BHARATHIDASAN UNIVERSITY

Tiruchirappalli- 620024, Tamil Nadu,
India

Programme: M.Sc., Biomedical Science

Course Title : Drug Discovery and Assay Development
Course Code : 18BMS48ES

Unit-V

Proteomics and Drug Designing

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DRUG DISCOVERY AND ASSAY DEVELOPMENT

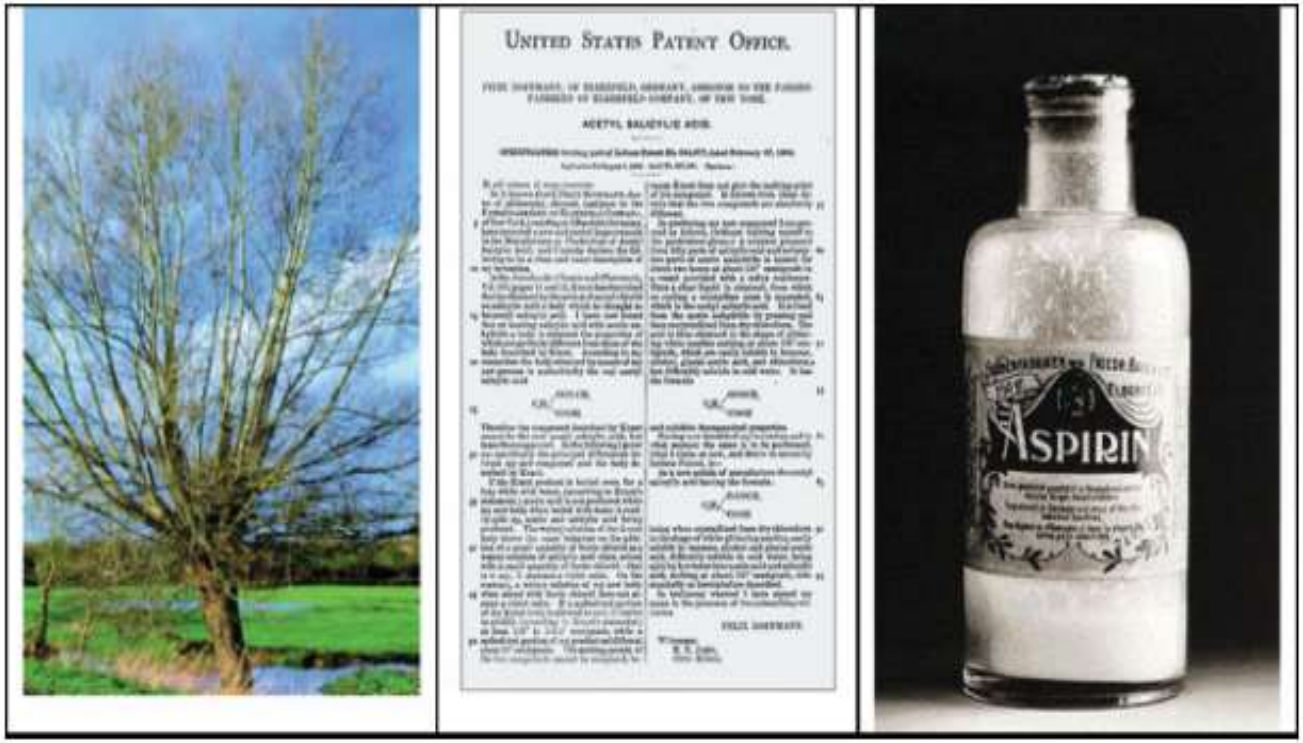


Figure 8. The white willow tree (*Salix alba*), the bark of which is rich in salicylates (left), US patent 1900 granted to Bayer's Felix Hoffmann for the synthesis of acetylsalicylic acid (middle) and an old bottle of aspirin (right).

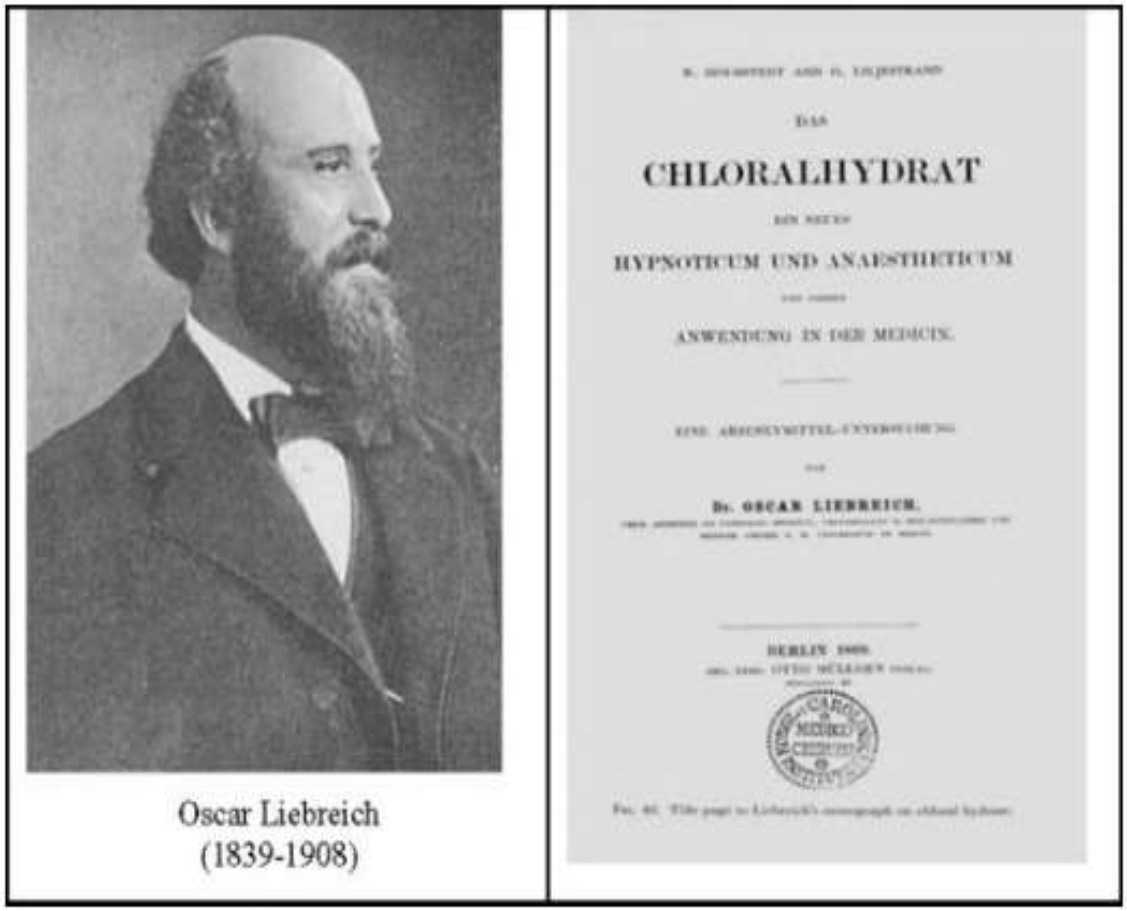


Figure 5. Portrait of Oscar Liebreich alongside the first page of his 1869 monograph on chloral hydrate and its use as a hypnotic.

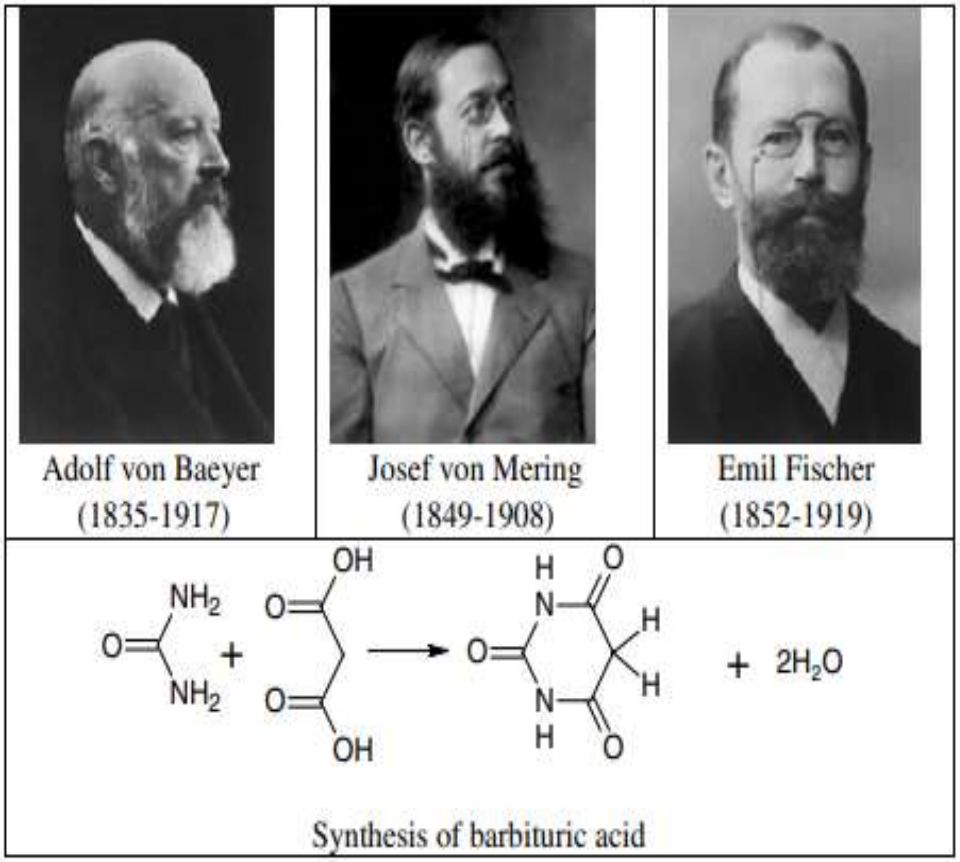


Figure 6. Scientists credited with the development of barbiturates and the synthesis of barbituric acid by Adolf von Baeyer in a condensation reaction between urea and malonic acid.

DRUG ?

- A substance recognized by an **official pharmacopeia or formulary.**
- A substance intended for use in the **diagnosis, cure, mitigation, treatment, or prevention of disease**.
- A substance (other than food) intended to affect the structure or any function of the body.
- Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process vs biological process)

DRUG NAME

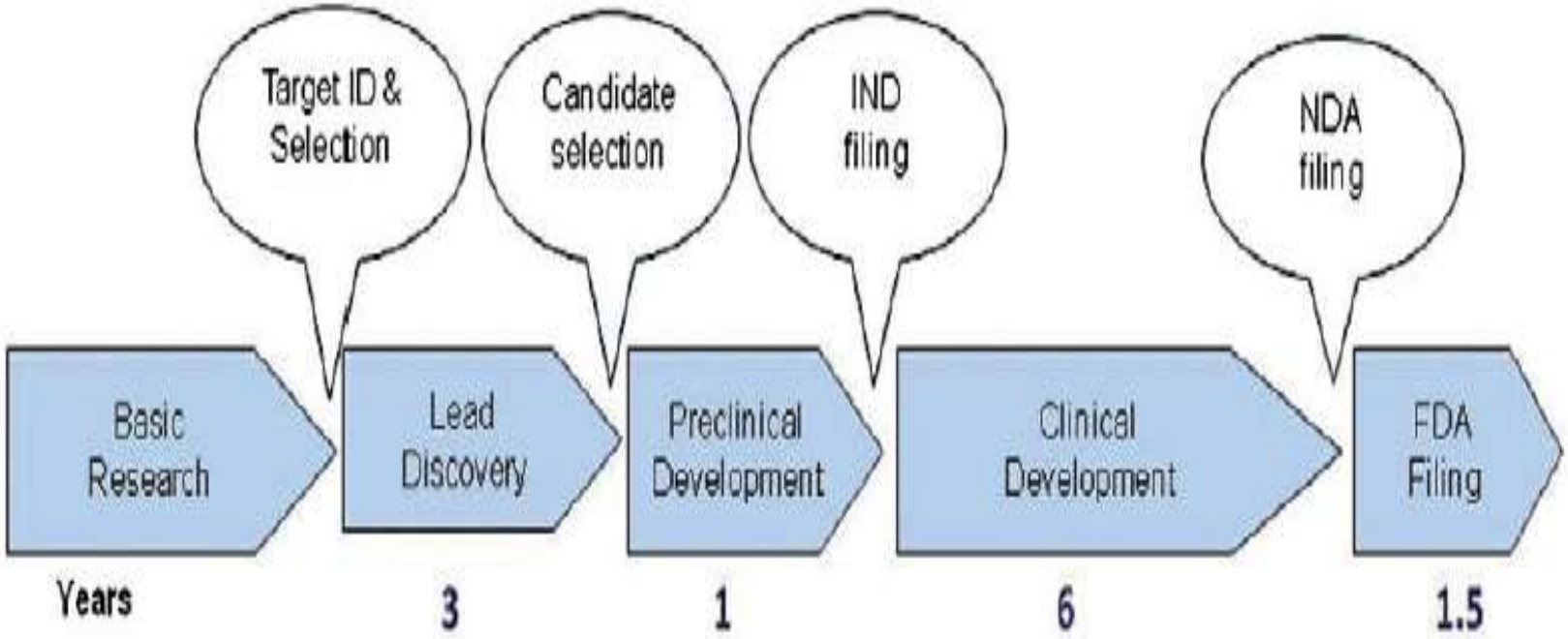
- **Trade or proprietary name**
  - (e.g., Lipitor)
- **Generic name, or nonproprietary name**
  - (e.g., atorvastatin)
- **Specific chemical name for the active ingredient**
  - (e.g., [*R*-(*R**,*R**)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate).

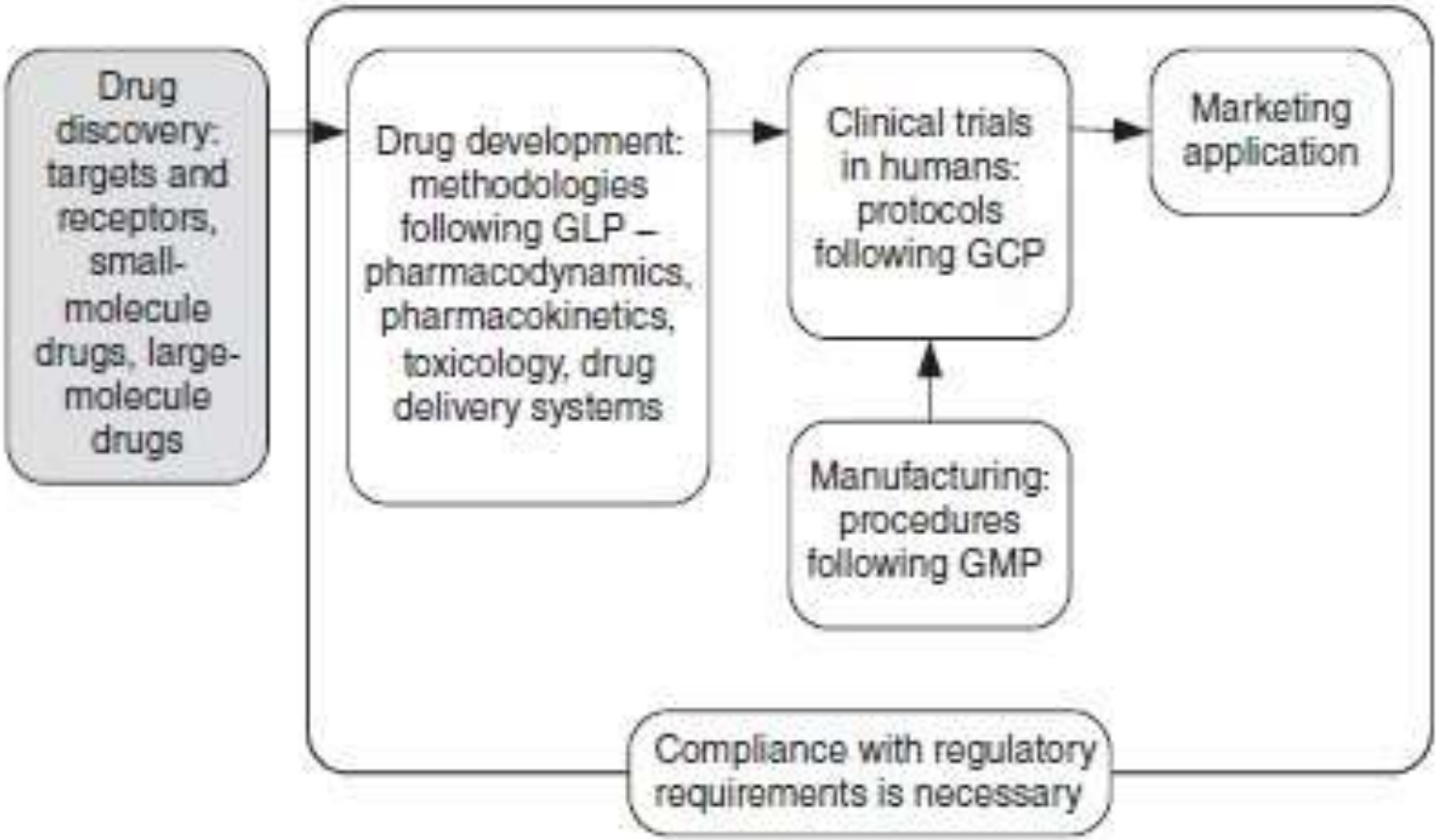
Drug Discovery

- The conventional method - Irrational approach.
- It involves scanning thousands of potential compounds from natural sources for a **hit against specific assays** that represent the **target advances** in drug discovery led to the rational approach.
- This approach starts by finding out about the **structure of the target** and then **designing a drug to fit the target** and **modify its functions.**

During lead discovery

- An intensive search ensues to find a drug-like small molecule or biological therapeutic, typically termed a development candidate,
- It will progress into preclinical, and if successful, into clinical development and ultimately be a marketed medicine.


Target ID & Selection
Candidate selection
IND filing
NDA filing
Basic Research
Lead Discovery
Preclinical Development
Clinical Development
FDA Filing
Years
3
1
6
1.5


Drug discovery: targets and receptors, small-molecule drugs, large-molecule drugs
Drug development: methodologies following GLP – pharmacodynamics, pharmacokinetics, toxicology, drug delivery systems
Clinical trials in humans: protocols following GCP
Marketing application
Manufacturing: procedures following GMP
Compliance with regulatory requirements is necessary

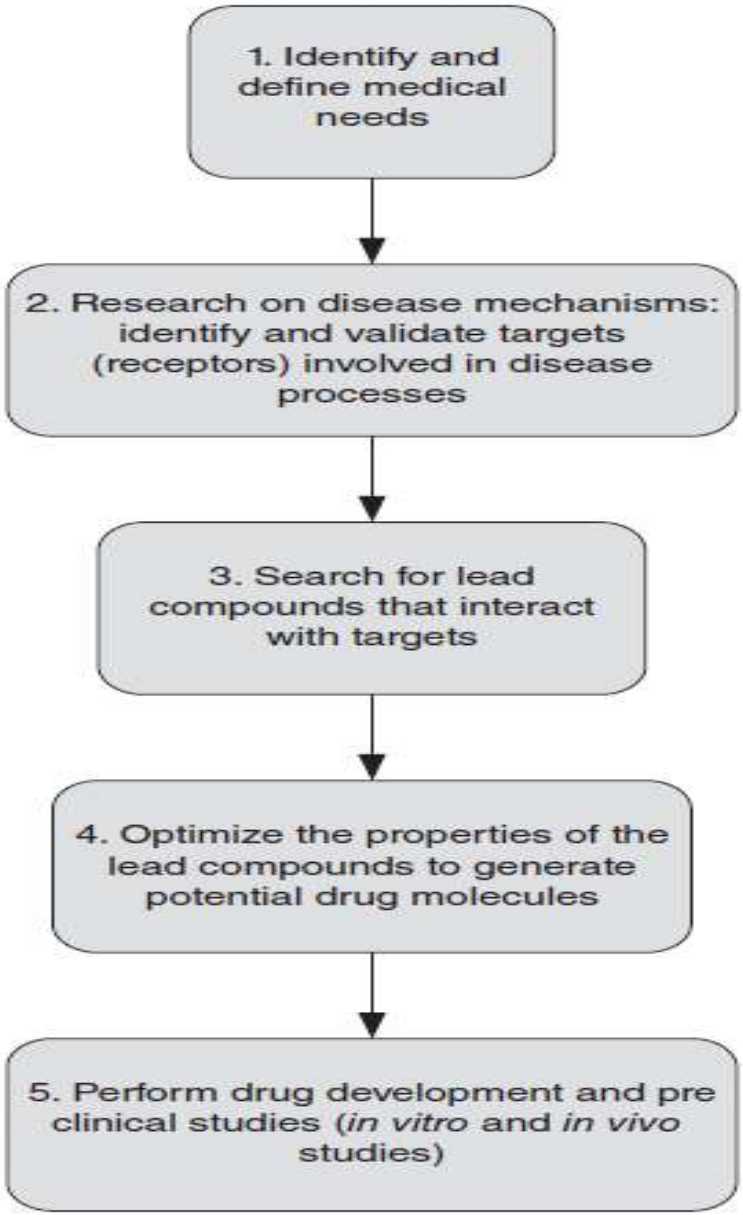
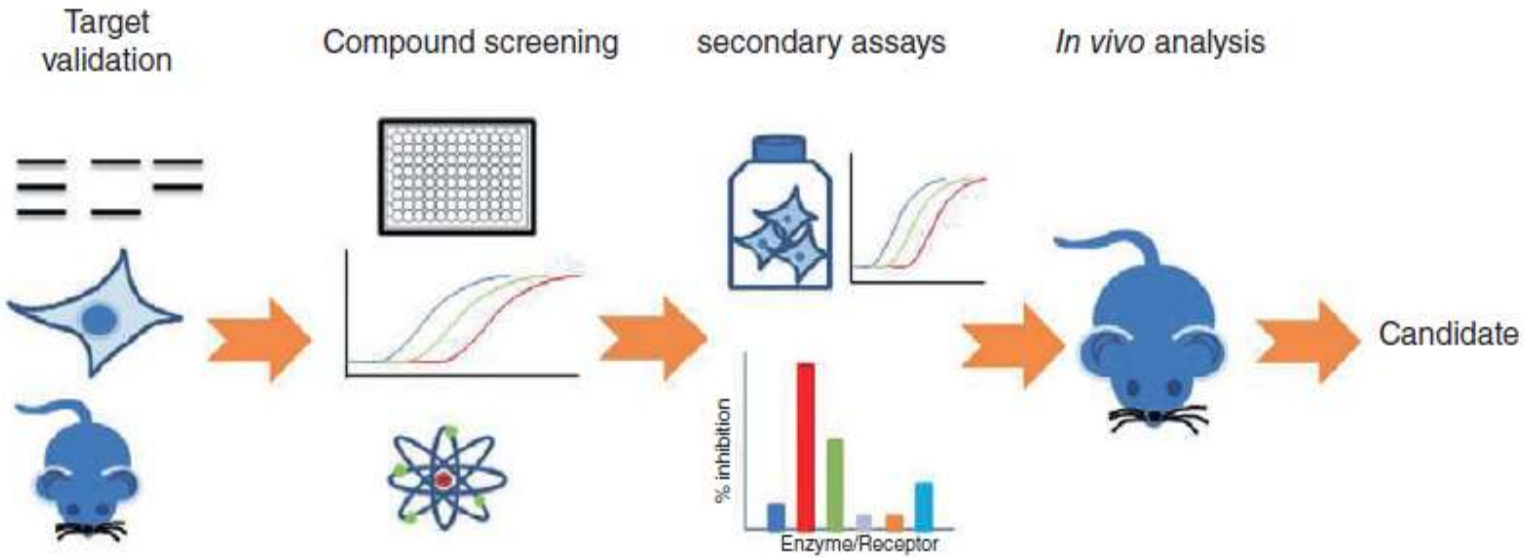


Figure 2.1 Flow chart of drug discovery processes.



- Genetic, cellular and *in vivo* experimental models to identify and validate target
- HTS & selective library screens; structure based design
- Reiterative directed compound synthesis to improve compound properties
- *in vitro* & *ex vivo* secondary assays (mechanistic)
- Selectivity & liability assays
- Compound pharmacology
- Disease efficacy models
- Early safety & toxicity studies
- Preclinical safety & toxicity package

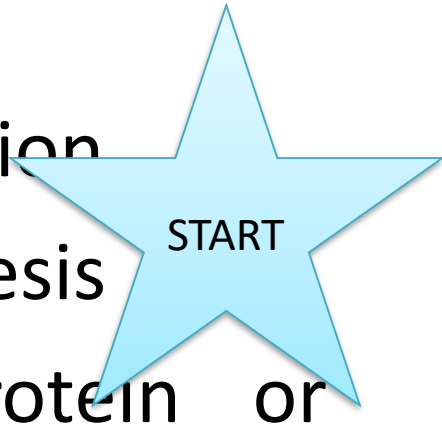
- 12–15 years
- Cost in excess of $1 billion.
- The idea for a target –

  Academic Research

  Clinical Research

  Commercial Sector
- It may take many years to build up a body of supporting evidence before selecting a target for a costly drug discovery programme.

- Disease or clinical condition without suitable medical products available
- Unmet clinical need - Driving motivation
- Academia Generates data - A hypothesis
- Inhibition or activation of a protein or pathway - therapeutic effect
- Selection of a target
- Validation prior to progression into the lead discovery



Review > Cancers (Basel). 2021 Jan 7;13(2):184. doi: 10.3390/cancers13020184.

Protein Tyrosine Kinases: Their Roles and Their Targeting in Leukemia

Kalpana K Bhanumathy [1], Amrutha Balagopal [1], Frederick S Vizeacoumar [2], Franco J Vizeacoumar [1 3], Andrew Freywald [2], Vincenzo Giambra [4]

Affiliations + expand

PMID: 33430292 PMCID: PMC7825731 DOI: 10.3390/cancers13020184

Free PMC article

Inhibitors of Protein Kinase Signaling Pathways

Emerging Therapies for Cardiovascular Disease

Thomas Force, Keisuke Kuida, Mark Namchuk, Keykavous Parang and John M. Kyriakis

Originally published 16 Mar 2004 | https://doi.org/10.1161/01.CIR.0000118538.21306.A9 | Circulation. 2004;109:1196–1205

Review > Semin Oncol. 2006 Aug;33(4):407-20. doi: 10.1053/j.seminoncol.2006.04.005.

New paradigms in anticancer therapy: targeting multiple signaling pathways with kinase inhibitors

Sandrine Faivre [1], Siham Djelloul, Eric Raymond

Affiliations + expand

PMID: 16890796 DOI: 10.1053/j.seminoncol.2006.04.005

Abstract

Signal transduction in cancer cells is a sophisticated process that involves receptor tyrosine kinases (RTKs) that eventually trigger multiple cytoplasmic kinases, which are often serine/threonine kinases. A number of tumor models have identified several key cellular signaling pathways that work independently, in parallel, and/or through interconnections to promote cancer development. Three major signaling pathways that have been identified as playing important roles in cancer include the phosphatidyl inositol-3-kinase (PI3K)/AKT, protein kinase C (PKC) family, and mitogen-activated protein kinase (MAPK)/Ras signaling cascades. In clinical trials, highly selective or specific blocking of only one of the kinases involved in these signaling pathways has been associated with limited or

TARGET IDENTIFICATION

I. **Genes and Biochemical Pathways**

II. **Targets**

   a. **Radioligand Binding**

   b. **DNA Microarray**

   c. **Expressed Sequence tags and In Silico Methods**

Genes and Biochemical Pathways

- The aim is to break down the disease process into the cellular and molecular levels.
- Status of genes and their associated proteins, biochemical pathways, and networks helps to pinpoint the cause of the disease.
- Drugs can be tailor-made to attack the “epicenter” of diseases.
- Drugs with fewer side effects and effective (with a high therapeutic index) can be discovered and manufactured to intervene or restore the cellular or molecular dysfunction.

Radioligand Binding

- To discover drug targets or receptors is to bind the potential receptors with radioligands so that targets can be picked out from a pool of other receptors.
- Bound receptors are then separated from the radioligands, sequenced, and their nucleotide sequence is decoded.
- Potential drug molecules are then studied with these receptors or their nucleotide sequences to determine their interactions in terms of biochemical and functional properties.

DNA Microarray

- DNA or gene chips, is a technology that investigates how genes interact with one another and how they control biological mechanisms in the body.
- The gene expression profile is dynamic and responds to external stimuli rapidly.
- By measuring the expression profile, scientists can assess the clues for the regulatory mechanisms, biochemical pathways, and cellular functions.
- Enable scientists to discover the target genes that cause disease.

Expressed Sequence tags and In silico Methods

- ESTs are short nucleotide sequences of cDNA 200–500 bps.
- Parts DNA code for the expression of particular proteins.
- Rapid method to scan for all the protein-coding genes and a tag for each gene on the genome.
- The scanning of nucleotide sequences is achieved through in silico (computer) methods.

DRUG DISCOVERY PROCESS

- Initial target identification and validation
- Through assay development
- High throughput screening
- Hit identification
- Lead Optimization
- Finally the selection of a candidate molecule for clinical development.

What is high-throughput screening?

- Automated testing of large numbers of chemical and/or biological compounds for a specific biological target
- Robotics and automation to quickly test the biological or biochemical activity of a large number of drugs.

- They **accelerate target analysis**, as large scale compound libraries can quickly be screened in a cost effective way.
- Assessing for instance pharmacological targets, Pharmacologically profiling agonists and antagonists for receptors (such as GPCRs) and enzymes.

High throughput screening (HTS)

- Automatic screening technique via a **YES/NO** sensitive detector to find inhibitors for therapeutic targets.
- It is a combination of robotics, data processing, and data control processes.
- Such screening may identify **one or few compounds from hundreds, thousands or even millions of compounds** with the ability to inhibit the activity of targets.

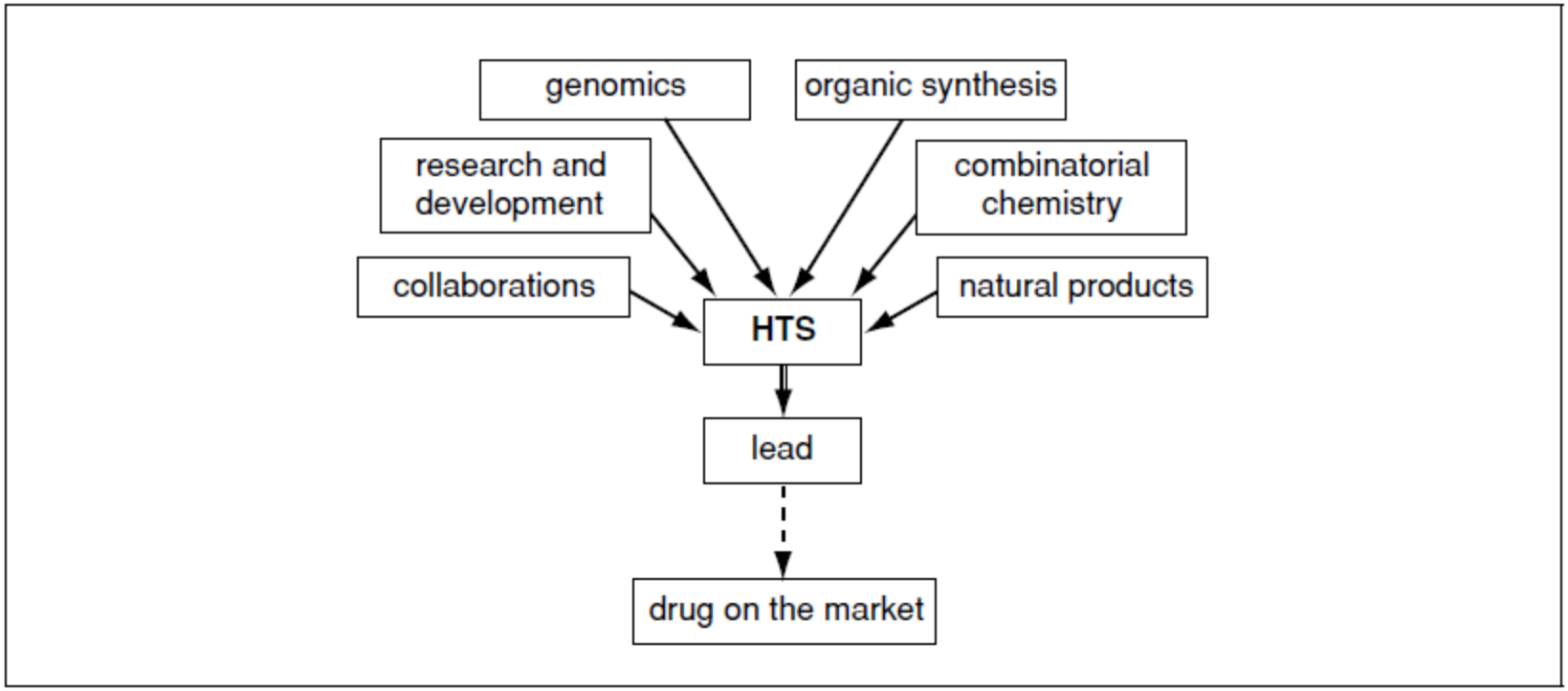


Figure 9.4.1 High-throughput screening (HTS) is one of the key methodologies used to find active compounds. HTS receives its input from numerous scientific disciplines and operational groups.

HTS

- The aim of HTS is to identify bioactive molecule from large compound collection and further development of active compounds to leads.

Types

- Biochemical - and cell-based assays.
- Depends on nature of target and assay feasibilities
- Assay optimization and validation

Fig. 11.1 Sequential steps involved in the high-throughput screening

- Identification of competent drug target.
- Target validation

(Biochemical assays and animal model Exp)

- Compounds modulating target identified.
- Assay development to screen modulators.
- Modulators -dose-dependent target modulation -lead compounds.
- Common pharmacophore can be developed from lead compounds showing common chemical properties.
- Structural activity relationship can be accessed
- Molecular descriptors can be optimized to improve selectivity and drug likeness of lead compounds; Lead optimization.
- Potential candidates for drug development.

(Animal models, and clinical trials)

- Drug discovery is designed to establish a scientific link between a biological target (e.g., an enzyme, G-protein-coupled receptor, ion channel, etc.) and a disease state model designed to mimic the human disease state.
- Process- target progression and target validation,
- Is accomplished through the use of molecular probes designed to identify multiple series of compounds that will modulate the activity of the biological target of interest.

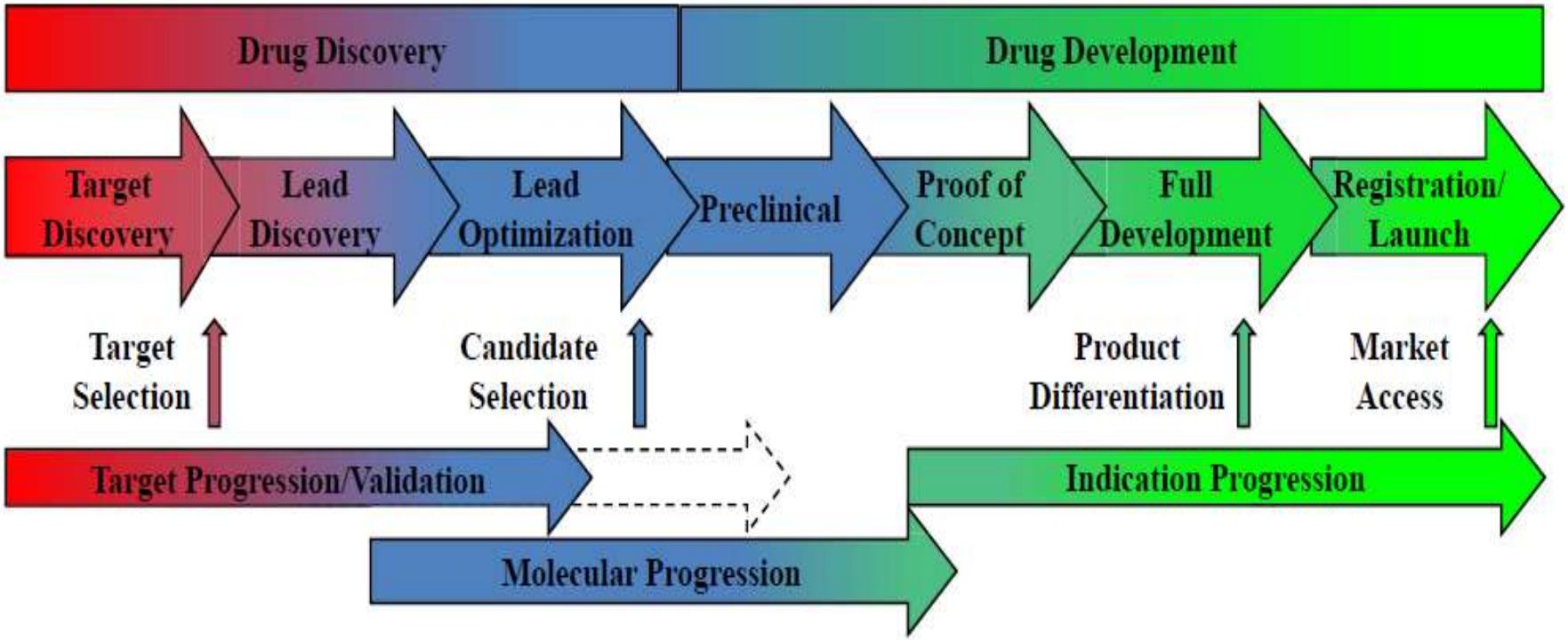
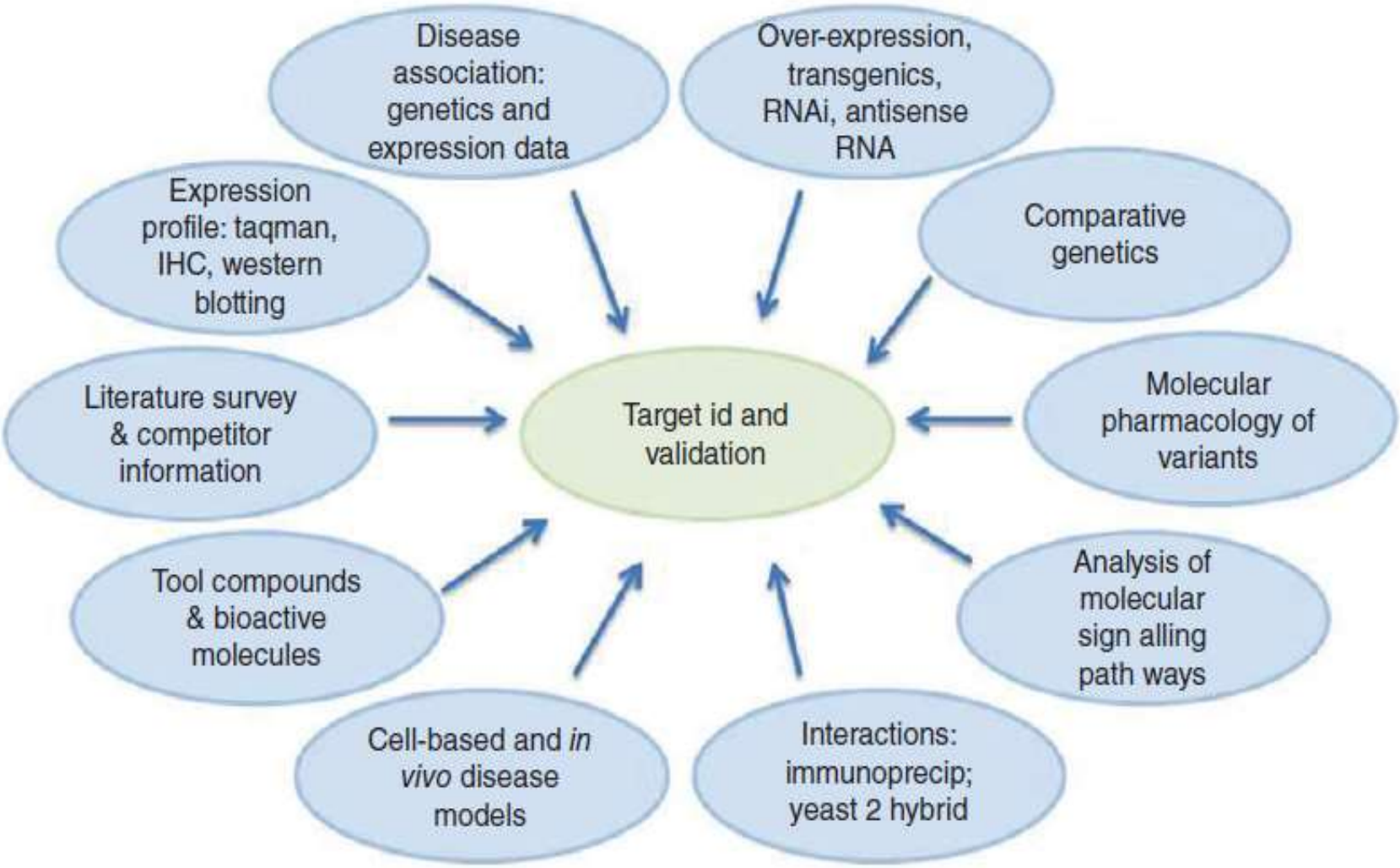


FIGURE 1.7 The drug discovery and development process viewed from "20,000 feet."

Target validation

- Once identified, the target then needs to be fully prosecuted.
- Validation techniques range from *in vitro tools through the* use of whole animal models, to modulation of a desired target


Disease association: genetics and expression data
Over-expression, transgenics, RNAi, antisense RNA
Expression profile: taqman, IHC, western blotting
Comparative genetics
Literature survey & competitor information
Target id and validation
Molecular pharmacology of variants
Tool compounds & bioactive molecules
Analysis of molecular sign alling path ways
Cell-based and *in vivo* disease models
Interactions: immunoprecip; yeast 2 hybrid

- Known compounds are employed to facilitate target selection,
- And are eventually transitioned into novel compounds through the processes of **lead discovery and lead optimization.**

In lead discovery phase,

- Sets of **structurally related compounds** with the desired biological activity are identified through biological screening of large numbers of compounds.
- Once a candidate series has been identified,
- **Lead optimization** phase begins.
- Structural analogs within a lead series are studied to identify a single compound

- Successful demonstration of *in vivo efficacy in an appropriate animal model employing* a compound that possess physical and chemical properties consistent with eventual clinical study in the drug development stage

Compound Libraries

- Natural product library,
- Target-specific libraries
- FDA approved drug library.
- Libraries consist of over 3000 molecules, and their biological and pharmacological activities
- Used for (HTS) and (HCS).

- Currently, there are over 70 million compounds registered in the Chemical Abstract Service database,
- Total number of possible compounds to consider as drug candidates is nearly infinite,
- so the question of where to start the process is significant.

- guidelines that have been developed in order to provide some guidance
- Lipinski's rule of 5
- (1) a molecular weight lower than 500
- (2) a logP below 5,
- (3) less than 5 hydrogen bond donors,
- (4) less than 10 hydrogen bond acceptors, and
- (5) less than 10 rotatable bonds

They each contain a para-fluorbenzene

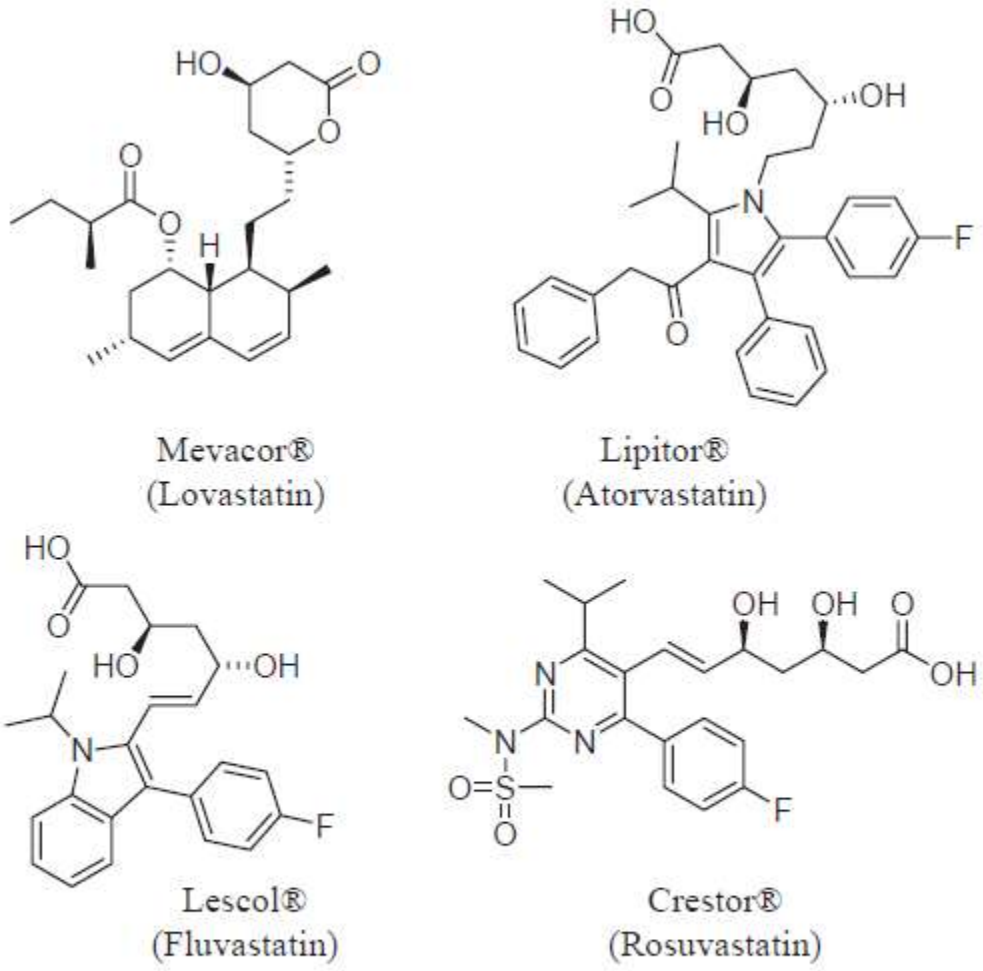


FIGURE 1.12 The HMG-CoA reductase inhibitors Mevacor® (lovastatin), Lipitor® (atorvastatin), Lescol® (Fluvastatin), and Crestor® (rosuvastatin) have some structural similarities, but there are a number of differences that make each unique.

- Physical high throughput screening (HTS) methods
- Virtual high throughput screening methods

- Physical high throughput screening approaches depend on the ability to screen large compound libraries containing hundreds, thousands, or even millions of samples.
- Large libraries are often designed to be chemically diverse in order to cover as much of the "druglike" chemical space as possible,
- Focused libraries designed to target specific types of biological targets (e.g., kinases, phosphatases) have also been employed.

- Chemical integrity of “hit” samples- assessed using High-performance liquid chromatography/ Mass spectroscopy (HPLC/MS) methods.
- Biological screening is often repeated with the “hit” compounds in order to validate the HTS results.

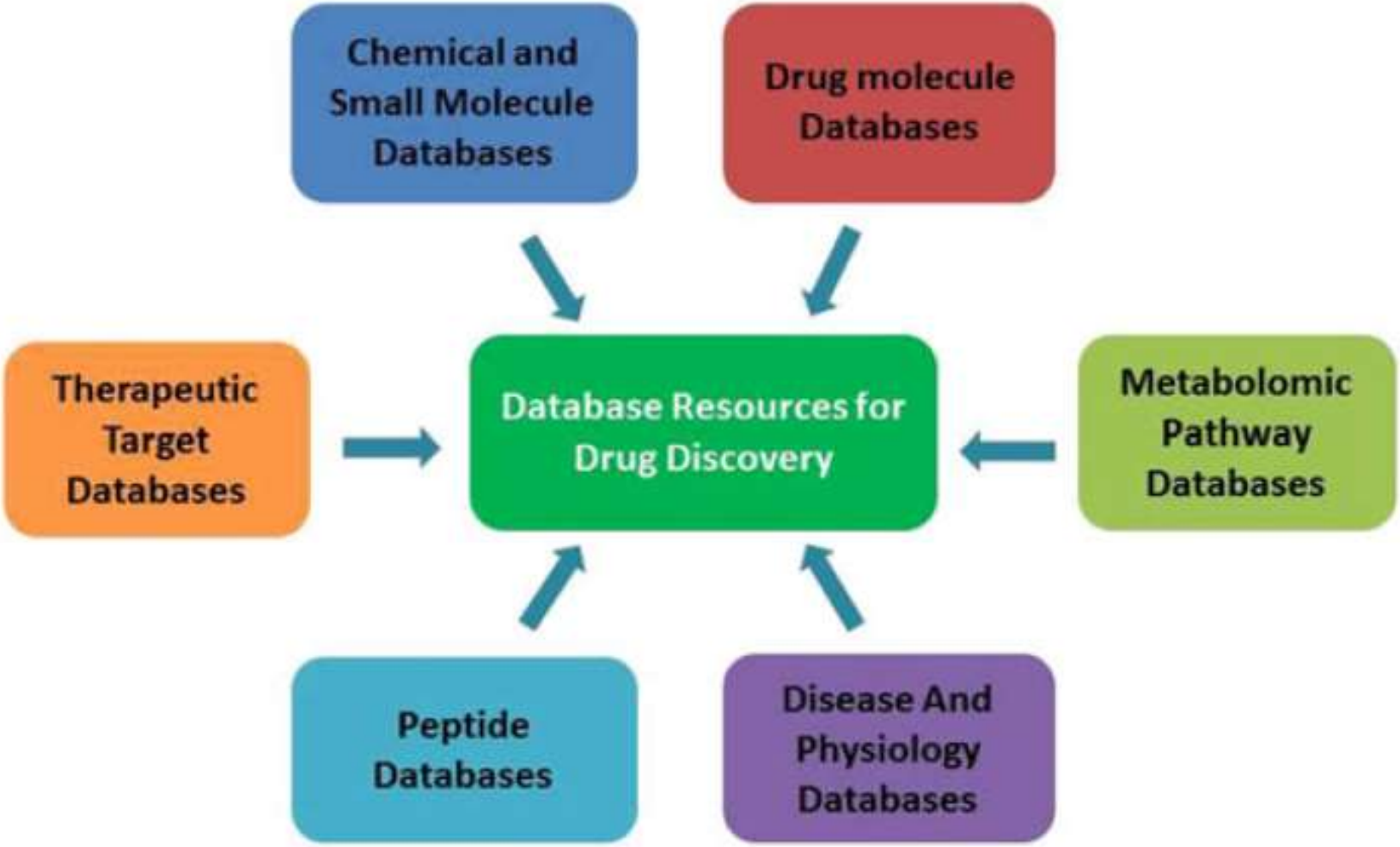


Fig. 5.1 Database resources for drug discovery

- The individual compounds of the chemical libraries can then be “docked” in a hypothetical binding site in the target of interest to determine a relative rank order for the entire set of compounds.

- It is the drug discovery scientist’s
- responsibility to identify a compound that will not only modulate the target of interest but also possesses the correct balance of properties required to create a usable drug.

- Kv1.5 channel
- Voltage-gated potassium channel - target of research programs atrial arrhythmia
- Many compounds have been identified that can block this channel with a high level of potency.
- Over 70 other voltage-gated potassium channels
- Varying degrees of similarity to the Kv1.5 channel
- Undesired activity at any of these related channels could create unwanted side effects in human or animal studies.

- For example, the Kv1.5 channel is closely related to the hERG channel.
- Blockade of the hERG channel has been linked to torsade de pointes and sudden cardiac death,
- so any compound moving forward in this area would need to be counter screened for hERG activity
- in order to ensure that advancing compounds do not present a risk of sudden cardiac death in a clinical setting

DISCOVER ANTIBODY

- On developing antibody drugs with high specific and affinity for research, diagnostic and therapeutic use.
- Discover antibody that can promote the desired biological response while avoiding off-target binding and toxicity.

Fragment Based Screening

- Biophysical techniques to measure low binding affinities of the fragments, like surface plasmon resonance (SPR), magnetic resonance spectrometry (NMR), X-ray crystallography.
- Orthogonal fragment screening technology allows us to discovery solutions to a wide array of target types.

BIOINFORMATICS

- Data mining of available biomedical data has led to a significant increase in target identification.
- Use of a bioinformatics approach to not only help in identifying but also selecting and prioritizing potential disease targets
- Sources - publications and patent information, gene expression, data, proteomics data, transgenic phenotyping and compound profiling data.

Examining mRNA/protein

- Identification approaches also include examining mRNA/protein levels to determine whether they are expressed in disease and if they are correlated with disease exacerbation or progression.

Identify Genetic Associations

- There a link between a genetic polymorphism and the risk of disease or disease progression or is the polymorphism functional.
- Familial Alzheimer's Disease (AD) patients commonly have **mutations in the amyloid precursor protein or presenilin genes** which lead to the production and deposition in the brain of increased amounts of the A beta peptide, characteristic of AD

Phenotypic screening

- Identify disease relevant targets.
- *phage-display antibody library were* to isolate human monoclonal antibodies (mAbs) that bind to the surface of tumour cells.
- By immunostaining- stain the malignant cells
- The antigens recognized by those clones were isolated by immunoprecipitation and identified by mass spectroscopy.

- Of 2114 mAbs with unique sequences they identified 21 distinct antigens highly expressed on several carcinomas, some of which may be useful targets for the corresponding carcinoma therapy

Drug Development

- Single compound has been identified,
- various studies designed to support its approval for sale by the appropriate regulatory bodies.
- Investigational New Drug (IND) Application that requests permission to move a clinical candidate into human study

In phase I clinical trials

- Safety and tolerability of an investigational new drug is examined in a small number of healthy individuals, typically 20 to 100 people, with the goal of determining if safety margins
- Pharmacokinetic and pharmacodynamic aspects of the candidate are closely monitored
- first in a single ascending dose (SAD) study, followed by a multiple ascending dose (MAD) study.

II trials

- phase IIA, the goal is to determine the dose required to provide the desired therapeutic impact or endpoint for the clinical candidate.
- phase IIB, the goal is to determine the overall efficacy of candidate compounds in a limited population of subjects.

Complex design of phase III

- Chronic medical conditions
- completion of phase III trials,
- New Drug Application is submitted to the appropriate regulatory body.

Phase iv

- The COX-2 selective non-steriodal anti-inflammatory agent Vioxx® (Rofecoxib), for example, - Ischemic
- Baycol® (cerivastatin), -coenzyme A (HMGCoA) reductase inhibitor marketed by Bayer AG for the treatment of high cholesterol and cardiovascular disease, was voluntarily removed from the market after reports of fatal rhabdomyolysis

Applications of CADD

- Identify novel potential active compounds
- Hit identification
- Optimize the bioactivity or LADMETox profile
- Assist in hit-to-lead process.

Classification of Computer-Aided Drug Design Methods

STRUCTURE-BASED METHODS

- Depend **3D information of the molecular target.**

Eg: Docking and Molecular dynamics (MD)

- App: Characterization of binding sites
- Elucidation of the MoA of active molecules at the molecular level
- Assessment of the kinetics and thermodynamics involved in ligand-target recognition.

Ligand-Based Methods

- Based on the information of the chemical **Structures of a set of ligands with known biological activity.**
- Identifying bioactive compounds or improving the activity of active molecules.
- Eg: Similarity searching and QSAR modeling

Hybrid Methods and Methods Based on End-Points

- When the structure of the target is known as well as the structure of active molecules,
- Combination of structure-based and ligand-based methods.
- Pharmacophore modeling.
- *in silico* approaches to predict bioactivity based on the biological profile of compounds tested vs. one or multiple targets

Big Data

- Era of information and the Internet
- Two zettabytes
- Doubling every 2 years
- mining this information offers a myriad of possibilities
- To enhance **competitivity and productivity**
- Data contains errors, duplicates, and missing values due to over collection.
- **Data curation** may be done differently by different research groups based on experience or previous reports.

Web Servers

- Need for informatic management of chemical data
- Gateway to virtual screening.

TABLE 5 Examples of Web Servers Useful for Chemoinformatics, Drug Discovery and/or Lead Optimization

Name and Website	Description	Type
Binding Database https://www.bindingdb.org/	Public repository containing ~1.1 million reports of binding affinity of protein-ligand complexes	Database
BRENDA https://www.brenda-enzymes.org/	Collection of enzymatic data manually curated from 82,568 proteins	Database
ChEMBL https://www.ebi.ac.uk/chembl/	Public database with more than 14 million activity values from ~ 11,000 targets	Database
Chemspider http://www.chemspider.com/	Repository of small molecules, with >63 million structures	Database
DrugBank https://www.drugbank.ca/	Contains information on more than 10,000 drugs and almost 5000 unique targets	Database
PubChem https://pubchem.ncbi.nlm.nih.gov/	Public database comprising an extensive number of records on compounds, bioactivity, assays and targets	Database
HEMD http://mdl.shsmu.edu.cn/HEMD/	Repository on epigenetic targets data and their chemical modulators	Database
GLIDA http://pharminfo.pharm.kyoto-u.ac.jp/services/glida/	Database providing data on G-coupled receptors and their ligands	Database
PUMA https://www.difacquim.com/d-tools/	Server implementing several analyses on chemical space and diversity of small molecules	Chemoinformatic tool
USR-VS http://usr.marseille.inserm.fr/	Server implementing ultrafast shape recognition algorithms for virtual screening. Queries are compared to almost 94,000 conformers from ZINC	Virtual screening tool
UFSRAT http://opus.bch.ed.ac.uk/ufsrat/	Server for virtual screening, based on the similarity principle. Queries can be compared to more than 10 million conformers from several sources	Virtual screening tool

T-COFFEE http://tcoffee.crg.cat/	Server for homology modeling	Homology modeling tool
SwissModel https://swissmodel.expasy.org/	Server for homology modeling	Homology modeling tool
SwissDock http://www.swissdock.ch/	Web implementation of EADock DSS software, allowing the docking of small molecules based on a manually curated database of protein-ligand interactions	Molecular docking server
Molecular Docking Server https://www.dockingserver.com/web	Web platform for protein and ligand preparation with several methods, while also offering docking and postprocessing capabilities	Molecular docking server
Hex Server http://hexserver.loria.fr/	Server for protein-protein docking based on shape and electrostatics of targets	Protein-protein docking
ZDOCK http://zdock.umassmed.edu/	Server for protein-protein docking based on Fourier transform, to evaluate energy on protein poses	Protein-protein docking

Workflows

- Case on virtual screening for lead identification and/or optimization.
- A protocol begins by acquiring pertinent data from repositories
- The next step is data curation
- Query or reference set is selected for comparison and filtering
- on chemical space or similarity metrics, for example, Tanimoto index.
- in silico testing would involve molecular docking as a means to select lead candidates.

- Schrodinger or Molecular Operating Environment
- Collection of scripts from a given programming language (R, python, Perl, etc.) advanced users may modify them to cover specific needs.
- Konstanz information miner (KNIME).

Konstanz Information Miner is **a modular environment which enables easy visual assembly and inter- active execution of a data pipeline**.

Machine Learning

- What is learning?
- Physiologically speaking, learning involves complex cognitive processes all leading to remembering
- This process can be replicated, to a certain extent, in machines and algorithms
- It begins with the recollection of previous experience/data to make a given choice.
- But to ensure said choice is the most adequate, superstition and/or false data must be filtered out and discarded
- Based on this, algorithms emulating learning can be developed.

Applications of Machine Learning in Drug Discovery

- Data repositories like PubChem or ChEMBL
- Data-driven discovery: making use of said to extract and identify patterns yielding predictions.
- Drug discovery.

TABLE 6 Examples of Applications of Machine Learning to Drug Discovery

Application	Result	References
Virtual screening	Lead structures for a novel target in tuberculosis were identified. Also, hit compounds are candidates for drug repurposing	Ekins et al. (2017)
High throughput screening	Fingerprints from imaging data were developed. These allowed the correlation of biological tests and provided activity prediction	Simm et al. (2018)
Protein-ligand interactions	Machine learning methods are good for interaction recognition, although the molecular diversity is not wide enough to allow complete assessment of binding and nonbinding molecules	Colwell (2018)
Side effects prediction	A novel clustering algorithm (K-Seeds) was developed. It showed higher enrichment than other methods	Dimitri and Lió (2017)
Classification of carcinogenic and mutagenic properties	Models showed agreement with experimental knowledge. Multicell descriptors were developed with 70% accuracy	Moorthy, Kumar, and Poongavanam (2017)
Molecular docking accuracy	Effective representations of protein-ligand complexes were developed using the DUD set	Pereira, Caffarena, and Dos Santos (2016)
Binding affinity prediction	Machine learning models can largely benefit from molecular dynamics data. In turn, this can benefit molecular dynamics by means of forcefield improvement	Pérez, Martínez-Rosell, and De Fabritiis (2018)

Deep Learning

- Scaling machine learning using multilayered neural networks
- Deep learning mimics the perception process using neural connections to extract features based on different observations.
- In other words, deep learning uses neural networks of several topologies trained to identify features corresponding to a complexity scale to recognize patterns in data

Artificial Intelligence

- Artificial intelligence (AI) is a branch of information and computer science concerned with the embedding of intelligence in machines and computers
- Apple's Siri, Amazon's Alexa, or Microsoft's Cortana.
- Digital assistants that serve as data sources and schedule optimizers.
- How about medical science?
- ICU care and surgical scheduling

Molecular Dynamics

- This is due to the reliance on intensive calculations for many particles, thus requiring a high CPU capability to handle the number of calculations needed to model the system.
- This has led to the development of a dedicated super clusters like Anton that achieves simulations on a microsecond scale.
- Briefly, this takes the simulation box and splits it into smaller systems

- Cheminformaticians
- Molecular similarity calculations.
- Well-known similarity/distance metrics are compared on a large dataset of molecular fingerprints with sum of ranking differences (SRD) and ANOVA analysis

Molecular Docking

- Docking intends to precisely fit the structure of a ligand inside the requirements of a receptor binding site and to accurately evaluate the strength of binding
- Binding site
- Sitespecific docking
- Flexible Docking
- Rigid Docking

Table 1.2 A summary of the highly cited molecular docking programs used in drug discovery

S. No.	Programs	Description	Availability	References
1	AutoDock	Used for molecular docking. It predicts the binding affinity and poses of a small molecule to a 3D structure target protein	http://autodock.scripps.edu/	Goodsell et al. (1996)
2	AutoDock Vina	Used for virtual screening and molecular docking	http://vina.scripps.edu/index.html	Trott and Olson (2010)
3	Glide Schrodinger	A complete package for molecular modeling and computer-aided drug discovery (CADD)	https://www.schrodinger.com/	Friesner et al. (2004)
4	Hex	Used for docking studies	http://hex.loria.fr/	Ritchie (2003)
5	Molecular operating environment (MOE)	A complete package for molecular modeling and computer-aided drug discovery	https://www.chemcomp.com/	Vilar et al. (2008)

Structure-Based Virtual Screening

- Virtual screening involves the docking and screening of a compound database against the drug target, followed by scoring based on their binding free energy with the target.

Pharmacophore Modeling

- Pharmacophore mapping is one of the real components in the drug designing program, without basic information of the target receptor
- Used to align compounds dependent on the 3D arrangement or to create prescient 3D QSAR models

Quantitative Structure–Activity Relationship (QSAR)

- Used to predict the biological activity of chemical compounds in drug designing.
- steric, electrostatic, hydrophobicity, and geometric behavior to interpret the molecular biological activity using multiple regression analysis
- Comparative molecular field analysis (CoMFA) and Comparative molecular similarity indices analysis (CoMSIA)

Homology or Comparative Modeling

- Identification of similar sequences with known structure
- Alignment of the target sequence with template structures,
- Modeling of structurally conserved regions using templates,
- Modeling of lateral chains and loops,
- Quality of the model being refined and evaluated by conformational sampling

ADMET Prediction and Analysis

- ADMET is one of the essential steps in any drug discovery program because it provides pharmacokinetics (ADME, i.e. Absorption, Distribution, Metabolism, and Excretion) and pharmacodynamics, i.e. toxicity (T) of lead molecules before going to wet-lab experimentation.

What is SMILES?

- (**S**implified **M**olecular **I**nput **L**ine **E**ntry **S**ystem)
- Chemical notation that allows a user to represent a chemical structure in a way that can be used by the computer.
- **SMILES** is an easily learned and flexible notation.
- You do not need to worry about ambiguous representations because the software will automatically reorder your entry into a unique **SMILES** string when necessary.

- Quantitative structure-property relationships (QSPR), (QSAR) are used to predict drug toxicity.
- The carcinogenicity, mutagenicity, and liver toxicity should be evaluated during drug designing.
- Lipinski's rule and some other principle descriptors such as polar surface area (2D), polarizability, van der Waals surface area, refractivity, etc.

Molecular Dynamics Simulation

- Molecular dynamics simulation (MDS) is one of the key tools for the theoretical and computational study of biomolecules
- The atoms and molecules can interact for a period of time during the simulation.
- The motion is calculated for each atom and can be used to check the overall behavior
- It has many advantages over docking because docking gives only binding free energy of ligand with the receptor.

- Additionally, we can predict the actual interaction of the ligand with receptors through MDS at the atomic level.
- During MDS, root mean square deviation (RMSD) is calculated for predicting the stability of receptor or ligand–receptor complexes, and it describes the conformational changes.
- Besides, root mean square fluctuation (RMSF) analysis is used to determine the flexibility with respect to time

The background of the MD simulation algorithm is generally based on three steps;

(1) determining the initial positions and speeds of each atom;

(2) calculating the forces applied to the identified atom using inter-atomic potentials;

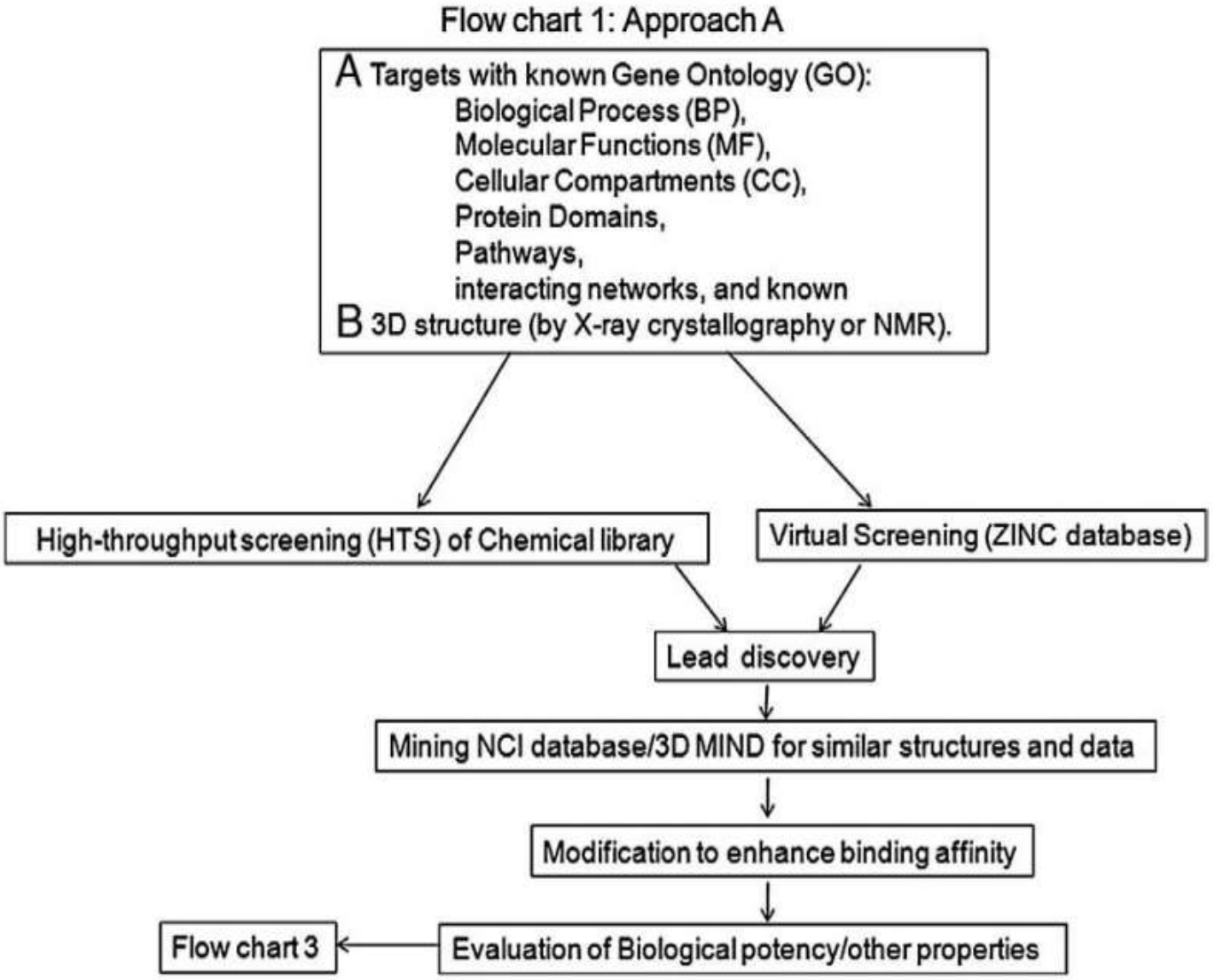
(3) the progression of atomic positions and speeds over the short period.

- vNN is a tool for assessments of the PK and toxic properties of a drug.
- vNN has 15 ADMET models, predict the important properties of drug
- Cytotoxicity, mutagenicity, cardiotoxicity, drug–drug interactions, microsomal stability, and drug-induced liver injury

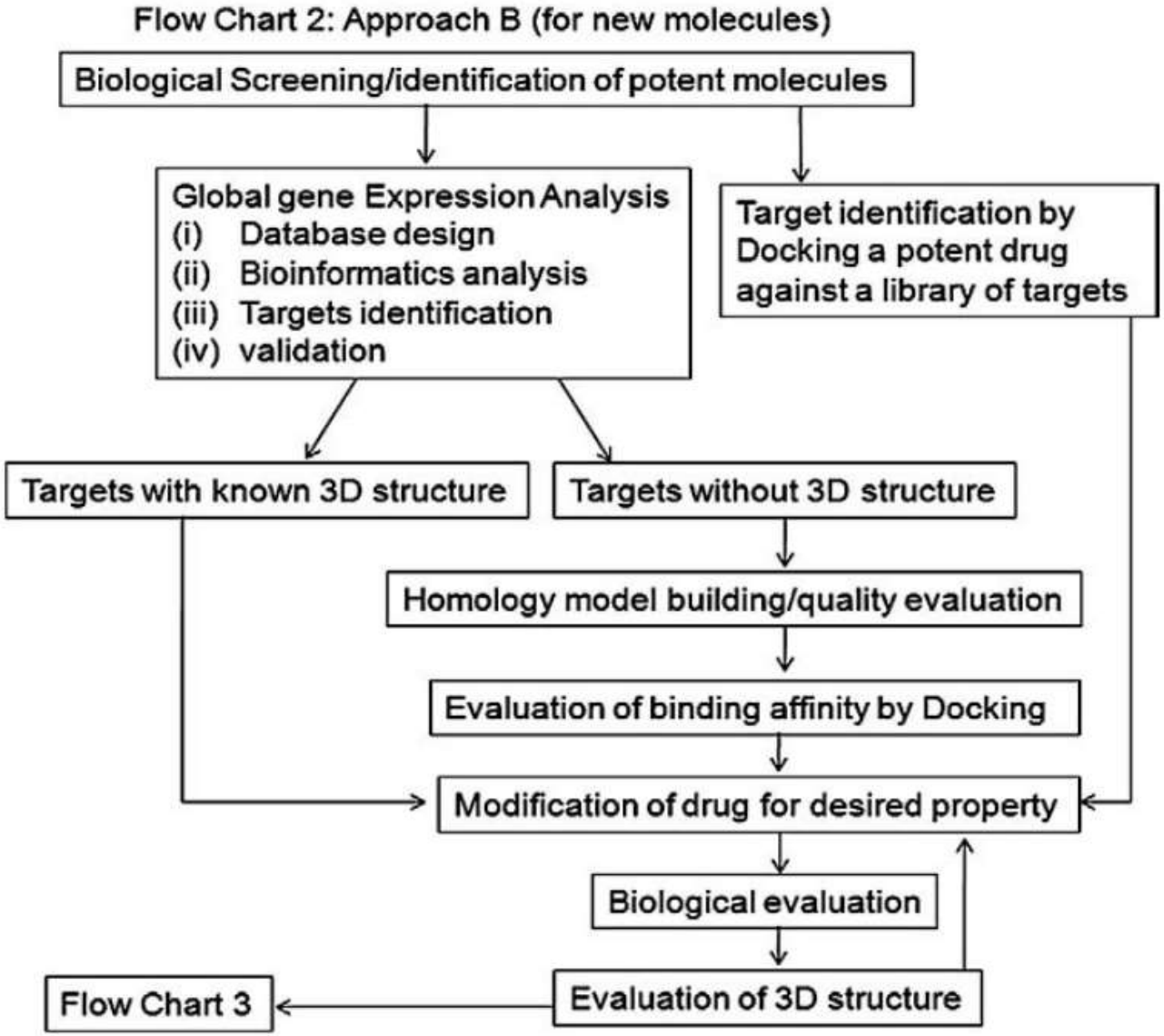
- ADMETopt is used for ADMET screening for lead optimization.
- This tool uses the information of 50,000 unique scaffolds extracted chemical compounds deposited in ChEMBL and Enamine database
- It predicts 7 physicochemical and 8 biological properties.

- PKKB includes 10,000 experimental
- ADMET data of 1685 drugs
- Provides information about octanol/ water partition coefficient, solubility, the dissociation constant, intestinal absorption, Caco-2 permeability, bioavailability, plasma protein binding, blood-plasma partitioning ratio, the volume of distribution, metabolism, half-life, excretion, urinary excretion, clearance, toxicity, half lethal dose.

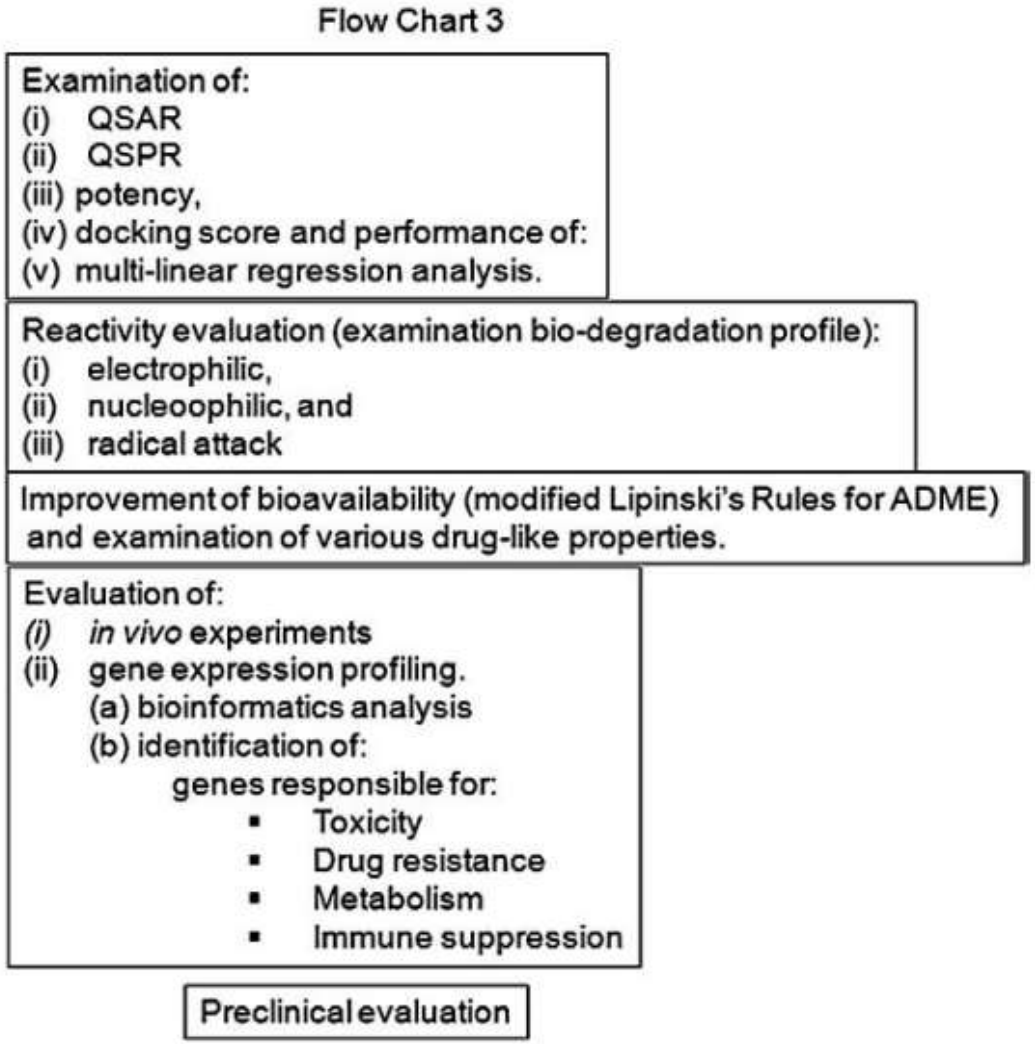
- QikProp tool is developed by Schrödinger, which is used for the prediction of ADMET related properties such as logPs, logS, BBB, CNS activity, Caco-2, and MDCK cell permeability, log K HSA for human serum albumin and log IC50 for HERG K + channel blockage.



Flow chart 1. Shows the possible steps in drug design for known targets.



Flow chart 2. Shows the possible steps in drug design for unknown targets.



Flow chart 3. Shows examination of additional properties towards the improvement of drug like properties.

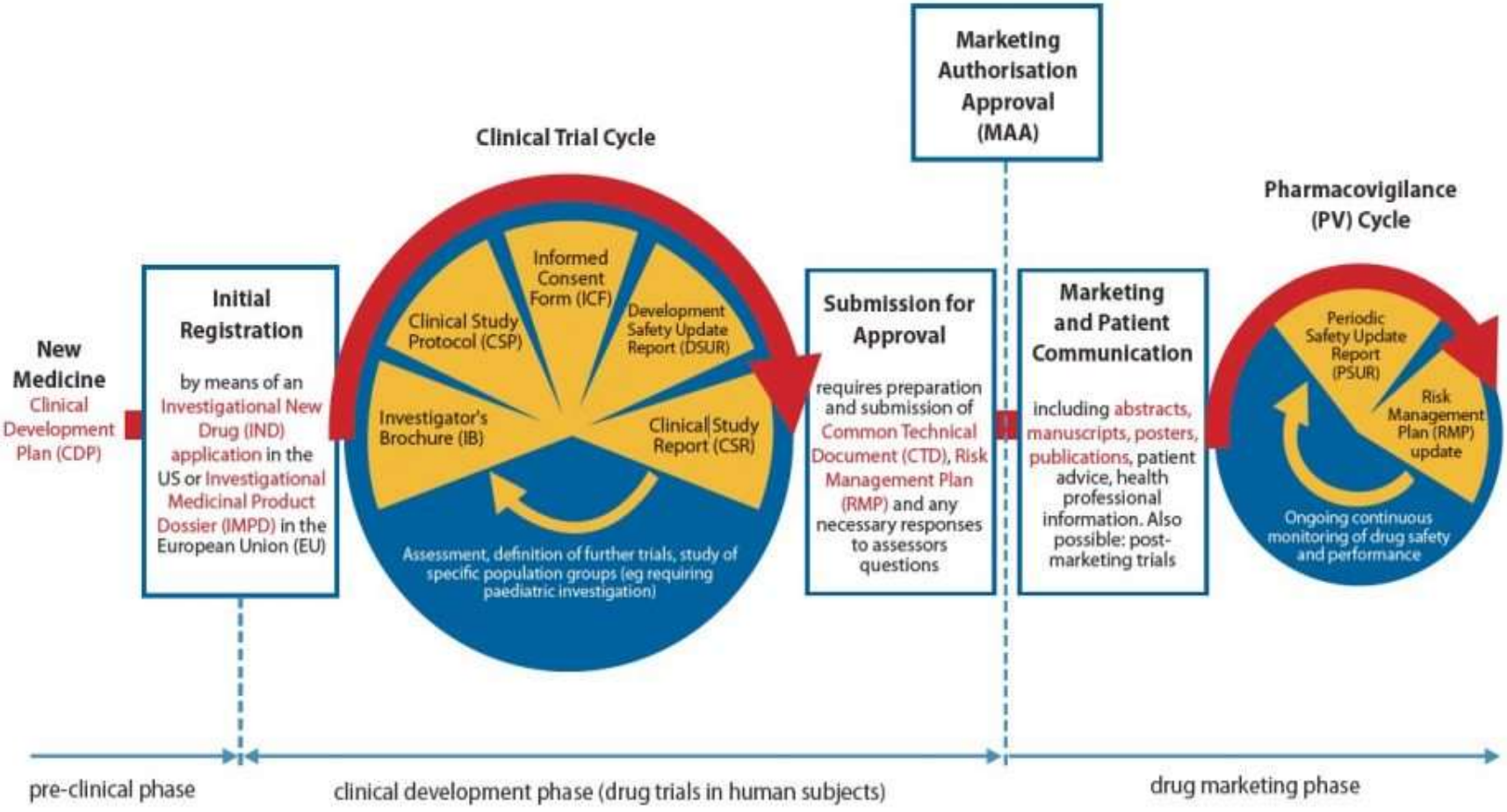


Figure 1: Documents in the drug lifecycle

Clinical Research In India

In 2007 - 221

2008 - 700(65%)

More than 100 companies conducting CR in India

Foreign companies

- Sun, Astra Zeneca, Merck, Novo nordisk, GSK, Pfizer, J&J, Novartis etc

Indian companies – CT –but could not sustain

2012 - 253 (480)

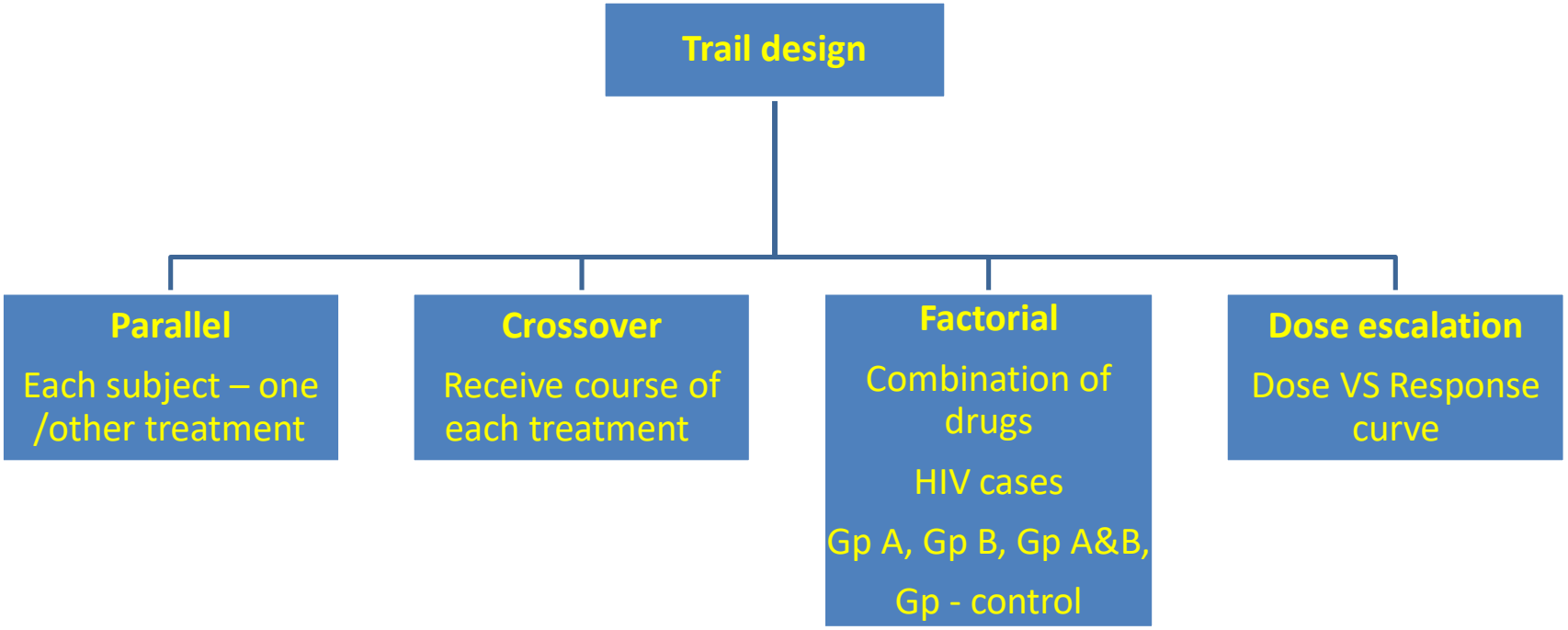
2013 - 73(207)

2013 - 17 global CT conducting in India

2014 - 87 global CT conducting in India

About 1.4% global CT – being – done in India

Types of trial design



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