The Power & Potential of Cord Blood

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Objectives

• Since 1988, umbilical cord blood (UCB) has proven to be a viable source of stem cells for treating patients with disorders of the hematopoietic system.
• Collected after the routine delivery of a healthy newborn, cord blood is processed and cryopreserved in accredited laboratories following Good Manufacturing Practice (cGMP).
• Typically used to reconstitute the blood forming system after treatment for malignant diseases, cord blood-derived cells are being studied for potential use in novel applications such as regenerative medicine and immunotherapy.

• This session will:
  – illustrate the manufacture of safe, high quality CB products
  – describe the regulatory framework under which CBBs operate
  – define current and potential therapeutic applications
Background

• Each year, thousands of people are diagnosed with leukemia, lymphoma, or immune system or genetic (inherited) disorders.

• People with these diseases have abnormal or non-functional blood-forming cells.

• A bone marrow transplant replaces a patient’s diseased blood-forming cells with healthy cells.

• Healthy cells from another individual must be matched.
Stem Cell Differentiation

Blood Stem Cells

Red Blood Cells

White Blood Cells
There are 3 primary sources of adult stem cells for patients needing a blood stem cell transplant:

- Bone Marrow
- Peripheral Blood
- Cord Blood
Cord Blood Is...

- Blood that remains in the umbilical cord and placenta after a child is born
- Rich source of adult stem cells
  - Similar to those found in bone marrow
  - Obtained from a developed person
  - Source of self-renewing production of red blood cells, platelets, and white blood cells
- Non-controversial
  - Collected after baby is born
  - No harm to mother or baby
Benefits of Cord Blood

- Abundant resource: 4 million births/year in the U.S.
- Donation is easy, safe, painless and free
- Prompt access - characterized, screened & typed
- Low attrition
- Placental barrier reduces environmental exposure & contamination from viruses
- Higher proliferative & self-renewal capacity in UCB HSC
- Immune tolerance –
  - Decreased incidence of graft vs host disease (GVHD) despite less stringent HLA-matching requirements
  - More flexible matches – supports patients with rare HLA types
  - Cross ethnic lines

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Timeline of Cord Blood Banking

• First UCB bank, established by Dr. Hal E. Broxmeyer, provided the donor graft for the historic 1988 UCB transplant
• Supported the establishment of unrelated cord blood banks
  – 1992: Dr. Pablo Rubinstein at the New York Blood Center
  – 1993: Dusseldorf
  – 1995: Milan & St. Louis
• Reports indicate >600,000 unrelated units banked globally
• Nearly 30,000 unrelated UCB transplants performed to date
• In 2011 alone, the World Marrow Donor Association reported that 4,093 UCB products were shipped for unrelated patients in 47 different countries compared to 3,743 BM grafts
Related (Family) Banking

• A number of private CBBs have been established worldwide
• Two of the largest private CBBs in US have recently reported
  • Storing the cord blood stem cells of 700,000 newborns
  • Each having distributed approximately 250 products for traditional transplantation and regenerative applications
Public vs Private Banking

**Public cord blood bank**

- No cost to donor
- Units available to *unrelated* recipients worldwide by HLA match
- Required testing for infectious diseases
- Subject to stringent regulations for good manufacturing practices

**Private cord blood bank**

- Initial collection fee and annual storage fee
- Units only available to donor and donor’s family
- Infectious disease testing may not required
- Minimum regulations since future use not based on disease treatment

The alternative to both is the trash can!

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St. Louis University Department of Pediatrics
Options for Umbilical Cord Blood

Expectant parents may choose to:

• Donate to a public cord blood bank:
  • Provided to patients in need of a transplant
  • No cost
• Store in a private family cord blood bank:
  • Saved for use by the donating family
  • Associated fee
• Donate for research
• Discard as medical waste
Donor Related Issues

• Recruitment
  – Role of OB
  – Early education

• Informed Consent
  – Understand ‘donation’ and commitments
  – Investigational vs procedural
Donor Eligibility – 21 CFR Part 1271

• Minimize transmission of relevant communicable disease agents and diseases (RCDAD)

• Health History & Medical Evaluation
  – Infectious exposures
  – Genetic history

• Donor Testing
  – Obtained with 7 days of delivery
  – donor screening vs diagnostic testing
  – FDA cleared tests; lab authorized to perform
Collection

- The delivery process is not affected by cord blood collection
- In Utero – performed by trained OB/MW
- Ex Utero – performed by dedicated staff
- Cleaning and cannulation of umbilical vein into CPD
- Packed, stored, and transported to the cell processing laboratory in a temperature-controlled environment
Transport to Laboratory

• Upon arrival, the CB unit is examined and evaluated by standardized criteria:
  – Volume by weight > 50 mL
  – TNC > 1.2 x 10^9
  – Proper labeling
  – Acceptable maternal history questionnaire
  – Maternal tubes for infectious disease testing

• Selected for further manufacturing
Processing

• Volume reduction and removal of red blood cells, enriched in mononuclear cell fraction
  – Sedimentation/centrifugation
  – Manual/automated
• Current Good Manufacturing Practice (cGMP)
  – Drug rules at 21 CFR Parts 210/211
  – Assure safety, purity, potency, and effectiveness
  – Standardize manufacturing processes using
    • reagents that have been approved for human use
    • systems and supplies that have been cleared by FDA
Manufacturing Method

• Cord blood unit mixed with RBC sedimenting agent

• Plasma rich with nucleated cells

• Centrifugation uses density gradient to form layer rich in nucleated cells

• Retain buffy coat layer and remove excess plasma
Cryopreservation

- Prevent cellular dehydration and ice crystal formation
- Slow cooling at a rate of 1°C/min
- Cryoprotectant = dimethyl sulfoxide (DMSO)
- Stored in liquid nitrogen at <-150°C
- Retention of viability and proliferative function for >23 years
Long term storage

• Post thaw testing on segments
  – Prior to distribution
  – Stability testing
  – Expiration dating
## Characterization and Quality Control Testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Method(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell counts – WBC, NRBC, HCT</td>
<td>Hematology analyzer, manual differential</td>
</tr>
<tr>
<td>CD34+ cell enumeration</td>
<td>Flow cytometry (single or dual platform)</td>
</tr>
<tr>
<td>Viability assay</td>
<td>Dye exclusion (light microscopy), fluorescence microscopy, flow cytometry</td>
</tr>
<tr>
<td>Clonogenic assay</td>
<td>CFU (most common in clinical lab), LTC-IC</td>
</tr>
<tr>
<td>Sterility testing</td>
<td>Aerobic/anaerobic, fungal culture</td>
</tr>
<tr>
<td>HLA typing</td>
<td>Molecular</td>
</tr>
<tr>
<td>ABO/Rh Typing</td>
<td>Serology</td>
</tr>
</tbody>
</table>
Recipient Related Issues

• Shipment
  – Dry shipper
  – Receipt prior to conditioning

• Preparation
  – Bed side thaw
  – Reconstitution with dextran & albumin – restore osmolarity and extend cell viability
  – Wash – reduce DMSO, free hemoglobin and volume; pediatric patients or those with underlying conditions

• Infusion
  – Limit time from thaw to administration
  – Intravenous drip or syringe push, filter

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Transplants by Cell Source

Source: National Marrow Donor Program FY 2012
Transplants by Cell Source
Pediatric Recipients (younger than 18 years)

Source: National Marrow Donor Program FY 2012
FDA proposes draft regulatory approach for autologous & allogeneic UCB under IND leading to BLA—Docket 96N-0002

FDA announces Proposed Approach to Regulation of Cellular and Tissue-Based Products (Section 361 PHS Act)

FDA requests Proposed Standards for Unrelated Allogeneic Peripheral and Placental/UCB HSCP — Docket 97N-0497

FDA releases Draft UCB Guidance

FDA releases Final UCB Guidance

HCT/Ps Establishment Rule— 21CFR 1271 Subparts A and B

HCT/Ps Donor Suitability Rule— 21CFR 1271 Subpart C

HCT/Ps cGTP Rule—21CFR 1271 Subparts D,E, and F

Cord Blood Licensure Workshop, March 2010, Used with permission of Liana Harvath
FDA Regulation & Licensure

• Due to intended use in allogeneic recipients, CB is classified as a biologic drug

• Regulated under the more stringent cGMP rules & biologics standards similar to pharmaceuticals – challenges...
  – Each cord = unique biological component; cells vs. chemicals
  – Lot sizes = single patient lot vs thousands of tablets
  – Manufacturing process controls = drugs can be terminally sterilized; CB manufacturers rely on aseptic processing

• Final FDA Guidance and Draft IND Documents released Oct 20 2009

• High profile – one of the first cellular therapies to undergo process

• Within 2 years, all public CBBs must be licensed (20+)

• 5 cord blood banks are approved; 1 closed
• Final FDA Guidance and Draft IND Documents were released Oct 20 2009
  – Guidance for Industry and FDA Staff: Investigational New Drug Applications (INDs) for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications
May 30, 2013 Approval Letter - ALLOCORD

Our STN: BL 125413/0

SSM Cardinal Glennon Children's Medical Center
Attention: Ms. Donna M Regan
3662 Park Avenue
St. Louis, MO 63110

Dear Ms. Regan:

We are issuing Department of Health and Human Services U.S. License No. 1873 to SSM Cardinal Glennon Children's Medical Center, St. Louis, Missouri under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce HPC, Cord Blood manufactured from the date of this authorization forward.

Under this license, you are authorized to manufacture the product HPC, Cord Blood. HPC, Cord Blood is an allogeneic cord blood hematopoietic progenitor cell therapy indicated 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 myeloablative treatment. The risk benefit assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and specific manifestations of the disease, on characteristics of the graft, and on other available treatments or types of hematopoietic progenitor cells.
Potential Stem Cell Therapies

- Stroke
- Baldness
- Blindness
- Deafness
- Amyotrophic lateral sclerosis
- Myocardial infarction
- Muscular dystrophy
- Diabetes
- Multiple sites: Cancers
- Traumatic brain injury
- Learning defects
- Alzheimer’s disease
- Parkinson’s disease
- Missing teeth
- Wound healing
- Bone marrow transplantation (currently established)
- Spinal cord injury
- Osteoarthritis
- Rheumatoid arthritis
- Crohn’s disease
“Adult” Stem Cells

Human Stem Cell

Adult Stem Cell

Eye

Limbal Stem cells

Retina

Pancreatic

Pancreas

Islets

Gut

Muscle

Mesenchymal

Pancreas

Tendon

Neuronal

Ligament

Epidermal

Cartilage

Hepatic

Fat

Marrow Adipose Cord Blood

Bone Marrow

Marrow Apheresis Cord Blood

Peripheral Blood
Potential Therapeutic Applications

• Hematopoietic Progenitor Cells (HPC)
  – Hemoglobinopathies – sickle cell disease, thalassemia
  – Immunotherapies
    • Natural killer (NK) cells
    • T-regulatory and dendritic cells
• Non-hematopoietic applications
• Mesenchymal Stem/Stromal Cells (MSC)
  – Promotion of engraftment
  – Immunomodulatory effect
    • Moderate GVHD
    • Induce tolerance / reduce rejection in organ transplant
    • Autoimmune disorders

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Regenerative Medicine

• Reconstruction trials in progress
  • Cartilage – knees & shoulders
  • Scaffolds – organs

• Mechanism of action for cardiac repair – direct, indirect or both?
  • Transdifferentiate
  • Exert paracrine signalling (cytokines)
  • Stimulate angiogenesis
The St. Louis Cord Blood Bank

• Established in 1995

• Serve to collect, process and store UCB for transplantation

• Community program – operate in collaboration with > 450 physicians at 29 hospitals in MO and IL, 5 hospitals in Kansas City

• One of the largest independent, public CBBs in the world, affiliated globally with transplant centers and registries

• The “ultimate recycling project”

• 2013 – FDA approval to manufacture biologic drug AlloCORD
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MISSION

Advancing cures through the development of effective cellular therapy products, exceptional manufacturing practices, and innovative applications.
More than 137,000 cord blood units have been donated
Over 29,000 met banking criteria & been processed
2,300 SLCBB products have been distributed... more than 80 different diseases...

... in 34 countries
... 20% for international patients
“The chemo I had when I was eight years old killed my cancer, but along with it my bone marrow. I wasn’t making anything on my own anymore.”

A bone marrow transplant could repopulate her blood-forming cells, but her parents and two younger sisters did not match her blood type. “Before we could worry, they told us, ‘But we have cord blood.’”
“Now I want to help other people.”
Thank you!