



Is stem cell treatment the answer?

by Dr Paul van Dam

Horse lovers know only too well that injuries to tendons and ligaments are one of the main causes abruptly ending the career of many equine athletes. Stem cell technology seems to offer a way of treating tendon and ligament injuries, allowing us to bring the truly great athletes back to the track after injury, albeit at a price.

During a recent visit to South Africa, David Mountford and Greg McCarrell of VetCell Biosciences, delivered a talk on stem cell technology in Kyalami. What follows is a synopsis of this presentation, with some information added from other sources.

Tendons

The horse is a “flight-response” animal, reacting to threats by running away as fast as it can. Its limbs have developed such that they allow for efficient locomotion – the distal limbs grew longer and stride length increased, while the main muscle mass was left behind at the top, with low mass at the lower part of the limb, allowing for more speed and easier movement. As a result, the digital flexor tendons are very long and act as springs, storing energy for efficient locomotion.

The digital flexor tendons and the suspensory ligament are loaded and stretched to their maximum during movement. When a horse gallops, the superficial digital flexor extends by up to 16%. Considering that during mechanical loading experiments in the laboratory, these same tendons rupture when extended to between 12-20%, it is understandable that they are prone to injury.

Immature tendons show the ability to adapt to loads placed on them, but mature tendons lose this ability. Exercising the horse continuously challenges the tendons, resulting in cumulative and progressive degeneration, often passing unnoticed. Obviously age also plays a role. Even without major exercise, the elasticity of the tendons gradually decreases because the tendons work continuously at close to maximum levels.

This gradual degeneration, when challenged by sudden overextension such as a horse slipping, is the cause of most injuries to the superficial digital flexor and suspensory ligament. These two structures are the ones most commonly involved in tendon and ligament injuries. The deep digital flexor tendon can also be injured, but this is less common, and usually the result of sudden and major overextension.

After injury, the tendon matrix is disrupted. Bleeding within the tendon is the first response to this disruption, followed rapidly by an often excessive inflammatory

reaction in which cellular infiltration and releases of proteolytic enzymes (which digest protein) can cause further damage to the injured tendon. Soon after injury the body reacts through a process called “fibroplasia” or the formation of scar tissue. Scar tissue is fibrous and not elastic, thereby reducing the capacity to stretch or for the tendon to act as a spring and to store energy.

Over months, the scar tissue becomes stronger, but also increases in stiffness – compromising the performance of the horse and increasing the risk of re-injury. The chances of recovery are determined primarily by the severity of the original injury. The prognosis for racehorses returning to racing after tendon injuries, is 63% in the case of a mild injury, 30% for moderate injury, and 23% after severe injury.

Treatment

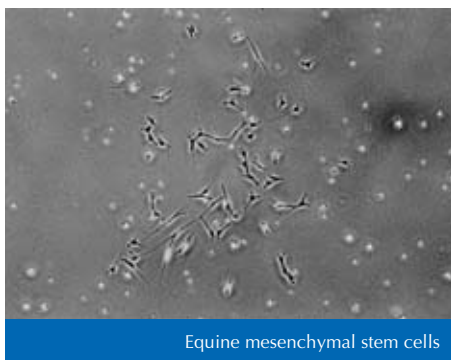
The best approach to deal with tendon injuries proved to be about ten days’ rest, followed by a controlled ascending exercise programme, and regular ultrasound examination approximately once every three months. The purpose of the exercise is to stimulate the scar tissue fibers to become in line with the long axis of the tendon, as this improves the prognosis. Thus, we have:

- An acute (inflammatory) stage, where the main emphasis is on minimising inflammation
- A subacute (reparative) stage, with the promotion of fibroplasia and attempts to optimise the organisation of scar tissue
- A chronic (remodeling) stage, where remodeling of the scar tissue is promoted.

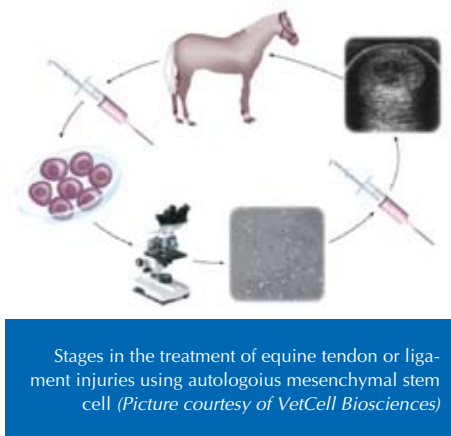
Over the past five years, research into the treatment of tendon injuries has focused on preventing scarring of the tissue and promoting reformation of normal tendon tissue to regain the “spring” and energy storage capabilities. This is where tissue engineering, and specifically the use of stem cells, comes into the picture.

What are stem cells?

Stem cells are found in the bodies of all adult animals and are the body’s repair mechanism for damaged or diseased tissues. They are unspecialised cells that have the ability to, under specific conditions, develop



Equine mesenchymal stem cells



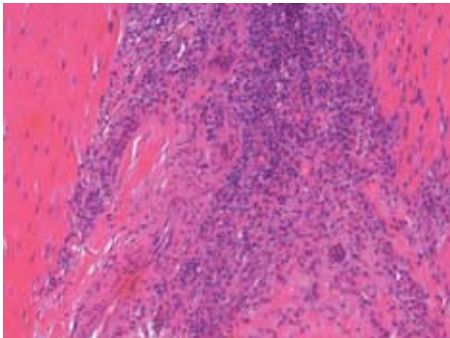
Stages in the treatment of equine tendon or ligament injuries using autologous mesenchymal stem cell (Picture courtesy of VetCell Biosciences)

into a limited number of adult cells with specific functions. Stem cells are subdivided into hemopoietic (blood cells lines) and mesenchymal stem cells, which can give rise to bone, cartilage, tendons and ligaments, scar tissue, muscle and fat.

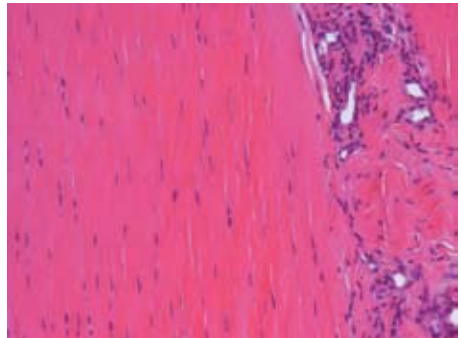
How is this possible, and how do we stimulate stem cells to become tendon cells? The following is of importance:

- The mechanical load experienced by the stem cells
- Contact with other cells
- Contact with the matrix in which they are placed
- Growth factors.

Equine tendons make the perfect model for studies to determine the effect of implanting



Untreated suspensory ligament lesion – note the scar tissue



Treated suspensory ligament lesion – scar tissue is almost absent (Pictures courtesy of VetCell Biosciences)

stem cells into a lesion. Equine digital flexor strain injuries almost invariably result in a central “core lesion” that is retained within the tendon, providing a hollow into which stem cells can be injected without leaking. Note that stem cells have to be autologous (harvested from the horse that is to be treated).

Work has been done on stem cells harvested from two main sources:

- From fat cells: Fat tissue is harvested from the base of the tail with the horse under sedation, and submitted to laboratory for stem cell recovery.
- From bone marrow (the technique on which VetCell have done their work): These stem cells appear to have better potential to develop into various specialised cells. Bone marrow is harvested from the breastbone of the horse under standing sedation. The bone marrow is submitted to a laboratory for isolation and multiplication of stem cells.

VetCell stresses that, after the stem cells have been injected into the core lesion, the horse must be given stable rest for five days. Then an ascending and carefully controlled exercise programme must be followed, with regular ultrasound examination to monitor progress. The exercise programme entails walking for three months, with trotting introduced three months after injection, cantering five months after injection and the horse going back to full work twelve months after injection.

To date, some 400 horses have been treated worldwide using this technique. Statistics are promising. Return-to-performance results in British jump racehorses that have suffered tendon injuries, is some 80% compared to the 30% for traditionally treated jump racehorses. The re-injury rate of horses after stem cell treatment of superficial digital flexor tendon injuries (17%) was significantly lower than for horses where stem cells were not used (56%).

More work needs to be done, but the results are promising. Costs might be a limiting factor at the moment, especially in South Africa, where no laboratory can currently isolate and multiply stem cells, and bone marrow has to be shipped off to Britain. But with further development, the technique is bound to become within reach.

The future

Storage of stem cells, frozen in liquid nitrogen, is very successful. With autologous stem cells available “on tap”, the lag phase between injury and treatment is shortened, possibly improving the prognosis even further. An interesting development is that stem cells are isolated from the umbilical cord after birth and frozen, ready for use when the animal later injures himself. Stem cells from bone marrow also can be frozen and stored.

Work is also being done on the use of stem cells to improve healing of fractures and cartilage injuries. Both fields show promising results.

(A list of references is available from the author) SAH