Orthobiologics: Fact, Fiction or Fantasy

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Disclosures

• Consultant
  – Arthrex (Royalties)
  – JRF
  – Johnson and Johnson and Depuy
    Mitek
  – Exactech
  – Geistlich
  – Regen Labs
  – Alter G
Stem Cell and Orthobiologics 2018
Hope or Hype...Fantasy

Tampa
Unscrupulous Actors Exploiting the gap between Hope and Knowledge!!!

...BRM
The Orthobiological Surgeon’s prayer

Ability to help when you can,

The judgment to know when can and can not help,

The wisdom to know the difference!

-BRM
4 P
Personalized Medicine
Personalized Medicine

“is the tailoring of medical treatment to the individual characteristics of each patient”

The Age of Personalized Medicine

“The science of individualized prevention and therapy”

National Institute of Health
Orthobiological Intervention
Personalized Medicine 4P

- Computing data cloud dumps.. **genomic sequencing**
- Artificial intelligence.. **facilitate knowledge**
- 3 D printing.. **Manufacturing of scaffolds and implants**
- Virtual and Augmented Reality.. **training**
- Robotics.. **Navigational arthroplasty etc**
- **Orthobiologics**

2017
100 million resistors/ 1 mm of 10 nm Intel chip
Orthobiologics
The Knee Joint is an Organ...
we must consider alignment, meniscal, ligament deficiency, molecular, tissue and matrix issues
Mechano-Orthobiologic Paradigm 2018

Performance

organ

tissue

cell/matrix

molecule

m  cm  mm  µm  nm
Orthobiologics
State of the Art
Objectives

- Cartilage Injury and OA
- ACL Injury
“Chondroprotection and Chondrofacilitation”

Management of knee articular cartilage injuries in athletes: chondroprotection, chondrofacilitation, and resurfacing

John R. Murray · Michael T. Beink · Bert R. Mandelbaum

Abstract Articular cartilage defects of the knee are common among athletes where the physical demands of sport result in significant stresses on joints. Chondral defects are associated with pain and functional impairment that limit sporting participation and may progress to joint degeneration and frank arthritis. Management of established chondral lesions aims to allow athletes to return to high-impact sports and can be considered in terms of prevention of existing cartilage, chondroprotection, and chondrofacilitation. Required and regenerated cartilage most closely resembles and functions like normal hyaline cartilage, and this ability may be the most significant factor for the return to sport. Based on our experiences and the available literature, we outline how athletes can best protect their cartilage, how physicians can facilitate intimate repair of established lesions, and which methods of cartilage restoration or resurfacing should be used in different situations.

Level of evidence: IV.

Keywords Cartilage injury · Return to sport · Knee articular cartilage · Cartilage resurfacing

Who is at risk?
Both acute traumatic injury and chronic repetitive damage to articular cartilage are increasingly recognized in athletes. The overall prevalence of focal chondral defects in the knee is 36% among all athletes compared with 86% of the general population [17]. Higher injury rates are noted in competition over practice, athletes with BMI over 30.5, and athletes in certain positions (for example, linemen) [7]. Increasing participation in recreational sports has also been associated with a rising incidence of cartilage injuries among non-competitive athletes [1]. In addition to being common, these injuries carry a high morbidity. Knee injuries account for 46% of career-ending injuries in professional soccer with over a quarter resulting from cartilage injuries, and athletes are up to 12 times more likely to develop osteoarthritis than the general population [17].

Natural history of athletic cartilage lesions
The rationale for each treatment approach is based on knowledge of the pathophysiology underlying chondral lesions. Without access to abundant nutrients or progenitor cells, cartilage lacks innate abilities to mount a regenerative response to injury. In partial-thickness defects, there is no involvement of the vasculature. Chondroprogenitor cells in medial and cartilage cannot enter the damaged region, and local articular chondrocytes do not migrate to the lesion. As such, the defect is not repaired and will progress.

Full-thickness cartilage injuries that penetrate subchondral bone have the potential for intrinsic repair due to communication with chondroprogenitors in bone marrow. Type I collagen is produced by these differentiating cells, resulting in fibrocartilage rather than the preferred hyaline cartilage.
(a) An HCT/P is regulated solely under section 361 of the PHS Act and the regulations in this part if it meets all of the following criteria:

(1) The HCT/P is minimally manipulated;

(2) The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;

(3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and
ACL injury is catabolic.
Articular Cartilage Injury

Alignment
Gender
Level of play
Age of Injury
Present age
Timing of RX
Modulators

Meniscus Injury

GAG
MMPs
Growth Factors

ACL
"Catabolic Injury"

Osteoarthritis
Prevalence of radiographic knee OA

Interventions Required
Regenerate, Repair or Reconstruct, restore
Orthobiological

- Non-operative
- Preoperative
- Timing and Staging
- Intra-operative
- Postoperative short and long term
Biological Paradigm
Resurfacing, Facilitation, Protection

RFP Approach

• Resurfacing Graft preservation, facilitation, protection
• Subchondral Bone and Bone integrity
  • blood flow
  • Bone integration, healing and substitution replacement
  • Role of BML cysts
• Chondrocyte and cell viability or repopulation
• Synovial anabolic Homeostasis
• Temporal signal requirements
The Regenerative Tissue Engineering Triad

Cells

Growth factors and Cytokines

Scaffolds/Biomaterials
Chondroprotection and Chondrofacilitation

**Performance Enhancing Adjuvants (PEAs)**

- GS/CS
- Hyaluronic Acid Injection
- PRP
- Cytokine Modulation
  - IL-Ira Inhibition of Inflammatory Response
- Stem Cells
  - Adipose derived
  - BMAC
  - Allogeneic stem cells
  - Induced pluripotential cells
- Amniotic Fluid
- Estrogens

*What is the ideal adjuvant combination?*
Chondroprotection and the Prevention of Osteoarthritis Progression of the Knee
A Systematic Review of Treatment Agents
Gallagher, Ciccotti et al 2015

**GS/CS** may protect joint cartilage and delay OA progression

Hyaluronic acid injections showed *variable efficacy*
Glucosamine / Chondroitin Sulfate
Monosaccharide precursor to GAG

Clinical Evidence

- GAIT Study NIH 2006
  - Beneficial to less severe
  - 2000 mg vs. placebo
  - 88% improved vs. 17% placebo
  - KOOS and KPS better
- RCT Reginster Lancet 2001
  - Improvement of Womac scores
  - Decrease in X-ray OA
  - Chondroprotective!
- RCT Pavelka Ann Int Med 2000
  - Less JSN
  - Better subjective scores

Mechanism of Action

Synergistic increased PG production and dec in degradative enzymes
Lipello Clin Orthop 2000

inhibition IL-1Beta and TNF-alpha, NO and PGE2 production in human Chondrocyte and inhibits inducible NO synthetase
Shikman et al J Immunol 2001

increases GAG content and cartilage thickness after injury
Oegema ORS 2001)
Hyaluronic Acid

• **Rationale**
  - Physiology: PGs and GAGs bind to collagen mesh and aid in hydration
  - Biomechanical: HA is for shock absorption and lubrication…aging and OA concentration and MW

• **Therapeutic Response**
  - Decrease inflammatory response and improve viscoelastic properties
    - (Abatangelo ’89 Clin Ortho. Rel Res.)
  - >chondrocyte density, >territorial matrix, >metabolism
    - (Guidolin et al OA Cartilage 2001)
  - **Protects cartilage degeneration** after meniscectomy
    - Enhances synthesis of GAGs
    - (Ameil ORS 2001)
32 Published or presented Clinical Trials for OA

- Supartz-Japan
- Healon-United States
- Hyalgan-France/Italy
- Synvisc- North America

In the past year significant number of presented studies.

**Conclusion**

- Intra-articular hyaluronan/hylan is superior to placebo in relieving symptoms associated with OA. (Wobig 98 Marshall 97)
- Produced similar results as NSAIDs and Corticosteroids. Lasting appx. 6 months (Dickson 98, Adams 95)
- Treatment is well tolerated and safe. (Lussier 96 Kotz 99)
The Orthobiologic Family

PRP

BMAC

Stem Cells
The Orthobiologic Family

PRP

BMAC

Stem Cells
The Orthobiologic Family

- PRP
- BMAC
- Stem Cells
<table>
<thead>
<tr>
<th>GROWTH FACTORS</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PD-EGF</strong> platelet-derived epidermal growth factor</td>
<td>Cell growth, recruitment, Differentiation, skin closure, Cytokine secretion</td>
</tr>
<tr>
<td><strong>PDGF A + B</strong> platelet-derived growth factor</td>
<td>Potent cell growth, recruitment Blood vessel growth, granulation Growth factor secretion; matrix formation with BMPs (collagen and bone)</td>
</tr>
<tr>
<td><strong>TGF-β1</strong> transforming growth factor</td>
<td>Blood vessel (±), collagen synthesis, Growth inhibition, apoptosis (cell death), Differentiation, activation</td>
</tr>
<tr>
<td><strong>IGF-I, II</strong> insulin-like growth factor</td>
<td>Cell growth, differentiation, recruitment, Collagen synthesis with PDGF</td>
</tr>
<tr>
<td><strong>VEGF, ECGF</strong> vascular endothelial growth factor, endothelial cell growth factor</td>
<td>Angiogenesis, Mitogenesis, Cell growth, migration, new blood vessel growth Anti-apoptosis (anti–cell death)</td>
</tr>
<tr>
<td><strong>bFGF</strong> basic fibroblast growth factor</td>
<td>Chemotaxis, Cell growth, Cell migration, blood vessel growth</td>
</tr>
</tbody>
</table>

Growth factors positive effect cartilage metabolism and regeneration Synovium, Meniscus, chondrocytes

Akeda K et al. Osteoarthritis Cartilage. 2006
Stimulation of the Superficial Zone Protein and Lubrication in the Articular Cartilage by Human Platelet-Rich Plasma

Sakata, Reddi et al 2015

- lubrication properties pin-on-disk tribometer.

- **Results:** PRP stimulated **proliferation in cells** derived from articular cartilage, synovium, and ACL

- **enhanced SZP secretion** from synovium- and cartilage-derived cells.

- high loads and low sliding speeds PRP **decreased the friction coefficient**

- **Conclusion:** PRP significantly stimulates cell proliferation and SZP secretion by articular cartilage and synovium of the human knee joint. Furthermore, PRP contains endogenous SZP and, in a functional bioassay, lubricates bovine articular cartilage explants.

**How does PRP work??**

SZP PRGF 4 Lubricin
PRPs EFFECTS ON CHONDROCYTES
PROLIFERATION AND GENE EXPRESSION


How does PRP work???

PROLIFERATION

% of Alamar Blue reduction

Day 0  Day 3  Day 7

P-PRP  L-PRP

PRPs EFFECTS ON CHONDROCYTES
PROLIFERATION AND GENE EXPRESSION


How does PRP work???

PROLIFERATION

% of Alamar Blue reduction

Day 0  Day 3  Day 7

P-PRP  L-PRP

GENE EXPRESSION

Collagen type II

Aggrecan

IL-1Beta

IL-6

MMP-13
ACP Excludes WBCs

Growth factor and catabolic cytokine concentrations are influenced by the cellular composition of platelet-rich plasma

Sundman, Cole, Fortier 2011

**MMP-9 and IL-1 beta** measured within ACP (PRP-1) and Biomet (PRP-2)
- Neutrophil-derived MMP-9 known to degrade collagen, causes poor healing
- IL-1 beta is primary cytokine for inflammation and matrix degradation

- Values correlated with WBCs (very minimal amount measured in ACP)
How does PRP work???

Jeremy Mao, PhD

Columbia University
The Effect of PRP on Autograft OATs in Rabbits
Smyth, Haleem et al

ICRS histology scores improved $p=0.002$
Bone graft integration improved $p=0.004$
EFFECTS OF PLATELET-RICH PLASMA ON TISSUE ENGINEERED CARTILAGE

Massimo Petrera*, MD - J. N. Amritha De Croos°, PhD - Jonathan Lu°, BSc - Mark Hurtig§, DVM - Rita A. Kandel°, MD - John S. Theodoropoulos*, MD

* University of Toronto Orthopaedic Sports Medicine
° Department of Pathology and Laboratory Medicine, CIHR-Bio Engineering of Skeletal Tissues Team, Mount Sinai Hospital, University of Toronto
§ Department of Biomedical Sciences, University of Guelph
EFFECTS OF PLATELET-RICH PLASMA ON TISSUE ENGINEERED CARTILAGE

Formation of Articular Cartilage in vitro

Courtesy: Dr. Rita Kandel
Results

Samples cultured in Ham’s F-12 supplemented with 20% PRP had significantly thicker tissue.

Intact cartilage layer and increased extracellular matrix in constructs cultured with 20% PRP.

Immunostaining: prevalence of type II collagen.
EFFECTS OF PLATELET-RICH PLASMA ON TISSUE ENGINEERED CARTILAGE

Results

Mechanical testing

Tissue engineered cartilage cultured with 20% PRP showed superior compressive mechanical properties with an equilibrium modulus of 38.1±3.6 kPa versus 15.6±1.5 kPa for 20% PPP (p=0.0002) and 20.4±3.5 kPa for 20% FBS (p=0.007).

Biochemistry - Proteoglican

Samples supplemented with 20% PRP had significantly higher GAG content (176.1±18.8µg GAG/mg dry wt) compared to those supplemented with 20% FBS (112±10.6µg GAG/mg dry wt, p=0.01) or 20% PPP (131.5±14.8µg GAG/mg dry wt, p=0.11).
Conclusions

• The presence of PRP in the culture media enhances the in vitro formation of cartilage with increased ECM and greater compressive mechanical properties, while maintaining features of hyaline phenotype

• This treatment may be a way to generate better tissue suitable to use for cartilage repair

• Further study to evaluate this tissue in vivo is required
Repeated platelet concentrate injections 5 injections of ACP post microfx: macroscopically, histologically, and biomechanically superior to microfx alone after 3, 6, and 12 months

Enhance reparative response of microfractures in the treatment of chondral defects of the knee: An experimental study in an animal model


**Arthroscopy**

The Journal of Arthroscopic and Related Surgery
## Meta Analysis

**Chahla, Mandelbaum 2018**

### PRP vs Placebo

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PRP Mean</th>
<th>PRP SD</th>
<th>Placebo Mean</th>
<th>Placebo SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel Am J Sports Med 2013</td>
<td>30.5</td>
<td>25.9</td>
<td>53.1</td>
<td>17.9</td>
<td>25</td>
<td>4.1%</td>
<td>-22.60 [-35.11, -10.09]</td>
<td></td>
</tr>
<tr>
<td>Smith Am J Sports Med 2016</td>
<td>3</td>
<td>3.6</td>
<td>9</td>
<td>3.6</td>
<td>15</td>
<td>95.9%</td>
<td>-6.00 [-8.58, -3.42]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>40</strong></td>
<td></td>
<td><strong>38</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td></td>
<td><strong>-6.68 [-9.20, -4.15]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 6.49, df = 1 (P = 0.01); I² = 85%
Test for overall effect: Z = 5.18 (P < 0.000001)

### PRP vs Steroid

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PRP Mean</th>
<th>PRP SD</th>
<th>CS Mean</th>
<th>CS SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
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</tr>
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<td><strong>25</strong></td>
<td></td>
<td><strong>23</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td></td>
<td><strong>-22.60 [-35.11, -10.09]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 3.54 (P = 0.0004)
# Meta Analysis

Chahla, Mandelbaum 2018

## PRP vs HA

### WOMAC 6mo

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [SD]</th>
<th>Total</th>
<th>Mean [SD]</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference [IV, Fixed, 95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duymus KSSTA 2017</td>
<td>42.8 [7.1]</td>
<td>41</td>
<td>44.5 [6.6]</td>
<td>40</td>
<td>33.3%</td>
<td>-1.70 [-4.68, 1.28]</td>
</tr>
<tr>
<td>Raeissadat Clin Med Insights 2015</td>
<td>0 [0]</td>
<td>0</td>
<td>0 [0]</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Sanchez Arthroscopy 2012</td>
<td>74 [42.7]</td>
<td>89</td>
<td>78.3 [48.1]</td>
<td>87</td>
<td>1.6%</td>
<td>-4.30 [-17.75, 9.15]</td>
</tr>
<tr>
<td>Vaquerizo Arthroscopy 2013</td>
<td>27.2 [15.1]</td>
<td>48</td>
<td>50.4 [23.2]</td>
<td>48</td>
<td>4.8%</td>
<td>-23.20 [-31.03, -15.37]</td>
</tr>
</tbody>
</table>

Total (95% CI): 440

Heterogeneity: $\chi^2 = 94.46$, df = 6 ($P < 0.00001$); $I^2 = 94$

Test for overall effect: Z = 10.62 ($P < 0.00001$)

### WOMAC 12mo

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [SD]</th>
<th>Total</th>
<th>Mean [SD]</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference [IV, Fixed, 95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duymus KSSTA 2017</td>
<td>-24.9 [6.3]</td>
<td>33</td>
<td>-24.2 [5]</td>
<td>5</td>
<td>55.8%</td>
<td>-0.70 [-3.43, 2.03]</td>
</tr>
<tr>
<td>Vaquerizo Arthroscopy 2013</td>
<td>-12.9 [10.6]</td>
<td>48</td>
<td>-0.5 [15.5]</td>
<td>48</td>
<td>14.7%</td>
<td>-12.40 [-17.71, -7.09]</td>
</tr>
</tbody>
</table>

Total (95% CI): 170

Heterogeneity: $\chi^2 = 15.47$, df = 2 ($P = 0.00004$); $I^2 = 87$

Test for overall effect: Z = 2.47 ($P = 0.01$)
Autologous Interleukin-1 receptor antagonist improvements RCT in OA
Yang et al Osteoarthritis and Cartilage 2008

- In theory? Incubation with CrSO₄-coated glass beads stimulates the synthesis of anti-inflammatory cytokines, **interleukin-1 receptor antagonist (IL-1ra)**
- 176 pts at 1 year
- WOMAC NSD
- KOOS improved symptom P < 0.002 and Sport p< 0.04 Domains
- Efficacy maybe not as robust as PRP!!!
Hyaluronic acid induces the release of growth factors from platelet-rich plasma
Lio et al Asia Pacific Sports Med and Arthroscopy 2016

• HA and PRP

What is the ideal adjuvant combination?
Concentrated Bone Marrow Aspirate for the Treatment of Chondral Injuries and Osteoarthritis of the Knee
A Systematic Review of Outcomes

Bone marrow aspirate concentrate for the treatment of osteochondral lesions of the talus: a systematic review of outcomes

Biological Therapies for Cartilage Lesions in the Hip: A New Horizon

Jorge Chahla, MD; Robert F. LaPrade, MD, PhD; Rodrigo Mardones, MD; Johnny Huard, PhD; Marc J. Philippon, MD; Shane Nho, MD; Omer Mei-Dan, MD; Cecilia Pascual-Garrido, MD
Treatment of Knee OA With Autologous Mesenchymal Stem Cells: A Pilot Study
Orozco et al Transplantation 2013

- 12 pts
- BMAC
- Significant improvement in VAS, WOMAC
- 27% improvement of T2 MRI

Minimal Evidence for stem cells... lots for PRP!
Clinical Outcome BMAC OA
Kristin S. Oliver, MD    St. Louis
J of Prolotherapy 2015

• 70 pts Angel BMAC + autologous lipoaspirate
• SOS outcomes
• Registry

Perhaps not as good as PRP!
Intra-Articular Injection of Mesenchymal Stem Cells for the Treatment of Osteoarthritis of the Knee: A Proof-of-Concept Clinical Trial
Jo et al 2014 Seoul, Korea

• 18 pts Adipose MSC 1.0 x 10^8th high vs. low dose
• WOMAC at 6 months
• Improvements no stats yet!

Minimal Evidence for stem cells...
Treatment of Knee OA With Allogeneic Mesenchymal Stem Cells: RCT
Vega et al Transplantation 2015 Vallaladid, Spain

- 30 pts
- randomized allogeneic with $40 \times 10^6$ cells. vs. HA
- 38% to 42% improvement in pain compared to 10% to 14% in active controls with hyaluronic acid

VAS
A randomized, double-blind, controlled study of adult human mesenchymal stem cells delivered via intra-articular injection to the knee joint following meniscectomy

C. Thomas Vangsness Jr., MD, David Fox, MD, David Dellaero, MD, David Griffin, MD, Jack Farr, MD, Joel Boyd, MD, John O’Donnell, MD
Improvement in VAS Pain Score through 2 years post meniscectomy surgery in patients with evidence of cartilage degeneration on MRI. Control: HA; Group A: 50 x 10^6 hMSCs; Group B: 150 x 10^6 hMSCs.

Look about the same as PRP data!!!
Amniotic fluid stem (AFS) cells

- Amniocentesis week 14 - 20 ultrasonography chromosomal analysis and levels of alpha fetoprotein
- AFS cells generated by selecting for ckit positive cells and single cell cloning
- can be expanded in vitro differentiated into cells of all three embryonic germ layers
Interim Analysis of Prospective, Multi-Center Outcome Observational Cohort Registry of **Amniotic Fluid Treatment for Osteoarthritis of the Knee** 2015 Report

*Douglas Beall, MD and **Sri Nalamachu, MD

- **Amniovisc**
- first 181 patients in a Registry Study designed for 470 patients suggest that use of a processed amniotic fluid allograft may offer a safe and effective treatment for osteoarthritis

![Graph 1](image1)

- % Improvement
- Mean VAS Score
- Time 0: 64, 59%, 63%
- 30 Days: 26, 24%
- 90 Days:

![Graph 2](image2)

- % Improvement
- Mean WOMAC Score
- Time 0: 1176, 59%, 60%
- 30 Days: 487, 473
- 90 Days: 0%
Incidence of TKR and THR for OA in Relation to Sex hormones in Women
Hussain, Cicuttini et al. Melbourne 2014

- Melbourne Collaborative Cohorts study
  2621 women Incidence of TKR and THR 2001-2011
- 115 TKR / 99 THR
- > Estradiol < incidence of TKR HR 0.70
- > Androstenedione < THR HR 0.70
- > Sex Hormone Binding Globulin (SHBG) > THR HR 1.70

Circulating Sex hormones have direct effect on OA pathogenesis
Estrogen reduced mechanical injury cell death
Imgenberg et al 2012

- 17 Beta Estradiol E2
- Cows explants
- Single load compression strain 50%
- 96 hours cell death

Estradiol E2 reduce cell death and release GAG
ACLR and Bioaugmentation
ACL Derived Stem Cells Transduced With BMP2 Accelerate Graft-Bone Integration After ACL Reconstruction
Kawakami, Huard et al 2017

• rat model of ACL injury
• ACL-derived CD34+ cells were isolated from remnant human ACL tissues
• virally transduced to express BMP2, and embedded within cell sheets wrapped around tendon autografts
• improved histological appearance and graft-bone interface biology along with tensile load to failure
Graft Maturation Beagles
PRP impact on Target Genes

Xie et al. JOR. 2013

• Randomized beagles to 1 of 4 groups
  • group 1 (PRP group—ACLR w/ BTB auto + PRP)
  • group 2 (control group—ACLR w/ BTB auto + Saline),
  • group 3 (sham group—no reconstruction)
  • group 4 (normal control group—no surgery)

• Increased expression of…
  • VEGF, TSP-1, neurotrophin-3, GAP-43, molecule 31, TSP-1, GAP-43, and nerve growth factor mRNA in group 1 at 2, 6, and 12 wk after surgery
  • Conclusion… “PRP alters the expression of some target genes at certain times, particularly during the early stages of graft remodeling….promoting revascularization and re-innervation, which might explain the enhancing effect of PRP on ACL graft maturation”
ACL Primary Repair
Porcine

**Scaffold + PRP importance**

- Suture repair after ACL transection + collagen hydrogel **scaffold** + PRP
  - significant improvement in load at yield, maximum load, and linear stiffness at 4 weeks compared with untreated
    » Murray et al. J Orthop Res. 2007

- Suture repair after ACL transection + PRP (No scaffold)
  - not improve AP knee laxity at 30 degrees ($p = 0.73$) or 60 degrees ($p = 0.65$).
  - not improve the maximum tensile load ($p = 0.64$) or linear stiffness ($p = 0.42$) of the ACL repairs after 14 weeks
The Bridge-Enhanced Anterior Cruciate Ligament Repair (BEAR) Procedure
An Early Feasibility Cohort Study
Murray, Micheli et al 2016

- Suture Repair Swivel lock to footprint
- Bridge TM scaffold over repair
  Collagen sponge and PRP
- 10 pts BEAR 10 HS

**Conclusion:**

The results of this study suggest that the BEAR procedure may have a rate of adverse reactions low enough to warrant a study of efficacy in a larger group of patients.
Acute Proximal Anterior Cruciate Ligament Tears: Outcomes After Arthroscopic Suture Anchor Repair Versus Anatomic Single-Bundle Reconstruction
Achtnich et al 2016

- 20 patients in each group
- correlation between poor results and failure rate ($P = .001$) in the refixation group
- **failure rate was 15% in the ACL refixation group and 0% in the reconstruction group ($P = .231$).**
- MRI homogeneous signal and proper ACL position in 100% of patients in the control group and 86% in the ACL repair group.

**Conclusions**
Proximal refixation of the ACL restores knee stability and results in comparable outcomes to a control group treated with single-bundle ACL reconstruction. **The results suggest that refixation of the ACL is a feasible treatment option in selected patients**
Acute Proximal Anterior Cruciate Ligament Tears: Outcomes After Arthroscopic Suture Anchor Repair Versus Anatomic Single-Bundle Reconstruction

Achtnich et al 2016

Repair Not For soccer players!!!!!
Orthobiological Interventions… FACT!

Conclusions

• Major frontier in Soccer Medicine will be led by molecular biology and our ability to utilize these techniques clinically.

• Think as an adjuvant “Ideal cocktail”… GS/CS HA + PRP + MSC

• Our present understanding of and maximizing the desired effect on the native tissue is at its infancy.. Good steps and lots of research so far!

• Basic and clinical science is essential to discover the complexities of optimal regeneration

• Need to be precise in not overstating the impact!.. it is the TRIAD