BROAD-SPECTRUM THERAPEUTICS FOR VIRAL DISEASES: A MEDICAL COUNTERMEASURE PLATFORM FOR EMERGING THREATS

Brilacidin As A Novel Broad-spectrum Antiviral Countermeasure Against Acutely Infectious Viruses

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Acutely infectious viruses, including those that are transmissible by the respiratory and aerosol routes, pose critical threats to the warfighter and the civilian population. Aerosol-transmissible pathogens, such as bunyaviruses (Rift Valley fever virus [RVFV]), and alphaviruses (Venezuelan Equine Encephalitis Virus [VEEV], Eastern Equine Encephalitis Virus [EEEV]), share a broad range of host tropism, retain high rates of infectivity as aerosols, attain high viral load in the host, cause damage to the blood brain barrier (BBB), impact neurological integrity and are likely to contribute to organ-damage. These viruses comprise nontrivial challenges to the warfighter because no FDA-approved therapeutics or vaccines are currently available that can be rapidly scaled up, and field-deployed, to potentially mitigate their deleterious consequences. There is an urgent, unmet need for the development of broad-spectrum intervention strategies that can ideally control the disease manifestations in the host and the spread of disease as a prophylactic countermeasure. Our ongoing studies with brilacidin, a host defense peptide (HDP)-based mimetic, have successfully demonstrated that brilacidin is able to interfere with viral integrity and exert an antiviral effect in vitro against candidate alphaviruses and bunyavirus. Furthermore, early indications support the potential of brilacidin to also act in an anti-inflammatory capacity by reducing inflammatory cytokine expression.

We have earlier successfully demonstrated that brilacidin can inhibit Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in a cell type- and strain-independent manner. We have since expanded our studies to alphaviruses and bunyaviruses. Appropriate cell lines were infected with RVFV (MP-12 strain), VEEV (TC-83 and TrD strains) and SINV +/- brilacidin. Culture supernatants and nucleic acid lysates were quantified for extracellular and intracellular viral load and impact on infectivity by plaque and qRT-PCR assays. Impact of brilacidin on cell viability and lack of toxicity were ascertained by CellTiter Glo assay. Impact of treatment on inflammatory events were quantified by a combination of PCR (gene expression) and ELISA (protein expression). Our overall assessment of brilacidin targets suggest that brilacidin exerts an impact on the virion integrity directly for several viruses, although the sensitivity to brilacidin differs for different viruses (SARS-CoV-2>RVFV>VEEV). Quantification of anti-inflammatory activities in VEEV infection by ELISA demonstrated decrease in IL-1b and IL-6 levels when treated with brilacidin. Assessment of innate immune activities included quantification of interferon gamma expression by PCR in the context of RVFV infection, which did not indicate a statistically significant change in IFN-β at the gene expression level.
Our observations with brilacidin in the context of acutely infectious viruses support the idea of brilacidin functioning in a broad-spectrum capacity as a novel antiviral compound. Of note, brilacidin was recently evaluated in Phase 2 clinical testing in moderate-to-severe cases of COVID-19 (NCT04784897), showing beneficial treatment effects and a well-tolerated safety profile. Brilacidin has also undergone several successful clinical studies in acute bacterial skin and skin structure infections. Research and development efforts are focused on identifying optimal dosing strategies to improve brilacidin in vivo effectiveness in the form of a nasally-delivered countermeasure.