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

Building A Molecular Atlas Of Blood Brain Barrier Disruption By Venezuelan Equine Encephalitis Virus

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Venezuelan equine encephalitis virus (VEEV) is a known weaponizable virus for which there are no therapeutics beyond supportive care. The natural route of infection with VEEV is via mosquito bite, however evidence from laboratory-acquired infections suggests that aerosolized VEEV is highly pathogenic with a high mortality rate, and thus is considered a category B biothreat virus. There is also growing concern about VEEV from a public health perspective, as climate change expands the habitat boundaries of the mosquitoes that harbor VEEV in the wild. VEEV invades and replicates within the central nervous system (CNS), causing breakdown of the blood brain barrier (BBB) and fatal encephalitis. Evidence from mouse models of infection suggests that BBB disruption is a critical component of fatal infection and preventing BBB disruption may be a viable therapeutic intervention. In order to gain a deeper mechanistic understanding of the molecular details regulating BBB permeability, we are conducting a molecular survey of BBB disruption during VEEV infection. To achieve this goal, we are employing two complimentary, state-of-the-art sequencing capabilities: single cell RNA-sequencing (scRNAseq) and spatial transcriptomics (ST), to profile the cellular and molecular changes that occur within different cell types of the brain while permeability of the BBB is being modulated via infection with VEEV. ScRNAseq allows for the deep profiling of gene expression within individual cells isolated from a complex tissue (such as brain), providing a high-resolution view of cellular differences and a better understanding of the functions of individual cell types. ST is then used to layer positional information on top of the deep characterization of specific cell types obtained using scRNAseq. Using these complimentary technologies, we are building a spatial molecular atlas of the BBB as permeability is being modulated. By generating a rich data set surrounding BBB disruption, we are providing key insight into the pathogenesis of a virus that is not only relevant from a biodefense standpoint, but also a public health concern, and identifying potential drug targets that would prevent BBB disruption following VEEV infection. Drug targets identified in this study may be appliable to infections with other encephalitic pathogens as well as neurodegenerative conditions.