Changing Paradigms in Drug Discovery

Hugo Kubinyi
Germany

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

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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)

Squill (Scilla alba, Urginea maritima)
1967-1978

KNOLL AG

Changing Paradigms in Cardiac Therapy

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

1967-1978
Yesterday's Drug Discovery Process

Natural Leads
Isolation
Synthetics
Animal Tests
Clinics

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

The Productivity Gap in Pharmaceutical Industry

FDA-Approved NCEs Over the Last Years


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?

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“


Is Target Focus the Best Strategy?

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

\[
\begin{align*}
K_i \text{ 5-HT}_{2A} &= 4 \text{ nM} & 2.5 \text{ nM} \\
K_i \text{ 5-HT}_{2B} &= 12 \text{ nM} \\
K_i \text{ 5-HT}_{2C} &= 11 \text{ nM} & 2.5 \text{ nM} \\
K_i \text{ 5-HT}_3 &= 57 \text{ nM} \\
K_i \text{ dop D}_1 &= 31 \text{ nM} & 119 \text{ nM} \\
K_i \text{ dop D}_2 &= 11 \text{ nM} \\
K_i \text{ dop D}_3 &= 27 \text{ nM} \\
K_i \text{ musc M}_1 &= 1.9 \text{ nM} & 2.5 \text{ nM} \\
K_i \text{ musc M}_2 &= 18 \text{ nM} \\
K_i \text{ musc M}_3 &= 25 \text{ nM} & 13 \text{ nM} \\
K_i \text{ musc M}_4 &= 13 \text{ nM} & 10 \text{ nM} \\
K_i \text{ musc M}_5 &= 6 \text{ nM} \\
K_i \text{ adr } \alpha_1 &= 19 \text{ nM} \\
K_i \text{ adr } \alpha_2 &= 230 \text{ nM} \\
K_i \text{ hist H}_1 &= 7 \text{ nM}
\end{align*}
\]

a) F. P. Bymaster et al., Neuropsychopharmacology 14, 87-96 (1996)
Smooth and Rough Structure-Activity Landscapes

\[
K_i \text{CRF1} = 70 \text{ nM}
\]

\[
K_i \text{CRF1} = 30 \text{ nM}
\]

\[
K_i \text{CRF1} > 10,000 \text{ nM}
\]


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

- Garbage filter: 90%
- Druglike / Non-druglike: 75%
- Bioavailability: 60%
- Cytotoxicity:
- hERG channel inhibition:
- Antitargets:
  - $\alpha_{1A}$ (orthostatic hypotension):
  - D2 (extrapyramidal syndrome):
  - 5-HT$_{2C}$ (obesity):
  - musc. M1 (hallucinations, memory):
  - CYP inhibition (3A4, 2C9, 2D6):
  - Pharmacophore searches:
  - Docking and scoring: 0%?

Reasons for Failure in Drug Development

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

(n = 198)

R. A. Prentis et al.,
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

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

- data from
Rodent, Dog, Primate and Human Bioavailability


The Role of Transporters in Drug Absorption and Elimination

Reasons for Failure in Drug Development

(n = 121; without antiinfectives)

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

T. Kennedy, Drug Discov. today 2, 436-444 (1997)
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)


“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

<table>
<thead>
<tr>
<th>Species</th>
<th>LD₅₀ 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>&lt; 0.06</td>
</tr>
<tr>
<td>Man</td>
<td>&gt; 0.003</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.

The 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.

Voltaire, by J. A. Houdon

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