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In Silico Identification of Oropouche Virus Protease-Binding Structures

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A Proposal for the Research & Creative Experiences for Undergraduates Program, Summer 2017

Faculty Research Mentor

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Project Summary

The overall goal of this research is to identify natural product structures that will bind to essential proteins in the Oropouche virus (OROV) and to refine these structures into a general pharmacophore, which will then be used to generate novel structures that exhibit maximal binding interactions. Computational investigations of emergent pathogens can provide unique and timely insights into potential targets and inhibitors when basic biological studies have not yet elucidated these details *in vivo* or *in vitro*. Oropouche virus[1-3] is a Bunyavirus transmitted by mosquitoes and other biting insects that is responsible for Oropouche fever, an infection with symptoms similar to that of chikungunya, dengue, yellow fever, Zika virus. It is among several arboviruses that fall under the classification of Neglected Tropical Diseases (NTD) and is prevalent in the Amazon region of Brazil (where its epidemic outbreaks rival only dengue in terms of numbers of infections), in Ecuador, Panama, Peru and the islands of the Caribbean. OROV is named after the region in which it was first isolated – the region around the Oropouche River in Trinidad and Tobago.

Oropouche virus occurs in nature in 28 known strains with three described genotypes. The genome is comprised of three single-stranded RNA sequences that encode large multifunction proteins, one of which is a polymerase. Several protein sequence segments have been generated from the complete genome of OROV, one of which corresponds to known protease sequences in other Bunyaviruses and has high sequence similarity specifically to the La Crosse virus protease, for which there is an X-ray crystal structure complexed with single-stranded RNA. This structure will serve as a template for the construction of a homology model for the OROV protease. Using molecular docking, an in-house set of natural products structures will be evaluated for their binding *in silico* to the RNA-binding pocket of the protease. These structures will then be used to generate a pharmacophore (a generalized set of structural features common to a set of binding structures) and new compound structures will be generated using the LigMerge[4] method, which takes common atom and bond coordinates and produces new permutations based on a set of chemical rules. These will then be re-docked to the protease and compared with the binding affinities for the original compounds. The pharmacophores generated from this will be put forward as scaffolds targeting the OROV protease. The traditional paradigm of virtual screening by molecular docking is augmented here through the generation of new structures and is a sort of methods development in computational drug discovery. The student's work here will be a proof of concept that should fit well into a summer project and yet yield sufficient material for publication in a peer-reviewed journal.

Student Prerequisites

There are no specific coursework or academic standing prerequisites for this project. Some familiarity with file handling in Windows or Unix enviroments is necessary.

Student Duties

Homology Modeling

The FASTA sequence of the OROV protease will be downloaded from the National Center for Biotechnology Information and the template crystal structures from the Research Collaboratory for Structural Bioinformatics PDB database. Sequence similarity will be evaluated using NCBI's BLAST utility. The homology models will be constructed from template

structures using SWISS-MODEL and refined with constrained minimization using the AMBER force field. The active site(s) of the enzyme will marked and used as the target for molecular docking.

Molecular Docking

An in-house data set of biologically active natural products structures will be docked into the binding pocket of the homology model for OROV protease and ranked according to goodness of fit using the Molegro docking program. Top hits here will be retained for further study and also used in the subsequent step of new structure generation.

Structure Generation

The top hits from molecular docking will be used to generate new structures by permutatively re-combining common molecular features among the hits using LigMerge. These new structures will then be re-docked to the receptor to identify the best possible leads and a pharmacophore structures will be generated.

Manuscript Preparation

The student is encouraged to assemble the results of this work in the form of a scientific journal article for publication. Dr. Byler will assist the student in this effort and may include the results of previous and concurrent studies into the final manuscript.

Expected Results

The hybrid structures generated by this method will arise from common chemical moieties found across several classes of natural products structures. As such, they may represent novel scaffold structures that may be readily modified from natural products using organic synthesis and starting from indigenous natural product sources. They may also comprise a biologically active region of chemical space as yet unexplored in the field of natural products and serve as a starting point for biological screening against any of the Bunyaviruses.

Mentor Supervision & Interaction

Dr. Byler will introduce key concepts in computational chemistry relevant to this research, such as homology modeling and molecular docking, and familiarize the student with the software and hardware associated with each technique. Dr. Byler is an expert in computational methods and routinely uses these methods in the study of chemical systems in computational drug discovery. Regular meetings will be held twice weekly with Dr. Byler; his office in MSB 223 is down the stairwell from the MSB computer lab in MSB 317.

References

1) "Oropouche virus disease – Peru" *WHO Disease Outbreak News* 3 June 2016. (http://www.who.int/csr/don/03-june-2016-oropouche-peru/en/)
2) Mourão MPG, Bastos MS, Gimaque JB, Mota BR, Souza GS, Grimmer GHN, *et al.* "Oropouche fever outbreak, Manaus, Brazil, 2007–2008" *Emerg Infect Dis* Dec 2009.
3) Nunes MRT, Martins LC, Rodrigues SG, Chiang JO, Azevedo RSS, Travassos da Rosa APA, *et al.* "Emergence and first isolation of Oropouche virus, southeast Brazil" *Emerg Infect Dis* Oct 2005.
4) Lindert S, Durrant JD, McCammon JA. "LigMerge: A Fast Algorithm to Generate Models of Novel Potential Ligands from Sets of Known Binders" *Chem Biol Drug Des* 80(3): 358–365, 2012.