Structure, Function and Drug Discovery of the G-protein Coupled Receptor Superfamily

Raymond Stevens1,2

The Scripps Research Institute1, La Jolla, CA 92037, USA
Shanghai Institute of Materia Medica2, Chinese Academy of Sciences
Shanghai 201203, China

G protein-coupled receptors comprise the largest family of human proteins that communicate signals across the membrane and recognize millions of diverse molecules such as adrenaline, opioids, caffeine, dopamine, chemokines to name only a few. Over the past 10 years we have built a process pipeline to determine representative members of the G protein-coupled receptor phylogentic tree in order to understand the similarities and differences within this protein superfamily. In 2007, we solved the crystal structures of the human β2-adrenergic receptor bound to the partial inverse agonist carazolol and timolol at 2.4 Å and 2.8 Å resolution and are now conducting NMR and HDX studies to understand receptor dynamics. In 2008, we determined the structure of the human adenosine A2A receptor bound to the antagonist ZM241385 at 2.6 Å resolution. More recently, we have determined the structures of the human CXCR4 chemokine, human dopamine D3, histamine H1 receptor structures, and agonist structure of the human adenosine A2a receptor. As part of a biotechnology start-up to use the technologies for specific drug discovery, Receptos has determined the structure of the human S1P1 receptor and the company now has a Phase I clinical trial underway to treat multiple sclerosis. The collective 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 G protein-coupled receptor phylogenetic tree including class A, B, and C G protein-coupled receptors, as well as the receptors bound to agonists and G-proteins in an activated state.

Raymond Stevens Professor, the Scripps Research Institute, USA; B.A., 1986, University of Southern Maine; Ph.D., 1988, University of Southern California; NIH Postdoctoral Fellowship, 1989-1992, Harvard University (advisor: William N. Lipscomb); Professor of Chemistry, University of California, Berkeley, 1992-2000; Structural neurobiology and G-protein coupled receptors; Tel: 858-784-9416, Fax: 858-784-9483, E-mail: stevens@scripps.edu