IUPAC Richter Prize Lecture
Wednesday September 10, 2014

Medicinal Chemistry, Quo Vadis?
The changing climate of Pharmaceutical R&D

Helmut Buschmann
Tapentadol - From Morphine and Tramadol to the Discovery Tapentadol
Tapentadol – A New Analgesic with a Dual Mode of Action

Tapentadol – The Path To The Market

- Start of the pre-clinical GLP-program
  - First synthesis of BN-200 (February 8, 1994)
- Start of clinical trials with oral IR formulation
- Start of the pre-clinical GLP-program INN for BN 200 (CG5503) base Tapentadol
- Start of clinical program in chronic pain
- Start of the pre-clinical GLP-program

- Start of co-operation with J&J
- First application to man
- First in man trial with PR formulation
- Start of Phase III program
- Completion EU registration procedure acute and chronic pain
- Extension of co-operation with J&J
- EU and US submission chronic pain
- US submission acute pain

- Start of co-operation with J&J
- Start of the pre-clinical GLP-program

- First study in patients (acute pain)
- Start of clinical trials with oral IR formulation
- Start of clinical program in chronic pain
- Completion EU registration procedure acute and chronic pain
- Extension of co-operation with J&J

Timeline:
- 1994
- 1996
- 1998
- 2000
- 2002
- 2004
- 2006
- 2008
- 2010
- 2012
- 2014
- 2016
Overview of the Different Types of Pain

- Physiological or nociceptive pain
  - Perioperative pain
  - Postoperative pain
  - Non-surgical trauma

- Inflammatory pain
  - Headache
  - Migraine
  - Visceral pain
  - Cancer pain
  - Back pain
  - Acute pain

- Neuropathic pain
  - Diabetic neuropathy
  - Phantom limb pain
  - Post-herpetic neuralgia

- Disease-related pain
  - Menstrual pain
  - Bone pain
  - AIDS pain
  - Rheumatic pain
  - Dental pain
  - Chronic pain
Significant Unmet Needs in Inflammatory/Nociceptive Pain Treatments

Safety and Tolerability

Pain Severity

- Severe
- Moderate
- Mild

Strong Opioids
- Morphine
- Oxycodone

Weak Opioids
- Tramadol

COX-2

NSAIDs

Acetaminophen

Unmet Need

Pain Research Today - The Unmet Needs
Significant Unmet Needs in Neuropathic Pain Treatments

- AEDs
- Tricyclics
- Gabapentin
- Pregabalin
- Duloxetine

Pain Research Today - The Unmet Needs
Tapentadol – A New Analgesic with a Dual Mode of Action
The Search for a New Morphine Without Side Effects

Tramadol
Tramadol is a racemate

(-) tramadol

(+) tramadol
Tramadol – Pharmacological Profile

Metabolites of Tramadol

Tramadol → M1 → M5 → M4 → M3 → M2

M1: OH
M5: O-H
M4: O-H
M3: OH
M2: O-CH₃

Tramadol
Tramadol’s mode of action - biochemical profile

- μ-Opioid
- Norepinephrine Uptake Inhibition
- Serotonin Uptake Inhibition
Tramadol’s mode of action - biochemical profile

- μ-Opioid
- Norepinephrine Uptake Inhibition
- Serotonin Uptake Inhibition

Tramadol – Pharmacological Profile
μ-Opioid binding of tramadol and tramadol-M1

Tramadol – Pharmacological Profile

µ Ki (µM)
Comparison of molecular structures

(+) Tramadol and Morphine
Tramadol’s mode of action - biochemical profile

Tramadol - Pharmacological Profile

- μ-Opioid
- Norepinephrine Uptake Inhibition
- Serotonin Uptake Inhibition
Norepinephrine-Uptake inhibition of tramadol and tramadol-M1

Desipramin | Venlafaxine | (+) Tramadol | (-) Tramadol | (+)-M1 | (-)-M1

NE-Uptake Inhibition Ki (µM)

- Desipramin: 0.002
- Venlafaxine: 0.14
- (+) Tramadol: 6.9
- (-) Tramadol: 0.6
- (+)-M1: 42
- (-)-M1: 1.8
Comparison of molecular structures

(+)-tramadol

(-)-tramadol

norepinephrine
Comparison of acute pain (Tail Flick) and chronic inflammatory pain (Randall Selitto)
Comparison of acute pain (Tail Flick) and neuropathic pain (Bennett)

Tailflick mouse i.v. (4.64mg/kg)  Bennett CP i.p. (21.5 mg/kg)
Occurrence of the Synthetic Analgesic Tramadol in an African Medicinal Plant

Ahcène Boumendjel, Germain Sotoing Taïwe,* Elisabeth Ngo Bum, Tanguy Chabrol, Chantal Beney, Valérie Sinniger, Romain Haudecoeur, Laurence Marcourt, Soura Challal, Emerson Ferreira Queiroz, Florence Souard, Marc Le Borgne, Thierry Lomberget, Antoine Depaulis, Catherine Lavaud, Richard Robins, Jean-Luc Wolfender, Bruno Bonaz, and Michel De Waard*
Tramadol – The Research Strategy

What have we learned from the Tramadol story?

Can both principles be combined in one molecule (one enantiomer)?
Tapentadol – A New Analgesic with a Dual Mode of Action

- Derivatisation of hydroxyl group: ester, ether, …
- Replacement of hydroxyl group by N, H, halogen
- Elimination resulting in olefins

- Substitution of cyclohexane ring
- Size of ring system
- Introduction of hetero atoms (e.g. O, N, S)
- Aromatic rings

- Phenyl ring substitution
- Replacement by heterocyclic aryl rings
- Replacement by acyclic ring systems

- Methylene group substitution
- N-Substitution
- N-containing ring systems

- Introduction of spacer groups between ring systems
Tapentadol – A New Analgesic with a Dual Mode of Action

Opening of the cyclohexane ring

Racemate with relative stereochemistry cis

From Prodrug to direct acting drug

Selecting of one enantiomer

Replacement of tert. OH group

Tramadol

Tapentadol
Tapentadol – A New Analgesic with a Dual Mode of Action

μ-Rezeptor-Agonism (MOR) and Noradrenalin Reuptake Inhibition (NRI)

50-fold weaker μ-receptor binding in comparison to Morphine
Tapentadol as a Multiple Ligand

Designed Multiple Ligand Continuum*)**)

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Tapentadol – A New Analgesic with a Dual Mode of Action

Spinal Mechanism of Action: MOR-NRI

Ascending Pathway

Descending Pathway

α2-R

NA

Pain signal

SP

Glut
Spinal Mechanism of Action: MOR-NRI

Ascending Pathway

Descending Pathway

α₂-R

Tapentadol

MOR

NA

+SP

Glut

Pain signal
Tapentadol – A New Analgesic with a Dual Mode of Action

Spinal Mechanism of Action: MOR-NRI

Ascending Pathway

Descending Pathway

NA

Tapentadol

MOR

α₂-R

SP

Glut

Pain signal
Tapentadol: Activity in MOR knock-out- and Wildtype-Mice

**Acute Pain (heat nociception), ip**

- Morphine: 10 mg/kg 20min
- Tapentadol: 31.6 mg/kg 15min

<table>
<thead>
<tr>
<th>(% MPE)</th>
<th>OPRM1 WT</th>
<th>OPRM1 KO</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td><img src="chart1" alt="" /></td>
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<tr>
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<tr>
<td>100</td>
<td><img src="chart9" alt="" /></td>
<td><img src="chart10" alt="" /></td>
</tr>
</tbody>
</table>

- * p<0.05 treatment vs vehicle
- # p<0.05 KO vs WT

**STZ diabetes (heat hyperalgesia), ip**

- Morphine: 3.16 mg/kg 30min
- Tapentadol: 3.16 mg/kg 30min

<table>
<thead>
<tr>
<th>(% MPE)</th>
<th>OPRM1 WT</th>
<th>OPRM1 KO</th>
</tr>
</thead>
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<tr>
<td>0</td>
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<tr>
<td>100</td>
<td><img src="chart19" alt="" /></td>
<td><img src="chart20" alt="" /></td>
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</tbody>
</table>

- * p<0.05 treatment vs vehicle
- # p<0.05 KO vs WT

Tapentadol remains partially active in MOR-Knock-out Mice
Pharmacology: Pain Models

- **Acute**
- **Chronic inflammatory**
- **Chronic neuropathic**
Analgesic Potency in Acute Pain

Tail Flick, mouse, i.v.

Values [mg/kg]

Analgesic ED*50

- Oxycodon: 0.80
- Morphin: 1.40
- Tapentadol: 4.20
- Tramadol: 13.7

Tapentadol – *in vivo* Pharmacology
Neuropathic pain model: Peripheral Mononeuropathy (Chung model)

Investigation of tactile allodynia after tight ligation of the dorsal root of spinal nerves (L5, L6)
High potency and efficacy in neuropathic pain (Chung)

**Analgesic ED\textsubscript{50}**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Value [mg/kg; i.v.]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tapentadol</td>
<td>1.64</td>
</tr>
<tr>
<td>Morphine</td>
<td>1.70</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>2.20</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>4.20</td>
</tr>
<tr>
<td>Tramadol</td>
<td>4.30</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>6.70</td>
</tr>
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</table>
Tapentadol – *in vivo* Pharmacology – Side Effects

**Tapentadol**

**Morphin**
Opioid Induced Side Effects: Emesis

Tapentadol – in vivo Pharmacology – Side Effects

Tapentadol shows a reduced emetic potential in comparison to Morphine

Opioid Induced Side Effects: Obstipation

- Increase of the intestinal charcoal passage
- Reduction of the PGE2 induced diarrhoe
Tapentadol – *in vivo* Pharmacology – Side Effects

**Opioid Induced Side Effects: Obstipation**

Tapentadol shows a reduced gastrointestinal inhibitory potential in comparison to Morphine.
Opioid Induced Side Effects: Tolerance Development

Chronic constriction injury, rat i.p.

Significant reduced tolerance development


Tapentadol – in vivo Pharmacology – Side Effects
Medicinal Chemistry, Quo Vadis?
The changing climate of Pharmaceutical R&D
New Drug Development: Some Facts

- **Global situation:**
  - Word population: 7 Billion with Growth rate of 1.1%
  - Word GDP: 70 Trillion Dollars with Growth rate of 5.2%
  - Word Pharma Market: 950 Billion Dollars with Growth rate of 6%

- **Drug discovery and development:**
  - To develop a new drug takes 10-15 years
  - The average cost of a new drug is in the range of $1.3 billion, this being a big financial risk
  - 20-30 new drugs are approved annually by the US-FDA: on average; 24 between 2000 and 2009;
  - Similar numbers by EMA
  - >3000 potential new drugs are under clinical development (Phase I, II, and III), however, the attrition rate has become very high
Creating New Medicines is a High Risk Journey

Pharmaceutical Industry – The R & D Process

- **Idea**
- **Synthesis of compounds**
  - **Screening**
  - **Formulations developed**
  - **Candidate**
  - **Extensive safety studies**
  - **Studies in healthy volunteers (Phase I)**
  - **Studies in 100-300 patients (Phase II)**
- **Risk assessment analysis**
- **Gaining approval**

- **Medicine**

- **Gaining approval**

- **Formulations developed**

- **Screening**

- **Extensive safety studies**

- **Studies in healthy volunteers (Phase I)**

- **Studies in 100-300 patients (Phase II)**

- **Risk assessment analysis**

- **Gaining approval**

- **Medicine**

- **Years**
Commonly Perceived Criticisms of the Pharmaceutical Industry

Pharmaceutical Industry – Changing Climate

Commonly Perceived Criticisms of the Pharmaceutical Industry

- Profits Over Cures
- Questionable Marketing
- Lack Of Innovation
- High Drug Prices
- Poor Access To Drugs
- Low R&D Budgets
- Block Drug Reimportation
- Delay Access To Generics

Pharmaceutical Industry – Changing Climate

Trends driving the evolution of the global healthcare environment

Blockbuster patent expirations

Pressure to control health care spending

R&D productivity crisis

Rise of Emerging markets

Source: Global Intelligence Alliance, Business Perspectives on Emerging Markets 2012-2017 Survey. Qn. Which are the top 5 Emerging Markets for your industry over the next 5 years? AN=38.
The recent years has brought considerable sales and erosions for most of the leading multinational pharmaceutical companies.

There is not a single reason for this development, many different causes happened at nearly the same time:

- Patent expiries of big blockbuster drugs and lack of innovative new drugs due to a decline in R&D productivity and efficiency;
- Worldwide economy crisis;
- Health care reforms in many countries with cost and price pressures and shift to cheap generics.

The traditional blockbuster model is more or less outdated;

Megamergers and acquisitions in this industry will surely continue, but will not be the solutions of the problems.

Also outsourcing of (newly-defined) non-core activities like manufacturing and parts of R&D will only give temporary cost relief.

A. Kleemann, Metamorphosis of the Pharmaceutical Industry; Pharm. Ind. 75(4), 562-574 (2013)
<table>
<thead>
<tr>
<th>Year</th>
<th>Number of jobs cut</th>
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<td>2000</td>
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<tr>
<td>2001</td>
<td>4,736</td>
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<td>2002</td>
<td>11,488</td>
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<td>2009</td>
<td>61,109</td>
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<td>53,636</td>
</tr>
<tr>
<td>2011</td>
<td>ca. 21,000</td>
</tr>
<tr>
<td>Total:</td>
<td>315,265</td>
</tr>
</tbody>
</table>

2009 Total layoffs: 61,109
thereof Pfizer (19,500), Merck & Co. (16,000), J&J (8,900), AstraZeneca (7,400), GSK (6,000), Eli Lilly (5,500)

2010 Total layoffs: 53,636
thereof AstraZeneca (8,550), Pfizer (8,480), GSK (5,201), Roche (4,800), Bayer (4,500), Abbott (3,000), Sanofi-Aventis (2,500), Takeda (1,400), Novartis (1,400), Genzyme (1,280)

A. Kleemann, Metamorphosis of the Pharmaceutical Industry; Pharm. Ind. 75(4), 562-574 (2013)
### Blockbuster Drug Patent Expirations between 2011 and 2016

<table>
<thead>
<tr>
<th>Year</th>
<th>Brand Name</th>
<th>2010 Sales (Billions of Dollars)</th>
<th>Company</th>
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<tbody>
<tr>
<td>2011</td>
<td>Actos®</td>
<td>4.6</td>
<td>Takeda</td>
</tr>
<tr>
<td>2011</td>
<td>Zyprexa®</td>
<td>5.0</td>
<td>Eli Lilly</td>
</tr>
<tr>
<td>2011</td>
<td>Lipitor®</td>
<td>12</td>
<td>Pfizer</td>
</tr>
<tr>
<td>2012</td>
<td>Levaquin®</td>
<td>1.4</td>
<td>Janssen</td>
</tr>
<tr>
<td>2012</td>
<td>Lexapro®</td>
<td>3.5</td>
<td>Forest</td>
</tr>
<tr>
<td>2012</td>
<td>Seroquel®</td>
<td>5.6</td>
<td>AstraZeneca</td>
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<tr>
<td>2012</td>
<td>Plavix®</td>
<td>9.1</td>
<td>BMS/Sanofi</td>
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<tr>
<td>2012</td>
<td>Singulair®</td>
<td>5.4</td>
<td>Merck</td>
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<tr>
<td>2012</td>
<td>Diovan®</td>
<td>6.1</td>
<td>Novartis</td>
</tr>
<tr>
<td>2013</td>
<td>Cymbalta®</td>
<td>3.5</td>
<td>Eli Lilly</td>
</tr>
<tr>
<td>2013</td>
<td>OxyContin®</td>
<td>2.4</td>
<td>Purdue</td>
</tr>
<tr>
<td>2013</td>
<td>Zometa®</td>
<td>1.5</td>
<td>Novartis</td>
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<tr>
<td>2014</td>
<td>Nexium®</td>
<td>5.0</td>
<td>AstraZeneca</td>
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<tr>
<td>2014</td>
<td>Celebrex®</td>
<td>2.7</td>
<td>Prizer</td>
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<tr>
<td>2014</td>
<td>Sandostatin®</td>
<td>1.3</td>
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<td>Gleevec®</td>
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<td>Novartis</td>
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<tr>
<td>2016</td>
<td>Crestor®</td>
<td>6.1</td>
<td>AstraZeneca</td>
</tr>
</tbody>
</table>

*aSource: ref 49.  bWorld-wide sales.  cBMS, Bristol-Myers Squibb.*
Pharmaceutical Industry – Productivity

Global pharmaceutical R&D expenditure, development time, NME output and sales 1992-2002p

Indexed values (1992 = 100)

Year

Global R&D expenditure
Global sales
Development time (3 year moving average)
Global NME output

Innovation Gap
FDA drug approvals since 1993.

New molecular entities and biologics license applications approved by the US Food and Drug Administration’s (FDA’s) Center for Drug Evaluation and Research, by year.
R&D Productivity – FDA-approved New Molecular Entities

The number of annual approvals since 1930

The average annual rates of approval by decade since 1930

Drug Discovery Today 19, 1033-1039 (2014)
# Ranking System for New Drug Approvals Using FDA Characterizations as Criteria

## Pharmaceutical Industry - Innovation

**New Drug Approval (NDA) Type** | **Level of Innovation**
---|---
Priority NMEs | Most Innovative
Standard NMEs |  
Priority IMDs |  
Standard IMDs |  
Other Drugs | Least Innovative

“New drugs to treat and cure sick patients are coming into the market in the United States at the slowest rate in a decade, despite billions invested by pharmaceutical companies on research and a costly expansion by the federal agency that”

“The decline in the number of new drugs is most pronounced in the category considered by the Food and Drug Administration to have the greatest promise for patients -- those listed as breakthrough "priority" drugs and "new molecular entities" that are different from any others on the market.”

Source: Washington Post, 11/18/02
New Drug Approvals by the FDA in 1989-2000

Two-third of new drugs approved in 1989-2000 used active ingredients already on the market
Source: FDA 2001

## New Drug Approvals by the FDA in 1989-2000*)

<table>
<thead>
<tr>
<th>Most Innovative</th>
<th>Least Innovative</th>
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</thead>
<tbody>
<tr>
<td>Priority NMEs</td>
<td>Other Drugs</td>
</tr>
<tr>
<td>Standard NMEs</td>
<td>Priority IMDs</td>
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<tr>
<td><strong>New Active Ingredients</strong></td>
<td><strong>Old Active Ingredients</strong></td>
</tr>
<tr>
<td><strong>15 %</strong></td>
<td><strong>46 %</strong></td>
</tr>
<tr>
<td><strong>20 %</strong></td>
<td><strong>11 %</strong></td>
</tr>
<tr>
<td><strong>8 %</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Distribution of NDAs, 1989-2000: Total 1.035 New Drugs**

Only 15 % of new drugs approved in 1989-2010 were highly innovative priority NMEs

Source: FDA 2001

*[/www.nihcm.org](http://www.nihcm.org); Changing Patterns of Pharmaceutical Innovation*
Pharmaceutical Industry - Innovation

R&D Productivity

R&D Productivity Data

All values inflation adjusted to 2013.
Sources: EvaluatePharma; US Food and Drug Administration (FDA); Boston Consulting Group (BCG) analysis

Eroom’s Law in pharmaceutical R&D.

The number of new drugs approved by the US Food and Drug Administration (FDA) per billion US dollars (inflation-adjusted) spent on research and development (R&D) has halved roughly every 9 years.

The Changing Climate in Pharmaceutical Research

- **Scientific Advances**
  - The Human Genome
  - Advances in Screening Technologies
  - Advances in Synthesis Technologies

- **Raising bar on drug-like characteristics**
  - Attrition rates too high
  - Increasing multi-parameter property optimization

- **Increasing Scale**
  - Data volumes and complexity soar
  - Global, multi-site, multi-cultural organizations
  - Rising costs of drug discovery and development

- The human body is complex
  - 100 organs,
  - 1500 different cell types,
  - 10,000 diseases

Pharmaceutical Industry – The R & D Process
Chemogenomics

10^{40} - 10^{120} compounds with C, H, O, N, P, S, F, Cl, Br, I, and MW < 500

Pharmaceutical Industry – The R & D Process
Venn diagram of the distribution of commonly used libraries in chemical space

Number of drug like molecules that could be synthesized per chemist per year

- **1970s**: 100 compounds per chemist per year
- **1980s**: 10,000 – 100,000 compounds per chemist per year
- **1990s**
- **2000s**
- **2010s**

$x \times 1.000$
Technological Inputs into Drug Research & Development

DNA Sequencing

1970s 1980s 1990s 2000s 2010s

1st Genome Sequence  Genomics

x 1,000,000,000 faster
R & D Performance: Drug Discovery Technologies

Technological Inputs into Drug Research & Development

X-ray Crystallography

1970s
1980s
1990s
2000s
2010s

1st Protein X-ray Structures
Structure-Based Design

x 1.000 faster calculation
Technological Inputs into Drug Research & Development

Three Dimensional Protein Structures

1970s 1980s 1990s 2000s 2010s

Some 100s Structures > 50,000 Structures

x 300 more entities in the last 25 years
The chart shows the trend in storage capacity needed to store biological data at EMBL-EBI (a terabyte is a million million bytes).
Potential outcome of new technologies

- Proteomics
- Genomics
- Genetics
- Imaging
- Tissue banks
- Disease definition
- Nanosciences
- Knowledge management

- Molecular definition of disease
- New Drug targets
- Prediction of Efficacy
- Prediction of Toxicity
- Better clinical trials design
- Reduced side-effects
- Diagnostic tools
- Personalised Treatments
Key R&D bottlenecks to overcome

- Discovery research
- Preclinical development
- Translational medicine
- Clinical development
- Pharmacovigilance

Predictive pharmacology
Predictive toxicology
Identification of biomarkers
Patient recruitment
Validation of biomarkers
Risk assessment with regulatory authorities

Efficacy
Safety

Data → Knowledge → Prediction
Preclinical models that are more predictive of clinical efficacy and safety
Drug Discovery Strategies Today – What Has Pharmaceutical Industry Learned From The Past?

Nothing
Clinical attrition statistics

Attrition rate by stage of development

Reasons for clinical failure in 1991

Reasons for clinical failure in 2000

Pharmaceutical Industry – The R & D Process

Drug Research was and is...

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

- An compound with an interesting structure has not necessarily a biological activity
- A compound with biological activity is not a hit
- A hit is not a lead
- An optimized lead is no candidate
- A candidate is not a drug
- A drug is not a success
- A successful drug is luck!

10100 Chemical Space of Organic Molecules

Pharmaceutical Industry – The R & D Process
The Evolution of Drug Discovery Strategies

1900

- **in vivo** screening of any available chemical compound: industrial chemicals, dyestuffs, natural compounds, copies of existing drugs, mimics of endogenous molecules
- Pharmacological tests on whole animals or isolated organs
- Objective: detection of the therapeutic effect
- Knowledge of mechanism of action was not considered as mandatory

1960

- Progress in biochemistry and Structural biology

1985

- Development of miniturized and automated bioassays
- Progress in molecular biology
- Receptor identification
- Cloning techniques
- Automatized combinatorial chemistry

1995

- High throughput screening programs
- Development of in silico technology
- Virtual screening
- Computational assessment of „drug likeness“
- screening of > 100,000 compounds/day
- timeconsuming and expensive process
- Many hits and too few leads
- low diversity of many libraries: large series of similar in house cpds, chemical catalog series,...
- low drug likeness
Four Possible Strategies in Research

- No hypotheses, no experiments
- Hypotheses but no experiments
- No hypotheses, only experiments
- Hypotheses and experiments

Rolf Zinkernagel (Nobel prize in Medicine 1996)
Chocolate consumption enhances cognitive function, which is a sine qua non for winning the Nobel Prize, and it closely correlates with the number of Nobel laureates in each country.

The early days of drug discovery at Grünenthal (1990)

*in vivo* activity
Writhing Mouse
ED$_{50}$, oral

*in vitro* Profile
µ-Opioid receptor affinity
Naloxon binding (K$_i$)
Drug discovery process

- Identify Target: Biomolecule Plays a Role in Disease
- Identify “Hits”: New Agents Interact with Target
- Optimize Leads: Molecules Active on Target & Bioavailable
- Preclinical Testing: Molecules Safe & Effective in Animals
- Clinical Research: Molecules Safe & Effective in Humans

Advantages of early *in vivo* testing

- Onset of Action
- CNS Side Effects
- Oral Bioavailability
- Duration of Action

**SAR based Lead Optimization**

- *in vivo* activity
- Writhing Mouse
- ED$_{50}$, oral

**in vitro Profile**

- μ-Opioid receptor affinity
- Naloxon binding (K$_i$)

**Early Clinical Proof of Concept**

- 1000 Compounds (14 scaffolds)
- 280 open chain lead series

The Future of Medicinal Chemistry & Medicinal Chemists
"Drug research needs a paradigm shift"

[By Kalle Lötberg]

According to earlier leading researchers, a paradigm shift is necessary that sees pharmaceutical research returning to animal testing in its primary stages.

- ...Top executives of global "Big Pharma" companies have to realise that pharmaceutical research needs a paradigm shift, moving away from the current practice of early stages protein target testing.
- A new paradigm is needed in which research returns to experiments based on animal testing models (phenotypic research)....
- ...People are very biased today. But medicinal chemists neither can nor have to know exactly how a substance acts.
- This has always been the case, since organisms are very much more complex than the sum of their receptors, enzymes and ion channels....

Kalle Lötberg, "Drug research needs a paradigm shift", Kemivärlden Biotech med Kemisk Tidskrift. Nr 3 March 2014
"Drug research needs a paradigm shift"

1970s – 1990s
- Disease models for animals were often developed in collaboration with hospital-based researchers.
- Newly synthesized compounds were tested in vivo directly on animals.
- Effect in animals were the all important driving force.

1990s – Today
- The golden era of the genome had begun, receptors were linked to specific genes, and an in vitro technique for measuring a protein’s affinity to synthetic substances was developed.
- The process became rational, efficient, simple, elegant and super-fast – and therefore also attractive.

The Future
- Focus on building disease models - for many years an area neglected in favour of for instance multi-chemistry.
- Use modern integrated screening directly on animals, including both behaviour and various analyte parameters.
- Synthesize carefully selected substances and test them all on animals.

The chemists were divided into those who worked at the early and the late testing stages respectively, and their previously acquired competence was often wasted.

It was taboo not to know the target and the mechanism already at the start of a new project.
in vivo Pharmacology
We have arguably the most talented and well-trained pool of synthetic chemists in the world, who could contribute innovative ideas to solve the most difficult challenges.

However, we have, instead, discouraged innovative and unconventional ideas in the practice of medicinal chemistry.

We have not raised the bar for our most capable and skilled chemists. We failed to provide them with the opportunity to achieve their full potential and push the boundaries of medicinal chemistry.

Steve Jobs once said, “When you grow up, you tend to get told that the world is the way it is, and your life is just to live your life inside the world. Try not to bash into the walls too much. Try to have a nice family life. Have fun, save a little money.”

Computers and drugs are not quite the same, but his statement captures the current mind-set of many medicinal chemists...
R&D Performance and Productivity

\[ \text{R&D productivity} = \frac{\text{R&D efficiency} \cdot \text{R&D effectiveness}}{\text{For the industry}} \]

- **For the industry**
  - \( \frac{\text{Volume of innovation}}{\text{Cost}} \cdot \text{Value} = \frac{\text{WIP} \cdot p \cdot (TS)}{CT} \cdot \frac{1}{C} \cdot V \)

- **For economists**
  - \( \frac{\text{R&D productivity}}{\text{R&D efficiency}} \cdot \text{Value} \)

Goal: maximize
Estimates of Where New Drugs Come From

1990 - 1999
- Pharmaceutical Industry (93.3%)
- Government/Public Sector (3.2%)
- Academic Labs (3.5%)

1998 - 2007
- Academic Labs (24%)
- Pharmaceutical Industry (76%)

Data taken from Kneller, 2010.

Data taken from DiMasi et al., 2003.