What is Regenerative Medicine?
What does it help?
What are the main types of treatments?

Using treatments and biological substances to help a non-healing structure to heal
Stimulates our innate healing response
Changes the biology of the structure treated by bringing blood flow to and activating the body’s healing system (pericytes & platelets)
3 Phases of Wound Healing

- Inflammatory phase (100 Hours)
  - Platelet aggregation and activation of the classical intrinsic coagulation cascade

- Granulation phase (4-5 Weeks)
  - Laying down scar tissue and early collagen formation

- Remodeling phase (4-5 Months)
  - Removing scar tissue and laying down more collagen

What do Regenerative Treatments help?

- Chronic tendinosis/tendonitis
  - Lateral epicondylitis, patellar or Achilles tendonitis

- Osteoarthritis
  - Improves joint biology, decreasing inflammatory cytokines, stimulates cartilage synthesis

- Ligament, fascia and muscle injuries
  - Partially torn soft tissue injuries and muscle tears
**EM - Normal Tendon (A) vs Tendinopathy (B)**

- **Normal**
- **Tendinopathy**
  - ↑ #, disorganization of tenocytes
  - (v) vessel ingrowth

**Lateral Epicondylitis Ultrasound**

- Thickening and hypoechoic loss of collagen
- High grade partial tear
- Neovascularization on Doppler
- Normal contralateral tendon

**Rotator cuff (Supraspinatus) tendinosis**

- Tendinosis w/ increased signal on T2 weighted MRI
- MSK Ultrasound
- Tendinosis w/ hypoechoic thickening & neovessels
MRI VS US IMAGING

Patellar Tendonitis (Tendinosis) Jumper’s Knee

- Long Axis view
- Short Axis view

Hypoechoic fusiform thickening w/ Neovascularization

Achilles Tendonitis (Tendinosis)

- Long Axis view
- Short Axis view

Hypoechoic thickening w/ vertical Interstitial Split Tear

Superiority of Ultrasound vs Landmark Based Injections

- Multiple studies demonstrate significantly improved accuracy of injection
- Many studies demonstrate significantly improved clinical outcomes
- Studies show improved patient satisfaction with Ultrasound compared to blind/fluoro guided injections

-AMSSM Position Paper on Interventional Ultrasound - 2014
What do Regenerative Treatments help?

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OA Definition

"Osteoarthritis is a disorder involving movable joints characterized by cell stress and extracellular matrix degradation, induced by micro- and macro-injury that activates multiple tissue repair responses including pro-inflammatory pathways to innate immunity. The disease manifests first as a molecular rearrangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function) that can culminate in illness."

What techniques/substances are used?

- Physical medicine, strengthening, eccentrics
- Needle tenotomy/fenestrations
- Dextrose Prolotherapy
- Platelet Rich Plasma
- Amniotic Membrane and Cells
- Autologous Stem Cells
  - Bone marrow, lipoaspirate

<table>
<thead>
<tr>
<th>Biologic Tx</th>
<th>ECM/Scaffold</th>
<th>Growth Factors</th>
<th>Pluripotent cells</th>
<th>Limitations</th>
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</thead>
<tbody>
<tr>
<td>Dextrose Prolo</td>
<td>None</td>
<td>++</td>
<td>No, may recruit</td>
<td>- Conc ≤ 25%</td>
</tr>
<tr>
<td>PRP</td>
<td>Single layer fibrinogen scaffold</td>
<td>++</td>
<td>++, +++</td>
<td>- No ECM/stem cells</td>
</tr>
<tr>
<td>Bone Marrow Aspirate</td>
<td>Single layer fibrinogen scaffold</td>
<td>++</td>
<td>++, +++</td>
<td>- Variability</td>
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<tr>
<td>Lipoaspirate</td>
<td>Complex adipose ECM structure</td>
<td>++</td>
<td>+, +, ++</td>
<td>- Thin scaffold, - invasive</td>
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<tr>
<td>Amniotic Tissues (cryopreserved)</td>
<td>Complex ECM structure</td>
<td>+++, ++++</td>
<td>?-+</td>
<td>- Cost, - Variability, - Small volumes</td>
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<tr>
<td>Amniotic Tissues (dehydrated)</td>
<td>Complex ECM structure</td>
<td>++, ++++</td>
<td>No, may recruit them</td>
<td>- Cost, - Small volumes, - No stem cells</td>
</tr>
</tbody>
</table>

Dextrose Prolotherapy

- 10-25% dextrose solution

Effects:

- Hyperosmolar/irritative effect
- Nerve calming effect
- Increases Growth Factors involved in healing of cartilage, tendon &ligament (alters DNA)
  - PDGF, TGFβ, bFGF, IGF
Platelets contain many clotting and growth factors that stimulate the healing process. Once activated, platelets change shape and develop branches that spread over injury. Growth factors are released which initiate cellular healing and recruit stem cells. PRP shown to be effective when platelets are concentrated at least 2-3x baseline.
Platelets
- Activated by Thrombin & Collagen

How do you get PRP?
- Various systems (1 or 2 spin systems)
- 30-60 cc venous blood draw from patient
- Centrifuge patient's blood 5-10 minutes

Images c/o Emcyte Corporation

Regenerative Injections
- Can use Ultrasound or Fluoroscopy
### Meta-analysis: PRP and degenerative cartilage lesions

<table>
<thead>
<tr>
<th>Level</th>
<th>PRP and HA comparison</th>
<th>Outcome 6 m</th>
<th>Complications</th>
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<tbody>
<tr>
<td>1</td>
<td>PRP vs HA</td>
<td>WOMAC</td>
<td>None observed</td>
</tr>
<tr>
<td>2</td>
<td>CaCl2-activated P-PRP or HA</td>
<td>Reduced pain</td>
<td>Mild, evenly distributed</td>
</tr>
<tr>
<td>3</td>
<td>Single or twice leukocyte-filtered PRP injection</td>
<td>Improved WOMAC</td>
<td>Self-resolved nausea and dizziness</td>
</tr>
</tbody>
</table>


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### Human Amniotic Membrane (HAM) and Amniotic Fluid cells

- **Immunoprivileged tissue donated at C-section**

- **HAM/Umbilical Cord Tissues:**
  - Rich extra-cellular matrix, heavy chain hyaluronan
  - Abundant growth factors
  - Anti-inflammatory/anti-fibrotic cytokines

- **Amniotic fluid/Cord blood cells (similar to MSCs):**
  - Amniotic epithelial cells (AECs)
  - Amniotic mesenchymal stromal cells (AMSCs)

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### Amniotic Tissue Evidence

- **KL Grade 1-3 Knee OA**
  - Single injection of cryopreserved amniotic suspension vs HA vs saline

- **KOOS and VAS scores superior in amniotic group compared to HA after 3 months and saline after 6 months**
  - Jack Farr, presented at TOBI 2018. At publisher
**Mesenchymal Stem Cells**
- Lipoaspirate and Bone Marrow derived

- Orchestrate healing response
  - Heal bone, cartilage, ligament, tendon tissues
  - via GF's and cell signaling after macrophage ingestion
- Anti-inflammatory/immunomodulatory effects
  - Respond to catabolic inflammatory environment, release cytokines, proteins to ↓ inflammation
  - Restore TH1/TH2 and M1/M2 ratios
- Anti-apoptotic effects
  - Rescues apoptic cells via growth factors & cytokines
- Anti-microbial effects

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**MSCs from Pericytes: “vessel huggers”**
- in response to environment, cell signaling following trauma

- After re-establishing a “healed” micro-environment, MSC returns to pericyte form, attached to local vessels

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**Evidence for Bone Marrow Aspirate in Knee OA**

- Bone Marrow + Platelet Products vs PT for knee OA
  - 48 pts, KSS, VAS, LEAS scores
  - BMA + Platelet Products superior to PT
- Bone Marrow + PPP vs Saline in pts w/ bilat knee OA
  - 25 pts, OARSI and VAS scores
  - 6 and 12 month f/u scores showed no sig diff b/w knees. Both knees were doing very well.
    - Shapiro et al, Cartilage. 2018 Aug 30:1947603518796142
Orthopedic injuries can heal in 3-4 months
If failing after 3-4 months, consider Regen Med

HAM and MSC’s have a limited but growing body of evidence
Dextrose Prolotherapy and PRP have Level 1 and Level 2 evidence for OA & tendinopathy
Ultrasound guidance is key to accurate diagnosis, treatment & optimal outcomes

Questions?

![Image]