

# Could Putting the Mesenchymal Stem Cells Technology into Practice Be an Optimistic Therapy for The Critically Ill COVID-19?

Laila Mahmoud Montaser

Professor of Clinical Pathology, Chair Founder Leader of Clinical Pathology Department, Chair of Stem Cell, Regenerative Medicine, Nanotechnology and Tissue Engineering (SRNT) Research Group, Faculty of Medicine, Menoufia University, Egypt

### Corresponding author

Laila Mahmoud Montaser, Professor of Clinical Pathology, Chair Founder Leader of Clinical Pathology Department, Chair of Stem Cell, Regenerative Medicine, Nanotechnology and Tissue Engineering (SRNT) Research Group, Faculty of Medicine, Menoufia University, Egypt

Submitted: 01 July 2020; Accepted: 07 July 2020; Published: 30 July 2020

## Perspective 2

### Abstract

COVID-19 comes to light, quickly developing status. Daily, we know more about the human new coronavirus (HCoV-19), which is extremely infective with heavy pneumonia connected with fast virus reproduction. Emerging in Wuhan China 31 December 2019, the contemporary COVID-19 outbreak has quickly overripe taking place directly between individuals so contagion extending to be a world health emergency at present on pandemic level. The pandemic has had deep impacts on everyday lifetime towards numerous of the world. Presently no therapy, no specified remedies or inoculations are ready to treat the patients with COVID-19 pollution and investigators here and there the globe are jostling to recognize present medication or synthesis that could be functional versus it. Therefore, there is a great unmet requirement for a secure and efficient therapy for COVID-19 contaminated cases, particularly the serious cases. What types of therapies might now assist? What are the lab craft strategies to restraining coronavirus? Ago mid-February, one tactic that has acquired rising attraction is stem cell therapy, curing that have often been saw as a potential magic bullet by despairing patients suffering from degenerative incurable conditions. In plentiful of these diseases, truth has so far to coincide with the hype. The cell based-therapy doings by supporting the body's precocious refractory reply in an orientation that could goal the coronavirus. Now stem cell-based therapy for COVID-19 is earning incentive in China. The tally of the world emergency has visible governments frequently proclamation the company global to develop in the search for a cure, and the Australian corporate Mesoblast – a global commander in cell-based therapies for a lot of illnesses – are earned recently the approval to start clinical trials of their possess stem cell based product against COVID-19. Taking into consideration that generality of the dead sick people were produced by serious inflammation reaction, it is extremely demanding to advance efficient curative factors and strategies for that cases. I present an accurate lab modality in preparing mesenchymal stem cells (MSCs) which might be a perfect option to cure the seriously sick novel COVID-19 cases. Beneath this situation, I suppose that blood derived MSCs generated from the critically ill novel COVID-19 patient itself (autologous) suggested as a treatment for him. Therefore, my viewpoint spots a modern curative strategy.

The total workflow involved in the suggested treatment of new COVID-19 cases using MSCs from the patient (autologous) schematic symbolized in figure 1

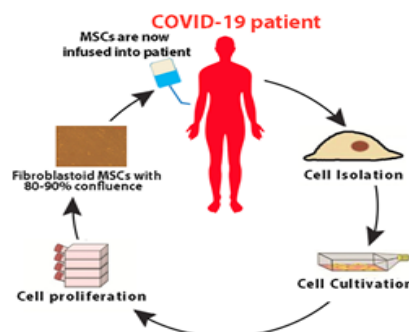


Figure 1: Schematic Sketching the Workflow of Proposition (Graphic Design by Sherin Design)

Blood obtained from the patient (autologous) for isolation, cultivation, proliferation of MSCs (in vitro) and subsequently transplanted into him. The start of fibroblast-like cell figuration of harvested MSCs could be spotted at day 3 or 4; MSCs cultivate as a layer one molecule thick of large flat cells. At day 7, display fibroblast-like cells having many poles and extremities and 60-70% confluence, which slowly grew to reach 80-90% confluence around the 9<sup>th</sup> day.

Ago January while the World Health Organization (WHO) specified the eruption of the new coronavirus disease, COVID-19, to be a “public health contingency of global anxiety”, strain grades anywhere have persisted to ascend. On the 23rd of March WHO has heraldic that the coronavirus disease pandemic is “quickenning”, with more than 300,000 patients at present proved. It took 67 days from the initial announced of Covid-19 to attain 100,000 patients, 11 days for another 100,000, and solely four days for the tertiary 100,000. But WHO Director General Tedros Adhanom Ghebreyesus told it was yet perspective to “modify the path” [1].

COVID-19 is a serious acute respiratory disease produced by a novel coronavirus designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Presently, treating COVID-19 cases, especially these stricken with severe pneumonia, is confronting despite no specified remedies or vaccines in opposed to SARS-CoV-2 are obtainable. Thence, MSC treatment prohibiting the too much energizing of the immune system and boosting internal reform by enhancing the lung microenvironment after the SARS-CoV-2 contagion is amazing [2].

In the role of WHO and health facilities towards the globe work to inhibit the pandemic, exhortation on safeguarding your authenticity and thus WHO requests for critical, violent measures to battle the virus? [3]. Thence, suggestion of a remedy with reachable, logic and viable manner is desperately required [4]. Every searcher is necessarily to cognize several significant lab technicalities to be competent in lab experimentations.

MSCs have been most applied in stem cell-based treatment; from requisite research to clinical experiments security and validation have been obviously certified in numerous clinical tests, particularly in the immune-mediated inflammatory illnesses [5].

The area of the proposition is to improve and use the MSCs from the patient itself, which could relieve the troubles correlated with the impairment of therapies or vaccines against the new coronavirus. Stem cells are suggested stand by for containing COVID-19. What we must be centering on immediately is performing accurate experiments so stem cells can contain COVID-19 patients.

This paper endeavors at serving as a guide for researchers and investigators, identifying my *in vitro* technology using MSCs and summarizing my prospects regarding COVID-19. My target is to find an optimum technique for curing the new coronavirus cases using MSCs acquired from the patient (autologous).

### Mesenchymal Stem Cell Preparation Protocol

MSCs are isolated under defined culture conditions as per the protocol standardized and optimized in my lab. Informed consent is taken from the patients before sampling. MSCs are produced by

drawing 100ml of blood (up to five multiples) from the patient in sterile heparinized ten 10 ml vacutainer tubes to be handled within 6 hours. Under complete aseptic conditions, the blood in each tube is diluted with sterile Calcium- and Magnesium-Free Phosphate-Buffered Saline (PBS) (Dulbecco's from Invitrogen) in the ratio of 1:1 and are mixed well then layer as two volume of blood to one volume of ficoll-hypaque (Bichrom AG, Leonorenstr, Berlin) in 15 ml conical centrifuge tubes to be centrifuged for 20 minutes at 1800 rpm. Collection of the mononuclear cells (MNCs) fraction is done using a pasteur pipette to be washed twice in sterile PBS and cell pellet is suspended in 1 ml DMEM-media (Thermo Scientific, Fermont, USA). Cell counting and viability are assessed by the vital stain trypan blue dye 0.4% (Sigma Aldrich) using a hemocytometer. MNCs suspensions of  $1 \times 10^6$  cells/ ml concentration are plated and allowed adhering to tissue culture plastic flasks 25 cm<sup>2</sup>. For proper adherence of the cells, the flasks are incubated in a horizontal position in a humidified incubator at 37°C and 5% CO<sub>2</sub>. The used nutrient media is constituted of the following: low glucose DMEM (DMEM-LG) with L-glutamine (2mmol/L) (Lonza), 10% FBS (Lonza), 2% penicillin-streptomycin (10,000 U/ml and 10,000 µg/ml) (Sigma Aldrich) and 1% Fungizone (250 mg/ml) (Bioscience). The media are examined by naked eye to look for signs of microbial contamination, and then examined under the inverted microscope (100-400X) for assessment of the cell morphology (fibroblast-like appearance, viability of cells, and microbial contamination). The first change of the media is accomplished at 3<sup>rd</sup> - 5<sup>th</sup> day to remove non-adherent cells; the adherent cells are kept in the flasks and are fed by fresh complete nutrient media. The media is changed twice weekly until reaching 80-90% confluence which is assessed by examination under the inverted microscope and then the cells are detached using trypsin-EDTA 0.25% solution. For trypsinization: one to 3 ml of trypsin-EDTA detachment solution is added to each flask. The closed flasks are gently shaken and taped on the sides to completely immerse the cells. After complete detachment, DMEM containing 1% serum is added at the same volume as the volume of trypsin used. The cells are transferred to centrifuge 15 ml falcon tubes and centrifuged at 1800 rpm for 10 minutes. The supernatant is removed and the cells are suspended in complete media as a single cell suspension. The harvested MSCs from primary culture are evaluated by flowcytometric characterization of MSCs according to the international guidelines for stem cell identification.

I'm studied and examined MSCs with my team for years and my leading profound-practice in this domain ago more than decennium as a model of a technological and research-based success may supply significant historic harbingers that are favorable, hopeful and worthy as humanness presently confronts the COVID-19 pandemic [6-20].

Two new studies from China have required, can MSC cure COVID-19 pneumonia, the 1st study is a case record of a seriously sick COVID-19 case on a ventilator who had deteriorated in spite of intense treatment, with signs exhibiting index of hepatic deterioration. This case was cured with allogeneic human umbilical cord MSC (hUCMSC) employing 3 intravenous injections of  $5 \times 10^7$  hUCMSC, every 3 days. During 4 days the 1st MSCs injection, the case was away the ventilator and capable to gait. Whole measured parameters returned towards normal levels. No apparent side sequels were spotted [21]. The 2nd study by Leng and colleagues announced that intravenous injection of clinical-grade human MSCs into seven patients with coronavirus disease 2019 (COVID-19) outputted in

amended effective results. This study explained that intravenous injection of MSCs is a secure and efficient manner for curing cases with COVID-19 pneumonia, inclusive aged cases exhibiting serious pneumonia [22].

An investigational study released to estimate the effectiveness of NestCell® (MSC) to cure critical COVID-19 pneumonia. NestCell® is a MSC remedy manufactured by Cellavita and manifested to be secure in former clinical experiments. The objective of the study is value the efficiency of NestCell® as a supplement treatment to criterion therapy to cure cases with serious COVID-19 pneumonia. Whole cases will get  $1 \times 10^6$  cells/kg weight every 3 days [5].

Mesoblast Limited (the regenerative medicine company), world commander in cellular drugs for inflammatory diseases, declared that it has gained redemption from the United States Food and Drug Administration (FDA) in the field of investigation Novel medicine implementation to cure cases with acute respiratory distress syndrome (ARDS) caused by coronavirus infection (COVID-19) with intravenous infusions of its allogeneic MSC manufacture applicant remestemcel-L [23].

FDA has presented contingency license, an increasing figure of clinicians utilize convalescent plasma (given blood from recovered COVID-19 cases) to transmit to critical ill cases. About the most progressing border, the FDA has provided the gesture to a numeral of stem cell treatment companies also; a motivating tactic due to their immunomodulatory drives furthermore their regenerative features which could be applicable on destroyed lungs [24].

My viewpoint coincides with the perspective of Chrzanowski et al who adduced that MSCs could be the extreme hopeful nominee for the therapy of COVID-19 contagions [25]. As the clef for the remedy of that crisis ambushes in the administration of the cytokine storm in the lungs, MSCs are fully-suitable taking into account their major process of work is via their immunomodulatory and dis-inflammatory effects [26].

My perspective agrees with the viewpoint of Golchin and colleagues who reported that next the intravenous injection of MSCs, a considerable number of cells collects in the lung, that they beside immunomodulatory impact could keep alveolar epithelial cells, adjust the microenvironment of lung, stop lung fibrosis, and healing deterioration of the lung function [28]. Also in their research, they theorized that novel tactic to ameliorate sick cases' immunological replies to COVID-19 utilizing MSCs. They reported that stem cell remedy and particularly MSCs may perhaps be one of the maximum idealistic therapeutics to cure new coronavirus cases [27].

In conclusion, respiratory distress murder many thousands of people yearly globe, and hundreds of clinical tests are experimenting medicines to cure it. During a pandemic, it's logical to do several experimentations of uncertain interferences like stem cells in tiny academic works, but outcomes from them must be explored in a programmatic, moderate modality till there is too proof. With life-menacing patients, we believe it's fundamental to utilize MSC therapy if no other soporific is obtainable. Requisition the MSC therapy as an interesting concept but the lone road is to attempt and vision. As the COVID-19 pandemic persists to expand, we are hoping driving it as better we mastery. Concurrently, we will

continue to make valuable research, studies analysis, and prudent comments. The precision of the lab modality in preparing MSCs is especially substantial for COVID-19 therapies for best clinical results. We may get to start somewhere. MSCs separated from blood or bone marrow (BM) are considered the gold criterion for MSC implementations. Since few months on Sunday (April 5 2020) the US FDA ratified MSC therapy for utilize in the highly diseased COVID-19 cases beneath what's recognized like widened merciful employ. We have to throw a decisive look on science inventions, explore emerging lab strategies for COVID-19 treatment. I present indispensable visions on the technologies leadership could lead to a revolt in humanitarian healthiness.

## References

1. WHO (2020). Coronavirus: Pandemic is 'accelerating', WHO warns as cases pass 300,000. Available at: <https://www.bbc.com/news/world-52010304>
2. Shetty AK (2020). Mesenchymal Stem Cell Infusion shows promise for Combating Coronavirus (COVID-19) - Induced Pneumonia. *Aging and disease*; 11: 462-464.
3. WHO (2020). Rolling updates on coronavirus disease (COVID-19). Available at: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen>
4. Montaser LM (2020). *Editorial: A therapeutic approach from lab to clinic in the domain of the disease caused by the novel coronavirus according to an Egyptian scientist*. *CPQ Medicine* 8: 1-7.
5. Brasil A (2020). NestCell® Mesenchymal Stem Cell to Treat Patients with Severe COVID-19 Pneumonia (HOPE). Available at: <https://clinicaltrials.gov/ct2/show/NCT04315987>
6. Montaser LM (2020). *Keynote speech: Contemporary Tissue Engineering Approaches for Cartilage Renovation*. Presented at: 31<sup>st</sup> European Congress on Nanotechnology and Materials Engineering. Available at: <https://nanotechnology-materialscience.materialsconferences.com/abstract/2020/contemporary-tissue-engineering-approaches-for-cartilage-renovation>
7. Montaser LM (2020). *Editorial: A Feminist Scientist Shouts Conveying I Am Here*. *Journal of Embryology & Stem Cell Research* 4: 1-3.
8. Montaser LM, El-Azab DS, Kotb EAZ (2020). Mesenchymal stem cell applications on the chronic liver disease. *Men Med J* 33: 236-242.
9. Montaser LM, El-Azab DS, Tawfeek GA, Saied SA (2019). Applications of bone marrow-derived cells in acute liver disease. *MMJ* 32: 1496-1500.
10. Montaser LM, Fawzy SM (2019). Novelities in Cartilage Tissue Regeneration using Nano Scaffolds. Presented at: 3rd International Conference on Materials Science and Research (ICMSR), *Int J Mater Sci Res.* 2: 22.
11. Montaser LM (2019). *Keynote Speech: Nano-approach in articular cartilage tissue regeneration*. Presented at: 4<sup>th</sup> Int Conf on Materials Chemistry & Science and 5<sup>th</sup> Int Conf on Nanotechnology for Renewable Materials, *J Chem Appl Chem Eng* 3: 41.
12. Montaser LM (2018). *Editorial: Outcomes of technology's epic success stories in the field of regenerative medicine and tissue engineering*. *Adv Tissue Eng Regen Med* 4:100-101.
13. Montaser LM, Fawzy SM (2018). Nanotechnology for articular cartilage regeneration. Presented at: Int Conf on Nanotechnology

- and Nanoengineering July 2018, Paris, France, J Nanomater Mol Nanotechnol; 7: 71-71.
14. Montaser LM (2018). *Keynote Speech: Hepatic Tissue Engineering and Regenerative Medicine*. Presented at: World Biotechnology Congress 2018, J Med Biotechnol 2: 16. Available at: <https://www.pulsus.com/conference-abstracts-files/biotechnology-2018-keynote.digital/files/assets/basic-html/page-5.html>
  15. Montaser LM (2017). *Editorial: Usage of Stem Cell, Regenerative Medicine, Nanotechnology and Tissue Engineering Science Education to Improve Stem Cell and Nano-Science Literacy*. Adv Tissue Eng Regen Med 2:168-169.
  16. Montaser LM (2016). *Editorial: Regenerative Medicine and Tissue Engineering-Driven Innovation of Medical Science and Technology*. Adv Tissue Eng Regen Med Open Access 1: 1.
  17. Montaser LM, Abbassy HA, Fawzy SM (2016). Articular cartilage tissue engineering with plasma-rich in growth factors and stem cells with Nano *scaffolds*. Proc. SPIE 9930, 99300V, San Diego, CA, USA.
  18. Montaser LM, Fawzy SM (2015). NANO *scaffolds* and stem cell therapy in liver tissue engineering. Proc SPIE 9550, 95500M, San Diego, CA, USA.
  19. Montaser LM, Fawzy SM (2014). Promising cell therapy achieves improvement outcomes. Presented at: Int. Society for Experimental Hematology (ISEH) 43 Annual Scientific Meeting, Experimental Hematology - J for hematology, stem cell biology and transplantation 42: 53-53.
  20. Montaser LM, Metwally HG, Elbasuoni MA, Tawfeek GA (2014). Human Mesenchymal Stem Cells as a Potential Source for Cell Therapy in Liver Disorders. World Academy of Science, Engineering and Technology. International Journal of Biotechnology and Bioengineering 8: 1. Available at: <https://waset.org/member/lailamontaser>
  21. Liang B, Chen J, Li T, Wu H, Yang W, et al. (2020). Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells. Available at: <http://chinaxiv.org/abs/202002.00084>
  22. Leng Z, Zhu R, Hou W et al (2020). Transplantation of ACE2-Mesenchymal Stem Cells Improves the Outcome of Patients with COVID-19 Pneumonia. Aging and disease 11: 216-228.
  23. Williams R (2020). Are mesenchymal stem cells a promising treatment for covid-19? Available at: <https://www.the-scientist.com/news-opinion/are-mesenchymal-stem-cells-a-promising-treatment-for-covid-19--67402>
  24. TRIALSITE NEWS (2020). The FDA Approving Experimental Stem Cell Therapies Targeting Patients with Severe COVID-19 Cases. Available at: <https://www.trialsitenews.com/the-fda-approving-experimental-stem-cell-therapies-targeting-patients-with-severe-covid-19-cases/>
  25. Chrzanowski W, Kim SY, McClements L (2020). Can Stem Cells Beat COVID-19: Advancing Stem Cells and Extracellular Vesicles Toward Mainstream Medicine for Lung Injuries Associated with SARS-CoV-2 Infections? Front Bioeng Biotechnol 8: 1-8.
  26. Fatima F, Ekstrom K, Nazarenko I, Maugeri M, Valadi H, et al. (2017). Non-coding RNAs in mesenchymal stem cell-derived extracellular vesicles: deciphering regulatory roles in stem cell potency, inflammatory resolve, and tissue regeneration. Front Genet 8: 1-13.
  27. Golchin A, Seyedjafari E, Ardeshirylajimi A (2020). Mesenchymal Stem Cell Therapy for COVID-19: Present or Future, Stem Cell Rev Rep 13: 1-7.

**Copyright:** ©2020 Laila Mahmoud Montaser. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.