PHARMACOKINETICS (ADME)

Lecture – 2

Second Semester

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Course Description

This course introduces the fundamental principles of pharmacology, focusing on:

- Drug classification systems
- Mechanisms of drug action
- Pharmacokinetics (ADME)
- Pharmacodynamics
- Drug–drug interactions
- Toxicology and drug safety

Week	Topic
1	Introduction to Pharmacology
2	Pharmacokinetics (ADME)
3	Pharmacodynamics
4	Steroid & Non-Steroid Drugs
5	Nervous System Pharmacology
6	Cardiovascular Pharmacology
7	Antimicrobial Agents
8	Endocrine & Metabolic Drugs
9	Hematology & Chemotherapy
10	General Toxicology
11	Clinical Toxicology & Drug Safety
12	Student Presentations & Review

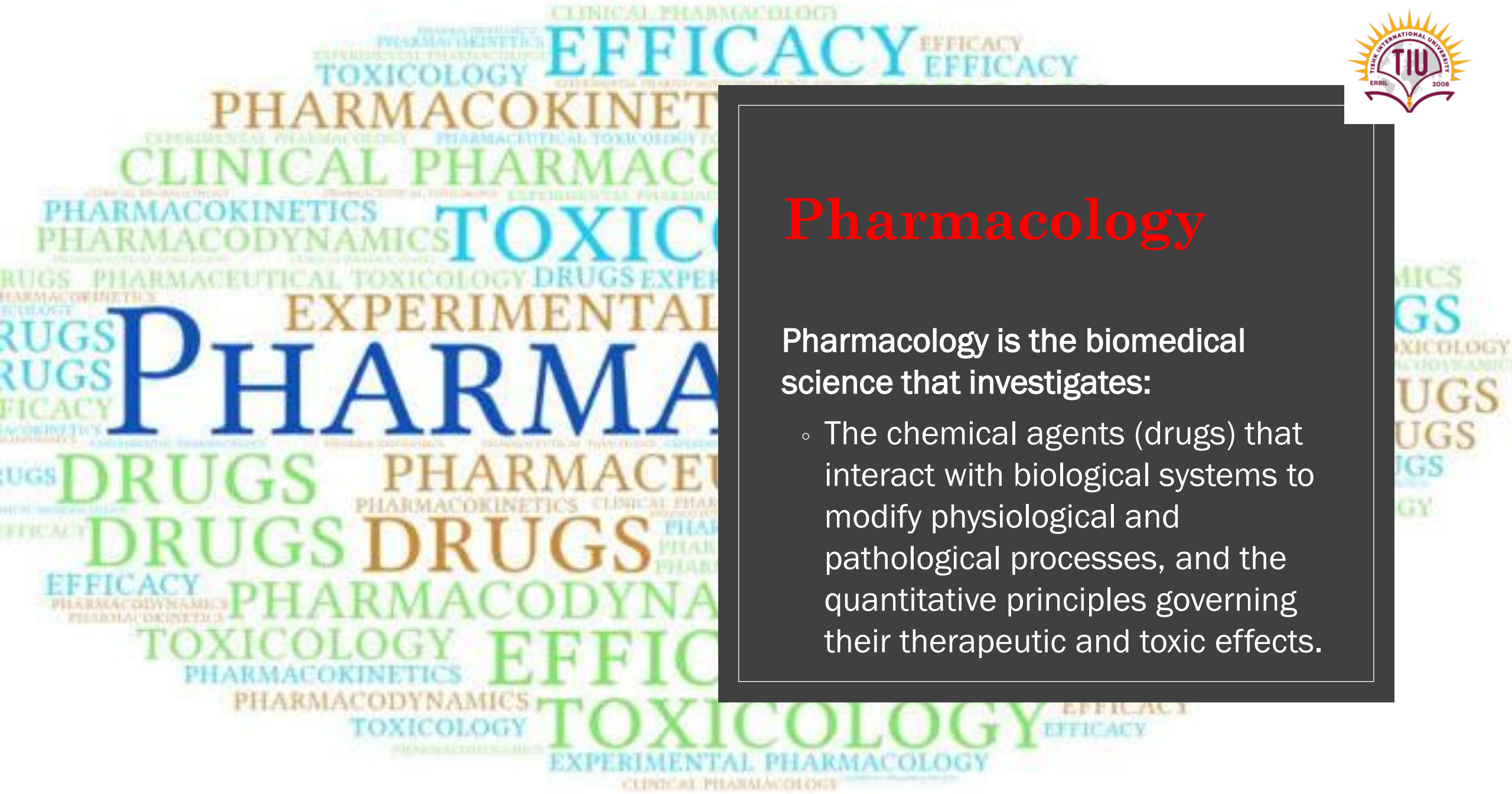
COURSE SYLLABUS

Outline

- Pharmacology
- Introduction to pharmacokinetics
- Detecting drugs & their metabolites
- Toxicology testing in clinical trials

Learning Objectives

- Outline the processes studied in pharmacokinetics.
- Describe how blood & urine test results determine the absorption & elimination rates.
- Establish the utility of screening for recreational drug metabolites in clinical trials.
- Outline how LCMS & GCMS work.



Pharmacology

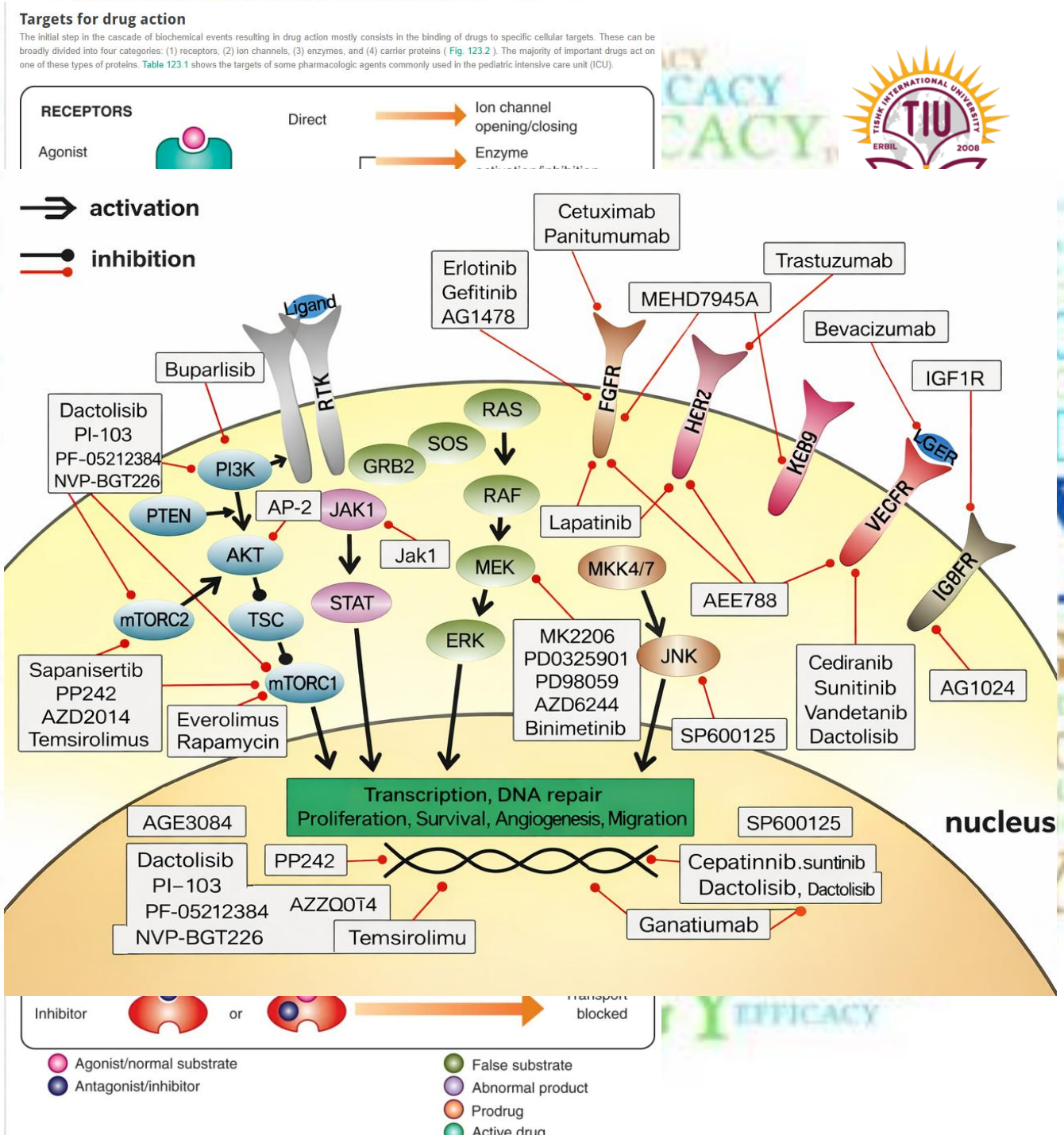
Pharmacology is the biomedical science that investigates:

- The chemical agents (drugs) that interact with biological systems to modify physiological and pathological processes, and the quantitative principles governing their therapeutic and toxic effects.

Pharmacology

Pharmacology examines:

- Molecular targets such as receptors, enzymes, ion channels, and transporters
- Signal-transduction pathways activated or inhibited by drugs
- Concentration–time relationships in plasma and tissues
- Dose–response behavior and therapeutic windows
- Mechanisms of toxicity, resistance, and adverse reactions
- Genetic and disease-related variability in drug response



Core Components of Pharmacology

Pharmacology has two main pillars:

- Pharmacokinetics (PK): What the body does to the drug → absorption, distribution, metabolism, excretion
- Pharmacodynamics (PD): What the drug does to the body → receptors, mechanisms, effects, toxicity

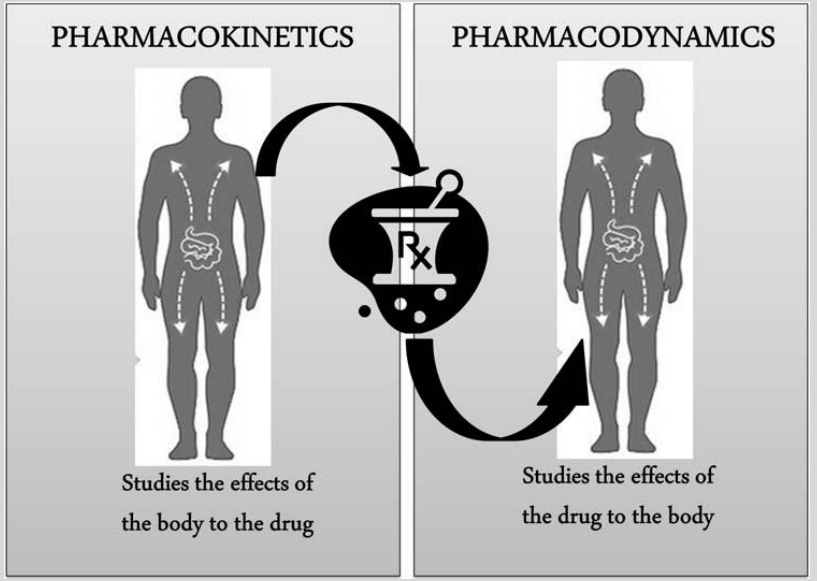
Pharmacokinetics (PK) & Pharmacodynamics (PD)

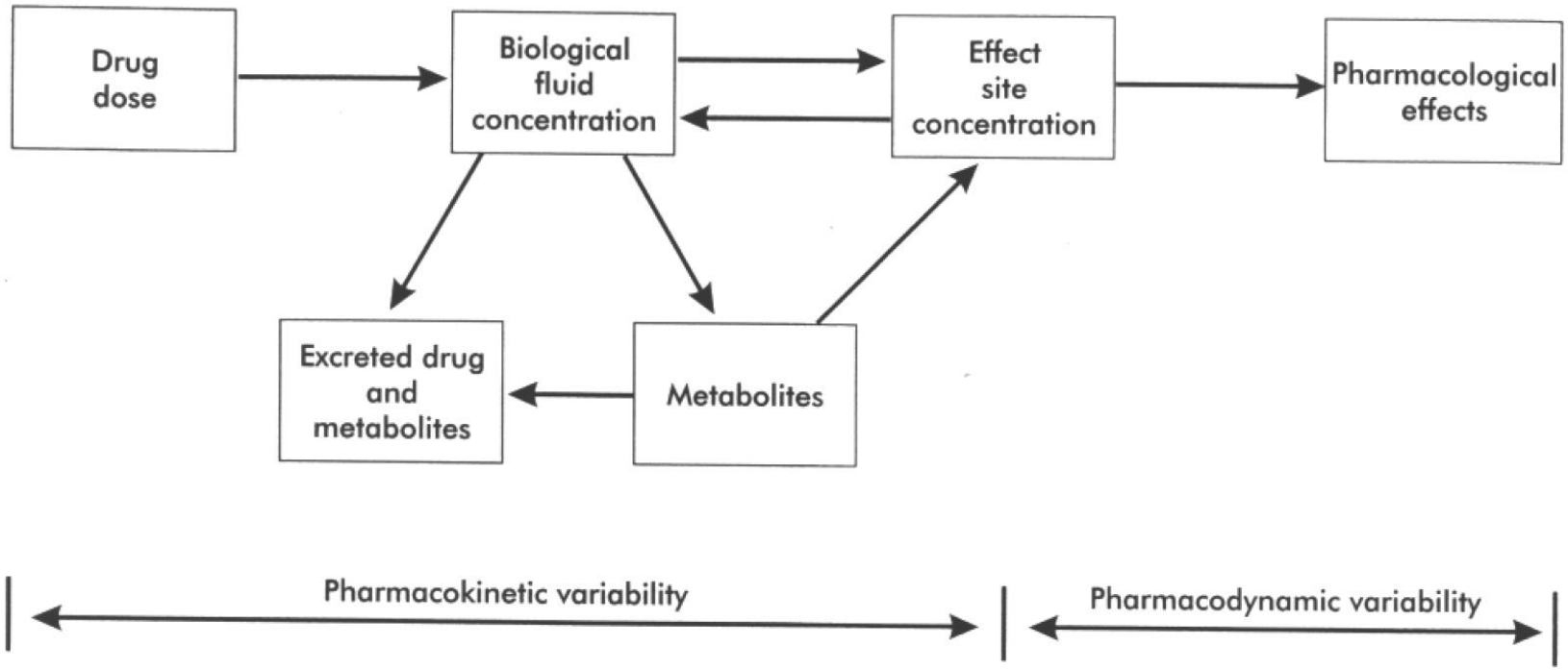
PK is what the body does to the drug (ADME)

- absorption
- distribution
- metabolism
- excretion

PD is what the drug does to the body

- molecular response
- biochemical effect
- physiological impact

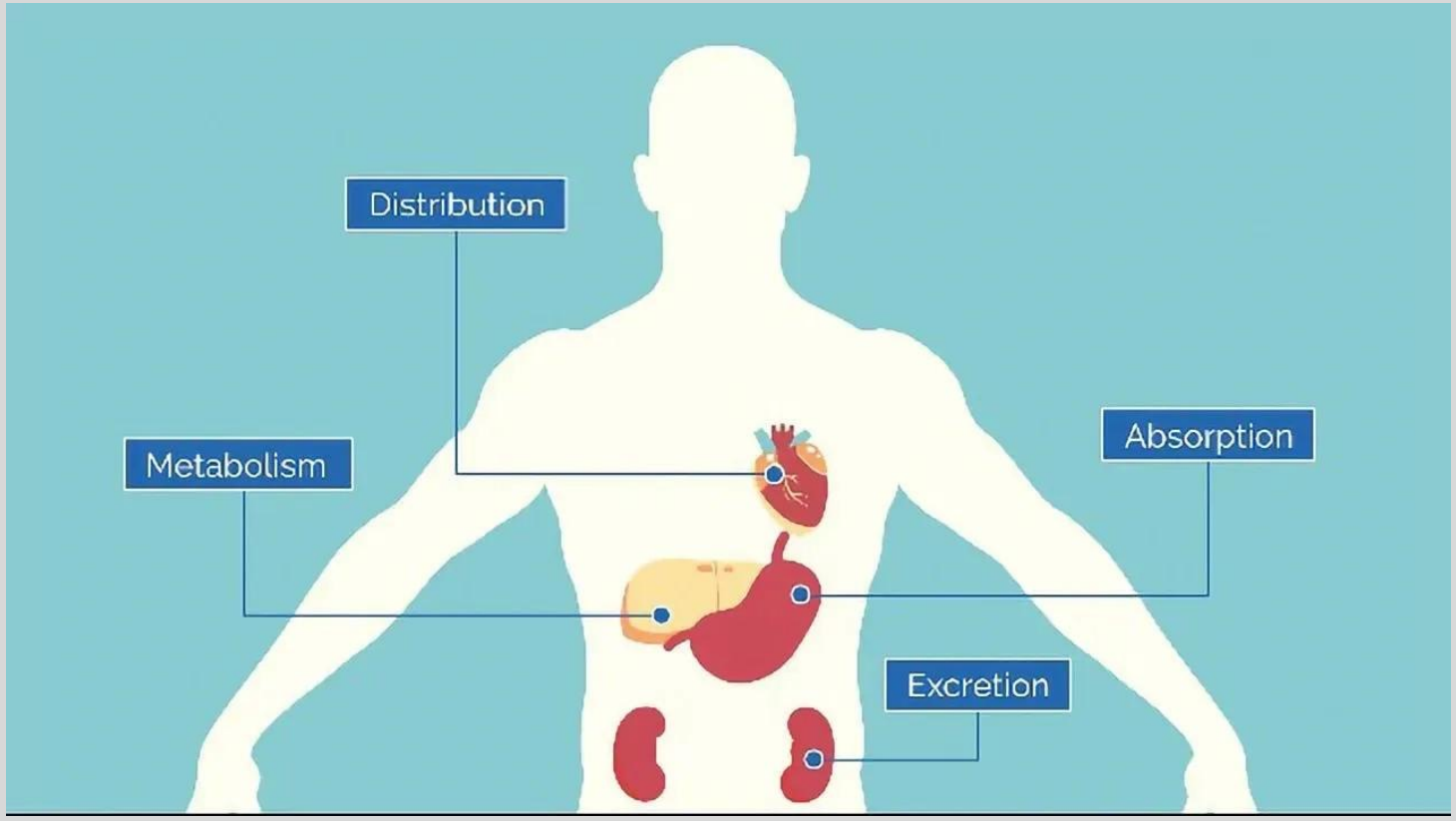




Pharmacokinetics (PK) & Pharmacodynamics (PD)

Pharmacokinetics

- Absorption
- Distribution
- Metabolism
- Excretion



Pharmacokinetics

Absorption

- depends on the route of administration

Distribution

- depends on solubility: water-soluble vs lipid-soluble
- depends on binding to blood proteins (albumin)

Metabolism

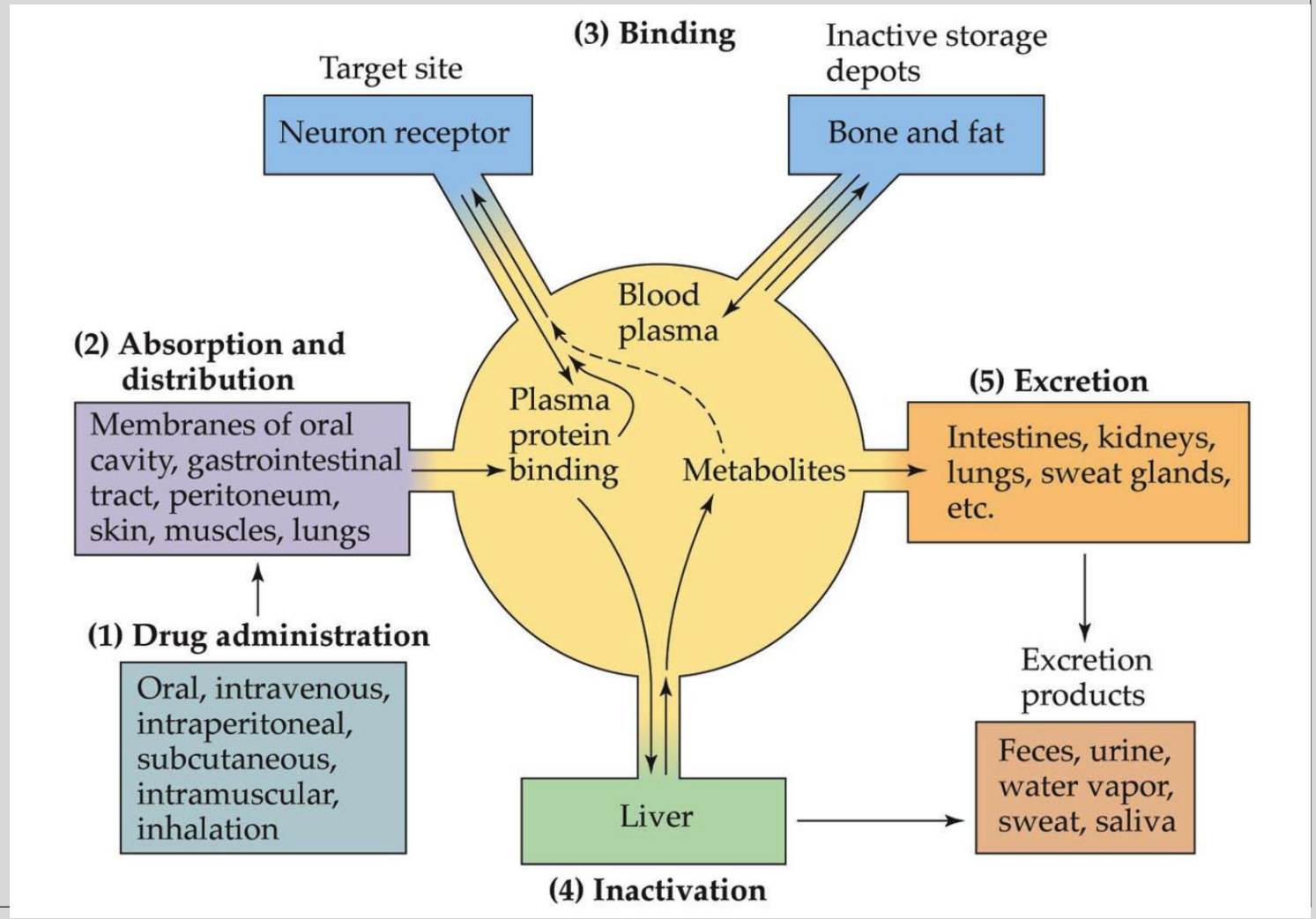
- mostly in the liver

Elimination

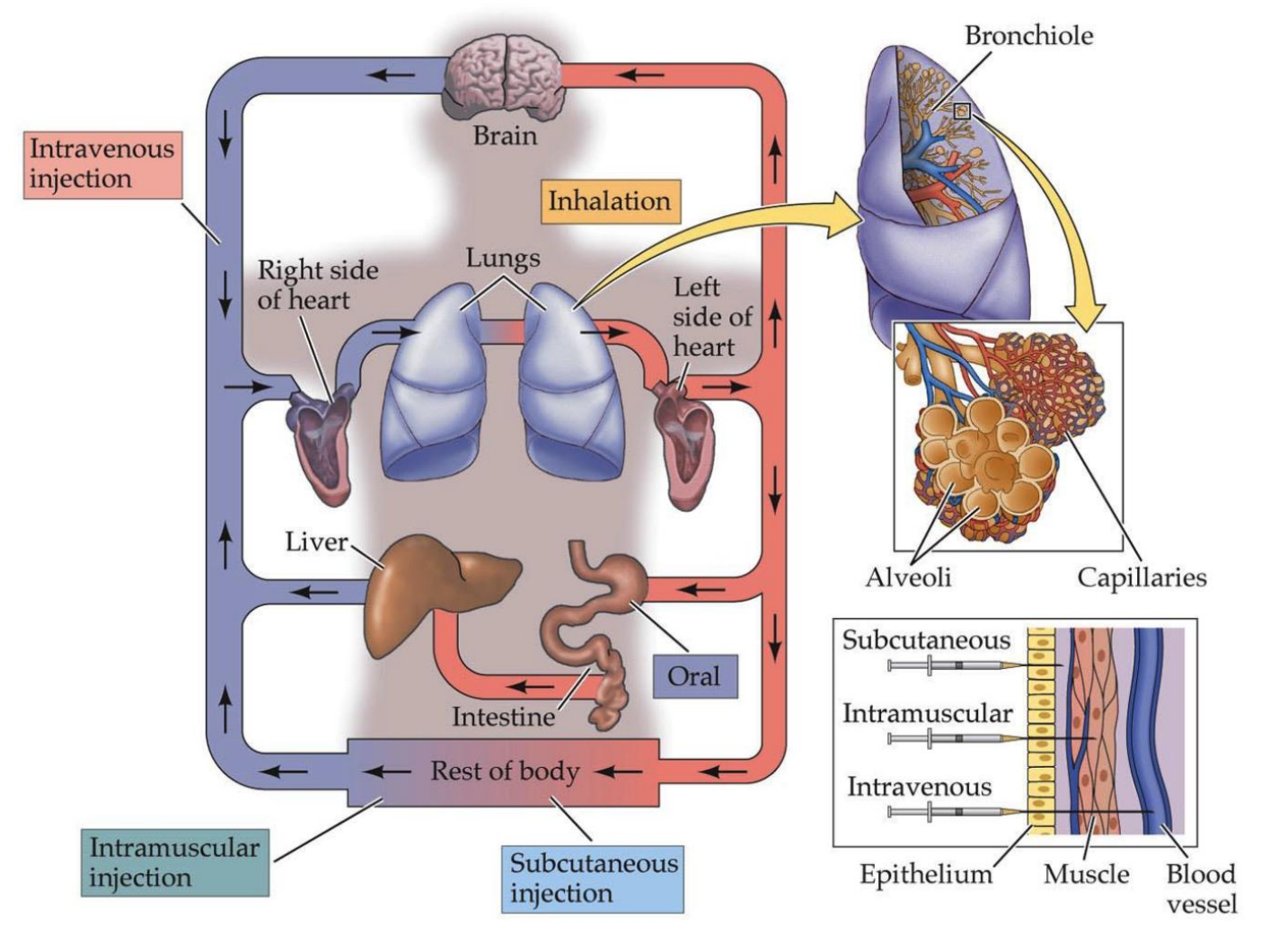
- excretion into urine
- elimination through feces, sweat, exhalation, saliva
- inactivation by enzymes in the liver

Drug Movement in the Body

- Most drugs move around the body through the blood
- Only a small percentage of drug molecules reach the target
- Some molecules become inactivated, deposited or excreted instead of reaching the target



Routes of Administration



SYSTEMIC

- Enteral: oral, sublingual, rectal
- Parenteral: inhalation, injection, transdermal

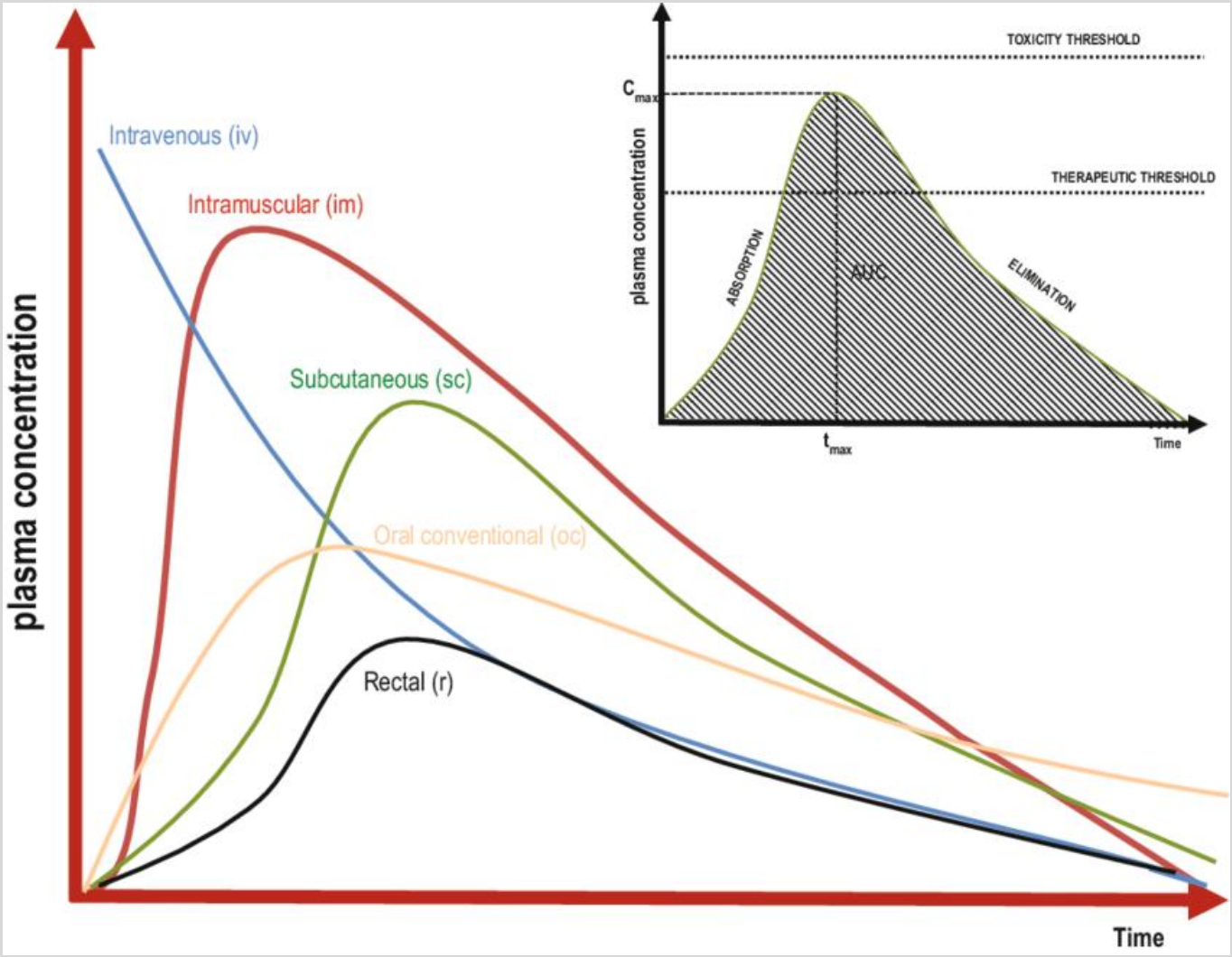
LOCAL

- topical,
- deeper tissues or organs,
- intraarterial (mostly to the brain)

Route of Administration vs Bioavailability

Route of administration determines:

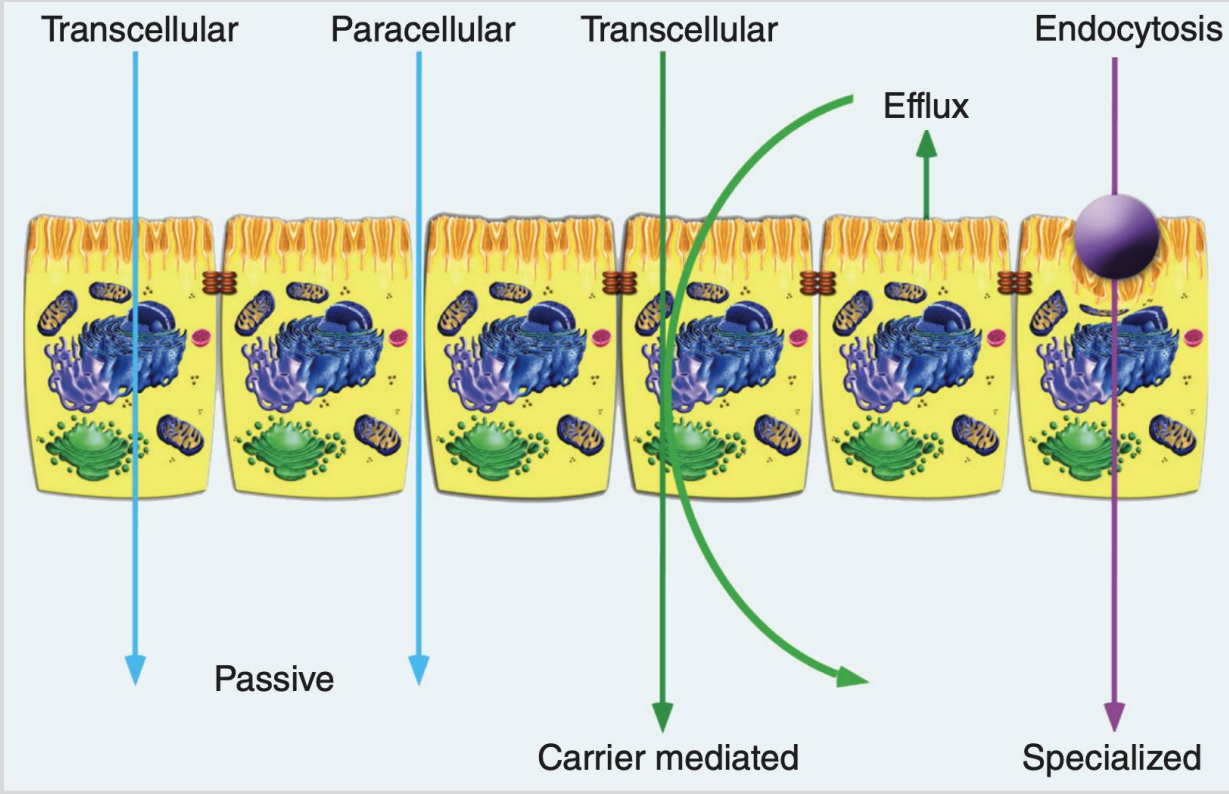
- bioavailability
- time of max concentration
- time of full elimination



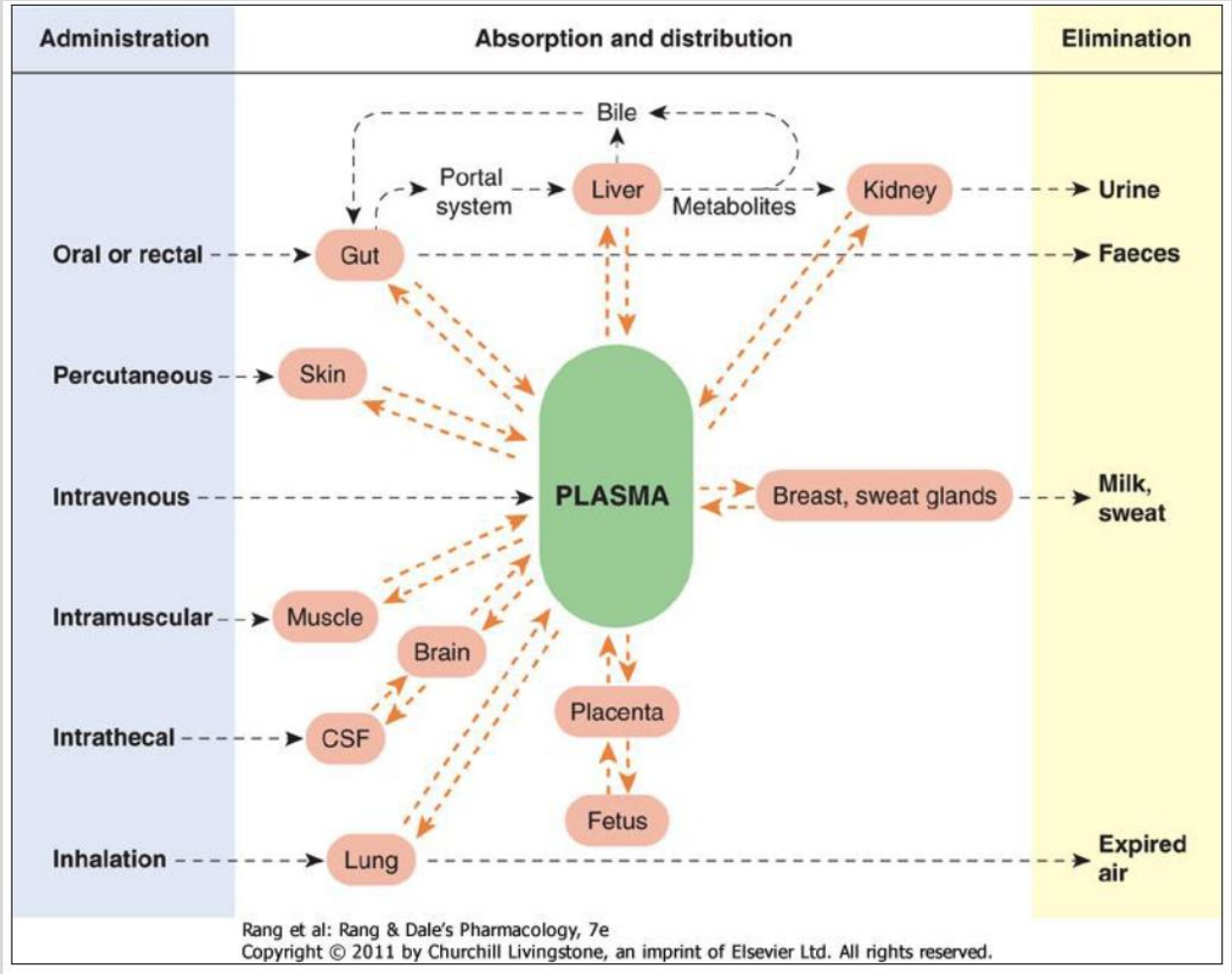
Absorption

Absorption is the movement of drugs from the administration site into circulation, which requires a movement across multiple cell membranes & cell layers.

- **Transcellular**
  - through the cell
  - passive or via carriers
- **Endocytosis**
  - via forming vesicles
- **Paracellular**
  - between the cells



Systemic Drug Administration & Absorption



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Distribution

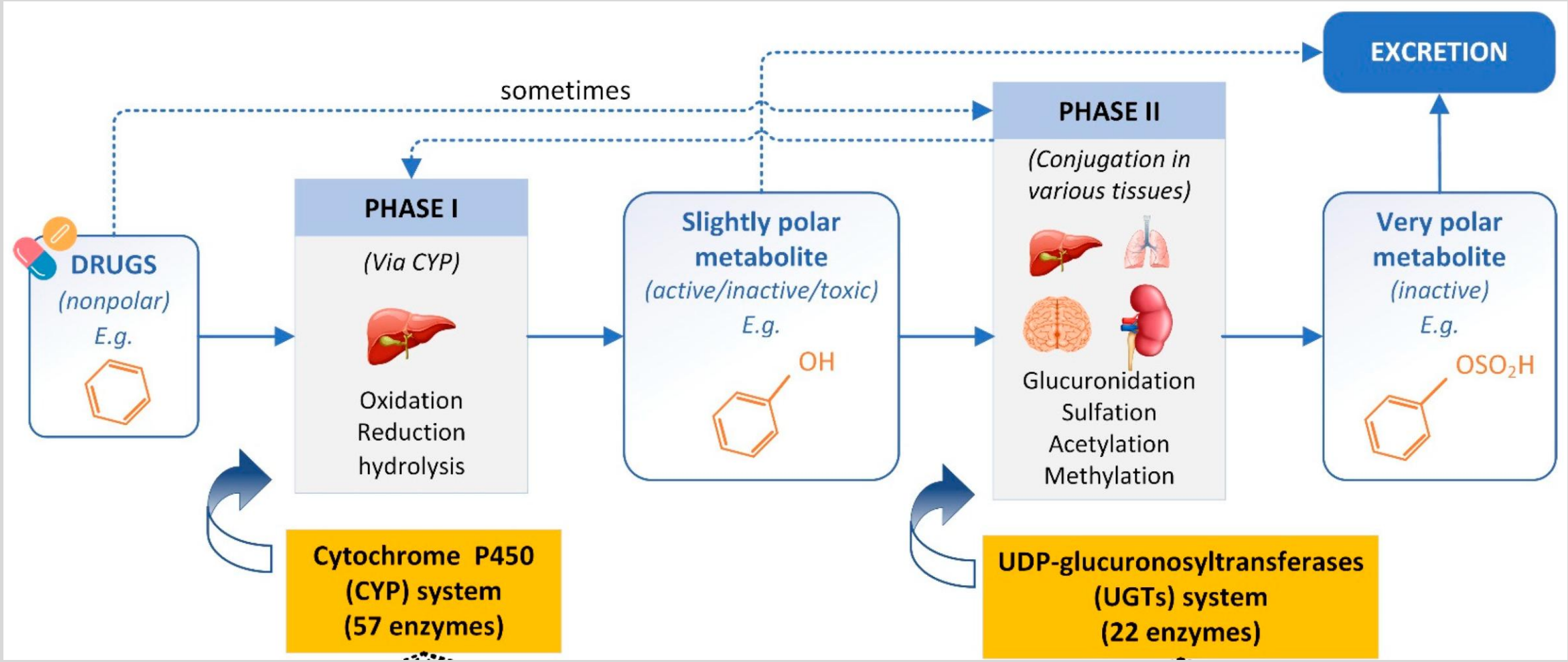
Drug distribution rates depend upon:

- Chemical structure of the drug
- Blood flow rates
- The efficiency of transport across the membrane
- Binding of the drug to proteins in the blood
- Rates of elimination processes

Metabolism

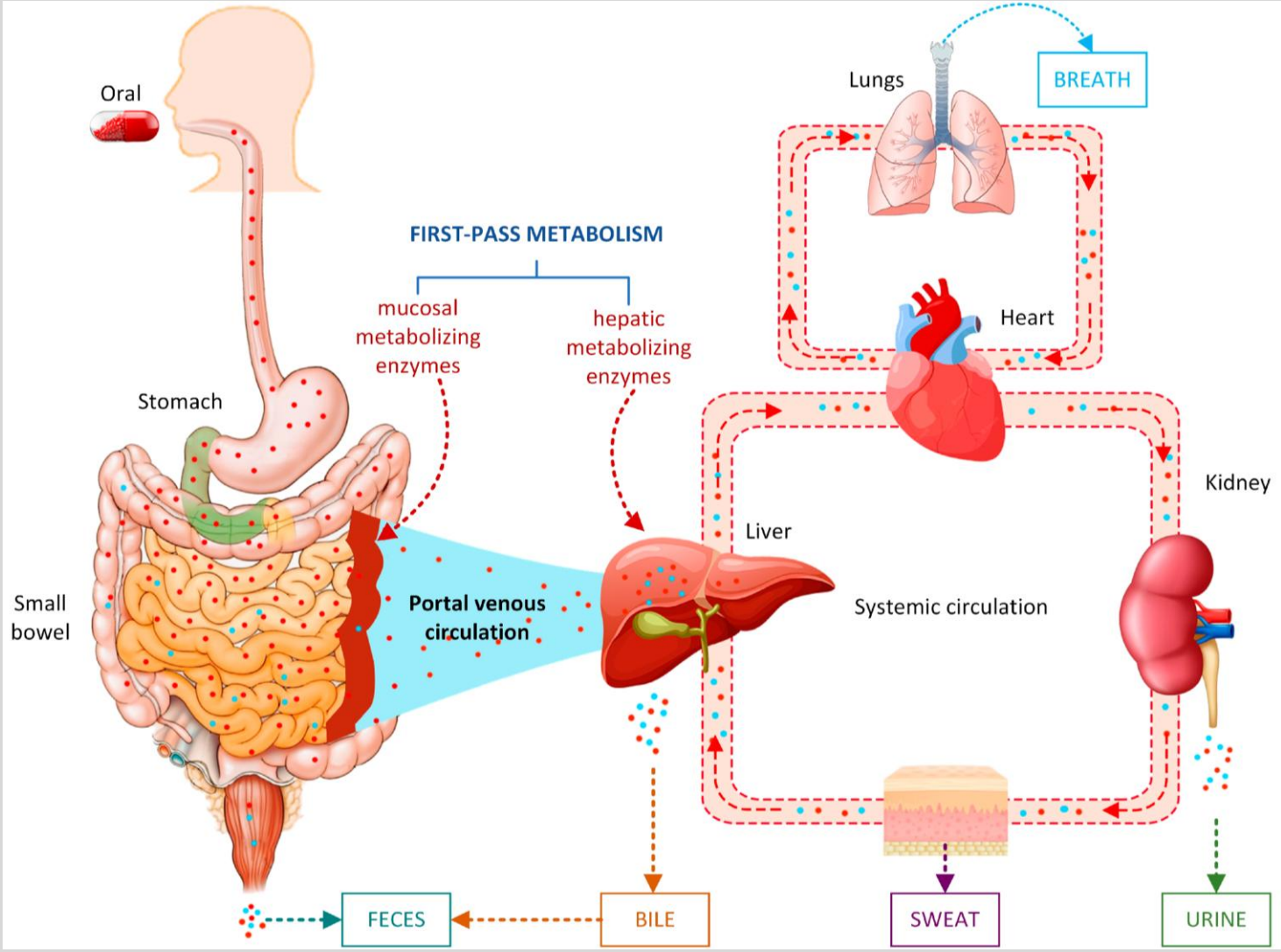
- Metabolism converts drugs into metabolites that can be easily eliminated.
- Metabolites can differ greatly from the original drug's physical and pharmacological characteristics.
- During metabolism, lipid-soluble (= non-polar) drugs become converted into more water-soluble metabolites. Water-soluble (= polar drugs) can be eliminated through the kidney system or bile.
- Non-polar drugs are often deposited in the fat tissues (bioaccumulation).
- The rate of metabolism dictates the length and strength of a drug's pharmacologic effect.

Metabolism


EXCRETION
sometimes
PHASE II
(Conjugation in various tissues)
PHASE I
(Via CYP)
DRUGS
(nonpolar)
E.g.
Oxidation
Reduction
hydrolysis
Slightly polar metabolite
(active/inactive/toxic)
E.g.
OH
Glucuronidation
Sulfation
Acetylation
Methylation
Very polar metabolite
(inactive)
E.g.
OSO_2H
Cytochrome P450 (CYP) system (57 enzymes)
UDP-glucuronosyltransferases (UGTs) system (22 enzymes)

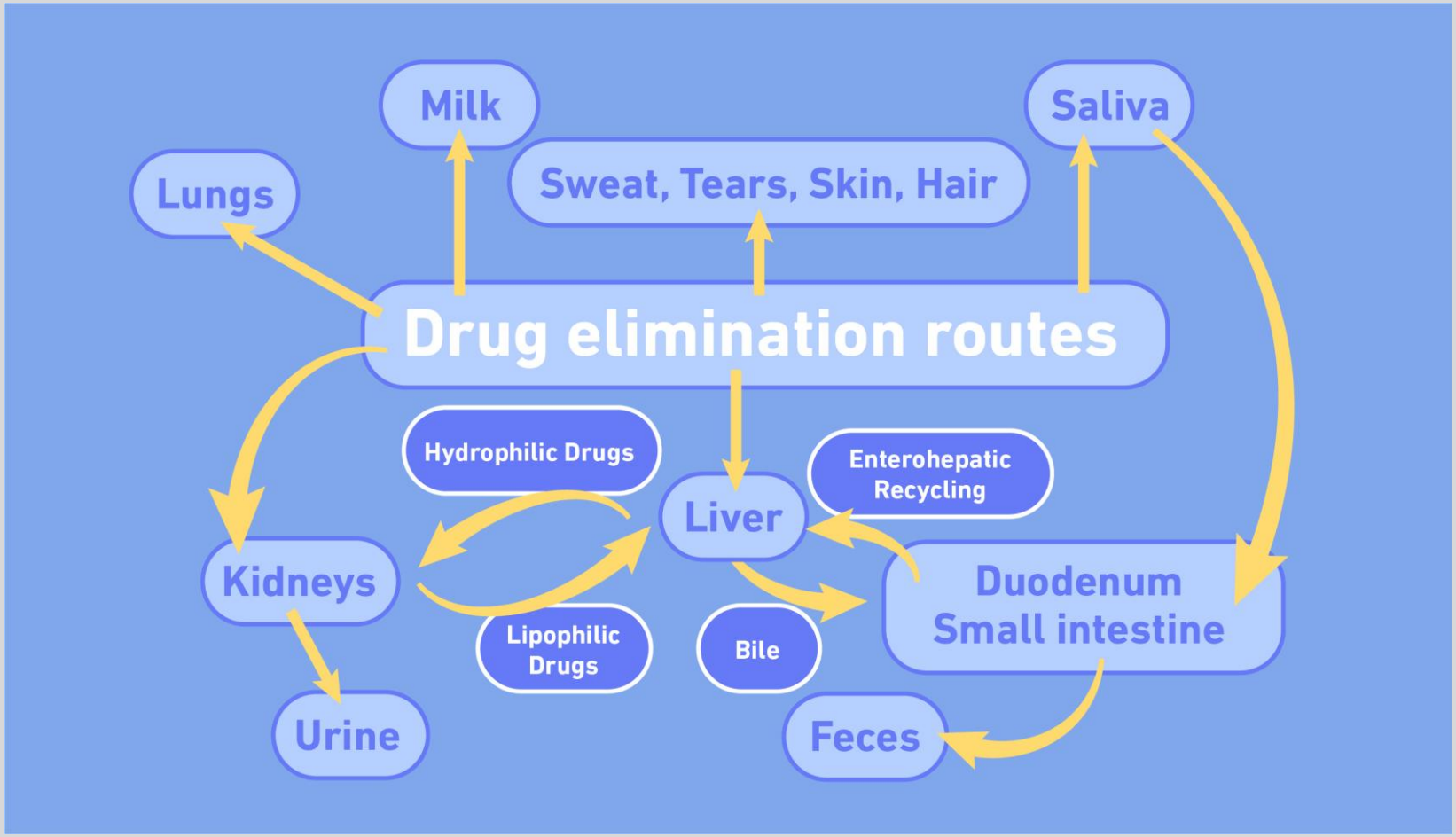
First-pass metabolism

- Occurs only via enteral administration
- Drugs pass through the GI and are delivered to the liver via the portal vein
- Drug concentration drops drastically in the liver
- First-pass metabolism lowers bioavailability



Elimination

- The kidney only eliminates polar, unbound drugs.
- Drugs eliminated with bile through the GI can get absorbed & returned to the liver.
- Lungs mainly eliminate volatile compounds.



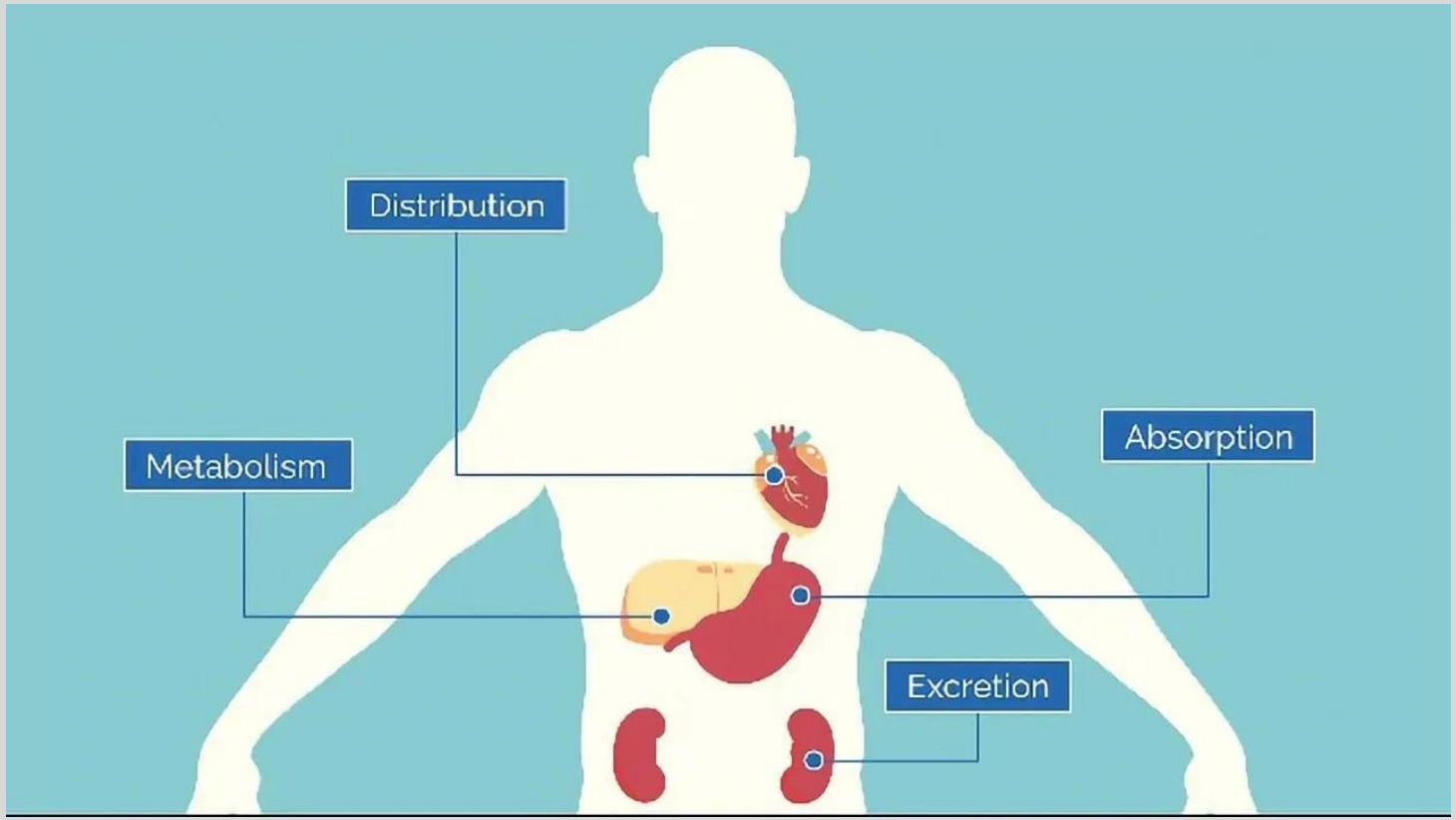
Pharmacokinetics

Absorption

Distribution

Metabolism

Excretion



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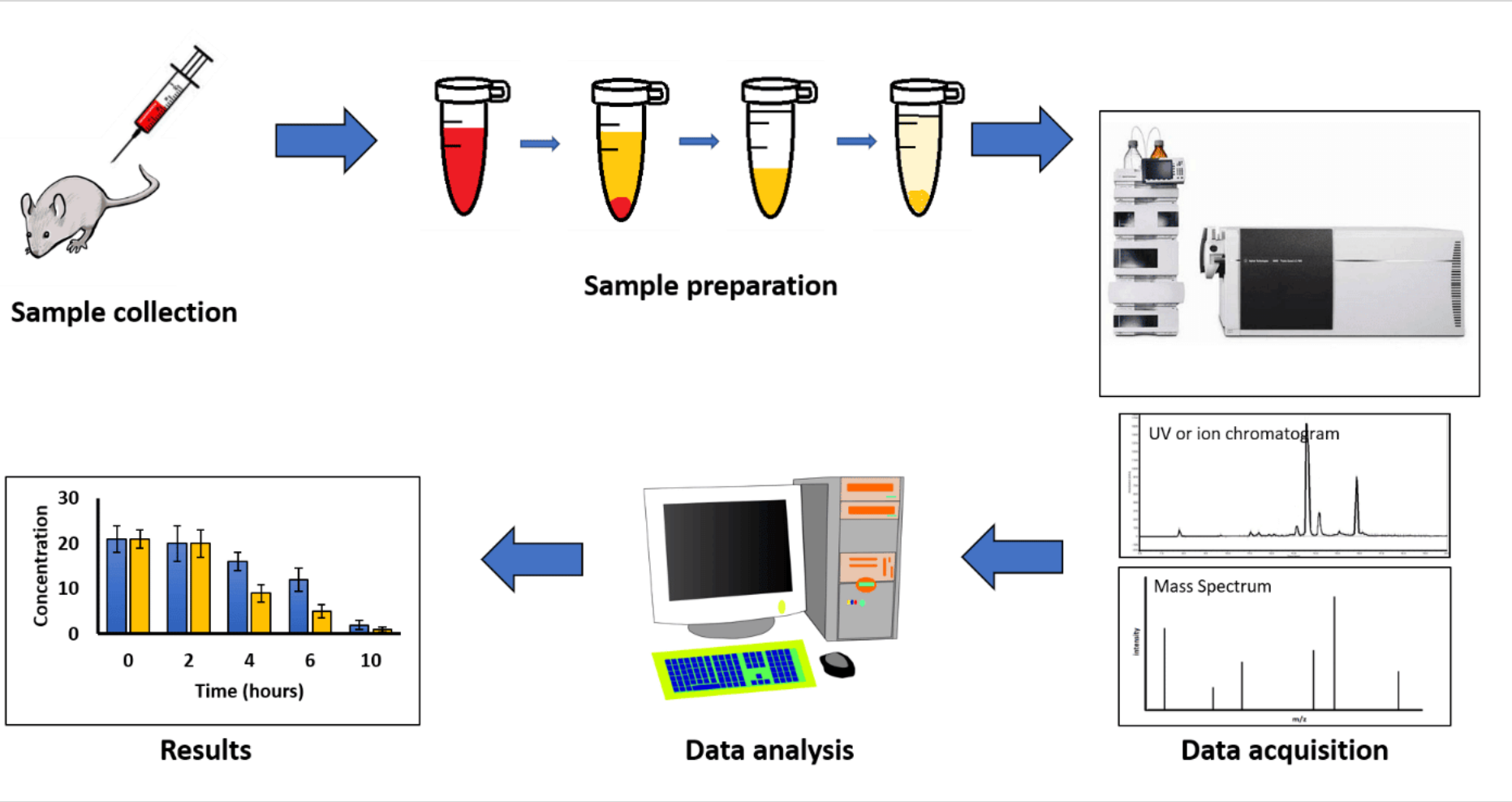
Pharmacokinetics testing in clinical trials

Drug PK Tests

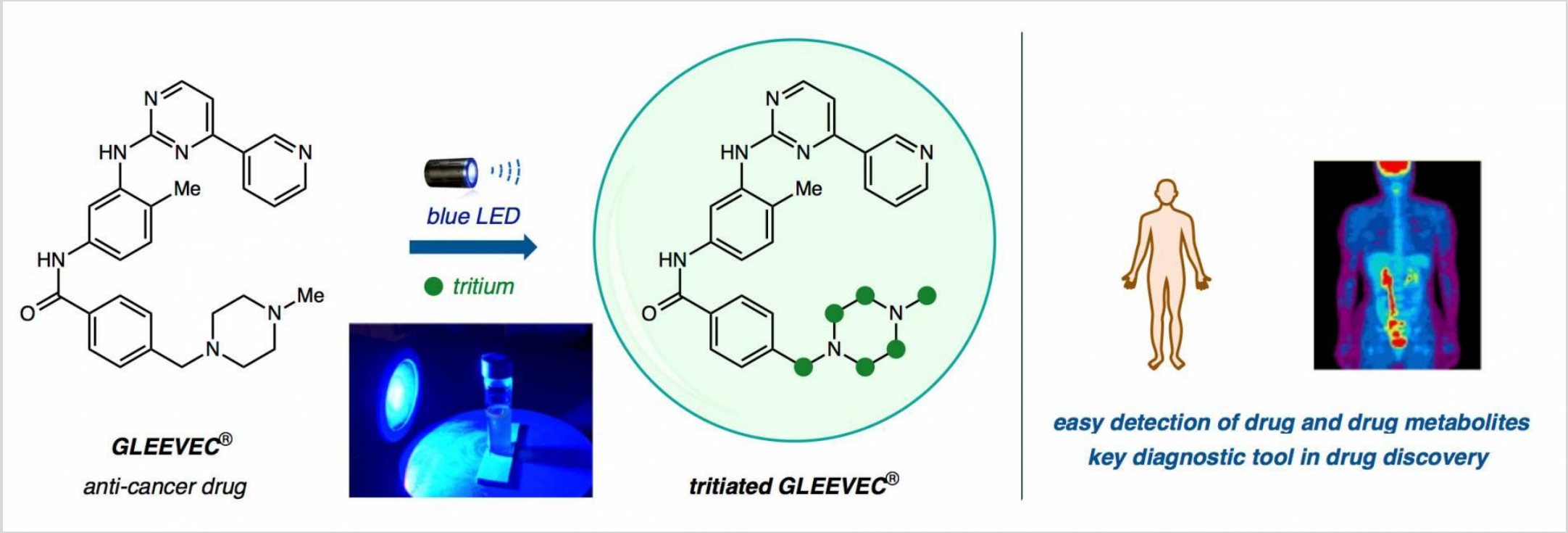
- **Blood test**
  - plasma drug concentration vs time ➪ therapeutic threshold
  - various routes of administration ➪ bioavailability & best route
  - plasma metabolite concentration vs time ➪ metabolic pathway & rates

- **Urine tests**
  - drug and/or metabolite concentration vs time ➪ metabolic pathways & rates

Drug PK Tests

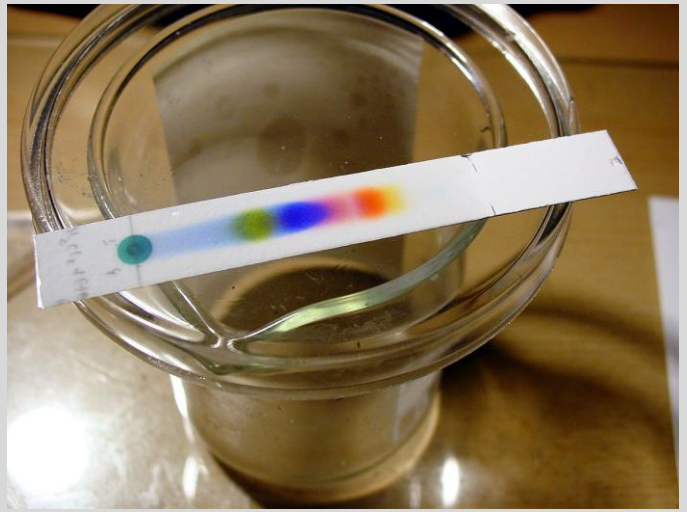


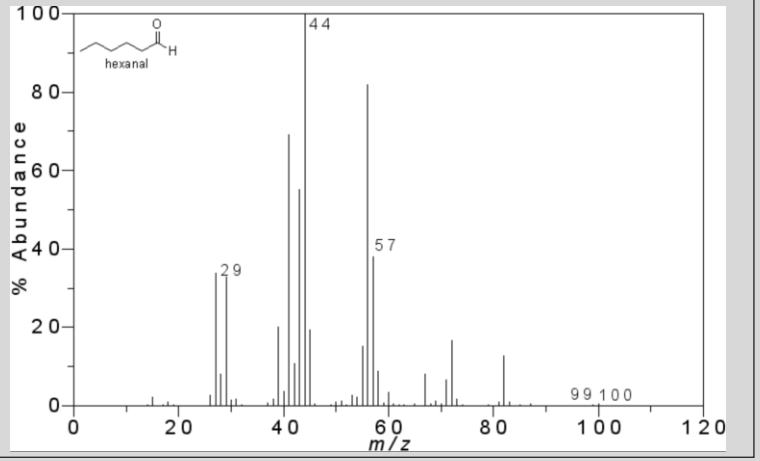
Drugs with Unknown Metabolism



How are Drugs Identified in Test Samples?

- To identify drugs & their metabolites in biological samples, researchers use **Liquid Chromatography-Mass Spectrometry (LC-MS).**
- The method combines two processes: **chromatography** & **mass spectrometry**.
- **Chromatography** allows the **separation** of chemicals by their mass.
- **Mass spectrometry** allows **identifying** fragments of the molecules by their mass-to-charge ratio.





How are Drugs Identified in Test Samples?

1. The sample is loaded into the chromatographer.
2. During chromatography, individual molecules in the sample are separated by mass.
3. The separated components are introduced into the mass spectrometer individually.
4. The detector in MS identifies molecule fragments based on their mass-to-charge ratios.
5. The peaks on the MS graph are analyzed, and the molecule is reconstructed.

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References

- Neal MJ. Medical Pharmacology at a Glance. Wiley-Blackwell.
- Hollinger MA. Introduction to Pharmacology.
- Additional journal articles will be provided during the semester.