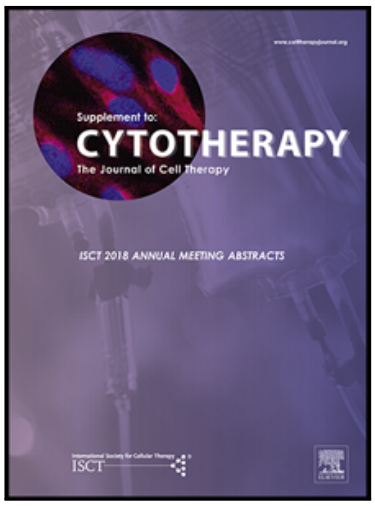

ISEV and ISCT statement on EVs from MSCs and other cells: considerations for potential therapeutic agents to suppress COVID-19

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PII: S1465-3249(20)30662-9
DOI: https://doi.org/10.1016/j.jcyt.2020.05.002
Reference: JCYT 1211

To appear in: *Cytotherapy*

Received date: 1 May 2020
Accepted date: 2 May 2020

Please cite this article as: Verena Börger , Daniel J. Weiss , Johnathon D. Anderson , Francesc E. Borràs , Benedetta Bussolati , David R.F. Carter , Massimo Dominici , Juan M. Falcón-Pérez , Mario Gimona , Andrew F. Hill , Andrew M. Hoffman , Dominique de Kleijn , Bruce L. Levine , Rebecca Lim , Jan Lötvall , S. Alex Mitsialis , Marta Monguió-Tortajada , Maurizio Muraca , Rienk Nieuwland , Anna Nowocin , Lorraine O'Driscoll , Luis A. Ortiz , Donald G Phinney , Ilona Reischl , Eva Rohde , Ralf Sanzenbacher , Clotilde Théry , Wei Seong Toh , Kenneth W. Witwer , Sai Kiang Lim , Bernd Giebel , ISEV and ISCT statement on EVs from MSCs and other cells: considerations for potential therapeutic agents to suppress COVID-19, *Cytotherapy* (2020), doi: https://doi.org/10.1016/j.jcyt.2020.05.002

ISEV and ISCT statement on EVs from MSCs and other cells: considerations for potential therapeutic agents to suppress COVID-19

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STATEMENT: The International Society for Cellular and Gene Therapies (ISCT) and the International Society for Extracellular Vesicles (ISEV) recognize the potential of extracellular vesicles (EVs, including exosomes) 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 storm, 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.

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 or those with existing chronic diseases are at greater risk of developing serious complications such as pneumonia or multiple organ failures. 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 chemoattractant protein-1 (MCP-1) (Chen et al., 2020; Diao et al., 2020; Yang et al., 2020). 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 (Chen et al., 2020; Diao et al., 2020; Qin et al., 2020). Since dysregulated immune responses and the cytokine storm are triggers for development of acute respiratory distress syndrome (ARDS), an increasing effort and current clinical trials are focused on immune therapeutic approaches such as IL-1 blockade (anakinra), IL-6 receptor blockade (tocilizumab) or Janus kinase (JAK) inhibition (Mehta et al., 2020). In parallel, there are a rapidly increasing number of cell-based therapy investigations, mostly utilizing mesenchymal stromal cells (MSCs) (Khoury et al., 2020a). 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 ARDS resulting from other etiologies (Laffey and Matthay, 2017; Matthay et al., 2019).

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 safe and effective, if not more effective than their parent cells (Mahida et al., 2020; Worthington and Hagood, 2020). The approach is further supported by a growing body of literature on the therapeutic potential and mechanisms of EVs in a wide range of diseases, including recent positive results in a steroid-refractory Graft-versus-Host Disease (GvHD) patient treated with MSC-EVs, and in a single centre, randomized, placebo-controlled phase II/III clinical pilot study on chronic kidney disease (CDK) patients treated with MSC-EVs (Kordelas et al., 2014; Nassar et al., 2016).

The mechanisms, by which EVs exert their beneficial effects, as well as their site(s) of action, remain incompletely understood. Nonetheless, effects observed in a range of pre-clinical non-COVID-19 model systems suggest that they may also have efficacy against COVID-19. For example, systemic administration of MSC-EV preparations modulated immune responses such as elevated cytokine storms in relevant lung disease models, including acute lung injury and sepsis (Liu et al., 2019; Mansouri et al., 2019; Monsel et al., 2015; Morrison et al., 2017; Park et al., 2019; Varkouhi et al., 2019; Willis et al., 2018; Zhu et al., 2014). Notably, in *E. coli* induced pneumonia mouse models, MSC-EV administration was found to enhance phagocytosis of bacteria (Hao et al., 2019; Monsel et al., 2015). In a pig model MSC-EVs were shown to attenuate influenza virus-induced acute lung injury, amongst others by inhibiting influenza virus replication (Khatri et al., 2018). Diseaseattenuating effects on inflammatory immune responses following MSC-EV administration have also been observed in other disease models (Börger et al., 2017). In an ischemic stroke model, for example, systemic MSC-EV administration reduced stroke-induced lymphopenia and pro-inflammatory immune responses in the brain and periphery, resulting in overall improvement of disease symptoms (Doeppner et al., 2015; Wang et al., 2020). These preliminary observations support MSC-EV administration as a potential treatment option for COVID-19.

However, the specific scientific rationale for MSC-EV and other EV administration to COVID-19 patients needs to be better understood and justified. For example, MSC-EVs do not necessarily suppress immune responses, but rather modulate them. Specifically, they seem to moderate acute immune responses towards regulatory responses, with the latter inducing tolerance and restoring homeostasis (Giebel and Hermann, 2019; Zhang et al., 2018; Zhang et al., 2014). While tolerance induction in GvHD and other non-infectious diseases may be beneficial, it might also have severe adverse effects in the presence of replicating pathogens. Although influenza and *E. coli* infections were attenuated in selected models (Hao et al., 2019; Khatri et al., 2018; Monsel et al., 2015), other viruses and bacteria might conceivably expand in uncontrolled manners in induced tolerogenic environments.

A number of additional issues should be considered before administering MSC-EVs to COVID-19 patients. These include the source of MSC-EVs. MSCs are a heterogeneous cell entity that can be obtained from different tissues. Even if derived from the same tissues, they may display interindividual and possibly clone specific functional differences (Phinney, 2012; Phinney et al., 1999; Radtke et al., 2016; Vogel et al., 2003). Indeed, side-by-side comparison of four MSC-EV preparations harvested from the conditioned media of different donor-derived bone marrow MSCs demonstrated significant variations in cytokine content (Kordelas et al., 2014). Whether this correlates with therapeutic potency is not yet clear; however, in the example of the ischemic stroke model, it was demonstrated that MSC-EV preparations with comparable particle and protein contents can significantly differ in potency. While some preparations effectively suppressed stroke symptoms, others failed to exert therapeutic activities (Wang et al., 2020). Furthermore, in an acute lung injury model, EVs from young but not from aged MSCs alleviated LPS-induced acute lung injury (Huang et al., 2019).

Potentially, heterogeneity of EV potency due to different sources, preparations, aging, and other factors could be resolved by generating immortalized clonal MSC lines that could be rigorously tested for EV production and potency (Chen et al., 2011). Still, apart from their immunomodulatory capabilities, MSC-EVs apparently also control additional biological processes, some with approved therapeutic functions (Arslan et al., 2013), and others that might trigger unforeseen side effects. Just recently, it was found that adipose-derived MSC-EVs had higher thrombogenic activities than bone-marrow-derived MSC-EVs (Chance et al., 2019; Silachev et al., 2019). Thus, the source of parental cells might increase thrombosis risks. Coupled to 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 (Magro et al., 2020), 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 (Lener et al., 2015; Reiner et al., 2017; Witwer et al., 2019). To date, many groups use in-house MSC-EV manufacturing and characterization strategies, mainly for preclinical studies (Börger et al., 2017). Protocols fulfilling good manufacturing practice (GMP) criteria are sparse, and just a few have been published (Gimona et al., 2017; Pachler et al., 2017; Rohde et al., 2019). For product candidates, studies focusing on safety and clinical pharmacology need to be performed. Results of such studies are mandatory to provide guidance for adjustment 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 (Khoury et al., 2020b) and one of the Italian StemNet[1], as many of the same considerations apply to MSC-EVs or other EVs. Governmental organizations, healthcare 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 (WHO) are a useful baseline.[2] 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 proxies, and otherwise comply with good clinical practice (GCP). 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 establishment of simplified clinical protocols for hospitalized patients, such as the WHO COVID-19 core protocol, minimizing risks to trial integrity,[3] changing logistics of trial participant visits (e.g. implementation of remote assessments), and protocol changes for the sake of hazard minimization that may need to be implemented and reported, in Europe, to the Institute for Research in Biomedicine (IRB) Barcelona after the fact. Certainly, regulatory flexibility and support is helpful to foster developments, such as the US Food and Drug Administration (FDA) special emergency program for possible therapies, the Coronavirus Treatment Acceleration Program (CTAP),[4] the European Medicines Agency (EMA) COVID-19 pandemic Task Force (COVID-ETF) activities,[5] the EMA guidance for medicine developers and companies on COVID-19[6] and the guidelines for clinical trials published by an EMA coordinated group[7,] or the Medicines and Healthcare products Regulatory Agency (MHRA),[8] respectively. Most or all of the considerations covered for cell-based therapies are also applicable to EV investigations.

[1] http://www.gismonline.it/images/filepdf/20200316_PostionSTEMNET_Covid19-MSCs.pdf

[2] Organisation WH. Guidance for managing ethical issues in infectious disease outbreaks. World Heal Organ 2016:62.

[3] FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic Guidance for Industry, Investigators, and Institutional Review Boards. 2020.

[4] Coronavirus Treatment Acceleration Program (CTAP) | FDA n.d. https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap (accessed April 1, 2020).

[5] COVID-19 EMA pandemic Task Force (COVID-ETF): "to help EU Member States and the European Commission to take quick and coordinated regulatory action on the development, authorisation and safety monitoring of treatments and vaccines intended for the treatment and prevention of COVID-19." https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/emas-governance-during-covid-19-pandemic#covid-19-ema-pandemic-task-force-section

[6] https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/guidance-medicine-developers-companies-covid-19

[7] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

[8] https://www.gov.uk/guidance/mhra-regulatory-flexibilities-resulting-from-coronavirus-covid-19#clinical-trials

In conclusion, to mitigate the risk of potential of 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.

Disclosures:

JDA: Co-founder of an exosome therapeutics company called Somos Therapeutics, Inc.

BG: Scientific advisory board member of Evox Therapeutics and Innovex Therapeutics SL.

MG: Consulting and Advisory Role: MDimune

BLL: Stock and Other Ownership Interests: Tmunity Therapeutics. Honoraria: Novartis, Terumo, AstraZeneca. Consulting or Advisory Role: Brammer Bio/ThermoFisher Viral Vector Services, Avectas, Immuneel, Ori Biotech, Vycellix.

SKL: Founder, Paracrine Therapeutics, Scientific advisory role: Ilias Biologics and ExoCo

S.A.M. is the inventor of Intellectual Property licensed by BCH to United Therapeutics Corp.

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