Clinical-Pathological Assessment of Severe (AIS A) Traumatic Acute Thoracic Spinal Cord Injury: Post-durotnomy/myelotomy Observations from the INSPIRE Trial

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Disclosures and Acknowledgements

• **Commercial disclosures**
• RT Layer, T Ulich, KM Neff and LK Masuoka are employees of In Vivo Therapeutics

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Clinical Approach for Acute SCI: The **Neuro-Spinal Scaffold™**

**Porous, biodegradable device**

*In vivo* residence time ~ 4-8 weeks

Intraparenchymal implantation within acute cavity following durotomy and often myelotomy

- **Control**
  - Cyst

- **Neuro-Spinal Scaffold**
  - Reduces cyst volume, spares white matter, and promotes generation of remodeled tissue in rat contusion model

- Remodeled tissue is rich in neuropermissive ECM and facilitates endogenous sprouting

[Images of scaffold and histological sections]
Neuro-spinal scaffolds

- Neuro-spinal scaffolds + Neural stem cell treatment reduced tissue loss from secondary injury processes as well as in diminished glial scarring
- Enhanced regenerative axons and motor functional recovery in a rat and a monkey SCI

Teng YD et al., PNAS 2002 and InVivo Therapeutics (http://www.invivotherapeutics.com)
The INSPIRE Study – Study Design

**InVivo Study of Probable Benefit of the Neuro-Spinal Scaffold™ for Safety and Neurologic Recovery in Subjects with Complete Thoracic AIS A Spinal Cord Injury**

- **Primary Objective:** To evaluate whether the Scaffold is safe and demonstrates probable benefit for the treatment of AIS A T2-T12/L1 spinal cord injury (within 96 hrs of injury)
- **Primary Endpoint:** AIS conversion by 6 month follow-up visit
- **Objective Performance Criterion:** At least 25% of subjects convert from complete paraplegia (AIS A) to partial paralysis by 6 months
  - Large, multinational, natural history databases consistently indicate that only 12-16% of subjects with complete (AIS A) thoracic injury will convert to an improved AIS grade within 6 months after injury
- **Additional Endpoints:** Sensory and motor scores, bladder and bowel function, Spinal Cord Independence Measure, pain, quality of life
- **Plan to enroll 20 subjects**
The INSPIRE Study: Site Update

23 Active Sites in the US and Canada

- Dr. Paul Arnold - KUMC
- Dr. Maxwell Boakye – Univ of Louisville
- Dr. Joseph Ciacci - UCSD
- Dr. Dom Coric, Dr. Bill Bockenek - CNSA
- Dr. Nadar Dahdaleh - Northwestern
- Dr. Travis Dumont – Univ of AZ Medical
- Dr. Michael Fehlings – Toronto Western
- Dr. James Harrop – Thomas Jefferson
- Dr. Bob Heary - Rutgers
- Dr. Eric Horn – Goodman Campbell
- Dr. Patrick Hsieh - USC
- Dr. Arthur Jenkins – Mount Sinai
- Dr. Kumar Kakarla – Barrow
- Dr. Kee Kim – UC Davis
- Dr. Shekar Kurpad – MC of WI
- Dr. Stuart Lee – Vidant Health
- Dr. Paul Okonkwo – UPMC
- Dr. Ahmed Raslan - OHSU
- Dr. Alex Ropper – Baylor
- Dr. Chris Shaffrey – UVA
- Dr. Paul Santiago, Dr. Zach Ray – WashU
- Dr. James Schuster – UPENN
- Dr. Steve Yocom – Cooper
The INSPIRE Study: 23 Active Sites (22US, 1Canada)
The INSPIRE Study: An Opportunity to Observe the Acutely Injured Human Spinal Cord

**InVivo Study of Probable Benefit of the Neuro-Spinal Scaffold™ for Safety and Neurologic Recovery in Subjects with Complete Thoracic AIS A Spinal Cord Injury**

- **Primary Objective:** To evaluate whether the Neuro-Spinal Scaffold, a biodegradable investigational device, is safe and demonstrates probable benefit for the treatment of complete T2-T12/L1 spinal cord injury.

- The Neuro-Spinal Scaffold is implanted via durotomy and often myelotomy into acutely injured (within 96 hours) spinal cord parenchyma to facilitate healing and possibly neural regeneration.

- The procedure provides a unique opportunity to classify injury types and correlate visible cord pathology with neurologic outcome following Scaffold implantation.

- Prior anatomic injury classifications have been performed following autopsy and tissue fixation (Bunge et al., 1993; Kakulas and Bedbrook, 1969).
• ‘Contusion-type’ injuries (5 subjects) displayed intact pial surface and peripheral white matter.

• Following dorsal myelotomy, gentle irrigation of loose necrotic debris revealed an intra-medullary cavity.

• Scaffolds implanted into the cavity were generally not visible but could be identified using ultrasound.

• ‘Compound-type’ injuries (3 subjects) displayed elements of contusion, pial-disruption, laceration, maceration, and damaged peripheral white matter but preserved cord continuity.

• Scaffolds implanted into compound-type injuries remained visible.
In ‘Contusion-Type’ injuries, the dorsal cord surface is intact.
‘Compound-Type’ Injuries

Subject 2
(103001)
45.6 hours
post-injury, A→A

Subject 5
(109001)
69.1 hours
post-injury, A→B

Subject 6
(104001)
8.8 hours
post-injury, A→B

In ‘Compound-Type’ injury, the pia is breached and there is visible but incomplete cord parenchymal separation.

In 'Compound-Type' injury, there is a cavity with maceration. 
The INSPIRE Study - Injury Type Is Not Predictive of AIS Conversion

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Sex</th>
<th>NLI</th>
<th>Time to Implant (h)</th>
<th>Neurologic Outcome to Date</th>
<th>Injury Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25 M</td>
<td>M</td>
<td>T11</td>
<td>9.2</td>
<td>Converted to AIS C at 1 month</td>
<td>Contusion</td>
</tr>
<tr>
<td>2</td>
<td>22 F</td>
<td>F</td>
<td>T7</td>
<td>45.6</td>
<td>Remains AIS A at 12 months</td>
<td>Compound</td>
</tr>
<tr>
<td>3</td>
<td>56 M</td>
<td>M</td>
<td>T4</td>
<td>82.6</td>
<td>Converted to AIS B at 1 month</td>
<td>Contusion</td>
</tr>
<tr>
<td>4</td>
<td>28 M</td>
<td>M</td>
<td>T3</td>
<td>52.9</td>
<td>Remains AIS A at 12 months</td>
<td>Contusion</td>
</tr>
<tr>
<td>5</td>
<td>18 F</td>
<td>F</td>
<td>T8</td>
<td>69.1</td>
<td>Converted to AIS B at 6 months</td>
<td>Compound</td>
</tr>
<tr>
<td>6</td>
<td>21 M</td>
<td>M</td>
<td>T10</td>
<td>8.8</td>
<td>Converted to AIS B at 2 months</td>
<td>Compound</td>
</tr>
<tr>
<td>7</td>
<td>25 M</td>
<td>M</td>
<td>T4</td>
<td>21.3</td>
<td>Remains AIS A at 3 months</td>
<td>Contusion</td>
</tr>
<tr>
<td>9</td>
<td>37 M</td>
<td>M</td>
<td>T3</td>
<td>40.4</td>
<td>Converted to AIS B at 3 months</td>
<td>Contusion</td>
</tr>
</tbody>
</table>

**NOTE:** Subjects 8 and 10 passed away with the cause of death deemed unrelated to Neuro-Spinal Scaffold™ or implantation.
Conclusions

• We observed either ‘Contusion-type’ injury with central necrosis and peripheral tissue sparing, or ‘Compound-type’ injury with focal laceration and pial-disruption.
  – Both injury types could be successfully implanted with the scaffold

• Neurological outcome has been assessed in 6 males and 2 females (aged 18-55) implanted with Scaffolds 9-83 hours after injury.

• Injury type was not predictive of AIS conversion.
  – Of 5 patients with contusion-type injury, one converted to AIS C by 1 month and two to AIS B by 1 and 3 months. Of 3 patients with compound-type injury, two converted to AIS B by 2 and 6 months.

• This work could provide the basis of a novel clinical-pathological classification system for severe blunt injury of the human spinal cord