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Review of Trials Currently Testing Stem Cells for Treatment of Respiratory Diseases: Facts Known to Date and Possible Applications to COVID-19

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Abstract

Therapeutic clinical and preclinical studies using cultured cells are on the rise, especially now that the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a "public health emergency of international concern", in January, 2020. Thus, this study aims to review the outcomes of ongoing clinical studies on stem cells in Severe Acute Respiratory Syndrome (SARS), Acute Respiratory Distress Syndrome (ARDS), and Middle East Respiratory Syndrome (MERS). The results will be associated with possible applications to COVID-19. Only three clinical trials related to stem cells are considered complete, whereby two are in Phase 1 and one is in Phase 2. Basically, the ongoing studies on coronavirus are using mesenchymal stem cells (MSCs) derived from bone marrow or the umbilical cord to demonstrate their feasibility, safety, and tolerability. The studies not related to coronavirus are all in ARDS conditions; four of them are in Phase 1 and three in Phase 2. With the COVID-19 boom, many clinical trials are being carried out using different sources with an emphasis on MSC-based therapy used to inhibit inflammation. One of the biggest challenges in the current treatment of COVID-19 is the cytokine storm, however MSCs can prevent or mitigate this cytokine storm through their immunomodulatory capacity. We look forward to the results of the ongoing clinical trials to find a treatment for the disease. Researchers around the world are joining forces to help fight COVID-19. Stem cells used in the current clinical studies are a new therapeutic promise for COVID-19 where pharmacological treatments seem insufficient.

Keywords Acute Respiratory Distress Syndrome · Clinical Trials · Mesenchymal Stem Cells · Microvesicles · Middle East Respiratory Syndrome

Introduction

On January 31st, 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a "public health emergency of international concern" [1]. The virus causing it is highly homologous to the coronavirus (CoV) that caused an outbreak of Severe Acute Respiratory Syndrome (SARS) in 2003 and is named SARS-CoV-2 [2]. Further, in 2011, the world also experienced outbreaks of a coronavirus infection that threatened to become a global pandemic called Middle East Respiratory Syndrome (MERS). In both cases, the causative agents (SARS-CoV and MERS-CoV, respectively) were newly identified coronaviruses from the genus *Betacoronavirus* having zoonotic origin [3]. Another lung disorder associated with CoV is the Acute Respiratory Distress Syndrome (ARDS) that developed in several patients causing pathological changes in the lungs such as diffuse alveolar damage leading to fibrotic lesions [4, 5].

Therapeutic clinical and preclinical studies using cultured cells are on the rise. Models for respiratory virus infections

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and relevant clinical studies related to the administration of stem cells in patients are essential to define the patient population that can benefit from cell therapy [6]. Thus, this study aims to review the outcomes of ongoing clinical studies on stem cells in SARS, ARDS, and MERS. The results will be associated with possible applications to COVID-19.

Stem Cells and Respiratory Diseases

Stem cells are specialized cells that differentiate into other cell types [7]. In certain organs, the stem cells produce descendants that maintain tissue homeostasis and also have the same function as the cells that are not generated from this differentiation [8]. This class of cells depicts a revolution in such studies enabling their application in patients with various disorders, including lung diseases, thus allowing to study cell-based therapies for their treatment. For the treatment of ARDS and sepsis, various cell types are used such as headStartembryonic stem cellsheadEnd (ESCs), headStartmesenchymal stem cellsheadEnd (MSCs), and epithelial progenitor cells (EpPCs). Currently, most of the preclinical studies are using MSCs, though headStartinduced pluripotent stem cellsheadEnd (iPSC) for the treatment of ARDS [9] are also being used.

The lungs were previously thought to be "post-mitotic" and unable to regenerate, while the stem cell populations, such as bone marrow, intestinal mucosa, and skin are considered regenerative. Yet it is known that different regions in the lungs are dependent on different cell populations, such as the endogenous stem cell complex for tissue repair demonstrating regenerative characteristics [10]. For example, idiopathic pulmonary fibrosis (IPF) is a fatal form of the disease characterized by scar tissue formation in the interstitial lungs with extracellular matrix deposited over time. The symptoms include cough, exertional dyspnea, functional and exercise limitation, acute respiratory failure, and death.

With the emergence of stem cell therapy in treating diseases, the murine bleomycin model became the best-characterized one, in which the administration of allogeneic bone marrow-derived-MSCs (BM-MSCs) reduces inflammation and collagen deposition [11–13]. Also, it was observed that stem cells from the placenta and human umbilical cord demonstrated reduced lung tissue damage in the mouse bleomycin models [14–16].

Another example of stem cells applied to lung disease is chronic obstructive pulmonary disease (COPD), a major devastating disease worldwide. COPD is characterized by chronic small airway inflammation, commonly known as chronic bronchitis, causing progressive poor airflow leading to damage of lung tissues (emphysema). MSCs, as a therapy, are considered a strong candidate in headStartclinical trialsheadEnd to repair damaged lung tissue in COPD or any other chronic lung disease [17–19].

Stem cells, particularly pluripotent cells such as ESCs or iPSCs, offer the potential to differentiate into lung cells reprogramming the immune response to reduce destructive inflammatory elements and directly replace damaged cells and tissues [20]. Thus, it can be a promising novel therapeutic strategy in ARDS to repair and resolve a lung injury restoring the whole epithelial and endothelial function [21]. They can also attenuate bacterial sepsis, directly associated with ARDS, via several mechanisms, such as improving the phagocytic ability, secreting anti-microbial peptides [22], and increasing bacterial clearance [23]. Furthermore, MSCs demonstrated a great potential when reducing the endotoxin-induced injury to explanted human lungs [24].

Mesenchymal Stem Cells

headStartMesenchymal stem cellsheadEnd can be isolated from bone marrow and expanded extensively *in vitro*. They play an important role in the repair process or may engraft the injured lung [25, 26]. Engraftment may initiate simultaneously, where MSCs differentiate into lung epithelial cells and can directly replace the damaged cells in alveoli during the treatment of ARDS [27, 28]. Their applicability has been reported in treating cardiovascular and pulmonary diseases [26, 29] along with severe inflammation [30, 31]. These properties are also very attractive due to the immunosuppressive/immunomodulatory abilities [32, 33] influencing an increase in Keratinocyte growth factor (KGF) on epithelial cells, and in the study models of lung injury. Thus, they play a protective role in inducing type II cell proliferation and edema clearance [34]. Additionally, KGF could upregulate alveolar fluid clearance in *ex vivo* human lungs injured by an endotoxin [24]. MSCs play an anti-inflammatory role secreting several mediators that down-regulate the inflammatory process [35] and secrete growth factors, including KGF [36, 37].

In animal models with lung injury, intravenous MSCs led to favorable outcomes, such as reduction in inflammation, pro-inflammatory cytokines, and lung edema [38]. In mouse models, the treatment involving MSCs reduced pulmonary edema and extended survival in *Escherichia coli* endotoxin-induced lung injury [39]. The outcomes of involving MSCs in experimental models of ALI/ARDS have been promising as a cell-based therapy [40].

Previously, ARDS was defined within two simple concepts, namely [1] the pro-inflammatory (leading to host damage) and [2] fibrotic (repair and fibrosis) phase. These two phases make the disease progression more complex [41]. Moreover, the mechanism of action of MSCs is also unknown due to the diverse array of paracrine mediators which are directly associated with the therapeutic effects [42]. Several factors that influence these effects are [1] differences between the cell surface epitopes and genomic stability between mice and humans involved in the

studies [43]; [2] different inflammatory environment [44]; and [3] the heterogeneity of MSCs and their subtypes [45]. However, the complete success of MSCs as a cell therapy for patients with ARDS will probably depend on a better understanding of their mechanism of action and on defining the best strategies for their use in a clinical setting [46].

The benefit of MSCs utilization is directly related to paracrine soluble factors, transfer of mitochondria, and histologically active microvesicles [47]. siRNA knockdown was utilized to analyze the paracrine soluble factors in cultured human type 2 cells during *in vitro* MSCs treatment and it was found that angiopoietin-1 secretion was partially responsible for the beneficial effect of MSCs [48–50]. The presence of MSCs upregulates lipoxin A4, a pro-resolving lipid mediator which could play an important role in MSC-mediated healing of lung injury [49, 50]. Additionally, MSCs mediate the release of microvesicles during cell-to-cell communication [51].

The resistance of pulmonary epithelial cells during inflammation is an important tool to combat pulmonary edema. The interaction between epithelial cells and MSCs in an inflammatory process represents a critical information point in revealing the mechanism of MSC-mediated therapeutic effects, thus allowing to design a better practical protocol to manage these cells [52]. However, the genetic manipulation to improve the therapeutic efficacy of MSCs, so that they could work at the low level of trophic factors in the damaged host tissue, remains a permanent challenge [53].

MSCs-derived Microvesicles

Among the MSC-derived extracellular vesicles (EVs) or microvesicles, the best- characterized ones are the exosomes. They have a conserved protein group known as tetraspanins which is important for cell targeting. These vesicles are rich in integrins, flotillins (lipid raft-associated), and cholesterol [54]. An important role of microvesicles is cell-cell-mediated communication and they are composed of small circular membrane fragments released from the endosomal cell membrane [33, 55]. MSC-derived EVs contain RNAs that are involved in transcription control, cell proliferation, and immune regulation [56], and interact using different mechanisms with the cell surface receptors [54, 57]. These exosomes activate molecules between the cells through the transfer of genetic material and specific organelles such as mitochondria [58]. Microvesicles derived from MSCs play an important role in the repair of lung injury in ARDS [59]. Zhu et al. [51] observed a decrease in lung edema and neutrophil counts by utilizing microvesicles from human bone marrow MSCs with an increased expression of KGF in this induced lung injury. Evidence from several studies supports the role of microvesicles in cell-based therapies associated with respiratory diseases [55, 60]. Furthermore, microvesicles from adult MSCs protect against acute tubular injury ischemia–reperfusion-induced acute and chronic kidney injury [61, 62].

In relation to cell-free therapeutics in lung diseases, Monsel et al. [63] displayed various advantages of using MSC-derived extracellular vesicles compared to the MSCs. The advantages are as follows: they are non-self-replicating, have reduced risk of iatrogenic tumor formation, can be stored without DMSO at − 80ºC to maintain a biologically active state, they do not express MHC I or II antigens, nor can be induced to express them, and they allow allogeneic transplantation.

Stem Cells From Other Sources

Induced Pluripotent Stem Cells

The headStartinduced pluripotent stem cellsheadEnd (iPSCs) produced by the method of Takahashi & Yamanaka [64] are based on the reprogramming of adult cells to a "stem cell state" through a gene transfection technique by manipulating them to undergo cellular differentiation, plasticity and behavioral transformation [64, 65].

There is a great potential of using iPSCs in ARDS and sepsis [9]. However, the associated problems arising from their use are unclear, and also their low efficiency during differentiation and the reprogramming process might be a concern. Thus, a possible genomic modification may be considered to address these drawbacks [66].

Embryonic Stem Cells

The human headStartembryonic stem cellsheadEnd (ESCs) derived from the inner cell mass of blastocysts are pluripotent and able to differentiate into all three primary germ layers. Their capacity to self-renew makes them a viable treatment option for tissue regeneration [67]. These ESCs promote the MSCs through reprogramming and differentiation with demonstrated efficacy in murine endotoxin and bleomycin-induced lung injury [68]. To develop cell-based strategies for repairing lung injury, Banerjee et al. [69] differentiated human headStartembryonic stem cellsheadEnd (hES) into lung epithelial lineage-specific cells. According to the authors, the study indicated an increase in progenitor cell numbers in the airway and significantly reduced the collagen content in bleomycin-treated mice, after the transplantation of differentiated hES cells.

Clinical Trials

Only three headStartclinical trialsheadEnd related to stem cells are considered complete, whereby two are in Phase 1 and one is in Phase 2. All the completed studies were

associated with ARDS in the United States (USA) (Table 1). Wilson et al. [70] conducted a Phase 1 trial, where no adverse events were reported in the nine patients evaluated. However, in three patients, serious adverse events were observed weeks after the infusion, but none were MSC-related. The study was considered for an extension trial by Matthay et al. [71]. These researchers carried out a Phase 2 trial in a double-blind study with placebo-control and allogeneic bone marrow-derived-MSCs in a 2 (MSCs):1(Placebo) randomization. The MSC group had significantly higher mean scores than the placebo group for Acute Physiology and Chronic Health Evaluation III (APACHE III) (Table 1). No results were posted in NCT02804945 by the authors.

The ongoing headStartclinical trialsheadEnd related to stem cells for various respiratory disorders such as SARS, MERS, and ARDS are presented in Table 2. Six studies related to coronavirus are in Phase 1, and four studies are already in Phase 2. Basically, the ongoing studies on coronavirus are using MSCs derived from bone marrow or the umbilical cord to demonstrate their feasibility, safety, and tolerability.

The studies not related to coronavirus are all in ARDS conditions; four of them are in Phase 1 and three in Phase 2. Two particularly interesting situations are being developed in Phase 1, where firstly, menstrual blood stem cells are utilized to determine whether these cells are effective in the treatment of infection, and secondly, another study is testing the drug administration of HCR040 (drug based on allogeneic adipose-derived adult headStartmesenchymal stem cellsheadEnd, expanded and pulsed with H_2O_2) (Fig. 1).

Emukah et al. [72] conducted a systematic review on the effects of mesenchymal stromal cell conditioned media (CdM) on many lung diseases. The findings were enthusiastic because it was demonstrated that CdM improved inflammation and was as effective as MSCs. Further studies must be conducted to determine the ideal site of CdM delivery, dosage, and timing of the treatment according to the lung disease [72]. Zhao et al. [73] also conducted a systematic review and meta-analysis evaluating the safety of cell therapies and the clinical variables critical for these lung disorders. The authors concluded that the cell therapies do not cause complications in gas exchange, spirometry, quality of life, cardiopulmonary circulation, and immune system of those suffering from the lung disease. Phases 2 and 3 are very important to determine the efficacy of the cell therapies related to dosage and safety approaches. Moreover, death rate was lower in the MSCs-treated group than in the non-MSCs-treated patients [73]. Preclinical studies examined the efficacy of MSCs-treatment compared to the control group across different animals and acute lung injury induction models [74]. A reduced number of deaths was also shown in acute lung injury (ALI) studies of preclinical models [74].

Possible Applications to COVID-19

Cytokines Storm

Lymphopenia and higher levels of cytokines are features of COVID-19-patients, being potential biomarkers for disease progression. In severely ill patients, a “cytokine storm” is induced due to the high levels of cytokines, and consequently, numerous adverse reactions in the human body are observed [75]. Cytokine storms include the interleukins IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10, Granulocyte colony stimulating factor (G-CSF), Granulocyte-macrophage colony-stimulating factor (GM-CSF), Interferon gamma inducible protein 10 kD (IP10), Monocyte chemoattractant protein-1 (MCP1), Macrophage inflammatory protein-1 alpha (MIP-1α), IFN-γ and TNF-α [75–79]. For COVID-19, IL-6 serves as a key mediator cytokine in cytokine storm development [80]. After infection, CD4 + T cells can be quickly activated in pathogenic helper T cells (Th) 1 secreting GM-CSF, which further induces CD14+, CD16 + monocytes providing high levels of IL-6, accelerating the inflammation process [75, 81].

Successful treatment involves influencing the immune response to SARS-CoV-2, including increasing antiviral immunity and inhibiting systemic inflammation. Therefore, using specific immunological profiles of COVID-19, such as the increase of lymphocytes or the inhibition of inflammation, may be essential for treatment in severe cases [75].

Given the potential of modular MSCs in sepsis and evolution of chronic conditions, strategies such as MSC-based therapy can be used to inhibit inflammation. One of the biggest challenges in the current treatment of COVID-19 is the cytokine storm, where some of them with a most important role, evolve to irreversible chronicity, and in this sense, MSCs can prevent or mitigate this cytokine storm through their immunomodulatory capacity [82]. Promising and unprecedented results for COVID-19 were obtained 14 days after the injection of MSCs in 7 patients with pneumonia at Youan Hospital of Beijing, China. Both, regulatory T cells and CD increased significantly after cell therapy. Before transplantation of MSCs, the patients in a severe condition had a significant increase in cells T $CXCR3^+$ $CD4^+$, T $CXCR3^+$ $CD8^+$ and CXCR3 + NK compared to the healthy control (without pathological manifestation), thus being reported as the cytokine storm. Nevertheless, once the transplantation of MSCs was performed in the patient, it could be observed on the 6th day that previously overactivated T and NK cells were drastically reduced, almost disappearing, and many other cells were restored to their normal dosages in the patient, especially the regulatory dendritic cells $CD14^+$ $CD11c^+$ CD11b. When transplanting MSCs, anti-inflammatory and trophic factors like TGF-β, HGF, LIF, GAL, NOA1, FGF, VEGF, EGF, BDNF e NGF were highly expressed in these cells confirming the immunomodulatory action of MSCs [82] (Fig. 2).

Table 1 Summary of completed headStartclinical trialsheadEnd related to stem cells in ClinicalTrials.gov

	ClinicalTrials.gov Identifier	Conditions	Study Design	Objective	Study Start / End	Country	Participants / Ages Eligible for Study	Interventions
Not related to coronavirus								
Phase 1	NCT01775774	ARDS	Multi-center	To assess the safety of hMSCs in patients with ARDS.	July, 2013 / February, 2015	United States	9 / 18	Allogeneic BM-MSCs
	NCT02804945	ARDS	Pilot study - interventional (clinical trial)	To learn about the safety of giving mesenchymal stem cellsheadEnd (MSCs) to patients who have ARDS. Researchers also want to learn if these cells can help control ARDS when given with drugs that are routinely used to treat ARDS.	February, 2017 / June, 2019	United States	20 / 18	Blood and marrow transplantation MSCs
Phase 2	NCT02097641	ARDS	Prospective, randomized, multi-center - interventional	This trial is the extension of the Phase 1 pilot trial (NCT01775774).	March, 2014 / February, 2018	United States	60 – 18	Allogeneic BM-MSCs Plasma-Lyte A

Angiotensin-converting Enzyme 2 (ACE2) Receptor

Both, the angiotensin-converting enzyme 2 (ACE2), widely distributed on cell's surfaces in humans, especially type II alveolar cells (AT2) and the capillary endothelium, as well as the presence of Transmembrane Protease Serine 2 (TMPRSS2), highly expressed by AT2 cells, are fundamental to the pathogenesis of HCoV-19, activating the Spike protein (S). Since many cells of the immune system are negative for ACE2, immune therapy may be an alternative in the treatment of infected patients [83].

According to the results of the above-mentioned study, MSCs have a natural immunity to HCoV-19, being ACE2- or TMPRSS2-negative according to transplant analyses. Thus, especially for patients critically ill with COVID-19 pneumonia, transplantation of MSCs was a safe and effective treatment regulating the inflammatory response and promoting tissue repair and regeneration [82].

Interferon-stimulated genes (ISGs) present in MSCs may explain why these cells are resistant to viral infections. MSCs, for example, express several ISGs, some of which are known to show typical antiviral responses. The member proteins of the Interferon Induced Transmembrane Family (IFITM) are peculiar because they prevent infection before the virus can cross the lipid bilayer on cells [84]. Cells cultivated by viruses such as SARS coronavirus, Ebola virus, influenza A and dengue were not infected because of the assigned activity to IFITM proteins [85]. Therefore, in this scenario of the COVID-19 respiratory viral infection, as suggested by Rajarshi et al. [84], the unique antiviral mechanisms of MSCs include constitutive elevation of MSC-specific ISG levels acting as regulators of antiviral protection and secondary response to IFN, which induces ISG, offering broad viral resistance [84].

In the case of hematopoietic stem / progenitor cells (HSPCs), evidence suggests that the SARS-CoV-2 virus input receptor (ACE2) and the angiotensin II receptor (AT1) are expressed and functional on the surface of these cells [86, 87]. Therefore, it is possible for SARS-CoV-2 upon binding to ACE2 via the Spike protein to directly activate the Nlrp3 inflammasome, contributing to the cytokine storm, affecting the mitochondrial function, leading to cell death by pyroptosis [87–93]. The Nlrp3 inflammasome, which can affect various tissues and organs as well as potentially hematopoiesis [93], may be responsible for certain complications during a SARS-CoV-2 infection.

In 2014, Min et al. [94] evaluated the therapeutic effects of human umbilical cord MSCs in the presence of angiotensinconverting enzyme 2 gene (ACE2; ACE2uMSCs) using bleomycin (BLM)induced lung injury and pulmonary fibrosis in mice. The injection of ACE2-uMSC demonstrated significantly more effective results in the treatment of bleomycin-induced pulmonary fibrosis

Table 2 Summary of ongoing headStartclinical trialsheadEnd related to stem cells and SARS, MERS and ARDS in ClinicalTrials.gov

	ClinicalTrials.gov Identifier	Conditions	Study design	Objective	Study Start	Locations	Participants / Ages Eligible for Study	Interventions	Status
Coronavirus									
Phase 1	NCT02215811	ARDS on extracorporeal membrane oxygenation (ECMO)	Multi-center, open-label, non-randomized controlled trial.	Patients will be enrolled and receive allogeneic BM-MSCs.	March 2014	Sweden	10 / 18	Allogeneic BM-MSCs	Unknown status
	NCT04276987	SARS	Single-arm design, open label, combined interventional clinical trial,	To explore the safety and efficiency of aerosol inhalation of the exosomes derived from allogenic adipose MSCs in the treatment of severe patients hospitalized with novel coronavirus pneumonia.	February 15, 2020	China	30 / 18–75	MSCs-derived exosomes	Not yet recruiting
	NCT04326036 (Early Phase I)	Pulmonary alveolar proteinosis COPD Idiopathic pulmonary fibrosis	Interventional, non-randomized	To use of autologous, cellular stromal vascular fraction (cSVF) deployed intravenously to examine the anti-inflammatory and structural potential to improve the residual, permanently damaged alveolar tissues of the lungs.	March 25, 2020	United States	10 / 18–90	Cellular stromal vascular fraction (cSVF)	Enrolling by invitation
Phase 1 Phase 2	NCT04333368	ARDS	Interventional, randomized	To treat intubated-ventilated patients with a SARS-CoV2-related ARDS of less than 96 h by three intravenous infusions of umbilical cord Wharton's jelly-derived mesenchymal stromal cells (UC-MSC).	April 6, 2020	France	60 / 18	UC-MSCs	Not yet recruiting
	NCT04355728 (Phase 1 Phase 2)	ARDS	Interventional, randomized	The trial has two groups, each with 12 subjects (n = 24). All eligible subjects will be randomized to either the treatment group or standard of care, and randomization will be stratified by ARDS severity.	April 25, 2020	United States	24 / 18	UC-MSCs	Recruiting
	NCT04346368	SARS	Interventional, randomized	To investigate the safety and efficacy of intravenous infusion of MSCs in severe patients with COVID-19.	April 2020	China	20 / 18–75	BM-MSCs	Not yet recruiting
Phase 2	NCT04288102	SARS	Prospective, double-blind, multi-center, randomized trial	To assess treatment with three intravenous doses of MSCs compared with placebo.	March 5, 2020	China	90 / 18–75	MSCs	Recruiting
	NCT04299152	SARS	Prospective, two-arm, partially masked, single center clinical study	To assess the safety, feasibility, and efficacy of Stem Cell Educator (SCE) therapy for the treatment of patients with SARS-CoV-2.	May 10, 2020	Not mentioned	20 / 18–60	SCE-Treated Mononuclear cells apheresis	Not yet recruiting
- Applicable	NCT04273646	Pneumonia	Interventional, randomized	To investigate efficiency and safety of UC-MSCs in treating severe	April 20, 2020	China	48 / 18–65	UC-MSCs	Not yet recruiting

Table 2 (continued)

	ClinicalTrials.gov Identifier	Conditions	Study design	Objective	Study Start	Locations	Participants / Ages Eligible for Study	Interventions	Status
				pneumonia patients infected with 2019-nCoV.					
Not related to coronavirus									
Phase 1 Phase 1 Phase 1 Phase 2	NCT02215811	ARDS	Multi-center, open-label, non-randomized controlled trial.	To treat ARDS with allogeneic bone marrow-derived MSCs.	March 2014	Sweden	10 / 18	Allogeneic BM-MSCs	Unknown
	NCT01902082	ARDS	Interventional, randomized	To assess the safety of allogeneic adipose-derived mesenchymal stem cellsheadEnd in patients with ARDS.	November 2012	China	20 / 18–90	MSCs	Unknown
	NCT02095444	ARDS Multiple organ failure	Interventional, single group assignment	To determine whether human menstrual blood-derived stem cells are effective in the treatment of infection of H7N9 virus-caused acute lung injury.	March 2014	China	20 / 18	Menstrual blood stem cells	Unknown
	NCT04289194 (Phase 1 Phase 2)	ARDS	Interventional, randomized	To assess the feasibility, safety, and tolerability of the administration of HCR040 in patients with ARDS.	December 10, 2019	Spain	26 / 18	HCR040, a drug whose active substance is HC016, allogeneic adipose-derived adult MSCs expanded and pulsed with H2O2	Active, not recruiting
Phase 2 Phase 2	NCT03818854A	ARDS	Randomized, double-blind, placebo-controlled, multi-center	An assignment will be made by computer-generated randomization to administer either hMSCs therapy or placebo with a 1:1 allocation to the hMSCs:placebo arms.	November, 2019	United States	120 / 18	BM-MSCs Cell reconstitution media	Recruiting
	NCT02112500	ARDS	Pilot study, interventional, single group assignment	To evaluate the efficacy and safety of MSCs treatment in patients with respiratory failure.	February 2014	Korea	10 / 20–80	MSCs	Unknown
-	NCT03608592	ARDS	Interventional, single group assignment	A package of 100 ml normal saline with 10^6/kg UC-MSCs suspension will be infused from central venous catheter.	June 1, 2018	China	26 / 18	UC-MSCs	Recruiting

BM-MSCs, Bone Marrow-Derived Mesenchymal Stem Cell; UC-MSCs, Umbilical cord derived MSCs

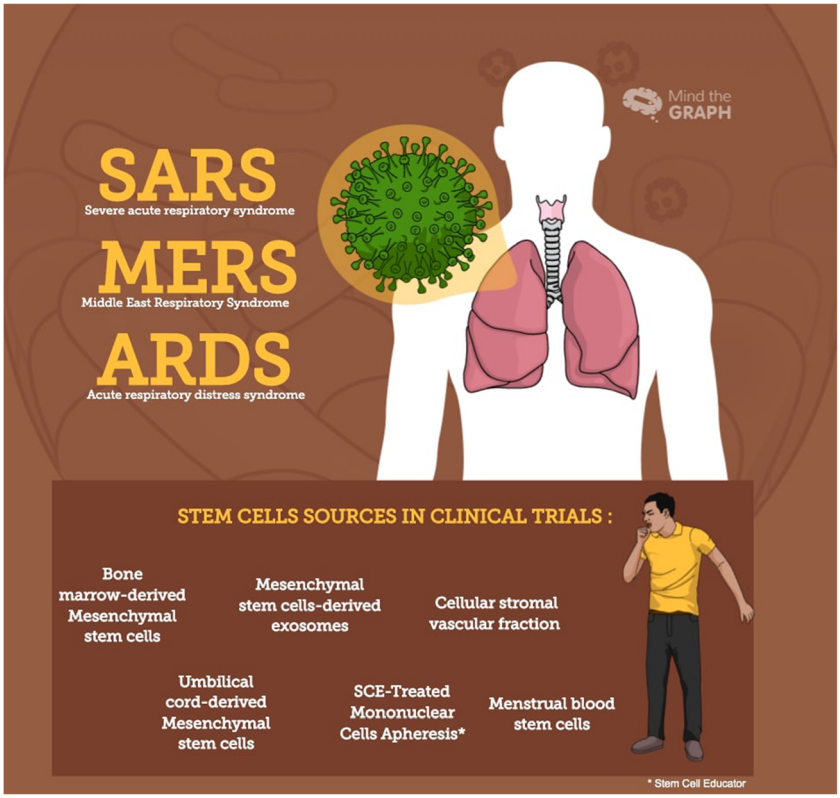

Fig. 1 Stem cells sources in headStartclinical trialsheadEnd

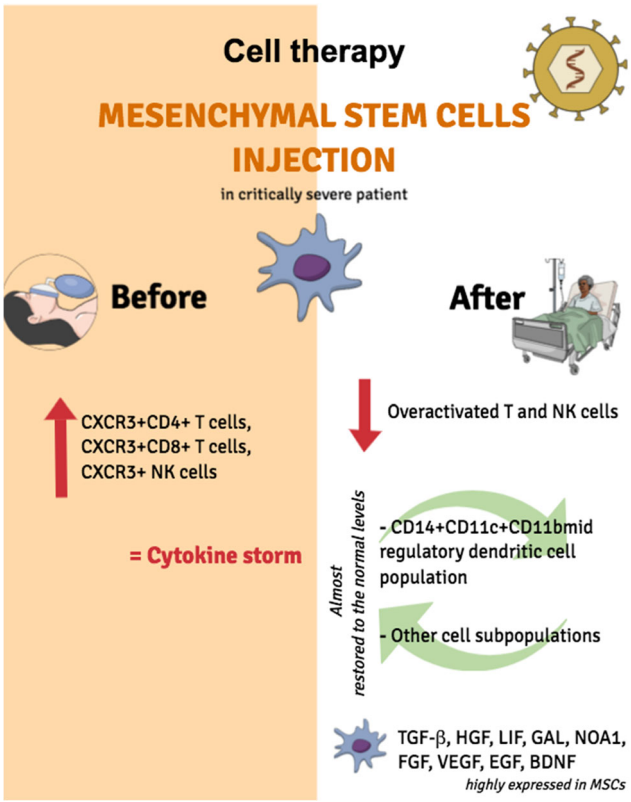

Fig. 2 Effects of MSCs-therapy before and after of transplantation on cytokine storm. Source: Leng, et al., (2020). Transplantation of ACE2-headStartMesenchymal Stem CellsheadEnd Improves the Outcome of Patients with COVID-19 Pneumonia. Aging and Disease, 11(2), 216–228

in vivo compared to those of the ACE2 and uMSC treatments alone. Thus, according to the authors suggestions, the synergistic effect of ACE2 and uMSCs may be used as a promising novel treatment for lung injury [94].

As suggested by Ulrich & Pillat [95], it is possible that CD147, the second incoming receptor for SARS-CoV-2, is expressed by untransformed lung stem and progenitor cells, but there is still no experimental evidence. This bone marrow receptor can be expressed by tissue-specific stem cells [96]. Soon, it is realized that the loss of airway epithelial cells caused by infection and viral replication suggests another possibility for the lack of cell regeneration considering that regenerating cells and stem cells can be equally lost or infected [95].

Final Considerations

Anti-inflammatory therapies for patients with ARDS have been developed using stem cells offering a great promise for managing ARDS [70, 97, 98]. MSCs related cell-therapies demonstrate high efficacy in preclinical data allowing their clinical usage [99]. For COVID-19 research and headStartclinical trialsheadEnd, it is important to consider the blood biomarkers involved in the pathophysiology of the disease which provide therapeutic targets and thus improve the clinical care. Moreover, it is essential to understand the role of endogenous lung progenitor cells during the repair of lung injury and also

the mechanism of lung development for developing novel therapeutic strategies [100, 101]. Han et al. [102] mentioned some obstacles in clinical practice that must be considered for COVID-19 as, for example, the low mobilization of transplanted MSCs at the injury site and their low survival rate. The comprehensive interaction between MSCs and the host tissue is a key to the successful therapeutic application whereby experimental studies play a major role in developing lung diseases in clinical translation [37].

Since we know that the mitochondrial disorder caused by the overactivation of Nlrp3 inflammasome is determinant to the pathogenesis of SARS-CoV-2, Nlrp3 inflammasome inhibitors must be taken into account regarding their therapeutic applicability [87–89, 92]. An example for this inhibitory potential is the MCC950 molecule which could affect the binding of SARS-CoV-2 to cells and inhibit the amplification of the intracellular virus, and also the ComC inhibitors that assist in modulating the activity of the innate immune system [93]. Another possible inhibition therapy against SARS-CoV-2 is the use of ACE2 + MSC-derived small extracellular vesicles (sEVs) overexpressed, as suggested by Inal [103].

Regarding the combat against the cytokine storm in the lungs during viral pneumonia, some studies highlighted that the leukemia inhibitor factor (LIF) released by the MSCs may not be expressed enough to supply the damage caused by the disease [104, 105]. As an innovative and technological alternative, there are MSCs with "LIFNano", nanotechnology that represents a 1000-fold increase in power compared to not using nanotechnology. "LIFNano" acts on damaged tissues and reduces the cytokine storm. Therefore, it represents a therapeutic agent ready to act beneficially against viral pneumonia [106].

Significant advances have been made in three-dimensional (3D) cell culture to develop organoids. These are able to recapitulate the complexity and functionality of different organs. Human lung organoids and bud tip progenitor organoids are composed of cells that are highly similar to the developing human lung. They are ideal for studying developmental biology and tissue engineering. Considering that the cells are specific to the patient's genetics, the organoids that mimic lung disease may be critical for designing personalized medicine and screening for therapeutic responsiveness [107].

Conclusion

With the COVID-19 boom, many headStartclinical trialsheadEnd are being carried out using different sources with an emphasis on MSCs. We look forward to the results of the ongoing headStartclinical trialsheadEnd to find a treatment for the disease. Researchers around the world are joining forces to help fight COVID-19. Stem cells used in the current clinical studies are a new therapeutic promise for COVID-19 where pharmacological treatments seem insufficient.

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Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflict of interest.

Research Involving Human Participants and/or Animals Not applicable.

Informed Consent Not applicable.

Abbreviations ACE 2, Angiotensin-convertingenzyme 2; ALI, Acute lung injury; ARDS, Acute respiratorydistress syndrome; CoV, Coronavirus; MSCs, Mesenchymal stemcells; iPSCs, Induced PluripotentStem Cells; ESCs, Embryonic Stem Cells; HSPCs, hematopoieticstem/progenitor cells; IFITM, Interferon InducedTransmembrane Family; ISGs, Interferon-StimulatedGenes; KGF, keratinocyte growthfactor; MERS, Middle EastRespiratory Syndrome; SARS, Severe acuterespiratory syndrome; TMPRSS2, TransmembraneProtease Serine 2

References

1. Zhou, M., Zhang, X., & Qu, J. (2020). Coronavirus disease 2019 (COVID-19): a clinical update. *Frontiers in Medicine, 14*(2), 126–135.
2. Yi, Y., Lagniton, P., Ye, S., Li, E., & Xu, R. H. (2020). COVID-19: what has been learned and to be learned about the novel coronavirus disease. *International Journal of Biological Sciences, 16*(10), 1753–1766.
3. Prompetchara, E., Ketloy, C., & Palaga, T. (2020). Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. *Asian Pacific Journal of Allergy and Immunology, 38*(1), 1–9.
4. Tian, S., Xiong, Y., Liu, H., Niu, L., Guo, J., Liao, M., & Xiao, S.-Y. (2020). Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. *Modern Pathology, 33*, 1007–1014.
5. Xu, Z., Shi, L., & Wang, Y. (2020). Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *The Lancet Respiratory Medicine, 8*(4), 420–422.
6. Khoury, M., Cuenca, J., Cruz, F. F., Figueroa, F. E., Rocco, P. R. M., & Weiss, D. J. (2020). Current status of cell-based therapies for respiratory virus infections: applicability to COVID-19. *European Respiratory Journal, 55*(6), 2000858.
7. Zakrzewski, W., Dobrzyński, M., Szymonowicz, M., & Rybak, Z. (2019). Stem cells: past, present, and future. *Stem Cell Research & Therapy, 10*(1), 68.

8. Bond, A. M., Ming, G., & Song, H. (2015). Adult mammalian neural stem cells and neurogenesis: five decades later. *Cell Stem Cell, 17*, 385–395.
9. Guillamat-Prats, R., Camprubí-Rimblas, M., Bringué, J., Tantinyà, N., & Artigas, A. (2017). Cell therapy for the treatment of sepsis and acute respiratory distress syndrome. *Annals of Translational Medicine, 5*(22), 446.
10. Jiang, J. X., & Li, L. (2009). Potential therapeutic application of adult stem cells in acute respiratory distress syndrome. *Chinese Journal of Traumatology, 12*(4), 228–233.
11. Liu, F., Mih, J. D., Shea, B. S., Kho, A. T., Sharif, A. S., Tager, A. M., & Tschumperlin, D. J. (2010). Feedback amplification of fibrosis through matrix stiffening and COX-2 suppression. *Journal of Cell Biology, 190*, 693–706.
12. Huang, X., Yang, N., Fiore, V. F., Barker, T. H., Sun, Y., Morris, S. W., Ding, Q., Thannickal, V. J., & Zhou, Y. (2012). Matrix stiffness-induced myofibroblast differentiation is mediated by intrinsic mechanotransduction. *American Journal of Respiratory Cell and Molecular Biology, 47*, 340–348.
13. Goldmann, W. H. (2012). Mechanotransduction and focal adhesions. *Cell Biology International, 36*, 649–652.
14. Samuel, M. S., Lopez, J. I., McGhee, E. J., Croft, D. R., Strachan, D., Timpson, P., Munro, J., Schroder, E., Zhou, J., Brunton, V. G., Barker, N., Clevers, H., Sansom, O. J., Anderson, K. I., Weaver, V. M., & Olson, M. F. (2011). Actomyosin-mediated cellular tension drives increased tissue stiffness and beta-catenin activation to induce epidermal hyperplasia and tumor growth. *Cancer Cell, 19*, 776–791.
15. Charbonney, E., Speight, P., Masszi, A., Nakano, H., & Kapus, A. (2011). beta-catenin and Smad3 regulate the activity and stability of myocardin-related transcription factor during epithelialmyofibroblast transition. *Molecular Biology of the Cell, 22*, 4472–4485.
16. Yang, J., & Jia, Z. (2014). Cell-based therapy in lung regenerative medicine. *Regenerative Medicine Research, 2*(1), 7.
17. Elnakish, M. T., Kuppusamy, P., & Khan, M. (2013). Stem cell transplantation as a therapy for cardiac fibrosis. *The Journal of Pathology, 229*, 347–354.
18. Le Blanc, K., & Fibbe, W. (2008). A new cell therapy registry coordinated by the European Group for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant, 41*, 319.
19. D'Agostino, B., Sullo, N., Siniscalco, D., De Angelis, A., & Rossi, F. (2010). Mesenchymal stem cell therapy for the treatment of chronic obstructive pulmonary disease. *Expert Opinion on Biological Therapy, 10*, 681–687.
20. Németh, K., Leelahavanichkul, A., Yuen, P. S. T., Mayer, B. Z., Parmelee, A., Doi, K., Robey, P. G., Leelahavanichkul, K., Koller, B. H., Brown, J. M., Hu, X., Jelinek, I., Star, R. A., & Mezey, E. (2009). Bone marrow stromal cells attenuate sepsis via prostaglandin E(2)-dependent reprogramming of host macrophages to increase their interleukin-10 production. *Nature Medicine, 16*, 42–49.
21. Hayes, M., Curley, G., Ansari, B., & Laffey, J. G. (2012). Clinical review: Stem cell therapies for acute lung injury/acute respiratory distress syndrome - hope or hype? *Critical Care, 16*(2), 205.
22. Krasnodembskaya, A., Song, Y., Fang, X., Gupta, N., Serikov, V., Lee, J.-W., & Matthay, M. A. (2010). Antibacterial effect of human mesenchymal stem cells is mediated in part from secretion of the antimicrobial peptide LL-37. *Stem Cells, 16,* 2229–2238.
23. Mei, S. H. J., Haitsma, J. J., Dos Santos, C. C., Deng, Y., Lai, P. F. H., Slutsky, A. S., Liles, W. C., & Stewart, D. J. (2010). Mesenchymal stem cells reduce inflammation while enhancing bacterial clearance and improving survival in sepsis. *American Journal of Respiratory and Critical Care Medicine, 16*, 1047–1057.
24. Lee, J. W., Fang, X., Gupta, N., Serikov, V., & Matthay, M. A. (2009). Allogeneic human mesenchymal stem cells for treatment of E. coli endotoxin-induced acute lung injury in the ex vivo perfused human lung. *Proceedings of the National Academy of Sciences of the United States of America, 16*, 16357–16362.
25. Mei, S. H. J., McCarter, S. D., Deng, Y., Parker, C. H., Liles, W. C., & Stewart, D. J. (2007). Prevention of LPS-induced acute lung injury in mice by mesenchymal stem cells overexpressing angiopoietin 1. *PLoS Medicine, 24*, e269.
26. Mei, S. H. J., & Stewart, D. J. (2010). Stem cells as vehicles for gene therapy in lung repair. In J. Polak (Ed.), *Cell Therapy for Lung Disease* (pp. 287–311). London: Imperial College Press.
27. Prockop, D. J. (1997). Marrow stromal cells as stem cells for nonhematopoietic tissues. *Science, 276*, 71–74.
28. Groove, J. E., Lutzko, C., Priller, J., Henegariu, O., Theise, N. D., Kohn, D. B., & Krause, D. S. (2002). Marrow-derived cells as vehicles for delivery of gene therapy to pulmonary epithelium. *American Journal of Respiratory Cell and Molecular Biology, 27*, 645–651.
29. Barry, F. P., & Murphy, J. M. (2004). Mesenchymal stem cells: clinical applications and biological characterization. *The International Journal of Biochemistry & Cell Biology, 36*, 568–584.
30. Ware, L. B., Matthay, M. A., Parsons, P. E., Thompson, B. T., Januzzi, J. L., Eisner, M. D., & National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network. (2007). Pathogenetic and prognostic significance of altered coagulation and fibrinolysis in acute lung injury/acute respiratory distress syndrome. *Critical Care Medicine, 35*(8), 1821–1828.
31. Nijnik, A., & Hancock, R. E. (2009). The roles of cathelicidin LL-37 in immune defences and novel clinical applications. *Current Opinion in Hematology, 16*, 41–47.
32. Stewart, D. J., & Mei, S. H. (2011). Cell-based therapies for lung vascular diseases: lessons for the future. *Proceedings of the American Thoracic Society, 8*(6), 535–540.
33. Xu, F., Hu, Y., Zhou, J., & Wang, X. (2013). Mesenchymal stem cells in acute lung injury: are they ready for translational medicine? *Journal of Cellular and Molecular Medicine, 17*(8), 927–935.
34. Matthay, M. A., Goolaerts, A., Howard, J. P., & Lee, J. W. (2010). Mesenchymal stem cells for acute lung injury: preclinical evidence. *Critical Care Medicine, 38*(10 Suppl), S569–S573.
35. Ghannam, S., Bouffi, C., Djouad, F., Jorgensen, C., & Noël, D. (2010). Immunosuppression by mesenchymal stem cells: mechanisms and clinical applications. *Stem Cell Research & Therapy, 1*(1), 2.
36. Boyle, A. J., McNamee, J. J., & McAuley, D. F. (2014). Biological therapies in the acute respiratory distress syndrome. *Expert Opinion on Biological Therapy, 14*(7), 969–981.
37. Walter, J., Ware, L. B., & Matthay, M. A. (2014). Mesenchymal stem cells: mechanisms of potential therapeutic benefit in ARDS and sepsis. *The Lancet Respiratory Medicine, 2*(12), 1016–1026.
38. Dushianthan, A., Grocott, M. P., Postle, A. D., & Cusack, R. (2011). Acute respiratory distress syndrome and acute lung injury. *Postgraduate Medical Journal, 87*(1031), 612–622.
39. Gupta, N., Su, X., Popov, B., Lee, J. W., Serikov, V., & Matthay, M. A. (2007). Intrapulmonary delivery of bone marrow-derived mesenchymal stem cells improves survival and attenuates endotoxin-induced acute lung injury in mice. *Journal of Immunology, 179*(3), 1855–1863.
40. Wang, Y. Y., Li, X. Z., & Wang, L. B. (2013). Therapeutic implications of mesenchymal stem cells in acute lung injury/acute respiratory distress syndrome. *Stem Cell Research and Therapy, 4*(3), 45.
41. Marshall, R. P., Bellingan, G., Webb, S., Puddicombe, A., Goldsack, N., McAnulty, R. J., & Laurent, G. J. (2000). Fibroproliferation occurs early in the acute respiratory distress syndrome and impacts on outcome. *American Journal of Respiratory and Critical Care Medicine, 162*, 1783–1788.

42. Ankrum, J., & Karp, J. M. Mesenchymal stem cell therapy: Two steps forward, one step back. *Trends in Molecular Medicine*, *16*, 203–209.
43. Peister, A., Mellad, J. A., Larson, B. L., Hall, B. M., Gibson, L. F., & Prockop, D. J. (2004). Adult stem cells from bone marrow (MSCs) isolated from different strains of inbred mice vary in surface epitopes, rates of proliferation, and differentiation potential. *Blood, 103*, 1662–1668.
44. Tomchuck, S. L., Zwezdaryk, K. J., Coffelt, S. B., Waterman, R. S., Danka, E. S., & Scandurro, A. B. (2008). Toll-like receptors on human mesenchymal stem cells drive their migration and immunomodulating responses. *Stem Cells, 26*, 99–107.
45. Ho, A. D., Wagner, W., & Franke, W. (2008). Heterogeneity of mesenchymal stromal cell preparations. *Cytotherapy, 10*, 320–330.
46. Masterson, C., Jerkic, M., Curley, G. F., & Laffey, J. G. (2015). Mesenchymal stromal cell therapies: potential and pitfalls for ARDS. *Minerva Anestesiologica, 81*(2), 179–194.
47. Matthay, M. A. (2015). Therapeutic potential of mesenchymal stromal cells for acute respiratory distress syndrome. *Annals of the American Thoracic Society, 12*(Suppl 1), S54–S57.
48. Fang, X., Neyrinck, A. P., Matthay, M. A., & Lee, J. W. (2010). Allogeneic human mesenchymal stem cells restore epithelial protein permeability in cultured human alveolar type II cells by secretion of angiopoietin-1. *Journal of Biological Chemistry, 285*(34), 26211–26222.
49. Fang, X., Abbott, J., Cheng, L., Colby, J. K., Lee, J. W., Levy, B. D., & Matthay, M. A. (2015). Human mesenchymal stem (stromal) cells promote the resolution of acute lung injury in part through lipoxin A4. *Journal of Immunology, 195*(3), 875–881.
50. Huppert, L. A., & Matthay, M. A. (2017). Alveolar fluid clearance in pathologically relevant conditions: In vitro and in vivo models of acute respiratory distress syndrome. *Frontiers in Immunology, 8,* 371.
51. Zhu, Y. G., Feng, X. M., Abbott, J., Fang, X. H., Hao, Q., Monsel, A., Qu, J. M., Matthay, M. A., & Lee, J. W. (2014). Human mesenchymal stem cell microvesicles for treatment of *Escherichia coli* endotoxin-induced acute lung injury in mice. *Stem cells, 32*(1), 116–125.
52. Li, J., Huang, S., Wu, Y., Gu, C., Gao, D., Feng, C., Wu, X., & Fu, X. (2014). Paracrine factors from mesenchymal stem cells: a proposed therapeutic tool for acute lung injury and acute respiratory distress syndrome. *International Wound Journal, 11*(2), 114–121.
53. Han, J., Li, Y., & Li, Y. (2019). Strategies to enhance mesenchymal stem cell-based therapies for acute respiratory distress syndrome. *Stem Cells International, 2019*, 5432134.
54. Abreu, S. C., Weiss, D. J., & Rocco, P. R. (2016). Extracellular vesicles derived from mesenchymal stromal cells: a therapeutic option in respiratory diseases? *Stem Cell Research and Therapy, 7*(1), 53.
55. Ratajczak, M. Z. (2011). The emerging role of microvesicles in cellular therapies for organ/tissue regeneration. *Nephrology Dialysis Transplantation, 26*, 1453–1456.
56. Tomasoni, S., Longaretti, L., Rota, C., Morigi, M., Conti, S., Gotti, E., Capelli, C., Introna, M., Remuzzi, G., & Benigni, A. (2013). Transfer of growth factor receptor mRNA via exosomes unravels the regenerative effect of mesenchymal stem cells. *Stem Cells and Development, 22*(5), 772–780.
57. Phinney, D. G., Di Giuseppe, M., Njah, J., Sala, E., Shiva, S., St Croix, C. M., Stolz, D. B., Watkins, S. C., Di, Y. P., Leikauf, G. D., Kolls, J., Riches, D. W., Deiuliis, G., Kaminski, N., Boregowda, S. V., McKenna, D. H., & Ortiz, L. A. (2015). Mesenchymal stem cells use extracellular vesicles to outsource mitophagy and shuttle microRNAs. *Nature Communications, 6*, 8472.
58. Horie, S., & Laffey, J. G. (2016). Recent insights: mesenchymal stromal/stem cell therapy for acute respiratory distress syndrome. *F1000Research, 5*, 1532.
59. Shah, T. G., Predescu, D., & Predescu, S. (2019). Mesenchymal stem cells-derived extracellular vesicles in acute respiratory distress syndrome: a review of current literature and potential future treatment options. *Clinical and Translational Medicine, 8*(1), 25.
60. Islam, M. N., Das, S. R., Emin, M. T., Wei, M., Sun, L., Westphalen, K., et al. (2012). Mitochondrial transfer from bone-marrow-derived stromal cells to pulmonary alveoli protects against acute lung injury. *Nature Medicine, 18*(5), 759–765.
61. Bruno, S., Grange, C., Deregibus, M. C., Calogero, R. A., Saviozzi, S., Collino, F., Morando, L., Busca, A., Falda, M., Bussolati, B., Tetta, C., & Camussi, G. (2009). Mesenchymal stem cell-derived microvesicles protect against acute tubular injury. *Journal of the American Society of Nephrology, 20*(5), 1053–1067.
62. Gatti, S., Bruno, S., Deregibus, M. C., Sordi, A., Cantaluppi, V., Tetta, C., & Camussi, G. (2011). Microvesicles derived from human adult mesenchymal stem cells protect against ischaemia-reperfusion-induced acute and chronic kidney injury. *Nephrology Dialysis Transplantation, 26*, 1474–1483.
63. Monsel, A., Zhu, Y. G., Gudapati, V., Lim, H., & Lee, J. W. (2016). Mesenchymal stem cell derived secretome and extracellular vesicles for acute lung injury and other inflammatory lung diseases. *Expert Opinion on Biological Therapy, 16*(7), 859–871.
64. Takahashi, K., & Yamanaka, S. (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell, 126*(4), 663–676.
65. Takahashi, K., Tanabe, K., Ohnuki, M., Narita, M., Ichisaka, T., Tomoda, K., & Yamanaka, S. (2007). Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell, 131*(5), 861–872.
66. Heffernan, C., Sumer, H., & Verma, P. J. (2011). Generation of clinically relevant "induced pluripotent stem" (iPS) cells. *Journal of Stem Cells, 6*, 109–127.
67. Horie, S., Curley, G. F., & Laffey, J. G. (2016). What's new in cell therapies in ARDS? *Intensive Care Medicine, 42*(5), 779–782.
68. Hao, Q., Zhu, Y. G., Monsel, A., Gennai, S., Lee, T., Xu, F., & Lee, J. W. (2015). Study of bone marrow and embryonic stem cell-derived human mesenchymal stem cells for treatment of *Escherichia coli* endotoxin-induced acute lung injury in mice. *Stem Cells Translational Medicine, 4*(7), 832–840.
69. Banerjee, E. R., Laflamme, M. A., Papayannopoulou, T., Kahn, M., Murry, C. E., & Henderson, W. R., Jr. (2012). Human embryonic stem cells differentiated to lung lineage-specific cells ameliorate pulmonary fibrosis in a xenograft transplant mouse model. *PLoS One, 7*(3), e33165.
70. Wilson, J. G., Liu, K. D., Zhuo, H., Caballero, L., McMillan, M., Fang, X., et al. (2015). Mesenchymal stem (stromal) cells for treatment of ARDS: a phase 1 clinical trial. *The Lancet Respiratory Medicine, 3*(1), 24–32.
71. Matthay, M. A., Calfee, C. S., Zhuo, H., Thompson, B. T., Wilson, J. G., Levitt, J. E., et al. (2019). Treatment with allogeneic mesenchymal stromal cells for moderate to severe acute respiratory distress syndrome (START study): a randomised phase 2a safety trial. *The Lancet Respiratory Medicine, 7*(2), 154–162.
72. Emukah, C., Dittmar, E., Naqvi, R., Martinez, J., Corral, A., Moreira, A., & Moreira, A. (2019). Mesenchymal stromal cell conditioned media for lung disease: a systematic review and meta-analysis of preclinical studies. *Respiratory Research, 20*, 239.
73. Zhao, R., Su, Z., Wu, J., & Ji, H. L. (2017). Serious adverse events of cell therapy for respiratory diseases: a systematic review and meta-analysis. *Oncotarget, 8*(18), 30511–30523.
74. McIntyre, L. A., Moher, D., Fergusson, D. A., Sullivan, K. J., Mei, S. H. J., Lalu, M., et al. (2016). Efficacy of mesenchymal stromal cell therapy for acute lung injury in preclinical animal models: A systematic review. *PLoS One, 11*(1), e0147170.

75. Yang, L., Liu, S., Liu, J., et al. (2020). COVID-19: immunopathogenesis and immunotherapeutics. *Signal Transduction and Targeted Therapy, 5,* 128.
76. Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., Gao, H., Guo, L., Xie, J., Wang, G., Jiang, R., Gao, Z., Jin, Q., Wang, J., & Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet, 395*(10223), 497–506.
77. Chen, N., Zhou, M., Dong, X., et al. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet, 395*(10223), 507–513.
78. Qin, C., Zhou, L., Hu, Z., et al. (2020). Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. *Clinical Infectious Diseases, 71*(15), 762–768.
79. Liu, J., Li, S., Liu, J., Liang, B., Wang, X., Wang, H., et al. (2020). Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. *EBioMedicine, 55,* 102763.
80. Yip, M. S., Leung, H. L., Li, P. H., et al. (2016). Antibody-dependent enhancement of SARS coronavirus infection and its role in the pathogenesis of SARS. *Hong Kong Medical Journal, 22*(3 Suppl 4), 25–31.
81. Zhou, Y., Fu, B., Zheng, X., et al. (2020). Aberrant pathogenic GM-CSF + T cells and inflammatory CD14 + CD16 + monocytes in severe pulmonary syndrome patients of a new coronavirus. *bioRxiv;* (Preprint).
82. Leng, Z., Zhu, R., Hou, W., Feng, Y., Yang, Y., Han, Q., et al. (2020). Transplantation of ACE2- mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. *Aging and Disease, 11*(2), 216–228.
83. Hamming, I., Timens, W., Bulthuis, M. L. C., Lely, A. T., Navis, G. J., & van Goor, H. (2004). Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *Journal of Pathology, 203*, 631–637.
84. Rajarshi, K., Chatterjee, A., & Ray, S. (2020). Combating COVID-19 with Mesenchymal Stem Cell therapy. *Biotechnology reports, 26*, e00467. Advance online publication. https://doi.org/10.1016/j.btre.2020.e00467.
85. Bailey, C. C., Zhong, G., Huang, I. C., & Farzan, M. (2014). IFITM-family proteins: the cell's first line of antiviral defense. *Annual Review of Virology, 1*, 261–283.
86. Park, T. S., & Zambidis, E. T. (2009). A role for the renin-angiotensin system in hematopoiesis. *Haematologica, 94*, 745–747.
87. Zambidis, E. T., Park, T. S., Yu, W., Tam, A., Levine, M., Yuan, X., et al. (2008). Expression of angiotensin-converting enzyme (CD143) identifies and regulates primitive hemangioblasts derived from human pluripotent stem cells. *Blood, 112*, 3601–3614.
88. Ratajczak, M. Z., Bujko, K., Cymer, M., Thapa, A., Adamiak, M., Ratajczak, J., et al. (2020). The Nlrp3 inflammasome as a "rising star" in studies of normal and malignant hematopoiesis. *Leukemia, 34*(6), 1–12.
89. Place, D. E., & Kanneganti, T. D. (2018). Recent advances in inflammasome biology. *Current Opinion in Immunology, 50*, 32–38.
90. Zhao, M., Bai, M., Ding, G., Zhang, Y., Huang, S., Jia, Z., et al. (2018). Angiotensin II stimulates the NLRP3 inflammasome to induce podocyte injury and mitochondrial dysfunction. *Kidney Dis (Basel), 4*, 83–94.
91. Sun, N. N., Yu, C. H., Pan, M. X., Zhang, Y., Zheng, B. J., Yang, Q. J., et al. (2017). Mir-21 mediates the inhibitory effect of Ang (1–7) on AngII-induced NLRP3 inflammasome activation by targeting Spry1 in lung fibroblasts. *Scientific Reports, 7*, 14369.
92. Pinar, A. A., Scott, T. E., Huuskes, B. M., Tapia Cáceres, F. E., Kemp-Harper, B. K., et al. (2020). Targeting the NLRP3 inflammasome to treat cardiovascular fibrosis. *Pharmacology & Therapeutics, 209*, 107511.
93. Ratajczak, M. Z., & Kucia, M. (2020). SARS-CoV-2 infection and overactivation of Nlrp3 inflammasome as a trigger of cytokine "storm" and risk factor for damage of hematopoietic stem cells. *Leukemia., 34*(7), 1726–1729.
94. Min, F., Gao, F., Li, Q., & Liu, Z. (2015). Therapeutic effect of human umbilical cord mesenchymal stem cells modified by angiotensin-converting enzyme 2 gene on bleomycin-induced lung fibrosis injury. *Molecular Medicine Reports, 11*(4), 2387–2396.
95. Ulrich, H., & Pillat, M. M. (2020). CD147 as a target for COVID-19 treatment: suggested effects of azithromycin and stem cell engagement. *Stem Cell Reviews and Reports, 16*(3), 434–440.
96. Amati, E., Perbellini, O., Rotta, G., et al. (2018). High-throughput immunophenotypic characterization of bone marrow- and cord blood-derived mesenchymal stromal cells reveals common and differentially expressed markers: identification of angiotensin-converting enzyme (CD143) as a marker differentially expressed between adult and perinatal tissue sources. *Stem Cell Research & Therapy, 16*(1), 10.
97. Wang, Y., Pati, S., & Schreiber, M. (2018). Cellular therapies and stem cell applications in trauma. *The American Journal of Surgery, 215*, 963–972.
98. Thompson, B. T., Chambers, R. C., & Liu, K. D. (2017). Acute respiratory distress syndrome. *New England Journal of Medicine, 377*, 562–572.
99. Laffey, J. G., & Matthay, M. A. (2017). Fifty years of research in ARDS. Cell-based therapy for acute respiratory distress syndrome. Biology and potential therapeutic value. *American Journal of Respiratory and Critical Care Medicine, 196*(3), 266–273.
100. Sueblinvong, V., & Weiss, D. J. (2010). Stem cells and cell therapy approaches in lung biology and diseases. *Translational Research, 156*(3), 188–205.
101. Spadaro, S., Park, M., Turrini, C., Tunstall, T., Thwaites, R., Mauri, T., et al. (2019). Biomarkers for acute respiratory distress syndrome and prospects for personalised medicine. *Journal of Inflammation, 16,* 1.
102. Han, J., Liu, Y., Liu, H., & Li, Y. (2019). Genetically modified mesenchymal stem cell therapy for acute respiratory distress syndrome. *Stem Cell Research & Therapy, 10*(1), 386.
103. Inal, J. M. (2020). Decoy ACE2-expressing extracellular vesicles that competitively bind SARS-CoV-2 as a possible COVID-19 therapy. *Clinical Science, 134*(12), 1301–1304.
104. Foronjy, R. F., Dabo, A. J., Cummins, N., & Geraghty, P. (2014). Leukemia inhibitory factor protects the lung during respiratory syncytial viral infection. *Immunology, 15*, 41.
105. Quinton, L. J., Mizgerd, J. P., Hilliard, K. L., Jones, M. R., Kwon, C. Y., & Allen, E. (2012). Leukemia inhibitory factor signaling is required for lung protection during pneumonia. *Journal of Immunology, 188*(12), 6300–6308.
106. Metcalfe, S. M. (2020). Mesenchymal stem cells and management of COVID-19 pneumonia. *Medicine in Drug Discovery., 5*, 100019.
107. Miller, A. J., Dye, B. R., Ferrer-Torres, D., Hill, D. R., Overeem, A. W., Shea, L. D., & Spence, J. R. (2019). Generation of lung organoids from human pluripotent stem cells in vitro. *Nature Protocols, 14*(2), 518–540.