If you are viewing this course as a recorded course after the live webinar, you can use the scroll bar at the bottom of the player window to pause and navigate the course.

This handout is for reference only. It may not include content identical to the PowerPoint. Any links included in the handout are current at the time of the live webinar, but are subject to change and may not be current at a later date.
Regenerative Medicine for the Musculoskeletal System

Matthew Vogt MD, David Hunnius DO

SMaRT
The Sports Medicine and Regenerative Therapeutics Institute
Regenerative Medicine

Why?

Joint Replacement – Astronomical cost

- 700,000 knee replacements in the U.S. each year and climbing
- 300,000 hip replacement surgeries [CDC]

- $55,000 avg cost for TKR - 2015
- $40,000 for THR – 2015
Joint Replacement – 10 Common Risks

1. Unrelieved chronic pain
   - 90% of patients believe they will have no pain after joint replacement
   - > 54% still have pain 5 years after knee replacement [Metsna]
   - 44% of TKR and 27% of THR patients still have pain 3-4 years after surgery [Wylde]
   - 15% TKR and 6% THR patients with severe pain 3-4 years after surgery [Wylde]

2. Activity levels lower than expected
   - Most joint replacement patients do not return to levels of activity shown in marketing ads
   - Many patients no more active than they were prior to surgery [Harding]

3. Heart Attack and Stroke Risk
   - Age 60 and over are 26x more likely to experience heart attack within two weeks following THR [Lalmohamed]
   - 31x more likely (MI) after TKR
   - Stroke risk increased 400-500%
Joint Replacement – 10 Common Risks

4. Blood Clots – DVT

5. Metal Ions in the Blood
   Wear particles particularly from metal on metal devices can lead to toxicity from heavy metals – chromium and cobalt [Catelas]
   [Friesenbichler]
   Several hip device manufacturers have undergone major recalls due to findings of heavy metal ions in the blood [Smeekes]

6. Allergies to Prosthetic Joint
   Allergies to metals contained in the components
   Having any allergy (such as pollen, cat dander) tied to increased pain/inflammation presumably due to hyperactive immune system [Hinarejos]

7. Bleeding stomach ulcers
   - Six fold increase lasting 12 weeks post op THR
   - 2-3 times increase in TKR lasting 6 wks [Lalmohamed]

8. Hip Fracture following knee replacement
   - 4% increase in hip fracture risk during 10 years following knee replacement
   [International Osteoporosis Foundation]
Joint Replacement – 10 Common Risks

9. Knee and Hip misalignment following Hip replacement
   - May affect walking, function, ankle, spine [Akiyama]

10. Complications in Smokers
    - 53% greater risk of infection
    - 161% greater risk of stroke
    - 34% greater risk pneumonia [Singh]

Regenerative Medicine

- Tissue engineering followed by reimplantation
- Regeneration of tissue in-vivo
Regenerative Medicine

- Tissue engineering in vitro with subsequent reimplantation
  - ACI – Autologous Chondrocyte Implantation
  - Cultured cartilage cells
    - Cartilage biopsy
    - Cartilage cells cultured (expanded)
    - Defect debrided
    - Reimplantation of cells
    - Return to activity 9-12 months
      - CARTICEL (no longer available June 30th, 2017)
      - MACI

Regenerative Medicine

- Regeneration of tissue in vivo
  - “You are ALIVE because you continuously renew (rejuvenate) various tissues/organs. Within the body, cells of the skin, gut, and blood, among others come to maturation, function for a time and then expire to be replaced by a continuous stream of cells which renew the tissue.”
  - “In every tissue in which this rejuvenation process occurs, a source exists which gives rise to these differentiated cells. The source is called a STEM CELL. Such a stem cell divides to produce like stem cells, some of which enter into a pathway of development and differentiation resulting in an end-phenotype which produces highly specialized molecules and/or functions and then, after a time, expires.”

Arnold Caplan PhD
Case Western Reserve
Regenerative Medicine

- **Mesenchymal Stem Cell**
  - MSC gives rise to:
    - Bone forming cells
    - Cartilage forming cells
    - Tendon
    - Ligament
    - Fat
    - Dermis
    - Connective tissue such as stromal tissue found in bone marrow

Continued

Mesenchymal Stem Cell

- **MSC**
  - Tissues are always regenerating
  - Pericytes (cells on capillaries and microvessels)
    - Sit on every single blood vessel in the body
    - Take on different morphology depending on tissue type
    - Injury ➔ Pericyte comes off vessel ➔ MSC ➔ activated MSC ➔ regenerative MSC
Pericytes: cells on capillaries and micro vessels. ALL MSCs are PERICYTES!
Mesenchymal Stem Cells

- "Stem Cells" infers that patients will receive direct medical benefit
  - Patients imagine that these cells will differentiate into the regenerating tissue-producing cells resulting in a cure

- Mesenchymal Stem Cells: Time to Change the Name!
  - MSCs ➞ "Medicinal Signaling Cells"
  - "More accurately reflects the fact that these cells home in on sites of injury or disease and secrete bioactive factors that are immunomodulatory and regenerative, meaning that these cells make therapeutic drugs that are medicinal. It’s the patient’s own site-specific and tissue-specific resident stem cells that construct the new tissue as stimulated by the bioactive factors secreted by the exogenously supplied MSCs."
Medicinal Signaling Cells

- MSCs can be isolated from every vascularized tissue
- Each separate tissue-specific stem cell is both in communication with its underlying vascular endothelial cells and neighboring specific pericyte/MSC.
- All pMSCs have both MSC-common and MSC-unique chemical and functional features
- In vitro MSCs of marrow are induced into chondrogenic lineage by TGF-B
- In vitro MSCs of fat require both TGF-B and BMP-6.

Cytokines

- Small secreted proteins having specific effects on interactions and communications between cells
  - Pro-inflammatory
  - Anti-inflammatory

Growth Factors

- Naturally occurring substance capable of stimulating cellular growth, proliferation, healing, and cellular differentiation, sometimes used interchangeably with term “cytokine”
- Act as signaling molecules between cells
  - Cytokines
  - Hormones
- Implies positive effect on cell division
  - BMPs – stimulate bone and cartilage cell differentiation
    - BMP 3 induces bone formation
    - BMPs 5 and 6 performs functions in cartilage development and joint integrity
  - VEGF – stimulate blood vessel differentiation
  - FGF – involved in angiogenesis and wound healing

Interventional Orthopaedics and Regenerative Medicine

- Precise image guided injections consisting of material or tissue that can facilitate healing of bone, tendon, ligaments, muscle, or cartilage.
Interventional what?

- Interventional Cardiology
  - Non-surgical techniques to diagnose and treat certain heart conditions
  - Catheter based therapies
    - Balloon angioplasty, intracoronary stent deployment, valvuloplasty, atherectomy
    - First coronary angioplasty 1977, Zurich, Switzerland
    - By 1990 angioplasty became more common than coronary artery bypass surgery (CABG)
- Interventional Radiology
  - At least 3 diagnostic and 22 therapeutic categories of procedures
    - Angiography, biopsy
    - Stents, aneurysm repair, embolization, dialysis interventions, vertebroplasty
    - First needle access arteriograms 1950s
    - 1980s specialty begun transition from diagnostic model to therapeutic

Interventional Orthopaedics and Regenerative Medicine

- PRP – Platelet Rich Plasma
- BMAC – Bone Marrow Aspirate Concentrate
- LIPOGEMS – Adipose tissue
- ALMI – autologous lipocyte micronized injection
- Amniotic membrane tissue graft
- Umbilical cord matrix (Whartons Jelly)
- Umbilical cord blood (UCB) derived allograft
Interventional Orthopaedics

- Degenerative joint disease
- Rotator cuff and other partial tendon tears
- Ligament tears (ACL, UCL)
- Chronic plantar fasciitis
- Chronic epicondylitis
- Achilles tendinosis
- Disc disease, facet joint arthropathy
- Muscle tears

MSK Ultrasound
MSK Ultrasound - supraspinatus

Hip ultrasound
Knee ultrasound – medial meniscus

- Right knee antemedial meniscus extension and hypersensitive area with criss-cross sign of meniscus for partial tear.
- Right knee medial meniscus with hyperemic meniscus retracted in joint space with visible stress.

Knee ultrasound - effusion

- Right knee suprapatellar pouch with needle visualized within effusion.
- Right knee suprapatellar pouch with yellow viscus effusion drainage.
Platelet Rich Plasma

**PLATELETS RELEASE GROWTH FACTORS**

- **PDGF** (Platelet derived growth factor)
  - Cell growth, new generation and repair of blood vessels, collagen production

- **EGF** (Epidermal growth factor)
  - Promotion of epithelial cell growth, angiogenesis, promotion of wound healing

- **KGF** (Keratinocyte growth factor)
  - Growth and new generation of keratinocytes

- **VEGF** (Vascular endothelial growth factor)
  - Growth and new generation of vascular endothelial cells

- **TGF-B** (Transforming growth factor beta)
  - Growth of epithelial cells, endothelial cells, promotion of wound healing
Platelet Rich Plasma

- 4-6x concentration
- Used for smaller tendon and ligament injuries
- Used in conjunction with micronized adipose or BMAC in DJD or large tendon injuries
- May repeat in 12 weeks if needed (booster)

---

Platelet Rich Plasma - Epicondylitis

- **Efficacy of Platelet-Rich Plasma for Chronic Tennis Elbow**
  
  A Double-Blind, Prospective, Multicenter, Randomized Controlled Trial of 230 Patients
  
  
  - 230 patients, at least 3 months of symptoms, failed conventional therapy
  - 116 tendon needling with PRP
  - 114 tendon needling alone

- Outcome: At 24 weeks PRP treated patients reported 71.5% improvement in pain score compared to 56% improvement in control group. No significant complications in either group.
Platelet Rich Plasma – Plantar Fasciitis

  - 60 heels, intractable plantar fasciitis
  - Failed conservative therapy

- Outcomes:
  - PRP as effective as steroid at 3 and 6 months
  - At 12 months PRP is significantly more effective than steroid

Bone Marrow Aspirate Concentrate

- Rich source of MSCs and thought to have greater potential to regenerate cartilage in OA and chondral defects
Bone Marrow Aspirate Concentrate


- 3 studies investigated efficacy of BMAC in OA
- 8 studies investigated efficacy in chondral defects
- All studies reported good to excellent overall outcomes with use of BMAC

Lipogems

- Advantages to using adipose:
  - Nobody seems to mind a mini liposuction
  - Easily accessible and easy to obtain
  - Many supportive and reparative cells that help promote a healing environment (many pericytes)
  - Fat maintains reparative properties (bone marrow may lose healing capacity with age)
  - 500-2500 times the number of MSCs than in marrow
Carried out in one surgical step (in office procedure)
Maintains stromal vascular niche containing mesenchymal cells and pericytes
Non-expanded microfractured adipose tissue for autologous use
Currently involved in over twenty clinical studies
Our Experience

- ACL tears
- Degenerative joint disease – hip and knee
- Rotator cuff tears
- Peroneal tendon tear and midfoot OA

- All excellent outcomes thus far in combination with physical therapy
  - Return to PT usually within 2 weeks
  - Typically see decreased pain within two weeks
  - Return of satisfactory pain relief and function within three months
  - Return to sport?

ALMI (autologous lipocyte micronized injection)

- Similar to Lipogems
- Less adipose tissue harvested
- Adipose micronized by passing tissue through filters connected to syringe
- Clinical studies underway
Amniotic membrane allograft

- Amniofix (MiMedx), Clarix Flo (Amniox)
  - Dehydrated amniotic membrane allograft
  - 226 different growth factors, cytokines, enzymes
    - TGF-B, FGF, PDGF AA & BB
  - Covered by BCBS – IL
- Our experience
  - Knee, shoulder, hip, midfoot, CMC joint osteoarthritis
  - Plantar fascial tear/plantar fasciitis
  - epicondylitis

Umbilical Cord Tissue Matrix

- Predictive Biotech – Corecyte
  - Cryopreserved stem cells from Whartons Jelly of the umbilical cord
  - Consider for patients 65+
  - Consider for patients with comorbidities – diabetes, chronic conditions
  - Use w/ PRP or use to augment Lipogems procedure
  - Stem cells are immune privileged – no concern for adverse reaction
- Our experience
  - Knee OA, lateral hip degenerative tendon tears – Excellent outcomes
What does the FDA say?

- Minimally manipulated tissue only
  - Cannot culture and expand cells
  - Unable to use enzymatic separation with adipose tissue processing
    - Mechanical processing only

Good candidates for regenerative therapies?

- Any patient interested in avoiding surgery
- Any patient where plateau is reached or has slow progression in PT
  - Epicondylitis
  - Plantar fasciitis
  - Rotator cuff tear
- Joint replacement candidates - Knee, Hip, Shoulder, CMC joint
- Partial or minimally-retracted tendon tears
- Ligament injuries
- Spine – facet arthritis, disc disease
Why SMaRT?

- Primary focus is Interventional Regenerative Orthopaedic Medicine
- Affiliated with BlueTail Medical Group – Dr. David Crane
  - National group of affiliated clinics interested in best practices
- Utilization of insurance covered procedures when able
- 45-60 minutes with new patients, MSK ultrasound
- Established relationships with therapists and other providers
- Outcome tracking
- Nutritionist on staff
- Accessible

What’s next?

- Can total joint surgery be avoided altogether?
- Nutrition – anti-inflammatory diet
- Hormone replacement therapy?
- Supplementation – Omega-3, Curcumin, ASU
- Earlier treatment?
Cost – single joint stem cell procedure

- Nationally – $4K-10K
- Large joint - $3500-$5500
- Small joint - $2300-$4400

- PRP - $990
- Amniofix/Clarix Flo – covered by BCBS-IL
  - $1500-$3200

Questions?