International Journal of Computational Bioinformatics and In Silico Modeling
Vol. 2, No. 4 (2013): 138-140
Editorial
Open Access

ISSN: 2320-0634

# Glimpse into GPCRs: a 'hot topic' for both academia and industry

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Received: 25 June 2013 Accepted: 25 June 2013 Online: 01 July 2013

G-protein coupled receptors (GPCRs) constitute the largest integral membrane protein family and in humanthey are encoded by more than 900 genes [1]. They have a typical structural topology consisting of 7 trans-membrane helices connected by intracellular and extracellular loops, with an extracellular N-terminal loop as well as intracellular C-terminal being responsible for the interaction with G-proteins, see figure 1. GPCRs primary function is to transduce extracellular stimuli into intracellular signal through interaction of their intracellular domains with heterotrimeric G-proteins.They convert extracellular massages into intracellular responses. GPCRs are essentially involved in all key physiological processes and responsible for our senses of vision, smell, taste, pain, regulation of many functions including heart rate and blood pressure, and they are the targets of 30% to 50% of all prescription drugs on the market today [1]. The therapeutic applications of GPCRs include pain, cancer, cardiovascular, gastrointestinal, visual, respiratory, allergies, hypertension, depression, obesity and various central nervous system disorders [2, 3]. On 2012 the Nobel Prize in chemistry was awarded to Robert Lefkowitz (Duke) and Brian Kobilka (Stanford) for their work on GPCRs that includes solving the first structures of a ligand activated GPCR [4-6] and the first activated GPCR in complex with G-protein [7]. In addition to the ingenuity of both scientists, this prize was also awarded due to the cardinal role of GPCRs, and it was one of the fast discoveries to Nobel prize transitions in recent decades.

Structural information is helpful for rational drug discovery and widely employed by academic and industrial researches for designing specific and potent modulators to target certain biological molecules involved in disease conditions [8]. GPCRs are not easily crystallized for structural evaluation since they are structurally unstable in purified form [3]. Rhodopsin was the first GPCR to be subjected to X-ray analysis [9] and since 2007, thirteen more unique GPCRs have been crystallized in their active/inactive forms, including the avian β1 adrenergic receptor [10], human β2adrenergic receptor [4], A2A adenosine receptor [11], Histamine H1 receptor [12], Sphingosine 1-phosphate receptor [13], Dopamine D3 receptor [14], CXCR4 chemokine receptor [15], Muscarinic M2 receptor [16], Muscarinic M3 receptor [17], Kappa opioid receptor[18], mu opioid receptor [19], delta opioid receptor [20] andnociceptin/orphanin FQ (N/OFQ) peptide receptor [21]. The structural data from these studies provides critical informationon the mechanics of drug-receptor interaction and help to rationally design allosteric modulators for some GPCRs.GPCRs remain a hot topic due to the continuing GPCR deorphanization and subsequent elucidation of their pharmacology and physiology.

Most drugs developed against GPCRs interact with the orthosteric ligand domain, see figure 1. However, other extracellular/intracellular parts can affect receptor activity/function and can be exploited as drug binding targets. Modulators acting on allosteric regions can be designed to be highly selective for individual GPCRs due to their binding pockets' uniqueness [22]. The first allosteric GPCR approved drug was Cinacalcet (Sensipar™). Contrary to orthosteric ligand, Cinacalcet binds to the trans-membrane region of the $Ca^{++}$ sensing receptor distal to the orthosteric binding domain in the N-terminus and alters the conformation to enhance

affinity to $Ca^{++}$ [23]. Recently, scientists started to talk about dualsteric ligands for GPCRs and their advantages over orthosteric and allosteric ligands. Since dualsteric ligands bind to the orthosteric and allosteric sites simultaneously, they are highly potent and selective. The first dualsteric ligands against M2 muscarinic receptor was described by Antony et al [24]. I believe that rational design of dualsteric GPCR ligands will have high impact in producing more effective and safer drugs in the future.

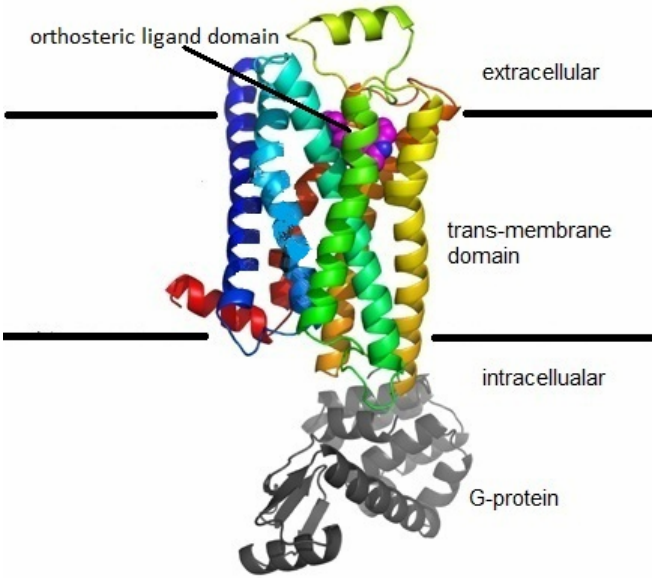


**Figure 1.** Structure of the Beta-2 adrenergic receptor. This shows the typical structural topology of GPCRs consisting of 7 trans-membrane helices connected by intracellular and extracellular loops, with an extracellular N-terminal loop as well as intracellular C-terminal. The N and C terminal structures were not fully determined by X-ray for this receptor and most of other GPCRs due to high flexibility. The orthosteric ligand domain of the adrenergic receptors reside in the upper half the trans-membrane domain while the allosteric domains could be in the trans-membrane domains or extracellular/intracellular regions. It affects receptor activity/function when being bounded.

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**News:**

**COST Action CM1207:"GLISTEN: GPCR-Ligand Interactions, Structures, and TransmembraneSignalling: a European Research Network"**

The kickoff meeting of COST Action CM1207 was held in Brussels, Belgium on 3rd of May 2013. Actually, the action started that day and will be ended on the 2nd of May 2017. Fifty renowned scientists from 23 countries belonging to various disciplines of chemical, physical and biological sciences are joining forces to deeply understand structure, function and physiology of GPCRs. This is aimed to facilitate the GPCR drug discovery process and make drug design efforts more efficient. Special efforts will be devoted to unravel details of the activation mechanism, ligand

binding, and effects of the membrane and other interaction partners on GPCRs (http://www.cost.eu/domains_actions/cmst/Actions/CM1207). Researchers from the academia and industry are taking part in this action and this may lead to high impact on GPCRs pharmaceutical research and industry.

**Editorial update:**

We are pleased to welcome Prof. Dr. Hubert G. Schwelberger (Medical University Innsbruck, Austria) and Prof. Francisca Sanchez-Jimenez (University of Malaga, Spain) for joining the editorial board staff. We continue to welcome suggestions for more editorial board members, so if you are a specialist scientist in one of the journal topics and interested in joining, please let us know. The editorial board members should support the journal in different ways: review and evaluate manuscripts, writing editorials and reviews, help to raise awareness of the journal and contribute ideas as to how to develop the journal to be a key medium for computational bioinformatics & modeling.

**Short Biography:**

Dr. Anwar Rayan Studied Chemistry (degree awarded with distinction) followed by a Ph.D. in Computational Chemistry. Postdoctoral Studies on Bioinformatics at the school of pharmacy in Jerusalem.Research fellowin FMP, Berlin, Germany. Dr. Anwar Rayan is currently CEO of GeneArrest LTD company and head of the Drug Discovery Informatics Lab at the QRC – Al Qasemi Academic College. Founder of five companies (IDD therapeutics, Pepticom, Sensotrade, GeneArrest and RAND Biotechnologies). Having more than 38papers in peer-reviewed journals and 5 patents.