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Past, present and future of the National Marrow Donor Program.

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Abstract

Allogeneic hematopoietic cell transplantation (alloHCT) is a potentially lifesaving therapy for many patients with hematologic malignant and non-malignant disorders. Although a human leukocyte antigen (HLA)-matched sibling is the preferred alloHCT donor source, the majority of patients in need of a transplant do not have a matched sibling and hence an alternative donor must be identified. The National Marrow Donor Program (NMDP)/Be The Match operates the world's largest registry of adult volunteer donors and cord blood units. Here we review the early years of the NMDP, efforts to advance the field through research, and global collaborations to facilitate transplants for all patients in need.

KEYWORDS: National Marrow Donor Program; NMDP; hematopoietic cell transplantation; HCT; unrelated donors

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Pasado, presente y futuro del Programa Nacional de Donación de Médula Ósea

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Resumen

El trasplante alogénico de células hematopoyéticas (TACH) es una terapia útil para muchos pacientes con enfermedades hematológicas malignas y no malignas. Aunque un hermano con antígeno leucocitario humano (HLA) compatible es el donador de elección para un TACH, la mayoría de los pacientes con necesidad de trasplantarse no tienen un hermano compatible, por tanto, debe identificarse a un donador alternativo. El Programa Nacional de Donadores de Médula Ósea de Estados Unidos (NMDP)/*Be The Match* opera el registro mundial más grande de adultos donadores y unidades de sangre de cordón umbilical. En este trabajo revisamos la actividad en los primeros años del NMDP y los esfuerzos realizados en este campo para llevar a cabo avances a través de la investigación, así como las colaboraciones globales para facilitar el trasplante a todos los pacientes que lo requieren.

PALABRAS CLAVE: Programa Nacional de Donadores de Médula Ósea, NMDP, trasplante de células hematopoyéticas, HCT, donadores no relacionados.

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INTRODUCTION

Allogeneic hematopoietic cell transplantation (alloHCT) is curative therapy for many malignant and non-malignant blood disorders. Historically alloHCT was restricted to patients with a human leukocyte antigen (HLA)-matched sibling. However, with over 70% of patients lacking a matched sibling, the majority of patients who could benefit from a transplant were not able to receive this potentially lifesaving treatment. Identifying an HLA-matched unrelated donor was impossible as no system existed for recruiting and HLA-typing potential donors from the general population. This changed in 1974 with the establishment of the Anthony Nolan Donor Registry in the United Kingdom. Several other registries followed including the National Marrow Donor Program (NMDP) Registry in 1986. NMDP/Be The Match is presently the world's largest registry of adult volunteer donors and cord blood units. Here we review the early years of NMDP, transplantation activity and trends over time, contributions by NMDP to advances in the field, and how we envision NMDP efforts will continue to shape the discipline of transplantation throughout the world.

Establishment and growth of the NMDP Network

Dr. Robert Graves, a veterinarian, was largely responsible for establishing NMDP.[1] In 1979, his daughter, Laura, suffered from relapsed acute lymphoblastic leukemia (ALL) and did not have a matched family donor. Dr. Graves sought the assistance of Dr. John Hansen of the Puget Sound Blood Center and Fred Hutchinson Cancer Research Center (FHCRC) in Seattle, Washington, United States (US). Dr. Hansen was conducting research on HLA matching in HCT, and he and his colleagues agreed to perform a transplant if an unrelated HLA-matched donor for Laura could be identified. Fortunately, Laura had a common HLA type and, in a search of the research laboratory database, an HLA-matched research donor (an FHCRC employee) was identified who agreed to be a bone marrow donor for Laura. Although Laura initially recovered from the transplant, unfortunately her disease recurred and she died in 1982. However, convinced of the lifesaving potential for unrelated donor transplantation, Dr. Graves continued to be a strong and vocal proponent for the establishment of a national registry of HLA-typed unrelated donor volunteers.

Over the ensuing years, ethical and legal issues and management of the potential risks to the donor from marrow collection were addressed and ultimately led to the development of a set of operating principles. Reports of successful HLA-matched unrelated donor transplants with donors identified through donor-based organizations including the Blood Center of Southeastern Wisconsin and the American Red Cross in St. Paul, Minnesota, and regional marrow donor programs, provided a strong rationale for a national program.[2-4] In 1986 efforts came to fruition with the establishment of the National Bone Marrow Donor Registry (NBMDR) through a contract with the US Navy. The program began to process search requests for donors in September 1987 followed by the first facilitated unrelated donor transplant in December 1987 for a child with acute leukemia. In June 1988 the organization was renamed the National Marrow Donor Program.

From 44 donor centers and 7 transplant and collection centers in 1986, the global NMDP Network has grown substantively (Figure 1). The Network is now composed of numerous domestic and international transplant, donor, apheresis and collection centers. A cord blood program was begun in 1998 that includes 67 affiliated cord blood banks (including 65 international banks), and an additional 24 member cord blood banks. Recruitment centers, testing

Figure 1. The National Marrow Donor Program Network.

laboratories, 41 cooperative registries and a donor-recipient sample repository complete the Network. NMDP headquarters and repository are based in Minneapolis, Minnesota, US. Beginning with 1 employee in 1986, the staff has grown to over 900. NMDP, supported in part through multiple federal contracts, operates what is now known as the congressionally authorized C.W. "Bill" Young Cell Transplantation Program and the Be The Match Registry.

NMDP Be The Match Registry

The growth of the NMDP Be The Match Registry has been exponential since the early years. Beginning with fewer than 10,000 adult donors, the founders set an immediate goal of 100,000 donors. That goal was quickly surpassed, reaching one million by 1994, and cord blood units were added in 2000. The growth in number of registered adult donors and cord blood units from 1988 to June 2015 is shown in Figure 2. NMDP is the world's largest registry with over 13.5 million registered adult donors and more than 225,000 cord blood units. The cord blood units represent a more diverse population (44% white; 47% people of color, including Hispanic or Latino; 9% unknown) compared with adult donors (52% white; 25% people of color; 23% unknown).

To better understand the impact of diversity, the NMDP built population-based genetic models for 21 US racial and ethnic groups to answer the question, "What is the likelihood of finding a suitable matched adult donor or cord-blood unit in the Registry?"[5] Population-based genetic models showed that the likelihood of finding an optimal donor (defined as 8/8 high-resolution HLA-matched at HLA-A, HLA-B, HLA-C, and HLA-DRB1 loci for adult donors, and matched at the antigen level at HLA-A and HLA-B and at high resolution at HLA-DRB1 for cord blood units) varied by racial and ethnic groups, with the highest probability (75%) among whites of European descent. The lowest probability (16%) of finding an optimal donor was among blacks of South or Central American descent. However, cord blood units mismatched at one or two HLA loci were available for the majority of patients regardless of racial and ethnic background. More recently, an NMDP analysis estimated the 8/8 and 10/10 (including HLA-DQB1) match rate for Hispanics to be 44% and 38%, respectively.[6] NMDP is focusing its efforts on recruiting donors from ethnic and racial groups as well as collaborating with international registries to increase the diversity of the Registry, and conducting research to investigate better ways to collect ethnic information, especially for multi-ethnic individuals.

Trends in unrelated donor transplants

Utilization of unrelated donor HCTs has risen steadily over the past 30 years. This is the result of numerous factors, including expanding disease indications for HCT, the emergence of umbilical cord blood transplantation with its less stringent HLA matching requirements, the development of non-myeloablative (NMA)/reduced intensity conditioning (RIC) regimens allowing HCT for

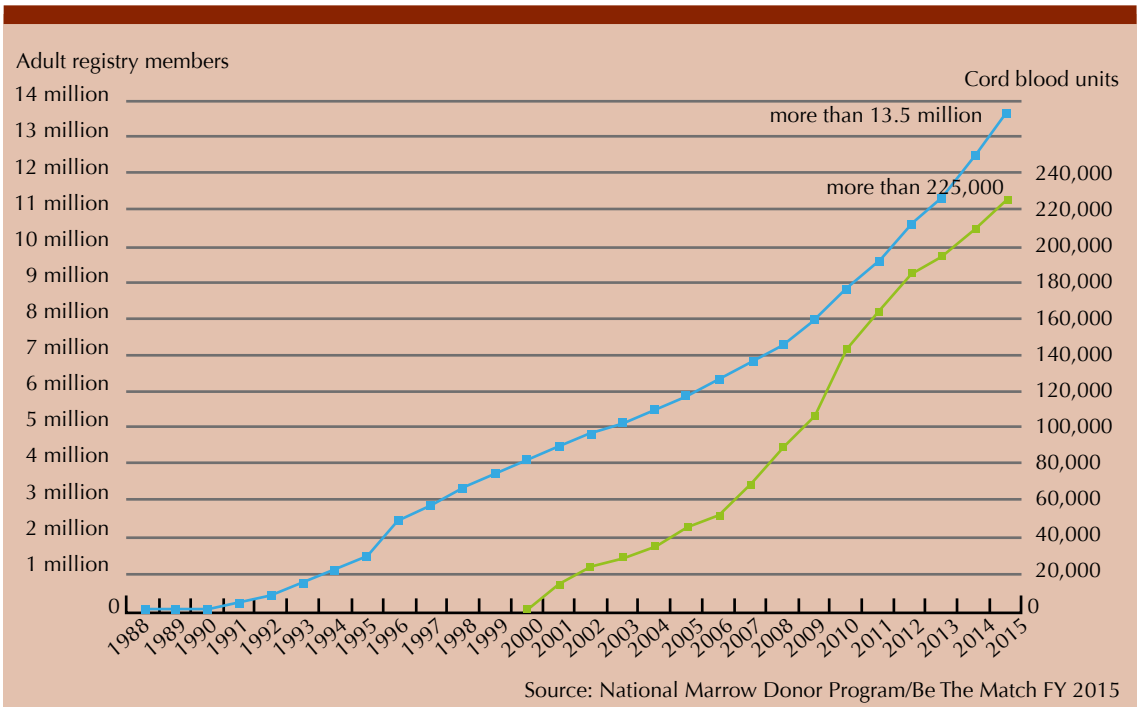

Figure 2. Be The Match Registry growth 1998-2015.

patients with co-morbidities or advanced age, and advances in HLA typing methods for improved donor selection with resultant fewer complications and better outcomes. Since 1987 NMDP has facilitated over 73,000 unrelated transplants for patients world-wide. The number of transplants for patients of Hispanic or Latino ethnic background since 2006 are shown in Figure 3. Trends in unrelated donor HCT, including graft sources, utilization in older adults, and by primary disease, are reviewed here.

Graft sources

In the early years the only graft source was bone marrow (Figure 4). Following the discovery of granulocyte-colony stimulating factor (G-CSF), subsequent manufacturing of recombinant drug and demonstrated safety and efficacy of mobilized peripheral blood stem cells in the autologous HCT and matched sibling alloHCT settings, in 1999 the NMDP began to facilitate unrelated donor PBSC transplant. By 2003 PBSC surpassed bone marrow as the preferred graft source. NMDP facilitated its first cord blood transplant in 2000. Over the ensuing years, cord blood grew in usage but has plateaued recently, as has the total number of unrelated transplants both in the US and globally. This plateau is most likely a result of several factors, including the increasing use of haploidentical donors for patients for whom a matched unrelated donor or suitable cord blood unit is unable to be identified, a greater number of novel therapies resulting in improved patient outcomes and obviating the need for alloHCT, and financial pressures on these high-cost procedures.

Graft sources vary by recipient age. Figures 5 and 6 depict graft sources for adult and pediatric patients, respectively. PBSC is the predominant graft source for adults; in contrast, marrow and cord

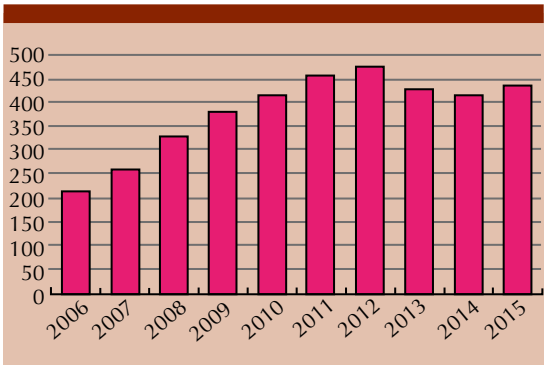

Figure 3. Unrelated donor transplants for patients of Hispanic or Latino ethnic background.

blood are more commonly used for pediatric recipients, likely reflecting that marrow is typically used as the graft source of non-malignant disorders affecting children, and that a cord unit may be identified with a minimum cell dose for successful engraftment in recipients of lower weight.

Recipient age

Less intense conditioning regimens demonstrating the feasibility of alloHCT for older patients or those with co-morbidities have resulted in a shift in utilization of unrelated donor transplants towards older patients. The number of unrelated HCTs by recipient age from 2003-2015 is shown in Figure 7. The increase in number of unrelated transplants is most prominent in the 51-64 and over 64 years age groups. In 2003, the number of transplants performed for patients 51-64 years of age was ~500, and rose to over 1900 transplants in 2014; similarly, the number of patients

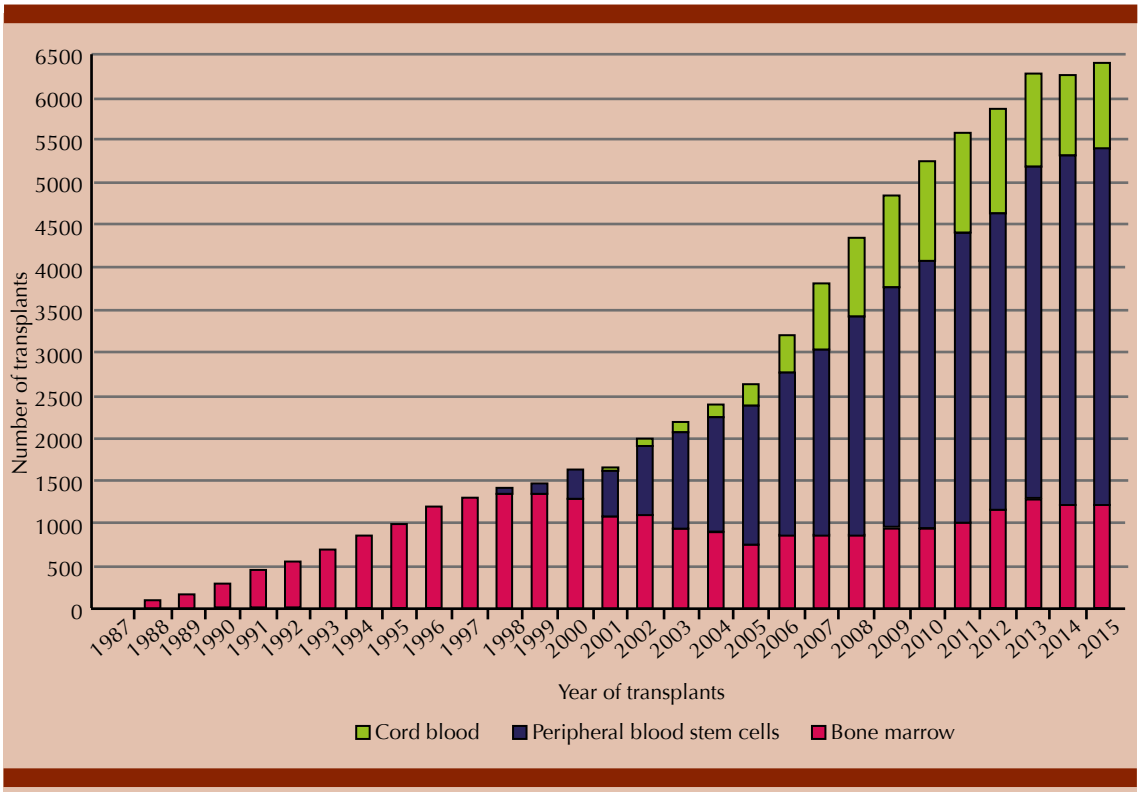

Figure 4. National Marrow Donor Program facilitated transplants 1987-2015 by graft source.

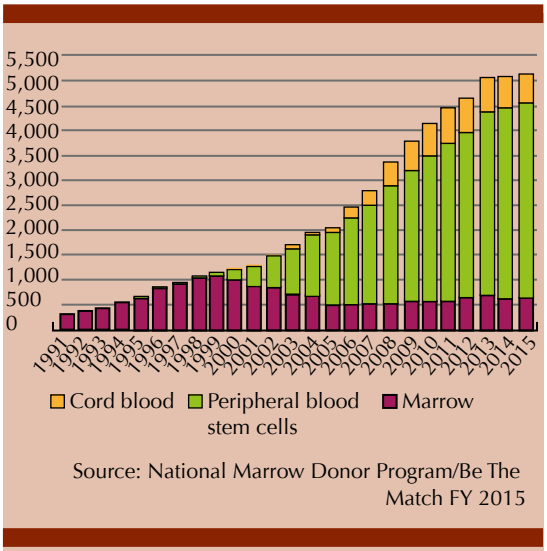

Figure 5. Transplants by cell source for adult patients 18 years and older, 1991-2015.

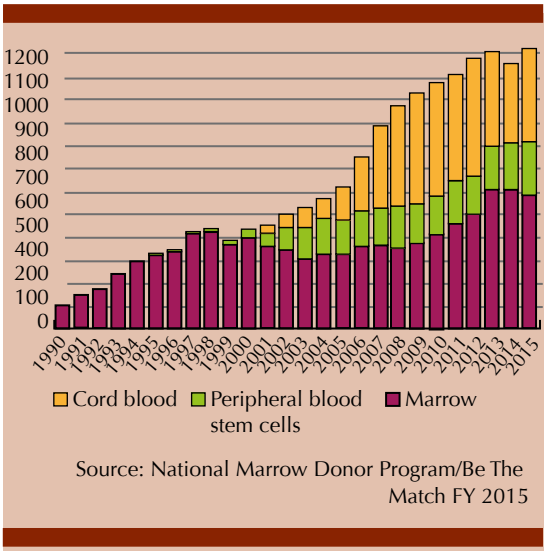

Figure 6. Transplants by cell source for pediatric patients younger than 18 years, 1990-2015.

over 64 years of age who received transplants in 2003 was ~50, and rose to over 1000 transplants in 2015.

Primary disease

AlloHCTs are performed for a variety of malignant and non-malignant diseases. Historically, most unrelated transplants have been performed for hematologic malignancies, predominantly chronic myeloid leukemia until the introduction of tyrosine-kinase inhibitor therapies. Today, the most common indications are acute myeloid leukemia (AML; >2200 in 2015) and myelodysplastic syndrome (MDS; >1200 in 2015) [Figure 8]. The most common non-malignant indication is severe aplastic anemia followed by inherited immune syndromes (225 and >200 unrelated transplants, respectively, in 2015).

Scientific contributions by NMDP

A commitment to research benefiting patients is a cornerstone of NMDP's mission. Here we review contributions made by NMDP to advancing the field of HLA typing for optimal donor selection and the conduct of clinical trials.

Selecting HLA-compatible donors

Since its inception, NMDP has been involved in developing and applying new methodologies to enable physicians to identify the best donor for their patients. For the first nine years of the Registry, serologic typing at HLA-A and –B was required; HLA-DR typing was both difficult and expensive.[8] The relatively high discrepancy rates were a major limitation, but additionally, as allosera for antigen recognition were derived from specific racial/ethnic populations, the methodology was not optimal for HLA testing in diverse populations.

Over the ensuing years, HLA typing and DNA sequencing methodologies were developed. NMDP research studies, in collaboration with the US Navy, the NMDP Histocompatibility Committee, laboratory principal investigators,

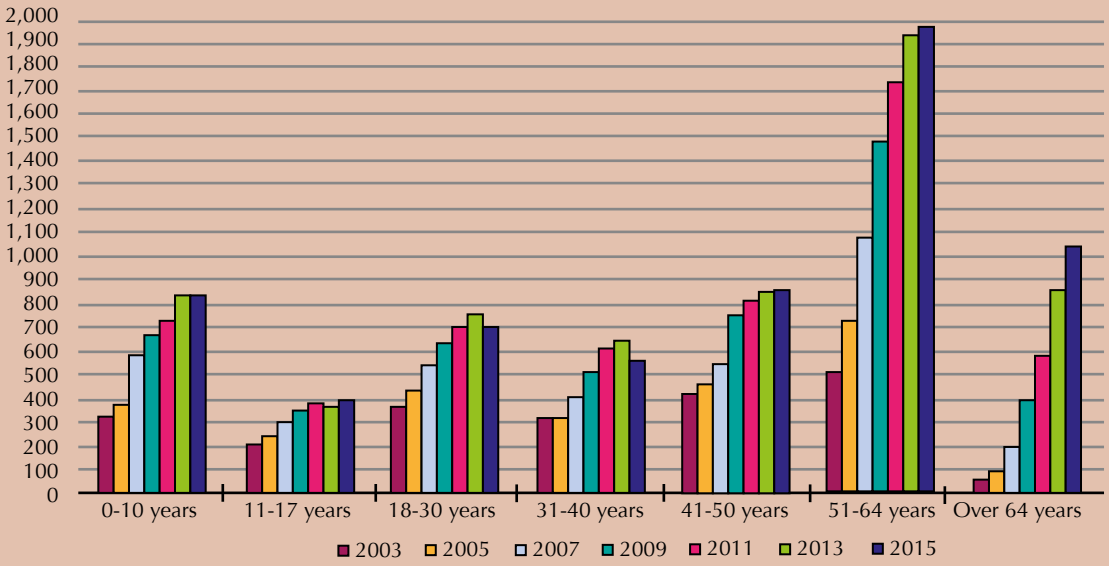

Figure 7. Number of unrelated transplants by recipient age from 2003-2015.

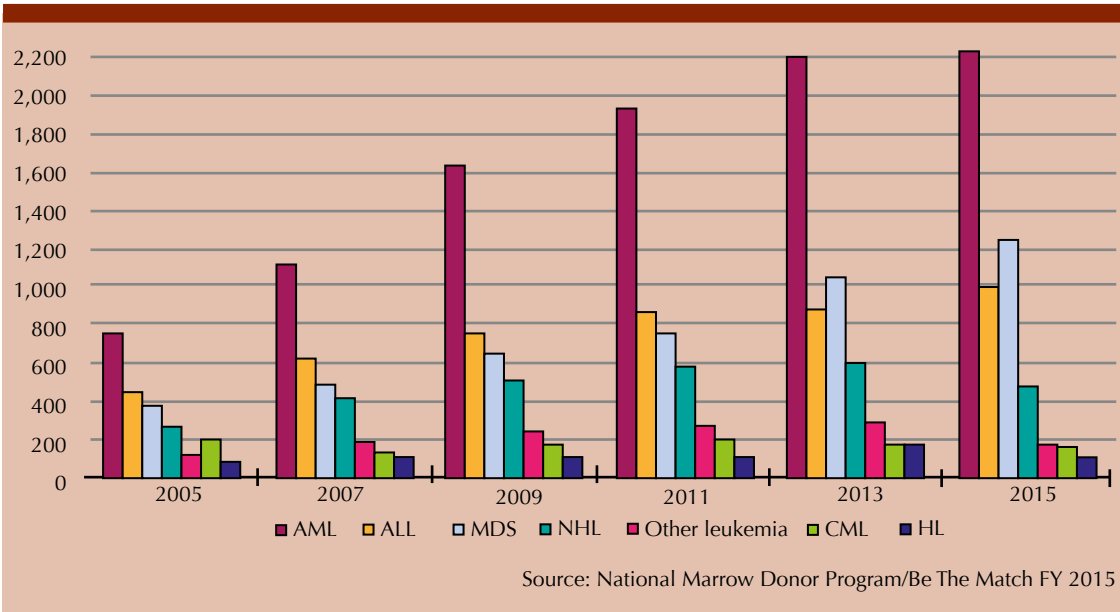

Figure 8. Unrelated donor transplants for hematologic malignancies.

and reagent/typing system manufacturers, incorporated rigorous sequencing strategies for high resolution DNA-based HLA typing methods for HLA-A, -B, -C, -DRB1 and –DQB1. The accuracy, quality and resolution of HLA assignments were enhanced, and the time needed to complete typing was reduced with lower cost. HLA typing through NMDP-contracted laboratories initially required 60 days, then 14 days in 2008, and currently is 3-4 days from time of sample receipt. Now, when physicians seek a donor, NMDP's patented HLA high-resolution imputation algorithm, HapLogic^{SM}, utilizes allele level haplotype frequency data to predict a probability score for the likelihood that a potentially matched adult donor or cord blood unit will be an allele match for the recipient at HLA-A, -B, -C, -DRB1 and -DQB1, irrespective of the original level of typing resolution.

Donor-recipient HLA data from NMDP-facilitated outcome studies has contributed to our understanding of the importance of HLA loci and level of resolution that results in optimal outcomes of unrelated alloHCT (Table 1) and provided a foundation for the recent guidelines for donor selection.[14] For recipients of unrelated donor HCT, overall survival is increased and transplantation-related mortality reduced when recipients are matched at high-resolution for HLA-A, -B, -C, -DRB1. Additional HLA loci (e.g., HLA-DPB1, DQB1, and DRB3/4/5) may assist in selecting donors with minimal mismatching at low expression loci and permissible HLA-DPB1 mismatches. In the 7/8-matched setting, prioritization for permissive HLA-C*03:03/03:04 mismatches or host-versus-graft mismatches may improve outcomes.

Retrospective and prospective studies

In 2004 NMDP formed an affiliation with the International Bone Marrow Transplant Registry (IBMTR) to create the Center for International Blood and Marrow Transplant Research (CIBMTR), expanding its research focus from solely unrelated alloHCT to include autologous and related alloHCTs. CIBMTR collaborates with the global scientific community of more than 500 transplant centers to design and conduct observational recipient and donor outcomes studies, immunogenetics research, and health services research. The NMDP sample repository serves as a rich resource for immunogeneticists and immunobiologists working towards an improved understanding donor characteristics that may impact outcomes. The repository contains approximately 2.1 million sample aliquots from more than 40,100 related and unrelated transplant donor/recipient pairs with complete, validated outcome data from the CIBMTR ob-

Table 1. National Marrow Donor Program-facilitated analyses of impact of HLA-typing on transplant outcomes

Author (reference)	Impact on transplant outcomes
Lee SJ[9]	A single mismatch in highly expressed HLA-A, -B, -C, and -DRB1 loci (HEL) is associated with worse outcomes
Hurley C[10]	Unidirectional graft-*versus*-host vector 7/8 HLA mismatches have the same level of risks for treatment related mortality and survival as bidirectional 7/8 mismatches. For HLA homozygous recipients, a mismatch at the homozygous locus is preferred over a mismatch at the heterozygous loci
Fernández-Viña M[11]	Three or more mismatches at the HLA-DP, -DQ, and- DRB3/4/5 low expression loci (LEL) may be associated with poor outcomes after 7/8 matched HCT
Fernández-Viña M[12]	The 7/8 HLA C*03:03/C*03:04 mismatch group was not significantly different from the 8/8 HLA matched transplants in any transplant outcome
Pidala J[13]	HLA-DPB1 nonpermissive mismatch increases mortality in otherwise 8/8 and 10/10 matched myeloablative unrelated transplants

servational database. CIBMTR also provides an infrastructure and scientific expertise in HCT clinical trial conduct and analysis for investigators conducting phase I and II trials through its Resource for Clinical Investigation in Blood and Marrow Transplantation (RCI BMT).

In 2001 the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) was established to conduct large, multi-institutional prospective interventional clinical trials to more rapidly answer critical questions to improve outcomes of HCT.[15] CIBMTR provides BMT CTN with its large observational database for planning trials. CIBMTR, the Emmes Corporation and the NMDP/Be The Match comprise the Data and Coordinating Center (DCC) for the BMT CTN. Since established, BMT CTN has opened 38 trials, enrolled more than 9,000 patients and published 57 papers.

The future of NMDP/Be The Match

Optimal donor selection

The development of successful strategies to perform transplants from haploidentical donors coupled with the documented success of unrelated adult donor and umbilical cord blood transplantation ensures that essentially all patients in need of an alloHCT will have a donor. For those recipients with multiple donor options, defining which donor is the optimal donor by underlying recipient disease status, disease risk and transplant variables will be paramount. Continued progress in HLA typing via next generation sequencing[16] and an improved understanding of the impact of other immunologic factors on outcomes, such as killer immunoglobulin-like receptors (KIR),[17,18] and will also affect donor selection. NMDP will continue to invest in information technology to provide physicians with an increasing array of information about potential donors in an easily accessible format.

Effect of advances in HCT technology and cellular therapies

Advances will continue to be made in technologies that expand the indications for alloHCT. NMDP, through the CIBMTR and BMT CTN, will continue to support prospective trials to clarify the role and optimal timing of alloHCT in the continuum of care from time of diagnosis, particularly in nonmalignant disorders for which the risk/benefit ratio of HCT deserves close scrutiny. The development of targeted therapies plus the rapidly evolving field of cellular therapies provides an opportunity for NMDP to engage with researchers in supporting delivery of novel therapies for patients with a variety of malignant and nonmalignant disorders. Such therapies may be used as a bridge to transplant, as post-transplant maintenance, or for therapy for patients whose disease relapses post-transplant.

Summary

AlloHCT is effective therapy for many life-threatening diseases, and its safety and effectiveness continue to improve. NMDP is committed to conducting thoughtful research to drive continuing improvements in donor selection and outcomes, and to working with countries around the world to establish registries, provide HLA typing services, and facilitate transplants.

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