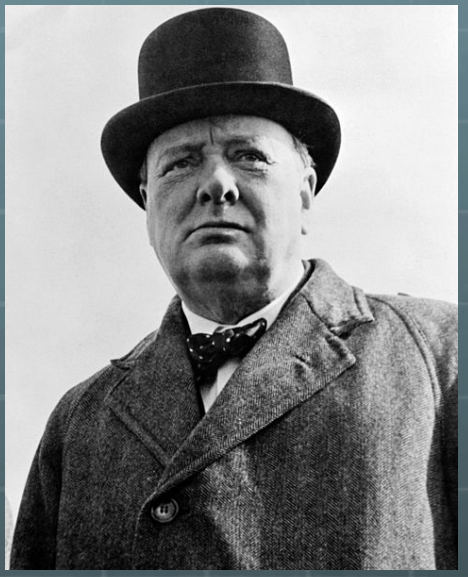
1. The Mission & Its Challenges

Painting by Joseph Karl Stieler. In the public domain.

I don't like standing near the edge of a platform when an express train is passing through. I like to stand right back and if possible get a pillar between me and the train. I don't like to stand by the side of a ship and look down into the water. A second's action would end everything. A few drops of desperation."

-- WINSTON CHURCHILL (1874-1965)

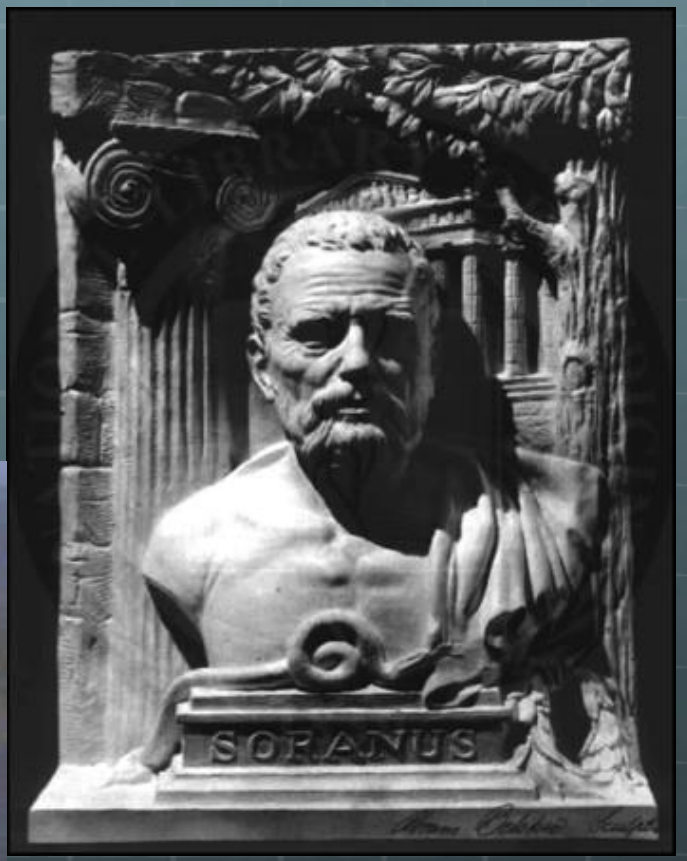


Photograph by the United Nations Information Office, New York. In the public domain.

Painting by Vincent van Gogh. In the public domain.

Courtesy of Mathias Gawlista. License: CC-BY.

In the 2nd century AD, Soranus of Ephesus treated melancholia and mania patients with alkaline waters which we now know contain ***very high levels of Li***.



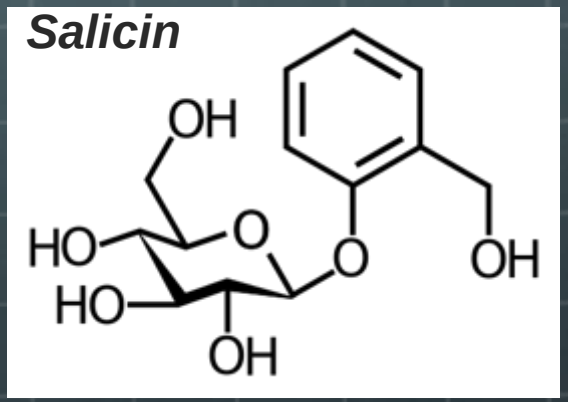
Bust of Soranus of Ephesus by the US National Library of Medicine, History of Medicine Division, and is in the public domain.

- Hippocrates, Galen, Pliny the Elder and others knew that willow bark could ease aches and pains and reduce fevers. It has long been used in Europe and China to treat these conditions and is also mentioned in texts from ancient Egypt, Sumer, and Assyria.

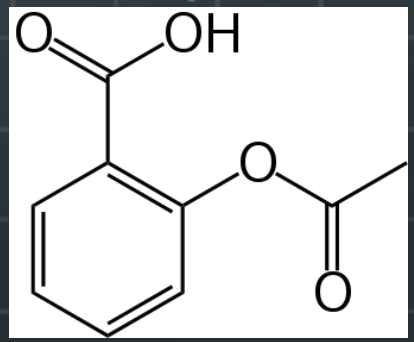
- The active extract of the bark, called ***salicin*** was isolated to its crystalline form in 1828. Soon thereafter, ***salicilic acid*** was separated in its pure state, and ***aspirin*** was discovered 40 years later.

Salix Alba (white willow)

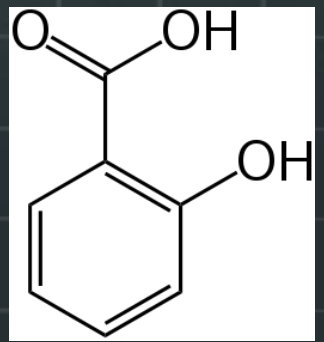
Salicin



Aspirin



Salicilic Acid



What is a Drug?

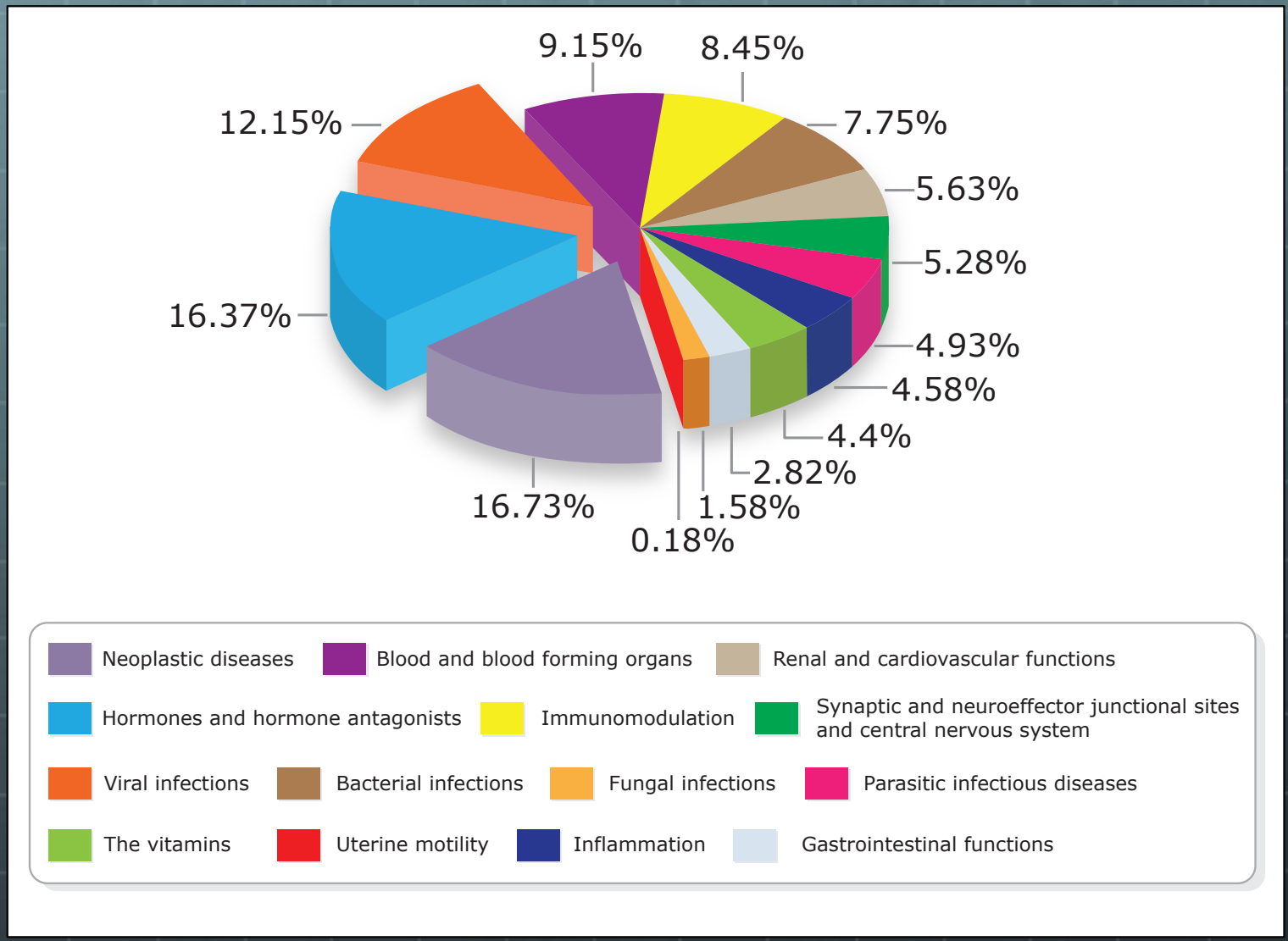
- A substance used as a medication or in the preparation of medication – it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.

- ***For our purposes***: a drug must be approved by a regulatory body and be recognized in an official pharmacopoeia or formulary.

Diverse Ways to Contribute to Discovering New Medicines

- Discovering therapeutics: many scientific disciplines
- Inventing new technologies that are used in R&D
- Clinical – POC; safety; defining medical needs; Dx; patient stratification
- Basic biology: understanding pathways, targets, etc.
- Scale up / manufacturing
- Drug delivery – formulations, nanoparticles, nano-factories, …
- Funding & Policy: NIH, FDA, CDC, insurance companies, congress, …
- Systems / process engineering, decision theory, etc.
- The human element - org structure, leadership, risk-taking, motivation
- Science journalism

Diseases Treated by Drugs



What is Medicine ?
What is "Therapy" ?

- ***Medicine*** is the applied science or practice of the diagnosis, treatment, and prevention of disease.
- ***Therapy*** refers to the whole collection of interlinked components used in medicine to treat a particular situation – drugs, devices, diagnostics, surgery, support services, and everything else.

The Fundamental Biochemical Hypothesis

- If you create a molecule that can intervene in a disease-relevant biochemical process in the body – for example, by blocking or activating the function of a receptor or enzyme – this may translate into clinical benefit.
- If it works – great! You've confirmed the biochemical hypothesis and you are on the way to a drug.
- If it fails –
  - Maybe your biochemical hypothesis was wrong
  - Maybe the body compensated for your drug somehow
  - Maybe you didn't deliver enough of the drug to the right place for long enough

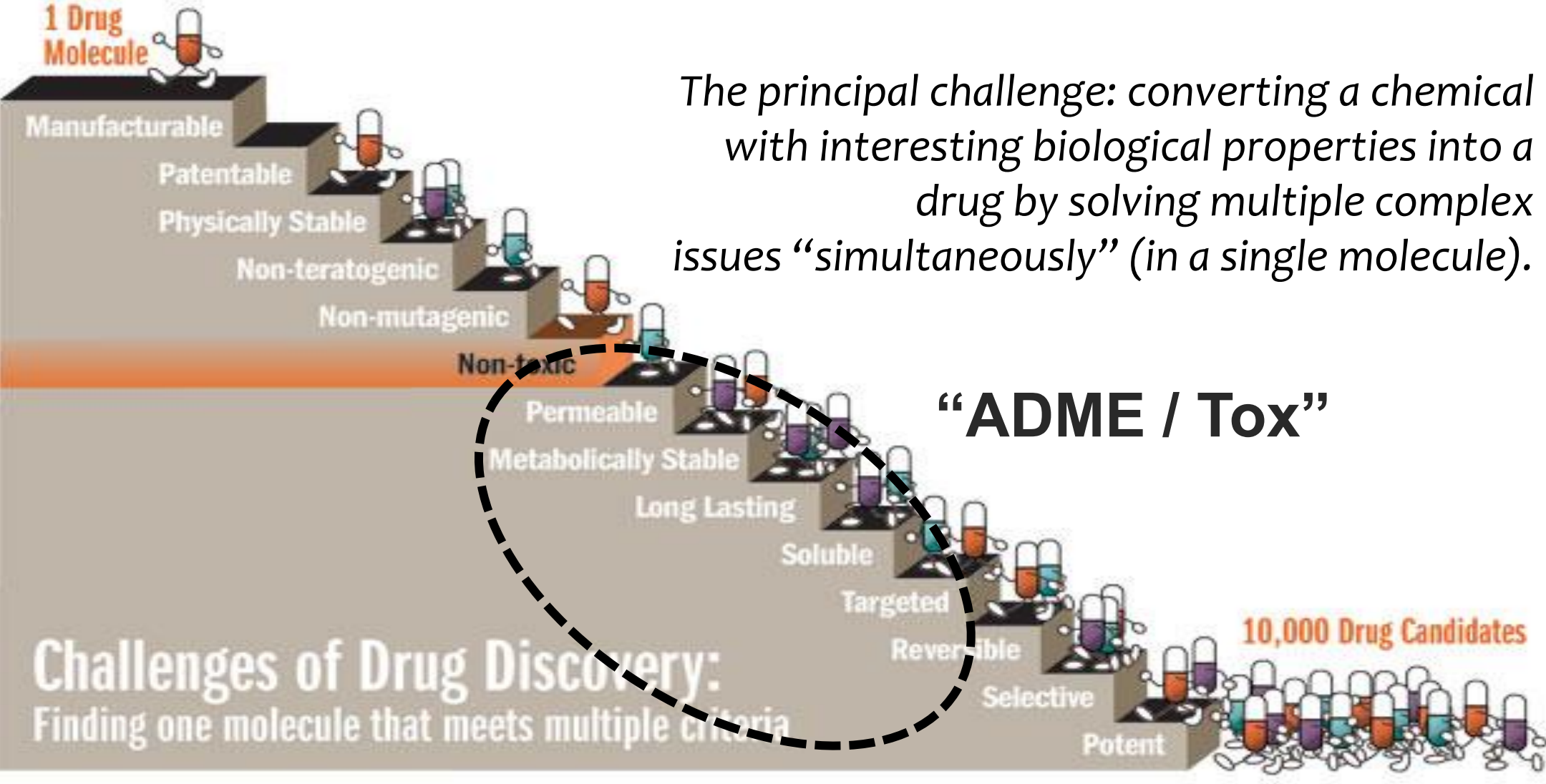
The Current Environment

- Many acute diseases are now well treated
- Chronic diseases, generally, are not:
  - Management vs. cure
  - Side effects
  - Lack of knowledge to identify patients early, track the progress of their disease, and to “customize” their treatment

What Problem Are We Solving?

- For diseases with no treatment, or poor treatments, we seek true breakthroughs.
- For diseases that are already well served by existing medicines (e.g. hypertension) we seek more incremental advantages in safety, cost, convenience, or effectiveness.
  - In the real world these improvements can be quite useful but are often belittled as “me-too”

The Multivariate Optimization Problem



The principal challenge: converting a chemical with interesting biological properties into a drug by solving multiple complex issues "simultaneously" (in a single molecule).

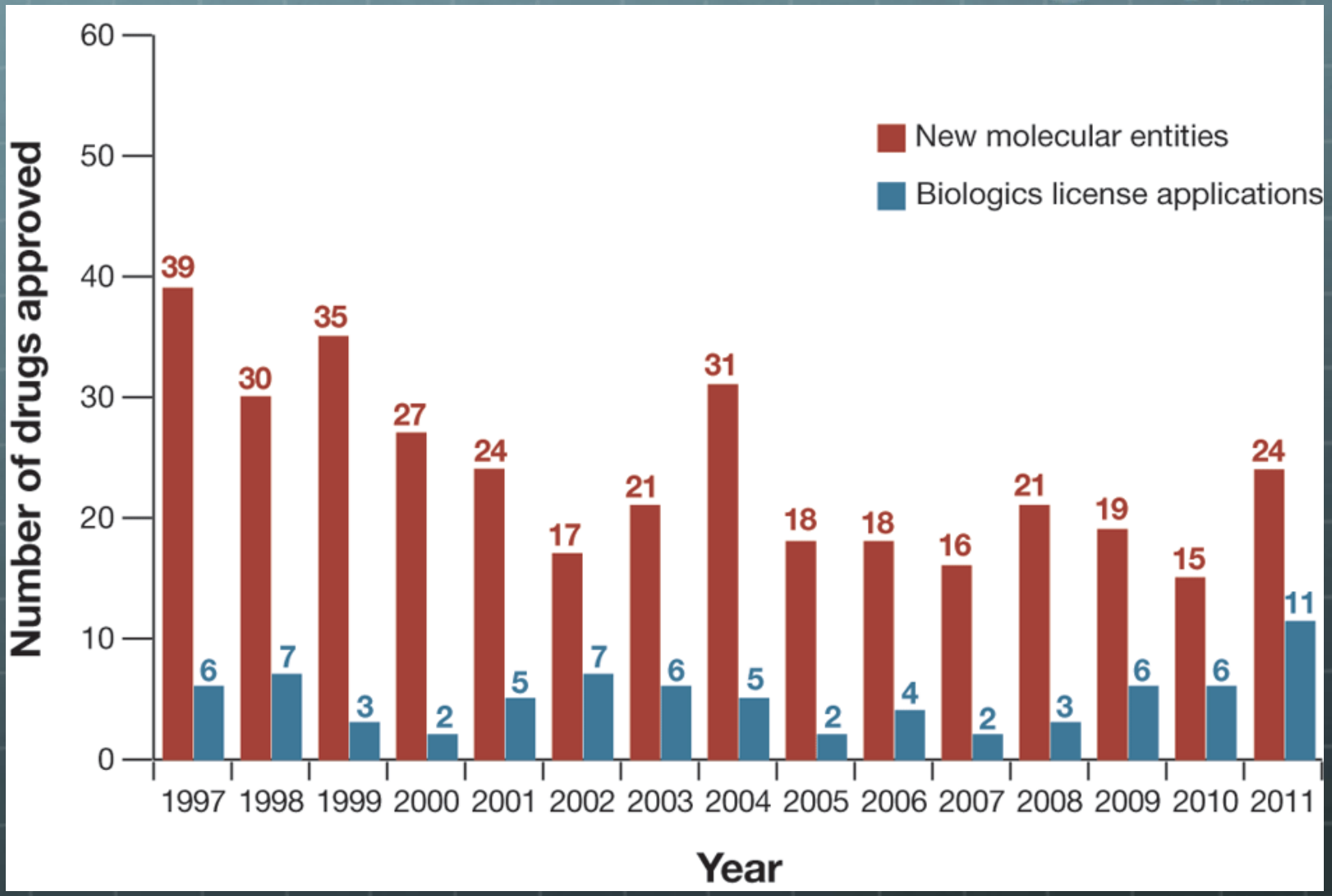
"ADME / Tox"

Figure modified from: Drug Discovery and Development; July 2004

ADME: You'll Hear This a Lot …

- **Absorption** - the process of a substance entering the blood circulation.
- **Distribution** - the dispersion of substances throughout the fluids and tissues of the body.
- **Metabolism** (or Biotransformation) - the irreversible chemical transformation of parent compounds into daughter *metabolites*.
- **Excretion** - the removal of the substances from the body. In rare cases, some drugs irreversibly accumulate in body tissue.

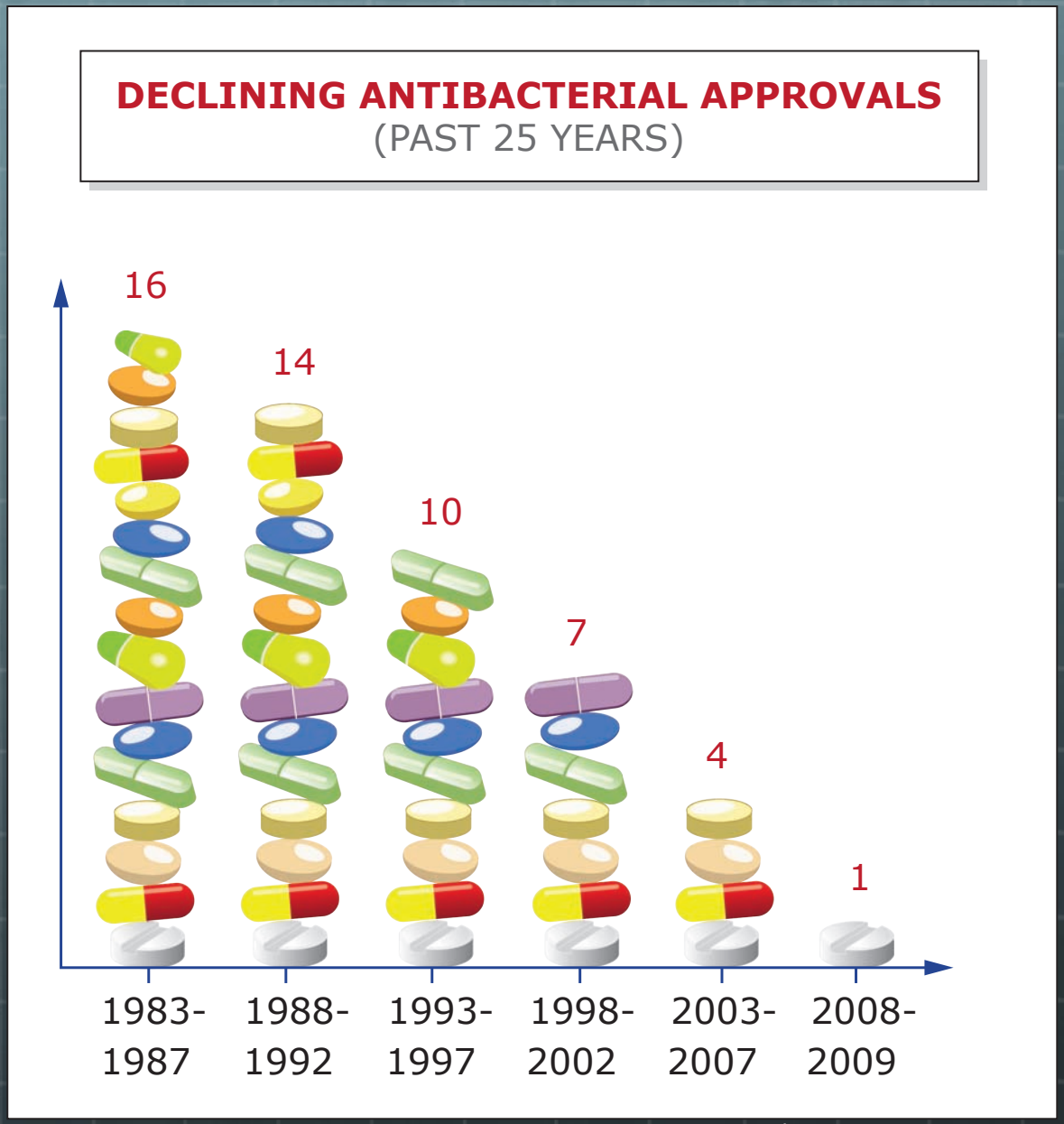
Downward Trends in New Drug Approvals



Source: Allison, Malorye. "Reinventing Clinical Trials." *Nature Biotechnology* 30, no. 1 (2012) : 41-9.

NME = New Medical Entities. BLA = Biologics License Applications.
*Nature Biotechnology (2012), **30**, pp 41-49*

Sharper Declines in Some Disease Areas

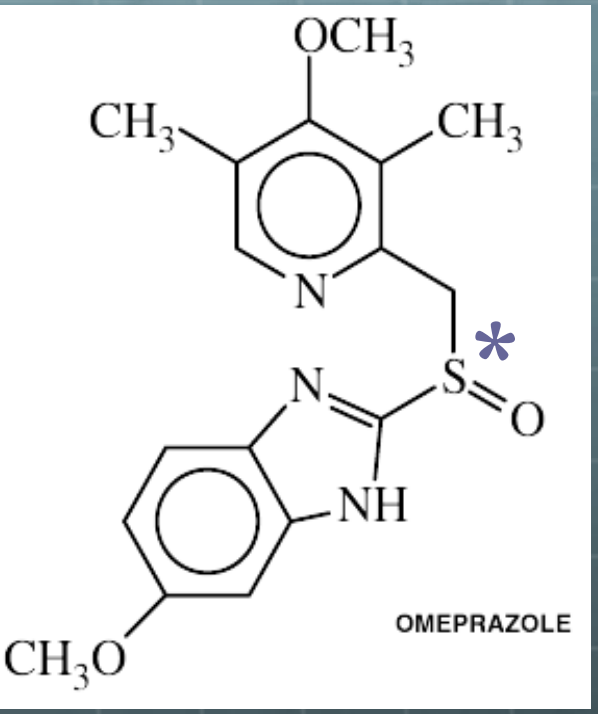


The Truly Staggering Cost of Inventing New Drugs

Company	# Drugs Approved	R&D Spending Per Drug ($Mil)	Total R&D Spending 1997-2011 ($Mil)
AstraZeneca	5	11,791	58,955
GlaxoSmithKline	10	8,171	81,708
Sanofi	8	7,909	63,274
Roche Holding AG	11	7,804	85,841
Pfizer Inc.	14	7,727	108,178
Johnson & Johnson	15	5,886	88,285
Eli Lilly & Co.	11	4,577	50,347
Abbott Laboratories	8	4,496	35,970
Merck & Co Inc	16	4,210	67,360
Bristol-Myers Squibb	11	4,152	45,675
Novartis AG	21	3,983	83,646
Amgen Inc.	9	3,692	33,229

Sources: (1) InnoThink Center For Research In Biomedical Innovation; (2) Thomson Reuters Fundamentals via FactSet Research Systems. Taken from Matthew Herper, Forbes Magazine, "The Medicine Show," 10 Feb 2012

Innovation?



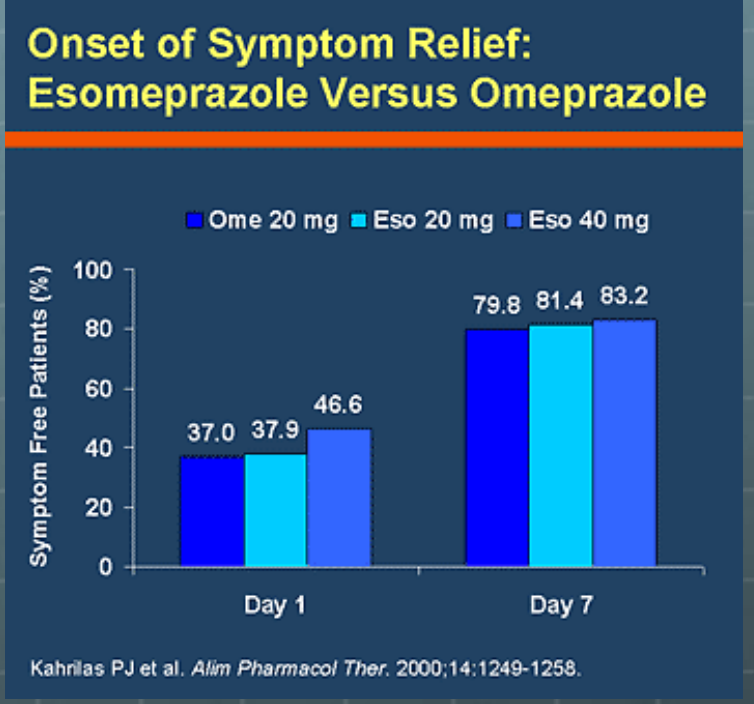
Omeprazole (Prilosec)
Racemate
Approved in 1989

Proton pump blocker - specific inhibition of H+/K+-ATPase in gastric parietal cells

Generally well tolerated drug

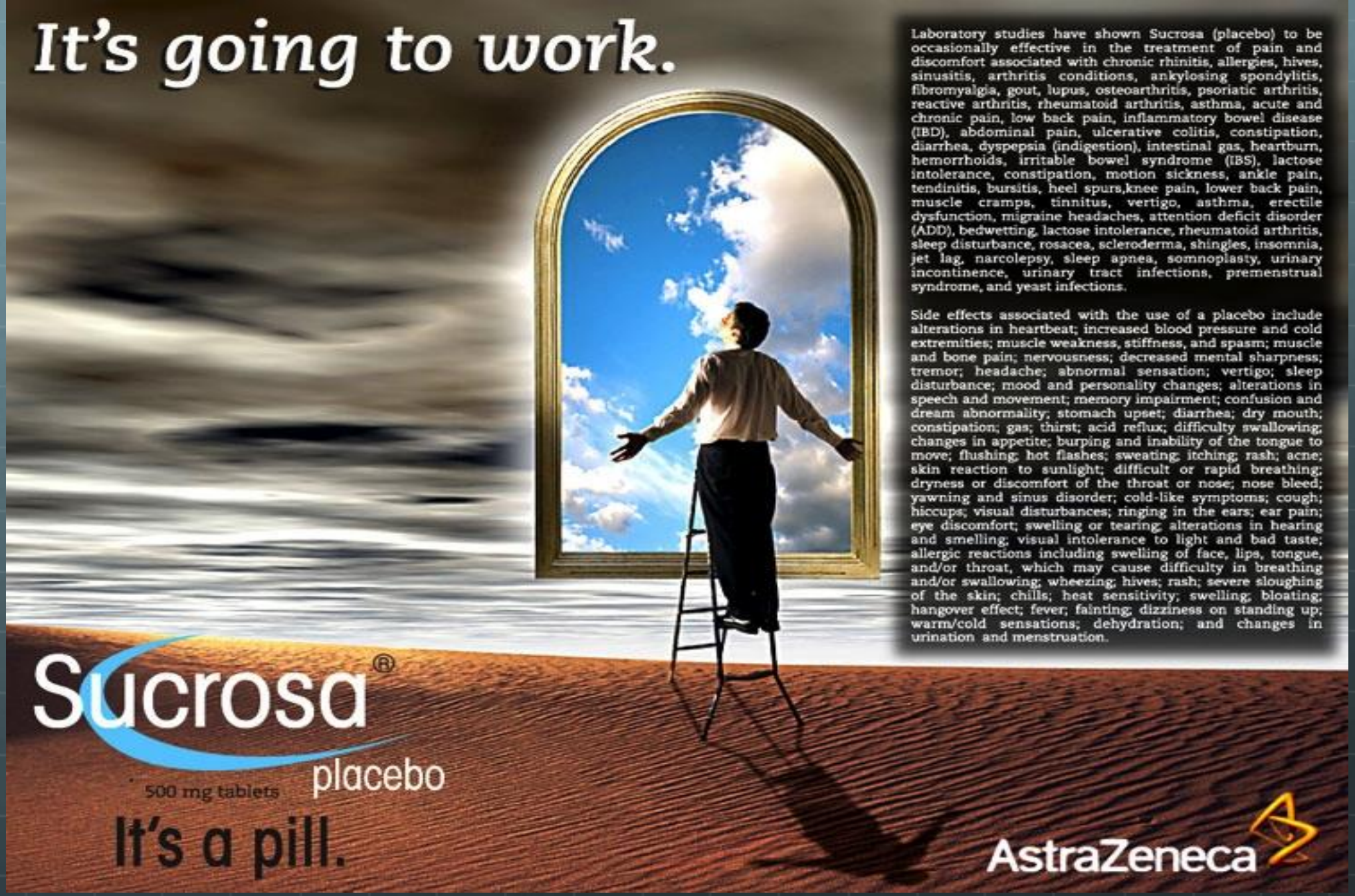
Both isomers get converted to active form of the drug

Going off patent in 2001



Esomeprazole (Nexium)
S-isomer of omeprazole
Approved in 2000

2001: $500M ad campaign
2003 sales: $3B



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FDA NEWS RELEASE

For Immediate Release: May 23, 2011
Media Inquiries: Erica Jefferson, 301-796-4988, erica.jefferson@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA approves Incivek for hepatitis C

The U.S. Food and Drug Administration today approved Incivek (telaprevir) to treat certain adults with chronic hepatitis C infection. Incivek is used for patients who have either not received interferon-based drug therapy for their infection or who have not responded adequately to prior therapies. Incivek is approved for use with interferon therapy made up of peginterferon alfa and ribavirin.

The current standard of care for patients with chronic hepatitis C infection is peginterferon alfa and ribavirin taken for 48 weeks. Less than 50 percent of patients respond to this therapy.

The safety and effectiveness of Incivek was evaluated in three phase 3 clinical trials with about 2,250 adult patients who were previously untreated, or who had received prior therapy. In all studies patients also received the drug with standard of care. In previously untreated patients, 79 percent of those receiving Incivek experienced a sustained virologic response (i.e. the infection was no longer detected in the blood 24 weeks after stopping treatment) compared to standard treatment alone.

The sustained virologic response for patients treated with Incivek across all studies, and across all patient groups, was between 20 and 45 percent higher than current standard of care.

The studies indicate that treatment with Incivek can be shortened from 48 weeks to 24 weeks in most patients. Sixty percent of previously untreated patients achieved an early response and received only 24 weeks of treatment (compared to the standard of care of 48 weeks). The sustained virologic response for these patients was 90 percent.

When a person achieves a sustained virologic response after completing treatment, this suggests that the hepatitis C infection has been cured.

Sustained virologic response can result in decreased cirrhosis and complications of liver disease, decreased rates of liver cancer (hepatocellular carcinoma), and decreased mortality.

The New York Times

Business Day

F.D.A. Approves New Cystic Fibrosis Drug

By ANDREW POLLACK
Published: January 31, 2012

The first drug that treats an underlying cause of cystic fibrosis, rather than just the symptoms, was approved by the Food and Drug Administration on Tuesday, more than 22 years after the gene responsible for the disease was first identified.

Enlarge This Image

The drug, called Kalydeco and developed by Vertex Pharmaceuticals, counters the effect of one specific mutation in the gene that accounts for 4 percent — or about 1,200 — cystic fibrosis cases in the United States.

"This is a breakthrough therapy for the cystic fibrosis community because current therapies only treat the symptoms of this genetic disease," Dr. Janet Woodcock, the director of the Center for Drug Evaluation and Research at the F.D.A., said in a statement issued by the agency.

mortality.

The New York Times

Business Day

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SEARCH

Popular Searches

F.D.A. Appr

By ANDREW POLLACK
Published: January 31, 2012

The first drug that t
than just the sympt
Administration on
responsible for the

Enlarge

FRIDAY, JULY 20, 2012

The Lung Function Scale...

80%!!!!!!!!

I can't believe it! I've gone from 67% to 80% in 5 weeks and I've also gained 3KG!!!!! AMAZING!

As I mentioned in my previous post I have had a cold and I went to the hospital to do blood tests, get antibiotics and do a sputum culture earlier in the week. I called the CF coordinator at the hospital yesterday to get the results from the tests and mentioned that I have still had a cold. I decided to go into the hospital yesterday to see my doctor to see if I could prevent my cold from getting worse. I was so nervous to do the lung function- I think I've secretly been avoiding doing it because I was so worried that it wouldn't be what I wanted it to be. Mum bought me a little home lung function monitor a couple of days ago and I refused to try it out of fear!! I bit the bullet and decided I needed to face reality whether I liked it or not. I did my first test and it was 78%! I was amazed but suddenly 80% was within reach and I was determined to make it. On my second try and I made it and I'd compare the feeing to winning Tattslotto!! I had not been at 80% since August 2009. After, my doctor and I looked at a graph that showed all my lung functions from 09 to present- I wish I had of got a copy to put on my blog. If I can get one I'll post it on here because it's a very good visual representation of my decline in health over the past 2-3 years and my rapid increase in the past 5 weeks on KALYDECO!!! :-D

2. Where Drugs Come From: An Introduction

Sources of Drugs

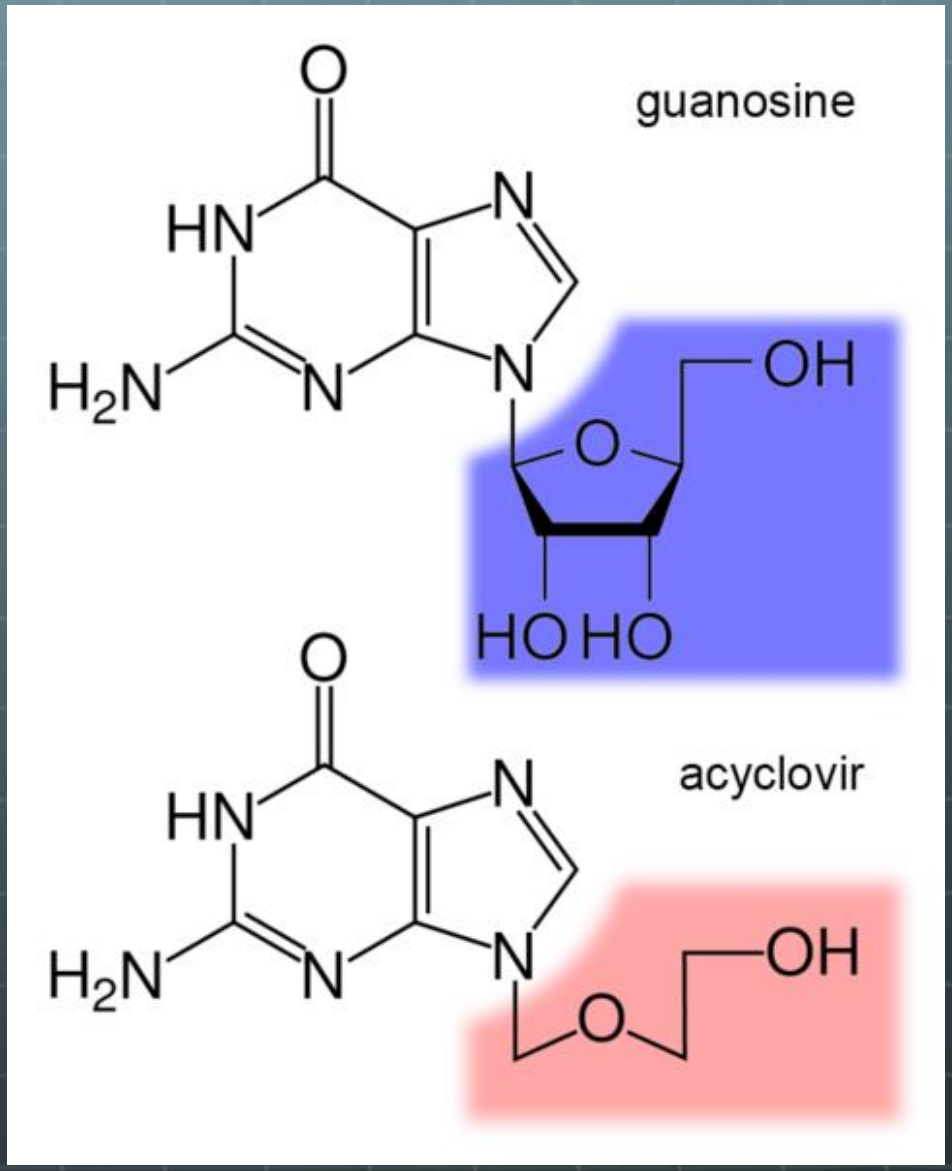
- "Nature"
  - "Natural Products" – plants, minerals
  - Animals – e.g. insulin, liver extracts
  - Microbiological sources – e.g. penicillin
- Synthetic / medicinal chemistry
  - Often copied in some fashion from nature
- Recombinant DNA -- biologicals (proteins, Ab)

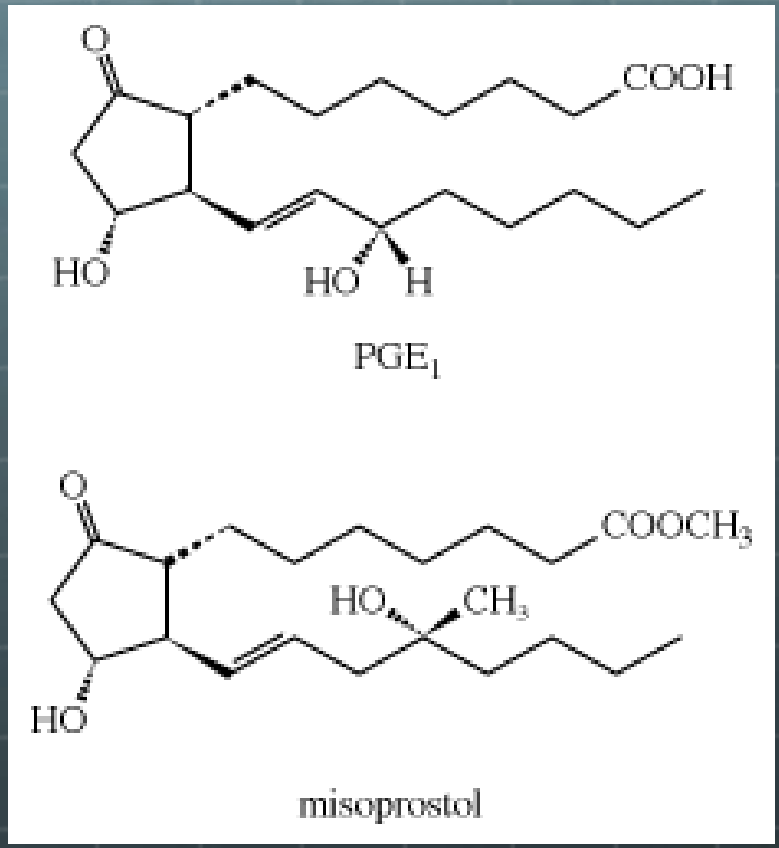
Where Hits and Leads Come From

- Random Screening
  - In-house collections
  - Purchased compounds
  - Known drugs/drug candidates
  - Combinatorial libraries (focused / diverse)
  - Fragment libraries
  - Natural products
- Directed Methods
  - Endogenous ligands / substrates
  - Known compounds
  - Active metabolites
  - Target families (chemogenomics)
  - Virtual screening / “structure-based design”
  - De novo design

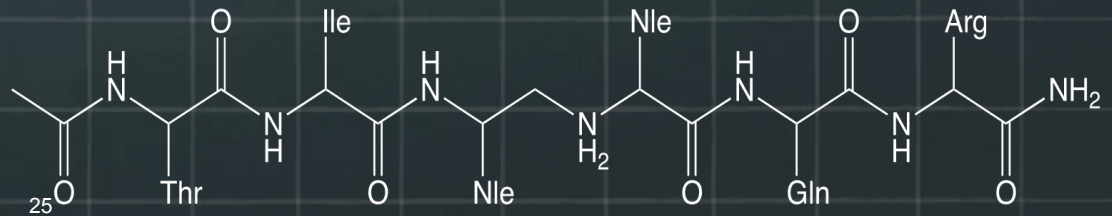
Rydzewski, p240

Many Drugs Copy From Nature





MVT-101 (NCI) – 1st gen HIV-PR inhibitor



Broad Mechanisms

- “Antagonists” / “inhibitors” – turn things down
- “Agonists” / “potentiators” – turn things up
- Orthosteric vs allosteric
- Competitive, uncompetitive, noncompetitive
- Fast on/off vs. slow on/off
- Covalent vs. noncovalent
  - If covalent - reversible vs irreversible

High-Throughput Screening

- Testing large libraries of compounds in multi-well plates in an automated, industrialized (robotic) way
- 96 wells per plate → 384 → 1,536 and even higher
- Biochemical (binding, function) or cellular
- Tiny quantities of material (by historical standards)
- Became popular in the 1990s
- Required completely different mindset …

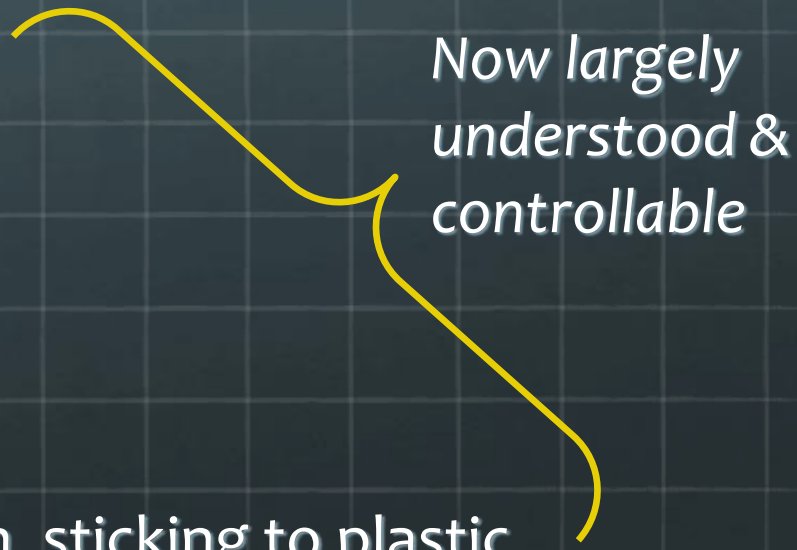
High-Throughput Screening Techniques

- Absorbance
- Fluorescence Intensity
- Fluorometric Imaging Plate Reader (FLIPR)
- Fluorescence Polarization (FP)
- Fluorescence Resonance Energy Transfer (FRET)
- Radioligand Displacement
- Scintillation Proximity Assay (SPA)
- Amplified Luminescent Proximity Assay (AlphaScreen)
- Surface Plasmon Resonance (SPR)

Rydzewski, p228

High-Throughput Screening Challenges

- Trade-offs: complexity, reagent availability, material requirements, equipment & reagent cost, data quality, …
- What to screen!?
  - "Diversity" … "drug-space" … "drug-likeness"
- Artifacts:
  - Compound fluorescence / quenching
  - Light scattering b/c of insolubility
  - Cytotoxicity
  - Reactive or aggregating compounds
  - Edge effects
  - Mechanical problems e.g. evaporation, sticking to plastic



Combinatorial Chemistry

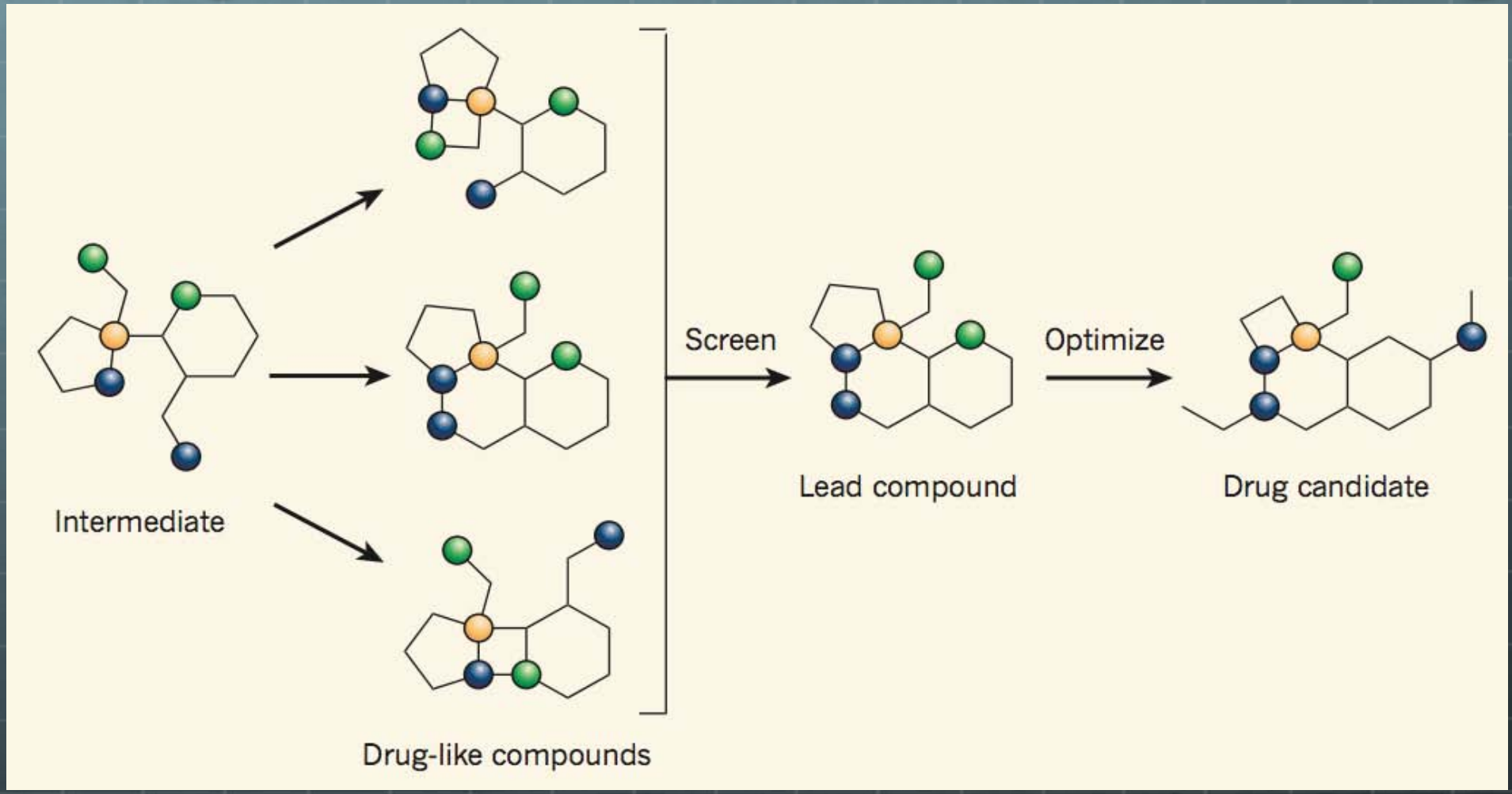
- "The solution to pharma's productivity problems" (!?)
- Based on a simplistic belief in sheer numbers
- But, there were a few problems:
  - $10^6 / 10^{60} = 0$
  - No clear definition of "diversity"
  - No clear idea of what "drug space" is, even for the targets we already know about
  - The chemistry was less robust than we all hoped; this led to boring cmpds with poor physical properties
  - Hard / expensive to intelligently screen 10^6 compounds
  - "Natural product-like" libraries that really weren't

Combi-Chem Then & Now

Circa 1995	Circa 2010
Large Libraries (~ 10^5)	Smaller libraries, typically < 10^3
Many "Rule of 5" violations	Mostly "rule of 5" compliant
Many solid phase syntheses	Many solution phase syntheses
Often multiple cmpds per well	Usually one cmpd per well
Minimal purification	Extensive purification typical
Primarily used for diversity screening	Primarily used for property optimization

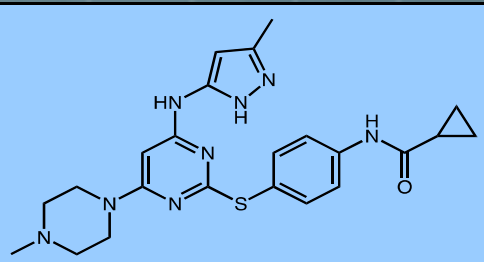
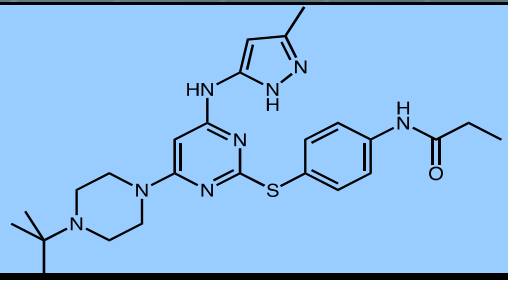
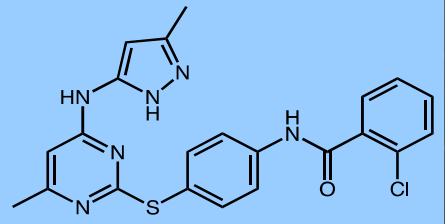
Rydzewski, p246

Diversity-Oriented Synthesis:
Blending Natural Products With Combinatorial Design



Source: Hajduk, Philip J., Warren RJD Galloway, et al. "Drug Discovery: A Question of Library Design." *Nature* 470, no. 7332 (2011): 42-3.

Aurora Inhibitors Exhibit Variable Cell Activity Despite Consistent Enzyme Activity

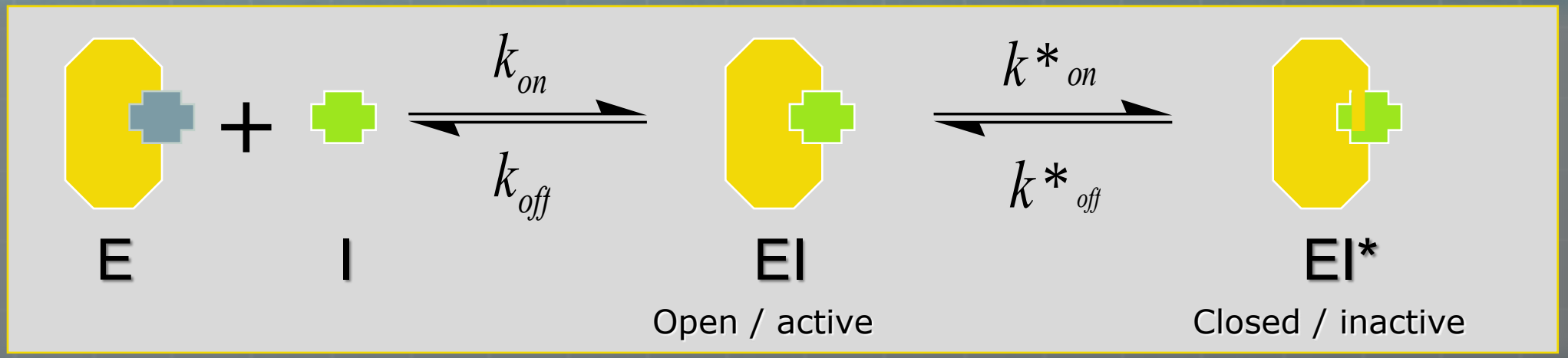
	MK-0457	VRT-426	VRT-960
			
Aur-A Ki (nM)	0.6	1.3	1.3
Aur-B Ki (nM)	18	11	10
Anti-Proliferation IC50 (nM)	19	4	250
Aur-A inhibition biomarker IC50 (nM)	43	9	29

Anti-proliferation: ^{3}H-thymidine incorporation at 96h in colo-205 cells

Aur inhibition biomarker: Auto-Pi of Aur-A at 2h in Hela cells

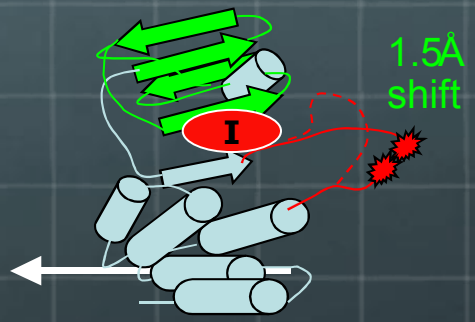
James Westcott, Philip Reaper, Mark Anderton, Peter Weber, Graham Cheetham, Peter Charlton, and John Pollard, Vertex UK, Presented at AACR annual meting, 14 April 2007

Kinetics Are Consistent With Structural Hypothesis



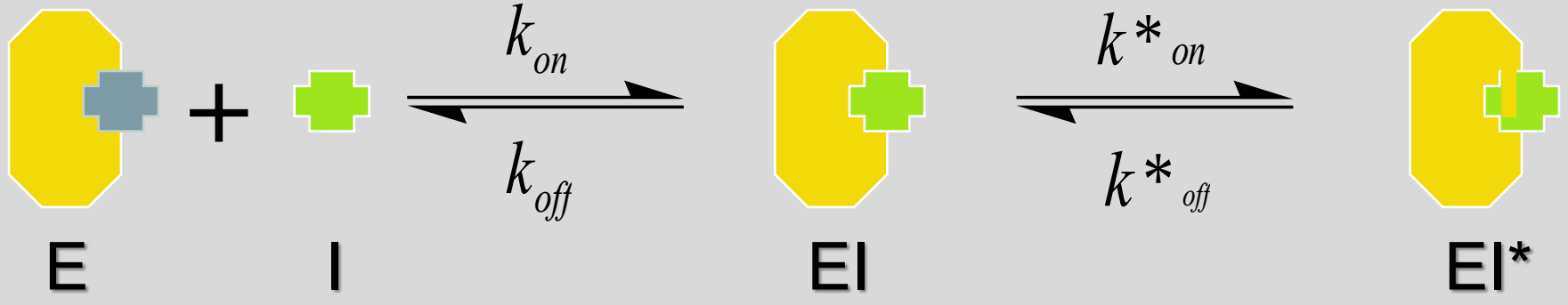
VRT-426

STEP 1: Moderate affinity
Ki = 11 nM



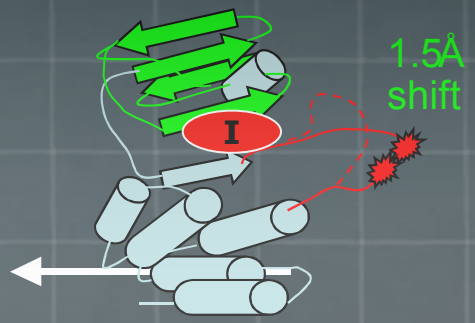
Source: Peter Charlton & John Pollard, Vertex Pharmaceuticals Ltd, UK

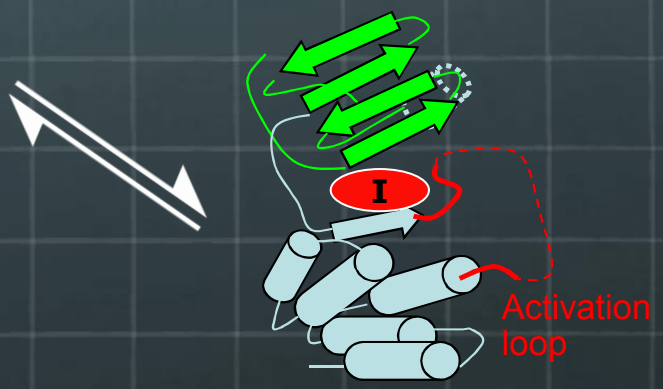
Kinetics Are Consistent With Structural Hypothesis



VRT-426

STEP 1: Moderate affinity
Ki 11nM





STEP 2: Isomerization and generation of tighter binding complex *Ki* = 0.75 nM*

Source: Peter Charlton & John Pollard, Vertex Pharmaceuticals Ltd, UK

Covalent Inhibitors

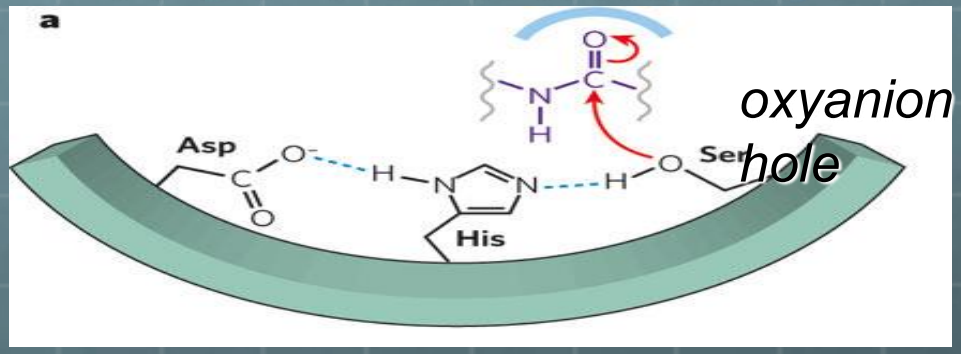
Table 2. Targets, Indications, and Mechanism of Action of Covalently Interacting Small Molecules

mechanism	target	indication	name of drug or representative drug[a]	reacting functionality	reversibility	dose (mg)[b]
acylation	serine-type D-Ala-D-Ala carboxypeptidase	bacterial infection	amoxicillin[c]	β-lactam	irreversible	100−500
	triacylglycerol lipase	obesity	orlistat	lactone	reversible	360
	acetylcholinesterase	Alzheimer's	rivastigmine	carbamate	reversible	6−12
	β-lactamase	bacterial infection	clavulanate[c]	β-lactam	irreversible	500
	prostaglandin endoperoxidase synthase	pain	aspirin	ester	reversible	1000
	vitamin K epoxide reductase (warfarin-sensitive)	anticoagulant	warfarin	coumarin		2−10
	enol−acyl carrier protein reductase	bacterial infection (tuberculosis)	*isoniazid*	hydrazide[d]	irreversible	300
	aldehyde dehydrogenase	alcoholism	*disulfiram*	disulfide	irreversible	500[e]
alkylation	UDP-*N*-acetylglucosamine-1-carboxyvinyltransferase	bacterial infection	fosfomycin	epoxide		3000
	alanine racemase	bacterial infection (tuberculosis)	D-cycloserine	amine[d]		>250
	GABA-AT[f]	epilepsy	vigabatrin	amine[d]	irreversible	3000[e]
metal/metalloid binding	aromatase	breast cancer	*exemstane*[c]	methyl	irreversible	25
	proteasome	multiple myeloma	bortezomib	boronic acid	reversible	3
disulfide bond formation	H^+/K^+ ATPase	gastresophageal reflux disease	*omeprazole*[c]	sulfenamide	irreversible	20
	P2Y12 purinoceptor antagonist	platelette aggregation inhibitor	*clopidogrel*	thiol	irreversible	75
(seleno-enzyme)	thyroxine 5′-deiodinase (type 1)	hyperthyroidism	propylthiouracil	thiourea		450
hemiketal formation	serine protease hepatitis C virus NS3[g]	viral infection	VX-950 (**1q**)	ketoamide	reversible	n/a
Michael addition	ribonucleoside diphosphate reductase	cancer	*gemcitabine*[c]	vinyl ketone		≥150−000[h]
	thymidylate synthase	cancer	floxuridine[c]	unsaturated amide	reversible	0.1−0.6 (mg/kg)/d
	ErbB1/2[g]	cancer (NSCLC)	HKI-272 (**1t**)	unsaturated amide	irreversible	n/a
	5-α-reductase	benign prostatic hyperplasia	finasteride[c]	unsaturated amide[d]	reversible	5
	MAO-B	Parkinson's disease[i]	*selegiline*[c]	aceylenic imine[d]	irreversible	1
Pinner reaction	DPP IV[g]	diabetes	vildagliptin	nitrile	reversible	100
	cathepsin K[g]	osteoporosis	odanacatib	nitrile	reversible	10−50[j]

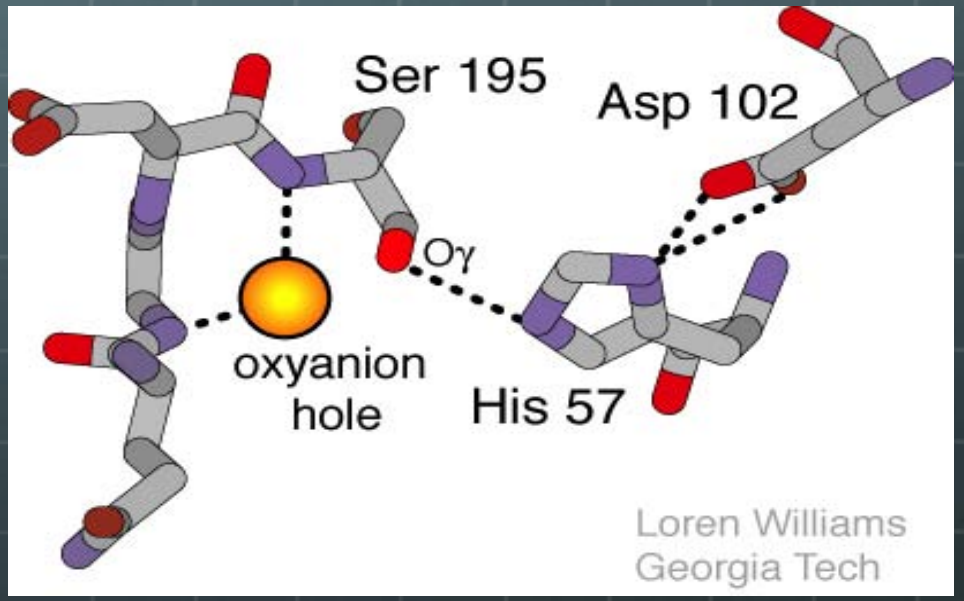
[a] Prodrugs are indicated in italics. [b] As determined from the FDA label or other medical references. [c] Because of the large number of drugs developed for these targets, one representative drug is indicated in the table. [d] Indicates functionality covalently modified by the cofactor. [e] Estimated dose. [f] Approved in Canada, U.K., and Mexico. [g] Under clinical investigation. [h] Dose = 1000 mg/m^2 weekly. The average body surface area of a person is approximately 1.5−2 mm^2. [i] Several irreversible MAO inhibitors are on the market for the treatment of depression. [j] Weekly dose used in the clinical trial "MK0822 (Odanacatib) Late Phase II Dose-Finding Study" described at www.clinicaltrials.gov.

Source: Potashman, Michele H., and Mark E. Duggan. "Covalent Modifiers: An Orthogonal Approach to Drug Design." *Journal of Medicinal Chemistry* 52, no. 5 (2009) : 1231-46.

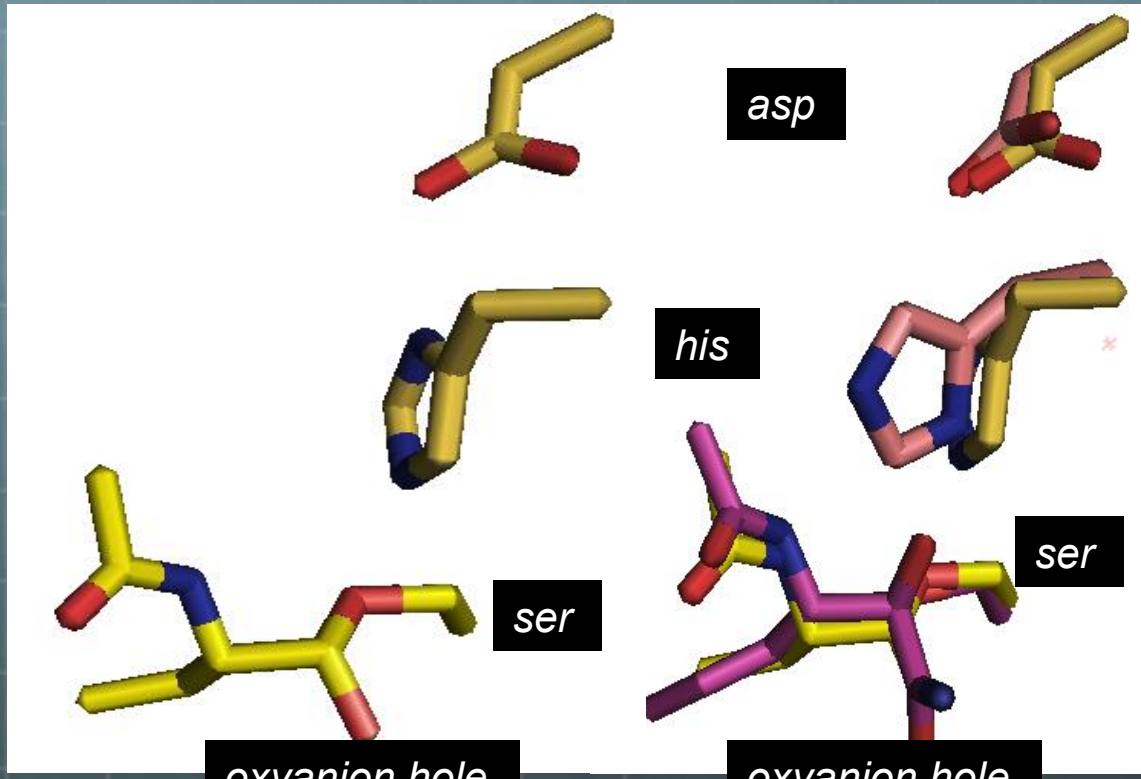
Telaprevir (Incivek): An Insurmountable HCV-PR Inhibitor

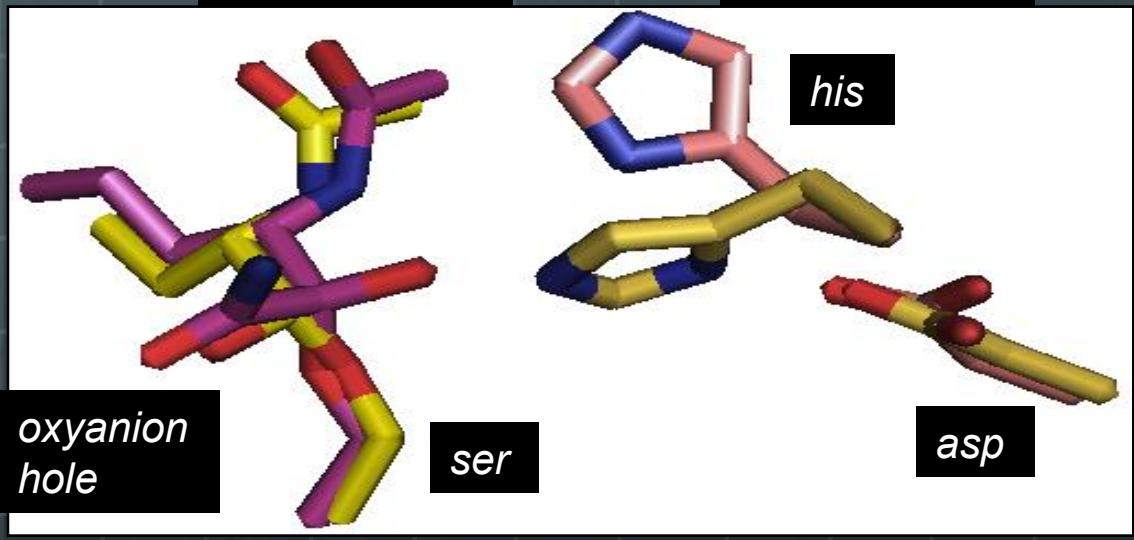


Courtesy of Macmillan Publishers Limited. Used with permission.
Source: Erez, Elinor, Deborah Fass, et al. "How Intramembrane Proteases Bury Hydrolytic Reactions in the Membrane." *Nature* 459, no. 7245 (2009) : 371-8.



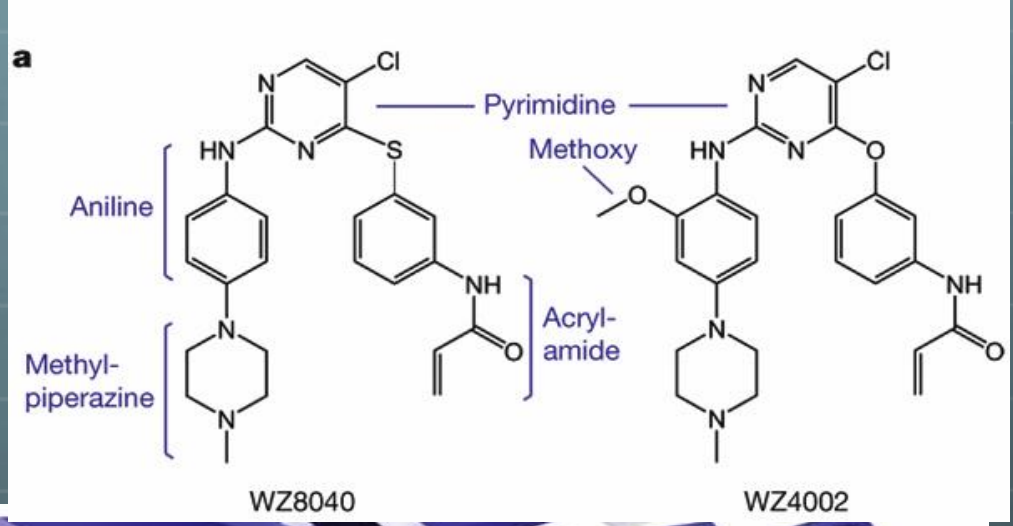
Courtesy of Loren Williams. Used with permission.

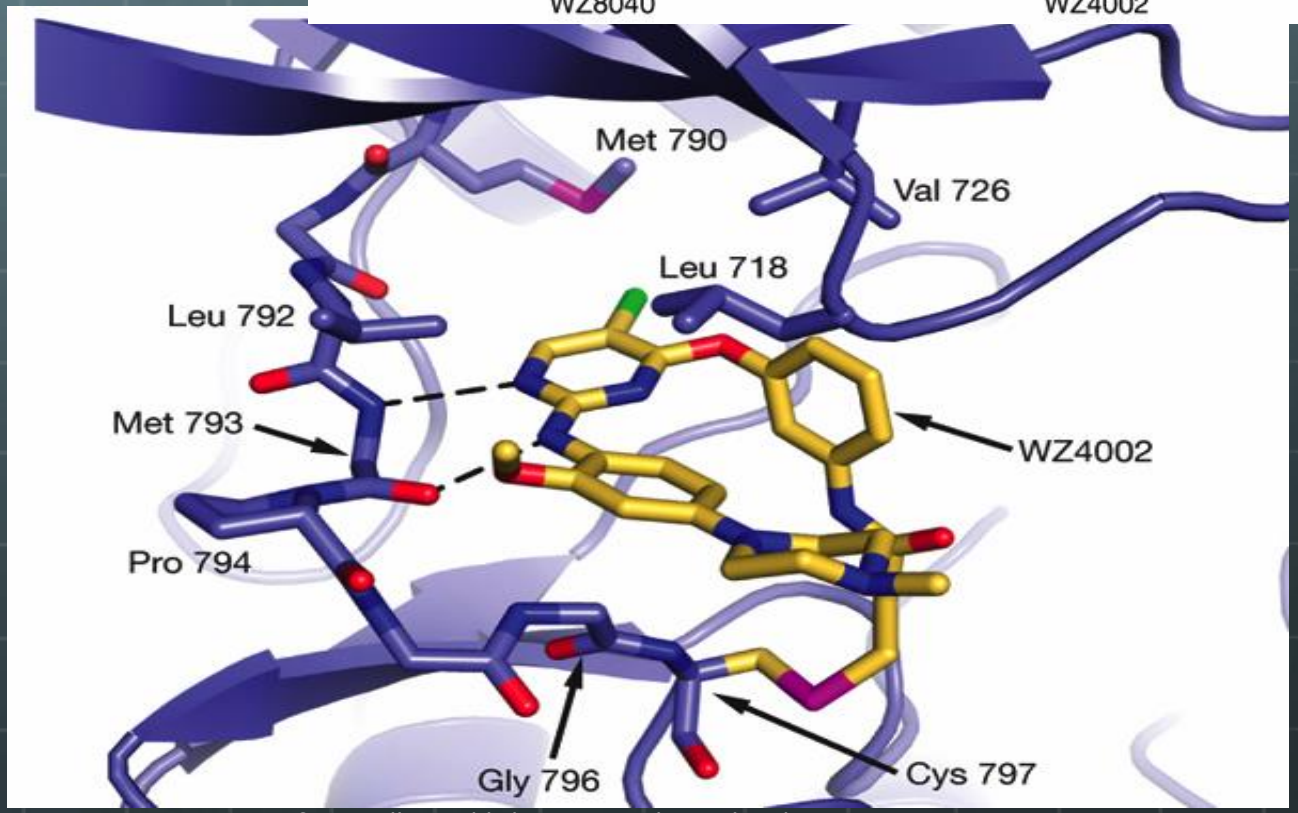




Irreversibles Don't Have to Use Catalytic Residues

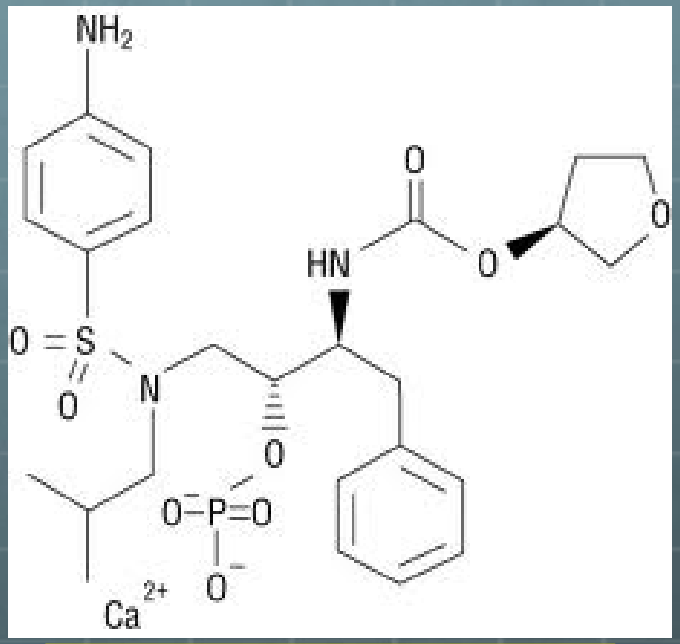
- Epidermal growth factor receptor (EGFR) kinase inhibitors
- Acrylamide moiety reacts with conserved cysteine
- Discovered by screening against mutants resistant to other EGFR inhibitors





Source: Zhou, Wenjun, Dalia Ercan, et al. "Novel Mutant-Selective EGFR Kinase Inhibitors Against EGFR T790M." *Nature* 462, no. 7276 (2009) : 1070-4.

Fosamprenavir: A Soluble Prodrug, A Better Product



Fosamprenavir calcium was approved by the FDA in October 2003 for use in combination with other antiretrovirals.

The HIV protease inhibitor amprenavir was approved by the FDA in 1999 but its limited water solubility requires the use of softgel formulation for delivery and multiple pills for a single dose.

After screening 60 prodrugs in in vitro and in vivo assays, the phosphate prodrug, fosamprenavir calcium (GW-433908), was selected for its high water solubility, solution and solid-state stability, and rapid conversion to the parent drug on the apical side of epithelium.

The prodrug is delivered from a solid dosage form with a lower pill burden, two tablets replacing eight amprenavir softgels.

Current Events With Commentary
Four Blogs Worth Checking Out

Derek Lowe
"In the Pipeline"

Bruce Booth
"lifeSciVC"

John LaMattina
Forbes

Matthew Herper
"The Medicine Show"

END OF PART 1

20.201 Mechanisms of Drug Actions

Fall 2013