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Stem Cell

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Stem Cell and COVID-19 Research Literatures

Dr. Mark Herbert

World Development Institute
39 Main Street, Flushing, Queens, New York 11354, USA, ma708090@gmail.com

Abstract: Stem cells are derived from embryonic and non-embryonic tissues. Most stem cell studies are for animal stem cells and plants have also stem cell. Stem cells were discovered in 1981 from early mouse embryos. Stem cells have the potential to develop into all different cell types in the living body. Stem cell is a body repair system. When a stem cell divides it can be still a stem cell or become adult cell, such as a brain cell. Stem cells are unspecialized cells and can renew themselves by cell division, and stem cells can also differentiate to adult cells with special functions. Stem cells replace the old cells and repair the damaged tissues. Embryonic stem cells can become all cell types of the body because they are pluripotent. Adult stem cells are thought to be limited to differentiating into different cell types of their tissue of origin. This article introduces recent research reports as references in the related studies.
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Key words: stem cell; COVID-19; life; research; literature

Introduction

The stem cell is the origin of an organism's life that has the potential to develop into many different types of cells in life bodies. In many tissues stem cells serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a red blood cell or a brain cell. This article introduces recent research reports as references in the related studies.

The following introduces recent reports as references in the related studies.

Abbaspanah, B., et al. (2021). "Stem Cell Therapy: A Promising Approach in Treatment of COVID-19." Curr Stem Cell Res Ther **16**(4): 406-413.

COVID-19 pandemic is a global health crisis of the 21st Century. There are currently no approved vaccines and no particular anti-viral treatment for coronavirus disease. As COVID-19 has a broad range of illnesses, it is necessary to find a safe and effective therapeutic method for COVID-19. An attractive approach for treating COVID-19 is cell therapy. Cell therapy aims to inject new and healthy stem cells into a patient's body, to repair the damaged cells and tissues. Stem cell therapy is one of the most studied and important approaches in the treatment of COVID-19 these days. The significant clinical outcome was observed by the adoptive transfer of stem cells, specifically mesenchymal stem cells. This study reviews the characteristics of stem cells and clinical trials that have used stem cells in treating COVID-19.

Abdelgawad, M., et al. (2021). "Mesenchymal stem cell-based therapy and exosomes in COVID-19: current trends and prospects." Stem Cell Res Ther **12**(1): 469.

Novel coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2. The virus causes an exaggerated immune response, resulting in a cytokine storm and acute respiratory distress syndrome, the leading cause of COVID-19-related mortality and morbidity. So far, no therapies have succeeded in circumventing the exacerbated immune response or cytokine storm associated with COVID-19. Mesenchymal stem cells (MSCs), through their immunomodulatory and regenerative activities, mostly mediated by their paracrine effect and extracellular vesicle production, have therapeutic potential in many autoimmune, inflammatory, and degenerative diseases. In this paper, we review clinical studies on the use of MSCs for COVID-19 treatment, including the salutary effects of MSCs on the pathophysiology of COVID-19 and the immunomodulation of the cytokine storm. Ongoing clinical trial designs, cell sources, dose and administration, and populations are summarized, and the paracrine mode of benefit is discussed. We also offer suggestions for optimizing MSC-based therapies, including genetic engineering, strategies for cell surface modification, nanotechnology applications, and combination therapies.

Adas, G., et al. (2021). "The Systematic Effect of Mesenchymal Stem Cell Therapy in Critical COVID-

19 Patients: A Prospective Double Controlled Trial." Cell Transplant **30**: 9636897211024942.

The aim of this clinical trial was to control the cytokine storm by administering mesenchymal stem cells (MSCs) to critically-ill COVID-19 patients, to evaluate the healing effect, and to systematically investigate how the treatment works. Patients with moderate and critical COVID-19 clinical manifestations were separated as Group 1 (moderate cases, n = 10, treated conventionally), Group 2 (critical cases, n = 10, treated conventionally), and Group 3 (critical cases, n = 10, treated conventionally plus MSCs transplantation therapy of three consecutive doses on treatment days 0, 3, and 6, (as 3 x 10(6) cells/kg, intravenously). The treatment mechanism of action was investigated with evaluation markers of the cytokine storm, via biochemical parameters, levels of proinflammatory and anti-inflammatory cytokines, analyses of tissue regeneration via the levels of growth factors, apoptosis markers, chemokines, matrix metalloproteinases, and granzyme-B, and by the assessment of the immunomodulatory effects via total oxidant/antioxidant status markers and the levels of lymphocyte subsets. In the assessment of the overall mortality rates of all the cases, six patients in Group-2 and three patients in Group-3 died, and there was no loss in Group-1. Proinflammatory cytokines IFNgamma, IL-6, IL-17A, IL-2, IL-12, anti-inflammatory cytokines IL-10, IL-13, IL-1ra, and growth factors TGF-beta, VEGF, KGF, and NGF levels were found to be significant in Group-3. When Group-2 and Group-3 were compared, serum ferritin, fibrinogen and CRP levels in Group-3 had significantly decreased. CD45 +, CD3 +, CD4 +, CD8 +, CD19 +, HLA-DR +, and CD16 + / CD56 + levels were evaluated. In the statistical comparison of the groups, significance was only determined in respect of neutrophils. The results demonstrated the positive systematic and cellular effects of MSCs application on critically ill COVID-19 patients in a versatile way. This effect plays an important role in curing and reducing mortality in critically ill patients.

Agrawal, N., et al. (2021). "Outcomes of COVID-19 in Hematopoietic Stem Cell Transplant Recipients: Multicenter Retrospective Analysis." Indian J Hematol Blood Transfus: 1-6.

COVID-19, caused by the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization on March 9, 2020. Hematopoietic stem-cell transplantation (HSCT) recipients may be highly susceptible to infection and related pulmonary complications due to nascent immune systems or organ damage from treatment-related toxicities. Poor outcomes in such group of patients were linked to older age, steroid therapy at the time of COVID-19 infection, and COVID-19 infection within a year of HSCT. We studied a cohort of 28 hematopoietic stem cell transplant recipients (male 17, M:F ratio of 1.5) with COVID-19 infection from 1st June 2020, through 31st December 2020 for outcome. Fever was the most common symptom at the time of presentation in 22 (78.5%) patients. Mortality rate at Day 28 and Day 42 was found to be 4/28 (14.3%) and 7/28 (25%) respectively. Patients within one year of HSCT and severe infection had higher day 28 mortality (with p values = 0.038)". There was no relation of mortality with type of transplant.

Ahmad Mulyadi Lai, H. I., et al. (2021). "Expression of Endogenous Angiotensin-Converting Enzyme 2 in Human Induced Pluripotent Stem Cell-Derived Retinal Organoids." Int J Mol Sci **22**(3).

Angiotensin-converting enzyme 2 (ACE2) was identified as the main host cell receptor for the entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its subsequent infection. In some coronavirus disease 2019 (COVID-19) patients, it has been reported that the nervous tissues and the eyes were also affected. However, evidence supporting that the retina is a target tissue for SARS-CoV-2 infection is still lacking. This present study aimed to investigate whether ACE2 expression plays a role in human retinal neurons during SARS-CoV-2 infection. Human induced pluripotent stem cell (hiPSC)-derived retinal organoids and monolayer cultures derived from dissociated retinal organoids were generated. To validate the potential entry of SARS-CoV-2 infection in the retina, we showed that hiPSC-derived retinal organoids and monolayer cultures endogenously express ACE2 and transmembrane serine protease 2 (TMPRSS2) on the mRNA level. Immunofluorescence staining confirmed the protein expression of ACE2 and TMPRSS2 in retinal organoids and monolayer cultures. Furthermore, using the SARS-CoV-2 pseudovirus spike protein with GFP expression system, we found that retinal organoids and monolayer cultures can potentially be infected by the SARS-CoV-2 pseudovirus. Collectively, our findings highlighted the potential of iPSC-derived retinal organoids as the models for ACE2 receptor-based SARS-CoV-2 infection.

Ahmad, N., et al. (2020). "Impact of Covid19 on a tertiary care pediatric oncology and stem cell transplant unit in Riyadh, Saudi Arabia." Pediatr Blood Cancer **67**(9): e28560.

Aitong, W., et al. (2021). "Visualized analyses of investigations upon mesenchymal stem/stromal cell-based cytotherapy and underlying mechanisms for COVID-19 associated ARDS." Curr Stem Cell Res Ther.

The outbreak of coronavirus disease 2019 (COVID-19) triggered by severe acute respiratory

syndrome coronavirus 2 (SARS-CoV-2) has become a widespread pandemic globally and seriously threatened the public health. Patients with COVID-19 infection, and in particular, those with severe pneumonia-associated acute respiratory distress syndrome (ARDS) manifested rapid disease progression and the resultant high mortality and morbidity. Advances in fundamental and clinical studies have suggested the feasibility of mesenchymal stem/stromal cell (MSC)-based therapy as an inspiring alternative for ARDS administration. However, the systematic characteristics of the MSC-based cytotherapy and underlying mechanism for COVID-19 associated ARDS by bibliometric analyses are still unknowable. Herein, we took advantage of visual analyses to reveal the overview of ARDS-associated updates, core authors and focused issues, as well as to summarize the comprehensive knowledge of the keywords, authors, institutions with the aid of indicated software. Meanwhile, we have provided a brief overview on the molecular mechanisms and discussed the safety and efficacy of MSC-based therapy for ARDS on the basis of clinical trials.

Akbari, A. and J. Rezaie (2020). "Potential therapeutic application of mesenchymal stem cell-derived exosomes in SARS-CoV-2 pneumonia." Stem Cell Res Ther **11**(1): 356.

BACKGROUND: The outbreak of a new virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has now become the main health concern all over the world. Since effective antiviral treatments have not been developed until now, SARS-CoV-2 is severely affecting countries and territories around the world. METHODS: At the present review, articles in PubMed were searched with the following terms: mesenchymal stem cells, exosomes, coronavirus, and SARS-CoV-2, either alone or in a combination form. The most relevant selected functions were mesenchymal stem cell-derived exosomes and SARS-CoV-2 virus infection. RESULTS: SARS-CoV-2 could damage pulmonary cells and induce secretion of different types of inflammatory cytokines. In the following, these cytokines trigger inflammation that damages the lungs and results in lethal acute respiratory distress syndrome (ARDS). The main characteristic of ARDS is the onset of inflammation in pulmonary, hyaline formation, pulmonary fibrosis, and edema. Mesenchymal stem cell-derived exosomes (MSC-Exo) are believed to have anti-inflammatory effects and immune-modulating capacity as well as the ability to induce tissue regeneration, suggesting a significant therapeutic opportunity that could be used to SARS-CoV-2 pneumonia treatment. Besides, exosomes may serve as a biomarker, drug delivery system, and vaccine for the management of the patient with SARS-CoV-2. CONCLUSION: MSC-Exo may serve as a promising tool in the treatment of SARS-CoV-2 pneumonia. However, further work needs to be carried out to confirm the efficacy of exosomes in the treatment of SARS-CoV-2 pneumonia.

Akkoc, T. (2020). "COVID-19 and Mesenchymal Stem Cell Treatment; Mystery or Not." Adv Exp Med Biol **1298**: 167-176.

On December 31, 2019, novel SARS-CoV2 spread from Wuhan China to more than 200 territories around world and the World Health Organization declared a COVID-19 pandemic on January 30, 2020. At this time there is no particular therapy, drug or vaccine available to deal with COVID-19. Today actual data indicates that about 17% of closed COVID-19 cases died. Health care professionals, ministry of health in countries and the public are trying to read the runes to see when the COVID-19 pandemic will be over. Although mild cases of COVID-19 can be controlled with antiviral, anti-inflammatory and immunomodulatory treatment, severe cases may need intensive care unit support and ventilation. Cytokine storms cause high inflammatory responses and pneumonia in severe cases. Mesenchymal stem cells are immunomodulatory and they have regenerative capacity. In this sense, mesenchymal stem cells may improve the patient's clinical and immunological response to COVID-19.

Ali, H., et al. (2021). "Safety and Tolerability of SARS-CoV2 Emergency-Use Authorized Vaccines for Allogeneic Hematopoietic Stem Cell Transplant Recipients." Transplant Cell Ther.

The safety and efficacy of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) emergency-use authorized (EUA) vaccines have been confirmed in the general population. However, there are no data on its safety and tolerability or efficacy in recipients of allogeneic hematopoietic stem cell transplant (HCT). We performed this study to identify the incidence of adverse events following SARS-CoV2 EUA vaccines, the incidence of new-onset graft-versus-host disease (GVHD) or worsening of existing GVHD after EUA vaccine administration, and the incidence SARS-CoV2 positivity in vaccinated HCT patients. We retrospectively reviewed 113 HCT patients who received at least one dose of EUA vaccine to describe the safety and tolerability, any impact on GVHD, and the incidence of SARS-CoV2 PCR positivity after vaccination. Patients received either Pfizer (BNT162b2) or Moderna (mRNA-1273) vaccines. Patients were included if they were 18 years or older and had received at least one dose of vaccine in the post-HCT setting. Most patients presented with myalgias/arthralgias (first dose, 7.7%; second dose, 14.6%), fatigue (first dose, 15.4%; second dose, 29.2%), and injection site pain (first dose, 40.4%; second dose, 43.8%). Other side-effects experienced by

patients included nausea, vomiting, diarrhea, headache, and injection-site rash and swelling. Liver function abnormalities occurred in 18.6% of patients. Neutropenia, thrombocytopenia, and lymphopenia occurred in 13.3%, 11.5%, and 8.8% of patients, respectively. Forty percent of patients had active chronic GVHD at the time of vaccination, and worsening chronic GVHD occurred in 3.5% of the patients. New chronic GVHD developed in 9.7% of patients after vaccination. The SARS-CoV2 EUA vaccines were well tolerated in allogeneic HCT recipients.

Alshukairi, A. N., et al. (2021). "Re-infection with a different SARS-CoV-2 clade and prolonged viral shedding in a hematopoietic stem cell transplantation patient." Int J Infect Dis **110**: 267-271.

Immunocompromised patients who have a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection pose many clinical and public health challenges. We describe the case of a hematopoietic stem cell transplantation patient with lymphoma who had a protracted illness requiring three consecutive hospital admissions. Whole genome sequencing confirmed two different SARS-CoV-2 clades. Clinical management issues and the unanswered questions arising from this case are discussed.

Amonoo, H. L., et al. (2021). "Distress in a Pandemic - The Association of the Coronavirus Disease-2019 (COVID-19) Pandemic with Distress and Quality of Life in Hematopoietic Stem Cell Transplantation (HSCT)." Transplant Cell Ther.

BACKGROUND: The global coronavirus disease 2019 (COVID-19) pandemic has drastically disrupted cancer care, potentially exacerbating patients' distress levels. Patients undergoing HSCT may be especially vulnerable to this pandemic stress. However, the associations of the COVID-19 pandemic with distress, fatigue, and QOL are not well understood in this population. METHOD: In a cross-sectional analysis of data from 205 patients undergoing HSCT enrolled in a supportive care trial, we compared baseline pre-HSCT distress (depression, anxiety, and posttraumatic stress disorder [PTSD]) symptoms, fatigue, and QOL between enrollees pre- (i.e., 03/2019-01/2020) and during (i.e., 03/2020-01/2021) the COVID-19 pandemic. We used linear regression models adjusting for sociodemographics and cancer diagnosis to examine the associations between enrollment period and patient-reported outcomes. We used semi-structured qualitative interviews in 20 allogeneic HSCT recipients who were >/=3-months post-HSCT to understand the impact of the COVID-19 pandemic on their recovery post-HSCT. RESULTS: Prior to COVID-19, 124 participants enrolled, while 81 participants enrolled during the pandemic. The cohorts had similar baseline demographics and disease risk factors. In multivariate regression models, enrollment during COVID-19 was not associated with pre-HSCT symptoms of depression, anxiety, PTSD, fatigue, or QOL impairment. COVID-19-era participants reported themes of negative (e.g., increased isolation) and positive (e.g., engagement with meaningful activities) implications of the pandemic on HSCT recovery. CONCLUSIONS: We found no differences in pre-HSCT distress, fatigue or QOL in patients undergoing HSCT prior to or during the COVID-19 pandemic. Patients in early recovery post-HSCT, however, report both negative and positive implications of the COVID-19 pandemic on their lives.

Arjmand, B., et al. (2021). "COVID-19 Pathology on Various Organs and Regenerative Medicine and Stem Cell-Based Interventions." Front Cell Dev Biol **9**: 675310.

Severe acute respiratory syndrome-coronavirus 2, a novel betacoronavirus, has caused the global outbreak of a contagious infection named coronavirus disease-2019. Severely ill subjects have shown higher levels of pro-inflammatory cytokines. Cytokine storm is the term that can be used for a systemic inflammation leading to the production of inflammatory cytokines and activation of immune cells. In coronavirus disease-2019 infection, a cytokine storm contributes to the mortality rate of the disease and can lead to multiple-organ dysfunction syndrome through auto-destructive responses of systemic inflammation. Direct effects of the severe acute respiratory syndrome associated with infection as well as hyperinflammatory reactions are in association with disease complications. Besides acute respiratory distress syndrome, functional impairments of the cardiovascular system, central nervous system, kidneys, liver, and several others can be mentioned as the possible consequences. In addition to the current therapeutic approaches for coronavirus disease-2019, which are mostly supportive, stem cell-based therapies have shown the capacity for controlling the inflammation and attenuating the cytokine storm. Therefore, after a brief review of novel coronavirus characteristics, this review aims to explain the effects of coronavirus disease-2019 cytokine storm on different organs of the human body. The roles of stem cell-based therapies on attenuating cytokine release syndrome are also stated.

Atanackovic, D., et al. (2021). "Anti-SARS-CoV-2 Immune Responses in Patients Receiving an Allogeneic Stem Cell or Organ Transplant." Vaccines (Basel) **9**(7).

Patients after autologous (autoSCT) and allogeneic stem cell transplantation (alloSCT) are at an increased risk of COVID-19-related morbidity and mortality, compounded by an immune system

weakened by the underlying malignancy and prior treatments. Allogeneic transplantation, including stem cell and solid organ transplants, requires intensive immunosuppressive prophylaxis, which may further undermine the development of a protective vaccine-induced anti-viral immunity. Herein, we report on short- and long-term antiviral immune responses in two peri-stem cell transplant recipients and a third patient who received a COVID-19 vaccination after kidney transplantation. Our data indicate that: (1) patients post-alloSCT may be able to mount an anti-COVID-19 immune response; however, a sufficient time interval between transplant and exposure may be of critical importance; (2) alloSCT recipients with preexisting anti-SARS-CoV-2 immunity are at risk for losing protective humoral immunity following transplantation, particularly if the stem-cell donor lacks antiviral immunity, e.g., vaccine-derived immunity; and (3) some post-transplant patients are completely unable to build an immune response to a COVID-19 vaccine, perhaps based on the prophylactic suppression of T cell immunity.

Atsuta, Y. and N. Doki (2021). "[Hematopoietic stem cell transplantation during the COVID-19 pandemic with reference to EBMT recommendation]." Rinsho Ketsueki **62**(2): 106-114.

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread worldwide and was classified as a pandemic by the World Health Organization in March 2020. However, its clinical manifestations and optimal management in immunosuppressed patients, including recipients of hematopoietic stem cell transplantation (HSCT), are unknown. There have been some international guidelines for the management of COVID-19 in HSCT recipients. In this issue, we describe the Japanese real-world clinical condition and careful points, explaining those international guidelines.

Azapira, N., et al. (2021). "Mesenchymal Stem Cell-Derived Extracellular Vesicles: Promising Treatment for COVID-19 Pandemic." Exp Clin Transplant.

The pandemic of severe acute respiratory syndrome coronavirus-2 infection has prompted the urgent need for novel therapeutic approaches, especially for patients in critically severe conditions. To date, the pathogenesis of COVID-19 is not completely understood, and finding an effective new drug is still inconclusive. Mesenchymal stromal cell-derived extracellular vesicles contain large amounts of proteins, messenger RNA, and microRNAs that act as vehicles that transfer the cargo between cells. These nanotherapeutic materials exert anti-inflammatory effects on the immune system, which are necessary for subsidence of acute inflammation and promotion of tissue repair and regeneration. Therefore, the consideration of mesenchymal stromal cell-derived extracellular vesicles as a new, safe, and effective therapeutic approach in the treatment of COVID-19 pneumonia is suggested.

Bacigalupo, A., et al. (2020). "Reducing infectious complications after allogeneic stem cell transplant." Expert Rev Hematol **13**(11): 1235-1251.

INTRODUCTION: Infections remain a significant problem, in patients undergoing an allogeneic hematopoietic stem-cell transplant (HSCT) and efforts have been made over the years, to reduce the incidence, morbidity and mortality of infectious complications. AREAS COVERED: This manuscript is focused on the epidemiology, risk factors and prevention of infections after allogeneic HSCT. A systematic literature review was performed using the PubMed database, between November 2019 and January 2020, with the following MeSH terms: stem-cell transplantation, infection, fungal, bacterial, viral, prophylaxis, vaccines, prevention. The authors reviewed all the publications, and following a common revision, a summary report was made and results were divided in three sections: bacterial, fungal and viral infections. EXPERT OPINION: Different infections occur in the early, intermediate and late post-transplant period, due to distinct risk factors. Improved diagnostic techniques, pre-emtive therapy and better prophylaxis of immunologic complications, have reduced the morbidity and mortality of infections. The role of the gut microbiota is under careful scrutiny and may further help us to identify high-risk patients.

Bagheri, H. S., et al. (2021). "Does the Global Outbreak of COVID-19 or Other Viral Diseases Threaten the Stem Cell Reservoir Inside the Body?" Stem Cell Rev Rep **17**(1): 214-230.

The COVID-19 pandemic has profoundly influenced public health and contributed to global economic divergences of unprecedented dimensions. Due to the high prevalence and mortality rates, it is then expected that the consequence and public health challenges will last for long periods. The rapid global spread of COVID-19 and lack of enough data regarding the virus pathogenicity multiplies the complexity and forced governments to react quickly against this pandemic. Stem cells represent a small fraction of cells located in different tissues. These cells play a critical role in the regeneration and restoration of injured sites. Because of their specific niche and a limited number of stem cells, the key question is whether there are different anti-viral mechanisms against viral infection notably COVID-19. Here, we aimed to highlight the intrinsic antiviral resistance in different stem cells against viral infection. These data could help us to understand the possible viral infections in different stem cells and the activation of specific molecular mechanisms upon viral entrance.

Balashov, D., et al. (2021). "SARS-CoV-2 convalescent plasma therapy in pediatric patient after hematopoietic stem cell transplantation." Transfus Apher Sci **60**(1): 102983.

Immunocompromised patients, including HSCT recipients, may have a poor prognosis after contracting COVID-19 due to the absence of a pathogen-specific adaptive immune response. One of the possible options for severe COVID-19 treatment may be the transfusion of hyperimmune SARS-CoV-2 convalescent plasma. A 9-month-old girl with juvenile myelomonocytic leukemia received an HSCT from a haploidentical donor. On day +99, during routine virologic monitoring, SARS-CoV-2 was detected without any clinical symptoms. On day +144, the child developed a polysegmental bilateral viral pneumonia with 60 % damage to the lung tissue and confirm a positive SARS-Cov-2 results in throat swab. The patient was treated with tocilizumab and three doses of fresh frozen plasma obtained from a SARS-CoV-2 convalescent patient. Therapy with tocilizumab and three doses of fresh frozen plasma was well tolerated. In spite of full resolution of the lung lesions, complete elimination of SARS-CoV-2 has not been achieved 4 months after the first detection, which is due to persistence of secondary immunodeficiency after HSCT and the lack of reconstitution of the adaptive immune response. This case represents a demonstration of an atypical course of COVID-19 and the delayed development of lung lesions, which was most likely associated with the features of the patient's immune status after HSCT. SARS-CoV-2 convalescent plasma in combination with other therapeutic approaches is one of the possible curative options for this clinical situation.

Bamba, C., et al. (2020). "Can mesenchymal stem cell therapy be the interim management of COVID-19?" Drug Discov Ther **14**(3): 139-142.

COVID-19 pandemic has accounted for ~ 4.3 million confirmed cases and ~ 292,000 deaths (till 12(th) May, 2020) across the globe since its outbreak. Several anti-viral drugs such as RNA dependent RNA polymerase inhibitors (remdesivir, favipiravir, ribavirin), protease inhibitors (lopinavir, ritonavir) and drugs targeting endocytic pathway (hydroxychloroquine) are being evaluated for COVID-19 but standard therapeutics yet not available. Severe health deterioration in critically ill patients is characterized by pulmonary edema, severe respiratory distress, cytokine storm and septic shock. To combat cytokine storm, immune-therapy targeting IL-1, IL-2, IL-6 and TNFalpha are being evaluated and one of the promising immune-modulator is the mesenchymal stem cells (MSCs) that can surmount the severity of COVID-19 infections. Recent studies have shown that MSC-therapy significantly dampens the cytokine storm in critically ill COVID-19 patients. This communication endows with the insight of stem cell therapy and summarizes the recent studies on COVID-19 patients.

Barhoom, D., et al. (2021). "Clinical Effects of COVID-19 on Hematopoietic Stem Cell Transplant Outcomes in Pediatric Patients." Exp Clin Transplant **19**(5): 501-507.

Coronavirus disease 2019 is the third zoonotic acute respiratory disease after SARS virus and Middle East respiratory syndrome. Most cases are mild in healthy children. In contrast, the infection is more severe in patients with underlying health conditions. Because there are few posttransplant reports in hematopoietic stem celltransplant patients, here we described COVID19 infection in 4 confirmed cases among pediatric hematopoietic stem cell transplant recipients: 3 boys and 1 girl with a median age of 6 years. Three patients presented with symptoms of lower respiratory tract disease, whereas 1 patient presented with extrapulmonary symptoms without fever or pulmonary involvement. All of the patients were on immunosuppressivedrugs, ie, 1patientforgraft-versus-hostdisease prophylaxis and 3 patients for graft-versus-host disease treatment.Thosewhowerediagnosedwith active graftversus-hostdisease requiredmechanical ventilationand intensive care. Two patients died from multiple organ dysfunction and resistant coinfection, and 1 patient developed pulmonary hypertension and mild cardiomegaly and remained at the hospital for more than 2 months, whereas the patient with no graft-versus-host disease was discharged and recovered. Our findings showed that COVID-19 infection among hematopoietic stem cell transplant recipients may be more severe and associatedwithlong-termhospitalization and complications. Active graft-versus-hostdisease, coinfections, and long-term use of immunosuppressive agents are risk factors for poor outcomes.

Basher, F., et al. (2021). "Aseptic Meningitis after Recovery from SARS-CoV-2 in an Allogeneic Stem Cell Transplant Recipient." Clin Med Insights Case Rep **14**: 11795476211009811.

SARS-CoV-2 emerged as a worldwide pandemic in late 2019 and initially was described as a primary respiratory illness. The clinical manifestations of COVID-19 are now known to encompass nearly all organ systems, including the central nervous system. We present a case of an allogeneic hematopoietic stem cell transplant recipient who recovered from documented SARS-CoV-2 infection and later presented with symptoms of meningitis. While cerebrospinal fluid analysis did not reveal any bacterial or viral etiologies, evidence of an inflammatory state, including ophthalmologic findings of episcleritis, indicate what is

likely the first reported case of aseptic meningitis associated with SARS-CoV-2 infection after initial clinical recovery.

Basiri, A., et al. (2021). "Stem Cell Therapy Potency in Personalizing Severe COVID-19 Treatment." Stem Cell Rev Rep **17**(1): 193-213.

Currently, there are no specific and efficient vaccines or drugs for COVID-19, particularly in severe cases. A wide range of variations in the clinical symptoms of different patients attributed to genomic differences. Therefore, personalized treatments seem to play a critical role in improving these symptoms and even similar conditions. Prompted by the uncertainties in the area of COVID-19 therapies, we reviewed the published papers and concepts to gather and provide useful information to clinicians and researchers interested in personalized medicine and cell-based therapy. One novel aspect of this study focuses on the potential application of personalized medicine in treating severe cases of COVID-19. However, it is theoretical, as any real-world examples of the use of genuinely personalized medicine have not existed yet. Nevertheless, we know that stem cells, especially MSCs, have immune-modulatory effects and can be stored for future personalized medicine applications. This theory has been conjugated with some evidence that we review in the present study. Besides, we discuss the importance of personalized medicine and its possible aspects in COVID-19 treatment, then review the cell-based therapy studies for COVID-19 with a particular focus on stem cell-based therapies as a primary personalized tool medicine. However, the idea of cell-based therapy has not been accepted by several scientific communities due to some concerns of lack of satisfactory clinical studies; still, the MSCs and their clinical outcomes have been revealed the safety and potency of this therapeutic approach in several diseases, especially in the immune-mediated inflammatory diseases and some incurable diseases. Promising outcomes have resulted in that clinical studies are going to continue.

Bauer, L., et al. (2021). "Replication Kinetics, Cell Tropism, and Associated Immune Responses in SARS-CoV-2- and H5N1 Virus-Infected Human Induced Pluripotent Stem Cell-Derived Neural Models." mSphere **6**(3): e0027021.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with a wide variety of neurological complications. Even though SARS-CoV-2 is rarely detected in the central nervous system (CNS) or cerebrospinal fluid, evidence is accumulating that SARS-CoV-2 might enter the CNS via the olfactory nerve. However, what happens after SARS-CoV-2 enters the CNS is poorly understood. Therefore, we investigated the replication kinetics, cell tropism, and associated immune responses of SARS-CoV-2 infection in different types of neural cultures derived from human induced pluripotent stem cells (hiPSCs). SARS-CoV-2 was compared to the neurotropic and highly pathogenic H5N1 influenza A virus. SARS-CoV-2 infected a minority of individual mature neurons, without subsequent virus replication and spread, despite angiotensin-converting enzyme 2 (ACE2), transmembrane protease serine 2 (TMPRSS2), and neuropilin-1 (NPR1) expression in all cultures. However, this sparse infection did result in the production of type III interferons and interleukin-8 (IL-8). In contrast, H5N1 virus replicated and spread very efficiently in all cell types in all cultures. Taken together, our findings support the hypothesis that neurological complications might result from local immune responses triggered by virus invasion, rather than abundant SARS-CoV-2 replication in the CNS. IMPORTANCE Infections with the recently emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are often associated with neurological complications. Evidence suggests that SARS-CoV-2 enters the brain via the olfactory nerve; however, SARS-CoV-2 is only rarely detected in the central nervous system of COVID-19 patients. Here, we show that SARS-CoV-2 is able to infect neurons of human iPSC neural cultures but that this infection is abortive and does not result in virus spread to other cells. However, infection of neural cultures did result in the production of type III interferon and IL-8. This study suggests that SARS-CoV-2 might enter the CNS and infect individual neurons, triggering local immune responses that could contribute to the pathogenesis of SARS-CoV-2-associated CNS disease.

Bergsten, E., et al. (2020). "Stem cell transplantation for children with hemophagocytic lymphohistiocytosis: results from the HLH-2004 study." Blood Adv **4**(15): 3754-3766.

We report the largest prospective study thus far on hematopoietic stem cell transplantation (HSCT) in hemophagocytic lymphohistiocytosis (HLH), a life-threatening hyperinflammatory syndrome comprising familial/genetic HLH (FHL) and secondary HLH. Although all patients with HLH typically need intensive anti-inflammatory therapy, patients with FHL also need HSCT to be cured. In the international HLH-2004 study, 187 children aged <18 years fulfilling the study inclusion criteria (5 of 8 diagnostic criteria, affected sibling, or molecular diagnosis in FHL-causative genes) underwent 209 transplants (2004-2012), defined as indicated in patients with familial/genetic, relapsing, or severe/persistent disease. Five-year overall survival (OS) post-HSCT was 66% (95% confidence interval [CI], 59-72); event-free survival (EFS) was 60% (95% CI, 52-67). Five-year OS was 81% (95% CI, 65-90) for children with a complete response and 59% (95% CI, 48-69) for those

with a partial response (hazard ratio [HR], 2.12; 95% CI, 1.06-4.27; P = .035). For children with verified FHL (family history/genetically verified, n = 134), 5-year OS was 71% (95% CI, 62-78) and EFS was 62% (95% CI, 54-70); 5-year OS for children without verified FHL (n = 53) was significantly lower (52%; 95% CI, 38-65) (P = .040; HR, 1.69; 95% CI, 1.03-2.77); they were also significantly older. Notably, 20 (38%) of 53 patients without verified FHL had natural killer cell activity reported as normal at diagnosis, after 2 months, or at HSCT, suggestive of secondary HLH; and in addition 14 (26%) of these 53 children had no evidence of biallelic mutations despite having 3 or 4 FHL genes analyzed (natural killer cell activity not analyzed after 2 months or at HSCT). We conclude that post-HSCT survival in FHL remains suboptimal, and that the FHL diagnosis should be carefully investigated before HSCT. Pretransplant complete remission is beneficial but not mandatory to achieve post-HSCT survival. This trial was registered at www.clinicaltrials.gov as #NCT00426101.

Beury, D., et al. (2020). "Use of whole-genome sequencing in the molecular investigation of care-associated HCoV-OC43 infections in a hematopoietic stem cell transplant unit." J Clin Virol **122**: 104206.

BACKGROUND: While respiratory viral infections are recognized as a frequent cause of illness in hematopoietic stem cell transplantation (HSCT) recipients, HCoV-OC43 infections have rarely been investigated as healthcare-associated infections in this population. OBJECTIVES: In this report, HCoV-OC43 isolates collected from HSCT patients were retrospectively characterized to identify potential clusters of infection that may stand for a hospital transmission. STUDY DESIGN: Whole-genome and S gene sequences were obtained from nasal swabs using next-generation sequencing and phylogenetic trees were constructed. Similar identity matrix and determination of the most common ancestor were used to compare clusters of patient's sequences. Amino acids substitutions were analysed. RESULTS: Genotypes B, E, F and G were identified. Two clusters of patients were defined from chronological data and phylogenetic trees. Analyses of amino acids substitutions of the S protein sequences identified substitutions specific for genotype F strains circulating among European people. CONCLUSIONS: HCoV-OC43 may be implicated in healthcare-associated infections.

Bulut, O. and G. U. I (2020). "Mesenchymal stem cell derived extracellular vesicles: promising immunomodulators against autoimmune, autoinflammatory disorders and SARS-CoV-2 infection." Turk J Biol **44**(3): 273-282.

Discovery of novel and broad-acting immunomodulators is of critical importance for the prevention and treatment of disorders occurring due to overexuberant immune responseincluding SARS-CoV-2 triggered cytokine storm leading to lung pathology and mortality during the ongoing viral pandemic. Mesenchymal stem/stromal cells (MSCs), highly regarded for their regenerative capacities, also possessesremarkable immunoregulatory functions affecting all types of innate and adaptive immune cells. Owing to that, MSCs have been heavily investigated in clinic for the treatment of autoimmune and inflammatory diseases along with transplant rejection. Extensive research in the last decaderevealed that MSCs carry out most of their functions through paracrine factors which are soluble mediators and extracellular vesicles (EVs). EVs, including exosomes and microvesicles, are an efficient way of intercellular communication due to their unique ability to carry biological messages such as transcription factors, growth factors, cytokines, mRNAs and miRNAs over long distances. EVs originate through direct budding of the cell membrane or the endosomal secretion pathway and they consist of the cytosolic and membrane components of their parent cell. Therefore, they are able to mimic the characteristics of the parent cell, affecting the target cells upon binding or internalization. EVs secreted by MSCs are emerging as a cell-free alternative to MSC-based therapies. MSC EVs are being tested in preclinical and clinical settings where they exhibit exceptional immunosuppressivecapacity. They regulate the migration, proliferation, activation and polarization of various immune cells, promoting a tolerogenic immune response while inhibiting inflammatory response. Being as effective immunomodulators as their parent cells, MSC EVs are also preferable over MSC-based therapies due to their lower risk of immunogenicity, tumorigenicity and overall superior safety. In this review, we present the outcomes of preclinical and clinical studies utilizing MSC EVs as therapeutic agents for the treatment of a wide variety of immunological disorders.

Cai, Q., et al. (2021). "Research Progress of Mesenchymal Stem Cell Therapy for Severe COVID-19." Stem Cells Dev **30**(9): 459-472.

Corona virus disease 2019 (COVID-19) refers to a type of pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Sixty million confirmed cases have been reported worldwide until November 29, 2020. Unfortunately, the novel coronavirus is extremely contagious and the mortality rate of severe and critically ill patients is high. Thus, there is no definite and effective treatment in clinical practice except for antiviral therapy and supportive therapy. Mesenchymal stem cells (MSCs) are not only characterized by low immunogenicity and homing but also have anti-inflammatory and immunomodulation characteristics.

Furthermore, they can inhibit the occurrence and development of a cytokine storm, inhibit lung injury, and exert antipulmonary fibrosis and antioxidative stress, therefore MSC therapy is expected to become one of the effective therapies to treat severe COVID-19. This article will review the possible mechanisms of MSCs in the treatment of severe COVID-19.

Chardon, M. L., et al. (2021). "Family Adjustment to Pediatric Hematopoietic Stem Cell Transplant During COVID-19." J Pediatr Psychol.

OBJECTIVE: The COVID-19 pandemic has been difficult for families across the world due to fears about infection risk, increased social isolation, and significant changes in family roles and routines. Families with a child undergoing pediatric hematopoietic stem cell transplant (HCT) may be at even greater risk for poor adjustment during COVID-19 given their child's increased risk for infection. The purpose of the current study was to qualitatively examine the impact of COVID-19 on family adjustment during pediatric HCT to inform clinical care. METHODS: Twenty-nine caregivers of children (</=12 years) who underwent an HCT within the past 2 years completed semi-structured qualitative interviews and demographic questionnaires in the first 4 months following initial COVID-19 quarantine. RESULTS: Twenty-two themes emerged from the interviews using grounded theory methodology. Although nearly half of caregivers described COVID-19 as a stressor, 69% of caregivers reported adequate adjustment to COVID-19. Caregivers generally attributed their positive adjustment to HCT preparing the family for COVID-19 and more difficult adjustment to increased physical or social isolation and COVID-19 amplifying germ fears. The child's HCT treatment status also had important implications on family adjustment to COVID-19. CONCLUSIONS: Results suggest that families undergoing pediatric HCT are uniquely prepared to cope with the impacts of a global pandemic; however, families experiencing certain risk factors (e.g., more recent transplant, impaired access to social support, reduced access to coping tools) may experience poorer adjustment during pandemics such as COVID-19 and may benefit from increased psychosocial support from their healthcare team.

Chiarucci, M., et al. (2021). "Immunological Response Against SARS-COV-2 After BNT162b2 Vaccine Administration Is Impaired in Allogeneic but Not in Autologous Stem Cell Transplant Recipients." Front Oncol **11**: 737300.

The efficacy of Covid-19 vaccine in hematopoietic stem cell transplantation (HSCT) recipients is still unknown. We planned a prospective study to evaluate the immune response after the administration of Covid-19 vaccine in HSCT recipients. Fifty patients previously submitted to HSCT (38 autologous and 12 allogeneic) received the mRNA-based SARS-CoV-2 vaccine BNT162b2 (Pfizer-BioNTech). Serum samples of all patients were tested for SARS-CoV-2 IgG against the Spike glycoprotein, 30 days after the second dose of vaccine. Antibody response was compared to a control group of 45 healthy subjects. Of the 50 patients tested, 12 did not develop any antibody response, including 6 patients undergoing autologous (16%) and 6 allogeneic HSCT (50%). Cyclosporine administration in allogeneic recipients and prior administration of Rituximab in the autologous setting correlated with lower antibody titers ($p < 0.0003$ and $p=0.000$, respectively). Flow cytometry of peripheral blood samples, performed 30 days after the vaccination, showed a significant correlation between the antibody response to Sars-COV2 and an increased number in CD19+ B lymphocytes ($p = 0.0003$) and CD56+ natural killer (NK) cells ($p = 0.00$). In conclusion, prior Rituximab before autologous HSCT and cyclosporine administration after allogeneic HSCT negatively affected the antibody response to Sars-COV2 vaccine, possibly due to their immunosuppressive action on CD20 +B cells and T cells, respectively. The correlation between seroconversion to Sars-COV2 and higher number of CD19 + B cells and CD56+ NK cells, suggests a central role for B and NK cells in the development of COVID-19 immunity after vaccination with a mRNA-based platform.

Choi, S. W., et al. (2020). "Antiviral activity and safety of remdesivir against SARS-CoV-2 infection in human pluripotent stem cell-derived cardiomyocytes." Antiviral Res **184**: 104955.

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is considered as the most significant global public health crisis of the century. Several drug candidates have been suggested as potential therapeutic options for COVID-19, including remdesivir, currently the only authorized drug for use under an Emergency Use Authorization. However, there is only limited information regarding the safety profiles of the proposed drugs, in particular drug-induced cardiotoxicity. Here, we evaluated the antiviral activity and cardiotoxicity of remdesivir using cardiomyocytes-derived from human pluripotent stem cells (hPSC-CMs) as an alternative source of human primary cardiomyocytes (CMs). In this study, remdesivir exhibited up to 60-fold higher antiviral activity in hPSC-CMs compared to Vero E6 cells; however, it also induced moderate cardiotoxicity in these cells. To gain further insight into the drug-induced arrhythmogenic risk, we assessed QT interval prolongation and automaticity of remdesivir-treated hPSC-CMs using a multielectrode array (MEA). As a result, the data indicated a potential risk of QT

prolongation when remdesivir is used at concentrations higher than the estimated peak plasma concentration. Therefore, we conclude that close monitoring of the electrocardiographic/QT interval should be advised in SARS-CoV-2-infected patients under remdesivir medication, in particular individuals with pre-existing heart conditions.

Choudhery, M. S. and D. T. Harris (2020). "Stem cell therapy for COVID-19: Possibilities and challenges." Cell Biol Int **44**(11): 2182-2191.

Since its eruption in China, novel coronavirus disease (COVID-19) has been reported in most of the countries and territories (>200) of the world with approximately 18 million confirmed cases (as of August 3, 2020). In most of the countries, COVID-19 upsurge is uncontrolled with a significant mortality rate. Currently, no treatment effective for COVID-19 is available in the form of vaccines or antiviral drugs and patients are currently treated symptomatically. Although the majority of the patients develop mild symptoms and recover without mechanical ventilation for respiratory management, severe respiratory illness develops in a significant portion of affected patients and may result in death. While the scientific community is working to develop vaccines and drugs against the COVID-19 pandemic, novel alternative therapies may reduce the mortality rate. Recent use of stem cells for critically ill COVID-19 patients in a small group of patients in China and subsequent Emergency Use Authorization of stem cells by Food and Drug Administration to Global Institute of Stem Cell Therapy and Research and Athersys has created excitement among the medical community. As a result, several clinical trials have been registered using stem cells for COVID-19 treatment that aim to use different cell sources, dosage, and importantly diverse targeted patient groups. In this brief review, the possibilities of stem cell use in COVID-19 patients and relevant challenges in their use have been discussed.

Chouw, A., et al. (2021). "Potency of Mesenchymal Stem Cell and Its Secretome in Treating COVID-19." Regen Eng Transl Med: 1-12.

Abstract: The COVID-19 disease, which is caused by the novel coronavirus, SARS-CoV-2, has affected the world by increasing the mortality rate in 2020. Currently, there is no definite treatment for COVID-19 patients. Several clinical trials have been proposed to overcome this disease and many are still under investigation. In this review, we will be focusing on the potency of mesenchymal stem cells (MSCs) and MSC-derived secretome for treating COVID-19 patients. Fever, cough, headache, dizziness, and fatigue are the common clinical manifestations in COVID-19 patients. In mild and severe cases, cytokines are released hyper-actively which causes a cytokine storm leading to acute respiratory distress syndrome (ARDS). In order to maintain the lung microenvironment in COVID-19 patients, MSCs are used as cell-based therapy approaches as they can act as cell managers which accelerate the immune system to prevent the cytokine storm and promote endogenous repair. Besides, MSCs have shown minimal expression of ACE2 or TMPRSS2, and hence, MSCs are free from SARS-CoV-2 infection. Numerous clinical studies have started worldwide and demonstrated that MSCs have great potential for ARDS treatment in COVID-19 patients. Preliminary data have shown that MSCs and MSC-derived secretome appear to be promising in the treatment of COVID-19. Lay Summary: The COVID-19 disease is an infection disease which affects the world in 2020. Currently, there is no definite treatment for COVID-19 patients. However, several clinical trials have been proposed to overcome this disease and one of them is using mesenchymal stem cells (MSCs) and MSC-derived secretome for treating COVID-19 patients. During the infection, cytokines are released hyper-actively which causes a cytokine storm. MSCs play an important role in maintaining the lung microenvironment in COVID-19 patients. They can act as cell managers which accelerate the immune system to prevent the cytokine storm and promote the endogenous repair. Therefore, it is important to explore the clinical trial in the world for treating the COVID-19 disease using MSCs and MSC-derived secretome.

De la Puerta, R., et al. (2021). "Common seasonal respiratory virus infections in allogeneic stem cell transplant recipients during the SARS-COV-2 pandemic." Bone Marrow Transplant **56**(9): 2212-2220.

The SARS-COV-2 pandemic has led to strict and generalized transmission prevention measures that may have changed the epidemiological landscape of common seasonal respiratory virus (CSRV). Through a prospective CSRV survey program conducted from 2016 onwards in allogeneic stem cell transplant (allo-HSCT) recipients with respiratory symptoms, we aimed to analyze and compare the epidemiology and characteristics of CSRV over three consecutive periods [from February 1 to September 30 of 2018 (P1), 2019 (P2), and 2020 (P3)]. CSRV screening was performed through multiplex PCR assays during the study period. We identified 188 consecutive allo-HSCT recipients with 406 episodes screened for CSRV during the study period, of which 147 developed 300 CSRV. In P1 and P2 we diagnosed 115 (38.3%) and 145 (48.3%) CSRV episodes, respectively, whereas in P3 only 40 (13.3%) episodes were detected ($p < 0.001$). During P3, we observed a reduction of 80.2% in Ev/Rh, 93.3% in RSV, 80% in hIV, 96.3% HPIV, 68.4% in hMPV, 77.7% in ADV, 100% in HBoV, and 53.6% in HCoV as compared to P1 and P2. Consequently, we also observed a decline in absolute numbers of lower

respiratory tract disease (68.1%), co-infections (91.7%), and hospitalizations (72.6%) during P3. We diagnosed SARS-COV-2 in nine allo-HSCT recipients, representing 23% of all CSRV detections in that period. In conclusion, we provide evidence of a significant drop in CSRV circulation during the SARS-COV-2 pandemic in our allo-HSCT recipients, indicating that prevention measures in the general population are highly effective in reducing CSRV prevalence and its complications in immunocompromised patients.

Deffune, E., et al. (2020). "Mesenchymal stem cell (MSc) secretome: A possible therapeutic strategy for intensive-care COVID-19 patients." Med Hypotheses **142**: 109769.

As an emerging global health challenge, COVID-19 requires international knowledge to reach novel possible therapeutic strategies, especially for intensive-care patients. During the early stages of infection, pneumocytes II are the primary infected cells, harming the respiratory system. We have previous evidence in murine models that MSc's secretome can be used to treat pulmonary injuries induced with bleomycin, due to its content: growth factors, extracellular vesicles, and exosomes. We hypothesize and strongly recommend MSc secretome testing and production, in xenofree conditions, to be used as an alternative approach in SARS-Cov-2 patients in critical conditions.

Desai, D. and P. Shende (2021). "Nanoconjugates-Based Stem Cell Therapy for the Management of COVID-19." Stem Cell Rev Rep **17**(1): 231-240.

A potential ability of stem cells (SCs) is to regenerate and repair tissues in the human body by providing great prospects for therapeutic applications in the field of medicine. Currently, SC therapy is used in various conditions like diabetes, neurodegenerative disorders, etc. but faces some limitations like patient biocompatibility and chances of cross-infection. SCs are further modulated with nanoconjugates to overcome such challenges and will offer an advantage in the treatment of COVID-19. This pandemic requires design and development of proper treatment to save the life of human beings. Advancements in SC-based nanoconjugated therapy will open new avenues and create a significant impact in the development of futuristic nanomedicine. It may also emerge as a potential therapy for the management of infection in patients suffering from SARS-CoV-2 and related diseases such as pneumonia and virus-induced lung injuries. Graphical abstract Mechanisms of stem cell-based nanoconjugates for inhibition of replication of corona virus.

Desterke, C., et al. (2021). "Molecular investigation of adequate sources of mesenchymal stem cells for cell therapy of COVID-19-associated organ failure." Stem Cells Transl Med **10**(4): 568-571.

The use of mesenchymal stem cells (MSC) derived from several sources has been suggested as a major anti-inflammation strategy during the recent outbreak of coronavirus-19 (COVID-19). As the virus enters the target cells through the receptor ACE2, it is important to determine if the MSC population transfused to patients could also be a target for the virus entry. We report here that ACE2 is highly expressed in adult bone marrow, adipose tissue, or umbilical cord-derived MSC. On the other hand, placenta-derived MSC express low levels of ACE2 but only in early passages of cultures. MSC derived from human embryonic stem cell or human induced pluripotent stem cells express also very low levels of ACE2. The transcriptome analysis of the MSCs with lowest expression of ACE2 in fetal-like MSCs is found to be associated in particularly with an anti-inflammatory signature. These results are of major interest for designing future clinical MSC-based stem cell therapies for severe COVID-19 infections.

Dorig, P., et al. (2021). "[Future therapeutic strategies for olfactory disorders: electrical stimulation, stem cell therapy, and transplantation of olfactory epithelium-an overview]." HNO **69**(8): 623-632.

Olfactory disorders may be temporary or permanent and can have various causes. Currently, many COVID-19 patients report a reduced or complete loss of olfactory function. A wide range of treatment options have been investigated in the past, such as olfactory training, acupuncture, medical therapy, transcranial magnetic stimulation, or surgical excision of olfactory epithelium, e.g., in severe qualitative smell disorders. The development of a bioelectric nose, e.g., in connection with direct electrical stimulation or transplantation of olfactory epithelium or stem cells, represent treatment options of the future. The basis of these developments and the state of knowledge is discussed in the following work.

Du, J., et al. (2020). "Stem cell therapy: a potential approach for treatment of influenza virus and coronavirus-induced acute lung injury." Stem Cell Res Ther **11**(1): 192.

Acute lung injury (ALI), an increasingly devastating human disorder, is characterized by a multitude of lung changes arising from a wide variety of lung injuries. Viral infection is the main cause of morbidity and mortality in ALI and acute respiratory distress syndrome (ARDS) patients. In particular, influenza virus, coronavirus, and other respiratory viruses circulate in nature in various animal species and can cause severe and rapidly spread human infections. Although scientific advancements have allowed for rapid progress to be made to understand the pathogenesis and develop therapeutics after each viral

pandemic, few effective methods to treat virus-induced ALI have been described. Recently, stem cell therapy has been widely used in the treatment of various diseases, including ALI. In this review, we detail the present stem cell-based therapeutics for lung injury caused by influenza virus and the outlook for the future state of stem cell therapy to deal with emerging influenza and coronaviruses.

Duan, F., et al. (2020). "Modeling COVID-19 with Human Pluripotent Stem Cell-Derived Cells Reveals Synergistic Effects of Anti-inflammatory Macrophages with ACE2 Inhibition Against SARS-CoV-2." Res Sq.

Dysfunctional immune responses contribute critically to the progression of Coronavirus Disease-2019 (COVID-19) from mild to severe stages including fatality, with pro-inflammatory macrophages as one of the main mediators of lung hyper-inflammation. Therefore, there is an urgent need to better understand the interactions among SARS-CoV-2 permissive cells, macrophage, and the SARS-CoV-2 virus, thereby offering important insights into new therapeutic strategies. Here, we used directed differentiation of human pluripotent stem cells (hPSCs) to establish a lung and macrophage co-culture system and model the host-pathogen interaction and immune response caused by SARS-CoV-2 infection. Among the hPSC-derived lung cells, alveolar type II and ciliated cells are the major cell populations expressing the viral receptor ACE2 and co-effector TMPRSS2, and both were highly permissive to viral infection. We found that alternatively polarized macrophages (M2) and classically polarized macrophages (M1) had similar inhibitory effects on SARS-CoV-2 infection. However, only M1 macrophages significantly up-regulated inflammatory factors including IL-6 and IL-18, inhibiting growth and enhancing apoptosis of lung cells. Inhibiting viral entry into target cells using an ACE2 blocking antibody enhanced the activity of M2 macrophages, resulting in nearly complete clearance of virus and protection of lung cells. These results suggest a potential therapeutic strategy, in that by blocking viral entrance to target cells while boosting anti-inflammatory action of macrophages at an early stage of infection, M2 macrophages can eliminate SARS-CoV-2, while sparing lung cells and suppressing the dysfunctional hyper-inflammatory response mediated by M1 macrophages.

Easdale, S., et al. (2021). "Serologic Responses following a Single Dose of SARS-Cov-2 Vaccination in Allogeneic Stem Cell Transplantation Recipients." Transplant Cell Ther **27**(10): 880 e881-880 e884.

Immunocompromised individuals were not included in formal trials of SARS-CoV-2 mRNA vaccines. Subsequent studies in patients with hematologic malignancies and solid organ transplantation recipients suggest inferior responses to vaccination. We determined antibody responses to a single dose of vaccines in one of the most vulnerable patient groups, allogeneic hematopoietic cell transplantation (allo-HCT) recipients. Pfizer-BioNTech (PB) or AstraZeneca (AZ) SARS-CoV-2 vaccines were administered at least 3 months post-transplantation to 55 adult allo-HCT recipients. We found that older age and concurrent use of immunosuppressive medications were significantly associated with lack of antibody response to vaccination. Only 21% of patients on systemic immunosuppression mounted a response, compared with 58% of patients not on immunosuppression (P = .006). We also show that responses to the AZ vaccine may be superior to responses to the PB vaccine in this cohort. These findings highlight the need for novel immunogenic vaccine formulations and schedules in these highest-risk patients, as well as continued public healthy safety measures to protect the most vulnerable members of our society.

Ebrahimi, M., et al. (2021). "The critical role of mesenchymal stromal/stem cell therapy in COVID-19 patients: An updated review." Cell Biochem Funct.

New coronavirus disease 2019 (COVID-19), as a pandemic disaster, has drawn the attention of researchers in various fields to discover suitable therapeutic approaches for the management of COVID-19 patients. Currently, there are many worries about the rapid spread of COVID-19; there is no approved treatment for this infectious disease, despite many efforts to develop therapeutic procedures for COVID-19. Emerging evidence shows that mesenchymal stromal/stem cell (MSC) therapy can be a suitable option for the management of COVID-19. These cells have many biological features (including the potential of differentiation, high safety and effectiveness, secretion of trophic factors and immunoregulatory features) that make them suitable for the treatment of various diseases. However, some studies have questioned the positive role of MSC therapy in the treatment of COVID-19. Accordingly, in this paper, we will focus on the therapeutic impacts of MSCs and their critical role in cytokine storm of COVID-19 patients.

Ernzen, K., et al. (2021). "Human Stem Cell Models of SARS-CoV-2 Infection in the Cardiovascular System." Stem Cell Rev Rep.

The virus responsible for coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has infected over 190 million people to date, causing a global pandemic. SARS-CoV-2 relies on binding of its spike glycoprotein to angiotensin-converting enzyme 2 (ACE2) for infection. In addition to fever, cough, and shortness of breath, severe cases of SARS-CoV-2 infection may result in the rapid overproduction of pro-

inflammatory cytokines. This overactive immune response is known as a cytokine storm, which leads to several serious clinical manifestations such as acute respiratory distress syndrome and myocardial injury. Cardiovascular disorders such as acute coronary syndrome (ACS) and heart failure not only enhance disease progression at the onset of infection, but also arise in hospitalized patients with COVID-19. Tissue-specific differentiated cells and organoids derived from human pluripotent stem cells (hPSCs) serve as an excellent model to address how SARS-CoV-2 damages the lungs and the heart. In this review, we summarize the molecular basis of SARS-CoV-2 infection and the current clinical perspectives of the bidirectional relationship between the cardiovascular system and viral progression. Furthermore, we also address the utility of hPSCs as a dynamic model for SARS-CoV-2 research and clinical translation.

Esagian, S. M., et al. (2021). "Challenges of Hematopoietic Stem Cell Transplantation in the Era of COVID-19." Exp Clin Transplant.

The coronavirus disease 2019 (COVID-19) pandemic raised unprecedented concerns in the hematopoietic stem cell transplant community. The diagnosis of COVID-19 in these transplant recipients may require extensive laboratory testing and high clinical suspicion, as atypical clinical manifestations or other respiratory viral infections are common in this patient population. The underlying malignancies, immunosuppressed state, frequently observed coinfections, and advanced age in some patients may also predispose them to worse clinical outcomes. Similar outcomes have been previously described with other human coronaviruses, including the severe acute respiratory syndrome coronavirus and the Middle East respiratory syndrome coronavirus. Many hematopoietic stem cell transplant organizations have issued elaborative guidelines that aim to prevent transmission and hence adverse patient outcomes. All potential donors are thoroughly screened, and donated products are cryopreserved in advance. Potential hematopoietic stem cell transplant recipients are also screened, and most nonurgent transplant cases with low risk of progression and/or death are deferred. Current hematopoietic stem cell transplant recipients should adhere to precaution and isolation measures, while their transplant units should also follow strict safety protocols, similar to other infectious outbreaks. The prolonged susceptibility of hematopoietic stem cell transplant recipients to respiratory viral infections might necessitate extending these measures even after the peak of the outbreak until a gradually return to normality is possible.

Esmail, S. and W. Danter (2021). "Viral pandemic preparedness: A pluripotent stem cell-based machine-learning platform for simulating SARS-CoV-2 infection to enable drug discovery and repurposing." Stem Cells Transl Med **10**(2): 239-250.

Infection with the SARS-CoV-2 virus has rapidly become a global pandemic for which we were not prepared. Several clinical trials using previously approved drugs and drug combinations are urgently under way to improve the current situation. A vaccine option has only recently become available, but worldwide distribution is still a challenge. It is imperative that, for future viral pandemic preparedness, we have a rapid screening technology for drug discovery and repurposing. The primary purpose of this research project was to evaluate the DeepNEU stem-cell based platform by creating and validating computer simulations of artificial lung cells infected with SARS-CoV-2 to enable the rapid identification of antiviral therapeutic targets and drug repurposing. The data generated from this project indicate that (a) human alveolar type lung cells can be simulated by DeepNEU (v5.0), (b) these simulated cells can then be infected with simulated SARS-CoV-2 virus, (c) the unsupervised learning system performed well in all simulations based on available published wet lab data, and (d) the platform identified potentially effective anti-SARS-CoV2 combinations of known drugs for urgent clinical study. The data also suggest that DeepNEU can identify potential therapeutic targets for expedited vaccine development. We conclude that based on published data plus current DeepNEU results, continued development of the DeepNEU platform will improve our preparedness for and response to future viral outbreaks. This can be achieved through rapid identification of potential therapeutic options for clinical testing as soon as the viral genome has been confirmed.

Fernandez-Francos, S., et al. (2021). "Mesenchymal Stem Cell-Based Therapy as an Alternative to the Treatment of Acute Respiratory Distress Syndrome: Current Evidence and Future Perspectives." Int J Mol Sci **22**(15).

Acute respiratory distress syndrome (ARDS) represents a current challenge for medicine due to its incidence, morbidity and mortality and, also, the absence of an optimal treatment. The COVID-19 outbreak only increased the urgent demand for an affordable, safe and effective treatment for this process. Early clinical trials suggest the therapeutic usefulness of mesenchymal stem cells (MSCs) in acute lung injury (ALI) and ARDS. MSC-based therapies show antimicrobial, anti-inflammatory, regenerative, angiogenic, antifibrotic, anti-oxidative stress and anti-apoptotic actions, which can thwart the physiopathological mechanisms engaged in ARDS. In addition, MSC secretome and their derived products, especially exosomes, may reproduce the therapeutic effects of MSC in lung injury. This last strategy of

treatment could avoid several safety issues potentially associated with the transplantation of living and proliferative cell populations and may be formulated in different forms. However, the following diverse limitations must be addressed: (i) selection of the optimal MSC, bearing in mind both the heterogeneity among donors and across different histological origins, (ii) massive obtention of these biological products through genetic manipulations of the most appropriate MSC, (iii) bioreactors that allow their growth in 3D, (iv) ideal culture conditions and (v) adequate functional testing of these obtaining biological products before their clinical application.

Fisler, G., et al. (2020). "Severe Coronavirus Disease 2019 Infection in an Adolescent Patient After Hematopoietic Stem Cell Transplantation." Chest **158**(4): e139-e142.

Infection with the severe acute respiratory syndrome coronavirus 2 causes severe acute lung injury in approximately 5% of infected adults, but few reports have been made of severe pediatric disease. We present an adolescent patient who contracted severe acute respiratory syndrome coronavirus 2 one week after a paternal haplo-identical hematopoietic stem cell transplant, with development of severe hyperferritinemic acute lung injury and macrophage activation-like syndrome. We present her case and a comparison of her laboratory data with those of a cohort of pediatric patients with coronavirus disease 2019 without severe disease.

Foss, F. M., et al. (2020). "Attenuated Novel SARS Coronavirus 2 Infection in an Allogeneic Hematopoietic Stem Cell Transplant Patient on Ruxolitinib." Clin Lymphoma Myeloma Leuk **20**(11): 720-723.

Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) has a high death rate in patients with comorbidities or in an immunocompromised state. We report a mild and attenuated SARS CoV-2 infection in a patient who is 17 months post stem cell transplantation and maintained on the JAK/STAT inhibitor ruxolitinib, a proposed novel therapy for SARS CoV-2 pneumonia.

Gardin, C., et al. (2020). "Could Mesenchymal Stem Cell-Derived Exosomes Be a Therapeutic Option for Critically Ill COVID-19 Patients?" J Clin Med **9**(9).

Coronavirus disease 2019 (COVID-19) is a pandemic viral disease originated in Wuhan, China, in December 2019, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The severe form of the disease is often associated with acute respiratory distress syndrome (ARDS), and most critically ill patients require mechanical ventilation and support in intensive care units. A significant portion of COVID-19 patients also develop complications of the cardiovascular system, primarily acute myocardial injury, arrhythmia, or heart failure. To date, no specific antiviral therapy is available for patients with SARS-CoV-2 infection. Exosomes derived from mesenchymal stem cells (MSCs) are being explored for the management of a number of diseases that currently have limited or no therapeutic options, thanks to their anti-inflammatory, immunomodulatory, and pro-angiogenic properties. Here, we briefly introduce the pathogenesis of SARS-CoV-2 and its implications in the heart and lungs. Next, we describe some of the most significant clinical evidence of the successful use of MSC-derived exosomes in animal models of lung and heart injuries, which might strengthen our hypothesis in terms of their utility for also treating critically ill COVID-19 patients.

Gholizadeh-Ghaleh Aziz, S., et al. (2021). "Critical roles of TLRs on the polarization of mesenchymal stem cells for cell therapy of viral infections: a notice for COVID-19 treatment." Comp Clin Path: 1-10.

Mesenchymal stem cells (MSCs), as one of the leading cell-based therapy, have provided a strong link between clinical investigation and basic research. MSCs have been successfully employed in treating graft versus host disease (GvHD), autoimmune disease, and several other diseases, particularly with high immune activity. Recently, MSCs have attracted attention to treating untreatable viral infections such as severe coronavirus disease 2019 (COVID-19). Given that the Toll-like receptors (TLRs) are directly able to detect internal and external hazard signals, and their stimulation has an intense effect on the ability to grow, differentiate, migrate, and maintain MSCs, it seems stimulation of these receptors can have a direct impact on the interaction of MSCs and immune cells, altering the ability to modify immune system responses. Hence, this mini-review focused on TLRs' critical roles in the polarization of MSCs for developing MSC-based therapy in viral infections. Consequently, according to the literature review, a polarization process, mediated by TLRs concerning anti-inflammatory and proinflammatory phenotype, may be considered for MSC-therapy against viral infections.

Giani, A. M. and S. Chen (2021). "Human pluripotent stem cell-based organoids and cell platforms for modelling SARS-CoV-2 infection and drug discovery." Stem Cell Res **53**: 102207.

The coronavirus disease 2019 (COVID-19) global pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected over 200 countries and territories worldwide and resulted in more than 2.5 million deaths. In a pressing search for treatments and vaccines, research models based on human stem cells are emerging as crucial tools to investigate SARS-CoV-2 infection mechanisms and cellular responses across different

tissues. Here, we provide an overview of the variety of human pluripotent stem cell-based platforms adopted in SARS-CoV-2 research, comprising monolayer cultures and organoids, which model the multitude of affected tissues in vitro. We highlight the strengths of these platforms, including their application to assess both the susceptible cell types and the pathogenesis of SARS-CoV-2. We describe their use to identify drug candidates for further investigation in addition to discussing their limitations in fully recapitulating COVID-19 pathophysiology. Overall, stem cell models are facilitating the understanding of SARS-CoV-2 and prove to be versatile platforms for studying infections.

Golchin, A., et al. (2020). "Mesenchymal Stem Cell Therapy for COVID-19: Present or Future." Stem Cell Rev Rep **16**(3): 427-433.

"COVID-19" is the word that certainly isn't forgotten by everybody who lives in the first half of the twenty-first century. COVID-19, as a pandemic, has led many researchers from different biomedical fields to find solutions or treatments to manage the pandemic. However, no standard treatment for this disease has been discovered to date. Probably, preventing the severe acute respiratory infection form of COVID-19 as the most dangerous phase of this disease can be helpful for the treatment and reduction of the death rate. In this regard, mesenchymal stem cells (MSCs)-based immunomodulation treatment has been proposed as a suitable therapeutic approach and several clinical trials have begun. Recently, MSCs according to their immunomodulatory and regenerative properties attract attention in clinical trials. After the intravenous transplantation of MSCs, a significant population of cells accumulates in the lung, which they alongside immunomodulatory effect could protect alveolar epithelial cells, reclaim the pulmonary microenvironment, prevent pulmonary fibrosis, and cure lung dysfunction. Given the uncertainties in this area, we reviewed reported clinical trials and hypotheses to provide useful information to researchers and those interested in stem cell therapy. In this study, we considered this new approach to improve patient's immunological responses to COVID-19 using MSCs and discussed the aspects of this proposed treatment. However, currently, there are no approved MSC-based approaches for the prevention and/or treatment of COVID-19 patients but clinical trials ongoing.

Greco, R., et al. (2021). "Hematopoietic stem cell transplantation for autoimmune diseases in the time of COVID-19: EBMT guidelines and recommendations." Bone Marrow Transplant **56**(7): 1493-1508.

Coronavirus disease-19 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), represents one of the biggest challenges of 21st century, threatening public health around the globe. Increasing age and presence of co-morbidities are reported risk factors for severe disease and mortality, along with autoimmune diseases (ADs) and immunosuppressive treatments such as haematopoietic stem cell transplantation (HSCT), which are also associated with adverse outcomes. We review the impact of the pandemic on specific groups of patients with neurological, rheumatological, and gastroenterological indications, along with the challenges delivering HSCT in adult and pediatric populations. Moving forward, we developed consensus-based guidelines and recommendations for best practice and quality of patient care in order to support clinicians, scientists, and their multidisciplinary teams, as well as patients and their carers. These guidelines aim to support national and international organizations related to autoimmune diseases and local clinical teams delivering HSCT. Areas of unmet need and future research questions are also highlighted. The waves of the COVID-19 pandemic are predicted to be followed by an "endemic" phase and therefore an ongoing risk within a "new normality". These recommendations reflect currently available evidence, coupled with expert opinion, and will be revised according to necessary modifications in practice.

Greiner, J., et al. (2021). "Characteristics and mechanisms to control a COVID-19 outbreak on a leukemia and stem cell transplantation unit." Cancer Med **10**(1): 237-246.

Immunosuppressed patients like patients with leukemia or lymphoma, but also patients after autologous or allogeneic stem cell transplantation are at particular risk for an infection with COVID-19. We describe a COVID-19 outbreak on our leukemia and stem cell transplantation unit (LSCT-Unit) originating from a patient with newly diagnosed acute myeloid leukemia. The patient was treated with intensive induction chemotherapy and we characterize the subsequent outbreak of COVID-19 on a LSCT-Unit. We describe the characteristics of the 36 contacts among the medical team, the results of their PCR and antibody tests and clinical aspects and features of infected employees. Of these 36 close contacts, 9 employees of the LSCT-Unit were infected and were tested positive by PCR and/or antibody-testing. 8/9 of them were symptomatic, 3/9 with severe, 5/9 with mild symptoms, and one person without symptoms. Due to stringent hygiene measures, the outbreak did not lead to infections of other patients despite ongoing clinical work. Moreover, we demonstrate that incubation period and clinical course of a COVID-19 infection in an immunosuppressed patient could be unusual compared to that of immunocompetent patients. Consistent PCR and antibody testing are helpful to understand, control, and prevent outbreaks. For the safety of health-care workers and patients alike, all employees wore FFP2

masks and were trained to adhere to several further safety guidelines. The implementation of rigorous hygiene measures is the key to controlling an outbreak and preventing infections of other patients.

Hade, M. D., et al. (2021). "Mesenchymal Stem Cell-Derived Exosomes: Applications in Regenerative Medicine." Cells **10**(8).

Exosomes are a type of extracellular vesicles, produced within multivesicular bodies, that are then released into the extracellular space through a merging of the multivesicular body with the plasma membrane. These vesicles are secreted by almost all cell types to aid in a vast array of cellular functions, including intercellular communication, cell differentiation and proliferation, angiogenesis, stress response, and immune signaling. This ability to contribute to several distinct processes is due to the complexity of exosomes, as they carry a multitude of signaling moieties, including proteins, lipids, cell surface receptors, enzymes, cytokines, transcription factors, and nucleic acids. The favorable biological properties of exosomes including biocompatibility, stability, low toxicity, and proficient exchange of molecular cargos make exosomes prime candidates for tissue engineering and regenerative medicine. Exploring the functions and molecular payloads of exosomes can facilitate tissue regeneration therapies and provide mechanistic insight into paracrine modulation of cellular activities. In this review, we summarize the current knowledge of exosome biogenesis, composition, and isolation methods. We also discuss emerging healing properties of exosomes and exosomal cargos, such as microRNAs, in brain injuries, cardiovascular disease, and COVID-19 amongst others. Overall, this review highlights the burgeoning roles and potential applications of exosomes in regenerative medicine.

Han, A., et al. (2021). "Persistent SARS-CoV-2 infectivity greater than 50 days in a case series of allogeneic peripheral blood stem cell transplant recipients." Curr Probl Cancer Case Rep **3**: 100057.

The coronavirus disease 19 (COVID-19) pandemic has infected tens of millions across the world, but there is a significant gap in our understanding about COVID-19 in the hematopoietic stem transplant (HSCT) recipient population. Prolonged viral shedding is frequently observed with severe acute respiratory syndrome coronavirus-2 (SARSCoV-2), but studies suggest viral loads decline 10 days after symptom onset. Current CDC guidance suggests that severely ill and immunocompromised hosts are no longer infectious after 20 days from symptom onset. Cycle threshold (Ct) values are inversely proportional to the viral load and are used to detect SARS-CoV-2 RNA concentration. Specimens with reverse transcriptase PCR (RT-PCR) Ct values > 33-34 have been associated with inability to culture virus, and have been used as a surrogate for diminished infectivity. We report two cases of allogeneic peripheral blood stem cell transplant (PBSCT) recipients who had prolonged durations of infectivity with SARSCov-2, based on culture positivity and persistently low Ct values for greater than 50 days.

Harschnitz, O. and L. Studer (2021). "Human stem cell models to study host-virus interactions in the central nervous system." Nat Rev Immunol **21**(7): 441-453.

Advancements in human pluripotent stem cell technology offer a unique opportunity for the neuroimmunology field to study host-virus interactions directly in disease-relevant cells of the human central nervous system (CNS). Viral encephalitis is most commonly caused by herpesviruses, arboviruses and enteroviruses targeting distinct CNS cell types and often leading to severe neurological damage with poor clinical outcomes. Furthermore, different neurotropic viruses will affect the CNS at distinct developmental stages, from early prenatal brain development to the aged brain. With the unique flexibility and scalability of human pluripotent stem cell technology, it is now possible to examine the molecular mechanisms underlying acute infection and latency, determine which CNS subpopulations are specifically infected, study temporal aspects of viral susceptibility, perform high-throughput chemical or genetic screens for viral restriction factors and explore complex cell-non-autonomous disease mechanisms. Therefore, human pluripotent stem cell technology has the potential to address key unanswered questions about antiviral immunity in the CNS, including emerging questions on the potential CNS tropism of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Huang, J., et al. (2020). "SARS-CoV-2 Infection of Pluripotent Stem Cell-Derived Human Lung Alveolar Type 2 Cells Elicits a Rapid Epithelial-Intrinsic Inflammatory Response." Cell Stem Cell **27**(6): 962-973 e967.

A hallmark of severe COVID-19 pneumonia is SARS-CoV-2 infection of the facultative progenitors of lung alveoli, the alveolar epithelial type 2 cells (AT2s). However, inability to access these cells from patients, particularly at early stages of disease, limits an understanding of disease inception. Here, we present an in vitro human model that simulates the initial apical infection of alveolar epithelium with SARS-CoV-2 by using induced pluripotent stem cell-derived AT2s that have been adapted to air-liquid interface culture. We find a rapid transcriptomic change in infected cells, characterized by a shift to an inflammatory phenotype with upregulation of NF-kappaB signaling and loss of the mature alveolar program. Drug testing confirms the efficacy of remdesivir as well as TMPRSS2 protease inhibition, validating a putative mechanism used for viral entry in alveolar cells. Our model system reveals

cell-intrinsic responses of a key lung target cell to SARS-CoV-2 infection and should facilitate drug development.

Huang, J., et al. (2020). "SARS-CoV-2 Infection of Pluripotent Stem Cell-derived Human Lung Alveolar Type 2 Cells Elicits a Rapid Epithelial-Intrinsic Inflammatory Response." bioRxiv.

The most severe and fatal infections with SARS-CoV-2 result in the acute respiratory distress syndrome, a clinical phenotype of coronavirus disease 2019 (COVID-19) that is associated with virions targeting the epithelium of the distal lung, particularly the facultative progenitors of this tissue, alveolar epithelial type 2 cells (AT2s). Little is known about the initial responses of human lung alveoli to SARS-CoV-2 infection due in part to inability to access these cells from patients, particularly at early stages of disease. Here we present an in vitro human model that simulates the initial apical infection of the distal lung epithelium with SARS-CoV-2, using AT2s that have been adapted to air-liquid interface culture after their derivation from induced pluripotent stem cells (iAT2s). We find that SARS-CoV-2 induces a rapid global transcriptomic change in infected iAT2s characterized by a shift to an inflammatory phenotype predominated by the secretion of cytokines encoded by NF-kB target genes, delayed epithelial interferon responses, and rapid loss of the mature lung alveolar epithelial program. Over time, infected iAT2s exhibit cellular toxicity that can result in the death of these key alveolar facultative progenitors, as is observed in vivo in COVID-19 lung autopsies. Importantly, drug testing using iAT2s confirmed an antiviral dose-response to remdesivir and demonstrated the efficacy of TMPRSS2 protease inhibition, validating a putative mechanism used for viral entry in human alveolar cells. Our model system reveals the cell-intrinsic responses of a key lung target cell to infection, providing a physiologically relevant platform for further drug development and facilitating a deeper understanding of COVID-19 pathogenesis.

Huang, Y., et al. (2020). "[Several Common Respiratory Viral Pathogens in Hematopoietic Stem Cell Transplantion Patients with Primary Immunodeficiency Disease]." Zhongguo Shi Yan Xue Ye Xue Za Zhi **28**(3): 1025-1031.

OBJECTIVE: To investigate the prevalence of respiratory viral infections in patients with primary immunodeficiency disease (PID) during hematopoietic stem cell transplantation. METHODS: 108 specimens of nasopharyngeal aspirate were collected from 22 PID patients before and after hematopoietic stem cell transplantation from July 2016 to July 2018 in the Department of Hematology. The TR-PCR was used to detect for respiratory viruses including respiratory syncytial virus(RSV)human metapneumoviros(hMPV)coronavirus(CoV) and parainfluenza 1-3 (PIV1-3). And the clinical characteristics and co-infection were analyzed. RESULTS: Among the total 108 specimens, viral pathogens were identified in 41 (37.96%) specimens. Among which the pathogens of highest detection rate was RSV (25.9%). Different types of PID showed different virus infection rates, among which the highest infection rate was severe combined immunodeficiency disease (SCID) patients, with the virus detection rate was 57.9%. The incidence of co-infection with two or more than two viruses was 19.5%. CONCLUSION: Patients with PID who undergo hematopoietic stem cell transplantation are more susceptible to respiratory viruses. RSV is an important respiratory tract virus pathogen after hematopoietic stem cell transplantation.

Ibrahim, C., et al. (2021). "Addressing the Importance of Stem Cell-Based Therapy: A Perspective in the Treatment of COVID-19." Curr Mol Med **21**(6): 441-456.

Severe acute respiratory syndrome-associated coronavirus 2 (SARS-CoV-2) is an extremely pathogenic virus belonging to the family of Coronaviridae. First identified in Wuhan, China in December 2019 after an epidemiological investigation of an emerging cluster of pneumonia of unknown etiology, SARS-CoV-2 was declared the cause of a pandemic on March 11 by the World Health Organization (WHO), pointing to the over 118000 cases of Coronavirus disease 2019 (COVID-19) in over 110 countries. Despite the promising results of drug repositioning studies in the treatment of COVID-19, the evidence of their safety and efficacy remains inconclusive. Cell based therapy has been proven safe and possibly effective in treating multiple lung injuries and diseases, but its potential use in the treatment of COVID-19 has not been yet elucidated. Our aim in this review is to provide an overview of the immunomodulatory effect and the regenerative capacity of stem cells and their secretome in the treatment of many diseases including lung injuries. Those findings may contribute to a better understanding of the potential of stem cell therapy in SARS-CoV-2 infection and its potential use in order to find a solution for this healthcare crisis.

Irmak, D. K., et al. (2020). "Stem Cell Based Therapy Option in COVID-19: Is It Really Promising?" Aging Dis **11**(5): 1174-1191.

The COVID-19 patients were first detected in China, in December 2019, then the novel virus with associated pneumonia and other diseases spread quickly to worldwide becoming a serious public health intimidation. Despite all the efforts, the pharmacological agents used for controlling or treating the disease, especially respiratory problems, have not been accomplished so far. Among various treatment

options, mesenchymal stem cell-based cellular therapies are being investigated, because of their regeneration ability and multipotency along with other features like immunomodulation, antifibrosis and anti-inflammatory effects. This paper intends to analyze the current clinical trials on stem cell treatment of novel virus, searching and reviewing the available information and the International Clinical Trials Registry Platform (ICTRP) of World Health Organization (WHO). We concluded that the stem cell treatment of COVID-19 is found promising with pilot studies' results, but still in the early development phase. There is an urgent need for large-scale investigations to confirm and validate the safety and efficacy profile of these therapies with reliable scientific evidence.

Jacob, F., et al. (2020). "Human Pluripotent Stem Cell-Derived Neural Cells and Brain Organoids Reveal SARS-CoV-2 Neurotropism." bioRxiv.

Neurological complications are common in patients with COVID-19. While SARS-CoV-2, the causal pathogen of COVID-19, has been detected in some patient brains, its ability to infect brain cells and impact their function are not well understood, and experimental models using human brain cells are urgently needed. Here we investigated the susceptibility of human induced pluripotent stem cell (hiPSC)-derived monolayer brain cells and region-specific brain organoids to SARS-CoV-2 infection. We found modest numbers of infected neurons and astrocytes, but greater infection of choroid plexus epithelial cells. We optimized a protocol to generate choroid plexus organoids from hiPSCs, which revealed productive SARS-CoV-2 infection that leads to increased cell death and transcriptional dysregulation indicative of an inflammatory response and cellular function deficits. Together, our results provide evidence for SARS-CoV-2 neurotropism and support use of hiPSC-derived brain organoids as a platform to investigate the cellular susceptibility, disease mechanisms, and treatment strategies for SARS-CoV-2 infection.

Jacob, F., et al. (2020). "Human Pluripotent Stem Cell-Derived Neural Cells and Brain Organoids Reveal SARS-CoV-2 Neurotropism Predominates in Choroid Plexus Epithelium." Cell Stem Cell **27**(6): 937-950 e939.

Neurological complications are common in patients with COVID-19. Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causal pathogen of COVID-19, has been detected in some patient brains, its ability to infect brain cells and impact their function is not well understood. Here, we investigated the susceptibility of human induced pluripotent stem cell (hiPSC)-derived monolayer brain cells and region-specific brain organoids to SARS-CoV-2 infection. We found that neurons and astrocytes were sparsely infected, but choroid plexus epithelial cells underwent robust infection. We optimized a protocol to generate choroid plexus organoids from hiPSCs and showed that productive SARS-CoV-2 infection of these organoids is associated with increased cell death and transcriptional dysregulation indicative of an inflammatory response and cellular function deficits. Together, our findings provide evidence for selective SARS-CoV-2 neurotropism and support the use of hiPSC-derived brain organoids as a platform to investigate SARS-CoV-2 infection susceptibility of brain cells, mechanisms of virus-induced brain dysfunction, and treatment strategies.

Jarmolinski, T., et al. (2021). "SARS-CoV-2 viral clearance during bone marrow aplasia after allogeneic hematopoietic stem cell transplantation-A case report." Pediatr Transplant **25**(5): e13875.

Respiratory viral infections are known causes of mortality after allogeneic hematopoietic stem cell transplantation (HSCT). Here, we report a unique case of a child with viral pneumonia caused by coinfection with human metapneumovirus (MPV), respiratory syncytial virus (RSV), and SARS-CoV-2 after HSCT. A 9-year-old girl with acute lymphoblastic leukemia underwent allogeneic HSCT from a matched, unrelated donor. During the post-transplant period, in profound leukopenia (below 10 leukocytes/microL), she was diagnosed with SARS-CoV-2, MPV, and RSV pneumonia and was treated with ribavirin and chloroquine. Before leukocyte recovery, the girl became asymptomatic, and SARS-CoV-2 and RSV clearance was achieved. The shedding of SARS-CoV-2 stopped before immune system recovery, and one may hypothesize that the lack of an inflammatory response might have been a contributing factor to the mild clinical course. Post-transplant care in HSCT recipients with COVID-19 infection is feasible in regular transplant units, provided the patient does not present with respiratory failure. Early and repeated testing for SARS-CoV-2 in post-transplant patients with concomitant infection mitigation strategies should be considered in children after HSCT who develop fever, respiratory symptoms, and perhaps gastrointestinal symptoms to control the spread of COVID-19 both in patients and in healthcare workers in hospital environments. Training of staff and the availability of personal protective equipment are crucial for containing SARS-CoV-2 infection.

Jayaramayya, K., et al. (2020). "Immunomodulatory effect of mesenchymal stem cells and mesenchymal stem-cell-derived exosomes for COVID-19 treatment." BMB Rep **53**(8): 400-412.

The world has witnessed unimaginable damage from the coronavirus disease-19 (COVID-19) pandemic. Because the pandemic is growing rapidly, it is important to consider diverse treatment options to

effectively treat people worldwide. Since the immune system is at the hub of the infection, it is essential to regulate the dynamic balance in order to prevent the overexaggerated immune responses that subsequently result in multiorgan damage. The use of stem cells as treatment options has gained tremendous momentum in the past decade. The revolutionary measures in science have brought to the world mesenchymal stem cells (MSCs) and MSC-derived exosomes (MSC-Exo) as therapeutic opportunities for various diseases. The MSCs and MSCExos have immunomodulatory functions; they can be used as therapy to strike a balance in the immune cells of patients with COVID-19. In this review, we discuss the basics of the cytokine storm in COVID-19, MSCs, and MSC-derived exosomes and the potential and stem-cell-based ongoing clinical trials for COVID-19. [BMB Reports 2020; 53(8): 400-412].

Jeyaraman, M., et al. (2021). "Fostering mesenchymal stem cell therapy to halt cytokine storm in COVID-19." Biochim Biophys Acta Mol Basis Dis **1867**(2): 166014.

The coronavirus disease 2019 (COVID-19) has been threatening the globe since the end of November 2019. The disease revealed cracks in the health care system as health care providers across the world were left without guidelines on definitive usage of pharmaceutical agents or vaccines. The World Health Organization (WHO) declared COVID-19 as a pandemic on the 11th of March 2020. Individuals with underlying systemic disorders have reported complications, such as cytokine storms, when infected with the virus. As the number of positive cases and the death toll across the globe continue to rise, various researchers have turned to cell based therapy using stem cells to combat COVID-19. The field of stem cells and regenerative medicine has provided a paradigm shift in treating a disease with minimally invasive techniques that provides maximal clinical and functional outcome for patients. With the available evidence of immunomodulatory and immune-privilege actions, mesenchymal stem cells (MSCs) can repair, regenerate and remodulate the native homeostasis of pulmonary parenchyma with improved pulmonary compliance. This article revolves around the usage of novel MSCs therapy for combating COVID-19.

Ji, H. L., et al. (2020). "Stem cell therapy for COVID-19 and other respiratory diseases: Global trends of clinical trials." World J Stem Cells **12**(6): 471-480.

Respiratory diseases, including coronavirus disease 2019 and chronic obstructive pulmonary disease (COPD), are leading causes of global fatality. There are no effective and curative treatments, but supportive care only. Cell therapy is a promising therapeutic strategy for refractory and unmanageable pulmonary illnesses, as proved by accumulating preclinical studies. Stem cells consist of totipotent, pluripotent, multipotent, and unipotent cells with the potential to differentiate into cell types requested for repair. Mesenchymal stromal cells, endothelial progenitor cells, peripheral blood stem cells, and lung progenitor cells have been applied to clinical trials. To date, the safety and feasibility of stem cell and extracellular vesicles administration have been confirmed by numerous phase I/II trials in patients with COPD, acute respiratory distress syndrome, bronchial dysplasia, idiopathic pulmonary fibrosis, pulmonary artery hypertension, and silicosis. Five routes and a series of doses have been tested for tolerance and advantages of different regimes. In this review, we systematically summarize the global trends for the cell therapy of common airway and lung diseases registered for clinical trials. The future directions for both new clinical trials and preclinical studies are discussed.

Jung, J. H., et al. (2021). "SARS-CoV-2-specific T cell memory is sustained in COVID-19 convalescent patients for 10 months with successful development of stem cell-like memory T cells." Nat Commun **12**(1): 4043.

Memory T cells contribute to rapid viral clearance during re-infection, but the longevity and differentiation of SARS-CoV-2-specific memory T cells remain unclear. Here we conduct ex vivo assays to evaluate SARS-CoV-2-specific CD4(+) and CD8(+) T cell responses in COVID-19 convalescent patients up to 317 days post-symptom onset (DPSO), and find that memory T cell responses are maintained during the study period regardless of the severity of COVID-19. In particular, we observe sustained polyfunctionality and proliferation capacity of SARS-CoV-2-specific T cells. Among SARS-CoV-2-specific CD4(+) and CD8(+) T cells detected by activation-induced markers, the proportion of stem cell-like memory T (TSCM) cells is increased, peaking at approximately 120 DPSO. Development of TSCM cells is confirmed by SARS-CoV-2-specific MHC-I multimer staining. Considering the self-renewal capacity and multipotency of TSCM cells, our data suggest that SARS-CoV-2-specific T cells are long-lasting after recovery from COVID-19, thus support the feasibility of effective vaccination programs as a measure for COVID-19 control.

Kaparou, M., et al. (2021). "Management of Allogeneic Stem Cell Transplantation for High-Risk AML following SARS-CoV-2 Associated Pancytopenia with Marked Bone Marrow Biopsy Alterations." Case Rep Hematol **2021**: 8843063.

The present study describes a patient aged 70 with very high-risk AML who successfully received a nonmyeloablative matched unrelated donor allograft shortly following SARS-CoV-2 infection, which manifested with mild cough, interstitial abnormalities on chest CT, and pancytopenia with profound bone marrow biopsy histological alterations. In parallel, our

study provides bone marrow biopsy data in a series of contemporary patients with serious haematological diseases who had a bone marrow biopsy performed within two weeks of PCR confirmation of SARS-CoV-2 infection. This study is notable because there are no published data describing the bone marrow biopsy changes observed in patients with haematological malignancies and SARS-CoV-2 infection. Finally, it is suggested that nonmyeloablative hematopoietic stem cell transplantation for very high-risk haematological malignancies can be successfully performed following recovery from SARS-CoV-2 infection.

Karatas, A., et al. (2021). "The clinical course of COVID-19 in hematopoietic stem cell transplantation (HSCT) recipients." Turk J Med Sci **51**(4): 1647-1652.

Background/aim: The disease caused by SARS-CoV-2 was named as COVID-19. There is as yet insufficient information about the effects of HSCT on the clinical course of COVID-19. In the present study, we aimed to investigate the clinical course of COVID-19 in patients who had undergone HSCT. Materials and methods: We analyzed baseline characteristics, clinical course and findings of COVID-19, hospitalization and death rates, overall survival, and case fatality rates of HSCT recipients diagnosed with COVID-19 retrospectively. Results: 57.6% of the patients underwent AHSCT, and 42.4% underwent allo-HSCT. 60.6%, 27.3%, and 12.1% of the patients had mild, moderate, and severe COVID-19 or critical illness, respectively. Overall, 45.5% were hospitalized, 12.1% required intensive care, and 9.1% necessitated invasive mechanical ventilation. The total CFR was 9.1% in HSCT recipients, 22.2% in patients with active hematologic malignancy, and 4.2% in patients without active hematologic malignancy. Conclusion: It can be concluded that mortality of HSCT recipients is lower in patients whose primary disease is in remission compared to ones that are not in remission. Further studies with larger group patients are needed in order to delineate the effects of COVID-19 on HSCT patients.

Katsura, H., et al. (2020). "Human Lung Stem Cell-Based Alveolospheres Provide Insights into SARS-CoV-2-Mediated Interferon Responses and Pneumocyte Dysfunction." Cell Stem Cell **27**(6): 890-904 e898.

Coronavirus infection causes diffuse alveolar damage leading to acute respiratory distress syndrome. The absence of ex vivo models of human alveolar epithelium is hindering an understanding of coronavirus disease 2019 (COVID-19) pathogenesis. Here, we report a feeder-free, scalable, chemically defined, and modular alveolosphere culture system for the propagation and differentiation of human alveolar type 2 cells/pneumocytes derived from primary lung tissue. Cultured pneumocytes express the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) receptor angiotensin-converting enzyme receptor type-2 (ACE2) and can be infected with virus. Transcriptome and histological analysis of infected alveolospheres mirror features of COVID-19 lungs, including emergence of interferon (IFN)-mediated inflammatory responses, loss of surfactant proteins, and apoptosis. Treatment of alveolospheres with IFNs recapitulates features of virus infection, including cell death. In contrast, alveolospheres pretreated with low-dose IFNs show a reduction in viral replication, suggesting the prophylactic effectiveness of IFNs against SARS-CoV-2. Human stem cell-based alveolospheres, thus, provide novel insights into COVID-19 pathogenesis and can serve as a model for understanding human respiratory diseases.

Kaye, R. J. (2020). "Overview of Stem Cell Therapy for Acute Respiratory Distress Syndrome with Focus on COVID 19." Pain Physician **23**(4S): S421-S432.

OBJECTIVE: There are as yet no effective strategies to treat the novel COVID-19 and to stem its symptoms, including ARDS. This review examines recent research studies in humans to determine whether mesenchymal stem cells (MSCs) may be used effectively and safely to target potentially deadly lung damage that may follow infection. METHODS: A literature search was conducted to find published manuscripts on the treatment of ARDS and COVID-19 symptoms, disease presentation, and available treatment regimens. Electronic data bases of scientific articles and records of printed documents of JAMA journals were searched to find research publications on MSC treatment of ARDS and COVID-19. Outcome variables included mortality over varying time periods, hospital days, days on ventilator, and biological factors. RESULTS: Two randomized double-blind clinical trials, 2 pilot studies, and 2 case reports described MSC use to treat ARDS with specific focus on COVID-19 and lung symptoms of cytokine storm. The MSCs were well-tolerated across studies. No significant differences in treatment outcome were found in randomized double-blind trials; however, results of 1 pilot study and 1 case report showed that MSCs led to lung symptom resolution and survival in severely ill treatment patients. CONCLUSIONS: There is little published research on disease and survival outcomes among patients suffering severe lung disease associated with ARDS and COVID-19, and studies available are limited by lack of consistency in design and numerous flaws and limitations. Comparisons across studies are difficult. Nevertheless, it is documented that 8 ARDS patients with COVID-19 experienced symptom recovery and survival subsequent to MSC administration. MSCs are potentially life-saving treatment approaches for some patients who exhibit severe lung distress and have not responded to standard treatments. This is an obviously exciting research and

treatment option for COVID-19 and other life-threatening diseases.

Khavinson, V. K., et al. (2021). "Results and Prospects of Using Activator of Hematopoietic Stem Cell Differentiation in Complex Therapy for Patients with COVID-19." Stem Cell Rev Rep **17**(1): 285-290.

The paper presents the results of a standard and complex treatment method using the peptide drug thymus thymalin in patients with COVID-19. One of the mechanisms of the immunomodulatory effect of thymalin is considered to be the ability of this peptide drug to influence the differentiation of human hematopoietic stem cells (HSCs). It was found that, as a result of standard treatment, patients in the control group showed a decrease in the concentration of the pro-inflammatory cytokine IL-6, C-reactive protein, D-dimer. The addition of thymalin to standard therapy accelerated the decline in both these indicators and the indicators of the T cell system. This has helped reduce the risk of blood clots in COVID-19 patients. The revealed properties of the thymus peptide preparation are the rationale for its inclusion in the complex treatment of coronavirus infection. Peptideswith potential biological activity against SARS-CoV-2 virus [29]. Note: Nitrogen atoms are shown in blue, oxygen atoms - in red, carbon atoms - in gray, hydrogen atoms - in white, and phosphorus atoms - in yellow.

Kheirkhah, A. H., et al. (2021). "Mesenchymal Stem Cell Derived-Exosomes as Effective Factors in Reducing Cytokine Storm Symptoms of COVID-19." Protein Pept Lett **28**(8): 945-952.

Given that conventional therapies are ineffective for COVID-19, obtained exosomes from stem cells have been proposed as a sustainable and effective treatment. Exosomes are subsets with lengths between 30 and 100 nanometers, and they can be secreted by different cells. Exosomes are containing different types of miRNAs, mRNAs, and different proteins. The role of immune system modulation of exosomes of mesenchymal stem cells has been studied and confirmed in more than one study. Exosome miRNAs detect and reduce cytokines that cause cytokine storms such as IL-7, IL-2, IL-6, etc. These miRNAs include miR-21, miR-24, miR-124, miR-145, etc. The risks associated with treatment with exosomes from different cells are relatively small compared to other treatments because transplanted cells do not stimulate the host immune system and also has reduced infection transmission. Due to the ineffectiveness of existing drugs in reducing inflammation and preventing cytokine storms, the use of immune-boosting systems may be suggested as another way to control cytokine storm.

Kikuchi-Taura, A., et al. (2021). "Gap junction-mediated cell-cell interaction between transplanted mesenchymal stem cells and vascular endothelium in stroke." Stem Cells **39**(7): 904-912.

We have shown previously that transplanted bone marrow mononuclear cells (BM-MNC), which are a cell fraction rich in hematopoietic stem cells, can activate cerebral endothelial cells via gap junction-mediated cell-cell interaction. In the present study, we investigated such cell-cell interaction between mesenchymal stem cells (MSC) and cerebral endothelial cells. In contrast to BM-MNC, for MSC we observed suppression of vascular endothelial growth factor uptake into endothelial cells and transfer of glucose from endothelial cells to MSC in vitro. The transfer of such a small molecule from MSC to vascular endothelium was subsequently confirmed in vivo and was followed by suppressed activation of macrophage/microglia in stroke mice. The suppressive effect was absent by blockade of gap junction at MSC. Furthermore, gap junction-mediated cell-cell interaction was observed between circulating white blood cells and MSC. Our findings indicate that gap junction-mediated cell-cell interaction is one of the major pathways for MSC-mediated suppression of inflammation in the brain following stroke and provides a novel strategy to maintain the blood-brain barrier in injured brain. Furthermore, our current results have the potential to provide a novel insight for other ongoing clinical trials that make use of MSC transplantation aiming to suppress excess inflammation, as well as other diseases such as COVID-19 (coronavirus disease 2019).

Kim, J. H., et al. (2020). "Diesel Particulate Matter 2.5 Induces Epithelial-to-Mesenchymal Transition and Upregulation of SARS-CoV-2 Receptor during Human Pluripotent Stem Cell-Derived Alveolar Organoid Development." Int J Environ Res Public Health **17**(22).

Growing evidence links prenatal exposure to particulate matter (PM2.5) with reduced lung function and incidence of pulmonary diseases in infancy and childhood. However, the underlying biological mechanisms of how prenatal PM2.5 exposure affects the lungs are incompletely understood, which explains the lack of an ideal in vitro lung development model. Human pluripotent stem cells (hPSCs) have been successfully employed for in vitro developmental toxicity evaluations due to their unique ability to differentiate into any type of cell in the body. In this study, we investigated the developmental toxicity of diesel fine PM (dPM2.5) exposure during hPSC-derived alveolar epithelial cell (AEC) differentiation and three-dimensional (3D) multicellular alveolar organoid (AO) development. We found that dPM2.5 (50 and 100 mug/mL) treatment disturbed the AEC differentiation, accompanied by upregulation of nicotinamide adenine dinucleotide phosphate oxidases and inflammation. Exposure to dPM2.5 also promoted

epithelial-to-mesenchymal transition during AEC and AO development via activation of extracellular signal-regulated kinase signaling, while dPM2.5 had no effect on surfactant protein C expression in hPSC-derived AECs. Notably, we provided evidence, for the first time, that angiotensin-converting enzyme 2, a receptor to mediate the severe acute respiratory syndrome coronavirus clade 2 (SARS-CoV-2) entry into target cells, and the cofactor transmembrane protease serine 2 were significantly upregulated in both hPSC-AECs and AOs treated with dPM2.5. In conclusion, we demonstrated the potential alveolar development toxicity and the increase of SARS-Cov-2 susceptibility of PM2.5. Our findings suggest that an hPSC-based 2D and 3D alveolar induction system could be a useful in vitro platform for evaluating the adverse effects of environmental toxins and for virus research.

Kim, M. and P. S. Knoepfler (2021). "Anticipated impact of stem cell and other cellular medicine clinical trials for COVID-19." Regen Med **16**(6): 525-533.

Aim: There is a critical need for safe and effective treatments for COVID-19. One possible type of treatment is cellular medicine such as stem cell therapy, but its potential is unclear. Here, our aim was to assess the potential impact of the many cellular medicine trials for COVID-19. Materials & methods: We collected and analyzed data for defined criteria from trial registries. Results: Our data suggest that relatively few of these COVID-19 trials will produce high-level evidence, but that on average they may be somewhat more rigorous than typical cell therapy trials unrelated to COVID-19. Conclusion: Most COVID-19 cellular medicine trials have relatively low potential for rapid, concrete impact. We discuss the findings in the context of the cellular medicine field overall.

Kim, Y. S., et al. (2020). "Cardiotoxicity induced by the combination therapy of chloroquine and azithromycin in human embryonic stem cell-derived cardiomyocytes." BMB Rep **53**(10): 545-550.

Combination therapy using chloroquine (CQ) and azithromycin (AZM) has drawn great attention due to its potential anti-viral activity against SARS-CoV-2. However, clinical trials have revealed that the co-administration of CQ and AZM resulted in severe side effects, including cardiac arrhythmia, in patients with COVID-19. To elucidate the cardiotoxicity induced by CQ and AZM, we examined the effects of these drugs based on the electrophysiological properties of human embryonic stem cellderived cardiomyocytes (hESC-CMs) using multi-electrode arrays. CQ treatment significantly increased the field potential duration, which corresponds to prolongation of the QT interval, and decreased the spike amplitude, spike slope, and conduction velocity of hESC-CMs. AZM had no significant effect on the field potentials of hESC-CMs. However, CQ in combination with AZM greatly increased the field potential duration and decreased the beat period and spike slope of hESC-CMs when compared with CQ monotherapy. In support of the clinical data suggesting the cardiovascular side effects of the combination therapy of CQ and AZM, our results suggest that AZM reinforces the cardiotoxicity induced by CQ in hESC-CMs. [BMB Reports 2020; 53(10): 545-550].

Kruger, J., et al. (2021). "Drug Inhibition of SARS-CoV-2 Replication in Human Pluripotent Stem Cell-Derived Intestinal Organoids." Cell Mol Gastroenterol Hepatol **11**(4): 935-948.

BACKGROUND AND AIMS: The COVID-19 pandemic has spread worldwide and poses a severe health risk. While most patients present mild symptoms, descending pneumonia can lead to severe respiratory insufficiency. Up to 50% of patients show gastrointestinal symptoms like diarrhea or nausea, intriguingly associating with prolonged symptoms and increased severity. Thus, models to understand and validate drug efficiency in the gut of COVID-19 patients are of urgent need. METHODS: Human intestinal organoids derived from pluripotent stem cells (PSC-HIOs) have led, due to their complexity in mimicking human intestinal architecture, to an unprecedented number of successful disease models including gastrointestinal infections. Here, we employed PSC-HIOs to dissect SARS-CoV-2 pathogenesis and its inhibition by remdesivir, one of the leading drugs investigated for treatment of COVID-19. RESULTS: Immunostaining for viral entry receptor ACE2 and SARS-CoV-2 spike protein priming protease TMPRSS2 showed broad expression in the gastrointestinal tract with highest levels in the intestine, the latter faithfully recapitulated by PSC-HIOs. Organoids could be readily infected with SARS-CoV-2 followed by viral spread across entire PSC-HIOs, subsequently leading to organoid deterioration. However, SARS-CoV-2 spared goblet cells lacking ACE2 expression. Importantly, we challenged PSC-HIOs for drug testing capacity. Specifically, remdesivir effectively inhibited SARS-CoV-2 infection dose-dependently at low micromolar concentration and rescued PSC-HIO morphology. CONCLUSIONS: Thus, PSC-HIOs are a valuable tool to study SARS-CoV-2 infection and to identify and validate drugs especially with potential action in the gut.

Lam, G., et al. (2021). "Targeting mesenchymal stem cell therapy for severe pneumonia patients." World J Stem Cells **13**(2): 139-154.

Pneumonia is the inflammation of the lungs and it is the world's leading cause of death for children under 5 years of age. The latest coronavirus disease 2019 (COVID-19) virus is a prominent culprit to severe pneumonia. With the pandemic running rampant for the past year, more than 1590000 deaths has occurred

worldwide up to December 2020 and are substantially attributable to severe pneumonia and induced cytokine storm. Effective therapeutic approaches in addition to the vaccines and drugs under development are hence greatly sought after. Therapies harnessing stem cells and their derivatives have been established by basic research for their versatile capacity to specifically inhibit inflammation due to pneumonia and prevent alveolar/pulmonary fibrosis while enhancing antibacterial/antiviral immunity, thus significantly alleviating the severe clinical conditions of pneumonia. In recent clinical trials, mesenchymal stem cells have shown effectiveness in reducing COVID-19-associated pneumonia morbidity and mortality; positioning these cells as worthy candidates for combating one of the greatest challenges of our time and shedding light on their prospects as a next-generation therapy to counter future challenges.

Lanza, F. and J. Seghatchian (2020). "Trends and targets of various types of stem cell derived transfusable RBC substitution therapy: Obstacles that need to be converted to opportunity." Transfus Apher Sci **59**(5): 102941.

A shortage of blood during the pandemic outbreak of COVID-19 is a typical example in which the maintenance of a safe and adequate blood supply becomes difficult and highly demanding. So far, human RBCs have been produced in vitro using diverse sources: hematopoietic stem cells (SCs), embryonic SCs and induced pluripotent SCs. The existing, even safest core of conventional cellular bioproducts destined for transfusion have some shortcoming in respects to: donor -dependency variability in terms of hematological /immunological and process/ storage period issues. SCs-derived transfusable RBC bioproducts, as one blood group type for all, were highly complex to work out. Moreover, the strategies for their successful production are often dependent upon the right selection of starting source materials and the composition and the stability of the right expansion media and the strict compliance to GMP regulatory processes. In this mini-review we highlight some model studies, which showed that the efficiency and the functionality of RBCs that could be produced by the various types of SCs, in relation to the in-vitro culture procedures are such that they may, potentially, be used at an industrial level. However, all cultured products do not have an unlimited life due to the critical metabolic pathways or the metabolites produced. New bioreactors are needed to remove these shortcomings and the development of a new mouse model is required. Modern clinical trials based on the employment of regenerative medicine approaches in combination with novel large-scale bioengineering tools, could overcome the current obstacles in artificial RBC substitution, possibly allowing an efficient RBC industrial production.

Li, J., et al. (2020). "Feasibility of Mesenchymal Stem Cell Therapy for COVID-19: A Mini Review." Curr Gene Ther **20**(4): 285-288.

Patients infected with SARS-CoV-2 carry the coronavirus disease 2019 (COVID-19) which involves multiple systems and organs with acute respiratory distress syndrome (ARDS) as the most common complication, largely due to cytokine storms or dysregulated immunity. As such, there are many severe patients with complications such as cytokine storm syndrome (CSS), who have a high fatality rate. Neither specific anti-SARS-CoV-2 drugs nor vaccines exist currently. Current treatment relies mainly on self-recovery through patients' immune function. Mesenchymal stem cells (MSCs) is a kind of multipotent tissue stem cells, which have powerful anti-inflammatory and immune regulatory functions, inhibiting the cytokine storms. In addition, MSCs have a strong ability to repair tissue damage and reduce the risk of severe complications such as acute lung injury and ARDS, and hopefully, reduce the fatality rate in these patients. There are several clinical types of research completed for treating COVID-19 with MSCs, all reporting restoration of T cells and clinical safety. Here we discuss the clinical prospect and conclude the therapeutic effects and potential mechanism for MSCs in treating COVID-19.

Li, Z., et al. (2021). "Complicated pulmonary human coronavirus-NL63 infection after a second allogeneic hematopoietic stem cell transplantation for acute B-lymphocytic leukemia: A case report." Medicine (Baltimore) **100**(25): e26446.

RATIONALE: Viruses are the most common pathogens that can cause infection-related non-recurrent death after transplantation, occurring mostly from the early stages of hematopoietic stem cell transplantation (HSCT) to within 1 year after transplantation. Human coronavirus (HCoV)-NL63 is a coronavirus that could cause mortality among patients with underlying disease complications. Serological tests are of limited diagnostic value in immunocompromised hosts and cases of latent infection reactivation. In contrast, macro-genomic high-throughput (DNA and RNA) sequencing allows for rapid and accurate diagnosis of infecting pathogens for targeted treatment. PATIENT CONCERNS: In this report, we describe a patient who exhibited acute B-lymphocytic leukemia and developed complicated pulmonary HCoV-NL63 infection after a second allogeneic HSCT (allo-HSCT). Six months after the second allo-HSCT, he developed sudden-onset hyperthermia and cough with decreased oxygen saturation. Chest computed tomography (CT) suggested bilateral multiple rounded ground-glass

opacities with the pulmonary lobules as units. DIAGNOSES: HCoV-NL63 was detected by metagenomic next-generation sequencing (NGS), and HCoV-NL63 viral pneumonia was diagnosed. INTERVENTIONS: The treatment was mainly based on the use of antiviral therapy, hormone administration, and gamma-globulin. OUTCOMES: After the therapy, the body temperature returned to normal, the chest CT findings had improved on review, and the viral copy number eventually became negative. LESSONS: The latest NGS is an effective method for early infection diagnosis. The HCoV-NL63 virus can cause inflammatory factor storm and alter the neutrophil-to-lymphocyte ratio (NLR). This case suggests that the patient's NLR and cytokine levels could be monitored during the clinical treatment to assess the disease and its treatment outcome in a timely manner.

Li, Z., et al. (2020). "Stem cell therapy for COVID-19, ARDS and pulmonary fibrosis." Cell Prolif **53**(12): e12939.

Coronavirus disease 2019 (COVID-19) is an acute respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 mainly causes damage to the lung, as well as other organs and systems such as the hearts, the immune system and so on. Although the pathogenesis of COVID-19 has been fully elucidated, there is no specific therapy for the disease at present, and most treatments are limited to supportive care. Stem cell therapy may be a potential treatment for refractory and unmanageable pulmonary illnesses, which has shown some promising results in preclinical studies. In this review, we systematically summarize the pathogenic progression and potential mechanisms underlying stem cell therapy in COVID-19, and registered COVID-19 clinical trials. Of all the stem cell therapies touted for COVID-19 treatment, mesenchymal stem cells (MSCs) or MSC-like derivatives have been the most promising in preclinical studies and clinical trials so far. MSCs have been suggested to ameliorate the cytokine release syndrome (CRS) and protect alveolar epithelial cells by secreting many kinds of factors, demonstrating safety and possible efficacy in COVID-19 patients with acute respiratory distress syndrome (ARDS). However, considering the consistency and uniformity of stem cell quality cannot be quantified nor guaranteed at this point, more work remains to be done in the future.

Lintzmaier Petiz, L., et al. (2021). "P2Y14 Receptor as a Target for Neutrophilia Attenuation in Severe COVID-19 Cases: From Hematopoietic Stem Cell Recruitment and Chemotaxis to Thrombo-inflammation." Stem Cell Rev Rep **17**(1): 241-252.

The global SARS-CoV-2 pandemic starting in 2019 has already reached more than 2.3 million deaths. Despite the scientific community's efforts to investigate the COVID-19 disease, a drug for effectively treating or curing patients yet needs to be discovered. Hematopoietic stem cells (HSC) differentiating into immune cells for defense express COVID-19 entry receptors, and COVID-19 infection hinders their differentiation. The importance of purinergic signaling in HSC differentiation and innate immunity has been recognized. The metabotropic P2Y14 receptor subtype, activated by UDP-glucose, controls HSC differentiation and mobilization. Thereon, the exacerbated activation of blood immune cells amplifies the inflammatory state observed in COVID-19 patients, specially through the continuous release of reactive oxygen species and extracellular neutrophil traps (NETs). Further, the P2Y14 subtype, robustly inhibits the infiltration of neutrophils into various epithelial tissues, including lungs and kidneys. Here we discuss findings suggesting that antagonism of the P2Y14 receptor could prevent the progression of COVID-19-induced systemic inflammation, which often leads to severe illness and death cases. Considering the modulation of neutrophil recruitment of extreme relevance for respiratory distress and lung failure prevention, we propose that P2Y14 receptor inhibition by its selective antagonist PPTN could limit neutrophil recruitment and NETosis, hence limiting excessive formation of oxygen reactive species and proteolytic activation of the kallikrein-kinin system and subsequent bradykinin storm in the alveolar septa of COVID-19 patients.

Liu, J., et al. (2021). "Homecare Encounters: An Organizational Response to Innovative Care for Patients Undergoing Hematopoietic Stem Cell Transplantation During COVID-19." Clin J Oncol Nurs **25**(4): 457-464.

BACKGROUND: Healthcare delivery has been significantly changed because of the COVID-19 pandemic. Patients undergoing hematopoietic stem cell transplantation (HSCT) are vulnerable to infections because of their immunocompromised status. The risk of nosocomial infection may be reduced by providing care to patients at home. OBJECTIVES: This article describes one cancer center's approach for delivering safe patient care through homecare encounters, the benefits of home care for HSCT, and future directions. METHODS: Patients received detailed information on home encounters. Advanced practice providers visited patients daily and then returned to the clinic to formulate a plan of care with the interprofessional care team. Transplantation RNs visited patients on the same day to provide the prescribed care. FINDINGS: Based on evaluations from 32 patients and 12 providers, the results indicated that home care was safe, feasible, and beneficial for patient care post-HSCT during the COVID-19 pandemic.

Ljungman, P., et al. (2021). "COVID-19 and stem cell transplantation; results from an EBMT and GETH multicenter prospective survey." Leukemia.

This study reports on 382 COVID-19 patients having undergone allogeneic (n = 236) or autologous (n = 146) hematopoietic cell transplantation (HCT) reported to the European Society for Blood and Marrow Transplantation (EBMT) or to the Spanish Group of Hematopoietic Stem Cell Transplantation (GETH). The median age was 54.1 years (1.0-80.3) for allogeneic, and 60.6 years (7.7-81.6) for autologous HCT patients. The median time from HCT to COVID-19 was 15.8 months (0.2-292.7) in allogeneic and 24.6 months (-0.9 to 350.3) in autologous recipients. 83.5% developed lower respiratory tract disease and 22.5% were admitted to an ICU. Overall survival at 6 weeks from diagnosis was 77.9% and 72.1% in allogeneic and autologous recipients, respectively. Children had a survival of 93.4%. In multivariate analysis, older age ($p = 0.02$), need for ICU ($p < 0.0001$) and moderate/high immunodeficiency index ($p = 0.04$) increased the risk while better performance status ($p = 0.001$) decreased the risk for mortality. Other factors such as underlying diagnosis, time from HCT, GVHD, or ongoing immunosuppression did not significantly impact overall survival. We conclude that HCT patients are at high risk of developing LRTD, require admission to ICU, and have increased mortality in COVID-19.

Lv, J., et al. (2020). "Stem cell 'therapy' advertisements in China: Infodemic, regulations and recommendations." Cell Prolif **53**(12): e12937.

During the COVID-19 pandemic, in addition to the pandemic itself, a phenomenon called an 'infodemic'-defined by the World Health Organization as the spread of misleading information on the pandemic-has also gained attention. In the field of stem cell research, researchers and regulators have been fighting against false and misleading information, particularly advertisements for unproven and unauthorized stem cell-based interventions for decades. However, how existing legal and regulatory measures, which vary by country, can be employed to combat such false information is unclear. In this article, we examine the situation in China, where the spread of unauthorized stem cell 'therapies' has drawn patients from not only within China but also from abroad. First, we assess how and to what extent online advertisements promote unproven and unauthorized stem cell-based interventions directly to patients and prospective health consumers in China. Next, we survey the landscape for existing regulatory and administrative measures that may be used to combat false and misleading advertisements in this area. Finally, based on our analysis, we provide three main recommendations that may improve the effectiveness and efficiency of the regulatory measures in curtailing illegitimate advertising of unproven and unauthorized stem cell-based interventions in China. In conclusion, we also call for international collaboration among researchers and regulators in studying and strengthening regulations in this critical area that has so far been neglected in scholarly and policy discussions.

Mahendiratta, S., et al. (2021). "Stem cell therapy in COVID-19: Pooled evidence from SARS-CoV-2, SARS-CoV, MERS-CoV and ARDS: A systematic review." Biomed Pharmacother **137**: 111300.

BACKGROUND: SARS-CoV-2, which majorly affects the lungs and respiratory tract is thought due to dysregulation of the immune system which causes an immense imbalance of the cytokines. However, till now no standard treatment has been developed in treating the disease. On the other hand, it becomes important to prevent the acute respiratory tract infection due to COVID-19 which is the most dangerous phase leading to increased mortality. Hence this systematic review has been framed by pooling the available data of the use of stem cells in SARS-CoV-2, SARS-CoV, MERS-CoV and ARDS. METHODS: 6 literature databases (PubMed, EMBASE, Scopus, Google Scholar, Clinicaltrials.gov, and Clinical trial registry of India) were searched for relevant studies till 10th August 2020 using keywords stem cells, mesenchymal stem cells, cell therapy, SARS CoV-2, SARS Coronavirus, Coronavirus 2, COVID-19, nCoV-19, Novel Coronavirus, MERS CoV, ARDS, acute respiratory distress syndrome. RESULTS: The observations of this systematic review suggest capability of MSCs in reducing the systemic inflammation and protecting against SARS-CoV-2 as evidenced by the available clinical data. CONCLUSION: MSCs can overcome the clinical challenges currently faced by SARS-CoV-2 infected patients, specifically who are seriously ill and not responding to conventional therapies. Though the available clinical data is motivating, still predicting the therapeutic potential of MSCs will be too early in COVID-19. Hence, further studies in a larger cohort of patients becomes a prerequisite to validate their potential efficacy.

Marchiano, S., et al. (2021). "SARS-CoV-2 Infects Human Pluripotent Stem Cell-Derived Cardiomyocytes, Impairing Electrical and Mechanical Function." Stem Cell Reports **16**(3): 478-492.

COVID-19 patients often develop severe cardiovascular complications, but it remains unclear if these are caused directly by viral infection or are secondary to a systemic response. Here, we examine the cardiac tropism of SARS-CoV-2 in human pluripotent stem cell-derived cardiomyocytes (hPSC-CMs) and smooth muscle cells (hPSC-SMCs). We find that that SARS-CoV-2 selectively infects hPSC-CMs through the viral receptor ACE2, whereas in hPSC-

SMCs there is minimal viral entry or replication. After entry into cardiomyocytes, SARS-CoV-2 is assembled in lysosome-like vesicles and egresses via bulk exocytosis. The viral transcripts become a large fraction of cellular mRNA while host gene expression shifts from oxidative to glycolytic metabolism and upregulates chromatin modification and RNA splicing pathways. Most importantly, viral infection of hPSC-CMs progressively impairs both their electrophysiological and contractile function, and causes widespread cell death. These data support the hypothesis that COVID-19-related cardiac symptoms can result from a direct cardiotoxic effect of SARS-CoV-2.

Mazini, L., et al. (2021). "Overview of current adipose-derived stem cell (ADSCs) processing involved in therapeutic advancements: flow chart and regulation updates before and after COVID-19." Stem Cell Res Ther **12**(1): 1.

Adipose-derived stem cells (ADSCs) have raised big interest in therapeutic applications in regenerative medicine and appear to fulfill the criteria for a successful cell therapy. Their low immunogenicity and their ability to self-renew, to differentiate into different tissue-specific progenitors, to migrate into damaged sites, and to act through autocrine and paracrine pathways have been altogether testified as the main mechanisms whereby cell repair and regeneration occur. The absence of standardization protocols in cell management within laboratories or facilities added to the new technologies improved at patient's bedside and the discrepancies in cell outcomes and engraftment increase the limitations on their widespread use by balancing their real benefit versus the patient safety and security. Also, comparisons across pooled patients are particularly difficult in the fact that multiple medical devices are used and there is absence of harmonized assessment assays despite meeting regulations agencies and efficient GMP protocols. Moreover, the emergence of the COVID-19 breakdown added to the complexity of implementing standardization. Cell- and tissue-based therapies are completely dependent on the biological manifestations and parameters associated to and induced by this virus where the scope is still unknown. The initial flow chart identified for stem cell therapies should be reformulated and updated to overcome patient infection and avoid significant variability, thus enabling more patient safety and therapeutic efficiency. The aim of this work is to highlight the major guidelines and differences in ADSC processing meeting the current good manufacturing practices (cGMP) and the cellular therapy-related policies. Specific insights on standardization of ADSCs proceeding at different check points are also presented as a setup for the cord blood and bone marrow.

Meng, F., et al. (2020). "Human umbilical cord-derived mesenchymal stem cell therapy in patients with COVID-19: a phase 1 clinical trial." Signal Transduct Target Ther **5**(1): 172.

No effective drug treatments are available for coronavirus disease 2019 (COVID-19). Host-directed therapies targeting the underlying aberrant immune responses leading to pulmonary tissue damage, death, or long-term functional disability in survivors require clinical evaluation. We performed a parallel assigned controlled, non-randomized, phase 1 clinical trial to evaluate the safety of human umbilical cord-derived mesenchymal stem cells (UC-MSCs) infusions in the treatment of patients with moderate and severe COVID-19 pulmonary disease. The study enrolled 18 hospitalized patients with COVID-19 (n = 9 for each group). The treatment group received three cycles of intravenous infusion of UC-MSCs (3 x 10(7) cells per infusion) on days 0, 3, and 6. Both groups received standard COVID-treatment regimens. Adverse events, duration of clinical symptoms, laboratory parameters, length of hospitalization, serial chest computed tomography (CT) images, the PaO2/FiO2 ratio, dynamics of cytokines, and IgG and IgM anti-SARS-CoV-2 antibodies were analyzed. No serious UC-MSCs infusion-associated adverse events were observed. Two patients receiving UC-MSCs developed transient facial flushing and fever, and one patient developed transient hypoxia at 12 h post UC-MSCs transfusion. Mechanical ventilation was required in one patient in the treatment group compared with four in the control group. All patients recovered and were discharged. Our data show that intravenous UC-MSCs infusion in patients with moderate and severe COVID-19 is safe and well tolerated. Phase 2/3 randomized, controlled, double-blinded trials with long-term follow-up are needed to evaluate the therapeutic use of UC-MSCs to reduce deaths and improve long-term treatment outcomes in patients with serious COVID-19.

Mengling, T., et al. (2021). "Stem cell donor registry activities during the COVID-19 pandemic: a field report by DKMS." Bone Marrow Transplant **56**(4): 798-806.

The COVID-19 pandemic has serious implications also for patients with other diseases. Here, we describe the effects of the pandemic on unrelated hematopoietic stem cell donation and transplantation from the perspective of DKMS, a large international donor registry. Especially, we cover the development of PBSC and bone marrow collection figures, donor management including Health and Availability Check (HAC), transport and cryopreservation of stem cell products, donor recruitment and business continuity measures. The total number of stem cell products provided declined by around 15% during the crisis with

a particularly strong decrease in bone marrow products. We modified donor management processes to ensure donor and product safety. HAC instead of confirmatory typing was helpful especially in countries with strict lockdowns. New transport modes were developed so that stem cell products could be safely delivered despite COVID-19-related travel restrictions. Cryopreservation of stem cell products became the new temporary standard during the pandemic to minimize risks related to transport logistics and donor availability. However, many products from unrelated donors will never be transfused. DKMS discontinued public offline donor recruitment, leading to a 40% decline in new donors during the crisis. Most DKMS employees worked from home to ensure business continuity during the crisis.

Meyer-Berg, H., et al. (2020). "Identification of AAV serotypes for lung gene therapy in human embryonic stem cell-derived lung organoids." Stem Cell Res Ther **11**(1): 448.

Gene therapy is being investigated for a range of serious lung diseases, such as cystic fibrosis and emphysema. Recombinant adeno-associated virus (rAAV) is a well-established, safe, viral vector for gene delivery with multiple naturally occurring and artificial serotypes available displaying alternate cell, tissue, and species-specific tropisms. Efficient AAV serotypes for the transduction of the conducting airways have been identified for several species; however, efficient serotypes for human lung parenchyma have not yet been identified. Here, we screened the ability of multiple AAV serotypes to transduce lung bud organoids (LBOs)-a model of human lung parenchyma generated from human embryonic stem cells. Microinjection of LBOs allowed us to model transduction from the luminal surface, similar to dosing via vector inhalation. We identified the naturally occurring rAAV2 and rAAV6 serotypes, along with synthetic rAAV6 variants, as having tropism for the human lung parenchyma. Positive staining of LBOs for surfactant proteins B and C confirmed distal lung identity and suggested the suitability of these vectors for the transduction of alveolar type II cells. Our findings establish LBOs as a new model for pulmonary gene therapy and stress the relevance of LBOs as a viral infection model of the lung parenchyma as relevant in SARS-CoV-2 research.

Milczarek, S., et al. (2021). "COVID-19 during Early Phase of Autologous Stem Cell Transplantation." Medicina (Kaunas) **57**(7).

We present one of few cases of COVID-19 occurrence during the early phase of autologous hematopoietic stem cell transplantation. We observed an interesting correlation between the patient's rapid clinical deterioration and myeloid reconstitution that cannot be assigned to engraftment syndrome. Our report emphasizes the need to investigate whether timely steroid therapy upon neutrophil engraftment in the setting of COVID-19 could limit the extent of lung injury and prevent ARDS. Furthermore, we discuss a significant issue of possible prolonged incubation of the virus in heavily pretreated hematological patients.

Mirgh, S., et al. (2021). "Clinical course of severe COVID19 treated with tocilizumab and antivirals post-allogeneic stem cell transplant with extensive chronic GVHD." Transpl Infect Dis **23**(4): e13576.

Recipients of allogeneic hematopoietic stem cell transplantation (allo-HSCT) are an immunocompromised group who are likely to develop severe complications and mortality because of coronavirus disease 2019 (COVID-19). We report here a 61-year-old male patient of primary myelofibrosis who underwent an allo-HSCT 6 years earlier, had chronic graft-versus-host disease (cGVHD) involving the liver, lung, eyes, and skin, (with recurrent episodes of pulmonary infections) who developed severe COVID-19. The patient was treated with tocilizumab, and a combination of lopinavir/ritonavir, ribavirin, interferon-beta1b. He was discharged after 31 days with full recovery. Tocilizumab, a humanized monoclonal antibody against IL6, has been shown to benefit respiratory manifestations in severe COVID19. However, this is first report, to our knowledge, of its use and benefit in a post HSCT recipient.

Mithal, A., et al. (2021). "Human Pluripotent Stem Cell-Derived Intestinal Organoids Model SARS-CoV-2 Infection Revealing a Common Epithelial Inflammatory Response." Stem Cell Reports **16**(4): 940-953.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection leading to coronavirus disease 2019 (COVID-19) usually results in respiratory disease, but extrapulmonary manifestations are of major clinical interest. Intestinal symptoms of COVID-19 are present in a significant number of patients, and include nausea, diarrhea, and viral RNA shedding in feces. Human induced pluripotent stem cell-derived intestinal organoids (HIOs) represent an inexhaustible cellular resource that could serve as a valuable tool to study SARS-CoV-2 as well as other enteric viruses that infect the intestinal epithelium. Here, we report that SARS-CoV-2 productively infects both proximally and distally patterned HIOs, leading to the release of infectious viral particles while stimulating a robust transcriptomic response, including a significant upregulation of interferon-related genes that appeared to be conserved across multiple epithelial cell types. These findings illuminate a potential inflammatory epithelial-specific signature that may contribute to both the multisystemic nature of COVID-19 as well as its highly variable clinical presentation.

Moret, F., et al. (2021). "Characteristics of respiratory virus infections in autologous hematopoietic stem cell transplantation patients, a prospective study, Bern, Switzerland, 2015-2017." Infect Dis (Lond) **53**(4): 274-280.

BACKGROUND: The epidemiology of respiratory virus infections (RVI) in patients undergoing autologous haematopoietic stem cell transplantation (auto-SCT) is not well described. METHODS: Our goal was to describe the epidemiology of respiratory virus infections (RVI) in patients undergoing autologous haematopoietic stem cell transplantation (auto-SCT) in a single tertiary centre observation study during two respiratory virus seasons (2015-2017). All symptomatic auto-SCT patients were tested for RVI by nasopharyngeal swab. RESULTS: 156 transplantation episodes were included, 69% were male and, the median age was 57 years. We detected 19 RVIs in 156 transplantation episodes (12%). The median time to RVI after hospitalization was 13 days [IQR 7-13] and 15/19 (79%) had a possible nosocomial origin (occurrence >/= 5 days after admission). The nosocomial infections included 5/15 (33%) 'severe' RVIs (3 influenza viruses, 1 parainfluenza virus, and 1 adenovirus) as well as 10/15 (66%) non-severe virus infections (including human rhinovirus and human coronavirus). CONCLUSION: In approximately 10% of auto-SCT transplantation episodes, an RVI with likely nosocomial origin was detected and included 'severe viruses' such as influenza. Our study suggests that infection prevention measures in auto-SCT patients can be improved. ABBREVIATIONS: AdV: adenovirus; ALL: acute lymphatic leukaemia; AML: acute myeloid leukaemia; auto-SCT: autologous haematopoietic stem cell transplantation; hCoV: human coronavirus; HD: Hodgkin's disease; hMPV: human metapneumovirus; HRV: human rhinovirus; HSCT: allogeneic haematopoietic stem cell transplantation; IQR: interquartile range; GCT: germ cell tumour; MM: multiple myeloma; NHL: non-Hodgkin lymphoma; PIV: parainfluenza virus; RSV: respiratory syncytial virus.

N, O. E., et al. (2021). "Clinical experience on umbilical cord mesenchymal stem cell treatment in 210 severe and critical COVID-19 cases in Turkey." Stem Cell Rev Rep.

OBJECTIVE: Treatment for COVID-19 is still urgent need for the critically ill and severe cases. UC-MSC administration has a therapeutic benefit for severe COVID-19 patients even in the recovery period. In this paper, we aimed to present our clinical experience with UC-MSC treatment in severe and critical severe COVID-19 patients. METHODS: In this study we evaluated the clinical outcome of severe/critically severe 210 COVID-19 patients treated with UC-MSCs, 1-2 x 10(6) per kilogram to 210 patients from 15/10/2020 until 25/04/2021. RESULTS: Out of 99 critically severe intubated patients we have observed good clinical progress/discharged from ICU in 52 (52.5%) patients. Where as 86 (77.5%) of 111 severe unintubated patients discharged from ICU. Intubated 47 (47.5%) patients and unintubated 25 (22.5%) patients pass away. Significantly higher survival was observed in patients who underwent UC-MSCs before intubation (OR = 1.475, 95% CI = 1.193-1.824 $p < 0.001$). It was observed that the SaO2 parameter tended to improve after UC-MSC therapy compared to all groups. But SaO2 parameter between intubated and unintubated groups was not statistically significant ($p > 0.05$), while in discharged cases SaO2 parameter was statistically significant ($p = 0.01$). Besides, there was a statistically significant relation with intubation status, age (OR = 3.868, 95% CI = 0.574-7.152 $p = 0.02$) and weigh (OR = 6.768, 95% CI = 3.423-10.112 $p < 0.001$) thus presented an elevated risk for COVID-19. The linear regression analysis confirmed that the high weight was associated with the risk of intubation in COVID-19 ($p = 0.001$). CONCLUSIONS: According to our results and from recent studies, UC-MSC treatment is safe with high potential to be used as an added therapeutic treatment for severe COVID-19 patients. Our experience showed that UC-MSC therapy may restore oxygenation and downregulate cytokine storm in patients hospitalized with severe COVID-19. We advice wider randomised studies to discover the detailed therapeutic pathophysiology of the MSCs on COVID-19 patients. MSCs transplantation improves the damaging effects of the cytokine storm through immunomodulation and improving tissue and organ repair. Severe patients who were unintubated were in the Phase I, while critical patients who were intubated were in the Phase II. The figure is created via biorender application, (BioRender.com).

Primorac, D., et al. (2021). "Compassionate mesenchymal stem cell treatment in a severe COVID-19 patient: a case report." Croat Med J **62**(3): 288-296.

COVID-19 presentations range from cold-like symptoms to severe symptoms with the development of acute respiratory distress syndrome (ARDS). We report on a severe COVID-19 patient who was mechanically ventilated and who developed ARDS and bacterial infection. Because of rapid clinical deterioration and the exhaustion of other treatment options, the family and attending physicians requested a compassionate use of adult allogeneic bone marrow-derived mesenchymal stem cells (MSC) in addition to commonly used immunosuppressive, antiviral, and supportive therapy. The clinical course is discussed thoroughly, with a special emphasis on the safety and effect of MSC therapy. Compassionate MSC treatment,

given in three rounds, affected ARDS regression. The patient was discharged from the intensive care unit after 31 days and from hospital after 49 days in a good general condition. MSC treatment was not associated with any side effects and was well tolerated in a three-week period; therefore, it should be studied in larger trials and considered for compassionate use.

Pryce, A., et al. (2021). "SARS-CoV-2 respiratory screening of asymptomatic stem cell donors on day of collection; to test or not to test. UK Aligned Stem Cell Donor Registry." Bone Marrow Transplant.

Purkayastha, A., et al. (2020). "Direct Exposure to SARS-CoV-2 and Cigarette Smoke Increases Infection Severity and Alters the Stem Cell-Derived Airway Repair Response." Cell Stem Cell **27**(6): 869-875 e864.

Current smoking is associated with increased risk of severe COVID-19, but it is not clear how cigarette smoke (CS) exposure affects SARS-CoV-2 airway cell infection. We directly exposed air-liquid interface (ALI) cultures derived from primary human nonsmoker airway basal stem cells (ABSCs) to short term CS and then infected them with SARS-CoV-2. We found an increase in the number of infected airway cells after CS exposure with a lack of ABSC proliferation. Single-cell profiling of the cultures showed that the normal interferon response was reduced after CS exposure with infection. Treatment of CS-exposed ALI cultures with interferon beta-1 abrogated the viral infection, suggesting one potential mechanism for more severe viral infection. Our data show that acute CS exposure allows for more severe airway epithelial disease from SARS-CoV-2 by reducing the innate immune response and ABSC proliferation and has implications for disease spread and severity in people exposed to CS.

Purkayastha, A., et al. (2020). "Direct exposure to SARS-CoV-2 and cigarette smoke increases infection severity and alters the stem cell-derived airway repair response." bioRxiv.

Most demographic studies are now associating current smoking status with increased risk of severe COVID-19 and mortality from the disease but there remain many questions about how direct cigarette smoke exposure affects SARS-CoV-2 airway cell infection. We directly exposed mucociliary air-liquid interface (ALI) cultures derived from primary human nonsmoker airway basal stem cells (ABSCs) to short term cigarette smoke and infected them with live SARS-CoV-2. We found an increase in the number of infected airway cells after cigarette smoke exposure as well as an increased number of apoptotic cells. Cigarette smoke exposure alone caused airway injury that resulted in an increased number of ABSCs, which proliferate to repair the airway. But we found that acute SARS-CoV-2 infection or the combination of exposure to cigarette smoke and SARS-CoV-2 did not induce ABSC proliferation. We set out to examine the underlying mechanism governing the increased susceptibility of cigarette smoke exposed ALI to SARS-CoV-2 infection. Single cell profiling of the cultures showed that infected airway cells displayed a global reduction in gene expression across all airway cell types. Interestingly, interferon response genes were induced in SARS-CoV-2 infected airway epithelial cells in the ALI cultures but smoking exposure together with SARS-CoV-2 infection reduced the interferon response. Treatment of cigarette smoke-exposed ALI cultures with Interferon beta-1 abrogated the viral infection, suggesting that the lack of interferon response in the cigarette smoke-exposed ALI cultures allows for more severe viral infection and cell death. In summary, our data show that acute smoke exposure allows for more severe proximal airway epithelial disease from SARS-CoV-2 by reducing the mucosal innate immune response and ABSC proliferation and has implications for disease spread and severity in people exposed to cigarette smoke.

Qatawneh, M., et al. (2021). "Hematopoietic Stem Cell Transplantation During the Era of COVID-19 in Queen Rania Children's Hospital." Mater Sociomed **33**(2): 131-137.

Background: Corona virus disease 2019 (COVID-19) is causing a health crisis nowadays, and all countries are following the recommendations of the WHO to decrease the spread of the disease. Till now, few data are available regarding the clinical course, severity of the disease and the duration of infectivity of COVID-19 in patients received Hematopoietic Stem Cell Transplantation (HSCT). Objective: To evaluate the medical protocols and outcome of patients who underwent HSCT during the pandemic of COVID-19. Methods: A retrospective review of the medical files of patients who underwent hematopoietic stem cell transplantation during the era of COVID-19. The following data were reviewed for all patients: age, gender, primary disease, viral screening protocols for donors and recipients, COVID-19 status and outcome. The European society for blood and marrow transplantation (EBMT) guidelines were applied strictly on all of our patients, donors and bone marrow transplant unit staff. Results: A total of 10 children were transplanted, 8 of them received allogenic transplant from matched donor and two patients received autologous transplant. Regarding allogenic transplants, all of our patients except two were transplanted as an emergency, 2 of them were Aplastic anemia, 2 patients were Fanconi anemia, one patient was Amegakaryocytic thrombocytopenia, and one patient was Acute myeloid leukemia. Only two patients were not an emergency as one of them had Thalassemia major and the other one was Sickle cell

anemia. The autologous transplant was done for two patients with Neuroblastoma stage 4 as part of their treatment protocol. At a median follow up of 5.5 months (range, 2 month-7 months) two patients (20%) developed COVID-19, which was asymptomatic in both of them. One of our patients (10%) died due to cytomegalovirus (CMV) pneumonia. No one of our patient was affected by the emergency regulations applied by the country and hospitals during the pandemic of COVID-19 virus. Conclusion: Hematopoietic stem cell transplantation can be performed safely for emergency cases, if we strictly follow the guidelines of EBMT.

Qin, H. and A. Zhao (2020). "Mesenchymal stem cell therapy for acute respiratory distress syndrome: from basic to clinics." Protein Cell **11**(10): 707-722.

The 2019 novel coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has occurred in China and around the world. SARS-CoV-2-infected patients with severe pneumonia rapidly develop acute respiratory distress syndrome (ARDS) and die of multiple organ failure. Despite advances in supportive care approaches, ARDS is still associated with high mortality and morbidity. Mesenchymal stem cell (MSC)-based therapy may be an potential alternative strategy for treating ARDS by targeting the various pathophysiological events of ARDS. By releasing a variety of paracrine factors and extracellular vesicles, MSC can exert anti-inflammatory, anti-apoptotic, anti-microbial, and pro-angiogenic effects, promote bacterial and alveolar fluid clearance, disrupt the pulmonary endothelial and epithelial cell damage, eventually avoiding the lung and distal organ injuries to rescue patients with ARDS. An increasing number of experimental animal studies and early clinical studies verify the safety and efficacy of MSC therapy in ARDS. Since low cell engraftment and survival in lung limit MSC therapeutic potentials, several strategies have been developed to enhance their engraftment in the lung and their intrinsic, therapeutic properties. Here, we provide a comprehensive review of the mechanisms and optimization of MSC therapy in ARDS and highlighted the potentials and possible barriers of MSC therapy for COVID-19 patients with ARDS.

Rachow, T., et al. (2020). "Detection of community-acquired respiratory viruses in allogeneic stem-cell transplant recipients and controls-A prospective cohort study." Transpl Infect Dis **22**(6): e13415.

BACKGROUND: Community-acquired respiratory viruses (CARV) cause upper and lower respiratory tract infections (URTI/LRTI) and may be life-threatening for recipients of an allogeneic stem cell transplantation (allo-SCT). METHODS: In a prospective study encompassing 4 winter-seasons, we collected throat gargles (TG) at random time points from allo-SCT recipients (patients) and controls and followed them up for at least 3 weeks including repetitive sampling and documentation of symptoms. A Multiplex-PCR system to identify 20 CARV and Mycoplasma pneumoniae was used to detect CARV. RESULTS: One hundred ninety-four patients with 426 TG and 273 controls with 549 TG were included. There were more patients with a positive test result (25% vs 11% in the controls), and the patients had a higher number of positive TG (70 = 16%) compared to controls (32 = 6%) ($P < .001$). Altogether, 115 viruses were detected. Multiple viruses in one TG (11/48, 34%) and prolonged shedding were only observed in patients (13/48, 27%). Patients had more RSV (18/83, 26%) and adenovirus (15/83, 21%) than controls (both viruses 2/32, 6%). Independent risk factors for the detection of CARV included age >40 years (OR 3.38, 95% CI 1.8-6.4, $P < .001$) and presence of URTI-symptoms (OR 3.22, 95% CI 1.9-5.5, $P < .001$). No controls developed a LRTI or died whereas 4/48 (8%) patients developed a LRTI (coronavirus in 2, RSV in 1 and influenza A H1N1 in 1 patient). One patient died of CARV (influenza A H1N1). CONCLUSION: Allo-SCT-recipients have more CARV-infections, exhibit a different epidemiology, have more cases of co-infection or prolonged shedding and have a higher rate of LRTI and mortality.

Rafiee, Z., et al. (2021). "Stem cell-based and mesenchymal stem cell derivatives for coronavirus treatment." Biotechnol Appl Biochem.

Coronavirus disease 2019 (COVID-19) as one of the diseases pneumonia was first reported in Wuhan, China in December 2019. COVID-19 is considered the third most common coronavirus among individuals after acute respiratory syndrome (SARS-CoV) and the Middle East respiratory syndrome (MERS-CoV) in the 20(th) century. Many studies have shown that cell therapy and regenerative medicine approaches have an impressive effect on different dangerous diseases in a way that using a cell-based experiment could be effective for improving humans with severe acute respiratory infections caused by the 2019 novel coronavirus. Accordingly, due to the stunning effects of mesenchymal stem cells and derivatives on the treatment of various diseases, this review focuses on the auxiliary role of mesenchymal stem cells and their derivatives in reducing the inflammatory processes of acute respiratory infections resulted from the 2019 novel coronavirus. The reported MSCs treatment outcomes are significant because these cells prevent the immune system from over-activating and improve, endogenous repair by improving the lung microenvironment after the SARS-CoV-2 infection. The MSCs can be an effective, autologous, and safe treatment, and therefore, share the results. To date, the

results of several studies have shown that mesenchymal stem cells and their derivatives can inhibit inflammation. Exosomes act as intercellular communication devices between cells for the transfer of active molecules. In this review, recent mesenchymal stem cells and their derivatives-based clinical trials for the cure of COVID-19 are introduced. This article is protected by copyright. All rights reserved.

Raghav, A., et al. (2021). "Mesenchymal Stem Cell-Derived Exosomes Exhibit Promising Potential for Treating SARS-CoV-2-Infected Patients." Cells **10**(3).

The novel coronavirus severe acute respiratory syndrome-CoV-2 (SARS-CoV-2) is responsible for COVID-19 infection. The COVID-19 pandemic represents one of the worst global threats in the 21st century since World War II. This pandemic has led to a worldwide economic recession and crisis due to lockdown. Biomedical researchers, pharmaceutical companies, and premier institutes throughout the world are claiming that new clinical trials are in progress. During the severe phase of this disease, mechanical ventilators are used to assist in the management of outcomes; however, their use can lead to the development of pneumonia. In this context, mesenchymal stem cell (MSC)-derived exosomes can serve as an immunomodulation treatment for COVID-19 patients. Exosomes possess anti-inflammatory, pro-angiogenic, and immunomodulatory properties that can be explored in an effort to improve the outcomes of SARS-CoV-2-infected patients. Currently, only one ongoing clinical trial (NCT04276987) is specifically exploring the use of MSC-derived exosomes as a therapy to treat SARS-CoV-2-associated pneumonia. The purpose of this review is to provide insights of using exosomes derived from mesenchymal stem cells in management of the co-morbidities associated with SARS-CoV-2-infected persons in direction of improving their health outcome. There is limited knowledge of using exosomes in SARS-CoV-2; the clinicians and researchers should exploit exosomes as therapeutic regime.

Rajarshi, K., et al. (2020). "Combating COVID-19 with mesenchymal stem cell therapy." Biotechnol Rep (Amst) **26**: e00467.

The COVID-19 disease is caused by a positive stranded RNA virus called SARS-CoV-2. The virus mainly targets the pulmonary epithelial cells as it's initial site of infection by letting its surface spike protein interact and bind to the host ACE2 receptor. The internalization and gradual replication of the virus results in an exaggerated immune response triggering release of many pro-inflammatory cytokines and chemokines. This immune storm is responsible for multiple health hazards in the host ultimately leading to multiple organ failure. Mesenchymal stem cell therapy offers a promising approach towards mitigating the delirious effects of the infection in the COVID-19 patients. This therapy has shown to reduce the expression of pro-inflammatory cytokines as well as repair of damaged tissues in COVID-19 patients. This review has been organized to put forward the positive aruments and implications in support of mesenchymal stem cell therapy as a necessary approach for treating COVID-19 patients.

Rezakhani, L., et al. (2021). "Mesenchymal stem cell (MSC)-derived exosomes as a cell-free therapy for patients Infected with COVID-19: Real opportunities and range of promises." Chem Phys Lipids **234**: 105009.

There are no commercially available effective antiviral medications or vaccines to deal with novel coronavirus disease (COVID-19). Hence there is a substantial unmet medical need for new and efficacious treatment options for COVID-19. Most COVID-19 deaths result from acute respiratory distress syndrome (ARDS). This virus induces excessive and aberrant inflammation so it is important to control the inflammation as soon as possible. To date, results of numerous studies have been shown that mesenchymal stem cells and their derivatives can suppress inflammation. Exosomes function as intercellular communication vehicles to transfer bioactive molecules (based on their origins), between cells. In this review, the recent exosome-based clinical trials for the treatment of COVID-19 are presented. Potential therapy may include the following items: First, using mesenchymal stem cells secretome. Second, incorporating specific miRNAs and mRNAs into exosomes and last, using exosomes as carriers to deliver drugs.

Riches, M. (2021). "The new world: hematopoietic stem cell transplant during a pandemic." Curr Opin Hematol.

PURPOSE OF REVIEW: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) impacted every facet of hematopoietic cell transplantation. This article reviews the adjustments to recipient and donor care that occurred in response to this unprecedented event. RECENT FINDINGS: Transplant centers modified algorithms, patient flow, education, and how we provided care. Our donor center partners reworked how donors were evaluated and products delivered to the transplant center. Our professional societies provided guidelines for patient and donor care and rapidly modified these based upon the never-ending stream of new data learned about SARS-CoV-2. Our research organizations provided rapid analyses to ensure the care modifications necessitated did not have a profound negative impact on our patients or donors. SUMMARY: The efforts of transplant providers and donor centers worldwide

allowed patients to receive the transplant needed with assurances that they were receiving the best care available despite the worldwide challenge.

Rozwadowski, M., et al. (2020). "Promoting Health and Well-Being Through Mobile Health Technology (Roadmap 2.0) in Family Caregivers and Patients Undergoing Hematopoietic Stem Cell Transplantation: Protocol for the Development of a Mobile Randomized Controlled Trial." JMIR Res Protoc **9**(9): e19288.

BACKGROUND: Cancer patients who undergo allogeneic hematopoietic stem cell transplantation are among the most medically fragile patient populations with extreme demands for caregivers. Indeed, with earlier hospital discharges, the demands placed on caregivers continue to intensify. Moreover, an increased number of allogeneic hematopoietic stem cell transplantations are being performed worldwide, and this expensive procedure has significant economic consequences. Thus, the health and well-being of family caregivers have attracted widespread attention. Mobile health technology has been shown to deliver flexible, and time- and cost-sparing interventions to support family caregivers across the care trajectory. OBJECTIVE: This protocol aims to leverage technology to deliver a novel caregiver-facing mobile health intervention named Roadmap 2.0. We will evaluate the effectiveness of Roadmap 2.0 in family caregivers of patients undergoing hematopoietic stem cell transplantation. METHODS: The Roadmap 2.0 intervention will consist of a mobile randomized trial comparing a positive psychology intervention arm with a control arm in family caregiver-patient dyads. The primary outcome will be caregiver health-related quality of life, as assessed by the PROMIS Global Health scale at day 120 post-transplant. Secondary outcomes will include other PROMIS caregiver- and patient-reported outcomes, including companionship, self-efficacy for managing symptoms, self-efficacy for managing daily activities, positive affect and well-being, sleep disturbance, depression, and anxiety. Semistructured qualitative interviews will be conducted among participants at the completion of the study. We will also measure objective physiological markers (eg, sleep, activity, heart rate) through wearable wrist sensors and health care utilization data through electronic health records. RESULTS: We plan to enroll 166 family caregiver-patient dyads for the full data analysis. The study has received Institutional Review Board approval as well as Code Review and Information Assurance approval from our health information technology services. Owing to the COVID-19 pandemic, the study has been briefly put on hold. However, recruitment began in August 2020. We have converted all recruitment, enrollment, and onboarding processes to be conducted remotely through video telehealth. Consent will be obtained electronically through the Roadmap 2.0 app.

Russo, D., et al. (2021). "Changes in Stem Cell Transplant activity and procedures during SARS-CoV2 pandemic in Italy: an Italian Bone Marrow Transplant Group (GITMO) nationwide analysis (TransCOVID-19 Survey)." Bone Marrow Transplant **56**(9): 2272-2275.

The Transplant Centers belonging to Gruppo Italiano per il Trapianto di Midollo Osseo (GITMO) conducted a survey with the aim of evaluating the effect of SARS-CoV2 pandemic on the allogeneic transplant activity in Italy. The pandemic period from 1/3/2020 to 31/7/2020 was compared with the same period in 2019. Overall, in 2020 there was a 2.4% reduction in the number of allo-HCT cases compared to 2019. Interestingly, this deflection did not affect the acute leukemia cases (+5.7% in 2020). The use of peripheral blood-derived stem cells (+10.7%) and cryopreservation (97.4% of the centers) was highly adopted in 2020. Despite the sanitary emergency, almost all of the surveyed centers declared no impact of SARS-CoV2 pandemic on the transplant timing and outcomes, and the sanitary policy was positively evaluated by the majority of centers. The emergency measures ensured that only a minority of the allo-HCT patients had been infected by SARS-CoV2; however, a mortality of 42.1% among the allo-HCT patients hospitalized for COVID-19 was recorded. This survey gives us the information that the GITMO Group reacted positively to the pandemic. Thanks to the emergency strategies, the Italian allo-HCT activity continued safely, showing only a minor deflection and offering the same probability of cure to the transplanted patients.

Sadeghi, S., et al. (2020). "Mesenchymal stem cell therapies for COVID-19: Current status and mechanism of action." Life Sci **262**: 118493.

The outbreak of COVID-19 in December 2019, has become an urgent and serious public health emergency. At present, there is no effective treatment or vaccine for COVID-19. Therefore, there is a crucial unmet need to develop a safe and effective treatment for COVID-19 patients. Mesenchymal stem cells (MSCs) are widely used in basic science and in a variety of clinical trials. MSCs are able to engraft to the damaged tissues after transplantation and promote tissue regeneration, besides MSCs able to secrete immunomodulatory factors that suppress the cytokine storms. Moreover, the contribution of MSCs to prevent cell death and inhibit tissue fibrosis is well established. In the current review article, the potential mechanisms by which MSCs contribute to the treatment of COVID-19 patients are highlighted. Also, current trials that evaluated the potential of MSC-based treatments for COVID-19 are briefly reviewed.

Saleh, M., et al. (2021). "Cell therapy in patients with COVID-19 using Wharton's jelly mesenchymal stem cells: a phase 1 clinical trial." Stem Cell Res Ther **12**(1): 410.

BACKGROUND: Mesenchymal stem cells (MSCs) have received particular attention because of their ability to modulate the immune system and inhibit inflammation caused by cytokine storms due to SARS-CoV-2. New alternative therapies may reduce mortality rates in patients with COVID19. This study aimed to assess the safety and efficacy of injecting intravenous Wharton's jelly-derived MSCs in patients with COVID-19 as a treatment. METHODS: In this study, five patients with severe COVID-19 were treated with Wharton's jelly-derived mesenchymal stem cells (150 x 106 cells per injection). These patients were subject to three intravenous injections 3 days apart, and monitoring was done on days 0, 3, 6, and 14 in routine tests, inflammatory cytokines, and flow cytometry of CD4 and CD8 markers. A lung CT scan was performed on base and days 14 and 28. In addition, IgM and IgG antibodies against SARS-CoV-2 were measured before and after treatment. RESULTS: The results showed that IL-10 and SDF-1 increased after cell therapy, but VEGF, TGF-beta, IFN-gamma, IL-6, and TNFalpha decreased. Routine hematology tests, myocardial enzyme tests, biochemical tests, and inflammation tests were performed for all patients before and after cell therapy on base and days 3, 6, and 14, which indicated the improvement of test results over time. COVID-19 antibody tests rose in 14 days after WJ-MSC injection. The total score of zonal involvement in both lungs was improved. CONCLUSIONS: In patients, the trend of tests was generally improving, and we experienced a reduction in inflammation. No serious complications were observed in patients except the headache in one of them, which was resolved without medication. In this study, we found that patients with severe COVID-19 in the inflammatory phase respond better to cell therapy. More extensive clinical trials should be performed in this regard. TRIAL REGISTRATION: IRCT, IRCT20190717044241N2 . Registered April 22, 2020.

Schultz, I. C., et al. (2021). "Mesenchymal Stem Cell-Derived Extracellular Vesicles Carrying miRNA as a Potential Multi Target Therapy to COVID-19: an In Silico Analysis." Stem Cell Rev Rep **17**(2): 341-356.

In the end of 2019 COVID-19 emerged as a new threat worldwide and this disease present impaired immune system, exacerbated production of inflammatory cytokines, and coagulation disturbs. Mesenchymal stem cell (MSC) derived extracellular vesicles (EVs) have emerged as a therapeutic option due to its intrinsic properties to alleviate inflammatory responses, capable to promote the restoring of injured tissue. EVs contain heterogeneous cargo, including active microRNAs, small noncoding sequences involved in post-transcriptional gene repression or degradation and can attach in multiple targets. This study investigated whether the MSC-EVs miRNA cargo has the capacity to modulate the exacerbated cytokines, cell death and coagulation disturbs present in severe COVID-19. Through bioinformatics analysis, four datasets of miRNA, using different stem cell tissue sources (bone marrow, umbilical cord and adipose tissue), and one dataset of mRNA (bone marrow) were analyzed. 58 miRNAs overlap in the four miRNA datasets analyzed. Sequentially, those miRNAs present in at least two datasets, were analyzed using miRWalk for the 3'UTR binding target mRNA. The result predicted 258 miRNAs for exacerbated cytokines and chemokines, 266 miRNAs for cell death genes and 148 miRNAs for coagulation cascades. Some miRNAs may simultaneously attenuate inflammatory agents, inhibit cell death genes and key factors of coagulation cascade, consequently preventing tissue damage and coagulation disturbs. Therefore, the MSC-derived EVs due to their heterogeneous cargo are a potential multitarget approach able to improve the survival rates of severe COVID-19 patients.

Schuster, M. A. (2021). "Creating the Hematology/Oncology/Stem Cell Transplant Advancing Resiliency Team: A Nurse-Led Support Program for Hematology/Oncology/Stem Cell Transplant Staff." J Pediatr Oncol Nurs **38**(5): 331-341.

Background: Burnout, moral distress, compassion fatigue, and posttraumatic stress disorder are concerns for health-care staff. Due to the high mental, physical, and emotional demands of the pediatric hematology/oncology profession, workplace supports should be in place to address the needs of the staff. A nurse-led support program is one strategy to enhance staff well-being. Methods: The Hematology/Oncology/Stem Cell Transplant Advancing Resiliency Team (HART) is a nurse-led peer-to-peer on-site support program for multidisciplinary staff caring for hematology/oncology patients. HART coaches, working 8-hour shifts, covering both day and night shift hours, are present 3 days a week on the unit. HART offers a confidential space for one on one or group interactions, educational sessions, assistance with work related, patient-care based, or personal concerns, and various forms of integrative therapies. Results: There have been over 1,100 coach consults and 98 HART shifts worked. The most commonly reported changes since HART began include staff feeling more supported by leadership and staff making time for breaks during the work shift. A 25.6% increase in staff reporting to be extremely satisfied with unit support was found. Discussion: Cultivating a culture of staff support is important. Due to COVID-19, physical HART coach presence was put on hold for 4 weeks and virtual interventions were

trialed. Since its return, coach consult numbers have been steadily rising. Having a support program led by coaches with direct experience understanding the emotional toll of caring for the pediatric hematology/oncology patient population was found to be well utilized, feasible through donor funding, and measurable via staff report.

Sever, T., et al. (2021). "Thoracic Air Leak Syndrome, Pulmonary Aspergillosis, and COVID-19 Pneumonia After Allogeneic Stem Cell Transplantation in a Child With Myelodysplastic Syndrome." J Pediatr Hematol Oncol.

Thoracic air leak syndromes (TALS) are very rare among the noninfectious pulmonary complications (PCs). They can either be idiopathic or have several risk factors such as allogeneic hematopoietic stem cell transplantation (allo-HSCT), graft versus host disease and rarely pulmonary aspergillosis. We present a 14-year-old girl with hypoplastic myelodysplastic syndrome who developed graft versus host disease on day 60, TALS on day 150, bronchiolitis obliterans syndrome on day 300, pulmonary aspergillosis on day 400 and COVID-19 pneumonia on day 575 after allo-HSCT. This is the first report of a child who developed these subsequent PCs after allo-HSCT. Therefore, the manifestations of these unfamiliar PCs like TALS and COVID-19 pneumonia, and concomitant pulmonary aspergillosis with management options are discussed.

Sharma, A., et al. (2021). "Clinical characteristics and outcomes of COVID-19 in haematopoietic stem-cell transplantation recipients: an observational cohort study." Lancet Haematol **8**(3): e185-e193.

BACKGROUND: Haematopoietic stem-cell transplantation (HSCT) recipients are considered at high risk of poor outcomes after COVID-19 on the basis of their immunosuppressed status, but data from large studies in HSCT recipients are lacking. This study describes the characteristics and outcomes of HSCT recipients after developing COVID-19. METHODS: In response to the pandemic, the Center for International Blood and Marrow Transplant Research (CIBMTR) implemented a special form for COVID-19-related data capture on March 27, 2020. All patients-irrespective of age, diagnosis, donor type, graft source, or conditioning regimens-were included in the analysis with data cutoff of Aug 12, 2020. The main outcome was overall survival 30 days after a COVID-19 diagnosis. Overall survival probabilities were calculated using Kaplan-Meier estimator. Factors associated with mortality after COVID-19 diagnosis were examined using Cox proportional hazard models. FINDINGS: 318 HSCT recipients diagnosed with COVID-19 were reported to the CIBMTR. The median time from HSCT to COVID-19 diagnosis was 17 months (IQR 8-46) for allogeneic HSCT recipients and 23 months (8-51) for autologous HSCT recipients. The median follow-up of survivors was 21 days (IQR 8-41) for allogeneic HSCT recipients and 25 days (12-35) for autologous HSCT recipients. 34 (18%) of 184 allogeneic HSCT recipients were receiving immunosuppression within 6 months of COVID-19 diagnosis. Disease severity was mild in 155 (49%) of 318 patients, while severe disease requiring mechanical ventilation occurred in 45 (14%) of 318 patients-ie, 28 (15%) of 184 allogeneic HSCT recipients and 17 (13%) of 134 autologous HSCT recipients. At 30 days after the diagnosis of COVID-19, overall survival was 68% (95% CI 58-77) for recipients of allogeneic HSCT and 67% (55-78) for recipients of autologous HSCT. Age 50 years or older (hazard ratio 2.53, 95% CI 1.16-5.52; p=0.020); male sex (3.53; 1.44-8.67; p=0.006), and development of COVID-19 within 12 months of transplantation (2.67, 1.33-5.36; p=0.005) were associated with a higher risk of mortality among allogeneic HSCT recipients, and a disease indication of lymphoma was associated with a higher risk of mortality compared with plasma cell disorder or myeloma (2.41, [1.08-5.38]; p=0.033) in autologous HSCT recipients.

Shetty, A. K. (2020). "Mesenchymal Stem Cell Infusion Shows Promise for Combating Coronavirus (COVID-19)- Induced Pneumonia." Aging Dis **11**(2): 462-464.

A new study published by the journal Aging & Disease reported that intravenous administration of clinical-grade human mesenchymal stem cells (MSCs) into patients with coronavirus disease 2019 (COVID-19) resulted in improved functional outcomes (Leng et al., Aging Dis, 11:216-228, 2020). This study demonstrated that intravenous infusion of MSCs is a safe and effective approach for treating patients with COVID-19 pneumonia, including elderly patients displaying severe pneumonia. COVID-19 is a severe acute respiratory illness caused by a new coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Currently, treating COVID-19 patients, particularly those afflicted with severe pneumonia, is challenging as no specific drugs or vaccines against SARS-CoV-2 are available. Therefore, MSC therapy inhibiting the overactivation of the immune system and promoting endogenous repair by improving the lung microenvironment after the SARS-CoV-2 infection found in this study is striking. Additional studies in a larger cohort of patients are needed to validate this therapeutic intervention further, however.

Shi, L., et al. (2021). "Mesenchymal stem cell therapy for severe COVID-19." Signal Transduct Target Ther **6**(1): 339.

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has placed a global

public burden on health authorities. Although the virological characteristics and pathogenesis of COVID-19 has been largely clarified, there is currently no specific therapeutic measure. In severe cases, acute SARS-CoV-2 infection leads to immune disorders and damage to both the adaptive and innate immune responses. Having roles in immune regulation and regeneration, mesenchymal stem cells (MSCs) serving as a therapeutic option may regulate the over-activated inflammatory response and promote recovery of lung damage. Since the outbreak of the COVID-19 pandemic, a series of MSC-therapy clinical trials has been conducted. The findings indicate that MSC treatment not only significantly reduces lung damage, but also improves patient recovery with safety and good immune tolerance. Herein, we summarize the recent progress in MSC therapy for COVID-19 and highlight the challenges in the field.

Simoneau, C. R. and M. Ott (2020). "Modeling Multi-organ Infection by SARS-CoV-2 Using Stem Cell Technology." Cell Stem Cell **27**(6): 859-868.

SARS-CoV-2, the virus causing the current COVID-19 pandemic, primarily targets the airway epithelium and in lungs can lead to acute respiratory distress syndrome. Clinical studies in recent months have revealed that COVID-19 is a multi-organ disease causing characteristic complications. Stem cell models of various organ systems-most prominently, lung, gut, heart, and brain-are at the forefront of studies aimed at understanding the role of direct infection in COVID-19 multi-organ dysfunction.

Singh, B., et al. (2021). "Stem cell therapies and benefaction of somatic cell nuclear transfer cloning in COVID-19 era." Stem Cell Res Ther **12**(1): 283.

BACKGROUND: The global health emergency of COVID-19 has necessitated the development of multiple therapeutic modalities including vaccinations, antivirals, anti-inflammatory, and cytoimmunotherapies, etc. COVID-19 patients suffer from damage to various organs and vascular structures, so they present multiple health crises. Mesenchymal stem cells (MSCs) are of interest to treat acute respiratory distress syndrome (ARDS) caused by SARS-CoV-2 infection. MAIN BODY: Stem cell-based therapies have been verified for prospective benefits in copious preclinical and clinical studies. MSCs confer potential benefits to develop various cell types and organoids for studying virus-human interaction, drug testing, regenerative medicine, and immunomodulatory effects in COVID-19 patients. Apart from paving the ways to augment stem cell research and therapies, somatic cell nuclear transfer (SCNT) holds unique ability for a wide range of health applications such as patient-specific or isogenic cells for regenerative medicine and breeding transgenic animals for biomedical applications. Being a potent cell genome-reprogramming tool, the SCNT has increased prominence of recombinant therapeutics and cellular medicine in the current era of COVID-19. As SCNT is used to generate patient-specific stem cells, it avoids dependence on embryos to obtain stem cells. CONCLUSIONS: The nuclear transfer cloning, being an ideal tool to generate cloned embryos, and the embryonic stem cells will boost drug testing and cellular medicine in COVID-19.

Singh, S., et al. (2021). "Mitigation of in-hospital risk of coronavirus disease 2019: Experience from a haematology-oncology and stem cell transplant setting." Natl Med J India **34**(1): 10-14.

Background: Coronavirus disease 2019 (Covid-19) was first described in December 2019 and has evolved into an ongoing global pandemic. Cancer patients on chemotherapy are immunocompromised and are at the highest risk of Covid-19-related complications. We describe our experience with the management of haematology-oncology and stem cell transplant (SCT) patients receiving curative chemotherapy in a hospital with a high influx of Covid-19 patients. Methods: . We did a prospective observational study at a 99-bedded cancer centre of a tertiary care teaching hospital from April 2020 to September 2020. Preventive measures taken were categorized as follows: (i) staff: screening, mandatory use of personal protective equipment (PPE), risk stratification of potential exposure and testing and isolation as needed; (ii) patients: mandatory viral polymerase chain reaction testing, segregation of positive and untested patients and testing of family members; and (iii) environment: mandatory regular cleaning, visitor restriction, telemedicine services and reassignment of priority to clinic visits. Treatment of the underlying conditions was continued with added precautions. Results: . A total of 54 patients were included in the analysis, including 48 with haematological malignancies and 6 for stem cell therapy. Preventive measures were universally applied, and chemotherapy with a curative intent was initiated as per protocol. Three patients were detected to have Covid-19 infection before admission and one after the institution of chemotherapy. Nine patients died after the first cycle of chemotherapy, 2 due to severe Covid-19-related illness and 7 due to complications of chemotherapy or disease progression. Conclusions: . In the wake of the Covid-19 pandemic, treatment for haematological malignancies must continue while balancing the risk of Covid-19 infections. Our report emphasizes the effectiveness of measures such as hand hygiene, social isolation, patient segregation, use of masks and PPE and universal pre-treatment testing for Covid-19 in reducing the risk of infection in a high-risk clinical setting.

Song, N., et al. (2021). "Mesenchymal stem cell immunomodulation: In pursuit of controlling COVID-19 related cytokine storm." Stem Cells **39**(6): 707-722.

The coronavirus disease 2019 (COVID-19) pandemic has grown to be a global public health crisis with no safe and effective treatments available yet. Recent findings suggest that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the coronavirus pathogen that causes COVID-19, could elicit a cytokine storm that drives edema, dysfunction of the airway exchange, and acute respiratory distress syndrome in the lung, followed by acute cardiac injury and thromboembolic events leading to multiorgan failure and death. Mesenchymal stem cells (MSCs), owing to their powerful immunomodulatory abilities, have the potential to attenuate the cytokine storm and have therefore been proposed as a potential therapeutic approach for which several clinical trials are underway.

Spinetti, G., et al. (2021). "Treatment of COVID-19 by stage: any space left for mesenchymal stem cell therapy?" Regen Med **16**(5): 477-494.

In many countries, COVID-19 now accounts for more deaths per year than car accidents and even the deadliest wars. Combating the viral pandemics requires a coordinated effort to develop therapeutic protocols adaptable to the disease severity. In this review article, we summarize a graded approach aiming to shield cells from SARS-CoV-2 entry and infection, inhibit excess inflammation and evasion of the immune response, and ultimately prevent systemic organ failure. Moreover, we focus on mesenchymal stem cell therapy, which has shown safety and efficacy as a treatment of inflammatory and immune diseases. The cell therapy approach is now repurposed in patients with severe COVID-19. Numerous trials of mesenchymal stem cell therapy are ongoing, especially in China and the USA. Leader companies in cell therapy have also started controlled trials utilizing their quality assessed cell products. Results are too premature to reach definitive conclusions.

Sukhanov, Y. V., et al. (2020). "Mesenchymal Stem Cell Therapy-Is the Vessel Half Full or Half Empty?" Russ J Dev Biol **51**(4): 267-270.

The urgency of the search and introduction into medical practice of the method for the therapy of severe forms of pneumonia COVID-19 is due to the lack of effective treatment methods that can destroy the pathogen. Expectations of a good clinical effect from the application of mesenchymal stem cells (MSCs) are not groundless: there is a scientific justification in using MSCs for the treatment of inflammatory diseases and of the proven mechanisms of their action. Along with this, there are very little reliable data about the mechanism of MSCs' action when they are systemically administrated to a human or on the distribution of cells in the body and the long-term consequences of such administration. Data from model experiments are contradictory both concerning the specific action of MSCs and their safety. If clinical studies show an acceptable risk/benefit ratio for the application of MSCs, countries in which such studies have been conducted can expect their introduction into medical practice. In Russia, it is necessary to initiate experimental verification of the specific action of MSCs and the risks of their use in COVID-19 conditions in a sufficient quantity, and, in parallel, to create a mechanism for accelerated but justified admission of biomedical cell products into practice.

Tiwari, S. K., et al. (2021). "Revealing Tissue-Specific SARS-CoV-2 Infection and Host Responses using Human Stem Cell-Derived Lung and Cerebral Organoids." Stem Cell Reports **16**(3): 437-445.

COVID-19 is a transmissible respiratory disease caused by a novel coronavirus, SARS-CoV-2, and has become a global health emergency. There is an urgent need for robust and practical in vitro model systems to investigate viral pathogenesis. Here, we generated human induced pluripotent stem cell (iPSC)-derived lung organoids (LORGs), cerebral organoids (CORGs), neural progenitor cells (NPCs), neurons, and astrocytes. LORGs containing epithelial cells, alveolar types 1 and 2, highly express ACE2 and TMPRSS2 and are permissive to SARS-CoV-2 infection. SARS-CoV-2 infection induces interferons, cytokines, and chemokines and activates critical inflammasome pathway genes. Spike protein inhibitor, EK1 peptide, and TMPRSS2 inhibitors (camostat/nafamostat) block viral entry in LORGs. Conversely, CORGs, NPCs, astrocytes, and neurons express low levels of ACE2 and TMPRSS2 and correspondingly are not highly permissive to SARS-CoV-2 infection. Infection in neuronal cells activates TLR3/7, OAS2, complement system, and apoptotic genes. These findings will aid in understanding COVID-19 pathogenesis and facilitate drug discovery.

Torres, J. P., et al. (2020). "[Respiratory viral infections during episodes of fever in children undergoing hematopoietic stem cell transplantation]." Rev Chilena Infectol **37**(4): 371-382.

BACKGROUND: Children undergoing hematopoietic stem cell transplant (HSCT) can develop respiratory viral infections (RVI) during fever episodes. There are few data about clinical outcomes in RVI and compared to bacterial infections (BI) in this population. AIM: To determine clinical outcome of RVI, compared to BI in children with HSCT. METHODS: Prospective study, patients </= 18 years with cancer and HSCT admitted with fever at a National Bone Marrow Transplant Center (Hospital Calvo Mackenna), Chile, (April-2016 to May-2019). Clinical assessment, laboratory tests, blood cultures, nasopharyngeal sample for multiplex-PCR

(Filmarray(R)), viral loads by PCR and cytokine panel (Luminex(R), 38 cytokines) were performed. The following outcomes were evaluated: upper/lower respiratory tract disease (RTD), admission to ICU, mechanical ventilation, mortality and antimicrobial withdrawal. RESULTS: Of 56 febrile episodes, 35 (63%) were RVI, 12 (21%) BI and 9 (16%) with unknown etiology (UE). Median of age was 8.5 years, 62% male gender. Rhinovirus (54%) and coronavirus (15%) were the more frequent detected viruses. No significant differences in cytokine levels were observed between RVI and BI. 94% of RVI patients had symptomatic RTD, versus 33% in BI and 33% in UE group ($p < 0.001$), with lower-RTD in 69% of RVI group ($p < 0,001$). Admission to ICU was 11% in RVI, 17% in BI and 11% in UE group ($p = 0.88$); only 2 patients required mechanical ventilation ($p = 0.37$) and no mortality was reported. After an RVI was detected by PCR, antimicrobials were withdrawal in 26% of patients with RVI (p: 0.04). CONCLUSION: RVI are frequent etiologic agents in febrile episodes of patients with HSCT. Viral detection might help to rationalize the use of antimicrobials in this population.

Ulrich, H. and M. M. Pillat (2020). "CD147 as a Target for COVID-19 Treatment: Suggested Effects of Azithromycin and Stem Cell Engagement." Stem Cell Rev Rep **16**(3): 434-440.

The expressive number of deaths and confirmed cases of SARS-CoV-2 call for an urgent demand of effective and available drugs for COVID-19 treatment. CD147, a receptor on host cells, is a novel route for SARS-CoV-2 invasion. Thus, drugs that interfere in the spike protein/CD147 interaction or CD147 expression may inhibit viral invasion and dissemination among other cells, including in progenitor/stem cells. Studies suggest beneficial effects of azithromycin in reducing viral load of hospitalized patients, possibly interfering with ligand/CD147 receptor interactions; however, its possible effects on SARS-CoV-2 invasion has not yet been evaluated. In addition to the possible effect in invasion, azithromycin decreases the expression of some metalloproteinases (downstream to CD147), induces anti-viral responses in primary human bronchial epithelial infected with rhinovirus, decreasing viral replication and release. Moreover, resident lung progenitor/stem are extensively differentiated into myofibroblasts during pulmonary fibrosis, a complication observed in COVID-19 patients. This process, and the possible direct viral invasion of progenitor/stem cells via CD147 or ACE2, could result in the decline of these cellular stocks and failing lung repair. Clinical tests with allogeneic MSCs from healthy individuals are underway to enhance endogenous lung repair and suppress inflammation.

Valentini, C. G., et al. (2021). "Coronavirus disease 2019 pandemic and allogeneic hematopoietic stem cell transplantation: a single center reappraisal." Cytotherapy **23**(7): 635-640.

BACKGROUND: The coronavirus disease 2019 (COVID-19) pandemic has deeply modified the complex logistical process underlying allogeneic hematopoietic stem cell transplant practices. AIM: In light of these changes, the authors compared data relative to allogeneic transplants carried out from 2018 at their center before (n = 167) and during the pandemic (n = 45). METHODS: The authors examined patient characteristics, donor and graft types, cell doses and main transplant outcomes. Moreover, the authors evaluated the rise of costs attributable to additional COVID-19-related procedures as well as the risk of adverse events these procedures conveyed to grafts or recipients. RESULTS: Overall, the number of transplants did not decrease during the pandemic, whereas patients at high relapse risk were prioritized. Transplants were mainly from matched unrelated donors, with a significant decrease in haploidentical related donors. Moreover, the use of bone marrow as a graft for haploidentical transplant was almost abandoned. Cryopreservation was introduced for all related and unrelated apheresis products, with a median storage time of 20 days. Notably, transplant outcomes (engraftment, acute graft-versus-host disease and non-relapse mortality) with cryopreserved products were comparable to those with fresh products. CONCLUSIONS: Considering that the emergency situation may persist for months, cryopreserving allogeneic grafts can offer a lifesaving opportunity for patients whose allogeneic transplant cannot be postponed until after the end of the COVID-19 pandemic.

Via, V. D., et al. (2021). "Possible Reactivation of SARS-CoV-2 in a Patient with Acute Myeloid Leukemia Undergoing Allogeneic Hematopoietic Stem Cell Transplantation: a Case Report." SN Compr Clin Med: 1-5.

Reactivation or reinfection cases of SARS-CoV-2 are known but there is scarce evidence about reactivation in immunocompromised patients. Here, we report the case of a 61-year-old male undergoing a conditioning regimen with fludarabine, cyclophosphamide, and 2-Gy total body irradiation in preparation of a haplo-identical allogeneic hematopoietic stem cell transplantation (allo-HSCT) for acute myeloid leukemia (AML). He received the first dose of a COVID-19 vaccine 6 weeks prior allo-HSCT and was hospitalized a month prior because of a COVID-19 bilateral pneumonia. On discharge, he showed two negative SARS-CoV-2 nasopharyngeal PCR swabs as well as a high SARS-CoV-2 antibody titer. On admission for allo-HSCT, he tested negative

for SARS-CoV-2 again. Conditioning with fludarabine, cyclophosphamide, and 2-Gy total body irradiation was started and the patient developed lymphopenia. During his hospital stay, he tested positive for SARS-CoV-2 in a PCR test twice but remained asymptomatic. The conditioning regimen was continued as planned. Later during his stay, the patient showed undetectable SARS-CoV-2 load four times. This case documents possible reactivation of SARS-CoV-2 and raises questions about reactivation risks among recipients of stem cell transplants and other immunocompromised patients.

Wang, H. C., et al. (2020). "Stem Cell Transplantation Therapy: A Potential Method for Treating Cytokine Storm Syndromes Induced by COVID-19." Cell Transplant **29**: 963689720965980.

Novel therapies are urgently needed to combat the severe cytokine storm syndromes induced by coronavirus disease 2019 (COVID-19). An increasing number of preclinical and clinical investigations of stem cell and derivatives therapy for COVID-19 were being carried out, among which several studies have preliminarily demonstrated the safety and possible efficacy of stem cell transplantation therapy, providing a hint to solve the tricky situation of anti-COVID-19.

Wang, L. T., et al. (2021). "Advances in mesenchymal stem cell therapy for immune and inflammatory diseases: Use of cell-free products and human pluripotent stem cell-derived mesenchymal stem cells." Stem Cells Transl Med **10**(9): 1288-1303.

Mesenchymal stem cell therapy (MSCT) for immune and inflammatory diseases continues to be popular based on progressive accumulation of preclinical mechanistic evidence. This has led to further expansion in clinical indications from graft rejection, autoimmune diseases, and osteoarthritis, to inflammatory liver and pulmonary diseases including COVID-19. A clear trend is the shift from using autologous to allogeneic MSCs, which can be immediately available as off-the-shelf products. In addition, new products such as cell-free exosomes and human pluripotent stem cell (hPSC)-derived MSCs are exciting developments to further prevalent use. Increasing numbers of trials have now published results in which safety of MSCT has been largely demonstrated. While reports of therapeutic endpoints are still emerging, efficacy can be seen for specific indications-including graft-vs-host-disease, strongly Th17-mediated autoimmune diseases, and osteoarthritis-which are more robustly supported by mechanistic preclinical evidence. In this review, we update and discuss outcomes in current MSCT clinical trials for immune and inflammatory disease, as well as new innovation and emerging trends in the field.

Williams, T. L., et al. (2021). "Human embryonic stem cell-derived cardiomyocyte platform screens inhibitors of SARS-CoV-2 infection." Commun Biol **4**(1): 926.

Patients with cardiovascular comorbidities are more susceptible to severe infection with SARS-CoV-2, known to directly cause pathological damage to cardiovascular tissue. We outline a screening platform using human embryonic stem cell-derived cardiomyocytes, confirmed to express the protein machinery critical for SARS-CoV-2 infection, and a SARS-CoV-2 spike-pseudotyped virus system. The method has allowed us to identify benztropine and DX600 as novel inhibitors of SARS-CoV-2 infection in a clinically relevant stem cell-derived cardiomyocyte line. Discovery of new medicines will be critical for protecting the heart in patients with SARS-CoV-2, and for individuals where vaccination is contraindicated.

Willis, C. M., et al. (2020). "Harnessing the Neural Stem Cell Secretome for Regenerative Neuroimmunology." Front Cell Neurosci **14**: 590960.

Increasing evidence foresees the secretome of neural stem cells (NSCs) to confer superimposable beneficial properties as exogenous NSC transplants in experimental treatments of traumas and diseases of the central nervous system (CNS). Naturally produced secretome biologics include membrane-free signaling molecules and extracellular membrane vesicles (EVs) capable of regulating broad functional responses. The development of high-throughput screening pipelines for the identification and validation of NSC secretome targets is still in early development. Encouraging results from pre-clinical animal models of disease have highlighted secretome-based (acellular) therapeutics as providing significant improvements in biochemical and behavioral measurements. Most of these responses are being hypothesized to be the result of modulating and promoting the restoration of key inflammatory and regenerative programs in the CNS. Here, we will review the most recent findings regarding the identification of NSC-secreted factors capable of modulating the immune response to promote the regeneration of the CNS in animal models of CNS trauma and inflammatory disease and discuss the increased interest to refine the pro-regenerative features of the NSC secretome into a clinically available therapy in the emerging field of Regenerative Neuroimmunology.

Wong, C. K., et al. (2020). "Human-Induced Pluripotent Stem Cell-Derived Cardiomyocytes Platform to Study SARS-CoV-2 Related Myocardial Injury." Circ J **84**(11): 2027-2031.

BACKGROUND: SARS-CoV-2 infection is associated with myocardial injury, but there is a paucity of experimental platforms for the condition.Methods and Results:Human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) infected by SARS-CoV-2 for 3 days ceased beating and exhibited cytopathogenic changes with reduced viability. Active viral replication was

evidenced by an increase in supernatant SARS-CoV-2 and the presence of SARS-CoV-2 nucleocaspid protein within hiPSC-CMs. Expressions of BNP, CXCL1, CXCL2, IL-6, IL-8 and TNF-alpha were upregulated, while ACE2 was downregulated. CONCLUSIONS: Our hiPSC-CM-based in-vitro SARS-CoV-2 myocarditis model recapitulated the cytopathogenic effects and cytokine/chemokine response. It could be exploited as a drug screening platform.

Wu, F., et al. (2021). "Generation of WAe001-A-58 human embryonic stem cell line with inducible expression of the SARS-CoV-2 nucleocapsid protein." Stem Cell Res **53**: 102197.

Excessive prostaglandin E2 (PGE2) is the key pathological basis for COVID-19 and a Celebrex treatment of hospitalized COVID-19 patients with comorbidities led to 100% discharged rate and zero death (Hong et al. 2020). It is also suggested that SARS-CoV-2 infected multiple organs and the SARS-CoV nucleocapsid (N) protein transcriptionally drives the expression of the host COX-2 gene. In order to test whether SARS-CoV-2 N protein activates COX-2 transcription in multiple human relevant cell types, an expression inducible human embryonic stem cell line was generated by piggyBac transposon system. This cell line maintained its pluripotency, differentiation potentials, normal morphology and karyotype.

Xiong, J., et al. (2021). "Mesenchymal Stem Cell-Based Therapy for COVID-19: Possibility and Potential." Curr Stem Cell Res Ther **16**(2): 105-108.

A novel coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV- 2) has emerged in Wuhan, China since the end of December 2019 and has quickly spread all over the world in a matter of two months. To date, no specific treatment has been proven to be effective for coronavirus (COVID-19). With the rapid increase of infected patients and deaths, it is vital to explore an effective treatment for COVID-19. Current studies suggest that there exists cytokine storm in SARS-CoV-2-infected patients; some of the them will develop acute respiratory distress syndrome (ARDS) and multiple organ dysfunction, and even death. Mesenchymal stem cells (MSCs) possess the property of immunomodulation. Given the previous preclinical and clinical studies, MSCs therapy has shown safety and efficacy in the treatment of respiratory failure or ARDS. Based on similar principles, MSCs therapy may also be an effective therapy in the treatment of COVID-19. In this study, we summarized the clinical outcomes of MSCs for ARDS patients in some preclinical and clinical studies and discussed the application of MSCs for patients with COVID-19 in China and the related important issues with MSCs used during the outbreak.

Yadav, P., et al. (2020). "Mesenchymal stem cell immunomodulation and regeneration therapeutics as an ameliorative approach for COVID-19 pandemics." Life Sci **263**: 118588.

The severe acute respiratory syndrome-novel coronavirus mediated COVID-19 has been recently declared a pandemic by the World Health Organization. The primary target of the SARS-CoV-2 virus is the human lungs governed by the ACE-2 receptor of epithelial type II cells/endothelial cells, which promote modulation of the immune response of host cells through generating cytokine storm, inflammation, severe pneumonia symptoms, and secondary complications such as acute respiratory distress syndrome. Although numerous antiviral and anti-parasitic drugs are under clinical trials to combat this pandemic, to date, neither a specific treatment nor any successful vaccine has been established, urging researchers to identify any potential candidate for combating the disease. Mesenchymal stem cells own self-renewal, differentiation, homing, immunomodulation and remains unaffected by the coronavirus on the virtue of the absence of ACE-2 receptors, indicating that MSC's could be used an ameliorative approach for COVID-19. MSCs have shown to combat the disease via various pathways such as repairing the lung epithelial and endothelial cells, reducing hyperimmune response, maintaining the renin-angiotensin system. Although MSCs-based treatment approaches for COVID-19 is still under consideration with limited data, many human clinical trials of MSC's has been initiated to explore their potential for COVID 19 treatment. The current review summarizes and emphasizes on how MSC's modulate the immune response, can repair the lungs from the impact of the virus, and various aspects of MSC's as a remedial source for COVID-19, to provide better insight for biomedical researchers and for those who are fascinated by stem cells as a therapeutic approach.

Yanagida, S., et al. (2021). "Comprehensive Cardiotoxicity Assessment of COVID-19 Treatments Using Human-Induced Pluripotent Stem Cell-Derived Cardiomyocytes." Toxicol Sci **183**(1): 227-239.

Coronavirus disease 2019 (COVID-19) continues to spread across the globe, with numerous clinical trials underway seeking to develop and test effective COVID-19 therapies, including remdesivir. Several ongoing studies have reported hydroxychloroquine-induced cardiotoxicity, including development of torsade de pointes (TdP). Meanwhile, human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) are expected to serve as a tool for assessing drug-induced cardiotoxicity, such as TdP and contraction impairment. However, the cardiotoxicity of COVID-19 treatments has not been fully assessed using hiPSC-CMs. In this study, we

focused on drug repurposing with various modes of actions and examined the TdP risk associated with COVID-19 treatments using field potential using multi-electrode array system and motion analysis with hiPSC-CMs. Hydroxychloroquine induced early after depolarization, while remdesivir, favipiravir, camostat, and ivermectin had little effect on field potentials. We then analyzed electromechanical window, which is defined as the difference between field potential and contraction-relaxation durations. Hydroxychloroquine decreased electromechanical window of hiPSC-CMs in a concentration-dependent manner. In contrast, other drugs had little effect. Our data suggest that hydroxychloroquine has proarrhythmic risk and other drugs have low proarrhythmic risk. Thus, hiPSC-CMs represent a useful tool for assessing the comprehensive cardiotoxicity caused by COVID-19 treatments in nonclinical settings.

Yang, L., et al. (2020). "A Human Pluripotent Stem Cell-based Platform to Study SARS-CoV-2 Tropism and Model Virus Infection in Human Cells and Organoids." Cell Stem Cell **27**(1): 125-136 e127.

SARS-CoV-2 has caused the COVID-19 pandemic. There is an urgent need for physiological models to study SARS-CoV-2 infection using human disease-relevant cells. COVID-19 pathophysiology includes respiratory failure but involves other organ systems including gut, liver, heart, and pancreas. We present an experimental platform comprised of cell and organoid derivatives from human pluripotent stem cells (hPSCs). A Spike-enabled pseudo-entry virus infects pancreatic endocrine cells, liver organoids, cardiomyocytes, and dopaminergic neurons. Recent clinical studies show a strong association with COVID-19 and diabetes. We find that human pancreatic beta cells and liver organoids are highly permissive to SARS-CoV-2 infection, further validated using adult primary human islets and adult hepatocyte and cholangiocyte organoids. SARS-CoV-2 infection caused striking expression of chemokines, as also seen in primary human COVID-19 pulmonary autopsy samples. hPSC-derived cells/organoids provide valuable models for understanding the cellular responses of human tissues to SARS-CoV-2 infection and for disease modeling of COVID-19.

Yao, D., et al. (2020). "Mesenchymal stem cell research progress for the treatment of COVID-19." J Int Med Res **48**(9): 300060520955063.

At the end of 2019, novel coronavirus (COVID-19) infection was detected in Wuhan City, Hubei Province, China. The COVID-19 infection characteristics include a long incubation period, strong infectivity, and high fatality rate, and it negatively affects human health and social development. COVID-19 has become a common problem in the global medical and health system. It is essentially an acute self-limiting disease. Patients with severe COVID-19 infection usually progress to acute respiratory distress syndrome, sepsis, metabolic acidosis that is difficult to correct, coagulation dysfunction, multiple organ failure, and even death within a short period after onset. There remains a lack of effective drugs for such patients clinically. Mesenchymal stem cells (MSCs) are expected to reduce the risk of complications and death in patients because they have strong anti-inflammatory and immunomodulatory capabilities, which can improve the microenvironment, promote neovascularization, and enhance tissue repair capabilities. China is currently conducting several clinical trials on MSCs for the treatment of COVID-19. Here, we review the research progress related to using stem cells to treat patients with COVID-19.

Yao, M., et al. (2020). "[Possibility of mesenchymal stem cell transplantation in the treatment of coronavirus disease 2019]." Zhonghua Wei Zhong Bing Ji Jiu Yi Xue **32**(9): 1139-1144.

2019 Novel coronavirus (2019-nCoV) infection has caused a global pandemic. Although researchers have carried out a lot of research on 2019-nCoV, analyzed the molecular structure and conducted evolutionary tree analysis, there is still insufficient understanding of its specific pathogenic mechanism, resulting in the lack of specific and effective therapeutic drugs and method. 2019-nCoV infection can cause inflammation and may deteriorate to acute respiratory distress syndrome (ARDS) and sepsis, which have become the main complication of its death. Therefore, using antiviral and symptomatic treatment with inflammation reduction can have a better therapeutic effect. Mesenchymal stem cells (MSCs) not only have a significant immune-regulation function, but also play a role in regeneration and repair, repairing damaged lungs, so they can be considered as a new effective method for the treatment of coronavirus disease 2019 (COVID-19). This article analyzes the main pathogenic mechanism of 2019-nCoV, and the process of developing into ARDS, combined with the research status of MSCs, to explore its significance and feasibility for the treatment of COVID-19. Finally, it will provide a substantial theoretical basis for clinical treatment now and in the future.

Yen, B. L., et al. (2020). "Current status of mesenchymal stem cell therapy for immune/inflammatory lung disorders: Gleaning insights for possible use in COVID-19." Stem Cells Transl Med **9**(10): 1163-1173.

The broad immunomodulatory properties of human mesenchymal stem cells (MSCs) have allowed for wide application in regenerative medicine as well as immune/inflammatory diseases, including unmatched allogeneic use. The novel coronavirus disease COVID-19 has unleashed a pandemic in record time

accompanied by an alarming mortality rate mainly due to pulmonary injury and acute respiratory distress syndrome. Because there are no effective preventive or curative therapies currently, MSC therapy (MSCT) has emerged as a possible candidate despite the lack of preclinical data of MSCs for COVID-19. Interestingly, MSCT preclinical data specifically on immune/inflammatory disorders of the lungs were among the earliest to be reported in 2003, with the first clinical use of MSCT for graft-vs-host disease reported in 2004. Since these first reports, preclinical data showing beneficial effects of MSC immunomodulation have accumulated substantially, and as a consequence, over a third of MSCT clinical trials now target immune/inflammatory diseases. There is much preclinical evidence for MSCT in noninfectious-including chronic obstructive pulmonary disease, asthma, and idiopathic pulmonary fibrosis-as well as infectious bacterial immune/inflammatory lung disorders, with data generally demonstrating therapeutic effects; however, for infectious viral pulmonary conditions, the preclinical evidence is more scarce with some inconsistent outcomes. In this article, we review the mechanistic evidence for clinical use of MSCs in pulmonary immune/inflammatory disorders, and survey the ongoing clinical trials-including for COVID-19-of MSCT for these diseases, with some perspectives and comment on MSCT for COVID-19.

Yigenoglu, T. N., et al. (2021). "Mesenchymal stem cell transfusion: Possible beneficial effects in COVID-19 patients." Transfus Apher Sci: 103237.

SARS-CoV-2 attaches to the angiotensin-converting enzyme 2 (ACE-2) receptor on human cells. The virus causes hypercytokinemia, capillary leak, pulmonary edema, acute respiratory distress syndrome, acute cardiac injury, and leads to death. Mesenchymal stem cells (MSCs) are ACE-2 negative cells; therefore, can escape from SARS-CoV-2. MSCs prevent hypercytokinemia and help the resolution of the pulmonary edema and other damages occurred during the course of COVID-19. In addition, MSCs enhance the regeneration of the lung and other tissues affected by SARS-CoV-2. The case series reported beneficial effect of MSCs in COVID-19 treatment. However, there are some concerns about the safety of MSCs, particularly referring to the increased risk of disseminated intravascular coagulation, and thromboembolism due to the expression of TF/CD142. Prospective, randomized, large scale studies are needed to reveal the optimum dose, administration way, time, efficacy, and safety of MSCs in the COVID-19 treatment.

Yildiz Kabak, V., et al. (2021). "Screening supportive care needs, compliance with exercise program, quality of life, and anxiety level during the COVID-19 pandemic in individuals treated with hematopoietic stem cell transplantation." Support Care Cancer **29**(7): 4065-4073.

PURPOSE: The primary aim was to assess supportive care needs, compliance with home exercise program, quality of life level (QOL), and anxiety level during the COVID-19 pandemic in individuals treated with hematopoietic stem cell transplantation (HSCT). The secondary aim was to investigate demographic and medical factors associated with the recorded outcomes. METHODS: The present study included individuals treated with HSCT and previously referred to physical therapy. The data were collected by interviews with the participants on the phone. Supportive care needs were assessed using the Supportive Care Needs Survey-Short Form 29(TR). Compliance with the exercise program was recorded as the number of patients regularly performed strengthening and stretching exercises and the ratio of the walking duration to the recommended duration. The European Cancer Research and Treatment Organization Quality of Life Questionnaire-Cancer30 was used to assess the QOL. The State-Trait Anxiety Inventory-I and the Visual Analogue Scale were used to assess anxiety level. RESULTS: The present study included 101 individuals treated with HSCT. The psychological and physical supportive care needs were predominant in participants. Compliance with exercise program was low. General anxiety level was low, yet anxiety about COVID-19 was moderate level in participants. Supportive care needs were related to female gender, performance level, time since HSCT, and QOL level ($p < 0.05$). Anxiety level was correlated with supportive care needs, COVID-19-related anxiety, and QOL ($p < 0.05$). Compliance with exercise program was associated with age, performance level, and QOL ($p < 0.05$). CONCLUSION: Our results offer that supportive telehealth interventions should be considered during the COVID-19 pandemic for individuals treated with HSCT to decrease unmet supportive care needs and isolation-related physical inactivity.

Youk, J., et al. (2020). "Three-Dimensional Human Alveolar Stem Cell Culture Models Reveal Infection Response to SARS-CoV-2." Cell Stem Cell **27**(6): 905-919 e910.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is the cause of a present pandemic, infects human lung alveolar type 2 (hAT2) cells. Characterizing pathogenesis is crucial for developing vaccines and therapeutics. However, the lack of models mirroring the cellular physiology and pathology of hAT2 cells limits the study. Here, we develop a feeder-free, long-term, three-dimensional (3D) culture technique for hAT2 cells derived from primary human lung tissue and investigate infection response to SARS-CoV-2. By imaging-based analysis

and single-cell transcriptome profiling, we reveal rapid viral replication and the increased expression of interferon-associated genes and proinflammatory genes in infected hAT2 cells, indicating a robust endogenous innate immune response. Further tracing of viral mutations acquired during transmission identifies full infection of individual cells effectively from a single viral entry. Our study provides deep insights into the pathogenesis of SARS-CoV-2 and the application of defined 3D hAT2 cultures as models for respiratory diseases.

Yu, B., et al. (2020). "Innate and Adaptive Immunity of Murine Neural Stem Cell-Derived piRNA Exosomes/Microvesicles against Pseudotyped SARS-CoV-2 and HIV-Based Lentivirus." iScience **23**(12): 101806.

By testing pseudotyped SARS-CoV-2 and HIV-based lentivirus, this study reports that exosomes/microvesicles (Ex/Mv) isolated from murine hypothalamic neural stem/progenitor cells (htNSC) or subtype htNSC(PGHM) as well as hippocampal NSC have innate immunity-like actions against these RNA viruses. These extracellular vesicles also have a cell-free innate antiviral action by attacking and degrading viruses. We further generated the induced versions of Ex/Mv through prior viral exposure to NSCs and found that these induced Ex/Mv were stronger than basal Ex/Mv in reducing the infection of these viruses, suggesting the involvement of an adaptive immunity-like antiviral function. These NSC Ex/Mv were found to be characterized by producing large libraries of P element-induced wimpy testis (PIWI)-interacting RNAs (piRNAs) against genomes of various viruses, and some of these piRNAs were enriched during the adaptive immunity-like reaction, possibly contributing to the antiviral effects of these Ex/Mv. In conclusion, NSC Ex/Mv have antiviral immunity and could potentially be developed to combat against various viruses.

Zengin, R., et al. (2020). "Mesenchymal stem cell treatment in a critically ill COVID-19 patient: a case report." Stem Cell Investig **7**: 17.

An outbreak of a new coronavirus causing severe respiratory disease (COVID-19) was first reported in China and rapidly spread worldwide. Clinical spectrum changes from asymptomatic infection to severe illness and even death, and no specific treatment is currently available. A range of antiviral, antimalarial and antibiotic agents are being used. We report a case of a COVID-19 patient that progressed to severe disease requiring intubation and intensive care. We performed mesenchymal stem cell (MSC) transplantation considering the signs showing persistent excessive immune response and deterioration despite all supportive and drug therapies. The two rounds of transplantation did not result in any severe complications and was well-tolerated. Clinical signs were improved. The use of MSC therapy may be considered for compassionate use in selected patients.

Zhao, R. C. (2020). "Stem Cell-Based Therapy for Coronavirus Disease 2019." Stem Cells Dev **29**(11): 679-681.

The novel coronavirus disease 2019 (COVID-19) has grown to be a global public-health emergency since patients were first detected in Wuhan, China, in December 2019. As of April 9, 2020, the novel coronavirus (named as SARS-CoV-2 by the International Committee on Taxonomy of Viruses on February 11) has infected 83,251 and 1,484,811 patients in China and the world, respectively. However, we have neither confirmed effective antiviral medications nor vaccines available to deal with this emergency. In this commentary, we offer an alternative promising therapy for COVID-19, that is, mesenchymal stem cell transplantation.

Zhou, H., et al. (2020). "A potential ex vivo infection model of human induced pluripotent stem cell-3D organoids beyond coronavirus disease 2019." Histol Histopathol **35**(10): 1077-1082.

The novel coronavirus disease 2019 (COVID-19) outbreak began in the city of Wuhan, whereupon it rapidly spread throughout China and subsequently across the world. Rapid transmission of COVID-19 has caused wide-spread panic. Many established medications have been used to treat the disease symptoms; however, no specific drugs or vaccines have been developed. Organoids derived from human induced pluripotent stem cells (iPSCs) may serve as suitable infection models for ex vivo mimicking of the viral life cycle and drug screening. Human iPSC-3D organoids, self-organised tissues with multiple cell environments, have a similar structure and function as real human organs; hence, these organoids allow greater viral infection efficiency, mimic the natural host-virus interactions, and are suitable for long-term experimentation. Here, we suggest the use of a functional human iPSC-organoid that could act as a reliable and feasible ex vivo infection model for investigation of the virus. This approach will provide much needed insight into the underlying molecular dynamics of COVID-19 for the development of novel treatment and prevention strategies.

Zumla, A., et al. (2020). "Reducing mortality and morbidity in patients with severe COVID-19 disease by advancing ongoing trials of Mesenchymal Stromal (stem) Cell (MSC) therapy - Achieving global consensus and visibility for cellular host-directed therapies." Int J Infect Dis **96**: 431-439.

As of May 17th 2020, the novel coronavirus disease 2019 (COVID-19) pandemic has caused 307,395 deaths worldwide, out of 3,917,366 cases reported to the World Health Organization. No specific

treatments for reducing mortality or morbidity are yet available. Deaths from COVID-19 will continue to rise globally until effective and appropriate treatments and/or vaccines are found. In search of effective treatments, the global medical, scientific, pharma and funding communities have rapidly initiated over 500 COVID-19 clinical trials on a range of antiviral drug regimens and repurposed drugs in various combinations. A paradigm shift is underway from the current focus of drug development targeting the pathogen, to advancing cellular Host-Directed Therapies (HDTs) for tackling the aberrant host immune and inflammatory responses which underlie the pathogenesis of SARS-CoV-2 and high COVID-19 mortality rates. We focus this editorial specifically on the background to, and the rationale for, the use and evaluation of mesenchymal stromal (Stem) cells (MSCs) in treatment trials of patients with severe COVID-19 disease. Currently, the ClinicalTrials.gov and the WHO Clinical Trials Registry Platform (WHO ICTRP) report a combined 28 trials exploring the potential of MSCs or their products for treatment of COVID-19. MSCs should also be trialed for treatment of other circulating WHO priority Blueprint pathogens such as MERS-CoV which causes upto 34% mortality rates. It's about time funding agencies invested more into development MSCs per se, and also for a range of other HDTs, in combination with other therapeutic interventions. MSC therapy could turn out to be an important contribution to bringing an end to the high COVID-19 death rates and preventing long-term functional disability in those who survive disease.

Zupanc, G. K. H., et al. (2021). "The Neurosphere Simulator: An educational online tool for modeling neural stem cell behavior and tissue growth." Dev Biol **469**: 80-85.

Until very recently, distance education, including digital science labs, served a rather small portion of postsecondary students in the United States and many other countries. This situation has, however, dramatically changed in 2020 in the wake of the COVID-19 pandemic, which forced colleges to rapidly transit from face-to-face instructions to online classes. Here, we report the development of an interactive simulator that is freely available on the web (http://neurosphere.cos.northeastern.edu/) for teaching lab classes in developmental biology. This simulator is based on cellular automata models of neural-stem-cell-driven tissue growth in the neurosphere assay. By modifying model parameters, users can explore the role in tissue growth of several developmental mechanisms, such as regulation of mitosis or apoptotic cell death by contact inhibition. Besides providing an instantaneous animation of the simulated development of neurospheres, the Neurosphere Simulator tool offers also the possibility to download data for detailed analysis. The simulator function is complemented by a tutorial that introduces students to computational modeling of developmental processes.

The above contents are the collected information from Internet and public resources to offer to the people for the convenient reading and information disseminating and sharing.

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