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

Optimization Of Next Generation Filovirus Therapeutics

Jonathan Bohmann Southwest Research Institute **Daniel Hinojosa** Southwest Research Institute **Rekha Panchal** USAMRIID
Jason De Meese WRAIR

Filovirus is an emerging infectious disease responsible for viral hemorrhagic fevers with high mortality rates (25-90%) that include Ebola virus (EBOV), Marburg virus (MARV), and Sudan virus (SUDV). The filovirus virion is protected by a highly-conserved glycoprotein (GP) envelope that recognizes and attaches to host cell membranes to initiate fusion toward replicating in many tissues and cells. In 2015, we discovered F1193-0102 to inhibit EBOV and MARV infections in Vero E6 and HeLa cells (micromolar activity), along with a handful of other small-molecules. A preliminary Tier 1 ADMET screen & safety profile was conducted and F1193-0102 was selected for further development.
Our discovery in 2015 was accelerated by Rhodium™, a proprietary computational docking program for in silico protein-targeted drug discovery. Rhodium™ screened a virtual library of 10 million small-molecules docked to a crystal structure of the Ebolavirus glycoprotein trimer (PDB ID: 3CSY). Currently, our high-performance docking program guides small-molecule drug development, candidate down-selection, and synthesis of F1193-0102 analogs. Virtual libraries can be generated automatically or manually for the purpose of identifying compounds designed to improve safety profiles, therapeutic index, target-selectivity, and to complete our drug development strategies and structure-activity relationship study.

Disrupting the fusion process with a prototype small-molecule (F1193-0102) to inhibit GP-mediated cellular entry and cell-attachment can lead to the approval of a broad-spectrum, orally bioavailable antiviral therapeutic. The highly-conserved viral filovirus GP is an opportunity to address the vulnerability of warfighter exposure to aerosolized viral biothreat agents and emerging threats, particularly MARV and SUDV and EBOV. Given the risks posed by EBOV/MARV/SUDV, a field-stable, bioavailable medication that could afford a level of protection against a variety of filovirus strains would be extremely valuable.

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