
VOLUME 1
GPCRs as Therapeutic Targets
Edited by Annette Gilchrist
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Contents

Preface

G protein-coupled receptors (GPCRs) are the largest group of cell surface receptors. They regulate nearly all known human physiological processes from the sensory modalities of vision, taste, and smell to hormones that control our growth and development to neurotransmitters that govern behavior. Given their role in normal homeostasis and a broad array of pathological conditions including cancer, diabetes, cardiovascular disease, and asthma to name just a few, they serve as the targets for hundreds of drugs and more recently biologics such as monoclonal antibodies. Yet our understanding of GPCRs continues to evolve and texts that discuss these receptors must constantly be revisited. For example, we are just beginning to appreciate the importance of genetic variation in targeted GPCRs.

In the 30 years I have studied GPCRs many novel pharmacological concepts have been advanced. We have seen the emergence of constitutively active GPCRs and inverse agonism, arrestin signaling and functional selectivity, receptor dimerization, and signaling through subcellular receptors. We have seen many GPCRs without known endogenous ligands (orphans) undergo deorphanization, and accepted that some orphan receptors may only function constitutively in a ligand-independent manner. Advances in our understanding of their basal activity, their ability to bind a diverse array of ligands, how they communicate a signal across the cell membrane or within the cells, when they dimerize, their crosstalk with other receptors, and that their genetic variation can lead to disease or differences in drug response has expanded our appreciation for GPCRs. In addition, the depth of our understanding of GPCR pharmacology has in turn altered the drug discovery process itself, expanding the ways in which they are screened for compounds that modulate their signaling.

This two volume book set is organized into 26 chapters and will serve as a resource for any scientists investigating GPCRs, be it in academia or industry. The first volume provides in-depth information about the molecular pharmacology of this important target class and presents up-to-date material on GPCR structures and structure based drug design. There are eight chapters on the evolving

pharmacology for GPCRs, including chapters discussing allosteric modulation, receptor dimerization, deorphanization, ubiquitination, intracellular trafficking, and subcellular GPCR signaling. The next six chapters discuss the rapidly growing field of GPCR structures and structure based drug design. Included in this section are chapters on the structural basis of G protein selectivity, as well as rational drug design for not only GPCRs but downstream signaling molecules such as phospholipase C. The second volume includes information on the role of GPCRs in disease and novel approaches for studying this receptor family. There are seven chapters addressing how GPCRs play a role in a wide range of pathological states including cancer, substance use disorders, cerebrovascular disease, and metabolic disease. The final five chapters present recent approaches employed to study GPCRs including mass spectrometry, bioluminescence, single molecule microscopy, and optogenetics. Together, the two volume book set provides a thorough overview of GPCRs in terms of their structure, pharmacology, function, and role in disease states, and provides information on novel approaches to measure GPCR activity.

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