

SARS_COV2 Pandemic

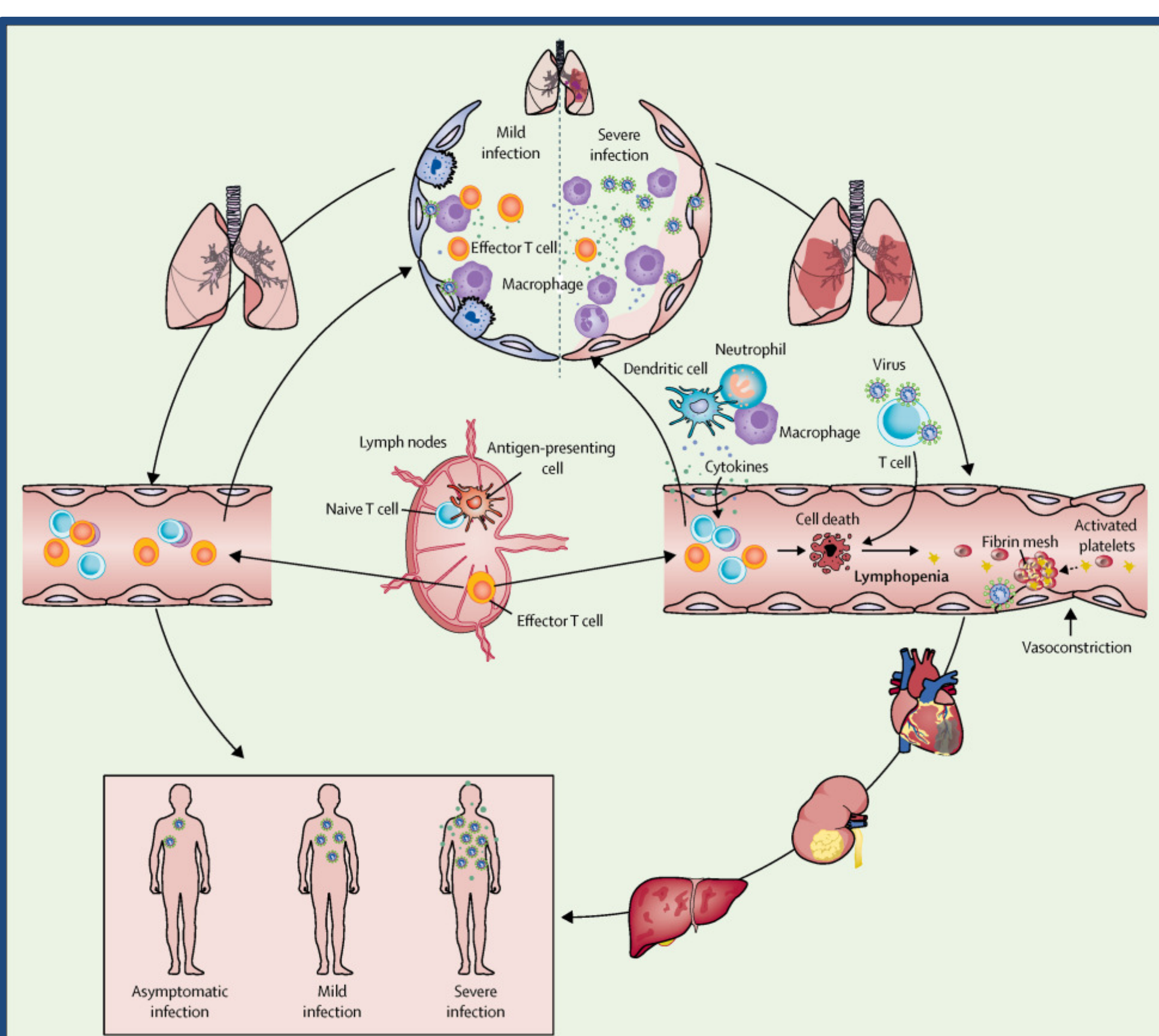
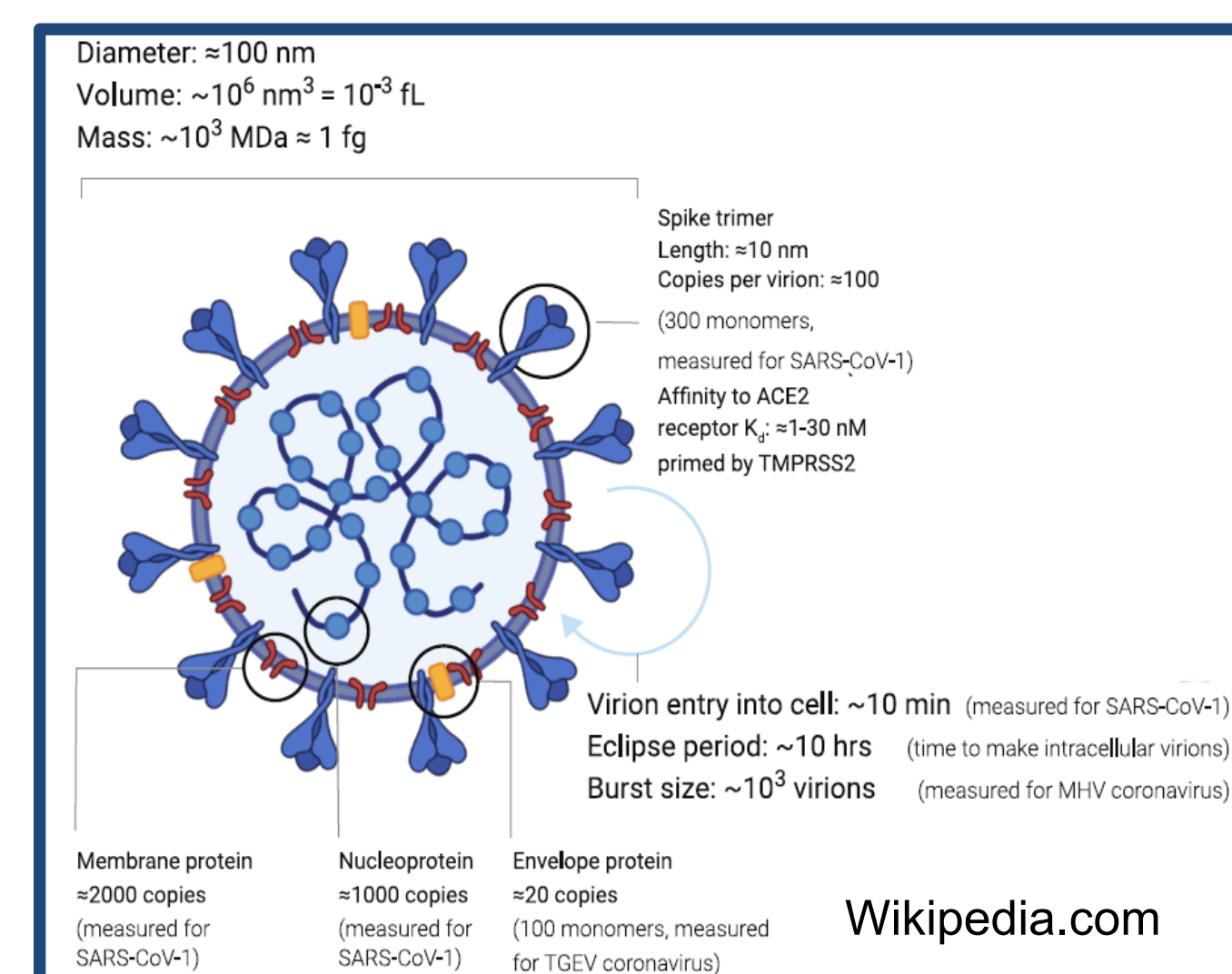
- Wuhan China Developed a Surge of a Unique SARS virus classified as SARS_COV2.
- The virus was unique from SARS_COV which generated a pandemic in Canada and parts of Europe.
- SARS_COV2 has a 5-14 incubation time before symptoms develop resulting in the lack of isolating the virus in China and the current global pandemic.
- Scientific communities around the world focused almost completely on issues related to treatment, containment and managing the socioeconomic consequences of the disease causing virus.
- Directives focused on minimizing viral multiplication, treating patients and understanding the host immune response related to the symptoms ranging from mild to severe.

Greater Cleveland Collaborative

- Case Western Reserve University
- Cleveland Clinic
- MetroHealth Medical Center
- University Hospitals
- Global Collegial/Clinical Interactives

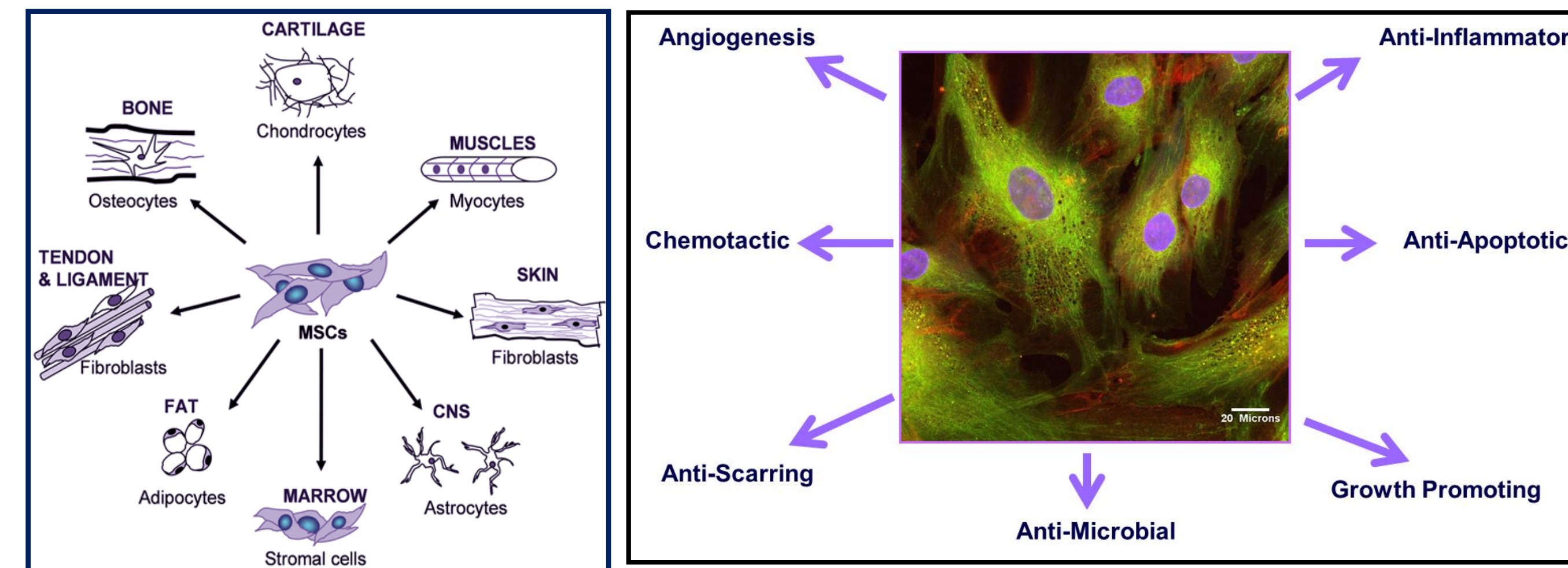
Case Western Reserve University

- Virology and Drug Discovery
- Immunology and Immunotherapeutic
 - T-cell
 - B-cell
 - Innate Immunity
 - Systems Biology
 - Cell Based Therapies
- Clinical Samples and Clinical Trials
- Behavioral Health and Population Outcomes
- Technology
- Safety



Sars-CoV-2 and viral sepsis: observations and hypotheses. Hui Li. Lancet. 2020. 395:1517-1520

Human Mesenchymal Stem Cells (hMSCs)



Mesenchymal Stem Cells (MSCs)

- Are multipotent cells that secrete a variety of bioactive factors that contribute favorably to their environment within damaged tissues
- Have anti-inflammatory, antimicrobial, immunomodulatory, and regenerative properties
- Express low levels of MHC-I molecules and no MHC-2 molecules making them relatively immune-evasive
- Have been evaluated in clinical trials of diseases involving multiple organ systems including bone, cartilage, lungs, pancreas, intestines, neurons, heart, and blood vessels

In clinical trials of CF, Influenza and Acute respiratory Distress Syndrome hMSCs.

- Attenuated pulmonary inflammation
- Decreased bacterial growth
- Enhanced antibiotic efficiency

Rationale

Mesenchymal stem cells have immunomodulatory properties and have previously been studied in a number of respiratory illnesses including ARDS (Lancet Respiratory Medicine 2015 Phase 1 Trial). Infusion of MSCs has been shown to be safe. A small trial of hMSCs in COVID-19 patients showed improvement in inflammatory markers (Aging and Disease) as well as showing by scRNA-seq that hMSCs do not express ACE2 or TMPRSS2, both of which are needed for viral infection of host cells, in significant amounts.

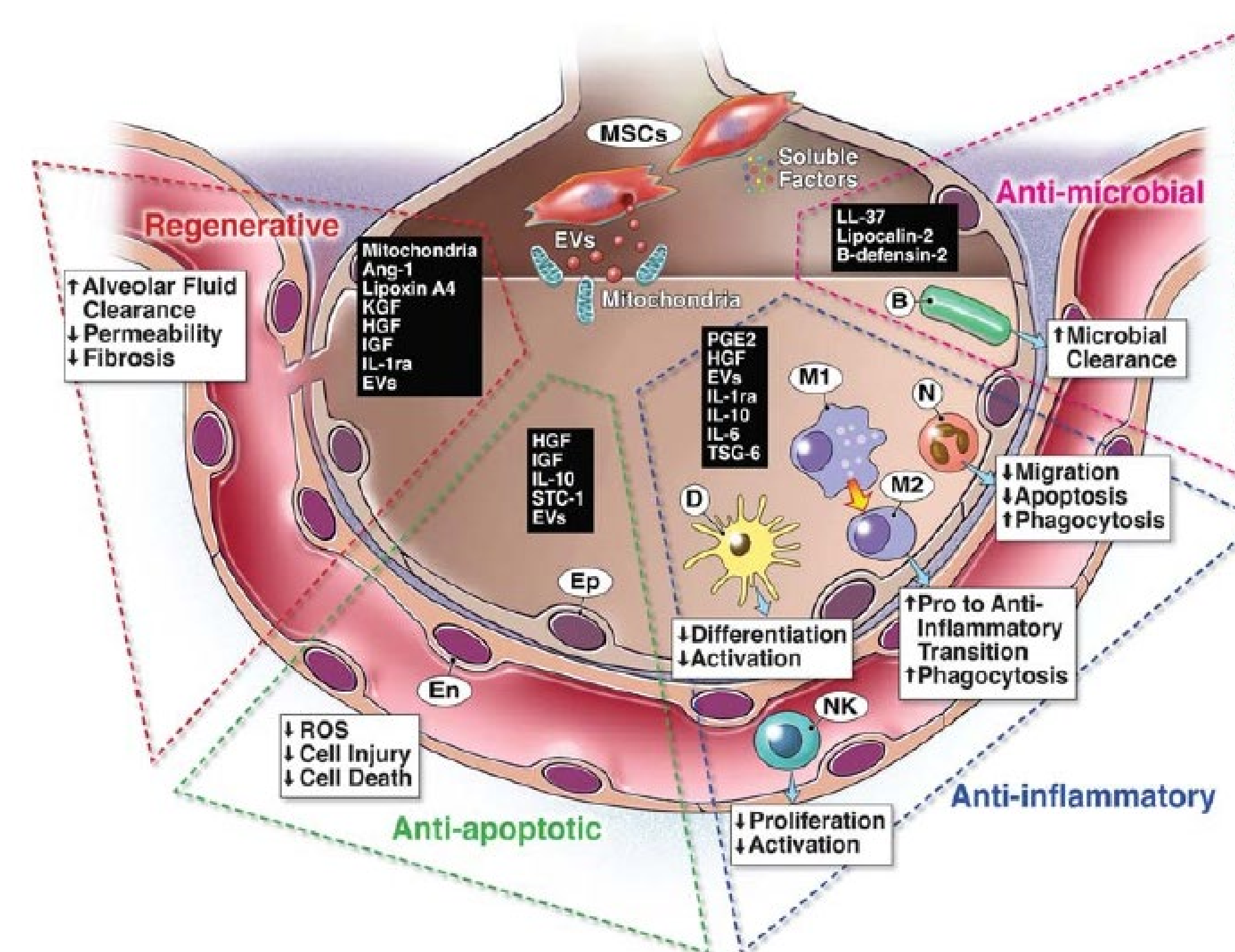


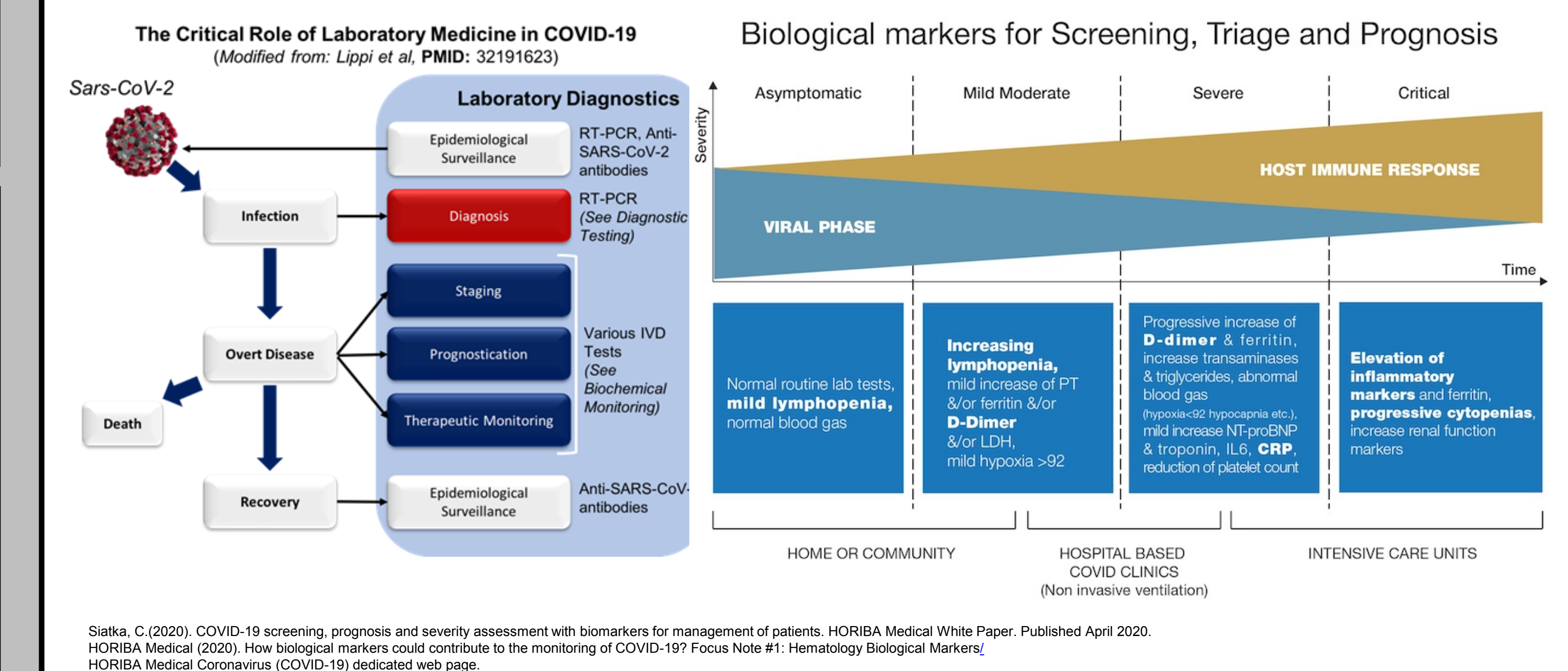
Figure 1. The multifunctional role of MSCs and their secreted factors for resolution of ARDS; B, bacteria; N, neutrophil; D, dendritic cell; NK, natural killer cell; Ep, epithelial cell; En, endothelial cell; PGE2, prostaglandin E2; HGF, hepatocyte growth factor; IL-1ra, interleukin 1 receptor antagonist; IL-10, interleukin 10; IL-6, interleukin 6; TSG-6, tumor necrosis factor-inducible gene 6 protein; IGF, insulin growth factor; STC-1, stanniocalcin 1; Ang-1, angiopoietin 1; ROS, reactive oxygen species.

Antebi et al. The promise of mesenchymal stem cell therapy for acute respiratory distress syndrome. J Trauma Acute Care Surg Volume 84, Number 1. 2017

NIH Clinical Trials of hMSCs in COVID_19 ARDS

Title	Status	Study Results	Conditions	Interventions	Locations
A Study to Collect Bone Marrow for Process Development and Production of BM-MSC to Treat Severe COVID-19 Pneumonia	Not yet recruiting	No Results Available	HC Bone Marrow Donation	Procedure: Bone Marrow Harvest	Cambridge University Hospitals NHS Foundation Trust, Cambridge, Cambridgeshire, United Kingdom
Phase 1 / 2 Clinical Study of Immunotherapy Based on Adoptive Cell Transfer as a Therapeutic Alternative for Patients With COVID-19 in Colombia	Not yet recruiting	No Results Available	COVID	Biological: Allogenic NK transfer	Fundacion Salud De Los Andes, Bogota, Bogota Distrito Capital, Colombia Universidad Nacional de Colombia, Bogota, Cundinamarca, Colombia
Changes in Cellular Immune Profile During COVID-19 Infection	Recruiting	No Results Available	COVID-19 SARS-CoV-2	Other: Leukapheresis	Sevagh Research Institute, Los Angeles, California, United States
Treatment of Coronavirus COVID-19 Pneumonia (Pathogen SARS-CoV-2) With Cryopreserved Allogeneic P-MSCs and UC-MMSCs	Recruiting	No Results Available	COVID-19	Procedure: Placenta-Derived MSCs; Cryopreserved Placenta-Derived Multipotent MSCs Drug: Antibiotics/ Hormones/ Anticoagulant Therapy/ Oxygen therapy	Institute of Cell Therapy, Kyiv, Ukraine
Study of F7516 for the Treatment of COVID-19 in Hospitalized Patients With Hypoxia	Recruiting	No Results Available	COVID-19	Drug: F7516	University of Minnesota, Minneapolis, Minnesota, United States
Treatment of Severe COVID-19 Pneumonia With Allogeneic Mesenchymal Stromal Cells (COVID_MSC)	Recruiting	No Results Available	COVID-19	Biological: Mesenchymal Stromal Cells Other: Placebo	Hospital Universitario Rio Hortega, Valladolid, Spain
Safety and Efficacy Study of Allogeneic Human Dental Pulp Mesenchymal Stem Cells to Treat Severe COVID-19 Patients	Recruiting	No Results Available	COVID-19	Biological: allogeneic human dental pulp stem cells (hDP-MSCs & hDP-BC) (BCT) Other: Intravenous saline injection (Placebo)	Renmin Hospital of Wuhan University (East Campus), Wuhan, Hubei, China
COVID-19 Specific T Cell Derived Exosomes (CSTC-Exo)	Active, not recruiting	No Results Available	Cov2 Infection Pneumonia	Biological: COVID-19 Specific T Cell derived exosomes (CSTC-Exo) Other: Placebo	GEMOIK, Kayseri, Melikgazi, Turkey
Mesenchymal Stem Cell Infusion for COVID-19 Infection	Recruiting	No Results Available	COVID-19	Drug: Mesenchymal stem cells	NIBMFT, Rawalpindi, Punjab, Pakistan
Use of hUC-MSC Product (UC-UMSC) for the Treatment of COVID-19 With ARDS	Not yet recruiting	No Results Available	COVID-19 ARDS	Biological: Human umbilical cord MSC + best supportive care	
Safety and Effectiveness of Mesenchymal Stem Cells in the Treatment of Pneumonia of Coronavirus Disease 2019	Active, not recruiting	No Results Available	COVID-19	Drug: Oxflamivir Drug: Normox; oxygen therapy Procedure: mesenchymal stem cells	Fuzhou General Hospital, Fuzhou, Fujian, China
Monocytes and NK Cells Activity in Covid-19 Patients	Recruiting	No Results Available	COVID-19 Severe ARDS_Cov 2	Diagnostic Test: Study of immune-mediated mechanisms in patients tested positive for SARS-CoV-2	ATS Insubria, Varese, Italy
Clinical Research of Human Mesenchymal Stem Cells in the Treatment of COVID-19 Pneumonia	Recruiting	No Results Available	COVID-19	Biological: UC-MSCs Other: Placebo	Puren Hospital Affiliated to Wuhan University of Science and Technology, Wuhan, Hubei, China

Biomarker for Diagnosis and Treatment



Outline of ARDS Trials and Applications

- Clinical Diagnostics**
- Need for non-invasive ventilator support
- Requirement for intubation and mechanical ventilation.
- Body Temperature, Duration of fever, Changes in systemic
- Biomarkers: C-reactive protein (>5mg/dL), D-dimer and ferritin (>1000mg/dL).
- Innovations in Biomarkers: Study Specific
- Secondary outcomes:**
- Mortality
- Duration of ICU stay
- Duration of hospital stay
- Development of fluid refractory shock
- Change in left ventricular ejection fraction
- SpO2 (<94% on 4L vs 94% on RA)
- Required FIO2
- Change in P/F ratio at 24, 48, 72 hours and 7 and 14 days post hMSC infusion
- Need for supplemental oxygen at 14 days after hMSC infusion

Acknowledgments and References

Inamdar AC, Inamdar AA. *Exp Lung Res.* Oct 2013;39(8):315-327.
Bonfield TL, Lennon DP, Ghosh SK, Dimarino AM, Weinberg A, Caplan AI. *Stem Cell Discovery.* 2013;3:138-159.