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61 MANAGEMENT OF AIRWAY REMODELING IN A MURINE MODEL OF ALLERGIC AIRWAY INFLAMMATION USING EXTRACELLULAR VESICLES FROM HUMAN BONE MARROW-DERIVED MESENCHYMAL STEM CELLS
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The aim of this study was to evaluate the therapeutic potential of extracellular vesicles (EV) derived from human bone marrow mesenchymal stem cells (MSCs), administered by intratracheal (IT) or systemic injection (S), to treat ovalbumin (OVA)-induced asthmatic Balb/C mice. This study was approved by Ethics Committee (number: 34309914.0.0000.0020) and Ethics Committee on Animal Use (number: 904). Forty-three male Balb/C mice were divided in four groups: control (C, n=11); asthmatic (AS, n=11); intratracheal treatment (EV-IT, n=10) and systemic treatment (EV-S, n=11). AS, EV-IT and EV-S groups were submitted to asthma induction by intraperitoneal injections of OVA (10µg in 100µL) at days 0, 2, 4, 7, 9 and 10. Then these animals received by IT injections OVA (20µg in 20µL) as allergenic challenge at days 15, 18 and 21. C group received sterile saline at these days. At day 22, animals were treated with EVs either locally (EV-IT) or intravenously (EV-S), while C and AS groups received sterile saline. Seven days after treatment, we performed bronchoalveolar lavage (BAL) to count total nuclear cells. The animals were euthanized using anesthetic overdose, and lungs were collected for histopathological analysis (HE, MT and PAS staining). It was performed a semi-quantitative analysis in 30 bronchioles/animal scoring for different parameters (presence and intensity of inflammatory infiltrate, epithelial and smooth muscle layer thickening, mucus production, collagen deposition). Data were analyzed using Kruskal-Wallis test followed by Dunn’s test for multiple comparisons, considering significant P<0.05. EV-IT group showed significant improvement in the evaluated criteria of presence and intensity of inflammatory infiltrate, epithelial and smooth muscle cell layer thickening, mucus production, collagen and deposition, as well as a reduction in total BAL cells, in comparison with AS group. EV-S group showed reduction only in total cell count in BAL fluid. In conclusion, the local application of EVs derived from hBM-MSCs is effective in controlling asthma.

62 MATERNAL OBESITY NEGATIVELY IMPACT HEART DEVELOPMENT IN OFFSPRING
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Background: The development of the heart is a sensitive and dependent process of stem cells present during its maturation. Changes in the population of these cells through modifications in the intracellular environment due to a metabolic program, such as during pregnancy of obese women is something of concern. It is estimated that 30% of pregnant women are obese and that 40% of these women gain excessive weight during pregnancy. Thus, the objective of this work is to analyze the impacts of maternal obesity on the heart of the offspring in neonate Swiss mice.

Methods: After birth, litters were adjusted to nine pups and divided into overfeeding Group - nine pups until the 3rd day, when the litter was reduced to three female pups, and control Group with nine pups. Three months old females of both groups were mated to healthy males and their offspring were euthanized at the day of birth, resulting in the Offspring Control Group (OCG) and Offspring Overfed Group (OOG). Biometric parameters were analyzed, and fragments of the heart were used to analyze fibrosis by Picro-Sirius Red staining and to analyze the population of c-kit and sca-1 cells. The results were expressed as mean ± SEM, analyzed by t-student test.

Results: OOG showed, at birth, 25% increased body mass compared to OCG. However, there was no difference in naso-anal length between groups, reflecting an increase of 93% in the Lee Index of OOG compared to OCG. Although the cardiac mass was 35% decreased in OOG, the analysis of collagen deposition in the heart showed an increased interstitial fibrosis (16%) in this group compared to the OCG. In addition, the quantification of cardiac stem cells demonstrated an increase of 229% in the c-kit+ cells and an increase of 218% in the sca+1 cells when compared to the OCG.

Conclusion: Together, results demonstrate that maternal metabolic programming negatively impacts offspring at birth, altering cardiac development, making the heart more immature at birth, as well as increasing adverse remodeling, which may be related to the development of cardiovascular diseases in adulthood.

63 MESENCHYMAL STEM CELL THERAPY FOR ACUTE KIDNEY DISEASE IN A CAT – CASE REPORT
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Background: Mesenchymal stem cells (MSCs) are attracted to the inflammatory microenvironment, where they act by producing cytokines and growth factors, which provide the immunomodulatory properties and can assist in the recovery of damaged tissue in cases of acute and chronic kidney disease. In this case report, the response of an animal with acute kidney disease to treatment with adipose tissue-derived MSC (ADSC) was evaluated.

Methods: A cat diagnosed with acute kidney disease – 14.29 mg/dL of creatinine and 402 mg/dL of urea – was conducted to BIO CELL Cell Therapy to receive the treatment with mesenchymal stem cells. Four applications of ADSC by intravenous route, with 21 days of interval, were performed. Quantification of creatinine and urea in the animal’s blood was performed 7 days after the second application to verify the animal’s response to treatment. The exams were repeated after 1 year.

Results: The animal showed an improvement in the clinical signs and in the evaluated exams. Clinically, the animal returned to eat, drink water and gained weight. In the initial exams, before cell therapy, the animal presented creatinine of 14.29 mg/dL and urea of 402 mg/dL, but between the applications, the parameters stabilized at 5.28 mg/dL of creatinine and 127.7 mg/dL of urea. One year after treatment, exams showed that the parameters improved to 2.74 mg/dL of creatinine and 171.00 mg/dL of urea. The values were still above the reference value between the applications, the parameters stabilized at 5.28 mg/dL of creatinine and 127.7 mg/dL of urea. The values were still above the reference value from 0.5 to 1.5 mg/dL of creatinine and 10 to 75 mg/dL of urea), but the animal showed clinical improvement, returning to eat, with no renal alteration observed in ultrasound even after 1 year of treatment.

Conclusion: Treatment with ADSC helped in the recovery of the animal’s kidneys, as demonstrated in the creatinine and urea values, demonstrating to be a promising therapy for acute renal disease. However, more clinical studies should be performed to evaluate the best protocol for this disease.
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**Background:** COVID-19 is an infectious disease characterized by a strong inflammatory response in severe cases. Treatment is limited, and mortality has surpassed 2.4 million deaths as in February, 2021. Therefore, several different therapeutic strategies are being investigated, including the use of mesenchymal stem cells (MSCs). Our group has previously published an analysis of the world-wide effort to investigate the use of stem cells for COVID-19 in July 2020 (Saldana-Nara-Araujo, 2020). Here, we provide an update to such a compendium of clinical trials.

**Methods:** Using the terms “COVID-19” and “stem cells”, we searched studies in the ClinicalTrials.gov database, the World Health Organization’s International Clinical Trials Registration Platform, and the European Union Registry of Clinical Trials in June 2020 and February 2021.

**Results:** A total of 119 clinical studies was considered, among which 99 studies aim to investigate the therapeutic efficacy of MSCs and derivatives in the treatment of COVID-19. The country with the higher number of studies was China. The most frequent tissue sources of MSCs were: umbilical cord, Wharton’s jelly, bone marrow, and adipose tissue. Six studies used MSC-derived exosomes. Most studies chose the intravenous route for cell therapy administration, but the inhalation route was also observed. Cell doses ranged between 0.5 × 10^6 and 1 × 10^7 cells/kg. Number of doses varied from 1 to 20 (twice/day inhalation for 10 days). Most studies are still in the recruitment process, and 2 have completed their studies and published their data. Several studies failed to describe MSC tissue source, administration route, and/or study phase.

**Conclusion:** Taken together, the present data reveals that stem cells and stem cell-derived strategies are still experimental therapies for COVID-19 treatment. Since July 2020, only one new scientific manuscript has been published describing clinical results from stem cell therapy for COVID-19. Similar to July 2020, published studies show that 51 patients received stem cell and stem cell-derived therapies and support the notion that the procedure is safe and effective in the short term for severe and critically ill patients. Long term follow-up and optimization of therapeutic regimen are still needed. The lack of complete detailed data from published studies are a challenge and compromise any further conclusions at this point.

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**65 MESENCHYMAL STEM CELLS FOR SCLERODERMA-LIKE GRAFT VERSUS HOST DISEASE: A CASE SERIES**

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**Background:** Refractory chronic GVHD (cGVHD) is a common and highly lethal complication after allogeneic hematopoietic stem cell transplantation (HSCT). Cutaneous manifestations of this disease, such as scleroderma, strongly decrease quality of life. Mesenchymal Stem Cells (MSCs) expanded in vitro are involved in modulating immune responses in vivo, as well as tissue repair.

**Methods:** three patients with scleroderma-like severe chronic steroid-refractory GVHD were infused with 2 × 10^6 MSCs/KG of body weight divided in two doses. The MSCs were obtained from the bone marrow of non-matched donors. The patients were followed up through clinical and laboratory exams.

**Results:** All three patients showed complete response to treatment, with full recovery and no remaining sign of the disease. Mobility was significantly improved. One patient discontinued use of all immunosuppressive agents. All patients survived. Response lasted up to 311, 470 and 1792 days since infusion. Survival lasted 1737, 1329 and 3504 days.

**Conclusion:** Bone marrow-derived Mesenchymal stem cells was safe and effective treatment for scleroderma-like steroid-resistant chronic GVHD for these patients and should be evaluated in larger prospective trials.

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**66 MESENCHYMAL STEM CELLS OF THE CANINE UMBILICAL CORD: ISOLATION, CHARACTERIZATION AND CLINICAL EVALUATION IN DOGS WITH NEUROLOGICAL SEQUELS OF DISTEMPER**

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**Background:** Distemper is a viral multisystem disease that affects dogs of all ages. So far, there are only palliative treatments and the consequence of the disease is decreasing the quality of life of the animals and in more severe cases is euthanasia. Mesenchymal stem cells (MSCs) are potential candidates for the treatment of distemper due mainly to their immunomodulatory and anti-inflammatory characteristics. Although the most explored source for the isolation of MSC in dogs is the adipose tissue, the collection results in invasive procedures, and the cells may be influenced by the age and physical conditions of the donor, so there is great interest in seeking alternative sources of MSC. Our objectives are to validate and define an optimized isolation protocol for canine umbilical cord MSCs for application in dogs diagnosed with neurological sequel of distemper.

**Methods:** The umbilical cords obtained in elective cesarean sections were processed according to the following protocols: Group 1 - 1 hour in collagenase 1 mg/ml, group 2 - 1 hour in trypsin 0.125% + 1 hour in collagenase 1 mg/ml, and group 3 - tissue explants. Following isolation, the cells were cultured in the same way, in DMEM culture medium, and a CO2 incubator at 37°C. After cultivation, the groups were subjected to evaluation of specific membrane markers by flow cytometry (CD90, CD44, CD29, CD45, CD34, CD14, and HLA-DR). Later in this project, we will carry out cell differentiation tests and the therapeutic evaluation will be carried out through the transplantation of umbilical cord MSCs in dogs diagnosed with neurological sequel of distemper.

**Results:** Using the same amount of starting material, groups 1 and 2 showed more adhered cells (at least ten times greater) than group 3, in addition to having greater expansion capacity along the passages. Groups 1 and 2 were similar in the number of cells obtained, with group 2 showing more homogeneous morphology from passage 2. In a preliminary study of membrane markers by cytometry, we observed that groups 1 and 2 show expression of the characteristic markers of MSC, however, group 1 showed a greater number of cells positive for CD90 and CD44 and negative for CD34 and HLA-DR.

**Conclusions:** So far, we have observed that the canine umbilical cord is a very relevant source of MSC, and that isolation by enzymatic methods is more effective than obtaining by explants.

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**67 MESENCHYMAL STROMAL CELLS FROM DIFFERENT EMBRYONIC ORIGINS SHOWED DISTINGUISHED GENE EXPRESSION BEFORE AND AFTER NEURONAL DIFFERENTIATION INDUCTION**

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