Licensing of Cord Blood Units for Indications other than currently approved

Joanne Kurtzberg

Cord Blood Association

January 30, 2018

Background and Rationale

- Treatments using umbilical cord blood for indications other than HSCT are undergoing evaluation in clinical trials around the world. Over 300 trials with UCB in regenerative applications are listed on clinicaltrials.gov.
- At Duke, we are conducting trials under INDs in babies with HIE, children with cerebral palsy and autism, and adults with acute ischemic stroke.
- Results of phase I and II studies in children with autism and CP, respectively have shown favorable safety profiles and encouraging efficacy results.
- Both autologous, related and unrelated cord blood units are being utilized.
- The mechanism of action using cord blood in these patients is that cord blood acts through paracrine signaling to instruct endogenous cells to repair damaged tissue and to build new connections in the brain.

Feasibility and Safety

- Cord blood is administered after thawing and washing, as an IV infusion in the outpatient clinic.
- Patients are pre-medicated with a single dose of IV diphenhydramine (0.5mg/kg) and solumedrol (0.5mg/kg).
- The cells are infused over 15 minutes.
- The patient is hydrated with standard IV fluids for 1-2 hours post infusion.
- In over 800 infusions over the past 10 years, the infusion reaction rate is <1%.
- Reactions were characterized as urticarial +/- cough or wheezing. All were self limited and deemed not serious.
- There have been no late ADEs.

Additional safety precautions

- **Eligibility limited to patients without genetic causes of their disease**
- **Patients must have normal ALC**
- **Patients with a PMH of cancer, immune deficiency, autoimmune disease, immunosuppressive or chemotherapy are ineligible**
- **Patients treated with other cell therapies are excluded**

Efficacy – Completed studies

- Safety
- CP
- Autism
- HIE
- Speech Apraxia
- Congenital Hydrocephalus
- Stroke

Safety

Published in final edited form as:
Transfusion. 2010 September ; 50(9): . doi:10.1111/j.1537-2995.2010.02720.x.

Differences in quality between privately and publicly banked umbilical cord blood units: a pilot study of autologous cord blood infusion in children with acquired neurologic disorders

Jessica Sun, **June Allison**, **Colleen McLaughlin**, **Linda Sledge**, **Barbara Waters-Pick**, **Stephen Wease**, and **Joanne Kurtzberg**
Pediatric Blood and Marrow Transplant Program and the Carolinas Cord Blood Bank, Duke University, Durham, North Carolina; and the EMMES Corporation, Rockville, Maryland

Autism

STEM CELLS TRANSLATIONAL MEDICINE
CORD BLOOD

Autologous Cord Blood Infusions Are Safe and Feasible in Young Children with Autism Spectrum Disorder: Results of a Single-Center Phase I Open-Label Trial

GERALDINE DAWSON,[a] JESSICA M. SUN,[b] KATHERINE S. DAVLANTIS,[a] MICHAEL MURIAS,[a,c] LAUREN FRANZ,[a] JESSE TROY,[b] RYAN SIMMONS,[b] MAURA SABATOS-DEVITO,[a] REBECCA DURHAM,[b] JOANNE KURTZBERG[b]

Authored by a member of CORD BLOOD ASSOCIATION

Key Words. Autism spectrum disorder • Autologous umbilical cord blood • Cell therapy

CP

STEM CELLS TRANSLATIONAL MEDICINE
CORD BLOOD

Effect of Autologous Cord Blood Infusion on Motor Function and Brain Connectivity in Young Children with Cerebral Palsy: A Randomized, Placebo-Controlled Trial

JESSICA M. SUN,[a] ALLEN W. SONG,[b] LAURA E. CASE,[c] MOHAMAD A. MIKATI,[d] KATHRYN E. GUSTAFSON,[e] RYAN SIMMONS,[a] RICKI GOLDSTEIN,[f] JODI PETRY,[c] COLLEEN MCLAUGHLIN,[a] BARBARA WATERS-PICK,[g] LYON W. CHEN,[b] STEPHEN WEASE,[h] BETH BLACKWELL,[h] GORDON WORLEY,[d] JESSE TROY,[a] JOANNE KURTZBERG[a]

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Key Words. Autologous stem cell transplantation • Cellular therapy • Clinical Trials • Cord blood • Human cord blood • Nervous system • Umbilical cord blood

HIE

THE JOURNAL OF PEDIATRICS • www.jpeds.com
ORIGINAL ARTICLES

Feasibility of Autologous Cord Blood Cells for Infants with Hypoxic-Ischemic Encephalopathy

C. Michael Cotten, MD[1], Amy P. Murtha, MD[2], Ronald N. Goldberg, MD[1], Chad A. Grotegut, MD[2], P. Brian Smith, MD[1], Ricki F. Goldstein, MD[1], Kimberley A. Fisher, PhD[1], Kathryn E. Gustafson, PhD[3], Barbara Waters-Pick, BS, MT(ASCP)[4], Geeta K. Swamy, MD[2], Benjamin Rattray, MD[1], Siddhartha Tan, MD[5], and Joanne Kurtzberg, MD[6]

Stroke

STEM CELLS TRANSLATIONAL MEDICINE

Allogeneic Umbilical Cord Blood Infusion for Adults with Ischemic Stroke (CoBIS): Clinical Outcomes from a Phase 1 Safety Study

Laskowitz, Daniel; Duke University Medical Center, Neurology
Bennett, Ellen; Duke University Medical Center, Neurology;
Durham, Rebecca; Duke University School of Medicine, Robertson Clinical and Translational Cell Therapy Center
Volpi, john; Eddy Scurlock Stroke Center, Houston Methodist Neurological Institute
Wiese, Jonathan; Eddy Scurlock Stroke Center, Houston Methodist Neurological Institute
Frankel, Michael; Emory University School of Medicine, Neurology
Shpall, Elizabeth; University of Texas, M.D. Anderson Cancer Center, Department of Stem Cell Transplant and Cellular Therapy
Wilson, Jeffry; MD Anderson Cancer Center
Troy, Jesse; Duke University Medical Center, Robertson Clinical and Translational Cell Therapy Program
Kurtzberg, Joanne; Duke University Medical Center, Department of Pediatrics

Congenital Hydrocephalus

Pediatr Res. 2015 Dec;78(6):712-6. doi: 10.1038/pr.2015.161. Epub 2015 Sep 2.

Repeated autologous umbilical cord blood infusions are feasible and had no acute safety issues in young babies with congenital hydrocephalus

Jessica M. Sun[1], Gerald A. Grant[2], Colleen McLaughlin[1], June Allison[1], Anne Fitzgerald[1], Barbara Waters-Pick[1] and Joanne Kurtzberg[1]

Speech Apraxia

Abstracts / Biol Blood Marrow Transplant 23 (2017) S18–S391 S149

Treatment of Childhood Apraxia with Autologous Cord Blood Infusions

Colleen A. McLaughlin, R. Anne Fitzgerald, June Allison, Barbara Waters-Pick, Jessica Sun, Joanne Kurtzberg

Ongoing Studies

- **CP**
  - **Phase II randomized trial comparing allogeneic unrelated donor cord blood infusions and third party cord tissue MSCs in young children with CP**
    - **100 children, 1:1:1 randomization, 6 and 12 month endpoints, change in GMFM level**
    - **Completion July 2019**
- **Autism**
  - **Duke ACT: Phase II, Placebo-Controlled, Cross-over, Randomized Trial Comparing autologous or unrelated donor allogeneic cord blood infusion to placebo in young children with ASD**
    - **177 children, 2:1 randomization, 6 month endpoint, Vineland Socialization Scale**
    - **Completion August 2018**
- **Adults with acute ischemic Stroke**
  - **COBIS II: Phase II randomized, placebo-controlled trial of infusion of unmatched, unrelated donor umbilical cord blood in adults with acute stroke, 3-10 days post stroke**
    - **110 patients, 1:1 randomization, 5 sites**
    - **Completion Q1 2019**
- **HIE**
  - **Babybac II: Phase II, randomized, placebo-controlled trial of fresh, volume and RBC reduced UCB infusion in newborn babies with moderate-severe encephalopathy treated with SOC hypothermia.**
    - **120-160 babies, 2:1 randomization, 12 sites**
    - **Completion 2020**

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Key Words. Autologous stem cell transplantation • Cellular therapy • Clinical Trials • Cord blood • Human cord blood • Nervous system • Umbilical cord blood

Authored by a member of

CORD BLOOD ASSOCIATION

[a]The Robertson Clinical and Translational Cell Therapy Program, [b]The Brain Imaging and Analysis Center, [c]Department of Physical and Occupational Therapy, [d]Division of Pediatric Neurology, [e]Department of Psychiatry, [f]Division of Neonatology, [g]Stem Cell Transplant Laboratory, Duke University, Durham, North California, USA; [h]The Emmes Corporation, Rockville, Maryland, USA

CPAC - Study Overview

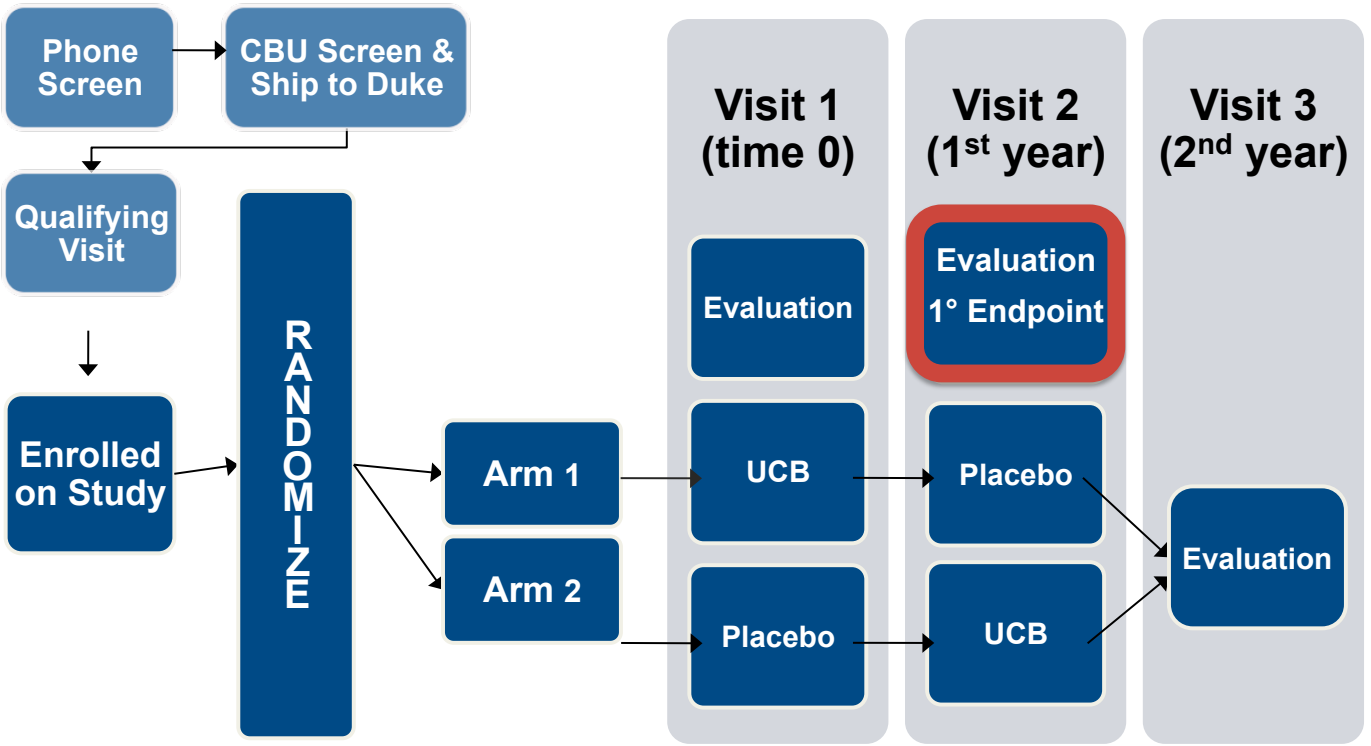
- 63 patients
- Ages 1-6 years
- Qualified autologous cord blood unit
  - 16 Banks
- CP with spasticity, GMFCS levels I-IV
- Randomized, placebo controlled cross over design
- Placebo = TC199 + 1% DMSO
- Primary endpoint: Change in GMFM score
- Follow up at 1 and 2 years

Table 1. Qualifying characteristics of autologous umbilical cord blood units

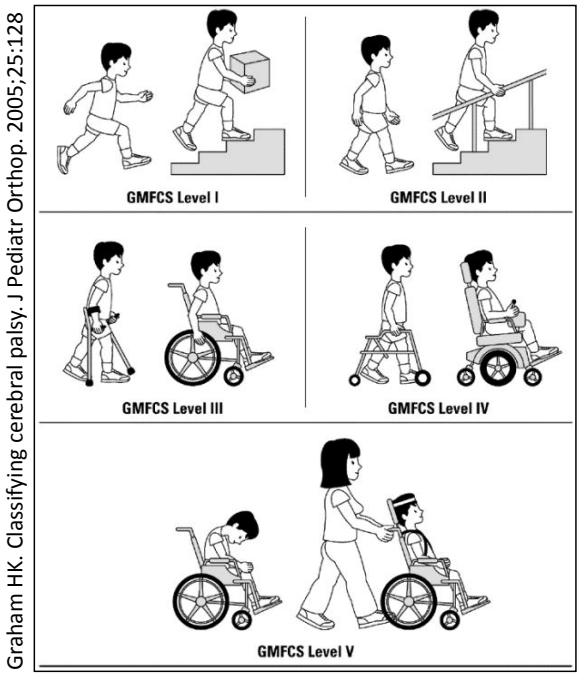
Characteristic	Specification
Precryopreservation characteristics	
Total nucleated cell count (TNCC)	$\geq 1 \times 10^7$/kg
Viability (total or CD34)	≥80%
Sterility culture	Negative
Maternal infectious disease screening[a]	Negative
Test sample available for confirmatory HLA typing	Yes
Cord blood test sample characteristics	
Identity confirmation via HLA testing of subject and cord blood sample	Confirmed
CD34 viability	≥60%
Colony forming units	Growth

[a]All mothers/units were tested for Hepatitis B, Hepatitis C, HIV, and syphilis. Most were also tested for HTLV I/II.
Abbreviation: HLA, Human Leukocyte Antigen.

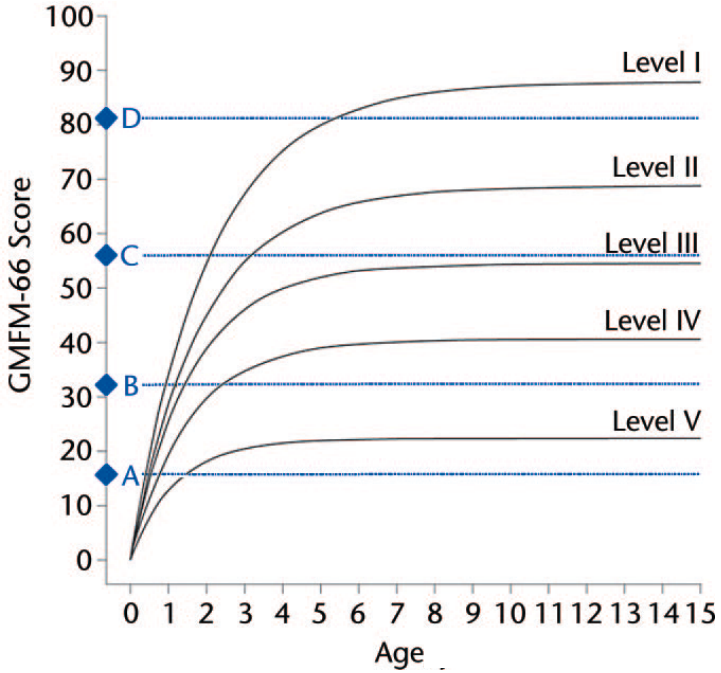
CP-AC Study Design



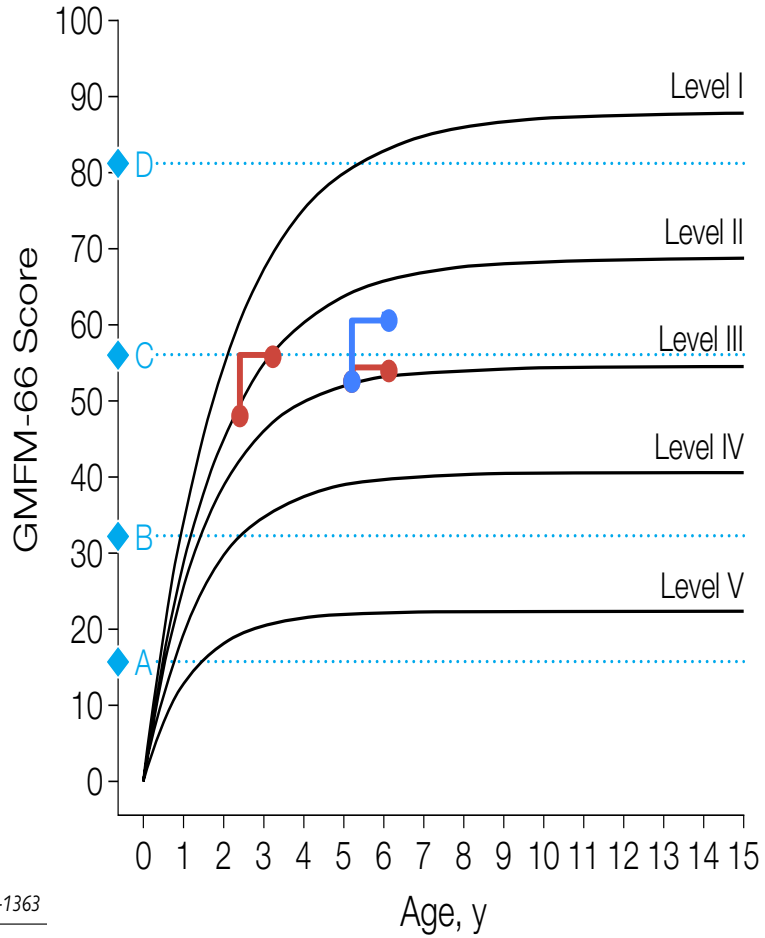
GMFM-66 Assessing Change in Study Subjects



Graham HK. Classifying cerebral palsy. J Pediatr Orthop. 2005;25:128

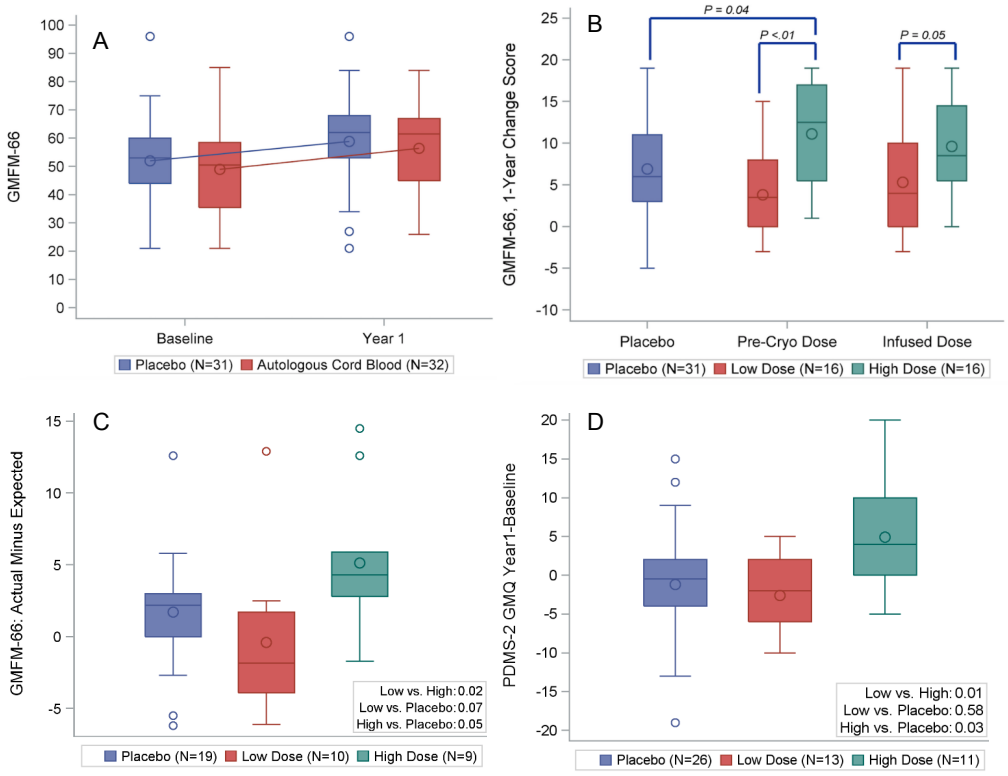


Assessing Change in Changing Subjects

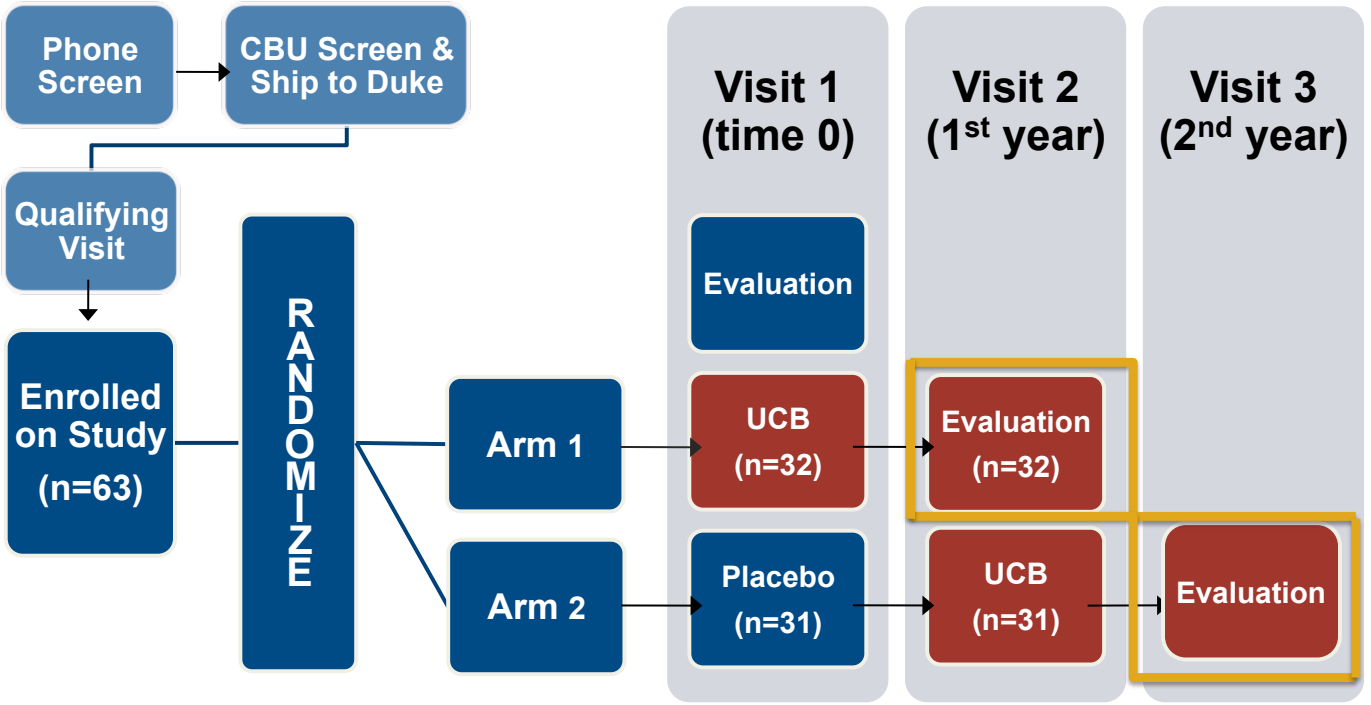


JAMA. 2002;288:1357-1363

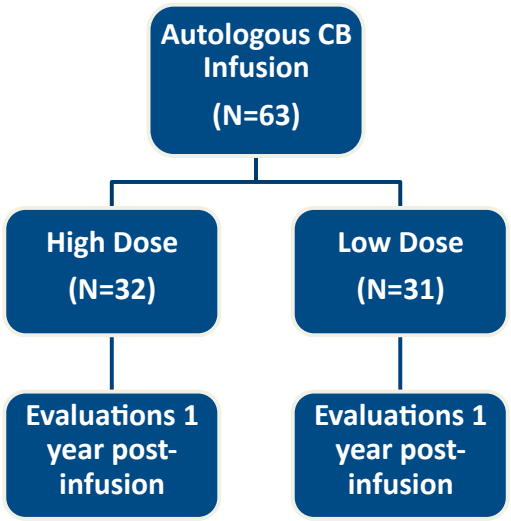
Figure 3: GMFM-66 Scores from Baseline to Year 1 by Randomized Treatment Assignment and Cell Dose



Analysis One Year after CB Infusion

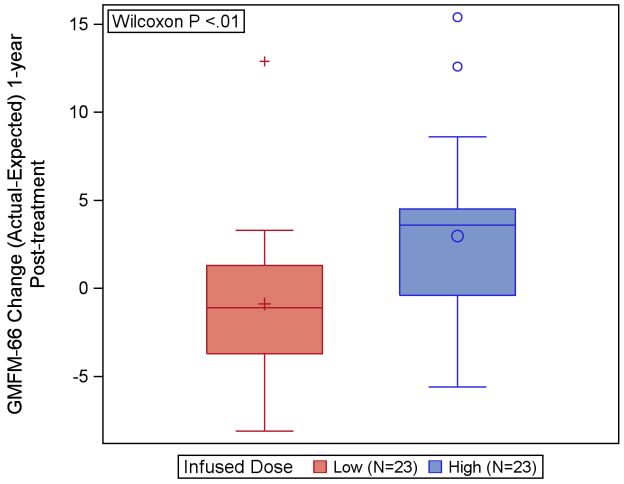


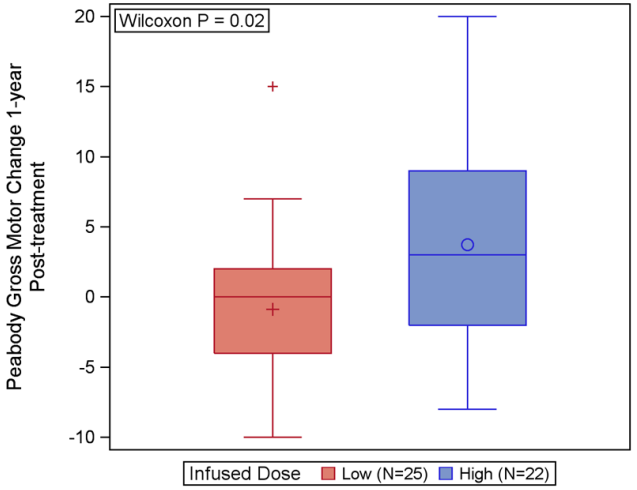
Dose Group Characteristics



	High ≥2x10^7/kg	Low <2x10^7/kg	p value
Age (median, range)	2.6 (1.1-6.3)	2.9 (1.2-8.0)	0.47
Sex			0.79
Male	22 (68.8%)	20 (64.5%)	
Female	10 (31.3%)	11 (35.5%)	
Type of CP			0.53
Hypotonic Quadriplegia	2 (6.3%)	2 (6.5%)	
Spastic Diplegia	5 (15.6%)	7 (22.6%)	
Spastic Hemiplegia	18 (56.3%)	12 (38.7%)	
Spastic Quadriplegia	7 (21.9%)	10 (32.3%)	
Baseline GMFCS level			0.19
I/II	24 (75%)	18 (58.1%)	
III/IV	8 (25%)	13 (41.9%)	
Infused TNC x10^7/kg (median, range)	3.1 (2.0-5.0)	1.5 (0.4-1.9)	<0.001

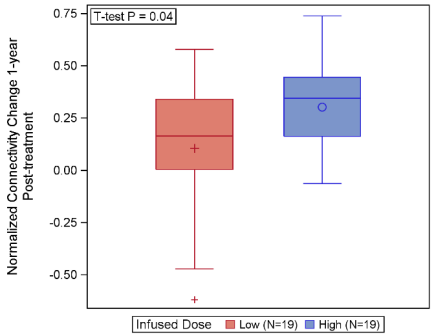
One year outcomes post UCB infusion
GMFM-66 Change and Peabody GM Scale



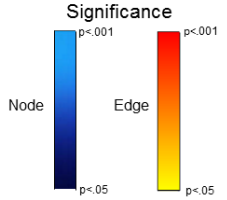


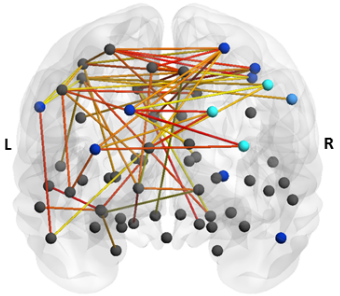
- **N = 38**
- **≥ 2 years old at the time of infusion**

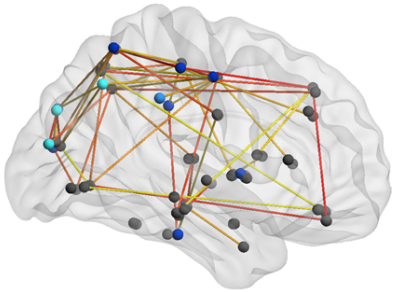
N = 47
≤ 72 months at time of follow-up

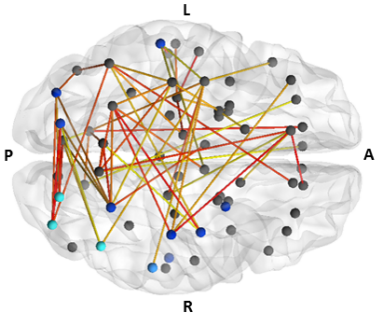


- **N = 38 with analyzable images**









UCB infusions in children with CP

- **Appropriately dosed autologous CB infusions increase motor function in children with CP. The regulatory pathway for approval of this therapy is being explored.**
- **Infusions of partially or fully-HLA matched sibling cord blood infusion are also safe and feasible in young children with cerebral palsy.**
- **There was no evidence of immune activation or persistence of donor cells in this cohort of patients treated with sibling cord blood.**
- **The efficacy of allogeneic, partially matched cord blood infusion should be studied in a Phase II clinical trial. A trial with allogeneic unrelated cord blood and cord tissue MSCs is planned.**

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Autologous Cord Blood Infusions Are Safe and Feasible in Young Children with Autism Spectrum Disorder: Results of a Single-Center Phase I Open-Label Trial

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Key Words. Autism spectrum disorder • Autologous umbilical cord blood • Cell therapy

Duke ABCs

Open-label clinical trial of autologous cord blood in young children with autism spectrum disorder

Hypothesis: Cord blood cells, acting through paracrine signaling, will modulate inflammation and suppress microglial activation in children with autism.

- **Open label trial with 25 children with autism, age 2-6 yrs (avg = 4.5), followed for 1 year**
- **Assess tolerability/safety of autologous CB infused IV x 1 with 6 and 12 month follow-up**
- **Evaluate the feasibility of the evaluation protocol**
- **Define primary and secondary endpoints for subsequent larger clinical trials**
- **Define optimal length of trial**

Open label clinical trial of autologous cord blood in young children with autism spectrum disorder

(Joanne Kurtzberg and Geraldine Dawson, Co-PIs)

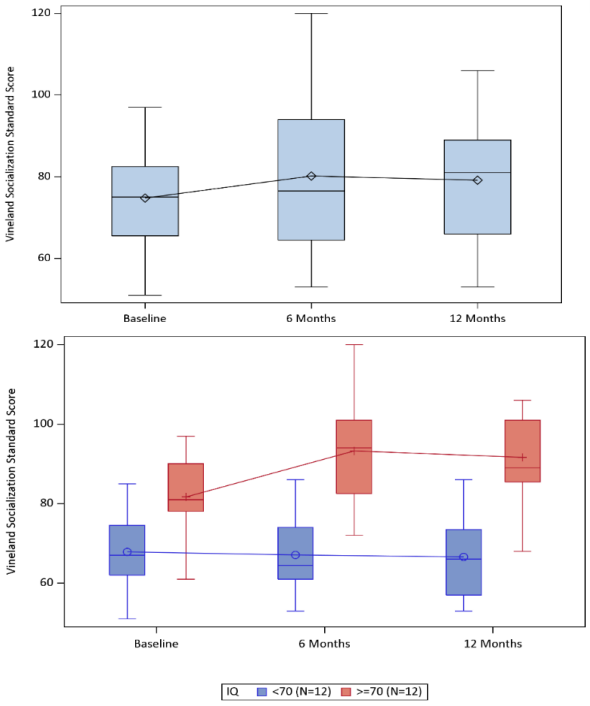
Participant Characteristics (N = 25)	
Age	2-6 years (M = 4.5 yrs)
Sex	21 males, 4 females
Diagnosis	DSM-5 ASD based on ADOS and ADI Known genetic syndromes (e.g. FraX) excluded
IQ	35 – 123 (M = 64.3)

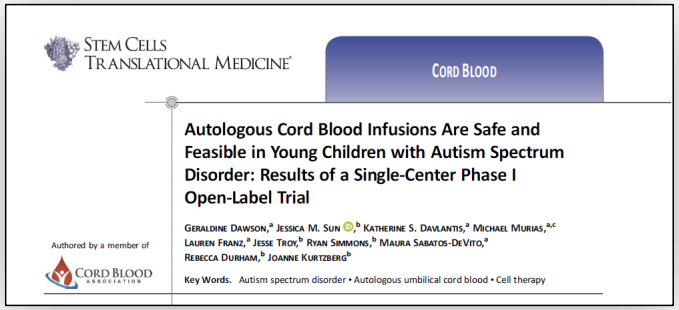
Autism Phase I - Safety results

- No serious adverse events reported
- 3 children had mild allergic reactions
  - Cough and hives during infusion (1 child)
  - Cough post-infusion (2 children)
- 1 parent reported that their child was more irritable for 2 days post-infusion
- **Conclusion: Preliminary safety/tolerability appears to be very good**
- **Endpoints were defined**

Improvements in social behavior

Primary endpoint: Vineland Adaptive Behavior Scale – Socialization Standard Score





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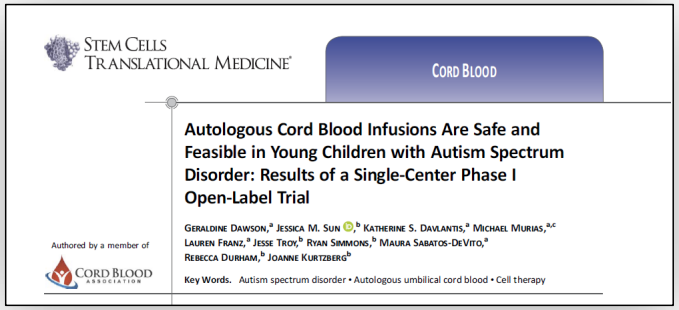
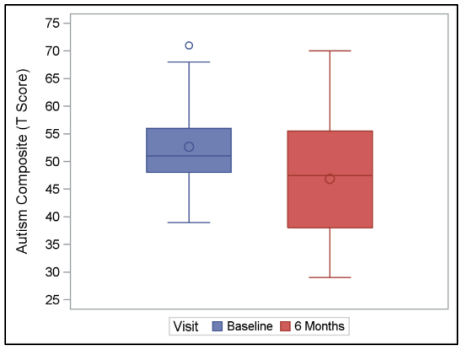
- Significant increase in socialization standard score ($p = 0.02$)
- Scores expected to *decrease* over time.
- 13/25 participants showed stable or increasing scores.
- Increase was not correlated with number of hours of behavioral intervention received.
- Children with higher baseline IQ had greater response.

Secondary Outcome Measures

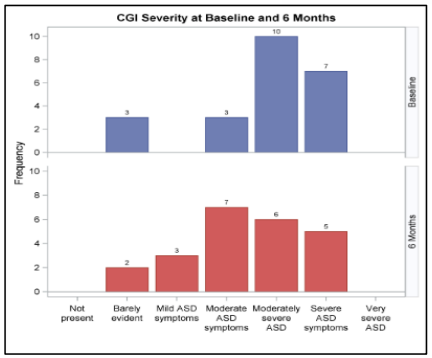


PDD-BI Total Autism Symptoms



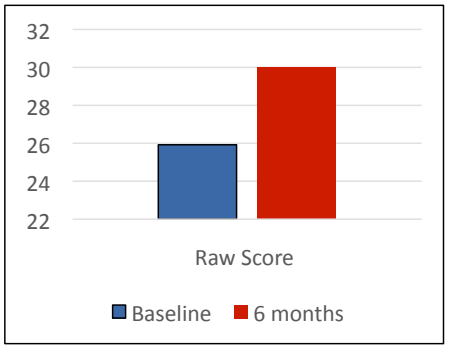
Autism symptom composite T-score; median change = 7 point decrease (p = 0.01)

CGI – Severity Ratings



The median change score is significantly different from zero (p=0.01, Wilcoxon signed rank test)

Expressive Vocabulary



Statistically significant increase in expressive vocabulary ($p < .0.001$); 15 of the 25 patients improved, 7 exhibited no change, 1 declined

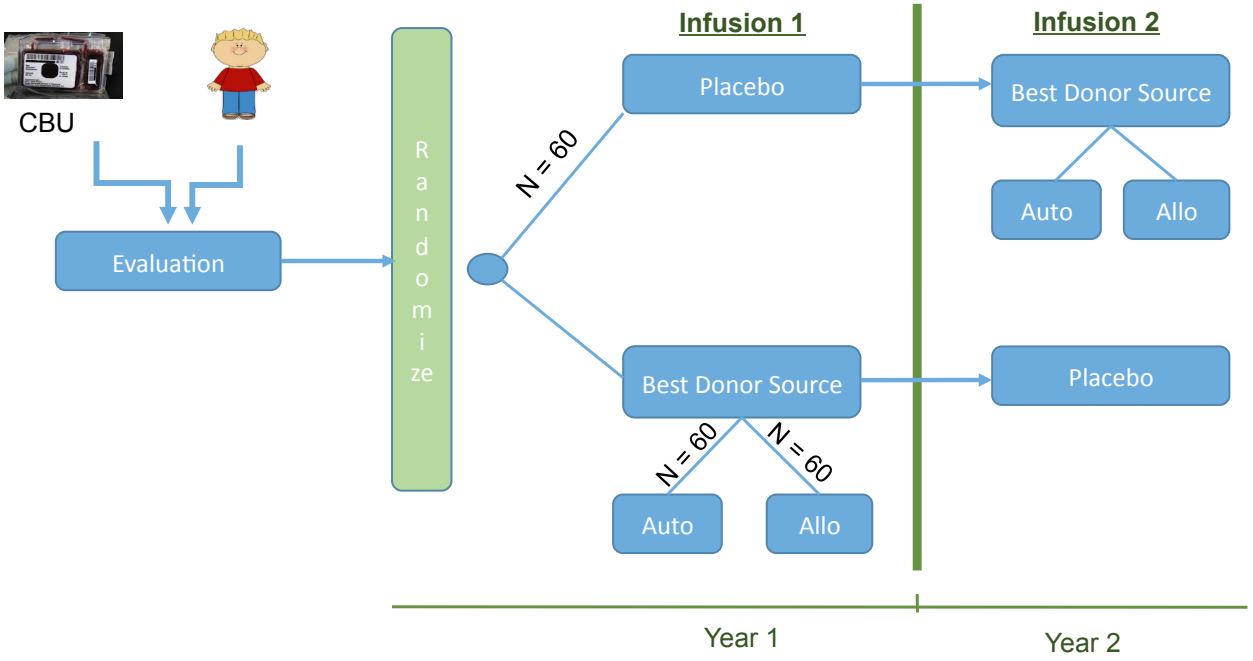
Duke Robertson Clinical and Translational Cell Therapy (CT²) Program

Duke Center for Autism and Brain Development

Phase II Study Design: DukeACT

- 180 Children with ASD 2-7 years of age
- Children evaluated at baseline and 6 months later and assessed remotely via parent questionnaire at 12 months
- **Primary endpoint**: Social communication skills assessed by Vineland Adaptive Behavior Scales Interview
- **Secondary endpoints**: Pervasive Developmental Disorder Behavior Inventory (parent report), Clinical Global Impression (clinician), Expressive One-Word Vocabulary (clinician), Safety and Tolerability
- **Exploratory**: GI symptoms, Eye-tracking, EEG, and MRI

Autism CBU "Best Donor" Trial Design



Expanded Access Protocol

- For infusions of autologous and haplo or fully matched qualified sibling cord blood in children with CP, ASD, HIE, and other related brain injuries.
- IND/IRB, parental informed consent
- Cost of care, not product, charged to third party payers
- 3 day visit: Outpatient
- IV infusion of washed cord blood cells on day 2 in the Duke CHC VDH
- Follow up remotely per diagnosis
- Data reported to the CIBMTR
- Hundreds of patients have approached Duke for enrollment on this protocol. Capacity is limiting.

? What are the next steps?

- **End of Phase 2 meeting with the FDA**
  - ✓ **Is this the appropriate meeting to have?**
- **Potential pathways to approval:**
  - ✓ **361 product**
    - **Homologous use**
    - **NMMM**
    - **Autologous or sibling**
  - ✓ **351 product**
    - **Conduct a single arm, open label phase III study to confirm observations in Phase II**
    - **Conduct a randomized, phase III study, multicenter**

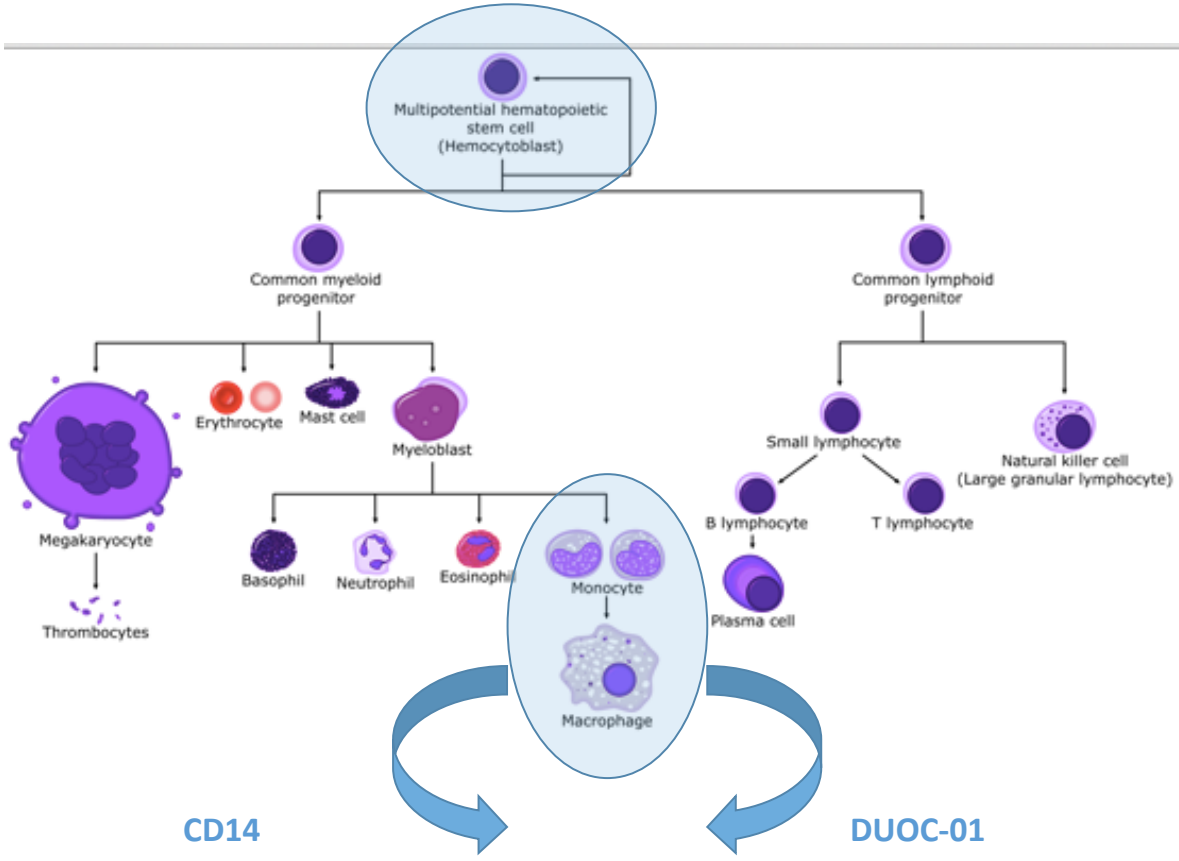
? About a BLA

- **If a BLA is required**
  - ✓ **Who obtains the BLA?**
    - **No guidance for private/family banks**
    - **Highly unlikely the private banks will do so.**
    - **Not practical for each bank to get its own BLA**
  - ✓ **Could treatment facility(ies) obtain a treatment BLA?**
    - **Consider the CBU from the private bank as source material**
    - **Use qualification specifications per IND**
    - **Is there a role for a shared BLA?**

? About homologous use

- For products with heterogeneous populations, can multiple homologous uses be identified?
- Will the FDA accept this approach for cord blood where there are many different types of therapeutic cells?
  - ✓HSCs
  - ✓T-cells
  - ✓NK cells
  - ✓Monocytes
    - CD14 cells

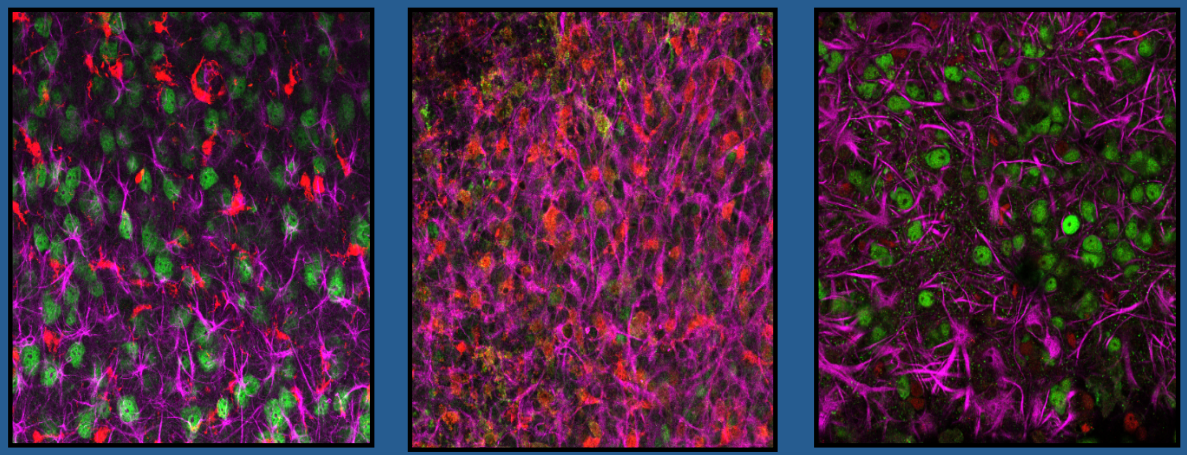
Types of Cells in Cord Blood



CD14
Hypoxic Injury

DUOC-01
Remyelination

Effects of CB CD14+ monocytes on OGD in brain slice cultures



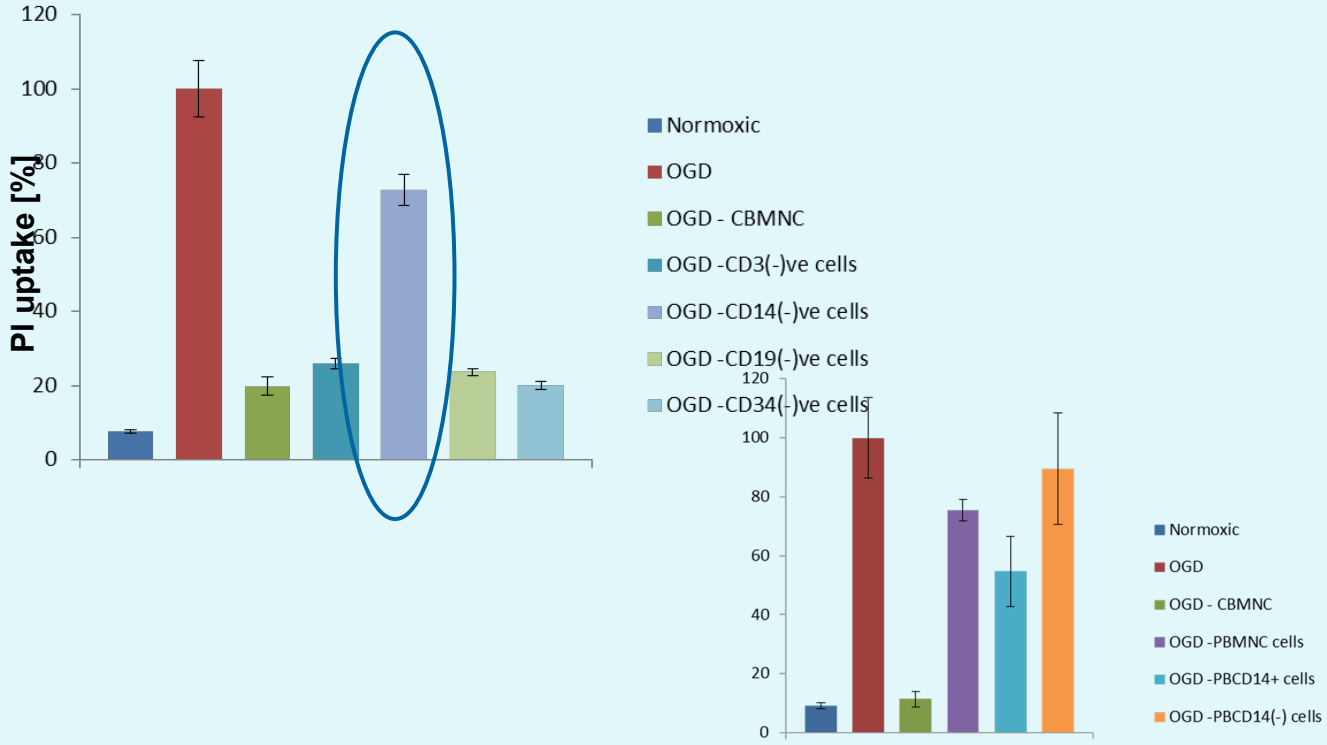
72h Control- No OGD

72-hr post OGD

72h post OGD
CB CD14 (+)

GFAP, NeuN, Iba1

Identification of CB populations that protect brain cells from OGD in cortical slice cultures



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Human Umbilical Cord Blood Cells Ameliorate Motor Deficits in Rabbits in a Cerebral Palsy Model

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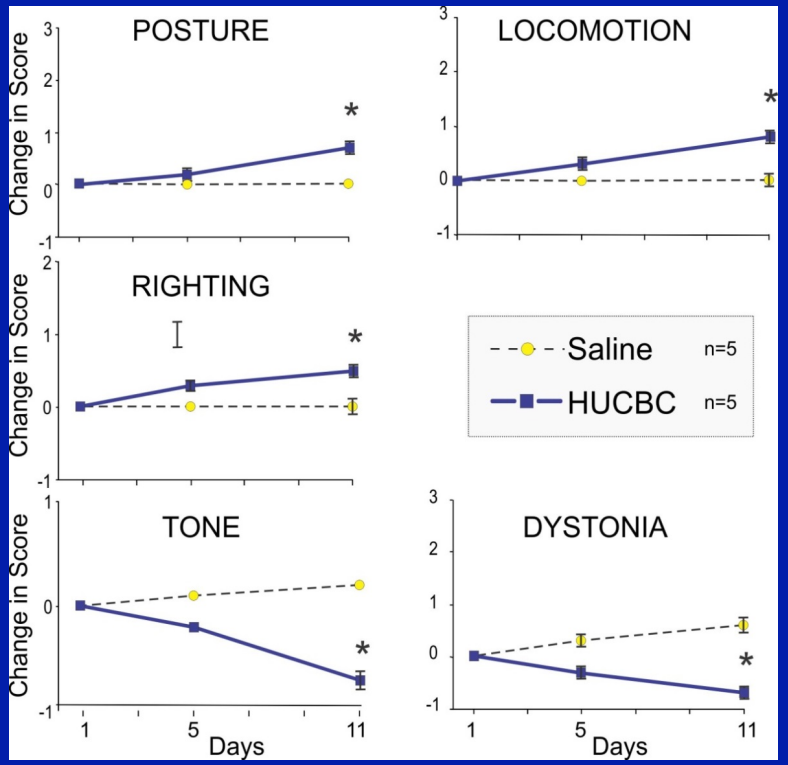
MOTOR FUNCTION AFTER CORD BLOOD

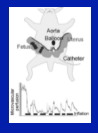
Intrauterine hypoxia e22
C/S e31
Severe phenotype
4 hours postnatal
2.5.0x10^6/ml saline IV

HUCB Cells improve Motor Function in rabbit CP model.

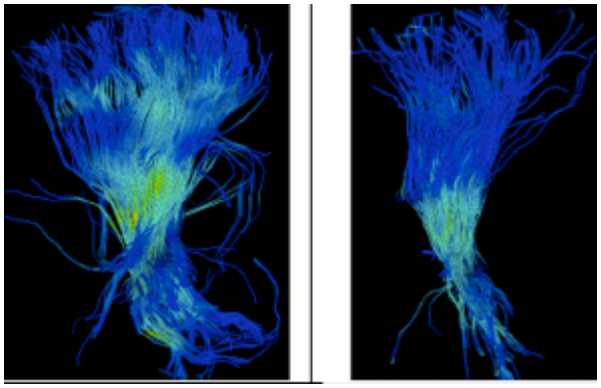
Replication
- **same volume (1 ml)**
- **lower dose (2.5 x 10^6)**
- **Compared cells to media+saline**
- **Improved outcome**
- **No increase in mortality**

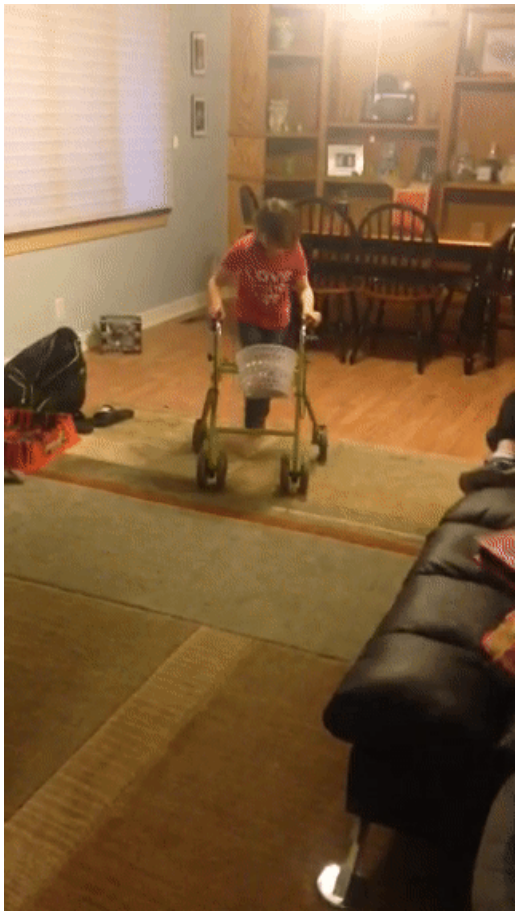


Drobyshevsky A, Cotten CM, Shi Z, Luo K, Jiang R, Derrick M, Tracy ET, Gentry T, Goldberg RN, Kurtzberg J, Tan S. Human Umbilical Cord Blood Cells Ameliorates Motor Deficits In Rabbits In a Cerebral Palsy Model. Developmental Neuroscience, *accepted for publication*, January 2015



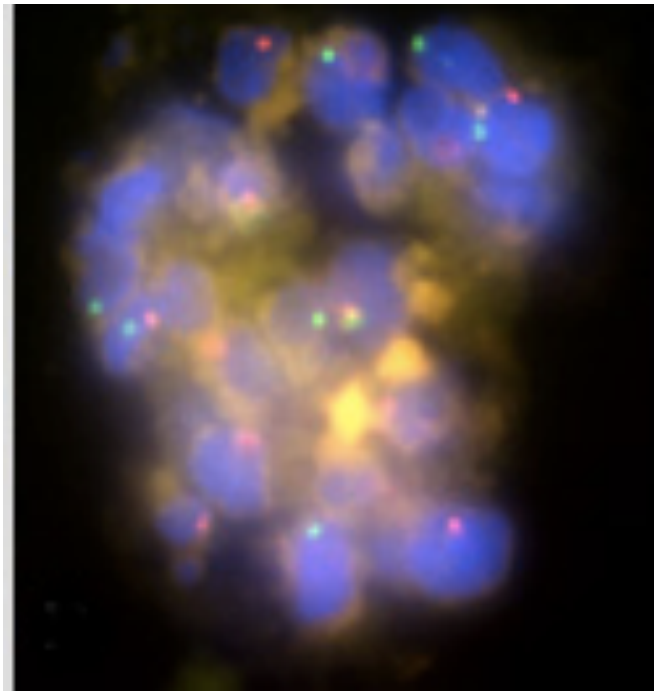
<u>UCBT for EIKD:</u>
Functional Outcomes vary with best outcomes in babies transplanted in the first month of life

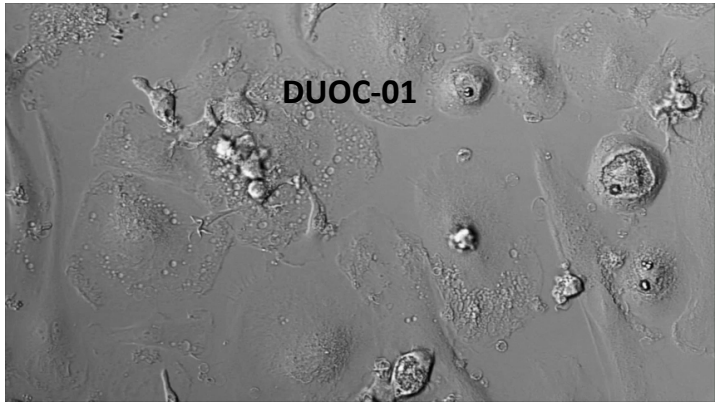


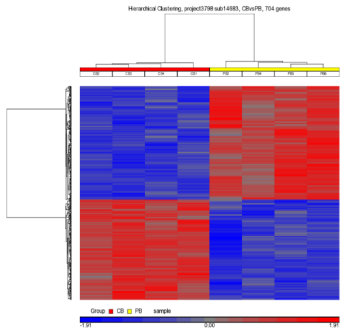


kids rule

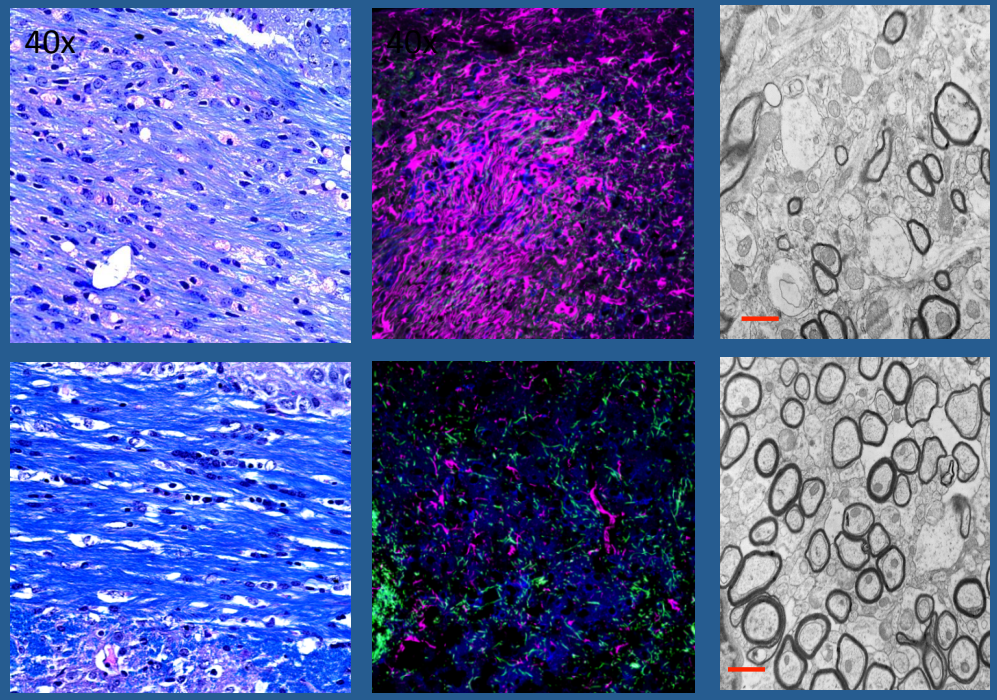
Donor Cells engraft in the brain after IV UCBT







DUOC-01 treatment accelerates remyelination of corpus collosum



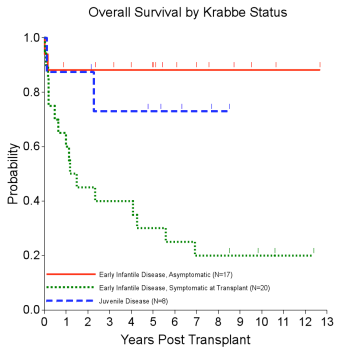
Potential mechanisms of DUOC-01 action

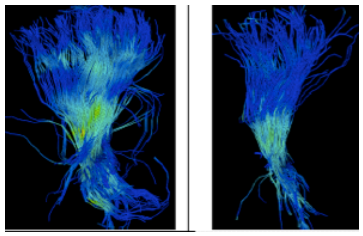
- Enzyme replacement
- "Clean up"
- Cytokine secretion:
  - Modulate inflammation
    - [IL10, IL6, TGF-beta]
  - Drives oligodendrocyte proliferation
  - Promotes myelination

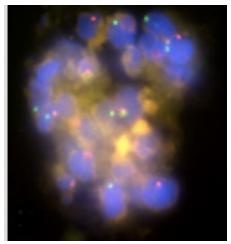
Gene name	Fold change Mean ±SEM	*P*-value
PDGF-α	**32.3**±8.3	≤0.01
IGF-1	**799**±294	≤0.05
SCF-1	**26.7**±4.8	≤0.033
MMP9	**632**±109	≤0.002
MMP12	**2057**±460	≤0.006
TREM2	**1634**±368	≤0.011

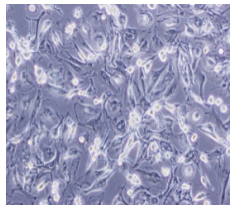
Fold increase DUOC-01 relative to CB CD14+ by RTqPCR. N>3

THE DEVELOPMENTAL PATHWAY FOR DUOC-01
2007-2015

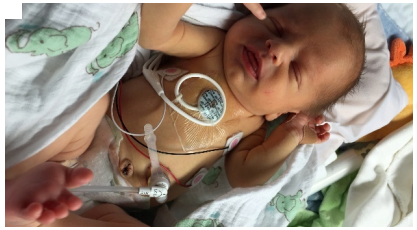








Day 0 IV



OUTCOMES

Day 28 IT

Begin D7

16 Patients treated with DUOC-01

17 and 18th patients pending

2 reversible reactions in 2/3 patients receiving different donor DUOC cells

Hard to assess efficacy in these diseases which have improvement and variable courses post transplant

Enhancing manufacturing using entire CBU

Planning clinical trials in adult demyelinating diseases

Conclusions

- Banked umbilical cord blood has great potential for use as a regenerative therapy.
- Results in children with ASD and CP are encouraging.
- There is a huge demand for use of 361 products at the current time.
- Pathways for regulatory approval for these products are unclear
  - If the homologous use premise is accepted by FDA, they can be utilized in the clinic under practice of medicine;
  - If not accepted, the entity obtaining a license is not clear and the pathway forward is also not clear.
  - Consideration of a use license considering 361 cord blood products as source materials may be a possible solution.
  - Would it be possible to have a broad license shared by multiple clinics?

BACK-UP SLIDES

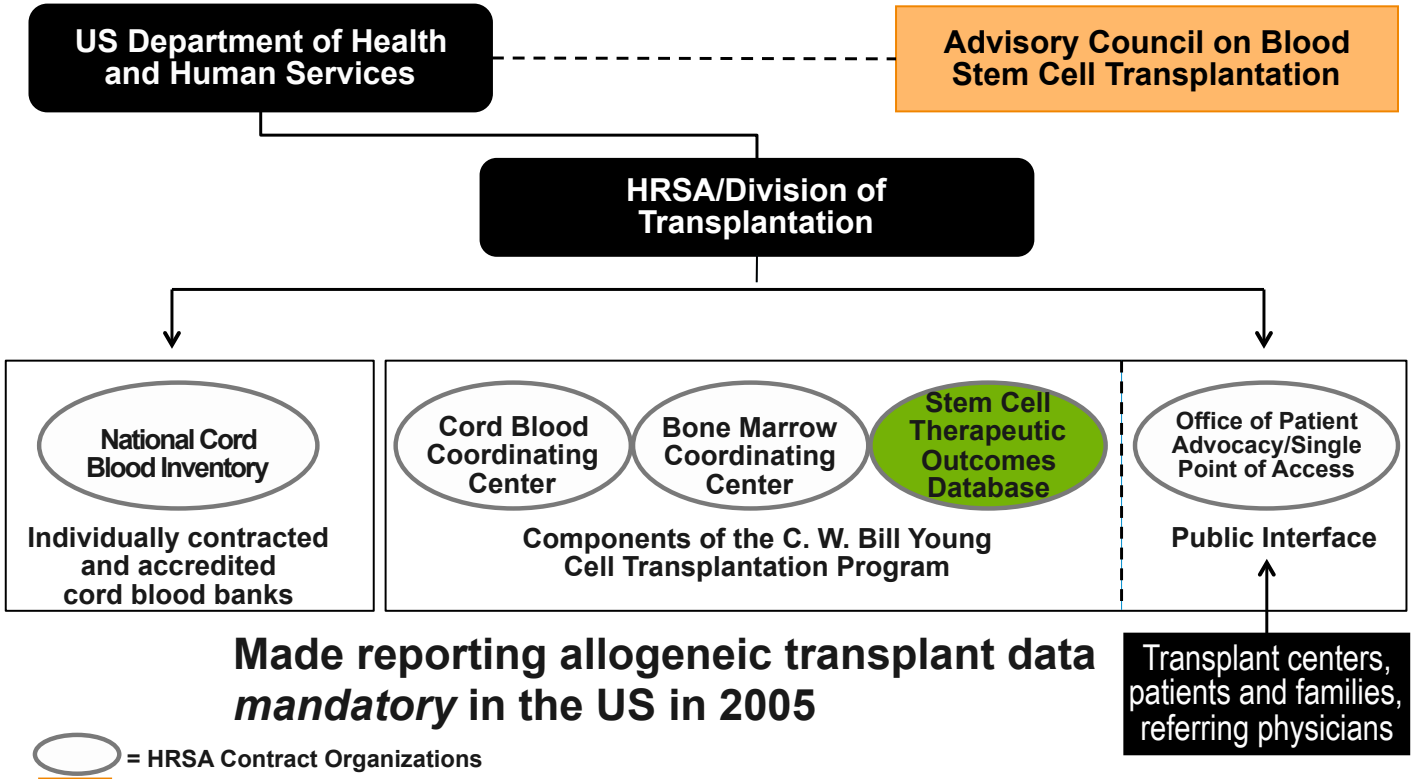
Timelines

- **1988- 1st UCBT (MRD – 5 yo with FA)**
- **1991- 1st US Public Bank (NYBC – Rubinstein)**
- **1993- 1st URD UCBT (4yo T-ALL, Duke/Kurtzberg)**
- **1996- Report of 1st 25 patients UCBT (Kurtzberg)**
- **1998- Report of 562 UCBT (Rubinstein)**
- **1999- COBLT Banking and Transplant Study (NIH)**
  - Establishment of 3 additional CBBs
  - Multiple prospective, multicenter Phase II clinical trials
- **2005- COBLT publications**

Timelines - 2005- Stem Cell ACT OF 2005

- Established ***CW Bill Young Cell Transplantation Program***
- Mandate to FDA to regulate/license public CBBs
- Established the ***NCBI*** network of public CBBs with subsidized funding to increase accrual of minority donors to the registry
- ***Single Point of Access Registry*** for adult and cord blood donors – contract to NMDP
- -Established the ***Stem Cell Transplant Outcomes Database*** – contract to CIBMTR
- Coordinating Centers for Adult and CB donors – contract to NMDP
- Advisory Council for Blood Stem Cell Transplantation

C.W. Bill Young Cell Transplantation Program*



Made reporting allogeneic transplant data *mandatory* in the US in 2005

= HRSA Contract Organizations

= Other New Organizations or Relationships

CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

* Created by the Stem Cell Therapeutic and Research Act of 2005 and the Stem Cell Therapeutic and Research Reauthorization Act of 2010

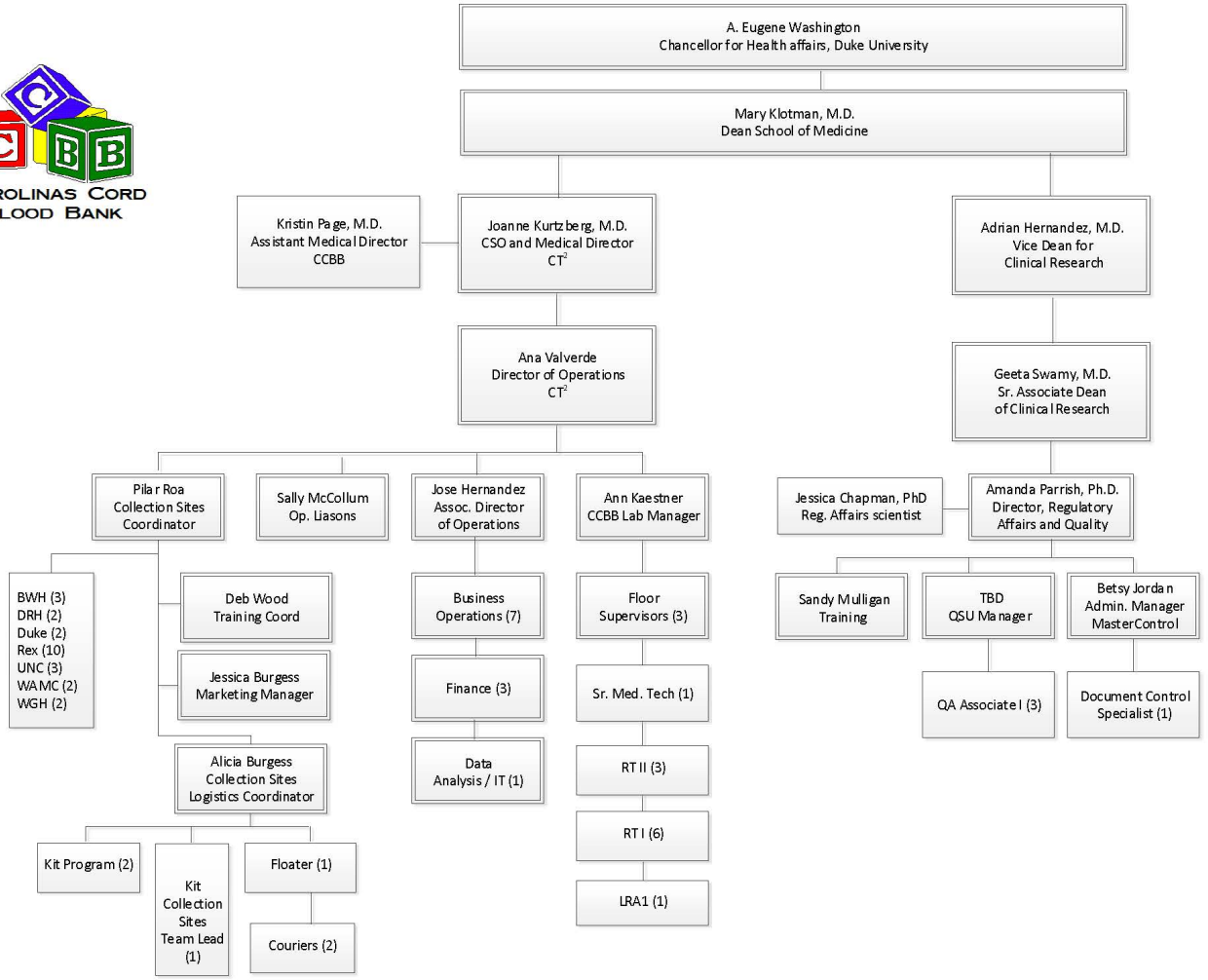
Timelines

- **2005- Mandate to FDA to regulate public CBBs**
- **2005- NMDP holds IND for public CBBs**
  - Center for Cord Blood (17 banks)
- **2005- FDA Docket to report UCBT outcomes**
  - Multiple TCs report to banks and CIBMTR
- **2011- FDA issues final guidance for CB licensure**
- **2012- First licenses issued to the NYBC, Colorado, Duke**
- **2017- Public inventory ~800K, Private inventory >5M**
- **2017- ~100 public banks registered with WMDA; hundreds of private banks worldwide**

Carolinas Cord Blood Bank - History

- Established 1997 through COBLT/NHLBI contract (IND)
- Current inventory ~40,000 units
- 10 collection sites with access to >55,000 births/year
- Staff, hybrid and kit collection models
- Units listed and distributed through NMDP for HSCT
- NMDP Member bank 2004-present (IND)
- FACT accreditation 2005-present
- FDA Masterfile 3/2005-closed at licensure
- HRSA: NCBI Bank 2006-present (cohorts 1 and 5)
- Netcord Bank 2007-present
- CAP Accreditation/CLIA Certified 2010 - present
- BLA received October 4, 2012

CAROLINAS CORD BLOOD BANK



Routine Testing of Cord Blood

Pre-Processing Sample (Whole Cord Blood + CPD)	Post-Processing Sample (HPC-C)
• Pre-processing TNCC	• Post-Processing TNCC
• ABO/Rh testing	• Viability
• Manual Diff (if applicable)	• Sterility (on CBU RBC/Plasma)
	• CMV PCR (on CBU Plasma) for CMV + Moms
	• Viable CD34+
	• CD3, 4, 8
	• Colony Forming Units (CFU)

Maternal IDMs
Maternal HLA
Baby NBS - hemoglobinopathies

Cord blood and maternal reference samples of whole blood, plasma, serum, FTA cards

Stem Cell Lab

HLA **DoD**

Release testing on Segment: ALDHbr, Viability of CD34 and CD45 cells, CFUs

Current Criteria for Banking and Release to Donor Registry under the BLA

- ≥60ml / ≥80ml collection volumes (Minority / Caucasian)
- ≥1x10e9 TNCC pre processing
- ≥0.9x10e9 TNCC post processing
- ≥90% Viability post processing
- ≥ 1.25x10e6 viable CD34
- + CFU Growth
- Negative Sterility Testing
- Negative donor screening tests (except CMV) and donor screening questionnaires
- Negative Hemoglobinopathy screen for homozygous disease

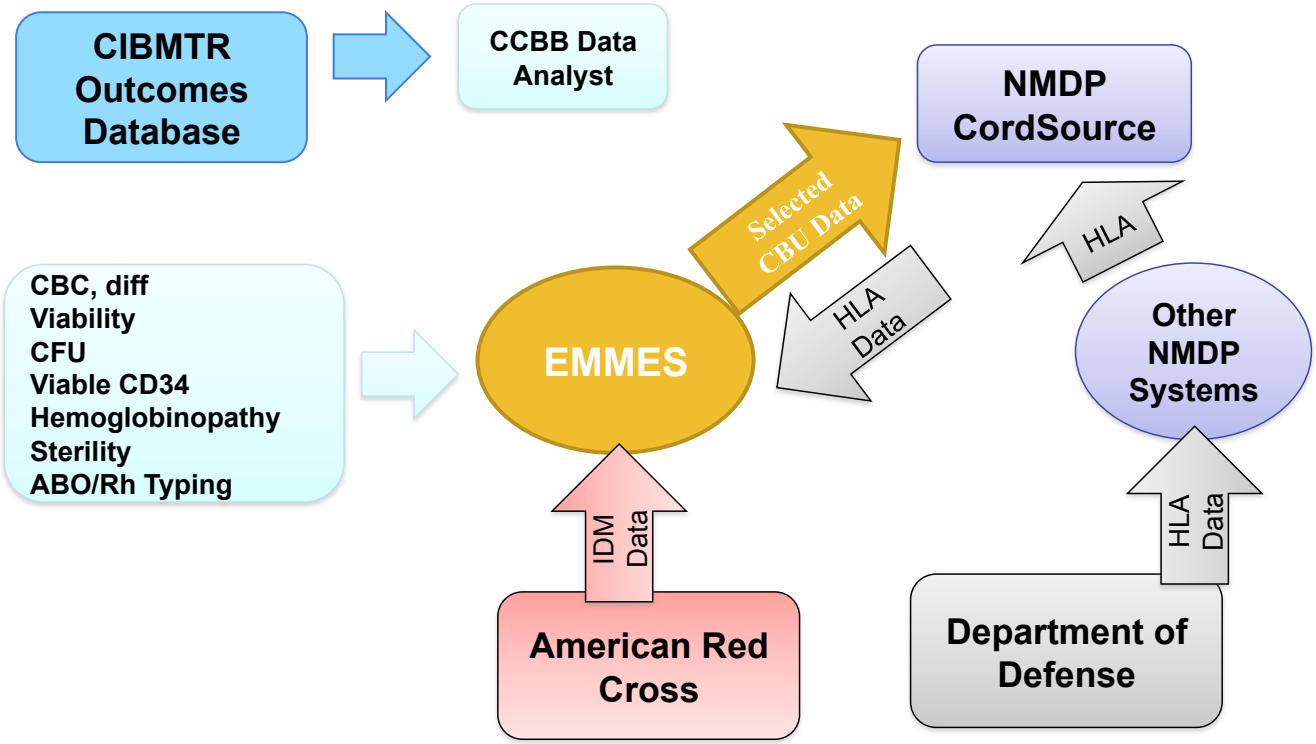
SAE and AE Reporting

- **SAE**
  - Transplant Centers report directly through the web-based FormsNet system which distributes the report to the NMDP and to the CBB in realtime.
- **AE**
  - Transplant Centers report to the CIBMTR on a scheduled basis. Reports are downloaded to the cord blood bank monthly.

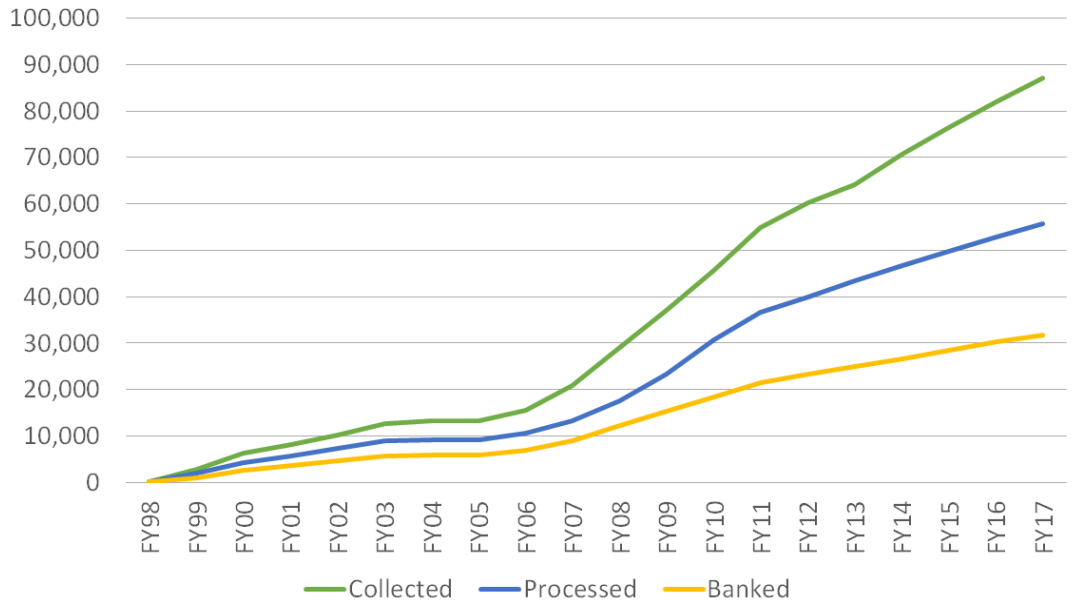
Investigations and Reporting

By the NMDP if the unit was distributed under IND
By the CBB if the unit was distributed under BLA

CCBB Information Systems



Collected vs. Bankable CBUs



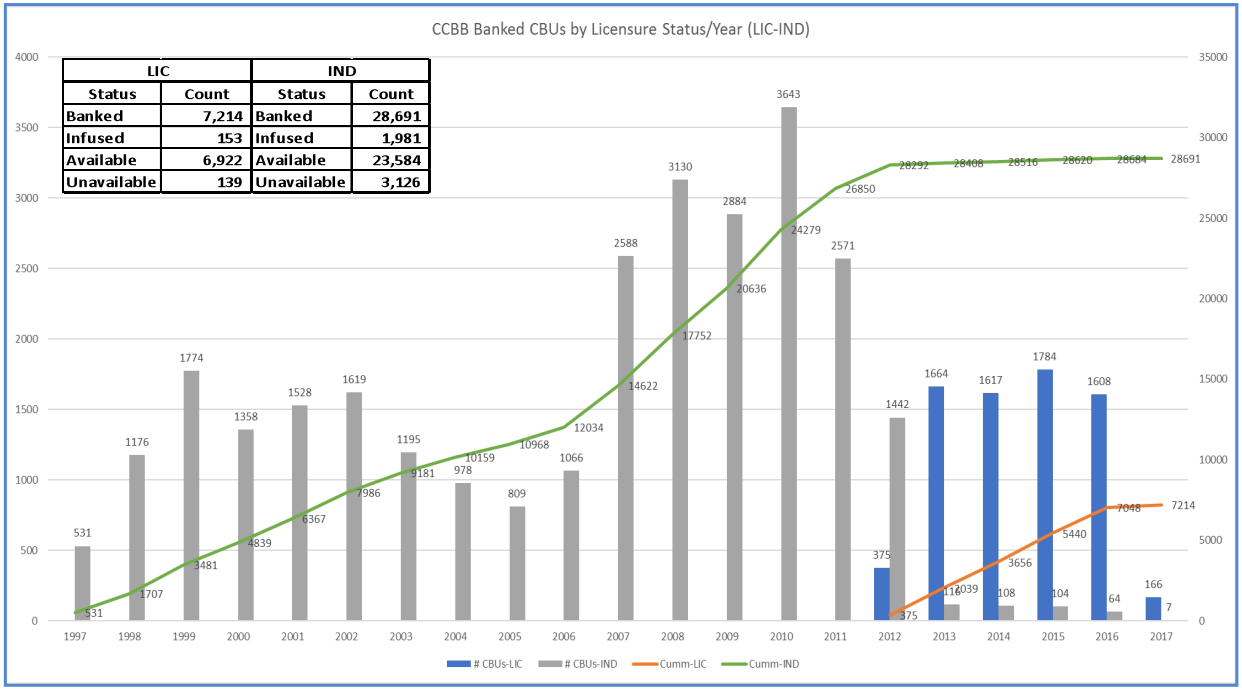
* FY defined as 7/1 – 6/30. Cumulative data for CCBB sites from EMMES data.

CCBB Total Units Banked by Licensure Status (1997-2017)

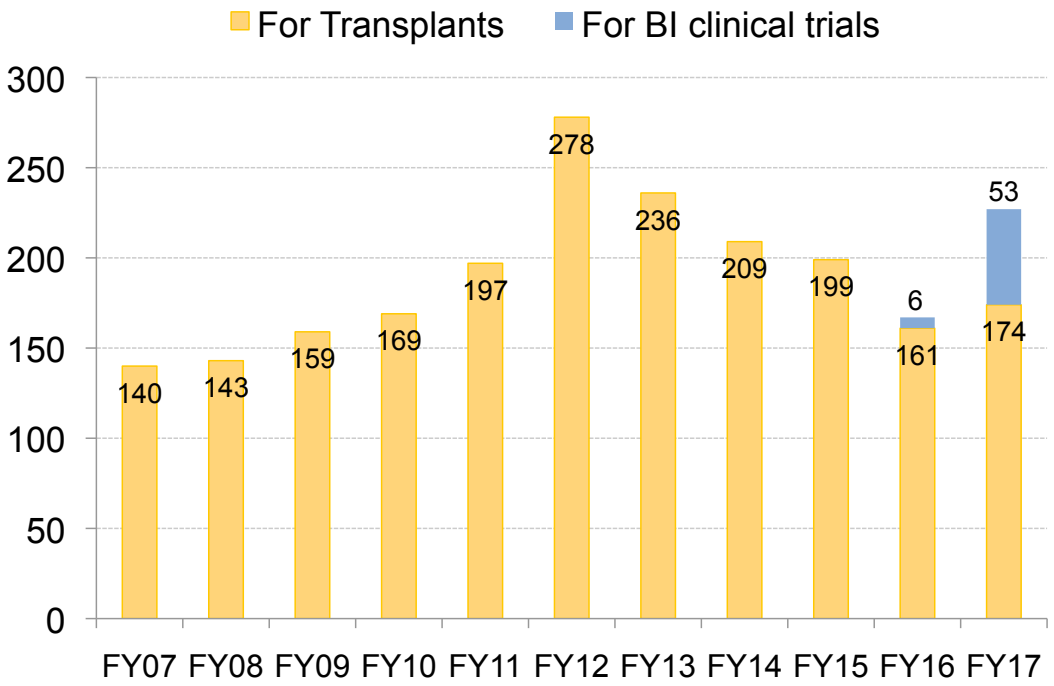
Source: CordSource as of 06/07/2017

Last units registered collected March2017

LIC		IND	
Status	Count	Status	Count
Banked	7,214	Banked	28,691
Infused	153	Infused	1,981
Available	6,922	Available	23,584
Unavailable	139	Unavailable	3,126



CCBB Units Distributed to Patients



FY defined as May-April

Applications of unrelated donor UCB

- **Provide a source of hematopoietic stem and progenitor cells for hematopoietic reconstitution after myeloablative therapy.**
- **Can substitute for BM in all proven indications:**
  - Hematological malignancies, hemoglobinopathies, bone marrow failure, congenital immunodeficiencies, certain inherited metabolic diseases.
- **Can be utilized without full HLA matching increasing access to HSCT for patients of minority ancestry.**

Applications of unrelated donor UCB

- **Lower relapse rates in patients with high risk HM, especially those with MRD at the time of transplant.**
- **Superior outcomes in pediatric patients with certain inherited metabolic diseases compared to adult donor sources.**
- **Newer applications in regenerative therapies in clinical trials.**