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

Approaches To Develop Icdna Clones Of Encephalitic Alphaviruses To Characterize Viral Disease And Evaluate Broad-spectrum Therapeutics

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There are currently no licensed vaccines or antivirals to treat infection caused by the Equine Encephalitis alphaviruses, and many of the existing animal models are unable to recapitulate the encephalitic disease often arising from infection. Of particular concern, is the increased potential for neuroinvasion following aerosol infection, which may result in an increased incidence of encephalitis in humans, and even death. There is limited clinical data relating to alphavirus pathogenesis, therefore well defined and robust in vivo models are required to further our understanding of the pathogenesis and development of encephalitis following infection with the New World alphaviruses, in particular for Eastern equine encephalitis virus (EEEV). The aim of this study was to use synthetic approaches to design and synthesize an infectious cDNA (icDNA) clone of EEEV strain v105 (a human isolate) that could be genetically modified to incorporate a light-emitting reporter to provide the ability to conduct in vivo imaging of EEEV in real-time. The icDNA clone would be used to study alphavirus pathogenesis using animal models, and in particular to track the migration of virus to the brain and to model alphavirus-induced encephalitis.

In this study, an icDNA clone of wild-type EEEV v105 was constructed and studies were conducted to confirm the replicase activity, in vitro growth characteristics and aerostability of the icDNA clone of EEEV. In addition, the virulence of icDNA clone of wild-type EEEV v105 was confirmed in an inhalational Balb/c mouse model where mice developed key features of disease such as acute onset of neurological signs with high titres of virus isolated from the brain. Further studies are in progress to genetically modify the wild-type icDNA clone to incorporate fluorescent/bioluminescent reporters to allow in vivo imaging of EEEV in real-time.

The synthetic approach described in this study is a design platform that can be adapted to construct optimized icDNA clones of Venezuelan- and Western Equine encephalitis viruses to study disease progression and brain exposure, and could be valuable tools in the development and evaluation of broad-spectrum antivirals, in particular therapeutics that target brain inflammation.

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