Cord blood in hematopoietic stem cell transplantation and beyond

Marcos de Lima, MD
Disclosures

Celgene and Seattle Genetics: consultant
Outline

Cord blood transplantation for hematologic malignancies: limitations and new strategies to improve engraftment

Use of cord blood cell subtypes

Family cord blood banking and potential new uses of cord blood to treat a variety of conditions
Allogeneic Stem Cell Transplantation

• Treatment of choice for selected high-risk patients with:
  - Acute Leukemia (ALL, AML)
  - Chronic Leukemia (CML, CLL)
  - Follicular Lymphomas
  - Aplastic Anemia
  - Several Genetic and Immunologic Diseases

• Less than 30% of patients have a related donor
Engraftment

Graft
Stem cell dose
T-cell dose (CD8)
Graft-facilitating cells
Stromal stem cells?

Host
Immunosuppression
Preparative Regimen
Post transplant Rx
Disease effects
Sensitization

Histocompatibility
Hematopoietic Stem Cell Transplantation

Preparative Regimen

Immunosuppression

Toxicities ?
Infections ?
GVHD ?
Umbilical cord blood (UCB) as a source of hematopoietic stem cells for hematopoietic reconstitution

Advantages

- Rapid procurement
- Less stringent HLA matching
- Expanded donor pool
- Less graft-versus-host disease

Disadvantages

- Low cell dose
- Delayed engraftment
- Poor immune reconstitution
- Increased graft failure rate

PBPC remains the “gold standard” against which performance of CB should be compared:

- Neutrophil engraftment (>500/µl) 11 days
- Platelets engraftment (>20,000/µl) 13 days
- Engraftment failure rate <1%
8/8 Allele, Available-Match Rates in the Adult Donor Registry

Courtesy Martin Maiers, NMDP Bioinformatics
7/8 and 8/8 Allele Adult and Cord, in the Adult Donor Registry

Courtesy Martin Maiers, NMDP Bioinformatics
Single unit CB transplant

- Cell dose is key
  
  Laughlin et al. NEJM, 344:1815-1822, 2001

- HLA matching is also key, but mismatches are better tolerated than with bone marrow or peripheral blood.

- Engraftment failure rate is 5-20%.

- Time to neutrophil and platelet engraftment is delayed.
Umbilical cord blood (UCB) as a source of hematopoietic stem cells for hematopoietic reconstitution: can we improve current outcomes?

- Improve collection procedures
- Double Cord Transplantation
- Ex Vivo Expansion
- Intra osseous transplant
- Haploidentical (CD34 selected) and CB co-transplantation
- Improve homing
Strategies to Improve the Results of Cord Blood Transplantation

Double Cord Blood Transplants
Double cord blood transplants

• one unit prevails (unable to predict which one)

• less relapses (improve survival (?) )

• no graft-versus-graft effect, but more GVHD

• Single versus double: controversy is unsolved!

Barker J, Brunstein C and Wagner J.
Strategies to Improve the Results of Cord Blood Transplantation

Ex vivo expansion of cord blood progenitor cells
MDACC Expansion Trial

Ex-Vivo Expansion with G-CSF, SCF, FLT3 ligand and TPO

100% fraction

CD133+ enrichment

14 days
MDACC Cord Blood Expansion Trial
 CB CD133+ cells cultured in SCF, Flt3L, G-CSF & TPO

Method developed by McNiece et al.
Patients with Hematologic Malignancies

Randomize (50 per arm)

Two Unmanipulated Cords

One Ex Vivo Expanded and One Unmanipulated Cord

MD Anderson Randomized Cord Blood Expansion Trial
P.I. Marcos de Lima - Protocol 02-407; IND 7166
Co P.I.: E. J. Shpall
Engraftment after Myeloablative Therapy

<table>
<thead>
<tr>
<th></th>
<th>Unmanipulated</th>
<th>Expanded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days to ANC &gt;500/µl</td>
<td>23 (21,NA)</td>
<td><strong>21</strong> (19, NA)</td>
</tr>
<tr>
<td>Days to platelet &gt;20,000/µl</td>
<td>50 (41, NA)</td>
<td><strong>48</strong> (40, NA)</td>
</tr>
</tbody>
</table>

Selection Data

- Post-selection CD34⁺ cell recovery: 46% (range 2-70%)

Expansion Data

- Median TNC expansion: 26-fold (range 0.4-275)
- Median CD34⁺ cell expansion: 2.2 fold (range 0-18)

Positive-selection reduces CD34⁺ cell yield
Mesenchymal Stem Cells (MSC)

- MSC are a stromal component of the hematopoietic microenvironment.

- They provide cellular and extracellular components of the stem cell “niche”.

- When isolated and used *in vitro* in combination with cytokines, MSC markedly increase the expansion of CB hematopoietic progenitors.
Co-culture with MSC significantly enhances ex vivo expansion of CB cells

Day 14 hematopoietic output from liquid culture of CD133+ (solid bar) vs. co-culture of non-selected CB cells with MSC (striped bar)

Robinson et al. Bone Marrow Transplantation (2006) 37, 359-399
Hypothesis

Double cord blood transplant in which one unit is expanded in MSC-based co-cultures will lead to more rapid hematopoietic engraftment
Part #1: MSC Generation (Family member, N=8)

- 100 mls bone marrow aspirate
- Ficoll density separation
- MNC cultured 2-3 days.
  - Non-adherent (hematopoietic) cells removed
  - Adherent cell (MSC) culture continued (7-10 days) to ~70% confluence

Medium: αMEM + 10% FBS

Passage: 6x150cm² flasks

3 weeks
Part #2: Cord blood expansion (Family member, N=8) Two-step culture system

Day 1 - culture
SCF
G-CSF
Flt-3L
TPO

Day 7-14 culture
1 liter
10 bags
10 flasks

Day 14: Cells washed and infused

Frozen CB unit
CB MNC thawed and washed

Day 1-7co-culture

3 weeks + 14 day ex vivo expansion culture
Limitations of the family member-derived MSC

- Family member donor not always available
- Logistics harvesting 100 ml marrow in clinic difficult
- Conscious sedation expensive
- MSC expansion procedure time consuming (approximately 3 weeks to generate sufficient cells)
Monoclonal Antibody S

Frozen aliquots of STRO-1-selected MSC from Angioblast required only 3-4 days to generate sufficient MSC for co-culture and provided comparable CB expansion to family member derived MSC.

Angioblast generate GMP-grade, BM-derived, 3rd party, “off-the-shelf” MSC isolated using the STRO-1 antibody.

Murine IgM monoclonal antibody STRO-1 identifies a cell surface antigen expressed by stromal elements in human bone marrow (BM). STRO-1 binds to approximately 10% of BM mononuclear cells, greater than 95% of which are nucleated erythroid precursors, but does not react with committed progenitor cells (colony-forming unit granulocyte-macrophage [CFU-GM], erythroid bursts [BFU-E], and mixed colonies [CFU-Mix]). Fibroblast colony-forming cells (CFU-F) are present exclusively in the STRO-1 population. Dual-color cell sorting using STRO-1 in combination with antibody to glycoporphin A yields a population approximately 100-fold enriched in CFU-F in the STRO-1/glycoporphin A population. When plated under long-term BM culture (LTBMC) conditions, STRO-1+ cells generate adherent cell layers containing multiple stromal cell types, including adipocytes, smooth muscle cells, and fibroblastic elements. STRO-1+ cells isolated from LTBMC at later times retain the capacity to generate adherent layers with a cellular composition identical to that of the parent cultures. The STRO-1-selected adherent layers are able to support the generation of clonogenic cells and mature hematopoietic cells from a population of CD34+ cells highly enriched in so-called long-term culture-initiating cells. We conclude that antibody STRO-1 binds to BM stromal elements with the capacity to transfer the hematopoietic microenvironment in vitro.

© 1991 by The American Society of Hematology.
M. D. Anderson CB Expansion Trial with “off-the-shelf” Angioblast MPC (N=24)

4 days + 14 day *ex vivo* expansion culture

Day 1-7 co-culture

Frozen CB unit

CB MNC thawed and washed

SCF G-CSF Flt-3L TPO

Day 7-14 culture

1 liter

10 bags

10 flasks

Day 14: Non-adherent cells washed and infused

Single vial of Angioblast MSC

4 days

10 bags

10 flasks

M. D. Anderson CB Expansion Trial with “off-the-shelf” Angioblast MPC (N=24)
MSC-CB Expansion Trial

Day -14
Thaw & wash CB#1

Ex vivo CB#1-MSC co-culture expansion for 14 days

Day –8 to –2 High-Dose Therapy

Day 0
Infuse unmanipulated CB unit AND
Ex vivo expanded CB unit

Day 0
Infuse unmanipulated CB unit
AND
Ex vivo expanded CB unit

Day Preparative regimen
-9 Hydration Therapy
-8 Melphalan 140 mg/m²
-7 Thiotepa 10 mg / Kg
-6 Fludarabine 40 mg/m²
-5 Fludarabine 40 mg/m²
-4 Fludarabine 40 mg/m² Rabbit-ATG
-3 Fludarabine 40 mg/m² Rabbit-ATG
-2 Rest
-1 Rest
0 CB Infusions

GvHD Prophylaxis: Tacrolimus and MMF
Eligibility
• Patients with a high-risk hematologic malignancy
• Two 4-6/6 HLA matched CB units with > 1x10^7 TNC/Kg each

Statistical Design
• Safety and feasibility phase I
• Primary endpoint = time to engraftment
• Stopping rule for engraftment failure or excessive GvHD

M. D. Anderson MSC-CB Expansion Trial
Protocol 05-0781, IND 13,034
### Table 1. Demographic and Clinical Characteristics of the Patients and Controls.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Haploidentical Mesenchymal Stromal Cells (N = 7)</td>
<td>STRO-3+ Mesenchymal Progenitor Cells (N = 24)</td>
</tr>
<tr>
<td>Weight — kg</td>
<td>79</td>
<td>75</td>
</tr>
<tr>
<td>Median</td>
<td>53–95</td>
<td>51–118</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age — yr</td>
<td>31</td>
<td>39</td>
</tr>
<tr>
<td>Median</td>
<td>26–55</td>
<td>18–61</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis — no. (%)</td>
<td>AML or MDS: 5 (71)</td>
<td>16 (67)</td>
</tr>
<tr>
<td></td>
<td>Non-Hodgkin's or Hodgkin's lymphoma: 0</td>
<td>3 (12)</td>
</tr>
<tr>
<td></td>
<td>CLL: 1 (14)</td>
<td>1 (4)</td>
</tr>
<tr>
<td></td>
<td>CML or other MPD: 0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Myeloma: 0</td>
<td>0</td>
</tr>
<tr>
<td>Disease status at time of transplantation — no. (%)</td>
<td>Complete remission: 1 (14)</td>
<td>12 (50)</td>
</tr>
<tr>
<td></td>
<td>First remission: 1 (14)</td>
<td>2 (8)</td>
</tr>
<tr>
<td></td>
<td>Second or subsequent remission: 0</td>
<td>10 (42)</td>
</tr>
<tr>
<td></td>
<td>Active disease: 6 (86)</td>
<td>12 (50)</td>
</tr>
<tr>
<td>Donor—recipient HLA compatibility — no. (%)</td>
<td>6/6: 0</td>
<td>1 (4)</td>
</tr>
<tr>
<td></td>
<td>5/6: 3 (43)</td>
<td>3 (12)</td>
</tr>
<tr>
<td></td>
<td>4/6: 4 (57)</td>
<td>20 (83)</td>
</tr>
<tr>
<td></td>
<td>3/6: 0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Not reported: 0</td>
<td>0</td>
</tr>
</tbody>
</table>

* ALL denotes acute lymphocytic leukemia, AML acute myeloid leukemia, CIBMTR Center for International Blood and Marrow Transplant Research, CLL chronic lymphocytic leukemia, CML chronic myeloid leukemia, MDS myelodysplastic syndrome, and MPD myeloproliferative disorder.

† Two controls from the M.D. Anderson Cancer Center (MDACC) were excluded owing to lack of engraftment and chimerism documentation.
Expansion of Cord Blood with Mesenchymal Stromal Cells.

A Total Nucleated Cells

B CD34+ Cells

C CFU-C

D Proportion of Various Types of Cells

E Doses in Units of Unmanipulated Cord Blood and Mesenchymal-Cell–Expanded Cord Blood (N=31)

<table>
<thead>
<tr>
<th></th>
<th>Unmanipulated Cord Blood</th>
<th>Expanded Cord Blood</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>median (range)</td>
<td>median (range)</td>
<td>median (range)</td>
</tr>
<tr>
<td>Total Nucleated Cells/kg\times10^-7</td>
<td>2.28 (1.57–4.82)</td>
<td>5.84 (0.03–14.37)</td>
<td>8.34 (1.66–19.19)</td>
</tr>
<tr>
<td>CD34+ Cells/kg\times10^-6</td>
<td>0.38 (0.07–1.74)</td>
<td>0.95 (1.60–9.34)</td>
<td>1.81 (0.09–9.88)</td>
</tr>
<tr>
<td>CFU-C/kg\times10^-5</td>
<td>Not done</td>
<td>3.00 (0.00–13.70)</td>
<td>3.00 (0.00–13.70)</td>
</tr>
</tbody>
</table>
Table 2. Engraftment in Recipients of Ex Vivo Expanded Cells and MDACC and CIBMTR Controls.

<table>
<thead>
<tr>
<th>Engraftment</th>
<th>Recipients of Ex Vivo Expanded Cells (N=24)</th>
<th>MDACC Controls (N=60)</th>
<th>P Value*</th>
<th>CIBMTR Controls (N=80)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil engraftment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>23</td>
<td>51</td>
<td></td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Time to engraftment — days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>15</td>
<td>21</td>
<td>0.08</td>
<td>24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Range</td>
<td>9–42</td>
<td>6–45</td>
<td></td>
<td>12–52</td>
<td></td>
</tr>
<tr>
<td>Cumulative incidence — % (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>By 26 days</td>
<td>88 (66–96)</td>
<td>62 (48–73)</td>
<td>0.006</td>
<td>53 (41–63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>By 42 days</td>
<td>96 (74–99)</td>
<td>83 (71–91)</td>
<td>0.05</td>
<td>78 (67–86)</td>
<td>0.005</td>
</tr>
<tr>
<td>Platelet engraftment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>18</td>
<td>38</td>
<td></td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Time to engraftment — days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>42</td>
<td>41</td>
<td>0.33</td>
<td>49</td>
<td>0.03</td>
</tr>
<tr>
<td>Range</td>
<td>15–62</td>
<td>26–126</td>
<td></td>
<td>18–264</td>
<td></td>
</tr>
<tr>
<td>Cumulative incidence — % (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>By 60 days</td>
<td>71 (48–85)</td>
<td>52 (38–63)</td>
<td>0.10</td>
<td>31 (21–41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>By 180 days</td>
<td>75 (53–88)</td>
<td>63 (50–74)</td>
<td>0.28</td>
<td>46 (35–58)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* P values are for the comparison between recipients of STRO-3+ mesenchymal precursor cells and MDACC controls.
† P values are for the comparison between recipients of STRO-3+ mesenchymal precursor cells and CIBMTR controls.
Cumulative Incidences of Neutrophil Engraftment and Platelet Engraftment.

A Neutrophil Engraftment

B Platelet Engraftment

What is next for MSC-based ex-vivo expansion?

Randomize

Two Unmanipulated Cords

One Ex Vivo Expanded and One Unmanipulated Cord

International, multicenter study sponsored by Mesoblast
Ex-vivo expansion

- Engineered Notch Ligands
  Delaney et al, Nat Med. 2010 Feb;16(2):232-6

  - StemRegenin-1 SR-1 (Novartis). Univ of Minnesota

- Gamida cell: nicotinamide-based ex vivo expansion

- TEPA (Tetraethylenepentamine) – StemEx
  de Lima et al, Bone Marrow Transplant. 2008;41:771-8
Limitations of double CB platform

Use of two units – expensive.

Possibly more GVHD.

Added costs of expansion technology to the cost of two units.
Intra-Osseous Co-Transplantation of Human Mesenchymal Stromal Cells and CD34-Selected Human Umbilical Cord Blood

Leland Metheny M.D.
Jane Reese-Koc
Alex Huang, MD
Methods

**Mouse:** NOD/SCID-gamma

**Non-lethal Radiation:** 300 rads

**6 Cohorts:**
- IV UCB
- IVUCB+IV MSC
- IO UCB
- IO UCB+IO MSC
- IO UCB+IV MSC
- IVUCB+IOMSC

**6 Week Analysis:**
- Right tibia flow
- Left tibia histology
Percent CD45 in the Right Tibia Bone Marrow at 6 weeks

- p<0.001
- p<0.001
- p<0.001
- p<0.001
- p>0.05

Bar graph showing percent CD45 for different conditions:
- IV UCB
- IO UCB
- IV UCB + IO MSC
- IV UCB + IV MSC
- IO UCB + IV MSC
- IO UCB + IO MSC
Cord blood as a source of cell subsets

NK cells

Regulatory T cells

Mesenchymal stromal cells

Other cell types.
Enhancing NK cell therapy through GSK3 inhibition

David Wald
Assistant Professor
CWRU/UH Hospitals
Case Medical Center
NK Cells

• Potent effectors of the innate immune response

• Make up from 1–32.6% of peripheral blood lymphocytes in normal subjects

• Large granular lymphocytes that can kill target cells

• Kill cells by cytokine/chemokine secretions (ex. IFN-γ) and/or perforin/granzyme and death receptor (ex. Fas) pathways
Glycogen Synthase Kinase 3

• Constitutively active serine/threonine kinase involved in a multitude of cellular processes (cell death, memory, inflammation) and signaling pathways (wnt/beta-catenin, mTor, p53, NFkB etc)

• GSK3 inhibition leads to growth inhibition, differentiation and cell death of many types of cancer cells

• Increase in NK cell-mediated AML killing in animal model and in vitro
Figure 2. Schema for NK cell manufacturing with aAPCs.

Irradiated K562 cells stably expressing a number of molecules such as CD64, CD86, CD137L and mIL-21

Incubation with GSK3 inhibitor and IL-15 super agonist
Human induced pluripotent stem cells (iPSCs):

- usually derived from human somatic cell types (blood, skin)
- generated with re-programming techniques
- differentiate into a variety of other cell types
Can cord blood banks transform into induced pluripotent stem cell banks?

_Cytobiotherapy_, 2015; 17: 756–764

HONGYAN ZHOU¹ & MAHENDRA S. RAO¹,²

¹New York Stem Cell Foundation Research Institute, New York City, New York, USA, and ²Q Therapeutics, Salt Lake City, Utah, USA
Family Cord Blood Banking
Reasons to family bank cord blood stem cells

Autologous cord blood stem cells are an exact match

Related stem cells remain the preferred choice of transplant by many physicians, as they cause fewer recipient problems.

- 25 percent probability of being a perfect match and a 50 percent probability of providing a suitable match for transplant use with a sibling (and possibly other family members).

Late onset diseases: possible benefit from having cells stored.

Minority populations are under-represented in transplant registries.
Family Cord Blood Banking

Figure 2. Autologous UCBT from family banks.

Umbilical cord blood donation
KK Ballen et al
Bone Marrow Transplantation (2015), 1–8
Family Cord Blood Banking

Figure 3. Allogeneic UCBT from family banks.

Umbilical cord blood donation
KK Ballen *et al*  
Bone Marrow Transplantation (2015), 1 – 8
Current FDA-Approved Cord Blood Uses and FDA IND-Approved Cord Blood Uses

**Cord Blood**

- **pCBB, allogenic**
  - CD34+ Cells → Hematologic Malignancies, Anemia, SCA

- **fCBB, autogenic**
  - MNC → Critical Limb Ischemia, Spinal Cord Injury
  - MSC → Diabetes Mellitus, Alzheimer's, Cartilage Injury, GvHD
  - CD4+ CD25+ T<sub>reg</sub> → Diabetes Mellitus
  - ALDH<sup>bright</sup> → Critical Limb Ischemia, Myocardial Ischemia, Stroke
  - Dendritic Cells → Vaccine (Ag Viral/Fungal Infections, Anti-Tumor)
  - Autism, Osteopetrosis, Hypoplastic Heart, Stroke, Cerebral Palsy, Chronic Traumatic Brain Injury, Transfusion for Preterm Neonates, Neonatal Hypoxic-Ischemic Encephalopathy, Chronic Injured Spinal Cord, Acquired Hearing Loss in Children

Serum/Plasma → Eye Abrasions
Current FDA **BLA**-Approved Cord Blood Uses and FDA **IND**-Approved Cord Blood Uses

**Cord Blood**

- **pCBB**, allogenic
- **fCBB**, autologous

- MNC → Critical Limb Ischemia, Spinal Cord Injury
- MSC → Diabetes Mellitus, Alzheimer's, Cartilage Injury, GvHD
- CD4+ CD25+ T_{reg} → Diabetes Mellitus
- ALDH^{bright} → Critical Limb Ischemia, Myocardial Ischemia, Stroke
- Dendritic Cells → Vaccine (Ag Viral/Fungal Infections, Anti-Tumor)
- Autism, Osteopetrosis, Hypoplastic Heart, Stroke, Cerebral Palsy, Chronic Traumatic Brain Injury, Transfusion for Preterm Neonates, Neonatal Hypoxic-Ischemic Encephalopathy, Chronic Injured Spinal Cord, Acquired Hearing Loss in Children
- Serum/Plasma → Eye Abrasions

→ Treatment/Cure

→ Treatment/Cure?
Contribution of the fCBB to Cord Blood Approvals for Alternative Uses
Homologous Use of Cord Blood

Homologous Use: “Use of the stem cells for the same type or purpose as the origin of that particular stem cell. A homologous use for stem cells obtained from the cord blood would be for a blood or hematological condition.” (PUBLIC CBB)

Non-Homologous Use: “Use of the stem cells for any other use or purpose, e.g., using umbilical cord blood stem cells to treat a disease such as multiple sclerosis, type I diabetes or ALS.” (FAMILY CBB)
What are the Odds of Requiring a Transplant?

In the USA, 1 in 217 people have a stem cell transplant by age 70
(Nietfeld et al., 2008)

http://parentsguidecordblood.org/odds.php; Table copyright Frances Verter, PhD 2014
# Summary of Clinical Trials with Cord Blood Using donor (allogeneic, + siblings) fCBB Cord Blood

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Occurrence in USA</th>
<th>Trial stage</th>
<th>Trial registry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cartilage Repair</td>
<td>10-25% adolescents have knee injuries</td>
<td>Approved by Korean FDA (Cartistem)</td>
<td>NCT01733186</td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td>2 per 1000 full term births</td>
<td>phase 2</td>
<td>NCT01193660, NCT01528436,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCT01639404, NCT01991145,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCT02025972</td>
</tr>
<tr>
<td>Critical Limb Ischemia</td>
<td>2.5 per 1000 people, over 80% of them diabetics</td>
<td>phase 1</td>
<td>NCT01019681</td>
</tr>
<tr>
<td>Premature Lungs (BPD)</td>
<td>25% births under 1500gm</td>
<td>phase 2</td>
<td>NCT01897987</td>
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<tr>
<td>Type 1 Diabetes</td>
<td>1.7 per 1000 ages birth-19</td>
<td>phase 2</td>
<td>NCT01350219, NCT01996228</td>
</tr>
</tbody>
</table>

[http://parentsguidecordblood.org/odds.php](http://parentsguidecordblood.org/odds.php); Table copyright Frances Verter, PhD 2014
## Summary of Clinical Trials with Cord Blood Using Autologous fCBB Cord Blood Stem Cells

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Occurrence in USA</th>
<th>Trial stage</th>
<th>Trial registry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired Hearing Loss</td>
<td>12.5% ages 6-19</td>
<td>phase 1</td>
<td>NCT01343394, NCT02038972, NCT01638819</td>
</tr>
<tr>
<td>Autism</td>
<td>1.5% (1 in 68) children</td>
<td>phase 2, phase 1</td>
<td>NCT01638819, NCT02176317</td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td>0.2% full term births, 2.2% premature births, 1 in 300 kids ages 5-10</td>
<td>phase 2</td>
<td>NCT01147653, NCT01072370, NCT01988584, Japan</td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td></td>
<td>phase 1</td>
<td>Romania, Slovakia, Spain, Spain</td>
</tr>
<tr>
<td>Hypoplastic Left Heart Syndrome</td>
<td>0.2 per 1000 births</td>
<td>phase 1</td>
<td>NCT01445041, NCT01856049, NCT00593242, NCT01506258, NCT01649648, Japan</td>
</tr>
<tr>
<td>Neonatal Oxygen Deprivation</td>
<td>0.2% full term births</td>
<td>phase 1</td>
<td>NCT01445041, NCT01856049, NCT00593242, NCT01506258, NCT01649648, Japan</td>
</tr>
<tr>
<td>Traumatic Brain Injury</td>
<td>435,000 per yr ages 0-14 #1 cause of death in kids</td>
<td>phase 1</td>
<td>NCT01251003, NCT01700166, NCT00989547, NCT00873925, CoRD</td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td>1.7 per 1000 ages birth-19</td>
<td>phase 1 &amp; 2</td>
<td>NCT01343394, NCT02038972, NCT01638819</td>
</tr>
</tbody>
</table>

[http://parentsguidecordblood.org/odds.php](http://parentsguidecordblood.org/odds.php); Table copyright Frances Verter, PhD 2014
USA Medical Society Opinion (Family Banking)

The following medical societies have issued Opinions about cord blood banking:

ASBMT - Mar. 2008
ACOG - Feb. 2008
AMA - Nov. 2007
AAP - Jan. 2007
WMDA - Jun. 2006
RCOG - Jun. 2006
EGE - Mar. 2004

None of the medical society opinions include therapies that are in clinical trials, which are not considered standard of care.

http://parentsguidecordblood.org/odds.php; Table copyright Frances Verter, PhD 2014
Benefit of Regenerative Medicine?

- Approximately 1 in 3 Americans could benefit from regenerative medicine.

- Children whose cord blood stem cells are available for their own potential use could be among the first to benefit from new therapies as they become available.

- With autologous cells, there is no risk of the immune system rejecting the cells.

Safety of Autologous Human Umbilical Cord Blood Treatment for Perinatal Arterial Ischemic Stroke (ClinicalTrials.gov Identifier: NCT02460484).

- **Principal Investigator:** James Baumgartner, MD.
- **Purpose:** to determine if hUCB infusion is safe, if late functional outcome is improved, if hUCB treatment improves physiologic response in the child's SSEP & EEG, and the effect of hUCB infusion in altering anatomic findings on MRI.
- **Primary Outcome Measures:** Hemodynamic Safety, Pulmonary Safety, Renal Safety, Neurological Safety
- **Secondary Endpoints:** EEG, Fine and Gross Motor
Principal Investigator: M. Haller, MD, University of Florida, Gainesville.

Purpose: To transfuse autologous UCB in attempt to re-establish immune tolerance and regenerate pancreatic islet insulin-producing beta cells.

Design: Open label, historic control, single group assignment efficacy study to determine if UCB can potentially be part of early treatment regimens for type 1 diabetes.
Safety of Autologous Human Umbilical Cord Blood Mononuclear Fraction to Treat Acquired Hearing Loss in Children (NCT01343394)

Cord Blood Registry
Speech Therapists for Children
The University of Texas Health Science Center, Houston
M.D. Anderson Cancer Center
Baylor College of Medicine
The Methodist Hospital System Research Institute – Houston.

Acquired hearing loss characterized by a loss of functioning hair cells in the Organ of Corti. Patients are 6 weeks to 18 months.
Cord Blood for Neonatal hypoxic-Ischemic Encephalopathy
(ClinicalTrials.govIdentifier: NCT00593242)

- **Principal Investigator:** J. Kurtzberg, MD.
- **Purpose:** Phase I open label, historic control, single group assignment safety study to test feasibility of collection, preparation and infusion of autologous UCB if the infant is born with signs of brain injury
- **Primary Outcome Measures:** AE rates in the pilot study population will be compared between UCB recipients and historic controls from the Network Hypothermia study
- **Secondary Endpoints:** preliminary efficacy as measured by neurodevelopmental function at 4-6 mo and 9-12 mo of age
Autologous Umbilical Cord Blood Infusion for Children With Autism Spectrum Disorder (ASD) (ClinicalTrials.gov Identifier: NCT02176317)

- **Principal Investigator**: J. Kurtzberg, MD.
- **Purpose**: Prospective phase 1 single-center trial designed to determine the safety of a single intravenous infusion of autologous umbilical cord blood in children with Autism Spectrum Disorder (ASD)
- **Primary Outcome Measures**: Evaluate the number of participants with non-serious and serious adverse events.
- **Secondary Endpoints**: Primary efficacy measure will be change in the Vineland Adaptive Behavior Scale

Hypothesis: umbilical cord blood cells (UCB) can offer neural protection/repair in the brain and reduction of inflammation associated with this disorder.
A Randomized Study of Autologous Umbilical Cord Blood Reinfusion in Children With Cerebral Palsy (ClinicalTrials.gov Identifier: NCT01147653)

- **Principal Investigator:** J. Kurtzberg, MD.
- **Purpose:** Is Autologous Umbilical Cord Blood Reinfusion Beneficial in Children With Cerebral Palsy: A Randomized, Blinded, Placebo-Controlled, Crossover Study
- **Primary Outcome Measures:** The primary measure of efficacy will be improvement of standardized measures of neurodevelopmental function.
- **Secondary Endpoints:** to determine effects on quality of life in these children and a secondary objective is to describe functional and morphologic changes on brain MRI in these children.
CB Infusion to Treat Type 1 Diabetes (NCT00305344)

- **Primary Outcome Measures**: peak C-peptide following mixed meal tolerance test.
- **Secondary outcomes**: insulin dose, autoantibody levels, T cell functional response assays, cytokine levels, to study potential changes in metabolism/immune function leading to islet regeneration.

NCT00518934: Safety and Efficacy of Therapeutic Angiogenesis for Limb Ischemia by Transplantation of Human UCB MNC

- **Principal Investigator:** D. Kim, MD, Samsung Med Center, Seoul, Korea.
- **Purpose:** to analyze the safety and efficiency of therapeutic angiogenesis for patients with limb ischemia by transplantation of UCB MNC.
- **Design:** Open label, historic control, single group assignment. Inclusion: patients with ischemic symptoms severe claudication, rest pain, or non-healing ischemic wound.
Conclusions

Umbilical Cord Blood offer the possibility of allogeneic transplantation to most patients in need.

Haploidentical donors and cord blood complement each other towards a new reality of donors for everybody.

Cord blood use is likely to rapidly diversify in the upcoming years.
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