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

Iminosugars Are Broad-spectrum Viral Inhibitors

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The coronavirus pandemic has demonstrated the need to develop drugs that can be used to minimize the impact of viral outbreaks. The pandemic has led to a particular interest in repurposed drugs that could be used to inhibit viral replication. Iminosugars are preapproved drugs that inhibit the ER α-glucosidases I and II (α-glu I and α-glu II), which are required for the production of many glycoproteins. Iminosugars have been shown to have antiviral properties against other enveloped RNA viruses including filoviruses and dengue virus. As such, we investigated two iminosugars, celgosivir, a prodrug of castanospermine, and UV-4B (N-(9-methoxynonyl)-1-deoxynojirimycin), a deoxynojirimycin derivative against SARS-CoV-2, Venezuelan Equine Encephalitis virus (VEEV), and Sin Nombre Hantavirus (SNV). Iminosugars were effective at inhibiting authentic SARS-CoV-2 and VEEV viral replication in a cell culture system. Celgosivir prevented SARS-CoV-2-induced cell death and reduced viral replication and Spike protein levels in a dose-dependent manner in culture with Vero E6 cells. The monocyclic UV-4B also prevented SARS-CoV-2-induced death and reduced viral replication after 24 h of treatment. The most successful iminosugar in vitro, Celgosivir, was then tested as an antiviral in the human ACE-2 transgenic mouse model of SARS-CoV-2 infection. Celgosivir was delivered as an intraperitoneal injection at 50 mg/kg/mouse of celgosivir twice daily for 5 days starting from day 0, when infection with 100,000 PFU of SARS-CoV-2 occurred. We examined weight loss as a readout of disease severity, mortality, and viral titer by lung PFU. Celgosivir treatment resulted in a one-day delay in time to death, but no statistically significant differences weight loss or lung viral titer. However, we hope to investigate celgosivir delivered prior to infection in the future, and determine the impact of the drug given prophylactically against SARS-CoV-2 and test the drug in the mouse model of VEEV infection.