Structure and Function of the G-protein Coupled Receptor Family

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G protein-coupled receptors comprise the largest family of human eukaryotic signal transduction proteins that communicate across the membrane. We recently solved the crystal structure of the human β_2-adrenergic receptor bound to the partial inverse agonist carazolol and timolol at 2.4 Å and 2.8 resolution Å, respectively. More recently, we determined the structure of the human adenosine A2a receptor bound to the antagonists ZM281345 at 2.6 Å resolution. The structures provide a high-resolution view of a human G protein-coupled receptor bound to diffusible ligands. Ligand-binding site accessibility is enabled by the extracellular loops which are held out of the binding cavity by a set of disulfide bridges and unique structural motifs. An exciting discovery is the role of cholesterol in receptor stability and potential function. Future studies include the determination of representative members from the different branches of the GPCR phylogenetic tree (Figure 1) including class A, B, and C GPCR's, as well as the receptors bound to agonists and G-proteins in an activated state.

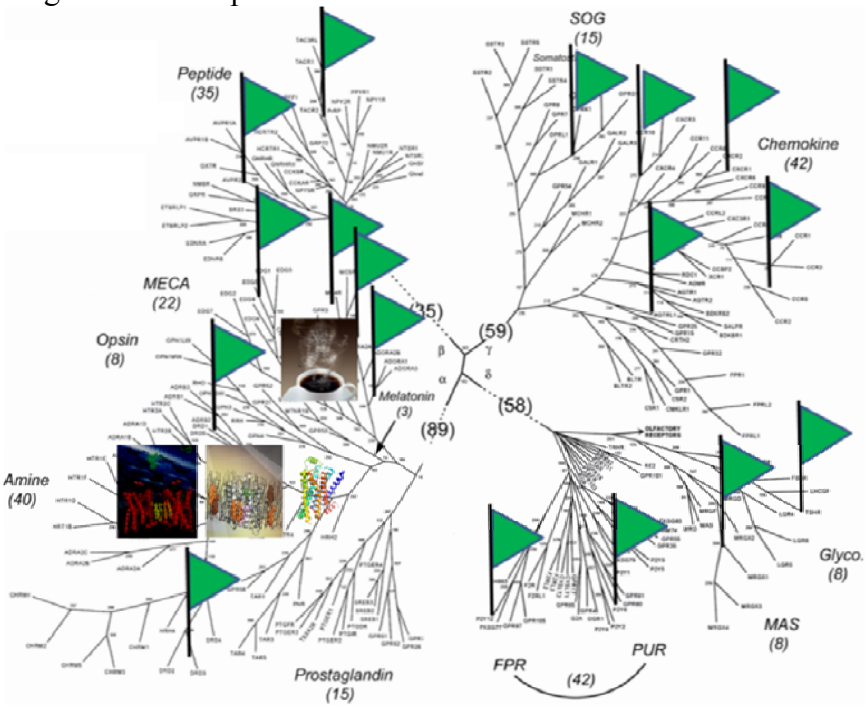

Figure 1. GPCR phylogenetic tree with green flags on the GPCR targets currently under structure investigation. Pictures are shown for the 4 structures currently known out of the several hundred class A GPCR's.

This work was supported by the NIGMS Protein Structure Initiative (ATCG3D) and the NIH Roadmap Initiative (JCIMPT).

Raymond Stevens is currently a Professor of Molecular Biology and Chemistry at The Scripps Research Institute in La Jolla, California where he focuses on understanding the basic principles of neurobiology and the associated disease states that affect mankind. After growing up in Maine and obtaining his B.A. degree there in 1986, Dr. Stevens obtained his Ph.D. in organic chemistry with Professors Robert Bau and George Olah (Nobel Prize 1994) at the University of Southern California in 1988 and conducted his post-doctoral research in structural biology with Professor William Lipscomb (Nobel Prize 1976) in the Chemistry Department at Harvard University. Prior to moving to Scripps in 1999, Dr. Stevens was a Professor of Chemistry and Neurobiology at the University of California, Berkeley. Dr. Stevens helped to pioneer the area of high throughput structural biology and has published more than 220 peer reviewed publications in the past 15 years, focusing primarily in the area of structural biology and structure based drug discovery including involvement in the development of TamiFlu™ for influenza, Phenoptin™ for mild phenylketonuria, Phenylase™ for classical phenylketonuria, and pegylated BoTox™ for neuromuscular disorders such as cerebral palsy. Dr. Stevens has received numerous awards for his research, including the Sidhu Award (1992), the National Science Foundation's Presidential Young Investigator Award (1994), Beckman Foundation's Young Investigator Award (1994), Lawrence Berkeley Laboratory Outstanding Performance Award (1995), Jouan Robotics Award (2003), and the USC Alumnus of the Year Award (2005). Dr. Stevens has also founded multiple biotech companies including Syrrx (acquired by Takeda), and MemRx (acquired by

Chiron/Novartis) and NIH research centers including the Joint Center for Structural Genomics and the Joint Center for Innovative Membrane Protein Technologies. Most recently, Dr. Stevens has been successful in his 16 year quest to generate GPCR structural data to provide insight into the basic science and drug discovery of this important family of human receptors.