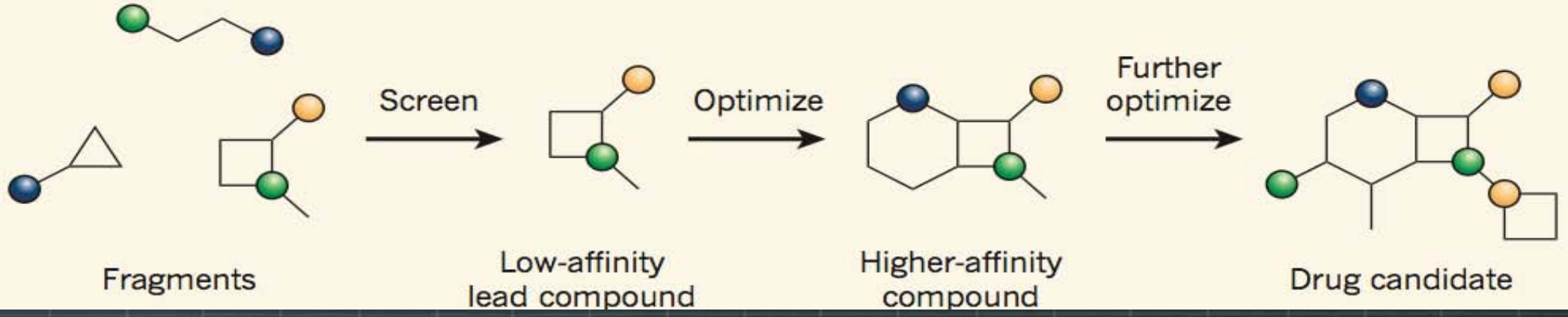
2b. Where Drugs Come From: SBDD versus Phenotype

Targets Which Have Yielded Clinical Candidates With the Help of Structure-Based Drug Design

Therapeutic Area	Targets
Cardiovascular	ACE, Renin, Thrombin, Factor VII, Factor Xa
Glaucoma	Carbonic anhydrase *(1st approved drug, Dorzolamide, 1995)*
Inflam / immun	Human neutrophil elastase, P38, IMPDH, ICE, COX2, MMP-X, JAK3
Cancer	Purine nucleoside phosphorylase, Thymidylate synthase, VEGF kinase (KDR), Aurora-2, CDK2, EGF kinase (erbB), Glycinamide ribonucleotide formyl-transferase, HSP90, BTK, ……
Antivirals	HIV protease, Influenza sialidase (neuraminidase), HCV protease, HCV polymerase, rhinovirus 3C protease, rhinovirus coat proteins
Sepsis	Caspases (broad), secretory PLA2
Diabetes	PPAR-gamma, DPP-IV, Aldose reductase
Osteoporosis	Cathepsin K
Various CNS	GSK3 kinase, Acetylcholinesterase, BACE

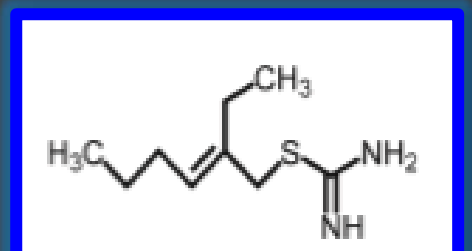
Fragment Based Design:
A Specialized Form of SBDD

- X-ray or NMR
- Yields weakly potent starting points -- ***but often with excellent physical properties***
- Linking is challenging

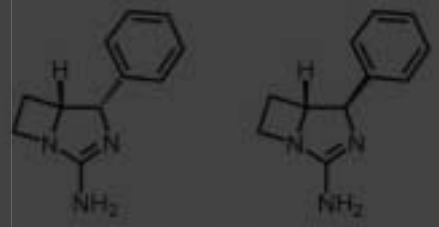


Source: Hajduk, Philip J., Warren RJD Galloway, et al. "Drug Discovery: A Question of Library Design." *Nature* 470, no. 7332 (2011): 42-3.

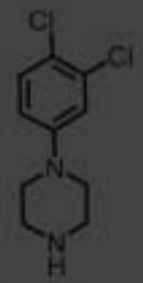
Fragment Based Design of BACE Inhibitors



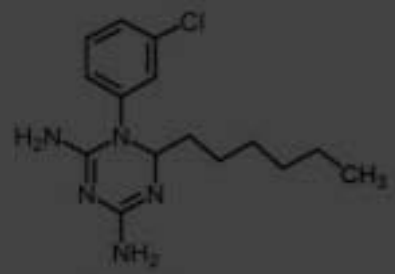
Isothioureas (2)
K_D(NMR) = 550±50 μM
204 analogs tested
X-ray structures of analogs



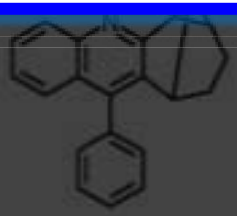
mino-diazobicycloheptenes
ndophenyl
Exophenyl



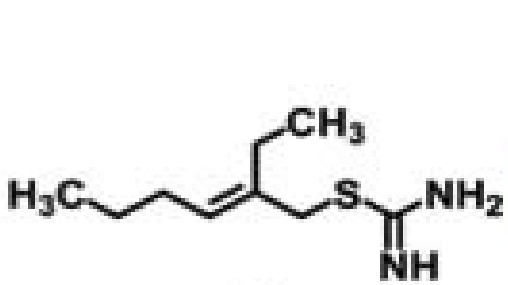
Piperazines
K_D(NMR) = 3.7±0.6 mM
134 analogs tested



Triazines
K_D(NMR) = 100±30 μM
69 analogs tested



Tropyl-quinolines
K_D(NMR) = 30±10 μM
98 analogs tested
X-ray structure



2
K_d(NMR) = 550±50 µM
MW = 186
LE = 0.37

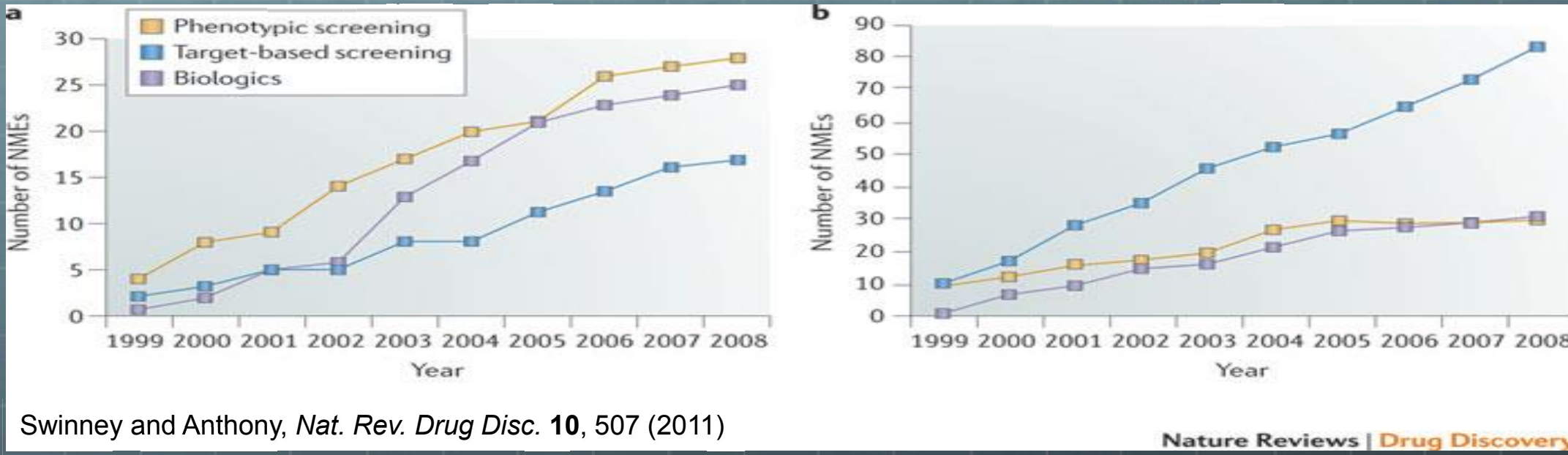
3
K_d(NMR) = 15±7 µM
IC_{50} (HTRF) = 210 µM
MW = 273
LE = 0.39
pKa ~ 8.6

Figure 1. Fragment-based NMR scree
screening 10000 compounds from a cus

Source: Wang, Yu-Sen, Corey Strickland, et al. "Application of Fragment-Based NMR Screening, X-ray Crystallography, structure-based Design, and Focused Chemical Library Design to Identify Novel µM Leads for the Development of nM BACE-1 (β-site APP cleaving enzyme 1) Inhibitors." *Journal of Medicinal Chemistry* 53, no. 3 (2009): 942-50.

Phenotypic Screening's Track Record

First-in-class *Followers*

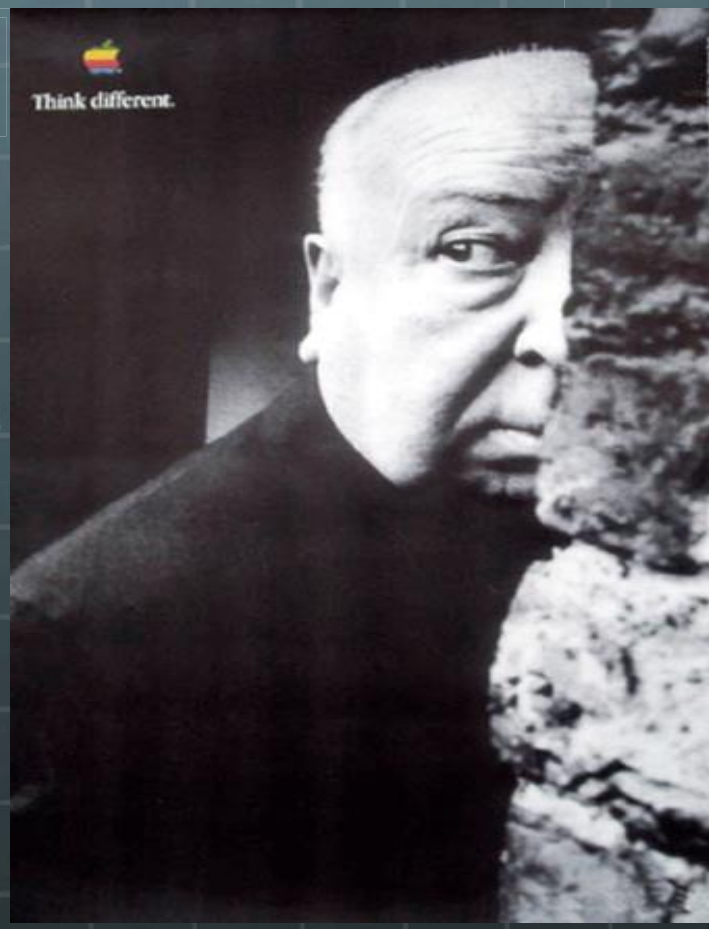


Swinney and Anthony, *Nat. Rev. Drug Disc.* **10**, 507 (2011)

- Probes entire pathway(s) - can be multiple classes of hits
- Hits are excellent tools for interrogating disease biology
- Encourages clear thinking about screening collection & assays
- Focuses chemistry on phenotype, pharmacology, tox

Phenotype-Driven Science Requires Different Thinking

- Biology:
  - Probes entire pathway(s) - can be multiple classes of hits doing different things
  - Target ID challenging (but cmpds are good tools)
  - Ineffective without clear link between assay & disease
  - Puts a huge emphasis on the quality of the assays
- Chemistry
  - Encourages clear thinking about screening collection
  - May serendipitously find cmpds that hit multiple targets
  - Provides a huge jump-start for chemistry teams
  - Focuses chemistry on phenotype, pharmacology, tox
  - Good starting molecules may be elusive
  - SAR may never make sense
- Development
  - May be harder to explain tox findings
  - There will be internal skeptics
  - Regulatory agencies may be nervous



3. How We Find Drugs: A Bit About Process & Philosophy

High-Level View of R&D Process

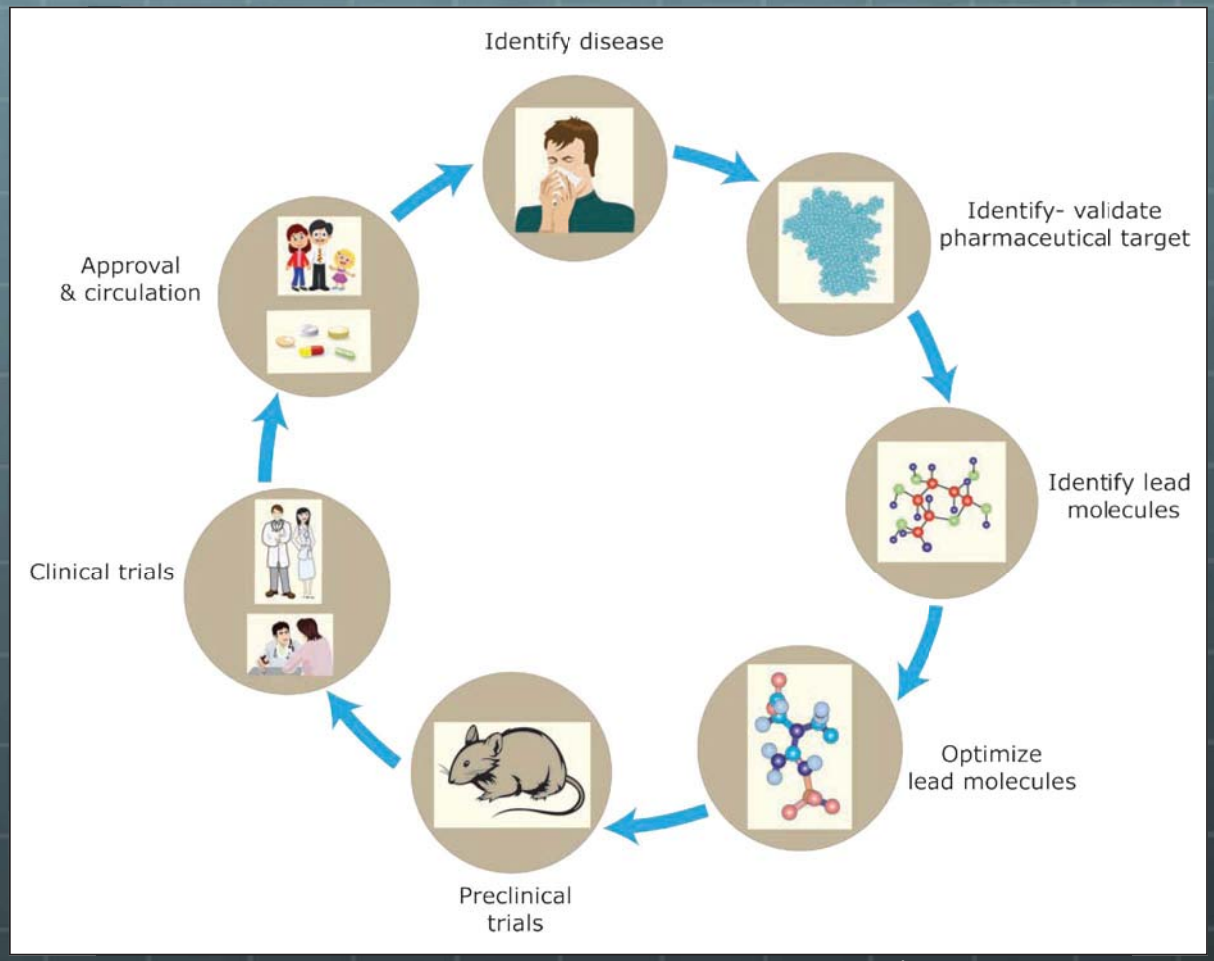
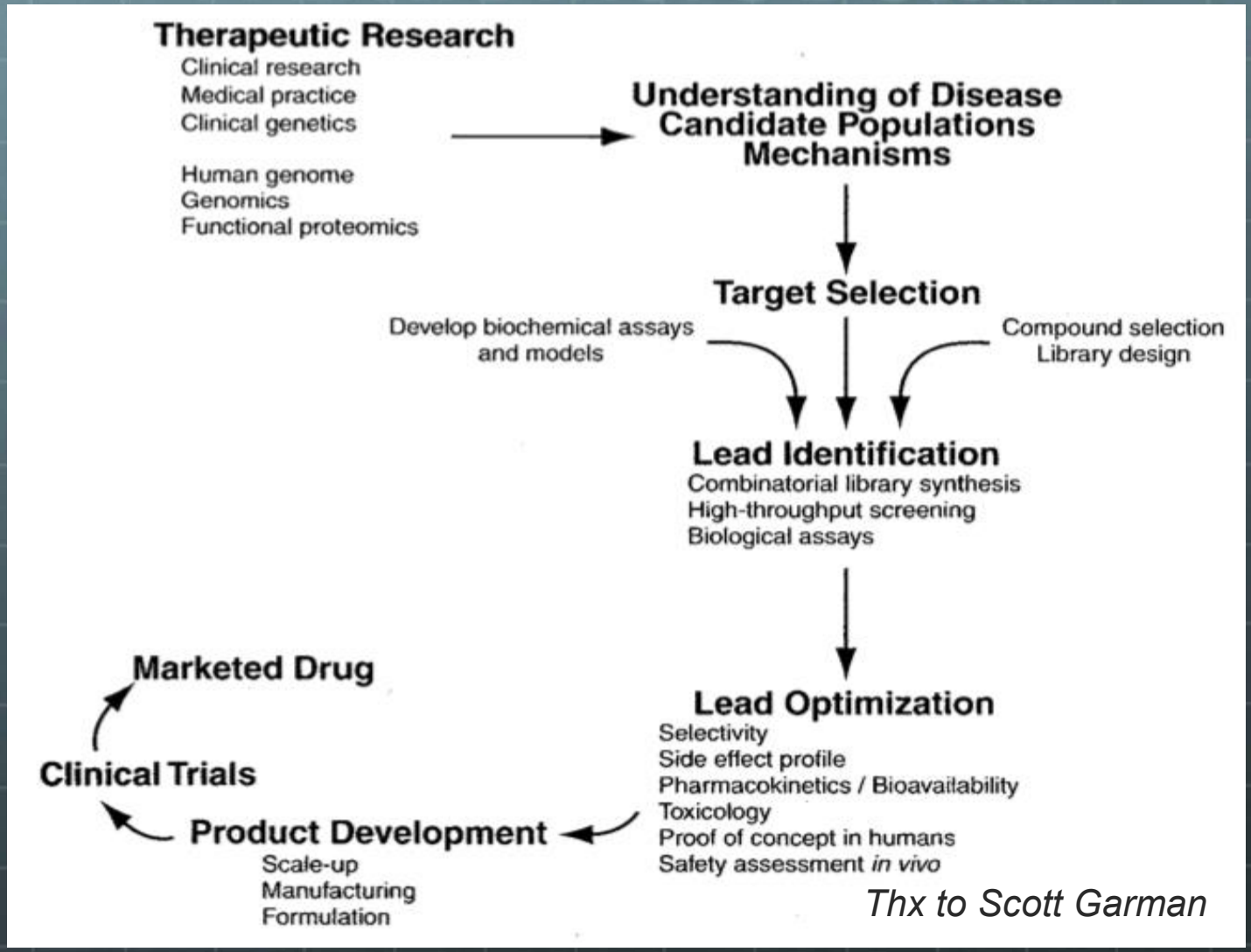


Image by MIT OpenCourseWare.

Of course reality isn't quite this clean and linear…

Idealized Drug R&D Process: A Little More Detail



Thx to Scott Garman

Lead Optimization Overview (1 of 2)

- Lead optimization: modifying the structure of a confirmed hit to improve its characteristics.
- ***Goal is to produce a preclinical drug candidate.***
- Confirmed hits are evaluated in secondary assays, and a set of related compounds, called analogs, are synthesized and screened.
- The testing of analog series results in structure-activity relationships (SAR): quantitative information that correlates changes in chemical structure to biological & pharmacological data.

Scott Garman

Lead Optimization Overview (2 of 2)

- ***"Lead opt" is highly iterative.***
- Leads are assessed in a range of assays. Med chemists modify cmpds to optimize pharmacological properties e.g. bioavailability or stability. These new analogs are then tested to determine potency, selectivity, and MOA.
- ***Biomarkers are essential to show cmpds are working as intended & get to the site of action in required amounts.***
- ***New information of all kinds comes in constantly, often changing the design parameters.***
- The "lead opt" process continues until a defined drug profile is achieved that warrants clinical testing.

Scott Garman

Formulation & Delivery

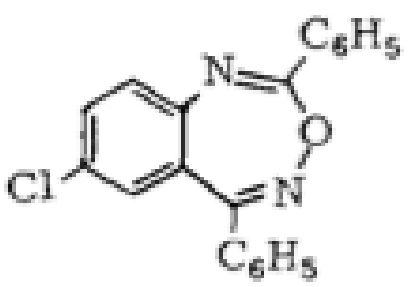
- Formulation & delivery are closely linked. i.v. delivery of a novel drug might require a different formulation than oral, b/c metabolic stability or solubility can differ significantly.
- Formulation can dramatically affect absorption, e.g. through their interaction with cell membrane of the GI tract.
- Formulation and delivery are highly specialized fields of research, and formulation scientists are ***now involved in drug discovery and development programs from the early stages***.
- Much effort is centered around new ways of formulating known drugs to increase their efficacy or safety profiles.

From “R” to “D”

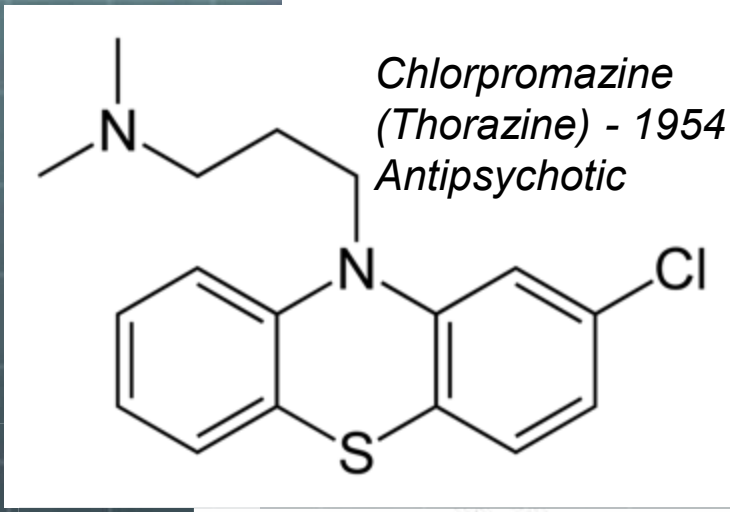
- The decision to take a new drug candidate into development entails a significant commitment in terms of money, resources, and time.
- ***90% failure, huge cost, average time 12 years.***
- Drug development requires rigorous attention to standards; it is a highly regulated process.
- ***Careful attention to development issues should begin at the start of discovery! (Systems perspective.)***
- Details of development covered later in the course.

4. Serendipity and Avoiding Micro-Management

Leo Sternbach reasoned that his old dyes, which reminded him of the chemical structure of thorazine, might make a decent starting point for his investigations. His idea was to add a basic amine to his old molecules since this was often necessary for biological activity.

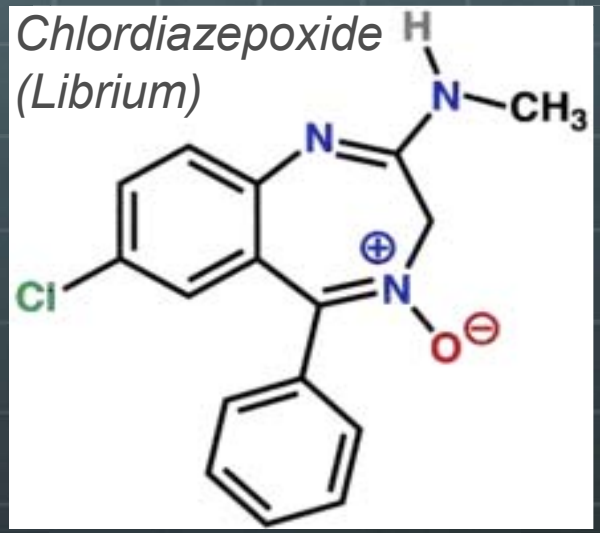


Sternbach prepared ~40 new cmpds and screened them for muscle relaxant, sedative, and anticonvulsant properties. Nothing worked… until the last compound!

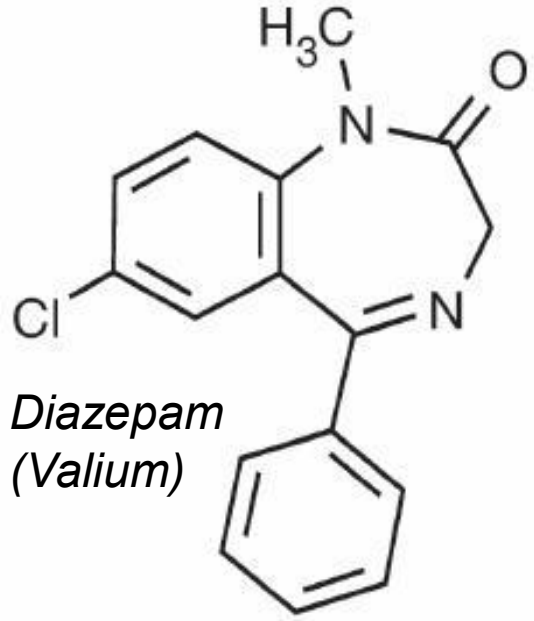


Chlorpromazine (Thorazine) - 1954 Antipsychotic

He investigated the chemistry and found that a key intermediate was entirely different -- this compound had undergone an unexpected molecular rearrangement to produce a different ring system called a ***benzodiazepine.*** This molecule eventually became a drug called ***Librium.***



He then came up with a better molecule: Valium.



Diazepam (Valium)

By 1970, in the USA 20% of women and 7% of men were using “minor tranquilizers and sedatives” – mostly benzodiazepines.

“Kids are different today” I hear every mother say
Mother needs something today to calm her down
And though she's not really ill
There's a little yellow pill
She goes running for the shelter of a mother's little helper
And it helps her on her way, gets her through her busy day…

“Mother’s Little Helper,” The Rolling Stones, 1966

How *Not* to Screw Up Research

"I construe my function as a director of research as mainly to create the kind of environment which is conducive to the advancement of learning. That sounds pompous, but this is all a director can do. You cannot *direct* people to have ideas, and no one can have a big enough grasp of the whole of biological science to be able to say which lines of research are certainly going to be fruitful and which are certainly going to be a waste of time. So what one has to do is simply create an environment and an atmosphere in which science flourishes."

—— *Peter Medawar*

Nobel Prize in Physiology or Medicine, 1960

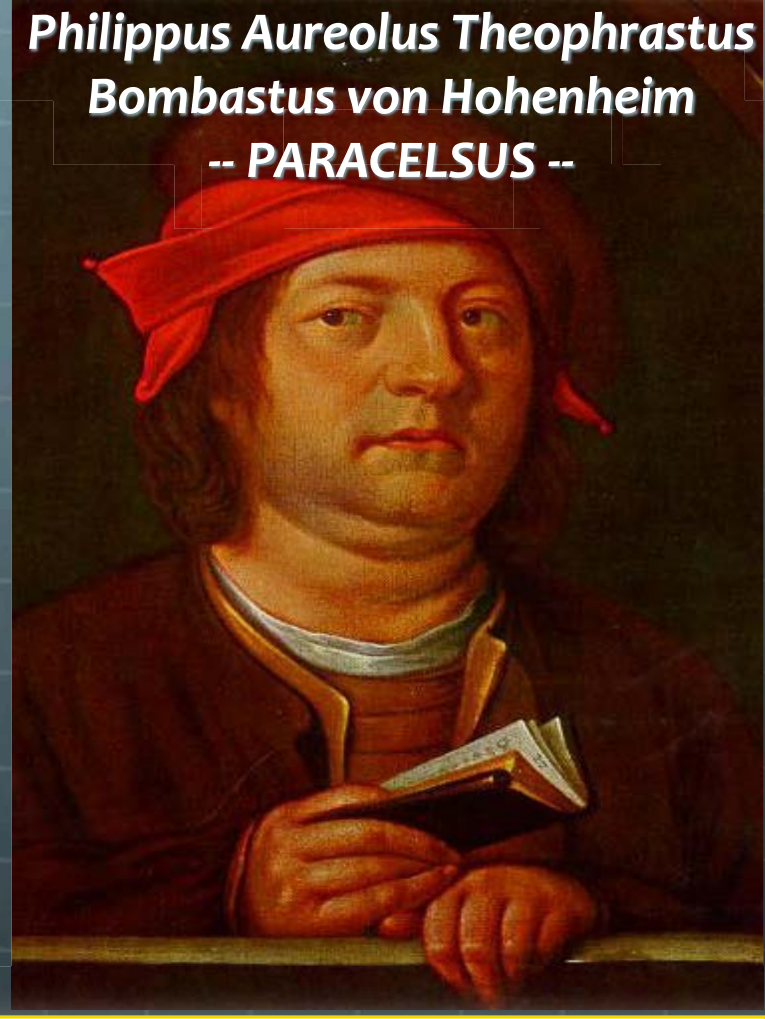
5. Why This is So Hard: Some Specific Challenges

5.1 Natural Products

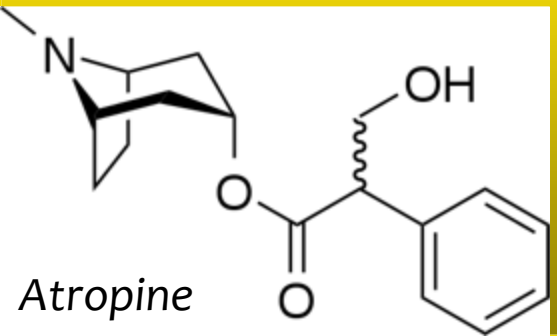
“The Dose Makes the Poison”

Atropa belladonna
(Belladonna,
Deadly Nightshade)

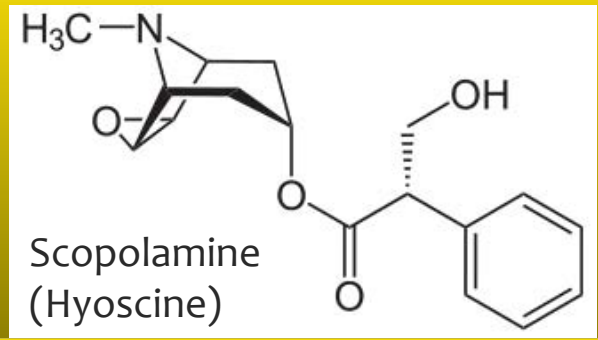
Agrippina the Younger
Sister of Caligula
Mother of Nero



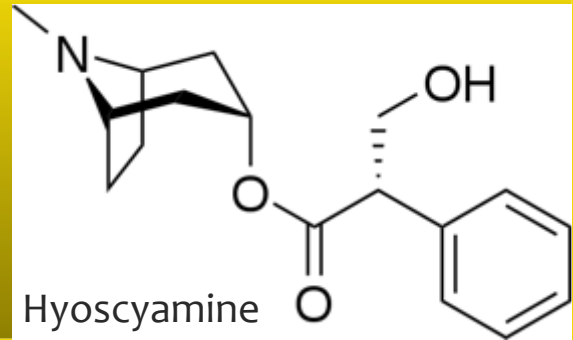
Muscarinic antagonists – parasympathetic system blockers



Atropine



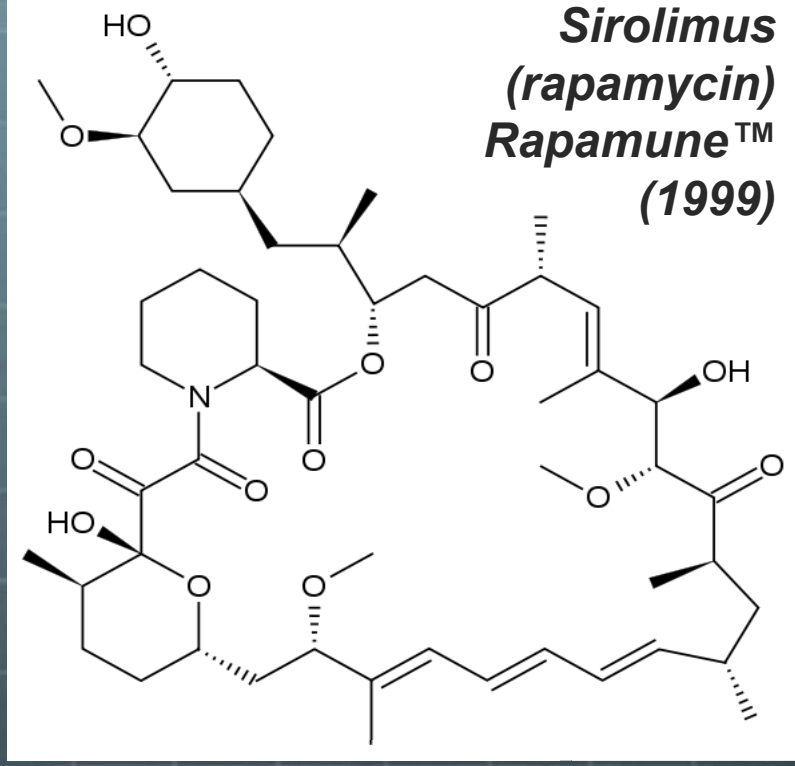
Scopolamine
(Hyoscine)



Hyoscyamine

Natural Products

- Source of MANY drugs
- However, the "rules" governing "drug-likeness" are mysterious
- If you need to chemically modify the drug – horrific synthetic & design challenges
- And, if you can't make it in bulk by fermentation – nightmare!



Sirolimus (rapamycin) Rapamune™ (1999)

Inhibits response to IL-2; approved for use in organ transplant rejection

- Product of the bacterium *Streptomyces hygroscopicus*
- Discovered in soil sample on Easter Island (Rapa Nui)
- First developed as antifungal agent; later discovered to be immunosuppressive
- In 2010 shown to prolong the life of middle-aged mice
- Antiproliferative; being studied in various cancers

5.2 Pharmacoeconomics

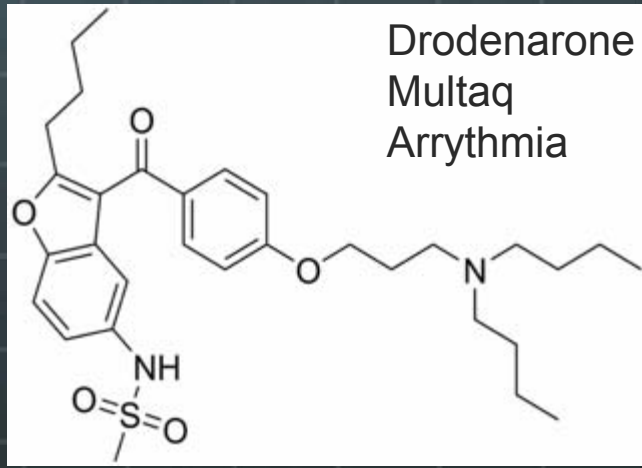
Is the Drug Worth the Cost?

Pharmacoeconomics:
1 January 2012 - Volume 30 - Issue 1 - pp 35-46
doi: 10.2165/11594280-000000000-00000
Review Articles

Dronedarone for the Treatment of Atrial Fibrillation: A NICE Single Technology Appraisal

McKenna, Claire[1]; Maund, Emma[2]; Sarowar, Muhammad[1]; Fox, David[2]; Stevenson, Matt[3]; Pepper, Chris[4]; Woolacott, Nerys[2]; Palmer, Stephen[1]

From the evidence presented by the manufacturer, dronedarone appeared highly cost effective in each of the population groups examined compared with using standard baseline therapy alone as first-line treatment, or compared with sotalol or amiodarone as first-line AAD, with incremental cost-effectiveness ratios (ICERs) well below £20 000 per QALY gained. The ICER for dronedarone relative to class 1c agents was around £19 000 per QALY. Although the evidence presented by the manufacturer indicated that dronedarone was cost effective, the estimates of treatment effect relative to other AADs and safety in the longer term were highly uncertain. The NICE Appraisal Committee in its preliminary guidance did not recommend the use of dronedarone for AF. However, following the response from a large number of consultees and commentators, NICE revised its preliminary guidance to allow the use of the drug in a specific subgroup of AF patients with additional cardiovascular risk factors.



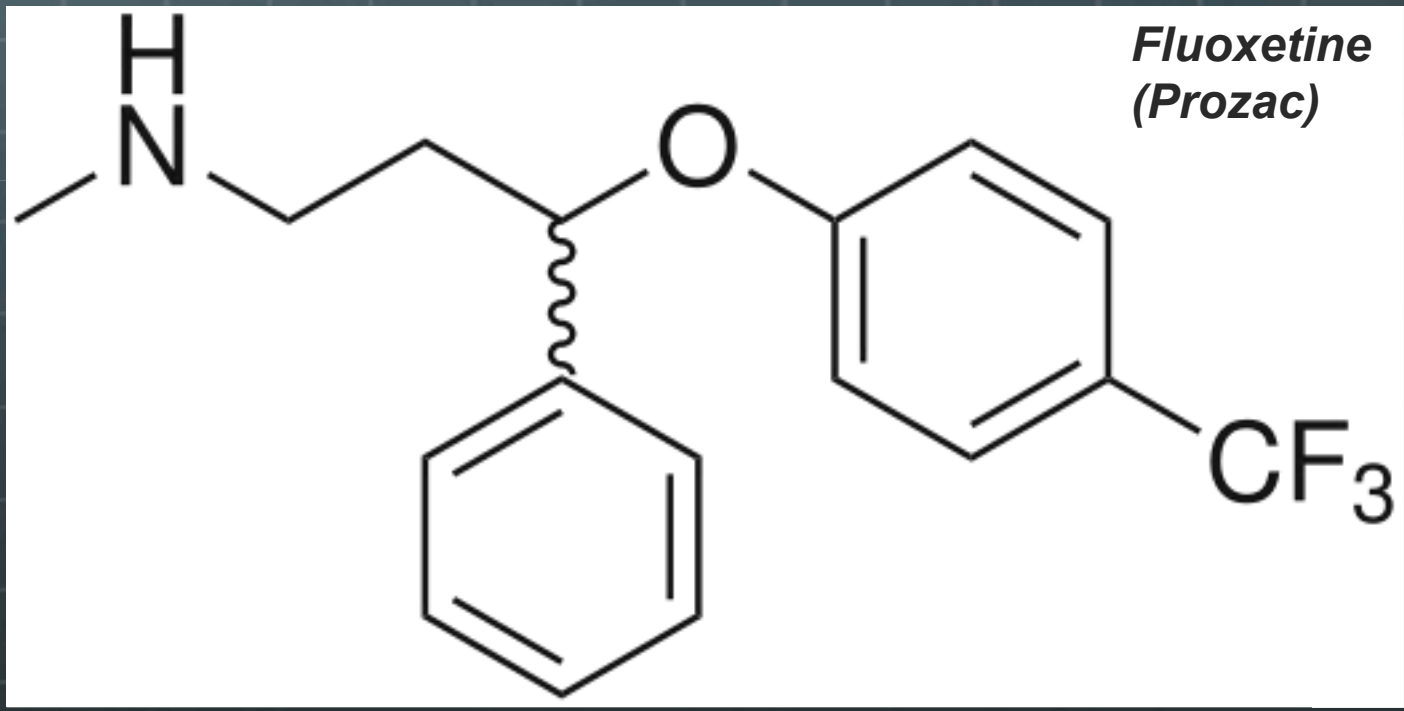
Drodenarone
Multaq
Arrythmia

Source: McKenna, Claire, Emma Maund, et al . "Dronedarone for the Treatment of Atrial Fibrillation."
Pharmacoeconomics 30, no. 1 (2012): 35-46.

5.3 Polypharmacy

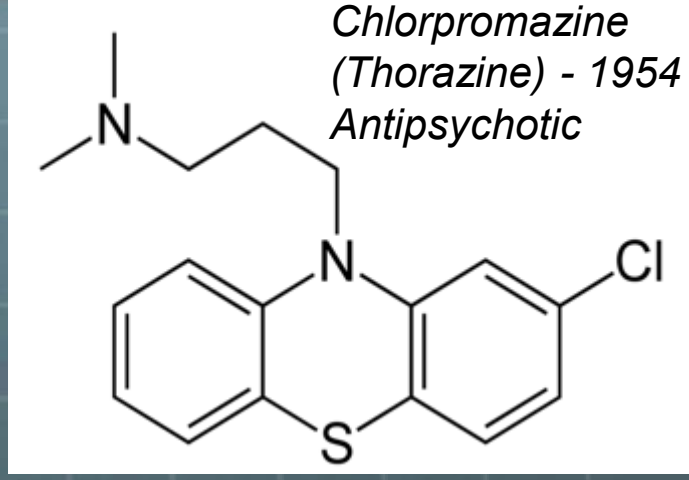
“Polypharmacology”

- Prozac is a used for major depression, obsessive-compulsive disorder, panic disorder, and other indication.
- Mechanism: selective serotonin reuptake inhibitor (SSRI) – block the serotonin transporter (SERT)
- However, also a potent 5-HT_{2C} receptor antagonist, and an agonist of the σ_1-receptor … unclear exactly how these activities contribute!



Fluoxetine (Prozac)

Threading a Needle



- A French army doctor was seeking drugs to relax surgical patients – "sedation without narcosis"
- Rats became tolerant of aversive stimuli
- The drug was superior in calming and reducing shock; patients reported improved well being.
- It was taken into manic patients: spectacular!

"The single greatest advance in psychiatric care"

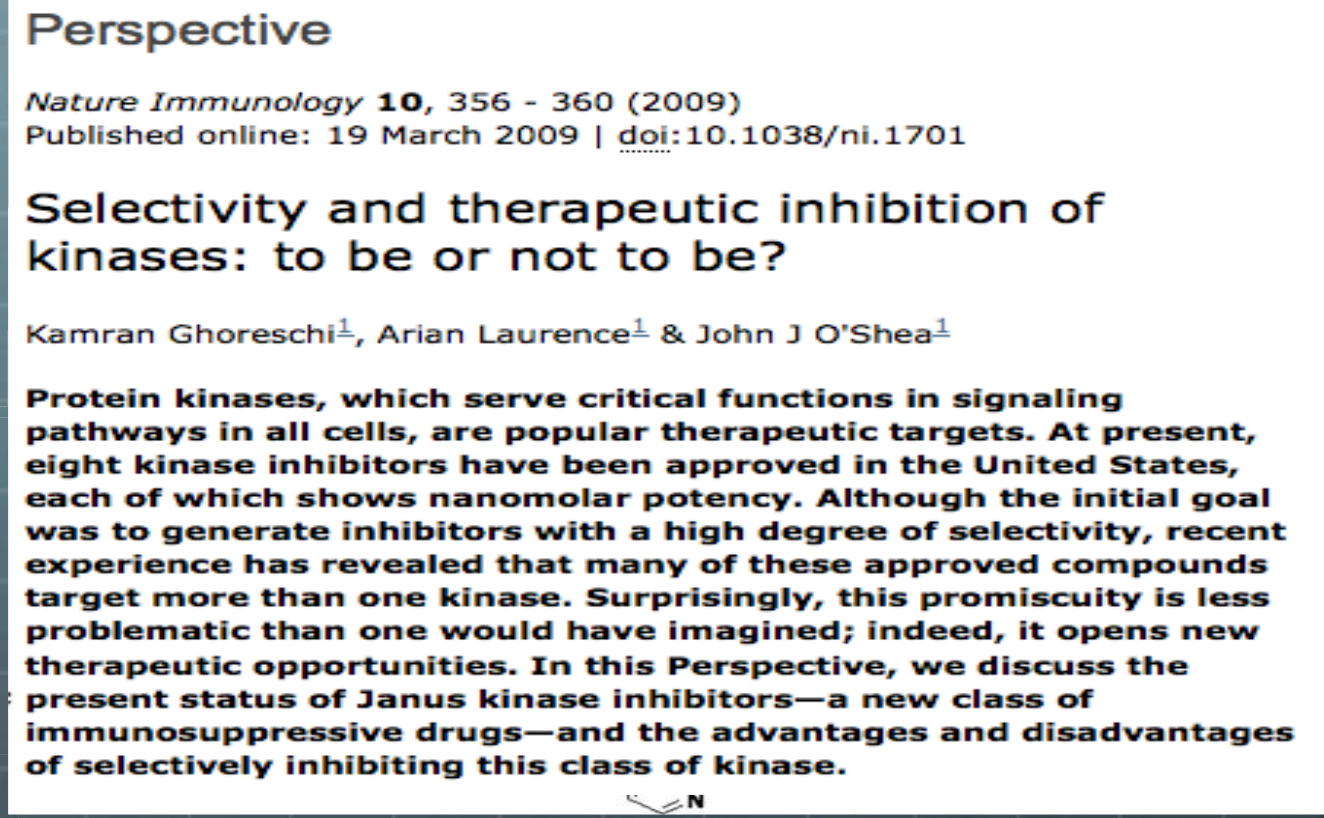
CLINICAL PHARMACOLOGY

The precise mechanism whereby the therapeutic effects of Chlorpromazine are produced is not known. The principal pharmacological actions are psychotropic. It also exerts sedative and antiemetic activity. Chlorpromazine has actions at all levels of the central nervous system —primarily at subcortical levels—as well as on multiple organ systems.

- What chlorpromazine blocks (A PARTIAL LIST): Dopamine receptors (subtypes D1 – D5); Serotonin receptors (5-HT1 and 5-HT2); Histamine receptor H1; α1- and α2-adrenergic receptors; M1 and M2 muscarinic acetylcholine receptors; ….

Threading a Needle

- Sorafenib is quite "dirty" but is nonetheless useful for some cancers (RCC, HCC). Its effectiveness is definitely related to its polypharmacy (VEGF, PDGF, raf).
- Gleevec is used in chronic myelogenous leukemia (CML), gastrointestinal stromal tumors (GIST), some myelodysplastic syndromes, and a range of other niche indications.
- Reasonably selective, Gleevec still hits TK domains of *abl* (Abelson proto-oncogene), c-kit and PDGF-R(platelet-derived growth factor receptor).



Perspective

Nature Immunology **10**, 356 - 360 (2009)
Published online: 19 March 2009 | doi:10.1038/ni.1701

Selectivity and therapeutic inhibition of kinases: to be or not to be?

Kamran Ghoreschi[1], Arian Laurence[1] & John J O'Shea[1]

Protein kinases, which serve critical functions in signaling pathways in all cells, are popular therapeutic targets. At present, eight kinase inhibitors have been approved in the United States, each of which shows nanomolar potency. Although the initial goal was to generate inhibitors with a high degree of selectivity, recent experience has revealed that many of these approved compounds target more than one kinase. Surprisingly, this promiscuity is less problematic than one would have imagined; indeed, it opens new therapeutic opportunities. In this Perspective, we discuss the present status of Janus kinase inhibitors—a new class of immunosuppressive drugs—and the advantages and disadvantages of selectively inhibiting this class of kinase.

5.4 Late Failure (Sometimes Even After Drug Launch)

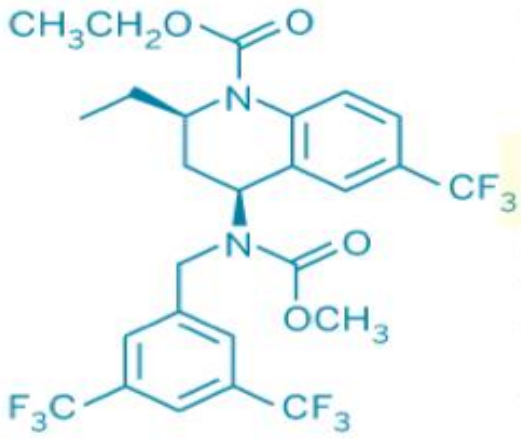
DECEMBER 4, 2006
PHARMACEUTICALS

Pfizer Pulls Torcetrapib

Loss leaves a gaping hole in company's late-stage pipeline

Lisa M. Jarvis

Pfizer dropped a bombshell over the weekend by pulling the plug on what is consid[illegible] in its new drug pipeline, the cholesterol agent torcetrapib. The company's shares were down as much as 15% on Monday, the first day of trading following the news.



"This spells the death of what is arguably the most important development program at Pfizer," says Morgan Stanley stock analyst Jami Rubin, who notes that the scientific community was particularly shocked by the news.

Pfizer halted development of the drug after an independent data safety monitoring board found a significant rise in mortality rates among patients taking both torcetrapib and Pfizer's Lipitor cholesterol drug. The board's analysis of a Phase III study of 15,000 patients showed that 82 deaths occurred in torcetrapib/Lipitor patients, compared with 51 deaths in patients taking Lipitor alone.

Torcetrapib is part of an emerging class of drugs that aim to raise levels of high-density lipoprotein, or "good" cholesterol, by blocking cholesterol ester transfer protein (CETP). The drug was meant to be a companion to Lipitor, Pfizer's top-selling product, which lowers low-density lipoprotein, or "bad" cholesterol.

Concerns over the safety of torcetrapib had been raised as early as last March, when Pfizer said it caused a rise in systolic blood pressure. But the company continued to display strong confidence in the drug, focusing on its blockbuster potential at a meeting with financial analysts just last week (**C&EN, Dec. 4, page 14**).

The loss of this critical product will undoubtedly push Pfizer to accelerate its plans to cut costs and improve operating efficiencies. Last week, Pfizer said it would trim its U.S. sales force by about 20%, eliminating roughly 2,000 jobs. The company will also ramp up its licensing efforts in order to maintain its goal of bringing six new drugs to the market annually starting in 2010.

The failure of torcetrapib puts a cloud over other CETP inhibitors in development, including products in the pipelines of **Merck** and **Roche**. "It's the result nobody wanted to see and probably means no CETP inhibitors will reach the market until their benefits have been clearly demonstrated in large outcomes trials," says Deutsche Bank analyst Barbara Ryan.

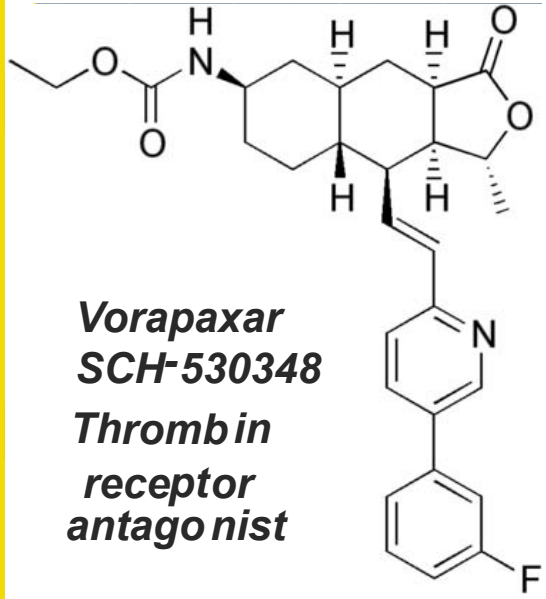
Interim Review Alters Phase Three Studies of Novel Antithrombotic Therapy

By Duke Medicine News and Communications

Following review of interim data by the independent Data Safety Monitoring Board (DSMB) for two large-scale, global phase three trials evaluating vorapaxar, an investigational anti-clotting medication, researchers at Brigham and Women's Hospital (BWH) and the Duke Clinical Research Institute (DCRI) announced today they are following the recommendations of the DSMB to discontinue study drug in one study among a subset of patients and discontinue study drug in the other trial in which the protocol target number of endpoint events had been reached.

Vorapaxar is a protease activated receptor-1 (PAR-1) inhibitor, which is a new class of anti-platelet heart medication that acts on a
standard therapy, including aspirin and drugs such a

The trials were designed to evaluate vorapaxar for th
of cardiac events among patients with acute coronar
prior heart attack, stroke, or peripheral arterial disea



Vorapaxar
SCH-530348
Thrombin receptor antagonist

PHARMA & HEALTHCARE | 8/27/2012 @ 4:03AM | 449 views

The Return Of Vorapaxar, This Time For Post-MI Patients

+ Comment now

The once highly-promising novel antiplatelet agent vorapaxar, widely thought to be dead on arrival after unacceptably high serious bleeding rates were found in two large clinical trials, has now returned to active duty. On Sunday the drug's sponsor, Merck, announced that it would seek approval of the drug, with a narrower indication than originally planned, based on new data from a prespecified analysis of the TRA 2P-TIMI 50 trial presented at the ESC and published simultaneously in the *Lancet*.

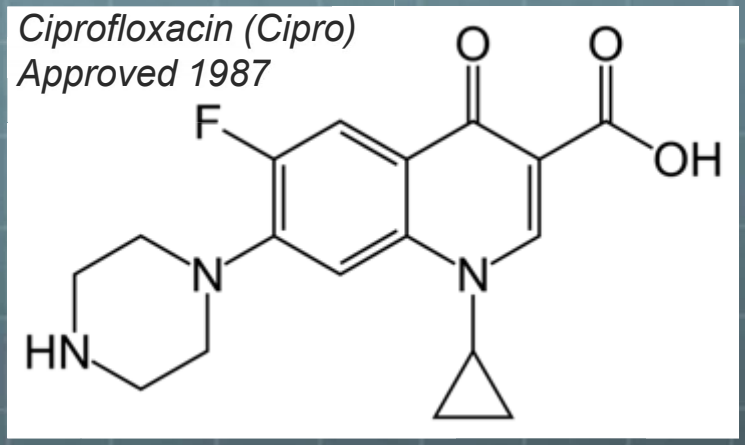
Source: Husten, Larry. "The Return of Vorapaxar, This Time for Post-MI Patients." Forbes.com. August 27, 2012.

Post Marketing recalls

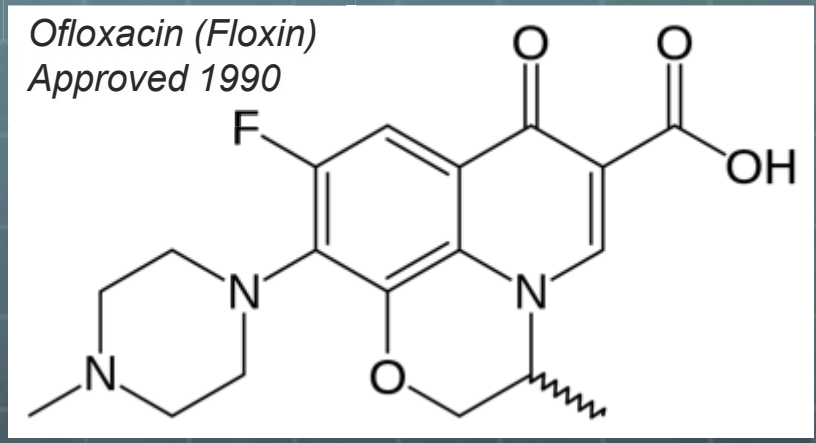
Drug (Indication)	On market	Withdrawn	Years Delay	Reason Drug Is Pulled	Company
Fenfluramine (weight loss)	1973	1997	24	Pulmonary hypertension, heart valve disease	Wyeth-Ayerst
Posicor (hypertension)	1985	1998	13	Reduced liver	Roche
Seldane (allergies)	1985	1997	12	Heart problems when taken with other drugs	Hoescht
Hismanal (allergies)	1988	1999	11	Heart arrhythmia	Janssen Pharmaceuticals
Propulsid (nocturnal heartbeat)	1993	2000	7	Cardiac arrhythmia	Janssen Pharmaceuticals
Vioxx (pain)	1999	2004	5	Heart attack, stroke	Merck
Baycol (anti-cholesterol)	1997	2001	4	Muscle deterioration	Bayer
Rezulin (anti-diabetes)	1997	2000	3	Liver toxicity	Pfizer
Razar (antibiotic)	1997	1999	2	Severe cardiovascular problems	Glaxo
Raplon (airway muscle relaxant)	1999	2001	2	Bronchospasm	Organon
Duract (pain)	1997	1998	1	Hepatitis, liver failure	Wyeth-Ayerst
Lotoronex (IBD)	2000	2000	9 mos	Ischemic colitis, constipation	Glaxo
Lumiracoxib (pain)	2006	2007	1	Hepatitis, liver failure	Novartis
Zelnorm (constipation)	2004	2007	3	Cardiac events	Novartis

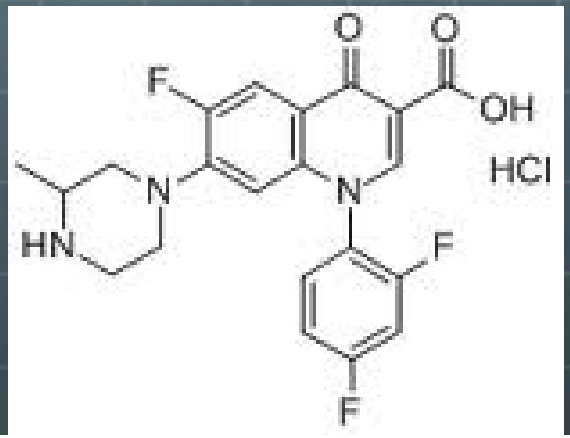
The Saga of the Floxacin (fluoroquinolone) Antibiotics

Ciprofloxacin (Cipro)
Approved 1987

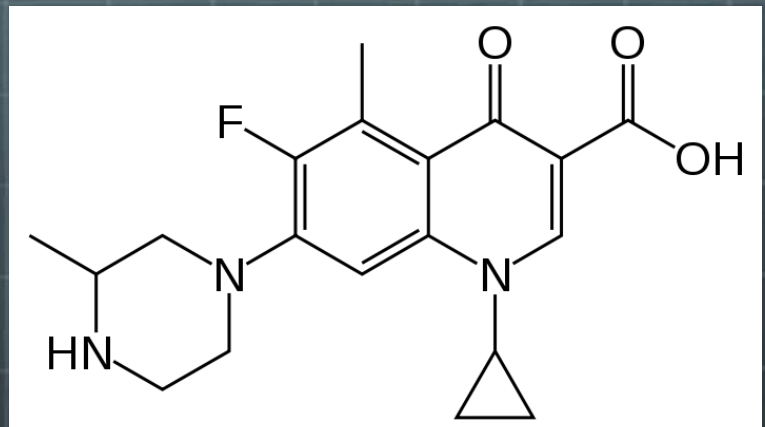


Ofloxacin (Floxin)
Approved 1990

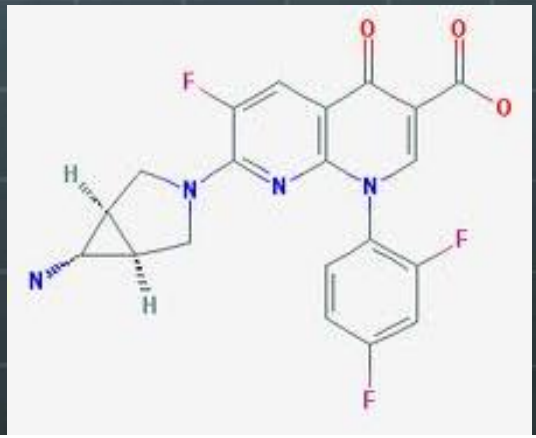




Temafloxacin (Omniflox)
Approved 1992, withdrawn 1992
Allergic rxns, hemolytic anemia



Grepafloxacin (Raxar)
Approved 1997, withdrawn 1999
QT prolongation



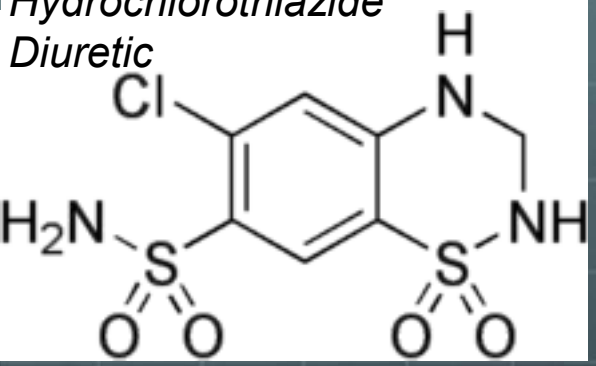
Trovafloxacin (Trovan)
Approved 1998, withdrawn 1999
Liver damage

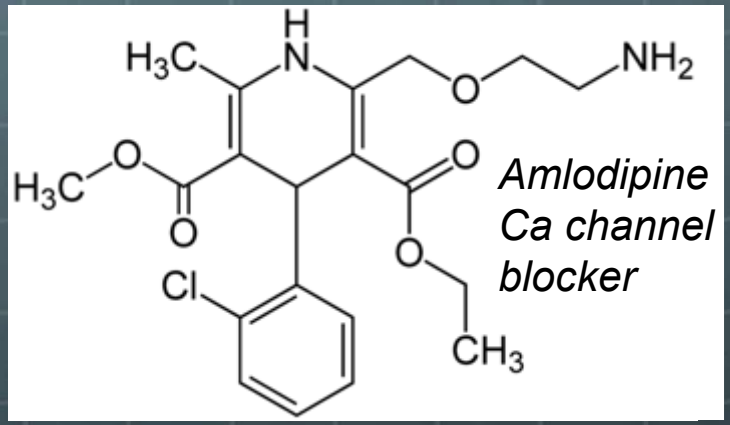
5.5 Generics: A Rising Bar

Past Successes → More Challenges Today

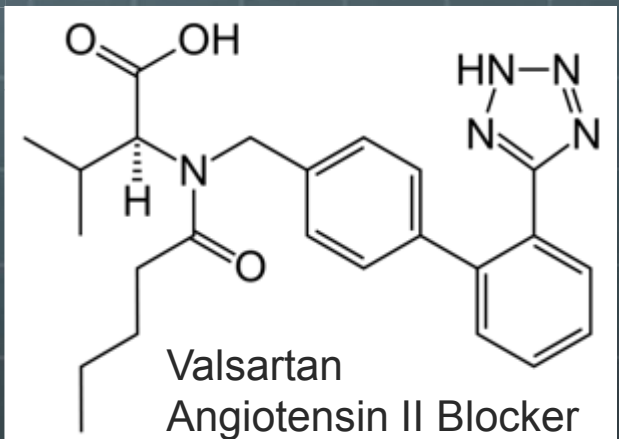
- Drugs with new mechanisms appear once in a while….
- Drugs with old mechanisms but better properties (e.g. once a day dosing, fewer side effects) come out regularly…
- Drugs become generic: cheaper, well understood

Hydrochlorothiazide
Diuretic

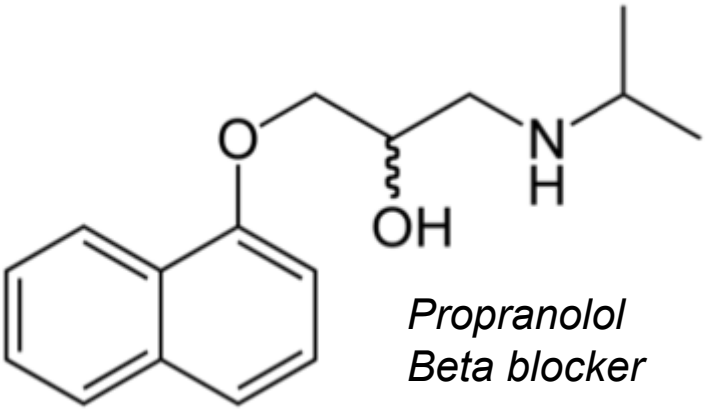




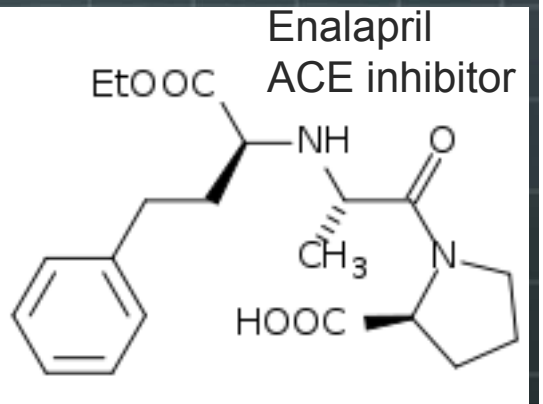
Amlodipine
Ca channel blocker



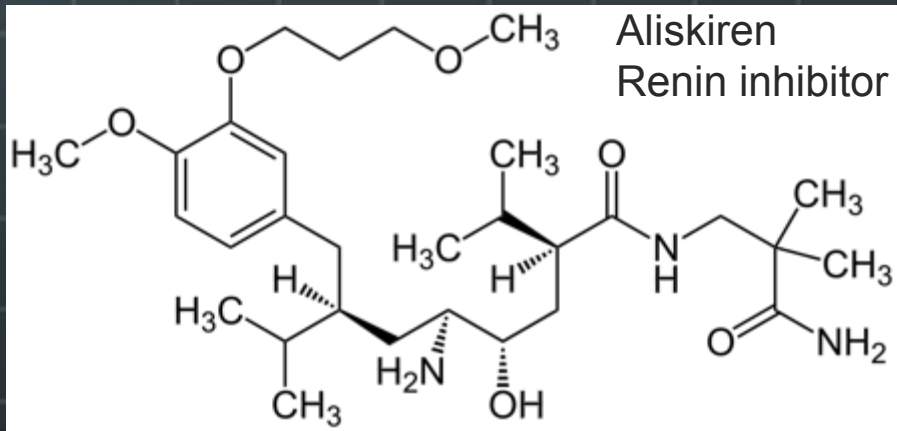
Valsartan
Angiotensin II Blocker



Propranolol
Beta blocker

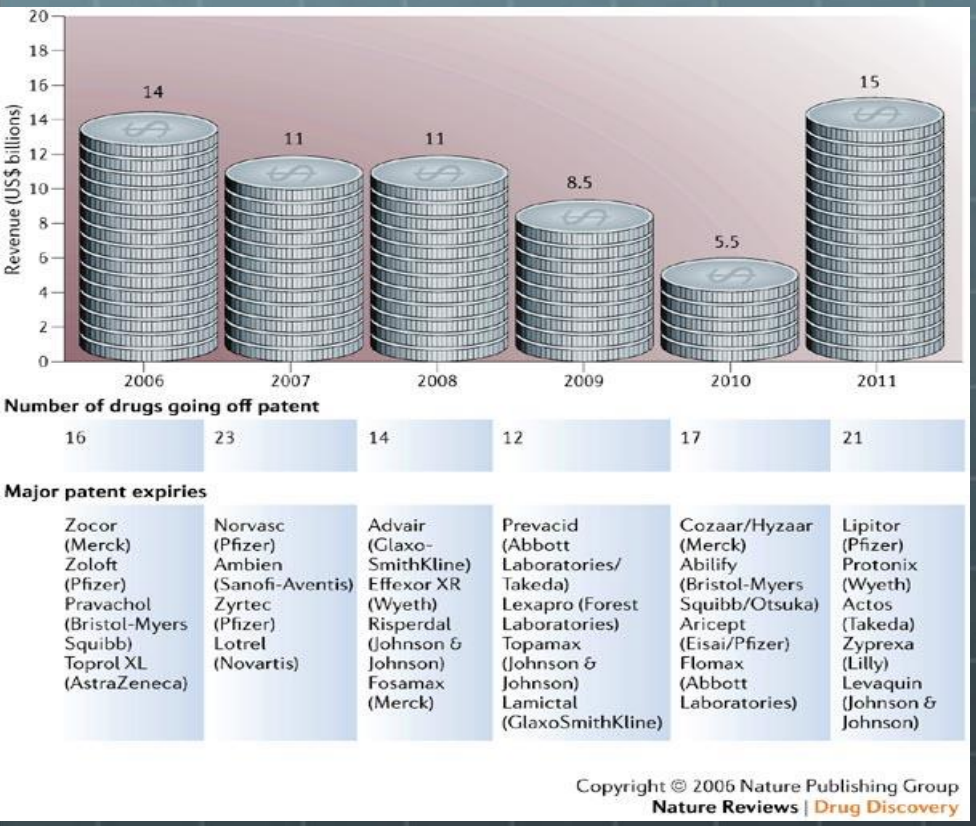


Enalapril
ACE inhibitor



Aliskiren
Renin inhibitor

Going Generic



Number of drugs going off patent					
16	23	14	12	17	21
Major patent expiries					
Zocor (Merck) Zoloft (Pfizer) Pravachol (Bristol-Myers Squibb) Toprol XL (AstraZeneca)	Norvasc (Pfizer) Ambien (Sanofi-Aventis) Zyrtec (Pfizer) Lotrel (Novartis)	Advair (Glaxo-SmithKline) Effexor XR (Wyeth) Risperdal (Johnson & Johnson) Fosamax (Merck)	Prevacid (Abbott Laboratories/ Takeda) Lexapro (Forest Laboratories) Topamax (Johnson & Johnson) Lamictal (GlaxoSmithKline)	Cozaar/Hyzaar (Merck) Abilify (Bristol-Myers Squibb/Otsuka) Aricept (Eisai/Pfizer) Flomax (Abbott Laboratories)	Lipitor (Pfizer) Protonix (Wyeth) Actos (Takeda) Zyprexa (Lilly) Levaquin (Johnson & Johnson)

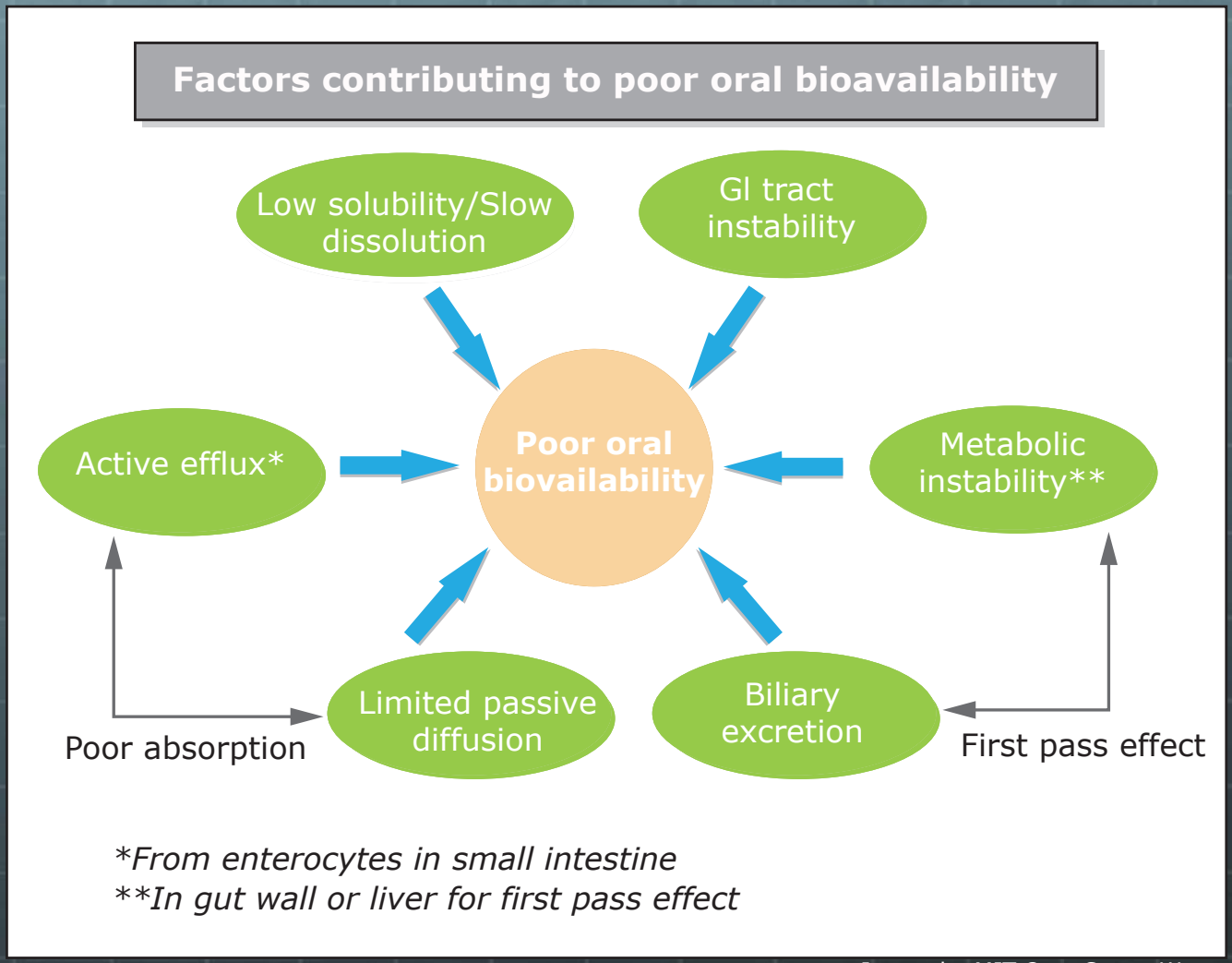
Nature Reviews | Drug Discovery

Table of projected annual sales figures for various drugs removed due to copyright restrictions.

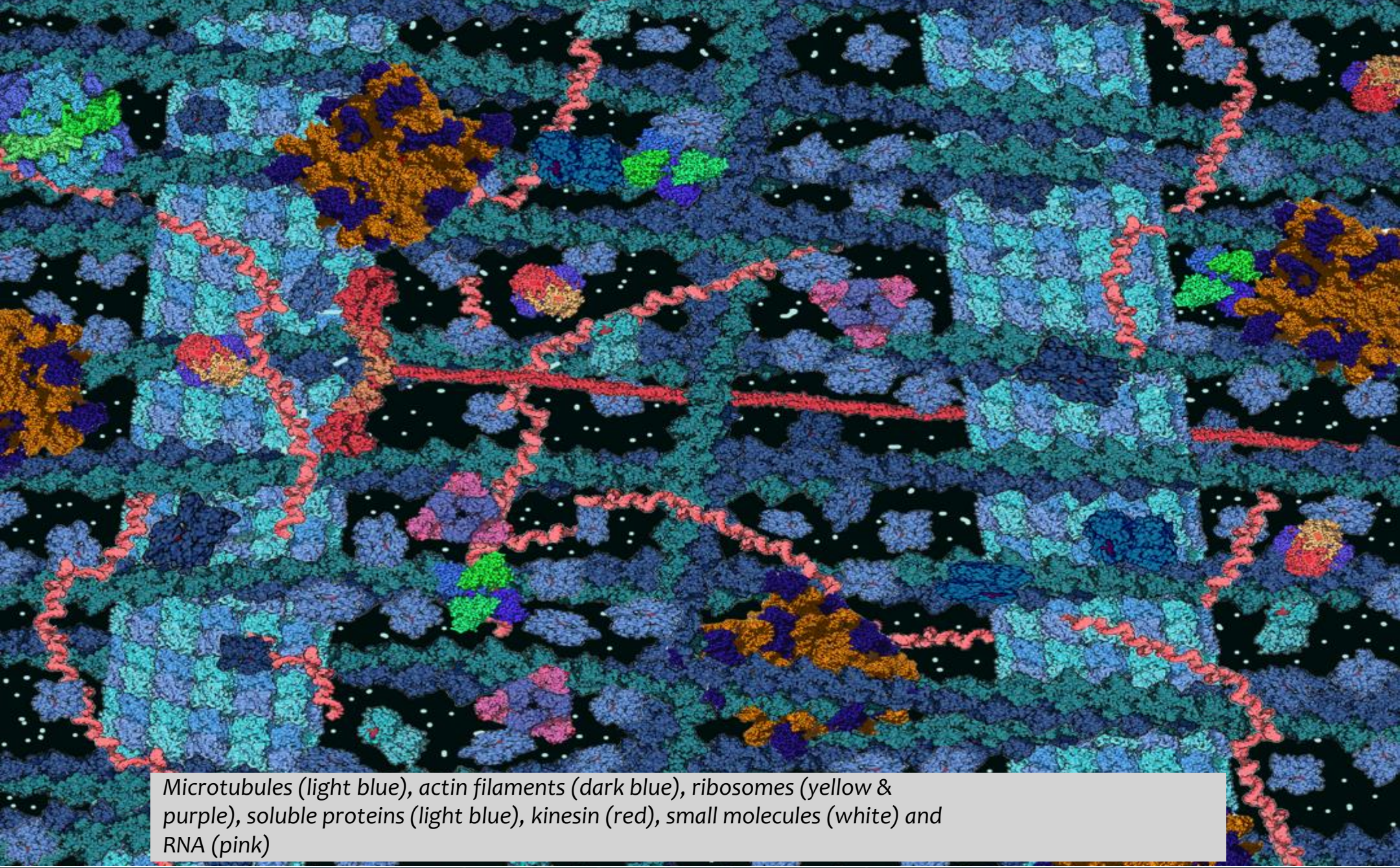
Source: Frantz, Simon. "Pharma Companies Becoming more Aggressive towards Generics Firms." *Nature Reviews Drug Discovery* 5, no. 8 (2006): 619-20.

5.6 Getting Across Barriers

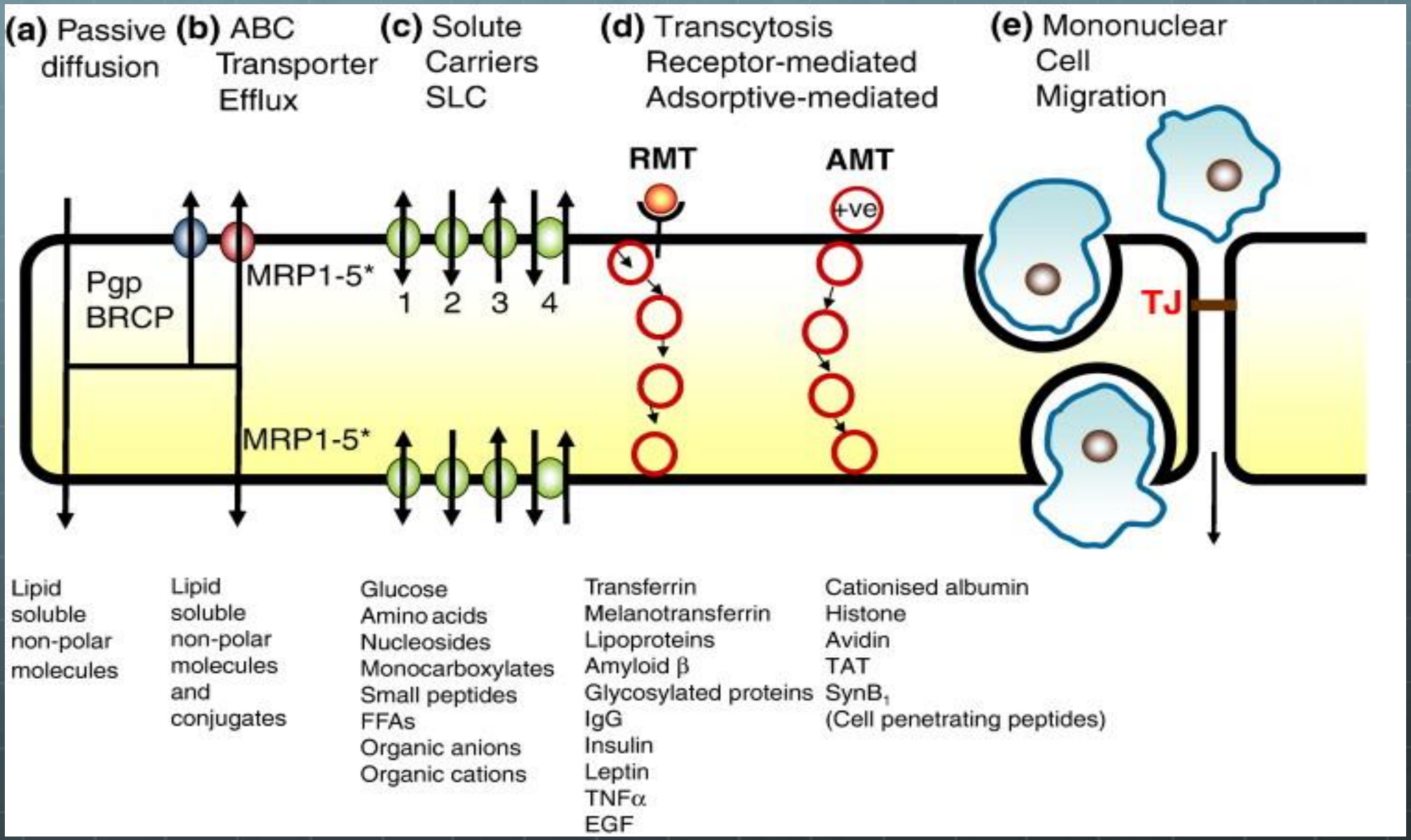
Oral Absorption: Balancing Many Factors



Real World Drug Discovery, Robert M. Rydzewski, p414

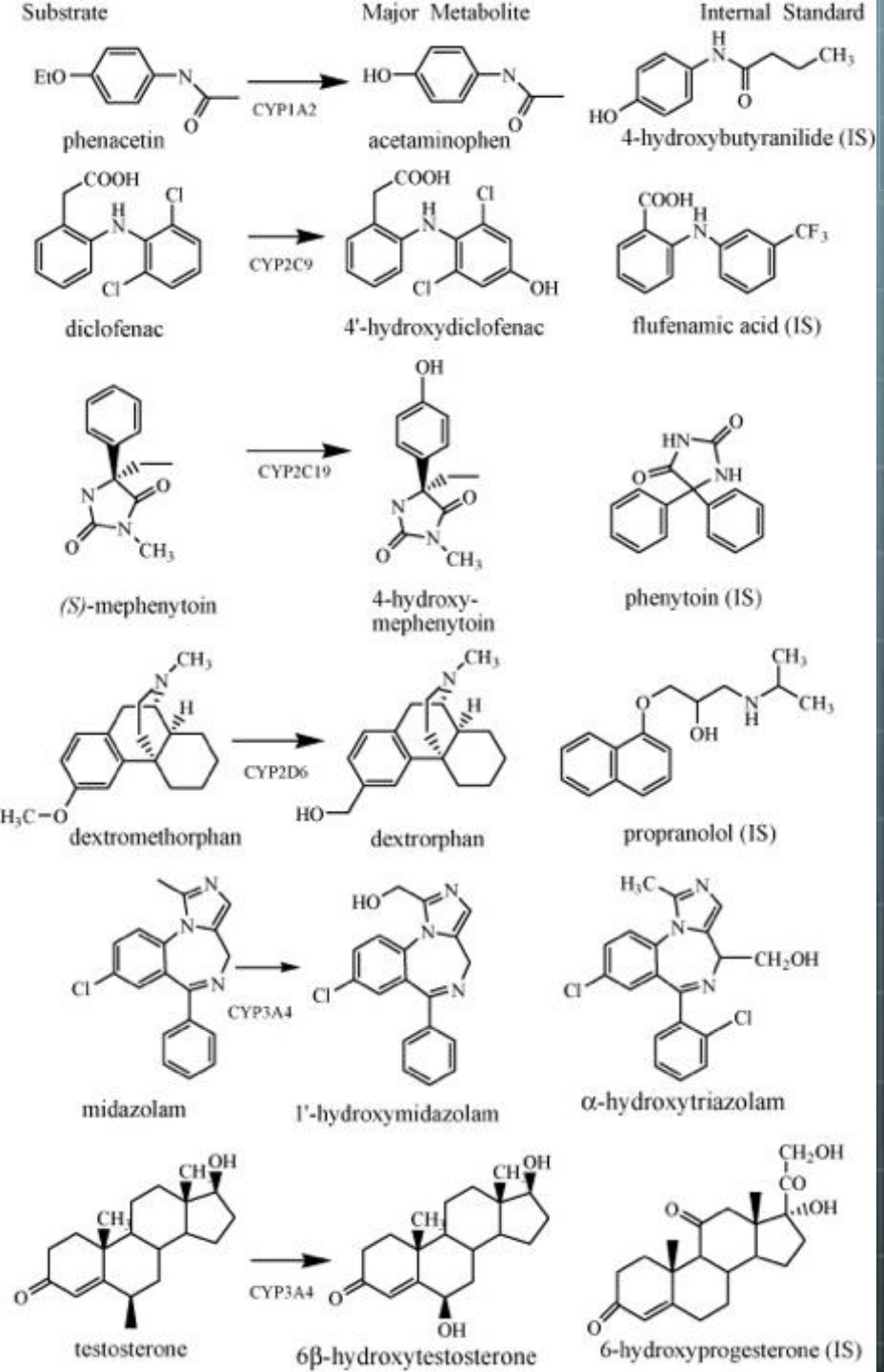


Microtubules (light blue), actin filaments (dark blue), ribosomes (yellow & purple), soluble proteins (light blue), kinesin (red), small molecules (white) and RNA (pink)



Source: Abbott, N. Joan, Adjanie AK Patabendige, et al. "Structure and Function of the Blood–Brain Barrier." *Neurobiology of Disease* 37, no. 1 (2010): 13-25.

5.7 Metabolism & Tox

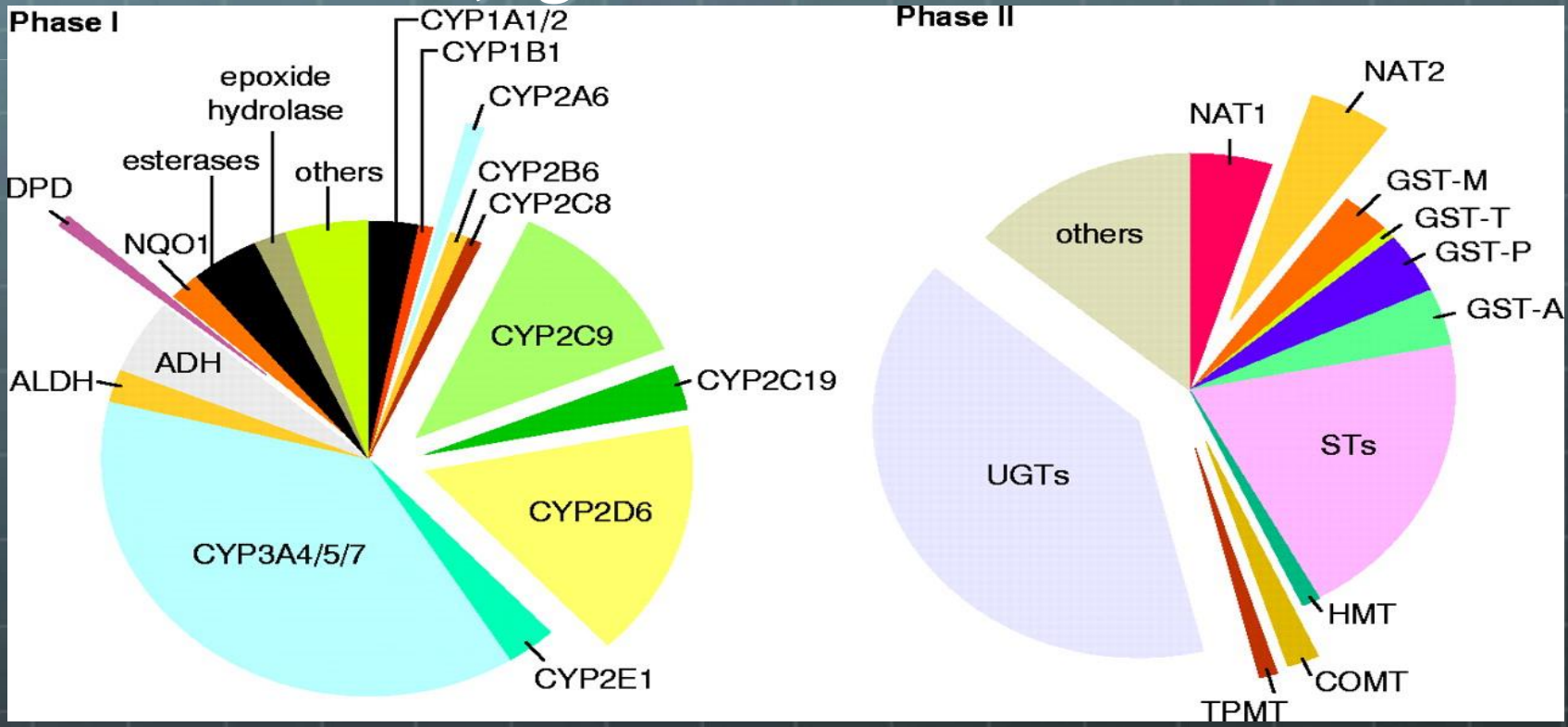


Cytochrome P450 ("CYPs")

- Family of enzymes that oxidize drugs
- CYP inhibition has important effects:
  - Some CYPs metabolize drugs into the bioactive form
  - Some CYPs help to eliminate drugs from the body by metabolizing them
- "Drug – drug interaction: Drug #1 blocks a CYP, which prevents the metabolism of Drug #2, causing Drug #2 to become toxic or fail to work.
- CYPs can also be induced, which can lead to the same issues.

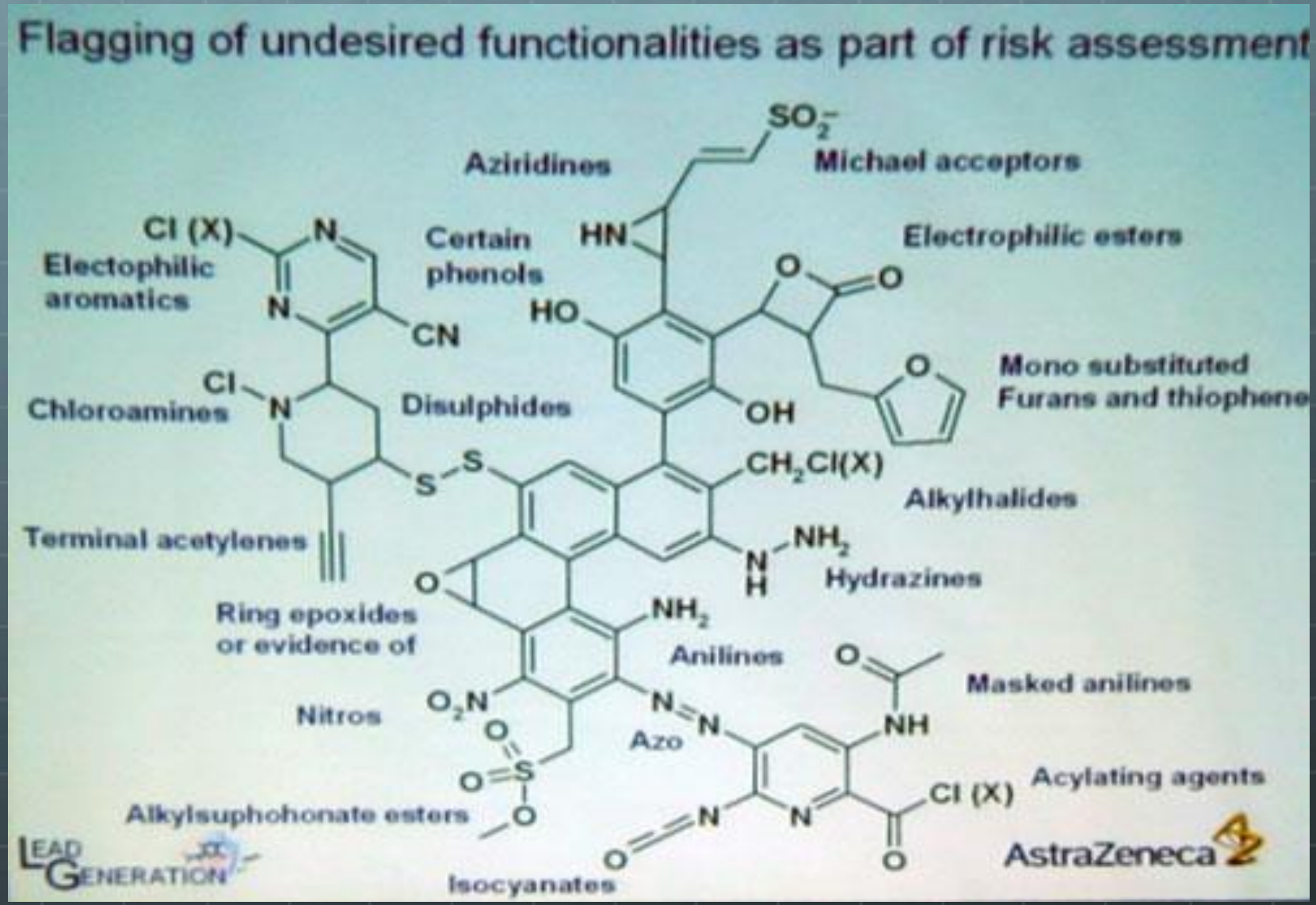
Metabolic Transformations: Many Enzymes

- Phase I: oxidation or hydrolysis
- Phase II: Conjugation



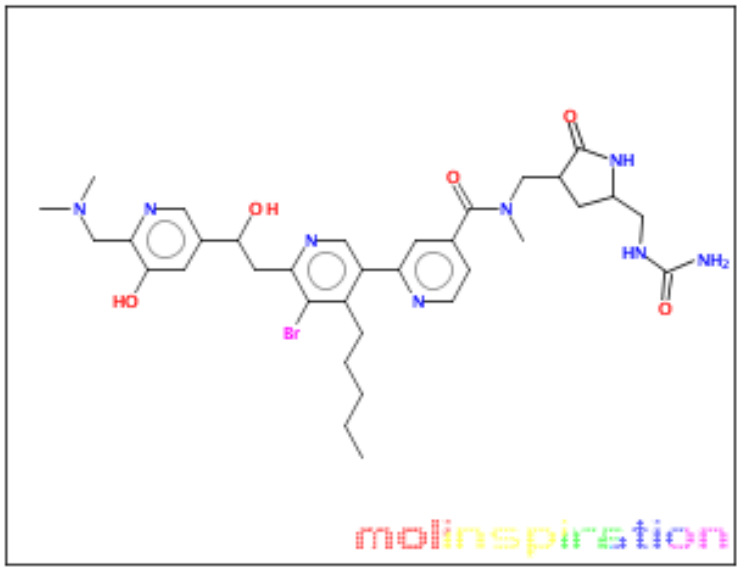
Source: Evans, William E., and Mary V. Relling. "Pharmacogenomics: Translating Functional Genomics into Rational Therapeutics." *Science* 286, no. 5439 (1999): 487-91.

Please, Don't Make This Molecule



5.8 “Drug-Likeness” & “Rules”

“Drug-Like” Compounds: Playing the Odds



Molinspiration property engine v2011.04

miLogP	3.206
TPSA	186.898
natoms	48.0
MW	725.689
nON	13
nOHNH	6
nviolations	3
nrotb	15
volume	624.026

Get data as text (for copy / paste).

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Have We Learned Anything?

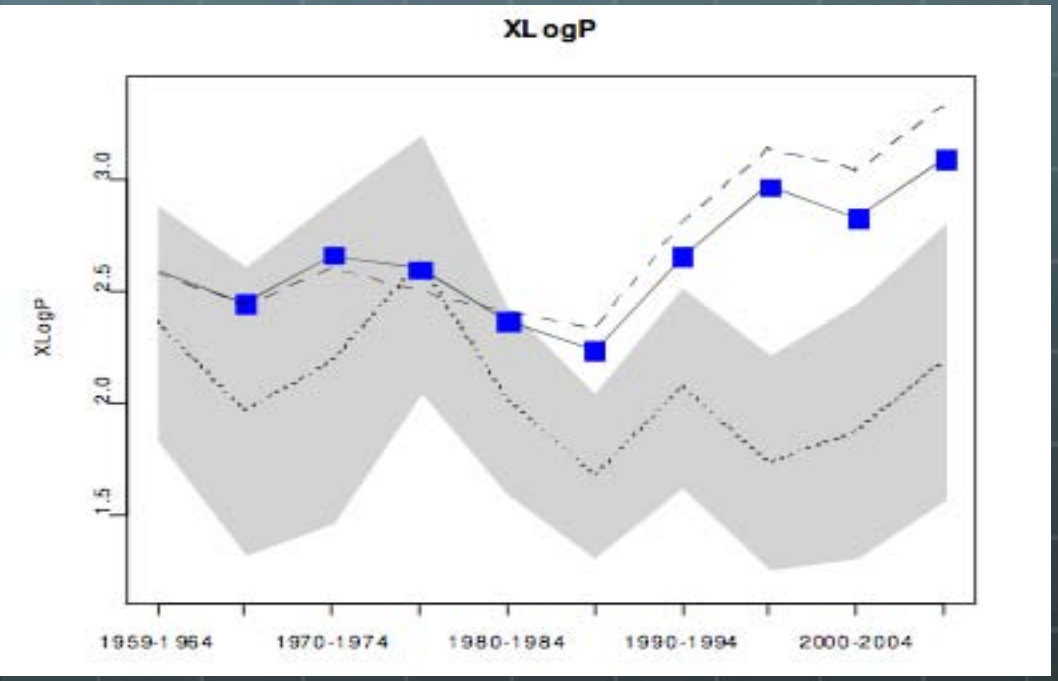
Journal of
Medicinal Chemistry

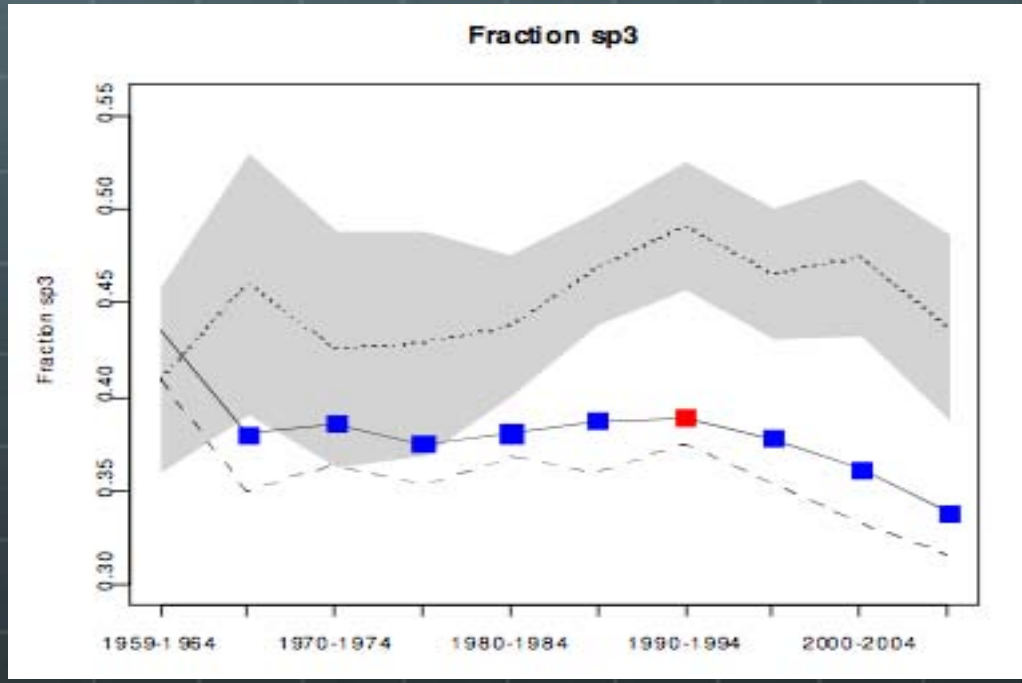
Perspective

What Do Medicinal Chemists Actually Make? A 50-Year Retrospective

W. Patrick Walters, Jeremy Green, Jonathan R. Weiss, and Mark A Murcko

J. Med. Chem., **Just Accepted Manuscript** • Publication Date (Web): 14 July 2011





Source: Walters, W. Patrick, Jeremy Green, et al. "What do Medicinal Chemists Actually Make? A 50-Year Retrospective." *Journal of Medicinal Chemistry* 54, no. 19 (2011): 6405-16.

END OF PART 2

20.201 Mechanisms of Drug Actions

Fall 2013