Living in Castalia?

The Pitfalls in “Rational” Design

Hugo Kubinyi
Weisenheim am Sand

E-mail kubinyi@t-online.de
HomePage www.kubinyi.de

Castalian Allocution at the EuroCUP II, Strasbourg, 2008

Papal Allocution
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
The Generation of Scaffold Diversity

FDA-Approved NCEs Over the Last Years


Drug Research is ....

the Search for a Needle in a Haystack
Success in Drug Research

- A compound is no hit
- is no lead optimization:
  - is no candidate
  - is no drug

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?

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, heterodimeric GPCRs, cross-talking)

→ the „druggable targetome“ ?

Balanced activity against a series of targets

→ the „druggable physiome“

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)
“Discouraging Data on the New Antidepressant”

The Problem of Prediction
inside: trivial
outside: wrong
at the edge: 50/50
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.


“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”)

The Storks and the Babies
pairs of brooding storks
millions of newborn babies

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.


“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”)

The Storks and the Babies
pairs of brooding storks
millions of newborn babies
A Common Situation in QSAR (and 3D QSAR)

A chemist synthesizes about 30 compounds.
The biologists determines the activity values.
Both ask the chemoinformatician to derive a QSAR model.
The chemoinformatician loads 1500 variables (e.g. from the program DRAGON, Roberto Todeschini) and derives a QSAR model, containing only a few variables, which meets all statistical criteria.
Chemist, biologist and chemoinformatician publish the results. Everybody is happy.

The Real Situation (e.g. the Selwood data set)

A chemist prepares some 20 compounds.
The biologist determines the activity values.
Both ask the chemoinformatician to derive a QSAR model.
The resulting model does not contain more than four variables, is selected from about fifty variables and is validated by all statistical criteria, including LOO/LMO cross-validation and $y$ scrambling.
How good is the predictivity of the model for a test set of 10 compounds?
The Real Situation (e.g. the Selwood data set)

A chemist prepares some 20 compounds.
The biologist determines the activity values.
Both ask the chemoinformatician to derive a QSAR model.
The resulting model does not contain more than four variables, is selected from about fifty variables and is validated by all statistical criteria, including LOO/LMO cross-validation and y scrambling.

How good is the predictivity of the model for a test set of 10 compounds? Lousy!!
“Activity landscapes are not continuous, they contain cliffs, like the Bryce Canyon”

rem: applies also to scoring functions!


Reasons for Failure in Drug Development (n = 198)

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

Human Absorption and Polar Surface Area

FDp = fraction of dose absorbed to the portal vein


The Role of Transporters in Drug Uptake and Elimination


Carrier-mediated cellular uptake of pharmaceutical drugs: an exception or the rule?

Paul D. Dobson and Douglas B. Kell

Abstract | It is generally thought that many drug molecules are transported across biological membranes via passive diffusion at a rate related to their lipophilicity. However, the types of biophysical forces involved in the interaction of drugs with lipid membranes are no different from those involved in their interaction with proteins, and so arguments based on lipophilicity could also be applied to drug uptake by membrane transporters or carriers. In this article, we discuss the evidence supporting the idea that rather than being an exception, carrier-mediated and active uptake of drugs may be more common than it is usually assumed — including a summary of specific cases in which drugs are known to be taken up into cells via defined carriers — and consider the implications for drug discovery and development.

Sites of Drug Metabolism:
(intestinal wall), liver, (organs)

Sites of Drug Elimination:
kidneys (polar compounds), bile, feces (lipophilic analogs), lung

Rodent, Dog, Primate and Human Bioavailability

Rodents green circles
Dog red triangles
Primates blue squares

data from:

Reasons for Failure in Drug Development

(n = 121; without antiinfectives)

- Pharmacokinetics: 46%
- Lack of efficacy: 7%
- Animal toxicity: 7%
- Adverse effects in man: 7%
- Commercial reasons: 17%
- Miscellaneous: 16%


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“
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.)

Pharmacophore Analyses Must Consider Correct Donor and Acceptor Properties of Ligands

The billion dollar question: how many acceptor positions has an ester group?

Correct answer: Two ...., but why?
Donor and Acceptor Properties of O and N

Brood (OpenEye) for Isostere Prediction

electrostatic isopotential contour surfaces of ester and oxazole fragments (www.eyesopen.com/products/applications/brood.html)
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

box: normal range of lead-to-drug optimization

Energies of Different Ligand Conformations? (Imatinib)

- c-abl kinase (1lep)
  - aryl-NH-aryl ≈ 90°

- syk tyrosine kinase (1xbb)
  - aryl-NH-aryl = 0°

S. Atwell et al., J. Biol. Chem. 279, 55827-55832 (2004)

Free Energy of Ligand Binding

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)
All things are poison and nothing without poison; only the dose determines, whether a thing be no poison"  
Salt, Fat, Alcohol ...  
Aspirin, Corticoids ...  
Phenacetin, Phenthepen, Cerivastatin ...

<table>
<thead>
<tr>
<th>Species</th>
<th>LD$_{50}$ in µg/kg</th>
</tr>
</thead>
<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>
**Dioxine Poisoning of Victor Yushchenko**

Victor Yushchenko, Ukraine's opposition leader, looks fit and healthy on August 02, 2004, before his mystery illness.


---

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

<table>
<thead>
<tr>
<th>Species</th>
<th>LD&lt;sub&gt;50&lt;/sub&gt; in mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>50-60</td>
</tr>
<tr>
<td>Rat</td>
<td>16.5</td>
</tr>
<tr>
<td>Rabbit</td>
<td>0.3</td>
</tr>
<tr>
<td>Elephant</td>
<td>« 0.06</td>
</tr>
<tr>
<td>Man</td>
<td>» 0.003</td>
</tr>
</tbody>
</table>

LSD

[Image of the chemical structure of LSD]
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

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 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