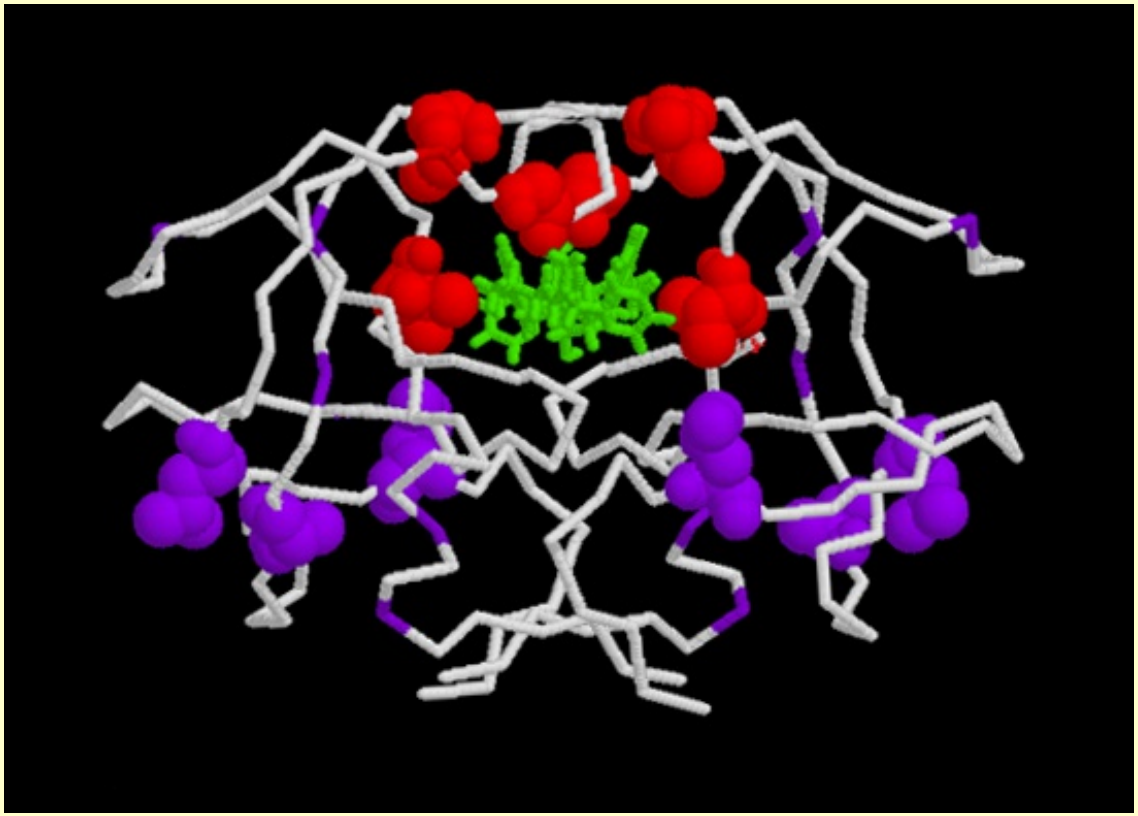
Genomics, Bioinformatics & Medicine

http://biochem118.stanford.edu/

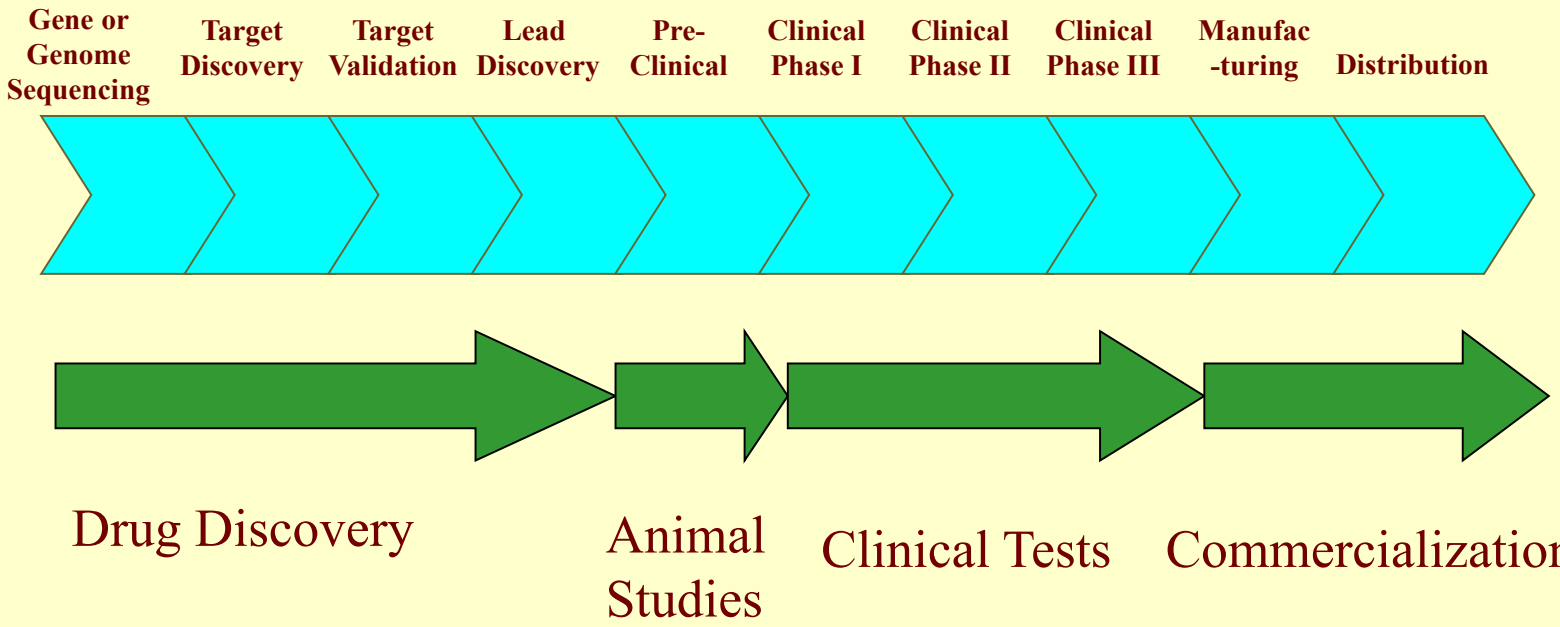
Drug Development

http://biochem118.stanford.edu/Drug-Development.html



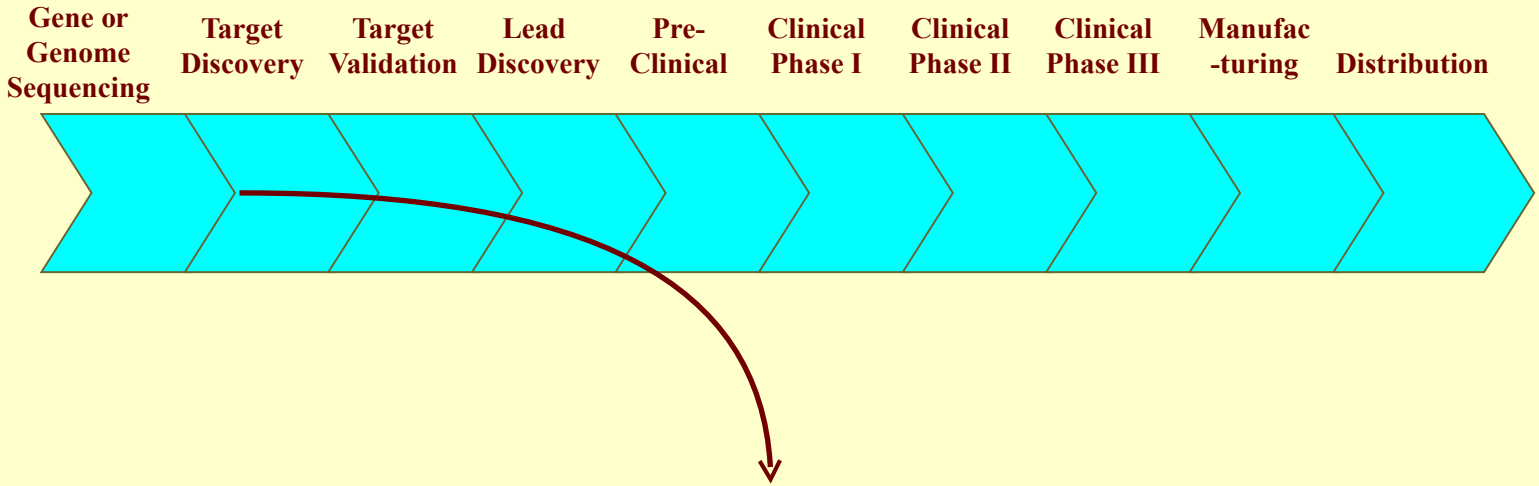
Doug Brutlag, Professor Emeritus of
Biochemistry and Medicine
Stanford University School of Medicine

The Pharma Value Chain



Courtesy of Doug Kalish

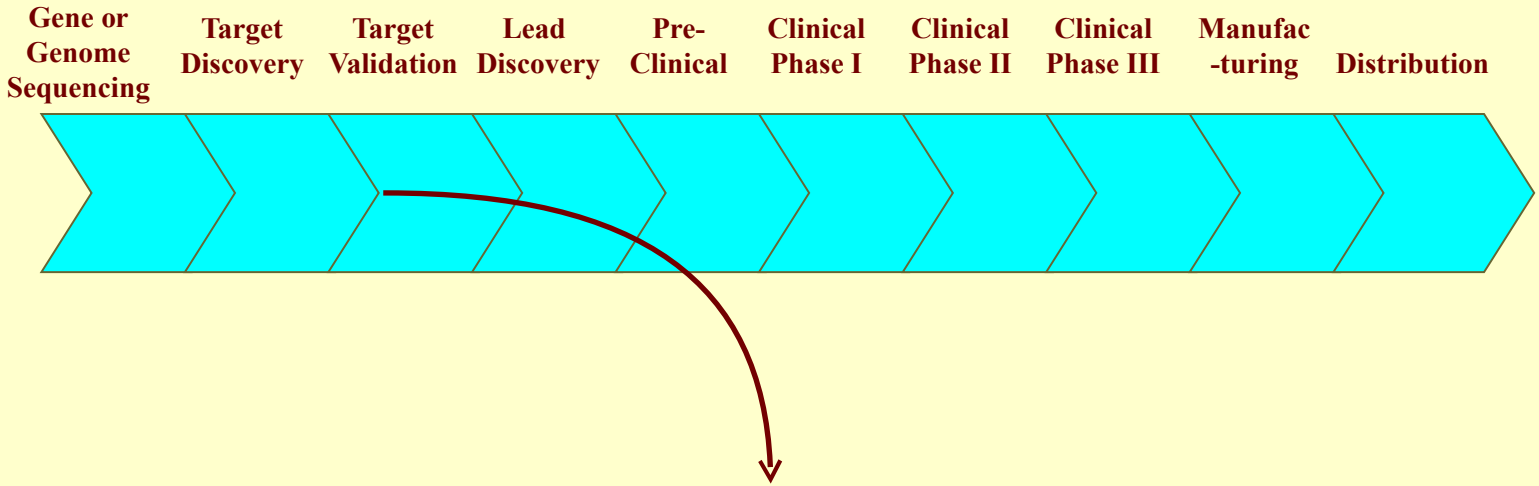
The Pharma Value Chain



Building a library of gene/protein (genome/proteome) sequences to mine for information

Courtesy of Doug Kalish

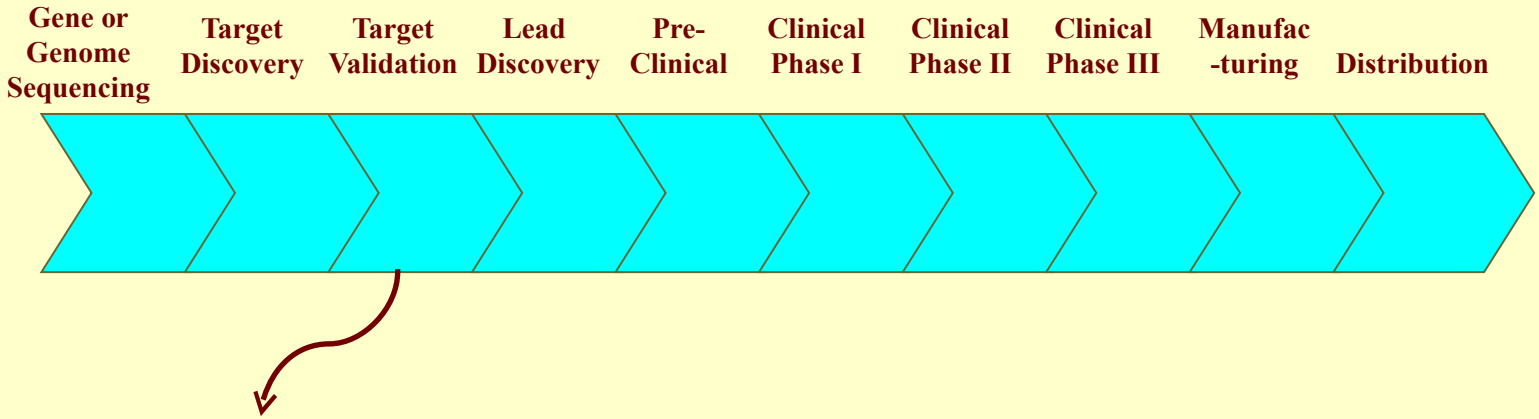
The Pharma Value Chain



- Look for proteins or mRNA expressed 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.
- Find regulatory pathways required for disease process.
- Look for genes/proteins essential for infectious agent and distinct from host genes/proteins.

Courtesy of Doug Kalish

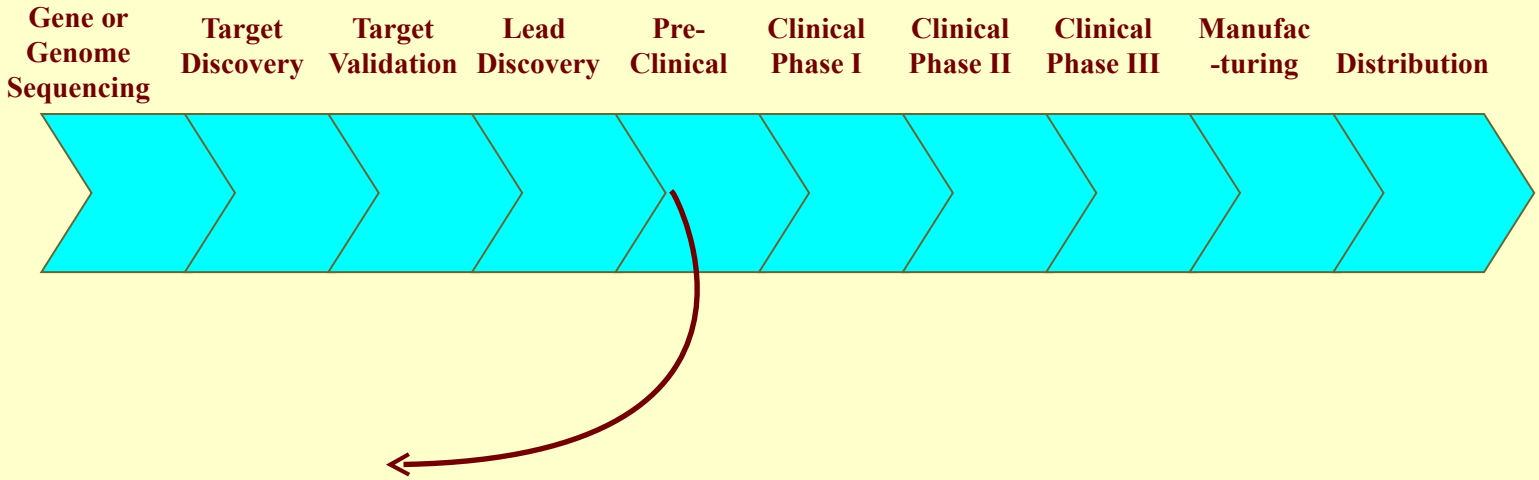
The Pharma Value Chain



- Molecular level
  - Screen enzyme inhibitors or activators
- Cellular Level
  - Verify the involvement of the protein in the disease state (use gene silencing iRNAs).
  - Understand the metabolic or cell signaling pathways and protein interactions.
- Organismal level
  - Verify critical nature of target and uniqueness.

Courtesy of Doug Kalish

The Pharma Value Chain

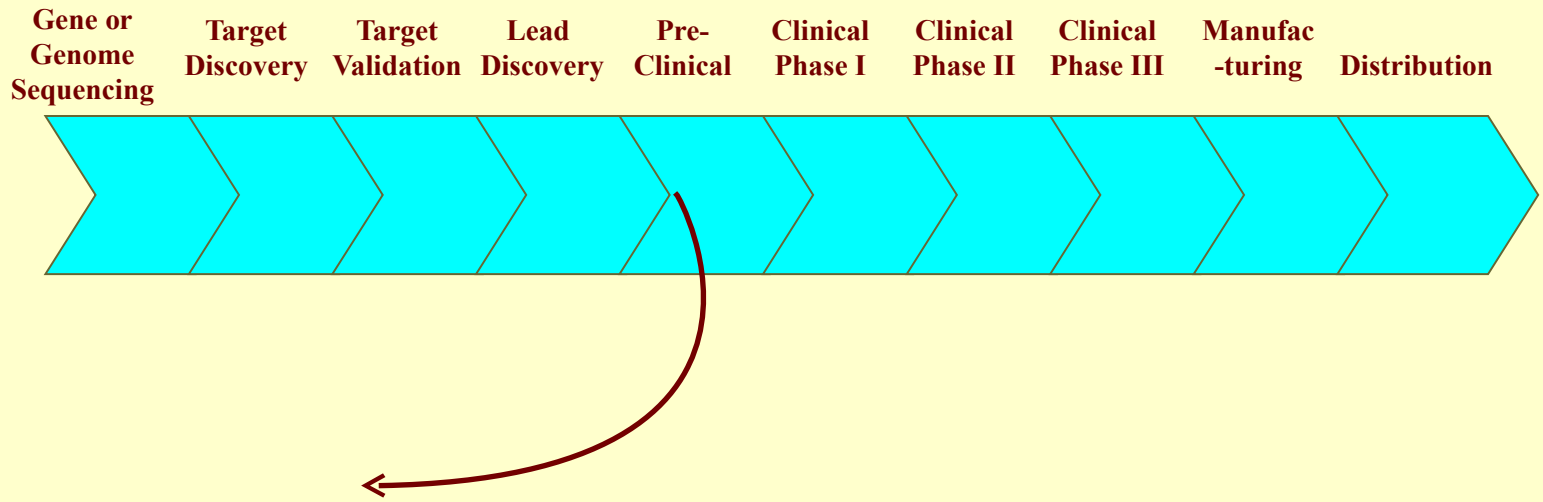


Discover leads that affect the target gene, protein or pathway

- Inhibit defective protein
- Activate a defective protein
- Inhibit expression of a protein/pathway
- Activate expression of required protein/pathway
- Stimulate protein modifications or cellular location

Courtesy of Doug Kalish

The Pharma Value Chain



Evaluate leads to ‘cure’ the problem, e.g.:

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

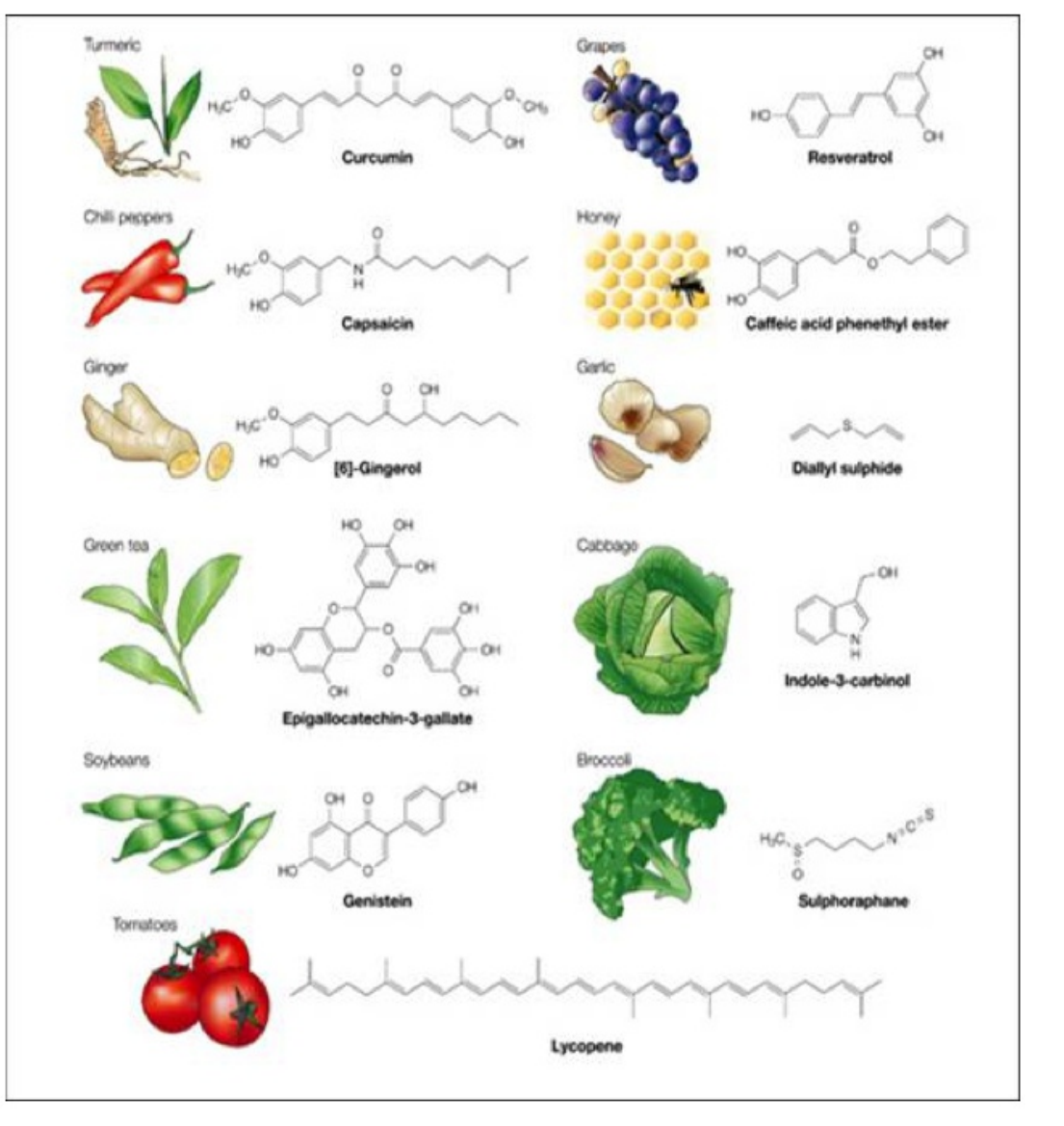
Courtesy of Doug Kalish

Drug Discovery Methods

- Screening natural compound collections

Courtesy of Doug Kalish

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

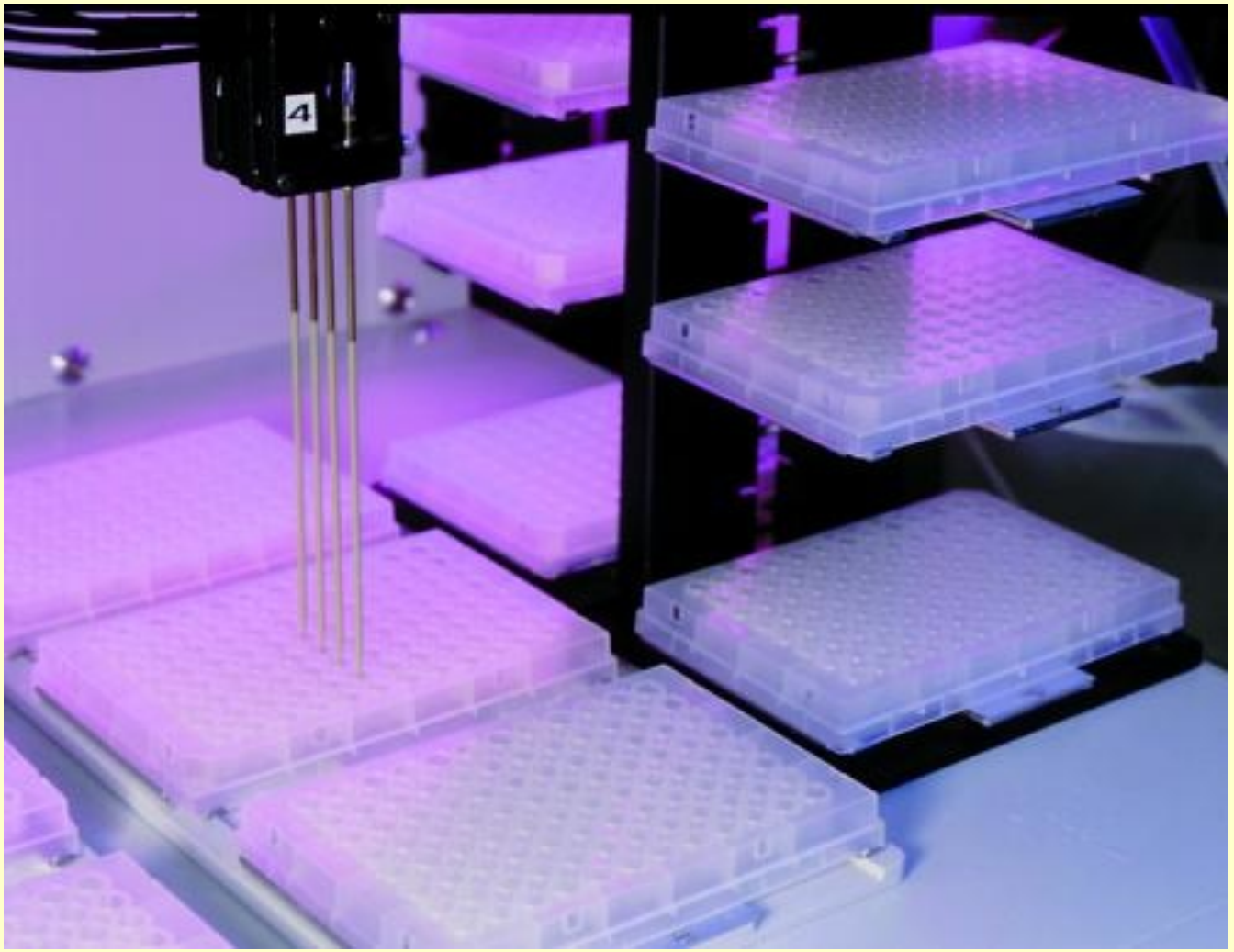
Plants

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

Drugs Derived from Wild Plants

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

Natural Compound Library Screening

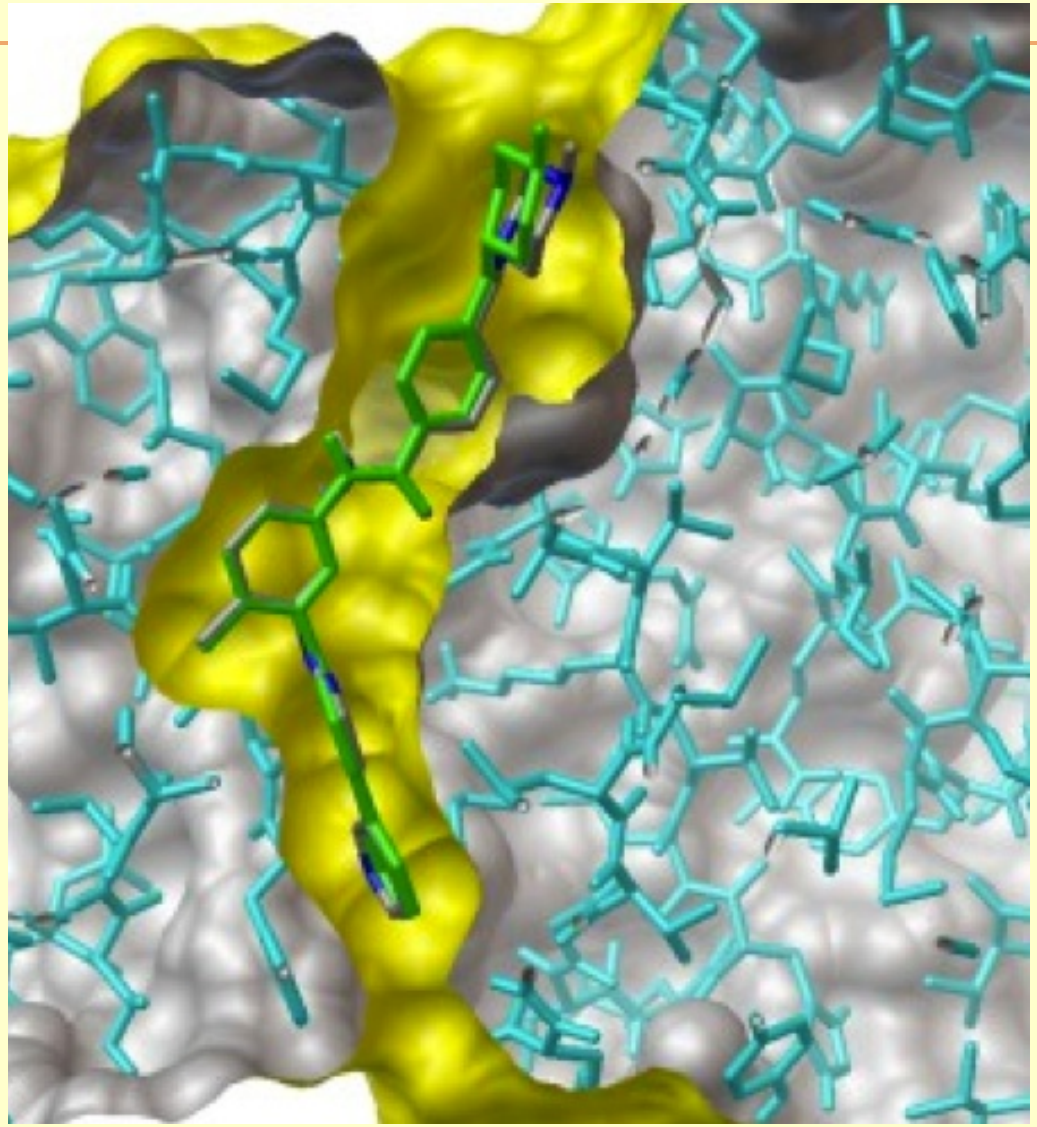


Drug Discovery Methods

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

Courtesy of Doug Kalish

In silico screening with Autodock



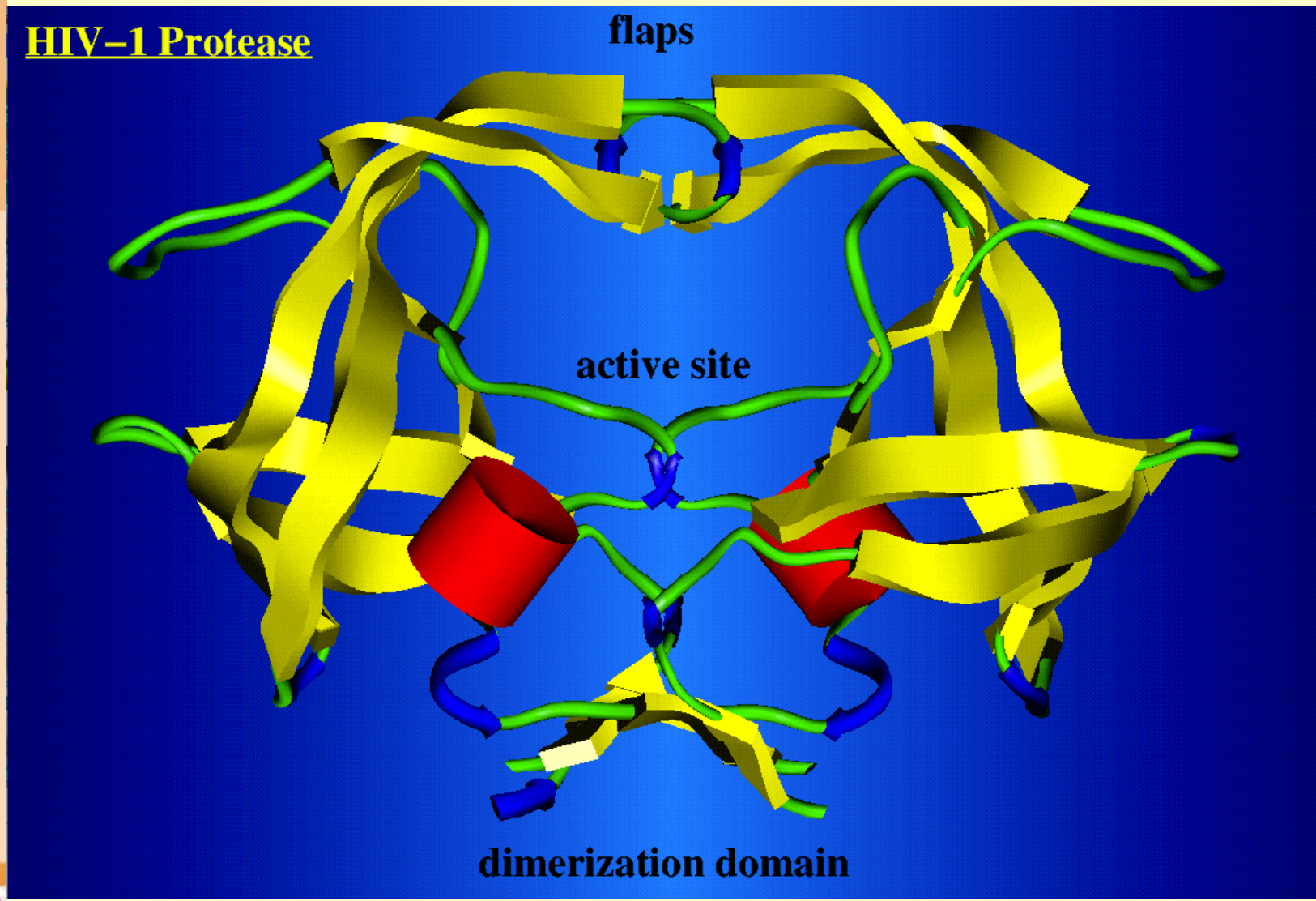
Gleevec (Imatinib) bound to BCR-Abl Protein

Drug Discovery Methods

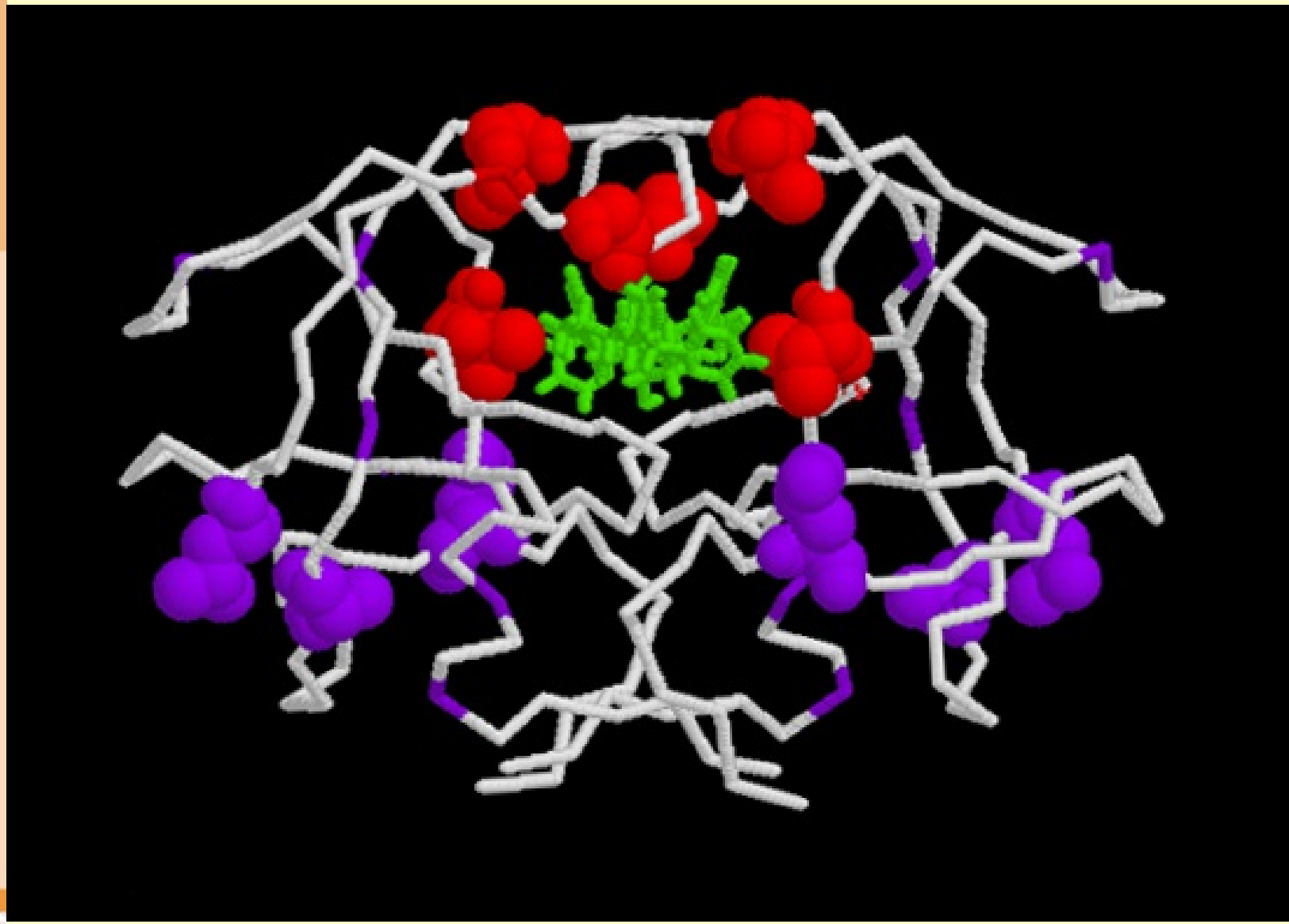
- Screening natural compound collections
- Screening corporate compound collections
- *In silico* screening (Autodock)
- Rational drug design

Courtesy of Doug Kalish

Rational Drug design for HIV Protease



Rational Drug Design for HIV Protease



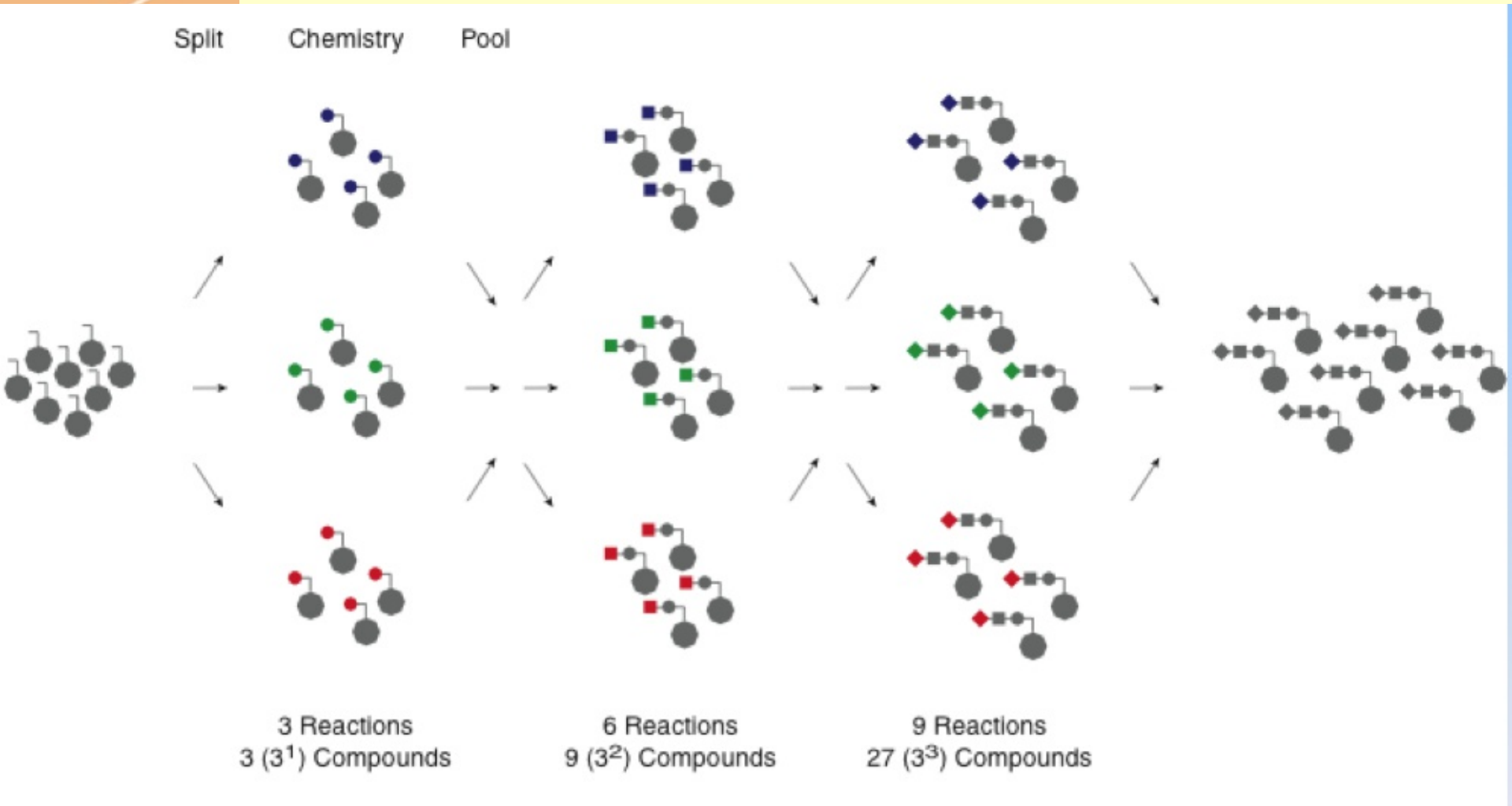
Indinavir bound to HIV Protease
Resistance mutations shown in red and purple

Drug Discovery Methods

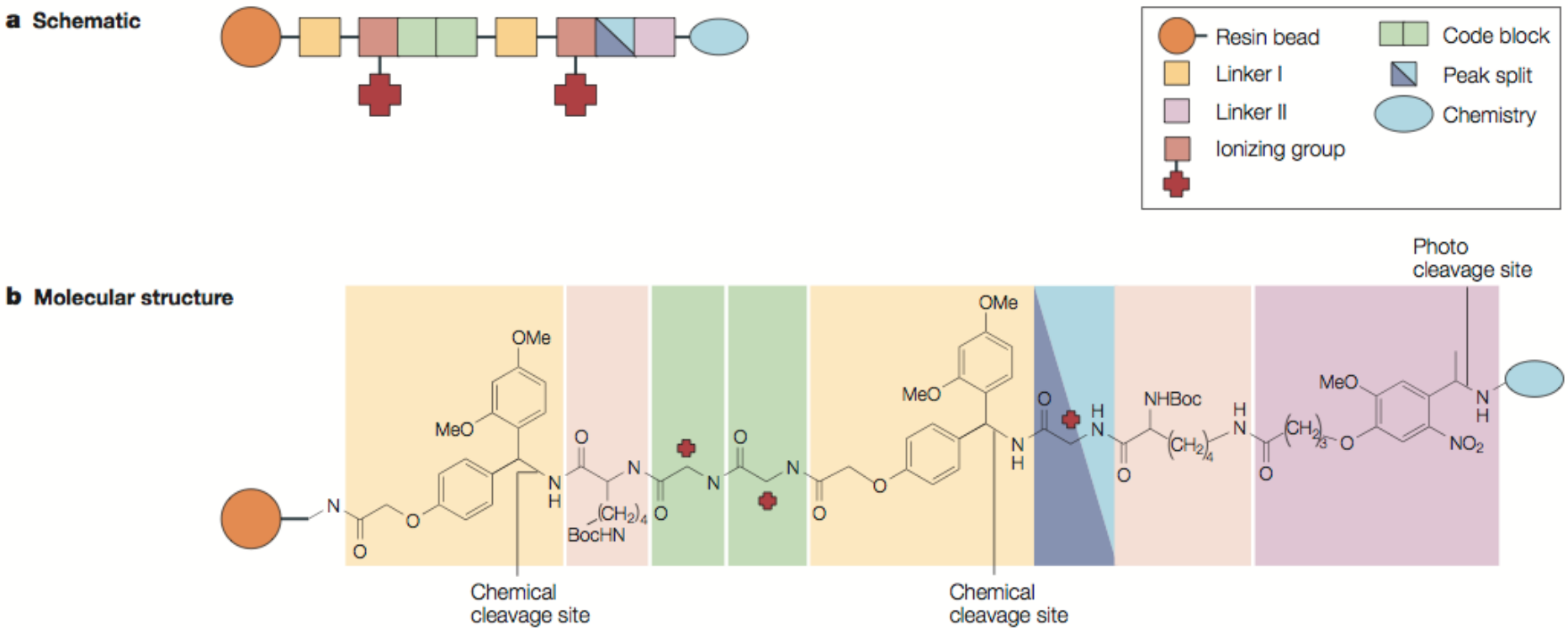
- Screening natural compound collections
- Screening corporate compound collections
- *In silico* screening (Autodock)
- Rational drug design
- Combinatorial chemistry

Courtesy of Doug Kalish

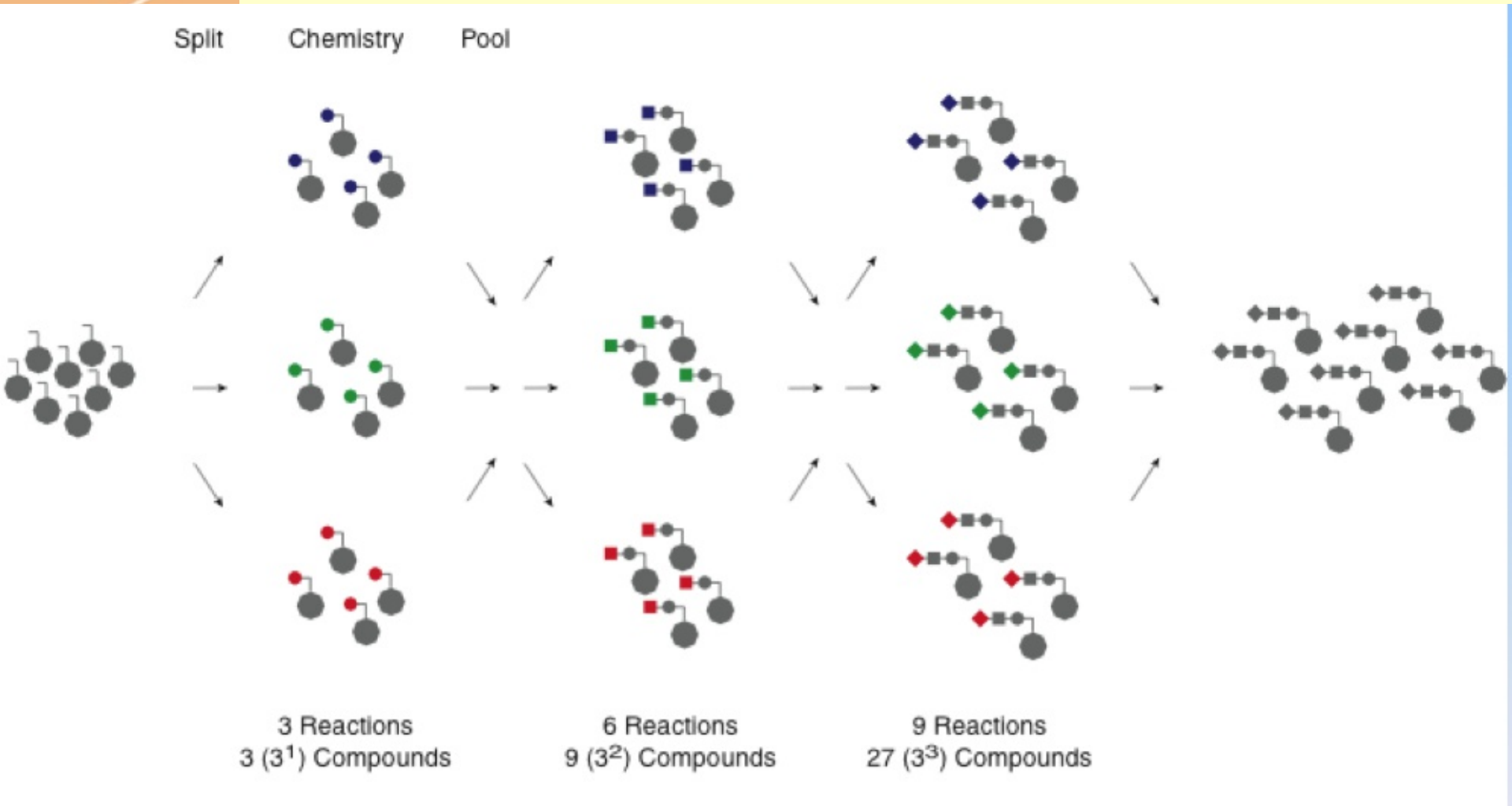
Combinatorial Chemistry



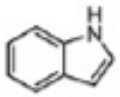
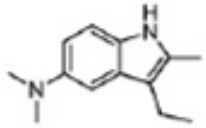
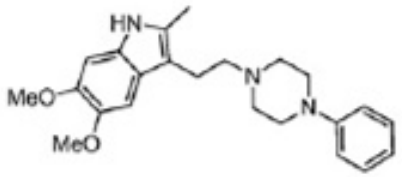
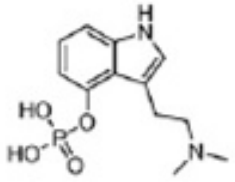
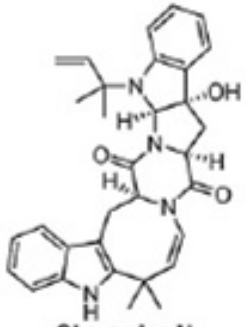
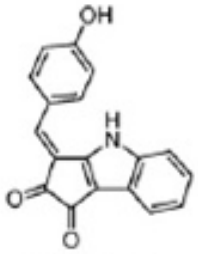
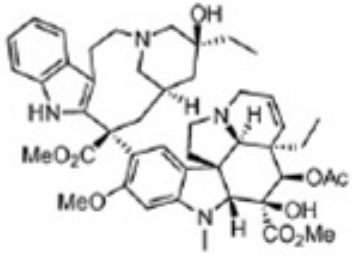
Resin Linker with Code Blocks and Light Sensitive Cleavage sites



Combinatorial Chemistry



Privileged Scaffolds

Privileged Scaffold	Structures
Indole 	*Drugs*  **Medmain** Therap Cat: Serotonin inhibitor  **Oxypertine** Therap Cat: Antidepressant  **Psilocybin** Therap Cat: Psychomimetic
	Natural Products  **Okaramine N** Source: Penicillium simplicissium Biological Activity: Insecticidal activity  **Nostodione A** Source: The terrestrial blue-green algae Nostoccommune Biological Activity: Mitotic spindle posion  **Vinblastine** Source: Leaves of Madagascar periwinkle plant (Cantharanthus roseus) Biological Activity: Anticancer agent; causes apoptosis by stopping spindle formation during mitosis

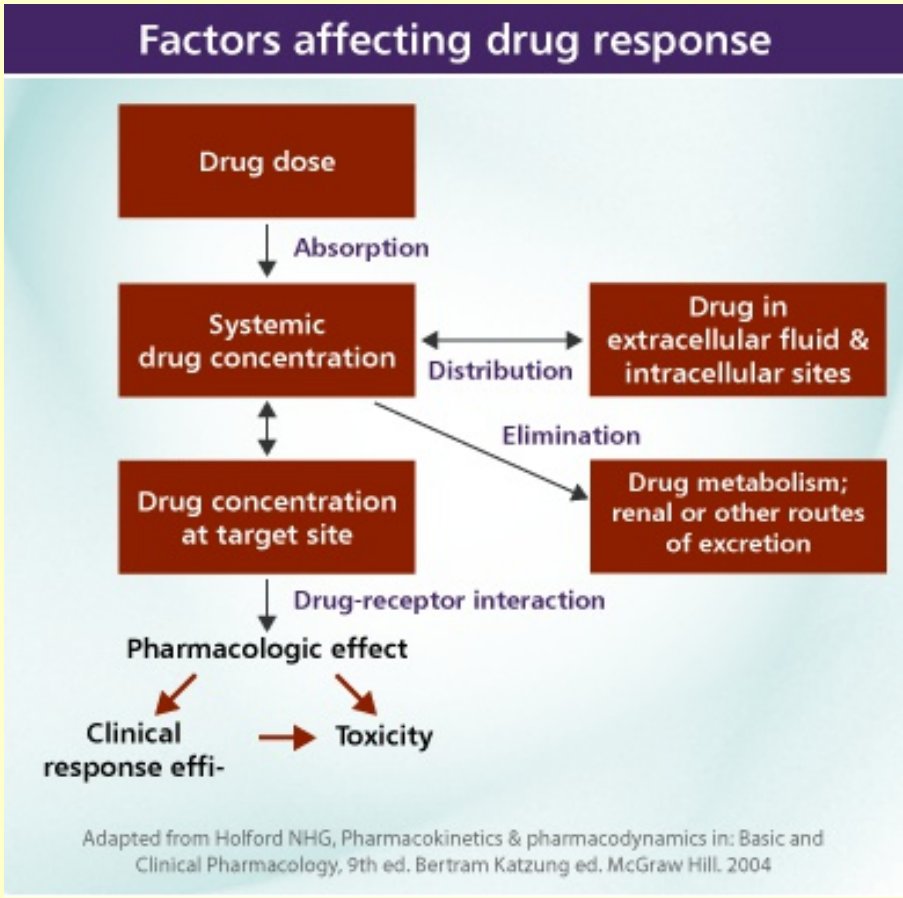
Drug Discovery Methods

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

Courtesy of Doug Kalish

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



Courtesy of Doug Kalish

Chris Lipinski's Rule of Five

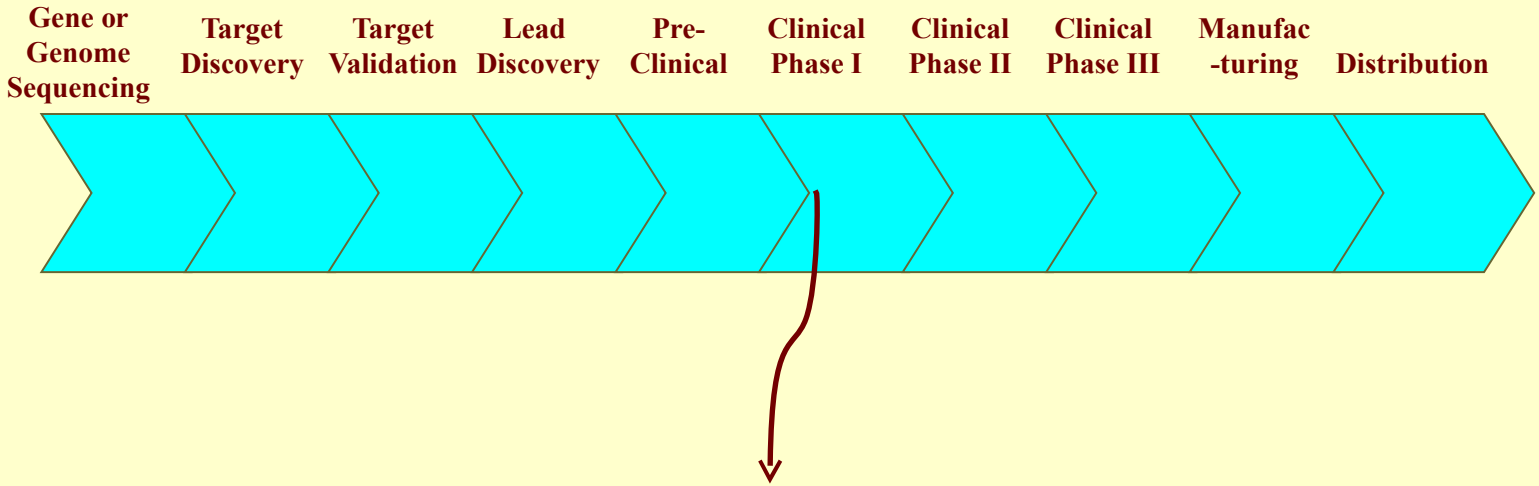
Lipinski and his Pfizer co-workers looked over a data set of drug candidates and noticed that there were some reasonably clear cutoffs for oral absorption and general cell permeability. They suggested that you need:

1. Fewer than five hydrogen bond donors (which can be estimated by counting the total number of OH and NH groups in the molecule.)
2. Fewer than 5 hydrogen-bond acceptors (estimated by the total of N and O atoms in the molecule.)
3. A molecular weight of less than 500
4. A partitioning coefficient (logP) of less than 5

The "rule of five" name came from the cutoffs all being multiples of five, in case you are wondering why there are only four rules.

Courtesy of Doug Kalish

The Pharma Value Chain

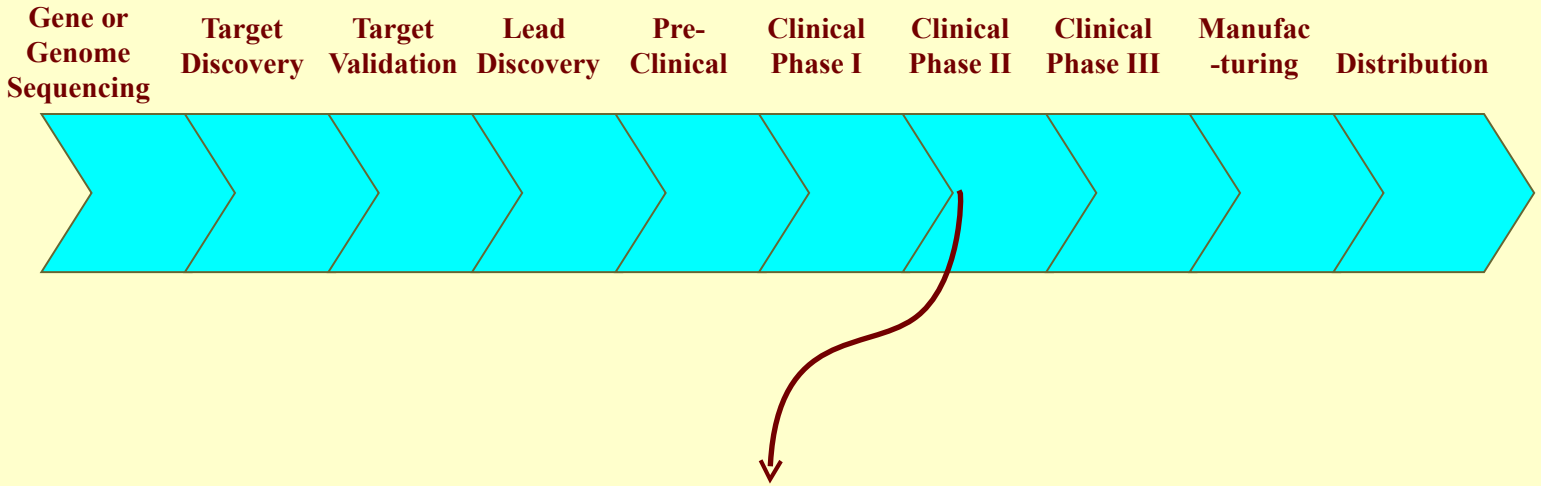


- Animal tests of toxicity and efficacy of therapy
  - Rodents (mice and rats)
  - Mammals (pigs)
  - Primates (monkeys and chimpanzees)
  - Mouse Lemurs (*Microcebus*)

Courtesy of Doug Kalish

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

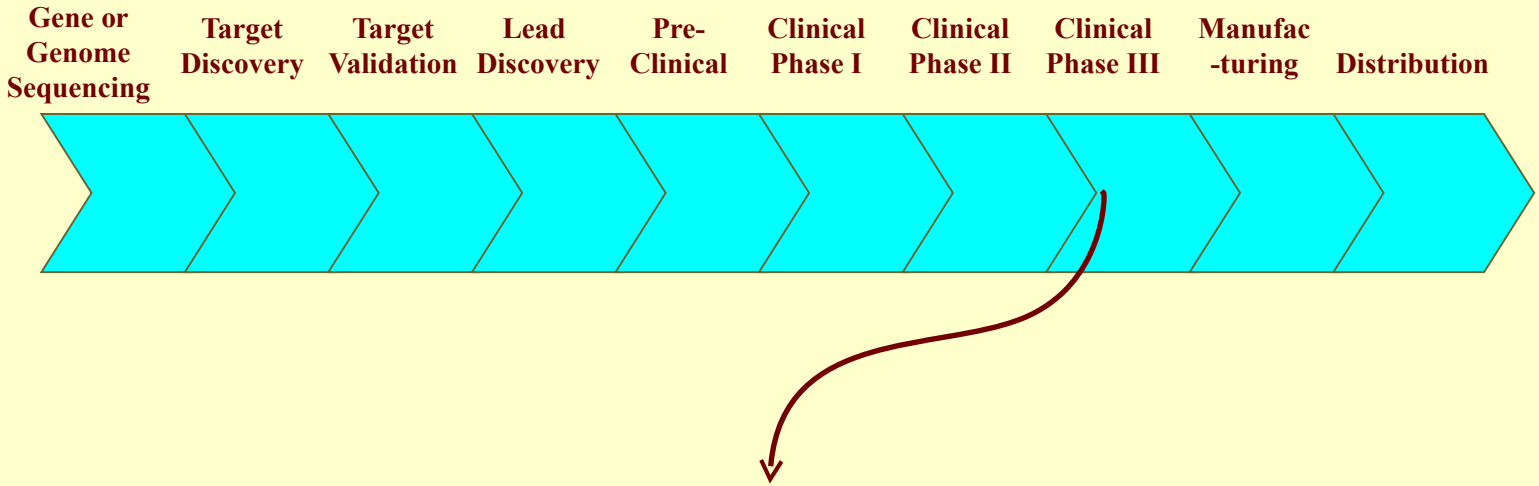
The Pharma Value Chain



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

Courtesy of Doug Kalish

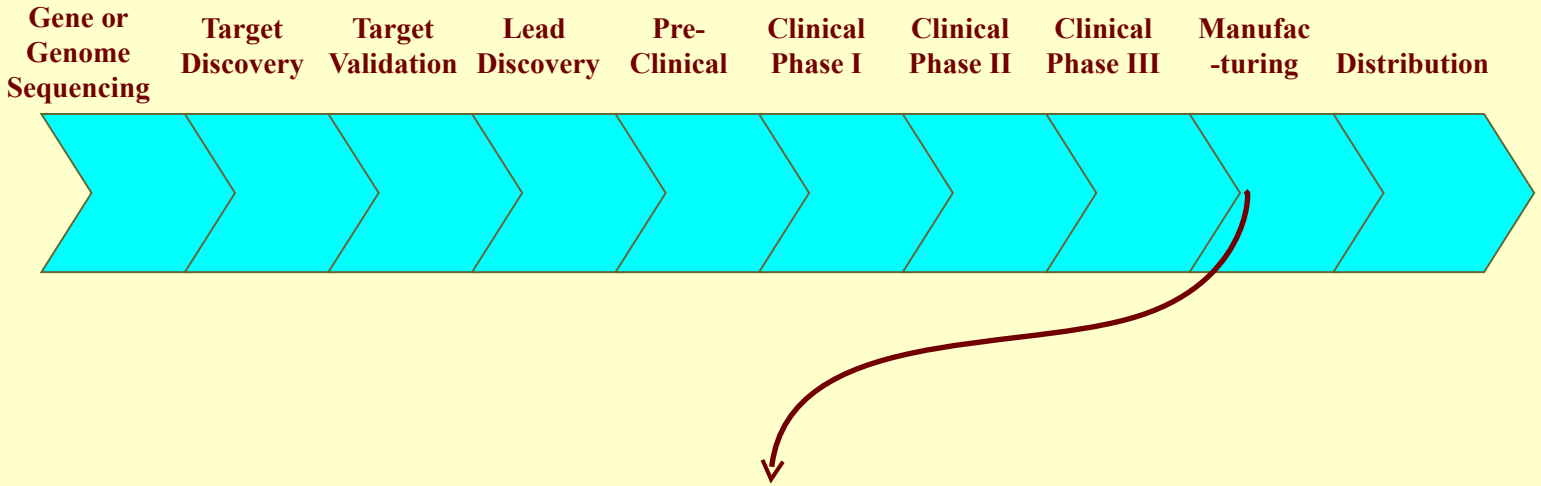
The Pharma Value Chain



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

Courtesy of Doug Kalish

The Pharma Value Chain

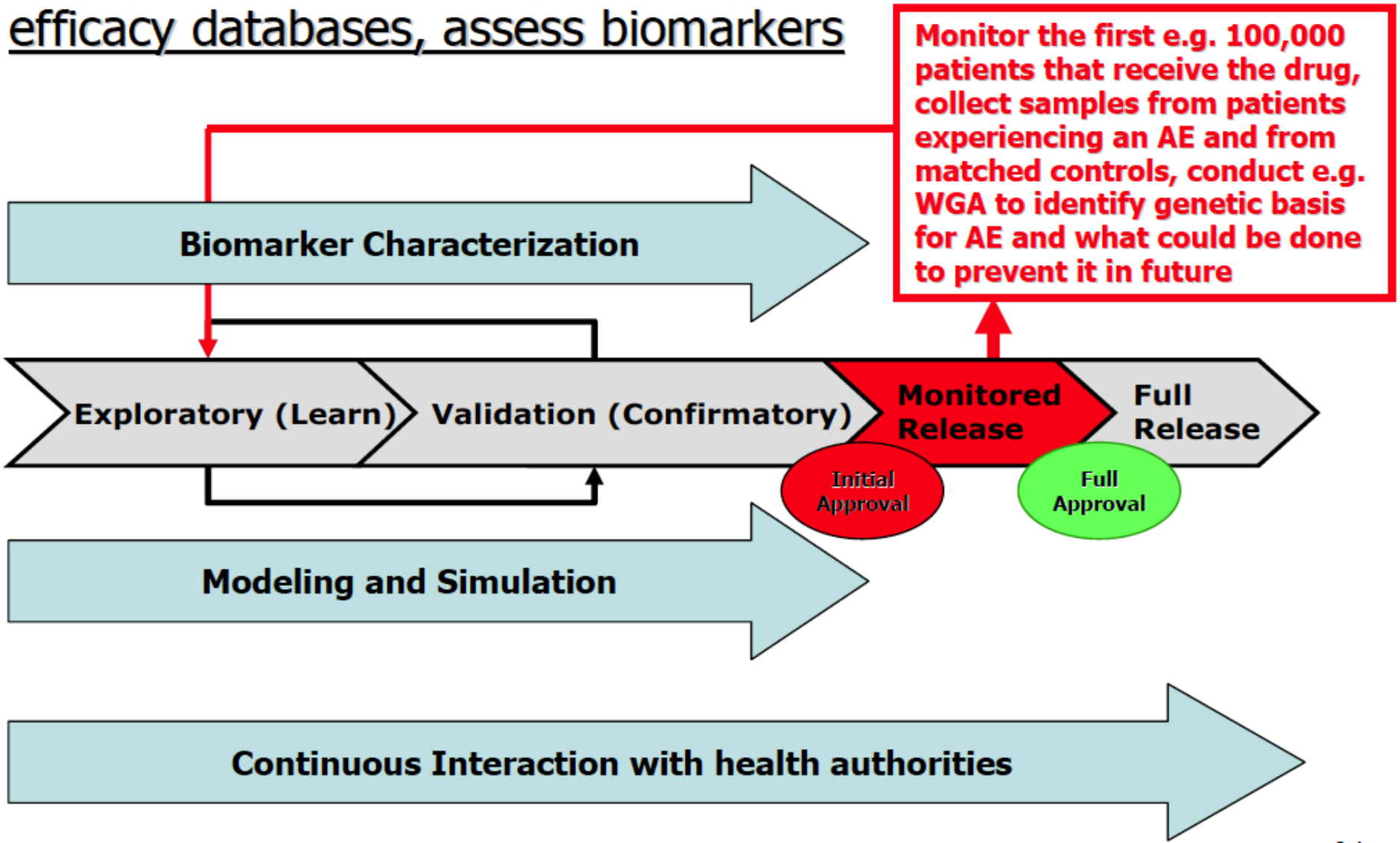


1000's of patients and controls (normals) to determine efficacy, dosage, safety, side effects, and interactions. Each prospective patient group (men, women, children, elderly and ethnic groups)

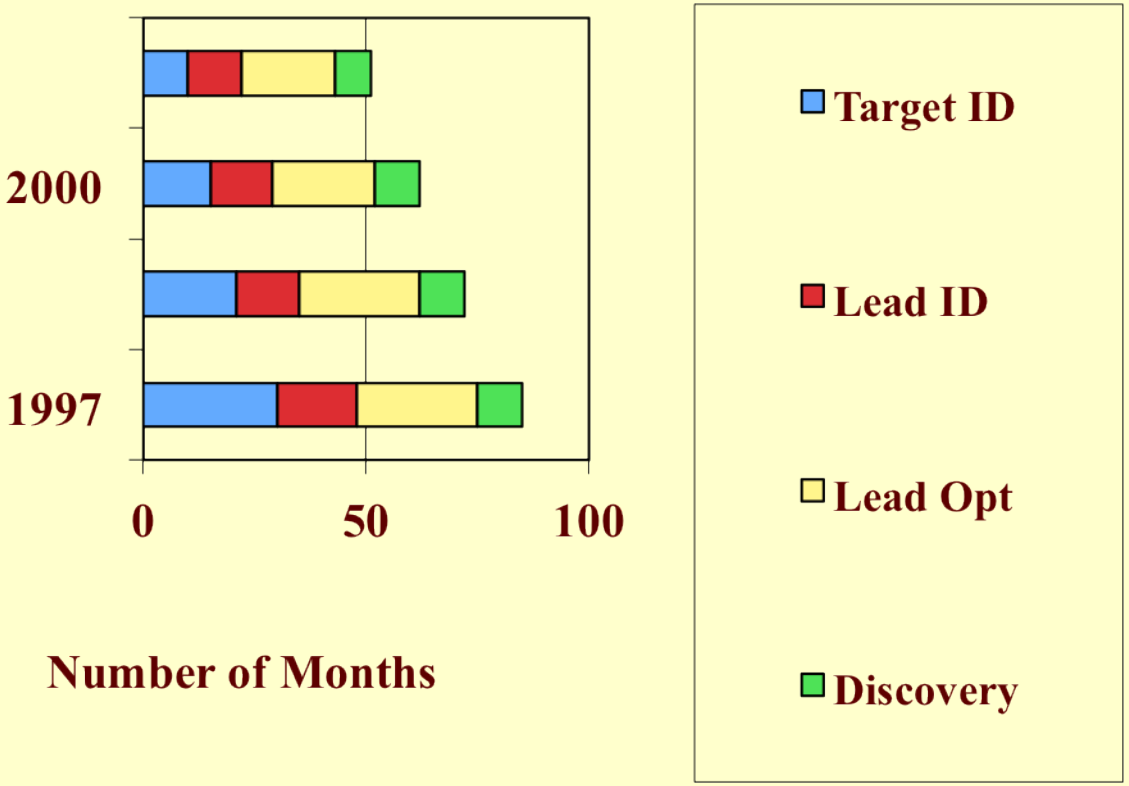
Courtesy of Doug Kalish

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

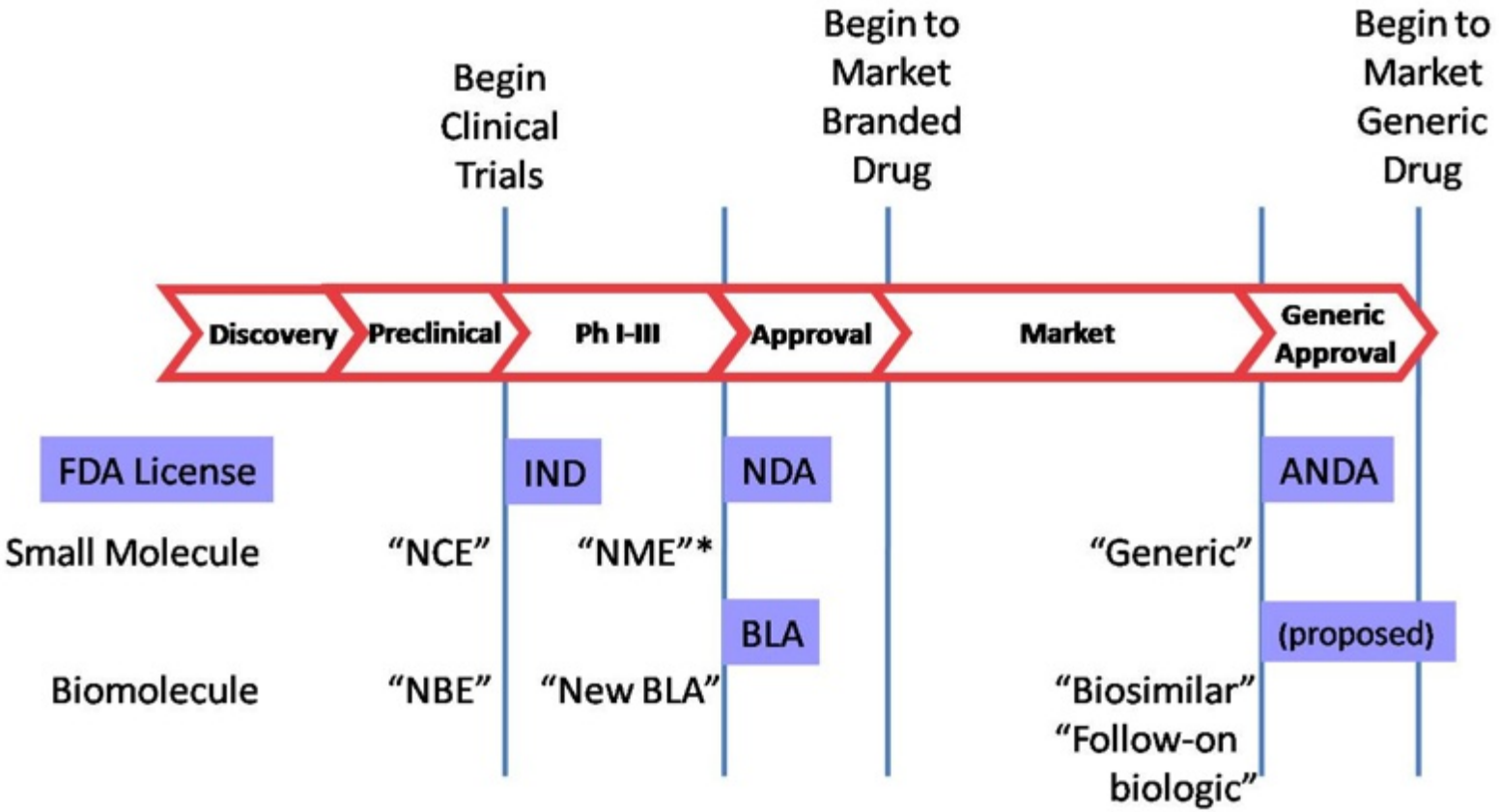


The Impact of Genomics and Bioinformatics on Drug Discovery Times



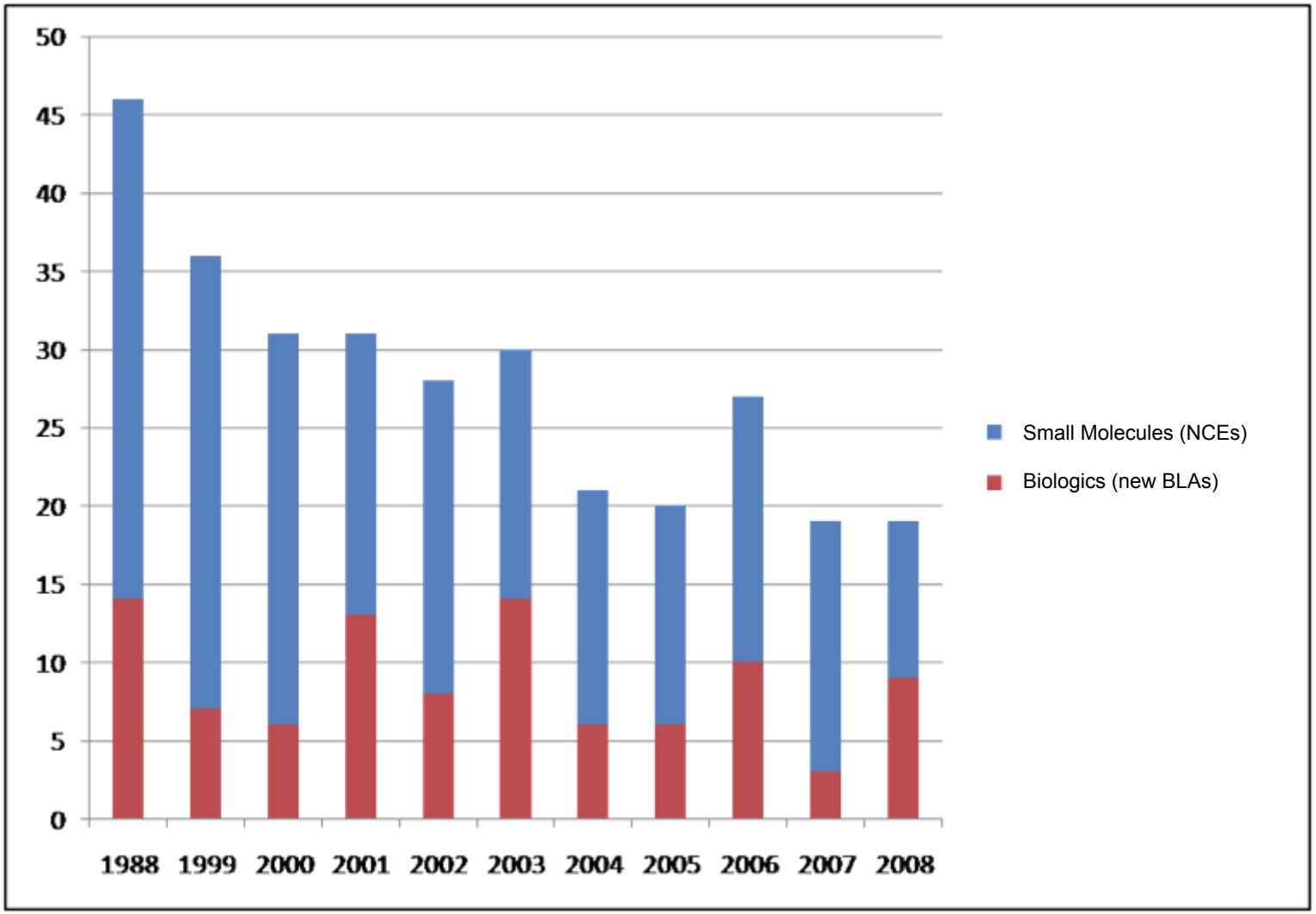
Courtesy of Doug Kalish

Short Market Time



C. Thomas Caskey, Annu. Rev. Med. 2007. 58:1–16

FDA Approved New Chemical Entities and Biological Derivatives



C. Thomas Caskey, Annu. Rev. Med. 2007. 58:1–16