Bio-Cellular Disc Interventions: New Evidence
Carlos J. Garcia, MD
Disclosures

NONE

Carlos J. Garcia, MD
The Regenerative Spine and Joint Institute
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".
SPINE RELATED CONDITIONS

- DISC
  - Symptomatic DDD
  - Symptomatic Herniated Discs

- NERVE ROOTS
  - Compressive Lesions
  - Inflammatory Lesions
  - Neuropathic Lesions
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
Cellular Respiration Dysfunction
NAD/NADH

Mitochondrial Dysfunction
Citric Acid Cycle
Glycolytic Pathways
ATP Production

Oxidative Stress
Alteration Gene Expression
Cytokine Imbalance

Alteration Cell Hemostasis
Decrease ECM

Increase Apoptosis
Inflammatory Cytokines

BIO-MOLECULAR PATHWAYS
BIO-MECHANICAL PATHWAYS

Reduction in cell density, proteoglycan, collagen (II, I, X), 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-arthropathy and spinal stenosis

Ref 16-23.
INTERNAL DISC DISRUPTION
ETIOLOGY

• Of the several insults previously described, IDD appears to be most closely associated with endplate fracture

• Experimental endplate fracture causes, over time: • reduction in water, proteoglycans • Delamination • reduction in pressure within the nucleus, autoimmune reaction


Haschtmann D, Stoyanov JV, Gédet P, Ferguson SJ. Vertebral endplate trauma induces disc cell apoptosis and promotes organ degeneration in vitro. Eur Spine J; 2008; 17:289-
INTERNAL DISC DISRUPTION
ETIOLOGY

· Endplate Fatigue Fracture
· Precipitates degradation of nuclear matrix
· Inflammatory response
· Nutritional / biochemical (pH) insults • Nuclear dehydration
· Unable to accept and disburse load
· Load to transferred to posterior annulus
· Radial Fissuring
# INTERVERTEBRAL DISC COMPLEX

<table>
<thead>
<tr>
<th>IVD</th>
<th>Collagen Type</th>
<th>Proteoglycan (Type and %wt)</th>
<th>Cell Density</th>
<th>Water (%wt)</th>
<th>Cell Type</th>
<th>Function</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleus</strong></td>
<td>Type II I,VI,IX,XI 5-10%</td>
<td>25-60 Aggrecan, Decorin, biglycan Fibromodulin, versican</td>
<td>Low</td>
<td>70-90</td>
<td>Chondrocyte</td>
<td>Compressive</td>
<td>CELL ECM, GAG</td>
</tr>
<tr>
<td><strong>Annulus</strong></td>
<td>Type I II, VI,IX,XI 10-15%</td>
<td>10-35 Aggrecan, Decorin ,biglycan Fibromodulin, versican</td>
<td>High</td>
<td>65-80</td>
<td>Fibroblast</td>
<td>Tensile</td>
<td>Lamellar, concentric</td>
</tr>
<tr>
<td><strong>End plate</strong></td>
<td>Type X 20-25%</td>
<td>5-10 Aggrecan, Decorin, biglycan Fibromodulin, versican</td>
<td>Low</td>
<td>50-60</td>
<td>Chondrocyte</td>
<td>Nutrition</td>
<td>CELL ECM, GAG</td>
</tr>
</tbody>
</table>
IVD CELL TYPES
CELL DENSITY AND AGING

Liebscher, T.; Wuertz, K.; Haefeli, M.; Nerlich, A.; Boos, N. University Hospital Balgrist, University of Zurich, Zurich, Switzerland

Paper No. 305 • 55th Annual Meeting of the Orthopaedic Research Society
IMMUNE PRIVILEGE

• Certain sites of the human body have immune privilege, meaning they are able to tolerate the introduction of antigens without eliciting an inflammatory immune response

• Tissue Grafts are normally recognized as foreign antigen by the body and attacked by the immune system

• Brain, Eye, Testes, Placenta, Disc
Recent report showed that the disc is an immune-privileged organ and Fas ligand expression may play important roles to maintain the immune privilege. It has been demonstrated that the expression of the Fas ligand is decreased in degenerated discs.

IMMUNE PRIVILEGE

TGF-beta

Suppresses Mitogen and antigen-driven T cells.

Suppresses mediators released by neutrophils.

Suppresses nitric oxide produced by macrophages.

Blocks the actions of Natural killer cells.
DEGENERATIVE CASCADE

Zygaphophyseal Joints
- Synovitis,
- Hypomobility
- Degeneration
- Capsular Laxity
- Subluxation
- Arthropathy

Intervertebral Disc
- Circumferential Tears
- Radial Tears
- Internal Disruption
- Disc Reasorption
- Osteophytes

SPINE CONDITIONS
- Normal Disc
- Degenerative Disc
- Bulging Disc
- Herniated Disc
- Thinning Disc
- Disc Degeneration with Osteophyte formation
STAGES OF DDD

EARLY MODERATE ADVANCED
Of the 61 patients undergoing surgery for extruded disc herniation in their series, in 46% of specimens growth of Propionibacterium Acnes [PA] was observed, and this correlated with a greater frequency of MC type I.

Intradiscal Environment (The Battle Zone)

- Lack of blood supply
- Low Oxygen tension
- Anabolic metabolism, Low Ph 6.9-7.1
- High levels of MMP, TNFa, ILB
- Extremely low cellular density
- Autoimmune “wars”
VARIABLES AFFECTING IDD

- Metabolic Conditions
- Genetic Influence
- Traumatic
- Nutritional
- Lifestyle (smoking, inflammatory diets)
- Infectious
- Core Instability
- Others
MODIC CLASSIFICATION

Type I

- T1: Hypo-intense signal
- T2: Hyper-intense signal

Bone marrow edema and inflammation

Type II

- T1: Hyper-intense
- T2: Iso or Hyper-intense

Often represents normal red haematopoietic bone marrow conversion into yellow fatty marrow as a result of marrow ischemia

Type III

- T1: Hypointense
- T2: Hypointense

Often represents sub-chondral bone sclerosis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Structure</th>
<th>Distinction of Annulus-Nucleus</th>
<th>Signal Intensity</th>
<th>Intervertebral Disc Height</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Homogeneous bright white</td>
<td>Clear</td>
<td>Hyperintense, Isointense to CSF</td>
<td>Normal</td>
</tr>
<tr>
<td>II</td>
<td>Inhomogeneous, w/w0 horizontal bands</td>
<td>Clear</td>
<td>Hyperintense, Isointense to CSF</td>
<td>Normal</td>
</tr>
<tr>
<td>III</td>
<td>Inhomogeneous, gray</td>
<td>Unclear</td>
<td>Intermediate</td>
<td>Normal to slightly decreased</td>
</tr>
<tr>
<td>IV</td>
<td>Inhomogeneous, gray to black</td>
<td>Lost</td>
<td>Intermediate to Hypointense</td>
<td>Normal to moderately decreased</td>
</tr>
<tr>
<td>V</td>
<td>Inhomogeneous, black</td>
<td>Lost</td>
<td>Hypointense</td>
<td>Collapsed</td>
</tr>
</tbody>
</table>
WHY REGENERATIVE MEDICINE INTERVENTIONS FOR IDD?

It is the only cost effective, therapeutic and preventive treatment for ADOSI syndrome, in patients with early to moderate IDD.
WHAT IS ADOSI SYNDROME?

• Affects over 300,000 patients a year in the US
• Cost of healthcare calculated in billions of dollars
• High prevalence
• It can be acquired while at the doctors office, dinner presentations, neighborhood parties
• The existing treatments can be associated with exacerbation of the condition and permanent side effects
ACQUIRED DEFICIENCY OF SPINAL INSTRUMENTATION (ADOSI)
Growth Factors
(Signaling Molecules)

- **Autologous**
- **Allogeneic**
- **Synthetic**

**PRP**

- Imbedded in Scaffolds, Amniotic Tissue
- GDF-5, BMP-2, Peptides (IGF-1)
CYTOKINES, WHERE DO THEY COME FROM?

Mitogenic (growth) factors

PDGF, FGF, HGF, IGF, etc: Roughly 80% stored in platelets, 20% soluble in plasma

• Angiogenic factors –primarily VEGF

Roughly 80% stored in platelets, 20% soluble in plasma

• Matrix-building proteins

Fibrinogen, fibronectin, vitronectin • Available in the plasma, not the platelets

• Anti-inflammatory proteins

Alpha-2-Macroglobulin (A2M), IL-1RAP (aka IRAP) • Available in the plasma, not the platelets
TISSUE SCAFFOLDS

Autologous
- Adipose, Fibrin (PPP)

Allogeneic
- Collagen, Amniotic BM, Fibrin

Synthetic
- Alginates, Polymer, Nano, Hyaluronic Acid
Cell-Based Therapies

Autologous

BMAC (Bone Marrow Aspirate Concentrate)
ADSVF (Adipose Derived Stromal Vascular Fraction)

BMMSC (Bone Marrow Mesenchymal Stem Cells)
ADMSC (Adipose Derived Mesenchymal Stem Cells)
UCMSC (Umbilical Cord Mesenchymal Stem Cells)

OTHER TISSUES (MUSCLE, SYNOVium, MENSTRUAL BLOOD, ETC)
Umbilical Cord Stem Cells (Grafts)

Point of Care

Ex-Vivo Expansion
Cell-Based Therapies

Allogeneic

Point of Care

BMMSC (Bone Marrow Mesenchymal Stem Cells)
ADMSC (Adipose Derived Mesenchymal Stem Cells)
UCMSC (Umbilical Cord SYNOVLIUM, MENSTRUAL BLOOD, ETC)

Ex-Vivo Expansion

Chondrocytes
Fibroblasts
REGENERATIVE APPROACH

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
“THE HOST DETERMINES THE OUTCOME MOST OF THE TIME”
INTRADISCAL PRP

Intradiscal Injection of Autologous Platelet-Rich Plasma releasate for the Treatment of Discogenic Low Back Pain-Preliminary Prospective Clinical Trial of 12 cases.

Akeda, K. et. Al. Poster presentation. ORS 2013

• Type: Open, Non Randomized Single ARM, Patients 12
• Diagnosis: Symptomatic DDD, Mainly back pain, discography, MRI
• Pfirrmann’s Grade III- IV, Grade IV- 4
Intradiscal Injection of Autologous Platelet-Rich Plasma Releasate to Treat Discogenic Low Back Pain: A Preliminary Clinical Trial.

Koji Akeda, Kohshi Ohishi, Koichi Masuda, Won C. Bae, Norihiko Takegami, Junichi Yamada, Tomoki Nakamura, Toshihiko Sakakibara, Yuichi Kasai, and Akihiro Sudo
PRP

• Outcome Measures: VAS, RDQ, X ray
• MRI (4, 12 months), DHI
• Source: Autologous PRP, Autologous Fibrin from coagulated whole blood and CaCl₂.
• Type: Growth factors, Fibrin Sealant
• Results: Average Follow Up: 11 months,
  • VAS: PRE- 7.7 POST 3.1 (+- 3.2)   RDQ: PRE- 13.5 POST-2.9 (+- 4.2)
  • MRI DHI unchanged, T2 mean values unchanged.
• Results: Average Follow Up: 11 months,

• VAS: PRE- 7.7 POST 3.1 (+- 3.2)      RDQ: PRE- 13.5 POST-2.9 (+- 4.2)

• DHI unchanged, T 2 mean values unchanged.
INTRADISICAL PRP

Lumbar Intradiskal Platelet-Rich Plasma (PRP) Injections: A Prospective, Double-Blind, Randomized Controlled Study. 1-10

Conclusion: Participants who received intradiskal PRP showed significant improvements in FRI, NRS Best Pain, and NASS patient satisfaction scores over 8 weeks compared with controls. Response rate 60%. N 28

Those who received PRP maintained significant improvements in FRI scores through at least 1 year of follow-up. Although these results are promising, further studies are needed to define the subset of participants most likely to respond to biologic intradiskal treatment and the ideal cellular characteristics of the intradiskal PRP

Inclusion: Low back pain 6>months, Failed conservative therapy, Pfirrmann II-IV

Study Design: Prospective

Intradiscal Injection of A2M, prior saline lavage for FAC analysis

Outcome Measurements: VAS, ODI
Duration of Follow Up: 6 months

Definition of Success: VAS reduction 3> points, ODI 20>
Treatment: 40 patients. Only 24 completed the 6 months follow up.

Results: FAC Positive Patients: 6 months- ODI 28 points, VAS 4 (declining trend), Patients # ?

FAC Negative Patients: 6 months- ODI 12., VAS 2.3 (declining trend), Patients # ?
Conclusion: Fibronectin-Aggrecan Complex (FAC) is a cartilage degradation product associated with tissue degeneration in the IVD. A2M **maybe be efficacious** in patient with symptomatic DDD FAC positive.

According to the author, “We cannot certainly ascribe all the therapeutic effects of A2M alone, these additional growth factors (PPP) may provide anabolic stimulus to the IVD and thus provide therapeutic benefit”.
AMNIOTIC FLUID CELL THERAPY TO RELIEVE DISC-RELATED LOW BACK PAIN AND ITS EFFICACY COMPARISON WITH LONG-ACTING STEROID INJECTION. BHATTACHARYA, NIRANJAN. (2012, DECEMBER 5). HUMAN FETAL TISSUE TRANSPLANTATION. 2013, PP 251-264

• Compared injection of intradiscal and paraspinous Methylprednisolone with fresh amniotic fluid

• Results at 3 months , steroid clinically superior

• Results at 24 months : 2/21 patients had sustained pain relief, while 12/24 patients had significant pain relief

• Changes noted on VAS, ODI, SF 36
Amniotic Membrane Microparticles Decrease Cytokine, Matrix Degradation and Associated Pain Marker Expression in Human Intervertebral Disc Explant Cultures.

Author(s):
Y.-P. Lee (1) R. Pichika (1) S. Garfin (1) M. Lenz (1) K. Masuda (1)
(1) UCSD San Diego, Orthopaedic Surgery, San Diego, CA, United States
Results

• Gene Expression: significantly suppressed the constitutive expression of the cytokines (IL-1β, IL-6, TNF-α; p<0.01).

• All matrix-degrading enzymes (MMP-3, ADAMTS4, ADAMTS5), were also significantly suppressed.

• Matrix genes, aggrecan and collagen II, were significantly upregulated by AMF.

• Protein levels in culture media: AMF dose-dependently decreased the release of MMP-3 and TNF-α into the media (both 10% and 20%; p<0.01).
Conclusions

Amniotic membrane tissue micro-particles suppressed the gene expression of cytokines and matrix-degrading enzymes and stimulated aggrecan and collagen II expression.
Intradiscal Injection of Fibrin Sealant for the Treatment of Symptomatic Lumbar Internal Disc Disruption: Results of a Prospective Multicenter Pilot Study with a 24-Month Follow Up.

• Content; Human Fibrin Sealant, Bovine Thrombin, Calcium Choride, Synthetic Aprotinin Acetate.

• Device: Biostat Biologx

• Proposed Mechanism of Action: Down regulation of pro-inflammatory Cytokines (Interleukin 1B, IL-6,8, TNF, Proteolytic Enzymes: MMP-3, MMP-1) Upregulation of Anabolic cytokines- IL-4.

• End Point: Up to 4ml or 100mmHg psi.

• Device: 18g Intradiscal Trochar

• Follow UP for 2 years

• No new disc bulges greater than 4 cm. One case of discitis. 3 cases of asymptomatic reactive changes (Modic I,II)
Intradiscal Allogeneic Fibrin Biostat

- Most subjects had improvement in pain and function in 4 weeks. Significant pain relief defined as > 30% improvement. 86% at 6 months.

- Improvement in function (>30%), 73% at 6 months.

- No change in reduction of medication use.

- No changes in T image or disc height.

- Phase III Trial failed
INTRA-DISCAL BMAC

BMAC

One-Year Results of the Use of Autologous Point-of-Care Bone Marrow Concentrate for the Treatment Discogenic Low Back Pain. October 2013. Online.

Kenneth Pettine, MD

Type: Prospective, Non randomized, 26 patients (13 one level, 13 two levels),
Product: BMAC (Bone Marrow Aspirate Concentrate)
Device: Celling Bio Science ART 21
Source: Autologous
• Construct Evaluation: CFU
• Endpoint: 2-3cc BMAC, no pressure manometry,
• No information as to the degenerative staging of the disc
• Evaluation Tools: VAS, ODI
• Results: 1 year. Average VAS reduction at 58%. ODI reduction 56%
• 1st study to correlate CFU and outcome.
• Regardless of CFU, all patients under 40, did well.
• Over 40 with CFU less than 2,000 CFU-F ml, less reduction in VAS, ODI
• No lumbar MRI follow up
INTRA-DISCAL BMAC

• Percutaneous Lumbar Intradiscal Injection of Autologous Bone Marrow Concentrated Cells Significantly Reduces Discogenic Pain through 24 Months

• Fernando Techy, MD

PERCUTANEOUS LUMBAR INTRADISCAL INJECTION OF AUTOLOGOUS BONE MARROW CONCENTRATED CELLS SIGNIFICANTLY REDUCES DISCOGENIC PAIN THROUGH 24 MONTHS

- Treatment: Intra-discal BMAC (Average 120 million TNC/ml and CFU 3,00) patients (median age 40), Levels: 13 One, 13 two

- Assessment Tool: VAS, ODI (Oswestry Dissability Index), Lumbar MRI

- Follow Up Period: 24 months (23/26)

- Results: Average reduction in ODI/VAS 77/78%, 8/20 One grade Pffirman improvement, 5/23 failed and underwent instrumented lumbar fusions. None of those patient improved ODI/VAS after surgery.
EFFECTS OF THE INTRADISCAL IMPLANTATION OF STROMAL VASCULAR FRACTION PLUS PLATELET RICH PLASMA IN PATIENTS WITH DEGENERATIVE DISC DISEASE.

COMELLA KRISTIN1*, SILBERT ROBERT2 AND PARLO MICHELLE1


• 1-3 cc of prp/svf (30-60 mill estimated, not tested)
• N 15 patients, no discography
• Average VAS scores improvement 40%, some increase in mobility at 6 months, 60 % improve at 6 month, 40% showed no improvement at 6 month
• ODI and BDI did not show statistically significant changes
INTRADISCAL SVF (STROMAL VASCULAR FRACTION)

- Lack of high quality and or comprehensive peer review evidence
- Animal data associated with significant autoimmune reaction
- FDA 351 product
INTRADISCAL ALLOGENEIC UMBILICAL CORD TISSUE GRAFT (AUCTG)

- Lack of comprehensive or clinically reliable peer review literature
- However, personal anecdotal excellent response in selected cases
- Unable to expand cells in the lab
EX-VIVO MSC EXPANSION

For illustration purposes only. This product has not been approved for use by the US Food and Drug Administration.
In 2010, Yoshikawa, et al. analyzed the regenerative ability of autologous MSCs in markedly degenerated IVDs of two patients with chronic low back pain, radiculopathy, and paresthesias [25].

MSCs isolated from bone marrow aspirate were coupled with collagen sponges and grafted percutaneously to the degenerated IVD following partial laminotomy. Two years after surgery, both patients had significant symptomatic relief as assessed by VAS, and T2-weighted MRIs showed high signal within the treated IVDs indicating high NP hydration without progressive degeneration.
EURO DISC RANDOMIZED TRIAL
AUTOLOGOUS CHONDROCYTE DISC TRANSPLANTATION (ACDT)

- 129 patients undergoing microdiscectomy. Age 18-60. BMI below 28.
- Sequestered cells expanded in culture and transplanted in the contralateral side, small bore cannula 12 weeks post procedure.
- Volume pressure measured prior to injection. 5 million cells injected per disc.
- Primary analysis at 12 months, interim analysis at 24 months and final analysis at 48 months. MRI used to assess the respective disc height from the sequestration date until the 2 year follow up. VAS, ODI, SF-36, QBPDI.
Interim Results at 2 years:

Trend to a decrease fluid content over the follow up period in the non-treated group. Treated group 41% preservation versus 25% control.

Adjacent disc one or two levels also had higher water content.

Patient who received ACDT had greater pain relief at 2 years.

EURO DISC RANDOMIZED TRIAL
AUTOLOGOUS CHONDROCYTE DISC TRANSPLANTATION (ACDT)

28 y/o woman undergoing discectomy at L5- S1

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post 1 day</th>
<th>Post 3 months</th>
<th>Post 12 months</th>
<th>Post 24 months</th>
<th>Post 60 months</th>
</tr>
</thead>
</table>
Orozco, L et al. 2011. Intervertebral Disc Repair by Autologous Mesenchymal Bone Marrow Cells: A Pilot Study. Transplantation 92; 7: 822

- 10 patients who failed conservative therapy for 6 months. Average age 35. Discogenic and Radicular pain.

- Cell expansion: Source Bone Marrow (90 ml, 800 million total nucleated). Expansion 25 million MSC. Viability 83%.

- Metrics: VAS, ODI, SF-36

- Response: Greatest improvement at 3 months and continue improving to 12 months. Significant improvement 71%.

- Imaging: The ratio of fluid content to the normal disc did not improve until month 6 to 12. Able to stop progression of degeneration.
INTERVERTEBRAL DISC REPAIR
BY AUTOLOGOUS MESENCHYMAL
BONE MARROW CELLS: A PILOT
STUDY.

• No improvement of disc height. In accordance to previous studies.
• Analgesic effect mainly due to the immune regulatory trophic effects of MSCs.
A RANDOMIZED, CONTROLLED TRIAL EVALUATING THE SAFETY AND EFFECTIVENESS OF IMMUNO SELECTED, ALLOGENEIC, MESENCHYMAL PRECURSOR CELLS FOR TREATMENT OF CHRONIC LOW BACK PAIN.”

24TH ANNUAL SCIENTIFIC MEETING OF THE SPINE INTERVENTION SOCIETY (SIS) HELD IN NEW ORLEANS JULY 27-30, AND RECEIVED THE 2016 DEPALMA, ET AL.
MESOBLAST STUDY

- Prospective, multi-center, randomized, double-blind, controlled study
- Patients and radiographic evaluators blinded to treatment
- Follow-up: 1, 3, 6, 12, 24 & 36 months
- Group A, N 20, Saline
- Group B, N 20, Hyaluronic Acid (HA)
- Group C, N 30, HA and 6 million MSC
- Group D, N 30, HA and 12 million MSC
MESOBLAST STUDY

- Success Defined as: VAS decrease >50% and ODI improvement >15 points
- Results 12 Months
  - Group A  Saline 12.%
  - Group B  Hyaluronic Acid 17.6%
  - Group C  HA and 6 million MSC 44%
  - Group D  HA and 12 million MSC 42.3%
Overall Treatment Success at 24months

- 38.5% of the 6 million MPC group
- 34.6% of the 18 million MPC group
- 17.7% of the hyaluronic acid group
- 12.5% of the saline group.
Phase 1/2 Clinical Trial Results Positive for SpinalCyte’s CybroCell™ Dermal Fibroblasts. Houston’s Business Wire.

Almost 70 percent of patients who were treated with the first off-the-shelf allogeneic HDF product for treatment of degenerative disc disease, called Cybro-Cell, reported significant therapeutic improvement. ...
Study Design

Group A - Saline  N-5

Group B - 10 million cells, N-6

Group C - 10 million cells and PRP, N 4
Results

Group A (Saline) ?

Group B (Cells Only )
4/6 patients, ODI improvement > 15 points

Group C (Cells and PRP)
1/4 patients, ODI improvement > 15 points

No mention of VAS, MRI, Discography, Duration of follow up, Group A outcome not reported
INTRADISICAL BIOLOGIC RECOMMENDATIONS

• Based on the available literature in human clinical trials, for early symptomatic DDD, the most cost effective and safe intervention is PRP releasate.

• For patients with more moderate degeneration which have failed PRP or have at least a Pfirrmann III, BMAC with or without scaffolding is a reasonable alternative.

• Micronized inner placental tissue can be used along PRP to enhance outcomes in patients with moderate DDD.

• Although BMAC is effective, there is not enough animal data. There is a significant incidence of inflammatory reaction.
• In patients with moderate to advanced DDD, even though the scientific validation is not reproducible, umbilical cord tissue grafts offers a distinct advantage due to the lack of a potential intradiscal autoimmune reaction.

• In patients who are not candidates for BMAC (due to contraindications), umbilical cord tissue along with PRP (releasate) is a prudent consideration.

• Autologous and Allogeneic Ex-vivo expanded stem cells are a viable alternative for patient with moderate DDD which have failed more cost effective alternatives. Not FDA approved.
MY WISH LIST

• Fresh amniotic fluid delivered daily to my clinic

• Autologous chondrocyte transplantation, tissue bank

• Autologous chondrocyte Ex-vivo expansion along with ADMSC or BMMSC co-culture

• Off the shelf, Allogeneic Umbilical Cord Ex-vivo expanded cells.

• Better absorbable scaffolds able to withstand compression forces in the spine

• Post surgical autologous chondrocyte transplantation in every patient undergoing a discectomy in the world (Ok, maybe starting in Texas)

• 3-D biologic printers at point of care with combination therapy (gene, crisper, others)
THANK YOU

REGENERATIVE
SPINE & JOINT
INSTITUTE
Pre-Lumbar MRI T2

6 Months Post-Lumbar MRI T2

12 Months Post-Lumbar MRI T2
P #1 AMNIOTIC GRAFT

PRE

6 Months POST
PLACENTAL-NEWBORN SOURCES

Amniotic Fluid (Growth Factors)

Placental Tissue (Growth Factors, Scaffolds)

Wharton’s Jelly (Scaffold, Growth Factors)

Umbilical Cord (Cells MSC)

Umbilical Cord Blood (Cells HSC)
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.
REGENERATIVE DISC CLASSIFICATION
STAGE I

- DHR 0 -25%  Herniation: 0-3mm  Stenosis- None
- Pfirman : I,II
- Modic O
- 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 0-50%  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 >50%  Herniation: >6mm  Stenosis- Mild-Moderate
- Pfirman: III-IV
- Modic: I-III
- Discography: Pain-Concordant, Grade 1-5
- Pain: Location: Back > Legs  Intensity: Moderate
- Instability: Spondylolisthesis I, Co-Morbidities: Mild-Severe
REGENERATIVE DISC CLASSIFICATION
STAGE IV

- DHR >80%  Herniation: >6mm  Stenosis- Mod-Severe
- Pfirman : IV-V
- Modic III
- Discography: Not indicated
- Pain: Location: Leg>Back
- Intensity :Severe
- Instability: Spondylolisthesis I-II,
- Mod-Severe Co-Morbidities: