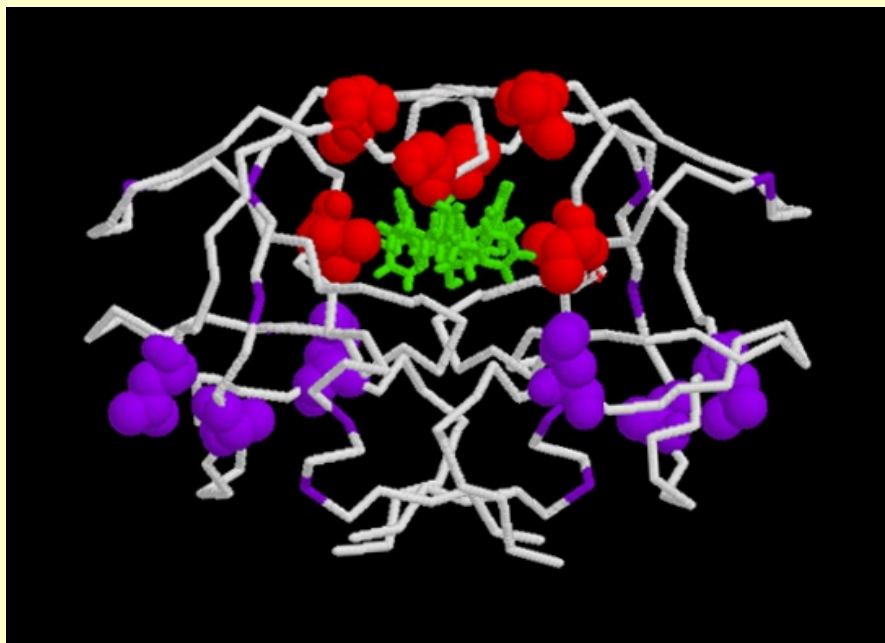


Your Genes and Your Health

<http://bio84.stanford.edu/>

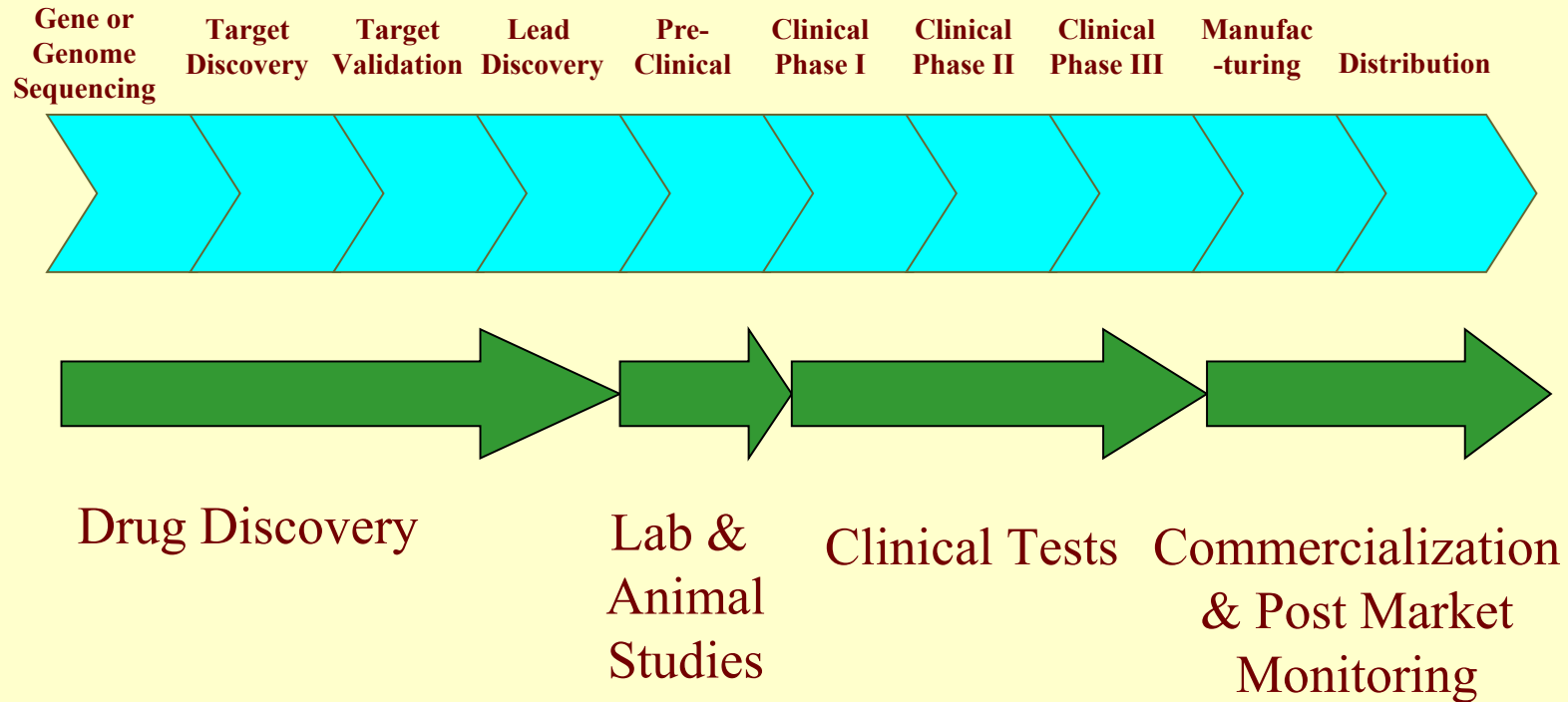
Drug Development

<http://bio84.stanford.edu/10%20Drug%20Development.html>

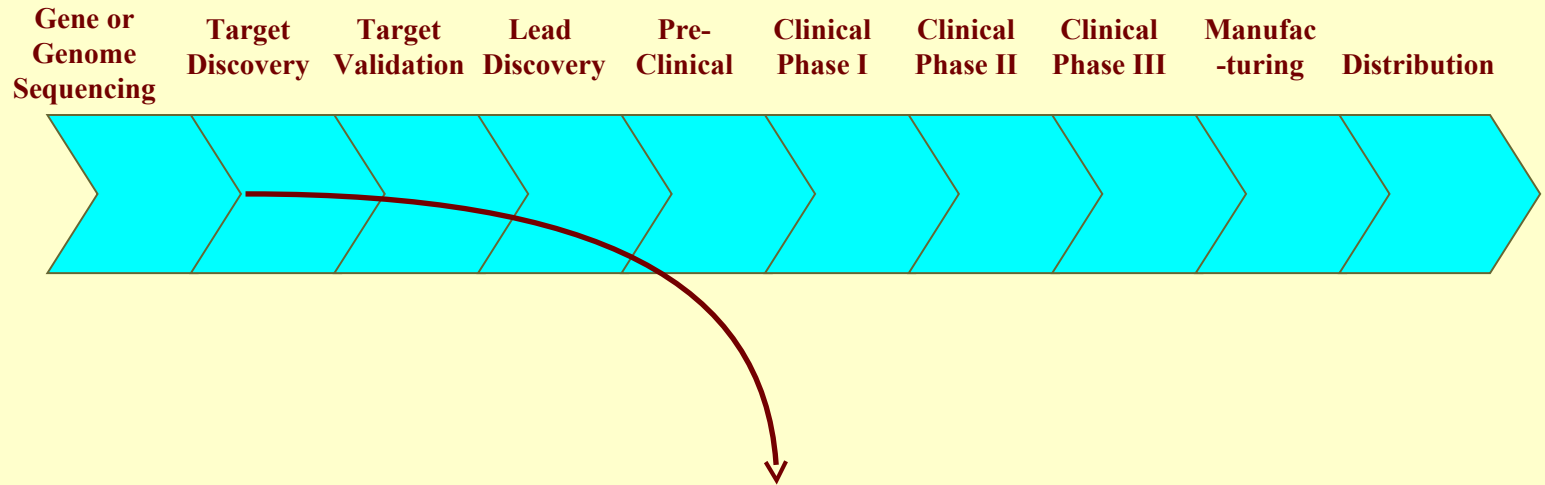


Doug Brutlag, Professor Emeritus
Biochemistry and Medicine (by courtesy)
Stanford University School of Medicine

The Pharma Value Chain

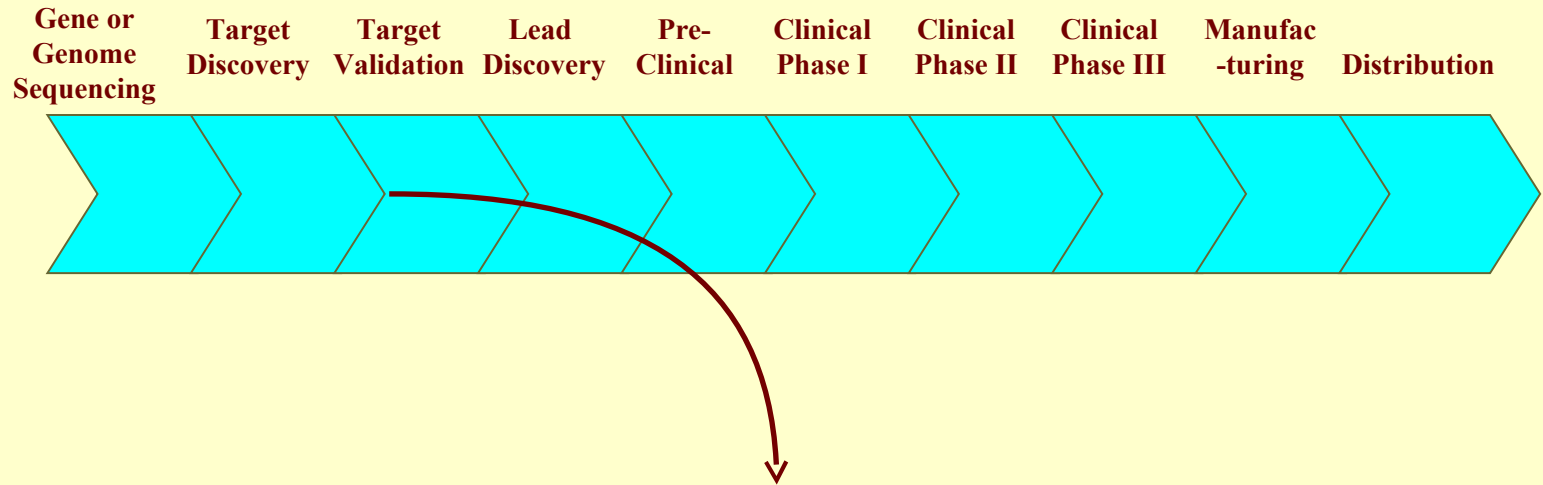


The Pharma Value Chain



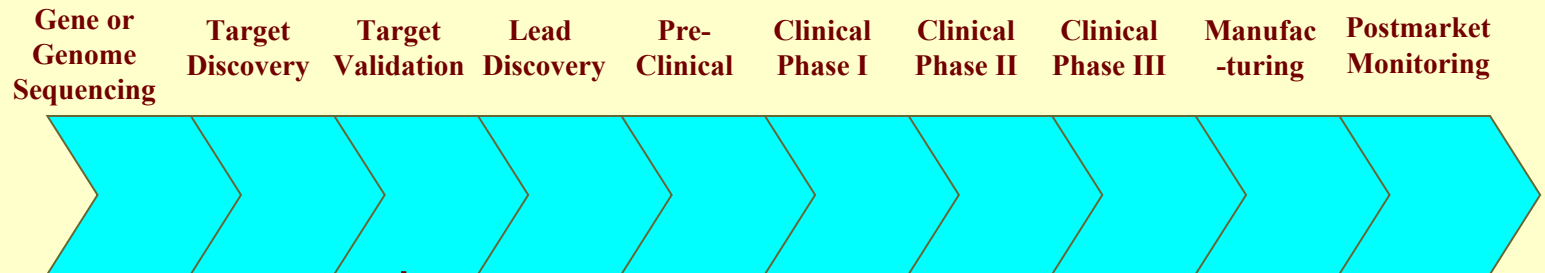
Building a library of gene/protein (genome/proteome) sequences to mine for potential drug targets (genes and proteins unique to disease process).

The Pharma Value Chain



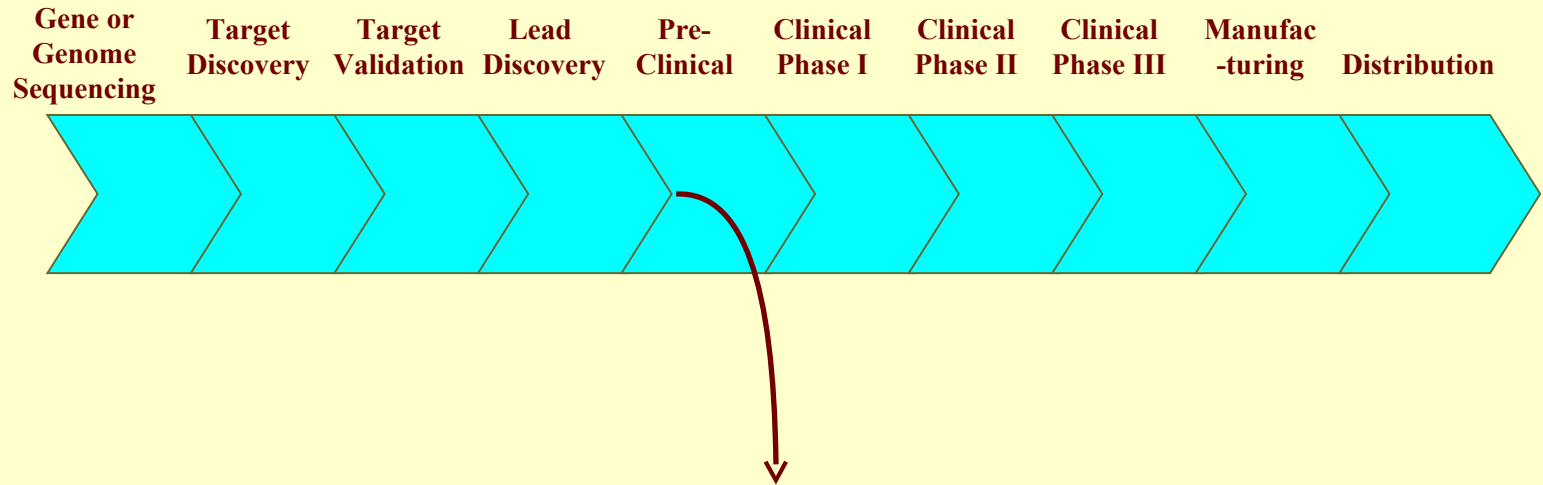
- Look for proteins or mRNA expressed (or not) in a disease.
- Comparative gene expression assays, Comparative proteomic profiles.
- Look for genes and gene modifications associated with a disease.
- Look for proteins or protein modifications associated with a disease.
- Look for metabolic pathways essential to the disease.
- Look for cell signaling pathways required for disease process.
- Look for genes/proteins essential for infectious agent and distinct from host genes/protein.

The Pharma Value Chain



- Molecular level
 - Screen enzyme inhibitors or activators or antibodies to enzyme
- Cellular Level
 - Verify the involvement of the protein in the disease state (often use gene silencing siRNAs).
 - Understand the protein pathways protein complexes and protein-protein interactions.
- Organismal level
 - Verify critical nature of target and uniqueness.

The Pharma Value Chain



Discover leads that affect the target gene, protein or pathway

Inhibit defective protein

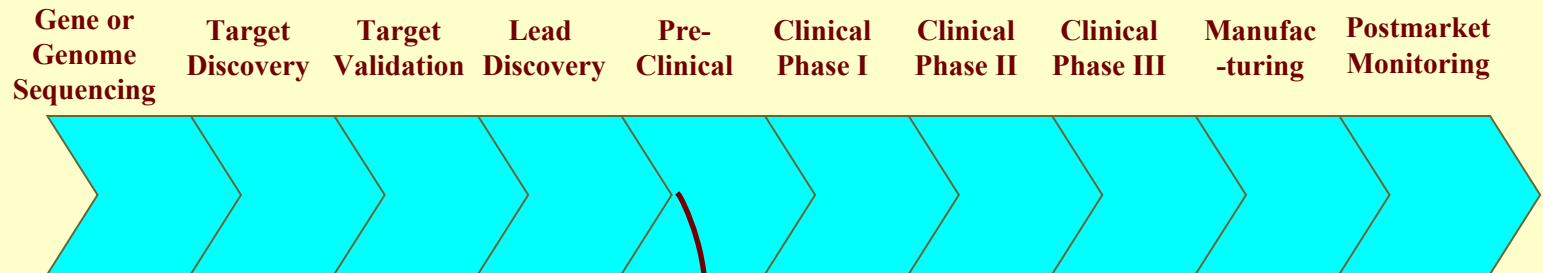
Activate a missing protein

Inhibit expression of a protein/pathway

Activate expression of required protein/pathway

Stimulate protein modifications or cellular location

The Pharma Value Chain



Evaluate leads to 'cure' the problem, e.g.:

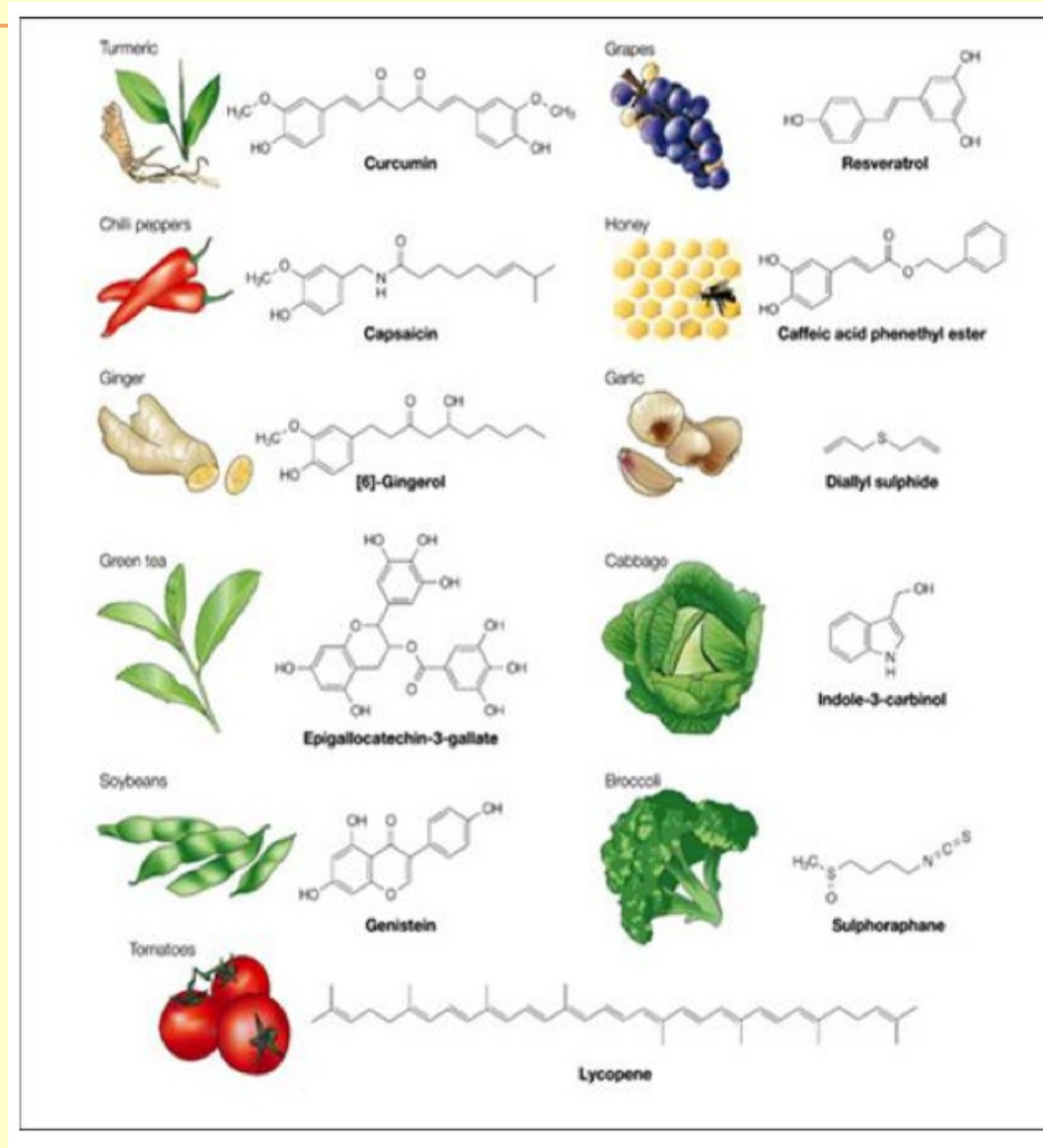
- Replace missing or defective protein with gene therapy
- Anti-sense or siRNA to prevent protein expression
- Antibody to remove or inhibit protein target
- Stimulation of synthesis to replace or activate protein
- Stimulate protein modification or cellular location

Drug Discovery Methods

- Screening natural compound collections



Natural Compound Collections



Drugs Derived from Wild Plants



Plant	Location	Drug	Use
Willow	Worldwide	Aspirin	Fever and pain
Cinchone	Tropics	Quinine	Malaria
Rosy Periwinkle	Madagascar	Vincristine	Leukemia
Rosy Periwinkle	Madagascar	Vinblastine	Hodgkin's disease
Pacific Yew	Pacific Northwest	Taxol	Ovarian cancer
Opium Poppy	Eurasia, Africa	Morphine	Pain
Curare	Amazon	Tubocurarine	Muscle relaxant
Snakeroot	India	Reserpine	Hypertension
Foxglove	Eurasia, Africa	Digoxin	Cardiac arrhythmia

Drug/Chemical	Action/Clinical Use	Plant Source
Acetyldigoxin	Cardio tonic	<i>Digitalis lanata</i>
Adoniside	Cardio tonic	<i>Adonis vernalis</i>
Aescin	Anti-inflammatory	<i>Aesculus hippocastanum</i>
Aesculetin	Anti-dysentery	<i>Frazinus rhychophylla</i>
Agrimophol	Anthelmintic	<i>Agrimonia supatoria</i>
Ajmalicine	Circulatory Disorders	<i>Rauwolfia serpentina</i>
Allantoin	Vulnery	Several plants
Allyl isothiocyanate	Rubefacient	<i>Brassica nigra</i>
Anabesine	Skeletal muscle relaxant	<i>Anabasis sphylla</i>
Andrographolide	Bacillary dysentery	<i>Andrographis paniculata</i>
Anisodamine	Anticholinergic	<i>Anisodus tanguticus</i>
Anisodine	Anticholinergic	<i>Anisodus tanguticus</i>
Arecoline	Anthelmintic	<i>Areca catechu</i>
Asiaticoside	Vulnery	<i>Centella asiatica</i>
Atropine	Anticholinergic	<i>Atropa belladonna</i>
Benzyl benzoate	Scabicide	Several plants
Berberine	Bacillary dysentery	<i>Berberis vulgaris</i>
Bergenin	Antitussive	<i>Ardisia japonica</i>
Betulinic acid	Anticancerous	<i>Betula alba</i>
Borneol	Antipyretic, analgesic, antiinflammatory	Several plants
Bromelain	Anti-inflammatory, proteolytic	<i>Ananas comosus</i>
Caffeine	CNS stimulant	<i>Camellia sinensis</i>
Camphor	Rubefacient	<i>Cinnamomum camphora</i>
Camptothecin	Anticancerous	<i>Camptotheca acuminata</i>
(+)-Catechin	Haemostatic	<i>Potentilla fragaroides</i>
Chymopapain	Proteolytic, mucolytic	<i>Carica papaya</i>
Cissampeline	Skeletal muscle relaxant	<i>Cissampelos pareira</i>
Cocaine	Local anaesthetic	<i>Erythroxylum coca</i>
Codeine	Analgesic, antitussive	<i>Papaver somniferum</i>
Colchicine amide	Antitumor agent	<i>Colchicum autumnale</i>
Colchicine	Antitumor agent, anti-gout	<i>Colchicum autumnale</i>
Convallatoxin	Cardio tonic	<i>Convallaria majalis</i>
Curcumin	Choleretic	<i>Curcuma longa</i>
Cynarin	Choleretic	<i>Cynara scolymus</i>
Danthron	Laxative	<i>Cassia species</i>
Demecolcine	Antitumor agent	<i>Colchicum autumnale</i>
Deserpidine	Antihypertensive, tranquilizer	<i>Rauwolfia canescens</i>
Deslanoside	Cardio tonic	<i>Digitalis lanata</i>
L-Dopa	Anti-parkinsonism	<i>Mucuna sp</i>
Digitalin	Cardio tonic	<i>Digitalis purpurea</i>
Digitoxin	Cardio tonic	<i>Digitalis purpurea</i>
Digoxin	Cardio tonic	<i>Digitalis purpurea</i>
Emetine	Amoebicide, emetic	<i>Cephaelis ipecacuanha</i>
Ephedrine	Sympathomimetic, antihistamine	<i>Ephedra sinica</i>
Etoposide	Antitumor agent	<i>Podophyllum peltatum</i>

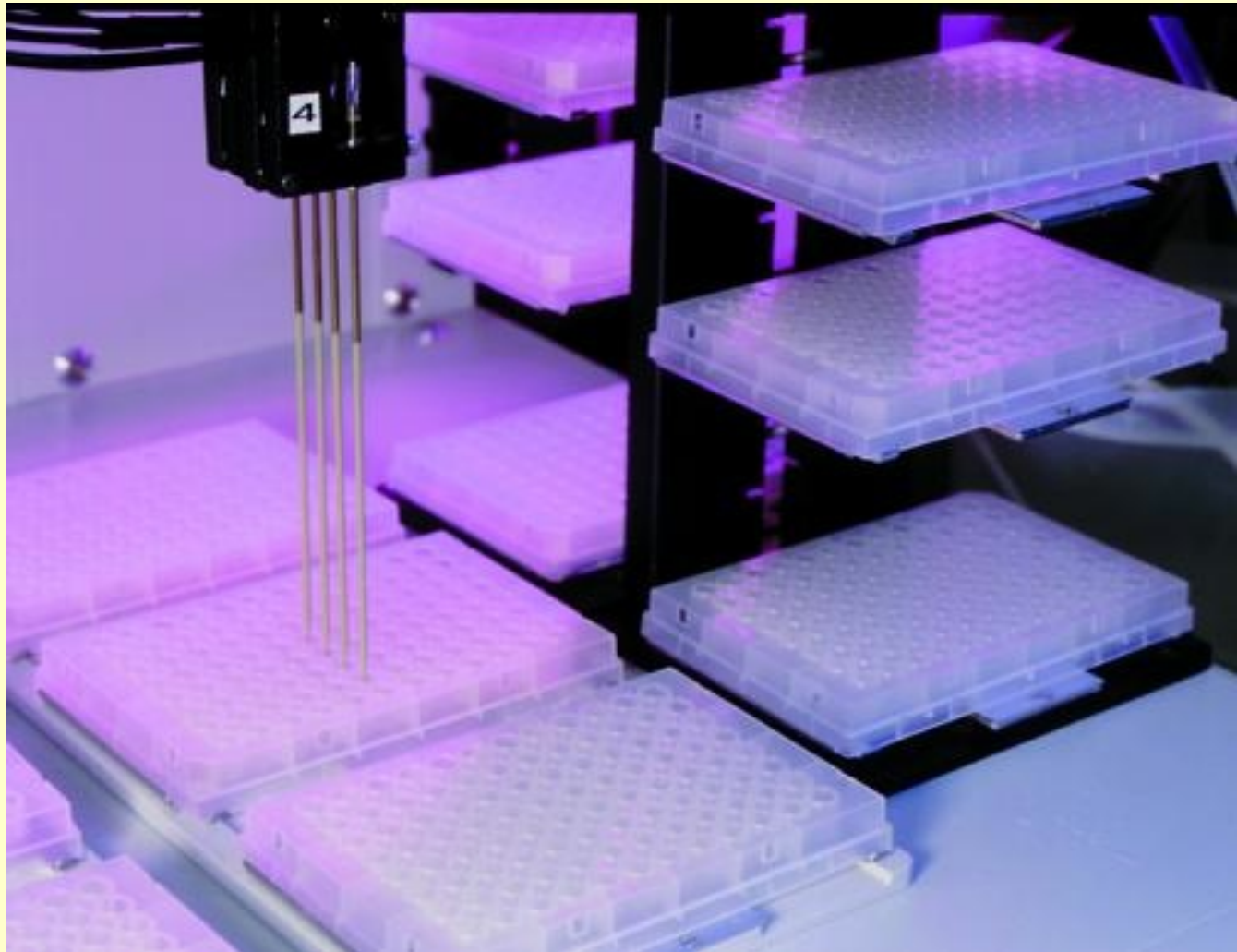
Drug/Chemical	Action/Clinical Use	Plant Source
Gossypol	Male contraceptive	<i>Gossypium species</i>
Hemseleyadin	Bacillary dysentery	<i>Hemseleya amabilis</i>
Hesperidin	Capillary fragility	<i>Citrus species</i>
Hydrastine	Hemostatic, astringent	<i>Hydrastis canadensis</i>
Hyoscyamine	Anticholinergic	<i>Hyoscyamus niger</i>
Irinote	Anticancer, antitumor agent	<i>Camptotheca acuminata</i>
Kaibic acid	Ascaricide	<i>Digenea simplex</i>
Kawain	Tranquillizer	<i>Piper methysticum</i>
Kheltin	Broncho dilator	<i>Ammi visaga</i>
Lanatosides A, B, C	Cardio tonic	<i>Digitalis lanata</i>
Lapachol	Anticancer, antitumor	<i>Tabebuia sp.</i>
a-Lobeline	Smoking deterrent, respiratory stimulant	<i>Lobelia inflata</i>
Menthol	Rubefacient	<i>Mentha species</i>
Methyl salicylate	Rubefacient	<i>Gaultheria procumbens</i>
Monocrotaline	Antitumor agent (topical)	<i>Crotalaria sessiliflora</i>
Morphine	Analgesic	<i>Papaver somniferum</i>
Neoandrographolide	Dysentery	<i>Andrographis paniculata</i>
Nicotine	Insecticide	<i>Nicotiana tabacum</i>
Nordihydroguaiaretic acid	Antioxidant	<i>Larrea divaricata</i>
Noscapine	Antitussive	<i>Papaver somniferum</i>
Ousabain	Cardio tonic	<i>Strophanthus gratus</i>
Pachycarpine	Oxytocic	<i>Sophora pschycarpa</i>
Palmatine	Antipyretic, detoxicant	<i>Coptis japonica</i>
Papain	Proteolytic, mucolytic	<i>Carica papaya</i>
Papavarine	Smooth muscle relaxant	<i>Papaver somniferum</i>
Phyllo dulcin	Sweetner	<i>Hydrangea macrophylla</i>
Physostigmine	Cholinesterase Inhibitor	<i>Physostigma venenosum</i>
Picrotoxin	Analeptic	<i>Anamirta cocculus</i>
Pilocarpine	Parasympathomimetic	<i>Pilocarpus jaborandi</i>
Pinitol	Expectorant	Several plants
Podophyllotoxin	Antitumor anticancer agent	<i>Podophyllum peltatum</i>
Protoveratrine A, B	Antihypertensives	<i>Veratrum album</i>
Pseudoephedrine*	Sympathomimetic	<i>Ephedra sinica</i>
Pseudoephedrine, nor-	Sympathomimetic	<i>Ephedra sinica</i>
Quinidine	Antiarrhythmic	<i>Cinchona ledgeriana</i>
Quinine	Antimalarial, antipyretic	<i>Cinchona ledgeriana</i>
Quisqualic acid	Anthelmintic	<i>Quisqualis indica</i>
Rescinamine	Antihypertensive, tranquillizer	<i>Rauwolfia serpentina</i>
Reserpine	Antihypertensive, tranquillizer	<i>Rauwolfia serpentina</i>
Rhomitoxin	Antihypertensive, tranquillizer	<i>Rhododendron molle</i>
Rorifone	Antitussive	<i>Rorippa indica</i>
Rotnone	Piscicide, Insecticide	<i>Lonchocarpus nicou</i>
Rotundine	Analgesic, sedative, tranquillizer	<i>Stephania sinica</i>
Rutin	Capillary fragility	<i>Citrus species</i>
Salicin	Analgesic	<i>Salix alba</i>
Sanguinarine	Dental plaque inhibitor	<i>Sanguinaria canadensis</i>
Santonin	Ascaricide	<i>Artemisia maritima</i>
Scillarin A	Cardio tonic	<i>Urginea maritima</i>
Scopolamine	Sedative	<i>Datura species</i>
Sennosides A, B	Laxative	<i>Cassia species</i>
Silymarin	Antihepatotoxic	<i>Silybum marianum</i>

Plants

Drugs Derived from Wild Plants

Drug/Chemical	Action/Clinical use	Plant source
Stevioside	Sweetener	<i>Stevia rebaudiana</i>
Strychnine	CNS stimulant	<i>Strychnos nux-vomica</i>
Toxol	Antitumor agent	<i>Taxus brevifolia</i>
Teniposide	Antitumor agent	<i>Podophyllum peltatum</i>
α -Tetrahydrocannabinol (THC)	Antiemetic, decrease ocular tension	<i>Cannabis sativa</i>
Tetrahydropalmatine	Analgesic, sedative, tranquilizer	<i>Corydalis ambigua</i>
Tetrandrine	Antihypertensive	<i>Stephania tetrandra</i>
Theobromine	Diuretic, vasodilator	<i>Theobroma cacao</i>
Theophylline	Diuretic, bronchodilator	<i>Theobroma cacao and others</i>
Thymol	Antifungal (topical)	<i>Thymus vulgaris</i>
Topotecan	Antitumor, anticancer agent	<i>Camptotheca acuminata</i>
Trichosanthin	Abortifacient	<i>Trichosanthes kirilowii</i>
Tubocurarine	Skeletal muscle relaxant	<i>Chondrodendron tomentosum</i>
Valprotriates	Sedative	<i>Valeriana officinalis</i>
Vasicine	Cerebral stimulant	<i>Vinca minor</i>
Vinblastine	Antitumor, Antileukemic agent	<i>Catharanthus roseus</i>
Vincristine	Antitumor, Antileukemic agent	<i>Catharanthus roseus</i>
Yohimbine	Aphrodisiac	<i>Pausinystalia yohimbe</i>
Yuanhuacine	Abortifacient	<i>Daphne genkwa</i>

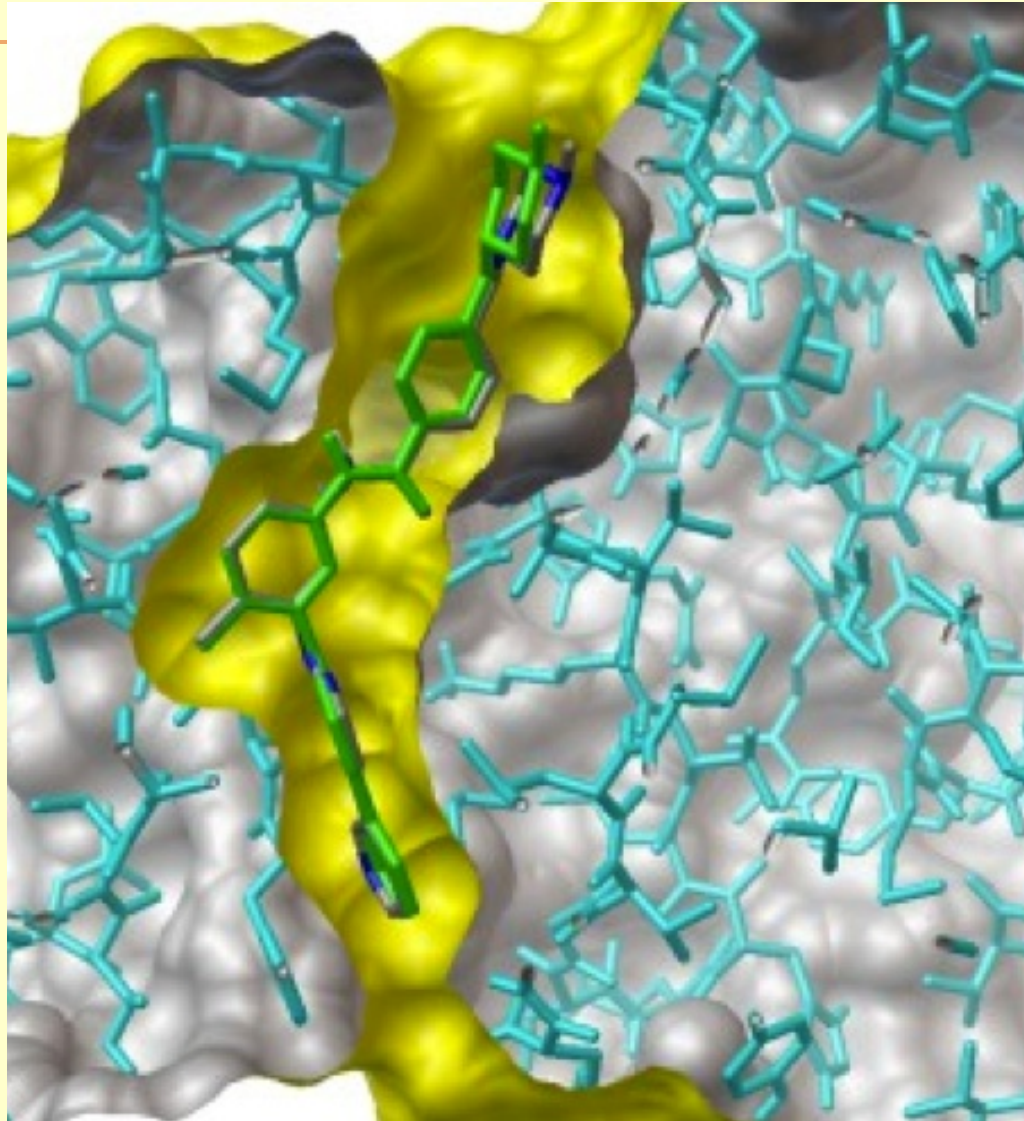
Natural Compound Screening



Drug Discovery Methods

- Screening natural compound collections
- Screening corporate compound collections
- *In silico* screening (Autodock)

In silico screening with Autodock



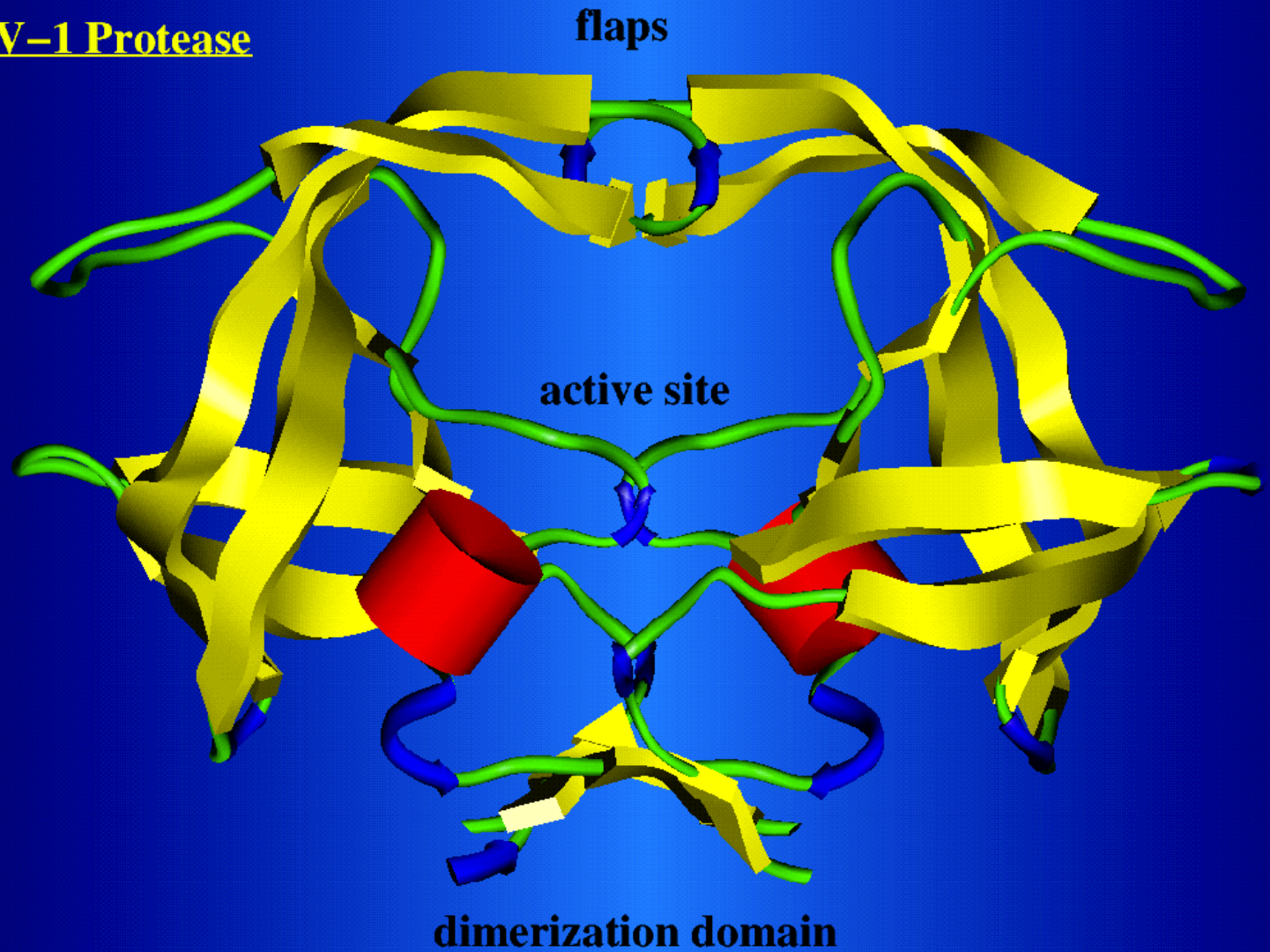
Gleevec (Imatinib) bound to BCR-Abl Protein

Drug Discovery Methods

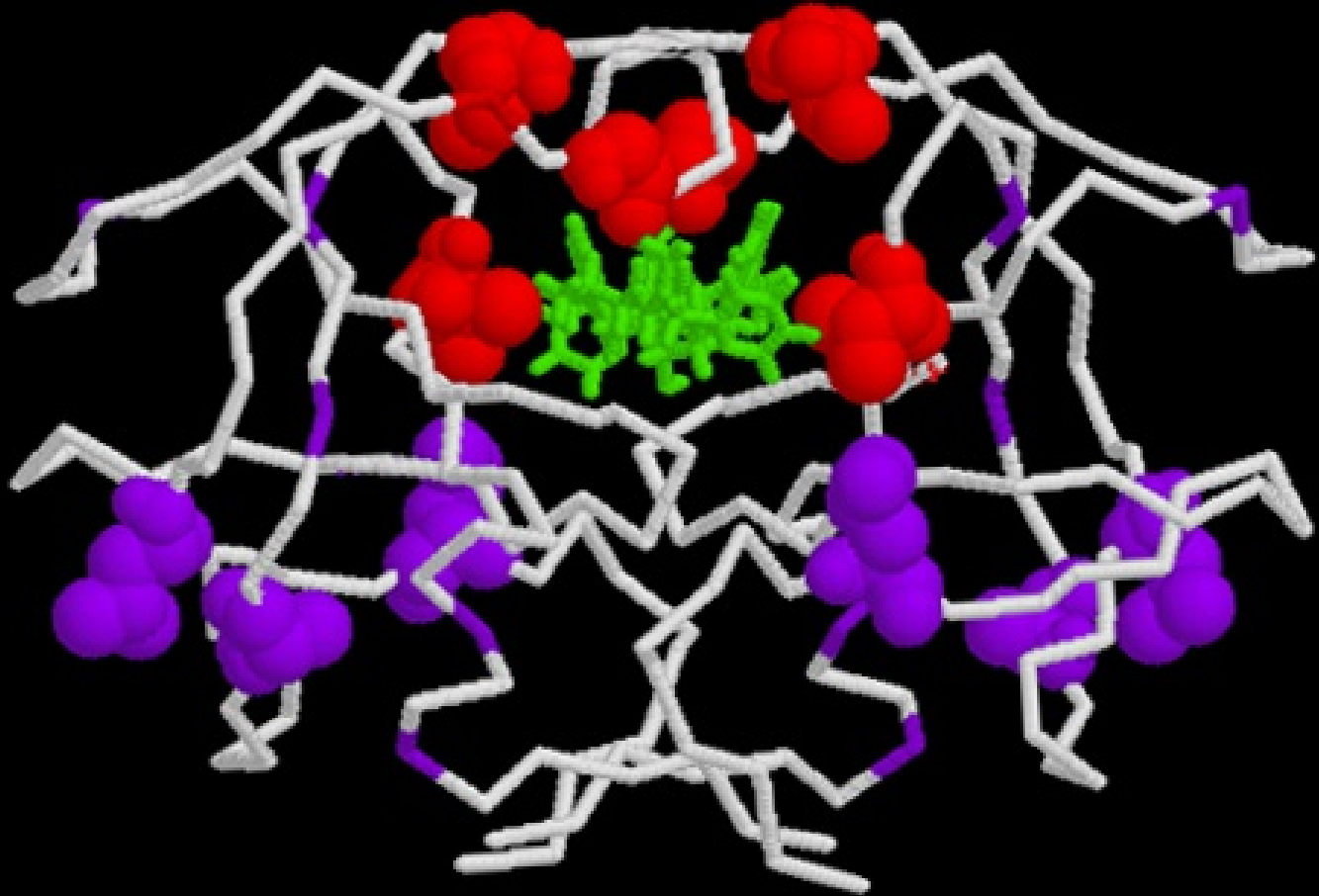
- Screening natural compound collections
- Screening corporate compound collections
- *In silico* screening (Autodock)
- Rational drug design

Rational Drug design for HIV Protease

HIV-1 Protease



Rational Drug Design for HIV Protease

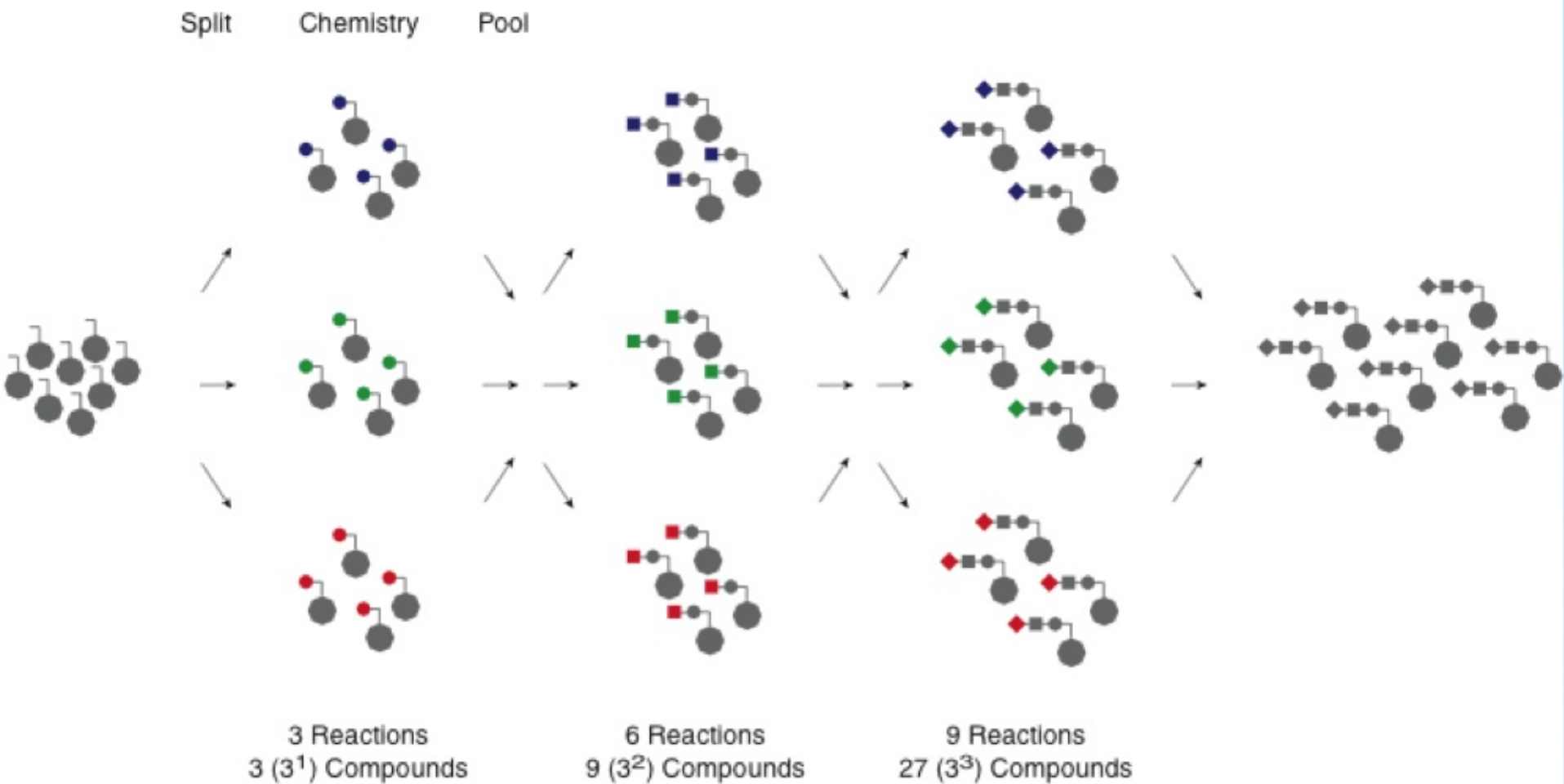


Indinavir bound to HIV Protease
Resistance mutations shown in red and purple

Drug Discovery Methods

- Screening natural compound collections
- Screening corporate compound collections
- *In silico* screening (Autodock)
- Rational drug design
- Combinatorial chemistry

Combinatorial Chemistry

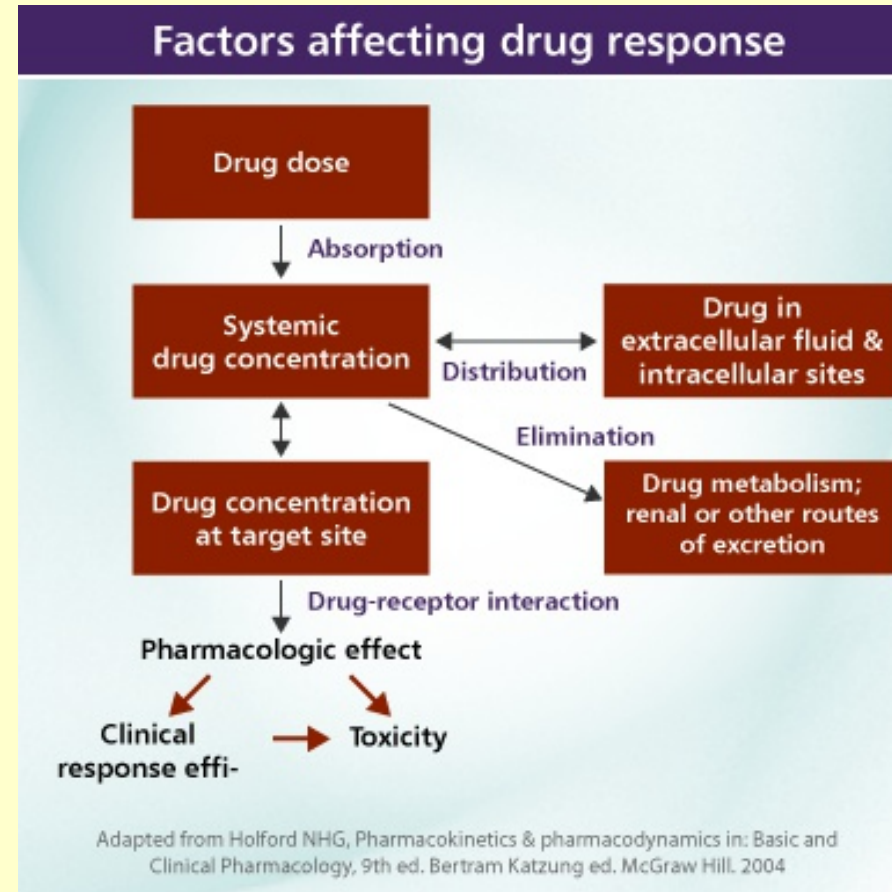


Drug Discovery Methods

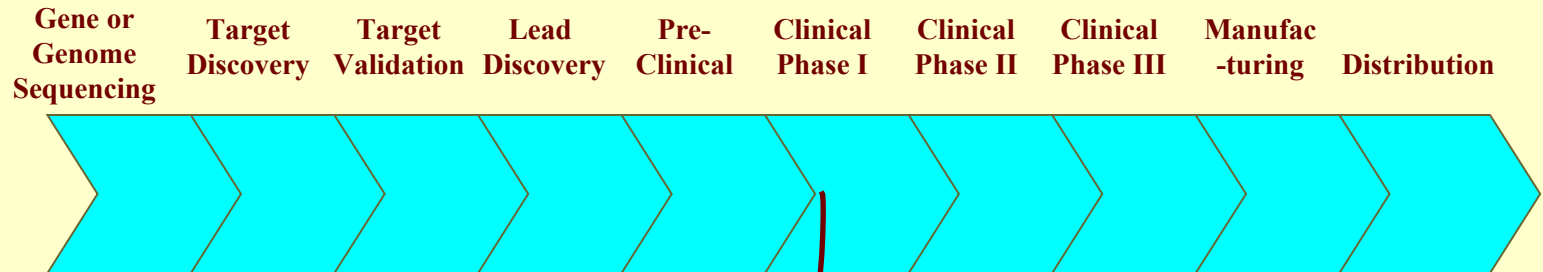
- Lead Discovery
 - Screening natural compound collections
 - Screening corporate compound collections
 - *In silico* screening (Autodock)
 - Rational drug design
 - Combinatorial chemistry
- Lead validation
- Lead optimization

ADMET: Ideal Properties of Drugs

- Absorption - Passes GI track into blood stream
- Distribution - Gets to target tissue (blood brain barrier)
- Metabolism – Not readily metabolized
- Excretion – Not readily secreted
- Toxicity – Not toxic to other cells or tissues



The Pharma Value Chain

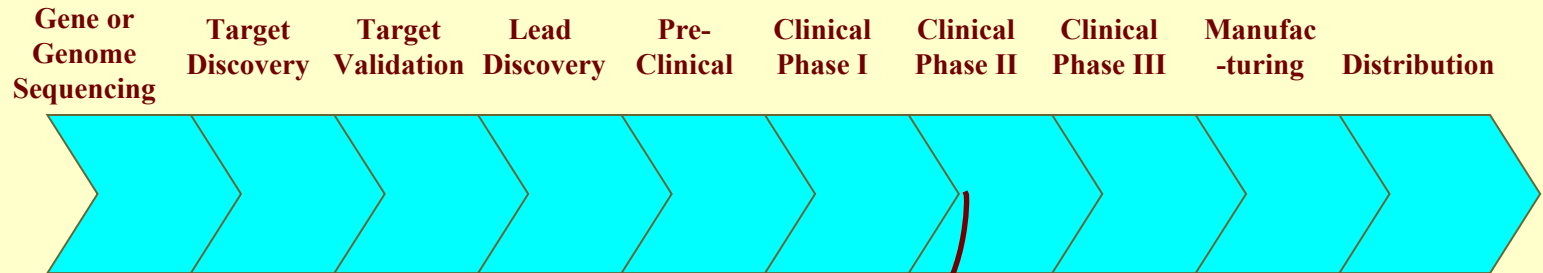


- Animal tests of toxicity and efficacy of therapy
 - Rodents (mice and rats)
 - Mammals (pigs)
 - Primates (monkeys and chimpanzees)
 - Mouse Lemurs (*Microcebus*)

The New Primate: Mouse Lemurs (*Microcebus margotmarshae*)

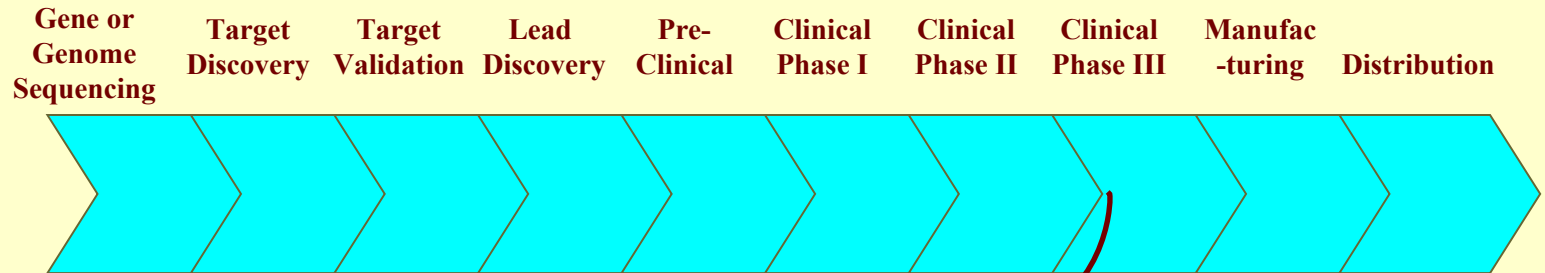


The Pharma Value Chain



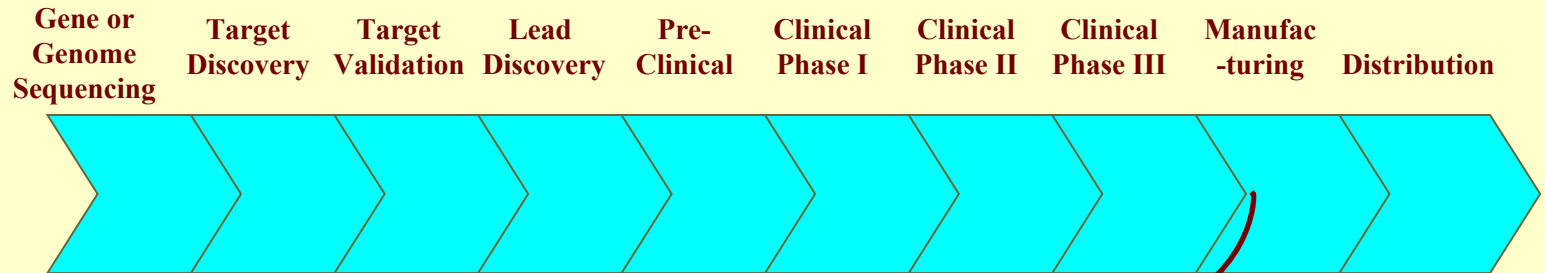
Small group of healthy volunteers (10's) to determine safety and toxicity. Maybe some members of target group

The Pharma Value Chain



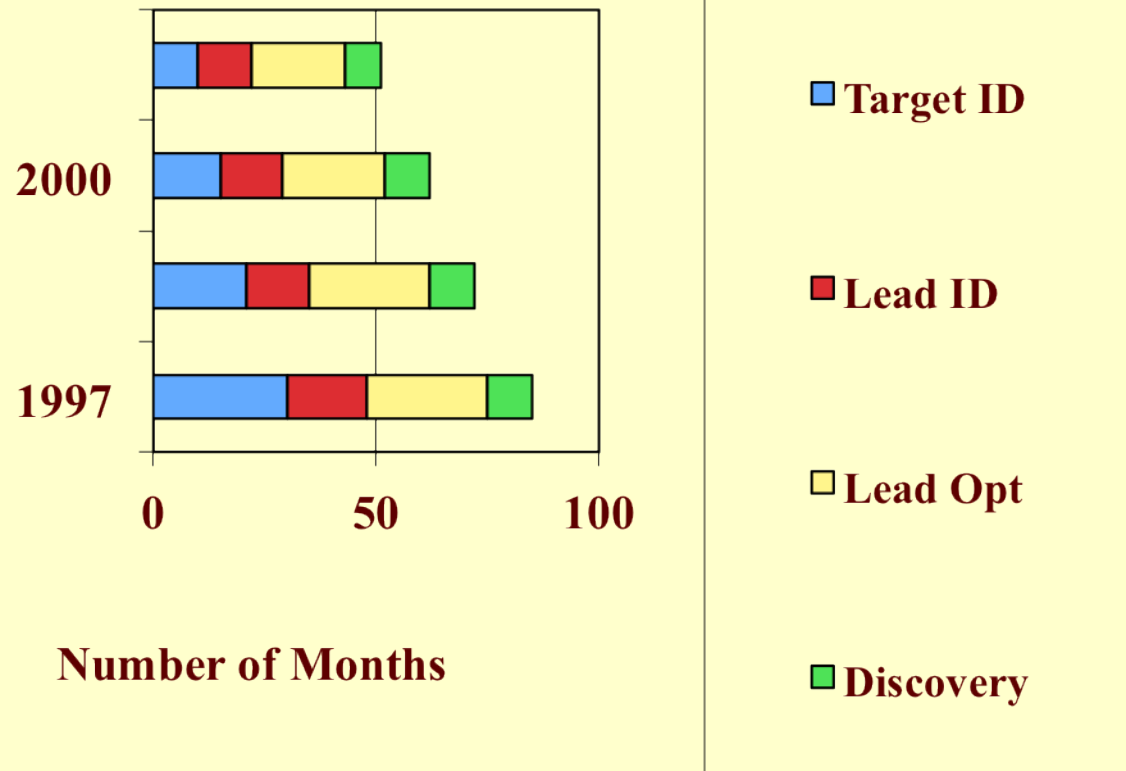
100's of patient population to determine efficacy, dosage, safety

The Pharma Value Chain



1000's of patients and controls (normals) to determine efficacy, dosage, safety, side effects, and interactions

The Impact of Genomics and Bioinformatics on Drug Discovery Times

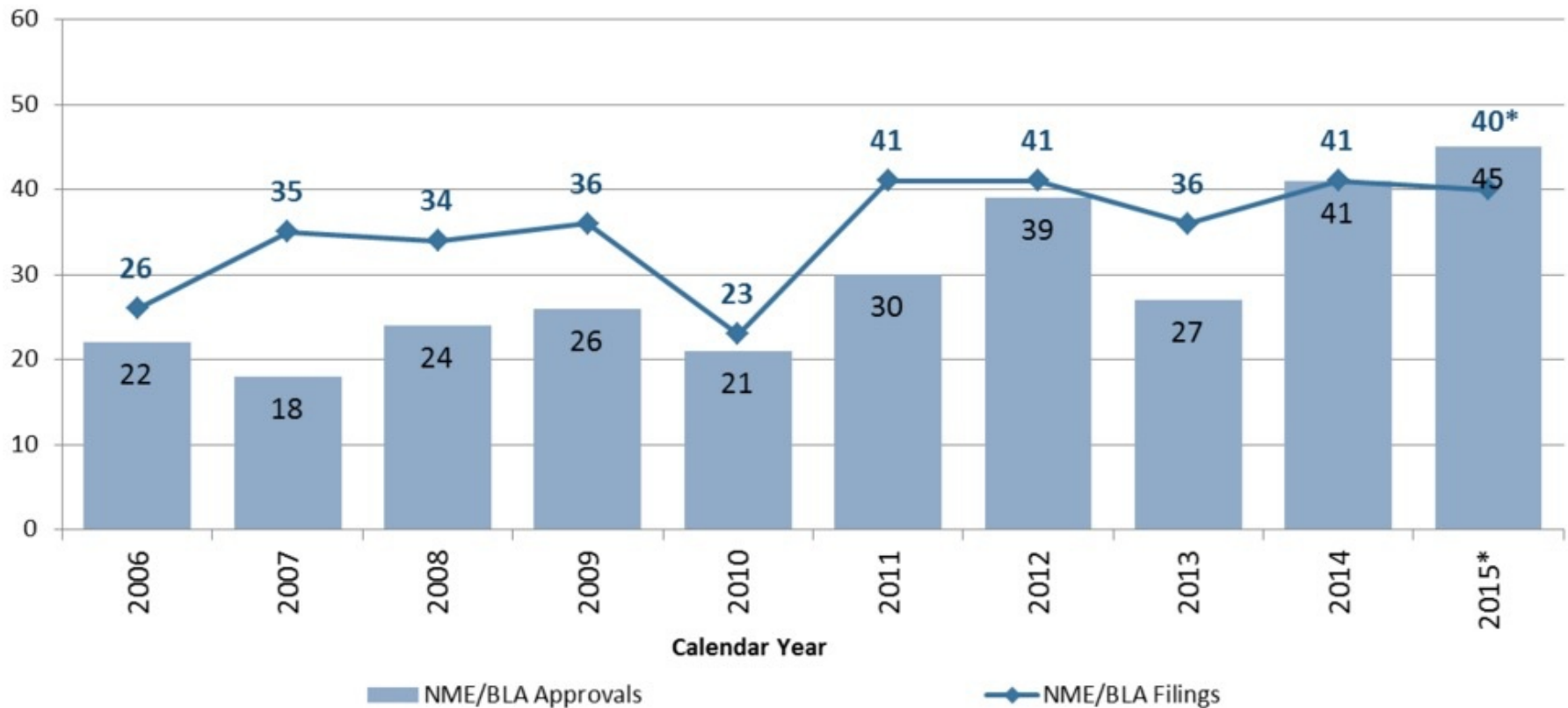




FDA Approved New Chemical Entities 2015

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm430302.htm>

CDER New Molecular Entity (NME) and New Biologic License Application (BLA) Filings and Approvals





FDA Approved New Chemical Entities 2014

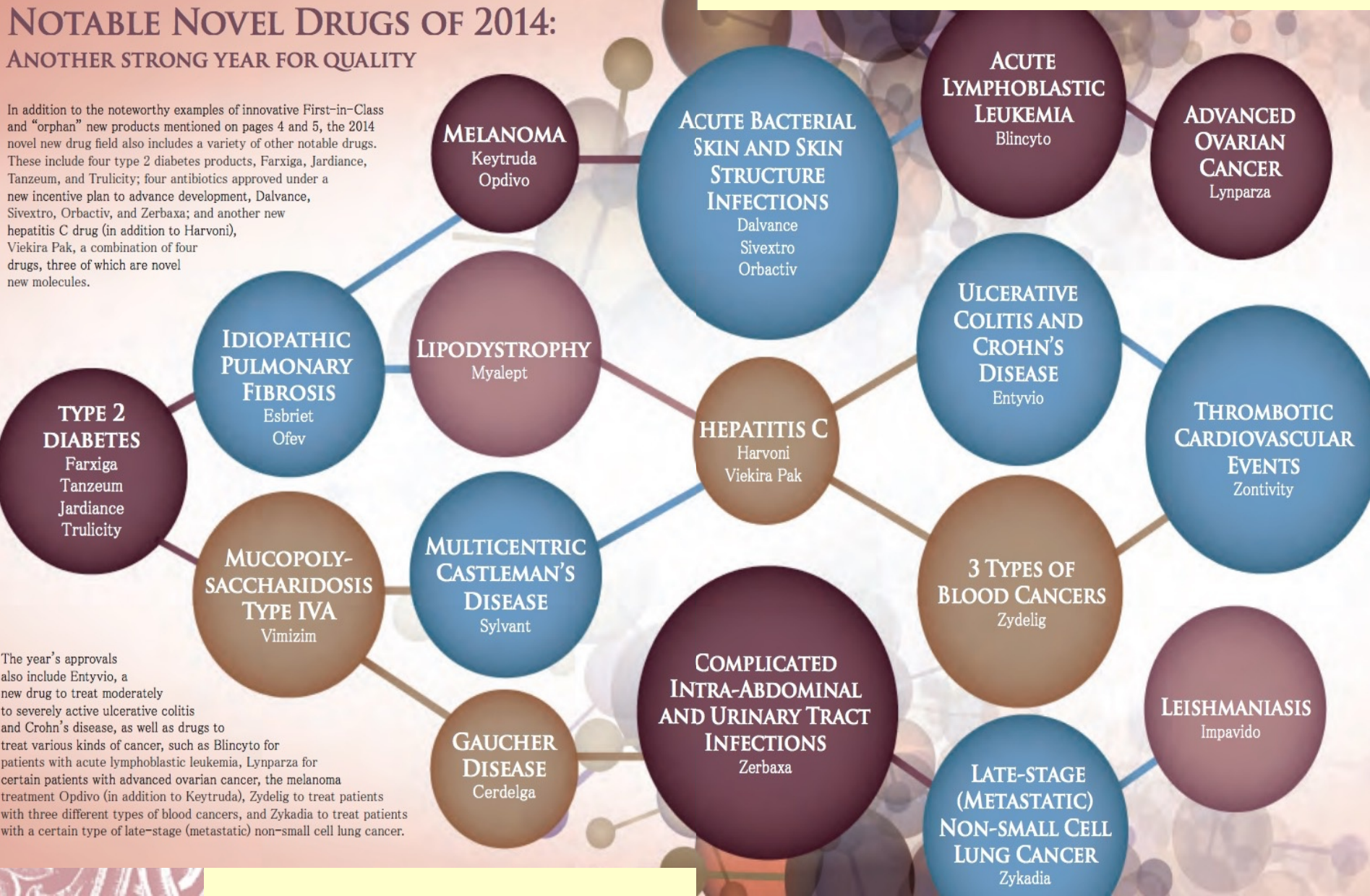
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM430299.pdf>

NOTABLE NOVEL DRUGS OF 2014:

ANOTHER STRONG YEAR FOR QUALITY

In addition to the noteworthy examples of innovative First-in-Class and "orphan" new products mentioned on pages 4 and 5, the 2014 novel new drug field also includes a variety of other notable drugs. These include four type 2 diabetes products, Farxiga, Jardiance, Tanzeum, and Trulicity; four antibiotics approved under a new incentive plan to advance development, Dalvance, Sivextro, Orbactiv, and Zerbaxa; and another new hepatitis C drug (in addition to Harvoni), Viekira Pak, a combination of four drugs, three of which are novel new molecules.

The year's approvals also include Entyvio, a new drug to treat moderately to severely active ulcerative colitis and Crohn's disease, as well as drugs to treat various kinds of cancer, such as Blinicyto for patients with acute lymphoblastic leukemia, Lynparza for certain patients with advanced ovarian cancer, the melanoma treatment Opdivo (in addition to Keytruda), Zydelig to treat patients with three different types of blood cancers, and Zykadia to treat patients with a certain type of late-stage (metastatic) non-small cell lung cancer.



MELANOMA
Keytruda
Opdivo

ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS
Dalvance
Sivextro
Orbactiv

ACUTE LYMPHOBLASTIC LEUKEMIA
Blinicyto

ADVANCED OVARIAN CANCER
Lynparza

IDIOPATHIC PULMONARY FIBROSIS
Esbriet
Ofev

LIPODYSTROPHY
Myalept

HEPATITIS C
Harvoni
Viekira Pak

ULKERATIVE COLITIS AND CROHN'S DISEASE
Entyvio

THROMBOTIC CARDIOVASCULAR EVENTS
Zontivity

TYPE 2 DIABETES
Farxiga
Tanzeum
Jardiance
Trulicity

MUCOPOLYSACCHARIDOSIS TYPE IVA
Vimizim

MULTICENTRIC CASTLEMAN'S DISEASE
Sylvant

3 TYPES OF BLOOD CANCERS
Zydelig

COMPLICATED INTRA-ABDOMINAL AND URINARY TRACT INFECTIONS
Zerbaxa

LATE-STAGE (METASTATIC) NON-SMALL CELL LUNG CANCER
Zykadia

GAUCHER DISEASE
Cerdelga

LEISHMANIASIS
Impavido

Genetic and Biomarker Followup

But why stop learning when the drug is on the market ?

A proposal to create larger safety and efficacy databases, assess biomarkers

