Topic 7 Drug Discovery and design Pt. 1

Chapter 9 Patrick
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Part 1: Sections 9.1-9.3

1. Target disease
2. Drug Targets
3. Testing Drugs
   3.1. In vivo Tests
   3.2. In vitro Tests
      3.2.1. Enzyme Inhibition Tests
      3.2.2. Testing with Receptors
DRUG DESIGN AND DEVELOPMENT

Stages

1) Identify target disease
2) Identify drug target
3) Establish testing procedures
4) Find a lead compound
5) Structure Activity Relationships (SAR)
6) Identify a pharmacophore
7) Drug design- optimising target interactions
8) Drug design - optimising pharmacokinetic properties
9) Toxicological and safety tests
10) Chemical development and production
11) Patenting and regulatory affairs
12) Clinical trials
1. TARGET DISEASE

Priority for the Pharmaceutical Industry

• Can the profits from marketing a new drug outweigh the cost of developing and testing that drug?

Questions to be addressed

• Is the disease widespread?  
  (e.g. cardiovascular disease, ulcers, malaria)
• Does the disease affect the first world?  
  (e.g. cardiovascular disease, ulcers)
• Are there drugs already on the market?  
• If so, what are there advantages and disadvantages?  
  (e.g. side effects)
• Can one identify a market advantage for a new therapy?
2. DRUG TARGETS-Remember?

A) LIPIDS
   Cell Membrane Lipids

B) PROTEINS
   Receptors
   Enzymes
   Carrier Proteins
   Structural Proteins (tubulin)

C) NUCLEIC ACIDS
   DNA
   RNA

D) CARBOHYDRATES
   Cell surface carbohydrates
   Antigens and recognition molecules
2. DRUG TARGETS

TARGET SELECTIVITY

Between species

- Antibacterial and antiviral agents
- Identify targets which are unique to the invading pathogen
- Identify targets which are shared but which are significantly different in structure

Within the body

- Selectivity between different enzymes, receptors etc.
- Selectivity between receptor types and subtypes
- Selectivity between isozymes
- Organ selectivity
3. TESTING DRUGS

- Tests are required in order to find lead compounds and for drug optimisation

- Tests can be *in vivo* or *in vitro*

- A combination of tests is often used in research programs
3.1 *in vivo* Tests

- Carried out on live animals or humans
- Measure an observed physiological effect
- Measure a drug’s ability to interact with its target and its ability to reach that target
- Can identify possible side effects
- Rationalization may be difficult due to the number of factors involved
- Transgenic animals - genetically modified animals
- Drug potency - concentration of drug required to produce 50% of the maximum possible effect
- Therapeutic ratio/index - compares the dose level of a drug required to produce a desired effect in 50% of the test sample (ED$_{50}$) versus the dose level that is lethal to 50% of the sample (LD$_{50}$)
3.2 *in vitro* Tests—See drug binding supplement

- Tests not carried out on animals/humans
  - Target molecules (e.g. isolated enzymes or receptors)
  - Cells (e.g. cloned cells)
  - Tissues (e.g. muscle tissue)
  - Organs
  - Micro-organisms (for antibacterial agents)
- More suitable for routine testing
- Used in high throughput screening
- Measure the interaction of a drug with the target but not the ability of the drug to reach the target
- Results are easier to rationalize - less factors involved
- Does not demonstrate a physiological or clinical effect
- Does not identify possible side effects
- Does not identify effective prodrugs
3.2.1 Enzyme Inhibition Tests

- Identify competitive or non competitive inhibition
- Strength of inhibition measured as IC$_{50}$
- IC$_{50}$ = concentration of inhibitor required to reduce enzyme activity by 50%
3.2.2 Testing with Receptors

- Not easy to isolate membrane bound receptors
- Carried out on whole cells, tissue cultures, or isolated organs
- Affinity - strength with which compounds bind to a receptor
- Efficacy - measure of maximum biochemical effect resulting from binding of a compound to a receptor.
- Potency - concentration of an agonist required to produce 50% of the maximum possible effect.
Part 2: Section 9.4 Lead compounds from the natural world

4. The Lead Compound
   4.1. Sources of Lead Compounds
   4.2. Identification of Lead Compounds
   4.3. Lead Compounds from the Natural World
      - Plant Extracts
      - Plants and Ancient Records
      - Herbal Remedies of Olde
      - Venoms and Toxins
      - Endogenous Compounds
4 The Lead Compound

Introduction

Def: A compound demonstrating a property likely to be therapeutically useful

- The level of activity and target selectivity are not crucial
- Used as the starting point for drug design and development
- Found by design (molecular modelling or NMR) or by screening compounds (natural or synthetic)
- Need to identify a suitable test in order to find a lead compound
- Active Principle - a compound that is isolated from a natural extract and which is principally responsible for the extract’s pharmacological activity. Often used as a lead compound.
4.1 Sources of Lead Compounds

A) The Natural World
- Plantlife (flowers, trees, bushes)
- Micro-organisms (bacteria, fungi)
- Animal life (frogs, snakes, scorpions)
- Biochemicals (Neurotransmitters, hormones)
- Marine chemistry (corals, bacteria, fish etc)

B) The Synthetic World
- Chemical synthesis (traditional)
- Combinatorial synthesis

C) The Virtual World
- Computer aided drug design
4.2 Identification of Lead Compounds

A) Isolation and purification
   solvent-solvent extraction
   chromatography
   crystallization
   distillation

B) Structure determination
   elemental analysis
   molecular weight
   mass spectrum
   infrared
   ultraviolet
   nmr (\(^1\)H, \(^{13}\)C, \(^2\)D)
   X-ray crystallography
4.3 Lead Compounds from the Natural World

PLANT EXTRACTS
4.3 Lead Compounds from the Natural World

PLANT EXTRACTS

MORPHINE

POPPY CAPSULE
4.3 Lead Compounds from the Natural World

PLANT EXTRACTS

- OPIUM - Morphine
- CINCHONA BARK - Quinine
- YEW TREE - Taxol
4.3 Lead Compounds from the Natural World

PLANT EXTRACTS

WILLOW TREE - SALICYLIC ACID

\[
\begin{align*}
\text{Salicylic Acid} & \xrightarrow{\text{Acetic anhydride}} \text{Aspirin} \\
\end{align*}
\]

Coca Bush - Cocaine

\[
\begin{align*}
\text{Coca Extract} & \xrightarrow{} \text{Procaine} \\
\end{align*}
\]
4.3 Lead Compounds from the Natural World

VENOMS AND TOXINS

Teprotide

Captopril (anti-hypertensive)
BUT WAIT....why do plants make these things??!!!
4.3 Lead Compounds from the Natural World

VENOMS AND TOXINS

Tubocurarine
(from curare)
4.3 Lead Compounds from the Natural World

VENOMS AND TOXINS

Tubocurarine (from curare)

Atracurium (Neuromuscular blocker)
4.3 Lead Compounds from the Natural World

ENDOGENOUS COMPOUNDS: found in YOU

NATURAL LIGANDS FOR RECEPTORS

ADRENALINE

SALBUTAMOL

5-HYDROXYTRYPTAMINE

SUMATRIPTAN

Agonist

Agonist
4.3 Lead Compounds from the Natural World

ENDOGENOUS COMPOUNDS

NATURAL LIGANDS FOR RECEPTORS

ADRENALINE

PROPRANOLOL

HISTAMINE

CIMETIDINE

Antagonist

Antagonist
4.3 Lead Compounds from the Natural World

ENDOGENOUS COMPOUNDS

NATURAL SUBSTRATES FOR ENZYMES

Enkephalins ↔ Enkephalinase inhibitors

HIV Peptides ↔ HIV Protease inhibitors

L-Phe-L-Pro

SAQUINAVIR
Part 3: Section 9.4 - Lead compounds from the synthetic world

4.4. Lead Compounds from the Synthetic World
- Organic Synthesis
- Combinatorial Synthesis
- Combinatorial Synthesis - Peptide Synthesis
- Combinatorial Synthesis - Heterocyclic Synthesis
4.4 Lead Compounds from the Synthetic World
4.4 Lead Compounds from the Synthetic World

PRONTOSIL: a dye
4.4 Lead Compounds from the Synthetic World

SULFANILAMIDE: not RED
4.4 Lead Compounds from the Synthetic World
4.4 Lead Compounds from the Synthetic World

ORGANIC SYNTHESIS
4.4 Lead Compounds from the Synthetic World

COMBINATORIAL SYNTHESIS

AUTOMATED SYNTHETIC MACHINES
4.4 Lead Compounds from the Synthetic World

COMBINATORIAL SYNTHESIS - PEPTIDE SYNTHESIS

RESIN BEAD

AMINO ACID

AMINO ACIDS

PEPTIDE
4.4 Lead Compounds from the Synthetic World

COMBINATORIAL SYNTHESIS - HETEROCYCLIC SYNTHESIS

RESIN BEAD
4.4 Lead Compounds from the Synthetic World

COMBINATORIAL SYNTHESIS - HETEROCYCLIC SYNTHESIS

\[
\text{Resin Bead} \quad \text{N} - \text{N} - \text{H} - \text{R}^2 - \text{R}^3
\]
4.4 Lead Compounds from the Synthetic World

COMBINATORIAL SYNTHESIS - HETEROCYCLIC SYNTHESIS

\[
\begin{align*}
\text{EtO} & \quad \text{R}^2 \\
\text{R}^3 & \quad \text{R}^4 \\
\text{R}^5 & \quad \text{RESIN} \\
\end{align*}
\]
4.4 Lead Compounds from the Synthetic World

COMBINATORIAL SYNTHESIS - HETEROCYCLIC SYNTHESIS
Contents

Part 4: Lead compounds - Impact of the human genome project

4.5. Lead Compounds
   - Impact of the human genome project
4.6. Lead Compounds - de novo design
4.7. Design of Lead Compounds using NMR Spectroscopy
4.5 Lead Compounds
- Impact of the human genome project

The Past

Lead Compound → Targets

The Future

Targets → Lead compounds
4.6 Lead Compounds - *de novo* design
4.6 Lead Compounds - *de novo* design

**X-RAY CRYSTALLOGRAPHY**
4.6 Lead Compounds - de novo design

PROTEIN STRUCTURE
4.6 Lead Compounds - *de novo* design
4.6 Lead Compounds - *de novo* design

THYMIDYLATE KINASE INHIBITOR

ANTICANCER AGENT

LEAD COMPOUND

Optimisation

ANTICANCER AGENT
4.7 Design of Lead Compounds using NMR Spectroscopy
4.7 Design of Lead Compounds using NMR Spectroscopy
4.7 Design of Lead Compounds using NMR Spectroscopy

Protein

NO OBSERVABLE BIOLOGICAL EFFECT
4.7 Design of Lead Compounds using NMR Spectroscopy

\[ ^{13}\text{C} \text{ NMR} \]
4.7 Design of Lead Compounds using NMR Spectroscopy
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Design of a lead compound as an immunosuppressant

Epitope A

Epitope B
4.7 Design of Lead Compounds using NMR Spectroscopy

Design of a lead compound as an immunosuppressant

Lead compound