Regenerative Medicine and Stem Cells for Joint/Articular Cartilage Disorders

The Advanced Musculoskeletal Ultrasound Skills Course
April 28-29, 2017

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Associate Professor of PM&R
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Harvard Medical School
Spaulding Rehabilitation Hospital

Goals of the Presentation

• Basic overview of the evolution of the current available techniques
• General principles in selecting amongst these treatments
• Patient Selection for regenerative treatments for knee OA

58 yo active tennis player with moderate knee OA

• Additional history
  - Aches in the evening after an active day
  - Difficulty with stairs and sports activity
  - No mechanical symptoms or recurrent synovitis
  - Uses aleve most days
  - Wants to wait until 65 as he has been told TKA lasts ~20 years

• Prior treatments:
  - Weight loss
  - PT
  - Steroid injection
  - Viscosupplementation no longer helps as much

• PMH: hypertension well controlled

27 yo professional running back with R knee pain

• Progressive R knee pain and intermittent sharp pain
• Had
  - ACL reconstruction
  - Several meniscal surgeries
  - PRP x 3
• 3 weeks to first pre-season game.
  6 weeks start of regular season

NO DISCLOSURES
Joanne Borg-Stein, MD
Harvard Medical School, Department of PM&R

Orthobiologics and Knee Osteoarthritis
A Recent Literature Review, Treatment Algorithm, and Pathophysiology Discussion

David M. Crane, MD, Stefan J. Oser, MD, Matthew C. Byers, MD

KEYWORDS
- Knee osteoarthritis
- Knee arthritis
- Orthobiologics
- Tissue engineering
- Stem cells
- Osteoarthritis
- Cartilage repair
- Cartilage restoration

KEY POINTS
- There has been a tremendous growth in the regenerative medicine industry
- By almost any measure, osteoarthritis is a problem of epidemic proportions
- Regenerative medicine has the potential to address this problem
- There is evidence that orthobiologics are effective in the treatment of knee osteoarthritis

52 yo executive with progressive medial L knee pain

- Had excision of femur tumor during childhood
- Knee pain since his 30’s
- No longer runs
- Wants to walk the golf course
- Friends tell him about PRP
- Surgeon: not great candidate for TKA
- Prior treatments
  - Excellent PT
  - Trainer
  - Steroids injections
  - High tibial osteotomy
  - Meniscal surgery

What has been the evolution/ convergence?

Baby Boomers and “tweeners”

- “In between” normal joint and arthroplasty

The “cult” of corticosteroid

Knee arthroscopy for OA and degenerative meniscus tears
Pathogenesis of Osteoarthritis: not just a mechanical disorder

Gupta et al. Stem Cell Research & Therapy 2012, 3: 25

Neuroanatomic Basis of Pain in OA

- Synovial joints are richly innervated: type IVa free nerve endings
  - Joint capsule
  - Tendons
  - Retinacula
  - Fat pads
  - Synovium
  - Subchondral bone
  - Ligaments
- Muscle and fascia: substance P and mechanoreceptors
- Periosteum: myelinated and unmyelinated sensory fibers


Anatomic targets for regenerative medicine

- Bone
- Enthesis
- Tendon
- Ligament
- Muscle
- Joint/cartilage
- Nerve


COMMON REGENERATIVE METHODS

Prolotherapy

Adipose

BMAC

PROLOThERAPY

Prolotherapy

PRP

Adipose

Amniotic Sac/Placenta/Cord Blood

Courtesy of Dr. Imran Sidiqqui

Figure 1 Schematic representation of the layered structures on the medial side of the knee joint. (A) Anterior view. (B) Superior view. AC = articular capsule; FC = fascia cruris; Gcm = medial head of gastrocnemius muscle; Gr = tendon of gracilis...
**Prolotherapy**

**Definition of Prolotherapy**

- **Prolotherapy** = “Proliferative therapy”
  - “Method of injection treatment using irritant solutions designed to stimulate healing and pain relief.
  - Targets: Joint space, ligament, tendon insertion

**Nomenclature: Dr Reeves**

- **Biologic Repair therapy**
  - Injection of biologics to repair connective tissue
- **Prolotherapy (Prolo)**
  - Injection to repair connective tissue (tendon, ligament, cartilage) not including biologics
- **PSI**: perineural subcutaneous injection (introduced as neural prolotherapy)
  - Subcutaneous injection to restore function in pain producing sensory nerves
- **Perineural deep injection** (also called hydrodissection)
  - Deep nerve treatment with ultrasound guidance

**Solutions Used in Prolotherapy and their proposed mechanisms of action**

<table>
<thead>
<tr>
<th>Injected Solution</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperosmolar dextrose</td>
<td>Creates hypertonic atmosphere, which leads to cell rupture, upregulates expression of platelet derived growth factors</td>
</tr>
<tr>
<td>Morrhuate Sodium</td>
<td>Attracts inflammatory mediators, vascular sclerosant</td>
</tr>
<tr>
<td>Phenol – glycerine - glucose</td>
<td>Cellular irritant * no longer used</td>
</tr>
</tbody>
</table>

**Proposed Mechanisms of Dextrose Prolotherapy**

- Natural GF elevation
- Stimulation of the healing cascade
- Needling effect
- Reduction of neurogenic inflammation (PSI, neural)
Growth factors the Dextrose Elevates (non inflammatory effect)

• Ligament/tendon healing:
  – PDGF, TGFβ, EGF, bFGF, CTGF
• Cartilage Healing
  – PDGF, TGFβ, IGF,


The “prolotherapy approach” to treatment

• Treat the region; not a point
• Postural models of assessment
• Combine with manual therapy**
• Meticulous knowledge of ligament and tendon anatomy

Best practice recommendations for dextrose prolotherapy in OA : 2017

• CMC/finger OA: (B)*
  – DPT preferable to steroid in chronic CMC OA
  – May reduce pain and stiffness in PIP and DIP OA
• Knee OA: (A)*
  – DPT effects are both positive and significantly beneficial in symptomatic knee OA.
• Low Back Pain
  – No definite recommendation at this time
• Sacroiliac Pain*
  – DPT lasted longer than steroid and provided significant relief of SI joint pain

Adapted with permission from Dr. Dean Reeves

Dextrose prolotherapy for knee osteoarthritis: results of a randomized controlled trial

• Double blind, prospective, randomized controlled trial
• 3 interventions
  – Dextrose prolotherapy
  – Saline injections
  – Home exercise program
• Injection arms
  – Injections at 1, 5 and 9 weeks with as needed repeat sessions at weeks 13 and 17
  – Extra and intra-articular injections with 15% and 25% dextrose respectively
  – At each session, both peri-articular and intra-articular injections were performed without image guidance.

Dextrose prolotherapy for knee osteoarthritis: results of a randomized controlled trial

• Outcome measures
  – WOMAC
  – Knee pain scale
• Results
  – Groups receiving dextrose prolo had significantly greater improvement in WOMAC scores at 52 weeks compared with saline and exercise
  – Knee pain scale scores similar in prolo and saline and exercise group.
  – High patient satisfaction in prolo group

Rabago, Miller, Zgierska. OA research society. 2011

Dextrose Prolotherapy for Knee Osteoarthritis: A Randomized Controlled Trial

David Rabago, MD1, Jeffrey J. Patterson, DO1, Marlon Mundt, PhD1, Richard Kjowksi, MD2, Jessica Grettie, BS1, Neil A. Segal, MD, MS1 and Aleksandra Zgierska, MD, PhD1

Annals of Family Medicine May/June 2013
Platelet Rich Plasma

- Platelet derived growth factor (PDGF)
- Transforming growth factor (TGF)
- Epidermal growth factor (EGF)
- Vascular endothelial growth factor (VEGF)
- Fibroblast growth factor (FGF)
- Connective tissue growth factor (CTGF)

Dense Granules
- Serotonin
- ADP
- Histamine
- Calcium
**PRP: level 1 metaanalyses: PRP and Knee OA**

- 2014: Chang et al: Effectiveness of PRP in treating cartilage degenerative change
  - RCs and single arm prospective studies:
  - "effectiveness of PRP was likely better and more prolonged than that of HA"
  - "patients with less severe OA achieved superior outcomes"
- 2015: Ribboh et al: Clinical outcomes and rates of adverse reactions between LP-PRP and LR-PRP
  - "LP-PRP significantly better WOMAC scores than HA or placebo"
  - LP-PRP highest ranked for WOMAC and IKDC
  - PRP: higher incidence of adverse reactions than HA
- Meheux et al: 2015: systematic review of level 1 studies
  - Patients with symptomatic knee OA: PRP results in significant clinical improvement up to 12 mos post injection

**Stem Cells**

**Mesenchymal stem cells**

- Mesenchymal Stem Cells
  1. Bone Marrow Derived MSCs
  2. Adipose Tissue Derived MSCs
  3. Synovium Derived MSCs
  - De Bari et al 2001
  4. Muscle Derived MSCs
  - Williams et al 1999
  5. Dermal Fibroblast
  - Connell et al N=12

**Best practice recommendations for PRP: 2017**

- **GOOD EVIDENCE**
  - Osteoarthritis
    - Knee is best studied and supported with L-PRP
    - Possibles: hip, ankle

**Mesenchymal stem cells**

- MSC: cells that have the ability to proliferate and differentiate into progenitors of different mesenchymal tissue
- They have unique cell surface markers, adhesion molecules, cytokines, growth factors and receptors
- Anti-inflammatory and immunomodulatory

**BMAC**

- Hemopoietic stem cells
- Nonhemopoietic cells: Mesenchymal Stem Cells
  - 0.001-0.01% of total cell population
  - 100k - 2M MSCs
  - Diminishes with age

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*Crane et al. PMR clinics 2016*


*Slide Courtesy of Dr. Joanne Borg Stein*
Mechanism of Action: Bone Marrow Mesenchymal Cells

- Not completely understood
- Replace degenerated tissue
- Through paracrine activity, exhibit a secretory or “trophic” function, with anti-inflammatory, immunomodulatory, pre-angiogenic, anti-apoptotic, anti-fibrotic, and wound healing properties with proliferative effects*


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Mesenchymal stem cells

- Bone marrow derived
- Adipose derived
- Synovium derived
- Muscle derived

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Slide from Dr Steve Sampson

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Slide From: Dr Chris Centenno

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Intra-Articular Injections of Mesenchymal Stem Cells for Knee Osteoarthritis

Enrique Carlos Rodríguez-Marchena, MD, PHD

- Only 3 randomized controlled trials (level II evidence) found pain relief and functional improvement over the short term. The other human studies also reported encouraging results, but their evidence level was very low (IV).
- Larger randomized controlled trials are needed to support these preliminary encouraging results. The relatively short duration of the studies is also a limitation for the technique at present.

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Concentrated Bone Marrow Aspirate for the Treatment of Chondral Injuries and Osteoarthritis of the Knee

A Systematic Review of Outcomes

Jorge Cherka, MD, Cheth S. Deen, MD, Gilbert Mejuto, MD, Cecilia Pascual-Ganobo, MD, Raphael Serra Cruz, MD, and Robert F. LaPrade, MD, PHD


- Conclusion: “there still remains a paucity of high-quality studies.......Studies reviewed reported varying degrees of beneficial results with the use of BMAC with and without an additional procedure for the treatment of chondral defects and early OA. Most articles present the use of BMAC as a safe procedure and report good results”
Bone marrow derived mesenchymal stem cells

- Preclinical Efficacy of MSCs in Cartilage Regeneration
  - Goat study demonstrates cartilage regeneration with IA injection of BMSCs suspended in hyaluronan (Murphy 2003)
  - Donkey study demonstrates reparative effect of injected MSCs clinically and radiologically (Mokbel 2011)
  - Undifferentiated BMSCs on biodegradable scaffolds yield encouraging results in rabbit and sheep models of OA

Gupta et al. 2012
Mokbel, Tantawy et al. BMC Musculoskeletal Disorders 2011

BMAC

- General Set up

Rate is not greater than that observed with other types of intra-articular injections
- Annual neoplasm 0.78% in adults 50 – 64 yo
  - This study showed 0.14%
- 13 possibly related SAEs among 2372 approximately 0.55% and only 4 of these SAE (0.17%) were deemed definitely related to the procedure
- Only 3 were possibly related to stem cells

BMAC

A multi-center analysis of adverse events among two thousand, three hundred and seventy two adult patients undergoing adult autologous stem cell therapy for orthopaedic conditions

Table 3: Description and proportion of adverse events among patients

<table>
<thead>
<tr>
<th>Type of SAE</th>
<th>Number</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse reaction</td>
<td>13</td>
<td>0.55%</td>
</tr>
<tr>
<td>Infection</td>
<td>4</td>
<td>0.17%</td>
</tr>
<tr>
<td>Inflammation</td>
<td>12</td>
<td>0.52%</td>
</tr>
<tr>
<td>Pain</td>
<td>12</td>
<td>0.52%</td>
</tr>
<tr>
<td>Other</td>
<td>13</td>
<td>0.55%</td>
</tr>
</tbody>
</table>

BMAC

- Rate is not greater than that observed with other types of intra-articular injections
- Annual neoplasm 0.78% in adults 50 – 64 yo
  - This study showed 0.14%
- 13 possibly related SAEs among 2372 approximately 0.55% and only 4 of these SAE (0.17%) were deemed definitely related to the procedure
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**Adipose Tissue**

- Human ADSCs
  - localize in the stromal vascular fraction (SVF)
  - The SVF consists of a heterogeneous mesenchymal population of cells
    - Adipose stromal stem and progenitor cells
    - Hematopoietic stem and progenitor cells
    - endothelial cells, erythrocytes, fibroblasts, lymphocytes, monocyte/macrophages, and pericytes

**Mesenchymal stem cells**

- Multipotent
- More prone to differentiate into muscle cells or even into cardiomyocytes compared with bone marrow MSCs
- Less efficient at osteogenic and chondrogenic differentiation

**Adipose Tissue**

- The stromal vascular fraction (SVF) is a heterogeneous cell population derived from manipulation of adipose tissue
  - homogenization
  - enzymatic digestion
  - differential centrifugation
  - red blood cells lysis and washing

**Adipose Tissue**

- When treated with growth factors
  - Upregulate expression of tendon related markers
  - They are found comparable scaffold adherence and proliferation potential
  - Suggesting AD-MSCs as alternative cell type for tendon tissue repair.

**Adipose Tissue**

- Easier to obtain
- Bioscaffold
Adipose Tissue

- General Set up
  - Lipogems kit contents (single-use)
    - 1L 240cc
    - 1 LG 60cc
    - 1 LG 240cc
    - 1 Aspirator infusion cannula 250x2.25 mm
    - 1 20G 100 polycarbonate vacuum syringe
    - 3 10 ml polycarbonate syringes
    - 2 10 ml polycarbonate syringes
    - 2 Female Luer transfer connectors

- Local Anesthetic
  - Connect the vacuum syringe to the blunt 13-gauge Lipoaspiration cannula
  - Advance and withdraw cannula in a “spokes-of-a-wheel” pattern

- Wash and Rinse
  - Shake vigorously at regular intervals of 30 seconds in a vertical motion
  - Re-open both clamps and allow saline to rinse through device and clear the cannister of debris between intervals
  - Repeat shaking for at least 1-2 minutes until the adipose tissue appears light yellow, and the saline solution is transparent

- Collection:
  - Pull down on syringe
  - Holding the cannister vertically, quickly squeeze the flanges on the full syringe with saline into the cannister
  - Take the syringes containing Liposapiration off and repeat until all of the Liposapiration is removed from the device

- 2002 national survey of 66,000 tumescent liposuction cases
  - No deaths were reported
  - Complication rate was 0.068 per 1000 cases

Stem Cell summary

BMAC
- 100k - 2M MSCs
- Chondrocyte
- Osteogenic
- More painful?
- Volume limit

Adipose
- 250k - 1.25M MSCs
- Bioscaffold
- Tendon defect filling
- Less painful?
- Larger volumes
Amniotic Tissue

- Human Amniotic suspension allografts
  - Human amniotic membrane
  - Human amniotic fluid-derived cells
- Contain anti-inflammatory factors
  - IL-10, IL-1
  - Matrix metalloproteases 1, 2, 3, and 4
  - HAFCs upregulate anti-inflammatory pathways
    - IL-10, Doleamine 2,3-dioxygenase, TGF-B1, leukocyte antigen G5
- Hyaluronic Acid and small amount so proteoglycans

Amniotic Tissue

- Human amniotic membrane
  - Growth factors including EGF, TGF-β, and FGF
    - Stimulate epithelial cell migration and proliferation
  - PDGF A and B
    - Stimulate many metabolic processes
      - General protein and collagen synthesis, collagenase activity, and chemotaxis of fibroblasts and of smooth muscle cells
      - TGF-β has been shown to significantly increase type I collagen production by tendon sheath fibroblasts

Amniotic Tissue

- Pain and functional measures
  - P, ADL, QOL, S, SR of the KOOS
  - Overall KOOS, IKDC, SANE
    - All scores demonstrated improvement at 1 year
    - Labs
      - No concerning changes in renal function, blood cell counts, or lymphocyte subsets
      - Statistically significant increase in IgG and IgE relative to baseline but not abnormal level

Amniotic Tissue

- Cryopreserved Amniotic Suspension for the Treatment of Knee Osteoarthritis
  - N = 6, KL grade 3,4
  - 12 weeks, 3,5,12 months
  - Primary goal feasibility of injection for treatment of OA
  - Secondary goal assessing safety and obtaining Preliminary data on safety and efficacy

Amniotic Tissue

- N = 23
  - 14 Corticosteroid
  - 9 c-hAM
  - Safe and comparable to steroid
Amniotic Tissue

Interim Analysis of Prospective, Multi-Center Outcome Observational Cohort Registry of Amniotic Fluid Treatment for Osteoarthritis of the Knee

Douglas Beall, MD and Sri Nalamachu, MD

*Clinical Radiology of Oklahoma, Edmond OK; **International Clinical Research Institute, Overland Park, KS

N=470: 181

- VAS, WOMAC
- KL 1-3 OA
- 30, 90, 120 days

Table 1. Average VAS Score Comparison by Sites

<table>
<thead>
<tr>
<th>Site</th>
<th>VAS Before</th>
<th>VAS After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site A</td>
<td>5.2</td>
<td>3.1</td>
</tr>
<tr>
<td>Site B</td>
<td>6.8</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Table 2. Average WOMAC Score Comparison by Sites

<table>
<thead>
<tr>
<th>Site</th>
<th>WOMAC Before</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Site A</td>
<td>12.3</td>
<td>8.7</td>
</tr>
<tr>
<td>Site B</td>
<td>15.6</td>
<td>11.2</td>
</tr>
</tbody>
</table>

FDA

- Regulation of Biologic products
  - 1913 – Virus-Serum Toxin Act
  - 1942 – Public Health Service Act
- Cells: “devices” “transplant”
  - 1980s Regulatory change
    - 1990s Carticel – autologous cartilage cells, cultured expanded for osteochondral flap
    - 1996 Center for Biologics Evaluation and Research Listed as Biologic
    - 1995 Carticel – autologous cartilage cells, cultured expanded for osteochondral flap
    - FDA approved as new medical device
  - 2006 – Changed regulatory focus – expanding regulation
- 2016 – Meeting in September

Centeno CJ, Bashir J, Safety and Regulatory Issues Regarding Stem Cell Therapies: One Clinic’s Perspective. PMR 2015 S4-S7
1. More than Minimally Manipulated
   - Centrifugation, crystalloids, water, cutting/shaping
2. Homologous use
   - Same structure / function
3. Processed in isolation
   - Same surgical procedure, no combinations
4. Limited systemic effect

**Adipose Tissue**

**FDA – NEJM Perspective**

**Clarifying Stem Cell Therapy’s Benefits and Risks**

Peter W. Marks, M.D., Ph.D., Cara M. Wilson, Ph.D., M.D., and Robert W. Cahill, M.D.

The current standard of care for intravitreal therapies is to perform photodynamic therapy or suppressive treatments to improve vision. However, in certain cases of AMD, the vision cannot be restored. The Food and Drug Administration (FDA) has approved the use of stem cells for the treatment of AMD, but there are concerns about the safety and efficacy of these therapies. It is important to consider the potential benefits and risks of stem cell therapy for AMD to ensure that patients are informed about their treatment options.

**Bioscaffolds**

A number of studies demonstrate that seeded constructs have better histological and biomechanical properties than scaffold alone.

- Studies
  - Synthetic biodegradable polymers
  - PLGA (polylactic-co-glycolide)
  - Acellularized tendon grafts
  - Collagen sponge
Silk Polymers

Cocoon Biotech to Explore New Treatments for Joint Disease using Silk Biomaterial Platform Developed at Tufts University

BOSTON (November 4th, 2014) — Cocoon Biotech today announced that it has entered into exclusive option and sponsored research agreements with Tufts University to explore the commercialization of new treatments for joint disease and arthritis using silk protein polymers.

Logistics

Patient Selection

- Age and medical factors
- Alignment
- Prior treatments
- Peri vs intra-articular component
- Severity of arthritis
- Candidacy for joint replacement
- Patient preference
- Particular joint
  - Knee
  - Hip
  - Shoulder

Patient education and counseling

- Literature
- Active rehabilitation
- Expense
- Benefits vs risks
- Set expectations
  - Pain
  - Function
  - Range of motion
  - Durability
  - “in season”

Selection of Treatment

- Accurate diagnosis
- Target tissue(s) and volume needs
- Severity and size of injury/defect
- Time frame (in season? geography)
- Cost
- Other medical co-morbidities
- Pain tolerance of patient
- Patient preference

Injectable, Biodegradable Hydrogels for Tissue Engineering Applications

Huaiping Tan 1 and Kacey G. Marra 2,3,*

1 Division of Plastic Surgery, Department of Surgery, University of Pittsburgh, Pittsburgh, PA, USA
2 Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA, USA
3 McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, PA, USA
* Author to whom correspondence should be addressed; Tel.: +1 412-385-8524; Fax: +1 412-648-2021.

Received: 19 November 2013; revised from: 16 February 2014; Accepted: 8 March 2014; Published: 10 March 2014
Treatment selection: osteoarthritis

<table>
<thead>
<tr>
<th>Injectate</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMAC</td>
<td>Paracrine effect</td>
<td>Immobile, expensive</td>
</tr>
<tr>
<td>Fat graft</td>
<td></td>
<td>No good research</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non FDA compliant</td>
</tr>
<tr>
<td>PROLOtherapy</td>
<td>Less expensive</td>
<td>Needing effect may be primary</td>
</tr>
<tr>
<td></td>
<td>Easy to obtain</td>
<td>Requires many visits</td>
</tr>
<tr>
<td>Platelet Rich Plasma</td>
<td>Knee best</td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td>Hip</td>
<td>Less data on small joints</td>
</tr>
</tbody>
</table>

58 yo active tennis player with moderate knee OA

- Additional history
  - Aches in the evening after an active day
  - Difficulty with stairs and sports activity
  - No mechanical symptoms or recurrent synovitis
  - Uses Aleve most days
  - Wants to wait until 65 as he has been told TKA lasts ~20 years

- Prior treatments:
  - Weight loss
  - PT
  - Steroid injection
  - Viscosupplementation no longer helps as much

TREATED WITH PRP: LR and 7% Hct
27 yo professional running back with R knee pain

- Progressive R knee pain and intermittent sharp pain
- Had
  - ACL reconstruction
  - Several meniscal surgeries
  - PRP x 3
- 3 weeks to first pre-season game.
  6 weeks start of regular season

TREATED WITH
BMAC and PRP

52 yo executive with progressive medial L knee pain

- Had excision of femur tumor during childhood
- Knee pain since his 30's
- No longer runs
- Wants to walk the golf course
- Prior treatments
  - Excellent PT
  - Trainer
  - Steroids injections
  - High tibial osteotomy
  - Meniscal surgery

TREATMENT PLAN:
BMAC and PRP: IA, meniscus, MCL

Summary: Cell Delivery for Musculoskeletal Regeneration

Conclusions

Future
The tissue engineering paradigm

- Biophysical stimuli
- Biochemical Signals
- Cells
- Scaffolds

Thank you!