Regenerative and Biological Treatment of the Spine

Texas Pain Society

Annual Scientific Meeting

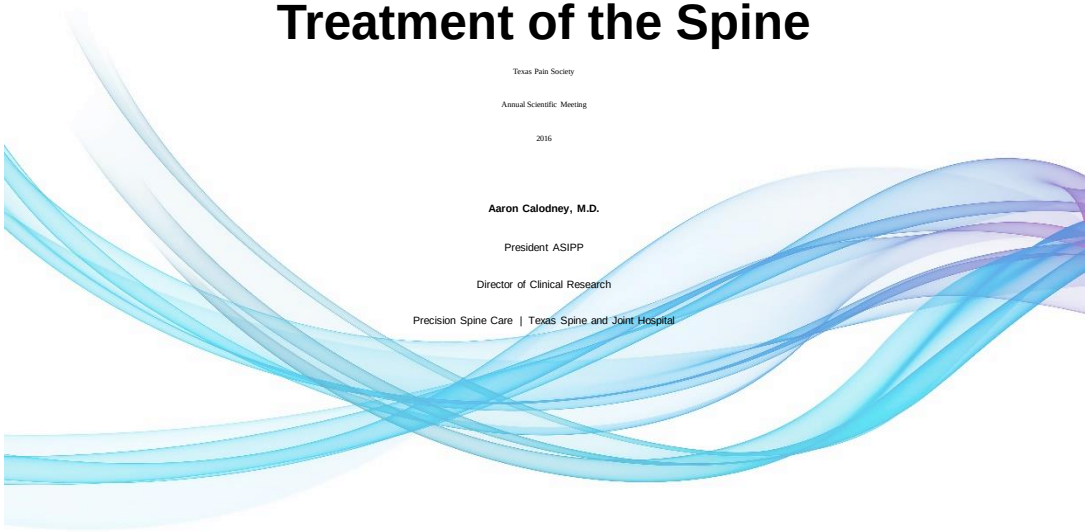
2016

Aaron Calodney, M.D.

President ASIPP

Director of Clinical Research

Precision Spine Care | Texas Spine and Joint Hospital



Texas Spine and Joint Hospital
Tyler, Texas

Disclosure

Investigator:

- Mesoblast Phase II Trial
  - Mesenchymal Precurser Cells (MPC's)
- Spinal Restoration Phase III Trial
  - Biostat Biologx (Fibrin Sealant)
- J and J
- rhGDF-5 Phase III Trial

What are we discussing?

- **Regenerative Medicine** involves delivering specific types of cells or cell products to diseased tissues or organs, where they will ultimately restore tissue and organ function.
- **Accomplished via** cell-based therapy or by using cell products, such as growth factors.

What are we discussing?

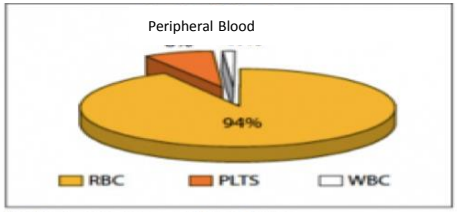
- Mesenchymal Stem Cells (MSC)
  - Adipose and Bone Marrow
- Platelet Rich Plasma (PRP)
- Amniotic derived products.

Sources of Regenerative Agents

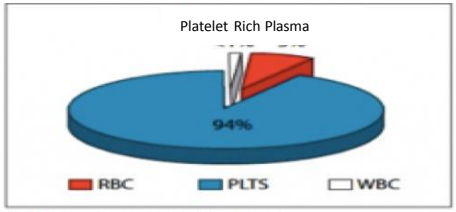
Component	Bone Marrow Aspirate	Blood (PRP)	Adipose	Amniotic/Placental
MSCs	++	–	+++	++
HSCs	+++	+	+	?
Endothelial PCs	+++	Low	+	?
Growth Factors	+	+	–	+
IL-1RAP	+++	+	?	?
Plasma Proteins (α-2 Macroglobulin)	+	+	–	+
Structural Protein (Fibrinogen)	If activated	If activated	–	In some formulations

What is PRP

A concentrated solution of platelets in
a small volume of plasma



Cell ratios in a normal blood clot.



Cell ratios in platelet rich plasma.

What is in platelets?

- Platelets contain a variety of growth factors, coagulation factors, adhesion molecules, cytokines, chemokines and integrins.
- After activation, the *platelets in PRP release these growth factors* at concentrations significantly higher than the baseline blood levels

Platelets

Thus, increased platelet count is a secondary measurement of growth factor concentration, which can be delivered to damaged tissues to promote healing.

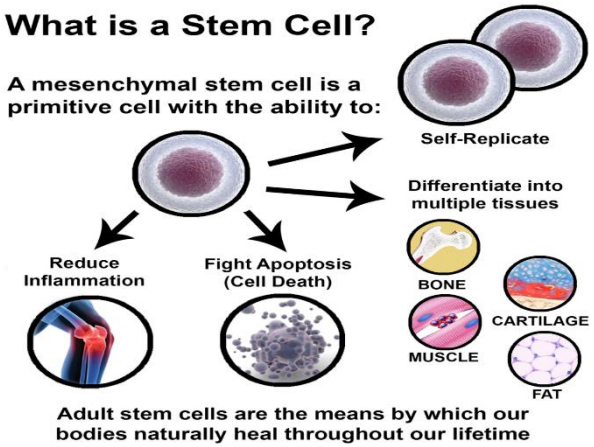
Platelet Derived Growth factors

- Stimulates cell replication
- Promotes angiogenesis
- Promotes tissue granulation formation
- Promote growth of extra-cellular matrix

Cytokines for Healing

- 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

Mesenchymal Stem Cells

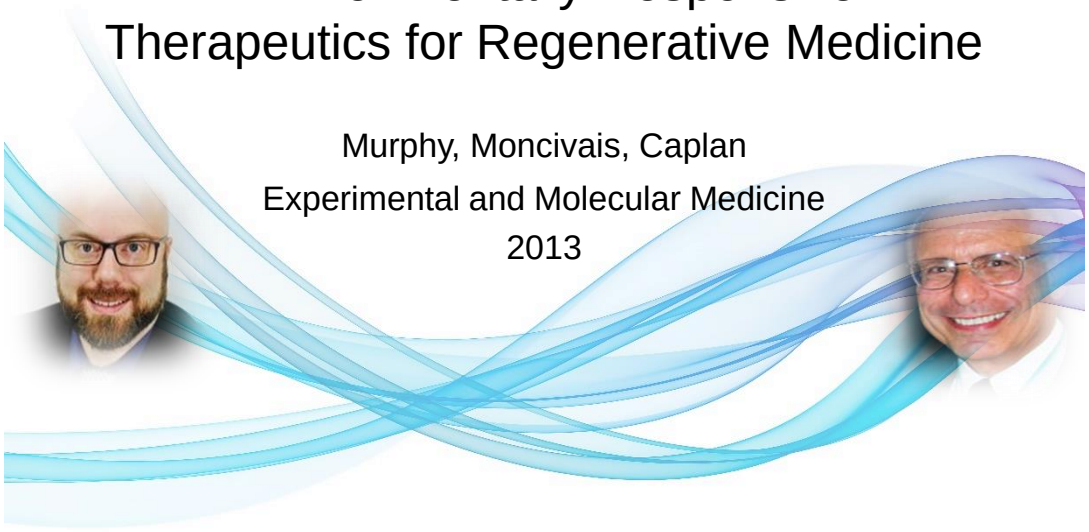


(undifferentiated state)

Mesenchymal Stem Cells:
Environmentally Responsive Therapeutics for Regenerative Medicine

Murphy, Moncivais, Caplan

Experimental and Molecular Medicine
2013



Autologous Sources of MSC’s

- Bone marrow
- Adipose
- Synovial fluid
- other sources

Allogenic Sources of ASC’s

- Amniotic tissue
- Umbilical cord blood
- Commercial stem cell lines are currently under development

Where do we obtain these cells?

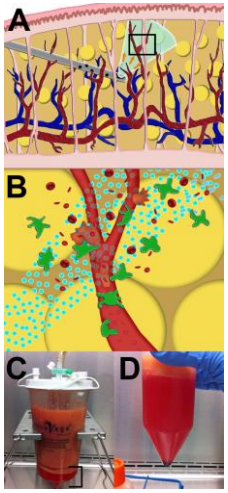
Human MSCs are generally isolated from bone marrow after separation by density gradient centrifugation or from processed lipoaspirate.

Bone Marrow or Adipose

Colter DC, Class R, DiGirolamo CM et al. Rapid expansion of recycling stem cells in cultures of plastic-adherent cells from human bone marrow. *Proc Natl Acad Sci U S A 2000;* ***97:3213–3218.***

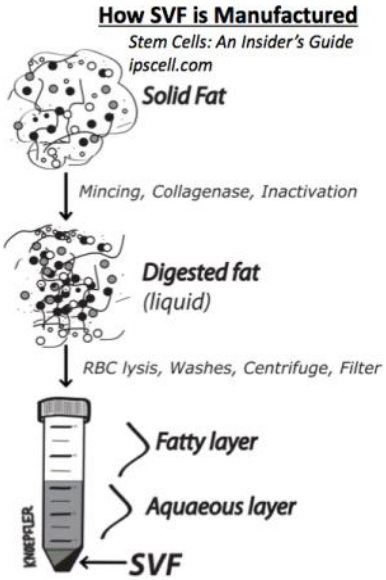
Processing to Yield SVF

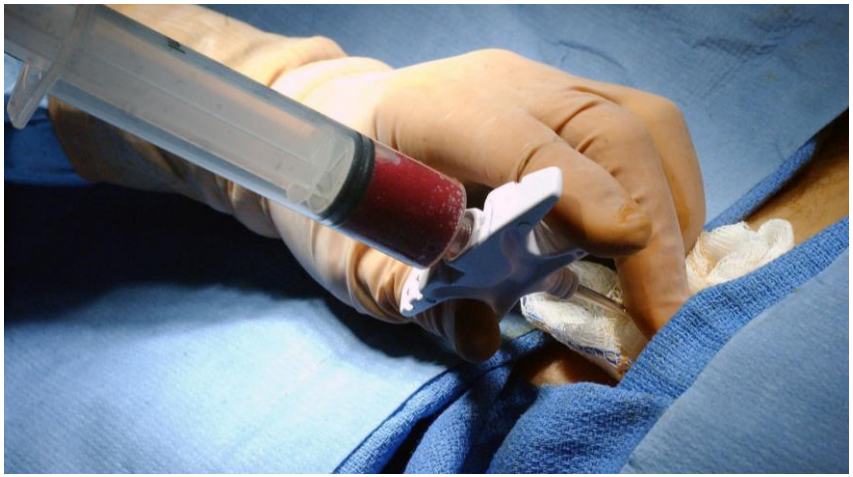
- Subcutaneous adipose is extracted through liposuction
- Connective tissue of the fat is disrupted by enzyme digestion (collagenase/neutral protease)
- Ultrasonic or mechanical disruption to free pericytes (MSCs) from vascular structures (not SVF)

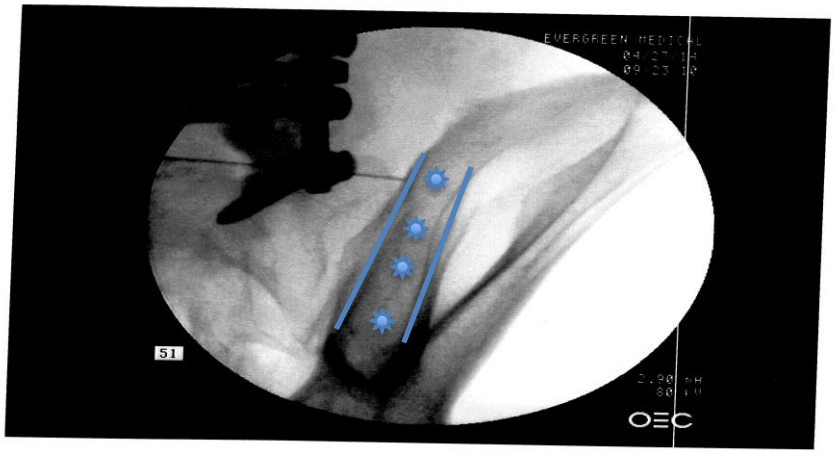


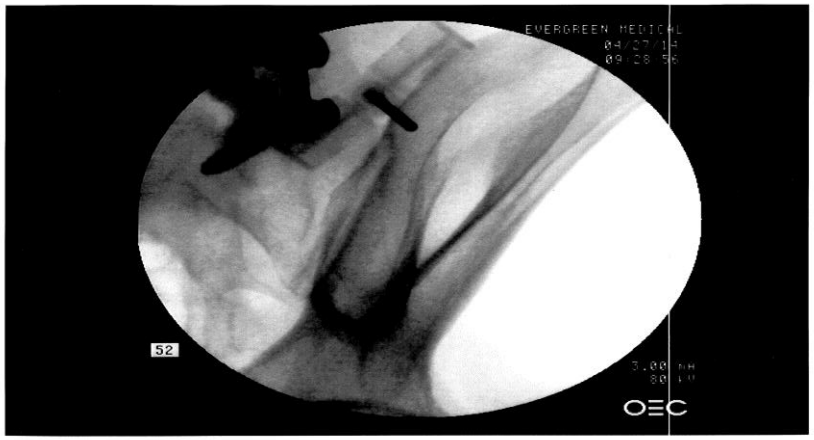
Processed lipoaspirate -derived Adult Stem Cells

Adipose tissue is an abundant source of mesenchymal stem cells






EVERGREEN MEDICAL
51
OEC


EVERGREEN MEDICAL
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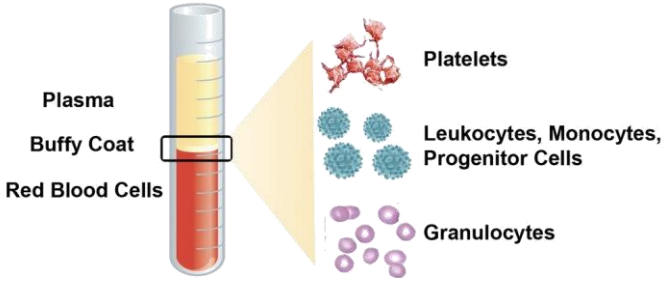
Bone marrow msc's exist in suspension - simple centrifugation can isolate the cells in the buffy coat layer.



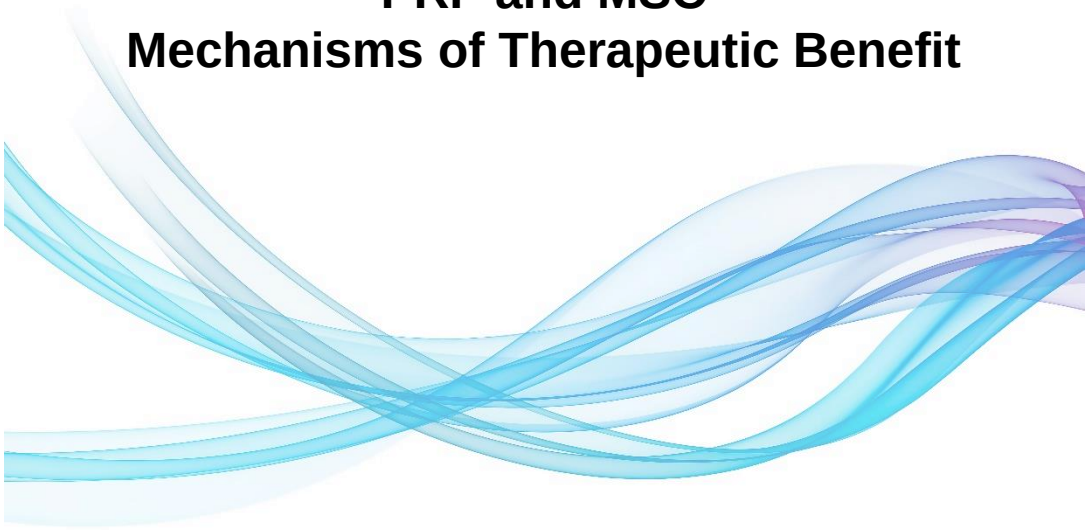
Concentrates cell numbers 2-4x (from a baseline
of 0.02% of cells up to 0.06%)

Dragoo Tobi 2015

Dr. Philippe Hernigou, MD

- Chief of Orthopaedic Surgery, Henri Mondor Hospital, University of Paris France
- Treated more than 5,000 patients with autologous bone marrow concentrate (BMC) since 1990
- Found correlations between stem cell content of BMC and clinical outcomes in non-unions, AVN, rotator cuff, and articular cartilage repair
- Established no increased risk of cancer when using the patient's own cells with 15+ years follow-up compared to the general French population

PRP and MSC
Mechanisms of Therapeutic Benefit



Framework for Regenerative Therapies

Types of Therapeutic Benefits

- Pain Relief
- Extracellular matrix repair/replacement

Therapeutic Strategies

- **Indirect** (e.g., PRP): Influence Host Cells
- Proteins, Enzyme Inhibitors, Growth Factors

Direct (e.g., BMC): Contains Viable Progenitor Cells

- Paracrine influence (releasing biochemical agents)
- Differentiation into adult tissue cells (less likely)

Inflammation

- Inflammation = Pain
- Pro-inflammatory cytokines stimulate anti-microbial agents (macrophages, granulocytes) to clean up a potentially contaminated wound and digest damaged parts of tissue/extracellular matrix (ECM)
- Inflammatory (e.g. TNF-a, interleukins) and mitogenic (e.g. PDGF, FGF) factors also recruit MSCs into the damaged site from nearby blood vessels
- Prolonged inflammation in a non-healing injury leads to cell death and further deterioration of the tissue

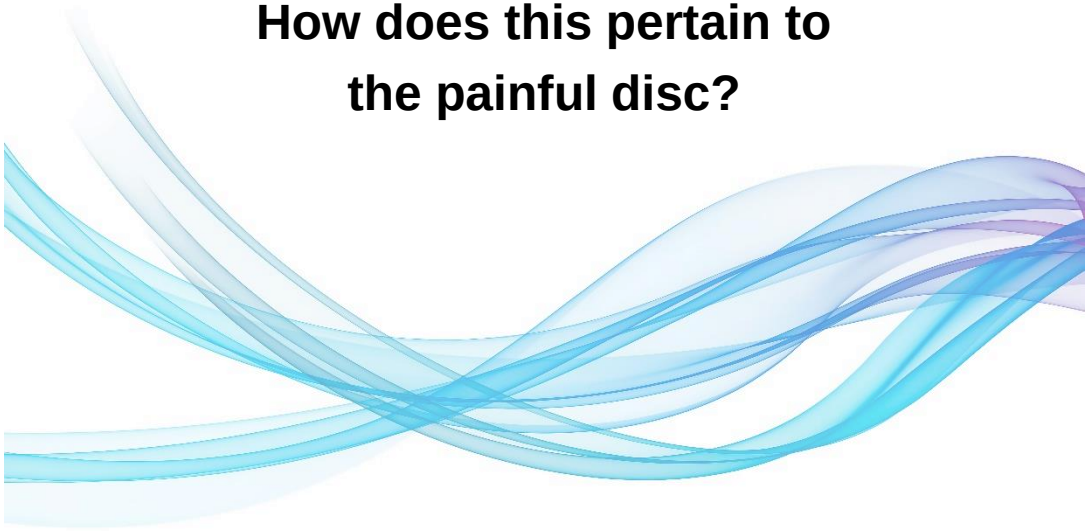
Why We Fail to Heal

- Injuries in or adjacent to vascular tissue release cytokines to recruit MSCs and other progenitors
- “Critical size defects” are non-healing injuries that do not have proximity to blood vessels or lack sufficient “scaffold” to build and remodel matrix proteins
- Most cartilaginous injuries cannot overcome the inflammation stage of healing

Non-Surgical Strategies

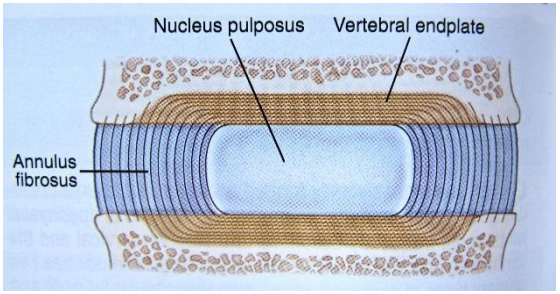
- Rest, icing, physical therapy
- Steroids – reduces inflammation (pain), long term is cytotoxic to chondrocytes
- Platelet-rich plasma (PRP) – **INDIRECT** therapy, objective is to release cytokines from platelets to stimulate local cells to move in, overcome inflammation generators, and remodel tissue
- Stem Cells (Bone Marrow Concentrate) – **DIRECT** therapy, delivers MSCs, HSCs, and other progenitor cells along with platelets to accelerate the healing process or provide cells where they are otherwise unavailable

How does this pertain to the painful disc?



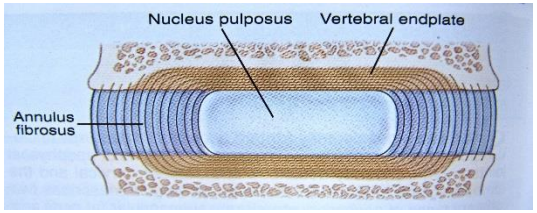
Disc Nucleus

- Nucleus Pulposus is a gel-like matrix containing proteoglycans and type II collagen. The negative charge of the glycosaminoglycans attracts and holds onto water.
- Hydration helps with maintenance of disc height and load-bearing capacity of the disc.
- Chondrocytes within the NP synthesize and maintain matrix.



The Lumbar Discovertebral Complex

- Homeostasis: Chondrocytes control synthesis and degradation of the nuclear metrix:
  - Proteoglycans, collagen, H_20
- Hostile biochemical environment
  - No direct blood supply
  - Low O_2 tension
  - Anabolic metabolism pH (6.9-7.1)
- A variety of insults may upset this homeostatic balance
  - Metabolic disease (DM, Ochronosis)
  - Genetic factors
  - Traumatic endplate injury
  - Nutritional (smoking, vascular disease)
  - Infectious



Disc Age Related Change or "Degeneration"

Consequence of Imbalance of Synthesis / Degradation

	Nuclear Matrix		Annulus
Molecular	Altered PGs Dehydration	Cross-linking	Cross-linking
Microscopic	Cracks Tears	Fibrosis	Fibrosis
Macroscopic		Thinning Fragmentation	
Biomechanical		Depressurized	Stiffening
Imaging		Loss of T2 signal	

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

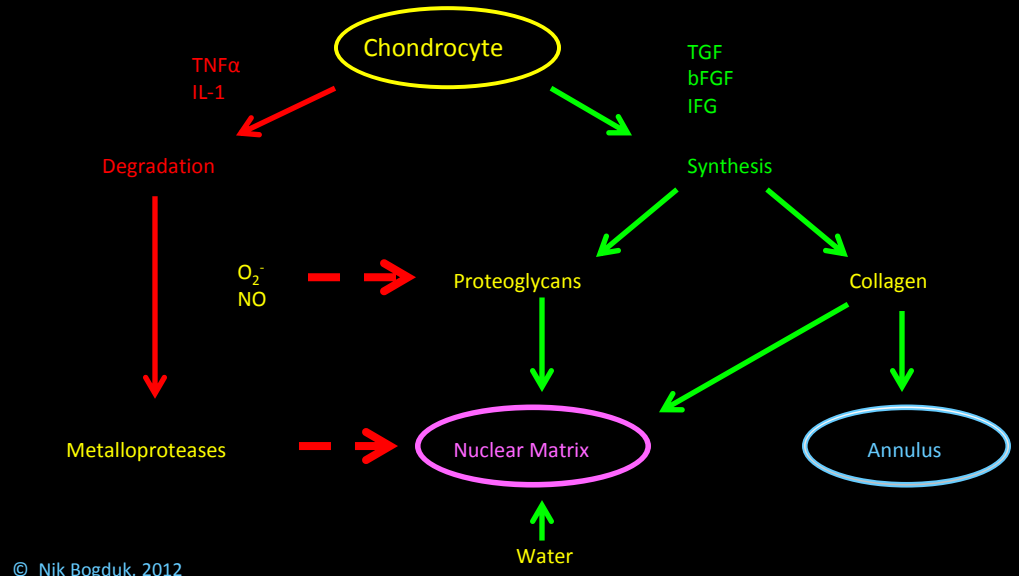
1. Holm S, Kaigle-Holm A, Ekstrom L, Karladani A, Hansson T. Experimental disc degeneration due to endplate injury. J Spinal Disord Tech 2004; 17:64-71.
2. Cinotti G, Della Rocca C, Romeo S, Vittur F, Toffanin R, Trasimeni G. Degenerative changes of porcine intervertebral disc induced by vertebral endplate injury. Spine 2005; 15:30-174-180.
3. Haschtmann D, Stoyanov JV, Gédet P, Ferguson SJ. Vertebral endplate trauma induces disc cell apoptosis and promotes organ degeneration in vitro. Eur Spin L; 2008; 17:289-299.

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

Homeostasis:

The Balance of
Synthesis and Degradation



Disc Degeneration

- Can biologics slow or even reverse the cascade of DDD?
- Will transplantation of cells into the disc improve the production of proteoglycan rich extraceullular matrix and lead to better hydration and biomechanical properties?

Therapeutic effect of MSC's intradiscal

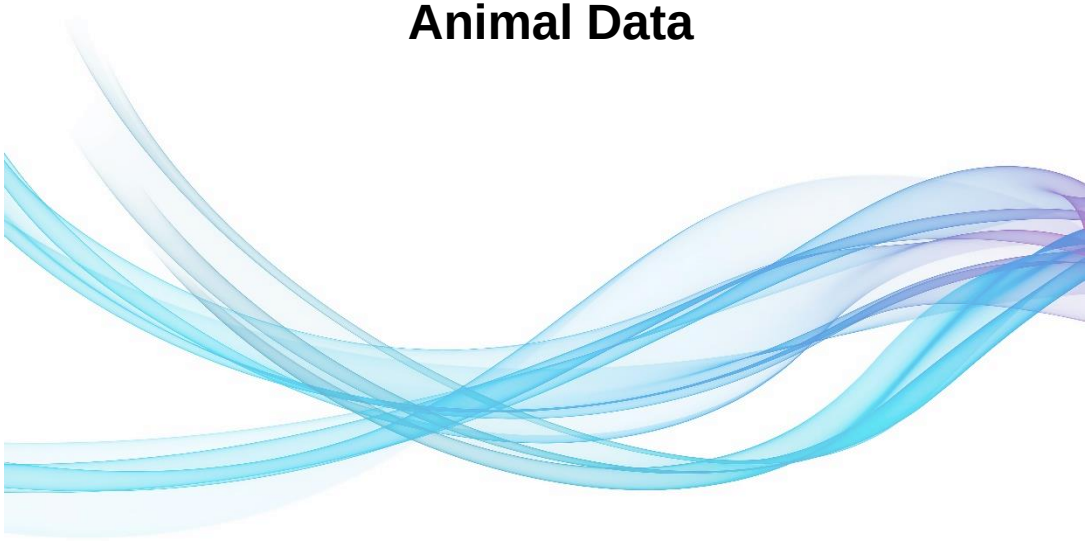
- MSC's have been shown to differentiate towards chondrocyte-like cells- phenotypically similar to NP cells.
- MSC's promote regeneration by stimulating native NP cells.
- Upregulation of extracellular matrix proteoglycan and Type II collegan synthesis by native NP cells has been demonstrated during coculture of MSC's with degenerative NP cells.
  - *Svanvik et al. 2010*

IT'S BEEN SAID….

The Disc
is where good therapies
go to

DIE

Animal Data



Meta-analysis of Animal Data

Gene 564 (2015) 1–8

Contents lists available at ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Research paper

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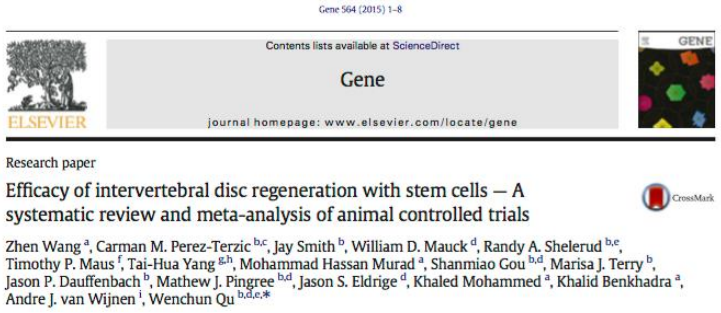
[d] Department of Anesthesiology Pain Division, Mayo Clinic, Rochester, MN 55905, USA
[e] Spine Center, Mayo Clinic, Rochester, MN 55905, USA
[f] Department of Radiology, Mayo Clinic, Rochester, MN 55905, USA
[g] Department of Biomedical Engineering, National Cheng Kung University, Taiwan
[h] Biomechanics Laboratory and Tendon and Soft Tissue Biology Laboratory, Division of Orthopedic Research, Mayo Clinic, Rochester, MN 55905, USA
[i] Department of Orthopedics, Rochester, MN 55905, USA

Meta-analysis of Animal Data

- 6 rct's in animals met criteria
- Looked at the association between disc stem cell transplant and subsequent change of disc height



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Meta-analysis of animal data

- Overall, IVD stem cell transplant was associated with 23.6% increase in disc height index (95% CI, 19.7-23.5; p<0.001)
- Of all the six studies, none showed decrease of disc height index
  in the transplant group compared with the controlled group.
- The increase in disc height index was statistically significant

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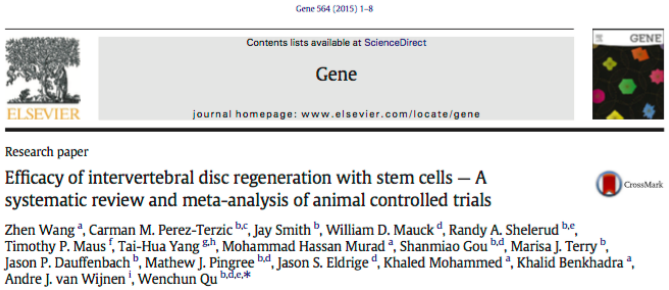
Meta-analysis of animal data

- The findings of this meta-analysis indicate that cell therapy may arrest or reverse the IVD degenerative process.



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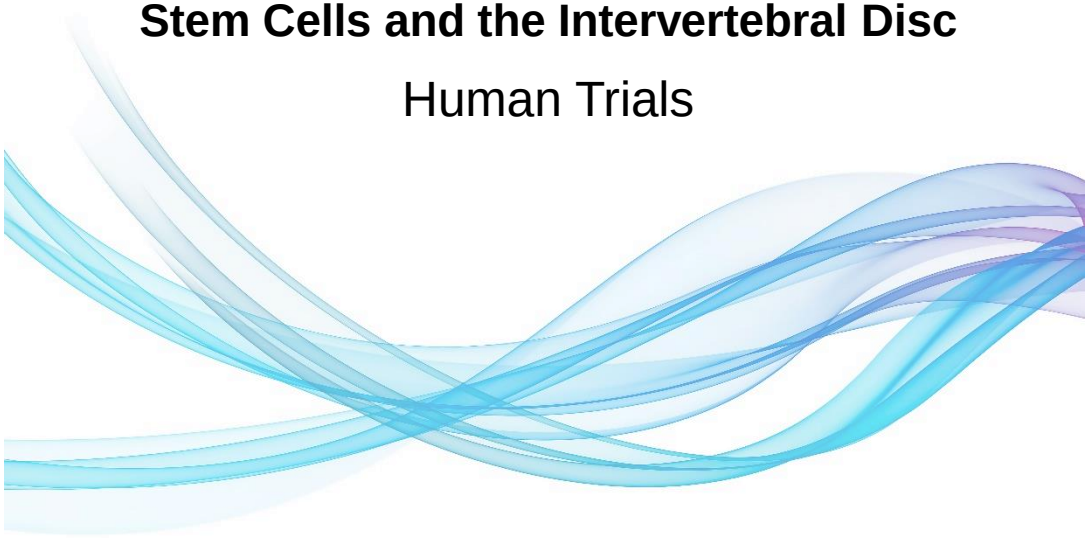
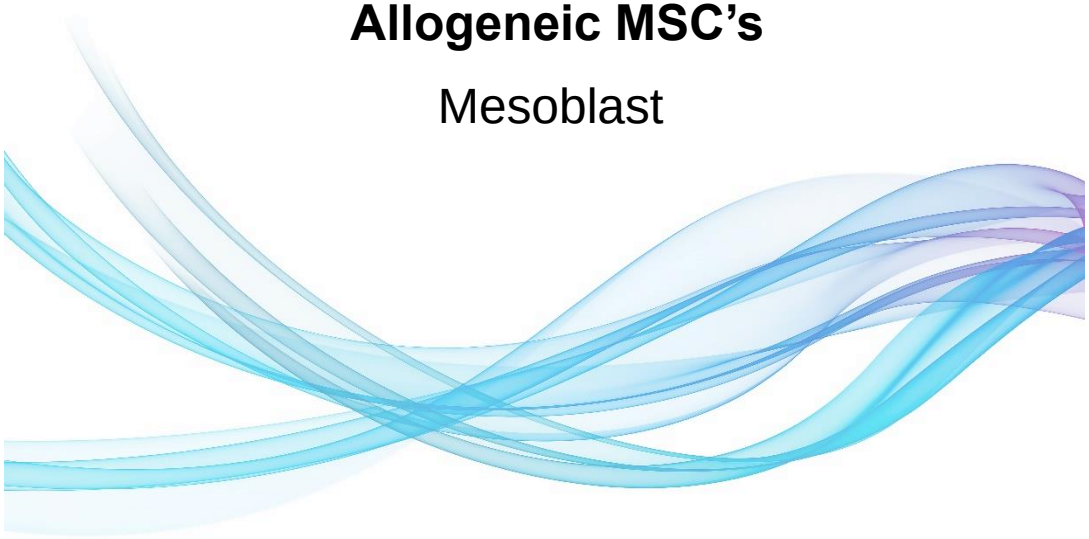
Stem Cells and the Intervertebral Disc

Human Trials



Allogeneic MSC’s

Mesoblast

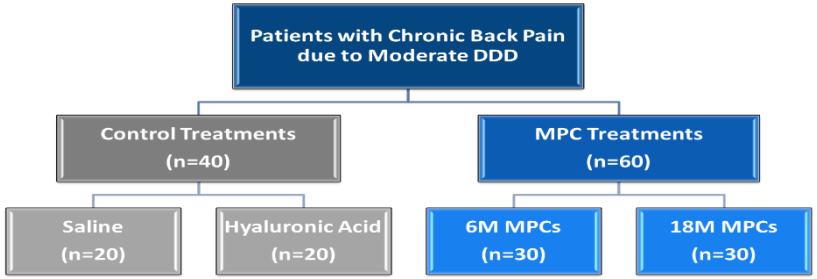


Safety and Preliminary Efficacy Study for Disc Repair (Mesoblast)

- MPC's for Lumbar Disc Disease in Adults
- Primary Objective: Safety @ 6 months
- Secondary Objective: Efficacy
- 100 Patients Worldwide
- Randomized to:
  - Normal Saline
  - Hyaluronic Acid (HA)
  - Low Dose (6 Million) MPC's in HA
  - High Dose (18 Million) MPC's in HA

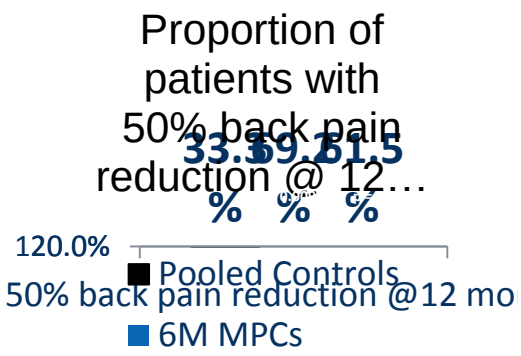
1. Safety and Preliminary Efficacy Study of Mesenchymal Precursor Cells (MPCs) in Subjects With Lumbar Back Pain

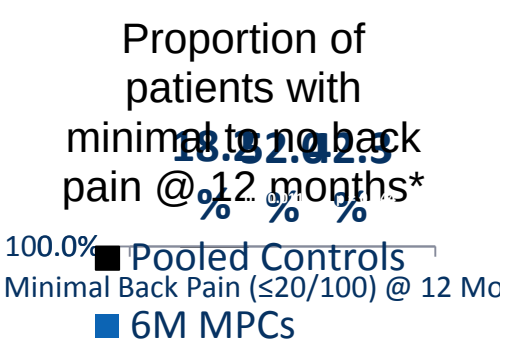
Study Design



- Prospective, multi-center, randomized, double-blind, controlled study
  - Patients and radiographic evaluators blinded to treatment
- Follow-up: 1, 3, 6, 12, 24 & 36 months

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



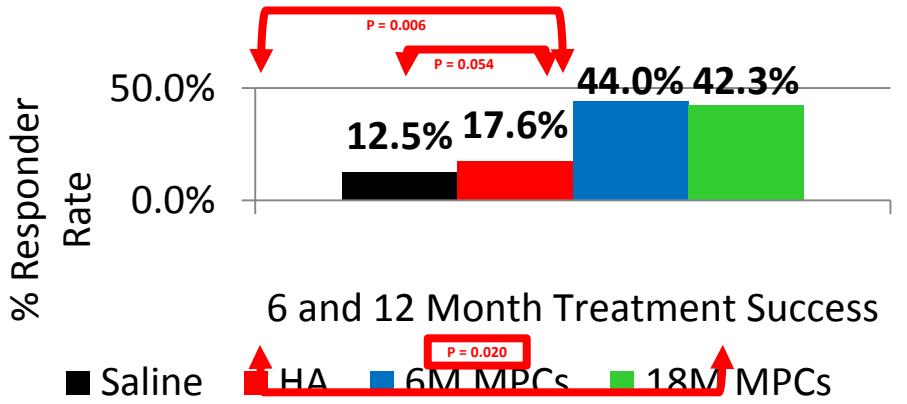


* from post-hoc analysis

MPC treated groups have significantly greater numbers of patients with treatment success at both 6 & 12 months

Treatment Success Over 12 Months

50% VAS back pain reduction AND 15 point ODI improvement AND no intervention at the treated level at both 6 and 12 months*



* from post-hoc analysis

Take away points from Mesoblast Study

- Allogeneic MPCs were well tolerated
  - No issues related to use of an allogenic product were identified

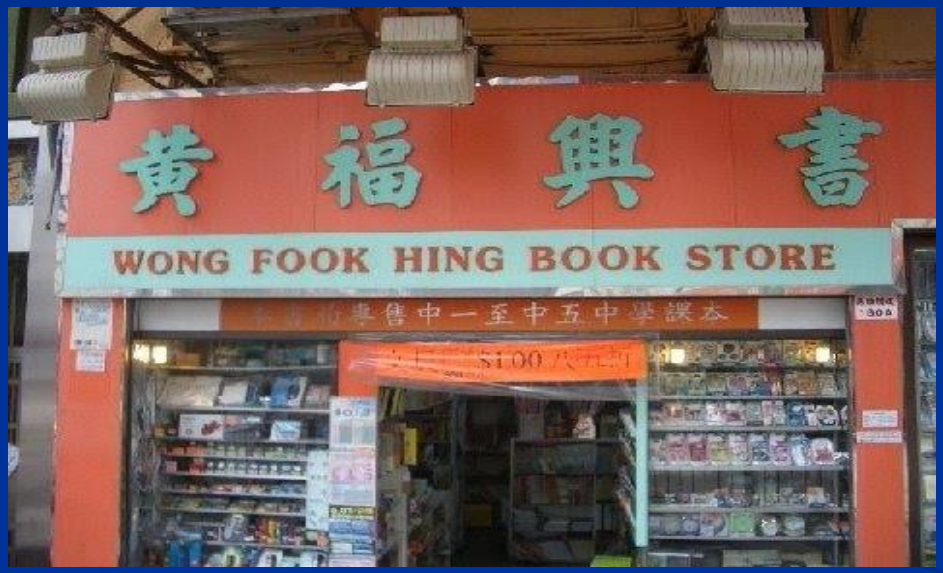
Take away points from Mesoblast Study

- Both MPC doses showed improvement relative to controls for pain and functional improvement and reduced interventions
  - There appears to be a minimal number of cells needed to exert a physiologic response but more may not always be better.

Take away points from Mesoblast Study

- Radiographic evidence demonstrating decreased abnormal vertebral movement, suggesting improvement in disc structure and stability

If you are in a book store and cannot find the book for which you search, you are obviously in the.....


黃福興書
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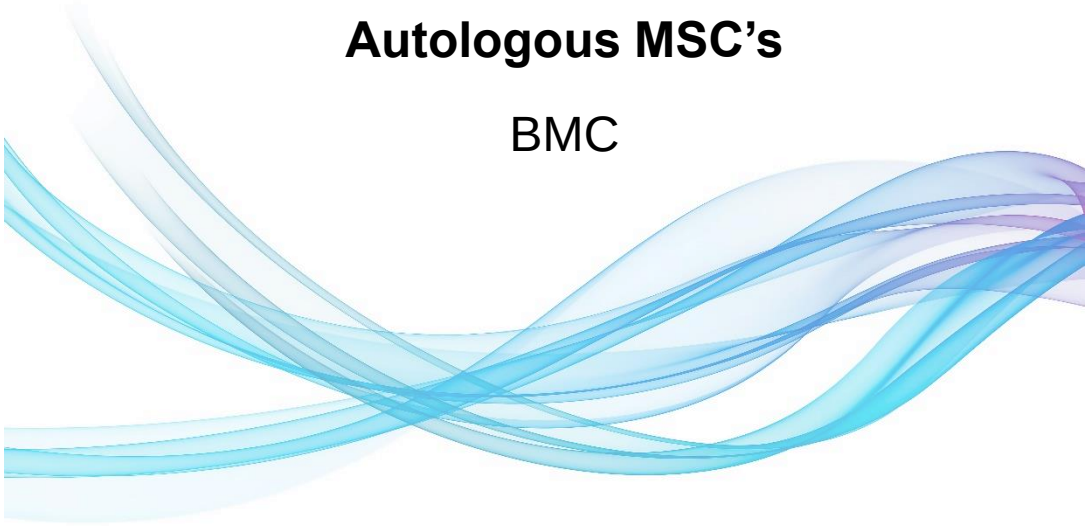
Autologous MSC's

BMC



Interventional Disc Repair by Autologous Mesenchymal Bone Marrow Cells: A Pilot Study

Lluis Orozco,[1] Robert Soler,[1] Carles Morera,[2] Mercedes Alberca,[3] Ana Sánchez,[3] and Javier García-Sancho[3,4]

- 10 pts with chronic LBP with Lumbar DDD
- Mesenchymal stem cells harvested from iliac crest, cultured (21-28 d), injected into nucleus pulposus
- 9:10 pts improved
- Analgesic effect approaching 71% efficacy
- No change in disc height

Orozco L, Soler R et al. Intervertebral disc repair by autologous mesenchymal bone marrow cells: a pilot study. Transplantation. 2011;92(7):82-8

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, M.D.*

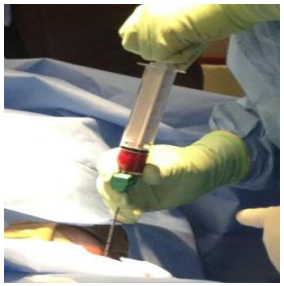
Stem Cells, 2015
(1-yr results)

Clinical Study

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

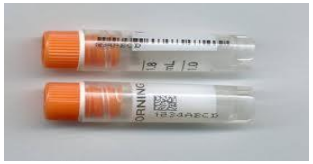
		One-Level	Two-Levels
Number of Patients		13	13
Median Age		40 Range 25-51	37 Range 18-61
Average BMI		27.1	26.1
Cause of Injury	Trauma	7	5
	Unknown	6	8
Discs of Modified Pfirrmann Grade:	IV	2	1
	V	3	6
	VI	5	11
	VII	3	8

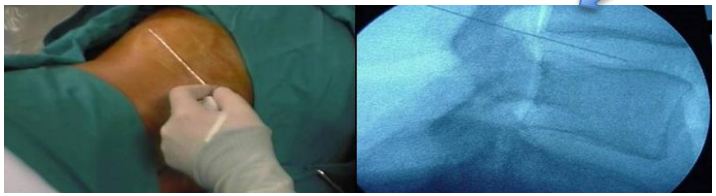
Disc Injection Therapy



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.

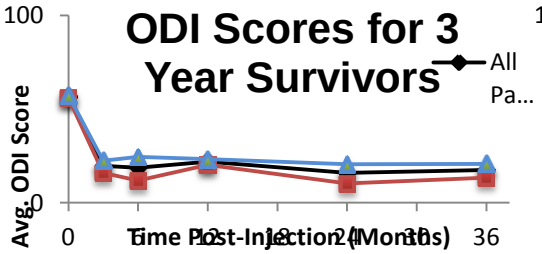
Disc Injection Therapy

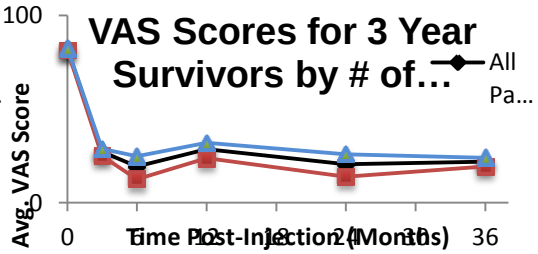
- Cell analysis was performed on samples from 20 patients
- No adverse events for bone marrow aspiration—no chronic pain (60 cc aspirated volume)
- No adverse events at the disc injection site(s)

	Avg. MSC dose per disc	% improv. 12 mo. ODI	% improv. 12 mo. VAS
All Patients	8,138	57%	58%
< 40 years, < 2,000 CFU-F/mL	3,852	65%	83%
< 40 years, > 2,000 CFU-F/mL	9,927	69%	64%
> 40 years, < 2,000 CFU-F/mL	4,433	34%	29%
> 40 years, > 2,000 CFU-F/mL	13,241	74%	74%

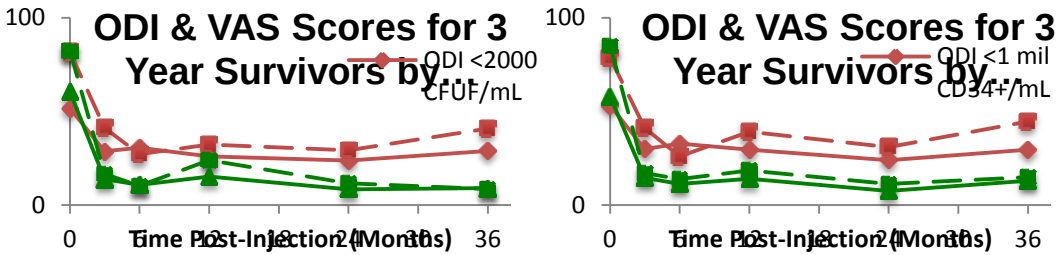
Disc Injection Therapy

3-year Survivor Cohort (n = 20)





Disc Injection Therapy
3-year Survivor Cohort



Effect of Progenitor Cell concentrations on pain reduction through 3 years
(ODI – solid lines, VAS – dashed lines, Lower cell counts – Red, Greater cell counts - Green)

Disc Injection Therapy

Patient Outcomes (September 2015)

- **8 patients showed a single grade level improvement in their Pfirrmann score at 1-yr (40% of enrolled patients)**

- **3 1-level and 3 2-level patients progressed to surgical repair by 3-yr (77% avoided surgery through three years)**

- **2 Patients received a 2nd injection two years ago; no additional 2nd injections have occurred**

- **73% average reduction in pain and 67% average improvement in ODI at 3-yr for the surviving 20 patients**
-
- **>2000 CFU-F patients: 86% improvement in ODI/90% reduction in VAS; <2000 CFU-F: 41% ODI/48% VAS**

Disc Injection Therapy

- The Degenerative disc contains:
  - Elavated levels of matrix metalloproteinases
  - Elavated levels of IL-1
- Bone marrow contains:
  - alpha-2-Macroglobulin (inhibitor of MMP's)
  - IL-1RAP (Interleukin-1 receptor accessory protein- reduces the pain associated with IL-1)

Disc Injection Therapy

- Thus BMC is a multi-modal therapeutic agent
- It contains:
  - Biochemical Modifiers
  - MSC's, EPC's (endothelial progenitor cells), HSC's and other progenitor cells
- Takes control of the "pro-inflammatory" environment in the disc

PRP DATA

Lumbar Intradiscal Platelet Rich Plasma Injections: A Prospective, Double-Blinded Randomized Controlled Study

Yetsa A. Tuakli-Wosornu, M.D., M.P.H. [1], Alon Terry, M.D. [1], Kwadwo Boachie-Adjei, B.S. , C.P.H. [1], Caitlin Gribbin, B.A. [1], Elizabeth E. LaSalle, B.S. [1], Julian Harrison, B.S.[1], Joseph Nguyen, M.P.H. [1], Jennifer Solomon, M.D. [1], Gregory Lutz, M.D. [1]

Funding: PR&EF

Harvest Technologies

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[1] Physiatry Department, Hospital for Special Surgery – New York, NY

Purpose

Determine if a single intradiscal PRP injection at time of discography has therapeutic value compared to control (contrast) injection

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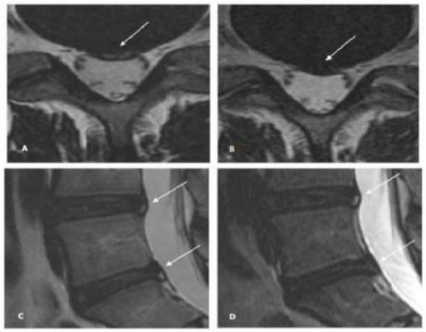

MRI imaging of study subject prior to study participation in 2011 (left) and post study participation in 2013 (right) (a) L5-S1 T2 axial image of individual in 2011 (b) L5-S1 T2 axial image of individual in 2013 with resolution of the HIZ (c) T2 Sagittal image 1 of individual in 2011 (d) T2 Sagittal image of individual in 2013 with 2 resolution of the HIZ at L5-S1. Of note is that the HIZ at L4-5 is the same or larger 3 despite also being treated with PRP.

Methodology

- 2:1 Randomization PRP vs contrast
- Double-blinded/crossover at 8 weeks
- Lumbar discogram 25G needle 3cc syringe
- Independent observer
- Injection of contrast first (0.5-1.5 cc)
- Followed by 1-2 cc contrast (control) or PRP (treatment)

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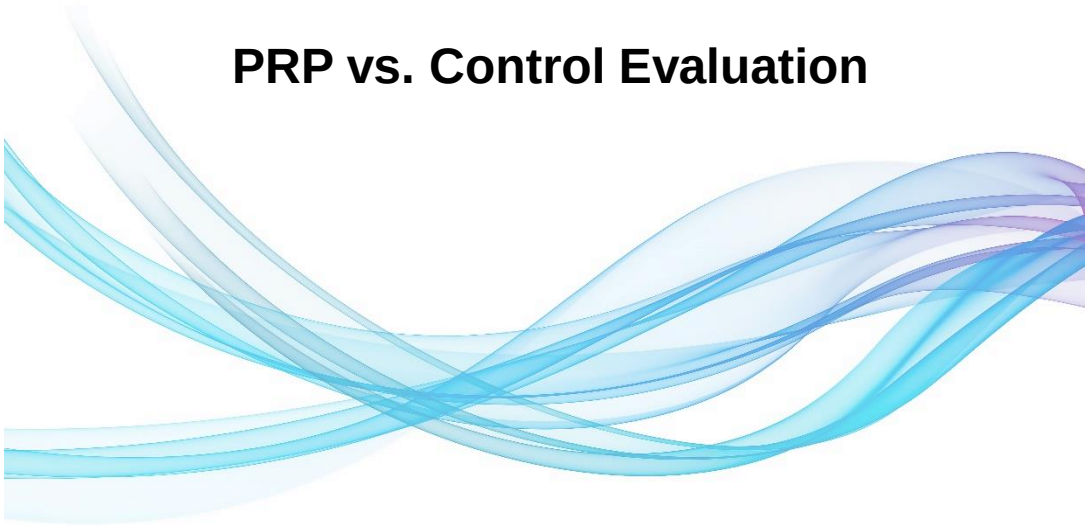
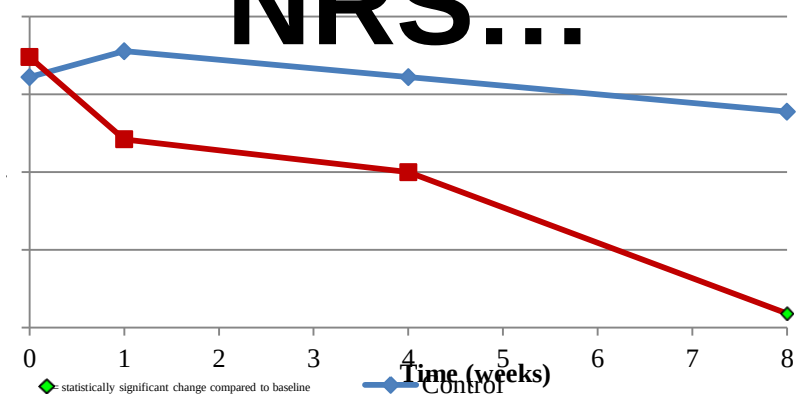
PRP vs. Control Evaluation



NRS…



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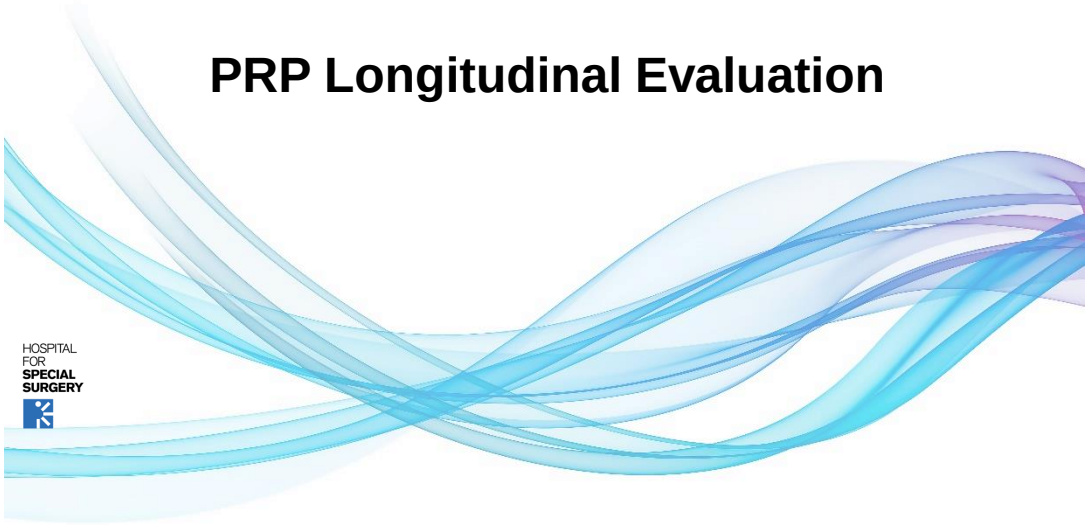
PRP Longitudinal Evaluation



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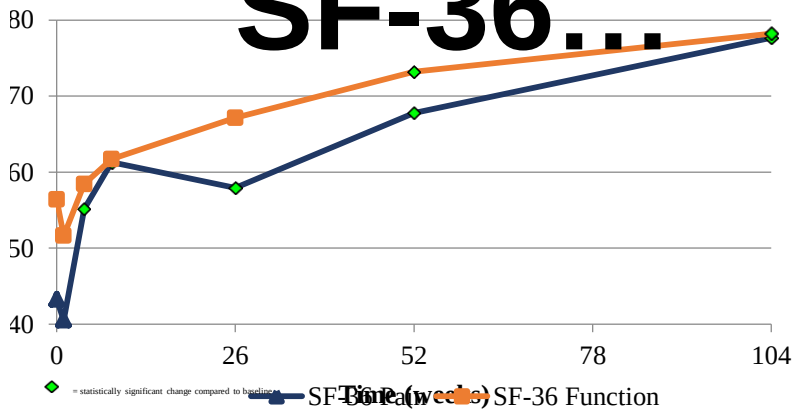

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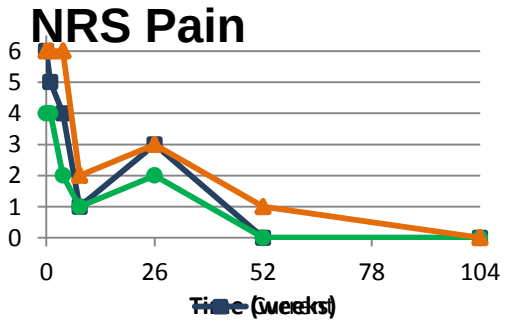
Progress through 24 mo. Post-PRP



	24 month Δ
Pain Right Now:	-6 points
Pain at Best:	-4 points
Pain at Worst:	-6 points

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Summary

- Intradiscal PRP is a readily available, safe, cost-effective treatment for IDD

Stem Cell Treatment for Disc Pain

What are the issues?

- Source of Cells
- Autologous (your cells) *vs*. Allogeneic (someone else's cells)
- Cellular induction
- Method of Transplantation
- Carrier
- Risks

Source of Cells

- Abundance
- Ease to obtain
- Capacity to differentiate into chondrocyte-like cells
- Viable in the hypoxic and hypoglycemic, and low pH environment
- Minimal or no immune response
- No risk for tumor growth

Source of Cells

- Bone Marrow and Adipose derived MSC's
  - Other sources are being developed commercially

Autologous vs. Allogeneic

- Allogeneic cells
  - Off-the-shelf availability
    - Specific dose (cell count known and optimized)
    - Cell behavior well studied
- Autologous Cells
  - Requires an invasive procedure to obtain
    - Contains much more than just MSC

Cellular Induction

- Induction techniques can increase the yield of differentiation of MSC's toward chondrocyte-like cells
  - Co-culture MSC's with NP cells
  - Stimulation factors IGF1, TGF Beta1, GDF5, BMP (PRP)
    - Hypoxia
    - Dexamethasone
    - Gene therapy sox-9

Method of Transplantation

- Disc is avascular- injection is necessary
- Successful transplantation by direct injection has been demonstrated in animal models

Carrier

- Characteristic of a favorable carrier or scaffold
  - Deter extravasation of injectate
  - Provide 3D environment for cellular proliferation
  - Enhance cell survival, proliferation and proper differentiation
- Collagen gel, hydrogel, hyaluran gel
- Fibrin Sealant

Risks

- Disk space infection
- Worsening of disc degeneration
- Tumorigenesis

MSC’s Intradiscal

- MSC’s have the capacity to repair degenerative discs
  - differentiation toward chondrocyte-like cells
  - producing proteoglycans and type II collagen
  - Supportive animal and human data

after Gou et al Am J Phys Med Rehab 2014

PRP Intradiscal

- Positive effects of PRP have been published in
  in-vitro studies of animal and human disc cells.
- Disc cells cultured with PRP demonstrate improved proteoglycan synthesis and annulus cell proliferation.

The End

Thank you for your time.

Aaron Calodney, M.D.

AaronCalodney@me.com