

## Investigation of equine fetlock joint immunopathology and the immunomodulatory effects of intra-articular therapeutics

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(Research Training Scholarship: USD 186,055)

The normal joint is composed of cartilage, an inner synovial membrane, and bathed in synovial fluid, along with additional supporting structures that surround the joint. Repetitive stress injury is a common cause for joint disease leading to osteoarthritis, which is commonly seen in racehorses. Osteoarthritis ultimately leads to joint inflammation, degeneration of the cartilage layer, bone proliferation along the joint edges, and alterations in the synovial fluid and synovial membrane layers. This inflammation and degeneration can lead to pain and reduced mobility, and is one of the most common causes for lameness in the horse. There is much unknown still about the immune cells participating in and propagating osteoarthritis, particularly in the horse. Our current therapeutic options can help mitigate the clinical signs of osteoarthritis for short periods of time but are unable to stop the development or progression of osteoarthritis.

Synovial fluid is composed of many proteins, all with a role in maintaining normal joint health. Lubricin is a protein present in synovial fluid with a primary role in boundary lubrication, or maintaining a friction-free surface within the joint at the cartilage surface; however, lubricin appears to have additional roles in the joint beyond lubrication. Lubricin acts as an anti-inflammatory on several types of immune cells that contribute to the development and progression of osteoarthritis. Numerous studies in rodents showed treatment with lubricin prevented cartilage degeneration in a model meant to induce osteoarthritis. These anti-inflammatory and chondroprotective effects make lubricin a promising therapeutic target in managing osteoarthritis. The function of lubricin depends on the sugars attached to it (glycosylation), and this sugar profile changes in osteoarthritis in humans and horses.

In aim 1 we will evaluate immune cell populations in cartilage, synovial fluid, and synovial membrane in healthy and osteoarthritic equine joints. Flow cytometry will be used to identify various types of immune cells, including M1 and M2 polarized macrophages, T cells, B cells, NK cells, neutrophils, and dendritic cells. The cell populations will be compared between healthy and osteoarthritic joints, as well as with disease severity. In aim 2 the glycosylation of synovial fluid lubricin will be evaluated and compared to the immune cell populations gathered in aim 1. For aim 3 cartilage and synovial membrane will be treated with lubricin, triamcinolone, or platelet rich plasma; the last two being common articular treatments used to manage osteoarthritis inflammation and pain. Cultures will be activated to induce inflammation, and the effects of treatment on inflammation, macrophage polarization, and cartilage degeneration evaluated.

The long-term objectives are to identify immune cell populations present in equine joints with osteoarthritis to improve the treatment of joint disease. Lubricin shows potential in early studies as a disease-modifying therapeutic, and evaluation of the anti-inflammatory and chondroprotective effects will identify the suitability of lubricin as a treatment option. The glycosylation profile of lubricin in joint disease may provide a simple marker that can identify horses with early osteoarthritis to allow for prompt treatment prior to the development of more severe disease.