California Institute for Regenerative Medicine
Overview of Current Umbilical Cord Blood Banking, Clinical, and Research Activities

Introduction

The following overview provides a high-level summary of current activities related to umbilical cord blood banking as well as clinical and research applications. It is designed to provide some background for our discussion and is not intended to be comprehensive or exhaustive.

I. Current Status

A. Overview of cord blood banking operations

1. Types of banks (1)

- The Institute of Medicine (IOM) defines three types of cord blood banks:
  - Public banks store cord blood units that are philanthropically donated for transplantation or research. Some public banks also store a limited number of units for autologous (self) or family use when a disease that is treatable by cord blood transplantation exists within the donor's family.
  - Private banks store cord blood units only for autologous or family use. These banks generally charge a fee for collection, processing, and storage and leave any decisions regarding the use of the unit to the donor or the donor's family.
  - Mixed banks collect units donated for transplantation to unrelated recipients and also operate facilities for cord blood banking for autologous use and use by family members. The money received from private banking can help offset the costs of public banking.

2. Number of cord blood banks in the US / CA

- Estimates vary as to the number of banks:
  - In preparation for a survey, the IOM identified 40 banks in the US (2).
  - The National Marrow Donor Program (NMDP) lists 27 banks, including:
    - 19 affiliated banks (including two outside the US) that are part of its registry, of which 3 are located in California (3).
    - 8 non-affiliated banks (including one outside the US), which are not part of its registry, of which 1 is located in California (4).
  - The AABB (formerly known as the American Association of Blood Banks) lists 25 accredited banks in the US (plus another 13 outside the US), of which 4 are located in California (4a).
  - The Foundation for the Accreditation of Cellular Therapy (FACT) lists 5 accredited banks in the US (plus another 6 outside the US), of which 1 is located in California (4b).

- The Parents' Guide to Cord Blood Banks lists:
  - 35 public banks in the US, of which 5 are located in California (5).
  - 30 private banks in the US, of which 3 are located in California (6).
  - 110 companies outside the US that engaged in cord blood banking (6a).

3. Sample banking

- Estimates also vary as to the number of samples banked:
  - Twenty-one cord blood banks responded to the IOM's survey. These banks have collected a total of about 255,000 samples, banked about 109,000, and have a total of about 63,000 samples available. The three California-based banks that responded have collected a total of about 18,000 samples, banked a total of about 11,000, and have a total of about 11,000 samples available (7).
  - One estimate suggests that the three largest banks in the US have stored more than 300,000 units of cord blood (7a).
  - There are roughly 4.2 million births in America each year and about 3% of new mothers nationwide elect to store the baby's cord blood in private banks (7b). This translates to roughly 126,000 new samples banked each year.

- The costs associated with banking cord blood are as follows:
  - Collection: Collection fees (which generally cover collection, processing, and freezing) for the companies listed on the Parents' Guide to Cord Blood Banks range from $846 to $1,925 (6a). Anecdotally, we have heard that collection costs can be as high as $4,000 to $5,000.
  - Storage: According to the Parents' Guide to Cord Blood Banks, commercial banks charge annual storage fees (for private banking) in the range of $90 to $149 per sample (6a). This is in line with what has been reported to us anecdotally.
  - Release: Private banks do not charge a family for the release of the sample(s) they have banked because they have already paid an initial collection fee as well as annual storage fees. It as been reported to us anecdotally those public banks (i.e. donated material) may charge between $20,000 and $30,000 for the release of a sample.
  - Transplantation: It has been reported to us that the costs of a cord blood transplant can range from $150,000 to $250,000.

4. Regulation (accreditation and quality)

- There is no single set of quality assurance guidelines or regulatory requirements in place, nor is there a single, universally recognized accrediting system or body.

- Most banks have developed practices and procedures independent of any consistent quality assurance or regulatory oversight, although many banks are accredited by independent organizations (8). These organizations include:
  - AABB (9)

- FACT, the Foundation for the Accreditation of Cellular Therapy (10)
- The International NETCORD Foundation (11)

  Note: NETCORD has established quality standards with FACT on the collection, cryopreservation, storage, and release of cord blood units (12).

- In July 2004, NMDP published a revised edition of its standards, intended to outline the most basic guidelines for facilities involved in the transplantation of hematopoetic progenitor cells (13).
- A few banks have volunteered to file an Investigational New Drug (IND) application with the FDA for their practices. This is not an FDA requirement and most banks do not file such applications.

B. Overview of current applications and limitations of cord blood

1. Research and Clinical Applications

- Clinical Uses
  - Over the past few decades, hematopoetic progenitor cells obtained from cord blood have been shown to be an alternative to adult bone marrow or peripheral blood in transplants for the treatment of leukemias, lymphomas, and aplastic anemia (14), primarily for children and as a choice of last resort for adults.
  - Cord blood has been used in the treatment of inherited diseases, including hematological disorders, such as sickle cell anemia, beta thalassemia, and Fanconi anemia (15).
  - Cord blood has also been used in transplants to treat patients with a variety of other diseases, including Gaucher disease, multiple myeloma, and Tay Sach Disease, among others (15aa).

- Clinical Research
  - A number of clinical research efforts regarding the use of cord blood for the treatment of disease have been completed or are underway; among these are the following:
    - A team of researchers in North Carolina transplanted umbilical-cord blood from unrelated donors into infants suffering from Krabbe's disease before and after development of symptoms. The study showed rates of donor-cell engraftment and survival of 100% and 100% among the asymptomatic infants (median follow-up, 3.0 years) and 100% and 43%, respectively, among the symptomatic infants (median follow-up, 3.4 years) (15a).
    - It has been reported to us that two clinical trials - a Phase I / II trial and a Phase II / III trial - are currently underway to study the impact of expanding select population(s) of umbilical cord cells ex vivo, prior to transplantation for the treatment of blood cancers.

- Basic Research
  - Understanding the basic biology and potential of stem cells in cord blood is a very new field. We found the following recent research findings:
    - In 2002, researchers at the Polish Academy of Sciences reported to have selected and expanded a neural-stem-cell-like subpopulation from umbilical blood cord cells. This clonogenic fraction of cells was devoid of hematopoetic or angiogenic properties and expressed nestin, one of the most specific markers of multipotent neural stem cells (16).
    - In 2005, researchers at Kingston University (UK) reported to have separated embryonic-like stem cells (that is, cells expressing embryonic stem cell markers) from cord blood and derived liver tissue from them (17).
    - Anecdotally, this UK team claims to have derived clonal lines of progenitor cells from cord blood and produced bone and cartilage cells from these lines, as well as produced insulin-secreting cells from cord blood.
    - We have also heard that mesenchymal stem cells (MSCs) have been derived from progenitors from cord blood, and investigators are looking closely for the presence of MAPC-like cells (multipotent adult progenitor cells) in cord blood.

2. Limitations in Clinical Use of Cord Blood

- Dosage of Total Nucleated Cell (TNC) per unit of cord blood
  - Cell dosage is a critical component of clinical therapy; each unit of cord blood is unique and finite.
  - Cord blood units have relatively small volumes (about 100 milliliters) and, therefore, a limited number of cells per unit. This can result in very low numbers of cells in the graft per kilogram of patient weight for larger children and adults, which has generally limited the use of cord blood based therapies to smaller children (19).
  - The Cord Blood Transplantation Study (COBLT), which was funded by the National Heart, Lung and Blood Institute (NHLBI), showed that a number of factors correlate with higher total nucleated cell (TNC), such as higher birth weight, delivery by Caesarian-section and increasing gestational age at delivery (not beyond 40 weeks) (20).
  - It has been reported to us anecdotally that an adult with leukemia was treated successfully by pooling 7 units of cord blood, using one highly matched and 6 closely matched units. On-going clinical trials are studying the efficacy of using two units of cord blood for adults.
  - Investigators have explored the *ex vivo* expansion of cord blood cells (see above), but this approach is still at the exploratory stage and is not a common practice.

- Need for recipient - donor compatibility (18)
  - Human leukocyte antigens (HLAs) are proteins found on the surface of white blood cells that control tissue compatibility.
  - At present, donated cord blood is routinely typed for six antigens, with notations such as 4/6 or 6/6 used to indicate the number of antigens a recipient has in common with a donor.
  - Disparities at these loci can affect the outcome of a transplant, with a greater mismatch increasing the likelihood of an unsuccessful transplant or the development of graft-versus-host disease (GVHD).

- Lack of standardization in sample identification and handling (21)
  - Centers that collect, process, and store cord blood differ in their organization and governance as well as in their processing methods.
  - When physicians attempt to access units for patients, they confront different search algorithms and informatics systems, depending on which bank or network of banks they search.
  - Likewise, HLA typing requests might come to banks in different formats on the basis of different transplant center preferences.
  - The Health Resources and Services Administration (HRSA) plans the creation of a development of a National Cord-blood Coordinating Center (NCCC) in part to address this issue (please see Section II-2 below for more details).

- Limited genetic diversity of currently banked samples
  - Existing cord blood collections lack sufficient ethnic and racial diversity, which limits the availability of HLA types for some groups of recipients (22).
  - Also, the COBLT study demonstrated that units collected from African American donors had lower cell counts per milliliter of blood collected (20).

II. Current Funding for Cord Blood

1. National Institutes of Health Funding (reported anecdotally)

- NIH funding of cord blood efforts has been as follows:
  - 2002 $21.0M
  - 2003 $17.0M
  - 2004 $18.5M
  - 2005 $18.6M
  - 2006 $18.6M

- Included in the above is a portion of the roughly $42M in funding the National Heart Lung and Blood Institute (NHLBI) has provided over the past 9 years for cord blood banks, mostly for transplant purposes.

2. Other Funding - The Stem Cell Therapeutic and Research Act of 2005 (23)

- H.R. 2520, the Stem Cell Therapeutic and Research Act of 2005, which became Public Law No. 109-129 on Dec 20, 2005, authorizes the Secretary of Health and Human Services to establish a national cord blood inventory by entering "…into one-time contracts with qualified cord blood banks to assist in the collection and maintenance of 150,000 new units of high-quality cord blood to be made available for transplantation …."

- Appropriations in the following amounts are called for:
  - $15M each year for fiscal years 2007 to 2010 to carry out a demonstration project where qualified cord blood banks will take part in the "…collection and storage of cord blood units for a family where a first-degree relative has been diagnosed with a condition that will benefit from transplantation."
  - $34M for fiscal year 2006 and $38M each year for fiscal years 2007 to 2010 for establishing and maintaining a database "…relating to patients who have been recipients of a stem cell therapeutics product (including bone marrow, cord blood, or other such product) from a donor."

- In April, 2006 Health Resources and Services Administration released a Request for Proposal around the development of a National Cord Blood Inventory (NCCBI), which aims to collect and bank 150,000 samples, and an associated National Cord-blood Coordinating Center (NCCC).
  - Approximately $22M is available for this effort, with $14M to be awarded in FY2006 and the remaining $8M in FY 2007.
  - The goals of this effort are to increase the size and quality of the cord-blood inventory, thereby increasing the likelihood of patients who need a transplant finding a suitable match (24) and to collaborate with cord blood banks across the US to identify and make available, through a single point of access, information on suitable cord blood units for transplantation (25).
  - The NCCC will establish a system for: (25)
    - Identifying available cord blood units;
    - Providing standardized information describing available cord blood units;
    - Facilitating the completion of additional tissue typing and infectious disease marker testing of cord blood units under consideration for searching patients;
    - Facilitating transplants with National Cord Blood Inventory (NCBI) cord blood units and other suitable cord blood units; and
    - Facilitating the collection of and making available outcomes data from unrelated umbilical cord blood transplants.
  - The NCCC will also facilitate collecting, verifying, and analyzing outcomes data of unrelated cord blood transplants (25).

III. Role for CIRM

1. Opinions from interviewees to date about possible CIRM initiatives

- The interviewees to date who have specifically discussed issues related to cord blood shared their thoughts on a number of "vital research opportunities" where CIRM might contribute. Suggestions included:
  - Supporting:
    - Studies related to variation in cord blood volumes / TNC counts based on birth conditions (i.e. Caesarian-section; pre-term vs. post-term birth).
    - Clinical investigations in areas of transplantation that have not been fully addressed (i.e. combining units for transplantation and understanding the limits of tolerance for HLA mismatch, etc.).
    - Basic research on demonstrating and verifying the presence of pluripotent stem cell in cord blood.
    - Research into how to efficiently and reproducibly generate multipotent adult stem cells (MAPC) from bone marrow or cord blood and to conduct research on their biology.
    - Research into developing ways to expand hematopoetic and other stem cell populations in cord blood prior to transplantation.
    - Studies into the differentiation of hematopoetic stem cells into immune cells that might be useful in the study of antivirals and treatments for leukemia.
    - Studies into the role that cells other than stem cells and progenitor cells, such as immune cells including natural killer cells, play in transplant success.
    - Gene expression studies to understand the role of particular genes in accelerating engraftment following transplantation.
  - Establishing a donor-sibling cord blood banking service for families in California. This could potentially provide cures and economic benefits.
  - Establishing high-quality cord blood banks in California to:
    - Serve the diverse population of California
    - Demonstrate that banks can be developed that are capable of longevity and self-sustainability.
    - Allow comparison of cord blood stem cells to other stem cells and expand the range of knowledge of what can be done with all types.

      Note: An anecdotal estimate of the start-up cost to establish such a bank, with roughly 10,000 – 20,000 units based on cost to establish National Cord Blood Bank was in the $20M to $25M range.

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