NATIONAL MARROW DONOR PROGRAM®

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GRANT AWARD N00014-05-1-0859
QUARTERLY
PERFORMANCE / TECHNICAL REPORT
for
JANUARY 1, 2006 to MARCH 31, 2006

GRANT AWARD N00014-05-1-0310
QUARTERLY
PERFORMANCE / TECHNICAL REPORT
for
JANUARY 1, 2006 to MARCH 31, 2006

Office of Naval Research

And

The National Marrow Donor Program
3001 Broadway Street N.E.
Minneapolis, MN 55413
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National Marrow
Donor Program®

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

National Coordinating Center
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Minneapolis, MN 55413-1753

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www.marrow.org

May 01, 2006

Commander Russell Shilling, USN
Program Officer, Medical Services Corps
Office of Naval Research (ONR 341)
875 N. Randolph St.
Arlington, VA 22203

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

Reference: Grant Award #N00014-05-1-0859 between the Office of Naval Research and the National Marrow Donor Program

Dear Commander Shilling:

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, 2006 to March 31, 2006.

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 Operating Officer - Patricia Coppo directly at 612-627-5815.

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: One (1) copy of SF298
One (1) copy of subject document

c: A. Cole – ACO (ONR-Chicago), letter and enclosure
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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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QUARTERLY PERFORMANCE / TECHNICAL REPORT

for

JANUARY 1, 2006 to MARCH 31, 2006

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And

The National Marrow Donor Program
3001 Broadway Street N.E.
Minneapolis, MN 55413
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Grant Award N00014-05-1-0859

Development of Medical Technology for Contingency Responses to Marrow Toxic Agents

Quarterly Performance / Technical Report

January 1, 2006 – March 31, 2006

National Marrow Donor Program®

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IIA.1.3	Patient Assessment Guidelines	Included
IIA.1.4	National Data Collection Model	Included
IIA.2.1	Contingency Response Network	Included
IIA.2.2	Standard Operating Procedures	Included
IIA.3.1	Information Technology Infrastructure	Included
IIB.1.1	Resolution Speeds Donor Selection	Included
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IIB.1.3	Evaluate HLA-C Typing of Donors	Included
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IIB.3.5	Bioinformatics Web Site	Included
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IID.1.3	Expand Immunobiology Research	Included

A. CONTINGENCY PREPAREDNESS

The primary goals of this project are to 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.

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 (A.1)

Efforts of these Aims are to engage transplant physicians in additional planning efforts to include opportunities to participate on subcommittees that will address specific, critical aspects of a contingency response plan.

Aim 1 (A.1.1)
Continue to secure the interest and participation of transplant physicians.

Activity:
A Core Contingency Network (CCN) meeting was held during the ASBMT/CIBMTR Tandem meeting on February 18, 2006. For the 2007 Tandem meeting a general training session was requested and approved. Dr. Weisdorf will present contingency related planning material to the audience during this session. The NMDPs Marketing and Communications department has identified a simple yet effective marketing campaign to increase awareness and interested of potential attendees for this session, this will begin in late fall 2006.

Aim 2 (A.1.2)
Refine protocols for patient assessment and use of GCSF in radiation exposure situations.

Activity:
During the CCN meeting held at the ASBMT/CIBMTR Tandem conference, the National Library of Medicine (NLM) demonstrated a draft of their web based version of the NMDP/ASBMT Acute Radiation Syndrome treatment guidelines to the Core Contingency Network physicians. Based on comments from the physicians the NLM is making improvements to the web based interface.

Aim 3 (A.1.3)

Refine guidelines for patient assessment, product selection and transplant in radiation exposure situations.

Activity:
The activity in Aim 2 A.1.2 related to the NLM web based ARS treatment guidelines is connected to the further development of this aim.

Information Systems (IS) department continues to implement system improvements to the processes and tools utilized by the Search and Transplant department. IS support is also responsible for helping to refine new processes and maintain data integrity until those processes are fully supported by the software. Improvements to tools used by Search included continued work on the STAR II application to ensure a rapid response to changing requirements. As guidelines and processes evolve regarding patient assessment, product selection and transplant, new transaction types containing new data elements need to be transported between NMDP and its satellite centers. In particular, the support of XML transaction in STAR II offers a great deal of flexibility when adding new data elements or business requirements. Every quarter, STAR II takes responsibility for a wider variety of transaction types including the acceptance of lab results from international affiliates and the related reporting.

Aim 4 (A.1.4)

Define and develop a national data collection and management model.

Activity:
The need to meet to further define a data collection model was discussed during the ASBMT/CIBMTR Tandem Conference Core Contingency Network meeting. A meeting to be held in July is being planned one objective is to present the data collection plan to the CCN members for review and approval.

A. CONTINGENCY PREPAREDNESS

The primary goals of this project are to 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.

Hypothesis 2 - Coordination of the care of casualties who will require hematopoietic support will be essential in a contingency situation. (A.2)

Efforts of these Aims will be to enhance the NMDP's ability to respond to casualties of a radiation exposure.

Aim 1 (A.2.1)

Develop a permanent organization of transplant centers to maintain a contingency response network.

Activity:
During this period Core Contingency Network participation was confirmed for another three transplant centers. This brings the total participating transplant centers to 11 of the 15 initially invited to join the Core Contingency Network. The NMDP continues to work with the remaining four centers that have not confirmed involvement in the Core Contingency Network.

Aim 2 (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.

Activity:
The working group held two meetings to identify requirements of an integrated system for management of sibling typing.

A. CONTINGENCY PREPAREDNESS

The primary goals of this project are to 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.

Hypothesis 3 - NMDP's critical information technology infrastructure must remain operational during contingency situations that directly affect the Coordinating Center. (A.3)

Efforts of this Aim will be to establish a functional disaster recovery site, enable real time replication of critical data systems, and configure disaster recovery site to be managed and operated remotely from the NMDP's Minneapolis Headquarters.

Aim 1 (A.3.1)

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.

Activity:

A Business Continuity Planner was hired to focus on the business recovery plan. Ken Hodnett will focus initially on updating the three year old Business Continuity Plan. He will also be instrumental in the development of a Critical Staff Recovery Site in the event the Minneapolis Coordinating Center is not available to occupy.

A working group met multiple times in reference to the Critical Staff Recovery Site for Coordinating Center staff, items discussed included:

- Determination of facility requirements
- In-sourcing versus out-sourcing of the facility
- Identification of key items needed to complete a cost comparison
- Review of staff identified as critical per the Business Continuity Plan
- Review of the recovery timeline set in current SOPs

In addition, two vendors (SunGard and IBM) were spoken with about services offered.

B. Development of Science and Technology for Rapid Identification of Matched Donors

The primary goal of this project is to increase operational efficiencies that accelerate the search process and increase patient access are key to preparedness in a contingency event.

Hypothesis 1 - Increasing the resolution and quality of the HLA testing of volunteers on the registry will speed donor selection. (B.1)

Efforts of these Aims are to increase the register diversity, evaluate HLA-DRB1 High Res Typing, evaluate HLA-C Typing of donors, and evaluate buccal swabs.

Aim 1 (B.1.1)

Expand the genetic diversity of the Registry through continued addition of adult donors and cord blood units, utilizing high volume HLA typing methodologies.

Activity: One year contracts were negotiated with five HLA laboratories and began March 26, 2006. The NMDP obtained a 14.1% reduction in the overall price per sample for HLA-A, B, DRB1 donor recruitment typing, in part due to the 20 bead pilot project and by reducing the number of contract laboratories. One laboratory is performing sequence based testing (SBT) on approximately 20% of the newly recruited samples and will report an average of 60-70 % high resolution results for class I and II. On average, 47% of new donors will have both antigens reported at allele level for class II from the three different methodologies used for this typing project; membrane bound SSOP, LABType® SSO and SBT.

Aim 2 (B.1.2)

Evaluate the impact on the typing process, cost and donor selection of high resolution DRB1 testing of new volunteers. Utilize high resolution data generated to optimize allele and haplotype frequency calculations.

Activity: Donors typed for high resolution DRB1 represented 32.5% of the donors recruited over a one year period. These donors accounted for 55.7% of the CT activity, 49.5% of the Customized HLA Typing activity and 50.6% of work ups. High resolution DRB1 results at recruitment had a significant impact on the likelihood of a donor being selected (P value <0.0005) by a searching patient.

Aim 3 (B.1.3)

Evaluate the impact of HLA-C typing donors and develop a strategy for future recruitment typing that will optimize identification of the best matched donors for patients.

Activity: No Activity

Aim 4 (B.1.4)

Evaluate the suitability of buccal swabs as a method to collect DNA samples to HLA type casualties and potential related donors in contingency situations, and to obtain research samples.

Activity: During the past quarter, two donor recruitment drives were piloted using buccal swabs and 150 samples were collected at each drive. The buccal swab samples were sent to two laboratories and HLA results were obtained for 100% of the donors. Ten buccal swab samples were sent in duplicate to two customized typing laboratories and high resolution HLA-A, B, C, DR, DQ and DP were reported for all 20 samples.

B. Development of Science and Technology for Rapid Identification of Matched Donors

The primary goal of this project is to increase operational efficiencies that accelerate the search process and increase patient access are key to preparedness in a contingency event.

Hypothesis 2 - Primary DNA typing data can be used within the Registry to improve the quality and resolution of volunteer donor HLA assignments (B.2)

Efforts of these Aims are to collect, validate, and reinterpretate primary data so as to interprert this data against genotype lists and matching algorithms.

Aim 1 (B.2.1)

Retrospective and prospective collection of supplemental primary data to complete the donor records in the interpretation database.

Activity:
During the past quarter software development took place to facilitate processing of primary data in an electronic reporting format called HML (version 0.3). An online message format validation system was developed based on e-mail to hmltest@nmdp.org. Implementation support for SBT typing results in recruitment typing is underway and should be completed during the next quarter. This includes storing and validating SBT data as well as allowing HLA typing results to be reported without multiple allele codes.

New versions of the SSO typing kits used by recruitment labs have been implemented for the new ABDR typing contract which began in March.

Aim 2 (B.2.2)

Validation of the logic utilized for interpretation of HLA-A and B primary data to ensure accuracy of this approach prior to integration into the NMDP matching algorithm.

Activity:
The primary data were analyzed to validate the accuracy of the interpretation logic, to confirm that the logic can read the binary messages and accurately generate an HLA type.

Primary data of approximately 40,000 QC samples typed for HLA-A, B at NMDP contract laboratories from 1999 to present were analyzed using a probe validation application developed by the Bioinformatics Department. The accuracy of the probe data was examined from two points:

- Interpreted probe data compared to the result the lab reported (Lab vs. Interp)
- Interpreted probe data compared to the expected results of the QC sample (QC vs. Interp).

The comparison of the interpreted probe data to the expected results (QC vs. Interp), or the interpreted probe data to the results reported by the lab (Lab vs. Interp) was used to categorize the majority of samples into three groups.

- Identical Samples
- Discrepant Samples
- Indeterminant

A statistically significant number of samples from the identical group were evaluated and all discrepant/indeterminant samples were reviewed.

Results:

The table summarizes the results of the approximately 40,000 QC samples that were evaluated by comparing reported HLA results to the interpreted probe data results. The discrepant samples were divided into additional categories listed in the table*. Over 99% of the class I (HLA-A and B) primary data were considered as identical. Discrepancies were less than 1% for each loci with more than half of those errors the result of random (not repeated) probe hit errors.

Summary of QC data Results

Description	HLA-A	Percent of A	HLA-B	Percent of B
Total Number of QC Samples	41,612		39,682	
Number Identical	41,448	99.6	39,439	99.3
Number Discrepant	156	0.4	239	0.6
Indeterminant	8	0.02	5	0.01
*Random Probe Hit Error	87	0.2	111	0.3
*Consistent Probe Hit Errors	49	0.1	106	0.3
*Completely Inaccurate Probe Scores	20	0.04	22	0.06

Aim 3 (B.2.3)

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

Activity:
Data processing and analysis of the genotype list data interpreted from stored primary (SSO/SSP) DNA typing results were incorporated into the algorithm for all available donors. Work is ongoing to make more data available for DRB1 and replace generic (XX) multiple allele codes for class I typings with NMDP codes derived from these genotype lists for display on search reports.

Aim 4 (B.2.4)

Interpretation of the primary data into genotype lists and integration into matching algorithm to optimize placement of donors onto patient searches.

Activity:
On February 27 the new NMDP matching algorithm HapLogic™ was implemented for all search reports. This provides a real-time DNA-based match that utilizes genotype list data in the up-front match computation. New symbols have been included on search reports to indicate situations where the genotype list data were used to compute the match based on underlying probe data. The symbols identify situations where an allele mismatch is indicated by the primary data where it was not apparent from the encoded results submitted by the laboratory.

B. Development of Science and Technology for Rapid Identification of Matched Donors

The primary goal of this project is to increase operational efficiencies that accelerate the search process and increase patient access are key to preparedness in a contingency event.

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. (B.3)

Efforts of these Aims are to support the hypothesis that HLA frequency data and primary DNA data can be used to predict the best-matched donor. Approaches to insure data validation and provide public dissemination of results will be included.

Aim 1 (B.3.1)
Incorporate EM haplotype estimation logic into matching algorithm.

Activity:
The first phase of allele match prediction has been implemented as part of the HapLogic™ algorithm. During the past quarter software was implemented to predict the DRB1 allele match rate for donors who are only typed for HLA-A and HLA-B. Validation was performed by applying the predictions of the algorithm to donors who were actually selected for DRB1 typings during the past two years, and comparing the predictions to the actual typing results.

Aim 2 (B.3.2)
Continue to enhance the EM algorithm to include additional loci and increased resolution for ethnic groups with input from consultants with expertise in population genetics.

Activity:
C-B and DRB1-DRB(345)-DQB1 haplotype frequency tables were produced for future extensions to the HapLogic algorithm. Automated quarterly updates to all HapLogic haplotype frequency tables are in development with the first update to begin in the next quarter.

More work was done in preparation for completing manuscripts on the EM algorithm and its application in analyzing several populations. Nei's genetic distance measure was implemented for comparison of populations. Automatic phylogram creation scripts were made for all genetic distance measurements (G, Fst, Nei, Wn) for each locus, two-locus haplotype, and full haplotype. Two-locus haplotype Hardy-Weinberg calculations were added to the EM. The W statistic was implemented for showing deviation from expected Hardy-Weinberg proportions.

Total observed and expected homozygosity and heterozygosity were added to the EM output spreadsheet. Detailed tables for systematic analysis of homozygote phenotypes were created to identify locations of deviation from expected Hardy-Weinberg proportions.

Aim 3 (B.3.3)

Use the EM algorithm to predict haplotypes for matching probabilities (revised Benchmark analysis) and Optimal Registry Size Analysis.

Activity:
The rewrite and extension of the registry size simulation program to four-locus/allele level typing was completed. A preliminary 8/8 allele level registry benchmark report was presented to NMDP's Histocompatibility Committee, HRSA, and the Navy on March 27, 2006. It is currently thought that the simulation over-estimates the match rate primarily because there are too few high resolution typed donor phenotypes available. Next steps are to find a way to correct for the lack of high resolution data or to try a different approach, such as a benchmark where "patients" are randomly selected, run through the search algorithm, and all potentially matched donors are typed to see how many real high resolution matches there are at four loci.

Additional registry size analysis reports were completed for Canadian and Greek registries using similar methodology.

Aim 4 (B.3.4)

Couple haplotype prediction methodology with donor demographic data (i.e., zip codes) to target recruitment to areas populated by individuals with underrepresented HLA phenotypes.

Activity:
A meeting was held at the NMDP Coordinating Center March 28 involving a panel of experts in geographical analysis of HLA. This meeting was a kickoff of the NMDP GeoCoding project to perform geographical HLA analysis of NMDP donors.

Aim 5 (B.3.5)

Develop a bioinformatics web site for frequency information.

Activity:
The Bioinformatics web site (www.nmdpresearch.org) was developed and deployed on schedule with the original IIB.3.5 Aim 5 proposal. Members of the NMDP Scientific Services working group and IT Bioinformatics group reviewed the content of the previous www.nmdpresearch.org

site with the NMDP web team. The existing content was given a new look, enhanced with new key information, and redeployed on Jan 30, 2006. Key enhancements included an updated publications list and addition of the Biannual Rare Allele List. Other related information and tools from ongoing projects will be added as they become available. The new Bioinformatics site map is listed below.

http://bioinformatics.nmdp.org/

HLA Resources

- *Biannual Rare Allele Lists*
  - *Version 2.12.0 (01/2006)*
- Allele Codes
  - Allele Code Lists
    - Sorted numerically
    - Sorted alphabetically
  - DNA Type Lookup Tool
  - Allele Code Mailing List
- HLA Typing
  - High Resolution Typing Procedures
    - SBT: HLA-A
    - SBT: HLA-B
    - SBT: HLA-C
    - SBT: HLA-DRB1/3/4/5
    - SBT: HLA-DQA1
    - SBT: HLA-DQB1
    - SBT: HLA-DPA1
    - SBT: HLA-DPB1
    - SSOP: HLA-DPA1
    - SSOP: HLA-DPB1
  - Histoimmunogenetics Markup Language (HML)
    - Document Type Definition 0.1 (DTD)
    - Version 0.2 Examples and DTD.
    - Version 0.3 Examples and DTD.
- NMDP Search Determinants
  - HLA-A Tables (PDF)
  - HLA-A Tables (TXT)
  - HLA-B Tables (PDF)
  - HLA-B Tables (TXT)
  - HLA-DRB1 Tables (PDF)
  - HLA-DRB1 Tables (TXT)

Search Strategies

- Unrelated Donor Search & Selection Strategies

Publications

- Abstracts (PDF)
- Manuscripts and Book Chapters (PDF)

Education

- HLA Educational Resources

Policies

- NMDP Confirmatory Typing Requirements (PDF)
- NMDP HLA Typing Discrepancy Review Process (PDF)
- NMDP Policy for Handling Recent HLA Nomenclature Changes (PDF)

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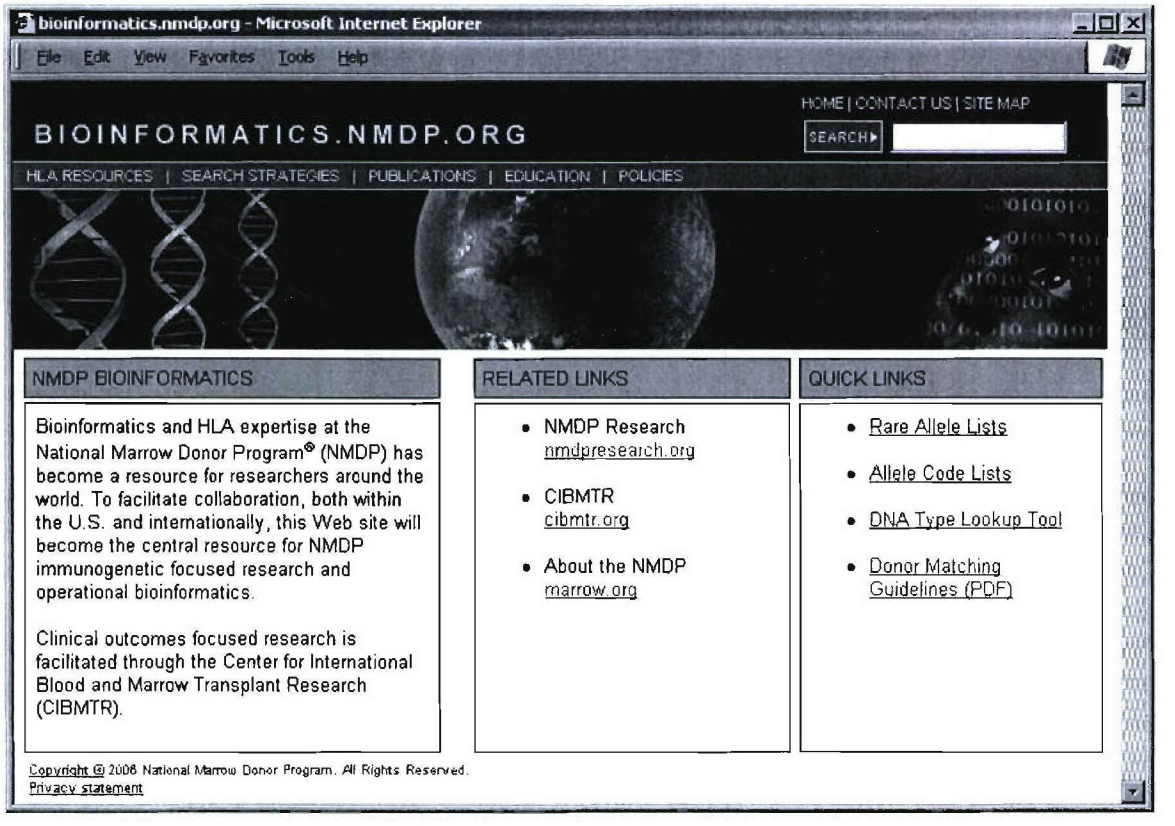

Aim 6 (B.3.6)

Use NMDP's expert HLA consultants as resources to further improve the matching algorithm and donor identification software applications with the goal to maximize the ability of the software to identify the best donors for each patient.

Activity:
The web-based application "Search Assistance Tools" (SAT 2.0) was developed and in February the new HapLogic™ algorithm was incorporated. The new algorithm was validated prior to its release by the Scientific Services Department and expert HLA consultants using the Web-based SAT 2.0 application. It continues to be enhanced as the platform for the next-generation matching algorithm.

It is also the platform for the "MultiCord" application which was beta tested by centers doing cord blood transplantation and by the expert HLA consultants. This application identifies the number of mismatches between the patient and the cord blood unit(s) and will allow the center to pick the level of resolution they require for matching at each locus (HLA-A, B and DRB1). The center can customize their cord searches to include allele or antigen level matching at these loci. When they select more than one cord unit the level of matching of each cord unit to the patient and the level of matching between the cord units is calculated. The TNC/kg for an individual cord or combined cord units is calculated and each cord blend can be saved and printed for their documentation to help determine the best combination. This application can include BMDW cord units and has the ability to manually add a cord unit from any other registry world wide to create cord blends.

B. Development of Science and Technology for Rapid Identification of Matched Donors

The primary goal of this project is to increase operational efficiencies that accelerate the search process and increase patient access are key to preparedness in a contingency event.

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. (B.4)

Efforts of these Aims are to expand the NMDP network communications and develop centralized search management proficiency for use during contingency situations.

Aim 1 (B.4.1)

Expand NMDP's automated communication capabilities to further streamline the electronic exchange of information throughout the Network.

Activity:
This aim affects many applications at NMDP in part. They include:

- Electronic receipt of IDM results via FormsNet
- Electronic receipt of cooperative registry data via EMDIS
- Electronic receipt of NMDP member center data via STAR II Transaction Broker
- Electronic receipt of NMDP operational data into the SIP database
- Interaction of SEARCH Link and TRANS Link with the SIP database

FormsNet

Work on this aim for FormsNet focused largely on the construction of a module to support the receipt of IDM results from labs. This module was written in a general way allowing it to also be adopted by the STAR II Transaction Broker for the receipt of electronic results. This included steps taken for development, quality assurance testing and migration plan to production. This project will greatly cut down on potential data entry errors of IDM data. Work in this quarter has focused less on development and more on the implementation and adoption (by labs) of the new submittal process.

More technical discussions were held concerning detailed architecture of FormsNet 2.0. Work on this project is underway.

Another I.S. development team has been focused on the gathering of requirements and coding for FormsNet 2.0.

During the past quarter, significant progress has been made in the architectural design and coding of FormsNet. The following has been accomplished:

- Completed requirements gathering from business users documenting their needs and business processes.
- Migrated development to the .Net platform so as to share existing and future code and resources with the STAR Link® application and team.
- Installed .Net development software on developer workstations.
- Completed basic architectural framework of the application.
- Implemented unit testing and coding standards for developers.

The FormsNet 2.0 project has been initiated to combine the existing legacy Registry data entry system into the web-based FormsNet data entry application. This will improve efficiency by eliminating duplicate applications and QA processes, allowing for the sharing of code and resources with the CORD Link® and STAR Link® applications, and allow for development staff to take over positions currently held by contractors. The first phase of this project is to make the harmonized forms available to the Research data entry staff in the FormsNet application.

EMDIS

EMDIS is responsible for the electronic communication with NMDP's cooperative registries. Routine maintenance was performed and enhancements made to the EMDIS system during the last quarter. Preparations were made for an EMDIS release to Australia. Also, a suite of administrative tools was created for EMDIS in this quarter. This will help when troubleshooting and maintaining the application.

STAR II Transaction Broker

Further enhancements were made to the STAR II Transaction Broker to support new transaction types from many different parties. New development has focused on the receipt of genotype list data to support the new Haplogic matching algorithm. HML .3 will support the transmission of genotype list data to NMDP.

SIP Database

As new information emerges from the increased electronic exchange of data, the SIP database must be modified to house new data elements. The SIP database facilitates management of the Search/Transplant process through data exchange with Donor Centers, Cord Blood Banks, Transplant Centers, etc. Also, work was done to ensure the continued security of all data stored in the SIP database.

SEARCH Link/TRANS Link

Ongoing maintenance occurred and improvements were made to both the SEARCH Link and TRANS Link applications. In particular, enhancements were made to support the electronic exchange of new information resulting from the new matching algorithm created by NMDP. This development effort occurred last quarter and was completed in this quarter. Many SEARCH Link/TRANS Link reports were modified to house the new information and express matching donors and cords more clearly. These reports were unified with those exchanged via the STAR II Transaction Broker in a batch format. The legacy reports, as a result, have been eliminated leaving a single unified architecture for creation of NMDP search reports.

Other enhancements were made to support new donor/cord summary matching information as well as ongoing changes to support new fields for cord blood and to unify information display with CORD Link. Lastly, work was done to electronically exchange information for BMDW cord blood units.

Aim 2 (B.4.2)

Develop central search management proficiency that can be utilized in contingency situations to assist transplant centers.

Activity:

Work performed under this Aim includes two projects:

- Search Assistance Tools
- Repository Reporting Utility.

Both of these projects provide tools to our internal search coordinators and, in part, to external search consultants to provide a centralized search management system capable of supporting and enhancing patient-donor matching processes in transplant centers. Due to their centralized nature and consolidated data-stores, these tools can also be used in lieu of localized search processes at transplant centers if the need arises.

The Multiple-cord selection tool was made available to the Transplant Center network. This program allows the user to select "blends" of multiple cord blood units (CBUs) considering degree of HLA match relative to the patient and between the CBUs. A number of features have been added including the ability to provide real-time BMDW results providing access to all 220,000 units with volume & TNC numbers.

A new version of the donor selection tool (v2.0) has been developed which implements the new HapLogic™ match algorithm for use by the internal donor selection team as well as the HLA expert consultants. This program is being used for validation of the results of the new matching algorithm.

C. Immunogenetic Studies

The goal of this project is to increase understanding of the immunologic factors important in HSC transplantation.

Hypothesis 1 - HLA mismatches may differ in their impact on transplant outcome, therefore, it is important to identify and quantitate 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. (C.1)

Efforts of this Aim will have important practical consequences for donor selection and patient management.

Aim 1 (C.1.1)

Evaluate HLA disparity and impact on HSC transplantation by adding selected pairs to the Donor/Recipient Pair project utilizing sample selection criteria that optimize the new data generated by the typing project.

Activity:
During the past quarter database design, development and testing progressed on the Immunobiology Project Results (IPR) database. This database is being developed to record the typing results of all immunobiology projects that utilize the NMDP research samples.

Sample groups were prepared for shipment from the Research Repository to laboratories participating in the HLA typing projects C1 and SG14 and the KIR SG02 typing project. Data processing and report generation activity are ongoing in support of the HLA SG13 typing project currently underway.

C. Immunogenetic Studies

The goal of this project is to increase understanding of the immunologic factors important in HSC transplantation.

Hypothesis 2 - Even when patient and donor are HLA matched, GVHD occurs, therefore, other loci may play a role. (C.2)

Efforts of this Aim will be to move technology forward from the current practice of locus level typing to high resolution typing, to disseminate information and protocols in an open source mechanism and to develop reference lines for use in individual laboratories.

Aim 1 (C.2.1)

Initiate the development of typing protocols for non-HLA immunogenetic loci, develop a lab network, implement database to capture non-HLA data and initiate analyses to evaluate genetic diversity in the transplant population.

Activity:

Bioinformatics and Scientific Services staff continued to refine the design of the Immunobiology Project Results (IPR) database for the capture of HLA and non-HLA data. The NMDP received reports of immunobiological test results including minor histocompatibility antigens and Killer Immunoglobulin-like Receptor genotypes generated through NMDP/CIBMTR approved studies. The data were validated for clinical outcome correlation and archived for transfer into the IPR database upon completion.

Aim 2 (C.2.2)

Establish a Related Pairs Research Repository; develop necessary operational procedures and supporting systems.

Activity:

During the past quarter, the NMDP presented an overview of the plan to collect research samples from related pair transplants to the Core Contingency Network Transplant Centers at the Tandem BMT meeting. The development of a sample collection and distribution process for samples from related transplant pairs through the Core Contingency Network will serve to establish a conduit for the handling of samples in support of family member HLA typing during contingency events. NMDP and CIBMTR staff continued planning for implementation of the

Repository and developed a vision document defining the scope and focus of the project. In addition, work began on the study protocol and IRB application for NMDP IRB approval of the project.

D. Clinical Research in Transplantation

The primary goal of this project is to create a platform that facilitates multicenter collaboration and data management. Many of the research protocols address issues important for managing the radiation exposure victim. Examples include exploration of alternative stem cell sources, acceleration of hematopoietic recovery, reduction of acute and chronic graft-versus-host disease, and others. Advancing the research capabilities facilitate a coordinated and effective contingency response.

Hypothesis 1 - (D.1)

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

Efforts of these Aims are for research targeting important transplant-related complications (e.g. GVHD or organ toxicity) or considering strategies that would allow broader application of transplantation to persons in need (e.g., use of HLA-mismatched cord blood for persons without a matched bone marrow donor).

Aim 1 (D.1.1)

Conduct observational research and interventional clinical trials.

Support for CIBMTR clinical trials

- **Prospective trials**
- **Data management systems**
- **Cord blood research**

Partnership with the intramural NIH transplant programs

Support for CIBMTR observational studies

Activity:

During this reporting period the first Advisory Committee meeting of the CIBMTR prospective trial internal program was held at the Tandem meeting in February. This meeting included the review of three trial proposals. Of the three studies, only one will move forward under conditional approval. There were several issues and revisions suggested by the committee that will need to be addressed prior to moving forward with forming a protocol team. Activity continued on developing templates, tracking tools, and processes for our trial program.

Development of a Cord Blood protocol continued. This is a Phase II, open-label, multicenter, prospective study of double unit UCBT in adult patients with hematologic malignancies. The protocol team has been created and has been meeting on a routine basis during this reporting period.

In January 2006 two master level statisticians were hired to directly support the Observational studies program. Each statistician was assigned Working Committees and participated in related meetings at Tandem.

D. Clinical Research in Transplantation

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Hypothesis 1 - (D.1)

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

Efforts of these Aims are for research targeting important transplant-related complications (e.g. GVHD or organ toxicity) or considering strategies that would allow broader application of transplantation to persons in need (e.g., use of HLA-mismatched cord blood for persons without a matched bone marrow donor).

Aim 2 (D.1.2)

Support research with NMDP donors and for donor studies proposed by outside investigators.

Activity:
Interviews are scheduled for the week of April 10 for the Sr. Research Specialist who will be the lead staff person on this project. I anticipate that this position will be filled and the person in place by the beginning of May. Concurrently, the first protocol from an outside investigator is under development.

D. Clinical Research in Transplantation

The primary goal of this project is to create a platform that facilitates multicenter collaboration and data management. Many of the research protocols address issues important for managing the radiation exposure victim. Examples include exploration of alternative stem cell sources, acceleration of hematopoietic recovery, reduction of acute and chronic graft-versus-host disease, and others. Advancing the research capabilities facilitate a coordinated and effective contingency response.

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Efforts of these Aims are for research targeting important transplant-related complications (e.g. GVHD or organ toxicity) or considering strategies that would allow broader application of transplantation to persons in need (e.g., use of HLA-mismatched cord blood for persons without a matched bone marrow donor).

Aim 3 (D.1.3)

Expand support for immunobiology research, statistical genetics and clinical research studies under CIBMTR Immunogenetics Working Committee.

Activity:

At the NMDP Histocompatibility Committee meeting in March the group discussed and refined the NMDP research priorities. The committee also developed a plan to prioritize studies within the CIBMTR that meet or support the NMDP's research interests. The committee will monitor study proposals submitted to or developed by the CIBMTR and identify studies of importance to the NMDP. Studies deemed high priority by the research community will be prioritized according to the standard working committee procedures of the CIBMTR. Studies that are deemed high priority by the NMDP, but not ranked highly by the CIBMTR working committees will be supported in one of two ways. The first mechanism will be to provide research support in the form of statistician hours or funds for laboratory testing to assist with study completion that would be unavailable through the CIBMTR. The second mechanism will be to take on a significant role in the completion of the study through support for study development and analysis through NMDP operations. The described plan will ensure that the NMDP's research priorities are reflected in the studies completed through or in collaboration with the CIBMTR.

During the last quarter NMDP Scientific Services staff announced the availability of limited funds for project support at the Immunobiology Working Committee (IBWC) meeting at the Tandem BMT Meetings. The committee was informed that the funds are available to approved IBWC studies that support the NMDP's research priorities, which are listed on the NMDP Web site. In addition, it was noted that the funding was not intended to provide comprehensive support, but rather subsidize additional lab tests, collection of samples or costs associated with usage of research samples from the NMDP Repository. A template for funding requests is under development and will be available in the next quarter.

To date, two studies have been identified for receipt of supplemental funding. The first award will support the preparation of purified DNA at a centralized processing facility for an International Histocompatibility Workshop study evaluating over 500 single nucleotide polymorphisms in HLA-A, B, C, DRB1 and DQB1 high resolution matched transplant pairs. The second award will support the HLA testing of cord blood unit (CBU) maternal samples for a study evaluating the role of non-inherited maternal antigens in unrelated CBU transplantation.

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May 01, 2006

Commander Russell Shilling, USN
Program Officer, Medical Services Corps
Office of Naval Research (ONR 341)
875 N. Randolph St.
Arlington, VA 22203

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

Reference: Grant Award #N00014-05-1-0310 between the Office of Naval Research and the National Marrow Donor Program

Dear Commander Shilling:

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, 2006 to March 31, 2006.

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.

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 Operating Officer - Patricia Coppo directly at 612-627-5815.

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, M.A.
Sr. Contracts Administrator

Enclosure: One (1) copy of SF298
One (1) copy of subject document

c: A. Cole – ACO (ONR-Chicago), letter and enclosures
Dr. Robert J. Hartzman, CAPT, MC, USN (Ret), letter and enclosures
DTIC (Ste 0944): letter and enclosures
NRL (Code 5227): letter and enclosures
Brian Bradley – Grants Officer (ONR-252), letter and enclosure
Patricia A. Coppo, Chief Operating Officer, NMDP, letter only

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14. ABSTRACT
Task 1 : Evaluate optimal short term storage parameters for stimulated and unstimulated leukapheresis (donor lymphocytes) and bone marrow products, including the type of storage media and the cell concentration, in addition to temperature and duration of storage before processing or infusion.

Task 2: The NMDP has developed an algorithm that "predicts' high resolution HLA typing results on donor samples that exist in the Registry with only low or intermediate results reported. Perform validation of the NMDP algorithm by selecting donors randomly from our Registry that have low or intermediate DRB1 typing results and using the algorithm to predict the high resolution results and test the ability of the algorithm to predict KIR ligand mismatching in the absence of existing HLA-C locus results.

15. SUBJECT TERMS
Research in HLA Typing, Hematopoietic Stem Cell Transplantation and Clinical Studies to Improve Outcomes

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U	U	U			19b. TELEPONE NUMBER *(Include area code)* (612) 627-5850

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Grant Award N00014-05-1-0310

QUARTERLY PERFORMANCE / TECHNICAL REPORT

for

JANUARY 1, 2006 to MARCH 31, 2006

Office of Naval Research

And

The National Marrow Donor Program
3001 Broadway Street N.E.
Minneapolis, MN 55413
1-800-526-7809

Grant Award N00014-05-1-0310
Performance Report
January 1, 2006 – March 31, 2006

National Marrow Donor Program®
HLA Typing for Bone Marrow Transplantation

Task 1: Product Validation

Description:
The objective of this study is to evaluate optimal short term storage parameters for stimulated and unstimulated leukapheresis (donor lymphocytes) and bone marrow products, including the type of storage media and the cell concentration, in addition to temperature and duration of storage before processing or infusion.

Project 1. Effects of Media Storage and Cell Concentration

Stimulated and unstimulated leukapheresis and bone marrow products that are representative of products collected and provided for NMDP transplant patients will be purchased. Aliquots of the product will be stored in different storage media at varying cell concentrations per mL of media. Standard graft characterization parameters will be tested.

Objectives:

1. Transportation factors: Determine the effects of different types of tissue media, nucleated cell concentration on CD34+ cell, CD3+ and total nucleated cell viability, and CFU-GM frequency during transport from collection sites to the transplant centers.

2. Overnight storage factors: Determine the effects of different type of tissue media, type of storage bags (gas permeable or non gas permeable), nucleated cell concentration on CD34+, CD3+ cell and total nucleated cell viability, and CFU-GM frequency during overnight storage.

Project 2. Effects of Time and Temperature

Stimulated and unstimulated leukapheresis and bone marrow products that are representative of products collected and provided for NMDP transplant patients will be purchased. Aliquots of the product will be stored at varying lengths of time and temperature. Standard graft characterization parameters will be tested.

Objectives:

1. Temperature factors: Determine the optimal short term storage temperature to preserve nucleated cell count, percent viable TNC, CD34+ and CD3+ cells, CFU-GM frequency and sterility.

2. Time factors: Determine the effect of time on nucleated cell count, percent viable TNC, CD34+ and CD3+ cells, CFU-GM frequency and sterility.

Grant Award N00014-05-1-0310
Performance Report
January 1, 2006 – March 31, 2006

National Marrow Donor Program®
HLA Typing for Bone Marrow Transplantation

Activity:
Due to the lack of response to the initial RFP released last fall, a twelve month extension (through February 2007) was requested and granted for completion of this study. The NMDP plans to revise the project Scope of Work to include both a better defined study design and better defined methodologies prior to re-release of the RFP next quarter. A panel of three experts in the field of cellular processing were recruited to assist in this effort and met, via conference call, with NMDP Scientific Services and Regulatory staff in late March. One of the major action items called for distribution of a "state-of-the-art" survey to the cellular processing community to more accurately assess current practices. The International Society for Cellular Therapy (ISCT), a collaborator on this study, agreed to circulate this survey to its membership for input early next quarter. Responses to the survey will be tabulated and findings incorporated into the study design of the revised RFP.

Government Signature _____ Date _____

Product Validation

Grant Award N00014-05-1-0310
Quarterly Performance / Technical Report
January 1, 2006 – March 31, 2006

National Marrow Donor Program®
HLA Typing for Bone Marrow Transplantation

Task 2: Validation of the Expectation – Maximization (EM) Algorithm

Description:

The NMDP has developed an algorithm that "predicts' high resolution HLA typing results on donor samples that exist in the Registry with only low or intermediate results reported. A modified version of this algorithm predicts HLA results at loci where there are no typings based on existing typings at other loci and the ethnic-specific haplotype frequencies observed in the population.

It is our intention to incorporate this logic into the mechanisms used to select matched donors for patient searches. Incorporation of this logic would improve the specificity of donors that appear on patient's searches, which then decreases the costs and time necessary to identify the optimally matched donor. This logic will also be used to provide estimates of the likelihood of finding matched donors in the Registry including matching at loci where some donors in the Registry do not currently have typings.

A portion of the funding would be used to assist in the validation of the NMDP algorithm by selecting donors randomly from our Registry who have low or intermediate DRB1 typing results and using the algorithm to predict the high resolution results. The HLA typing results would be used to validate the accuracy of this method in an unbiased data set.

The remaining portion of the funding would be used to test the ability of the algorithm to predict KIR ligand mismatching in the absence of existing HLA-C locus results. Randomly selected donors from the Registry without HLA-C would be run through a modified version of the algorithm to predict the C locus KIR ligand status. The HLA intermediate resolution typing would validate the accuracy of this method in an unbiased data set.

A laboratory would perform the high resolution HLA-DRB1 testing and/or intermediate resolution HLA-B and C from stored samples of the donors. Quality control and performance criteria will be monitored by a Scientific Services Specialist. The results will be analyzed by a programmer in the Bioinformatics group to verify the accuracy of each prediction technique.

In addition to assisting with the validation of the algorithm, this typing project has potential to impact subsequent patient searches simply due to the increased level of resolution for the Registry donors whose typings have been upgraded. A portion of this typing may be selected on behalf of searching patients in order to further validate the approach and provide direct positive impact on these searches.

Grant Award N00014-05-1-0310
Quarterly Performance / Technical Report
January 1, 2006 – March 31, 2006

National Marrow Donor Program®
HLA Typing for Bone Marrow Transplantation

Activity:

The following activities have been completed:

- Three laboratories HLA typed 2500 samples for high resolution A,B,C,DRB1/3/4/5: completed in May. Laboratory performance was evaluated:
  - QC error rate for all labs = 1.13% (less than 2.0% required)
  - Turnaround time for all labs = 95.6% (greater than 90% required)
- Prediction of the HLA-A, B and DRB1 results of these samples using the NMDP algorithm was completed and results were validated by Bioinformatics staff.
- The receiver operator characteristic (ROC) analysis by the Bioinformatics Department (published - Mori/Beatty/Graves/Milford, Oct 1996 BBMT) was completed.
- The high resolution HLA typing data on this unbiased data set increased the number of minority haplotypes represented in our Registry. This was part of the haplotype data that was used to predict the ability of the donor to match a searching patient. The enhanced NMDP search algorithm, which uses these haplotypes to make those predictions, was introduced in February 2006.