Drug Discovery Technologies - A Closer Look

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Yesterday's Drug Discovery Process

Natural Leads
Isolation
Synthetics
Animal Tests
Clinics
Today’s Drug Discovery Process

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

Bottlenecks of the Past

<table>
<thead>
<tr>
<th>Problem</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target search</td>
<td>genome information</td>
</tr>
<tr>
<td>Target validation</td>
<td>knock-outs, RNA silencing</td>
</tr>
<tr>
<td>Lead search</td>
<td>in vitro test models, HTS</td>
</tr>
<tr>
<td>Lead optimization</td>
<td>parallel syntheses, chemogenomics</td>
</tr>
<tr>
<td>Absorption, permeability</td>
<td>Lipinski rules, Caco cells, prodrugs</td>
</tr>
<tr>
<td>Metabolism</td>
<td>liver microsomes</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Ames test, hERG models</td>
</tr>
<tr>
<td>Drug drug interactions</td>
<td>CYP inhibition/induction</td>
</tr>
</tbody>
</table>
FDA-Approved NCEs Over the Last Years

B. Hughes, Nature Rev. Drug Discov. 8, 93-96 (2009)

The Medicinal Chemistry Space

Drug Research is ....

the Search for a Needle in a Haystack

New Technologies: Open Questions

Is there a „druggable genome“ ?
Is a target focus always best ?
Is QSAR predictive ?
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?

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“


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Kinase Inhibitor Specificity

Sunitinib, Sutent® approved by FDA in January 2006


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)

<table>
<thead>
<tr>
<th></th>
<th>a)</th>
<th>b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_i$ 5-HT$_{2A}$</td>
<td>4 nM</td>
<td>2.5 nM</td>
</tr>
<tr>
<td>$K_i$ 5-HT$_{2B}$</td>
<td>12 nM</td>
<td>12 nM</td>
</tr>
<tr>
<td>$K_i$ 5-HT$_{2C}$</td>
<td>11 nM</td>
<td>2.5 nM</td>
</tr>
<tr>
<td>$K_i$ 5-HT$_3$</td>
<td>57 nM</td>
<td>57 nM</td>
</tr>
<tr>
<td>$K_i$ dop D$_1$</td>
<td>31 nM</td>
<td>119 nM</td>
</tr>
<tr>
<td>$K_i$ dop D$_2$</td>
<td>11 nM</td>
<td>11 nM</td>
</tr>
<tr>
<td>$K_i$ dop D$_3$</td>
<td>27 nM</td>
<td>27 nM</td>
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<tr>
<td>$K_i$ musc M$_1$</td>
<td>1.9 nM</td>
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<td>$K_i$ musc M$_5$</td>
<td>6 nM</td>
<td>6 nM</td>
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<td>19 nM</td>
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<tr>
<td>$K_i$ adr $\alpha_2$</td>
<td>230 nM</td>
<td>230 nM</td>
</tr>
<tr>
<td>$K_i$ hist H$_1$</td>
<td>7 nM</td>
<td>7 nM</td>
</tr>
</tbody>
</table>

“Good” QSAR
- parameters with biophysical relevance
- few variables to select
- few variables in the model
- validation by LOO, LMO, y scrambling

“Poor” QSAR
- artificial parameters
- too many variables to select
- too many variables in the model
- no test set predictivity (“Kubinyi paradox”)
Sir – There is concern in West Germany over the falling birth rate. The accompanying graph might suggest a solution that every child knows makes sense. H. Sies, Nature 332, 495 (1988)

Reasons for Failure in Drug Development (n = 198)

- Pharmacokinetics: 39%
- Lack of efficacy: 30%
- Animal toxicity: 11%
- Adverse effects in man: 10%
- Commercial reasons: 5%
- Miscellaneous: 5%

FDp = fraction of dose absorbed to the portal vein


Rodent, Dog, Primate and Human Bioavailability

- Rodents: green circles
- Dog: red triangles
- Primates: blue squares

Data from:


The Role of Transporters in Drug Uptake and Elimination

Species Differences of Caffeine Oxidation

F. Berthou et al., Xenobiotica 22, 671-680 (1992); figure from S. D. Krämer and B. Testa, Chemistry & Biodiversity 5, 2465-2578 (2008)

The Ultimate (Unavoidable) Bottlenecks?

Reasons for failure in clinical development, 1964-1985
(n = 121; without antiinfectives)
T. Kennedy, Drug Discov. today 2, 436-444 (1997)

Reasons for failure in clinical development, 1992-2002 (n = 73)
(reasons for market withdrawal, n = 17: toxicity 93%, efficacy 7%)
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

<table>
<thead>
<tr>
<th>Tools</th>
<th>remaining</th>
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</thead>
<tbody>
<tr>
<td>Garbage filter</td>
<td>90%</td>
</tr>
<tr>
<td>Druglike / Non-druglike</td>
<td>75%</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>60%</td>
</tr>
<tr>
<td>Cytotoxicity</td>
<td></td>
</tr>
<tr>
<td>hERG channel inhibition</td>
<td></td>
</tr>
<tr>
<td>Antitargets</td>
<td></td>
</tr>
<tr>
<td>$\alpha_{1a}$ (orthostatic hypotension)</td>
<td></td>
</tr>
<tr>
<td>D2 (extrapyramidal syndrome)</td>
<td></td>
</tr>
<tr>
<td>5-HT$_{2c}$ (obesity)</td>
<td></td>
</tr>
<tr>
<td>musc. M1 (hallucinations, memory)</td>
<td></td>
</tr>
<tr>
<td>CYP inhibition (3A4, 2C9, 2D6)</td>
<td></td>
</tr>
<tr>
<td>Pharmacophore searches</td>
<td></td>
</tr>
<tr>
<td>Docking and scoring</td>
<td>0%</td>
</tr>
</tbody>
</table>
Problems in Pharmacophore Generation

Isomers, enantiomers, diastereomers
Superposition of flexible molecules
Ionization and dissociation
  (Sadowski rules)
Tautomeric and protomeric forms
  (program AGENT, ETH Zurich; ChemoSoft tautomer recognition, ChemDiv)
Acceptor properties of oxygen and sulfur atoms
  (esters, aromatic ethers, oxazoles, isoxazoles, thiazoles, etc.)

Factors to be Considered in Scoring Functions

Desolvation enthalpy and entropy (ligand and protein)
Protonation state of the ligand and the binding site
Distortion energy of the ligand and its binding site
Loss of translational and rotational degrees of freedom of the ligand
MEP + dielectric constant at the binding site
Dipole moment of the ligand and local dipole moment at the binding site
Binding enthalpy of the ligand-protein complex
Repulsive effects (e.g. -O----O-)
Inserted water molecules
Solvation enthalpy and entropy of the complex
pK_i values of HIV Protease Inhibitors: VALIDATE II Predictions

exp. pK_i

box: normal range of lead-to-drug optimization

calcd. pK_i

Species Specificity of Renin Inhibitors

**Remikiren (Roche)**
- $IC_{50} = 0.8 \text{ nM}$ (human)
- $1.0-1.7 \text{ nM}$ (monkeys)
- $107 \text{ nM}$ (dog)
- $3600 \text{ nM}$ (rat)

**Aliskiren (Novartis)**
- $IC_{50} = 0.6 \text{ nM}$ (human)
- $2 \text{ nM}$ (marmoset)
- $7 \text{ nM}$ (dog)
- $11 \text{ nM}$ (rabbit)
- $63 \text{ nM}$ (guinea pig)
- $80 \text{ nM}$ (rat)
- $150 \text{ nM}$ (pig)
- $8500 \text{ nM}$ (cat)


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“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

\[\text{Cl} \begin{array}{c} \text{O} \\ \text{Cl} \\ \text{Cl} \end{array} \text{Cl} \begin{array}{c} \text{O} \\ \text{Cl} \end{array} \text{2,3,7,8-Tetrachlorodibenzodioxin} \]

<table>
<thead>
<tr>
<th>Species</th>
<th>LD50 in µg/kg</th>
</tr>
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<tbody>
<tr>
<td>Mouse</td>
<td>114-280</td>
</tr>
<tr>
<td>Rat</td>
<td>22-320</td>
</tr>
<tr>
<td>Hamster</td>
<td>1,150-5,000</td>
</tr>
<tr>
<td>Guinea Pig</td>
<td>0.5-2.5</td>
</tr>
<tr>
<td>Mink</td>
<td>4</td>
</tr>
<tr>
<td>Rabbit</td>
<td>115-275</td>
</tr>
<tr>
<td>Dog</td>
<td>&gt; 100 &lt; 3,000</td>
</tr>
<tr>
<td>Monkey</td>
<td>&lt; 70</td>
</tr>
<tr>
<td>Man</td>
<td>??</td>
</tr>
</tbody>
</table>

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.

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.

Patients

plus other disease(s)
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.

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