Journal of Animal & Plant Sciences, 32(6): 2022, Page: 1501-1512
ISSN (print): 1018-7081; ISSN (online): 2309-8694
https://doi.org/10.36899/JAPS.2022.6.0558

REVIEW ARTICLE

ADVANCES IN THE USE OF STEM CELLS THERAPY IN VETERINARY CLINICAL PRACTICE

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ABSTRACT

Stem cells are self-organized, unspecialized cells which are produced from various types of cells in all tissues of the body. They can be derived through a proper methodology from embryos, fetus, and adults. Stem cells can divide into specific cell types, such as nerves or muscles. These cells are a source of information about cell differentiation processes and tissue homeostasis, but they are also one of the main biological tools for treating degenerative diseases. In the past 20 years, researchers have paid great attention to stem cell biology. Therefore, an understanding of its characteristics has greatly enhanced regarding to its therapeutic potential in all aspects in past few years. Role of stem cells is important for veterinary medicine in various ways. Several stem cell treatments for animals are currently being developed, such as treatment of equine tendinopathies disease through mesenchymal stem cells. In addition, animal models are widely being used to study the properties of stem cells and their potential in human medicine. These cells are now being artificially grown and transformed into special types of cell cultures that are compatible with cells from different tissues. This paper summarizes the current knowledge of stem cells potential in veterinary medicine.

Keywords: animal, regenerative medicine, stem cell therapy, stem cells, veterinary

Published first online June 10, 2022 Published final November 20, 2022

INTRODUCTION

Research in stem cells gains eminent heed in the past two decades because of the self-renewability into many cell types (Markoski 2016). Two daughter cells of stem cells are obtained after division asymmetrically by mitosis (Berika *et al*. 2014). Because of this, there was a surge in the understanding of the characteristics as well as their therapeutic potential in different areas (Lane *et al*. 2014). But there is limited legislation about the use of stem cells in veterinary medicine and as well as in human medicine in any country (Dhar and others 2009; Kimmelman *et al*. 2016).

Stem cells are broadly categorized into two categories as either adult or embryonic stem cells. Most of the stem cells have ability of self-renewability in which they are residing. These cells have rapid turnover rate such as intestine, epidermis and blood (Post and Clevers 2019). These are called as adult stem cells (ASCs) and are multipotent in nature but embryonic stem cells (ESCs) obtained from the embryo are in lieu pluripotent which can give rise to all cell types (Lewandowski and Kurpisz 2016). Embryo cells at the blastocysts stage are totipotent in nature which can generate all cell types forming an entire organism (Condic 2014). The field of stem cells in veterinary

medicine is rapidly developing both experimentally and clinically. Stem cell technology in veterinary medicine was first used by Herthel to treat equine ligament dermatitis (Herthel 2002). Stem cells are now most often used in clinical veterinary therapy applications to treat musculoskeletal injuries in horses (Bonilla-Gutiérrez *et al*. 2019; Colbath *et al*. 2020) and dogs (Taroni *et al*. 2017; Prządka *et al*. 2021). In order to protect endangered animal species, new assisted reproductive technologies are being developed that utilize the properties of spermatogonial stem cells (Fayomi and Orwig 2018). Any animal tissue can be repaired or regenerated by using stem cells (Kwon *et al*. 2018).

This article aims to illustrate the properties of stem cells and their derivation with clinical uses of stem cells, along with a discussion of their future horizon.

Types of Potency:

Totipotent: Embryonic and extra embryonic cells can be generated from these stem cells, developing into a complete organism. Cells of first few divisions of fertilized egg are totipotent in nature (Zakrzewski *et al*. 2019).

Pluripotent: All three germ layer cells can be produced resulting in rise of all types of body cells (Hanna *et al*. 2010). These pluripotent cells have the capacity of self-renewability (Nichols and Smith 2012). Embryonic stem cells are pluripotent in nature (Wobus and Boheler 2005).

Multipotent: Stem cells after division resulted in the production of closed related cells. Cord blood stem cells and adult stem cells are considered as multipotent stem cells (Baksh *et al*. 2004).

Oligopotent: Only a few cells can be differentiated after division, like myeloid cells (Zakrzewski *et al*. 2019).

Unipotent: These cells can be differentiated into only one type having the property of self-renewability. These cells are distinguishable from other non-stem cells such as muscle stem cells (Zakrzewski *et al*. 2019).

Types of Stem Cells: Stem cells can be differentiated into many cell types as shown in Figure 1. Stems are broadly categorized into two main types i.e. Embryonic stem cells (ESCs) and Adult stem cells (ASCs).

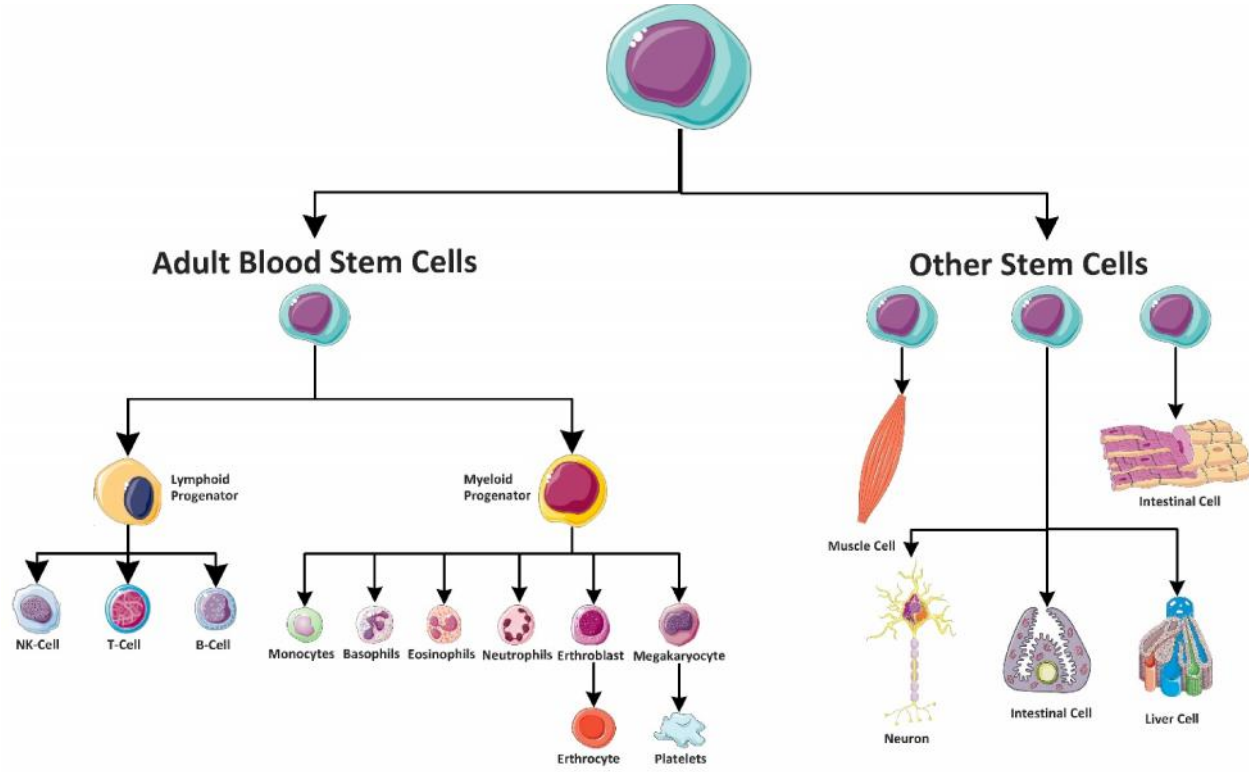

Figure 1: Self renewal and differentiation of stem cells into different cell types

Embryonic stem cells (ESCs): Embryos at the developmental stage are source of ESCs which are usually at the 32 cell stage i.e. blastocyst before the attachment to uterus (De Paepe *et al*. 2014). ESCs were isolated more than 35 years ago from inner cell line of mice blastocyst and grown in vitro (Evans and Kaufman 1981; Martin 1981). Bongso in 1994 first isolated the ESCs from humans (Bongso *et al*. 1994a,b), while

Thomson developed first human embryonic stem cell line from blastocyst in 1998 (Thomson *et al*. 1998). ESCs are capable of symmetrical self-renewal divisions and are pluripotent having capacity to differentiate into all types of fetal and adult cells from all three layers of embryonic germ layers i.e. ectoderm, mesoderm and endoderm. Different type of proteins have been described for the pluripotency of the ESCs such as Nanong, Oct 4 protein and Wnt-B-catenin signaling etc (Ye and Blelloch 2014).

Adult stem cells (ASCs): ASCs are undifferentiated cells found in all over the body possessing the capability of stem cells to replenish the dying cells of body and regeneration of damaged tissues. It was previously assumed that their function is limited to the organ from which they are derived and used for the regeneration of that tissue only but with the advancement in recent years it is suggested that these ASCs can be differentiated into many cell lines as shown in Figure 2.

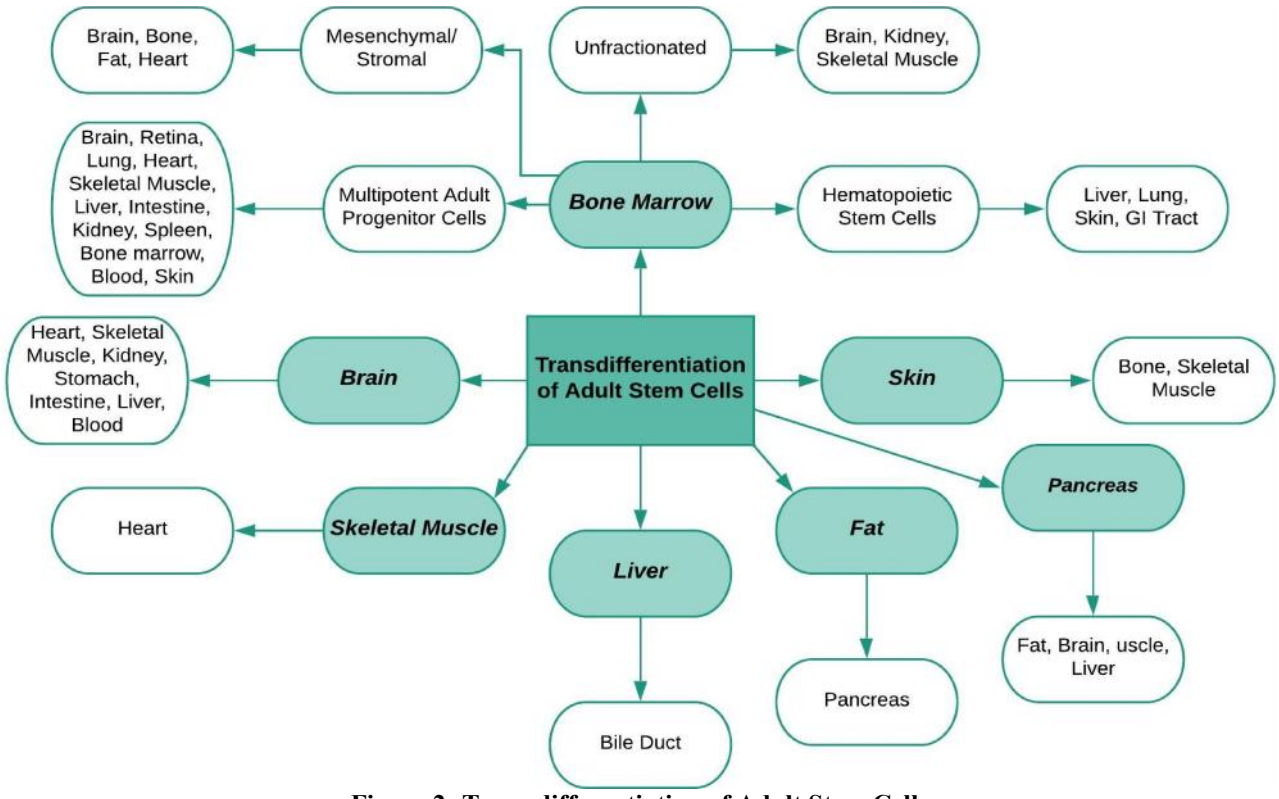

Figure 2: Trans differentiation of Adult Stem Cells

Bone marrow stem cells: Bone marrow stem cells are major reservoir of ASCs. These cells are further divided into two main types:

Bone marrow derived hematopoietic stem cells: Hematopoietic stem cells (HSCs) are the building block of the final hematopoiesis i.e. production of all types of blood cells during entire life of an organism (Ng and Alexander 2017) and can foster the bone marrow after depletion by any disease or irradiation (Troeger *et al*. 2005). Both myeloid (erythrocytes, basophils, eosinophils, neutrophils, monocytes and macrophages, megakaryocytes/platelets and some dendritic cells) and lymphoid cells lines (B cells, T cells, NK cells and some dendritic cells) can be generated from HSCs (Sachin *et al*., 2008).

Bone marrow derived stromal stem cells: Traditionally postnatal bone marrow can be divided into hemopoietic tissue proper and the supporting stroma (Paolo *et al*. 2009). Bone marrow stromal stem cells (BMSSCs) are multipotent in nature and have the capability to undergo differentiation into mesodermal origin type cells, viz osteocytes, chondrocytes and adipocytes (Polymeri *et al*. 2016).

Neural stem cells (NSCs): All three cell types of central nervous system (CNS) can be generated from these NSCs (Kornblum 2007). Reynolds et. al initially cultured the NSCs from brain of adult and embryonic murine as floating neurospheres in the presence of epidermal growth factor (EGF) (Reynolds and Weiss 1992; Reynolds *et al*. 1992).

Olfactory adult stem cells (OASCs): OASCs harvested from human olfactory mucosa have been a source of cell regeneration because of limited availability of stem cells present within CNS (Roisen *et al*. 2001).

Adipose derived adult stem cells (AASCs): MSCs obtained from bone marrow are suboptimal for clinical use because of their highly invasive aspiration and decrease in both proliferation and differentiation potential with increasing senescence (Koobatian *et al*. 2015). Zuk *et al*. introduced alternative stem cells that were morphologically and phenotypically same as of MSCs obtained from adipose tissue (Zuk *et al*. 2002). ADSCs show superiority over MSCs because of their repeated and easy accessibility by subcutaneous adipose tissue with minimal invasion. ADSCs have simple isolation procedure and their quality and proliferation capacity doesn't decreases with patient's age (Zuk *et al*. 2001; Beane *et al*. 2014).

Multipotent adult progenitor cells (MAPCs): The adult bone marrow also harbors nonhematopoietic stem cells i.e., MAPCs which can be grown extensively leading to generation of cells that possess the phenotype and gene profile same as the cells obtained from endoderm, ectoderm and mesoderm (Kovacsovics-Bankowski *et al*. 2006). It has been suggested that MAPCs comprises a population of stem cells obtained from or closely related to ESCs (Jiang *et al*. 2002).

Induced Pluripotent Stem Cells (iPSCs): iPSCs were first developed by the Takahashi and Yamanaka in 2006 by retroviral induction of 4 transcription factors (octamer-binding transcription factor (Oct)3/4, proto-oncogene MYC (c-MYC), Krüppel-like factor (KLF4) and SRY-Box (SOX2) (Takahashi and Yamanaka 2006). These stem cells were found to have the similar properties of ESCs involving the morphology, marker expression and differentiation potential (Takahashi and Yamanaka 2006). iPSCs are now being generated for humans as well as for a variety of animal species such as wild felines, primates, equines, bovine and rodents etc.

Stem cells in veterinary medicine

Equine/Camels

Tendinitis/Tendon repair: Scar tissue formed after the recovery of damaged tendon repercussed in decreased performance and considerable risk of reinjury. That's why, to avoid poor functional outcome, it is essential to substitute the tissue with a tendon like matrix instead of scar. Many studies unveiled beneficial effects on organization of tissue along with composition and mechanics of stem cells implanted tendons (Butler *et al*. 2008; Schnabel *et al*. 2009; Crovace *et al*. 2010). All these studies differ in experimental design regarding number of BMSSCs ($0.5\text{-}10\times10^6$), suspension of vehicle (bone marrow supernatant, phosphate-buffered saline, plasma) as well as post injury time of injection. In 2003, first application of BMSSCs was reported in horses (Smith *et al*. 2003). Recent study unveiled that 90% of horses treated with BMSSCs returned to athletics with no re-injury of superficial digital flexor tendon after two years, although recurrence of injury observed in horses of controlled group (Pacini *et al*. 2007). Godwin and Smith treated the 141 horses with BMSSCs with 3 years follow up. Significant decrease in recurrence of injury was noted in National Hunt race horses but not in Thoroughbred racing horses (Godwin *et al*. 2012). Adipose derived mesenchymal stromal stem cells also used in the treatment showed better recovery of tendon as compared to control group horses (de Mattos Carvalho *et al*. 2011).

Cartilage injury/osteoarthritis: Wilke evaluate the BMSSCs in six young horses creating acute cartilage injury with 15 mm diameter cartilage lesions in femoropatellar articulations (Wilke *et al*. 2007). BMSSCs was injected with autogenous fibrin as a vehicle and autogenous fibrin alone in control animals. Arthroscopy scores as well as biopsy assessment were better in lesions treated with BMSSCs as compared to autogenous fibrin alone. Animals euthanized after 8 months, repaired cartilage tissue and surrounding cartilage were examined by histochemistry, collagen type I and type II immunohistochemistry, histology, and matrix biochemical assays. There was no significant difference in both control and treatment groups. Another study comparatively evaluates the clinical, histologic and biochemical effects of adipose-derived stromal vascular fraction (AD-SVF) and BMSSCs in equine model of osteoarthritis (OA) (Frisbie *et al*. 2009). Both AD-SVF and BMSSCs were injected in the affected joints 14 days post induction of OA. Lower prostaglandin E2 (PGE2) level along with less synovial effusion was found in the joints treated with BM-MSCs in comparison with AD-SVF. Moreover, there was no difference recorded in cartilage histology and biochemistry profile, synovial fluid analysis as well as other clinical parameters (Frisbie *et al*. 2009). Many other preclinical studies in OA models of sheep, goat, rats and rabbits have shown that BM-MSCs enhances cartilage regeneration as well as meniscus (Murphy *et al*. 2003; Izuta *et al*. 2005).

Canine/Feline

Dilated Cardiomyopathy: Myocardial infarction has been given more attention in regenerative medicine as compared to nonischemic cardiac diseases, although myocardial infarction is seldom seen in dogs and cats. Companion animals have high rate of many nonischemic cardiac diseases, also found in humans, such as canine dilated cardiomyopathy (DCM), feline hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular dysplasia/cardiomyopathy and mitral valve disease-prolapse (MVP). This non-ischemic heart disease

in dogs provides a unique opportunity to develop therapeutic interventions that weaken biomarkers that improve heart reperfusion, progressing to cardiac arrest, fatal arrhythmias, and the diagnosis and prognosis of these diseases. The only study that used stem cells in non-ischemic heart disease in dogs and cats was carry out in DCM (Pogue *et al*. 2013). DCM has similar processes and phenotypes in humans and dogs (Simpson *et al*. 2015). Study involves the 15 dogs with DCM were coronary venously injected with allogeneic ADSCs transduced employing adenoviral associated virus subtype 2 (AAV2). Only 1 out of 15 dogs burgeon malignant ventricular arrhythmias after injecting cells and died because of cardiac arrest, while 14 dogs discharged after the treatment. There were no differences in echocardiography and hematological index after 2-year follow-up, between the treated dog and the previous control group. No AAV2 antibodies were developed in dogs. The model of non-ischemic heart diseases in dogs can be used for research in the field of regenerative medicine, taking into account the high prevalence and significant similarity of pathology with human DCM, MVP and HCM.

Atopic Dermatitis (AD): AD is a skin condition affecting 8.7% dogs (Hillier and Griffin 2001) while 10%-20% in human child and 3%-4% in human adults (Watson and Kapur 2011). Hall conducted a trial in 5 dogs employing single dose of AD-MSC. No benefit of this treatment was recorded in this trial because the dose used in this study was less than the other studies. Contrarily, a human trial showed positive result in atopic dermatitis treatment (Liang *et al*. 2010). Choice of dosage for pets is usually modeled according to human studies and is not formulated in rodents with significantly higher doses per kilogram of body weight. So, further trials need to be conducted in order to evaluate the effect of stem cells in atopic dermatitis.

Feline Chronic Kidney Disease (CKD): CKD is widespread in aged cats, estimating about 85% of cats over 15 years of age with some kind of renal function impairment. Stem cell therapy for CKD in cats has been studied with both allogenic and autologous MSCs (Quimby and Dow 2015). In a study, six cats (2 healthy and 4 with CKD) were injected once intravenously 1×10^5 autologous ADSCs or BMSSCs per injection (Quimby *et al*. 2011). Nuclear scintigraphy showed mild improvement in renal function of two cats having CKD. A second trial was conducted in the 11 cats. Cats received three infusions of allogenic ADSCs intravenously with 2 weeks intervals either 4×10^6 per kg body weight (six cats) or 2×10^6 per kg body weight (five cats) (Quimby *et al*. 2013). Cats receiving high doses of ADSCs showed adverse effects such as dyspnea, salivation and vomiting while no adverse effects observed in cats receiving low doses. No improvement in renal function parameters were observed. Altogether, these two studies of ADSCs have shown that the intravenous administration of MSC may not be especially effective in treating relatively advanced CKD in cats.

Alzheimer's Disease, Amyotrophic Lateral Sclerosis, and Epilepsy: Other 3 CNS conditions found in dogs corresponds to human neurologic diseases including Alzheimer's disease (Canine Cognitive Dysfunction Syndrome), amyotrophic lateral sclerosis (canine degenerative myelopathy), and epilepsy (canine epilepsy). It has been shown that MSCs mitigate progression of epilepsy or chronic epilepsy (Agadi and Shetty 2015) and ALS (Thomsen *et al*. 2014). That's why stem cell therapies are being utilized for the treatment of these diseases and dogs are being used as model for this objective.

Livestock: One of the main concerns today is getting the contribution of agriculture and livestock inputs to increase the nutrition of the world's population. In this way, the cows to be slaughtered are very concerned, and in order to obtain better meat and reproductive potential, it is necessary to take into account the livestock environment (pasture or confine) and physical development. Still, stem cells are rarely studied in livestock area, but some goat models also exists for treatment of cell types such as cartilage injuries (Im and Ko 2018) and iPSCs under study (Chen *et al*. 2017). Cattle designed to produce fatty meat with high tender ability (may be the maximum weight) can cause problems related to bones and cartilages. Moreover, it can also affect movement, especially when grazing. Nam *et al*. identifies and established of MSCs methods for the treatment of caprine chondral injuries (Nam *et al*. 2013). Mastitis, an acute inflammatory and economically important disease of the mammary glands, especially in bovines results in dramatic reductions in milk production (Peralta *et al*. 2020). The disease directly affects farmers' income through reducing milk quantity, quality and animal value as well , while at the same time leading to drug costs, the risk of animal removal and the potential for death (Hill *et al*. 2019). Furthermore, the epithelial cells of bovine mammary glands and their stem cells are also of great importance in the field of biotechnology and also in sense of milk production. Therefore, Sharma and Jeong have shown the possibility of stem cell treatment from cows, which offers great potential for tissue regeneration (Sharma and Jeong 2013). The diseased sweat glands can potentially be repaired or regenerated by these tissues, suggesting that isolated stem cells differentiate into epithelial and muscular epithelial reducing risk after injection (Sharma and Jeong 2013; Hill *et al*. 2019; Peralta *et al*. 2020). Authors believed that iPSCs can also be used alternatively for the treatment purposes. iPSCs are termed as differentiated cells and are experimentally reprogrammed into pluripotent cells to

achieve a state similar to embryonic stem cells. MSCs and fibroblasts can be used for this purpose, and there are many studies to obtain iPSCs for cattle, sheep, pigs goats, buffalo and other farm animals (Kumar *et al*. 2015).

There are certain large animal models that are more closely related to the anatomy and physiology of humans. These models can mimic human physiological process more effectively as compared to murine models for rapid clinical intervention and therapies (Dixon and Spinale 2009). Large animal stem cell technologies can serve as a basic guiding path for development of human stem cell treatment targeting injuries (ligaments and tendon rupture) and diseases (osteochondrosis, osteoarthritis, muscular dystrophy, stroke, and myocardial infarction) in large animals and in humans as well (Chen *et al*. 2001). Table 1 summarizes the application of the stem cells used in livestock sector.

Table 1: Summary of the potential use of stem cells in different livestock animal species.

Specie	Use	Reference
Cattle/Buffalo	Stem cells are being used in cattle/buffalo to ameliorate meat and milk production as well as increasing biopharming using transgenic milch animals.	(Singh *et al*. 2009; Niemann *et al*. 2011).
	MSC are also being used in reduction of greenhouse gases emission and production of in-vitro meat using muscle stem cells	(Datar and Betti 2010; Pandurangan and Kim 2015; Hossain 2019)
Sheep/Goat	Transgenic animal are being produced to enhance biopharming as well as in vitro mutton production	(Mauro *et al*. 2010; Azari *et al*. 2011).
	Osteochondral defects can be treated by using the stem cells obtained from the goats.	(Gugjoo *et al*. 2019)
	Many different bone tissue engineering techniques are being used that involves the use of bones such as mandible, femur and tibia.	(El Hadidi *et al*. 2016; Zhao *et al*. 2017)
	Used as model for the research of various human diseases such as Intervertebral disc disease, human stress urinary incontinence disorder, and Broncho pleural fistula.	(Beckstein *et al*. 2008; Petrella *et al*. 2014; Burdzinska *et al*. 2017)
Pig	Cell, tissue and organ development for xenotransplantation, improved biopharmaceuticals through transgenic animals and in vitro pork production	(Niemann *et al*. 2011)

Poultry: Avian embryos are powerful models for studying stem cell development and biology (Stern 2004, 2005). They have many advantages to be used as models for studying the biology of stem cells, because of their size and easy access to eggs, availability throughout the year and ease of embryos for processing (Berg *et al*. 1999). So far, the only stable non-mammalian embryonic stem cell and germ cell lines are established from poultry. Chick embryonic stem cells (cESc) and embryonic germ cells (cEGs) are thought as pluripotent (Petitte *et al*. 2004). However, it has been demonstrated that cESc cells can only take part in somatic cells while germ cells are not included (Pain *et al*. 1996), and germ cells in chicken embryos may take part in germ cells (Van de Lavoir *et al*. 2006). Surprisingly, little attention has been paid to the biological properties of avian stem cells, in particular the similarities and differences between embryonic chicken stem cells, stem cells and germ cells derived from adult and / or other embryonic tissues.

Retroviral vectors have been used to transduce foreign genes into early chicken placenta and somatic stem cells, but LacZ-containing constructs can be transfected into placental cells to create chicken chimeras (Naito *et al*. 1994; Inada *et al*. 1997). Unlike, lentiviral vectors have been successfully used to produce several transgenic avian strains, including quail and chicken (McGrew *et al*. 2004; Poynter *et al*. 2009; Seidl *et al*. 2013).

Now a days, this method has been used routinely, and most of the laboratories are going to establish gene transduction lines for avian species, such as universal expression of GFP (membrane or cytoplasmic position) or tissue specific promoters as well as other cell clines used such as reporters for many signal pathways are useful for research purpose. A principally promising transformation technique to introduce large inserts using Tol2 and piggyBac transposons has been recently described (Macdonald *et al*. 2012).

Instead of successful development of transgenic poultry, lentiviral transduction is still not easy to perform a targeted mutagenesis on selected genetic loci because transgenes are randomly inserted into multiple loci. Although a well-thought-out selection allows isolation and purification of the strain as a single integrator, it is

still not possible to target a specific location with this method. To do this, cell methods using homologous recombination in ESCs or Primordial germ cells (PGCs) are needed. Homologous recombination in poultry cells is possible, but relatively simple, howbeit has not yet been achieved (Acloque *et al*. 2004; Takata *et al*. 2009; Ishiai *et al*. 2012; Han and Park 2018). The main obstacle is the accessibility of cell lines for homologous recombination (the recombinant lines can be kept in culture so that they can be successfully isolated like mice) and the germline, Suitable for their contribution too (Pain *et al*. 1996; Van de Lavoir *et al*. 2006; Zhang *et al*. 2013). In stage X embryos, the early blastocyst cells containing PGCs had some success, results in germline chimeras production and somatic cells (Thoraval *et al*. 1994; Kagami *et al*. 1995; Etches *et al*. 1996). Although fresh cells are more efficient, chimeras can be generated using fresh, or cryopreserved blastodermic cells (Etches *et al*. 1996; Kino *et al*. 1997). A study has shown that using transgenic marrow cells of chicks, which were inserted into testicles, results in genetically modified chicks (Heo *et al*. 2011).

The germ-cell obtained for chicken transgenesis was described in studies long ago using crescent-derived PGCs and replication-defective retroviral vectors (Vick *et al*. 1993). The introduction of genes into gonadal PGCs were also being made by Lenti virus vectors (Shin *et al*. 2008). Blood-derived PGCs are also used in transgenic chickens to deliver electroporation genes (Van de Lavoir *et al*. 2006). Transgenic birds production methods which are PGCs based are termed as "embryo-mediated system" (Han 2009). "Testis mediated system" was introduced as an alternate system (Lee *et al*. 2006). Reduction in test cross time and exception of PGCs retrieval are advantages of above described method (Han 2009). However, to increase yield and efficiency in the production of transgenic chicks there was no appraisal between testis and embryo mediated systems.

Thus, cellular methods have the potential for targeted mutagenesis in chicks, but this has not been achieved successfully. Currently, Transgene which produced by using lentivirus as vector seems to be most effective way to generate strains of transgenic birds, but mutagenesis of specific endogenous loci can't be done by this method.

Conclusion: Regenerative veterinary medicine is an active area of research. In recent years, significant progress has been made in the development of safe and effective stem cell therapies. Although stem cell therapy has shown remarkable results, especially in orthopedic conditions in dogs and horses, but this therapy has also made significant advances in the treatment of other conditions such as DCM, CKD, CAD and wound healing. The positive results from many studies open up broad prospects for the future of stem cell therapy for various animal diseases, but there are still many problems that need to be solved. One of them is the best source to isolate stem cells. While most studies have used bone marrow and AASCs, most are readily available and easy to use. Therefore, in future, different stem cells harvested from different tissues, may be better suited to treat certain diseases. We live in an exciting time and new methods of regenerative therapy are emerging. Further research in this area is expected to make stem cell therapy not only a treatment option for many incurable diseases, but also a realistic and user-friendly option for veterinarians and human patients.

Acknowledgements: No acknowledgement

Competing interests: No conflict of interests

Funding: No funding received

REFERENCES

Acloque, H., A. Mey, A.M. Birot, H. Gruffat, B. Pain, and J. Samarut. (2004). Transcription factor cCP2 controls gene expression in chicken embryonic stem cells. Nucleic Acids Res. 32(7): 2259–2271.

Agadi, S., and A.K. Shetty. (2015). Concise review: prospects of bone marrow mononuclear cells and mesenchymal stem cells for treating status epilepticus and chronic epilepsy. Stem Cells. 33(7): 2093–2103.

Azari, O., H. Babaei, A. Derakhshanfar, S.N. Nematollahi-Mahani, R. Poursahebi, and M. Moshrefi. (2011). Effects of transplanted mesenchymal stem cells isolated from Wharton's jelly of caprine umbilical cord on cutaneous wound healing; histopathological evaluation. Vet. Res. Commun. 35(4): 211–222.

Baksh, D., L. Song, and R.S. Tuan. (2004). Adult mesenchymal stem cells: characterization, differentiation, and application in cell and gene therapy. J Cell Mol Med. 8.

Beane, O.S., V.C. Fonseca, L.L. Cooper, G. Koren, and E.M. Darling. (2014). Impact of aging on the regenerative properties of bone marrow-, muscle-, and adipose-derived mesenchymal stem/stromal cells. PLoS One. 9(12): e115963.

Beckstein, J.C., S. Sen, T.P. Schaer, E.J. Vresilovic, and D.M. Elliott. (2008). Comparison of animal discs used in disc research to human lumbar disc: axial compression mechanics and glycosaminoglycan content. Spine (Phila. Pa. 1976). 33(6): E166--E173.

Berg, C., K. Halldin, A.-K. Fridolfsson, I. Brandt, and B. Brunström. (1999). The avian egg as a test system for endocrine disrupters: effects of diethylstilbestrol and ethynylestradiol on sex

organ develo. Sci. Total Environ. 233(1–3): 57–66.

Berika, M., M.E. Elgayyar, and A.H.K. El-Hashash. (2014). Asymmetric cell division of stem cells in the lung and other systems. Front. Cell Dev. Biol. 233.

Bongso, A., C.Y. Fong., S.C. Ng., and S.S. Ratnam. (1994a). The growth of inner cell mass cells from human blastocysts. Theriogenology. 41(1): 167.

Bongso, A., C.Y. Fong, S.C. Ng, and S. Ratnam. (1994b). Isolation and culture of inner cell mass cells from human blastocysts. Hum. Reprod. 9(11): 2110–2117.

Bonilla-Gutiérrez, A.F., C. López, and J.U. Carmona. (2019). Regenerative therapies for the treatment of tenodesmic injuries in horses. J. Equine Vet. Sci. 73139–147.

Burdzinska, A., B. Dybowski, W. Zarychta-Wisniewska, A. Kulesza, R. Zagozdzon, Z. Gajewski, and L. Paczek. (2017). The anatomy of caprine female urethra and characteristics of muscle and bone marrow derived caprine cells for autologous cell therapy testing. Anat. Rec. 300(3): 577–588.

Butler, D.L., N. Juncosa-Melvin, G.P. Boivin, M.T. Galloway, J.T. Shearn, C. Gooch, and H. Awad. (2008). Functional tissue engineering for tendon repair: A multidisciplinary strategy using mesenchymal stem cells, bioscaffolds, and mechanical stimulation. J. Orthop. Res. 26(1): 1–9.

Chen, H., Q. Zuo, Y. Wang, J. Song, H. Yang, Y. Zhang, and B. Li. (2017). Inducing goat pluripotent stem cells with four transcription factor mRNAs that activate endogenous promoters. BMC Biotechnol. 17(1): 1–10.

Chen, J., Y. Li, L. Wang, Z. Zhang, D. Lu, M. Lu, and M. Chopp. (2001). Therapeutic benefit of intravenous administration of bone marrow stromal cells after cerebral ischemia in rats. Stroke. 32(4): 1005–1011.

Colbath, A.C., S.W. Dow, C.W. McIlwraith, and L.R. Goodrich. (2020). Mesenchymal stem cells for treatment of musculoskeletal disease in horses: Relative merits of allogeneic versus autologous stem cells. Equine Vet. J. 52(5): 654–663.

Condic, M.L. (2014). Totipotency: What It Is and What It Is Not. Stem Cells Dev. 23(8): 796–812.

Crovace, A., L. Lacitignola, G. Rossi, and E. Francioso. (2010). Histological and immunohistochemical evaluation of autologous cultured bone marrow mesenchymal stem cells and bone marrow mononucleated cells in collagenase-induced tendinitis of equine superficial digital flexor tendon. Vet. Med. Int. 2010.

Datar, I., and M. Betti. (2010). Possibilities for an in vitro meat production system. Innov. Food Sci. Emerg. Technol. 11(1): 13–22.

de Mattos Carvalho, A., A.L.G. Alves, P.G.G. de Oliveira, L.E.C. Álvarez, R.L. Amorim, C.A. Hussni, and E. Deffune. (2011). Use of adipose tissue-derived mesenchymal stem cells for experimental tendinitis therapy in equines. J. Equine Vet. Sci. 31(1): 26–34.

De Paepe, C., M. Krivega, G. Cauffman, M. Geens, and H. de Velde. (2014). Totipotency and lineage segregation in the human embryo. Mol. Hum. Reprod. 20(7): 599–618.

Dhar, D., and others. (2009). Stem cell research policies around the world. Yale J. Biol. Med. 82(3): 113–115.

Dixon, J.A., and F.G. Spinale. (2009). Large animal models of heart failure: a critical link in the translation of basic science to clinical practice. Circ. Hear. Fail. 2(3): 262–271.

El Hadidi, Y.N., M. El Kassaby, S.A.E.F. Ahmed, and N.S. Khamis. (2016). Effect of mesenchymal stem cell application on the distracted bone microstructure: an experimental study. J. Oral Maxillofac. Surg. 74(7): 1463--e1.

Etches, R.J., M.E. Clark, A. Toner, G. Liu, and A.M. Verrinder Gibbins. (1996). Contributions to somatic and germline lineages of chicken blastodermal cells maintained in culture. Mol. Reprod. Dev. Inc. Gamete Res. 45(3): 291–298.

Evans, M.J., and M.H. Kaufman. (1981). Establishment in culture of pluripotential cells from mouse embryos. Nature. 292154.

Fayomi, A.P., and K.E. Orwig. (2018). Spermatogonial stem cells and spermatogenesis in mice, monkeys and men. Stem Cell Res. 29207–214.

Frisbie, D.D., J.D. Kisiday, C.E. Kawcak, N.M. Werpy, and C.W. McIlwraith. (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.

Godwin, E.E., N.J. Young, J. Dudhia, I.C. Beamish, and R.K.W. Smith. (2012). 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. 44(1): 25–32.

Gugjoo, M.B., Amarpal, M.-U.R. Fazili, M.A. Gayas, R.A. Ahmad, and K. Dhama. (2019). Animal mesenchymal stem cell research in cartilage regenerative medicine--a review. Vet. Q. 39(1): 95–120.

Han, J.Y. (2009). Germ cells and transgenesis in chickens. Comp. Immunol. Microbiol. Infect. Dis. 32(2): 61–80.

Han, J.Y., and Y.H. Park. (2018). Primordial germ cell-

mediated transgenesis and genome editing in birds. J. Anim. Sci. Biotechnol. 9(1): 19.

Hanna, J.H., K. Saha, and R. Jaenisch. (2010). Pluripotency and cellular reprogramming: facts, hypotheses, unresolved issues. Cell. 143(4): 508–525.

Heo, Y.T., S.H. Lee, J.H. Yang, T. Kim, and H.T. Lee. (2011). Bone marrow cell-mediated production of transgenic chickens. Lab. Investig. 91(8): 1229–1240.

Herthel, D.J. (2002). Suspensory desmitis therapies.

Hill, A.B.T., F.F. Bressan, B.D. Murphy, and J.M. Garcia. (2019). Applications of mesenchymal stem cell technology in bovine species. Stem Cell Res. Ther. 10(1): 1–13.

Hillier, A., and C.E. Griffin. (2001). The ACVD task force on canine atopic dermatitis (I): incidence and prevalence. Vet. Immunol. Immunopathol. 81(3–4): 147–151.

Hossain, M.S. (2019). Consumption of Stem Cell Meat: An Islamic Perspective. IIUM Law J. 27(1): 233–257.

Im, G.-I., and J.-Y. Ko. (2018). SOX-6, 9-transfected adipose stem cells to treat osteoarthritis in a goat osteoarthritis model. Osteoarthr. Cartil. 26S36--S37.

Inada, S., M.A. Hattori, N. Fujihara, and K. Morohashi. (1997). In vivo gene transfer into the blastoderm of early developmental stage of chicken.

Ishiai, M., E. Uchida, and M. Takata. (2012). Establishment of the DNA repair-defective mutants in DT40 cells.

Izuta, Y., M. Ochi, N. Adachi, M. Deie, T. Yamasaki, and R. Shinomiya. (2005). Meniscal repair using bone marrow-derived mesenchymal stem cells: experimental study using green fluorescent protein transgenic rats. Knee. 12(3): 217–223.

Jiang, Y., B. Vaessen, T. Lenvik, M. Blackstad, M. Reyes, and C.M. Verfaillie. (2002). Multipotent progenitor cells can be isolated from postnatal murine bone marrow, muscle, and brain. Exp. Hematol. 30(8): 896–904.

Kagami, H., M.E. Clark, A.M.V. Gibbins, and R.J. Etches. (1995). Sexual differentiation of chimeric chickens containing ZZ and ZW cells in the germline. Mol. Reprod. Dev. 42(4): 379–387.

Kimmelman, J., I. Hyun, N. Benvenisty, T. Caulfield, H.E. Heslop, C.E. Murry, D. Sipp, L. Studer, J. Sugarman, and G.Q. Daley. (2016). Policy: global standards for stem-cell research. Nature. 533(7603): 311–313.

Kino, K., B. Pain, S.P. Leibo, M. Cochran, M.E. Clark, and R.J. Etches. (1997). Production of chicken chimeras from injection of frozen-thawed blastodermal cells. Poult. Sci. 76(5): 753–760.

Koobatian, M.T., M.-S. Liang, D.D. Swartz, and S.T. Andreadis. (2015). Differential effects of culture senescence and mechanical stimulation on the proliferation and leiomyogenic differentiation of MSC from different sources: implications for engineering vascular grafts. Tissue Eng. Part A. 21(7–8): 1364–1375.

Kornblum, H.I. (2007). Introduction to Neural Stem Cells. Stroke. 38(2): 810 LP – 816.

Kovacsovics-Bankowski, M., P.R. Streeter, W.J. Van't Hof, R.J. Deans, and R.T. Maziarz. (2006). Multipotent Adult Progenitor Cells (MAPC) are non-immunogenic and display immunosuppressive properties on activated T cells. Biol. Blood Marrow Transplant. 12(2): 106–107.

Kumar, D., T.R. Talluri, T. Anand, and W.A. Kues. (2015). Induced pluripotent stem cells: Mechanisms, achievements and perspectives in farm animals. World J. Stem Cells. 7(2): 315.

Kwon, S.G., Y.W. Kwon, T.W. Lee, G.T. Park, and J.H. Kim. (2018). Recent advances in stem cell therapeutics and tissue engineering strategies. Biomater. Res. 22(1): 1–8.

Lane, S.W., D.A. Williams, and F.M. Watt. (2014). Modulating the stem cell niche for tissue regeneration. Nat Biotechnol. 32(8): 795–803.

Lee, Y.M., J.G. Jung, J.N. Kim, T.S. Park, T.M. Kim, S.S. Shin, D.K. Kang, J.M. Lim, and J.Y. Han. (2006). A testis-mediated germline chimera production based on transfer of chicken testicular cells directly into heterologous testes. Biol. Reprod. 75(3): 380–386.

Lewandowski, J., and M. Kurpisz. (2016). Techniques of human embryonic stem cell and induced pluripotent stem cell derivation. Arch. Immunol. Ther. Exp. (Warsz). 64(5): 349–370.

Liang, J., H. Zhang, B. Hua, H. Wang, L. Lu, S. Shi, Y. Hou, X. Zeng, G.S. Gilkeson, and L. Sun. (2010). Allogenic mesenchymal stem cells transplantation in refractory systemic lupus erythematosus: a pilot clinical study. Ann. Rheum. Dis. 69(8): 1423–1429.

Macdonald, J., L. Taylor, A. Sherman, K. Kawakami, Y. Takahashi, H.M. Sang, and M.J. McGrew. (2012). Efficient genetic modification and germ-line transmission of primordial germ cells using piggyBac and Tol2 transposons. Proc. Natl. Acad. Sci. 109(23): E1466–E1472.

Markoski, M.M. (2016). Advances in the Use of Stem Cells in Veterinary Medicine: From Basic Research to Clinical Practice. Scientifica (Cairo). 201612.

Martin, G.R. (1981). Isolation of a pluripotent cell line from early mouse embryos cultured in medium conditioned by teratocarcinoma stem cells. Proc.

Natl. Acad. Sci. U. S. A. 78(12): 7634–7638.

Mauro, A., M. Turriani, A. Ioannoni, V. Russo, A. Martelli, O. Di Giacinto, D. Nardinocchi, and P. Berardinelli. (2010). Isolation, characterization, and in vitro differentiation of ovine amniotic stem cells. Vet. Res. Commun. 34(1): 25–28.

McGrew, M.J., A. Sherman, F.M. Ellard, S.G. Lillico, H.J. Gilhooley, A.J. Kingsman, K.A. Mitrophanous, and H. Sang. (2004). Efficient production of germline transgenic chickens using lentiviral vectors. EMBO Rep. 5(7): 728–733.

Murphy, J.M., D.J. Fink, E.B. Hunziker, and F.P. Barry. (2003). Stem cell therapy in a caprine model of osteoarthritis. Arthritis Rheum. Off. J. Am. Coll. Rheumatol. 48(12): 3464–3474.

Naito, M., E. Sasaki, M. Ohtaki, and M. Sakurai. (1994). Introduction of exogenous DNA into somatic and germ cells of chickens by microinjection into the germinal disc of fertilized ova. Mol. Reprod. Dev. 37(2): 167–171.

Nam, H.Y., P. Karunanithi, W.C.P. Loo, S.V. Naveen, H.C. Chen, P. Hussin, L. Chan, and T. Kamarul. (2013). The effects of staged intra-articular injection of cultured autologous mesenchymal stromal cells on the repair of damaged cartilage: a pilot study in caprine model. Arthritis Res. Ther. 15(5): R129.

Ng, A.P., and W.S. Alexander. (2017). Haematopoietic stem cells: past, present and future. Cell Death Discov. 317002.

Nichols, J., and A. Smith. (2012). Pluripotency in the embryo and in culture. Cold Spring Harb. Perspect. Biol. 4(8): a008128.

Niemann, H., B. Kuhla, and G. Flachowsky. (2011). Perspectives for feed-efficient animal production. J. Anim. Sci. 89(12): 4344–4363.

Pacini, S., S. Spinabella, L. Trombi, R. Fazzi, S. Galimberti, F. Dini, F. Carlucci, and M. Petrini. (2007). Suspension of bone marrow--derived undifferentiated mesenchymal stromal cells for repair of superficial digital flexor tendon in race horses. Tissue Eng. 13(12): 2949–2955.

Pain, B., M.E. Clark, M. Shen, H. Nakazawa, M. Sakurai, J. Samarut, and R.J. Etches. (1996). Long-term in vitro culture and characterisation of avian embryonic stem cells with multiple morphogenetic potentialities. Development. 122(8): 2339–2348.

Pandurangan, M., and D.H. Kim. (2015). A novel approach for in vitro meat production. Appl. Microbiol. Biotechnol. 99(13): 5391–5395.

Paolo, B., R. Mara, G. Stan, and R.P. Gehron. (2009). Bone Marrow Stromal Stem Cells: Nature, Biology, and Potential Applications. Stem Cells. 19(3): 180–192.

Peralta, O.A., C. Carrasco, C. Vieytes, M.J. Tamayo, I. Muñoz, S. Sepulveda, T. Tadich, M. Duchens, P. Melendez, A. Mella, (Add here the name of all other researchers/co-authors and others. (2020). Safety and efficacy of a mesenchymal stem cell intramammary therapy in dairy cows with experimentally induced Staphylococcus aureus clinical mastitis. Sci. Rep. 10(1): 1–12.

Petitte, J.N., G. Liu, and Z. Yang. (2004). Avian pluripotent stem cells. Mech. Dev. 121(9): 1159–1168.

Petrella, F., F. Toffalorio, S. Brizzola, T.M. De Pas, S. Rizzo, M. Barberis, P. Pelicci, L. Spaggiari, and F. Acocella. (2014). Stem cell transplantation effectively occludes bronchopleural fistula in an animal model. Ann. Thorac. Surg. 97(2): 480–483.

Pogue, B., A.H. Estrada, I. Sosa-Samper, H.W. Maisenbacher, K.E. Lamb, B.D. Mincey, K.E. Erger, and T.J. Conlon. (2013). Stem-cell therapy for dilated cardiomyopathy: a pilot study evaluating retrograde coronary venous delivery. J. Small Anim. Pract. 54(7): 361–366.

Polymeri, A., W. V Giannobile, and D. Kaigler. (2016). Bone Marrow Stromal Stem Cells in Tissue Engineering and Regenerative Medicine. Horm. Metab. Res. = Horm. und Stoffwechselforsch. = Horm. Metab. 48(11): 700–713.

Post, Y., and H. Clevers. (2019). Defining Adult Stem Cell Function at Its Simplest: The Ability to Replace Lost Cells through Mitosis. Cell Stem Cell. 25(2): 174–183.

Poynter, G., D. Huss, and R. Lansford. (2009). Japanese quail: an efficient animal model for the production of transgenic avians. Cold Spring Harb. Protoc. 2009(1): pdb. emo112.

Prządka, P., K. Buczak, E. Frejlich, L. Gąsior, K. Suliga, and Z. Kiełbowicz. (2021). The Role of Mesenchymal Stem Cells (MSCs) in Veterinary Medicine and Their Use in Musculoskeletal Disorders. Biomolecules. 11(8): 1141.

Quimby, J.M., and S.W. Dow. (2015). Novel treatment strategies for feline chronic kidney disease: A critical look at the potential of mesenchymal stem cell therapy. Vet. J. 204(3): 241–246.

Quimby, J.M., T.L. Webb, D.S. Gibbons, and S.W. Dow. (2011). Evaluation of intrarenal mesenchymal stem cell injection for treatment of chronic kidney disease in cats: a pilot study. J. Feline Med. Surg. 13(6): 418–426.

Quimby, J.M., T.L. Webb, L.M. Habenicht, and S.W. Dow. (2013). Safety and efficacy of intravenous infusion of allogeneic cryopreserved mesenchymal stem cells for treatment of chronic kidney disease in cats: results of three sequential pilot studies. Stem Cell Res. Ther. 4(2): 48.

Reynolds, B.A., W. Tetzlaff, and S. Weiss. (1992). A multipotent EGF-responsive striatal embryonic progenitor cell produces neurons and astrocytes. J. Neurosci. 12(11): 4565–4574.

Reynolds, B.A., and S. Weiss. (1992). Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. Science. 255(5052): 1707–1710.

Roisen, F.J., K.M. Klueber, C.L. Lu, L.M. Hatcher, A. Dozier, C.B. Shields, and S. Maguire. (2001). Adult human olfactory stem cells. Brain Res. 890(1): 11–22.

Sachin Avasthi, R. N. Srivastava, Ajai Singh, A., and M.S. MS. (2008). Stem Cell: Past, Present and Future- A Review Article. Internet J. Med. Updat. 3(1): 22–30.

Schnabel, L. V, M.E. Lynch, M.C.H. Van Der Meulen, A.E. Yeager, M.A. Kornatowski, and A.J. Nixon. (2009). Mesenchymal stem cells and insulin-like growth factor-I gene-enhanced mesenchymal stem cells improve structural aspects of healing in equine flexor digitorum superficialis tendons. J. Orthop. Res. 27(10): 1392–1398.

Seidl, A.H., J.T. Sanchez, L. Schecterson, K.M. Tabor, Y. Wang, D.T. Kashima, G. Poynter, D. Huss, S.E. Fraser, and R. Lansford. (2013). Transgenic quail as a model for research in the avian nervous system: a comparative study of the auditory brainstem. J. Comp. Neurol. 521(1): 5–23.

Sharma, N., and D.K. Jeong. (2013). Stem cell research: a novel boulevard towards improved bovine mastitis management. Int. J. Biol. Sci. 9(8): 818.

Shin, S.S., T.M. Kim, S.Y. Kim, T.W. Kim, H.W. Seo, S.K. Lee, S.C. Kwon, G.S. Lee, H. Kim, and J.M. Lim. (2008). Generation of transgenic quail through germ cell-mediated germline transmission. FASEB J. 22(7): 2435–2444.

Simpson, S., J. Edwards, T.F.N. Ferguson-Mignan, M. Cobb, N.P. Mongan, and C.S. Rutland. (2015). Genetics of human and canine dilated cardiomyopathy. Int. J. Genomics. 2015.

Singh, B., M.S. Chauhan, S.K. Singla, S.K. Gautam, V. Verma, R.S. Manik, A.K. Singh, M. Sodhi, and M. Mukesh. (2009). Reproductive biotechniques in buffaloes (Bubalus bubalis): status, prospects and challenges. Reprod. Fertil. Dev. 21(4): 499–510.

Smith, R.K.W., M. Korda, G.W. Blunn, and A.E. Goodship. (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.

Stern, C.D. (2005). The chick: a great model system becomes even greater. Dev. Cell. 8(1): 9–17.

Stern, C.D. (2004). The chick embryo-past, present and future as a model system in developmental biology. Mech. Dev. 1211011–1013.

Takahashi, K., and S. Yamanaka. (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 126(4): 663–676.

Takata, M., M. Ishiai, and H. Kitao. (2009). The Fanconi anemia pathway: insights from somatic cell genetics using DT40 cell line. Mutat. Res. Mol. Mech. Mutagen. 668(1–2): 92–102.

Taroni, M., Q. Cabon, M. Fèbre, T. Cachon, N. Saulnier, C. Carozzo, S. Maddens, F. Labadie, C. Robert, and E. Viguier. (2017). Evaluation of the effect of a single intra-articular injection of allogeneic neonatal mesenchymal stromal cells compared to oral non-steroidal anti-inflammatory treatment on the postoperative musculoskeletal status and gait of dogs over a 6-month period a. Front. Vet. Sci. 483.

Thomsen, G.M., G. Gowing, S. Svendsen, and C.N. Svendsen. (2014). The past, present and future of stem cell clinical trials for ALS. Exp. Neurol. 262127–137.

Thomson, J.A., J. Itskovitz-Eldor, S.S. Shapiro, M.A. Waknitz, J.J. Swiergiel, V.S. Marshall, and J.M. Jones. (1998). Embryonic stem cell lines derived from human blastocysts. Science (80-.). 282.

Thoraval, P., F. Lasserre, F. Coudert, and G. Dambrine. (1994). Somatic and germline chicken chimeras obtained from brown and white leghorns by transfer of early blastodermal cells. Poult. Sci. 73(12): 1897–1905.

Troeger, A., R. Meisel, T. Moritz, and D. Dilloo. (2005). Immunotherapy in allogeneic hematopoietic stem cell transplantation--not just a case for effector cells. Bone Marrow Transpl. 35.

Van de Lavoir, M.-C., J.H. Diamond, P.A. Leighton, C. Mather-Love, B.S. Heyer, R. Bradshaw, A. Kerchner, L.T. Hooi, T.M. Gessaro, and S.E. Swanberg. (2006). Germline transmission of genetically modified primordial germ cells. Nature. 441(7094): 766–769.

Vick, L., Y. Li, and K. Simkiss. (1993). Transgenic birds from transformed primordial germ cells. Proc. R. Soc. London. Ser. B Biol. Sci. 251(1332): 179–182.

Watson, W., and S. Kapur. (2011). Atopic dermatitis. Allergy Asthma. Clin. Immunol. 7 Suppl 1S4.

Wilke, M.M., D. V Nydam, and A.J. Nixon. (2007). Enhanced early chondrogenesis in articular defects following arthroscopic mesenchymal stem cell implantation in an equine model. J. Orthop. Res. 25(7): 913–925.

Wobus, A.M., and K.R. Boheler. (2005). Embryonic stem

cells: prospects for developmental biology and cell therapy. Physiol Rev. 85(2): 635–678.

Ye, J., and R. Blelloch. (2014). Regulation of Pluripotency by RNA Binding Proteins. Cell Stem Cell. 15(3): 271–280.

Zakrzewski, W., M. Dobrzyński, M. Szymonowicz, and Z. Rybak. (2019). Stem cells: past, present, and future. Stem Cell Res. Ther. 10(1): 1–22.

Zhang, Y., H. Yang, Z. Zhang, Q. Shi, D. Wang, M. Zheng, B. Li, and J. Song. (2013). Isolation of chicken embryonic stem cell and preparation of chicken chimeric model. Mol. Biol. Rep. 40(3): 2149–2156.

Zhao, W., J.-Y. Lu, Y.-M. Hao, C.-H. Cao, and D.-R. Zou. (2017). Maxillary sinus floor elevation with a tissue-engineered bone composite of deciduous tooth stem cells and calcium phosphate cement in goats. J. Tissue Eng. Regen. Med. 11(1): 66–76.

Zuk, P.A., M. Zhu, P. Ashjian, D.A. De Ugarte, J.I. Huang, H. Mizuno, Z.C. Alfonso, J.K. Fraser, P. Benhaim, and M.H. Hedrick. (2002). Human adipose tissue is a source of multipotent stem cells. Mol. Biol. Cell. 13(12): 4279–4295.

Zuk, P.A., M. Zhu, H. Mizuno, J. Huang, J.W. Futrell, A.J. Katz, P. Benhaim, H.P. Lorenz, and M.H. Hedrick. (2001). Multilineage cells from human adipose tissue: implications for cell-based therapies. Tissue Eng. 7.