

## Mesenchymal stem cell licensing for improved tendon healing

Lauren Schnabel, North Carolina State University, US  
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Superficial digital flexor tendon (SDFT) injuries occur frequently in athletic horses and are particularly debilitating and costly due to both their extensive healing time and their high re-injury rate (50% to 70%). Rehabilitation from a typical tendon injury takes at least 6 months and often up to 1 year for full return to work. A re-injury during or after this rehabilitation period is devastating to any horse's career, but is especially devastating to that of a racehorse with a limited age and time frame for peak performance. SDFT injuries in racehorses can also negatively affect their ability to be adopted out after their racing career due to concerns about their performance ability in a second career. As such, SDFT injuries have a major impact on equine welfare.

SDFT injuries are characterized by tearing of fibers within the center of the tendon commonly referred to as core lesions and most often affect the forelimb SDFT at the level of the mid-third metacarpus. Current treatment strategies include rest, non-steroidal anti-inflammatory drugs (NSAIDs), controlled rehabilitation, and administration of local regenerative therapies, all in an effort to improve healing and return the horse to its previous level of competition. Mesenchymal stem cell (MSC) therapy has been shown to be effective at improving tendon architecture and also reducing reinjury rate in horses. Historically, MSCs have been administered following resolution of inflammation due to the extended time to diagnosis of tendon injury combined with the time required to isolate and expand patient-specific, or autologous, MSCs for therapy. However, recent work has revealed that the secretion of growth factors and immunomodulatory cytokines by MSCs needed for optimal healing can actually be enhanced through exposure to inflammation, termed MSC licensing. For these reasons, our group has been working diligently to characterize the tendon inflammatory environment post-injury and to assess how this tendon inflammatory environment affects MSC gene and protein expression. To date, we have characterized the cytokine environment in acute tendon injury with novel ultrafiltrate probes implanted in surgically induced core lesions of the SDFT. More recently, we demonstrated that licensing of MSCs with the inflammatory cytokine IL-1B and the immunomodulatory cytokine TGF-B2 markedly increases the expression of key genes related to tendon healing and are now investigating protein expression levels.

The purpose of this current proposal is to evaluate the ability of IL-1B and TGF-B2 licensed MSCs to improve tendon healing with the hypothesis that licensed MSCs will significantly enhance tendon healing compared to naïve MSCs in terms of improved lameness and ultrasonographic assessments in addition to biomechanics and histologic evaluation. If our hypothesis is correct, the findings of this proposal would substantially alter clinical application of MSC therapy with the potential to markedly improve treatment outcomes and improve racehorse welfare by preventing early retirement or euthanasia and allowing them to more easily find homes after racing as sound horses with the ability to have a second career.