Stem Cells and Development

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Perspective

The coronavirus pandemic: a pitfall or a fast-track for validating cell therapy products?

Maroun Khoury[1,2], Laertis Ikonomou[3], Massimo Dominici[4], Katarina LeBlanc[5], Bruce L. Levine[6] and Daniel J. Weiss[7]*

[1] Laboratory of Nano-Regenerative Medicine, Faculty of Medicine, Universidad de los Andes, Santiago, Chile.

[2] Cells for Cells and Consorcio Regenero, Chilean Consortium for Regenerative Medicine, Santiago, Chile

[3] Department of Oral Biology, University at Buffalo, The State University of New York, Buffalo, NY, USA.

[4] Department of Medical and Surgical Sciences for Children and Adults, Division of Oncology, University Hospital of Modena, Italy.

[5] Department of Laboratory Medicine, Karolinska Institutet, CAST, Patient Area Cell Therapies and Allogeneic Stem Cell Transplantation, Karolinska University Hospital, Stockholm, Sweden.

[6] Center for Cellular Immunotherapies, Department of Pathology and Laboratory Medicine, and Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA.

[7] Department of Medicine, University of Vermont, Burlington, VT, USA

*To whom correspondence may be addressed:

Daniel J. Weiss, MD, PHD

Department of Medicine,

University of Vermont,

Burlington, VT USA

Phone: +1 802-847-1158

E-mail: daniel.weiss@med.uvm.edu

Abstract:

The global COVID-19 pandemic has prompted urgent need for potential therapies for severe respiratory consequences resulting from coronavirus infection. New therapeutic agents that will attenuate ongoing inflammation and at the same time promote regeneration of injured lung epithelial cells are urgently needed. Cell-based therapies, primarily involving mesenchymal stromal cells (MSCs) and their derivatives are currently being investigated worldwide for SARS-CoV-2-induced lung diseases. A significant number of academic centers and companies globally have already initiated such trials. However, at a time of unprecedented need, it is also foreseen that families and caregivers will seek all available options including access to cell-based and other investigational products, even prior to proven safety and efficacy as well as regulatory approval. This should not be an excuse for opportunists to sell or advertise unproven therapies of any kind. "Compassionate use" should be conducted in the context of a clinical investigation framed by strict ethical and regulatory permissions, with the goal of obtaining mechanistic information wherever possible.

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The serious consequences of the COVID-19 pandemic have prompted a global initiative to develop effective therapies that can lessen disease severity in infected patients, particularly those with severe respiratory disease. Cell-based approaches, primarily using mesenchymal stromal cells (MSCs), have demonstrated an acceptable safety profile in patients with non-SARS-CoV-2 related acute respiratory distress syndrome (ARDS) in the limited currently available information.[1] However, whether these therapies are effective for treating respiratory virus-induced ARDS, including that resulting from SARS-CoV-2, is unknown.[1] This is despite several recent case reports and uncontrolled case series suggesting potential efficacy.[2,3] Regardless, there are an increasing number of both academic and industry-sponsored trials of cell-based therapies for COVID-19 patients initiated over the past several months. Most are investigating use of MSCs, but some are investigating MSC-derived products including extracellular vesicles (EVs) and some are utilizing other cell types. In parallel, there has been a worrisome increase in the number of businesses offering unproven and untested cell-based therapy approaches in uncontrolled and unregulated settings.[4] This creates a potentially dangerous situation for patients, families, and care-givers in often desperate situations.

An overview of the rationale, pre-clinical data, and clinical experience of cell-based therapy in non-COVID-related ARDS provides a strong platform underlying legitimate investigations. There is a wealth of pre-clinical data in both small and large animal models as well as in explanted human lungs in which either systemic or direct airway administration of MSCs mitigates experimentally-induced acute lung injuries resulting from bacteria or bacterial product, for example gram-negative bacterial endotoxin, administration.[5,6] The postulated mechanisms largely focus on paracrine actions of the administered MSCs including release of anti-inflammatory cytokines, anti-bacterial peptides, and extracellular vesicles that mitigate inflammation in the setting of acute lung injuries (**Figure 1**).[7] These encouraging results have provided a basis for the growing number of academic and industry-sponsored investigations of systemically administered MSCs in (non-COVID) ARDS patients.[1] While these studies have uniformly demonstrated a good safety profile, there remains uncertainty about potential efficacy. One major academic-based trial did not demonstrate clinical efficacy[8], whereas improvement in clinically relevant endpoints including increased ventilator-free and ICU-free days and

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decreased one month mortality, was suggested in one major industry trial.[9] However, neither of these trials have specifically targeted patients with respiratory virus-induced ARDS. Further, there are only a small number of pre-clinical studies in models of respiratory virus infection and these all involve influenza rather than coronavirus. Notably, there were contrasting results of efficacy in these studies, possibly related to the type of influenza (swine vs. avian) infection utilized. This furthers adds to uncertainty about whether MSC or other cell or cell product administration will have specific efficacy in SARS-CoV-2 induced respiratory failure. There is almost no available clinical data with respect to MSC administration in other types of respiratory virus infections with only a case report in a patient with H1N1 flu-related ARDS (allogeneic bone marrow-derived MSCs)[10] and a case series following H7N9 flu infection (allogeneic menstrual blood-derived MSCs).[11]

A recent search (November, 2020) of the NIH clinical trial database and the World Health Organization-International Clinical Trial Registry Platform (WHO-ICTRP) revealed over 3,787 recently registered clinical trials for COVID-19. Among these are 154 cell and gene therapy-based trials worldwide, with most registered in China (41) and the the USA (36). Most of these utilize MSCs or their secreted products, including EVs or conditioned media. In a previous comprehensive review, we had presented an exhaustive summary of ongoing studies registered in the Chinese Clinical Trial Registry (chictr.org.cn) also accessible from the World Health Organization-International Clinical Trial Registry Platform (WHO-ICTRP).[1] Following the continued spread of the pandemic, we complement that information with an updated list of trials with investigational new drug (IND) clearance from the US.FDA (**Table 1**). Notably, a wide range of protocols with allogeneic MSCs of different origins, different doses, and different dosing strategies are being utilized. The dose of injected cells ranges from 0.5 to 2 x 10^6 cells/kg or the equivalent in a predefined infusion dose. The number of injections varies between a single dose and up to three doses separated between 3- 5 days with one trial utilizing up to 4 separate doses. . Importantly, there is also a wide range of patient groups being targeted including those with mild or moderate disease in addition to those with severe disease. A variety of enrollment designs are being utilized including emergency and compassionate use, with only a small proportion of trials using a randomized, double-blinded placebo control format. Also, the use of autologous MSC derived from the patient's adipose tissue is used

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in 3 registered trials. It is unclear whether the cells were obtained previous to infection through adult stem cell banking or harvested after infection. In two trials, MSC are being used as prophylaxis not only in asymptomatic COVID-19 patients but also in healthy individuals at high or very high exposure risk of contracting COVID-19. While the majority of investigations are utilizing modified MSCs, one industry trial is evaluating the safety and feasibility of MSCs RNA-engineered to secrete a combination of DNases (**Table 1**). Further, although there is a less robust mechanistic and pre-clinical platform, at least seven investigations are utilizing other cell types including, among others, cytotoxic T cells (CTL), dendritic cells (DC), primary natural killer cells (NK) and induced pluripotent stem cell (iPSC)-derived NK cells already being used to treat cancer patients [12]. There is a paucity of direct evidence for the protective or pathological role of NK cells in the response to SARS-Cov-2 infection. In the context of non-respiratory viral infections by human immunodeficiency virus (HIV) and hepatitis C virus (HCV), NK cells appear to prevent T cell-mediated autoimmunity through their cytotoxic properties [13]. However, NK cells are one of the main producers of the pro-inflammatory mediator IFN-γ, hence, they may be involved in the induction or perpetuation of inflammation-mediated lung injuries, and subsequent mortality associated with COVID-19 [14].

Despite the lack of preclinical information in COVID-19 or any other respiratory virus pathophysiology, there has been clearance by the FDA of an investigational new drug (IND) application for the use of NK cells in clinical testing.[15] Whether these approaches are even safe for COVID-19 patients has yet to be clarified. As such we urge the FDA and other regulatory agencies to take a careful position with respect to approving cell-based products with unclear track records in either pre-clinical or clinical studies in lung diseases or critical illnesses for use in COVID 19 patients.

Convalescent T-cells isolated from COVID-19 patients are also being considered. Recently, SARS-CoV-2 -specific T-cells were shown to be polyfunctional and can be expanded from convalescent individuals. These T-cell were able to target structural viral proteins, including the C-terminus of membrane protein, making them good candidate for the prevention or early treatment of SARS-CoV-2 infection in immunocompromised patients with blood disorders [16].

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Of the recent published reports and small case series from both academic and industry sources suggesting potential efficacy of systemic MSC administration in COVID-19 patients, the available data presented is either anecdotal or from incompletely presented, poorly controlled investigations.[2,17] The situation is also further complicated by lack of consensus or full understanding with respect to MSC source of origin, dose, dosing strategy, use of freshly thawed vs. continuously cultured cells, and other factors involved in potential use of MSC-based cell therapies. The same holds for a recent published initial safety investigation utilizing MSC-derived EVs in which no information about the actual biological substance being administered was provided.[18] Therefore, while there may be a potential role for MSCs and other cell-based therapies in treatment of COVID-19, these need to be investigated in a rationally designed, controlled approach if safety and efficacy are to be demonstrated accurately. Importantly, in addition to legitimate peer-reviewed academic trials being conducted globally, one industry-sponsored prospective randomized, double blinded, placebo-controlled phase II (intramuscular injection of Placental-MSC, ClinicalTrials.gov Identifiers: NCT04389450) and two phase III trials of intravenously administered marrow-derived MSC-like products for severe COVID-19 have been initiated in the USA (NCT04367077 and NCT04371393). The hope is these and comparable studies will provide robust data informing the utility of systemic MSC administration for COVID-related ARDS (Table 1).

At a time of unprecedented need, it is natural for patients, families, and caregivers to seek all available options including access to cell-based and other investigational products, even prior to adequate demonstration of safety and efficacy and according regulatory approval. This should not be an excuse for opportunists to sell or advertise unproven therapies of any kind. “Compassionate use” should be conducted in the context of a clinical investigation framed by strict ethical and regulatory permissions, such as expanded access authorization, with the goal of obtaining mechanistic information wherever possible. There must be a strong stance against the rogue stem-cell clinic industry which has already begun to offer unproven therapies for COVID-19. A number of global organizations, including the International Society for Cell and Gene Therapy (ISCT) and the International Society for Stem Cell Research (ISSCR), have taken positions against this predatory behavior.[19] The FDA has recently increased oversight activities against businesses

offering unproven therapies, but more regulatory oversight and action are needed.[20] These actions are necessary to develop rationale evidence-based platform for potential use of cell-based therapies both for COVID-19 but also for a wider range of respiratory and other diseases potentially amenable to these advanced therapies.

Author Disclosure Statement

Maroun Khoury PHD is assistant professor at the faculty of medicine of the University of los Andes, Santiago, Chile and Chief Scientific Officer of Cells for Cells and Regenero (Chile), spin-offs of the same University. He receives research support from the Chilean National Agency for Research and Development (ANID), the Economic Development Agency of the Chilean Government (CORFO), Cells for Cells-Regenero and from the University of Los Andes.

Laertis Ikonomou PhD is Associate Professor of Oral Biology at the University at Buffalo, The State University of New York and the Chair of the International Society for Cell & Gene Therapy Presidential Task Force (PTF) on the Use of Unproven and/or Unethical Cell and Gene Therapy. He has written an expert report in a class action lawsuit filed against a business selling unproven stem cell interventions and wrote the report on a pro bono basis.

Massimo Dominici, MD is Professor of Oncology at the University of Modena, Italy. He is a specialist physician at the Department of Medical and Surgical Sciences for Children and Adults, University Hospital of Modena, Italy. He receives research support from Associazione Italiana Ricerca Cancro (AIRC), the Associazione Sostegno Ematologia e Oncologia Pediatrica (ASEOP), the Associazione ASLEM and MIUR (Progetto Dipartimenti Eccellenti 2017). He has been chair of the ISCT Presidential Task Force on Unproven cell and gene therapy (2014-2020).

Katarina LeBlanc, MD PHD is Professor of Clinical Stem Cell Research at the Division of Clinical Immunology and Transfusion Medicine, Karolinska Institutet and Senior Consultant, Center of Allogeneic Stem Cell Transplantation and Cellular Therapy (CAST), Karolinska University Hospital Huddinge, Stockholm, Sweden. She receives research

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Bruce L. Levine is the Barbara and Edward Netter Professor of Cancer Gene Therapy at the Perelman School of Medicine at the University of Pennsylvania and President of the International Society for Cell and Gene Therapy. Disclosures of equity: Tmunity Therapeutics. Honoraria: Novartis, Terumo, AstraZeneca. Consulting or Advisory Role: Brammer Bio/ThermoFisher Viral Vector Services, Avectas, Immuneel, Ori Biotech, Vycellix.

Daniel J. Weiss MD PhD is Professor of Medicine at the University of Vermont and Chief Scientific Officer of the International Society for Cell & Gene Therapy. He receives research support from the National Institutes of Health, Department of Defense, Cystic Fibrosis Foundation, and the University of Vermont. He has written an expert report in a class action lawsuit filed against a business selling unproven stem cell interventions and wrote the report on a pro bono basis.

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Table 1: US-FDA approved MSC-based clinical trials for COVID-19

	Date of registration/ Completion date	Study phase/Allocation	ID/Sponsor/ Location	Title	Cell type/Dose	Number of total participants / Intervention or treatment
1	April-2020/ May 2022	1/randomized	NCT04345601/ Baylor College of Medicine Houston, Texas	Mesenchymal Stromal Cells for the Treatment of SARS-CoV-2 Induced Acute Respiratory Failure (COVID-19 Disease)	BM-MSC / 100 x 10^6	**30** Experimental group: up to two infusions of MSC. Control group: Supportive care or treatment designed by their physician.

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2	April-2020/ NC	Expanded access	NCT04366830/ Mesoblast, NY, New York	Intermediate-size Expanded Access Program (EAP), Mesenchymal Stromal Cells (MSC) for Acute Respiratory Distress Syndrome (ARDS) Due to COVID-19 Infection	BM-MSC / 1 x 10^6/kg	NC 2 infusions of Remestemcel-L administered intravenously (IV).
3	April-2020/ August-2022	2/3 randomized	NCT04367077/ Athersys, Akron and Cleveland, Ohio.	A Phase 2/3 Study to Assess the Safety and Efficacy of MultiStem® Therapy in Subjects With Acute Respiratory Distress Syndrome (ARDS) Due to	BM-MSC/ NC	400 Experimental group: 1 infusion of Multisem, IV Control group: Placebo treatment

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				Coronavirus Disease (COVID-19)		
4	April-2020/ April-2022	3 / randomized	NCT04371393/ Mesoblast, NY, New York	Mesenchymal Stem Cells for the Treatment of Moderate to Severe COVID-19 Acute Respiratory Distress Syndrome	BM-MSC / 1 x 10^6/kg	300 Experimental group: Intravenous infusion of remestemcel-L plus standard of care, administered twice during the first week, with the second infusion at 4 days following the first injection (± 1 day) Control group: Placebo (Plasma-

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						Lyte) plus standard of care
5	May-2020/ June-2021	1b / Recruiting	NCT04397796/ Nantkwest, Lynwood, California	Phase 1b Randomized, Double-Blind, Placebo-Controlled Study Of The Safety Of Therapeutic Treatment With Immunomodulatory Mesenchymal Stem Cells In Adults With COVID-19 Infection Requiring Mechanical Ventilation	BM-MSC/ NC	45 Experimental group: Allogenic BM-MSC. Control group: plasmalyte and human albumin.
6	April 2020/ December 2020	1 / 2 randomized	NCT04355728/ University of Miami Miami,	Umbilical Cord-derived Mesenchymal Stem Cells for COVID-19 Patients With	UC-MSCs 100x10^6 cells/infusion	24 Experimental group: Two infusions of

			Florida	Acute Respiratory Distress Syndrome (ARDS)		MCSs along with heparin in addition to standard of care treatment. The first infusion will be administered within 24 hours of study enrollment and the second within 72 hours. Control group: Best supportive care treatment per the treating hospital protocol, with 2

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						infusion of vehicle + heparin.
7	June-2020/ July-2021	1/2 randomized	NCT04399889/ Duke University, Durham, North Carolina	Pilot Study of Safety and Efficacy of Cord Tissue Derived Mesenchymal Stromal Cells (hCT-MSC) in COVID-19 Related Acute Respiratory Distress Syndrome (ARDS)	UC-MSCs/ NC	30 Experimental group: UC-MSC Control group: Standard of care
8	June-2020/ June-2021	1 / not-randomized	NCT04452097/ Baylx, Irvine, California	A Phase 1 Study of the Safety and Tolerability of BX-U001 for the Treatment of Severe COVID-19 Pneumonia With Moderate to Severe Acute Respiratory Distress	UC-MSCs 0,5 or 1 or 1,5 x 10^6/kg	9 Experimental group: Low, medium, high dose, Single injection of MSCs.

				Syndrome (ARDS).		
9	June-2020/ July-2024	1 /2 randomized	NCT04490486/ University of Miami Miami, Florida	Phase I, Randomized, Double Blinded, Placebo Control Study to Evaluate the Safety and Potential Efficacy of Intravenous Infusion of Umbilical Cord Tissue (UC) Derived Mesenchymal Stem Cells (MSCs) Versus Placebo to Treat Acute Pulmonary Inflammation Due to COVID-19 With Moderate to Severe Symptoms	UC-MSCs/ 100x10^6 cells/infusion	21 Experimental group: Two intravenous (IV) UCMSCs intervention on on day 0 and day 3. Control group:

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						Placebo, a solution of 1% human serum albumin in Plasmalyte A, delivered via peripheral intravenous infusion
10	May-2020/ October-2020	1 / 2 randomized	NCT04398303/ Aspire Health Science, Orlando, Florida	A Phase 1/2 Randomized, Placebo-Controlled Trial of ACT-20 in Patients With Severe COVID-19 Pneumonia	UC-MSCs/ 1x10^6/kg + CM/ 100ml	70 Experimental group1: MSCs + CM Experimental group 2: CM Control group: Conventional treatment plus placebo (MEM-α)
11	July-2020/ Novemb	1/2 randomized	NCT04494386/ Restem, Sioux Falls,	Phase 1/2a Study of Umbilical Cord	UC-MSC 100x10^6 cells/dose	Experimental group: IV infusion

	er-2021		South Dakota	Lining Stem Cells (ULSC) in Patients With ARDS Due to COVID-19		of MSC in sterile saline for injection Control group: IV infusion of carrier control consisting of sterile saline for injection
12	April-2020/ April-2021	2 / randomized (healthy prophilaxis)	NCT04348435/ Hope Biosciences Sugar Land, Texas	A Randomized, Double-Blind, Single Center, Efficacy and Safety Study of Allogeneic HB-adMSCs to Provide Immune Support Against COVID-19	Adipose-MSCs 50, 100 or 200 x10^6/dose	100 Experimental group1: 5 intravenous infusions of HB-adMSCs at 200 million cells/dose. Infusions will occur at weeks 0, 2, 6, 10, and 14. Experimental group2:

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						5 intravenous infusions of HB-adMSCs at 100 million cells/dose. Infusions will occur at weeks 0, 2, 6, 10, and 14. Experimental group3: 5 intravenous infusions of HB-adMSCs at 50 million cells/dose. Infusions will occur at weeks 0, 2, 6, 10, and 14 Control group: 5 intravenous

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						infusions of placebo intervention (saline). Infusions will occur at weeks 0, 2, 6, 10, and 14.
13	April-2020/ December-2020	2/ NC (infected prophilaxis)	NCT0434963/ Hope Biosciences Sugar Land, Texas	A Phase II, Open Label, Single-Center, Clinical Trial to Assess Efficacy of HB-adMSCs to Provide Immune Support Against Coronavirus Disease	Adipose-MSCs/ NC	56 Experimental group: Five IV infusions of autologous, adipose-derived mesenchymal stem cells.
14	April-2020/ April-2026	1 / Non-randomized	NCT04352803/ Regeneris Medical, North Attleborough, MA,	IV Infusion of Autologous Adipose Derived Mesenchymal Cells for Abatement of Respiratory Compromise in	Adipose-MSCs 0,5 x10^6/kg	20 Experimental group: Conventional treatment plus MSC. Control

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				SARS-CoV-2 Pandemic (COVID-19		group: Conventional treatment only
15	April-2020/ October-2020	2 / randomized	NCT04362189/ Hope Biosciences Houston, Texas	A Randomized, Placebo-Controlled, Double-Blind, Efficacy and Safety Study of Allogeneic HB-adMSCs for the Treatment of COVID-19	Adipose-MSCs 100x10^6 cells/infusion	100 Experimental group: 4 intravenous infusions of MSC at day 0, 3, 7, and 10. Control group: 4 intravenous infusions of placebo (saline solution) at day 0, 3, 7, and 10.
16	June-2020/ January 2022	2 / randomized	NCT04428801 / Celltex Therapeutics Corporation, Houston, Texas	Clinical Study for the Prophylactic Efficacy of Autologous Adipose Tissue-	Adipose-MSCs 200x10^6 cells/infusion	200 Experimental group: Three doses of autologous adipose

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				Derived Mesenchymal Stem Cells (AdMSCs) Against Coronavirus 2019 (COVID-19).		derived mesenchymal stem cells via intravenously infusion every three days Control group: Three doses of placebo via intravenously infusion every three days.
17	July-2020/ January-2021	1 / NC	NCT04486001/ Personalized Stem Cells Fresno, California	COVID-19 Stem Cell Therapy: A Phase I Study of Intravenous Administration of Allogeneic Adipose Stem Cells	Adipose-MSCs/ NC	20 Experimental group: adipose stem cells derived from screened donor lipoaspirate and culture expanded
18	May-2020/ March-2022	2/ randomized	NCT04389450/ Pluristem, Multicentric: California,	A Randomized, Double-Blind, Placebo-	Placental-MSCs/ NC	140 Experimental group 1: interval high

			Florida, Georgia, Mississippi, New Jersey, New York, Pennsylvania.	Controlled, Multicenter, Parallel-Group Phase II Study to Evaluate the Efficacy and Safety of Intramuscular Injections of PLX PAD for the Treatment of Severe COVID-19		dose 15 Intramuscular (IM) injections (1 mL each). Each subject will be treated twice, with an interval of 1 week between treatments. Experimental group 2 : low dose single administration, second administration of placebo after 1 week. Experimenta group 3 : high dose Single administration Control group 1-2:

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						Placebo, two administrations, 1 week apart. Control group 3: Placebo, single administration/
19	September-2020/ April-2021	1/ randomized	NCT04565665/ M.D. Anderson Cancer Center, Houston, Texas	Emergency Use Pilot Study of Cord Blood Derived Mesenchymal Stem Cells for Treatment of COVID-19 Related Acute Respiratory Distress Syndrome	Cord blood-MSC	70 Experimental: Pilot study Patients receive MSCs IV over 1-2 hours on day 1. Patients may receive a second infusion of MSCs within 7 days after the first infusion per physician discretion Experimental: Phase II Arm I Patients

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						receive MSCs as in the Pilot study. Control group: standard of care.
20	June-2020/ July-2021	1/2 randomized	NCT04445220/ Sentien Biotechnologies, Inc. NA	A Multi-center, Randomized, Case Controlled, Double-blind, Ascending-dose Study of Extracorporeal Mesenchymal Stromal Cell Therapy (SBI-101 Therapy) in COVID-19 Subjects With Acute Kidney Injury Receiving Renal Replacement	MSC-extracorporal/ 250 or 750 x10^6	22 Experimental group 1: high dose. MSC and plasmapheresis device, administered via integration into a Continuous Renal Replacement Therapy circuit and is designed to regulate inflammation and promote repair of injured tissue. Experimental group 2: low

				Therapy		dose. Control group: standard-of-care treatment
21	July-2020/ December -2021	2/ randomized	NCT04466098/ University of Minnesota, Minneapolis, Minnesota.	Multi-center, Randomized, Placebo Controlled, Interventional Phase 2A Clinical Trial Evaluating the Safety and Potential Efficacy of Multiple Dosing of Mesenchymal Stromal Cells in Patients With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-	MSC (unkown source)/ 300x10^6	30 Experimental group: Three fixed doses of thawed MSC approximately 48 hours apart, containing DMSO resuspended 1:1 with Dextran 40 + 5% human serum albumin [total volume 60 mL] Control group:

				2)		Dextran 40 + 5% human serum albumin [total volume 60 mL]
22	August-2020/ Septembe r-2022	1/2 NA	NCT0452496 2/ Cartesian Therapeutics, Boston, Massachuset ts Oklahoma City, Oklahoma.	Phase I/IIA Study of Descartes-30 in Acute Respiratory Distress Syndrome	MSC (unkown source)- genetically modified	30 Experimental group: Mesenchymal Stem Cells or MSCs RNA-engineered to secrete a combination of DNases

UC-MSCs, Umbilical cord derived-mesenchymal stem cells; BM-MSCs, bone marrow derived-mesenchymal stem cells.

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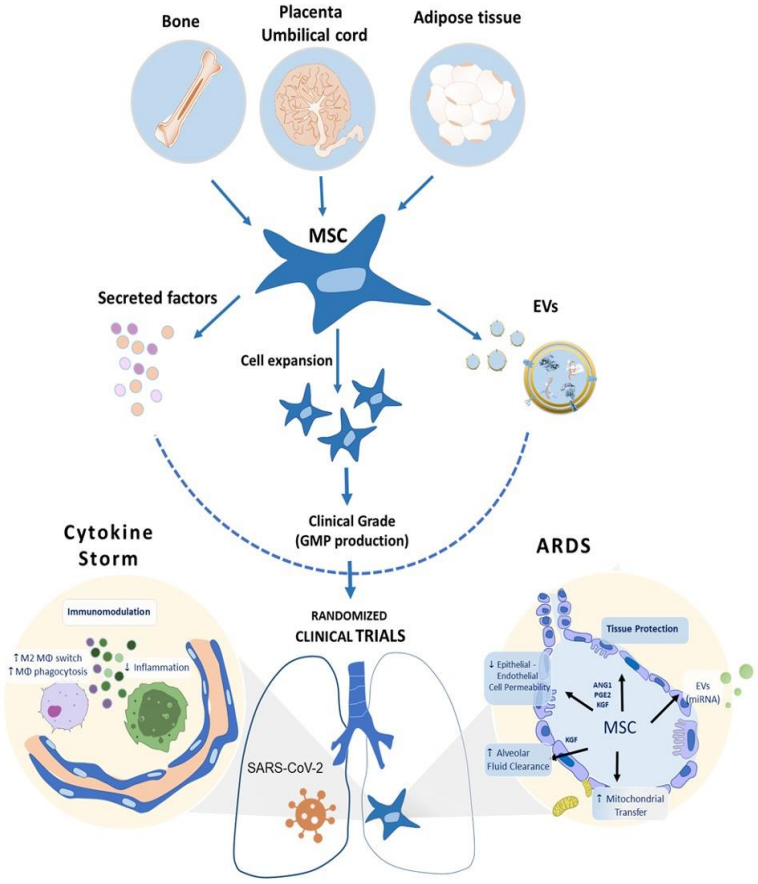

Figure 1: Overview of MSC properties relevant for potential use in COVID-19 related severe respiratory disease.