American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Review Article

Advances in Mesenchymal Stem cell Therapy for Equine Osteoarthritis

Wenyi Guo[1,2], Carolina Bluguerman[3], Adrian Mutto[1,3], David Whaley[1], Todd Scott[4], Mike K S Chan[5,6], Michelle B F Wong[4,5], Michael Alexander[7] and Jonathan RT Lakey[1,7,8*]

[1]*Global Innovative Health Solutions, Carrollton, Georgia, USA.*

[2]*Department of Pancreatic Surgery, General Surgery, Qilu Hospital of Shandong University, Jinan, China.*

[3]*Instituto de Investigaciones Biotecnologicas, Universidad Nacional de San Martín, CONICET, Buenos Aires, Argentina.*

[4]*Crestwood Veterinary Clinic, Edmonton, Canada.*

[5]*European Wellness Biomedical Group, Klosterstrasse 205ID, Edenkoben, Germany, 67480.*

[6]*Baden R&D Laboratories GmbH, z.Hd.v., Sabine Conrad Ferdinand-Laselle-Strasse 40 Germany, 72770.*

[7]*Department of Surgery, University of California Irvine, Irvine, California, USA, 92868.*

[8]*Department of Biomedical Engineering, University of California Irvine, Irvine, California, USA, 92868.*

***Corresponding author:** Jonathan R T Lakey, Global Innovative Health Solutions, Carrollton, Georgia, Department of Surgery, University of California Irvine, Irvine, California, USA, 92868, Department of Biomedical Engineering, University of California Irvine, Irvine, California, USA, 92868.

To Cite This Article: *Wenyi Guo, Carolina Bluguerman, Adrian Mutto, David Whaley, Todd Scott, Mike K S Chan, Michelle B F Wong, Michael Alexander and Jonathan RT Lakey*, Acute Cerebral Ischemia in Patient with COVID 19: Debut of the Thrombectomy Service in Kuwait - Case Report. Am J Biomed Sci & Res. 2024 22(3) AJBSR.MS.ID.002958,* DOI: 10.34297/AJBSR.2024.22.002958

Received: : April 28, 2024; **Published:** May 02, 2024

Abstract

Stem cell-based regenerative therapies have gained attention from equine veterinarians in the past two decades responding to the pressing need posed by the high prevalence of musculoskeletal disorders among horses and the limited success of conventional treatment options. Given their remarkable regenerative potential and versatility, mesenchymal stem cells (MSCs) have merged as a focal point of interest within this field. As a prevalent and debilitating musculoskeletal disorder, osteoarthritis (OA) poses significant challenges for equine veterinarians and owners alike, affecting the well-being and performance of affected animals. This review aims to provide valuable insights into evidence-based treatments using MSCs in equine veterinary medicine, ultimately improving outcomes for horses affected by OA and contributing to ongoing efforts to advance equine musculoskeletal health.

Keywords: Stem cell therapy, Mesenchymal stem cell, Osteoarthritis, Horse, Equine

Introduction

Animals, like human beings, undergo aging, an inevitable natural process that affects all living beings. With aging, animals frequently experience the development of articular cartilage lesions, a condition known as osteoarthritis (OA). Sporting and working animals are more likely to develop OA due to the chronic strain they endure, which can lead to damage and deterioration of bone and muscle tissue, resulting in clinical signs [1-3] characterized by chronic pain and increasing disability as a result of progressive joint degeneration [1].

In OA, chondrocytes transition from a quiescent state to an "activated" state, marked by cell proliferation, matrix degradation and remodeling, and inappropriate hypertrophy-like maturation, leading to degradation of the articular cartilage, thickening of the subchondral bone, osteophyte formation, and synovial inflammation.

The primary characteristic of OA is the progressive degeneration of articular cartilage and surrounding periarticular tissues.

Unfortunately, due to relative avascularity and therefore the lack of systemic regulation, cartilage has limited intrinsic repair capacity, making regeneration challenging [4]. Therefore, OA is a progressive condition that cannot currently be cured [3]. The absence of a cure for OA requires management strategies to alleviate pain and inflammation, restore normal cartilage and joint function, and prevent further damage [5]. The primary characteristic of OA is the progressive degeneration of articular cartilage and surrounding periarticular tissues. These conditions are primarily associated to either injury, aging or over exertion. After an injury, the affected area of cartilage forms fibrous tissue and loses its structural properties of hyaline tissue. In some cases, the cartilage defect may even penetrate through the entire cartilage to the subchondral bone, resulting in pain, deformity, loss of function of the entire joint, and even disability [6,7]. Similar to humans, horses also experience OA as a result of aging and extended periods of exercise.

As such, animal health is a major concern for the industry, especially in equine, given that the cost of injuries and illnesses in sports animals worldwide amounts to billions of dollars each year. The types and anatomical location of injuries vary among sporting disciplines, levels of competition, and age, but in all cases, articular and musculoskeletal injuries are the most clinically relevant in most sports disciplines, mainly because of their poor healing capacity and the consequent tendency to develop chronic or degenerative disorders [8].

This implies, in a large number of cases, animals are unable to return to training or competition and often must wait for long periods of time to do so. Even in the most severe cases, euthanasia may be necessary [9]. Numerous investigations have shown that orthopedic problems are the main reason for loss of training ability and death in athletic horses [10-13] accounting for more than 70% of lost training days in both jumping and racing horses [14].

Current methods for OA treatment in animals include systemic or intra-articular application of non-steroidal anti-inflammatory drugs (NSAIDs), hyaluronic acid, and other substances [15,16], or even surgical treatment [17]. However, these therapeutic options do not halt the progression of the disease, and always associated with some side effects [18] and at best provide short-term solutions, where the repaired tissue does not have the same characteristics of elasticity and strength as the original tissue, and thus result in a high rate of injury recurrence. In fact, partial healing of the lesion usually ends in fibrosis that is difficult to treat, due to an over-accumulation of extracellular matrix components [19]. This is why veterinary medicine is an active search for therapeutic alternatives that allow the animal to regenerate the damaged tissue, reduce recovery time and improve its overall quality of life.

Stem cells are generally characterized by their capacity for self-renewal and differentiation into different cell types both *in vitro* and *in vivo* [20,21]. These cells are responsible for the development and regeneration of an individual's organs and tissues. There are multiple types of stem cells according to their potency levels and the source from which they are obtained. The best known are embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and mesenchymal stem cells (MSCs). Due to their characteristics, they have become a fundamental tool in regenerative medicine. In recent years, their study and application has grown enormously due to their proven therapeutic action in different pathologies, from tissue damage to degenerative diseases or immune disorders [22].

Unlike ESCs and iPSCs, MSCs are classified as adult stem cells, derived from various tissues of an adult organism, such as skin, adipose tissue, bone marrow, brain, heart, and reproductive organs [23]. The physiological function of these cells in the body is to maintain tissue homeostasis and promote tissue recovery in case of damage, among others [14]. MSCs have a more restricted differentiation potential than pluripotent stem cells, being able to differentiate only to mesoderm-derived cell types [24].

They were first discovered in 1963 and have since been extensively studied [25]. Stem cells have been widely used in clinics and have demonstrated considerable therapeutic value in treating various conditions, including diabetes mellitus [26], OA [27], and macular degeneration [28]. Additionally, stem cell therapy has been utilized in treating animal diseases for many years [29]. In 2003, *Smith, et al*. applied mesenchymal stem cells (MSCs) to treat superficial flexor tendon injuries in racehorses [30]. This paved the way for the use of stem cells in equine disease treatment, with a focus on osteoarthritic diseases, which is the subject of this review. The aim of the current review article is to provide a clear overview of currently reported equine OA research on MSC application, with a main focus on different sources of MSC. Special attention is given to the distinctive features, differentiation potential for tissues of interest and regeneration outcomes. We aspire to provide valuable insights that can benefit animal health.

MSCs therapy for OA

Given the limitations of current osteoarthritis (OA) management, researchers are exploring new and promising options. Biological therapies utilizing mesenchymal stem cells (MSCs) have emerged as a significant focus in both human and veterinary OA research. Because of their multipotentiality, these adult stem cells have the potential to repopulate cartilage defects. Moreover, MSCs possess immunomodulatory properties that can reduce local and systemic inflammation. Additionally, they release signaling molecules that stimulate local repair cells, potentially aiding in cartilage healing. MSCs also exhibit homing capabilities, enabling them to be recruited to sites of tissue injury, both locally and systemically.

MSCs were first described in 1970 as a population morphologically similar to fibroblasts and with the ability to adhere to plastic. The researchers isolated these cells from bone marrow (naming BM-MSCs) and found that they could later differentiate into osteocytes. Later, it was discovered that MSCs could be isolated from other adult tissues, such as the umbilical cord and placenta. It was then shown that with proper stimulation, these cells could differentiate into various cell types in addition to osteocytes, such as adipocytes and chondrocytes [31]. MSCs are present in various adult tissues, such as bone marrow and adipose tissue, so they can be

isolated and cultured *in vitro* with relative ease [32-34]. However, in most cases, surgical intervention is required to obtain the tissue of which cell will be derived [35]. In addition, MSCs isolated from different tissues show certain differences in their *in vitro* amplification capacity or differentiation potential, which influences their subsequent applicability [36,37]. Also, besides of the origin from which they are sourced, tissue donor age greatly influences the cell yield obtained from a certain amount of tissue as well as cell proliferation rate. Therefore, the selection of a suitable cell source for clinical use must consider logistical, practical, and functional issues [38]. Currently, MSCs derived from bone marrow and adipose tissue are the most commonly used. Because MSC are nonimmunogenic this makes them a great candidate to be used in both autologous and allogeneic approaches [39-41].

Initially, MSC differentiation and direct incorporation into regenerating tissues were speculated to be a primary mechanism of MSC action; however, the contribution of trans-differentiation and direct incorporation are somewhat controversial [42]. Rather, MSCs were shown to secrete various growth factors and cytokines including interleukin 6 (IL-6), interleukin 1 beta (IL1 β), Tumor necrosis factor alpha (TNF- α), Interleukin 8 (IL-8), Interleukin 10 (IL-10), monocyte chemoattractant protein -1 (MPC-1), vascular cell adhesion molecule (VCAM), Vascular endothelial growth factor (VEGF) and Transforming growth factor β (TGF- β) among others.

Bone Marrow-Derived Mesenchymal Stem Cells (BMSCs)

BMSCs are widely used in veterinary medicine. However, in equines, marrow procurement is usually performed from a sternal puncture [43], a practice that is very risky due to its proximity to the pericardial cavity, and associated risks of serious infection and bleeding [44].

BMSCs are commonly used in equine OA due to their superior chondrogenic differentiation potential compared to adipose tissue-derived MSCs and peripheral blood-derived MSCs [45,46]. Intra-articular injection of BMSCs has been shown to improve cartilage repair quality by increasing aggreging content and tissue strength, as well as facilitating cartilage fracture healing [47]. *David, et al*. found that intra-articular injection of BMSCs resulted in significantly lower levels of prostaglandin E2 in the synovial fluid compared to the group that received adipose-derived stromal vascular fraction injection in an equine OA model [48]. Additionally, BMSCs are believed to have superior therapeutic effects for OA compared to cord blood MSCs (CB-MSCs) [49,50].

Furthermore, it has been demonstrated that exosomes derived from BMSCs possess therapeutic effects for OA: Hotham and *Manon, et al*. have reported that vesicles derived from BMSCs can be taken up by autologous chondrocytes and may have anti-inflammatory properties [51]. Numerous preclinical studies in humans have demonstrated that exosomes play a significant role in facilitating information exchange among chondrocytes and modulating the physiological functions of these cells. Due to their complex composition, current research still has a considerable gap in fully understanding the diverse landscape of exosomes derived from various types of mesenchymal stem cells (MSCs) for osteoarthritis (OA) treatment. Among the various contents of exosomes, microRNA (miRNA) has emerged as a primary focus of research and is found in the majority of MSCs. It is worth noting that exosomes derived from certain sources have the ability to sustain cell homeostasis and inhibit cellular apoptosis progression [52-54].

Adipose-Derived Mesenchymal Stem Cells (AD-MSCs)

AD-MSCs, derived from equine adipose tissue, offers a safer and more economical alternative to BMSCs, while retaining the same potential for multidirectional differentiation [55]. Due to its ease of collection and abundance of cells present in adipose tissue [56] it has become a preferred choice [57]. AD-MSCs are morphologically and immunophenotypically identical to BMSCs, yet exhibit significantly greater proliferative potential than BMSCs [58,59]. Ad-MSCs have also been shown to be more active in the autocrine production of some growth factors and immunomodulators at equal cell number than BM-MSCs [60,61].

AD-MSCs have been shown to have a therapeutic role in OA. *Luis, et al*. demonstrated that one or two intra-articular injections of AD-MSCs could reduce lameness in horses with OA and decrease the need for anti-inflammatory medication [62]. The study by *Delco, et al*. revealed that AD-MSCs with high expression of integrin α10 significantly improved joint damage in horses and activated intra-articular immunomodulation [63]. AD-MSCs can enhance their osteogenic differentiation by binding to macromolecular biomaterials and experiencing fluid shear stress [64].

Embryonic Tissue Mesenchymal Stem Cells

Embryonic tissues, such as umbilical cord blood, placenta, and amniotic membrane [55], are also a rich source of stem cells. These tissues are convenient since normally are discarded after the foal is born. Moreover, they possess a longer survival time attributed to their extended telomerase activity [65, 66]. Stem cells derived from embryonic tissues express markers associated with the embryonic phenotype, thus affording them a broader differentiation capacity [67,68].

Cord blood MSC (CB-MSCs) possess similar potential for treating OA. While BMSCs are frequently used in equine musculoskeletal disorders, it has been suggested that CB-MSCs may have a more robust chondrogenic phenotype. *White, et al*. demonstrated that CB-MSCs proved to be superior overall in chondrogenic differentiation than BMSCs, with a functionality index >50% of native equine patellar cartilage, as well as collagen production and alkaline phosphatase activity comparable to those of native equine articular cartilage [69]. Additionally, cartilage formed by CB-MSCs has significantly higher chondrogenic differentiation indices than that of the BMSCs source [70].

Mesenchymal Stem Cells from other Tissues

Other tissues, such as peripheral blood and tendon tissue, have been explored for their potential application in equine diseases. Studies have indicated that tendon tissue-derived stem cells demonstrate the ability to differentiate towards osteogenesis and

lipogenesis, rendering them promising candidates for osteoarthritis studies [71-73], even better than BMSCs [74]. Due to its ease of procurement, peripheral blood MSCs were considered a good candidate, however their low recovery rated and diminished differentiation potential they are not widely used [46,75]. Furthermore, it has been described that stem cells derived from peripheral blood may not possess the capability to differentiate into chondrocytes [46], thus limiting their potential for treating OA.

Prospective

OA is a prevalent joint disease, particularly among middle-aged and elderly individuals. Equine OA treatment is of particular importance as horses are considered a relevant model for human OA [49] hence all equine research holds great translational promise. MSCs have a promising future in regenerative medicine due to their cellular plasticity. In equine OA, MSC-derived chondrocytes can replace diseased tissue and provide a complete cure, which cannot be achieved through current conventional means such as drug therapy and surgery.

Although both BMSCs and CB-MSCs have shown favorable chondrogenic effects, the advantages and disadvantages of each need to be further explored.

One factor to consider is the availability and accessibility of MSC sources. BMSCs requires invasive procedures such as bone marrow aspiration while CB-MSCs, on the other hand, can be derived from umbilical cord blood, which is a non-invasive and readily available source.

Another consideration is the differentiation potential of MSCs. BMSCs were historically regarded as the preferred treatment for OA due to their robust chondrogenic differentiation capacity. However, in recent years, CB-MSCs have also demonstrated excellent chondrogenic potential, challenging the long-standing dominance of BMSCs in this field.

In addition, the immunomodulatory properties of MSCs should be considered. Originally, their use in cell replacement therapies was considered, i.e., it was thought that by injecting stem cells into a damaged tissue, due to their differentiation potential, cells would differentiate into the specific cell type, thus replacing the damaged tissue [76]. However, it was later shown that the exposure of these cells to a pathological environment did not necessarily allow cells to receive the appropriate signals to carry out a differentiation process to the cell type of interest. MSCs, in particular, were shown to have a beneficial, regenerative effect at the sites of treated [77] and, therefore, other hypotheses about their therapeutic benefits arose. It began to be considered that these cells could play an immunomodulatory role in the inflammatory environment of the wound, or that they could influence the migration and activation of the individual's own cells [78]. Both BMSCs and CB-MSCs have demonstrated immunomodulatory capacity [79,80], which can aid in reducing inflammation and promoting OA tissue repair. However, the specific mechanisms and effects of immunomodulation by these two types of MSCs may differ. Further research and clinical trials are necessary to provide more conclusive evidence and guidance on the selection of MSCs.

Despite the promising therapeutic effects of MSCs and their extracellular vesicles in OA, it is important to be aware of potential complications. Complications following stem cell therapy were observed in horse studies, including swelling, redness, and joint effusion at the injection site, and exacerbations [81,82]. *Berglund, et al*. demonstrated that recipient horses produced a cytotoxic antibody response after injection of MHC-mismatched MSCs, capable of killing donor MSCs *in vitro* [83]. Moreover, although not reported in horses, graft-versus-host disease (GVHD) after hematopoietic stem-cell transplantation is possible in dogs [17].

Future research studies employing state-of-the-art technology can be key to validate the effectiveness and safety of MSC therapies and their derivatives allowing these cells to become a leading candidate for the treatment of various diseases, including arthritic diseases.

References

1. Johnston SA (1997) Osteoarthritis. Joint anatomy, physiology, and pathobiology. Vet Clin North Am Small Anim Pract 27(4): 699-723.
2. Venable RO, Stoker AM, Cook CR, Cockrell MK and Cook JL (2008) Examination of synovial fluid hyaluronan quantity and quality in stifle joints of dogs with osteoarthritis. Am J Vet Res 69(12): 1569-1573.
3. Rychel JK (2010) Diagnosis and treatment of osteoarthritis. Top Companion Anim Med 25(1): 20-25.
4. Im GI (2018) Tissue Engineering in Osteoarthritis: Current Status and Prospect of Mesenchymal Stem Cell Therapy. BioDrugs 32(3): 183-192.
5. Freitag J, Bates D, Boyd R, Shah K, Barnard A, et al (2016) Mesenchymal stem cell therapy in the treatment of osteoarthritis: reparative pathways, safety and efficacy - a review. BMC Musculoskelet Disord 17: 230.
6. Li M, Yin H, Yan Z, Li H, Wu J, et al (2022) The immune microenvironment in cartilage injury and repair. Acta Biomater 140: 23-42.
7. Buckwalter JA (1998) Articular cartilage: injuries and potential for healing. J Orthop Sports Phys Ther 28(4): 192-202.
8. Van Weeren PR and Back W (2016) Musculoskeletal Disease in Aged Horses and Its Management. Vet Clin North Am Equine Pract 32(2): 229-247.
9. Whitton RC, Jackson MA, Campbell AJ, Anderson GA, Parkin TD, et al (2014) Musculoskeletal injury rates in Thoroughbred racehorses following local corticosteroid injection. Vet J 200(1): 71-76.
10. Bertuglia A, Bullone M, Rossotto F and Gasparini M (2014) Epidemiology of musculoskeletal injuries in a population of harness Standardbred racehorses in training. BMC Vet Res 10:11.
11. Egenvall A, Tranquille CA, Lonnell AC, Bitschnau C, Oomen A, et al (2013) Days-lost to training and competition in relation to workload in 263 elite show-jumping horses in four European countries. Prev Vet Med 112(3-4): 387-400.
12. Jeffcott LB, Rossdale PD, Freestone J, Frank CJ and Towers-Clark PF (1982) An assessment of wastage in thoroughbred racing from conception to 4 years of age. Equine Vet J 14(3): 185-198.
13. Ramzan PH and Palmer L (2011) Musculoskeletal injuries in Thoroughbred racehorses: a study of three large training yards in Newmarket Vet J 187(3): 325-329.
14. Ribitsch I, Oreff GL and Jenner F (2021) Regenerative Medicine for Equine Musculoskeletal Diseases. Animals (Basel) 11(1): 234.
15. Donnell JR and Frisbie DD (2014) Use of firocoxib for the treatment of equine osteoarthritis. Vet Med (Auckl) 5: 159-168.

16. Gupta RC, Lall R, Srivastava A and Sinha A (2019) Hyaluronic Acid: Molecular Mechanisms and Therapeutic Trajectory. Front Vet Sci 6: 192.

17. Wang Y, Alexander M, Scott T, Cox DCT, Wellington A, et al (2023) Stem Cell Therapy for Aging Related Diseases and Joint Diseases in Companion Animals. Animals (Basel) 13(15): 2457.

18. Nurul AA, Azlan M, Ahmad Mohd Zain MR, Sebastian AA, Fan YZ, et al (2021) Mesenchymal Stem Cells: Current Concepts in the Management of Inflammation in Osteoarthritis. Biomedicines 9(7): 785.

19. Usunier B, Benderitter M, Tamarat R and Chapel A (2014) Management of fibrosis: the mesenchymal stromal cells breakthrough. Stem Cells Int 14: 340257.

20. Kolios G and Moodley Y (2013) Introduction to stem cells and regenerative medicine. Respiration 85(1): 3-10.

21. Reya T, Morrison SJ, Clarke MF and Weissman IL (2001) Stem cells, cancer, and cancer stem cells. Nature 414(6859): 105-111.

22. Joel MDM, Yuan J, Wang J, Yan Y, Qian H, et al (2019) MSC: immunoregulatory effects, roles on neutrophils and evolving clinical potentials. Am J Transl Res 11(6): 3890-3904.

23. Sampogna G, Guraya SY and Forgione A (2015) Regenerative medicine: Historical roots and potential strategies in modern medicine. J Microsc Ultrastruct 3(3): 101-107.

24. Zomer HD, Vidane AS, Goncalves NN and Ambrosio CE (2015) Mesenchymal and induced pluripotent stem cells: general insights and clinical perspectives. Stem Cells Cloning 8: 125-134.

25. McCulloch EA and Till JE (2005) Perspectives on the properties of stem cells. Nat Med 11(10):1026-1028.

26. Kroon E, Martinson LA, Kadoya K, Bang AG, Kelly OG, et al (2008) Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells *in vivo*. Nat Biotechnol 26(4): 443-452.

27. Freitag J, Wickham J, Shah K and Tenen A (2022) Real-world evidence of mesenchymal stem cell therapy in knee osteoarthritis: a large prospective two-year case series. Regen Med 17(6): 355-373.

28. Schwartz SD, Regillo CD, Lam BL, Eliott D, Rosenfeld PJ, et al (2015) Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies. Lancet 385(9967): 509-516.

29. Pinheiro LL, de Lima AR and Branco E (2019) Is Stem Cell Commerce in Small Animal Therapies Scientifically and Morally Justified? Stem Cell Rev Rep 15(4): 506-518.

30. Smith RK, Korda M, Blunn GW and Goodship AE (2003) Isolation and implantation of autologous equine mesenchymal stem cells from bone marrow into the superficial digital flexor tendon as a potential novel treatment. Equine Vet J 35(1): 99-102.

31. Wang S, Qu X and Zhao RC (2012) Clinical applications of mesenchymal stem cells. J Hematol Oncol 5: 19.

32. Buzhor E, Leshansky L, Blumenthal J, Barash H, Warshawsky D, et al (2014) Cell-based therapy approaches: the hope for incurable diseases. Regen Med 9(5): 649-672.

33. Mehrabani D, Seghatchian J and Acker JP (2019) Platelet rich plasma in treatment of musculoskeletal pathologies. Transfus Apher Sci 58(6): 102675.

34. Holkar K, Vaidya A, Pethe P, Kale V and Ingavle G (2020) Biomaterials and extracellular vesicles in cell-free therapy for bone repair and regeneration: Future line of treatment in regenerative medicine. Materialia 12: 100736.

35. Ullah I, Subbarao RB and Rho GJ (2015) Human mesenchymal stem cells - current trends and future prospective. Biosci Rep 35(2): e00191.

36. Nancarrow-Lei R, Mafi P, Mafi R and Khan W (2017) A Systemic Review of Adult Mesenchymal Stem Cell Sources and their Multilineage Differentiation Potential Relevant to Musculoskeletal Tissue Repair and Regeneration. Curr Stem Cell Res Ther 12(8): 601-610.

37. Elahi KC, Klein G, Avci-Adali M, Sievert KD, MacNeil S, et al (2016) Human Mesenchymal Stromal Cells from Different Sources Diverge in Their Expression of Cell Surface Proteins and Display Distinct Differentiation Patterns. Stem Cells Int 2016: 5646384.

38. Heo JS, Choi Y, Kim HS and Kim HO (2016) Comparison of molecular profiles of human mesenchymal stem cells derived from bone marrow, umbilical cord blood, placenta and adipose tissue. Int J Mol Med 37(1): 115-125.

39. Carrade Holt DD, Wood JA, Granick JL, Walker NJ, Clark KC, et al (2014) Equine mesenchymal stem cells inhibit T cell proliferation through different mechanisms depending on tissue source. Stem Cells Dev 23(11): 1258-1265.

40. Carrade DD and Borjesson DL (2013) Immunomodulation by mesenchymal stem cells in veterinary species. Comp Med 63(3): 207-217.

41. Whitworth DJ and Banks TA (2014) Stem cell therapies for treating osteoarthritis: prescient or premature? Vet J 202(3): 416-424.

42. Pittenger MF and Martin BJ (2004) Mesenchymal stem cells and their potential as cardiac therapeutics. Circ Res 95(1): 9-20.

43. Peters AE and Watts AE (2016) Biopsy Needle Advancement during Bone Marrow Aspiration Increases Mesenchymal Stem Cell Concentration. Front Vet Sci 3: 23.

44. Kasashima Y, Ueno T, Tomita A, Goodship AE and Smith RK (2011) Optimisation of bone marrow aspiration from the equine sternum for the safe recovery of mesenchymal stem cells. Equine Vet J 43(3): 288-294.

45. Vidal MA, Robinson SO, Lopez MJ, Paulsen DB, Borkhsenious O, et al (2008) Comparison of chondrogenic potential in equine mesenchymal stromal cells derived from adipose tissue and bone marrow. Vet Surg 37(8): 713-724.

46. Koerner J, Nesic D, Romero JD, Brehm W, Mainil-Varlet P, et al (2006) Equine peripheral blood-derived progenitors in comparison to bone marrow-derived mesenchymal stem cells. Stem Cells 24(6): 1613-1619.

47. McIlwraith CW, Frisbie DD, Rodkey WG, Kisiday JD, Werpy NM, et al (2011) Evaluation of intra-articular mesenchymal stem cells to augment healing of microfractured chondral defects. Arthroscopy 27(11): 1552-1561.

48. Frisbie DD, Kisiday JD, Kawcak CE, Werpy NM and McIlwraith CW (2009) Evaluation of adipose-derived stromal vascular fraction or bone marrow-derived mesenchymal stem cells for treatment of osteoarthritis. J Orthop Res 27(12): 1675-1680.

49. Bertoni L, Jacquet Guibon S, Branly T, Desance M, Legendre F, et al (2021) Evaluation of Allogeneic Bone-Marrow-Derived and Umbilical Cord Blood-Derived Mesenchymal Stem Cells to Prevent the Development of Osteoarthritis in An Equine Model. Int J Mol Sci 22(5): 2499.

50. Contentin R, Demoor M, Concari M, Desance M, Audigie F, et al (2020) Comparison of the Chondrogenic Potential of Mesenchymal Stem Cells Derived from Bone Marrow and Umbilical Cord Blood Intended for Cartilage Tissue Engineering. Stem Cell Rev Rep 16(1):126-143.

51. Hotham WE, Thompson C, Szu Ting L, Henson FMD (2021) The anti-inflammatory effects of equine bone marrow stem cell-derived extracellular vesicles on autologous chondrocytes. Vet Rec Open 8(1): e22.

52. Yu H, Huang Y and Yang L (2022) Research progress in the use of mesenchymal stem cells and their derived exosomes in the treatment of osteoarthritis. Ageing Res Rev 80: 101684.

53. Liu Y, Lin L, Zou R, Wen C, Wang Z, et al (2018) MSC-derived exosomes promote proliferation and inhibit apoptosis of chondrocytes via lncRNA-KLF3-AS1/miR-206/GIT1 axis in osteoarthritis. Cell Cycle 17(21-22): 2411-2422.

54. Wang Z, Wang Z, Zhang B, Zhao Q, Liu Y, et al (2021) Effect of Activated Platelet-Rich Plasma on Chondrogenic Differentiation of Rabbit Bone Marrow-Derived Mesenchymal Stem Cells. Stem Cells Int 2021: 9947187.

55. Przadka P, Buczak K, Frejlich E, Gasior L, Suliga K, et al (2021) The Role of Mesenchymal Stem Cells (MSCs) in Veterinary Medicine and Their Use in Musculoskeletal Disorders. Biomolecules 11(8): 1141.

56. Bacakova L, Zarubova J, Travnickova M, Musilkova J, Pajorova J, et al (2018) Stem cells: their source, potency and use in regenerative therapies with focus on adipose-derived stem cells - a review. Biotechnol Adv 36(4): 1111-1126.

57. Petrova V and Vachkova E (2023) Outlook of Adipose-Derived Stem Cells: Challenges to Their Clinical Application in Horses. Vet Sci 10(5): 348.

58. Marx C, Silveira MD and Beyer Nardi N (2015) Adipose-derived stem cells in veterinary medicine: characterization and therapeutic applications. Stem Cells Dev 24(7): 803-813.

59. Burk J, Ribitsch I, Gittel C, Juelke H, Kasper C, et al (2013) Growth and differentiation characteristics of equine mesenchymal stromal cells derived from different sources. Vet J 195(1): 98-106.

60. Hsiao ST, Asgari A, Lokmic Z, Sinclair R, Dusting GJ, et al (2012) Comparative analysis of paracrine factor expression in human adult mesenchymal stem cells derived from bone marrow, adipose, and dermal tissue. Stem Cells Dev 21(12): 2189-2203.

61. Melief SM, Zwaginga JJ, Fibbe WE and Roelofs H (2013) Adipose tissue-derived multipotent stromal cells have a higher immunomodulatory capacity than their bone marrow-derived counterparts. Stem Cells Transl Med 2(6): 455-463.

62. Marinas Pardo L, Garcia Castro J, Rodriguez Hurtado I, Rodriguez Garcia MI, Nunez Naveira L, et al (2018) Allogeneic Adipose-Derived Mesenchymal Stem Cells (Horse Allo 20) for the Treatment of Osteoarthritis-Associated Lameness in Horses: Characterization, Safety, and Efficacy of Intra-Articular Treatment. Stem Cells Dev 27(17): 1147-1160.

63. Delco ML, Goodale M, Talts JF, Pownder SL, Koff MF, et al (2020) Integrin alpha10beta1-Selected Mesenchymal Stem Cells Mitigate the Progression of Osteoarthritis in an Equine Talar Impact Model. Am J Sports Med 48(3): 612-623.

64. Elashry MI, Baulig N, Wagner AS, Klymiuk MC, Kruppke B, et al (2021) Combined macromolecule biomaterials together with fluid shear stress promote the osteogenic differentiation capacity of equine adipose-derived mesenchymal stem cells. Stem Cell Res Ther 12(1): 116.

65. Oliver Vila I, Coca MI, Grau Vorster M, Pujals Fonts N, Caminal M, et al (2016) Evaluation of a cell-banking strategy for the production of clinical grade mesenchymal stromal cells from Wharton's jelly. Cytotherapy 18(1): 25-35.

66. Kogler G, Sensken S, Airey JA, Trapp T, Muschen M, et al (2004) A new human somatic stem cell from placental cord blood with intrinsic pluripotent differentiation potential. J Exp Med 200(2): 123-135.

67. Moretti P, Hatlapatka T, Marten D, Lavrentieva A, Majore I, et al (2010) Mesenchymal stromal cells derived from human umbilical cord tissues: primitive cells with potential for clinical and tissue engineering applications. Adv Biochem Eng Biotechnol 123: 29-54.

68. Lepage SIM, Lee OJ and Koch TG (2019) Equine Cord Blood Mesenchymal Stromal Cells Have Greater Differentiation and Similar Immunosuppressive Potential to Cord Tissue Mesenchymal Stromal Cells. Stem Cells Dev 28(3): 227-237.

69. White JL, Walker NJ, Hu JC, Borjesson DL and Athanasiou KA (2018) A Comparison of Bone Marrow and Cord Blood Mesenchymal Stem Cells for Cartilage Self-Assembly. Tissue Eng Part A 24(15-16): 1262-1272.

70. Berg L, Koch T, Heerkens T, Bessonov K, Thomsen P, et al (2009) Chondrogenic potential of mesenchymal stromal cells derived from equine bone marrow and umbilical cord blood. Vet Comp Orthop Traumatol 22(5): 363-370.

71. Lovati AB, Corradetti B, Lange Consiglio A, Recordati C, Bonacina E, et al (2011) Characterization and differentiation of equine tendon-derived progenitor cells. J Biol Regul Homeost Agents 25(2 Suppl): S75-84.

72. Youngstrom DW, LaDow JE and Barrett JG (2016) Tenogenesis of bone marrow-, adipose-, and tendon-derived stem cells in a dynamic bioreactor. Connect Tissue Res 57(6): 454-465.

73. Ni Q, Zhu J, Li Z, Li B, Wang H, et al (2023) Simvastatin promotes rat Achilles tendon-bone interface healing by promoting osteogenesis and chondrogenic differentiation of stem cells. Cell Tissue Res 391(2): 339-355.

74. Rui YF, Lui PP, Lee YW and Chan KM (2012) Higher BMP receptor expression and BMP-2-induced osteogenic differentiation in tendon-derived stem cells compared with bone-marrow-derived mesenchymal stem cells. Int Orthop 36(5): 1099-1107.

75. Spaas JH, De Schauwer C, Cornillie P, Meyer E, Van Soom A, et al (2013) Culture and characterisation of equine peripheral blood mesenchymal stromal cells. Vet J 195(1): 107-113.

76. Ilic D and Polak JM (2011) Stem cells in regenerative medicine: introduction. Br Med Bull 98: 117-126.

77. Spees JL, Lee RH and Gregory CA (2016) Mechanisms of mesenchymal stem/stromal cell function. Stem Cell Res Ther 7(1): 125.

78. Merimi M, El Majzoub R, Lagneaux L, Moussa Agha D, Bouhtit F, et al (2021) The Therapeutic Potential of Mesenchymal Stromal Cells for Regenerative Medicine: Current Knowledge and Future Understandings. Front Cell Dev Biol 9: 661532.

79. Reesink HL, Sutton RM, Shurer CR, Peterson RP, Tan JS, et al (2017) Galectin-1 and galectin-3 expression in equine mesenchymal stromal cells (MSCs), synovial fibroblasts and chondrocytes, and the effect of inflammation on MSC motility. Stem Cell Res Ther 8(1): 243.

80. Tessier L, Bienzle D, Williams LB and Koch TG (2015) Phenotypic and immunomodulatory properties of equine cord blood-derived mesenchymal stromal cells. PLoS One 10(4): e0122954.

81. Duddy HR, Schoonover MJ and Hague BA (2022) Outcome following local injection of a liquid amnion allograft for treatment of equine tendonitis or desmitis - 100 cases. BMC Vet Res 18(1): 391.

82. Ursini TL, Amelse LL, Elkhenany HA, Odoi A, Carter Arnold JL, et al (2019) Retrospective analysis of local injection site adverse reactions associated with 230 allogenic administrations of bone marrow-derived mesenchymal stem cells in 164 horses. Equine Vet J 51(2): 198-205.

83. Berglund AK and Schnabel LV (2017) Allogeneic major histocompatibility complex-mismatched equine bone marrow-derived mesenchymal stem cells are targeted for death by cytotoxic anti-major histocompatibility complex antibodies. Equine Vet J 49(4): 539-544.