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

Discovery and Development of Filovirus Inhibitors: Managing Off-target Risk of Sodium Channel Block with Pharmacophore Modeling

Mariavictoria Moreno Southwest Research Institute **Daniel Hinojosa** Southwest Research Institute **Jonathan Bohmann** Southwest Research Institute

Sodium voltage (NaV) ion channels play a vital role in producing action potentials in excitable cells. The transmembrane NaV ion channel facilitates the movement of ions to regulate the membrane action potential of the cell. Specific subtypes of NaV ion channels are expressed in the central nervous system, skeletal muscles, cardiac muscles, and pancreatic cells to regulate physiological processes.

State-dependent nonselective NaV inhibitors will display different affinities against the closed resting state, open conducting state, and the nonconducting inactivated state of the ion channel subtype. Use-dependent inhibition requires the ion channel pore to be open for the inhibitor to bind. Tonic block inhibition of the ion channel occurs when the pore is in a closed state. The purpose of this project was to build a counter-screening model using bioactivity data of state-dependent NaV inhibitors and apply a predictive NaV model in the design of novel filovirus inhibitors with improved off-target profile.

The NaV pharmacophore model filters the virtual library of synthetic targets designed to inhibit filovirus glycoproteins in Ebola virus (EBOV), Marburg virus (MARV), and Sudan virus (SUDV). Motifs such as indoles, pyridines, and cyclopentyl groups are featured in the latest virtual library. Indoles with branched lipophilic handles and substituted pyridines are predicted to be less selective for NaV. Reducing the likelihood of off-target effects from earlier prototype compounds has focused our medicinal chemistry campaign to optimize the drug-likeness of our broad-spectrum small molecule glycoprotein inhibitors against filoviruses.

Funding by Award MCDC2102-003