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Natural Products as New Treatment Option for Trichmomoniasis

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Natural Products as New Treatment Options for Trichomoniasis

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 Trichomoniasis using a molecular docking approach. Trichomoniasis is a sexually transmitted disease (STD) caused by the parasitic protozoan *Trichomonas vaginalis*, and is the most common non-viral STD with an estimated 3.7 million cases in the United States.[1] Only about 30% of individuals infected with *T. vaginalis* experience symptoms of genital discomfort, itching, burning, or discharge, but there can be severe inflammation in some cases, and there is increased risk of HIV infection, cervical cancer, preterm delivery, and low birth weight.[1] Trichomoniasis can be treated with antibiotics, usually metronidazole or tinidazole, but there are increasing reports of resistance to these drugs.[2] There are currently no alternative drugs approved for treatment of refractory cases of trichomoniasis, emphasizing the need for new treatment options. Natural products have served and continue to serve as potential medicinal agents for a variety of human ailments, including parasitic protozoal diseases.[3]

There are several proteins of *T. vaginalis* that have been identified as potential drug targets.[4] The research will involve downloading and processing all known *T. vaginalis* 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 antiprotozoal natural products using the Molegro molecular docking software package. This project is a way to rapidly and inexpensively screen numerous compounds without the need to expose students to pathogenic organisms. ***We are very experienced in molecular docking of protein targets***.[5]

Student Prerequisites: There are no coursework or academic standing prerequisites. We will instruct and oversee all the student needs to carry out the project. This project does involve building organic small molecules and interactions between small molecules and proteins. Some understanding of organic chemicals and proteins would be beneficial.

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 cysteine proteases (TvCPs), triosephosphate isomerase (TvTPI), lactate dehydrogenase (TvLDH), methionine gamma-lyase (TvMGL), thioredoxin reductase (TvTrxR), and purine nucleoside phosphorylase (TvPNP). Structures of TvMGL, TvPNP, TvTPI, and TvLDH are currently available from the PDB. Structures for TvCP (papain-like cysteine protease), TvCP (cathepsin L-like cysteine protease), and TvTrxR will be prepared by homology modeling of the protein sequences (available from the Protein Database, http://www.ncbi.nlm.nih.gov/protein) with the SWISS-MODEL software, using homologous protein crystal structures as models.

Molecular Docking of Natural Product Small Molecule Ligands. The student will carry out molecular docking of our in-house library of antiprotozoal natural products with the *T. vaginalis* 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 as well as selectivity for the parasite protein compared to homologous human proteins), and drug likeness (according to Lipinski's rule of five[6]).

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 two weeks. 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 anti-*Trichomonas* agents or may demonstrate promising structural motifs for further trichomoniasis drug development. 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 and computational chemistry collaborator, Dr. Kendall Byler. Manuscript preparation will be supervised by Dr. Setzer. We will hold regular group meetings each week. 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 emerging infectious 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 170 individuals at UAH) and publishing their results (56 peer-reviewed publications based on undergraduate research have appeared since 2010).

References

1. Centers for Disease Control and Prevention. Trichomoniasis – CDC Fact Sheet. http://www.cdc.gov/std/trichomonas/STDFact-Trichomoniasis.htm.
2. Dunne RL, Dunn LA, Upcroft P, O'Donoghue PJ, Upcroft JA. Drug resistance in the sexually transmitted protozoan *Trichomonas vaginalis*. *Cell Research*, **2003**, *13*, 239-249.
3. Gehrig S, Efferth T. Development of drug resistance in *Trichomonas vaginalis* and its overcoming with natural products. *Open Bioactive Compounds Journal*, **2009**, *2*, 21-28.
4. Huang KY, Chien KY, Lin YC, Hsu WM, Fong IK, Huang PJ, Yueh YM, Gan RRC, Tang P. A proteome reference map of *Trichomonas vaginalis*. *Parasitology Research*, **2009**, *104*, 927-933.
5. Powers CN, Setzer WN. An *in-silico* investigation of phytochemicals as antiviral agents against dengue fever. *Combinatorial Chemistry & High Throughput Screening*, **2016**, *19*, 516-536.
6. 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.