Mackow Cover Page and Project Summary

REVISE AND RESUBMIT SEED GRANT PROGRAM PROPOSAL:

Goal: Enhance Previously Scored NIH submission scored 35 by adding preliminary results and rebutting mistaken reviewer statements that SARSCOV2 infects ECs. Published data from COVID-19 patient lungs demonstrates that pulmonary ECs are not infected, and our published studies demonstrate that primary human ECs from lung, kidney, brain, dermis and umbilical vein are not SARSCOV2 infected unless they are transduced to express recombinant ACE2. In fact no studies have shown SARSCOV2 antigen colocalizes with PECAM1 positive endothelial cells, and studies have shown that PECAM1 fails to colocalize with ACE2.

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TITLE: SARS-CoV-2 Infected Alveolar Epithelial Cells Aberrantly Activate Endothelial Cells

R21 Submitted July 15 2021. **Scored 35 VIRB Study Section Nov. 7 2021. (score of 30 is funded).**

Project Summary:

SARS-CoV-2 (SCoV2) causes an acute respiratory distress syndrome associated with endotheliitis and obstructive microvascular thrombosis. SCoV2 uses ACE2 receptors to infect alveolar type II (AT2) epithelial cells (AEpCs). AEpCs share basement membranes with pulmonary microvascular endothelial cells (PMECs) forming a functional unit that controls oxygen exchange and activation of the vasculature. PMECs normally regulate coagulative, inflammatory and thrombotic responses that are aberrantly activated in COVID-19 patients. PMECs lack ACE2 receptors and are not SCoV2 infected, however activating the vasculature does not require PMECs to be infected.

Our findings indicate that SCoV2 infected AEpCs release factors that externally activate PMECs. Roles for SCoV2 infected AEpCs in activating coagulative/inflammatory PMEC responses found in severe COVID-19 patients remain to be resolved. We found that SCoV2 infected AEpCs induce inflammatory alarmins that act on PMEC receptors. In addition, conditioned media from SCoV2 infected AEpCs directs the shedding of a critical coagulation inhibitor, thrombomodulin (TM), from PMECs. Shedding of TM is observed in PMECs from COVID-19 patients and provides a fundamental mechanism for activating vascular coagulation and thrombotic programs. We propose defining the mechanism of SCoV2 infected AEpCs activation of coagulative/thrombotic PMEC responses. These studies are aimed at revealing therapeutic targets for preventing severe COVID-19 disease.