cases to evaluate the service. In addition, two network member TCs began using the service. The volume of CSS reviews for this quarter was the highest to date with 271 reviews completed.
IIB.4.3 Aim 2: Benchmarking Analysis	**Period 5 Activity:** • This task is closed.
IIB.4.4 Aim 2: Expand Capabilities of Collection and Apheresis Centers	**Period 5 Activity:** • This task is closed.

IIC. 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.	
IIC.1.1 Aim 1: Donor Recipient Pair Project	**Period 5 Activity:** In 1994 a retrospective Donor/Recipient Pair HLA typing project to characterize class I and class II alleles of donor/recipient paired samples from NMDP's Repository was initiated. The goals of this ongoing research project are to assay 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 and finally to promote the development of DNA-based high resolution HLA typing methodologies. • Sample Group 21 (SG21) period of performance came to a close on December 31, 2008. During the quarter discrepancy, no make and linkage analyses were completed. 491 pairs (98%) of SG21 were audited and made available for research. • Scientific Services staff compiled all outstanding typing issues from prior SGs and distributed samples to a tie-breaker laboratory for final resolution. Results are due next quarter. • The project period for SG22 began January 2, 2009 and will come to a close on April 30, 2009. The contracts for SG22 (273 pairs) testing includes intermediate and high resolution HLA and also presence/absence testing for 14 KIR loci (2DL1-5, 2DS1-5, 3DL1-3 and 3DS1). • Scientific Services and Bioinformatics staff initiated sample selection and database preparation for SG23, which will consist of 400 pairs and will begin next quarter with a project period from April 30, 2009 to August 31, 2009.
IIC. Immunogenetic Studies – Hypothesis 2: Even when patient and donor are HLA matched, GVHD occurs so other loci may play a role.	
IIC 2.1 Aim 1: Analysis of non-HLA loci	**Period 5 Activity:** In 2005 a pilot study to perform high resolution KIR gene typing was launched. The primary objectives of the study were to move technology forward from the current practice of locus level typing to high resolution typing, disseminate information and protocols in an open source mechanism and develop reference lines for

	use in individual laboratories. • Resolution of new alleles found within Phase 1, 2 and 3 of the KIR Typing Pilot Project were shipped to the DNA Project Officer and resolution/typing began late this quarter. • Manuscript preparation for the KIR Typing Pilot Project was initiated. A meeting to discuss the data obtained and further analysis of this data is scheduled for early next quarter at the NMDP coordinating center. The Immunobiology Project Results (IPR) database and its applications will allow for storage and analysis of all immunogenetic data collected on NMDP research samples. This database will replace the existing HLA donor/recipient pairs database and facilitate storage and analysis of data from other immunogenetic loci (KIR, microsatellites, single nucleotide polymorphisms, etc). • The Scientific Services and Bioinformatics departments continued to collaborate on the design and development of the IPR database application and tools. • Development was mostly completed on an application that will transfer data from the existing legacy database to IPR. • Development was mostly completed for acceptance, validation, and storage of incoming HLA and KIR typing data via Histoimmunogenetics Markup Language (HML), including genotype lists. This functionality will move to testing.
IIC 2.2 Aim 2: Related Pairs Research Repository	**Period 5 Activity:** • Related transplant research sample collection continued with a pilot project initiated at seven TCs in December 2007. By the end of the reporting period, five TCs had submitted 460 samples (208 donor/recipient pairs) to the Repository. Development continues on the Research Sample Repository Tools suite to facilitate management of samples. Several enhancements were tested and released to production. • The whole genome amplification (WGA) project continued with the evaluation of the effectiveness of WGA using cord blood samples. In March of 2009 WGA was performed on 10 samples; five of which were of DNA extracted from cord blood and the other five of filter paper samples spotted with cord blood. All samples achieved amplification close to the expected amount of 40ug from an initial

	input of 10ng. In order to validate the effectiveness and reliability of WGA at producing unbiased, high quantity and quality DNA products, the amplified DNA samples will be high resolution typed at HLA- A, B, C, DRB1, DQB1, and DPB1 by SBT. Typing results will be completed early next quarter.
IID. Clinical Research in Transplantation – Hypothesis 1: Clinical research in transplantation improves transplant outcomes and supports preparedness for a contingency response.	
IID.1.1 Aim 1: Observational Research, Clinical Trials and NIH Transplant Center	**Period 5 Activity:** **Observational Research** • Staff continued work on various observational studies within the area of Immunobiology and GVHD and Graft Sources Working Committees. • All CIBMTR Working Committees held their annual meetings at the Tandem meeting in February. A total of 68 new proposals were reviewed and prioritized during these meetings. • A total of 15 manuscripts were published, three accepted and 7 submitted from the CIBMTR Working Committees during this reporting period. **Prospective Studies; RCI BMT** • Activity related to the BMT CTN PBSC vs. Marrow trial continued with a total of 483 donor/patient pairs randomized at the end of this reporting quarter. Accrual at the end of September was 88% complete. We continue to see an increase in work-ups and randomizations which directly reflects efforts made to increase accrual and the goal of completion in 2009. • Adult Double Cord trial activity during this period included one patient being enrolled for a total of 12 patients giving us a 22% completion rate. Staff continue to coordinate and complete monthly PI and coordinator calls, manage data collection and monitor sites. • Revlemid trial activity continued to progress forward. The trial was official opened at two sites in February with a total of one patient accrued during this reporting period. It is anticipated that an additional five sites will open to accrual during the next period.

- Activity continued on protocol development for the AZA study titled *Low Intensity Therapy of MDS Prior to Non-Ablative Allogeneic Stem Cell Transplantation.* Additional funding continues to be explored to support portions of this study.

Work began on a requirements document for the FormsNet platform development to support donor data management and clinical trial management.

The Cord Blood Research sub-Committee met monthly to discuss study priorities and plan analyses. Activity during the past quarter focused on the following areas:

- Continued work on several research projects
  - Data analysis continued on a study to evaluate differential cellular recoveries for CBUs from various race groups with a focus on determining root causes of low cell yields from African American CBUs. MD Anderson Cancer Center, Duke and the St. Louis Cord Blood Bank compiled the results of pre and post processing cell yield s for CBUs from various racial/ethnic groups.
  - The cell processing laboratory at Memorial Sloan-Kettering Cancer Center (MSKCC) recently developed a modified gating strategy for CD34 viability assessment that correlates with engraftment potential in a single center study. MD Anderson Cancer (MDACC) confirmed the feasibility of applying the modified gating strategy to archived pre-transplant flow cytometry files. Reanalysis of the MDACC files is in process and will be evaluated for engraftment correlation upon completion.
  - Work began to prepare a challenge grant application to the NHLBI to support a study to investigate biomarkers associated with cord blood engraftment. The study will evaluate a panel of assays on cord blood segments distributed for HLA confirmatory typing by the NMDP cord blood bank Network and correlate the results with engraftment data from the CIBMTR.
  - The protocol and study design for a retrospective observational study of single versus double cord blood transplants in adult patients was presented by PI E. J. Shpall during the CIBMTR Graft Sources Working Committee meeting at the BMT Tandem meetings. The study received a high priority score and has been placed on a fast track to complete the analysis in time to submit an abstract to the 2009 ASH meeting.

	o A group met at the BMT Tandem meetings to discuss the development of an adverse event reporting form for CBU shipments. The form was distributed to the full committee for review and comment prior to implementation.
IID.1.2 Aim 2: Research with NMDP Donors	**Period 5 Activity:** • Staff continued support of a Donor Ethnicity study with Dr. Galen Switzer from the University of Pittsburgh. • Staff continued to collaborate on a COG KIR study. Activities include facilitating the collection of a donor blood sample and shipment to the study lab. To date, 17 patients have been enrolled and 52 donor sample requests being facilitated. • Staff continued to develop a protocol for centralizing the NMDP long-term donor follow-up. The protocol is on track for approvals processes in spring 2009. • During this review period staff began to explore support of two additional studies.
IID.1.3 Aim 3: Expand Immuno-biology Research	**Period 5 Activity:** The CIBMTR IBWC met monthly during the quarter to discuss progress on ongoing research studies • Two manuscripts were accepted for publication: o S Spellman, M Warden, M Haagenson, B Pietz, E Goulmy, E Warren, T Wang, T Ellis. **Effects of mismatching for Minor Histocompatibility Antigens on clinical outcomes in HLA-matched, unrelated hematopoietic stem cell transplants.** Accepted by Biology of Blood and Marrow Transplantation. o L Baxter-Lowe, M Maiers, S Spellman, M Haagenson, T Wang, M Fernandez-Vina, S Marsh, M Horowitz, C Hurley. **HLA-A Disparities illustrate challenges for ranking the impact of HLA mismatches on bone marrow transplant outcomes in the United States.** Accepted by Biology of Blood and Marrow Transplantation. • Five abstracts were presented at the 2009 Tandem BMT meetings: o S Arai, D Tyan, T Vayntrub, S Vail, A Hassebroek, C Brady, S Spellman, DMiklos. **Antibodies**

are detected against mismatched HLA class II alleles and not class I following allogeneic hematopoietic cell transplantation. Accepted for poster presentation.

- B Sahaf, B Narasimhan, K Miller, K Spencer, S Spellman and D Miklos. Female **Donor H-Y Seropositivity Does not Predict Male Recipient HCT outcomes, including cGVHD**. Accepted for poster presentation.
- J Venstrom, T Gooley, S Spellman, R Hasan, J Pring, M Malkki, B Dupont, E Petersdorf', K Hsu. **Donor KIR 3DS1 is associated with Less Acute GvHD Following Unrelated Allogeneic Hematopoietic Cell Transplantation for Hematologic Malignancies.** Accepted for oral presentation.
- S Cooley, P Parham**,** E Trachtenberg, , X Luo, C Le, J Klein, S Marsh, D Weisdorf, and J Miller. **The Relapse-free Survival Benefit Associated with Group B KIR Haplotype Donors for Unrelated Hematopoietic Cell Transplantation is Unique to Acute Myelogenous Leukemia.**

- Three abstracts were presented at the 2009 EBMT meeting:
  - M Stern, A Gratwohl, M Malkki, Y Morishima, S Spellman, T Gooley, E Petersdorf on behalf of the International Histocompatibility Working Group in Hematopoietic Cell Transplantation. **HLA-DR15 and Outcome of Unrelated Donor Hematopoietic Stem Cell Transplantation – An IHWG Analysis.** Accepted for poster presentation.
  - B Shaw, E Petersdorf, T Gooley, M Malkki, K Fleischhauer, S. Spellman, Y Morishima, E Zino. **Significant differences in outcome following unrelated donor HCT can be better predicted using an algorithm incorporating both allele and epitope level matching for HLA-DPB1.** Accepted for oral presenation.
  - Z Shamim, L Ryder, M Haagenson , S Spellman, T Wang, S Lee, K Müller. **Polymorphism in the genes encoding human interleukin-7 Receptor-alpha (IL-7Ra) and outcome after allogeneic hematopoietic cell transplantation (HCT) with matched unrelated donor (MUD)**. Accepted for poster presentation and nominated for a best poster award.
- IBWC staff and principal investigators prepared posters and slides for 5 Tandem and 3 EBMT abstract presentations.

	• 7 new proposals were reviewed and accepted for implementation in FY10 at the IBWC meeting during the BMT Tandem Meetings. • The IBWC co-scientific director attended the BMT Tandem Meetings and the EBMT meeting. Funding for CIBMTR IBWC studies: • Research funds supported a prospective research sample collection protocol for a study of cGVHD in long-term surviving male recipients who received HSCT from female donors. Prospective blood samples were submitted by 24 of 28 consented participants. A final attempt at collection from the remaining participants will occur early next quarter. Sample analysis also continues next quarter. • Research funds were approved to support sample costs for a study investigating the role of mutations in the P53 gene pathway implicated in long-term survival after HCT.

ACRONYM LIST

AABB	American Association of Blood Banks	ICRHER	International Consortium for Research on Health Effects of Radiation
AGNIS	A Growable Network Information System	IS	Information Services
AML	Acute Myelogenous Leukemia	IT	Information Technology
ARS	Acute Radiation Syndrome (also known as Acute Radiation Sickness)	IRB	Institutional Review Board
ASBMT	American Society for Blood and Marrow Transplantation	JCAHO	Joint Commission on Accreditation of Healthcare Organizations
ASHI	American Society for Histocompatibility and Immunogenetics	KIR	Killer Immunoglobulin-like Receptor
B-LCLs	B-Lymphoblastoid Cell Lines	NCI	National Cancer Institute
BARDA	Biomedical Advanced Research and Development Authority	MHC	Major Histocompatibility Complex
BMT CTN	Blood and Marrow Transplant - Clinical Trials Network	MICA	MHC Class I-Like Molecule, Chain A
BRT	Basic Radiation Training	MICB	MHC Class I-Like Molecule, Chain B
C&A	Certification and Accreditation	MDACC	MD Anderson Cancer Center
CBMTG	Canadian Blood and Marrow Transplant Group	MSKCC	Memorial Sloan-Kettering Cancer Center
CBB	Cord Blood Bank	MUD	Matched Unrelated Donor
CBC	Congressional Black Caucus	NEMO	
CBS	Canadian Blood Service	NCBM	National Conference of Black Mayors
CBU	Cord Blood Unit	NHLBI	National Heart Lung and Blood Institute
CHTC	Certified Hematopoeitic Transplant Coordinator	NIH	National Institutes of Health
CIBMTR	Center for International Blood & Marrow Transplant Research	NIMS	National Incident Management System
CLIA	Clinical Laboratory Improvement Amendment	NK	Natural Killer
CME	Continuing Medical Education	NMDP	National Marrow Donor Program
CMF	Community Matching Funds	NRP	National Response Plan
COG	Children's Oncology Group	NST	Non-myeloablative Allogeneic Stem Cell Transplantation

CREG	Cross Reactive Groups	OCR/ICR	Optical Character Recognition/Intelligent Character Recognition
CSS	Center Support Services	OIT	Office of Information Technology
CT	Confirmatory Testing	OMB	Office of Management and Budget
CTA	Clinical Trial Application	ONR	Office of Naval Research
DC	Donor Center	P2P	Peer-to-Peer
DIY	Do it yourself	PBMC	Peripheral Blood Mononuclear Cells
DKMS	Deutsche Knochenmarkspenderdatei	PBSC	Peripheral Blood Stem Cell
DMSO	Dimethylsulphoxide	PCR	Polymerase Chain Reaction
DNA	Deoxyribonucleic Acid	PSA	Public Service Announcement
D/R	Donor/Recipient	QC	Quality control
EBMT	European Group for Blood and Marrow Transplantation	RCC	Renal Cell Carcinoma
EM	Expectation Maximization	RCI BMT	Resource for Clinical Investigations in Blood and Marrow Transplantation
EMDIS	European Marrow Donor Information System	REAC/TS	Radiation Emergency Assistance Center/Training Site
ERSI	Environment Remote Sensing Institute	RFP	Request for Proposal
FBI	Federal Bureau of Investigation	RFQ	Request for Quotation
FDA	Food and Drug Administration	RG	Recruitment Group
FDR	Fund Drive Request	RITN	Radiation Injury Treatment Network
Fst	Fixation Index	SBT	Sequence Based Typing
GETS	Government Emergency Telecommunications Service	SCTOD	Stem Cell Therapeutics Outcome Database
GCSF	Granulocyte-Colony Stimulating Factor (also known as filgrastim)	SG	Sample Group
GIS	Geographic Information System	SLW	STAR Link® Web
GvHD	Graft vs Host Disease	SSA	Search Strategy Advice
HCT	Hematopoietic Cell Transplantation	SSO	Sequence Specific Oligonucleotides
HHS	Health and Human Services	SSP	Sequence Specific Primers
HIPAA	Health Insurance Portability and Accountability Act	SSOP	Sequence Specific Oligonucleotide Probes

HLA	Human Leukocyte Antigen	STAR®	Search, Tracking and Registry
HML	Histoimmunogenetics Mark-up Language	TC	Transplant Center
HR	High Resolution	TED	Transplant Essential Data
HRSA	Health Resources and Services Administration	TNC	Total Nucleated Cell
HSC	Hematopoietic Stem Cell	TSA	Transportation Security Agency
IBWC	Immunobiology Working Committee	UI	User Interface
IDM	Infectious Disease Markers	URD	Unrelated Donor
IHWG	International Histocompatibility Working Group	WGA	Whole Genome Amplification
IPR	Immunobiology Project Results	WMDA	World Marrow Donor Association
IND	Investigational New Drug	WU	Work-up