Editorial

Cell-surface G protein-coupled receptors (GPCRs) constitute nearly 5% of the human genome, making them the largest superfamily of all receptor proteins. Approximately 300 – 350 of a total of 700 – 1000 GPCRs are the "non-sensory" GPCRs, which represent the main drug targets for the majority of medicines currently available. In particular, the "rhodopsin-like" Class I (Family A) GPCRs are pre-eminent therapeutic targets. Given that half of the non-sensory GPCRs are "orphan" receptors, it is evident that GPCR-based drug discovery will remain a vital practice well into the new millennium.

The classic approach to GPCR-based drug discovery has long been the optimization of lead molecules to target the "orthosteric" site on the receptor, i.e., the site that is recognized by the endogenous agonist for that receptor. Orthosteric ligands have traditionally been classed as agonists, neutral (competitive) antagonists and inverse agonists. However, it is now becoming recognized that many GPCRs possess additional, "allosteric", binding sites that modulate receptor activity through conformational changes transmitted to the orthosteric site or directly to effector coupling sites. The structure-activity relationships that govern orthosteric effects do not apply to allosteric binding sites, leading to a greater scope for ligand fishing in the chemical space encompassing biologically active molecules. Furthermore, allosteric modulator ligands of GPCRs possess a number of advantages over classic orthosteric drugs, including a greater potential for receptor selectivity and a higher safety in overdose due to a ceiling level to their effect.

Despite their theoretical advantages, allosteric interactions are more complex than orthosteric interactions, and the manifestations of allosterism at GPCRs are many and varied. Thus, the successful detection, validation and quantification of allosteric phenomena at GPCRs require modifications of standard approaches used to screen for orthosteric ligands. The current paucity of allosteric modulators in the known population of biologically active molecules is likely due to the fact that classic high-throughput screens are biased towards the detection of orthosteric ligands, but functional assays have now overtaken radioligand-binding assays as the high-throughput method of choice, and allosteric ligands that have minimal effects on orthosteric binding are being discovered through their effects on receptor signalling. Nevertheless, the optimal detection of novel allosteric ligands requires the combination of both standard functional and modulator-optimized binding assays.

This issue of Mini-Reviews in Medicinal Chemistry contains three reviews from international leaders in the study of Class I GPCR allosterism. Birdsall and Lazareno provide an excellent overview on the methodological approaches and pitfalls associated with the detection and quantification of allosteric modulator ligands, using the muscarinic acetylcholine receptors as a prototypical example. A structure-activity focus is provided in the review by Gao, Kim, IJzerman and Jacobson on allosteric modulators of the adenosine family of receptors. Finally, Schetz outlines the various modes of modulation of the dopamine family of GPCRs. These reviews are particularly timely, as there are now a number of allosteric modulators in clinical trials with many more likely to eventuate from current drug discovery programs. I am extremely grateful to the contributors for ensuring that this issue will become a valuable resource to others in the growing field of GPCR allosterism.

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