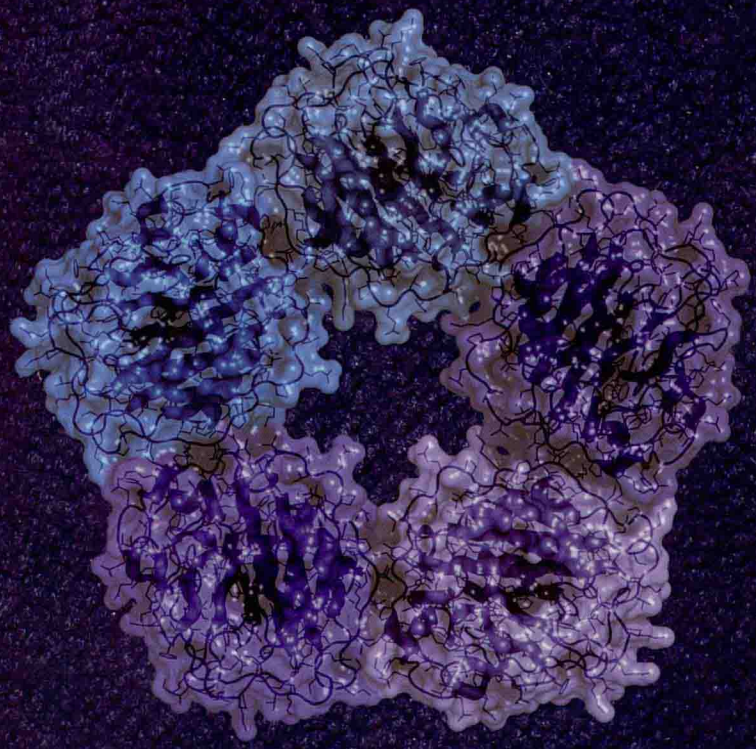
Biased Signaling in Physiology, Pharmacology and Therapeutics



Edited by
Brian J. Arey

BIASED SIGNALING IN PHYSIOLOGY, PHARMACOLOGY AND THERAPEUTICS

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BRIAN J. AREY

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BIASED SIGNALING IN PHYSIOLOGY, PHARMACOLOGY AND THERAPEUTICS

Dedication

This book is dedicated to my wife Tiffany, my sons James and Alexander and my stepson Nicholas. You have been my inspiration, motivation and refuge; I am eternally grateful.

> ...I will conclude with an hypothesis which – in its simplest message argues that biological communication consists of a complex meshwork of structures in which G proteins, surface receptors, the extracellular matrix, and the vast cytoskeletal network within cells are joined in a community of effort, for which my life and those of my colleagues is a metaphor.
>
> **Martin Rodbell 1994 Nobel Lecture**

Preface

As a beginning to this book, I would like to take a brief moment to explain the motivation and objectives of this text. The ultimate objective of the book is to provide a single but comprehensive source of information (for both personal and educational purposes) concerning signal transduction as it is understood in the present with the addition of a personal vision on receptor signaling.

The first chapter is purposefully basic and intended to provide both a general historical backdrop and description of basic pharmacological principles as a launching point to the more detailed descriptions of other topics provided by my co-authors. As the focus of the book is on common themes in receptor signaling across classes of receptors, there are natural redundancies apparent from chapter to chapter. With limited space, we have attempted to provide a comprehensive view of the field including understanding how we can model and assess signaling bias in the practical sense. I am motivated to put these topics together in order to provide a more complete view of how we envision receptor signaling and to put it in the context of evolution and a more universal view of receptor signaling. That is, despite clear and significant differences between classes of receptors, there are also universal principles to their function that have been selected and carried forward throughout evolution.

As this book is published, it occurs to me that the concepts of biased signaling are just coming to the popular forefront of the minds of the research world. However, in my mind, the contents of this book are a culmination of my thoughts and my journey in science.

There are several key moments in the development of these thoughts on signal transduction and the potential of multiple signaling outputs provided by activated receptors. The first being the observations made by my fellow graduate student, Tom Burris, in the late 1980s that dopamine could not only inhibit prolactin secretion from isolated anterior pituitary cells through Gi activation but also stimulate it through a Gs mechanism, and the discussions that followed within the lab that included Marc Freeman (my graduate advisor) and Béla Kanyicska. My exposure to research in nuclear receptors and the development of selective estrogen and progesterone receptor modulators at Wyeth also had a profound impact on my views since it was through this research that I came to the realization that cell background and associated proteins provided another level of regulation and possibilities for the development of better therapeutics. Lastly, the observation that naturally occurring ligands could also induce signaling bias in collaboration with Francisco López (on glycoprotein hormone receptors) and the development of synthetic biased agonists to the FSH and calcium-sensing receptors have rounded out this view.

In compiling this resource, I have sought out fellow authors who are well-respected experts in their domains and who have had significant impact on their research fields for the topics they provided. I would like to thank them for their commitment to this project and for the outstanding chapters they have written. It is my sincere hope that you, the reader, will find this book useful and compelling.

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Biased Signaling in Physiology, Pharmacology and Therapeutics is accompanied by a website featuring discussion questions, summaries, full color images and additional resources compiled by the authors. To access these companion resources, please visit http://booksite.elsevier.com/9780124114609.

About the Editor

Brian J. Arey received the Bachelor of Science degree in biology from Saint Louis University where as an undergraduate he performed research on estrogen and progesterone receptors and their interactions with chromatin. He then moved to Florida State University where he received both Master's and Doctorate degrees studying neuroendocrine physiology with Dr. Marc Freeman.

In 1992, his work in graduate school led to an National Institutes of Health (NIH) Postdoctoral Fellowship in the NIH Center for Reproductive Sciences at Northwestern University, where he studied the expression and signaling mechanisms of the mouse and rat prolactin receptors.

While at Wyeth in the mid-1990s, Dr. Arey collaborated to develop some of the first described allosteric agonists, antagonists and partial agonists to the follicle-stimulating hormone receptor (FSHR). As part of this research he was the first to demonstrate that the FSH receptor could activate multiple G-protein signaling pathways. In addition, he proposed the concepts of biased agonism/conformational dynamics as a natural physiological phenomenon in relation to glycoprotein hormone receptors.

Dr. Arey ultimately moved to Bristol-Myers Squibb where he and his colleagues developed allosteric modulators to a number of other receptors including novel allosteric modulators to the calcium-sensing receptor (CaSR). Throughout his tenure in pharmaceutical research, he has contributed to the discovery or development of multiple marketed medicines. Dr. Arey writes reviews and is requested to speak internationally on the topics of allosteric activation of GPCRs and the role of biased signaling.

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