SHARE THE SCIENCE

TODAY:

Novel Applications of Cord Blood Derived Therapies for Genetic and Acquired Brain Diseases

Presented by

JOANNE KURTZBERG, MD
WHAT IS SHARE THE SCIENCE?

A webinar series focused on cellular therapy topics and trends
Breakthroughs and research | News | Opinions | Distinguished experts

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Share the Cord Foundation | Mediware
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Developed the first blood transfusion software to be FDA 510(k) cleared to secure the safety of the US blood supply

**Innovator**
Breakthrough software solutions that allow healthcare and public health providers and payers to be more efficient and effective

**Leader**
+5,000 customer facilities around the world, including USA, Canada, Ireland, UK, South Africa, Holland, Belgium, and Singapore
Solutions that empower healthier communities

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Blood Banks & Centers
HME/DME
Rehabilitation
Respiratory
Behavioral Health
Institutional Pharmacy

Cellular Therapy
Home Health
Hospice
Home Infusion
Specialty Pharmacy
Homeless Management
Long-Term Services & Supports
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- **Optimize processes** with tools for comprehensive management of stem cell transplants

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- **Manage multiple business lines** with one, comprehensive system

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Transtem Patient™
The solution for cancer centers and bone marrow transplant programs
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Learn more about Save the Cord Foundation and saving cord blood

savethecordfoundation.org
Joanne Kurtzberg, MD

- Medical Director of Carolinas Cord Blood Bank
- Chief Scientific Officer and Medical Director of the Robertson Clinical and Translational Cell Therapy Program at Duke
TREATING BRAIN DISORDERS WITH CORD BLOOD THERAPIES

Joanne Kurtzberg, MD
Duke University Medical Center
UCBT History

- 1st Transplant, France 1988 – MRD
- 1st unrelated donor CB bank, NYBC 1992
- 1st unrelated transplant, Duke 1993
- Now >40,000 transplants and >160 banks worldwide
- Public Inventory ~230K US, >700K worldwide
- Private Inventory ~5M worldwide

Legislation: CW Bill Young Cell Transplantation Program
- Coordinating centers, registry, outcomes database
- NCBI banking network

Regulations: Guidance for FDA Licensure 10/20/2011
- Now 7 licensed CBBs in the USA
- ~4,000 transplants annually around the world
- Novel uses in CT and RMbare emerging
Key Observations about UCBT

- Cord blood could substitute for bone marrow as a donor for HSCT for all standard allogeneic indications
  - Hematological malignancies, marrow failure, immunodeficiencies, hemoglobinopathies, certain inherited metabolic diseases
- Cell dose matters and single cord blood unit may be on the cusp or too small for larger individuals
- HLA matching also matters, but lesser matches can be utilized when higher cell doses are administered
- Immune reconstitution is delayed
- GvHD is decreased as compared to adult HSCT sources
- Results are comparable to MRD and MUD
- Relapse may be lower post CBT versus other HSCT sources
Types of Cells in Cord Blood
Autologous UCB Trials at Duke

- Safety
  - Cryopreserved UCB, 184 patients
  - Sun et al, Transfusion, 2010
- HIE Study “Babybac”
  - Fresh, VR, RR, UCB
  - Cotten et al, J Peds, 2014
- Congenital Hydrocephalus
  - Multiple doses of auto UCB
  - Sun et al, Pediatric Research, 2015
- HLHS/ECMO
  - Fresh and cryopreserved
- CP
  - Cryopreserved
- Autism
  - Cryopreserved
  - 25 patient safety/endpoint finding study in progress
Allogeneic Cord Derived Therapies

Ongoing:

- **DUOC-01, Phase I/II**
  - Acute Stroke in Adults, Phase II
  - Non HLA Matched
  - ABO/Rh matched
  - 4 sites
  - 110 patients to be enrolled
    - Phase I, 10 patients, completed

- **Sibling CP**
  - 15 patients treated, in follow up phase

**Best donor in children with ASD, Phase II**

- 165 patients, 2:1 randomization against placebo

- Cord tissue MSCs (huCT-MSC) in ASD, Phase I

Planned:

- **Allogeneic CP Phase II**
- MSC versus CB Autism Phase II
Diseases Treated (N=>350)
Median follow-up 10.3 years

Krabbe Disease
Metachromatic Leukodystrophy
Adrenoleukodystrophy
Mucopolysaccharidoses
  Hurler, Hunter, Sanfilippo
Neimann Pick Disease
Maroteau Lamy
PMD
Batten Disease
Others

Unrelated cord blood donor
Myeloablative chemotherapy
Average 56 day hospitalization
12-18 month recovery
Risk of GvHD and TRM
Types of Cells in Cord Blood

Multipotential hematopoietic stem cell (Hemocytoblast)

Common myeloid progenitor
- Erythrocyte
- Mast cell
- Myeloblast
- Basophil
- Neutrophil
- Eosinophil
- Monocyte
- Macrophage

Common lymphoid progenitor
- Small lymphocyte
- Natural killer cell (Large granular lymphocyte)
- B lymphocyte
- T lymphocyte
- Plasma cell

CD14
Hypoxic Injury

DUOC-01
Remyelination
Donor Cells engraft in the brain after IV UCBT
DUOC-01 treatment accelerates remyelination of corpus collosum.

Control

DUOC-01

Luxol Fast Blue

Iba1(blue), GFAP (pink), MBP(green)

Myelination & myelin quality
Potential mechanisms of DUOC-01 action

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

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Fold change Mean ±SEM</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDGF-α</td>
<td>32.3±8.3</td>
<td>≤0.01</td>
</tr>
<tr>
<td>IGF-1</td>
<td>799±294</td>
<td>≤0.05</td>
</tr>
<tr>
<td>SCF-1</td>
<td>26.7±4.8</td>
<td>≤0.033</td>
</tr>
<tr>
<td>MMP9</td>
<td>632±109</td>
<td>≤0.002</td>
</tr>
<tr>
<td>MMP12</td>
<td>2057±460</td>
<td>≤0.006</td>
</tr>
<tr>
<td>TREM2</td>
<td>1634±368</td>
<td>≤0.011</td>
</tr>
</tbody>
</table>

Fold increase DUOC-01 relative to CB CD14+ by RTqPCR. N>3
THE DEVELOPMENTAL PATHWAY FOR DUOC-01 2007-2015

OUTCOMES

Day 0 IV

Day 28 IT

Begin D7
Types of Cells in Cord Blood

Multipotent hematopoietic stem cell (Hemocytoblast)

- Common myeloid progenitor
  - Erythrocyte
  - Mast cell
  - Myeloblast
  - Basophil
  - Neutrophil
  - Eosinophil
  - Monocyte
  - Macrophage
  - Plasma cell

- Common lymphoid progenitor
  - Small lymphocyte
  - Natural killer cell (Large granular lymphocyte)
  - B lymphocyte
  - T lymphocyte

CD14
Hypoxic Injury

DUOC-01
Remyelination
Effects of CB CD14+ monocytes on OGD in brain slice cultures

GFAP, NeuN, Iba1
Identification of CB populations that protect brain cells from OGD in cortical slice cultures

PI uptake [%]

- Normoxic
- OGD
- OGD - CBMNC
- OGD - CD3(-)ve cells
- OGD - CD14(-)ve cells
- OGD - CD19(-)ve cells
- OGD - CD34(-)ve cells

For detailed analysis, please refer to the accompanying graphs.
CP-AC Trial
A prospective, randomized, placebo-controlled, blinded, cross-over trial of autologous cord blood infusion in young children with spastic cerebral palsy
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
- Primary endpoint: Change in GMFM score
- Follow up at 1 and 2 years
CP-AC Study Design

1. Phone Screen
2. CBU Screen & Ship to Duke
3. Qualifying Visit
4. Enrolled on Study
5. RANDOMIZE
   - Arm 1
   - Arm 2
6. Visit 1 (time 0)
   - Evaluation
   - UCB
   - Placebo
7. Visit 2 (1st year)
   - Evaluation
   - 1° Endpoint
   - Placebo
   - UCB
8. Visit 3 (2nd year)
   - Evaluation
Cord Blood Eligibility & Infusion

- Pre cryo TNCC $\geq 1 \times 10^7$ cells/kg
- Pre-cryo viability (total/CD34+) $\geq 80$
- Sterility culture performed & negative
- Maternal infectious disease markers performed & negative
- Identity confirmed (HLA)
- Auto infusions washed and volume reduced
- Infused via PIV after IV Benadryl and Solumedrol
- Placebo = TC 199 + 1% DMSO
GMFM-66 Assessing Change in Study Subjects

Figure 3: GMFM-66 Scores from Baseline to Year 1 by Randomized Treatment Assignment and Cell Dose
Analysis One Year after CB Infusion

Enrolled on Study (n=63)

Qualifying Visit

Phone Screen

CBU Screen & Ship to Duke

Randomize

Arm 1

Arm 2

Visit 1 (time 0)

Evaluation

UCB (n=32)

Placebo (n=31)

Visit 2 (1st year)

Evaluation (n=32)

UCB (n=31)

Visit 3 (2nd year)

Evaluation
## Dose Group Characteristics

**Autologous CB Infusion (N=63)**

<table>
<thead>
<tr>
<th></th>
<th>High ( \geq 2 \times 10^7/\text{kg} )</th>
<th>Low (&lt; 2 \times 10^7/\text{kg} )</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, range)</td>
<td>2.6 (1.1-6.3)</td>
<td>2.9 (1.2-8.0)</td>
<td>0.47</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td>Male</td>
<td>22 (68.8%)</td>
<td>20 (64.5%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10 (31.3%)</td>
<td>11 (35.5%)</td>
<td></td>
</tr>
<tr>
<td>Type of CP</td>
<td></td>
<td></td>
<td>0.53</td>
</tr>
<tr>
<td>Hypotonic Quadriplegia</td>
<td>2 (6.3%)</td>
<td>2 (6.5%)</td>
<td></td>
</tr>
<tr>
<td>Spastic Diplegia</td>
<td>5 (15.6%)</td>
<td>7 (22.6%)</td>
<td></td>
</tr>
<tr>
<td>Spastic Hemiplegia</td>
<td>18 (56.3%)</td>
<td>12 (38.7%)</td>
<td></td>
</tr>
<tr>
<td>Spastic Quadriplegia</td>
<td>7 (21.9%)</td>
<td>10 (32.3%)</td>
<td></td>
</tr>
<tr>
<td>Baseline GMFCS level</td>
<td></td>
<td></td>
<td>0.19</td>
</tr>
<tr>
<td>I/II</td>
<td>24 (75%)</td>
<td>18 (58.1%)</td>
<td></td>
</tr>
<tr>
<td>III/IV</td>
<td>8 (25%)</td>
<td>13 (41.9%)</td>
<td></td>
</tr>
<tr>
<td>Infused TNC ( x10^7/\text{kg} ) (median, range)</td>
<td>3.1 (2.0-5.0)</td>
<td>1.5 (0.4-1.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
- \( N = 38 \)
- \( \geq 2 \) years old at the time of infusion

Wilcoxon \( P < 0.01 \)
- $N = 47$
- $\leq 72$ months at time of follow-up
- $N = 38$ with analyzable images
Plans for auto CB in CP

• Expanded Access trial for auto and sibling CB
• End of phase II meeting with FDA
  – 361 product
  – Homologous use
  – NMM manufacturing
  – ?approvable without further studies?
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

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)

<table>
<thead>
<tr>
<th>Participant Characteristics (N = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>IQ</strong></td>
</tr>
</tbody>
</table>
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

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

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

Statistically significant increase in expressive vocabulary (p < .001); 15 of the 25 patients improved, 7 exhibited no change, 1 declined
Baseline - 6 month MRI/DTI Changes

Increased social approach behaviors (PDD-BI) associated with increased functional connectivity with left occipital, left globus pallidus, and right superior temporal gyrus regions.

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Function</th>
<th>rho</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIDDLE OCCIPITAL GYRUS left</td>
<td>Visual processing</td>
<td>0.497</td>
<td>0.03</td>
</tr>
<tr>
<td>GLOBUS PALLIDUS left</td>
<td>Regulation of voluntary movement</td>
<td>0.497</td>
<td>0.03</td>
</tr>
<tr>
<td>SUPERIOR TEMPORAL GYRUS right</td>
<td>Processing of speech sounds</td>
<td>0.475</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Results of open label trial are encouraging

- Improvements in core autism symptoms, attention, brain activity and structure
- Next step: Randomized, double-blind, placebo controlled trial

Feasibility/endpoints

- Protocol feasible for young, moderately affected children
- Endpoints show sensitivity to change.

Safety

- Preliminary data suggest safety/tolerability are good.

Future trial design

- Account for effects of IQ and dose
- Feasibility and justification of 6 month endpoint
- Biomarkers (blood, EEG, MRI) will be explored.
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
Phase II Study: Flowchart

1. Patient Screening
   - Review Records, Labs, Videos, Photos
2. CBU Screening
   - Review CBU Report, HLA & Potency testing
3. Qualifying Visit
   - Final Eligibility Determination
4. Enroll & Randomize
   - Sequence A
   - Sequence B
5. Baseline Evaluations & Infusion
   - CB
   - Placebo
6. 6 Month Evaluations (Primary Endpoint) & Infusion
   - Placebo
   - CB
7. 12 Month Evaluations
   - Remote Assessments

Best source CB:
- Qualified autologous (if available)
- Unrelated donor otherwise
### Duke ACT - Enrollment Status as of 6OCT2017

#### Cell Source

<table>
<thead>
<tr>
<th>ELIGCELLSOURCE</th>
<th>Frequency</th>
<th>Percent</th>
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<tbody>
<tr>
<td>Allogeneic</td>
<td>78</td>
<td>58.21</td>
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<tr>
<td>Autologous</td>
<td>56</td>
<td>41.79</td>
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</table>

#### Age Category

<table>
<thead>
<tr>
<th>agecat</th>
<th>Frequency</th>
<th>Percent</th>
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<tbody>
<tr>
<td>&lt; 5</td>
<td>59</td>
<td>44.03</td>
</tr>
<tr>
<td>=&gt; 5</td>
<td>75</td>
<td>55.97</td>
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</table>

#### Age Group (years)

<table>
<thead>
<tr>
<th>agegroup</th>
<th>Frequency</th>
<th>Percent</th>
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</thead>
<tbody>
<tr>
<td>2</td>
<td>6</td>
<td>4.48</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>11.94</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>27.61</td>
</tr>
<tr>
<td>5</td>
<td>18</td>
<td>13.43</td>
</tr>
<tr>
<td>6</td>
<td>21</td>
<td>15.67</td>
</tr>
<tr>
<td>7</td>
<td>34</td>
<td>25.37</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>1.49</td>
</tr>
</tbody>
</table>

#### Non-Verbal IQ Category

<table>
<thead>
<tr>
<th>iqcat</th>
<th>Frequency</th>
<th>Percent</th>
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</thead>
<tbody>
<tr>
<td>&lt; 55</td>
<td>38</td>
<td>28.36</td>
</tr>
<tr>
<td>=&gt; 55</td>
<td>96</td>
<td>71.64</td>
</tr>
</tbody>
</table>

N= 134 (2 pilots)
hCT-MSC

- Healthy, screened, term male Caucasian babies
- Delivery by elective C-section
- Retrieval of sterile CT in OR
- Transport to GMP Lab
- Digestion with enzymes - Miltenyi Octo
- Plating to P0 – Master cell bank
- Expansion to P1 – Working cell bank
- Expansion to P2 – Cryopreservation
- Thawed P2 = therapeutic product
- Characterize by phenotype, functional properties, gene and protein expression and potency
Cord Tissue Collection

Prepare sterile table inside OR

Place placenta & cord in sterile tray and cut clamp

Clean cord

Place cord in bucket

Drive to lab at Duke
**MSC Isolation from Umbilical Cord - GMP Procedure**

- **Sterile Umbilical Cord from C-Section**
  - Place each piece into a separate tube
  - ~4 gram pieces
  - ~36 grams Total

**Miltenyi Octo™ Dissociator**

- Digests tissue using 5 different enzymes
- Temperature controlled
- Gentle tissue disruption
- 75'-180' incubation

**Place into Cellstack**

**Expand**

**Plate into**

**7-14 days**

**Harvest**

- P0
  - Yield 2 x 10^7 cells
  - Freeze
  - MCB

**Harvest**

- P1
  - Yield 2.4 x 10^8 cells
  - Freeze
  - WCB

**Harvest**

- P2
  - Yield 3-5 x 10^9 cells

**Cryopreserve Multiple Cell Doses**

- Expand

- Thaw & Plate into Hyperflasks (n=~60)

- Expand

- Thaw & Plate into Hyperflasks (n=~4)
Developing a signature Immunophenotype

Flow cytometry

CD73

CD31

CD90

CD90

CD105

CD146

CD166

CD45
Developing a Signature: Potency Inhibition of T-cell Proliferation

No Interferon (IFN)

With Interferon (IFN) and/or MT
D7 after cell addition

No LPC

LPC

LPC, 25K Cells

CD68
Objectives of the Study

• To determine the safety of a single and repeated intravenous doses of hCT-MSC in children with ASD

Study Design

• Open label, dose escalation; Up to three doses of $2 \times 10^6$ cells/kg will be administered
• 12 children with ASD, 2-11 years
• Outcomes assessed at baseline and 6 months later; remote assessments at 12 months
• Endpoints: Safety, Vineland Parent Interview, PDD-BI autism symptoms, and CGI Clinician Rating
Phase 1 study of hCT-MSC in Children with ASD

- **Cohort 1**
  - N=3
  - MSCs
  - Infusion
  - Evaluate in person
    - F/U
  - F/U

- **Cohort 2**
  - N=3
  - MSCs
  - Infusion
  - Evaluate remotely
    - F/U
  - F/U

- **Cohort 3**
  - N=6
  - MSCs
  - Infusion
  - Evaluate remotely
    - F/U
  - 6 mos

Baseline, 2 mos, 4 mos, 6 mos, 12 mos from final dose
## CT MSC Phase I Schedule

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Infusion</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; Infusion</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; Infusion</th>
<th>6-month return visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>N = 3</td>
<td>Complete</td>
<td>--</td>
<td>--</td>
<td>12/6/2017 1/10/2018 1/24/2018</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10/11/2017 10/25/2017 10/25/2017</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>N = 3</td>
<td>Complete</td>
<td>10/11/2017 10/25/2017</td>
<td>---</td>
<td>2/7/2018 2/14/2018 2/14/2018</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10/18/2017 11/1/2017 11/14/2017 11/14/2017 12/13/2017</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12/13/2017 12/20/2017 12/20/2017 1/16/2018 1/24/2018 2/14/2018</td>
</tr>
</tbody>
</table>

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**Duke Robertson Clinical and Translational Cell Therapy (CT<sup>2</sup>) Program**

**Duke Center for Autism and Brain Development**
Inclusion Criteria

• Age ≥ 2 years to ≤ 12 years
• Confirmed clinical DSM-5 diagnosis of ASD with a moderate severity level of ASD as reflected by SRS score ≥ 66.
• Fragile X testing performed and negative; CMA and/or whole exome sequencing performed and results not linked to ASD
• Stable on current psychiatric medication regimen
• Normal absolute lymphocyte count (≥1500/uL)
• Participant and parent/guardian are English speaking
• Able to travel to Duke University up to four times, and parent/guardian is able to participate in interim surveys and interviews
• Parental consent
Exclusion Criteria

- General:
  - ASD diagnosis not likely
  - Known diagnosis of any of the following coexisting psychiatric conditions: depression, bipolar disorder, schizophrenia, obsessive compulsive disorder associated with bipolar disorder, Tourette syndrome
  - Screening data suggests that participant would not be able to comply with the requirements of the study procedures as assessed by the study team
  - Family is unwilling or unable to commit to participation in all study-related assessments, including protocol follow up
  - Sibling is enrolled in this (Duke hCT-MSC) study
- Genetic:
  - Records indicate that child has a known genetic syndrome such as (but not limited to) Fragile X syndrome, neurofibromatosis, Rett syndrome, tuberous sclerosis, PTEN mutation, cystic fibrosis, muscular dystrophy or a genetic defect definitively known to be associated with ASD
  - Evaluation by geneticist indicates a genetic cause for ASD.
- Current/Prior Therapy:
  - History of prior cell therapy
  - Current or prior use of IVIG or other anti-inflammatory medications with the exception of NSAIDs
  - Current or prior immunosuppressive therapy
- Medical:
  - Known metabolic disorder
  - Known abnormal thyroid function
  - Known mitochondrial dysfunction
  - History of unstable epilepsy or uncontrolled seizure disorder, infantile spasms, Lennox Gastaut syndrome, Dravet syndrome, or other similar chronic seizure disorder
  - Active malignancy or prior malignancy that was treated with chemotherapy
  - History of a primary immunodeficiency disorder
  - History of autoimmune cytopenias (i.e., ITP, AIHA)
  - Coexisting medical condition that would place the child at increased risk for complications of study procedures
  - Concurrent genetic or acquired disease or comorbidity(ies) that could require a future stem cell transplant
  - Significant sensory (e.g., blindness, deafness, uncorrected hearing impairment) or motor (e.g., cerebral palsy) impairment
  - Impaired renal or liver function
  - Significant hematologic abnormalities defined as: Hemoglobin <10.0 g/dL, WBC < 3,000 cells/mL, ALC <1000/µL, Platelets <150 x 10e9/µL
  - Evidence of clinically relevant physical dysmorphology indicative of a genetic syndrome
- Infectious:
  - Known active CNS infection
  - Evidence of uncontrolled infection based on records or clinical assessment
  - Known HIV positivity
## Safety Assessments

<table>
<thead>
<tr>
<th>Time Points</th>
<th>Baseline (Visit 1)</th>
<th>Each hCT-MSC dose</th>
<th>7-10 days post-MSCs</th>
<th>2 mo.</th>
<th>4 mo.</th>
<th>6 mo.</th>
<th>6 mo.</th>
<th>After last MSC dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History &amp; Physical</strong></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>CBCD, CMP, Direct &amp; Indirect Coombs (T&amp;S), HLA Antibody Screen (PRA), ESR, CRP, Immune Reconstitution Panel, Humoral Immune Profile, Donor Referral Panel</strong></td>
<td>X</td>
<td>X (CBC/CM P only)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>hCT-MSC infusion</strong></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Safety Assessment – in person</strong></td>
<td>X (Day after MSCs)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>Safety Assessment – phone call/survey</strong></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
# ASD Assessments

<table>
<thead>
<tr>
<th>Respondent</th>
<th>Measure</th>
<th>Domain</th>
<th>Length of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Assessments with the Child</td>
<td>Autism Diagnostic Observation Schedule, Second Edition (ADOS-2)</td>
<td>ASD Diagnosis</td>
<td>45-50 minutes</td>
</tr>
<tr>
<td></td>
<td>Mullen Scales of Early Learning, AGS Edition (MSEL) or the Differential Ability Scales, Second Edition (DAS-II)</td>
<td>Cognitive/ Language</td>
<td>45-60 minutes</td>
</tr>
<tr>
<td>Clinician Observation of Parent/Child</td>
<td>Parent-Child Interaction (PCI) with Noldus EthoVision Camera</td>
<td>Parent-Child Interaction</td>
<td>12 minutes</td>
</tr>
<tr>
<td>Caregiver Interviews and Questionnaires (conducted with the caregiver only)</td>
<td>Vineland Adaptive Behavior Scales (VABS) - 3 Survey Interview Form</td>
<td>Social and Communicative Behavior</td>
<td>60-120 minutes</td>
</tr>
<tr>
<td></td>
<td>Pervasive Developmental Disorder Behavior Inventory (PDDBI)</td>
<td>Social behavior and ASD symptoms</td>
<td>30 minutes</td>
</tr>
<tr>
<td></td>
<td>Clinical Global Impression Parent Interview</td>
<td>Global Clinical Improvement</td>
<td>30-45 minutes</td>
</tr>
</tbody>
</table>
hCT-MSC in ASD – Results to Date

• 12/12 children enrolled
• 11/12 received 1 or 2 doses
• Others continue on study
• No safety issues have been noted to date
• Too early to assess efficacy
Planned future studies with MSC

• Randomized Phase II in CP: MSC vs UCB vs Placebo
• MSC Phase II: Autism
• Allo UCB in ALS
• MSC in osteoarthritis – knees and shoulders
• MSC in HIE
• MSC in premie IVH
In Summary

• Cord blood therapies show highly promising results for treatment of diseases with no currently available therapies
• Results using autologous cells in babies and children with HIE, CP and Autism suggest efficacy
• Safety of allogeneic cells has been demonstrated
• Safety & Efficacy studies with allogeneic cord blood and cord tissue cells are underway
• Regulatory pathways for autologous and allogeneic cells as regenerative therapies need clarification
“It takes a village”  
Hillary Clinton

- Pediatric Blood and Marrow Transplant Team  
  - MDs, APNs, NCs, SC, SW, FA, FSP
- Stem Cell Laboratory
- Carolinas & MDAnderson CBBs
- CT2: Andy Balber, Arjun Saha and team
- Allen Song, Jim Provenzale
- Jessica Sun, Mohamad Mikati
- Amy Murtha, Haywood Brown
- Sid Tan, Mike Cotten, Ron Goldberg
- Geri Dawson and team
- Danny Laskowitz and team
- EJ Shpall, John Wingard, Mike Frankel
- NHLBI, HRSA, NMDP, EMMES Corp
- The Julian Robertson Foundation
- The Legacy of Angels Foundation
- Cure CP Foundation
- The Katz Foundation
- The Marcus Foundation

FDA LICENSURE  
‘hematopoietic reconstitution after myeloablative chemotherapy’
Questions?
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Save the Cord Foundation

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