Stem cell therapy

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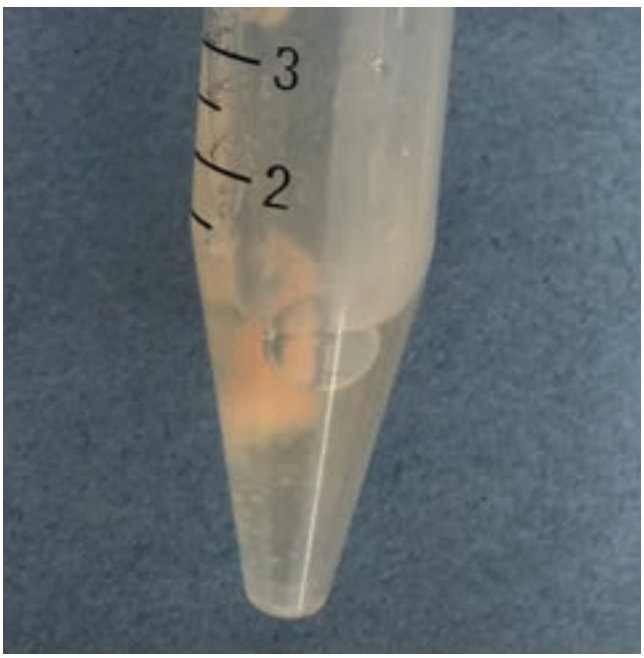

Figure 1: Stem-cell isolate following extraction from adipose tissue.

Mesenchymal stem cells (MSC) have been discovered in most adult tissues examined, where they lie in wait to initiate repair. The number of these specialised cells are very low but can be isolated. In 1970, the successful isolation and culture of the non-haematopoietic portion from bone marrow of fibroblast-like adherent cells was not deemed initially, as a stem cell discovery. Later, it became evident that these undifferentiated cells were precursors of cells from the mesenchymal lineage, ie. adipocytes, chondrocytes and osteocytes. These MSCs had the ability to expand and differentiate into these different cell lines. Since this discovery, there has been an exponential growth of research into these cells producing a very large number of experimental studies and publications. The popular media have promoted stem-cell therapy on the back of these and other clinical studies. Overall, these experimental studies have produced consistently promising results that have led to the use of these cells in clinical practice and their promotion commercially.

Experimental studies have teased out how these cells work in a disease process. MSC provide significant anti-inflammatory effect, immunomodulation, cell differentiation/renewal, angiogenesis and antifibrosis (see Figure 1). The mechanisms of how they accomplish these effects are understood to be multifactorial including cell-to-cell interaction, endocrine, paracrine, growth factors and cytokine release. The local chemical environment and oxygen tension also influence how the MSC behave. Hypoxia induces a homing activation in the MSC which releases growth factors and cytokines such as vascular endothelial growth factor (VEGF), stromal derived factor (SDF-1), fibroblast growth factor (FGF-2&7), matrix metalloproteinases (MMP-9) and interleukins (IL-1&6). Currently, it is believed that the main effect of MSC is through the release of such chemical mediators. A further effect of MSC is the inhibition of T lymphocytes by the production of nitric oxide. So, essentially, the MSC seem to act like governors of regeneration in a diseased tissue. It has also been shown experimentally that the MSC also differentiate into chondrocytes to repair cartilage defects with hyaline-like cells (see Figure 2). Furthermore, the MSC stop ongoing chondrocyte death. The MSC have been shown to survive as injected for up to 30 days in a diseased joint, but the positive effects are much longer lasting with claims of up to a few years.

MSC AS A THERAPEUTIC MODALITY

There is a wealth of preclinical and clinical data making claims for MSC as a therapeutic modality. The current therapeutic options for MSC in human and veterinary medicine are purported to be, but not limited by, osteogenesis imperfecta, osteoporosis, osteoarthritis, hypophosphatasia, bone defects and fracture repair, intervertebral disc regeneration, tendon and ligament

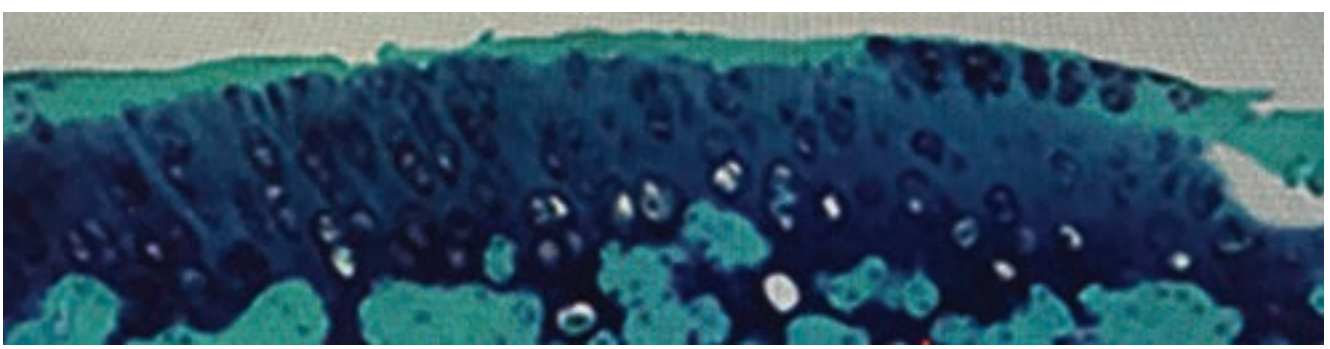

Figure 2: Cartilage regeneration following experimental defect creation and MSC implantation with growth factors.

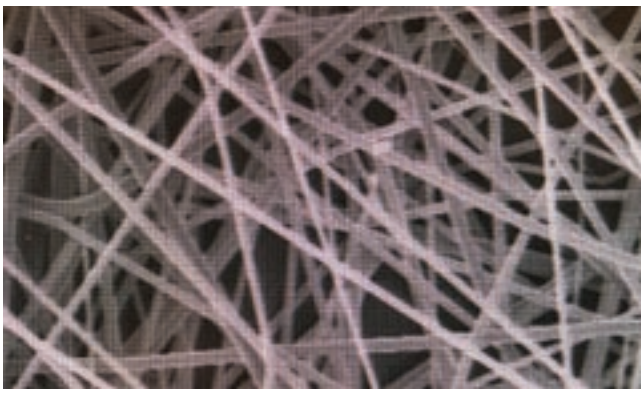

Figure 3: Injectable biodegradable whiskers for intraarticular use, acting as scaffold for MSC.

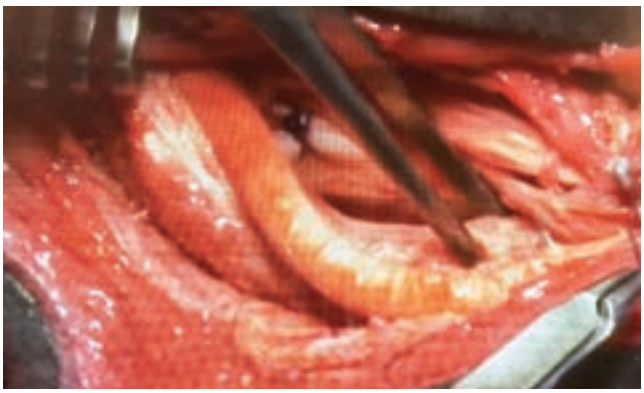

Figure 4: Synthetic fibre impregnated with MSC being surgically implanted into a repair of an equine SDF.

repair and spinal defects. The clinical evidence for these conditions is very encouraging but there is a lack of large double blind randomised controlled studies. The first clinical trials in humans using MSC intra-articularly with knee osteoarthritis was carried out in 2002. There have been small double-blind randomised studies in human-knee osteoarthritis since then, which have shown that there was a significant improvement in function, pain relief and cartilage structure as determined by MRI. The trials have moved on from phase I to phase II trials in humans at this point in time. It is a difficult and long drawn-out process to produce a large, double-blind, random controlled study, and even more complex to complete in veterinary medicine.
A number of companies are offering commercial stem-cell therapy kits for osteoarthritis and tendon/ligament repair in veterinary medicine for the last five years or more, especially in the US.
To date, there have been thousands of stem-cell therapy cases completed using these kits. Treatment of canine and equine osteoarthritis has become a big industry. But, not all cases are suitable and prudent assessment is required prior to embarking on the route to stem cell therapy. As the osteoarthritic joint is in a catabolic state, alternative treatments do not offer a solution to this disease process. MSC therapy provides symptomatic relief and the possibility of cartilage repair/renewal. The treatment is claimed to be effective in up to 90% of cases and safe, as the cells are simply re-implanted.
A further advantage for MSC therapy for osteoarthritis is not relying on owner compliance to administer treatment, which has been shown in some studies to be surprising low.

USE IN EQUINE SECTOR

The equine industry has been well ahead of most sectors in the use of MSC therapeutically. Typically, for a veterinary sector, most of the published work on MSC therapy is based on small studies. In the case of superficial digital tendon (SDF) injury (see Figure 3), the use of MSC has been in use for, perhaps, long enough to reach some conclusions.
MSC therapy has been shown to improve the quality of the SDF repair with better histological characteristics. This repair has been confirmed also by ultrasound to be a more normal matrix architecture compared to non-MSC SDF repair studies. With MSC therapy, a racehorse may not return to previous racing form but they can still be used for breeding purposes. One of the conclusions in the equine sector is that using MSC therapy reduces the SDF re-injury rate. So, although MSC therapy initially was announced with great fanfare for SDF injury the story has evolved to more enlightened view of MSC therapy. But because the science behind the therapy, ie. the tendon does repair to a more normal state, MSC therapy is recommended in those cases that are suitable.
A relook at the MSC therapy process by equine surgeons has highlighted some issues which need addressing as quickly as possible. There is no standard method of isolation, cell source, cell processing and diluents usage. We don't know what is the optimum processing method for collecting MSC. Therefore, immediately, many of the studies are not directly comparable. The same situation applies to platelet rich plasma (PRP), which is often used in conjunction with MSC to provide extra growth factors. The variability in the MSC sample produced is a problem that needs proper scientific clarification. Furthermore, there is no certain optimised timing of MSC injections and there is no agreed optimised rehabilitation process.
As with many studies, the method of measuring outcomes also varies between studies so there is difficulty comparing studies. Then, there is the issue of bioscaffolds, which are available commercially to attempt to aid the adherence of the stem cells to the injury site. These scaffolds have again shown promising results and further development is inevitable. Such scaffolds can be as fibres for tendon repair, injectable biodegradable whiskers for joints and patches for skin defects (see Figure 4).

SUMMARY

In conclusion, MSC therapy is a really useful therapy and is still developing in terms protocols and new conditions that are treatable. We wait for a large, double-blind controlled study to confirm the data we have now from smaller double-blind random controlled studies.
The future looks promising for further use of MSC therapy with the development of optimised processes, addition of targeted growth factors and the development of improved bioscaffolds.