Accelerating Therapeutic Development for Nervous Systems Disorders: Traumatic Brain Injury

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  – NIDRR
  – Department of Defense

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• Personal opinion. Does not reflect views of Department of Defense or Federal Government
Traumatic Brain Injury
A selective factor in early human evolution

<table>
<thead>
<tr>
<th>Site</th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peru</td>
<td>40%</td>
<td>25%</td>
<td>31%</td>
</tr>
<tr>
<td>Conchopata</td>
<td>25%</td>
<td>31%</td>
<td>26%</td>
</tr>
<tr>
<td>Beringa</td>
<td>50%</td>
<td>31%</td>
<td>33%</td>
</tr>
<tr>
<td>La Real</td>
<td>41%</td>
<td>19%</td>
<td>31%</td>
</tr>
<tr>
<td>Chile</td>
<td>10%</td>
<td>15%</td>
<td>12%</td>
</tr>
<tr>
<td>Early Intermediate (200 BC – 600 AD)</td>
<td>1.7%</td>
<td>10.3%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Middle Horizon (AD 600 – 950)</td>
<td>12.2%</td>
<td>9.3%</td>
<td>10.9%</td>
</tr>
<tr>
<td>Late Intermediate (AD 950 – 1400)</td>
<td>26.0%</td>
<td>38.9%</td>
<td>29.2%</td>
</tr>
<tr>
<td>Terminal Late Intermediate</td>
<td>14.3%</td>
<td>0%</td>
<td>7.0%</td>
</tr>
<tr>
<td>Late Horizon (AD 1400 – 1532)</td>
<td>3.5%</td>
<td>3.2%</td>
<td>3.4%</td>
</tr>
</tbody>
</table>

Epidemiology of TBI

An estimated 1.7 million TBIs occur in the United States annually.

- 52,000 Deaths
- 275,000 Hospitalizations
- 1,365,000 Emergency Department Visits
- ??? Receiving Other Medical Care or No Care*

Division of Injury Response, National Center for Injury Prevention and Control,
Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, 2010
Epidemiology of TBI

- Incidence of 1.7 million ED visits per year in the United States
  - 80% mild, 10% moderate, 10% severe
  - 275,000 hospitalizations
- 52,000 fatalities annually
- 5.3 million Americans—2% of the U.S. population—live with disabilities resulting from TBI
- The single most common cause of death and permanent disability in young people (under age 45).
- Total costs estimated at $56.3 billion per year
Outline of Presentation

1. Heterogeneity of traumatic brain injury
2. Imaging biomarkers show promise for:
   a. Identification of injury subtypes
   b. Surrogate outcome markers in Phase 2
3. Promising molecular targets and novel therapies
Subtypes of TBI

EDH

Contusion/Hematoma

SDH

SAH/IVH

DAI

Diffuse Swelling

Courtesy of Alisa Gean, UCSF
Cortical ADC and DWI abnormalities in TBI
Subcortical ADC/DWI abnormalities in TBI
Cerebral Atrophy after Focal TBI

Acute scan

Rescan

Latour et al, CNRM/NINDS

FLAIR

T1
Cerebral Atrophy after Diffuse TBI

Acute scan

Rescan

18 year old Male, GCS 5, WBV change 9.5%, GOSE 3

Ding et al, J. Neurotrauma 2009
Post-traumatic Cerebral Atrophy Correlates to Acute Hyperintensity Lesion Volume

Ding et al, J. Neurotrauma 2009
Diffusion Tensor Imaging after TBI
Voxel-Based Morphometry Analysis

2 days

6 months

Oldenkamp et al, AAN 2011
Correlation Between Patients’ Progressions on a DCA Map and Long-term Cognitive Outcome

### Post-Traumatic Cerebral Atrophy

#### Freesurfer Analysis

<table>
<thead>
<tr>
<th></th>
<th>Scan 1</th>
<th>Scan 2</th>
<th>% Change</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole brain volume</td>
<td>1346 ± 134</td>
<td>1287 ± 146</td>
<td>-4.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Whole white matter</td>
<td>564 ± 73</td>
<td>531 ± 66</td>
<td>-5.8</td>
<td>0.003</td>
</tr>
<tr>
<td>Whole gray matter</td>
<td>755 ± 77</td>
<td>722 ± 91</td>
<td>-3.7</td>
<td>0.056</td>
</tr>
<tr>
<td>L lat ventricle</td>
<td>4.5 ± 3.4</td>
<td>8.2 ± 4.8</td>
<td>+82.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>R lat ventricle</td>
<td>4.8 ± 3.4</td>
<td>7.4 ± 3.5</td>
<td>+80.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Acute MRI scans were not statistically different from controls*

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Freesurfer Analysis – Subcortical

% Volume Change

Amygdala | Thalamus | Hippocampus | Caudate | Cerebellum

L | R | L | R | L | R

*Significant after correction for multiple comparisons

Warner et al, Arch Neurol 2010;67(11):1336-44
Freesurfer Analysis – Cortical

- Cortical atrophy regionally selective
- Greatest atrophy seen in:
  - Precuneus
  - Posterior Cingulate
  - Superior Parietal Cortex
  - Superior Frontal Cortex

## Relationship with Outcome

Probability of disability or severe disability with whole brain atrophy

<table>
<thead>
<tr>
<th></th>
<th>Any Disability</th>
<th>Severe Disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Atrophy</td>
<td>10%</td>
<td>3%</td>
</tr>
<tr>
<td>5% Atrophy</td>
<td>37%</td>
<td>15%</td>
</tr>
<tr>
<td>10% Atrophy</td>
<td>76%</td>
<td>48%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>% Change in Pilot Study</th>
<th>Detectable % change between two groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Brain Volume</td>
<td>-4.38</td>
<td>20.0</td>
</tr>
<tr>
<td>White Matter Volume</td>
<td>-5.85</td>
<td>17.6</td>
</tr>
<tr>
<td>Ventricular Volume</td>
<td>60.00</td>
<td>-12.4</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>-11.46</td>
<td>10.5</td>
</tr>
<tr>
<td>Amygdala</td>
<td>-17.14</td>
<td>8.6</td>
</tr>
<tr>
<td>Thalamus</td>
<td>-11.98</td>
<td>8.6</td>
</tr>
<tr>
<td>Cuneus</td>
<td>-12.31</td>
<td>14.8</td>
</tr>
<tr>
<td>Precuneus</td>
<td>-12.32</td>
<td>11.4</td>
</tr>
<tr>
<td>Superior Parietal</td>
<td>-14.98</td>
<td>9.5</td>
</tr>
</tbody>
</table>
Default Mode Network in TBI

Averinas et al, INS 2011
Pathology of Diffuse Vascular Injury after TBI


Assessment of vessel reactivity with CO₂


TOPOLOGICAL DATA ANALYSIS

TRACK-TBI

Courtesy of Geoff Manley, UCSF, and TRACK-TBI Investigators
CT FINDINGS

CT Positive

CT Negative

Courtesy of Geoff Manley, UCSF, and TRACK-TBI Investigators
GOSE: 3 MONTHS

GOS-E 2

GOS-E 8

Courtesy of Geoff Manley, UCSF, and TRACK-TBI Investigators
PTSD

PTSD Negative

PTSD Positive

Courtesy of Geoff Manlev, UCSF, and TRACK-TBI Investigators
Anti-Nogo

- Nogo-A is a protein in CNS myelin that inhibits neurite growth
- Models of spinal cord injury (SCI) treatment with antibodies of Nogo-A results in
  - Upregulation of growth-specific proteins
  - Enhanced regenerative and compensatory sprouting of fibers
  - Formation of new functional connections
- In TBI animals with unilateral sensorimotor cortex lesions treatment with Nogo-A antibody results in
  - Fibers from the intact corticofugal system crossed the midline, innervating brainstem and spinal cord
  - Improvements of functional recovery
- Phase I clinical trial using intrathecal anti-Nogo-A antibody (Novartis) to subjects with acute SCI has been completed
- Multicenter Phase II trial is currently in preparation (Novartis)
Anti-Nogo in Experimental TBI

Anti-Nogo in Experimental SCI in Macaques

Freund et al, Nat Med 2006;12:790
Freund et al, J Comp Neurol 2007;502:644
Endothelial Progenitor Cells

Candidate Therapies to Stimulate Angiogenesis

- Erythropoietin
- Sildenafil
- Statins
- G-CSF
- VEGF
- Pioglitazone
- Enriched Endothelial Progenitor Cells
  - From cord blood or bone marrow
- Exercise
Bone-Marrow Derived Mesenchymal Stem Cells

- SB623 cells are human bone-marrow derived mesenchymal stromal cells (SanBio, Inc)
  - Transfected with *Notch Intracellular Domain*
  - Off the shelf, allogenic product
  - Preclinical data in
    - Stroke
    - Parkinson’s disease
    - Spinal Cord Injury
    - TBI
- First-in-human studies ongoing in MCA stroke
  - Stanford
  - Univ. of Pittsburgh
- Produced by SanBio, Inc.
SB623 cells promote functional recovery and regeneration. Intracranial delivery of SB623 significantly increases host cell proliferation (Ki67, top panel) and neural progenitors (nestin, middle panel) in the subventricular zone (SVZ) and cortex (CTX) 1 and 3 months post-controlled cortical impact injury. Representative images of the injured cortex are shown (20X lens). SB623 cells also significantly improve sensory-motor ability (Rotarod test shown in bottom plot; similar results were obtained for the elevated body swing test and neuroscore). Mean SD; *p < 0.05 versus Vehicle Control; 300,000 SB623 cells implanted at 1 week post-TBI.
Collaborators

- **Center for Neuroscience and Regenerative Medicine**
  - Dan Perl
  - Carol Moore
  - Kimbra Kenney
  - Carlee Culver
  - Tanya Bogoslovsky
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  - Dzung Pham
  - John Butman

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  - Jun-Yi Wang
  - Khamid Bakhadirov
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  - Matthew Warner
  - Lifang Peng
  - Nasreen Sayed
  - Christopher Paliotta
  - Chris Madden
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  - Anne Hudak
  - Mike Devous
  - Roderick McColl
  - Tony Whittemore

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  - Randi Dubiel
  - Cindy Dunklin
  - Eva Wooster
  - Elizabeth Callender

- **Department of Defense**

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