Practical Use of Growth Cells in Athletics

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Introduction

- Objectives:
  - Define Growth Cells/Biologics
  - Define types of Growth Cells Available
  - Tendon and Ligament Healing
  - The problem
  - Discuss Clinical Uses of Growth Cells
  - Further Understand Dehydrated Human/Chorion Membrane

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Intoduction

- Definition of Biologics:
  - Composed of Sugars, Proteins or Nucleic Acids or combinations of these substances OR may be living entities such as cells or tissues
  - Isolated from natural sources (human, animal, microorganism) OR produced by biotechnology methods
  - Biologics are complex mixtures that are not easily identified or characterized - Unlike most drugs that are synthesized and have known structures
  - Tend to be heat sensitive and prone to microbial contamination and therefore must be processed aseptically

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Introduction

- Continually trying to improve outcomes
- Biologic manipulation f the healing tableau
- Optimally achieve tissue regeneration not healing by “scar”
- Growth Factors, Cytokines, Stem Cells

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The Problem

- Healing of acutely injured tissue
- Healing of chronically degenerative tissue
- Restoration of complete strength and functionality
- More rabid and robust healing response

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The Problem

- Current Strategies to Augment Healing
  - Growth Factors
  - Stem Cells
  - Growth Factors with Stem cells
  - Tissue Scaffolds

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Types of Cells

- Definition of Growth Cells
  - Progenitor Cells
    - STEM Cells
      - Mesenchymal STEM Cells (MSCs)
    - Growth Factors
  - Embryonic STEM Cells (ESCs)
    - Autograft – Controversial – Obtained from embryo in first stages
      - Ethical Issueas
      - Oncogenic potential – Teratomas, etc
    - Allograft – from Placental membrane

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Types of Cells

- Sources of STEM cells
  - Autologous vs Allogenic
  - Adult, Embryonic, or Induced Pluripotent Cells
  - Native vs Culture expanded
- Sources of STEM cells
  - Bone Marrow
  - Adipose Tissue
  - Embryonic

Growth Factors

- Proteins that bind on a cells surface stimulating cellular growth proliferation, healing, and differentiation
- Growth Factor implies a positive effect on cell division
- Cytokines are a class of signaling protiens used for signaling communications
- Cytokine is a neutral term with respect to whether a molecule affects proliferation
  - Some cytokines can be growth factors, such as G-CSF and GM-CSF
  - Some cytokines have an inhibitory effect on cell growth or proliferation, such as Fas ligand (cause target cells to undergo programmed cell death)

Growth Factors

- Tendon Injury increases production of growth factors
- Early phases of healing
- Increases cell activity and tissue volume
- Increases cell migration
- Increases mitogenesis
- Increases collagen production

Growth Factors

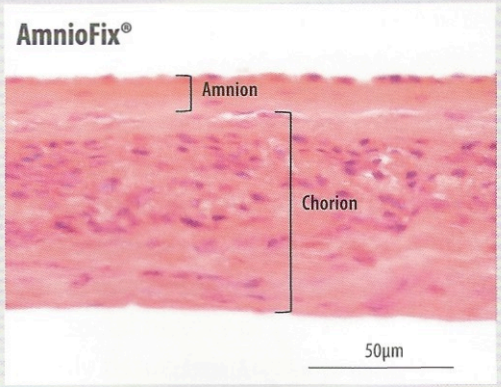
- Sources of Growth Factors:
  - Dehydrated human Amnion/Chorion membrane (dHACM)
    - Tissue Allograft
    - Laminated layers from donated human placenta
    - Non-viable cells with intact extracellular matrix
      - Contains Collagens I, III, IV, V and VII
      - Contains laminin, fibronectin and proteoglycans
    - Retains Growth Factors, cytokines, interleukins
  - PRP

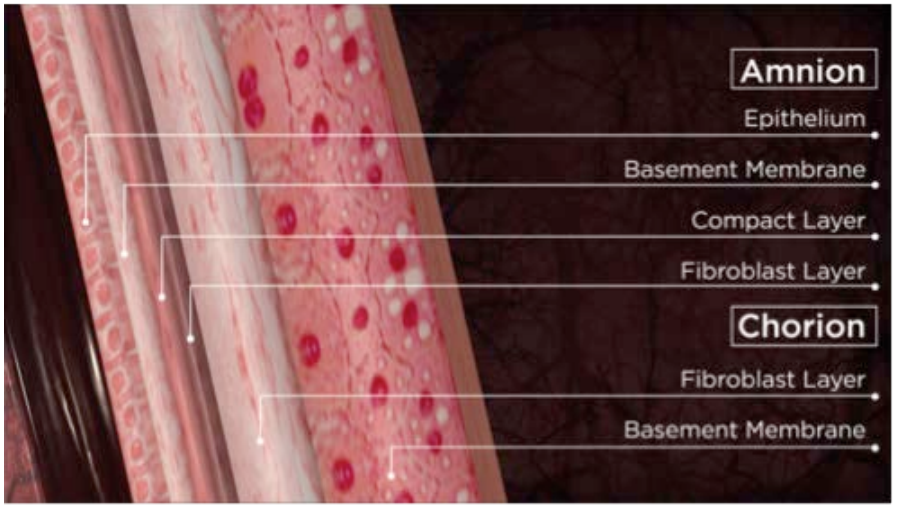
dHACM - AmnioFix

FIGURE 1 Micrograph of Hematoxylin and Eosin (H&E) stained cross section of AmnioFix®, with cell nuclei.

Amnion
Structural Proteins – Collagen I, III, IV
Cell-binding Domains – Fibronectin, Collagen V, VII
Growth Factor Binding – Proteoglycans, Laminin

Chorion
Structural Proteins – Collagen I, III, IV; Elastin Fibers
Cell-binding Domains – Fibronectin, Collagen V, VII
Growth Factor Binding – Proteoglycans, Laminin





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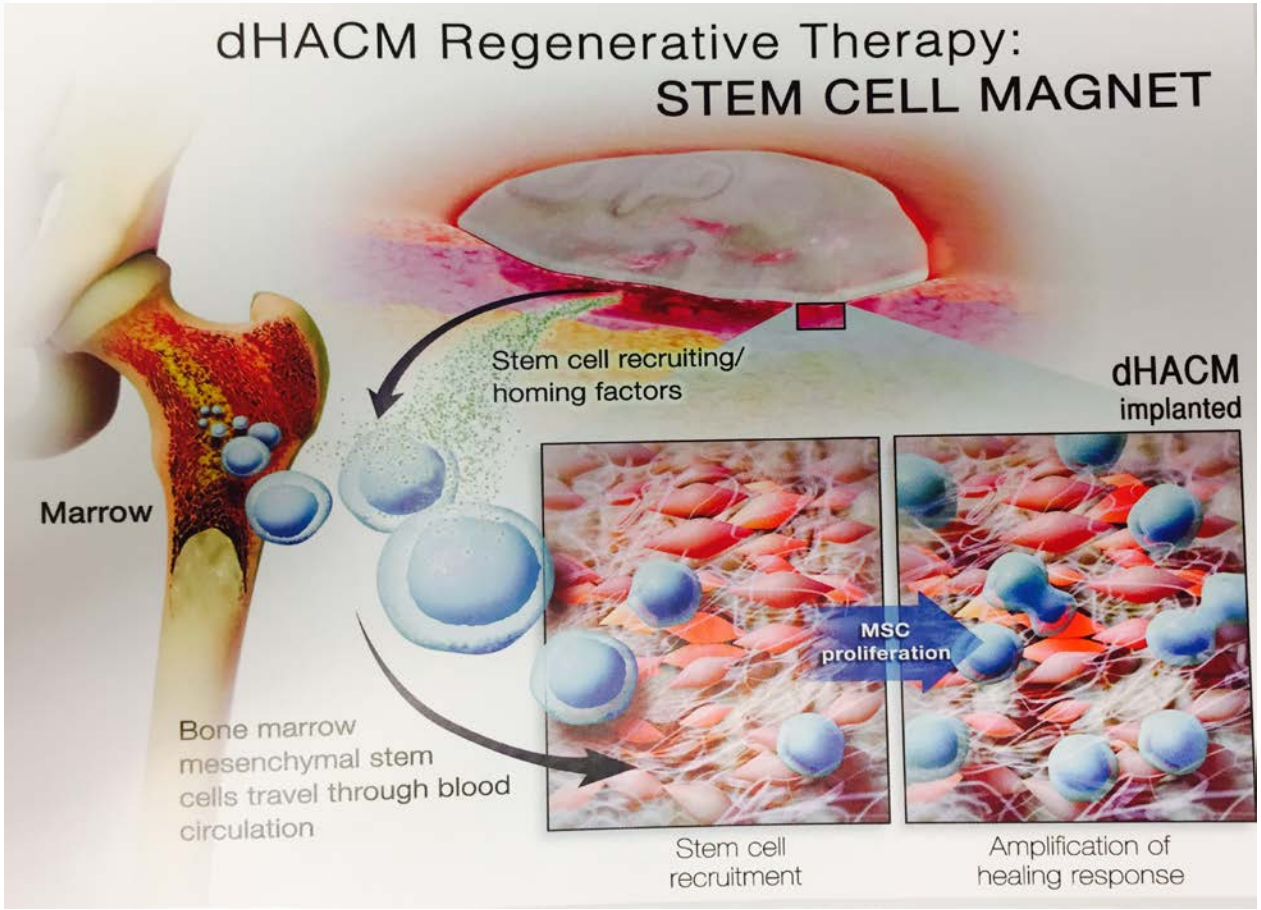

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dHACM

- Properties of dHACM
  - Immune privileged
  - Reduces Inflammation
  - Reduces Scar Tissue Formation
  - Mediates Tissue Repair
  - Antibacterial properties
  - Hemostatic properties
  - Pain Reduction properties

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dHACM

- Our focus for today's discussion
  - Dehydrated Human Amnion/Chorion Membrane
    - AmnioFix Injectable (40mg, 100mg)
    - AmnioFix Injectable used as a paste
    - AmnioFix Injectable used as a powder
    - AmnioFix Sheets/Membranes (multiple sizes)
    - AmnioCord – Thicker, derived from umbilical cord
      - 2 x 3 cm, 3 x 5 cm

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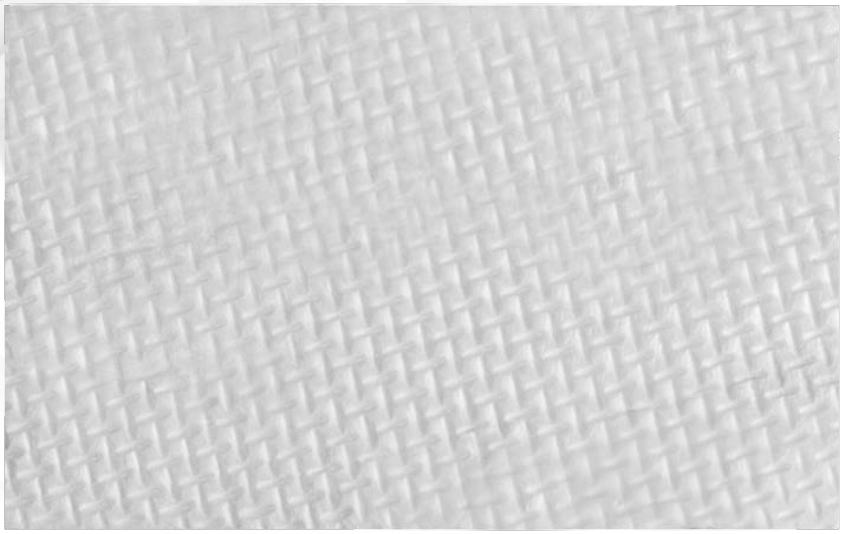

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dHACM

- dHACM Uses in Orthopedics:
  - Cartilage Defects (paste and amniocord)
  - Bone union/non-union (paste)
  - Tendon Repairs (wrap/injectable)
  - Tendonopathy/Partial Tendon Tears (injectable)
  - Tendonitits (injectable)
  - Other Itis's (Fasciitis)

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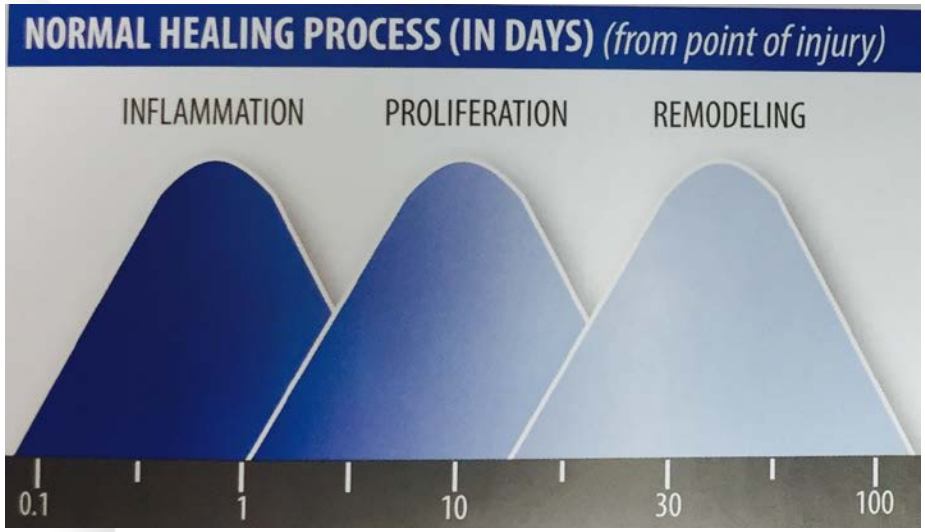
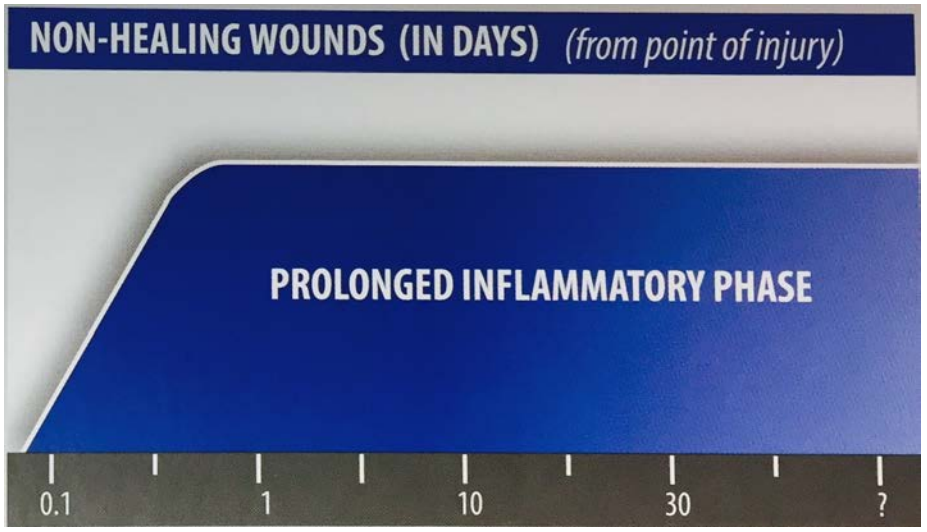
Stages of Healing





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Ligament Healing

- Phases of Healing
  - Inflammatory Phase
    - Occurs at days 1-7
    - Influx of neutrophils and macrophages
    - Production of type III collagen
    - Growth Factors
      - TGF-β1
      - IGF
      - PDGF
      - BMPs -12 and -13
      - bFGF

Ligament Healing

- Phases of Healing
  - Proliferation Phase
    - Occurs at 7-21 days
    - Gradually replaced by type I collagen
    - Tendons and ligaments are weakest at days 5-21
  - Remodeling Phase
    - Occurs at >14 days
  - Maturation Phase
    - Up to 18 months

Ligament Healing

- Factors that Impair Healing
  - Intra-articular
  - Increasing age
  - Immobilization
  - Smoking
  - NSAIDS
  - Diabetes
  - Alcohol intake
  - Decreased Growth Factors
  - Decreased expression of genes involved with tendon and ligament healing

Ligament Healing

- Factors that Improve Healing
  - Extra-articular
  - Compromised immune response
  - Mesenchymal stem cells
  - Growth Factors
  - Scaffold to help primary ligament healing
  - Neuropeptides

Tendon Anatomy

- Composition
  - Water
  - Collagen
    - Type I makes up 85% of dry weight
    - Type II make sup 0-5% of dry weight
  - Proteoglycans
    - Makes up 0-5% of dry weight
    - Decorin
      - Most predominant proteoglycan in tendons
      - Regulates collagen fiber diameter
    - Aggrecan
      - Found in areas of tendon compression

Tendon Healing

Hemostasis	**Platelets initiate coagulation cascade Fibrin clot and fibronectin interaction leading to chemotaxis to stabilize torn tendon edges**	**5-15 minutes**
Inflammation	**Fibroblasts produce type III collagen Macrophages help initiate healing and remodeling**	**1-7 days**
Organogenesis	**Tissue modeling via large amounts of disorganized collagen and angiogenesis**	**7-21 days**
Remodeling	**Tissue remodeling replacing type III collagen to type I collagen**	**Up to 18 months**

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Tendon Surgical Repair

- Strength following repair
  - Tendon repairs are weakest at 7-10 days
  - Most of strength by 21-28 days
  - Maximum strength at 6 months
    - Final strength only reaches 2/3 of normal even after years
- Early mobilization
  - Allows earlier ROM but decreased tendon repair strength
  - Beneficial for the flexor tendon healing to prevent adhesion formation

Pathology

- Definitions:
  - Tendonpoathy
    - Failed Healing or Repetitive Trauma/Microtrauma
  - Tendonitis
    - Acute Injury
    - Inflammation

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Pathology

- Most Common Tendon Injury
  - Rotator Cuff
  - Achilles Tendon
  - Posterior Tibialis
  - Patellar Tendon

Practical Uses

- Wound Healing
- Tendon Healing
- Cartilage Repair
  - Inherently low cellular activity
  - Avascularity
  - Limited regenerative capacity
  - Fibrocartilage (short term fix)

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Practical Uses

- Non-surgical
  - Osteitis Pubis
  - Lateral Epicondylitis
  - Hamstring Injury
  - Chronic Tendonopathies
  - Acute Ligament Injury
  - Osteoarthritis
  - Plantar Fasciitis

Practical Uses

- Surgical
  - Tendon Repair
    - Rotator Cuff
    - Achilles
    - Hamstring
    - Quadriceps and Patella
    - Posterior Tibialis
  - ACL Reconstruction
  - Meniscus Repair
  - Cartilage Repair

Practical Uses-Surgical

- Peroneal Tendon Repairs – AmnioFix Sheet and Injectable

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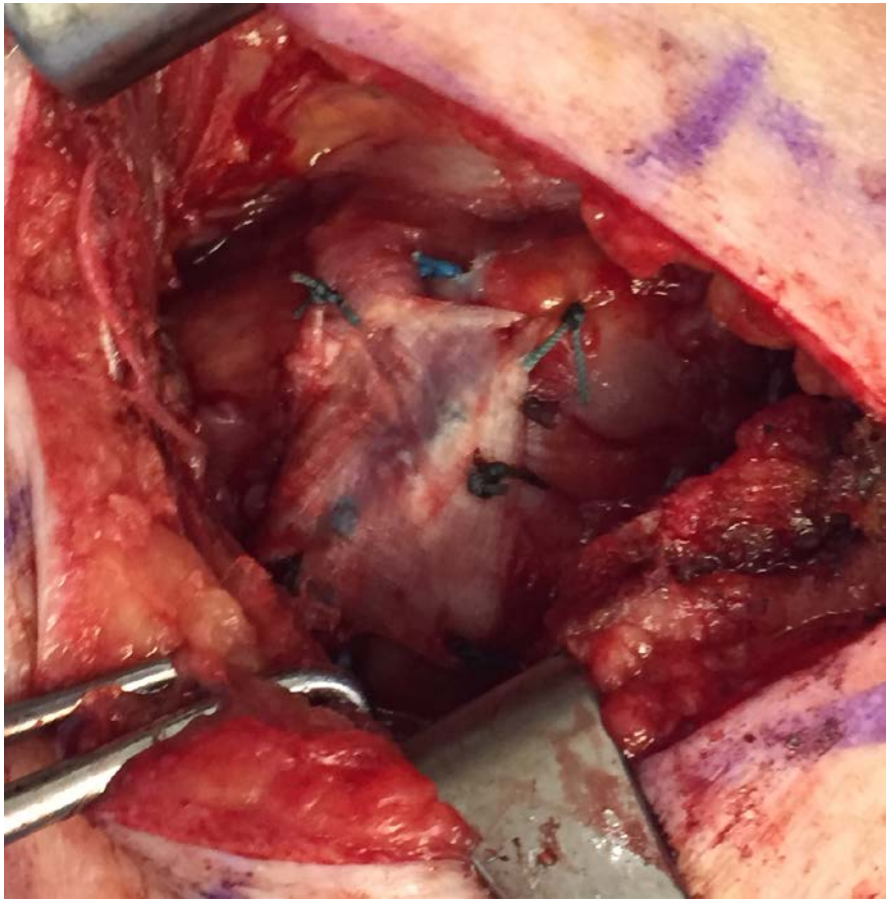
Practical Uses-Surgical

- Rotator Cuff Repairs - AmnioCord



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Practical Uses-Surgical

- Achilles Tendon Repair – AmnioFix Sheet

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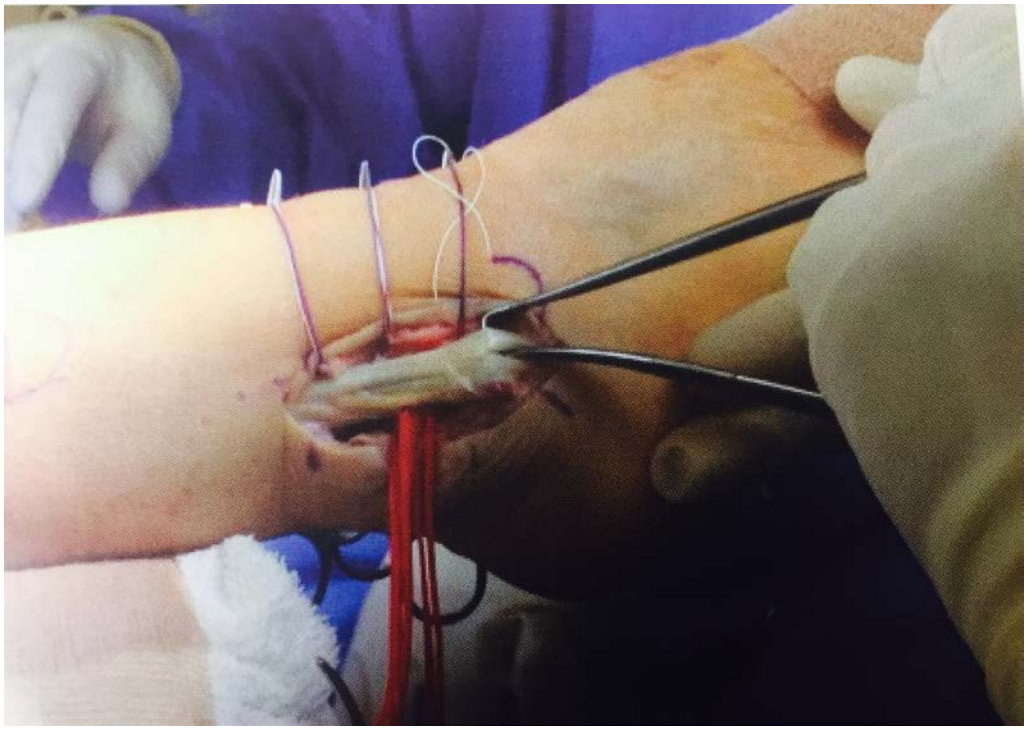
Practical Uses-Surgical

- Peroneal Longus Tendon Repair – AmnioFix Sheet



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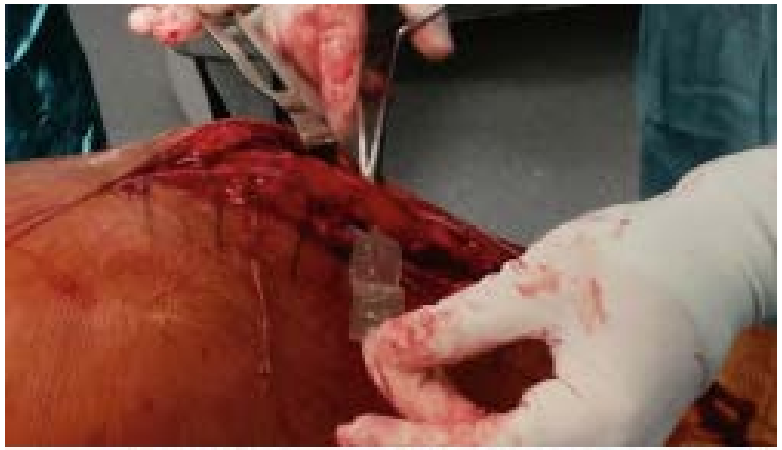
Practical Uses-Surgical

- Patellar Tendon Repair



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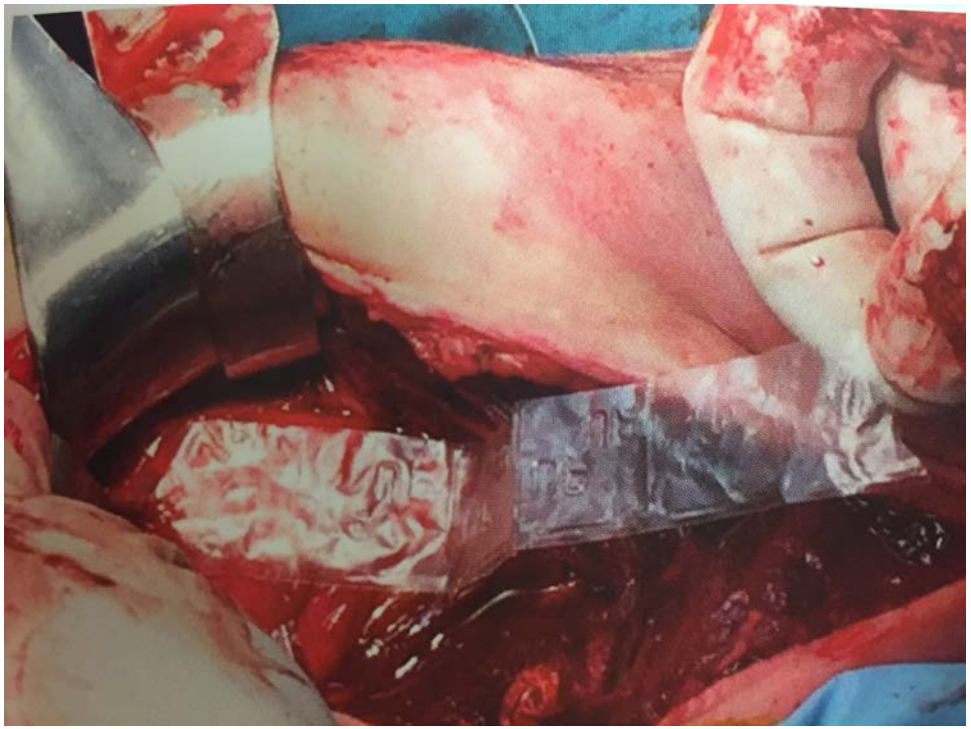
Practical Uses-Surgical

- Total knee Arthoplasty –Extensor Mechanism



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Practical Uses-Surgical

- Chondral Injuries

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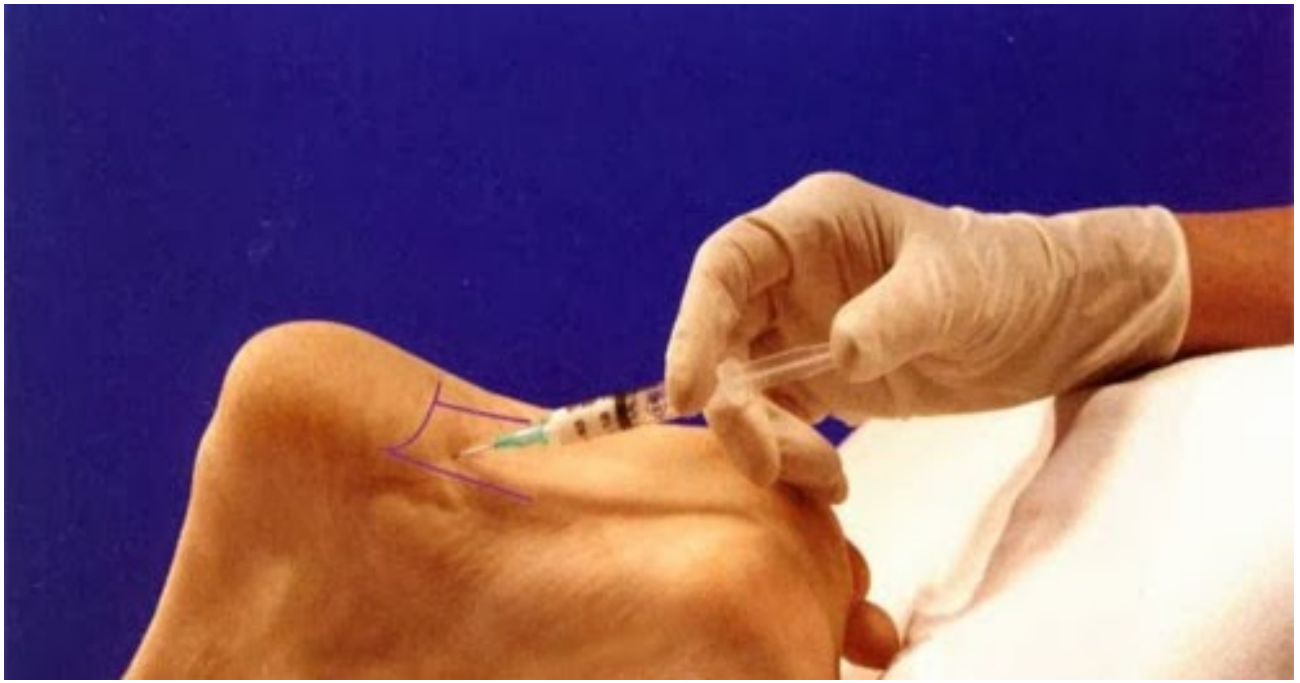
Practical Uses – Non-surgical

- Plantar Fasciitis



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Practical Uses – Non-surgical

- Achilles Tendonopathy

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Practical Uses – Non-surgical

- Lateral Epicondylitis

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Science

- Very little science in peer reviewed journals regarding Sports medicine/tendonapthies
- Some articles in orthodontia and podiatry
  - Still not well run studies
- 16 animal model studies
- 9 cell culture studies
- Numerous case reports
- Anecdotal

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Science

- Human Studies Completed – both Plantar Fasciitis
  - Hanselman et al (2015) *Foot Ankle Int*
    - Human RCT
    - Cryopreserved human AM - 23 patients
    - No difference between cryopreserved AM and corticosteroids for the treatment of plantar fasciitis; no adverse side effects from AM injection
  - Zelen et al (2013) *Foot Ankle Int*
    - Human RCT
    - Micronized dehydrated human AM - 45 patients
    - AOFAS and pain scores improved with micronized AM compared with saline injections
- Human Studies Ongoing – only 3 in Orthopedics
  - Scar reduction in TKR
  - Zone II Flexor tendon repairs
  - Comparing injection of AM allograft with HA vs placebo in knee OA

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Unsolved Issues

- Amount and concentration of cells needed
- Stem cells with or without growth factors??
- Scaffolds??
- Optimal method of delivery
- No known protocols for each given entity
- How to assess results and outcomes

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Thank YOU!

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