# Effects of Inflammatory Cytokines on MSC Homing

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**This study will investigate how mesenchymal stem cells traffic to injuries after delivery to the bloodstream to inform the best time to deliver cells relative to initial injury in future animal models.**

Mesenchymal stem cells (MSCs) are a special type of stem cell that can turn into a variety of cell types, such as bone, cartilage, and muscle cells. They also can help repair damaged tissues, which makes them important for therapies aimed at healing injuries.

One of the challenges in using MSCs for therapy is understanding how they get to the site of injury, especially after they are introduced into the bloodstream—a process called vascular perfusion. Vascular perfusion means that the MSCs are delivered directly into the blood vessels that supply the injured area. Once they are in the bloodstream, MSCs need to "home" to the site of damage in order to participate in the healing process. This proposal aims to address how MSCs move from the bloodstream, across the tissues, and arrive at a site of injury. This information is critical to understanding how to best utilize MSCs to treat localized injuries in horses.

When MSCs are injected into the bloodstream, they don't automatically go to the injury site. Studying how MSCs move or "traffic" through the body to the injured area helps us better understand the steps that need to happen for healing to begin. Additionally, right after an injury occurs, the body goes through several stages of repair, from inflammation to tissue rebuilding. If we know how quickly and because of which signals MSCs can travel to the injury site, we can determine the best time to deliver them for maximum healing. For example, if MSCs are most effective during the inflammation phase, we need to time their delivery right after injury.

We will engage in a series of experiments aimed at identifying the specific inflammatory signals required for MSCs to interact with the blood vessel wall, migrate across it, and eventually reach a site of inflammation. Eventually we plan to employ cell tracking techniques to follow MSCs after they are introduced into the bloodstream in a horse. For example, advanced imaging technologies can help visualize where the cells go over time, while cell trackers can indicate when the cells arrive at the injury.

**Importance to the Equine Industry:** The lower limb and the hoof are the areas in which most performance limiting lameness in the equine athlete are found. Distal limb injury treatments could be improved with biological therapeutics, which are recognized for their potent anti-inflammatory effects and promotion of wound healing. Biologic therapies like Mesenchymal Stem Cells (MSCs) are becoming increasingly requested by horse owners and used in the clinical settings. Despite this, there is currently no agreement on the types of injuries well suited for MSC treatments, ideal treatment delivery methods, or when to give cell treatments after injury.
To enhance the effectiveness of MSC therapies, it is necessary to maximize the delivery of MSCs to the target injury.
The positive effects of MSC therapies has been shown to improve when more MSCs are delivered to an injury.

As such, it is critical to understand how MSCs move around the horse's body after being given as a treatment. Many clinicians opt to directly inject MSC into a wound in an effort to increase the number of cells delivered to the area. However, some injuries are inaccessible with a needle. Additionally, this route of administration can lead to complications such as further tissue damage and adverse reactions like swelling or lameness. Regional limb perfusion (RLP) commonly used in equine medicine, and could be used to deliver MSCs to the equine lower limb via the bloodstream. Unfortunately, there is minimal information regarding the efficacy of this technique to deliver MSCs to injured horse legs. This study will investigate how MSCs interact with their environment to travel out of the bloodstream and into the wound site. The study will address gaps that are paramount to creating clinical guidelines for MSC therapies, especially as it relates to timing of cell treatments. Ultimately, our goal is to clarify optimal usage of cell therapies so that better, more accessible cell treatments are available.

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