Introduction

The nervous system is a complex entity, derived during development from a sheet of neural stem cells (NSCs). Although a small number of NSCs and glial cells exist in the CNS, their capacity for repair is extremely limited. Regenerative therapies to augment or replace natural cellular or tissue repair have been a focus of research for decades. Multiple cell types and biologies have been investigated, including mesenchymal stromal or stem cells (MSCs), embryonic stem cells, NSCs, neural precursor cells, and induced pluripotent stem cells (iPSCs) and their derivatives. An overview of the discussed therapies is included (Figure 1). However, few studies have investigated the use of cellular therapies for neurologic disease in veterinary species. The goal of this narrative is to review the pertinent veterinary literature regarding a variety of regenerative therapies for neurological disease, highlighting proposed mechanisms of action, indications for use, administration techniques, potential benefits, and safety concerns. Studies were selected from PubMed and Web of Science Core Collection from January 1, 2000, to January 1, 2023; search criteria included cellular therapies and neurological diseases and were not initially restricted to veterinary species. The authors determined salient articles for inclusion focusing on horses and dogs but included research in potential cellular therapies supported by experimental studies in other species.

Potential Benefits of Cellular Therapies

Cellular therapies may provide benefits by 3 mechanisms: cellular replacement, immune modulation, and paracrine signaling. Cellular replacement...
imparts that the administered cells replace the original neural cells. Immune modulation of either the central or peripheral nervous system may be facilitated through direct cell-to-cell contact or secretion of molecules such as cytokines (eg, IL-10 and TGF-β) and enzymes that modulate immune responses (eg, indoleamine 2,3-dioxygenase and arginase). The third mechanism involves the release of neurotrophic factors like brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and glial-derived neurotrophic factor processes, promoting generation and repair.

The field of cellular therapy has advanced significantly in the last 10 years. For example, liver tissue repair and regeneration are substantial targets. In 2013, Takebe et al reported the ability to produce a functional human liver in vitro from iPSCs. Since then, other organ tissues have been developed in vitro (cardiac, thymic, kidney, and small intestine) as well as various nervous system components (cortical projection neurons, dopaminergic neurons, and cortical motor neurons).

Although the technology to generate equine and canine organs has not been developed yet, multiple studies have focused on the immunomodulatory functions of equine MSCs. Using MSCs cocultured with stimulated lymphocytes, these studies have shown a decrease in lymphocyte proliferation, indicating an anti-inflammatory or immune suppression effect. Recent in vitro work may suggest that inflammation is necessary to push MSCs into an immunosuppressive phenotype. Namely, Barrachina et al demonstrated MSCs immune modulatory factors increased when MSCs were exposed to the inflammatory cytokines interferon-γ and tumor necrosis factor-α. The influence of the environment on MSCs is still under investigation and comprises an important focus of future research. Contrary to in vitro work, in vivo work in rat traumatic brain injury reveals a short period following implantation in which a portion of the stem cells undergo hypoxia-mediated cell death, inflammatory cell invasion, and neoangiogenesis.

Le Blon et al speculated that regenerative processes following stromal or stem cell engraftment may be due to paracrine secretion coupled with an in vivo inflammatory reaction.

Recent reports have focused on determining the pathways by which MSCs may exert their anti-inflammatory effects. Prostaglandin-E2 has been implicated in the pathway of immune suppression by allogeneic MSCs, but immune modulation is likely multifactorial, depending on cellular and environmental factors. In fact, the immune-modulating effects of MSCs extend beyond the typical trophic mechanisms and include direct immune cell interactions by both living or dead and fragmented MSCs. For example, Benvenuto et al have determined that human MSCs are able to affect lymphocyte cell adhesion and extravasation by influencing the expression of important cell surface adhesion molecules on both lymphocytes and endothelial cells. This could be of particular importance when treating neurological conditions that result in T-cell extravasation across the blood-brain barrier. Further, studies in musculoskeletal injury have identified inflammatory cytokines, such as IL-1β, that prime MSCs for healing and increase their production of anti-inflammatory cytokines such as prostaglandin-E2.

### Treatment of Neurologic Disease with MSCs

Most research using equine or canine stem cells has employed MSCs derived from bone marrow, adipose, or umbilical tissues, but MSCs may come from a variety of other sources including synovium and skin. These cells are multipotent, meaning that they are able to develop into multiple cell types. For MSCs, stem cell characterization requires the ability to undergo trilineage differentiation: developing into fat, bone, and cartilage. Normally, MSCs express very low levels of neural factors. However, if MSCs are exposed to specific cytokines they may be conditioned to a neural cell-like morphology with expression of neural markers such as neuron-specific enolase, NeuN (a neural-specific nuclear protein), neurofilament-M, and tau proteins. Other methods of differentiation include exposure to other neural cells such as Schwann cells or astrocytes. Differentiation of equine MSCs into cells of neural lineage was achieved by Cruz Villagran et al using nitrogen-coated tissue plates. In addition, neuronal cells have been induced from equine adipose tissue-derived MSCs and bone marrow-derived MSCs in culture using lentiviral vectors. Furthermore, equine Schwann-like cells induced from adipose-derived and bone marrow-derived MSCs have been promoted as a potentially promising new strategy for peripheral nerve injury including equine motor neuron disease. That stated, clinical or experimental studies supporting their use in equine peripheral nerve injury have not been completed. Perineural injection of autologous MSCs for treatment of recurrent laryngeal neuropathy has been described in 5 horses using guidance from an electrical nerve
stimulator. Although the injection was well tolerated, no improvement in laryngeal function was noted at 1, 7, or 28 days following injection. It is clear that further research is needed to support the use of MSCs or Schwann-like cells induced from MSCs in equine peripheral nerve injury.

As an example of the use of stem cells to release neurotrophic factors, dogs have been used as a preclinical model of peripheral nerve injury with separate studies investigating MSCs graft on various scaffolds resulting in some restoration of locomotor activity following removal of a portion of the sciatic nerve. Further, a study comparing the efficacy of platelet-rich plasma or bone marrow–derived MSCs in combination with a saphenous vein graft for facial nerve transection in dogs found subjects treated with MSCs showed a significant improvement in clinical signs 4 weeks postoperatively compared to graft alone. Further, an experimental study using IV administration of MSCs in a small study of 3 German Shepherd Dogs with naturally occurring intervertebral disk disease did not show clinical improvement in comparison to control dogs but did not have any adverse effects. In horses, autologous MSCs have been administered intrathecally with no changes in clinical signs or cerebrospinal fluid parameters compared to a control group. These various studies indicate that autologous MSCs are well tolerated and may provide beneficial effects in canine spinal cord injury. Although such evidence is promising, more double-blinded, placebo-controlled, clinical trials are needed before making definitive conclusions.

There is a significant, unresolved debate over the use of allogeneic ("nonself") stem cells. Allogeneic bone marrow–derived and adipose tissue–derived MSCs administered intrathecally, IV, intraspinally, and directly into the disk for canine spinal cord injury. In a small preliminary study, autologous bone marrow–derived MSCs were administered to dogs and cats suffering from chronic (> 2 months) intravertebral disk extrusion; no adverse reactions were recorded and all animals showed significant clinical recovery. No control group was included as the therapy was only administered following the failure of traditional treatment, and no improvement in disk extrusion was seen on MRI 90 days following treatment. In a canine experimentally induced spinal cord injury model, intrathecal delivered labeled stem cells were identified by histopathology at the damaged site 1 and 4 weeks after injury; both allogeneic and autologous MSCs improved clinical, MRI, and histopathological outcomes compared to the control group, and RNA expression for neurotrophic factors was higher in both MSC-treated groups compared to the control group. In an experimental study where Beagles (n = 6/group) underwent complete spinal cord transection, those animals treated with MSCs on a collagen/heparin sulfate scaffold had improved bladder function, nerve function, and imaging compared to those treated with collagen/heparin sulfate scaffold alone. Further, an experimental study using IV administration of heat shock–treated MSCs implanted into Beagles with acute spinal cord injury showed significant improvement in hindlimb function compared to control animals; clinical findings were supported by histological and Western blot analysis of fibrosis, myelination, and neural markers. Kim et al suggested that MSCs administered IV for spinal cord injury may work through anti-inflammatory and antioxidative mechanisms. In a compelling study of 22 dogs undergoing hemilaminectomy following spinal compression, half the animals were administered MSCs epidurally following surgery; although all animals recovered locomotion, those that received MSCs recovered locomotion faster (7 days vs 21 days) and were discharged sooner. Intrascal application of MSCs in a small study of 3 German Shepherd Dogs with naturally occurring intervertebral disk disease did not show clinical improvement in comparison to control dogs but did not have any adverse effects. In horses, autologous MSCs have been administered intrathecally with no changes in clinical signs or cerebrospinal fluid parameters compared to a control group. These various studies indicate that autologous MSCs are well tolerated and may provide beneficial effects in canine spinal cord injury. Although such evidence is promising, more double-blinded, placebo-controlled, clinical trials are needed before making definitive conclusions.

There is a significant, unresolved debate over the use of allogeneic ("nonself") stem cells. Allogeneic bone marrow–derived and adipose tissue–derived MSCs administered IV in a mouse model of stroke, using middle cerebral artery occlusion, showed significant functional improvement, decreased cell death, and increased cell proliferation as well as an increase in neurogenesis, oligodendrogenesis, synaptogenesis, and angiogenesis markers. Experimental trials surrounding allogeneic and xenogenic neural cell and MSC engraftment, show that engraftment of neural cells into the CNS results in immune recognition by T lymphocytes. However, T lymphocytes appear to have little involvement in immune reaction to MSCs, which seem to be dominated by macrophages and microglia. The clinical success of allogeneic MSCs may be linked to their ability to modulate the immune response.

Multiple in vitro reports have indicated that allogeneic bone marrow–derived MSCs retain their immune suppressive properties in vitro while expressing very low levels of major histocompatibility complex II. In agreement with these in vitro reports, allogeneic MSCs have been used to treat knee osteoarthritis in humans and musculoskeletal disease in the horse with good success. However, conflicting results exist both in vitro and in vivo, indicating a host immune response may occur when allogeneic MSCs are administered. The significance of this response is unclear. Intradermal and intra-articular allogeneic MSC use has been reported to result in alloantibodies. Therefore, repeated injections of allogeneic non-cross–matched MSCs should potentially be avoided.

A small preliminary investigation of allogeneic amniotic membrane–derived MSCs administered at the time of surgery in dogs with intervertebral disc disease resulted in no adverse effects and significant neurological improvement in some patients; however, no improvement was seen on MRI, and histological outcomes were not performed as clinical cases were enrolled. Further, multiple injections of allogeneic adipose tissue–derived MSCs were administered to 4 dogs with fracture of the sacral vertebral or fracture of the seventh lumbar vertebrae and lumbosacral displacement; no adverse side effects were noted and all dogs showed significant neurological improvements. These studies suggest allogeneic MSCs may be beneficial in dogs with spinal cord injury or intervertebral disc disease. However,
controlled, experimental studies with clinical and histological outcomes are necessary to confirm these preliminary clinical studies.

Repeated allogeneic MSC administration has been investigated in horses. Repeated IV administration of allogeneic equine MSCs resulted in no clinically adverse reactions but an increase in circulating CD8+ T lymphocytes, indicating an alloantigen cytotoxic response. However, the significance of this response remains unclear. Allogeneic MSCs may act differently in the presence of inflammation with inflammation acting as a trigger for the release of anti-inflammatory mediators. Recent in vitro studies suggest equine MSCs may decrease their expression of major histocompatibility complex II in response to the presence of inflammatory cytokines. Further, interferon-γ-treated MSCs inhibit production of IL-10 by B cells and result in strong immune modulation.

Allogeneic bone marrow–derived MSCs have been administered intrathecally in healthy dogs; no differences were seen in a neurodisability score, CSF, analysis, and magnetic resonance imaging between dogs administered allogeneic versus autologous MSCs at 1 or 5 days following injection. Likewise, intrathecal administration of 100 million allogeneic MSC in horses resulted in no adverse changes in blood, CSF, or neurological examinations. Intraspinal administration of allogeneic MSCs in 6 client-owned dogs with ventral compression fracture resulted in significant improvement in locomotor status and sensory function without adverse effects.

Technetium-labeled, canine allogeneic MSCs administered intraspinally were detectable at the injection site for at least 24 hours postinjection. Likewise, equine allogeneic umbilical cord–derived MSCs were detectable in the spinal cord up to 14 days following intraspinous injection in healthy, experimental horses undergoing cervical ventral interbody fusion. However, equine allogeneic MSCs given intrathecally were not detectable at the injury site 7 or 15 days following injection in a small study population (n = 3 horses).

It is important that we recognize the influence of the environment on MSCs; these cells may adapt and alter their function in response to environmental cues. It is, therefore, important that regenerative therapies be tested for their specific condition before clinical use and not just in healthy animals.

Further randomized, controlled, prospective studies are necessary for the horse and dog before widespread clinical use for neurologic disease.

**Neu trophic Treatments**

Axons in the adult nervous system do not regenerate effectively. However, during development, neurotrophic factors such as NGF, BDNF, and neurotrophin-3 allow for growth and extension of axons. It is reasonable, therefore, that these neurotrophic factors may be harnessed to promote axonal survival and function in the adult.

These neurotrophic factors still have significant limitations. NGF has the unfortunate characteristic

**Cell Replacement with NSCs in Spinal Cord Injury and Neurodegenerative Diseases**

NSCs are resident stem cells of the nervous system. As such, they demonstrate the ability to differentiate into neurons, astrocytes, and oligodendrocytes in vitro. The growth factors fibroblast growth factor and epidermal growth factor are important for NSC differentiation. These cells were first harvested in the late 1980s from the mouse subventricular zone and have since been isolated from humans and dogs but not horses. Recently, canine NSCs have been successfully isolated from adult cervical spinal cord and fetal canine spinal cord and differentiated into neural lineage and glial cells including astrocytes, neurons, and oligodendrocytes in vitro. Although these cells have been isolated, creating specific neuronal tissue has not been perfected. With multiple different neuron types comprising the complicated nervous system, Irion et al indicated “no universal neuron will be able to fulfill the exquisitely specialized function of a neuronal subclass.” A further complication arises; MSC expansion may result in the loss of neurogenic capacity and the increasing production of glial cells. Due to these limitations, NSCs have not been used clinically in horses or dogs.

**Embryonic Stem Cells as a Source of Neural Precursor Cells**

In contrast, to multipotent stem cells, pluripotent stem cells can develop into all cell types within the body excluding extraembryonic cells such as placental cells. The development of all cell types and the extraembryonic cell types is referred to as totipotency and is achieved only by embryonic stem cells. Although embryonic stem cells have the advantage of being totipotent, they have many logistical disadvantages. Most importantly embryonic stem cells must be acquired from a blastocyst. This process can result in ethical considerations, as the blastocyst...
must be sacrificed to harvest the cells. This also makes autotransplantation impossible. Therefore, embryonic stem cells cannot be used in situations where autologous stem cells are preferred. For these reasons, researchers have sought alternative cell sources for the treatment of neurological diseases.

**Neural Precursor Cells**

Oligodendrocyte precursor cells are precursors to oligodendrocytes. This cell population forms a homogenous population throughout the white and gray matter of the brain. Although these cells are primarily thought of as precursors to oligodendrocytes, controversy exists on whether they can be differentiated into neurons. Oligodendrocyte precursors may be modified before transplantation. For example, Yao et al. used lentivirus to increase platelet-derived growth factor production, a growth factor that promotes their survival, proliferation, migration, and differentiation into oligodendrocytes in a rat model of spinal cord injury resulting in increased tissue repair and neurologic function. Neurologic insults are often complex, resulting in damage to multiple subtypes and, therefore, may require a more plastic cell source. However, oligodendrocyte precursors may provide a viable treatment for diseases affecting the myelin sheath of the CNS.

Researchers have also examined the use of a less differentiated, precursor cell, the neural crest cells. The neural crest forms early in the vertebrate embryo, and cells from the neural crest later differentiate into neurons, glia, smooth muscle cells, endocrine cells, etc. These cells are multipotent and therefore are a good, potential model for complex cellular repair. They have been successfully isolated from human embryonic, fetal, and adult tissues and are referred to as neural crest stem cells. However, adult neural crest cells are rare, and difficult to isolate. Therefore, researchers have recently focused on differentiating embryonic or iPSCs into neural crest stem cells. As such, embryonic stem cells or iPSCs could provide an unlimited cell source to generate neural crest stem cells. In a mouse study, neural crest stem cells had improved motor recovery in spinal cord injury and nerve regeneration in peripheral nerve injury. The authors are unaware of any equine studies using neural crest cells. However, a study by McMahon and colleagues established the survival of neural crest cells injected into the spinal cords of healthy dogs.

**Treatment of Neurodegenerative Disease with MSCs or Neural Precursor Cells**

Neurotrophic factors delivered by MSCs may be a more promising treatment in neurodegenerative diseases. MSCs administered to sites of nerve injury are known to produce neurotrophic factors including BDNF and NGF. Administration of MSCs has shown some promise in amyotrophic lateral sclerosis, a human condition linked to a mutation in Cu/Zn superoxide dismutase gene with similar features to canine degenerative myelopathy. A new multilineage-differentiating stress-enduring cell derived from human MSCs, known as a “muse cell,” has shown safety and some positive clinical effects in a phase 2 clinical trial in Japan. A canine study utilizing a combination of allogeneic MSCs and in-hospital neurorehabilitation (n = 8) in canine degenerative myelopathy resulted in an increased mean survival time and open field score in comparison to ambulatory neurorehabilitation alone (n = 5).

MSCs and NSCs have been investigated as a treatment for Alzheimer disease in humans with success in multiple animal models. Canine cognitive dysfunction and Alzheimer disease share many commonalities including progressive neurodegeneration with behavioral manifestations including disorientation. In a compelling phase 2/2A veterinary clinical trial in dogs with canine cognitive dysfunction, 4 out of 5 dogs treated with autologous skin-derived neural precursor cells into the hippocampus improved clinically with 2 having a full reversal of symptoms for 2 years.

**Treatment of Spinal Cord Injuries with iPSCs**

Dr. Shinya Yamanaka and Dr. John Gurdon received a Nobel Prize in 2012 for discovering the ability to create iPSCs from mature cells. Since this time, interest in the use of iPSCs has accelerated. iPSCs are pluripotent cells that can give rise to all cell types except placental or amnionic cells. iPSCs are generated from adult cells by manipulating the genome. Therefore, these cells provide a valuable alternative to embryonic stem cells, without the same ethical considerations as they can be harvested from any adult cell in the body. iPSCs are immortal whereas MSCs are thought to lose their “stemness” after several passages. However, small genetic variations called single-nucleotide variations may occur with continued replication. Despite some of the benefits of immortality as a therapeutic agent source, iPSCs carry the risk of being teratogenic. Therefore, these cells are most valuable as an intermediary state. Namely, iPSCs are used to derive another cell type, such as astrocytes or oligodendrocytes, which may then be implanted. The partially or fully differentiated progeny of iPSCs may be therapeutically effective by replacing or regenerating lost neurons, remyelinating axons, or providing immune modulatory cells or trophic support.

Initial methods of generating iPSCs have relied on the use of viral vectors. These vectors contain the genes associated with pluripotency (Oct4, Sox2, Klf4, and c-Myc). Although successful, viral vectors introduce the possibility of negative side effects including reactivation of the viral genes resulting in malignancy. Therefore, additional techniques have been developed including mRNA reprogramming and nucleofection using episomatic plasmids.

Recent reports have outlined the development of equine and canine iPSCs derived from...
fibroblasts. Sharma et al\textsuperscript{88} were able to generate functional neurons from equine iPSCs in vitro. Although the field of equine and canine iPSCs is in its infancy, we are likely to see an increased focus on iPSC-derived cell lines for the treatment of neurologic and musculoskeletal diseases.

Much research has focused on cellular therapy for traumatic spinal cord injury. Spinal cord injury is unique, in that, the initial insult is followed by a debilitating and prolonged secondary injury cascade. Researchers have sought to utilize iPSCs for spinal cord injury, as these cells are able to create multiple different cell types simultaneously. Cells derived from iPSCs include dopaminergic neurons,\textsuperscript{89} motor neurons,\textsuperscript{90} and cerebral cortical neurons.\textsuperscript{91} Studies\textsuperscript{89,92,93} using iPSC-derived neural progenitor cells in rodents and nonhuman primates have shown that iPSC-derived neural progenitor cells are able to differentiate into neurons and glia in vivo. Researchers have shown improvement in remyelination, axonal regeneration, and improved clinical outcomes. Canine iPSCs have been induced into canine neural cells including glial cells and neurons and implanted into 2 dogs with chronic spinal cord injury; although no adverse effects were recorded, no significant clinical improvement was observed.\textsuperscript{94}

Although iPSCs and their cellular derivatives remain a promising therapeutic in the future, they have multiple disadvantages to overcome before clinical use. Creating iPSCs is labor intensive and extremely time consuming. Culture periods are significantly longer than traditional stem cell therapies, and the efficiency of all techniques remains low. This makes autologous use, especially for acute injury, unlikely, iPSCs also carry significant safety concerns. Namely, these cells result in teratomas. As a result, iPSCs are not meant to be used as a regenerative medicine therapeutic. Instead, it is the cellular derivatives that are employed.

Challenges Associated with Delivery of Cellular Therapies

Just as there are many options for cellular therapies, there are also multiple options for implantation. Cells can be administered intrasensionally, intrathecally, within a scaffold, or systemically (IV or intra-arterial).

In many ways, intrasensional or scaffold-facilitated therapy may be considered the gold standard as it ensures delivery of the cells to the site of injury. However, when lesions are diffuse or inaccessible, other regional or systemic methods of administration may be beneficial. Indirectly, one may take advantage of the immune modulatory or anti-inflammatory properties of stem cells with systemic administration.

A murine study\textsuperscript{95} of spinal cord injury sought to determine the optimal method of administration (intrasensionally, IV, or intrathecal administration) and determined intrasensional administration resulted in the highest number of persistent grafted cells. However, it is unclear how engraftment correlates to clinical improvement. For example, a similar study\textsuperscript{96} sought to compare 6 administration methods and determined intralosomal administration. The authors\textsuperscript{96} concluded that IV administration may be an attractive, less invasive, treatment for stroke. This is in agreement with a rat model of spinal cord disease that found intrasensional, intracisternal, and IV administration all resulted in improved functional recovery.\textsuperscript{97}

**Neurologic Diseases Where Cellular Therapy Is Most Likely To Be of Benefit**

A few characteristics create the ideal environment for cellular therapy. Evidence is prevalent that MSCs are immunomodulatory.\textsuperscript{10,11,98} Therefore, acute inflammatory or autoimmune-mediated diseases may be rational targets for stem cell therapy.

A murine model of acute traumatic brain injury using IV administration of MSCs demonstrated multiple parameters of immune modulation including a decrease in macrophages and peripheral leukocytes, reduced proinflammatory cytokines, and increased anti-inflammatory cytokines.\textsuperscript{99} Likewise, subarachnoid hemorrhage may be considered an acute inflammatory environment that carries a high morbidity and mortality. When MSCs were employed in an experimental model in rats, improved clinical recovery and enhanced neuroplastic effects were found.\textsuperscript{99}

Single-cell diseases may also provide an attractive target for the regenerative characteristics of cellular therapy. If a single cell target can be identified, a regenerative method becomes more attractive and, in many ways, attainable. Parkinson disease fills the criteria, caused by the death of dopaminergic neurons of the substantia nigra, and therefore has become a substantial target for extensive cellular therapy.

Autologous cellular therapies may be appropriate in slowly progressive diseases such as canine cognitive dysfunction or degenerative myelopathies. Although allogeneic cellular therapies remain controversial, they provide a distinct benefit when immediate therapy is necessary. Because of this, we believe continued research in allogeneic cellular therapies is imperative.

**Promise and Challenges: the Future of Cellular Therapy for Neurologic Disease in Companion Animals**

Much promise exists in utilizing cellular therapies for veterinary neurologic conditions. Although the field remains in its infancy, it is rapidly advancing with extensive animal research being pursued, often modeling human disease. Many equine and canine neurologic conditions provide challenging...
therapeutic targets with few established surgical or medical treatments. Cellular therapies provide 2 distinct mechanisms for treating these diseases. One mechanism targets inflammation and results in immune modulation. The second relies on the replacement of cells of interest. New cellular technologies, such as iPSC or allogeneic stem cells, may provide the clinician with an off-the-shelf weapon in their armamentarium. Future studies are necessary to determine the efficacy of these cellular therapies and help guide clinicians in selecting the optimal cellular therapy, timing of application, dosage, and method of delivery for a particular condition.

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