Biologic Treatments for Spinal Disc Regeneration

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Chronic Axial Lumbar Back Pain
Patient Profile

- 12.5M Patients annually present with chronic (>6 months), low back pain in the United States
- Only 20% present with evidence of an easily imaged pathology or anatomic source of pain

- 10M U.S. patients annually present with symptoms of discogenic pain:
  - Chronic axial low back pain (>6 months)
  - Referred leg pain that is less than back pain
  - Mild to moderate disc generation at 1 or more adjacent levels
  - No significant instability or disc height loss
  - Minimal central canal or foraminal stenosis

Intervertebral Disc Repair – Preclinical Study

Baseline 3 Months

Inject Chondroitinase ABC

Control

Disc
Degenerated Disc

Inject Chondroitinase ABC

Control

Disc
Degenerated Disc

Inject Chondroitinase ABC

Control

Disc
Degenerated Disc
**Intervertebral Disc Repair – Preclinical Study**

MRI 6 months after injecting 0.5 million MPC showing similar H₂O signal (white) to normal control ovine disc.

- Non-Degenerated Control Disc
- MPC/HA Treated Disc
- Degenerated Disc (No Treatment)

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**Human Spinal Disease**

**THEN**

I’ll Be BACK

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**Human Spinal Disease**

**NOW**

Oh My BACK
Structure and Vascularity of the Disc

- Nucleus pulposus poorly vascularized
  - No blood vessels penetrate the inner annulus
  - Pressure on the nucleus is 5-15 times greater than blood pressure.
  - It is hypothesized that the tissue is hypoxic.

Pre-Op MRI

- Clinical Study
  - Biostat System
    - Phase III
    - Internal disc disruptions (IDD) of lumbar intervertebral discs
    - 15 sites, N=260
    - One or two level, randomized, blinded
    - First patient in February 2010
The findings of these studies highlight a possible novel treatment options for intervertebral disc repair. Although the intent was to investigate novel treatment effects using sham procedures* in future clinical injection trials, differentiate between a placebo effect and a true saline effect for novel treatments to improve upon!

Future directions include:

- Establishing the threshold for novel treatments to improve upon
- Developing mechanisms of action
- Understanding the impact of saline in disc cells to high salt, sorbitol, and urea

Further research is needed to determine a biologic mechanism of action is needed.

* Current Randomized Clinical Trial Designs include a sham treatment group when intradiscal high-pressure injection of saline in patients with extruded lumbar herniated disc cells to high salt, sorbitol, and urea. J Cell Physiol. 2012 Mar;227(3):1179-87.

**References**

For your reference, please consider the following studies:

- Fukui S, Iwashita N, Nitta K, Tomie H, Nosaka S. The results of percutaneous intradiscal high-pressure injection of saline in patients with extruded lumbar herniated disc degeneration, not related to the underlying reason for the patients a chance for some pain resolution, decreased disability, or may merely introduce less substance reaction than to treatment or carriers and injection trauma.

**Results**

Noting the 50% or greater improvement observed for saline injected patients in this study provides a potentially saline-associated clinical improvement provides a potential signal for saline effect using sham procedures* in future clinical injection trials!
Results

• Four RCT using saline as control
  • 58.5% decrease in patients at 12 months treated with saline
  • 36.6% decrease in patients at 12 months treated with investigational drug
  • p<0.04

Allogeneic Stem Cells – The Future?
The image contains three sections with different content:

1. **Bioreactor Cell Processing**
   - Image of a bioreactor setup.
   - Text: "Bioreactor Cell Processing"

2. **Commercial Viability**
   - Logos of Uber and Facebook.
   - Text: "Commercial Viability" and "Scaability"

3. **Phase II Results**
   - Title: "POSITIVE SPINAL DISC REPAIR TRIAL RESULTS USING MESOBLAST ADULT STEM CELLS"
   - Summary: Single injection of Mesenchymal Precursor Cells into Degenerating Intervertebral Disc Reduced Low Back Pain and Improved Function for at Least 12 Months.
   - Notes: The phase II trial was designed to assess the safety and efficacy of Mesenchymal Precursor Cells for the treatment of low back pain. Patients were followed for at least 12 months after the initial injection.

4. **Additional Text**
   - Text: "5/27/2016"
Study Design

- Prospective, multi-center, randomized, double-blind, controlled study
  - Patients and radiographic evaluation standards established
- Follow-up: 6, 12, 18, 24 & 36 months
- Safety Evaluations
  - Efficacy Evaluations
    - Clinical
    - Radiographic Changes
      - MRI
      - X-ray & Validity
      - MRI: Proportion of patients with at least a 50% improvement in back pain or minimal/no residual back pain at 12 months relative to Controls
      - DDD: Proportion of patients with at least a 50% improvement in back pain or minimal/no residual back pain at 12 months relative to Controls
      - Discs with full thickness tears with free flowing contrast through the annulus fibrosus
      - Lumbar intervertebral foraminal stenosis at the affected level(s) resulting in clinically significant spinal nerve root compression

Phase 2 Clinical Study Patient Population

A prospective, multi-center, double-blinded, controlled clinical study of two doses of immunoselected, culture-expanded, nucleated, allogeneic MPCs when combined with hyaluronic acid in subjects with chronic low back pain (≥6 months) due to moderate DDD at one lumbar level from L1 to L5 and an exacerbation to conservative therapy for at least 3 months (including physical therapy) and evaluated at 1, 3, 6, 12, 24, & 36 months.

Inclusion Criteria
- DDD with back pain ≥6 months
- Failed 3 Months Non-Operative Care
- Patients with a modified Pfirrmann score of 3, 4, 5, or 6
- With or without contained disc herniation up to a 3 mm protrusion with no radiographic evidence of neurological compression
- Disc height loss of ≥50% compared to a normal adjacent disc based upon radiographic evaluation
- VAS back pain ≥80
- ODI Score ≥30

Exclusion Criteria
- Modified Pfirrmann score of 1 & 2 or 7 & 8
- Clinically significant nerve or sacroiliac joint pain
- Clinically significant facet pain as determined by a diagnostic medial branch block or facet joint injection
- Symptomatic involvement of more than one lumbar disc level
- Intact disk: vague/unclear or focal herniation at the symptomatic level(s) >3 mm or presence of disc extrusion or sequestration
- Discs with full thickness tears with free flowing contrast through the annulus fibrosus
- Lumbar intervertebral foraminal stenosis at the affected level(s) resulting in clinically significant spinal nerve root compression

MPC groups have a greater proportion of patients with at least a 50% improvement in back pain or minimal/no residual back pain at 12 months relative to Controls
MPC groups have a significantly greater proportion of patients with a 50% pain reduction with no intervention compared to saline @ 24 months.

50% pain reduction with no intervention @ 24 months

- 60.9% for 18 million MPCs vs. saline
- 47.9% for 6 million MPCs vs. saline
- p = 0.009 vs. saline
- p = 0.038 vs. saline
- p = 0.024 vs. saline

MPC groups have a significantly greater proportion of patients with clinically significant function improvement and no intervention compared to saline @ 24 months.

15 point ODI improvement with no intervention @ 24 months

- 60.9% for 18 million MPCs vs. saline
- 56.5% for 6 million MPCs vs. saline
- p = 0.009 vs. saline
- p = 0.020 vs. saline
- p = 0.093 vs. saline

Missing Link

Evidence Based Efficacy
Mesoblast Phase III Study

- 60 investigative sites across US and Australia
- 660 subjects
- 2 identical protocols:
  - MSB-DR002
  - MSB-DR003
- Only MSB-DR003 will undergo interim analysis
- Study period (subject): ~15 months
- Randomization scheme - 1:1:1
  - rexlemestrocel-L + saline
  - rexlemestrocel-L + HA
  - Saline
- First patient screen target date: 05 March 2015
- Last patient screen target date: 09 November 2016

THANK YOU!!!