Problems in Drug Design

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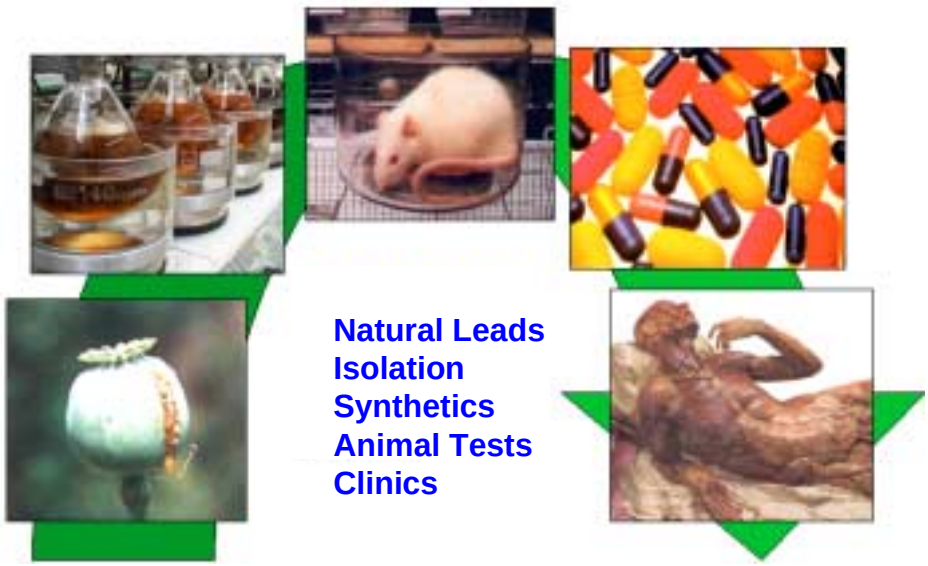
Yesterday's Drug Discovery Process



Natural Leads
Isolation
Synthetics
Animal Tests
Clinics

Technological Changes in Drug Research

Up to the 70s

- Chemistry and hypotheses guide the syntheses
- Bottleneck: Animal experiments, isolated organs

Up to the 90s

- Molecular Modelling
- *In vitro* models (enzyme inhibition, receptor binding)
- Bottleneck: Dedicated syntheses of drugs

Up to the year 2000:

- Gene technology (production of proteins)
- Combinatorial chemistry (mixtures, chemistry-driven)
- Structure-based design of ligands
- High-throughput test models (HTS)
- Bottleneck: ADMET properties

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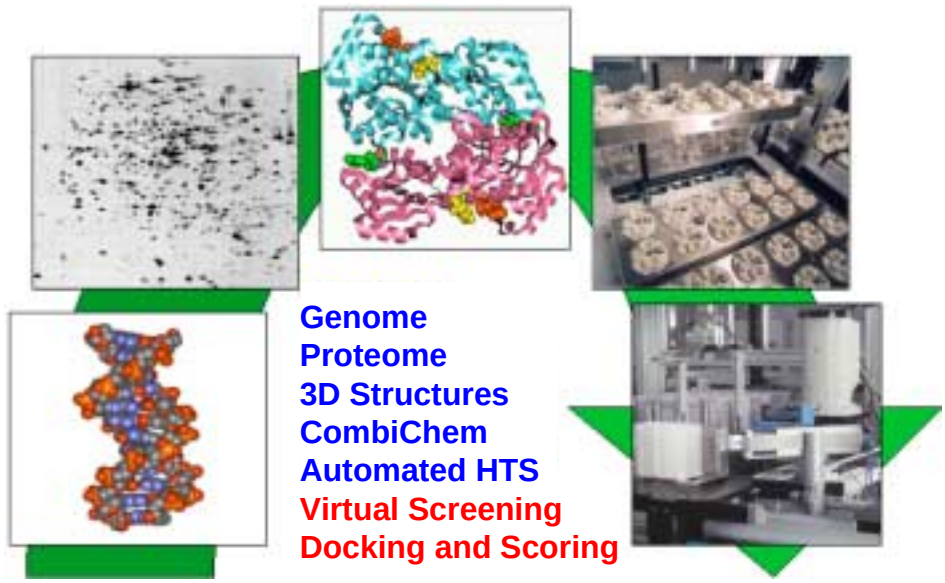
Today's Drug Discovery Process



Genome
Proteome
3D Structures
CombiChem
Automated HTS
Virtual Screening
Docking and Scoring

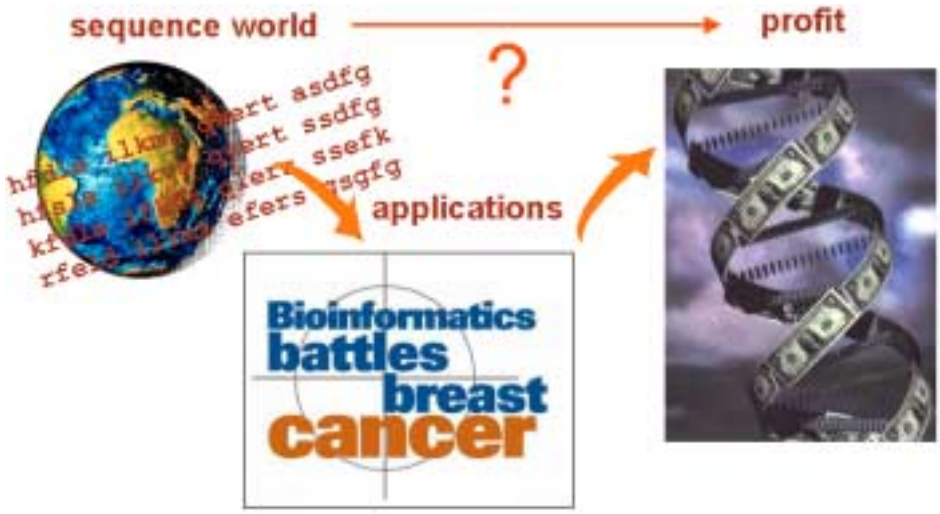
Technological Changes in Drug Research

Today:

- Genomics, proteomics and bioinformatics
- Transgenic animals for proof of concept
- Combinatorial chemistry
  (single compounds, design-driven)
- Structure-based and computer-aided design
  of ligands
- Ultra-high-throughput test models (u-HTS)
- Data mining
- Virtual screening
- ADMET profiles (HTS and *in silico*)

Bottleneck: Target validation, "drugable" targets

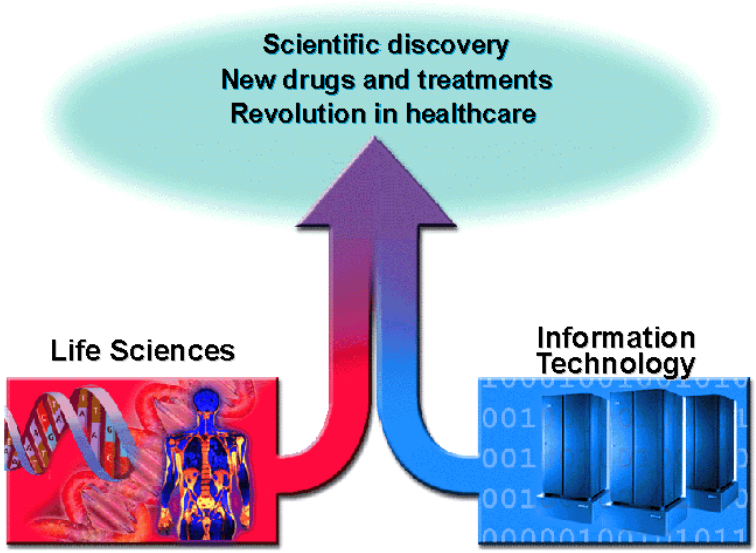
Bioinformatics: The Promise



Modern Drug Discovery, 3(1), 28-34 (2000).

Drug Design Made Simple

© IBM DiscoveryLink™



The New Technologies

Do we already live in Castalia, the land of Hermann Hesse's novel „The Glass Bead Game", where the Magister Ludi (sic!) organizes and plays the most wonderful, brilliant, exciting and elaborate game ... without any practical relevance?

D. F. Horrobin, Modern biomedical research: an internally self-consistent universe with little contact with medical reality, Nature Rev. Drug Discov. 2, 151-154 (2003).

New Technologies: Open Questions

Is there a „druggable genome“ ?

Is a target focus always best ?

Is poor ADME the main problem ?

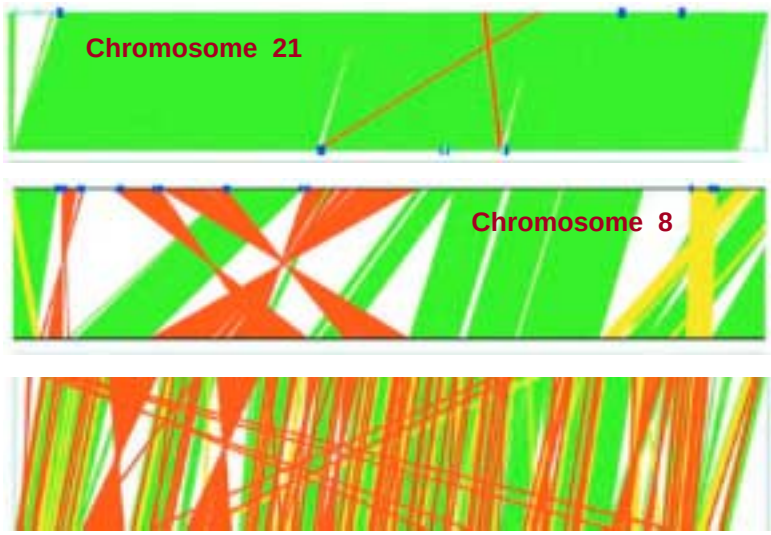
Are we using the right virtual screening techniques?

What are the problems in virtual screening ?

What‘s wrong and could we do better?

H. Kubinyi, Drug Research: Myths, Hype and Reality, Nature Rev. Drug Discov. 2 (8), 665-668 (2003)

Errors in the Humane Genome, April 2001



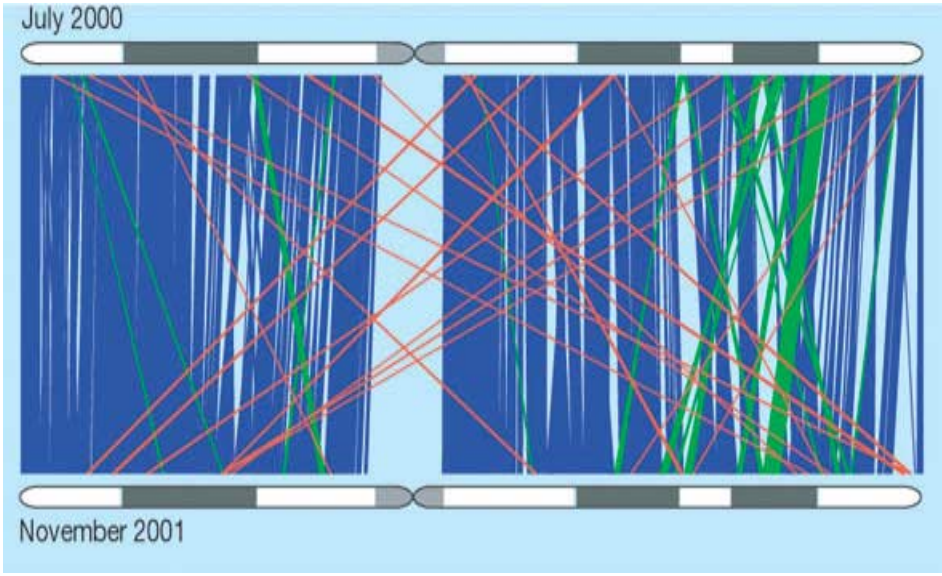
green: o.k.

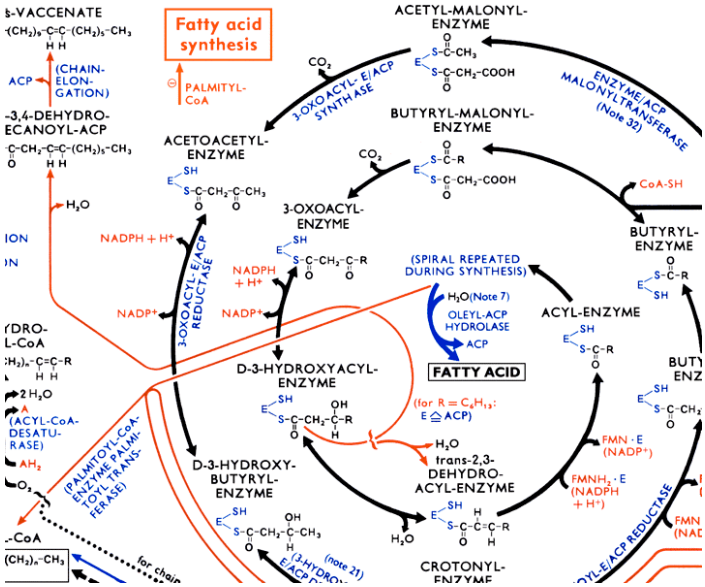
yellow: out of order

red: wrong direction

a 1 Mb section of Chromosome 8

Revised Sequence of Chromosome 20





Fatty Acid Biosynthesis Pathway

Source: „Biochemical Pathways“

(one of 120 segments)

biochem.boehringer-mannheim.com/prodinfo_fst.htm?/techserv/metmap.htm

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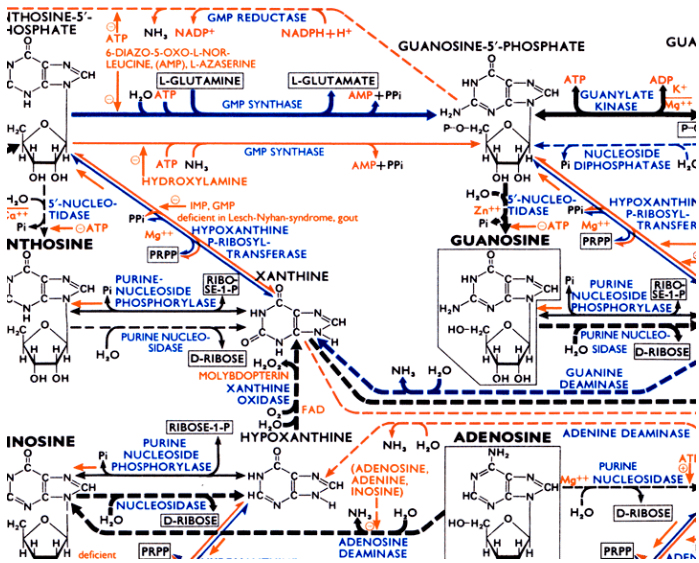

DNA- and RNA Base Biosynthesis

Source: „Biochemical Pathways“

(one of 120 segments)

biochem.boehringer-mannheim.com/prodinfo_fst.htm?/techserv/metmap.htm

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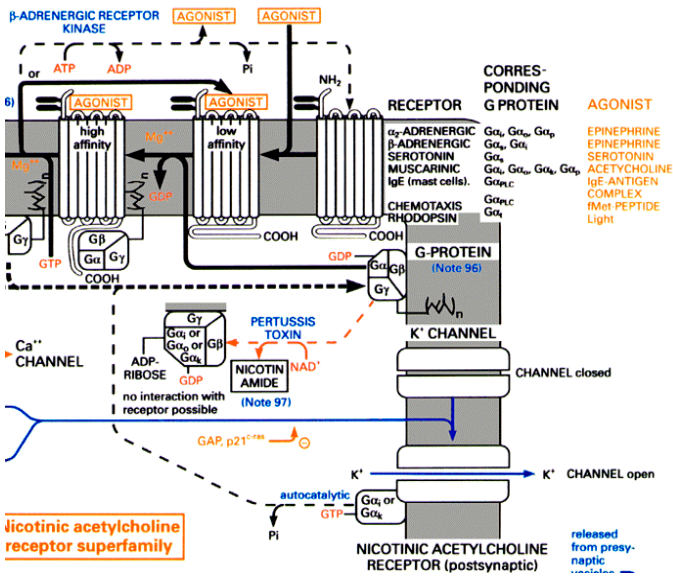
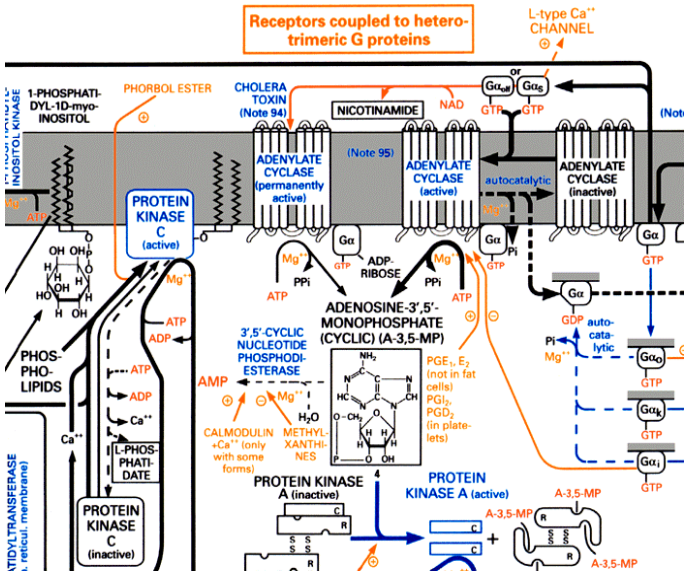


GPCRs and Ion Channels

Source: „Cellular and Molecular Processes“

(one of 100 segments)

biochem.boehringer-mannheim.com/prodinfo_fst.htm?/techserv/metmap.htm



Adenylate cyclase and Protein Kinase C

Source: „Cellular and Molecular Processes“

(one of 100 segments)

biochem.boehringer-mannheim.com/prodinfo_fst.htm?/techserv/metmap.htm

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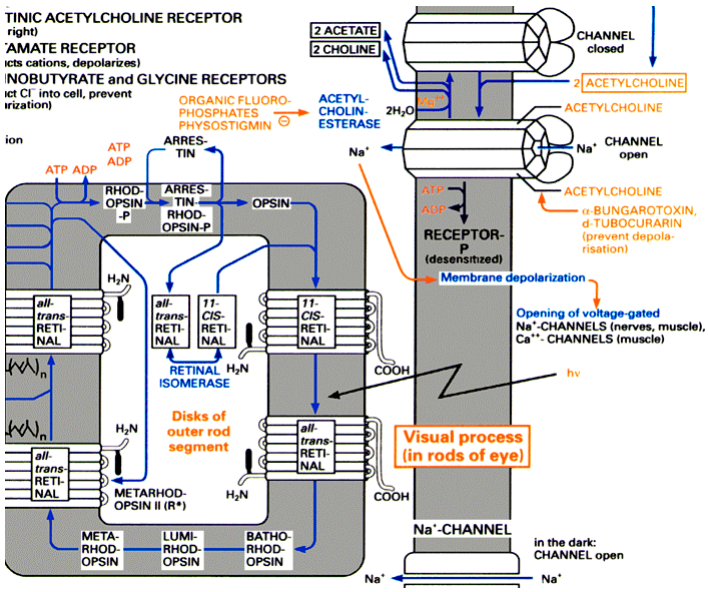


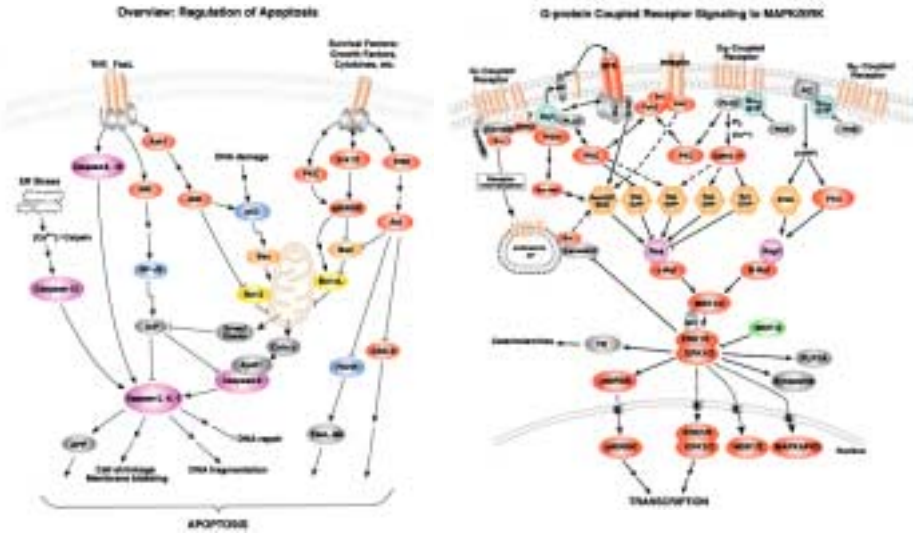
nACh Receptor and Visual Process

Source: „Cellular and Molecular Processes“

(one of 100 segments)

biochem.boehringer-mannheim.com/prodinfo_fst.htm?/techserv/metmap.htm

Signalling by Protein-Protein Interaction



www.cellsignal.com

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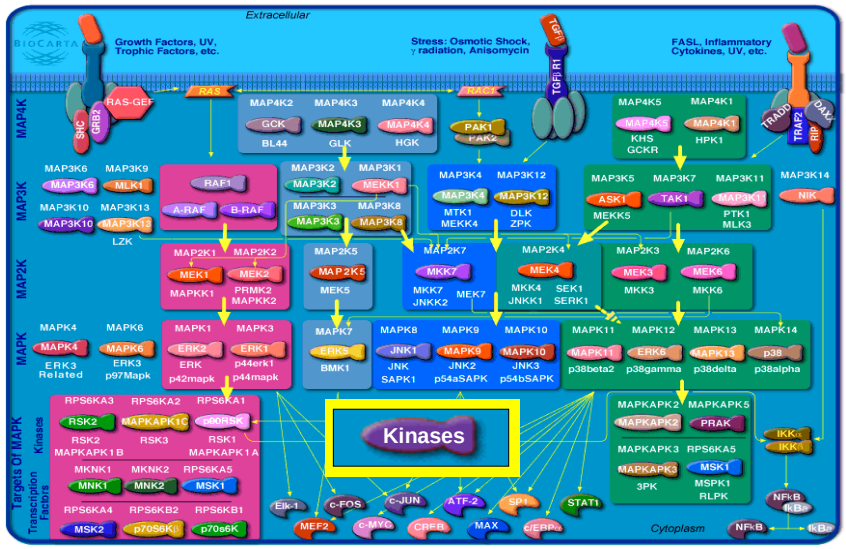
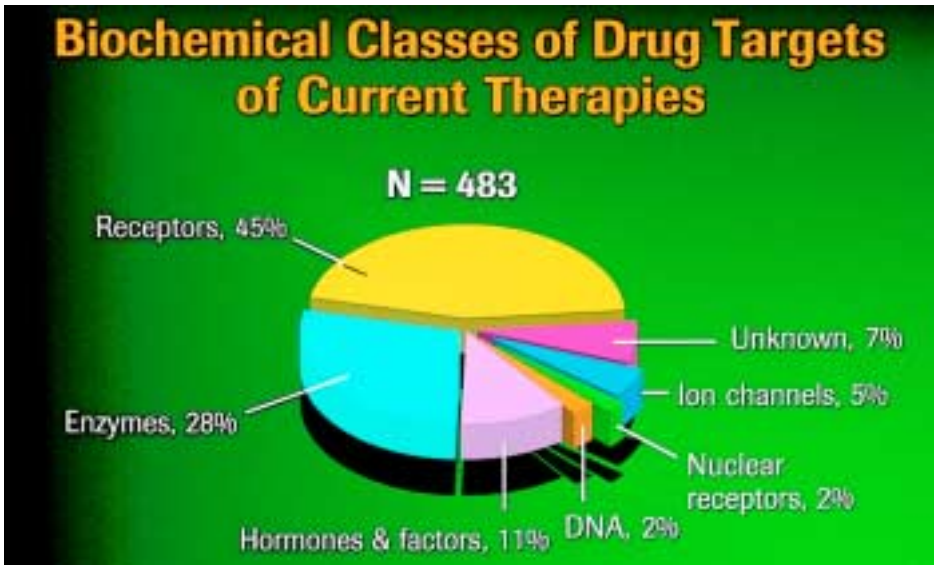
MAP Kinase Pathways



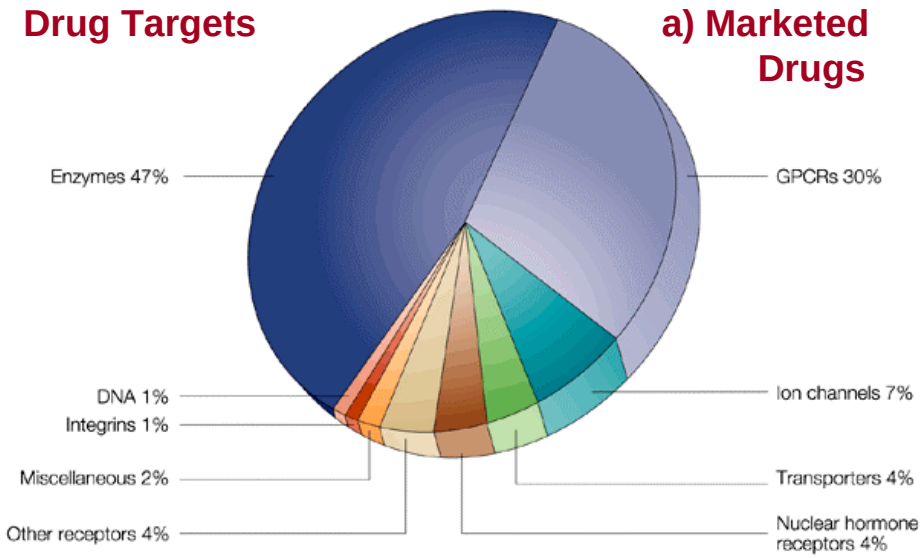
www.biocarta.com/pathfiles/h_mapkPathway.asp



© J. Drews, Science 287, 1960-1964 (2000)

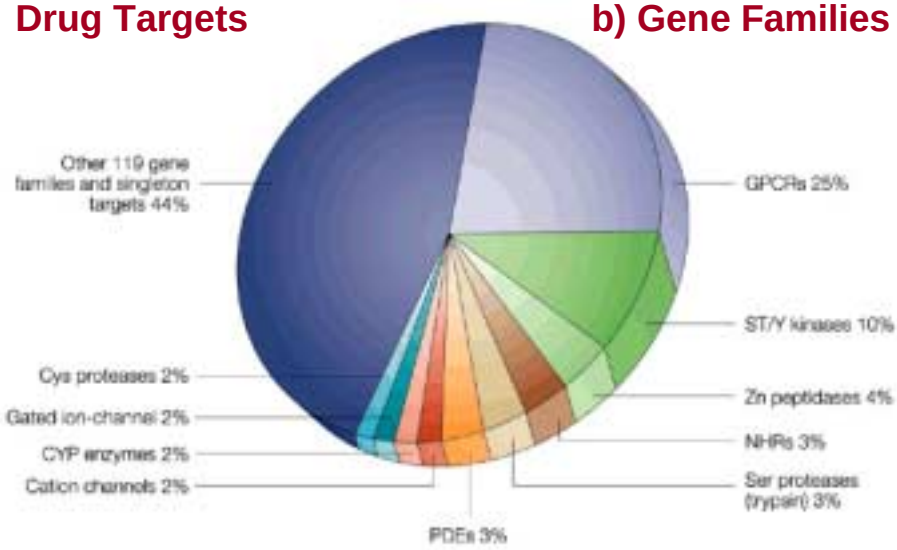
Drug Targets

a) Marketed Drugs



A. L. Hopkins and C. R. Groom, Nature Rev. Drug Discov. 1, 727-730 (2002); © Nature Reviews Drug Discovery

Drug Targets b) Gene Families



A. L. Hopkins and C. R. Groom, Nature Rev. Drug Discov. 1, 727-730 (2002); © Nature Reviews Drug Discovery

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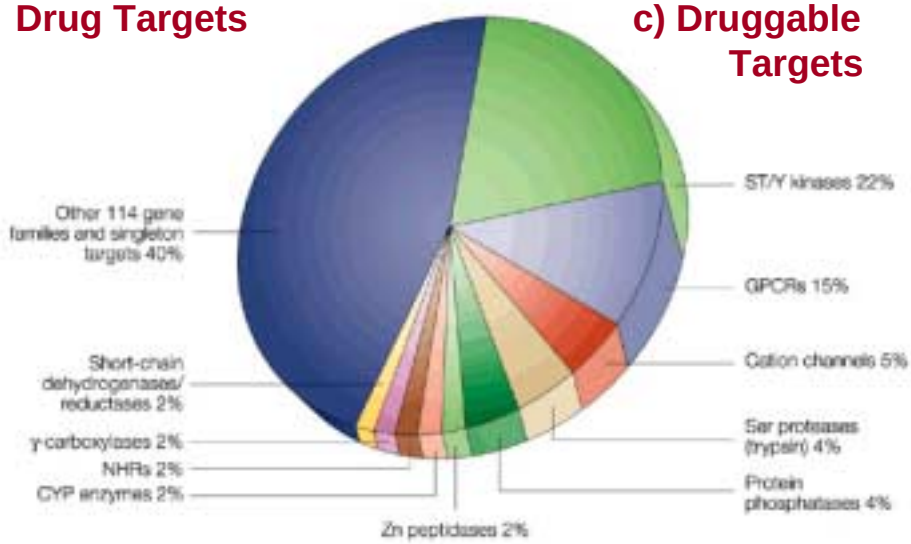
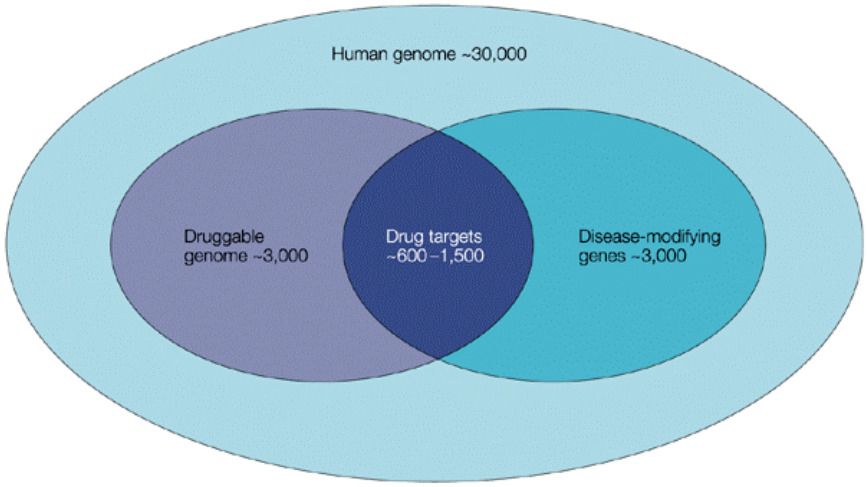
Drug Targets c) Druggable Targets



A. L. Hopkins and C. R. Groom, Nature Rev. Drug Discov. 1, 727-730 (2002); © Nature Reviews Drug Discovery

Genome, Druggable Genome and Drug Targets



A. L. Hopkins and C. R. Groom, Nature Rev. Drug Discov. 1, 727-730 (2002); © Nature Reviews Drug Discovery

Estimation on Druggable Targets

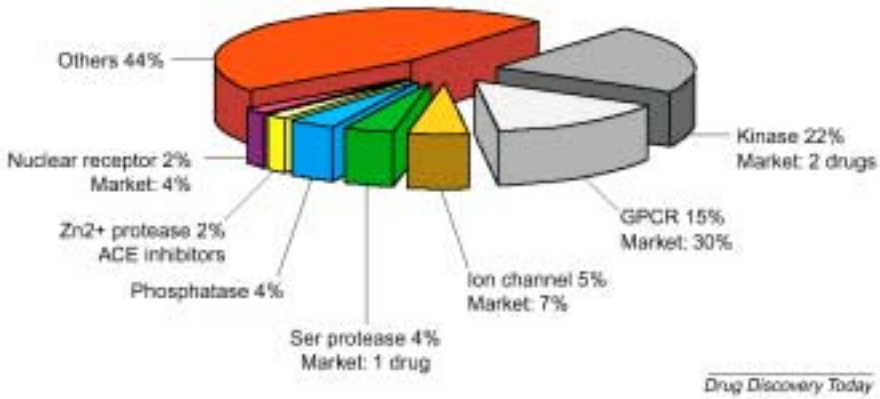


Figure 2. Schematic presentation of the target family distribution within the human 'druggable genome'. If drugs that target members of the given families are on the market, the percentage of their market share, or number of released drugs, is given explicitly.

G. Müller, Drug Discov. today 8, 681-691 (2003)

Is there really a „druggable genome“ ?

Alternative splicing and posttranslational modification generate a multitude of proteins

→ **the „druggable proteome“ ?**

Protein complexes (nAChR, GABA-R, integrins, hetero-dimeric GPCRs, cross-talking)

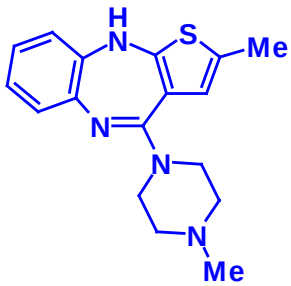
→ **the „druggable targetome“ ?**

Balanced activity against a series of targets

→ **the „druggable physiome“**

H. Kubinyi, Drug Research: Myths, Hype and Reality, Nature Rev. Drug Discov. 2 (8), 665-668 (2003)

Is Target Focus the Best Strategy?



Olanzapine, a clozapine-like „atypical“ neuroleptic with a promiscuous binding pattern

a) F. P. Bymaster et al., Neuropsychopharmacology 14, 87-96 (1996)
b) F. P. Bymaster et al., Schizophrenia Research 37, 107-122 (1999)

	a)	b)
K_i 5-HT$_{2A}$ =	4 nM	2.5 nM
K_i 5-HT$_{2B}$ =		12 nM
K_i 5-HT$_{2C}$ =	11 nM	2.5 nM
K_i 5-HT$_3$ =	57 nM	
K_i dop D$_1$ =	31 nM	119 nM
K_i dop D$_2$ =	11 nM	
K_i dop D$_4$ =	27 nM	
K_i musc M$_1$ =	1.9 nM	2.5 nM
K_i musc M$_2$ =	18 nM	
K_i musc M$_3$ =	25 nM	13 nM
K_i musc M$_4$ =	13 nM	10 nM
K_i musc M$_5$ =		6 nM
K_i adr α_1 =	19 nM	
K_i adr α_2 =	230 nM	
K_i hist H$_1$ =	7 nM	

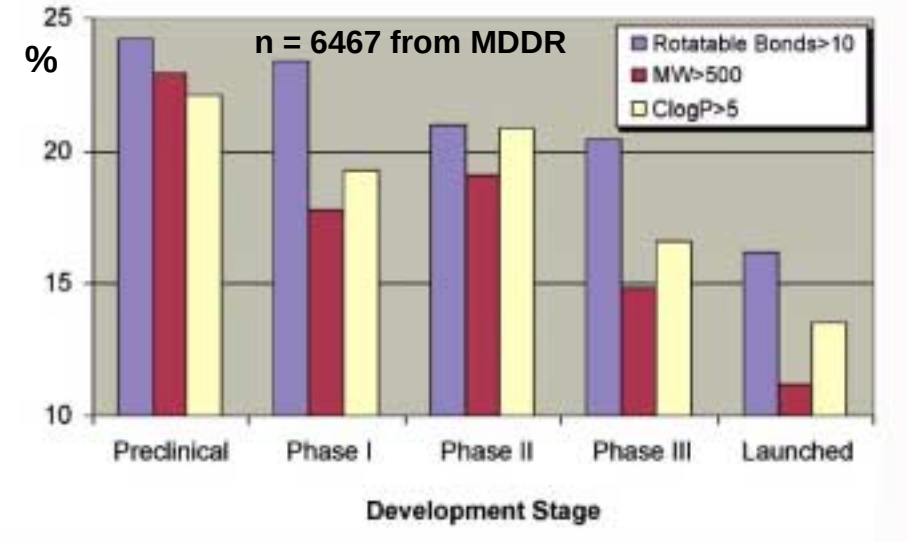
The New Pharma Strategy: Fail early ?

Percentage of medicines dropped at different stages of development

Year	Pre-clin	Phase I	Phase II	Phase III	Registration
1997	70	7.2	15	5.4	1.7
1998	66	9.4	15	6.2	2.4
1999	56	10.0	19	9.4	4.3
2000	61	9.1	17	8.3	3.1
2001	53	11.0	27	5.0	3.4

Source: SCRIP Magazine, February 2002, page 72 (data from Pharmaprojects)

Properties of Development Candidates and Drugs



J. F. Blake, BioTechniques 34, S16-S20 (June 2003)

Success in Drug Research

➔ A compound	hundred thousands
is no hit	thousands
➔ is no lead	dozens
optimization:	thousands
is no candidate	some
is no drug	1

Costs of Drug Research

A compound	1,000
is no hit	100,000
is no lead	10 millions
is no candidate	100-200 millions
is no drug	1 - 2 billions US-$

Pharma Sales and Earnings, 1999-2002

Company	Sales in bill$				Earnings in bill$			
Year	2002	2001	2000	1999	2002	2001	2000	1999
Merck	51.8	47.7	40.4	32.7	7.2	7.3	6.8	5.9
Johnson & Johnson	36.3	33.0	29.1	27.5	6.8	5.9	4.8	4.2
Pfizer	32,4	32.3	29.6	16.2	9.9	8.4	6.5	3.2
GlaxoSmithKline	31.9	30.8	27.2	25.2	7.0	6.6	5.6	4.8
Novartis	20.8	20.3	23.0	20.9	4.7	4.5	4.6	4.3
Aventis	19.5	21.7	21.1	11.9	2.1	1.5	0.0	-0.8
Hoffmann-La Roche	19.1	18.7	18.4	17.7	-2.6	2.4	5.6	3.7
Bristol-Myers Squibb	18.1	18.0	17.5	16.5	2.0	2.0	3.8	3.4
Astra Zeneca	17.8	16.2	17.9	18.3	2.8	2.9	2.3	1.3
Abbott Laboratories	17.7	16.3	13.7	13.2	3.2	2.9	2.8	2.4
Wyeth	14.6	14.1	13.3	13.6	3.0	2.9	2.5	2.2
Pharmacia	14.0	13.8	18.1	7.3	2.0	1.9	1.9	0.8
Eli Lilly	11.1	11.5	10.9	10.0	2.8	2.8	2.9	2.5
Schering-Plough	10.2	9.8	9.8	9.2	2.1	2.3	2.4	2.1

Source: C&EN, July 07, 2003, pp. 26-45

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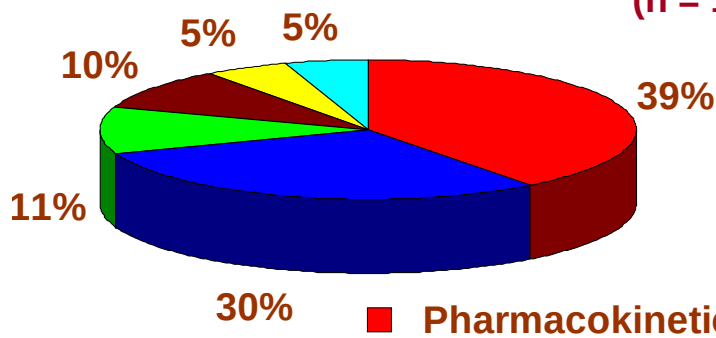
Top 20 Drugs, Sales in mio $,

		year	2000	/ 2004est.
Losec / omeprazole	ion channel	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 channel	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	GPCR	1986	2,574	525
Zyprexa / olanzapine	GPCR	1996	2,350	4,445
Seroxat / paroxetine	GPCR	1991	2,348	3,409
Vioxx / rofecoxib	enzyme	1999	2,160	3,800
Zoloft / sertraline	GPCR	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)

Reasons for Failure in Drug Development (n = 198)



R. A. Prentis et al., Br. J. Clin. Pharmacol. 25, 387-396 (1988); T. Kennedy, Drug Discov. today 2, 436-444 (1997)

- Pharmacokinetics
- Lack of efficacy
- Animal toxicity
- Adverse effects in man
- Commercial reasons
- Miscellaneous

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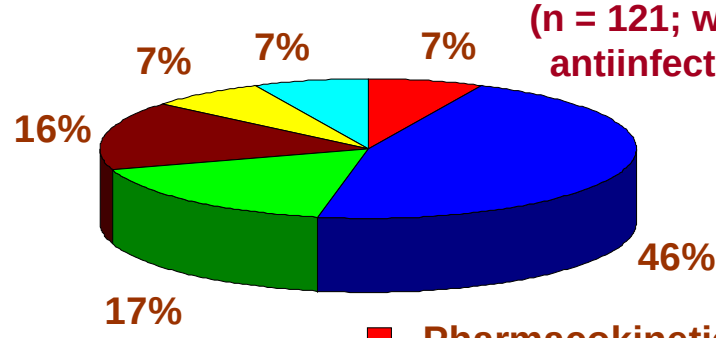
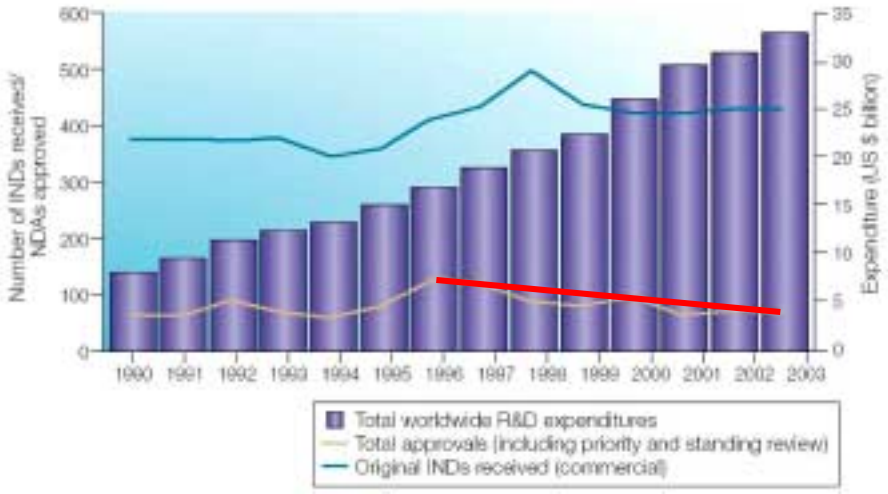
Reasons for Failure in Drug Development (n = 121; without antiinfectives)



R. A. Prentis et al., Br. J. Clin. Pharmacol. 25, 387-396 (1988); T. Kennedy, Drug Discov. today 2, 436-444 (1997)

- Pharmacokinetics
- Lack of efficacy
- Animal toxicity
- Adverse effects in man
- Commercial reasons
- Miscellaneous

The Productivity Gap in Pharmaceutical Industry



T.T. Ashburn and K.B. Thor, Nature Rev. Drug Discov. 3, 673-683 (2004)

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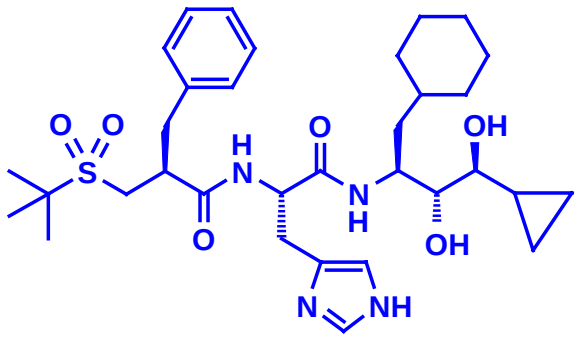
Gene Technology in Drug Research

- **Identification of a therapeutically relevant protein: Identification of a gene and determination of its sequence yield the protein sequence. Elucidation of its function and 3D-structure prediction**
- **Proof of therapeutic concept: Introduction, amplification or knock-out of the gene in animals**
- **Development of a molecular test system: Screening with human protein, reduction of animal experiments**
- **Production of the protein: finally leads to the three-dimensional structure and to structure-based design.**

Species Specificity of a Renin Inhibitor



Remikiren

IC_{50} =

0.8 nM (human)

1.0-1.7 nM (monkeys)

107 nM (dog)

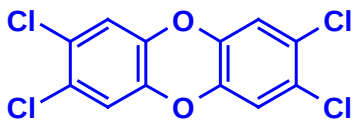
3 600 nM (rat)

Alle Dinge ſind Gift
und nichts ohn Gift;
allein die Doſis macht,
daß ein Ding kein Gift iſt.

„All things are poison and nothing without poison; only the dose determines, whether a thing be no poison“

Salt, Fat, Alcohol ...
Aspirin, Corticoids ...
Phenacetin, Phenphen, Cerivastatin ...

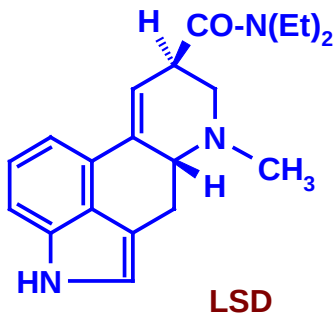
Acute Toxicity of Tetrachlorodibenzodioxin



2,3,7,8-Tetrachloro-dibenzodioxin

Species	LD_{50} in µg/kg
Mouse	114-280
Rat	22-320
Hamster	1,150-5,000
Guinea Pig	0.5-2.5
Mink	4
Rabbit	115-275
Dog	> 100 < 3,000
Monkey	< 70
Man	??

Acute Toxicity of Lysergic Acid Diethylamide in Animals and Maximum Tolerated Dose in Man



LSD

Species	LD_{50} in mg/kg
Mouse	50-60
Rat	16.5
Rabbit	0.3
Elephant	« 0.06
Man	» 0.003

Prediction is very difficult, especially about the future (Niels Bohr, also attributed to Mark Twain)

"Everything that can be invented has been invented."
Charles H. Duell, U.S. Office of Patents, 1899.

"I think there is a world market for maybe five computers." Thomas Watson, Chairman IBM, 1943

"Computers in the future may weigh no more than 1.5 tons." Popular Mechanics, forecasting the relentless march of science, 1949

"There is no reason anyone would want a computer in their home." Ken Olson, President, Chairman and Founder of Digital Equipment Corp., 1977

"640 k ought to be enough for anybody."
Bill Gates, Founder of Microsoft, 1981

Important Mispredictions in Drug Therapy

There is no market for cyclosporin, because there are too few organ transplants.

The breakthrough in transplantation medicine was enabled by cyclosporin.

There is no market for Cimetidin. Gastric and duodenal ulcera can be treated conventionelly (by surgery!)

In 1983, six years after its market introduction, cimetidin had yearly sales of one billion US-$.

Omeprazole will „dry out“ the stomach, because of its complete blockade of gastric acid production.

Omeprazole developed to the most successful drug of all time (more than six billions US-$/year).

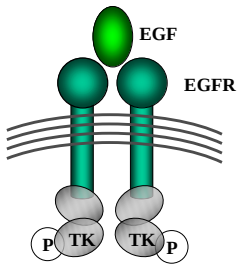
Hugo Kubinyi, www.kubinyi.de

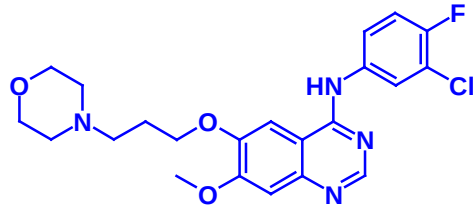
The Future: Pharmacogenomics - New Opportunities from Personalized Medicine

Genotyping of drug targets and metabolic enzymes enables

- **cost savings in drug development through better design of clinical trials**
- **selection of the „best drug“ for a certain patient**
- **individual dose ranges (variance in target sensitivity, reduced or increased metabolism)**
- **fewer toxic side effects**
- **fewer unexpected drug-drug interactions**

Gefitinib®, Iressa, ZD1839 (EGFR TK inhibitor)





cell proliferation ⇧
apoptosis ⇩
angiogenesis ⇧
metastasis ⇧

third-line therapy for non-small-cell lung cancer (75% of lung cancer cases)

clinical response to Iressa ~ 10%

J. G. Paez et al.
EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy
Science 304 (5676), 1497-1500 (2004)

T. J. Lynch et al.
Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non-Small-Cell Lung Cancer and Gefitinib
New Engl. J. Med. 350, 2129-2139 (2004)

8 out of 9 Iressa-responsive patients showed mutations in the kinase domain
0 out of 7 non-responsive patients showed mutations
2 out of 25 non-treated patients showed mutations (8%)

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