ASV 2021
40TH ANNUAL MEETING July 19-23

INNOVATION PHARMACEUTICALS INC.

GEORGE MASON UNIVERSITY

Oral Presentation

Brilacidin, a Host Defense Protein/Peptide Mimetic, Shows Potential as a Broad-Spectrum Inhibitor of Acutely Infectious Viruses

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Abstract ID #: 3562525; Session: W28 Antiviral Therapies II; Session Day & Time: July 21, 2021 (6:00 PM to 9:00 PM); Program Number: W28-3

Contents

Background: Brilacidin as a peptidomimetic

Acutely infectious viruses (targets)

Unmet Need and Proposed Solution

Results: Coronaviruses (SARS-CoV-2)

Alphaviruses (VEEV, EEEV)

Bunyaviruses (RVFV)

Ongoing Research and Future Directions

A First-in-Class Host Defense Protein (HDP)/Defensin Mimetic

Brilacidin: The Molecule

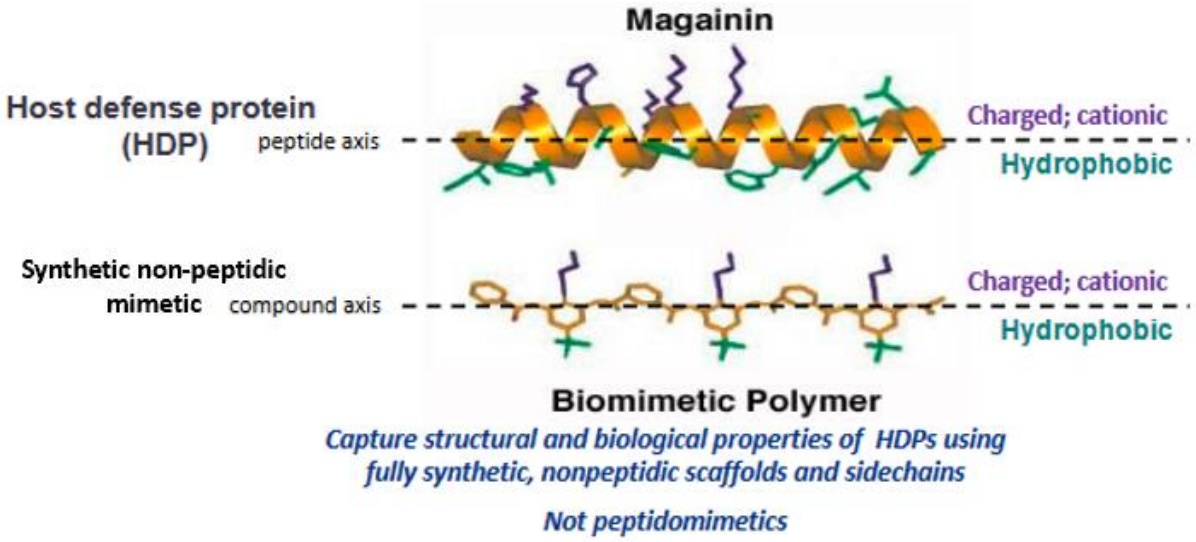
Host Defense Protein (HDP)/Defensin Mimetic

Brilacidin is a fully synthetic, non-peptidic, small molecule HDP/Defensin Mimetic

Design Approach

Biological activities of defensins depend on an amphiphilic helix

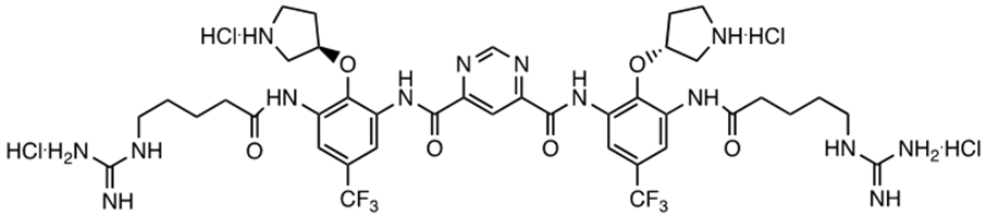
- Cationic (charged)
- Hydrophobic



Brilacidin is the result of *de novo* biocomputational drug design, producing a drug candidate exhibiting tailored exposure and efficacy across multiple clinical indications

Brilacidin

- Mimics HDP/Defensin structure and activity



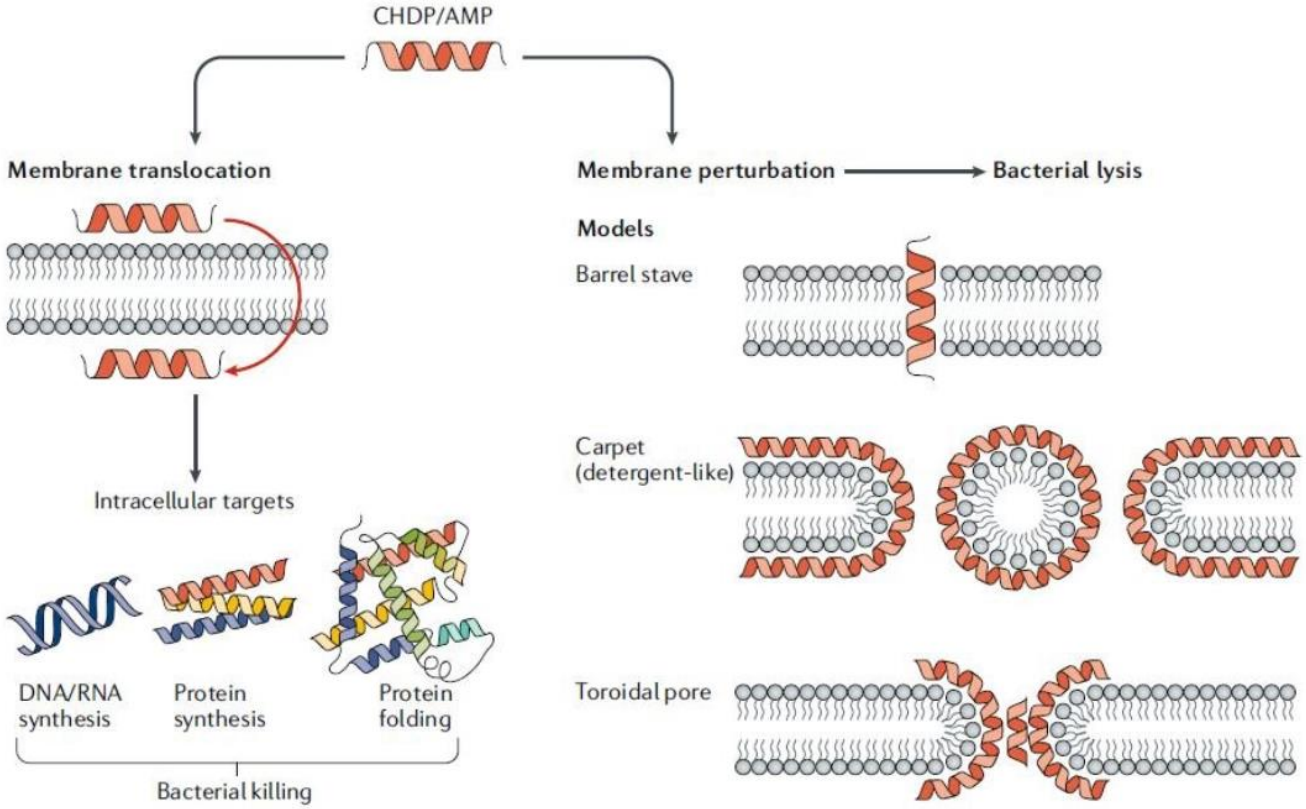
Molecular Wt: 1082.7 (tetrahydrochloride)
936.9 (free base)

See: Scott RW and Tew GN (2017). "Mimics of Host Defense Proteins; Strategies for Translation to Therapeutic Applications" (pdf). *Current Topics in Medicinal Chemistry*; 17:576-89; Som A, et al (2012). "Identification of Synthetic Host Defense Peptide Mimics That Exert Dual Antimicrobial and Anti-Inflammatory Activities." *Clin Vaccine Immunol*; 19(11):1784-91; Ergene C, et al (2018). "Biomimetic Antimicrobial Polymers: Recent Advances in Molecular Design." (pdf) Review Article. *Polym. Chem.*, 2018, 9, 2407-2427; Scott RW, DeGrado WF, Tew GN (2008). "De Novo Designed Synthetic Mimics of Antimicrobial Peptides." *Curr Opin Biotechnol*; 19:620-7.

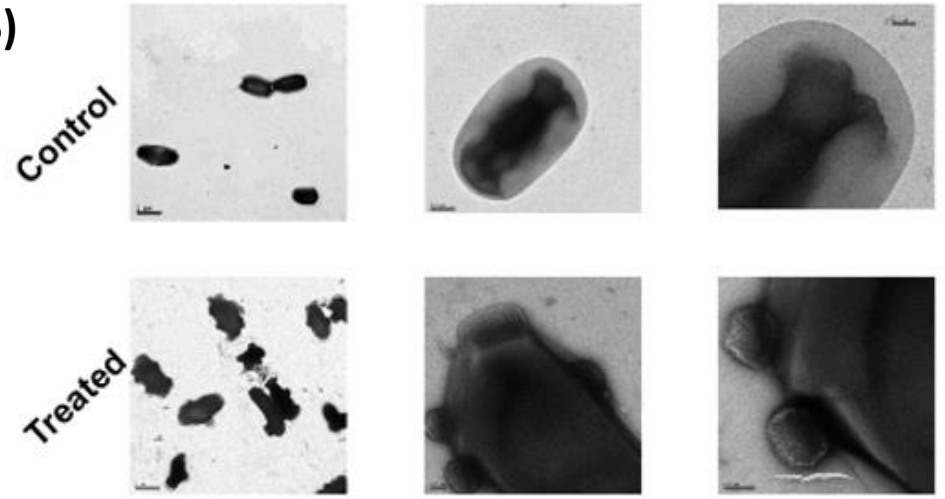
Brilacidin: Mechanism of Action—(Antimicrobial - Bacteria)

Disrupts Membrane Integrity (Polarity) of Pathogens Leading to Bacterial Cell Death

A)



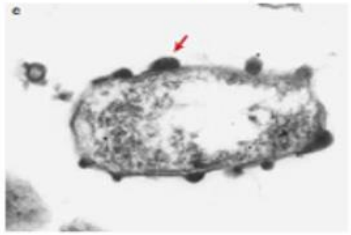
B)



60 minutes; 10x MIC concentrations

C)

TEM of *P. aeruginosa* on SMAP29 (3 hrs)



Brogden, K. 2005. Nature Reviews, Microbiology *3*: 238 (2005)

Cidal concs. of a HDP mimic cause visible signs of vesiculation (blebbing) at the E. coli membrane.

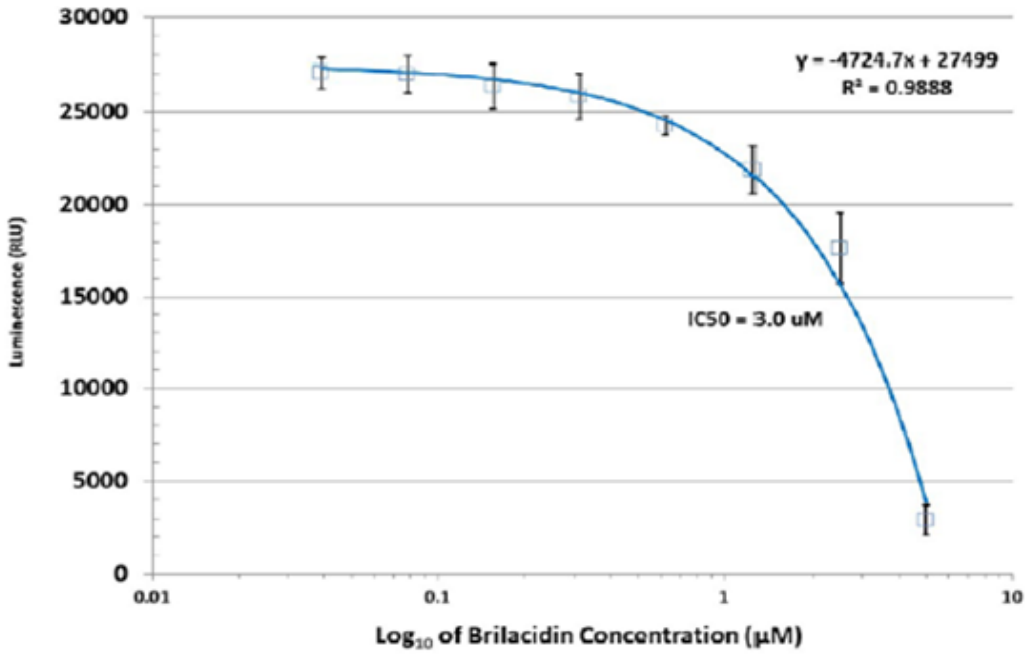
Similar morphological response reported for SMAP29 and P. aeruginosa.

Source: Mookherjee et al. (2020)

Brilacidin: Mechanism of Action—(Immunomodulatory)

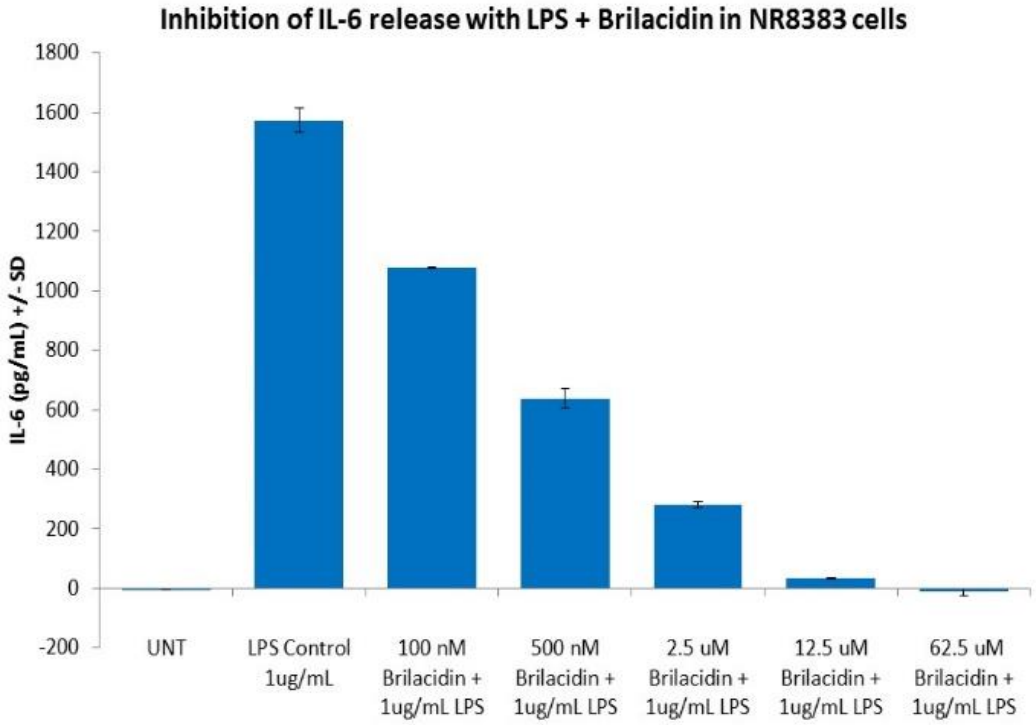
Inhibits PDE4/PDE3 through Cyclic AMP/GMP Pathways Reducing Inflammation (via Cytokines/Chemokines)

Brilacidin inhibits PDE4



Brilacidin has been shown to inhibit numerous pro-inflammatory cytokines and chemokines, e.g., TNF-α, IL-1β, IL-6, IL-8, MIP2-α, MCP-1, MMP-9, and CINC-3

Brilacidin inhibits IL-6 release

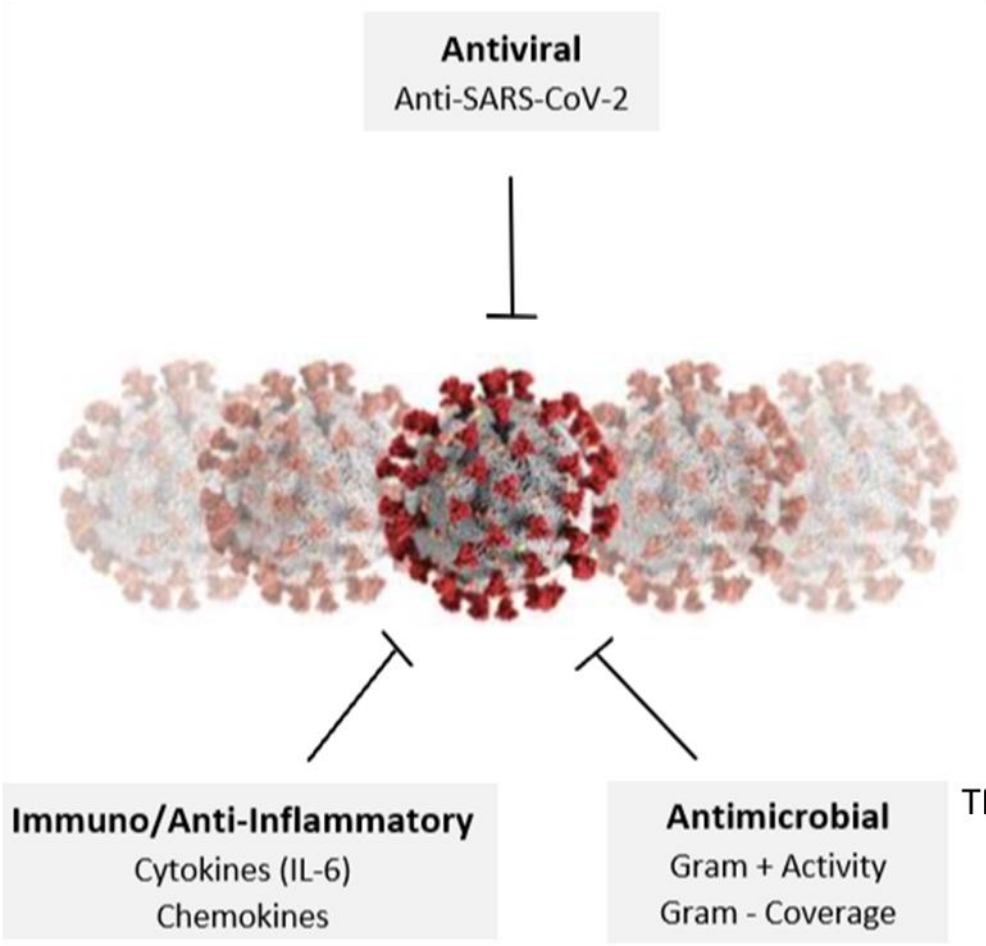


Brilacidin: Therapeutic Profile

Completed Successful Phase 2 Trials

- **Acute Bacterial Skin and Skin Structure Infection** (ABSSSI) (FDA QIDP): Phase 2b (NCT02052388), *intravenous delivery*
- **Inflammatory Bowel Disease** (IBD): Phase 2 Proof-of-Concept in Ulcerative Proctitis/Ulcerative Proctosigmoiditis (UP/UPS), *enema formulation*; currently being developed as an *oral tablet* in Ulcerative Colitis (UC), Phase 2 planning underway
- **Oral Mucositis** (OM) (FDA Fast Track): Phase 2 (NCT02324335), *oral rinse delivery;* Phase 3 planning underway

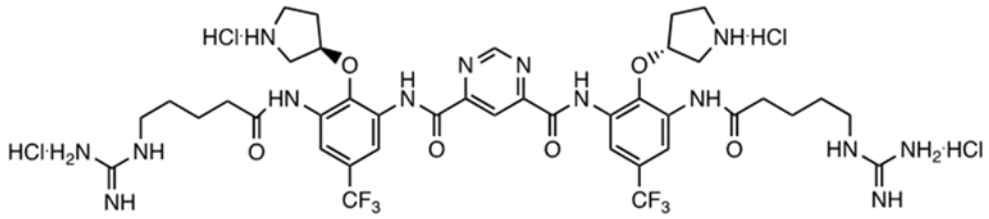
3-in-1 Combination of Therapeutic Properties (TP)



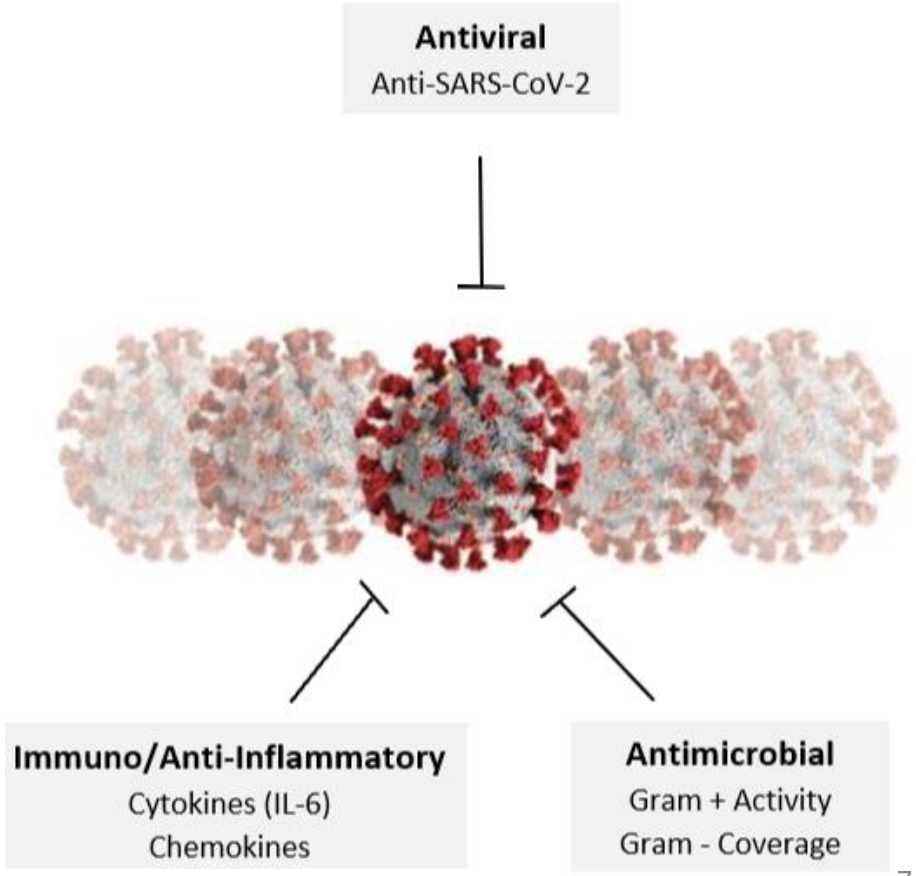
Unmet Need and Proposed Solution

Brilacidin

- A broad-spectrum antiviral therapeutic/prophylactic intervention strategy
- Robust immunomodulatory properties
- Broadly antimicrobial (secondary infections)
- Well-tolerated in humans

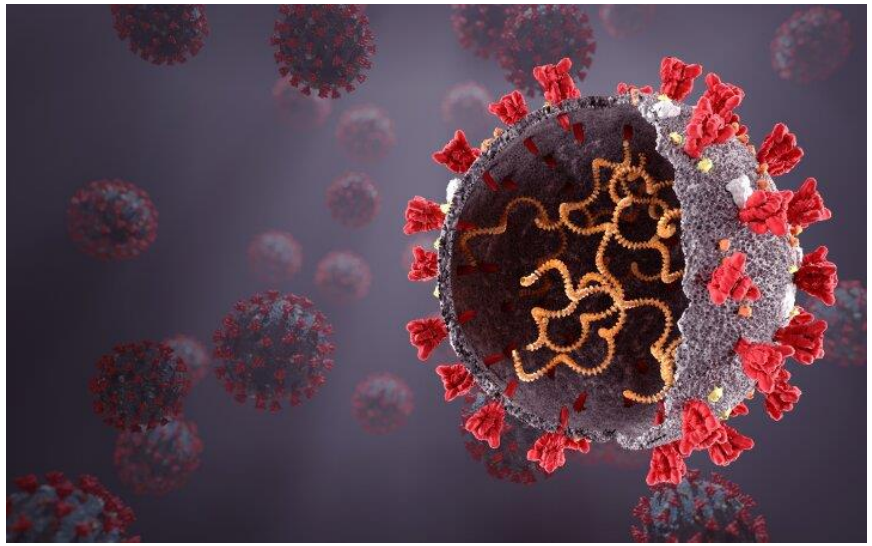


Molecular Wt: 1082.7 (tetrahydrochloride)
936.9 (free base)



Acutely Infectious Virus Targets

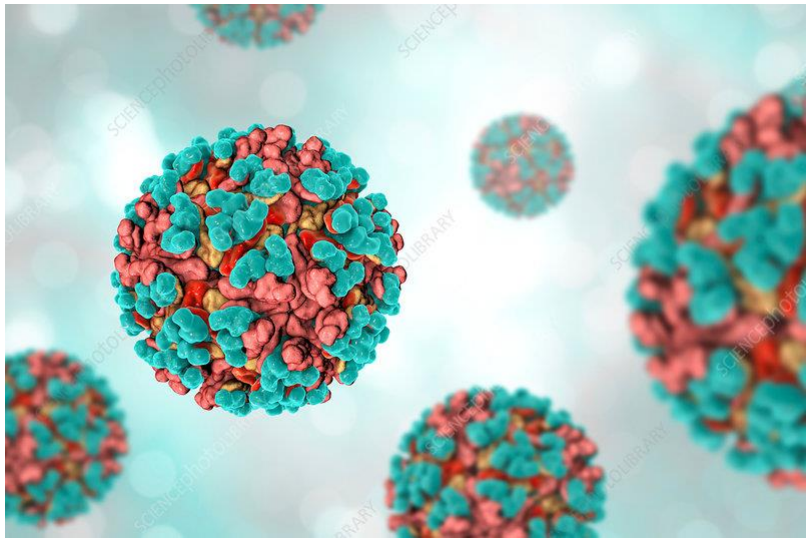
(Respiratory and/or Aerosolized Pathogens)



https://www.geneproof.com/geneproof-sars-cov-2

Coronavirus

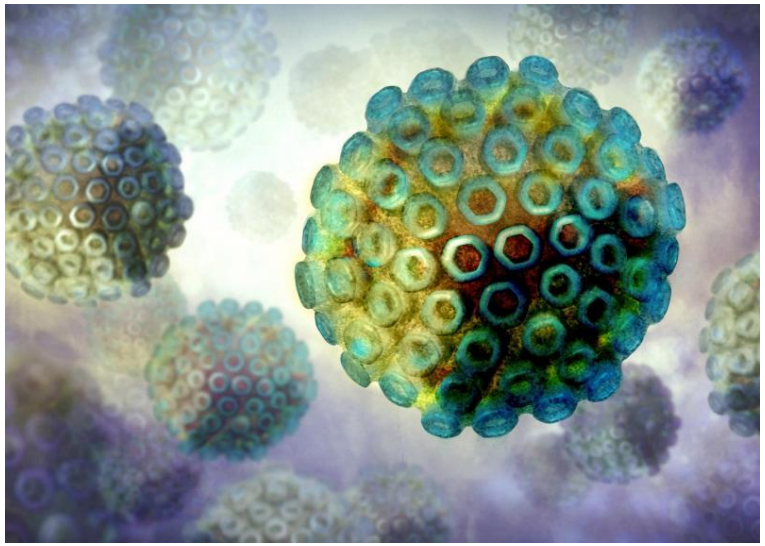
SARS-CoV-2
SARS-CoV
MERS-CoV
Human (Endemic) CoVs



https://www.sciencephoto.com/media/879506/view/venezuelan-equine-encephalitis-virus-illustration

Alphavirus

Venezuelan Equine Encephalitis Virus
Eastern Equine Encephalitis Virus



https://medicalxpress.com/news/2015-05-rift-valley-fever-virus-proteins.html

Bunyavirus

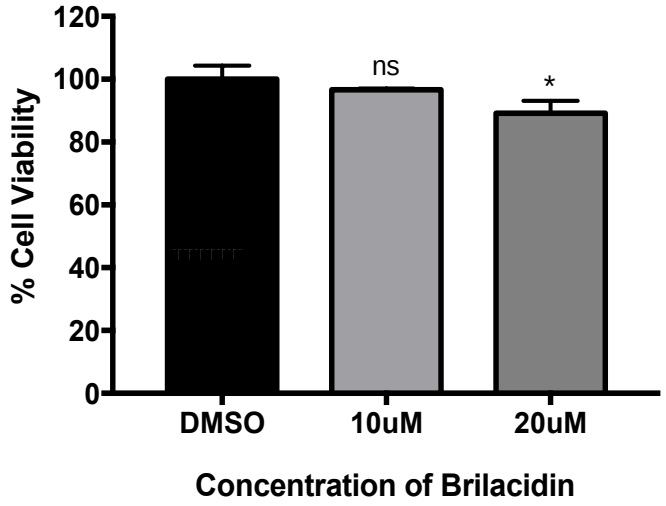
Rift Valley Fever Virus

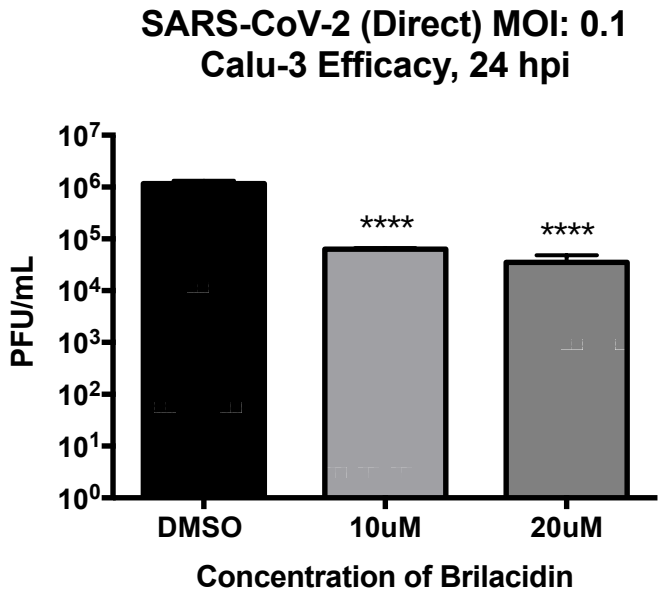
Results – Coronavirus (SARS-CoV-2)
PoC*: Inhibitory Potential

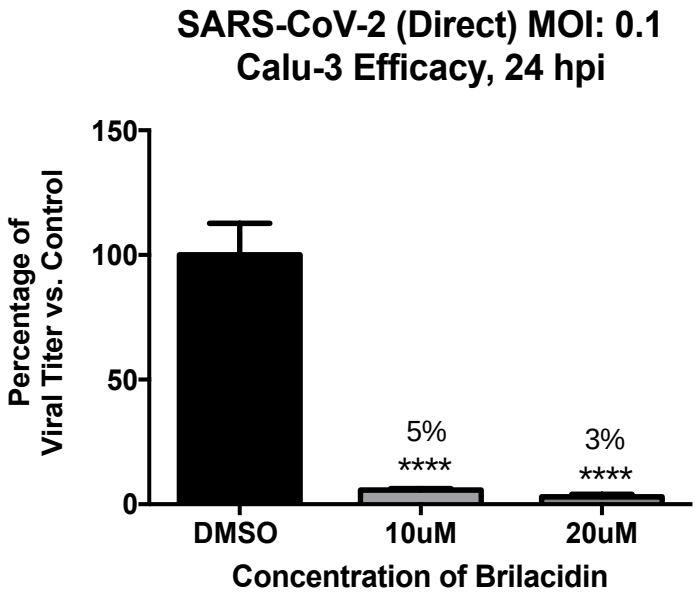
A)

Plate cells, then Pre-treat cells +BRI (2h) → Pre-treat virus +BRI (1h) at 37 °C → Infect cells virus+BRI mix (1h) → Post-treat cells +BRI (24h)

B)



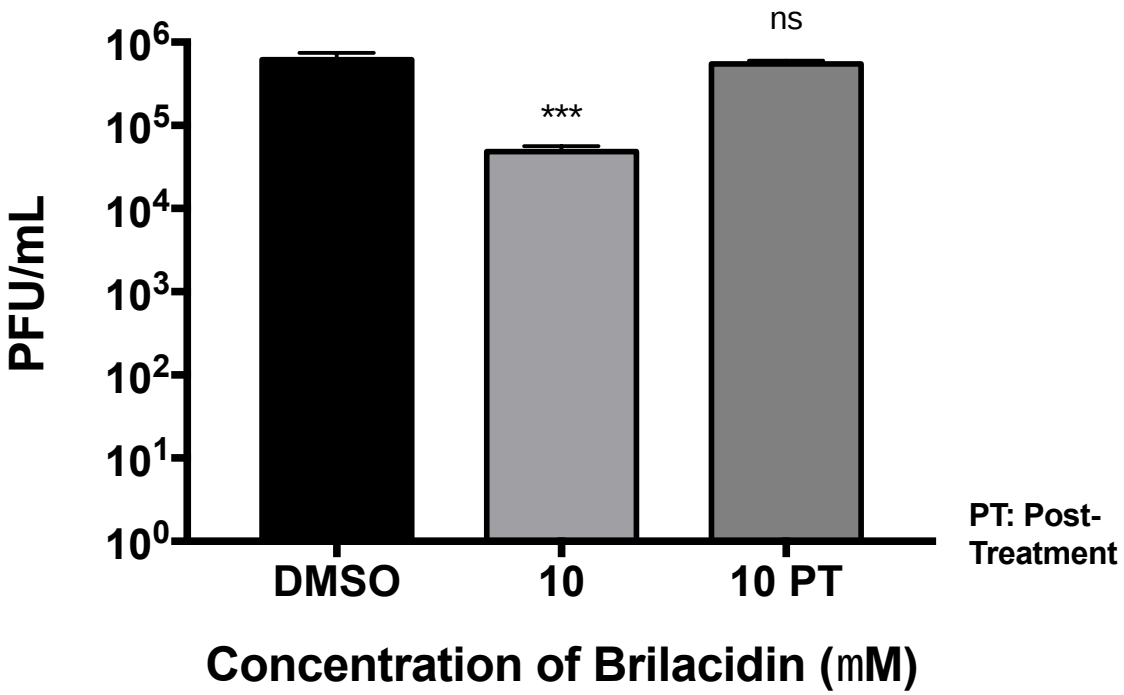


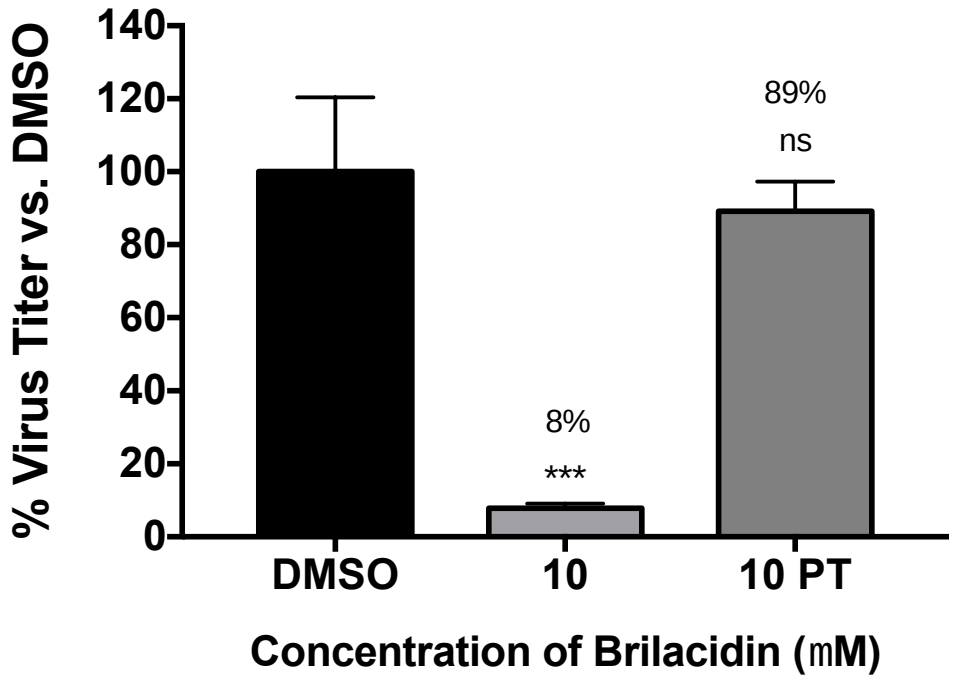


CC50 = 241µM

*Proof of Concept

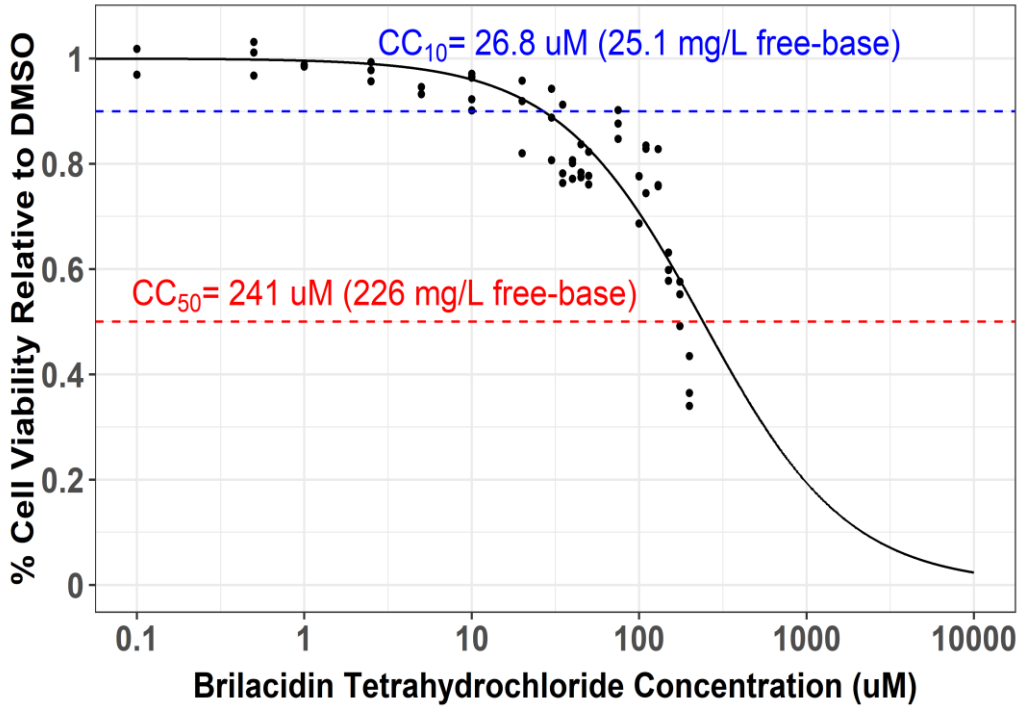
Results – Coronavirus (SARS-CoV-2)
Primary MOA*: Direct Impact on Virus

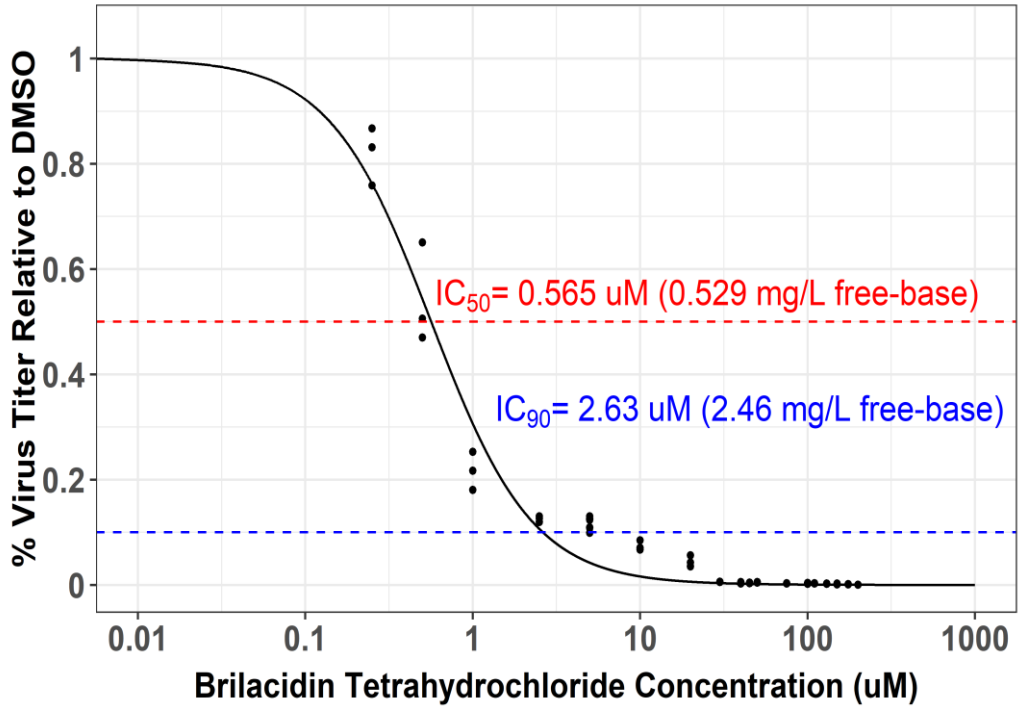




*Mechanism of Action

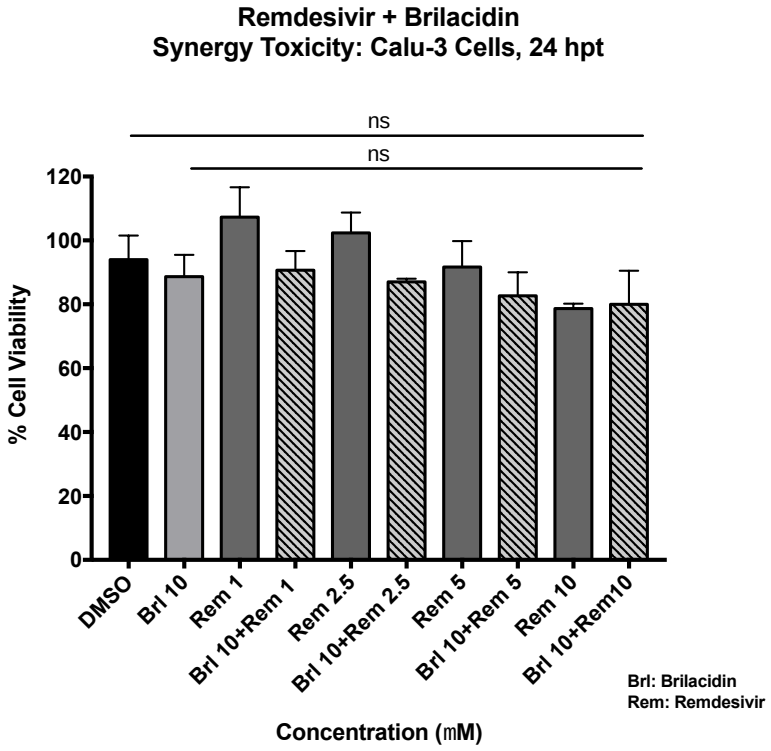
Results – Coronavirus (SARS-CoV-2) CC50, IC50 and SI*

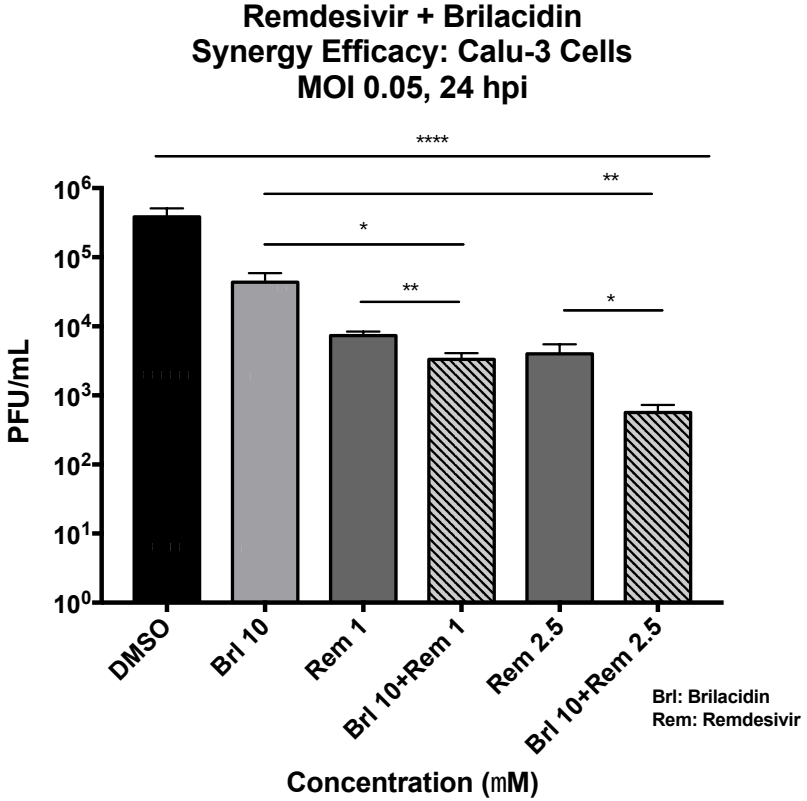


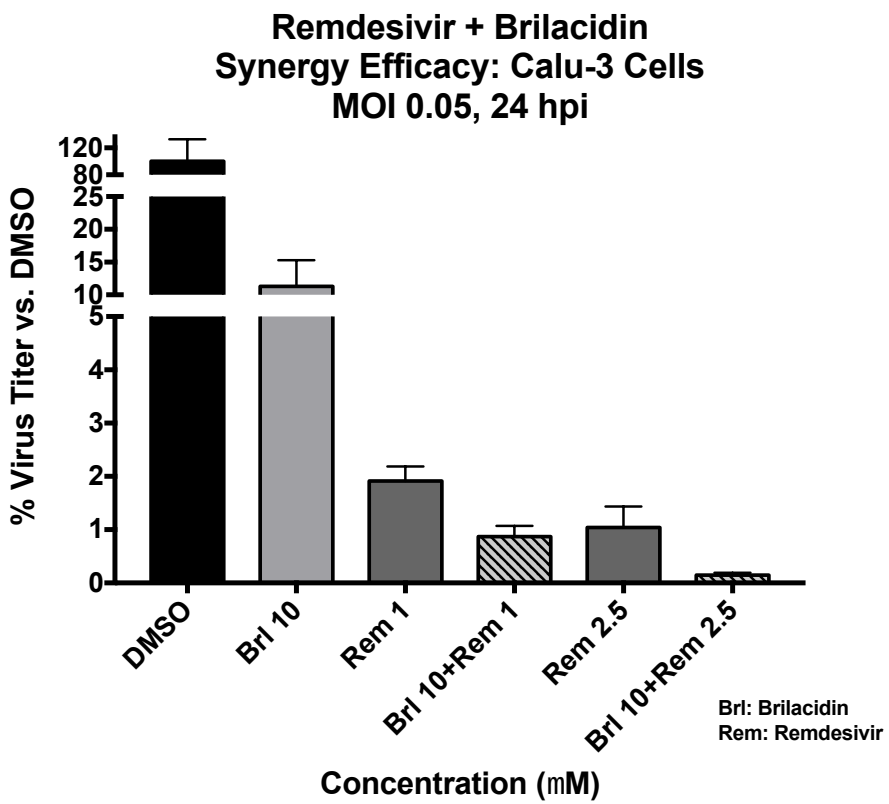


***Selectivity Index:** Brilacidin achieved 90% inhibition at a concentration of 2.63 µM and 50% inhibition at 0.565 µM, yielding a Selectivity Index of 426 (CC50 = 241 µM/IC50 = 0.565 µM)

Results – Coronavirus (SARS-CoV-2) Synergy with Remdesivir

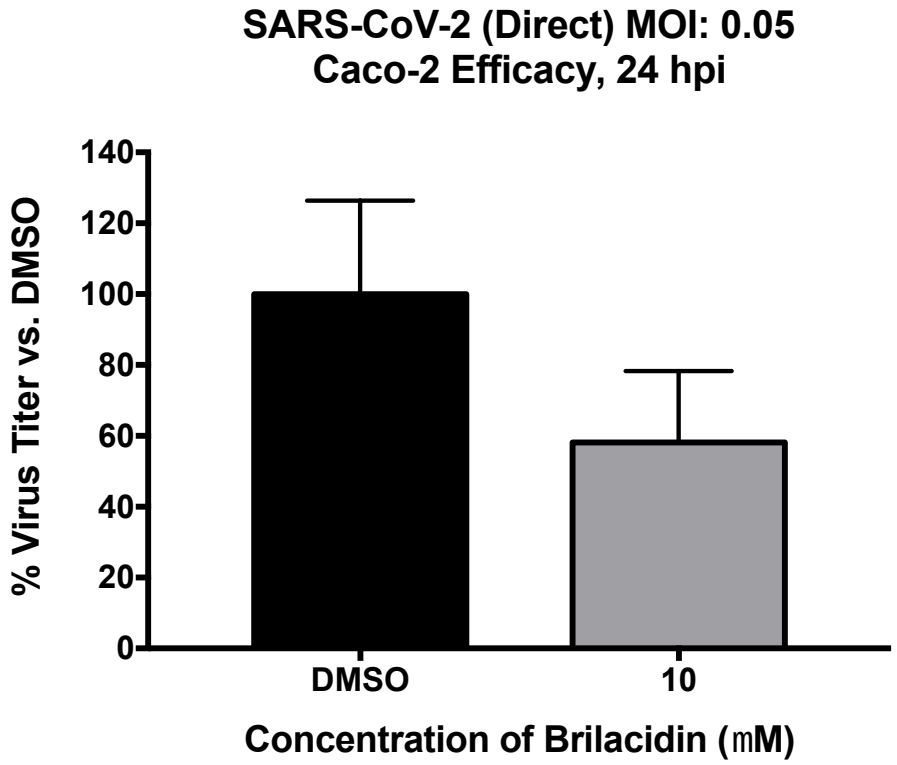


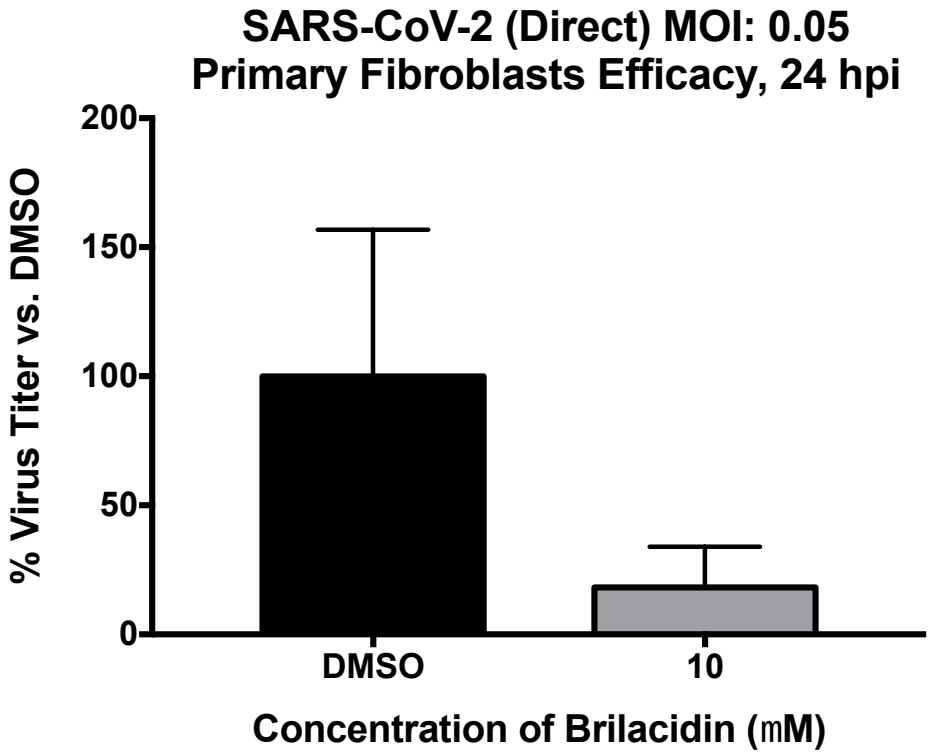




Results – Coronavirus (SARS-CoV-2)

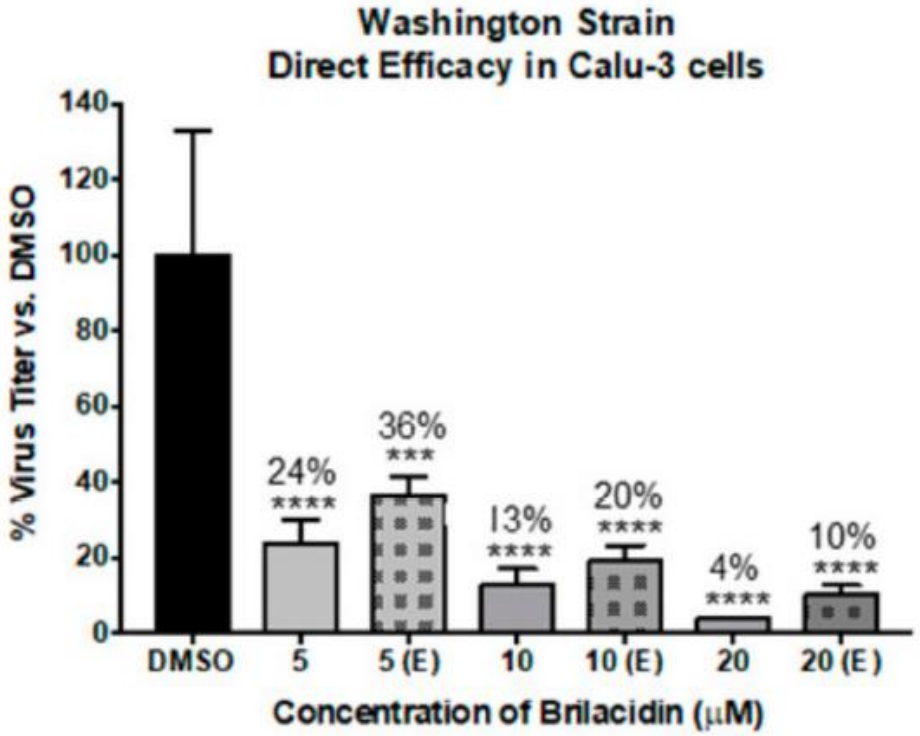
Inhibitory Potential: Cell Type Independent

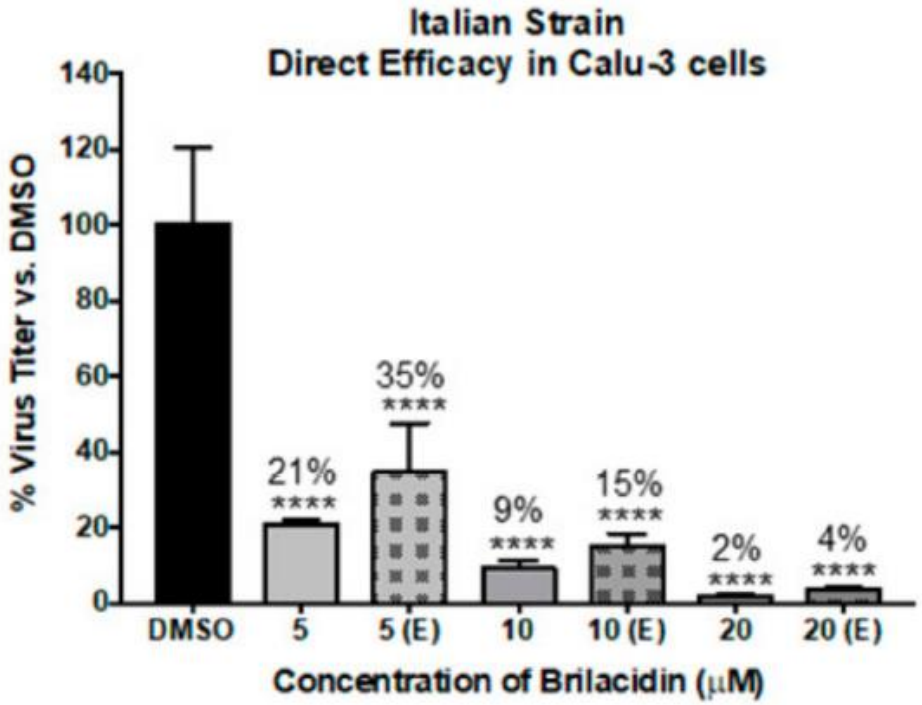




Results – Coronavirus (SARS-CoV-2)

Inhibitory Potential: Extends to Different Strains





Brilacidin – In-Human Trial

Brilacidin for COVID-19—Phase 2 Clinical Trial Fully Enrolled

Randomized, Placebo-Controlled; Moderate-to-Severe COVID-19; FDA Fast Track Designated

Study Design Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	120 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled, Multi-center Study to Evaluate the Efficacy and Safety of Brilacidin in Hospitalized Participants With COVID-19
Actual Study Start Date :	February 22, 2021
Estimated Primary Completion Date :	June 2021
Estimated Study Completion Date :	July 2021

- *Trial 100% enrolled*
- *Dosing Increased to 5 Days from 3 Days based on DMC recommendation*

Primary Endpoint

- Time to sustained recovery through Day 29 using a clinical status ordinal scale based on that used in the series of National Institute of Allergy and Infectious Diseases (NIAID) Adaptive COVID-19 Treatment Trials (ACTTs)

Additional Endpoints

Including:

- In-hospital outcomes (e.g., duration of hospitalization, time to discharge)
- All-cause mortality
- Measurement of disease biomarkers (e.g., CRP, ferritin) and inflammation-related biomarkers (e.g., IL-1β, IL-6, IL-10, total IL-18, TNF-α)
- Changes to SARS-CoV-2 viral load

Brilacidin: Coronaviruses – Salient Observations

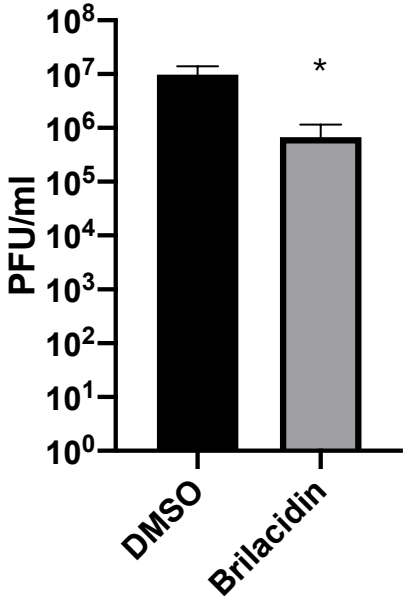
- Inhibition appears to impact viral integrity in a manner that interferes with entry and/or early post-entry steps
- Inhibition extends to different strains of SARS-CoV-2 (alpha, beta, gamma and delta strain assessments are planned)
- Synergistic activity with remdesivir without any apparent increase in toxicity
- Cell type independent inhibition of SARS-CoV-2 (Calu-3, Caco-2, primary lung fibroblasts)

Results – Alphavirus (VEEV)
PoC*: Inhibitory Potential

TC-83 infection of U87MG cells followed by quantification of infectious titer by plaque assay in Vero cells

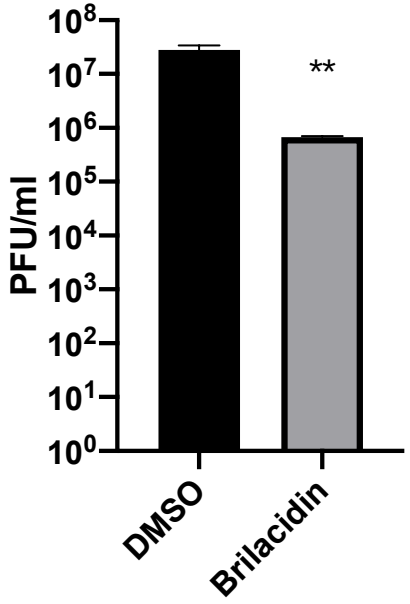
A)

B) TC-83



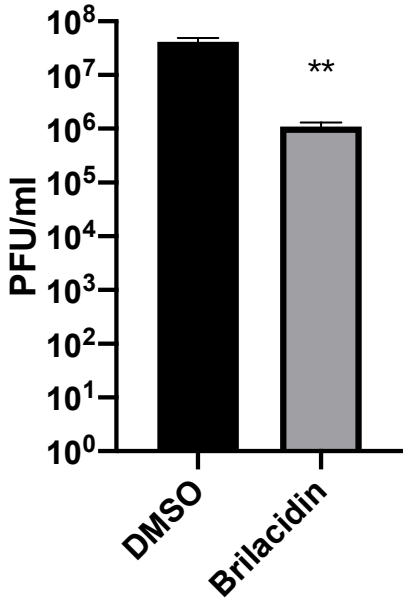
Pre and Post Treatment (20μM)

C) TC-83



Direct Viral Treatment (20μM)

D) TC-83



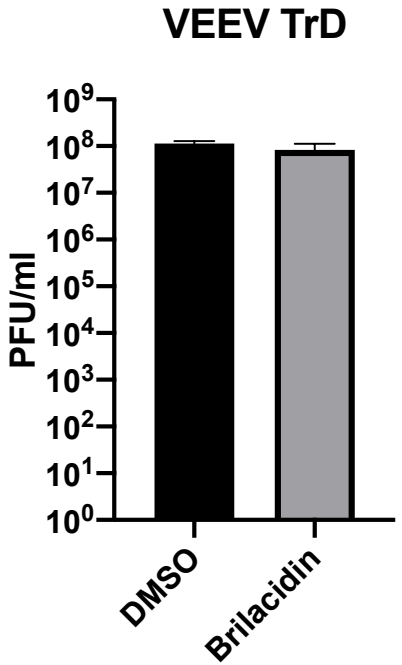
Pre, Post, and Direct Viral Treatment (20μM)

*Proof of Concept

Results – Alphavirus Broad-Spectrum Inhibition

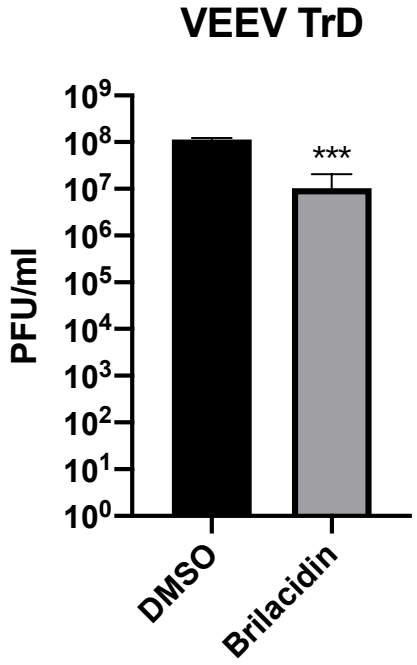
A)

B)



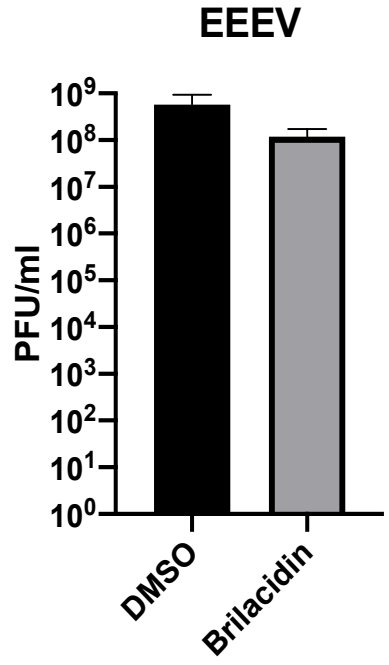
Pre and Post Treatment (20µM)

C)



Pre, Post, and Direct Viral Treatment (20µM)

D)

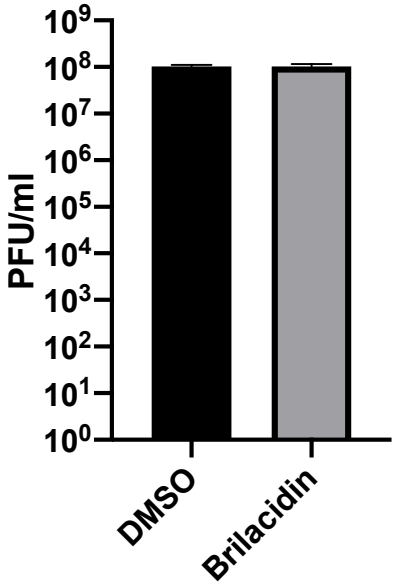


Pre, Post, and Direct Viral Treatment (20µM)

Results – Bunyavirus (RVFV)
PoC*: Inhibitory Potential

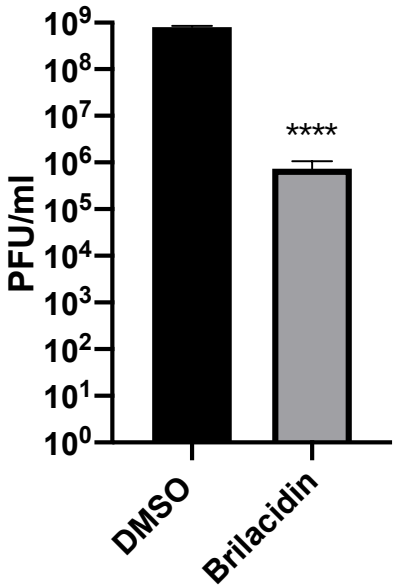
A)

B) RVFV MP-12



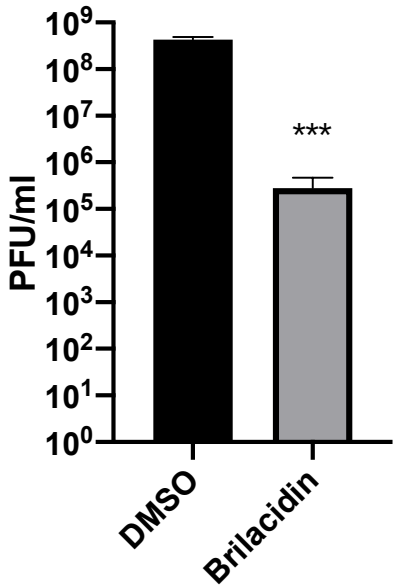
Pre and Post Treatment (20μM)

C) RVFV MP-12



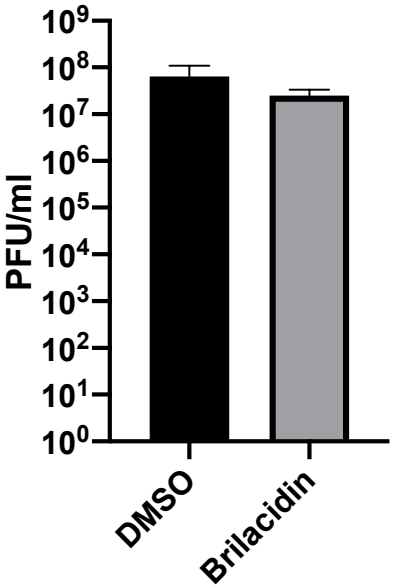
Direct Viral Treatment (20μM)

D) RVFV MP-12



Pre, Post, and Direct Viral Treatment (20μM)

E) RVFV MP-12



Post Treatment (20μM)

*Proof of Concept

Conclusion: Brilacidin Exhibits Broad-Spectrum Antiviral Properties

- Inhibition appears to impact viral integrity in a broad-spectrum manner by interfering with viral entry and/or early post-entry steps – Post-entry mechanisms remain to be investigated
- Cell type independent inhibition that extends to multiple cell types

Ongoing and Future Studies

Ongoing Studies

- Additional research with coronaviruses, alphaviruses and bunyaviruses
- Expansion to other cell types and in vivo models (SARS-CoV-2)
- Mechanisms of action insights—impact on entry and post-entry stages

Future Studies

- Exploratory work on the anti-inflammatory properties of the compound during infection
- Testing Brilacidin against new SARS-CoV-2 variants
- Delivery and dosing strategies