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

Development Of Small-molecule Antivirals Targeting Host Vps34 Complex For Treatment Of Emerging Virus Threats

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Development of antivirals targeting a host process is an attractive strategy to effectively counteract diverse emerging pathogens dependent on the same host mechanism to replicate. We and others previously identified Beclin-1 and UV radiation associated gene (UVRAG) proteins, components of the host VPS34 complex, as essential for Ebola virus (EBOV) productive infection. VPS34, a class III phosphatidylinositol 3-phosphate kinase, associates with different host factors to facilitate diverse cellular processes, including vesicular trafficking and cellular homeostasis through autophagy. Our data show that indiscriminate pharmacological targeting of VPS34 complexes leads to toxicity and compromised host survival, thus signifying a critical need to identify strategies to target a virus-specific VPS34 subset. Our proprietary machine learning and docking platform, RhodiumTM, has used the Beclin-1/UVRAG interface within the complex to rapidly identify several chemotypes of potential inhibitors targeting infection of live EBOV. One of the compounds, M7, blocked virus in primary human macrophages, a clinically relevant cell target, at nanomolar concentrations, with the selectivity index >180. Notably, M7 efficiently inhibited EBOV spread in a 3D human tissue model, suggesting a high potential for translation to future efficacy studies in animals. In addition, we determined that M7 treatment blocked virus pseudotyped with EBOV glycoprotein, thus targeting virus cell entry, likely by macropinocytosis. Studies on autophagic flux kinetics and uptake of high-molecular weight dextran, a marker of macropinocytosis, confirmed that M7 specifically blocked endosomal trafficking. Our work highlights a potential for M7 to be developed into a preclinical development drug candidate targeting EBOV and potentially other pathogens that require the VPS34 complex to replicate.

This work was supported in part by National Institutes of Health grants AI154336 and AI151717 and to OS.