Future Directions in RCR
Facts and Myths

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Anatomic Failure

- Early = Failure to Heal
- Late = Re-Tear
- Multi-Factorial
  - Anchor from bone
  - Suture from tendon
  - Tendon from bone

Anatomic Failure

- 10 – 90%
- Associations
  - #1 Size
  - #2 Chronicity

Pain relief and functional return can occur in the face of anatomic failure

Prevention
Reduced Tension

- Capsular Release
- Side to Side
Prevention

**DR/TOE**

<table>
<thead>
<tr>
<th>Single Row</th>
<th>Double Row</th>
</tr>
</thead>
<tbody>
<tr>
<td>275N-300N</td>
<td>300-350 N</td>
</tr>
<tr>
<td>No footprint</td>
<td>Footprint</td>
</tr>
<tr>
<td>Gap formation</td>
<td>Resistance to shear</td>
</tr>
<tr>
<td></td>
<td>Minimal “gap formation”</td>
</tr>
</tbody>
</table>

**TOE**

<table>
<thead>
<tr>
<th>350-400 N</th>
<th>Footprint</th>
<th>Resistance to shear</th>
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<tbody>
<tr>
<td>Minimal “gap formation”</td>
<td></td>
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</tbody>
</table>

### Intervention

- **ECM Scaffolds**
- **Synthetics**
- **Growth Factors**
- **Other**

### Biologics “101”

- **Normal RC Insertion**
  - Unmineralized FC → Mineralized FC → Bone
- **RC Healing**
  - Fibrovascular Scar
- **Patches** promote material properties
- **GF** improve structural properties
  - Increased cellularity and scar tissue volume at repair site

### Scaffolds

- **ECM Scaffolds**
  - Augmentation not bridge
  - Allograft or Xenograft
  - Architecture
    - Acellular
    - Crosslinked
    - Collagen (Types I,II,III,IV)
    - Elastin
    - CS:PG
    - GF (FGF-2, VEGF)
- **ECM Scaffolds**
  - Allografts
    - GraftJacket™
    - Dermis
    - Freeze Dried
    - SS/IS
    - Fresh Frozen
    - Soft Tissue
    - Allopatch™
      - Fascia Lata

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510K Class II: “Product X is intended for reinforcement of soft tissues that are repaired by suture or suture anchors, during tendon repair surgery including reinforcement of rotator cuff, patellar, Achilles, biceps, or quadriceps tendons”
**ECM Scaffolds**

**Xenografts**
- **Restore®** • Porcine SIS
- Permacol ZCR™ • Porcine Dermis
- TissueMend® • Fetal Bovine Dermis
- CuffPatch™ • Porcine SIS
- OrthoADAPTM • Equine Pericardium

**Synthetics**
- Synthasome RCR Device
  - PLA/PGA
- Artelon® Sport Mesh
  - Polyurethane Urea
- Biomerix RCR Patch®
  - Polyurethane
- Gore-tex

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**Outcomes Pre-Clinical**

**Pre-Clinical Outcomes**

- **Tissue Engineered Rotator Cuff Tendon Using Swine Small Intestine Submucosa in Canines**
  - Dejardin LM, Arnoczky SP, Ewers BJ et al

- **Load (mean ± sd - N)**
  - Control: 0, 3, 6 months
  - SIS: 0, 50, 100, 150, 200, 250, 300

- **Sham**

**SEM image of patch material**

**Collagen fibers from SIS infiltrating patch**

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**Outcomes Pre-Clinical**

- **Polyurethane scaffold mesh in ovine chronic tear**
- **12 weeks post-op**
  - Increased force to failure compared to non-augmented repairs (74.2%)
  - Increased stiffness (55.4%) and global displacement at failure (21.4%)

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**Outcomes Pre-Clinical**

- **Polycarbonate polyurethane patch for RTC repair**
- **Rat RTC repair model (n = 12)**
- **6 weeks post-op**
  - No histologic evidence of an inflammatory reaction
  - Tissue in-growth noted in 79.9% of specimens

**SEM image of patch material**

**Collagen fibers from SIS infiltrating patch**

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**Outcomes Pre-Clinical**

- **Woven poly-L-lactic acid graft in cadaver**
- **Compared to non-augmented repairs**
  - Yield load: 56-92%
  - Ultimate load: 56-76%
  - No change in initial stiffness

**Compared to non-augmented at time zero**
- 23% in ultimate load
- No increase in stiffness
- At 12 weeks post-op augmented repairs had significantly
  - Less retraction
  - Greater cross-sectional area
  - Higher ultimate load (35%)
  - Higher stiffness (28%)
Prospective evaluation of porcine dermal collagen implant to augment massive RTC tear
- 10 patients mean age of 66 years (range 46-80)
- Significant improvements seen w respect to
  - Pain
  - Abduction power
  - ROM
- Post-op Ultrasound/MRI at mean of 4.5 years
  - Intact grafts in 80%
  - 2 cases of graft detachment

Outcomes

Clinical

Implantation of a Polyurethane Patch for RC Repair
Augmentation
Encalada I and Cole BJ

Conclusions

Scaffolds

- Is there a need?
- Biology drives failure
  - NOT A GAP FILLER
- Arthroscopically challenging
- Cost $$
- Data to date…not convincing
- Impossible to recommend one over another

Synthetic and Permanent = Paradigm Shift

Growth Factors

ligand (GF)

recycled degradation

bioactive

nucleus

transcription: DNA → mRNA
translation: mRNA → protein

Time, Dose and Delivery Dependent
Growth Factors

Cytokines that induce mitosis, ECM production, neovascularization, cell maturation and differentiation.

<table>
<thead>
<tr>
<th>GF</th>
<th>Activity Phase</th>
<th>Function</th>
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</thead>
<tbody>
<tr>
<td>IGF-1</td>
<td>Inflammation, proliferation</td>
<td>Promotes proliferation and migration of cells, stimulates matrix production</td>
</tr>
<tr>
<td>TGF-β</td>
<td>Inflammation</td>
<td>Regulates cell migration, proteinase expression, fibronectin-binding interactions, termination of cell proliferation, stimulation of collagen production</td>
</tr>
<tr>
<td>VEGF</td>
<td>Proliferation, remodeling</td>
<td>Promotes angiogenesis</td>
</tr>
<tr>
<td>PDGF</td>
<td>Proliferation, remodeling</td>
<td>Regulates protein and DNA synthesis at injury site, regulates expression of other growth factors</td>
</tr>
<tr>
<td>bFGF</td>
<td>Proliferation, remodeling</td>
<td>Promotes cellular migration, angiogenesis</td>
</tr>
</tbody>
</table>

Growth Factors

Pre-Clinical

- **Animal Models**
  - Acute vs Chronic repair
  - Collagenase
  - Rat RC Overuse (Soslowsky)
  - Traumatic injury (Flatow)

Pre-Clinical

- **Growth factor treated repairs**
  - Stronger with more organized healing
  - rhBMP-12 in a collagen or HA sponge improved healing

Emerging Technology

- **Autologous PRP to enhance tendon healing**
  - **Methods**
    - Rabbit (n=9) tendon stem cell culture w/o PRP
  - **Results (PRP Effects)**
    - TSC proliferation and differentiation into tenocytes
    - Upregulation of tenocyte-specific genes
    - 103%↑ in TGF-b1 and 8-fold↑ in collagen production
  - **Conclusion**
    - PRP may enhance tendon repair by stimulating TSCs to differentiate into active tenocytes

Emerging Technology

- **Type I collagen w rhPDGF-BB for RCR**
  - **Methods**
    - Sheep RCR (n=60)
    - Groups
      - Suture
      - Suture + Collagen + LD/MD/HD rhPDGF-BB
  - **Results**
    - Dose dependent improvement in biomechanics
    - Tendon repair with better interdigitation of collagen with bone
  - **Conclusion**
    - Type I collagen matrix w rhPDGF-BB significantly enhanced RTC repair in a dose-dependent manner
Emerging Technology

- MSCs transduced with Scleraxis (drives tendon and cartilage development) to enhance RCR

Methods

- MSCs vs Scleraxis transduced MSCs in Rat RCR (n=60)

Results

- Increased cartilage formation with Scleraxis
- No differences in collagen organization
- Improved biomechanics

Conclusion

- MSCs expressing Scleraxis helps regenerate FC tendon-bone insertion site during RTC repair

### Blood Derived GF

**Pre-Clinical**

The effect of fibrin clot on healing rat supraspinatus tendon defects

**Clinical**

Comparison of Surgically Repaired Achilles Tendon Tears Using Platelet-Rich Fibrin Matrices

No effect on tendon healing except at 3 weeks where decreased material properties where demonstrated

Coehet of 6 patients w/ RTS quicker and smaller x.s. area of Achilles by U/S compared to cohort w/o PRP

### Blood Derived GF

**Poster 11**

Bone Marrow-Derived Mesenchymal Cells Transduced with Scleraxis Improve Rotator Cuff Healing in a Rat Model

Laurencin C, Quak H, New York, NY; David Kemper MD, Evanston, IL; Jonathan D. Reher MD, New York, NY; Scott A. Nachman MD, New York, NY, NY

**PRP...its much more than platelets**

**Platelets and WBCs The Good and Bad**

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Platelets (fold change)</th>
<th>WBC (fold change)</th>
<th>RBC reduction (%)</th>
<th>Platelet/WBC</th>
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</thead>
<tbody>
<tr>
<td>ACP (Arthrex)</td>
<td>2.3</td>
<td>0.09</td>
<td>99</td>
<td>800</td>
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<tr>
<td>GPS II (Biorx)</td>
<td>8.1</td>
<td>5.4</td>
<td>80</td>
<td>51</td>
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<tr>
<td>PRP Human (Harvest Tech/Symphony)</td>
<td>7.6</td>
<td>2.5</td>
<td>52</td>
<td>61</td>
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<tr>
<td>PRP Equine (Harvest Tech/Symphony)</td>
<td>4.5</td>
<td>1</td>
<td>99</td>
<td>60</td>
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<tr>
<td>Magellan (Medtronic)</td>
<td>7.5</td>
<td>3.2</td>
<td>40</td>
<td>84</td>
</tr>
</tbody>
</table>

* Primarily a function of neutrophils

McCarrel & Fortier, JOR, 2010
Conclusions

Growth Factors

- Goal: improve local biology (FC) at insertion
- Many questions
- Timing
- Carrier
- Cost $$
- Data to date…very little

Other Modalities

Gene Therapy

- In Vivo: Direct injection of the vector
- Ex Vivo: Harvest cells, transduce with vector, re-administer cells into repair site

Other Modalities

Embryonic vs Mesenchymal (Adult) Stem Cells

Embryonic: Totipotent stem cells (pink) are capable of three germ lineages.
Adult: Multipotential progenitors (blue and green) yield multiple limbs within a single germ lineage.

Other Modalities

Gene Therapy

- In Vivo: Direct injection of the vector
- Ex Vivo: Harvest cells, transduce with vector, re-administer cells into repair site

Other Modalities

Sutures dipped in GDF-5 resulted in similar biomechanics with improved histology
Conclusion

So many variables….

- Need
- Cost
- Timing
- Delivery

Ultimate Goal: Reversing the irreversible and normalizing the tendon bone interface creating material property changes in the tendon (and muscle)….we are just not there yet

THANK YOU