



CORE PRINCIPLES OF PHARMACOLOGY: A SELF-STUDY GUIDE FOR GRADUATE STUDENTS

Rationale for this document. Students admitted to the M.Sc. and Ph.D. programs in Pharmacology at the University of Toronto come from diverse academic backgrounds. While all our incoming graduate students normally have solid background preparation in biochemistry and physiology, the amount of exposure to pharmacology that students have had at the undergraduate level varies considerably. Regardless of academic background, it is essential that ALL Pharmacology graduate students achieve a solid understanding of the core principles of pharmacology. This document has been prepared to assist students with achieving this goal.

How to make use of this document. During the first year in the Pharmacology graduate program, normally while taking the Graduate Pharmacology PCL1002Y course, students should conduct a self-assessment of their mastery of the core principles of pharmacology listed in this document. During the first year and on an on-going basis throughout the program, students should undertake self-directed study as needed to achieve a solid understanding of these principles. The resources outlined in this document should help students accomplish this essential task.

How mastery of the principles will be evaluated. A primary opportunity to evaluate students' knowledge of pharmacological principles arises in the Graduate Pharmacology PCL1002Y course. Students are expected to display a solid understanding of these principles in the oral presentations of research paper critiques, in the grant-writing exercise, and especially on the exams in this course. Each exam in PCL1002Y will test knowledge of course content as well as basic principles. Beyond this course, there are multiple opportunities for the evaluation of students' mastery of the core principles throughout the M.Sc. and Ph.D. programs.

Resources to be used in concert with this document. To assist you with mastering the basic principles of our discipline, you are also welcome (although not required) to make use of various courses offered at the undergraduate level. The courses that are particularly relevant with respect to basic principles of pharmacology and toxicology are the following:

- PCL201H: Introduction to Pharmacology and Pharmacokinetic Principles
- PCL302H: Pharmacodynamic Principles
- PCL362H: Introductory Toxicology
- PCL469H/470H: Systems Pharmacology I & II (graduate equivalent is PCL1400H/1500H)

If you wish to attend lectures in these courses and/or access the on-line course materials, please contact the relevant course coordinators for permission.

The catalogue of core principles below includes a listing of relevant chapters from our currently recommended textbook, the 15th edition of Katzung's "Basic & Clinical Pharmacology". Studying these chapters will assist you in mastering the material. This book is generally available in the University of Toronto Bookstore and in the University of Toronto Library system (books and/or electronic online resources). It can also be purchased from several online retailers. The full bibliographic information for this book is as follows:

- Basic & Clinical Pharmacology, 15th Edition. Edited by BG Katzung & TW Vanderah. McGraw-Hill, New York (2021). ISBN: 978-1-260-45231-0

1. Principles of Pharmacokinetics & Toxicokinetics

(a) Absorption [Chapters 1 & 3]

- routes of drug administration and factors that influence choice
- mechanisms of drug movement across biological membranes and factors that influence drug solubility and membrane permeability
- factors that influence drug bioavailability

(b) Distribution [Chapters 1 & 3]

- the volume of distribution and its relationship to physiological body volumes
- factors influencing drug binding to plasma proteins and tissue reservoirs

(c) Biotransformation / Metabolism [Chapter 4]

- relationship of drug metabolism to excretion of drugs and termination of drug effects
- metabolism as a determinant of bioavailability: the first-pass effect
- pathways of drug metabolism: phase I (oxidation, reduction, hydrolysis) and phase II (glucuronidation, sulfation, acetylation, methylation, glutathione conjugation)
- enzyme multiplicity and broad substrate selectivity of drug-metabolizing enzymes, with the cytochromes P450 as a prime example
- role of drug metabolism in adverse drug reactions: factors that control the balance between drug bioactivation and detoxification
- drug-metabolizing enzymes as key sites for drug-drug interactions: inhibition and induction of drug metabolism

(d) Excretion [Chapters 1 & 3]

- major sites of drug elimination: liver and biliary excretion, kidney, lungs
- factors influencing hepatic and renal clearance of drugs

(e) Mathematical Analysis of the Time-Course of Drug Action [Chapter 3]

- relationship between dose, plasma drug concentration and effect
- plasma concentration-time curves following oral drug administration: absorption, distribution, and elimination phases
- definitions and mathematical relationships among the following terms: volume of distribution, half-life, clearance, bioavailability, area under the concentration-time curve
- pseudo-zero-order and first-order kinetics of drug elimination
- rational dosing to achieve a target steady-state drug concentration: loading dose and maintenance dose

2. Principles of Pharmacodynamics & Toxicodynamics

(a) Quantitation of Drug-Receptor Interactions [Chapters 1 & 2]

- nature and properties of biological drug receptors
- definitions and mathematical relationships among the following terms: equilibrium dissociation constant, total number of specific receptor binding sites
- receptor saturation: the simple hyperbolic relationship between drug concentration and the concentration of drug-receptor complex, and the mathematical analysis that is analogous to the Michaelis-Menten treatment of enzyme-substrate interactions
- chemical determinants of selectivity in drug-receptor interactions

(b) Quantitative Relationship Between Receptor Occupancy and Effect [Chapters 1 & 2]

- the relationship between drug concentration or dose and the biological effect, as defined by the log-dose-response curve
- analysis of log-dose-response curves to gain understanding of the following drug properties: median effective concentration or dose, median lethal concentration or dose, therapeutic index,

potency, efficacy

- classification of drugs based on their effects on receptors: full agonist, partial agonist, inverse agonist, antagonist (competitive, non-competitive, etc.)

(c) Major Drug Targets as Defined by Molecular Class [Chapters 1 & 2]

- enzymes (e.g., dihydrofolate reductase) and structural proteins (e.g., tubulin) as drug targets
- G protein-coupled receptors as drug targets: structure of G protein-coupled receptors, their signal transduction systems, and major categories of intracellular second messengers, e.g., cAMP, calcium, phosphoinositides
- receptor tyrosine kinases as drug targets: structure and mechanisms of regulation of receptor tyrosine kinases, e.g., epidermal growth factor receptor
- cytokine receptors as drug targets: structure and mechanisms of regulation of cytokine receptors using a separate tyrosine kinase not intrinsic to the receptor, e.g., growth hormone receptor
- ion channels as drug targets: structure and mechanisms of regulation of ligand-gated and voltage-gated ion channels
- nuclear receptor transcription factors as drug targets: structure and mechanisms of regulation of the steroid receptor superfamily, e.g., glucocorticoid receptor
- transporters as drug targets and determinants of drug actions: neurotransmitter transporters, ATP-binding cassette transporters
- regulation of receptors: receptor desensitization, receptor internalization and trafficking, receptor down-regulation

3. Factors Contributing to Variability in Drug Response

(a) Pharmacogenetics & Pharmacogenomics [Chapter 5]

- genetic basis for differences among humans in drug therapeutic response and/or toxicity; role in individualization of drug and dose selection
- genotype vs. phenotype
- genetic polymorphisms in drug-metabolizing enzymes (e.g. CYP2D6 and TPMT) and drug targets (e.g. VKORC1)

(b) Drug Interactions [Chapter 67]

- types and examples of interactions by mechanism: pharmacokinetic, pharmacodynamic
- types and examples of interactions by outcome: additivity, synergy, antagonism
- drug interactions related to induction or inhibition of drug metabolism
- importance of drug-food interactions, e.g., P450 inhibition by grapefruit juice

(c) Other Factors Affecting Therapeutic Outcome

- Age: the special cases of perinatal/pediatric and geriatric pharmacology [Chapters 59 & 60]
- Tolerance: a decreased response to the effects of a drug, necessitating larger doses to achieve the same effect; its importance to understanding drugs of abuse [Chapter 32]

4. Adverse Drug Reactions and Toxicology [Chapters 2 and 56]

- adverse drug reactions that are extensions of the principal pharmacological action of the drug
- adverse drug reactions that are idiosyncratic in nature, i.e., relatively rare, unrelated to the principal action of the drug, difficult to predict; role of host susceptibility factors, immune system, etc.
- beneficial and toxic drug effects mediated by the same or different receptors
- basic concepts relevant to occupational and environmental toxicology: acceptable daily intake, hazard, risk, acute vs. chronic exposure, bioaccumulation and biomagnification, endocrine disruption
- mechanisms of chemical teratogenesis [Chapter 59]

5. *Drug Development and Regulation* [Chapter 1]

- approaches for the discovery and development of new drugs
 - preclinical testing of new drugs: in vitro and in vivo animal studies required to bring a new chemical entity to the stage of clinical investigation
 - clinical trials: the phases of clinical testing of new drugs; factors to consider in the design of clinical trials; ethical issues
 - post-marketing surveillance of drugs; adverse drug reaction reporting
 - drug regulatory systems with the FDA in the United States as an example
 - sources of unbiased information about the clinical uses of drugs, e.g., “The Medical Letter on Drugs and Therapeutics”, etc.
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David S. Riddick, Ph.D.
PCL1002Y Course Coordinator
Department of Pharmacology & Toxicology
University of Toronto

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