From Bench to Phase 2a Clinical Trial in SCI

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Disclosure Statement

- Dr. Lisa McKerracher is the Founder and CEO of BioAxone BioSciences, Inc. and a shareholder in the company.
- Dr. Lisa McKerracher will present data on an investigational drug, BA-210, that is not approved for human use.
- BA-210 is the generic name for Cethrin™.
Learning Objectives

At the conclusion of this activity the participant will be able to

- Describe the types of growth inhibitory protein that exist in the spinal cord to block regeneration and their signalling pathways
- Explain the important steps are required to translate preclinical studies to an IND (Investigation of a New Drug) application submitted to the FDA (Food and Drug Administration)
- Discuss measurable outcomes in a clinical study designed to test safety of a drug to treat spinal cord injury
Spinal Cord Injury

- 80’s: Growth inhibitory proteins block regeneration
- 90’s: Identify inhibitors
  - Nogo
  - MAG
  - OMgp
- Glial scar
- 2000’s Clinical trials
Growth inhibitory proteins block regeneration

- Myelin-Derived inhibitors
  - MAG
  - Nogo
  - OMgP
- Gliar scar – CSPG
- Chemorepulsive proteins

![Diagram showing growth inhibitory proteins blocking regeneration](image)
Rho is key convergent point that integrates multiple growth inhibitory signals.
Challenge: Translate research on growth inhibitory proteins to treatments for SCI

- Basic research
  - Rho biology → BA-210
  - Preclinical studies
- Translational research
  - Focus pre-clinical studies toward clinical
  - Good Laboratory practice (GLP) safety
  - Making the drug under GMP (quality control for purity, potency and stability)
- Clinical Research
  - Phase 1/2a results
- Next Steps
BA-210 inactivates RHO GTPase

- Rho acts as an on/off switch
  - Cytoskeleton
  - Cell cycle/cell death
  - Motility
- C3 toxin from Closteridium botulinum inactivates Rho
- ADP ribosylation of active domain is irreversible
- BA-210 is a recombinant fusion protein composed of bacterial C3 transferase and a transport sequence
Inhibitors in the CNS activate neuronal Rho

Pull down assays detect active Rho

Rho is active when cells are placed on inhibitory substrates

21 kDa
Blocking Rho activation promotes regeneration on CNS inhibitory substrates

C3-05 (BA-210)

Myelin

Myelin

Myelin + CSPG
Preclinical efficacy studies
There is abnormal activation of Rho in CNS injury

<table>
<thead>
<tr>
<th></th>
<th>Mouse Hemisection</th>
<th>Rat Contusion</th>
<th>Rat Transection</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Lesion</td>
<td>Treated</td>
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<tr>
<td>GTP-Rho</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
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<tr>
<td>Total Rho</td>
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<td><img src="image8.png" alt="Image" /></td>
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<td>C3-05</td>
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<td><img src="image14.png" alt="Image" /></td>
<td><img src="image15.png" alt="Image" /></td>
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</tbody>
</table>
Local delivery was developed to enhance safety and efficacy

80% of SCI patients have surgery within 1 week of injury

Fibrin tissue sealants are used in neurosurgery for hemostasis and to repair dural tears
Preclinical studies show extradural delivery is effective.

BA-210 penetrates into neurons in grey matter.
Inactivation of Rho promotes regeneration

Lesion

Control

10 mm from lesion
Cethrin has dual activity
Cethrin is neuroprotective in addition to pro-regenerative

Neuroprotection of RGCs after axonal transection

Rodents show functional recovery after SCI and treatment with BA-210

Motor recovery in rats (Contusion injury)

Motor recovery in mice

Open field test

Grid-walk

BBB=Basso, Beattie and Bresnahan
Robust methods are needed to predict effective dose in humans

- Dose experiments were completed in mouse, rat, and pig

- Different methods were used to calculate dose
  - **Biochemistry:** Activity assays (Rho pull-down)
  - **Drug penetration:** Immunodetection in intact spinal cord (bots, microscopy)
  - **Efficacy:** Motor recovery
  - **Safety:** Toxicity studies

- Effective dose in humans was predicted to be 1-5 mg.
Translational Research
Goals to treat SCI

Good preclinical rational for BA-210

- Stimulate axon growth and repair
  - Stimulate regeneration: regrowth of cut axons ✓
  - Stimulate plasticity: growth from spared axons

- Limit Early Damage
  - Neuroprotection ✓
  - Reduce inflammatory damage ✓

- Replace lost cells
  - Cell transplantation
Investigation of a New Drug (IND)

- CMC (Chemistry, manufacture and control)
- Non-clinical (Preclinical efficacy, safety (2 species), pharmacokinetics, toxicology)
- Clinical
GLP (Good Laboratory Practice) a GMP (Good Manufacturing Practice)

- Supporting safety studies and drug synthesis and characterization assays must be GLP/GMP
- GLP is a system of Quality Control
  - Documentation is key
  - Audit trail for all aspects of an experiment
  - Study protocols and study reports
  - SOPs (standard operating procedures): from buffers to inventory control
CMC (Synthesis) : BA210

- Made by Good Manufacturing Process (GMP)
- Outsourced to contract manufacturing facility
- All processes validated for reproducibility
- Drug substance characterized by GLP assays
  - Identity (MCB testing; sequencing)
  - Purity (HPLC; SDS PAGE; IEF)
  - Potency (GH enzyme assay; bioassay not validated)
  - Stability (GH assay; SDS page)
- Acceptance criteria designed
- Formulation and delivery protocol
- Bottling and labeling
Lots of effort was committed to drug manufacturing protocols.

Drug Substance

- Fermentation
  - Extract soluble BA-210
- Filtration
  - Centrifugation
- FPLC
  - 3 columns for purification & endotoxin removal

Drug Product

- Buffer exchange, Concentration sterile filtration
- Vial fill, capping, labeling

![Dose-Diagram](https://via.placeholder.com/150)
CMC: Commercial Scale-up is complete
Potential to be available in all trauma centers

Bacterial Fermentation and Purification
- E. coli fermentation (500L)
- Purification: 3 Chromatography steps
- Filtration, bottle fill and storage of bulk drug substance
  - Drug substance has freeze-thaw stability over multiple cycles
- Drug Product: Liquid formulation
- Supplied to hospital as a packaged kit

Drug delivery kit
- BA-210
- Fibrin kit
- Syringe
BA-210 Clinical Assays

- All SOPs and GLP assays were developed in-house

- Analytical methods for detecting the drug in animal and human plasma
  - ELISA for drug concentration in plasma
  - Assays to detect anti-drug antibodies

- Analytical methods to determine drug stability and purity
Safety testing was done by a GLP compliant CRO

- Preclinical safety
  - Non-GLP pharmacokinetic to determine dose range
  - GLP safety testing

- 6 GLP safety studies were completed
  - 2 IV in rat (single dose and repeat dose)
  - 1 IV in Dog
  - 2 Extradural in rat
  - Wound healing in pig
Clinical study
FDA and Regulatory Process

- Pre-IND meeting with FDA (Submit 30 days in advance)
  - Guidance on safety studies, CMC, clinical protocol
- Submit IND (Outcome in 30 days)
  1. Cover sheet
  2. Table of Contents
  3. Introductory statement
  4. General Investigational plan
  5. Investigator's Brochure
  6. Clinical Protocol
  7. CMC
  8. Non-Clinical (Relevant animal data, Pharmacology and toxicology)
  9. Previous human experience
PI/IIa Clinical Study Objectives

- Primary Objectives
  - To determine the safety and tolerability of a single application of BA-210

- Secondary Objectives
  - To evaluate the pharmacokinetic profile of BA-210
  - The neurological status of patients by ASIA scores
  - MRI evaluation
  - Dose range in humans
PI: Dr. Michael Fehlings (U of Toronto)

Multi-center trial with 9 sites

- Vancouver, BC.
- Seattle, WA.
- Montreal, QC.
- Toronto, ON.
- Toronto, ON.
- Philadelphia, PA.
- Cincinnati, OH.
- Charlottesville, VA.
- Phoenix AZ.
Phase I/IIa was planned for safety
Open label, ASIA A, recruit thoracic patients first

- Thoracic patient group is safety group. *They are less likely to be detrimentally effected, but unlikely to show improvement.*
- 5 doses tested (0.3 mg, 1 mg, 3 mg, 9 mg)
- After shown safe with thoracic patients, cervical recruited, for each dose group
- Multi-center: 9 sites in USA and Canada
Patient recruitment planned for safety and ASIA measurement

<table>
<thead>
<tr>
<th>Thoracic</th>
<th>DSMB</th>
<th>Cervical</th>
<th>DSMB</th>
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<tbody>
<tr>
<td>0.3 mg</td>
<td>➡</td>
<td>0.3 mg</td>
<td>➡</td>
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<tr>
<td>1 mg</td>
<td>➡</td>
<td>1 mg</td>
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<tr>
<td>3 mg</td>
<td>➡</td>
<td>3 mg</td>
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<tr>
<td>6 mg</td>
<td>➡</td>
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</tr>
<tr>
<td>9 mg</td>
<td>➡</td>
<td>9 mg</td>
<td>End of enrollment</td>
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DSMB = Data Safety Monitoring Board
Patients were recruited within one week of SCI.
BA-210 was considered safe at all doses tested

- **48 patients**
  - Normal clinical parameters
    - Vitals
    - Clinical labs
    - Neurological exams (MRI, ASIA)
  - DSMB: No drug related adverse events
  - No dose dependent adverse events
  - Low systemic exposure (PK parameters)
Improvement in ASIA motor scores in cervical cohort

Treated patients in cervical cohort improve over time

<table>
<thead>
<tr>
<th>Cethrin (Cervical cohort)</th>
<th>All doses</th>
<th>18.6 ± 19.3</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>3 mg dose</td>
<td>27.3 ± 13.3</td>
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</table>

| Untreated (Historical data) | Untreated | ~ 10 over 2 years |
Sensory Improvement in Thoracic patients
Pin Prick EMSCI/Sygen compared with BA-210

Steeves, unpublished

BA-210

N=29
N=28
N=27
N=20

Percent

B to 4w  B to 12w  B to 24w  B to 48w

W6  Mo3  Mo6  Mo12

<=-3  -2  -1  0  1  2  >=3)
Impressive conversion rates

66% of patients in 3 mg cervical cohort convert from motor complete to motor incomplete compared to 8% expected

Cervical patients improving to ASIA C or ASIA D

<table>
<thead>
<tr>
<th>Cethrin (A to C/D)</th>
<th>(Fehlings et al., 2011)</th>
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</thead>
<tbody>
<tr>
<td>All doses</td>
<td>Thoracic: 6%</td>
</tr>
<tr>
<td></td>
<td>Cervical: 31%</td>
</tr>
<tr>
<td>3mg</td>
<td>Cervical: 66%</td>
</tr>
</tbody>
</table>

Spontaneous (Fawcett et al, 2007, ICCP)

| AIS A – AIS A       | ~80% (78-82%)          |
| AIS A – AIS B       | ~12% (7-17%)           |
| AIS A – AIS C       | ~8% (5-10%)            |
Lower UTI rates in cervical patients

- Urinary tract infections were consistent at all dose levels (mean 75%). However, the UTI rate was lower in the cervical cohort (50%).
- None of the patients in the 3 mg cervical cohort had UTI.
Next Steps for BA-210

- Clinical Development
  - Phase IIIB: placebo controlled trial
  - (Phase III)
- Business Development
  - Technology was licensed with milestone-based development goals
  - License has reverted to BioAxone
  - Looking for a new development partner
  - $$
A single pivotal trial could lead to approval

- End of Phase 2 minutes with FDA indicate potentially approval with single placebo control trial because of urgent unmet need

- Phase 2b timelines
  - One year recruitment (20 sites)
  - One year follow-up

- Planned endpoints
  - Primary endpoint: motor scores
  - Secondary endpoints: bladder, pain, Autonomic dysreflexia and SCIM (spinal cord independence measure)
  - Trial planned with global regulatory requirements in mind
The business of translational research

- Patent protection is critical. BA-210 is covered by issued patents.
- Market is important; SCI is a small market, making it less attractive to investors.
- Phase 2b is a critical inflection point from a risk – reward stand point.
- Challenges exist in a risk-adverse economy but BA-210 clinical program is attracting interest.
BA:210 is positioned to be first drug to treat SCI that promotes regeneration

- BA-210: Biologic drug that stimulates regeneration of damaged axons
- Safe at all doses tested
- Patients continued to improve over 12 months they were followed
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- Université de Montreal, Dept. Pathology and Cell Biology
Obtaining CME Credit

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http://www.pesgce.com/PVAsummit2011/

• This information can also be found in the Summit 2011 Program on page 8.