Regenerative and Cellular Therapies: A new and emerging technology

- What are these therapies?
  - Cells, tissues, genes
- What is their potential for the field of medicine?
  - To provide effective therapies for currently unmet medical needs
    - Neurology, Cardiology, Arthritis, Diabetes, etc
  - Current applications are exciting but unproven
- Why are they unique?
  - Manufacturing, packaging, distribution and administration are different than the systems currently in place for drugs
- How will they challenge the current health care delivery system?
  - Gaps in the current workforce (esp manufacturing for GMP)
  - Storage is different, not in the bandwidth of a typical clinical or pharmacy
  - Administration requires expertise in processing & handling of cells
The Marcus Center for Cellular Cures: Who are we?

Translationally-focused, scientifically-based center developing cell-based therapies to treat brain diseases with a goal and a track record of rapid translation from the laboratory to the clinic

BLA – DUCORD 2012

MC3 Product Matrix

<table>
<thead>
<tr>
<th>Mechanisms of Action</th>
<th>Allogeneic Cord Blood</th>
<th>DUOC-01</th>
<th>Allogeneic Cord Tissue MSCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce inflammation</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Reduce CNS inflammation</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Promote oligodendrocyte proliferation</td>
<td>?</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Modulate brain connectivity</td>
<td>✓</td>
<td>?</td>
<td>✓</td>
</tr>
<tr>
<td>Rescue for hypoxia</td>
<td>✓</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Promote remyelination</td>
<td>?</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

Indications under study

| HIE, CP, Autism, Stroke | LeukodystrophiesMS | HIE, CP, MS | Autism, OA |

Stem Cell Lab 14 FTEs
GMP 14 FTEs
Clinical Trials 18 FTEs
Regulatory 7.0 FTEs
CCBB 49 FTEs
R&D 10 FTEs
Faculty 5.0 FTEs
Admin 13 FTEs
The Science, Policy, and Potential of Cell and Gene Therapies

Types of Cells in Cord Blood

Cord blood is not a bag of stem cells

Active cells are cord blood monocytes

Human umbilical cord blood monocytes, but not adult blood monocytes, rescue brain cells from hypoxic-ischemic injury: Mechanistic and therapeutic implications
Donor Cells engraft in the brain after IV UCBT – Idea for DUOC
A cord blood monocyte derived therapeutic cell

DUOC Activities
- Enzyme replacement
- “Clean up”
- Cytokine secretion:
  - Modulate inflammation
  - [IL10, IL6, TGF-beta]
  - Inhibits cellular infiltration
- Drives oligodendrocyte proliferation
- Promotes myelination

DUOC-01 activities include:
- Enzyme replacement
- “Clean up”
- Cytokine secretion:
  - Modulate inflammation
  - [IL10, IL6, TGF-beta]
  - Inhibits cellular infiltration
- Drives oligodendrocyte proliferation
- Promotes myelination

UCBT for early Infantile Krabbe Disease:
- Functional Outcomes vary with best outcomes in babies transplanted in the first month of life

Newborn Screening
DUOC-01, a bridging therapy augmenting UCBT in LSDs

27 pediatric patients treated in 4 years
Intrathecal injections well tolerated; formulated in NS and HC
Planning trials in adult MS as a stand-alone cell therapy product

OUTCOMES

Siblings (haplo/full match)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline Mean (SD)</th>
<th>6 month Mean (SD)</th>
<th>Change Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMFM-66</td>
<td>37.5 (10.1)</td>
<td>40.8 (8.8)</td>
<td>4.8 (2.5)*</td>
</tr>
<tr>
<td>PDMS – Gross Motor Quotient</td>
<td>47.7 (7.7)</td>
<td>48.7 (8.4)</td>
<td>1.0 (2.9)</td>
</tr>
<tr>
<td>PDMS – Fine Motor Quotient</td>
<td>63.3 (15.9)</td>
<td>63.4 (12.9)</td>
<td>0.1 (7.2)</td>
</tr>
<tr>
<td>AHA Interval Score</td>
<td>44.6 (20.4)</td>
<td>49.9 (19.6)</td>
<td>5.3 (3.2)</td>
</tr>
</tbody>
</table>

Cerebral Palsy - Auto
Established dose of 25M/kg
Autologous cord blood infusions in young children with cerebral palsy improve motor function; effect is dose dependent (25M/kg)

Cell therapies in children with ASD

MSCs and CB CD14 cells Inhibit Microglial Activation
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

Objective endpoints are needed: Eye tracking

Duke ACT Trial Design

- During dyadic bid condition, there was a 20% increase in odds of gazing at actress' eyes from baseline to 12 months (p = 0.048).
- 7-point change in VABS-II socialization standard score was associated with a 14% increase in odds of gazing at the actress (p<.001).
Market Size
(# affected patients in the USA)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIE</td>
<td>6 Thousand</td>
</tr>
<tr>
<td>CP</td>
<td>0.8 Million</td>
</tr>
<tr>
<td>ASD</td>
<td>3.5 Million</td>
</tr>
<tr>
<td>Stroke</td>
<td>6 Million</td>
</tr>
<tr>
<td>OA</td>
<td>30 Million</td>
</tr>
</tbody>
</table>

Conclusions and Challenges

- 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.
- Clinical trials are expensive
- Complex endpoints requiring novel clinical trial designs
- Point of care delivery
  - Complex products
  - Handling, storage, preparation for administration
  - Compliance with FDA regulations
- Work force gaps and shortages
  - GMP technicians
- Harmonization of FDA regulations and point of care therapies