COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

Omaveloxolone As A Broad-spectrum Intervention Strategy Against Vector Transmitted Rna Viruses

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Single-stranded, acutely infectious RNA viruses including alphaviruses such as Venezuelan equine encephalitis virus (VEEV) and Eastern equine encephalitis virus (EEEV); Orthoflaviviruses, such as West Nile virus (WNV) and dengue virus (DENV); and Rift Valley fever virus (RVFV) and Crimean Congo hemorrhagic fever virus (CCHFV), belonging to bunyavirales, are some of the most prevalent arboviruses that cause serious disease in both humans and animals. They are the source of emerging and re-emerging infectious diseases worldwide, accounting for almost 20% of global human diseases (World Health Organization 2020). In addition to civilians and livestock being at high risk, especially in endemic regions with periodic outbreaks of vector-borne viruses, as the largest contributor of humanitarian and military aid globally, U.S. civilian volunteers and military population abroad are at risk of vector-borne diseases and their potential for spread around the world. There is a prominent unmet need for FDA-approved therapeutic intervention strategies available for treatment of human diseases resulting from vector-transmitted viral infections.

In our efforts, we have focused on the potential application of omaveloxolone (OMA), an FDA-approved Nuclear factor erythroid 2-related factor 2 (Nrf2) activator, as a broadly effective intervention strategy against acutely infectious RNA viruses. Our previous work demonstrated the efficacy of Omaveloxolone (OMA), an FDA-approved small molecule targeting the host Nrf2 function, in inhibiting virulent strains of encephalic alphaviruses. Moreover, our studies unveiled that OMA preserves the blood-brain barrier (BBB) integrity and effectively reduces the viral and inflammatory load of VEEV in the three-dimensional organ-on-chip (OOC) model of the human BBB. To determine the mechanisms by which OMA exerts robust antiviral activities and affects human brain microvascular endothelial cells (HBMVECs) to modulate inflammatory load in the BBB during VEEV infection, we investigated enzymatic effects of OMA in HBMVECs through kinome activity profiling. Our findings revealed several kinases in the Src-family that are downregulated in the presence of OMA, thus identifying novel host-based candidates that can provide underlying mechanistic insights. Ongoing proteomic analysis of host signaling mechanisms that are modulated by OMA in infected cells are expected to dovetail with the kinome studies. Independent examination of OMA's impact on VEEV viral non-structural proteins (nsPs) demonstrated a reduction in the synthesis of nsP2 and nsP3 proteins up to 6 hours post-infection. Mass Spectrometry-based analysis indicated that OMA treatment affects the ubiquitination of both viral and host proteins in VEEV-infected HBMVECs. Notably, OMA also demonstrated inhibitory effects against CCHFV, Chikungunya Virus, Lassa Virus, and WNV, but demonstrated less effectiveness against Ebola Virus. Ongoing studies are focused on intracellular signaling pathways associated with Src-family kinases through reverse phase protein microarray (RPPA) analysis. Further investigations include quantitative assessment of gene expression changes in key signaling pathways, including Nrf2 signaling, inflammation, and antiviral signaling mechanisms, to provide mechanistic insights into molecular underpinnings that result in broad-spectrum inhibition of multiple RNA viruses.

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