

**FINAL
TECHNICAL REPORT**

**OFFICE OF NAVAL RESEARCH
COOPERATIVE AGREEMENT
NO. N00014-96-2-0016**

**National Marrow Donor Program
3433 Broadway Street N.E.
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Minneapolis, MN 55413**

February 10, 2000

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13. SUPPLEMENTARY NOTES

14. ABSTRACT The objectives of activities conducted through this cooperative agreement were to: increase the availability of hematopoietic stem cell transplantation; improve scientific understanding of factors leading to successful post-transplant outcomes; and develop and test centralized contingency responses for the treatment of military and/or civilian casualties exposed to nuclear or biological marrow toxic agents. These objectives were successfully met through the following activities. The transition from serologic to DNA-based (molecular) technology for large-scale HLA-A,B typing of newly recruited donors increased donor file size while improving the accuracy of the data used to match patients and donors. Continued molecular HLA-DR typing of large numbers of donors increased the percentage of patients identifying at least one potential donor from 78% to 86% during the period of the agreement. The increase in donor file size, complete and highly accurate typing of donors and enhancements to the NMDP computer system resulted in decreased search times. The data obtained from high resolution DNA-based typing of samples from stem cell recipients and their donors were correlated with post-transplant outcome data to evaluate the relationship between degree of match and successful patient outcomes. The results of these studies were disseminated through publications in peer-reviewed scientific journals and presentations at national conferences. Contingency plans for rapidly identifying stem cell donors for military or civilian casualties were developed. The plans were tested in conjunction with exercises led by the Department of Defense donor center.

15. SUBJECT TERMS
HLA Typing for Bone Marrow Transplantation

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Proposal Section)

(Sec.1.) HLA TYPING AND RESEARCH

(Sec. 1.a.1.) Description: Continued Class II Allele Level Typing of Donor Recipient Samples

Activity:

This project was initiated in 1994 with funding from Navy Grant N00014-93-1-0658 and continued in 1995-1996 with funding from Navy Grant N00014-95-1-0055. The Navy Cooperative Agreement N00014-96-2-0016 provided funding for ongoing work from October 1996 through September 1999. The project's ongoing primary objectives are: 1) to expand the capacity and technology for allele level Class II HLA typing, 2) to increase the accuracy of allele level typing, 3) to reduce the costs of allele level typing and 4) to determine the impact of HLA matching, defined by high resolution molecular typing, on transplant outcome.

During this cooperative agreement period, 1,600 samples (800 donor and recipient pairs) were shipped to laboratories from the Irwin Research Sample Repository for HLA-DRB1, DRB3, DRB4, DRB5, DQA1, DQB1, DPA1 and DPB1 typing. Allele level results were achieved using Sequence Specific Oligonucleotide Probe (SSOP) technology and results were interpreted according to the 1994 WHO HLA Nomenclature Committee Report. One laboratory performed duplication on separate samples utilizing Sequence-Based Typing (SBT) methods to monitor the quality of the typings (see Section 1.d.2). An NMDP computer program compared the duplicated typings with each other and the non-duplicated typings with the previously reported results from transplant centers and loaded the confirmed consensus typings into the database. These data were then made available for use by investigators. Any discrepant typing results were handled through a standardized discrepancy resolution process.

The results of these typings generated eight abstracts that were presented at the 1997 and 1998 American Society of Histocompatibility and Immunogenetics (ASHI) annual meetings. One abstract was presented at the 1997 American Society of Hematology annual meeting and one abstract was presented at the 1998 Annual Meeting of the European Blood and Marrow Transplantation group. Five manuscripts have been published. Five additional manuscripts are in progress utilizing the Class II data.

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Sec. 1.a.2.) Description: Continued Class I Allele Level Typing of Donor Recipient Samples

Activity:

This project was initiated in 1995 with funding from Navy Grant N00014-95-1-0055. The Navy Cooperative Agreement N00014-96-2-0016 provided funding for ongoing work from February 1997 through September 1999. The project's ongoing primary objectives are: 1) to expand the capacity and technology for allele level Class I HLA typing, 2) to increase the accuracy of allele level typing, 3) to reduce the costs of allele level typing and 4) to determine the impact of HLA matching, defined by high resolution molecular typing, on transplant outcome.

During the cooperative agreement period, 1,312 donor and recipient pairs were characterized for HLA-A, B and C loci. Approximately 13,400 aliquots were shipped to laboratories from the Irwin Research Sample Repository to facilitate the HLA-A, B and C typing. To incorporate the rapid discovery rate of new alleles into this project, the laboratories were required to update their software interpretation systems and to interpret alleles according to the most recently published Class I Sequence Database report of confirmed alleles.

Because the typing technology used in this project was new and still evolving, the quality of typings was monitored through the use of a complete duplicate typing strategy (see Section 1.d.2). Every sample was typed once by a laboratory using SSOP methodology and once by a partner laboratory using SBT methods. The NMDP computer system compared the duplicate typings and entered confirmed consensus results into the database. These data were then made available for use by investigators to report on project progress or technical issues. Any discrepant typing results were resolved through a standardized discrepancy resolution process.

The results of these typings generated 14 abstracts that were presented at the 1997, 1998 and 1999 American Society of Histocompatibility and Immunogenetics (ASHI) annual meetings. One abstract was presented at the 1997 Annual Meeting of the American Society of Hematology. One abstract was presented at the 1998 Annual Meeting of the European Blood and Marrow Transplantation group. Four manuscripts have been published, and six manuscripts are in development following release of additional data.

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(Sec. 1.b.) Description: Intermediate Level DNA Class II Typing

Activity:

The Intermediate Level Class II typing project was implemented in 1992 and has been primarily supported since that time with Navy funding. This typing project is a continuation of that program with the primary objectives to: 1) facilitate large scale, prospective, DNA-based HLA DR typing of NMDP donors to increase the likelihood that a patient will identify a completely matched donor during the preliminary search process, 2) improve the accuracy of HLA-DR typing and 3) optimize the typing methodology and level of resolution for large-scale Registry typing.

During this cooperative agreement period, a total of 343,343 donor samples were shipped from the NMDP DNA Repositories to contract laboratories for HLA-DR typing. The laboratories typed HLA-DRB1, DRB3 and DRB5 at an intermediate level of resolution. Results were reported electronically to the NMDP database to update the donors' records.

During this timeframe, the percentage of searching patients that identified at least one HLA-A, B and DR matched donor increased from 78% to 86%. This increase was in large part due to the prospective HLA-DR typing performed under this cooperative agreement and previous Navy grants. A recent NMDP analysis shows that 95% of all transplants are facilitated with volunteer donors who were already fully typed when identified on the preliminary search. These statistics show the first objective of this project has been met.

An important initiative over the last two years of this project was the standardization of Exon 2 polymorphisms tested for by sequence specific oligonucleotide probes and primers. This standardization allowed the NMDP to proceed towards collection of the raw typing data (i.e., the probe and primer reactions) in an effort to "immortalize" the typing results and allow reinterpretation of the raw data as new alleles are described. In January 1998 the NMDP began requiring the contract laboratories to send probe and primer data and scores with each reported result. An NMDP probe reinterpretation

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(Sec. 1.b. continued)

program analyzed the raw data and rejected messages that contained insufficient or non-interpretable probe data. As of October 1999, 668,246 incoming electronic data messages were reinterpreted by the NMDP program.

Seven abstracts using data generated from this project were presented at the 1997, 1998 and 1999 ASHI annual meetings and one was presented at the 1998 Annual Meeting of the European Blood and Marrow Transplantation group.

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(Sec. 1.c.) Description: Intermediate Level DNA Class I Typing

Activity:

Intermediate Level Class I typing was initiated in June 1997 and continued through December 1999 utilizing funding from Navy Cooperative Agreement N00014-96-2-0016. The objectives of this project were: 1) to advance the technology of molecular typing for HLA-A and B, 2) to develop a large-scale, DNA-based HLA-A, B typing network robust enough to support the donor recruitment typing requirements of the NMDP, 3) to improve the accuracy of typings for donors listed on the Registry and 4) to disseminate the acquired knowledge through the preparation of abstracts and manuscripts.

To investigate and select the optimal typing methodology for large-scale Registry typing, the NMDP placed contracts with a diverse group of laboratories using a variety of HLA typing techniques (custom-made SSOP sets, commercially purchased SSOP kits, custom-made sequence specific primer [SSP] sets and commercially purchased SSP kits). Sixteen laboratories participated initially, each receiving weekly shipments of 50-100 samples. By the end of the project, there were 12 laboratories continuing with weekly shipment volumes ranging from 100-900 samples per week.

During the methods optimization portion of this project (June 1997 through October 1998), the laboratories typed minority donor samples from the DNA Repositories that had previous serologic HLA-A, and B results defined and reported to the NMDP. These samples were selected for typing because it had been shown in previous NMDP analyses that there were high error rates associated with serologic HLA typing of minority individuals due to limitations of the typing reagents. In November 1998 all stored samples from minority donors had been typed and the selection process was changed to focus on retyping donor samples that were presumed to be at high risk for a serologic mistyping (samples reported with "X" and/or "blank" antigens). A cumulative total of 176,945 donor samples were typed and reported during this project.

Similar to the Intermediate Level Class II typing project, raw typing data for the NMDP probe reinterpretation program was collected for the purpose of reinterpretation. In order to reduce some of the complexity of the data collection, the number of typing methods

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(Section 1.c. continued)

that laboratories were allowed to use was condensed into five groups prior to the start of this program:

1. commercially purchased SSOP probe sets covering defined polymorphic regions
2. a custom designed SSOP probe set utilizing probes placed in α -helical regions
3. a custom designed SSOP probe set utilizing dimorphic B locus amplification
4. a reverse dot blot SSOP kit
5. a custom designed SSP set

The laboratories were required to send raw probe and primer data to the NMDP beginning July 1, 1999. By the end of the project, 103,360 typings had been reinterpreted by the NMDP program.

Data from this project have been analyzed and presented in seven abstracts at the 1997, 1998 and 1999 ASHI annual meetings. One abstract was presented at the 1998 Annual Meeting of the European Blood and Marrow Transplantation group. One manuscript has been published and three are in progress.

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Sec. 1.c.2) Description: Resolve Discrepancies by Retyping Samples (New category)

Activity:

This project was initiated following the review of the data comparing DNA-based HLA-A, B typing results to serologic HLA-A, B results from the first six months of the Intermediate Level Class I typing project. Funding was added to support this effort in Year 2 of this cooperative agreement.

The number of discrepancies between the new DNA-based typing and the previously reported serologic typing provided a unique and plentiful data set for analysis. A total of 42,160 reported molecular typings were analyzed and compared to the serologic results. The discrepant typings (approximately 25% of the total comparisons made) were divided into categories according to the probable source and type of error. Then a statistically significant number of samples was selected for retyping by a third laboratory to resolve the discrepancy. A subcontract was placed with a laboratory that could provide sequence-based typing, SSP and SSOP with alternate primer pairs as necessary to resolve the discrepancies. The laboratory received, inventoried and tested a total of 670 samples that were returned from the original Intermediate Level Class I typing laboratories and shipped from the DNA Repositories. Final results are now being analyzed and a manuscript is in progress.

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(Sec. 1.d.1.) Description: Quality Control of Serologic HLA-A, B Typing

Activity:

Funding from the Navy Cooperative Agreement N00014-96-2-0016 supported a short-term project to monitor the accuracy of results being reported by the serologic typing laboratory network. In November 1998 the NMDP placed a subcontract with one laboratory to perform, by DNA-based methods, duplicate typing of approximately 1% of the samples typed by NMDP contract HLA-A, B serology laboratories. A monthly quality control report was generated and sent to each laboratory that documented discrepancies between the DNA results and their reported serology. Specifications for satisfactory performance required that laboratories achieve a monthly error rate of less than 15%. Over the course of this project, the Quality Control laboratory retyped a total of 1,983 samples. The average error rate for all 26 participating serology laboratories was 4% with a range of 0%-22%. Seven laboratories exceeded the limitation of 15% per month and were required to submit and implement written plans of corrective action.

The Quality Control laboratory was terminated effective September 30, 1999 to coincide with the termination of the NMDP serologic typing network of contract laboratories.

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(Sec. 1.d.2.) Description: Quality Control of DNA-based HLA Typing

Activity:

The Navy Cooperative Agreement provided funding for staff support to administrate the quality control monitoring of the DNA-based typing programs.

Four DNA typing programs were included in this project: Intermediate Level Class II typing, Intermediate Level Class I typing, Allele Level Class II typing of donor-recipient pair samples and Allele Level Class I typing of donor-recipient pair samples.

The quality of HLA typing results received by the Intermediate Level Class II laboratories was monitored through a blind Quality Control (QC) program. A panel of well-characterized quality control cells was maintained at the C.W. Bill Young Marrow Donor and Research Program. The cells were strategically selected and shipped to the NMDP DNA Repositories for inclusion into every shipment of donor samples going to the laboratories. The control cells were indistinguishable from the donor samples. An NMDP computer program sorted out the incoming testing results by ID number and generated a monthly report comparing the laboratory's typings with the consensus QC result. Specifications for satisfactory performance required maintaining a monthly accuracy rate of greater than 98.0% until October 1998. At that time the specification was increased slightly to 98.5%. The overall average accuracy rate for all laboratories participating in this large-scale program was consistently > 99 %.

The design of the Quality Control monitoring system for the Intermediate Level Class I laboratories was identical to that of the Class II laboratories described above. Specifications for satisfactory performance during the methods optimization period of this project (June 1997-April 1998) required maintaining a monthly accuracy rate of greater than 96.0%. The requirement was then increased to 98.0% and remained at that specification until the end of the project. The overall accuracy rate improved significantly during the project period from 97.2% the first month to 99.8% in the last month as laboratories gained experience with this relatively new typing methodology.

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(Sec. 1.d.2. continued)

A duplicate-typing program monitored the quality of the typing results received in the Allele Level Class II Donor-Recipient Pair Project. The percentage of samples incorporated into this strategy decreased over the course of the project period (from 25% - 10%). In addition, duplicate typing of the DRB1 locus was discontinued due to low discrepancy rates. With this strategy of comparing two typings reported on the same sample, the outcome was described as a "discrepancy" rate as opposed to the Intermediate Level Class I and II QC program where typings were compared to a consensus result and the outcome was "error" rate. The discrepancy rates for results reported during this funding period are summarized below:

LOCUS	1996-1997	1997-1998	1998-1999
DQA1	8.1	7.1	6.1
DQB1	5.2	5.7	8.1
DPA1	0.6	4.3	3.0
DPB1	2.8	4.3	1.0

The increase in percent of discrepancies noted over time was primarily related to the smaller number of duplicate typings performed in more recent years. In the Class I Allele Level Project (where 100% of the samples were tested in duplicate), the discrepancy rates for all three loci decreased significantly since the start of the cooperative agreement period. This is a reflection of the improvements in technology and the operational systems and procedures developed and instituted by the laboratories. The discrepancy rates for results reported during this funding period are summarized below:

LOCUS	1997	1998	1999
A	10.7	2.5	3.9
B	15.4	8.1	4.6
C	6.6	5.0	3.1

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Sec. 1.e.) Description: Staff Immunogeneticist

Activity:

Yoon Choo, M.D., was hired on August 1, 1997, as the NMDP Immunogeneticist. He shared a joint appointment with the NMDP and the University of Minnesota where he acted as Assistant Professor, Department of Laboratory Medicine and Pathology. Dr. Choo worked within the NMDP Search Coordinating Unit, under the direction of the NMDP Chief Medical Officer, to provide HLA expertise during the process of unrelated donor searches, advise on difficult search cases, and evaluate the internal NMDP search process. Dr. Choo was available for consultation from transplant centers or referring physicians.

During his tenure at the NMDP, Dr. Choo served as an ex officio member of the NMDP Histocompatibility Committee and contributed to the development of network education about search strategies at NMDP Council Meetings and Transplant Center Spring Meetings. At the April 1999 Transplant Center Spring Meeting, Dr. Choo served as an expert panel member and presenter for the workshop "How to Take Advantage of HLA Expertise and Search Assistance."

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Sec. 1.f.) Description: Contract Laboratory for Reference/Pre-test Cells

Activity:

This project was not initiated as funds for this initiative were reallocated to higher priority projects. Funding for this project was requested and provided in the Navy Cooperative Agreement N00014-99-2-0006.

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Sec. 1.g.) **Description: Central CD34+ Testing Laboratory**

Activity:

This project was not initiated as funds for this initiative were reallocated to higher priority projects. Funding for this project was requested and provided in the Navy Cooperative Agreement N00014-99-2-0006.

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Sec 1.h.) Description: Repository Sample Storage

Activity:

The Navy Cooperative Agreement N00014-96-2-0016 provided funding that contributed to the operation of the NMDP DNA Repository. The Repository held an ongoing subcontract to store frozen (-20°C) aliquots of volunteer donor samples to be accessed for future DNA-based HLA typing. During the first fiscal year the funds were used for the receipt of 92,859 new donor samples, the retrieval and shipment of 64,579 samples and the discarding of 26,027 samples. In addition, the funding contributed to the monthly costs of storing approximately 2 million frozen samples.

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Sec. 1.i.) Description: Class I Sequencing Database

Activity:

Funds from Navy Cooperative Agreement N00014-96-2-0016 were utilized to support the previously placed contract with Stanford University (Peter Parham, Ph.D.) for the maintenance of an updated HLA Class I sequence database. Quarterly reports and sequence alignments were provided to the NMDP for distribution to our contract laboratories. The final report covering the period of June through September 1998 was received in November 1998. Funding from private donations has supported this effort since that time.

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Sec. 1.j.) Description: NMDP Match vs. Outcome Research

Activity:

The Cooperative Agreement provided funding for data extract and statistical support for researchers conducting NMDP-approved studies on the correlation between degree of HLA match and post-transplant outcome. During the project period there were 13 abstracts published and 4 manuscripts published (or in press). An additional 13 manuscripts are in progress. The match versus outcome research projects supported under this category are as follows:

MANUSCRIPTS PUBLISHED/IN PRESS

- Unrelated Donor Bone Marrow Transplantation in 5075 Patients with Malignant and Non-Malignant Disease: Effect of Graft-Versus-Host Disease Prophylaxis on Treatment Outcome.
Principal Investigator: John E. Wagner, M.D.
- Unrelated Donor Marrow Transplantation for Chronic Myelogenous Leukemia: Nine Years Experience of the National Marrow Donor Program.
Principal Investigator: Philip B. McGlave, M.D.
- The Extent of HLA Class II Allele Level Disparity in Unrelated Bone Marrow Transplantation: Analysis of 1,259 National Marrow Donor Program Donor-Recipient Pairs.
Principal Investigator: Carolyn Hurley, Ph.D.
- Marrow Transplantation from Unrelated Donors for Patients with Severe Aplastic Anemia Who have Failed Immunosuppressive Therapy.
Principal Investigator: H. Joachim Deeg, M.D.

MANUSCRIPTS/PROJECTS IN PROGRESS

- Outcome of URD Stem Cell Transplantation for Children with ALL in Second Remission
Principal Investigator: Nancy Bunin, M.D.
- Bone Marrow Transplantation from URD for Patients with CLL
Principal Investigator: Steven Pavletic, M.D.

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(Sec. 1.j. continued)

- Unrelated Donor BMT in JCML Transplants
Principal Investigators: Frank Smith, M.D./Stella Davies, M.B.B.S., Ph.D.
- Comparison of Autologous BMT with Unrelated Donor BMT for AML
Principal Investigator: Hillard Lazarus, M.D.
- High Risk ALL study
Principal Investigator: Jan Cornelissen, M.D.
- Unrelated Donor BMT versus Autologous BMT in ALL
Principal Investigators: Daniel Weisdorf, M.D.
- Analysis of NMDP CML Transplants: Effect of Allele-Level Matching on Outcome.
Principal Investigator: Effie Petersdorf, M.D.
- Matched Unrelated Allogeneic BMT for Non-Hodgkin's Lymphoma
Principal Investigator: Philip Bierman, M.D.
- Effect of Allele-Level Matching on Outcome for Unrelated Donor BMT for CML
Principal Investigator: Effie Petersdorf, M.D.
- Analysis of Class II Disparity in Bone Marrow Transplants Utilizing Unrelated Donors
Principal Investigator: Lee Ann Baxter-Lowe, Ph.D.
- Influence of HLA Genetic Determinants on the Risk of Developing Pediatric Acute Lymphocytic Leukemia
Principal Investigator: Elizabeth A. Trachtenberg, Ph.D.
- Analysis of Class I Disparity in Transplant Outcome
Principal Investigator: Harriet Noreen, CHS
- Analysis of Class I CREG in Transplant Outcome
Principal Investigator: Judith Wade

ABSTRACTS PUBLISHED

- HLA-Matched Unrelated Donor (MUD) Bone Marrow Transplantation for B-Cell Chronic Lymphocytic Leukemia (Results from the CLL Working Group, National Marrow Donor Program)
Principal Investigator: Steven Pavletic, M.D.

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(Sec. 1.j. continued)

- Marrow Transplantation from Unrelated Donors for Patients with Aplastic Anemia (AA) – Optimization of a Conditioning Regimen.
Principal Investigator: H. Joachim Deeg, M.D.
- Comparison of Total Body Irradiation (TBI)-Based Regimens and Non-TBI Regimens in Marrow Transplantation from Unrelated Donors.
Principal Investigator: Joseph P. Uberti, M.D., Ph.D.
- Matched Unrelated Donor (MUD) Allogeneic Bone Marrow Transplantation for Non-Hodgkin's Lymphoma (NHL): Results from the National Marrow Donor Program® (NMDP).
Principal Investigator: Philip Bierman, M.D.
- Bone Marrow Transplantation From Unrelated Donors For Adult Patients With Poor-Risk Acute Lymphoblastic Leukemia: A Report From The National Marrow Donor Program (NMDP).
Principal Investigator: Jan J. Cornelissen, M.D., Ph.D.
- Unrelated Donor Bone Marrow Transplantation (UBMT) in 5075 Patients with Malignant and Non-Malignant Disorders: Impact of Marrow T Cell Depletion (TCD).
Principal Investigator: John Wagner, M.D.
- Frequent and Early Relapse After Unrelated Donor BMT for Juvenile Myelomonocytic Leukemia (JMML).
Principal Investigator: Franklin O. Smith, M.D.
- Predictive Value of High Resolution Class II HLA Typing in Bone Marrow Transplantation Using Unrelated Donors.
Principal Investigator: Lee Ann Baxter-Lowe, Ph.D.
- Unrelated Donor Marrow Transplantation for Myelodysplastic Syndromes (MDS).
Principal Investigator: Hugo Castro-Malaspina, M.D.
- Engraftment of Unrelated Donor Bone Marrow: A Report from the National Marrow Donor Program (NMDP).
Principal Investigator: Stella M. Davies, M.B.B.S., Ph.D.
- Use of Molecular HLA Analysis to Examine the Relationship Between Class II HLA Disparity and Outcome of Unrelated Bone Marrow Transplants.
Principal Investigator: Lee Ann Baxter-Lowe, Ph.D.

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(Sec. 1.j. continued)

- Marrow Transplantation from Unrelated Donors for Patients with Aplastic Anemia (AA) Who Failed Immunosuppressive Therapy.
Principal Investigator: H. Joachim Deeg, M.D.
- Analysis of 390 Marrow Transplants for the Treatment of Chronic Myeloid Leukemia from Unrelated Donors Facilitated by the U.S. National Marrow Donor Program® (NMDP): Effect of HLA-DRB1 Allele Disparity on Clinical Outcome.
Principal Investigator: Effie W. Petersdorf, M.D.

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Sec. 1.k.) Description: Intermediate Level DNA Class I & II Typing (NEW CATEGORY)

Activity:

This project was not initiated during this cooperative agreement. Due to the impact of unexpected delays in the implementation of this project, funds were de-obligated and reallocated to higher priority projects. Funding for this project was requested and provided in the Navy Cooperative Agreement N00014-99-2-0006.

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(Proposal Section)

(Sec. 2.) **ELECTRONIC COMMUNICATION**

(Sec. 2.a.) **Description: Expansion of STAR[®] to Accommodate Alternative Sources of Stem Cells & Blood Products**

Activity:

In general, the successful computer automation initiatives reported in Section 2. (Electronic Communication) provide some of the following benefits. As intended, they:

- Help streamline the overall transplant process and minimize the time required to deliver search match results to physicians and patients by introducing automation to assist NMDP network and Coordinating Center personnel.
- Continue to maximize access by patients to a variety of sources of stem cell products and timely data (e.g., via the World Wide Web).
- Ensure military preparedness and centralized contingent response for treatment in case of a nuclear or biologic disaster.
- Continue timely collection and analysis of research data relative to the efficacy of various treatment regimes.

Automation for Primary Peripheral Blood Stem Cell (PBSC) Treatment

During the term covered by this cooperative agreement, significant enhancements have been made to the NMDP Search, Tracking and Registry (STAR[®]) System, based on additional requirements from users. These significant enhancements permit the tracking and follow-up of donors who provide stimulated peripheral blood stem cells, following the controlled administration of G-CSF, rather than bone marrow for recipients. This serves to expand the treatment options available to recipients.

This ongoing effort will be continued under the new cooperative agreement (N00014-99-2-0006) to help increase transplants, shorten times to delivery and reduce costs associated with the services offered by the NMDP. The research value of these data is also significant and the STAR system will collect all pertinent information about the primary PBSC option.

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(Section 2.a. continued)

CORD Blood Processing Enhancements to STAR

Expansion of the STAR system to incorporate the tracking and management of Cord Blood Stem Cells (CBSCs) ensures that recipients have another potential treatment option. All searches performed against the STAR system will access both the available volunteer donor pool and the data associated with available CBSCs, thereby maximizing each recipient's options in one operation. The vital research required to determine the long-term outcome and efficacy of CBSCs relative to marrow will also be accommodated by use of the STAR system stored data.

The first cord confirmatory typing search request was made through the NMDP in November 1999. Currently, five cord units are active in the STAR system. Transplant centers continue to be added to the cord search process as training sessions are completed. Future enhancements to STAR based upon requirements from Search and Transplant Services and Finance are scheduled in 2000. These enhancements will continue under Navy Cooperative Agreement N00014-99-2-0006.

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(Sec. 2.b.) Development and Implementation of Client Software Products

Activity:

CORD Link™ (Cord Blood Bank software – interfaces with STAR)

The CORD Link application permits NMDP contracted Cord Blood Banks (CBBs) to list the data associated with available frozen Cord Blood Units (CBUs) which have been collected in order to provide CBSCs (see Sec. 2.a. above) for recipients. CORD Link was developed by the NMDP, with the support of funding provided under Navy cooperative agreements, and is provided to participating CBBs. CORD Link offers the CBB a suite of tools to list, manage and report on the CBUs available to NMDP recipients. In addition, it provides a means to store and report maternal risk factors, infectious disease test results and a variety of other factors considered by the transplant physician before use. An extensive inventory control system is inherent in CORD Link, ensuring that cord units are available as soon as data is entered into the system. Ongoing, two-way communication between CORD Link and STAR via the Internet is designed to efficiently transfer data records to be used by the search process as well as requests for additional information, shipping, etc., from intended recipients.

Conversions of existing CBBs that meet minimum requirements for participation in the NMDP network are ongoing. Recently, for example, Bonfils Cord Blood Services at Bonfils Blood Center in Denver, with the assistance of the NMDP Information Systems department, completed the conversion of approximately 500 cord blood units. These CBUs are now listed on the STAR registry system. All such efforts are directly aimed at increasing the numbers of transplants performed by offering new alternatives for treatment to transplant centers. Additional conversions and installations of CORD Link will continue under Navy Cooperative Agreement N00014-99-2-0006. Also, additional versions of the CORD Link (and related) software will be developed and implemented in the months to come.

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(Sec. 2.b. continued)

TRANS Link™ (Transplant Center Software – interfaces with STAR)

The first version of the Transplant Center Software (TRANS Link) was developed with the support of the Navy cooperative agreement. This software provides considerable utility to NMDP transplant centers. Some of the important features include:

- Instantaneous “window shopping” search capabilities over the Internet, such that subscribing centers can quickly evaluate the availability of best-matched donors.
- Automation of NMDP preliminary and formal searches over the Web.
- Additional recipient data via a centralized database.
- Provision for transplant center controlled multiple search strategies.
- On-line, automated Workflow Management to help streamline transplant operations.
- Forms tracking indicating forms due, completed or overdue.
- Provision for initial reporting needs.

A subsequent phase of this software will be developed starting in 2000. Phase II enhancements will include:

- On-line forms entry to reduce paperwork and simplify transplant center reporting.
- Integration with IBMTR.
- Automated CPI management.
- Additional reporting needs.
- An ability to set a “Fast-Track” in order to streamline the search process for urgent situations.
- Centralized management of searches by the NMDP in case of a disaster.

Development and programming during Phase I progressed rapidly throughout the last three months with specific iterations established ahead of the published project timeline. A training initiative and course outline was established. It is anticipated that training of all NMDP affiliated transplant centers will begin in March 2000 and continue until completed. More than 140 transplant centers are scheduled for training and conversion to use of the new TRANS Link project developed with Navy support.

Continuation of the development of TRANS Link and reengineering of the search process to reduce the time required to bring patients to transplant will continue under Navy Cooperative Agreement N00014-99-2-0006.

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(Sec. 2.b. continued)

CRIS Link™ - (Computerized Repository Information System – interfaces with STAR)

The CRIS Link application replaced an outdated Paradox application, called "DNACR" with a more fully featured and reliable application written in an object-oriented database language that NMDP can support and continue to enhance. The first objective in developing this software was to create a more stable and scalable application. Secondly, the effort was aimed at refining the processes automated by the application so that data recovery did not require time consuming, manual intervention by NMDP support staff members.

The CRIS Link application stores samples and processes them into units to be sent to NMDP contract typing laboratories. It serves the purpose of automating entry of the sample donor IDs (DIDs), automating storage location (box and slot) allocation, and tracking of the anomalies that can occur during the aliquoting or filter paper splitting processes. Samples are received from the various donor centers, and the samples (blood) are placed into the Central Repository Frozen Sample Inventory or into a Filter Paper Sample Inventory.

The DNA Repository Sample Shipping portion of the solution serves the purpose of tracking shipments, by using the sample DIDs, to contract typing laboratories, expediting the shipping process. The samples are assigned to a typing laboratory shipment by the priority and typing category. The new version of the software will permit handling, shipping, tracking and management of samples by the funding source being used to pay for the laboratory work.

CRIS Link was installed at both NMDP repositories in early November 1999. Enhancements to CRIS Link will continue under Navy Cooperative Agreement N00014-99-2-0006. Additionally, the functionality of CRIS Link will be expanded to incorporate the needs of other repository operations (e.g., donor and recipient sample pair collections, etc.).

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(Section 2.b. continued)

STAR Link™ (Donor Center Software – interfaces with STAR)

In early December 1999, the latest version of STAR Link was released to the NMDP donor centers. Installation of this release will continue through January 2000. The latest release incorporates functions for better management of recruitment drives, modifications to existing STAR Link reports, additional security measures, and enforces certain requirements for recruitment typing of donors. Other enhancements on the queue for future STAR Link releases will continue to be reviewed and implemented under Navy Cooperative Agreement N00014-99-2-0006.

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(Sec. 2.c.) **Description: STAR[®] Enhancements to Support DNA Polymorphism Data**

Activity:

STAR Enhancements to Support DNA Polymorphism Data

Navy funds on this line item ensured a successful and significant evolution in NMDP automated systems to support DNA Polymorphism Data. Highlighted below are just a few examples of accomplishments that have recently been completed and are being continued under the new Navy Cooperative Agreement (N00014-99-2-0006). Many of these changes to the STAR system to support DNA polymorphism data have been summarized by a five-step plan. Navy funding has helped with the analysis, design, programming and system testing required to complete Step I of the NMDP/Navy DNA projects which were completed during the terms of this cooperative agreement.

Specifically, Step I provided for:

- the acceptance, storage and use of Class I typing results on the STAR system;
- significant modifications with regard to the electronic, automated exchange of data between the NMDP and its contract sample repositories;
- enhancements to the internal HLA override functions within the system, and
- quality control processing on DNA (serology) labs under contract with the NMDP.

The NMDP then went on to address the needs defined by Step II, including changes to the STAR system, such as:

- “refining” the use of DNA typings within the system to provide for matching by “search determinants;”
- an expansion of antigen typing fields within the system to 5 digits to incorporate expanded allele codes;
- implementation of a new “sub-sort” paradigm to provide more informative reports from the match system; and
- many other enhancements to prepare the system for eventual DNA based matching.

Step III was undertaken by the NMDP to incorporate modifications to the STAR system and certain ancillary applications in order to:

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- accept and utilize DNA probe scores obtained from NMDP contract labs around the country;
- interpret probes for use by the STAR system;
- provide Research & Scientific Services staff with improved tools for maintaining probe data;
- validate antigen and DNA specific data on the systems on the basis of search determinant tables rather than antigen-specific global parameters;
- improve the system-based process of determining effective HLA overrides; and
- integrate all the required system and management reporting functions modified during this step.

Step III is not yet complete, but will include the work summarized below.

Probe interpretations for Class I and II intermediate resolution typing continues. Modifications have been made to the probe interpretation program within the STAR system to refine multiple allele codes for homozygous typings. A new system was developed to process incoming typing results with probes and interprets them as they are received during the day. Interpretation reports are now sent to laboratories within minutes of receipt of their probes. All of these measures help to reduce errors and ensure timesaving in the process of matching recipients with available sources of treatment.

During the term of the cooperative agreement, new systems were put in place to process incoming Class II typing results with probes and interpret them as they were received during the day. This system has worked extremely well and the percentage of uninterpretable typings went from over 9% in December 1998 to less than 1% in March 1999. A probe interpretation report is generated and sent back to the laboratories within 30 minutes of the original message, thereby ensuring timely correction of any problems.

The labs have reported that this on-line interpretation process has helped them identify some problems with their internal interpretation and reporting systems. Additionally, since the feedback obtained from the NMDP about uninterpretable typings is delivered so quickly, the lab is often able to repeat typings while the original setups are still in place, thereby saving time and other valuable resources.

Step IV involves the design and implementation of a DNA data model to accommodate the complex nature of molecular data storage.

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WISE – DNA Virtual Sequence Database

A Virtual Sequence Database (WISE) is a new conceptual data model that is capable of representing all typing information in a consistent way regardless of typing method (SSO, SSP, SBT, etc.). This data format immortalizes the data for future interpretation and analysis while preserving all typing results in a consistent representation that can capture: negative typing results, cis/trans linkages, insertion/deletion mutations, group specific amplification and intron sequence features. The WISE is a key component of the NMDP/Navy DNA Step IV.

The virtual sequence working group met on October 18 to discuss the results of a pilot project. HLA-DRB1 typings on 128,000 simulated and 30,000 real donors were assembled to test different matching approaches that make use of the raw reactivity data. Three different storage representations were evaluated for matching against 10 test patients:

1. Conversions of patient typing to the expected probe/primer reactivity pattern with direct comparison to the donor's probe/primer reactivity pattern.
2. Conversions of all donor typings to a standardized data format (using symbolic expressions about nucleotides) and then matched based on polymorphisms found in patient typing.
3. Conversion of donor typings to a pair of consensus sequence strings that represent the positive and negative reactivity data and then matched to the patient typing.

The conclusions from the meeting are that all three approaches require patient typings at the allele level for all loci covered by the donor typing kits (HLA-DRB1, DRB3 and DRB5 for this pilot project). The group also concluded that if the system is going to be flexible and allow different typing kits which use different methodologies (or over different polymorphisms), then the matching system will need to reference an allele list during the matching process.

Another conclusion from the pilot project is that partial interpretation (separation of polymorphisms into separate alleles) is a critical step in the use of SSO and SSP data.

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Step V will involve the rewrite of the STAR system to provide for full DNA matching.

Several examples of other specific additional improvements accomplished during the same period are summarized briefly below. The aims of these projects included:

- HLA Override programming within STAR to incorporate logic specific to DNA typing data;
- the capturing and storing of Molecular HLA-A, B data within the STAR system;
- automation to manage the exchange of information specific to the interaction between the NMDP and AB contract labs;
- a system to track and maintain Quality Control over various lab typing results;
- modification to the STAR search algorithm in order to fully utilize and report on the basis of DNA data;
- enhancements to the STAR system in order to provide for the storage (and update typings) of data based upon DNA polymorphisms; and
- ongoing expansion of the allele codes within the STAR system.

STAR System Summary Count and Match Grade Changes

In October 1999, changes to search summary count and match grades were put into STAR and the resultant reports provided to the transplant centers. The benefits of these enhancements included:

- The ability to distinguish allele codes with overlapping values from those without overlapping values.
- More realistic representation of the type of matching donors available.
- More accurate representation of how closely donors match. Better capability to display match results, placing the 6/6 HLA-DRB1 allele matches in a best-match order at the top of reports.
- Timesaving improvements in the search process associated with the provision of allele-specific information.

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New HLA-A,B & DRB Typing Result Monitoring Capabilities

A series of new reports has been created within the STAR system to better monitor the complex yet critical reporting of typing results by contract laboratories. By improving the NMDP's ability to monitor the progress of labs and avoid difficulties, fewer delays are passed on to searching patients, thereby helping to shorten the time between the initial search and the ultimate transplant activity. Several recent changes are summarized below by way of example:

New laboratory performance monitoring reports have been developed for the HLA-A,B & DRB intermediate resolution typing contract which began January 2000. A new turnaround time report was developed which monitors the number of days between the shipment of samples to the lab and the date the results are received in STAR. The sample completion report was modified to track typing requests for HLA-A, B only, HLA-DR only and HLA-A,B & DRB separately.

Class I Search Determinants

Towards the eventual storage and use of DNA polymorphism data, the STAR system has undergone extensive modification in order to accept and store Class I DNA typing results from contract laboratories, and convert DNA typing results to search determinants. The NMDP is capable of accepting typing results from newly established contract laboratories. The system will be further modified through the development of a Class I and II DNA search routine.

As a result of the NMDP Histocompatibility Committee meeting on November 15, 1999, the Class I search determinants for alleles have been approved. An algorithm to specify the search determinants for Class I allele codes has been developed based on the committee's recommendations.

The STAR HLA Override System has been revised to reflect new requirements for evaluating typings based on decisions made at the committee meeting. A timeline has been developed to implement the changes to Class I search determinants early in the year 2000 that involves remapping the search determinants on 225,000 donors.

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On-line DNA Matching

A system has been developed to perform real-time matching for donors and cords. This system will be integrated with TRANS Link to provide on-line matching results. The on-line matching system uses the new DNA matching rules, developed during the term of this agreement, which consider an allele mismatch at HLA-DRB1 to be a major mismatch.

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(Sec. 2.d.) **Description: Enterprise Upgrades to STAR[®] System for Registry Growth and Diversification**

Activity:

Infrastructure Enhancements

During the period covered by this agreement, there have been many improvements made to the STAR infrastructure, supporting environment and many ancillary systems. Some of these include:

- Year 2000 compliance, including date processing changes on all systems.
- STAR server upgrades to provide additional memory, processing speed and flexibility.
- Improve the office system applications on all NMDP computers.
- Enhance the operating system environment by introducing the latest versions and tools.
- Develop an internal Internet (Intranet) to support extensive new automation applications at the NMDP national headquarters (e.g., calendaring systems, fully integrated E-Mail, internal status reporting, forms generation, human resources information, project management systems, Navy time reporting system, etc.).
- Improved networking capabilities with more efficient connections between various systems, faster access to the Internet, remote access terminal server capabilities, and improved remote office support.
- Significant improvements to security measures, including regular testing of off-site disaster recovery.
- Telecommunication enhancements including capacity upgrades to telephone systems, improved 800 number services, faster FAX receipt and transmission facilities, voice messaging upgrades, etc.
- Database tuning and the introduction of new testing and development environments to speed the delivery of final solutions.
- Development and implementation of a new and improved data dictionary service, including process improvements to speed the review and acceptance of newly developed code and STAR enhancements.
- Improved forms processing applications to better handle the complex data reported by NMDP network centers in regard to donor and recipient follow up.

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(Sec. 2.d. continued)

- Data audits to verify the integrity of STAR data.
- Implementation of new Help Desk software to monitor reported problems and track resolutions.
- Enhancements to the NMDP Continuous Process Improvement (CPI) processing.
- Develop and implement a batch simulation system for use during Navy Contingency Exercises.
- Creation of tools to help with the stratified selection of donors for retention studies.
- Ongoing enhancement to the STAR Alternative Blood Processing (ABP) modules.
- Development of a STAR Donor Activity Reimbursement (DAR) tracking system to facilitate automated payment to donor centers for services rendered.
- Creation of a medical Cost Tracking System (MCTS) linked to STAR to monitor costs associated with procedures performed by transplant centers.
- Provision of a case management tool for use by the NMDP Office of Patient Advocacy to help monitor potential recipients who might otherwise not go forward to transplant.
- Completion of many research studies, data extracts and analyses using STAR data.

Web-based Development Efforts

The NMDP Information Systems web development group is working with several departments within the organization to continue adding new material and applications to the NMDP Internet and Intranet sites.

Recent enhancements have included the design and implementation of a new web site directed towards research called <http://www.NMDPResearch.org>. The site was created to communicate the results of NMDP-sponsored research, to assist physicians and scientists in conducting research through the NMDP and to promote opportunities in stem cell transplant studies.

Other NMDP web sites include:

http://www.NMDP.org	the main NMDP web site
http://www.BMTinfo.org	a physician and patient education site
http://www.sequence.org	a site to house DNA data
http://www.marowfoundation.org	The Marrow Foundation home page

Continued enhancements used to communicate critical information to donors, recipients and NMDP staff will continue under Navy Cooperative Agreement N00014-99-2-0006.

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(2.e.)

Description: Studies on Effects of Exposure to Ionizing Radiation

Activity:

The NMDP Information Systems personnel have supported the efforts of the International Consortium for Research on the Health Effects of Radiation (ICRHER), as required, during the term of the cooperative agreement. Ongoing support to the ICRHER will be provided under the new cooperative agreement (N00014-99-2-0006) in the form of database and data management consulting.

Selected personnel from the NMDP will attend the annual meeting of the ICRHER in the spring of 2000.

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(Proposal Section)

(Sec. 3.) Donor Recruitment and Retention

(Sec. 3.a.) Description: Minority Donor Serologic and DNA HLA-A,B Typing

Activity:

Education, recruitment, and serologic HLA-A, B typing and DNA HLA-A, B typing of minority volunteer donors.

- During the three years of this cooperative agreement, the NMDP expended, committed or obligated funds for the education, recruitment, serologic HLA-A,B and DNA HLA-A, B typing of 426,300 minority volunteer donors.
- Donor centers conducted educational sessions and made presentations to minority and community groups to aid in the retention of volunteer donors once they were recruited for the NMDP Registry. These education sessions led to the donor centers conducting 18,629 recruitment drives during the three years of this cooperative agreement.
- Each month donor centers participated in an average of 517 minority focused recruitment.
- The NMDP utilized funding from this cooperative agreement to implement a network of contract serologic HLA-A, B typing laboratories that would provide standardized, accurate and timely low-cost typings for newly recruited volunteer donors. Contracts were placed with 26 laboratories and work began in August 1998.
- In February 1999 the NMDP began a process to transition from serologic typing to complete DNA-based HLA-A, B typing for newly recruited donors whose recruitment and HLA typing were supported with government funding. The transition was completed June 30, 1999, and this network of serologic typing

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(Sec. 3.a. continued)

laboratories was terminated effective June 30, 1999. The total number of donor samples typed by this network for the ten-month duration of the contracts was 107,151.

- DNA HLA-A, B contract laboratories began typing all Navy funded samples by DNA July 1, 1999. NMDP donor centers are required to use this group of laboratories for all NMDP funded typing, including minority donor typing and typing performed with community matching funds.

Please see Section 1.c for additional information on DNA HLA-A, B typings.

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(Sec. 3.b.) Description: National Minority Campaigns and Donor Recruitment

Activity:

- Results of the 1999 follow-up survey of individuals who call the NMDP's public information 800 number, MARROW-2, revealed that 19% of callers go on to join the Registry. This is up 2% from the 1994-95 survey. The most significant increases were seen among Hispanics and African Americans.
- Traffic on the www.marow.org web site has increased annually, with the largest increases coming in the past year. We went from approximately 8,000 visits a month in October 1998, to more than 30,000 visits a month in September of 1999. The number of visitors to the site was significantly increased through enhancements to the site and several new marketing initiatives. Numerous additions were made to the web site including: frequently asked questions, more personal stories, a new media room, cord blood information and the ability for volunteers on the Registry to update their address online. A site survey continues to provide helpful insight about additional information to be added and ways to make the site easier to use. The Communications & Education Department and the Information Systems Department collaborate on the development and implementation of the site.
- The media team responds to media inquiries, provides hands-on support for the network centers, pitches new stories and produced a record 30 news releases in 1999. Topics included: donor/recipient meetings, outstanding cancer survivors, award and grant winners, special events and numerous releases about minority recipients and minority donors. We have continued to build on the success of using feature-style news releases to emphasize the need for minority donors during special months such as Black History Month, Native American Heritage Month and others.
- A public service announcement featuring National Football League player and Super Bowl Champion Charles Haley, members of the Dallas Cowboys and minority patients received 1,227 telecasts in 26 markets for an estimated time value of \$191,746.
- The NMDP continued its efforts to build relationships with ethnic media by participating in the UNITY '99 conference, the world's largest gathering of journalists of color.

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- Promotional and hands-on support was provided to The Marrow Foundation and the 20 NMDP donor centers that participated in National Minority Donor Awareness Day.
- The NMDP's first-ever art calendar was created in 1999. The 18-month calendar was introduced at the UNITY conference. It features artwork from last year's art contest and milestones in NMDP history. Each month carries a message about the need for minority donors, donor commitment, or services available through the NMDP. The calendar was well received at the conference.
- A new, multicultural recruitment and educational video, *The Missing Piece*, was created to provide a more detailed overview of marrow and PBSC donation.
- Brochures, posters, fliers and other marketing collateral items for ethnic and minority audiences were updated and reprinted throughout the year. A glossary of common NMDP and medical terms was translated in Chinese, Japanese, Korean and Vietnamese and serves as a standard for developing the translations of the brochures and other educational materials.

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(Sec. 3.c.) Description: Community Matching Funds for Caucasian Donor HLA-A,B Typing

Activity:

Education, recruitment and HLA-A, B and DNA HLA-A, B typing of Caucasian volunteer donors.

- During this cooperative agreement, the NMDP expended or obligated funds to educate, recruit and HLA-A, B and DNA HLA-A, B tissue type 329,035 Caucasian volunteer donors.
- Donor centers coordinated activities with families and community focused groups to make presentations, conduct workshops, etc. These coordinated efforts resulted in donor centers conducting 8,291 community-focused drives during this agreement.
- Each month donor centers participated in an average of 230 Caucasian donor education and recruitment efforts during this agreement.

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(Sec. 3.d.) Description: Donor Center Waiting List Funds for HLA-A,B Typing

Activity:

No effort was performed on this line during this cooperative agreement. All funds were reallocated to other critical projects.

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(Sec. 3.e.) Description: HLA Typing of Cord Blood Stem Cell Samples

Activity:

No effort was performed on this line during this cooperative agreement. All funds were reallocated to other critical projects.

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Proposal Section)

(Sec. 4.) **EDUCATION AND AWARENESS**

(Sec. 4.a.) **Description: Physician and Transplant Center Coordinator Education**

Activity:

This cooperative agreement provided funding for several important educational events:

Two symposia, held preceding the 1996 and 1997 American Society of Hematology (ASH) meetings, were attended by hematologists and oncologists worldwide. Funding was used to provide the required acceptance fee to ASH, printing and postage of the brochures describing the program, as well as modest travel expenses for speakers and minimal refreshments for attendees.

The 1997 and 1998 Transplant Center Spring Meetings. Each had an emphasis on search strategies, as well as searching for patients with unusual HLA types. Funding was used to cover lodging and food costs for one representative from each transplant center.

A special DNA Symposium for transplant center coordinators was held at the 1997 Council Meeting in Minneapolis. Funding was used to cover the extra night of lodging and food for transplant center coordinators.

In addition, the cooperative agreement was used to produce and distribute a set of slides and background material (updated annually) to NMDP transplant and donor center physicians in 1996, 1997 and 1998.

A booklet entitled *A Physician's Guide to the National Marrow Donor Program* was also printed with support from this cooperative agreement.

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(Sec. 4.b.) **Description: Patient Education**

Activity:

Patient materials, including the *Transplant Center Access Directory*, *Unrelated Bone Marrow Transplants: A Patient's Guide* and *A Patient's Resource: Information About Unrelated Marrow Transplants*.

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(Sec. 4.c) Description: Registry Wide Newsletter and Follow-up Mailings

Activity:

Two volumes of the Registry-wide newsletter *The Marrow Messenger* were produced. A new editorial process was created to include more input from NMDP network centers and staff. The major messages of education, motivation and commitment were sprinkled liberally throughout the stories. Volunteers are now encouraged to go to the NMDP web site to change their address online.

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Sec. 4.d.) Description: Phase II National Public Service Campaign

Activity:

Costs were incurred for duplication and distribution of a television public service announcement featuring professional football players and minority patients. The PSA received 1,227 telecasts in 26 markets for an estimated time value of \$191,746.

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Proposal Section)

(Sec. 5.) Description: PROGRAM ADMINISTRATION

(Sec. 5.a.) Description: Technical and Administrative Support

There are three parts to this section.

Activity:

- 1) NMDP staff administered the cooperative agreement by tracking expenditures, coordinating with ONR on contractual documents and preparing financial and technical reports.

- 2) Ionizing Radiation Exposure Study Subcontractor and Office Expense

Activity:

The subcontractor provided support for the ICRHER. Funds under this section of the cooperative agreement supported personnel, office rent, and supplies of the subcontractor. Throughout the course of the agreement, the subcontractor expended efforts for negotiations with participating institutions and provided planning for the annual investigator meetings.

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(Sec. 5.a. continued)

- 3) Military Preparedness Planning for Military Personnel Exposed to Ionizing Radiation or Biological Warfare Weapons in a Combat Situation

Contingency Planning Committees

The NMDP has formed several committees composed of NMDP staff, and physicians and coordinators from participating centers. These committees have been charged with responsibility to develop network-wide contingency plans. At the National Coordinating Center, the Contingency Planning Committee is composed of NMDP staff from each department. This committee has identified internal processes that would be impacted by a contingency event and has begun writing and refining department contingency procedures. These procedures will be tested during internal drills and external drills with NAMRI. A subcommittee of this group, the HLA Matching Team, participated in the selection of donors for the first DOD/NMDP contingency drill April 27 – May 4.

In an emergency event, it is critical that the NMDP have medical treatment and data collection plans in place. The NMDP Patient Care Committee is composed of network physicians. The goals of this committee include:

- Developing guidelines for performing hematopoietic stem cell transplants to treat radiation injuries.
- Developing guidelines for non-transplant/pre-transplant management of radiation victims.
- Developing guidelines for determining which radiation victims should receive transplants.

These activities will be pursued under Cooperative Agreement N00014-99-2-0006.

Contingency Planning Education

In October 1998, the NMDP Chief Medical Officer presented introductory contingency planning training to the NMDP staff and Board of Directors. An introduction to contingency planning and centralized searching was first presented to the NMDP network at the Spring Coordinator Meeting for transplant centers (Park City, Utah April 12-13) and donor centers (Denver, April 23-25).

NMDP Chief Medical Officer, Dr. Dennis Confer attended a REAC/TS-sponsored course in the care of radiation victims from April 26-30. Materials and information from this

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course were used to develop the first Patient Care Committee Meeting. Dr. Confer was invited back to REAC/TS to present a seminar on stem cell transplantation on September 28, 1999.

The NMDP Chief Medical Officer and Manager, Special Search and Transplant Projects attended a CDC/USAMRIID/FDA satellite training course entitled "Biological Warfare and Terrorism; The Military and Public Health Response" in St. Paul, Minnesota. The course provided several examples of actual or potential interactions between public health and military organizations, which will prove valuable in the development of the NMDP network response plan.

Urgent Search and Streamlined Search Management.

In a contingency situation, it would be necessary to match rapidly and reliably stem cell donors with casualties who might require stem cell support. The NMDP devised several pilot projects that test NMDP management of patient searches using a variety of typing methods, including centralized confirmatory typing, centralized high resolution DNA testing (HR-DNA), and improved utilization of repository samples.

HR-DNA Pilot 1

The NMDP completed the first centralized high resolution DNA (HR-DNA) pilot initiated in May 1999. NMDP reviewed recipient searches and selected potentially matched donors for typing. Freshly drawn donor blood samples were shipped to a central laboratory for HR-DNA DRB1 and intermediate resolution HLA-DQB1, DRB3, DRB4, and DRB5 testing. Recipients were selected for inclusion in the project based on the following enrollment criteria:

- Recipient diagnosis of CML, chronic phase, stable condition.
- Low or high resolution HLA-A, B typing and high resolution HLA-DRB1 recipient typing available.
- No potential donor matches with HLA-DRB1 allele level typing.
- Available domestic NMDP donors with low resolution or serologic HLA-DRB1 typing that are potential matches.
- Recipient enrollment at a domestic transplant center.
- Recipient transplant center was willing to allow NMDP to select donors for HR-DNA testing.

(Section continued on next page.)

Government Comments:

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(Sec. 5.a. continued)

The NMDP reviewed 128 patient searches from 5/28/99-6/30/99 and accrued 10 patients of various ethnic backgrounds and a total of 114 donors were selected for HR-DNA testing as shown in Table 1. Five searches progressed to the confirmatory typing (CT) stage with pilot donors and three recipients subsequently transitioned to a marrow work-up. Although 18% of the pilot donors were identified as potential matches for transplant, upon conclusion of the HR-DNA testing it was determined that the most suitable matches for two patients were international donors. International donors were not included in this first pilot project, so the transplant centers performed CT testing of potential international donors at their centers and then compared the results with the domestic HR donors. The rate of unavailable donors was 42%, indicating that large numbers of donors should be requested for typing when possible.

Government Comments:

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(Sec. 5.a. continued)

Table 1: Results of HR-DNA Pilot I

Patient	Race	Number of Donors Selected for HR-DNA	Donor/Patient Match Grade	Matched Donors/ Donors Typed	Search Resolution
1	CAU	10	111	2/7	TX with pilot donor 9/99.
2	CAU	4	111	0/2	TX with NMDP international donor.
3	CAU	3	111	0/3	No matches identified.
4	AFA	11	111	4/4	Work-up in progress with pilot donor.
5	CAU	27	211(1) 121(4) 311 (15) 131(7)	5/16	Suitable matches. TX with 111 donor outside NMDP.
6	CAU	2	111	0/0	Patient not interested in TX.
7	AFA	10	111(1) 211(4) 311(5)	5/5	No further activity at this time.
8	HIS	9	111	1/7	One pilot donor at CT.
9	HIS	28	111	2/16	TX with pilot donor in 10/99.
10	AIND	10	111(3) 211(1) 121(2) 311(3) 131(1)	1/4	One donor at CT.

(Section continued on next page).

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HR-DNA Pilot II

The NMDP selected donors for testing for 6 patients in August and September 1999. Donor blood samples were drawn and shipped to a central laboratory for HR-DNA DRB1, DQB1 and intermediate resolution DRB3, DRB4, and DRB5 testing. During September, typing was temporarily halted due to a reagent problem. The manufacturer provided a new reagent lot in early October and typing efforts have resumed. Results are pending and will be described in the next quarterly report.

Currently, the NMDP is modifying the HR-DNA laboratory contract to include a rapid turn-around time for ultra-urgent searches. In the next phase, the project will be repeated with an urgent time frame to evaluate the process speed. Future strategies will also include centralized HR-DNA HLA-A, B testing and CT. The NMDP will also consider the role of international donors.

Government Comments: