# PHAR1922: HOW DRUGS WORK

## MODULE 1: DRUG SOURCES AND TARGETS

### *1.1 INTRODUCTION TO DRUG TARGETS*

**learning outcome one: understand the range of drug targets**

| TARGET | MECHANISM |
|---|---|
| **Enzyme** | Enzymes catalyse steps in the biosynthesis of many cellular products, drugs acting by:<br>- **Inhibiting an enzyme** (reversible or irreversible) to prevent a normal reaction (Eliquis)<br>- Acting as a **false substrate** to produce an abnormal product.<br>**ACE (Angiotensin-converting)** inhibitors treat heart failure and high blood pressure (hypertension) by acting on the **Renin-Angiotensin-Aldosterone system (RAAS)** to control blood pressure and fluid balance (water retention).<br>*Angiotensinogen →(renin) angiotensin I →(ACE) angiotensin II →(angiotensinases) angiotensin III*<br>- Carboxypeptidase (CPA) enzyme undergoes hydrolysis to convert from an ionic → ion-dipole → H-bond → hydrophobic interaction. Similar mechanism and function to ACE, zinc important for binding and polarising carbonyl group and breaks amide bond (H-bonds with active site of enzyme).<br>- Sulfonamides - specific and synthetic antibacterials (e.g. folic acid synthesis is inhibited by dihydropteroate synthetase (DHPS) |
| **Receptor** (present in cell membrane) | **Drugs bind to receptors (regulatory macromolecuels) can function as agonist or antagonist, measured by efficacy (produce a biological response) and affinity (liking) - such as spirivia and symbicort. Includes Beta blockers, ACE inhibitors**<br>- Agonist drug binds to receptor, binding with an affinity to produce a biological response (high efficacy is a full agonist and intermediate efficacy is a partial agonist)<br>- Antagonist drug binds to receptor, binding with an affinity and produces no biological response.<br><u>Analgesic (Opioid) Receptors</u><br>There are three types: mu, kappa and delta - all are G proteins. The binding of agonist induces conformational change in uOR; activates the Gi protein and leads to a series of events which result in analgesia.<br>Codeine affinity is 200x less than morphine - has to be metabolised to morphine to exert its optimal analgesic activity.<br>***Pharmacophore*** is the group is structural features required for the optimal interaction of a drug with its target (e.g. morphine has ionic bonds, is aromatic and contains HBD/HBA to bind as an agonist) |
| **Nucleic Acid** | **Intercalator, substrate mimic or modifier**<br>Nucleic acids are targets for chemotherapeutic agents (cytotoxic). Drugs can be<br>- Chain terminators (e.g. antiviral agents terminates chain elongation)<br>- Covalent binders (e.g. alkylating agents covalently bond to electron rich sites in DNA)<br>- Intercalators (e.g. anthracycline antibiotics - planar molecules sliding between base pairs) |
| **Ion Channel** (present in cell membrane) | **Blocker or openers** that are responsible for transport of ions across membranes, essential for electrical signalling for organ systems and hormone secretion.<br>**Calcium Channel Blockers** (e.g. lercanidipine - zandip) |
| **Transporters** (present in cell membrane) | **Uptake inhibitors**<br>- Porins transport polar molecules across the outer membrane (lipid bilayer) of Gram negative bacteria.<br>- Protein transports cholesterol across lipid membranes of gastrointestinal tract epithelial cells. |

**learning outcome two: understand how drugs interact with these targets in terms of the functional groups in their structure**

*Drug-Target Interaction:*

- Covalent bond 50-150 (strongest type, irreversible when drug forms covalent bond with target - target won't be used again unless it is degraded and new synthesis takes place)
- Ionic bond 5-10 (moderate strength, most common)
- Hydrogen bond 2-5 (single is weak but multiple stabilises drug-target complex, HBA/HBD)
- Hydrophobic interaction 0.5-1 (Van Der Waals / London Dispersion forces, non-polar molecules, very weak)

**Bioisosteric groups** are substituents or functional groups with related physical and/or chemical properties.

- bioisosteric replacement can be used to decrease toxicity, modify activity or change pharmacokinetics
- bioisosteric replacement aims to enhance biological / physical properties by making small changes in a structure
- isosteric replacements may modulate size, conformation, H- bonding, pKa, solubility, stability

**Prodrug** is a drug in an inactive form - once administered it is metabolised to give an action form of a drug. Strategies include altering solubility, improve membrane permeability by masking groups as less polar to increase lipophilicity, slow release of active agent and masking drug toxicity or side effects (e.g. Erythromycin with ester group)

**Lipinski's Rule of 5 ORAL SUITABILITY -** no more than 5 HBD (N/O with H attached), 10 HBA (N/O atoms), molecular weight less than 500 g/mol and a partition coefficient logP < 5.

## *1.2.1 DRUG DEVELOPMENT OVERVIEW*

**LEARNING OUTCOMES**

- Describe the critical activities required for each stage of the drug development pathway.
- Outline the ethical considerations for researchers participating in drug development.
- Explain the process involved in introducing a new chemical entity to market in Australia
- Outline the key features of the common technical document
- Access and describe guidelines for drug development according the ICH

**CORE PHARMACOLOGY CONCEPTS -** linkage between **pharmacokinetics** (drug travelling from administration to reach target, removal from body as it metabolises in the liver to become polar to be excreted) and **pharmacodynamics** (binding and cellular/physiological response)

***learning outcome one: describe the critical activities required for each stage of the drug development pathway***

**Stage One: Discovery** (*preclinical)* - understanding drug target and treatment indication (understand molecular level of receptor), finding lead molecules (natural products, ligand or structure-based design)

**Stage Two: Development** (*clinical)* - cells to animals to humans, pre-clinical pharmacology (pharmacdybamics and pharmacokinetics), pre-clinical toxicology, clinical trials

**Stage Three: Registration** (*regulatory)* - TGA Approval (prescribing in Australia, Government subsidisation PBS)

- Investment in research is primarily allocated to cancer, diabetes/endocrine/metabolic and psychiatric, and investment in drug target classes are protein kinases/GPCR's (cell surface receptor). Investment in Drug Design Approach is dominated by high-throughput screening.

Drug treatment modalities: new molecular entities (NME - most common) and biological license application (BLA)

**Drug Development Pipeline:**

1. High-throughput screening (IC50 determination, hit triage)
2. Hit to Lead (selecticity assays, in vitro [cells] efficacy assays)
3. Lead to Optimisation (in vivo [whole animals] efficacy assays)
4. Candidate Seeking (second species PK/PD)
5. Clinical Development - GLP toxicology studies (genetic toxicology, safety pharmacology, in vivo toxicology in two species)
    a. Phase one (measure SAFETY): safety and tolerability in normal volunteers