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Introduction

THE THERAPEUTIC PROMISE OF HEMATOPOIETIC PROGENITOR CELL TRANSPLANTATION

Stem cells are a primitive cell type found in all animals and are capable of both self-renewal and differentiation. Some stem cell types are more committed to a particular developmental fate than others. For example, they divide and mature into cells of a specific type or limited spectrum of types (e.g., heart, muscle, blood, or brain cells). In contrast, pluripotent stem cells are less committed and retain the potential to differentiate into most other types of cells.¹ One example of a pluripotent stem cell is the embryonic stem cell, found in the blastocyst stage of the developing embryo. It is believed that stem cells form reservoirs of repair cells to replace cells and tissues that degenerate over the lifespan of the organism. It is this capacity for self-renewal and for differentiation into repair cells that offers great potential for regenerative medicine.

This report focuses on the development of an integrated system for the use of one specific type of stem cell, the hematopoietic progenitor cell (HPC), which is a multipotent stem cell responsible for the continual production of the diverse array of normal blood cells.² HPCs can be obtained from a variety of sources including bone marrow, peripheral blood, and umbilical cord blood collected from the placentas of recently delivered infants. Because of the potential of HPCs to reconstitute bone marrow and peripheral blood, their use for the treatment of patients with bone marrow damage from either chemotherapy or underlying hematological failure has been under investigation for several decades. Transplantation of HPCs from healthy individuals could also reconstitute bone marrow or blood in individuals with a variety of blood-related disorders (human-to-human transfer is called “allogeneic transplantation”).

Early research specifically into cord blood transplantation was based on the hypothesis that the immune cells in cord blood may be less mature than those in adult bone mar-

¹Pluripotent cells can differentiate into all cell types except those that make up the extraembryonic membranes (placenta, umbilical cord, and amnion) which are derived from the trophoblast.

²Throughout this report the committee uses the term hematopoietic progenitor cell and the abbreviation HPC to avoid confusion with other forms or sources of stem cells.

row or peripheral blood. Consequently, the risk of graft-versus-host disease (GVHD)³ after a cord blood transplant might be less than that after a bone marrow transplant or peripheral blood transplant. Other advantages of cord blood over bone marrow include its ready availability, its low potential for infectious disease transmission, and the minimal risk at the time of collection. This opens up the possibility of HPC transplantation to patients who either could not find a match within the bone marrow donor pool or were too ill to be able to wait for the process of searching and harvesting of bone marrow from adult donors.

Since the first transplants in the late 1980s and early 1990s, cord blood has been shown to be a suitable alternative to adult bone marrow or peripheral blood as a source of HPCs for the treatment of leukemia, lymphoma, aplastic anemia, and inherited disorders of immunity and metabolism. Whether cord blood is as good as or superior to adult graft sources in all of these situations is as yet unknown. Factors already shown to influence the outcome of cord blood transplantation include the numbers of cells in the cord blood, the size of the recipient, and the degree of human leukocyte antigen (HLA) match⁴ between the donor and the recipient. The committee holds the view that cord blood and marrow are complementary sources of HPC, each having specific advantages and disadvantages, and that the choice between the two should be made on a case-by-case basis, depending on the status of the patient.

The rate of use of cord blood for transplantation has increased rapidly, and in the US, Europe, and Japan exceeds the use of bone marrow for childhood transplant. Clinical investigations indicate promising results in a variety of settings although utilization and success are limited by several obstacles common to any form of transplantation, including the need for an HLA match (Kernan et al., 1993; Confer, 1997; Rubinstein et al., 1998; Goldberg et al., 2000; Rocha et al., 2000; de Lima and Champlin, 2001; Barker et al., 2001; Laughlin et al., 2001; Wagner et al., 2002; Barker et al., 2003; Barker and Wagner, 2003; Grewal et al., 2003; Barker et al., 2005).

Without a close match for HLA, HPC transplantation from any source is associated with high risk of rejection, in which the recipient's immune cells react against the donor cells, and of GVHD. Even with HLA compatibility, immunosuppressive therapy is required to prevent rejection and to reduce the incidence and severity of GVHD. Immunosuppressive therapy, plus the delay in reestablishing normal immune functions as donor cells restore recipient lymphohematopoiesis⁵, places patients at a high risk for bacterial,

³GVHD occurs when donor cells attack the recipient's normal tissues after transplant, and can lead to organ damage.

⁴HLA stands for *human leukocyte antigen*, the major histocompatibility complex in humans. The closer the donor's and recipient's HLA antigens match, the less likely it is that the T cells (immune system cells) of the donated marrow will react against the patient's body. Within a family, siblings have one-in-four chance of being HLA-identical. Outside the family, the situation is very different. HLA antigens are highly polymorphic with hundreds of different HLA antigens found in the human population (there are roughly 750,000 possible combinations of three HLA antigens alone). To find an unrelated HLA-matched donor requires searching very large numbers of people (Beatty et al., 1988).

⁵Development of new lymphocytes

viral, and fungal infections. In the case of donor-patient HLA disparity, infection is an even greater problem.

IN SEARCH OF A MATCH

HLA matching is critical for all types of transplant, regardless of the source. The number of patient candidates for an HPC transplant is estimated to be 11,700 annually, of whom only 3,500 have an HLA-identical sibling donor.

In an attempt to make HPCs more widely available to the large number of patients who do not have an HLA-identical sibling, large international volunteer bone marrow and peripheral blood donor registries were created in the 1980s (Beatty et al., 1988). Unrelated adult donors are generally identified through these donor registries. As of December 2003, more than 9 million registered volunteer donors were listed in more than 40 registries worldwide (BMDW, 2004). Registries maintain list of the HLA types (and other clinically relevant information) of individuals willing to allow the harvesting of HPCs from their bone marrow or peripheral blood for transplantation should a need arise.

Despite the large numbers of donors recruited over the past two decades, volunteer donor registries still face several challenges. These include:

- an inability to identify fully or closely HLA-matched donors for a significant proportion of transplant candidates, particularly non-Caucasian groups;
- a permanent or transient unavailability of the potential donor, even if the individual was identified in a registry on the basis of HLA match criteria (Wagner et al., 2002); and
- the prolonged interval (as many as four months) between the time of the request for a search and the time of HPC acquisition (Linch and Brent, 1989; Nash et al., 1992; Kurtzberg et al., 2000; Thomson et al., 2000; Barker et al., 2002).

Moreover, the donation of HPCs is not without risk for adults. In the case of bone marrow donation (Gluckman et al., 1997; Barker et al., 2002), the bone marrow must be surgically removed, generally by large-bore needle aspiration while the donor is under general or spinal anesthesia (Locatelli et al., 1999). Although less than 1 percent of donors experience serious complications, the procedure can result in significant postoperative discomfort to the donor at the aspiration site and may be a factor in recruiting donors to a registry (Buckner et al., 1984). Alternatively, HPCs can be collected from peripheral blood through a process called leukapheresis after the administration of drugs to mobilize HPCs so that they move out of the bone marrow and into the bloodstream. Leukapheresis

can be associated with bone pain from the mobilization drugs, hypocalcemia,⁶ decreased platelet counts, spleen enlargement or (rarely) rupture, and complications from venous catheter placement.

These registries of unrelated donors provide suitable donors for only about a third of the patients without a sibling donor; thus a shortage of suitable donors persists. In addition, the distribution of HLA alleles and haplotypes⁷ found in individuals varies among different ethnic and racial groups. Some alleles and haplotypes are common to several populations; others are predominantly confined to one population group. Thus, some populations are more likely to be underserved by these registries.

DEVELOPMENT OF UMBILICAL CORD BLOOD BANKS

Several groups recognized the need to obtain HPCs more easily, more safely, and from a broader cross-section of the population and for this reason established cord blood banks with the central mission of maintaining a supply of HPCs for therapeutic use in transplantation. (More information about banks and banking can be found in Chapter 4.)

In 1992, the New York Blood Center (NYBC) recognized the need for a dedicated inventory of cord blood units for patients lacking an HLA-matched sibling and established a program for public cord blood banking (Rubinstein et al., 1998). In 1998, NYBC published a report summarizing the results of the first 562 transplants performed with units from its inventory. The results, primarily pediatric cases, indicated consistent engraftment, low rates of GVHD, and survival rates that appeared to be similar to those obtained with bone marrow transplantation (Rubinstein et al., 1998). Other banks were soon established, and today there are at least 40 cord blood banks in the United States. Of those known banks, 20 store donations for unrelated transplants. (More information about all banks can be found in Appendix C.) The remaining banks are private; that is, they store cord blood at the expense of the donor for potential future use by the donor or a member of the donor's family.

In 1998, the National Marrow Donor Program (NMDP), which also recognized the potential of cord blood as an alternative graft source, extended its network to include cord blood banks (GAO, 2002). NMDP grew out of the congressionally established National Bone Marrow Donor Registry (NBMDR), which began operation in July 1986. The Organ Transplants Amendment Act of 1988 reauthorized NBMDR by directing the establishment of a national registry. In June 1988, the NBMDR board changed the name to the National Marrow Donor Program (NMDP). In 1990, NMDP became a separate nonprofit organization and took over the administration of the federal contract from the American Red Cross. The Transplant Amendments Act of 1990 further defined and expanded the

⁶Abnormally low calcium concentration that can result in muscle cramps, abdominal cramps, spasms, and hyperactive deep tendon reflexes – from <http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=hypocalcemia&action=Search+OMD> accessed 3/23/05

⁷Haplotyping is the determination of the HLA type of a patient or cord blood unit.

functions of NMDP. The act wrote into law the network of centers, addressed the need for diversity, consolidated all of the registries and established a system for patient advocacy.⁸ At present, 14 cord blood banks in the United States and internationally are affiliated with NMDP.⁹

THE CHALLENGES OF A FRAGMENTED SYSTEM

Although independence often leads to innovation, it can also lead to inconsistency in quality from bank to bank and a need for transplant centers to access multiple banks. Thawing and processing the units received from different banks can also vary depending on the bank accessed. The proliferation of cord blood banks has raised the challenges of accessibility, the adequacy of the inventories, the standardization of techniques and documentation, and quality control. In addition, most cord blood banks have developed practices and procedures independent of any consistent quality assurance or regulatory oversight, although many banks are accredited by independent organizations such as the American Association of Blood Banks (AABB) and the Foundation for the Accreditation of Cellular Therapy (FACT).

The complexity of the search and matching process for cord blood units remains an issue for many transplant physicians. No standardized search algorithm is available, and the level of HLA typing differs from registry to registry and between cord blood units and bone marrow donors. At present, transplant coordinators must often search multiple registries and banks to find potential adult donors or cord blood units for a given patient before deciding on the best graft source. Within the United States, searches of the vast majority of adult donors in national and international registries (and the 14 participating cord blood banks) can be accomplished with a single search process through NMDP, although this process may sometimes take weeks, time that ill patients may not have. However, no single point exists for access to the entire cord blood inventory. In 2001, NetCord, an international organization, was established to facilitate searches of multiple cord blood banks to seek a match. This organization is an affiliation of 15 international

⁸http://www.marow.org/NMDP/history_of_transplants.html.

⁹Those banks are the American Red Cross North Central Blood Services in St. Paul, Minnesota; American Red Cross Western Area Community Cord Blood Bank in Portland, Oregon; Ashley Ross Cord Blood Program of the San Diego Blood Bank in San Diego, California; Bonfils Cord Blood Services Belle Bonfils Memorial Blood Center in Denver, Colorado; Carolinas Cord Blood Bank in Durham, North Carolina; Children's Hospital of Orange County Cord Blood Bank in Orange, California; ITxM Cord Blood Services in Glenview, Illinois; J.P. McCarthy Cord Stem Cell Bank in Detroit, Michigan; LifeCord in Gainesville, Florida; New Jersey Cord Blood Bank at the Coriell Institute for Medical Research in Camden, New Jersey; Puget Sound Blood Center in Seattle, Washington; St. Louis Cord Blood Bank in St. Louis, Missouri; StemCyte International Cord Blood Center in Arcadia, California; and StemCyte Taiwan National Cord Blood Center in Taipei County, Taiwan.

banks with a combined inventory of 86,914 units.¹⁰ (NetCord, 2005). Because not all banks belong to this network, one-request searches are still not possible.

Recent reports suggest that cord blood searches are becoming more uniform, but no uniform search algorithm exists. However, lack of a single portal and the absence of an evidence based HPC search algorithm have hampered the increased use of cord blood. Therefore, until this uniform outcomes reporting is established, such an algorithm cannot be developed, and there will be no mechanism by which to establish a single search system.

In the 2004 appropriations bill for the U.S. Department of Health and Human Services, the U.S. Congress, recognizing the potential contributions of cord blood transplantation and the need for a system that better serves patients, provided \$10 million for the establishment of a new national cord blood stem cell bank program under the leadership of the Health Resources and Services Administration (HRSA).

Although consensus on the need for a national banking program exists, major differences in perspectives on how that might be accomplished remain. These differences are over governance, database management, unit selection processes, sources of material, financing and competition, and standards, among other issues. Many of these differences in perspective can be understood by examining the evolution and focus of the two major U.S. programs currently involved in HPC transplantation.

TWO VIEWS OF A NATIONAL CORD BLOOD PROGRAM

The federally funded NMDP is the hub of a worldwide network of more than 500 medical facilities engaged in both bone marrow and blood cell transplantation. Through this network, NMDP has facilitated approximately 350 cord blood transplants since 1999, in addition to the 20,000 bone marrow transplants that it has facilitated since 1987. It neither collect or bank cord blood. NMDP, however, has a long-standing history of linking patients in need to the best possible stem cell match, initially from adult bone marrow or peripheral cells, but now its efforts have been extended to cord blood via member cord blood banks. It also has strong patient advocacy and education functions. Supported by \$73,753,000 in search and procurement fees, \$40,707,000 in federal contracts and cooperative agreements, \$3,854,000 in contributions, and \$1,864,000 in other income, NMDP represents a comprehensive program that has devoted a great deal of its effort to developing an informatics infrastructure to support the search and procurement process, as well as the collection and use of outcomes data for research (NMDP, 2004).

¹⁰They are: AusCord (Australia), Barcelona (Spain), Düsseldorf (Germany), France Cord (France); Helsinki (Finland), Jerusalem (Israel), Leiden (The Netherlands), Leuven (Belgium), Liege (Belgium), London (Great Britain), Milan (Italy), New York (United States), Prague (Czech Republic), Tel Hashomer (Israel), and Tokyo (Japan)

The National Cord Blood Program of NYBC¹¹ is the single largest U.S. cord blood bank and since 1993 has shipped more than 1,765 units for transplantation into 1,660 patients.¹² It is not a part of NMDP's cord blood network. This program started as one of NYBC's research activities and later became a separate center. The program works directly with transplant physicians seeking a unit from those in their inventory to ensure the best match for patients and has devoted substantial energy toward promoting cord blood transplantation and research. The program is supported by \$23 million from the recovery of the costs for units shipped for transplantation, \$9 million in individual contributions, and \$10.6 million from NYBC. Between 1992 and 1997, it has also received \$4.2 million in federal grants (Stevens, 2004). The program collects extensive outcome data which it uses to publish research to promote a better understanding of cord blood transplantation and science.

In the committee's view, the NMDP, NYBC, and other interested parties agree on several key goals for a national program:

- **Simplicity.** A national program needs to avoid duplication of effort in terms of both services provided and the steps necessary for a transplant center to access appropriate graft sources.
- **Quality.** The ultimate goal of a program should be to promote the best possible chance of patient recovery by establishing an inventory of high-quality, HLA-diverse cord blood units
- **Patient, physician, and donor support.** Support and education for all individuals involved in the program are integral and necessary parts of the program.

However, each organization describes the preferred shape of the program differently in ways that are not readily integrated. Table 1-1, describes the ideal shape of a national program according to NYBC and NMDP.

¹¹This is the name of the New York Blood Center's cord blood bank and is not to be confused with the topic of this report. Unless otherwise specified, references to NYBC in this report should be taken as references to that cord blood program

¹²Some patients received multiple units or follow-up transplants

TABLE 1-1 Views from NYBC and NMDP on an Ideal National Stem Cell Cord Blood Bank Program

Component	New York Blood Center	National Marrow Donor Program
Governance	The network should be independent, with its own board of directors to set policy and monitor participants' compliance with network rules and regulatory agencies.	The network should operate under already existing NMDP infrastructure. Time and money can be saved by not re-creating that which already exists. The NMDP board should be representative of parties who should provide oversight. Committees of the board should be in place to oversee issues unique to cord blood.
Search Database	The best chance of finding a match is obtained when each bank searches its up-to-date local database. A centralized database would duplicate banks' databases and would be expensive to maintain or almost always out of date.	A centralized database would allow transplant coordinators a location for 'one-stop shopping' for both adult HPC donors and cord blood units and would avoid the potential for the same unit to be reserved through more than one channel.
Unit Selection	Banks must be able to interact directly with the transplant centers to help select the best units for transplantation. If a central search mechanism is adopted, it must be transparent to everyone. Banks must have input in the development of the search algorithm used to define, sort and display matches and must be able to monitor whether their units are listed appropriately.	The program must establish and maintain a standard mechanism to search for units, confirm the HLA type, and to reserve and select the units. A mechanism should be available to update the HLA search algorithm as new alleles are developed or new match criteria are identified.
Source of transplant material	Cord blood and adult donors compete as sources of stem cells for hematopoietic reconstitution.	Cord blood, peripheral blood, and bone marrow are complementary alternative sources for HPCs.

Component	New York Blood Center	National Marrow Donor Program
Finances	Banks distribute manufactured products, are reimbursed, and should become self-sufficient, like regular blood and tissue banks. To jumpstart that process, federal appropriations funding should be in the form of direct grants to the network banks.	Funds should be distributed through the program to all banks meeting the criteria under the oversight of HRSA in a manner that ensures the equitable distribution of responsibility. Goals include the collection of an appropriately diverse registry of units should be established.
Cord blood bank selection	Cord blood banks should compete for participation in the national program according to criteria that should be published in advance of the competition.	Role of competition is misplaced, as goal should be ensuring a large, diverse registry of units that meet current standards regardless of where collected and stored. The registry and its network should be competed every five years to assure they are functioning well as a unit.
Standards	Regulatory rules and standards should be the responsibility of the Food and Drug Administration.	Standards should be established by the program and should include Food and Drug Administration regulations, as they become available.
Patient support	The network's board of directors should establish patient, donor, and physician education programs.	The program should address issues of access to transplant therapy for all patients including financial ability, literacy, language, patient advocacy, etc.
Outcomes data	Collection of the outcomes of transplants is a responsibility of each bank. Banks should obtain these data as part of quality control whether or not there is a central mechanism for outcomes data collection.	The program should establish and maintain a means to define and collect outcomes data for transplants performed as part of the program. Data submission should be monitored, and a formal error correction mechanism should be used. Data should be available to the wider research community to support the submission of peer-reviewed journal article submission to professional scientific journals to expand knowledge of cord blood transplantation.

BACKGROUND OF THIS STUDY

In its 2004 appropriation of \$10 million for the establishment of a National Cord Blood Banking Program, the U.S. Congress recognized the different views on how such a program might be established. A portion of the appropriation was allocated to the Institute of Medicine (IOM) to provide HRSA with an assessment of existing cord blood programs and inventories and to make recommendations on the ideal structure, function, and utility of a national cord blood stem cell bank program. The charge to the IOM committee is as follows:

In response to Conference Report on H.R. 2673, Consolidated Appropriation Act 2004 (H. Rept. 108-401), the Institute of Medicine (IOM) will assemble a committee of experts to conduct a study that will consider relevant issues related to the establishment of a National Cord Blood Stem Cell Bank Program within the Health Resources and Services Administration, DHHS. The IOM study will make recommendations for the optimal structure for the cord blood program and address pertinent issues related to maximizing the potential of this technology (e.g., collection, storage, standard setting, information sharing, distribution, reimbursement, research and outcome measures).

The following are among the more specific issues to be considered:

- What is the role of cord blood in HPC transplantation in the context of other sources of HPCs?
- What is the current status of the cord blood banks already in existence?
- What is the optimal structure for the cord blood program?
- What is the current use and utility of cord blood for stem cell transplants?
- What is the best way to advance the use of cord blood units for HPC transplantation (i.e., setting storage standards, collection procedures, information sharing, distribution, and outcome measures)?
- What is the best way to make cord blood units available for research?
- What consent procedures should be followed to obtain informed consent for both research and transplantation use?
- Should the cord blood program set practice guidelines for all banks or just the public banks (e.g., what kind of HLA-typing would need to be done before blood goes into the cord blood bank, and how are the databases advertised)?

IOM formed the Committee on Establishing a National Cord Blood Stem Cell Bank Program, which consists of experts in the fields of economics, HPC transplantation, outcomes analysis, biostatistics, stem cell biology, cord blood quality and standards, public health, health technology assessment, patient advocacy, ethics, and obstetrics and gynecology.

cology. Throughout the course of its work, the committee's perspective was that the program that is eventually established should have as its primary mission the goal to maximize access to high-quality HPC sources for patient care and research in the most efficient, cost-effective, and ethical manner possible. All committee findings and recommendations were weighed against this core perspective, and were developed after careful consideration of current experience with cord blood banking, the lessons learned from other organ and tissue transplant programs, and the current and potential uses of HPCs derived from cord blood. (Information on the methods and information gathering strategy that the committee used can be found in Appendix A.)

In the course of its work, the committee made every effort to consider all points of view on the establishment of a national program, hearing from patient advocates, transplant physicians, individuals from existing banking facilities, and the research community, all of whom have expressed concerns about the need for openness and fairness in policymaking about cord blood banking.

ORGANIZATION OF THIS REPORT

This report is structured as follows: Chapter 2 describes the history of HPC transplantation and the current use and utility of cord blood for this purpose. Chapter 3 explains the current research applications of cord blood and potential future uses. Chapter 4 discusses banking processes and the current status of cord blood banking in the United States. Chapter 5 describes some of the ethical and legal implications of cord blood banking and of a national program. Chapter 6 discusses the inventory needs for a national program. Finally, Chapter 7 presents the committee's view of the ideal structure of a national program. Though the structure chapter comes last, there will be references to structural elements throughout the report. The committee believed it was necessary to discuss the background of banking, HPC transplantation, and other relevant matters prior to discussing the structure.

REFERENCES

- Barker JN, Wagner JE. 2003. Umbilical-cord blood transplantation for the treatment of cancer. *Nature Reviews Cancer* 3(7):526–532.
- Barker JN, Weisdorf DJ, Wagner JE. 2001. Creation of a double chimera after the transplantation of umbilical-cord blood from two partially matched unrelated donors. *New England Journal of Medicine* 344(24):1870–1871.
- Barker JN, Krepski TP, DeFor TE, Davies SM, Wagner JE, Weisdorf DJ. 2002. Searching for unrelated donor hematopoietic stem cells: Availability and speed of umbilical cord blood versus bone marrow. *Biology of Blood and Marrow Transplantation* 8(5):257–260.

- Barker JN, Weisdorf DJ, DeFor TE, Blazar BR, Miller JS, Wagner JE. 2003. Rapid and complete donor chimerism in adult recipients of unrelated donor umbilical cord blood transplantation after reduced-intensity conditioning. *Blood* 102(5):1915–1919.
- Barker JN, Weisdorf DJ, DeFor TE, Blazar BR, McGlave PB, Miller JS, Verfaillie CM, Wagner JE. 2005. Transplantation of 2 partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy. *Blood* 105(3):1343–1347.
- Beatty PG, Dahlberg S, Mickelson EM, Nisperos B, Opelz G, Martin PJ, Hansen JA. 1988. Probability of finding HLA-matched unrelated marrow donors. *Transplantation* 45(4):714–718.
- BMDW (Bone Marrow Donors Worldwide). 2004. Bone Marrow Donors Worldwide Annual Report 2003. Leiden, The Netherlands: Europdonor Foundation.
- Buckner CD, Clift RA, Sanders JE, Stewart P, Bensinger WI, Doney KC, Sullivan KM, Witherspoon RP, Deeg HJ, Appelbaum FR. 1984. Marrow harvesting from normal donors. *Blood* 64(3):630–634.
- Confer DL. 1997. Unrelated marrow donor registries. *Current Opinion in Hematology* 4(6):408–412.
- de Lima M, Champlin R. 2001. Unrelated donor hematopoietic transplantation. *Reviews in Clinical and Experimental Hematology* 5(2):100–134.
- GAO (General Accounting Office). 2002. Bone Marrow Transplants: Despite Recruitment Successes, National Program May Be Underutilized. Washington, DC: General Accounting Office.
- Gluckman E, Rocha V, Boyer-Chamman A, Locatelli F, Arcese W, Pasquini R, Ortega J, Souillet G, Ferreira E, Laporte JP, Fernandez M, Chastang C. 1997. Outcome of cord-blood transplantation from related and unrelated donors. Eurocord Transplant Group and the European Blood and Marrow Transplantation Group. *New England Journal of Medicine* 337(6):373–381.
- Goldberg SL, Chetid S, Jennis AA, Preti RA. 2000. Unrelated cord blood transplantation in adults: A single institution experience. *Blood* 96:208a.
- Grewal SS, Barker JN, Davies SM, Wagner JE. 2003. Unrelated donor hematopoietic cell transplantation: Marrow or umbilical cord blood? *Blood* 101(11):4233–4244.
- Kernan NA, Bartsch G, Ash RC, Beatty PG, Champlin R, Filipovich A, Gajewski J, Hansen JA, Henslee-Downey J, McCullough J, McGlave P, Perkins HA, Phillips GL, Sanders J, Stroncek D, Thomas ED, Blume KG. 1993. Analysis of 462 transplantations from unrelated donors facilitated by the National Marrow Donor Program. *New England Journal of Medicine* 328(9):593–602.
- Kurtzberg J, Scaradavou M, Wagner J, et al. 2000. Banked umbilical cord blood is an excellent source of donor hematopoietic stem cells for infants with malignant and non malignant conditions lacking a related donor. *Blood* 96:587a.
- Laughlin MJ, Barker J, Bambach B, Koc ON, Rizzieri DA, Wagner JE, Gerson SL, Lazarus HM, Cairo M, Stevens CE, Rubinstein P, Kurtzberg J. 2001. Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors. *New England Journal of Medicine* 344(24):1815–1822.
- Linch DC, Brent L. 1989. Marrow transplantation. Can cord blood be used? *Nature* 340(6236):676.
- Locatelli F, Rocha V, Chastang C, Arcese W, Michel G, Abecasis M, Messina C, Ortega J, Badell-Serra I, Plouvier E, Souillet G, Jouet JP, Pasquini R, Ferreira E, Garnier F, Gluckman E. 1999. Factors associated with outcome after cord blood transplantation in children with acute leukemia. Eurocord-Cord Blood Transplant Group. *Blood* 93(11):3662–3671.

- Nash RA, Pepe MS, Storb R, Longton G, Pettinger M, Anasetti C, Appelbaum FR, Bowden RA, Deeg HJ, Doney K. 1992. Acute graft-versus-host disease: analysis of risk factors after allogeneic marrow transplantation and prophylaxis with cyclosporine and methotrexate. *Blood* 80(7):1838–1845.
- NetCord. 2005. *NetCord By-Laws*. [Online] Available: https://www.netcord.org/netcord_bylaws.pdf [accessed January 2005].
- NMDP (National Marrow Donor Program). 2004. *2003 Report to the Community*. [Online] Available: http://www.marrow.org/NMDP/report_to_community03.pdf [accessed January 2005].
- Rocha V, Arcese W, Sanz G. 2000. Prognostic factors of outcome after unrelated cord blood transplantation. *Blood* 96:567a.
- Rubinstein P, Carrier C, Scaradavou A, Kurtzberg J, Adamson J, Migliaccio AR, Berkowitz RL, Cabbad M, Dobrila NL, Taylor PE, Rosenfield RE, Stevens CE. 1998. Outcomes among 562 recipients of placental-blood transplants from unrelated donors. *New England Journal of Medicine* 339(22):1565–1567.
- Stevens CE. 2004. *Unrelated cord blood for transplantation: Collections and processing*. Presentation at the meeting of the Committee on Establishing a National Cord Blood Stem Cell Bank Program, Meeting 2, August 18, 2004. Beckman Center, Irvine, CA.
- Thomson BG, Robertson KA, Gowan D, Heilman D, Broxmeyer HE, Emanuel D, Kotylo P, Brahmi Z, Smith FO. 2000. Analysis of engraftment, graft-versus-host disease, and immune recovery following unrelated donor cord blood transplantation. *Blood* 96(8):2703–2711.
- Wagner JE, Barker JN, DeFor TE, Baker KS, Blazar BR, Eide C, Goldman A, Kersey J, Krivit W, MacMillan ML, Orchard PJ, Peters C, Weisdorf DJ, Ramsay NKC, Davies SM. 2002. Transplantation of unrelated donor umbilical cord blood in 102 patients with malignant and nonmalignant diseases: Influence of CD34 cell dose and HLA disparity on treatment-related mortality and survival. *Blood* 100(5):1611–1618.

