



Stanford - South Africa

*Biomedical Informatics Program*



# Pharmacology: Basic Principles

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# Different types of drugs

- Oral (Most common)
  - Pills & Coated pills (drugs in solid base)
  - Capsules (powder in digestible container)
- Intravenous
  - Mostly for compounds that can not tolerate digestive system (e.g. Vancomycin)
- Intramuscular
  - For slow release and uptake (e.g. progesterone)
- Subcutaneous
  - For quick absorption (e.g. insulin)



# Lipinski's Rules

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Christopher Lipinski created rules to predict which drugs would fail because of poor pharmacokinetics.

- Molecular mass > 500 Da
- High lipophilicity
- More than 5 hydrogen bond donors
- More than 10 hydrogen bond acceptors

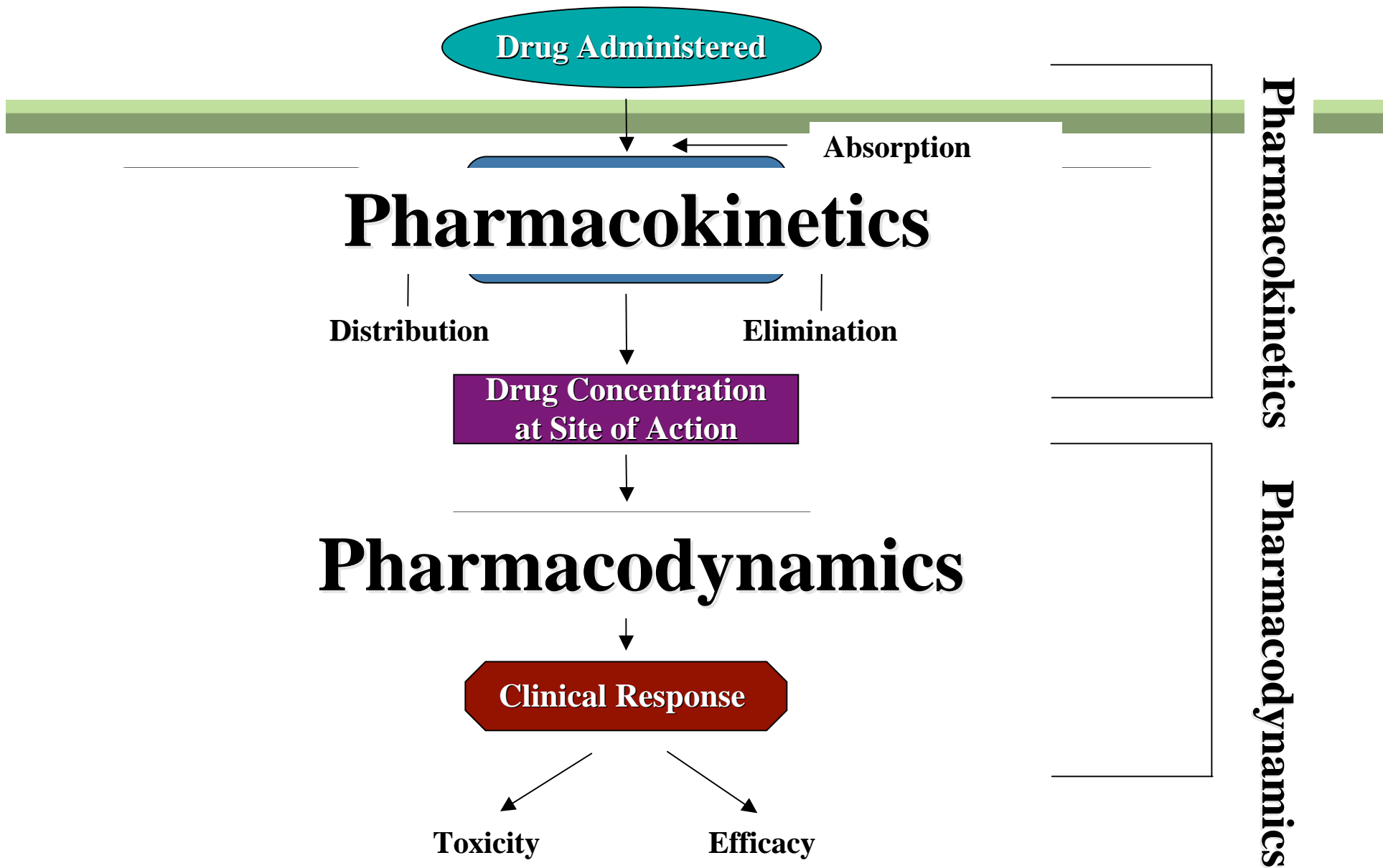


# Two key concepts

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- Pharmacokinetics: how a drug gets in and out of the body. Kinetics = movement of the drug.
- Pharmacodynamics: how the drug acts on the body to produce good effects (as well as bad effects).





# Pharmacokinetics: ADME

- **A**bsorption--passive, active, or cotransport?
- **D**istribution--fat or water soluble?
- **M**etabolism
  - Phase I oxidation/reduction
  - Phase II conjugation (methylation, sulfation, acetylation, glucuronidation)
- **E**limination--renal excretion to urine, liver excretion to bowel



# Pharmacodynamics: target

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- Target = the place in the cell that the drug targets for its effect
- Most common target classes:
  - G-protein coupled receptors
  - Large family of receptors (1-3% of genome) that detect signal, and start intracellular cascade in response.
  - 160 receptors with known ligand
  - 200+ receptors with unknown ligands = OPPORTUNITY



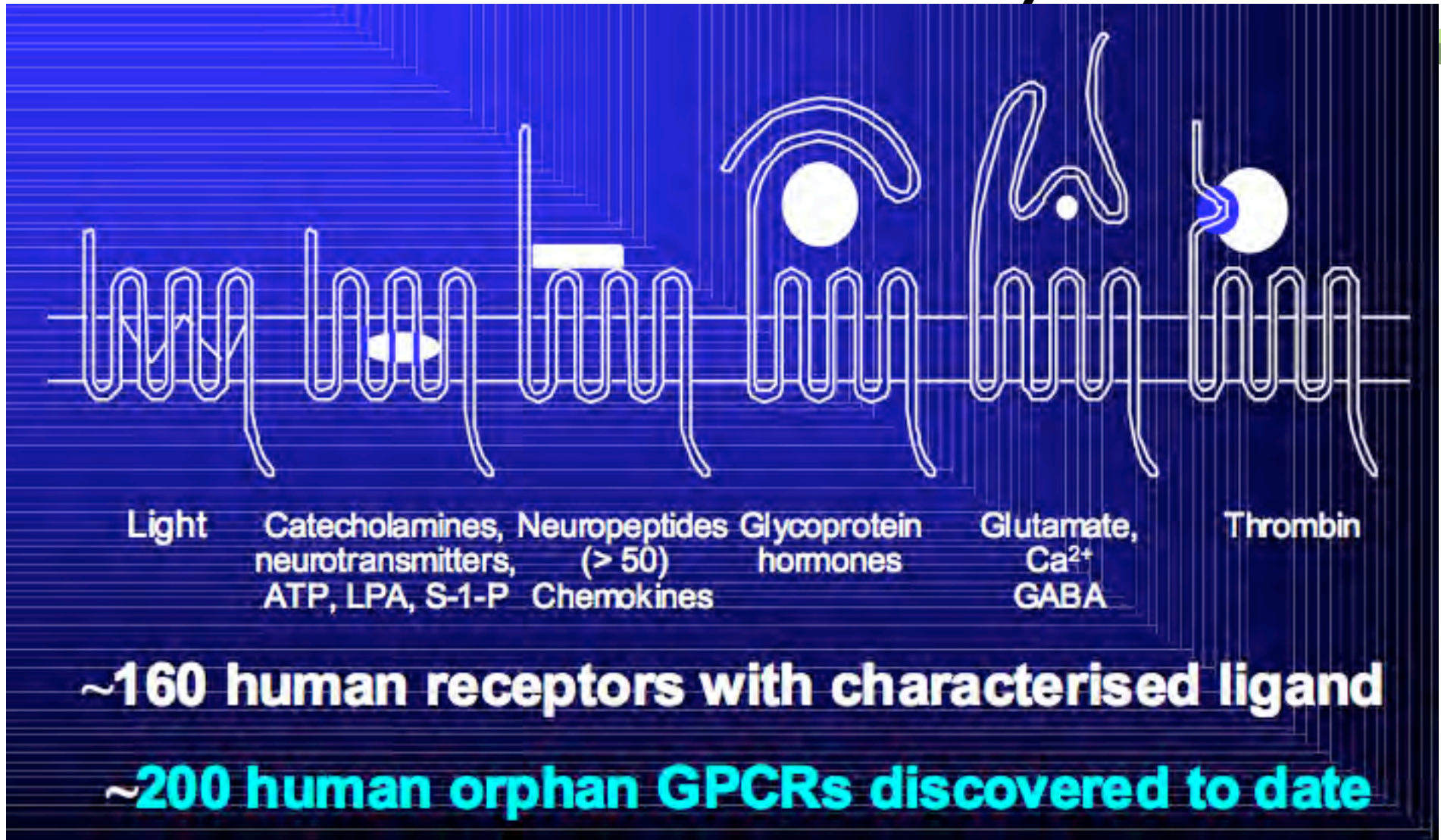
# Top Drug Targets (1997)

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- G-protein coupled receptors
- Enzymes (non-protease)
- Ion channels
- Non-human ribosomes
- Biotherapeutics
- Proteases
- Symporters
- Pumps



# GPCR Diversity



# Types of interactions with target

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- Competitive inhibition
  - Competes with natural compound to bind target
- Noncompetitive inhibition
  - Binds target independently from natural compounds
- Activation
  - Competitive
  - Noncompetitive



# Measuring pharmacodynamics

Can measure the action of a drug in many ways:

Molecular assays (e.g. drug binding, target function)

Cellular assays (cellular changes, e.g. expression)

Organ-based assays (e.g. liver cell response)

Organism-based (e.g. clinical measures, e.g. desired effect of drug)



# Pharmacogenes

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Now, we can define pharmacogenes more precisely:


Genes that are involved in either the PK or PD of a drug = pharmacogenes











































## Legend

Φ phenotype data available

 genotype data available

 literature annotations available

## Literature Annotations

Related Genes	Relationship 	Details
   <a href="#">ABCB1</a>	FAGN	
   <a href="#">ABCC1</a>	FAGN	
   <a href="#">ABCG2</a>	FAGN	
 <a href="#">BCHE</a>	FA	
   <a href="#">CES1</a>	FA	
   <a href="#">CES2</a>	FA	
   <a href="#">CYP3A4</a>	PD PK FAGN	
   <a href="#">CYP3A5</a>	PK FA	
   <a href="#">UGT1A1</a>	COPD PK FAGN	
 <a href="#">UGT1A7</a>	FAGN	
  <a href="#">UGT1A9</a>	FAGN	



# Defining P-etics vs. P-omics

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- Pharmacogenetics = study of individual gene-drug interactions, usually the gene that has the dominant effect on a drug response. (SIMPLE relationship)
- Pharmacogenomics = study of the full set of PK/PD genes, often using high-throughput data (sequencing, expression, proteomics) (COMPLEX interactions)



# Informatics Challenge in PGx

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- Standards for data representation & exchange
  - Genotype
  - Phenotype
  - High throughput data
- Analysis of literature
  - Find pgx papers
  - Extract gene-drug interactions



# Informatics challenges II

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- Integration of data from multiple sources
  - Gene sequence, protein sequence
  - SNP databases
  - Drug info databases
- Representation and manipulation of pathways
  - PK pathways
  - PD pathways



# Informatics challenges III

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- Standard terminologies for PGx
  - Genes
  - Drugs
  - Diseases
  - Symptoms (Adverse events)
- Machine learning for associating genotypes to phenotypes



# Informatics challenges IV

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- Creating databases that have adequate security and privacy mechanisms
- Information systems for point of care delivery

