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Title: Response to Maccio et al., "Multifactorial Pathogenesis of COVID-19-related Coagulopathy: Can defibrotide have a role in the early phases of coagulation disorders?"

Authors:

Edward Richardson[1*], Carmelo Carlo-Stella[2], Ruben Jara[3], Israel Vlodavsky[4], Massimo Iacobelli[5], Jawed Fareed[6], Clifton Mo[7], Peter O'Gorman[8], Gregory Yanik[9], Marta Palomo[10], Maribel Diaz-Ricart,[11] and Jose M. Moraleda[12**], on behalf of the DEFACOVID Study Group.

Affiliations:

[1] Frank H. Netter M.D. School of Medicine at Quinnipiac University, North Haven, Connecticut, USA; Department of Surgery, Yale University School of Medicine, New Haven, Connecticut, USA.

[2] Department of Oncology and Hematology, Humanitas Clinical and Research Center - IRCCS, Rozzano-Milano,Italy; Department of Biomedical Sciences, Humanitas University, Rozzano-Milano, Italy.

[3] Intensive Care Unit. Virgen de la Arrixaca University Hospital, University of Murcia, Spain.

[4] Technion Integrated Cancer Center, Rappaport Faculty of Medicine, Technion, Haifa, Israel.

[5] Techitra s.r.l., Milan, Italy.

[6] Department of Molecular Pharmacology and Therapeutics, Hemostasis and Thrombosis Research Laboratories, Loyola University Medical Center, Chicago, Illinois, USA.

[7] Department of Hematologic Oncology, Dana Farber Cancer Institute, Boston, Massachusetts, USA.

[8] Mater University Hospital, UCD School of Medicine and Medical Science, Dublin, Ireland.

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[9] Department of Pediatrics, Blood and Marrow Transplantation Program, University of Michigan, Ann Arbor, MI, USA; Department of Internal Medicine, Blood and Marrow Transplantation Program, University of Michigan, Ann Arbor, MI, USA.
[10] Josep Carreras Leukaemia Research Institute, Hospital Clinic, University of Barcelona, Barcelona, Spain; Barcelona Endothelium Team, Barcelona, Spain.
[11] Hematopathology, Centre Diagnostic Biomedic, Hospital Clinic, Institut d'Investigacions Biomediques August Pi i Sunyer, Universitat de Barcelona, Barcelona, Spain; Barcelona Endothelium Team, Barcelona, Spain.
[12.] Department of Hematology, Stem Cell Transplant and Cell Therapy Unit, IMIB-Arrixaca, Virgen de la Arrixaca University Hospital, University of Murcia, Spain.

Institution: Frank H. Netter M.D. School of Medicine at Quinnipiac University, 370 Bassett Road, North Haven, CT 06473, USA.

***Corresponding Author:** Edward Richardson, B.S. MMSc.
Email: edward.richardson@quinnipiac.edu Phone: (781) 290-7059
Address: 275 Winchester Avenue, New Haven, CT 06511 USA

****Senior Author:** Jose M. Moraleda M.D.
Email: jmoraled@um.es

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Edward Richardson and Jose M. Moraleda contributed to the composition, scholarship and revision of the manuscript.
Carmelo Carlo-Stella, Ruben Jara, Israel Vlodavsky, Massimo Iacobelli, Jawed Fareed, Clifton Mo, Peter O'Gorman, Gregory Yanik, Marta Palomo, and Maribel Diaz-Ricart all contributed to the scholarship and revision of the manuscript.

Conflict of Interest:
Edward Richardson has no actual or potential conflict of interest to declare.

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Response to Maccio et al., "Multifactorial Pathogenesis of COVID-19-related Coagulopathy: Can defibrotide have a role in the early phases of coagulation disorders?"

We read with interest the letter by Maccio et al., which postulates a role for defibrotide (DF) in the treatment of coagulation disorders observed in COVID-19 [1]. Their commentary effectively explores the contribution of macrophages towards the coagulopathy observed in COVID-19, while highlighting the similarities between COVID-19 associated vascular lesions and veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS) and commonly referred to as VOD/SOS. DF has indeed been shown to improve overall survival in patients with severe VOD/SOS [2] and may be beneficial in the treatment of COVID-19, but not exclusively because of the observed similarities to VOD/SOS.

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In detailing the role of macrophages in COVID-19-related coagulopathy, the letter overlooks some other etiologies. While macrophages may drive endothelial dysfunction by production of reactive oxygen species (ROS) and pro-inflammatory cytokines, the endotheliopathy observed in COVID-19 may also be driven by direct infection of endothelial cells by SARS-CoV-2 [3].

Angiotensin converting enzyme 2 (ACE2) receptors mediate the entry of SARS-CoV-2 into the cell, via direct interaction between ACE2 and primed viral spike proteins. ACE2 is expressed abundantly on lung alveolar epithelial cells and enterocytes of the small intestine but is also present in arterial and venous endothelial cells, pericytes, and vascular smooth muscle cells across numerous organ systems [4]. Direct infection and apoptotic death of endothelial cells by SARS-CoV-2 has been demonstrated across vascular beds of several organs via post mortem histology [3].

The p38 MAPK pathway may be a critical factor in COVID-19-related endotheliopathy. Similar to other respiratory RNA viruses, SARS-CoV-2 infection induces upregulation of p38 MAPK, perhaps enhancing viral replication [5]. More notably, however, the entry mechanism of SARS-CoV-2 disables a key homeostatic process employed by the cell to diminish p38 MAPK downstream of Angiotensin II (Ang II) signaling. ACE2 on the cell surface converts Ang II into Angiotensin 1-7, which binds the Mas receptor and downregulates the vasoconstrictive and proinflammatory effects driven by Ang II through p38 MAPK activation. Binding of ACE2 by SARS-CoV-2 leads to endocytosis and proteolytic cleavage, resulting in decreased ACE2 expression and functionality, thereby diminishing the counterbalancing effect served by ACE2 [4]. The result is upregulation of p38 MAPK, which activates the transcription of proinflammatory cytokines such as IL-6, TNF-alpha, and IL-1beta, all of which are detected at high levels in patients with COVID-19. Unchecked p38 MAPK activity may thereby promote endotheliitis, vasoconstriction, and thrombosis while also augmenting the viral life cycle [6].

DF has been demonstrated to decrease p38 MAPK activation through direct interaction with endothelial cells [7], and DF treatment of COVID-19 may serve to target this signaling axis in COVID-related endotheliopathy. Studies have demonstrated increased integrin ligand expression, disrupted endothelial cell membranes, and perivascular inflammation in COVID-19,

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all of which may also contribute to endothelial cell dysfunction and disseminated intravascular coagulation observed clinically [7, 8]. In murine models, DF down-regulates the expression of endothelial cell adhesion molecules that are critical to platelet activation and leukocyte migration such as P-selectin, E-selectin, V-CAM and ICAM-1, and lowers endothelial cell release of pro-inflammatory cytokines [9]. In addition, the severity of COVID-19 has been linked to heparanase activity, with significant elevations of heparanase reported in COVID-19 patients [10]. As a key regulator of inflammation at the endothelium, heparanase likely plays a central role in COVID-related vasculitis and thrombosis. DF potently inhibits both heparanase expression and enzymatic activity, furthering its significant potential as a treatment for COVID-19 [2, 7, 9].

In the ongoing Spanish DEFACOVID phase IIb randomized clinical trial (clinicaltrials.gov: NCT04348383), as well as other international studies either planned or already underway in Italy, the United States, Ireland and the United Kingdom, patients treated with DF are being comprehensively assessed for serum plasma inflammatory markers, including heparanase, pro-inflammatory and anti-inflammatory cytokines, immune subpopulation cells, and prothrombotic / antifibrinolytic markers such as Von Willebrand factor and soluble thrombomodulin. Preliminary results are encouraging to date, and these data will hopefully serve to demonstrate the effects of DF on the proposed targets in COVID-19.

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