Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company’s public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Coronavirus disease 2019 (COVID-19)-related respiratory failure is a significant cause of morbidity, mortality and health care utilization. Further, long-term respiratory consequences including fibro-proliferative changes and chronic respiratory dysfunction remain an unclear but a growing problem. Vaccinations including boosters have decreased the incidence of COVID-19 severe respiratory disease, but significant numbers remain unvaccinated. In addition, some patients remain particularly vulnerable to severe acute respiratory syndrome coronavirus 2 infection regardless of vaccine and booster administration. For instance, patients with significant immunosuppression continue to have significantly greater rates of symptomatic COVID-19 infection and mortality [1–7].

While the main tool in combating the pandemic is prevention, drug-discovery pipelines are still required, especially when vaccine development and deployment are slower than the appearance of new variants. Current therapies including remdesivir, corticosteroids and immunotherapies such as tocilizumab and baricitinib have only partially decreased the incidence, severity and sequelae of respiratory disease [8,9]. Two new antiviral treatments available, molnupiravir [10] and a combination of nirmatrelvir and ritonavir (Paxlovid), may continue to lessen respiratory sequelae [11]. However, molnupiravir may result in mutagenic activities [12] for the host, whereas nirmatrelvir/ritonavir can interfere with a number of commonly used drugs [7,13]. In addition, specific antibodies against severe acute respiratory syndrome coronavirus 2 have shown efficacy in tempering respiratory symptoms and preventing major complications only when administered in the very early phases of infection and for not all the viral variants [14].

In this setting, cell-based therapy approaches using systemic administration of mesenchymal stromal cells (MSCs) and their derived products have a strong mechanistic rationale and pre-clinical track record [15]. A number of case series and uncontrolled trials of both academic and industry sponsorship have demonstrated safety of systemic MSC administration in patients with COVID-19 with different degrees of respiratory severity [16]. This has provided a platform for a growing number of randomized, blinded, placebo-controlled trials of systemic MSC administration [17]. MSC administration has consistently been found safe without significant inflammatory toxicities or attributable serious adverse events. Importantly, a growing number of studies, although not all, have demonstrated efficacy [18–21]. Of note, the published trials to date are from academic centers. Despite suggestive results in press releases, industry-sponsored, randomized, blinded, placebo-controlled trials have not yet undergone peer-reviewed publication.

These trials have been reviewed in several recent systematic reviews and meta-analyses. Overall, these have demonstrated safety and positive end points, including reduction of mortality rate [22–24]. They are, however, limited by the relatively small numbers of patients studied to date. The meta-analyses have also highlighted significant issues and lack of consensus on critical study parameters including but not restricted to the source of MSCs. Of the 11 clinical investigations included in the recent systematic reviews, including open label non-randomized or non-controlled trials, eight used MSCs derived from cord blood or umbilical cord tissue whereas others used MSCs derived from menstrual blood or bone marrow mononuclear cells. Another variable included differences in critical process parameters used to manufacture the MSCs including medium supplementation (some studies used fetal bovine serum [25], some used different types of platelet lysate [18,21], another used serum free medium [26]), Passage numbers varied between studies [26,27] as well as the cryopreservant used, reported in only one study [18]. Two studies reported infusing freshly thawed MSCs, whereas others lacked these details in the methods [18,21]. Other variables downstream of manufacturing included dose (typically trials used 1–3 x 10⁶/kg, although one trial used 240 million MSCs over 3 doses [21] (mand dosing (one to four infusions), time of administration, patient population, symptom heterogeneity, illness severity, and outcome measures.

Overall, these investigations support that use of MSCs as a treatment option for COVID-19 appears to be promising; however, potential risk of bias was detected in all studies. Although the latest meta-analyses demonstrated reduced mortality (relative risk of death 28 days after treatment 0.19; 95% confidence interval 0.05–0.78), outcome measures were not reported consistently and pooled estimates were not calculated. MSC administration tended to improve radiographic findings, pulmonary function (lung compliance, tidal volumes, arterial oxygen partial pressure/fractional inspired oxygen, alveolo-capillary injury), and inflammatory biomarker levels. Circulating interleukin-6 level was the most commonly reported cytokine and were consistently decreased compared with controls at early but not later time points [22]. However, no comparisons were made between MSCs of different sources within any trial. There is further heterogeneity, as demonstrated by one recently published study from France using umbilical cord-derived MSCs (not included in the most-recent meta-analyses) [23]. This study showed that among the
45 enrolled patients, arterial oxygen partial pressure/fractional inspired oxygen did not change between day 0 and day 7 as well as between MSC and placebo groups. Repeated MSC infusions were not associated with any serious adverse events.

In short, the optimal approaches for MSC administration and potential approval by regulatory agencies remain uncertain. On the one hand, this prompts for investigations toward deeper fundamental understanding on potential mechanisms of MSC actions, as a basis to precisely define required MSC attributes and to design rational clinical investigations, particularly those identifying patients more likely to respond [15]. On the other hand, this is in part due to the relatively limited numbers of patients involved in the published trials to date, which limits the power of observations on potential efficacy. To this end, a combined global registry of all patients enrolled in these trials, both academic and industry-sponsored, will provide an invaluable tool to better understand and apply MSC-based cell therapies to patients with COVID-19 respiratory disease [28–30]. Data in the registry could include information on patient phenotypes and inflammatory status, in addition to other clinical outcome measures, as these are increasingly recognized to influence potential MSC actions and efficacy. In addition, a registry approach provides the opportunity to collect information on critical process parameters used to manufacture the MSCs, and characterization data which can be harmonized to reflect MSC critical quality attributes. These data will support efforts such as “living systematic reviews” that are updated in real-time to provide researchers, patients and decision-makers with the most up-to-date information [31,32]. Moreover, a registry would facilitate individual patient data meta-analysis, which will help identify patient, disease and cell product characteristics that may modify MSC efficacy. Notwithstanding the logistics of collating and managing a registry and the need for buy-in from the wide range of investigators, the critical nature of the COVID-19 pandemic is a strong impetus for the biomedical community to join forces [33].

As the leading organization promoting development and application of MSC-based cell therapies, the International Society for Cell and Gene Therapy is well situated as an unbiased neutral agency to coordinate with comparable interested organizations, funding agencies and regulatory agencies globally to develop plans to manage the database and to serve as a central source for communication between the investigative groups. With focus on COVID-19—associated acute respiratory distress syndrome investigations, this will be a pilot endeavor that can serve as a basis for larger more broad ranging databases. To this end, we call upon all investigators and the International Society for Cell and Gene Therapy to join in this endeavor and strive to help make MSC-based approaches for COVID-19 respiratory diseases an effective therapy.

Daniel J. Weiss
Anthony Filiano
Jacques Galipeau
Maroun Khoury
Mauro Krampera
Manoj Lalu
Katarina Le Blanc
Jan Nolta
Donald G. Phinney
Patricia R.M. Rocco
Yufang Shi
Karin Tarte
Sowmya Viswanathan
Ivan Martin

University of Vermont College of Medicine, Burlington, Vermont, USA

Department of Immunology, Duke University, Durham, North Carolina, USA
Marcus Center for Cellular Cures, Duke University, Durham, North Carolina, USA
Department of Pathology, Duke University, Durham, North Carolina, USA
Department of Neurosurgery, Duke University, Durham, North Carolina, USA
Department of Medicine, University of Wisconsin Carbone Cancer Center, Madison, Wisconsin, USA
IMPACT-Center for Interventional Medicine for precision and advanced cellular therapy, Universidad de los Andes, Santiago, Chile
Cells for Cells and Consorcio Regenero, Chilean Consortium for Regenerative Medicine, Santiago, Chile
Department of Medicine, Section of Hematology, University of Verona, Verona, Italy
Cellular and Molecular Medicine, University of Ottawa, Ottawa, Ontario, Canada
Anesthesiology and Pain Medicine, University of Ottawa, Ottawa, Ontario, Canada
Clinical Epidemiology, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
Regenerative Medicine, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden
Department of Cellular Therapy and Allogeneic Stem Cell Transplantation, Karolinska University Hospital, Stockholm, Sweden
Department of Internal Medicine, Stem Cell Program and Institute for Regenerative Cures, University of California Davis, Sacramento, California, USA
UF Scripps Biomedical Research, Jupiter, Florida, USA
Laboratory of Pulmonary Investigation, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil
The First Affiliated Hospital, Soochow University Institutes for Translational Medicine, Suzhou, China
Institute of Health Sciences, Chinese Academy of Sciences, Shanghai, China
UMR U1236-MICMAC, Immunology and Cell Therapy Lab, Rennes University Hospital, Rennes, France
Osteoarthritis Research Program, Division of Orthopedic Surgery, Schroeder Arthritis Institute, University Health Network, Toronto, Canada
Krembil Research Institute, University Health Network, Toronto, Canada
Institute of Biomedical Engineering, University of Toronto, Toronto, Canada
Department of Medicine, Division of Hematology, University of Toronto, Toronto, Canada
Department of Biomedicine, University Hospital Basel, University of Basel, Basel, Switzerland

References
[1] Passamonti F, Cattaneo C, Arcaini L, Bruna R, Cavo M, Merli F, Angelucci E, Krampera M, Cairoli R, Della Porta MG, Fracchiola N, et al. Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: A retrospective, multicentre, cohort study. Lancet Haematol 2020;7:e737–45.
[2] Visco C, Marcheselli L, Mina R, Sassone M, Guidetti A, Penna D, Cattaneo C, Bonuomo V, Busca A, et al. A prognostic model for patients with lymphoma and COVID-19: A multicentre cohort study. Blood Adv 2022;6:327–38.
[3] Jiménez M, Roldán E, Fernández-Naval C, Villacampa G, Martínez-Gallo M, Medina-Gil D, Peralta-Garzón S, Pujadas G, Hernández C, et al. Cellular and
humoral immunogenicity of the mRNA-1273 SARS-CoV-2 vaccine in patients with hematologic malignancies. Blood Adv 2022;6:774–84.

[4] Lyski ZL, Kim MS, Lee DX, Raue HP, Raghunathan V, Griffin J, Ryan D, Brunton AE, Curlin ME, Silfka MK, Messier WB, Spurgeon SE. Cellular and humoral immune response to mRNA COVID-19 vaccination in subjects with chronic lymphocytic leukemia. Blood Adv 2022;6:1207–11.

[5] Mittelman M, Magen O, Barca N, Dagan N, Oster HS, Leader A, Balicer R. Effectiveness of the BNT162b2 mRNA COVID-19 vaccine in patients with hematological neoplasms in a nationwide mass vaccination setting. Blood 2022;139:1439–51.

[6] Pagano L, Salmantongo J, Marchesi F, López-Garcia A, Lamure S, Itri F, Gomes-Silva M, Dragonevt G, Falces-Romero I, van Doesen J, Sili U, Laborador J, et al. COVID-19 in vaccinated adult patients with hematological malignancies: Preliminary results from EPICCOVIDHA. Blood 2022;139:1588–92.

[7] Heskin J, Pallette SJ, Mughal N, Davies GW, Moore LSP, Raymond M, Jones R. Caution required with use of ritonavir-boosted PF-07321332 in COVID-19 management. Lancet 2022;399:21–2.

[8] Huang E, Jordan SC. Tocilizumab for COVID-19 therapy. N Engl J Med 2020: 383.

[9] Marconi FC, et al. Efficacy and safety of baricitinib for the treatment of hospitalized adults with COVID-19 (COV-BARRIER): A randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med 2021;9:1407–18.

[10] Jayk Bernal A, et al. Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. N Engl J Med 2022;389:506–20.

[11] Wen W, et al. Efficacy and safety of three new oral antiviral treatment (molnupiravir, favunavir and Paxlovid) for COVID-19: A meta-analysis. Ann Med 2022;54:516–23.

[12] Kabinger f, Skiller C, Schmitzova J. Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis. Nat Struct Mol Biol 2021;28:740–6.

[13] Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid TM. <https://www.fda.gov/media/155050/download> [accessed XXX] 2022.

[14] van de Veerdonk FL, Giamarellos-Bourboulis E, Pickkers P, Derde N, Leavis H, van der Zee A, et al. A guide to immunotherapy for COVID-19. Lancet 2022;399:21–2.

[15] Lu K, et al. Clinical efficacy and mechanism of mesenchymal stromal cells in treatment of COVID-19. Stem Cell Res Ther 2022;13:1–15.

[16] Leng Z, Zhu R, Hou W, et al. Transplantation of ACE2- mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. Aging Dis 2020;11:216–28.

[17] Meng F, Xu R, Wang S, Xu Z, Zhang C, Li Y, Yang T, Shi L, Fu J, Jiang T, et al. Human umbilical cord-derived mesenchymal stem cell therapy in patients with COVID-19: A phase 1 clinical trial. Signal Transduct Target Ther 2020;5:172.

[18] Shu L, Niu C, Li R, Huang T, Wang Y, Huang M, Ji N, Zheng Y, Chen X, Shi L, et al. Treatment of severe COVID-19 with human umbilical cord mesenchymal stem cells. Stem Cell Res Ther 2020;11(1):361.

[19] Kusuma GD, Carthew J, Lim R, Finth R. Effect of the microenvironment on mesenchymal stem cell paracrine signaling: Opportunities to engineer the therapeutic effect. Stem Cells Dev 2017;26(9):617–31.

[20] Dunbar H, Weiss DJ, Roldansson Enes S, Laffey JS, English K. The inflammatory lung microenvironment: a key mediator in MSC licensing. Cells 2021;10(11).

[21] Roldansson Enes S, Hampton TH, Barar J, McKenna DH, Dos Santos CC, Amiel E, et al. Healthy versus inflamed lung environments differentially affect mesenchymal stem cells. Eur Respir J 2021;58(4).

[22] Elliot J, et al. Decision makers need constantly updated evidence synthesis. Nature 2021;600(7889):383–5.

[23] Monaghan M, Bailey AJM, Monaghan J, Shorr R, Lalu MM, Ferguson DA, Allan DS. Updated living systematic review and meta-analysis of controlled trials of mesenchymal stromal cells to treat COVID-19: A framework for accelerated synthesis of trial evidence for rapid approval – FASTER Approval. Stem Cells Transl Med 2022;11(7):857–87.

[24] Qui W, et al. Cell-based therapy to reduce mortality from COVID-19: Systematic review and meta-analysis of human studies on acute respiratory distress syndrome. Stem Cells Transf Med 2020;9:1007.

[25] Kirkham AM, Bailey AJM, Monaghan J, Shorr R, Lalu MM, Ferguson DA, Allan DS. Updated living systematic review and meta-analysis of controlled trials of mesenchymal stromal cells to treat COVID-19: A framework for accelerated synthesis of trial evidence for rapid approval – FASTER Approval. Stem Cells Transl Med 2022;11(7):857–87.

[26] Zhu R, Yan T, Feng Y, Liu Y, Cao H, Peng G, et al. Mesenchymal stem cell treatment improves outcome of COVID-19 patients via multiple immunomodulatory mechanisms. Cell Res 2021;31(12):1244–62.

[27] Monsel A, et al. Treatment of COVID-19-associated ARDS with mesenchymal stromal cells: A multicenter randomized double-blind trial. Crit Care 2022;26.

[28] Kirkham AM, Bailey AJM, Monaghan J, Shorr R, Lalu MM, Ferguson DA, Allan DS. Updated living systematic review and meta-analysis of controlled trials of mesenchymal stromal cells to treat COVID-19: A framework for accelerated synthesis of trial evidence for rapid approval – FASTER Approval. Stem Cells Transl Med 2022;11(7):857–87.

[29] Qu J, et al. Cell-based therapy to reduce mortality from COVID-19: Systematic review and meta-analysis of human studies on acute respiratory distress syndrome. Stem Cells Transf Med 2020;9:1007.