Biomaterials Translational

Mesenchymal stem cells and COVID-19: the process of discovery and of translation

*Arnold I. Caplan**

Key Words:
COVID-19; discovery research; mesenchymal stem cell; translation

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ABSTRACT

Mesenchymal stem cells were developed as a cell-based therapeutic in the 1990's. The translation of culture expanded mesenchymal stem cells from a basic science focus into a modern therapeutic has taken 30 years. The current state of the basic science information argues that mesenchymal stem cells may be curative for coronavirus disease 2019 (COVID-19). Indeed, early small-scale clinical trials have shown positive results. The issue raised is how to assemble the resources to get this cell-based therapy approved for clinical use. The technology is complex, the COVID-19 viral infections are life threatening, the cost is high, but human life is precious. What will it take to perfect this potentially curative technology?

Skeletal Research Center, Department of Biology, Case Western Reserve University, Cleveland, OH, USA.

***Corresponding author:**
Arnold I. Caplan, arnold.caplan@case.edu.

http://doi.org/10.12336/biomatertransl.2021.04.006

How to cite this article:
Caplan, A. I. Mesenchymal stem cells and COVID-19: the process of discovery and of translation. *Biomater Transl.* **2021**, *2*(4), 307-311.

Introduction

The process of discovery and translation are very different, with different rules and rewards. Both have unimagined timeframes (very long), and the end-rewards turn out to be personal, potentially societal but, in many cases, not financial. I detail these events and focus on these two very different logics not to discourage the young, naïve investigators and entrepreneurs but rather to document that, at the goal line, there is the opportunity for a huge personal satisfaction and pride (both rare and expensive commodities in terms of human currency). This treatise also allows me the opportunity to lay out in a limited way, both the good and the bad of these processes, the pitfalls and the summits that one must overcome. A scholarly treatise like this must be properly referenced; but, here, I will be skimpy with references because no matter whose work I reference, many other contributors will be left out and offended. Clearly, I will over-reference my own publications, many of which are more suitably and broadly referenced.

Today: Mesenchymal Stem Cells Can Be Curative for Coronavirus Disease 2019 Infections

In 1991, I named rare, cell culture isolated and expanded human bone marrow derived cell populations, mesenchymal stem cells (MSCs).[1] I felt justified in using this "stem cell" nomenclature because, *in vitro*, my colleagues and I could show using powerful inductive conditions and reagents that these cells could form fat, muscle, cartilage and other connective tissues in culture. The dogma of the day was that what we saw in culture is what happened *in vivo*. We now know that these MSCs do not differentiate in your body into any of these phenotypes.[2] Moreover, the stem cell nomenclature has been currently grossly misused by a (relatively few) number of bad actors (some clinics and practitioners) to promise stem cell and regenerative therapies in situations where MSCs are not provided such as the situations where platelet rich plasma or concentrated bone marrow are provided. Many thousands of publications have used this MSC nomenclature,[3, 4] and in some cases, inappropriately focuses on the capacity of these pliable cells to differentiate in cell culture into a number of adult phenotypes. Again, I was wrong in calling them stem cells, they are not, and I have, for reasons listed below, renamed these cells **M**edicinal **S**ignaling **C**ells.[5]

MSCs are not *stem cells* and, we now know, that they arise from perivascular cells, pericytes, that sit on the outside of every blood vessel in your

body.[6,7] When the blood vessels break or become inflamed, the pericyte detaches from their basement membrane anchorage of the blood vessel and, these released cells, then differentiate into MSCs. These newly differentiated MSCs survey the surrounding environment and have a built-in secretome response to that sensed unique microenvironment.[8] This response involves the synthesis and secretion of a variety of bioactive molecules. The MSCs function in its genetically controlled paracrine capacity which affects the local biology of that tissue and sets up the functioning of other effector cells, such as monocytes, macrophage and T-cells, that have entered into this localize site of tissue damage.[9,10] Indeed, MSCs isolated and expanded in cell culture when infused into the blood system or injected into a specific tissue site, home to the injured tissue because that's where these MSCs normally do business.[11]

MSCs have been shown in animal models and in human clinical trials to:

1. Manage the local immune system and thus provide immunomodulatory capabilities.

2. Produce *trophic factors*[12] which:

A. Sit on opioid receptors and manage pain.[13]

B. Inhibit scar formation and stimulate the removal of scar.[14]

C. Produce tissue specific mitogens for tissues specific and tissue intrinsic progenitors to organize and stimulate true innate tissue regeneration.[15]

D. Stimulate angiogenesis.

E. Stabilize newly formed and fragile blood vessels by becoming pericytes again.[11]

F. Produce antibiotic peptides that kill bacteria on contact and, also, have antiviral capabilities.[16,17]

G. Stimulate wound closure.[18]

Currently, there are over 1200 listings of clinical trials on clinicaltrials.gov, testing MSCs in over 900 medical conditions. Such clinical trial successes will depend on one or more of the trophic activities listed above. These trial listings include over 100 clinical trials to treat patients with severe acute respiratory syndrome-associated coronavirus 2 (SARS-CoV-2) infections, coronavirus disease 2019 (COVID-19).

The hypotheses behind these MSC-COVID-19 clinical trials are that MSCs:

- can manage the inflammatory cytokine and other bioactive factor surges,
- can facilitate lung tissue regeneration,
- can close the holes in the lung blood vessel system,
- can kill the bacteria that are massively infected in the lung,
- can stop the lung pain,
- and based on the new research now being done in my laboratory with talented colleagues from Case Western Reserve University, can produce antibiotic/antiviral proteins in the lung; these unique peptides, cathelicidin LL-37 and human beta-defensin 2, can bind to both the spike protein of the SARS-CoV-2 virus and/or the angiotensin-converting enzyme 2 receptors and, thus, effectively take the virus out of its normal, expansive re-infection cycles.[19] Another group likewise recently published similar findings.[20]

Based on these suppositions, I predict that MSCs have the possibility to be curative for COVID-19 patients.

Translation

This brings us to the translation of cell-based therapies using MSCs from basic science through clinical trials to Food and Drug Administration of USA (FDA) or regulatory agency approval. If all that I have written above is correct or even half of it is correct, hundreds, if not thousands, of COVID-19 patients should now be involved in MSC-clinical trials using both commercially produced and academically available in investigator-and company-initiated trials. This is not the case because:

1. Over 160 new drug applications have been approved by the FDA for the use of cells, drugs and devices for COVID-19 patients, and, thus, producing a vigorous competition in various intensive care units for COVID-19 patients to be enrolled in one or more of these approved trials.

2. The pharmaceutical industry has influenced regulators and clinicians to believe that only a single-action drug whose mechanism of action is known should be used for the ailments involved in COVID-19 infections and, indeed, none of these are thought to be curative (they are palliative) although some multiple monoclonal antibody drugs are quite useful.

3. Moreover, the enrollment of 3000 to 5000 patients in placebo controlled, double-blinded trials have become the pharmaceutical industry's gold-standard and, thus, MSC-trials should, likewise, test this number of patients. Yet, MSCs are known to produce multiple agents at multiple sites, which together produce a therapeutic outcome. This makes it difficult to predict the exact "the mechanism of therapeutic action" of MSCs as now is considered essential by the FDA. The cost of producing enough MSCs for 3000 patients is, in itself, staggering.

4. The USA Federal Government has invested many billions of dollars in the development of vaccines, while knowing that 20% to 40% of the USA population will not be vaccinated. Relatively sparse resources have been devoted to developing treatments that are curative for COVID-19 infection.

5. The non-responder rate for drugs now on the market, whether over-the-counter or by prescription, is 20% to 40%. If you have a headache and taking Tylenol does not work, you are a non-responder for Tylenol because it works for headaches. MSC administration can be expected to have patients with non-responder outcomes.[21] My view is that these non-responders should be used as a base onto which MSC-therapy must be responsible for significantly improved outcomes; and thus, the placebo controls should be eliminated during this pandemic. Therefore, all patients in the trial would receive the same MSC preparation and blinding would only be necessary for outcome evaluation.

6. Cell-based therapeutics were initiated over 50 years ago with the start of the use of bone marrow transplantation for cancer patients.[22] Today, all bone marrow transplantations are registered on a website, CIBMTR (https://www.cibmtr.org) and the outcomes are entered into a standardized and informative format. All MSC-trial participants should, likewise, be registered on a universal website, a registry, that can be viewed by both health professionals and members of the lay-public. The bad actors never list outcomes because they are highly variable or non-existent.

7. The MSC therapy should not be confused with the therapies used by bad actors of the stem cell clinics who promise stem cell regenerative medicine therapies but certainly do not provide MSCs. Some of these non-MSC therapies may, indeed, produce therapeutic outcomes but the equating of this stem cell promise with MSCs, as their advertisements state, negatively clouds the practitioner's opinion of the use of MSCs.

8. Last, the cardiac stem cell field has had recent controversies and published articles have been retracted which has reflected badly on the entire cell-based therapy industry.[23, 24] Again, cardiac stem cells should not be equated to MSCs.[25]

Translation of technology requires expertise in both academic and for-profit sectors and these require huge amounts of money and long timeframes. The COVID-19 pandemic and its critical clinical issues, raise the perfect opportunity to test the efficacy of MSCs for providing multi-modal therapeutics as outlined above. This cell-based therapy needs to be set-free of the roadblocks and naysayers[26, 27] to be honestly and expeditiously tested. I do not know of any better opportunity or test for MSC-therapy then we now have with this COVID-19 epidemic.

Now

The current regulatory drill for approving a drug or cell-based technology is to complete Phase I, II, and III clinical trials. This process was established by guidelines which are supported by Big Pharma. Academics have now taken responsibility for some of the Phase I and II trials as proofs of concepts of the basic science behind the cell-based technologies that they have developed. In the case of COVID-19, these trials have shown rather excellent results in saving lives.

Most interesting, in the historic sense, is the fact that from January 23, 2020 to February 16, 2020 in Beijing Youan Hospital, China, seven patients were assessed after MSC infusions.[28] MSCs cured or significantly improved the functional outcomes of these seven patients without adverse effects. The pulmonary function and symptoms were significantly improved in two days after exposure to MSCs. Two common and one severe patient were sufficiently recovered to be discharged 10 days after receiving treatment. After treatments, the peripheral lymphocytes were increased, the C-reactive protein decreased, and the overactive cytokine secreting immune cells (both CD-4 and CD-8 T cells and natural killer cells) disappeared in 3 to 6 days. In addition, the blood stream level of tumor necrosis factor-alpha was significantly decreased while interleukin-10 increased in the MSC-treated patients compared to the placebo control group. The physicians concluded that infusion of MSCs was safe and effective for treatment in patients with COVID-19 pneumonia especially for patients with critically severe conditions.

More recently, two Phase II trials were completed in Miami (FL, USA) by two different medical groups using either umbilical cord MSCs or marrow derived MSCs that were culture expanded.[29, 30] As reported by Lanzoni et al.[29] a double blind, Phase I/IIa randomized controlled trial was performed with subjects with severe acute respiratory distress syndrome secondary to COVID-19 at a single institution in Miami. Participants received two intravenous infusions of 100 million umbilical cord MSCs or vehicle alone on day 0 or day 3. The primary endpoint was safety defined by recurrence of pre-specified infusion associated adverse events ascertained at infusion or during the 28-day follow-up. At 28 days post last infusion, patient survival was 91% in patients infused with umbilical cord MSCs and 41% in the control group. No serious adverse events were observed, and the conclusion was that exposure to MSCs provided increased survival and decreased time to recovery compared to controls.

In another study published by Kaushal et al.,[30] involved case-control study of critically ill patients with laboratory-confirmed COVID-19, with acute respiratory distress syndrome. To evaluate clinical responsiveness, the most critically ill patients were examined with the outcomes in a sub-group of those requiring extracorporeal membrane oxygenation (ECMO) supports. Patients (n = 9) were administered three infusions of intravenous allogenic marrow derived culture expanded MSCs and compared to a local ECMO control group (n = 31). The primary outcome was safety, and the secondary outcomes were all-cause mortality (or rate of hospital discharge), cytokine levels, and viral clearance.

MSC infusions were well tolerated, and no side effects occurred. Of ECMO patients receiving MSC infusions, two out of nine died compared with a mortality of 15 of 31 in the ECMO control group. Isolated plasma exosomes from patients containing the SARS-COV-2 spike protein decreased after MSC infusions between day 14 or 21 after administration (P = 0.003 and P = 0.005, respectively) and was associated with a decrease in COVID-19 IgG spike protein titer at same time points (P = 0.006 and P = 0.007, respectively). Control ECMO patients receiving convalescent plasma did not clear COVID-19 IgG over the same time frame. Together these findings suggest that MSC intravenous infusion is well tolerated in patients with a broad range of severity including the most severe COVID-19 acute respiratory distress syndrome patients requiring ECMO. These data also raise the possibility that MSCs, in addition to exerting an immunomodulatory effect, contribute to viral clearance probably by mechanism explained elsewhere.[19, 20]

With these rather impressive results, it should be noted that the funds to support these trials came almost exclusively through philanthropy. Yes philanthropy, not National Institute of Health or any other USA federal agency. Somehow the USA government can allocate many billions of dollars for vaccines but not for therapeutics that potentially can be curative for very sick and dying COVID-19 patients.

Indeed, some for-profit companies have also conducted MSC-based clinical trials with COVID-19 patients with very positive results but with insufficient endpoints to provide "statistically significant" results (I speculate that this is probably because of high non-responder rates). Why cannot the saving of lives and the relief of severe symptoms in some of the COVID-19 patients be enough to merit approval. Oh yes, we need 95% effectiveness to be a value (yet breakthrough infections in vaccinated patients are OK?). Again, MSCs can be curative but where will the $20+ million come from to do a "proper" Phase III trial that is controlled and run by my fellow academics?

The unfortunate generalization can be made that to translate a new technology, one needs several things. First and foremost, one needs huge amounts of money. This is emphasized because one would have thought that one needs to have a great technology. Even with a great technology, there is a need for it to be optimized and perfected. Some of this can be supported by National Institute of Health through maddeningly slow and politically complex application and review processes somewhat geared against discovery research. The most efficient way to translate this technology is either through the start of a for-profit company or through well-placed and clever philanthropy with both of these being money centric. New companies live and die by one variable and one variable only: the quality of the chief executive officer or management. Great management will find money and hire talented employees. Philanthropy will also accomplish this, but the academic route is slower and more complex than a for-profit company outside of academics. A company will hire unique specialists for each activity that is needed to bring the technology forward. Indeed, the currency for success in academics is quite different from the currency for success in the private sector. In fact, the end validation for a new technology in academia is that the technology is taken over by a for-profit company preferably a large well-established enterprise. Although the University of Pennsylvania developed the chimeric antigen receptor T-cell immunotherapy technology, Novartis got it approved by the FDA. The profits from this will be obtained by Novartis with the University of Pennsylvania and its investigators sharing a small proportion of these profits. The University of Pennsylvania investigators, however, will have had the satisfying knowledge that they translated a basic science technology into a clinically relevant protocol to save the lives of cancer patients. These academics and their workforce will have worked out all of the kinks in the process before Novartis took the technology over. Is there a Nobel Prize here? Nobel Prize would be nice but how many of the tens of people who added pieces to this complex puzzle will be financially rewarded or share in the notoriety of a Nobel Prize? These workers and investigators will, however, have the satisfaction of knowing that they helped carry this complex chimeric antigen receptor T-cell immunotherapy technology over the goal line. Likewise, the philanthropic contributors and their managing agencies will feel part of the satisfaction at having invested in the resources to help with this huge task of turning this good idea into a great medical technology for saving lives.

The MSC story has all of the above: large number of academic laboratories contributing to the knowledge base, the support of federal funding agencies such as National Institute of Health, the US Army, Department of Defense, etc. and the very key contributions by philanthropic agencies and the individuals associated with these agencies. We still have a long way to go to get this technology over the finish line. That said, if I contracted COVID-19, I am finding a way to get MSCs into my bloodstream because I know that they work, and I know how they work on COVID-19 even though they are currently not approved by the regulatory agencies. My only hesitation is the thought that I might be a non-responder.

Author contributions

AIC is the sole author, who conceived and drafted the review, and approved the final version of the manuscript.

Financial support

The work was supported by the Virginia and David Baldwin Fund.

Acknowledgement

I thank all of the scientists and clinicians who have so diligently worked with MSCs and COVID-19 patients.

Conflicts of interest statement

None.

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Received: August 18, 2021
Revised: October 19, 2021
Accepted: November 16, 2021
Available online: December 28, 2021