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Brief Overview on "Brilacidin Demonstrates Inhibition of SARS-CoV-2 in Cell Culture"

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Abstract

The COVID-19 pandemic remains a pressing global challenge. Worldwide mortality attributable to COVID-19 now exceeds 4 million deaths. There is an urgent need for developing novel therapeutics to treat SARS-CoV-2. Our recent study showed brilacidin, a synthetic small molecule with peptide-like properties, potently inhibits SARS-CoV-2 in cell culture. Additionally, brilacidin exhibited *in vitro* inhibition in combination with remdesivir, the only FDA-approved drug for treatment of COVID-19. Brilacidin is currently undergoing Phase 2 clinical testing for treatment of moderate-to-severe COVID-19 in hospitalized patients.

Keywords: Severe acute respiratory syndrome; Coronavirus; SARS-CoV-2

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Description

SARS-CoV-2, the novel coronavirus that has led to the global COVID-19 pandemic, is characterized by extreme contagiousness and significant associated mortality/morbidity [1]. Worldwide, almost 193 million people have been infected by COVID-19, resulting in over 4.1 million deaths. Research also shows approximately 25 percent of people who initially experience mild forms of COVID-19 will exhibit lingering symptoms, affecting overall wellbeing and ability to function--a condition that has been termed "Long COVID" [2]. Approximately 1 in 2 hospitalized COVID-19 patients have been later observed to develop health complications [3]. Finally, the rise of more transmissible, virulent, and even drug- and vaccine-resistant strains of SARS-CoV-2, coupled with a relaxation of precautionary measures (mandatory masking, physical distancing), has further complicated controlling the contagion [4].

Current COVID-19 treatments are limited to a handful of antiviral therapies and anti-inflammatory drugs, which have proven only moderately effective in fighting the disease. As a result, there exists a large unmet need for developing new therapeutics capable of safely and effectively treating SARS-CoV-2 and potentially helping prevent future viral outbreaks [5,6].

Antimicrobial peptides, also called Host Defense Proteins/Peptides (HDPs), comprise potentially effective countermeasures against COVID-19, having shown pre-clinical inhibitory activity against different types of viruses, including SARS-CoV-2 [7-12].

Brilacidin (PMX-30063) is a synthetic, nonpeptidic, mimetic of HDPs that was designed *de novo* to be much smaller, more stable, more potent, more selective, and more economical to manufacture than natural HDPs. Brilacidin has already been shown to exhibit potent antibacterial activity in Phase 2 clinical trials for treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI), and immuno/anti-inflammatory activity, as supported in Phase 2 clinical trials for treatment of Ulcerative Proctitis/Ulcerative Proctosigmoiditis (a type of Inflammatory Bowel Disease), and Oral Mucositis (a complication of chemoradiation) [13-16]. In total, brilacidin has been tested in 9 clinical trials, providing established safety and efficacy data on over 500 subjects. Additionally, two independent predictive machine learning studies identified brilacidin as one of the most promising inhibitors of SARS-CoV-2 based on its molecular properties [17,18].

Within the broader context of the global COVID-19 pandemic and the potential therapeutic role for HDPs, brilacidin was evaluated in pre-clinical experiments to determine if the compound might exhibit antiviral properties against SARS-CoV-2 [19].

We demonstrated brilacidin exerts potent *in vitro* antiviral activity against different strains of SARS-CoV-2 (2019-nCoV/USA-WA1/2020 and Italy-INMI1), in a cell-type independent manner. Brilacidin achieved a high Selectivity Index (SI) of 426 (CC50=241 µM/IC50=0.565 µM) in a human lung cell line (Calu-3). Brilacidin also showed potent inhibition in Calu-3 cells in combination

with remdesivir, the only FDA-approved drug for the treatment of COVID-19. A vast majority of other drugs being evaluated as potential COVID-19 treatments, including repurposed drugs, have SIs that are much lower than that achieved by brilacidin, with most drugs failing to show anti-SARS-CoV-2 potency in the <1 µM range [20]. Of note, the IC50 (0.565 µM) and IC90 (2.63 µM) values for brilacidin seen in the Calu-3 cell line are within clinically-achievable concentrations based on pharmacokinetics observed in a Phase 2 clinical trials of brilacidin for the treatment of ABSSSI, e.g., median Cmax (maximum concentration) plasma was 7.67 µM brilacidin (free-base) from a single IV dose of 0.6 mg/kg.

A proposed primary antiviral mechanism of action of brilacidin, along with blocking viral entry, is disrupting viral integrity. Destabilizing viral integrity is a particularly desirable antiviral property, especially in relation to pan-coronavirus agents, as the viral membrane is highly conserved and similar in construct across different coronavirus strains. Drugs that can disrupt viral integrity would be less prone to resistance due to mutation, unlike many antiviral therapies, antibody-based treatments and vaccines currently in use for COVID-19 [21,22].

In development under U.S. FDA Fast Track designation, brilacidin is being studied in a Phase 2 randomized, blinded, placebo-controlled clinical trial for treatment of moderate-to-severe COVID-19 in hospitalized patients via intravenous delivery (NCT04784897). Among patients experiencing later-stage SARS-CoV-2 infection, it is anticipated brilacidin's immunomodulatory and anti-inflammatory properties--inhibiting various pro-inflammatory cytokines/chemokines, such as TNF-α, IL-1β, and IL-6--may prove beneficial and complementary to the compound's antiviral properties [23].

Pre-clinical work is ongoing to further assess brilacidin's potential as a broad-spectrum antiviral, with promising preliminary data observed in additional viruses, including human coronaviruses (HCoV-OC43, HCoV-229E, HCoV-NL63), alphaviruses and bunyaviruses. These new brilacidin findings are being prepared for academic presentation and publication. Formulation feasibility work also is planned to assess brilacidin for prophylactic use, *via* intranasal and/or lung delivery.

Conclusion

Our experiments support brilacidin's anti-SARS-CoV-2 properties in cell culture, suggesting the drug candidate has potential to treat COVID-19. An effective COVID-19 therapeutic, or therapeutics used in combination, ideally would control both viral load and the corresponding inflammatory damage due to SARS-CoV-2, as well as help mitigate bacterial co-infections. Exhibiting three-in-one properties--antiviral, immuno/anti-inflammatory and antibacterial--our hope is that brilacidin may be able to address these different COVID-19 disease parameters within a single treatment, as is being investigated in a Phase 2 clinical trial. The trial was fully enrolled (n=120 patients) and is awaiting the unblinding of study data and statistical analyses, to be followed by the reporting of topline results. Beyond targeting SARS-CoV-2, extending the study of brilacidin to other acutely infectious viruses due to brilacidin's broad-spectrum antiviral profile may well be warranted.

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