Rational Drug Discovery and Protein Modeling

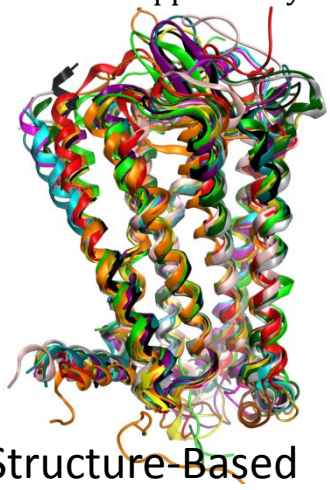
THE UNIVERSITY OF MEMPHIS

Members of the **Rational Drug Discovery and Protein Modeling Lab** utilize a suite of computational medicinal chemistry and protein modeling techniques to prioritize candidates for experimental studies in the early-stage drug discovery process. This team is led by Professor of Chemistry and Associate Dean in the College of Arts and Sciences, Abby Parrill.

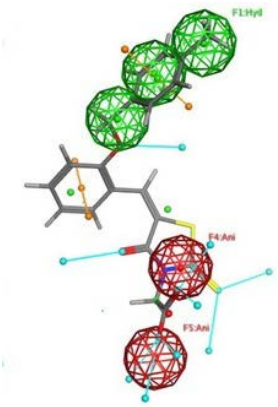
-Research Interests and Expertise-

Dr. Parrill's group approaches the drug discovery process through the use of computational methods to guide investments of time and resources into experimental studies that are most likely to identify candidate drugs with the desired biological activity. Computational pharmacophore models can identify the ligand features and geometry required for recognition of a biological target. Quantitative structure activity models are applied to predict potencies of candidate compounds. These types of methods are ligand-based drug discovery methods, not requiring knowledge of the biological target structure.

Additional computational techniques such as docking do require three-dimensional structural details about the biological target. Such details can come from experimental structural biology approaches, but can also come from protein modeling efforts when experimental structural information is not available. The Parrill group specializes in modeling membrane proteins, particular members of the G protein-coupled receptor family, which serve as targets for ~35% of FDA-approved drugs on the market. Dr. Parrill's research is supported by the National Institutes of Health.



Structure-Based Drug Discovery



Ligand-Based Drug Discovery

-Representative Publications-

Gacasan, S.; Baker, D.L.; Parrill, A.L. "G Protein-Coupled Receptors: The Evolution of Structural Insight", AIMS Biophysics, **2017**, 4(3): 491-527..

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McMillan, J.E.; Bukiya, A.N.; Terrell, C.L.; Patil, S.A.; Miller, D.D.; Dopico, A.M.; Parrill, A.L. "Multi-generational pharmacophore modeling for ligands to the cholane steroid-recognition site in the β1 modulatory subunit of the BKCa channel", J. Mol. Graph. Model., **2014**, 54C:174-183. doi: 10.1016/j.jmgm.2014.10.008.

Valentine, W.J.; Godwin, V.I.; Osborne, D.A.; Liu, J.; Fujiwara, Y.; Van Brocklyn, J.; Bittman, R.; Parrill, A.L.; Tigyi, G. "FTY720 (Gilenya) phosphate selectivity of sphingosine 1-phosphate receptor subtype 1 ($S1P_{1}$) G protein-coupled receptor requires motifs in intracellular loop 1 and transmembrane domain 2", J. Biol. Chem., **2011**, 286(35), 30513-30525. http://www.jbc.org/cgi/doi/10.1074/jbc.M111.263442.

Fells, J.I.; Tsukahara, R.; Liu, J.; Tigyi, G.; Parrill, A.L. "Structure-based Drug Design Identifies Novel LPA_3 Antagonists", Bioorg. Med. Chem., **2009**, 17(21), 7457-7464.

Jo, E.; Sanna, M. G.; Gonzalez-Cabrera, P. J.; Thangada, S.; Tigyi, G.; Osborne, D. A.; Hla, T.; Parrill, A. L.; Rosen, H. "$S1P_1$-selective in vivo-active agonists from high throughput screening: Off-the-shelf chemical probes of receptor interactions, signaling and fate". Chemistry & Biology, **2005**, 12, 703-715.

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