CALIFORNIA STATE SCIENCE FAIR
2013 PROJECT SUMMARY

Name(s)

Eric S. Chen

Project Number

33772

Project Title

Discovery of Novel Influenza Endonuclease Inhibitors to Combat Flu Pandemic

Abstract

Objectives/Goals

The objective is to discover novel influenza endonuclease inhibitors as leads for a new type of anti-flu medicine that is effective against all influenza viruses including pandemic strains.

New anti-flu medicines are urgently needed as current drugs are losing their effectiveness due to emerging resistant strains. Since the influenza endonuclease is well-conserved and essential for viral propagation, inhibitors of this enzyme can potentially block any influenza virus and reduce the chance of developing resistance.

Methods/Materials

I used ROCS software to construct pharmacophore models and performed virtual screening of large compound libraries with over 450,000 chemicals. I set up a fluorescence-based enzyme assay to validate the virtual screening hits as endonuclease inhibitors. In parallel, I used TACC Ranger supercomputers to run molecular dynamics (MD) simulation of influenza endonucleases and FTMap software to perform solvent mapping. Molecular docking experiments of new inhibitors to the enzyme were performed by using the Glide module in Schrodinger software. I also examined structure and activity relationship using analogs of the new inhibitors.

Results

Through the pharmacophore model-based virtual screening, I identified 237 hits of potential endonuclease inhibitors, and among them, six compounds were confirmed to have potent inhibitory activities. They exhibit structural diversity and belong to five distinct classes. Two compounds were found to block influenza propagation with negligible cell toxicity. In addition, MD simulation and solvent mapping construct a comprehensive map of binding pockets and druggable hot spots within the endonuclease active site. Molecular docking of the new inhibitors to the endonuclease active sites provides valuable information for designing even more potent inhibitors.

Conclusions/Discussion

I have successfully identified a number of new, potent and structurally diverse endonuclease inhibitors with great potential to be developed into new anti-influenza drugs. The structural analysis also laid the ground work for further optimizing the new inhibitors. Therefore, my findings will help combat influenza and save lives. A patent was filed on my discoveries.

Summary Statement

By combining computational research and biological assays, I identified novel and potent influenza endonuclease inhibitors and performed comprehensive structural analysis, which laid the ground work for developing new anti-flu medicine.

Help Received

Used computers in Dr. Rommie Amaro's lab at UCSD; used lab equipment in Dr. Gen-Sheng Feng's lab at UCSD.

Preliminary