Translational Approaches to Brain Injury Treatment

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Traumatic Brain Injury (TBI)

- TBI is a bump, blow, or jolt to the head or a penetrating or blast head injury that disrupts the normal function of the brain.

Football images courtesy of SI.com; blast image courtesy of www.brainline.org
Mechanism of Injury

United States, 2013

- Falls: 47%
- Struck by or against: 16%
- Assault: 8%
- MVC: 14%
- Other: 15%
Figure 1. Annual age-adjusted rates of TBI-related Emergency Department (ED) visits, hospitalizations, and deaths—United States, 2001-2010
# TBI Statistics

<table>
<thead>
<tr>
<th>United States TBI Related Event</th>
<th>Number of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED Visits</td>
<td>2.5 million</td>
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<tr>
<td>Hospitalizations</td>
<td>282,000</td>
</tr>
<tr>
<td>Deaths</td>
<td>56,000</td>
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<tr>
<td>Total</td>
<td>2.8 million in 2013</td>
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Treatment for TBI

• Few successful interventions
• Improvements in emergency and ICU care
• Still lacking in improvements in functional outcome

Guidelines for Field Triage of Injured Patients
Recommendations of the National Expert Panel on Field Triage, 2011
Research for TBI

- Basic science – laboratory research (bench)
- Clinical trials – clinical research (bedside)
- Translational Research
  - bench to bedside
  - bedside to the bench
Progesterone

- Females do better after experimental TBI
- Less brain swelling
- Pseudopregnant female rats do even better
  – progesterone
- Male rats - impact acceleration model of TBI
- Progesterone administered daily starting 30min after injury
Progesterone

• Protects/rebuilds BBB
• Reduces cerebral edema
• Downregulates inflammatory cascade
  – Antagonism of cytokine release
  – Inhibition of immune cell activation and migration
• Decreases apoptosis
• Phase III multinational double-blind RCT
• 1195 patients
• GCS ≤ 8
• Enrolled within 8 hours
• 120 hours of progesterone treatment vs placebo
• Primary Outcome: GOS at 6mo

SyNAPSe: Study of the Neuroprotective Activity of Progesterone in Severe Traumatic Brain Injuries
• Phase III multicenter double-blind RCT
• 49 trauma centers in US; 882 patients
• GCS 4-12
• Enrolled within 4 hours of injury
• 96 hours of progesterone treatment vs placebo
• Primary outcome: GOSE at 6 months
No effect of progesterone

- No improvement in outcome
- No statistical differences between groups
What went wrong?
Very Early Administration of Progesterone for Acute Traumatic Brain Injury

David W. Wright, M.D., Sharon D. Yeatts, Ph.D., Robert Silbergleit, M.D., Yuko Y. Palesch, Ph.D., Vicki S. Hertzberg, Ph.D., Michael Frankel, M.D., Felicia C. Goldstein, Ph.D., Angela F. Caveney, Ph.D., Harriet Howlett-Smith, R.N., Erin M. Bengelink, M.A., Geoffrey T. Manley, M.D., Ph.D., Lisa H. Merck, M.D., M.P.H., L. Scott Janis, Ph.D., and William G. Barsan, M.D., for the NETT Investigators*
Efficacy and safety of dexanabinol in severe traumatic brain injury: results of a phase III randomised, placebo-controlled, clinical trial

Andrew I R Maas, Gordon Murray, Herbert Henney III, Nadim Kassem, Valerie Legrand, Miriam Mangelus, Jan-Paul Muizelaar, Nino Stocchetti, Nachshon Knoller; on behalf of the Pharmos TBI investigators*

Effect of intravenous corticosteroids on death within 14 days in 10 008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial

CRASH trial collaborators*
Efforts in Last 2 Decades

- Over 4000 preclinical studies on TBI
- Over 200 Phase 2 or greater clinical trials

Data from clinicaltrials.gov
• 30 year old male
• Assaulted
• Brief loss of consciousness
• Nausea / vomiting
• Neurologically intact
• Watched in hospital overnight
• 1 month later:
  – No headaches
  – Mild difficulty with problem solving
  – Returned to work
• 40 year old male
• Fall at work
• Brief loss of consciousness
• Headaches
• Neurologically intact
• Discharged from ED
• 1 month later:
  – Continued headaches
  – Significant cognitive difficulties
  – Unable to return to work
Classification by Injury Severity

- Mild (GCS 13-15)
- Moderate (GCS 9-12)
- Severe (GCS 3-8)

<table>
<thead>
<tr>
<th>Points</th>
<th>Eye Opening</th>
<th>Verbal Response</th>
<th>Motor</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>-</td>
<td>-</td>
<td>follows commands</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>oriented</td>
<td>Localizes</td>
</tr>
<tr>
<td>4</td>
<td>spontaneous</td>
<td>confused</td>
<td>normal flexion</td>
</tr>
<tr>
<td>3</td>
<td>to voice</td>
<td>words</td>
<td>abnormal flexion</td>
</tr>
<tr>
<td>2</td>
<td>to pressure</td>
<td>sounds</td>
<td>Extension</td>
</tr>
<tr>
<td>1</td>
<td>none</td>
<td>none</td>
<td>none</td>
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</table>
Severe TBI Patients

Intervention

Improved Outcome

Non-significant study results
Every patient is not the same
Modified from Geoffrey T Manley, MD, PhD UCSF
InTBIR
International Initiative for Traumatic Brain Injury Research

TRACK-TBI
Transforming Research and Clinical Knowledge in Traumatic Brain Injury

NINDS
Common Data Elements
Harmonizing information, streamlining research.

CENTER-TBI
Study Sites

Washington
UCSF
UTSW
Baylor/UT Houston
Austin
Miami
Cincinnati
Pittsburgh
VCU
Maryland
Harvard
Penn

Many additional collaborative sites for data analysis
Precision Medicine Approach

Pathology

Targeted intervention

Appropriate Outcome
Translational Targets
Abnormal Protein Accumulations
Phosphorylated Tau

• Rationale:
  – Abnormally folded proteins may be part of pathology of chronic TBI
  – Identification of those with abnormal protein patterns may lead to treatment

• Pre-clinical studies:
  – Abnormal proteins found in brains of some with repetitive TBI
  – Abnormal protein patterns similar to those found in other known degenerative diseases
Chronic Traumatic Encephalopathy

- NFL Players
- Boxers
- Diagnosed on pathology of deceased individuals

Mez J, et al. 2017 JAMA
Antemortem PET Scans in patient with CTE
Cell Generation Strategies
• Rationale:
  – Cells die after TBI
  – Stem cells may be able to replace cells lost
  – Stem cells may release factors to encourage recovery

• Pre-clinical studies:
  – Grafting of stem cells improves outcome
  – Improvements often seen without integration of stem cells
Study of Modified Stem Cells in TBI (STEMTRA)

• Phase II – patients >1 year from TBI with motor deficit
• SB623 adult bone-marrow derived cells transfected with Notch-1
  – Produce trophic factors
  – Control arm of sham partial burr hole surgery
• Recruiting now
  – 6 sites in CA (UCLA)
  – Ohio Health Research (Columbus)
  – Rehabilitation Institute of Chicago
  – University of Pittsburgh Medical Center
Inflammation and Metabolism
Hyperbaric oxygen

- **Rationale:**
  - Targets TBI induced ischemia
  - Increases amount of O2 inspiration
  - 100% O2 at >1 ATA
  - Increased O2 concentration in plasma and increased delivery of O2 for diffusion to brain tissue

- **Pre-clinical studies:**
  - Reduced lesion size
  - Decreased cell death
  - Reduced inflammatory response
HBO2 Treatment

• Some clinical trials suggest benefit, but systemic reviews/meta-analysis have not confirmed
  – No recommendations that HBO2 effective in mild TBI patients for cognitive or post-concussive symptoms
  – For moderate to severe TBI may be some benefit
    • More studies needed
Acute HBO2 Treatment

- Hyperbaric Oxygen Brain Injury Treatment (HOBIT) trial
  - 200 TBI patients within 6-12 hours of injury, with defined imaging on CT
  - Phase II – efficacy of HBO2
    - Starting March 2018
    - Different ATA of HBO2 +/- NBH compared to placebo and to NBH
Acute Physiological Alterations
Brain tissue oxygen

- **Rationale:**
  - Treating ICP alone may not be sufficient as other abnormal physiologic events in severe TBI
  - Poor brain tissue oxygen puts brain at risk of further injury
  - Need to identify patients / episodes to treat

- **Pre-clinical studies:**
  - Independent episodes of decreased brain tissue oxygen separate from increased ICP
  - Identifying and treating low brain tissue oxygen improves outcomes
Brain Oxygen Optimization in Severe Traumatic Brain Injury - BOOST II

- Primary outcome = physiologic efficacy of PbtO2 treatment from continuous PbtO2 monitoring

<table>
<thead>
<tr>
<th>PbtO2 ≥ 20</th>
<th>PbtO2 &lt; 20</th>
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<tbody>
<tr>
<td>ICP &lt; 20</td>
<td>ICP ≥ 20</td>
</tr>
<tr>
<td>Type A</td>
<td>Type B</td>
</tr>
<tr>
<td>No interventions directed at PbtO2 or ICP needed</td>
<td>Interventions directed at lowering ICP</td>
</tr>
<tr>
<td>Type C</td>
<td>Type D</td>
</tr>
<tr>
<td>Interventions directed at increasing PbtO2</td>
<td>Interventions directed at lowering ICP and increasing PbtO2</td>
</tr>
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Okonkwo D, 2017. Critical Care Medicine
BOOST II Trial

GOS-E at 6 Months

PbtO2 + ICP
- 13% 11% 9% 8% 19% 13% 2% 25%

ICP Only
- 6% 8% 9% 8% 23% 9% 4% 34%

8 = Upper Good Recovery; 7 = Lower Good Recovery; 6 = Upper Disability; 4 = Upper Severity Disability; 3 = Lower Disability

Okonkwo D, 2017. Critical Care Medicine
Spreading Depolarizations

**Rationale:**
- Abnormal electrical activity after TBI
- SDs often seen when tissue undergoes ischemic damage
- Identifying SDs can allow treatment target

**Pre-clinical studies:**
- SDs occur in stroke, SAH, TBI models
- Fewer / no SDs correlated with improved tissue viability
What are SDs?

- Self-propagating wave of near complete breakdown of hemostasis of ion gradients in neurons and astrocytes
- Near-complete sustained depolarization in individual neurons
- Neuronal swelling and distortion of dendritic spines
- Loss of electrical activity
- Causes brain electrical silence
SDs in TBI Patients

- Occur in 53% of patients
- Peak within first 36hr
- Exist independent of other measurable physiological abnormalities
- Associated with worse outcomes

Detecting SDs
SDs with Continuous EEG

Spreading Depolarizations II: Development and validation of spreading depolarization monitoring for TBI management

- University of Cincinnati – coordinating site
- PI: Jed Hartings, PhD
- 6 Additional TRACK-TBI Sites
  - UCSF, Baylor, U Miami, U Pittsburgh, MGH, U Penn
- UC Site PI: Laura Ngwenya, MD, PhD
Clinical observations

Laboratory Investigations

New Intervention
Precision Medicine Approach

- Targeted patient population
- Specific Intervention
- Targeted outcome goals
References

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http://uchealth.com/neurotrauma

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