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In-Silico Screening of Natural Products as Alphavirus Inhibitors

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A Proposal for the Research or Creative Experience for Undergraduates (RCEU) Program
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Project Summary: The overall goal of this research is to identify natural products for the treatment of alphavirus infections using a molecular docking approach. There are several alphaviruses that cause human infections, including Old World alphaviruses, Barmah Forest virus (BFV), Chikungunya virus (CHIKV), O'Nyong-Nyong virus (ONNV), Ross River virus (RRV), Semliki Forest virus (SFV), and Sindbis virus (SINV), and New World alphaviruses, Auravirus (AURV), Eastern equine encephalitis virus (EEEV), Venezuelan equine encephalitis virus (VEEV), and Western equine encephalitis virus (WEEV).[1] Recently, there has been an increasing interest in CHIKV.[1] Chikungunya virus fever was formerly limited to Africa, but this disease has over the past ten years transformed into a global menace.[2] The disease is spread by the Asian tiger mosquito (*Aedes albopicta*) and *Aedes aegypti*, both species of which have been spreading to new areas around the world. Incidences of CHIKV fever have been increasing in China, southern Europe, Brazil, Mexico, and the United States. There have already been more than 1 million CHIKV infections in Latin America and the Caribbean. The mosquito vectors are expected to spread northward into North American either through adaptation or global climate change.[3] Currently, there are no antiviral treatment options for alphavirus infections. There are, however, several non-structural proteins that have been identified as potential drug targets.[1] The research will involve downloading and processing all known non-structural virus protein targets that have had structures determined. These structures are freely available from the Protein Data Bank (PDB). Protein targets for which there are no crystal structures will be prepared by homology modeling using known homologous crystal structures. Each of the protein structures will be screened against our *in-silico* library of natural products using the Molegro molecular docking software package. This project is a way to rapidly and inexpensively screen thousands of compounds without the need to expose students to pathogenic organisms. ***We are very experienced in molecular docking of protein targets***.[4]

The student will be supervised by Dr. Setzer every day during the conduct of this research. Dr. Setzer's office (MSB 315) is next door to the departmental computer facility (MSB 317), so he will be available at all times during the day and evenings for consultation. The student's work will fit directly into our overall efforts in structure-based natural products drug discovery directed at neglected tropical diseases. In addition, the project is ideal in terms of scope for an undergraduate summer research project. Dr. Setzer has a good track record in working with undergraduate researchers (more than 165 individuals at UAH) and publishing their results (50 peer-reviewed publications based on undergraduate research have appeared since 2010).

Student Duties:

Downloading and Processing Protein Crystal Structures. The student will use the Molegro Virtual Docking program (MolDock) to download and prepare protein crystal structures from the Protein Data Bank (PDB: http://www.rcsb.org/pdb/home/home.do). Currently recognized protein targets include NSP2 protease and the NSP3 macro domain. The PDB currently lists crystal structures for CHIKV and VEEV proteases, CHIKV and VEEV macro domains. Structures of the NSP2 protease and NSP3 macro domain for the other human pathogenic alphaviruses will be prepared by homology modeling of the protein sequences (available from the Protein Database, http://www.ncbi.nlm.nih.gov/protein) with the Molecular Operating Environment (MOE) software, using the CHIKV and VEEV protein structures as models.

Molecular Docking of Natural Product Small Molecule Ligands. We currently have a virtual library of nearly 100,000 structures of natural products. The student will carry out molecular docking of our natural product library with the dengue virus protein targets using the Molegro Virtual Docking program. Molecular

docking "hits" will be determined based on docking energies (how exothermic the docking energies are), protein target selectivity (to determine if the ligand is a selective- or a promiscuous-binding ligand), and drug likeness (according to Lipinski's rule of five[5]).

Manuscript Preparation. Dr. Setzer encourages all undergraduate student researchers to write up their results in the form of a manuscript for publication. The RCEU participant, under the supervision of Dr. Setzer, will help prepare the manuscript(s), which may include data from other undergraduate or graduate students.

Expected Results and Deliverables. Initial protein structure downloads and preparation will take approximately one week. Molecular docking of our virtual natural products library will probably take two months. The results of this *in-silico* screening project should identify natural products that may themselves be effective antiviral agents, may demonstrate promising structural motifs for further antiviral drug development, and may identify readily available treatment options for underdeveloped tropical locales. Additionally, the project affords the opportunity for students to delve closely into biochemical target – ligand interactions, medicinal chemistry, and toxicology of drug-like molecules.

Mentor Supervision and Interaction: All computational work, software familiarization, and data analysis will be supervised by Dr. Setzer. Manuscript preparation will be supervised by Dr. Setzer. We will hold regular group meetings each week.

References

1. Gould, *et al*. Understanding the alphaviruses: Recent research on important emerging pathogens and progress towards their control. *Antiviral Research*, **2010**, *87*, 111-124.
2. Weaver SC. Arrival of chikungunya virus in the New World: Prospects for spread and impact on pubic health. *PLoS Neglected Tropical Diseases*, **2014**, *8(6)*, e2921.
3. Morens DM, Fauci AS. Chikungunya at the door – Déjà vu all over again?. *New England Journal of Medicine*, **2014**, *371*, 885-887.
4. Powers CN, Setzer WN. A molecular docking study of phytochemical estrogen mimics from dietary herbal supplements. *In Silico Pharmacology*, **2015**, *3*, 4.
5. Lipinski CA, *et al*. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced Drug Delivery Reviews*, **2012**, *64*, 4-17.