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Preventing SARS-CoV-2 infection by blocking a tissue serine protease

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***Abstract*:** Currently, there are no proven pharmacologic interventions to reduce the clinical impact and prevent complications of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, the cause of the ongoing Coronavirus Disease of 2019 (COVID-19) pandemic. Selecting specific pharmacological targets for the treatment of viral pathogens has traditionally relied in blockage of specific steps in their replicative lifecycle in human cells. However, an alternative approach is reducing the molecular cleavage of the viral surface spike protein of SARS-CoV-2 to prevent viral entry into epithelial cells.

Keywords: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2); COVID-19; Serine proteases; COVID-19 drug treatment

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Currently, there are no proven pharmacologic interventions to reduce the clinical impact and prevent complications of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, the cause of the ongoing Coronavirus Disease of 2019 (COVID-19) pandemic. This pandemic has produced substantial global economic and social disruptions, and it has caused devastating medical consequences in terms of morbidity and mortality in 180 countries to date. Acute respiratory distress syndrome (ARDS) is a cause of major life-threatening end-organ damage of this novel coronavirus infection.[1]

Selecting specific pharmacological targets for the treatment of viral pathogens has traditionally relied on blockage of specific steps in their replicative lifecycle in human cells. However, an alternative approach is reducing the molecular cleavage of the viral surface spike protein of SARS-CoV-2 to prevent viral entry into epithelial cells. The pathogenesis of influenza virus infection of the respiratory epithelium is illustrative of this approach. Influenza viruses require priming of the viral hemagglutinin (HA) by tissue serine-proteases in the human host before infecting epithelial cells. The HA is cleaved at a single basic amino acid by tryptase clara, a serine-protease present in normal lung secretions.[2] Highly pathogenic avian influenza strains, such as influenza A H_5N_1, have more highly cleavable HA sites involving multiple basic amino acids, which may potentially explain the severe clinical outcomes of this infection.[2–4] Like in the HA of highly pathogenic influenza viruses, the SARS-CoV-2 S protein can be primed by a transmembrane serine protease (TMPRSS2). TMPRSS2 is required for infection of cells, unlike other proteases with activity at this site. After being primed, S protein binds to ACE2 receptors on epithelial cells and initiates fusion.[5] TMPRSS2 is present in the gastrointestinal tract, which could explain the commonly reported GI effects with COVID-19.

Given viral invasion of respiratory epithelial ($ACE2^+$) cells, the pathogenesis of ARDS likely starts with the death of the epithelial cells, as seen in highly pathogenic avian influenzas and the Severe Acute Respiratory Syndrome (SARS) coronavirus of 2002.[6,7] To prevent host immune-caused lung inflammation, corticosteroids have been tried in small trials of viral-induced ARDS, like SARS. However, there have been no clinical benefits of corticosteroids in viral-induced ARDS.[8] Targeting this disease at an earlier step in the pathogenesis is much more likely to be beneficial as a prophylactic or therapeutic drug.

TMPRSS2 is the required protease in S protein activation but is not necessary for homeostasis[5]. Camostat mesylate is a TMPRSS2 inhibitor

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approved in Japan for the treatment of chronic pancreatitis in humans.[5,9] Phase I/II trials are active in the US for oral camostat mesylate for pain in patients with chronic pancreatitis with minimal side effects.[9] Separately, a small American study tested the safety of intranasal camostat mesylate as a potential agent to increase ENaC activity in cystic fibrosis (CF) patients. Mild adverse effects such as nasal irritation and rhinorrhea were seen in patients with CF and, in some patients, higher doses may cause hematuria.[10] Though oral camostat mesylate has a high volume of distribution, including to the lung, inhaled camostat mesylate would be the most direct route of administration to inhibit SARS-CoV-2 priming in the respiratory tract. There is now a clinical trial underway in Denmark: The Impact of Camostat Mesilate on COVID-19 Infection (CamoCO-19) [ClinicalTrials.gov identifier: NCT04321096]. We are urgently following up research results from clinical trials to assess the efficacy of oral and inhaled camostat mesylate in patients with severe manifestations of COVID-19, and recommend studies assessing its potential as a prophylactic agent.

Author contributions

Katherine C. Jankousky: Investigation, writing—original draft, writing—reviewing and editing. Carlos Franco-Paredes: Conceptualization, investigation writing—original draft, writing—reviewing and editing. Andrés F. Henao-Martínez: Conceptualization, writing—reviewing and editing. Jonathan Schultz: Writing—review and editing. Samuel Windham: Writing—review and editing. Leland Shapiro: Conceptualization, investigation, writing—review and editing.

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