CORD BLOOD TRANSPLANTATION: PAST, PRESENT AND FUTURE

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Hematopoietic Stem Cell Transplantation (HSCT)

• The transplantation of pluripotential hematopoietic stem cells derived from bone marrow, peripheral blood, umbilical cord blood or placental tissue.
What Defines a Stem Cell?

• The ability for self renewal through cell division

• Ability to differentiate into organ or tissue specific cells
Classification of stem cells?

- **Embryonic Stem Cells**
  - cells derived from human embryos; can form all cell types (pluripotent)
- **Somatic or Adult Stem Cells**
  - undifferentiated cells which are formed in a particular tissue or organ and can differentiate to produce the specialized cells of that organ or tissue.
- **Induced Pluripotent Stem Cells (iPSC)**
  - adult cells which have been genetically reprogrammed to be embryonic stem cell-like
A Brief History of Haematopoietic Stem Cell Transplantation

• **1956** - Dr. E. Donnell Thomas performed the first successful bone marrow transplant on a young male suffering from leukemia.
  – Donor was identical twin (syngeneic transplant)

• **1958** - Dr. Georges Mathé, a French oncologist performed bone marrow transplants on 5 Yugoslavian physicists injured in a nuclear reactor accident. The transplants failed.

• **1968** - Dr. Robert Good, University of Minnesota, performed the first successful bone marrow transplant on 5 month old male suffering from a profound immune deficiency.
  – Donor was his 8 year old sister (related allogeneic transplant)

• **1972** - Drs. Milton Ende and Norman Ende, reported the use of umbilical cord blood to treat leukemia

• **1973** - First successful bone marrow transplant from an unrelated donor, MSKCC
A Brief History of Hematopoietic Cord Blood Stem Cell Transplantation

• **1988**- Dr. Eliane Gluckman, performs the first successful cord blood transplant on a 5 y.o. male suffering from Fanconi anemia
  - Cord blood cells were collected from the patients sister at birth

• **1990**- Dr. John Wagner, University of Minnesota performs the first successful cord blood transplant for the treatment of leukemia

• **1993**- Dr. Joanne Kurtzberg, Duke University performs the first unrelated cord blood transplant

• **1998**- COBLT Study begins accrual

• **1999**- First double cord transplants performed in Europe

• **2009**- FDA releases guidance for the licensing of umbilical cord bloods intended for transplant
The Birth of Cord Blood Banking

  - Three banks, six transplant centers, and one medical coordinating center (MCC) were funded with the overall goal of banking cord blood units (CBU) using a single manual of operations.

- Enrollment in the Cord Blood Stem Cell Transplantation Study (COBLT) begins in 1998
  - To evaluate if HLA-mismatched, unrelated-donor umbilical cord blood stem and progenitor cell units (UCBU) offered a clinically acceptable alternative to matched unrelated-donor allogeneic bone marrow for transplantation with 180-day disease free survival as the endpoint.
    - Patients with "true" HLA 3/6 and 4/6 matches were evaluated.
  - A separate study in adults addressed the problem of limited cell dose and engraftment failure.
  - The study was not planned as a randomized comparative clinical trial. Instead, it was a phase II/III efficacy study.
Conditions Addressed in the COBLT Study

• Aplastic Anemia
• Fanconi Anemia
• Hematologic Diseases
• Leukemia
• Neoplasms
• Severe Combined Immunodeficiency
• Hematopoietic Stem Cell Transplantation
  Myelodysplastic Syndromes
COBLT Results

• A total of 34,799 potential donors were screened and 20,710 (60%) consented.

• A total of 17,207 (83%) ethnically diverse units were collected between 1998 and 2001.

• A total of 11,077 (64%) units were cryopreserved and quarantined.
  – Of these, 79 percent met eligibility criteria and were HLA-typed and entered into the search registry.

• Higher CB volumes and cell counts were obtained from cesarean sections compared to vaginal deliveries.

• Units from African American persons contained lower cell counts per volume compared to other ethnicities.

• Birth weight correlated with volume and cell content.
The National Cord Blood Inventory (NCBI)


  - The NCBI portion of the Stem Cell Acts of 2005 and 2010 provides funding for the collection and storage of at least 150,000 cord blood units.

  - These cord blood units will be available through the C.W. Bill Young Cell Transplantation Program (Program) to treat patients who need an umbilical cord blood or bone marrow transplant.
Goals of the NCBI

• Encourage more cord blood donations, with special emphasis on parents of racially or ethnically diverse backgrounds.

• Collect and store cord blood units and make them available through the Program.

• Ensure the cord blood units are of high-quality and meet specified criteria such as having a certain number of blood-forming cells.
  – Cord blood units that do not meet these criteria may be available for research to improve patient outcomes.

• Protect the rights of donating mothers by obtaining consent to donate from the mother and maintaining confidentiality of the mother and baby.

• Provide cord blood unit data to the Program's Stem Cell Therapeutic Outcomes Database contractor.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
October 2009
This 2009 FDA guidance document provides recommendations for the submission of a biologics license application (BLA) (21 CFR Part 601) for placental/umbilical cord blood products that are:

• Manipulated minimally and

• Intended for hematopoietic reconstitution in patients with any of the following diseases:
  – Hematological malignancies
  – Certain lysosomal storage and peroxisomal enzyme deficiency disorders
    • Hurler Syndrome (MPS I)
    • Krabbe Disease (Globoid Leukodystrophy)
    • X-linked Adrenoleukodystrophy
  – Primary immunodeficiency diseases
  – Bone marrow failure
  – Beta thalassemia
  – Intended to be used in recipients unrelated to the donor.
Guidance for Industry Biologics License Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
March 2014
This 2014 guidance document provides recommendations for the submission of a biologics license application (BLA) under Title 21 of the Code of Federal Regulations Part 601 (21 CFR Part 601) for placental/umbilical cord blood products that are:

- Manipulated minimally

- Intended for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloblastic treatment

- For the purpose of this guidance, HPC, Cord Blood refers to the final drug product (cryopreserved or thawed) of minimally manipulated hematopoietic stem/progenitor cells from placental/umbilical cord blood, sourced from an unrelated allogeneic cord blood donor and intended for hematopoietic and immunologic reconstitution.
FDA Required Testing

• For **Safety**, cord blood banks must test for:
  – Infectious Diseases
    • Maternal blood
  – Sterility
    • HPC product
  – Hemoglobinopathies
    • Neonatal blood

• For **Purity and Potency**, cord blood banks must assess:
  – Total Nucleated Cell Count
    • Must be greater than ≥500 x10^6 cells/unit
  – Viable nucleated cells
    • ≥85% viable nucleated cells
  – Viable CD34+ cells (by flow cytometry)
    • ≥1.25 x10^6 CD34+ cells/unit

• For **Identity**:
  – HLA Typing of the cord blood pre processing
  – Confirmatory HLA typing of unit attached segment
  – Blood group and Rh typing
Haploidentical Transplantation (Half Match Transplant)

- Haploidentical stem cell transplantation is a treatment option for the approximately 70% of patients who do not have an HLA-identical sibling donor.

- The procedure requires just a half-match, meaning that a patient’s parents or children could be suitable donors.
  - Three days after the transplant, the patient is given a high dose of cyclophosphamide, which “re-boots” the immune system.
  - The cyclophosphamide spares the donor's stem cells and allows them to establish a new immune system. The new immune system is in essence re-trained to see the patient's body as self, preventing the patient from rejecting the donor stem cells.
Transplants by Cell Source

Source: National Marrow Donor Program/Be The Match FY 2014
Numbers of Allogeneic HCTs in the US
By Year and Donor Type

Data provided by CIBMTR

Excludes twins, related CB, 0-1 mism relatives
“Alternative Donor” Transplants in the US by Year and Graft Type

Data provided by CIBMTR
Umbilical Cord Blood & Haploidentical Transplants in the US by Year & HLA Match

Data provided by CIBMTR
Mesenchymal Stromal Cells (MSCs)

- Self renewing multi-potent cells that can be induced to differentiate into a variety of cell types by chemical means
  - osteoblasts
  - chondrocytes
  - adipocytes
  - cardiomyocytes
What’s the Process?
The umbilical cord blood is collected in a blood bag containing anticoagulant. The tubing is clamped under sterile conditions. The needle is discarded and the unit is transported to the laboratory.
Diagrammatic Representation of the Sepax Processing Kit
After the HES has been added, seal the port and remove the HES filter.
System Configuration
Kit Component Containing Buffy Coat (BC)
Overwrap the freezing bag.
Place freezing bag inside a metal cassette. Place the cassette in the control rate freezer.

Once the unit(s) has reached -80 degrees Celsius and the freezing process is complete, transfer the cassette(s) to a dedicated quarantine LN$_2$ freezer.
NJ Cord Blood Bank Stem Cells Shipped for Transplant

(as of 3/30/2015)
New Jersey Cord Blood Stem Cell Bank

- **1996** - The New Jersey Cord Blood Bank was created and operated as a program within the Coriell Institute for Medical Research in Camden, NJ.
- **1997** - Bergen Community Regional Blood Center created its cord blood bank in Bergen County.
- **1998** - Coriell receives a $5 MM loan from the state to operate the cord blood program and bank 5,000 transplantable units.
- **2005** - Governor Richard Cody designates the NJCBB and the Elie Katz Umbilical Cord Blood Program at BCRBC as New Jersey’s state designated cord blood programs and awards each $350K grants to bolster collections and build awareness for public cord blood banking.
- **2009** - The New Jersey Cord Blood Bank is awarded a 5 year HRSA contract and becomes one of thirteen NCBI banks.
- **2014** - NJCBB HRSA contract renewed for an additional 5 years.
Advantages of Cord Blood Derived Stem Cells for Hematopoietic Reconstitution

- Ready availability
- Ability to target specific racial and ethnic minorities
- Successful transplants with 1 or 2 HLA mismatches
- Less severe GVHD
- Less risk for transmission of blood borne pathogens
Disadvantages of Cord Blood Derived Stem Cells for Hematopoietic Reconstitution

• Large inventories with low cell doses

• Slower engraftment of neutrophiles
  – Longer hospitalizations
  – Increased utilization of resources

• Slow immune system reconstitution
  – Increase risk of infection

• Cost
The Future

• Stem cell expansion

• Protocols to decrease time to engraftment

• The use of CB derived stem cells to treat diseases other than hematologic malignancies and genetic disorders
  – Cerebral Palsy
  – Type 1 Diabetes
  – Neonatal Hypoxic-ischemic Encephalopathy
  – Autism Spectrum Disorder (ASD)

• There are presently over 1,000 clinical trials listed on clinicaltrials.gov
Thank You!