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In-Silico Screening of Natural Dengue Fever Virus 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 dengue fever using a molecular docking approach. Dengue fever is an acute viral infection caused by all four serotypes (1, 2, 3, or 4) of the dengue virus, and is one of the seventeen "Neglected Tropical Diseases" (NTDs) defined by the World Health Organization.[1] The highest incidence of dengue fever is in Southeast Asia, India, and the Neotropics; where the principal vector, the *Aedes aegypti* mosquito is found.[2] Currently, there are no treatment options for Dengue fever; there is no known cure or vaccine. There are, however, several dengue virus proteins that have been identified as potential drug targets.[3] The research will involve downloading and processing all known dengue virus protein targets that have had structures determined. These structures are freely available from the Protein Data Bank (PDB). Each of the proteins 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. Dr. Setzer has a good track record in working with undergraduate researchers (more than 160 individuals at UAH) and publishing their results (49 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 dengue virus (DENV) protease, DENV helicase, DENV RNA-dependent RNA polymerase (RdRp), DENV methyl transferase (MTase), and DENV envelope protein. The PDB currently lists 81 structures of these dengue virus protein targets.

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 [need to calculate this out]. 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. Bhatt S, *et al*. (**2013**) The global distribution and burden of dengue. *Nature*, ***496***, 504-507.
2. Guzman MG, Kouri G.. (**2002**) Dengue: an update. *Lancet Infect Dis*, ***2***, 33-42.
3. Geiss BJ, *et al*. (**2009**) Focus on flaviviruses: current and future drug targets. *Future Med Chem*, ***1(2)***, 327.
4. McCulley SF, Setzer WN. (**2014**) An *in-silico* investigation of anti-Chagas phytochemicals. *Curr Clin Pharmacol*, ***9***, 205-247.
5. Lipinski CA, *et al*. (**1997**) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Del Rev*, ***23***, 3-25.