Changing Paradigms in Drug Discovery

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Nauta Award Lecture
XXth ISMC, Vienna, August 31, 2008

Pheromone of the Silk Moth

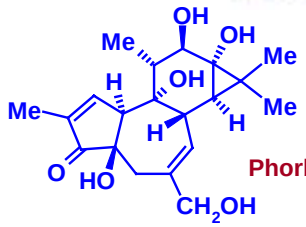
PhD Thesis on Tumor Promotors (1962-1965)

MPI of Biochemistry, Munich

Adolf Butenandt
1903-1995
(Nobel prize 1939)

Erich Hecker
(later Director
at the DKFZ)

Croton tiglium



Phorbol

KNOLL AG

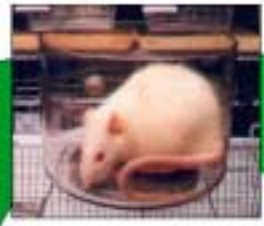
Squill (Scilla alba,
Urginea maritima)

Changing Paradigms in Cardiac Therapy

1967-1978

Proscillaridin-4'-methyl ether
Ky-18, Meproscillarin, CLIFT®

Yesterday's Drug Discovery Process

Natural Leads
Isolation
Synthetics
Animal Tests
Clinics

Josephinum

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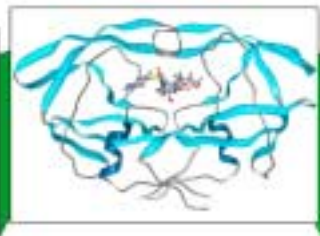
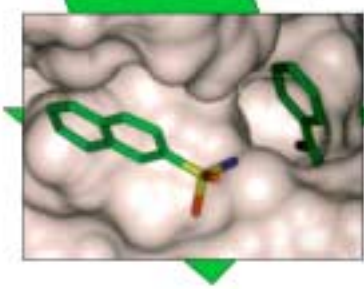
Changing Paradigms in Drug Discovery

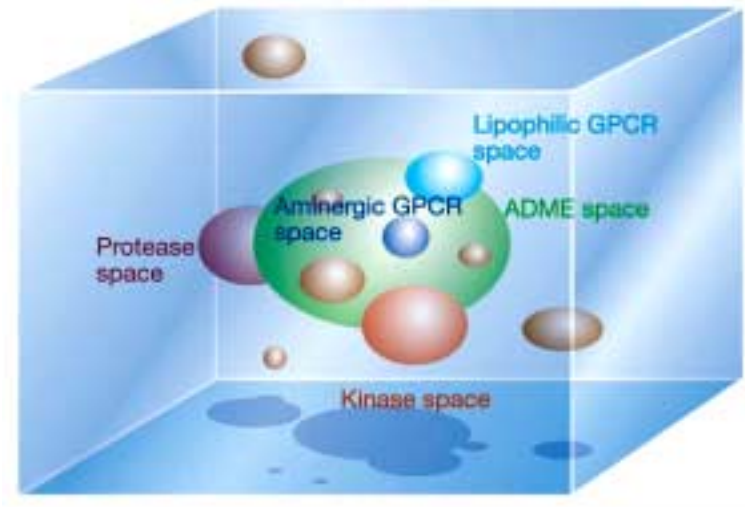
Serendipity
Rational design
Structure-based design
High-throughput hype
Virtual screening and fragment-based design



Drug Research is ....

the Search for a Needle in a Haystack

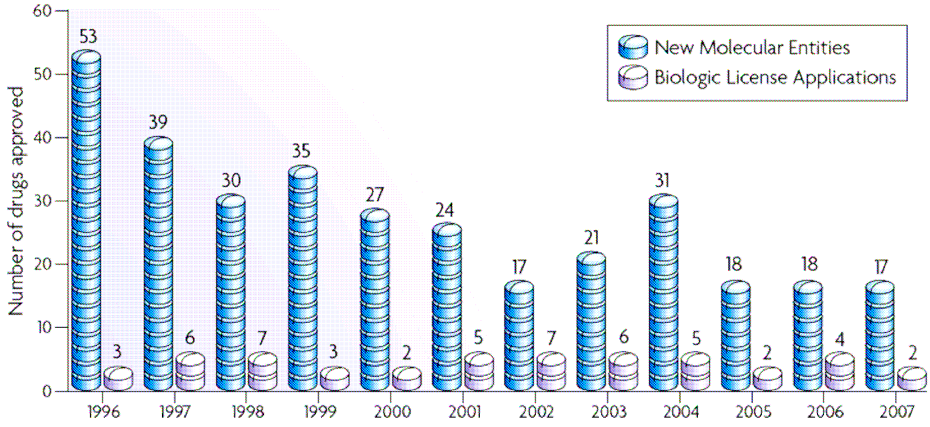
The Medicinal Chemistry Space



C. Lipinski and A. Hopkins, Nature 432, 855-861 (2004)

The Productivity Gap in Pharmaceutical Industry

FDA-Approved NCEs Over the Last Years



B. Hughes, Nature Rev. Drug Discov. 7, 107–108 (February 2008)

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).

How many targets? The „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)

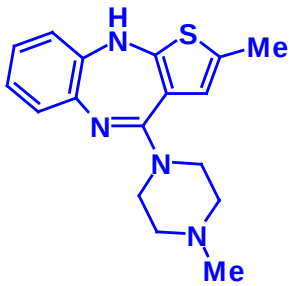
→ **the „druggable targetome“ ?**

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?

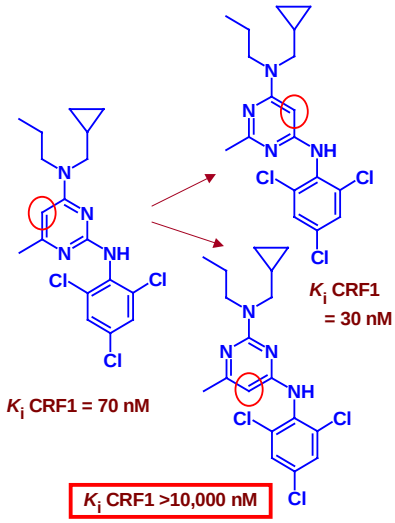


Olanzapine, a clozapine-like „atypical“ neuroleptic with a promiscuous binding pattern

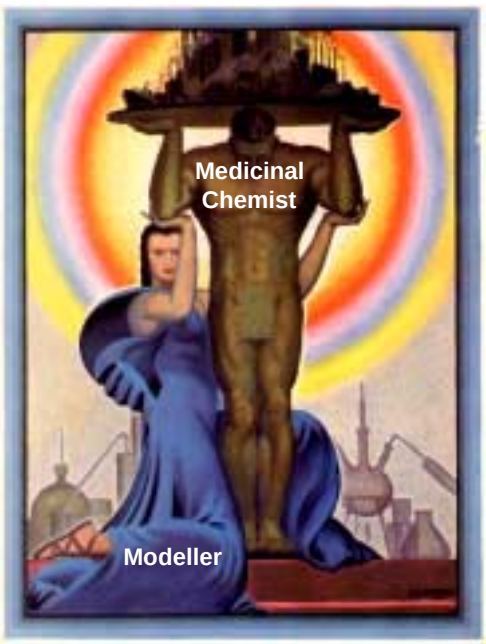
a) F. P. Bymaster et al., Neuropsychopharmacology 14, 87-96 (1996)
b) F. P. Bymaster et al., Schizophrenia Research 37, 107-122 (1999)

	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	

Smooth and Rough Structure-Activity Landscapes



C. Chen et al., J. Med. Chem. 39, 4358-4360 (1996)



A. Cressy Morrison

Man in a Chemical World
The Service of Chemical Industry

Ch. Scribner's Sons, NY, 1937

„Chemical Industry, Upheld by Pure Science, Sustains the Production of Man's Necessities"

Tools for Virtual Screening

	remaining
Garbage filter	90%
Druglike / Non-druglike	75%
Bioavailability	60%
Cytotoxicity	:
hERG channel inhibiton	:
Antitargets	:
α_{1a} (orthostatic hypotension)	:
D2 (extrapyramidal syndrome)	:
5-HT_{2c} (obesity)	:
musc. M1 (hallucinations, memory)	:
CYP inhibition (3A4, 2C9, 2D6)	:
Pharmacophore searches	:
Docking and scoring	0% ?

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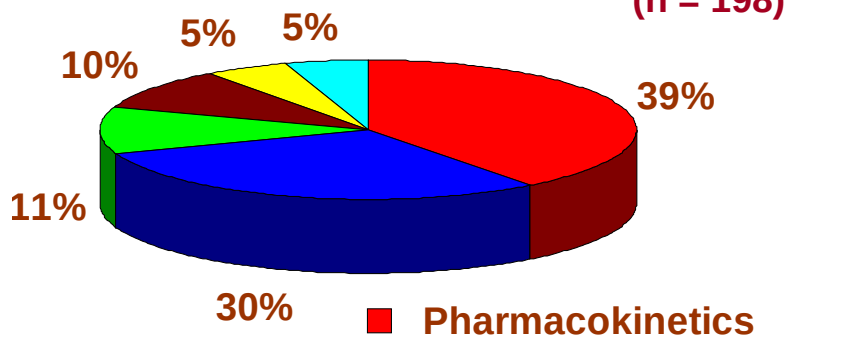
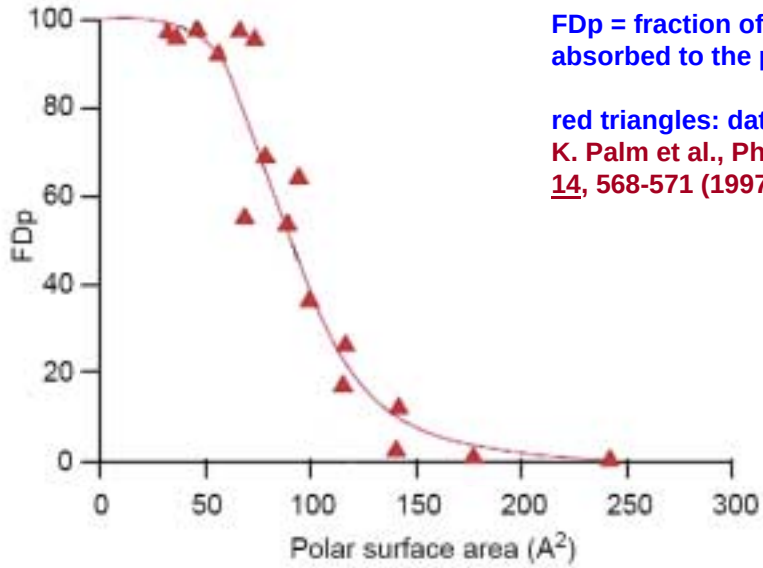
Reasons for Failure in Drug Development (n = 198)



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

Human Absorption and Polar Surface Area



FDp = fraction of dose absorbed to the portal vein

red triangles: data from K. Palm et al., Pharm. Res. 14, 568-571 (1997)

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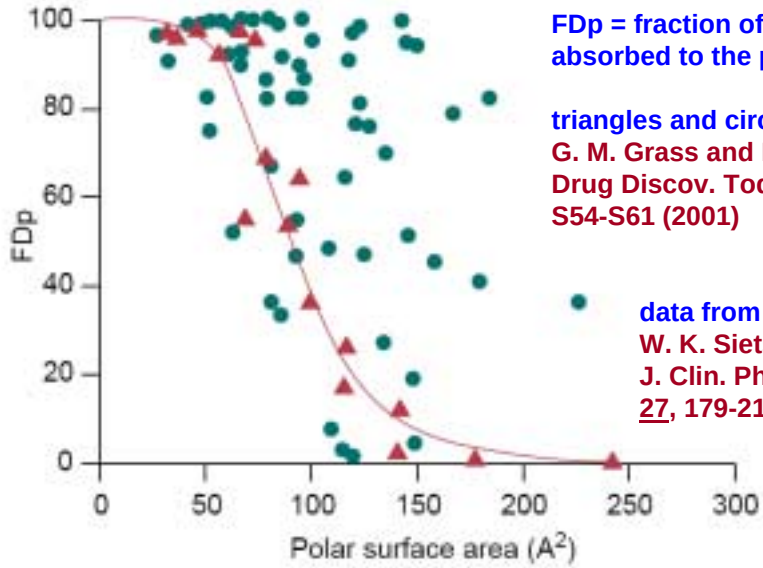
Human Absorption and Polar Surface Area

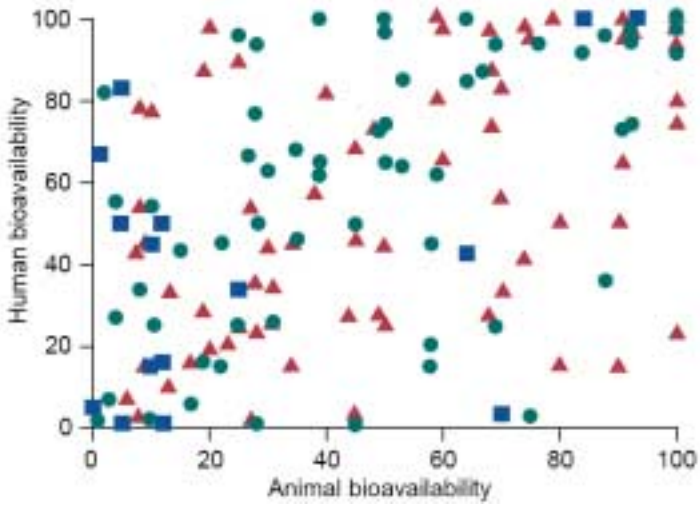


FDp = fraction of dose absorbed to the portal vein

triangles and circles: G. M. Grass and P. J. Sinko, Drug Discov. Today 6, S54-S61 (2001)

data from W. K. Sietsema, Int. J. Clin. Pharmacol. 27, 179-211 (1989)

Rodent, Dog, Primate and Human Bioavailability



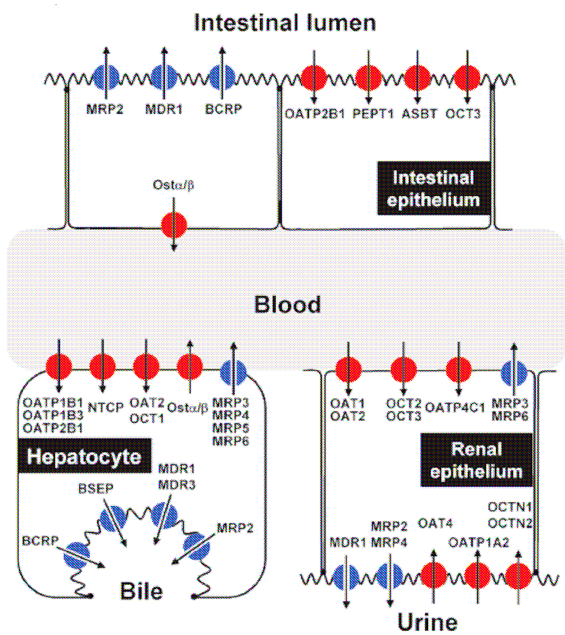
Rodents
green circles

Dog
red triangles

Primates
blue squares

data from:
W. K. Sietsema, Int. J. Clin. Pharmacol. 27, 179-211 (1989)

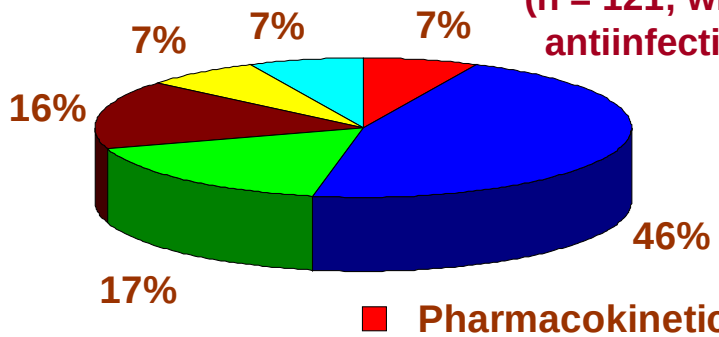
G. M. Grass and P. J. Sinko, Drug Discov. Today 6, S54-S61 (2001)



The Role of Transporters in Drug Absorption and Elimination

H. Gleaser et al., in R. J. Vaz and T. Klabunde, Antitargets, Wiley-VCH, 2008, pp. 341-366

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)

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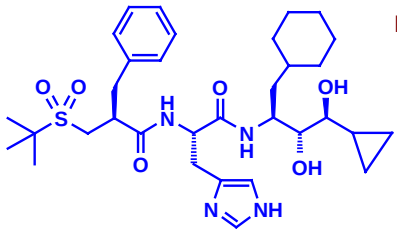
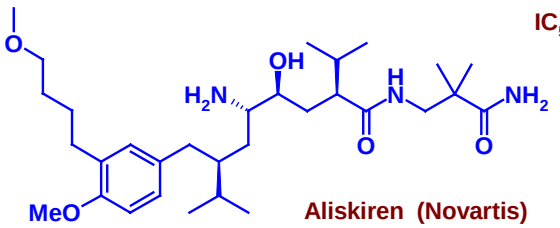
Species Specificity of Renin Inhibitors



Remikiren (Roche)

IC_{50} =	0.8 nM	(human)
	1.0-1.7 nM	(monkeys)
	107 nM	(dog)
	3 600 nM	(rat)



Aliskiren (Novartis)

IC_{50} =	0.6 nM	(human)
	2 nM	(marmoset)
	7 nM	(dog)
	11 nM	(rabbit)
	63 nM	(guinea pig)
	80 nM	(rat)
	150 nM	(pig)
	8 500 nM	(cat)

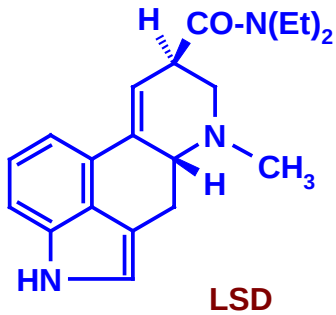
J. M. Wood et al., Biochem. Biophys. Res. Comm. 308, 698-705 (2003)

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 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

Albert Hofmann, LSD - My Problem Child, McGraw Hill, 1980

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An Early Clinical Study - Coffee or Tea ?

In late 18th century Gustav III, King of Sweden, performed a "clinical study" to confirm the negative effects of coffee drinking on health.
One convicted murder had to drink only coffee, another one tea, instead.
Two physicians supervised the study.

First, one physician died.
Then the other physician died.
Then the king was murdered.
The tea drinker died in the age of 83.
The coffee drinker survived all others.

Nevertheless, in 1794 coffee drinking was forbidden in Sweden and later again, in 1822.

An early clinical trial, Ann. Int. Med. 117, 1, 30 (1992)

Clinical Studies - the Typical Volunteer

Phase I

healthy volunteers, age 18-55 years, males and females (however, no females who could be or could become pregnant), normal weight, no smokers, no alcohol (ab)use, standard food, drug taken with 150 ml water, no other therapy, no intake of fruit juices or illegal drugs.

The Patients

plus other disease(s)

Voltaire, by J. A. Houdon

The Past

Voltaire (1694-1778):

**Doctors
pour drugs of which
they know little,
to cure diseases of which
they know less,
into human beings
of whom
they know nothing.**

Many thanks - to all friends and colleagues

Erich Hecker, MPI of Biochemistry and DKFZ
Ott-Hermann Kehrhahn, KNOLL

**Hans-Joachim Böhm, BASF
(now at Roche)
Gerhard Klebe, BASF
(now at Univ. Marburg)**

**as well as many other colleagues of former KNOLL AG and the
BASF Drug Design and Combinatorial Chemistry Groups**