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MESENCHYMAL STEM CELLS APPLIED TO THE TREATMENT OF NEUROLOGICAL SEQUELS OF CANINE DISTEAM DISEASE- LITERATURE REVIEW

Ramon Ricarte Muniz Andrade

Anderson Pinto Almeida

Mônica Aline Parente Melo Maciel

Vanessa Amaral Lemos

Abstract: Regenerative Medicine is the branch of medicine that aims to replace damaged organs, tissues and cells with healthy ones and, within the scope of stem cell biology, it is not restricted to embryonic stem cells, but stem cells from a variety of sources as what are all the potential tools to stimulate regeneration. Mesenchymal stem cells are undifferentiated cells that are present in the adult organism and are responsible for tissue homeostasis. Distemper is a disease caused by the canine distemper virus, which is also neurodegenerative. Regenerative medicine through mesenchymal stem cells can act in the regeneration of nervous tissue affected by the disease and attenuate the neurological symptoms of the neurological sequelae of the disease in question. The objective of the present study is to evaluate the effectiveness of treatment with mesenchymal stem cells for the treatment of neurological sequelae of distemper, in view of the scientific literature.
Keywords: Regenerative therapy. Cell therapy. Regeneration.

INTRODUCTION

Regenerative medicine is an interdisciplinary field involving the life, physical and engineering sciences that seeks to develop functional cells, tissues and replacement organs in order to repair, replace or improve biological function that has been lost due to congenital abnormalities, injuries, diseases. , or aging. It uses a combination of several existing and emerging converging technology approaches that go beyond traditional transplantation and replacement therapies. These approaches may include, but are not limited to, the use of soluble molecules, gene therapy, stem and progenitor cell therapy, tissue engineering, and the reprogramming of cells and tissue types.

Regenerative medicine aims to direct and expand the repair process and replacement of injured tissues. This potentiation of repair can be accomplished by providing the required cellular elements, the cellular proliferation and differentiation factors that can guarantee the generation of a sufficient amount of new cells, and the supramolecular structures that provide the fully functional spatial organization of newly generated tissues and their systemic integration (SOARES; SANTOS, 2002).

In the last decades, regenerative medicine through knowledge about stem cells has evolved significantly, in particular about the ability of stem cells to expand and differentiate. These special properties of stem cells make them an important tool for a vast array of diseases or illnesses that cannot be treated in the traditional way. Due to its ability to colonize an entire organism or regenerate parts of an injured tissue, its activity is related to the treatment of organic dysfunctions caused by trauma, diseases, natural precocious degenerative processes or by environmental aggression, or by the degenerative process of aging of the body. body. The development of treatment methods has raised great expectations due to its wide variety of possibilities, which makes this cutting-edge therapy of modern medicine, the hope for intractable diseases (ZAKRZEWSKI et al., 2019).

Thus, due to the great therapeutic potential of these cells, either for their ability to maintain adult tissues, for the promotion of responses to injuries or for their potential in the treatment of the most varied cellular and tissue injuries caused by accidents, stem cells have been proving to be a very favorable alternative form of therapy in the veterinary clinic, applied in several diseases (CARVALHO; 2001), especially in those that are found, to date, unsuccessful with conventional therapies or whose therapies required a very long recovery period. The use of stem cells in recent years has gradually increased and this growing

interest is related to the ability that these cells offer in revolutionizing the understanding of tissue repair and regeneration mechanisms, for example, the treatment of various diseases, such as nerve injuries, arthritis, tendon injuries and rupture of suspensory ligaments in horses (FRANCIOLLI, 2012).

According to Alvarenga (2011), the therapeutic application of stem cells in veterinary medicine is a field that is on the rise, as is the case of the use of stem cells in horses in the treatment of various diseases such as nerve injuries, arthritis, tendons, and rupture of suspensory ligaments. The therapeutic application of stem cells in small animals is still in an expansion phase, so there is little bibliography on its application. However, there are some experimental studies on the use of mesenchymal stem cells as a therapeutic treatment for the neurological sequelae of canine distemper (GONÇALVES et al., 2018). Canine distemper is a multisystemic viral infectious disease caused by the canine distemper virus which, with its advancement, destroys the myelin sheath, compromising the animal's motor and neurological functions. (PINHEIRO et al., 2009). Due to the high rate of morbidity and mortality associated with distemper, alternatives have been sought to minimize symptoms and sequelae in affected patients. Thus, regenerative medicine through the use of mesenchymal stem cells appears as a promising therapeutic option for the treatment of the neurological sequelae of distemper for the reestablishment of the patient's motor function through the recovery of the myelin sheath.

In this context, the objective of this study is to evaluate the effectiveness of the use of mesenchymal stem cells in the treatment of neurological sequelae of canine distemper through the analysis and comparison of existing bibliographies on the subject, in order to compare the results obtained with the infusion of cells mesenchymal trunk in the treatment of neurological sequelae of canine distemper.

If the effectiveness of the use of mesenchymal stem cells in the restoration of the neurological functions of infected animals is confirmed, this therapy will be a promising option for the treatment of the neurological sequelae of distemper, promoting the well-being of the animals, as well as interfering in the reduction of high rate of morbidity and mortality associated with canine distemper.

REGENERATIVE MEDICINE: CONCEPTS AND APPLICATIONS

According to Nature Insight editor Natalie Dewitt (2008), "Life is regenerative, by definition". Some of our cells have the innate ability to replenish themselves and, in doing so, repair aged or injured tissues and organs. The tissue regeneration capacity depends on the type of cell, tissue or organ affected by the injury, also depending on the cell's ability to multiply and whether the cells involved are able to regenerate, but at different levels of capacity.

Unfortunately, injuries from injury, illness and age wreak havoc on those who don't and even organs that can regenerate eventually succumb to the ravages of aging or some injuries. To understand the importance of Regenerative Medicine, it is necessary to know its concept and applicability.

Regenerative Medicine is an area that has been developing more and more in the context of Biomedicine, based on the use of living cells for the regeneration or replacement of injured tissues and organs with the objective of restoring the normal functions of the organism, both in Human Medicine. as in Veterinary Medicine (OLIVEIRA, 2012). The author points out that tissue engineering, stem cell therapy, regeneration factors, extracellular matrices and therapeutic cloning were united

under a single term called regenerative medicine.

According to Mason and Dunnill (2008), the concepts for regenerative medicine are numerous, long and difficult to define if we want to explain them in a few words. One of the complications is that regenerative medicine has developed from a good deal of previous activities. This includes surgery, surgical implants such as artificial hips, increasingly sophisticated biomaterial scaffolds. Still in the same article, the authors point out that the goal of regenerative medicine "is to regenerate more fundamentally by supplying cells, particularly stem cells that can stimulate wider regeneration. Likewise, in classical terms, 'repair is the replacement of lost tissue with granulation tissue that matures to form scar tissue'."

Daar and Greenwood (2007) define regenerative medicine as an interdisciplinary field of research and clinical applications focused on repair, replacement or regeneration of cells, tissues, or organs to restore impaired function resulting from any cause, including birth defects, disease, trauma, and aging. It uses a combination of several converging technologies with approaches, existing and emerging, that go beyond traditional transplantation and replacement therapies. The conditions for the applicability of regenerative medicine are broad. Examples include chronic degenerative (eg Alzheimer's), metabolic (eg diabetes) and ischemic (eg stroke) diseases, many of which lead to organ failure.

Regeneration goes beyond repairing what is damaged or simply replacing it from the outside. In regeneration, the body is stimulated to produce new and young cells, tissues and organs (HASELTINE, 2003). Many research activities in regenerative medicine are focused on determining the developmental pathways of stem cells, with the aim of understanding how to stimulate their differentiation.

Finally, Greenwood et al.(2021) highlights that regenerative medicine is an emerging interdisciplinary field of research and clinical applications focused on the repair, replacement or regeneration of cells, tissues or organs to restore impaired function resulting from any cause, including birth defects. , illness and trauma. It uses a combination of several technological approaches that go beyond traditional transplantation and replacement therapies. These approaches may include, but are not limited to, the use of stem cells, soluble molecules, genetic engineering, tissue engineering, and advanced cell therapy. It seeks to combine the knowledge and experience of diverse disciplines aimed at the goal of curing impaired function in the body. Its purpose is not just to replace what is defective, but to provide the elements necessary for in vivo repair, to design replacements that seamlessly interact with the living body, and to stimulate the body's intrinsic capabilities for regeneration.

The use of stem cells for the repair of damaged organs and tissues in regenerative medicine opens the door to a new era, rich in possibilities, in which, according to some researchers, it presents a revolutionary potential comparable to the advent of penicillin.

STEM CELLS: DEFINITION AND CLASSIFICATION

To understand how stem cells can participate in the recovery of tissue damaged by damage, trauma or aging, it is necessary to know the concepts that define stem cells. According to Salomone (2015), stem cells are cells that have the ability to self-replicate and differentiate, that is, they can generate other stem cells in addition to differentiating into any other cell type and can be found in any tissue of the human or animal body.

However, some tissues such as hematopoietic and adipose connective tissue have a greater number of stem cells than more specialized tissues such as nervous tissue. According to Pereira (2009), stem cells (SCs) are cells with prolonged, unlimited proliferation capacity, and capable of generating more specialized offspring.

Stem cells have three general characteristics: they divide, giving rise to cells similar to them, they are undifferentiated because they do not have any tissue-specific structure that allows them to perform specialized functions, such as producing saliva, contracting or transmitting impulses. Nerve cells, however, can give rise to specialized or differentiated cells. Stem cells are able to renew themselves for a long period and unlike differentiated cells such as muscle, blood or nerve, which do not divide anymore, stem cells replicate many times. An initial population of stem cells can multiply many times in the laboratory and this characteristic defines them as self-renewable (DESSEN, 2007).

Marshall (2018) highlights that, currently, stem cells are generally considered to be undifferentiated cells that self-renew and produce differentiated cells as progeny. The same author states that within this broad definition, there are many types of stem cells that differ based on their long- or short-term self-renewal capacity and the number of different cell types they produce. In addition to the definitions mentioned above, Souza et al. (2003) classifies stem cells as totipotent, pluripotent and multipotent, taking into account some distinctions, such as the level of plasticity these cells have, the number of different pathways they can follow, and to what portion of a functional organism they can contribute. Melton (2014) points out that the multipotent stem cell is at the top of a lineage hierarchy and can generate different types of differentiated cells, the latter cells having distinct morphologies and gene expression patterns.

According to Wodewotzky (2008), the classification of TC is proposed in a diversified way by many authors around the world, but a clear and objective description was presented by Mingroni-Netto and Dessen (2006), who propose that TC can be subdivided into based on two criteria: the degree of potentiality, which is the cell's ability to generate different cell lineages, or according to the place where they originate, in embryonic and non-embryonic. And finally, a concept proposed by Slack (2018) suggests that actual stem cells comprise two fundamentally different types: pluripotent stem cells that exist only in vitro, and tissue-specific stem cells that exist in vivo in the postnatal organism. Pluripotent stem cells comprise embryonic stem cells (ESC) and induced pluripotent stem cells (iPSC).

REGARDING THE ORIGIN AND POTENTIAL FOR DIFFERENTIATION

According to Kolios and Moodley (2013) embryonic stem cells (ESCs) are pluripotent, derived from the inner cell mass of the blastocyst, a preimplantation embryo stage, between 5 and 6 days after fertilization and these cells can differentiate into tissue of the 3 primary germ layers, but can also be maintained in an undifferentiated state for a prolonged period of culture. These cells are capable of unlimited symmetric self-renewal and in addition to maintaining clonality as they provide a potential source of differentiated cells for a variety of therapeutic uses (BHATTACHARYA et al., 2004). While totipotent cells form the embryonic and extra-embryonic tissue, thus forming the embryo and placenta, they are the most undifferentiated cells and are found early in development (KOLIOS and MOODLEY, 2013). Conventionally, the term totipotent is

now reserved for cells that can form an entire conceptus, comprising the trophectoderm as well as the inner cell mass. According to this definition, the only totipotent cells in mammals are the zygote itself and the first blastomeres formed by the division of the zygote.

Carrion et al. (2009), defines adult or postnatal stem cells as multipotent cells capable of generating cell types that make up tissues and organs.

They have the ability to generate cells from other organs and tissues and are responsible for tissue replenishment throughout life and are present in most tissues. Machado et al. (2014), emphasizes that adult stem cells (ASC) can be extracted from various human tissues, such as bone marrow, nervous system, dental tissue, epithelium, blood, liver, umbilical cord and placenta; and, the embryonic ones (ETC) can only be found in the embryos.

Another type of stem cell, according to Ghaedi and Niklason (2019), induced pluripotent stem cells (iPSCs), are the product of reprogramming adult somatic cells to an embryonic state by inducing a "forced" expression of specific genes. Takahashi and Yamanaka (2006) successfully performed this somatic cell reprogramming by retroviral delivery and forced expression of four key transcription factors Oct4, Sox2, cMyc and Klf4. These are similar to natural pluripotent stem cells such as embryonic stem cells (ES) in many ways, such as the expression of certain stem cell genes and potency and differentiability.

ADULT STEM CELLS

According to Grifield et al (2004), somatic or adult stem cells are undifferentiated, rare cells found in tissues that are responsible for tissue regeneration during their existence and have been identified in the skin, kidney, adipose tissue and dental pulp. Adult stem cells include hematopoietic CT, mesenchymal CT, neural CT, skin CT, umbilical cord CT, and countless others. However, the best characterized are those derived from bone marrow, which produce two types of SC: hematopoietic SC, which classically give rise to all blood lines; and mesenchymal stromal SCs, which give rise to various connective tissues, mainly bone and adipose tissue (VATS et al., 2002).

HEMATOPOIETIC STEM CELLS (HSCS)

For Abdelhay et al. (2009), HSCs are the most extensively studied. Because mature blood cells are predominantly short-lived, HSCs need to be renewed throughout the life of the individual to produce multilineage progenitors and precursors targeting individual hematopoietic lineages. Although rare, HSCs are programmed to allow the continuous and efficient production of functionally mature blood cell components, including platelets, red and white blood cells (SANTOS, 2017). Cell proliferation of HSCs is possible due to its ability to self-renew and to be a multipotent cell, that is, to be able to differentiate into lymphoid, myeloid, erythrocyte and megakaryocytic lineages (COVAS, 2009)

NEURAL STEM CELLS (NSCS)

Neural Stem Cells (NSCs) are multipotent cells capable of self-renewal and unlimited proliferation, for the production of progenitor cells that terminally differentiate into neurons, astrocytes and oligodendrocytes (MATTIS et al., 2015). According to Clarke (2003), the characterization of these cells indicates that these oligodendrocyte progenitors resemble neonatal progenitors, and not adults, and that the generation of these cells from the adult brain opens new possibilities to explore their potential in repairing disorders. of myelin.

For Marconi et al. (2004) studies have demonstrated that NSCs are capable of migrating to areas of the CNS affected by disease or injury and that due to their relative ease of propagation and manipulation in vitro, NSCs may represent a readily available and replenishable source for cell-based therapies. for the above-mentioned conditions.

MESENCHYMAL STEM CELLS (MSCS)

MSCs are non-hematopoietic stromal cells that have the ability to differentiate, and contribute to the regeneration of mesenchymal tissues, such as bone, cartilage, muscle, ligament, tendon and adipose tissue (CHAMBERLAIN et al., 2007). This type of behavior suggests that, despite originating from the bone marrow (BM), MSCs are circulating, passing through organs and tissues when they need to be repaired. This occurs through a physiological process closely regulated by a complex interaction of cytokines, particularly after mobilization of OM cells (WODEWOTZKY, 2008).

Thus, as they are multipotent stem cells, MSCs can differentiate, both in vitro and in vivo, and exhibit remarkable plasticity due to their ability to transdifferentiate or undergo an abrupt change in phenotype, giving rise to cells that have characteristics of different lineages (SQUILLARO et al., 2016).

Characterization and identification of mesenchymal stem cells

Some criteria were established to characterize mesenchymal stem cells such as adherence to plastic if kept under basic culture conditions; being positive for CD105, CD73 and CD90 and negative for CD45, CD34, CD14 and CD11b; and capable of differentiating into fibroblasts, osteoblasts, adipocytes and chondroblasts when exposed in vitro to the corresponding strains (DOMINICI et al .2006). MSCs are a heterogeneous population of cells that proliferate, in vitro, as cells adherent to plastic, having a morphology similar to fibroblasts, with a spindle shape and that during their initial growth in vitro, form colonies called, in analogy with hematopoietic stem cells , of colony forming fibroblast units (CFU-f) (BYDLOWSKI, SP et al., 2009).

Although MSCs do not express MHC class II and only express MHC class I at low levels, in addition to not expressing Fas ligand and co-stimulatory molecules, such as B7 and CD40, they have been suggested as hypoimmunogenic cells. MSCs do not appear to cause rejection because they are hypoimmunogenic, modulate the T cell phenotype, and immunosuppress the local environment. (ATOUI et al., 2012).

Mesenchymal stem cells and their capacity for homing and migration

Stem cell homing, according to Liesveld et al. (2020), refers to the ability of circulating stem cells or exogenously administered stem cells to locate and enter an environmental niche. Throughout its life, a stem cell can migrate between niches during embryonic development and also during adulthood. In the case of marrow mesenchymal stem cells, targeting to injured tissues may also occur.

Clinical trials have shown that MSCs function similarly to leukocytes because they express several homing receptors, which are typically activated during leukocyte extravasation, and because some of these receptors are definitely functional and necessary for their tissue localization in certain physiological or other contexts. pathological (HENSCHELER et al., 2008). Homing, according to Ullah et al. (2019), covers systemic and non-systemic homing. In systemic homing, MSCs are administered or recruited endogenously into the bloodstream and then must go through a multi-step process (tethering and roll, activation, entrapment,

transmigration or diapedesis and migration) to exit the circulation and migrate into the body. injury site; whereas in non-systemic homing, MSCs are locally transplanted into the target tissue and then guided to the lesion site by means of a chemokine gradient.

According to Sordi (2009), MSC homing, even if the signaling pathways are still unknown, may be a potential strategy for tissue regeneration, since in this process there is a probable involvement of chemokines and chemokine receptors. Chamberlain et al. (2007) emphasizes that, when transplanted, MSCs are able to migrate to the lesion sites and this process involves adhesion molecules, chemokine receptors and their ligands. Furthermore, the study on MSC homing indicates that the expression of chemokine receptors helps in trafficking to various tissues, including the bone marrow, and highlights the performance of CXCR4, the receptor for SDF-1, produced by stromal cells (BOBIS et al. 2021).

Immunomodulatory capacity of MSCs

Studies have shown that MSCs are cells with unique immunological properties, both in vitro and in vivo, inhibiting lymphocyte proliferation. Faced with the interaction of these cells with interferon-gamma (INF-Δ), which is a protein produced by cells of the immune system, or even due to the direct contact of these cells with transplanted tissues, MSCs enhance the release of soluble factors that will act in the cells of the immune system, inhibiting the production and proliferation of T and B lymphocytes, avoiding alloreactivity stimuli and escaping the cytotoxic activity of natural killer cells and T lymphocytes (MORAES, 2016).

For Lee et al. (2011), MSCs have potent immunosuppressive effects by inhibiting the activity of innate and adaptive immune cells, mediated by mechanisms dependent and independent of cell contact through the release of soluble factors. The list of candidate mediators released or induced by MSCs include transforming growth factor-b, tumor necrosis factor a (TNFa) - gene/stimulated protein 6 (TSG-6), PGE2, indoleamine 2,3-dioxygenase, interleukin-10 (IL-10) and IL-1ra, among others. Furthermore, studies have shown that MSCs affect various properties of T cells and definitively suppress proliferation of CD4+ and CD8+ T cells (Di Nicola et al., 2002). Likewise, their ability to hinder the proliferation of activated T cells, MSCs, prolongs the survival of T cells in a quiescent state. In this context, mesenchymal stem cells efficiently inhibit maturation, cytokine production, and the ability to stimulate T cells from dendritic cells. They can also prevent proliferation, cytokine secretion and the cytotoxic potential of T lymphocytes. In addition, mesenchymal stem cells are able to inhibit the differentiation of B cells into plasma cells by inhibiting their ability to produce antibodies (MARTI et al., 2011).).

CANINE DISEASE

Canine distemper is an infectious and multisystemic disease caused by a Morbillivirus, which affects the epithelia, the immune system and the central nervous system of domestic canids, and may present acute, subclinical and chronic clinical manifestations. In dogs, the disease is characterized by diarrhea, pneumonia, hyperkeratosis of the cushions and nasal plane, ocular secretion and neurological alterations. The disease is recognized for high mortality rates in the canine population (MANGIA; PAES, 2018). The disease can be systemic in puppies, producing respiratory, gastrointestinal and neurological signs due to involvement of the meninges and neuraxis. Lesions affect both white and gray matter. It affects dogs of any age, sex, breed and with

a tendency to different patterns, depending on the age group. In immature animals, it has a characteristic of systemic disease and multifocal neurological signs; in adult dogs, encephalitis is multifocal (chronic, progressive, multifocal neurological disease not associated with systemic disease; may be seen in vaccinated animals, where lesions are predominantly located in the brainstem and cerebellum); encephalitis in elderly dogs is characterized by non-systemic signs, visual and cerebral signs, with pathology of the perivascular sheath in the CNS and demyelination; Post-vaccination encephalitis, seen only in young animals (less than 6 months of age) showing signs one to two weeks after vaccination, is a non-systemic disease, often with severe personality change (FENNER et al., 1985).

In addition to the main clinical manifestations that include respiratory and gastrointestinal signs, immunosuppression and demyelinating leukoencephalitis (CARVALHO et al., 2012), histological studies showed the presence of eosinophilic intracytoplasmic inclusion bodies, characteristic of canine distemper, found in the epithelium of the lung, kidney, bowel and urinary bladder (VAN DE BILDT et al., 2002).

According to Summers and Appel (1994), the transmission of canine distemper virus is spread by aerosols and the initial signs of infection in dogs are pyrexia and mucopurulent conjunctivitis, rhinitis and pneumonia, and some dogs present gastrointestinal disorders. The agent is highly immunosuppressive and secondary bacterial infections of the respiratory tract usually occur. Classically, neurological signs develop a few days to weeks after respiratory tract infection, but often CNS disorders are the only signs present. According to Deem et al. (2000), the clinical signs of canine distemper are influenced by the virulence of the virus strain, environmental conditions, host age and immune status, and the identity of the infected species. In all species, the respiratory, gastrointestinal, integumentary, and CNS systems are most commonly affected, with biphasic fever and malaise that are usually associated with viremia. Infections, probably secondary to leukopenia, are common and can complicate the clinical course of the disease.

NEUROLOGICAL SEQUELAE OF DISTEMPER AND ITS SYMPTOMS

In the central nervous system (CNS), canine distemper virus infection causes severe demyelinating lesions which occur through two main processes that are related to damage to the myelin itself or by myelinogenic cells (primary demyelination) or axonal damage that promotes a secondary effect on myelin degeneration (secondary demyelination) (CARVALHO et al., 2012).

According to Beineke et al. (2009), canine distemper virus infection in dogs is characterized by a systemic and/or nervous clinical course and viral persistence in selected organs, including the central nervous system (CNS) and lymphoid tissue, the main manifestations being respiratory and gastrointestinal signs, immunosuppression and demyelinating leukoencephalomyelitis (DL). The initial phase of LD is a sequela of direct virus-mediated damage and infiltration of CD8+ cytotoxic T cells associated with upregulation of pro-inflammatory cytokines such as interleukin (IL)-6, IL-8, tumor necrosis factor (TNF) -α and IL-12 and lack of response of immunomodulatory cytokines, such as IL-10 and transforming growth factor (TGF) -β. A delayed-type hypersensitivity mediated by CD4+ and cytotoxic CD8+ T cells contribute to the loss of myelin in the chronic phase. In addition, upregulation of interferon-γ and IL-1 may occur in advanced lesions. Furthermore, an altered balance

between matrix metalloproteinases and their inhibitors appears to play a central role in the pathogenesis of LD. Thus, LD represents a biphasic disease process consisting of a direct virus-mediated initial process and immune-mediated plaque progression.

Greene and Vandevelde (2012) mention the neurological complications of canine distemper as the most significant factors that affect the prognosis and the recovery from infection and emphasizes that neurological signs, whether acute or chronic, are typically progressive and vary according to the area of the CNS involved. According to these authors, hyperesthesia and cervical or paravertebral stiffness can be found in some dogs as a result of meningeal inflammation, although parenchymal rather than meningeal signs usually predominate. As well as seizures, cerebellar and vestibular signs, paraparesis or tetraparesis with sensory ataxia and myoclonus are common. Seizures can be of any type, depending on which region of the forebrain has been damaged by the virus. The "chewing gum" type of seizure, classically associated with CDV infection, frequently occurs in dogs that develop temporal lobe polioencephalomalacia. However, damage to these lobes from other causes can produce similar seizures. Hippocampal changes have been observed in dogs that develop generalized tonic-clonic seizures that can progress to status epilepticus. Myoclonus, the involuntary contraction of muscles in a simultaneous forceful contraction, may be present without other neurological signs. With more extensive spinal cord injury, the dog may have upper motor neuron paresis of the affected limb associated with myoclonus. Rhythmic contractions may be present while the dog is awake, although they most commonly occur during sleep. The neural mechanisms of myoclonus arise from local irritation of lower motor neurons in the spinal cord or cranial nerve nuclei.

Moro et al., 2004, believe that, despite being much studied, the pathogenesis of distemper demyelination is still far from being fully clarified. However, he points out that more recent studies show that apoptosis of astrocytes and neurons may be participating in this process and that this is a new facet to be focused on as this virus can cause demyelination and nervous symptomatology.

CONVENTIONAL AND UNCONVENTIONAL TREATMENTS FOR CANINE DISTEMPER SEQUELAE

Sigwalt (2009) points out that despite distemper being a globally distributed and exhaustively studied disease, it remains a matter of concern both in small animal clinics and for zoo animals. And it highlights some problems that must be taken into account such as the lack of early diagnosis; the treatment to be instituted, as there is no effective antiviral therapy; the evaluation of the general picture as well as the degree of involvement of the organism, in order to establish how much it is worth investing in a treatment and what to use. And it points out the frequency of choice for euthanasia in cases where the central nervous system is compromised and in cases of severe systemic disease.

Nascimento et al. (2019), reported a treatment with phenobarbital at a dose of 2mg/kg (VO/BID) and supplementation with an antioxidant complex composed of docosahexaenoic acid, eicosapentaenoic acid, vitamin E, vitamin C, selenium and amino acid chelate (VO/SID), with success. in a canine patient who had distemper sequelae, which presented ambulation with ataxia, postural deformities and multifocal myoclonus in moderate degrees, with considerable accentuation of clinical signs within 15 days, culminating in a convulsive

episode, intense myoclonus and difficulty in maintaining in season. At the end of the treatment, the patient had a lower intensity and frequency of myoclonus crises, as well as a considerable improvement in balance and motor coordination. One hundred days after starting the new protocol, the patient had mild, sometimes imperceptible, myoclonus and improved coordination and balance, and was able to perform normal activities. According to the author, the established therapy obtained a satisfactory result in this patient, significantly reducing the neurological signs and stabilizing the convulsive condition.

For Greene and Vandevelde (2012), therapy for neurological disorders in canine distemper is not very rewarding. According to the authors, progressive multifocal encephalitis usually causes quadriplegia, semicoma, and such disability that euthanasia must be recommended. Despite ineffective therapy, dogs must not be euthanized unless the neurological disorders are progressive or incompatible with life. Variable or temporary success in stopping neurological signs in some dogs may result from a single 2.2 mg/kg dose given intravenously (IV) of dexamethasone. For these authors, myoclonus is usually intractable and irreversible; many forms of therapy have been tried without success. Drugs that facilitate y-aminobutyric acid, such as commonly used anticonvulsants, have been tried; however, they are not effective because they are intended for cortical-induced myoclonus. Drugs such as benzodiazepines or levetiracetam have been used with varying effectiveness.

With myoclonus in humans, treatment can lessen the severity of muscle contractions, but rarely eliminates it. Seizures are best treated with parenteral diazepam (0.5 to 2 mg/kg rectal or slow IV) for status epilepticus and phenobarbital for maintenance prevention. Primidone or potassium bromide are alternative choices, and combinations or higher doses may be necessary in refractory cases.

However, other authors such as Brito et. al., 2010, report the treatment in 11 dogs that presented neurological disorders with pre-diagnosis of distemper, 7 with recent clinical manifestations and 4 with chronic clinical signs, which received allogeneic bone marrow mononuclear cell transplantation from adult dogs in doses between 1.00 x 108 and 2.50 x 108 injected intravenously. At the end of treatment, of the 7 animals with acute or recent distemper, 5 showed complete remission of clinical signs; of these, only 2 did not have complete improvement, and their guardians opted for euthanasia, one of them less than 1 month after the transplant and the other, 2 weeks after a second transplant, the latter still showing signs associated with the viremic phase of the disease, with severe pneumonia and conjunctivitis. Of the animals with chronic signs, 3 showed visible improvement in the first week after transplantation, however, 2 of them, after a short period of stability, showed again the same clinical signs seen before transplantation. The animal that had ablepsy had improvement in the other signs, but did not recover its sight.

Gonçalves et al.(2019), in a case report in which he used Neural Therapy (NT) focused on the full recovery of the neurological sequelae caused by distemper. Neural therapy is based on the use of local anesthetics in low concentrations in different areas of the patient's body, chosen by the patient's life history. The dog that received the therapy had hematochezia and tetraparesis and confirmed distemper by examination. In all sessions, 0.7% procaine hydrochloride was used, totaling a dose of 10 ml. The acupuncture points used varied between sessions, and the amount administered to the points ranged from 0.3 mL to 1.0 mL. The animal was discharged

after 5 sessions of Neural Therapy, as it showed complete recovery from the distemper motor sequelae. The author, due to his case report, emphasizes the importance of neural therapy for the sequelae from canine distemper due to the impressive results obtained.

According to Bezerra (2017), the conventional treatment for distemper is not very effective, as the sequelae are constant, and euthanasia is an indication. The author defends acupuncture (AP) as an alternative to the treatment of these conditions due to its effects with sensory stimulation, due to the fact that it causes the release of local and distant neuropeptides, due to the involvement of the central and peripheral nervous systems. The therapeutic purpose comprises analgesia, motor recovery, regulation of organic, immunological and endocrine functions and activation of neuroskeletal regenerative processes. In his article, he added the electroacupuncture technique (EA) as an alternative treatment since the electrical stimuli connected to acupuncture needles potentiate the consistent therapeutic effects in patients with neurological sequelae, which can lead to clinical efficacy to the general condition of the animal and that electroacupuncture is a treatment that can help in the clinical picture of the animal comparing the symptoms before and after the treatment. E concluded that the use of the electroacupuncture technique in dogs with neurological disorders was clinically effective in the symptoms of pain, lameness, paresis, myoclonal and vocalization, solution for either tetraparesis or plegia in most animals, cure of urinary retention and alterations of cranial nerves and mental status and improvement or cure of myoclonus in all animals and thus avoiding euthanasia, which is an indication for cases with paralysis.

Baldotto (2019) in a study with 10 dogs with encephalomyelitis caused by the canine distemper virus, evaluated the effectiveness of using a single transplant of 10 x 106 of allogeneic CMTs intrathecally, in which, according to the final results, there was a reduction in the degree of the Neurodeficiency Scale evidenced by the clinical improvement of the neurological signs presented in Posture, Gait, Coordination, Cranial Nerves and Epileptic Seizures. The author concluded that the intrathecal route for allogeneic ASC transplantation in dogs is viable and safe, as it has been shown to be minimally invasive, rapid and allows for the transplantation of a large number of cells into the subarachnoid space.

TREATMENT WITH MSCS FOR THE NEUROLOGICAL SEQUELAE OF CANINE DISTEMPER

According to Björklund and Lindvall (2000), the nervous system, unlike many other tissues, has a limited capacity for self-repair because mature nerve cells do not have the ability to regenerate and stem cells that are neural networks, although they exist even in the adult brain, have a limited ability to generate new functional neurons in response to injury. For this reason, there is great interest in the possibility of repairing the nervous system by transplanting new cells that can replace those lost due to damage or disease.

Regarding the use of MSCs, the isolation rate of MSC-TA (Mesenchymal Stem Cells from Adipose Tissue) is 40 times higher compared to bone marrow, conferring high potential in regenerative medicine. In vivo studies have determined the survival, migration and engraftment of transplanted MSC-TA and suggest a neuroprotective mechanism for its use. Thus, MSC-TA have high potential for application to neurological diseases and injuries (MASSUMOTO et al., 2014). The advantage of using adipose tissue is that it is a rich source of mesenchymal stem cells, especially attractive due to its

ease of collection, clonogenic potential and proliferative capacity (BAGNO et al., 2012).

Carvalho et al. (2011) emphasizes that MSCs, when applied to the central nervous system (CNS), are considered cytotrophic mediators, as their secretome is rich in neurotrophic factors, which promote neurogenesis and increase neuronal survival. Teixeira et al. (2013) reinforces that it has been demonstrated, both in vitro and in vivo, that MSCs are capable of secreting a wide range of neuroregulatory factors that promote an increase in neurogenesis, inhibition of apoptosis and glial scar formation, immunomodulation, angiogenesis, survival neuronal and glial cells, as well as relevant neuroprotective actions in different pathophysiological contexts. Considering its protective action at lesion sites, MSC secretome may also improve the integration of local progenitor cells in neuroregeneration processes.

Monteiro (2017), using infusions of MSCs applied epidurally, for the treatment of demyelinating leukoencephalitis in dogs with neurological sequelae of distemper, proved to be effective and safe and did not cause adverse effects in animals undergoing therapeutic treatment and prevented the dispersion of cells. to unwanted areas. The author adds that tissue regeneration after the application of MSCs can be explained by the release of cytokines and trophic factors at the site of injury. Thus, the therapeutic potential as well as the regenerative capacity of MSCs can be explained by the ability to self-regulate the factors of the inflammation cascade without inducing an immune response in the host, thus representing another therapeutic opportunity to be used.

As for the nervous system, after transplantation, MSCs interact with the injured tissue and can control the gene expression of genes related to inflammation and apoptosis, in addition to stimulating the neuroprotective effect of gene expression (OLIVERI et al., 2014). In addition, these cells produce an extracellular matrix and neurotrophic factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) that modify the injury microenvironment and accelerate tissue repair. neural tissue (DE FEO et al., 2012).

Gonçalves et al. (2018) investigated the effects of an allogeneic infusion of mesenchymal stem cells derived from adipose tissue in the treatment of dogs with neurological sequelae secondary to virus infection in the canine nervous system. Of the seven dogs selected, all were PCR positive for distemper and later, after clinical treatment, were PCR negative, but retaining at least one post-infection neurological sign. Therapy consisted of an allogeneic infusion of mesenchymal stem cells derived from adipose tissue, administered at a dose of 5.0x 106 cells / 3.0 mL of PBS (Phosphate Buffered Saline Solution), in three applications 15 days apart. All animals showed post-therapy clinical neurological improvement, mainly for ambulation and urinary and fecal incontinence parameters, and this improvement was significant throughout the evaluation period, which proved to be efficient and can be considered a treatment option in cases of distemper. chronic.

Gonçalves et al. (2018) opted for therapy in patients with chronic signs and not in dogs that showed clinical signs characteristic of the acute phase of distemper, because in the acute phase there is a high rate of virus replication in the lymphoid tissues of dogs and leads to lymphopenia by depletion. transient CD21 + B, CD8 + T and CD4 + T cells (CARVALHO et al, 2012), profound immunosuppression due to leukocyte necrosis and apoptosis (Carvalho et al., 2012; Beineke et al., 2015),

and inhibition of responses of interferon and cytokines secreted by lymphoid cells (Greene and Vandevelde, 2012) and that, therefore, this immunosuppression could be potentiated by exogenous use of MSC.

Uccelli et al. (2011) suggest that MSCs are a promising approach to achieving neural repair and protection. However, current data do not support the possibility that most of the reported effects occur through cell replacement. And they believe that many other paracrine mechanisms, including a potent anti-inflammatory capacity, the direct release of anti-apoptotic and neurotrophic factors, the ability to induce other cells, such as microglia, to acquire a protective phenotype, and to induce proliferation of local neural progenitor cells, possibly leading to reduced demyelination, probably ensure the protective effects observed in preclinical models.

FINAL CONSIDERATIONS

Considering that the neurological sequelae of canine distemper are considered irreversible and have been treated symptomatically, or with indication of euthanasia, which occurs in most cases of severe sequelae, therapy with infusion of mesenchymal stem cells proved to be effective for the regeneration of the central and peripheral nervous system. Mesenchymal stem cells will act mainly through their paracrine effect, which is the ability to secrete numerous substances that will act in the repair, regeneration and protection of normal cells within the injured tissue and not by a direct regeneration mechanism, although they do, but in a much smaller amount compared to their paracrine effect. The average concentration of application doses 5.0 x 106 cells / 3.0 mL of PBS, derived from adipose tissue, meet all requirements for adhesion to plastic substrate, differentiation in culture medium and consistent membrane receptor expression profile with a population of mesenchymal stem cells, from the fourth passage.

The use of MSCs for the treatment of neurological sequelae of canine distemper demonstrates the potential to be one of the best, safest and most promising options, as it allows complete remission of clinical signs or partial and momentary improvement. It is concluded that, according to the results obtained from the reading of the scientific literature, stem cells prove to be effective for the treatment of neurological sequelae of canine distemper. It is worth noting that treatment with mesenchymal stem cells can have even more encouraging results with other therapies that can potentiate the rehabilitative effects of mesenchymal stem cells, such as acupuncture, electroacupuncture and physical therapy itself.

However, there is still a lack of information in the scientific literature on how the migration and establishment of mesenchymal stem cells occurs in the injured tissue and what biological mechanisms are involved, exemplifying, for example, chemokines and their ligands, which are involved in this process, or explaining in a satisfactory as the homing process occurs.

REFERENCES

A. HASELTINE, WILLIAM. Regenerative Medicine 2003: An Overview. **The Journal of Regenerative Medicine**,[S. l.], v. 4, n. 3, p. 15-18, 6 jul. 2004. DOI:10.1089/152489003321222844.https://doi.org/10.1089/152489003321222844. Acesso em: 4 out. 2021.

ABDEHLAY, Eliana S. F. W. et al. Células-tronco de origem hematopoética: expansão e perspectivas de uso terapêutico: Hematopoietic stem cells: expansion and perspectives for therapeutic use. **Revista brasileirade hematologia e hemoterapia**, [s. l.], v. 31, n. 1, p. 2-8, 2009. DOI 10.1590/S1516- 84842009005000019. Disponível em: https://doi.org/10.1590/S1516-84842009005000019. Acesso em: 18 ago. 2021.

ALVARENGA,Marina Landim e **. Uso de células- tronco para o tratamento de tendinite em equinos.** 2011.1 CD-ROM. Trabalho de conclusão de curso (bacharelado- Medicina Veterinária)-Universidade Estadual Paulista, Faculdade de Medicina Veterinária e Zootecnia, 2011. Disponível em https://hdl.handle.net/11449/118005 . Acesso em 07/12/2021

ATOUI, Rony et al. Immunomodulatory Propertiesof Mesenchymal Stem Cells in CellularTransplantation: Update, Controversies, and Unknowns: Concise Review. **Tissue-specific progenitor and stem cells: stem cells translational medicine, usa**, v. 1, ed. 3, p. 200-205, 2012. DOI 10.5966/sctm.2011-0012. Disponível em: https://stemcellsjournals.onlinelibrary.wiley.com/doi/full/10.5966/sctm.2011-0012. Acesso em: 11 out. 2021.

BAGNO, Luiza e Lima e Silva et al. Células Tronco Derivadas de Tecido Adioso. In: CARVALHO, Antnio Carlos Campos de et al. **Células-Tronco Meenquimais:** Conceitos, Métodos de Obtenção e Aplcações. São Paulo: Atheneu, 2012. cap.

BALDOTTO, S. B. **Efeitos da terapia com células estromais mesenquimais multipotentes em cães com encefalomielite pelo virus da cinomose** 2019. 35 páginas. Tese (Pós-graduação em Medicina Veterinária) – Faculdade de Medicina Veterinária e zootecnia (FMVZ) – Botucatu, Botucatu, 2019; Disponível em: <http://hdl.handle.net/11449/180951>.

BHATTACHARYA, Bhaskar et al. Molecular signature of human embryonic stem cells: Gene expression in human embryonic stem cell lines: unique molecular signature. **Hematopoiesis, ash publication**, v. 103, ed. 8, p. 2956-2964, Abril 2004. DOI 10.1182/blood-2003-09-3314. Disponível em: https://doi.org/10.1182/blood- 2003-09-3314. Acesso em: 9 set. 2021.

BEINEKE, Andreas et al. Cross-species transmission of canine distemper virus—an update. **Scienc Direct,** Germany, v. 1, p. 49-59, 13 set. 2015. DOI DOI: 10.116/j.onehlt.2015.09.002. Disponível em: https://doi.org/10.1016/j.onehlt.2015.09.002. Acesso em: 29 out. 2021.

BEINEKE, Andreas et al. Pathogenesis and immunopathology of systemic and nervous canine distemper. **Veterinary Immunology and Immunopathology**, [s. l.], v. 127, n. 2, ed. 1, p. 1-18, Janeiro 2009. DOI DOI:10.1016/j.vetimm.2008.09.023. Disponível em: https://doi.org/10.1016/j.vetimm.2008.09.023. Acesso em: 29 out. 2021.

BEZERRA, Karina Machado. **Tratamento com eletroacupuntura em cães com seqüelas neurológicas causadas pelo vírus da cinomose**. 2017. 15 p. Artigo (Pós Graduação em Acumputura) - Faculdade FASERRA, Manaus, 2017. Disponível em: portalbiocursos.com.br › ohs › data. Acesso em: 12 out. 2021.

BJÖRKLUND , Anders et al. Cell replacement therapies for central nervous system disorders: Review. **Nature Neuroscience**, [s. l.], v. 3, n. 6, p. 537-44, Junho 2000. DOI doi:10.1038/75705. Disponível em: https://pubmed.ncbi.nlm.nih.gov/10816308/. Acesso em: 26 out. 2021.

BOBIS, Sylwia et al. Mesenchymal stem cells: characteristics and clinical applications. Folia Histochemica et Cytobiologica, **folia histochemica et cytobiologica**, v. 44, n. 4, p. 215-230, 2007. DOI DOI: 10.5603/4554. Disponível em: https://www.researchgate.net/publication/307803623. Acesso em: 1 nov. 2021.

BRITO, Harald F. V. et al. --"Tratamento de sequelas neurológicas em cães,causadas por infecção pelo vírus da cinomose,através do transplante alogênico de células mononucleares de medula óssea":: Bone marrow mononuclear cells as a treatment for neuronal sequels in dogs, caused by canine distemper vírus. **Revista Científica de Medicina Veterinária - Pequenos Animais e Animais de Estimação**, [s. l.], v. 8, ed. 24, p. 26-29, Abril 2010. Disponível em: https://www.researchgate.net/publication/265250963. Acesso em: 18 out. 2021.

BRITO, Harald Fernando Vicente de. "**Utilização de células mononucleares de medula óssea para o tratamento de sequelas neurológicas de cinomose canina.** 2015. Tese de doutorado (Doutor em Ciências Veterinárias. Medicina Veterinária). Universidade Federal Do Paraná, CURITIBA, 2015. http://educapes.capes.gov.br/handle/1884/41363. Acesso em: 27 out. 2021.

BYDLOWSKI, Sergio P et al. Características biológicas das células- tronco mesenquimais: Revisão. **Hemoter-Revista Brasileira de Hematologia,** São Paulo- SP, v. 31, ed. 1, p. 25-35, 10 maio 2009. DOI https://doi.org/10.1590/ S1516- 84842009005000038. Disponível em: https://www.scielo.br/j/rbhh/a/ qZ47zKnRRRhJnR6hzrMqGZk/?format=html. Acesso em: 20 abr. 2020.

CARRION, Maria Julia M. et al. Potencial terapêutico das células-tronco de medula óssea no tratamento da Epilepsia: Therapeutic potential of bone marrow stem cells in epilepsy treatment. **Revista Brasileira de Hematologia: Artigo de Revisão,** [s. l.], v. 31, ed. 1, p. 112-119, 2009. DOI Doi: 10.1590/S1516-84842009005000023. Disponível em: https://1library.org/title/potencial-terapeutico-celulas-tronco-medula- ossea... Acesso em: 5 set. 2021.

CARVALHO, A. C. C. Células-tronco: medicina do futuro. **Revista Ciência Hoje,** v. 29, n. 172, p. 26-31, 2001.

CARVALHO, Miguel M. et al. Mesenchymal Stem Cells in the Umbilical Cord: Phenotypic Characterization, Secretome and Applications in Central Nervous System Regenerative: Medicine Current Stem Cell Research & Therapy. **Bentham Science Publishers,** [s. l.], v. 6, ed. 3, p. 221-228, 2011. DOI 10.2174/157488811796575332. Disponível em: http://hdl.handle.net/1822/18615. Acesso em: 19 out. 2021.

CHAMBERLAIN, GISELLE et al. Concise Review: Mesenchymal Stem Cells: Their Phenotype, Differentiation Capacity, Immunological Features, and Potential for Homing: TISSUE SPECIFIC STEM CELL. **STEM CELLS EXPRESS** , Stem cells journals, v. 25, n. 11, p. 2740-2749, 17 jul. 2007. DOI doi: 10.1634/ Stemcells .2007- 0197. Disponível em: https://stemcellsjournals.onlinelibrary.wiley.com/doi/pdf/10.1634/stemcells.2007- 0197. Acesso em: 5 out. 2021.

CLARKE, Diana L. Neural stem cells. **Bone Marrow Transplantation,** USA, v. 32, ed. 1, p. 13-17, September 2003. Disponível em: https://www.researchgate.net/publication/10603750_Neural_stem_cells. Acesso em: 27 out. 2021.

COVAS, Dimas Tadeu. Biologia das células tronco adultas. In: VOLTARELLI, Julio C. **Transplante de células-tronco hematopoiéticas**. 1. ed. São Paulo: Atheneu, 2009. v. 1, cap. 2, p. 43-55. ISBN 978-85-388-0081-1.

DAAR, Abdallah S; GREENWOOD, Heather L. A proposed definition of regenerative medicine: PERSPECTIVE. **Journal of tissue engineering and regenerative medicine**, Canada, v. 1, p. 179–184, 17 set. 2007. DOI 10.1002/term.20. Disponível em: www.interscience.wiley.com. Acesso em: 15 mar. 2021.

DEEM, Sharon L. et al. Canine distemper in terrestrial carnivores: a review. **Journal of Zoo and Wildlife Medicine**, SourcePubMed, v. 31, n. 4, p. 441–451, 1 dez. 2000. Disponível em: https://www.researchgate.net/publication/11913087_Canine_Distemper_in_Terrestria l_Carnivores_A_Review/link/02bfe50d31daf65e09000000/download. Acesso em: 29 out. 2021.

DE FEO, D., MERLINI, A., LATERZA, C., MARTINO, G., 2012. Neural stem cell transplantation in central nervous system disorders: from cell replacement to neuroprotection. **Curr. Opin. Neurol.** 25 (3), 322–333. doi: 10.1097/WCO.0b013e328352ec45. https://journals.lww.com/co- neurology/Abstract/2012/06000/Neural_stem_cell_transplantation_in_central.17.aspx . Acesso em 09/12/2021

DE OLIVEIRA, Mílton Paulo. Aspectos evolutivos da Medicina Regenerativa. **Arquivos catarinenses de medicina**, Santa Catarina, v. 41, ed. 01, 2012. Disponível em: http://www.acm.org>revista>pdf.fartigos. Acesso em: 6 mar. 2021.

DESSEN, Eliana Maria Beluzzo. O básico sobre células-tronco. desvendando as células-tronco: dos sonhos à realidade. Centro de Estudos do Genoma Humano Depto. de Genética e Biologia Evolutiva Instituto de Biociências Universidade de São Paulo: [s. n.], 16/07/2007. Disponível em: http://stemcells.nih.gov/info/basics/basics1.asp. Acesso em: 2 maio 2021.

DEWITT, Natalie DeWitt. Regenerative Medicine. **Nature Insight,** [S. l.], v. 453, n. 7193, p. 301, 15 maio 2008. Disponível em: Https://doi.org/10.1038/453301a. Acesso em: 4 out. 2021.

DI NICOLA, Massimo et al. Human bone marrow stromal cells suppress T- lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli: TRANSPLANTATION. BLOOD, **American Society of Hematology,** v. 99, ed. 10, p. 3838-3843, 15 maio 2002. DOI DOI:10.3838/1684678. Disponível em: http://ashpublications.org/blood/article- pdf/99/10/3838/1684678/h810020038.38.pdfbyguest. Acesso em: 4 nov. 2021.

DOMINICI, M et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement: POSITION PAPER. **Cytotherapy journal**, [S. l.], v. 8, n. 4, p. 315-317, 1 jan. 2006. DOI DOI 10.1080/14653240600855905. Disponível em: DOI:https://doi.org/10.1080/14653240600855905. Acesso em: 28 out. 2021.

FENNER, William R. Distúrbios que acometem difusamente o SNC: Infecções: Cinomose. In: FENNER, Willian R. et al. **Manual de Prática Clínica Veterinária.** Brasil: Guanabara Koogan S.A, 1985. cap. Capítulo 11 Distúrbios Neurológicos, p. 224-225. ISBN 85-226-0130-5.

FRANCIOLLI, A. L. R. **Medicina veterinária regenerativa:** multipotencialidade das células da membrana amniótica e do saco vitelino no modelo equino (Equus caballus, Linnaeus 1758). 2012. Tese de Doutorado. Universidade de São Paulo.Medicina veterinária regenerativa - Biblioteca Digital de Teses https://www.teses.usp.br › disponiveis › publico. Acesso em 07/12/2021.

GHAEDI, Mahboobe; NIKLASON, Laura E. Human Pluripotent Stem Cells (iPSC) Generation, Culture, and Differentiation to Lung Progenitor Cells. In: TURKSEN, Kursad. **Methods in Molecular Biology:** Organoids: Stem Cells, Structure, and Function. 1. ed. USA: Humana Press, 2019. cap. 1, p. 55-92.ISBN 978-1-4939-7617- 1. Disponível em: https://doi.org/10.1007/978-1-4939-7617-1. Acesso em: 9 set. 2021.

GONÇALVES, Bruna Aparecida Lima et al. "Tratamento com Terapia Neural em cão com sequela de cinomose: Relato de caso". **PUBVET,** [s. l.], ano a363, v. 13, n. 7, p. 1-6, Julho 2019. Disponível em: http:s//doi.org/10.31533/pubvet.v13n7a363.1-6. Acesso em: 26 out. 2021.

GONÇALVES, D.S.V. et al. Mesenchymal stem cell infusion for the treatment of neurological sequelae of canine distemper virus: a clinical study. **Genetics and Molecular Research,** Brasil, v. 17, ed. 4, p. 1-13, 9 out. 2018. DOI Doi:10.428/gmr18088. Disponível em: DOI http://dx.doi.org/10.4238/gmr18088. Acesso em: 16 set. 2021.

GREENE, Craig E. e VANDEVELDE, Marc. Canine Distemper. In: GREENE, Craig E. **Infectious dieseases of the dog and cat**. 4. ed. [S. l.]: Elsevier, 2012. cap. 3, p. 25-42.

GREENWOOD, Heather L et al. Regenerative Medicine and the Developing World. **Plos medicine journal**, [S. l.], v. 3, n. 9, 15 set. 2021. e-381, p. 1496-1500. DOI DOI: 10.1371. Disponível em: www.plosmedicine.org. Acesso em: 24 mar. 2021.

GRIFIELD, Sara; GOMES, Roberta Gondim da Costa. Células tronco: um breve estudo: Stem Cells: a brief study. IJD. **International journal of dentistry**, Recife-Pe, v. 3, n. 1, p. 324-329, 20 jun. 2004. Disponível em: https://periodicos.ufpe.br › dentistry › article › view. Acesso em: 21 mar. 2021.

HENSCHLER, Reinhard et al. Homing of Mesenchymal Stem Cells. **Transfusion Medicine and Hemotherapy**, [s. l.], v. 35, p. 306-312, 2008. Disponível em: https://www.academia.edu/18055031/Homing_of_Mesenchymal_Stem_Cells. Acesso em: 27 out. 2021.

KOLIOS, George; MOODLEY, Yuben. Introduction to Stem Cells and Regenerative Medicine. **Respiration: Thematic Review Series,** [s. l.], v. 83, n. 1, p. 3–10, 2013. DOI: 10.1159/000345615. Disponível em: https://doi.org/10.1159/000345615. Acesso em: 11 ago. 2021.

LEE, Jae W. LEE et al. Concise Review: Mesenchymal Stem Cells for Acute Lung Injury: Role of Paracrine Soluble Factors: STEM CELLS -TRANSLATIONAL AND CLINICAL RESEARCH. **STEM CELLS EXPRESS**, USA, v. 29, ed. March 28, 2011, p. 913–919, 28 mar. 2011. DOI doi: 10.1002/stem.643. Disponível em: www.StemCells.com. Acesso em: 4 nov. 2021.

LIESVELD, Jane L. et al. Stem cell homing: From physiology to therapeutics: CONCISE REVI EW. **Stem Cells Journals**, [s. l.], v. 38, ed. 10, p. 1241–1253, 2000. DOI DOI: 10.1002/stem.3242. Disponível em: https://stemcellsjournals.onlinelibrary.wiley.com/doi/full/10.1002/stem.3242. Acesso em: 25 out. 2021.

MACHADO , Mariana Rezende et al. Dentes como Fonte de Células-Tronco: uma Alternativa aos Dilemas Éticos: Teeth as Source of Stem Cells: an Alternative to Ethical Dilemmas. **Revista de Bioética y Derecho,** Barcelona, v. 31, p. 66-80, 2014.. Disponível em: https://dx.doi.org/10.4321/S1886-58872014000200006. Acesso em: 2 ago. 2021.

MANGIA , Henrique; PAES, Antono Carlos. Cinomose: Seção 2: Vírus. In: MEGID, Jane et al. **Doenças infecciosas em animais de produçao e companhia**. [S. l.]: ROCA, 2018. cap. Capítulo 51, p. 560-579. ISBN 978-85-277-2891.

MARCONI, et al. Neural Stem Cells From In Vivo to In Vitro and Back Again— Practical Aspects. In: SELL, STEWART. **Stem Cell Handbook**. USA: HUMANA PRESS, 2004. cap. 17, p. 191-208. ISBN 1-58829-113-8.

MARSHALL, Clement D. et al. Stem Cell Regeneration and Repair – Overview. In: WILEY, John; & SONS, & Sons. **Wound Healing:** Stem Cells Repair and Restorations, Basic and Clinical Aspects. 1. ed. USA: Kursad Turksen, 2018. cap. 1, p. 1-14. ISBN 1119282519. Disponível em: https://zlibrary.org. Acesso em: 10 set. 2021.

MARTI, Luciana Cavalheiro et al. O efeito imunomodulatório de células-tronco mesenquimais: Review. **Einstein,** São Paulo, v. 9, ed. 2, p. 224-8, Apr-Jun 2011. DOI DOI: 10.1590/S167945082011RW1843. Disponível em: https://www.scielo.br/j/eins/a/vRT97hp3ZKZqhxhcqxdDx7R/abstract/?lang=pt. Acesso em: 29 out. 2021.

MASON, Chris; DUNNILL, Peter. A brief definition of regenerative medicine. **Regenerative Medicine,** [s. l.], v. 3, ed. 1, p. 1-5, 2008. Disponível em: https://www.futuremedicine.com. Acesso em: 15 mar. 2021.

MASSUMOTO et al. O TECIDO Adiposo. In: MASSUMOTO, Celso et al**. Células- Tronco:** da coleta aos protocolos terapêuticos. São Paulo: Atheneu, 2014. cap. 5, p. 29-33. 383 p.

MATTIS, Virginia et al. Neural Stem Cells: Identification, Function, Culture, and Isolation. STEMCELL Technologies, **Nature Neuroscience,** April 2015. Disponível em: https://www.stemcell.com/neural-stem-cells-lp.html. Acesso em: 27 out. 2021.

MELTON, Douglas. 'Stemness': Definitions, Criteria, and Standards. In: LANZA, R. et al. **Essentials of Stem Cell Biology.** 3. ed. USA: Elsevier, 2014. cap. 2, p. 7-17. Disponível em: http://dx.doi.org/10.1016/B978-0-12-409503-8.00002. Acesso em: 5 out. 2021.

MINGRONI-Netto, Regina Célia e DESSEN, Eliana Maria Beluzzo. Células-tronco: o que são e o que serão. **Genética na Escola**, v.1, n.1, p. 12-15, 2006.

MONTEIRO, Bianca Andriolo Monteiro. **Efeitos da terapia com células tronco mesenquimais em afecções do sistema nervoso de cães.** 2017. 68 p. Tese de doutorado (Obtenção do Título de Doutor em Biotecnologia Animal) - Universidade Estadual Paulista Faculdade De Medicina Veterinária E Zootecnia, Botucatu-Sp, 2017. Disponível em: https://repositorio.unesp.br/handle/11449/151543. Acesso em: 8 dez. 2021.

MORAES, Daniela Abreu De. **Estudo da função de cd90 na proliferação e diferenciação de células-tronco mesenquimais humanas**. Orientador: Prof. Dr. Orlando Ayrton de Toledo. 2016. 106 p. Tese de doutorado (Título de Doutora em Ciências da Saúde) - Ciências da Saúde da Universidade de Brasília., BRASÍLIA, 2016. Disponível em: http://repositorio.unb.br/handle/10482/22330. Acesso em: 19 out. 2021.

MORO, Luciana; ALVES, Cristiane de Morais; SANTOS, Francisco Glauco de Araújo; MARTINS, Almir de Sousa; VASCONCELOS, Anilton César. Artigo de Revisão : Apoptose na desmielinização da cinomose canina. **Bioscience Journal, Uberlandia-Brasil**, v. 20, ed. 2, p. 171-178, Abril 2004. Disponível em: https://www.researchgate.net/publication/265250853. Acesso em: 14 out. 2021.

NASCIMENTO, Tainá Gentil do et al. Tratamento de sequela de cinomose em cão com fenobarbital associado à complexo antioxidante: relato de caso. **UNINGÁ Review Journal:** v. 34 n. S1. Anais do II CICLOVET - Ciclo de Palestras do curso de Medicina Veterinária, Maringá, v. 34, ed. 1, p. 45-45, Julho/Setembro 2019. Disponível em: http://34.233.57.254/index.php/uningareviews/article/view/3107/2077. Acesso em: 16 nov. 2021.

OLIVERI, R.S., BELLO, S., BIERING-SORENSEN, F. Mesenchymal stem cells improve locomotor recovery in traumatic spinal cord injury: systematic review withmeta-analyses of rat models. **Neurobiol. Dis.,** v. 62, p. 338–353, 2014.. Disponível em: https://pubmed.ncbi.nlm.nih.gov/24148857/. Acesso em 09/12/2021

PEREIRA, Lygia da Veiga. Células tronco – promessas e realidades da terapia celular. **Cadernos de História da Ciência,** Cadernos de História da Ciência – Instituto Butantan, v. V, ed. 2, 2009. Disponível em: bibliotecadigital.butantan.gov.br › arquivos. Acesso em: 21 mar. 2021.

PINHEIRO, Luane Lopes et al. Mesenchymal stem cells in dogs with demyelinating leukoencephalitis as an experimental model of multiple sclerosis. **Heliyon journal,** Brasil, v. 5, ed. 4, p. 1-7, 2009. Disponível em: https://doi.org/10.1016/j.heliyon.2019.e01857. Acesso em: 6 dez. 2021.

SALOMONE, Raquel. **XIII Manual de Otorrinolaringologia Pediátrica da IAPO:** Células-Tronco: Uma Nova Esperança na Regeneração Neural?. 13. ed. Interamerican Association of Pediatric Otorhinolaryngology (IAPO): Copyright ©, 2015. pagina 59-63 p. Disponível em: bibliotecadigital.butantan.gov.br › arquivos. Acesso em: 21 mar. 2021.

SANTOS, Enrico Jardim. Análise da Aplicação Terapêutica das Células Tronco na Medicina Veterinária. **Revista Científica Multidisciplinar Núcleo do Conhecimento,** Ano 02, v. 01. p 269-295, Abr. 2017.

SIGWALT, Desirée. **Cinomose em carnívoros.** 2009. 34 f. TCC (Graduação em Medicina Veterinária) - Universidade Federal do Rio Grande do Sul, Porto Alegre, 2009/2. Disponível em: https://www.lume.ufrgs.br/handle/10183/22948. Acesso em: 16 nov. 2021

SQUILLARO, Tiziana et al. **Review Clinical Trials With Mesenchymal Stem Cells:** An Update. Cell Transplantation, USA, v. 25, p. 829–848, 2016. DOI 10.3727/096368915X689622. Disponível em: http://dx.doi.org/10.3727/096368915X689622. Acesso em: 9 set. 2021.

SLACK, Jonathan M. W. Pluripotent Stem Cells. In: SLACK, Jonathan M. W. **The Science of Stem Cells**. USA: Wiley Blackwell, 2018. v. 1, cap. 6, p. 93-105. ISBN 9781119235231 (pdf) |. Disponível em: https://lccn.loc.gov/2017028793. Acesso em: 6 ago. 2021.

SOARES, M. B. P.; SANTOS, R. R. dos. Terapia com células-tronco: a medicina do futuro. **Parcerias Estratégicas,** Brasília, n. 16, out. p. 153-161, 2002. https://www.arca.fiocruz.br/handle/icict/14255. Acesso em 5/12/2021

SORDI, Valeria. Mesenchymal Stem Cell Homing Capacity. **The Transplantation Society** , [s. l.], v. 87, ed. 9, p. 42-45, 2009. DOI doi: 10.1097/TP.0b013e3181a28533. Disponível em: https://journals.lww.com/transplantjournal/Fulltext/2009/05151/Mesenchymal_Stem_ Cell_Homing_Capacity.4.aspx. Acesso em: 4 nov. 2021.

SOUZA, Verônica Ferreira de et al. Células-tronco: uma breve revisão. **Revista de Ciências Médicas e Biológicas**, Salvador, v. 2, ed. 2, p. 251-256, jul/dez 2003. Disponível em: https://repositorio.ufba.br/ri/handle/ri/20334. Acesso em: 18 out. 2021.

SUMMERS , B. A.; APPEL, M. J. G. Aspects of canine distemper virus and measles vírus encephalomyelitis: Review. **Neuropnthology and Applied Neurobiology- British Neuropathological Society**, USA, v. 20, ed. 6, p. 525-534, Dezembro 1994. DOI DOI:10.111/J.1365-2990. Disponível em: https://doi.org/10.1111/j.1365- 2990.1994.tb01006. Acesso em: 20 out. 2021.

TAKAHASHI, Kazutoshi; YAMANAKA, Shinya. Induction of pluripotent stem cells from mouse embryonic. **Stem Cell Discovery,** Japan, v. 4, n. 2, p. 663-676, 2006. DOI 10.1016/j.cell.2006.07.024 SUMMARY. Disponível em: https://www.cell.com/cell/pdf/S0092-8674(06)00976-7.pdf. Acesso em: 30 jun. 2021.

TEIXEIRA, Fábio G. et al. SalgadoMesenchymal stem cells secretome: a new paradigma for central nervous system regeneration?: Review. **Cellular and Molecular Life Sciences**, Portugal, p. 3871–3882, 4 fev. 2013. Disponível em: http://hdl.handle.net/1822/25128. Acesso em: 6 out. 2021.

UCCELLI, Antonio et al. Neuroprotective features of mesenchymal stem cells. **Best Practice & Research Clinical Haematology**, Italy, v. 24, p. 59–64, 2011. doi:10.1016/j.beha.2011.01.004. Disponível em: www.elsevier.com/locate/beha. Acesso em: 27 out. 2021.

ULLAH, Mujib et al. Mesenchymal Stromal Cell Homing: Mechanisms and Strategies for Improvement. **IScience, Science Direct Journal,** v. 15, n. 31, p. 421–438, 31 maio 2019. Disponível em: https://doi.org/10.1016/j.isci.2019.05.004. Acesso em: 3 nov. 2021.

VAN DE BILDT, Marco W.G. et al. Distemper Outbreak and Its Effect on African Wild Dog Conservation. **Emerging Infectious Diseases** , [s. l.], v. 8, ed. 2, p. 212-213, Fevereiro 2002. Disponível em: https://www.researchgate.net/publication/11466837_Distemper_Outbreak_and_Its_E ffect_on_African_Wild_Dog_Conservation. Acesso em: 7 out. 2021.

VATS, A. et al. Stem cells: sources and applications: a review article. **Clinical Otolaryngology ,** UK, v. 27, p. 227–232, 25 mar. 2002. Disponível em: https://doi.org/10.1046/j.1365-2273.2002.00579. Acesso em: 27 out. 2021.

WODEWOTZKY, Thaila Isabel. **Células - tronco e terapia celular:** suporte didático para o ensino fundamental e médio. 2008. 76 p. TCC (Título de Licenciatura em Ciências Biológicas.) - Universidade Estadual Paulista "Júlio De Mesquita Filho" Instituto De Biociências Campus De Botucatu/Sp, Botucatu- SP, 2008. Disponível em: https://1library.org/document/dy4465rycelulas-tronco-terapia-celular suporte- didatico-ensino-fundamental.html. Acesso em: 6 jul. 2021.

ZAKRZEWSKI, Wojciech et al. "Stem cells: past, present, and future": Review. **Stem Cell Research & Therapy**, v. 10, ed. 68, p. 1-22, 26 fev. 2019. .Disponível em: https://doi.org/10.1186/s13287-019-1165-5. Acesso em: 6 dez. 2021.

GLOSSARY

THE

-Self-replication: ability to generate an identical copy of itself.

- Ablepsia: lack or loss of vision; blindness.

-Adipocytes: cells that store fat and regulate body temperature. These are cells that are part of adipose tissue.

-Adhesion: ability to adhere to a surface

-Ataxia: impaired coordination

-Alloreactivity: related to rejection of allogeneic transplants (from different individuals, but of the same species).

B

-Blastocyst: We call blastocyst the set of embryonic structures that includes blastocytes, primordial cells of the embryo and embryonic annexes, the blastocoel, the cavity that divides these two cell types, and the zona pellucida of the ovum, primarily responsible for keeping these cells together. .

-Blastomers: structure that results from the division of the fertilized egg during embryonic development. Cells resulting from the segmentation of the fertilized egg. Ç

- Cytokines: are proteins that have the function of signaling, mediating cellular functions. They are produced by innate and adaptive immunity in a brief and self-limiting manner, which only occurs in response to antigens. They are agents secreted by one type of immune cell that stimulates another type of cell. Cytokines are proteins with diverse activities such as mediating immune and inflammatory responses; acting on various types of cells; acting on mRNA synthesis processes.

-Cytotoxic: able to destroy certain cells

- Cerebellum: region of the brain whose function is to control voluntary body movements, posture, motor learning, balance and muscle tone.

-Natural Killer Cells: or NK (Natural Killer) cells are defense cells of the innate immune system that have the function of recognizing cells foreign to the body, cells infected by viruses or with some type of alteration that can lead to the emergence of cancer, actively participating in the immune surveillance mechanism.

- Dendritic cells: are cells that express receptors that recognize molecules produced by microorganisms and respond with the production of cytokines and in response to activation by pathogens become motile, migrate to lymph nodes and present antigens to T lymphocytes, being a type of antigen-presenting cell.

-T cells: same as T lymphocyte

-B cells: same as B lymphocyte

-Chondroblasts: Chondroblasts are cells that secrete collagen, mainly type II, and the ground substance (proteoglycans, glycosaminoglycans and adhesion glycoproteins, such as chondronectin. They are cells of cartilaginous tissue. D

-Walking: simply means walking, walking.

- Demyelination: for example, a demyelinating disease is any disease in the brain or spinal cord in which an inflammation-like change occurs in the myelin sheath of the nerves – hence the term demyelination.

-Differentiation: In developmental biology, differentiation is the process in which living cells

"specialize", generating a cellular diversity capable of performing certain functions.
E
- Erythrocyte: or erythrocyte lineage, it is the one that will develop red blood cells or erythrocytes.
- Stromal: Stromal cells are connective tissue cells. The most common types are fibroblasts, immune cells, pericytes, endothelial cells, and inflammatory cells.
- Encephalitis: Inflammation of the brain, usually because of an infection. Eosinophilic:
F
-Fibroblasts: have the function of synthesizing connective tissue fibers and matrix proteoglycans and glycoproteins.
- Biphasic fever: two-phase fever, intermittent fever. H
-Hematopoietic: relating to hematopoiesis, which is the process of formation, development and maturation of blood elements (erythrocytes, leukocytes and platelets) from a common, undifferentiated cell precursor called a hematopoietic cell or stem cell
-Hyperesthesia: tendency to transform ordinary sensations into painful sensations.
-Hypoimmunogenic: relative to which a low immune response develops.
-Hyperkeratosis: is the thickening of the stratum corneum (the outermost layer of the epidermis), often associated with the presence of an abnormal amount of keratin and also usually accompanied by an increase in the granular layer.
-Hippocampal: relating to the hippocampus, which is an important part of the limbic system, a cortical region that regulates motivation, emotion, learning, and memory. I
-Undifferentiated: consists of a cell that does not yet have a specific biological function and specific tissue structure.
-Intrathecal: intrathecal or subarachnoid route, it is an administration route that consists of injecting substances into the spinal canal, directly into the subarachnoid space, thus avoiding the blood-brain barrier, thus acting on the nervous system.
-In vivo: In vivo (Latin: within the vivo) means "that takes place or takes place within an organism or in living tissue." In science, in vivo refers to experimentation done within or on the living tissue of a living organism.
-In vitro: In vitro is a Latin expression that designates all biological processes that take place outside living systems, in the controlled and closed environment of a laboratory and which are normally carried out in glass containers.
L
- Leukocytes: also known as white blood cells, they are the cells responsible for defending the body against infections, diseases, allergies and colds.
-Leukopenia: Leukopenia is considered to be the total white blood cell count below the lower limit of normal for the population.
-Leukocytosis: When white blood cells are above the normal range, this is called leukocytosis.
- Lymphopenia: is defined as a total lymphocyte count below the reference limit.
-B lymphocytes: they are responsible for a defense modality called Humoral Immunity. They do not form clones. Each time they detect the presence of agents with foreign antigens, initially transform into larger cells called plasmoblasts. These then go on to form hundreds of cells called plasma cells.
-T lymphocytes: The main functions of T lymphocytes include the activation of phagocytes, killing infected cells and helping B cells. That is, these functions require them to interact with

other cells, which can be phagocytes, the infected host cells , or B lymphocytes.
- Ligands: a ligand is defined as any molecule or atom that binds irreversibly to a receptor protein molecule, if not known as a receptor.
-Lymphoid: Cells of the lymphoid lineage include B lymphocytes, T lymphocytes and NK ("natural killer") cells.
M
-Megakaryocytic: either megakaryocytic lineage or megakaryocytic lineage, will give rise to platelets.
-Myelin: is a structure formed by a lipid membrane rich in glycophospholipids and cholesterol, and covers the axons, facilitating rapid communication between neurons.
-Myoclonus: refers to rapid and sudden spasms (twitches) in a muscle or group of muscles.
-Multisystem: relative that affects several body systems, such as lymphatic, musculoskeletal and nervous systems.
-Multifocal: or multiple focuses
-Multipotent: like multipotent stem cells, which, unlike the others, can differentiate into only a few cell types. This type of cell is most easily found in our body and is responsible for the renewal of certain organs.
No
-Neurons: These are the cells responsible for transmitting nerve impulses. They are basically made up of three structures: a cell body, dendrites and axons.
-Neuroaxis: composed of brain and spinal cord
O
-Osteoblasts: osteoblasts are young cells with intense metabolic activity and responsible for the production of the organic part of the bone matrix, composed of type I collagen, glycoproteins and proteoglycans. ... They are cubic or cylindrical and are found on the surface of the periosteum bone (thin membrane that covers the bone).
P
-Pyrexia: the same as fever
-Immune-mediated plate:
-Plasmocyte: Correspond to active B lymphocytes (antibody production)
- Pluripotent: are cells capable of transforming into any cell type of an adult individual, with the exception of extra-embryonic tissues.
-Polioencephalomalacia: or (PEM) is a descriptive term that designates the morphological diagnosis for necrosis with softening (malacia) of the gray matter (polio) of the brain.
-Potentiality: is the ability of the cell to originate other cell types. Q
-Chemokines: form a large family of small cytokines, generally of low molecular weight, ranging from 7 to 15kDa. Chemokines and their receptors are able to control the migration and residence of all immune cells.
s
-Systemic: able to affect the whole organism.
-Subarachnoid: Arachnoid-mater + pia-mater interface ("subarachnoid space"), the only real space that contains LCS (cerebrospinal fluid), trabecular cells, arteries and veins and that manifests normally, without the need for bloody collection.
T

-Embryonic tissue: The embryonic layer, also called the germ layer, is an embryonic tissue responsible for the origin of the organs and tissues of adult animals.
-Extra-embryonic tissue: or extra-embryonic structures, the amniotic cavity, the amnion, the yolk sac, the connecting stalk and the chorionic sac.
-Trofectoderm: cellular layer that externally delimits the blastocyst, is responsible for the formation of the embryonic annexes, that is, the tissues of maternal-fetal communication.
-Totipotent: Totipotent stem cells: they are capable of forming cells from any tissue in the body, including embryonic and extraembryonic tissues. It is often said that this type of cell is capable of originating an entire organism.
- Brainstem: The brainstem or brainstem is situated between the spinal cord and the brain. It is the area of the CNS responsible for controlling blood pressure, swallowing, breathing and heartbeat. The brainstem has three portions: the medulla oblongata, the pons (bulge), and the midbrain.