

Cell-based treatments for COVID-19

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The COVID-19 pandemic, caused by the SARS-COV-2 coronavirus, has ripped through the globe with severe social and economic impact. The significant morbidity and mortality of COVID-19 and the resulting overburden on healthcare systems everywhere highlight the pressing need for new therapies, including cell- and gene-based therapies. It is heartening to witness the international coordinated scientific efforts from various disciplines (immunology, virology, cell biology etc.) to understand the structure, transmission mechanisms, and cellular tropism of SARS-COV-2 and the pathophysiology of COVID-19 ¹. Such studies provide several potential targets for drug and cell therapy.

Indeed, multiple pharmacological and cell-based treatments are currently under investigation in numerous interventional studies, including placebo-controlled studies ²⁻⁴. Proposed cell-based approaches include use of mesenchymal stromal cells (MSC), natural killer (NK) cells, and exosomes and they are mostly immunomodulatory in nature, e.g. tackling COVID-19-associated “cytokine storm”.

At the same time, and perhaps not surprisingly, profiteers have started taking advantage of the fear and desperation caused by the pandemic. There is a surge of unproven and questionable treatments and test kits for coronavirus, some of which are outright fraudulent ⁵. These also include direct-to-consumer cell-based or cell-derived interventions marketed as allegedly effective treatments or even cures for COVID-19. Regulatory agencies, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have taken notice ^{6,7}. Indeed the FDA has issued letters to businesses offering unproven treatments for COVID-19 and has warned against unfounded therapeutic claims ^{8,9}.

Several scientific and professional organizations have also stepped up and issued statements of concern regarding marketing of unproven “stem cell” treatments (see **Table 1** for a list of statements from eight organizations). The ISCT released its statement on March 20 and followed up on March 25 with a proposed plan of action to counteract such practices. There are a few points worth emphasizing in the ISCT statement as well as in the other statements of concern. Unfortunately, purported “stem cell” treatments for various conditions have been around for a long time and present a borderless, global challenge to the legitimate development of cell and gene therapies ^{10,11}. Similar offerings for COVID-19 are the latest example of businesses flouting regulatory and ethical rules related to clinical translation of cell-based treatments ¹². Another fact highlighted in all the statements is that there are currently **no approved and proven cell-based therapies for either the prevention or treatment of COVID-19**. This important point should frame the discussion about current options and future development of cell-based therapeutics for COVID-19.

For example, there are lay press reports, based mostly on company press releases and non-peer-reviewed pre-prints, of allegedly highly effective cell-based interventions for COVID-19 induced acute respiratory distress syndrome (ARDS) ¹³⁻¹⁵. Talk about patients “saved by stem cell therapy”, miraculous and/or complete recovery, and COVID-19 cures amounts to irresponsible and sensationalist reporting. Most importantly, uncritically positive press reports obscure the limited utility of such clinical findings. These are preliminary results, mostly coming from compassionate use of cells, without any control groups or long-term patient follow-up. They cannot and should not substitute for well-designed, blinded and appropriately powered clinical trials to demonstrate safety and efficacy. In a similar vein, regenerative medicine products that have been green-lighted for COVID-19 patient clinical studies should not advertised as “approved” by regulatory agencies.

Likewise, pleas to use the current pandemic as a “deregulatory opportunity”, extensive use of US Right-to-Try laws for COVID-19 drug development, and bypassing of established regulatory pathways by being “bold and innovative” ^{14,16} must be resisted by the regenerative medicine community and our Society. Until a preventive SARS-COV-2 vaccine is clinically validated and mass produced, we may expect several resurgent waves of COVID-19 ¹⁷. Thus, wide availability of untested and unproven treatments, including cell-based interventions, may sound appealing due to the severity, extent, and potential recurrence of the COVID-19 pandemic. Yet, it threatens time-tested approaches for drug evaluation, which also cover cell- and gene-based treatments, as has been convincingly argued elsewhere ¹⁸⁻²⁰.

In these unprecedented times, ISCT should continue leading the scientific and ethical way “to translate cellular therapy into safe and effective therapies to improve patients' lives”. We need to be continuously vigilant about efforts to undermine this mission and offers of cell and gene products without established therapeutic value for COVID-19 and its complications.

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Table 1. Statements of concern on unproven cell-/cell-derived interventions for COVID-19

Organization	Web link
International Society for Cell and Gene Therapy (ISCT)	https://isctglobal.org/news/news.asp?id=494824 https://isctglobal.org/news/497106/ISCT-takes-a-stand-against-organizations-marketing-unproven-COVID-19-cell-and-gene-therapies.htm
International Society for Stem Cell Research (ISSCR)	https://www.isscr.org/news-publicationsss/isscr-news-articles/article-listing/2020/03/06/isscr-statement-regarding-the-marketing-of-unproven-stem-cell-treatments-for-covid-19
EuroStemCell	https://www.eurostemcell.org/stem-cells-and-covid-19

Canadian Stem Cell Network	https://stemcellnetwork.ca/warning-claims-of-stem-cell-treatments-for-covid-19-unfounded-and-misleading/
Centre for Stem Cell Systems (The University of Melbourne)	http://www.stemcellsaustralia.edu.au/News---Events/News/Warning-about-unproven-stem-cell-treatments-for-COVID-19.aspx
German Stem Cell Network	https://gscn.org/
Stem Cell Network North Rhine-Westphalia	https://www.stammzellen.nrw.de/en/newsroom/article/statements-on-covid-19-and-stem-cells
Alliance for Regenerative Medicine	https://alliancerm.org/bioethics/stem-cell-clinical-trials/

References

- Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*. 2020;181(2):271-280.
- Alliance for Regenerative Medicine. Ongoing Regenerative Medicine Clinical Trials to Treat COVID-19 & Related Complications. 2020; <https://alliancerm.org/wp-content/uploads/2020/03/Clinical-Trials-3.pdf>. Accessed April 17, 2020.
- Khoury M, Cuenca J, Cruz FF, Figueroa FE, Rocco PRM, Weiss DJ. Current Status of Cell-Based Therapies for Respiratory Virus Infections: Applicability to COVID-19. *Eur Respir J*. 2020;doi: 10.1183/13993003.00858-2020.
- Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *JAMA*. 2020;doi: 10.1001/jama.2020.6019.
- Ormseth M, Rubin J. Fake cures, scams, phony medications and price gouging: Predators pounce during coronavirus. 2020; <https://www.latimes.com/california/story/2020-04-14/coronavirus-home-test-treatment-scams>. Accessed April 17, 2020.
- Food and Drug Administration. Coronavirus (COVID-19) Update: FDA Alerts Consumers About Unauthorized Fraudulent COVID-19 Test Kits. 2020; <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-alerts-consumers-about-unauthorized-fraudulent-covid-19-test-kits>. Accessed April 17, 2020.
- European Medicines Agency. COVID-19: Beware of falsified medicines from unregistered websites. 2020; <https://www.ema.europa.eu/en/news/covid-19-beware-falsified-medicines-unregistered-websites>. Accessed April 17, 2020.
- Food and Drug Administration. April 1 2020 Untitled Letter - Dynamic Stem Cell Therapy. 2020; <https://www.fda.gov/media/136668/download>. Accessed April 1, 2020.
- Food and Drug Administration. April 7 2020 Warning Letter - Savvy Holistic Health dba Holistic Healthy Pet 2020; <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/savvy-holistic-health-dba-holistic-healthy-pet-605915-04072020>. Accessed April 14, 2020.

10. Berger I, Ahmad A, Bansal A, Kapoor T, Sipp D, Rasko JEJ. Global Distribution of Businesses Marketing Stem Cell-Based Interventions. *Cell Stem Cell*. 2016;19(2):158-162.
11. Turner L, Knoepfler P. Selling Stem Cells in the USA: Assessing the Direct-to-Consumer Industry. *Cell Stem Cell*. 2016;19(2):154-157.
12. Harris E. ISCT On The Marketing Of Unproven COVID-19 Cell And Gene Therapies. 2020; <https://www.cellandgene.com/doc/isct-on-the-marketing-of-unproven-covid-cell-and-gene-therapies-0001>. Accessed April 17, 2020.
13. Jaffe-Hoffman M. Israeli COVID-19 treatment shows 100% survival rate - preliminary data. 2020; <https://www.jpost.com/HEALTH-SCIENCE/Israeli-COVID-19-treatment-shows-100-percent-survival-rate-preliminary-data-624058>. Accessed April 17, 2020.
14. Chen S. Coronavirus: critically ill Chinese patient saved by stem cell therapy, study says 2020; <https://www.scmp.com/news/china/society/article/3053080/coronavirus-critically-ill-chinese-patient-saved-stem-cell>. Accessed April 17, 2020.
15. Parry R. Chinese doctor claims he made a breakthrough in coronavirus pandemic with stem cell injections - having 100% success rate after treating nine mostly elderly patients. 2020; <https://www.dailymail.co.uk/news/article-8116881/Doctor-claims-breakthrough-stem-cell-injections-treat-coronavirus.html>. Accessed April 17, 2020.
16. Mulligan CB. The COVID-19 Plague Considered as a Deregulatory Opportunity. 2020; <https://www.nationalreview.com/magazine/2020/05/04/the-covid-19-plague-considered-as-a-deregulatory-opportunity/>. Accessed April 17, 2020.
17. Kissler SM, Tedijanto C, Goldstein E, Grad YH, Lipsitch M. Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. *Science*. 2020;doi: 10.1126/science.abb5793:eabb5793.
18. Rome BN, Avorn J. Drug Evaluation during the Covid-19 Pandemic. *N Engl J Med*. 2020;doi: 10.1056/NEJMp2009457.
19. Robertson C, Bateman-House A, Lynch HF, Joiner K. In the rush to innovate for COVID-19 drugs, sound science is still essential. 2020; https://theconversation.com/in-the-rush-to-innovate-for-covid-19-drugs-sound-science-is-still-essential-134638?utm_source=twitter&utm_medium=bylinetwitterbutton. Accessed April 17, 2020.
20. Goodman JL, Borio L. Finding Effective Treatments for COVID-19: Scientific Integrity and Public Confidence in a Time of Crisis. *JAMA*. 2020;doi: 10.1001/jama.2020.6434.