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Re: "Exosomes Derived from Bone Marrow Mesenchymal Stem Cells as Treatment for Severe COVID-19" by Sengupta et al.

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The catastrophic COVID-19 pandemic demands urgent development and testing of potential new therapeutics. However, these need to be developed in a transparent way including rigorous peer-reviewed and appropriately conducted, regulated, and reported clinical investigations.

Recently, Sengupta et al. reported on intravenous application of exosomes in 24 patients suffering from COVID-19 with moderate-to-severe acute respiratory distress syndrome [1]. Although we welcome rigorous investigations of extracellular vesicles (EVs) in this setting, key details were lacking that allow adequate assessment of the medical value and scientific rationale of this study. Specifically, little information was provided about the investigational new drug "ExoFlo™," including EV characterization, biological properties, and proposed biological or therapeutic actions. The website of one manufacturer offering ExoFlo ("Direct Biologics") (https://directbiologics.com/#aboutus) does not provide this information and there are no other obvious sources of the relevant product details. Although we understand that ExoFlo was produced under current good manufacturing practice (cGMP) conditions in an U.S. Food and Drug Administration (FDA)-certified and inspected facility, it is not clear as to what was actually being administered to the patients. The information provided in the article is thus insufficient for critical analyses and comprehension of the results as well as for potential replication of the investigation.

We, therefore, request clarification of the following points regarding the ExoFlo product and application:

(1) Are the FDA-registered facilities that meet cGMPs and current good tissue practices specifically FDA registered for the manufacture of exosome drug products?
(2) What is the evidence that ExoFlo is a truly exosomal agent, as opposed to a general EV product or cell releasate, and that it is derived from bone marrow mesenchymal "stem" cells [2,3]?
(3) What is the biological activity of ExoFlo as compared with other products that were cited to rationalize the use of ExoFlo in this publication.
(4) What was the actual dose? The description of "15 ml of ExoFlo" is meaningless without some measure of concentration per unit volume.
(5) What vital signs were monitored during and after the infusion periods, such as continuous ECG and pulse oximetry?
(6) Appreciating the severity and broad manifestations of SARS-CoV-2 infection, how could the data and safety monitoring board conclude that events occurring >72 h after application were unrelated?
(7) To what extent does EVs reporting comply with field consensus standards as summarized by the MISEV2018 criteria [4]? Important parameters required to be reported are provided by the EV-TRACK knowledgebase (www.evtrack.org). We therefore encourage to enter important information about methods and product characteristics of ExoFlo into the EV-TRACK database.

As members of leading scientific societies (International Society for Cell and Gene Therapy [ISCT] and International Society for Extracellular Vescles [ISEV]) promoting the study and clinical applications of cell-based therapies, including those utilizing cell-derived EVs, we are hopeful that these will contribute to treatment of COVID-19 patients [4]. However, during the COVID-19 pandemic, transparent disclosures

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are more critical than ever to validate new therapies, reduce potential harm, and avoid creating unrealistic expectations. We call on the authors to provide more information about this potentially important product.

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Author Disclosure Statement

S.K.L. is founder of Paracrine Therapeutics and has scientific advisory role at Ilias Biologics and ExoCo. B.G. is scientific advisory board member of Evox Therapeutics and Innovex Therapeutics SL. The others authors have nothing to disclose.

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