



# InVivo Therapeutics

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Developing Innovative Products for  
Spinal Cord Injury

# Forward-Looking Statements

Before we begin, we would like to remind everyone that during our presentation, we will be making forward-looking statements about our business, plans, and objectives. These statements are based on how we see things today. These statements can be identified by words such as believes, estimates, expects, or similar references to the future, and include statements we may make regarding our product development strategy, business prospects, and clinical and operational milestones. We wish to caution you that actual events or results may differ materially from those expressed in forward-looking statements made by us or on our behalf. For more information on the many factors that can result in actual performance differing from our forward-looking statements, please see our filings made with the SEC, including our 2015 Annual Report on Form 10-K filed on March 4, 2016 and our Quarterly Reports on Form 10-Q filed on May 6, 2016 and August 4, 2016.



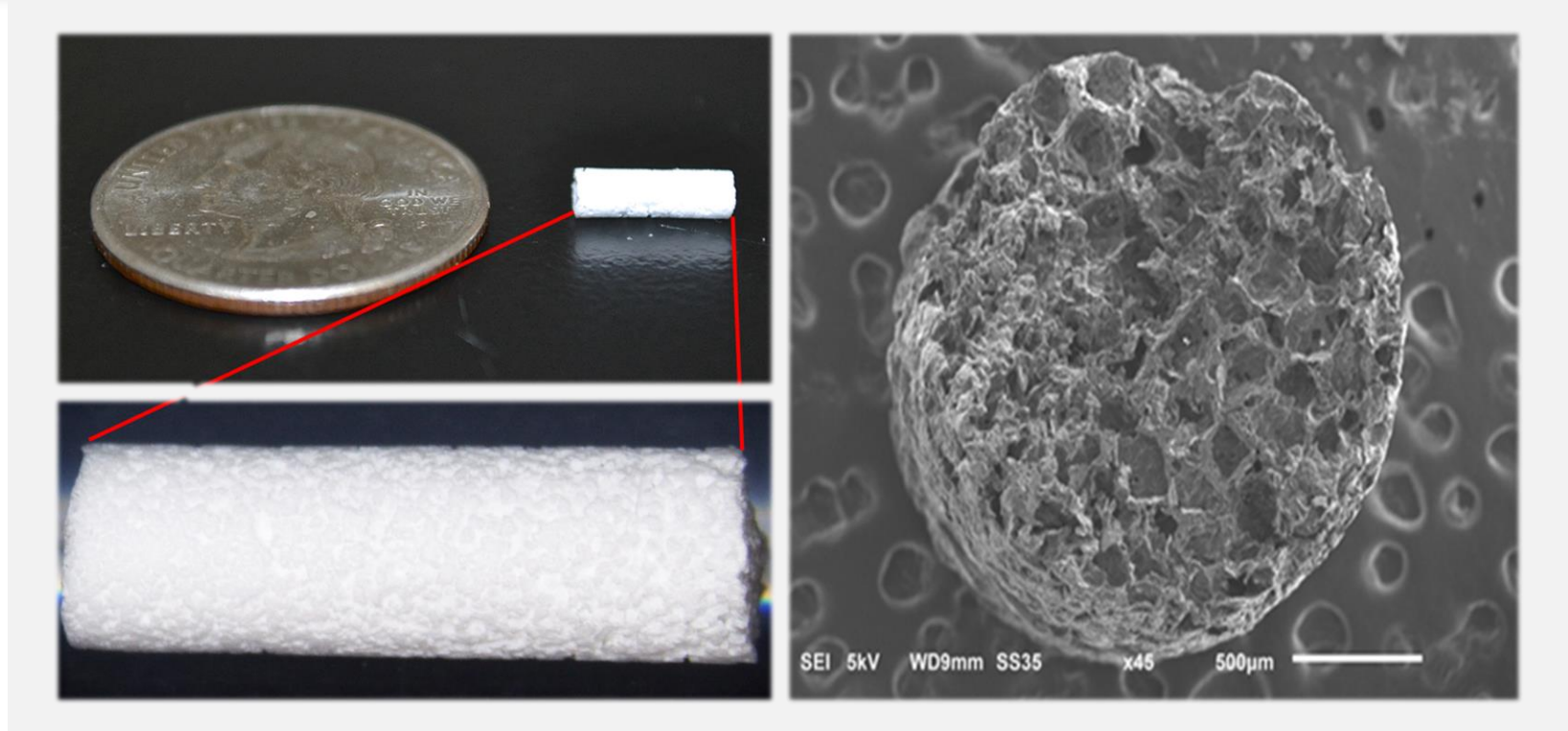


## *Neuro-Spinal Scaffold™* for Acute SCI

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Designed to Promote Healing in  
Spinal Cord Injury

# InVivo's Pioneering Clinical Approach for Acute SCI: The *Neuro-Spinal Scaffold*™

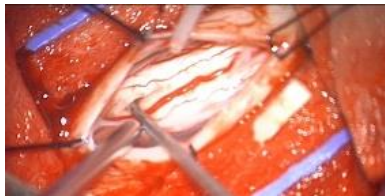
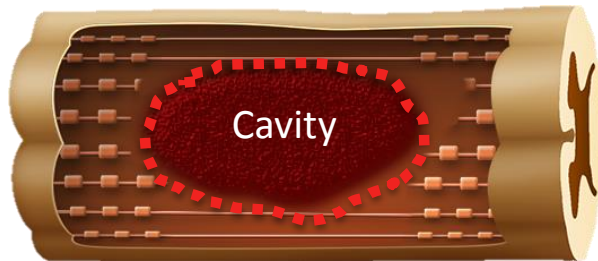


- Highly porous biopolymer *Neuro-Spinal Scaffold*
- Composition:
  - PLGA is the biodegradable skeleton along which cells can grow
  - Poly-L-Lysine promotes cellular adhesion



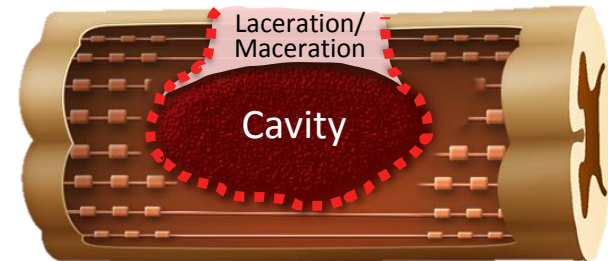
# Two Types of Spinal Cord Injury: Closed (Contusion) vs Open (Compound) Injury

## Closed (Contusion) Injury



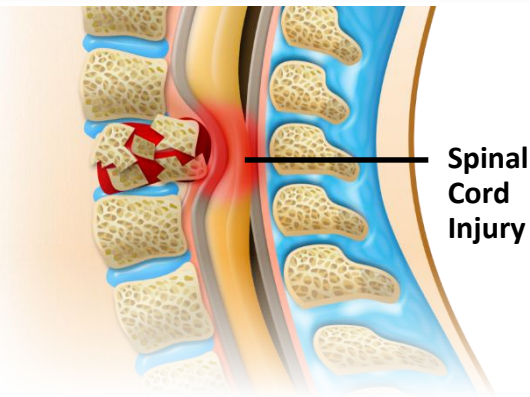
- Outer region of cord is preserved and cord appears intact externally
- Injury leads to cavity filled with necrotic material
- Pressure builds inside the cord, which may lead to further injury
- Preclinical model: contusion injury

## Open (Compound) Injury



- Outer region of cord is breached and injury is visible externally
- Myelotomy (cutting into the cord) may not be required
- Minimal added pressure inside cord
- Preclinical model: hemicordecotomy

# Progression of Acute SCI to Post-Traumatic Cavity in Contusion Injuries



Hemorrhage  
&  
Spinal Cord  
Swelling

Reduced  
Blood Flow  
&  
Ischemic  
Necrosis

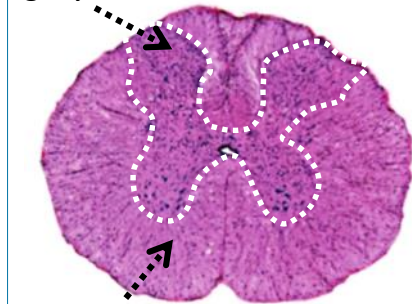
Cavity  
Development  
&  
White Matter  
Reduction

Chronic injury  
and mature  
cavity formation

Time

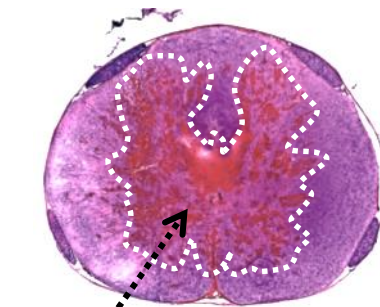
**Normal**

*Highly vascularized  
gray matter*



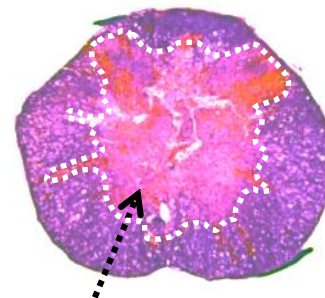
*White matter*

**2 hours after SCI**



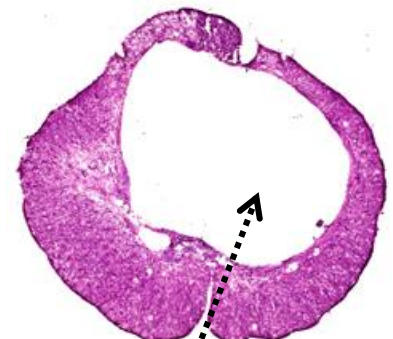
*Acute hemorrhage &  
necrosis*

**24 hours after SCI**



*Liquefactive necrosis*

**12 weeks after SCI**



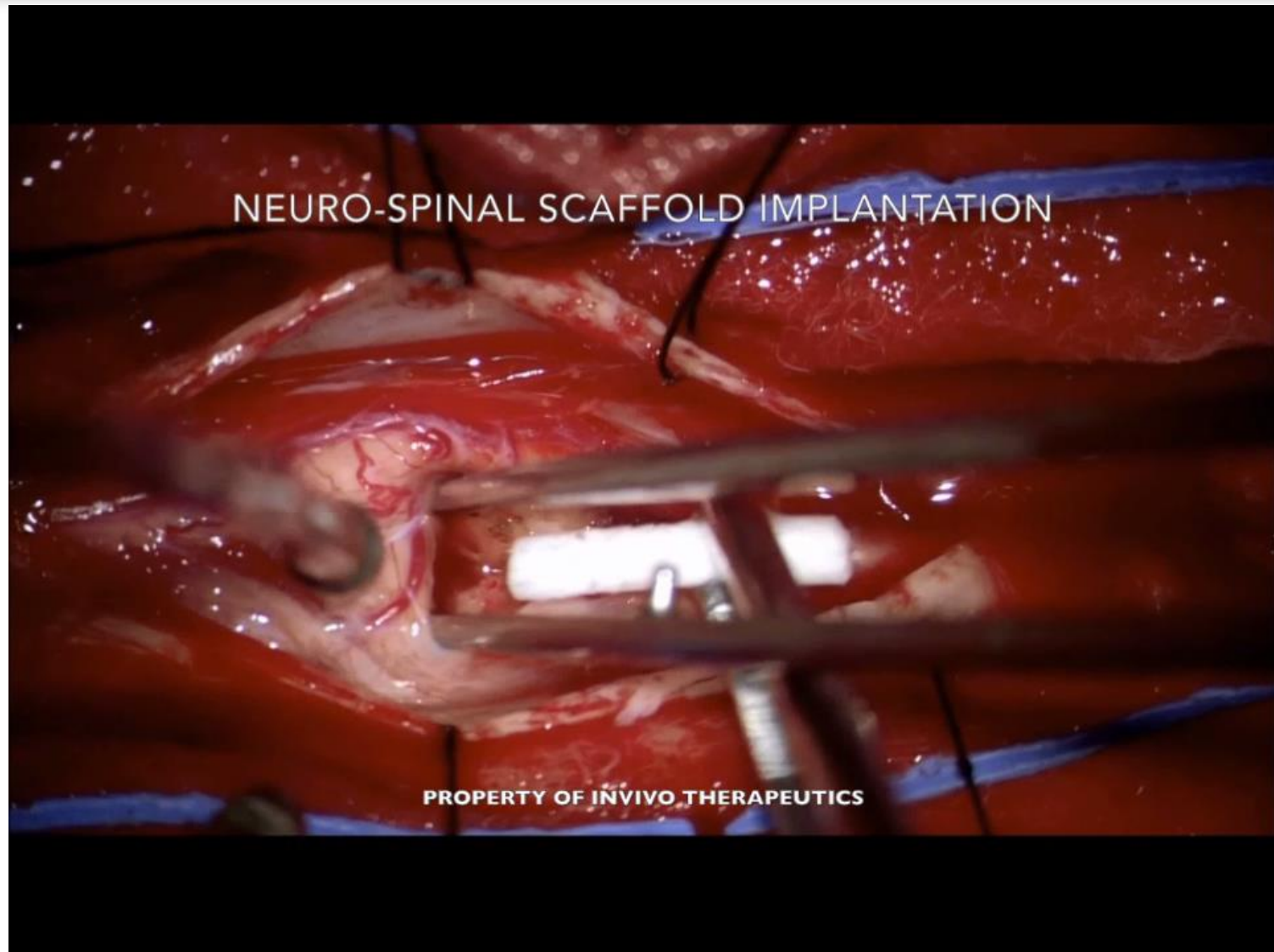
*Mature cavity*

*Histology from rat contusion model of SCI*

Poster D8-06; National Neurotrauma  
Society 2015 Symposium; Santa Fe, NM.



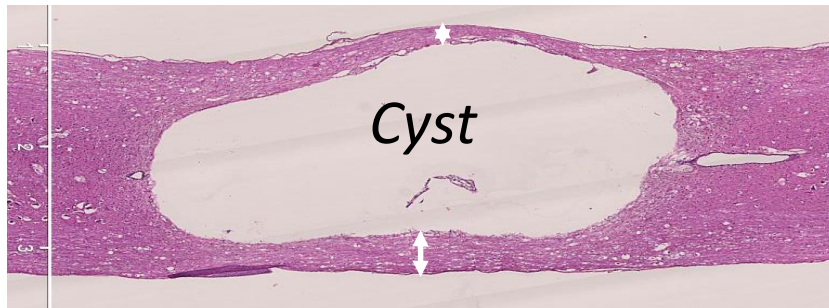
# First *Neuro-Spinal Scaffold*™ Implantation in Human Contusion Injury



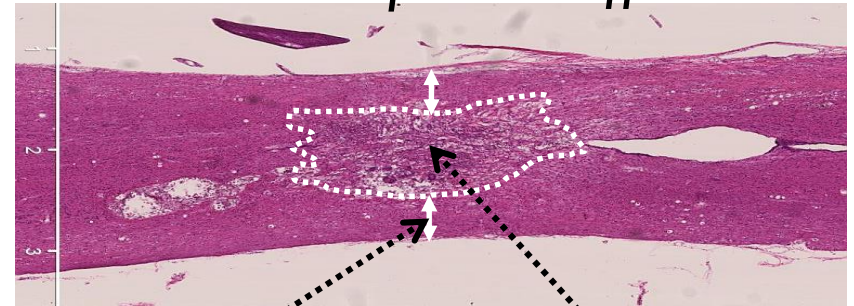
# The *Neuro-Spinal Scaffold*<sup>TM</sup> Preserves Macroscopic Spinal Cord Architecture

## Rat Acute Spinal Cord Contusion Injury (at 12 weeks)

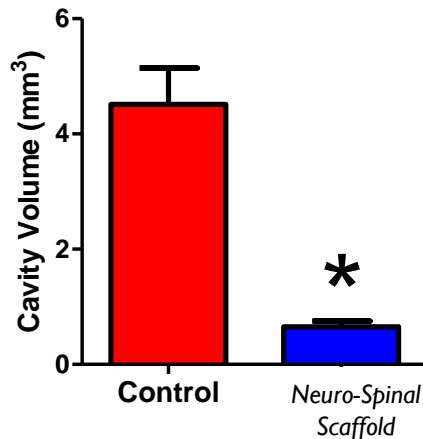
Control



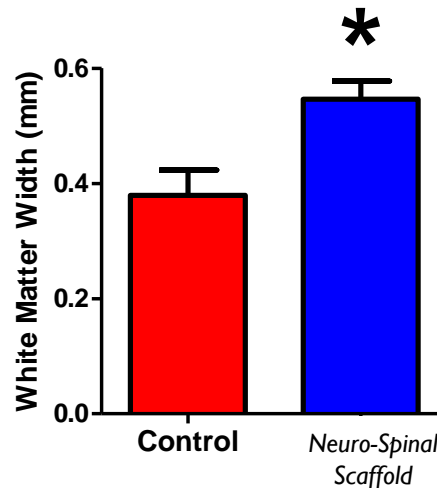
*Neuro-Spinal Scaffold*



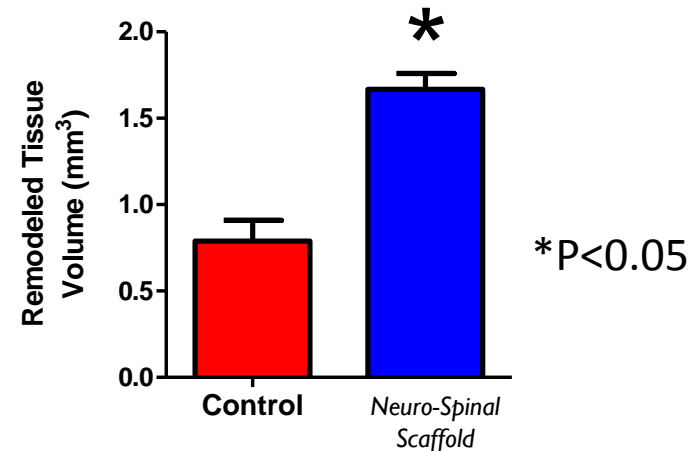
Cyst Reduction



White Matter Sparing



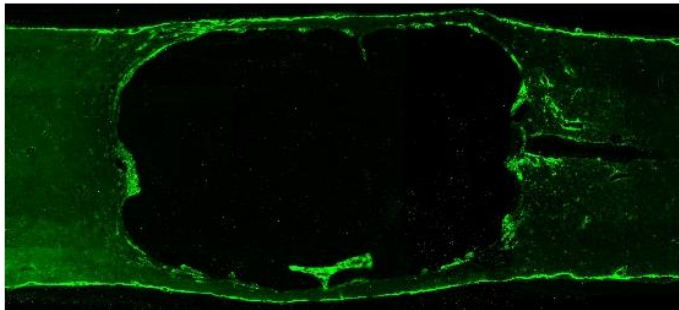
Remodeled Tissue





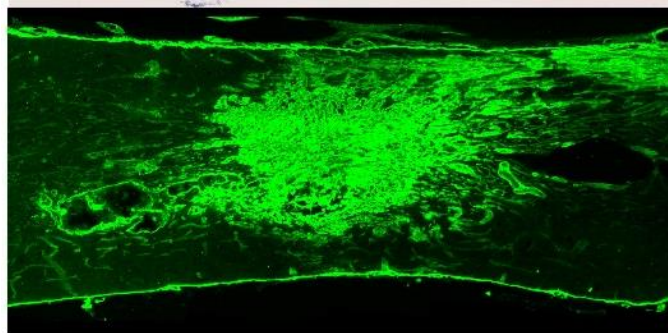
# The *Neuro Spinal Scaffold*<sup>TM</sup> Increases Remodeled Tissue Supporting Neural Regeneration

Rat Acute Spinal Cord Contusion Injury (at 12 weeks)  
Control

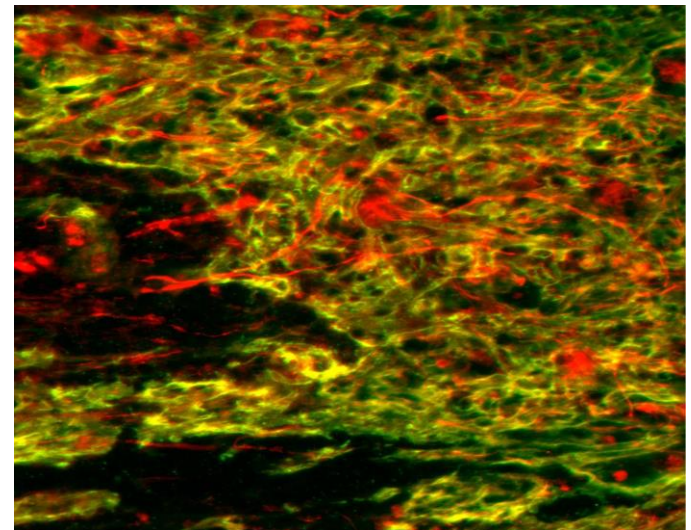


Minimal neuro-permissive matrix

*Neuro-Spinal Scaffold*



Remodeled tissue with extensive  
neuro-permissive matrix

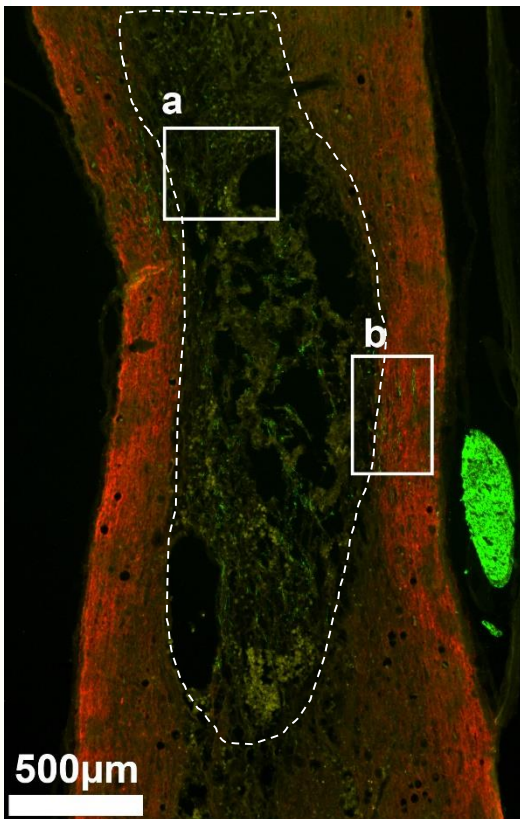


Neuro-permissive matrix supports  
neural regeneration

# Neural Regeneration and Remyelination with Schwann Cells after *Neuro-Spinal Scaffold*<sup>TM</sup> Implantation

## Contusion Injury

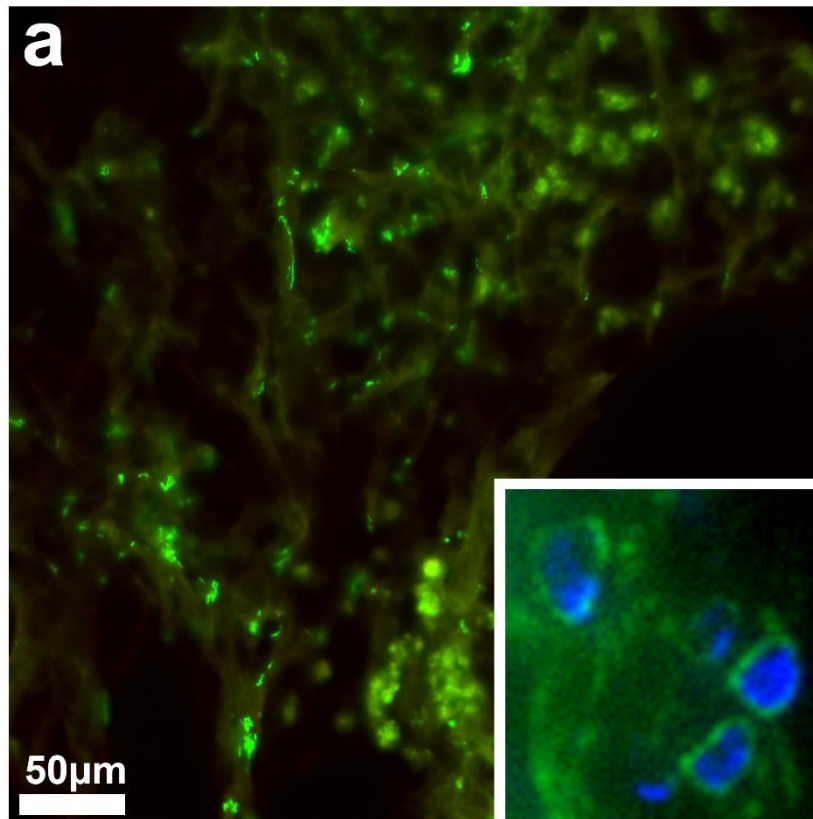
Central epicenter (a) and white matter (b)



Rat Acute Spinal Cord Contusion Injury (at 12 weeks)

## Epicenter

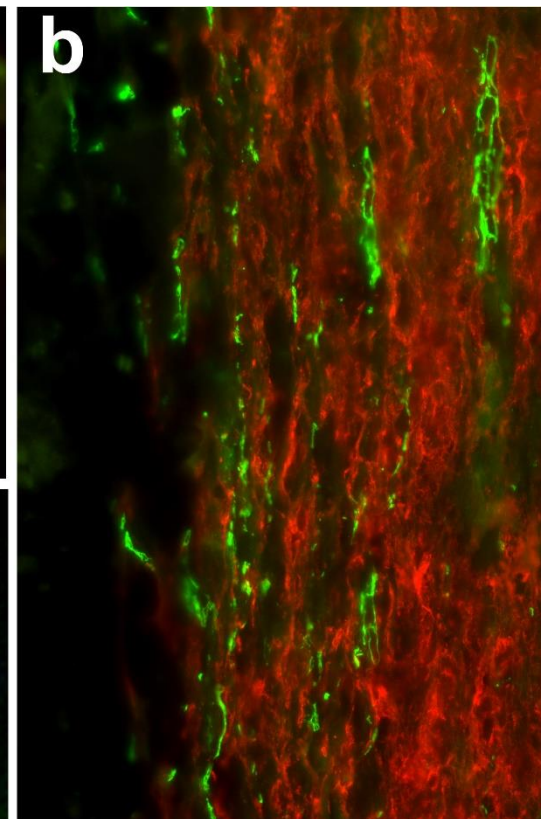
Schwann Cells aid neural regeneration



Inset: Schwann cells ensheathing axons  
Oligodendrocytes Schwann Cells

## White Matter

Schwann Cells restore signal transduction

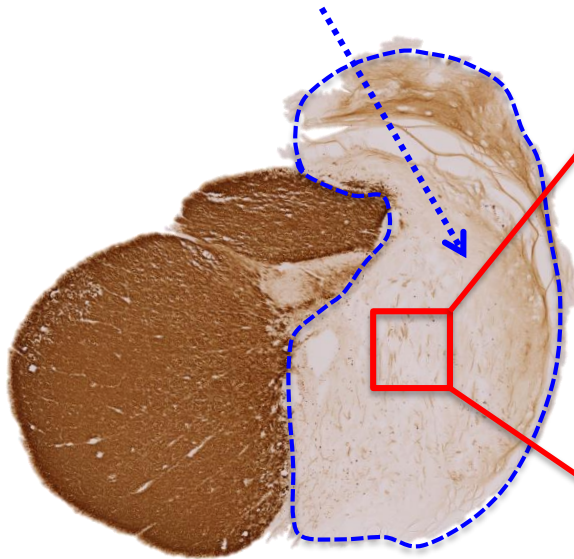




# Neuro-Spinal Scaffold™ Promotes Neural Regeneration and Functional Recovery

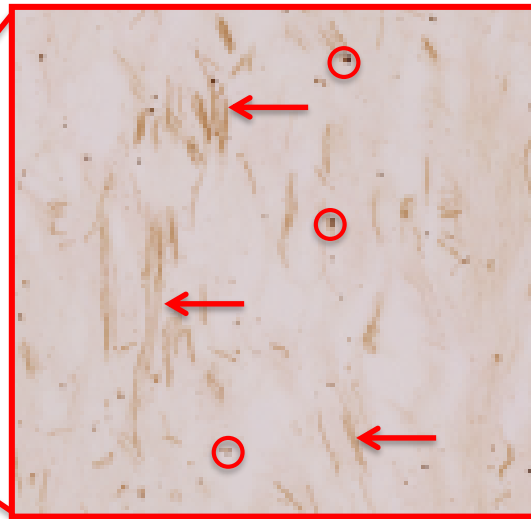
## Primate Hemicorpectomy Model (at 3 Months)

**Increased remodeled tissue**

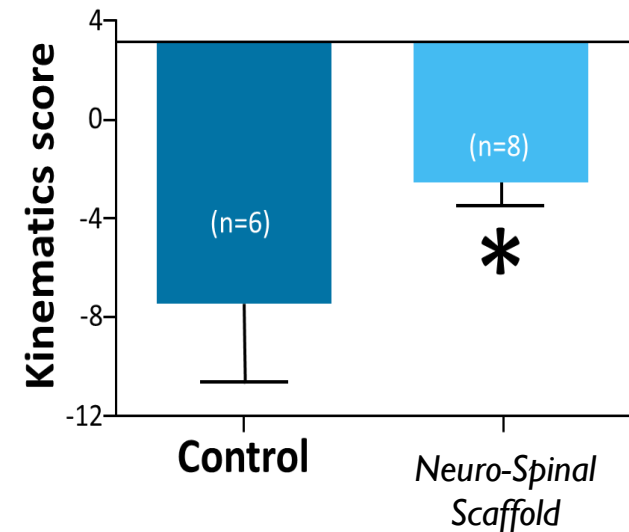


**Neural regeneration**

*Myelin basic protein stained axons in remodeled tissue*



**Improved functional recovery**



Hemicorpectomy Model

# The INSPIRE Study

## 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

- Designed as 20-patient pivotal study to be used for HDE application
  - Endpoint: improvement in ASIA Impairment Scale (AIS) grade by 6 months
- Objective Performance Criterion (study success definition) – at least 25% of patients improve AIS grade by 6 months
- Additional Endpoints: sensory and motor scores, bladder and bowel function, Spinal Cord Independence Measure, pain, quality of life
- 23 clinical sites (US and Canada)
  - Plan also to include United Kingdom clinical sites in 2016

NOTE: FDA has recommended inclusion of a control arm in the study as part of a Study Design Consideration (SDC). As is typical of the regulatory process, InVivo has previously addressed a number of SDCs regarding the study. InVivo is engaged in a discussion with the FDA regarding this SDC and will provide an update if substantial changes are made to the study protocol. InVivo continues to believe that the current study design is sufficient to demonstrate safety and probable benefit in support of an HDE application for marketing approval.



# Promising Neurologic Outcomes and Favorable Safety Profile in The INSPIRE Study

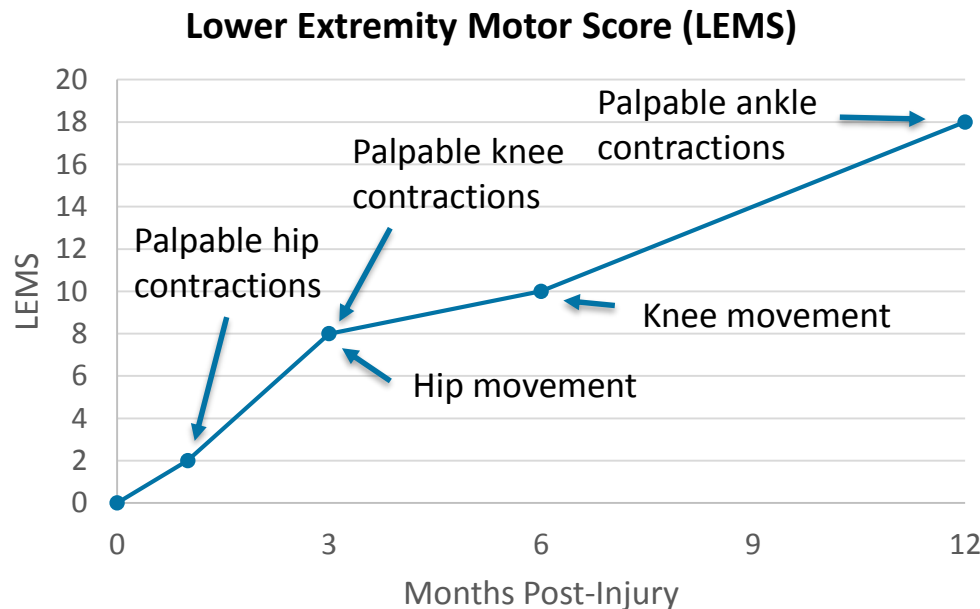
Subject	Neurologic Level of Injury	Injury Type	Time to Implant	Neurologic Outcome to Date
1	T11	Closed	9 hrs.	Converted to AIS C at 1 month
2	T7	Open	46 hrs.	Remains AIS A at 12 months
3	T4	Closed	83 hrs.	Converted to AIS B at 1 month
4	T3	Closed	53 hrs.	Remains AIS A at 6 months
5	T8	Open	69 hrs.	Converted to AIS B at 6 months
6	T10	Open	9 hrs.	Converted to AIS B at 2 months
7	T3	Closed	21 hrs.	Remains AIS A at 3 months
9	T4	Open	40 hrs.	Converted to AIS B at 3 months

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

- No obvious correlations between AIS conversions and injury level or type or time to implant
- Conversions observed with open injuries unlikely to benefit from surgical decompression alone
- **Delayed and prolonged recoveries indicate that neural regeneration may be taking place beyond the acute injury period**

# Marked Long-term Improvement in First Patient

- Improved from T11 complete AIS A to AIS C at 1 month
  - <5% of AIS A patients with a T10-T12 injury progress to AIS C or D at 1 month <sup>1</sup>
- Regained bowel function and improved bladder function
- Continued significant motor improvement from months 6 to 12



<sup>1</sup> Zariffa *et al.*, Spinal Cord (2011)





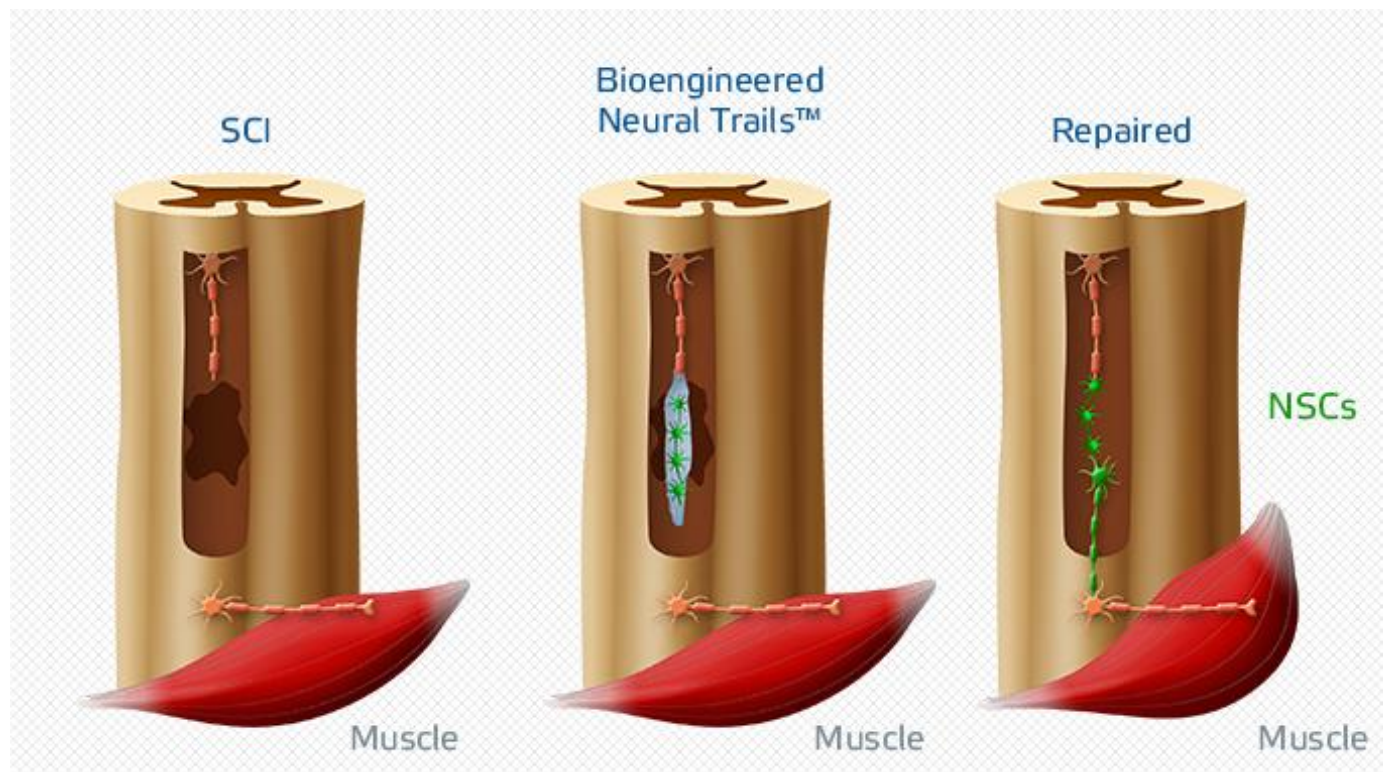
## InVivo's Chronic SCI Product: Bioengineered Neural Trails™

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Neural Stem Cells Incorporated into an  
Injectable Scaffold for Minimally-  
Invasive Delivery

# Bioengineered Neural Trails™: InVivo's Novel Neural Stem Cell Product for Chronic SCI

- Neural stem cells incorporated into an injectable scaffold for minimally-invasive delivery designed to:
  - Bridge the site of injury to create neuronal detour circuits
  - Activate the resting potential of network below injury site





# Bioengineered Neural Trails Provide Many Advantages Over Conventional Bolus Injections

## **Bolus approach**

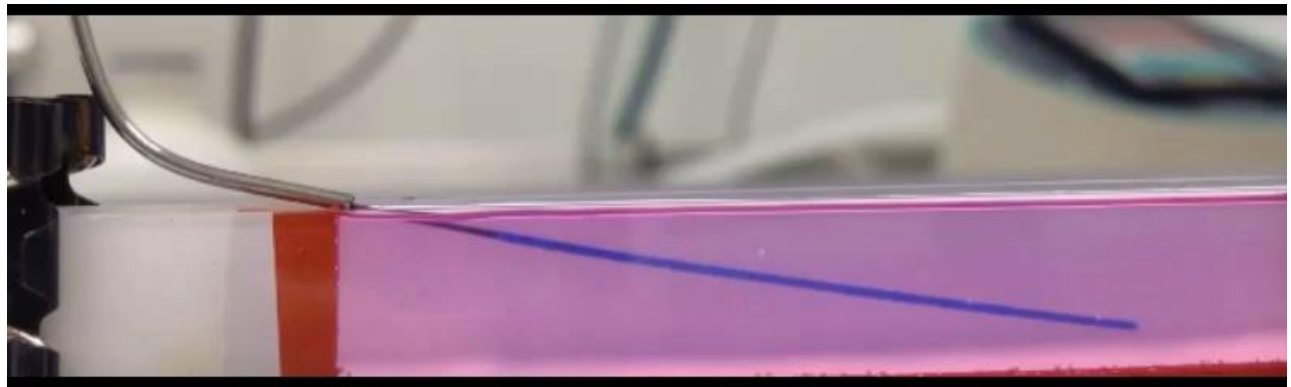
- Reflux at multiple injection sites
- Sub-optimal cell distribution
- No longitudinal connectivity



Collagen matrix to simulate spinal cord

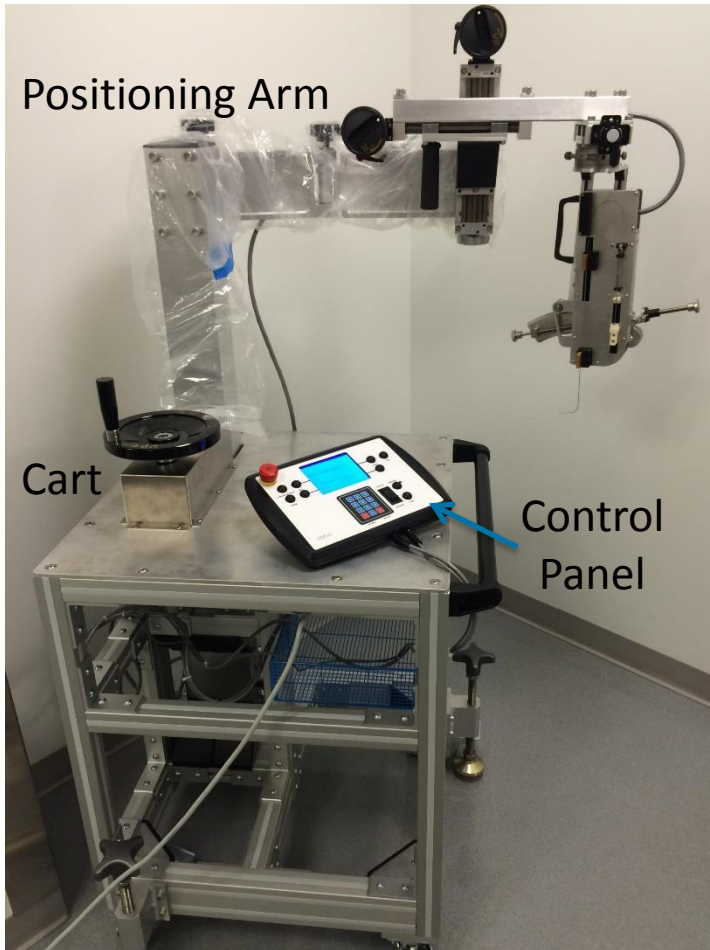
## **Trail approach**

- No reflux at single injection site
- Homogeneous cellular suspension
- Immediate longitudinal connectivity

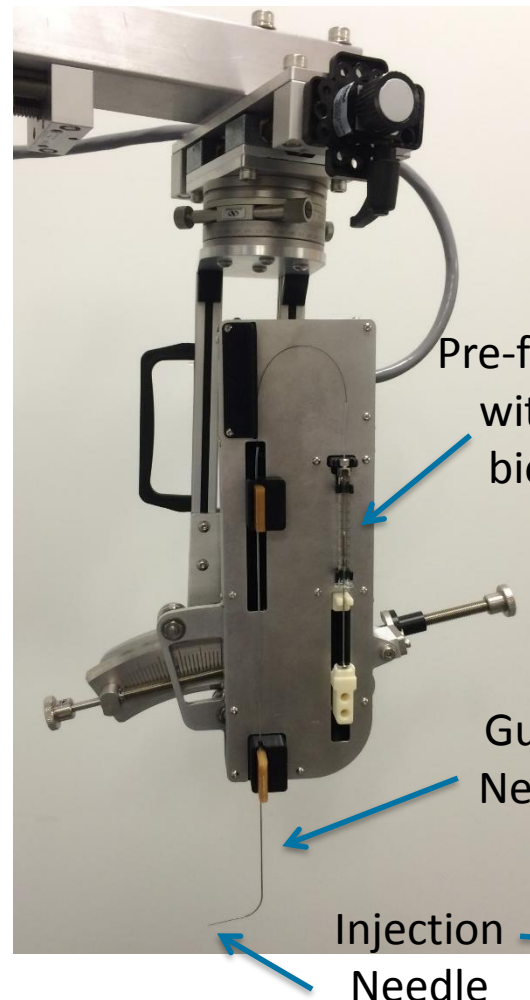


# A Novel Surgical Device for Creation of Bioengineered Neural Trails™

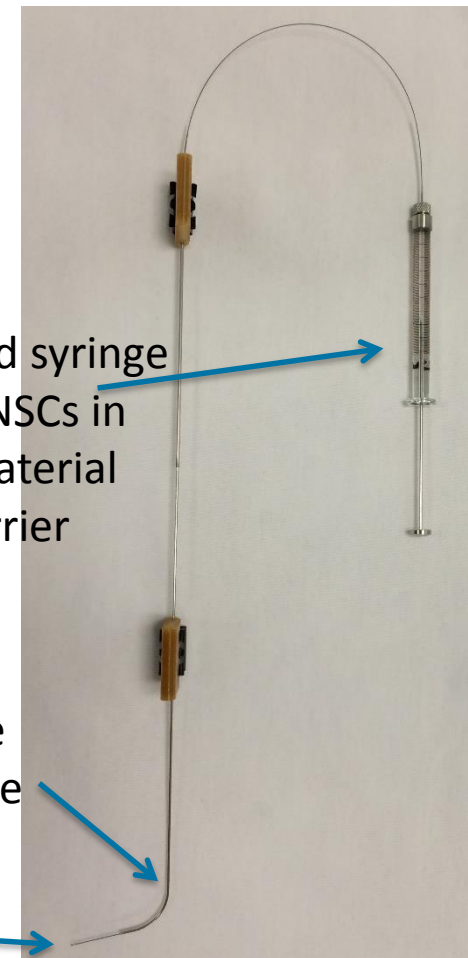
**Complete Device**



**Dispensing System**



**Disposable Injection Assembly**



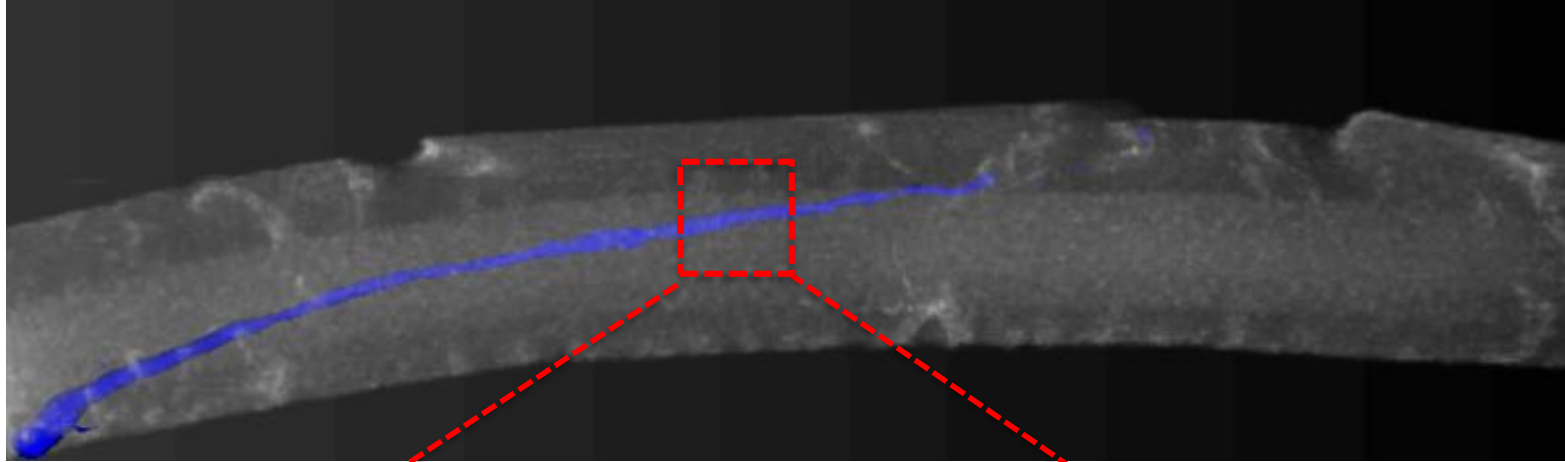


# Feasibility of Proprietary Device Demonstrated in Pilot Porcine Study

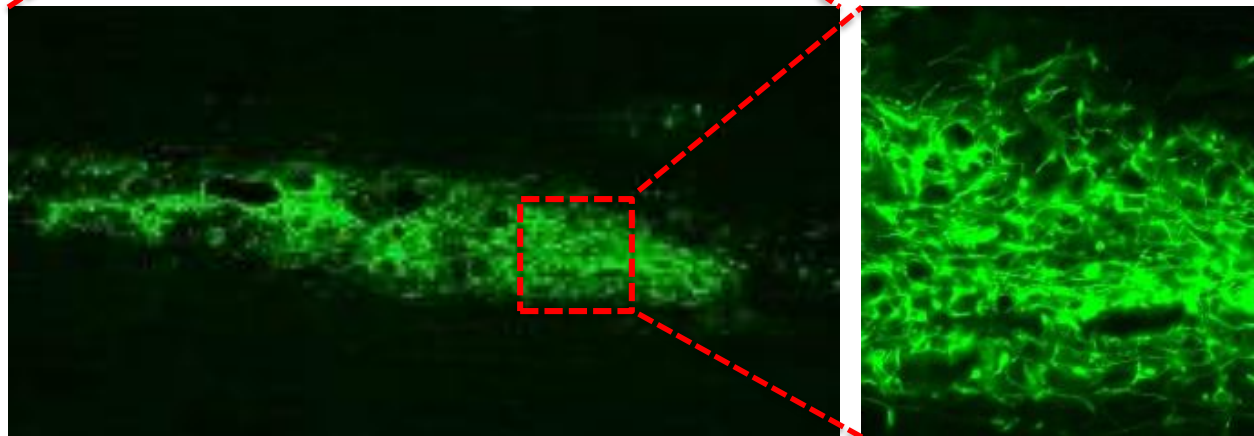


# The Bioengineered Neural Trail Creates a Continuous Neural Plexus Bridging the Injury

**3D MRI reconstruction demonstrating continuous Bioengineered Neural Trail in a pig spinal cord**



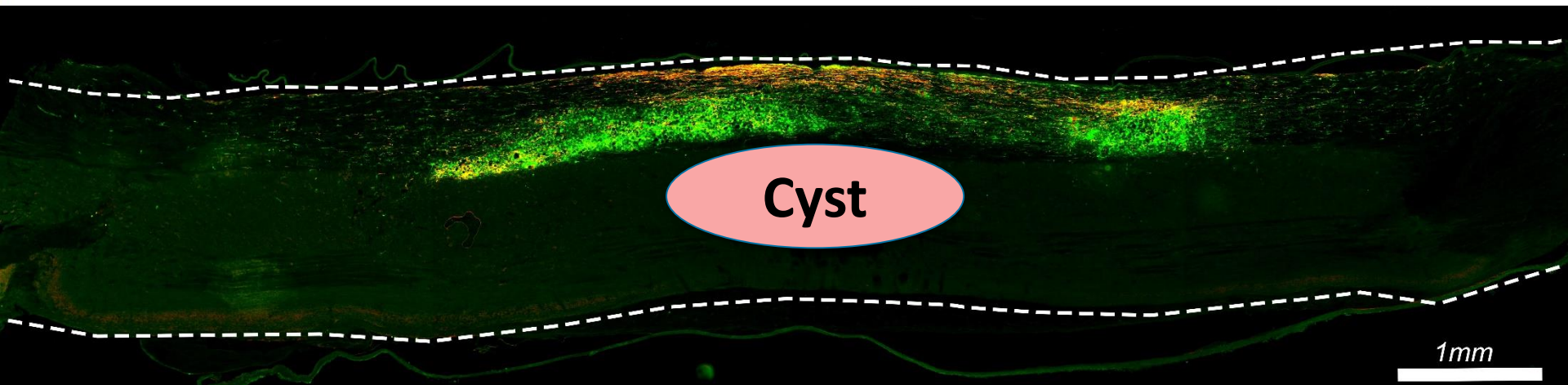
**Histology  
demonstrating  
interconnected  
human cells in a  
pig spinal cord**





# Next Steps for Bioengineered Neural Trails™

- Optimize all aspects of product profile in preparation for IND: instrumentation, biomaterial, and NSCs
- Strengthen and broaden intellectual property portfolio
- Partner with a stem cell company to accelerate project timelines



**Human Cells (STEM121) and Neural Progenitors (DCX)**