CALIFORNIA STATE SCIENCE FAIR
2016 PROJECT SUMMARY

Name(s)

Meghana B. Reddy

Project Number

S1524

Project Title

Computer Aided Discovery of Inhibitors of the VP35 Protein of the Ebola Virus

Abstract

Objectives/Goals

VP35 is a polymerase cofactor and multifunctional protein that interferes with host-cell antiviral resistance mechanisms and it is essential for viral replication and immune-system evasion. Without functional VP35, the ebola virus cannot replicate, making the protein a good drug target. VP35 is also a transcription cofactor and contains an interferon inhibitory domain. With computer-aided drug discovery, will it be possible to identify molecule(s) that inhibit the protein, leading to a novel treatment for the virus?

Methods/Materials

Nine VP35 inhibitors, identified from the Protein Data Bank, were used as positive controls. The other (uncharacterized) molecules included in the virtual screen came from the National Cancer Institute (NCI). Different docking scoring functions were used with different protein models to identify combinations that were particularly good at separating the known compounds from the other molecules, as measured by the area under the ROC curve. The best combination involved docking the NCI compounds into the 4IJE crystal structure with AutoDock Vina and then rescoring the docked poses with a scoring function called rf2013_best_vina.

This same predictive combination was then used to pick potential VP35 inhibitors from among ~110,000 compounds that are commercially available through Chembridge. In this Chembridge screen, the area under the ROC curve was an impressive 0.97.

Results

By using the NCI compounds for #benchmarking# the proteins, the data yielded that through the cutoffs there were a possible of 5 proteins. The top performing protein with the scoring function rf2013_best_vina was used to on a larger Chembridge set in which the known ligands ranked among the top ~7% leaving possibilities for potential drug targets.

Conclusions/Discussion

There were 5 compounds that made the virtual screening cutoffs for RMSD, early performance, and ROC out of 26 receptors, 11 docking scoring functions, and 286 virtual screens, leading to a possibility of 5 compounds that have a potential to inhibit the VP35 protein of the ebolavirus.

Summary Statement

In an effort to further the development of novel drugs against this deadly pathogen, computer-aided drug discovery was used to identify several predicted low-micromolar inhibitors of the polymerase cofactor VP35 from a larger compound libr

Help Received

At the outset, I would like to thank Dr. Rommie Amaro for giving me the opportunity to work on my project at the Amaro Lab at the University of California, San Diego. Further, I am extremely grateful to the National Biomedical Computation Resource center for giving me the resources to advance my project