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

In Vitro And In Vivo Evaluation Of Small Molecule S-adenosylhomocysteinase (ahcy) Inhibitor Against Ebola Virus

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Ebola virus (EBOV) a member of the filoviridae family is a negative-sense single-stranded RNA virus that causes severe hemorrhagic disease characterized by high case fatality rates. The virus, which initially infects monocytes, macrophages, and dendritic cells, spreads systemically to produce a primary viremia that leads to infection of other cell types, including vascular endothelial cells. Virus replication leads to a rise in inflammatory cytokine levels and development of coagulopathies, resulting in vascular leakage, hypovolemic shock, and multi-organ failure. To date there are no FDA approved small molecule therapeutics for the treatment of EBOV disease (EVD).
In collaboration with MRL, Merck & Co., several small molecule chemical libraries were screened using our in vitro high content image based phenotypic screening assay to quantitate Ebola virus infection. A small molecule S-adenosylhomocsteinase (AHCY) inhibitor was identified that exhibited broad-spectrum Filovirus activity with EC50 100. This compound was subsequently evaluated in a mouse model of Ebola infection. A dose-dependent increase in mouse survival was observed when the therapeutic was given via the oral route. Based on efficacy in the mouse model, the AHCY inhibitor, delivered by the oral route, was evaluated for efficacy in a nonhuman primate model of Ebola infection. In this model, the small molecule inhibitor was unable to provide adequate protection against morbidity and mortality. Efforts are ongoing to meet our key deliverable of a portfolio of confirmed screening leads that target key viral pathogens to support DoD countermeasure efforts.
Disclaimer: Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the U.S. Army.

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