Introduction to Drug Design and Discovery

Course: Drug Design
Course code: 0510412

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Learning Outcomes
At the end of this lesson students will be able to

- Outline the entire process involved in the drug discovery and drug design.
- Understand the interdisciplinary contribution as well as the key role of medicinal chemists in drug discovery and drug design.
- Gain an idea of clinical trials in drug discovery process.
- Understand and to apply the ligand-based drug design and the structure-based drug design in new drug discovery.
- Use of virtual screening approaches in drug design.
- Understand the common concepts of computer aided drug design techniques.
Medicinal Chemistry is the science that deals with the discovery and design of new therapeutic chemicals or biochemicals and their development into useful medicines.

**Medicines:** substances used to treat diseases.

**Drugs:** molecules used as medicines or as components in medicines to diagnose, cure, mitigate, treat, or prevent disease.
Role of Medicinal Chemists

- Isolation of compounds from nature.
- Synthesis of new molecules.
- Investigations of the relationships between the structure of compounds (natural and/or synthetic) and their biological activities (SAR).
- Elucidation of the drug-protein interactions.
- Determination of pharmacokinetic (PK) properties of drugs.
  - Absorption (A)
  - Distribution (D)
  - Metabolism (M)
  - Elimination (E)
  - Toxicity (T)
Drug Discovery Process

1. Lead compound
2. Synthetic modification
3. Drug candidate
4. Extensive pharmacological studies
5. Clinical drug
6. Clinical trials
7. Drug
Drug Discovery—Merging of Disciplines

- Combinatorial Chemistry
- Synthetic Chemistry
- Patent Law
- Physiochemistry
- Biochemistry
- Immunology
- Pharmacology
- Design
- Novel Molecule
- Intellectual Property
- Structural Activity
- Pharmacodynamics
- Pharmacokinetic Properties
- In Vivo activity
- Safety
- Safety Assessment
- Pharmacology
- Pathology
- Physical Chemistry
- Physiology
- Enzymology
- Modelling
- Information Technology
- Physiology
- Metabolism
- Pharmacology
- Pathology
- Behavior
- Physiology
• Problem: development of a drug takes 12 to 15 years and costs approximately 800 million dollars.
Drug Candidate safety testing

Animal Studies - relevant species - transgenic KO/KI mice - conditional KOs - agonists/antagonists - antibodies - antisense - RNAi

Studies of Disease Mechanisms

Molecular Studies

Target - receptor; - ion channel; - transporter; - enzyme; - signalling molecule

Lead Search - Develop assays (use of automation) - Chemical diversity - Highly iterative process

Target selection & validation

Discovery

Development

Human Studies Phases I, II, III

Drug Approval and Registration

Lead optimization - selectivity - efficacy in animal models - tolerability: AEs mechanism-based or structure-based? - pharmacokinetics - highly iterative process

Target - receptor; - ion channel; - transporter; - enzyme; - signalling molecule

Molecular Studies

Animal Studies - relevant species - transgenic KO/KI mice - conditional KOs - agonists/antagonists - antibodies - antisense - RNAi

Studies of Disease Mechanisms

Target selection & validation
Development

Pre-Clinical

Safety Assessment
Toxicology

Drug Metabolism
(ADME)

Pharmacology

Pharmaceutical R&D
Formulation

Clinical Investigator
& patient

Clinical Pharmacology
Clinical Research

Statistics & Epidemiology
Data Coordination
Research Information Systems
Information Services

Process R&D
Chem Eng. R&D
Manufacturing

Bio Process R&D

Regulatory Affairs
Project Planning & Management
Marketing

Clinical
**Phase I**

- Absorption and metabolism
- Effects on organs and tissue
- Side effects as dosage is increased

**Outcome**

1. Effectiveness in treating disease
2. Short-term side effects in health-impaired patients
3. Dose range

**Phase II**

- Several hundred health-impaired patients
- Treatment Group
- Control Group

**Outcome**

1. Benefit/risk relationship of drug
2. Less common and longer term side effects
3. Labeling information

**Phase III**

- Hundreds or thousands of health-impaired patients

**Compassionate Use**
Clinical trials-Different Phases

- Phase-I (lasts for 1 month - 1 year): Evaluation of the safety, tolerability, pharmacokinetic and pharmacological activity of drugs on 20-100 volunteers.

- Phase-II (lasts for 1-3 years): further assess the efficacy, safety of drugs in addition to dosing regimen in 300-600 patients.

- Phase-III (last for 2-6 years): covers several thousands of patients in clinics or hospitals; study the activity and possible side effects on the long term.

- Phase-IV: Post marketing feedback, after prescribing drugs to the out patients.
Clinical Trials Continued

Submit to Regulatory Agencies

Advisory Committee

New Drug Application (NDA)

Regulatory Review Team

Reviews, comments, and discussions

Drug Co./Regulatory liaison activities

APPROVAL PROCESS (Ex. FDA)

Submit to Regulatory Agencies

Worldwide Marketing Authorization (WMA) in other countries
Drug Design

Structure based

Ligand based

Protein Structure

Known

Unknown

Structure-Based Design

QSAR Pharmacophores Alignment

De Novo Design

Library Design/Analysis Diversity
**Ligand (analog) based drug design**
- Receptor structure is not known
- Mechanism is known/unknown
- Ligands and their biological activities are known/unknown

**Target (structure) based drug design**
- Receptor structure is known
- Mechanism is known
- Ligands and their biological activities are known/unknown

**Ligand-based Approach:**
- Statistical analysis of the relationships between molecular structures and their descriptors to provide correlations for predicting biological activities (QSAR)
- Exploring common pharmacophore features amongst a set of active compounds (Pharmacophore modeling)
- Deriving predictive models if SAR data is available (QSAR and Pharmacophore modeling)
- Searching for compounds with similar properties (Library analysis & Pharmacophore modeling)
Molecular Modeling

1. Quantum Mechanics
2. Molecular Mechanics
3. Molecular Dynamics

- Structure-based
  - Crystal Structure analysis
  - Homology Modeling
  - Computational Analysis of Protein-Ligand Interactions
  - Modification of ligands within the active-site for better binding

- Ligand-based
  - SAR, 2D- & 3D-QSAR
  - Lead Identification
  - In-Silico BBB, Solubility, Caco-2 & Toxicity Predictions

- Lead Optimization

- Lead Hopping

- Pharmacophore Development
  - Hits from Database Searches
  - Prioritization of Hits
Virtual Screening (VS)

The process of screening large databases on the computer for molecules having desired properties and biological activity and also to predict their binding to a target receptor.

OR

Use of high-performance computing to analyze large database of chemical compounds in order to identify possible drug candidates.

It has evolved over the past decade as a well accepted strategy in the discovery of new lead compounds.
Significance of Virtual Screening?

- **VS is a computational filter:**
  - Reduces the size of a chemical library to be screened experimentally—**Saves time & money**

- May improve likelihood of finding interesting compounds
  - As opposed to random screening
  - Enhance “hit rates”

**HTS versus VS:**

Use VS to exclude compounds which are predicted not to bind, helping to “enrich” the library

VS can also help to identify false-negatives in HTS
VIRTUAL SCREENING

Virtual screening

Ligand-based
- Similarity searching
- Pharmacophore mapping
- Machine learning

Structure-based
- Protein-ligand docking
- Scoring & ranking

Drug-like & Lead like
Toxicity
PAINS
ADME

Filtering rules