

Using Stem Cells to Combat Multidrug Resistant Bacterial Infections

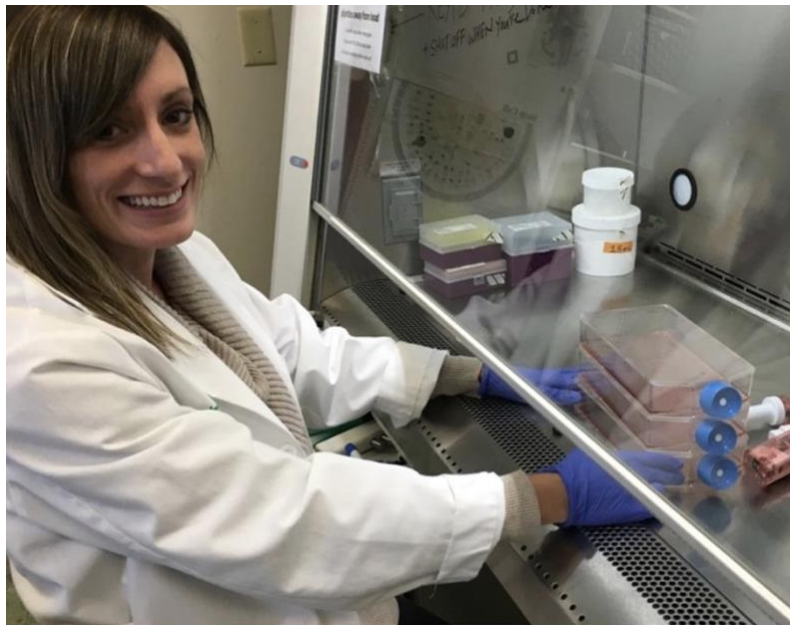
The mission of the C. Wayne McIlwraith Translational Medicine Institute is to improve the lives of animals and humans through biologic therapies created via the collaborative work of leading scientists and clinicians; to expediate the availability of these therapies, and to promote education related to these goals. Towards that goal, collaborators from the Orthopaedic Research Center and the Laboratory for Immunotherapy are investigating a novel approach to treat multi-drug resistant bacterial infections using mesenchymal stem cells (MSC) activated to prime the body's immune response to infection. This work has been driven by the increased incidence of bacterial infections with multi-drug resistance in both people and animals. Mesenchymal stem cells have been shown to have antibacterial properties and represent a particularly attractive alternative to antibiotics as they are not subject to development of resistance.

Mesenchymal stem cells possess properties that reduce bacteria and stimulate the immune system and are vital participants in the body's own healing and repair processes. Stem cells directly promote resolution of infection through secreting proteins that fight infection. They also recruit cells of the immune system to fight-off infection. Furthermore, MSC have proteins on their surfaces called toll-like receptors, that are involved in priming the body's response to inflammation and infection. By stimulating these toll-like receptors in culture in the laboratory prior to injecting stem cells into sites of infection, collaborators from Dr. Dow's laboratory have demonstrated enhanced antibacterial action of MSC through more rapid recruitment of immune cells already in the patient's own body resulting in a synergistic action with antibiotics administered in unison. This overall reduces bacterial loads far beyond what antibiotics can do on their own. Inspired by promising results in mouse models of implant infection and pet dogs with naturally occurring wounds, Orthopaedic Research Center Director, Laurie Goodrich, equine surgeon and clinician scientist, and Laboratory for Immunotherapy Director, Steven Dow, immunologist and internal medicine specialist, set out to investigate the effect of TLR-activated cellular therapy in treating horses with joint infections. They recognized that developing therapies to augment antibiotics through a combination of "priming" the immune system and cellular therapy, will be vitally important to address the increasing threat of antimicrobial resistance in healthcare which is a leading cause of death in humans in the US.

The team assembled to bring specialists in the fields of veterinary and human surgery, immunology, and internal medicine. With exciting preliminary benchtop data and findings in small animal species, funding was sought to explore this technology further in horses,

and ultimately granted by the Grayson Jockey Club Research Foundation and American College of Veterinary Surgeons. Studies investigating the effect of activated stem cell therapy on bacterial reduction and priming the immune system in horses with joint infections are currently being carried out by PhD Candidate/Postdoctoral Fellow Dr. Lynn Pezzanite, an equine surgeon and PhD student co-mentored by Drs. Laurie Goodrich and Steven Dow, and Dr. Lyndah Chow, PhD research scientist, who completed her graduate work under the supervision of Dr. Dow with a strong background in immunology and Dr. Wayne McIlwraith, Founding Director of the Orthopedic Research Center. The design and implementation of this work is strengthened by collaborations with and input from leaders in their respective fields at Cornell (Drs. Doug Antczak and Don Miller, immunology), University of Pennsylvania (Drs. Tom Schaer and Julie Engiles, surgery and histopathology, respectively) and North Carolina State University (Drs. Lauren Schnabel and Jess Gilbertie, equine surgery and bacteriology, respectively). The findings of these studies are expected to directly impact treatment of multidrug resistant infections not only in horses, but also determine how these cells have their mechanistic effects with the ultimate goal of saving the lives of both horses and people with life threatening bacterial infections.

At the completion of these studies, the team assembled, aims to determine the mechanisms by which activated stem cells both suppress infection and “prime” the immune system. Highlighting the translational goal of the TMI, the anti-infective stem cell program is the ongoing collaboration with the Gates Center for Regenerative Medicine at the University of Colorado Anschutz medical campus in Aurora, CO. This group is currently in the process of



initiating a clinical trial of activated human MSC for treatment of chronic infections in human patients. The clinical trial in people will be led by Dr. Jason Stoneback, Chief of Orthopedic Trauma and Fracture Surgery Service and Director of the Limb Restoration Program at the University of Colorado Hospital. Dr. Stoneback is also on the PhD committee of Dr. Lynn Pezzanite whose work is described here. This work will further foster the research and clinical connections between the veterinary and human

health programs at our two institutions.

The above photo shows Dr. Lynn Pezzanite, equine surgeon and postdoctoral Fellow at the C. Wayne McIlwraith Translational Medicine Institute cultures equine mesenchymal stem cells. With co-investigators from the Center for Immune and Regenerative Medicine and Orthopaedic Research Center, anti-infective cellular technology will be delivered in horses

with infected joints to further investigate mechanisms by which TLR-activated stem cells exert antimicrobial action and modulate inflammation, towards the ultimate goal of application in a Phase I human clinical trial.