



Mitigating Damage to the Spinal Cord

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Disclosures

- Consultant Precision Spine
- Research Grant Support
 - Invivo Therapeutics
 - Vertex Pharmaceuticals, Inc



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Spinal Instability

The loss of the ability of the spine under physiologic loads to maintain relationships between vertebrae in such a way that there is neither initial nor subsequent damage to the spinal cord or nerve roots



Cervical-Thoracic Instability



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Cervical-Thoracic Instability



Cervical-Thoracic Instability



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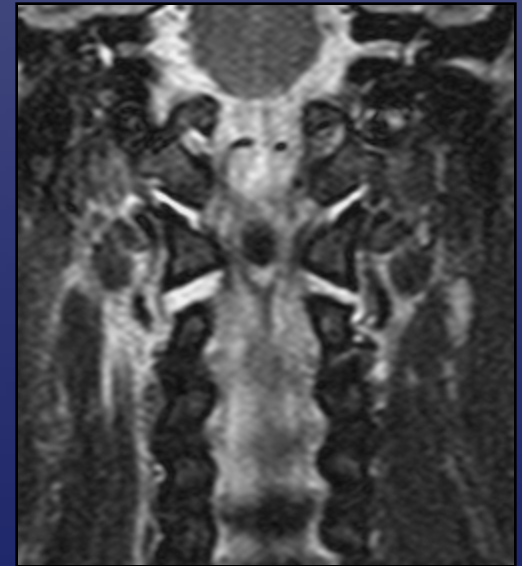
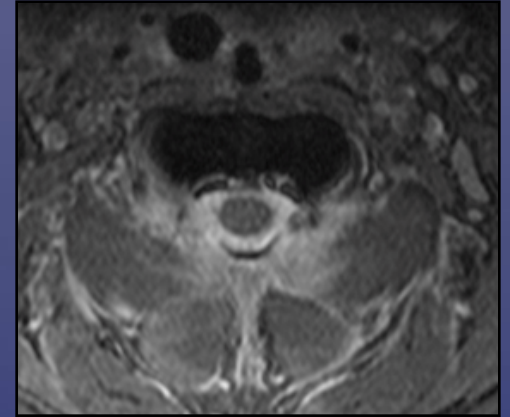
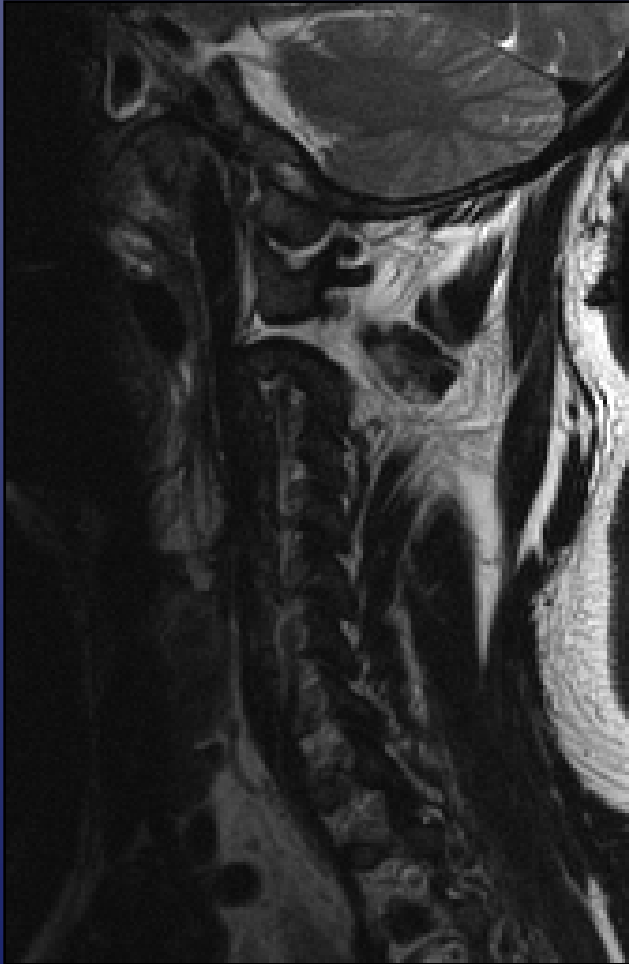
Occipital Cervical Stabilization



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Occipital Cervical Stabilization

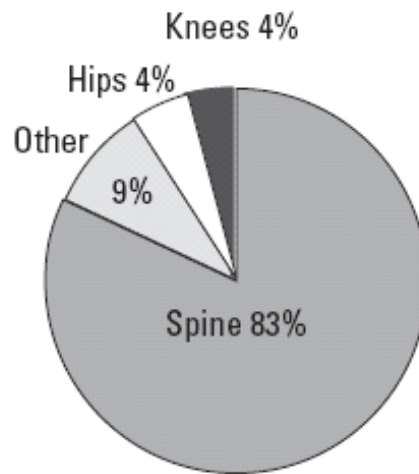


Occipital Cervical Stabilization

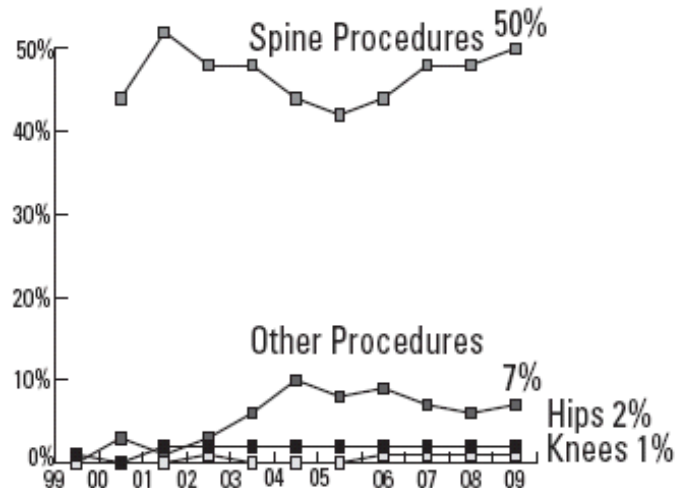


Usage of Bone Grafts and Substitutes by Procedure Type

**% of Dollars for Bone Grafts
By Procedure Type, 2009**



**% of Procedures with Bone Graft and
Bone Substitute**



Source: www.ImplantData.com data for 2009. Cases with GIC61>0 assigned to constructs for primary hips and knees, or spinal fusion cases.



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Comparison of Surgical Graft Types

Autograft:

ICBG/ BMA

PRP

Allograft:

HCT/P's, DBM*, cancellous chips, cortical spacers

Xenograft:

Bovine/ Porcine (collagens used for improved handling in DBM's)

Synthetic:

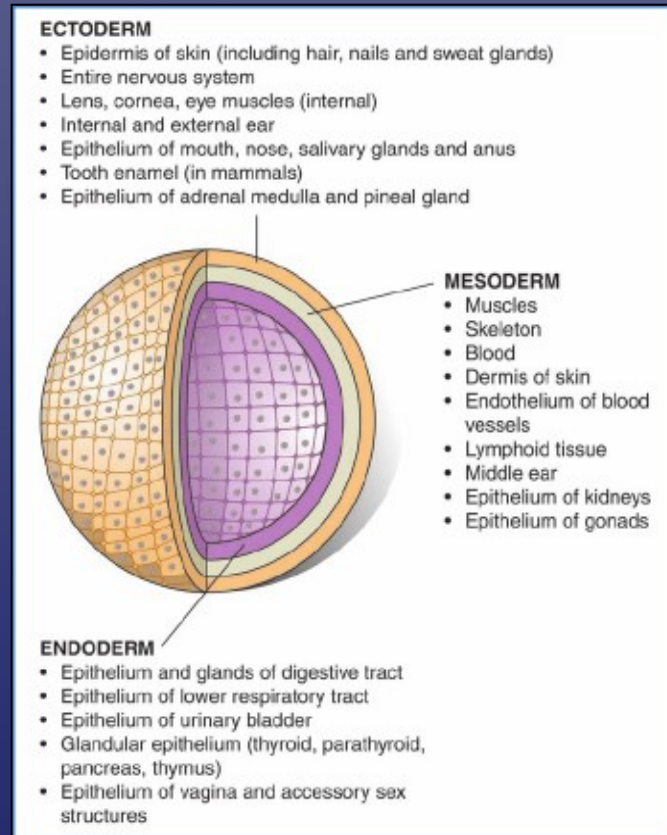
HA, TCP, CaSu, BioGlass, Glycerol



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Amniotic Fluid MSC's



Zerucha, T. (2004). *Your Body: How it Works - Human Development*. New York, New York, Infobase Publishing.



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Advantages of MSC's

Regenerate tissue types

Bone (yes)

Cartilage (yes)

= Bi-lineage differentiation: Osteogenesis, chondrogenesis

Immune Privileged: Do not express

HLA class II molecules (essential for activation of immune response)

Accessory molecules CD 40, 80, & 86 (essential for T-cell activation)



FDA Regulatory Guidelines

Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P's) Products

Regulated under 21 CFR 1271.3(d)(1) and Section 361 of the PHS Act

- be minimally manipulated;
- be intended for homologous use only
- not be combined with a drug or device, except for water, crystalloids, or a sterilizing, preserving, or storage agent
- not have a systemic effect and not be dependent on the metabolic activity of living cells for its primary function

FDA regulations further define "minimal manipulation" for structural tissue as "processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement."



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FDA Regulatory Guidelines

Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P's) Products

Regulated under 21 CFR 1271.3(d)(1) and
Section 361 of the PHS Act

NOT INCLUDED= Drugs and Biologic Products/Compounds

CULTURED CARTILAGE CELLS

CULTURED NERVE CELLS

LYMPHOCYTE IMMUNE THERAPY

GENE THERAPY PRODUCTS

HUMAN CLONING

HUMAN CELLS USED IN THERAPY INVOLVING THE TRANSFER OF GENETIC MATERIAL
(cell nuclei, oocyte nuclei, mitochondrial genetic material in ooplasm, genetic material
contained in a genetic vector)

UNRELATED ALLOGENEIC HEMATOPOIETIC STEM CELLS

UNRELATED DONOR LYMPHOCYTES FOR INFUSION



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Key Components

- Rich supply of trophic proteins, growth factors, multipotential cells
- These cells are multipotential*, providing a highly regenerative platform .
- Amnion from single donor
 - No chorion, consistent/ non-controversial source/ age
 - Cells are suspended in cryopreservative and stored at -80 deg F to maintain viability
 - cellECT added to any matrix provides the triad of induction, conduction, and genesis.



MSC's have an Important Role in Regenerative Medicine

- Amniotic tissues at the site of repair activate and stimulate production of proteins and growth factors at physiologic levels.
- cellECT provides a reliable and reproducible quantity of trophic proteins, growth factors- cytokines, collagens, and cells with demonstrated viability, providing a natural biologic enhancement for wound healing without the morbidity of autograft harvest.





Protocol Number VX15-210-101

Protocol Name A Phase 2b/3, Double-blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Efficacy and Safety of VX-210 in Subjects With Acute Traumatic Cervical Spinal Cord Injury

Protocol Version 2.0 – 14April2017

Sponsor Vertex Pharmaceuticals Incorporated

Axonal Regeneration and Sprouting Can Form New Functional Corticospinal Connections

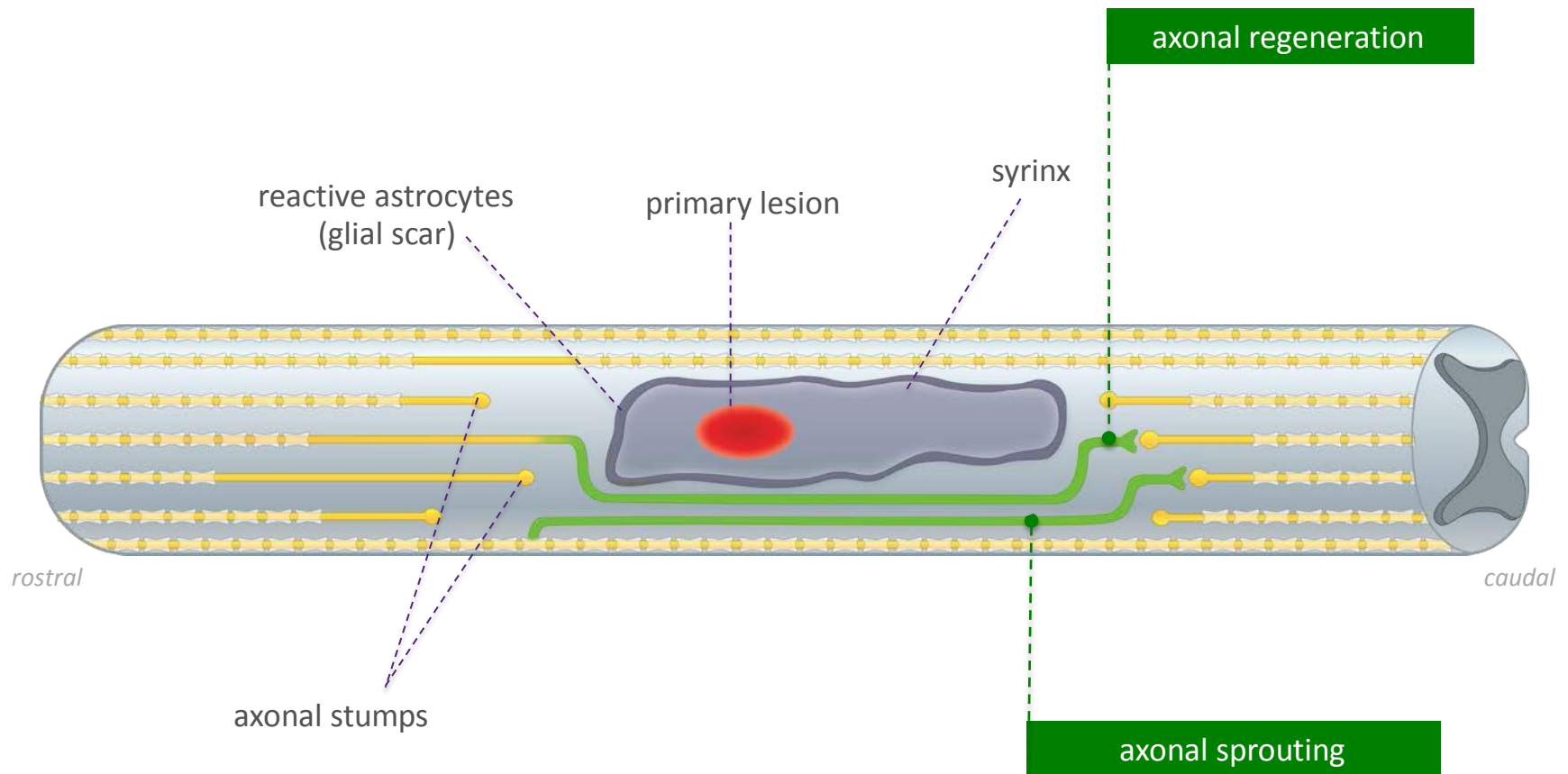


Image adapted from Schwab JM, et al. *Prog Neurobiol* 2006;78:91-116

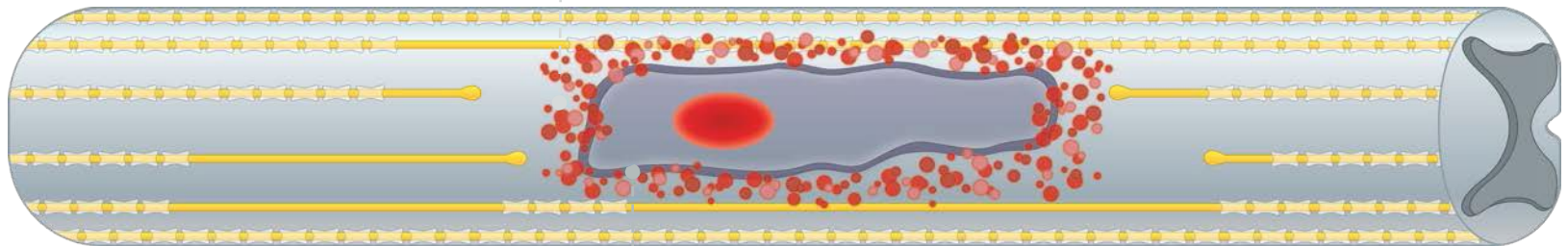


Two Main Obstacles Block Axonal Regeneration & Sprouting After Spinal Cord Injury

Chemical Barriers to Growth

Axonal Growth Inhibitory Proteins

- Multiple extracellular inhibitors of growth cone activity that block axonal regeneration
- First discovered to be released by **myelin debris**
- Also released by **glial scar** and **inflammation**

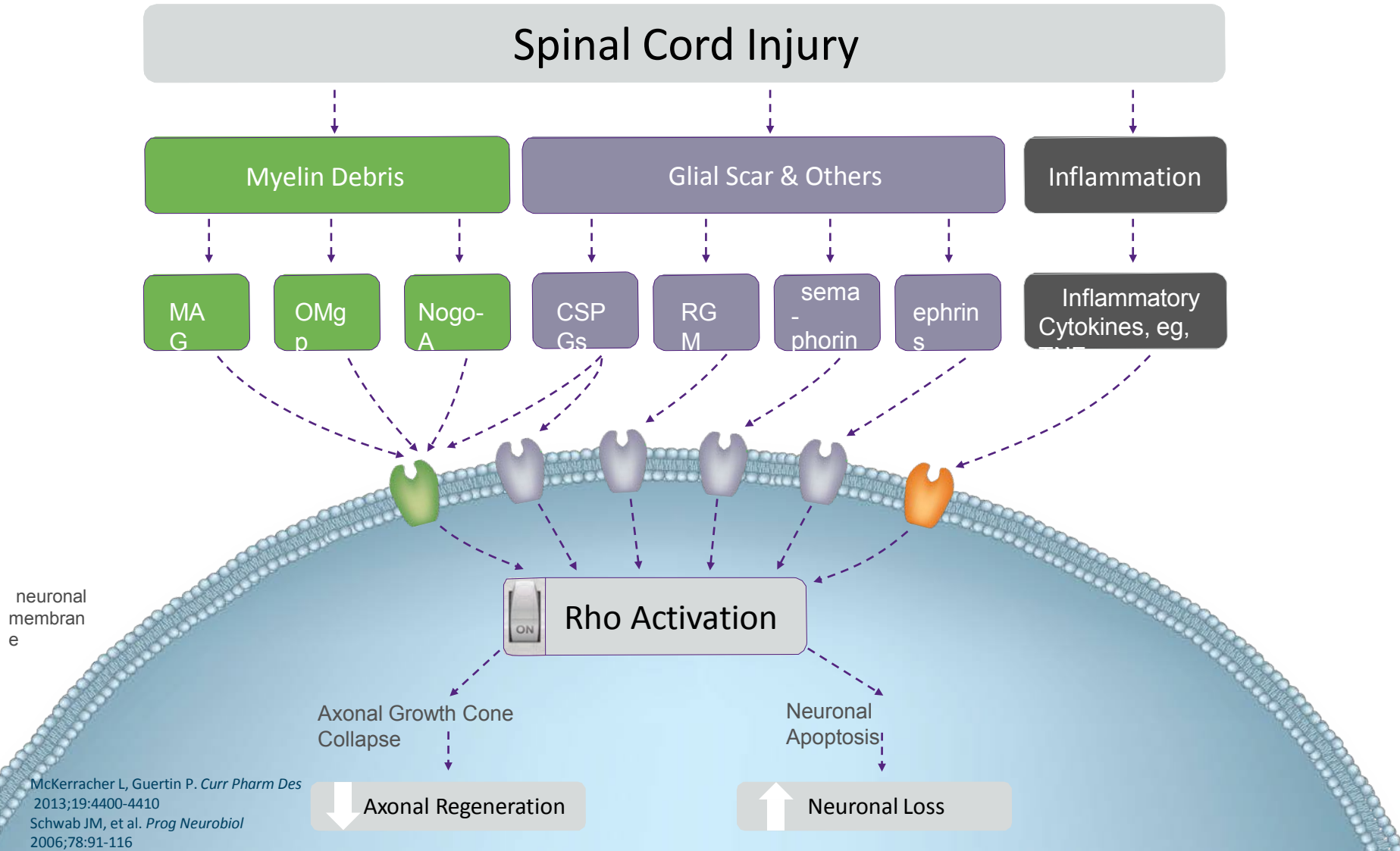


Physical Barrier to Growth

Glial Scar

- Formed by astrocytes
- Presents a physical barrier to growth
- Upregulate axonal growth inhibitory proteins

Rho Activation Is A Major Factor in Blocking Axonal Regeneration and Increasing Neuronal Loss After SCI



VX-210:

A Potent Rho Inhibitor with Excellent Cell Penetration

- Cell penetration by wild-type C3 transferase is very low¹
- This limits its use for *in vivo* applications¹
- VX-210—a cell-permeable C3 transferase—was developed to effectively penetrate cells while maintaining potent Rho inhibition²

		Rho Inactivation	Cell Penetration	Tissue Penetration
C3 Wildtype	SS + C3 transferase	YES	NO	NO
VX-210	C3 transferase + TS	YES	YES	YES

SS Signal Sequence

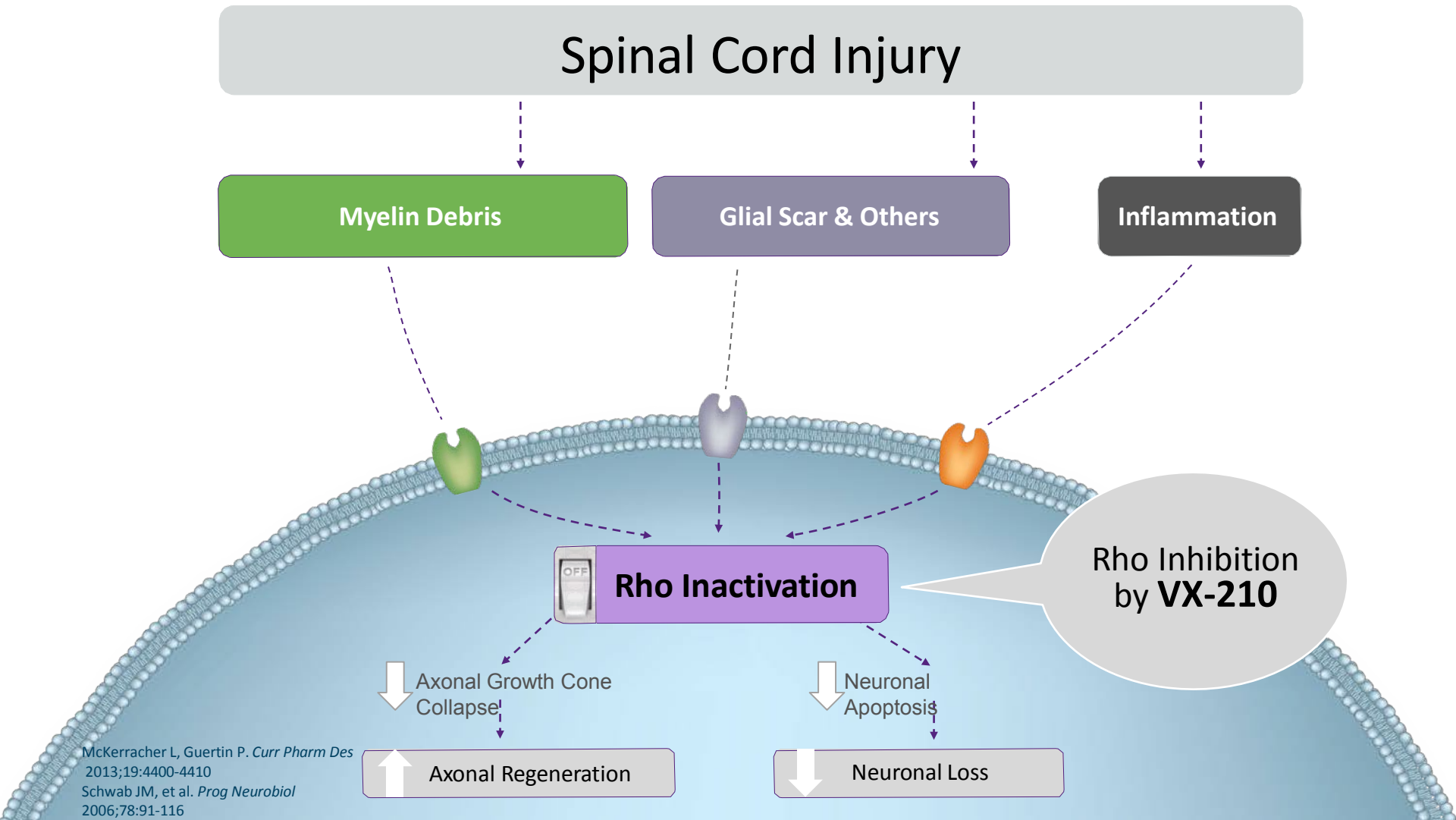
TS Transport Sequence

1. McKerracher L, Guertin P. *Current Pharmaceutical Design* 2013;19:4400-4410

2. Lord-Fontaine S, et al. *J Neurotrauma* 2008;25:1309-1322

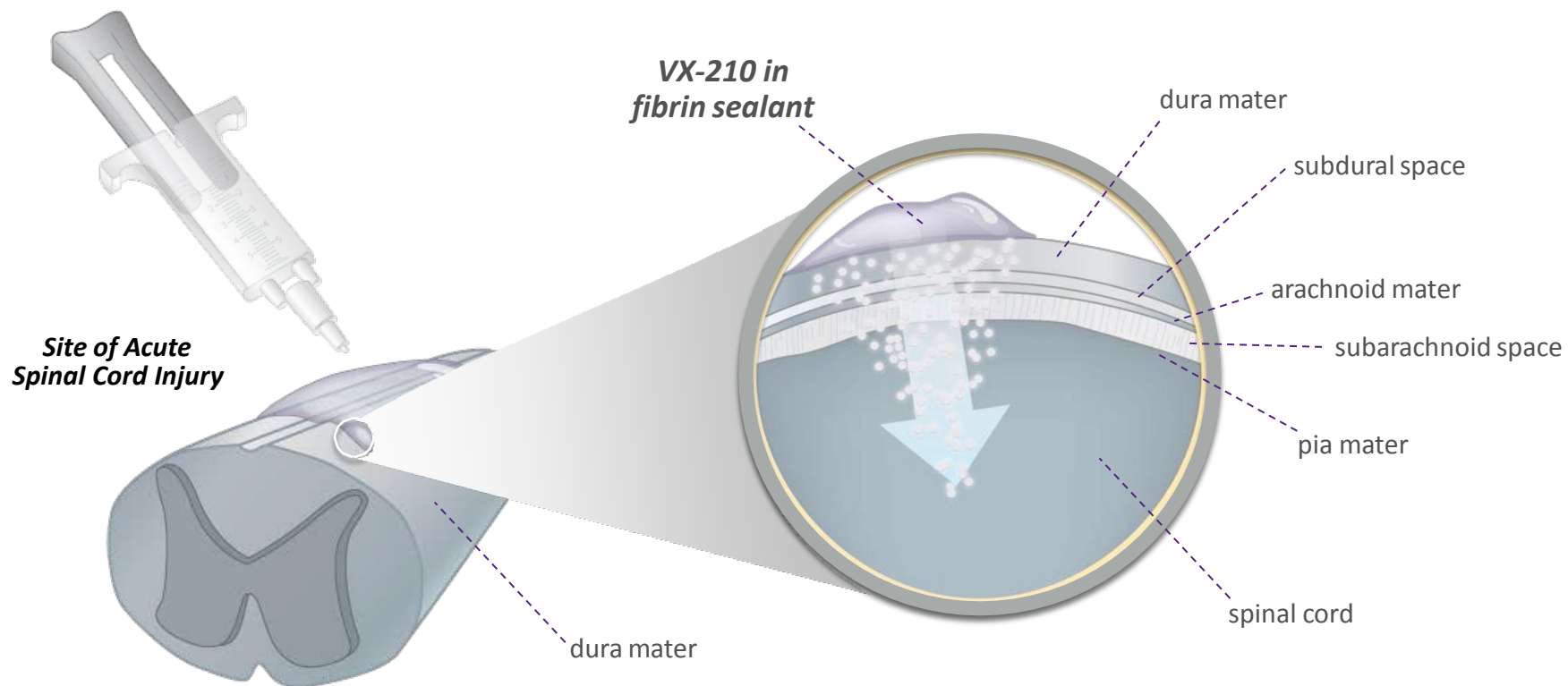


By Inhibiting Rho Activation After SCI, VX-210 Enhances Axonal Regeneration and Reduces Neuronal Loss



McKerracher L, Guertin P. *Curr Pharm Des* 2013;19:4400-4410
Schwab JM, et al. *Prog Neurobiol* 2006;78:91-116

VX-210 Applied Directly on the Dura Penetrates into Spinal Cord

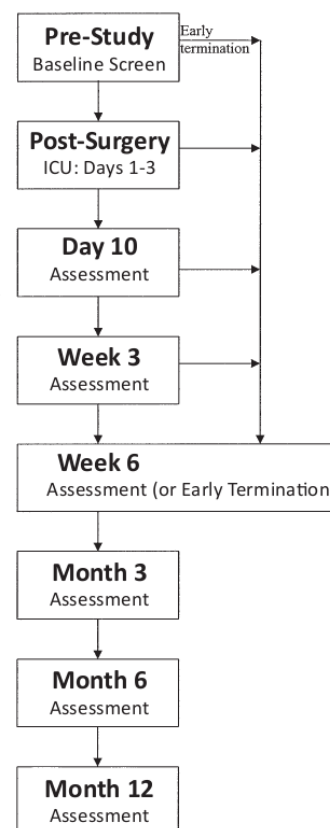


Phase 1/2a Clinical Trial: Overview

A Phase 1/2a Dose-Ranging Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of BA-210 and the Neurological Status of Patients Following Administration of a Single Extradural Application of Cethrin During Surgery for Acute Thoracic and Cervical Spinal Cord Injury

- **Open Label Study**
- **Primary Objective:** Evaluate safety and tolerability
- **Dosing:** Single extradural dose \leq 7 days post-injury
- **Inclusion:**
 - Acute, Traumatic, AIS A Thoracic and Cervical
 - Ages 16 – 70
- **Number of Sites:** 9 sites; United States, Canada
- **Number of Subjects:** 48 Subjects (16 Cervical)
 - All 48 subjects exposed to VX-210
- **Number of Arms:** 5 arms (0.3, 1, 3, 6, 9 mg VX-210)
 - Lowest dose selected based on assigned nonclinical NOAEL
- **Study Period:** February 2005 – November 2008

Overview of Study Visits



Target Spinal Cord Injury Population

VX-210 Target Population: Subjects with acute, traumatic cervical spinal cord injury

Acute Spinal Cord Injury

- Subject is within days of initial injury

Traumatic Spinal Cord Injury

- Injury caused by trauma, e.g. fall, motor vehicle accident

Cervical Spinal Cord Injury

- Injury to spinal cord in neck region



Specific Population Subset Eligible for VX15-210-101 (Based on Study Eligibility Criteria)

- AIS grade A or AIS grade B
- C4 - C7 Motor Levels (Subset)
- 14 through 75 years of age
- Decompression/stabilization begins within 72 hrs after injury

Inclusion Criteria, VX15-210-101

Inclusion Criteria:

1. Subject (or a witness, or his or her legally appointed and authorized representative) will sign and date an informed consent form (ICF).
2. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, contraceptive guidelines, and other study procedures.
3. Subjects are male or female between 14 and 75 years of age, inclusive.
4. Acute traumatic cervical spinal cord injury, motor level of C4, C5, C6 or C7 on each side
 - Screening UEMS score must be ≤ 16 points on each side
 - AIS A subjects with a C4 motor level on both sides must have at least 1 point of motor activity between C5 and T1 on at least 1 side
 - AIS B subjects with a C4 motor level on both sides must have at least 1 point of motor activity between C5 and C7 on at least 1 side.
5. American Spinal Injury Association Impairment Scale (AIS) Grade A or AIS Grade B.
6. Scheduled and planned to undergo a spinal decompression/stabilization surgery that commences within 72 hours after the initial injury.
7. Computed tomography (CT) scan or magnetic resonance imaging (MRI) is consistent with the subject's neurological deficit.

Exclusion Criteria, VX15-210-101 (Part 1 of 2)

Exclusion Criteria:

1. Participation in any other clinical study for acute spinal cord injury (SCI) without approval by the sponsor (Vertex).
2. Inability to undergo decompression/stabilization surgery that commences within 72 hours after injury.
3. One or more upper extremity muscle groups untestable during screening International Standards for Neurological Classification of SCI (ISNCSCI) examination.
4. Acute SCI from gunshot or penetrating/stab wound; non-traumatic SCI (e.g., transverse myelitis, acute disc herniation); brachial plexus injury; complete spinal cord transection; or multifocal SCI.
5. Females who are breastfeeding or have a positive serum pregnancy test.
6. Body mass index (BMI) of ≥ 40 kg/m² at screening.
7. History of an adverse reaction to a fibrin sealant or its human or bovine components.

Exclusion Criteria, VX15-210-101 (Part 2 of 2)

Exclusion Criteria:

8. Unconsciousness or other mental impairment that precludes reliable ISNCSCI examination.
9. Known immunodeficiency, including human immunodeficiency virus, or use of immunosuppressive or cancer chemotherapeutic drugs.
10. Any significant medical or psychiatric comorbidities (e.g., neurologic, cardiac, respiratory, hepatic, bleeding/coagulation disorder, renal, active malignancy) that would significantly increase the risk of study enrollment and/or significantly interfere with study outcomes or assessments, in the judgment of the investigator.

Note: Subjects with chronic medical conditions that are well controlled are eligible for the study, e.g. a subject with mild and well-controlled asthma or diabetes would be eligible, whereas a subject with severe congestive heart failure limiting activity or severe cardiopulmonary disorder limiting exercise would not be eligible.

11. Subject, or close relative of the subject, is the investigator or a sub-investigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site.

Overview of VX15-210-101 Endpoints

PRIMARY ENDPOINT

Change from baseline in **Upper Extremity Motor Score (UEMS)** at 6 months after treatment

SECONDARY ENDPOINTS

- **SCIM III Self-Care Score** at 6 months after treatment
- **CUE-T Score** at 6 months after treatment
- **GRASSP Quantitative Prehension Score** at 6 months after treatment
- **AIS Grade Conversion** from baseline to 6 months after treatment
- **Motor Level Change** from baseline to 6 months after treatment
- **Pharmacokinetic Parameters of VX-210**

OTHER ENDPOINTS

- **SCIM III Total Score**
- **Total Motor Score**
- **Total Sensory Score**
- **EuroQol Questionnaire (EQ-5D-5L) Index**
- **36-Item Short Form Health Survey (SF-36) Scores**

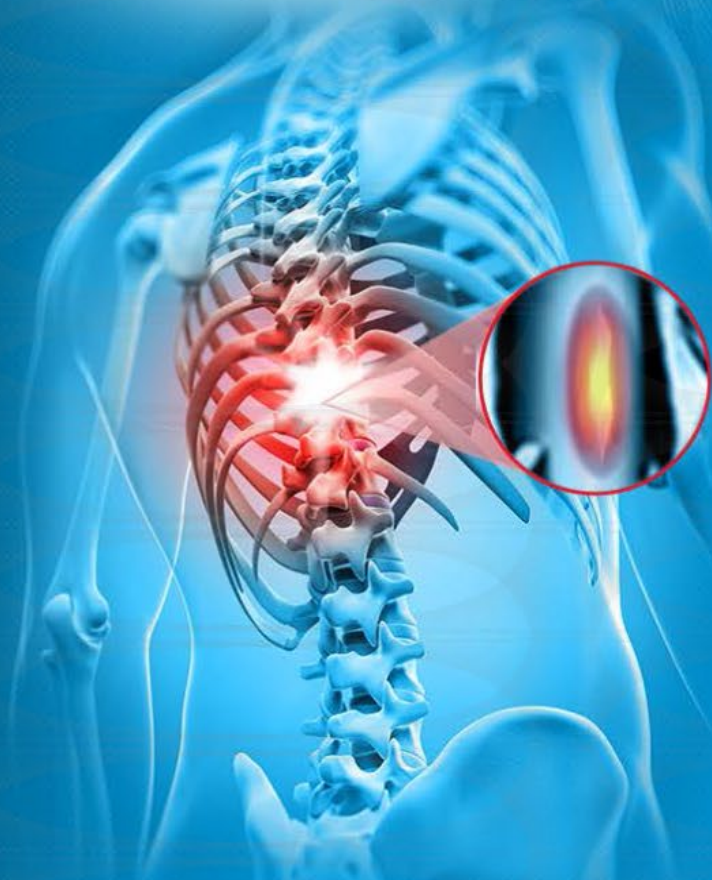


The INSPIRE Study:

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

PROTOCOL OVERVIEW

Protocol v11.3 dated 30 June 2016



Summary of Study Design

- Pivotal/Probable Benefit
- Open label
- Non-randomized
- Single-arm
- Multicenter

PROBABLE BENEFIT PER FDA:

- Sufficient information to determine that the device does not pose an unreasonable or significant risk of illness or injury
- That the **probable benefit** to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment

Summary of Study Design

NUMBER OF SITES:

Up to **40** sites in the United States, Canada, and the European Union

NUMBER OF SUBJECTS:

Up to **30** subjects to ensure **20** subjects in the Primary Endpoint Analysis Set *(defined as subjects with a successful Scaffold implant, no major protocol deviations, and a complete 6 Month Primary Endpoint Follow-up Visit)*



Study Objectives

- **PRIMARY OBJECTIVE:** To evaluate whether the Scaffold is safe and demonstrates probable benefit for the treatment of complete T2-T12/L1 spinal cord injury.
- **REGULATORY OBJECTIVE:** This is a Humanitarian Device Exemption (HDE) Probable Benefit study to demonstrate safety and probable benefit in support of future studies and an HDE application with subsequent approval.

An **HDE application** is needed to obtain approval for an **Humanitarian Use Device (HUD)**, which is a device that is intended to benefit patients by treating or diagnosing **a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year.**

An HDE is similar in both form and content to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA.

Investigational Product - *Neuro-Spinal Scaffold*TM

- Porous bioresorbable polymer scaffold comprised of a synthetic biomaterial: poly(lactic-co-glycolic acid)-b-poly(L-lysine) or PLGA-PLL
- Cylindrical shape
- Comes in 2 sizes
 - 2mm x 10 mm in length
 - 3mm x 10 mm in length
- Trimmed if necessary to a specific length
- Expected to be resorbed from the site of implant within 4-8 weeks





Inclusion/Exclusion Criteria

Primary Objective in Assessing Eligibility

- Subject should be a good candidate for standard of care spine stabilization surgery
 - Even if subject is eligible for spine surgery and this surgery is medically indicated, should not recruit subjects at higher than usual risk for postoperative (30-day) mortality.
- Recruitment into the study should not alter the plan for spine stabilization surgery to any significant degree
 - Subjects should not be held over for long periods of time to enter the study if early intervention is indicated (e.g., significant cord compression)
 - Subjects should not be brought into surgery earlier than medically warranted for standard of care procedures
 - Subjects should however, be implanted as soon as the SOC surgery is medically warranted (earlier implantation may be beneficial but should not adversely drive decision making for standard of care)

Inclusion Criteria

1. AIS A classification of traumatic spinal cord injury at neurological spinal cord level within T2-T12/L1 inclusive, confirmed by a qualified medical professional by the time of open spine surgery
2. Recent injury (must receive Scaffold implanted within 96 hours from time of injury)
3. Non-penetrating SCI (i.e., contusion injury) that is no less than approximately 4 mm in diameter by MRI
4. Requires open spine surgery allowing access to the injured spinal cord (subjects requiring either posterior surgical approach or posterior plus anterior approach will be eligible)
5. Written Informed consent obtained from subject or Legally Authorized Representative
6. 16 - 70 years of age, inclusive
7. Hemodynamically stable and deemed a suitable candidate for surgery

Potential Benefits of *Neuro-Spinal Scaffold*[™]

1. Improvement of AIS grade with related motor and sensory function recovery
2. Improvement in motor or sensory function at any level
3. Decreased incidence of repeat hospitalizations related to SCI complications
4. Decreased pain

Study Assessments – Screening (Visit 1)

Screening Visit

Visit Window: After injury and prior to open spine surgery (clinical assessments conducted during post injury care, but prior to Informed Consent may be used as part of the Screening Assessments)

ASSESSMENTS

1. Informed consent
2. Demographics
3. Medical and surgical history
4. Complete physical examination
5. Lab tests including screening laboratory tests - pregnancy serum test, blood alcohol and urine drug toxicology, blood type and coagulation test
6. Erythrocyte Sedimentation Rate (ESR) & C-Reactive Protein (CRP)
7. Measurement of resting vital signs
8. Vital Capacity for subjects not ventilator dependent*
9. Neurological examinations
10. ISNCSCI Exam - ANY variable that may affect the ability to obtain a reliable ISNCSCI exam should be eliminated.
11. MRI without contrast
12. Prior and concomitant medications, interventions and procedures
13. **For subjects ages 16 & 17**, assessment of skeletal maturity* must be performed prior to hospital discharge, but is not required prior to open spine surgery/Scaffold implant. X-rays obtained during the preoperative period may be used for this assessment.

Study Assessments – Visit 2 – Before Surgery

Visit 2: BEFORE SURGERY

ASSESSMENTS:

1. Confirmatory ISNCSCI Exam within the 8 hours prior to surgery
 - * *Any variables which may affect the reliability of the ISNCSCI Exam should be removed*
2. Clinical laboratory tests
3. Measurement of resting vital signs
4. Vital Capacity for subjects not ventilator dependent
5. Neurological examinations

Study Assessments – Visit 2 – Post Surgery

Visit 2: POST SURGERY

ASSESSMENTS

1. Clinical laboratory tests
2. Measurement of resting vital signs
3. Neurological examinations
4. Concomitant medications, interventions and procedures
5. Safety event monitoring
6. For 72 hours after Scaffold implant, **monitor for ventilator changes due to worsening of pulmonary function** – site to document changes due to worsening of pulmonary function, and assess if the worsening is due to the Scaffold or the procedure to implant the Scaffold

Study Assessments – Post-Scaffold Implant Follow-up (Visits 3 – 6)

Post-Scaffold Implant Follow-up Visits:

- Visit 3 - **24 hrs ± 6 hrs**
- Visit 4 - **48 hrs ± 6 hrs**
- Visit 5 - **72 hrs ± 8 hrs**
- Visit 6 - **1 week ± 1 day**



ASSESSMENTS

1. Clinical laboratory tests
2. Vital Signs
3. Vital Capacity for subjects not ventilator dependent
4. Neurological Examinations
5. Non-contrast MRI* **at 72 hours only**
 - Note: If MRI is not medically possible for any follow-up visit, a CT Scan without contrast can be performed
6. Concomitant Medications, Interventions and Procedures
7. Safety Event Monitoring
8. **For 72 hours after Scaffold implant, monitor for ventilator changes due to worsening of pulmonary function**
 - Site to document changes due to worsening of pulmonary function, and assess if the worsening is due to the Scaffold or the procedure to implant the Scaffold

Study Assessments – Follow-up Visits (8 – 10)

Post-Discharge FU Visits:

- Visit 8 - **1 month** ± 3 days
- Visit 9 - **2 mos.** ± 4 days
- Visit 10 - **3 mos.** ± 7 days

ASSESSMENTS

1. Clinical laboratory tests, ESR and CRP
2. Measurement of resting vital signs
3. Neurological examinations
4. ISNCSCI Exam
5. Pain assessment
6. Bowel and bladder functions assessments
7. SCIM III, QLI-SCI III, BDI-II
8. Rehabilitation Therapy Log
9. Concomitant meds, interventions, procedures
10. Safety event monitoring
11. **MRI without contrast at 3 months**

Study Assessments – PRIMARY ENDPOINT 6 Month Follow-up Visit (11)

Primary Endpoint Visit:

➤ Visit 11 – 6 mos. ± 30 days
from Scaffold implantation

Because this is the
**Primary Endpoint
Visit**, it is **CRITICAL**
for all subjects to
complete this visit

ASSESSMENTS

1. Clinical laboratory tests
2. Measurement of resting vital signs
3. Neurological examinations
4. Complete physical exam
5. ISNCSCI Exam
6. Pain assessment
7. Bowel and bladder functions assessments
8. SCIM III, QLI-SCI III, BDI-II
9. MRI without contrast
10. Rehabilitation Therapy Log
11. Concomitant meds, interventions, procedures
12. Safety event monitoring

Statistical Analysis – Efficacy

- **Primary Efficacy:** The primary efficacy endpoint will be the proportion of subjects in the Primary Endpoint Analysis Set with an AIS improvement from baseline of one or more grades at the 6 Month Primary Endpoint Follow-up Visit (6 months post-Scaffold implantation).
- **Additional Efficacy Endpoints:**
 - Proportion of subjects with improvement in sensory scores
 - Proportion of subjects with improvement in motor scores
 - Proportion of subjects with improvement in hip abduction, hip adduction or great toe flexion/extension
 - Proportion of subjects with improvement in bowel function
 - Proportion of subjects with improvement in bladder function
 - Proportion of subjects with decreased pain
 - Proportion of subjects with improvement in SCIM III
 - Proportion of subjects with improvement in QLI-SCI III

InVivo-100-101 Site Update – 31 open

Site ID	PI/Location
101	Dumont/Univ of AZ in Tucson, AZ
102	Kakarla/Barrow in Phoenix, AZ
103	Coric/CNSA and Bockenek/Carolinas Rehab in Charlotte, NC
104	Santiago/Barnes-Jewish in St. Louis, MO
105	Raslan/OHSU in Portland, OR
106	Okonkwo/UPMC in Pittsburgh, PA
107	Arnold/Univ of Kansas in Kansas City, KS
108	Jenkins/Mount Sinai in New York City, NY
109	Hsieh/USC-Keck in Los Angeles, CA
110	Kurpad/MC Wisconsin & Froedtert in Milwaukee, WI
111	Horn/Goodman Campbell & Indiana Univ in Indianapolis, IN
112	Yocom/Cooper Neurological Institute in Camden, NJ
113	Kim/UC-Davis in Sacramento, CA
114	Heary/Rutgers, NJ Med in Newark, NJ
115	Ciacchi/UCSD in San Diego, CA

Site ID	PI/Location
116	Boakye/Univ of Louisville in Louisville, KY
117	Lee/Vidant Medical in Greenville, NC
118	Schuster/PENN in Philadelphia, PA
119	Shaffrey/Univ of VA in Charlottesville, VA
120	Harrop/Jefferson in Philadelphia, PA
121	Fehlings/Toronto Western in Toronto, ON
122	Ginsberg/St. Michael's in Toronto, ON
125	Dahdaleh/Northwestern in Chicago, IL
127	Ropper/Baylor in Houston, TX
128	Stippler/BIDMC in Boston, MA
129	Lewis/Univ of NM in Albuquerque, NM
130	Hitchon/Univ of IA in Iowa City, IA
131	Casha/Univ of Calgary, Calgary AB
132	Oyelese/RI Hospital in Providence, RI
133	Lu/Brigham & Women's in Boston, MA
134	Julien/Allegheny in Pittsburgh, PA

US, UK & Canadian Sites in Study Start-up Phase

Site ID	PI/Location
123	Purcell/Queen Elizabeth Univ. Hospital in Glasgow, Scotland
124	Prasad/James Cook Univ. Hospital in Middlesbrough, England
126	Desai/Stanford University in San Francisco, CA
135	Grandhi/Univ. of Texas Health in San Antonio, TX
136	Pritchard/University of Alabama in Birmingham, AL
137	Schroepfel/UC Memorial Hospital in Colorado Springs, CO
139	Cameron/Virginia Commonwealth University in Richmond, VA
140	Sansur & Ludwig/Univ of Maryland in Baltimore, MD
141	Thumbikat/Sheffield Teaching Hospital NHS Foundation Trust