

# Molecules and Medicine:an overview

The drug concept and history of  
natural products as medicinal  
agents



**St. John's Wort**



**Echinacea**



**Ginkgo Biloba**



**Valerian**

# Folk/Herbal Medicines

Truths and Myths

and

The Art and Science of  
Pharmacognosy

*“O, mickle is the powerful grace that lies  
In plants, herbs, stones and their true qualities;  
For nought so vile that on the earth doth live  
But to the earth some special good doth give,  
Nor aught so good that strained from that fair use  
Revolts from true birth, stumbling on abuse  
Virtue itself turns vice, being misapplied;  
And vice sometime by action dignified  
Within the infant rind of this weak flower  
Poison hath residence and medicine power “  
-Romeo and Juliet ACT 11: SC 111*



*“The Mystery Man got nervous  
and he fidgeted around a bit  
he reached into the pocket of his Mystery Robe  
and whipped out his shaving kit...  
‘With the Oil of Aphrodite and  
The Dust of the Grand Wazoo  
He said you might not believe this little fellow  
But it will cure your asthma, too.’  
And I said... look here brother  
who you jivin’ with that Cosmik Debris?”  
-Frank Zappa, *Cosmik Debris**

# Myth #1

We don't need natural and herbal products since all truly effective medicines have been synthesized by modern organic chemistry in the past 50 years

How are medicines discovered anyway?

# Historical use-Ebers papyrus

c. 1534 B.C.E

- See <http://www.crystalinks.com/egyptmedicine.html>

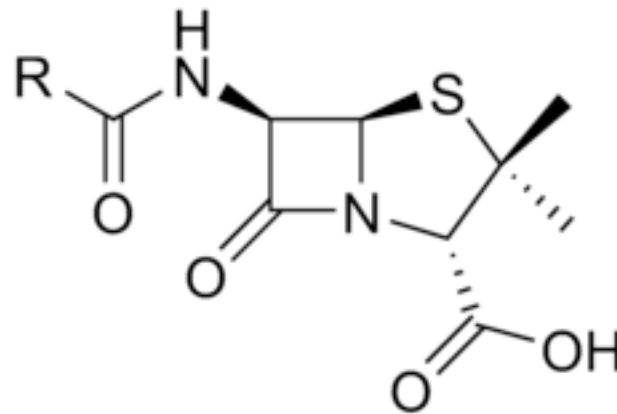
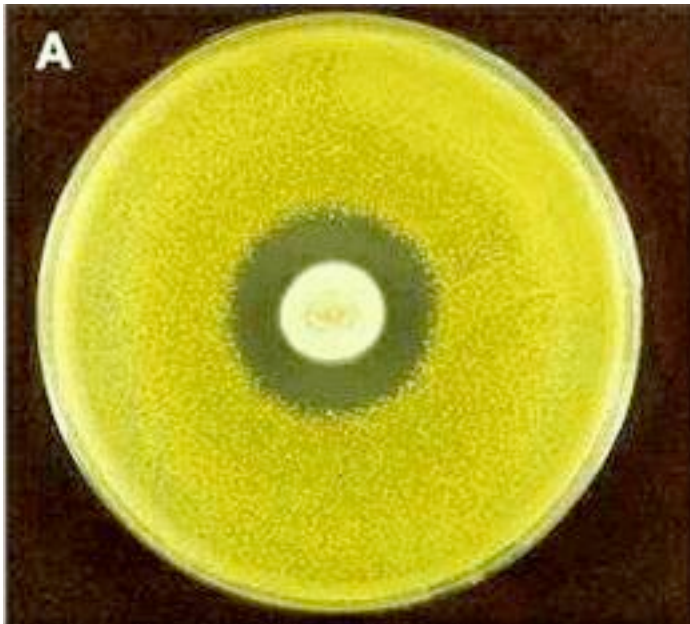


- Acacia (acacia nilotica)- vermifuge, eases diarrhea and internal bleeding, also used to treat skin diseases.
- Aloe vera - worms, relieves headaches, soothes chest pains, burns, ulcers and for skin disease and allergies.
- Basil (ocimum basilicum)- excellent for heart.
- Balsam Apple (malus sylvestris)or Apple of Jerusalem - laxative, skin allergies, soothes headaches, gums and teeth, for asthma, liver stimulant, weak digestion.
- Bayberry(Myrica cerifera) - stops diarrhea, soothes ulcers, shrinks hemorrhoids, repels flies.
- Belladonna - pain reliever;camphor tree - reduces fevers, soothes gums, soothes epilepsy.
- Caraway (Carum carvi; Umbelliferae)- soothes flatulence, digestive, breath freshener.
- Myrtle(Myrtus) leaves for rheumatic and back pain  
**AND MANY MORE**

# Serendipitous discovery-

Penicillin: when bad technique is good?

1928- A. Fleming contaminated plates with *Penicillium*.  
Little therapeutic promise shown until  
1940's Ernst Chain figured out  
purification

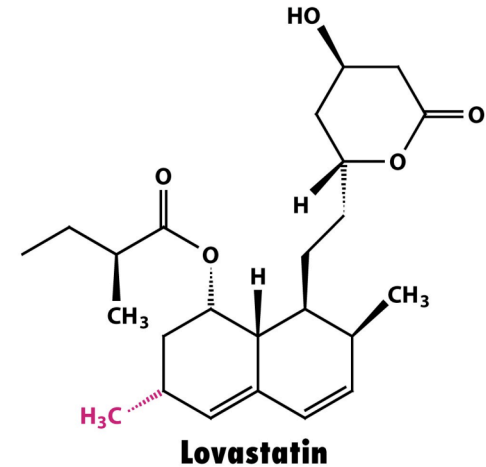
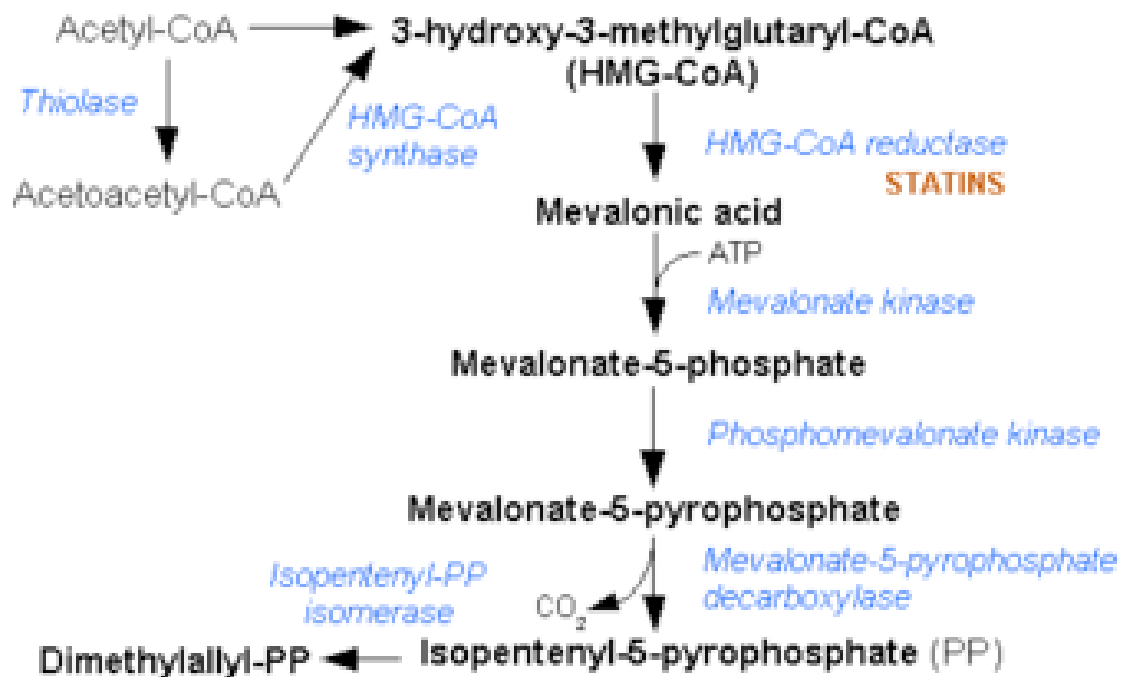




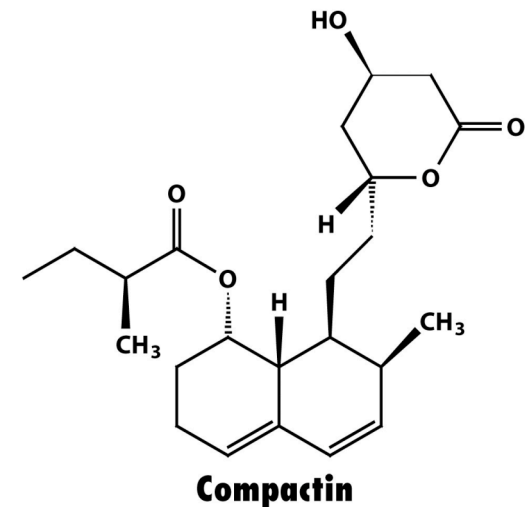
# Bare Knuckles Science!-

**Statins:** fungal natural products- took two years and involved more than 6,000 microbes looking for microbial secreted products that would inhibit the incorporation of carbon-14 acetate into lipids!!

[\\*http://www.world-of-fungi.org/Mostly\\_Medical/Mark\\_Gilson/Mark\\_Gilson.htm](http://www.world-of-fungi.org/Mostly_Medical/Mark_Gilson/Mark_Gilson.htm)



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# Natural Product Medicine Sampler

<b>Medicine</b>	<b>From:</b>
penicillin	mold
streptomycin	bacteria
tetracycline, etc,etc	need I say more
digitoxin	foxglove
atropine, scopolamine	belladonna
morphine	poppy
codeine	poppy
magainin(LOCILEX)	frog
caspofungin	fungus
squalamine	shark
quinine	Cinchona
diosgenin (hormones)	Mexican Yam
taxol, vinblastine	yew, periwinkle

# Natural Product Medicine Facts

- 78% of antibacterials and 74% of anticancer compounds are natural products or derivatives
- 61% (535) new drugs from 1981-2002 were natural products ,derivatives or inspirations
- High-tech combinatorial organic chemistry has produced 0 new drugs between 1981-2002

C&E News October 13, 2003 Volume 81, Number 41

## Myth #2

The “green” myth: If it’s natural, it must be safe. Plants are here to help us.

# Synthetic and *Natural* Substances

**Substance**                      **LD<sub>50</sub> mg/kg\***

Aspirin                              1,500

Caffeine                            130

Arsenic trioxide                15

Sodium Cyanide                15

Rotenone                            3

Strychnine                        1.2

Tabun (nerve gas)              0.6

Tubocurarine                    0.6

Palytoxin(coral)                0.00015

VX (nerve gas)                 0.000075

Ricin                                0.0000003

Botulinum toxin                0.00000003

\* mostly in rats

# Myth #3

It's been used for 2000 years so it  
must be effective

or

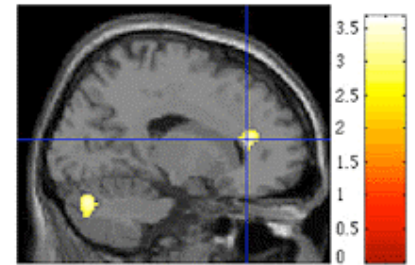
It was used 2000 years ago so it  
must be phony

# Mode of discovery.....

## Doctrine of Signatures

- Ginseng-looks “human”, good for every thing
- Lungwort-pulmonary complaints
- Red plants-blood disorders
- Goldenrod-for jaundice
- Rhino horn-take a guess
- Tiger parts-teeth are protective
- Beijings penis emporium!- increases potency
- Perceived effects may be “placebo” *L. I shall please*

# However, the Placebo effect...is not “nothing”



- “pointing the bone”
- works about 35% of the time (Turner et al. JAMA (1994) 271,1609-14)
- Placebos activate the *same* part of the brain as opiates (Science, Vol 295, Issue 5557, 947 , 8 February 2002)
- Modern placebos like therapeutic “touch”, many vitamins, Zicam, Head-on, Airborne, homeopathy, herbal diet patches, etc. are very popular
- works even better when goal involves:
  - behavioral change (drowsiness, wakefulness)
  - subjective sensation (pain, discomfort; see [this report on aspirin](#) for example)
  - endocrine or autonomic response (blood pressure, asthma, acid stomach)



# Myth #4

If an herbal remedy *really* worked, there would be hundreds of pharmaceutical scientists looking at it

or

Natural remedies can't be proven by "Western" science, and there is a conspiracy to suppress them (by drug companies, doctors, etc..)

# Problems with Herbal Remedies

- Do they work?
  - health claims may not be directly made even where evidence exists (U.S.) w/o FDA new drug approval (or “old” drug status)
- Dose uncertainty
  - What is the minimum/maximum safe and effective dose?
  - How much is in the capsule?
- Purity/Quality
  - parts, individual plants may vary
- Toxicity
  - How much is too much? Are there chronic/mutagenic effects?
  - Effects on liver metabolism
  - Disclaimers may frighten but not inform

# What Can/Should be Done

- Rational Herbal Regulation *a la* Germany, U.K. or Canada
  - Relies on historical use, clinical experience and pharmaceutical research (e.g. German Commission “E” monographs)
  - Requires quality control, labeling (but...new FDA proposal for GMP for herbals, 2003)

**Pharmacognosy and clinical research by pharmaceutical/herbal companies should be encouraged (tax breaks like the Orphan Drug Act?) and by academic institutions. In Germany, drug companies make big \$\$\$ on herbals**

# Modern Drugs and Drug Discovery: the scientific era

# Top Prescription Pharmaceuticals

<b>Top 20 Drugs, Sales in mio \$,</b>		<b>year</b>	<b>2000 / 2004est.</b>
Losec / omeprazole	ion transporter	1988	6,260 / 2,575
Zocor / simvastatin	enzyme	1988	5,280 / 9,653
Lipitor / atorvastatin	enzyme	1997	5,031 / 11,304
Norvasc / amlodipine	ion channel	1990	3,362 / 4,260
Takepron / lansoprazole	ion transporter	1992	3,046 / 4,877
Claritin / loratadine	GPCR	1988	3,011 / 1,900
Procrit / erythropoetin	agonist	1988	2,709 / 2,875
Celebrex / celecoxib	enzyme	1999	2,614 / 3,411
Prozac / fluoxetine	transporter	1986	2,574 / 525
Zyprexa / olanzapine	GPCR	1996	2,350 / 4,445
Seroxat / paroxetine	transporter	1991	2,348 / 3,409
<b>Vioxx / rofecoxib</b>	enzyme	1999	2,160 / 3,800
Zoloft / sertraline	transporter	1990	2,140 / 2,750
Epogen / erythropoetin	agonist	1988	1,963 / 2,155
Glucophage / metformin	unknown		1,892 / 1,400
Premarin / oestrogens	nucl. receptor		1,870 / 2,300
Augmentin / amox.+clav.acid	enzyme		1,847 / 2,603
Pravachol / pravastatin	enzyme	1989	1,817 / 2,581
Vasotec / enalapril	enzyme	1984	1,790 / 575
Cozaar / losartan	GPCR	1994	1,715 / 2,764

Source: Nature Rev. Drug Discov. 1, 176 (2002)

## Development of Drug Research

<b>Time</b>	<b>Materials</b>	<b>Test systems</b>
- ancient time	plants, venoms minerals ...	humans
- 1806	morphine	
- 1850	chemicals	
- 1890	synthetics, dyes	animals
- 1920		animals, isolated organs
- 1970		enzymes, membranes
- 1990	combinatorial libraries	human proteins, HTS
- 2000	focused libraries	uHTS, virtual screening

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## Important Results in Drug Research, 1806-1981

1806	Morphine	Hypnotic agent
1875	Salicylic acid	Antiinflammatory agent
1884	Cocaine	Stimulant, local anesthetic agent
1888	Phenacetin	Analgesic and antipyretic agent
1899	Acetylsalicylic acid	Analgesic and antipyretic agent
1903	Barbiturates	Sedatives
1909	Arsphenamine	Antisymphilitic agent
1921	Procaine	Local anesthetic agent
1922	Insulin	Antidiabetic agent
1928	Estrone	Female sex hormone
1928	Penicillin	Antibiotic agent
1935	Sulphachrysoidine	Bacteriostatic agent
1944	Streptomycin	Antibiotic agent
1945	Chloroquine	Antimalarial agent
1952	Chlorpromazine	Neuroleptic agent
1956	Tolbutamide	Oral antidiabetic agent
1960	Chlordiazepoxide	Tranquillizer
1962	Verapamil	Calcium channel blocker
1963	Propranolol	Antihypertensive agent (beta-blocker)
1964	Furosemide	Diuretic agent
1971	L-Dopa	Anti-Parkinson agent
1975	Nifedipine	Calcium channel blocker
1976	Cimetidine	Anti-ulcus agent (H <sub>2</sub> blocker)
1981	Captopril	Antihypertensive agent (ACE inhibitor)
1981	Ranitidine	Anti-ulcus agent (H <sub>2</sub> blocker)

## Important Results in Drug Research, 1983-2001

1983	Cyclosporin A	Immunosuppressant
1984	Enalapril	Antihypertensive agent (ACE inhibitor)
1985	Mefloquine	Antimalaria agent
1986	Fluoxetine	Antidepressant (5-HT transporter)
1987	Artemisinin	Antimalaria agent
1987	Lovastatin	Cholesterol biosynthesis inhibitor
1988	Omeprazole	Anti-ulcus agent (H/K-ATPase inhibitor)
1990	Ondansetron	Antiemetic agent (5-HT <sub>3</sub> blocker)
1991	Sumatriptan	Anti-migraine agent (5-HT <sub>1</sub> blocker)
1993	Risperidon	Antipsychotic agent (D <sub>2/5</sub> -HT <sub>2</sub> blocker)
1994	Famciclovir	Anti-herpes (DNA polymerase inhibitor)
1995	Losartan	Antihypertensive agent (A II antagonist)
1995	Dorzolamide	Glaucoma (Carbonic anhydrase inhib.)
1996	Meloxicam	Anti-arthritis agent (COX 2 inhibitor)
1996	Nevirapin	HIV reverse transcriptase inhibitor
1996	Indinavir, Ritonavir, Saquinavir	HIV protease inhibitors
1997	Nelfinavir	HIV protease inhibitor
1997	Finasteride	Hair loss
1997	Sibutramine	Adipositas (uptake blocker)
1998	Orlistat	Adipositas (lipase inhibitor)
1998	Sildenafil	Erectile dysfunction (PDE inhibition)
1999	Celecoxib, Rofecoxib	Anti-arthritis agents (COX-2 inhibitors)
1999	Amprenavir	HIV protease inhibitor
1999	Zanamivir, Oseltamivir	Influenza (neuraminidase inhibitors)
2001	Fondaparinux	Thrombosis (synthetic LMWH)
2001	Imatinib	CML (specific abl-TK inhibitor)



# Top Prescription Pharmaceuticals-Natural vs Synthetic

**Table 1.** Top 35 Worldwide Ethical Drug Sales for 2000, 2001, and 2002<sup>a</sup> with Natural Product-Derived Drugs in Blue,<sup>b</sup> Biologically Derived Drugs in Magenta,<sup>c</sup> and Synthetically Derived Drugs in Black<sup>d</sup>

Rank	2000	2001	2002
1	Omeprazole	Atorvastatin	Atorvastatin
2	Atorvastatin	Omeprazole	Simvastatin
3	Simvastatin	Simvastatin	Omeprazole
4	Amlodipine	Lansoprazole	Erythropoietin (J&J)
5	Lansoprazole	Amlodipine	Amlodipine
6	Loratadine	Erythropoietin (J&J)	Lansoprazole
7	Erythropoietin (J&J)	Loratadine	Olanzapine
8	Celecoxib	Celecoxib	Paroxetine
9	Fluoxetine	Olanzapine	Celecoxib
10	Olanzapine	Paroxetine	Sertraline
11	Paroxetine	Sertraline	Interferon $\alpha$ -2b+ribarvarin
12	Sertraline	Metformin/Metformin+Glyburide	Rofecoxib
13	Rofecoxib	Rofecoxib	Salmeterol+Fluticasone propionate
14	Erythropoietin (Amgen)	Erythropoietin (Amgen)	Gabapentin
15	Metformin/Metformin+Glyburide	Pravastatin (BMS)	Pravastatin (BMS)
16	Estrone	Estrone	Erythropoietin (Amgen)
17	Amoxicillin + Clavulanic acid	Amoxicillin + Clavulanic acid	Alendronate Sodium
18	Enalapril	Fluoxetine	Losartan/Losartan+Hydrothiazide
19	Pravastatin (BMS)	Risperidone	Risperidone
20	Insulin	Losartan/Losartan+Hydrothiazide	Venlafaxine
21	Ciprofloxacin	Insulin	Esomeprazole magnesium
22	Losartan/Losartan+Hydrothiazide	Ciprofloxacin	Fexofenadine
23	Pravastatin (Sankyo)	Gabapentin	Clopidogrel bisulfate
24	Risperidone	Alendronate sodium	Insulin
25	Paclitaxel	Leuprolide acetate	Estrone
26	Leuprolide Acetate	Fexofenadine	Loratadine
27	Azithromycin	Venlafaxine	Amoxicillin+Clavulanic acid
28	Interferon $\alpha$ -2b+Ribarvarin	Sildenafil	Sildenafil
29	Sildenafil	Azithromycin	Valsartan
30	Gabapentin	Interferon $\alpha$ -2b+Ribarvarin	Citalopram hydrobromide
31	Fluticasone propionate	Pravastatin (Sankyo)	Leuprolide Acetate
32	Clarithromycin	Filgrastim	Oxycodone HCl
33	Filgrastim	Fluticasone propionate	Azithromycin
34	Cyclosporin	Enoxaparin	Montelukast sodium
35	Lisinopril	Vaccines (Aventis)	Rituximab

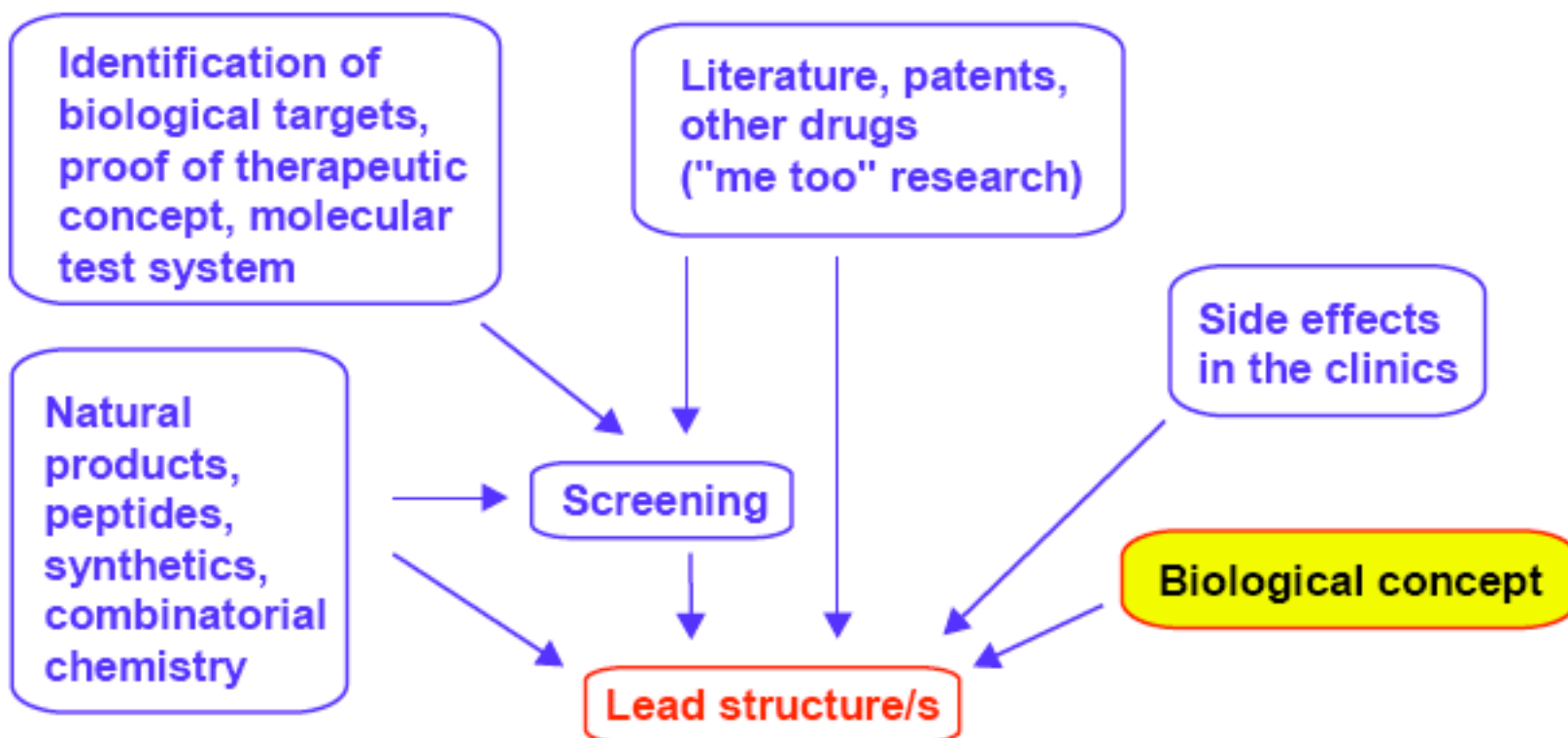
## Lead Structure Search

- Identification of a pathophysiologically relevant molecular target, e.g. an enzyme, receptor, ion channel, or transporter
- Determination of the DNA and protein sequence
- Elucidation of the function and mechanism of the protein
- Proof of the therapeutic concept in animals
- High-throughput molecular test system
- Synthesis program and/or mass screening
- Selection of one or several lead structures

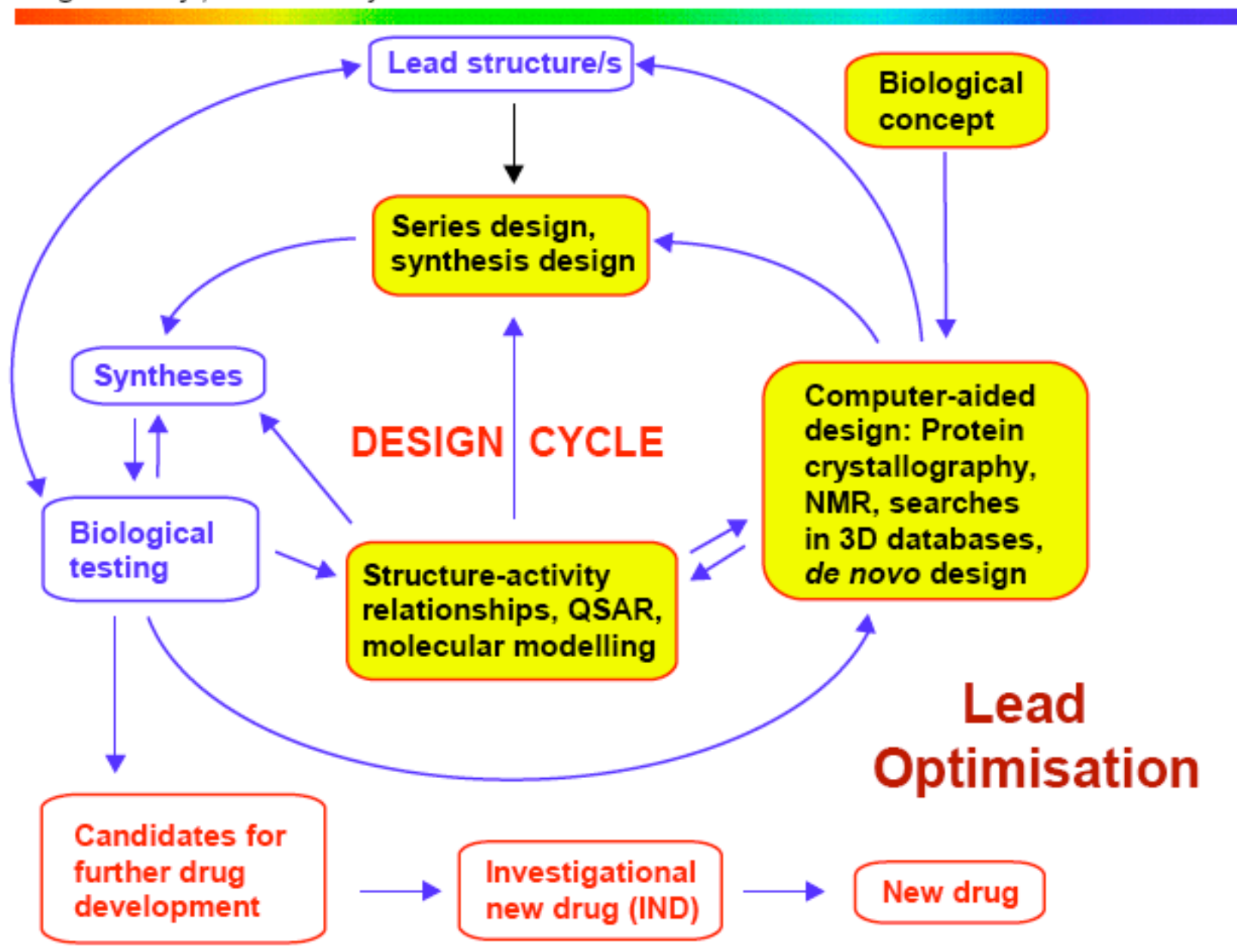
## Lead Optimization and Drug Development

- 3D structure determination of the molecular target and its complexes with low-molecular weight ligands
- Molecular modelling and design of new ligands
- Further syntheses and biological tests of selected candidates
- Optimization of selectivity, bioavailability and pharmacokinetics
- Pharmaceutical formulation
- Preclinical and clinical development
- Drug approval and market introduction

## The Design Cycle: Lead Structure Search



The **design cycle** describes the optimization of a lead structure to one or several development candidates. It is an iterative process with evolutionary character.



# HIV Protease Inhibitors: Structure-based design

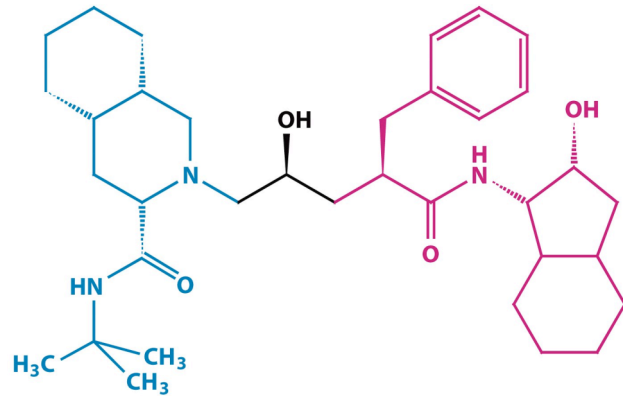


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Blue: improves solubility

Red: inhibitor

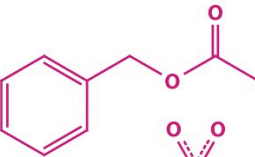


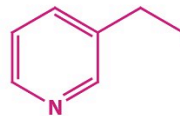
R =	IC <sub>50</sub> (nmol)	log (P)	c <sub>max</sub> (μM)
	0.4	4.67	< 0.1
	0.01	3.70	< 0.1
	0.3	3.69	0.7
	0.6	2.92	11

Figure 35-22  
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## Causes of Death: age 24-44 in US

Advent of protease inhibitors and combination RT inhibitor cocktails

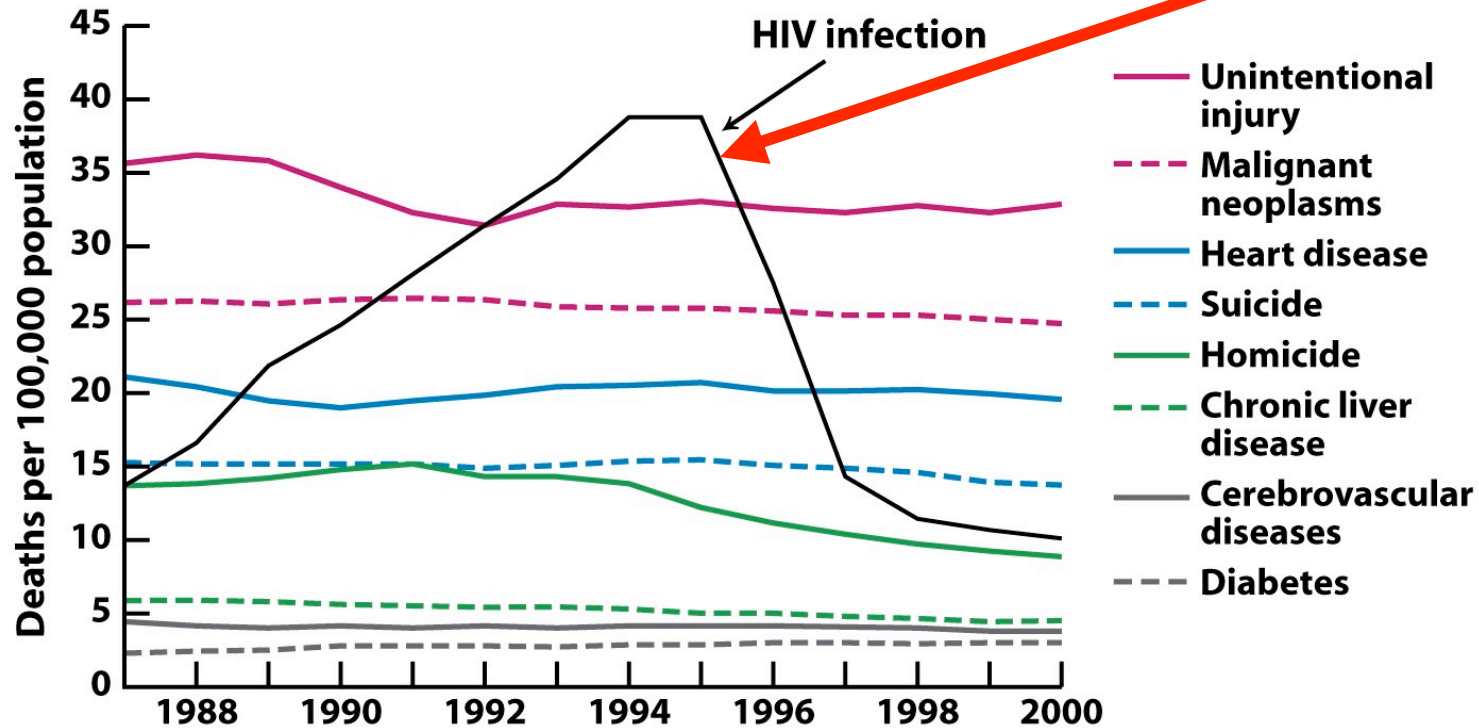


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# The Future: Pharmacogenomics?

$\beta$ 1 adrenergic blocker metoprolol reduces blood pressure *but* only people with most common alleles SR show large reductions. Pre-screening could determine which drug and dose is best.

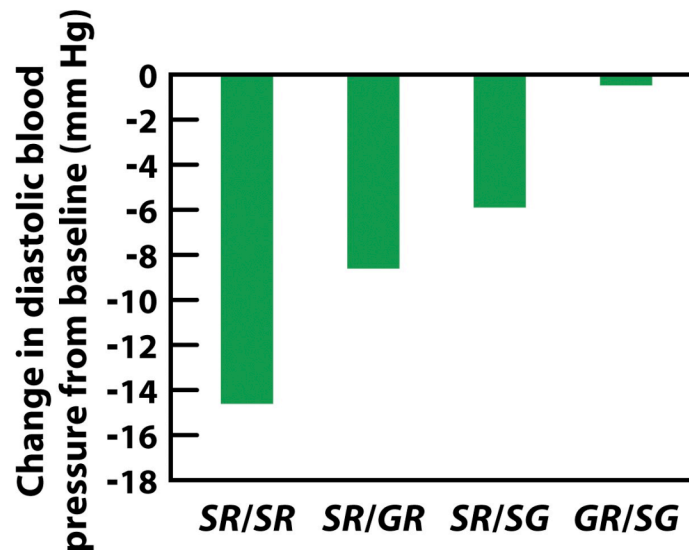
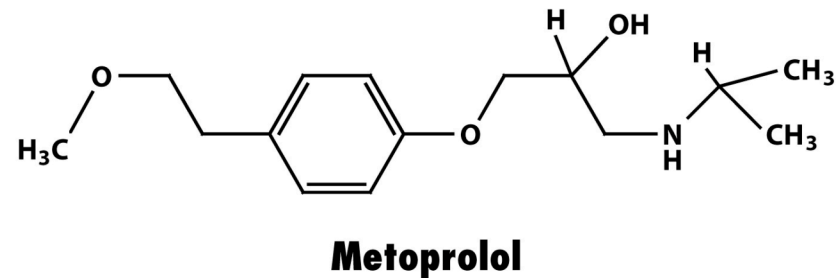


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