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Stem Cell

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# COVID-19, Vaccine and Stem Cell Research Literatures

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**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. Coronavirus disease 2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first known case was identified in December 2019. The disease has since spread worldwide, leading to an ongoing pandemic. Symptoms of COVID-19 are variable, but often include fever, cough, headache, fatigue, breathing difficulties, and loss of smell and taste. Symptoms begin 1 - 14 days after exposure to the coronavirus. This article introduces recent research reports as references in the related studies. The use of face masks or coverings has been recommended in public settings to minimize the risk of transmissions. Management involves the treatment of symptoms, supportive care, isolation, and experimental measures. (https://en.wikipedia.org/wiki/COVID-19). Upto 12/1/2021 in USA, Total Cases are 48,377,531, Total accines Administered are 460,773,508, Total Deaths 778,489 (https://www.cdc.gov/coronavirus/2019-ncov/index.html).
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**Key words**: COVID-19; vaccine; stem cell; pandemic; life; research; literature

## Introduction

Coronavirus disease 2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first known case was identified in December 2019. The disease has since spread worldwide, leading to an ongoing pandemic. Symptoms of COVID-19 are variable, but often include fever, cough, headache, fatigue, breathing difficulties, and loss of smell and taste. Symptoms begin 1 - 14 days after exposure to the coronavirus. At least 30% of people who are infected do not develop noticeable symptoms. Of those people who develop symptoms noticeable enough to be classed as patients, around 80% develop mild to moderate symptoms, while 14% develop severe, and 5% suffer critical symptoms. Some people continue to experience a range of effects for months after recovery, and damage to organs has been observed. Multi-year studies are underway to further investigate the long-term effects of the disease. COVID-19 transmits when people breathe in air contaminated by droplets and small airborne particles containing the virus. People remain contagious for up to 20 days, and can spread the virus even if they do not develop symptoms. The standard diagnostic method is by detection of the virus' nucleic acid by real-time reverse transcription polymerase chain reaction (rRT-PCR), transcription-mediated amplification (TMA), or by reverse transcription loop-mediated isothermal amplification (RT-LAMP) from a nasopharyngeal swab. Several COVID-19 vaccines have been approved and distributed in various countries, which have initiated mass vaccination campaigns. Other preventive measures include physical or social distancing, quarantining, ventilation of indoor spaces, covering coughs and sneezes, hand washing, and keeping unwashed hands away from the face. The use of face masks or coverings has been recommended in public settings to minimize the risk of transmissions. Management involves the treatment of symptoms, supportive care, isolation, and experimental measures. (https://en.wikipedia.org/wiki/COVID-19).

Upto 12/1/2021 in USA, Total Cases are 48,377,531, Total accines Administered are 460,773,508, Total Deaths 778,489 (https://www.cdc.gov/coronavirus/2019-ncov/index.html).

Omicron is a variant of SARS-CoV-2, the virus that causes COVID-19. The variant was first reported to the World Health Organization (WHO) from South Africa on 11/24/2021. On 11/26/2021, the WHO designated it as a variant of concern and named it after omicron, the `5th letter in the Greek

alphabet. The variant has an unusually large number of mutations, several of which are novel and several of which affect the spike protein used for most vaccine targeting at the time of its discovery. This level of variation has led to concerns regarding transmissibility, immune system evasion, and vaccine resistance. As a result, the variant was quickly designated as being "of concern", and travel restrictions were introduced by several countries to limit or slow its international spread. The variant has a large number of mutations, of which some are concerning. 32 mutations affect the spike protein, the main antigenic target of antibodies generated by infections and of many vaccines widely administered. Many of those mutations had not been observed in other strains. The variant is characterised by 30 amino acid changes, 3 small deletions and 1 small insertion in the spike protein compared with the original virus, of which 15 are located in the receptor binding domain (residues 319-541). It also carries a number of changes and deletions in other genomic regions. Additionally, the variant has three mutations at the furin cleavage site. The furin cleavage site increases SARS-CoV-2 infectivity. The mutations by genomic region are the following. Spike protein: A67V, Δ69-70, T95I, G142D, Δ143-145, Δ211, L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F (Half (15) of these 30 changes are located in the receptor binding domain-RBD (residues 319-541). ORF1ab: nsp3: K38R, V1069I, Δ1265, L1266I, A1892T; nsp4: T492I; nsp5: P132H; nsp6: Δ105-107, A189V; nsp12: P323L; nsp14: I42V. Envelope protein: T9I. Membrane protein: D3G, Q19E, A63T. Nucleocapsid protein: P13L, Δ31-33, R203K, G204R. (https://en.wikipedia.org/wiki/SARS-CoV-2_Omicron_variant).

A vaccine is a biological preparation that provides active acquired immunity to a particular infectious disease. A vaccine typically contains an agent that resembles a disease-causing microorganism and is often made from weakened or killed forms of the microbe, its toxins, or one of its surface proteins. The agent stimulates the body's immune system to recognize the agent as a threat, destroy it, and to further recognize and destroy any of the microorganisms associated with that agent that it may encounter in the future. Vaccines can be prophylactic or therapeutic. Some vaccines offer full sterilizing immunity, in which infection is prevented completely. The administration of vaccines is called vaccination. Vaccination is the most effective method of preventing infectious diseases; widespread immunity due to vaccination is largely responsible for the worldwide eradication of smallpox and the restriction of diseases such as polio, measles and tetanus from much of the world. The effectiveness of vaccination has been widely studied and verified; for example, vaccines that have proven effective include the influenza vaccine, the HPV vaccine, and the chickenpox vaccine. The World Health Organization reports that licensed vaccines are currently available for 25 different preventable infections. (https://en.wikipedia.org/wiki/Vaccine).

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. (https://en.wikipedia.org/wiki/Stem_cell).

Mesenchymal stem cells (MSCs) have been recently under investigation in this regard, and the achieved clinical outcomes show promising evidence for stem cell-based therapy of COVID-19. MSCs therapy and Convalescent Plasma Therapy have emerged as a promising therapeutic strategy against SARS-CoV-2 virion. Human pluripotent stem cell (hPSC) cardiovascular derivatives were rapidly recognized as an invaluable tool to address this, not least because one of the major receptors for the virus is not recognized by SARS-CoV-2 in mice. Here, we outline how hPSC-derived cardiovascular cells have been utilized to study COVID-19, and their potential for further understanding the cardiac pathology and in therapeutic development (Yiangou, et al., 2021).

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

Afarid, M. and F. Sanie-Jahromi (2021). "Mesenchymal Stem Cells and COVID-19: Cure, Prevention, and Vaccination." Stem Cells Int **2021**: 6666370.

COVID-19 disease has been a global health problem since late 2019. There are many concerns about the rapid spread of this disease, and yet, there is no approved treatment for COVID-19. Several biological interventions have been under study recently to investigate efficient treatment for this viral disease. Besides, many efforts have been made to find a safe way to prevent and vaccinate people against COVID-19 disease. In severe cases, patients suffer from acute respiratory distress syndrome usually associated with an increased level of inflammatory cytokines, called a cytokine storm. It seems that reequilibrating the hyperinflammatory response of the host immune system and regeneration of damaged cells could be the main way to manage the disease. Mesenchymal stem cells (MSCs) have been recently under investigation in this regard, and the achieved clinical outcomes show promising evidence for stem cell-based therapy of COVID-19.

MSCs are known for their potential for immunomodulation, defense against virus infection, and tissue regeneration. MSCs are a newly emerged platform for designing vaccines and show promising evidence in this area. In the present study, we provided a thorough research study on the most recent clinical studies based on stem cells in the treatment of COVID-19 while introducing stem cell exclusivities for use as an immune disorder or lung cell therapy and its potential application for protection and vaccination against COVID-19.

Aleem, A. and A. K. Slenker (2021). Monoclonal Antibody Therapy For High-Risk Coronavirus (COVID 19) Patients With Mild To Moderate Disease Presentations. StatPearls. Treasure Island (FL).

Since being declared a global pandemic by the World Health Organization WHO), Coronavirus disease 2019 (COVID-19), the illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had a devastating effect on global health and the world economy. The virus primarily affects the respiratory system and is spread from person to person via respiratory particles from coughing and sneezing. The majority of transmission occurs from close contact with presymptomatic, asymptomatic, or symptomatic carriers. The early course of the pandemic was characterized by the rapid spread of the virus that created an urgency to mitigate this new viral illness with experimental therapies and drug repurposing. Since then, due to an intense global research effort, significant progress has been made that has resulted in the development of novel therapeutics and vaccines at an unprecedented speed, leading to favorable patient outcomes. Currently, a variety of therapeutic options that include antiviral medications, monoclonal antibodies, and immunomodulatory agents are available in the management of COVID-19. However, the therapeutic potential and clinical use of these drugs are limited and specifically based on the stage of the illness. The pathogenesis of COVID-19 illness occurs in two distinct phases, an early stage characterized by profound SARS-CoV-2 viral replication followed by a late phase characterized by a hyperinflammatory state induced by the release of cytokines such as tumor necrosis factor-alpha (TNF alpha), granulocyte-macrophage colony-stimulating factor (GM-CSF), Interleukin (IL) 1, IL-6, interferon (IFN)-gamma, and activation of the coagulation system resulting in a prothrombotic state. Antiviral therapy and antibody-based treatments are likely to be more effective if used during the early phase of the illness, and immunomodulating therapies either alone or in combination with antiviral and antibody-based therapies may be more effective when used in the later stage to combat the cytokine-mediated hyperinflammatory state that causes severe illness.[1] Individuals of all ages are at risk for infection and severe disease. However, individuals aged >/=65 years and with underlying medical comorbidities (obesity, cardiovascular disease, chronic kidney disease, diabetes, chronic lung disease, smoking, cancer, solid organ or hematopoietic stem cell transplant recipients) are at increased risk of developing severe COVID-19 infection. The percentage of COVID-19 patients requiring hospitalization was six times higher in those with preexisting medical conditions than those without medical conditions (45.4% vs. 7.6%) based on an analysis by Stokes et al. of confirmed cases reported to the US Centers for Disease Control and Prevention (CDC) during January 22 to May 30, 2020.[2] A promising approach to address the COVID-19 associated mortality and prevent the increased utilization of healthcare resources is by terminating the progression of viral replication, thereby preventing the progression to the hyperinflammatory stage of COVID-19, which causes severe illness in high-risk nonhospitalized patients. Initially, the focus of treatment was directed mainly towards hospitalized patients with COVID-19 illness. However, the clinical focus throughout the pandemic has expanded toward combatting the illness early on by reducing the viral load in patients with early disease, thus attempting to halt the disease progression. Monoclonal antibodies targeting the spike protein of the SARS-CoV-2 have yielded positive in vitro results.[3][4] They are considered a promising approach in managing nonhospitalized patients with mild to moderate COVID-19 who are at high risk of developing severe illness. This review discusses the mechanism of action of monoclonal antibodies against SARS-CoV-2 and current clinical indications of monoclonal antibody therapy for nonhospitalized patients with mild to moderate COVID-19 illness who are at high risk of developing severe illness. According to the US National Institutes for Health (NIH), management of nonhospitalized patients with COVID-19 includes:[5]: Supportive/symptomatic care, reducing the risk of transmission, and advising patients when to seek in-person medical evaluation. Advising patients with dyspnea to seek in-person medical evaluation. Anti-SARS-CoV-2 monoclonal antibodies are recommended for mild to moderate severity outpatients that are at high risk of progressing to severe disease. For patients discharged from the emergency department on supplemental oxygen, they recommend dexamethasone 6 mg once daily for the duration of oxygen supplementation, not to exceed ten days. For patients not on oxygen therapy, they recommend against the use of dexamethasone. They found insufficient evidence for or against the use of remdesivir in patients discharged from the emergency department on supplemental oxygen. Monoclonal Antibodies in COVID-19 Monoclonal antibodies (mAbs) are immune system proteins developed from a single cell lineage that demonstrate a high affinity for their

target cell. Monoclonal antibodies were first developed by Kohler and Milstein in 1975 using hybridoma technology.[6] Since then, significant progress has been made in the molecular engineering world that has enabled the establishment of monoclonal antibodies as targeted therapies in various neoplastic conditions, autoimmune, post-transplant immunosuppression, and infectious diseases.[7] When used as antiviral therapies, neutralizing antibodies play an integral part in achieving passive antiviral immunity and are also instrumental in preventing or regulating many viral illnesses. Over the years, passive immunization against many viral diseases was achieved by administering polyclonal sera obtained from convalescent human donors or animals. However, polyclonal antibody preparations are increasingly being replaced by monoclonal antibodies by virtue of them, demonstrating a favorable safety profile and target specificity when used in different viral diseases.[8] Palivizumab was the first antiviral monoclonal antibody approved by the US Food and Drug Administration (FDA) for prophylaxis of respiratory syncytial virus (RSV) in high-risk infants.[9] Over the years, significant developments in antibody engineering, improved understanding of the biology of viruses, and the direct and indirect effect of monoclonal antibodies on viral infections has resulted in the development of many novel monoclonal antibodies. Like other antiviral drugs, monoclonal antibodies, when used as antiviral agents, are also susceptible to developing resistance as a result of alterations in the viral genome which can alter the pathogenic potential of the virus resulting in the emergence of viral escape mutants, which may render the virus-resistant to a specific monoclonal antibody. To counter this viral escape phenomenon, a combination of monoclonal antibodies, commonly referred to as antibody cocktails, have been proposed with the rationale that combining two specific monoclonal antibodies that complement each other can prevent neutralization escape by targeting multiple viral epitopes. There are an estimated 70 monoclonal antibodies currently in development or clinical trials to treat COVID-19. The FDA has granted four agents an emergency use authorization (EUA) for clinical use as combination antibody cocktails and one agent as monotherapy.

Algwaiz, G., et al. (2020). "Real-World Issues and Potential Solutions in Hematopoietic Cell Transplantation during the COVID-19 Pandemic: Perspectives from the Worldwide Network for Blood and Marrow Transplantation and Center for International Blood and Marrow Transplant Research Health Services and International Studies Committee." Biol Blood Marrow Transplant **26**(12): 2181-2189.

The current COVID-19 pandemic, caused by SARS-CoV-2, has impacted many facets of hematopoietic cell transplantation (HCT) in both developed and developing countries. Realizing the challenges as a result of this pandemic affecting the daily practice of the HCT centers and the recognition of the variability in practice worldwide, the Worldwide Network for Blood and Marrow Transplantation (WBMT) and the Center for International Blood and Marrow Transplant Research's (CIBMTR) Health Services and International Studies Committee have jointly produced an expert opinion statement as a general guide to deal with certain aspects of HCT, including diagnostics for SARS-CoV-2 in HCT recipient, pre- and post-HCT management, donor issues, medical tourism, and facilities management. During these crucial times, which may last for months or years, the HCT community must reorganize to proceed with transplantation activity in those patients who urgently require it, albeit with extreme caution. This shared knowledge may be of value to the HCT community in the absence of high-quality evidence-based medicine. (c) 2020 American Society for Transplantation and Cellular Therapy. Published by Elsevier Inc.

Atluri, S., et al. (2020). "Expanded Umbilical Cord Mesenchymal Stem Cells (UC-MSCs) as a Therapeutic Strategy in Managing Critically Ill COVID-19 Patients: The Case for Compassionate Use." Pain Physician **23**(2): E71-E83.

COVID-19 has affected the United States leading to a national emergency with health care and economic impact, propelling the country into a recession with disrupted lifestyles not seen in recent history. COVID-19 is a serious illness leading to multiple deaths in various countries including the United States. Several million Americans satisfy the Center for Disease Control and Prevention (CDC) criteria for being high risk. Unfortunately, the available supply of medical beds and equipment for mechanical ventilation are much less than is projected to be needed. The World Health Organization (WHO) and multiple agencies led by the CDC in the United States have attempted to organize intensive outbreak investigation programs utilizing appropriate preventive measures, evaluation, and treatment. The clinical spectrum of COVID-19 varies from asymptomatic forms to conditions encompassing multiorgan and systemic manifestations in terms of septic shock, and multiple organ dysfunction (MOD) syndromes. The presently approved treatments are supportive but not curative for the disease. There are multiple treatments being studied. These include vaccines, medications Remdesivir and hydroxychloroquine and potentially combination therapy. Finally, expanded umbilical cord mesenchymal stem cells or (UC-MSCs) may have a role and are being studied. The cure of COVID-19 is essentially dependent on the patients' own immune system. When the immune system is over activated in an attempt to kill the virus, this can lead to the production of a large number of

inflammatory factors, resulting in severe cytokine storm. The cytokine storm may induce organ damage followed by the edema, dysfunction of air exchange, acute respiratory distress syndrome (ARDS), acute cardiac injury, and secondary infection, which may lead to death. Thus, at this point, the avoidance of the cytokine storm may be the key for the treatment of HCOV-19 infected patients.In China, where there was limited availability of effective modalities to manage COVID-19 several patients were treated with expanded UC-MSCs. Additionally, the Italian College of Anesthesia, Analgesia, Resuscitation and Intensive Care have reported guidelines to treat coronavirus patients with stem cells in the hope of decreasing the number of patients going to the ICU, and, also relatively quickly getting them out of ICU. In this manuscript, we describe the urgent need for various solutions, pathogenesis of coronavirus and the clinical evidence for treatment of COVID-19 with stem cells. The limited but emerging evidence regarding UC MSC in managing COVID-19 suggests that it might be considered for compassionate use in critically ill patients to reduce morbidity and mortality in the United States. The administration and Coronavirus Task Force might wish to approach the potential of expanded UC-MSCs as an evolutionary therapeutic strategy in managing COVID-19 illness with a 3-pronged approach: If proven safe and effective on a specific and limited basis...1. Minimize regulatory burden by all agencies so that critically ill COVID-19 patients will have access regardless of their financial circumstance.2. Institute appropriate safeguards to avoid negative consequences from unscrupulous actors.3. With proper informed consent from patients or proxy when necessary, and subject to accumulation of data in that cohort, allow the procedure to be initiated in critically ill patients who are not responding to conventional therapies. KEY WORDS: Coronavirus, COVID-19, cytokine storm, multiorgan failure, expanded umbilical cord mesenchymal stem cells.

Aviv, A. (2020). "Telomeres and COVID-19." FASEB J **34**(6): 7247-7252.

The medical, public health, and scientific communities are grappling with monumental imperatives to contain COVID-19, develop effective vaccines, identify efficacious treatments for the infection and its complications, and find biomarkers that detect patients at risk of severe disease. The focus of this communication is on a potential biomarker, short telomere length (TL), that might serve to identify patients more likely to die from the SARS-CoV-2 infection, regardless of age. The common thread linking these patients is lymphopenia, which largely reflects a decline in the numbers of CD4/CD8 T cells but not B cells. These findings are consistent with data that lymphocyte TL dynamics impose a limit on T-cell proliferation. They suggest that T-cell lymphopoiesis might stall in individuals with short TL who are infected with SARS-CoV-2.

Bahrampour Juybari, K., et al. (2020). "Melatonin potentials against viral infections including COVID-19: Current evidence and new findings." Virus Res **287**: 198108.

Viral infections are dangerous diseases for human health worldwide, which lead to significant morbidity and mortality each year. Because of their importance and the lack of effective therapeutic approaches, further attempts should be made to discover appropriate alternative or complementary treatments. Melatonin, a multifunctional neurohormone mainly synthesized and secreted by the pineal gland, plays some roles in the treatment of viral infections. Regarding a deadly outbreak of COVID-19 across the world, we decided to discuss melatonin functions against various viral infections including COVID-19. Therefore, in this review, we summarize current evidence on melatonin therapy for viral infections with focus on possible underlying mechanisms of melatonin actions.

Bhandari, R., et al. (2021). "Pharmacological insight into potential therapeutic agents for the deadly Covid-19 pandemic." Eur J Pharmacol **890**: 173643.

Coronaviruses are pleomorphic, enveloped, or spherical viruses, which have a size ranging from 80 to 120 nm. These viruses act on receptors that cause the triggering of fusion. Coronaviruses were first described after cultivation from patients with common colds by Tyrell and Bynoe in 1966. There are various subtypes of coronavirus, 7 out of these can cause infection in human beings. The Alpha subtype is responsible for mild infection showing symptoms or infection without any prevailing symptoms. On the other hand, the beta subtype is responsible for very serious diseases leading to fatality. The lineage of this novel SARS-CoV-2 falls under the beta lineage of the beta coronavirus which has been observed to have a relation to the MERS and SARS coronavirus. In the Huanan market selling seafood, the transition of this novel virus in humans from animals has occurred. It has the potential to be the cause of widespread fatality amongst the people of the globe. On August 16, 2020, the World Health Organisation had reported 2,1294,845 cases which are confirmed to date out of which 413,372 deaths have occurred. Currently, no targeted antiviral vaccines or drugs to fight against COVID-19 infection have been approved for use in humans. This pandemic is fast emerging and drug repurposing is the only ray of hope which can ensure quick availability. Vaccine development is progressing each day with various platforms such as DNA, Live Attenuated Virus, Non-Replicating Viral Vector, Protein Subunit, and RNA, being utilized for the development. COVID-19 attacks the immune system of the host & this can result in a cytokine storm. As a result, various herbal agents both acting as antivirals and immunomodulatory can also be used.

Convalescent Plasma Therapy and Mesenchymal Stem Cell therapy are also being explored as a plausible therapeutic. There remains a considerable unmet need for therapeutics to be addressed. The development and availability of accessible and efficient therapy are essential for the treatment of patients. This review discusses the epidemiology, pathogenesis, the tale of origin, and transmission of COVID-19 or Sars-Cov2 virus and gives evidence of potential therapeutic agents that can be explored to cast away this pandemic.

Borlongan, M. C., et al. (2020). "The Disillusioned Comfort with COVID-19 and the Potential of Convalescent Plasma and Cell Therapy." Cell Transplant **29**: 963689720940719.

Coronavirus disease 2019 or COVID-19 is highly infectious, which can lead to acute and chronic debilitating symptoms, as well as mortality. The advent of safe and effective vaccines or antiviral drugs remains distant in the future. Practical public health measures, such as social distancing, hand washing, and wearing a face mask, are the current recommended guidelines by the Centers for Disease Control and Prevention for limiting the spread of the virus. Weakened immune system and aberrant inflammation represent a major pathological symptom of COVID-19 patients. Based on the unique immunomodulatory properties of both convalescent plasma and stem cells, we discuss here their potential use for treating COVID-19.

Brumeanu, T. D., et al. (2021). "A Human-Immune-System (HIS) humanized mouse model (DRAGA: HLA-A2. HLA-DR4. Rag1 KO.IL-2Rgammac KO. NOD) for COVID-19." bioRxiv.

We report the first Human Immune System (HIS)-humanized mouse model ("DRAGA": HLA-A2.HLA-DR4.Rag1KO.IL-2RgammacKO.NOD) for COVID-19 research. This mouse is reconstituted with human cord blood-derived, HLA-matched hematopoietic stem cells. It engrafts human epi/endothelial cells expressing the human ACE2 receptor for SARS-CoV-2 and TMPRSS2 serine protease co-localized on lung epithelia. HIS-DRAGA mice sustained SARS-CoV-2 infection, showing deteriorated clinical condition, replicating virus in the lungs, and human-like lung immunopathology including T-cell infiltrates, microthrombi and pulmonary sequelae. Among T-cell infiltrates, lung-resident (CD103(+)) CD8(+) T cells were sequestered in epithelial (CD326(+)) lung niches and secreted granzyme B and perforin, indicating cytotoxic potential. Infected mice also developed antibodies against the SARS-CoV-2 viral proteins. Hence, HIS-DRAGA mice showed unique advantages as a surrogate in vivo human model for studying SARS-CoV-2 immunopathology and for testing the safety and efficacy of candidate vaccines and therapeutics.

Chen, Y., et al. (2020). "Efficacy and safety of mesenchymal stem cells for the treatment of patients infected with COVID-19: a systematic review and meta-analysis protocol." BMJ Open **10**(12): e042085.

INTRODUCTION: To date, no specific antivirus drugs or vaccines have been available to prevent or treat the COVID-19 pandemic. Mesenchymal stem cell (MSC) therapy may be a promising therapeutic approach that reduces the high mortality in critical cases. This protocol is proposed for a systematic review and meta-analysis that aims to evaluate the efficacy and safety of MSC therapy on patients with COVID-19. METHODS AND ANALYSIS: Ten databases including PubMed, EMBASE, Cochrane Library, CINAHL, Web of Science, Chinese National Knowledge Infrastructure (CNKI), Chinese Scientific Journals Database (VIP), Wanfang database, China Biomedical Literature Database (CBM) and Chinese Biomedical Literature Service System (SinoMed) will be searched from inception to 1 December 2020. All published randomised controlled trials, clinical controlled trials and case series that meet the prespecified eligibility criteria will be included. The primary outcomes include mortality, incidence and severity of adverse events, respiratory improvement, days from ventilator, duration of fever, progression rate from mild or moderate to severe, improvement of such serious symptoms as difficulty breathing or shortness of breath, chest pain or pressure, and loss of speech or movement, biomarkers of laboratory examination and changes in CT. The secondary outcomes include dexamethasone doses and quality of life. Two reviewers will independently perform study selection, data extraction and assessment of bias risk. Data synthesis will be conducted using RevMan software (V.5.3.5). If necessary, subgroup and sensitivity analysis will be performed. Grading of Recommendations Assessment, Development and Evaluation system will be used to assess the strength of evidence. ETHICS AND DISSEMINATION: Ethical approval is not necessary since no individual patient or privacy data have been collected. The results of this review will be disseminated in a peer-reviewed journal or an academic conference presentation. PROSPERO REGISTRATION NUMBER: CRD42020190079.

Coelho, A., et al. (2020). "Mesenchymal Stem Cells (MSCs) as a Potential Therapeutic Strategy in COVID-19 Patients: Literature Research." Front Cell Dev Biol **8**: 602647.

In 2019, an outbreak of an unknown coronavirus - SARS-CoV-2 - responsible for COVID-19 disease, was first reported in China, and evolved into a pandemic of huge dimensions and raised serious concerns for global health. The number of critical cases continues to increase dramatically, while vaccines and specific treatments are not yet available. There are several strategies currently being studied for the treatment of adverse symptoms of COVID-19, that encompass Acute Lung Injury (ALI)/Acute Respiratory Distress Syndrome

(ARDS), extensive pulmonary inflammation, cytokine storm, and pulmonary edema, due to virus-induced pneumonia. Mesenchymal stem cells (MSCs) are at the origin of new revolutionary treatments, which may come to be applied in such as Regenerative Medicine, Immunotherapy, Tissue Engineering, and Cell and Molecular Biology due to immunomodulation and anti-inflammatory activity. MSCs have already been studied with positive outcomes for other lung pathologies, thus representing and being identified as an important opportunity for the treatment of COVID-19. It has recently been shown that these cells allow hopeful and effective therapies for serious or critical COVID-19, minimizing its adverse symptoms. In this study we will analyze the MSCs, their origin, differentiation, and therapeutic potential, making a bridge with the COVID-19 disease and its characteristics, as a potential therapeutic strategy but also reporting recent studies where these cell-based therapies were used for the treatment of COVID-19 patients.

Copcu, H. E. (2020). "Potential Using of Fat-derived Stromal Cells in the Treatment of Active Disease, and also, in Both Pre- and Post-Periods in COVID-19." Aging Dis **11**(4): 730-736.

The whole world is fighting with the COVID-19 pandemic, which traps people home, causing high business and economic losses, and above all, leads to very serious deaths. The lack of a valid, accepted treatment protocol and vaccine that leads to continued treatment searches. Leng et al published their article in the Aging and Disease journal, which demonstrates that mesenchymal stem cells (MSCs) can be used for COVID-19 treatment. Adipose tissue is one of the most important MSCs sources in the body, and adipose derived stromal cells (ADSCs) from adipose tissue are also one of the most valuable components of stromal vascular fraction (SVF). Finally, Gentile and Sterodimas, have also published their article for the potential use of SVF in COVID-19 treatment in Aging and Disease journal. Their publication has been a guide in many ways. Adipose tissue-derived stromal cells have three main features: Immunomodulatory, anti-inflammatory and regenerative. Immunomodulator effects are used as a preventive in patients prone to disease; its anti-inflammatory effects may allow them to be used as a therapeutic during active disease period and finally regenerative effects to repair post-disease sequale. Those cells can be obtained not only enzymatically, but also mechanically with very benefits. They can be delivered not only systemically through the IV route but also to the target organ with a carrier. While suggesting any adipose tissue-derived treatment method possibility, the relation of adipose tissue COVID-19 should not be ignored. Because, COVID-19 shows its effect through ACE-2 and adipose tissue is very rich and important tissue in terms of ACE-2.

Cui, C., et al. (2020). "Review on the Clinical Pharmacology of Hydroxychloroquine Sulfate for the Treatment of COVID-19." Curr Drug Metab **21**(6): 427-435.

BACKGROUND: As the number of severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infected people is greatly increasing worldwide, the international medical situation becomes very serious. Potential therapeutic drugs, vaccine and stem cell replacement methods are emerging, so it is urgent to find specific therapeutic drugs and the best treatment regimens. After the publications on hydroxychloroquine (HCQ) with anti- SARS-COV-2 activity in vitro, a small, non-randomized, open-label clinical trial showed that HCQ treatment was significantly associated with reduced viral load in patients with coronavirus disease-19 (COVID-19). Meanwhile, a large prophylaxis study of HCQ sulfate for COVID-19 has been initiated in the United States. HCQ offered a promising efficacy in the treatment of COVID-19, but the optimal administration is still being explored. METHODS: We used the keyword "hydroxychloroquine" to conduct a literature search in PubMed to collect relevant literature on the mechanism of action of HCQ, its clinical efficacy and safety, pharmacokinetic characteristics, precautions for clinical use and drug interactions to extract and organize information. RESULTS: This paper reviews the mechanism, clinical efficacy and safety, pharmacokinetic characteristics, exposureresponse relationship and precautions and drug interactions of HCQ, and summarizes dosage recommendations for HCQ sulfate. CONCLUSION: It has been proved that HCQ, which has an established safety profile, is effective against SARS-CoV-2 with sufficient pre-clinical rationale and evidence. Data from high-quality clinical trials are urgently needed worldwide.

Dash, P., et al. (2020). "A Scoping Insight on Potential Prophylactics, Vaccines and Therapeutic Weaponry for the Ongoing Novel Coronavirus (COVID-19) Pandemic- A Comprehensive Review." Front Pharmacol **11**: 590154.

The emergence of highly virulent CoVs (SARS-CoV-2), the etiologic agent of novel ongoing "COVID-19" pandemics has been marked as an alarming case of pneumonia posing a large global healthcare crisis of unprecedented magnitude. Currently, the COVID-19 outbreak has fueled an international demand in the biomedical field for the mitigation of the fast-spreading illness, all through the urgent deployment of safe, effective, and rational therapeutic strategies along with epidemiological control. Confronted with such contagious respiratory distress, the global population has taken significant steps towards a more robust strategy of containment and quarantine to halt the total number of positive cases but such a strategy can only delay the spread. A substantial number of potential vaccine candidates

are undergoing multiple clinical trials to combat COVID-19 disease, includes live-attenuated, inactivated, viral-vectored based, sub-unit vaccines, DNA, mRNA, peptide, adjuvant, plant, and nanoparticle-based vaccines. However, there are no licensed anti-COVID-19 drugs/therapies or vaccines that have proven to work as more effective therapeutic candidates in open-label clinical trial studies. To counteract the infection (SARS-CoV-2), many people are under prolonged treatment of many chemical drugs that inhibit the PLpro activity (Ribavirin), viral proteases (Lopinavir/Ritonavir), RdRp activity (Favipiravir, Remdesivir), viral membrane fusion (Umifenovir, Chloroquine phosphate (CQ), Hydroxychloroquine phosphate (HCQ), IL-6 overexpression (Tocilizumab, Siltuximab, Sarilumab). Mesenchymal Stem Cell therapy and Convalescent Plasma Therapy have emerged as a promising therapeutic strategy against SARS-CoV-2 virion. On the other hand, repurposing previously designed antiviral agents with tolerable safety profile and efficacy could be the only promising approach and fast response to the novel virion. In addition, research institutions and corporations have commenced the redesign of the available therapeutic strategy to manage the global crisis. Herein, we present succinct information on selected anti-COVID-19 therapeutic medications repurposed to combat SARS-CoV-2 infection. Finally, this review will provide exhaustive detail on recent prophylactic strategies and ongoing clinical trials to curb this deadly pandemic, outlining the major therapeutic areas for researchers to step in.

Feldmeier, J. J., et al. (2021). "Physiologic and biochemical rationale for treating COVID-19 patients with hyperbaric oxygen." Undersea Hyperb Med **48**(1): 1-12.

The SARS-Cov-2 (COVID-19) pandemic remains a major worldwide public health issue. Initially, improved supportive and anti-inflammatory intervention, often employing known drugs or technologies, provided measurable improvement in management. We have recently seen advances in specific therapeutic interventions and in vaccines. Nevertheless, it will be months before most of the world's population can be vaccinated to achieve herd immunity. In the interim, hyperbaric oxygen (HBO2) treatment offers several potentially beneficial therapeutic effects. Three small published series, one with a propensity-score-matched control group, have demonstrated safety and initial efficacy. Additional anecdotal reports are consistent with these publications. HBO2 delivers oxygen in extreme conditions of hypoxemia and tissue hypoxia, even in the presence of lung pathology. It provides anti-inflammatory and anti-proinflammatory effects likely to ameliorate the overexuberant immune response common to COVID-19. Unlike steroids, it exerts these effects without immune suppression. One study suggests HBO2 may reduce the hypercoagulability seen in COVID patients. Also, hyperbaric oxygen offers a likely successful intervention to address the oxygen debt expected to arise from a prolonged period of hypoxemia and tissue hypoxia. To date, 11 studies designed to investigate the impact of HBO2 on patients infected with SARS-Cov-2 have been posted on clinicaltrials.gov. This paper describes the promising physiologic and biochemical effects of hyperbaric oxygen in COVID-19 and potentially in other disorders with similar pathologic mechanisms.

Gentile, P., et al. (2020). "Research progress on Mesenchymal Stem Cells (MSCs), Adipose-Derived Mesenchymal Stem Cells (AD-MSCs), Drugs, and Vaccines in Inhibiting COVID-19 Disease." Aging Dis **11**(5): 1191-1201.

Mesenchymal Stem Cells (MSCs), and Adipose-Derived Mesenchymal Stem Cells (AD-MSCs) have been used for many years in regenerative medicine for clinical and surgical applications. Additionally, recent studies reported improved respiratory activity after intravenous administration of MSCs into patients affected by coronavirus disease 2019 (COVID-19) caused by the Coronavirus 2 (SARS-CoV-2) suggesting their role as anti-viral therapy. Severe COVID-19 patients usually progress to acute respiratory distress syndrome, sepsis, metabolic acidosis that is difficult to correct, coagulation dysfunction, multiple organ failure, and even death in a short period after onset. Currently, there is still a lack of clinically effective drugs for such patients. The high secretory activity, the immune-modulatory effect, and the homing ability make MSCs and in particular AD-MSCs both a potential tool for the anti-viral drug-delivery in the virus microenvironment and potential cellular therapy. AD-MSCs as the most important exponent of MSCs are expected to reduce the risk of complications and death of patients due to their strong anti-inflammatory and immune-modulatory capabilities, which can improve microenvironment, promote neovascularization and enhance tissue repair capabilities. In this literature review, the role of regenerative strategies through MSCs, AD-MSCs, and adipocyte-secreted exosomal microRNAs (A-SE-miRs) as a potential antiviral therapy was reported, comparing the results found with current research progress on drugs and vaccines in COVID-19 disease.

Golchin, A. (2021). "Cell-Based Therapy for Severe COVID-19 Patients: Clinical Trials and Cost-Utility." Stem Cell Rev Rep **17**(1): 56-62.

The race among countries and companies to develop efficacious vaccines and therapeutics for the COVID-19 is ongoing fast, with many trials underway. Among this, cell-based therapy is focused on moderate to severe phases of COVID-19, and there have been promising outcomes. Mesenchymal stem cells (MSCs) due to their pro/anti-inflammatory and immune-modulatory behavior, Natural Killer (NK) cells thanks to their capacity of lysing virus-

infected cells and regulate the resulting immune response, Dendritic cells thanks to immunotherapy and cell-based vaccine engineering, SARS-CoV2-specific T cells due to stimulate and promote the immune system and MSC-derived exosomes because of cell-free therapy and beneficial manufacturing aspects, hold great promises for cell-based therapy applications for treating COVID-19 and similar viral infections. Moreover, recently, an innovative approach to COVID-19 based on engineered human MSC has been introduced, which is continuously evacuated and degraded by the body's immune system during the antigen recognition process. However, the economic situation of governments and nations, and the cost of therapeutics influence the clinical approaches to manage and exit from this pandemic. This summary describes cell-based clinical trials and the cost-utility aspects of cell therapy. In this regard, limited clinical studies have been reported; while, several clinical trials have been approved for starting phases 2 and 3 of their trials for treating COVID-19 patients with acute respiratory distress syndrome. Regarding the cost of cell therapy, many believe that the high cost of cell-based therapy will decrease substantially. Hence, there are hopes that cellular therapy can be approved soon for the treatment of viral diseases such as COVID-19. Graphical abstract.

Goldman, J. D., et al. (2021). "COVID-19 in immunocompromised populations: implications for prognosis and repurposing of immunotherapies." J Immunother Cancer **9**(6).

SARS-CoV-2 is the virus responsible for the COVID-19 pandemic. COVID-19 has highly variable disease severity and a bimodal course characterized by acute respiratory viral infection followed by hyperinflammation in a subset of patients with severe disease. This immune dysregulation is characterized by lymphocytopenia, elevated levels of plasma cytokines and proliferative and exhausted T cells, among other dysfunctional cell types. Immunocompromised persons often fare worse in the context of acute respiratory infections, but preliminary data suggest this may not hold true for COVID-19. In this review, we explore the effect of SARS-CoV-2 infection on mortality in four populations with distinct forms of immunocompromise: (1) persons with hematological malignancies (HM) and hematopoietic stem cell transplant (HCT) recipients; (2) solid organ transplant recipients (SOTRs); (3) persons with rheumatological diseases; and (4) persons living with HIV (PLWH). For each population, key immunological defects are described and how these relate to the immune dysregulation in COVID-19. Next, outcomes including mortality after SARS-CoV-2 infection are described for each population, giving comparisons to the general population of age-matched and comorbidity-matched controls. In these four populations, iatrogenic or disease-related immunosuppression is not clearly associated with poor prognosis in HM, HCT, SOTR, rheumatological diseases, or HIV. However, certain individual immunosuppressants or disease states may be associated with harmful or beneficial effects, including harm from severe CD4 lymphocytopenia in PLWH and possible benefit to the calcineurin inhibitor ciclosporin in SOTRs, or tumor necrosis factor-alpha inhibitors in persons with rheumatic diseases. Lastly, insights gained from clinical and translational studies are explored as to the relevance for repurposing of immunosuppressive host-directed therapies for the treatment of hyperinflammation in COVID-19 in the general population.

Hossein-Khannazer, N., et al. (2020). "Novel therapeutic approaches for treatment of COVID-19." J Mol Med (Berl) **98**(6): 789-803.

To date, there is no licensed treatment or approved vaccine to combat the coronavirus disease of 2019 (COVID-19), and the number of new cases and mortality multiplies every day. Therefore, it is essential to develop an effective treatment strategy to control the virus spread and prevent the disease. Here, we summarized the therapeutic approaches that are used to treat this infection. Although it seems that antiviral drugs are effective in improving clinical manifestation, there is no definite treatment protocol. Lymphocytopenia, excessive inflammation, and cytokine storm followed by acute respiratory distress syndrome are still unsolved issues causing the severity of this disease. Therefore, immune response modulation and inflammation management can be considered as an essential step. There is no doubt that more studies are required to clarify immunopathogenesis and immune response; however, new therapeutic approaches including mesenchymal stromal cell and immune cell therapy showed inspiring results.

Iovino, L., et al. (2021). "Shared inflammatory pathways and therapeutic strategies in COVID-19 and cancer immunotherapy." J Immunother Cancer **9**(5).

COVID-19, the syndrome caused by the infection with SARS-CoV-2 coronavirus, is characterized, in its severe form, by interstitial diffuse pneumonitis and acute respiratory distress syndrome (ARDS). ARDS and systemic manifestations of COVID-19 are mainly due to an exaggerated immune response triggered by the viral infection. Cytokine release syndrome (CRS), an inflammatory syndrome characterized by elevated levels of circulating cytokines, and endothelial dysfunction are systemic manifestations of COVID-19. CRS is also an adverse event of immunotherapy (IMTX), the treatment of diseases using drugs, cells, and antibodies to stimulate or suppress the immune system. Graft-versus-host disease complications after an allogeneic stem cell transplant, toxicity after the infusion of chimeric antigen receptor-T cell therapy and monoclonal antibodies can all lead to CRS. It is

hypothesized that anti-inflammatory drugs used for treatment of CRS in IMTX may be useful in reducing the mortality in COVID-19, whereas IMTX itself may help in ameliorating effects of SARS-CoV-2 infection. In this paper, we focused on the potential shared mechanisms and differences between COVID-19 and IMTX-related toxicities. We performed a systematic review of the clinical trials testing anti-inflammatory therapies and of the data published from prospective trials. Preliminary evidence suggests there might be a benefit in targeting the cytokines involved in the pathogenesis of COVID-19, especially by inhibiting the interleukin-6 pathway. Many other approaches based on novel drugs and cell therapies are currently under investigation and may lead to a reduction in hospitalization and mortality due to COVID-19.

Kared, H., et al. (2021). "SARS-CoV-2-specific CD8+ T cell responses in convalescent COVID-19 individuals." J Clin Invest **131**(5).

Characterization of the T cell response in individuals who recover from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is critical to understanding its contribution to protective immunity. A multiplexed peptide-MHC tetramer approach was used to screen 408 SARS-CoV-2 candidate epitopes for CD8+ T cell recognition in a cross-sectional sample of 30 coronavirus disease 2019 convalescent individuals. T cells were evaluated using a 28-marker phenotypic panel, and findings were modelled against time from diagnosis and from humoral and inflammatory responses. There were 132 SARS-CoV-2-specific CD8+ T cell responses detected across 6 different HLAs, corresponding to 52 unique epitope reactivities. CD8+ T cell responses were detected in almost all convalescent individuals and were directed against several structural and nonstructural target epitopes from the entire SARS-CoV-2 proteome. A unique phenotype for SARS-CoV-2-specific T cells was observed that was distinct from other common virus-specific T cells detected in the same cross-sectional sample and characterized by early differentiation kinetics. Modelling demonstrated a coordinated and dynamic immune response characterized by a decrease in inflammation, increase in neutralizing antibody titer, and differentiation of a specific CD8+ T cell response. Overall, T cells exhibited distinct differentiation into stem cell and transitional memory states (subsets), which may be key to developing durable protection.

Kounis, N. G., et al. (2021). "Allergic Reactions to Current Available COVID-19 Vaccinations: Pathophysiology, Causality, and Therapeutic Considerations." Vaccines (Basel) **9**(3).

Vaccines constitute the most effective medications in public health as they control and prevent the spread of infectious diseases and reduce mortality. Similar to other medications, allergic reactions can occur during vaccination. While most reactions are neither frequent nor serious, anaphylactic reactions are potentially life-threatening allergic reactions that are encountered rarely, but can cause serious complications. The allergic responses caused by vaccines can stem from activation of mast cells via Fcepsilon receptor-1 type I reaction, mediated by the interaction between immunoglobulin E (IgE) antibodies against a particular vaccine, and occur within minutes or up to four hours. The type IV allergic reactions initiate 48 h after vaccination and demonstrate their peak between 72 and 96 h. Non-IgE-mediated mast cell degranulation via activation of the complement system and via activation of the Mas-related G protein-coupled receptor X2 can also induce allergic reactions. Reactions are more often caused by inert substances, called excipients, which are added to vaccines to improve stability and absorption, increase solubility, influence palatability, or create a distinctive appearance, and not by the active vaccine itself. Polyethylene glycol, also known as macrogol, in the currently available Pfizer-BioNTech and Moderna COVID-19 mRNA vaccines, and polysorbate 80, also known as Tween 80, in AstraZeneca and Johnson & Johnson COVID-19 vaccines, are excipients mostly incriminated for allergic reactions. This review will summarize the current state of knowledge of immediate and delayed allergic reactions in the currently available vaccines against COVID-19, together with the general and specific therapeutic considerations. These considerations include: The incidence of allergic reactions and deaths under investigation with the available vaccines, application of vaccination in patients with mast cell disease, patients who developed an allergy during the first dose, vasovagal symptoms masquerading as allergic reactions, the COVID-19 vaccination in pregnancy, deaths associated with COVID-19 vaccination, and questions arising in managing of this current ordeal. Careful vaccine-safety surveillance over time, in conjunction with the elucidation of mechanisms of adverse events across different COVID-19 vaccine platforms, will contribute to the development of a safe vaccine strategy. Allergists' expertise in proper diagnosis and treatment of allergic reactions is vital for the screening of high-risk individuals.

Luellen, E. (2020). "A Machine Learning Explanation of the Pathogen-Immune Relationship of SARS-CoV-2 (COVID-19), and a Model to Predict Immunity and Therapeutic Opportunity: A Comparative Effectiveness Research Study." JMIRx Med **1**(1): e23582.

Background: Approximately 80% of those infected with COVID-19 are immune. They are asymptomatic unknown carriers who can still infect those with whom they come into contact. Understanding what makes them immune could inform public health policies as to who needs to be protected and why, and possibly lead to a novel

treatment for those who cannot, or will not, be vaccinated once a vaccine is available. Objective: The primary objectives of this study were to learn if machine learning could identify patterns in the pathogen-host immune relationship that differentiate or predict COVID-19 symptom immunity and, if so, which ones and at what levels. The secondary objective was to learn if machine learning could take such differentiators to build a model that could predict COVID-19 immunity with clinical accuracy. The tertiary purpose was to learn about the relevance of other immune factors. Methods: This was a comparative effectiveness research study on 53 common immunological factors using machine learning on clinical data from 74 similarly grouped Chinese COVID-19-positive patients, 37 of whom were symptomatic and 37 asymptomatic. The setting was a single-center primary care hospital in the Wanzhou District of China. Immunological factors were measured in patients who were diagnosed as SARS-CoV-2 positive by reverse transcriptase-polymerase chain reaction (RT-PCR) in the 14 days before observations were recorded. The median age of the 37 asymptomatic patients was 41 years (range 8-75 years); 22 were female, 15 were male. For comparison, 37 RT-PCR test-positive patients were selected and matched to the asymptomatic group by age, comorbidities, and sex. Machine learning models were trained and compared to understand the pathogen-immune relationship and predict who was immune to COVID-19 and why, using the statistical programming language R. Results: When stem cell growth factor-beta (SCGF-beta) was included in the machine learning analysis, a decision tree and extreme gradient boosting algorithms classified and predicted COVID-19 symptom immunity with 100% accuracy. When SCGF-beta was excluded, a random-forest algorithm classified and predicted asymptomatic and symptomatic cases of COVID-19 with 94.8% AUROC (area under the receiver operating characteristic) curve accuracy (95% CI 90.17%-100%). In total, 34 common immune factors have statistically significant associations with COVID-19 symptoms (all c<.05), and 19 immune factors appear to have no statistically significant association. Conclusions: The primary outcome was that asymptomatic patients with COVID-19 could be identified by three distinct immunological factors and levels: SCGF-beta (>127,637), interleukin-16 (IL-16) (>45), and macrophage colony-stimulating factor (M-CSF) (>57). The secondary study outcome was the suggestion that stem-cell therapy with SCGF-beta may be a novel treatment for COVID-19. Individuals with an SCGF-beta level >127,637, or an IL-16 level >45 and an M-CSF level >57, appear to be predictively immune to COVID-19 100% and 94.8% (AUROC) of the time, respectively. Testing levels of these three immunological factors may be a valuable tool at the point of care for managing and preventing outbreaks. Further, stem-cell therapy via SCGF-beta and M-CSF appear to be promising novel therapeutics for patients with COVID-19.

Park, Y. J., et al. (2021). "Fighting the War Against COVID-19 via Cell-Based Regenerative Medicine: Lessons Learned from 1918 Spanish Flu and Other Previous Pandemics." Stem Cell Rev Rep **17**(1): 9-32.

The human population is in the midst of battling a rapidly-spreading virus- Severe Acute Respiratory Syndrome Coronavirus 2, responsible for Coronavirus disease 2019 or COVID-19. Despite the resurgences in positive cases after reopening businesses in May, the country is seeing a shift in mindset surrounding the pandemic as people have been eagerly trickling out from federally-mandated quarantine into restaurants, bars, and gyms across America. History can teach us about the past, and today's pandemic is no exception. Without a vaccine available, three lessons from the 1918 Spanish flu pandemic may arm us in our fight against COVID-19. First, those who survived the first wave developed immunity to the second wave, highlighting the potential of passive immunity-based treatments like convalescent plasma and cell-based therapy. Second, the long-term consequences of COVID-19 are unknown. Slow-progressive cases of the Spanish flu have been linked to bacterial pneumonia and neurological disorders later in life, emphasizing the need to reduce COVID-19 transmission. Third, the Spanish flu killed approximately 17 to 50 million people, and the lack of human response, overcrowding, and poor hygiene were key in promoting the spread and high mortality. Human behavior is the most important strategy for preventing the virus spread and we must adhere to proper precautions. This review will cover our current understanding of the pathology and treatment for COVID-19 and highlight similarities between past pandemics. By revisiting history, we hope to emphasize the importance of human behavior and innovative therapies as we wait for the development of a vaccine. Graphical Abstract.

Pocsfalvi, G., et al. (2020). "COVID-19 and Extracellular Vesicles: An Intriguing Interplay." Kidney Blood Press Res **45**(5): 661-670.

BACKGROUND: The outbreak of severe acute respiratory syndrome beta-coronavirus 2 (SARS-CoV-2) has the potential to become a long-lasting global health crisis. The number of people infected with the novel coronavirus has surpassed 22 million globally, resulting in over 700,000 deaths with more than 15 million people having recovered (https://covid19.who.int). Enormous efforts are underway for rapid vaccine and treatment developments. Amongst the many ways of tackling the novel coronavirus disease 2019 (COVID-19) pandemic, extracellular vesicles (EVs) are emerging. SUMMARY: EVs are lipid bilayer-enclosed structures secreted from all types of cells, including those lining the respiratory tract. They have

established roles in lung immunity and are involved in the pathogenesis of various lung diseases, including viral infection. In this review, we point out the roles and possible contribution of EVs in viral infections, as well as ongoing EV-based approaches for the treatment of COVID-19, including clinical trials. Key Messages: EVs share structural similarities to viruses and recent findings demonstrate that viruses exploit EVs for cellular exit and EVs exploit viral entry mechanisms for cargo delivery. Moreover, EV-virus interplay could be exploited for future antiviral drug and vaccine development. EV-based therapies, especially the mesenchymal stem cell-derived EVs, are being intensively studied for the treatment of COVID-19.

Pooladanda, V., et al. (2020). "The current understanding and potential therapeutic options to combat COVID-19." Life Sci **254**: 117765.

The ongoing wreaking global outbreak of the novel human beta coronavirus (CoV) pathogen was presumed to be from a seafood wholesale market in Wuhan, China, belongs to the Coronaviridae family in the Nidovirales order. The virus is highly contagious with potential human-human transmission which was named as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has spread across six continents and emerged as a global pandemic in short span with alarming levels of spread and severity. This virus associated symptoms and infectious respiratory illness is designated as coronavirus disease 19 (COVID-19). The SARS-CoV-2 possesses enveloped club-like spike protein projections with positive-sense large RNA genome and has a unique replication strategy. This virus was believed to have zoonotic origin with genetical identity to bat and pangolin CoV. In the current review, we introduce a general overview about the human CoVs and the associated diseases, the origin, structure, replication and key clinical events that occur in the COVID-19 pathogenicity. Furthermore, we focused on possible therapeutic options such as repurposing drugs including antimalarials, antivirals, antiparasitic drugs, and anti-HIV drugs, as well as monoclonal antibodies, vaccines as potential treatment options. Also we have summarized the latest research progress on the usage of stem cell therapy, human convalescent serum, interferon's, in the treatment of COVID-19.

Riches, J. C. (2021). "Impact of COVID-19 in patients with lymphoid malignancies." World J Virol **10**(3): 97-110.

The first cases of coronavirus disease 2019 (COVID-19) were detected in Wuhan, China, in December 2019. Since this time a concerted global effort of research and observational data gathering has meant that a great deal has been learnt about the impact of COVID-19 in patients with lymphoid malignancies. Approximately one-third of patients with lymphoid malignancies who acquire COVID-19 and have it severely enough to require hospital assessment will die from this infection. Major risk factors for a poor outcome are age and co-morbidities, but when these are taken into account lymphoma patients have a slightly greater than 2-fold increased risk compared to the general population. Notably, despite early concerns regarding the particular vulnerability of lymphoma patients due to the immunosuppressive effects of therapy, active treatment, including B-cell depleting agents such as rituximab, do not appear to be associated with an increased risk of a poorer outcome. Indeed, some treatments such as ibrutinib may be beneficial due to their modulation of the potential fatal hyperinflammatory phase of infection. There are risks associated with hemopoietic stem cell transplantation, but the collective experience is that these can be minimized by preventive strategies and that the majority of transplant recipients with COVID-19 infection will survive. Many questions remain including those regarding the outcome of COVID-19 infection in the rarer lymphoid malignancies and the efficacy of COVID-19 vaccines in lymphoma patients. This review aims to discuss these issues and present a summary of the current knowledge of the impact of COVID-19 in lymphoid malignancies.

Rnjak, D., et al. (2021). "COVID-19 convalescent plasma as long-term therapy in immunodeficient patients?" Transfus Clin Biol **28**(3): 264-270.

OBJECTIVES: The patients with hematological malignancies are a vulnerable group to COVID-19, due to the immunodeficiency resulting from the underlying disease and oncological treatment that significantly impair cellular and humoral immunity. Here we report on a beneficial impact of a passive immunotherapy with convalescent plasma to treat a prolonged, active COVID-19 infection in a patient with a history of nasopharyngeal diffuse large B-cell lymphoma treated with the therapy inducing substantial impairment of particularly humoral arm of immune system. The specific aim was to quantify SARS-CoV2 neutralizing antibodies in a patient plasma during the course of therapy. MATERIALS AND METHODS: Besides the standard of care treatment and monitoring, neutralizing antibody titers in patient's serum samples, calibrated according to the First WHO International Standard for anti-SARS-CoV-2 immunoglobulin (human), were quantified in a time-dependent manner. During the immunotherapy period peripheral blood flow cytometry immunophenotyping was conducted to characterize lymphocyte subpopulations. RESULTS: The waves of clinical improvements and worsening coincided with transfused neutralizing antibodies rises and drops in the patient's systemic circulation, proving their contribution in controlling the disease progress. Besides the patient's lack of own humoral immune system, immunophenotyping analysis revealed also the reduced level of helper T-

lymphocytes and immune exhaustion of monocytes. CONCLUSION: Therapeutic approach based on convalescent plasma transfusion transformed a prolonged, active COVID-19 infection into a manageable chronic disease.

Rodriguez, H. C., et al. (2021). "Umbilical cord: an allogenic tissue for potential treatment of COVID-19." Hum Cell **34**(1): 1-13.

The COVID-19 pandemic has placed an unprecedented burden on health care systems and economies around the globe. Clinical evidences demonstrate that SARS-CoV-2 infection produces detrimental levels of pro-inflammatory cytokines and chemokines that can lead to acute respiratory distress syndrome (ARDS) and significant systemic organ damage. Currently, there is no definitive therapy for COVID-19 or associated complications, and with the hope of a safe and effective vaccine in the distant future, the search for an answer is paramount. Mesenchymal stem cells (MSCs) provide a viable option due to their immunomodulatory effects and tissue repair and regeneration abilities. Studies have demonstrated that compassionate use of MSCs can reduce symptoms associated with SARS-CoV-2 infection, eliminate fluid buildup, and act as a regenerative technique for alveolar damage; all in a safe and effective way. With multiple autologous sources available for MSCs, each with their own respective limitations, allogenic umbilical cord (UC) and/or UC-derived Wharton's jelly (WJ) seem to be best positioned source to harvest MSCs to treat COVID-19 and associated symptoms. As an allogenic source, UC is readily available, easily obtainable, and is rich in immunomodulatory and regenerative factors. In this manuscript, we reviewed the current evidences and explored the potential therapeutic use of allogenic UC and/or WJ-derived MSCs for the treatment of COVID-19. Although, preliminary preclinical and clinical studies indicate that their use is safe and potentially effective, more multi-center, randomized, controlled trials are needed to adequately assess the safety and efficacy of UC and/or WJ-derived MSCs for the treatment of COVID-19.

Saburi, E., et al. (2021). "The use of mesenchymal stem cells in the process of treatment and tissue regeneration after recovery in patients with Covid-19." Gene **777**: 145471.

In addition to causing health concerns, the new coronavirus has been considered in the world with its unknown mechanism of physiopathogenesis and long-term effects after patient recovery. Pulmonary, renal, hepatic and cardiac complications have been reported so far. Beside the researchers' focus on finding vaccines and using conventional therapies, cell-based therapy might be an effective therapeutic strategy. The use of mesenchymal stem cells (MSCs) is one of the options due to their immunomodulatory properties and their proven effects in the treatment of many diseases. As MSCs are not infected with covid-19, there is evidence that it modulates the immune system and prevents the virus from clotting. Despite the beginning of numerous clinical trials in the use of mesenchymal stem cells, it is necessary to set a practical guideline that specifies items such as cell origin, number of cells, frequency of injection, injection site, etc.

Sahu, K. K., et al. (2021). "Mesenchymal Stem Cells in COVID-19: A Journey from Bench to Bedside." Lab Med **52**(1): 24-35.

The COVID-19 pandemic has led to a major setback in both the health and economic sectors across the globe. The scale of the problem is enormous because we still do not have any specific anti-SARS-CoV-2 antiviral agent or vaccine. The human immune system has never been exposed to this novel virus, so the viral interactions with the human immune system are completely naive. New approaches are being studied at various levels, including animal in vitro models and human-based studies, to contain the COVID-19 pandemic as soon as possible. Many drugs are being tested for repurposing, but so far only remdesivir has shown some positive benefits based on preliminary reports, but these results also need further confirmation via ongoing trials. Otherwise, no other agents have shown an impactful response against COVID-19. Recently, research exploring the therapeutic application of mesenchymal stem cells (MSCs) in critically ill patients suffering from COVID-19 has gained momentum. The patients belonging to this subset are most likely beyond the point where they could benefit from an antiviral therapy because most of their illness at this stage of disease is driven by inflammatory (over)response of the immune system. In this review, we discuss the potential of MSCs as a therapeutic option for patients with COVID-19, based on the encouraging results from the preliminary data showing improved outcomes in the progression of COVID-19 disease.

Sarwar, Z., et al. (2020). "Potential approaches to combat COVID-19: a mini-review." Mol Biol Rep **47**(12): 9939-9949.

The outbreak of a novel coronavirus namely SARS-CoV-2, which first emerged from Wuhan, China, has wreaked havoc not only in China but the whole world that now has been engulfed in its wrath. In a short lapse of time, this virus was successful in spreading at a blistering pace throughout the globe, hence raising the flag of pandemic status. The mounting number of deaths with each elapsing day has summoned researchers from all around the world to play their part in driving this SARS-CoV-2 pandemic to an end. As of now, multiple research teams are immersed in either scrutinizing various antiviral drugs for their efficacy or developing different types of vaccines that will be capable of providing long-term immunity against this deadly virus. The mini-review sheds light on the possible approaches that can be undertaken to curb the

COVID-19 spread. Possible strategies comprise viral vector-based, nucleic acid-based, protein-based, inactivated and weakened virus vaccines; COVID-19 vaccine being developed by deploying Hyleukin-7 technology; plant-based chimeric protein and subunit vaccines; humanized nano-bodies and human antibodies; intravenous immunoglobulin (IVIG) infusion therapy; inhibitors for ACE-2, Angiotensin 1 receptor (AT1R), complement system, viral proteins, host cell protease and endocytosis; shield immunity; IL-6R, NKG2A and hACE2-SARS-CoV-2-RBD interaction blocking monoclonal antibodies; SARS-CoV RdRp-based drugs, traditional Chinese medicine, repositioned and anti-viral drugs. These vaccines and drugs are currently being screened in the clinical trials as several of them have manifested positive results, hence increasing the probability of becoming one of the potential treatments for this disease.

Siam, M. H. B., et al. (2020). "Stopping the COVID-19 Pandemic: A Review on the Advances of Diagnosis, Treatment, and Control Measures." J Pathog **2020**: 9121429.

With the continued spread of COVID-19 across the world, rapid diagnostic tools, readily available respurposable drugs, and prompt containment measures to control the SARS-CoV-2 infection are of paramount importance. Examples of recent advances in diagnostic tests are CRISPR technology, IgG assay, spike protein detection, and use of artificial intelligence. The gold standard reverse transcription polymerase chain (RT-PCR) has also been upgraded with point-of-care rapid tests. Supportive treatment, mechanical ventilation, and extracorporeal membrane oxygenation (ECMO) remain the primary choice, while therapeutic options include antivirals, antiparasitics, anti-inflammatories, interferon, convalescent plasma, monoclonal antibody, hyperimmunoglobulin, RNAi, and mesenchymal stem cell therapy. Different types of vaccines such as RNA, DNA, and lentiviral, inactivated, and viral vector are in clinical trials. Moreover, rapidly deployable and easy-to-transport innovative vaccine delivery systems are also in development. As countries have started easing down on the lockdown measures, the chance for a second wave of infection demands strict and rational control policies to keep fatalities minimized. An improved understanding of the advances in diagnostic tools, treatments, vaccines, and control measures for COVID-19 can provide references for further research and aid better containment strategies.

Singh, V. K., et al. (2020). "Emerging Prevention and Treatment Strategies to Control COVID-19." Pathogens **9**(6).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), has now become a serious global threat after inflicting more than 8 million infections and 425,000 deaths in less than 6 months. Currently, no definitive treatment or prevention therapy exists for COVID-19. The unprecedented rise of this pandemic has rapidly fueled research efforts to discover and develop new vaccines and treatment strategies against this novel coronavirus. While hundreds of vaccines/therapeutics are still in the preclinical or early stage of clinical development, a few of them have shown promising results in controlling the infection. Here, in this review, we discuss the promising vaccines and treatment options for COVID-19, their challenges, and potential alternative strategies.

Thakkar, A., et al. (2021). "Seroconversion rates following COVID-19 vaccination among patients with cancer." Cancer Cell **39**(8): 1081-1090 e1082.

As COVID-19 adversely affects patients with cancer, prophylactic strategies are critically needed. Using a validated antibody assay against SARS-CoV-2 spike protein, we determined a high seroconversion rate (94%) in 200 patients with cancer in New York City that had received full dosing with one of the FDA-approved COVID-19 vaccines. On comparison with solid tumors (98%), a significantly lower rate of seroconversion was observed in patients with hematologic malignancies (85%), particularly recipients following highly immunosuppressive therapies such as anti-CD20 therapies (70%) and stem cell transplantation (73%). Patients receiving immune checkpoint inhibitor therapy (97%) or hormonal therapies (100%) demonstrated high seroconversion post vaccination. Patients with prior COVID-19 infection demonstrated higher anti-spike IgG titers post vaccination. Relatively lower IgG titers were observed following vaccination with the adenoviral than with mRNA-based vaccines. These data demonstrate generally high immunogenicity of COVID-19 vaccination in oncology patients and identify immunosuppressed cohorts that need novel vaccination or passive immunization strategies.

Ueda Oshima, M., et al. (2021). "Blood and marrow transplantation during the emerging COVID-19 pandemic: the Seattle approach." Bone Marrow Transplant **56**(2): 305-313.

On January 20, 2020, the first patient with coronavirus disease 2019 (COVID-19) in the United States of America was diagnosed in Washington state, which subsequently experienced rapidly increasing numbers of COVID-19 cases, hospitalizations, and deaths. This placed the Seattle Blood and Marrow Transplant Program at Fred Hutchinson Cancer Research Center (Fred Hutch) in the national epicenter of this pandemic. Here, we summarize the experience gained during our rapid response to the COVID-19 pandemic. Our efforts were aimed at safely performing urgent and potentially life-saving stem cell transplants in the setting of pandemic-related stresses on healthcare resources and shelter-in-place public health measures. We describe the unique circumstances and

challenges encountered, the current state of the program amidst evolving COVID-19 cases in our community, and the guiding principles for recovery. We also estimate the collateral impact of directing clinical resources toward COVID-19-related care on cancer patients in need of stem cell transplantation. Although our experience was influenced by specific regional and institutional factors, it may help inform how transplant programs respond to COVID-19 and future pandemics.

Wang, J., et al. (2020). "Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: Review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts." J Leukoc Biol **108**(1): 17-41.

Clinical evidence indicates that the fatal outcome observed with severe acute respiratory syndrome-coronavirus-2 infection often results from alveolar injury that impedes airway capacity and multi-organ failure-both of which are associated with the hyperproduction of cytokines, also known as a cytokine storm or cytokine release syndrome. Clinical reports show that both mild and severe forms of disease result in changes in circulating leukocyte subsets and cytokine secretion, particularly IL-6, IL-1beta, IL-10, TNF, GM-CSF, IP-10 (IFN-induced protein 10), IL-17, MCP-3, and IL-1ra. Not surprising, therapies that target the immune response and curtail the cytokine storm in coronavirus 2019 (COVID-19) patients have become a focus of recent clinical trials. Here we review reports on leukocyte and cytokine data associated with COVID-19 disease in 3939 patients in China and describe emerging data on immunopathology. With an emphasis on immune modulation, we also look at ongoing clinical studies aimed at blocking proinflammatory cytokines; transfer of immunosuppressive mesenchymal stem cells; use of convalescent plasma transfusion; as well as immunoregulatory therapy and traditional Chinese medicine regimes. In examining leukocyte and cytokine activity in COVID-19, we focus in particular on how these levels are altered as the disease progresses (neutrophil NETosis, macrophage, T cell response, etc.) and proposed consequences to organ pathology (coagulopathy, etc.). Viral and host interactions are described to gain further insight into leukocyte biology and how dysregulated cytokine responses lead to disease and/or organ damage. By better understanding the mechanisms that drive the intensity of a cytokine storm, we can tailor treatment strategies at specific disease stages and improve our response to this worldwide public health threat.

Yamamoto, V., et al. (2020). "COVID-19: Review of a 21st Century Pandemic from Etiology to Neuro-psychiatric Implications." J Alzheimers Dis **77**(2): 459-504.

COVID-19 is a severe infectious disease that has claimed >150,000 lives and infected millions in the United States thus far, especially the elderly population. Emerging evidence has shown the virus to cause hemorrhagic and immunologic responses, which impact all organs, including lungs, kidneys, and the brain, as well as extremities. SARS-CoV-2 also affects patients', families', and society's mental health at large. There is growing evidence of re-infection in some patients. The goal of this paper is to provide a comprehensive review of SARS-CoV-2-induced disease, its mechanism of infection, diagnostics, therapeutics, and treatment strategies, while also focusing on less attended aspects by previous studies, including nutritional support, psychological, and rehabilitation of the pandemic and its management. We performed a systematic review of >1,000 articles and included 425 references from online databases, including, PubMed, Google Scholar, and California Baptist University's library. COVID-19 patients go through acute respiratory distress syndrome, cytokine storm, acute hypercoagulable state, and autonomic dysfunction, which must be managed by a multidisciplinary team including nursing, nutrition, and rehabilitation. The elderly population and those who are suffering from Alzheimer's disease and dementia related illnesses seem to be at the higher risk. There are 28 vaccines under development, and new treatment strategies/protocols are being investigated. The future management for COVID-19 should include B-cell and T-cell immunotherapy in combination with emerging prophylaxis. The mental health and illness aspect of COVID-19 are among the most important side effects of this pandemic which requires a national plan for prevention, diagnosis and treatment.

Yiangou, L., et al. (2021). "Using Cardiovascular Cells from Human Pluripotent Stem Cells for COVID-19 Research: Why the Heart Fails." Stem Cell Reports **16**(3): 385-397.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) led to the coronavirus disease (COVID-19) outbreak that became a pandemic in 2020, causing more than 30 million infections and 1 million deaths to date. As the scientific community has looked for vaccines and drugs to treat or eliminate the virus, unexpected features of the disease have emerged. Apart from respiratory complications, cardiovascular disease has emerged as a major indicator of poor prognosis in COVID-19. It has therefore become of utmost importance to understand how SARS-CoV-2 damages the heart. Human pluripotent stem cell (hPSC) cardiovascular derivatives were rapidly recognized as an invaluable tool to address this, not least because one of the major receptors for the virus is not recognized by SARS-CoV-2 in mice. Here, we outline how hPSC-derived cardiovascular cells have been utilized to study COVID-19, and their potential for further understanding the cardiac pathology and in therapeutic development.

Yuan, C., et al. (2020). "Potential of Immune-Related Therapy in COVID-19." Front Pharmacol **11**: 609212.

At the beginning of 2020, a sudden outbreak of new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), infections led to anxiety, panic, and crisis among people worldwide. The outbreak first occurred in Wuhan, China, in late December 2019 and then spread rapidly across the globe, thus becoming a major public health emergency. Although the current epidemic situation in China tends to be stable, coronavirus disease 2019 (COVID-19) continues to spread globally. At present, no specific therapeutic drugs and vaccines are available against COVID-19. Also, the pathogenesis of the SARS-CoV-2 is not fully clear. Human immunity is important in SARS-CoV-2 infection. Studies have shown that excessive inflammation caused by SARS-CoV-2 infection and subsequent induced uncontrolled cytokine storm are the main causes of disease deterioration and death of severe patients. Therefore, immune-related research is of great significance for the prevention, control, and prognosis of COVID-19. This study aimed to review the latest research on immune-related treatment of COVID-19.

Zani-Ruttenstock, E., et al. (2021). "The Role of Exosomes in the Treatment, Prevention, Diagnosis, and Pathogenesis of COVID-19." Eur J Pediatr Surg **31**(4): 326-334.

The novel coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), continues to be a major health concern. In search for novel treatment strategies against COVID-19, exosomes have attracted the attention of scientists and pharmaceutical companies worldwide. Exosomes are small extracellular vesicles, secreted by all types of cells, and considered as key mediators of intercellular communication and stem-cell paracrine signaling. Herein, we reviewed the most recent literature about the role of exosomes as potential agents for treatment, prevention, diagnosis, and pathogenesis of COVID-19. Several studies and ongoing clinical trials have been investigating the anti-inflammatory, immunomodulatory, and reparative effects of exosomes derived from mesenchymal stem/stromal cells for COVID-19-related acute lung injury. Other studies reported that exosomes play a key role in convalescent plasma therapy for COVID-19, and that they could be of use for the treatment of COVID-19 Kawasaki's-like multisystem inflammatory syndrome and as drug delivery nanocarriers for antiviral therapy. Harnessing some advantageous aspects of exosome biology, such as their endogenous origin, capability of crossing biological barriers, high stability in circulation, and low toxicity and immunogenicity, several companies have been testing exosome-based vaccines against SARS-CoV-2. As they carry cargos that mimic the status of parent cells, exosomes can be isolated from a variety of sources, including plasma, and employed as biomarkers of COVID-19. Lastly, there is growing evidence supporting the role of exosomes in COVID-19 infection, spread, reactivation, and reinfection. The lessons learned using exosomes for COVID-19 will help determine their efficacy and applicability in other clinical conditions.

Zhang, J., et al. (2020). "Current status of potential therapeutic candidates for the COVID-19 crisis." Brain Behav Immun **87**: 59-73.

As of April 15, 2020, the ongoing coronavirus disease 2019 (COVID-2019) pandemic has swept through 213 countries and infected more than 1,870,000 individuals, posing an unprecedented threat to international health and the economy. There is currently no specific treatment available for patients with COVID-19 infection. The lessons learned from past management of respiratory viral infections have provided insights into treating COVID-19. Numerous potential therapies, including supportive intervention, immunomodulatory agents, antiviral therapy, and convalescent plasma transfusion, have been tentatively applied in clinical settings. A number of these therapies have provided substantially curative benefits in treating patients with COVID-19 infection. Furthermore, intensive research and clinical trials are underway to assess the efficacy of existing drugs and identify potential therapeutic targets to develop new drugs for treating COVID-19. Herein, we summarize the current potential therapeutic approaches for diseases related to COVID-19 infection and introduce their mechanisms of action, safety, and effectiveness.

Zhang, Y., et al. (2020). "Intravenous infusion of human umbilical cord Wharton's jelly-derived mesenchymal stem cells as a potential treatment for patients with COVID-19 pneumonia." Stem Cell Res Ther **11**(1): 207.

The novel coronavirus disease 2019 (COVID-19) has grown to be a global public health emergency since patients were first detected in Wuhan, China. Thus far, no specific drugs or vaccines are available to cure the patients with COVID-19 infection. The immune system and inflammation are proposed to play a central role in COVID-19 pathogenesis. Mesenchymal stem cells (MSCs) have been shown to possess a comprehensive powerful immunomodulatory function. Intravenous infusion of MSCs has shown promising results in COVID-19 treatment. Here, we report a case of a severe COVID-19 patient treated with human umbilical cord Wharton's jelly-derived MSCs (hWJCs) from a healthy donor in Liaocheng People's Hospital, China, from February 24, 2020. The pulmonary function and symptoms of the patient with COVID-19 pneumonia was significantly improved in 2 days after hWJC transplantation, and recovered and discharged in 7 days after treatment.

After treatment, the percentage and counts of lymphocyte subsets (CD3(+), CD4(+), and CD8(+) T cell) were increased, and the level of IL-6, TNF-alpha, and C-reactive protein is significantly decreased after hWJC treatment. Thus, the intravenous transplantation of hWJCs was safe and effective for the treatment of patients with COVID-19 pneumonia, especially for the patients in a critically severe condition. This report highlights the potential of hWJC infusions as an effective treatment for COVID-19 pneumonia.

Zhu, Y., et al. (2020). "Human Umbilical Cord Mesenchymal Stem Cells for Adjuvant Treatment of a Critically Ill COVID-19 Patient: A Case Report." Infect Drug Resist **13**: 3295-3300.

Background: COVID-19 (coronavirus disease 2019) has become a global public health emergency since patients were first detected in Wuhan, China, in December 2019. Currently, there are no satisfying antiviral medications and vaccines available. Case Presentation: We reported the treatment process and clinical outcome of a 48-year-old man critically ill COVID-19 patient who received transfusion of allogenic human umbilical cord mesenchymal stem cells (UC-MSCs). Conclusions: We proposed that UC-MSC transfusion might be a new option for critically ill COVID-19. Although only one case we were shown, more similar clinical cases are inquired for further evidence providing the potential effectiveness of UC-MSC treatment.

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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