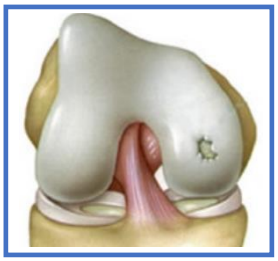
Musculoskeletal Models for Evaluating the Therapeutic Efficacy of Biomaterials & Stem Cells





ORTH X
Laboratory of Orthopaedic Tissue Regeneration And Orthobiologics

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Background: Osteoarthritis (OA) and intervertebral disc (IVD) degeneration (IVDD) are two of the most common musculoskeletal pathologies which impart significant socio-economic burden. These pathologies are mediated by increased concentrations of pro-inflammatory cytokines and proteases which ultimately result in cartilage and IVD tissue destruction, loss of mechanical function and debilitating pain. The development of regenerative strategies to repair damaged tissue and mitigate disease progression using biomaterials and stem cells, respectively should be evaluated using *in vitro* and *in vivo* models which mimic the salient hallmarks of OA and IVDD, respectively. Thus, our lab has focused on developing an expertise in characterizing and utilizing such models. Additionally, we have significant experience in isolating and studying the therapeutic efficacy of human mesenchymal stem cells (MSCs) in these models, including MSCs derived from amnion (hAMSCs), adipose (hADSC), and bone marrow (hBMSC) tissues.

In Vitro Model of Osteoarthritis: We have reported on the development and characterization of an *in vitro* co-culture model of patient-matched human OA cartilage and synovium. Biopsies of these tissues are cultured together using indirect contact for up to 14 days. This model accurately reflects the tissue-level hallmarks and complex cellular signaling commonly observed in the human joint space *in vivo* during late-stage OA. This includes impaired chondrocyte viability and progressive cartilage degradation in the presence of several pro-inflammatory and degradative mediators including synovial macrophages, interlukin-1β, and MMP-13. Moreover, we have demonstrated that hAMSCs are more effective at chondroprotection in the OA microenvironment as compared to hADSCs. We have also used this model to assess the efficacy and mechanism of action of currently marketed therapies in collaboration with medical device companies.

In Vivo Model of Osteoarthritis: Our group has also gained significant experience in using the male Dunkin Hartley guinea pig as a naturally-occurring model of knee OA. This model demonstrates several key similarities to human pathophysiology including; medial compartment load bearing, persistence of synovial inflammation, progressive chondrocyte death and proteoglycan loss which eventuates in cartilage destruction, osteophyte formation, and subchondral bone sclerosis. This model can be used to evaluate the efficacy of therapies across the continuum of OA progression (i.e. from early-stage prophylactic treatments to end-stage approaches for cartilage regeneration). We are currently using this model to assess the efficacy of different MSC sources to mitigate OA progression.

In Vivo Model of Intervertebral Disc Degeneration: In collaboration with Colorado State University, our lab has developed and characterized a sheep model of lumbar IVDD. Sheep were chosen as their IVDs have similar geometry, range of motion, matrix composition and intradiscal pressures compared to humans. Degeneration is induced via fluoroscopically-guided intradiscal injection of an enzyme which initiates degradation of the central region of the IVD. IVD degradation progresses through 17-weeks with no evidence of spontaneous regeneration and can be tracked longitudinally via magnetic resonance and radiographic imaging. Hallmarks of human IVDD are present in this model including progressive loss in IVD hydration, height, and tissue micro-architectural organization. Additionally, inflammation is present in conjunction with altered spinal kinematics. The ability of our nucleus pulposus replacement (NPR) and annulus fibrosus repair patch (AFRP) implants with and without MSCs have been evaluated using this model.

Future Model Development: Our lab is currently working on establishing rabbit and goat osteochondral defect models to evaluate our osteochondral plug (OCP) constructs. We have also recently received funding to evaluate the use of MSCs to mitigate post-traumatic OA progression in a rat meniscectomy / anterior cruciate ligament transection model.