BHARATHIDASAN UNIVERSITY

Tiruchirappalli- 620024, Tamil Nadu,
India

Programme: M.Sc., Biomedical Science

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

Unit-I

Introduction to Drug Discovery

Dr. P.S.Dhivya
Guest Lecturer
Department of Biomedical Science

DRUG DISCOVERY AND ASSAY DEVELOPMENT

UNIT-1

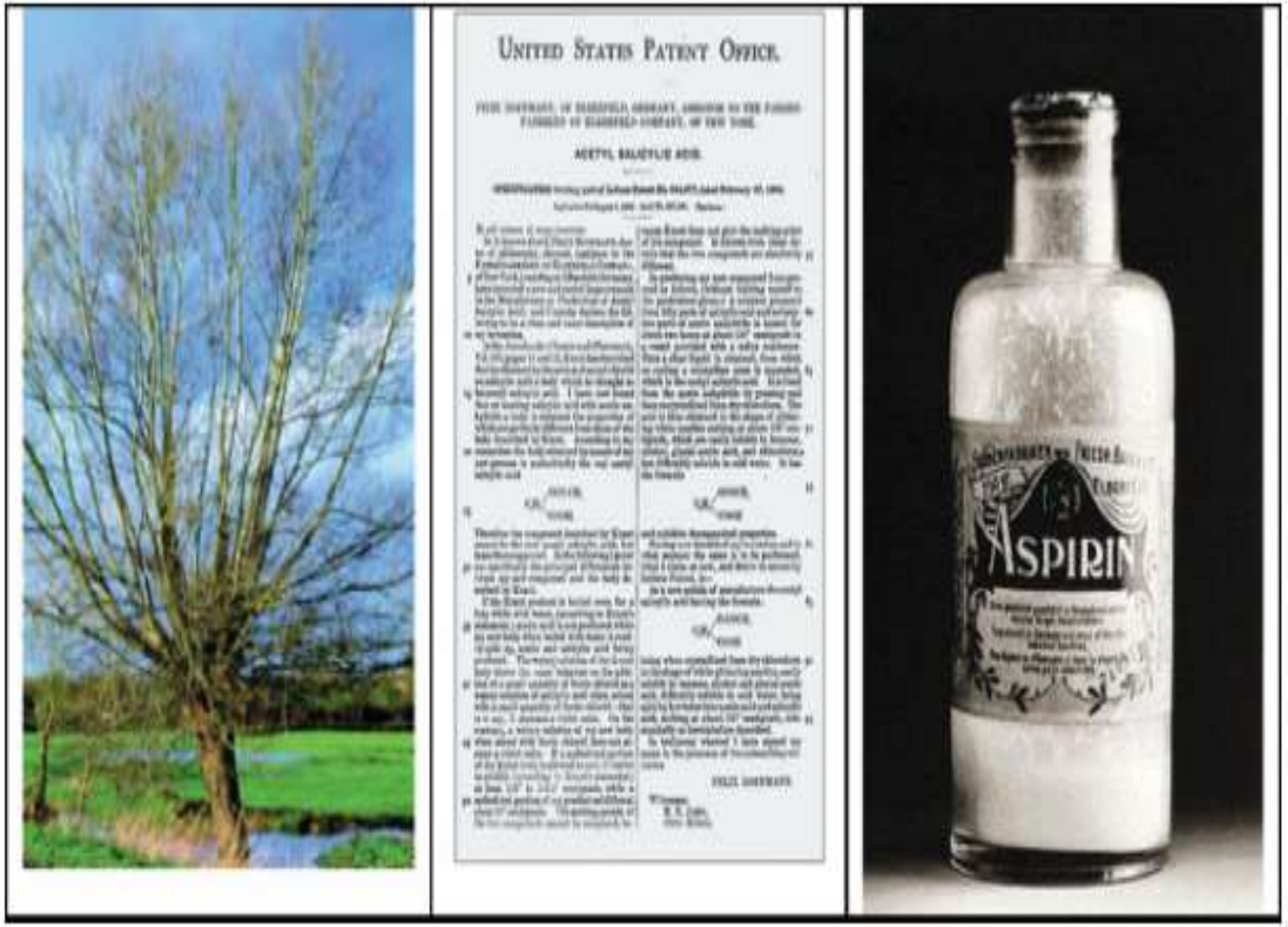


Figure 8. The white willow tree (*Salix alba*), the bark of which is rich in salicylates (left), US patent 1900 granted to Bayer's Felix Hoffmann for the synthesis of acetylsalicylic acid (middle) and an old bottle of aspirin (right).

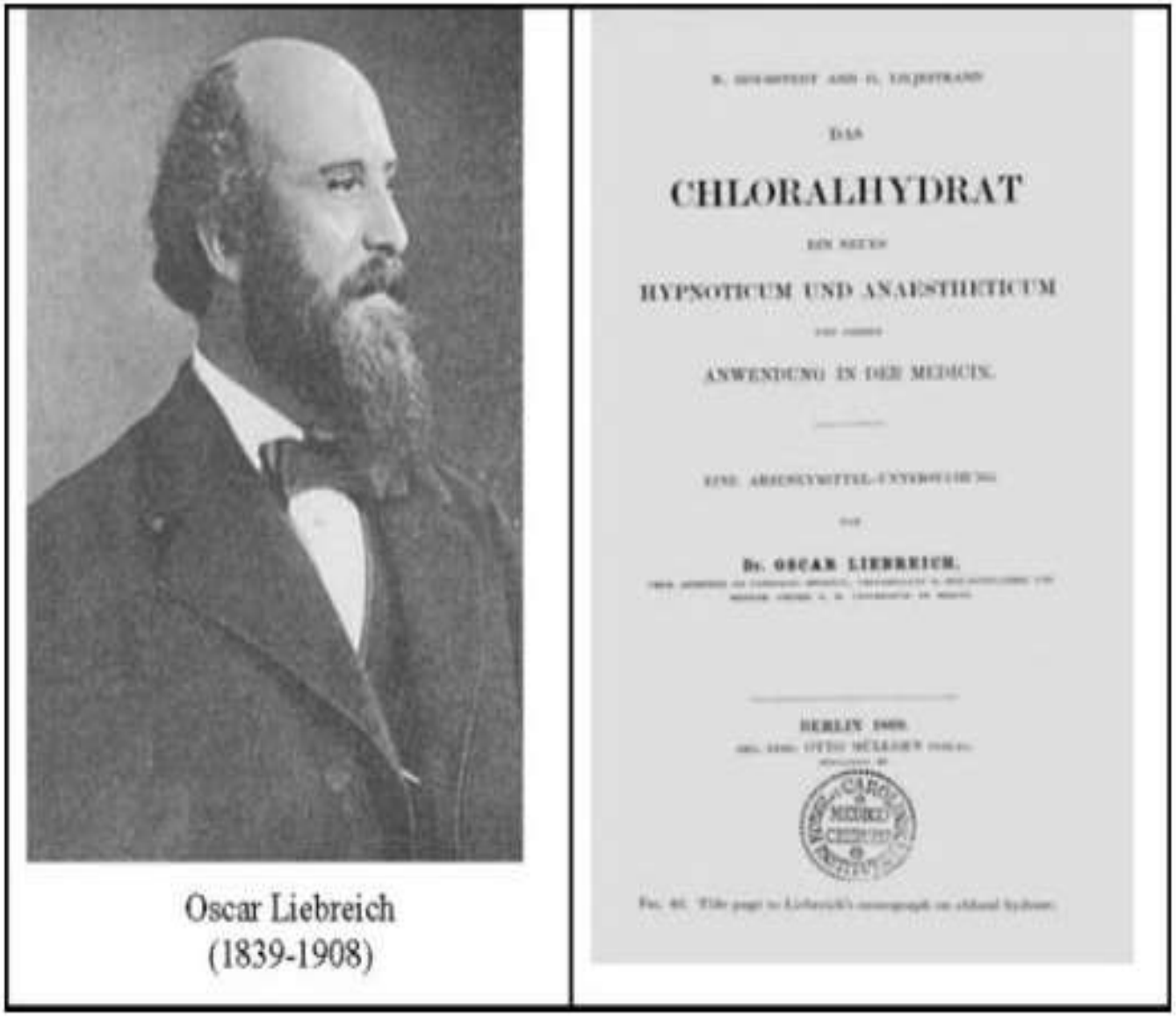


Figure 5. Portrait of Oscar Liebreich alongside the first page of his 1869 monograph on chloral hydrate and its use as a hypnotic.

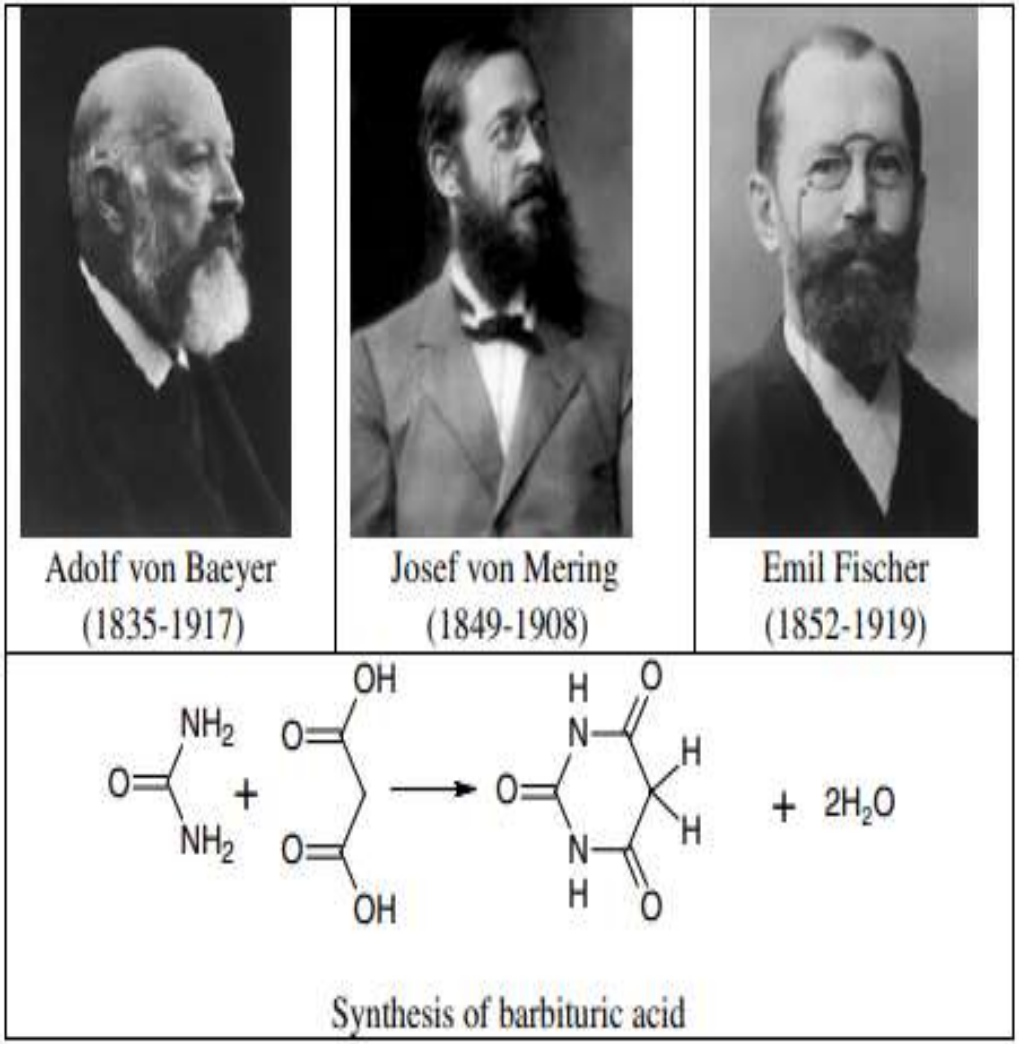


Figure 6. Scientists credited with the development of barbiturates and the synthesis of barbituric acid by Adolf von Baeyer in a condensation reaction between urea and malonic acid.

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).

Identification of a single marketed drug

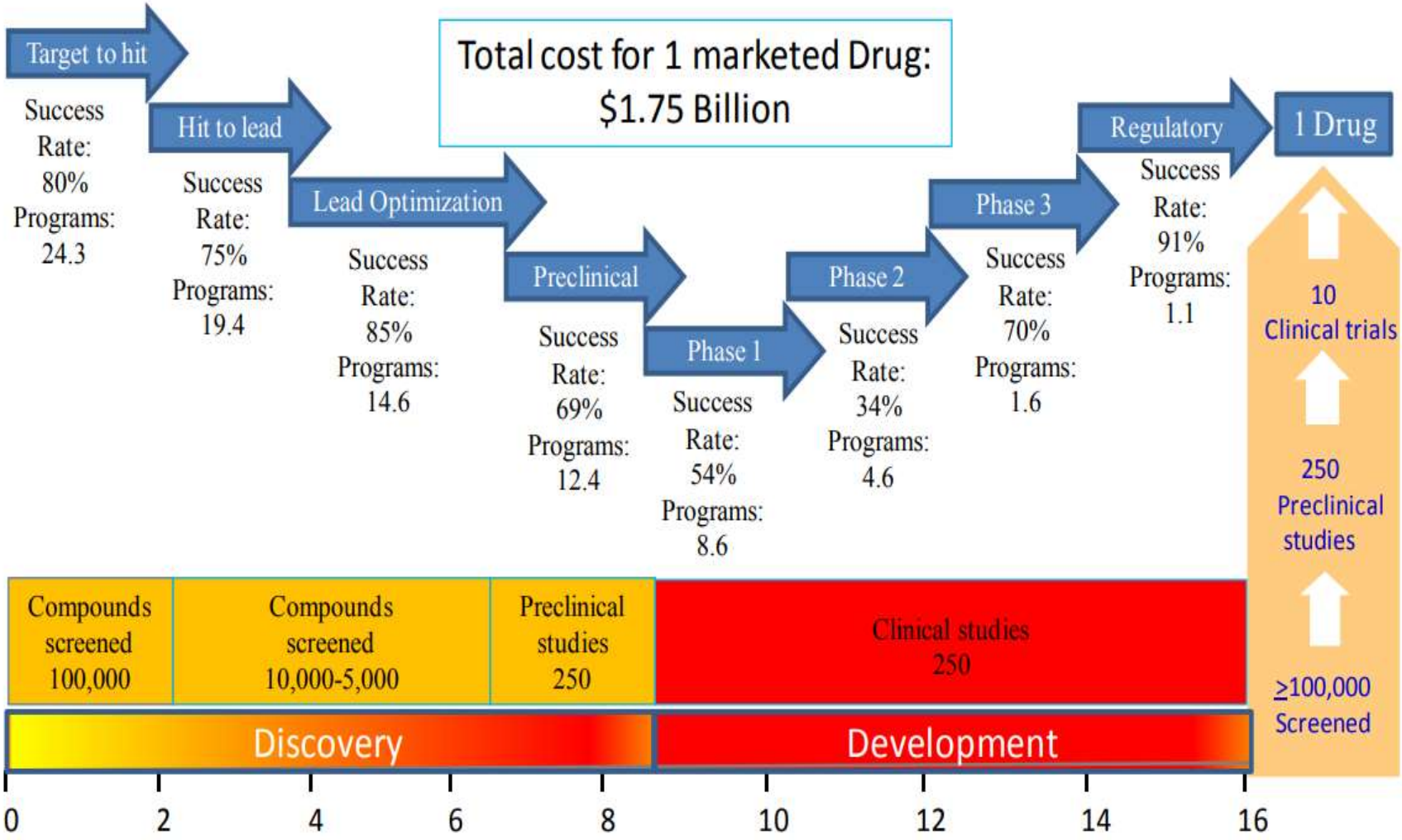
- Initial examination of over **100,000** candidate compounds
- Hundreds of preclinical animal studies
- Numerous clinical trials - thousands of patients.
- Clinical trial success
- Only **1 out of every 10** clinical candidates.
- Success rate of less than 0.001%

- 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.


Total cost for 1 marketed Drug:
$1.75 Billion
Target to hit
Success Rate: 80%
Programs: 24.3
Hit to lead
Success Rate: 75%
Programs: 19.4
Lead Optimization
Success Rate: 85%
Programs: 14.6
Preclinical
Success Rate: 69%
Programs: 12.4
Phase 1
Success Rate: 54%
Programs: 8.6
Phase 2
Success Rate: 34%
Programs: 4.6
Phase 3
Success Rate: 70%
Programs: 1.6
Regulatory
Success Rate: 91%
Programs: 1.1
1 Drug
10 Clinical trials
250 Preclinical studies
≥100,000 Screened
Compounds screened 100,000
Compounds screened 10,000-5,000
Preclinical studies 250
Clinical studies 250
Discovery
Development
0
2
4
6
8
10
12
14
16

$1.75billion

- 17 Boeing 737 jet aircrafts (based on 2012)
- Purchase approximately 7000 homes
- 70,000 automobiles (average price $25,000)
- Provide for the raising 7000 children born in 2010 to the age of 18.

ANNUAL SALES

- Lipitor® (Atorvastatin)- $13billion,
- Prozac® (Fluoxetine, peak sales $2.8billion),
- Singulair® (Monteluclast, $5.5billion)

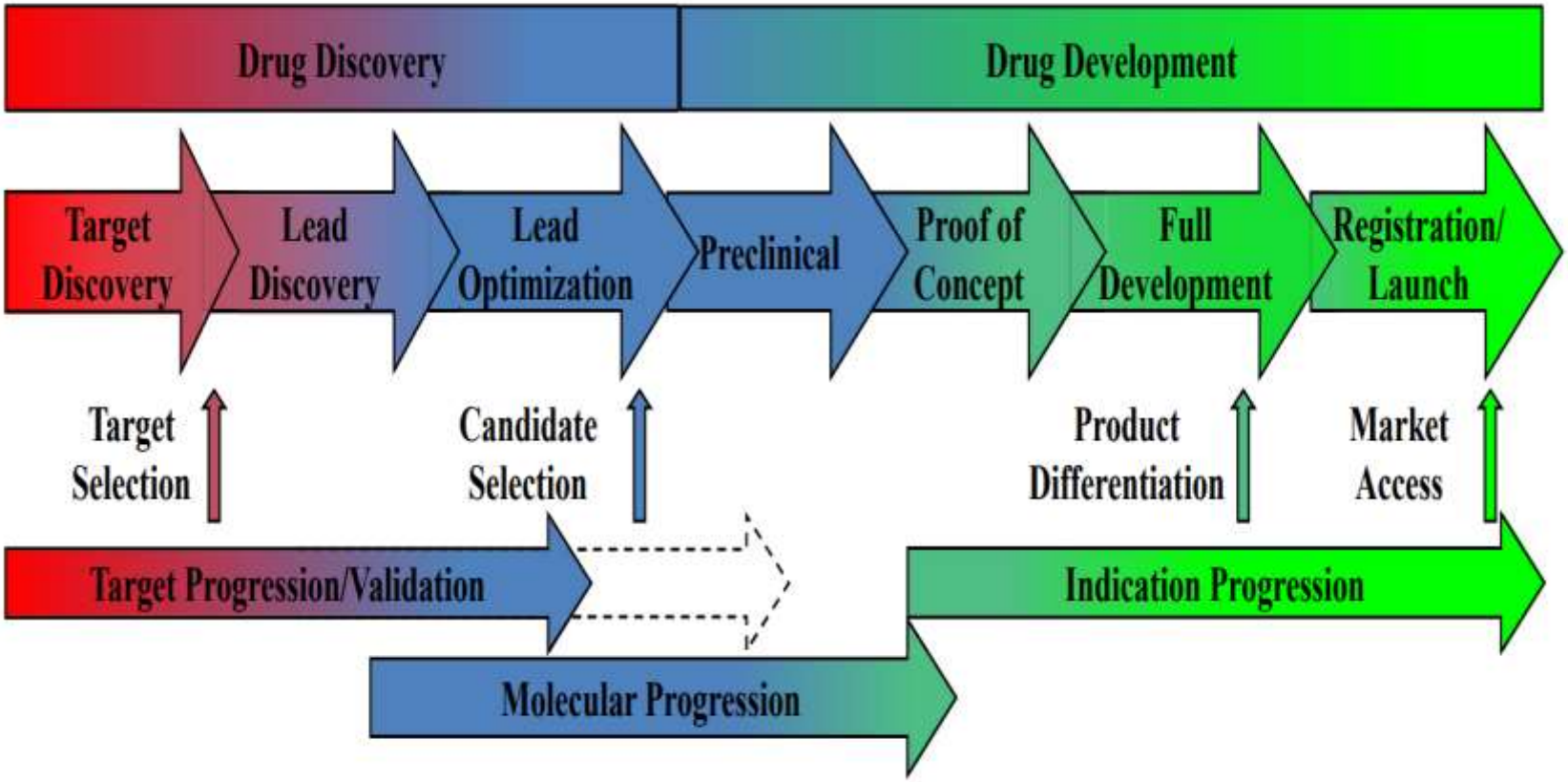


FIGURE 1.7 The drug discovery and development process viewed from "20,000 feet."

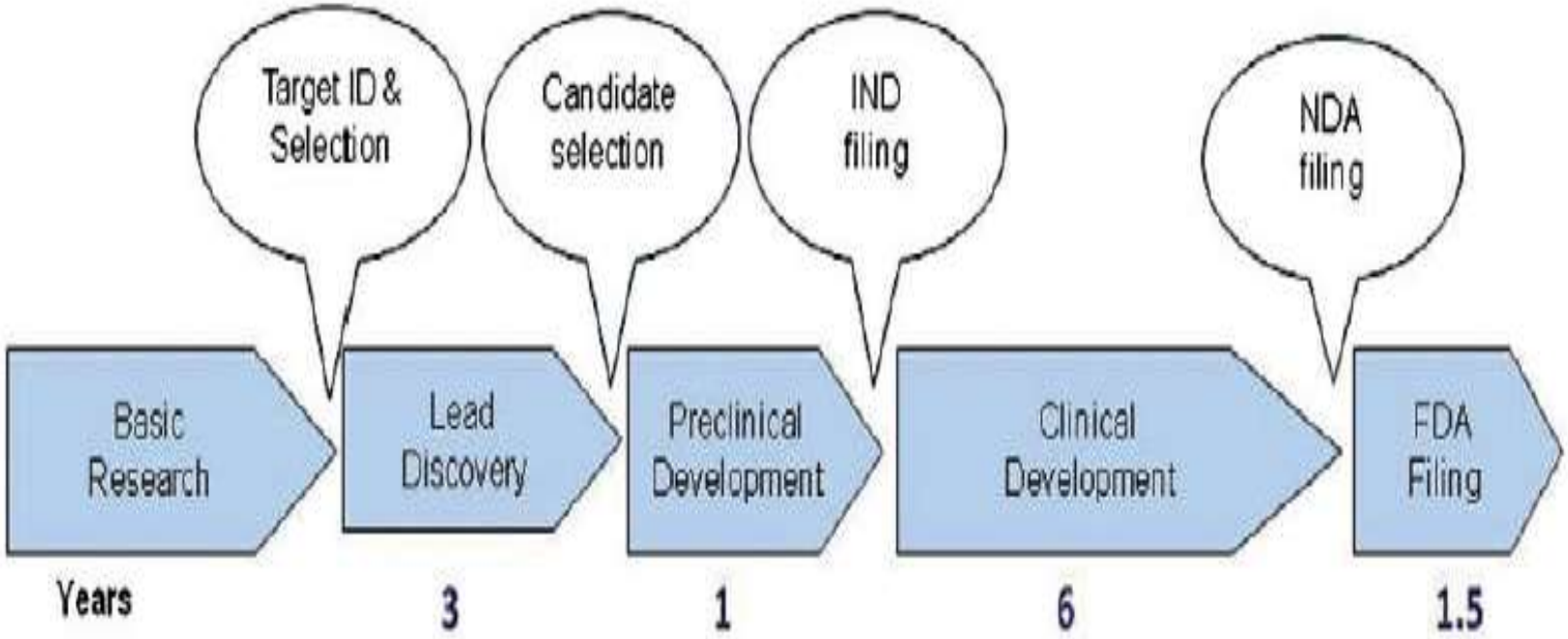
Drug Discovery

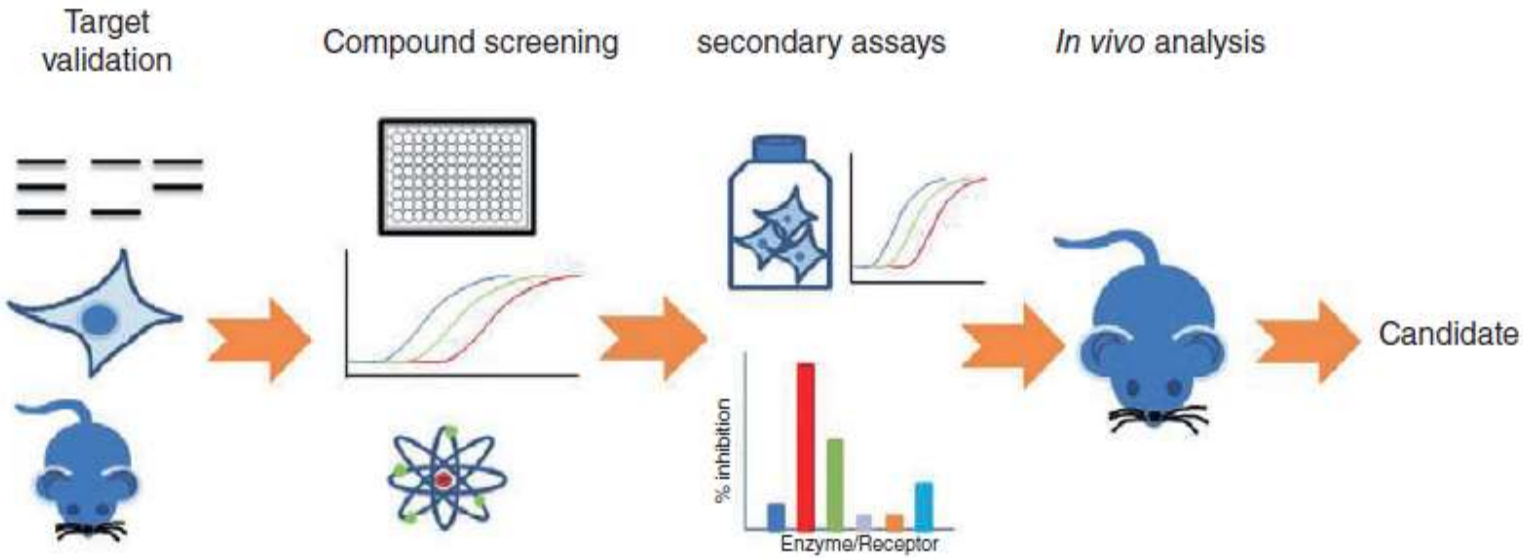
- Target discovery
- Lead discovery
- Lead optimization

- A biological target (e.g., an enzyme, G-protein-coupled receptor, ion channel, etc.)
- Disease state model designed to mimic the human disease state.
- **Target Identification and target validation**
- Use of **MOLECULAR PROBES** designed to identify multiple series of compounds that will modulate the activity of the biological target of interest

In lead discovery phase

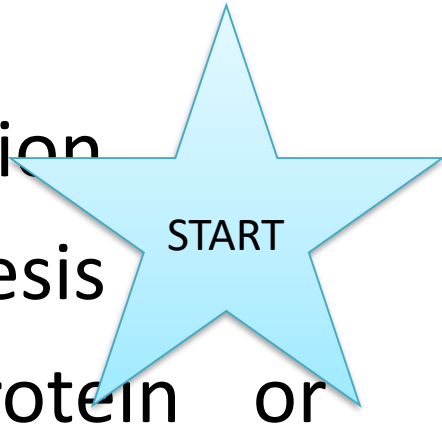
- Sets of structurally related compounds with the desired biological activity are identified (lead discovery) through biological screening of large numbers of compounds.
- An intensive search ensues to find a drug-like small molecule or biological therapeutic, typically termed a development candidate,
- 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



- 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

- 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

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.

TARGET IDENTIFICATION

- A good target needs to be efficacious, safe, meet clinical and commercial needs and, above all, be ‘druggable’.
- A ‘druggable’ target is accessible to the putative drug molecule,
- G-protein-coupled receptors (GPCRs),
- whereas antibodies are good at blocking protein/protein interactions.

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.

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.

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

Target validation

- Validation techniques range from *in vitro tools through the* use of whole animal models, to modulation of a desired target in disease patients.

Antisense technology

- Utilizes RNA-like chemically modified oligonucleotides
- Designed to be complimentary to a region of a target mRNA
- Binding of the antisense oligonucleotide to the target mRNA
- Prevents binding of the translational machinery
- Blocking synthesis of the encoded protein.
- Abbott Laboratories - Antisense probes to the rat P2X3 receptor
- By intrathecal minipump, had marked anti-hyperalgesic activity in the Complete Freund's Adjuvant model
- Demonstrating an unambiguous role for this receptor in chronic inflammatory states.
- After antisense discontinued algesic responses returned

Transgenic Animals

- Use of the P2X7 knockout mouse to confirm a role for this ion channel in the development and maintenance of neuropathic and inflammatory pain.
- In mice lacking P2X7 receptors, inflammatory and neuropathic hypersensitivity is completely absent to both mechanical and thermal stimuli, while normal nociceptive processing is preserved.
- These transgenic animals were also used to confirm the mechanism of action for this ablation in vivo as the transgenic mice were unable to release the mature pro-inflammatory cytokine IL-1beta from cells although there was no deficit in IL-1beta mRNA expression

Gene knock-ins

- Non-enzymatically functioning protein replaces the endogenous protein.
- Protein has structural as well as enzymatic functions and these mice should ostensibly mimic more closely what happens during treatment with drugs, that is, the protein is there but functionally inhibited.

small interfering RNA (siRNA)

- Double-stranded RNA (dsRNA) specific to the gene to be silenced is introduced into a cell or organism, where it is recognized as exogenous genetic material and activates the RNAi pathway.
- The ribonuclease protein Dicer is activated which binds and cleaves dsRNAs
- These short double-stranded fragments are called siRNAs

siRNAs

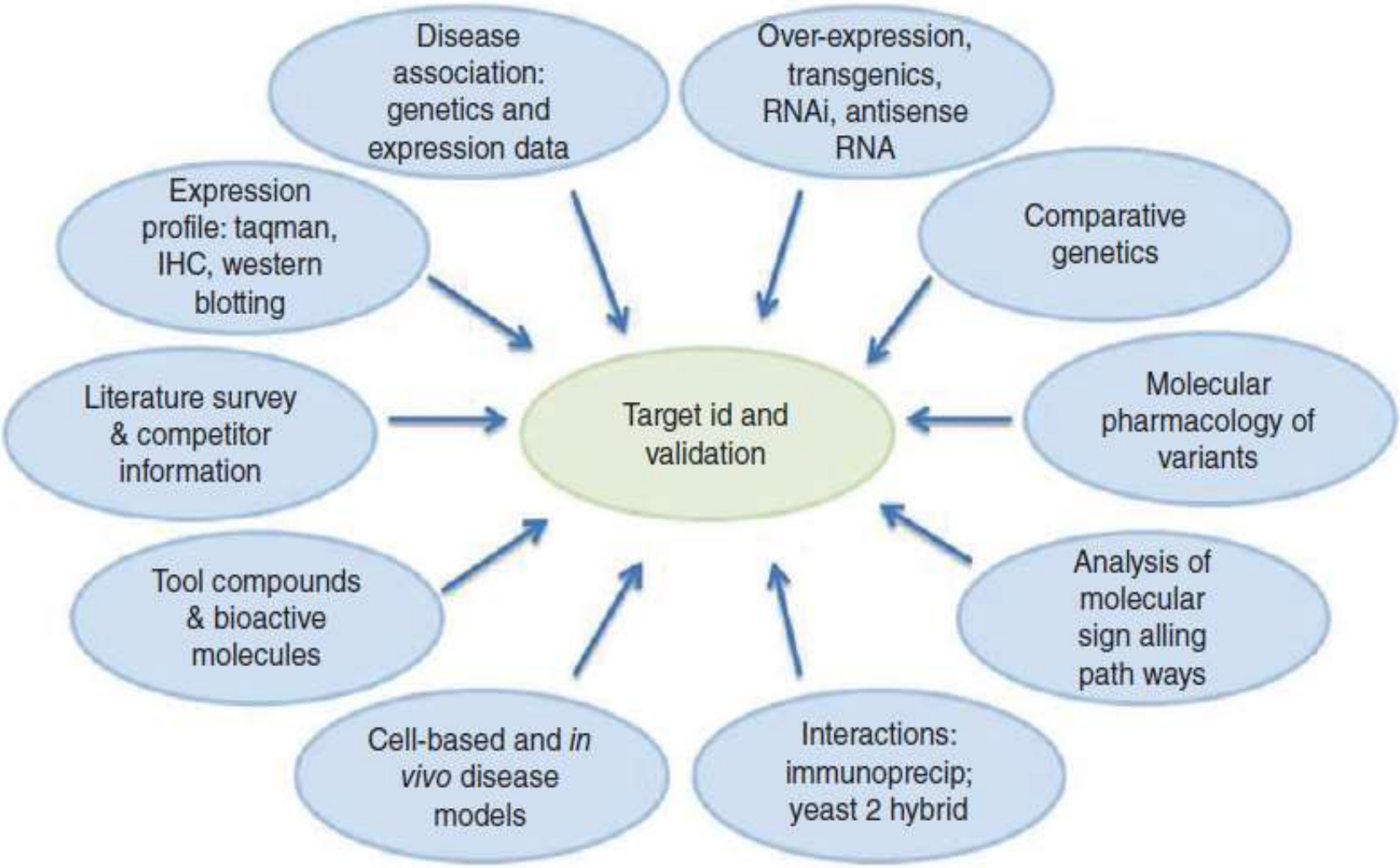
- These siRNAs are then separated into single strands and integrated into an active RNA-induced silencing complex (RISC).
- After integration into the RISC, siRNAs basepair to their target mRNA and induce cleavage of the mRNA, thereby preventing it from being used as a translation template.

Monoclonal antibodies

- Monoclonal antibodies are an excellent target validation tool as they interact with a larger region of the target molecule surface, allowing for better discrimination between even closely related targets and often providing higher affinity.

Chemical genomics

- Chemical genomics can be defined as the study of genomic responses to chemical compounds.
- Goal is the rapid identification of novel drugs and drug targets
- Chemical genomics brings together diversity-oriented chemical libraries and high-information-content cellular assays, along with the informatics and mining tools necessary for storing and analysing the data generated
- Goal of this approach is to provide chemical tools against every protein encoded by the genome.
- Evaluate cellular function prior to full investment in the 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

HIT IDENTIFICATION

- In this process, the right small molecules, also called hits, which binding to the target and modifying its function are identified.
- High quality of the starting hits make faster progress with lower attrition rates in drug discovery project.

HIT IDENTIFICATION: FINDING A STARTING POINT

- To identify a single compound
- 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.

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).

- 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,
- (5) less than 10 rotatable bonds.

MODERN DRUG DISCOVERY PROGRAMS

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

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.

PHER Astar FSX plate readers integrated in a HighRes Biosolutions modular robotic workstation at AstraZeneca UK

- Large libraries -Chemically diverse
- Libraries designed to target specific types of biological targets (e.g., kinases, phosphatases)
- Physical samples for screening are available from commercial sources (e.g., Maybridge, Enamine, Aldrich, etc.), and pharmaceutical companies.

- False positives and false negative results
- Manipulations
- Error may occur during some facet of reagent handling (such as a clogged pipette tip).
- Screening sample may have degraded over time, creating “ghost samples”
- Structure no longer matches the material originally entered into the library

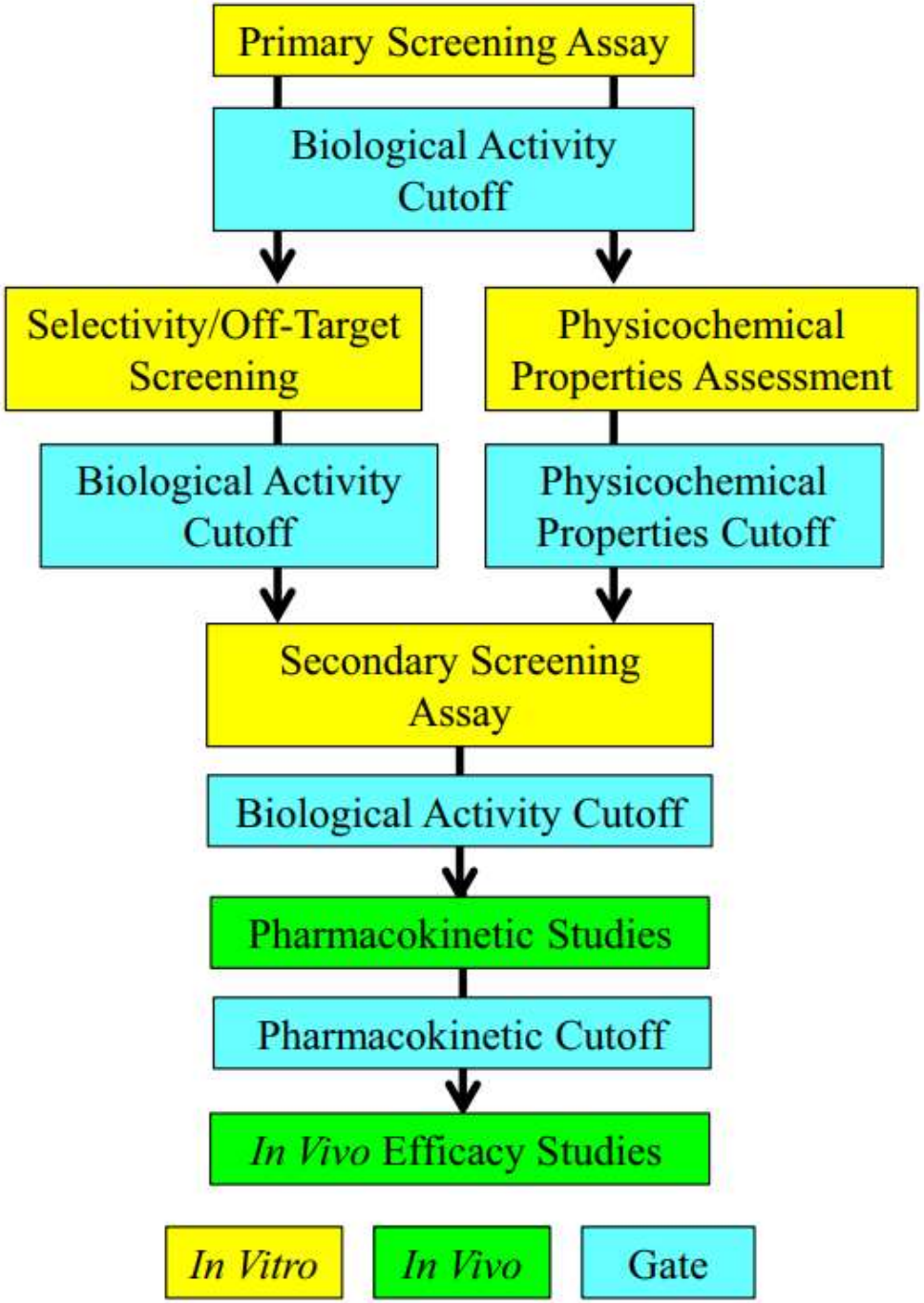
Fragment Based Screening

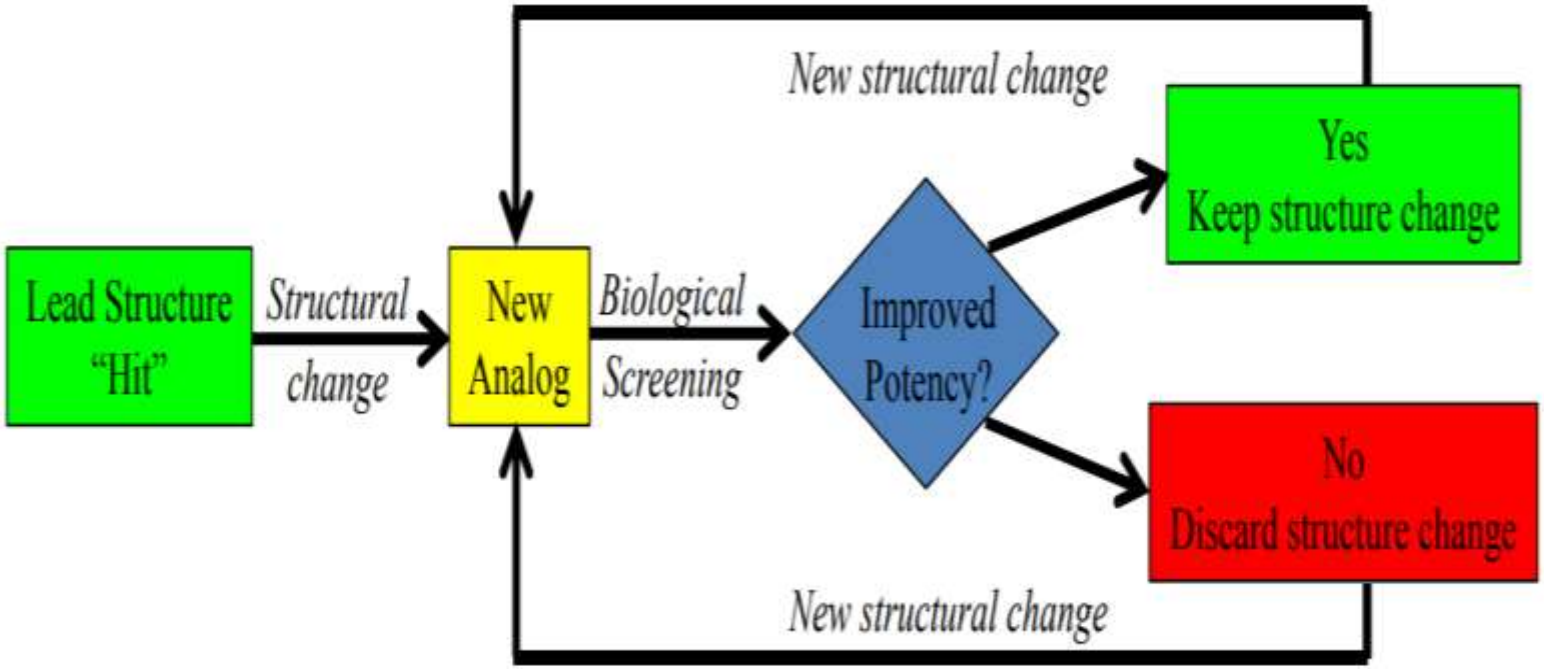
- Biophysical techniques to measure low binding affinities of the fragments, like surface plasmon resonance (SPR), magnetic resonance spectrometry (NMR), X-ray crystallography.
- Orthogonal fragment screening technology allows us to discovery solutions to a wide array of target types.

Integrity of “hit”

- Samples is generally assessed using High-performance liquid chromatography/ Mass spectroscopy (HPLC/MS) methods.
- In addition, biological screening is often repeated with the “hit” compounds in order to validate the HTS results

- If 500,000 compounds are screened and only 0.1% of the compounds in the library provide interesting biological results, this still leaves 500 compounds to be evaluated.

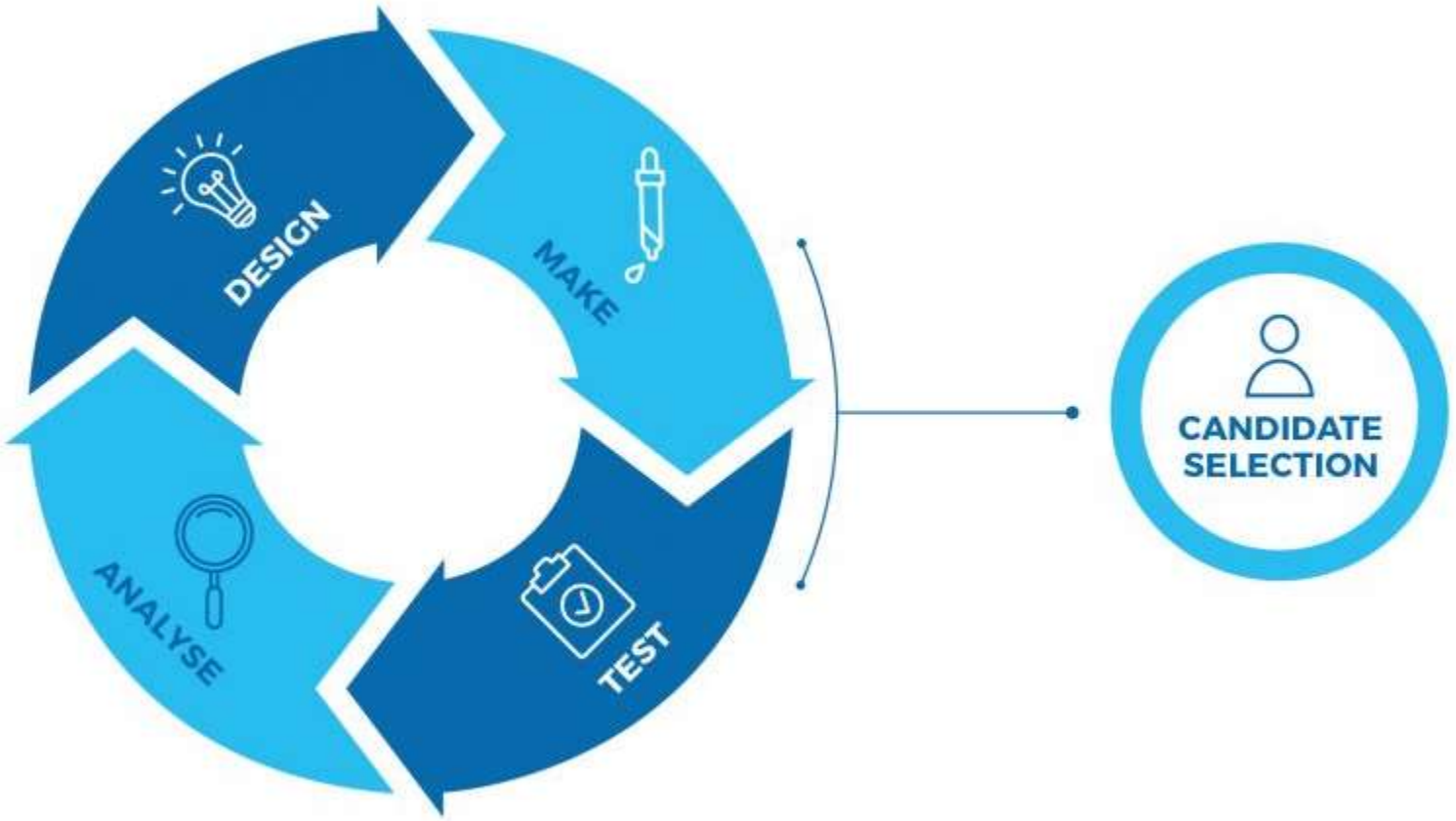

Primary Screening Assay
Biological Activity Cutoff
Selectivity/Off-Target Screening
Physicochemical Properties Assessment
Biological Activity Cutoff
Physicochemical Properties Cutoff
Secondary Screening Assay
Biological Activity Cutoff
Pharmacokinetic Studies
Pharmacokinetic Cutoff
In Vivo Efficacy Studies
In Vitro
In Vivo
Gate

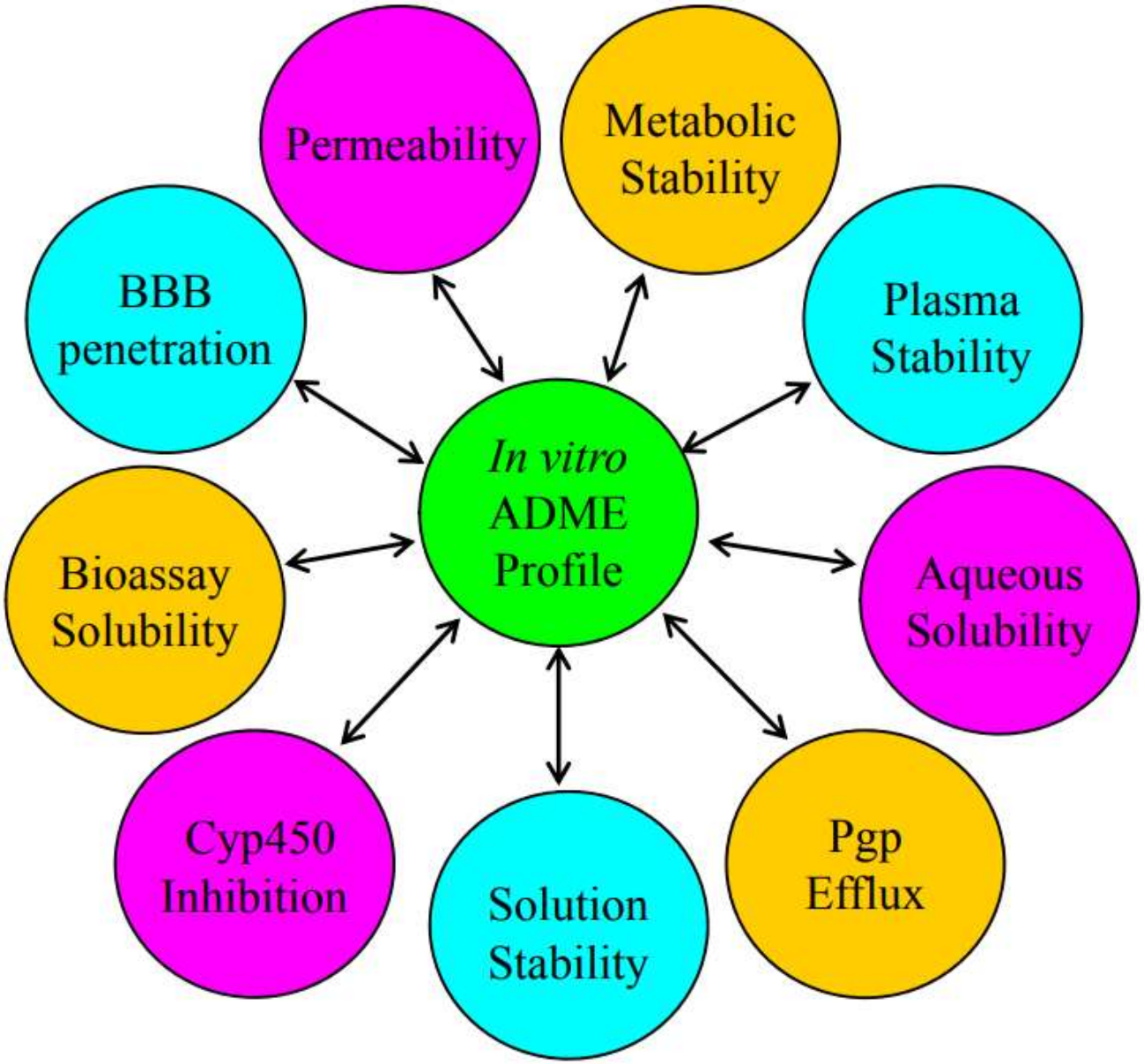

New structural change
Lead Structure
"Hit"
Structural
change
New
Analog
Biological
Screening
Improved
Potency?
Yes
Keep structure change
No
Discard structure change
New structural change

Lead Optimisation

To deliver one or more clinical candidate for evaluation in a formal regulatory (GLP) programme prior to human clinical trials.

Interdisciplinary team must monitor and manipulate multiple parameters pertaining to ADMET properties -potency and selectivity -within a patentable chemical space.




Permeability
Metabolic Stability
BBB penetration
Plasma Stability
In vitro ADME Profile
Bioassay Solubility
Aqueous Solubility
Cyp450 Inhibition
Solution Stability
Pgp Efflux

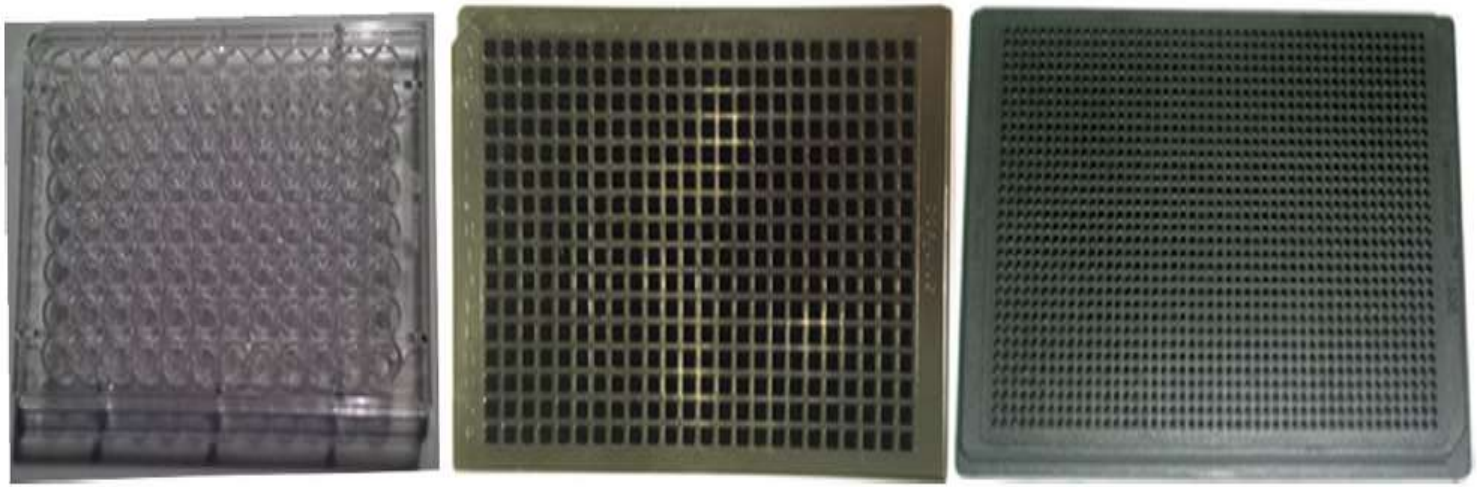
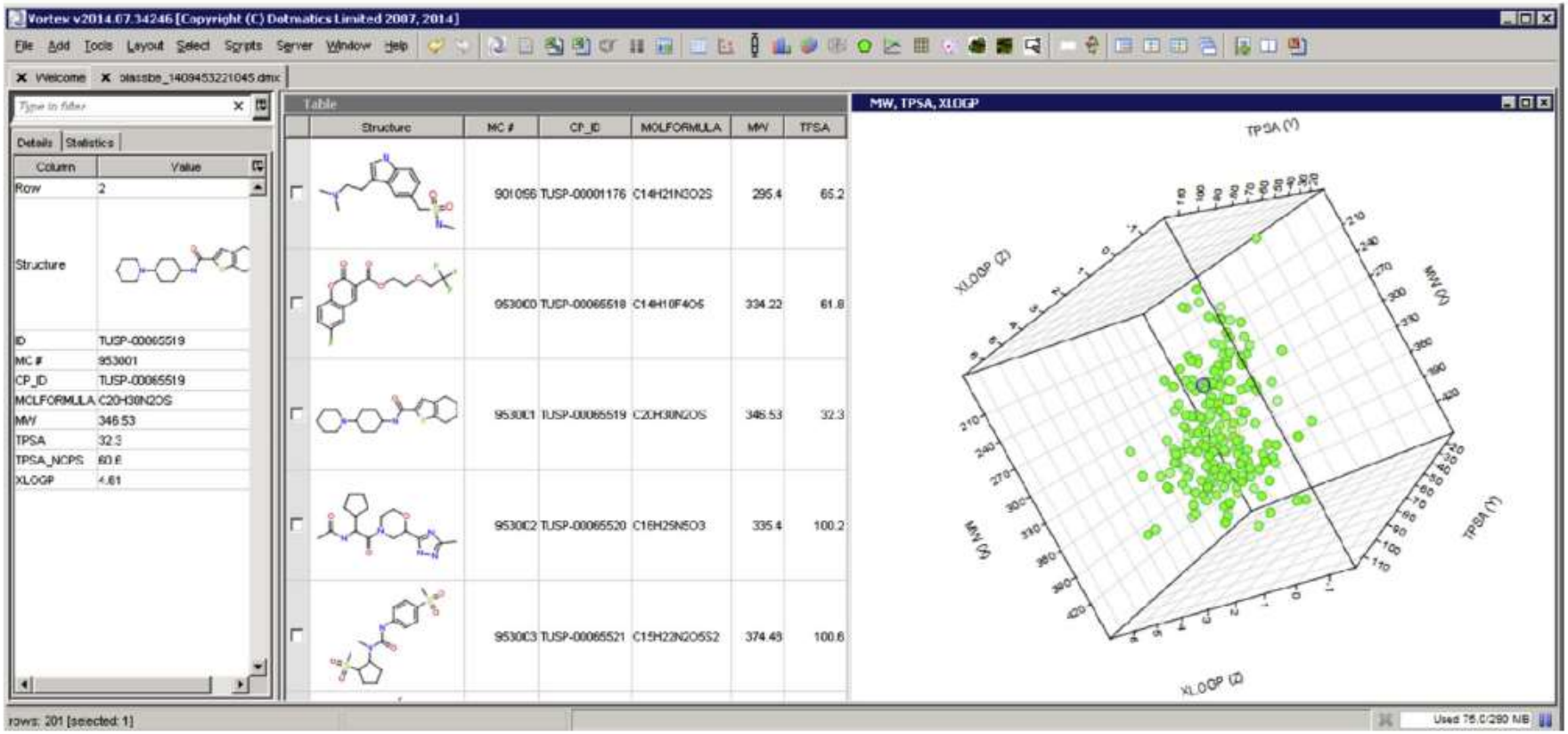


FIGURE 2.18 The typical *in vitro* screening assay employs 96 (left), 384 (middle), or 1536 (right) well plates. As the plates increase in well number (density), the well volume decreases and reagent requirements drop accordingly. The cost saving associated with higher density plates can be substantial.

Virtual high throughput screening

- in silico screening
- Advanced molecular modeling techniques are combined with virtual chemical libraries and structural data on the biological target in order to assess a compound's ability to interact with the target of interest.
- Virtual chemical libraries are often freely available from commercial vendors **(the largest of which is the ZINC database; http://zinc.docking.org/)**



Cheminformatics software platforms provide scientist with the ability to link compound structures to physicochemical properties (e.g., molecular formula, molecular weight, Topological Polar Surface Area (TPSA), solubility, etc.) and screening data from multiple sources in a searchable database.

National Library of Medicine
National Center for Biotechnology Information

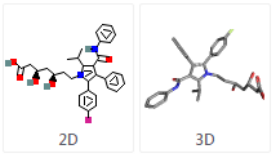
PubChem About Blog Submit Contact Search PubChem

COMPOUND SUMMARY

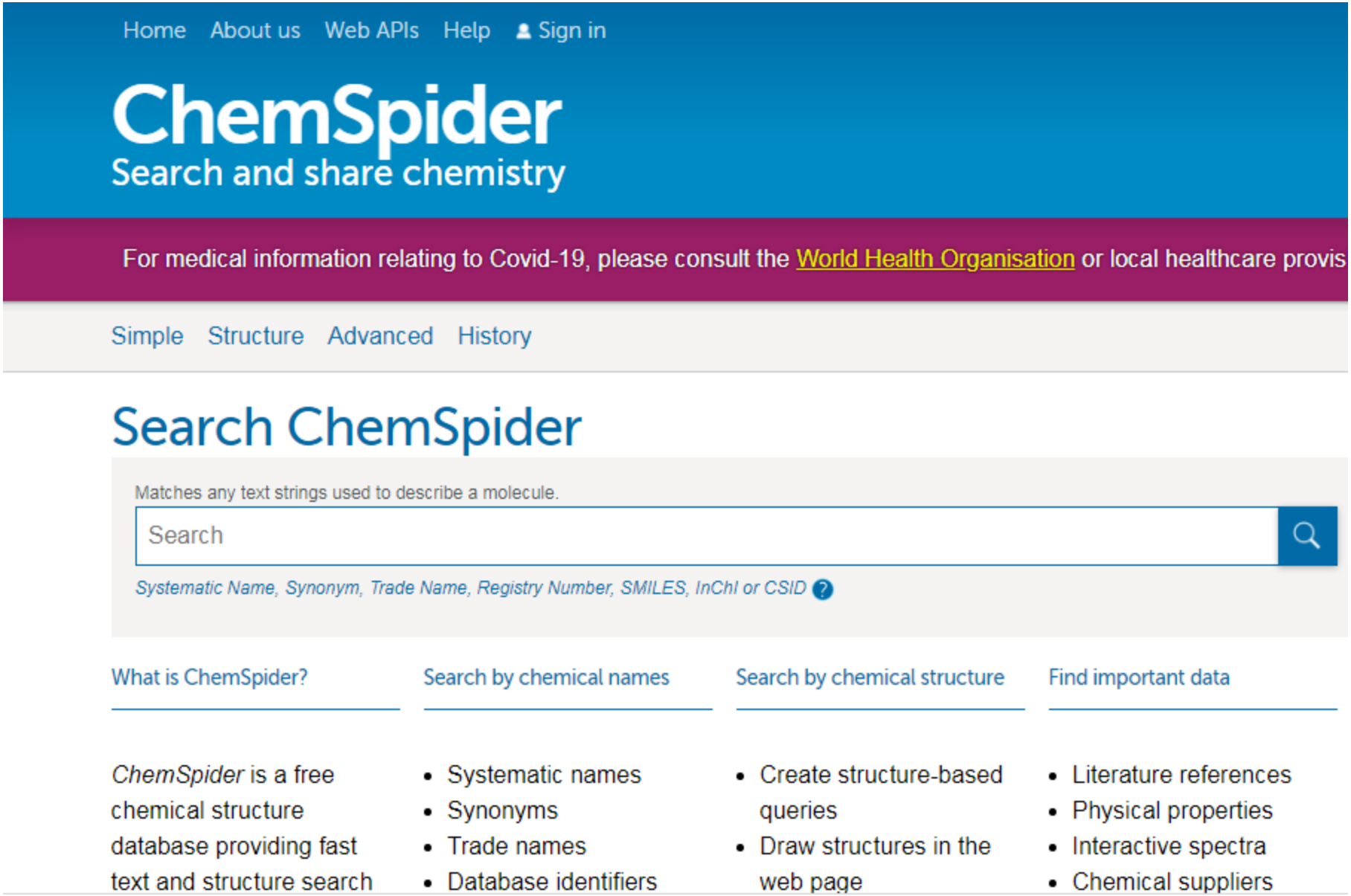
Atorvastatin

Cite Download

CONTENTS

PubChem CID	60823
Structure	 2D 3D

Find Similar Structures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Simple Structure Advanced History
Search ChemSpider
Matches any text strings used to describe a molecule.
Search
Systematic Name, Synonym, Trade Name, Registry Number, SMILES, InChI or CSID
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ChemSpider is a free chemical structure database providing fast text and structure search
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Systematic names
Synonyms
Trade names
Database identifiers
Search by chemical structure
Create structure-based queries
Draw structures in the web page
Find important data
Literature references
Physical properties
Interactive spectra
Chemical suppliers

- Structural information on biological targets may be available through X-ray crystallography, as a large number of protein crystal structures are available through the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (http://www.rcsb.org/pdb/home/home.do)

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RCSB PDB PROTEIN DATA BANK

187844 Biological Macromolecular Structures Enabling Breakthroughs in Research and Education

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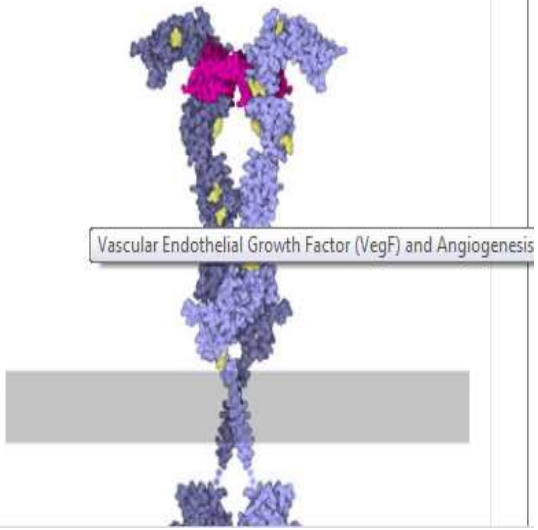
A Structural View of Biology

This resource is powered by the Protein Data Bank archive-information about the 3D shapes of proteins, nucleic acids, and complex assemblies that helps students and researchers understand all aspects of biomedicine and agriculture, from protein synthesis to health and disease.

As a member of the wwPDB, the RCSB PDB curates and annotates PDB data.

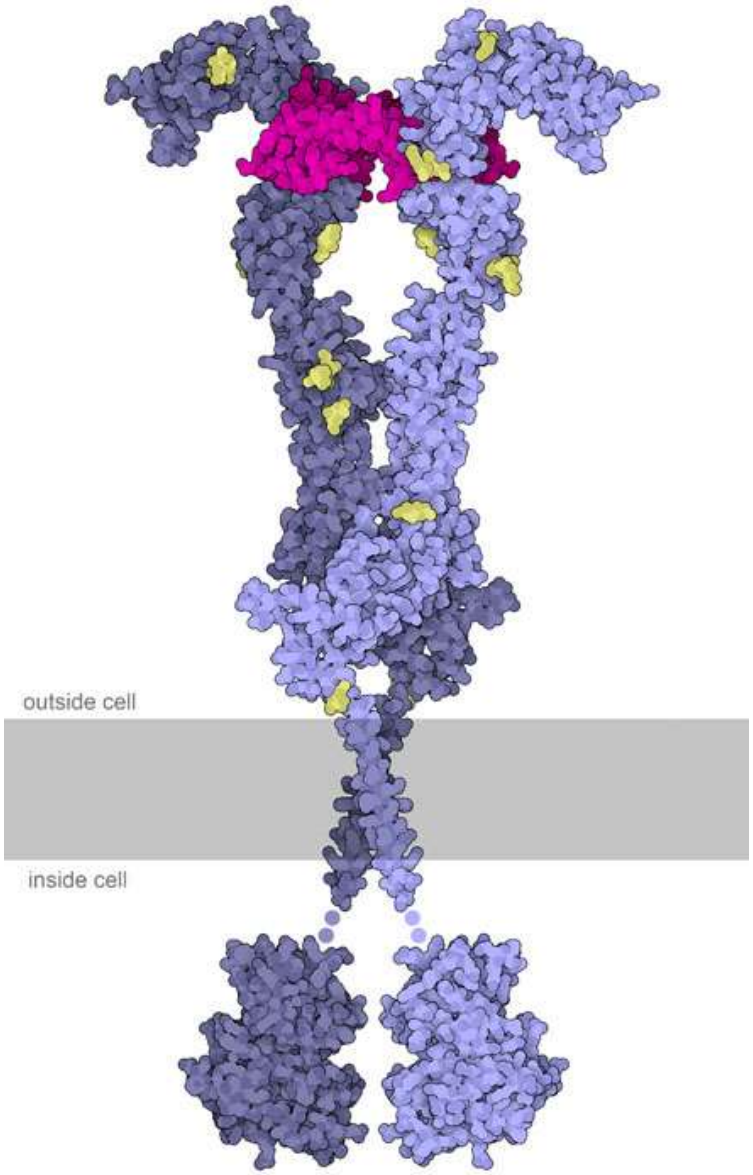
The RCSB PDB builds upon the data by creating tools and resources for research and education in molecular biology, structural biology, computational biology, and beyond.

March Molecule of the Month

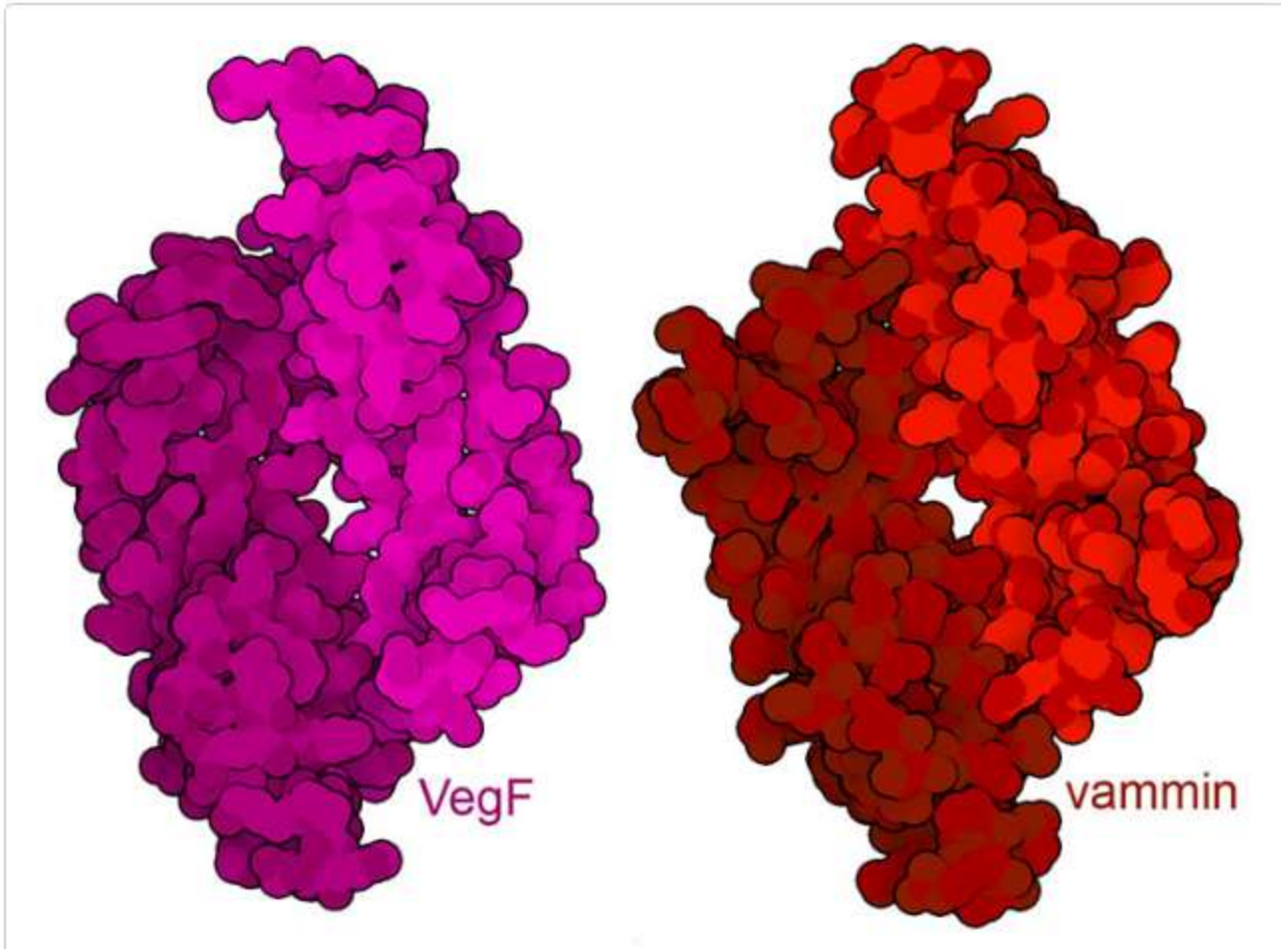


Vascular Endothelial Growth Factor (VegF) and Angiogenesis

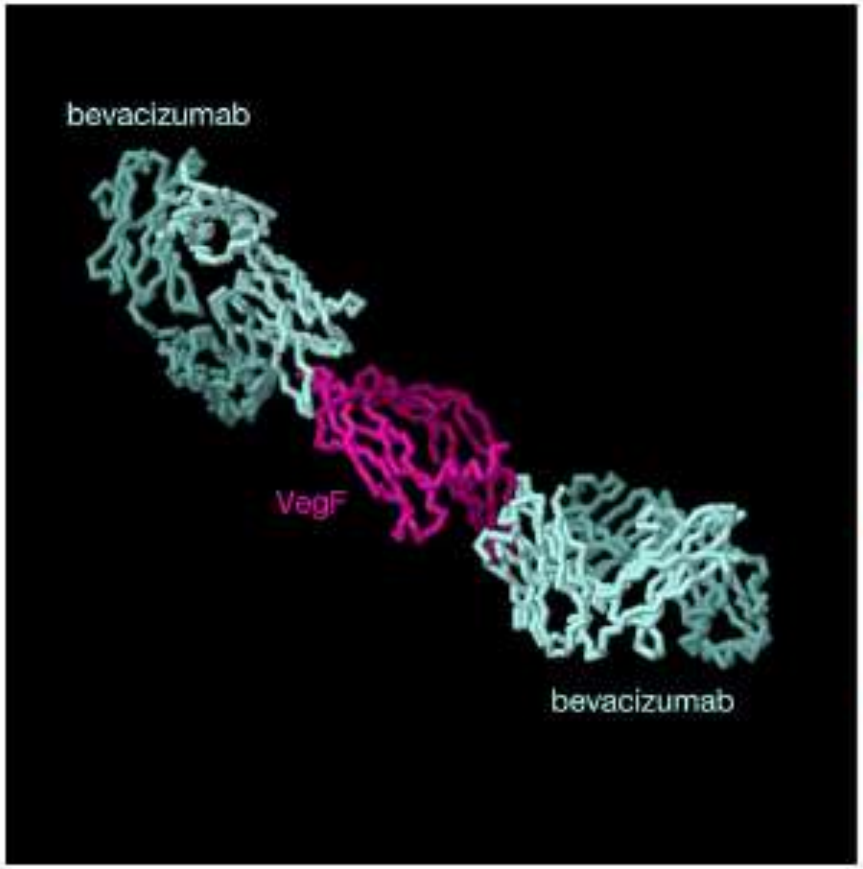
1.rcsb.org/motm

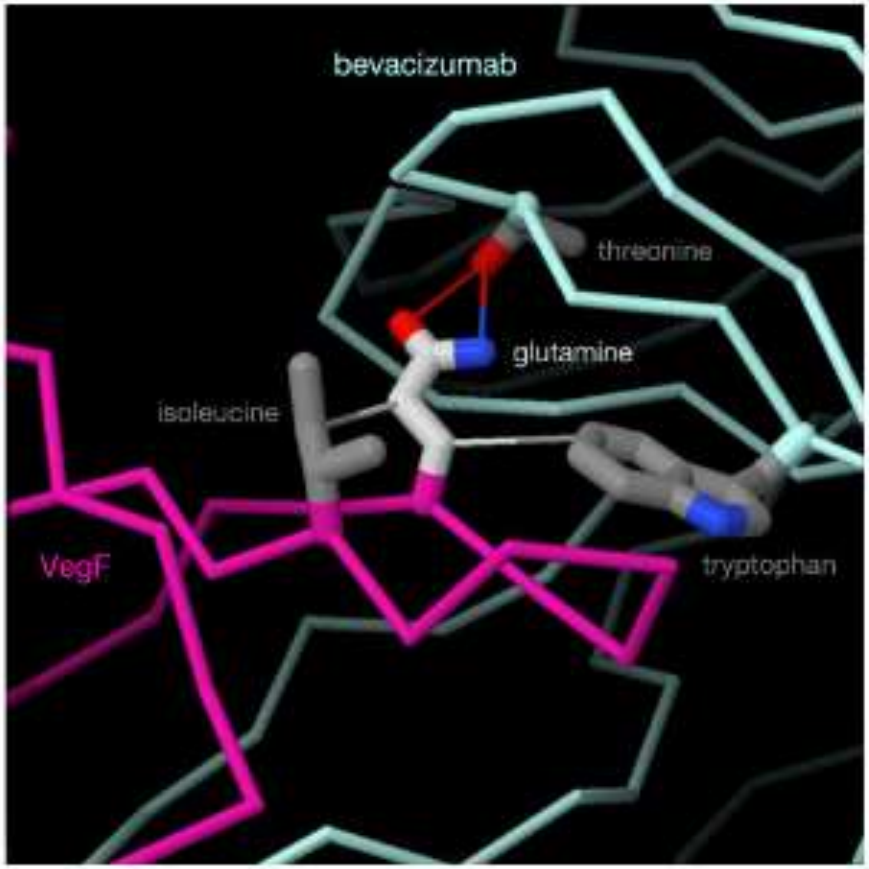


Vascular Endothelial Growth Factor (VegF)


VegF
vammin

VegF and Bevacizumab





- The structure of bevacizumab with VegF (PDB ID 1bj1) shows that two bevacizumab molecules interact with VegF, blocking both ends of the VegF dimer (as seen on the left).
- Thus, it is unable to dimerize the receptor and unable to activate the angiogenic signaling cascade.
- As with most antibodies, highly-complementary interactions are formed between bevacizumab and VegF.
- For example, a set of three molecular interactions centered around a glutamine are critical for the binding of bevacizumab to VegF. These include hydrogen bonding interactions with a neighboring threonine, and hydrophobic interactions with tryptophan and isoleucine that constrain the glutamine in the proper conformation.
- To explore this structures in more detail, click on the image for an interactive JSmol.

DRUG DEVELOPMENT

- Single compound -Identified
- Designed - Approval for sale by regulatory bodies.
- Submission of an Investigational New Drug (IND)
- Permission to move a **CLINICAL CANDIDATE INTO HUMAN STUDY.**
- This document provides regulatory agencies with detailed preclinical data describing animal pharmacology and toxicology studies, chemical manufacturing information (including formulation, stability studies, and quality control measures), how the clinical compounds will be studied in human populations if the studies are approved.

IN PHASE I CLINICAL TRIALS

- Safety and tolerability of an investigational new drug is examined in a SMALL NUMBER OF HEALTHY INDIVIDUALS
- 20 to 100 people- 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.
- The cycle is repeated until intolerable side effects appear in order to determine the maximum tolerated dose (MTD).

PHASE II

- 100 to 300 patients
- Designed to determine whether or not the **Clinical candidate provides the desired biological impact.**
- **IIA,** the goal is to determine the dose required to provide the **desired therapeutic impact or endpoint** for the clinical candidate.
- **IIB** studies to determine the **overall efficacy of candidate compounds** in a limited population of subjects.
- Only 34% of phase II clinical candidates successfully reach phase III studies.

Phase III clinical trials

- The number of subjects, time requirements, and complex design of (especially in chronic medical conditions) dictate that they are the most expensive aspect of drug discovery and development.
- New Drug Application is submitted to the appropriate regulatory body.
- Comprehensive details of both animal and human studies.

Phase IV studies

- Alterations to labeling based on safety results
- Contraindication for use of the new drug in combination with other medications
- Even the withdrawal of marketing approval if the findings are severe enough.
- The COX-2 selective nonsteriodal anti-inflammatory agent Vioxx® (Rofecoxib), for example, was removed from the market after phase IV studies indicated that it increased the risk of ischemic events in patients.

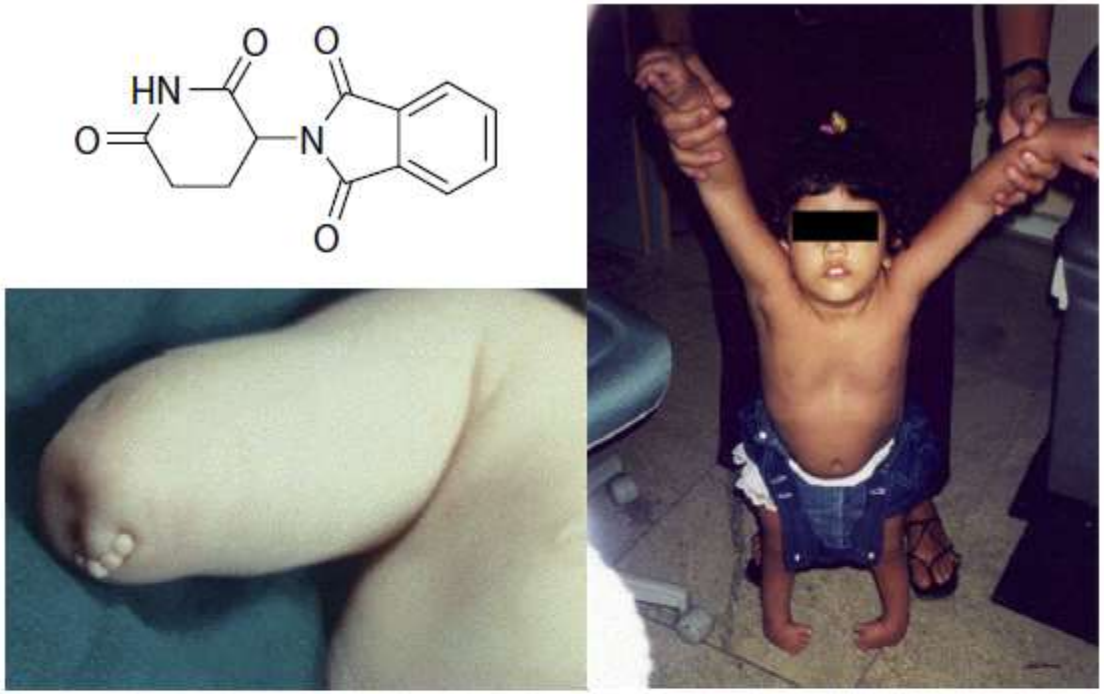
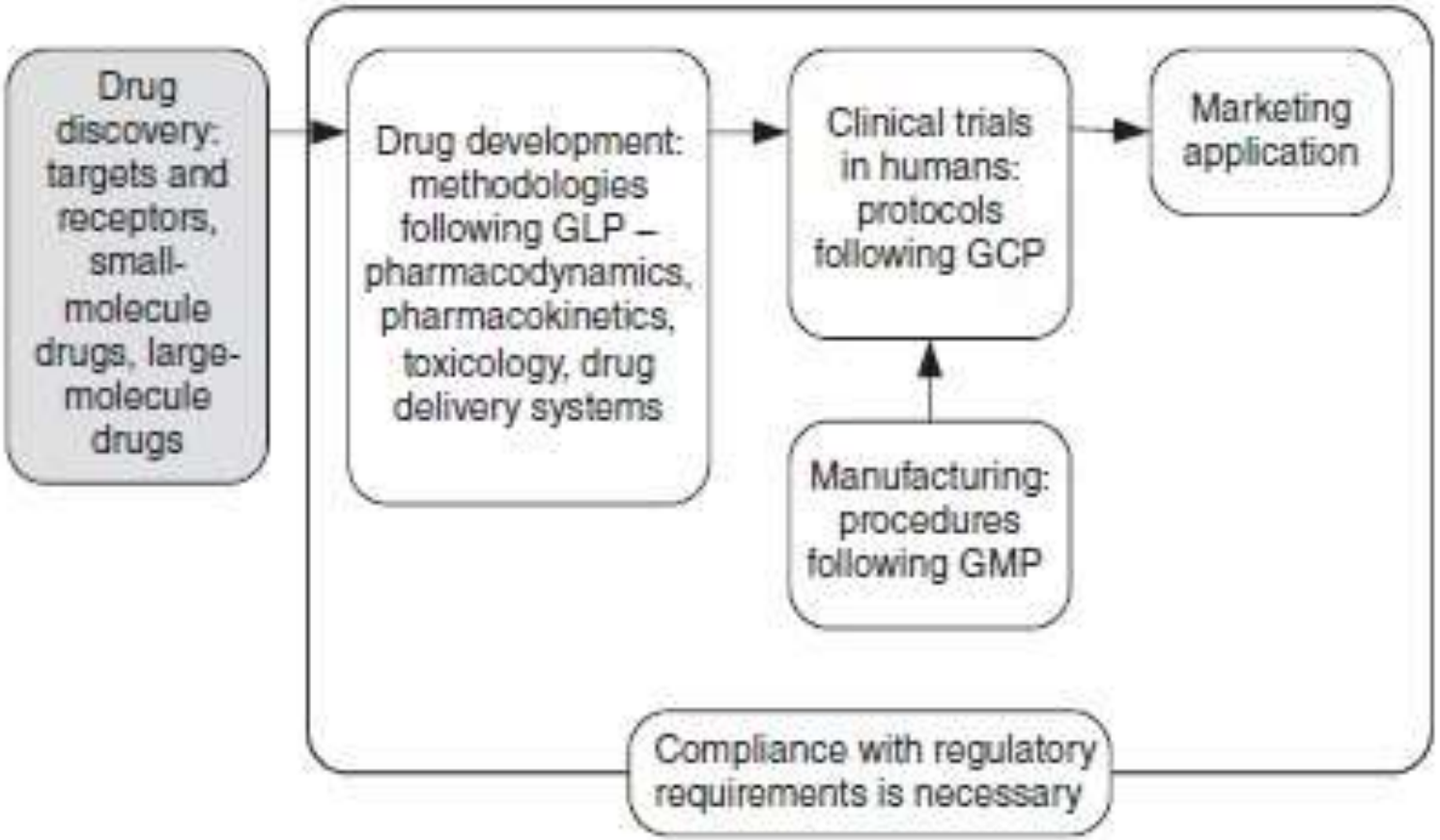


FIGURE 2.25 Thalidomide was brought to market in 1956 by Chemie Grünenthal GmbH as an over the counter treatment for morning sickness in pregnant women. By 1962, it had been withdrawn from markets across the globe as it had been definitively linked to severe birth defect in the children of woman that used it during their pregnancies. *Source: Lower left: Reprinted with permission from Davies, D. P.; Evans, D. J. R. Clinical dysmorphology: understanding congenital abnormalities. Curr. Paediatrics, 13 (4), 288–297, copyright 2003, with permission from Elsevier. Right: Reprinted from Miller, M. T.; Strömland, K.; Ventura, L.; Johansson, M.; Bandim, J. M.; Gillberg, C. Autism associated with conditions characterized by developmental errors in early embryogenesis: a mini review. Int. J. Dev. Neurosci., 23 (2-3), 201–219, copyright 2005, with permission from Elsevier.*


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

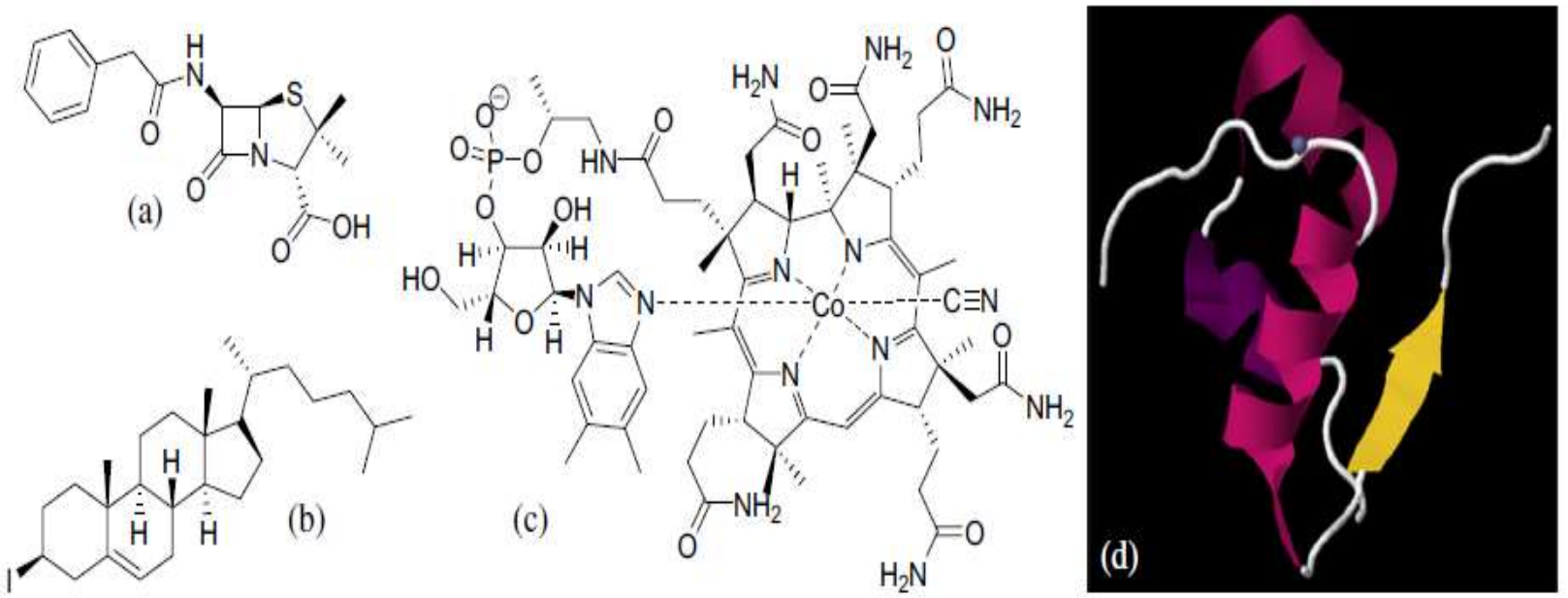


FIGURE 2.12 Dorothy Crowfoot Hodgkin (1910–1994), a graduate of the University of Cambridge, was an earlier pioneer in the field of X-ray crystallography, especially with respect to its application to biomolecules. She is credited with providing definitive structures for a variety of important molecules including (a) benzylpenicillin, (b) cholesteryl iodide, (c) vitamin B_{12}, and (d) insulin (RCSB 4INS).

PAUL EHRLICH: THE FATHER OF MODERN DRUG DISCOVERY[10]

There are many additional examples of useful drugs that were discovered in the preindustrial era, such as morphine,[11] cocaine,[12] and aspirin,[13] but it was Paul Ehrlich's (Figure 2.4) efforts that are most often cited as the

FIGURE 2.4 Paul Ehrlich (1854–1915), the founder of modern drug discovery was a physician and scientist noted for his discoveries in the fields of hematology, immunology, and chemotherapy. In 1908, he received the Nobel Prize in Physiology or Medicine in recognition of his work. *Source: NIH U.S. National Library of Medicine* http://ihm.nlm.gov/luna/servlet/view/search?q=B07744.

Acknowledgement

- The Presentation is being used for educational and non commercial Purposes
- Thanks are due to all the original contributors and entities whose pictures were used in the creation of this presentation.