toward rSeV(hPIV-1HN) was superior to that of the effect on rSeV(hPIV-3FHN) as well as the effect of BCX 2855 against both recombinant viruses. Our data indicate that BCXs are highly potent compounds for prophylaxis/treatment of hPIV infections.

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11
Evaluation of Interferon Inducers, Ribavirin and Mouse Hyperimmune Serum in a Pathogenesis/Lethal Mouse Model Using a Mouse-adapted SARS-CoV

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SARS-CoV causes an untreatable severe acute respiratory syndrome. Thus, anti-SARS-CoV agents need to be developed and tested. In vitro active compounds have yet to be evaluated in an animal model where death and lung pathogenesis occur as happens in human disease. Passaging the SARS-CoV human isolate strain Urbani 25 times through mouse lungs and then plaque purifying the virus 3 times yielded a virus causing severe lung disease and mortality in infected mice. ELISA, PCR analysis and RNA sequencing confirmed the SARS-CoV identity. At least eight amino acid changes throughout the virus genome were found. Using this virus, a number of compounds were tested for efficacy in BALB/c mice. The virus inoculum used resulted in 70% death of exposed animals, with all deaths occurring from 3 to 5 days after virus exposure. Untreated, infected mice lost 30% of their initial weight or more from days 3 to 7, but survivors gained back the weight by day 14. Lungs of infected mice at day 3 after virus exposure were characterized by swollen cells lining the bronchiolar epithelium, hypereosinophilia, neutrophil infiltration of area surrounding the bronchioles, scattered alveolar septae widened by foamy macrophages, aggregates of neutrophils and macrophages in the airways, and moderate amounts edema and neutrophils surrounding some of the large vessels. Ampligen and poly IC:LC were effective in reducing virus lung scores, yet neither compound reduced virus lung titers at day 3. Both compounds significantly protected mice against death. Ribavirin did not protect against death; in fact the drug prolonged and enhanced virus lung replication. Four of five mice treated with mouse hyperimmune serum (MHS) diluted 1:100 survived the 14-day experiment. Animals not losing significant amounts of weight (>30%) at days 3–7 survived the infection. The data demonstrate that mice infected with a lethal dose of mouse-adapted SARS-CoV virus and treated with interferon stimulators were protected from weight loss and death.

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12
Therapies and Mechanisms of West Nile Virus Encephalitis and Neurological Sequelae

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West Nile virus (WNV) patients can have persistent movement disorders, cognitive complaints, and functional disability that can occur during acute viral infection or thereafter. These disorders include acute flaccid paralysis and limb weakness. Despite the importance of neurological sequelae in WNV infection, little is known about potential treatments, and the transition between acute infection and development of sequelae. The role of the virus, the immunopathology, and the neuropathology of sequelae are largely unknown because of the lack of a laboratory animal model. In this study, we have developed a hamster model for disease phenotypes, such as acute flaccid paralysis having poliomyelitis and for neurological sequelae, which to our knowledge is the first neurological sequelae model for investigations occurring after resolution of the WNV in rodents, and for that matter, for any viral encephalitis laboratory animal model. As a direct measure of neurological disease and nerve function, we performed electrophysiological nerve conduction studies. Specifically, M-waves or H-reflexes were suppressed or aberrant in hind limbs of hamsters during acute viral infection of the CNS and in later stages after acute infection. We have identified two antiviral agents and neuroprotective agents with the potential for treating WN fever, meningitis, encephalitis, and neurological sequelae in this hamster model.

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