Problems in Drug Design

Hugo Kubinyi

Germany

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

Yesterday's Drug Discovery Process

Natural Leads
Isolation
Synthetics
Animal Tests
Clinics
Technological Changes in Drug Research

Up to the 70s
Chemistry and hypotheses guide the syntheses
**Bottleneck:** Animal experiments, isolated organs

Up to the 90s
Molecular Modelling
*In vitro* models (enzyme inhibition, receptor binding)
**Bottleneck:** Dedicated syntheses of drugs

Up to the year 2000:
Gene technology (production of proteins)
Combinatorial chemistry (mixtures, chemistry-driven)
Structure-based design of ligands
High-throughput test models (HTS)
**Bottleneck:** ADMET properties

Today’s Drug Discovery Process

- **Genome**
- **Proteome**
- **3D Structures**
- **CombiChem**
- Automated HTS
- Virtual Screening
- Docking and Scoring
Technological Changes in Drug Research

Today:

- Genomics, proteomics and bioinformatics
- Transgenic animals for proof of concept
- Combinatorial chemistry
  - (single compounds, design-driven)
- Structure-based and computer-aided design of ligands
- Ultra-high-throughput test models (u-HTS)
- Data mining
- Virtual screening
- ADMET profiles (HTS and \textit{in silico})

\textbf{Bottleneck:} Target validation, “drugable” targets

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Bioinformatics: The Promise

\textit{Modern Drug Discovery, 3(1), 28-34 (2000).}
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 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?

Revised Sequence of Chromosome 20

Fatty Acid Biosynthesis Pathway

Source: "Biochemical Pathways"
(one of 120 segments)

biochem.boehringer-mannheim.com/prodinfo_fst.htm?/techserv/metmap.htm
Adenylate cyclase and Protein Kinase C

Source: "Cellular and Molecular Processes"
(one of 100 segments)

nACh Receptor and Visual Process

Source: "Cellular and Molecular Processes"
(one of 100 segments)
**Biochemical Classes of Drug Targets of Current Therapies**

- Receptors, 45%
- Enzymes, 28%
- Known, 7%
- Ion channels, 5%
- Nuclear receptors, 2%
- DNA, 2%
- Hormones & factors, 11%
- **N = 483**


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**Drug Targets**

- Enzymes 47%
- DNA 1%
- Integrins 1%
- Miscellaneous 2%
- Other receptors 4%
- GPCRs 30%
- Ion channels 7%
- Transports 4%
- Nuclear hormone receptors 4%

**a) Marketed Drugs**

Drug Targets

b) Gene Families


Drug Targets
c) Druggable Targets

Genome, Druggable Genome and Drug Targets


Estimation on Druggable Targets

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“


Is Target Focus the Best Strategy?

\[
\begin{align*}
K_{i} 5-\text{HT}_{2A} &= 4 \text{ nM} \quad 2.5 \text{ nM} \\
K_{i} 5-\text{HT}_{2B} &= 12 \text{ nM} \\
K_{i} 5-\text{HT}_{2C} &= 11 \text{ nM} \quad 2.5 \text{ nM} \\
K_{i} 5-\text{HT}_{3} &= 57 \text{ nM} \\
K_{i} \text{ dop } D_{1} &= 31 \text{ nM} \quad 119 \text{ nM} \\
K_{i} \text{ dop } D_{2} &= 11 \text{ nM} \\
K_{i} \text{ dop } D_{3} &= 27 \text{ nM} \\
K_{i} \text{ musc } M_{1} &= 1.9 \text{ nM} \quad 2.5 \text{ nM} \\
K_{i} \text{ musc } M_{2} &= 18 \text{ nM} \\
K_{i} \text{ musc } M_{3} &= 25 \text{ nM} \quad 13 \text{ nM} \\
K_{i} \text{ musc } M_{4} &= 13 \text{ nM} \quad 10 \text{ nM} \\
K_{i} \text{ musc } M_{5} &= 6 \text{ nM} \\
K_{i} \text{ adr } \alpha_{1} &= 19 \text{ nM} \\
K_{i} \text{ adr } \alpha_{2} &= 230 \text{ nM} \\
K_{i} \text{ hist } H_{1} &= 7 \text{ nM}
\end{align*}
\]

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

a) F. P. Bymaster et al., Neuropsychopharmacology 14, 87-96 (1996)
The New Pharma Strategy: Fail early?

Percentage of medicines dropped at different stages of development

<table>
<thead>
<tr>
<th>Year</th>
<th>Pre-clin</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Registration</th>
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<tr>
<td>1997</td>
<td>70</td>
<td>7.2</td>
<td>15</td>
<td>5.4</td>
<td>1.7</td>
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<tr>
<td>1998</td>
<td>66</td>
<td>9.4</td>
<td>15</td>
<td>6.2</td>
<td>2.4</td>
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<tr>
<td>1999</td>
<td>56</td>
<td>10.0</td>
<td>19</td>
<td>9.4</td>
<td>4.3</td>
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<tr>
<td>2000</td>
<td>61</td>
<td>9.1</td>
<td>17</td>
<td>8.3</td>
<td>3.1</td>
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<tr>
<td>2001</td>
<td>53</td>
<td>11.0</td>
<td>27</td>
<td>5.0</td>
<td>3.4</td>
</tr>
</tbody>
</table>


Properties of Development Candidates and Drugs

n = 6467 from MDDR

J. F. Blake, BioTechniques 34, S16-S20 (June 2003)
Success in Drug Research

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

Costs of Drug Research

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

### Pharma Sales and Earnings, 1999-2002

<table>
<thead>
<tr>
<th>Company</th>
<th>Sales in bill$</th>
<th>Earnings in bill$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merck</td>
<td>51.8</td>
<td>47.7</td>
</tr>
<tr>
<td>Johnson &amp; Johnson</td>
<td>36.3</td>
<td>33.0</td>
</tr>
<tr>
<td>Pfizer</td>
<td>32.4</td>
<td>32.3</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>31.9</td>
<td>30.8</td>
</tr>
<tr>
<td>Novartis</td>
<td>20.8</td>
<td>20.3</td>
</tr>
<tr>
<td>Aventis</td>
<td>19.5</td>
<td>21.7</td>
</tr>
<tr>
<td>Hoffmann-La Roche</td>
<td>19.1</td>
<td>18.7</td>
</tr>
<tr>
<td>Bristol-Myers Squibb</td>
<td>18.1</td>
<td>18.0</td>
</tr>
<tr>
<td>Astra Zeneca</td>
<td>17.8</td>
<td>16.2</td>
</tr>
<tr>
<td>Abbott Laboratories</td>
<td>17.7</td>
<td>16.3</td>
</tr>
<tr>
<td>Wyeth</td>
<td>14.6</td>
<td>14.1</td>
</tr>
<tr>
<td>Pharmacia</td>
<td>14.0</td>
<td>13.8</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>11.1</td>
<td>11.5</td>
</tr>
<tr>
<td>Schering-Plough</td>
<td>10.2</td>
<td>9.8</td>
</tr>
</tbody>
</table>

Source: C&EN, July 07, 2003, pp. 26-45

### Top 20 Drugs, Sales in mio $,

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year</th>
<th>2000</th>
<th>2004est.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losec / omeprazole</td>
<td>1988</td>
<td>6,260</td>
<td>2,575</td>
</tr>
<tr>
<td>Zocor / simvastatin</td>
<td>1988</td>
<td>5,280</td>
<td>9,653</td>
</tr>
<tr>
<td>Lipitor / atorvastatin</td>
<td>1997</td>
<td>5,031</td>
<td>11,304</td>
</tr>
<tr>
<td>Norvasc / amlodipine</td>
<td>1990</td>
<td>3,362</td>
<td>4,260</td>
</tr>
<tr>
<td>Takepron / lansoprazole</td>
<td>1992</td>
<td>3,046</td>
<td>4,877</td>
</tr>
<tr>
<td>Claritin / loratadine</td>
<td>1988</td>
<td>3,011</td>
<td>1,900</td>
</tr>
<tr>
<td>Procrit / erythropoetin</td>
<td>1988</td>
<td>2,709</td>
<td>2,875</td>
</tr>
<tr>
<td>Celebrex / celecoxib</td>
<td>1999</td>
<td>2,614</td>
<td>3,411</td>
</tr>
<tr>
<td>Pravachol / fluoxetine</td>
<td>1986</td>
<td>2,574</td>
<td>525</td>
</tr>
<tr>
<td>Zyprexa / olanzapine</td>
<td>1996</td>
<td>2,350</td>
<td>4,445</td>
</tr>
<tr>
<td>Seroxat / paroxetine</td>
<td>1991</td>
<td>2,348</td>
<td>3,409</td>
</tr>
<tr>
<td>Vioxx / rofecoxib</td>
<td>1999</td>
<td>2,160</td>
<td>3,800</td>
</tr>
<tr>
<td>Zoloft / sertraline</td>
<td>1990</td>
<td>2,140</td>
<td>2,750</td>
</tr>
<tr>
<td>Epogen / erythropoetin</td>
<td>1988</td>
<td>1,963</td>
<td>2,155</td>
</tr>
<tr>
<td>Glucophage / metformin</td>
<td>unknown</td>
<td>1,892</td>
<td>1,400</td>
</tr>
<tr>
<td>Premarin / oestrone</td>
<td>unknown</td>
<td>1,870</td>
<td>2,300</td>
</tr>
<tr>
<td>Augmentin / amox.+clav.acid</td>
<td>1989</td>
<td>1,847</td>
<td>2,603</td>
</tr>
<tr>
<td>Pravachol / pravastatin</td>
<td>1984</td>
<td>1,817</td>
<td>2,581</td>
</tr>
<tr>
<td>Vasojet / enalapril</td>
<td>1984</td>
<td>1,790</td>
<td>575</td>
</tr>
<tr>
<td>Cozaar / losartan</td>
<td>1994</td>
<td>1,715</td>
<td>2,764</td>
</tr>
</tbody>
</table>

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: 11%

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: 17%
The Productivity Gap in Pharmaceutical Industry


Gene Technology in Drug Research

- Identification of a therapeutically relevant protein: Identification of a gene and determination of its sequence yield the protein sequence. Elucidation of its function and 3D-structure prediction

- Proof of therapeutic concept: Introduction, amplification or knock-out of the gene in animals

- Development of a molecular test system: Screening with human protein, reduction of animal experiments

- Production of the protein: finally leads to the three-dimensional structure and to structure-based design.
Species Specificity of a Renin Inhibitor

![Remikiren molecule]

**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, Phenytoin, Cerivastatin ...

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**Acute Toxicity of Tetrachlorodibenzodioxin**

2,3,7,8-Tetrachlorodibenzodioxin

<table>
<thead>
<tr>
<th>Species</th>
<th>LD50 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>
# Acute Toxicity of Lysergic Acid Diethylamide in Animals and Maximum Tolerated Dose in Man

<table>
<thead>
<tr>
<th>Species</th>
<th>LD$_{50}$ 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 molecule](image)

Prediction is very difficult, especially about the future (Niels Bohr, also attributed to Mark Twain)

"Everything that can be invented has been invented."

"I think there is a world market for maybe five computers."
Thomas Watson, Chairman IBM, 1943

"Computers in the future may weigh no more than 1.5 tons."
Popular Mechanics, forecasting the relentless march of science, 1949

"There is no reason anyone would want a computer in their home."
Ken Olson, President, Chairman and Founder of Digital Equipment Corp., 1977

"640 k ought to be enough for anybody."
Bill Gates, Founder of Microsoft, 1981
Important Mispredictions in Drug Therapy

There is no market for cyclosporin, because there are too few organ transplants.
   The breakthrough in transplantation medicine was enabled by cyclosporin.

There is no market for Cimetidin. Gastric and duodenal ulcers can be treated conventionally (by surgery!)
   In 1983, six years after its market introduction, cimetidin had yearly sales of one billion US-$.  

Omeprazole will „dry out“ the stomach, because of its complete blockade of gastric acid production.
   Omeprazole developed to the most successful drug of all time (more than six billions US-$/year).

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
Gefitinib®, Iressa, ZD1839 (EGFR TK inhibitor)

third-line therapy for non-small-cell lung cancer (75% of lung cancer cases)

clinical response to Iressa ~ 10%

J. G. Paez et al.
EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy
Science 304 (5676), 1497-1500 (2004)

T. J. Lynch et al.
Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non-Small-Cell Lung Cancer and Gefitinib

8 out of 9 Iressa-responsive patients showed mutations in the kinase domain
0 out of 7 non-responsive patients showed mutations
2 out of 25 non-treated patients showed mutations (8%)
References


