

# The Use of Stem Cells in the Treatment of Animal Diseases and Injuries

Ziad Ahmad Alabdallah \*

Department of Anatomy -Histology and Embryology, Al Furat University, Deirez-ZOR, College of Veterinary, Syria.

\*Correspondence Author: Ziad Ahmad Alabdallah, Department of Anatomy -Histology and Embryology, Al Furat University, Deirez-ZOR, College of Veterinary, Syria.

Received Date: July 17, 2023 | Accepted Date: August 02, 2023 | Published Date: August 09, 2023

Citation: Ziad A. Alabdallah (2023), The Use of Stem Cells in the Treatment of Animal Diseases and Injuries, *Clinical Reviews and Case Reports*, 2(4); DOI:10.31579/2835-7957/033

Copyright: © 2023, Ziad Ahmad Alabdallah. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

## Abstract

Stem cells are considered a scientific renaissance because of their use in regenerative therapy and diseases in the field of veterinary medicine. Therefore, it is necessary to learn about their types and sources, how to take, preserve, and store them, methods of use, and the mechanism of their impact on injuries and diseases that affect animals that may not respond to conventional treatment.

**Keywords:** stem cells; regenerative therapy; injuries; diseases

## Introduction

Although stem cells (SCs) are undifferentiated cells, they can change into other cell types to perform a variety of tasks. The therapeutic use of stem cells in veterinary medicine makes use of their capacity to differentiate into various cell types. SCs come from four primary sources: embryos, fetuses, umbilical cords, and adult body cells. Once more, stem cells are divided into totipotent, multipotent, pluripotent, and unipotent categories depending on their capacity to differentiate. Multipotent ASCs are employed in treatments because they are easier to get and grow from a variety of sources, have lower immunogenicity, and don't run the danger of developing teratomas. SCs have been used to treat a variety of issues in animals, including heart problems, diabetes mellitus, tendonitis, ligament defects, wounds, cartilage defects, and spinal injuries. However, due to their dynamic complexity, biology, potential for teratoma formation, and histocompatibility, clinical uses of stem cells are constrained. Despite the fact that many degenerative conditions are difficult to treat because they don't respond to current medications, the therapeutic use of stem cells in veterinary medicine hasn't been generally adopted. This manuscript's goal is to discuss the therapeutic use of stem cells in the regeneration of a wide range of difficult illnesses that are not responding to conventional forms of treatment.

## Main text:

### Types of stem cells

The two primary types of stem cells used in contemporary regenerative treatment are allogeneic and autologous. Experts throughout the world are constantly debating the differences in the safety and efficacy of using these cells in treatment. Depending on the donor-recipient connection, MSCs can be classified as being of allogeneic, autologous, or xenogeneic origin. The individual receiving allogeneic cells belongs to the same species as the donor. Successful in vitro production of these cells reduces the duration of the therapy significantly as compared to autologous cells. Horses were given therapeutic injections of the antlerogenic stem cells MIC-1 (obtained

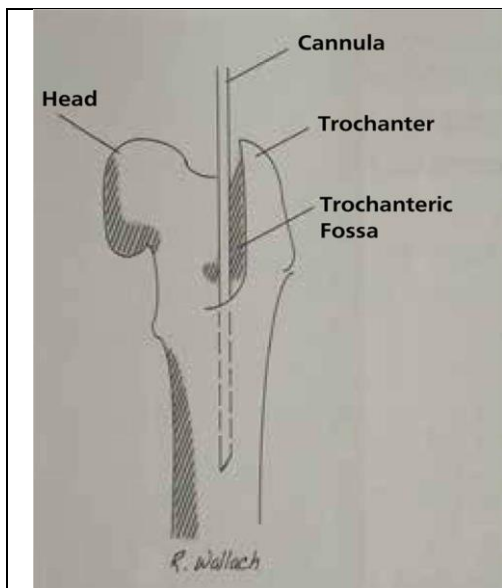
from a deer), and injured rabbits had the cells experimentally implanted into their tissues. [75].

### Isolation and purification of stem cells

Practically any tissue in a living body can be efficiently harvested to produce mesenchymal stem cells. Nevertheless, the best results are obtained when cells are isolated from adult tissues like adipose tissue (AD-MSCs), bone marrow (BM-MSCs), peripheral blood (PB-MSCs), or fetal tissue like the placenta (P-MSCs), umbilical cord blood (UCB-MSCs), or umbilical cord (UC-MSCs) [7;26]. This is a result of these cells' capacity for proliferation and differentiation. It was found that the type of cells, based on their origin, has a significant impact on both their capacity for in vivo differentiation and their physiologically significant properties [100]. When selecting the source of those cells, a crucial factor to take into account is how the MSCs will be used in the therapy. Similar to human medicine, one of the most extensively studied sources of MSC origin in veterinary medicine is bone marrow [39]. Unfortunately, gathering the samples requires an invasive procedure done while the animals are sedated, with or without local anesthetic in the case of dogs, and under general anesthesia in the case of horses. Both of these procedures have a risk of postoperative complications, including infection and/or hemorrhage [73]. A number of significant inadvertent cardio-thoracic punctures have been reported [45]. as well as nonfatal pneumopericardium in horses [29;44]. But with these animals, there is little to no risk of the aforementioned issues when doing the BM-MSC collection procedure on a standing animal. The 4th or 5th sternbra is the best place to perform a sternal biopsy with a Jamshidi needle, according to current consensus [24; 47]. Age-related declines in the number of BM-MSCs, which make up a relatively small percentage of all bone marrow stromal mononuclear cells [77]. The donor's previously removed aspirate is used for MSC passage and culture in vitro. The maximum number of cultivated MSCs that can be passed through four times determines the exact therapeutic amount of MSCs. This culture goes through several stages, including starting the culture, cell growth, media changes, and finishing the culture by

identifying the cell phenotype. Despite the fact that research first concentrated on MSCs produced from bone marrow, the large concentration of MSCs in adipose tissues (100–1000 times that in bone marrow) led to the use of adipose-derived MSCs in regenerative stem cell treatment [15;66;109]. The need for numerous purification processes to exclude non-MSC cell types (such as hematopoietic stem cells and blood cells) when collecting chicken MSCs using bone marrow from non-compact bone sources is one of the main problems [48]. These methods of purification frequently result in cytotoxicity, modifications to MSC functioning, and poor MSC yields [103]. There haven't been any reports of MSCs isolated from chicken compact bones, which might circumvent these restrictions because there aren't as many contaminating cell types [74]. Hematopoietic stem cells and MSCs are the two principal stem cell groups that exist in bone marrow [74; 108]. The contamination of blood cells and hematopoietic stem cells that results from the isolation of MSCs from bone marrow is a severe disadvantage. The MSC population extracted from bone marrow has been purified or enriched using a variety of methods, including density gradient centrifugation and preferential attachment to culture plastic [105], antibody-based cell sorting and the

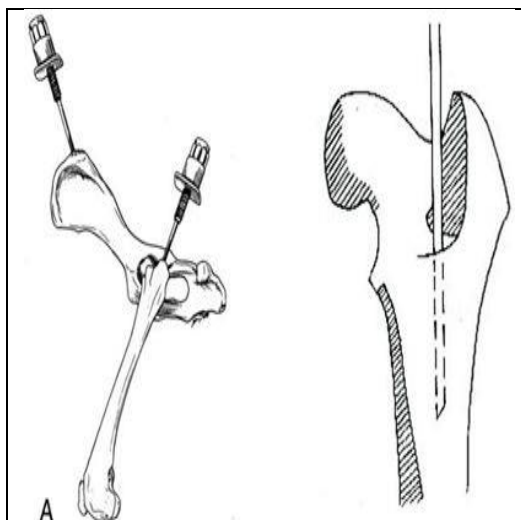
application of ficole to remove blood cells [30;97], techniques for low- and high-density cultivation [31], as well as regular media change [88]. However, there are a number of drawbacks to these techniques for purifying MSCs that have been isolated from bone marrow. A phenotypically and functionally heterogeneous cell population might be produced via preferential attachment to cell culture plates [95]. Using immune depletion strategies decreased the expression of several genes involved in cell growth and cell cycle progression [3]. Insulin-like growth factor or leukemia inhibitory factor exposure of MSCs obtained from immunodepleted cells reversibly decreased the cells' capacity to develop into adipocytes, chondrocytes, and osteoblasts in vitro [3]. Only around 27 fibroblastoid colonies of 5 or more cells were produced using low-density culture out of a total of 200 culture discs [102]. Multiple multi-lineage MSCs were recovered from hematopoietic cells using cell sorting techniques, but these MSCs had less osteogenic capacity and less clonogenicity than unilinear MSCs [97]. MSCs can be easily and cheaply extracted from compact bones, eliminating the need for further purification procedures and lowering the risk of hematopoietic cell contamination in isolated cultures [41;108].



**Diagram to show a catheter placed into the proximal femur**



**Taking stem cells from the pelvic bone in dogs**



**Taking stem cells from the pelvic bone and femur in dogs**



**Taking stem cells from the humerus of dogs**

**Preservation and storage of stem cells**

To get enough MSCs for clinical usage, they must be separated and grown in vitro for therapeutic use. It may occasionally be necessary to apply a

second or third time; however, prolonged culture before therapeutic use is not advised since the cells might lose their stemness characteristics and get contaminated with germs. For these reasons, it is highly helpful to cryopreserve these cells in order to obtain a fast and regulated supply of many autologous stem cells that maintain the vitality and pluripotent phenotype of the freshly separated cells while maintaining the unmodified properties of the cells. Di Bella et al. [25] assessed the outcomes of a 7-year cryopreservation procedure utilizing 10% DMSO and various FBS concentrations (ranging from 10% to 90%). In both fresh and thawed cells, the phenotypes of morphology, cell viability, differentiation, and proliferative capacity, as well as the expression of pluripotency markers, were examined. According to the results of this investigation, canine adipose tissue MSCs that were cryopreserved with more than 50% FBS and thawed after 7 years had similar proliferative potential and morphological and molecular properties to fresh cells. Usually, after being expanded in vitro in the lab, fresh or frozen-thawed cells are returned to the attending doctors. As mentioned above, the effectiveness of the therapy depends on maintaining the MSCs' properties while they travel from the laboratory to the clinic. Various storage methods, temperatures, and durations have been investigated during the past ten years due to the significance of this subject for veterinary regenerative medicine [32;36]. Iacono et al. [42] showed that various kinds of MSCs react differently to the storage conditions often employed to transport them from the laboratory to the clinic for horse MSCs isolated from AT and Wharton's jelly (WJ). These circumstances affect MSC survivability and, based on the cell type, can also affect certain MSC features. Equine WJMSCs in particular must be utilized right away to keep them viable. However, it is important to compare the information gained in vitro with that obtained in vivo using cells transported under controlled circumstances and with that obtained using frozen-thawed cells that were implanted immediately. The ideal circumstances (medium, temperature, hours of travel, etc.) for moving horse MSCs from a lab to a clinic have been sought by several writers in this context. When Bronzini et al. [10] examined the effects of media, temperature, and storage time on equine peripheral blood MSCs in 2012, they discovered that neither varying media nor temperature could keep the cells alive during shipping; in fact, cell mortality ranged from 30 to 40 percent in each experimental group. The same was shown to apply to horse peripheral blood MSCs, bone marrow MSCs, and equine adipose tissue MSCs, respectively, by Mercati et al. [63], Espina et al. [32], and Garvican et al. [36]. Both the differentiation and clonogenic potential of stored eATMSCs and eBMMSCs are still present [32;63], although it is debatable whether or not ePBMSCs can retain their molecular characteristics [10]. Indeed, while CD44 and CD105 expression levels were the same in fresh and stored cells, CD90 expression declined after 9 and 12 hours of storage, indicating, as stated by the authors, that these cells were unable to preserve the characteristics of MSCs after this time [10]. To obtain therapeutic dosages, autologous MSC treatment entails cell separation and growth. As a result, there is a delay between their collection and utilization, endangering the treatment's efficacy. Donor variability, tissue of origin, tissue quantity, and culture conditions are additional crucial criteria for MSC isolation [17]. However, due to their decreased immunogenicity, MSCs produced from fetuses and placentas have been proven to be preferable to adult MSCs as candidates for allogeneic therapeutic applications [70;107]. The preservation and pooling of MSCs by cryopreservation is an effective way to get the cell numbers needed for clinical applications. By harvesting samples and then isolating, growing, and storing cells for later use, logistics from collection through transplanting may be made as efficient as possible. As a result, the development of allogeneic cell treatments depends on MSCs' capacity to endure prolonged storage while still maintaining their quality. It is crucial to preserve MSCs' functional traits, such as their capacity for multilineage differentiation and immunomodulatory abilities, after cryopreservation. Prior to their use in clinical settings, cryopreserved MSCs must also undergo a biosafety assessment [106]. The clinical use of MSCs necessitates instantaneous access to a ready supply of effective therapeutic dosages. Cell dose is not specified for every particular treatment and fluctuates greatly depending on the application. Due to their low cell density, MSCs require prolonged culture extension, and as the length of the culture increases, so do the dangers of genetic contamination and mutation. In order to get a quick and regulated supply of many autologous

stem cells that keep the original properties of the freshly separated cells by preserving their vitality and maintaining their pluripotent phenotype, it is highly helpful to cryopreserve these cells for this purpose. Aliquots of cells might be biobanked for administration later, either right away after revitalization or right after brief growth. MSC availability is further increased by cryopreservation since frozen cells may be supplied far away [28]. Most cryopreservation protocols for stem cells use dimethyl sulfoxide (DMSO) at a concentration of 10% (v/v), often combined with fetal bovine serum (FBS) in concentrations ranging from 10% to 90% (v/v) [12;60;84;104]. FBS is frequently added to freezing solutions because of its advantages for regulating cell osmotic pressure and stabilizing the cell membrane [4]. However, because of its xenobiotic nature, it is always accompanied by the danger of infection [96].

### **Injuries and diseases treated with stem cells in animals and the mechanism of their effect**

In veterinary medicine, there is mounting evidence in favor of MSC-based treatments. There is a long history of using MSC to treat orthopedic problems, particularly in horses [8;9;34;39;69;78;86], Equine Recurrent Uveitis [81], Equine Immune Mediated Keratitis [54], Equine Persistent Breeding-Induced Endometritis [33; 67;80], Endometriosis [18;59;58], Ovarian Diseases [40;91;101], Testicular Diseases [23], Equine Metabolic Syndrome [62], Equine Asthma [6], Wounds [65;90;92], Decubitus Ulcers [42;43;52], Laminitis [1;27;64;87], Peripheral Nerve Injury [13;98], Wobblers Syndrome [55; 5], Laryngeal Hemiplegia or Left Recurrent Laryngeal Neuropathy [82] and Endotoxemia [51]. Bovine MSCs used for Clinical Treatments Chronic Wound Healing [20;21;22], Mastitis [37;38;94] and Reproductive System [14;57;71]. MSC is also becoming increasingly widely used in canine treatment. Numerous in vivo studies have employed canine MSC with great success, particularly for the treatment of osteoarthritis [53;56;83], but also for a number of other ailments including atopic dermatitis [49;99], diabetes mellitus [79], inflammatory bowel disease [72], or to aid in the recovery of neurons after spinal compression fractures [85]. Processes for producing canine MSC need to be streamlined and enhanced simultaneously. The in vitro culture of MSC before giving it to the patient is one of the crucial elements. In this context, the cell culture medium is a critical component of the cell culture process and may have a significant impact on the effectiveness and standard of care [46]. Regarding left ventricular ejection fraction (LVEF), La Mantia et al. [50] described the use of stem-cell therapy against acute or chronic ischemic cardiomyopathies in large animal models. The authors' meta-analysis revealed that the pig species is proven to be a useful animal model in the field of cardiovascular research and that stem-cell treatment may enhance heart function in big animal models. In this perspective, Garcia-Mendivil et al.'s paper [35] on the creation of in vitro cellular models for prion neurodegenerative diseases affecting both people and animals, notably ruminants, is also relevant. demonstrate that MSCs have therapeutic benefits by secreting bioactive substances that provide an advantageous milieu for the healing and regeneration of damaged tissues [11]. The paracrine function of MSCs is crucial because it affects the target tissue's angiogenesis, neuroprotection, and immunoregulation by producing vital growth and trophic factors or bioactive compounds [16; 93]. For instance, MSCs release a variety of chemokines that draw in and control the activity of various cell types, as well as growth factors like vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), or leukemia inhibitory factor (LIF) that support cell survival and stimulate resident cell proliferation. Some of these growth factors, like VEGF, also have important pro-angiogenic effects, which are crucial for the regeneration of injured tissues since blood supply must be restored [19]. Additionally, MSCs release a variety of cytokines and mediators, including nitric oxide (NO), transforming growth factor (TGF), interleukin (IL)-6 and 10, prostaglandin E-2 (PGE-2), and IL-10, which have immunomodulatory effects such as preventing T lymphocyte proliferation [61], lysed by cytotoxic T cells [76], and NK cell activation [89] macrophages, too [68], or modulate B cell proliferation [2]. Treatment of ailments like mastitis has a lot of promise because of the antibacterial activity of MSCs and their derivatives. In addition to having a direct effect on milk production in the dairy sector, it would offer a substitute for the use of antimicrobials, lowering the likelihood of antibiotic resistance and

the amount of antibiotics in milk. Treatment with MSCs may reduce the time needed to recover from numerous illnesses that influence output, boosting profitability [110].

## Conclusion:

This review aims to highlight the importance of using stem cells in the treatment of many injuries and diseases in different animals when conventional treatment does not have any effect on the pathological condition and stem cell therapy can be combined with conventional treatment in order for the therapeutic results to be faster, thus preserving the health of the animal and its productive capacity.

## Acknowledgment

None.

## Conflict of Interest

None.

## References

- Angelone M., Conti V., Biacca C., Battaglia B., Pecorari L et al. (2017) The contribution of adipose tissue-derived mesenchymal stem cells and platelet-rich plasma to the treatment of chronic equine laminitis: A proof of concept. *Int. J. Mol. Sci.* 18:2122.
- Asari S., Itakura S., Ferreri K., Liu C., Kuroda Y. (2009). Mesenchymal stem cells suppress B-cell terminal differentiation. *Exp. Hematol.* 37:604–615.
- Baddoo, M., Hill, K., Wilkinson, R., Gaupp, D., Hughes, C. et al. (2003). Characterization of mesenchymal stem cells isolated from murine bone marrow by negative selection. *J. Cell Biochem.* 89, 1235–1249.
- Bahsoun S., Coopman K., Akam E.C. (2019). The impact of cryopreservation on bone marrow-derived mesenchymal stem cells: A systematic review. *J. Transl. Med.* 17:397.
- Barberini D.J., Aleman M., Aristizabal F., Spriet M., Clark K.C. (2018). Safety and tracking of intrathecal allogeneic mesenchymal stem cell transplantation in healthy and diseased horses. *Stem Cell Res. Ther.* 9:96.
- Barussi F.C.M., Bastos F.Z., Leite L.M.B., Frago F.Y.I., Senegaglia A.C. et al. (2016). Intratracheal therapy with autologous bone marrow-derived mononuclear cells reduces airway inflammation in horses with recurrent airway obstruction. *Respir. Physiol. Neurobiol.* 2016; 232:35–42.
- Bearden, R.N.; Huggins, S.S.; Cummings, K.J.; Smith, R.; Gregory, C.A. et al. (2017). In-vitro characterization of canine multipotent stromal cells isolated from synovium, bone marrow, and adipose tissue: A donor-matched comparative study. *Stem Cell Res. Ther.*
- Broeckx, S.; Zimmerman, M.; Crocetti, S.; Suls, M.; Mariën, T et al. (2014). Regenerative therapies for equine degenerative joint disease: A preliminary study.
- Broeckx, S.Y.; Seys, B.; Suls, M.; Vandenberghe, A.; Mariën, T.; Adriaensen, E.; Declercq, J.; Van Hecke, L.; Braun, G.; Hellmann, K.; et al. Equine Allogeneic Chondrogenic Induced Mesenchymal Stem Cells Are an Effective Treatment for Degenerative Joint Disease in Horses. *Stem Cells Dev.* 2019, 28, 410–422. [Google Scholar] [CrossRef]
- Bronzini, I.; Patruno, M.; Iacopetti, I.; Martinello, T. Influence of Temperature, Time and Different Media on Mesenchymal Stromal Cells Shipped for Clinical Application. *Vet. J. Lond. Engl.* 1997 2012, 194, 121–123. [Google Scholar] [CrossRef]
- Caplan, A.I. Mesenchymal Stem Cells: Time to Change the Name! *Stem Cells Transl. Med.* 2017, 6, 1445–1451. [Google Scholar] [CrossRef] [PubMed][Green Version]
- Carvalho K.A.T., Cury C.C., Oliveira L., Cattaned R.I.L., Malvezzi M., Francisco J.C., Pachalok A., Olandoski M., Faria-Neto J.R., Guarita-Souza L.C. Evaluation of bone marrow mesenchymal stem cell standard cryopreservation procedure efficiency. *Transpl. Proc.* 2008;40:839–841. doi: 10.1016/j.transproceed.2008.03.004. [PubMed] [CrossRef] [Google Scholar]
- Casañas J., de la Torre J., Soler F., Garcia F., Rodellar C., Pumarola M., Climent J., Soler R., Orozco L. Peripheral nerve regeneration after experimental section in ovine radial and tibial nerves using synthetic nerve grafts, including expanded bone marrow mesenchymal cells: Morphological and neurophysiological results. *Injury.* 2014;45:S2–S6. doi: 10.1016/S0020-1383(14)70003-8. [PubMed] [CrossRef] [Google Scholar]
- Chang, L.-B.; Peng, S.-Y.; Chou, C.-J.; Chen, Y.-J.; Shiu, J.-S.; Tu, P.-A.; Gao, S.-X.; Chen, Y.-C.; Lin, T.-K.; Wu, S.-C. Therapeutic Potential of Amniotic Fluid Stem Cells to Treat Bilateral Ovarian Dystrophy in Dairy Cows in a Subtropical Region. *Reprod. Domest. Anim.* 2018, 53, 433–441. [Google Scholar] [CrossRef] [PubMed][Green Version]
- Choudhery, M.S.; Badowski, M.; Muise, A.; Harris, D.T. Comparison of human mesenchymal stem cells derived from adipose and cord tissue. *Cytotherapy* 2013, 15, 330–343. [Google Scholar] [CrossRef] [PubMed]
- Cizkova, D.; Cubinkova, V.; Smolek, T.; Murgoci, A.-N.; Danko, J.; Vdoviakova, K.; Humenik, F.; Cizek, M.; Quanicco, J.; Fournier, I.; et al. Localized Intrathecal Delivery of Mesenchymal Stromal Cells Conditioned Medium Improves Functional Recovery in a Rat Model of Spinal Cord Injury. *Int. J. Mol. Sci.* 2018, 19, 870. [Google Scholar] [CrossRef][Green Version]
- Colleoni, S.; Bottani, E.; Tessaro, I.; Mari, G.; Merlo, B.; Romagnoli, N.; Spadari, A.; Galli, C.; Lazzari, G. Isolation, Growth and Differentiation of Equine Mesenchymal Stem Cells: Effect of Donor, Source, Amount of Tissue and Supplementation with Basic Fibroblast Growth Factor. *Vet. Res. Commun.* 2009, 33, 811. [Google Scholar] [CrossRef]
- Corradetti B., Correani A., Romaldini A., Marini M.G., Bizzaro D., Perrini C., Cremonesi F., Lange-Consiglio A. Amniotic membrane-derived mesenchymal cells and their conditioned media: Potential candidates for uterine regenerative therapy in the horse. *PLoS ONE.* 2014;9:e111324. doi: 10.1371/journal.pone.0111324. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- da Silva Meirelles L., Fontes A.M., Covas D.T., Caplan A.I. Mechanisms involved in the therapeutic properties of mesenchymal stem cells. *Cytokine Growth Factor Rev.* 2009;20:419–427. doi: 10.1016/j.cytogfr.2009.10.002. [PubMed] [CrossRef] [Google Scholar]
- Das, J.; Behera, S.S. Successful treatment of inter digital chronic ulcerative wound by mesenchymal stem cell therapy in a cow. *Indian J. Vet. Sci. Biotechnol.* 2013, 9, 66–67. [Google Scholar]

21. Das, J.; Nath, I.; Das, R.K.; Routray, P.; Behera, S.S. Autologous Stem Cell Therapy to Treat Chronic Ulcer in Heifer-A Case Study. Available online: [https://scholar.google.com/citations?view\\_op=view\\_citation&hl=en&user=V8kdet8AAAAJ&citation\\_for\\_view=V8kdet8AAAAJ:UeHWp8X0CEIC](https://scholar.google.com/citations?view_op=view_citation&hl=en&user=V8kdet8AAAAJ&citation_for_view=V8kdet8AAAAJ:UeHWp8X0CEIC) (accessed on 15 July 2021).
22. Das, J.; Routray, N.P.; Das, R.K. Autologous Bone Marrow Derived Mesenchymal Stem Cells (BM-MSCs) Therapy for Treatment of Chronic Limb Wound in a Bull. *Indian J.* Available online: <https://www.indianjournals.com/ijor.aspx?target=ijor:ipo&volume=14&issue=1&article=023> (accessed on 9 December 2021).
23. de Papa P.M., Guasti P.N., De Vita B., Nakazato N.G., Maia L., de Freitas Dell'Aqua C.P., da Scheeren V.F.C., Segabinazzi L.G.T.M., de Andrade Junior L.R.P., Silva L.F.M.C., et al. Clinical safety of intratesticular transplantation of allogeneic bone marrow multipotent stromal cells in stallions. *Reprod. Domest. Anim.* 2020;55:429–437. doi: 10.1111/rda.13624. [PubMed] [CrossRef] [Google Scholar]
24. Désévaux, C.; Laverty, S.; Doizé, B. Sternal bone biopsy in standing horses. *Vet. Surg.* 2000, 29, 303–308. [Google Scholar]
25. Di Bella, S.; Cannella, V.; Mira, F.; Di Marco, P.; Lastra, A.; Gucciardi, F.; Purpari, G.; Guercio, A. The Effect of a 7 Year-Long Cryopreservation on Stemness Features of Canine Adipose-Derived Mesenchymal Stem Cells (CAD-MSC). *Animals* 2021, 11, 1755. [Google Scholar] [CrossRef]
26. Ding, D.-C.; Shyu, W.-C.; Lin, S.-Z. Mesenchymal Stem Cells. *Cell Transplant.* 2011, 20, 5–14. [Google Scholar] [CrossRef] [PubMed][Green Version]
27. Dryden V.C., Morrison S., Bras R., Morrell S.A. Using stem cells in clinical cases. *J. Equine Vet. Sci.* 2013;33:872–873. doi: 10.1016/j.jevs.2013.08.057. [CrossRef] [Google Scholar]
28. Duan W., Lopez M.J., Hicok K. Adult multipotent stromal cell cryopreservation: Pluses and pitfalls. *Vet. Surg.* 2018;47:19–29. doi: 10.1111/vsu.12730. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
29. Durando, M.M.; Zarucco, L.; Schaer, T.P.; Ross, M.; Reef, V.B. Pneumopericardium in a horse secondary to sternal bone marrow aspiration. *Equine Vet. Educ.* 2006, 18, 75–79. [Google Scholar] [CrossRef]
30. El-Sayed, K. M., Paris, S., Graetz, C., Kassem, N., Mekhemar, M., Ungefroren, H., et al. (2015). Isolation and characterisation of human gingival margin-derived STRO-1/MACS(+) and MACS(-) cell populations. *Int. J. Oral. Sci.* 7, 80–88. doi: 10.1038/ijos.2014.41. [PubMed] [CrossRef] [Google Scholar]
31. Eslaminejad, M. B., and Nadri, S. (2009). Murine mesenchymal stem cell isolated and expanded in low and high density culture system: surface antigen expression and osteogenic culture mineralization. *In vitro Cell Dev. Biol. Anim.* 45, 451–459. doi: 10.1007/s11626-009-9198-1. [PubMed] [CrossRef] [Google Scholar]
32. Espina, M.; Jülke, H.; Brehm, W.; Ribitsch, I.; Winter, K.; Dellling, U. Evaluation of Transport Conditions for Autologous Bone Marrow-Derived Mesenchymal Stromal Cells for Therapeutic Application in Horses. *PeerJ* 2016, 4, e1773. [Google Scholar] [CrossRef] [PubMed][Green Version]
33. Ferris R.A., Frisbie D.D., McCue P.M. Use of mesenchymal stem cells or autologous conditioned serum to modulate the inflammatory response to spermatozoa in mares. *Theriogenology.* 2014;82:36–42. doi: 10.1016/j.theriogenology.2014.02.015. [PubMed] [CrossRef] [Google Scholar]
34. Ferris, D.J.; Frisbie, D.D.; Kisiday, J.D.; McIlwraith, C.W.; Hague, B.A.; Major, M.D.; Schneider, R.K.; Zubrod, C.J.; Kawcak, C.E.; Goodrich, L.R. Clinical outcome after intra-articular administration of bone marrow derived mesenchymal stem cells in 33 horses with stifle injury. *Vet. Surg.* 2014, 43, 255–265. [Google Scholar] [CrossRef][Green Version]
35. García-Mendivil, L.; Mediano, D.R.; Hernaiz, A.; Sanz-Rubio, D.; Vázquez, F.J.; Marín, B.; López-Pérez, Ó.; Otero, A.; Badiola, J.J.; Zaragoza, P.; et al. Effect of Scrapie Prion Infection in Ovine Bone Marrow-Derived Mesenchymal Stem Cells and Ovine Mesenchymal Stem Cell-Derived Neurons. *Animals* 2021, 11, 1137. [Google Scholar] [CrossRef] [PubMed]
36. Garvican, E.R.; Cree, S.; Bull, L.; Smith, R.K.; Dudhia, J. Viability of Equine Mesenchymal Stem Cells during Transport and Implantation. *Stem Cell Res. Ther.* 2014, 5, 1. [Google Scholar] [CrossRef][Green Version]
37. Ghai, S.; Saini, S.; Ansari, S.; Verma, V.; Chopra, S.; Sharma, V.; Devi, P.; Malakar, D. Allogenic Umbilical Cord Blood-Mesenchymal Stem Cells Are More Effective than Antibiotics in Alleviating Subclinical Mastitis in Dairy Cows. *Theriogenology* 2022, 187, 141–151. [Google Scholar] [CrossRef]
38. Ghai, S.; Verma, V.N.; Ansari, S.; Saini, S.; Thakur, A.; Kumar, A.; Kumar, S.; Malakar, D.; Ghai, S.; Verma, V.N.; et al. 157 Mesenchymal Stem Cells as a Regenerative Therapy for the Prevention of Subclinical Mastitis in Cattle. *Reprod. Fertil. Dev.* 2021, 34, 316–317. [Google Scholar] [CrossRef] [PubMed]
39. Godwin, E.E.; Young, N.J.; Dudhia, J.; Beamish, I.C.; Smith, R.K.W. Implantation of bone marrow-derived mesenchymal stem cells demonstrates improved outcome in horses with overstrain injury of the superficial digital flexor tendon. *Equine Vet. J.* 2012, 44, 25–32. [Google Scholar] [CrossRef] [PubMed]
40. Grady S.T., Watts A.E., Thompson J.A., Penedo M.C.T., Konganti K., Hinrichs K. Effect of intra-ovarian injection of mesenchymal stem cells in aged mares. *J. Assist. Reprod. Genet.* 2019;36:543–556. doi: 10.1007/s10815-018-1371-6. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
41. Guo, Z., Li, H., Li, X., Yu, X., Wang, H., Tang, P., et al. (2006). In vitro characteristics and in vivo immunosuppressive activity of compact bone-derived murine mesenchymal progenitor cells. *Stem Cells* 24, 992–1000. doi: 10.1634/stemcells.2005-0224. [PubMed][CrossRef][Google Scholar]
42. Iacono E., Lanci A., Merlo B., Ricci F., Pirrone A., Antonelli C., Mariella J., Castagnetti C. Effects of amniotic fluid mesenchymal stem cells in carboxymethyl cellulose gel on healing of spontaneous pressure sores: Clinical outcome in seven hospitalized neonatal foals. *Turkish J. Biol.* 2016;40:484–492. doi: 10.3906/biy-1507-147. [CrossRef] [Google Scholar]
43. Iacono E., Merlo B., Pirrone A., Antonelli C., Brunori L., Romagnoli N., Castagnetti C. Effects of mesenchymal stem

- cells isolated from amniotic fluid and platelet-rich plasma gel on severe decubitus ulcers in a septic neonatal foal. *Res. Vet. Sci.* 2012;93:1439–1440. doi: 10.1016/j.rvsc.2012.04.008. [PubMed] [CrossRef] [Google Scholar]
44. Iacono, E.; Lanci, A.; Gugole, P.; Merlo, B. Shipping Temperature, Time and Media Effects on Equine Wharton's Jelly and Adipose Tissue Derived Mesenchymal Stromal Cells Characteristics. *Animals* 2022, 12, 1967. [Google Scholar] [CrossRef] [PubMed]
  45. Jacobs, R.M.; Kociba, G.J.; Ruoff, W.W. Monoclonal Gammopathy in a Horse with Defective Hemostasis. *Vet. Pathol.* 1983, 20, 643–647. [Google Scholar] [CrossRef]
  46. Karnieli, O.; Friedner, O.M.; Allickson, J.G.; Zhang, N.; Jung, S.; Fiorentini, D.; Abraham, E.; Eaker, S.S.; Yong, T.K.; Chan, A.; et al. A consensus introduction to serum replacements and serum-free media for cellular therapies. *Cytotherapy* 2017, 19, 155–169. [Google Scholar] [CrossRef] [PubMed]
  47. Kasashima, Y.; Ueno, T.; Tomita, A.; Goodship, A.E.; Smith, R.K.W. Optimisation of bone marrow aspiration from the equine sternum for the safe recovery of mesenchymal stem cells. *Equine Vet. J.* 2011, 43, 288–294. [Google Scholar] [CrossRef] [PubMed]
  48. Khatri, M., O'Brien, T. D., and Sharma, J. M. (2009). Isolation and differentiation of chicken mesenchymal stem cells from bone marrow. *Stem Cells Dev.* 18, 1485–1492. doi: 10.1089/scd.2008.0223. [PubMed] [CrossRef] [Google Scholar]
  49. Klinger, C. Mesenchymal stem cells: A potential therapy for canine atopic dermatitis? *Vet. Rec.* 2018, 183, 651. [Google Scholar] [CrossRef] [PubMed]
  50. La Mantia, D.; Bernardini, C.; Zannoni, A.; Salaroli, R.; Wang, C.; Bencivenni, S.; Forni, M. Efficacy of Stem Cell Therapy in Large Animal Models of Ischemic Cardiomyopathies: A Systematic Review and Meta-Analysis. *Animals* 2022, 12, 749. [Google Scholar] [CrossRef]
  51. Lalu M.M., Sullivan K.J., Mei S.H.J., Moher D., Straus A., Fergusson D.A., Stewart D.J., Jazi M., Macleod M., Winston B., et al. Evaluating mesenchymal stem cell therapy for sepsis with preclinical meta-analyses prior to initiating a first-in-human trial. *Elife.* 2016;5:1–28. doi: 10.7554/eLife.17850. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
  52. Lanci A., Merlo B., Mariella J., Castagnetti C., Iacono E. Heterologous Wharton's Jelly derived mesenchymal stem cells application on a large chronic skin wound in a 6-month-old filly. *Front. Vet. Sci.* 2019;6:9. doi: 10.3389/fvets.2019.00009. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
  53. Lima, V.P.; Tobin, G.C.; Jesus Pereira MR de Silveira, M.D.; Witz, M.I.; Nardi, N.B. Chondrogenic effect of liquid and gelled platelet lysate on canine adipose-derived mesenchymal stromal cells. *Res. Vet. Sci.* 2019, 124, 393–398. [Google Scholar] [CrossRef]
  54. Lin H.-B., Li W.-L., Zhuo X., He A.-Q. Application effect of soft corneal contact lens on corneal limbal stem cell transplantation in elderly patients with pterygium. *Int. J. Ophthalmol.* 2019;19:329–331. [Google Scholar]
  55. Maia L., da Cruz Landim-Alvarenga F., Taffarel M.O., de Moraes C.N., Machado G.F., Melo G.D., Amorim R.M. Feasibility and safety of intrathecal transplantation of autologous bone marrow mesenchymal stem cells in horses. *BMC Vet. Res.* 2015;11:63. doi: 10.1186/s12917-015-0361-5. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
  56. Maki, C.B.; Beck, A.; Wallis, C.-B.C.C.; Choo, J.; Ramos, T.; Tong, R.; Borjesson, D.L.; Izadyar, F. Intra-articular Administration of Allogeneic Adipose Derived MSCs Reduces Pain and Lameness in Dogs With Hip Osteoarthritis: A Double Blinded, Randomized, Placebo Controlled Pilot Study. *Front. Vet. Sci.* 2020, 7, 570. [Google Scholar] [CrossRef] [PubMed]
  57. Malard, P.F.; Peixer, M.A.S.; Grazia, J.G.; Brunel, H.D.S.S.; Feres, L.F.; Villarroel, C.L.; Siqueira, L.G.B.; Dode, M.A.N.; Pogue, R.; Viana, J.H.M.; et al. Intraovarian Injection of Mesenchymal Stem Cells Improves Oocyte Yield and in Vitro Embryo Production in a Bovine Model of Fertility Loss. *Sci. Rep.* 2020, 10, 8018. [Google Scholar] [CrossRef]
  58. Mambelli L.I., Mattos R.C., Winter G.H.Z., Madeiro D.S., Morais B.P., Malschitzky E., Miglino M.A., Kerkis A., Kerkis I. Changes in expression pattern of selected endometrial proteins following mesenchymal stem cells infusion in mares with endometrosis. *PLoS ONE.* 2014;9:e97889. doi: 10.1371/journal.pone.0097889. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
  59. Mambelli L.I., Winter G.H.Z., Kerkis A., Malschitzky E., Mattos R.C., Kerkis I. A novel strategy of mesenchymal stem cells delivery in the uterus of mares with endometrosis. *Theriogenology.* 2013;79:744–750. doi: 10.1016/j.theriogenology.2012.11.030. [PubMed] [CrossRef] [Google Scholar]
  60. Martinello T., Bronzini I., Maccatrozzo L., Mollo A., Sampaolesi M., Mascarello F., Decaminada M., Patruno M. Canine adipose-derived-mesenchymal stem cells do not lose stem features after a long-term cryopreservation. *Res. Vet. Sci.* 2011;91:18–24. doi: 10.1016/j.rvsc.2010.07.024. [PubMed] [CrossRef] [Google Scholar]
  61. Martinet L., Fleury-Cappellesso S., Gadelorge M., Dietrich G., Bourin P., Fournie J.J., Pouput R. A regulatory cross-talk between V $\gamma$ 9V $\delta$ 2 T lymphocytes and mesenchymal stem cells. *Eur. J. Immunol.* 2009;39:752–762. doi: 10.1002/eji.200838812. [PubMed] [CrossRef] [Google Scholar]
  62. Marycz K., Szłapka-Kosarzewska J., Geburek F., Kornicka-Garbowska K. Systemic administration of rejuvenated adipose-derived mesenchymal stem cells improves liver metabolism in equine metabolic syndrome (EMS)—New approach in veterinary regenerative medicine. *Stem Cell Rev. Rep.* 2019;15:842–850. doi: 10.1007/s12015-019-09913-3. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
  63. Mercati, F.; Pascucci, L.; Curina, G.; Scocco, P.; Tardella, F.M.; Dall'aglio, C.; Marini, C.; Ceccarelli, P. Evaluation of Storage Conditions on Equine Adipose Tissue-Derived Multipotent Mesenchymal Stromal Cells. *Vet. J. Lond. Engl.* 1997 2014, 200, 339–342. [Google Scholar] [CrossRef]
  64. Morrison S. Successful use of allogenic umbilical cord-derived stem cells in nonresponsive chronic laminitis cases. *J. Equine Vet. Sci.* 2011;31:603. doi: 10.1016/j.jevs.2011.09.053. [CrossRef] [Google Scholar]
  65. Mund S.J.K., Kawamura E., Awang-Junaidi A.H., Campbell J., Wobeser B., MacPhee D.J., Honaramooz A., Barber S. Homing and engraftment of intravenously administered

- equine cord blood-derived multipotent mesenchymal stromal cells to surgically created cutaneous wound in horses: A pilot project. *Cells*. 2020;9:1162. doi: 10.3390/cells9051162. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
66. Nakao, N.; Nakayama, T.; Yahata, T.; Muguruma, Y.; Saito, S.; Miyata, Y.; Yamamoto, K.; Naoe, T. Adipose tissue-derived mesenchymal stem cells facilitate hematopoiesis in vitro and in vivo: Advantages over bone marrow-derived mesenchymal stem cells. *Am. J. Pathol.* 2010, 177, 547–554. [Google Scholar] [CrossRef] [PubMed]
  67. Navarrete F., Saravia F., Cisterna G., Rojas F., Silva P.P., Rodríguez-Alvarez L., Rojas D., Cabezas J., Mançanaras A.C.F., Castro F.O. Assessment of the anti-inflammatory and engraftment potential of horse endometrial and adipose mesenchymal stem cells in an in vivo model of post breeding induced endometritis. *Theriogenology*. 2020;155:33–42. doi: 10.1016/j.theriogenology.2020.06.010. [PubMed] [CrossRef] [Google Scholar]
  68. Nemeth K., Keane-Myers A., Brown J.M., Metcalfe D.D., Gorham J.D., Bundoc V.G., Hodges M.G., Jelinek I., Madala S., Karpati S., et al. Bone marrow stromal cells use TGF- $\beta$  to suppress allergic responses in a mouse model of ragweed-induced asthma. *Proc. Natl. Acad. Sci. USA*. 2010;107:5652–5657. doi: 10.1073/pnas.0910720107. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
  69. Pacini, S.; Spinabella, S.; Trombi, L.; Fazzi, R.; Galimberti, S.; Dini, F.; Carlucci, F.; Petrini, M. Suspension of bone marrow-derived undifferentiated mesenchymal stromal cells for repair of superficial digital flexor tendon in race horses. *Tissue Eng.* 2007, 13, 2949–2955. [Google Scholar] [CrossRef][Green Version]
  70. Papait, A.; Vertua, E.; Magatti, M.; Ceccariglia, S.; De Munari, S.; Silini, A.R.; Sheleg, M.; Ofir, R.; Parolini, O. Mesenchymal Stromal Cells from Fetal and Maternal Placenta Possess Key Similarities and Differences: Potential Implications for Their Applications in Regenerative Medicine. *Cells* 2020, 9, 127. [Google Scholar] [CrossRef] [PubMed][Green Version]
  71. Peng, S.-Y.; Wu, T.-H.; Lin, T.-Y.; Hii, L.-Y.; Chan, K.-S.; Fu, T.-Y.; Chang, S.-C.; Shen, P.-C.; Liu, K.-Y.; Shaw, S.W. Application of Cattle Placental Stem Cells for Treating Ovarian Follicular Cyst. *World J. Stem Cells* 2020, 12, 1366–1376. [Google Scholar] [CrossRef]
  72. Pérez-Merino, E.M.; Usón-Casaús, J.M.; Zaragoza-Bayle, C.; Duque-Carrasco, J.; Mariñas-Pardo, L.; Hermida-Prieto, M.; Barrera-Chacón, R.; Gualtieri, M. Safety and efficacy of allogeneic adipose tissue-derived mesenchymal stem cells for treatment of dogs with inflammatory bowel disease: Clinical and laboratory outcomes. *Vet. J.* 2015, 206, 385–390. [Google Scholar] [CrossRef]
  73. Peters, A.E.; Watts, A.E. Biopsy Needle Advancement during Bone Marrow Aspiration Increases Mesenchymal Stem Cell Concentration. *Front. Vet. Sci.* 2016, 3, 23. [Google Scholar] [CrossRef][Green Version]
  74. Pittenger, M. F., Mackay, A. M., Beck, S. C., Jaiswal, R. K., Douglas, R., Mosca, J. D., et al. (1999). Multilineage potential of adult human mesenchymal stem cells. *Science* 284, 143–147. doi: 10.1126/science.284.5411.143.[PubMed] [CrossRef] [Google Scholar]
  75. Prządka, P.; Kielbowicz, Z.; Osiński, B.; Dzimira, S.; Madej, J.A.; Nowacki, W.; Kubiak, K.; Reichert, P.; Cegielski, M. Reconstruction of cranial cruciate ligament in rabbits using polyester implants saturated with PRP, antlerogenic stem cells MIC-1 and their homogenate. *Connect. Tissue Res.* 2017, 58, 464–478. [Google Scholar] [CrossRef] [PubMed]
  76. Rasmusson I., Uhlin M., Le Blanc K., Levitsky V. Mesenchymal stem cells fail to trigger effector functions of cytotoxic T lymphocytes. *J. Leukoc. Biol.* 2007;82:887–893. doi: 10.1189/jlb.0307140. [PubMed] [CrossRef] [Google Scholar]
  77. Rebelatto, C.K.; Aguiar, A.M.; Moretão, M.P.; Senegaglia, A.C.; Hansen, P.; Barchiki, F.; Oliveira, J.; Martins, J.; Kuligovski, C.; Mansur, F.; et al. Dissimilar Differentiation of Mesenchymal Stem Cells from Bone Marrow, Umbilical Cord Blood, and Adipose Tissue. *Exp. Biol. Med.* 2008, 233, 901–913. [Google Scholar] [CrossRef]
  78. Renzi, S.; Riccò, S.; Dotti, S.; Sesso, L.; Grolli, S.; Cornali, M.; Carlin, S.; Patruno, M.; Cinotti, S.; Ferrari, M. Autologous bone marrow mesenchymal stromal cells for regeneration of injured equine ligaments and tendons: A clinical report. *Res. Vet. Sci.* 2013, 95, 272–277. [Google Scholar] [CrossRef]
  79. Rhew, S.-Y.; Park, S.-M.; Li, Q.; An, J.-H.; Chae, H.-K.; Lee, J.-H.; Ahn, J.-O.; Song, W.-J.; Youn, H.-Y. Efficacy and safety of allogeneic canine adipose tissue-derived mesenchymal stem cell therapy for insulin-dependent diabetes mellitus in four dogs: A pilot study. *J. Vet. Med. Sci.* 2021, 83, 592–600. [Google Scholar] [CrossRef]
  80. Rink B.E., Beyer T., French H.M., Watson E., Aurich C., Donadeu F.X. The fate of autologous endometrial mesenchymal stromal cells after application in the healthy equine uterus. *Stem Cells Dev.* 2018;27:1046–1052. doi: 10.1089/scd.2018.0056. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
  81. Saldinger L.K., Nelson S.G., Bellone R.R., Lassaline M., Mack M., Walker N.J., Borjesson D.L. Horses with equine recurrent uveitis have an activated CD4+ T-cell phenotype that can be modulated by mesenchymal stem cells in vitro. *Vet. Ophthalmol.* 2020;23:160–170. doi: 10.1111/vop.12704. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
  82. Sandersen C., Ceusters J., Fourez A., Tosi I., Graide H., Lejeune J.P., Serteyn D. Nerve stimulator-guided injection of autologous stem cells near the equine left recurrent laryngeal nerve. *J. Vis. Exp.* 2018;2018:58023. doi: 10.3791/58023. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
  83. Shah, K.; Drury, T.; Roic, I.; Hansen, P.; Malin, M.; Boyd, R.; Sumer, H.; Ferguson, R. Outcome of Allogeneic Adult Stem Cell Therapy in Dogs Suffering from Osteoarthritis and Other Joint Defects. *Stem Cells Int.* 2018, 2018, 7309201. [Google Scholar] [CrossRef][Green Version]
  84. Shahid M.A., Kim W.H., Kweon O.K. Cryopreservation of heat-shocked canine adipose-derived mesenchymal stromal cells with 10% dimethyl sulfoxide and 40% serum results in better viability, proliferation, anti-oxidation, and in-vitro differentiation. *Cryobiology.* 2020;92:92–102. doi: 10.1016/j.cryobiol.2019.11.040. [PubMed] [CrossRef] [Google Scholar]
  85. Sharun, K.; Rawat, T.; Kumar, R.; Chandra, V.; Saxena, A.C.; Pawde, A.M.; Kinjavdekar, P.; Amarpal; Sharma,

- G.T. Clinical evaluation following the percutaneous transplantation of allogenic bone marrow-derived mesenchymal stem cells (aBM-MSC) in dogs affected by vertebral compression fracture. *Vet. Anim. Sci.* 2020, 10, 100152. [Google Scholar] [CrossRef]
86. Smith, R.K.W.; Werling, N.J.; Dakin, S.G.; Alam, R.; Goodship, A.E.; Dudhia, J. Beneficial effects of autologous bone marrow-derived mesenchymal stem cells in naturally occurring tendinopathy. *PLoS ONE* 2013, 8, e75697. [Google Scholar] [CrossRef]
  87. Sole A., Spriet M., Galuppo L.D., Padgett K.A., Borjesson D.L., Wisner E.R., Brosnan R.J., Vidal M.A. Scintigraphic evaluation of intra-arterial and intravenous regional limb perfusion of allogeneic bone marrow-derived mesenchymal stem cells in the normal equine distal limb using <sup>99m</sup>Tc-HMPAO. *Equine Vet. J.* 2012;44:594–599. doi: 10.1111/j.2042-3306.2011.00530.x. [PubMed] [CrossRef] [Google Scholar]
  88. Soleimani, M., and Nadri, S. (2009). A protocol for isolation and culture of mesenchymal stem cells from mouse bone marrow. *Nat. Protoc.* 4, 102–106. doi: 10.1038/nprot.2008.221. [PubMed] [CrossRef] [Google Scholar]
  89. Sotiropoulou P.A., Perez S.A., Gritzapis A.D., Baxevas C.N., Papamichail M. Interactions between human mesenchymal stem cells and natural killer cells. *Stem Cells.* 2006;24:74–85. doi: 10.1634/stemcells.2004-0359. [PubMed] [CrossRef] [Google Scholar]
  90. Spaas J.H., Broeckx S., Van De Walle G.R., Poletini M. The effects of equine peripheral blood stem cells on cutaneous wound healing: A clinical evaluation in four horses. *Clin. Exp. Dermatol.* 2013;38:280–284. doi: 10.1111/ced.12068. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
  91. Takehara Y., Yabuuchi A., Ezoe K., Kuroda T., Yamadera R., Sano C., Murata N., Aida T., Nakama K., Aono F., et al. The restorative effects of adipose-derived mesenchymal stem cells on damaged ovarian function. *Lab. Investig.* 2013;93:181–193. doi: 10.1038/labinvest.2012.167. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
  92. Textor J.A., Clark K.C., Walker N.J., Aristizobal F.A., Kol A., LeJeune S.S., Bledsoe A., Davidyan A., Gray S.N., Bohannon-Worsley L.K., et al. Allogeneic stem cells alter gene expression and improve healing of distal limb wounds in horses. *Stem Cells Transl. Med.* 2018;7:98–108. doi: 10.1002/sctm.17-0071. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
  93. The Secretion Profile of Mesenchymal Stem Cells and Potential Applications in Treating Human Diseases [Signal Transduction and Targeted Therapy. Available online: <https://www.nature.com/articles/s41392-022-00932-0> (accessed on 2 May 2022).
  94. Ting, W.-J.; Shaw, S.W.; Hii, L.-Y.; Lin, T.-Y.; Chang, S.-C.; Liu, K.-Y.; Shen, P.-C.; Chen, T.-J.; Peng, S.-Y. Therapeutic Effects of Conditioned—DPBS from Amniotic Stem Cells on Lactating Cow Mastitis. *Taiwan. J. Obstet. Gynecol.* 2020, 59, 520–526. [Google Scholar] [CrossRef]
  95. Tremain, N., Korkko, J., Ibberson, D., Kopen, G. C., DiGirolamo, C., and Phinney, D. G. (2001). MicroSAGE analysis of 2,353 expressed genes in a single cell-derived colony of undifferentiated human mesenchymal stem cells reveals mRNAs of multiple cell lineages. *Stem Cells* 19, 408–418. doi: 10.1634/stemcells.19-5-408. [PubMed][CrossRef][Google Scholar]
  96. Tripathy S. Cryopreservation of Mesenchymal Stem Cells (MSCs): Different approaches and applications. *Int. J. Adv. Sci. Technol.* 2017;1:435–456. [Google Scholar]
  97. Van Vlasselaer, P., Falla, N., Snoeck, H., and Mathieu, E. (1994). Characterization and purification of osteogenic cells from murine bone marrow by two-color cell sorting using anti-Sca-1 monoclonal antibody and wheat germ agglutinin. *Blood* 84, 753–763. [PubMed] [Google Scholar]
  98. Villagrán C.C., Schumacher J., Donnell R., Dhar M.S. A novel model for acute peripheral nerve injury in the horse and evaluation of the effect of mesenchymal stromal cells applied in situ on nerve regeneration: A preliminary study. *Front. Vet. Sci.* 2016;3:80. doi: 10.3389/fvets.2016.00080. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
  99. Villatoro, A.J.; Hermida-Prieto, M.; Fernández, V.; Fariñas, F.; Alcoholado, C.; Rodríguez-García, M.I.; Mariñas-Pardo, L.; Becerra, J. Allogeneic adipose-derived mesenchymal stem cell therapy in dogs with refractory atopic dermatitis: Clinical efficacy and safety. *Vet. Rec.* 2018, 183, 654. [Google Scholar] [CrossRef]
  100. Voga, M.; Adamic, N.; Vengust, M.; Majdic, G. Stem Cells in Veterinary Medicine—Current State and Treatment Options. *Front. Vet. Sci.* 2020, 7, 278. [Google Scholar] [CrossRef]
  101. Wang S., Yu L., Sun M., Mu S., Wang C., Wang D., Yao Y. The therapeutic potential of bone marrow mesenchymal stem cells in premature ovarian failure. *Stem Cell Res. Ther.* 2018;9 doi: 10.1186/s13287-018-1008-9. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
  102. Wang, Q. R., and Wolf, N. S. (1990). Dissecting the hematopoietic microenvironment. VIII. Clonal isolation and identification of cell types in murine CFU-F colonies by limiting dilution. *Exp. Hematol.* 18, 355–359. [PubMed][Google Scholar]
  103. Wee, A. S., Lim, C. K., Merican, A. M., Ahmad, T. S., and Kamarul, T. (2013). Total cell pooling in vitro: an effective isolation method for bone marrow-derived multipotent stromal cells. *In vitro Cell Dev. Biol. Anim.* 49, 424–432. doi: 10.1007/s11626-013-9626-0. [PubMed] [CrossRef] [Google Scholar]
  104. Xiang Y., Zheng Q., Jia B., Huang G., Xie C., Pan J., Wang J. Ex vivo expansion, adipogenesis and neurogenesis of cryopreserved human bone marrow mesenchymal stem cells. *Cell Biol. Int.* 2007;31:444–450. doi: 10.1016/j.cellbi.2006.11.012. [PubMed] [CrossRef] [Google Scholar]
  105. Yamamoto, Y., Itoh, S., Yamauchi, Y., Matsushita, K., Ikeda, S., Naruse, H., et al. (2015). Density gradient centrifugation for the isolation of cells of multiple lineages. *J. Cell Biochem.* 116, 2709–2714. doi: 10.1002/jcb.25270. [PubMed] [CrossRef] [Google Scholar]
  106. Yong, K.W.; Wan Safwani, W.K.Z.; Xu, F.; Wan Abas, W.A.B.; Choi, J.R.; Pinguan-Murphy, B. Cryopreservation of Human Mesenchymal Stem Cells for Clinical Applications: Current Methods and Challenges. *Biopreserv. Biobank.* 2015, 13, 231–239. [Google Scholar] [CrossRef]
  107. Yu, Y.; Valderrama, A.V.; Han, Z.; Uzan, G.; Naserian, S.; Oberlin, E. Human Fetal Liver MSCs Are More Effective than Adult Bone Marrow MSCs for Their Immunosuppressive, Immunomodulatory, and Foxp3+ T Reg Induction Capacity.



- Stem Cell Res. Ther. 2021, 12, 138. [Google Scholar] [CrossRef] [PubMed]
108. Zhu, H., Guo, Z. K., Jiang, X. X., Li, H., Wang, X. Y., Yao, H. Y., et al. (2010). A protocol for isolation and culture of mesenchymal stem cells from mouse compact bone. *Nat. Protoc.* 5, 550–560. doi: 10.1038/nprot.2009.238. [PubMed] [CrossRef] [Google Scholar]
109. Zuk, P.A.; Zhu, M.; Mizuno, H.; Huang, J.; Futrell, J.W.; Katz, A.J.; Benhaim, P.; Lorenz, H.P.; Hedrick, M.H. Multilineage cells from human adipose tissue: Implications for cell-based therapies. *Tissue Eng.* 2001, 7, 211–228. [Google Scholar] [CrossRef] [PubMed][Green Version]
110. Merlo, Barbara, Penelope Maria Gugole, and Eleonora Iacono. "An Update on Applications of Cattle Mesenchymal Stromal Cells." *Animals* 12.15 (2022): 1956. [Google Scholar] [CrossRef]

**Ready to submit your research? Choose ClinicSearch and benefit from:**

- fast, convenient online submission
- rigorous peer review by experienced research in your field
- rapid publication on acceptance
- authors retain copyrights
- unique DOI for all articles
- immediate, unrestricted online access

**At ClinicSearch, research is always in progress.**

Learn more <http://clinicsearchonline.org/journals/clinical-reviews-and-case-reports->



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.