THE USE OF AI AND ADVANCED COMPUTER SYSTEMS TO DEVELOP DRUGS AGAINST NEW EMERGING THREATS

A Structure-based Drug Design Approach Towards The Discovery And Lead Optimization Of Inhibitors Of Alphavirus NsP2 Helicase

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Venezuelan, Eastern, and Western equine encephalitis viruses (VEEV, EEEV, and WEEV) are zoonotic and potentially fatal New World alphaviruses that can cause fever, encephalitis, sustained neurological disorders, and mortality in humans. Surprisingly, only a few small molecule inhibitors have been reported to improve survival in VEEV mouse models of infection, and no therapeutic studies to date have been reported in nonhuman primates. Our efforts to target a novel binding site led us to a structure-based drug design approach to develop inhibitors of the alphavirus nsP2 helicase. The nsP2 protein functions as protease and helicase and are required for replication. The helicase ‘unpacks’ genes by using energy from ATP hydrolysis, thus inhibitors targeting the ATP binding site are expected to limit energy required for helicase unwinding activity and inhibit replication. Given the high sequence identity among VEEV, EEEV, and WEEV helicases, it is possible that a compound with high affinity for nsP2 helicase in VEEV would be pan-inhibitory. Importantly, since the alphavirus helicases are structurally different from human helicase proteins, selectivity is not expected to be an issue.

Using in silico models based on the structure of the CHIKV nsP2 helicase domain, a set of ~3 million commercially available compounds were virtually screened to provide a prioritized set of a few hundred compounds predicted to fit and bind well in the ATP pocket. Validation of the virtual screening hits in vitro using VEEV cell culture and VEEV nsP2 helicase biochemical assays identified several small molecule lead compounds in the 10-30 μM potency range. Ongoing lead optimization efforts has led to key compounds with increased potency (1-10 μM range) and favorable in vitro ADME properties. In vitro results, including pan-alphavirus inhibition, in vitro ADME data, and in vivo pharmacokinetics and tolerability in mice for key compounds will be presented. This poster describes a series of small molecule alphavirus helicase inhibitors and progress towards an in vivo proof-of-concept in a mouse model of VEEV infection.