

Stem cells in canine osteoarthritis. Part 1: sources, effects and modes of action

Osteoarthritis represents the most prevalent joint pathology diagnosed in both human and veterinary medicine, and it is characterised by progressive degenerative changes and remodelling of synovial joints. These pathological alterations lead to compromised biomechanical function and nociceptive pain responses. In humans, osteoarthritis is associated with severe pain and can evolve into a chronic, debilitating condition. The aetiology is often multifactorial, involving systemic and local biomechanical disruptions. Clinical observations in canines, such as gait abnormalities and a favourable response to analgesic interventions, suggest a comparable pain experience and effect on quality of life in affected dogs.

<https://doi.org/10.12968/coan.2024.0046.1>

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Key words: osteoarthritis | platelet-rich plasma | regenerative medicine | stem cells

Submitted: 4 October 2024; accepted for publication following double-blind peer review: 20 November 2024

Osteoarthritis is widely recognised as a complex, multifactorial disease with a significant genetic predisposition. In canine populations, the manifestation and severity of osteoarthritis is also influenced by various lifestyle factors, including diet and physical activity levels. In veterinary contexts, osteoarthritis is frequently classified as secondary, emerging subsequent to primary joint abnormalities, such as dysplasia, cranial cruciate ligament rupture or patellar luxation, as well as primary trauma. These primary conditions are hypothesised to precipitate the onset of osteoarthritic changes. The precise epidemiological data regarding the proportion of canines that develop secondary osteoarthritis because of these predisposing factors remain undetermined.

The prevalence of osteoarthritis in dogs ranges from 6.6% (based on primary care data) to 20% (based on referral data) in the UK dog population. Estimates from North America report prevalence from 20% in dogs older than one year up to 80% in dogs older than eight years, based on radiographic and clinical data from referral clinics (Anderson et al, 2018).

Treatment options for canine osteoarthritis

Treating canine osteoarthritis often requires a multimodal approach. Stem cell techniques have been developed out of the necessity to add to veterinary ability to best help

patients, where there is no simple solution to what is considered a chronic, complex disease process. Stem cell therapy may be used alone or in combination with a variety of other treatment modalities which should be considered in every case. These include, but are not limited to:

- Analgesics: pure analgesics and centrally-acting analgesics acting at various levels of the pain pathway:
 - Transduction: non-steroidal anti-inflammatory drugs, steroids, piprants, anti-nerve growth factor monoclonal antibodies
 - Transmission: opioids, N-methyl-D-aspartate antagonists, gabapentoids, cannabinoids
 - Modulation: opioids, tricyclic antidepressants, N-methyl-D-aspartate antagonists, paracetamol, cannabinoids
 - Perception: opioids, non-steroidal anti-inflammatory drugs, paracetamol, gabapentinoids, N-methyl-D-aspartate antagonists
- Anti-inflammatories: non-steroidal anti-inflammatory drugs, piprants and steroids
- Dietary modification
- Environmental modification, with particular attention to the home environment and travel aids
- Exercise modification
- Rehabilitation including physiotherapy and hydrotherapy
- Other modalities, including acupuncture, dry needling, shockwave therapy and laser therapy (Alves et al, 2022)

- Surgery including joint replacement techniques and end stage procedures, such as amputation, arthrodesis and femoral head and neck excision
- Other intra-articular techniques, including autologous-conditioned serum, platelet-rich plasma and intra-articular high molecular weight hyaluronic acid and polyacrylamide gel treatments, as well as intra-articular steroids (methylprednisolone and triamcinolone) and alpha-2 macroglobulin therapy
- Supplements, for example glucosamine, chondroitin, cannabidiol oils, green-lipped mussels, turmeric and essential fatty acids
- Weight management
- Pentosan polysulphate (osteopen/cartrophen) and polysulfated glycosaminoglycans (Adequan)

Reviews and current evidence for the use of these modalities and treatment options are described (Pye et al, 2022; 2024). Several resources, such as the Aim-OA multimodal system (AIM OA, 2024) and a 5-stage grading system developed by Canine Arthritis Management (2024) are available to serve as guidance as to when to introduce one or more of these modalities. *Table 1* summarises the stages of osteoarthritis and some treatment options. It may be helpful to note that management options for late-stage disease are limited (arthrodesis, joint replacement, amputation and euthanasia) and that treatment modalities

should be tailored to each individual to prevent or delay the onset of late-stage disease.

A brief history of stem cell therapy

Stem cell therapy involves the use of stem cells to repair or replace damaged cells, tissues or organs, and has potential applications in a wide range of conditions. The history of stem cell therapy spans more than a century, with key discoveries contributing to its evolution as one of the most promising areas of regenerative medicine. Stem cell therapy is currently an active area of clinical research, including in areas such as Parkinson's disease, diabetes, heart disease, multiple sclerosis and Alzheimer's disease.

Three-dimensional bioprinting and tissue engineering using stem cells are emerging fields, with the potential to create replacement tissues and organs for transplantation. Gene editing technologies have further enhanced the possibilities for stem cell therapies by allowing precise modifications to stem cells before they are used therapeutically.

The history of stem cell therapy in dogs is closely tied to the progress made in human and equine medicine. Research into stem cell therapy has focused on mesenchymal stem cells, which are multipotent stromal cells capable of differentiating into various cell types, including bone, cartilage, muscle and fat. These cells were initially studied for their potential to treat

Table 1. Stages of osteoarthritis

Disease stage	Main pathological changes	Focus for management	Management strategy
Pre-clinical	Cartilage only Early synovitis	Prevention Prophylaxis Lifestyle alteration	Diet Environment Essential fatty acids
Early clinical	Cartilage Synovitis Synovial effusion or altered synovial fluid Early changes elsewhere in the joint	Disease modification Acute inflammation and pain control Prevention of neurosensitisation	Additionally: Disease-modifying drugs Regenerative therapy (autologous-conditioned serum, platelet-rich plasma) Intra-articular polyacrylamide/hydrogel
Established clinical	Established cartilage damage Chronic synovitis Altered synovial fluid Bone changes Extra-articular fibrosis of joint capsule Musculoskeletal effects Neurological alterations	Pain management Prevent sensitisation Control of secondary pathologies Preservation of mobility	Additionally: Adjunctive analgesia Transmission Regenerative therapy (adipose-derived stem cell treatment and platelet-rich plasma or autologous-conditioned serum) Hydrotherapy or physiotherapy Laser therapy Environmental modification Shockwave therapy Home and travel environmental modifications
Late-stage	As the established clinical stage Neurological alterations Fibrosis/mechanical limitations Muscle pathology/atrophy	Chronic pain control Increase mobility Increase exercise Address weakness Address behavioural changes Enhance quality of life	Additionally: Adjunctive analgesia: ● Modulation ● Perception Intra-articular steroids (triamcinolone/depomedrone)
End-stage	Immobile joint Extensive joint pathology Neuropathology	Reduce pain Restore mobility Enhance quality of life	Surgical salvage (joint replacement/ arthrodesis) Amputation Euthanasia

musculoskeletal injuries in horses. By the early 2000s, stem cell treatments were being used in practice to treat equine tendon and ligament injuries, and this laid the groundwork for extending similar therapies to dogs for orthopaedic conditions.

Although stem cell therapy in dogs has primarily been used for orthopaedic conditions, research has expanded to other areas, such as cardiac conditions, kidney disease and autoimmune disorders. The potential of stem cell therapy in treating canine cognitive dysfunction has also been evaluated (Chandrasekaran et al, 2021). Emerging research has also focused on the use of stem cells to modulate the immune system in conditions like diabetes mellitus (Gooch et al, 2019), inflammatory bowel disease (Pérez-Merino et al, 2015) and atopic dermatitis (Villatoro et al, 2018), where the immunomodulatory properties of mesenchymal stem cells have shown promise in reducing inflammation and managing symptoms.

Categories of stem cells

Stem cells are classified based on their origin and potential to differentiate into various cell types (Table 2). There are four main categories of stem cells:

- Embryonic stem cells are considered pluripotent in that they can differentiate into any cell type in the body. In humans, embryonic stem cells are obtained from the inner lining of blastocysts produced by in vitro fertilisation at around 3–5 days of development
- Adult stem cells (also known as tissue specific or somatic stem cells) can differentiate into a limited number of cell types, usually to those that form the tissue from which they are harvested
- Mesenchymal stem cells (Figure 1) are derived from bone marrow or fat and can differentiate into multiple cell types. They also express immunomodulatory behaviour and plastic adherence, and are the cell types used in canine osteoarthritis therapy
- Induced pluripotent stem cells are differentiated cells that have been manipulated to revert to embryonic stem cell type.

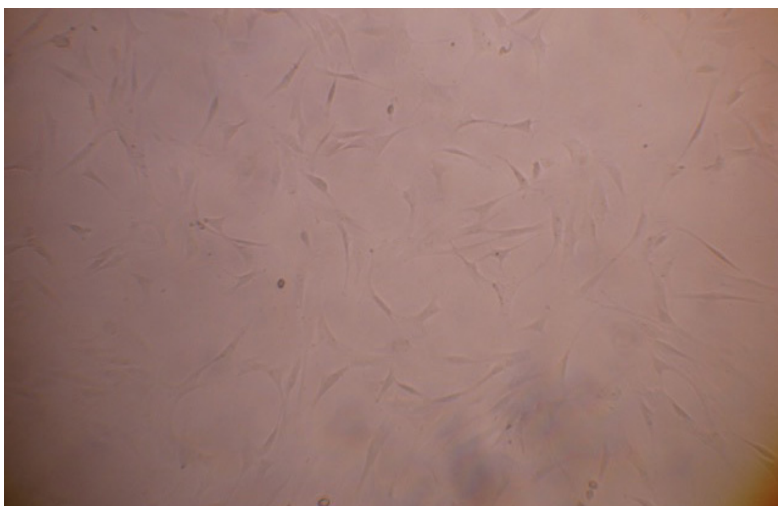


Figure 1. Stem cells in vitro – microscope photograph (x100).

Effects of stem cells

Mesenchymal stem cells have been extensively studied for their therapeutic potential because of their unique properties. The effects of mesenchymal stem cells in osteoarthritis are multifaceted:

- Regenerative effects
 - Tissue repair and regeneration: mesenchymal stem cells can differentiate into various cell types, including osteoblasts, chondrocytes, adipocytes and myocytes. This makes them valuable for regenerating damaged tissues, particularly in orthopaedic conditions (Caplan, 1991)
 - Promotion of angiogenesis: mesenchymal stem cells secrete factors that promote the formation of new blood vessels. This is critical in tissue repair, as it ensures an adequate blood supply to healing tissues
- Immunomodulatory effects
 - Mesenchymal stem cells suppress the activation and proliferation of T-cells, B-cells, natural killer cells and dendritic cells. This makes them useful in treating autoimmune diseases and in reducing the risk of transplant rejection
 - Induction of immune tolerance: mesenchymal stem cells can promote immune tolerance, making them beneficial in conditions where immune system suppression is useful
- Anti-inflammatory effects
 - Mesenchymal stem cells secrete anti-inflammatory cytokines and other molecules that can reduce inflammation in various conditions, including osteoarthritis
 - They can also influence macrophages to adopt an anti-inflammatory phenotype, which supports tissue repair and reduces chronic inflammation
- Paracrine effects
 - Secretion of bioactive molecules: mesenchymal stem cells exert many of their effects through the secretion of bioactive molecules, including growth factors, cytokines and extracellular vesicles. These factors promote cell survival, proliferation and tissue repair, even when the mesenchymal stem cells themselves do not directly differentiate into new tissue
 - Stimulation of resident stem cells: mesenchymal stem cells can enhance the activity of local stem cells in damaged tissues, thereby promoting endogenous repair mechanisms
 - Paracrine effects are considered to contribute to most of the beneficial effects of stem cell therapy in clinical application in dogs
- Anti-apoptotic effects
 - Mesenchymal stem cells release factors that can protect cells from apoptosis (programmed cell death), which is particularly important in preserving tissue integrity during injury or disease

Table 2. Types of stem cells

Type	Origin	Potency	Application
Embryonic	Inner cell mass of blastocysts	Pluripotent	Research, cloning and regenerative therapies, though their use is ethically controversial
Adult	Found in various tissues of the adult body, such as bone marrow, fat, skin and brain	Multipotent, can develop into a limited range of cell types related to their tissue of origin	Bone marrow transplants and regenerative treatments for specific tissues
Induced pluripotent stem cells	Somatic (adult) cells that have been genetically reprogrammed to an embryonic stem cell-like state	Pluripotent	Disease modelling, drug testing and potential regenerative therapies, offering an alternative to embryonic stem cells without the associated ethical concerns
Perinatal stem cells	Derived from perinatal tissues, including the placenta, umbilical cord and amniotic fluid	Typically multipotent, although research suggests they may have pluripotent characteristics	Research and potential therapies, particularly in regenerative medicine
Mesenchymal stem cells	Commonly bone marrow, but also in fat and umbilical cord tissue	Multipotent, with the ability to differentiate into bone, cartilage, fat and muscle cells	Regenerative medicine, particularly in osteoarthritis and bone and cartilage repair, and for immunomodulatory properties.
Haematopoietic stem cells	Bone marrow, peripheral blood and umbilical cord blood	Multipotent, specifically giving rise to various types of blood cells	Bone marrow transplants for treating blood disorders such as leukaemia and lymphoma
Neural stem cells	Specific regions of the brain and spinal cord	Multipotent, capable of differentiating into neurons, astrocytes and oligodendrocytes	Research into neurodegenerative diseases and potential therapies for conditions like Parkinson's and spinal cord injuries
Epithelial stem cells	Epithelial tissues of the skin and intestine	Multipotent, contributing to the regeneration of epithelial layers	Wound healing and research into tissue regeneration
Trophoblast stem cells	Derived from the early embryo, specifically from the cells that will form the placenta	Multipotent, with the potential to differentiate into various types of placental cells	Research into pregnancy and placental development

- Neuroprotective effects
 - Mesenchymal stem cells can support the survival and function of neurons and other neural cells, and are being investigated for their potential to treat neurodegenerative diseases and traumatic injuries to the nervous system
- Fibrosis reduction
 - Mesenchymal stem cells have been shown to reduce the formation of fibrotic tissue (excessive scar tissue), which can be beneficial in conditions like osteoarthritis
- Mitochondrial transfer from adult stem cells to somatic cells (Spees et al, 2006).

The mode of action of mesenchymal stem cells

There are two primary known modes of action of stem cells, when injected either locally (for example via the intra-articular route) or parenterally (intravenous route):

1. Stem cells can replace diseased cells by engrafting and differentiating into the required cell type. It was previously thought that the main mechanism of action

of stem cells was that, once injected into the site of an osteoarthritis lesion, they undergo differentiation into chondrocytes, helping to repair the lesion (Scharstuhl et al, 2007; Kriston-Pál et al, 2017)

2. Via a paracrine effect, donor cells act to stimulate the patient's cells to repair the diseased tissue, without the donor cells contributing directly to the new tissue. In effect, they orchestrate the healing response that may result in new tissue formation. It is thought that the effects of mesenchymal stem cells are exerted primarily through their secreted factors, including extracellular vesicles and bioactive molecules such as chemokines, cytokines and growth factors (Tofiño-Vian et al, 2018). These paracrine factors can have a range of immunomodulatory, anti-inflammatory, angiogenic and anti-apoptotic properties (Phinney and Pittenger, 2017; Mocchi et al, 2020). Therefore, the therapeutic effect may last longer than, and not be correlated with, stem cell viability.

Donor cells secrete growth factors that signal to the recipient's cells to change their behaviour. This signalling from one cell to another is called the paracrine effect, and

in this way, donor cells do not have to persist or populate damaged recipient tissue, to achieve tissue regeneration.

Damaged patient cells secrete cytokines and regulatory proteins that act as mediators to generate an immune response that attracts the donor cells. In turn, the donor cells secrete their own chemotactic proteins that stimulate the patient’s stem cells and help to reduce inflammation, promote cell proliferation and increase vascularisation and blood flow into areas of damaged tissue. Paracrine effect cells also secrete factors that inhibit the death of recipient cells because of injury or disease, and are able to ‘dampen’ the immune response that occurs during autoimmune disease (Najar et al, 2010).

This paracrine effect is considered the most important aspect of the regenerative process provided by the therapeutic use of stem cells. It is also thought to be responsible for the long-term effects of stem cell therapy where mesenchymal stem cells have a long-term effect on tissue regeneration, even though the cells themselves are short-lived (Abe et al, 2020), and it has been proposed that mesenchymal stem cells should now be known as ‘medicinal signalling cells’ (Caplan, 2017).

Mesenchymal stem cell homing

Besides their complex mechanisms of immunomodulation, one of the key advantages of mesenchymal stem cell-based

therapies is their ability to home to damaged tissue (Ullah et al, 2019).

When tissues are damaged, mesenchymal stem cells are naturally released into the circulation (as capillary pericytes), where they migrate to the site of injury and secrete molecules with immune-modulating, angiogenic and anti-apoptotic effects to create a microenvironment that promotes regeneration. Mesenchymal stem cells can home to damaged tissue and act as a ‘drug store’ to aid in repair or tissue regeneration (Caplan, 2009).

Homing can be systemic or non-systemic. In systemic homing, they are administered or endogenously released into the bloodstream and undergo a multi-step process to exit circulation and migrate to an injury site. The process of systemic homing can be divided into five steps: tethering and rolling, activation, arrest, transmigration or diapedesis, and migration (Ullah et al, 2019). In non-systemic homing, mesenchymal stem cells are transplanted locally at the target tissue and guided to the site of injury via a chemokine gradient.

Sources of stem cells

Stem cells can be harvested from various sources (Table 3). In clinical situations, stem cells are isolated from the patient (Table 4) from either adipose tissue or bone marrow, which are good sources of mesenchymal stem cells (Zhu et al, 2008). It is possible to isolate stem cells from peripheral blood, but these circulating cells are very low in numbers for the volume of blood sample required and as a result, cell culture and doubling time is very slow. Stem cells may also be derived from dental pulp, umbilical cord, placenta and synovium (Humenik et al, 2022). Adipose tissue-derived autologous mesenchymal stem cells are currently the preferred source for clinical use in the dog (Voga et al, 2020). Once an adipose sample has been collected, mesenchymal stem cells may be isolated and cultured in vitro, or prepared patient-side as a stromal vascular fraction for intra-articular injection (Table 5).

Routes of administration

Adipose-derived stem cells for osteoarthritis therapy can be administered intra-articularly, intravenously or via a scaffold. Intra-articular administration directly into the joint space of the affected joint is the most commonly adopted method in studies and in clinical practice to date (Kriston-Pál et al, 2017; Daems et al, 2019; Olsson et al, 2021).

Intravenous administration

As mesenchymal stem cells are known to have homing capacities (Ullah et al, 2019), studies have investigated the effectiveness of intravenous administration (Olsen et al, 2019) and consider that this route may be useful because the mesenchymal stem cells may interact with the immune system more than locally delivered cells.

Based on labelled mesenchymal stem cell detection studies, the principle of mesenchymal stem cells homing after intra-articular and intravenous administration

Table 3. Sources of stem cells
Autologous stem cells
● Source: harvested from the same dog that will receive the treatment ● Advantages: reduced risk of immune rejection because the cells are derived from the patient’s own body. Ability to culture potentially unlimited cell numbers, check for sterility, cell viability and freeze for future use ● Common use: osteoarthritis, ligament injuries and other musculoskeletal issues in dogs ● Disadvantages: requires sample collection from dog, culture and expansion of cells in lab over 14–21 days depending on cell numbers required and rate of cell growth
Allogeneic stem cells
● Source: derived from a donor dog and used to treat other dogs ● Advantage: easier and quicker to administer because the cells are pre-harvested and stored, eliminating the need for a harvesting procedure on the patient ● Common use: not currently in clinical use but have been used for research purposes (Harman et al, 2016) ● Disadvantages: Allogeneic stem cells are not currently commercially available in the dog and there is potential for immune reactions
Zoogeneic stem cells
● Source: derived from a different species to the recipient ● Advantage: easier and quicker to administer since the cells are pre-harvested and stored, eliminating the need for a harvesting procedure on the patient (Daems et al, 2019). Commercially available in the dog in the UK as equine umbilical cord mesenchymal stem cells ● Common use: osteoarthritis in hips and elbows ● Disadvantage: Potential for immune reactions. High cost for treating multiple joints compared to autologous cells. License restricted to elbows and hips and for one treatment. Small study sample size.

Table 4. Sources of autologous stem cells

Bone marrow aspiration
● Procedure: bone marrow is typically aspirated from the iliac crest or proximal humerus. The procedure is performed under general anaesthesia or heavy sedation to minimise discomfort ● Processing: the aspirated bone marrow is processed to isolate mesenchymal stem cells. This often involves density gradient centrifugation or similar techniques to separate the stem cells from other components of the bone marrow ● Advantages: bone marrow is a well-established source of mesenchymal stem cells with a high yield of cells that can differentiate into various tissues ● Disadvantages: the procedure is invasive and requires anaesthesia, and there is potential discomfort and complications associated with bone marrow aspiration
Adipose tissue harvesting
● Procedure: adipose tissue is commonly collected from falciform or omental fat via midline laparotomy ● Processing: the harvested adipose tissue is enzymatically digested to release the mesenchymal stem cells, which are then isolated and culture expanded ● Advantages: adipose tissue is abundant, easily accessible and the procedure is less invasive compared to bone marrow aspiration. Adipose-derived mesenchymal stem cells can be harvested in relatively large quantities ● Disadvantages: variability in the quality and differentiation potential of mesenchymal stem cells derived from adipose tissue compared to bone marrow. Use of subcutaneous adipose in dogs is prone to low yields and seroma formation
Peripheral blood collection
● Procedure: mesenchymal stem cells can be obtained from peripheral blood, although they are present in much lower concentrations compared to bone marrow and adipose tissue. Mobilisation agents like granulocyte colony-stimulating factor may be used to increase the number of circulating stem cells before collection ● Processing: the blood is processed using techniques such as density gradient centrifugation to isolate mesenchymal stem cells ● Advantages: less invasive than bone marrow aspiration or adipose tissue harvesting, as it involves only blood collection ● Disadvantages: the yield of mesenchymal stem cells is typically low, and the process may require pre-treatment with mobilising agents, which can add complexity
Umbilical cord collection
● Procedure: mesenchymal stem cells can be collected from the umbilical cord of newborn puppies. The umbilical cord is typically harvested immediately after birth during routine caesarean sections or natural deliveries ● Processing: the umbilical cord tissue is processed to extract mesenchymal stem cells, often involving enzymatic digestion and subsequent cell isolation techniques ● Advantages: the procedure is non-invasive for the dog and the cells obtained are very potent with high proliferative capacity ● Disadvantages: the opportunity to collect these cells is limited to the immediate postpartum period and there may be ethical considerations regarding the use of neonatal tissue. Commercially available only in the USA
Dental pulp extraction
● Procedure: mesenchymal stem cells can be obtained from the dental pulp, particularly from deciduous teeth that are naturally shed. Teeth may be collected opportunistically or extracted during routine dental procedures ● Processing: the dental pulp is removed from the tooth and processed to isolate mesenchymal stem cells, often involving enzymatic digestion and cell culture techniques ● Advantages: dental pulp mesenchymal stem cells are easily accessible, particularly in younger dogs, and the procedure is minimally invasive if performed during natural shedding ● Disadvantages: the yield of mesenchymal stem cells from dental pulp is relatively low, and the procedure is limited by the availability of suitable teeth
Synovial fluid and synovial membrane harvesting
● Procedure: mesenchymal stem cells can be collected from the synovial fluid or synovial membrane of joints. This is typically performed during arthroscopy or joint surgery, or via joint aspiration ● Processing: the synovial fluid or membrane is processed to isolate mesenchymal stem cells, often requiring centrifugation and culture to expand the cell population ● Advantages: these mesenchymal stem cells are considered particularly relevant for treating joint-related conditions, as they are already present in the joint environment ● Disadvantages: the procedure is invasive, typically requiring anaesthesia and surgical intervention, and the yield of mesenchymal stem cells can be low

seems to be promising for animals with osteoarthritis. However, there is a discrepancy between study results after intra-articular and intravenous mesenchymal stem cell administration in dogs.

Mesenchymal stem cell homing capacities were assessed by a model-based study on autologous bone marrow-derived

mesenchymal stem cells, which performed fluorescence analysis. Labelled mesenchymal stem cells were detected in new cartilage 2 and 8 weeks after intra-articular injection, confirming local or non-systemic mesenchymal stem cell homing (Mokbel et al, 2011a). These results are comparable to a similar model-based study in donkeys which assessed

KEY POINTS

- Treatment for osteoarthritis in dogs requires a multimodal approach.
- Stem cell techniques have been developed out of the necessity to improve the ability to help the patients under veterinary care, where there is no simple solution to a chronic, complex disease process.
- Autologous, adipose-derived cultured mesenchymal stem cells are currently considered ideal for intra-articular stem cell therapy in osteoarthritis in dogs.
- Paracrine effects are the most important aspect of the regenerative process provided by the therapeutic use of stem cells.

Table 5. Comparison table of patient side vs laboratory-cultured mesenchymal stem cells

	Laboratory-cultured mesenchymal stem cells	Patient-side stromal vascular fraction
Advantages	Can request specific cell numbers depending on number and size of joint(s) to be treated Does not contain other cell types Can carry out cell count Can carry out sterility testing Can carry out cell viability testing Can store cells for future use (-180°C)	Adipose collection and intra-articular injection of cells may be carried out in the same visit Less expensive
Disadvantages	Takes 14–28 days for cell culture Requires second patient visit Requires second anaesthetic or sedation More expensive	Less stem cells/ml Contains other cell types such as endothelial cells, pericytes and immune cells (Franklin et al, 2018) Cannot carry out cell count Cannot carry out sterility testing Cannot carry out cell viability testing Requires specialised in-house lab equipment Requires specialised training Cannot store cells for future use

the homing capacity of intra-articular injected, labelled, autologous bone marrow-derived mesenchymal stem cells where fluorescence microscopy confirmed the incorporation of labelled mesenchymal stem cells in newly formed cartilage 1, 2 and 6 months post-treatment (Mokbel et al, 2011b).

In a study on intravenous injection of allogeneic adipose tissue-derived mesenchymal stem cells, those labelled with cell membrane dye were only occasionally detected in synovial fluid (Olsen et al, 2019). In rabbit and equine studies, homing of intravenous autologous and allogeneic mesenchymal stem cells to areas of tissue injury was also confirmed (Ueda et al, 2017; Mund et al, 2020). Olsen et al (2019) suggested

pulmonary trapping, early assessment of the synovial fluid, attachment to synovial membrane and inadequate cell labelling as possible causes of insufficient mesenchymal stem cell homing detection on intravenous administration. To bypass problems associated with lung capillaries when stem cells are introduced intravenously, where mesenchymal stem cells are relatively large cells (with an average size of 30 µm in comparison to pulmonary capillaries which are on average, only 14 µm in diameter) causing mechanical entrapment of mesenchymal stem cells in the lungs, intra-arterial and intraperitoneal routes of administration have been trialled.

Scaffold administration

Scaffolds are tissue-engineered cartilage and bone, transplanted into osteochondral defects as a template for new tissue formation and organisation. Mesenchymal stem cells can be seeded on these scaffolds (Yang et al, 2011; Duan et al, 2013; Qiang et al, 2014). Based on a matched-pair study, mesenchymal stem cell administration on a scaffold was more beneficial to clinical and arthroscopic outcomes in humans with stifle osteoarthritis than mesenchymal stem cell administration via intra-articular injection alone (Kim et al, 2015).

Conclusions

Stem cell therapy has undergone significant development from its theoretical origins to clinical applications, and regenerative medicine holds great promise for treating a wide array of conditions and diseases. Despite challenges, the potential for stem cell therapy to revolutionise medicine remains immense. In dogs, stem cell therapy may be used as part of a multimodal approach to best manage osteoarthritis where there is no simple generic solution to what is considered a chronic, complex disease process. CA

Conflicts of interest

The author declares that there are no conflicts of interest.

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