1

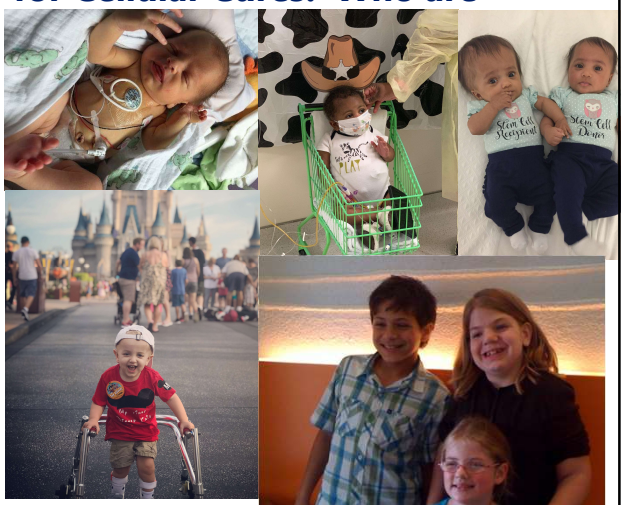
Regenerative and Cellular Therapies: A new and emerging technology

- 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

2

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



Marcus Center for Cellular Cures
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BLA – DUCORD 2012

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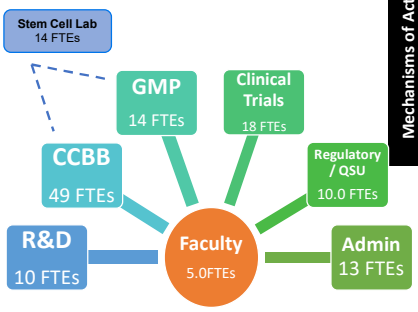
MC3 Product Matrix



	Allogeneic Cord Blood	DUOC-01	Allogeneic Cord Tissue MSCs
Mechanisms of Action			
Reduce inflammation	√	√	√
Reduce CNS inflammation	√	√	√
Promote oligodendrocyte proliferation	?	√	?
Modulate brain connectivity	√	?	√
Rescue for hypoxia	√	?	?
Promote remyelination	?	√	?
Indications under study	HIE, CP, Autism, Stroke	Leukodystrophiesms	HIE, CP, MS Autism, OA

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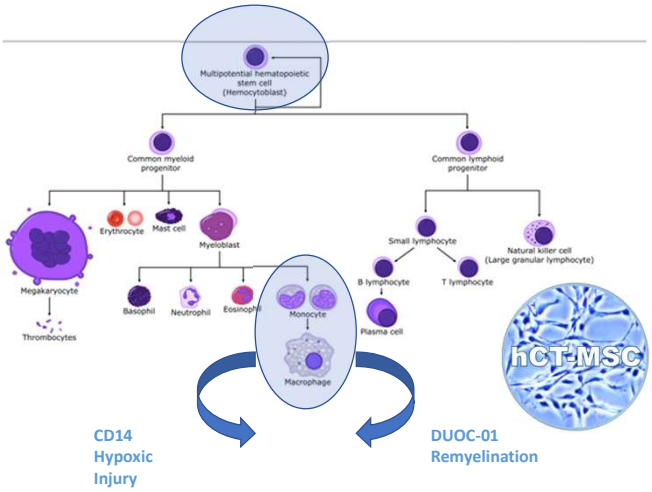
Types of Cells in Cord Blood



Cord blood is not a bag of stem cells

5

5

Active cells are cord blood monocytes

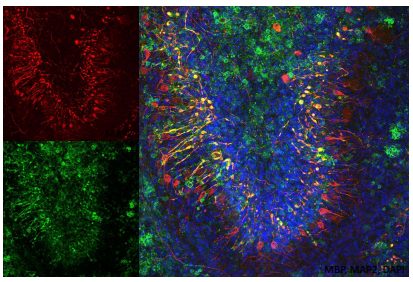
PLOS ONE

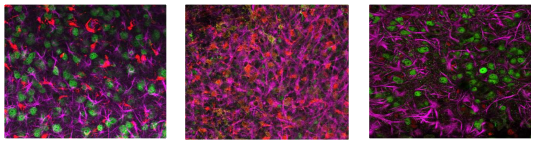
RESEARCH ARTICLE

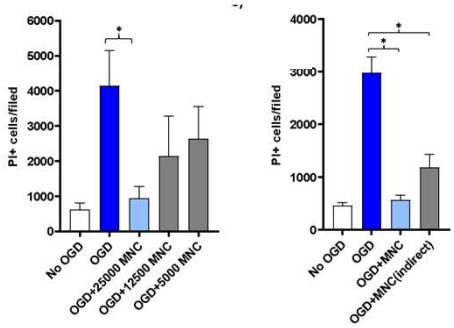
Human umbilical cord blood monocytes, but not adult blood monocytes, rescue brain cells from hypoxic-ischemic injury: Mechanistic and therapeutic implications

Arjun Saha*, Sachit Patel, Li Xu, Paula Scotland, Jonathan Schwartzman, Anthony J. Filiano, Joanne Kurtzberg, Andrew E. Balber

Marcus Center for Cellular Cures (MC3), Duke University School of Medicine, Durham, North Carolina, United States of America

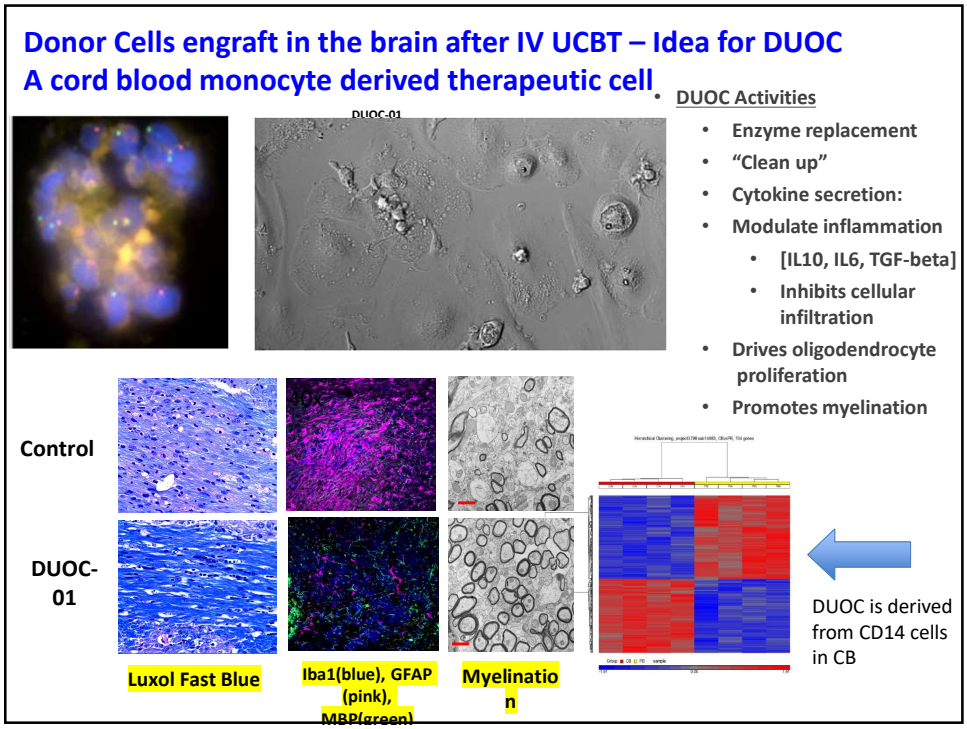






MAP2 MBP DAPI

6


Donor Cells engraft in the brain after IV UCBT – Idea for DUOC
A cord blood monocyte derived therapeutic cell
DUOC-01
DUOC Activities
Enzyme replacement
"Clean up"
Cytokine secretion:
Modulate inflammation
[IL10, IL6, TGF-beta]
Inhibits cellular infiltration
Drives oligodendrocyte proliferation
Promotes myelination
Control
DUOC-01
Luxol Fast Blue
Iba1(blue), GFAP (pink), MBP(green)
Myelination
DUOC is derived from CD14 cells in CB

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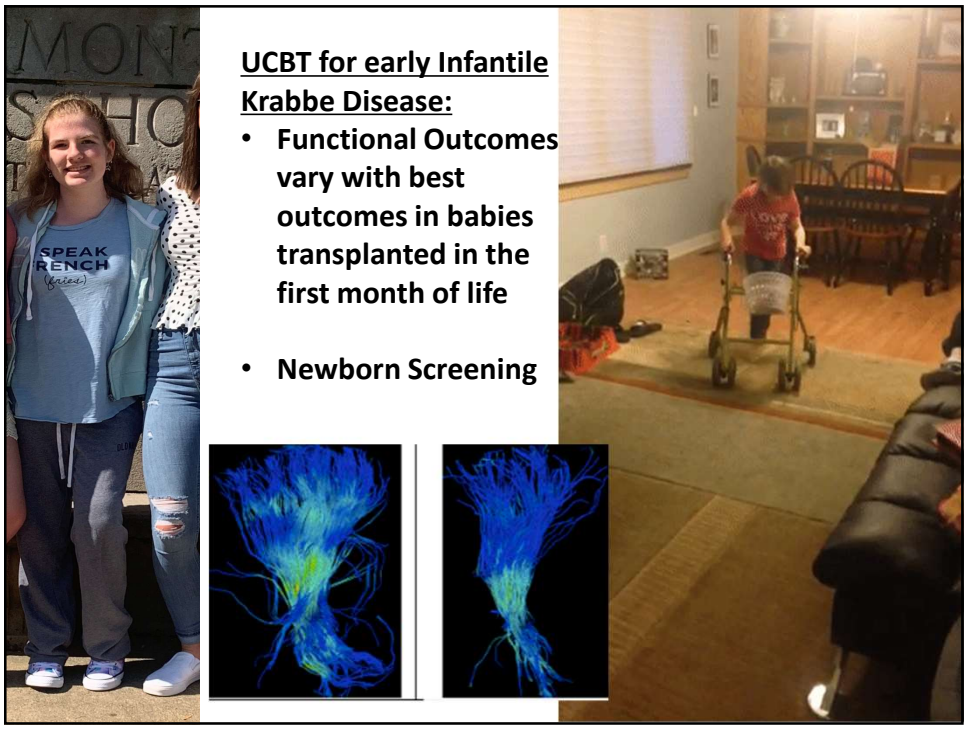
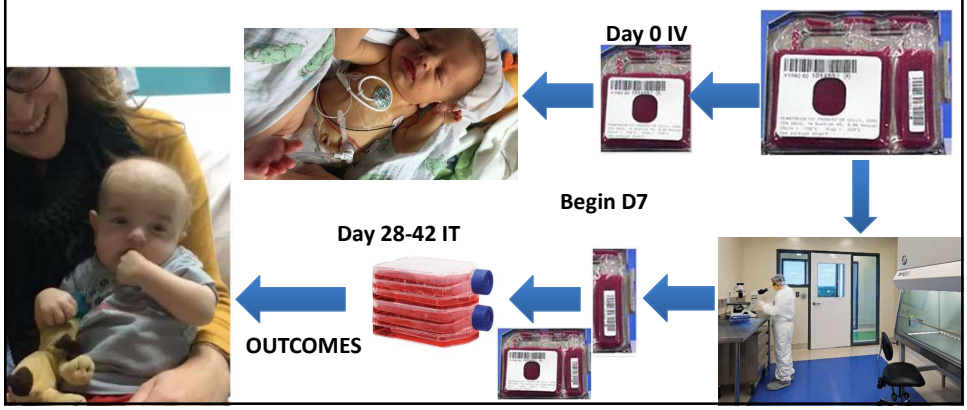

UCBT for early Infantile Krabbe Disease:
Functional Outcomes vary with best outcomes in babies transplanted in the first month of life
Newborn Screening

8

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



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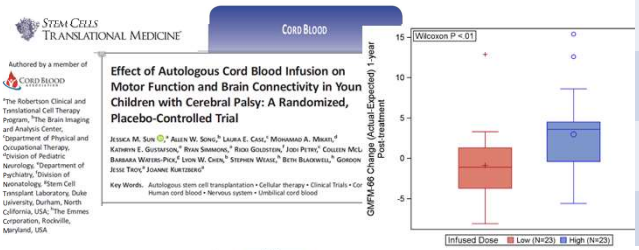
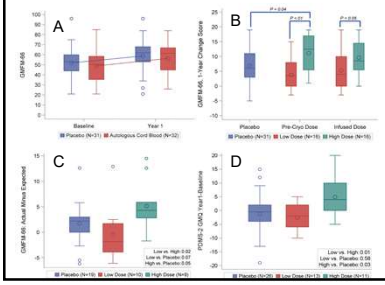
Cerebral Palsy - Auto

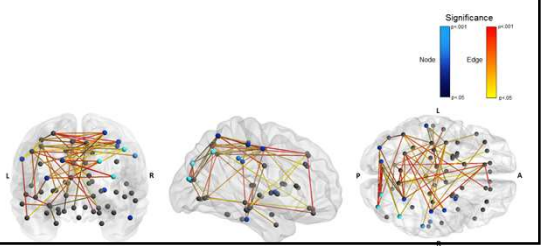
Established dose of 25M/kg

Siblings (haplo/full match)

Measure	Mean (SD) Baseline	6 months	Change score
GMFM-66	37.5 (10.1)	40.8 (8.8)	4.8 (2.5)#
PDMS – Gross Motor Quotient	47.7 (7.7)	48.7 (8.4)	1.0 (2.9)
PDMS – Fine Motor Quotient	63.3 (15.9)	63.4 (12.9)	0.1 (7.2)
AHA Interval Score	44.6 (20.4)	49.9 (19.6)	5.3 (3.2)







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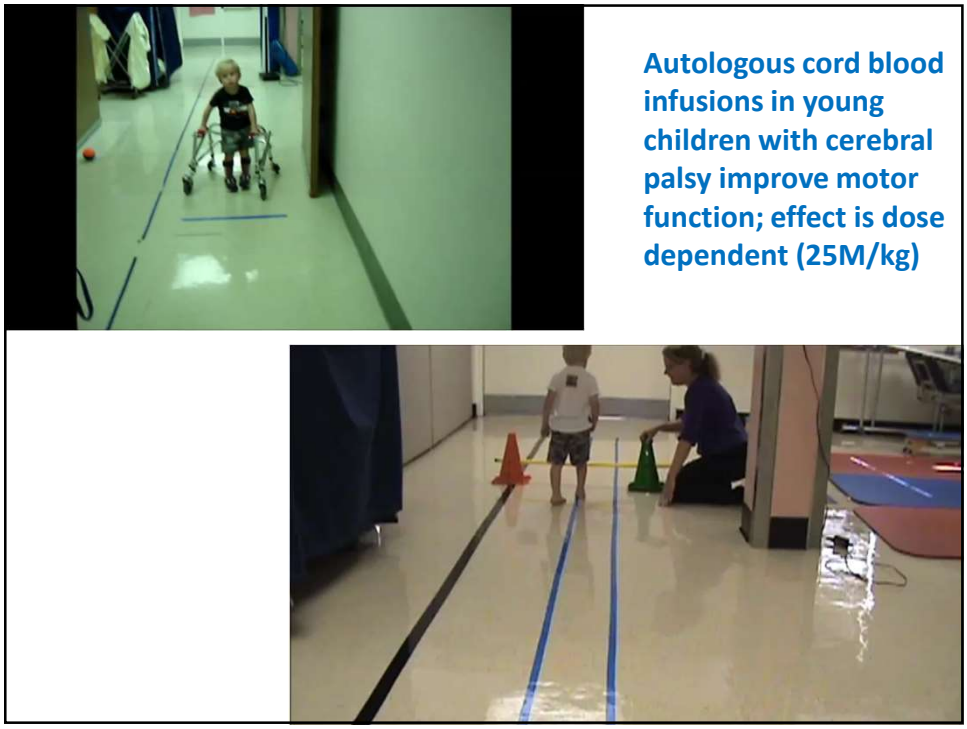
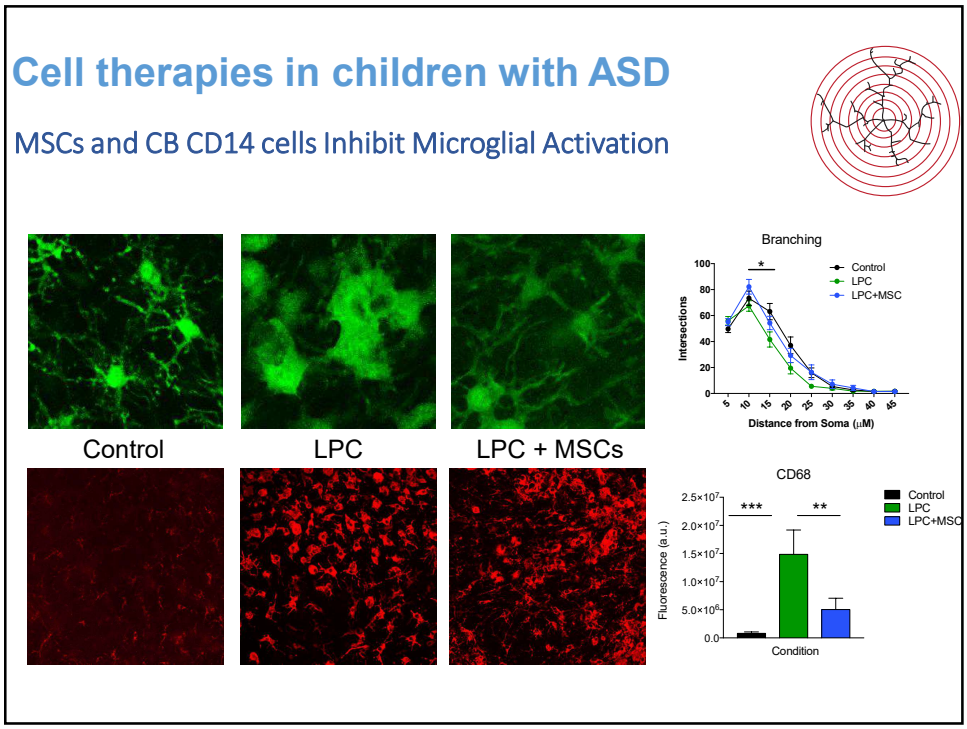

Autologous cord blood infusions in young children with cerebral palsy improve motor function; effect is dose dependent (25M/kg)

11


Cell therapies in children with ASD
MSCs and CB CD14 cells Inhibit Microglial Activation
Control
LPC
LPC + MSCs
Branching
Control
LPC
LPC+MSC
Intersections
Distance from Soma (μM)
CD68
Control
LPC
LPC+MSC
Fluorescence (a.u.)
Condition

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Autism Spectrum Disorder

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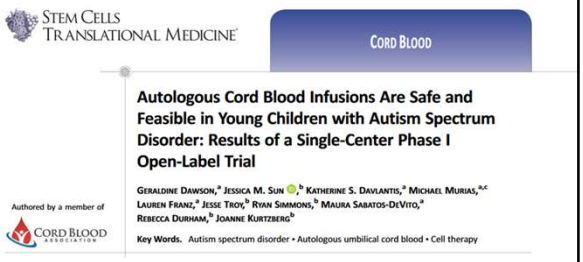
- **Difficulties forming relationships and communicating**
- **1 in 59 children in US affected**
- **Annual cost to society - $265 billion**
- **No FDA-approved medicines that improve core symptoms of autism**


Stem Cells Translational Medicine

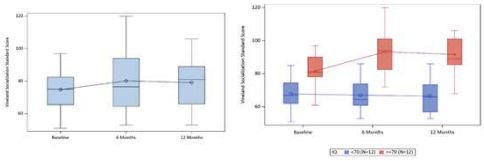
Cord Blood

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



- Significant increase in socialization standard score (p = 0.02)
- Children with higher baseline IQ had greater response
- No safety concerns

Duke Center for Autism and Brain Development

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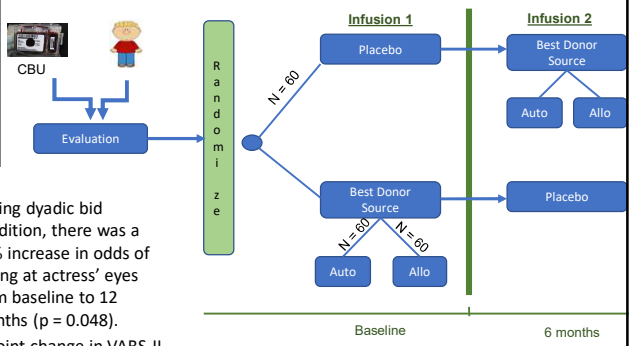
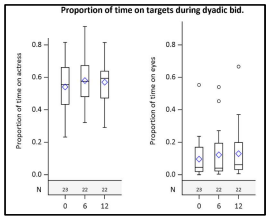
Objective endpoints are needed: Eye tracking

DUKE ACT

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).

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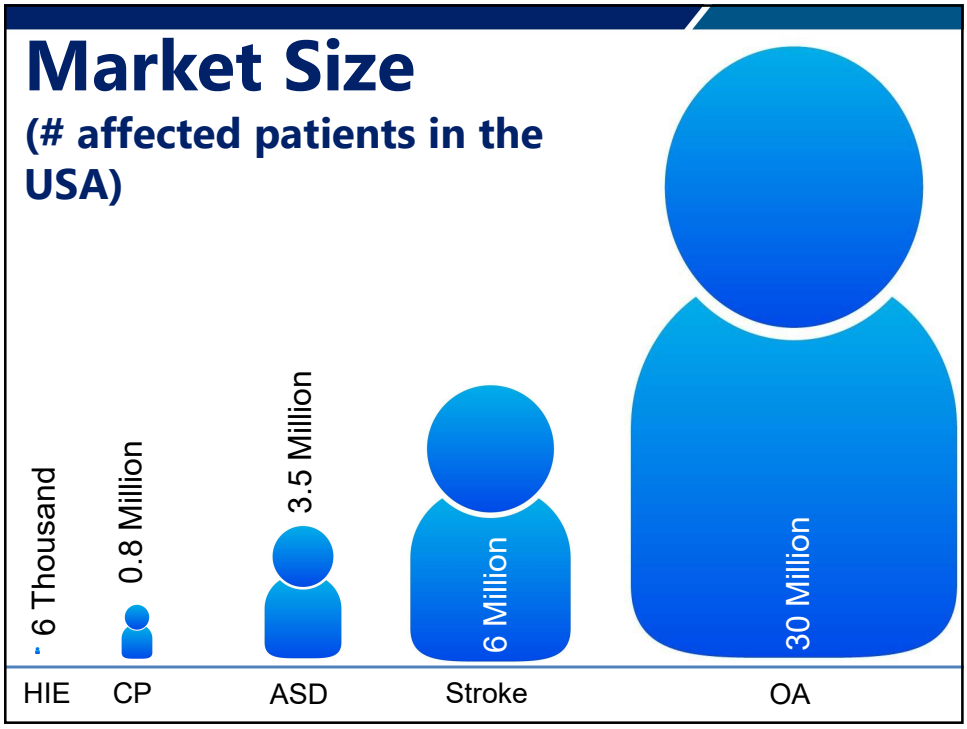

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Conclusions and Challenges

- 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

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