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2-pyrimidone compound series prevents acute viremia and chronic chikungunya virus disease in a mouse model of infection

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Abstract

Alphaviruses are arthropod-transmitted RNA viruses, including the NIAID Category B priority pathogens Eastern equine encephalitis (EEEV), Venezuelan equine encephalitis (VEEV) and chikungunya (CHIKV) viruses. In November of 2023, the first chikungunya virus vaccine became FDA approved for use in individuals 18 years of age and older who are at increased risk of exposure to CHIKV, although no FDA-licensed antiviral therapeutics are available to treat alphavirus infection or disease, thus demonstrating a need in the field of public health. We identified a small molecule antiviral hit using a screen against CHIKV. Derivatives of the hit were made by medicinal chemistry, and we identified a first-in-class, orally available, non-nucleoside small molecule (SRI-42718) that targets a conserved region in nsP4-RdRp. The SRI-42718 chemical series blocks both gRNA and sgmRNA synthesis as well as viral protein production. The compound has shown no adverse toxicity in mice as repeat dosing at 40 mg/kg, TID, is a well-tolerated treatment for up to 10 days. *In vivo* PK analysis indicates that the compound has good bioavailability by oral delivery in mice and nonhuman primates, and the compound was distributed to several mouse tissues including joints and muscles. Importantly, oral administration of the compound prevents viremia at a dose of 40 mg/kg three times per day (TID) in acutely infected mice. Viral tissue burden and virus-induced foot/ankle swelling (tissue disease) are also significantly reduced in treated animals compared to vehicle controls. A seven-day treatment of mice beginning at 28 days post infection during the persistent phase reduced the viral RNA level in joint-associated tissue. Combined, our data indicate that SRI-42718 is capable of blocking CHIKV replication *in vivo* during both the acute and persistent phases, which increases the

therapeutic potential for this compound. SRI-42718 promises to be an important preclinical candidate and the compound has entered early drug development studies.