Round Table: Chemogenomics and Drug Discovery

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Drug Discovery - The Ancient Times

Folk medicine (mainly plants)

pro: thousands years of human experience

con: lack of reproducibility (varying doses)

Experiments in humans
(J. Lind, 1747, treatment of scurvy)

pro: the “right” object

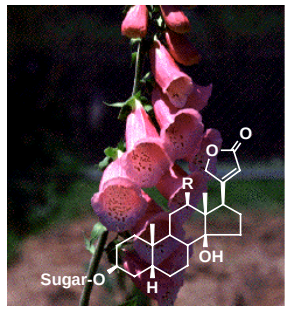
con: toxicity

Drug Discovery - The Early Times

Natural products and their analogs

pro: high percentage of actives
large chemical diversity

con: availability may pose problems
most often difficult chemistry

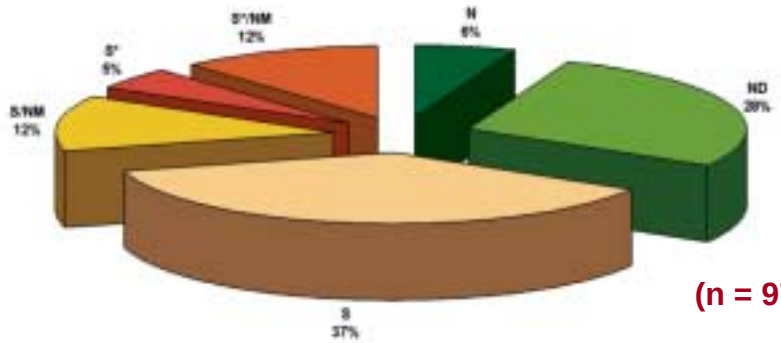


Animal experiments

pro: ADMET included

con: slow, expensive
ethical issues

All NCE's, 01/1981 - 06/2006, by Source (without biologicals and vaccines)



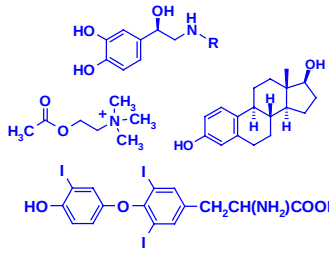
(n = 974)

N = natural products **ND = derived from natural products**
S = synthetic products **NM = natural product mimics**
S* = synthetics but pharmacophore derived from natural product

D. J. Newman and G. M. Cragg, J. Nat. Prod. 70, 461-477 (2007)

Drug Discovery - The Golden Age

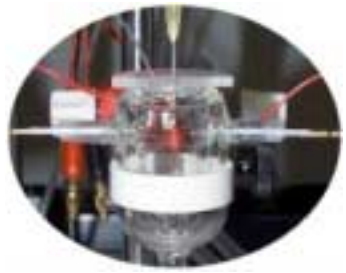
Endogenous transmitters and hormones



pro: active lead structures
involved in many different diseases

con: limited number of lead structures

Isolated organs as test models

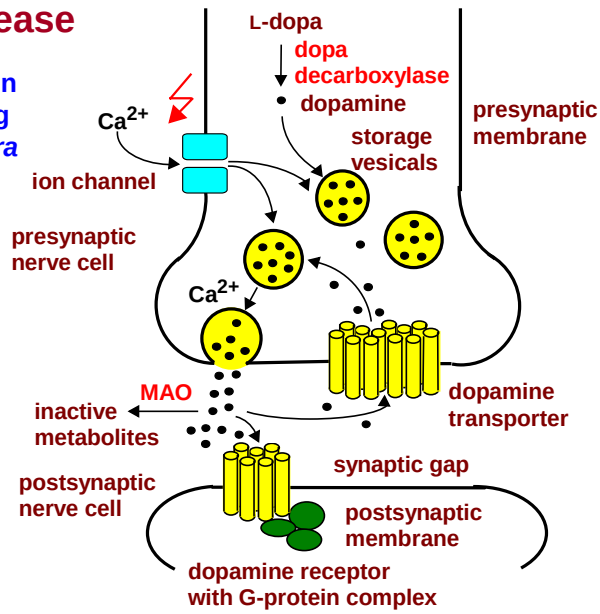


pro: includes membrane permeability

con: slow, expensive
no ADMET
ethical issues

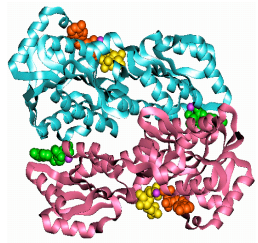
Parkinson's Disease

caused by degeneration of dopamine-producing cells in *Substantia nigra*



Drug Discovery - “Rational” Approaches

Structure-based and computer-aided design



pro: straightforward approach

con: only targets with known 3D structure
only ligand design - no ADMET
risk of failure

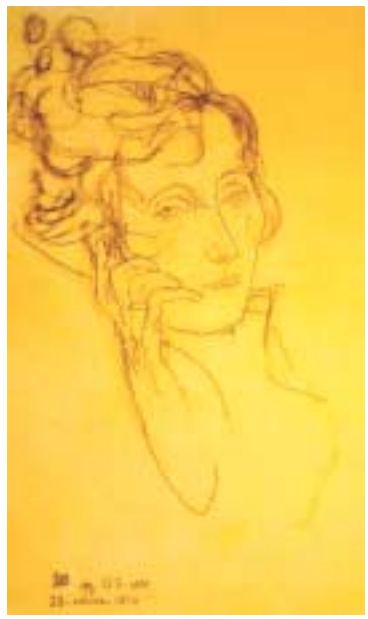
***In vitro* test models**

pro: very fast (up to 100,000’s / day)
target-oriented

con: no ADMET
single target

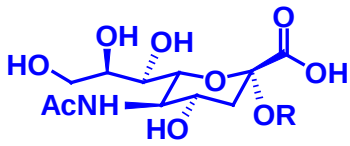
Influenza

In 1918/19, the „Spanish Flu“ killed about 20-40 mio people. Especially young and very old people died from influenza. The heavy death toll of this pandemic disease has to be compared to the number of 11 mio victims of World War I.

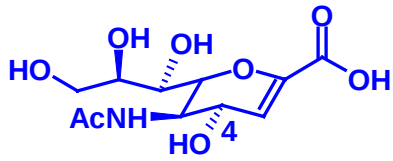


Egon Schiele prepared this drawing of his wife, one day before her death and four days before he died himself, only 28 years old.

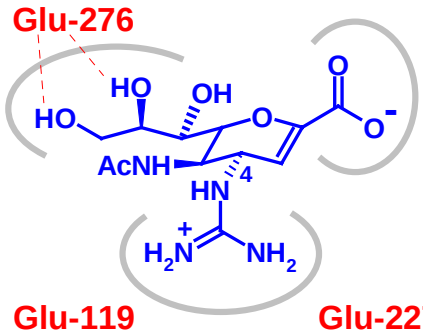
Design of Neuraminidase Inhibitors



sialic acid, R = H



Neu5Ac2en
K_i = 1 000 nM



Arg-371
Arg-292
Arg-118

4-Guanidino-Neu5Ac2en
K_i = 0.1-0.2 nM
Zanamivir (Relenza, Glaxo-Wellcome)

Drug Discovery - Nowadays

Combinatorial chemistry, chemical libraries

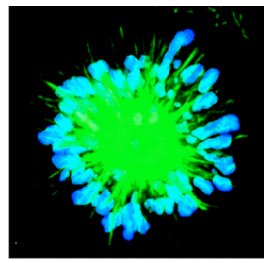
pro: generate a multitude of compounds

con: limited chemical diversity
chemistry-driven libraries most often outside of biological space

Chemical biology

pro: fast screening in biological systems
membran permeability included

con: no ADMET in cellular models
target/s remain/s unknown

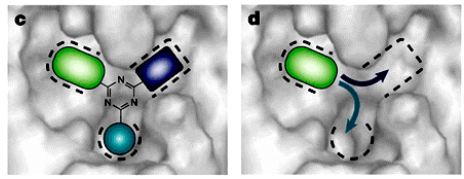


Drug Discovery - Nowadays

Virtual screening and fragment-based design

pro: straightforward approach
saves time and resources

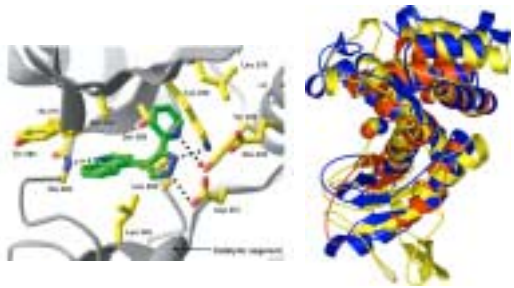
con: only ligand design
still some risk of failure



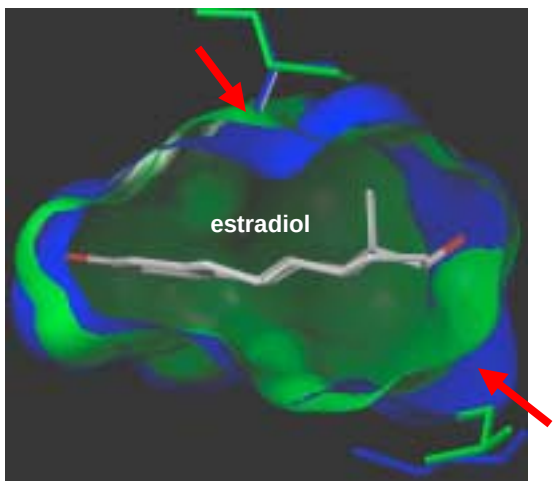
Chemogenomics

pro: multitarget-oriented
quick information on
selectivity

con: no ADMET



Design of Selective ERα and ERβ Ligands



blue: hERα LBD
(crystallography)

green: hERß LBD
(homology model)

hERα → hERß

„upper“ side:
Leu384 → Met336

„lower“ side:
Met421 → Ile373

A. Hillisch et al., Ernst Schering Res. Found. Workshop 46, 47-62 (2004); A. Hillisch et al., Mol. Endocrinol. 18, 1599-1609 (2004)

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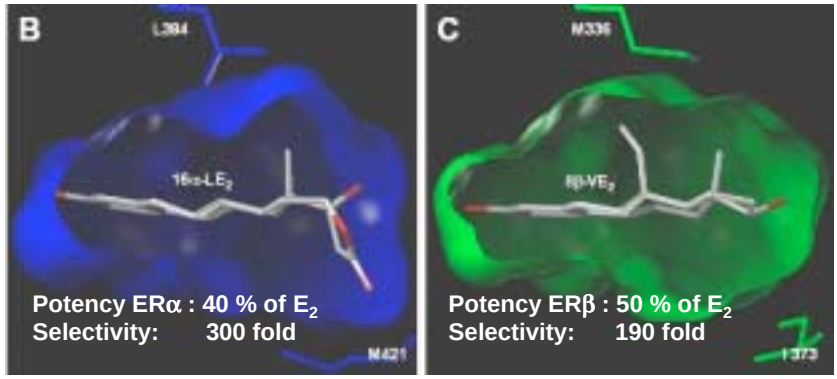
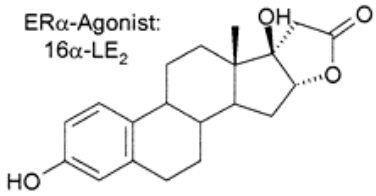
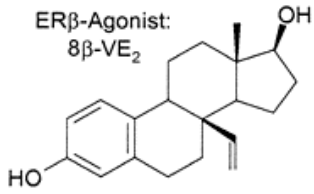


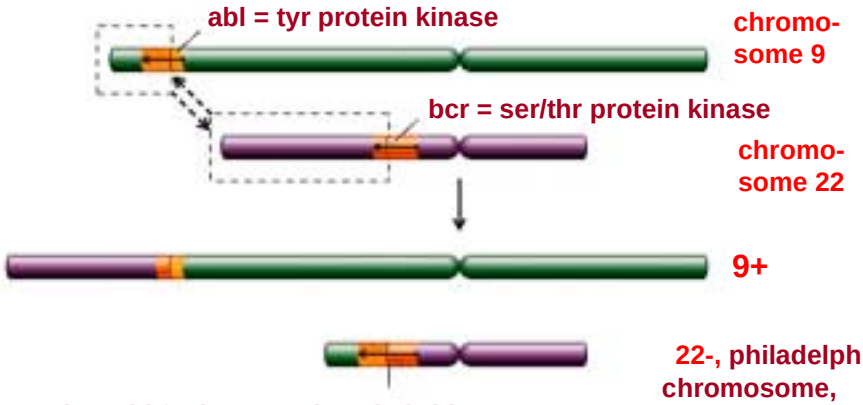
ERα-Agonist: 16α-LE_2



ERβ-Agonist: 8β-VE_2



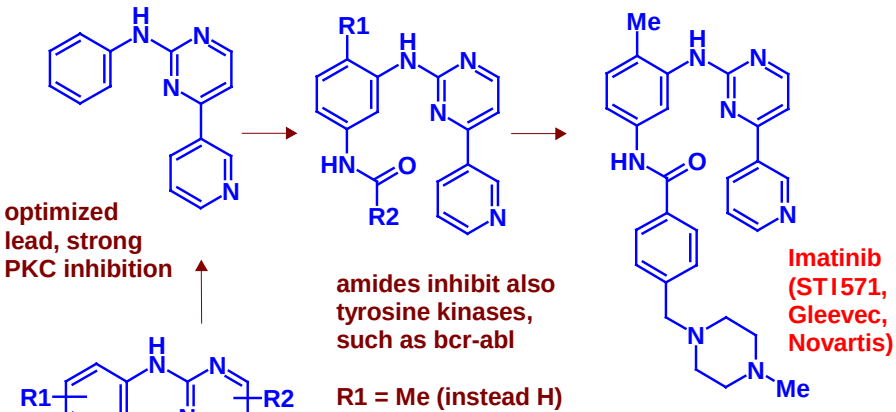
Chromosome Translocation in CML



bcr-abl fusion protein, a hybrid with constitutionally enhanced tyrosine protein kinase activity

22-, philadelphia chromosome, present in 90+% of all cases of chronic mye-logenous leukemia

Development of Imatinib (STI 571, Gleevec®)

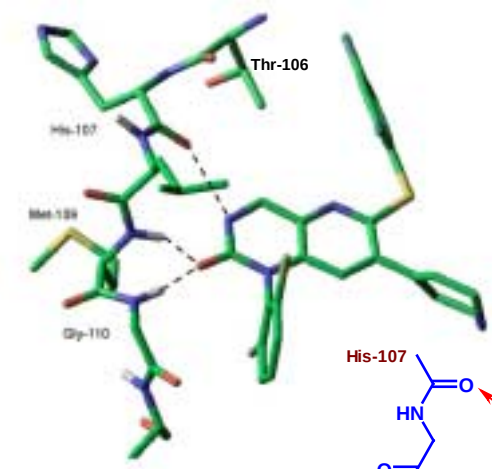


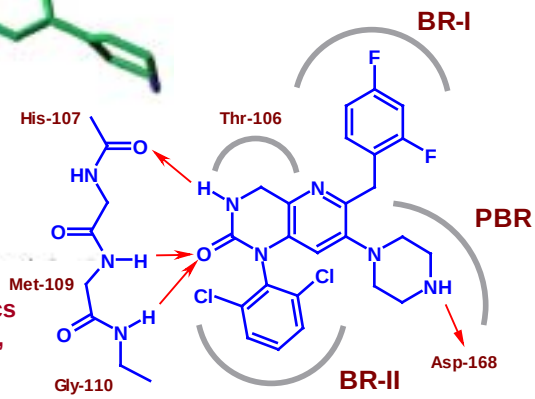
R. Capdeville et al., Nature Rev. Drug Discov. 1, 493-502 (2002)

ATP Binding Site Pockets of Protein Kinases

R. Buijsman, in: H. Kubinyi, G. Müller, Chemogenomics in Drug Discovery, Wiley-VCH, 2004, pp. 191-219

Binding Mode of a Kinase Inhibitor





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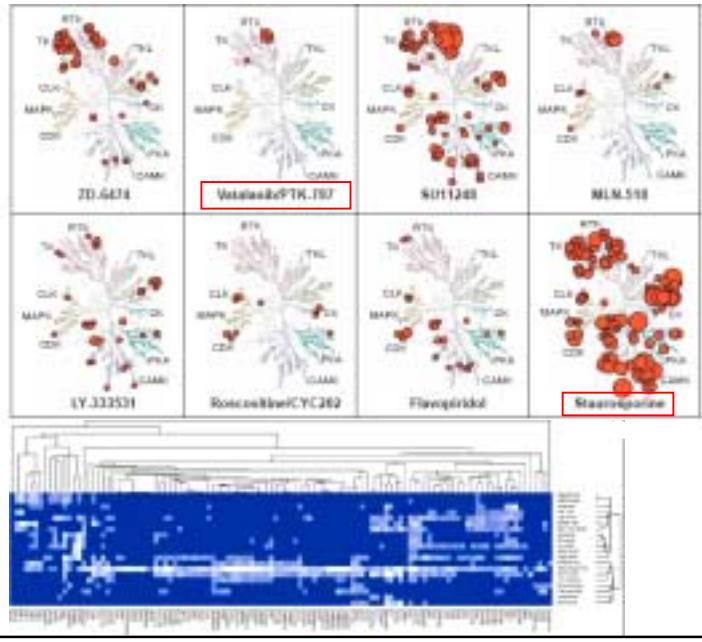
Selectivity of Kinase Inhibitors

(20 inhibitors tested vs. 113 kinases)

M. A. Fabian et al., Nature Biotech. 23, 329-336 (2005)



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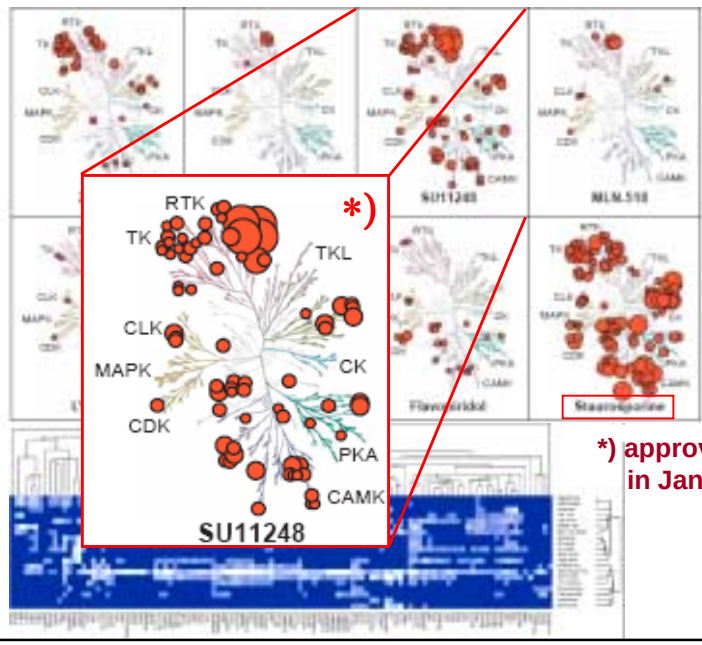

Selectivity of Kinase Inhibitors

(20 inhibitors tested vs. 113 kinases)

***) approved by FDA in January 2006**

M. A. Fabian et al., Nature Biotech. 23, 329-336 (2005)

Chemogenomics and Drug Discovery - The Impact on Society

Drug discovery phases (H2L, L2C) much faster than years before, due to the progress in structure-based and computer-aided design, virtual screening, and fragment-based design

Early information on specificity, due to parallel screening against (all) evolutionary related targets (chemogenomics strategy)

Significant progress in cancer therapy: before following the chemogenomics paradigm, kinases were considered to be non-druggable targets - now there are valuable cancer therapeutics

Progress to be expected in the design of resistance-breaking anti-virals, anti-bacterials, and antitumor agents

Progress to be expected in pharmacogenetics