Mackow Cover Page and Project Summary

COVID-19 SEED GRANT PROGRAM PROPOSAL

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TITLE: Therapeutic Targeting SARS-CoV-2 Induced ACE2/Bradykinin Pulmonary Edema

Project Summary:

SARS-CoV-2 causes an acute respiratory distress syndrome (ARDS) in COVID-19 patients. SARS-COV-2 uses ACE2 receptors to infect pulmonary epithelial and endothelial cells (ECs). Infection of pulmonary epithelial cells fosters respiratory spread, while the underlying pulmonary endothelium regulates pulmonary fluid accumulation (edema) and inflammation that contribute to ARDS. SARS-CoV-2 binding to ACE2 receptors on ECs disrupts a balanced system that normally regulates pulmonary edema, hypoxia and inflammation that results in ARDS. ACE2 is highly expressed in lung, heart and kidney endothelium, and ACE2 regulates the accumulation of bradykinin, a vasoactive peptide that causes angioedema and acts on ECs to increase permeability, cytokine release and inflammation associated with ARDS. In fact, ACE2 knockout mice display more severe ARDS and recombinant expressed ACE2 protects mice from ARDS.

My lab studies acute respiratory distress caused by hantavirus regulation of EC responses. Here we propose related studies that analyze the role of SARS-CoV-2 regulation of ACE2 functions in primary human pulmonary ECs. We will determine whether ACE2 dysfunction is directed by the SARS-CoV-2 Spike protein and assess the therapeutic potential of recombinant expressed ACE2, and FDA approved bradykinin inhibitors, to inhibit SARS-CoV-2 directed EC permeability, sensitivity to hypoxia and induction of inflammatory cytokine responses.