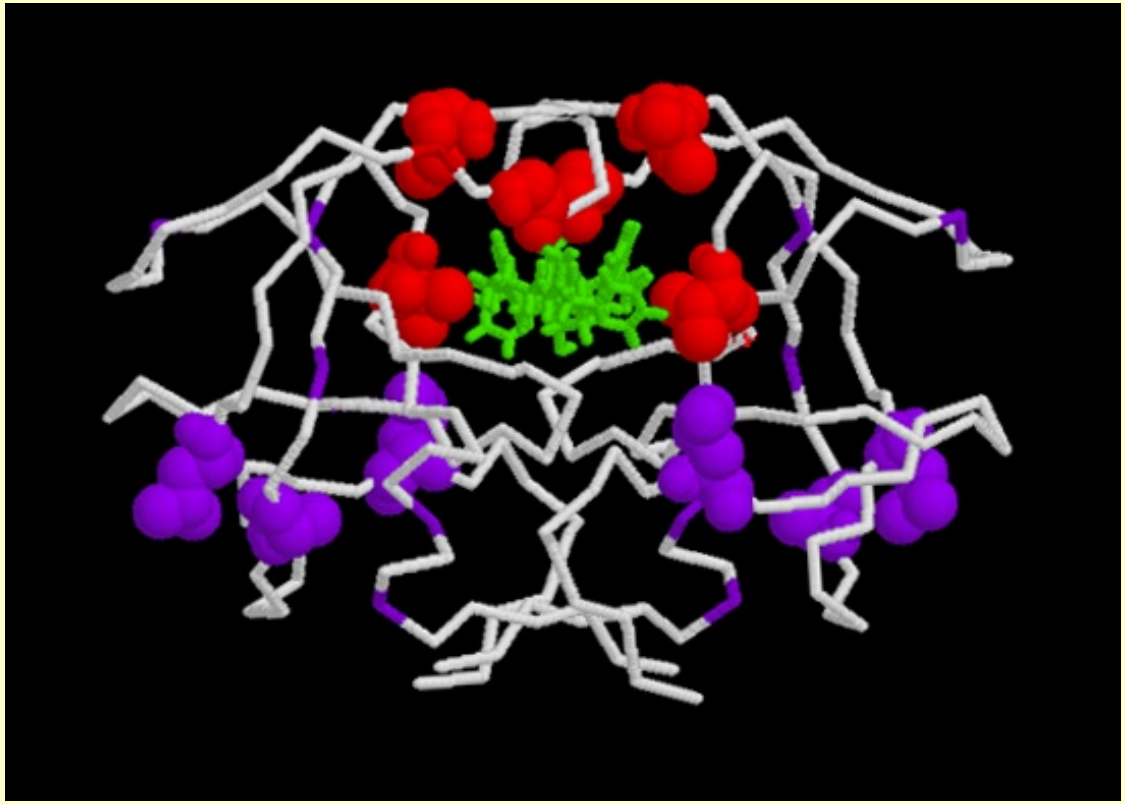
# Genomics, Bioinformatics & Medicine

http://biochem158.stanford.edu/

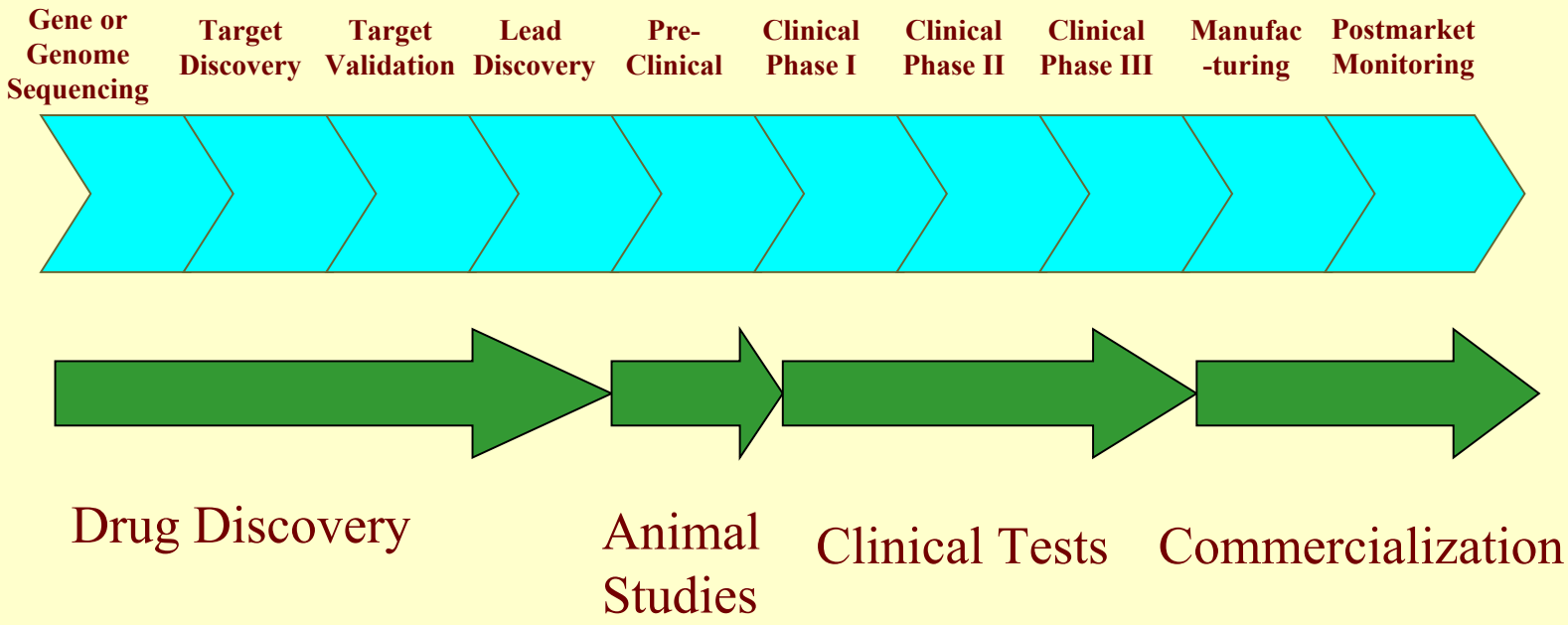
## Drug Development

http://biochem158.stanford.edu/Drug-Development.html



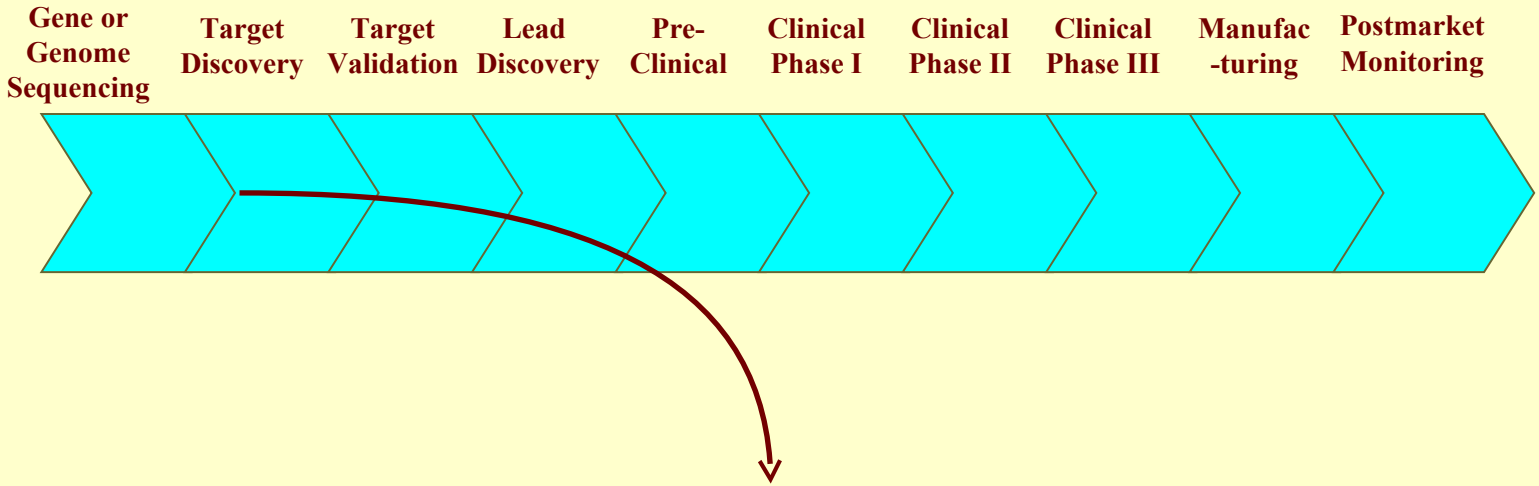
Doug Brutlag
Professor Emeritus of Biochemistry and Medicine
Stanford University School of Medicine
brutlag@stanford.edu

# The Pharma Value Chain




Courtesy of Doug Kalish

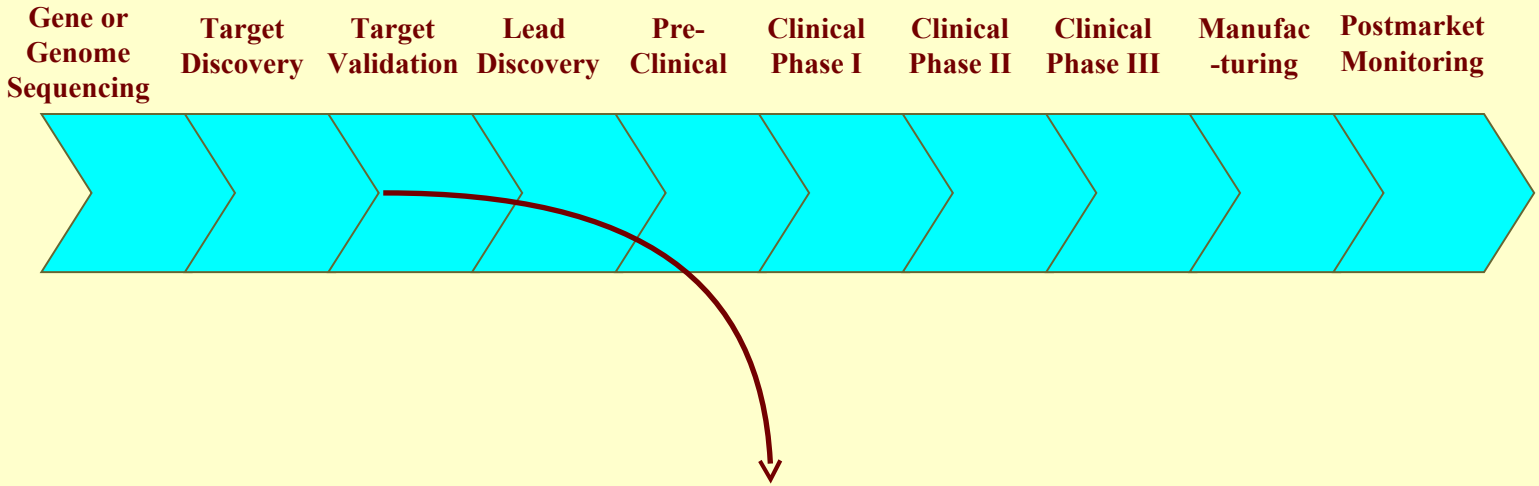
# The Pharma Value Chain




- Build a library of gene/protein (genome/proteome) sequences to mine for information
- Look for genes known to cause a disease
- Look for genes associated with a disease
- Look for genes in pathways unique to the disease

Courtesy of Doug Kalish

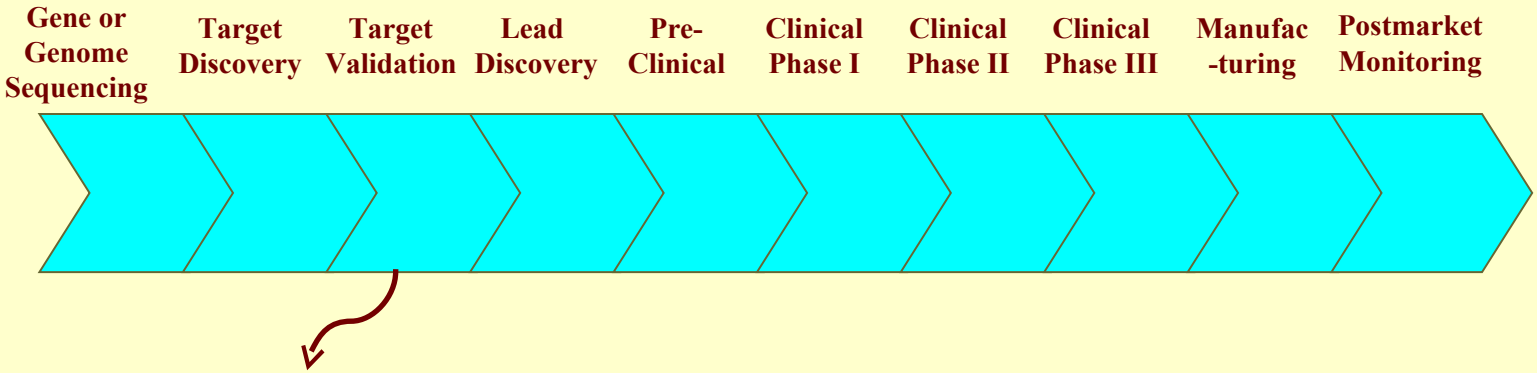
# The Pharma Value Chain




- 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/proteins.

Courtesy of Doug Kalish

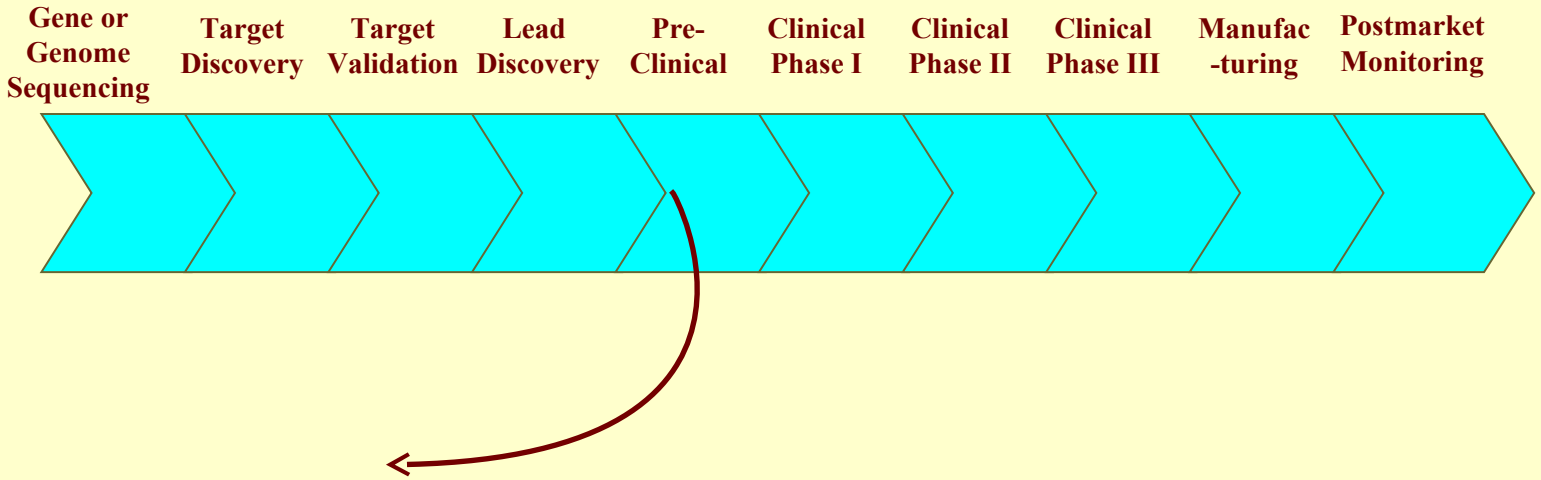
# The Pharma Value Chain




- 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.

Courtesy of Doug Kalish

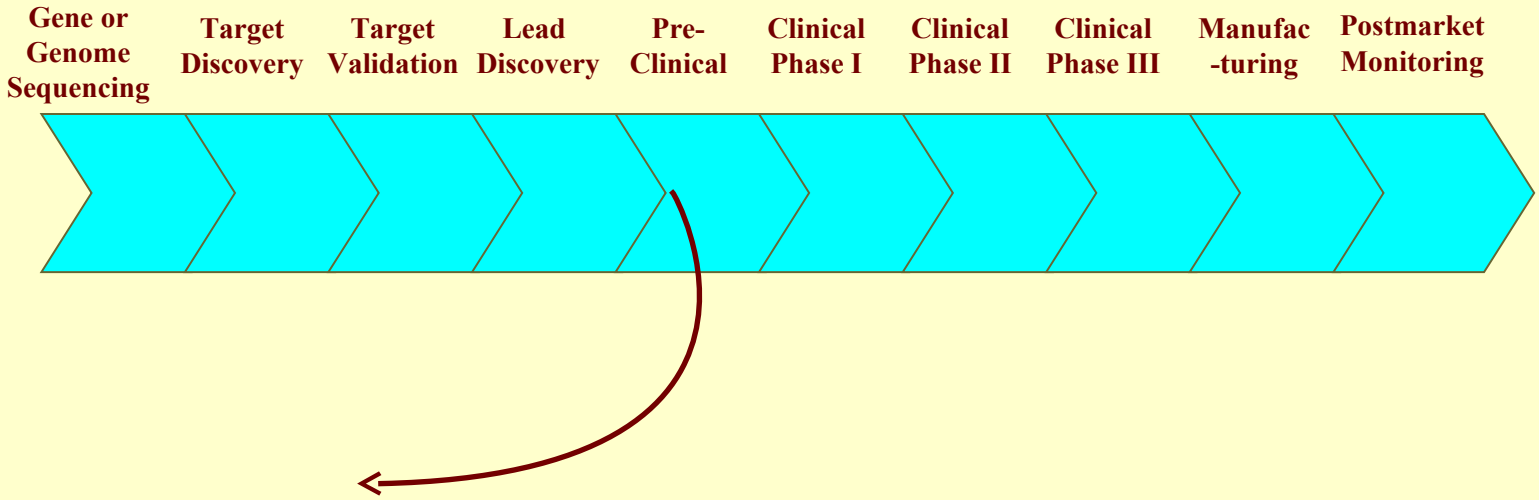
# The Pharma Value Chain




Discover leads that affect the target gene, protein or pathway
Inhibit defective protein
Activate a normal 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 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

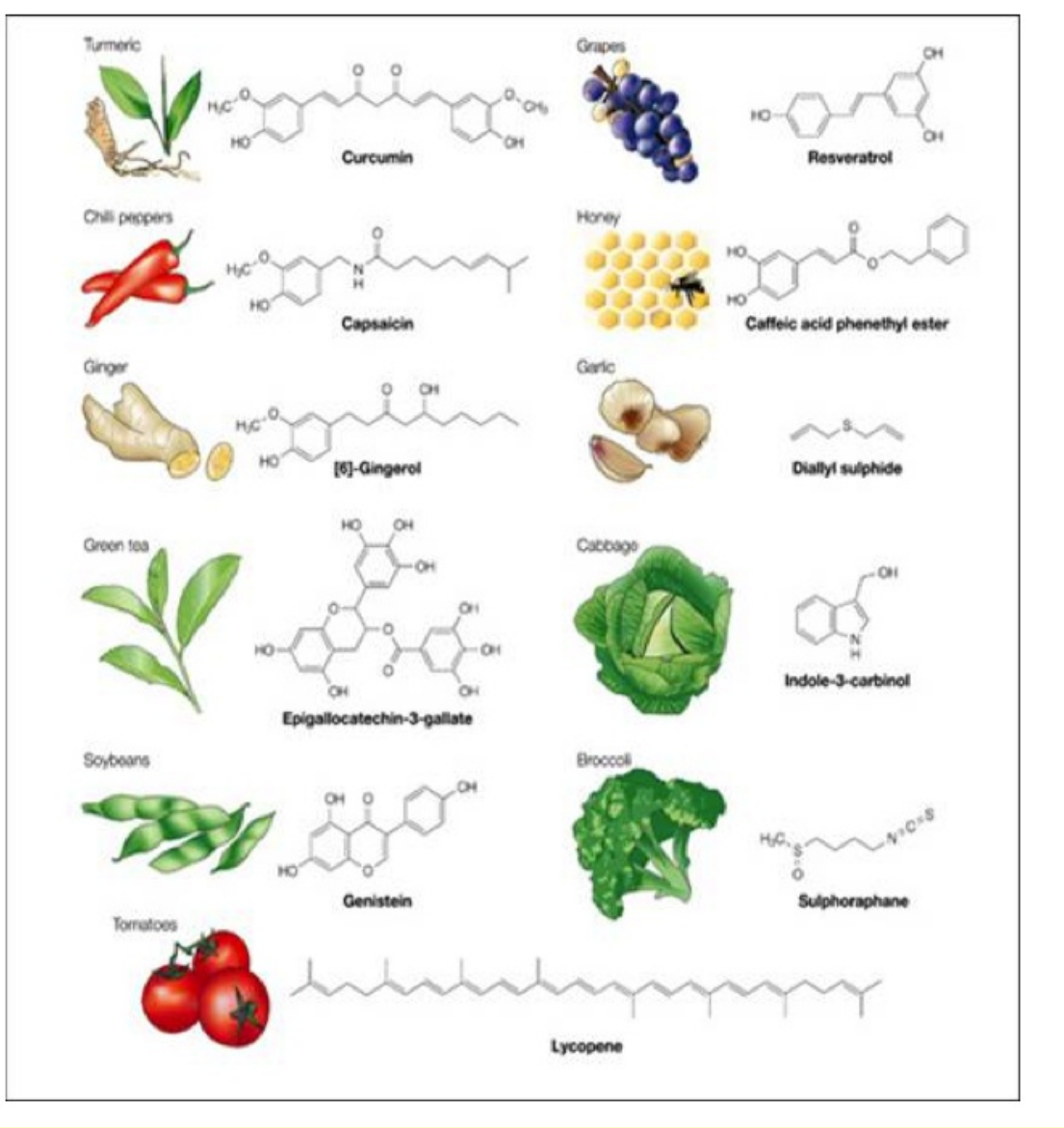
Courtesy of Doug Kalish

# 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* |
| Adonisside | 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* |

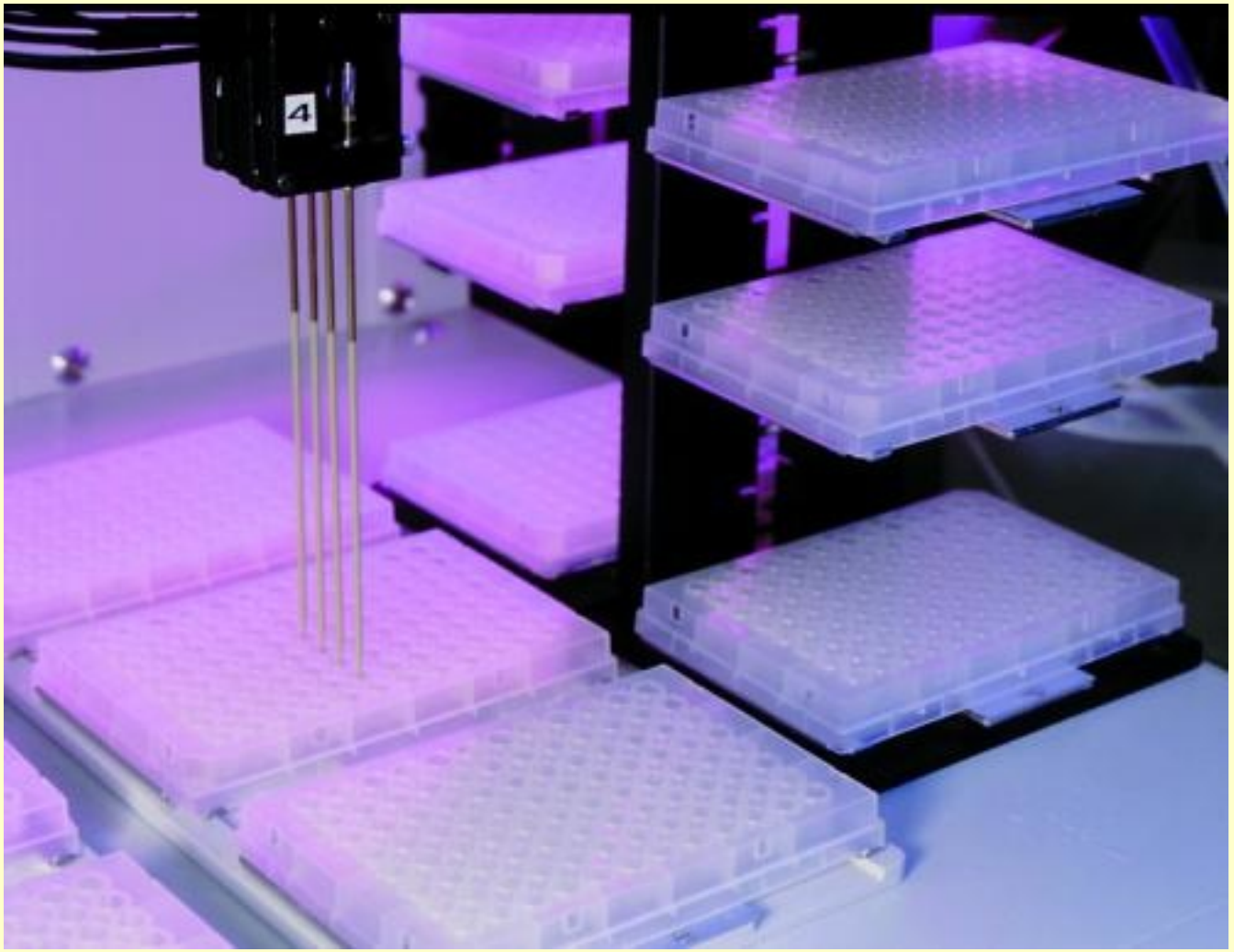
# Plants

| 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* |
| Qulsqualic 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

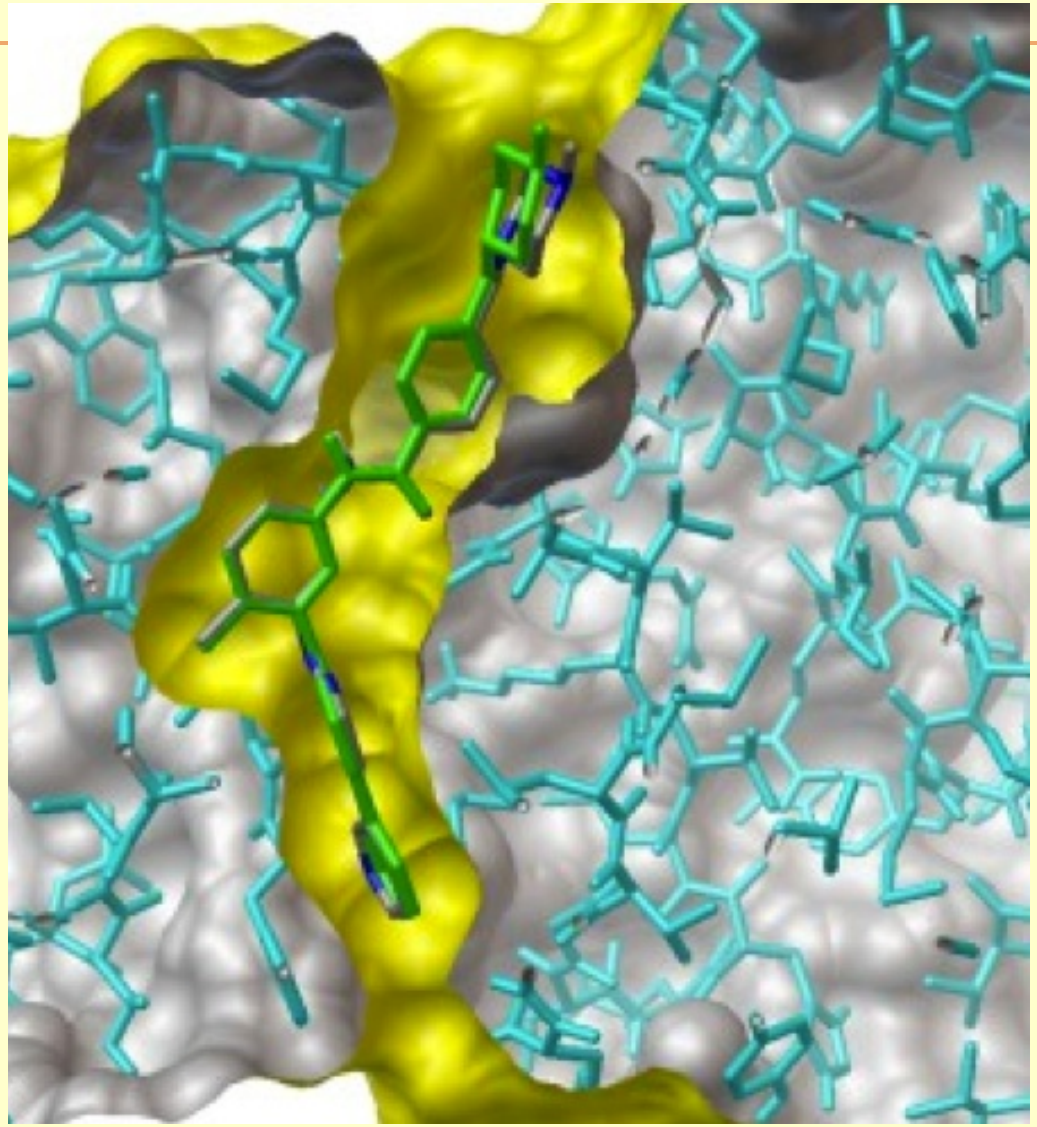


# Drug Discovery Methods

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

Courtesy of Doug Kalish

# *In silico* screening with Autodock



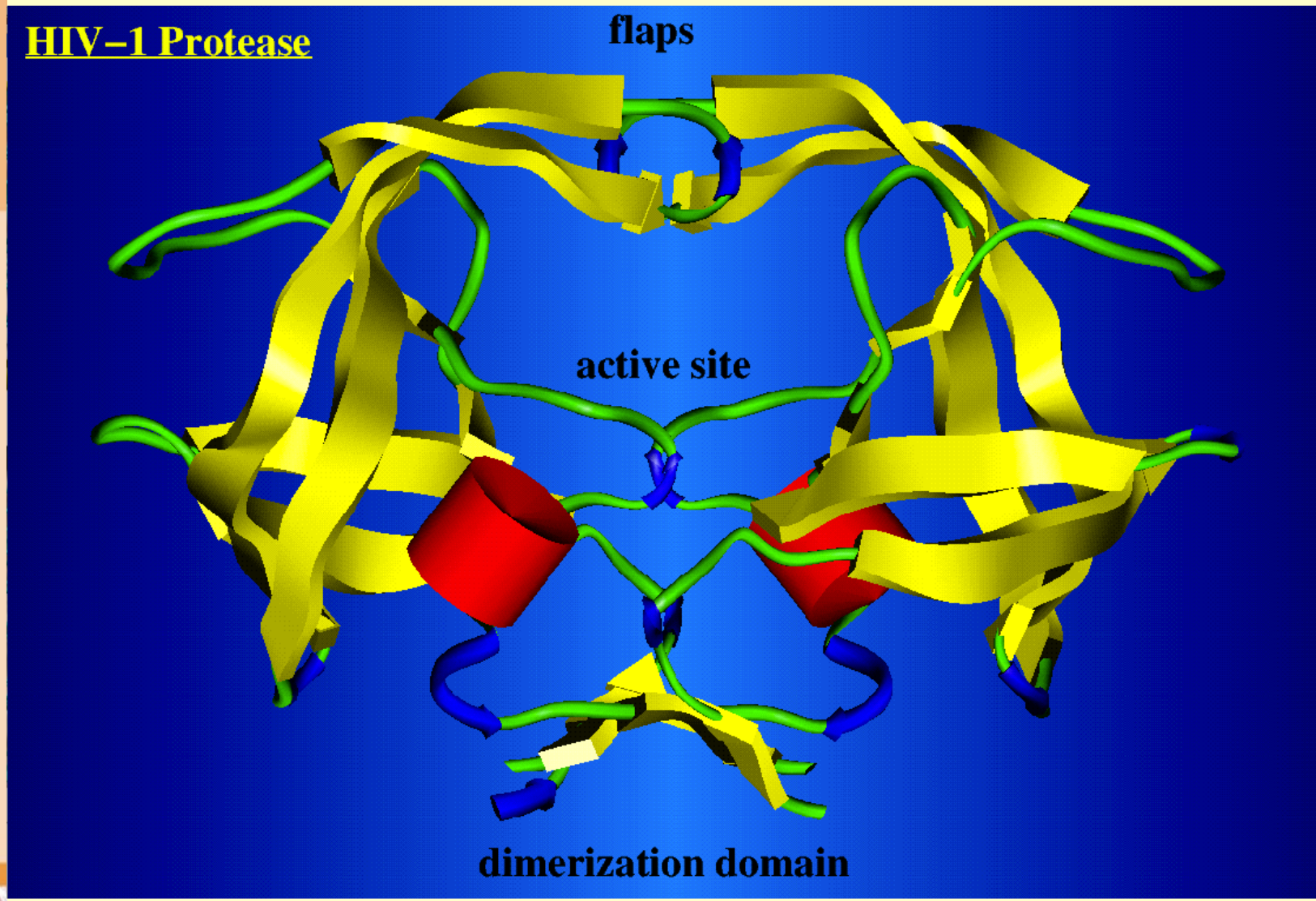
Gleevec (Imatinib) bound to BCR-Abl Protein

# Drug Discovery Methods

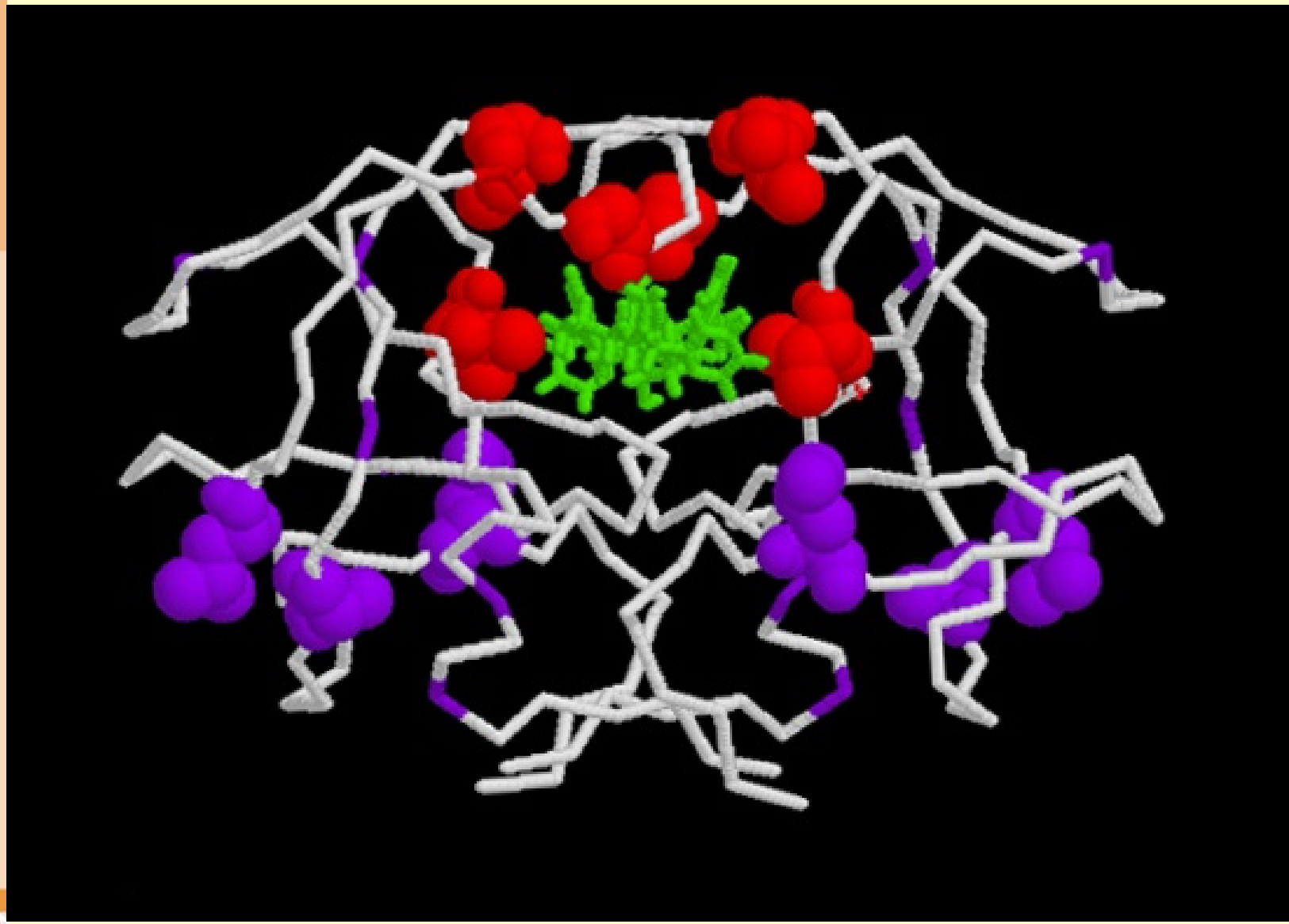
- Screening natural compound collections
- Screening corporate compound collections
- *In silico* screening (Autodock)
- Rational drug design

Courtesy of Doug Kalish

# Rational Drug design for HIV Protease



# Rational Drug Design for HIV Protease



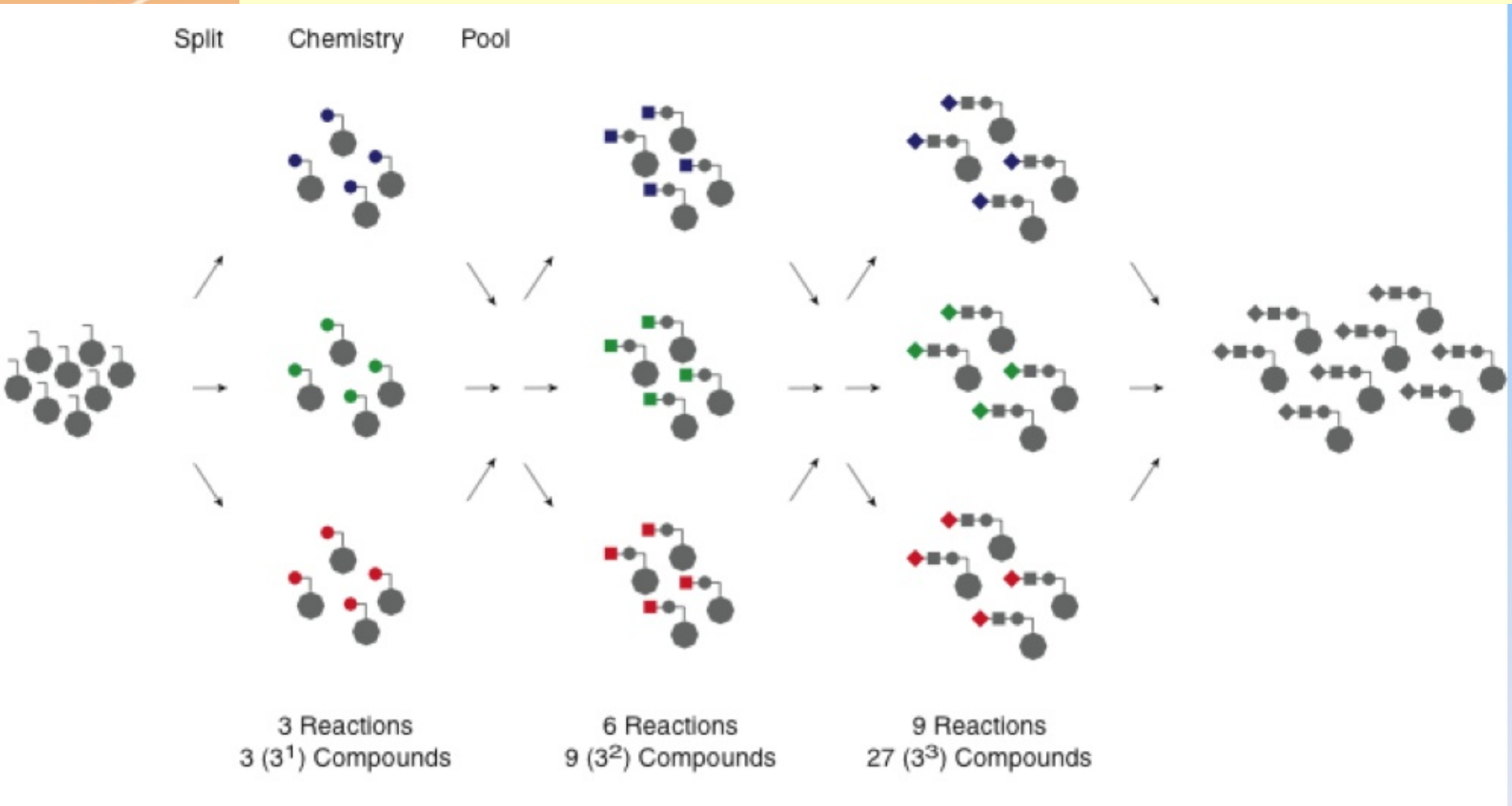
Indinavir bound to HIV Protease
Resistance mutations shown in red and purple

# Drug Discovery Methods

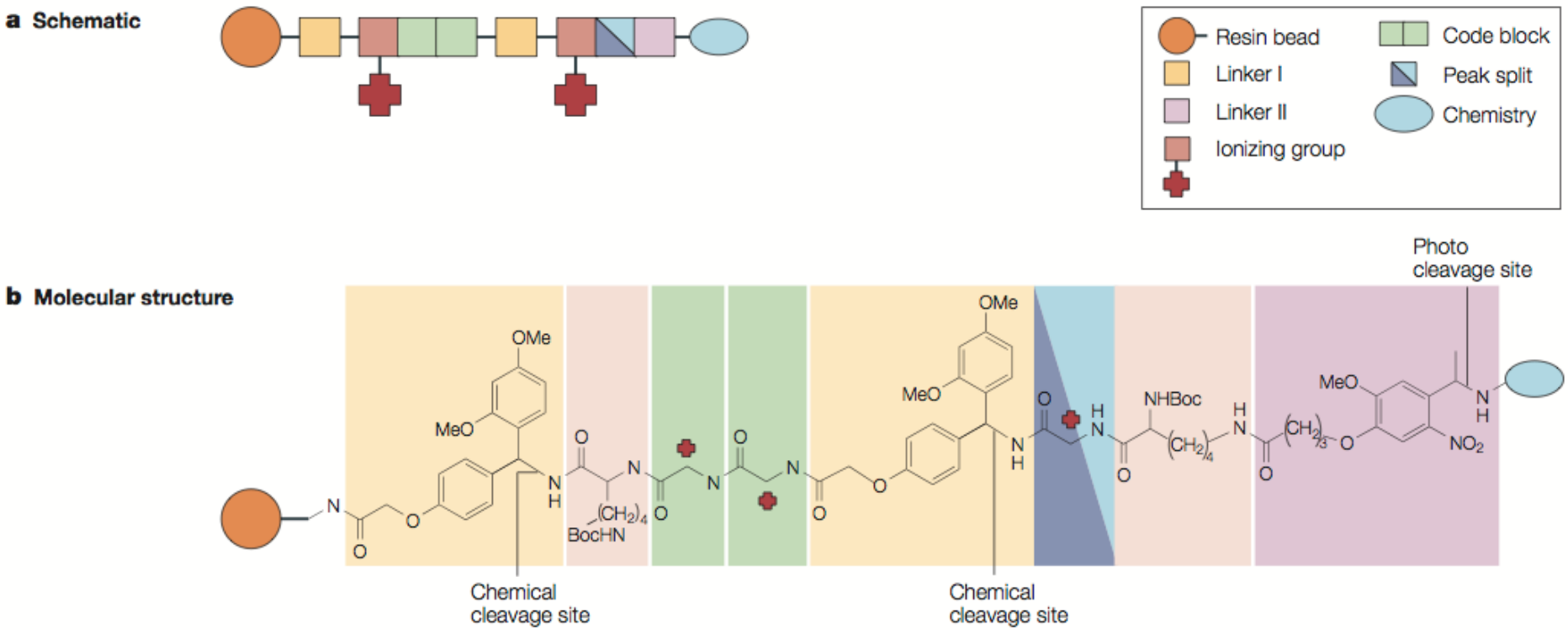
- Screening natural compound collections
- Screening corporate compound collections
- *In silico* screening (Autodock)
- Rational drug design
- Combinatorial chemistry

Courtesy of Doug Kalish

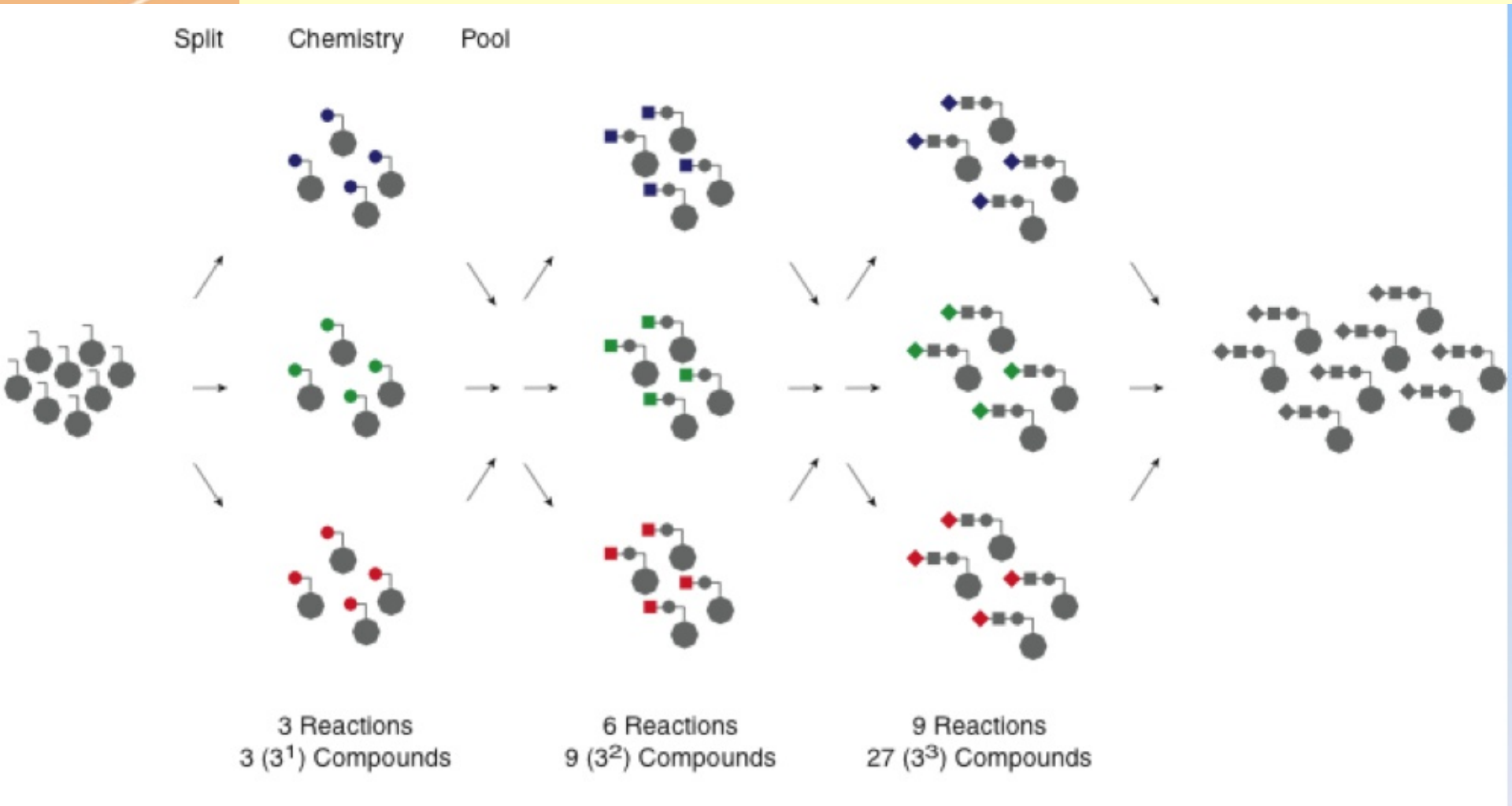
# Combinatorial Chemistry



# Resin Linker with Code Blocks and Light Sensitive Cleavage sites



# Combinatorial Chemistry



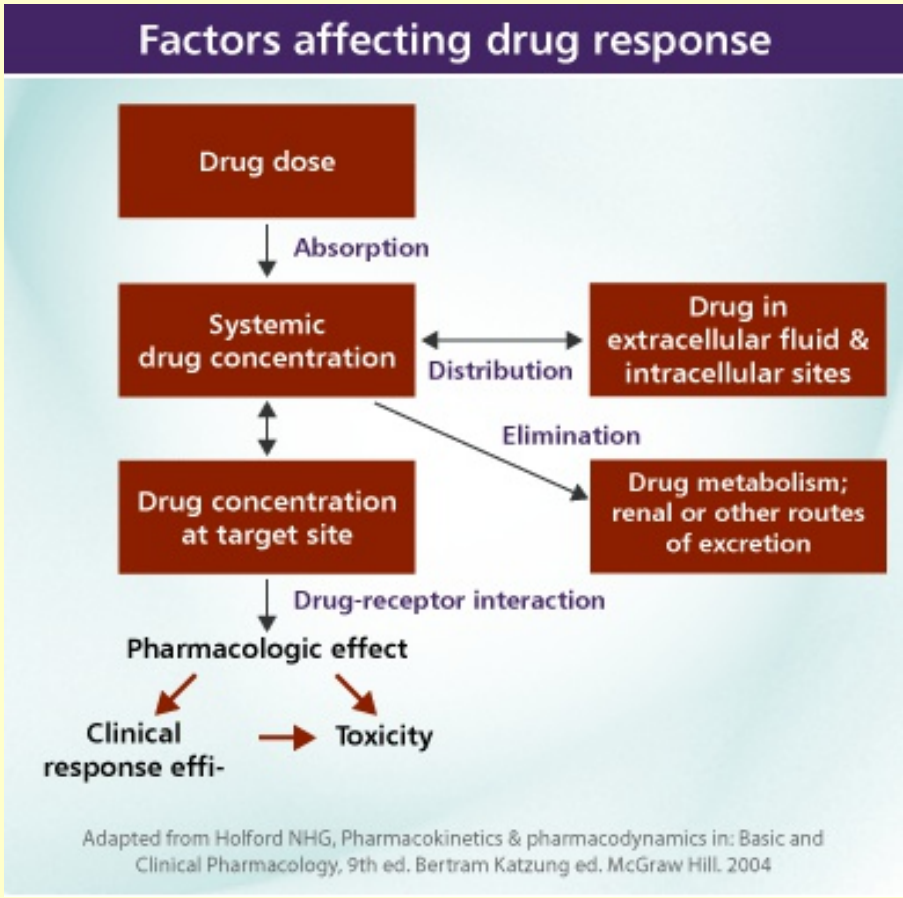
# Drug Discovery Methods

- 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

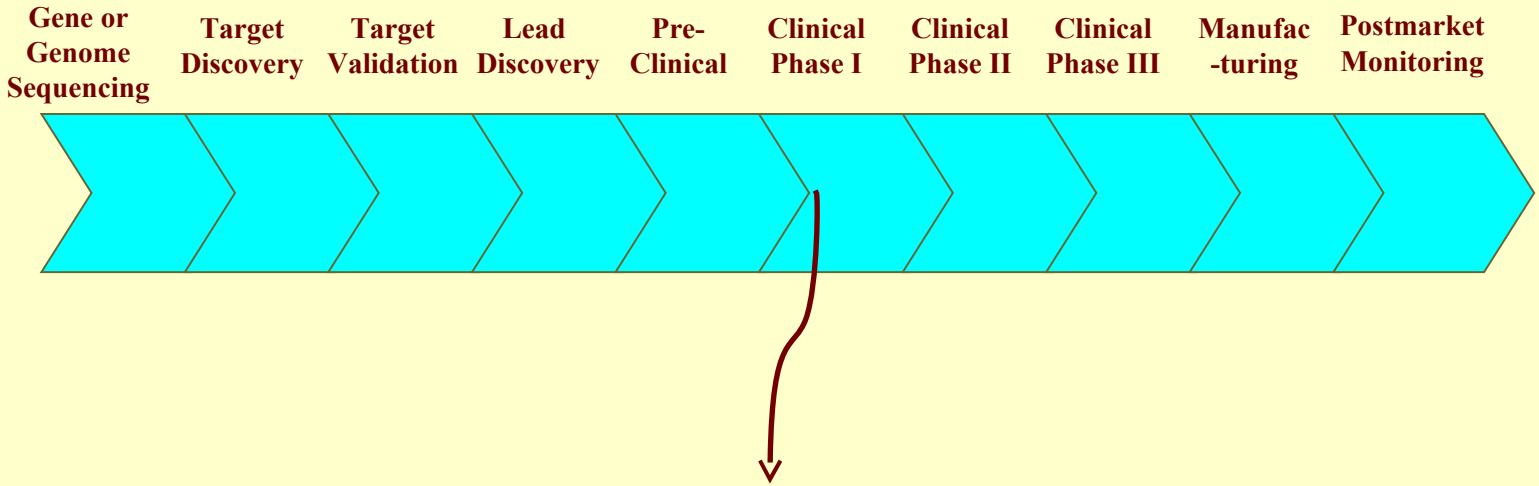
Lipinski and his Pfizer co-workers looked over a data set of drug candidates and noticed that there were some reasonably clear cutoffs for oral absorption and general cell permeability. They suggested that you need:

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

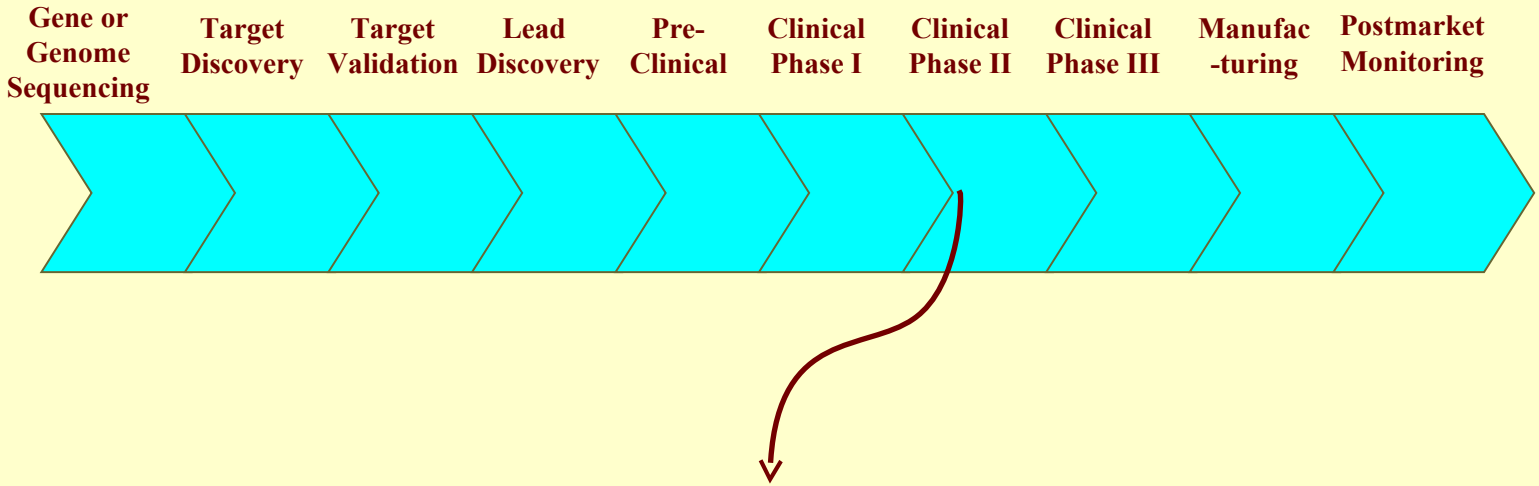



- Animal tests of toxicity and efficacy of therapy
  - Rodents (mice and rats)
  - Larger mammals (pigs)
  - Primates (monkeys and chimpanzees)
  - Mouse Lemurs (*Microcebus*)

Courtesy of Doug Kalish

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

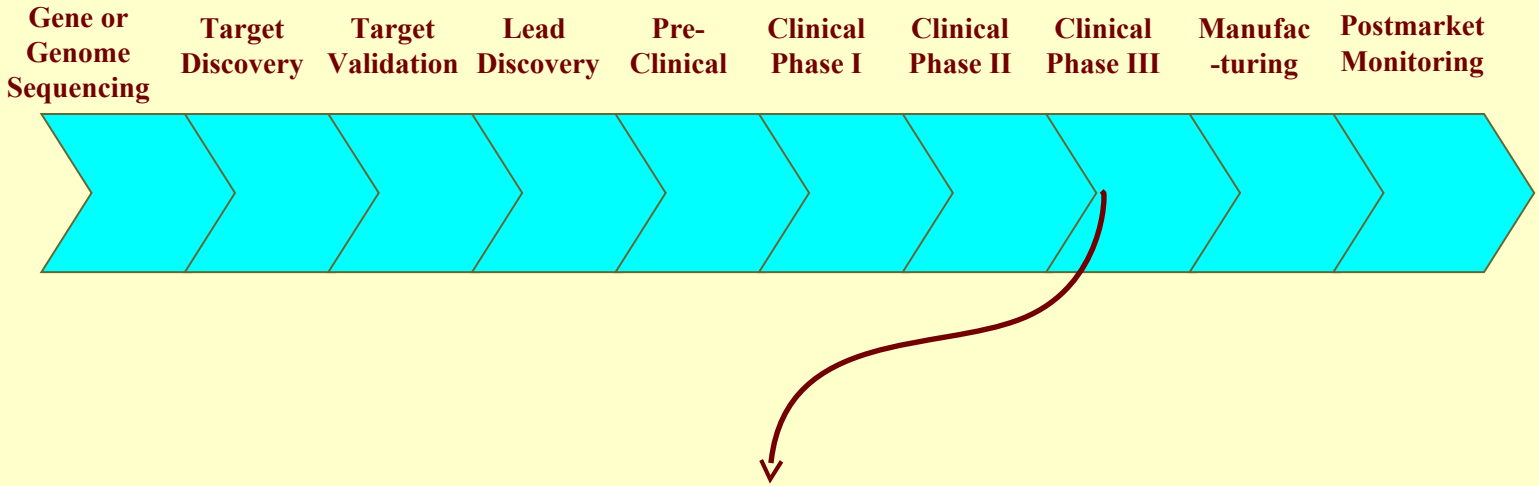
# The Pharma Value Chain




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

Courtesy of Doug Kalish

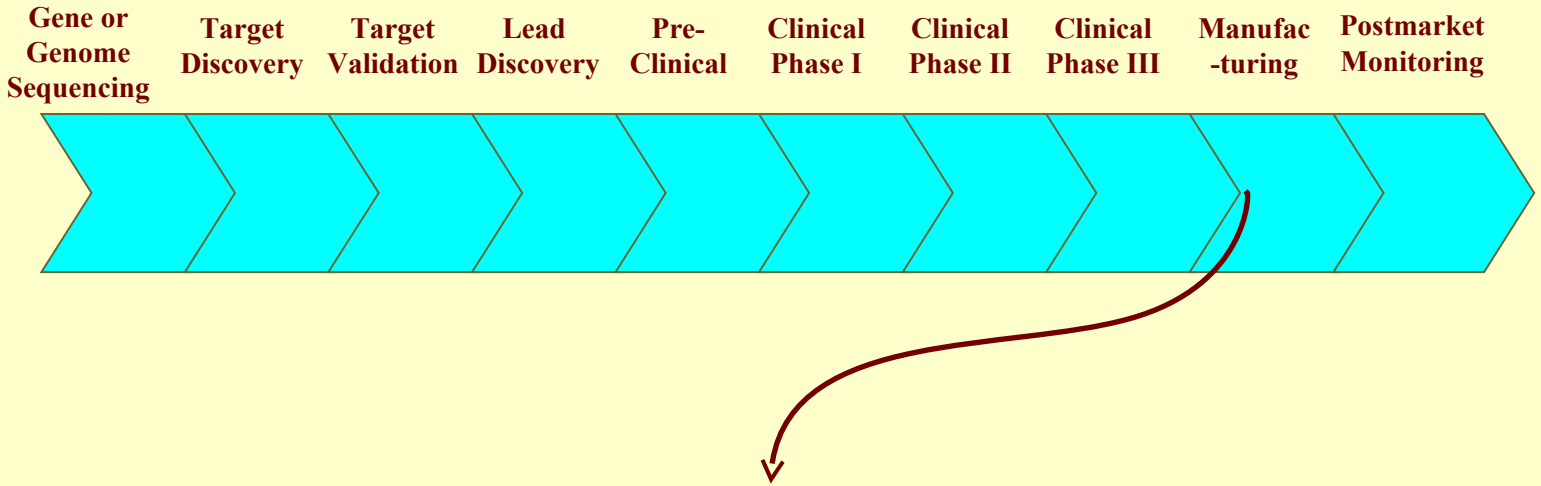
# The Pharma Value Chain




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

Courtesy of Doug Kalish

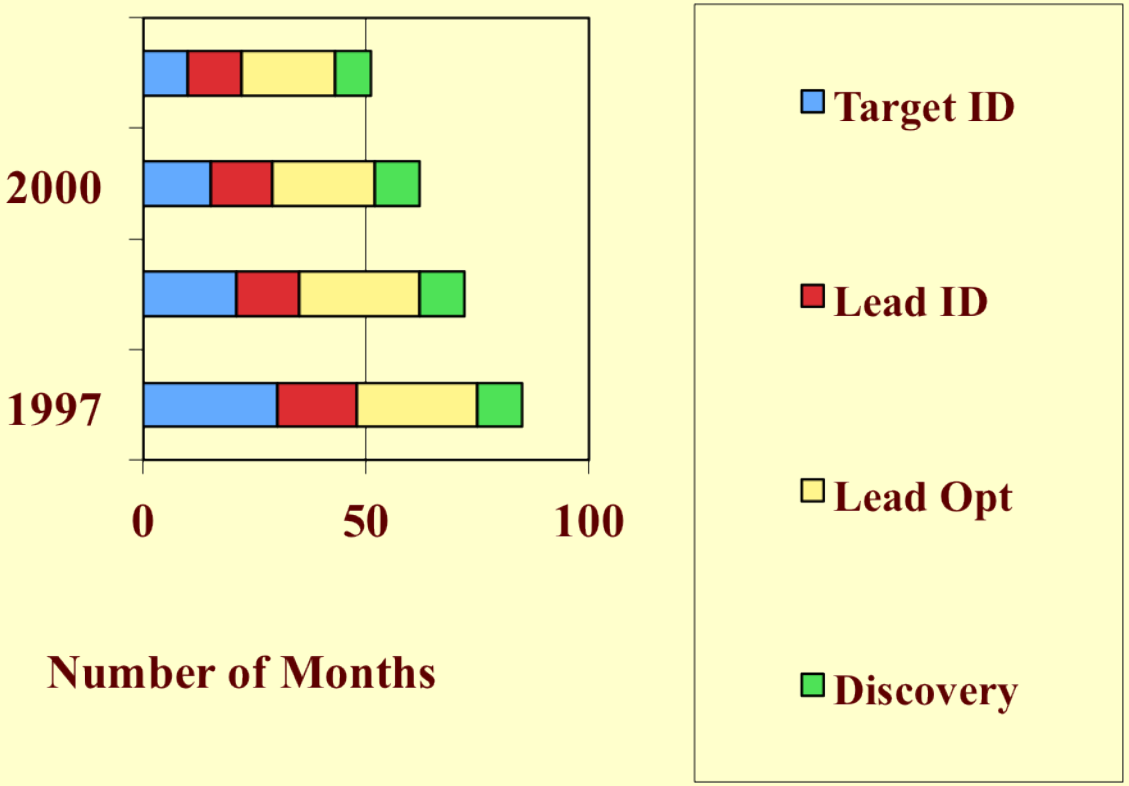
# The Pharma Value Chain




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)

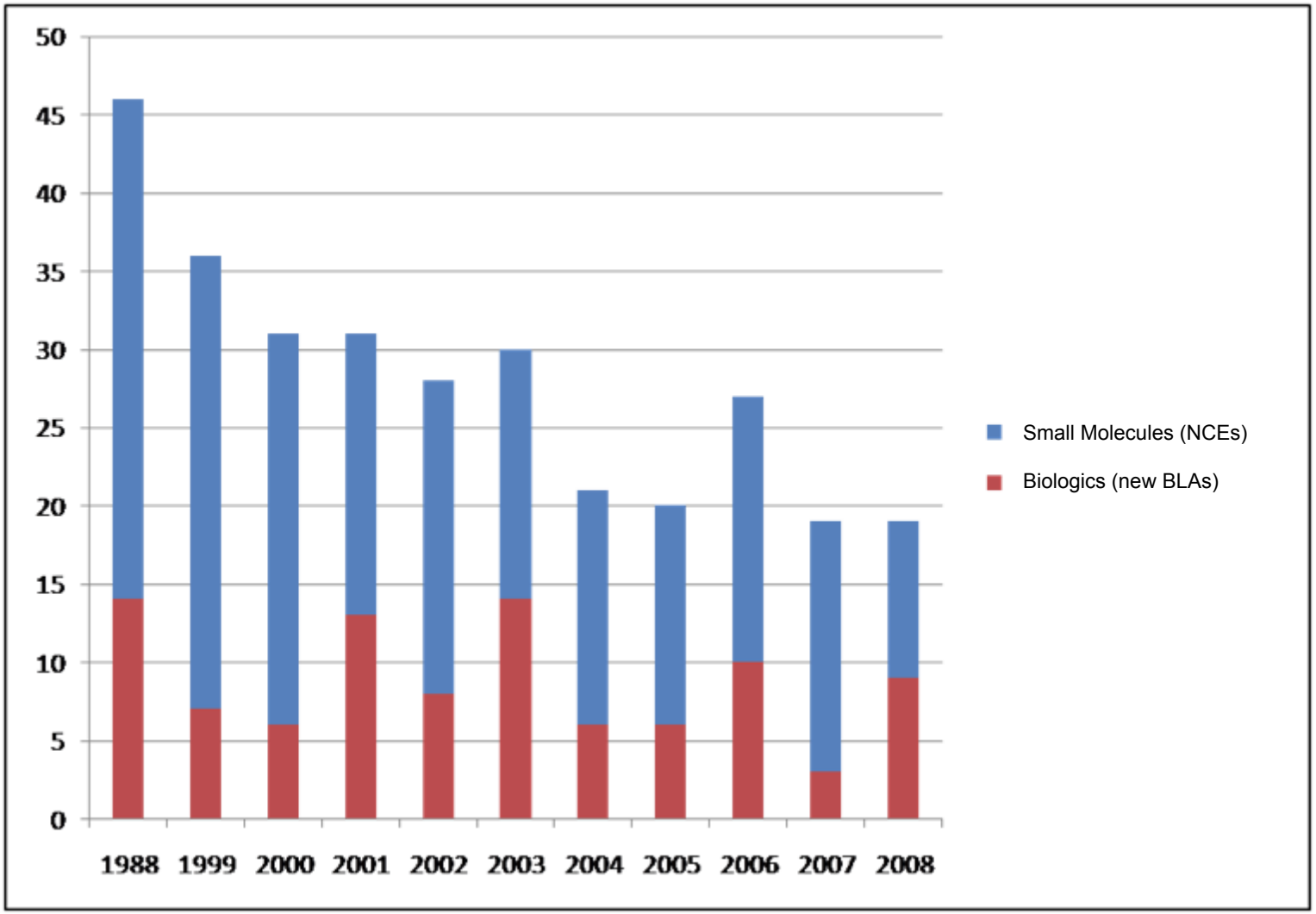
Courtesy of Doug Kalish

# The Impact of Genomics and Bioinformatics on Drug Discovery Times




Courtesy of Doug Kalish

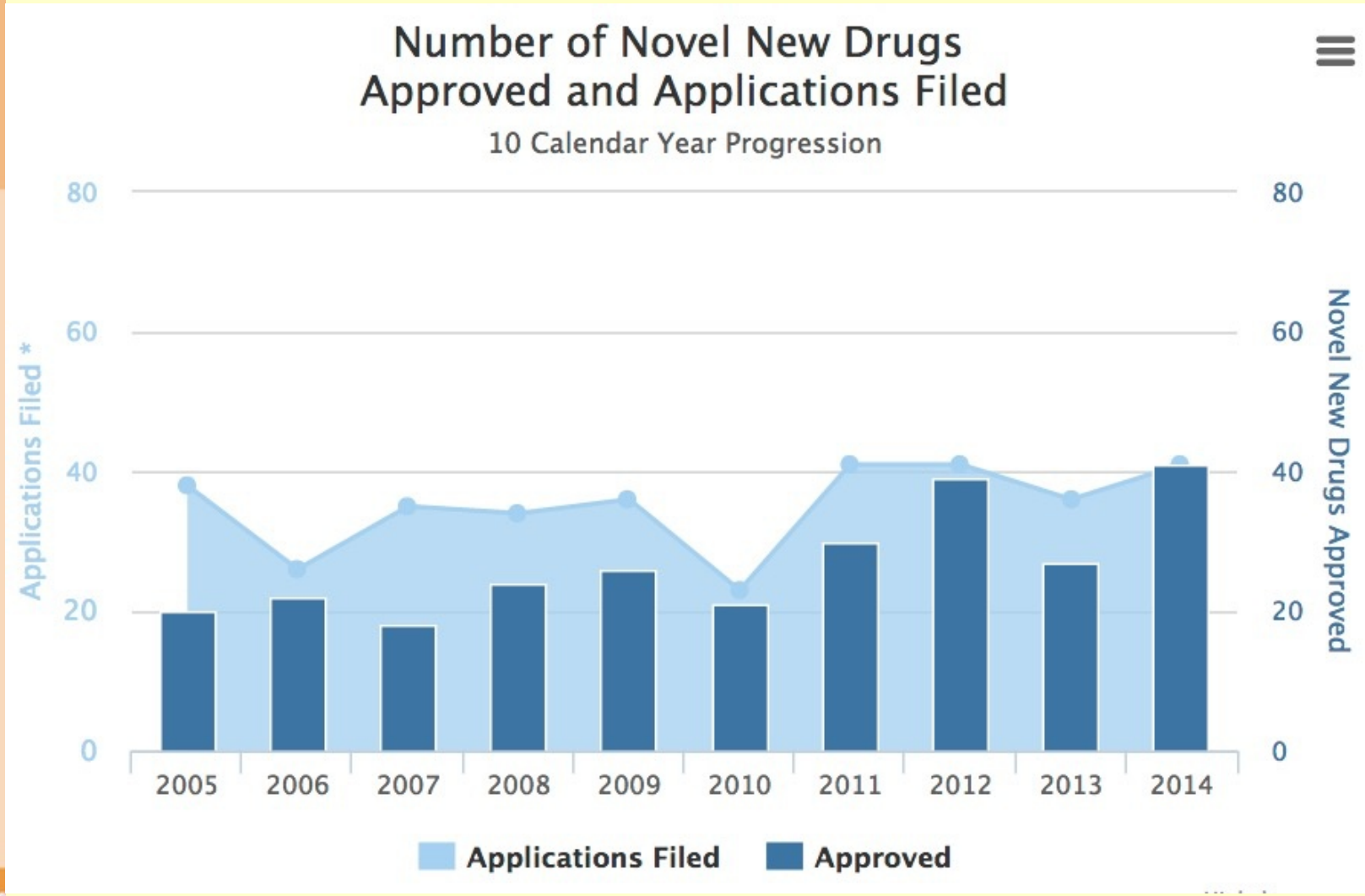
# FDA Approved New Chemical Entities and Biological Derivatives




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

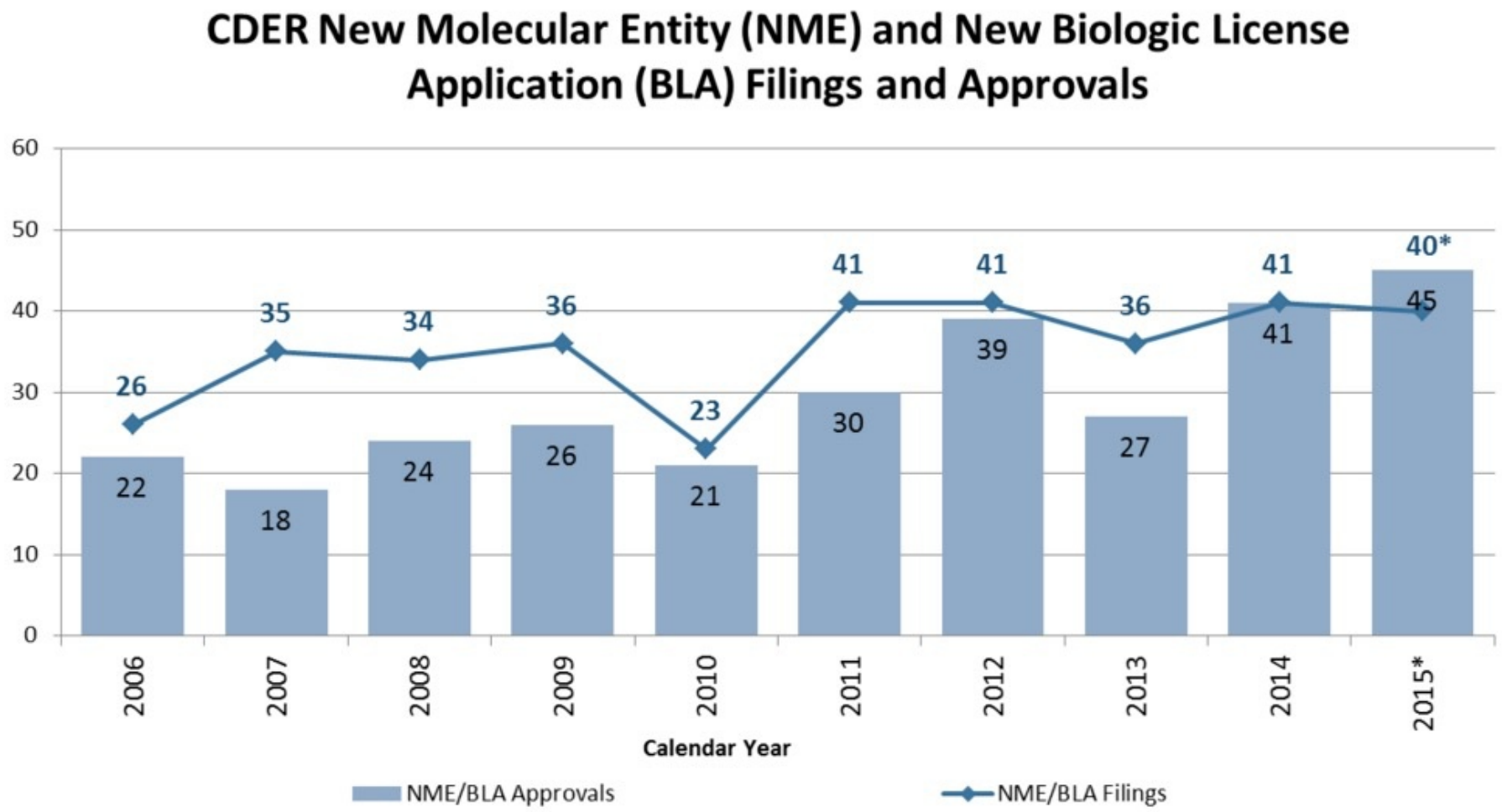
# FDA Approved New Chemical Entities 2014

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



# FDA Approved New Chemical Entities 2015

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



# FDA Approved New Chemical Entities 2015

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

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

| Calendar Year | NME/BLA Filings | NME/BLA Approvals |
|---|---|---|
| 2006 | 26 | 22 |
| 2007 | 35 | 18 |
| 2008 | 34 | 24 |
| 2009 | 36 | 26 |
| 2010 | 23 | 21 |
| 2011 | 41 | 30 |
| 2012 | 41 | 39 |
| 2013 | 36 | 27 |
| 2014 | 41 | 41 |
| 2015* | 40 | 45 |

# U.S. Food and Drug Administration

http://www.fda.gov/

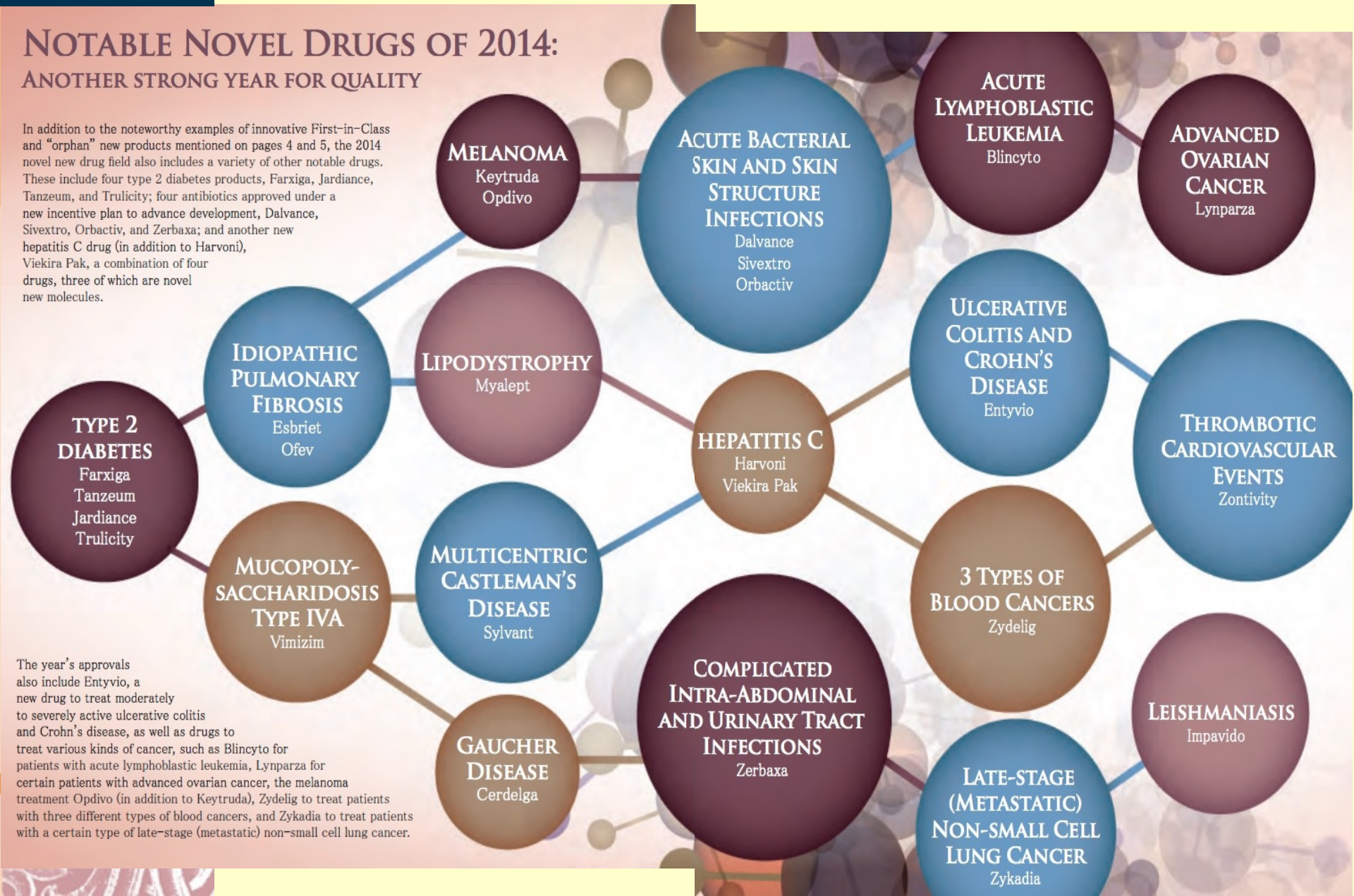
# FDA Approved New Chemical Entities 2014

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 Blincyto 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.

FI 2014

http://  CM430299.pdf

# INNOVATION

## METHODS FOR EXPEDITING INNOVATIVE NOVEL NEW DRUGS TO MARKET

CDER used a number of regulatory methods to expedite the approval of novel new drugs in 2014. These involved the following four expedited development and review pathways: Fast Track, Breakthrough, Priority Review, and Accelerated Approval.

## FAST TRACK

Seventeen of the 2014 novel new drugs (41%) were designated by CDER as Fast Track, meaning drugs with the potential to address unmet medical needs. Fast Track speeds new drug development and review, for instance, by increasing the level of communication FDA allocates to drug developers and by enabling CDER to review portions of a drug application ahead of the submission of the complete application.

1. BELEODAQ
2. CYRAMZA
3. DALVANCE
4. ENTYVIO
5. ESBRIET
6. HARVONI
7. IMPAVIDO
8. MYALEPT
9. NORTHERA
10. OFEV
11. OPDIVO
12. RAPIVAB
13. VIEKIRA PAK
14. VIMIZIM
15. ZERBAXA
16. ZONTIVITY
17. ZYDELIG*.

## BREAKTHROUGH

CDER designated nine of the 2014 novel new drugs (22%) as Breakthrough therapies, meaning drugs with preliminary clinical evidence demonstrating that the drug may result in substantial improvement on at least one clinically significant endpoint (i.e., study result) over other available therapies. A breakthrough therapy designation includes all of the Fast Track program features, as well as more intensive FDA guidance on an efficient drug development program. Breakthrough status is designed to help shorten the development time of a promising new therapy.

1. BLINCYTO
2. ESBRIET
3. HARVONI
4. KEYTRUDA
5. OFEV
6. OPDIVO
7. VIEKIRA PAK
8. ZYDELIG*
9. ZYKADIA

## PRIORITY REVIEW

Twenty-five of the 2014 novel new drugs (61%) were designated Priority Review, in which CDER determined the drug to potentially provide a significant advance in medical care and set a target to review the drug within six months instead of the standard 10 months.

1. BELEODAQ
2. BLINCYTO
3. CERDELGA
4. CYRAMZA
5. DALVANCE
6. ENTYVIO
7. ESBRIET
8. HARVONI
9. HETLIOZ
10. IMPAVIDO
11. KEYTRUDA
12. LYNPARZA
13. MYALEPT
14. NORTHERA
15. OFEV
16. OPDIVO
17. ORBACTIV
18. SIVEXTRO
19. SYLVANT
20. VIEKIRA PAK
21. VIMIZIM
22. XTORO
23. ZERBAXA
24. ZYDELIG*
25. ZYKADIA

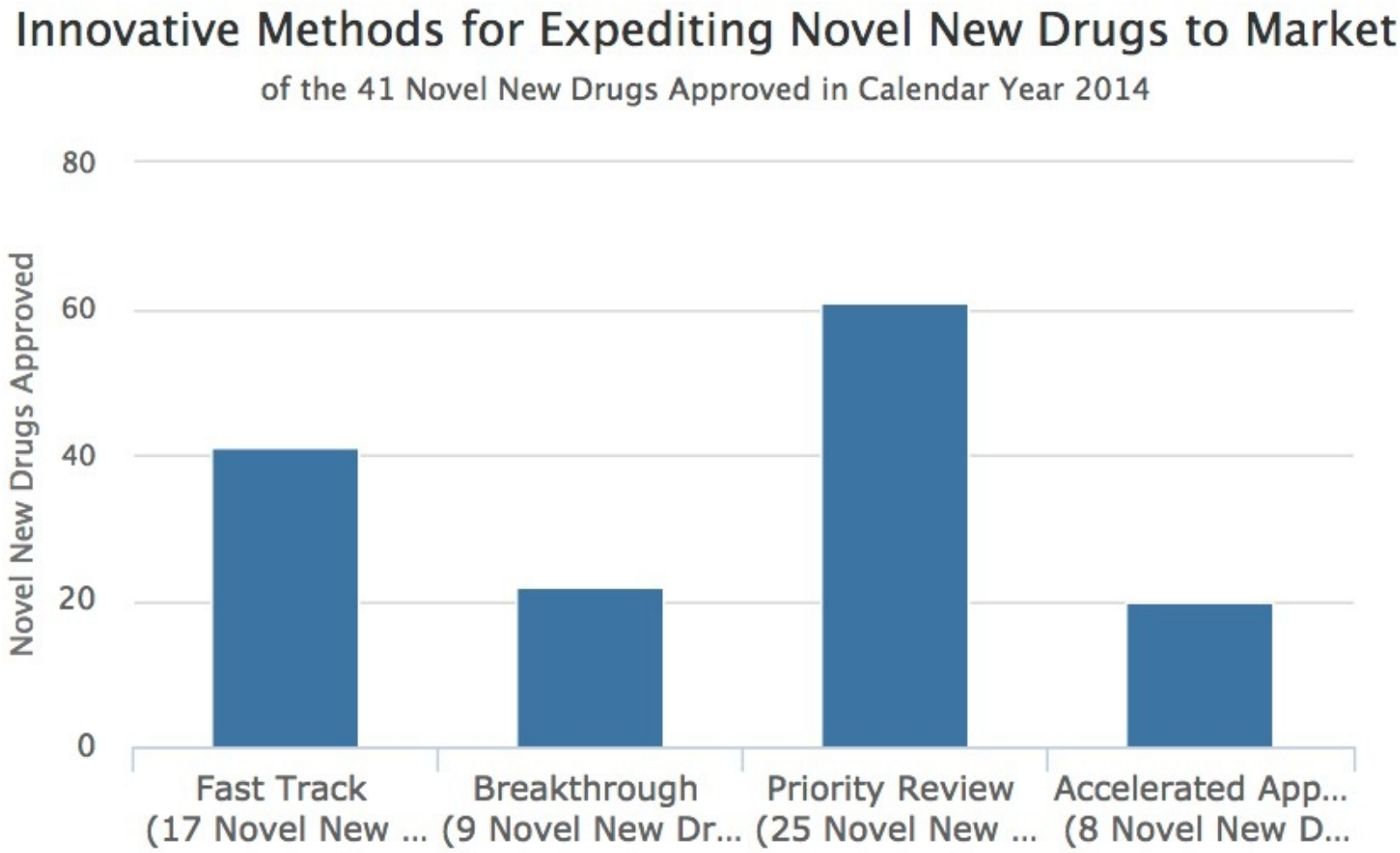
## ACCELERATED APPROVAL

CDER approved eight of the 2014 novel new drugs (20%) under FDA's Accelerated Approval program, which allows early approval of a drug for a serious or life-threatening illness that offers a benefit over current treatments. This approval is based on a "surrogate endpoint" (e.g., a laboratory measure) or other clinical measure that we consider reasonably likely to predict a clinical benefit of the drug. Once Accelerated Approval is granted, the drug must undergo additional testing to confirm that benefit; this speeds the availability of the drug to patients who need it.

1. BELEODAQ
2. BLINCYTO
3. KEYTRUDA
4. LYNPARZA
5. NORTHERA
6. OPDIVO
7. ZYDELIG*
8. ZYKADIA

# FDA Approved New Chemical Entities 2014

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



# 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