Protocol Title:

Single Donor Banked Bone Marrow Mesenchymal Stromal Cells for the Treatment of COVID-19 Induced ARDS: A Non-Blinded Randomized, Controlled Study

Principal Investigators:
LaQuisa Hill, MD
Adrian Gee, PhD
Zhuyoung Mei, MD

Co-Investigators:
Helen Heslop, MB, ChB, MD, DSC (Hon), FRACP, FRCPA
George Carrum, MD
Rammurti Kamble, MD
Premal Lulla, MBBS
Carlos Ramos, MD
Sai Pingali, MD
Jenny Chang, MD
Bambi Grilley, RPh

Statistician
Tao Wang, PhD

IND # 21643

Center for Cell and Gene Therapy

Houston Methodist Hospital
6565 Fannin Street
Houston, TX 77030-2707

Dan L. Duncan Comprehensive Cancer Center
Baylor College of Medicine

Table of Contents

CHECKLIST FOR PATIENT ELIGIBILITY FOR TREATMENT

YES	NO	VALUE/DATE	
Any "**NO**" answers will make a patient **ineligible** for study participation.			
			18 years or older
			Confirmed SARS-CoV2 infection real-time reverse transcription polymerase chain reaction (RT-PCR) assay
			Moderate **OR** severe acute respiratory distress syndrome (ARDS), based on the degree of impairment of oxygenation as defined by the ratio of arterial oxygen tension to fraction of inspired oxygen (PaO2/FiO2): a. Moderate ARDS: PaO2/FiO2 100-200 mmHg **OR** b. Severe ARDS: PaO2/FiO2 ≤100 mmHg
			If on invasive or non-invasive (BiPAP) mechanical ventilator,PEEP ≥5 cm H2O
			Bilateral opacities present on chest radiograph or computed tomographic (CT) scan, that are not fully explained by pleural effusions, lung collapse, or lung nodules.
YES	**NO**	**VALUE/DATE**	
Any "**YES**" answers will make a patient **ineligible** for study participation.			
			Currently receiving extracorporeal membrane oxygenation (ECMO)
			Severe chronic respiratory disease requiring current use of home oxygen prior to COVID-19 diagnosis
			Pregnant or lactating
			Known hypersensitivity to dimethyl sulfoxide (DMSO)
			Unstable hemodynamics as deemed by the treating physician/investigator including but not limited to unstable , ventricular tachycardia or new cardiac arrythmia requiring cardioversion
			Uncontrolled bacterial or fungal co-infection
			Any end-stage organ disease or condition, which in the opinion of the Investigator, makes the patient an unsuitable candidate for treatment
			Inability to obtain informed consent (from patient or legally appropriate proxy)
			Presence of any contraindication to receiving prophylactic low dose unfractionated or low molecular weight heparin
			Respiratory failure explained or complicated by cardiac failure or fluid overload

Signature of MD _____ **Date** _____

PROTOCOL SYNOPSIS

Single Donor Banked Bone Marrow Mesenchymal Stromal Cells for the Treatment of COVID-19 Induced ARDS: A Non-Blinded Randomized Controlled Study

Principal Investigator: LaQuisa Hill, MD

Study Design: Single center, open-label, non-blinded randomized controlled study

Objective: To evaluate the safety and clinical benefits of banked mesenchymal stromal cells (MSCs) versus controls for treatment of patients with ARDS due to COVID-19

Eligibility Criteria:

Inclusion Criteria

1) 18 years or older
2) Confirmed SARS-CoV2 infection real-time reverse transcription polymerase chain reaction (RT-PCR) assay
3) Moderate **OR** severe acute respiratory distress syndrome (ARDS), based on the degree of impairment of oxygenation as defined by the ratio of arterial oxygen tension to fraction of inspired oxygen (PaO_2/FiO_2):
    a. Moderate ARDS: PaO_2/FiO_2 100-200 mmHg

    OR

    b. Severe ARDS: PaO_2/FiO_2 ≤100 mmHg
4) If on invasive or non-invasive (BiPAP) mechanical ventilator PEEP ≥5 cm H_2O
5) Bilateral opacities present on chest radiograph or computed tomographic (CT) scan, that are not fully explained by pleural effusions, lung collapse, or lung nodules.

Exclusion Criteria

1) Currently receiving extracorporeal membrane oxygenation (ECMO)
2) Severe chronic respiratory disease requiring current use of home oxygen prior to COVID-19 diagnosis
3) Pregnant or lactating
4) Known hypersensitivity to dimethyl sulfoxide (DMSO)
5) Unstable hemodynamics as deemed by the treating physician/investigator including but not limited to unstable , ventricular tachycardia or new cardiac arrythmia requiring cardioversion

6) Uncontrolled bacterial or fungal co-infection
7) Any end-stage organ disease or condition, which in the opinion of the Investigator, makes the patient an unsuitable candidate for treatment
8) Inability to obtain informed consent (from patient or legally appropriate proxy)
9) Presence of any contraindication to receiving prophylactic low dose unfractionated or low molecular weight heparin
10) Respiratory failure not fully explained by cardiac failure or fluid overload.

1 Background and Rationale

1.1 Acute Respiratory Distress Syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) is an acute, life-threatening form of respiratory failure caused by diffuse inflammatory mediated alveolar injury leading to impaired gas-exchange, decreased compliance and fluid accumulation in the airspaces. Excessive inflammation is a major contributor to lung injury in ARDS leading to activation of the complement system by alveolar macrophages and the release of pro-inflammatory cytokines such as TNF, IL-1, IL-6, and IL-17, as well as multiple chemokines such as IL-8, CCL-2, and CCL-7 [1]. This leads to the accumulation of neutrophils and monocytes to the site of injury where they release toxic substances that damage the capillary endothelium and alveolar epithelium [1]. The ensuing cytokine storm leads to systemic inflammatory response, septic shock, and multi-organ failure [2, 3]. Multiple etiologies may trigger ARDS, including respiratory infections, sepsis/shock, trauma, pancreatitis, smoke inhalation, hematopoietic stem cell transplant, and transfusion-related acute lung injury.

ARDS is currently diagnosed based on the Berlin Definition of ARDS published in 2012 based on expert consensus [4]. It is clinically manifested by dyspnea and poor arterial oxygenation which is determined by the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FIO2), along with bilateral opacities on chest imaging. ARDS is divided into 3 groups based on the degree of hypoxemia: mild (PaO2/FIO2 201-300 mm Hg), moderate (PaO2/FIO2: 101-200 mm Hg), and severe (PaO2/FIO2 ≤ 100 mm Hg) and ventilator settings with a positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) ≥5 cm H_2O. The mortality rate has been reported to be up to 50%, with increasing severity of ARDS leading to higher likelihood of mortality [5]. To date, no pharmacologic therapies have shown any benefit in reducing the high mortality of ARDS, and the primary treatment relies on treating underlying causes and supportive measures such as mechanical ventilation and fluid management [1]. Thus, effective therapies are needed.

1.2 Coronavirus Disease 2019 (COVID-19)

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and was first reported in Wuhan, China in December 2019 [6] . In January 2020, the World Health Organization (WHO) declared the outbreak a global emergency after rapid spread to multiple other countries including the United States, Italy, Japan, Iran and others. The number of cases continues to increase exponentially with the number of cases surpassing 1,500,000 globally by April 10, 2020 [7].

SARS-CoV2 belongs to the Coronavirus (CoV) family which also includes the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory

syndrome coronavirus (MERS-CoV) which led to epidemics 2003 and 2012, respectively. While COVID-19 shares a similar clinical presentation with SARS-CoV, it appears to have a higher transmission rate although the estimated basic reproductive number (R0) has been very dynamic as the number of cases continues to rise with increased testing availability [8-11]. The most common clinical symptoms of COVID-19 at onset are fever, cough, dyspnea, myalgia, and/or fatigue [10, 12, 13]. Less common symptoms included anosmia, headache, diarrhea, nausea, and vomiting. However, the clinical spectrum ranges widely from asymptomatic or mild illness to critical illness in a subset of patients with progression to ARDS, shock, and/or multi-organ failure leading to a case fatality rate variously estimated as 1%-4%. [14].

1.3 ARDS due to COVID-19 Disease

Angiotensin converting enzyme-2 receptor (ACE-2) has been identified as a primary host receptor for cell entry utilized by SARS-CoV-2 similar to SARS-CoV [15, 16]. ACE-2 is highly expressed in multiple organs including but not limited to the oral cavity, human airway epithelia, myocardial cells, and kidney proximal tubule cells, and high expression may increase susceptibility to viral damage. It has been reported that approximately 50% of patients with COVID-19 pneumonia will progress to ARDS [12, 13, 17], with mortality approaching 50% in various studies [10, 12, 13, 17, 18]. Risk factors for ARDS and increased mortality include age (older than 60 years), presence of comorbidities such as hypertension, diabetes, heart disease, COPD, immunocompromised states, elevated markers of inflammation and higher disease severity as evidenced by high APACHE II, SOFA, and CURB-65 scores [10, 18-21]. At present, no effective antiviral treatment or vaccine is available; however, multiple clinical trials are evaluating the safety and efficacy of pharmacologic agents.

1.4 COVID-19-associated coagulopathy (CAC)

Abnormalities in coagulation parameters have been observed in patients hospitalized with COVID-19 disease [12, 19, 22, 23]. Most common are elevations in fibrinogen and D-dimer, which may correlate with a rise in inflammatory markers. However, some patients with severe COVID-19 disease develop classic disseminated intravascular coagulopathy (DIC) with moderate to severe thrombocytopenia, prolongation of PT/aPTT, elevated D-dimer, and fibrinogen less than 100 mg/dL. Tang et al reported that use of low molecular weight (LMWH) or unfractionated (UFH) heparin was associated with decreased mortality in patients with severe COVID-19 disease [24]. Conversely, progressively increasing D-dimer levels were associated with increased mortality. Based on these (and related) findings, monitoring of platelet counts, PT/aPTT, D-dimer and fibrinogen levels is strongly recommended. While the use of therapeutic anticoagulation in patients with severe COVID-19 disease is still under study, prophylactic low dose heparin anticoagulation is recommended in the absence of active bleeding or other contraindications.

1.5 Mesenchymal Stromal Cells (MSCs) for Inflammatory Disorders, including ARDS

Mesenchymal stromal cells have shown benefit in patients with inflammatory and immune-related disorders, such as inflammatory bowel disease [25], rheumatoid arthritis [26], type 1 diabetes mellitus [27-29], systemic lupus erythematosus [30-33], multiple sclerosis [34], and acute graft versus host disease (aGVHD) [35] as well as lung disease [36-38]. MSCs are a cellular component of the supportive microenvironment that function as multipotent progenitor cells with the capacity to differentiate into mesodermal lineages, such as adipocytes, osteocytes, and chondrocytes [39, 40]. MSCs also contribute to tissue repair [41-43]. They also have anti-inflammatory properties and increase the activity of T regulatory cells, which may benefit development of immune tolerance [44-47]. Since MSCs do not express class II human histocompatibility antigens (HLA) or co-stimulatory molecules (CD40, CD40L, CD80, and CD86) required for T cell activation, even allogeneic (banked) MSC appear to induce little alloreactivity after administration [48, 49]. MSCs also secrete antimicrobial peptides that enhance bacterial clearance and improve survival [50-52]. These inherent qualities of MSCs make them a promising candidate for the treatment of lung injury without toxicities.

Multiple preclinical studies have shown that MSCs can be used for treating lung injury [53-55]. Chan et al showed that human MSCs administered to aged mice infected with H5N1 prevented or reduced lung injury, thereby increasing oxygenation. The MSCs reduced pro-inflammatory cytokines and increased survival [56]. MSC administration similarly reduced proinflammatory cytokines and chemokines, and pulmonary inflammation in mice with H9N2 avian influenza induced lung injury [57]. MSCs also attenuate lung injury in mice and *ex* vivo human lungs after injury by live bacterial infections [51, 58]. In addition, MSCs may secrete paracrine factors that improve the rate of alveolar fluid clearance [59, 60]. Based on these preclinical findings, MSCs were deemed to be a promising form of adoptive cell therapy for the treatment of ARDS.

Several phase 1 and 2 studies evaluating the safety of MSCs as treatment for a variety of lung diseases (idiopathic pulmonary fibrosis, COPD and ARDS) have confirmed tolerability of this approach [36-38, 61, 62]. A case report of two patients with severe, refractory ARDS treated with MSC from allogeneic bone marrow (2 million cells/kg i.v.) had significant improvement of respiratory and end-organ failure, as well as reduction in inflammatory cytokines [63]. In a phase 1, dose-escalation study using bone marrow derived allogeneic MCSs for moderate to severe ARDS, no infusion or treatment related adverse events were reported in 9 recipients [62]. Two patients died, but this was considered unrelated to infusion of the MSCs. Given the mortality associated with COVID-19 induced ARDS, Leng et al. conducted a pilot study of MSC administration in patients with confirmed SARS-CoV-2 pneumonia. They reported improvement in pulmonary function and symptoms, and a decrease in pro-inflammatory cytokines such as TNF-α and an increase in anti-inflammatory IL-10 [21]. They were also able to show improvement, although not statistically significant, in the disease severity scores such as SOFA.

1.6 Procoagulant effects of MSCs

Although MSCs have been safely used in numerous clinical trials, preparations of these cells may express Tissue Factor and therefore pose an increased thrombogenic risk [64-67]. Thus the general safety of bone marrow derived MSCs [68] has been accompanied by reports of thrombotic and embolic complications in animal and human studies when the MSCs were derived from alternative sources such as adipose tissue or placental tissue [65, 69-73]. MSC from these sources may express higher levels of TF [74, 75] than BM derived MSCs, potentially accounting for the observed "instant blood-mediated inflammatory reactions" (IBMIR) [76, 77].

The TF expression of adipose and placenta derived MSC shows significant variation depending on donor and culture passage [66, 70, 78, 79]. Although these thrombotic complications are rarely seen after infusion of BM derived MSCs, low dose anticoagulation has been used preclinically and in human studies [72, 74, 75, 80, 81]. These additives block activation of coagulation and complement, decreasing the risk of IBIM-triggering. Thus, supplementation with anticoagulants appears to be a simple method to reduce activation of coagulation pathways following MSC infusion, which might also enhance the therapeutic effect. Thus in an effort to mitigate any putative additional procoagulation activity following infusion of MSCS, patients with active COVID 19 disease must be eligible for prophylaxis with LMWH/UFH.

2 Study Design

2.1 Study Overview

This study is a single center open label, non-blinded randomized, controlled study designed to evaluate the use of single donor banked bone marrow derived MSCs versus standard of care as therapy for patients with ARDS due to COVID-19 disease. The study will first enroll and treat six patients with MSCs for safety run in. If no more than 2 treatment-related severe adverse events (tSAEs) are observed, the study will enroll and randomize additional 60 patients in a ratio of 1:1 to receive either MSCs or routine/supportive care.

2.2 Hypothesis and Specific Objectives

2.2.1 Primary Hypothesis

The primary hypothesis is that banked, bone marrow derived mesenchymal stromal cells can be safely used to mediate the severe inflammatory response seen in moderate or severe ARDS resulting from COVID-19 disease compared to the control group receiving routine supportive care.

2.3 Study Objective:

To evaluate the safety and clinical benefits of banked mesenchymal stromal cells (MSCs) versus control for treatment of patients with COVID-19 induced ARDS.

2.3.1 Primary endpoints:

1. Treatment-related serious adverse events (tSAEs)
2. Improvement by at least two categories on a six category ordinal scale at day 14 post randomization. The six-category ordinal scale is as follows: 6 = death; 5 = hospitalization, requiring extracorporeal membrane oxygenation (ECMO) and/or invasive mechanical ventilation (IMV); 4 = hospitalization, requiring non-invasive mechanical ventilation (NIV) and/or High-flow nasal cannula (HFNC) therapy; 3 = hospitalization, requiring supplemental oxygen (but not NIV/HFNC); 2 = hospitalization, not requiring supplemental oxygen; 1 = hospital discharge.

2.3.2 Secondary endpoints:

1. Clinical status at day 28 as determined by 6-point ordinal scale
2. Severity of ARDS at day 14
3. Oxygenation free days at day 28
4. Progression to mechanical ventilation or ECMO
5. Duration of mechanical ventilation and/or ECMO (ventilation/ECMO free days at day 28)
6. Duration of ICU stay (ICU free days at day 28)
7. Duration of hospital stay (time to discharge)
8. Overall survival
9. All-cause mortality at day 28

2.3.3 Exploratory endpoints

1. Changes in inflammatory markers (CRP, IL-6, IL-10, TNF-α)
2. Negative SARS-CoV-2 RT-PCR by day 28 (if available)
3. Changes in blood safety laboratories (CBC with differential, electrolytes, renal indices, liver function studies, LDH, coagulation studies if available)
4. Corticosteroid use and duration
5. Changes in chest imaging
6. Evolution of other end-organ damage (hepatic, renal, cardiovascular)
7. Changes in disease severity score (SOFA, CURB-65)
8. Duration of vasopressor use

3 Eligibility Criteria

3.1 Inclusion Criteria

1) 18 years or older

2) Confirmed SARS-CoV2 infection real-time reverse transcription polymerase chain reaction (RT-PCR) assay
3) Moderate OR severe ARDS, based on the degree of impairment of oxygenation as defined by the ratio of arterial oxygen tension to fraction of inspired oxygen (PaO_2/FiO_2):
    a. Moderate ARDS: PaO_2/FiO_2 100-200 mmHg

    OR

    b. Severe ARDS: PaO_2/FiO_2 ≤100 mmHg
4) If on invasive or noninvasive (BiPAP) mechanical ventilator, PEEP ≥5 cm H_2O
5) Bilateral opacities present on chest radiograph or computed tomographic (CT) scan, that are not fully explained by pleural effusions, lung collapse, or lung nodules.

3.2 Exclusion Criteria

1) Currently receiving extracorporeal membrane oxygenation (ECMO)
2) Severe chronic respiratory disease requiring current use of home oxygen prior to COVID-19 diagnosis
3) Pregnant or lactating
4) Known hypersensitivity to dimethyl sulfoxide (DMSO)
5) Unstable hemodynamics as deemed by the treating physician/investigator including but not limited to unstable , ventricular tachycardia or new cardiac arrythmia requiring cardioversion
6) Uncontrolled bacterial or fungal co-infection
7) Any end-stage organ disease or condition, which in the opinion of the Investigator, makes the patient an unsuitable candidate for treatment
8) Inability to obtain informed consent (from the patient or legally appropriate proxy)
9) Presence of any contraindication to receiving prophylactic low dose unfractionated or low molecular weight heparin
10) Respiratory failure not fully explained by cardiac failure or fluid overload.

4 Mesenchymal Stromal Cells (MSCs) Manufacturing

All manufacturing procedures will be performed in our GMP facility as dictated by Standard Operating Protocols (SOP). Brief summaries are given here.

4.1 Source Material. The cell product will consist of allogeneic mesenchymal stromal cells

MSCs) generated from the bone marrow of an eligible normal donor. Up to 100 ml of marrow is obtained by aspiration under local anesthesia following informed consent. The donor will meet the eligibility requirements as described in 21 CFR Parts 1271 Subpart C. Testing (Table 1) will be performed using FDA-approved, cleared and/or licensed kits by Gulf Coast Regional Blood Center within 7 days of collection of the

marrow for manufacturing. Manufacturing commences within four hours of marrow collection by following SOP L03.05.XX. (Expansion of Human Mesenchymal Stromal Cells from Bone Marrow Using the Quantum Cell Expansion System).

Table 1 Infectious Disease Testing on Marrow Donor

Test	Specification
Chagas Disease	Negative
Hepatitis B Surface Antigen	Negative
Hepatitis B Core	Negative
Hepatitis C Virus	Negative
HIV 1 and 2	Negative
HTLV I and II	Negative
TAQ Screen MPX (HBV,HCV, HIV-1 Group M RNA, HIV-1 Group O)	Negative
NAT West Nile Virus	Negative
Serological Test for Syphilis	Negative

4.2 Ex vivo cell expansion. In order to meet the cell dose requirements for the protocol, a

primary cell bank will be established. This will consist of MSCs cultured to passage 2 from the marrow using the Terumo Quantum Bioreactor (a Master File on this device has been filed by Terumo BCT). This system avoids the multiple open procedures associated with culturing the cells in cell culture flasks, thereby considerably decreasing the risk of contamination. The cell culture bioreactor and all tubing are sterile and completely disposable, thereby avoiding the possibility of cross-contamination. The Quantum is capable of generating more than 1.5 billion MSC at Passage 2.

4.3 Freezing. For this proposal, we will use cells that were previously grown to

passage 2 and frozen in aliquots suitable for future expansion. The pooled passage 2 cells were tested for sterility, endotoxin, and mycoplasma following previously validated SOPs. The cells are frozen in Plasma Lyte containing a final concentration of 10% v/v DMSO using a controlled-rate freezer and stored in the vapor phase of liquid nitrogen (SOP C03.34.XX). The cell products for administration will be thawed Passage 3 cells generated from aliquots of the Passage 2 frozen cell bank. Passage 2 cells will be thawed and seeded into the Quantum bioreactor, cultured and harvested, washed, counted, and cryopreserved using a controlled rate freezer in Plasma Lyte A containing 10% DMSO following standard operating procedures (SOPs L03.05.XX and C03.34.XX).

4.4 Testing. Products that meet study specific release criteria, as detailed on the certificate of analysis (CofA), will be infused as per Section 4.0.

5 Patient Enrollment and Evaluation

5.1 Informed Consent

Informed consent should be obtained prior to enrollment on the study. All patients and/or their legal guardian must sign a document of informed consent consistent with local institutional and federal guidelines stating that they are aware of the investigational nature of this protocol and of the possible side effects of treatment. Further, patients must be informed that no efficacy of this therapy is guaranteed, and that unforeseen toxicities may occur. Patients have the right to withdraw from this protocol at any time. No patient will be accepted for treatment without such a document signed by him or his legal guardian. Full confidentiality of patients and patient records will be provided according to institutional guidelines.

5.2 Registration and Randomization

All consented patients will be registered in the online collaborative research environment (Forte's OnCore® eResearch CTMS), a Clinical Research Management System available at BCM Dan L. Duncan Comprehensive Cancer Center. Prior to enrollment in the study, the eligibility data must be reviewed and verified by the study coordinator and treating physician. After the eligibility status is verified, the subject will be assigned to a unique study sequence number. After safety run in, additional patients will be randomized in a 1:1 ratio to either the MSC or control arm. Randomization will use the permuted block method and be stratified by severity of ARDS (moderate and severe). Randomization information will be stored on a secure, access-restricted server at Baylor College of Medicine.

5.3 Treatment Plan

5.3.1 Dosing

Patients who are randomized to the MSC arm will be administered an intravenous infusion of MSCs at a dose of 1×10^8. A second infusion at the same dose will be allowed if the patient does not have improvement in respiratory parameters per discretion of the investigator, or ARDS clinically worsens, within 3-5 days following the initial infusion. When a patient is enrolled on the protocol a sufficient number of aliquoted cells will be thawed to provide the required cell dose. Thawing will be initiated on the planned date of administration according to the completed and signed Prescription for Administration received from the Principle Investigator on the study or designee. The thawed cells will be pooled, washed and formulated to the required final dose for administration. The release tests will be performed on the pooled cells prior to administration.

5.3.2 Administration and Monitoring of MSC Infusion

The MSCs will be given by intravenous injection, and the IV flushed with saline upon completion of the infusion. The expected volume is 20-30 mL. The rate of infusion may be tailored to patient fluid status, but the duration of infusion should not exceed 60 minutes. No other medications should be given during the infusion unless determined medically necessary by the treating physician. Patients randomized to the MSC arm must be receiving prophylactic low dose anticoagulation (or therapeutic anticoagulation if indicated for a separate etiology [i.e. atrial fibrillation, venous thromboembolism, etc.) or be considered eligible to receive at the time of study entry.

Patients may be pre-medicated with diphenhydramine up to 1mg/kg IV (max 50 mg) and/or acetaminophen up to 15mg/kg PO (max 650 mg) at least 30 minutes prior to infusion.

Monitoring will be undertaken according to institutional standards for administration of blood products, and at a minimum will be monitored according to below:

- Vitals signs (HR, BP, RR, oxygen saturation, and temperature) will be taken and recorded at the below times
    - Just prior to the start of the infusion
    - at 15, 30, 60, and 120 minutes (± 5 minutes) after the start of the infusion

- During MSC administration, infusion *should be stopped if:*
    - the patient shows signs or symptoms of worsening respiratory status (such as tachypnea, cyanosis, complains of worsening shortness of breath, etc.) regardless of the oximetry reading.
    - there is an adverse event (AE) that the treating physician believes is related to the MSC infusion.

- No other medications should be given during the infusion unless determined medically necessary by the treating physician.

- Infusion reactions should be managed per institutional standards. Appropriate medications should be readily available at the bedside, including epinephrine, hydrocortisone, and diphenhydramine.

- If an anaphylactic reaction is suspected, the MSC administration should be stopped immediately and should not be resumed, **nor** should the patient receive any additional doses.

5.3.3 Supportive Care for the control arm

Patients who are randomized to the control arm will receive supportive care or treatment designated by their treating physicians

6 Patient Evaluation

6.1 Study Calendar

Treatment Protocol Days	Pre-treatment (baseline)	Day 0	1	2	3	4	5	6	7	14	21	28
Visit window										**±2**	**±2**	**±2**
Informed consent	X											
Randomization		X										
Demographics[%]	X											
History*[b]	X	X	X	X	X	X	X	X	X[b]	X[b]	X[b]	X[b]
Physical Exam	X	X	X	X	X	X	X	X	X[b]	X[b]	X[b]	X[b]
Vital signs[a]	X	X	X	X	X	X	X	X	X[b]	X[b]	X[b]	X[b]
Weight (kg) and height	X											
MSC Infusion for MSC arm		X			X[#]	X[#]	X[#]					
APACHE II Score	X											
SOFA/CURB-65 Score	X											X[c]
ARDS Assessment[c]	X	X	X	X	X	X	X	X	X	X	X	X
6-point Ordinal Scale	X	X	X	X	X	X	X	X	X[b]	X[b]	X[b]	X[b]
SAR-CoV-2 PCR	X											
CBC w/ diff	X	X	X	X	X	X	X	X	X	X[d]	X[d]	X[d]
CMP	X	X	X	X	X	X	X	X	X	X[d]	X[d]	X[d]
Coagulation Studies[@]	X	X[e]	X[e]		X[e]		X[e]		X[e]	X[e]	X[e]	X[e]
LDH	X	X[e]	X[e]		X[e]		X[e]		X[e]	X[e]	X[e]	X[e]
C-Reactive Protein (CRP)	X	X[e]	X[e]		X[e]		X[e]		X[e]	X[e]	X[e]	X[e]
Research Cytokine Profile and labs		X[&]	X		X		X		X	X[d]		X[d]
Chest X-Ray/ Computerized Tomography (CT scan)[e]	X	X[e]	X[e]		X[e]		X[e]		X[e]	X	X	X
Pregnancy test (if CBP)	X											
Adverse Events		X	X	X	X	X	X	X	X	X	X	X

a - vital signs to include HR, BP, Temp (max temp for the day), RR, Oxygen Saturation (O_2 sat)
b - Should be done **daily** if patient still hospitalized
c - if remains in the ICU and ABG available per SOC. ARDS severity requires PaO2 to calculate
d- only required if patient remains hospitalized at this time point
e- done per SOC; not mandated by study. Date will be collected from medical record at these timepoints if available
*- includes concurrent medications
%- includes age, gender and ethnicity
- if inadequate response to initial infusion, a second infusion may be given within 3-5 days following the first infusion; no more than 2 infusions will be administered
@ - coagulation studies = PT/aPTT, d-dimer, fibrinogen
& - collected pre-infusion and 3-4 hours post-infusion

7 Evaluations

For patients randomized to the control arm, day 0 will be the day of randomization. For patients randomized to the MSC arm, day 0 will be the day of infusion. Patients in both treatment arms will be evaluated as follows:

7.1 Baseline Pre-treatment Evaluation

7.1.1 History and physical (including vitals and oxygenation requirements)
7.1.2 SARS-CoV-2 RT-PCR testing
7.1.3 ARDS assessment
7.1.4 Complete Blood Count and differential (CBC)
7.1.5 Complete Metabolic Panel (CMP)
7.1.6 Coagulation studies: PT/aPTT, d-dimer, fibrinogen
7.1.7 Lactate Dehydrogenase (LDH)
7.1.8 C-Reactive Protein (CRP)
7.1.9 CXR and/or CT chest imaging
7.1.10 Urine or serum pregnancy test for females of childbearing potential
7.1.11 APACHE II score
7.1.12 Medical record review for concomitant medications
7.1.13 Clinical status assessed by the six-category ordinal scale (1 = discharged; 6 = death)

7.2 Post-randomization/treatment Evaluation

7.2.1. History and physical (including vitals and oxygenation requirements) daily during hospitalization

7.2.2 ARDS assessment daily day 0 through 7, then weekly until day 28 if remains intubated in the ICU or until extubated, whichever occurs first, and ABG data available

7.2.2. The following routine laboratory investigations will be obtained through day 7, then weekly until day 28 or hospital discharge, whichever comes first

- CBC
- CMP

7.2.3. PT/aPTT, d-dimer, fibrinogen, CRP and LDH will be collected from the medical record, if available, at timepoints noted in the study calendar.

7.2.4. CXR and/or CT chest imaging will be done at baseline, then as then as clinically indicated per treating physician discretion. Data will be collected from the medical record, if available, at timepoints noted in the study calendar.

7.2.5. SOFA/CURB-65 score day 0, and day 28, if patient remains in the ICU and ABG available per SOC (for SOFA calculation).

7.2.6. Research cytokine profile and labs day 0 pre-infusion, 3-4 hours post-infusion, day 1, 3, 5, 7, 14 and day 28 if remains hospitalized. Optional if patient has

been discharged.

7.2.7. Medical record review for data collection on supportive interventions, including but not limited to:

- Respiratory support (high flow nasal canula, AirVO, proning, high frequency oscillatory ventilation (HFOV), etc.)
- Pharmacologic interventions (corticosteroids, vasopressors, paralytics, pulmonary vasodilators, etc.)

7.2.8. Medical record review for data collection on concurrent medications (such as antibiotics, antivirals, antihypertensives, anticoagulants), concurrent infections, and other end-organ damage daily through day 28 or hospital discharge, whichever occurs first

7.2.10. Clinical status assessed by the six category ordinal scale daily until hospital discharge or death, whichever occurs first.

7.3 Follow up

7.3.1. If discharged from the hospital prior to day 28, patients will followed up with (in clinic or by telephone) through day 28 as outlined in study calendar Section 6.1. Additional visits or telephonic contacts will be obtained as clinically indicated for patients with toxicities deemed to be related to the MSC infusion, which will be followed until resolved.

7.4 Drug Toxicity and/or Adverse Reactions

7.4.1. For consistency, toxicity for all patients will be evaluated using the NCI Common Toxicity Criteria scale (version 5.X; http://ctep.cancer.gov).

7.4.2. Adverse events will be collected as per SOP J02.05.XX and J02.75.XX. Data on all new adverse experiences/toxicities (regardless of seriousness) and worsening of baseline toxicities by at least one grade following infusion will be collected for documentation purposes for 4 weeks after the last dosing of the study drug/biologic with the exception of all toxicities which were deemed to be related to the MSC infusion, which will be followed until resolved.

7.4.3. Serious Adverse event data will be collected and reported as per SOP J02.06.XX until 28 days after the last dosing of study drug/biologic or until time of discharge, whichever comes first, and should consist of both solicited and volunteered events reported by the patient.

7.4.4. Infusion/allergic reactions will be evaluated by continuous monitoring the patient's vital signs from the time of administration until two hours after starting the infusion.

7.4.5. Treatment-related serious adverse events (tSAE) will be considered as those directly related to the investigational infusion product. Adverse event grading

will be as defined by the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 5. In making this assessment, there should be consideration of the probability of an alternative cause (for example, COVID-19 itself or some other condition preceding randomization) and the timing of the event with respect to study treatment. The safety endpoint of the study is tSAE, defined as:

- Any grade 5 AE
- Any grade 4 AE that fails to return to grade 2 within 72 hours post-infusion
- Grade 2 to 4 allergic reactions (severe rash, bronchospasm, and immediate-type allergic reactions)
- Arterial or venous thromboembolic event occurring within 48 hours of infusion
- Serious Adverse Event (SAE) that, in the treating physicians' judgment, is considered related to MSC infusion and requires withdrawal from the study

8 Statistical Considerations

8.1 Clinical Trial Design

This is a single-center, open label, non-blinded randomized controlled, parallel study designed to evaluate the safety and clinical benefits of banked, allogeneic bone marrow MSCs versus control (routine supportive care) for treatment of COVID-19 related ARDS. The primary safety endpoint will be treatment-related serious adverse events (tSAE), defined in Section 7.4.5. The primary efficacy endpoint will be improvement in clinical status by at least two categories at day 14 post randomization, assessed by a six-category ordinal scale. The study will first enroll and treat 6 patients with MSCs for safety run in, then additional 60 patients will be randomized to receive either MSCs or supportive care designated by their treating physician.

8.2 Sample size

This early phase study will accrue a total of 66 patients with 6 patients for safety run in and additional 30 patients in each treatment arm by randomization. MSCs will be manufactured in our GMP facility and available to treat at least 36 patients. The study primary efficacy endpoint is improvement in clinical status at least two categories on a six-category ordinal scale at day 14 post randomization. The six-category ordinal scale ranges from 6 to 1 with a higher score indicates worse clinical outcome, i.e. 6 = death; 5 = hospitalization, requiring ECMO and/or IMV; 4 = hospitalization, requiring NIV and/or HFNC therapy; 3 = hospitalization, requiring supplemental oxygen (but not NIV/HFNC); 2 = hospitalization, not requiring supplemental oxygen; 1 = hospital discharge. The scale will be used to evaluate patients' status daily from baseline to day hospital discharge. Patients' clinical status at day 14 post randomization will be dichotomized as 'improved' (decreased by at least two categories) or 'not improved'. Patients who died before day 14 will be deemed as 'not improved'. Public data about the novel COVID-19 are limited and the data varies between all studies. Based on reported data, the time to improvement in patients with supportive care were about 22-23 days [20, 82] we expect 10% patients in the control group and 35%

patients in the MSC group will achieve 'improved' status at day 14, a total sample size of 66 (36 in the MSC arm and 30 in the control arm) will provide 84% power to detect a difference in clinical improvement of 25% between control (10%) and MSC (35%) at a 7.5% one-sided significance level using a Chi-square test.

8.3 Randomization and Stratification

After safety run in, patients will be randomized in a 1:1 ratio to receive either MSCs or supportive care. Randomization will be stratified by severity of ARDS (moderate and severe), and employ permuted blocks method.

8.4 Safety monitoring and stopping rule

This study will enroll the first 6 patients to the MSC arm for safety run in. Based on experience, we expect the toxicity of MSC is low about 5-10%. The chance of observing tSAEs in more than two out of six patients is 1.6%. After the first six patients complete safety monitoring at day 28, we will halt the study if more than two patients have tSAEs. Otherwise, the study will continue to enroll additional patients

The study will continuously monitor the safety of MSCs infusions in patients who are randomized to the MSC arm so that the accrual can be halted early if there is an unexpectedly high rate of treatment-related serious adverse events (tSAE) at day 28, defined in Section 7.4.5. Patients who don't complete the 28-day observation due to a reason other than tSAE will be deemed not evaluable for tSAE. However, those patients in the randomization phase are evaluable for efficacy and will not be replaced. A tSAE rate of greater than or equal to 25% is considered excessive. The occurrence of tSAEs will be monitored using a stopping guideline based on a Pocock-type boundary method [83]. The following sequential stopping boundaries will be used:

Number of Patients	1-3	4-5	6-7	8-9	10-12	13-14	15-17	18-20	21-23	24-26	27-28	29-30
Number of tSAEs <	-	4	5	6	7	8	9	10	11	12	13	14

The accrual will be halted if the number of tSAEs is equal to or exceeds the boundary in the above table. Under this sequential stopping rule, the probability of early stopping is 5% if the true tSAE rate is 25%, and the probability of early stopping will be high at 81% if the true tSAE rate is 50%.

8.5 Statistical Analysis

All patients who received any MSC infusions in the MSCs arm or supportive care in the control arm will be included in the safety analyses. All efficacy analysis will be based on the intent to treat (ITT) population, defined as eligible and randomized subjects.

Adverse event data and corresponding toxicity grades after treatment will be summarized descriptively by treatment arms. All adverse events, grades, and attributions

will be listed and tabulated. Toxicity information including the type, severity, time of onset, time of resolution, and the probable association with the study regimen will be tabulated and summarized by treatment arms. Rate of tSAEs in patients treated with MSCs will be reported as proportion and its 95% confidence interval overall and by cancer status (cancer patients versus non-oncologic patients).

Clinical outcome data (increase in oxygen saturation, decrease in oxygen supplementation, progression to mechanical ventilation or ECMO, evolution of other end-organ damage, severity of ARDS, mortality rate, cause of death, duration on ventilation, durations of ICU stay and hospital stay, duration of vasopressor use, negative SARS-Co-V-2 RT-PCR by day 28, and change in disease severity scores and corticosteroid use) will be summarized descriptively. Categorical variables will be summarized by frequencies and percentages. Continuous variables will be summarized by means, standard deviations, medians, interquartile ranges.

Proportion of patients who have an improvement of at least two categories on a six category ordinal scale at day 14 and day 28 will summarized using rate and their 95% confidence interval by treatment arms and compared with Chi-square tests. Proportion of patients with improvement will also be reported by cancer status. As exploratory analyses, improvement in clinical status will also be assessed using logistic regression, adjusting for potential confounders such as age, race/ethnicity, underline condition, and severity of ARDS. Changes in the six-point ordinal scale, oxygen saturation, required FiO2, severity scores from baseline will be presented graphically and compared with paired t-tests or Wilcoxon singed rank tests, whichever are appropriate (comparisons are considered exploratory). Duration of overall survival will be days from date of randomization to date of death or date of last follow-up for censoring. Overall survival will be calculated using Kaplan-Meier survival curves with estimates of medians and 95% confidence intervals by each treatment arm and compared with a log-rank test (comparison is considered exploratory).

Laboratory data, which include inflammatory markers and chest imaging will be reported with appropriate summary statistics. Changes from baseline to post-treatment will be plotted for each patient over time and assessed using paired test methodologies when appropriate. Comparison between the two treatment groups will be exploratory with appropriate two-sample tests.

9 Off Treatment and Off Study Criteria

9.1 Off Treatment Criteria

9.1.1. Infusion related anaphylactic reactions

9.1.2. Occurrence of thrombotic event within 48 hours after initial infusion

9.1.3. Patient/legal guardian decline second infusion

9.1.4. Treating physician determines second infusion would not be beneficial for patient

9.2 Off Study Criteria

9.2.1. Completion of all study specified procedures

9.2.2. Refusal of further study follow-up by patient or legal guardian

9.2.3. Lost to follow up

9.2.4. Death

10 Clinical Trial Oversight and Monitoring

10.1. This protocol will be conducted in accordance with the Cell and Gene Therapy Monitoring Plan on file with the FDA.

10.2. This protocol will be monitored in accordance with the current Dan L Duncan Cancer Center Data Safety Monitoring Board Plan.

10.3. The conduct of this clinical trial will be evaluated in accordance with the Texas Children's Cancer Center for Cell and Gene Therapy Quality Assurance/Quality Control Policy and Procedure Plans.

REFERENCES

1. Thompson, B.T., R.C. Chambers, and K.D. Liu, *Acute Respiratory Distress Syndrome.* N Engl J Med, 2017. **377**(6): p. 562-572.
2. Arango Duque, G. and A. Descoteaux, *Macrophage cytokines: involvement in immunity and infectious diseases.* Front Immunol, 2014. **5**: p. 491.
3. Beutler, B.A., *The role of tumor necrosis factor in health and disease.* J Rheumatol Suppl, 1999. **57**: p. 16-21.
4. Force*, T.A.D.T., *Acute Respiratory Distress Syndrome: The Berlin Definition.* JAMA, 2012. **307**(23): p. 2526-2533.
5. Bellani, G., et al., *Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries.* JAMA, 2016. **315**(8): p. 788-800.
6. Goh, K.J., et al., *Rapid Progression to Acute Respiratory Distress Syndrome: Review of Current Understanding of Critical Illness from COVID-19 Infection.* Ann Acad Med Singapore, 2020. **49**(1): p. 1-9.
7. WHO, *Coronavirus disease 2019 (COVID-19)-Situation Report – 63.*
8. Bauch, C.T., et al., *Dynamically modeling SARS and other newly emerging respiratory illnesses: past, present, and future.* Epidemiology, 2005. **16**(6): p. 791-801.
9. Li, Q., et al., *Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia.* N Engl J Med, 2020. **382**(13): p. 1199-1207.
10. Liu, Y., et al., *Clinical features and progression of acute respiratory distress syndrome in coronavirus disease 2019.* medRxiv, 2020.
11. Wu, J.T., K. Leung, and G.M. Leung, *Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study.* Lancet, 2020. **395**(10225): p. 689-697.
12. Huang, C., et al., *Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.* Lancet, 2020. **395**(10223): p. 497-506.
13. Wang, D., et al., *Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China.* JAMA, 2020.
14. Worldmeter, *Worldmeter-coronavirus.*
15. Y Zhao, Z.Z., Y Wang, Y Zhou, Y Ma, W Zuo *Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov.* BioRxiv. 2020; (published online Jan 26.), Jan 26 2020.
16. Letko, M., A. Marzi, and V. Munster, *Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses.* Nat Microbiol, 2020.
17. Yang, X., et al., *Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study.* Lancet Respir Med, 2020.
18. Wu, C., et al., *Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China.* JAMA Intern Med, 2020.

19. Chen, H., et al., *Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records.* Lancet, 2020. **395**(10226): p. 809-815.
20. Zhou, F., et al., *Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.* Lancet, 2020.
21. Leng, Z., et al., *Transplantation of ACE2 -Mesenchymal Stem Cells Improves the Outcome of Patients with COVID-19 Pneumonia.* Aging and Disease, 2020. **11**: p. 216-228.
22. Tang, N., et al., *Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia.* J Thromb Haemost, 2020. **18**(4): p. 844-847.
23. Zhou, F., et al., *Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.* Lancet, 2020. **395**(10229): p. 1054-1062.
24. Tang, N., et al., *Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy.* J Thromb Haemost, 2020.
25. Adak, S., S. Mukherjee, and D. Sen, *Mesenchymal Stem Cell as a Potential Therapeutic for Inflammatory Bowel Disease- Myth or Reality?* Curr Stem Cell Res Ther, 2017. **12**(8): p. 644-657.
26. Ansboro, S., A.J. Roelofs, and C. De Bari, *Mesenchymal stem cells for the management of rheumatoid arthritis: immune modulation, repair or both?* Curr Opin Rheumatol, 2017. **29**(2): p. 201-207.
27. Davies, L.C., et al., *Type 1 Diabetes Mellitus Donor Mesenchymal Stromal Cells Exhibit Comparable Potency to Healthy Controls In Vitro.* Stem Cells Transl Med, 2016. **5**(11): p. 1485-1495.
28. Katuchova, J., et al., *Mesenchymal stem cells in the treatment of type 1 diabetes mellitus.* Endocr Pathol, 2015. **26**(2): p. 95-103.
29. Wu, H. and R.I. Mahato, *Mesenchymal stem cell-based therapy for type 1 diabetes.* Discov Med, 2014. **17**(93): p. 139-43.
30. Fathollahi, A., N.B. Gabalou, and S. Aslani, *Mesenchymal stem cell transplantation in systemic lupus erythematous, a mesenchymal stem cell disorder.* Lupus, 2018. **27**(7): p. 1053-1064.
31. Wang, D., et al., *Umbilical cord mesenchymal stem cell transplantation in active and refractory systemic lupus erythematosus: a multicenter clinical study.* Arthritis Res Ther, 2014. **16**(2): p. R79.
32. Wang, D., et al., *Allogeneic mesenchymal stem cell transplantation in severe and refractory systemic lupus erythematosus: 4 years of experience.* Cell Transplant, 2013. **22**(12): p. 2267-77.
33. Sun, L., et al., *Umbilical cord mesenchymal stem cell transplantation in severe and refractory systemic lupus erythematosus.* Arthritis Rheum, 2010. **62**(8): p. 2467-75.
34. Karussis, D., et al., *Safety and immunological effects of mesenchymal stem cell transplantation in patients with multiple sclerosis and amyotrophic lateral sclerosis.* Arch Neurol, 2010. **67**(10): p. 1187-94.
35. Leyendecker, A., Jr., et al., *The Use of Human Mesenchymal Stem Cells as Therapeutic Agents for the in vivo Treatment of Immune-Related Diseases: A Systematic Review.* Front Immunol, 2018. **9**: p. 2056.

36. Weiss, D.J., et al., *A placebo-controlled, randomized trial of mesenchymal stem cells in COPD.* Chest, 2013. **143**(6): p. 1590-1598.
37. Tzouvelekis, A., et al., *A prospective, non-randomized, no placebo-controlled, phase Ib clinical trial to study the safety of the adipose derived stromal cells-stromal vascular fraction in idiopathic pulmonary fibrosis.* J Transl Med, 2013. **11**: p. 171.
38. Chambers, D.C., et al., *A phase 1b study of placenta-derived mesenchymal stromal cells in patients with idiopathic pulmonary fibrosis.* Respirology, 2014. **19**(7): p. 1013-8.
39. Pittenger, M.F., et al., *Multilineage potential of adult human mesenchymal stem cells.* Science, 1999. **284**(5411): p. 143-7.
40. Haynesworth, S.E., et al., *Characterization of cells with osteogenic potential from human marrow.* Bone, 1992. **13**(1): p. 81-8.
41. Chamberlain, G., et al., *Concise review: mesenchymal stem cells: their phenotype, differentiation capacity, immunological features, and potential for homing.* Stem Cells, 2007. **25**(11): p. 2739-49.
42. Orlic, D., et al., *Bone marrow cells regenerate infarcted myocardium.* Nature, 2001. **410**(6829): p. 701-5.
43. Orlic, D., et al., *Mobilized bone marrow cells repair the infarcted heart, improving function and survival.* Proc Natl Acad Sci U S A, 2001. **98**(18): p. 10344-9.
44. Le Blanc, K. and O. Ringden, *Immunobiology of human mesenchymal stem cells and future use in hematopoietic stem cell transplantation.* Biol Blood Marrow Transplant, 2005. **11**(5): p. 321-34.
45. Di Nicola, M., et al., *Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli.* Blood, 2002. **99**(10): p. 3838-43.
46. Bartholomew, A., et al., *Mesenchymal stem cells suppress lymphocyte proliferation in vitro and prolong skin graft survival in vivo.* Exp Hematol, 2002. **30**(1): p. 42-8.
47. Le Blanc, K., et al., *Mesenchymal stem cells inhibit and stimulate mixed lymphocyte cultures and mitogenic responses independently of the major histocompatibility complex.* Scand J Immunol, 2003. **57**(1): p. 11-20.
48. Ryan, J.M., et al., *Mesenchymal stem cells avoid allogeneic rejection.* J Inflamm (Lond), 2005. **2**: p. 8.
49. Tse, W.T., et al., *Suppression of allogeneic T-cell proliferation by human marrow stromal cells: implications in transplantation.* Transplantation, 2003. **75**(3): p. 389-97.
50. Mei, S.H., et al., *Mesenchymal stem cells reduce inflammation while enhancing bacterial clearance and improving survival in sepsis.* Am J Respir Crit Care Med, 2010. **182**(8): p. 1047-57.
51. Gupta, N., et al., *Mesenchymal stem cells enhance survival and bacterial clearance in murine Escherichia coli pneumonia.* Thorax, 2012. **67**(6): p. 533-9.
52. Walter, J., L.B. Ware, and M.A. Matthay, *Mesenchymal stem cells: mechanisms of potential therapeutic benefit in ARDS and sepsis.* Lancet Respir Med, 2014. **2**(12): p. 1016-26.
53. Moodley, Y., et al., *Human umbilical cord mesenchymal stem cells reduce fibrosis of bleomycin-induced lung injury.* Am J Pathol, 2009. **175**(1): p. 303-13.

54. Tashiro, J., et al., *Therapeutic benefits of young, but not old, adipose-derived mesenchymal stem cells in a chronic mouse model of bleomycin-induced pulmonary fibrosis.* Transl Res, 2015. **166**(6): p. 554-67.
55. Rojas, M., et al., *Bone marrow-derived mesenchymal stem cells in repair of the injured lung.* Am J Respir Cell Mol Biol, 2005. **33**(2): p. 145-52.
56. Chan, M.C., et al., *Human mesenchymal stromal cells reduce influenza A H5N1-associated acute lung injury in vitro and in vivo.* Proc Natl Acad Sci U S A, 2016. **113**(13): p. 3621-6.
57. Li, Y., et al., *Mesenchymal stromal cell treatment prevents H9N2 avian influenza virus-induced acute lung injury in mice.* Stem Cell Res Ther, 2016. **7**(1): p. 159.
58. Lee, J.W., et al., *Therapeutic effects of human mesenchymal stem cells in ex vivo human lungs injured with live bacteria.* Am J Respir Crit Care Med, 2013. **187**(7): p. 751-60.
59. Lee, J.W., et al., *Allogeneic human mesenchymal stem cells for treatment of E. coli endotoxin-induced acute lung injury in the ex vivo perfused human lung.* Proc Natl Acad Sci U S A, 2009. **106**(38): p. 16357-62.
60. Goolaerts, A., et al., *Conditioned media from mesenchymal stromal cells restore sodium transport and preserve epithelial permeability in an in vitro model of acute alveolar injury.* Am J Physiol Lung Cell Mol Physiol, 2014. **306**(11): p. L975-85.
61. Glassberg, M.K., et al., *Allogeneic Human Mesenchymal Stem Cells in Patients With Idiopathic Pulmonary Fibrosis via Intravenous Delivery (AETHER): A Phase I Safety Clinical Trial.* Chest, 2017. **151**(5): p. 971-981.
62. Wilson, J.G., et al., *Mesenchymal stem (stromal) cells for treatment of ARDS: a phase 1 clinical trial.* Lancet Respir Med, 2015. **3**(1): p. 24-32.
63. Simonson, O.E., et al., *In Vivo Effects of Mesenchymal Stromal Cells in Two Patients With Severe Acute Respiratory Distress Syndrome.* Stem Cells Transl Med, 2015. **4**(10): p. 1199-213.
64. Coppin, L., E. Sokal, and X. Stephenne, *Thrombogenic Risk Induced by Intravascular Mesenchymal Stem Cell Therapy: Current Status and Future Perspectives.* Cells, 2019. **8**(10).
65. Moll, G., et al., *Intravascular Mesenchymal Stromal/Stem Cell Therapy Product Diversification: Time for New Clinical Guidelines.* Trends Mol Med, 2019. **25**(2): p. 149-163.
66. Moll, G., et al., *Are therapeutic human mesenchymal stromal cells compatible with human blood?* Stem Cells, 2012. **30**(7): p. 1565-74.
67. Christy, B.A., et al., *Procoagulant activity of human mesenchymal stem cells.* J Trauma Acute Care Surg, 2017. **83**(1 Suppl 1): p. S164-S169.
68. Lalu, M.M., et al., *Safety of cell therapy with mesenchymal stromal cells (SafeCell): a systematic review and meta-analysis of clinical trials.* PLoS One, 2012. **7**(10): p. e47559.
69. Wu, Z., et al., *Thromboembolism Induced by Umbilical Cord Mesenchymal Stem Cell Infusion: A Report of Two Cases and Literature Review.* Transplant Proc, 2017. **49**(7): p. 1656-1658.
70. George, M.J., et al., *Clinical Cellular Therapeutics Accelerate Clot Formation.* Stem Cells Transl Med, 2018. **7**(10): p. 731-739.

71. Vulliet, P.R., et al., *Intra-coronary arterial injection of mesenchymal stromal cells and microinfarction in dogs.* Lancet, 2004. **363**(9411): p. 783-4.
72. Stephenne, X., et al., *Bivalirudin in combination with heparin to control mesenchymal cell procoagulant activity.* PLoS One, 2012. **7**(8): p. e42819.
73. Shiratsuki, S., et al., *Enhanced survival of mice infused with bone marrow-derived as compared with adipose-derived mesenchymal stem cells.* Hepatol Res, 2015. **45**(13): p. 1353-9.
74. Moll, G., et al., *Different Procoagulant Activity of Therapeutic Mesenchymal Stromal Cells Derived from Bone Marrow and Placental Decidua.* Stem Cells Dev, 2015. **24**(19): p. 2269-79.
75. Ringden, O., et al., *Placenta-Derived Decidua Stromal Cells for Treatment of Severe Acute Graft-Versus-Host Disease.* Stem Cells Transl Med, 2018. **7**(4): p. 325-331.
76. Moberg, L., et al., *Production of tissue factor by pancreatic islet cells as a trigger of detrimental thrombotic reactions in clinical islet transplantation.* Lancet, 2002. **360**(9350): p. 2039-45.
77. Bennet, W., et al., *Isolated human islets trigger an instant blood mediated inflammatory reaction: implications for intraportal islet transplantation as a treatment for patients with type 1 diabetes.* Ups J Med Sci, 2000. **105**(2): p. 125-33.
78. Tatsumi, K., et al., *Tissue factor triggers procoagulation in transplanted mesenchymal stem cells leading to thromboembolism.* Biochem Biophys Res Commun, 2013. **431**(2): p. 203-9.
79. Oeller, M., et al., *Selection of Tissue Factor-Deficient Cell Transplants as a Novel Strategy for Improving Hemocompatibility of Human Bone Marrow Stromal Cells.* Theranostics, 2018. **8**(5): p. 1421-1434.
80. Liao, L., et al., *Heparin improves BMSC cell therapy: Anticoagulant treatment by heparin improves the safety and therapeutic effect of bone marrow-derived mesenchymal stem cell cytotherapy.* Theranostics, 2017. **7**(1): p. 106-116.
81. Baygan, A., et al., *Safety and Side Effects of Using Placenta-Derived Decidual Stromal Cells for Graft-versus-Host Disease and Hemorrhagic Cystitis.* Front Immunol, 2017. **8**: p. 795.
82. Wang, Y., et al., *Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial.* Lancet, 2020. **395**(10236): p. 1569-1578.
83. Ivanova, A., B.F. Qaqish, and M.J. Schell, *Continuous toxicity monitoring in phase II trials in oncology.* Biometrics, 2005. **61**(2): p. 540-5.