Multipotent mesenchymal stem cells in clinical veterinary practice

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Abstract. Multipotent mesenchymal stem cells have a high therapeutic uniqueness. Their potential extends to the treatment numerous of animal diseases. This is due to their properties. They have the ability to self-renew in the culture for a long time. Upon induction to differentiation, cells are able to form cells within the same germ layer. When introduced into the body of an animal, they can exhibit an immunomodulatory effect, anti-inflammatory, anti-apoptotic and anti-fibrotic. In this regard, multipotent mesenchymal stem cells are considered as promising cellular material for the regeneration of animal tissues and organs. We conditionally divided the achievements of regenerative cell medicine described in the scientific literature using multipotent mesenchymal stem cells into groups. The division was carried out according to the nature of the pathological process (degenerative, immunological, inflammatory).

1. Introduction
Cell therapy (CT) is widely used in veterinary medicine. This therapy is represented by the introduction of donor cells into the organism in order to replace the cells damaged by the disease or lost after an injury (blood transfusion, to combat the lack of blood cells or the introduction of healthy lymphocytes, to regenerate the functions of the immune system). CT has only a substitution function and is able to provide a temporary result alone. In contrast to regenerative cell therapy (RCT), which is able to restore the tissue damaged by a disease or injury by the methods of activation of endogenous stem cells, direct transplantation of them, or the use of both methods.

The contemporary veterinary medicine uses the RCT based on the multipotent mesenchymal stem cells (MSCs) and progenitor cells that are capable of producing numerous biologically active substances: growth factors, chemokines, cytokines and extracellular vesicles in its practice [1]. MSCs have such properties as the ability to self-renew in culture, differentiation during induction in osteo-, chondro- and adipogenic directions. In vivo, they maintain hematopoiesis, have an influence on vascularization, block apoptosis, fibrosis and inflammation and modulate the immune system [2].

In this regard, in our laboratory are being conducted investigations on the study of the biology of these cells as well as actively studying the therapeutic potential of RCT in veterinary medicine both in vitro and in vivo. The objective of our work was to summarize the data on the use of MSCs in the clinic and discuss the achievements of the application of these cells in RCT in veterinary medicine.
2. Literature review

Over the twenty-year period of clinical testing of RCT based on MSCs, many studies have been published in which wide ranges of pathologies in animals were treated. However, the number of questions is only increasing. As the whole RCT is at the level of clinical application and scientific research the questions arise from specialists of these two areas. Doctors are interested in the therapeutic effect of MMSCs and the way it happens and what diseases they are potentially applicable to. In turn, scientists are concerned about the mechanism of action of MSCs and their ability to change under the influence of various biological parameters, under the conditions of the same or different species with the same pathologies. The scientific literature does not provide answers to all these questions but the spectrum of positive therapeutic results and the use of MSCs are extensive. It is connected not only with their properties but also with the weakness of contemporary traditional and veterinary medicine. A lot of diseases are incurable both in humans and in animals and the methods used in the treatment only retard their further development. In this regard, all medical specialists are constantly in search of alternative methods of treatment giving an incentive to the development of RCT. In order to optimize the analysis and clinical achievements of RCT in veterinary medicine by MSCs, they have been conditionally divided into three groups based on the types of pathological processes: degenerative, immunological and inflammatory diseases. Table 1. The corresponding systematization is convenient for both doctors and scientists.

2.1. The degenerative diseases of animals

Arthritis is an inflammatory pathology resulting from damage to articular cartilage. This pathological process can lead to irreversible changes in the joint as it does not have the ability to be regenerated due to its structure (avascular, aneurysm and lymphatic). Considering these circumstances, arthritis is often a painless process which leads to the absence of obvious clinical signs and treatment. This provokes its further progression by damaging all tissues surrounding the joint. The veterinary practice has shown great clinical success in the intra-articular transplantation of MSCs while animal arthritis. It is due to the ability of MSCs to restore cartilage and reduce pain by the immunomodulation and anti-inflammatory properties [3]. Wherein, the objectivity of analysis of different teams’ results becomes more complicated by the lack of a differential diagnosis protocol. The veterinarians are often diagnosis arthritis in animals by the assessment of pain reaction (the presence or absence of chromate in the standing position while running, the reaction to raising the diseased limb, its flexion and extension) before and after RCT. The instrumental methods for confirming the results usually are not used, except the radiography, which in the case of RCT application is not objective.

Hip dysplasia (HD) in veterinary medicine is one of the main bone-articular pathologies that usually affect dogs. HD is a violation in the development mainly of the femur, which results in varying stage of hip joint weakness, and the development of arthritis and osteoarthritis [4]. As the animal grows, weight increases, sometimes abruptly which causes subluxations and abnormalities in the development of all joint structures. This leads to excessive wear of the cartilage. At present, the effective treatment of HP is provided only by its complete replacement [5]. However, such procedures are extremely rare conducted in veterinary medicine because of the high financial costs. The use of RCT based on MSCs to improve the restoration of cartilage tissue in HD separately or in conjunction with surgical methods of treatment shows positive therapeutic effects [6].

The intervertebral disc diseases are characterized by the degeneration, loss of biomechanical properties and a tendency of occurring spinal discs herniation. It causes acute neurological syndromes with subsequent loss of the animal's life quality. This pathology is often observed in veterinary medicine especially in dogs. The veterinarian usually notes the neglected degenerative cases with the presence of many hernias that require urgent surgical decompression. Moreover, the traditional methods of treatment are directed only on the facilitation of the neurological syndromes. The use of RCT based on MSCs injections in combination with various hydrogels is able to provide a positive therapeutic effect. At the same time pain decreases and disappears. The result depends on the properties of MSCs to isolate biologically active substances with anti-inflammatory and immunomodulation properties, which in turn
are able to influence the metabolic processes of the microenvironment of the intervertebral discs due to modulation of lymphocytes, normalization of the water balance of the pulposus nucleus and fibrous ring. This increases the biomechanical capabilities of the intervertebral disc and contributes to its regeneration. Thus, the injection of MSCs into the pulp nucleus leads to reduce the discogenic pain and degenerative processes of the intervertebral discs [7-8].

Table 1. Clinical achievements of regenerative cell medicine.

| Degenerative diseases | Immunological diseases | Inflammatory diseases |
|-----------------------|------------------------|----------------------|
| Arthritis             | Atopic dermatitis      | Cruciate ligament injuries |
| Hip dysplasia         | Pemphigus foliage      | Acute liver failure   |
| Intervertebral disc diseases | Chronic autoimmune stomatitis | Tendonitis |
| Cardiovascular disease | Keratoconjunctivitis Sikka | Laminitis |
| Kidney failure        | Asthma                 | Non-healing wounds   |
|                       | Autoimmune hemolytic anemia |
|                       | Diabetes mellitus      |
|                       | Systemic lupus erythematosus |
|                       | Anal furunculosis      |
|                       | Immuno-mediated cutaneous vasculitis |
|                       | Autoimmune colitis and enteritis |

Cardiovascular disease can be primary or secondary etiology. In pets, it manifests itself quite often with high mortality rates. The traditional treatment can only temporarily improve the functional abilities of the heart muscle only by slowing down the development of pathological processes. This is due to the limited possibilities of self-regeneration of the heart. The RCT based on MSCs for the treatment of animal cardiovascular failure had originated two decades ago. During this time, it was not possible to determine the mechanism of regeneration of the heart muscle [9-10]. The researchers several times changed the concept of the therapeutic effect of MSCs on the heart muscle searching the truth. It was previously believed that MSCs are capable of differentiation into cardiomyocytes and vascularization [9]. More recent studies have shown the dependence of the therapeutic effect on the secretion of MSCs the biologically active substances having anti-inflammatory, anti-fibrotic properties and are also able to stimulate endogenous regional stem cells. The introduction of MSCs by various approaches can reduce the size of cicatricial tissue; improve the functional capabilities of the heart evidenced by the improvement of cardiac blood markers and the quality of animals’ life [9-12].

Kidney failure is a degenerative process in the kidney that is clinically characterized by a gradual or sudden loss of kidney function. A veterinarian usually notes the disorders in the excretion of toxins of
kidney and water-electrolyte balance in the body of animals. In this case, the treatment of renal failure in animals is based on the introduction of fluid by the regeneration of metabolic acidosis, monitoring of urine and blood tests, the use of diuretics, sometimes antidotes for nephrotoxins and dialysis [13]. It means that all treatment while renal failure is focused on the relief of developing symptoms and compensation of renal dysfunctions. The injections of MSCs during renal failure can improve the kidney function. The researchers believe that therapeutic efficacy occurs by reducing inflammation and renal fibrosis and depends on the methods of MSCs injection. It is known that only the direct introduction of stem cells into the area of the affected kidneys (in corticomedullary junction and renal vein) can lead to a positive therapeutic effect. This is confirmed by a decrease in the number of inflammatory markers in the urine (interleukins and protein) as well as a decrease in levels of nitrogen, creatinine and urea in blood [14].

Thus, the studies of RCT by MSCs can be an alternative tool in the treatment of degenerative processes as arthritis, HD, diseases of the intervertebral discs, cardiovascular and kidney diseases in animals [3]-[14].

2.2. Immunological diseases of animals.
In veterinary practice, there is a constant increase in registrations of the number of diseases with impaired immune systems. The usual treatment regimens are aimed only at slowing down the progression of the cascade of pathological processes of the immune system and consist of symptomatic therapy (steroid drugs and immunosuppressant). The need for their application is often a necessity for life. This can cause side effects, exacerbating the further development of the disease. [15]. Therefore, the use of RCTs using MSCs is increasingly used in the treatment of various immune-mediated animal pathologies. Success is due to the properties of MSCs. They have low immunogenicity and immunomodulation abilities [16-17]. MSCs can affect all types of immunity. This process is complex and not fully understood. However, MSCs can produce many anti-inflammatory and pro-inflammatory biologically active substances (prostaglandins, cytokines, chemokines). RCT of immune-mediated pathological processes can provide a high degree of positive therapeutic efficacy without the use of steroids and immunosuppressant [18].

Atopic dermatitis is a generally chronic skin disease with number etiological factors. During its development, the disorders of the functional abilities of the skin barriers occur which leads to the penetration of many allergens and as a result of its infection by pathogens. All these changes in the epidermis also cause clinical symptoms in the form of inflamed, often soaked, fetid smell and itchy skin. This occurs under the influence of gradual changes in the stratum corneum lipids (ceramide) and protein (filaggrin) structural components and transepidermal water loss. As a result, the skin begins to produce less antimicrobial substances. The allergens penetrate into the epidermis and an inflammatory process is developed which later due to the loss of barrier properties of the skin and comb of the animal becomes infected. In this regard, a clinical deterioration of atopic dermatitis developing into pyoderma and otitis occurs. This can provoke allergic sensitization in relation to microflora and other allergens that penetrate into the deeper layers of the skin and produce a large amount of Ig E. The use of RKT for the treatment of atopic dermatitis can achieve positive results even in cases that cannot be treated. Due to the properties of MSCs (anti-inflammatory cytokines, inhibition of lymphocytes and, as a consequence, the production of Ig E) [18-20].

Pemphigus foliage is an autoimmune pathological condition of the skin characterized by acantholysis. As a result of cascading immunological disorders with the presence of a large number of etiological factors, immunoglobulins G4 and G1 are activated against desmosome glycoproteins connecting keratinocytes. The formation of immune complexes destroys the intercellular contact of keratinocytes which leads to acantholysis. The clinical picture of the pemphigus foliage is characterized by the intraepidermal vesicles and pustules with the spread of which dermatosis develops. Only half of the registered cases with this pathology have a duration of life for more than a year. The positive therapeutic effect of RCT in the treatment of PV is caused by the immunomodulatory and anti-inflammatory properties of MSCs. Their local and general transplantation is able to provide a powerful
inhibitory effect on T-lymphocytes which leads to immunosuppression and relief of clinical signs as a result [18] [21].

**Chronic autoimmune stomatitis** (gingivitis) is usually a chronic inflammatory disease of the oral cavity often not treatable. The veterinary specialists prefer to remove all the teeth of the animal while this pathology. This can provide a positive result in some animals. The corresponding measure deteriorates the quality of life of the animal with the potential impact on their life duration. In this regard, the researchers and clinicians use the RCT (MSCs), as an alternative and effective method of treating chronic autoimmune stomatitis. At the same time, the therapy is conducted to those who have not helped tooth extraction. In order to obtain positive therapeutic results, the researchers recommend using two MSCs injections with an interval of 3-4 weeks [22-23].

**Keratoconjunctivitis Sikka** (KCS) or dry eye syndrome is an ophthalmic pathology often observed in veterinary practice. It is an etiologically multifactorial disease consisting in violation of the lacrimal gland function directed either at reducing the amount of lacrimal secretion or in the disorders of its composition. This result in dryness and potential disruption of the eyeball functions which even more exacerbates the destruction of the tissues of the lacrimal gland. The authors demonstrate that the use of RCT for the treatment of dry eye syndrome can reduce the inflammatory process already after two months of MSCs injections [24].

**Asthma** is a chronic immune-mediated disease of the lower respiratory tract. This process is characterized by eosinophilia, inflammation and remodeling of the airways. Treatment of asthma in animals by RCT with the introduction of MSCs shows a positive therapeutic dynamic, which is enhanced by the immunomodulating and anti-inflammatory properties of the cellular material. After five to six intravenous injections of cells, a gradual improvement in asthma symptoms is observed [19, 22].

**Autoimmune hemolytic anemia** is an autoimmune blood disease. While its development, the autoreactive antibodies and complement opposes membrane proteins. As a result, premature destruction of red blood cells is triggered. Dogs and cats are usually affected. The researchers use RCT with systemic administration of MSCs in the treatment of autoimmune anemia of animals, which demonstrates a positive therapeutic effect provided by their immunosuppressive properties [25].

**Diabetes mellitus** is an endocrine disease in which there is a violation of the function of the pancreatic beta cells (producing insulin) or insulin resistance of the cells. These pathological processes can develop both together and separately. This leads to hyperglycemia [26]. The use of RCTs for the treatment of diabetes in animals can give a positive therapeutic result. MSCs can suppress inflammatory processes in the tissues of the pancreas, protect it from apoptosis. They are able to positively influence the insulin resistance of peripheral tissue cells. So RCT (MSC) All these properties ultimately provide a positive therapeutic effect in the treatment of diabetes in animals [27, 28].

The **systemic lupus erythematosus** is a multisystem, immune-related disease that affects connective tissue. A large number of different autoantibodies are produced that form immune complexes circulating throughout the body. They trigger a hypersensitivity reaction of the second type (cytotoxic) and the third type (immunocomplex). The RCT by MSCs transplantation represents an important treatment strategy for lupus erythematosus. Moreover, it was shown that the use of autologous MSCs does not give positive results, which are associated with their participation in the pathological process. The allogeneic transplantation of MSCs demonstrates clinical remission in half of the clinical cases [21, 29].

**Anal furunculosis** (perianal fistulas) is an immune-mediated, chronic, peptic ulcer disease often affecting small domestic animals. It is clinically characterized by the inflamed and infected canals located along with the anus as a result of a chain of dysfunctions of the immune system as pathological activation of T-lymphocytes, pathological macrophages polarization and the release of metalloproteases. It leads to furunculous inflammation and ulceration if in the area of the rectum numerous infectious sources are presented. The RCT in anal furunculosis shows a positive therapeutic effect including the severe and resistant to therapy cases as a result of the anti-inflammatory and immunomodulating properties of MSCs. The biologically active substances that MSCs are capable of secret suppress the inflammatory process by the inhibition of T cells proliferation and promote regeneration [30].
**Immuno-mediated cutaneous vasculitis** is an inflammatory process that affects the blood vessels and damages the blood flow in the affected area. The development of the pathological process begins with the deposition of immunocomplexes in the vessel walls and the development of a hypersensitivity reaction of the third type. As a result, there is a lesion and ulceration of the vessel walls and the release of formed elements outside the vessels. Immunomodulating RCT of cutaneous immuno-mediated animal vasculitis using MSC transplantation eliminates the need for other immunosuppressants [31].

**Autoimmune colitis and enteritis** are the chronic inflammation of the intestines. The clinical signs are characterized by chronic or periodical gastrointestinal (GI) disorders that do not respond to the treatment. The etiology of autoimmune intestinal inflammation in animals has not been studied. It is known that as a result the impaired immune responses in the mucosa of gastrointestinal and loss of the tolerance to the surrounding it antigens occur. More often the treatment is lasting for a lifetime. The compliance of all requirements of treatment does not provide positive dynamics in all cases. The use of MSCs as an alternative treatment for autoimmune inflammatory processes of the intestine is considering as the latest therapeutic method. However, the use of this method in clinical experiments with immune disorders of the gastrointestinal tract of animals has been effective. Moreover, the authors recommend using RCT at least twice [32-33].

2.3. **Inflammatory diseases of animals.**

**Cruciate ligament injuries** in dogs and horses. The rupture of the cruciate ligament leads to the disturbances in the stability of the articular structure and the development of various forms of arthritis which causes lameness of the hind limb. Traditionally, veterinarians are using the surgical methods, physiotherapy and corticosteroids in the treatment of cruciate ligament injuries. All the above methods are not able to avoid the rapidly progressing degenerative process in the joint and achieve the desired therapeutic effect apart from animals whose weight does not reach 15 kg [34]. The results of RCTs in the treatment of cruciate ligament injuries show greater resistance to complications (relapses). Injections of MSCs into the zone of the damaged ligament can affect the organization of its fibers, improving the type of collagen tissue, which helps to reduce inflammation [35].

**Acute liver failure** is a life-threatening clinical syndrome in which necrosis develops as a result of acute liver damage caused by hepatotoxins. The usual treatment, when registering an acute renal failure aimed at preventing its development which often does not bring positive results. The authors related this to the properties of MSCs: to differentiation (hepatocyte-like cells), anti-inflammatory, immunomodulatory, antiapoptotic, as well as the ability to influence angiogenesis. All these properties can improve liver functionality of the liver, inhibit apoptosis and promote the restoration of hepatocytes, which can potentially lead to regeneration of liver tissue [36, 37]. However, the therapeutic mechanism of the MSCs effect on liver tissue has not yet been fully studied. In clinical conditions, doctors prove a positive therapeutic effect by lowering the levels of the enzymes ALT, AST and protein in the blood [38].

**Tendonitis** is an inflammatory process of tendons tissue. The treatment of tendonitis in animals is complex and relapses are not uncommon. The histological studies of the inflamed tendon tissues indicate a loss of collagen density, an increase in proteoglycan concentrations. A prolonged progression of inflammation can lead to foci of mineralization and changes in bone tissue at the attachment sites with the tendon [39]. It has been shown that the use of traditional methods leads either to a lack of response to treatment or to frequent relapses due to a violation of tendon morphology, after the inflammatory process. The RCT has demonstrated a positive effect on tendon healing. Injections of MSCs into the area of tendon inflammation due to their anti-inflammatory and anti-fibrotic properties contribute to the healing of the ligamentous apparatus. It is known that MSCs have an influence on the increase of collagen fibers density improving their biomechanical strength which significantly reduces the number of relapses [40].

**Laminitis** is a disease of the feet of ungulates. As a result of the progression of laminitis, complex pathological processes of lamellar structures of the hoof that support the skeleton is occurring. This leads to the development of disorders of hematological homeostasis and inflammation of the foot. In chronic
forms, the phalanx is detached from the hoof wall and lowered damaging the sole of the hoof. It is known that any inflammatory disease in ungulates causes the laminitis. So, the pathogenesis resembles those observed in metabolic disorders, organ failure or “systemic inflammatory response syndrome”. The severe pain, lameness and lack of desire of the animal to rely on a sick limb are noted while the neglected form of the disease. It is very difficult to treat laminitis. The clinical examination of ungulates with laminitis has shown normalization of the general condition after RCT application. It has been reported by authors that after MSCs injections, horses are able to return to a normal quality of life and sometimes to an initial level of activity [41, 42].

Non-healing wounds. After damaging the skin, a complex chain of processes occurs as a temporary violation of homeostasis and inflammation inside the tissue. The general pathological conditions as metabolic disorders, prolonged immunosuppressive therapy, extensive damage, can lead to a delay or complete non-healing of wounds [43]. The results of using MSCs for the treatment of long-term non-healing wounds, has shown an improvement in the regeneration of the skin confirmed by the histological studies that described a decrease of inflammation and ameliorating of epithelization. In this case, the autologous RCT takes a lot of time from cell collection to their use and requires healthy host stem cells. However, this is often not possible with non-healing wounds. The allogeneic RCT has an advantage in the treatment of non-healing wounds as its immediate application with cellular material from a healthy donor [44, 45].

3. Conclusion
Today, there are numerous animal diseases that do not receive full treatment. This encourages clinicians and scientists to join forces in the search for new methods of treatment, which led to the collection of a large amount of clinical data on the use of RCTs based on MSCs. An analysis of the literature showed not only the positive therapeutic effect of MSCs, but also the absence of a positive and negative clinical effect. However, due to the large number of reports on effective RCTs, the number of negative results is negligible. The effectiveness of applying MSCs directly depends on their properties. MSCs are able to differentiate into different types of cells within the same germ layer. They have anti-inflammatory, anti-apoptotic, anti-fibrotic and immunomodulation potential, which ensures success in the treatment of degenerative, immunological and inflammatory diseases of animals. Nevertheless, the tasks of studying the mechanism of action and safety of RCTs are still very relevant for scientists and doctors. The solution to these problems is complicated by the methods of conducting clinical experiments. Many authors do not pay attention to the methods of introducing MSCs, since what tools were used, whether the cells were introduced separately or in combination with other components. This generally complicates the comparison of studies of different authors, does not provide objective statistical data and requires the further development of unified clinical protocols. Nevertheless, the currently known potential of MSCs and the number of reports of positive therapeutic results with their application may surprise clinicians and inspire new research teams.

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Reference
[1] Angelone M et al. 2017 Int J Mol Sci 18(10) 2122
[2] Escalhão C C M et al. 2017 Stem Cells Int 2017 11
[3] Sasaki A, Mizuno M and Mochizuki M 2019 World J Stem 11(5) 254–69
[4] Syrcele J 2017 Vet Clin North Am Small Anim Pract 47(4) 769–75
[5] Roush J K 2012 Surgical therapy of canine hip dysplasia In: Tobias K M, Johnston S A editors Veterinary surgery small animal (Missouri Elsevier) 849–64
[6] Ettinger S J 2017 Textbook of veterinary internal medicine (Missouri Elsevier) p 8
[7] Kriston-Pál É et al. 2017 Can J Vet Res 81(1) 73–8
[8] Dittmar R 2014 Eindhoven: Technische Universiteit Eindhoven 90
[9] Bagno L, Hatzistergos K E, Balkan W and Hare J M 2018 Mol Ther 26(7) 1610–23
[10] Vulliet P R et al. 2004 Lancet 363 783–784
[11] Caplan A I and Dennis 2006 J Cell Biochem 98(5) 1076–84
[12] Pei Z et al. 2017 Sci. Rep 7 6296
[13] Ross I 2011 J Small Anim Pract 41(1) 1–14
[14] Quimby J M, Webb T L, Habenicht L M, Dow S W 2013 Stem Cell Res Ther 4(2) 48
[15] Dias I E et al. 2019 BMC Vet Res 15 358
[16] Klinker M W and Wei C H 2015 World J Stem Cells 7 556–67
[17] Villatoro A J et al. 2017 Int J Mol Sci 18 2264
[18] Jiménez A J and Guerrero F F 2017 Clindervet 9 8–18
[19] Inzucchi S E 2002 JAMA 287(3) 360–72
[20] Caplan A I and Dennis J E 2006 J Cell Biochem 98(5) 1076–84
[21] Nakagawa H et al. 2005 Br J Dermatol 153 29–36
[22] Ferrer L et al. 2016 Regen Med 11(1) 33–43
[23] Arzi B, Clark K and Sundaram A. 2017 Stem Cells Transl Med 6 1710–22
[24] Villatoro A J et al. 2015 Biomed Res Int 2015 10
[25] Trzil, JE, Masseau I and Webb T L 2014 Clin Exp Allergy 44 1546–57
[26] Villatoro A J et al. 2018 Vet Rec 183(21) 654
[27] Hare J M et al. 2012 JAMA 308(22) 2369–2379
[28] Hawsawi Y M et al. 2018 Technology in Cancer Research & Treatment 17 1–12
[29] Pérez-Merino E M et al. 2015 Vet J 206 1–23
[30] Quimby J M and Borjesson D L 2018 J Feline Med Surg 20(3) 208–16
[31] Webb T L and Webb C B 2015 J Feline Med Surg 17(10) 901-8
[32] Zang L et al. 2017 Diabetol Metab Syndr 9 36
[33] Cuervo B et al. 2014 Int J Mol Sci 15(8) 13437–60
[34] Bodderker J et al. 2012 Vet Comp Orthop Traumatol 25 11–21
[35] Smith R K et al. 2013 PLoSOne 8(9) 25
[36] Yuan S et al. 2013 Biomed Res Int 2013 9
[37] Wang Y H, Wu D B, Chen B, Chen E Q and Tang H 2018 Stem Cell Res Ther 9(1) 227
[38] Cai Y et al. 2015 Int J Clin Exp Pathol 8 107–16
[39] Canapp S O Jr et al. 2016 Front Vet Sci 3 61
[40] Zhang X et al. 2016 Stem Cells Int 2016 14
[41] Angelone M et al. 2017 Int J Mol 18(10) 2122
[42] Eustace R A 2010 Vet. Clin. North Am. Equine Pract 26 391–405
[43] Kim B C et al. 2003 J Cell Physiol 195 331–36
[44] Malhotra S et al. 2016 Stem Cells Int 2016 6
[45] Enciso N, Avedillo L, Ferníe M L, Fragio C and Tejero C 2020 Acta Vet Scand 62(1) 13