Clinical trials using cord blood and cord tissue cells in children with cerebral palsy, autism and related conditions

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- Duke University Medical Center
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Types of Cells in Cord Blood

- Multipotent hematopoietic stem cell (Hemocytoblast)
  - Common myeloid progenitor
    - Erythrocyte
    - Mast cell
    - Myeloblast
    - Megakaryocyte
      - Thrombocytes
  - Common lymphoid progenitor
    - Small lymphocyte
    - Natural killer cell (Large granular lymphocyte)
    - B lymphocyte
    - T lymphocyte
  - Macrophage
  - Monocyte
  - Plasma cell

- CD14
  - Hypoxic Injury
- DUOC-01
  - Remyelination
Innovative Cord Blood Therapies at Duke (All under IND with the FDA)

HSCT
- Children with IMD
- DUOC as a bridging therapy to accelerate CNS engraftment in children with IMD
- Requires myeloablative conditioning

Infusion therapy
- Cord Blood
  - HIE
  - CP
  - ASD
  - Acute Stroke in adults
  - EAP
- HCT-MSCs
  - HIE
  - CP
  - ASD
  - OA knee in adults
- Direct Infusion, no conditioning
Cord Blood Monocytes and hCT-MSCs: How are the cells working?

• Paracrine signaling
• Trophic effects

• Cross talk with endogenous cells resulting in:

  ✓ Modulation of neuroinflammation
    • Suppression of microglial activation
    • Suppression of activated lymphocytes

  ✓ Promotion of 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
MSCs Inhibit Microglial Activation after Chemical Induced Demyelination
Autism Spectrum Disorder

• Difficulties forming relationships and communicating
• 1 in 59 children in US affected
• Annual cost to society - $265 billion
• No FDA-approved medicines that improve core symptoms of autism
25 children with ASD
Ages 2-6, 80% males
Non-verbal IQ 35-123 (median 64)
Assess endpoints at 6 and 12 months
Assess feasibility and safety
Excluded children with genetic causes of autism
Improvements in social behavior

Primary endpoint: Vineland Adaptive Behavior Scale – Socialization Standard Score

- Significant increase in socialization standard score (p = 0.02)
- Children with higher baseline IQ had greater response
- No safety concerns
- Primary endpoint for ongoing Phase II randomized, placebo controlled trial comparing autologous versus allogeneic cord blood to placebo.
  - 178 patients
  - Results Oct 2018
Eye tracking

- During dyadic bid condition, there was a 20% increase in odds of gazing at actress’ eyes from baseline to 12 months ($p = 0.048$).
- Proportion of time child spent looking at the actress increased but was not statistically significant.
- 7-point change in VABS-II socialization standard score was associated with a 14% increase in odds of gazing at the actress ($p < 0.001$).
DukeACT Trial Design

Evaluation

Randomize

N = 60

Infusion 1

Placebo

Best Donor Source

Auto

Allo

Infusion 2

Best Donor Source

Placebo

Auto

Allo

Baseline

6 months
Phase 1 hCT-MSC in Children with ASD

Cohort 1
N=3
MSCs

Cohort 2
N=3
MSCs

Cohort 3
N=6
MSCs

Infusion
Infusion
Infusion

Evaluate in person
Evaluate remotely

F/U
F/U

F/U
F/U

F/U
F/U

Baseline
2 mos
4 mos
6 mos
12 mos from final dose
Phase 1 MSC study – 6 month data

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• 58% of patients (7/12) showed improvement on at least 2/3 measures.
  o 42% (5/12) showed improvement on 3/3 measures.
  o 16% (2/12) showed improvement on 2/3 measures.
  o No clear dose effect, although there are too few patients to determine this definitively.

* Clinically significant improvement ≥ 3 points.
Phase 2 MSC study in ASD: IMPACT

- **Baseline**: Placebo
- **3 mos**: MSCs 6M / Kg
- **6 mos**: Placebo

Infusion
- In person evaluation
- Remote evaluation

**N = 82 - 150**
63 patients, ages 1-6 years
Qualified autologous CBU – 16 banks
CP with spasticity, GMFCS Levels I-IV
Placebo TC199 + 1% DMSO
Primary Endpoint: Change in GMFM score at 1 year
Assessing Change in Changing Subjects

![Graph showing GMFM-66 Score vs Age for different levels of GMFCS (Gross Motor Function Classification System).]

- Level I
- Level II
- Level III
- Level IV
- Level V

GMFCS Level I
GMFCS Level II
GMFCS Level III
GMFCS Level IV
GMFCS Level V

JAMA. 2002;288:1357-1363
N = 38 with analyzable images
Increases in motor function at 1 year that were 30% higher than predicted for age and level of function were scored a response to cord blood cells.
Expanded Access Protocol

• In SEP 2017 we opened an Expanded Access Protocol (EAP) under IND for IV infusion of autologous or sibling umbilical cord blood for children with brain injuries, including:
  o Autism
  o Cerebral Palsy
  o Congenital Hydrocephalus
  o Apraxia
  o Stroke
  o Hypoxic Brain Injury

• Assessing safety up to 12 months post infusion
• 320+ patients treated to date
• Waiting list of thousands of patients
Conclusions

▪ CB, both autologous and allogeneic, show excellent safety profiles and suggestions of efficacy in Phase I and Phase II clinical trials in children with brain injury.

▪ The CB monocytes appear to be the active cells in this heterogeneous cell product.

▪ Additional, well designed Phase III studies, will be required to confirm efficacy and to obtain regulatory approvals.

▪ These therapies have the potential to treat diseases with unmet needs and to change human lives.
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“It takes a Village”

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