Brilacidin
First-in-Class Defensin-Mimetic Drug Candidate

Mechanism of Action, Pre/Clinical Data and Academic Literature
Supporting the Development of Brilacidin
as a Potential Novel Coronavirus (COVID-19) Treatment

April 20, 2020

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I. Brilacidin: Background Information

Brilacidin (PMX-30063) is Innovation Pharmaceutical’s lead Host Defense Protein (HDP)/Defensin-Mimetic drug candidate targeting SARS-CoV-2, the virus responsible for COVID-19. Laboratory testing conducted at a U.S.-based Regional Biocontainment Laboratory (RBL) supports Brilacidin’s antiviral activity in directly inhibiting SARS-CoV-2 in cell-based assays. Additional pre-clinical and clinical data support Brilacidin’s therapeutic potential to inhibit the production of IL-6, IL-1β, TNF-α and other pro-inflammatory cytokines and chemokines (e.g., MCP-1), identified as central drivers in the worsening prognoses of COVID-19 patients. Brilacidin’s antimicrobial properties might also help in fighting secondary bacterial infections, which can co-present in up to 20 percent of COVID-19 patients. Collectively, these data support Brilacidin as a promising and unique—3 in 1 combination: antiviral, immune/anti-inflammatory, and antimicrobial—anti-COVID-19 drug candidate. Additional drug delivery work (e.g., developed as an inhalant) might complement Brilacidin’s anti-COVID-19 therapeutic potential. Brilacidin has been tested in multiple Phase 2 human trials for other clinical indications, providing an established safety and efficacy profile, thereby potentially enabling it to help confront the worldwide coronavirus crisis.

Exhibiting antiviral, immunomodulatory/anti-inflammatory and antimicrobial properties, Brilacidin has shown therapeutic benefit in successful Phase 2 clinical trials (see Section V for summary safety and efficacy data), including:

- **Acute Bacterial Skin and Skin Structure Infection (ABSSSI) (FDA Qualified Infectious Disease Product, 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
- **Oral Mucositis (OM) (FDA Fast Track):** Phase 2 (NCT02324335), oral rinse delivery; Phase 3 planning

Referred to as the “Swiss Army Knife” of the human body, defensins are small antimicrobial peptides (AMPs) expressed widely in the animal kingdom that serve as the first line of defense against pathogenic invasion of the body. Defensin-based therapeutics—of which Brilacidin is the leading example, and the most advanced drug candidate among this class in clinical testing—represent an attractive possible intervention to combat the coronavirus given their innate and multifaceted immune functions. Defensins exhibit a number of distinct and favorable therapeutic characteristics, including among others: immunomodulatory, antiviral, anti-inflammatory and antimicrobial.

Brilacidin, a fully synthetic non-peptidic mimetic of defensins, was computationally designed de novo to be smaller (1/10th the size), more stable, more potent (by a 100-fold), more selective (by a 1000-fold), and more easily manufactured, than natural defensins, so as to overcome many of the shortcomings (e.g., degradation, toxicity, lack of efficacy, malabsorption, cost to produce, etc.) that have complicated their clinical development. Brilacidin has shown tailored exposure and efficacy across multiple clinical indications.
II. Brilacidin: Two Primary Mechanisms of Action

HDPs/Defensins are Small Antimicrobial Peptides

- Expressed widely in the animal kingdom
- Evolutionarily conserved
- Produced in skin, mucosal surfaces, neutrophils
- Target membranes (primary MOA)
- Modulate immune response (primary MOA)
- Properties act in synergistic fashion

Serve as First Line of Defense Against Pathogens

- Part of innate and adaptive immunity
- Maintenance of epithelial barrier function
- Regulate microbiota
- Immunomodulatory/Anti-Inflammatory properties
- Antimicrobial properties
- Antiviral properties

Brilacidin

1) Membrane Disruption MOA

- Amphiphilic Structure
- Cationic/Hydrophobic

2) Immunomodulatory MOA

- cAMP Pathway
- PDE4/PDE3 Inhibition

Source
Membrane Disruption Mechanism of Action

As to bacterial/viral invasion, AMP/defensins and mimetics, like Brilacidin—via an amphiphilic topology: both positively charged and hydrophobic (water-hating, lipid-loving) properties—target the structural plasticity/thermodynamic instability of invading toxins, thus increasing their susceptibility to proteolysis and degradation. Other intra-cellular mechanisms beyond membrane-active properties—a capacity for acting on numerous targets and by means of a variety of mechanisms—also play an important role in contributing to the overall antibacterial/antiviral efficacy of AMP/defensin-based therapies, via what’s been referred to as a “multiple-hit model.” For additional detailed information on the biophysics of this process, including mechanistic studies conducted on Brilacidin, refer to the two articles linked below:


Teicoplanin-based glycopeptide antibiotics (Dalbavancin, Telavancin, Oritavancin) have been shown to inhibit viral entry of MERS and SARS/SARS-CoV-2 viruses. Interestingly, Vancomycin did not. Researchers attributed this lack of anti-MERS and anti-SARS efficacy due to the drug not having a hydrophobic property, again, which Brilacidin possesses. In the 2014 Mensa et al article cited above, the authors reference Brilacidin showing certain membrane-lytic properties similar to those of Telavancin.

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2 “Transcriptional response studies have shown a strong induction of the VraSR regulon in response to telavancin treatment, as observed for brilacidin treatment and as expected from a cell wall synthesis inhibitor.”
Fully synthetic non-peptidic mimetic drugs, such as Brilacidin, an arylamide foldamer, are considered attractive therapeutic candidates given favorable characteristics, including being: (i) highly selective (potent against target while leaving host cells unaffected); (ii) not prone to resistance mechanisms; (iii) relatively easy to produce at low costs; (iv) and stable during storage or upon administration.

This biocomputational aspect of Brilacidin’s development (de novo design\(^3\)) has resulted in the drug candidate having much better exposure and efficacy in terms of its pharmacokinetics, contributing to broad and robust properties.

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Current view on MOA for optimized arylamides

- Muted membrane and capsule stress but no large-scale leakage from the cytoplasmic membrane
- Damage/leakage evident in outer membrane of Gram-negative E. coli
- Accumulation of unprocessed secreted proteins by mal-functioning translocon
  - Caused by change in membrane properties and/or plasma membrane depolarization
- Up-regulation of chaperones and proteases that target mis-folded proteins
- Blockade of protein secretion and/or accumulation of toxic aggregates leads to cell death

Advantages: Mimetic Approach

- Narrow and broad-spectrum antimicrobial agents have been produced
  - 0.5 to 2 μg/ml MICs vs Gram-positives
  - 0.5 to 8 μg/ml MICs vs Gram-negatives
- Wide selectivity for bacteria over mammalian cells
  - Significant improvements in cytotoxicity versus HDPs
  - >100 to 1,000 fold selectivities
- Medicinal chemistry enables “fine-tuning” for specific activities
- Straightforward synthesis
  - Common starting materials
- Metabolically stable and active in vivo
- Developed for systemic and topical uses
**Immunomodulatory Mechanism of Action**

Brilacidin, through its modulation of the cyclic adenosine monophosphate (cAMP) pathway, has been shown to be a potent regulator of immune response.

Pre-clinical studies have demonstrated that Brilacidin inhibits PDE4B2 and PDE3A *in vitro*, in a dose dependent manner. Brilacidin demonstrated similar IC50 values against both PDE4 (biochemical) and cytokine release in cell-based assays, suggesting Brilacidin has good cell membrane permeability. Localized clinical administration enables Brilacidin concentrations that markedly exceed *in vitro* IC50 values, and, consequently, provides for increased concentrations of cAMP. Drugs that elevate intracellular cAMP levels reduce pro-inflammatory mediators and increase anti-inflammatory factors in numerous immune cells. The effect of Brilacidin’s ability to modulate cAMP levels—complementing other aspects of its mechanisms of action—supports its potential to treat a number of chronic, autoimmune and inflammatory diseases related to issues of innate immunity, such as: Inflammatory Bowel Disease, Atopic Dermatitis, and potentially COVID-19.

Brilacidin, as an inhibitor of PDE4/PDE3, might provide added benefit as a result of this particular mechanism by 1) disrupting viral replication; and 2) enhancing the protective role of natural surfactants in the lung, helping resolve respiratory problems common to COVID-19. Defensins play a key role in pulmonary and mucosal host defense. In March 2020, a Deep Learning AI program\(^4\) was used by researchers to screen (pdf) almost 5,000 approved drugs and identified Roflumilast, a PDE4 inhibitor, like Brilacidin, as one of only ten most promising anti-SARS-CoV-2 drug candidates.

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Additional Commentary on Relevance to COVID-19

In normal physiology, on initial encounter with viruses, resident alveolar macrophages become activated and secrete pro-inflammatory cytokines and chemokines, resulting in the recruitment of neutrophils, macrophages, and lymphocytes. A pro-inflammatory positive feedback loop between the tissue-resident macrophages and recruited cells amplifies the immune response, and promotes further immune cell recruitment. As the infection is cleared, a second wave of anti-inflammatory cytokines is produced to dampen the immune response to avoid immune-mediated damage.

This cycle of immune response amplification followed by response attenuation has been demonstrated to be less robustly regulated in older patients. The innate immune response to tissue damage caused by the novel coronavirus could lead to Acute Respiratory Distress Syndrome (ARDS) in which respiratory failure is characterized by rapid onset of widespread inflammation in the lungs and subsequent death. The level of inflammatory cytokines is highly expressed in the lungs of hospitalized COVID-19 patients. Key molecular players include IL-6, TNF-α, and IL-1. Recent autopsies have confirmed that the lungs are filled with clear liquid jelly, which is similar to that caused by hyaluronan associated with ARDS. Hyaluronan increases MMP9.

Brilacidin has been shown to inhibit IL-6, as well as other pro-inflammatory cytokines and chemokines (e.g., TNF-α, IL-1β, IL-6, IL-8, MIP2-α, MCP-1, MMP-9, and CINC-3), thereby positioning the drug as a promising intravenous treatment for COVID-19 patients. Given the redundancy of cytokine actions, targeting a single cytokine may have only limited effects on the complex inflammatory process.

Brilacidin, through its modulation of the cyclic adenosine monophosphate (cAMP) pathway acting to inhibit PDE4/PDE3, has the ability to affect multiple immune-related steps and regulate multiple cytokines and chemokines to mitigate severity of complex inflammatory processes, including respiratory distress implicated in COVID-19.

Source
The three Review Articles on coronaviruses, linked below, also suggest immunomodulators, like Brilacidin, might be beneficial therapeutic options for treating coronaviruses, potentially acting synergistically when combined with other antiviral drugs.

III. Brilacidin: Several Complementary Ways of Targeting COVID-19

Formula: \[ \text{C}_{40} \text{H}_{50} \text{F}_{6} \text{N}_{14} \text{O}_{6} \]
Molar Mass: 936.9 g/mol

3-in-1 Combination of Therapeutic Properties

- **Antiviral**
  - Anti-SARS-CoV-2

- **Immuno/Anti-Inflammatory**
  - Cytokines (IL-6)
  - Chemokines

- **Antimicrobial**
  - Gram + Activity
  - Gram - Coverage
**Antiviral**

The antiviral testing of Brilacidin was conducted at one of the U.S. Regional Biocontainment Laboratories (RBLs). Based on a recent review article, few compounds show activity against SARS-CoV-2, an enveloped virus.

VERO cells, a monkey kidney cell line commonly used to screen small molecule inhibitors of viruses, were used to test whether Brilacidin inhibits SARS-CoV-2. Cells were pretreated with Brilacidin at increasing concentrations (at 2 µM and at 10 µM) for two hours prior to the infection. Cells treated with the vehicle alone (Dimethyl sulfoxide or DMSO) were maintained alongside, as controls.

At 16 hours post-infection (16hpi), researchers observed a dose-dependent reduction in the SARS-CoV-2 infectious viral titers from the Brilacidin treated cells as compared to the vehicle-alone control, as shown in the graphic below. (The higher number of asterisks denote higher statistical significance compared to control.) Additional laboratory testing of Brilacidin against SARS-CoV-2, the novel coronavirus responsible for COVID-19, is to commence shortly. This is based on recommendations made by the lead researcher at the RBL who performed the preliminary testing of Brilacidin, characterizing the results as “extremely encouraging.” Immediate next steps include conducting studies in human lung cells, exploring dosing/treatment windows and evaluating the drug’s effect on the viral envelope.
Of note, two recent journal articles, summarized and linked below, also support Brilacidin as a promising potential inhibitor of SARS-CoV-2.


Based on a molecular docking-based virtual screening of 11,552 structurally diverse compounds either already FDA-approved or in clinical testing—Brilacidin, due to its unique molecular properties, was identified as one of the most promising potential inhibitors of SARS-CoV-2 by targeting the spike 1 glycoprotein (S1) (see image below). The researchers concluded: “Clearly, these compounds should be further evaluated in experimental assays and clinical trials to confirm their actual activity against the disease.”


In this article, human defensin 5 (HD5) was shown to lower the ability of the novel coronavirus (nCoV) spike 1 glycoprotein (S1) to bind to angiotensin-converting enzyme-2 (ACE2), a receptor that nCoV uses to mediate entry into host cells. Researchers currently evaluating Brilacidin’s anti-SARS-CoV-2 therapeutic potential theorize that Brilacidin, as a defensin-mimetic, may show similar nCoV inhibitory activity due to this particular mechanism of action, in addition to potentially disrupting the nCOV viral envelope directly due to the Brilacidin’s hydrophobic properties.
**Immuno/Anti-Inflammatory**

An excessive immune response to fight the novel coronavirus (triggering a “cytokine storm”) is theorized to play an important role in COVID-19 disease severity, which can lead to Acute Respiratory Distress Syndrome (ARDS)—a serious respiratory complication necessitating mechanical ventilation and leading cause of death among COVID-19 patients. Scientists at the University of Science and Technology of China (USCT) have identified interleukin 6 (IL-6), a pro-inflammatory cytokine, as the “main culprit” in the body’s overreaction when trying to fend off the virus.

Brilacidin, through its modulation of the cyclic adenosine monophosphate (cAMP) pathway, has been shown to be a potent regulator of immune response. Brilacidin has been shown to inhibit IL-6, as well as other pro-inflammatory cytokines and chemokines (e.g., TNF-α, IL-1β, IL-6, IL-8, MIP-2α, MCP-1, MMP-9, and CINC-3), thereby positioning the drug as a potential promising treatment for COVID-19 patients.

### Anti-inflammatory Nonclinical Studies: in vitro and ex vivo

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Test System</th>
<th>IPI Study Number</th>
<th>Brilacidin IC₅₀</th>
<th>Unit</th>
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<tbody>
<tr>
<td>Inhibition of human PDE-4B2</td>
<td>in vitro PDE-Glo™ PDE assay</td>
<td>2014-05-29</td>
<td>3 mg</td>
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<tr>
<td>Inhibition of human PDE3A</td>
<td>in vitro PDE-Glo™ PDE assay</td>
<td>2014-07-18</td>
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<tr>
<td>Inhibition of LPS-induced TNF-α release</td>
<td>Rat alveolar macrophage (NR8341) cells; ELISA assay</td>
<td>2014-08-21</td>
<td>442 pg</td>
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<tr>
<td>Inhibition of LPS-induced MIP-9 release</td>
<td>Rat alveolar macrophage (NR8341) cells; ELISA assay</td>
<td>2014-11-10</td>
<td>2.3 pg</td>
<td></td>
</tr>
<tr>
<td>Inhibition of LPS-induced MCP-1 release</td>
<td>Rat alveolar macrophage (NR8341) cells; ELISA assay</td>
<td>2014-11-13</td>
<td>750 pg</td>
<td></td>
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<tr>
<td>Inhibition of LPS-induced IL-6 release</td>
<td>Rat alveolar macrophage (NR8341) cells; ELISA assay</td>
<td>2014-12-03</td>
<td>274 pg</td>
<td></td>
</tr>
<tr>
<td>Inhibition of LPS-induced IL-1β release</td>
<td>Rat alveolar macrophage (NR8341) cells; ELISA assay</td>
<td>2015-02-10</td>
<td>702 pg</td>
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<tr>
<td>Inhibition of LPS-induced CINC-3 release</td>
<td>Rat alveolar macrophage (NR8341) cells; ELISA assay</td>
<td>2015-02-16</td>
<td>425 pg</td>
<td></td>
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<tr>
<td>Inhibition of LPS-induced TNF-α release</td>
<td>Human monocytic leukemia (THP-1) cells; ELISA assay</td>
<td>2016-07-21</td>
<td>23.4 pg</td>
<td></td>
</tr>
<tr>
<td>Inhibition of LPS-induced IL-8 release</td>
<td>Human monocytic leukemia (THP-1) cells; ELISA assay</td>
<td>2016-08-02</td>
<td>16.8 pg</td>
<td></td>
</tr>
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</table>

**IL-6 Human Tissue Biopsy at Day 42 (Phase 2 UP/UPS Trial)**

![IL-6 Human Tissue Biopsy at Day 42 (Phase 2 UP/UPS Trial)](chart)
Brilacidin

**Inhibition of IL-1β, IL-6 (Mouse Model, Ulcerative Colitis)**

Brilacidin reduced the severity of Ulcerative Colitis (UC) induced by DSS administered through drinking water in mice. Brilacidin 400mg/kg were given intra-rectally once per day for 5 days. 5-amino salicylic acid (5-ASA) was used as a positive control. At the end of experiments, animals were anaesthetized. Their abdomens were opened directly with co-opened PBS (pH7) and immediately cut into small 1cm piece (distal portion) and transferred to liquid nitrogen container for further study. Frozen colon tissues were lysed and protein concentrations were measured and all samples were diluted to equal concentration. IL-6 and IL-1β were measured according to manufacturer’s instruction.

**Mouse Ulcerative Colitis: IL-1β**

Effects of Brilacidin on DSS-induced IL-1β. The data were normalized to the total proteins. Levels of IL-1β levels presented as treated UC with Brilacidin (400mg/kg) relative to untreated UC. 5-ASA were used as positive control.

**Mouse Ulcerative Colitis: IL-6**

Effects of Brilacidin on DSS-induced IL-6. The data were normalized to the total proteins. Levels of IL-6 levels presented as treated UC with Brilacidin (400mg/kg) relative to untreated UC. 5-ASA were used as positive control.

**Brilacidin**

**Inhibition of TNF-α, IL-1β, IL-6**

**Fig. 1** Effects of Brilacidin on LPS-induced TNF-α release in NR8838 cells. Rat macrophages (NR8838) were pretreated with Brilacidin with concentrations shown for 45 minutes, followed by LPS (1μg/ml) treatment for 8 hrs. After 8 hrs, supernatants were collected for TNF-α measurement by ELISA.

**Fig. 2** Effects of Brilacidin on LPS-induced IL-6 release in NR8838 cells. Rat macrophages (NR8838) were pretreated with Brilacidin with concentrations shown for 45 minutes, followed by LPS (1μg/ml) treatment for 8 hrs. After 8 hrs supernatants were collected for IL-6 measurement by ELISA.

**Fig. 3** Effects of Brilacidin’s on IL-1β production in rat macrophage cells pretreated with the compound. Brilacidin demonstrated a strong inhibition of IL-1β induction after LPS stimulation. There was more than 50% decrease in IL-1β production within 8 hrs of treatment at 2.5μM concentration of Brilacidin.
Brilacidin
Inhibition of IL-8, MIP2-α

Effects of Brilacidin on LPS-induced IL-8 production in THP-1 cells. THP-1 cells were pretreated with Brilacidin with concentrations shown for 45 minutes, followed by LPS (1μg/ml) treatment for 8 hrs. After 8 hours, IL-8 concentrations were determined by ELISA using an immunoassay kit specific for human IL-8 (Thermo Fisher). Brilacidin inhibited the LPS-induced IL-8 production in THP-1 cells in a dose-dependent manner.

Brilacidin
Inhibition of MCP-1, MMP-9

Effects of Brilacidin on LPS-induced MCP-1 release in NR8383 cells. Rat macrophages (NR8383) were pretreated with Brilacidin with concentrations shown for 45 minutes, followed by LPS (1μg/ml) treatment for 8 hrs. After 8 hrs, supernatants were collected for MCP-1 measurement by ELISA.

Effects of Brilacidin on LPS-induced MIP-2α (Rat CINC-3) release in NR8383 cells. Rat macrophages (NR8383) were pretreated with Brilacidin with concentrations shown for 45 minutes, followed by LPS (1μg/ml) treatment for 8 hrs. After 8 hrs, supernatants were collected for MIP-2α (Rat CINC-3) measurement by ELISA. A 65% decrease in CINC-3 levels at a 2.5μM concentration of Brilacidin was observed.
**Antimicrobial**

Even though a vast majority of COVID-19 patients are administered IV antibiotics, bacterial infections can co-present, in up to 15 percent of patients according to one study (even as high as 20 percent according to another study), with 50 percent of those who have died having had a secondary infection.

Brilacidin may help fight secondary infections among COVID-19 patients given its robust activity against opportunistic pathogenic bacteria, both gram positive and gram negative, including Methicillin-resistant Staphylococcus aureus (MRSA) and other drug-sensitive/drug-resistant bacteria. Julie L. Gerberding, Director of the CDC from 2002 to 2009, has called antibiotic resistance “an even larger threat lurking behind” the current COVID-19 pandemic.\(^5\)

Bacterial superinfections, tied to secondary bacterial pneumonia caused by *Staphylococcus aureus* or *Streptococcus pneumoniae*, accompany flu outbreaks and might be expected in the current novel coronavirus pandemic. The attenuation of AMP/defensin production by lung epithelial cells may play a key role in patient susceptibility to secondary bacterial pneumonia.

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**Brilacidin for ABSSSI**

**ABSSSI** Phase 2b Clinical Trial Results—Single-Dose Brilacidin Comparable to 7-Day Regimen of Daptomycin

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number Assessed</th>
<th>Clinical Response (%</th>
<th>95% CI</th>
<th>Current Perspectives</th>
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</thead>
<tbody>
<tr>
<td>Brilacidin 0.6 mg/kg IV x 1 day (N=53)</td>
<td>53</td>
<td>46</td>
<td>52</td>
<td>50</td>
</tr>
<tr>
<td>Brilacidin 0.8 mg/kg IV x 1 day (N=53)</td>
<td>86 (91.0)</td>
<td>99 (99.0)</td>
<td>91 (94.1)</td>
<td>50 (95.9)</td>
</tr>
<tr>
<td>Brilacidin x 3 days (N=53)</td>
<td>53</td>
<td>46</td>
<td>52</td>
<td>50</td>
</tr>
<tr>
<td>Daptomycin x 7 days (N=50)</td>
<td>99 (96.1)</td>
<td>99 (99.0)</td>
<td>99 (99.9)</td>
<td>99 (99.9)</td>
</tr>
</tbody>
</table>

**Pre-treatment**

**Day 3**

**Day 10**

*Acute Bacterial Skin and Soft Tissue Infection

**Current Perspectives**

- Safe and effective in TWO Phase 3 studies
- Highly active against MRSA
- Convenient 3-day-DOT regimen
- Pharmacoeconomic advantages
- Efficacy comparable to 7-day regimen of robust comparator (daptomycin x 7 days)
- GDS designation (Nov 2014) under the GAVA Act
  - Eligibility for Fast Track and Priority Review
  - 5-year Market Exclusivity
- Minimal potential for development of resistance
  - Novel class, with no cross resistance
  - Novel mechanism of action: anti-biofilm advantage for bacterial resistance
  - Single dose ensures patient non-compliance as risk of resistance
- Phase 3 Ready
  - Application to Special Protocol Assessment (SPA) confirmed to FDA

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**Brilacidin—Mechanism of Action (Antimicrobial)**

**Rapid Killing Ability Makes Antibiotic Resistance Less Likely**

**Bacterial Resistance Unlikely**

**Membrane Activity supported by:**

- Coarse grain molecular dynamic simulations
- Vesicle leak assays
- Membrane permeabilization and potentiation assays
- Transcriptional profiling, proteomics and deep sequencing
- Transmission electron microscopy

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\(^5\) Dr. Gerberding: "As we come together to fight today’s Covid-19 crisis, we must also look ahead to the next one. We cannot be short-sighted, and we cannot be complacent, especially about antibiotic resistance. We must put measures in place to ensure that we have the antibiotics we need — today and in the future. The time to act is now.”
Innovation Pharmaceuticals: Mechanism of Action, Pre/Clinical Data and Academic Literature
Supporting the Development of Brilacidin as a Potential Novel Coronavirus (COVID-19) Treatment (April 20, 2020)

Brilacidin has broad spectrum in vitro antimicrobial activity

MIC for antimicrobial activity was assessed for brilacidin. Brilacidin has potent Gram positive activity, Gram negative coverage, but low cytotoxicity against mammalian cells.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Gram +MIC90s (µg/ml)</th>
<th>Gram - MIC range (µg/ml)</th>
<th>Mammalian cytotoxicity (EC50, µM)</th>
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</thead>
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<tr>
<td>MSSA</td>
<td>1</td>
<td>0.5 - 1</td>
<td>&gt;500</td>
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<tr>
<td>MRSA</td>
<td>1</td>
<td>1 - 2</td>
<td>430</td>
</tr>
<tr>
<td>CoNS</td>
<td>1</td>
<td>1 - 4</td>
<td>1,031</td>
</tr>
<tr>
<td>E. coli</td>
<td>1</td>
<td>0.5 - 1</td>
<td>&gt;500</td>
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<tr>
<td>K. pneumonia</td>
<td>1</td>
<td>1 - 2</td>
<td>430</td>
</tr>
<tr>
<td>Entero. bact.</td>
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<td>1 - 2</td>
<td>1,031</td>
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<tr>
<td>RBCs</td>
<td>1</td>
<td>0.5 - 1</td>
<td>&gt;500</td>
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<tr>
<td>3T3</td>
<td>1</td>
<td>0.5 - 1</td>
<td>&gt;500</td>
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<tr>
<td>HepG2</td>
<td>1</td>
<td>0.5 - 1</td>
<td>&gt;500</td>
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</table>

Brilacidin has rapid (0.5 to 6 hrs) bactericidal activity

Antimicrobial activity vs. Gram-positive clinical isolates

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC (µg/ml)</th>
<th>S. aureus</th>
<th>Staph. epidermidis</th>
<th>Staph. saprophyticus</th>
<th>Staph. spp. (coagulase-)</th>
<th>Strept. anginosus</th>
<th>Strept. pneumonia</th>
<th>Strept. pyogenes</th>
<th>Strept. viridans</th>
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<tbody>
<tr>
<td>Enter. faecalis</td>
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<td>1</td>
<td>1 - 2</td>
<td>0.5 - 1</td>
<td>0.25 - 0.5</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Enter. faecalis (VRE)</td>
<td>1</td>
<td>1</td>
<td>1 - 2</td>
<td>&gt;128</td>
<td>&gt;64</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>S. aureus (MRSA)</td>
<td>0.5</td>
<td>0.5 - 1</td>
<td>0.5 - 1</td>
<td>2</td>
<td>16 - 32</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td>0.5</td>
<td>0.25 - 0.5</td>
<td>0.5 - 1</td>
<td>2</td>
<td>16 - 32</td>
<td>1</td>
<td>1</td>
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<tr>
<td>S. saprophyticus</td>
<td>0.5</td>
<td>0.25 - 0.5</td>
<td>0.5 - 1</td>
<td>2</td>
<td>16 - 32</td>
<td>1</td>
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</tr>
<tr>
<td>S. spp. (coagulase-)</td>
<td>0.5</td>
<td>0.25 - 0.5</td>
<td>0.5 - 1</td>
<td>2</td>
<td>16 - 32</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Strept. agalactiae</td>
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<td>0.5</td>
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</tr>
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<td>Strept. pneumonia</td>
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<td>0.25</td>
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<td>0.25</td>
<td>0.25</td>
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<tr>
<td>Strept. pyogenes</td>
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<td>1</td>
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<td>0.25</td>
<td>0.25</td>
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<tr>
<td>Strept. viridans</td>
<td>0 - 10</td>
<td>2 - 5</td>
<td>1</td>
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<td>0.25</td>
<td>0.25</td>
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Antimicrobial activity vs. Gram-negative clinical isolates

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC (µg/ml)</th>
<th>S. aureus</th>
<th>Staph. epidermidis</th>
<th>Staph. saprophyticus</th>
<th>Staph. spp. (coagulase-)</th>
<th>Strept. agalactiae</th>
<th>Strept. pneumonia</th>
<th>Strept. pyogenes</th>
<th>Strept. viridans</th>
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<tr>
<td>Enterococcus faecalis</td>
<td>2 - 4</td>
<td>2 - 4</td>
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<td>&gt;128</td>
<td>&gt;64</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Citrobacter freundii</td>
<td>2 - 4</td>
<td>2 - 4</td>
<td>1 - 2</td>
<td>&gt;128</td>
<td>&gt;64</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>2 - 4</td>
<td>2 - 4</td>
<td>1 - 2</td>
<td>&gt;128</td>
<td>&gt;64</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>2 - 4</td>
<td>2 - 4</td>
<td>1 - 2</td>
<td>&gt;128</td>
<td>&gt;64</td>
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<tr>
<td>Klebsiella oxytoca</td>
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<td>1 - 2</td>
<td>&gt;128</td>
<td>&gt;64</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>2 - 4</td>
<td>2 - 4</td>
<td>1 - 2</td>
<td>&gt;128</td>
<td>&gt;64</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Morganella morganii</td>
<td>2 - 4</td>
<td>2 - 4</td>
<td>1 - 2</td>
<td>&gt;128</td>
<td>&gt;64</td>
<td>2</td>
<td>2</td>
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<td>2</td>
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<tr>
<td>Proteus mirabilis</td>
<td>2 - 4</td>
<td>2 - 4</td>
<td>1 - 2</td>
<td>&gt;128</td>
<td>&gt;64</td>
<td>2</td>
<td>2</td>
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<td>2</td>
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<tr>
<td>Proteus vulgaris</td>
<td>2 - 4</td>
<td>2 - 4</td>
<td>1 - 2</td>
<td>&gt;128</td>
<td>&gt;64</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>2 - 4</td>
<td>2 - 4</td>
<td>1 - 2</td>
<td>&gt;128</td>
<td>&gt;64</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Salmonella typhimurium</td>
<td>2 - 4</td>
<td>2 - 4</td>
<td>1 - 2</td>
<td>&gt;128</td>
<td>&gt;64</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>2 - 4</td>
<td>2 - 4</td>
<td>1 - 2</td>
<td>&gt;128</td>
<td>&gt;64</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>2 - 4</td>
<td>2 - 4</td>
<td>1 - 2</td>
<td>&gt;128</td>
<td>&gt;64</td>
<td>2</td>
<td>2</td>
<td>2</td>
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</tr>
</tbody>
</table>

Table 1. Susceptibility of Clinical Isolates

<table>
<thead>
<tr>
<th>Organism (# isolates)</th>
<th>Gram + / -</th>
<th>Fluoroquinolone</th>
<th>brilacidin (µg/ml)</th>
<th>MIC range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staph. aureus (25)</td>
<td>+</td>
<td>S</td>
<td>0.25</td>
<td>0.13 - 0.5</td>
</tr>
<tr>
<td>Staph. aureus (25)</td>
<td>+</td>
<td>R</td>
<td>0.25</td>
<td>0.13 - 1</td>
</tr>
<tr>
<td>Staph. epidermidis (25)</td>
<td>+</td>
<td>S</td>
<td>0.13</td>
<td>0.03 - 0.25</td>
</tr>
<tr>
<td>Staph. epidermidis (25)</td>
<td>+</td>
<td>R</td>
<td>0.13</td>
<td>0.03 - 0.25</td>
</tr>
<tr>
<td>Strept. pneumoniae (24)</td>
<td>+</td>
<td>S</td>
<td>1</td>
<td>0.5 - 16</td>
</tr>
<tr>
<td>Strept. viridans (25)</td>
<td>+</td>
<td>S</td>
<td>4</td>
<td>1 - 32</td>
</tr>
<tr>
<td>Pseud. aeruginosa (25)</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>0.5 - 8</td>
</tr>
<tr>
<td>Serrat. marcescens (25)</td>
<td>-</td>
<td>-</td>
<td>8</td>
<td>2 - 32</td>
</tr>
</tbody>
</table>
IV. Brilacidin: COVID-19 Clinical Development Pathways

Brilacidin, a leading defensin-mimetic drug candidate tested successfully in Phase 2 human trials for other clinical indications, is a promising and unique novel coronavirus (COVID-19) therapeutic candidate given Brilacidin exhibits three therapeutic properties (a 3 in 1 combination) in a single drug—antiviral, immuno/anti-inflammatory and antimicrobial.

Drug

Evaluated as an anti-inflammatory antibiotic, the Company completed a Phase 2b trial of Brilacidin, delivered as a single intravenous dose, where the drug compared favorably to a 7-day dosing regimen of daptomycin (Cubicin™).

Brilacidin could be developed, most immediately based on existing safety and efficacy data, as an intravenous drug (direct treatment), whether administered as a monotherapy or in combination, potentially leveraging synergies with other drugs or antivirals, as is being done (e.g., Hydroxychloroquine and azithromycin; antivirals and anti-inflammatories⁶, e.g., remdesivir and sarilumab).

Importantly, Brilacidin is one of the few drugs currently in clinical development and among drugs already approved that has shown direct antiviral properties against SARS-CoV-2, the novel coronavirus responsible for COVID-19, in a cell-based assay, with additional research planned by academic collaborators.

Drugs that are even modestly active⁷ against the novel coronavirus, particularly ones with safe therapeutic profiles having been evaluated earlier in rigorous placebo-controlled clinical trials, might not only save the lives of severely ill patients, but might also be given prophylactically to protect health care workers and others at risk of infection. Such treatments may also reduce the time patients spend in ICUs, freeing up hospital beds.

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⁷ See: The Brussels Times (March 4, 2020), Gates Foundation Commissions Large Coronavirus Study from KU Leven: “But a little bit is good enough,” Prof Neyts said. “Or better still, a couple of substances that each slow it down a little, that we can combine to help seriously ill patients to hopefully get better.”
Additional drug delivery development work (e.g., intranasal/nebulized dosing, the use of nanotechnologies\(^8\)) may further complement Brilacidin’s anti-COVID-19 therapeutic potential.

---

Vaccine

Vaccines containing defensins as adjuvants have been shown, in vivo and in vitro, to activate the primary innate antiviral immune response and mediate other immunomodulatory activities against a number of viruses, including coronaviruses. A vaccine based on Brilacidin, a defensin-mimetic, is another potential clinical development pathway, though developing Brilacidin as a vaccine would involve a longer process (12-18 months) than advancing it as a COVID-19 drug candidate. Legislative and regulatory authorities, however, have indicated (pdf) a willingness to expedite vaccine development, including eliminating the need for animal studies, assigning promising vaccines Breakthrough Therapy status and making COVID-19 vaccines eligible for Priority Review Vouchers, etc. Information below and posted to the Company website includes links to literature detailing the potential of defensins developed as antiviral vaccines.

Human β-defensin 2 plays a regulatory role in innate antiviral immunity and is capable of potentiating the induction of antigen-specific immunity

Ju Kim¹, Ye Lin Yang², Sun-Hee Jang¹ and Yong-Suk Jang¹* (*)

Abstract

Background: Antimicrobial peptides (AMPs) are primarily known for their innate immune defense against invading microorganisms, including viruses. In addition, recent research has suggested their modulatory activity in immune induction. Given that most subunit vaccines require an adjuvant to achieve effective immune induction through the activation of innate immunity, AMPs are plausible candidate molecules for stimulating not only innate immune but also adaptive immune responses.

Results: In this study, we investigated the ability of human β-defensin (HBD) 2 to promote antiviral immunity in vitro and in vivo using a receptor-binding domain (RBD) of Middle East respiratory syndrome-coronavirus (MERS-CoV) spike protein (S RBD) as a model antigen (Ag). When HBD 2-conjugated S RBD was used to treat THP-1 human monocyctic cells, the expression levels of antiviral (IFN-β, IFN-γ, MxA, PKR, and RnaseL) and primary immune-inducing (NO2, TNF-α, IL-1β, and IL-6) molecules were enhanced compared to those expressed after treatment with S RBD only. The expression of chemokines capable of recruiting leukocytes, including monocytes/macrophages, natural killer cells, granulocytes, T cells, and dendritic cells, was also increased following HBD 2-conjugated S RBD treatment. More importantly, immunization of mice with HBD 2-conjugated S RBD enhanced the immunogenicity of the S RBD and elicited a higher S RBD-specific neutralizing antibody response than S RBD alone.

Conclusions: We conclude that HBD 2 activates the primary antiviral innate immune response and may also mediate the induction of an effective adaptive immune response against a conjugated Ag.

Keywords: Adjuvant, Antigen, Antibody, Human β-defensin, MERS-CoV

Background

In general, vaccination materials consist of a specific antigen (Ag) and an adjuvant capable of potentiating the immunogenicity of the Ag to achieve efficient Ag-specific adaptive immunity [1]. Vaccines made up of live attenuated and/or killed whole pathogens usually contain endogenous adjuvants, such as bacterial cell wall components, genomic nucleic acids, and various pathogen-derived materials, that act as pathogen-associated molecular patterns and are sufficient to induce Ag-specific adaptive immunity by potentiating immunogenicity through the activation of innate immunity [2, 3]. However, subunit vaccines that utilize recombinant and/or purified Ags usually lack these endogenous innate immune stimulators. Consequently, the addition of exogenous materials with adjuvant activity is required to mimic natural infection to draw effective pathogenic Ag-specific adaptive immunity [4].

The innate immune response includes the production of interferons (IFNs), complements, and antimicrobial peptides (AMPs) and is crucial for controlling infectious diseases and inducing adaptive immunity [5]. AMPs have been proposed as multifunctional peptides that participate

Table 1: Summary of the development of antiviral agents and vaccine development against Coronavirus (CoV).

<table>
<thead>
<tr>
<th>S. No</th>
<th>Drug</th>
<th>Status</th>
<th>References</th>
</tr>
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<tr>
<td>1</td>
<td>Favipiravir</td>
<td>Phase III</td>
<td>[25]</td>
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<td>2</td>
<td>Aluminum’s intranasal vaccine</td>
<td>stage I clinical trial</td>
<td>[26]</td>
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<td>3</td>
<td>INO-4800</td>
<td>Pre-clinical testing</td>
<td>[27]</td>
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<td>4</td>
<td>NP-120 (Ivermectin)</td>
<td>Phase-I pilot trial</td>
<td>[28]</td>
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<td>5</td>
<td>AP501</td>
<td>Phase-I clinical trial</td>
<td>[29]</td>
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<tr>
<td>6</td>
<td>mRNA-1273</td>
<td>Phase-I clinical trial</td>
<td>[30]</td>
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<td>7</td>
<td>Avian CoV infectious Bronchitis virus vaccine</td>
<td>Pre-clinical trials</td>
<td>[31]</td>
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<tr>
<td>8</td>
<td>Brilacidin</td>
<td>Pre-clinical stage</td>
<td>[32]</td>
</tr>
<tr>
<td>9</td>
<td>Clover - recombinant subunit vaccine</td>
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<td>[33]</td>
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<td>10</td>
<td>Vaxxart’s CoV vaccine</td>
<td>Pre-clinical stage</td>
<td>[34]</td>
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<td>11</td>
<td>CytoDyn-Leronlimus</td>
<td>Phase II clinical trial</td>
<td>[35]</td>
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<tr>
<td>12</td>
<td>Lisan DNA vaccine – Takis Biotech</td>
<td>Pre-clinical stage</td>
<td>[36]</td>
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<td>13</td>
<td>Randevir (GS-5734)</td>
<td>Phase-III clinical trials</td>
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<td>14</td>
<td>Chloroquine or hydroxychloroquine</td>
<td>clinical trial</td>
<td>NCT04261517</td>
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<tr>
<td>15</td>
<td>Camo/izumab and thymosin</td>
<td>Phase II trials</td>
<td>NCT04685337</td>
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<td>16</td>
<td>Azadirone</td>
<td>Phase I</td>
<td>C5CTR20002953</td>
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</table>

Source: Kumar D. “Understanding the Molecular Mechanism(s) of SARS-CoV2 Infection and Propagation in Human to Discover Potential Preventive and Therapeutic Approach.” OSF Preprints. April 14, 2020.
Defensins - Non-antibiotic Use for Vaccine Development

Arya Biragyn*

Laboratory of Immunology, Gerontology Research Center, National Institute on Aging, National Institutes of Health, Baltimore, Maryland 21224, USA

Abstract: Vaccines should elicit protective and long lasting immune memory, which depends on well choreographed responses between innate and acquired immunity. Defensins are small host defense peptides of innate immunity hitherto reported to have antimicrobial activity, which also orchestrate chemotaxis and activation of effector immune cells, including immature dendritic cells. This review analyzes the biological meaning of the immunomodulatory and immunoenhancing features of defensins and their use for the development of novel vaccines to combat cancer and clinically relevant diseases.

Keywords: Antimicrobial peptides, dendritic cells, vaccine carrier.

Fig. (1). Defensins as carrier for vaccines to target APCs. Marine β-defensin 2–fused antigens target to APCs via the CCR6 chemokine receptor CCR6, which is internalized to deliver the complex to early/late endosomal compartments. The internalized defensin-antigen is processed and presented to both MHC class II and MHC class I to elicit CD4 and CD8 T cell responses. At the same time, marine β-defensins 2 fused antigens induce maturation of IDCs and the the production of Th1 polarizing cytokines.

Conclusion: “Taken together, these features of the defensins and other antimicrobial peptides have to be considered when they are utilized as adjuvant and vaccine carriers for non-immunogenic or weakly immunogenic antigens. Use of different defensins may enable induction of controlled and polarized immune responses individually tailored for the specific disease at will.” [emphasis added]

Next Steps

The Company is engaged in discussions within government, the pharmaceutical industry, and among health care provider networks and hospitals both in the United States and Europe, toward rapidly advancing Brilacidin testing into human trials to evaluate its potential as a novel coronavirus (COVID-19) therapeutic. Their interest in Brilacidin as a treatment for COVID-19 and associated complications is based on the drug’s promising antiviral activity against SARS-CoV-2, as supported in preliminary testing conducted in a monkey epithelial cell line (with testing planned to continue), and the drug’s established anti-inflammatory and antimicrobial properties—a 3-in-1 treatment combination. In advance of potential clinical testing, the Company is investigating procurement of appropriate drug supply (i.e., manufacture of intravenous drug product), and preparing for engagement with regulatory authorities. While there can be no assurance that a Brilacidin for COVID-19 clinical trial will commence, though that is the goal of the Company, a recent announcement by the National Institutes of Health (NIH) to launch a public-private partnership to speed COVID-19 therapeutics is a hopeful sign—that promising drugs, such as Brilacidin, might be rapidly developed to help address the COVID-19 pandemic.
V. Brilacidin: Phase 2 Clinical Trial Data in Other Indications

Exceptionally Strong Pipeline, Novel Mechanisms of Action

<table>
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<th>Drug Candidate</th>
<th>Indication</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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<td>Oral Mucositis¹</td>
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<td></td>
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<tr>
<td></td>
<td>ABSSSI²,3</td>
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<tr>
<td></td>
<td>IBD: Ulcerative Colitis⁴</td>
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<tr>
<td></td>
<td>IBD: Crohn’s Disease</td>
<td></td>
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<tr>
<td></td>
<td>IBD: UP/UPS⁵</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atopic Dermatitis</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Acne</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kevetrin</td>
<td>Ovarian Cancer⁶</td>
<td></td>
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</tr>
</tbody>
</table>

1 Awarded Fast Track Designation
2 Acute Bacterial Skin and Skin Structure Infection
3 Awarded Qualified Infectious Disease Product (QIDP) Designation (qualifies for Fast Track and Priority Review)
4 Oral formulation mode of administration
5 Inflammatory Bowel Disease: Ulcerative Proctitis/Ulcerative Proctitis/Rectitis, licensed to Alfasigma S.p.A. July 2019
6 Awarded Orphan Drug Designation

Leveraging data from clinical studies in other indications to expedite development.
Brilacidin for Acute Bacterial Skin and Skin Structure Infection (ABSSSI)

FDA Qualified Infectious Disease Product, QIDP; Phase 2b (NCT02052388), intravenous delivery

**Study Design**

**Efficacy/Safety**

**Baseline Pathogens**

*Source* (ECCMID 2015)
Brilacidin for 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 (NCT04240223) in Ulcerative Colitis (UC), Phase 2 planning underway

Brilacidin for IBD: Phase 2 UP/UPS
Rectal Enema Formulation demonstrated Clinical remission, supported by Endoscopic improvement

Clinical Remission in majority of patients at Week 6 (Day 42)
Similar across cohorts
- 60% (3 of 5) in Cohort A, 50 mg Brilacidin
- 67% (4 of 6) in Cohort B, 100 mg Brilacidin
- 75% (3 of 4) in Cohort C, 200 mg Brilacidin

Examples Clinical Remission
Treated with 100 mg Brilacidin (Cohort B) per retention enema

Clinical Remission defined as:
- Endoscopy subscore ≤ 1
- Rectal Bleeding subscore of 0
- Stool Frequency subscore improvement or no change from baseline

Colonic tissue biopsies at Week 6 (D42) demonstrate reduction in inflammatory biomarkers

Source: Innovation Pharmaceuticals Inc.
Brilacidin for Oral Mucositis (OM)

FDA Fast Track; Phase 2 (NCT02324335), oral rinse delivery; Phase 3 planning underway

CTIX-BRI-205: Oral Mucositis Phase 2 Study

Efficacy and Safety of Brilacidin oral rinse administered tid for 7 weeks (49 days)

- Phase 2, multi-center (USA), randomized, double-blind, placebo-controlled study
- Daily treatment aimed at attenuating Oral Mucositis (OM) in subjects with Head and Neck Cancer receiving concurrent chemoradiation therapy

**Designs:**
- 7 weeks of treatment, with two study visits per week
- 2 treatment groups:
  - Brilacidin (45 mg/23 mL WFI, tid)
  - Placebo (55 mL WFI, tid)
- Oral rinse (15 mL), “swish” for 1 min, then “spit” out
- 3 x daily oral rinse (tid), approximately 6 hours apart

**Patients:**
- Recently diagnosed (within previous 3 months), pathologically confirmed, non-metastatic squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or supraglottic larynx
- Radiation Therapy: at least 2 oral sites to receive single daily fractions of 2.0-2.2 Gy with a cumulative radiation dose ≥ 55 Gy and ≤ 72 Gy
- Chemotherapy: cisplatin weekly (30-40 mg/m²) or approximately every 21 days (60-100 mg/m²)

CTIX-BRI-205: Oral Mucositis Phase 2 Study

Primary Efficacy Endpoint met

**Brilacidin oral rinse met primary endpoint of reduced incidence of severe OM (WHO Grade ≥ 3) experienced by subjects during chemoradiation therapy.**

**Incidence of SOM (WHO Grade ≥ 3)**

**Relative Difference (Reduction) in Incidence of SOM, Brilacidin vs Placebo**

- Greatest efficacy demonstrated in cisplatin q4w subgroup
- Incidence of SOM on placebo was 60% (in this study)

CTIX-BRI-205: Phase 2 Oral Mucositis Trial

**Positive Results: Delayed Time to Onset of Severe Oral Mucositis marked in 21-day Cisplatin subgroup**

**Kaplan-Meier Curves for Time to Onset, in Days, of Severe OM, 21-day Cisplatin Schedule (PP Population)**

Note: Time start from approximately 19-49 days during which SOM incidence rises sharply in Placebo while not in the Brilacidin group

Source: Innovation Pharmaceuticals
**Brilacidin Platform Potential**

*Gateway Concept Given Wide Range of HDP-M Therapeutic Activity*

---

### Innate Immunity

#### Pathogen Defense
- **Bacterial**
  - *ABSSSI (skin)*
  - *Bone and Joint*
  - *DFIs*
  - *Respiratory*
  - *Blood Stream*
  - *STDs*
- **Fungal**
  - *Oral Candidiasis*
  - *Disseminated Candidiasis*
  - *Aspergillosis*
- **Parasitic**
  - *Malaria*
  - *Sleeping Sickness*
  - *Glarulasis*
- **Viral**
  - *Coronavirus (tbd)*
  - *Influenza*
  - *Herpes*
  - *RSV*

#### Barrier Function
- **GI Mucosa**
  - *IBD: Ulcerative Proctitis (Distal Colitis)*
  - *IBD: Ulcerative Colitis*
  - *Oral Mucositis*
  - *IBD: Crohn’s*
  - *Irritable Bowel Syndrome*
  - *GI-Acute Radiation Sickness*
  - *Periodontitis*
- **Skin/Eye**
  - *Atopic Dermatitis*
  - *Acne*
  - *H. Suppurativa*
  - *Diabetic Ulcers*
  - *Keratitis*
  - *Burns/Abrasions*

---

*ABSSSI gateway for antibiotic opportunities*

*Ulcerative Proctitis (Distal Colitis) gateway for anti-inflammatory opportunities*
VI. AMPs/Defensins (Mimetics): Antiviral Properties

Antiviral properties of natural AMPs/defensins and their synthetic mimics are actively being studied by scientists the world over, with newer understandings elucidating their direct mechanisms of action against non-enveloped and enveloped viruses alike, along with their role in the regulation of inflammation and chemoattraction. Relevant review articles, with select excerpts, are inked below:


“Progress has been made in the last decade to elucidate the mechanisms of action of various AMPs. The primary mechanism of AMP-mediated antiviral activity has been attributed to direct interference with, and destabilization of, viral envelopes. However, AMPs have also demonstrated selective immune modulation. Antiviral activity against both enveloped and non-enveloped viruses has been reported with the latter hinting at the presence of undiscovered activities of AMPs, in addition to the known direct interaction with viral envelopes. [...] In vulnerable individuals, prophylactic expression of AMPs has the potential to become a preventative strategy against viral infections, especially during emerging pandemics. In addition, the simplicity of AMPs makes the development of synthetic peptide analogues a cost-effective measure to treat established viral infections. AMPs and their synthetic derivatives are a promising avenue to yield new strategies to control and treat a wide range of viral diseases but their application is still at the preliminary stages. Therefore, further research is warranted to understand AMP antiviral activity both in vivo and in vitro and to determine underlying mechanisms involved in AMP-mediated immune modulation for clinical applications.”

[emphasis added]
Innovation Pharmaceuticals: Mechanism of Action, Pre/Clinical Data and Academic Literature
Supporting the Development of Brilacidin as a Potential Novel Coronavirus (COVID-19) Treatment (April 20, 2020)


“Due to their common structural features, including an amphipathic structure and cationic charge, they [HDPs] have been widely shown to interact with and disrupt microbial membranes. Thus, it is not surprising that human HDPs have activity against enveloped viruses as well as bacteria and fungi. However, these peptides also exhibit activity against a wide range of non-enveloped viruses as well, acting at a number of different steps in viral infection. [...] The broad spectrum of antiviral activity of these peptides, both in vitro and in vivo suggest that they play an important role in the innate antiviral defense against viral infections. Furthermore, the literature suggests that they may be developed into antiviral therapeutic agents.” [emphasis added]

Table 1. Known antiviral activities of human defensins against enveloped DNA viruses [21].

<table>
<thead>
<tr>
<th>Virus/Defensin</th>
<th>HNP1</th>
<th>HNP2</th>
<th>HNP3</th>
<th>HNP4</th>
<th>HD5</th>
<th>HD6</th>
<th>HD1</th>
<th>HD2</th>
<th>HD3</th>
<th>HD4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpesviruses</td>
<td>NE</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CMV</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>HSV-1</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>HSV-2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VZV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VACCIA</td>
<td>NE</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
</tr>
</tbody>
</table>

NE: Tested HDP had no effect. U: Antimicrobial mechanism is undetermined. *: Yet to be tested. Table shows most common result of HDP antiviral test.

Table 7. Direct comparisons of human HDP activity against viruses.

<table>
<thead>
<tr>
<th>Virus</th>
<th>Direct comparison of HDP activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV-1</td>
<td>HNP1, HNP2, and HNP3 were about equal in effectiveness</td>
</tr>
<tr>
<td>HSV-2</td>
<td>HNP1 and HD5 were most effective among defensins tested. HD3 was more effective than HDB1</td>
</tr>
<tr>
<td>VZV</td>
<td>HBD2 and LL-37 had similar activities, but unlike with HDB1, LL-37 pre-incubation of virus and peptide before infection increased antiviral activity compared to after infection</td>
</tr>
<tr>
<td>Vaccinia</td>
<td>HBD2, but not HD1 or HDN1/2 had effect. This effect was more potent than LL-37</td>
</tr>
<tr>
<td>HADV</td>
<td>For HNP1 and HD5, viral species A, B1, B2, C, and E susceptible, but D and F are not. HD5 was more effective than HNP1 against HADV5 and HDADV5. HBD2 and HD6 mostly ineffective. Defensins and LL-37 inhibit different species.</td>
</tr>
<tr>
<td>HPV</td>
<td>HD5 had highest efficacy. HBD1/2 and HD6 had no effect. HNP1-4 and LL-37 had similar efficacies</td>
</tr>
<tr>
<td>BKV</td>
<td>HD5 had highest efficacy. HNP1 and HBD2 had similar effect, while HBD1 had no effect</td>
</tr>
<tr>
<td>JCV</td>
<td>HD5 had highest efficacy. Discrepancy for activity of HNP1 and HBD1/2. No effect seen in HNP9 or HBD4</td>
</tr>
<tr>
<td>SV40</td>
<td>HD5 inhibited, while HNP1 and HBD1/2 did not</td>
</tr>
<tr>
<td>HCV</td>
<td>Mixture of HNP1-4 (about as effective as LL-37) was more effective than mixture of HBD1-5+116</td>
</tr>
<tr>
<td>Influenza A virus</td>
<td>HNP1, HBD1, and HBD2 did not increase IA' uptake by neutrophils, unlike HNP1 and HD5. HNP1/2 (with slight edge to HNP2) more effective than HDs or LL-37. HNP1/2 work synergistically with LL-37</td>
</tr>
<tr>
<td>RSV</td>
<td>HBD2 had most activity while HBD1 was ineffective. LL-37 was less effective than HBD2</td>
</tr>
<tr>
<td>HIV-1</td>
<td>LL-37 and HNP4 are more effective than HNP1-3, most likely due to HNP4 less binding to serum. Combination of HBD2 and HBD3 was more effective than either HBD alone. Conflicting data about HBD1 activity, with HBD2/3 having more activity. HBD2 inhibits single stage infection and provides long term antiviral activity, unlike HBD1.</td>
</tr>
</tbody>
</table>

Comparisons are only between HDPs tested in the same experiment.

“While scientific advances have led to large-scale production and widespread distribution of vaccines and antiviral drugs, viruses still remain a major cause of human diseases today. The ever-increasing reports of viral resistance and the emergence and re-emergence of viral epidemics pressure the health and scientific community to constantly find novel molecules with antiviral potential. This search involves numerous different approaches, and the use of antimicrobial peptides has presented itself as an interesting alternative. Even though the number of antimicrobial peptides with antiviral activity is still low, they already show immense potential to become pharmaceutically available antiviral drugs. Such peptides can originate from natural sources, such as those isolated from mammals and from animal venoms, or from artificial sources, when bioinformatics tools are used. This review aims to shed some light on antimicrobial peptides with antiviral activities against human viruses and update the data about the already well-known peptides that are still undergoing studies, emphasizing the most promising ones that may become medicines for clinical use.” […]

Human coronaviruses are positive-sense RNA enveloped viruses that belong to the Coronaviridae family. So far, six coronaviruses (CoV) have been reported to infect humans: HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, severe acute respiratory syndrome coronavirus (SARS-CoV), and the Middle East respiratory syndrome coronavirus (MERS-CoV) [160]. While HCoV-229E and HCoV-OC43 are associated with upper and mild respiratory tract infections, SARS-CoV and MERS-CoV cause a variety of severe flu-like symptoms and were responsible for recent epidemics (in 2002/3 and 2015, respectively) [161, 162]. […]

The peptides named 229E-HR1P and 229E-HR2P both showed inhibition of cell–cell spread, and inhibition of the pseudovirus infection, but 229E-HR2P was much more effective. Besides, in vivo assays showed that 229E-HR2P could retain its antiviral activity in both upper and lower respiratory tracts when administered intranasally. In the end, the authors suggested that 229E-HR2P could become an antiviral drug to be used along with different antiviral molecules with a different mechanism of action, possibly exerting synergistic activity.”
VII. AMPs/Defensins (Mimetics): Anti-Coronavirus Potential

*Direct Anti-Coronavirus Properties (SARS-CoV/MERS-CoV)*

In the search for effective therapies to treat SARS-CoV infections, a comprehensive 2016 review article highlighted small molecule drugs and drugs that mimic peptides and proteins, like Brilacidin.


Recently, intestinal lectin-like defensins were shown in cellular assays to inhibit SARS-CoV-2 binding to ACE2 and that their exogenous supplement to the lung might be therapeutic. Other research shows the AMP rhesus θ-defensin 1 (RTD-1) to have an anti-SARS-CoV effect in animal studies when administered intranasally. Note: Mice in the study were protected from lethal SARS-CoV via mechanisms that were independent of an antiviral effect, as RTD-1 was not virus neutralizing: “RTD-1 administration appeared to protect infected animals by reducing pulmonary inflammation and suppressing IL-1α, IL-1β, IL-6, IL-12, CXCL1 (KC), CCL2 (MCP-1), CCL3 (MIP-1α), and CCL5 (RANTES) 2–4 days post-infection.” Further research on RTD-1 suggests the suppression of pro-inflammatory cytokines and blockade of TNF may be RTD-1’s primary mechanism of action against SARS-CoV infections.


A February 13, 2020, Review Article—“Potential Interventions for Novel Coronavirus in China: A Systematic Review” (pdf)—refers to a peptide mimetic (Mucroporin-1) of scorpion venom, a research area of great interest among academics, that has also been shown, in pre-clinical studies, to have antiviral activity, in measles, influenza H5N1 and SARS-CoV.

“[A]pproved or universally recommended therapies have been lacking for SARS-CoV and influenza H5N1 infections until now, even though more and more antiviral agents against SARS-CoV and influenza H5N1 have been reported [8], [17], [24]. Therefore, the development of new antiviral agents is needed to provide more options for managing cases of diseases caused by RNA viruses in both developed and developing countries. [...] This report provides evidence that host defense peptides from scorpion venom can be modified for antiviral activity by rational design and represents a practical approach for developing broad-spectrum antiviral agents, especially against RNA viruses.” [emphasis added]

A novel synthetic peptide (P9) derived from mouse β-defensin-4 has shown, in pre-clinical studies, broad and potent antiviral activity against respiratory viruses, including against SARS-CoV and MERS-CoV.

Two Review Articles, excerpted below, suggest AMPs/defensins can be successful therapeutic options for treating Middle East Respiratory Syndrome coronavirus (MERS-CoV), particularly those approaches that have been biocomputationally-designed (mimetics) to deliver greater efficacy (see Falanga, A et al, 2017 “Cyclic Peptides as Novel Therapeutic Microbicides: Engineering of Human Defensin Mimetics”).


“Currently, several therapeutic options have been employed, such as convalescent plasma (CP), intravenous immunoglobulin (IVIG), monoclonal antibodies and repurposing of existing clinically approved drugs. However, these therapeutic options have drawbacks, thus the need for an alternative approach. The requirement for effective therapeutic treatment has brought the necessity for additional MERS treatments. We suggest that antimicrobial peptides (AMPs) may be used as alternative therapeutic agents against MERS-CoV infection. In addition, we propose the feasibility of developing effective agents by repurposing the existing and clinically approved anti-coronavirus and antiviral peptide drugs.” [emphasis added]

“It is for these reasons we propose that antimicrobial peptides (AMPs) can be used as effective therapeutic agents against MERS. Several peptides have been extensively studied and identified as anti-MERS-CoV peptides [9–12] and anti-MERS-CoV AMPs in the past few years [13]. […] Our computational study confirms that four AMPs were able to bind clearly to the specific binding site of S protein (5X59). From our results, it may confirm that these AMPs may be suitable for inhibiting MERS-CoV virus entry into the host cell by binding and preventing fusion. However, the results are preliminary and certainly need experimental confirmation using in vitro and in vivo experiments essential to validate them. Special assays studies are needed to confirm the mechanism of action. Considering all the structural aspects and binding affinity studies of the four AMPs may possibly be the first choice as an anti-MERS-CoV AMPs which could be exploited to design potential inhibitors for treating MERS.”

<table>
<thead>
<tr>
<th>Rank</th>
<th>Peptide</th>
<th>Length</th>
<th>Definition</th>
<th>Species</th>
<th>Representative</th>
<th>Member</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AP00166</td>
<td>25</td>
<td>Pleurocidin</td>
<td>Fish</td>
<td>Center</td>
<td>134</td>
</tr>
<tr>
<td>2</td>
<td>AP00641</td>
<td>33</td>
<td>Pardaxin 1</td>
<td>Fish</td>
<td>Center</td>
<td>134</td>
</tr>
<tr>
<td>3</td>
<td>AP00444</td>
<td>23</td>
<td>Magainin 2</td>
<td>Frog</td>
<td>Center</td>
<td>117</td>
</tr>
<tr>
<td>4</td>
<td>AP00771</td>
<td>23</td>
<td>Magainin 1</td>
<td>Frog</td>
<td>Center</td>
<td>117</td>
</tr>
<tr>
<td>5</td>
<td>AP01644</td>
<td>30</td>
<td>Brevinin-2-RNI</td>
<td>Frog</td>
<td>Center</td>
<td>117</td>
</tr>
<tr>
<td>6</td>
<td>AP00764</td>
<td>24</td>
<td>Dermaseptin-S9</td>
<td>Frog</td>
<td>Center</td>
<td>110</td>
</tr>
<tr>
<td>7</td>
<td>AP02571</td>
<td>31</td>
<td>Cyclovicon VYI (cytolides)</td>
<td>Plant</td>
<td>Center</td>
<td>110</td>
</tr>
<tr>
<td>8</td>
<td>AP00275</td>
<td>31</td>
<td>Circulin B (cytolides)</td>
<td>Plant</td>
<td>Center</td>
<td>107</td>
</tr>
<tr>
<td>9</td>
<td>AP01022</td>
<td>31</td>
<td>Cyclovicon A (cytolides)</td>
<td>Plant</td>
<td>Center</td>
<td>107</td>
</tr>
<tr>
<td>10</td>
<td>AP01061</td>
<td>31</td>
<td>Circulin D (cytolides)</td>
<td>Plant</td>
<td>Center</td>
<td>107</td>
</tr>
</tbody>
</table>

(a) Prefusion stage  (b) Postfusion stage
VIII: The Broader Context: Characteristics of the COVID-19 Pandemic

Prevalence and Impact

The novel coronavirus (COVID-19) pandemic poses a significant life-threatening and economic risk throughout the world, with the potential eventually to infect hundreds of millions (or more) of people. Epidemiologists estimate 50 to 70 percent of the world’s population will become infected. As of April 19, 2020, over 2.37 million cases have been diagnosed in at least 185 countries, resulting in almost 164,000 reported deaths, including over 742,000 cases and over 16,000 fatalities in the U.S. Presently, there are no effective approved therapies to treat COVID-19. Efforts globally are focused on aggressive containment and quarantine strategies to “flatten the curve” of the contagion so COVID-19 cases do not overwhelm a country’s health care system’s capacity to treat patients. Without such interventions, based on modeling performed (pdf) in 2006 by Australian researchers who studied the potential financial impact of a worldwide flu pandemic (a scenario comparable to the current COVID-19 outbreak), the monetary loss to the worldwide economy—as a measure of lost GDP—could be in the many trillions of dollars. Which this global pandemic already has surpassed.

Note: Average case-fatality rates and transmission numbers are shown. Estimates of case-fatality rates can vary; and numbers for the new coronavirus are preliminary estimates.

Source

Source
Innovation Pharmaceuticals: Mechanism of Action, Pre/Clinical Data and Academic Literature

Supporting the Development of Brilacidin as a Potential Novel Coronavirus (COVID-19) Treatment (April 20, 2020)

Source (data as of 4.19.2020)
Epidemiological Information

While mortality rates differ by location and by the method of calculation, there is evidence COVID-19—which has been shown to be of natural origin through genomic analyses—may be at least 10-20x more deadly than the seasonal flu (see this analysis), with an overall case mortality rate of 1.38% (1.23-1.53, 95% CrI). And it is proving to be many times more deadly among symptomatic cases and certain patient populations. Children under the age of 5 may (pdf) also be more susceptible to COVID-19 than previously thought, though suffering less severely than adults.

Additional data: Digestive symptoms are (pdf) common and blood Type O people may be more resistant to COVID-19, along with women. Genetics is likely to play a role. The disease may at first seem to build slowly (“a slow burn”), only to intensify quickly. Serious cardiac-related complications may accompany COVID-19 disease. Warmer temperatures may help to slow the spread of the disease. Questions concerning potential reinfection have been raised by Korean health authorities. Also see “seven important things” about the coronavirus and “facts and myths” about SARS-CoV-2.

Elderly and Compromised Most at Risk, but Younger People Severely Affected Too

Approximately 1 in 7 patients develop difficulty breathing and other severe complications, requiring hospitalization, while 6 percent become critical. These patients typically suffer failure of the respiratory and other vital systems, and can be susceptible to septic shock, according to a report (pdf) by the World Health Organization. About 10-15 percent of mild-to-moderate patients progress to severe and of those, 15-20 percent progress to critical.

According to the largest study conducted to date in China, COVID-19 patients at the highest risk for poor outcomes include people age 60 and older (especially those over 80, ~15 percent die) and those with underlying conditions, such as hypertension, cancer, diabetes and cardiovascular disease. Those with two chronic conditions were shown to be at a 2.6 greater risk, compared to individuals with none. Nearly 20 percent of COVID-19 patients who had at least one chronic condition had poor outcomes, compared with 4.5 percent of those without any chronic ailments.

An estimated 60 percent of all Americans have at least one chronic health condition, and 40 percent have more than one, putting a large number of people at greater risk of succumbing to COVID-19, particularly if elderly.

Data compiled by the U.S. Center for Disease Control, however, shows that younger people may also be at risk of severe outcomes. Among hospitalized adults, from February 12 through March 16, 2020, 1 in 5 were 20 to 44 years old, as were 12 percent of those admitted to the ICU. Adults 45 to 64 years old made up 35 percent of hospitalized patients and 36 percent of ICU patients.

Source
Asymptomatic Transmission

A stealth contagion, the novel coronavirus (SARS-CoV-2) can be shed by people before symptoms arise, lurking up to 14 days in the body before the emergence of any outward signs (e.g., cough, fever, sore throat, shortness of breath) of COVID-19. It is estimated about 85 percent of infected travelers leaving Wuhan, prior to a January 31st lockdown, went undetected while they were still contagious, at which time containing COVID-19 was now near impossible. Outbreaks in other countries inevitably started to appear.

Other transmission dynamics, based on frontline observations by scientists in China:

“[I]n the early stage of the epidemic, the average incubation period was 5.2 days; the doubling time of the epidemic was 7.4 days, i.e., the number of people infected doubled every 7.4 days; the average continuous interval (the average interval time of transmission from one person to another) was 7.5 days; the basic regeneration index (R0) was estimated to be 2.2 to 3.8, meaning that each patient infects 2.2 to 3.8 people on average.”

The virus can also remain in the body well-after recovery. According to a study in the Lancet, based on research in China, the median length of time the virus stays in the respiratory tract of a patient after symptoms begin is 20 days. Among patients who survived the disease, the virus continued to be shed for between eight and 37 days. SARS-CoV-2 can remain even longer in the stool, for up to 5 weeks after a patient tests negative for the virus based on respiratory samples.
Viability Outside the Body

Experiments (pdf) conducted by Vincent Munster, Chief of the Virus Ecology Section of Rocky Mountain Laboratories, and others in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), show (see NEJM article) the novel coronavirus can stay infectious for days in different environments, depending on the type of surface and the surrounding temperature. Some coronavirus can potentially remain viable—capable of infecting a person—for up to 24 hours on cardboard and up to three days on plastic and stainless steel. When aerosolized into fine, floating particles, the virus remained viable for three hours. On a copper surface, it was four hours. Median length of viability for the virus on stainless steel was 13 hours, and 16 hours on polypropylene, a common type of plastic.

<table>
<thead>
<tr>
<th>Different environments</th>
<th>Temperature</th>
<th>Survival time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>50 ~ 59°F</td>
<td>4 hours</td>
</tr>
<tr>
<td></td>
<td>77°F</td>
<td>2 ~ 3 minutes</td>
</tr>
<tr>
<td>Droplets</td>
<td>&lt;77°F</td>
<td>24 hours</td>
</tr>
<tr>
<td>Nasal mucus</td>
<td>132.8°F</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Liquid</td>
<td>167°F</td>
<td>15 minutes</td>
</tr>
<tr>
<td>Hands</td>
<td>68 ~ 86°F</td>
<td>&lt;5 minutes</td>
</tr>
<tr>
<td>Non-woven fabric</td>
<td>50 ~ 59°F</td>
<td>&lt;8 hours</td>
</tr>
<tr>
<td>Wood</td>
<td>50 ~ 59°F</td>
<td>48 hours</td>
</tr>
<tr>
<td>Stainless steel</td>
<td>50 ~ 59°F</td>
<td>24 hours</td>
</tr>
<tr>
<td>75% alcohol</td>
<td>Any temperature</td>
<td>&lt;5 minutes</td>
</tr>
<tr>
<td>Bleach</td>
<td>Any temperature</td>
<td>&lt;5 minutes</td>
</tr>
</tbody>
</table>

Source
Pathogenesis, Role of IL-6 (Inflammatory Cytokines)

According to recent article in JAMA, as well as another article in Nature, the pathogenesis of COVID-19 is still not completely understood, though an excessive immune response by the body to fight off the novel coronavirus (triggering a “cytokine storm”) and viral evasion of cellular immune responses are thought to play important roles in disease severity. This can lead to Acute Respiratory Distress Syndrome (ARDS)—a leading cause of death among the sickest COVID-19 patients. Scientists at the University of Science and Technology of China (USCT) have identified interleukin 6 (IL-6), a pro-inflammatory cytokine, as the “main culprit” in the body’s overreaction when trying to fend off the virus. This has led health authorities in China to recommend Roche’s arthritis drug, Actemra (tocilizumab), a monoclonal antibody that inhibits IL-6, to be used in treating patients with COVID-19. A randomized clinical trial evaluating Actemra has commenced, according to Chinese Clinical Trial Registry, with investigators planning to enroll a total of 188 patients—half on Actemra, half on placebo. Regeneron and Sanofi have announced, alongside smaller companies like Tiziana Life Sciences, similar plans to target IL-6 inhibition as a potential novel anti-COVID-19 strategy.
With a 3-in-1 treatment potential—as an antiviral, immuno/anti-inflammatory and antimicrobial drug—Brilacidin might help strengthen the body’s innate immune response at early stages of COVID-19, as well as help stem inflammatory reactions and bacterial complications in later stages of the disease.

![Diagram of Early and Severe Stage of COVID-19 Response]

After an incubation period, the invading COVID-19 virus causes non-severe symptoms and elicits protective immune responses. The successful elimination of the infection relies on the health status and the HLA haplotype of the infected individual. In this period, strategies to boost immune response can be applied. If the general health status and the HLA haplotype of the infected individual do not eliminate the virus, the patient then enters the severe stage, when strong damaging inflammatory response occurs, especially in the lungs. At this stage, inhibition of hyaluronan synthase and elimination of hyaluronan can be prescribed. Cytokine activated mesenchymal stem cells can be used to block inflammation and promote tissue reparation. Vitamin B3 can be given to patients starting to have lung CT image abnormalities.

Source
Secondary Infections

Bacterial infections (10-20%) can often co-present in COVID-19 patients. In one retrospective study of 191 patients in China, 95 percent received antibiotics, compared to 21 percent of patients receiving antiviral treatment, 30 percent corticosteroids, and 24 IV immunoglobulin. Half of non-survivors experienced a secondary infection, and ventilator-associated pneumonia occurred in ten (31%) of 32 patients requiring invasive mechanical ventilation. The duration of antibiotic treatment in another study of 99 cases in Wuhan China was between 3 and 17 days, with a median duration of 5 days.

Source

Experts Warn Of Secondary COVID-19 Infections, Antibiotic Resistance

By Kelly Lienhard / March 3, 2020 at 2:59 PM

Several antimicrobial resistance experts have begun to cite concerns about a possible wave of secondary bacterial and fungal infections in COVID-19 patients that could evolve into antimicrobial-resistant diseases and said the lack of new antibiotic development could exacerbate an already-climbing death rate from the epidemic. The president on Tuesday (March 3) reinstated an advisory council on antibiotic-resistant bacteria coming as stakeholders press Congress to boost incentives for development of new antibiotics. The Antimicrobial Innovation Alliance’s top priority on Capitol Hill...
Forward-Looking Statements: There is no assurance made or implied that clinical testing of Brilacidin against any coronavirus will be conducted or successful. This informational document contains forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 including statements concerning future drug development plans, other statements regarding future product developments, and markets, including with respect to specific indications, and any other statements which are other than statements of historical fact. These statements involve risks, uncertainties and assumptions that could cause the Company’s actual results and experience to differ materially from anticipated results and expectations expressed in these forward-looking statements. The Company has in some cases identified forward-looking statements by using words such as “anticipates,” “believes,” “hopes,” “estimates,” “looks,” “expects,” “plans,” “intends,” “goal,” “potential,” “may,” “suggest,” and similar expressions. Among other factors that could cause actual results to differ materially from those expressed in forward-looking statements are the Company’s need for, and the availability of, substantial capital in the future to fund its operations and research and development; including the amount and timing of the sale of shares of common stock under securities purchase agreements; the fact that the Company’s licensee(s) may not successfully complete pre-clinical or clinical testing and the Company will not receive milestone payments, or the fact that the Company’s compounds may not successfully complete pre-clinical or clinical testing, or be granted regulatory approval to be sold and marketed in the United States or elsewhere. A more complete description of these risk factors is included in the Company’s filings with the Securities and Exchange Commission. You should not place undue reliance on any forward-looking statements. The Company undertakes no obligation to release publicly the results of any revisions to any such forward-looking statements that may be made to reflect events or circumstances after the date of this press release or to reflect the occurrence of unanticipated events, except as required by applicable law or regulation.