SEQT

Divisione di Chimica Farmaceutica

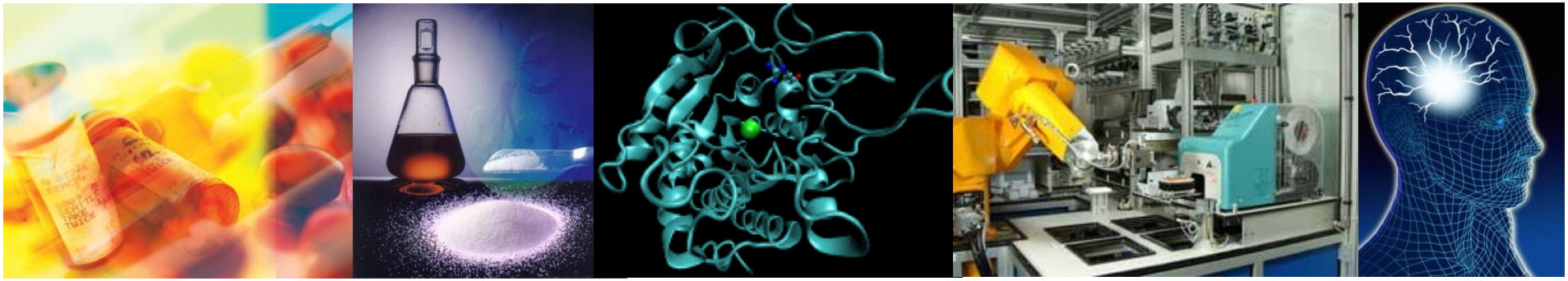
SIMCC 2015

SPANISH-ITALIAN MEDICINAL CHEMISTRY CONGRESS

BARCELONA, SPAIN - JULY 12-15, 2015

**SIMCC 2015, Barcelona**

**July 12-15, 2015**



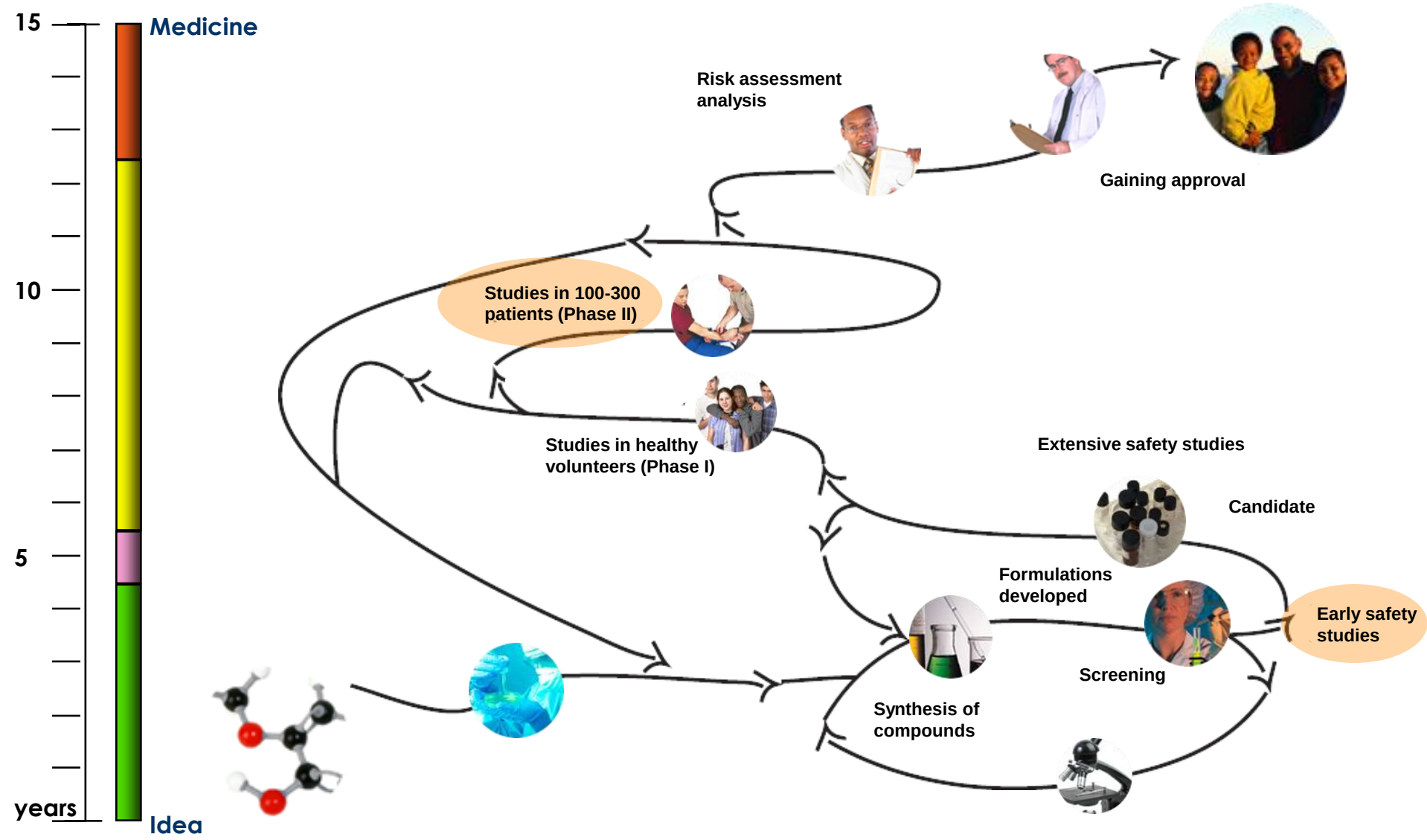
# Medicinal Chemistry, Quo Vadis?

## A personal view backwards on successful drug discoveries within the changing climate of Pharmaceutical R&D

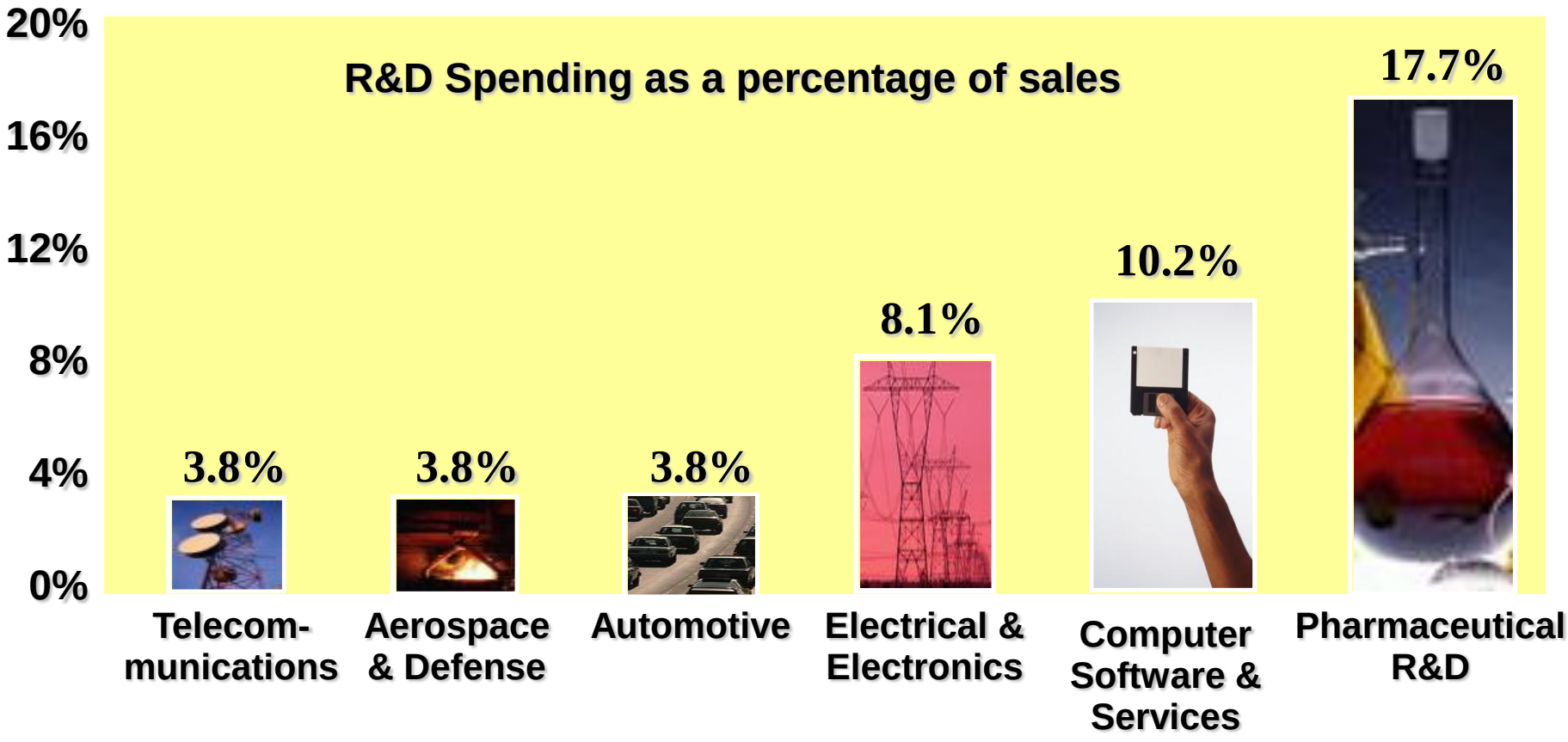
Helmut Buschmann

# Pharmaceutical Industry – The R & D Process

## Creating New Medicines is a High Risk Journey

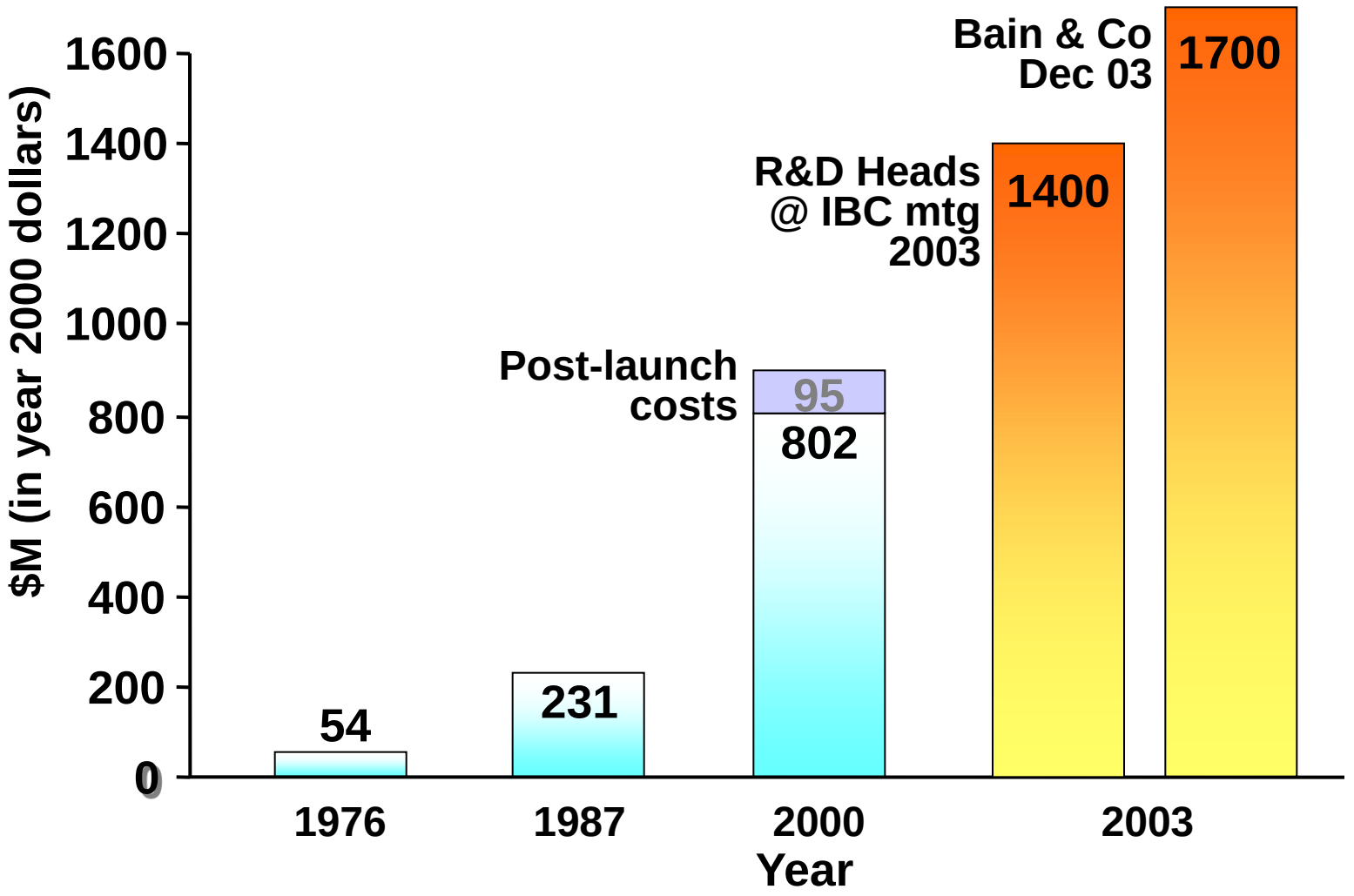


# Pharmaceutical R&D investment is substantial

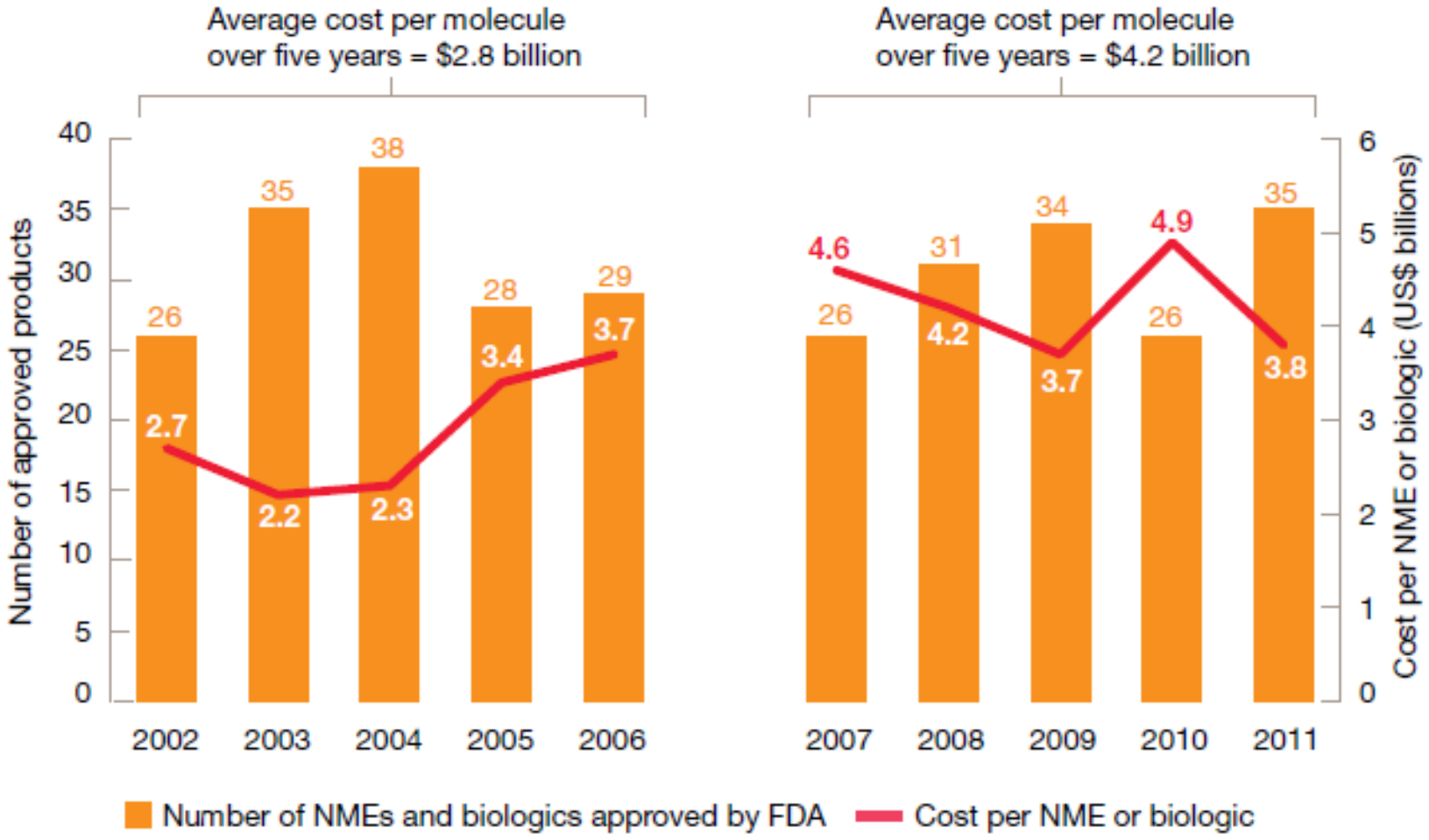


# Pharmaceutical Industry – The R & D Process

## Average R&D costs per NCE medicine launched

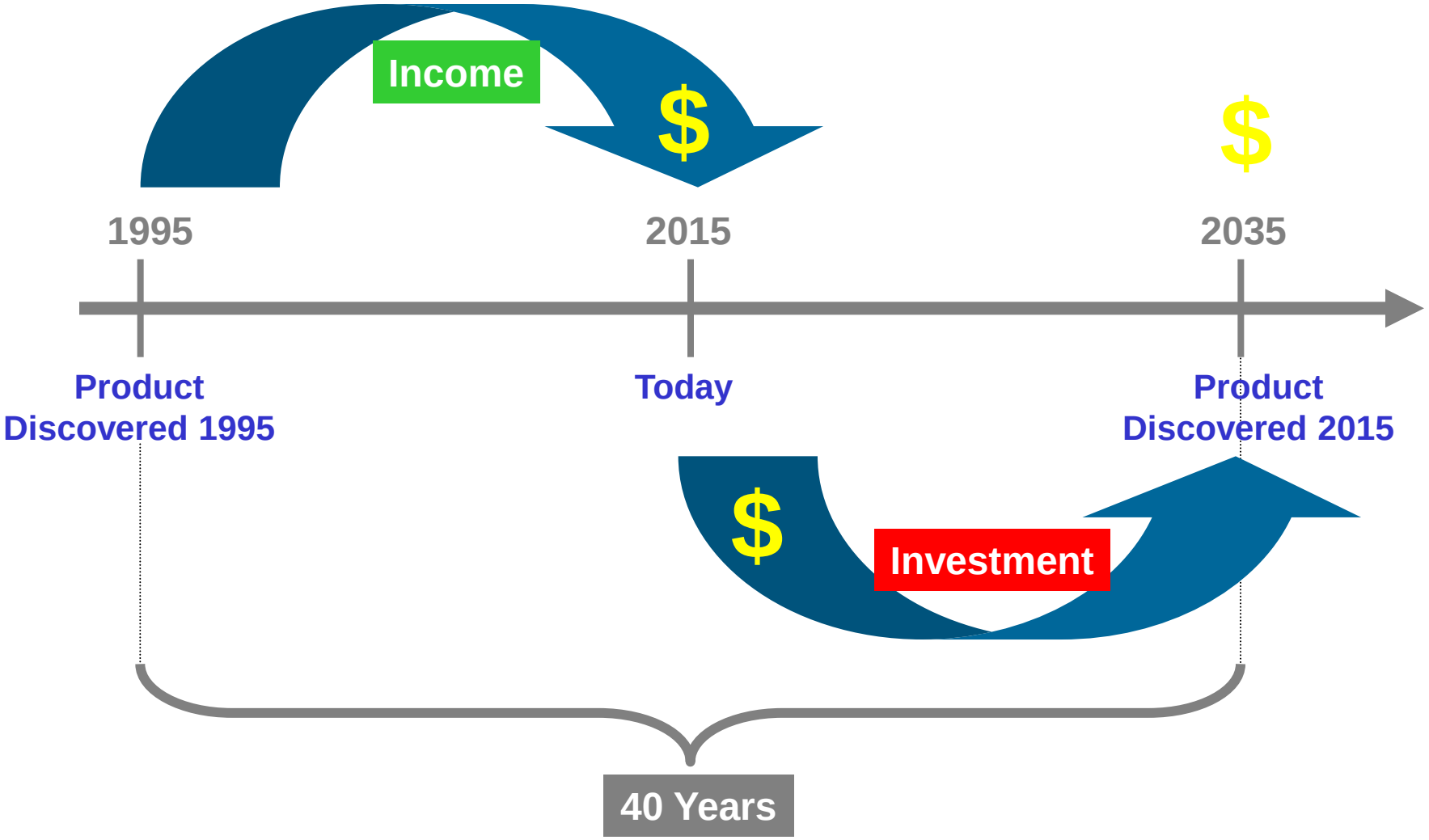


# Costs per approved molecule are unsustainably high




*From vision to decision* Pharma 2020 www.pwc.com/pharma2020

# Forty-Year Coupling of Investments and Return in the Pharmaceutical Industry



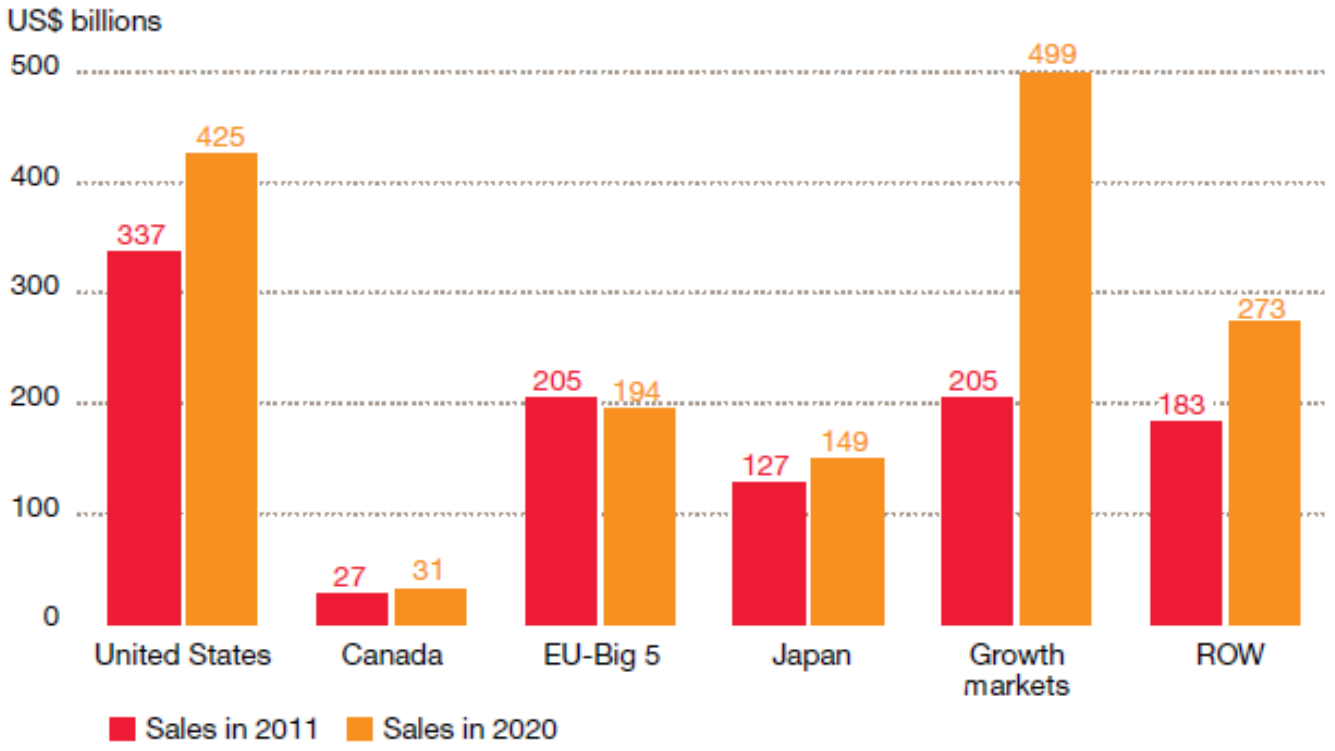
# Pharma has an additional lever in the form of outcomes data





*From vision to decision* Pharma 2020 www.pwc.com/pharma2020

# The global pharmaceutical market could be worth nearly $1.6 trillion by 2020

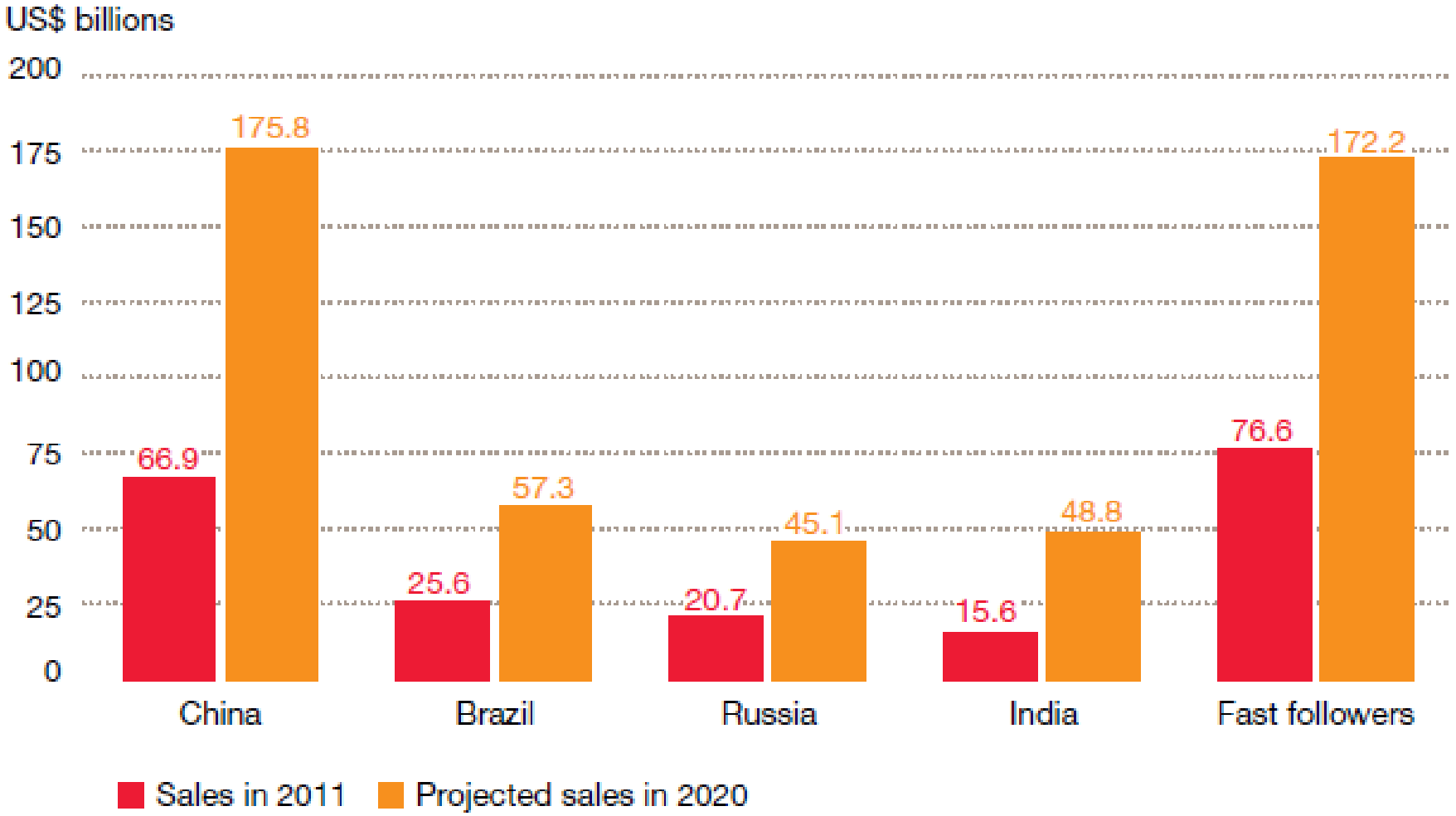



*Source: Business Monitor International*

Notes: (1). All sales are expressed in US dollars at constant exchange rates; (2). The growth markets include, in descending order of size, China, Brazil, Russia, India, Mexico, Turkey, Poland, Venezuela, Argentina, Indonesia, South Africa, Thailand, Romania, Egypt, Ukraine, Pakistan and Vietnam. (3) EU-Big 5 is France, Germany, Italy, Spain and United Kingdom.

*From vision to decision* Pharma 2020 www.pwc.com/pharma2020

# Demand for medicines is rising rapidly in the growth markets




*From vision to decision* Pharma 2020 www.pwc.com/pharma2020

# 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%

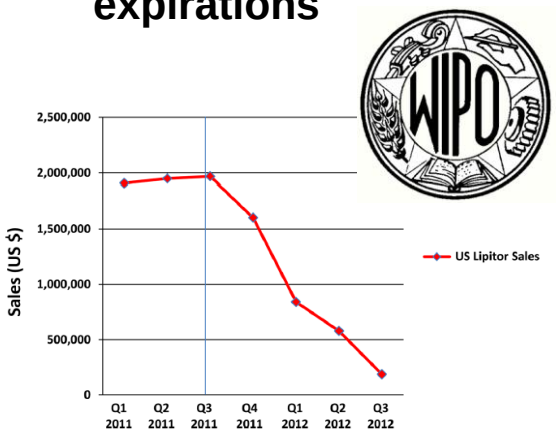
- **Drug discovery and development:**
  - To develop a new drug takes 10-15 years
  - The average cost of a new drug is in the range of $ 1.3 billion, this being a big financial risk
  - 20-30 new drugs are approved annually by the US-FDA: on average; 24 between 2000 and 2009;
  - Similar numbers by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

# Commonly Perceived Criticisms of the Pharmaceutical Industry


Magid Abou-Gharbia and Wayne E. Childers, Discovery of Innovative Therapeutics: Today's Realities and Tomorrow's Vision. 1. Criticisms Faced by the Pharmaceutical Industry, J. Med. Chem 56, 5659-5672 (2013)

# Trends driving the evolution of the global healthcare environment

## Blockbuster patent expirations



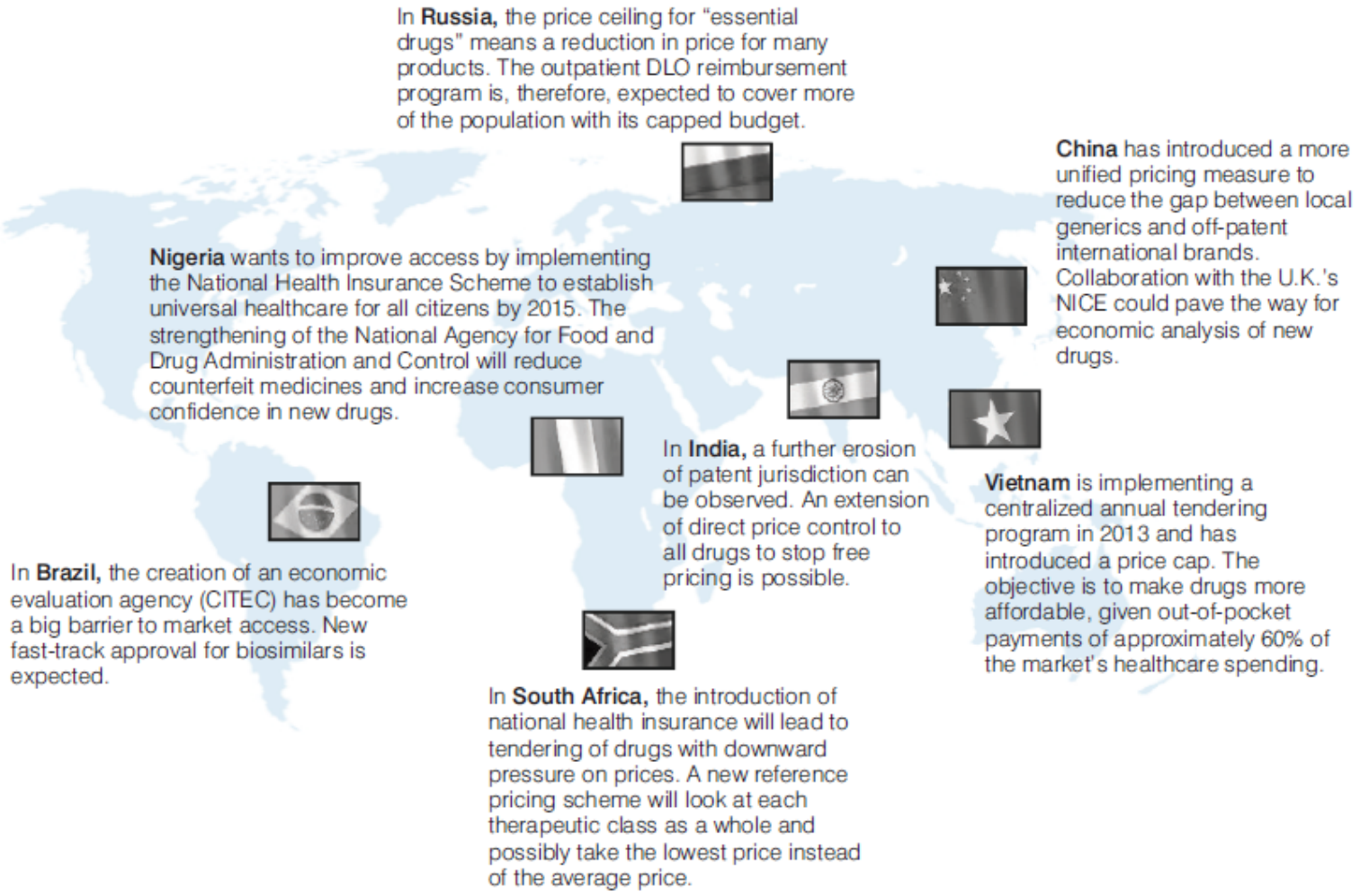

## Pressure to control health care spending


## 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? N=38*

# Examples of Healthcare Policy Changes for Selected Emerging Markets




Source: IMS Health; UNIDO; SCRIP; Booz & Company analysis

# Metamorphosis of the Pharmaceutical Industry

- 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 productivityand efficiency;
  – Wordwide economy crisis;
  – Health care reforms in many countries with cost and price pressures and shift to cheap generics.

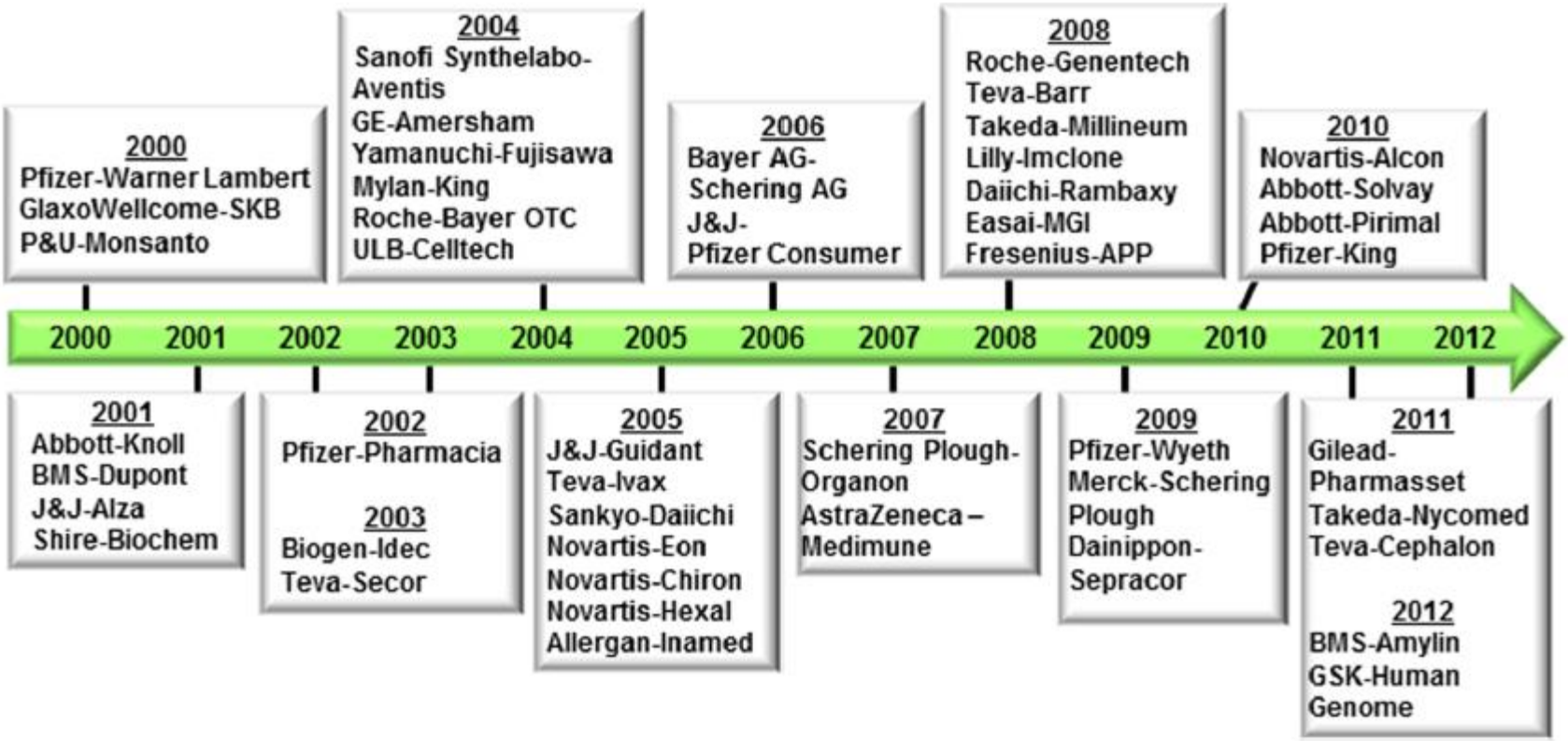
- The traditional blockbuster  model is more or less outdated;

- 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)

# Timeline of mergers and acquisitions with values ≥$2 billion that occurred from 2000 to 2012




Magid Abou-Gharbia and Wayne E. Childers, Discovery of Innovative Therapeutics: Today's Realities and Tomorrow's Vision. 2. Pharma's Challenges and Their Commitment to Innovation, J. Med. Chem 57, 5525–5553 (2014)

# Pharma Industry Layoffs (2000-2011)

| Year | Number of jobs cut |
|---|---|
| 2000 | 2,453 |
| 2001 | 4,736 |
| 2002 | 11,488 |
| 2003 | 28,519 |
| 2004 | 15,640 |
| 2005 | 26,300 |
| 2006 | 15,638 |
| 2007 | 31,732 |
| 2008 | 43,014 |
| 2009 | 61,109 |
| 2010 | 53,636 |
| 2011 | ca. 21,000 |
| Total: | 315,265 |

*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 2011and 2016

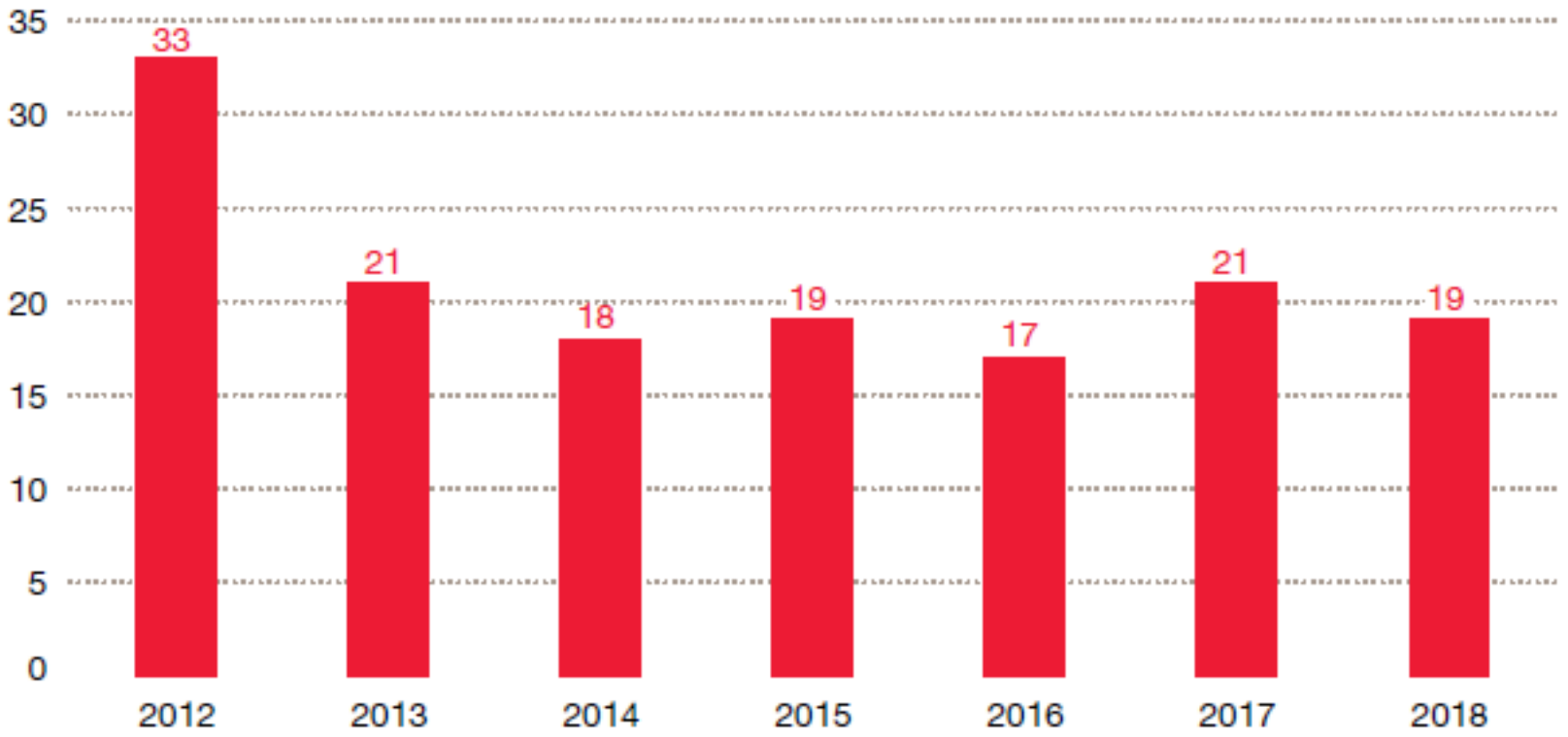
| year | brand name | 2010 sales (billions of dollars)[b] | company |
|---|---|---|---|
| 2011 | Actos® | 4.6 | Takeda |
| 2011 | Zyprexa® | 5.0 | Eli Lilly |
| 2011 | Lipitor® | 12 | Pfizer |
| 2012 | Levaquin® | 1.4 | Janssen |
| 2012 | Lexapro® | 3.5 | Forest |
| 2012 | Seroquel® | 5.6 | AstraZeneca |
| 2012 | Plavix® | 9.1 | BMS[c]/ Sanofi |
| 2012 | Singulair® | 5.4 | Merck |
| 2012 | Diovan® | 6.1 | Novartis |
| 2013 | Cymbalta® | 3.5 | Eli Lilly |
| 2013 | OxyContin® | 2.4 | Purdue |
| 2013 | Zometa® | 1.5 | Novartis |
| 2014 | Nexium® | 5.0 | AstraZeneca |
| 2014 | Celebrex® | 2.7 | Prizer |
| 2014 | Sandostatin® | 1.3 | Novartis |
| 2015 | Abilify® | 4.6 | BMS[c] |
| 2015 | Gleevec® | 4.3 | Novartis |
| 2016 | Crestor® | 6.1 | AstraZeneca |

[a]Source: ref 49. [b]World-wide sales. [c]BMS, Bristol-Myers Squibb.

Magid Abou-Gharbia and Wayne E. Childers, Discovery of Innovative Therapeutics: Today's Realities and Tomorrow's Vision. 2. Pharma's Challenges and Their Commitment to Innovation, J. Med. Chem 57, 5525–5553 (2014)

# Big Pharma's earnings are tumbling over the patent cliff

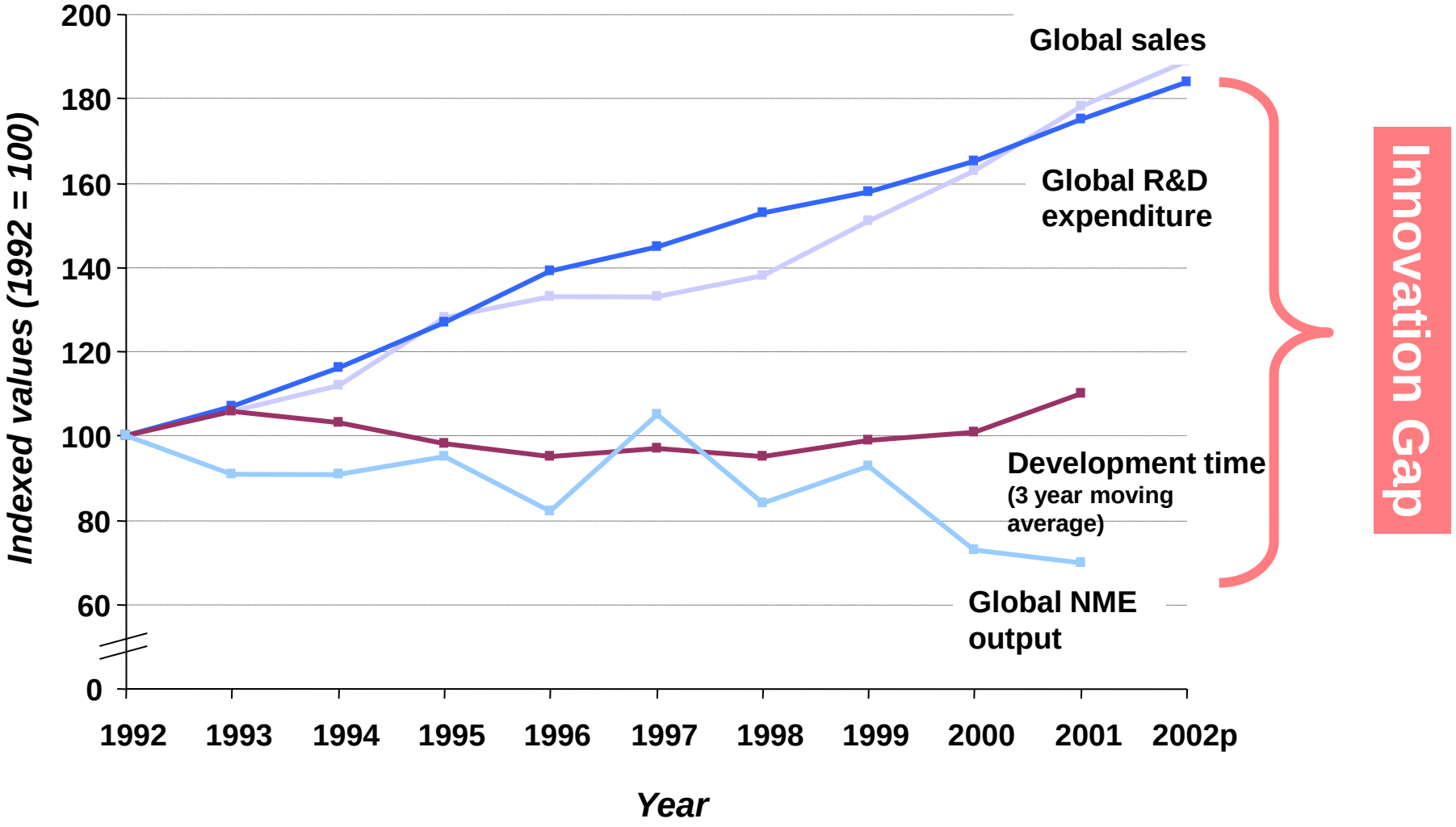
**Expected sales losses (US$ billions)**




*From vision to decision* Pharma 2020 www.pwc.com/pharma2020

# Pharmaceutical Industry – Productivity

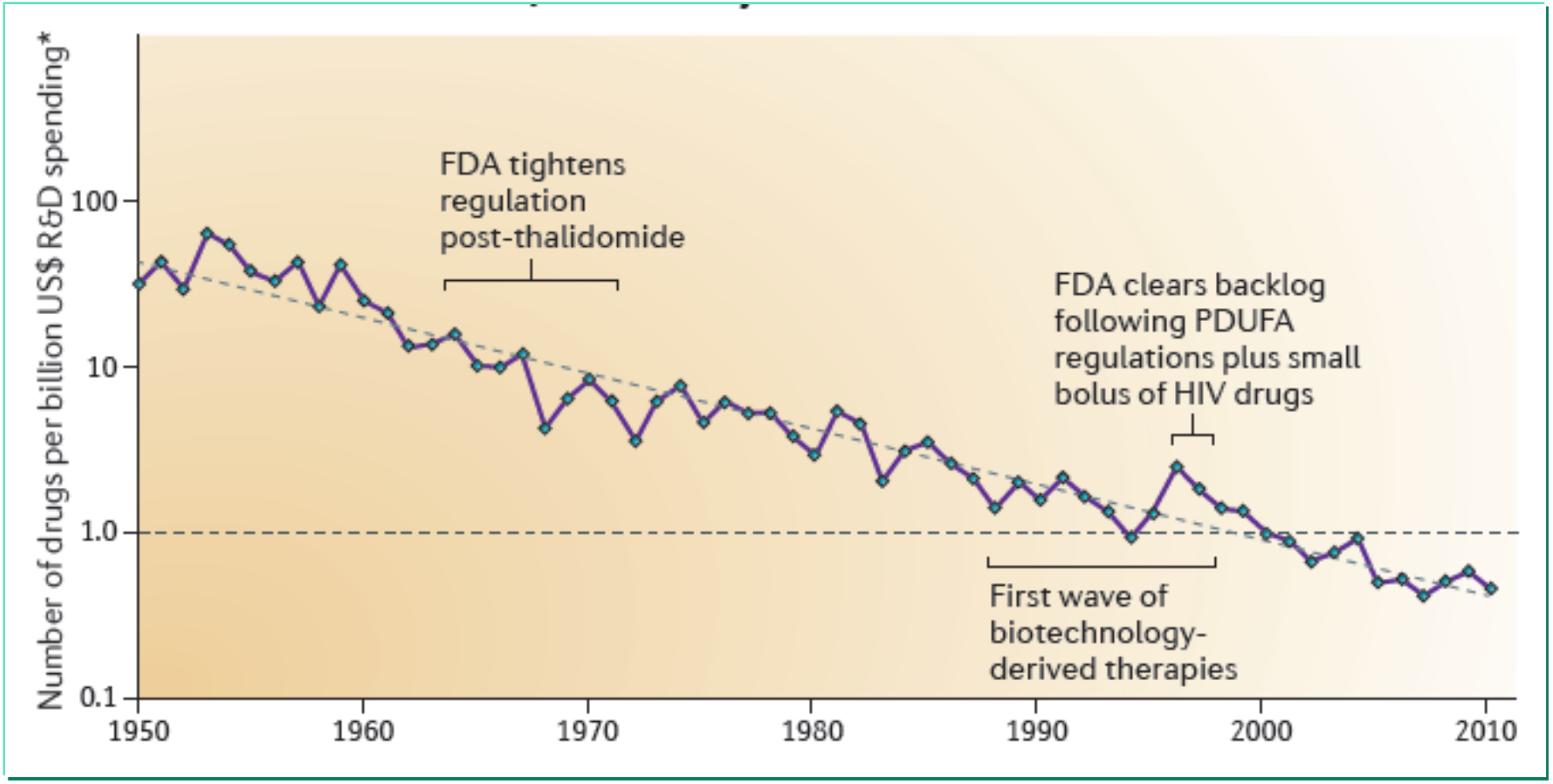
## Global pharmaceutical R&D expenditure, development time, NME output and sales 1992-2002p



# Pharmaceutical Industry – Productivity

## Eroom's Law in pharmaceutical R&D.

**Overall trend in R&D efficiency (inflation-adjusted)**



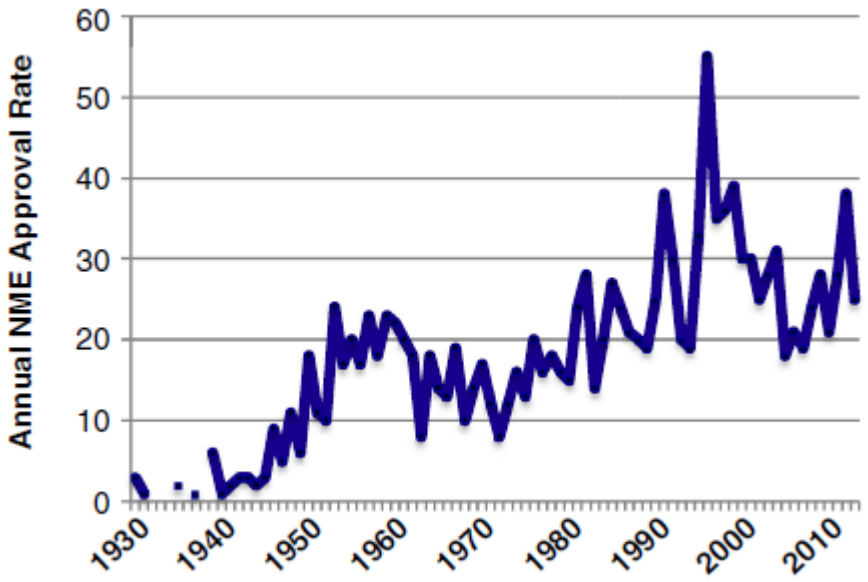

The number of new drugs approved by the US Food and Drug Administration (FDA) per billion US dollars (inflation-adjusted) spent on research and development (R&D) has halved roughly every 9 years.

J.W. Scannel, A. Blanckley, H. Boldon, B. Warrington, Diagnosing the decline in pharmaceutical R&D efficiency, Nature Reviews Drug Discovery **2012**, 11, 191-200.

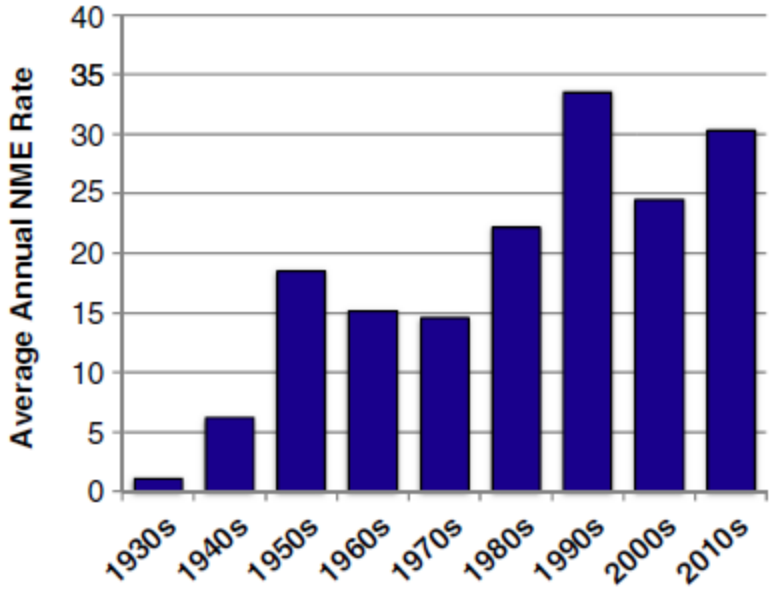
# Pharmaceutical Industry – Productivity

## 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**

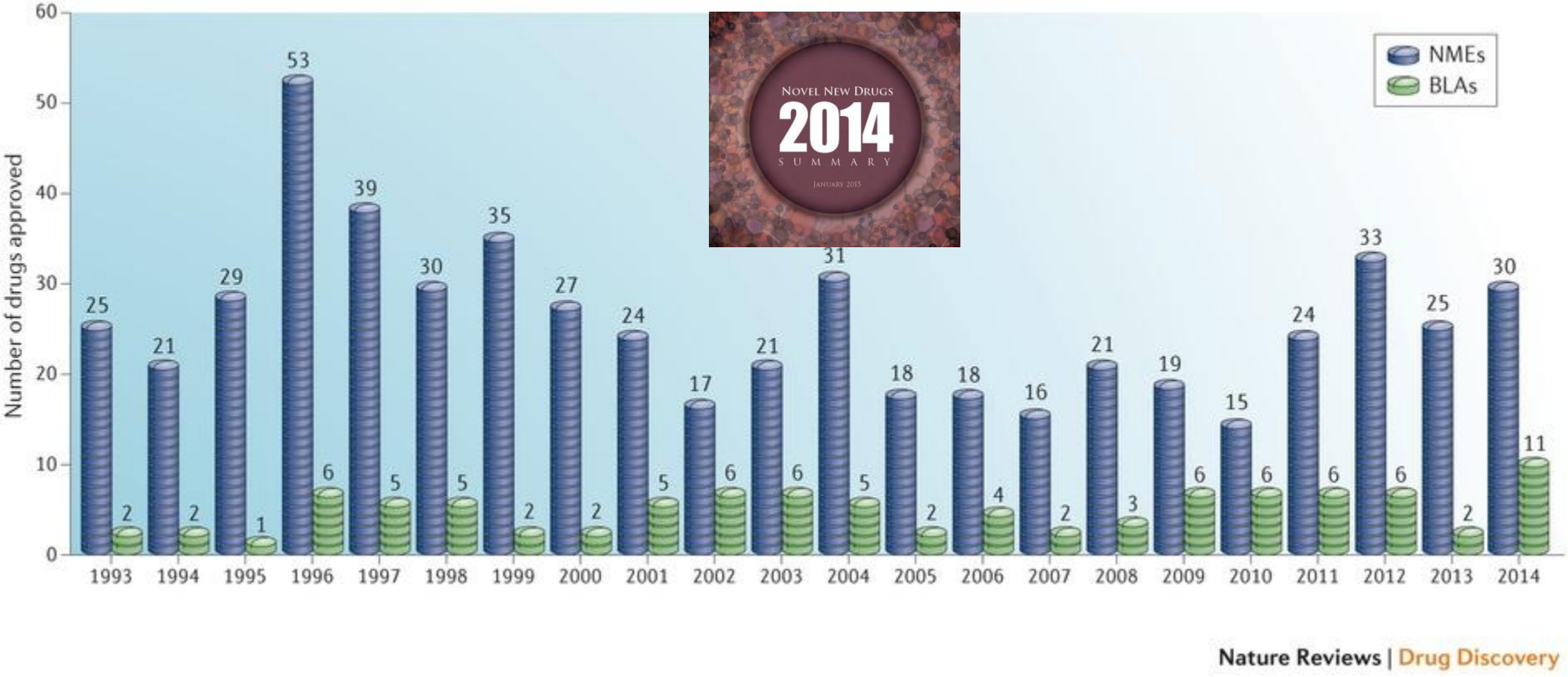



M.S. Kinch, S. L. Kinch, D. Hoyer, An overview of FDA-approved new molecular entities: 1827–2013
Drug Discovery Today 19, 1033-1039 (2014)

# Pharmaceutical Industry – Productivity

## 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.**

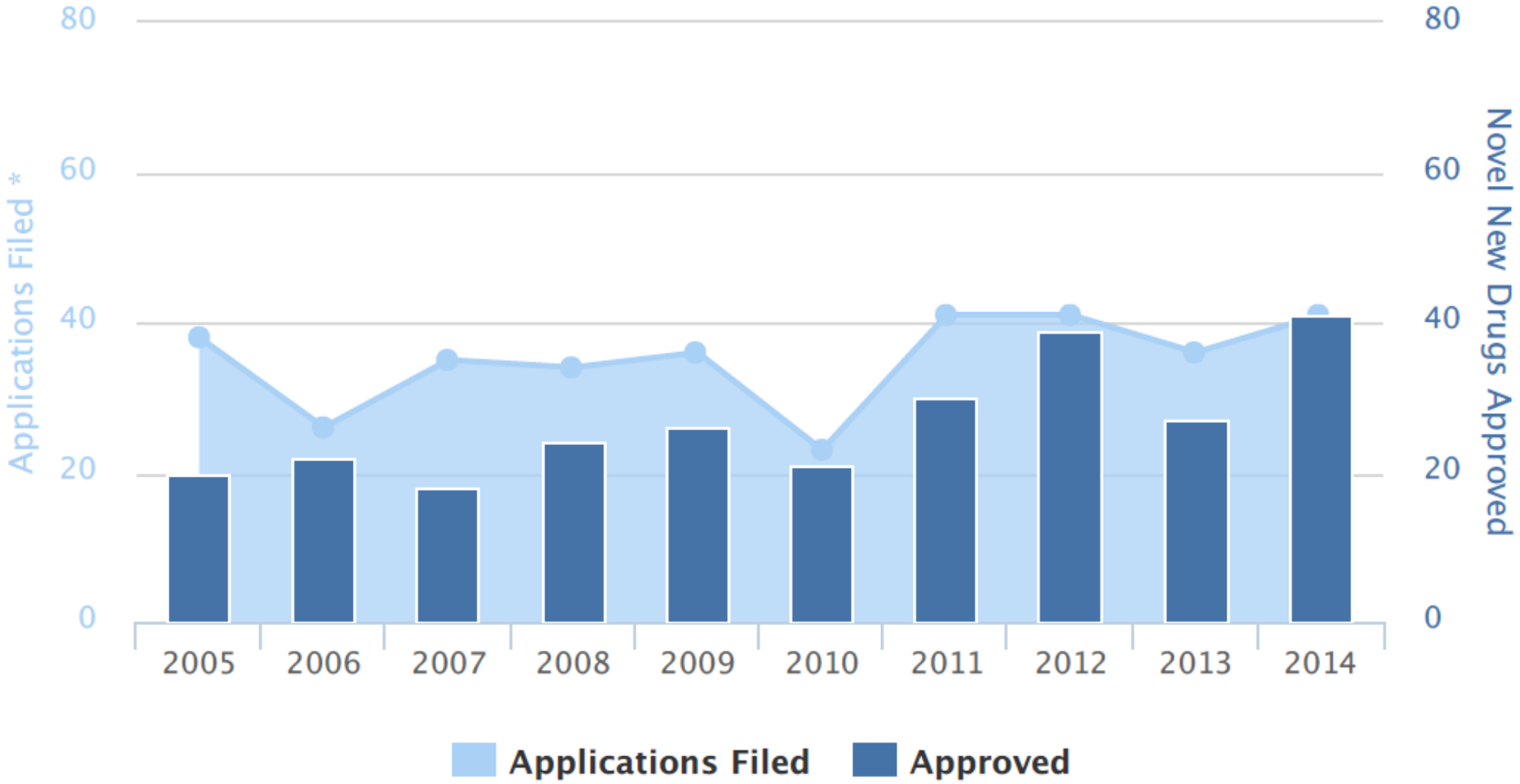



This figure shows the new molecular entities (NMEs) and biologics license applications (BLAs) approved by the Center for Drug Evaluation and Research (CDER) since 1993. Approvals by the Center for Biologics Evaluation and Research (CBER) are not included in this drug count. Data are from Drugs@FDA and the US Food and Drug Administration (FDA).

Nature Reviews Drug Discovery14, 77-81 (2015)

# Pharmaceutical Industry – Productivity

## Number of Novel New Drugs Approved and Applications Filed




http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm429873.htm

# Selected drugs that were rejected or withdrawn* from FDA review in 2014

| Drug | Sponsor | Properties | Indications |
|---|---|---|---|
| Cangrelor | The Medicines Company | P2Y12 platelet ADP-receptor inhibitor | Acute coronary syndrome and following coronary artery bypass graft |
| Serelaxin | Novartis | Agonist for relaxin receptors 1–4 | Acute decompensated heart failure |
| Macrilen | Æterna Zentaris | Ghrelin-receptor agonist | Short stature or growth-hormone deficiency |
| Daclatasvir* | Bristol-Myers Squibb | NS5A inhibitor | Hepatitis C virus |
| Daclatasvir plus asunaprevir* | Bristol-Myers Squibb | An NS5A inhibitor plus an NS3 protease inhibitor | Hepatitis C virus |

Nature Reviews Drug Discovery 14, 77-81 (2015)

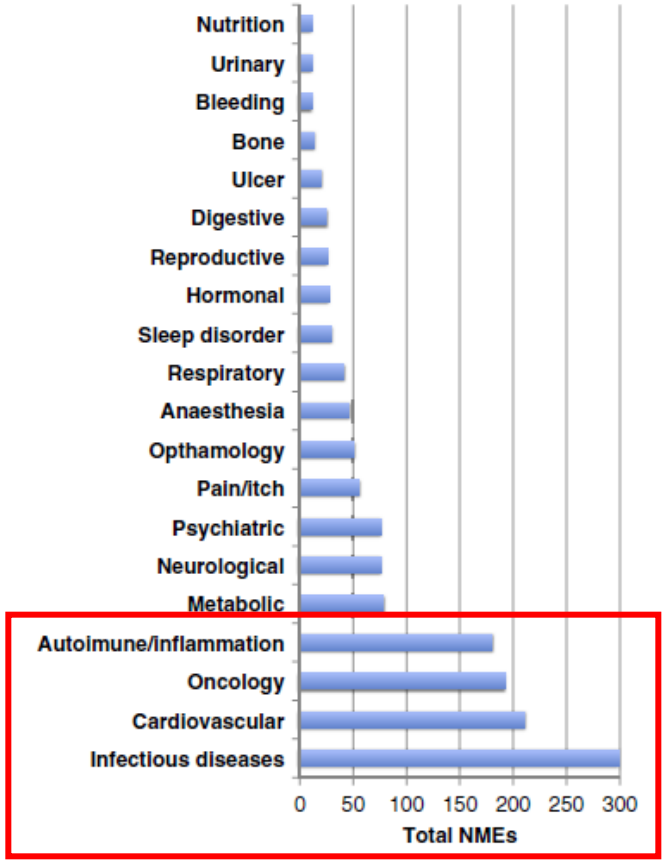
# Top 10 Phase III disasters of 2014

| Drug | Company | Comments |
|---|---|---|
| **Darapladib** | GlaxoSmithKline | GlaxoSmithKline ($GSK) gambled big on darapladib, enrolling 30,000 cardio patients in two big Phase III studies and tracking them for more than two years. This atherosclerosis drug was one of the key attractions to the Human Genome Sciences buyout |
| **Tecemotide (Stimuvax)** | MERCK | This is a cancer vaccine that was in-licensed from Oncothyreon ($ONTY) which failed, badly, in its maiden Phase III journey. |
| **MAGE-A3** | GlaxoSmithKline | Cancer vaccines once captured the industry's attention with the compelling notion that if you could rev up the immune system to send out its soldiers to attack cancer, you could change the course of the disease. That didn't really prove to be the case, though. |
| **Cabozantinib** | EXELIXIS | The problem with Exelixis, and it's a big one, is that its first Phase III trial of cabozantinib for prostate cancer had flunked out in a big Phase III study in September – A clear evidence of failure |
| **Serelaxin** | NOVARTIS | The synthetic version of the hormone relaxin that aids pregnant women works by relaxing the blood vessels. But serelaxin only met one primary endpoint and missed the other in a Phase III trial to treat acute heart failure. |

http://www.fiercebiotech.com/special-reports/top-10-phase-iii-disasters-2014

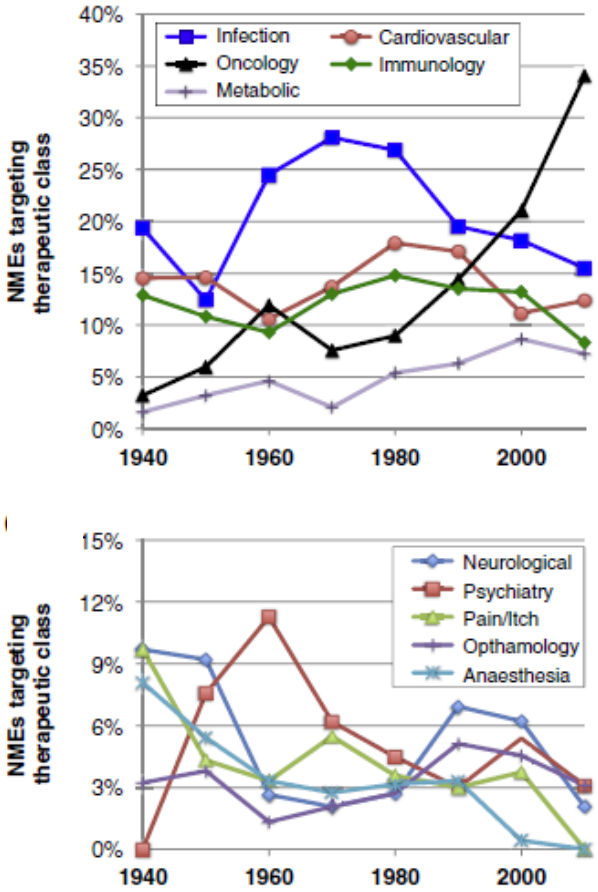
# Trends in pharmaceutical targeting of clinical indications: 1930–2013

## The leading 20 therapeutic applications for NMEs




**60%**

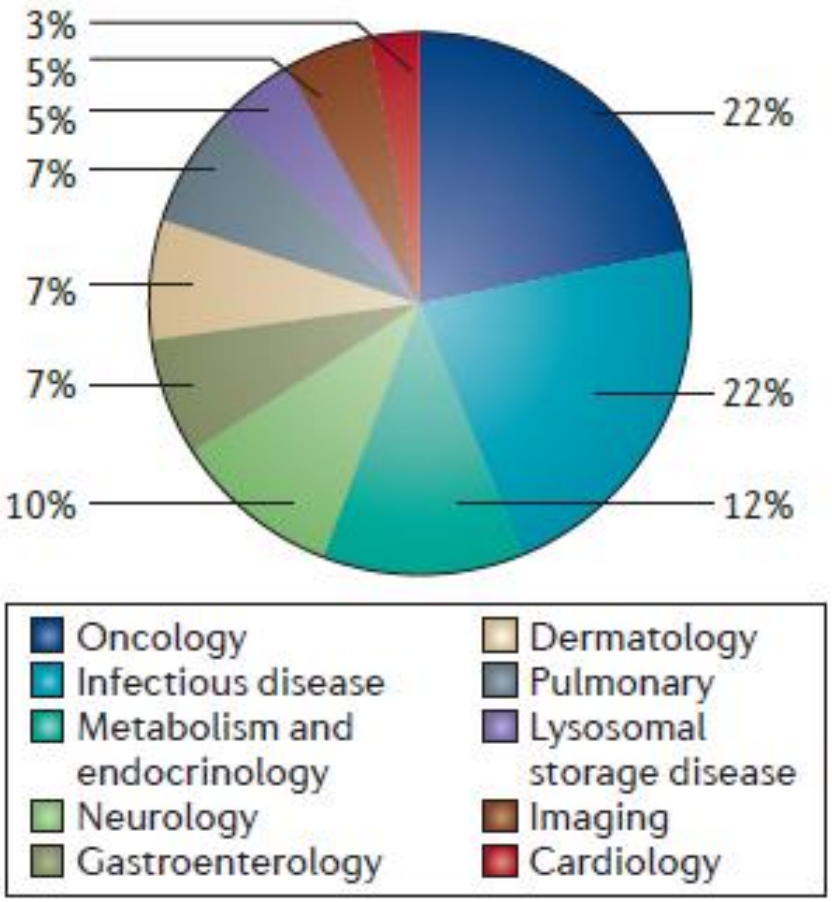
## The top ten indications over time on a decade-by-decade basis




M. S.Klinch, J. Merkel, S. Umlauf, Trends in pharmaceutical targeting of clinical indications: 1930–2013, Drug Discovery Today 2014, 19(11), 1682-1685.

# Pharmaceutical Industry – Productivity

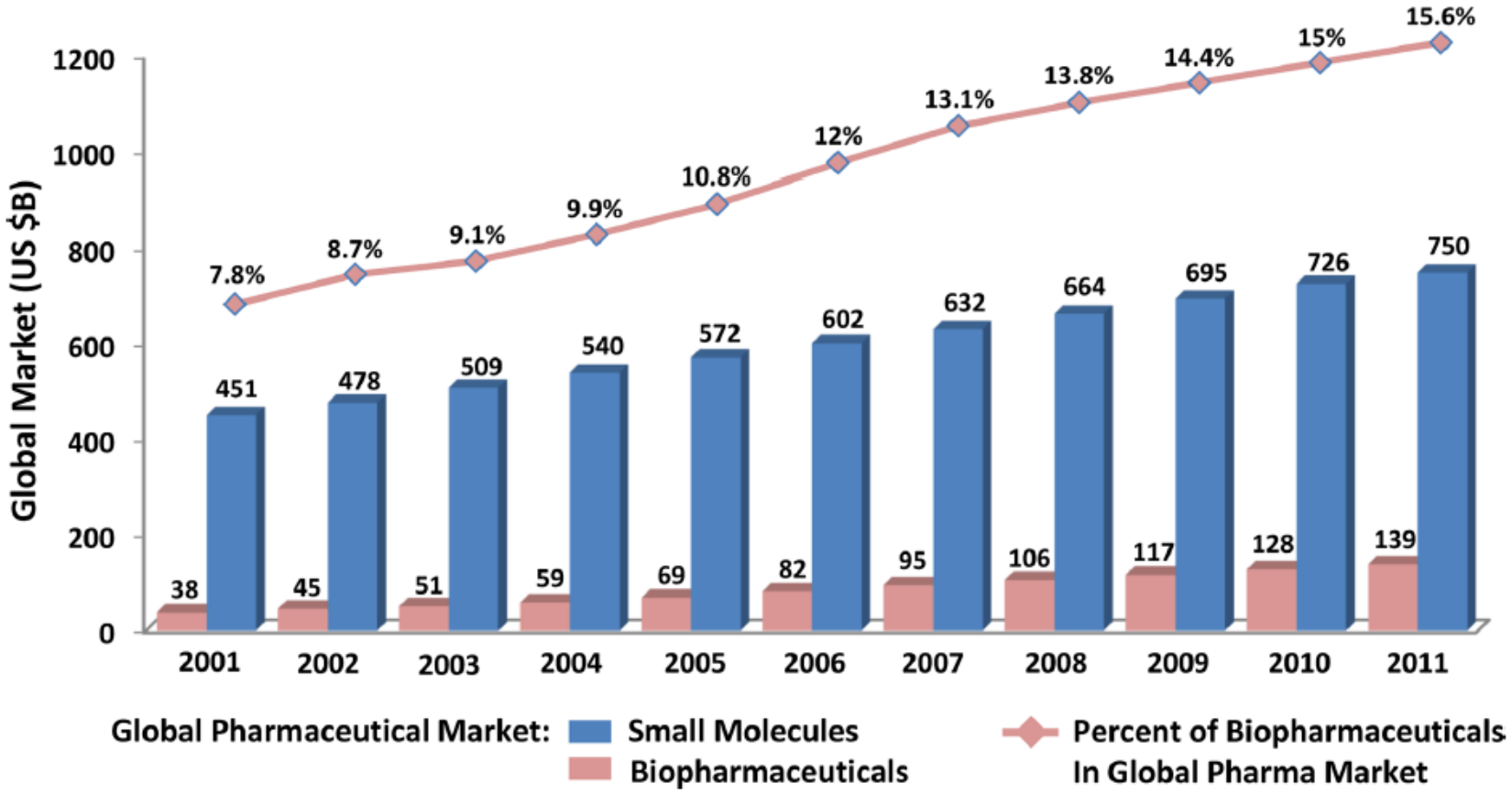
## Approvals by therapeutic area
## FDA Approved Drugs in 2014




Nature Reviews Drug Discovery 14, 77-81 (2015)

# Pharmaceutical Industry – Productivity

## Percentage of biopharmaceuticals in the pharmaceutical market, 2001–2011

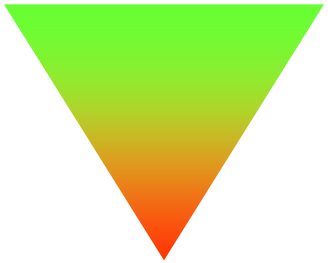



Magid Abou-Gharbia and Wayne E. Childers, Discovery of Innovative Therapeutics: Today's Realities and Tomorrow's Vision. 2. Pharma's Challenges and Their Commitment to Innovation, J. Med. Chem 57, 5525–5553 (2014)

# Pharmaceutical Industry - Innovation

## Ranking System for New Drug Approvals Using FDA Characterizations as Criteria*)

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



*) www.nihcm.org; Changing Patters of Pharmaceutical Innovation, May 2002.

# The Pharmaceutical Marketplace

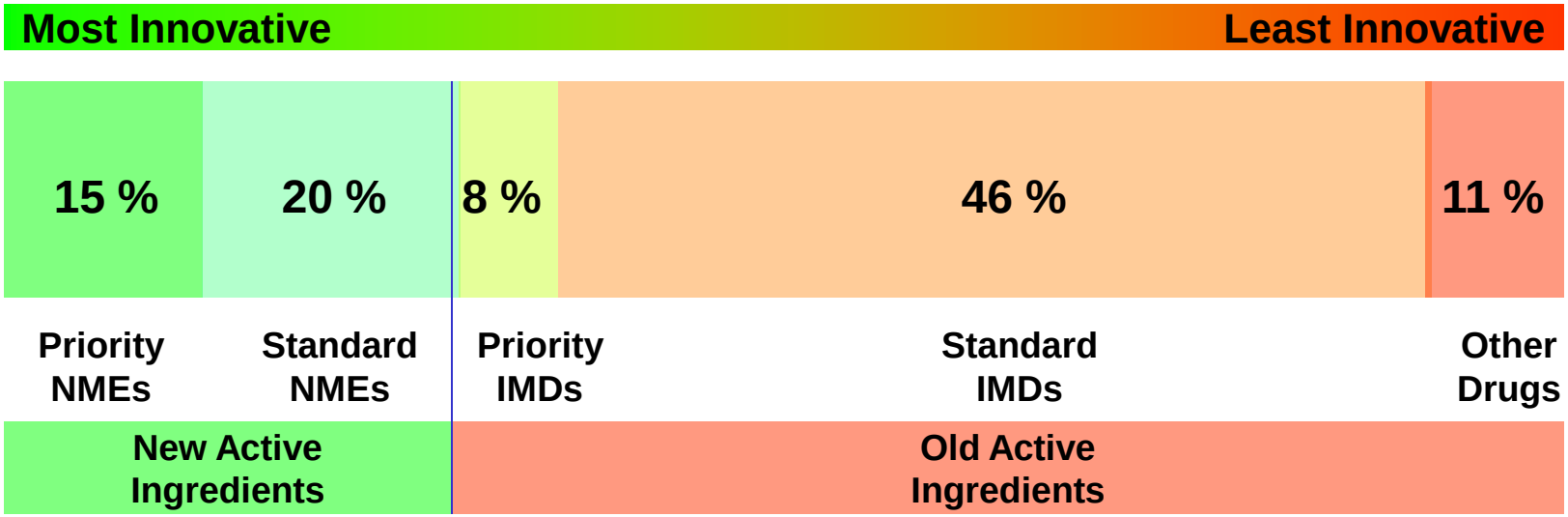
**“New drugs to treat and cure sick patients are coming into the market in the United States at the slowest rate in a decade, despite billions invested by pharmaceutical companies on research and a costly expansion by the federal agency that”**

**“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**

# Pharmaceutical Industry - Innovation

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

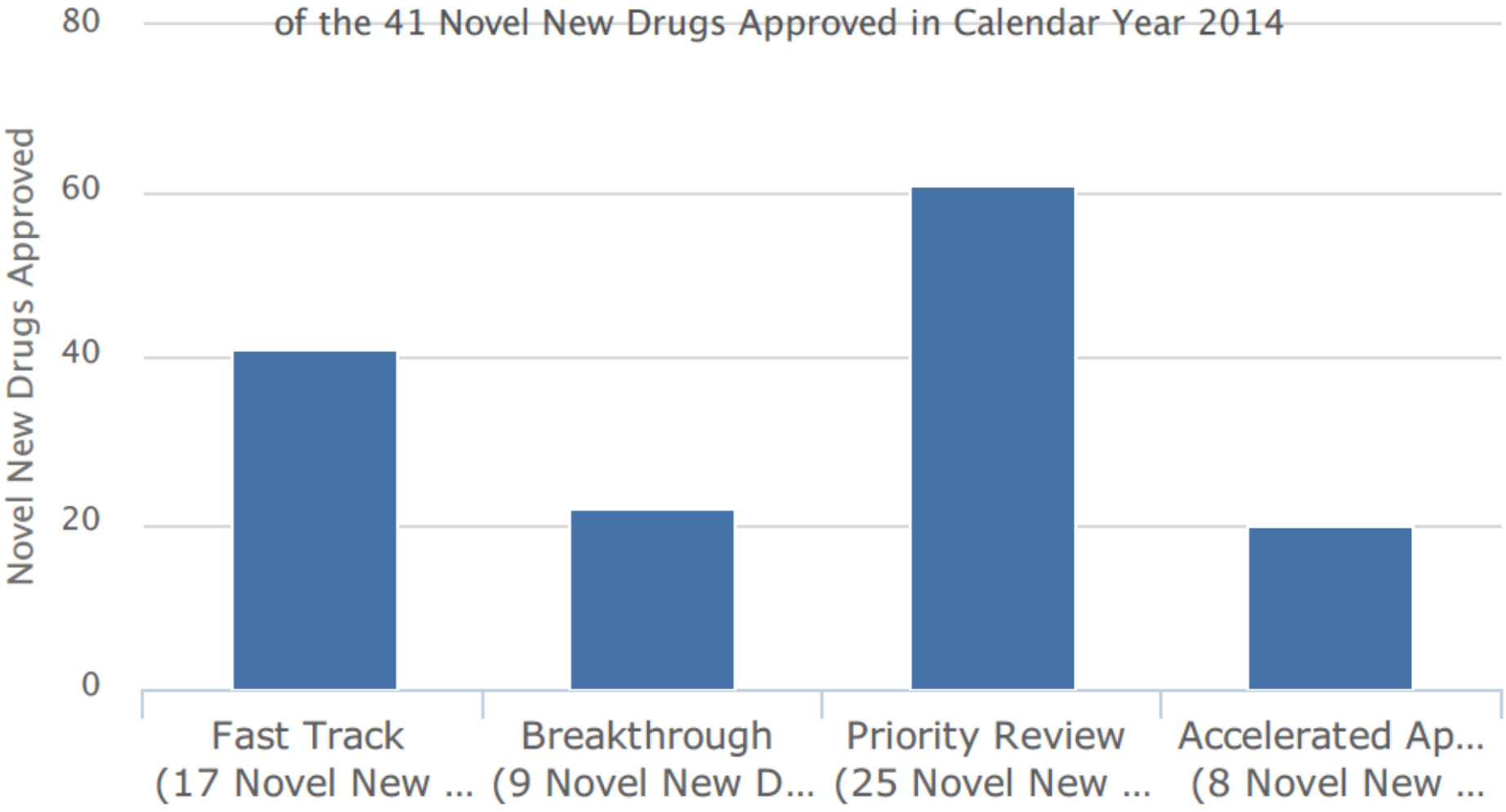



**Distribution of NDAs, 1989-2015: Total 1.035 New Drugs**

**Only 15% of new drugs approved in 1989-2000 were highly innovative priority NMEs**
**Source: FDA 2000**

*) www.nihcm.org; Changing Patters of Pharmaceutical Innovation

# Innovative Methods for Expediting Novel New Drugs to Market

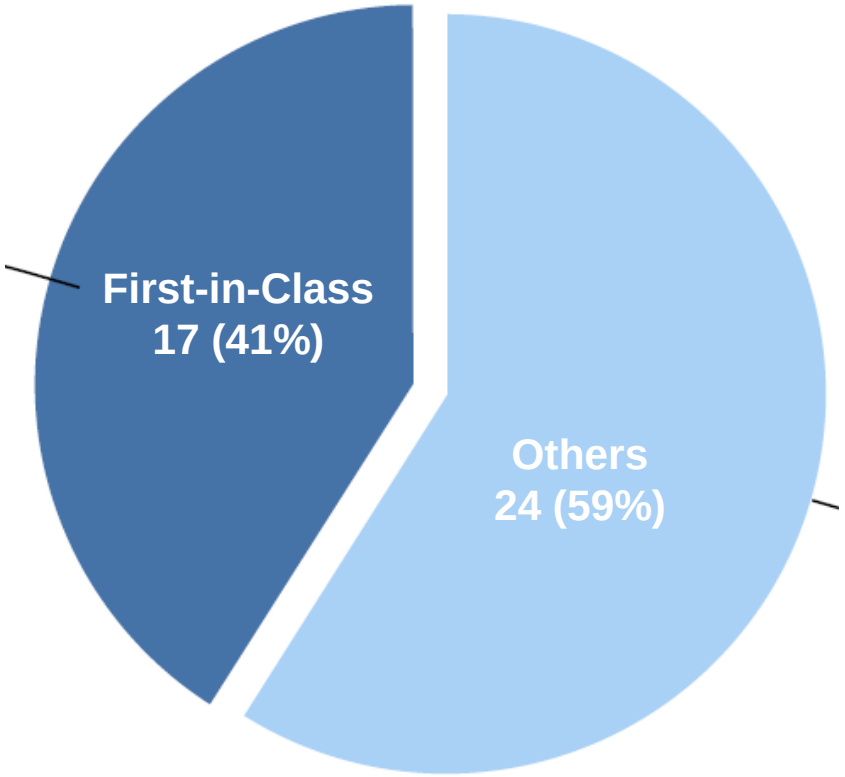



http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm429873.htm

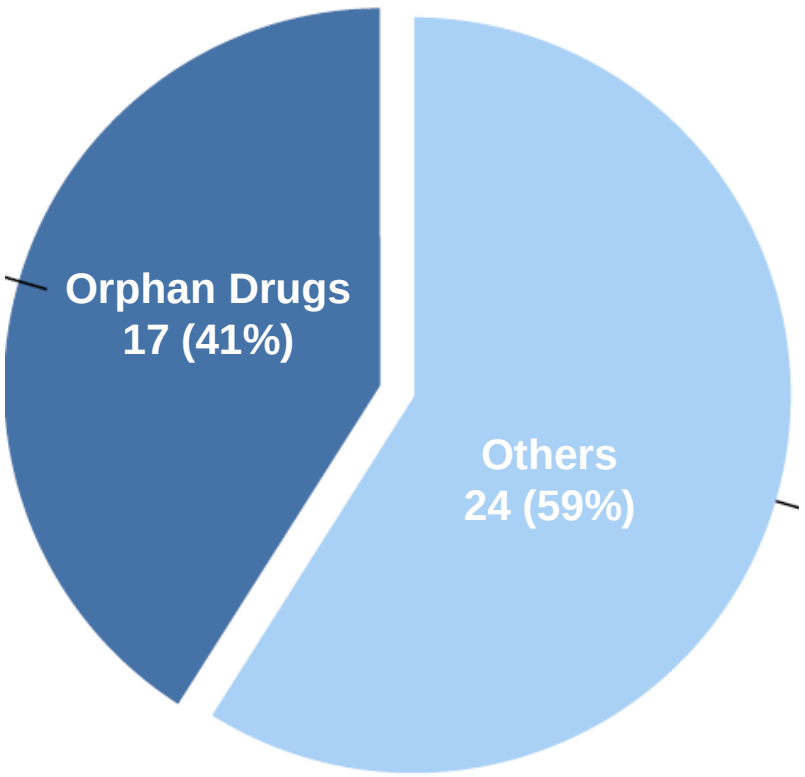
# Pharmaceutical Industry - Innovation

## Novel New Drugs Approved in Calendar Year 2014 (41)

### First-in-Class Designation



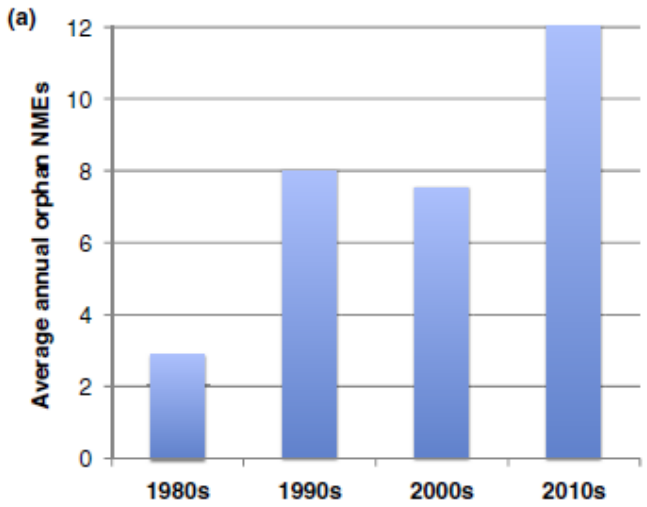

### Orphan Drug Designation



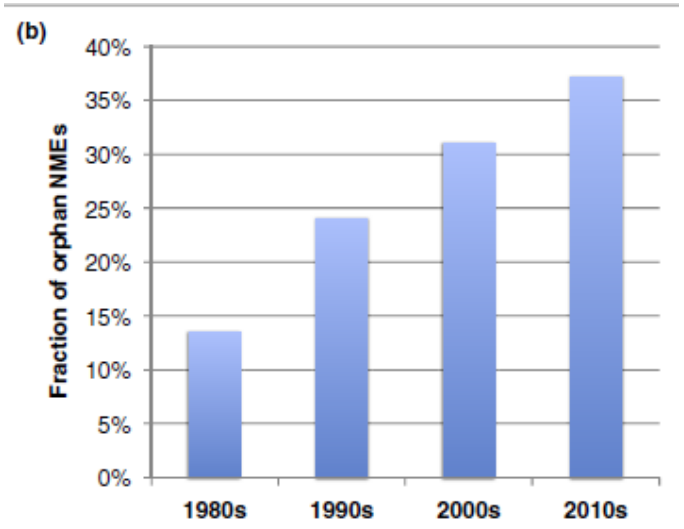

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm429873.htm

# Trends in pharmaceutical targeting of clinical indications: 1930–2013

**The average annual rate of new molecular entities (NMEs) initially approved for targeting of orphan disease indications**




**The relative proportion of orphan indications (compared with all approvals)**

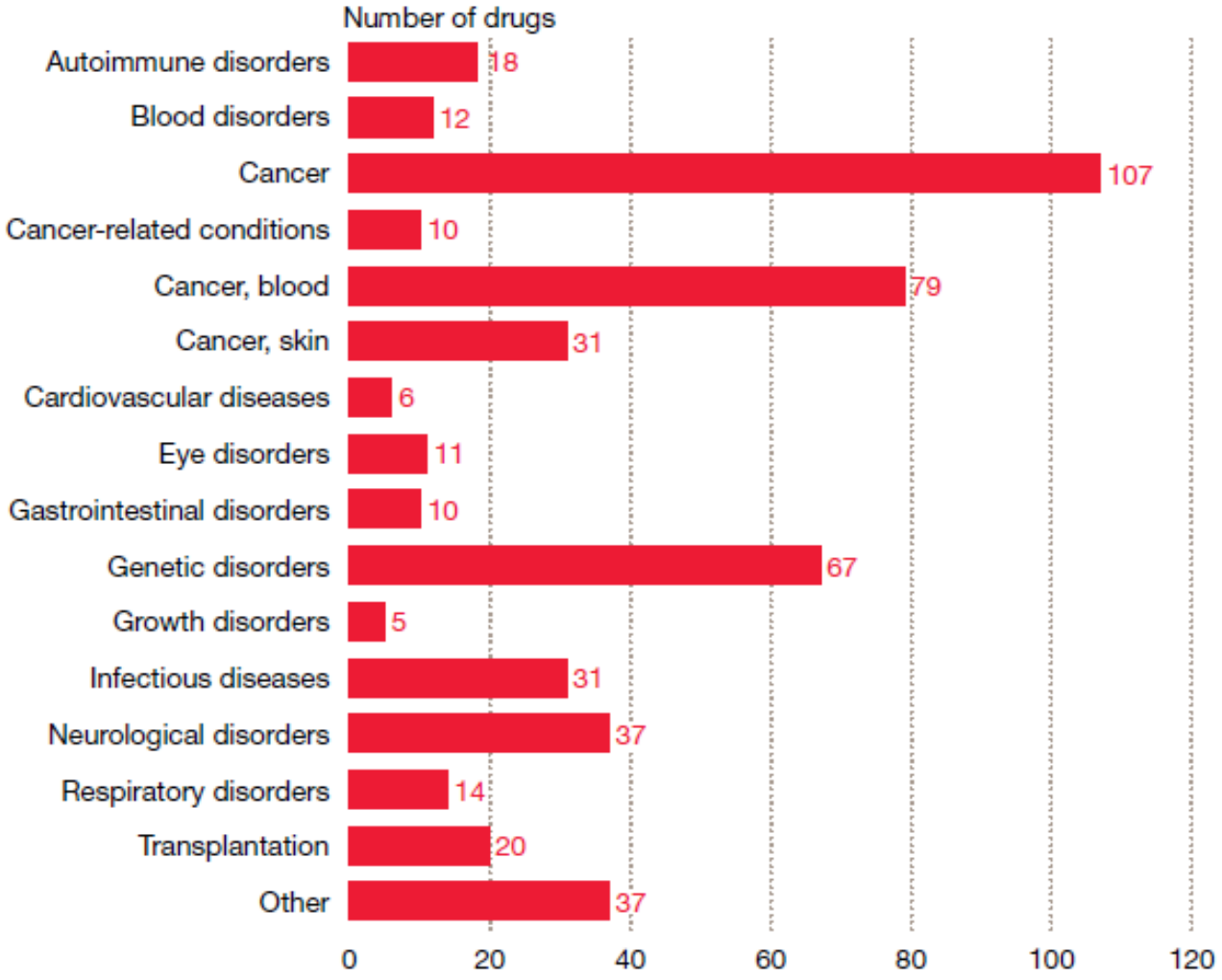



**The proportion of drugs initially approved for orphan indications was compared between pharmaceutical and biotechnology industries.**

| | Orphan NMEs | Orphan fraction |
|---|---|---|
| Biotechnology | 88 | 45% |
| Pharmaceutical | 97 | 14% |

M. S.Klinch, J. Merkel, S. Umlauf, Trends in pharmaceutical targeting of clinical indications: 1930–2013, Drug Discovery Today 2014, 19(11), 1682-1685.

# There are 460 therapies for rare diseases in the pipeline

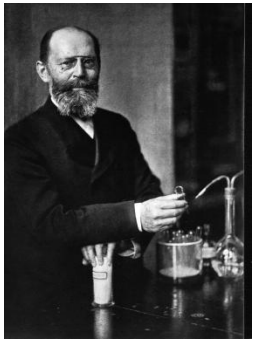


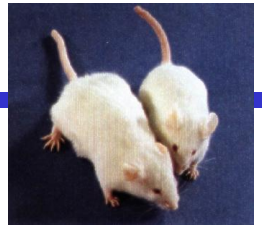

*From vision to decision* Pharma 2020 www.pwc.com/pharma2020

# Pharmaceutical Industry – Evolution of the R & D Process

## The Evolution of Drug Discovery Strategies

„blind fisching“ → rational design → high throughput screening → „blind screening“ → ?





- Progress in biochmistry and
- Structural biology

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

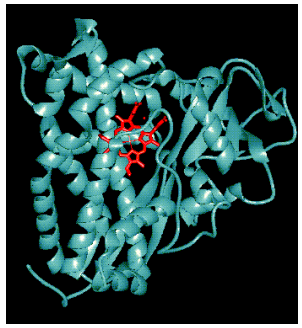
- Development of in silico technology
- Virtual screening
- Computational assessment of „drug likeness“

**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 not considered as mandatory

**1960**

- use of *in vitro* screening based on a mechanism of action hypothesis



**1985**

- High throughput screening programs

**1995**

- 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

# Pharmaceutical Industry – Evolution of the R & D Process

## Drug Discovery – The Ancient Times

**Folk Medicine (mainly plants)**

*Public theriak preparation at a market.*

- pro: Thousands years of human experience
- con: Lack of reproducibilit (varying doses)

**Experiments in Humans**

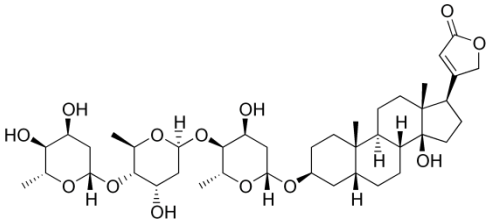
*J. Lind, 1747, „Treatmant of Scurvy“*

- pro: The „right“ object
- con: Toxicity

# Pharmaceutical Industry – Evolution of the R & D Process

## Drug Discovery – The Early Times

**Natural Products and their Analogues**




**Animal Experiments**

- **pro:**
  - **High percentage of active compounds**
  - **Large chemical diversity**

- **con:**
  - **Availability may pose problems**
  - **Most often difficult chemistry**

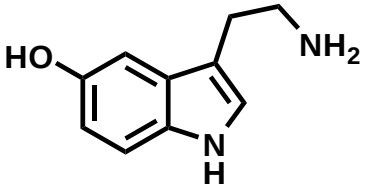
- **pro:**
  - **ADMET included**
  - **Disease models**

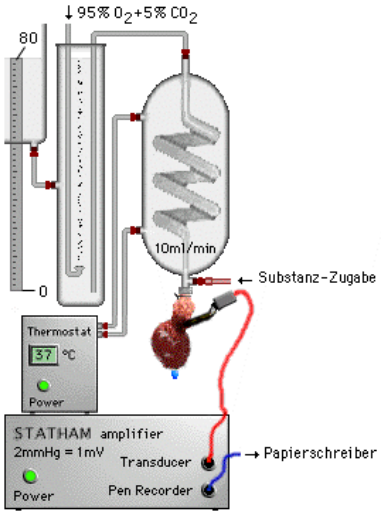
- **con:**
  - **Slow, expensive**
  - **Ethical issues**
  - **Species differences**

# Pharmaceutical Industry – Evolution of the R & D Process

## Drug Discovery – The Golden Age

**Endogenous Transmitters & Hormones** → **Isolated Organs as Test Models**



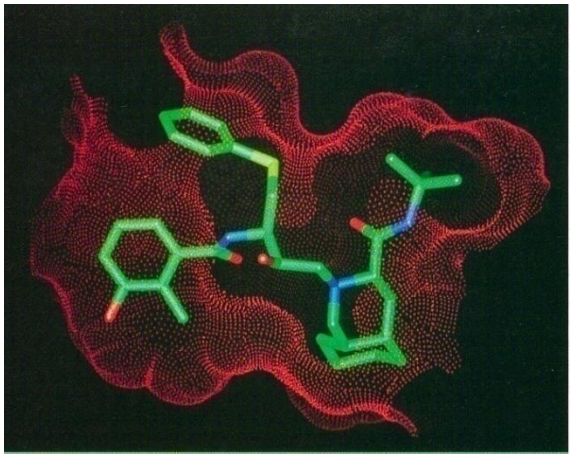

- **pro:**
  - Active lead structures with defined biological function
  - Involved in many different diseases
- **con:**
  - Limited number of lead structures

- **pro:**
  - Include membrane permeability

- **con:**
  - Slow, expensive
  - No ADME(T)
  - Ethical issues

# Drug Discovery – „Rational“ Approaches

## Sructure-based & Computer Aided Design



*HIV - VIRACEPT*

- **pro:**
  - Straightforward approach
- **con:**
  - Only targets with 3Dstructures
  - Only ligand design
  - No ADMET
  - High risk of failure

## *In vitro* Test Models

*Different Types of Microtiterplates*

- **pro:**
  - Very fast: 100.000`s a day
  - Target focussed
- **con:**
  - No ADMET
  - Single target approach

# Pharmaceutical Industry – Evolution of the R & D Process

## Drug Discovery – Nowadays

### Combinatorial Chemistry Compound Libraries

- **pro:**
  - Generate a multitude of compounds
- **con:**
  - Limited chemical diversity
  - Chemistry driven libraries (most often outside the biological space)

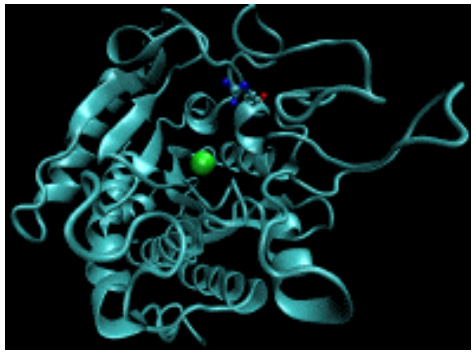
### Chemical Biology

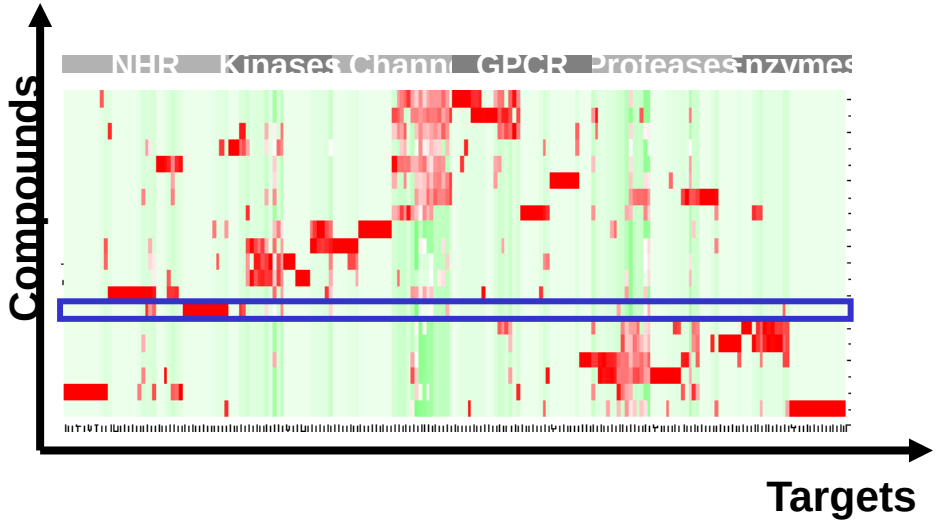
- **pro:**
  - Fast screening in biological systems
  - Membrane permeability included
- **con:**
  - No ADMET in cellular systems
  - Target(s) remain(s) unknown

# Pharmaceutical Industry – Evolution of the R & D Process

## Drug Discovery – Nowadays

**Virtual Screening & Fragment-Based Design** → **Chemogenomics**



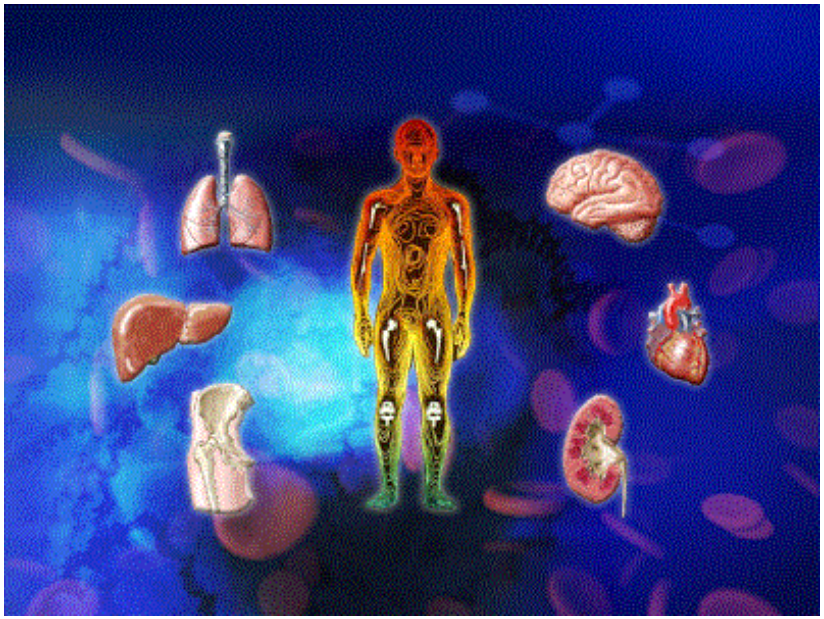




- **pro:**
  - Straight forward approach
  - Saves time and resources
- **con:**
  - Only ligand design
  - Risk of failure is remaining

- **pro:**
  - Fast information on multitarget.orientated selectivity
- **con:**
  - No ADMET

# The Changing Climate in Pharmaceutical Research

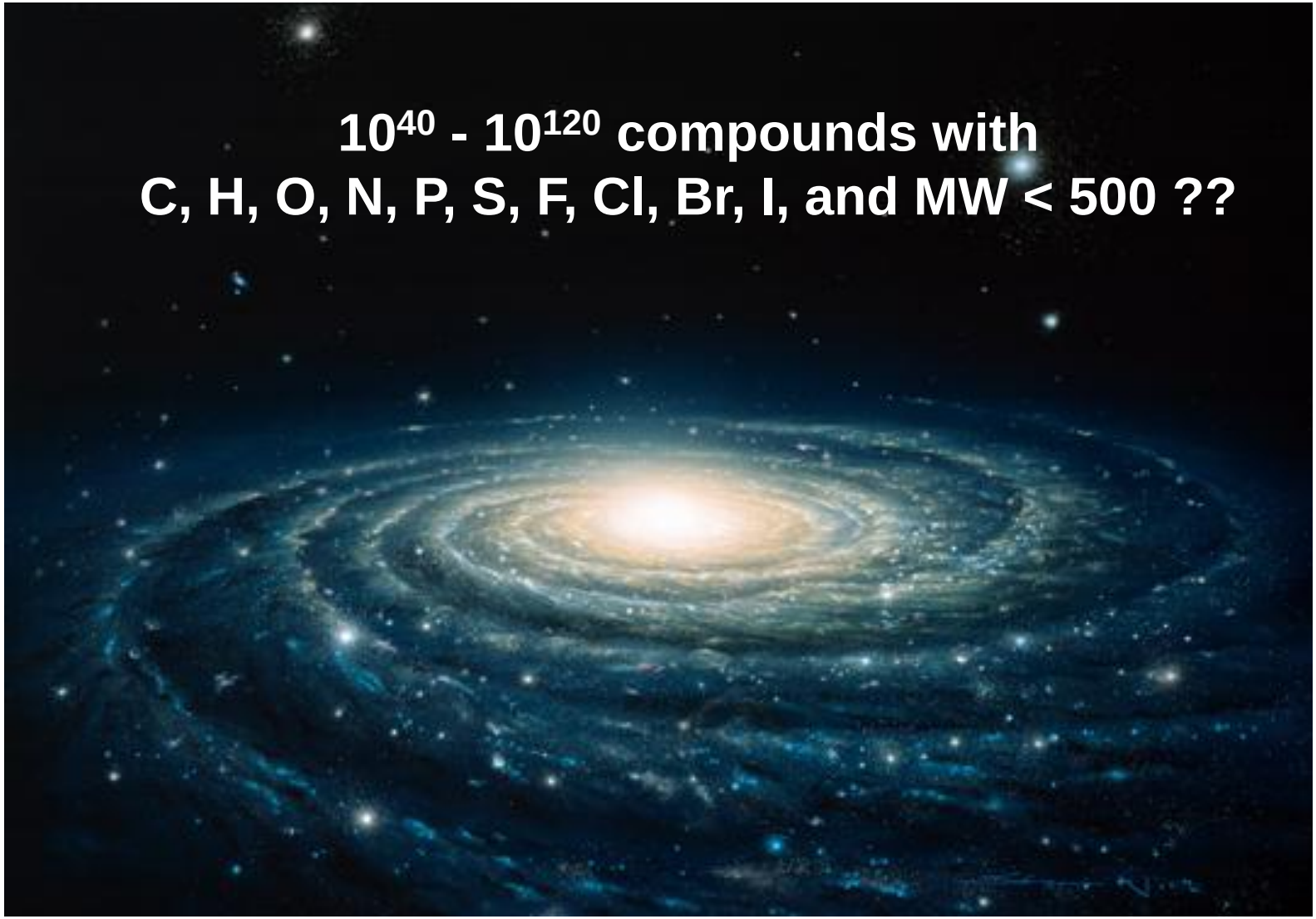
**The human body is complex**



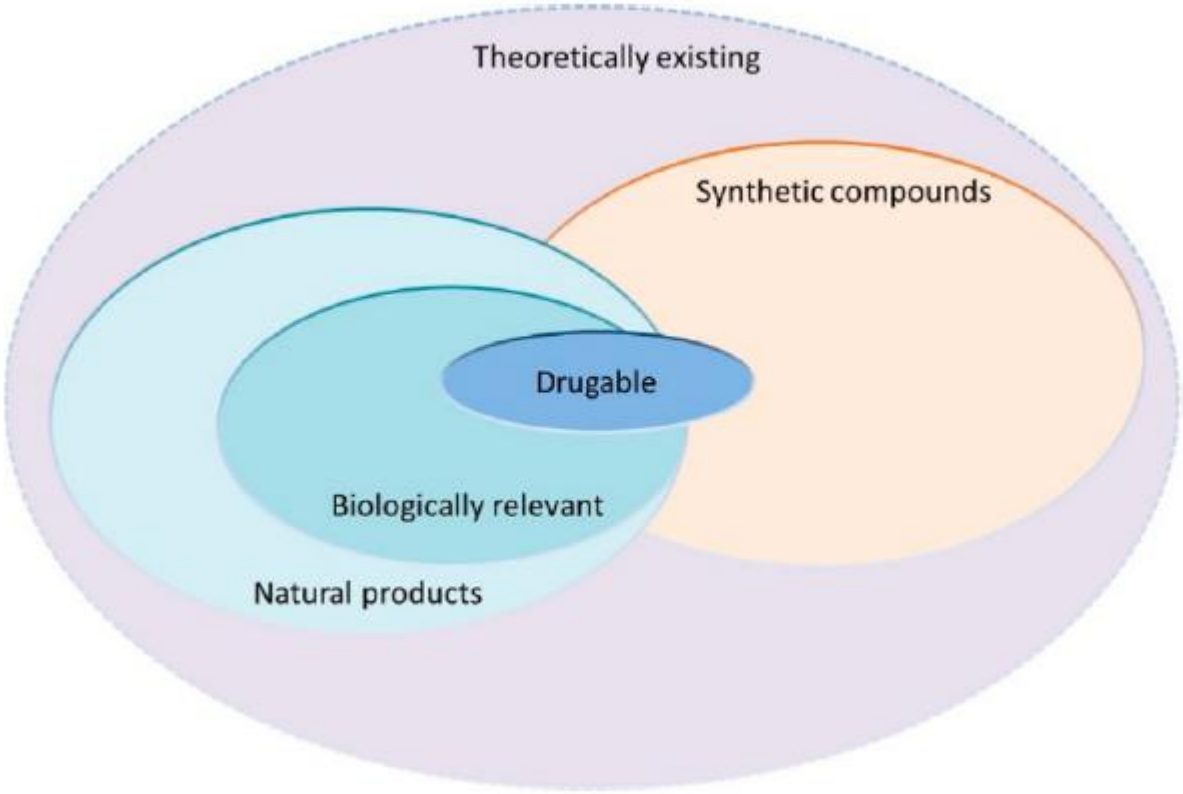
**100** organs,
**1500** different cell types,
**10.000** diseases

- **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 Chemical Universe



# Venn diagram of the distribution of commonly used libraries in chemical space

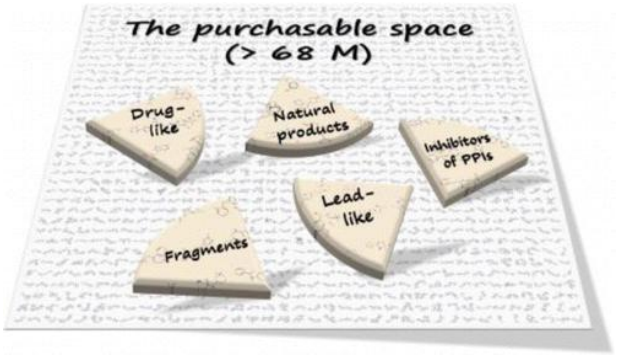


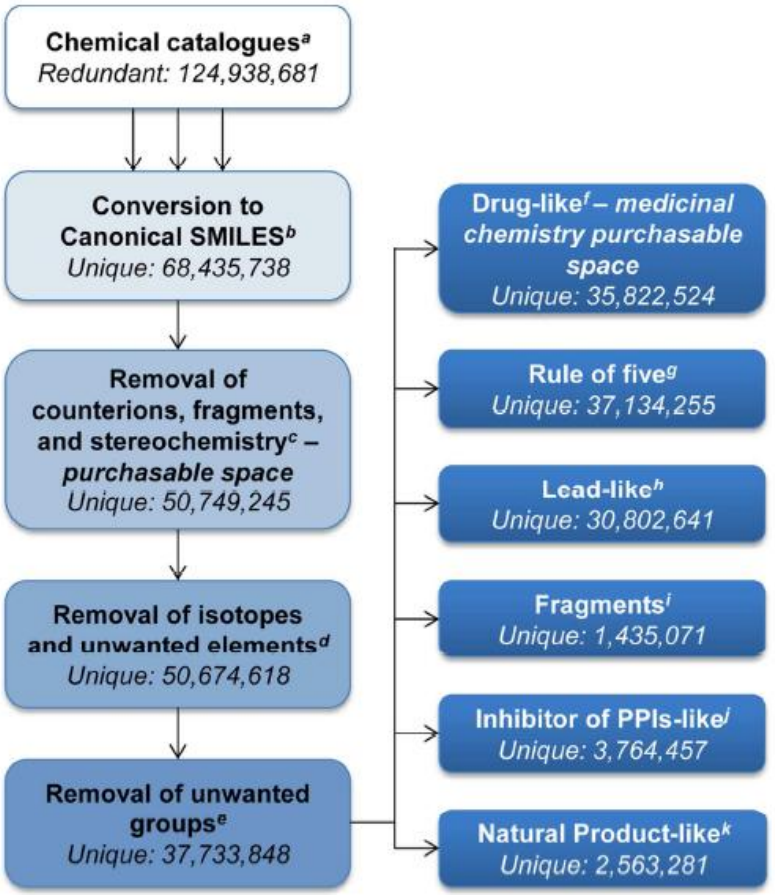

Zhi-Luo Deng et al., Exploring the Biologically Relevant Chemical Space for Drug Discovery 53, 2820–2828 (2013)

# The Purchasable Chemical Space: a Detailed Picture

**Workflow used to collect, filter, and partition the purchable space**

- The ZINC database is nowadays routinely used to freely access and screen millions of commercially available compounds.
- From ~125 million collected compounds from chemical catalogs and the ZINC database more than 68 million were investigated
- The data set was filtered using advanced medicinal chemistry rules to remove potentially toxic, promiscuous, metabolically labile, or reactive compounds.

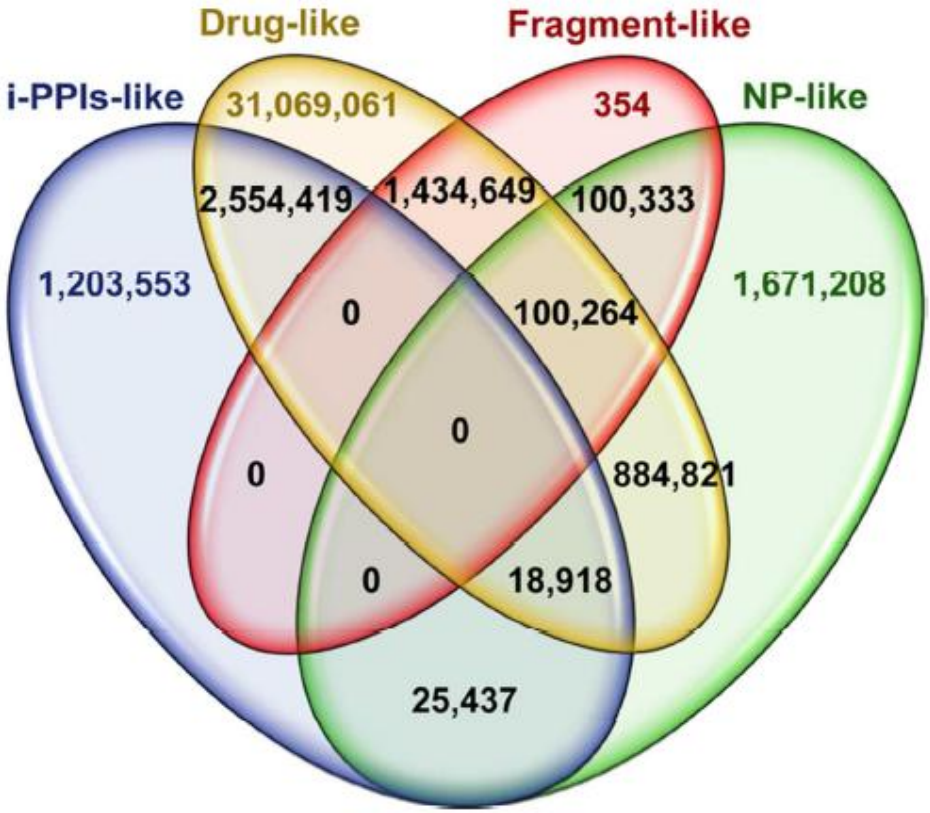



X. Lucas, B.A. Grüning, S. Bleher, S. Günther, The Purchasable Chemical Space: a Detailed Picture, *J. Chem. Inf. Model.*, 2015, 55 (5), pp 915–924

# The Purchasable Chemical Space: a Detailed Picture

**Venn diagram representing the amount of overlapping and unique molecules contained in the focused libraries of i-PPIs-like, drug-like, fragment-like, and NP-like.**




X. Lucas, B.A. Grüning, S. Bleher, S. Günther, The Purchasable Chemical Space: a Detailed Picture, *J. Chem. Inf. Model.*, 2015, 55 (5), pp 915–924

# April 2003 : *99 % of the Human Genome Sequenced*

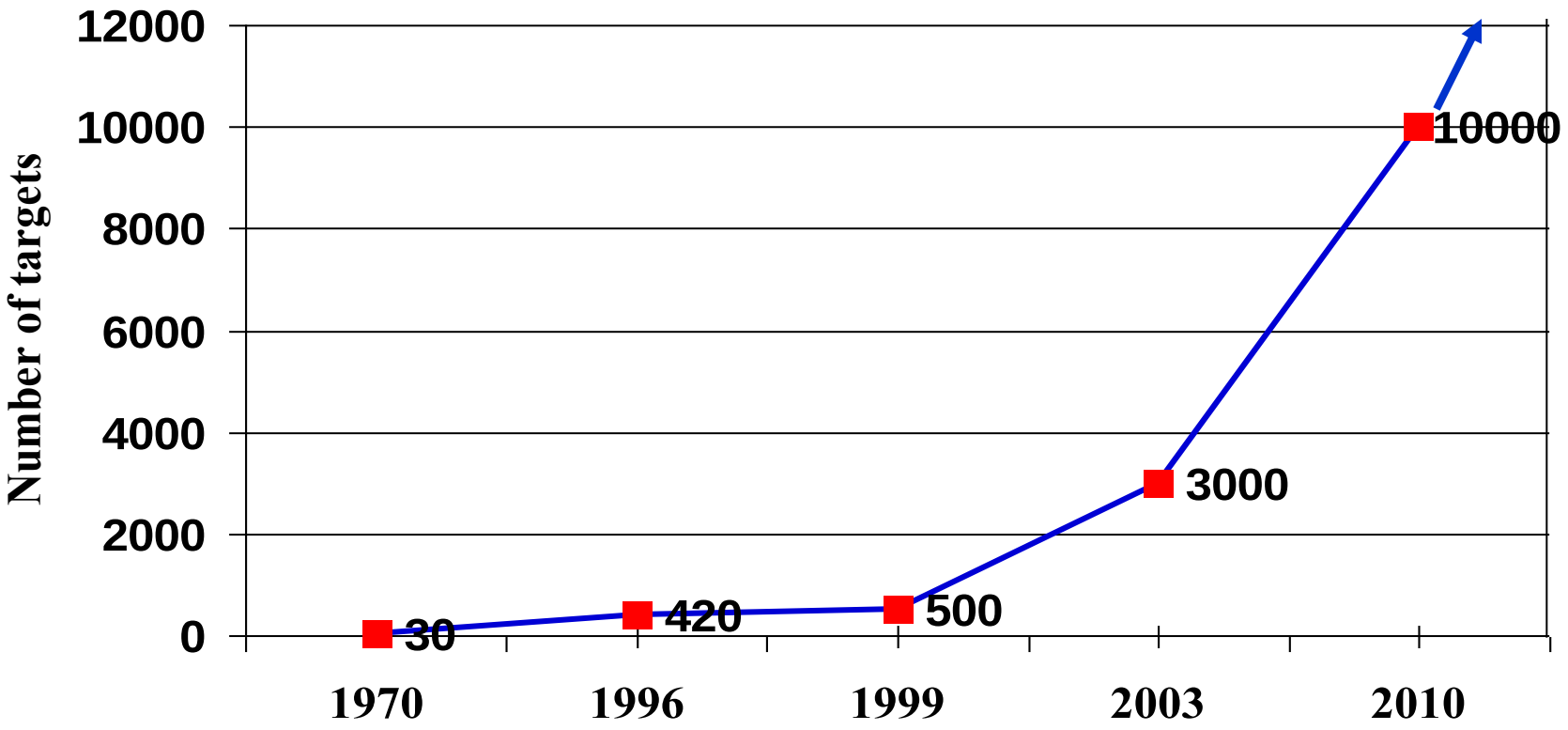
**3.12 billion nucleotides**

**(cf. 200 telephone books worth of information)**

# Pharmaceutical Industry – Evolution of the R & D Process

## Development of target identification

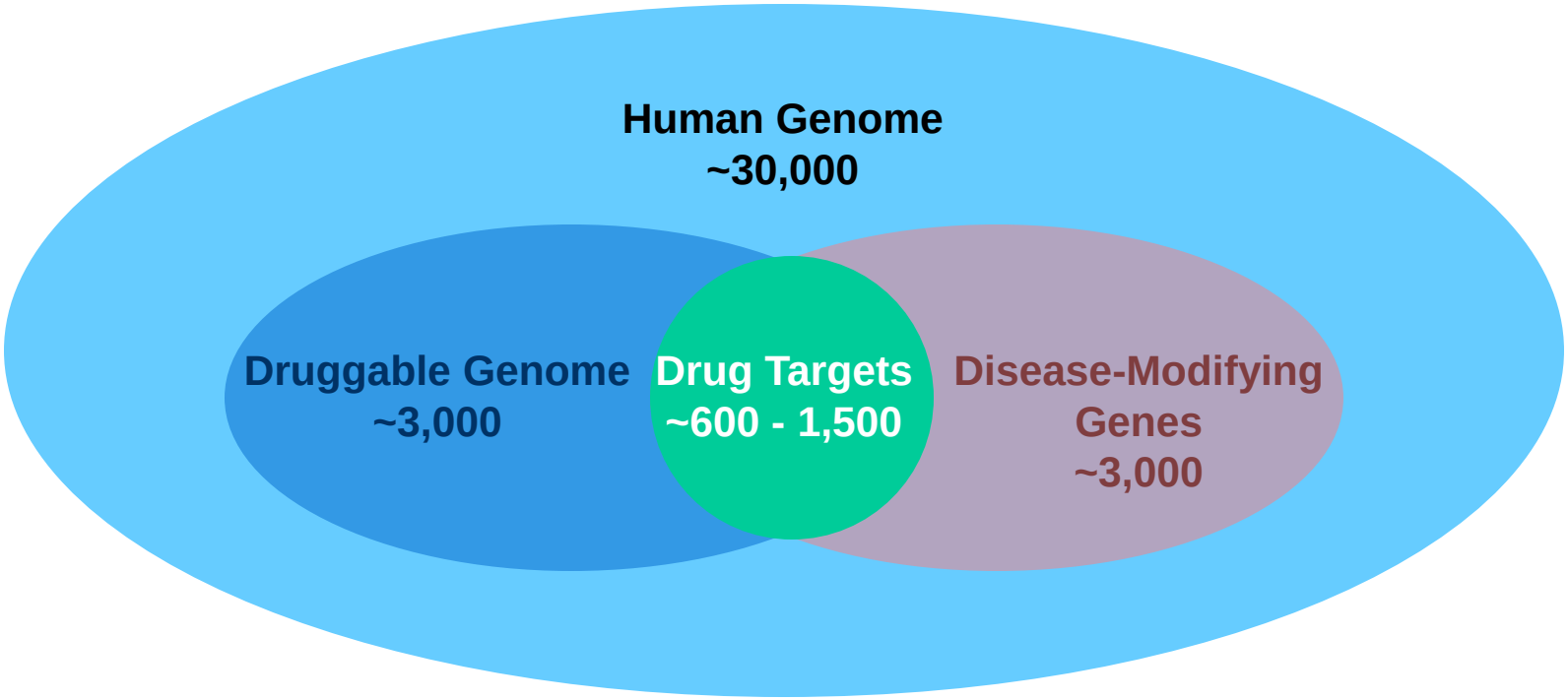
*(Number of targets)*




**Source:** J. Drews, *Nature Biotechnology*, Volume 14; November 1996.

# Pharmaceutical Industry – Evolution of the R & D Process

## Number of Drug Targets



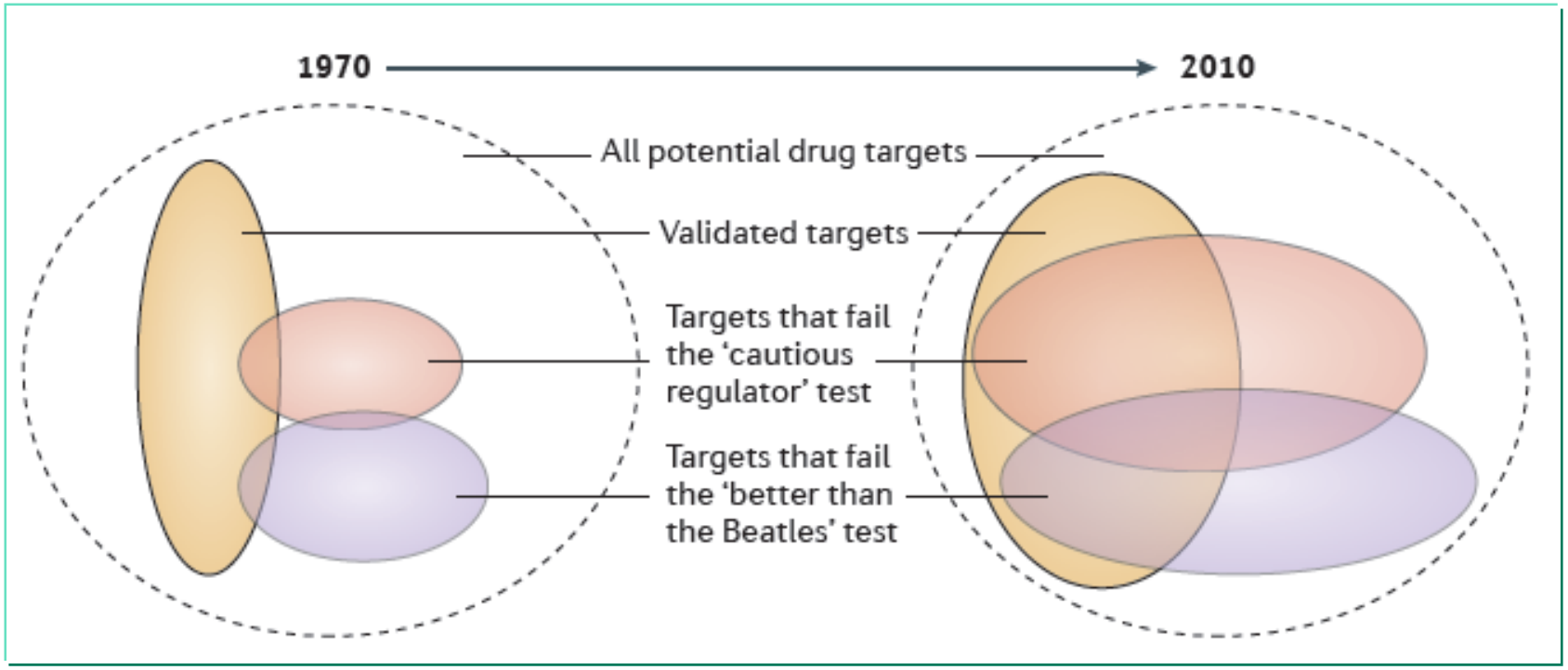

**The effective number of exploitable drug targets can be determined by the intersection of the number of genes linked to disease and the 'druggable' subset of the human genome.**

A.L. Hopkins, C.R. Groom, The Druggable Genome, *Nature Reviews Drug Discovery* 2002, *1*, 727-730.

# Pharmaceutical Industry – Evolution of the R & D Process

## Eroom's Law in pharmaceutical R&D.

**Venn diagram illustrating hypothetical headwinds to R&D efficiency**



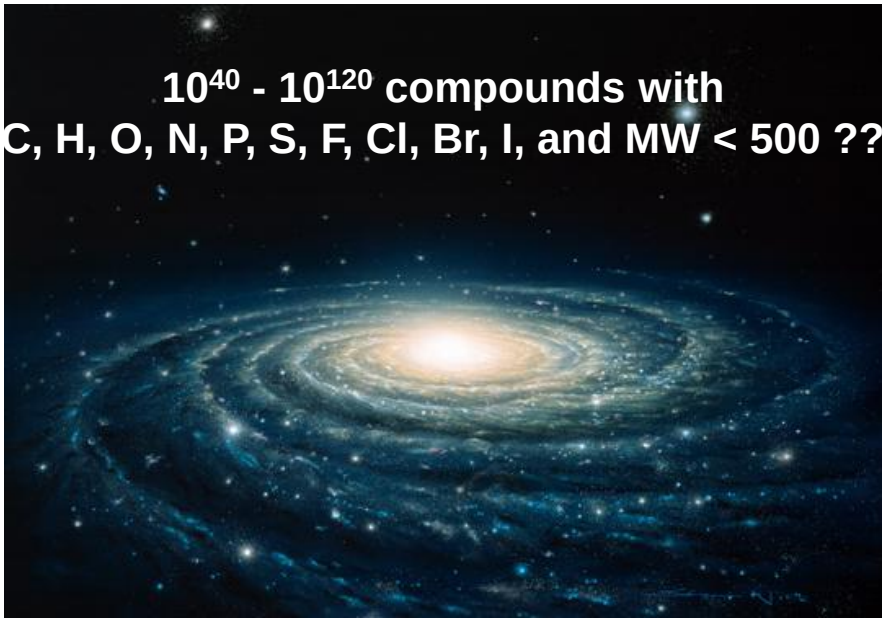

- **Research and development (R&D) efficiency could decline if scientific, technical and managerial improvements are offset by other factors.**
- **For example, R&D efficiency could be limited by the supply of validated targets that could be drugged without failing the 'cautious regulator' test and/or the 'better than the Beatles' test.**
- **In this hypothetical illustration, the increase in the number of validated targets between 1970 and 2010 is outweighed by increasing regulatory caution and an improving catalogue of approved drugs.**

J.W. Scannel, A. Blanckley, H. Boldon, B. Warrington, Diagnosing the decline in pharmaceutical R&D efficiency, Nature Reviews Drug Discovery **2012**, 11, 191-200.

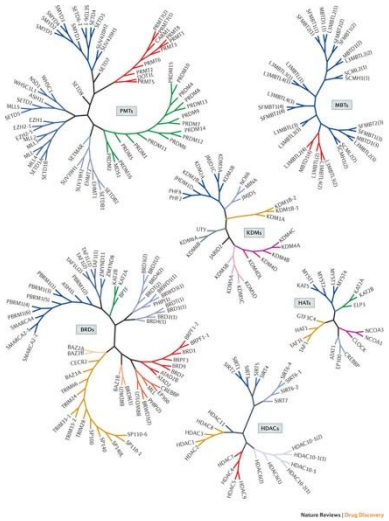
# Pharmaceutical Industry – Evolution of the R & D Process

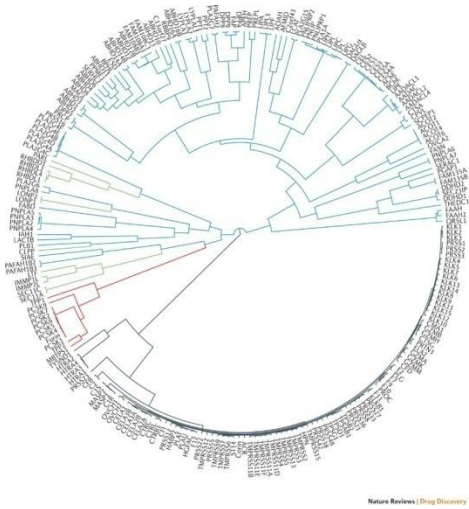
## Chemogenomics

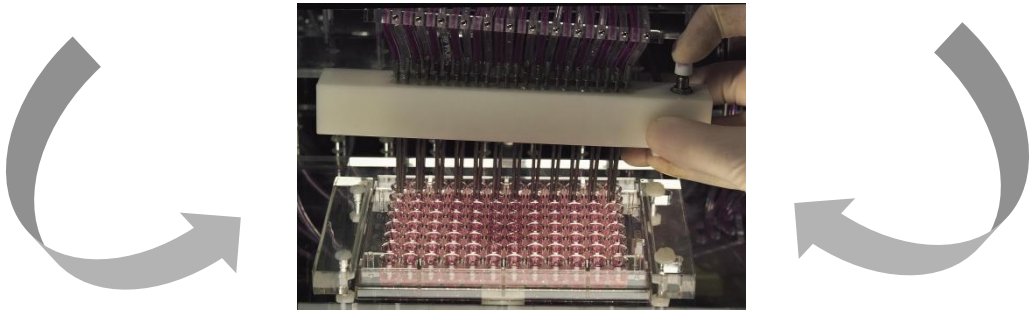
**Cemical Universe**




**Target Universe**

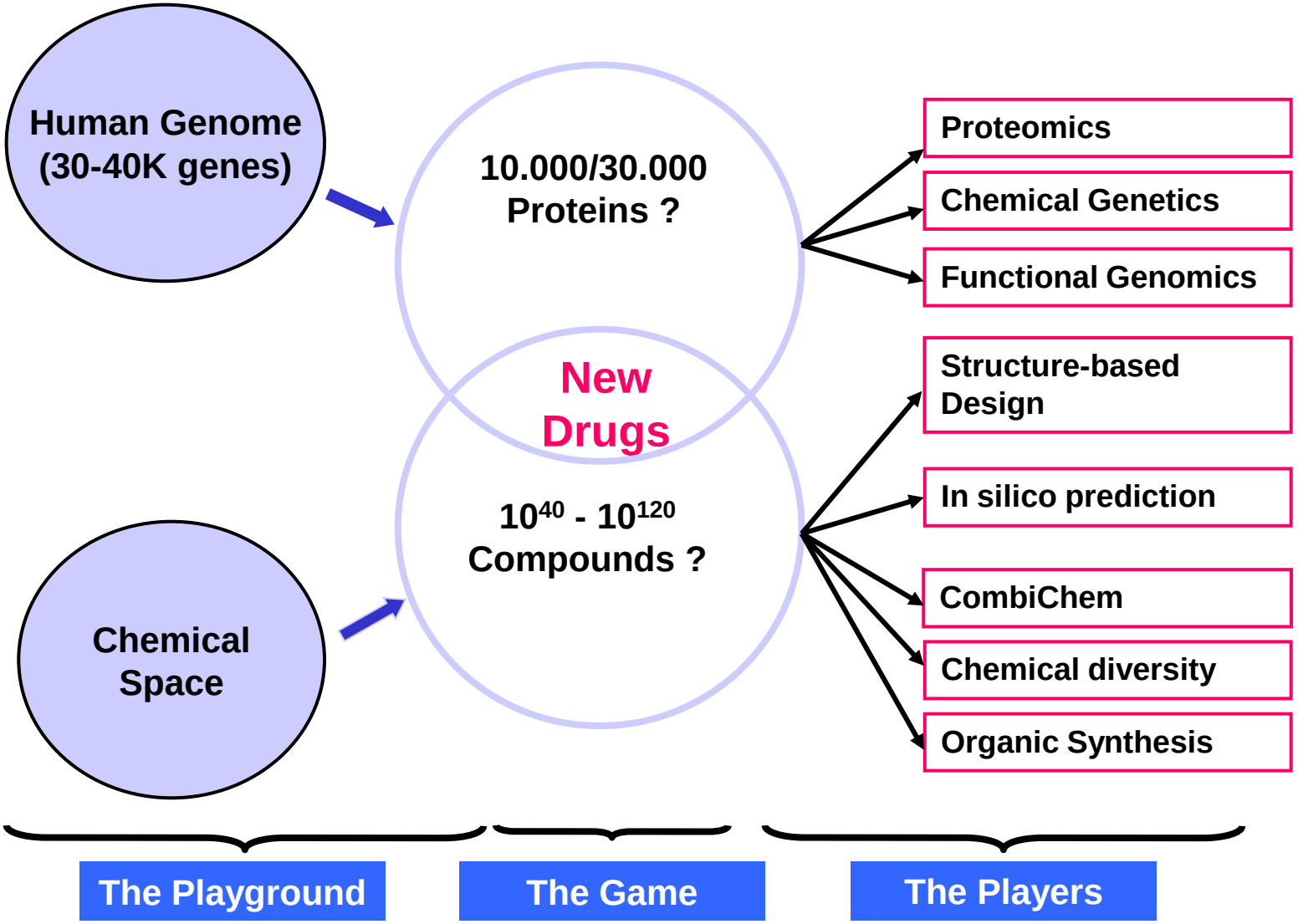






# Pharmaceutical Industry – Evolution of the R & D Process

## Drug Discovery in the 21st Century



# Technological Inputs into Drug Research & Development

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




1970s | 1980s | 1990s | 2000s | 2010s

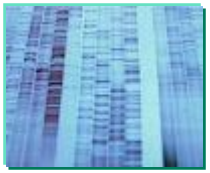
**100 compounds per chemist per year**

**10.000 – 100.000 compounds per chemist per year**

**x 1.000**

# Technological Inputs into Drug Research & Development

## DNA Sequencing

1970s | 1980s | 1990s | 2000s | 2010s

1st Genome Sequence

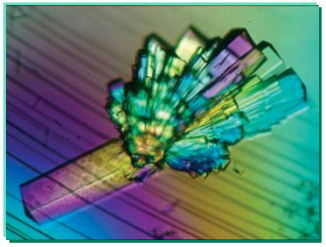
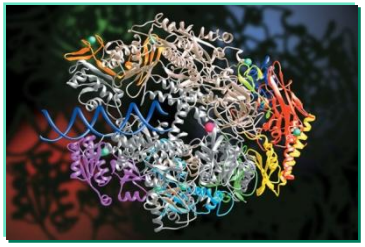
Genomics

x 1.000.000.000 faster

# Technological Inputs into Drug Research & Development

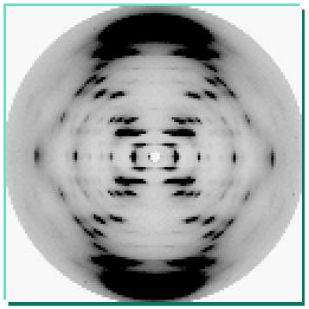
## X-ray Crystallography



1970s | 1980s | 1990s | 2000s | 2010s

1st Protein X-ray Structures



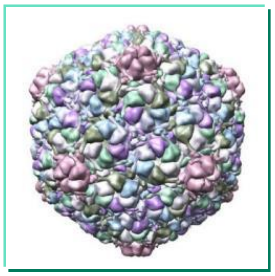
Structure-Based Design

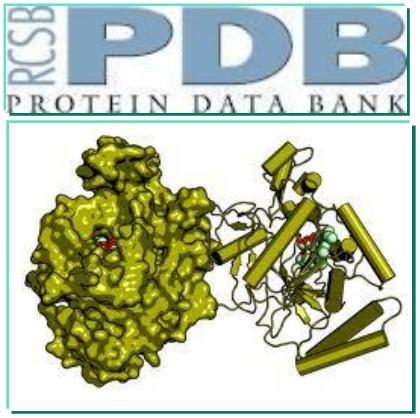
x 1.000 faster calculation

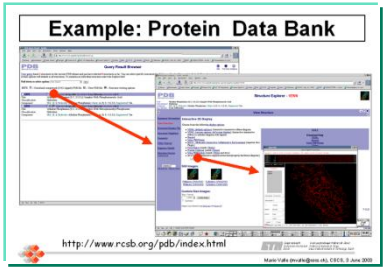
# R & D Performance: Drug Discovery Technologies

## Technological Inputs into Drug Research & Development

### Three Dimensional Protein Structures



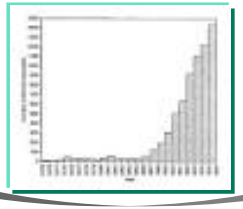



1970s | 1980s | 1990s | 2000s | 2010s

Some 100s Structures

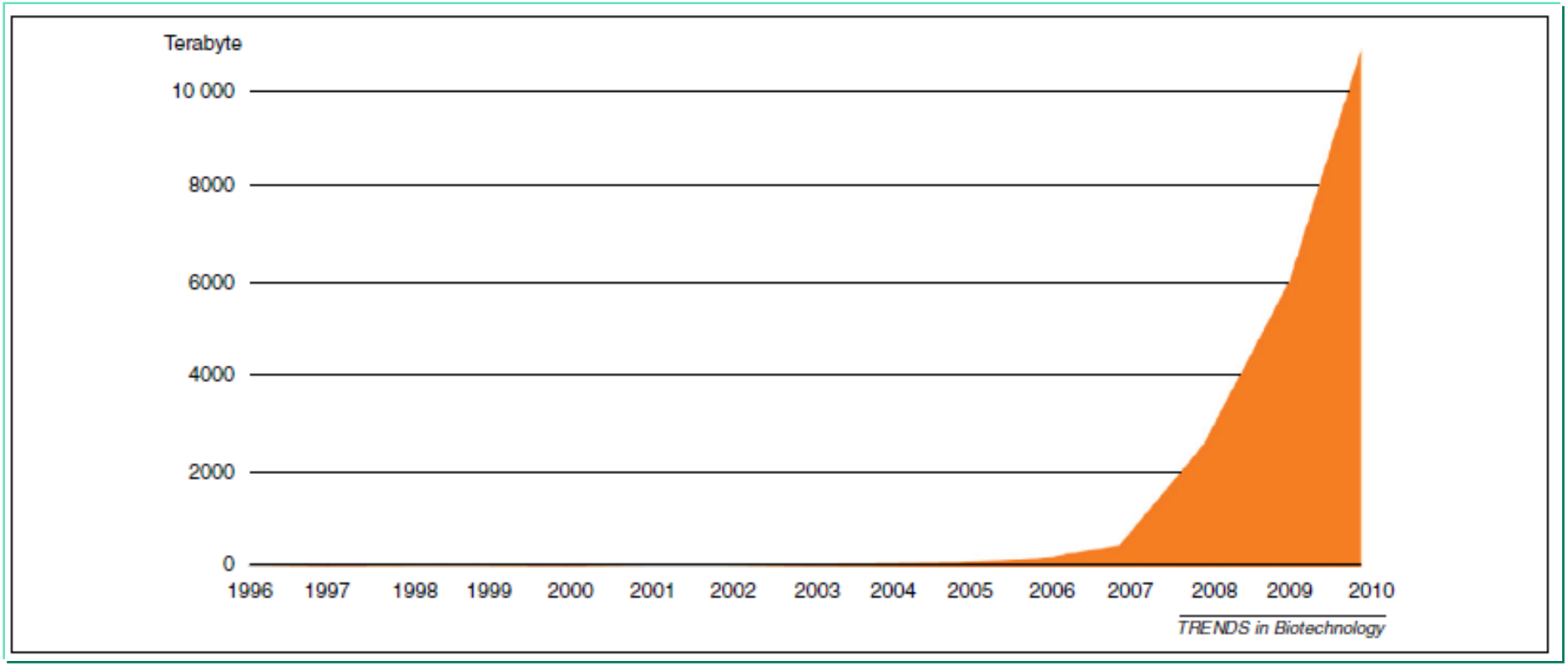
> 50.000 Structures



**x 300 more entities in the last 25 years**

# Technological Inputs into Drug Research & Development

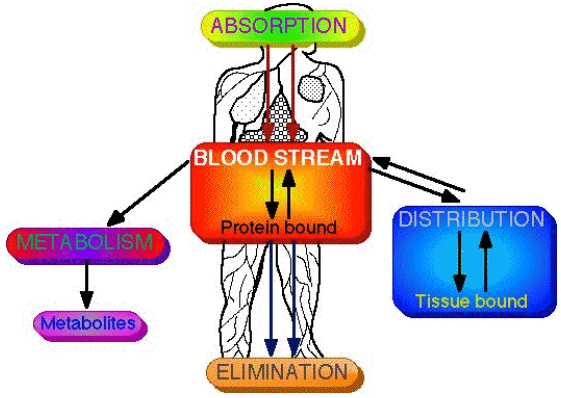
**The scale of data growth**




**The chart shows the trend in storage capacity needed to store biological data at EMBL-EBI (a terabyte is a million million bytes).**

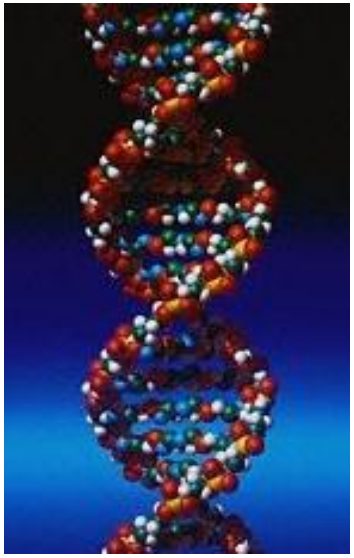
# Technology Changes in Drug Research

| | Technology | Bottlenecks |
|---|---|---|
| Up to the 70s | ▪ Chemistry & Hypotheses guide the synthesis | ▪ Animal experiments<br>▪ Isolated organs |
| Up to the 90s | ▪ Molecolar Modelling<br>▪ *In vitro* models<br>  ▪ enzyme inhibition<br>  ▪ receptor binding | ▪ Dedicated synthesis of compounds |
| Up to the year 2000 | ▪ Gene technology<br>  ▪ Production of proteins<br>▪ Combinatorial chemistry<br>  ▪ Mixtures, chemistry driven<br>▪ Structure-based design of ligands<br>▪ High-throughput test models (HTS) | ▪ ADMET Properties |



# Technology Changes in Drug Research

**Today**

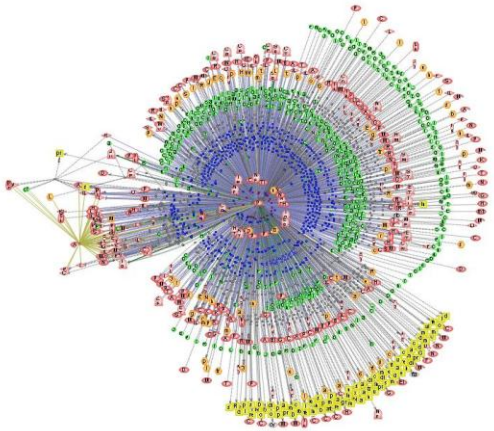


**Technology**

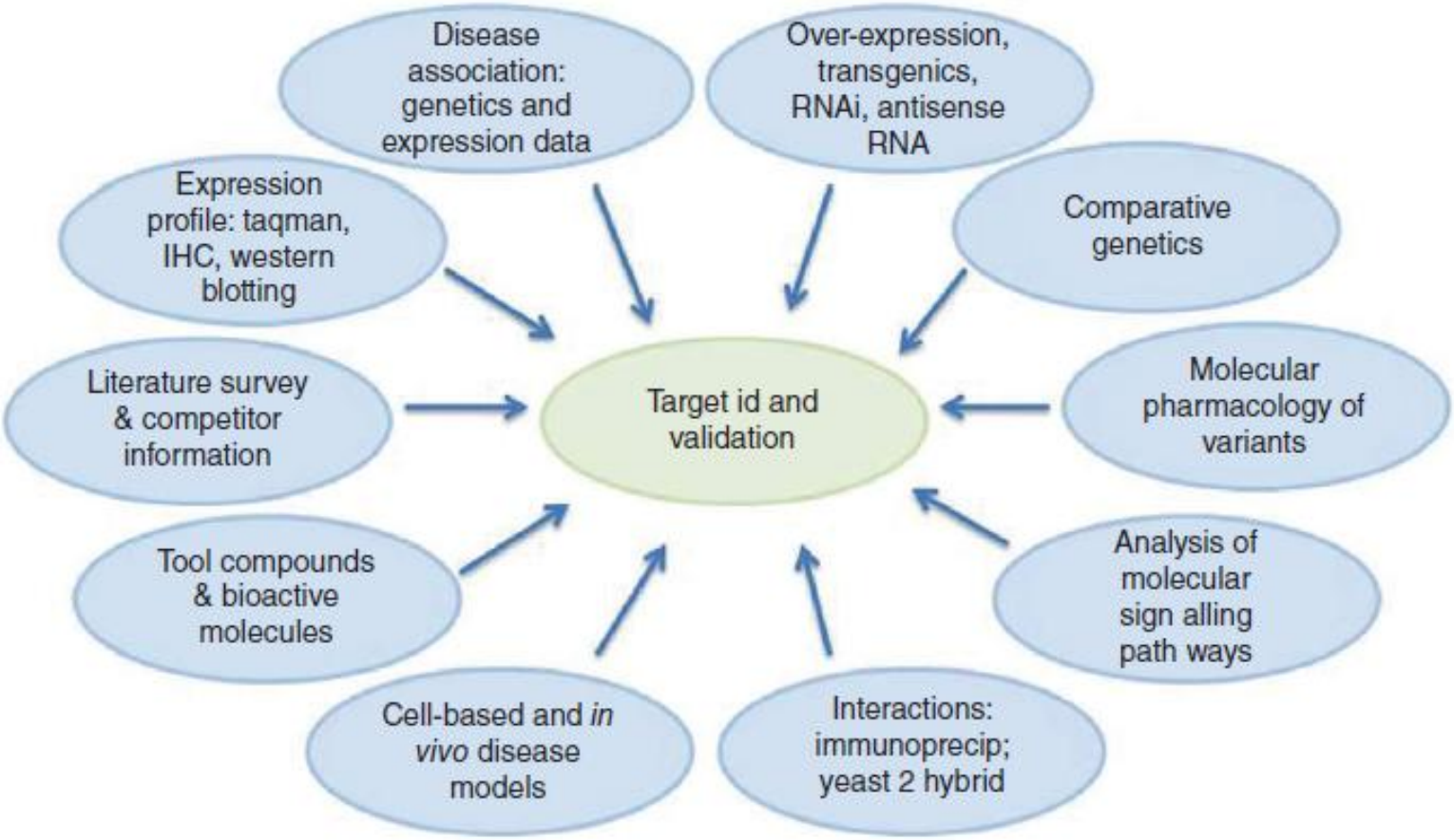
- Genomics
  - Proteonomics & bioinformatic
- Transgenic animals for proof of concept
- Combinatoriual chemistry
  - Single compounds
  - Design driven
- Structure-based and computer-aided design of ligands
- Ultra-high-throughput test models (uHTS)
- Data mining
- Virtual screening
- ADMET properties
  - HTS & *in silico*

**Bottlenecks**

- Target validation
  - „Drugable“ targets



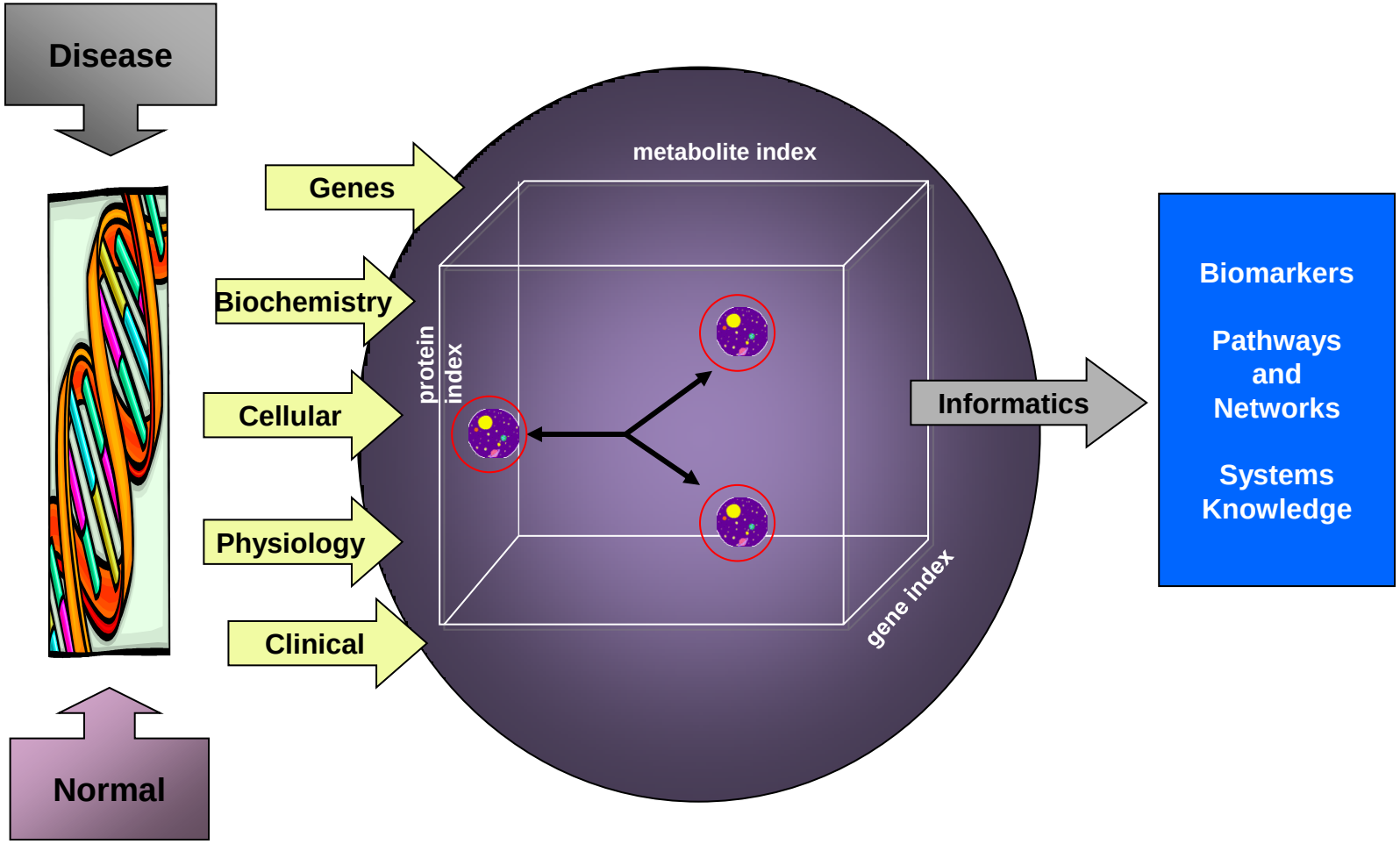
# Target Identification and validation is a multifunctional process.




J.P. Hughes, s. rees, S.B. Kalinjian, K.L. Philpott, Principles of early drug Discovery, British Journal of Pharmacology (2011) **162** 1239–1249

# R & D Performance: Drug Discovery Technologies

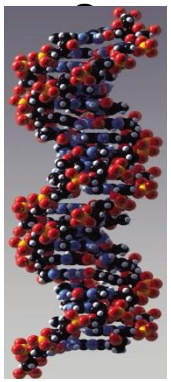
## Schematic of conceptual architecture behind systems biology



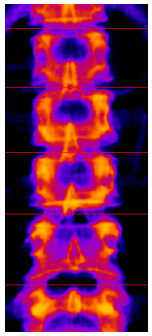

**A series of measurements ranging from genetic/genomic through to clinical are made and a comparison between normal versus perturbed (eg diseased/drug treated/toxin administration) populations is performed. Complex datasets are integrated and a variety of informatic, biostatistical and knowledge assembly tools are used to produce new knowledge and understanding about the perturbed system compared to the normal system. The output can range from molecular and cellular biomarkers to pathways and networks of the system under investigation.**

# Science and technology advances present significant opportunities

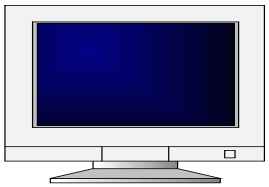
'omic



Understanding human physiology



Imaging



IT

Public investment

Pre-competitive collaborative research

Industry investment

Better understanding of disease/drug mechanisms

More efficient drug discovery and development

Better medicines, faster

Health benefits for EU citizens

# R & D Performance: Drug Discovery Technologies

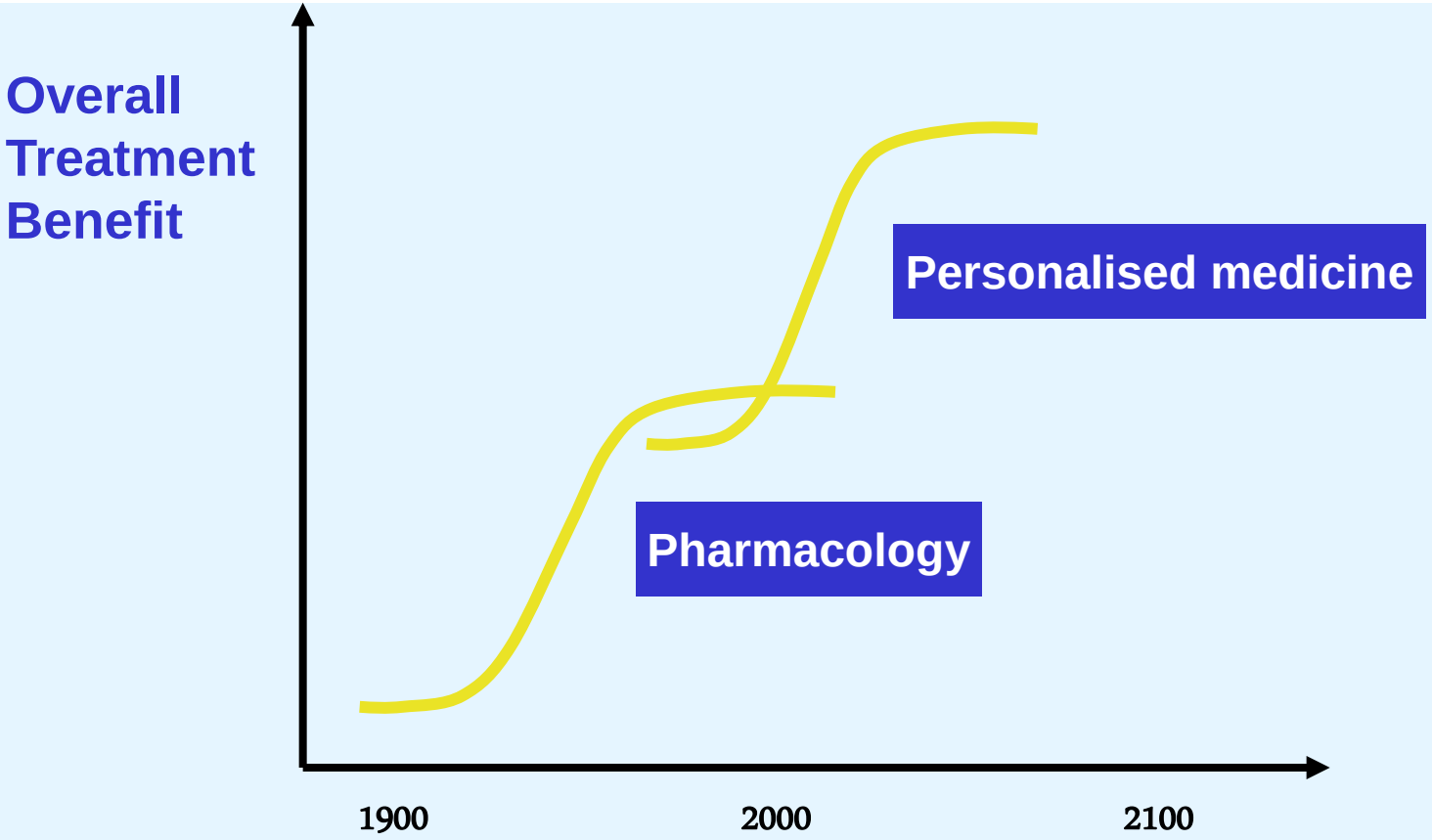
## Potential outcome of new technologies

- 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

# Innovation in the Pharmaceutical Industry

*What is the future?*

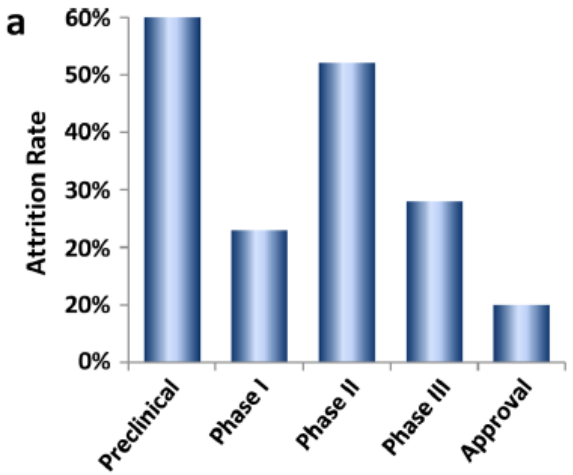


**Drug Discovery & Development Strategies Today –**
***What Has Pharmaceutical Industry Learned From The Past?***

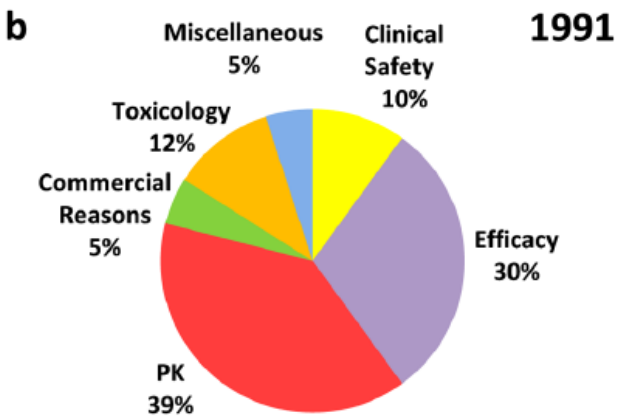
**Nothing**

# Clinical attrition statistics

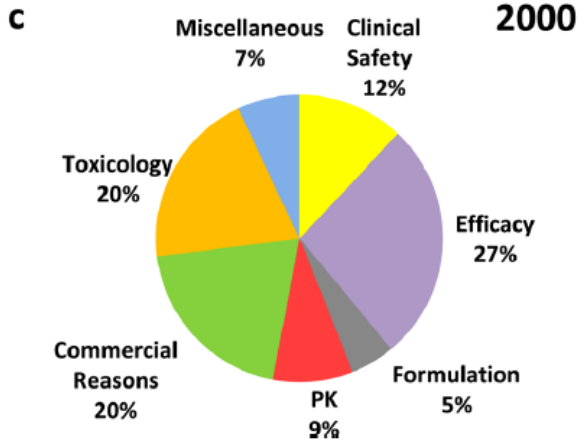
**Attrition rate by stage of development**




**Reasons for clinical failure in 1991**



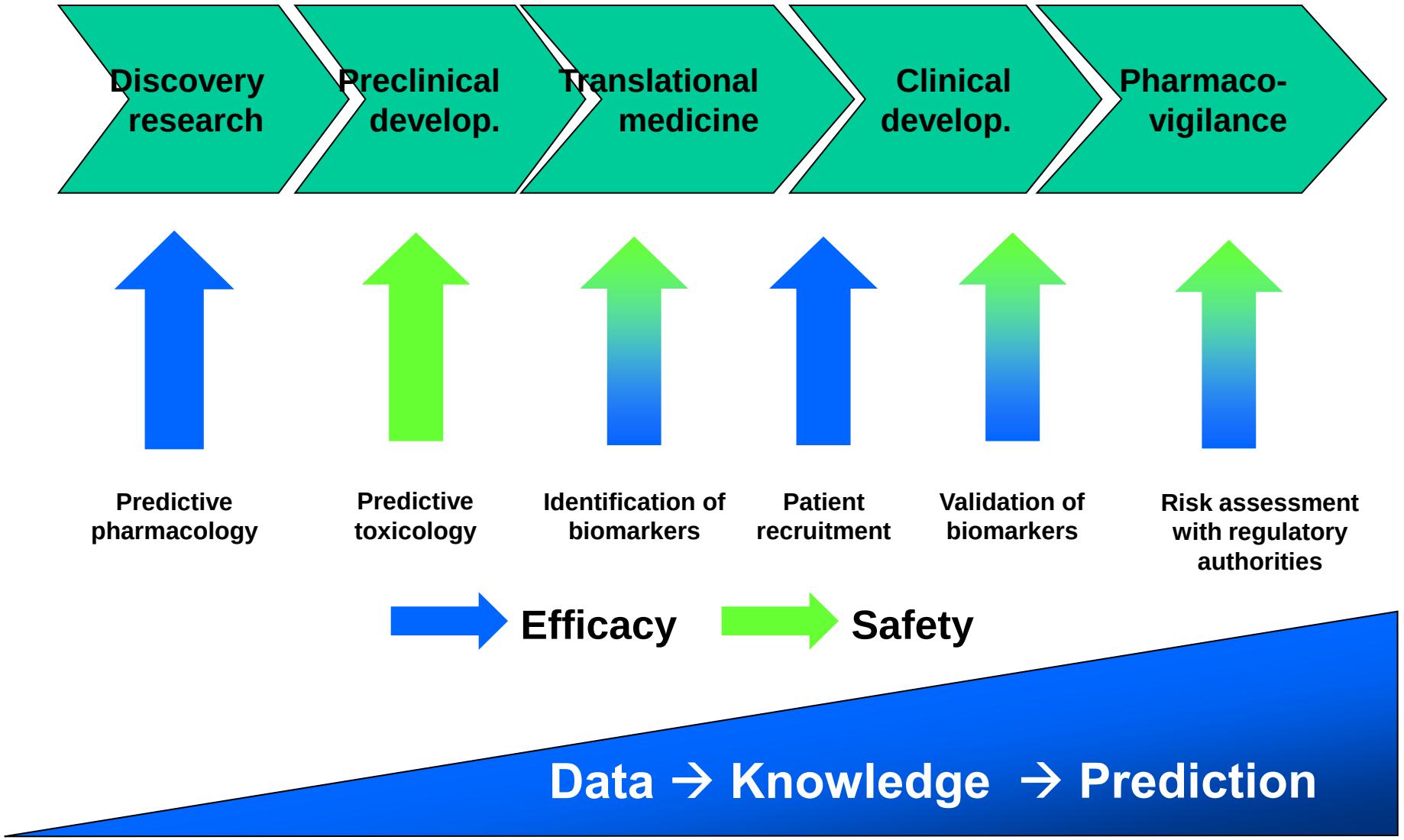

**Reasons for clinical failure in 2000**




Magid Abou-Gharbia and Wayne E. Childers, Discovery of Innovative Therapeutics: Today's Realities and Tomorrow's Vision. 2. Pharma's Challenges and Their Commitment to Innovation, J. Med. Chem 57, 5525–5553 (2014)

# R & D Performance: Drug Discovery Technologies

## Key R&D bottlenecks to overcome



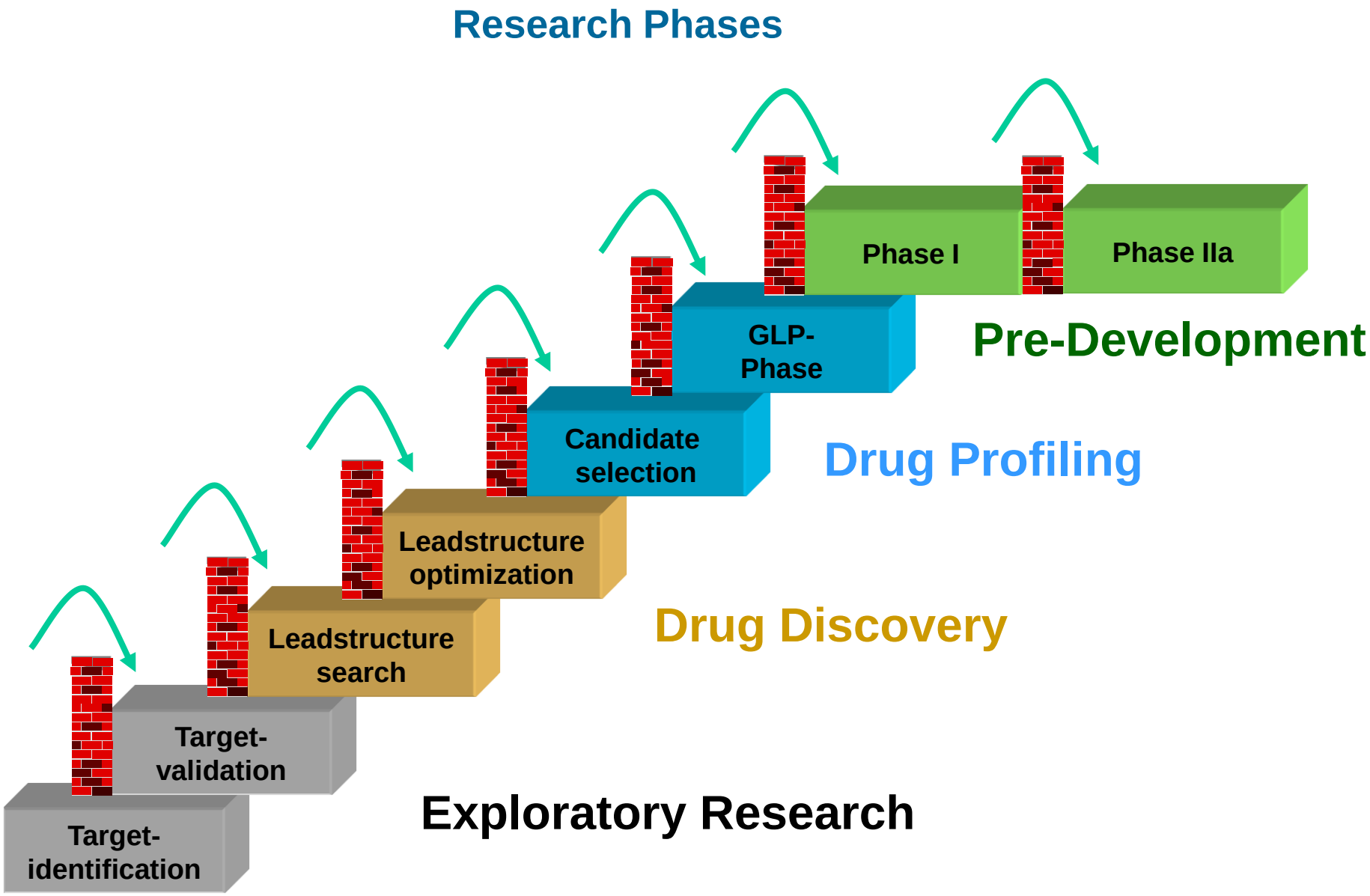
# EFFICACY in Pharmacology

**TRANSLATIONAL MEDICINE**

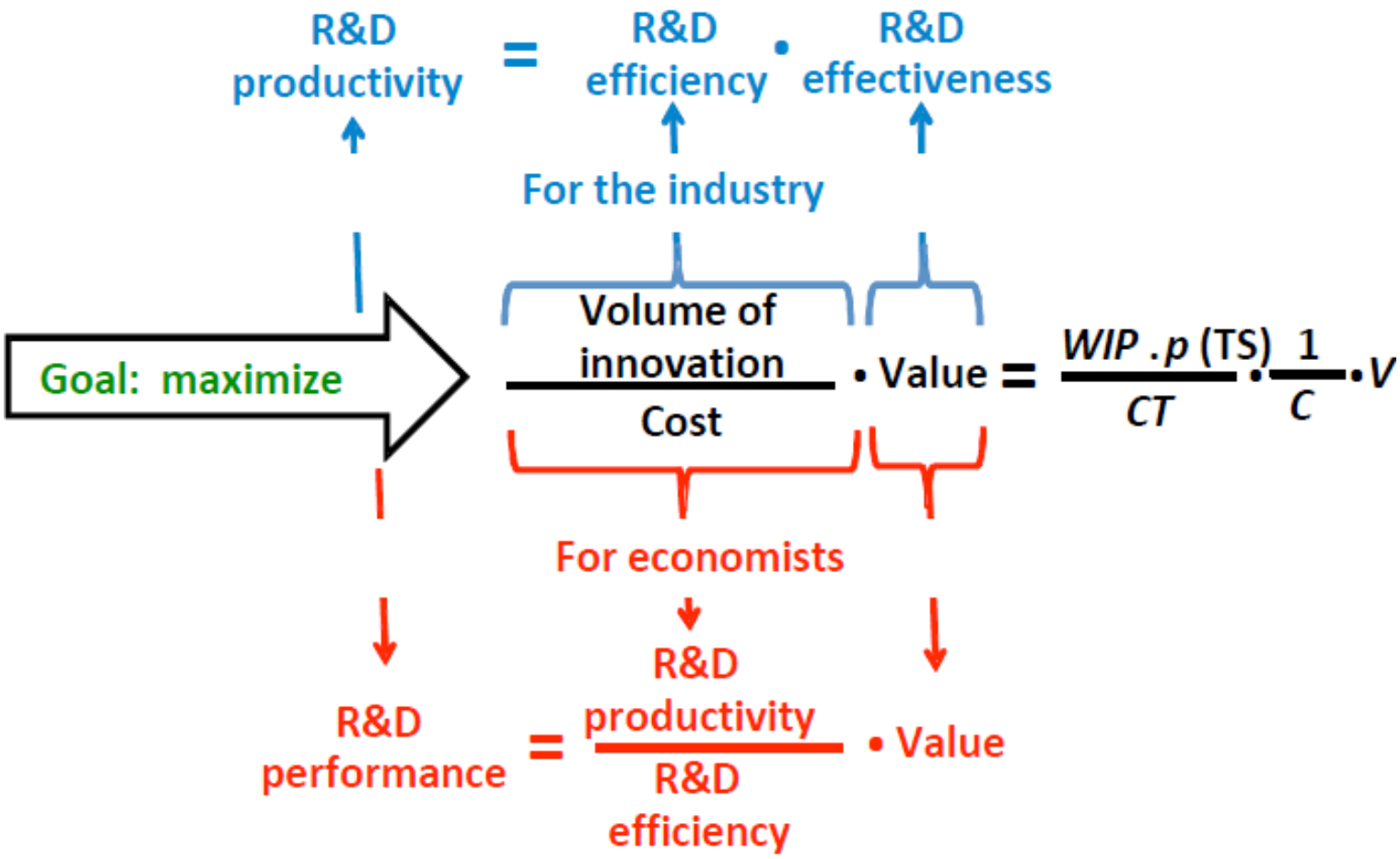
**Preclinical models that are more predictive of clinical efficacy and safety**

**Drug Research was and is…**

**…the Search for a Needle in a Haystack**


Research Phases
Phase I
Phase IIa
GLP-Phase
Pre-Development
Candidate selection
Drug Profiling
Leadstructure optimization
Leadstructure search
Drug Discovery
Target-validation
Target-identification
Exploratory Research

# R&D Performance and Productivity



# The Future of Medicinal Chemistry & Medicinal Chemists

## Success in Drug Research

An compound with an interesting structure has not nessecarily a biological activity

↓

Á 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

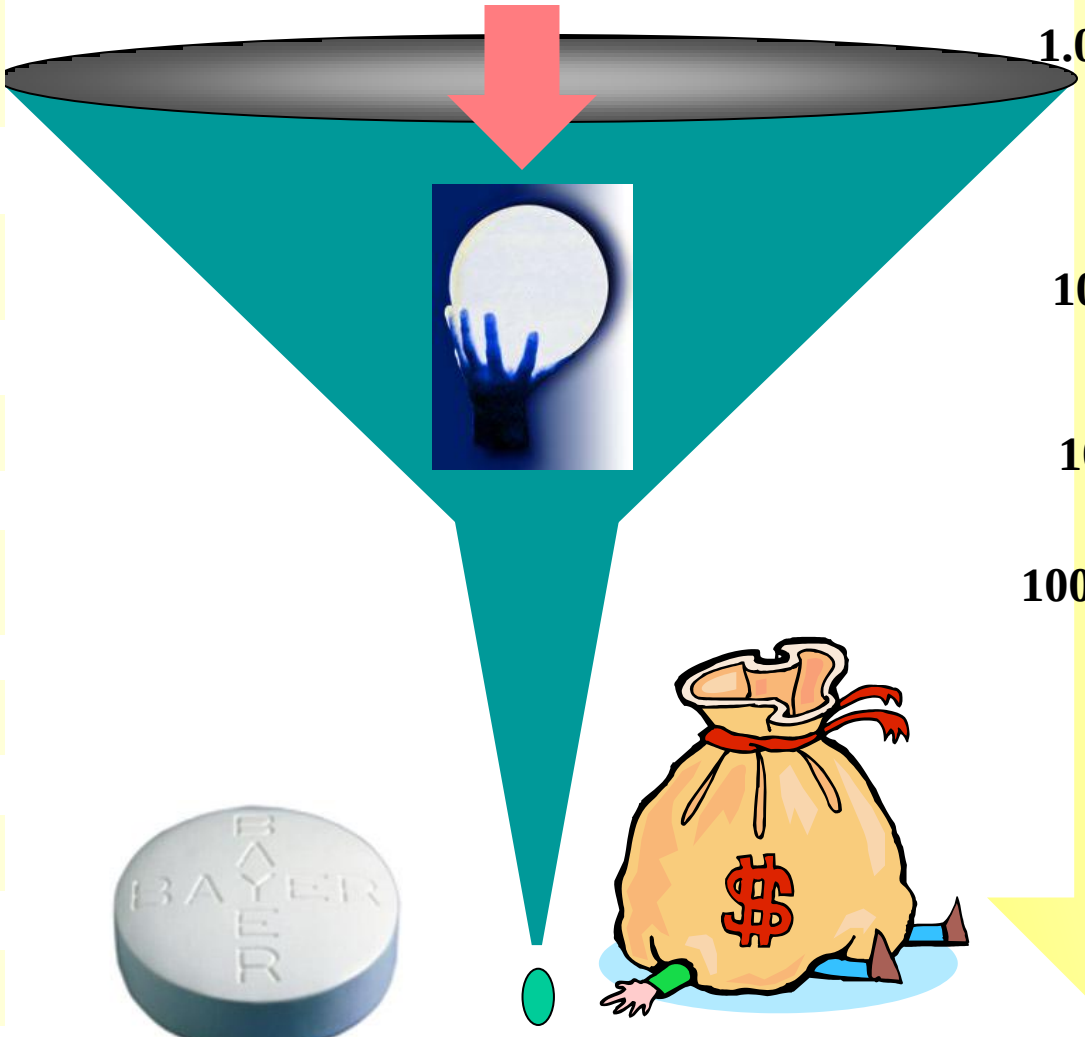
↓

A drug is not a success

↓

A successful drug is luck!

$10^{100}$ Chemical Space of Organic Molecules




1.000.000s

↓

100.000s

↓

10.000s

↓

100s - 1000

↓

10s

↓

1

↓

0 -1

# R & D Performance: Clinical Trials

## The big clinical trial problem

900 → >4,000

Number of patients per pivotal trial for a new oral antidiabetic drug

Simvastatin (Merck)

4,400

Anacetrapib (Merck)

>30,000

1948 | 1987 | 1993 | 2001 | 2006 | 2010s

1990s

First randomized controlle trial:

- 109 patients were recruited
- 107 were randomized

Number of patients per pivotal trial for an antihypertensive agent

Post marketing study long-lasting bronchodilator

>53,000

100 → 200 → 450

# R & D Performance: Clinical Trials

## 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.

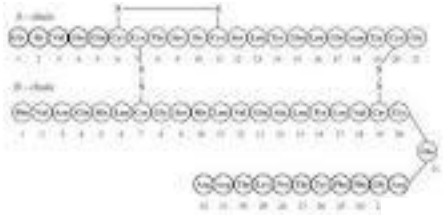
- First, one physician died.
- Then the other physician died.
- Then the king was murdered.
- The tea drinker died in the age of 83.
- The coffee drinker survived all others.

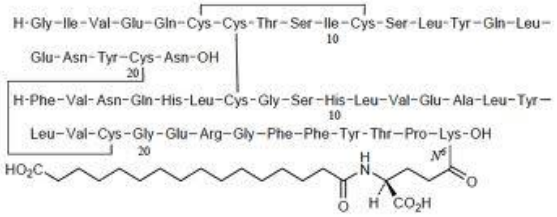
**Nevertheless, in 1794 coffee drinking was forbidden in Sweden and later again, in 1822.**

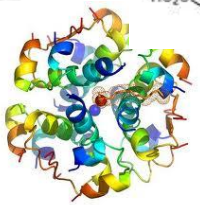
**An early clinical trial, Ann. Int. Med. 117, 1, 30 (1992)**

# R & D Performance: Clinical Trials

## The big clinical trial problem





**Glargine**

**Degludec**

**1999**

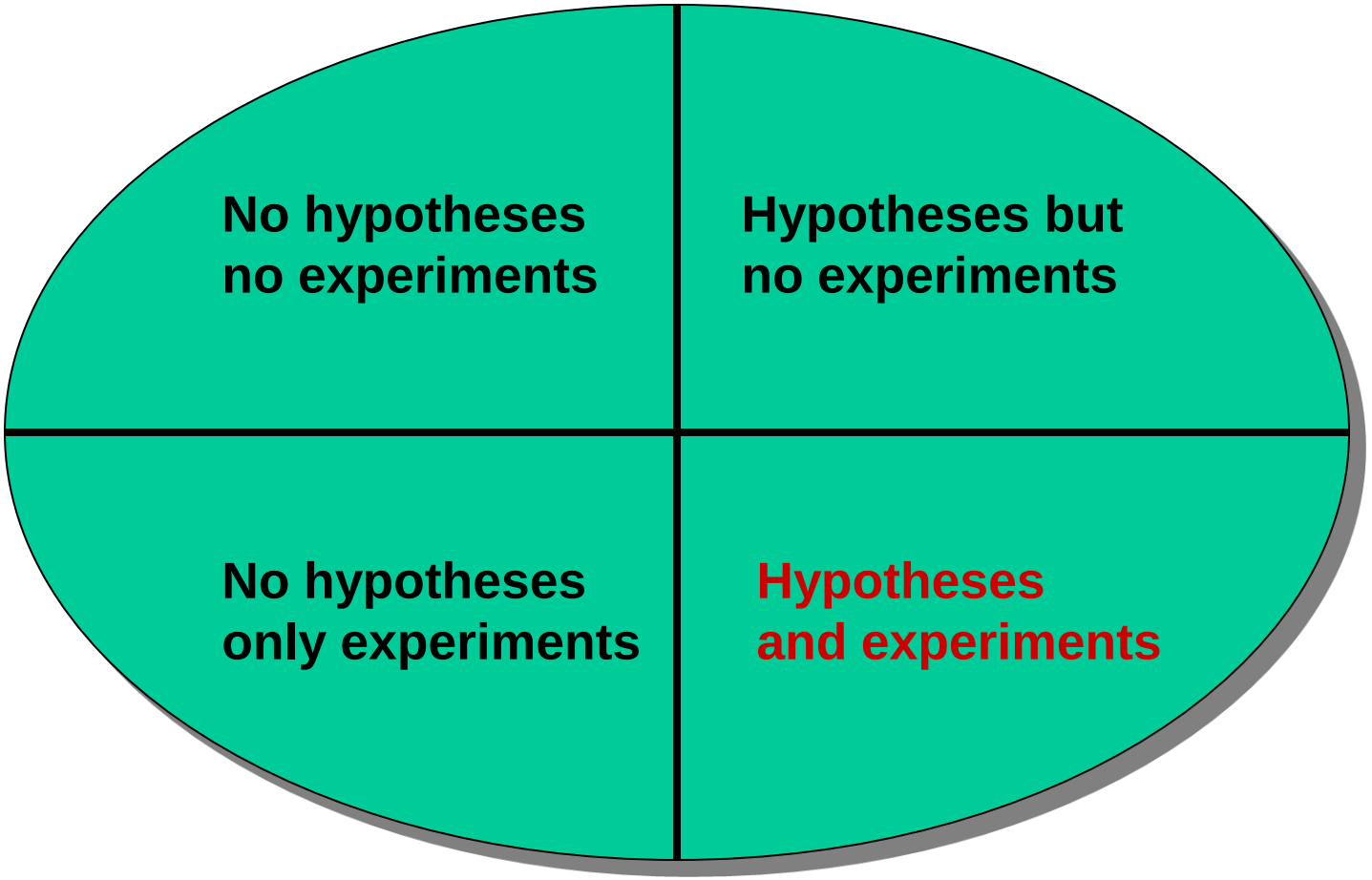
**2011**



**3 pivotal Phase III trials**

**12 pivotal Phase III trials**

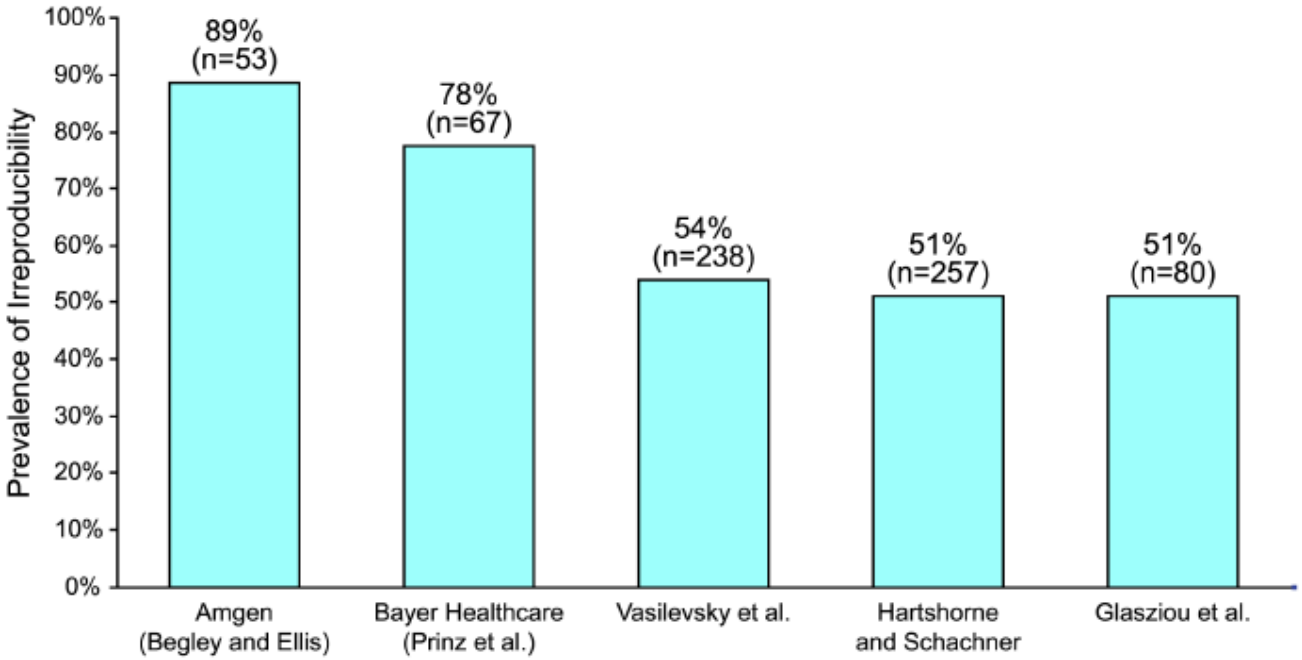
# Four Possible Strategies in Research




**Rolf Zinkernagel (Nobel prize in Medicine 1996)**

# The Economics of Reproducibility in Preclinical Research

**Studies reporting the prevalence of irreproducibility**

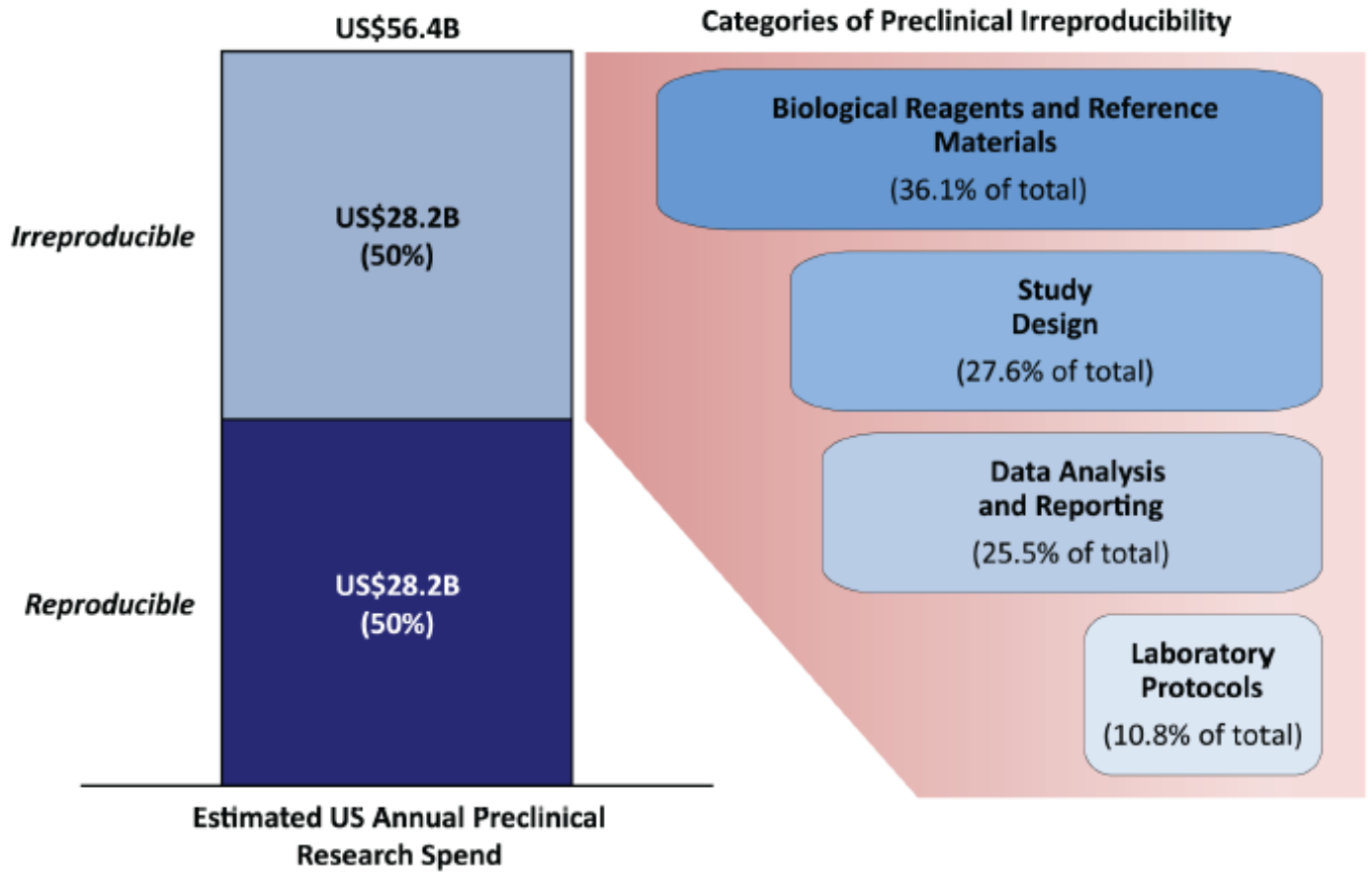



- Low reproducibility rates within life science research undermine cumulative knowledge production and contribute to both delays and costs of therapeutic drug development.
- An analysis of past studies indicates that the cumulative (total) prevalence of irreproducible preclinical research exceeds 50%, resulting in approximately US$28,000,000,000 (**US $28B)/year** spent on preclinical research that is not reproducible—in the United States

Freedman LP, Cockburn IM, Simcoe TS (2015) The Economics of Reproducibility in Preclinical Research. PLoS Biol 13(6): e1002165. doi:10.1371/journal.pbio.1002165

# The Economics of Reproducibility in Preclinical Research

**Estimated US preclinical research spend and categories of errors that contribute to irreproducibility.**




Freedman LP, Cockburn IM, Simcoe TS (2015) The Economics of Reproducibility in Preclinical Research. PLoS Biol 13(6): e1002165. doi:10.1371/journal.pbio.1002165

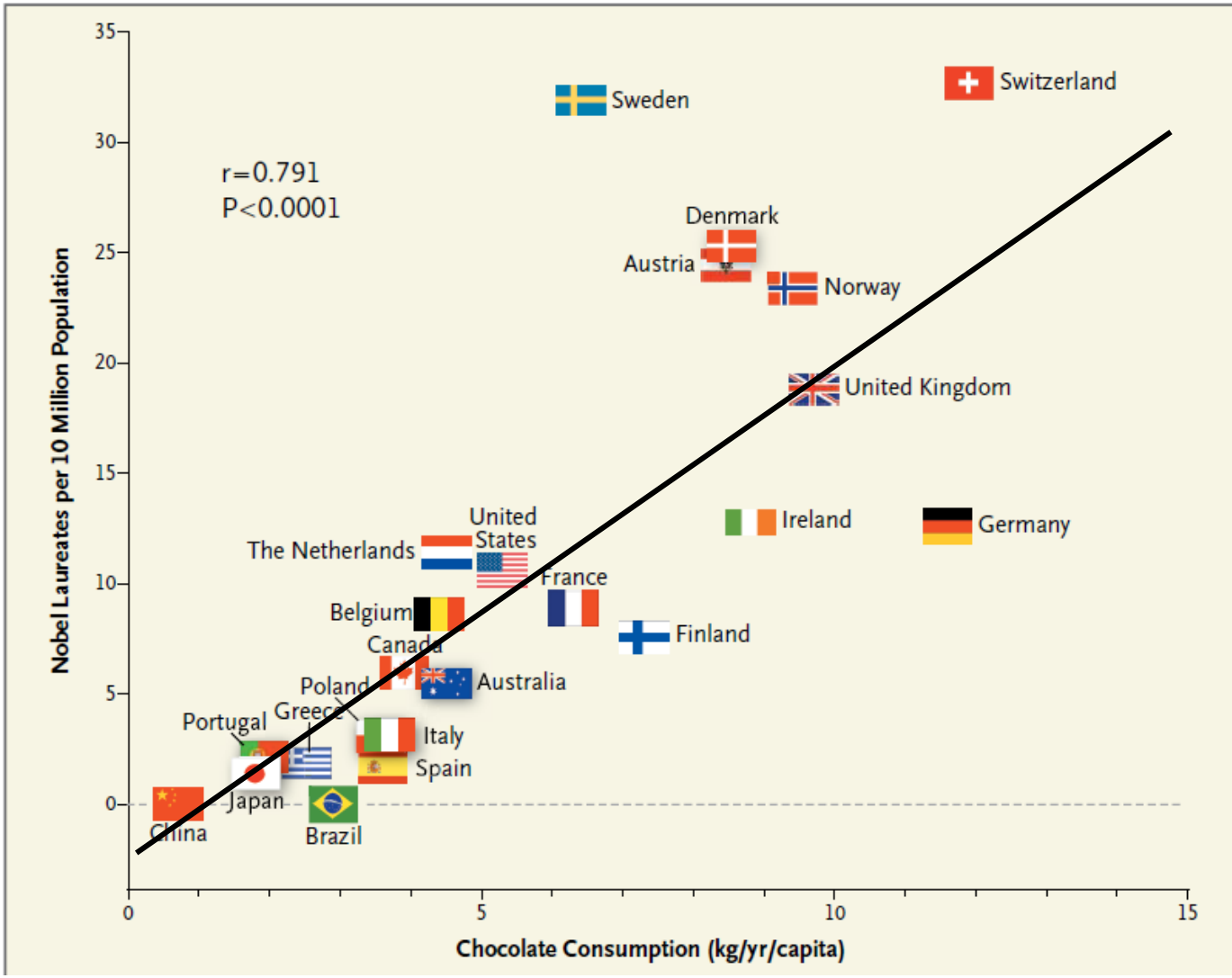
# The Future of Medicinal Chemistry & Medicinal Chemists

## Correlation between Countries' Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population.

**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.**




Franz H. Messerli, Chocolate Consumption, Cognitive Function, and Nobel Laureates, The New England Journal of Medicine 367 (16), 2012 , 1562-1564.

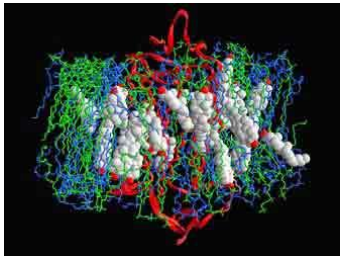
# Chocolate Consumption, Cognitive Function, and Nobel Laureates

- **Chocolate consumption could hypothetically improve cognitive function not only in individuals but also in whole populations.**
- There was a close, significant linear correlation ($r = 0.791$, $P<0.0001$) between chocolate consumption per capita and the number of Nobel laureates per 10 million persons in a total of 23 countries.
- When recalculated with the exclusion of Sweden, the correlation coefficient increased to 0.862. Switzerland was the top performer in terms of both the number of Nobel laureates and chocolate consumption.
- The slope of the regression line allows us to estimate that it would take about 0.4 kg of chocolate per capita per year to increase the number of Nobel laureates in a given country by 1.
- For the United States, that would amount to 125 million kg per year.

Franz H. Messerli, Chocolate Consumption, Cognitive Function, and Nobel Laureates, The New England Journal of Medicine 367 (16), 2012 , 1562-1564.

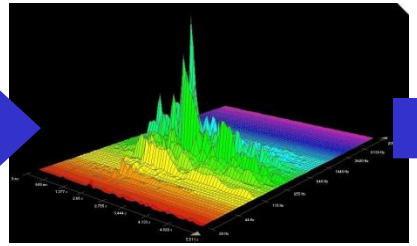
## The Selectivity of Ligands

- Over the past decades, one of the key goals of drug design has been the discovery of maximally selective ligands for specific binding sites on individual molecular targets.
- The assumption being that if a ligand´s potency and selectivity for the desired target is increased, there should be a corresponding decrease in undesirable side effects that may arise from binding in secondary targets.

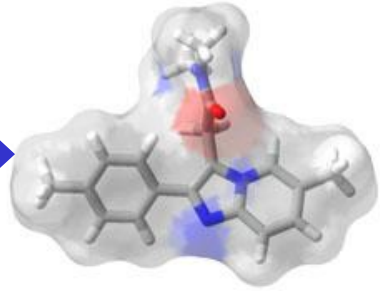


One Target

Hightroughput Assay



Optimizing the Biological Fingerprint



Highly Selective Ligand

## The Key Lock Principle

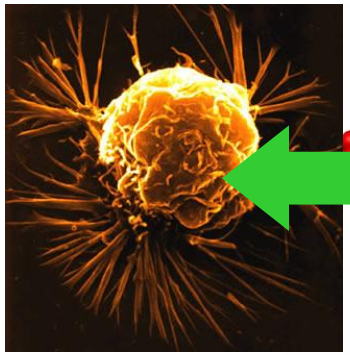
*Emil H. Fischer (1852-1919)*
*Nobel Price 1902*

**“Um ein Bild zu gebrauchen, will ich sagen, daß Enzym und Glucosid wie Schloß und Schlüssel zueinander passen müssen, um eine chemische Wirkung aufeinander ausüben zu können”**

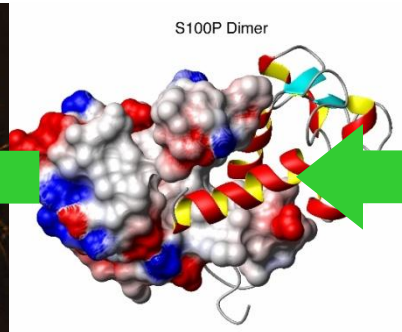
***„To use a model I would like to say, that an enzyme and an glycoside have to fit to each other like a lock and a key to be able to have a chemical reaction on each other.“***

***E. Fischer, 1894***

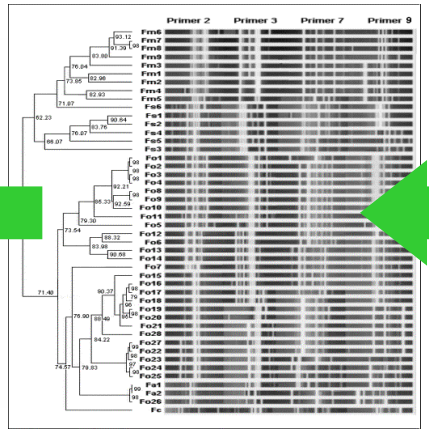
# R & D Performance: Drug Discovery Technologies



Cell Structure and Function

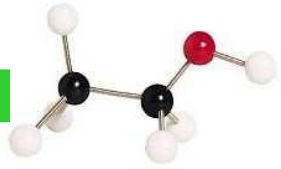



Proteine

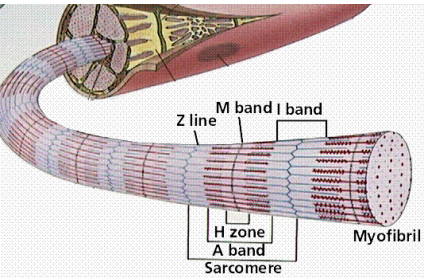



Genome

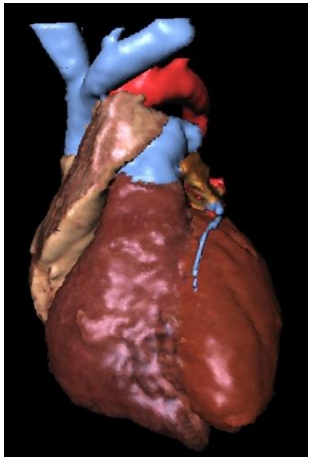
Gene



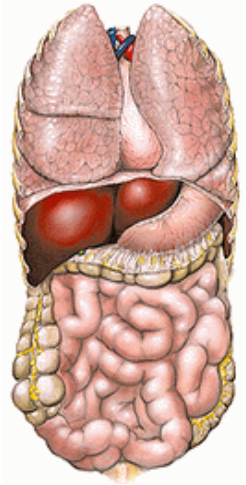
Molecule



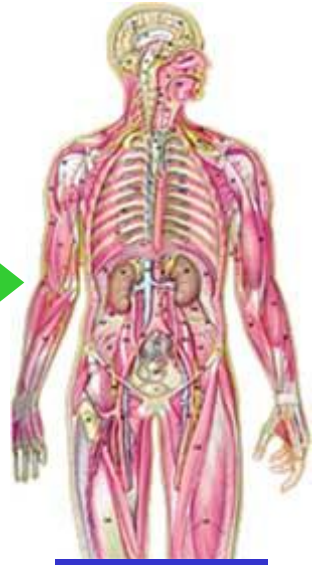

Tissue Structure and Function



Organ Structure and Function



Organ System

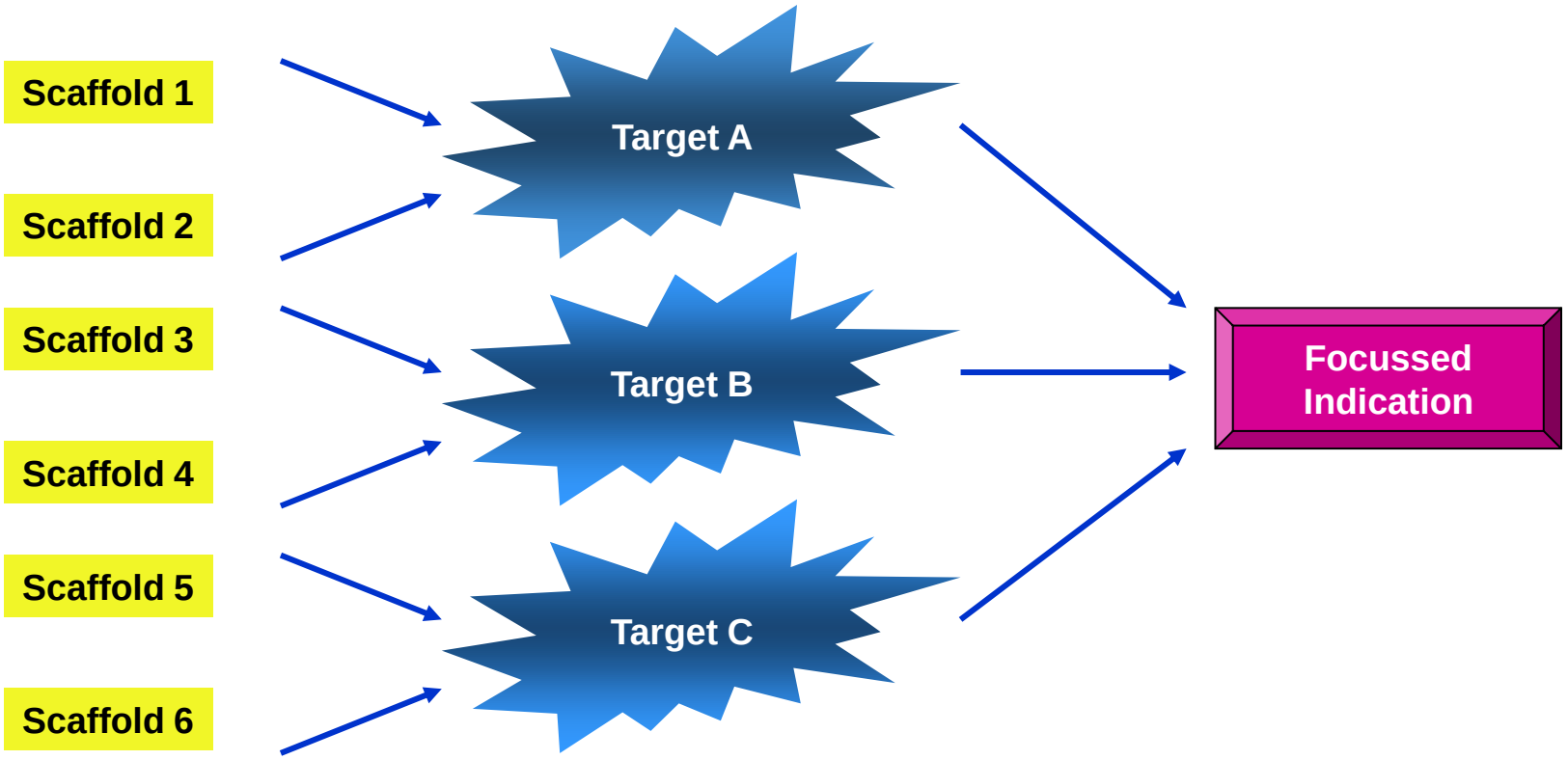


Organism

# The Future of Medicinal Chemistry & Medicinal Chemists

## Indication Orientated Drug Research

***Scaffold - Target - Indication***



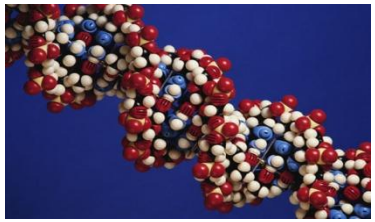

**Highly Diverse Chemistry**

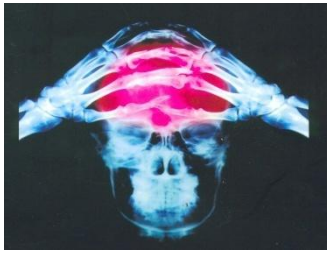
**Diverse *in vitro* Screening**

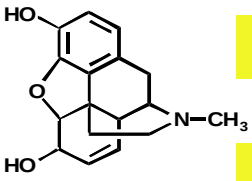
**Focussed *in vivo* Screening**

# Target Orientated Drug Research

## *Scaffold - Target - Indication*

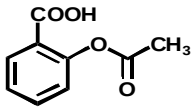







**Scaffold 1**

**Scaffold 2**




**Scaffold 3**

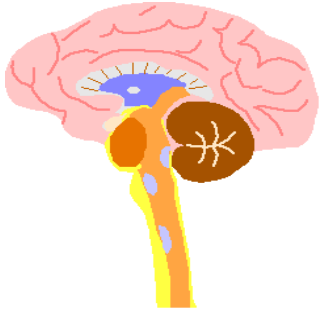
**Scaffold 4**

**Target**

**Indication A**

**Indication B**

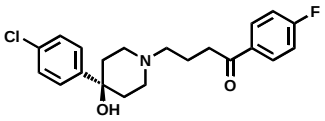
**Indication C**

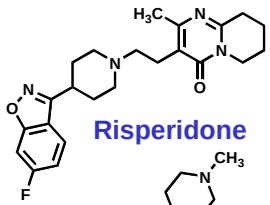


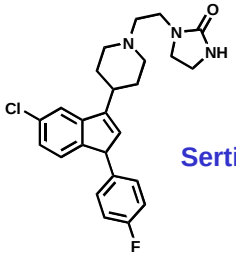
# The Future of Medicinal Chemistry & Medicinal Chemists

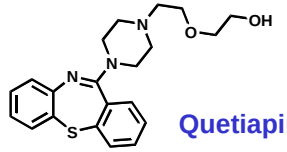
## Affinities of Some Antipsychotics for Various Neuronal Receptors*)

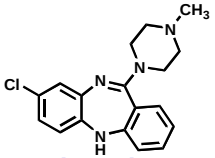
| | Affinity, $K_i$ (nM) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Compound** | $D_1$ | $D_2$ | $D_3$ | $D_{4.2}$ | 5-$HT_{2A}$ | 5-$HT_{2C}$ | $\alpha_1$ | $\alpha_2$ | Muscarinic receptors | $H_1$ |
| **Haloperidol** | 270 | 1.4 | 21.0 | 11 | 25.00 | >5000.0 | 19.0 | >5000.0 | 4670 | 730.0 |
| **Clozapine** | 540 | 150.0 | 360.0 | 40 | 3.30 | 13.0 | 23.0 | 160.0 | 34 | 2.1 |
| **Risperidone** | 620 | 3.3 | 13.0 | 16 | 0.16 | 63.0 | 2.3 | 7.5 | >5000 | 2.6 |
| **Olanzapine** | 250 | 17.0 | 54.0 | 28 | 1.90 | 7.1 | 60.0 | 230.0 | 26 | 3.5 |
| **Sertindole** | 210 | 7.4 | 8.2 | 21 | 0.85 | 1.3 | 1.8 | 1680.0 | >5000 | 570.0 |
| **Quetiapine** | 4240 | 310.0 | 650.0 | 1600 | 120.00 | 3820.0 | 58.0 | 87.0 | 1020 | 19.0 |
| **Ziprasidone** | 330 | 9.7 | 7.5 | 39 | 0.30 | 13.0 | 12.0 | 390.0 | >5000 | 5.3 |
| **Zotepine** | 84 | 13.0 | 16.0 | 39 | 0.91 | 2.9 | 3.4 | 960.0 | 550 | 3.4 |

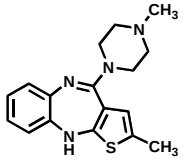

Haloperidol

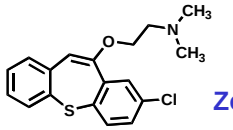

Risperidone

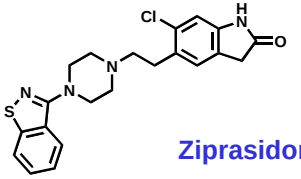

Sertindole


Quetiapine


Clozapine


Olanzapine


Zotepine


Ziprasidone

*) J. Schaus, F.P. Bymaster, *Dopaminergic Approaches to Antipsychotic Agents*, Annual Reports in Medicinal Chemistry, Academic Press; San Diego, CA, 1998, pp 1-10.

# The Future of Medicinal Chemistry & Medicinal Chemists

drugs research

## ”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.

**Per Lindberg**

- …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

# The Future of Medicinal Chemistry & Medicinal Chemists

## ”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 im portant 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.*

# The Future of Medicinal Chemistry & Medicinal Chemists

ACS Medicinal Chemistry Letters

Viewpoint

pubs.acs.org/acsmedchemlett

## Tough Times for Medicinal Chemists: Are We to Blame?

Takashi Tsukamoto*

Department of Neurology and Brain Science Institute, Johns Hopkins University, Baltimore, Maryland 21205, United States

ABSTRACT: In the United States, medicinal chemists continue to face job insecurity and high rates of unemployment. The situation is unlikely to improve in the near future. Is there a light at the end of the tunnel? Is there anything we can do to revitalize our community? The answer may be right in front of us.

- ….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…

Takashi Tsukamoto, Tough Times for Medicinal Chemists: Are We to Blame?, ACS Med. Chem. Lett. 2013, 4, 369−370

# The Future of Medicinal Chemistry & Medicinal Chemists

ChemPubSoc Europe

DOI: 10.1002/cmdc.201500133

CHEMMEDCHEM Viewpoints

## Medicinal Chemists of the 21st Century—Who Are We and Where to Go?

Peter Nussbaumer*[a]

*Dedicated to all medicinal chemists and to ChemMedChem on the occasion of its 10th volume*

Many recent articles have dealt with the future challenges in medicinal chemistry. Here, I discuss my concerns over the future of medicinal chemists, who have to be skilled and knowledgeable in many different fields, particularly in the context of the ever-growing requirements, the request for even broader diversification, and the substantial structural change in industrial drug discovery. In my opinion, we have to do the following in order to ensure sustained high quality and achievements: 1) to focus on superior design without excluding complex structures a priori; 2) to proactively shape the future of our discipline; 3) to discuss specialization; 4) to intensify exchange between academia and industry; and 5) to remodel education of the next generation of medicinal chemists. By providing my opinion on these aspects, I hope to stimulate discussions and change within the community.

# The Future of Medicinal Chemistry & Medicinal Chemists

Pharmacology
Clinical Medicine
Toxicology
Physiology
ADME Expertise

Systems Biology
Cellular Biology
Molecular Biology
Biochemistry
Chemical Biology

Medicinal Chemist

Bioinformatics
Cheminformatics
Computational Chemistry
Data Mining

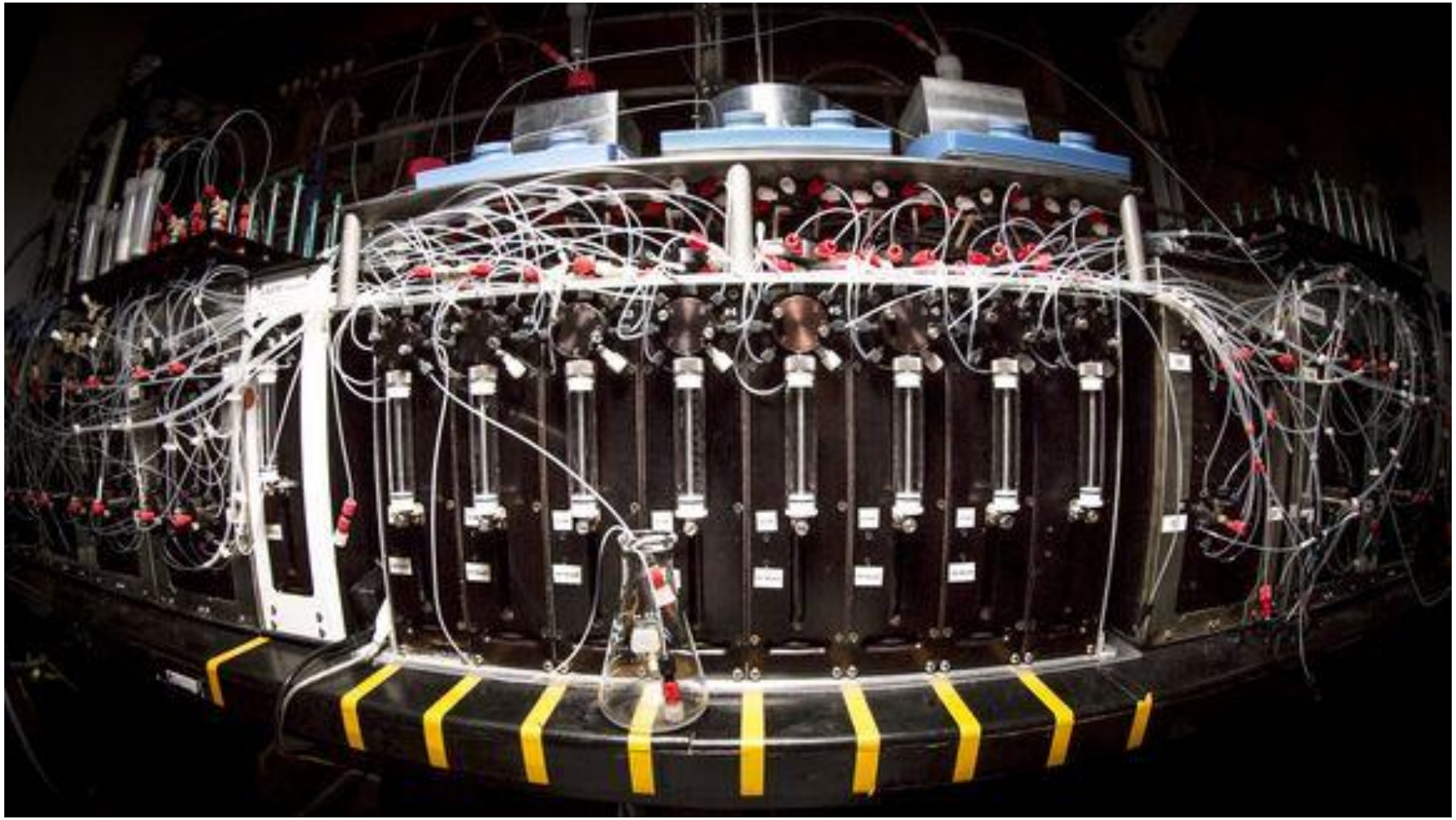
Regulatory Expertise
Pharmaceutical technology
Ecology (Green Chemistry)
Process Chemistry

Design of new molecules

Synthesis new molecules

# The Synthesis Engine

By Martin Burke, University of Illinois



# The Future of Medicinal Chemistry & Medicinal Chemists

Pharmacology

Clinical Medicine

Toxicology

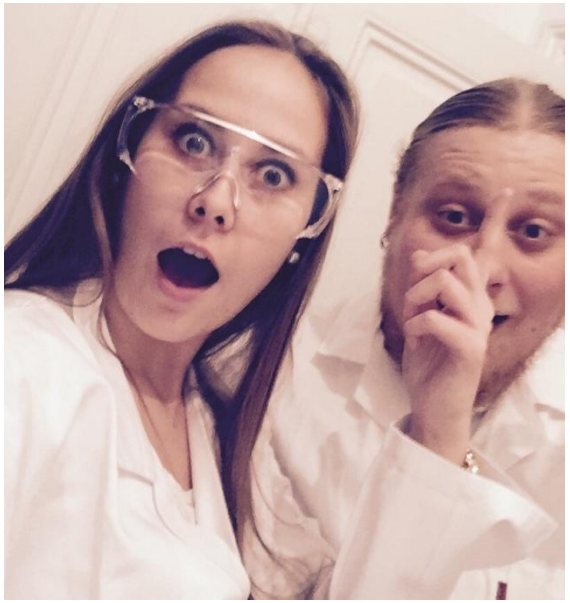
ADME Expertise

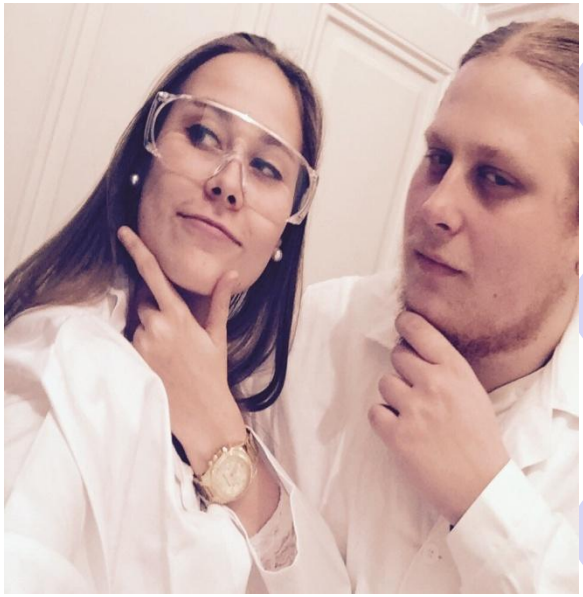
Molecular Biology

Cellular Biology

Systems Biology

Physiology





Biochemistry

Cheminformatics

Regulatory Expertise

Computational Chemistry

Ecology (Green Chemistry)

Data Mining

Bioinformatics

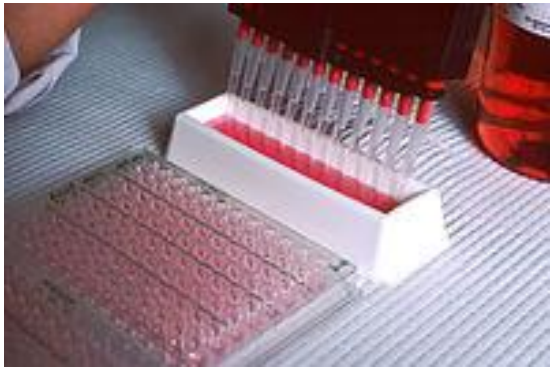
Process Chemistry

Pharmaceutical technology

Chemical Biology

# 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 ($K_I$)**

# The Future of Medicinal Chemistry & Medicinal Chemists

## *in vivo* Pharmacology

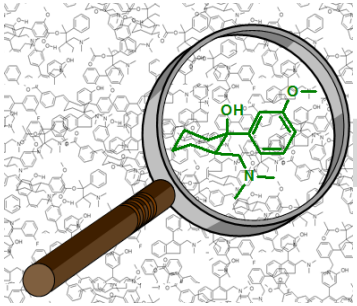
# Advantages of early *in vivo* testing

**Onset of Action**

**CNS Side Effects**

**Oral Bioavailability**

**Duration of Action**




**SAR based**
**Lead Opzimization**

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

***in vitro* Profile**
**μ-Opioid receptor affinity**
**Naloxon binding ($K_i$)**

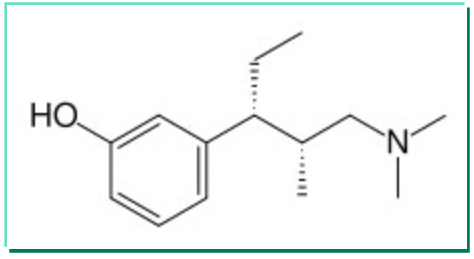
**Early Clinical**
**Proof of Concept**

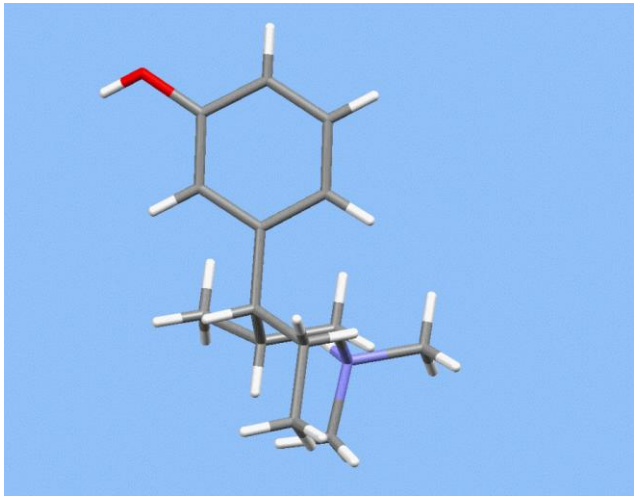
**1000 Compounds (14 scaffolds)**
**280 open chain lead series**

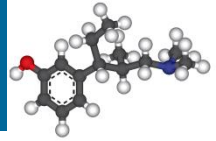
# Tapentadol – A New Analgesic with a Dual Mode of Action

PALEXIA®
TAPENTADOL


# Tapentadol - From Morphine and Tramadol to the Discovery Tapentadol





# Tapentadol – The Path To The Market

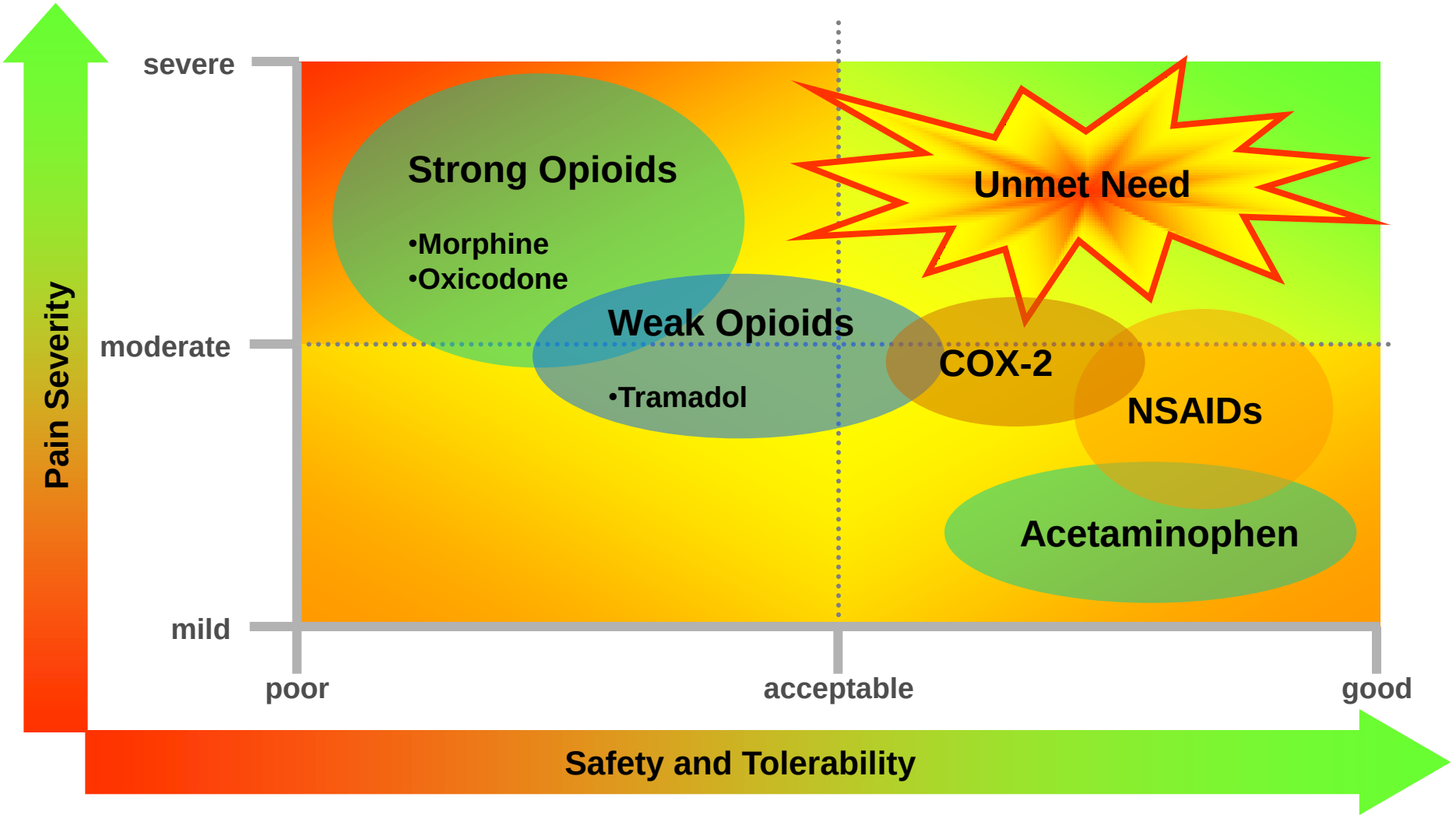
- Start of the pharmaceutical development
- First application to man
- Start of clinical trials with oral IR formulation
- First in man trial with PR formulation
- Start of co-operation with J&J
- US submission acute pain
- EU submission acute pain
- EU and US submission chronic pain

1994 1996 1998 2000 2002 2004 2006 2008 2010 2012 2014 2016

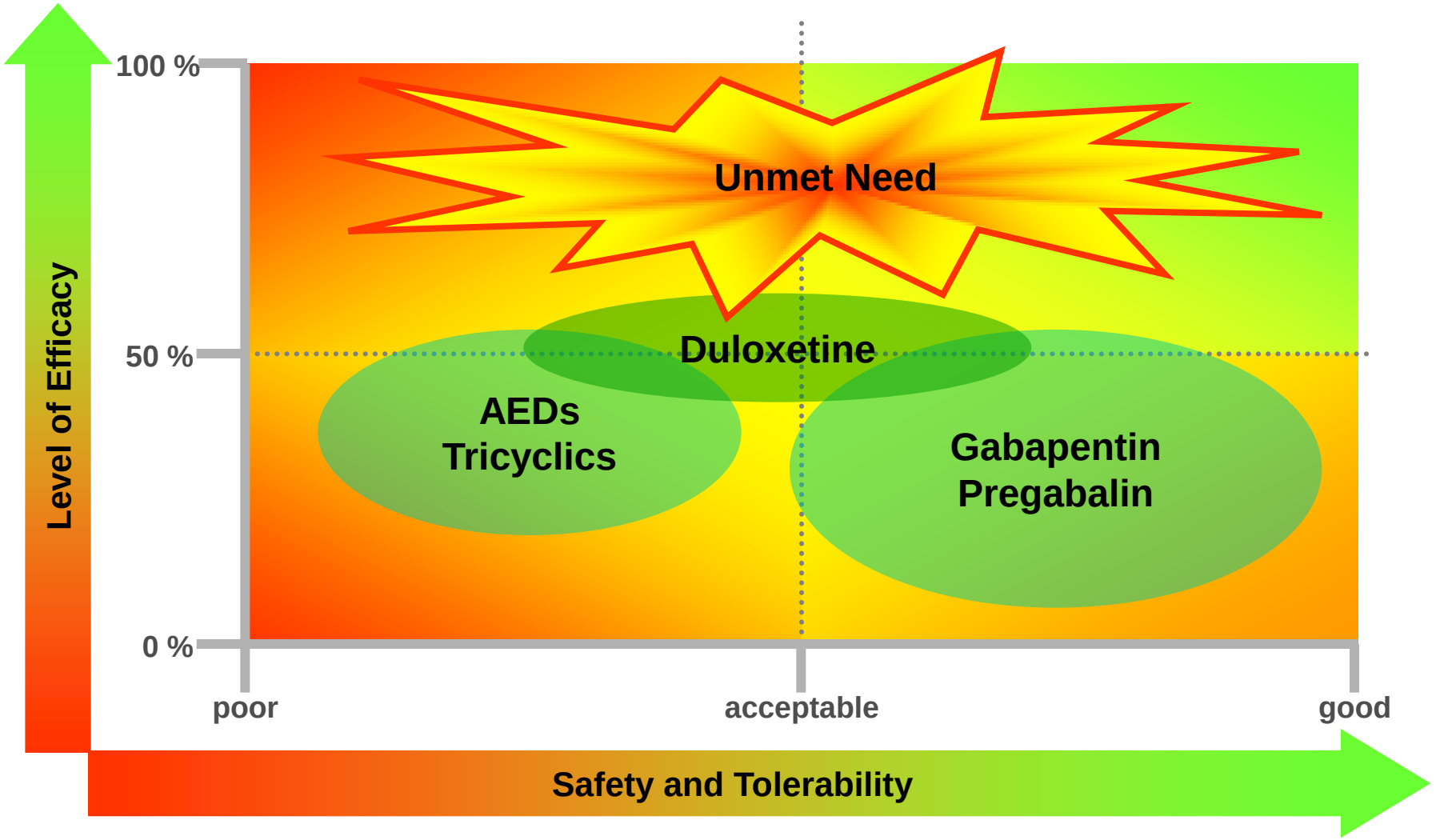
- First synthesis of BN-200 (February 8, 1994)
- Start of the pre-clinical GLP-program
- First study in patients (acute pain)
- Start of the pre-clinical GLP-programINN for BN 200 (CG5503) base Tapentadol
- Start of clinical program in chronic pain
- Start of Phase III program
- First national EU registration
- Completion EU registration procedure acute and chronic pain
- Extension of co-operation with J&J

# Pain Research Today - The Unmet Needs

## Significant Unmet Needs in Inflammatory/Nociceptive Pain Treatments

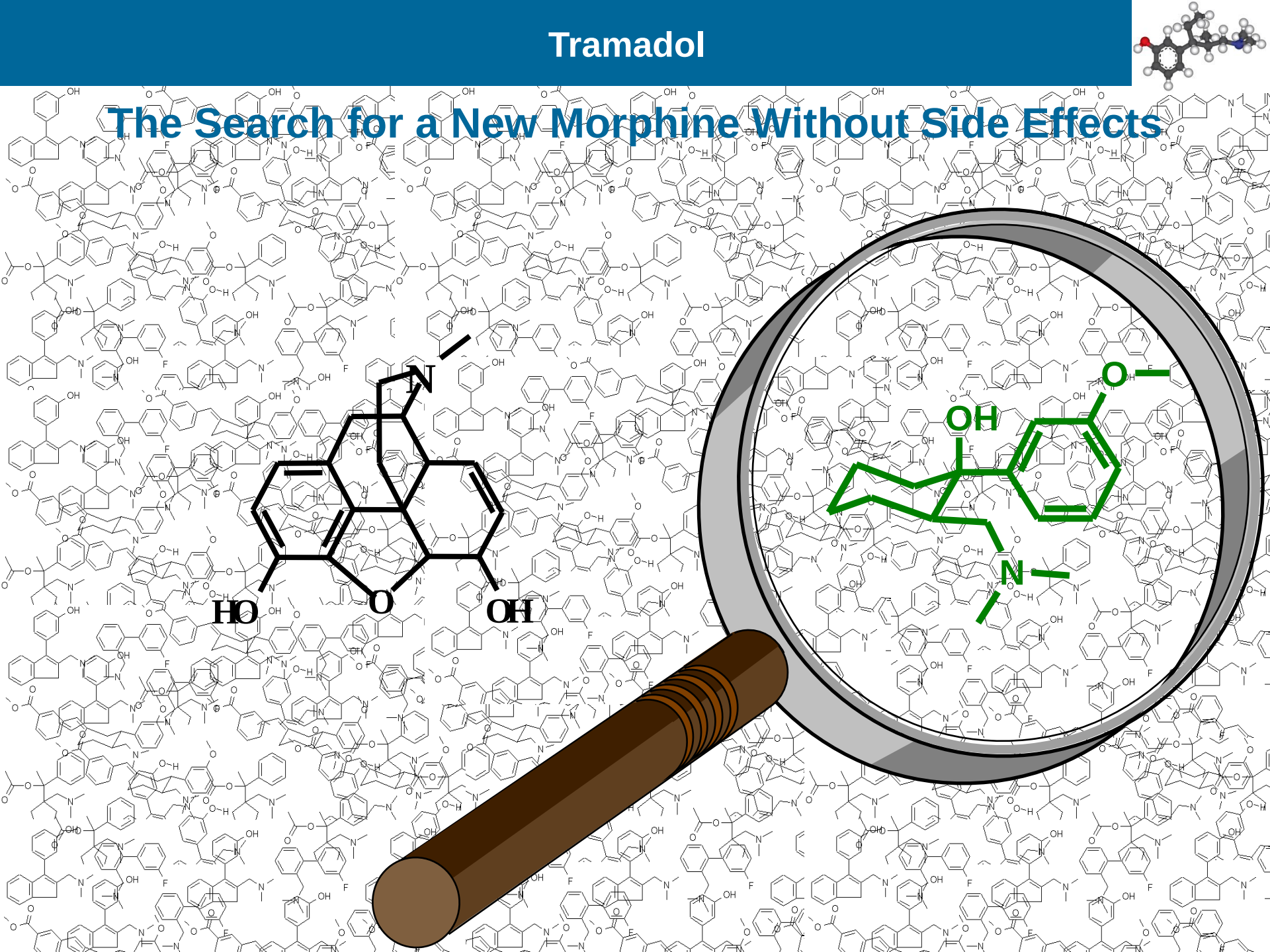


# Significant Unmet Needs in Neuropathic Pain Treatments

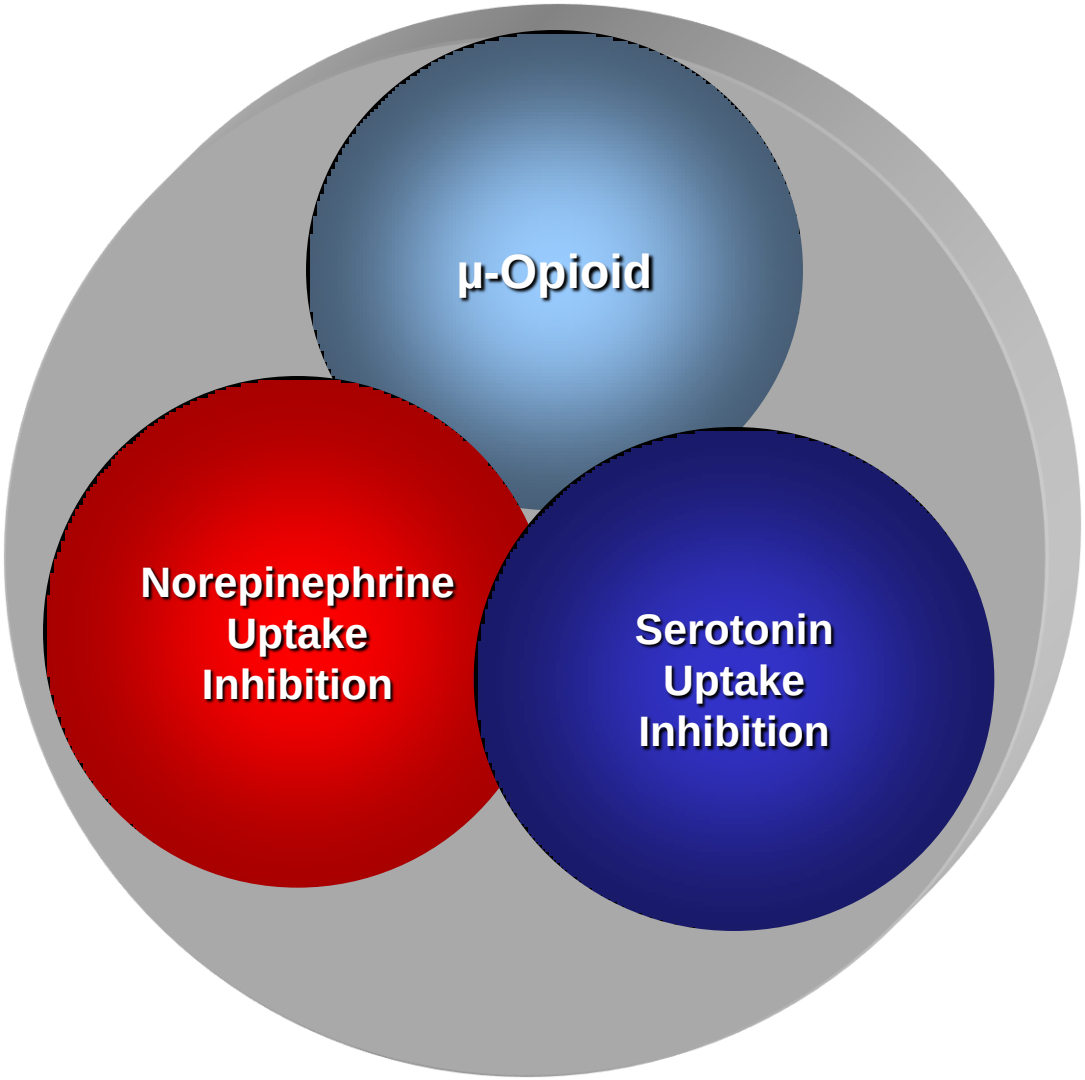


# Tramadol

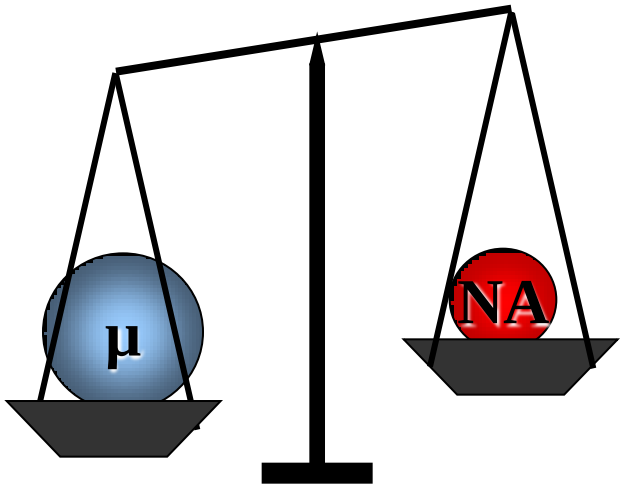
## The Search for a New Morphine Without Side Effects



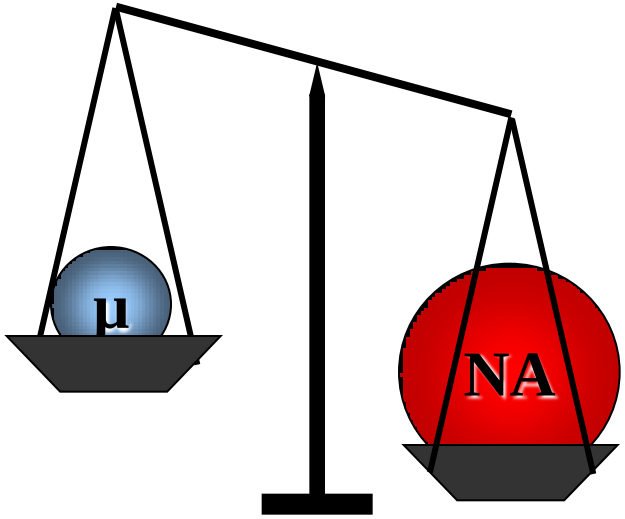
# Tramadol‘s mode of action - biochemical profile



# What have we learned from the Tramadol story?



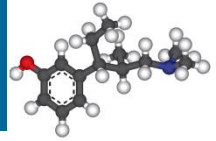

(+)-Tramadol




(-)-Tramadol

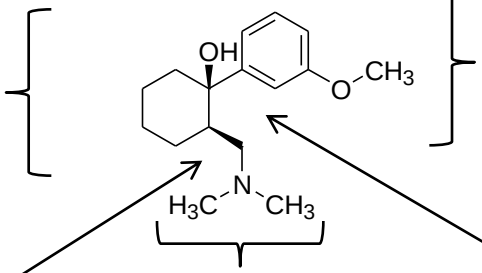
**Can both principles be combined in one molecule (one enantiomer) ?**

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



- Derivatisation of hydroxyl group: ester, ether, …
- Replacement of hydroxylgroup 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

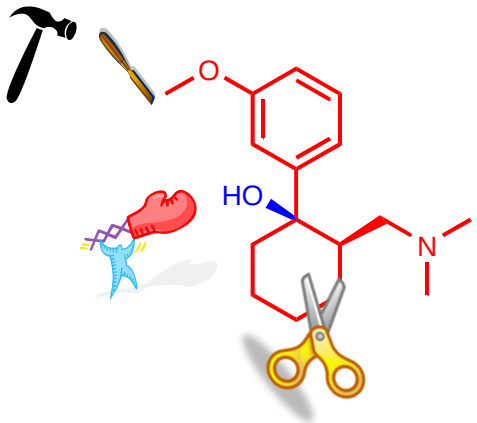



- Phenyl ring substitution
- Replacement by heterocyclic aryl rings
- Replacement by acyclic ring systems

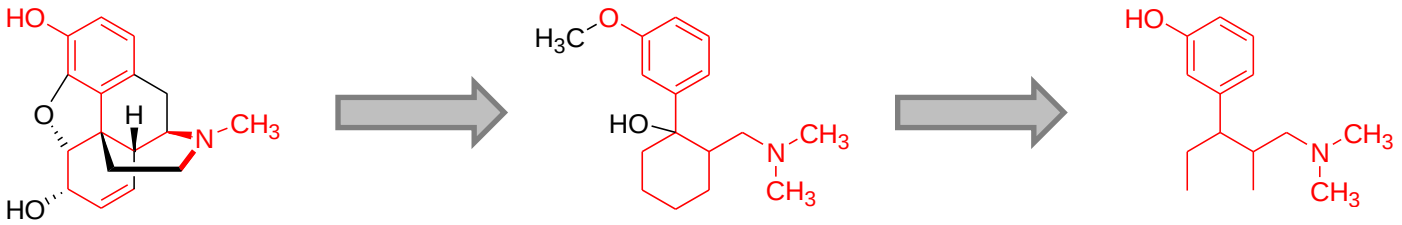
- Methylen group substitution

- N- Substitution
- N-containing ring systems

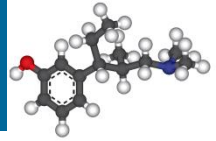
- Introduction of spacer groups between ring systems

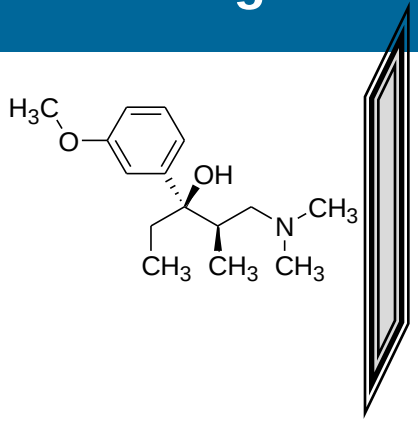


# Tapentadol – A New Analgesic with a Dual Mode of Action

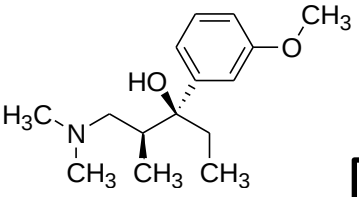


# Tapentadol – A New Analgesic with a Dual Mode of Action

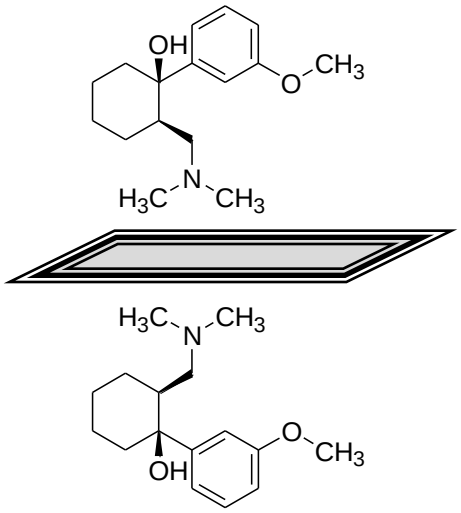




Opening of the cyclohexane ring

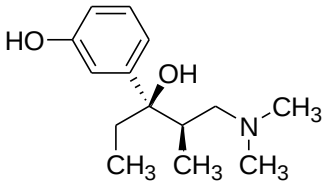


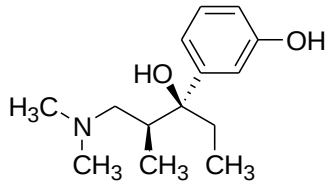
From Prodrug to direct acting drug



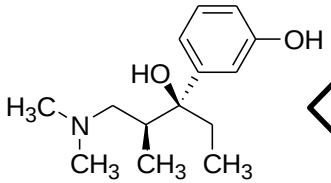
Tramadol

Racemate with relative stereochemistry cis

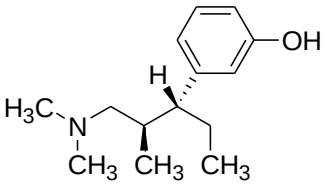




Selecting of one enantiomer



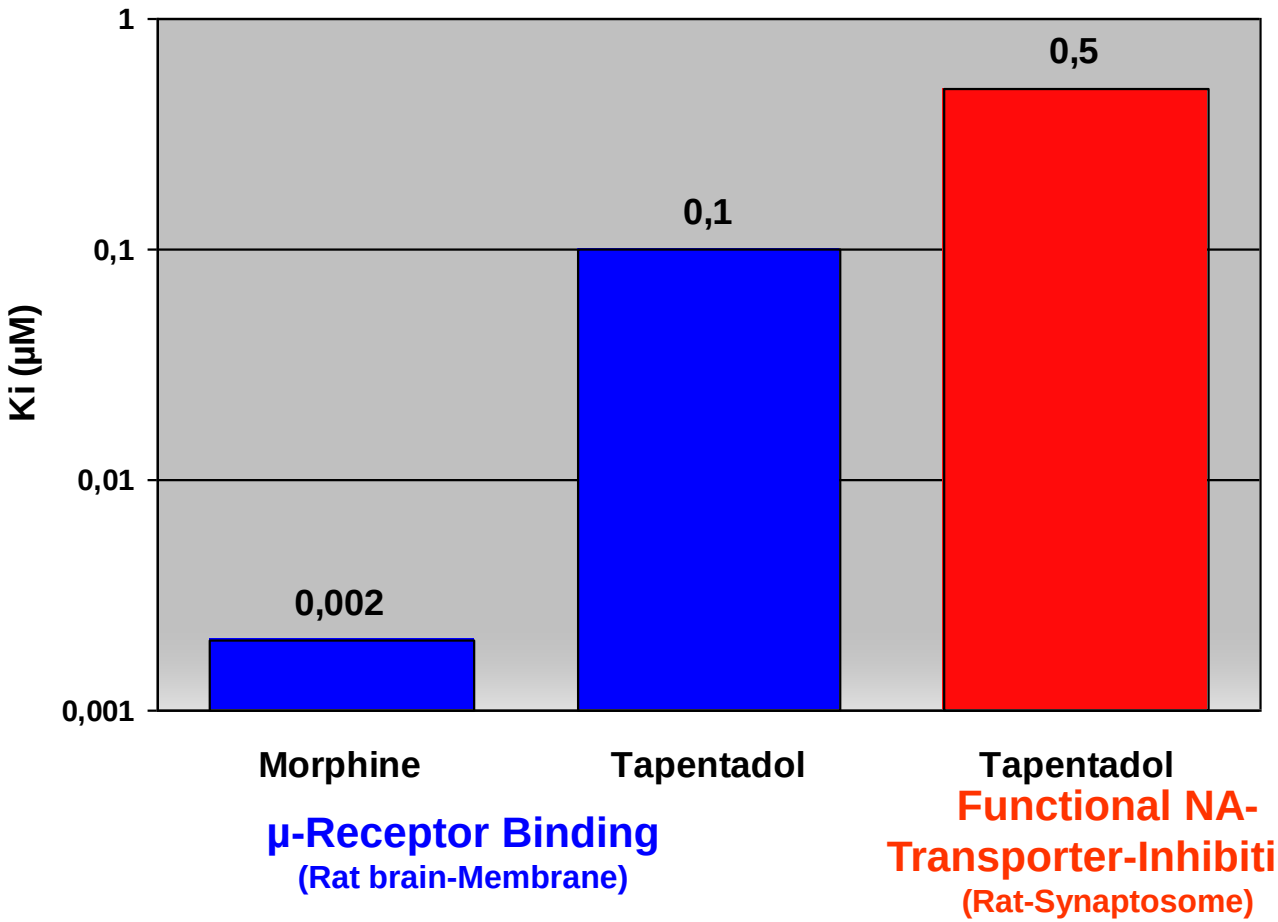
Replacement of *tert.* OH group



Tapentadol

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

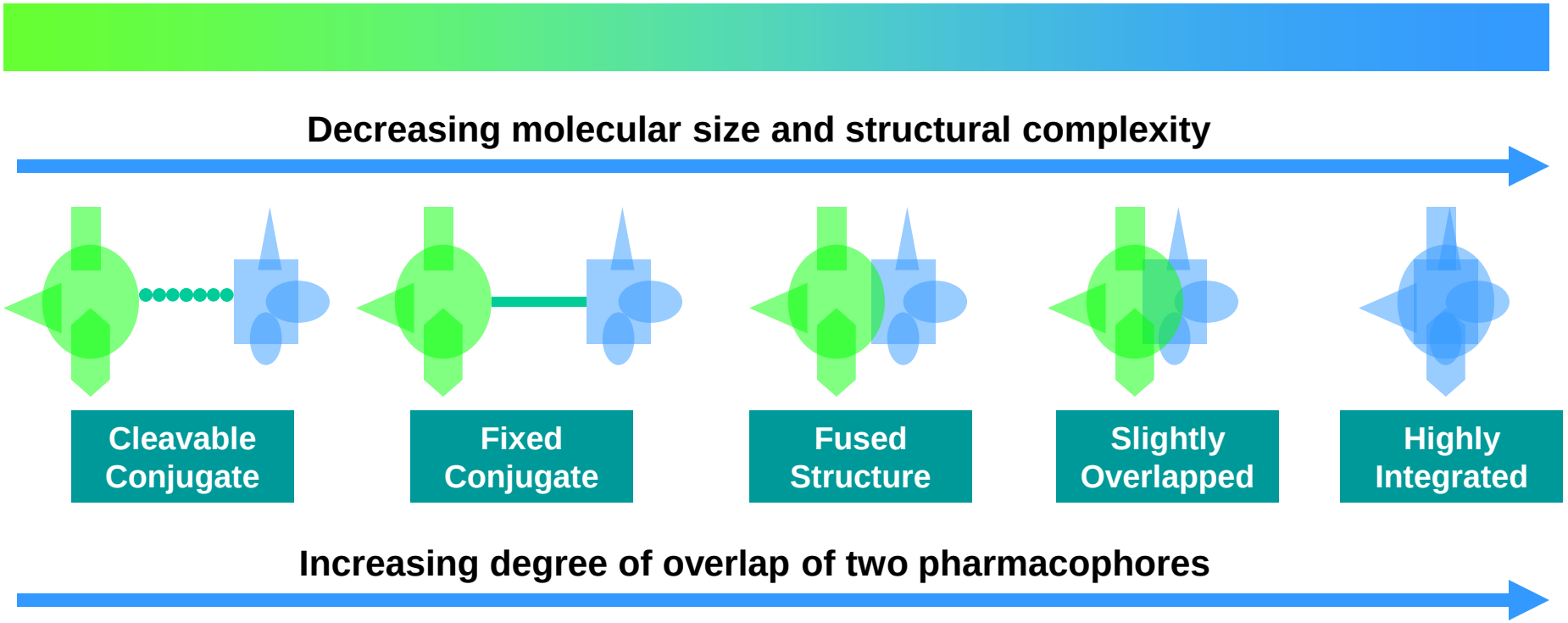
## μ-Rezeptor-Agonism (MOR) and Noradrenalin Reuptake Inhibition (NRI)




**50-fold weaker μ-receptor binding in comparison to Morphine**

# Tapentadol as a Multiple Ligand

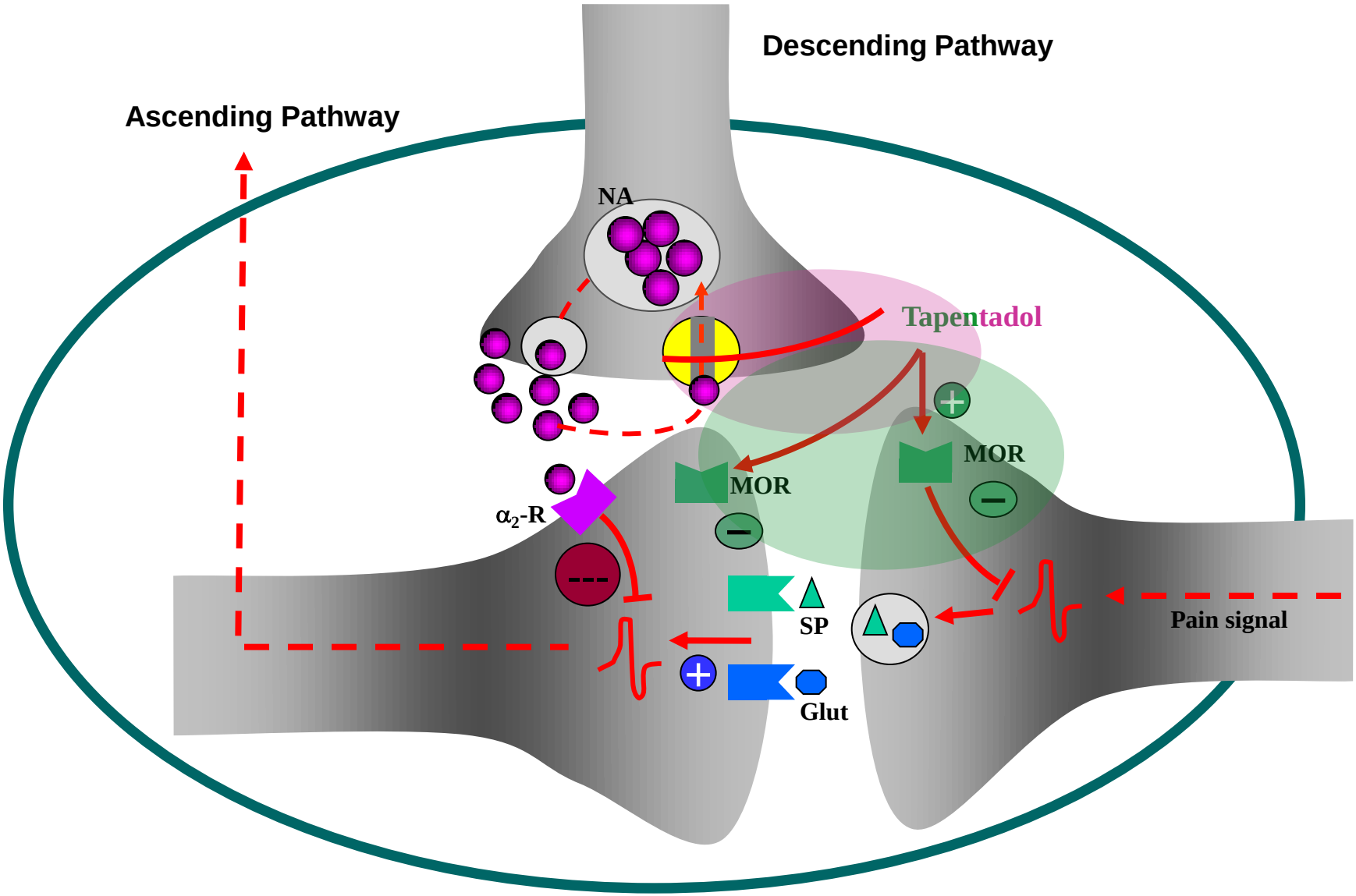
## Designed Multiple Ligang Continuum*)**)



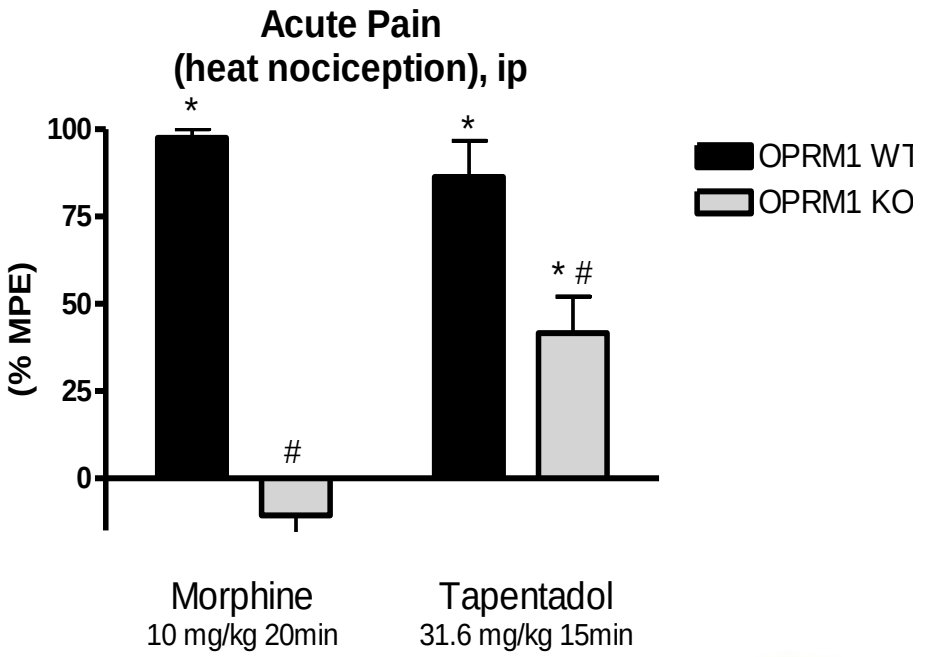

*) R. Morphy, Z. Rankovic, *Designed Multiple Ligands. An Emerging Drug Discovery Paradigm*, J. Med. Chem. 2005 (48), 6523-6543.

**) R. Morphy, C. Kay, Z. Rankovic, *From Magic Bullets to Designed Multiple Ligands*, Drug Discovery Today 2004 (9), 641-651.

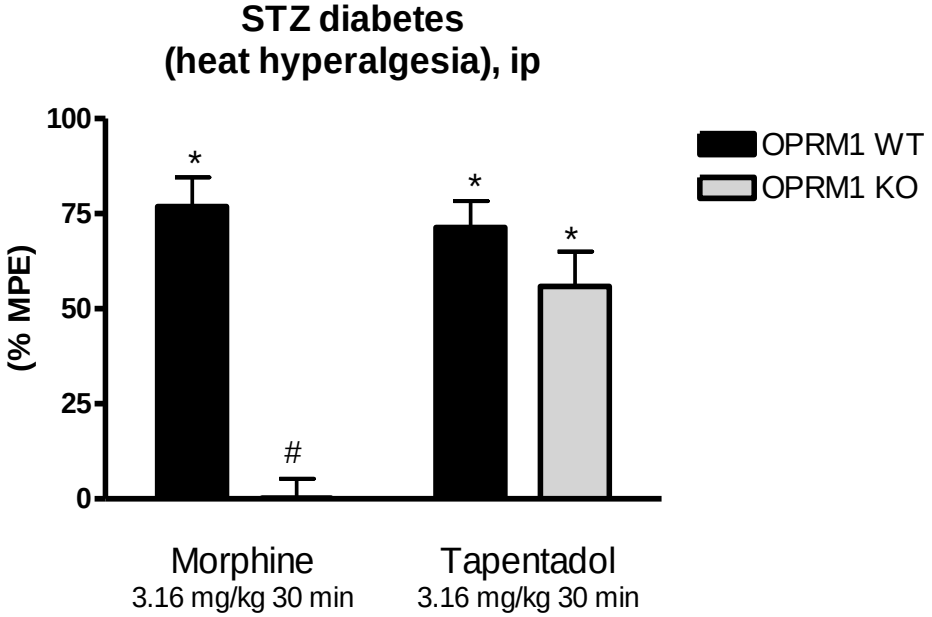
# Spinal Mechanism of Action: MOR-NRI



# Tapentadol: Activityt in MOR knock-out- und Wildtype-Mice



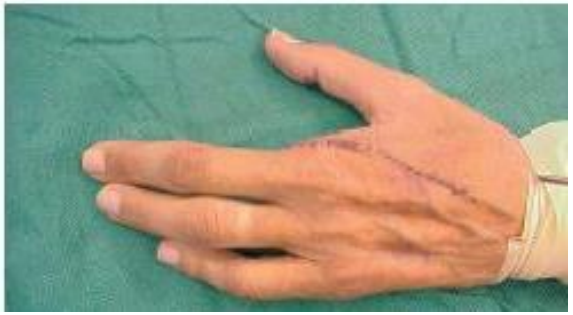

* p<0.05 treatment vs vehicle
# p<0.05 KO vs WT



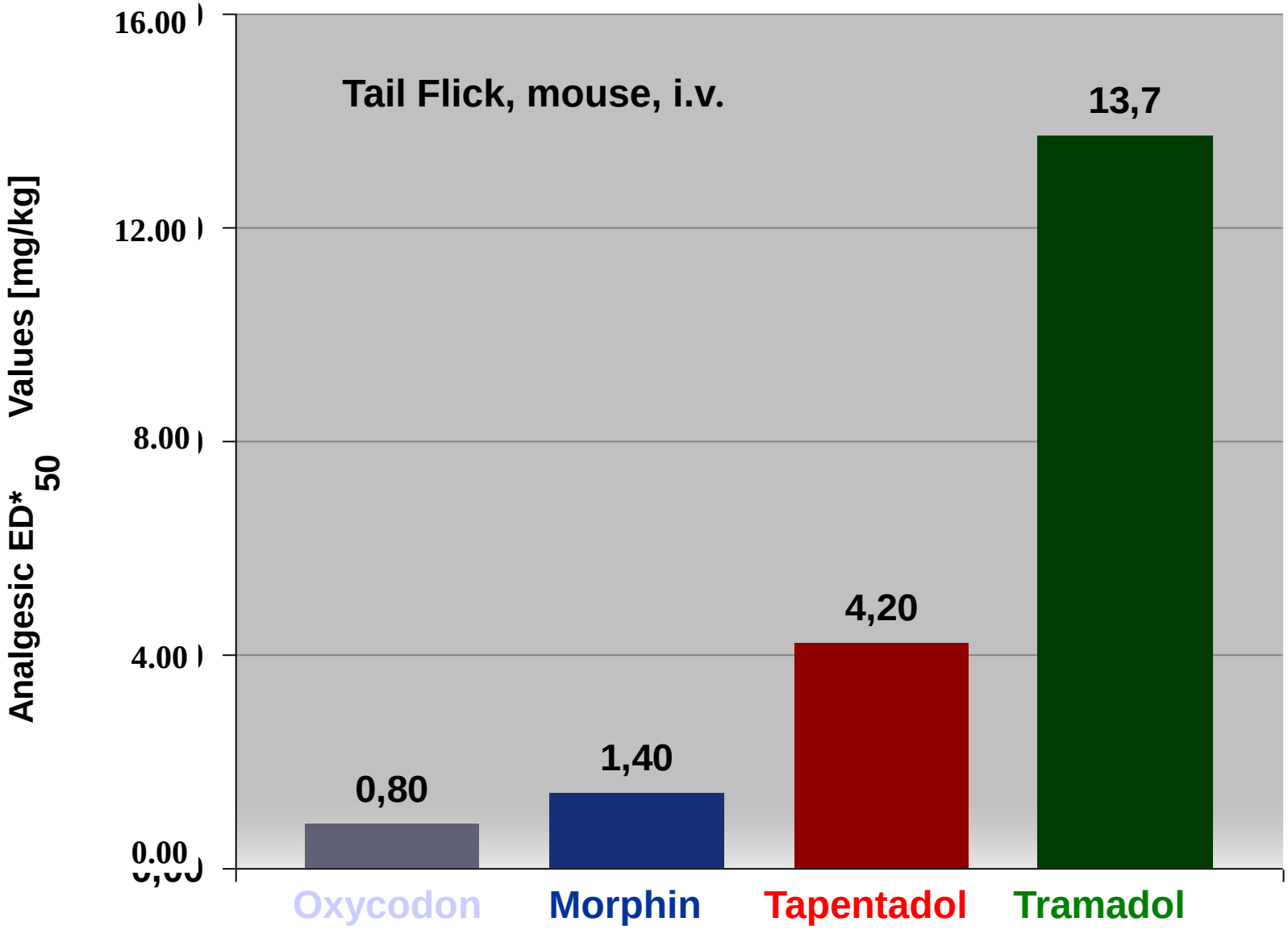

* p<0.05 treatment vs vehicle
# p<0.05 KO vs WT


**Tapentadol remains partially active in MOR-Knock-out Mice**

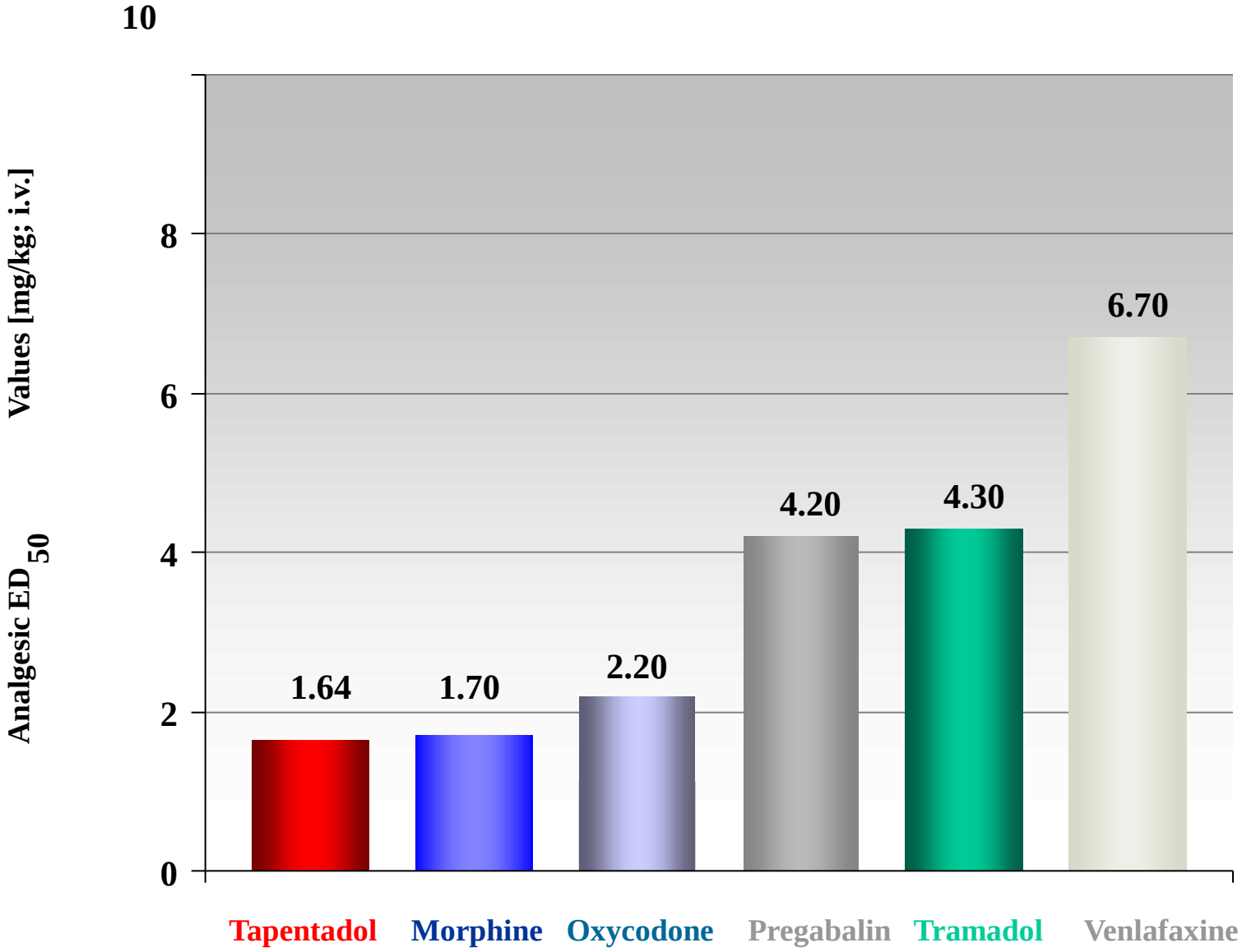
# Pharmacology: Pain Models

| Acute | Chronic inflammatory | Chronic neuropathic |
| --- | --- | --- |
|  |  |  |
|  |  |  |

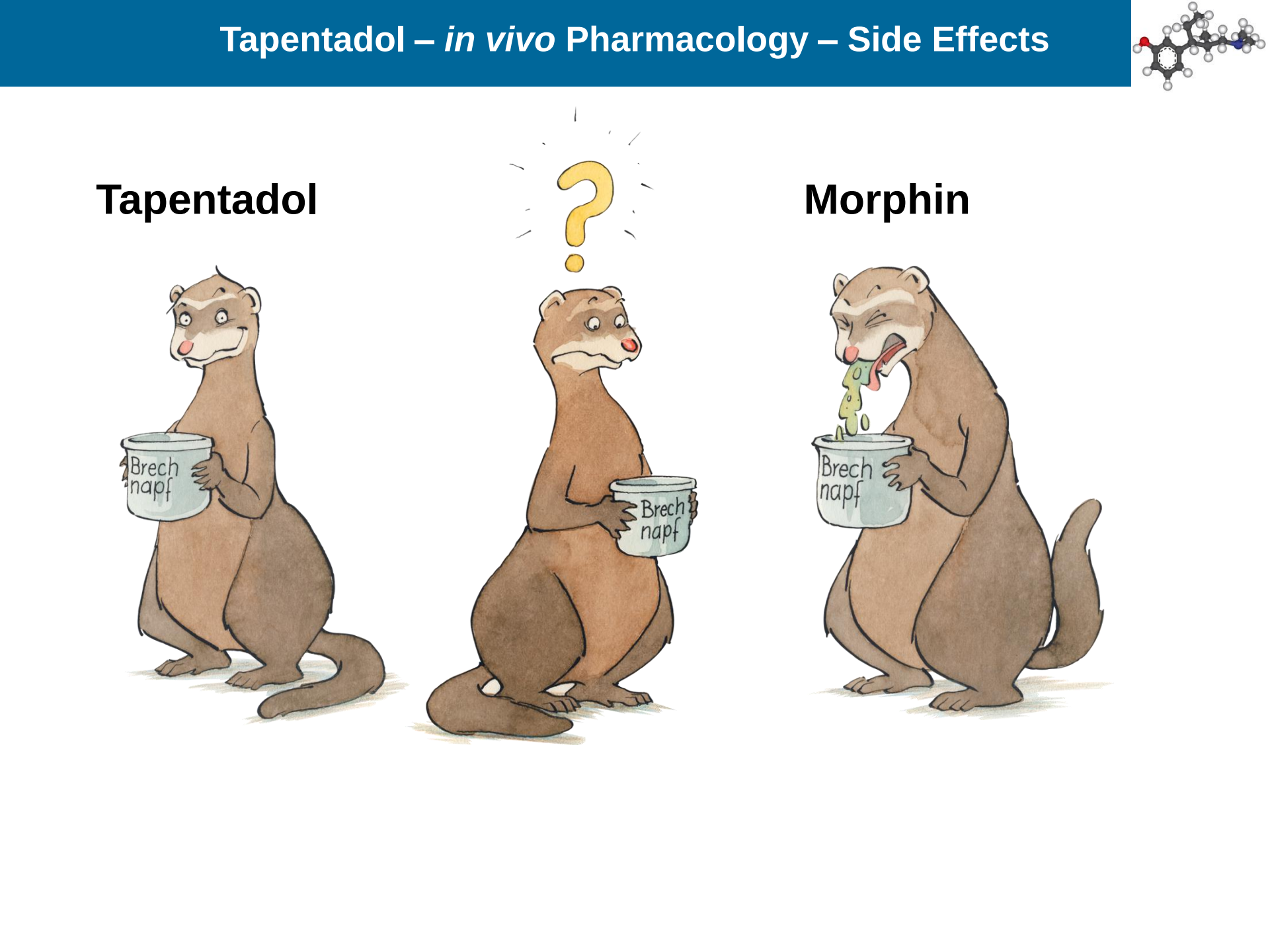
# Analgesic Potency in Acute Pain



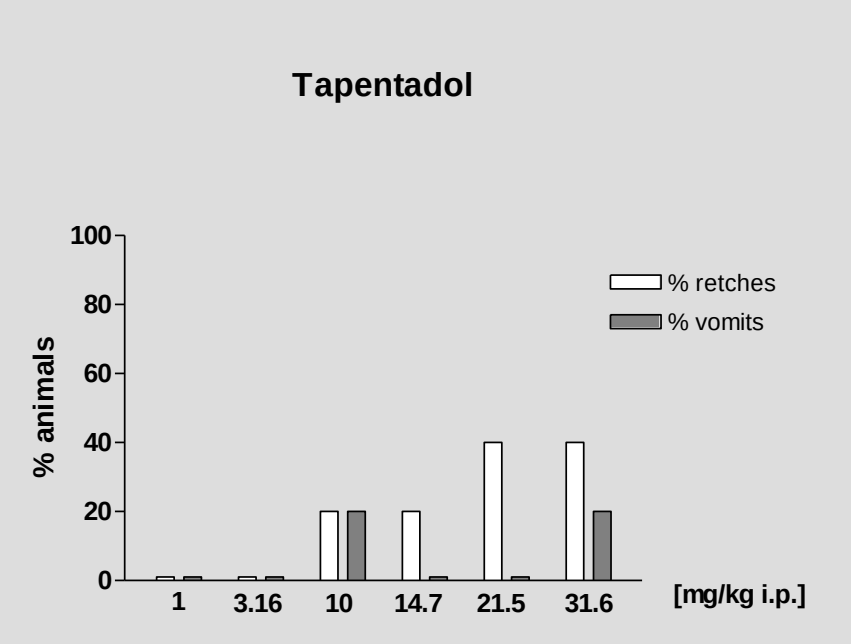
# High potency and efficacy in neuropathic pain (Chung)

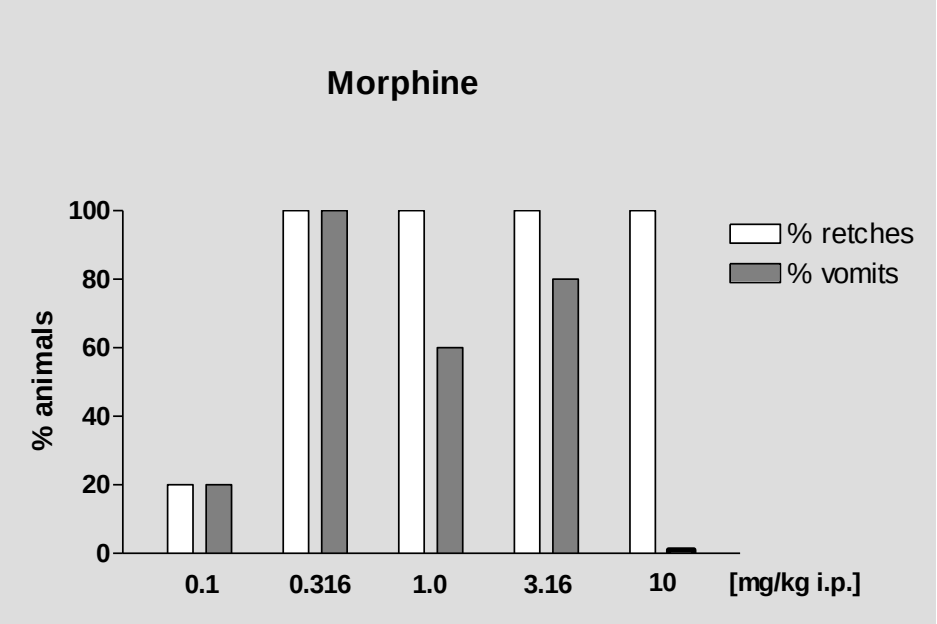


# Tapentadol – *in vivo* Pharmacology – Side Effects



# Opioid Induced Side Effects: Emesis



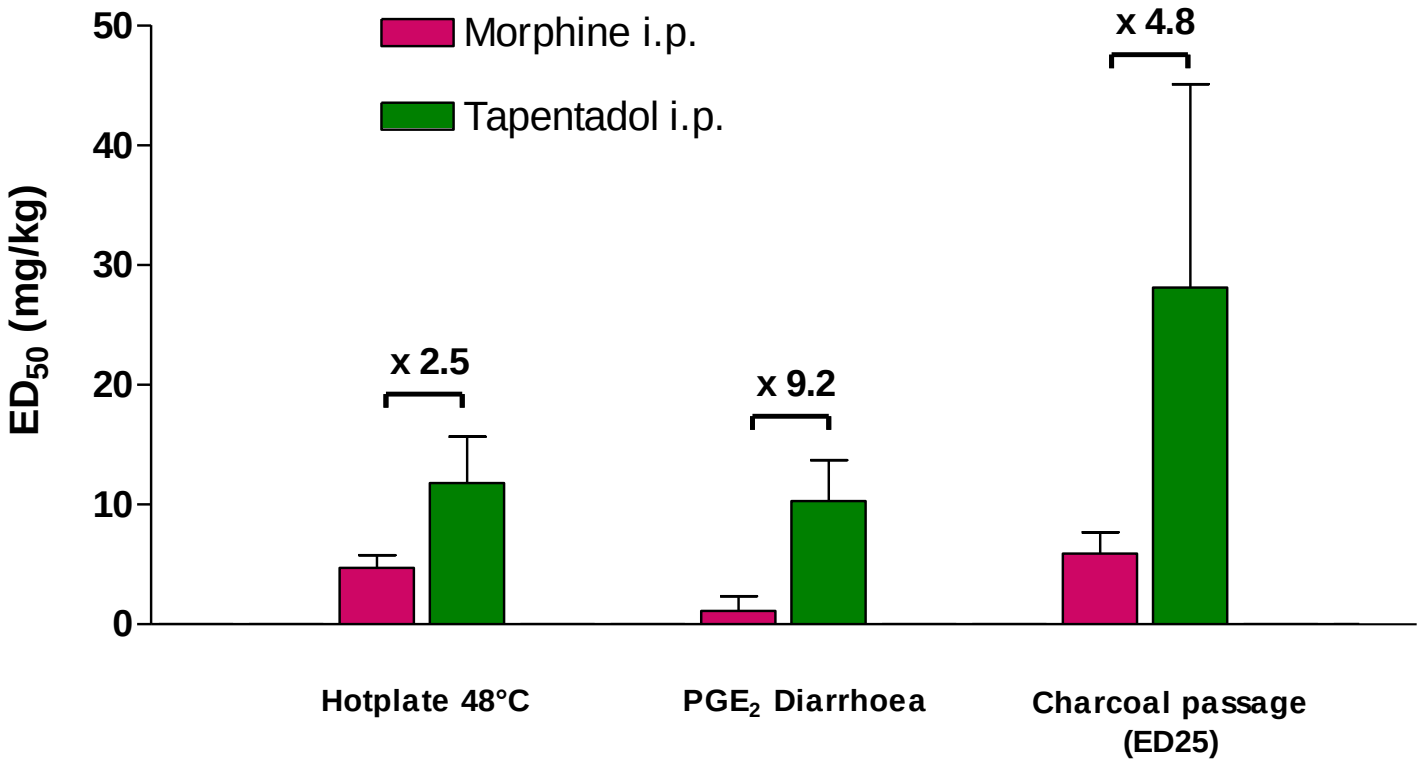

Tzschentke et al (2006) Drugs Fut 31:1053ff

**Tapentadol shows a reduced emetic potential in comparison to Morphine**

# Opioid Induced Side Effects: Obstipation

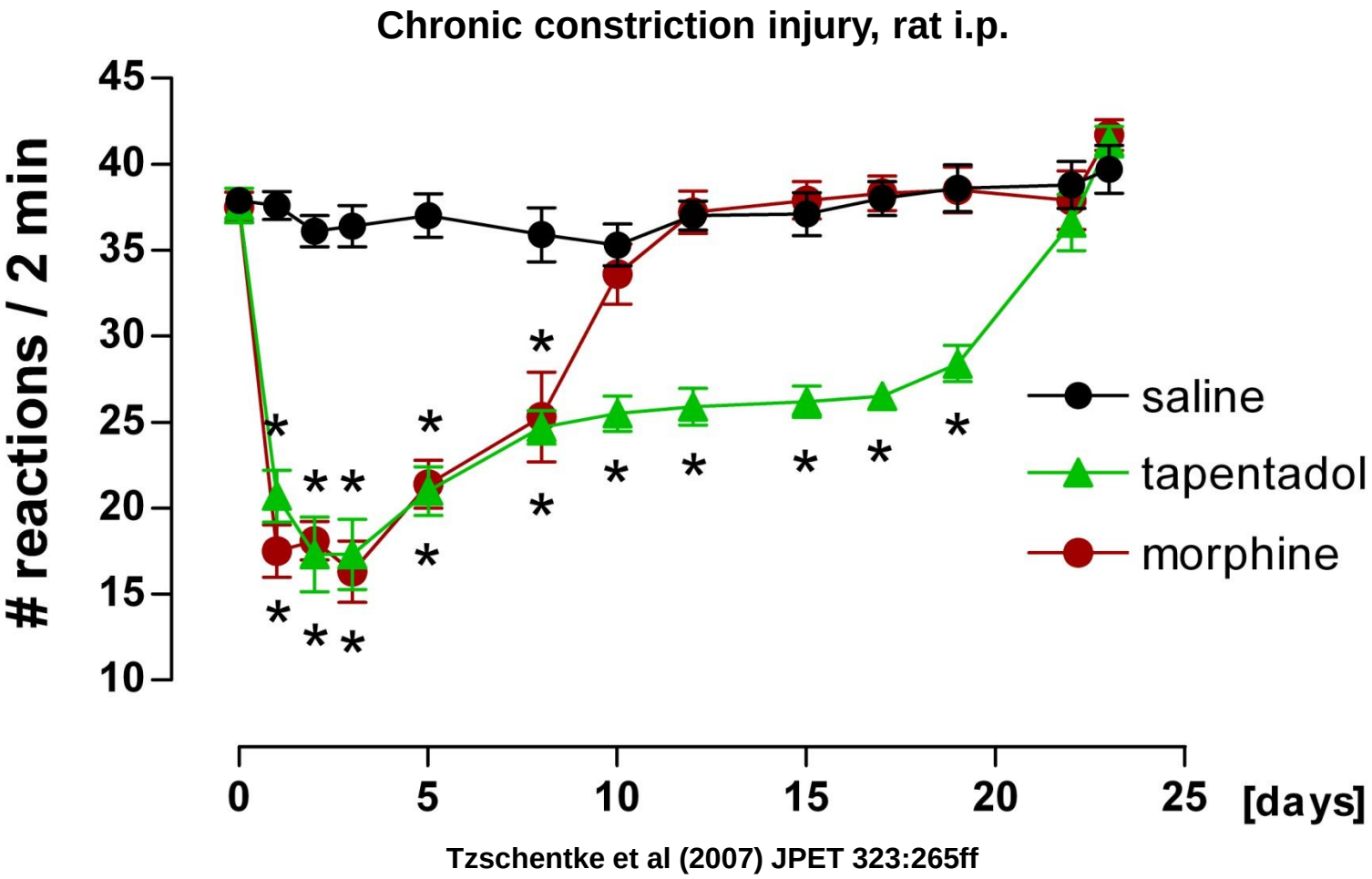
- **Increase of the intestinal charcoal passage**
- **Reduction of the PGE2 induced diarrhoe**

# Opioid Induced Side Effects: Obstipation




**Tapentadol shows a reduced gastrointestinal inhibitory potential in comparison to Morphine**

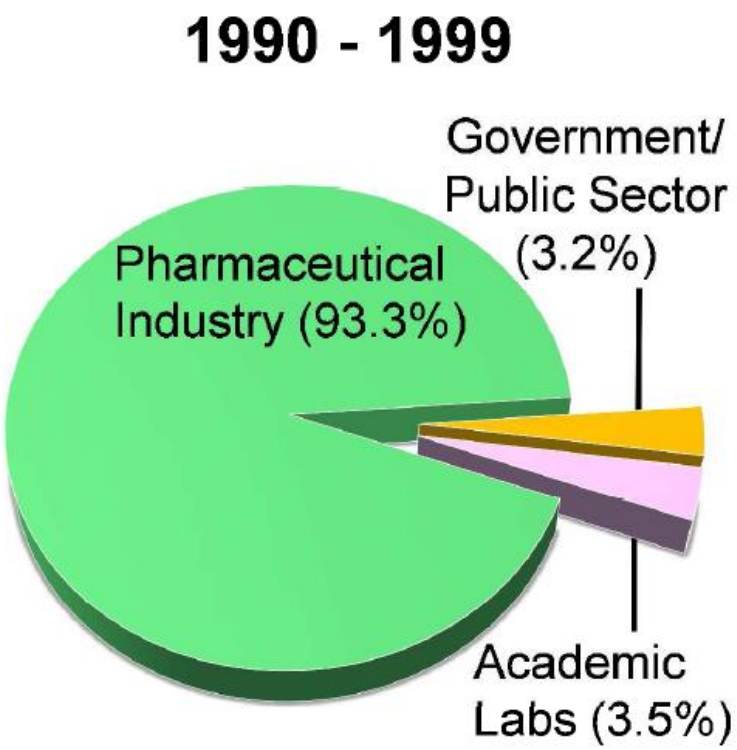
# Opioid Induced Side Effects: Tolerance Development

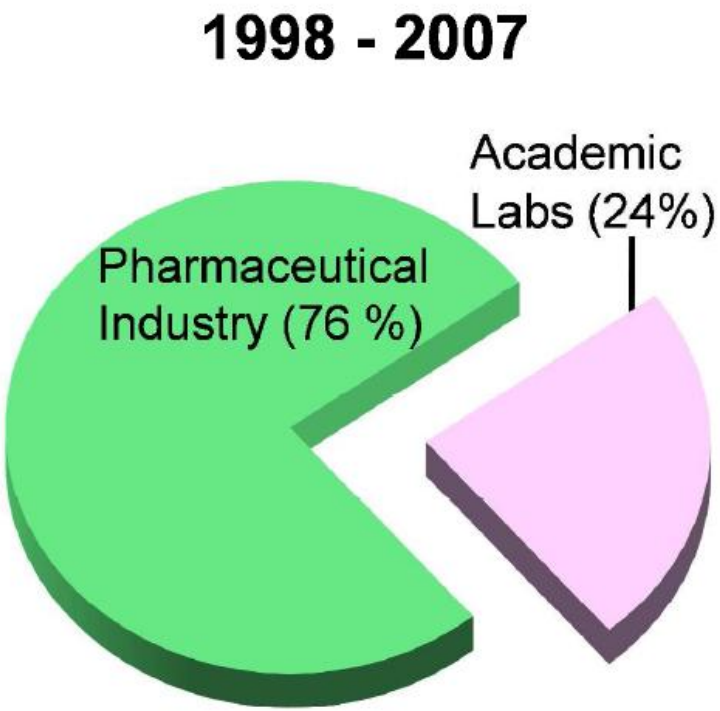



Tzschentke et al (2007) JPET 323:265ff

**Significant reduced tolerance development**

# Estimates of Where New Drugs Come From




**Data taken from Kneller, 2010.**

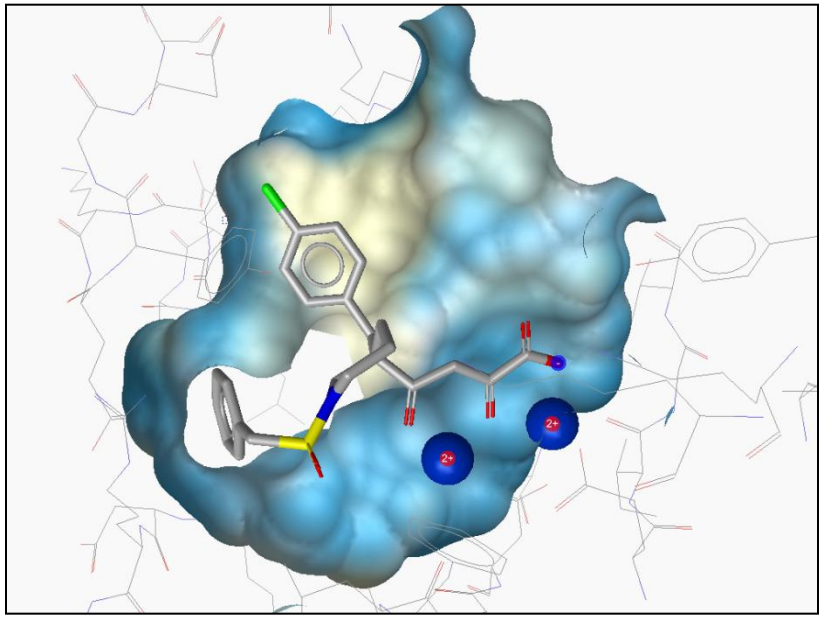
**Data taken from DiMasi et al., 2003.**

Magid Abou-Gharbia and Wayne E. Childers, Discovery of Innovative Therapeutics: Today's Realities and Tomorrow's Vision. 1. Criticisms Faced by the Pharmaceutical Industry, J. Med. Chem 56, 5659-5672 (2013)

# Influenza Polymerase: Endonuclease & Cap Binding Inhibitors

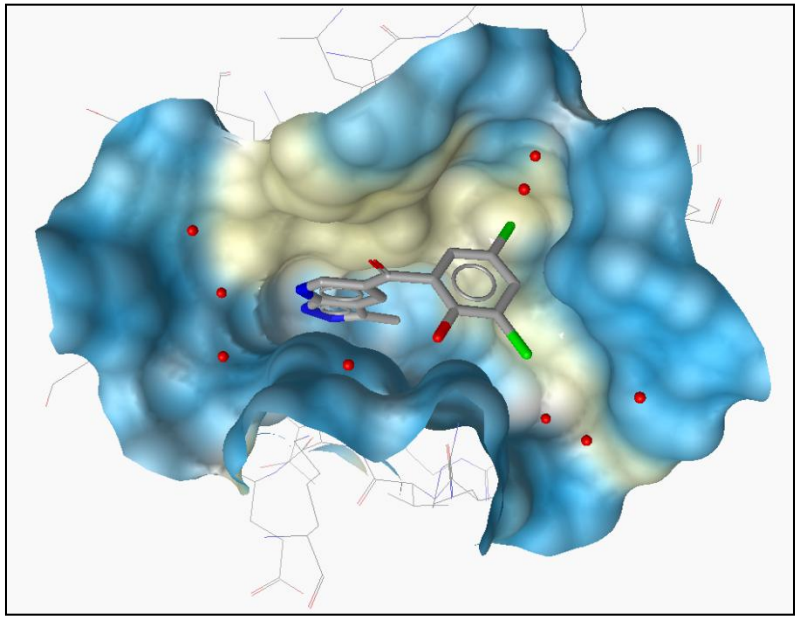
## Influenza Virus Polymerase Inhibitors

### Endonuclease Inhibitors




SAV-6004 H1N1 Cocrystal

### Cap Binding Inhibitors

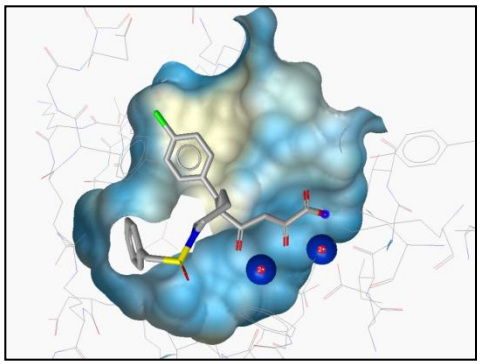


SAV-7125 H5N1 Cocrystal

# Influenza Polymerase Program @ Savira

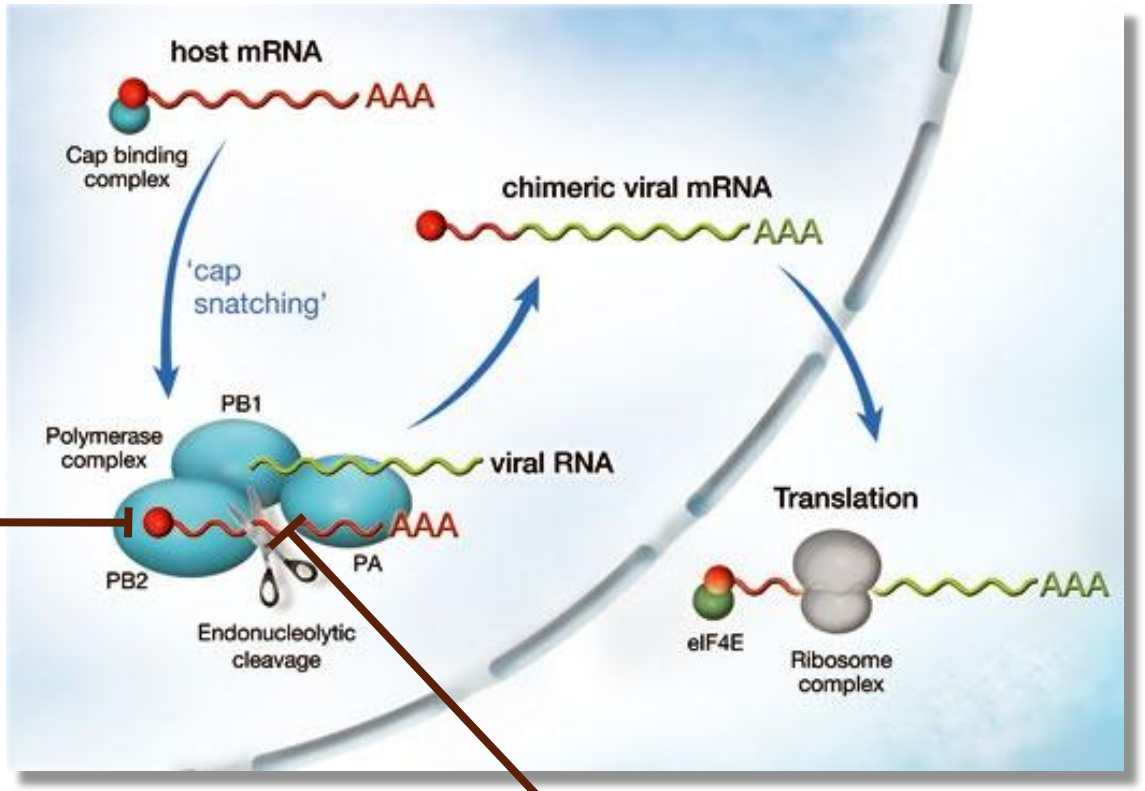
savira pharmaceuticals

EMBL



- Savira focuses on innovative anti-influenza drug discovery and development
- Influenza is amongst the top three viral diseases with an expected market value for therapeutics of $8 billion in 2014
- Currently, the market is dominated by neuraminidase inhibitors such as Tamiflu (Roche), Relenza (GSK), Rapiacta (Shionogi) and Invavir (Daiichi-Sankyo)
- There is a strong medical need for new influenza therapeutics as several influenza strains are already resistant against the few marketed drugs
- The influenza virus polymerase is currently being regarded as one of the most promising targets in the fight against influenza. This concept has been validated for several other viral diseases
- Savira has followed a structure-based development approach based on highly resolved crystal structures for both targets

# Influenza Polymerase Preoject: Savira & FLUPHARM




Cap-binding site inhibitor

Endonuclease inhibitor

Source: *http://www.scienceinschool.org/print/788*

# Influenza Polymerase Preoject: Savira & FLUPHARM

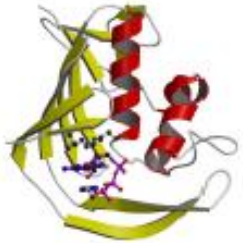
## Evaluation of potency of drug candidates

- fragment flexibility
- assay conditions

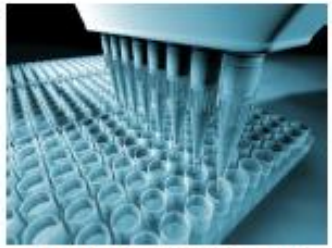
- influence of entire architecture on active site

- Absorption
- Metabolism
- dynamics of infection
- host factor

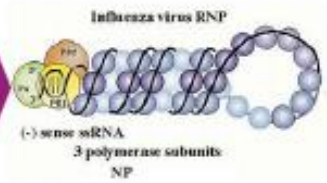
- DMPK



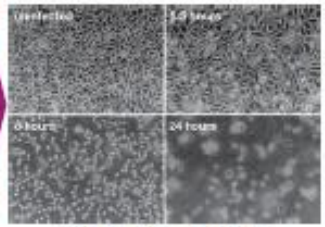
In-silico screen



Polypetide fragment-based assay

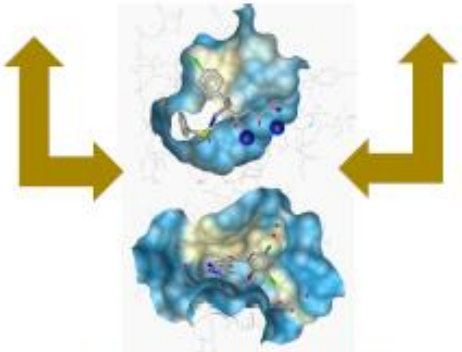



RnP assay

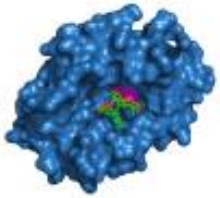


Cellular assay

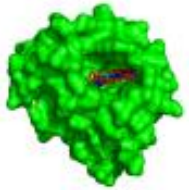
In-vivo assay



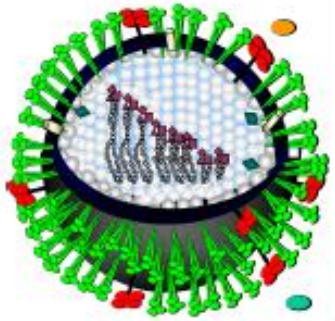
Co-crystal structures



ENDO



CAP

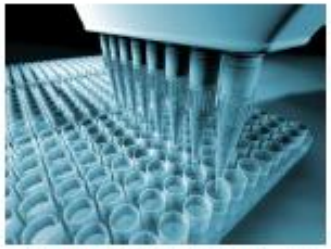


# Influenza Polymerase Preoject: Savira & FLUPHARM

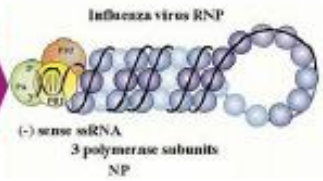
## Evaluation of potency of drug candidates

prediction to more complex biological level
requires knowledge of additional factors

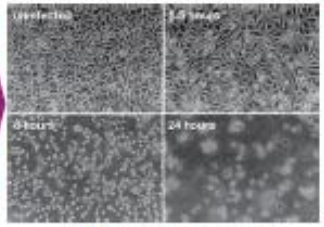
In-silico screen



Polypetide fragment-based assay

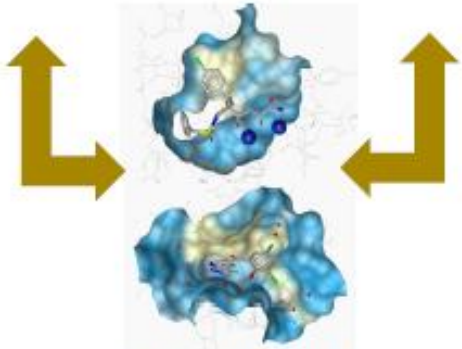



RnP assay



Cellular assay

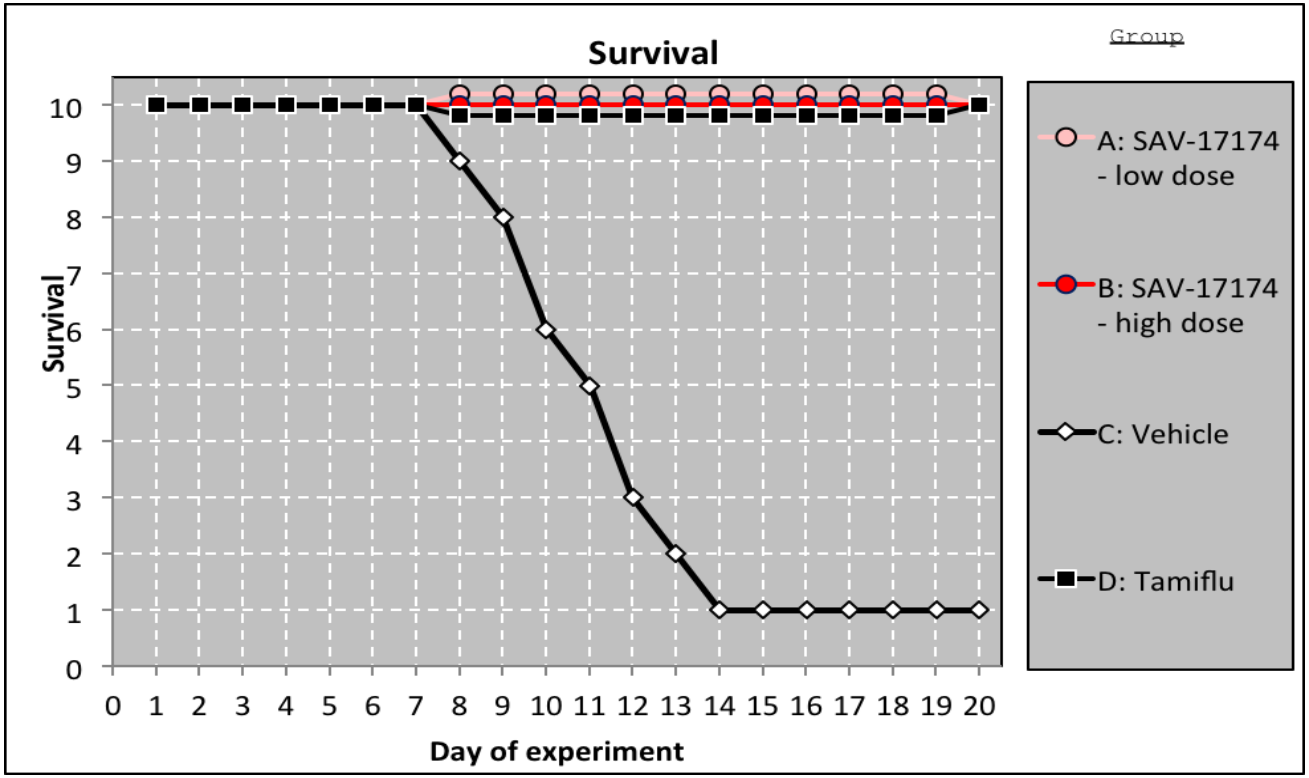
In-vivo assay



Co-crystal structures

prediction to less complex
biological level confirms target

# In vivo Efficacy Study of SAV-17174




- The most active compound with cellular activity (IC50) of 240pM was tested in the in vivo efficacy model and resulted in full protection of the animals at the lowest dose of 10mg/kg/d upon oral application!

- Within FLUPHARM projectit was possible to deliver a new and patentable compound with high biochemical and cellular activity which translated to in vivo efficacy upon oral administration, with a superior profile to the reference standard compound (Tamiflu).

# My Journey in the Pharmaceutical Industry

RWTH
RHEINISCH-
WESTFÄLISCHE
TECHNISCHE
HOCHSCHULE
AACHEN

GRÜNENTHAL

ESTEVE

savira
pharmaceuticals

AiCuris
Anti-infective Cures


RD&C
Research
Developement
& Consulting

EMBL

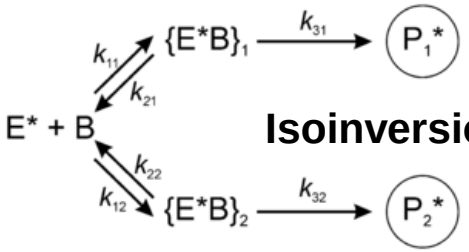
# Acknowledgement

RWTH
RHEINISCH-
WESTFÄLISCHE
TECHNISCHE
HOCHSCHULE
AACHEN

**Prof. Dr. Dr. h.c.**
**Hans-Dieter Scharf**
**18.7.1930-27.2.1998**

**Prof. Dr. Carsten Bolm**
**Organic Chemistry**
**RWTH Aachen**

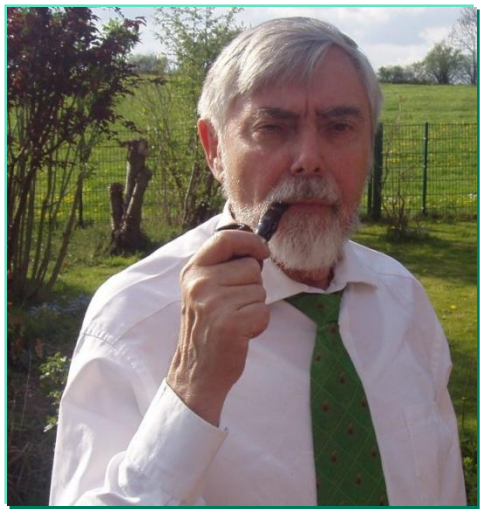
**Prof. Dr. Dieter Enders**
**Organic Chemistry**
**RWTH Aachen**




**Isoinversion Principle**

# Acknowledgement



**Prof. Werner Winter**
**(1980s – 1990s)**

**Peter Jansen**
**1997**

**Dr. Klausdieter Langner**
**Managing Director**
**Grünenthal**

**Prof. Dr. Eric-Paul Paques**
**CEO Grünenthal**

# Acknowledgement

Joerg Holenz, Ph.D., Director, Discovery & Preclinical Sciences, AstraZeneca Pharmaceuticals

Dr Bernd Sundermann

Bernd Sundermann
Global Advisor to the Site Head at Fresenius Kabi Oncology Ltd.

Dr. Corinna Sundermann
Senior Vice President Intellectual Property

Prof. Dr. Detlef Heller
LIKAT, Rostock

Peter Klemm
*Proteomics CEO*

CEO Predictive BioSciences
May 2008 – July 2011

# Acknowledgement

**Antoni Esteve Cruella & Alberz Esteve**

**Jose Miguel Vela Hernández**
**Director de Drug Discovery & Preclinical Development**

**Head of Chemical Collaborations & Strategic Alliances en Esteve**

**Jordi Quintana, Head of Business Development, Director of Drug Discovery Platform, PCB**

**Ana Guerra Enrique**

# Acknowledgement

savira pharmaceuticals

EMBL

**Oliver Szolar**
**CEO Savira**

**Stephen Cusack**
**Head of EMBL Grenoble**

WINGS 4 INNOVATION
WE ACCELERATE LIFE SCIENCE RESEARCH

FLUPHARM
NEW DRUGS TARGETING INFLUENZA VIRUS POLYMERASE

# Acknowledgement

AiCuris
Anti-infective Cures

**Prof. Dr. Rübsamen-Schaeff**
**Founder AiCuris**

**Dr. Holger Zimmermann**
**CEO AiCuris**

**Dr. Alex Birkmann**
**CSO AiCuris**

**Gerrit van Dyken**
**Legal Affairs**

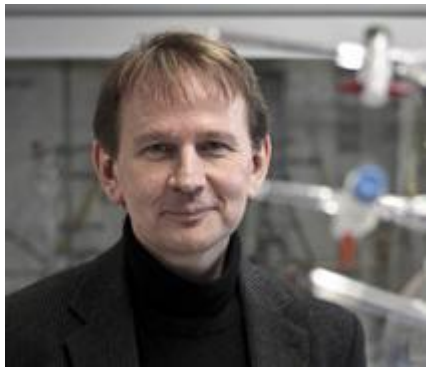
**Daniela Höltig**
**HR AiCuris**

**Dr. Yogesh Bacchav**
**Pharmaceutical Development**

**Dr. Burkhard Klenke**
**Director Chemistry**

**Dr. Daniela Paulsen**
**Project leader AiCuris**

# Acknowledgement



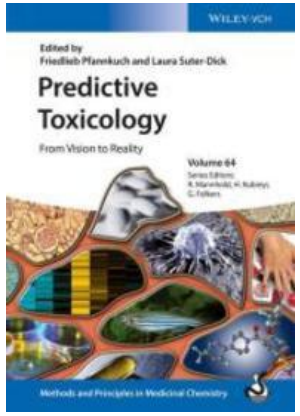
Prof. Dr. Matthias Beller
Leibnitz Institute for Catalysis, Rostock
LIKAT

Prof. Miquel A. Pericàs
Director & Group Leader at Institut Català d'Investigació Química

Prof. Hugo Kubinyi

Prof. Raimund Mannhold

WILEY-VCH





Catalysis
Leibniz-Institut für Katalyse e.V.

ICIQ
Institut Català d'Investigació Química

CRYSFORMA

# Acknowledgement

**Dr. Norbert Handler**
**Managing Director**
**RD&C**

**Dr. Andrea Wolkerstorfer**
**Managing Director**
**RD&C**