CALIFORNIA STATE SCIENCE FAIR
2012 PROJECT SUMMARY

Name(s)

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Project Number

S0521

Project Title

Modeling and Molecular Dynamics Simulations of Membrane-Bound Aromatase Reveal Novel Druggable Sites

Abstract

Objectives/Goals

The objectives of the project are to: 1) Develop a new method of modeling full-length membrane-bound proteins systems for the application of molecular dynamics; 2) Use molecular dynamics and computational solvent mapping for the identification of novel druggable sites; 3) Identify the pharmacophores of inhibitors targeting these sites, and 4) Compare the quality of analysis derived from molecular dynamics simulation over analysis derived from the crystal structure.

Methods/Materials

The system (consisting of the protein, heterogeneous membrane, and waterbox) was constructed using CHARMM-GUI and Maestro. NAMD 2.7b on the SDSC Trestles and TACC Ranger supercomputers ran minimization and equilibration of the system, as well as 250 nanoseconds of free molecular dynamics. The resulting data was analyzed and visualized using VMD, UCSF Chimera, and Tcl scripts. FTMap performed computational solvent mapping, and DelphiElec computed electrostatics.

Results

Data from the molecular dynamics simulation was highly consistent with experimental data, validating the novel procedure used to build the model and process it for molecular dynamics. In addition, computational solvent mapping discovered two novel druggable sites for next-generation aromatase inhibitors to target - the heme proximal cavity and the active site channel. Furthermore, the overlapping of organic solvent molecules revealed a general pharmacophore for new inhibitors targeting these sites. The comparison of the ensemble-averaged electrostatics with the crystal structure electrostatics also pointed out flaws of the current theory of a higher-order aromatase structure, which was based on analysis of the crystal structure alone.

Conclusions/Discussion

The method used in this project in to construct a system of full-length membrane-bound protein was validated with experimental data, and is much more efficient than previously used methods. This method can be used as a precedent for the molecular dynamics of other membrane-bound proteins of interest. Furthermore, the use of molecular dynamics for the discovery of novel druggable sites was validated with the identification of the heme proximal cavity and the active site channel. The project also indicated the flaws of using the crystal structure for making conclusions, as evidenced in the example of aromatase oligomerization and electrostatics.

Summary Statement

I developed a novel method of preparing membrane-bound proteins for molecular dynamics and applied to to aromatase to discover new binding sites that future inhibitors can target to treat estrogen-dependent breast cancer.

Help Received

Dr. Rommie Amaro mentored my project and allowed me to access the computational resources available to the Amaro Lab. Additionally, she and Dr. Luke Czapla answered any questions I had, gave me advice, suggested various things, helped me with programs, and edited my report.