HARNESSING THE POWER OF PARALLEL COMPUTING FOR COMPUTER-AIDED DRUG DISCOVERY

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My research revolves around the study of the cellular targets of drugs, the identification and pharmacological characterization of molecules that modulate their activity, and the examination of the cellular consequences resulting from such pharmacological intervention. Through the application of computational and experimental biochemical pharmacology techniques, the ultimate goal of my laboratory is to rationally identify molecules potentially endowed with a desired pharmacological activity and subsequently test their biological effect on mammalian cells that express the target of interest either naturally or artificially. The main research focus is on the discovery of compounds that act through G protein-coupled receptors (GPCRs), the single family of cellular targets most exploited by currently marketed medicines.

The Zorro High-Performance Computing System of American University is instrumental to all the computational aspects of my research.

The computations are mainly based on two software packages:

1. The Schrödinger platform (Schrödinger, www.schrodinger.com), which is the main tool that we utilize for ligand-based screenings, molecular docking-based screenings, conformational searches and molecular dynamics simulations;
2. The Molecular Operating Environment (MOE, Chemical Computing group, www.ccg.com), which is the main tool that we utilize for homology modeling.

Both platforms are installed on all local computers in my laboratory as well as the Zorro parallel computing cluster. The local computers are connected to the cluster, to which all the molecular modeling calculations are submitted in a seamless way. The excellent graphic capabilities of the local computers, the computational power of the cluster constitute an outstanding hardware platform for computer-aided drug discovery.

Two specific projects on which my students and I are currently working are described below.

A rational campaign for the discovery of CNS-active P2Y₁₂ blockers in the hunt for potential agents for the treatment of neuropathic pain

P2Y₁₂ is a G protein-coupled receptor (GPCR) activated by adenosine diphosphate (ADP) and coupled to the inhibition of adenyl cyclase. In humans, it is found in platelets and the central nervous system (CNS), primarily microglial cells, and acts as a sensor for cellular injury. Nucleotides released by injured cells activate the P2Y₁₂ receptor, which in platelets triggers aggregation, while in the CNS triggers microglia activation. The latter is at the basis of the etiology of neuropathic pain, a debilitating condition associated with many disorders, among which are nerve injury, diabetes, cancer, shingles, AIDS, alcoholism and multiple sclerosis (MS). Since, intrathecally administered P2Y₁₂ blockers suppress neuropathic pain in mice, we envision that BBB-permeable P2Y₁₂ blockers would provide an effective pharmacological avenue to the treatment of neuropathic pain. Through this project, we aim to identify blockers for the P2Y₁₂ receptor permeable to the blood brain barrier (BBB) through a computer-aided molecular recognition approach. These compounds would be
extremely valuable for the characterization, in animal models, of the effectiveness of P2Y12-blockage in the treatment of neuropathic pain and might ultimately provide leads for drug development.

Development of a systematic method for the assessment of the accuracy of computational models of G protein-coupled receptors in complex with their modulators through site-directed mutagenesis.

G protein-coupled receptors (GPCRs) are integral membrane proteins of high pharmaceutical interest. Notably, compounds that bind to them and modulate their activity constitute a large share of the currently marketed drugs. The experimental determination of the three-dimensional (3D) structure of these receptors has proven particularly challenging. As a result, despite the fact that humans have about 1000 different GPCRs, 3D structures have been experimentally elucidated for only 17 of them. Through our research, we have demonstrated that, in the absence of experimental structures, accurate models of the receptors in complex with their modulators can be constructed through computational techniques. We have also demonstrated that accurate models provide an excellent platform for the discovery of novel modulators of the receptors through computer-aided screening campaigns. However, only accurate models are useful and, currently, there are no validated systematic methodologies that allow an estimation of said accuracy. In light of these premises, the goal of this project is the development of a systematic methodology intended to identify, among a number of alternative models, those that most closely resemble the actual three-dimensional (3D) structure of the receptor-modulator complex.

Specifically, through controlled experiments conducted using as a case study a receptor with known 3D structures, we intend to demonstrate that the structural accuracy of models can be predicted through a quantitative evaluation of the correlation between computational and experimental mutagenesis data. The significance of the project lies in the fact that, as mentioned, accurate models can be effectively employed in computer-aided drug discovery campaigns. Because of my proven expertise in molecular modeling and molecular pharmacology of GPCRs, we are in a unique position to successfully develop this systematic methodology.

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