## Computer Aided Drug Discovery and Development

*Structure Based Drug Discovery Targeting the Complement System,* **DIMITRIOS MORIKIS** (Department of Bioengineering, University of California, Riverside, Riverside, CA; dmorikis@ucr.edu).

The complement system is part of innate immunity and a link between innate and adaptive immunity. It consists of over 30 proteins, receptors and regulators, and has been characterized as the bloodstream patrol against invading pathogens. However, in cases of inappropriate regulation the complement system is capable of attacking own tissues, resulting to inflammatory and autoimmune diseases, or looses pathogen-fighting ability. Our drug discovery efforts target the function of complement protein C3, the converging point of all three complement activation pathways, and its proteolytic fragments C3a and C3d. We use structure-activity relations, molecular dynamics simulations, pharmacophore modeling, virtual screening, docking, and free energy calculations to design peptidic inhibitors, agonists, and antagonists of complement system proteins, receptors, and bacterial regulators. We will present our latest efforts in designing peptides of the compstatin family that inhibit the cleavage of C3 to C3a and C3b, and have the potential to become therapeutics for macular degeneration. We will also present the design of C3a-derived peptides that are agonists and antagonists of C3a receptor (C3aR), and are candidates for the treatment of complement-mediated inflammatory diseases. Finally, we will present the discovery of chemical compounds that target C3d and have the potential to be developed as biomarkers to diagnose, monitor and treat complement-mediated chronic pathological conditions. Our computationally designed/discovered molecules are experimentally tested using binding, biochemical, and cell-based assays, as well as NMR and fluorescence spectroscopies.

*Bridging Calorimetry and Simulation through Precise Calculation of Binding Enthalpies in Host-Guest and Protein-Ligand Systems*, **ANDREW FENLEY* and MICHAEL GILSON** (Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, San Diego, CA; afenley@ucsd.edu).

Recent technological advances in both hardware and software have increased the throughput of explicit solvent molecular simulations to the point where we can now start making numerically precise connections to the thermodynamic data provided by isothermal titration calorimetry (ITC). Here, we present the direct calculation of the enthalpy of binding using microsecond timescale simulations for eight guests bound to cucurbit[7]uril (CB7) and two potent inhibitors bound to HIV protease. The computed binding enthalpies show reasonable agreement with experiment with block averaging analysis yielding numerical uncertainty estimates of the binding enthalpies to be on par with experimental error from previously published ITC data. For the CB7 system, the estimates are able to discern between the five high-affinity aliphatic guests and the three low affinity aromatic guests. And for HIV, the relative change in binding enthalpy between the inhibitors closely agrees with experiment. Furthermore, since we are using canonical simulations with additive potentials, we are able to extract the direct enthalpic contributions of the nonbonded interactions (electrostatic and van der Waals) which are critical for molecular recognition in binding. A similar decomposition using temperature derivatives of the free energy does not seem to be nearly as accessible. The presented approach to calculating binding enthalpies using explicit solvent simulations allows for a direct comparison with experimental values and thus could be used as an additional constraint when tuning future force field parameters specifically with the goal of increasing the predictable power of binding free energy calculations.

*Activation Mechanisms of the M2 Muscarinic Receptor and Design of Allosteric Modulators*, **YINGLONG MIAO* and ANDY McCAMMON** (Howard Hughes Medical Institute, University of California, San Diego, San Diego, CA; afenley@ucsd.edu).

G-protein coupled receptors (GPCRs) are important cell signaling proteins that have been targeted by ~1/3 of current marketed drugs for treating many human diseases such as cancer and heart failure. While significant advances have been made in recent structural and computational studies, detail mechanisms of GPCR activation that occurs on the millisecond timescales remain unclear. The X-ray crystal structure of the M2 muscarinic receptor, a key GPCR that regulates the human heart rate and contractile forces of cardiomyocytes, was first determined in an antagonist-bound inactive state. Starting from the inactive X-ray structure with antagonist removed, we captured activation of the apo M2 receptor through hundred-of-nanosecond accelerated molecular dynamics (aMD) simulations1. The receptor activation is characterized by large-scale structural rearrangements of the transmembrane helices via an intermediate state. With the simulation-derived activation-associated conformers, a fragment-based site mapping program FTMAP is applied to explore druggable allosteric binding sites in the M2 receptor2. Virtual screening is then performed to select small-molecule drugs that bind these allosteric sites and modulate the receptor signaling. In contrast to highly conserved residues in the orthosteric site where the endogenous ligand binds, residues in the allosteric sites exhibit large diversity across different GPCR subtypes. Therefore, GPCR allosteric modulators are able to provide highly selective therapeutics.

(1) Miao, Y.; Nichols, S. E.; Gasper, P. M.; Metzger, V. T.; McCammon, J. A. *Proc Natl Acad Sci U S A* 2013, *110*, 10982.
(2) Miao, Y.; Nichols, S. E.; McCammon, J. A. *Chem Bio Drug Des* 2013, 237.

*Using Model Systems to Improve Binding Free Energy Calculations for Drug Discovery*, **DAVID MOBLEY** (Department of Pharmaceutical Sciences and Department of Chemistry, University of California, Irvine, Irvine, CA; dmobley@uci.edu).

I will survey our work using molecular dynamics simulations to predict binding free energies in blind tests in a series of different model binding sites, highlighting lessons learned and major challenges still facing work in this area. In general, we find that RMS errors in the vicinity of 1.5 kcal/mol are possible with today's force fields, at least for small molecules like those studies here. I also discuss how these techniques might find practical use in discovery applications, and work calculating other properties and how it can impact force field development.

*Deciphering and Engineering Chromodomain-Methyllysine Peptide Recognition*, **WEI HE, NAN LI, RICHARD STEIN, ELIZABETH KOMIVES and WEI WANG*** (Department of Chemistry and Biochemistry, University of California, San Diego, San Diego, CA; wei-wang@ucsd.edu).

Post-translational modifications (PTMs) play critical roles in regulating protein functions and mediating protein-protein interaction. An important PTM is lysine methylation that orchestrates

chromatin modifications and regulates functions of non-histone proteins. Methyllysine peptides are bound by modular domains, of which chromodomains are representative. Here, we conducted the first comprehensive study of all chromodomains in the human proteome interacting with both histone and non-histone methyllysine peptides. We observed significant degenerate binding between chromodomains and histone peptides, i.e. different histone sites can be recognized by the same set of chromodomains, and different chromodomains can share similar binding profiles to individual histone sites. Such degenerate binding is not dictated by amino acid sequence or PTM motif but rather rooted in the physiochemical properties defined by the PTMs on the histone peptides. This molecular mechanism is confirmed by the accurate prediction of the binding specificity using a computational model that captures the structural and energetic patterns of the domain-peptide interaction. Furthermore, guided by the computational model, we completed the first targeted engineering of the chromodomain binding profiles towards hundreds of peptides by mutating only three residues on the interaction interface. This study presents a systematic approach to deciphering the domain-peptide recognition and pinpointing the critical residues of which mutation could manipulate this recognition.

*CADD and Translational Science: Interfacing Industry Practices with Academia*, **VICTORIA A. FEHER* and ROMMIE AMARO** (Department of Chemistry and Biochemistry, University of California, San Diego, San Diego, CA; vfeher@ucsd.edu).

Recently two events have put increased pressure on the productivity and success of academic CADD projects; a. the increased funding by the NIH on translational science and b. the movement by big pharma away from internally discovered drug leads to academic partnerships for new biology, validated targets or chemical entities. At a time when many academic research labs are utilizing HTS, through virtual screening or HTS research Centers, for novel target hit discovery, our group is instead utilizing small target-focused libraries of several hundred compounds purchased from commercial vendors for *in vitro* screening. This approach incorporates a "Best Practices Workflow" borrowed from small start up companies that incorporates cheminformatics, structure- and ligand-based computational methods for target-focused compound selection. Several examples will be discussed, including a recent successful approach for influenza endonuclease. A workflow incorporating Open Eye's Omega, Filter and a three-dimensional structure- and ligandbased pharmacophore developed using VROCs will be presented. Cheminformatics filtered a library from ~450,000 compounds to allow a virtual screen of ~110,000 compounds. The VS yielded 264 compounds selections for testing in a FRET-based endonucleaseinhibition assay. Sixteen inhibitors ($IC50 < 50\ \mu M$) that span 5 molecular classes novel to this endonuclease were found (6.1% hit rate). Two compounds suppress viral replication with negligible cell toxicity.

*Drug Repurposing and Adverse Event Mitigation via an Integrated Molecular Modeling and Systems Pharmacology Approach*, **DONG XU** (Department of Biomedical and Pharmacrutical Sciences, College of Pharmacy, Idaho State University; dxu@pharmacy.isu.edu).

It has been shown that the current paradigm of "one drug, one target" in drug discovery no longer holds true. Most drugs bind to multiple targets, leading to side effects and also potential new uses. In addition to the polypharmacological implications, new possibilities arise from medication regimen of two or more drugs. In silico methods spanning molecular modeling, systems biology and database mining are being developed to facilitate drug repurposing, detect adverse events, and predict mitigating effects of combination therapy. Advances in these areas are creating the foundation of the next paradigm in drug discovery: multiple drugs, multiple targets.