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Ethical issues and public communication in the development of cell-based treatments for COVID-19: Lessons from the pandemic

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SUMMARY

The significant morbidity and mortality of coronavirus disease 19 (COVID-19) prompted a global race to develop new therapies. These include interventions using cell- or cell-derived products, several of which are being tested in well-designed, properly controlled clinical trials. Yet, the search for cell-based COVID-19 treatments has also been fraught with hyperbolic claims; flouting of crucial regulatory, scientific, and ethical norms; and distorted communication of research findings. In this paper, we critically examine ethical issues and public communication challenges related to the development of cell-based therapeutics for COVID-19. Drawing on the lessons learned from this ongoing process, we argue against the rushed development of cell-based interventions. We conclude by outlining ways to improve the ethical conduct of cell-based clinical investigations and public communication of therapeutic claims.

INTRODUCTION

The coronavirus disease-19 (COVID-19) that first emerged in Wuhan, China, in late 2019 (Zhu et al., 2020) rapidly transformed into a serious pandemic that has resulted in more than 222 million infected individuals and in excess of more than 4.5 million deaths worldwide as of September 9, 2021 (Johns Hopkins University, 2021). COVID-19, caused by the SARS-CoV-2 coronavirus strain, can present with complex pathophysiology, including progressive respiratory failure, pericarditis, and coagulopathy (blood clot formation), which is exacerbated by underlying conditions such as diabetes, chronic kidney or lung disease, heart conditions, and cancer (Centers for Disease Control and Prevention, 2020). Furthermore, the emergence of prolonged symptoms after the acute phase of the disease in certain COVID-19 patients, known as "long COVID" (Burke and Del Rio, 2021; Davis et al., 2021), points to the long-term health toll of the pandemic. Socioeconomic inequalities have enabled the spread of the virus, as have ineffective and inconsistent government responses, widespread misinformation about the virus and purported treatments and preventive measures, and inadequate use of nonpharmaceutical interventions such as mask use and physical distancing.

From the early days of the pandemic, through relentless scientific effort, researchers around the world have sought to understand the pathology of COVID-19 and use basic science approaches to inform the development of preventive vaccines and therapeutic products. A variety of interventions, including anti-inflammatory and antiviral drugs, convalescent plasma, and cell-based treatments, have been tested in clinical investigations for either prevention of COVID-19 infection or treatment of COVID-19 patients with varied disease severity (Welte et al., 2021). Following expedited clinical testing that demonstrated safety and high levels of efficacy, several COVID-19 vaccines, based on either established (viral vector) or novel (mRNA) delivery technologies, have been approved or granted emergency use authorization or similar status (provisional registration, conditional market authorization) in the United States and elsewhere. Large-scale public vaccination campaigns are now underway around the world, although many lower- and middle-income nations continue to suffer from inadequate supply of COVID-19 vaccines (Creech et al., 2021). The development of safe and efficacious vaccines in combination with other public health strategies and better clinical management of patients with COVID-19 offers hope for eventual pandemic control, despite significant challenges, such as the emergence of variants and the rising counts of cases and fatalities in such countries as Afghanistan, India, Indonesia, Japan, and Nepal. Acknowledging the impressive translational process that resulted in the development of multiple vaccine products, the search for COVID-19 therapies has been fraught with hyperbolic claims, miscommunication of research findings, poorly designed and underpowered clinical studies, science-by-press-release, and commercial efforts to exploit for profit the public's fears and anxieties (Caulfield et al., 2021; Turner, 2020). In this perspective, we examine and critically discuss ethical issues and public communication challenges that emerged during efforts to develop and test cell-based interventions for COVID-19.

ETHICAL ISSUES WITH RUSHED DEVELOPMENT OF CELL-BASED TREATMENTS

The unprecedented global effort to rapidly identify interventions capable of limiting the spread of SARS-CoV-2,

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reducing mortality and morbidity, and alleviating the suffering of individuals with COVID-19 is to be commended. Many researchers made substantial efforts in challenging personal and professional circumstances to contribute their expertise to the pandemic response. Furthermore, efforts to accelerate the development of vaccines and therapies are laudable when appropriate safeguards are preserved and research is conducted in a rigorous and reproducible manner.

Since the beginning of the pandemic, numerous cell-based interventions have been proposed and investigated as potential therapies for COVID-19 patients. As a hallmark of COVID-19 is a dysregulated immune response, mesenchymal stromal cells (MSCs) or their derivatives (e.g., exosomes) comprise a large part of tested cell products due to their immunomodulatory properties (Khoury et al., 2020). In addition to MSCs, other cell types tested in clinical trials include natural killer (NK) cells, cytotoxic T cells, and T cells from convalescent patients. More than 150 trials of cell- and gene-based interventions have been initiated, mostly in China and the United States (Khoury et al., 2021). Importantly, numerous cell-based interventions that are already under clinical investigation as potential treatments for other diseases or are approved for other indications have been repurposed as potential treatments for individuals diagnosed with COVID-19 (Lanzoni et al., 2021; Sharma and Zhao, 2021). A similar process has occurred with drug development, as existing medications have been tested to see whether they prevent COVID-19 or ameliorate its symptoms. Acknowledging the case for attempting to repurpose cell-based interventions and other medical products with well-known safety profiles (Sharma and Zhao, 2021), there are also clinical trials conducted by study sponsors who may be embarking on cell-based strategies for the first time and whose product is less defined and characterized. In such cases, preclinical research is sometimes quite limited, and there is reason to question whether sufficient evidence exists to proceed to clinical trials involving human research participants.

Acknowledging the urgency of developing safe and efficacious treatments, efforts to rapidly develop therapeutic interventions should never occur at the expense of the ethical and scientific standards that are at the heart of responsible clinical research and therapeutic innovation. Scientists, regulators, policy makers, and other parties must guard against "pandemic research exceptionalism" and insist upon rigorous well-designed studies rather than a proliferation of poorly designed, underpowered, and duplicative small studies that are developed and conducted with undue haste and are unlikely to provide insight into clinically meaningful effects (London and Kimmelman, 2020).

Demanding robust standards for the conduct of research includes ensuring that there is a sound scientific justification for the selection of a particular intervention based on sufficient evidence from preclinical studies or prior trials. Clinical studies should be prospectively registered, appropriately designed, and, following completion of preliminary studies, include randomization, blinding, and control arms, as well as being sufficiently powered to generate usable findings that address a key therapeutic challenge. Whenever feasible, groups should coordinate their research efforts to support larger trials to optimize time, funds, clinical support, and patient participation. Findings, whether they are encouraging or not, need to be shared with colleagues through high-quality peer-reviewed publications and not via press releases or using the news media to propagate unsubstantiated scientific claims. "Negative" results also need to be disclosed, even though researchers sometimes encounter pressures to publish "positive" results and not report that particular investigational products are unsafe or ineffective (Dwan et al., 2013).

Finally, expanded or compassionate use of investigational cell-based interventions, while an important means of access for individuals who are ineligible to receive such products in clinical studies, should not be portrayed as an adequate substitute for systematic scientific evaluation of products in a clinical trial context. Although these standards are not unique to cell-based interventions for COVID-19, the heightened community interest in regenerative medicine remedies, as well as the long history of expanded use as a justification for premature applications of unproven interventions, means that now more than ever we need to maintain rigor in how we present such applications (Khoury et al., 2020).

Multiple studies have reviewed clinical trial registries to describe and evaluate the evolving landscape of cell-based clinical research targeting various symptoms of COVID-19 (Kim and Knoepfler, 2021; Liao et al., 2020). Based on searches conducted in August 2020, one study found 70 clinical trials examining various stem cell-based interventions—predominantly MSCs—and another 9 exploring the use of NK cells to target COVID-19 symptoms (Kim and Knoepfler, 2021). Most trials were relatively small (mean: 51.8 participants) and only 22% (18/79) were randomized, double blinded, and controlled, leading the authors of this analysis to conclude that ongoing clinical trials that utilized cell-based interventions for COVID-19 symptoms were likely to have "relatively small collective clinical impact" (Kim and Knoepfler, 2021). These results prompt concerns that many studies testing cell-based products to treat or prevent COVID-19 exhibit troubling signs of pandemic research exceptionalism, much like the broader effort to develop COVID-19 therapeutics, with one FDA report estimating that only "6% of clinical trials are yielding results the agency deems actionable" (Baumann, 2020). Another

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possible interpretation is that clinical studies testing cell-based investigational products for COVID-19 have not generated sufficiently encouraging and robust results to warrant initiating large-scale randomized controlled trials.

RESPONSIBLE SCIENTIFIC COMMUNICATION OF COVID-19 THERAPEUTIC CLAIMS

In the context of the COVID-19 pandemic, with urgent need for improved treatments, accurate and accessible scientific communication is both critical and challenging. It is critical because countless people, experts and nonexperts alike, are scouring the latest COVID-19 science to glean insight into appropriate policy choices and guidance on everyday decisions, and these decisions can collectively help us slow and manage the pandemic (Saitz and Schwitzer, 2020). It is challenging because of the ways in which the urgency of the COVID-19 pandemic interacts with the complicated contemporary communication environment and the roles of some profit-driven businesses and clinics that use this unique environment as an opportunity to exploit the fears and anxieties of vulnerable persons (Turner, 2020).

Given the urgency of the ongoing pandemic, even the smallest morsel of COVID-19 science is often deemed newsworthy and rapidly enters a social media landscape where—regardless of its accuracy—it can be widely and rapidly shared with a global audience. This prompt and widespread distribution of novel research findings can be helpful and contribute to public understanding when trustworthy, credible information is broadly dispersed. However, it can also be highly problematic, as new and often poorly vetted information either intentionally or unintentionally spreads confusion and undermines responsible personal and collective decision-making. In addition to peer-reviewed articles, information about COVID-19 science comes from preprints, press releases, media reports, and a host of other non-peer-reviewed sources (Fraser et al., 2021; Gupta, 2020). Even when scientific information is initially communicated with appropriate context and caveats identifying limitations, this critical information can easily be stripped away as new claims circulate through multiple communication channels. Furthermore, because many people are desperate for positive news, even a hint of progress toward a treatment for COVID-19 can easily be communicated in an overly positive manner rather than with suitable qualifiers and appropriate context. This overpromising is perhaps most prevalent when science is communicated by press release, a form of communication designed explicitly to garner media coverage. This mode of publicizing scientific research has been shown to regularly hype scientific advances, inadequately convey study limitations, and insufficiently place findings in proper context (Caulfield and Condit, 2012; Caulfield et al., 2016). Examples of COVID-19 hype can be seen in discussion of "cures" based on small and preliminary studies (Chen, 2020; Jaffe-Hoffman, 2020) as well as in reports that omit forthright acknowledgment of study limitations, such as a small number of research participants or the lack of a control group (Londoño et al., 2021; Parry, 2020).

In this highly charged communication environment, it is especially important for researchers, clinicians, and companies working to advance understanding of the potential and limitations of cell-based approaches for COVID-19 to avoid overhyping science and to provide an appropriate context for the general public to understand research findings and associated limitations in study research methods and results. This obligation to promote responsible communication of research also extends to university-based press officers, company publicists, journalists, and others involved in the process of translating scientific knowledge for the public. This publicly accountable approach to science communication includes clearly and accurately explaining how a new therapeutic approach might fit into the COVID-19 treatment process and the level of evidence upon which any claims are based (e.g., peer-reviewed journal article, preprint, press release, etc.).

Those tasked with communicating the state of cell-based approaches for potential treatment and management of COVID-19 symptoms should start by ensuring they have an accurate understanding of the science and then clearly state the findings of new research without exaggeration or rhetorical flourish (Kueffer and Larson, 2014). They should also situate new research findings in the translational research process, articulating the required steps for the science to move forward toward clinical use without exaggerating the speed at which this process is likely to advance. Highlighting the need for responsible oversight of research, especially for clinical studies, is also important and appropriate. Beyond these efforts to provide accurate information, it is also beneficial to draw upon evidence-based best practices for scientific communication and public engagement (as reviewed in Cooke et al., 2017; Newman, 2020). For example, communicators striving to provide accurate information and increase understanding of the relevant science (as opposed to, for example, those marketing unproven cell therapies) should, at the very least, reject the deficit model of science communication (Simis et al., 2016). They should instead strive for engaged or dialogue-based communication approaches that, although more time intensive, promote better understanding, especially in contentious areas (Reincke et al., 2020; Smith et al., 2013), and consider the use of framing techniques (Nisbet, 2010; Nisbet and Mooney, 2007) or diverse

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and trusted messengers (Kahan, 2010, 2013) to overcome challenges posed by cultural cognition and motivated reasoning in the communication of scientific knowledge.

If those charged with science communication and development of cell-based therapies consistently followed these best practices, it would likely improve the overall quality of the discourse surrounding cell-based therapeutics for COVID-19. The magnitude of this improvement may be small, however, especially given the complicated and fragmented communication environment, with many voices not committed to this sort of accurate communication. Both profit-driven and politics-driven voices will continue to contribute to and, potentially, dominate the conversation, yielding a complicated and confusing communication environment. Despite these challenges, efforts to promote clear, accurate, and hype-free communication, especially by members of the scientific enterprise, can help build and maintain trust in science, scientists, and the biotech sector (Caulfield et al., 2016), an important outcome and public good in its own right.

INACCURATE REPRESENTATIONS MADE BY DIRECT-TO-CONSUMER (DTC) BUSINESSES

Commercial investment by biotechnology companies attempting to develop cell therapies has predominantly been directed toward testing cell-based interventions for COVID-19 in well-designed and rigorously conducted clinical trials. However, numerous other businesses less invested in the demanding and costly process of generating the safety and efficacy data required to seek premarketing authorization for cell-based interventions have made unsubstantiated and inaccurate claims about purported "stem cell" products for COVID-19, emboldened by hyperbolic reporting on cell-based interventions that are in preliminary stages of clinical testing (Kimberlin, 2020). Some clinics advertise unproven and unlicensed "mesenchymal stem cell treatments" or "exosome therapies" as "immune boosters" capable of repairing and regenerating the lungs, improving respiratory health, "interrupting viral replication," and reducing the likelihood of being infected with SARS-CoV-2 (Turner, 2020). These businesses typically promote cell-based products as preventive measures. While most facilities advertise on-site "stem cell" treatments available via infusion or injection, an "anti-aging" clinic in California sold "mesenchymal stem cell exosome" kits that it shipped to its clients. The clinic's customers were then expected to self-administer the product at home using a nebulizer and mask. Other businesses advertise the service of cell banking, claiming that stored stem cells might have therapeutic value for individuals subsequently diagnosed with COVID-19. Companies use their websites, Facebook pages, YouTube videos, and other online marketing platforms and social media sites to reach prospective customers worried about being infected with SARS-CoV-2. In an initial review of marketing claims made by businesses selling supposed stem cell treatments and preventive interventions for COVID-19, we were unable to find published findings from preclinical studies and clinical trials that supported their commercial activities. To persuade potential customers, they attempt to link the purported stem cell products they are advertising to uncritical news media reports and preliminary clinical studies or case reports in which stem cell interventions were administered to individuals diagnosed with COVID-19. While such studies and case reports have not conclusively demonstrated that stem cell products used to treat COVID-19 or COVID-19-related acute respiratory distress syndrome (ARDS) are safe and efficacious, businesses selling "stem cell" interventions for COVID-19 on a DTC basis attempt to persuade clients that a convincing evidence base exists for their advertised products. Such marketing techniques, which involve misrepresentations that undermine the ability of prospective patients to make informed decisions, have been particularly prominent in DTC promotion of alleged cell and stem cell therapies (Sipp et al., 2017). While the provision of accurate scientific information alone is not sufficient to obtain informed consent from patients, it is necessary to ensure that they have the basic information they require to make meaningful decisions about their medical care.

Exactly how many businesses are selling on a DTC basis unlicensed and unproven stem cell interventions for COVID-19 is unknown, although several such companies have been identified (Turner, 2020). Also unknown is how much clinics typically charge for these interventions, as well as how many individuals have decided to purchase and have administered to them such products in the hope of reducing the chance that they would subsequently be infected with the virus or would limit the severity of the condition if infected. While companies vary in terms of exactly what products they sell, the most common claims made by businesses selling cell-based products for COVID-19 appear to involve mesenchymal "stem cells," exosome products derived from stem cells, and perinatal tissue products (Turner, 2020, and Table 1).

Commercial and clinical activity involving marketing and administration of unproven and unapproved cell-based products for COVID-19 raises numerous ethical and legal concerns and could have variety of harmful effects.

First, there is the real possibility of physical and financial harms, as the safety and efficacy of these products was not established before they entered the marketplace and such businesses use misrepresentations routinely in

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Table 1. Warning/untitled letters to businesses selling or manufacturing and distributing for sale unapproved cell/cell-based interventions for COVID-19

Issuing authority	Business name	Date	Web link
FDA CBER	Dynamic Stem Cell Therapy	04/01/2020	https://www.fda.gov/media/136668/download
FDA CBER	Kimera Labs, Inc.	04/10/2020	https://www.fda.gov/media/137129/download
FDA CBER	Regenerative Solutions of New Jersey	04/10/2020	https://www.fda.gov/media/137396/download
FDA CBER	Sparrow Health & Performance LLC	05/11/2020	https://www.fda.gov/media/137974/download
FDA CBER	21st Century LaserMed Pain Institute dba Create Wellness Clinics	07/21/2020	https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/21st-century-lasermed-pain-institute-dba-create-wellness-clinics-607654-07212020
FDA CBER	PA Green Wellness LLC dba a Predictive Biotech certified facility	08/17/2020	https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/pa-green-wellness-llc-dba-predictive-biotech-certified-facility-608144-08172020
FDA CBER	Predictive Biotech	08/17/2020	https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/predictive-biotech-608322-08172020
FDA CBER	Vibrant Health Care, Inc.	11/18/2020	https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/vibrant-health-care-inc-608426-11182020
FDA CBER	The Dahlia Center LLC	07/15/2021	https://www.fda.gov/media/150856/download
FDA OBPO	EUCYT Laboratories LLC	06/04/2020	https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/eucyt-laboratories-llc-607182-06042020
FDA OCBQ	Lattice Biologics Ltd.	08/27/2020	https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/lattice-biologics-ltd-607852-08272020
FTC	Vidaful Medicine	04/10/2020	https://www.ftc.gov/system/files/warning-letters/covid-19-letter_to_dap-vidaful-medicine.pdf
FTC	Absolute Health Clinic	04/16/2020	https://www.ftc.gov/system/files/warning-letters/covid-19-letter_to_absolute-health-clinic.pdf
FTC	Center for Regenerative Cell Medicine	04/17/2020	https://www.ftc.gov/system/files/warning-letters/covid-19-letter_to_center-regenerative-cell-medicine.pdf
FTC	Stemedix, Inc.	04/17/2020	https://www.ftc.gov/system/files/warning-letters/covid-19-letter_to_stemedix-inc.pdf

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Table 1. *Continued*

Issuing authority	Business name	Date	Web link
FTC	Brexo Bio	05/27/2020	https://www.ftc.gov/system/files/warning-letters/covid-19-letter_to_brexo_bio.pdf
FTC	Colts Neck Stem Cells and Regenerative Medicine	06/01/2020	https://www.ftc.gov/system/files/warning-letters/covid-19-letter_to_colts_neck_stem_cells_and_regenerative_medicine.pdf
FTC	BioXcellerator	06/05/2020	https://www.ftc.gov/system/files/warning-letters/covid-19-letter_to_bioxcellerator.pdf
FTC	American Regenerative Clinic	09/09/2020	https://www.ftc.gov/system/files/warning-letters/ftc-covid-19-letter-american_regenerative_clinic.pdf
FTC	Health and Wellness of Carmel	09/21/2020	https://www.ftc.gov/system/files/warning-letters/ftc-covid-19-letter-health_and_wellness_of_carmel.pdf
FTC	Rocky Mountain Regenerative Medicine	11/05/2020	https://www.ftc.gov/system/files/warning-letters/covid-19-letter-rocky-mountain-regenerative-medicine.pdf
FTC	The Karlfeldt Center	02/08/2021	https://www.ftc.gov/system/files/warning-letters/covid-19-letter-karlfeldt-center.pdf

CBER, Center for Biologics Evaluation and Research; dba, doing business as; FDA, US Food and Drug Administration; FTC, Federal Trade Commission; OBPO, Office of Biological Products Operations; OCBQ, Office of Compliance and Biologics Quality.

their advertising. Serious adverse events have been documented as a result of clinics selling unlicensed "stem cell" products for vision loss and other indications (Bauer et al., 2018; Richardson, 2021). While research on harms associated with the administration of unlicensed and unproven stem cell products has understandably focused on physical injuries to patients, financial harms based on inaccurate marketing claims matter and can be particularly consequential for patients with limited personal savings. These issues become particularly salient in the context of the COVID-19 pandemic, where vulnerable populations, such as individuals with pre-existing conditions or long COVID patients, are more likely to suffer such harms.

Second, while researchers have not yet documented how patient behavior changes after individuals are provided what has been represented to them as supposed "stem cell" treatments or preventive interventions for COVID-19, individuals who believe they have received an "immune boosting" stem cell intervention intended to "prevent" COVID-19 may have an exaggerated sense of safety and decide not to be vaccinated and/or take insufficient steps to engage in physical distancing, masking, and other basic preventive measures intended to reduce the likelihood SARS-CoV-2 infection. It is conceivable that misrepresentations can therefore compromise public health as well as the safety of individual patients. Those who believe they are "immune" or have had their immune systems "boosted" through such interventions may also initially ignore or dismiss symptoms and delay seeking medical care.

Third, the sale of unproven "stem cell" products could have the effect of reducing the number of individuals eligible for participating in well-designed and properly conducted trials testing various investigational products intended to treat or prevent COVID-19. Individuals who disclose they have received unlicensed cell-based products for COVID-19 will typically be excluded from participating in such trials. In this respect, the DTC marketplace for unproven and unlicensed "stem cell" products for COVID-19 could undermine efforts to conduct legitimate scientific research intended to test investigational products for COVID-19 and lead to the development of safe, efficacious, and approved cell-based therapies.

Finally, the widespread circulation of misinformation has been a persistent and pervasive feature of the pandemic. Businesses selling unlicensed and unproven "stem cell" products have contributed to the spread of

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Table 2. Statements of concern addressing promotion of unproven cell/cell-derived interventions for prevention or treatment of COVID-19

Organization	Web link
International Society for Cell & 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/
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/

misinformation, not only by making misleading claims about the safety and efficacy of the "stem cell" products they sell, but also in contributing to misleading rhetoric about "immune boosting" and blocking viral replication of SARS-CoV-2. The prolonged nature of symptoms and significant disability presenting in the emerging subset of infected patients with long COVID may signify they are vulnerable to marketed cell-based treatments that purport to increase and/or restore patient "wellness." Some companies have exacerbated the spread of misinformation and conspiracy theories by claiming that evidence-based cell therapies already exist, and regulatory bodies have been obstructionist by not approving such products. The spread of such misinformation has potential to cause real harm to patient safety and public health by making it difficult or impossible for patients and other members of the public to distinguish evidence-based scientific claims from pseudoscience and quackery. Such rhetoric, when coupled with attacks on regulatory agencies, also threatens to undermine the reputation of public bodies that have integral roles to play in addressing the pandemic. In this respect the distribution of misinformation is not just a threat to individual patients, but can pose a threat to core public institutions and their efforts to promote responsible science communication (Murthy, 2021).

SCIENTIFIC SOCIETIES AND THEIR RESPONSES TO COVID-19 THERAPEUTIC HYPE

The therapeutic hype on cell-based treatments for COVID-19 generated by DTC businesses has generated a critical response from scientific organizations (Ikonomou, 2020). Early in the pandemic, appreciating the urgency of the situation, scientific and professional societies issued forceful statements to counteract unfounded claims of efficacious "stem cell" treatments (Table 2). Societies such as the International Society for Cell & Gene Therapy (ISCT) and the International Society for Stem Cell Research (ISSCR) and professional organizations such as the Alliance for Regenerative Medicine warned the public against businesses engaged in DTC marketing of cell-based treatments that have not been proven safe and effective in treating or preventing COVID-19. For example, the ISCT Presidential Task Force on the Use of Unproven and/or Unethical Cell and Gene Therapies has consistently argued against both the deceptive marketing of unproven cell-based interventions and the rushed development of cell-based therapies for COVID-19 (Harris, 2020; Ikonomou, 2020). These actions reflect the important role of scientific and medical societies in the global scientific enterprise and their ability to inform their members while also supporting patient education and public understanding (Sipp et al., 2017; Weiss et al., 2018).

Acknowledging the important messages conveyed by these statements, it is unclear whether such cautionary efforts reached patients and their loved ones or have had a significant effect upon public understanding of risks associated with receiving unlicensed and unproven stem cell interventions to prevent or treat COVID-19. Whereas businesses selling such products use Facebook, YouTube, and other platforms to circulate and amplify their marketing claims, evidence-based warnings from scientific societies and professional associations may not necessarily reach their intended audiences or benefit from widespread circulation (e.g., on social media). It is also unclear whether scientific societies and other professional organizations have had an important role to play in convincing regulatory bodies to increase their enforcement efforts in this space. It is possible that scientific societies could have a greater impact by more explicitly lobbying regulatory bodies to better enforce existing laws and regulations by targeting companies selling unlicensed stem cell products for COVID-19. Drawing specific noncompliant business practices and marketing claims to the attention of regulators and law enforcement agencies might also have a public impact that exceeds issuing general statements of concern.

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While such calls could likely not be made public due to concerns that businesses would respond with threat of litigation, behind-the-scenes interaction with regulators could help draw the attention of such agencies to the most egregious commercial operations and in this respect contribute to both patient safety and public health. How much such activity already occurs is unclear.

REGULATORY AGENCIES AND THEIR RESPONSES TO COVID-19 THERAPEUTIC CLAIMS

To curtail the sale and distribution of unlicensed stem cell and regenerative medicine products advertised as treating or preventing COVID-19, regulatory agencies such as the US Food & Drug Administration (FDA) and the Federal Trade Commission (FTC) increased their enforcement actions, such as issuing warning and untitled letters documenting noncompliant commercial activity. As shown in Table 1, as of this writing, there have been 22 letters issued by the FTC and FDA in response to businesses selling unproven and unlicensed cell-based interventions for COVID-19. The offered products range from purported "stem cells" of perinatal origin (Wharton's jelly, amniotic fluid, umbilical cord blood) to exosomes; the therapeutic claims typically emphasized supposed immunomodulatory effects. The letters highlighted the deceptive nature of such claims propagated by these businesses. They also noted that offerings of specific products, such as exosomes, require premarket approval, and therefore the sale and distribution of such unlicensed products occur in apparent violation of FDA regulations.

Enforcement activity has resulted in some businesses ceasing to market stem cell and regenerative medicine products as purported therapies or preventive measures for COVID-19. However, other companies continue to make such advertising claims. Their presence suggests that there is still an important role for regulatory bodies to play in curtailing the activities of businesses selling unapproved and unproven stem cell and regenerative medicine products for COVID-19. One important issue regulatory agencies need to consider is whether actions such as issuing warning letters and untitled letters provide sufficient disincentives to clinicians and other parties interested in selling unlicensed products. If companies and affiliated clinicians are not fined, forced to return to patients whatever profits they have made, confronted with criminal charges, subject to revocation of medical licensure, or otherwise subject to serious legal and financial consequences, it is possible that more businesses will be drawn to this space because of the profits that can be generated from selling unlicensed and unproven cell-based products in the midst of a pandemic. Regulatory agencies and other law enforcement bodies could likely reduce such commercial activity by making greater use of disincentives such as pursuing criminal charges when warranted and seeking disciplinary action in cases where licensed health care providers are involved in the marketing, sale, and administration of unlicensed and unproven cell-based interventions for COVID-19.

CONCLUSIONS

The COVID-19 pandemic has taken a heavy toll on human life and, on a global scale, caused massive disruption of social life and economic activities. The sense of urgency in finding new therapeutic modalities, albeit understandable, has also led to pleas to use the current pandemic as a "deregulatory opportunity" and to bypass established regulatory pathways by being "bold and innovative" (Ikonomou, 2020). More than a year after the emergence and rapid spread of SARS-CoV-2, and in the light of extensive clinical investigations, these arguments for lowered regulatory standards seem misguided. For example, drugs such as hydroxychloroquine, which were surrounded with hype at the beginning of the pandemic, proved to be ineffective for the treatment of severely ill COVID-19 patients following large-scale, well-designed clinical trials. At the same time, the FDA's rigorous and meticulous approach in the evaluation of COVID-19 vaccine safety and efficacy offers a valuable blueprint for the development of cell and gene products for COVID-19 and future public health emergencies (Sharfstein et al., 2021). Rushed development and premature commercialization of cell- and gene-based therapeutics for COVID-19 and other respiratory virus infections and hyped communication of related clinical and research findings will inevitably harm the field of regenerative medicine, increase risks to patients, and erode the public's trust. Evidence-based approaches to developing safe and efficacious cell-based interventions and other medical products remain crucial even amid the challenges and intense pressures of the pandemic.

CONFLICTS OF INTEREST

On a *pro bono* basis, L.T. has written an expert report in a class action lawsuit filed against a business alleged to have marketed unproven "stem cell"-based interventions. In a separate criminal case, L.T. has served as a compensated expert witness for the US government. L.T. is an unpaid member of the International Society for Cell & Gene Therapy (ISCT) and the International Society for Stem Cell Research (ISSCR). He serves on the ISCT Presidential Task Force on the Use of Unproven and/or Unethical Cell & Gene Therapies and the ISSCR Ethics and Membership Committees and has served on the 2021 ISSCR Guidelines Taskforce.

M.M. is vice president of the Australasian Society for Stem Cell Research and serves on the ISCT Presidential Task Force on the

Use of Unproven and/or Unethical Cell & Gene Therapies and the ISSCR Ethics Committee, has served on the 2021 ISSCR Guidelines Taskforce, and is a nonexecutive board member of the National Stem Cell Foundation of Australia. She is not paid for these roles.

A.L. is a member of the ISCT and the ISSCR and he serves on the ISCT Presidential Task Force on the Use of Unproven and/or Unethical Cell & Gene Therapies. He is also an elected member of the board of directors for the American Society for Bioethics and Humanities (ASBH). He is not paid for these roles.

L.I. has written an expert report in a class action lawsuit filed against a business selling unproven "stem cell"-based interventions, and wrote the report on a *pro bono* basis. He is a member of the ISCT and the ISSCR and the chair of the ISCT Presidential Task Force on the Use of Unproven and/or Unethical Cell & Gene Therapies. He is not paid for these roles.

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