I will address three major areas:
1. Tendonopathy
2. Tendon healing
3. Articular cartilage healing/regeneration

I will emphasize 2 major pathophysiologic principles related to tendonopathy and tendon healing:

1. Emerging data suggests that there is fundamental and important interaction between:
   i. mechanical load
   ii. inflammatory mediators
   iii. matrix metalloproteinases (MMP's)

2. Fetal wounds heal by tissue regeneration in contrast to reactive scar formation in post-natal human. We can use lessons from embryologic development and studies of fetal wound healing (“scarless healing”) to discover novel methods for connective tissue healing.

Consideration of these mechanisms suggests novel treatments....

Role of Mechanical Load:
Stress deprivation leads to up-regulation of inflammatory mediators (IL-1) and MMP's (collagenase). These MMP’s affect matrix remodeling, usually leading to detrimental changes in material properties.

Mechanism of Tendonopathy (Steve Arnoczky):
Microscopic collagen fiber failure → cells in injured area are exposed to less load → resulting stress deprivation leads to upregulation of interleukin-1 and MMP-13 → decreased structural and mechanical properties

Clinical implications: We need to consider how modulation of mechanical load (magnitude, frequency, onset of loading, etc.) affects tendon healing.

Inflammation in Healing:
- Fetal wounds heal by tissue regeneration in contrast to reactive scar formation in post-natal human
  “Scarless healing” in fetal wounds
- Absence of inflammatory response in fetal tissue appears to be a primary mechanism for this phenomena
- Cell signals expressed during inflammation lead to healing by fibrosis
- Inflammation is very complex       Inflammatory cells have both catabolic and anabolic actions
- Inflammatory mediators may have very different effect on early versus late healing events
- During early tendon repair, a cyclooxygenase-2 inhibitor had a detrimental effect
- Late treatment had beneficial effect

Clinical implications:
Inflammation may have negative effect on tendon remodeling, thus cyclooxygenase-2 inhibitors might be of value given later in healing.

Novel anti-inflammatory mediators that are being evaluated in clinical trials:
- Adalimumab (TNF-α blocker)
- Anakinra (IL-1 antagonist)
- Tropisetron (serotonin-3 receptor antagonist with anti-inflammatory properties)

Matrix metalloproteinases
- MMP inhibitors may positively affect tendon biology
- Aprotinin is an MMP inhibitor that is being evaluated in clinical trials of tendonopathy (Orchard et al. Successful management of tendinopathy with injections of the MMP-inhibitor aprotinin. Clin Orthop Relat Res. 2008).
- We have found that doxycycline administered in the peri-operative period improves structure, composition, and function of the healing tendon-to-bone attachment in rat rotator cuff repair model (Bedi et al, in press Amer. J. Sports Medicine)

Clinical implications:
MMP inhibitors hold promise for treatment of both tendonopathy and for improvements in healing after tendon-to-bone repair.

Vascularity also plays a role in tendonopathy:
Tendon degeneration and rupture often occurs at water-shed area
- Higher prevalence of tendonosis in hypercholesterolemia and diabetes
- Likely due to microangiopathy, local tissue hypoxia

Clinical implications:
Topical nitroglycerin patches have been found to be effective in randomized clinical trial for supraspinatus and Achilles tendonosis (Paoloni J et al. Topical glyceryl trinitrate application in the treatment of chronic supraspinatus tendinopathy: a randomized, double-blinded, placebo-controlled clinical trial. Am J Sports Med. 2005).
Although mechanism unclear, may act via vasodilation.

Lessons from Developmental Biology
Our long-term goal is to induce tissue regeneration by recapitulating signals that occur during development. Work in our laboratory demonstrates that the following molecules have promise for improving tendon healing.

1. MT1-MMP (aka MMP14)
   - Membrane bound MMP
   - Embryologic development of the junction between calcified and uncalcified cartilage and enthesis.(Apte 2997, Holmbeck 2003)
   - Work in our laboratory demonstrates cells transfected with MT1-MMP gene improves healing tendon-to-bone attachment in rat rotator cuff repair model (Gulotta et al, in press Amer. J. Sports Medicine).
2. Scleraxis
   - Transcription factor responsible for tendon development
   - Expressed with Sox-9 at tendon/cartilage junctions.
   - Work in our laboratory demonstrates improved histology at 4 weeks, and improved biomechanical testing at 2 and 4 weeks in rat rotator cuff repair model.

3. BMP-12 (GDF-7) and BMP-13 (GDF-6)
   - Distinct from BMP-2, 4, 7 (osteogenic)
   - Expressed at insertion site during embryonic development
   - Induce formation of tendon/fibrocartilage

4. TGF-β3
   - Expressed in the developing rotator cuff tendon in early embryogenesis
   - Leads to tissue regeneration
   - In contrast, TGFβ-1 is associated with adult wound healing and scar formation
   - Transition from TGF-β3 to TGF-β1 coincides with the end of regenerative fetal healing phase
   - Exogenous TGF-β3 improves healing in our rat rotator cuff repair model

5. Platelet-rich plasma (PRP)
   - PRP is another method to deliver cytokines
   - α-granules and dense granules contain a variety of cytokines and other bio-active molecules in physiologic proportions
   - Biologic rationale is compelling but currently very little data
   - Important questions:
     - How to deliver to repair site?
     - Serial applications?

Articular Cartilage
- Many of the same principles as above can be applied to articular cartilage healing/regeneration.
- Cell-based approaches hold promise for cartilage regeneration
  - Stem cells:
    Adult-derived (marrow, adipose tissue)
    Embryonic
    Induced
    Allograft (juvenile allograft chondrocytes currently available for clinical use)

  - Stem cell biology can be improved by cell transfection with transcription factors (i.e., SOX-9) that are known to play role in chondrocyte differentiation.
    - Tissue engineering approaches to form tissue ex-vivo for later transplantation: cells are suspended in a matrix and then exposed to mechanical stimulation

*There is currently no level 1 or level 2 evidence to support these biologic interventions in connective tissue healing