A Pharmacology Primer: Theory, Applications, and Methods

Third Edition

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As always . . . for Debbie
... more ceterum censeo is perhaps necessary in order to rouse pharmacology from its sleep. The sleep is not a natural one since pharmacology, as judged by its past accomplishments, has no reason for being tired...

—Rudolph Buchheim (1820–1879)
I am indebted to GlaxoSmithKline Research and Development for support during the preparation of this book and for the means and scientific environment to make the science possible.

T.P.K., Research Triangle Park, NC
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It has been an interesting experience as an author and pharmacologist to see the changes that the discipline has experienced through the drug discovery process. While the definition of the human genome has undoubtedly marked pharmacology forever (and advanced it immeasurably), the more we learn, the more we are humbled by nature’s complexity. With the genome, knowing the road map is still a long way from completing the journey and recent experience seems to reinforce the idea that pharmacology must be used to understand integrated systems, not just the pieces they are made of.

This edition incorporates a new trend in drug discovery; namely the consideration of pharmacokinetics and ADME properties of drugs (absorption, distribution, metabolism, excretion) early in the process. As prospective new drugs are tested in more complex systems (with concomitantly more complex dependent variable values), the trend in screening is to test fewer compounds of higher (“druglike”) quality. Finally, this edition also hopefully fills a previous void whereby the ideas and concepts discussed can be applied to actual problems in pharmacological drug discovery in the form of questions with accompanying answers. The expanded version now spans pharmacology from consideration of the independent variable (drug concentration in the form of pharmacokinetics) to the dependent variable (system-independent measurement of drug activity). As with previous editions, the emphasis of this book is still on the chemist–biologist interface with special reference to the use of pharmacology by non-pharmacologists.

Terry Kenakin, Ph.D.
Research Triangle Park, NC, 2008
Preface to the Second Edition

With publication of the human genome has come an experiment in reductionism for drug discovery. With the evaluation of the number and quality of new drug treatments from this approach has come a re-evaluation of target-based versus systems-based strategies. Pharmacology, historically rooted in systems-based approaches and designed to give systems-independent measures of drug activity, is suitably poised to be a major, if not the major, tool in this new environment of drug discovery.

Compared to the first edition, this book now expands discussion of tools and ideas revolving around allosteric drug action. This is an increasingly therapeutically relevant subject in pharmacology as new drug screening utilizes cell function for discovery of new drug entities. In addition, discussion of system-based approaches, drug development (pharmacokinetics, therapeutics), sources of chemicals for new drugs, and elements of translational medicine have been added. As with the first edition, the emphasis of this volume is the gaining of understanding of pharmacology by the nonpharmacologist to the mutual enrichment of both.

Terry Kenakin, Ph.D.
Research Triangle Park, NC, 2006
If scientific disciplines can be said to go in and out of vogue, pharmacology is exemplary in this regard. The flourishing of receptor theory in the 1950s, the growth of biochemical binding technology in the 1970s, and the present resurgence of interest in defining cellular phenotypic sensitivity to drugs have been interspersed with troughs such as that brought on by the promise of the human genome and a belief that this genetic road map may make classical pharmacology redundant. The fallacy in this belief has been found in experimental data showing the importance of phenotype over genotype which underscores a common finding with roadmaps; They are not as good as a guide who knows the way. Pharmacology is now more relevant to the drug discovery process than ever as the genome furnishes a wealth of new targets to unravel. Biological science often advances at a rate defined by the technology of its tools; that is, scientists cannot see new things in old systems without new eyes. A veritable explosion in technology coupled with the great gift of molecular biology have definitely given pharmacologists new eyes to see.

This book initially began as a series of lectures at GlaxoSmithKline Research and Development on receptor pharmacology aimed at increasing the communication between pharmacologists and chemists. As these lectures developed it became evident that the concepts were useful to biologists not specifically trained in pharmacology. In return, the exchange between the chemists and biologists furnished new starting points from which to view the pharmacological concepts. It is hoped that this book will somewhat fill what could be a gap in present biological sciences, namely the study of dose-response relationships and how cells react to molecules.

Terry P. Kenakin, Ph.D.
Research Triangle Park, 2003