Stem Cell Applications in Orthopedic Surgery

R. Tyler Boone, MD
Spinal Surgery

- Spine fusion
- Management of degenerative disc disease/annual tear
- Spinal cord injury
Other Clinical Applications

- Rotator cuff repair
- Achilles tendon repair
- Metatarsal Jones fracture
- Long Bone Non-union
- Acetabular labral repair
- SI joint Injections
- ACL allograft reconstruction
- Cell augmented meniscal repair
- Osteonecrosis
- Facet Injections
- Pars Fracture
Stem Cells and Spinal Fusion

- Overview
  - 300,000 fusion procedures performed yearly.
  - Autograft, most commonly from the iliac crest, is the historical gold standard for obtaining bone fusion.
Autograft

- Low cost and no concerns with tissue compatibility and disease transmission
- Quality is variable
  - Age (low cellularity)
  - Metabolic abnormalities (diabetics)
  - Smoking
  - 30% donor site morbidity
  - 10 to 15% pseudoarthrosis
  - Leads spine surgeons to investigate alternatives (bone graft substitutes, graft extenders, osteobiologic materials)
  - Including the use of mesenchymal stem cells
Successful Spinal Fusion
Requirements

- Bone forming cell or precursors
- Appropriate biologic signals directing bone synthesis
- Biocompatible scaffold
- Bone forming cell (osteoblast) or its precursor (mesenchymal stem cells) are the most critical components
Mesenchymal stem cell

- First discovered 1966
- Adult stem cells that have ability to self-renew (replicate)
Multipotent Cells

- Bone, cartilage, fat, nerve, muscle, tendons, fibrous tissue
- Differentiation dependent on intrinsic/extrinsic factors in local environment.
- Less differentiation potential than embryonic stem cells
- Highest concentration in bone marrow of pelvic girdle and vertebral bodies
Mesenchymal stem cells continued

- Can be isolated from placenta umbilical cord blood, connective tissue, skin synovial fluid, fat and teeth
- Bone marrow contains two types of stem cells
  - Mesenchymal stem cells and hematopoietic stem cells
  - MSC’s make up only 0.01% of all nucleated bone marrow cells
  - Aspiration of iliac crest bone marrow contains between 1 to 5 MSC’s per 500,000 nucleated cells
  - MSC's differentiate into osteoblasts
Mimicking Natural Healing

- Multiple cell types
- Access stem cells in bone marrow
- Provide a microenvironment that maximizes stem cell function
- Importance of effective osteoconductive scaffold
Bone marrow aspiration
Maximizing BMA Cellularity

Benefits of small volume and small syringe for bone marrow aspirations of mesenchymal stem cells

Philippe Hernigou · Yasuhiro Homma · Charles Henri Flozat Lachaniette · Alexandre Poignard · Jerome Allain · Nathalie Chevallier · Helene Rouard

- Studied impact of syringe volume and level of fill in the syringe
- **300% increase in the MSC content of 10-ml syringe aspirations** compared to 50-ml syringe aspirations
- Partial filling to 10-20% of full volume gave higher MSC yields
  - Use a 30-ml syringe, draw to 15-ml level, fill, rotate needle position,
  - draw to 30-ml level
What exactly is bmc anyway?
Creating BMC: Going for A Spin
Buffy Coat Contents

- Mesenchymal Stem Cells
- Hematopoietic Stem Cells
- Endothelial Progenitor Cells
- Platelets
Plasma Contents

→ Clotting Proteins
  → Fibrinogen, Prothrombin
  → Factors (Factor VIII, Factor IX)
→ Growth Factors
  → VEGF, PDGF, FGF, TGF-β, IGF, etc.
→ Other Proteins
  → Fibronectin, Vitronectin (Matrix remodeling and healing)
→ Alpha-2-Macroglobulin
  → Multi-functional enzyme inhibitor:
  Matrix metaloproteinases
→ IRAP (IL-1RA Protein)
  → IL-1 Inhibitor
Cell-based Therapy

1. Obtain maximum cell number
2. Recover maximum progenitor cell number
3. Remove unwanted cells (RBCs)
4. Apply to patient without damaging cells
Spine 2014, Robert Johnson, MD

Prospective randomized study
• Iliac crest bone graft is the gold-standard in spinal fusions.
• 25 patients receiving 1-, 2- or 3-level posterolateral lumbar fusions were enrolled.
• Each patient received ICBG and BMC with cancellous chips.
• CT scans at 1-year were evaluated for degree of fusion.
• Two blinded unrelated assessments of the images showed no statistically significant difference between the two treatments.
• Provides an alternative to BMP therapy and the co-morbidities of the ICBG procedure.
Cellular Bone Matrices

- Allogenic bone grafts containing live Mesenchymal stem cells
CBM’s

- Currently 6 different brands on the market
- Retrospective studies show fusion rate from 90-92% (industry supported)
- No independent studies exist
- Safe
- Expensive
CBM processing and use

- Cadaver bone harvested
- Isolation of cancellous chips
- Demineralization of cortical bone
- Selective immunodepletion to remove hematopoietic cells
- Combined with cryoprotectant and frozen at -70 to -80 degrees C
- Shelf life 18-60 months
- Thawed, decanted, and placed in sterile saline
Stem Cells and Management of Degenerative Disc Disease

- Clinical manifestations of degenerative disc disease have huge impact in society and economy
- Direct and indirect costs of $50 to $90 billion per year in United States
- Nonsurgical and surgical therapies do not deal with inherent loss of functional native disc tissue
- Failure to regenerate or cure the degenerated painful disc tissue
Stem Cells and Degenerative Disc Disease continued

- Current research emphasis on in vitro cell cultures using mesenchymal stem cell
- In vivo animal models.
Two-Year Results of the Use of Autologous Point-of-Care Bone Marrow Concentrate for the Treatment of Discogenic Low Back Pain

International Orthopaedics 2015
Kenneth Pettine, MD

Stem Cells, 2015
(1-yr results)

<table>
<thead>
<tr>
<th>Clinical Study</th>
<th>One-Level</th>
<th>Two-Levels</th>
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<tbody>
<tr>
<td>• Failed conventional therapy &gt;3 mo.</td>
<td>13</td>
<td>13</td>
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<tr>
<td>• Eligible for surgical relief</td>
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<tr>
<td>• IRB cleared protocol</td>
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<table>
<thead>
<tr>
<th>Discs of Modified Pfirrmann Grade:</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
<th>VII</th>
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<tbody>
<tr>
<td>One-Level</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>3</td>
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<tr>
<td>Two-Levels</td>
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<td>6</td>
<td>11</td>
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<tr>
<th>Cause of Injury</th>
<th>Trauma</th>
<th>Unknown</th>
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<tr>
<td>One-Level</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Two-Levels</td>
<td>5</td>
<td>8</td>
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<table>
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<tr>
<th>Median Age</th>
<th>Range</th>
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<tr>
<td>One-Level</td>
<td>40</td>
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<tr>
<td>Two-Levels</td>
<td>37</td>
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Average BMI

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<th></th>
<th>One-Level</th>
<th>Two-Levels</th>
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<tr>
<td>Average BMI</td>
<td>27.1</td>
<td>26.1</td>
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</table>

Clinical Study
- Failed conventional therapy >3 mo.
- Eligible for surgical relief
- IRB cleared protocol

Stem Cells, 2015
1-yr results
Disc Injection Therapy

60cc BMA drawn from the posterior iliac crest

BMA centrifuged for 12 min. 6cc bone marrow concentrate (BMC) drawn

Total procedure time: 30-45 min.
Disc Injection Therapy

- Cell analysis was performed on samples from 20 patients
- No adverse events for bone marrow aspiration —no chronic pain (60 cc aspirated volume)
- No adverse events at the disc injection site(s)

<table>
<thead>
<tr>
<th></th>
<th>Avg. MSC &quot;dose&quot;</th>
<th>% improv. 12 mo. ODI</th>
<th>% improv. 12 mo. VAS</th>
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<tbody>
<tr>
<td>All Patients</td>
<td>8,138</td>
<td>57%</td>
<td>58%</td>
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<tr>
<td>&lt; 40 years, &lt; 2,000 CFU-F/mL</td>
<td>3,852</td>
<td>65%</td>
<td>83%</td>
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<td>&lt; 40 years, &gt; 2,000 CFU-F/mL</td>
<td>9,927</td>
<td>69%</td>
<td>64%</td>
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<tr>
<td>&gt; 40 years, &lt; 2,000 CFU-F/mL</td>
<td>4,433</td>
<td>34%</td>
<td>29%</td>
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<tr>
<td>&gt; 40 years, &gt; 2,000 CFU-F/mL</td>
<td>13,241</td>
<td>74%</td>
<td>74%</td>
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Disc Injection Therapy
3-year Survivor Cohort (n = 20)

ODI Scores for 3 Year Survivors

- All Patients
- One Level
- Two Level

VAS Scores for 3 Year Survivors by # of Discs Injected

- All Patients
- One Level
- Two Level
Conclusion

- Future of spine surgery evolving
- Recent advancements in stem cell based technologies for both spine fusion and treatment of degenerative disc disease are promising and exciting
Questions