Short Communication

International Society for Extracellular Vesicles and International Society for Cell and Gene Therapy statement on extracellular vesicles from mesenchymal stromal cells and other cells: considerations for potential therapeutic agents to suppress coronavirus disease-19

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First described in December 2019, the severe acute respiratory syndrome associated with coronavirus disease-19 (COVID-19) quickly evolved into a pandemic, with severe and increasing worldwide morbidity and mortality. Although most infected patients have mild to moderate symptoms or are even asymptomatic, older patients and those with pre-existing chronic diseases are at greater risk of developing serious complications, such as pneumonia or multiple organ failure. COVID-19 respiratory infection is marked by dysregulated immune responses leading to significant respiratory pathology as well as increased probabilities for multi-organ pathologies. While the inflammatory pathways are still being elucidated, notable components include increased circulating levels of pro-inflammatory cytokines and other mediators, including interleukin-6 (IL-6), interleukin-1β (IL-1β), induced protein 10 (IP10) and monocyte chemotactic protein-1 (MCP-1) [4, 6, 41]. There are also significant alterations in circulating inflammatory cell populations, with initial lymphocytosis followed by severe lymphopenia, with increased ratios of helper to regulatory T cells [4, 6, 30]. Since dysregulated immune responses and the cytokine storm are triggers for development of acute respiratory distress syndrome, an increasing effort and current clinical trials are focused on immune therapeutic approaches, such as IL-1 blockade (anakinra), IL-6 receptor blockade (tocilizumab) and Janus kinase inhibition [22]. In parallel, there are a rapidly increasing number of cell-based therapy investigations, mostly utilizing mesenchymal stromal cells (MSCs) [12]. These are based on supporting pre-clinical data for use of MSCs delivered either systemically or intratracheally in pre-clinical models of acute lung injuries and on demonstration of safety of systemic MSC administration in recent trials for acute respiratory distress syndrome resulting from other etiologies [15, 21].

Among the cell-based therapy investigations for COVID-19, some registered clinical trials aim to utilize extracellular vesicles (EVs) prepared from MSC-conditioned media rather than the cells themselves. MSC-EVs will be administered intravenously (ChiCTR2000030484) or by inhalation (NCT04276987, ChiCTR2000030261). The rationale for these approaches is based on a relatively small but growing number of investigations in pre-clinical lung injury and sepsis models in which MSC-EV preparations were described as being as safe and effective as—if not more than—their parent cells [19, 40]. The approach is further supported by a growing body of literature on the therapeutic potential and mechanisms of EVs from mesenchymal stromal cells (MSCs) and possibly other cell sources as treatments for COVID-19. Research and trials in this area are encouraged. However, ISEV and ISCT do not currently endorse the use of EVs or exosomes for any purpose in COVID-19, including but not limited to reducing cytokine storms, exerting regenerative effects or delivering drugs, pending the generation of appropriate manufacturing and quality control provisions, pre-clinical safety and efficacy data, rational clinical trial design and proper regulatory oversight.

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others that might trigger unforeseen side effects. Just recently, it was found that adipose-derived MSC-EVs had higher thrombogenic activity than bone marrow-derived MSC-EVs [3, 34]. Thus, the source of parental cells might increase thrombosis risk. Coupled with the finding that activation of complement pathways and an associated procoagulant state seem to result in catastrophic microvascular injury syndrome in a proportion of severe COVID-19 cases [18], MSC-EV administration could even be counterproductive in COVID-19.

To this end, it is imperative that stringent “identity” and “potency” parameters are defined and potential side effects addressed before MSC-EV or other EV preparations are released for therapeutic applications [16, 32, 39]. To date, many groups use in-house MSC-EV manufacturing and characterization strategies, mainly for pre-clinical studies [2]. Protocols fulfilling Good Manufacturing Practice (GMP) criteria are sparse, and just a few have been published [8, 26, 33]. For product candidates, studies focusing on safety and clinical pharmacology need to be performed. Results of such studies are mandatory to provide guidance for administration of manufacturing, storage, dosing and administration of EV-based therapeutics in specific target diseases.

We would like to refer to a recent statement by ISCT on the use of MSCs in COVID-19 [13] and one by the Italian STEMnet, as many of the same considerations apply to MSC-EVs or other EVs. Governmental organizations, health care providers and clinical investigators must take the lead by insisting that clinical uses of EVs follow appropriate scientific, regulatory and ethical guidelines and are approved only after a rigorous review by duly empowered agencies. The ethical guidelines produced by the World Health Organization are a useful baseline. The urgency of the current outbreak does not justify administration of EVs in uncontrolled compassionate use settings and does not obviate the need to register clinical trials, obtain informed consent from patients or protocols and otherwise comply with good clinical practice. In particular, even limited compassionate use should employ well-characterized MSC-EV preparations produced through strict GMP conditions under the oversight of the relevant national regulatory entity. Additional outbreak-specific measures may be needed, including establishing simplified clinical protocols for hospitalized patients, such as the World Health Organization COVID-19 core protocol; minimizing risks to trial integrity; and changing logistics of trial participant visits (e.g., implementation of remote assessments) as well as protocol changes for the sake of hazard minimization, which may need to be implemented and reported, in Europe, to the Institute for Research in Biomedicine Barcelona after the fact. Certainly, to foster developments, it is helpful to have regulatory flexibility and support from sources such as the US Food and Drug Administration special emergency program for possible therapies, the Coronavirus Treatment Acceleration Program, the European Medicines Agency (EMA) COVID-19 Pandemic Task Force, the EMA guidance for medicine developers and companies on COVID-19 and the guidelines for clinical trials published by an EMA-coordinated group and the Medicines and Healthcare Products Regulatory Agency, respectively. Most or all of the considerations covered for cell-based therapies are also applicable to EV investigations.

In conclusion, to mitigate the risk of potentially life-threatening side effects, ISCT and ISEV strongly urge that the potential benefits and risks in the use of MSC-EVs for COVID-19 be weighed carefully against available pre-clinical data in relevant animal models and clinical data from relevant MSC clinical trials and that any use of EVs be carefully evaluated through rational clinical trial design, employing well-characterized EV preparations produced under strict GMP conditions and under the proper regulatory oversight.

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Declaration of competing interest
JDA is the co-founder of an exosome therapeutics company called Somos Therapeutics, Inc. BG is a scientific advisory board member with Evox Therapeutics and Innovex Therapeutics SL. MG has a consulting and advisory role with MDMune. BLL has stock and other ownership interests with Tmunity Therapeutics; has received honoraria from Novartis, Terumo and AstraZeneca; and has a consulting or advisory role with Bramer Bio/ThermoFisher Viral Vector Services, Avectas, Immuneel, Ori Biotech and Vycellix. SKL is the founder of Paracrine Therapeutics and has a scientific advisory role with Ilia Biologics and ExoCo. SAM is the inventor of intellectual property licensed by BCH to United Therapeutics Corp.

Author contributions
Drafting the manuscript: VB, DJW, KWW, SKL, BG. All authors have approved the final article.

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