Progenitor Cell Therapies for Pediatric Traumatic Brain Injury

NHLBI Workshop

UT·HOUSTON MEDICAL SCHOOL

Children's MEMORIAL HERMANN Hospital

Autologous Bone Marrow Mononuclear Cell Therapy for Severe Traumatic Brain Injury in Children

Charles S. Cox, Jr, MD*
James E. Baumgartner, MD*
Matthew T. Harting, MD*†
Laura L. Worth, MD, PhD§
Peter A. Walker, MD*†
Shinil K. Shah, DO*†
Linda Ewing-Cobbs, PhD*
Khader M. Hasan, PhD‡
Mary-Clare Day, RN, BSN*
Dean Lee, MD, PhD§
Fernando Jimenez, MS*
Adrian Gee, PhD¶

*Departments of Pediatric Surgery, †Surgery, and ‡Diagnostic & Interventional Imaging, University of Texas Medical School at Houston, Houston, Texas; Children's Memorial Hermann Hospital, University of Texas, Houston, Texas; §Department of Pediatrics, Division of Cell Therapy, MD Anderson Cancer Center, Houston, Texas; ¶Baylor College of Medicine Center for Cell and Gene Therapy, Houston, Texas

Correspondence:
Charles S. Cox Jr, MD,
6431 Fannin, MSB 5.236,
Houston, TX 77030.
E-mail: Charles.S.Cox@uth.tmc.edu

BACKGROUND: Severe traumatic brain injury (TBI) in children is associated with substantial long-term morbidity and mortality. Currently, there are no successful neuroprotective/neuroreparative treatments for TBI. Numerous preclinical studies suggest that bone marrow-derived mononuclear cells (BMMNCs), their derivative cells (marrow stromal cells), or similar cells (umbilical cord blood cells) offer neuroprotection.

OBJECTIVE: To determine whether autologous BMMNCs are a safe treatment for severe TBI in children.

METHODS: Ten children aged 5 to 14 years with a postresuscitation Glasgow Coma Scale of 5 to 8 were treated with 6×10^6 autologous BMMNCs/kg body weight delivered intravenously within 48 hours after TBI. To determine the safety of the procedure, systemic and cerebral hemodynamics were monitored during bone marrow harvest; infusion-related toxicity was determined by pediatric logistic organ dysfunction (PELOD) scores, hepatic enzymes, Murray lung injury scores, and renal function. Conventional magnetic resonance imaging (cMRI) data were obtained at 1 and 6 months postinjury, as were neuropsychological and functional outcome measures.

RESULTS: All patients survived. There were no episodes of harvest-related depression of systemic or cerebral hemodynamics. There was no detectable infusion-related toxicity as determined by PELOD score, hepatic enzymes, Murray lung injury scores, or renal function. cMRI imaging comparing gray matter, white matter, and CSF volumes showed no reduction from 1 to 6 months postinjury. Dichotomized Glasgow Outcome Score at 6 months showed 70% with good outcomes and 30% with moderate to severe disability.

CONCLUSION: Bone marrow harvest and intravenous mononuclear cell infusion as treatment for severe TBI in children is logistically feasible and safe.

KEY WORDS: Cellular therapy, Clinical trial, Mononuclear cell, Pediatric, Stem cell, Traumatic brain injury

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10 Leading Causes of Death by Age Group, United States – 2006

Rank	Age Groups										
	<1	1-4	5-9	10-14	15-24	25-34	35-44	45-54	55-64	65+	Total
1	Congenital Anomalies 5,819	Unintentional Injury 1,610	Unintentional Injury 1,044	Unintentional Injury 1,214	Unintentional Injury 16,229	Unintentional Injury 14,954	Unintentional Injury 17,534	Malignant Neoplasms 50,334	Malignant Neoplasms 101,454	Heart Disease 510,542	Heart Disease 631,636
2	Short Gestation 4,841	Congenital Anomalies 515	Malignant Neoplasms 459	Malignant Neoplasms 448	Homicide 5,717	Suicide 4,985	Malignant Neoplasms 13,917	Heart Disease 38,095	Heart Disease 65,477	Malignant Neoplasms 387,515	Malignant Neoplasms 559,888
3	SIDS 2,323	Malignant Neoplasms 377	Congenital Anomalies 182	Homicide 241	Suicide 4,189	Homicide 4,728	Heart Disease 12,339	Unintentional Injury 19,675	Chronic Low. Respiratory Disease 12,375	Cerebro-vascular 117,010	Cerebro-vascular 137,119
4	Maternal Pregnancy Comp. 1,683	Homicide 366	Homicide 149	Suicide 216	Malignant Neoplasms 1,664	Malignant Neoplasms 3,656	Suicide 6,591	Liver Disease 7,712	Unintentional Injury 11,446	Chronic Low. Respiratory Disease 106,845	Chronic Low. Respiratory Disease 124,583
5	Unintentional Injury 1,147	Heart Disease 161	Heart Disease 90	Heart Disease 163	Heart Disease 1,076	Heart Disease 3,307	HIV 4,010	Suicide 7,426	Diabetes Mellitus 11,432	Alzheimer's Disease 71,660	Unintentional Injury 121,599
6	Placenta Cord Membranes 1,140	Influenza & Pneumonia 125	Chronic Low. Respiratory Disease 52	Congenital Anomalies 162	Congenital Anomalies 460	HIV 1,182	Homicide 3,629	Cerebro-vascular 6,341	Cerebro-vascular 10,518	Diabetes Mellitus 52,351	Diabetes Mellitus 72,449
7	Respiratory Distress 825	Septicemia 88	Cerebro-vascular 45	Chronic Low. Respiratory Disease 63	Cerebro-vascular 210	Diabetes Mellitus 673	Liver Disease 2,551	Diabetes Mellitus 5,692	Liver Disease 7,217	Influenza & Pneumonia 49,346	Alzheimer's Disease 72,432
8	Bacterial Sepsis 807	Perinatal Period 65	Influenza & Pneumonia 40	Cerebro-vascular 50	HIV 206	Cerebro-vascular 527	Cerebro-vascular 2,221	HIV 4,377	Suicide 4,583	Nephritis 37,377	Influenza & Pneumonia 56,326
9	Neonatal Hemorrhage 618	Benign Neoplasms 60	Septicemia 40	Septicemia 44	Influenza & Pneumonia 184	Congenital Anomalies 437	Diabetes Mellitus 2,094	Chronic Low. Respiratory Disease 3,924	Nephritis 4,368	Unintentional Injury 36,689	Nephritis 45,344
10	Circulatory System Disease 543	Cerebro-vascular 54	Benign Neoplasms 38	Benign Neoplasms 38	Complicated Pregnancy 179	Influenza & Pneumonia 335	Septicemia 870	Viral Hepatitis 2,911	Septicemia 4,032	Septicemia 26,201	Septicemia 34,234

Source: National Vital Statistics System, National Center for Health Statistics, CDC.
Produced by: Office of Statistics and Programming, National Center for Injury Prevention and Control, CDC.

TBI is the leading cause of death in the Injury Category

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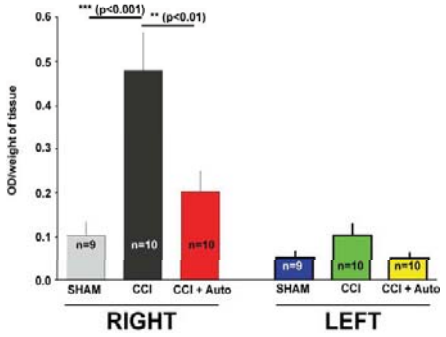
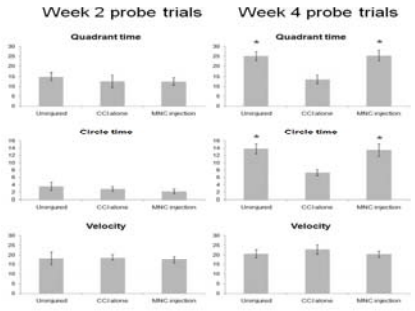
Rationale

There is NO reparative therapy for TBI.

There are strong pre-clinical data supporting cell therapy for TBI.

Autologous BMMNC reduce BBB permeability and improve spatio-temporal memory.





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Barriers to Development/Opportunities

Finances-Organizational/Logistical Solutions

Sample size and Outcomes Measures-
Novel/Adaptive Designs-(see Finances).

Regulatory-Pooled Safety Master Files;
acceptance of surrogates.

Finances

Patchwork cost sharing: NIH budget shrink, over-commitment on time.

Network organization opportunity for disease themes (neuroscience, CV, hematologic/metabolic).

No Pediatric Cell Therapy home.

cGMP infrastructure.

CIRM – Disease Team Working Group Approach.

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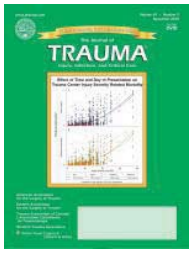
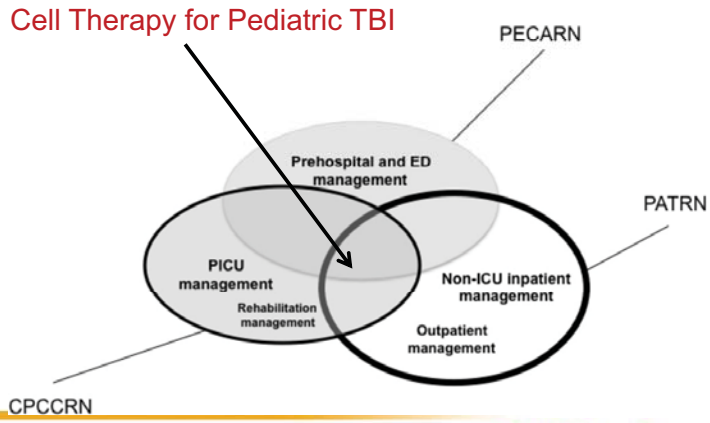
Finances: Pediatric/TBI Networks

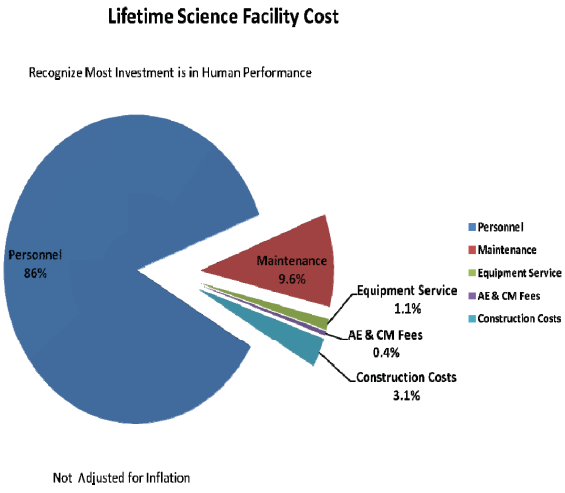
No funded research for INTERVENTIONS or CELL THERAPY in TBI in PEDIATRIC patients in ANY of these networks. The sole network proposed to study TBI in children (PATRN) was not funded by NICHD: USC-CHOLA, Harvard-Children's, UT-Children's Memorial Hermann, Ohio State-Nationwide, UM-Mott, GW-Children's National.





Finances: cGMP Infrastructrure Costs

Rarely accounted for in grant submissions



Program Balance Sheet

GMP Personnel/Supplies-600K/yr
IND Development-100K-1M/submission
Medical Monitors-50K/study
Legacy Recordkeeping-?

Well suited to regional network approach to mitigate costs.

Clinical Outcomes Measures

Bagiella et al., 2010- Global test procedures-the movement away from the dichotomized GOS. CORBIT trial still requires 1426 randomized patients!!!!!

Narayan et al., 2002-Clinial Trials in Head Injury-explains the problem with current clinical trial design/GOS.

McGrayne- 2011-Bayesian analysis for dummies. Smaller sample sizes and surrogate markers.

Outcomes Measures: The case for surrogates

Biological rationale

- ICP-degree of ischemia known to impact almost every organ.
- Issues in past relative to techniques of measurement.
- Composite functional outcomes have problems too!

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Regulation

For any rule to be durable and effective, it must be fair, based upon some goal (safety), articulated easily, and uniformly applied. *From Cox's Rulebook of Parenting Teenagers*.

In a statement on Wednesday, Perry spokesman Mark Miner called the procedure "successful" and confirmed that it included "the innovative use of his own adult stem cells."-Texas Tribune

FDA must review all non-homologous uses, or risk becoming irrelevant.

Regulation: FDA and Translation

Substantial Evidence

"well controlled trial"—see Bayesian approach

FDA Modernization Act-1 trial and confirmatory evidence=substantial evidence.

When can surrogates be used for approval: serious illness, no treatment options, outcome endpoints are difficult, large safety database.

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Conclusions

Focus on more rapid (and safe) movement of treatments into practice for high impact diseases.

Fund Cell Therapy RWGs (not networks) in cross-disciplinary centers with FDA representatives on the team.

> " It's the National Institutes of Health, not the National Institutes of Biology"
>
> - Newt Gingrich

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