“Always a student, frequently a mentor and never an expert”.

**Disclaimers**

- Bio-Cellular Disc Interventions (BDI) are not designed as stand-alone therapies.
- Some of the BDI may considered investigational and proper consents should be obtained.
- Consult with your State Medical Board and the FDA for regulatory guidance.
- BDI should only be performed by practitioners with significant expertise in interventional spine techniques.
- BDI should only be considered when reasonable conservative therapies have failed or conservative treatment is not feasible.
**Definitions**

**Regenerative Medicine**
Multi-disciplinary approach in which different therapeutic interventions are utilized, in order to induce biologic enhancement of tissue repair, regeneration and functional restoration.

**Bio-Cellular Disc Interventions**
Interventions in which growth factors, scaffolds and cells are utilized, in order to induce biologic enhancement of tissue repair, regeneration and functional restoration of the intervertebral disc complex.

**Definitions**

**Tissue Engineering**
The first definition of tissue engineering is attributed to Drs. Langer and Vacanti who stated it to be "an interdisciplinary field that applies the principles of engineering and life sciences towards the development of biological substitutes that restore, maintain, or improve tissue function or a whole organ".

**Degenerative Disc Disease**
- Is a chronic progressive degenerative condition with no known cure
- High prevalence and frequently symptomatic
- It is associated with the normal aging process and is influenced by many factors, known and unknown
- The hallmark change is reduced disc height due to loss of extracellular matrix and cell death, resulting in decrease capacity of the IVD to absorb water
- The condition can deteriorate and cause pain, motion instability and ultimately collapse of the IVD
- It affects the Annulus Fibrosis, Nucleus, Cartilaginous End Plate and Vertebral Bone Marrow
Bio-Molecular Pathways

- Cellular Respiration Dysfunction
- Mitochondrial Dysfunction
- Citric Acid Cycle Glutamic Pathways
- Glycolytic Pathways ATP Production
- Oxidative Stress Alteration Gene Expression Cytokine Imbalance
- Apoptosis Decrease ECM
- Inflammatory Cytokines

Bio-Mechanical Pathways

- Reduction in cell density, proteoglycan, collagen (II,IX), water binding capacity, axial loading function
- Mechanical dysfunction of the annulus, nucleus and end plate
- Cell death, fibrosis, catabolic cytokines and proteases creating structural failure
- Resulting in annular tears, end plate sclerosis, herniated discs, spondylo-arthritis and spinal stenosis

Degenerative Cascade

- Synovitis
- Hypomobility
- Degeneration
- Capsular Laxity
- Subluxation
- Arthropathy
- Zygaphophyseal Joints
- Intervertebral Disc
- Circumferential Tears
- Radial Tears
- Internal Disruption
- Disc Resorption
- Osteophytes

Ref 16-23.
Symptomatic DDD Treatment Challenges

- Multifactorial etiology
- Presence of systemic pro-inflammatory conditions modulating pain pathways: Obesity, RA, SLE, DM, Diets
- Lack of specific biologic markers
- Lack of correlation significant between diagnostic imaging and pain
- Non-specific symptoms and non-specific physical findings
- Diagnostic test such as provocative discography and MRI, considered the "gold standards" have concerns with specificity and sensitivity
- Lack of consensus
- Lack of an integrated regenerative approach
- Pain cannot be imaged. Maybe.

Dr. McCoy’s Lab

- Bio Computer
- Bio Bed
- Scanner
- Bones

Degenerative Disc Disease STAGING

- RSJI STAGING SYSTEM: Evaluation tool designed to standardized evaluation of symptomatic DDD from a regenerative perspective.
- It is utilized to assist in biologic tool selection and intervention prognosis
- Utilizes four imaging classifications: MRI, Pfirrmann (MRI), Modic (MRI, X-rays), Dynamic Video Discography
- Co-Morbidity factors assessment that affect the overall cell function
**Dynamic Video Discography**

- Utilizes real time video recording during discography
- Allows for evaluation of contrast flow analysis based on volume, not pressure
- Provides critical information regarding volumetric capacity of the IVD
- Better assessment of annular tear dynamics
- Essential in designing tissue engineering constructs

**Modic Classification**

Type I
- T1: Hypointense signal
- T2: Hypointense signal

Type II
- T1: Hyperintense signal
- T2: Iso or Hyperintense signal
  - Often represents normal red hematopoiesis
  - Some may represent bone marrow conversion to yellow fatty marrow as result of marrow ischemia

Type III
- T1: Hypointense signal
- T2: Hypointense signal
  - Often represents sub-chondral bone sclerosis

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**Pffirmann Magnetic Resonance Classification**

**Intervertebral Disc Degeneration**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Structure</th>
<th>Description of Nucleus</th>
<th>Signal Intensity</th>
<th>Intervertebral Disc Height</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Normal</td>
<td>Homogeneous bright white</td>
<td>Clear Hyperintense</td>
<td>Normal to slightly decreased</td>
</tr>
<tr>
<td>II</td>
<td>Mild</td>
<td>Inhomogeneous, W0 horizontal bands</td>
<td>Clear Hyperintense, Isointense to CSF</td>
<td>Normal to slightly decreased</td>
</tr>
<tr>
<td>III</td>
<td>Moderate</td>
<td>Inhomogeneous, gray</td>
<td>Unclear Intermediate</td>
<td>Normal to moderately decreased</td>
</tr>
<tr>
<td>IV</td>
<td>Severe</td>
<td>Inhomogeneous, gray to black</td>
<td>Lost Hypointense</td>
<td>Collapsed</td>
</tr>
<tr>
<td>V</td>
<td>Failed</td>
<td>Inhomogeneous, black</td>
<td>Lost Hypointense</td>
<td>Collapsed</td>
</tr>
</tbody>
</table>
CO-MORBIDITY FACTORS

- Translational Instability
- Poor Core Biomechanics
- Advanced Auto Immune Diseases
- Nutritional Depletion
- Severe Systemic Diseases
- Morbid Obesity
- Substance Abuse
- Psychological Dysfunction
- Prior Back Surgery
- Chronic Infections

CO-MORBIDITY FACTORS

- Greater than 2 symptomatic discs
- Chronic Neuropathic Pain
- Smoking History
- Non-ambulatory
- Failed Spinal Cord Stimulation
- Failed Intra Thecal Therapies
- Disability Seeking Behavior
- Hormonal Deficiencies

Regenerative Disc Classification
Stage I

- DHR 0-25%  Herniation: 0-3mm  Stenosis: None
- Pfirman: I,II
- Modic 0
- Discography: Pain-Concordant, Grade 1-3
- Pain: Location: Mainly back  Intensity: Mild-Moderate
- Instability: None  Co-Morbidities: None-Mild
Regenerative Disc Classification

Stage II
- DHR 0-25% Herniation: 0-6mm Stenosis: None
- Pfirman: III
- Modic: O/I
- Discography: Pain Concordant, Grade 1-5
- Pain: Location: Back> Leg  Intensity: Mild-Moderate
- Instability: None  Facet Hypertrophy – Hypo-Hyper Mobility
- Co-Morbidities: None-Moderate

Regenerative Disc Classification

Stage III
- DHR 25-50% Herniation: >6mm Stenosis: Mild-Moderate
- Pfirman: III-IV
- Modic: I-III
- Discography: Pain Concordant, Grade 1-5
- Pain: Location: Leg>Back  Intensity: Moderate
- Instability: Spondylolisthesis I, Co-Morbidities: Mild-Severe

Regenerative Disc Classification

Stage IV
- DHR >50% Herniation: >6mm Stenosis: Mod-Severe
- Pfirman: IV-V
- Modic: III
- Discography: Not indicated
- Pain: Location: Leg>Back
- Intensity: Severe
- Instability: Spondylolisthesis I-III,
- Mod-Severe Co-Morbidities:
The Regenerative Approach

Integrated Regenerative Approach
Degenerative Disc Disease

All Stages

Bio-Mechanical
- Core strengthening
- Weight reduction
- Exercise
- PT, Chiropractic, Acupuncture, Low level laser, Yoga, Bio feedback, TENS

Nutritional Optimization
- Anti-inflammatory Diet
- Supplements

Hormonal Optimization
- Cortisol, Testosterone, Progesterone, Thyroid, Estrogen

Primary End Point
- Safety
- Pain Relief

Secondary End Point
- Functional Restoration (Regenerate, Repair, Restore)

Tertiary End Point
- Prevention of Further Degeneration
- Prevention of Adjacent Level Degeneration
- Restoration of Disc Height

Bio-cellular Therapies for IVD
Bio-Regenerative Disc Index Prognostic Model

- Stage I: Very Good – Excellent
- Stage II: Good – Very Good
- Stage III: Fair – Good
- Stage IV: Poor

*At this time, there is not enough clinical data to validate this prognostic model.

Biologic Tools

- Cells
- Growth Factors
- Signaling Molecules
- Scaffolds

- Polypeptides found in tissue extracts such as blood, synovial fluid, cells, etc., involved in stimulation of cell proliferation, migration, modulation, differentiation and matrix synthesis
- Essential in stimulating cells such as chondrocytes, fibroblasts, endothelial cells needed for connective tissue repair
- Found in small concentration in tissue extracts
- Can be genetically engineered

Growth Factors
Mechanism of Action

Autologous

Synthetic

Allogeneic

Growth Factors (Stimulating Molecules)

PRP

Imbedded in Scaffolds, Amniotic Tissue

GDF-5, BMP-2, Peptides (IGF-1)
## PRP Growth Factors

<table>
<thead>
<tr>
<th>Growth Factor</th>
<th>Units</th>
<th>Concentration above baseline</th>
<th>Final Platelet Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-1</td>
<td>ng/ml</td>
<td>1x-10x</td>
<td>2x-6x</td>
</tr>
<tr>
<td>PDGF</td>
<td>ng/ml</td>
<td>3x-10x</td>
<td>2x-6x</td>
</tr>
<tr>
<td>TGF-b1</td>
<td>pg/ml</td>
<td>4x-10x</td>
<td>2x-6x</td>
</tr>
<tr>
<td>EGF</td>
<td>pg/ml</td>
<td>2x-3x</td>
<td>2x-6x</td>
</tr>
</tbody>
</table>

Unpublished data from companies: [www.biomet.com](http://www.biomet.com), [www.arthrex.com](http://www.arthrex.com), [www.harvesttech.com](http://www.harvesttech.com)

## Types of Growth Factors

### Anabolic Regulators

- Insulin Like Growth Factor IGF-1
- Transforming Growth Factor TGF-B
- Bone Morphogenic Protein BMP-2

### Catabolic Regulators

- Secreted by macrophages infiltrated in granulation tissue and apoptotic cells. Metalloproteinases MMP and Aggrecanases create loss of matrix. TNF alpha, Interleukin-1 (IL-1) PG inhibition at low concentration and aggrecan degradation at higher concentration.

- Interleukin-1 (IL-1)
- Metalloproteinases MMP
- Aggrecanases

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Endocrine: Affect multiple distant tissues, usually carried in the blood.

Paracrine: Cells are the source of growth factors, usually close contact.

Autocrine: Cell produces growth factors which act on the same cell.

Growth Factors

Mechanism of Action

- Endocrine
- Paracrine
- Autocrine

Scaffolds

Scaffolds provide a provisional matrix in a three-dimensional microenvironment, to localize cells for cellular and molecular interactions appropriate for cell survival and differentiation.

- Natural
- Synthetic
- Low immunogenicity
- Biodegradable and bio-compatible
- Optimal Mechanical and Architectural Properties
- Non-toxic
- Preferably hydrophilic

Autologous

Adipose, Fibrin (PPP)

Allogeneic

Collagen, Amniotic BM, Fibrin

Synthetic

Alginate, Polymer, Nano, Hyaluronic Acid

A normal constituent of both connective tissue matrix and synovial fluid, is a large mucopoly saccharide produced by synoviocytes and chondrocytes, respectively. Large molecular weight with cross-linking are preferable (Synvisc).

Fibrin Gel
Fibrin Gel contains large amounts of fibrinogen and thrombin. Ideal for growth factor delivery. Autologous processed from PRP.

Collagen

Sponges, micronized, allogeneic, most effective with cell therapy.

Human Amniotic Membrane
Decellularized basement membrane from the innermost placental layer, composed of a thick basement membrane, avascular matrix.
Cell Based Therapies

- Treatment in which stem cells are induced to differentiate into the specific cell type required to repair damaged or destroyed cells or tissues.
- Produce significant growth factors to induced stimulate endogenous stem cell population.
- Successful cell to cell interaction with the Niche.
- Survive in the recipient after transplant.
- Engraft into the surrounding tissue after transplant.
- Produce enough trophic growth factors to achieve desired effect.
- Avoid harming the recipient in any way.

Cell Based Therapy

Coehlem, a German pathologist almost 130 years ago proposed the existence of non hematopoietic stem cells. He suggested that bone marrow cells can assist in the repair of the process of various peripheral tissues.

In 1970, Friedenstein discovered that bone marrow contained fibroblastoid cells with clonogenic potential in vitro capable of forming colonies. CO was able to regenerate bone in different transplants. This provided evidence of cell renewal potential of these cells.


Autologous Point of Care Cell Based Therapies

- BMAC (Bone Marrow Aspirate Concentrate)
- ADSVF (Adipose Derived Stromal Vascular Fraction)
- BMMSC (Bone Marrow Mesenchymal Stem Cells)
- ADMSC (Adipose Derived Mesenchymal Stem Cells)
- UCMS (Umbilical Cord Mesenchymal Stem Cells)
- OTHER TISSUES (MUSCLE, SYNOVIAL, MENSTRUAL BLOOD, ETX)
Cell Based Therapy

Bone Marrow Aspirate Concentrate (BMAC)
Non hematopoietic fraction composed of endothelial progenitor cells (EPC), mesenchymal stem cells (MSC), very small embryonic like cell (VSEL), platelets, lymphocytes, growth factors and other extracellular matrix factors.
- Mesenchymal stem cell population less than \(0.01\) - \(0.02\%\) of total nucleated cells.
- Current clinical trials: critical limb ischemia trials, cardiac (ischemia and heart failure), stroke, diabetes (I,II), autoimmune, etc.

Cell Based Therapy

Adipose Derived Stromal Vascular Fraction (ADSF)
Endothelial progenitor cells (EPC), mesenchymal stem cells (MSC), very small embryonic like cell (VSEL), lymphocytes, pericytes, growth factors and other extracellular matrix factors.
- Mesenchymal stem cell population 5\%-10\% of total nucleated cells.
- Current clinical trials: graft vs. host, tissue reconstruction, cosmetic surgery, orthopedics, spinal cord injury, RA, SLE, etc.

Niche and Homing
- Cell behavior is induced by encoding proteins and cytokines secreted by the local tissue or niche.
- SDF-1 molecules bind with the local surface receptors and integrins of the MSC outer membrane (CXCR4)
- Cell are then induced to differentiate into specific phenotype or proliferate.
- Niche signaling pathways are critical for regenerative therapies to be successful.
Interventional Regenerative Approach
Degenerative Disc Disease

**Diagnosis:** Stage I DDD
**Biologic Tools:** Growth Factors (PRP)
Peptides (P)
**Technique:** Intra-Discal Injection, Peri-annular
Interventional Regenerative Approach
Degenerative Disc Disease

Diagnosis: Stage II DDD
Biologic Tools: BMAC (CBT) + HA (S) + Peptides (GF)
- Amniotic (CBT) + HA (S) + Peptides (GF)
- ADSVF (CBT) + AF (S) PRP + Peptides (GF)
Technique: Intra-Discal Injection, Lipoaspirate or Bone Marrow Aspirate

Interventional Regenerative Approach
Degenerative Disc Disease

Diagnosis: Stage III DDD
Biologic Tool: ADSVF + BMAC
- HA, Collagen, Fibrin
Technique: Lipoaspirate (50-100cc) + Bone Marrow Aspirate
- Intra-discal Injection, Transpedicular

Interventional Regenerative Approach
Degenerative Disc Disease

Stage IV Severe
Complex Spine Operative Care

- Main role as enhancement of tissue repair
- Growth Factors (PRP, BMP-2, GDF-5)
- Scaffolds (Amniotic BM, Bone Allografts, DBM, Hyaluronic Acid)
- Cell Therapy (ADSVF, BMSVF, Expanded MSC)
Treatment of Lumbar Degenerative Disc Disease with Adipose-Derived Stromal Vascular Fraction, Point of Care

- A 48 y/o female patient with intractable low back and left lower extremity radicular symptoms
- Duration 6 years, not responding to conservative care and interventional pain management therapeutics
- Patient obtained prior neurosurgical consultation recommending an inter-body fusion with instrumentation or a total disc arthroplasty at L-5

Garcia, C. Treatment of Lumbar Degenerative Disc Disease with Adipose-Derived Stromal Vascular Fraction/Point of Care. Abstract. IFATS, Oct 2012, Quebec.

Lumbar MRI consistent with a L5 central disc herniation (3mm), significant disc desiccation, end plate changes and a “black disc”

Garcia, C. Abstract. IFATS, Oct 2012, Quebec.

Biologic Construct

Adipose Derived SVF
- Standard procedures were used for SVF isolation from autologous lipo-aspirate 50cc.
- Cells processed via a lecithin based emulsification
- 93% viability
- 80% CD34+, CD45-, CD39+, CD90+, CD105+
- Estimated MSC injected 5 x 10^6

PRP: Platelet Rich Plasma (20%) Fragmented Collagen (porcine)
Results

- Lumbar MRI at 6 and 12 months post procedure was positive for an increased in the T2 weighted signal at the L5 nucleus, consistent with ECM deposition
- Preservation of disc height at the treated level (L5) and the adjacent level (L4)
- No ectopic bone formation

Visual Analog Scale

![Visual Analog Scale Graph]

<table>
<thead>
<tr>
<th>Pre</th>
<th>Month 1</th>
<th>Month 3</th>
<th>Month 6</th>
<th>Month 9</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS</td>
<td>8</td>
<td>7</td>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

![MRI Images]
MRI Results
Lumbar MRI  T2 weighted
Pre  12 Months Post

Conclusion

- A biologic construct with autologous AD-SVF at point of care was successful in treating a patient with advanced symptomatic Lumbar DDD

- ECM production in the nucleus pulposus at 6 and 12 months post-transplantation was confirmed by increased T2 Lumbar MRI

- Prevention of further disc degeneration at the treated L-5 and adjacent L-4 disc was achieved
Transpedicular Vertebral BMAC
Intra-Discal BMAC/Synvisc

Transpedicular Vertebral BMAC
Intra-Discal BMAC/Synvisc

IT'S THE ONLY PROCEDURE HER H.M.O. WILL PAY FOR.
Thank You