Synthetic Proteoglycan Replacement For Osteoarthritis

Kyla Ortved, University of Pennsylvania –Two Year Grant

This proposal seeks to establish a new class of injectable, cartilage-penetrating compounds made from synthetic polyelectrolytes that replace proteoglycans that are critically lost in osteoarthritis.

Joint cartilage is a remarkably strong tissue capable of withstanding considerable force. The strength of the tissue is conferred by the robust extracellular matrix (ECM) that is composed mainly of proteoglycans and collagen. Despite the impressive strength of cartilage, it is susceptible to damage and trauma, especially in equine athletes. Following joint injury, inflammation in the joint leads to breakdown of the ECM with notable loss of proteoglycan. Early osteoarthritis (OA) is marked by a loss of proteoglycans in cartilage which leads to further cartilage degradation because in healthy cartilage, proteoglycans create an osmotic pressure from their negative charge, which supports compressive loads. Clinical features of OA include pain, decreased range of motion, and joint effusion. In severe cases, permanent loss of joint function occurs. Joint injury and OA are the second leading cause of retirement in the equine athlete and currently there are no effective disease-modifying OA drugs to halt or reverse OA; therefore, there is a critical need for the development of new approaches for cartilage repair and prevention of OA.

In healthy articular cartilage, compressive mechanical loads are supported by a stiff ECM and an internal pressure generated by proteoglycans. Early in OA, posttraumatic inflammation and increased enzymatic degradation result in loss of proteoglycans from the ECM. In an effort to treat OA, approaches have turned towards developing glycosaminoglycan (GAG) and proteoglycan mimics that can restore healthy ECM properties in damaged cartilage, thereby restoring mechanical functions of the tissue and supporting overall joint health. However, despite the immense economical cost and prevalence of OA, and the importance of proteoglycans in cartilage function, there are currently no such proteoglycan treatments that stabilize the ECM. A key technical challenge is that proteoglycan replacements need to be able to diffuse throughout cartilage to achieve therapeutic benefit. However, any proteoglycan replacement that can easily diffuse into cartilage will also easily diffuse out. To overcome this limitation, our team has developed a fully synthetic proteoglycan replacement based on thermal polymers. As a liquid at room temperature, poly(N-isopropylacrlyamide) (PNiPAm) diffuses rapidly through the joint and into the cartilage. As the polymer reaches body temperature, it undergoes thermal gelation and is “locked in” the cartilage. This thermal gelation is a new strategy in OA to overcome the historical challenge of delivering and retaining proteoglycan replacements in the ECM. Although PNiPAm is widely used in drug delivery, and PSS (polystyrene sulfonate) is an FDA-approved treatment for an unrelated disease, the combination of the two into a copolymer is a synthetic challenge and a novel treatment strategy for cartilage damage. Our robust preliminary data in vitro demonstrates the ability of this compound to penetrate cartilage concentrating in areas of proteoglycan depletion, retain in cartilage for up to 5 days and likely beyond, and most critically, restore biomechanical function in degraded cartilage.

Our proposal seeks to evaluate this promising synthetic compound in the horse to establish a new class of injectable, tissue penetrating compounds made from synthetic polyelectrolytes that will replace the function of lost proteoglycans and, critically, are retained within damaged cartilage for long durations (weeks to months). Our central hypothesis is that by diffusing our polymer into damaged cartilage, and enabling its long-term retention via thermal gelation, the biomechanical properties of cartilage will be enhanced to nearly its undamaged form, thus improving the load-bearing function and reducing a potent contributor to cartilage degradation. Our primary outcome measures will include histological and biomechanical assays, while our secondary outcome measures will assess downstream effects of a proteoglycan stabilization including gait assessments and synovial fluid biomarkers. This proposal has the potential to develop a new treatment option that directly targets the biomechanical function of the ECM, thereby preventing OA progression.

Importance to the Equine Industry: Joint injuries often have serious, long-term effects that lead to OA which remains one of the leading causes of retirement in horses. Currently, there are no effective disease-modifying therapies that halt or reverse the progression of OA. This proposal addresses this critical, unmet need in the equine industry as it seeks to establish a new therapeutic that will bolster the ECM and preserve the biomechanical function of the joint thereby preventing the progression of OA.
Historically, horses with OA were treated symptomatically with rest, systemic non-steroidal anti-inflammatories drugs (NSAIDs), and intra-articular corticosteroids.

Although these approaches can temporarily decrease pain and inflammation, they do not reverse joint damage and are associated with side effects including gastrointestinal ulceration and renal damage with prolonged NSAID use, and steroid arthropathies and laminitis with repeated intra-articular corticosteroid injection. Newer generation intra-articular treatments including orthobiologics such as platelet rich plasma, autologous protein solution and stem cells can decrease inflammation and promote healing and homeostasis within the joint. However, there are currently no treatments that directly address the loss of proteoglycan in the ECM and reverse the deteriorating biomechanical strength of the articular cartilage. Here, we seek to establish a new category of joint therapy that can be used in conjunction with anti-inflammatories to provide synthetic support to the ECM and prevent further joint degradation.

Funded by Grayson-Jockey Club Research Foundation