

# Preface

Functional selectivity refers to the observation that different ligands acting at one subtype of receptor that couples to multiple signaling pathways can vary in their ability to activate the signaling pathways; that is, one drug can be an agonist at pathway A and an antagonist or partial agonist at pathway B, and another drug can have the reverse profile. As discussed by Bryan L. Roth in his introductory chapter, this is not a new notion, with evidence for functional selectivity accumulating over the past 20 years. During the 1990s, as molecular cloning of G protein-coupled receptors (GPCRs) facilitated the unequivocal demonstration that coupling of one type of receptor to multiple signaling pathways is a general characteristic of GPCRs, a number of investigators also demonstrated that ligands differed in their ability to activate those signaling pathways. In other words, the ligands were functionally selective.

During the late 1990s and the early part of this decade, Terry Kenakin and other investigators placed functional selectivity within a theoretical framework, sophisticated structural studies of GPCRs provided a mechanistic basis for the phenomenon by identifying ligand-specific and signaling pathway-specific receptor conformations, the concept of ligand-selective signaling was expanded to include other responses to receptor activation such as phosphorylation and internalization, and functionally selective ligands were identified for many more classes of receptors. The purpose of this book is to review that work.

This phenomenon has many names, including agonist-directed stimulus trafficking, ligand-biased signaling, and ligand-induced differential signaling. The authors and I debated the best name to use in this book, with Ligand-Induced Bias in Downstream Outcome (LIBIDO) being a brief front-runner, and eventually compromised on the use of *functional selectivity*, despite the concerns of some that it is too broad and could include both cell-specific and ligand-specific aspects of differential signaling. In spite of the cell-specific factors that influence selective responses to ligands, I sought to focus this book on the aspect of ligand-selective signaling that can best be controlled for drug development – the ability of ligands to stabilize receptor conformations with distinct functional properties.

The attentive reader will note that the authors are not in complete agreement concerning what functional selectivity is or what its significance is for the basic tenets of pharmacology, with some followers of Hume believing that there are no ligand-specific characteristics, that everything depends on the cellular context in which the

receptor is expressed, and, therefore, that there is no basis for ascribing any property such as intrinsic efficacy to a ligand. My own view is more Kantian; I believe that intrinsic efficacy is an invariant characteristic of a ligand–receptor pair that results from the receptor conformation(s) stabilized by that ligand, but that when referring to the intrinsic efficacy of a ligand we must also specify a particular functional response. Cell-specific factors have always been important because, for example, binding of isoproterenol to a  $\beta$ -adrenergic receptor will not stimulate cyclic AMP accumulation if the cell lacks  $G\alpha_s$  or adenylate cyclase, but whereas previously one would refer to isoproterenol as a full agonist at the  $\beta$ -adrenergic receptor despite its seeming lack of efficacy in cells lacking the necessary components, now it is also necessary to add “for stimulation of adenylate cyclase.” Despite the differences of opinion, the authors agreed not to dispose of the concept of intrinsic efficacy. (Some of the authors may be mouthing “yet” as they read the end of that sentence.)

This book is organized into two parts, with Part I containing six chapters that focus on theoretical or mechanistic aspects of functional selectivity and that cut across subfamilies of GPCRs, and Part II being composed of seven chapters that focus on subfamilies of therapeutically relevant receptors where there is considerable evidence of ligand functional selectivity. This format intentionally produces considerable overlap between the two parts, so that each chapter in one part collects information that is scattered throughout several chapters of the other part. Although, ideally, the reader would begin with the introductory chapter, my goal was to produce a book in which any of the chapters would be an appropriate point of entry into the topic.

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