BPS2022

Drug Discovery and Design

Comprehensive Study Notes

HD 86 • Monash University

Table of Contents

BPS2022 Drug Discovery and Design

BPS2022 Drug Discovery and Design

Drug development - from then to now

Lipinski's rule of 5

- Function:
    - Improve physicochemical properties of drugs
        - Used to improve compound solubility
        - Used to make compounds smaller
    - Improve oral bioavailability (for orally delivered drugs)
    - Make compounds smaller and more soluble which was designed to contribute to increased bioavailability
    - *The Ro5 is a guideline for drug development. It is not an absolute measure of whether a drug will be absorbed or not.*
- Parameters:
    - Hydrogen bond donors ≤ 5 (sum of OHs and NHs)
    - Hydrogen bond acceptors ≤ 10 (sum of Os and Ns)
    - Molecular mass < 500 Da
    - Log P ≤ 5
- Compounds that fail Ro5:
    - Antibiotics, antifungals, vitamins, and cardiac glycosides
    - These drugs are delivered orally, bioavailable drugs that can cross membranes
    - Two rules must be violated for Lipsinki's rule to be failed

Developing drugs

- Factors to develop drugs
    - Potency, safety, efficacy, stability, toxicity, compatibility with other drugs, suitability for different demographics, and cost
        - Selective toxicity = drugs able to act on (injure, modify) specific cells while leaving others unaffected
    - Compounds can increase in size and complexity to improve potency
    - Hydrophobicity can increase and solubility is reduced
    - Reduce toxicity over the development process
    - Requirements for an effective drug
        - Able to treat the indication e.g. disease
        - Not too toxic
        - Able to be delivered
- Modern Small-Molecule Drugs
    - Consist of C, H, N, O, and halogens
    - Include metals = for imaging
    - Pure and dont contain toxophores or reactive chemical groups
    - MW not too high but may exceed 500 Daltons
- Target Product Profile

    - Desired target properties for a drug development program
    - properties/parameters that need to be optimized or considered
- Properties that change during drug development
    - Increase in size and complexity to improve potency
    - Hydrophobicity will increase and solubility reduce
    - Reduce toxicity over the development process
- What makes an effective drug
    - Able to treat the indication
    - Not too toxic (all drugs have some toxic effects, even if rare/low)
    - Able to be delivered (e.g. oral drugs must be bioavailable)
- Important factors for the patient
    - Not too difficult to take (e.g. not large numbers of tablets, inconvenient dosing requirements)
    - Oral is well understood and convenient. Injections can be OK if infrequent or in clinic or live-preserving (e.g. insulin)

Changes to drug discovery and development over time

- Then: Less ethical and safe → human testing was the norm
- Now: More ethical regulation and safety criteria → in vitro and in vivo testig before first in human dose
    - FDA and TGA regulate drugs and medicines to ensure public health and safety
- Now: technological advances → screening techniques aiding in TDD and PDD
- Then: Relied heavily on serendipity and chance
- Now: Increased prevalence of biologics in the markets (more complex molecules)
- Now: Release and development of blockbuster drugs
- Now: Increased purity of drugs
- Now: Strict preclinical and clinical studies undertaken to ensure safety and efficacy
    - To avoid disasters such as thalidomide (e.g. testing for teratogenic effects - causing birth defects)

Drug development - target selection

- Drug development
    - Categories:
        - Discovery
            - Target selection
            - Target validation
            - Lead discovery
            - Lead optimisation
        - Development
        - Commercialisation

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Target Identification

- Methods
    - Pathophysiology
    - Phenotypic drug effects
    - Genetic studies
- Drug target acts at a molecular level (interact with proteins)
    - Drug action at cellular level, tissues level, and system level
    - Therapeutic use in humans
- Drug targets
    - GPCR, ion channels, growth hormone receptors, enzymes, DNA, and nuclear receptors
    - Criteria:
        - Selected based on function not structure (can target be inhibited or activated)
        - Ability to establish an assay (ability to measure functional response)
        - Selected with an educated guess - likelihood of finding a drug like inhibitor/activator - chemical tractibility
        - Strong rationale for disease link or suitable models to test the theory behind the drug action
        - Ability to separate required effects from undesirable effects
        - Ability to demonstrate drug efficacy in clinical settings
        - Market (a potential commercial market)
        - Be testable
    - Then demonstrate that the drug can:
        - Produce the required/desired effects at the drug target
        - Possess minimal adverse effects at the drug target
        - Possess efficacy in a clinical setting

- Pathophysiology
    - Incorporates disease pathways and underlying mechanisms involved
    - Steps:
        - Understand the primary disturbance to normal physiological function and how it arised
        - Identify the molecular/biochemical pathways likely to respond to therapeutic intervention
        - Select key molecules from pathway as possible drug targets
    - Disadvantage - identification technique is very SLOW
- Phenotypic drug effects
    - Therapeutic agents already identified and on the market are further studied and analysed for other uses

- Genetic studies
    - Gene therapy - using animal models to test for possible molecular targets

- Knockout (KO) animal models
    - 'Genetically engineered' animal that has had a specific gene altered/removed to recreate a particular pathophysiology
    - Benefits:
        - Allows for a better understanding of the role of genes in diseases
        - Allows researcher to 'tinker' with possible drug targets to try and reverse/fix the problem
    - Steps:
        - Embryonic stem (ES) cells are cultured from mouse blastocysts
        - Construction of targeting vector which contains pieces of DNA homologous to target gene
        - The targeting vector is introduced into ES cells (transfection)
        - Homologous recombination allows the targeting vector to find and combine with the target gene
        - Selection of targeted ES cells for the presence of neo and absence of HSV-tk (cells that contain the wanted gene)
        - Injection of ES cells into blastocytes
        - Implantation of blastocysts into surrogate mother where they develop into chimeric embryos
        - Birth and breeding of chimeric mice to produce gene-targeted and normal offspring
        - Birth of gene-targeted mice = knockout mice
    - Questions:
        - Correlation between human and mouse
        - Relevance of KO phenotype to developing a small molecule drug
        - Compensation of other genes for the KO
        - Relevance of KO throughout the development of adult behavior
        - embryonic lethality prevents target identification

Target Validation

- What:
    - Experimental approaches by which a potential drug target can be tested and given further credibility
        - Pharmacological approach
        - Genetic approach
- Criteria (questions about the drug target):
    - Where is it expressed?
        - Look for a 'message' (mRNA → microarray or RNA sequencing)
        - E.g. expression of a receptor

PREVIEW

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