Orthobiologics in Shoulder Surgery

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“The future ain’t what it used to be”

“You've got to be very careful if you don't know where you're going, because you might not get there.”

Yogi Berra
What’s so special about shoulder surgery?

- Often working with chronic, degenerative conditions
- Rotator cuff tears are very common
  - If you live long enough, you probably will have a cuff tear
- Re-tear rates after traditional surgery is much higher than previously appreciated
  - 40-95% retear rate!
- Annual financial burden of $3 billion on the US economy
My Introduction to Orthobiologics

• What is it?
  – “highly inductive, scaffolding material”
    » Steve Arnockzy

• How does it work?
  – “I haven’t the slightest idea”
    » Steve Arnockzy

"I think you should be more explicit here in step two."
Realities of the “Orthopaedic Marketplace”

• Most surgeons know nothing about “orthobiologics”
• Many surgeons know nothing about soft tissue healing
• Many surgeons are desperate for anything to give them better results
• Some surgeons will try anything to get a “competitive edge” over other surgeons
Biologics in Shoulder Surgery

• Soft tissue substitutes
  – Biologic
  – Structural

• Hard tissue substitutes
  – Graft extenders
  – Graft substitutes

• Healing “enhancers”
Orthobiologics in Orthopaedic Surgery

• Alternatives:
  – Bone Substitutes
    • Tricalcium phosphate
    • Amorphous Calcium Phosphate
    • Dicalcium Phosphate Dihydrate Precursors
    • Demineralized bone matrix
  – Soft tissue scaffolds
    • ECM grafts
  – Cell based healing response
    • Platelet Rich Plasma
  – Factor based healing
## Bone Graft Substitutes

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allograft based</td>
<td>Allograft bone used alone or in combination with other materials</td>
<td>Allogro, Othroblast, Opteform, Grafton</td>
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<tr>
<td>Factor based</td>
<td>Natural and recombinant growth factors used alone or in combination with other materials</td>
<td>TGF-beta, PDGF, FGF, BMP</td>
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<tr>
<td>Cell based</td>
<td>Cells used to generate new tissue alone or seeded onto a support matrix</td>
<td>Mesenchymal stem cells, Cellect</td>
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<tr>
<td>Ceramic based</td>
<td>Includes calcium phosphate, calcium sulfate, and bioglass used alone or in combination</td>
<td>Osteograf, Norian SRS, ProOsteon, Osteoset, Conduit</td>
</tr>
<tr>
<td>Polymer based</td>
<td>Both degradable and nondegradable polymers used alone and in combination with other materials</td>
<td>Cortoss, OPLA, Immix</td>
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</tbody>
</table>
Bone Graft Substitutes

• 1998 - >300K bone grafts, 1999 ~500K
• Total cost ~ $2.5 billion/year
• However:
  – Relatively high complication rate ~20-30%
  – Donor site pain
  – Increased operative times
  – Increased operative costs (supplies, OR time, etc)
  – Limited supply/availability
Bone Morphogenetic Protein

- Also known as BMP
  - Synthetics: INFUSE® and OP-1®
- Signaling protein that tells mesenchymal stem cells what to become (i.e. bone, muscle or connective tissue)
- 30 known human BMPs
- “Key” that fits into one keyhole on the surface of the MSC
Problems with BMP

- Needs MSC’s
- Expensive
- Non-reimbursable
- Questions of using factor in far greater than normal quantities
Problems with Factor Based Healing

• Not only are the factors important
  – Relationship of the combination of factors
  – Quantity of factors
  – ? 3 dimensional presentation of factors
  – Host status
• Most important wound healing tissue factors are platelet derived
  – PDGF – platelet derived growth factor
  – VEGF – vascular/endothelial growth factor
  – TGFβ – transforming growth factor
  – IFG-I – insulin like growth factor
• Can we enhance healing by application of a platelet concentrate at the time of surgery?
• Various systems available to concentrate autologous plate
Multiple studies have shown enhanced wound healing, improved hemostasis and improved bone formation with application of PRP and PPP. However, other studies have shown no benefit and even decreased bone formation with PRP.
PRP Causes Migration of MSCs

Chemotactic Test Solution

Cell number/chamber

SF 10% PPP 10% PRP
PRP Causes Proliferation of MSCs

*P<0.05 compared to PPP
PRP and Implant Coating

• Most studies are in dental, ENT and maxillofacial areas

PRP in My Practice
Observations

• No longer need drain post-op
• Less swelling and ecchymosis
• Better/earlier range of motion and function
• Incisions “mature” sooner
• *Patients have been using significantly less post-op narcotics
Humeral Nonunion 68yo female heavy smoker 1 year s/p failed ORIF
3 mos s/p Revision with PRP and TCP
Humeral Osteotomy Nonunion in 28 yo male now 1 month s/p revision with PRP and TCP
Revision shoulder arthroplasty
PRP + TCP
PRP plus DBM/Cancellous Bone
72 yo home $\text{O}_2$ dependent, EF 25%
3 weeks s/p revision ORIF c/ PRP, 15cc IC Graft
Soft Tissue Scaffolds

- **CuffPatch** *(Arthrotek)*
  - Porcine SIS
- **Graftjacket** *(Wright Medical)*
  - Human dermal tissue
- **Graftjacket Xpress** *(Wright Medical)*
  - Flowable Soft Tissue Scaffold
  - Micronized human dermal tissue
- **AlloPatch** *(MTF)*
  - Human fascia lata,

- **Permacol** *(Tissue Science Lab/Zimmer)*
  - Porcine dermal tissue
- **Restore** *(DePuy Ortho)*
  - Porcine SIS
- **TissueMend** *(Stryker Howmedica)*
  - Bovine fetal dermal tissue
- **OrthADAPT** *(Pegasus Biologics)*
  - Equine Pericardium
Uses of the Restore® Graft

- FDA approved for:
  - Rotator cuff repair
    - 1 and 2 tendon repairs
    - NOT TO BE USED WITH MORE THAN MILD FATTY DEGENERATION
  - Reinforcement of soft tissue where weakness exists
- Replacement of torn/ruptured ligaments
- Replacement of torn/ruptured tendons
• 6 years post-op revision left rotator cuff repair
• Patient rates left shoulder as “normal”
• MRI at 1, 3 and 6 year f/u show intact left cuff
• Patient has re-ruptured right RC repair done without Restore
  – Revised 10/2004 with Restore
6 year postop MRI & CT
5 weeks postop Right revision
Lateral Retinacular Defect in 36yo w/HIV – failed 2 prior attempts at primary repair

Pre-op

6 mos post-op
Reinforcement of Triceps Rupture

“Overlay Technique”
Levator Scapulae Avulsion Repair
Post-acromioplasty deltoid avulsion
Subscapularis Reinforcement

The “Taco” Technique
Subscapularis reinforcement
Pectoralis Rupture
History

• Cook and Arnoczky:
  – SIS appears to induce regeneration of meniscal-like tissue in large, avascular meniscal defects in dogs
  – Control dogs had significantly more articular cartilage damage than grafted dogs
History

• Fox and Arnoczky:
  – SIS disks underwent cellular and extracellular matrix modification resulting in fibrocartilage-like tissue when placed free in dog joints
  – Suggested that SIS scaffolds can support cell attachment and ingrowth in a diarthrodial joint
    – Tissue Eng 2004 Jan;10(1-2):129-37
Glenoid Resurfacing Arthroplasty

Not FDA approved for this application
Glenoid Resurfacing Arthroplasty

Not FDA approved for this application
Dog Glenoid Resurfacing Study
Dog Glenoid Resurfacing Results

- There was significantly less surface erosion (12% VS. 39%, p>0.05%) in the group with SIS resurfacing by 6 months.
- Good remodeling on histopathology assessment was also seen in the SIS group at both 3 and 6 months.
- There were no differences in lameness at 3 and 6 months and no difference in surface erosions at 3 months.
3 months

Control | SIS
6 months

Control (2x)  SIS (10x)
Necropsy photos obtained at 6 months

Control

SIS
Where Are We Going With Soft Tissue Grafts
Concerns:

- Only 1 controlled study
  - Questionable patient selection
- Difficult to prove effectiveness in humans
  - Especially difficult in rotator cuff tears
    - No good studies showing long-term effectiveness in cuff repairs
  - What is a success?
    - No pain
    - Good function
    - Intact cuff on re-imaging

"You WANT proof? I'll GIVE you proof!"
ECM’s in Rotator Cuff Surgery

- 2-year follow-up of 12 patients
- Arthroscopic repair of massive chronic rotator cuff tears
- Restore SIS as an augmentation device.
- MRI scans showed significant thickening of the cuff tendon with the incorporation of the SIS graft in 11 patients
- Clinical failure was observed within 12 weeks with complete resorption of the graft in 1 patient
- No evidence of local or systemic rejection or infection in any patient
- Mean postoperative UCLA score was 19.9 (out of 35)
  - Preoperative 9.9 ($P\leq0.01$)
- Functional improvement in all patients based on Simple Shoulder Test
2 year Canadian Multicenter Study

• Chronic one and two tendon tears
• Within FDA clearance for use
  – No more than mild fatty infiltration
  – No significant retraction
• One year data:
  – Restore patch decreased re-tear rate by at least 25%
  – No significant rejection or hyper-immune responses
ECM’s in Rotator Cuff Surgery

- Sclamberg et al evaluated the use of Restore as an augmentation device in a cohort of 11 patients undergoing open repair of large or massive rotator cuff tears.
- At 6 months postoperatively, MRI scans revealed that 10 of 11 Restore augmented repairs had failed.

Use of Restore Orthobiologic Implant for Agumentation of Chronic Two Tendon Rotator Cuff Tears: A Controlled Randomized Study

Joseph P. Iannotti MD, PhD, Jim Ciccone CRNA, Michael Codsi MD, Young Kwon MD, PhD, Kathe Derwin PhD, John Brems MD

JBJS, 2006
Results

• Prospective, randomized, controlled trial of 30 patients with repairable, large 2-tendon cuff tears

• The unaugmented group was 7% more likely to heal than the Restore augmented group

• The postoperative PENN scores in the unaugmented group (91 points) were also significantly higher than those in the augmented group (83 points) ($P \: .007$)
“Larger Sized Tear”
Moderate to Severe Atrophy: Group II
Problem with these studies

- Restore patch was used in clinical setting contraindicated by the FDA clearance
  - Massive cuff tears with fatty degeneration and retraction
- Is it reasonable to use a graft material in a non-indicated setting and then question its value?
Cellular Hysteria

• Cellular elements
  • Is this functional DNA?
  • What are the chances of cross – species DNA disease transmission versus species specific?
What I Have Learned:

• There is a great deal of misunderstanding about the healing of rotator cuff
  – What is the goal of surgery?
    • A functional muscle unit
• There is great deal of misunderstanding about ECMs
• There has been a great deal of “spin” by the manufacturers
“...there is no such thing as an irreparable cuff...”
Native nerve orientation

Suprascapular nerve

Scapular notch

First motor branch to supraspinatus

3cm retraction

Suprascapular nerve

Scapular notch

First motor branch to supraspinatus

Biology of a Cuff Tear

- Cytokine-mRNAs in the shoulder synovium expressed more significantly in full-thickness tears
- Significant increase in collagenase-3 (MMP-13) mRNA levels
- Decrease in stromelysin-1 (MMP-3) mRNA levels
- Decrease in tissue inhibitor of metalloproteinase-2, -3, and -4 mRNA levels
- Increase in the active form of collagenase-3 (MMP-13) in rotator cuff tendon tears.
Can We Change the Biology?

• In theory, inhibition of collagenases and cytokines should promote healing
• If so, why do nonsteriodal anti-inflammatory drugs decrease healing?
What’s The Point of No Return?

- There are numerous adaptive and “maladaptive” responses to a cuff tear
- These include biological, mechanical and neurological changes
- Some of these make any attempt repair futile
- Repair of these tears need to consider not only the mechanics of the repair but also the biology of the repair
Thank You

Moo-shoe pork
Comparative study of Soft Tissue Scaffolds

- Badylak studied 5 different extracellular soft tissue scaffolds and compared them with an autologous tissue graft
  - GraftJacket – Wright Medical
  - Restore – DePuy
  - TissueMend – TEI Biosciences
  - Permacol – Tissue Sciences
  - CuffPatch – Arthrotek

- Critical abdominal wall defect model
Results – Autologous Graft

- Replaced with poorly organized collagen consistent with scar

A = 1 week
C = 16 weeks
Results – Restore Graft

• Rapidly infiltrated with dense mononuclear cells
• Followed by progressive organization into a mixture of skeletal muscle and organized connective tissue

A = 1 week
C = 16 weeks
Results – CuffPatch

- Prolonged infiltration by mononuclear cells AND foreign body giant cells
- Followed by partial scaffold remodeling into organized connective tissue

A = 1 week
C = 16 weeks
Results – GraftJacket

- Intense cellular infiltrate
- Eventual replacement by partially organized, dense connective tissue

A = 1 week
C = 16 weeks
Results – TissueMend

- Little cellular infiltration
- Eventually surrounded by fibrous connective tissue and adipose tissue

A = 1 week
C = 16 weeks
Results – Permacol

- Remained intact with virtually no cellular infiltration
- Eventually enveloped by a dense fibrous capsule

A = 1 week
C = 16 weeks
Concussion

• Host response to different soft tissue scaffolds will vary based on their composition and processing
• Stronger with less inflammation is not necessarily better