Out-Sourcing Stem Cells for Clinical Applications

Osteoarthritis is a progressive, degenerative disease of joints that significantly impacts quality of life in both companion animals and people. Articular cartilage damage is the hallmark of osteoarthritis, but the disease generates pathological changes in several articular and peri-articular tissues as well, such as the synovium, joint capsule, and subchondral bone. Most available therapies modulate clinical signs of arthritis but do relatively little to arrest or reverse the disease process. However, several biological and gene-based strategies show promise as authentic ‘disease-modifying’ therapies.

The manuscript in this edition of VCOT by Pigott et al. addresses the response to intra-articular injections of mesenchymal stem cells (MSC) from different sources into the fetlock joints of adult horses (1). The group addressed a very critical aspect of cell-based therapies: can we use pre-prepared allogeneic or xenogeneic cell sources as therapeutic agents, or does stem cell therapy require autologous cell stocks?

The responses to both naïve and (human bone morphogenetic protein-2 [BMP-2]) adenovirally-infected autologous MSC populations were assessed in the study, as well as allogeneic and xenogeneic (human) MSC. The responses to intra-articular MSC administration were monitored over the four weeks following the injections, using a panel of assays that addressed the clinical appearance of the fetlock joints (joint circumference, limb oedema, pain-free range-of-motion) and several synovial fluid parameters (total and differential cell counts, total protein, interleukin [IL]-6 and IL-10 concentrations) (1).

All four MSC sources induced an acute inflammatory response, although the response to autologous cell administration was, not surprisingly, less severe and more transient than the responses to allogeneic and xenogeneic cells (1). Infecting autologous MSC with a human BMP-2 adenoviral vector did not increase the host response to any degree. This finding provides strong support for the development of genetically engineered stem cells to augment their therapeutic value, as has been previously demonstrated (2–4). Of particular interest, the xenogeneic MSC (of human origin) elicited reactions almost identical to allogeneic cells and, as the authors point out, the clinical signs of joint and peri-articular inflammation that followed the injections would likely have been easily controllable through routine bandaging and anti-inflammatory medication (1). This finding is critical to the clinical feasibility of cell-based therapies, since access to ‘off the shelf’ cell stocks avoids the need for collection and in vitro expansion of the patient’s own MSC; a process that usually takes several weeks.

The specific mechanisms by which stem cells influence the clinical signs and progression of osteoarthritis remains unclear. Mesenchymal stem cells do not appear to adhere or localize to articular cartilage after intra-articular administration (5–8). Instead, MSC preferentially localize to the soft tissue structures within the joint. Given this, any beneficial consequences of intra-articularly administered MSC are likely mediated by the release of soluble ‘trophic’, immune-modulatory factors, by primary effects on other articular tissues, or some combination of these factors, as has been documented to occur in inflammatory arthritic states (9–12).

Impressive beneficial responses to intra-articular MSC administration have been demonstrated in the rabbit cranial cruciate ligament transection models (13, 14). In horses, the current evidence suggests that equine arthritis is unlikely to be responsive to MSC injections where significant articular cartilage damage exists, although a recent study by McIlwraith et al. demonstrated that MSC administration did improve cartilage defect repair following micro-fracture (15, 16).

Accepting the concerns with MSC therapy for cartilage pathology, MSC do appear to be particularly indicated for the treatment of meniscal and other intra-articular...
soft tissue injuries in performance horses (17). In a multi-centre clinical trial, in which stifle injuries with meniscal damage comprised the majority of cases (20 of 39), the success rates compared very favourably with other published outcomes following surgical treatment of meniscal injuries in horses (18, 19). Clearly, the timing of MSC administration following a joint injury, along with the specific pathological changes in affected joints, are critical determinants of stem cell efficacy (15, 16).

The study by Pigott et al. used horses with no clinical evidence of metacarlo-/metatarso-phalangeal joint disease. In this respect, the joint swelling, limb oedema and synovial fluid changes that were detected developed against an essentially baseline background. Self-evidently, arthritic joints are variably inflammatory environments and the disease state itself will undoubtedly impact stem cell activities after administration (20, 21). The degree to which pre-existing joint disease influences the response to MSC administration and the activities of these cells after administration requires considerably more investigation, using clinical cases or an appropriate experimental model.

Finally, the horses in this study received single MSC injections. Although it is unlikely to be relevant to autologous MSC administration, the possibility that repeated injections of genetically altered, allogeneic or xenogeneic cells would result in immunological sensitization also needs to be addressed, since it is unlikely that cell-based therapy will permanently ‘cure’ arthritic joint disease and pre-empt the need for further treatments.

References
12. Lozito TP, Tuan RS. Mesenchymal stem cells inhibit both endogenous and exogenous MMPs via secreted TIMPs. J Cell Physiol 2011; 226: 385–396.