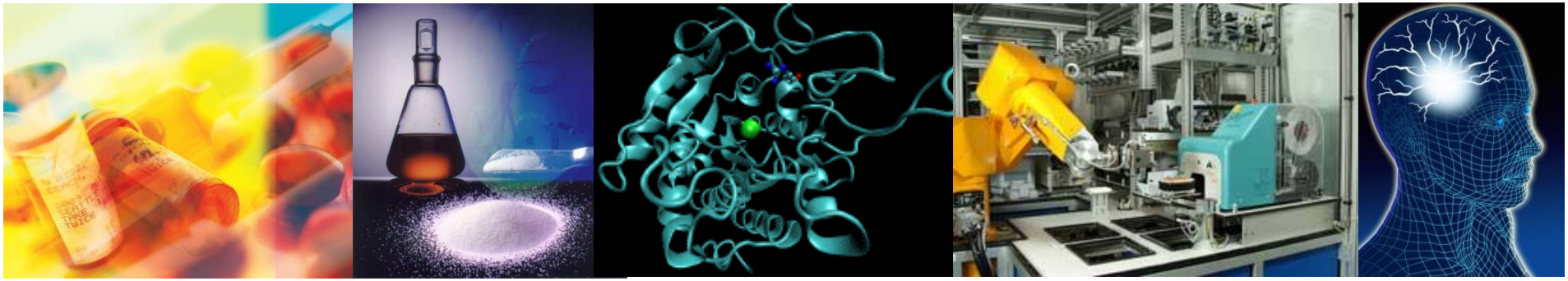
EFMC | ISMC 2014
XXIII International Symposium on Medicinal Chemistry

IUPAC Richter Prize Lecture

Wednesday September 10, 2014

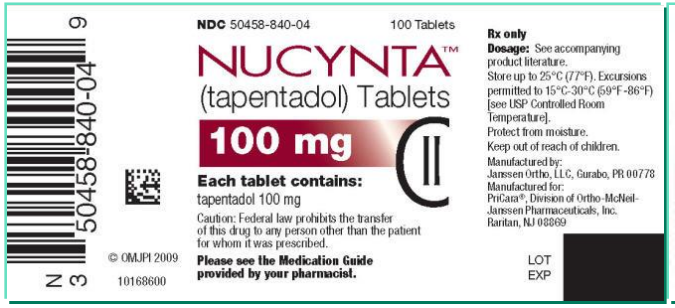


Medicinal Chemistry, Quo Vadis?
The changing climate of Pharmaceutical R&D

Helmut Buschmann

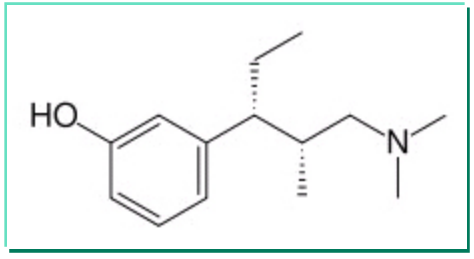
Tapentadol – A New Analgesic with a Dual Mode of Action

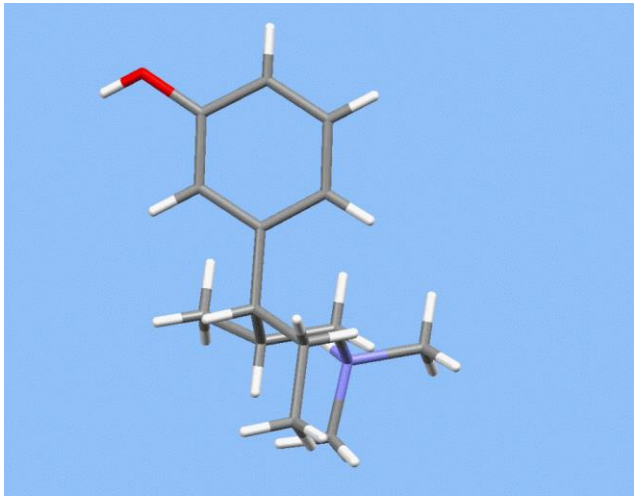
PALEXIA®
TAPENTADOL

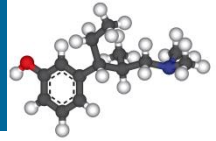


PALEXIA®

Tapentadol - From Morphine and Tramadol to the Discovery Tapentadol







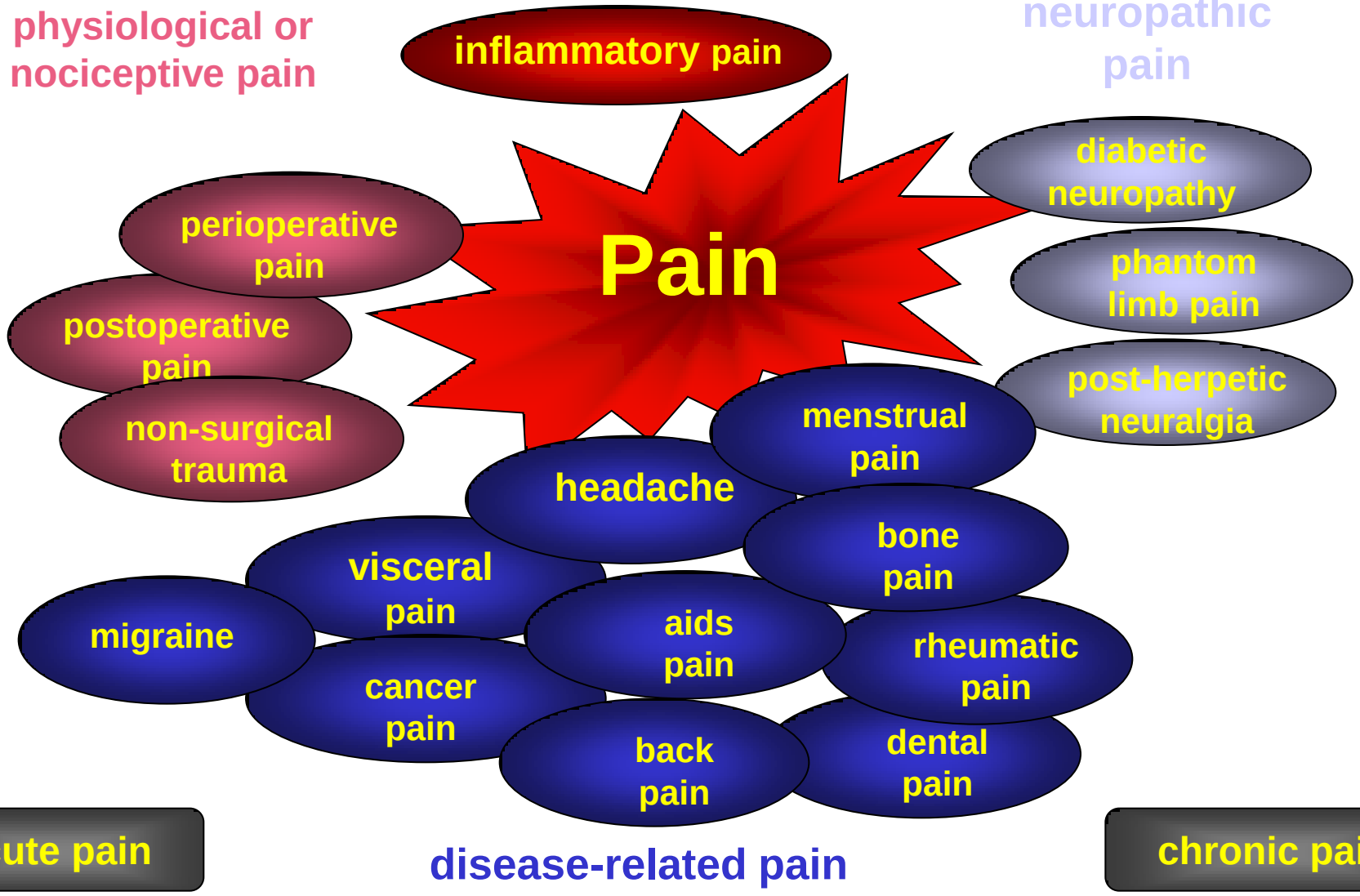
Tapentadol – The Path To The Market

- Start of the pharmaceutical development
- First synthesis of BN-200 (February 8, 1994)
- Start of the pre-clinical GLP-program
- First application to man
- First study in patients (acute pain)
- Start of clinical trials with oral IR formulation
- First in man trial with PR formulation
- Start of the pre-clinical GLP-programINN for BN 200 (CG5503) base Tapentadol
- Start of co-operation with J&J
- Start of clinical program in chronic pain
- Start of Phase III program
- US submission acute pain
- EU submission acute pain
- EU and US submission chronic pain
- First national EU registration
- Completion EU registration procedure acute and chronic pain
- Extension of co-operation with J&J

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

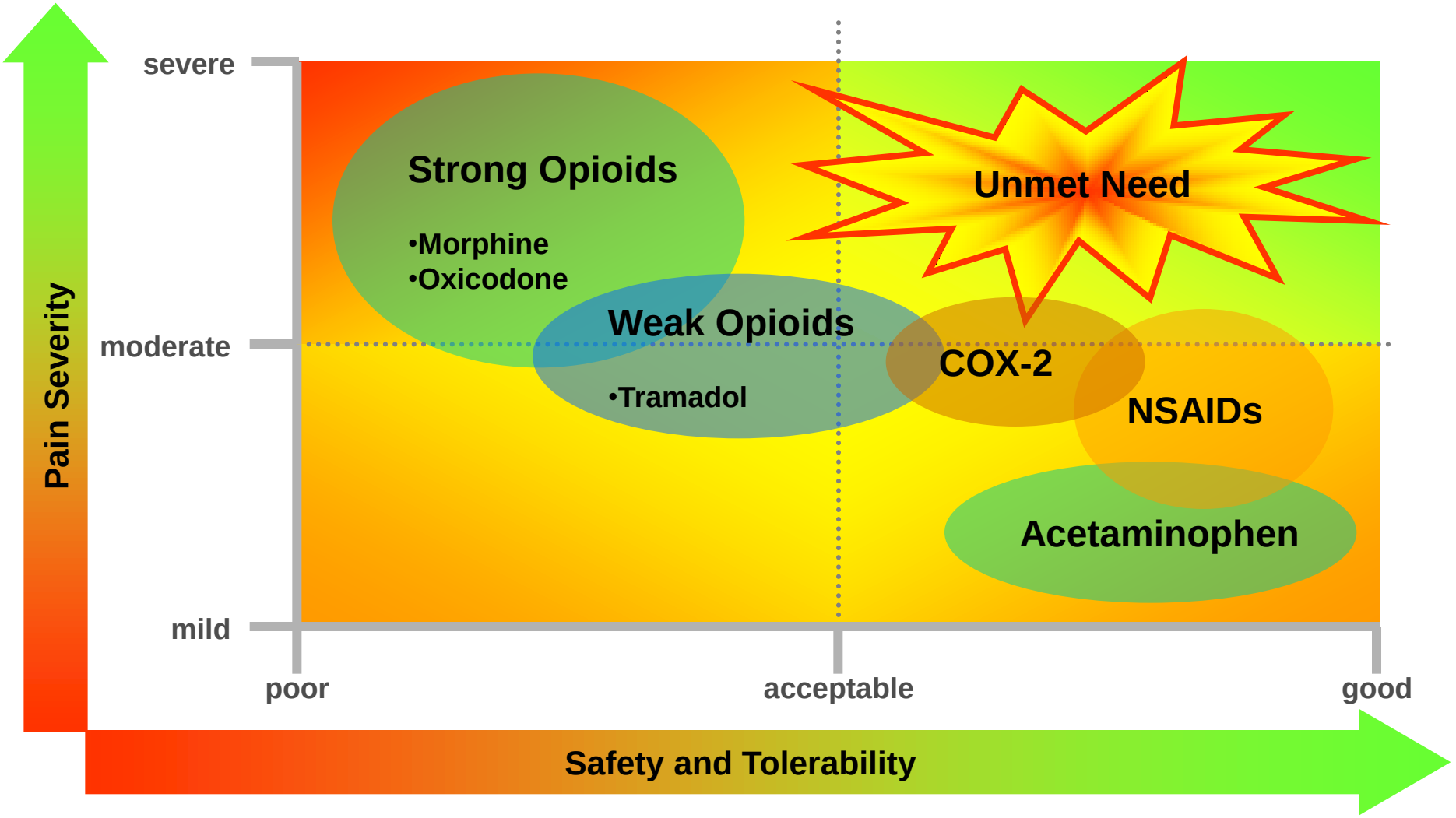
Pain Transduction

Overview of the Different Types of Pain

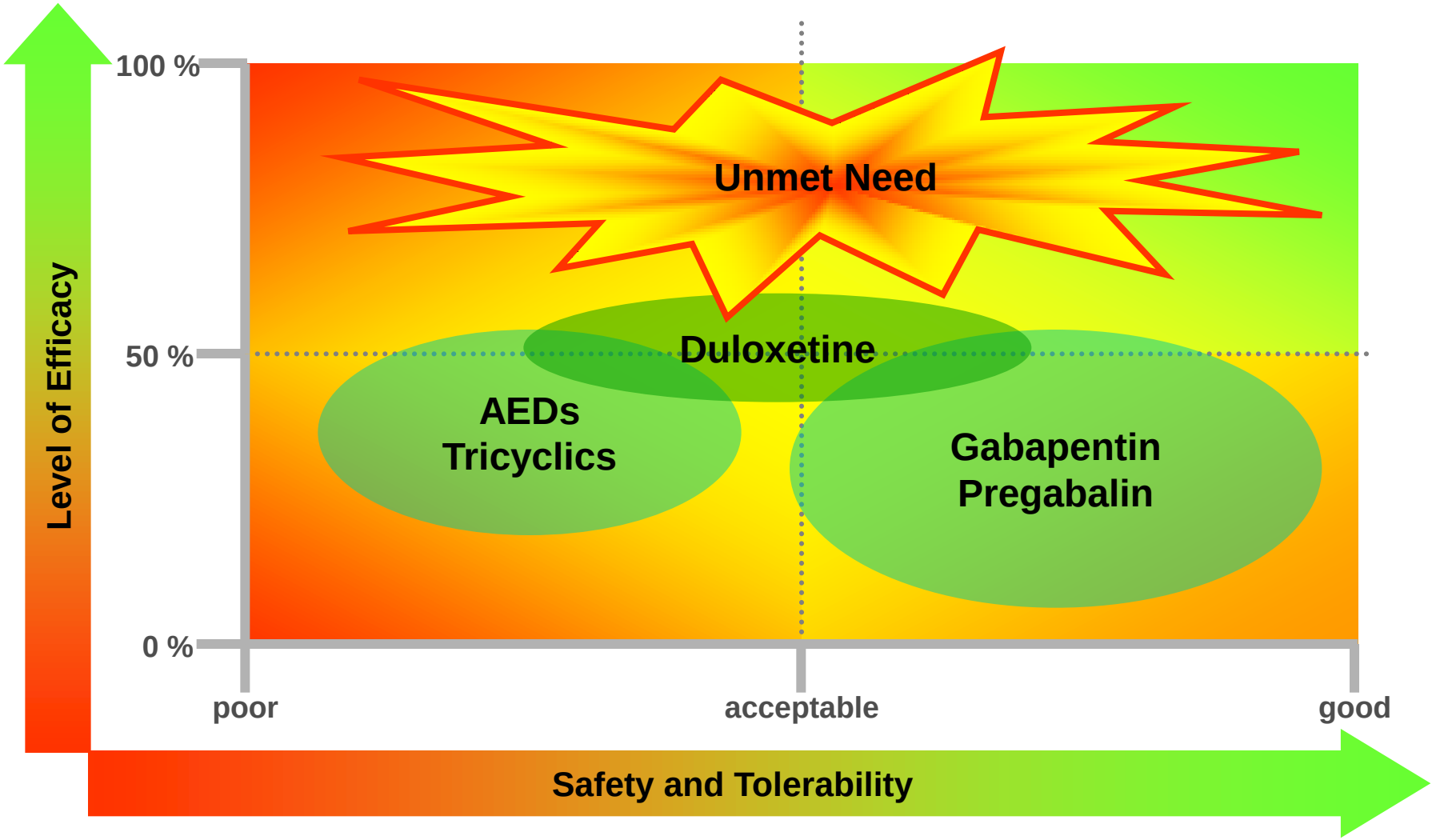


Pain Research Today - The Unmet Needs

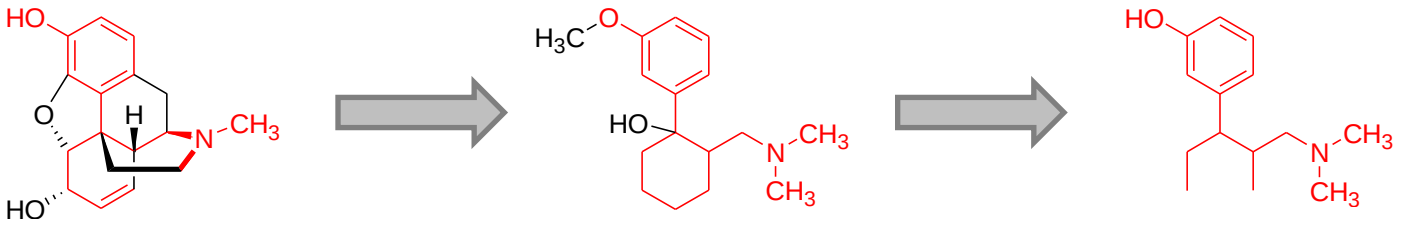
Significant Unmet Needs in Inflammatory/Nociceptive Pain Treatments



Significant Unmet Needs in Neuropathic Pain Treatments

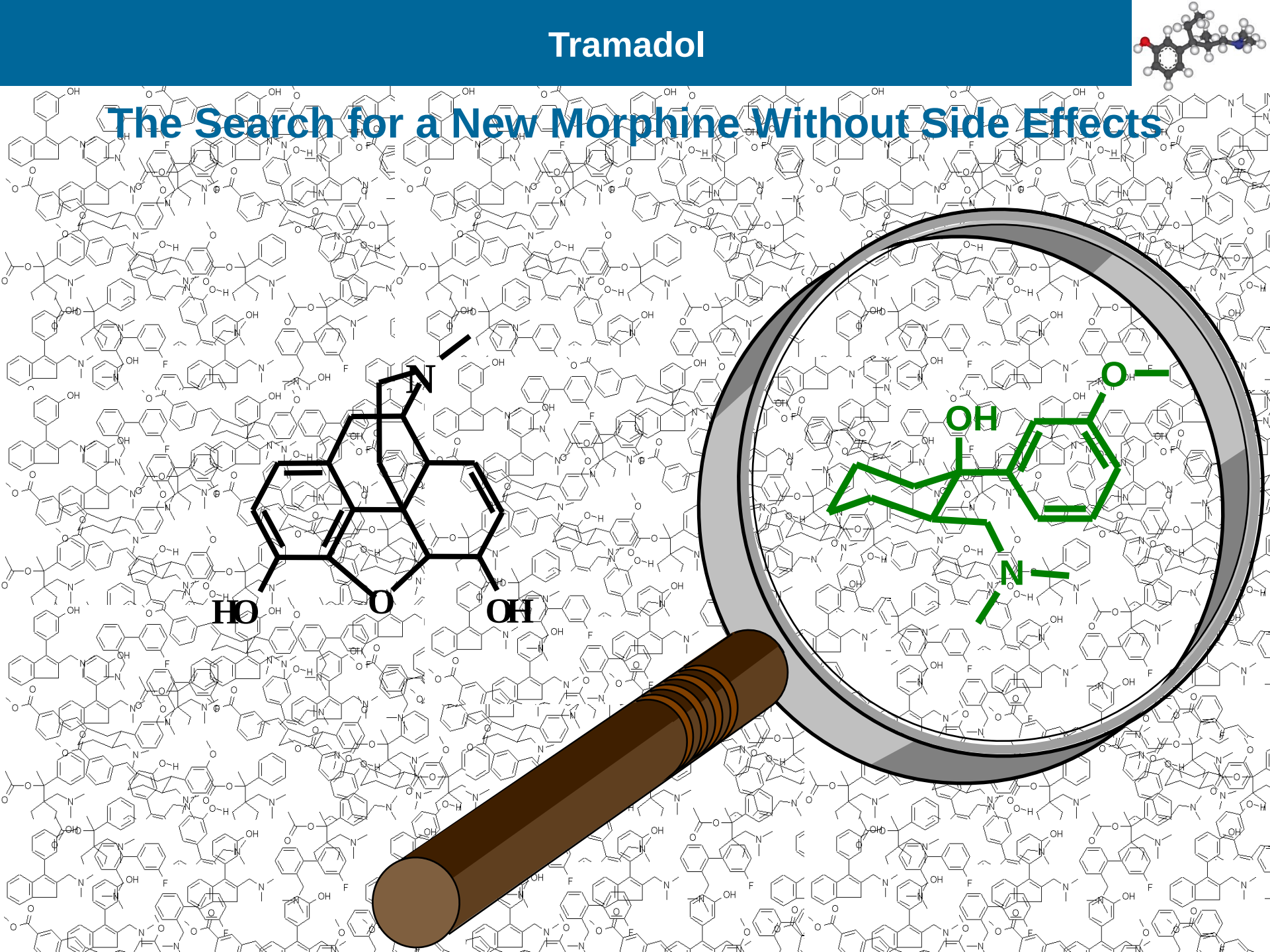


Tapentadol – A New Analgesic with a Dual Mode of Action



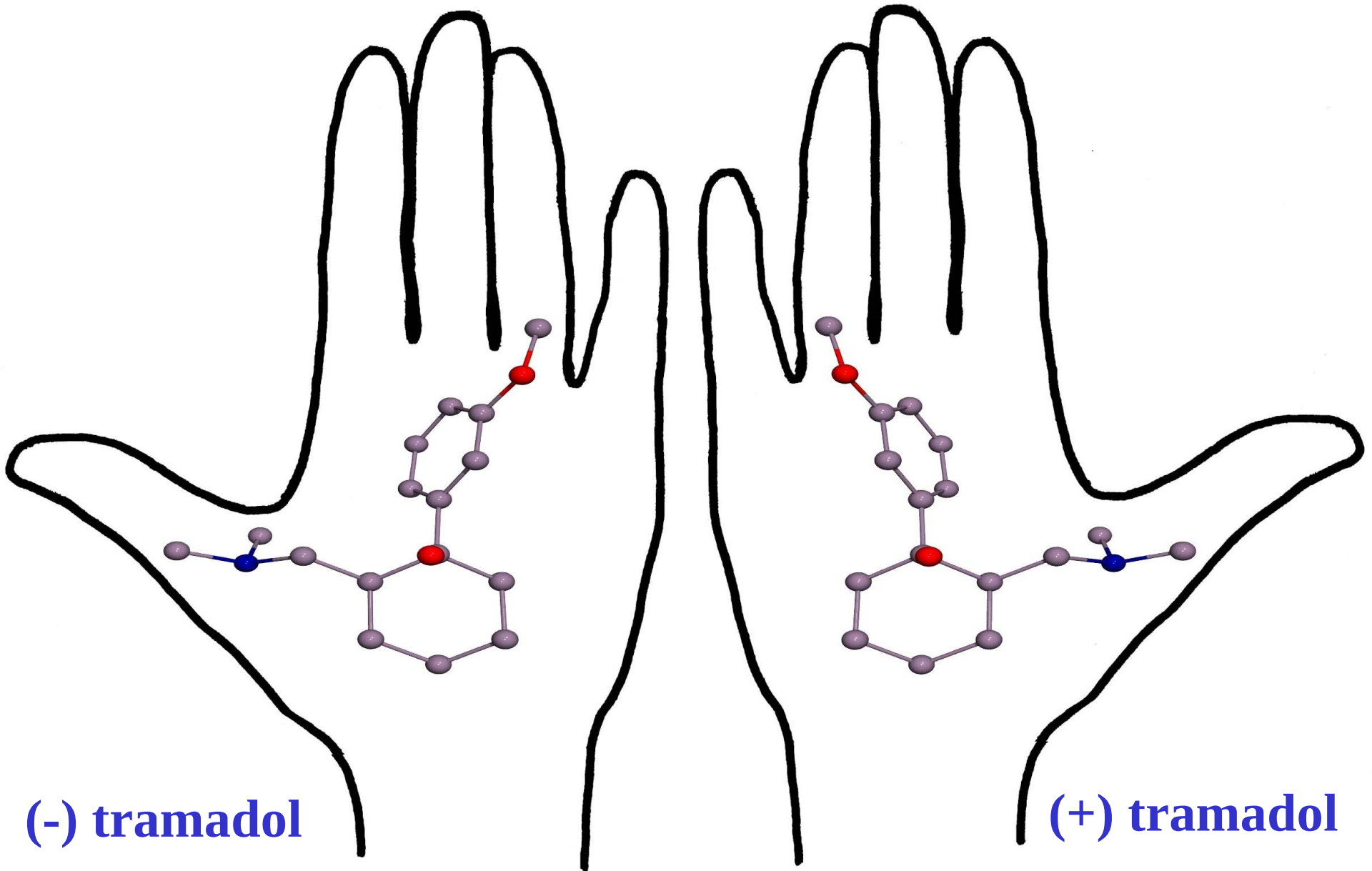
Tramadol

The Search for a New Morphine Without Side Effects



Tramadol – Pharmacological Profile

Tramadol is a racemate

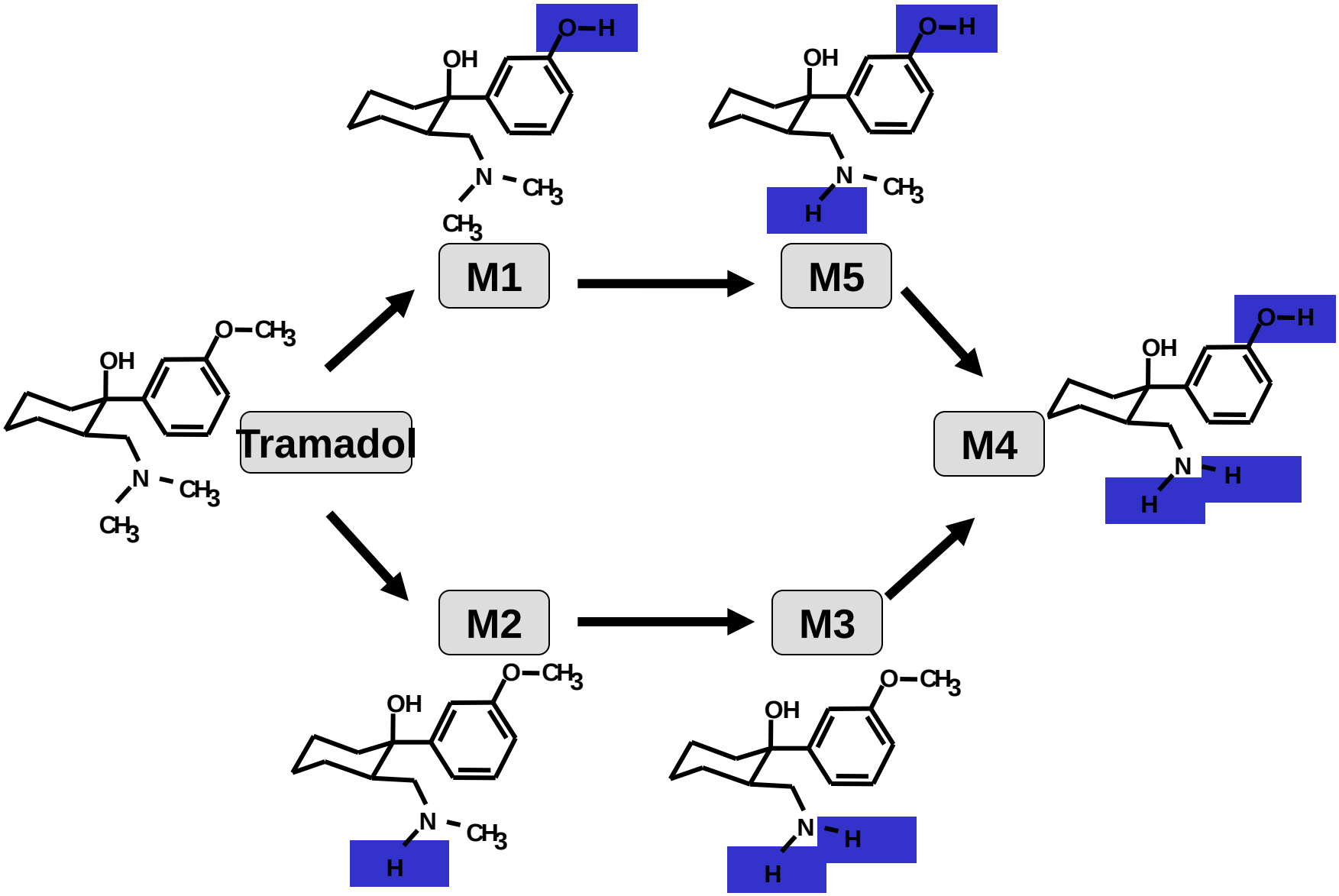


(-) tramadol

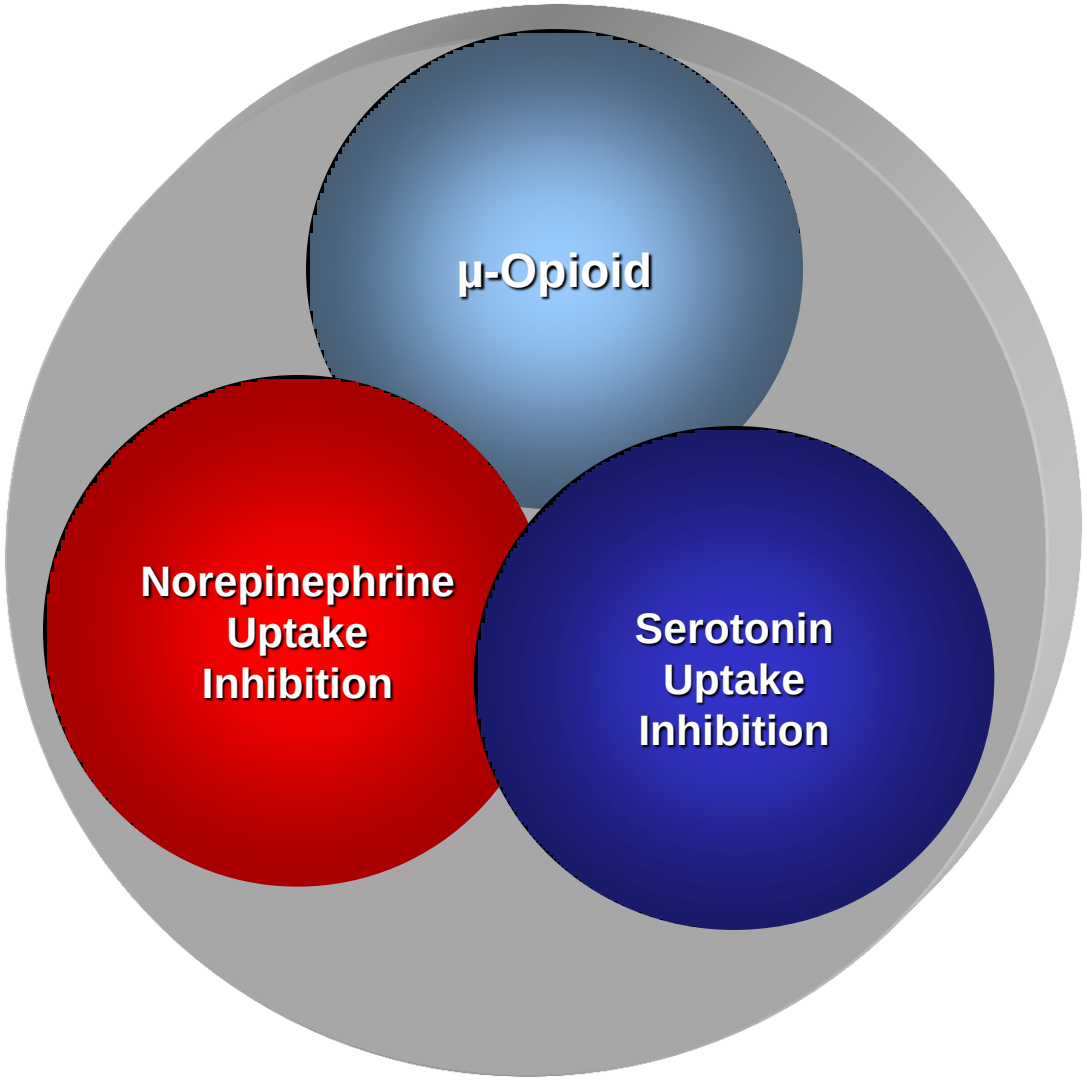
(+) tramadol

Tramadol – Pharmacological Profile

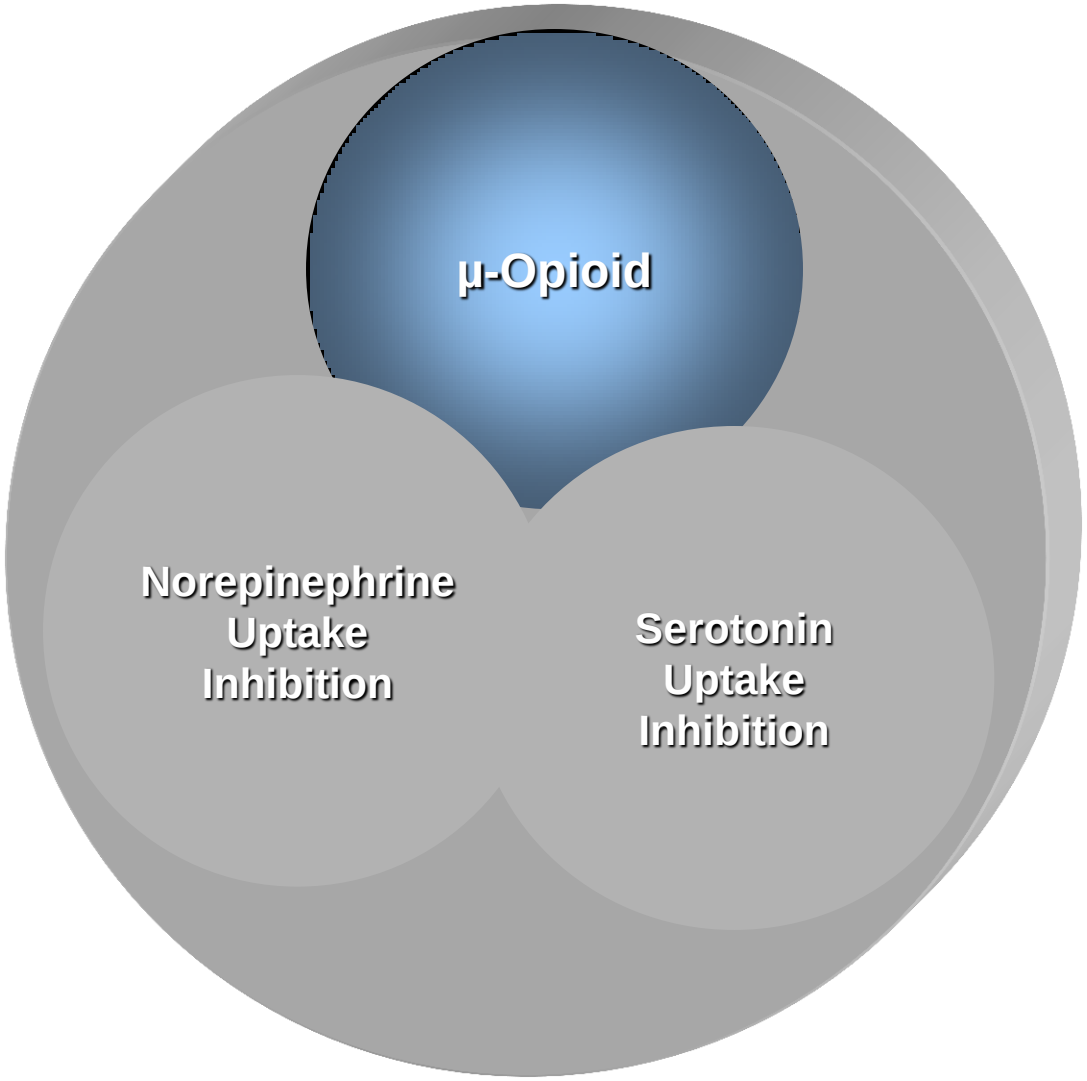
Metabolites of Tramadol



Tramadol‘s mode of action - biochemical profile

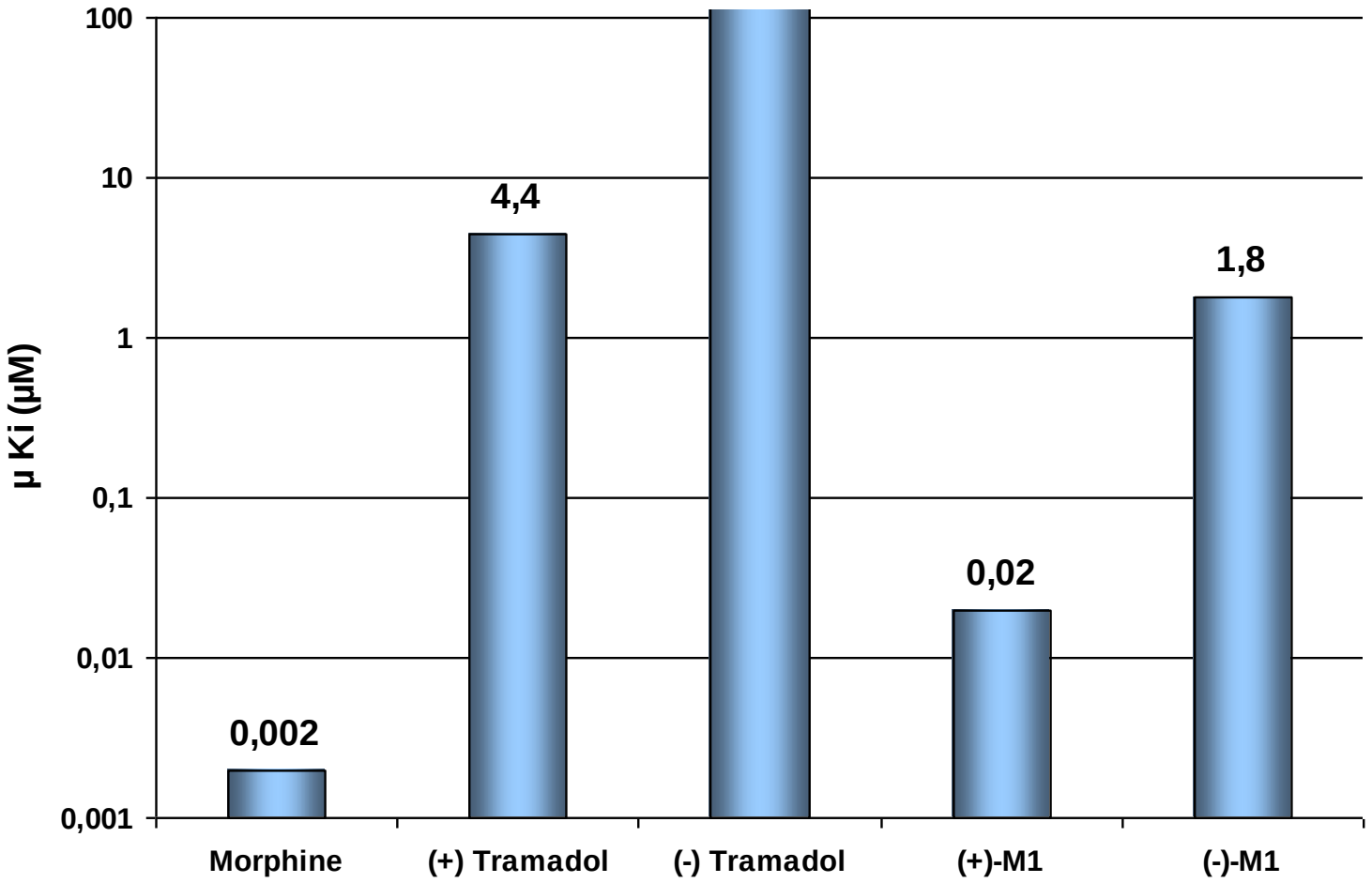


Tramadol‘s mode of action - biochemical profile

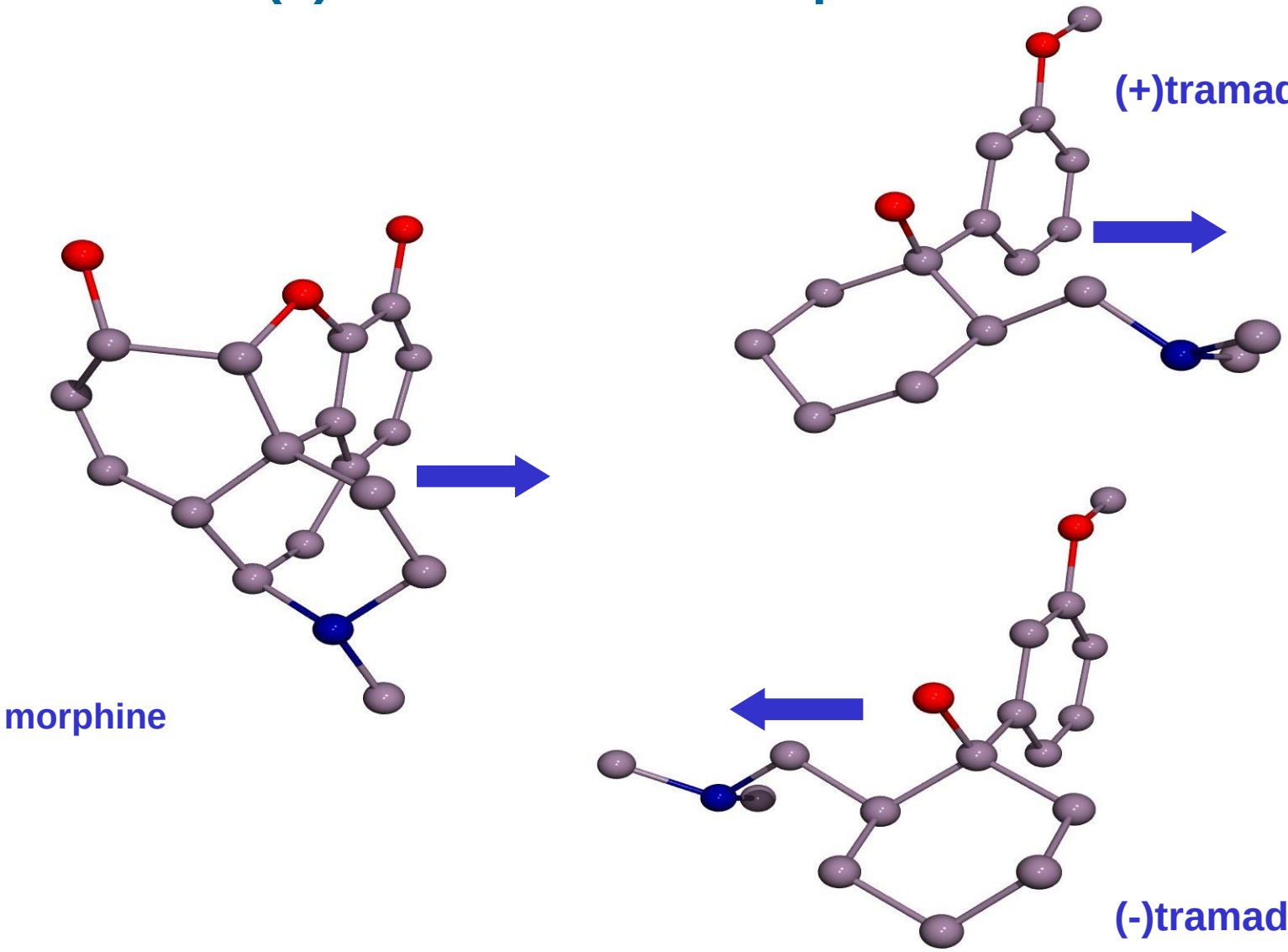


Tramadol – Pharmacological Profile

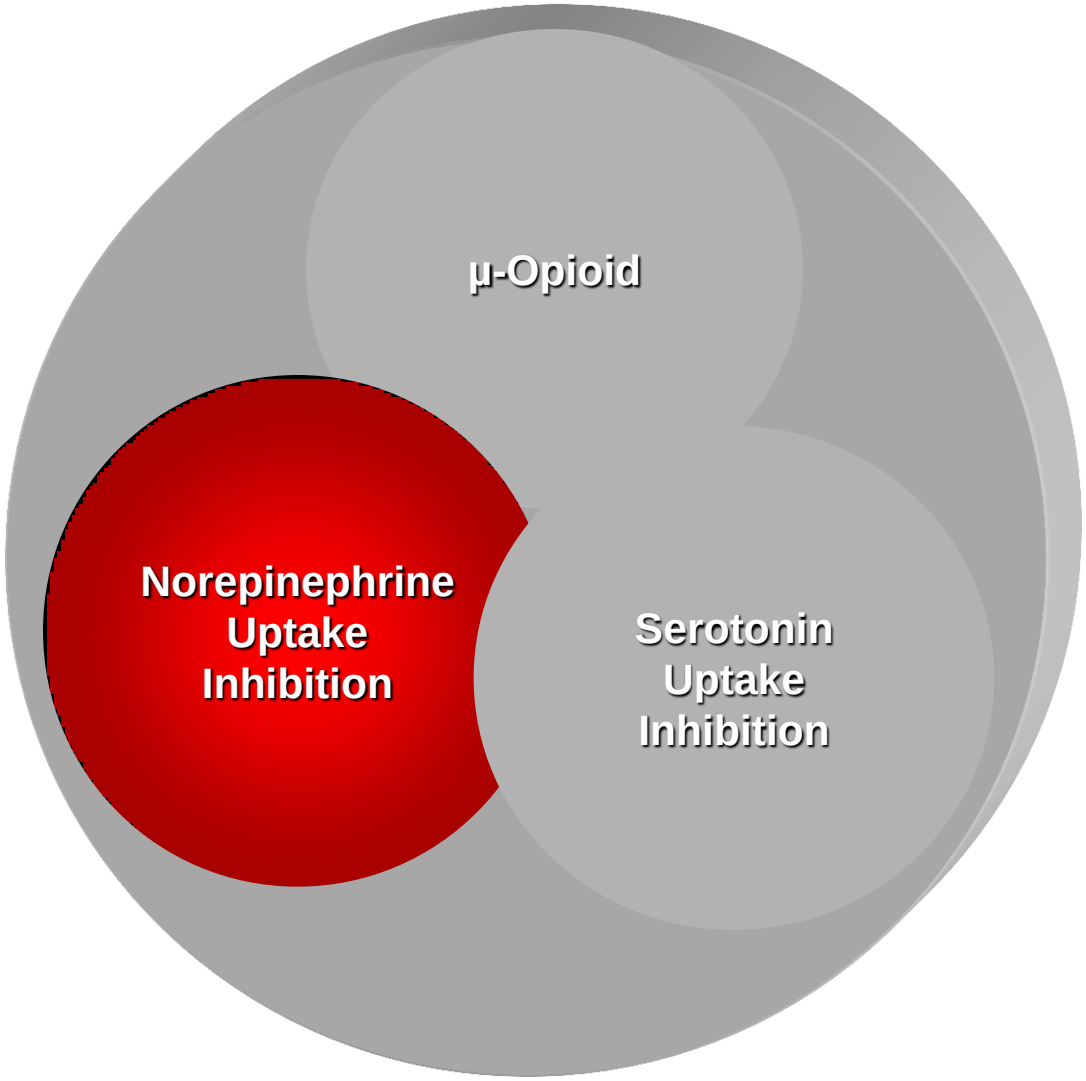
μ-Opioidbinding of tramadol and tramadol-M1



Comparison of molecular structures (+) Tramadol and Morphine

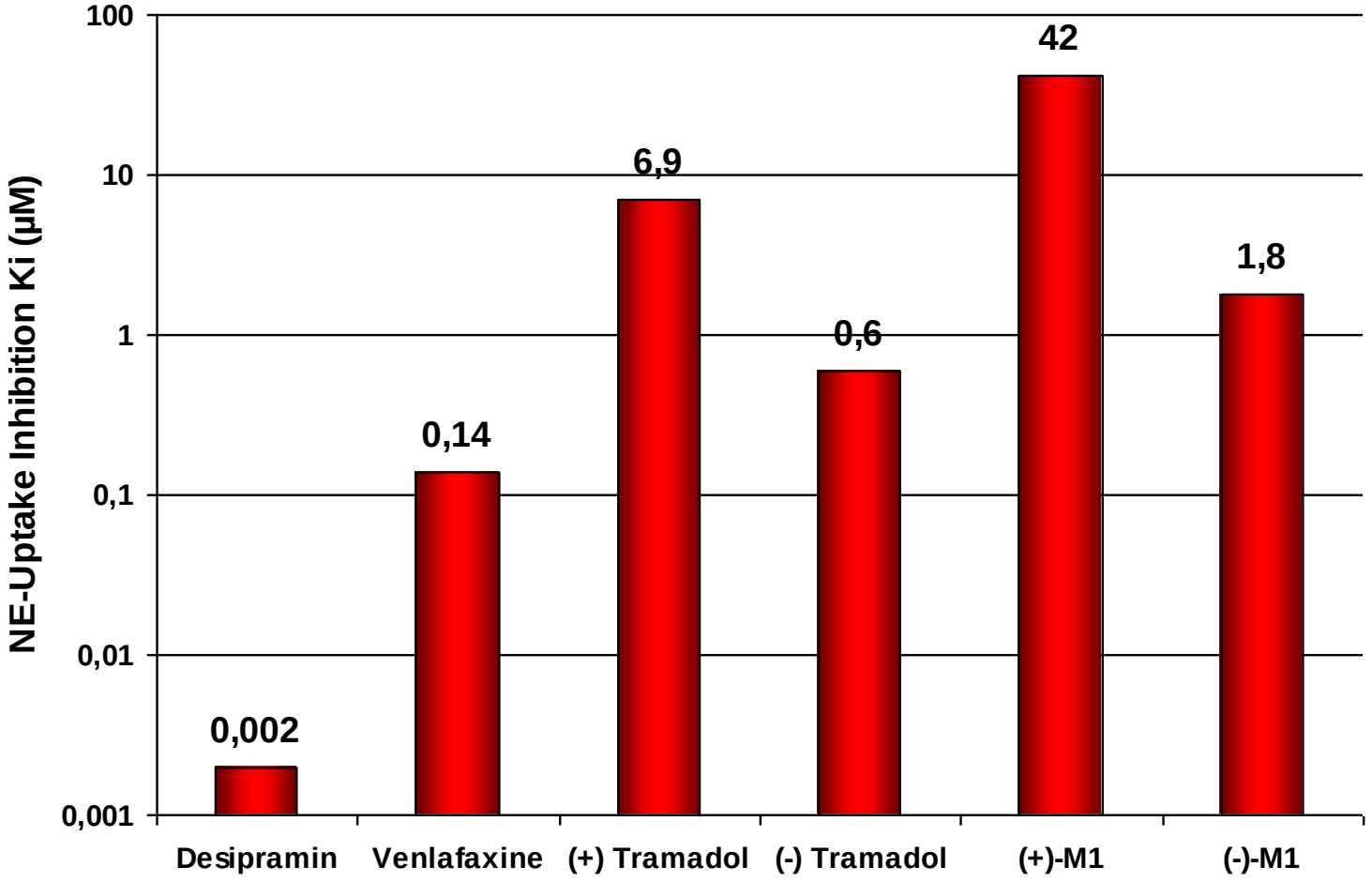


Tramadol‘s mode of action - biochemical profile

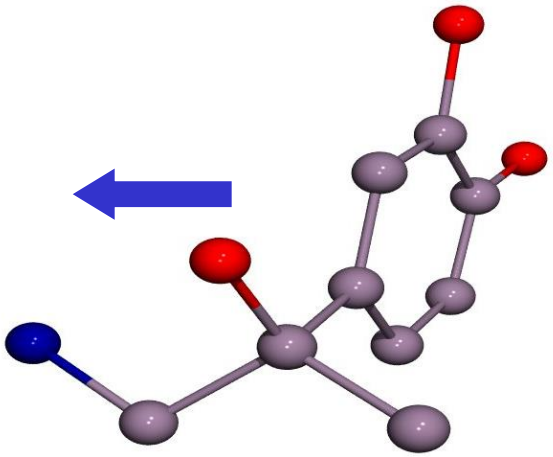


Tramadol – Pharmacological Profile

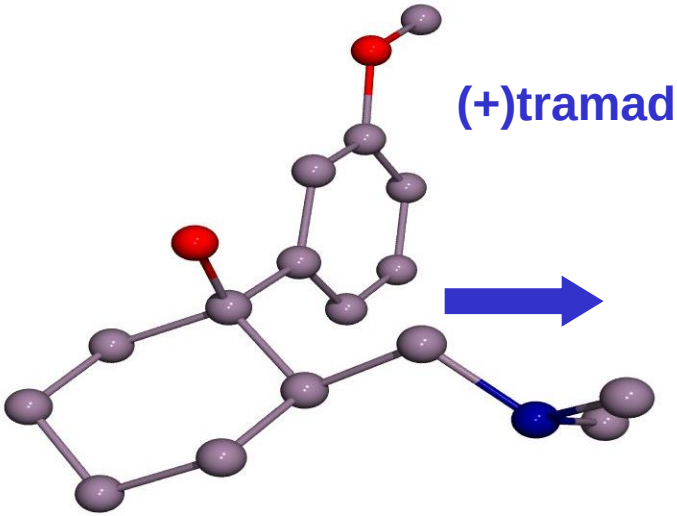
Norepinephrine-Uptake inhibition of tramadol and tramadol-M1



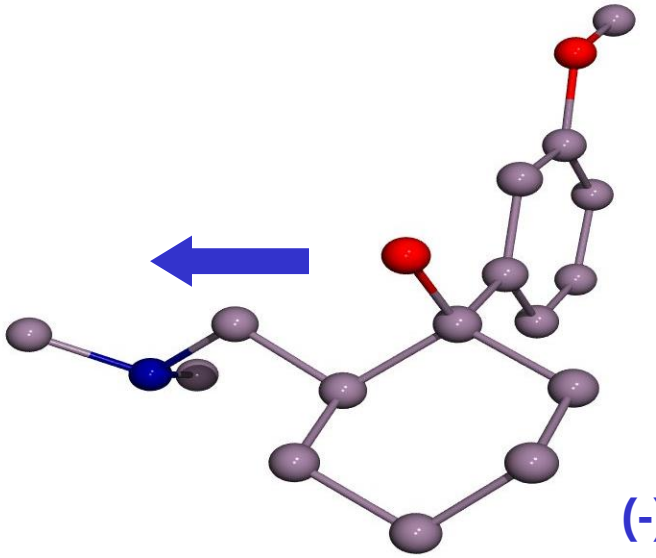
Comparison of molecular structures



norepinephrine

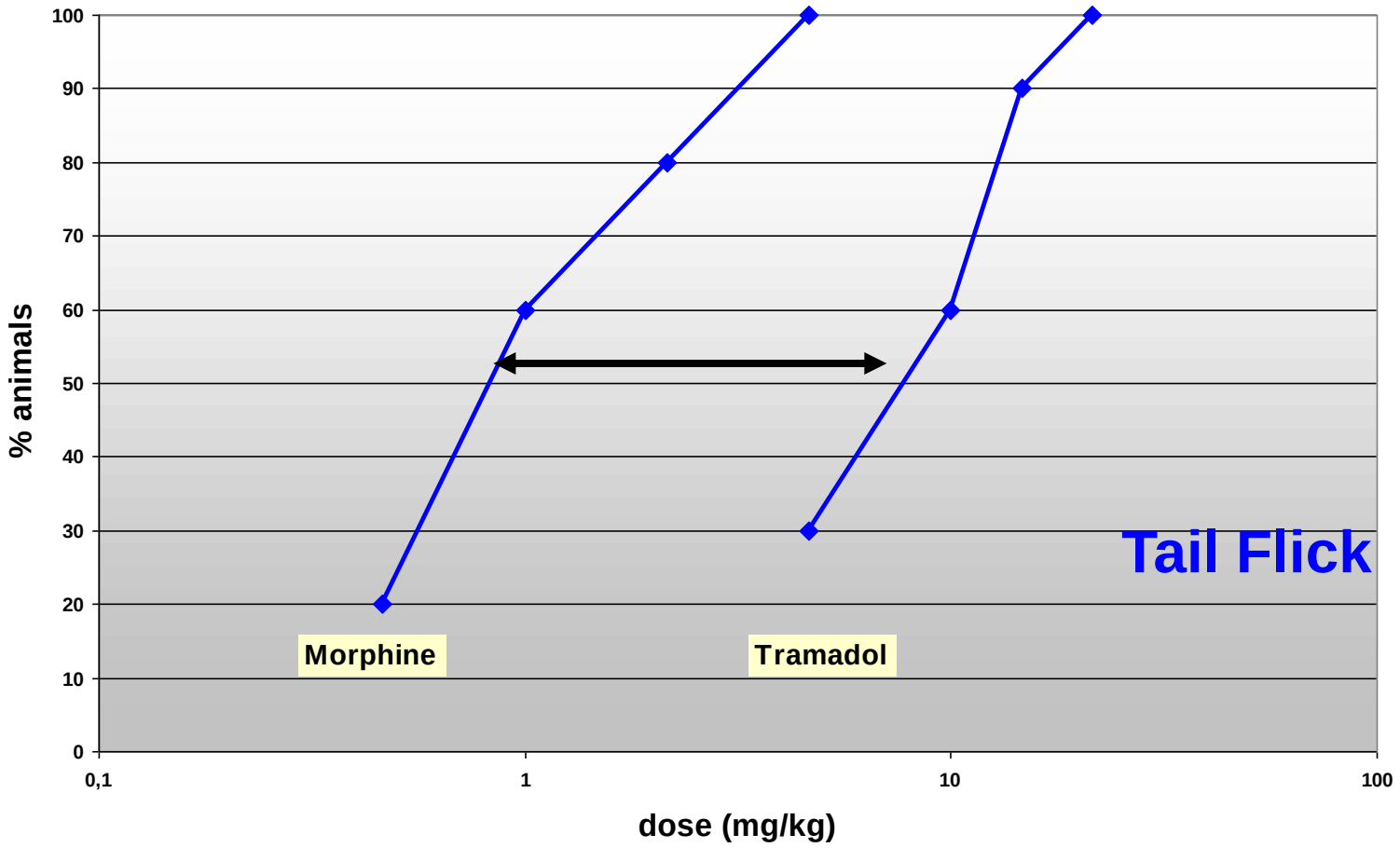


(+)tramadol

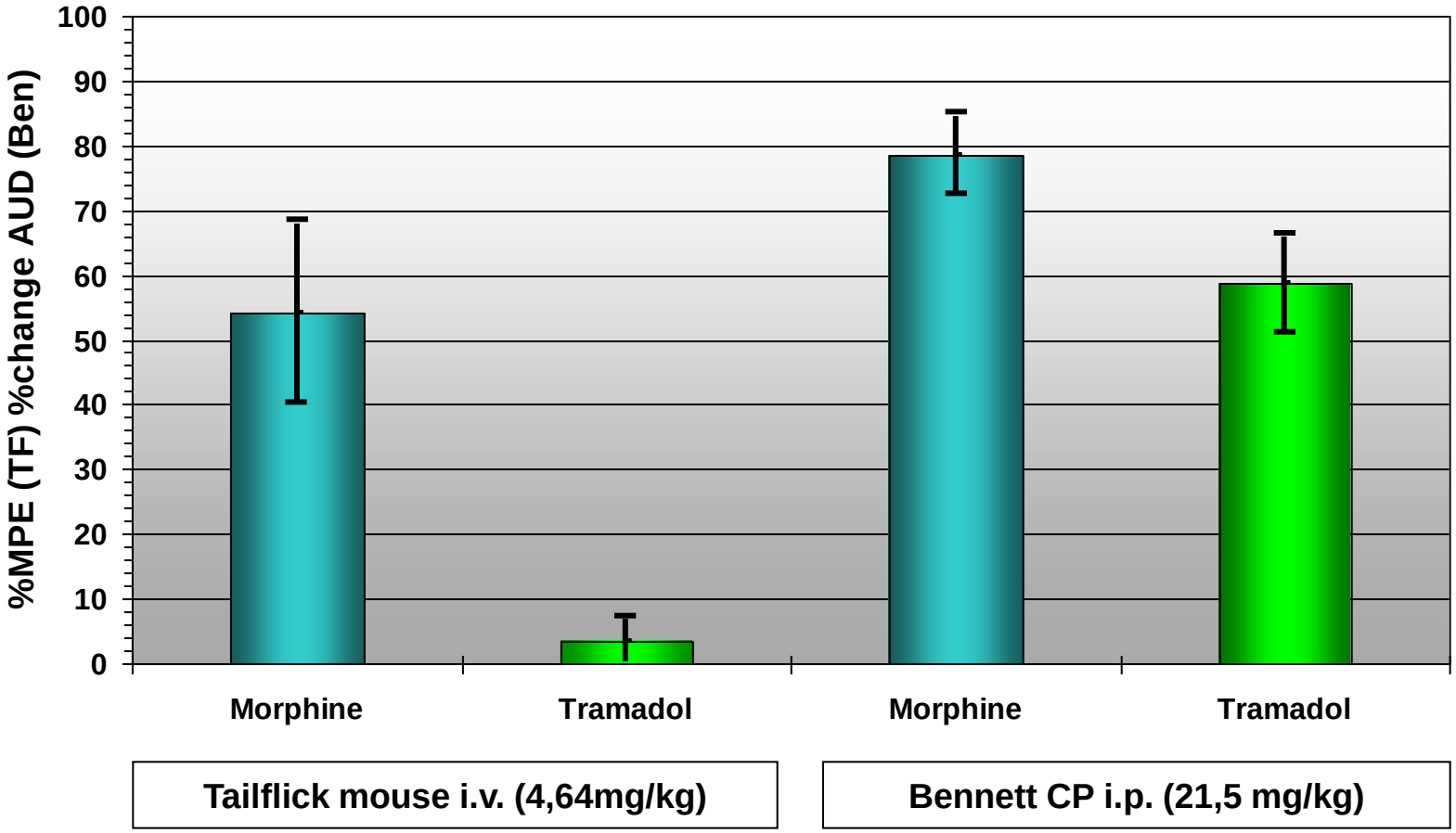


(-)tramadol

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



Comparison of acute pain (Tail Flick) and neuropathic pain (Bennett)



Occurrence of the Synthetic Analgesic Tramadol in an African Medicinal Plant

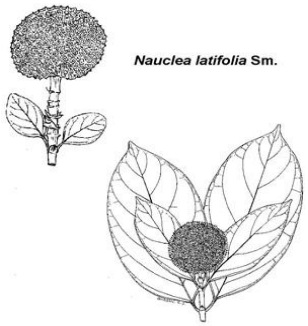
Angewandte Chemie

Natural Products

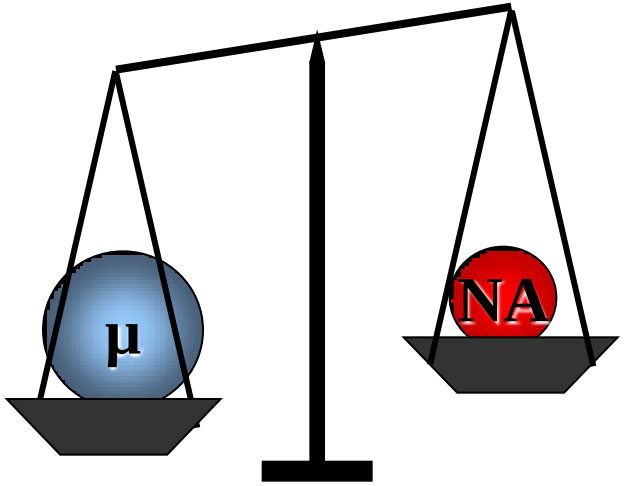
DOI: 10.1002/ange.201305697

Occurrence of the Synthetic Analgesic Tramadol in an African Medicinal Plant**

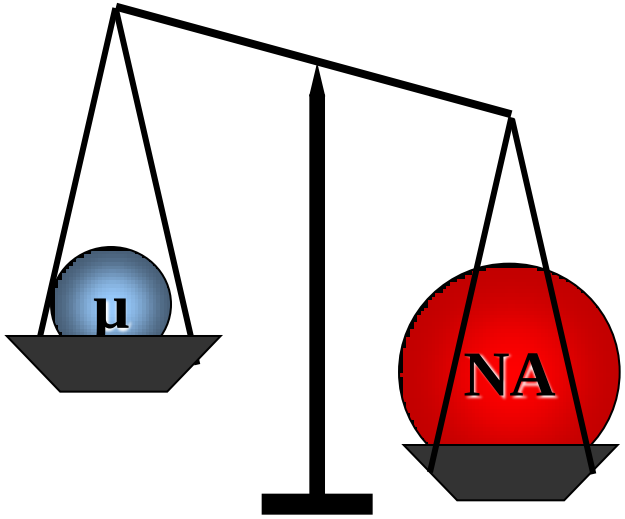
Ahcène Boumendjel, Germain Sotoing Taïwe, Elisabeth Ngo Bum, Tanguy Chabrol, Chantal Beney, Valérie Sinniger, Romain Haudecoeur, Laurence Marcourt, Soura Challal, Emerson Ferreira Queiroz, Florence Souard, Marc Le Borgne, Thierry Lomberget, Antoine Depaulis, Catherine Lavaud, Richard Robins, Jean-Luc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



What have we learned from the Tramadol story?



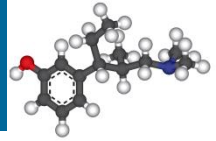
(+)-Tramadol



(-)-Tramadol

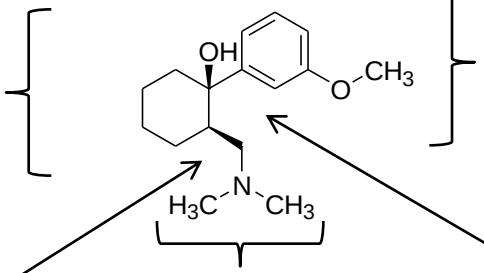
Can both principles be combined in one molecule (one enantiomer) ?

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

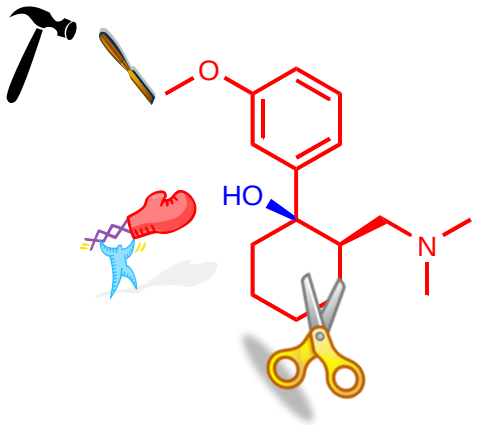


- Phenyl ring substitution
- Replacement by heterocyclic aryl rings
- Replacement by acyclic ring systems

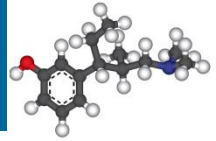
- Methylen group substitution

- N- Substitution
- N-containing ring systems

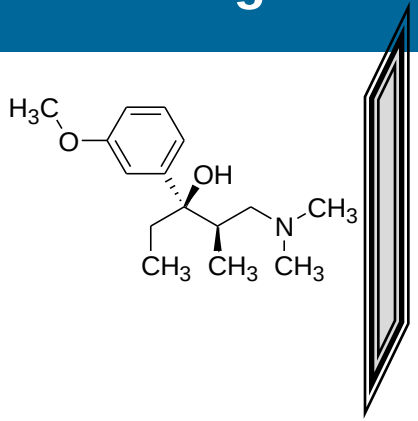
- Introduction of spacer groups between ring systems

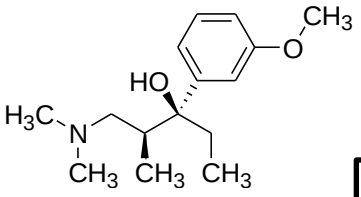


Tapentadol – A New Analgesic with a Dual Mode of Action

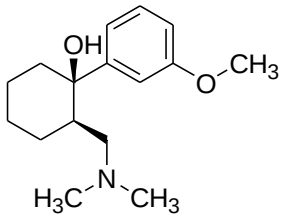


Opening of the cyclohexane ring

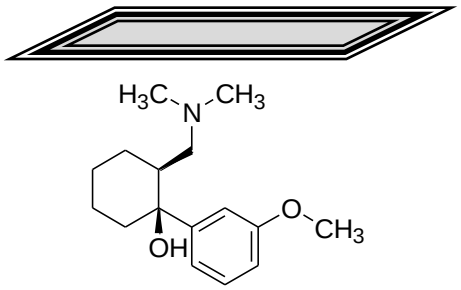




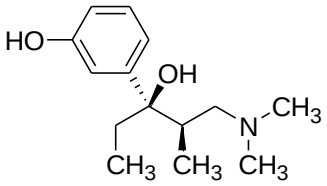
From Prodrug to direct acting drug

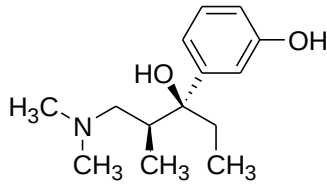


Tramadol

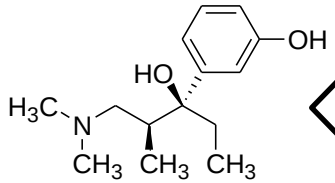


Racemate with relative stereochemistry cis

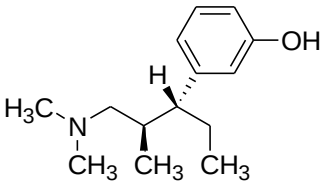




Selecting of one enantiomer



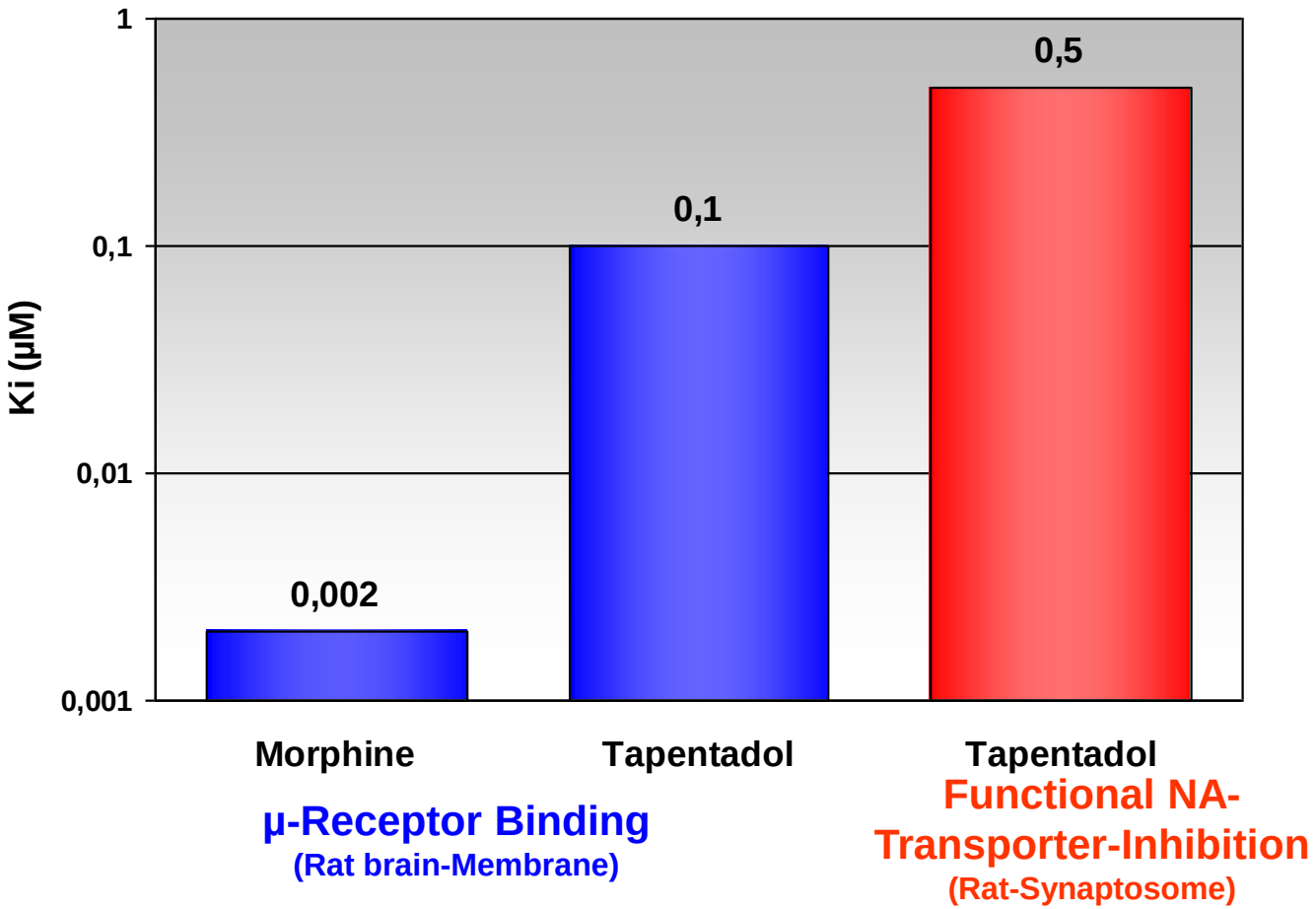
Replacement of *tert.* OH group



Tapentadol

Tapentadol – A New Analgesic with a Dual Mode of Action

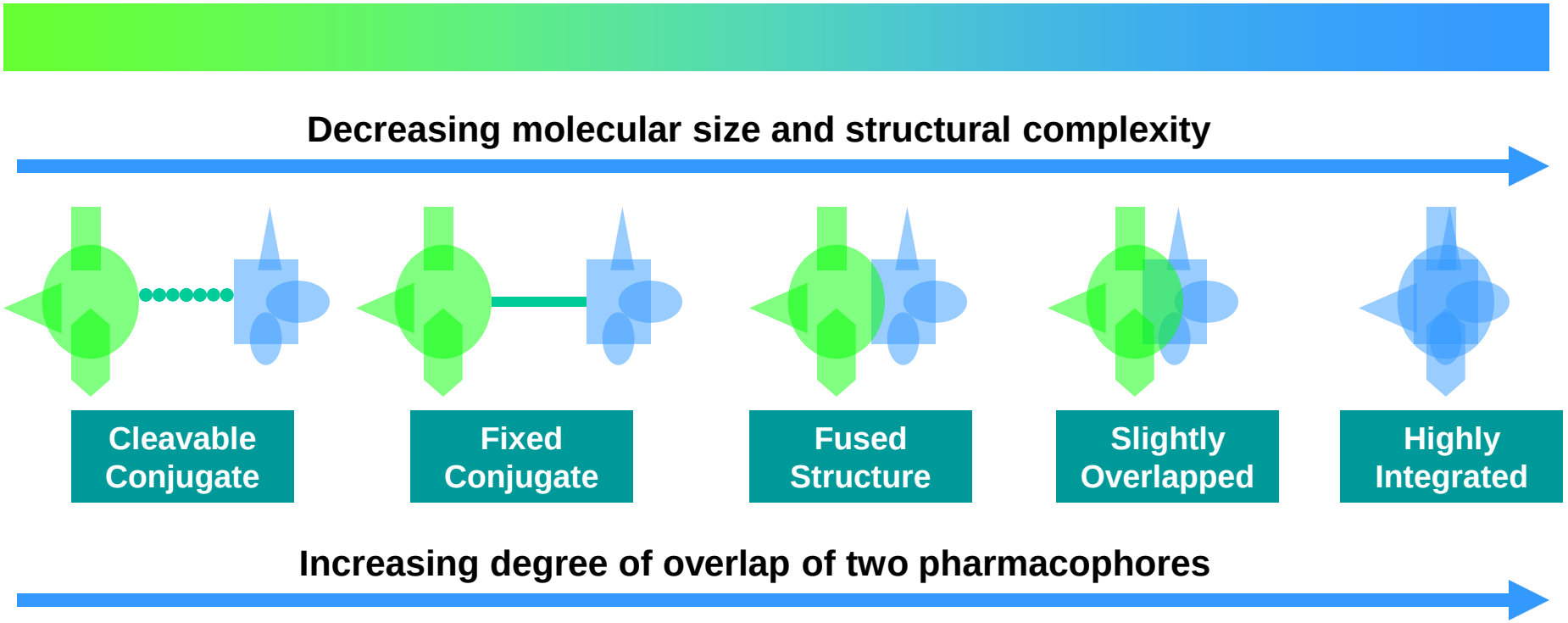
μ-Rezeptor-Agonism (MOR) and Noradrenalin Reuptake Inhibition (NRI)



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

Tapentadol as a Multiple Ligand

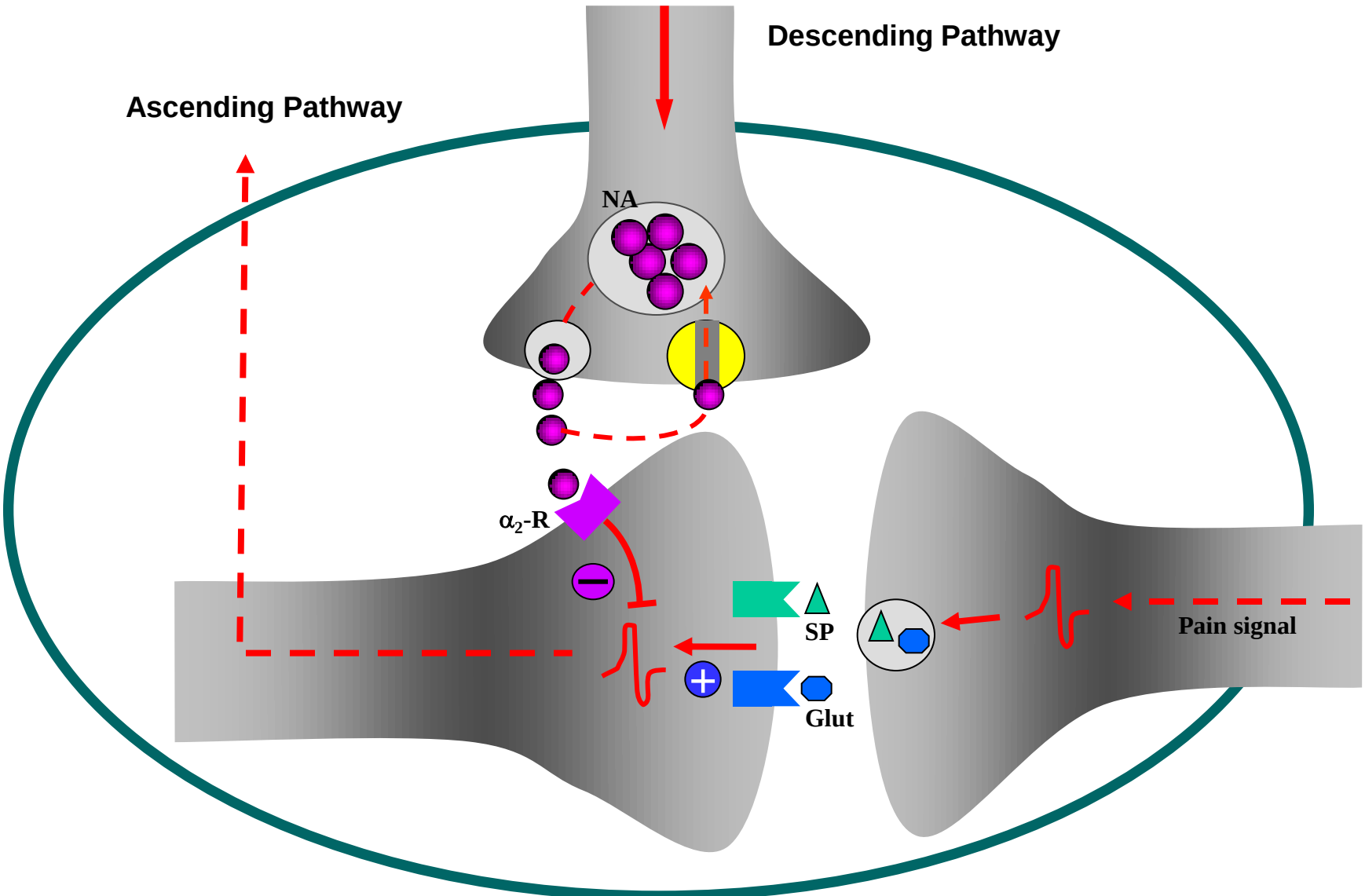
Designed Multiple Ligang Continuum*)**)



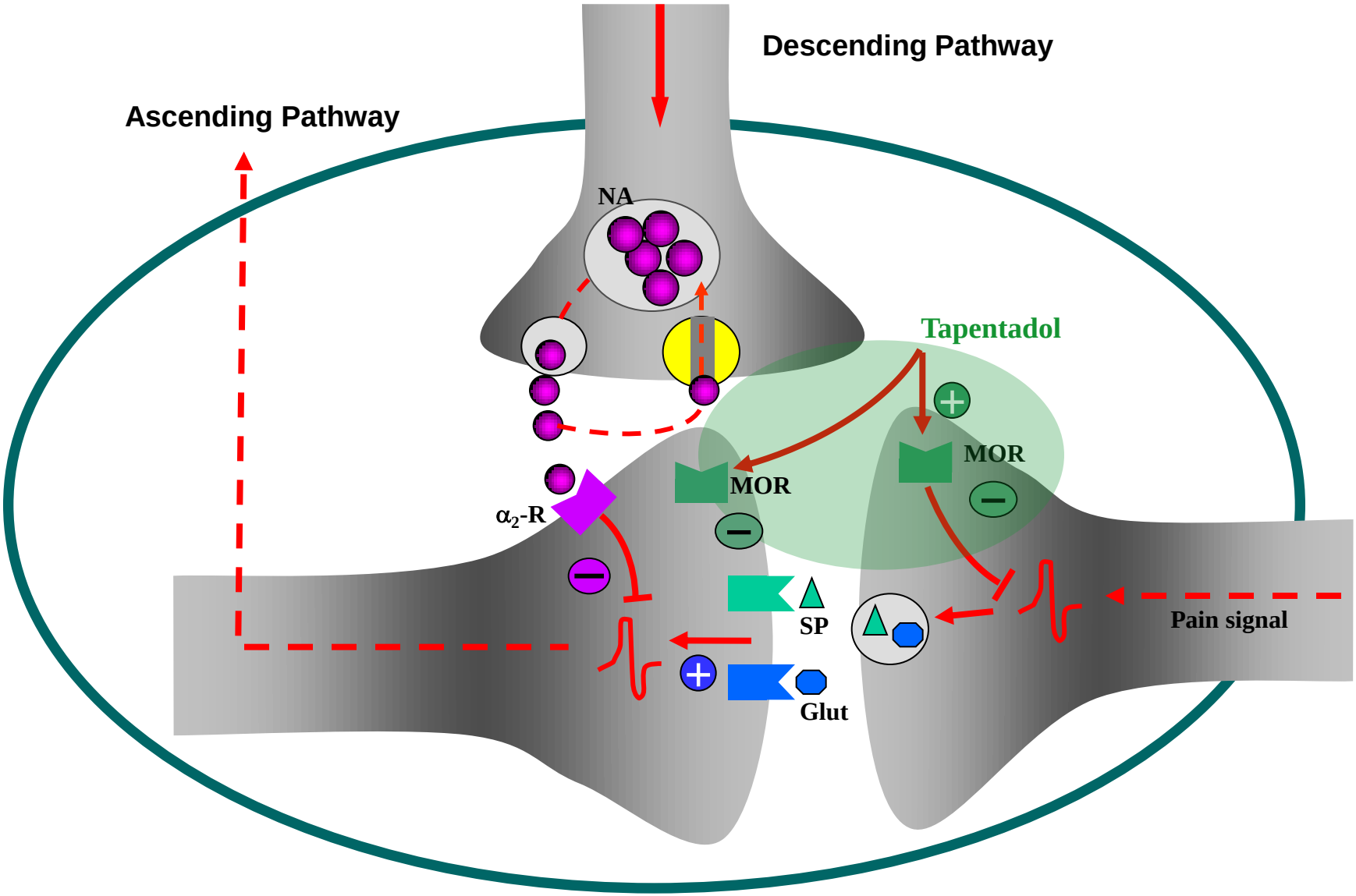
*) R. Morphy, Z. Rankovic, *Designed Multiple Ligands. An Emerging Drug Discovery Paradigm*, J. Med. Chem. 2005 (48), 6523-6543.

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

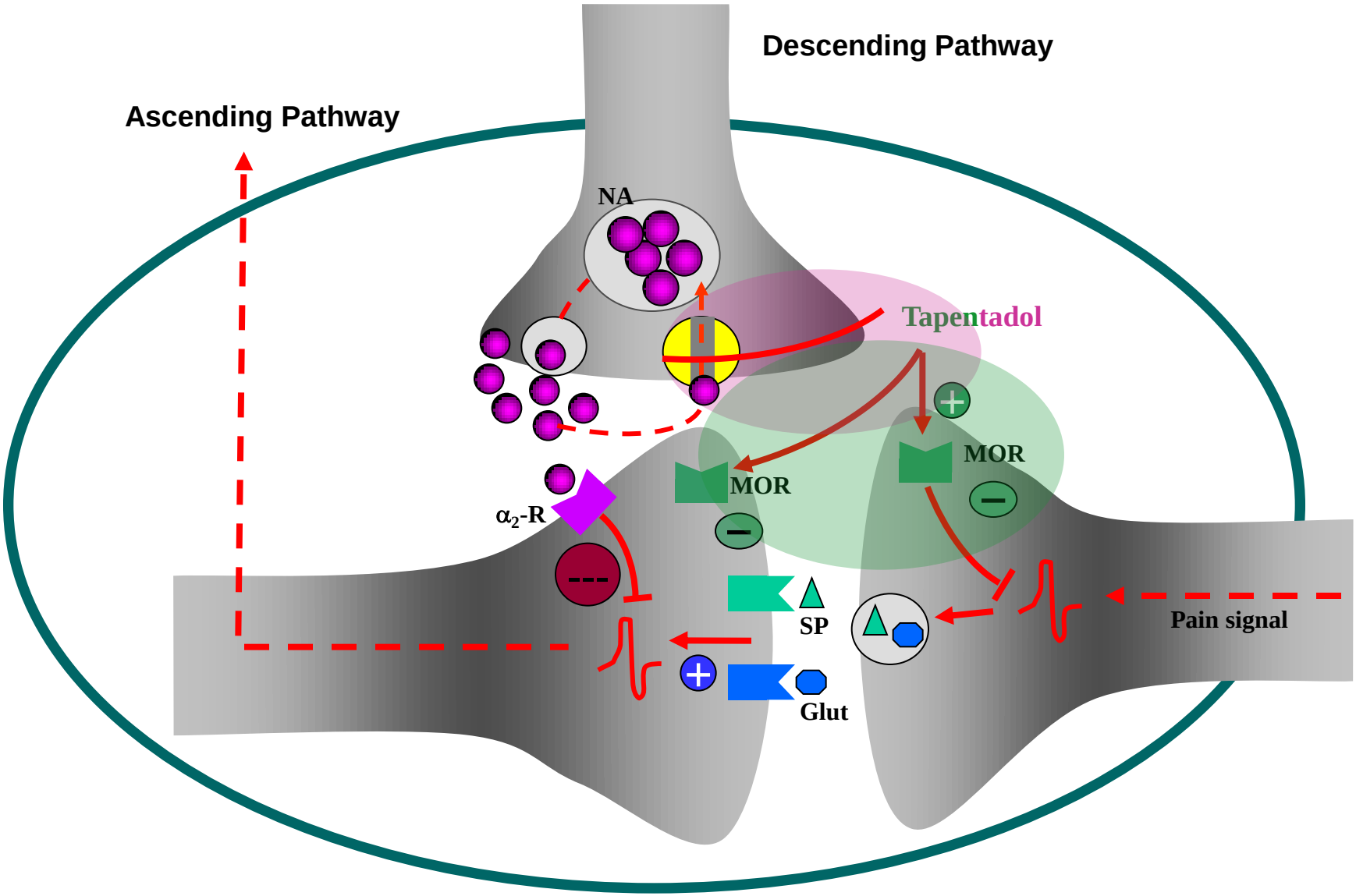
Spinal Mechanism of Action: MOR-NRI



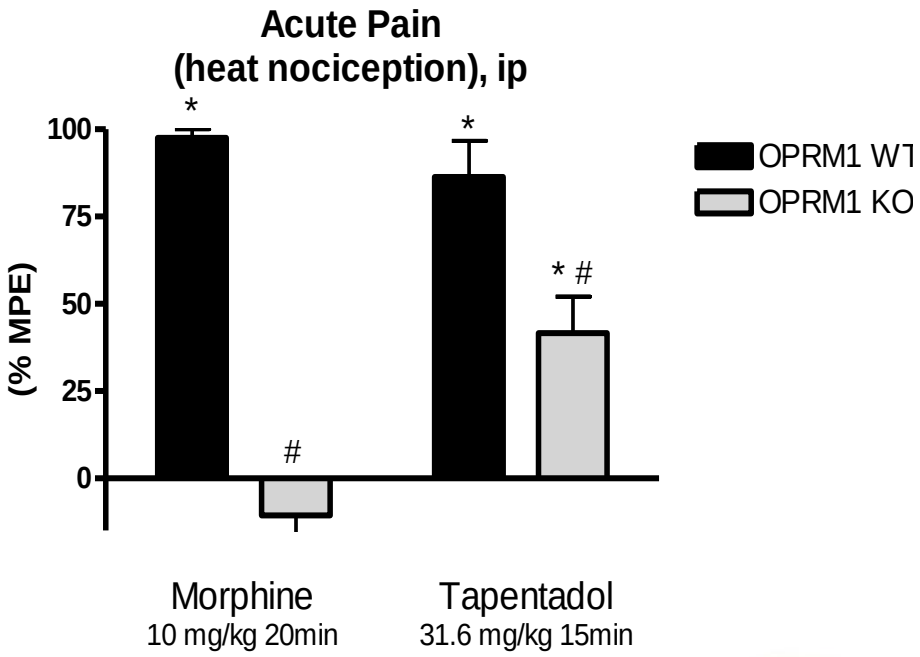
Spinal Mechanism of Action: MOR-NRI



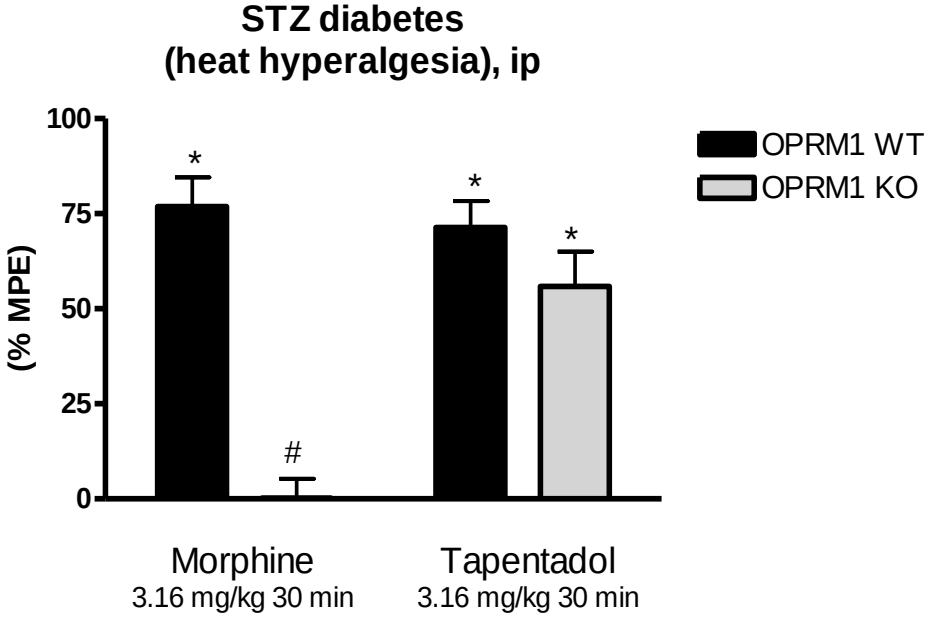
Spinal Mechanism of Action: MOR-NRI



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



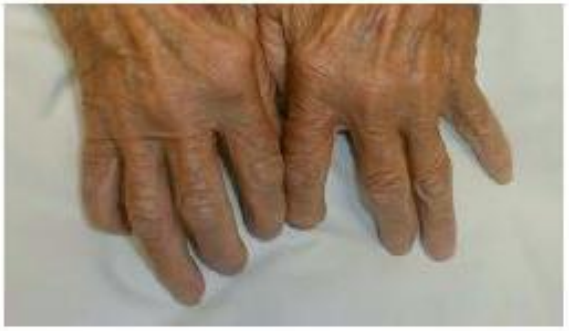
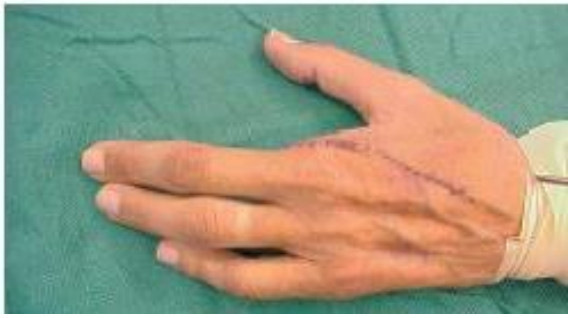
* p<0.05 treatment vs vehicle
# p<0.05 KO vs WT



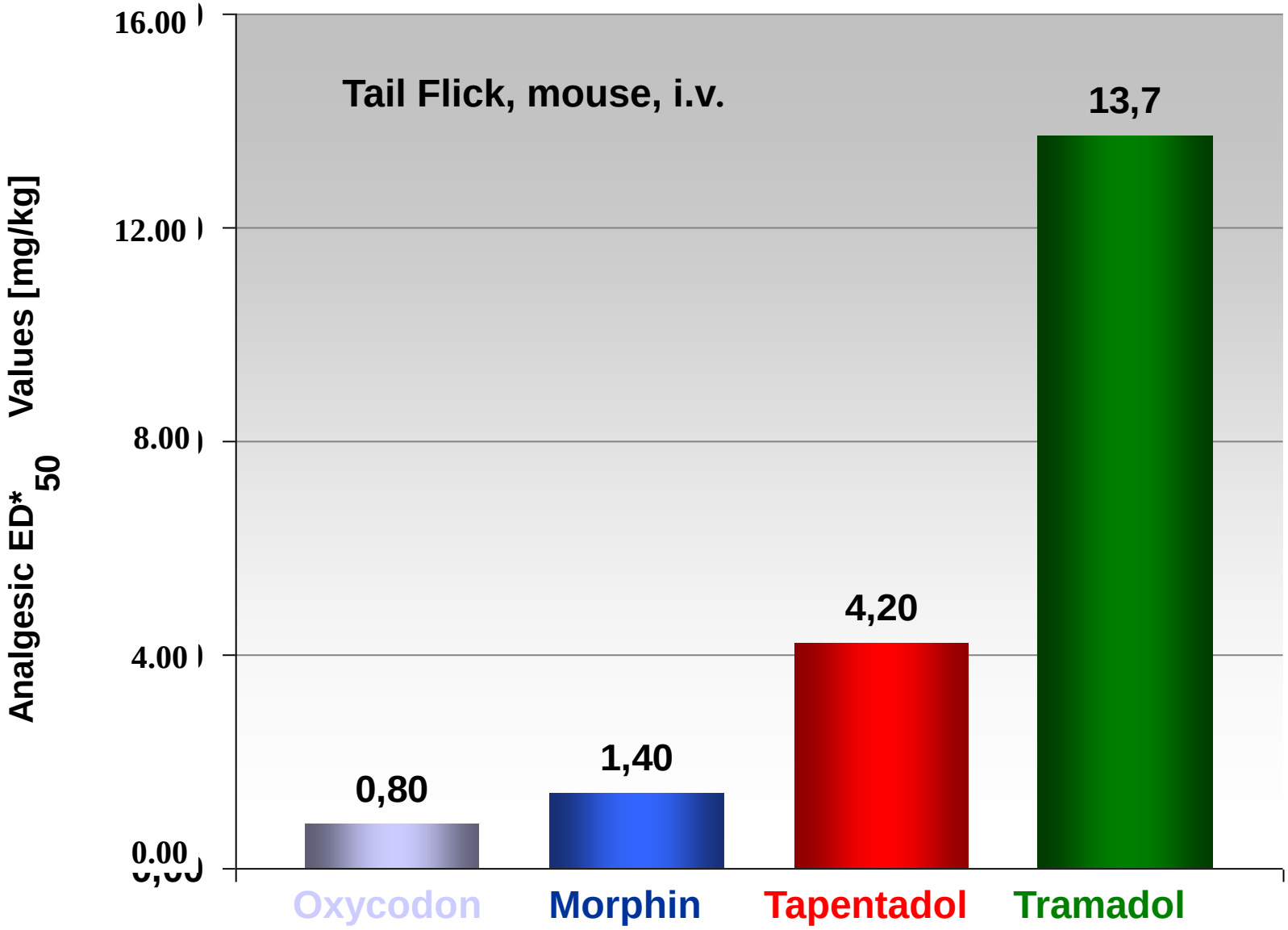
* p<0.05 treatment vs vehicle
# p<0.05 KO vs WT

Tapentadol remains partially active in MOR-Knock-out Mice

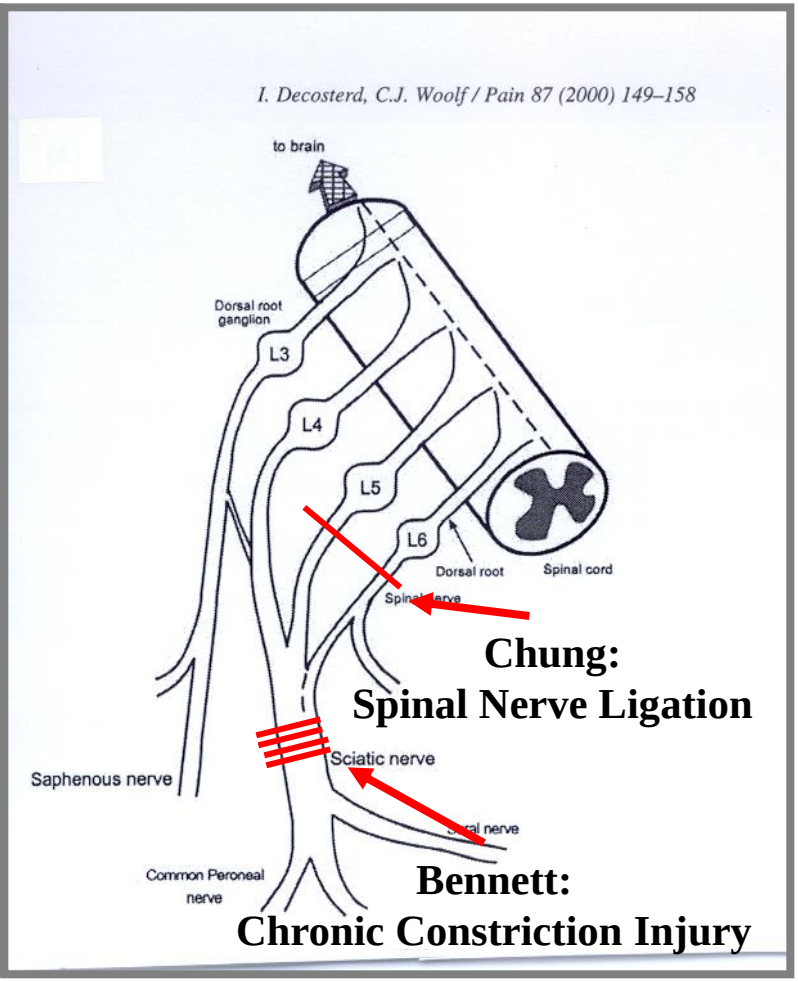
Pharmacology: Pain Models

Acute	Chronic inflammatory	Chronic neuropathic
		
		

Analgesic Potency in Acute Pain

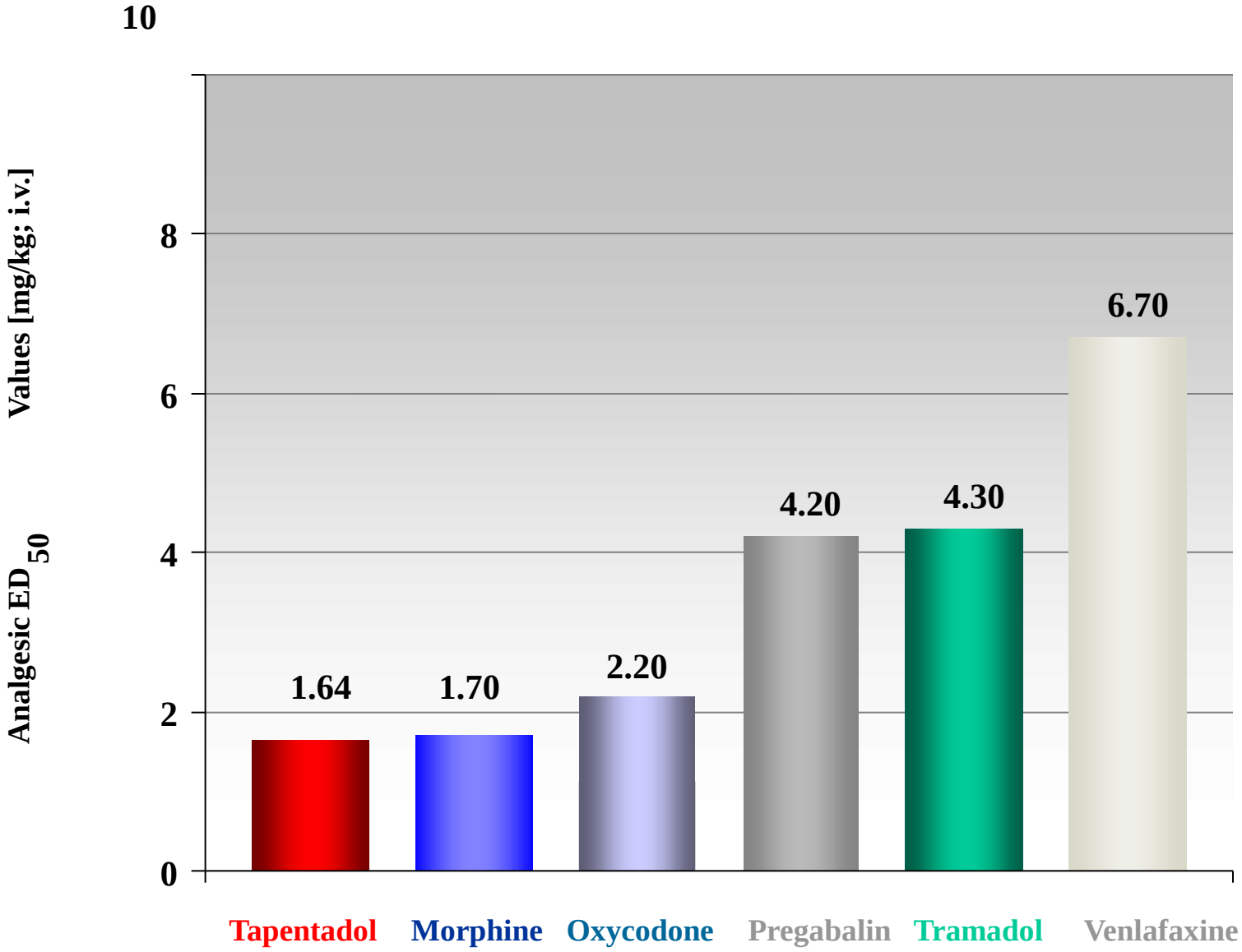


Neuropathic pain model: Peripheral Mononeuropathy (Chung model)



Investigation of tactile allodynia after tight ligation of the dorsal root of spinal nerves (L5, L6)

High potency and efficacy in neuropathic pain (Chung)

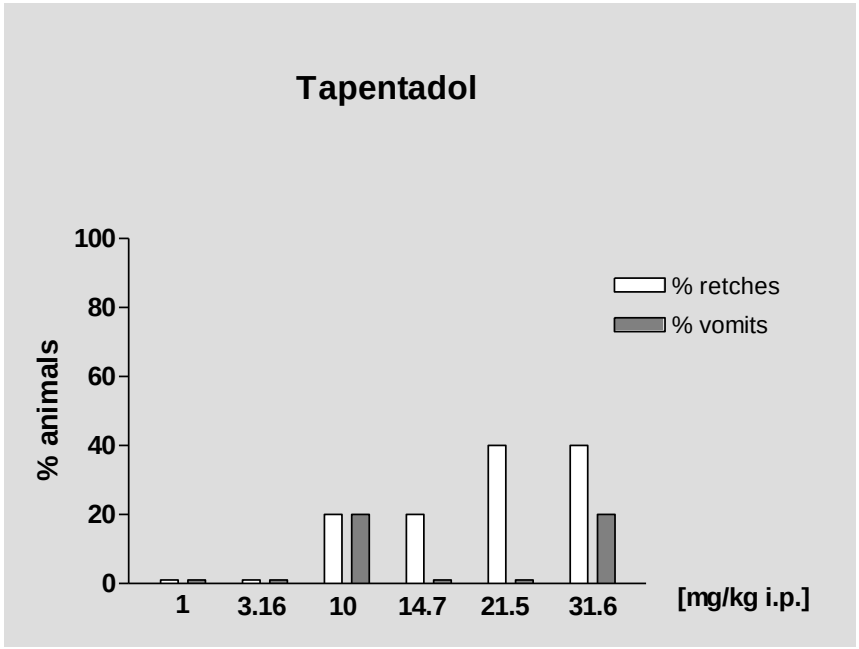


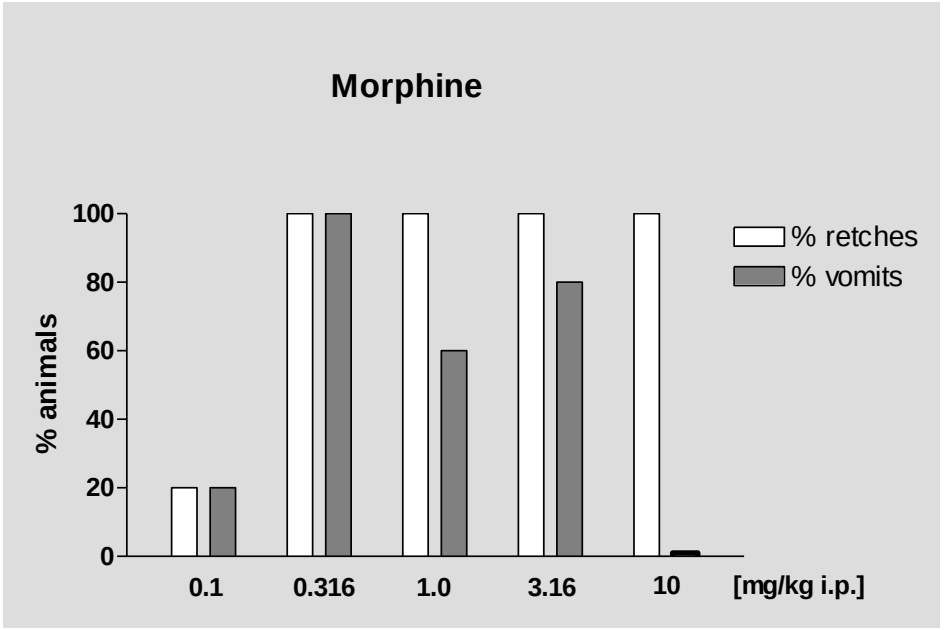
Tapentadol – *in vivo* Pharmacology – Side Effects

Tapentadol

Morphin

Opioid Induced Side Effects: Emesis





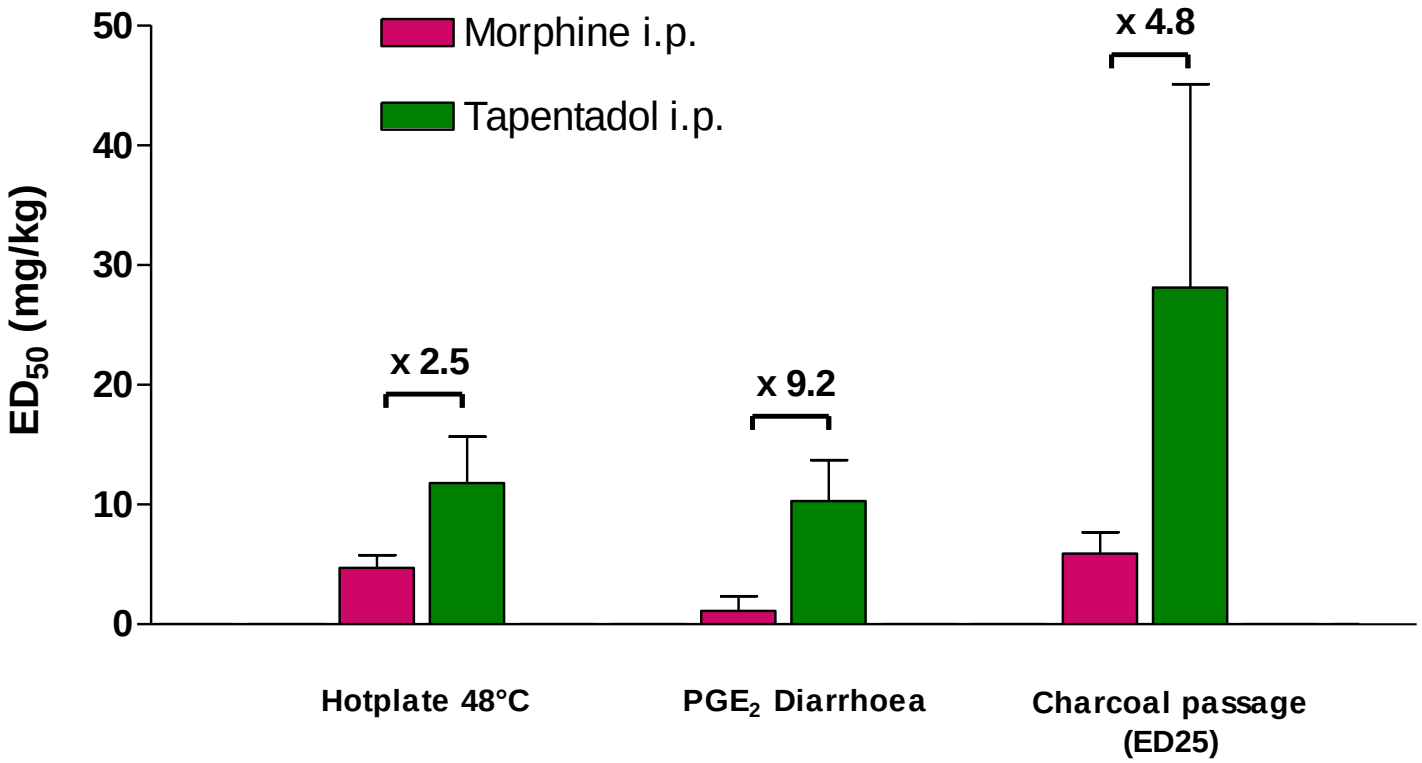
Tzschentke et al (2006) Drugs Fut 31:1053ff

Tapentadol shows a reduced emetic potential in comparison to Morphine

Opioid Induced Side Effects: Obstipation

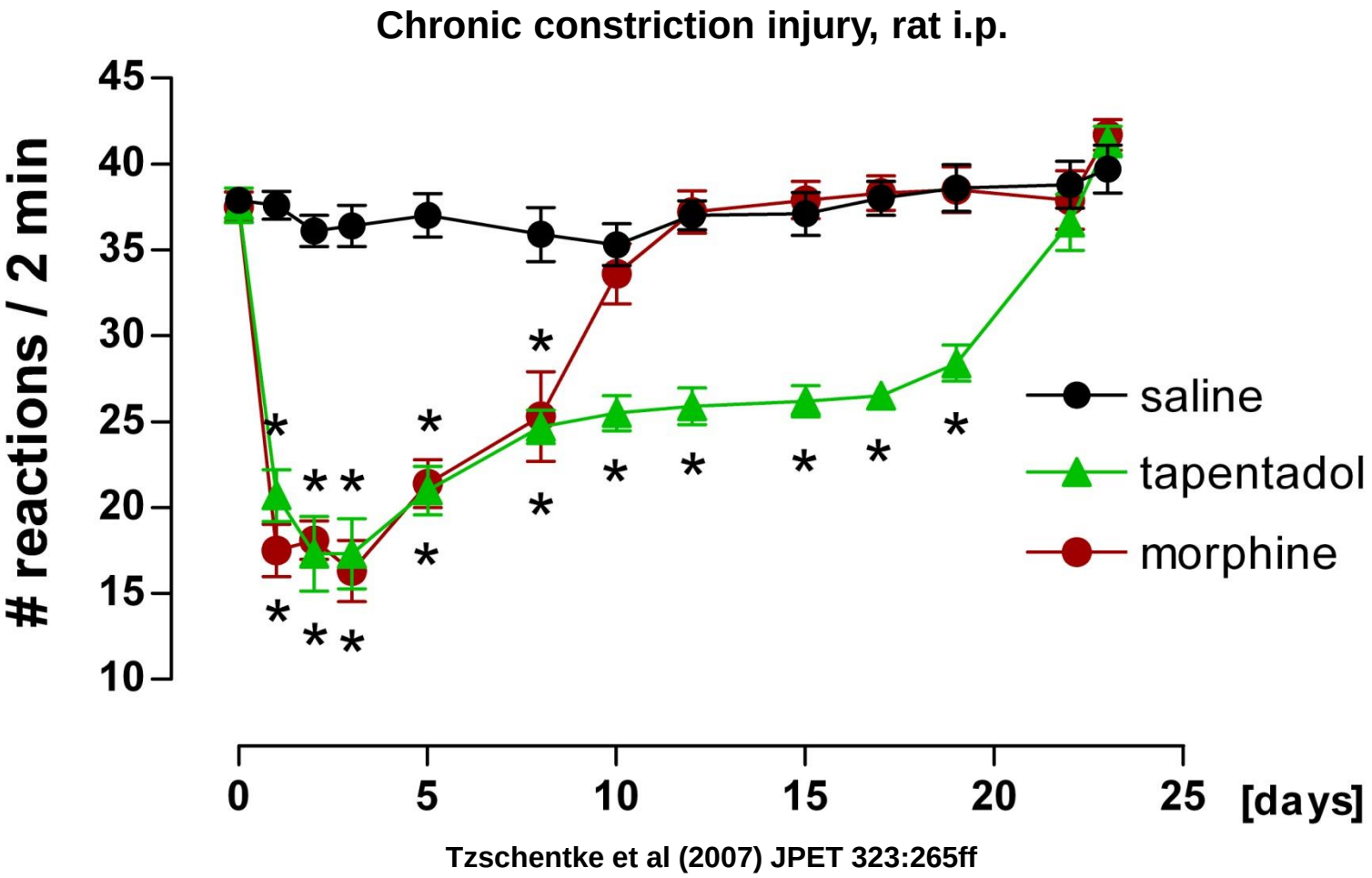
- **Increase of the intestinal charcoal passage**
- **Reduction of the PGE2 induced diarrhoe**

Opioid Induced Side Effects: Obstipation



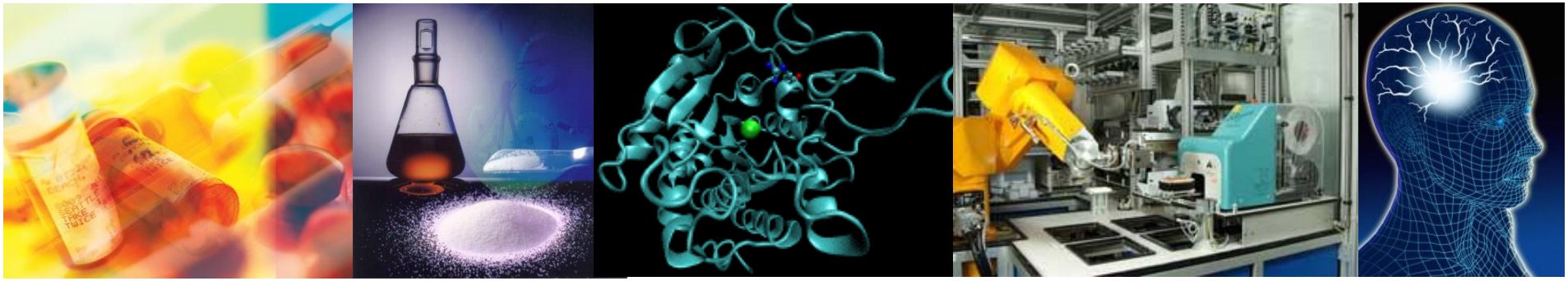
Tapentadol shows a reduced gastrointestinal inhibitory potential in comparison to Morphine

Opioid Induced Side Effects: Tolerance Development



Tzschentke et al (2007) JPET 323:265ff

Significant reduced tolerance development



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

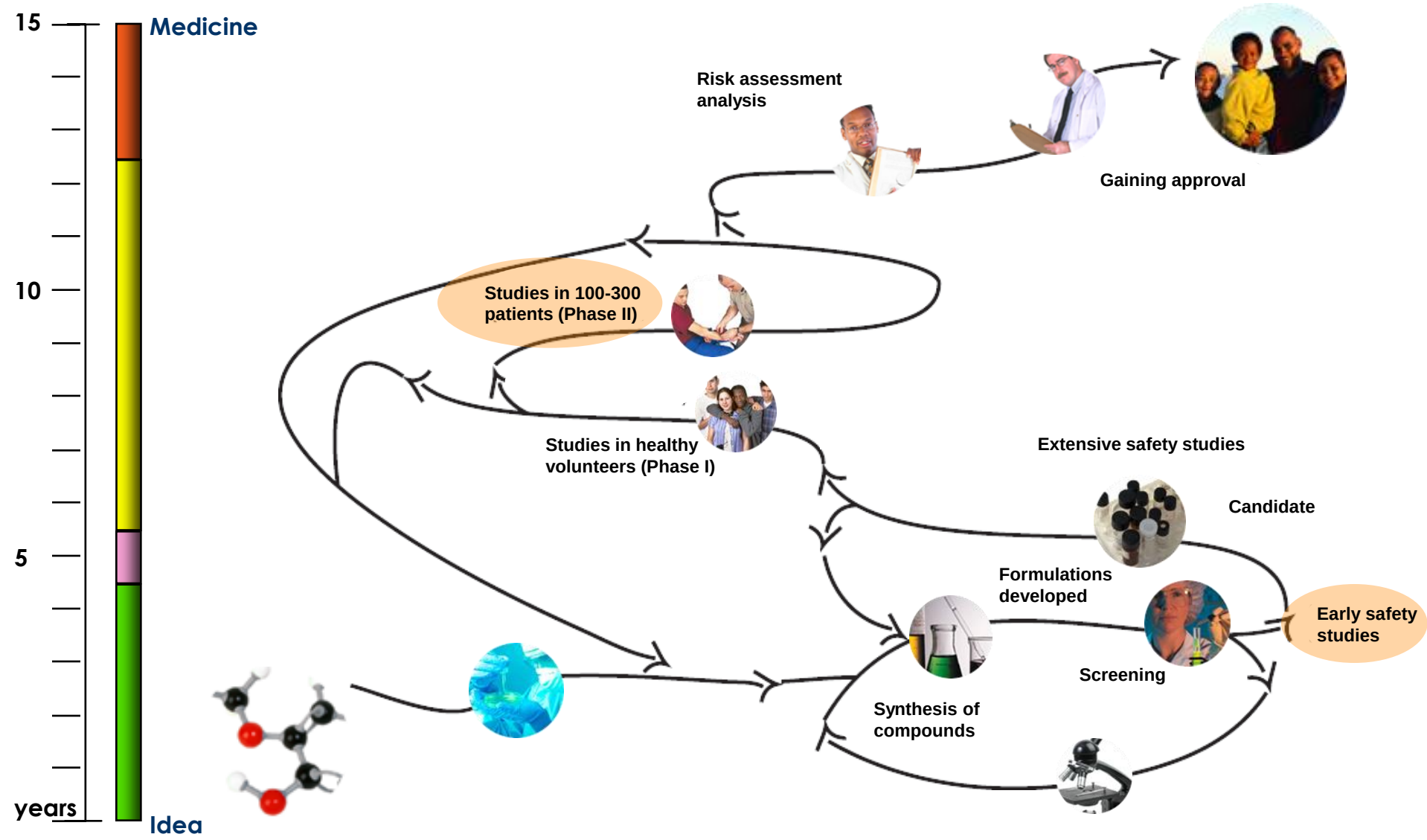
New Drug Development: Some Facts

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

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

Pharmaceutical Industry – The R & D Process

Creating New Medicines is a High Risk Journey

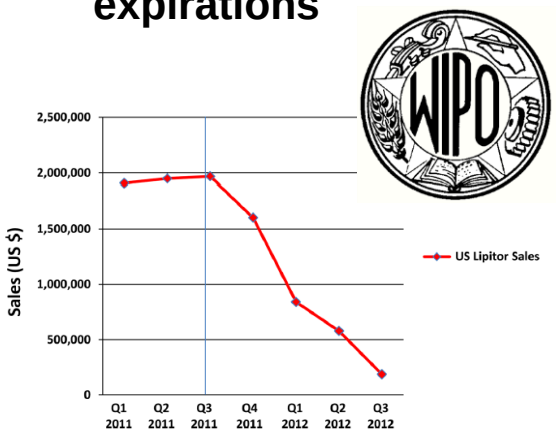


Commonly Perceived Criticisms of the Pharmaceutical Industry

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*

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.

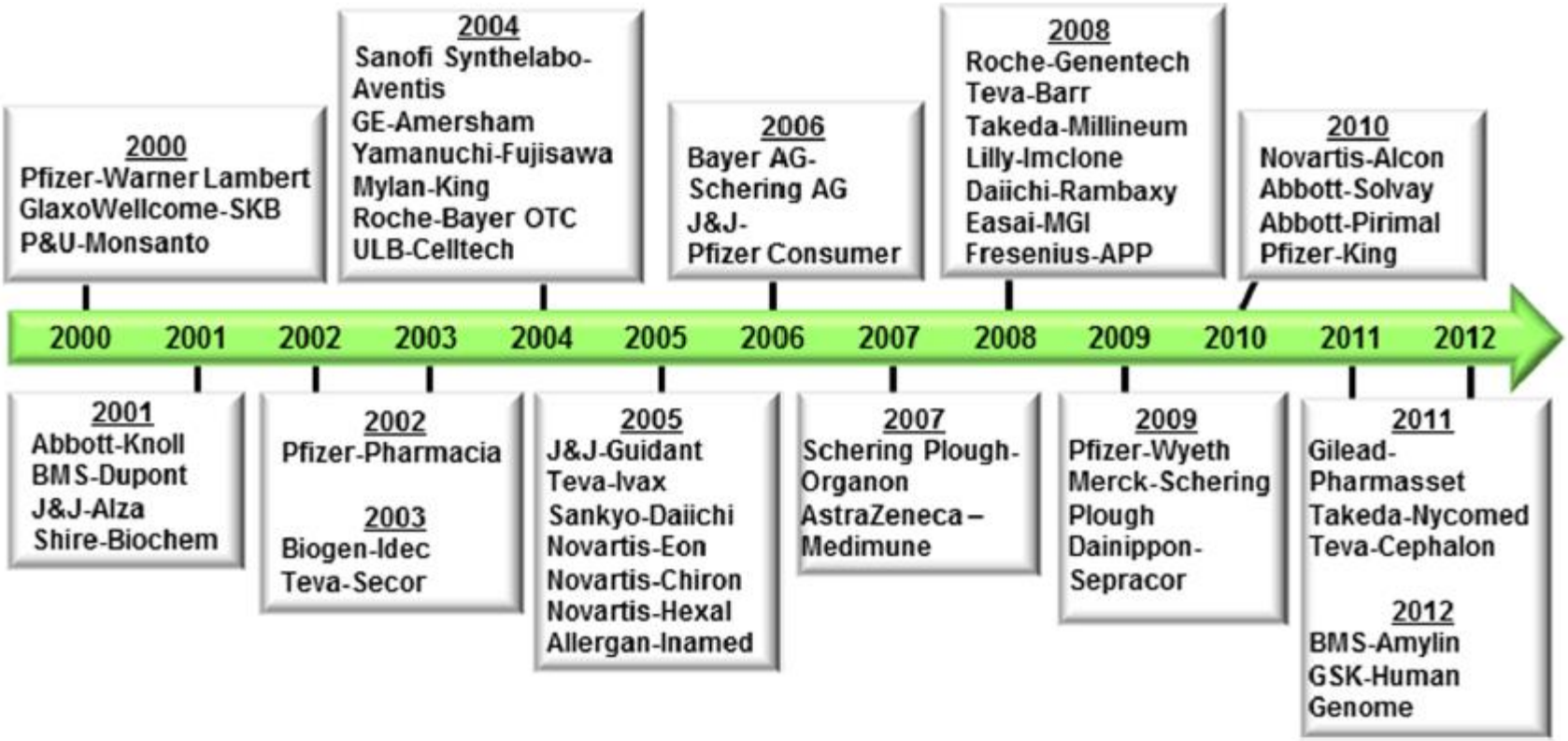
- The traditional blockbuster model is more or less outdated;

- 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

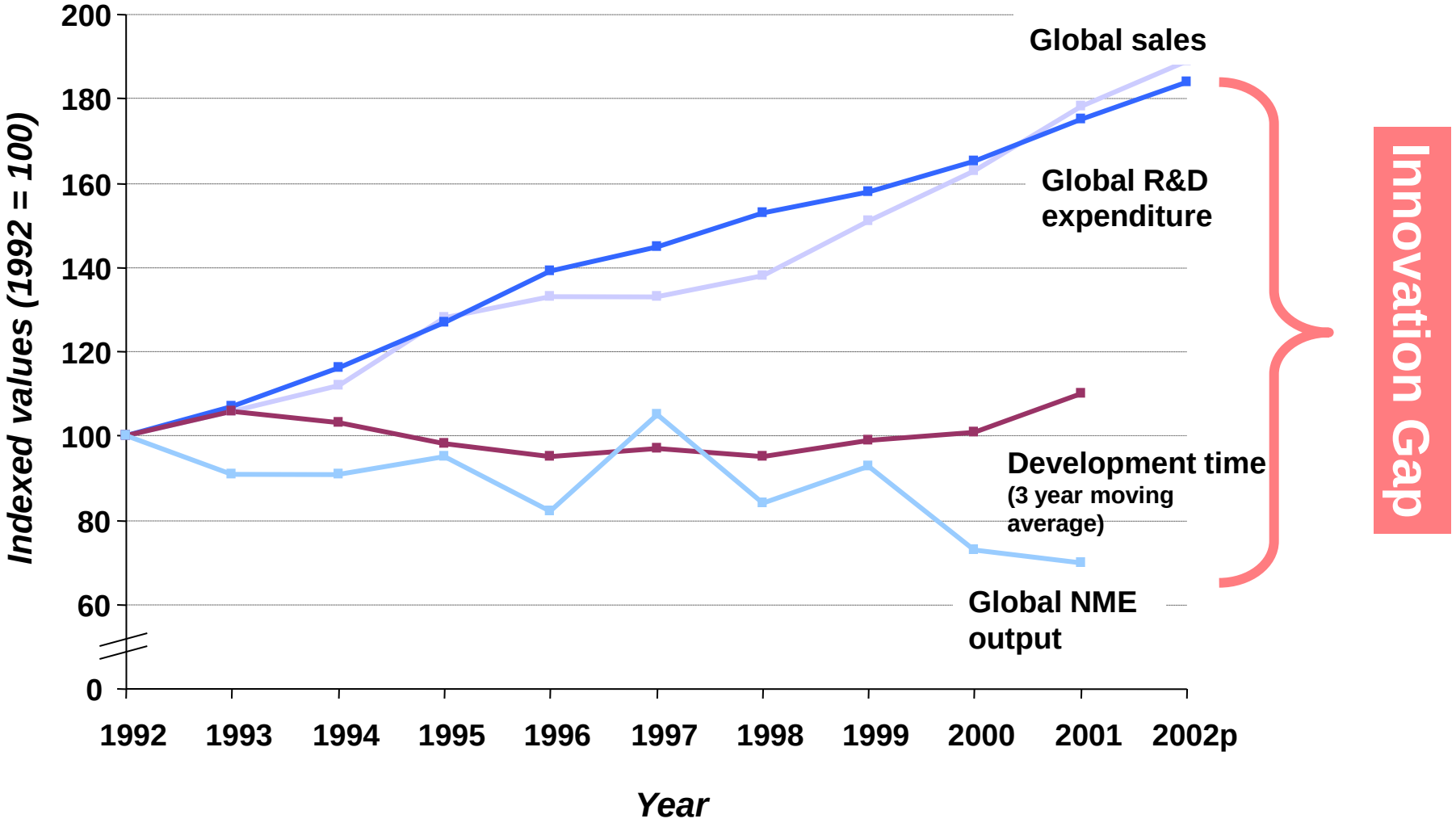
year	brand name	2010 sales (billions of dollars)[b]	company
2011	Actos®	4.6	Takeda
2011	Zyprexa®	5.0	Eli Lilly
2011	Lipitor®	12	Pfizer
2012	Levaquin®	1.4	Janssen
2012	Lexapro®	3.5	Forest
2012	Seroquel®	5.6	AstraZeneca
2012	Plavix®	9.1	BMS[c]/ Sanofi
2012	Singulair®	5.4	Merck
2012	Diovan®	6.1	Novartis
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)

Pharmaceutical Industry – Productivity

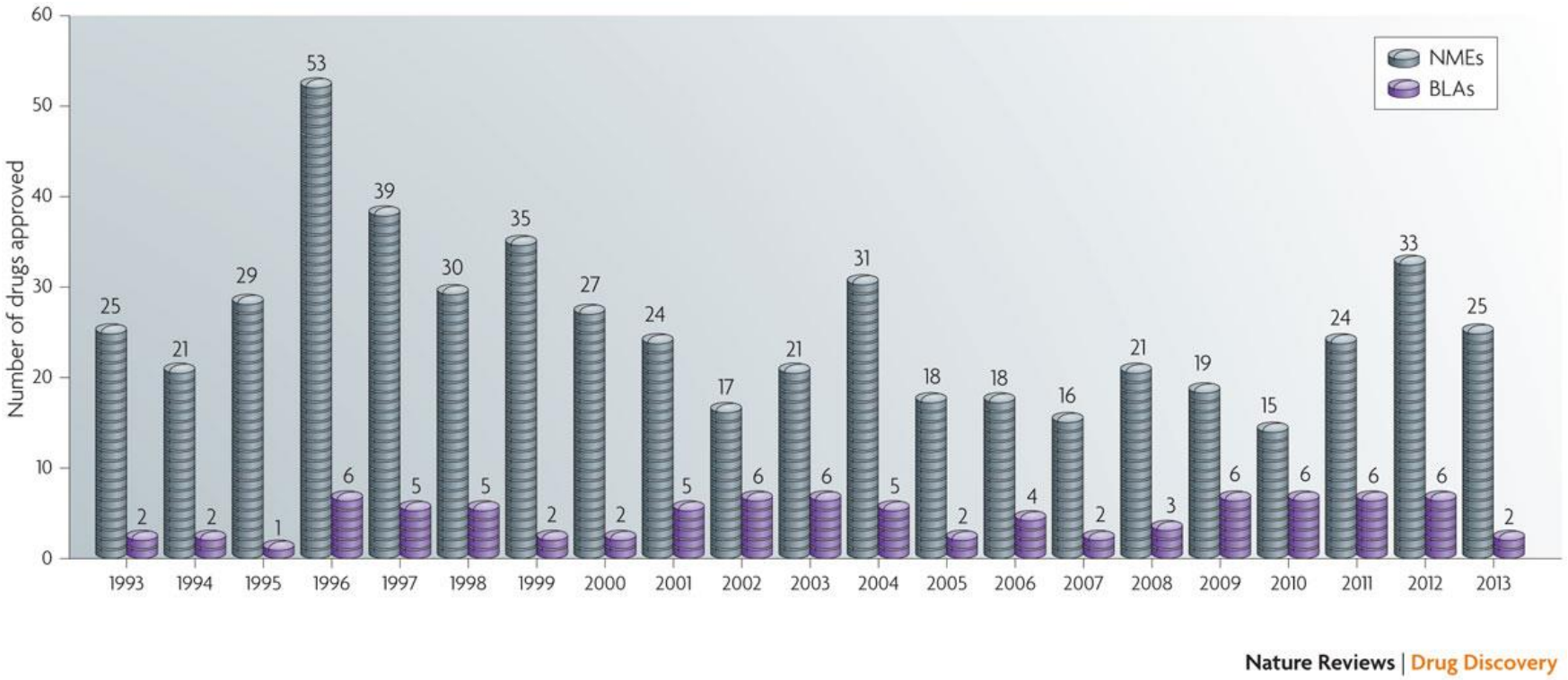
Global pharmaceutical R&D expenditure, development time, NME output and sales 1992-2002p



Pharmaceutical Industry – Productivity

FDA drug approvals since 1993.

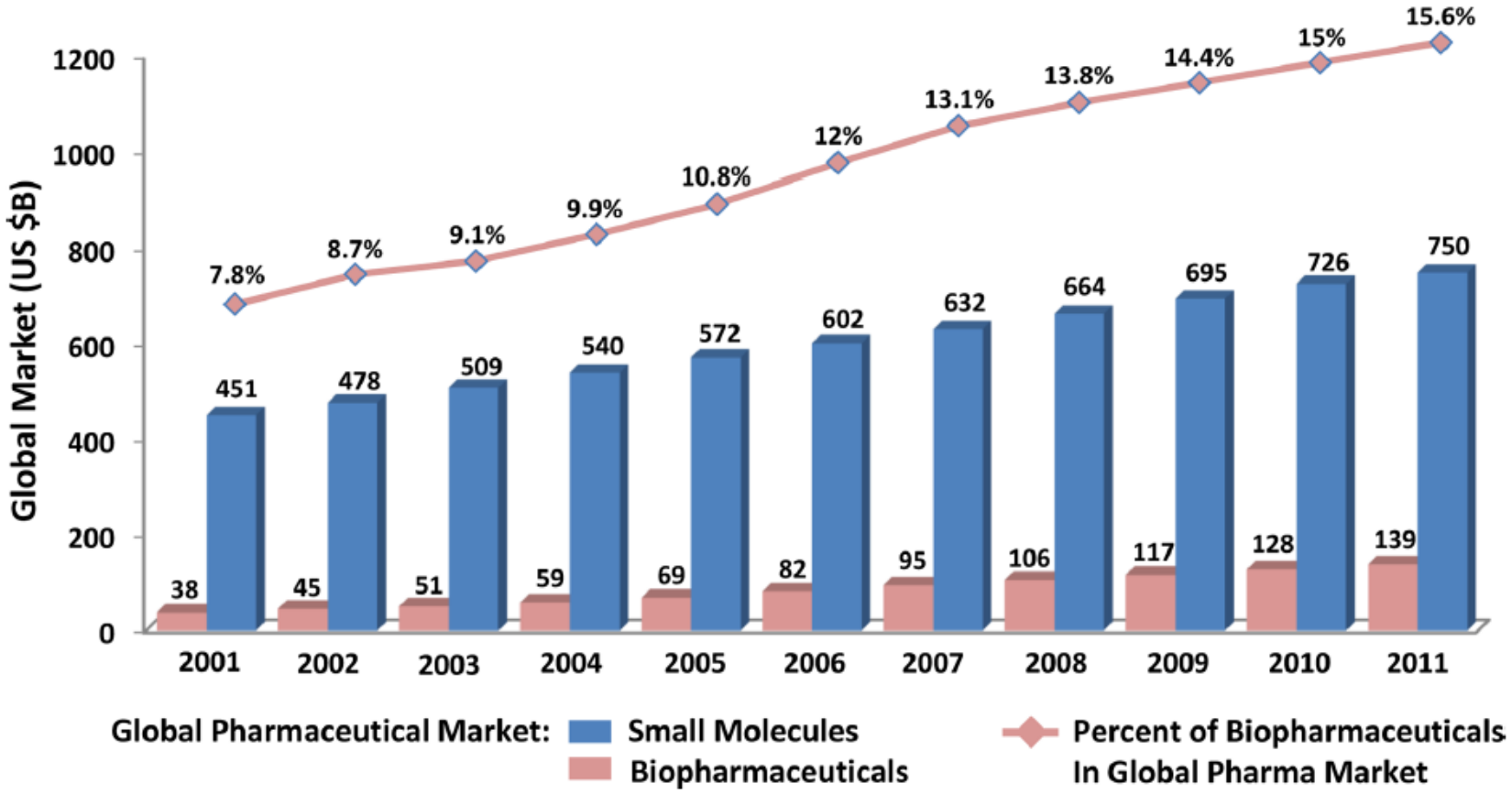
New molecular entities and biologics license applications approved by the US Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research, by year.



Nature Reviews Drug Discovery13, 85–89 (2014)

Pharmaceutical Industry – Productivity

Percentage of biopharmaceuticals in the pharmaceutical market, 2001–2011

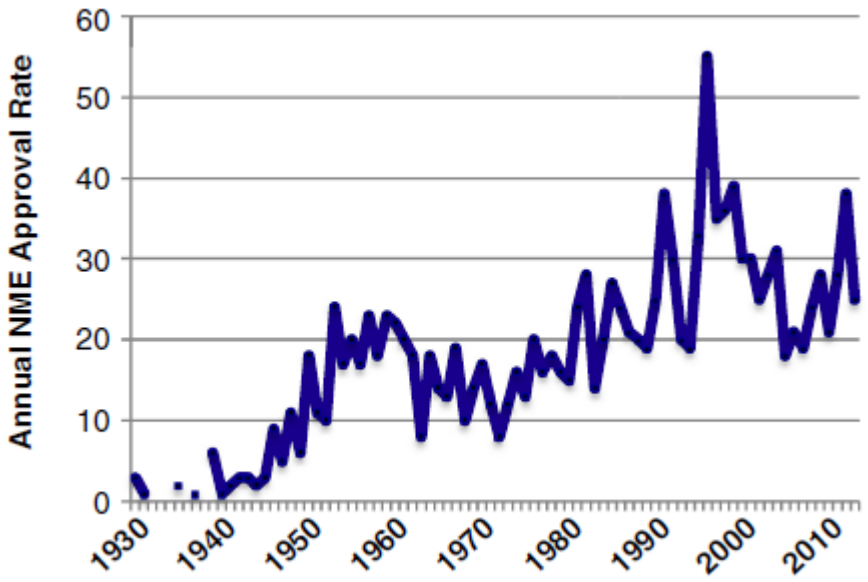


Magid Abou-Gharbia and Wayne E. Childers, Discovery of Innovative Therapeutics: Today's Realities and Tomorrow's Vision. 2. Pharma's Challenges and Their Commitment to Innovation, J. Med. Chem 57, 5525–5553 (2014)

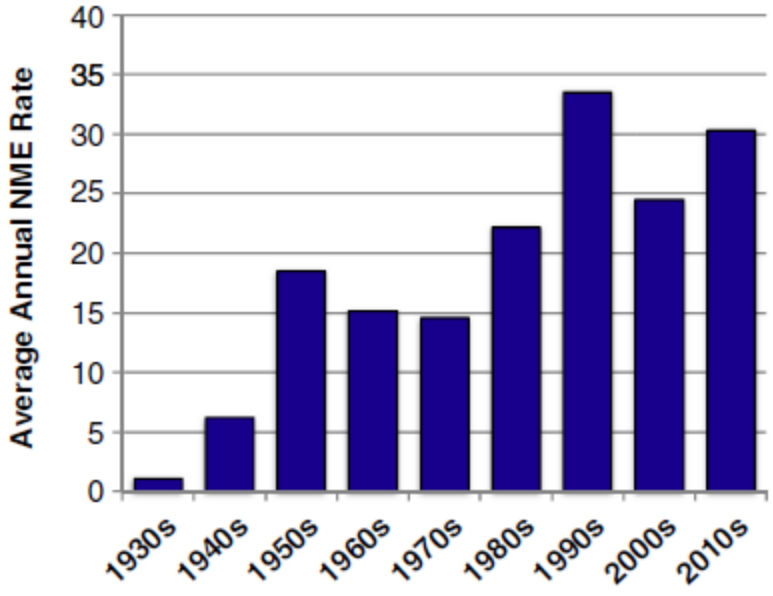
Pharmaceutical Industry – Productivity

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

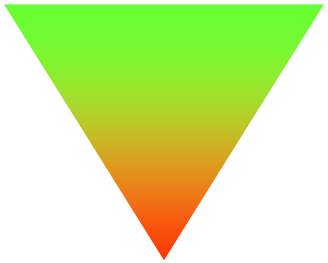


M.S. Kinch, S. L. Kinch, D. Hoyer, An overview of FDA-approved new molecular entities: 1827–2013
Drug Discovery Today 19, 1033-1039 (2014)

Pharmaceutical Industry - 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

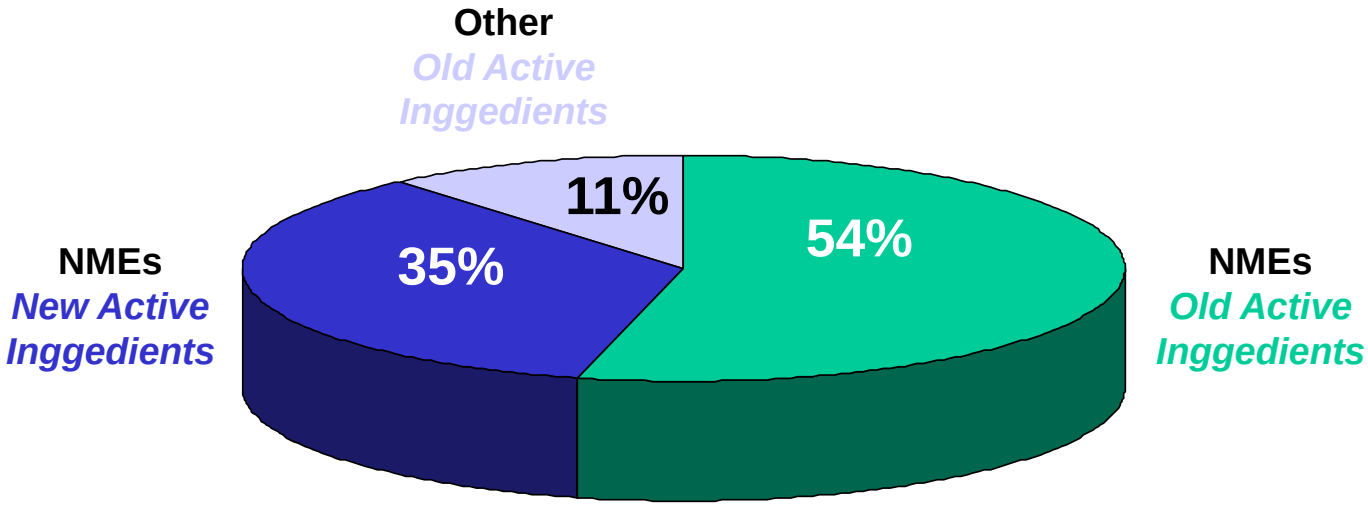
“New drugs to treat and cure sick patients are coming into the market in the United States at the slowest rate in a decade, despite billions invested by pharmaceutical companies on research and a costly expansion by the federal agency that”

“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*)

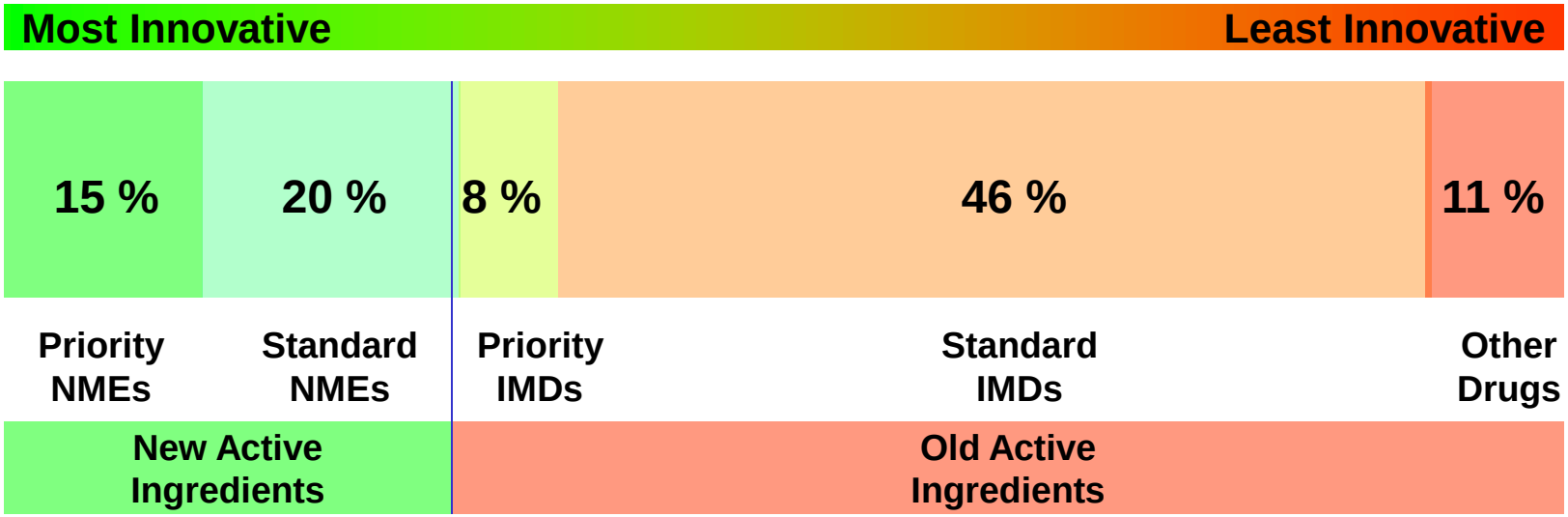


Two-third of new drugs approved in 1989-2000 used active ingredients already on the market
Source: FDA 2001

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

Pharmaceutical Industry - Innovation

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



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

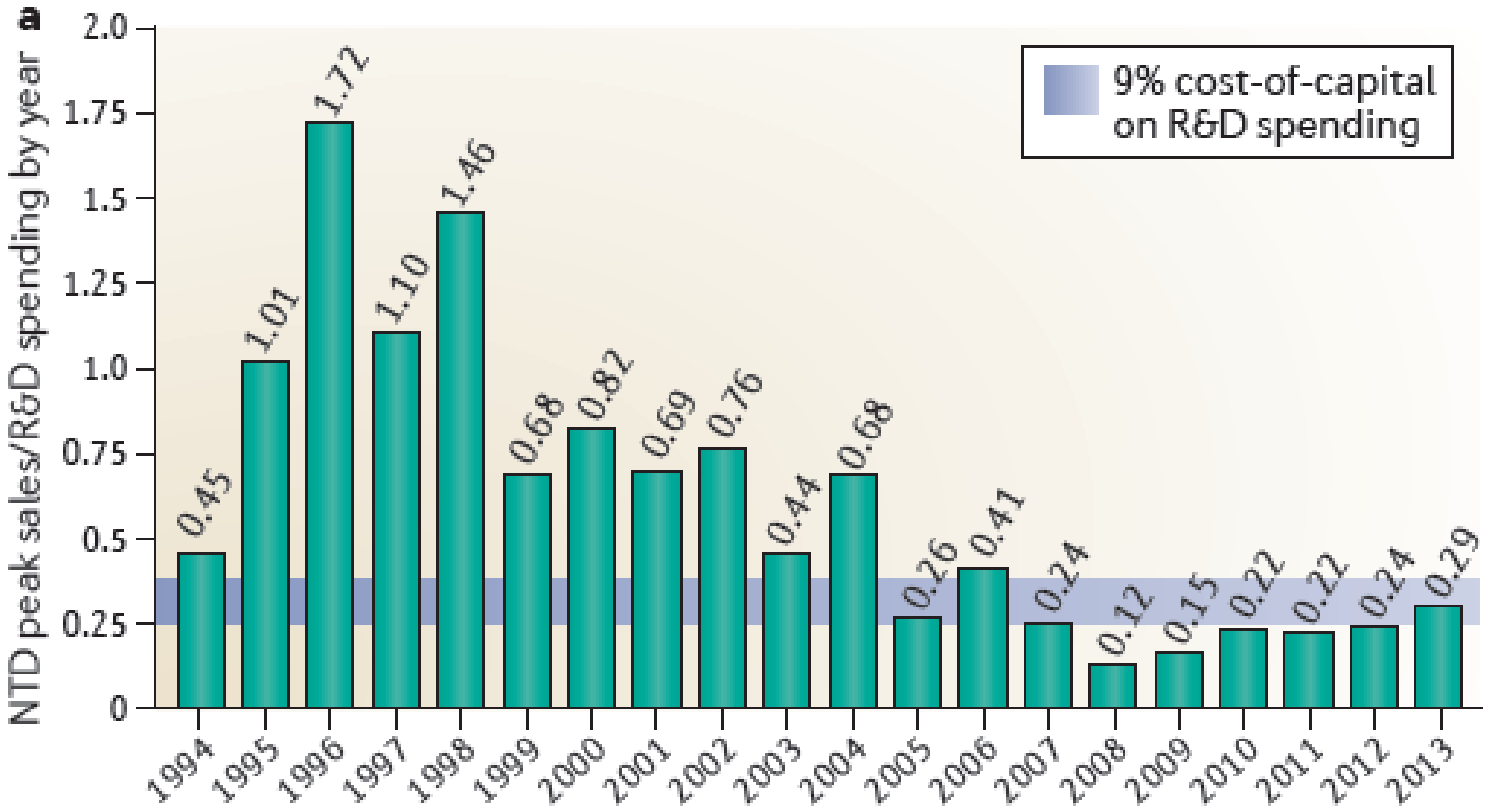
Only 15 % of new drugs approved in 1989-2010 were highly innovative priority NMEs
Source: FDA 2001

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

Pharmaceutical Industry - Innovation

R&D Productivity

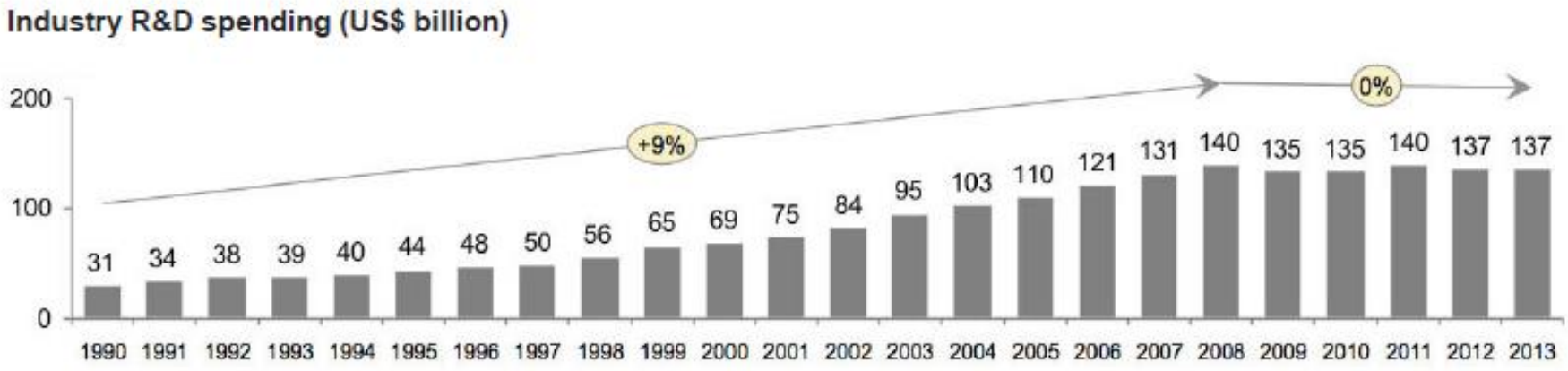
R&D Productivity Data



U. Schulze, M. Baedeker, Yen Ting Chen, D. Greber, R&D productivity: on the comeback trail, Nature Reviews Drug Discovery 13, 331–33, (2014)

R&D Productivity

Aggregate industry spending on research and development



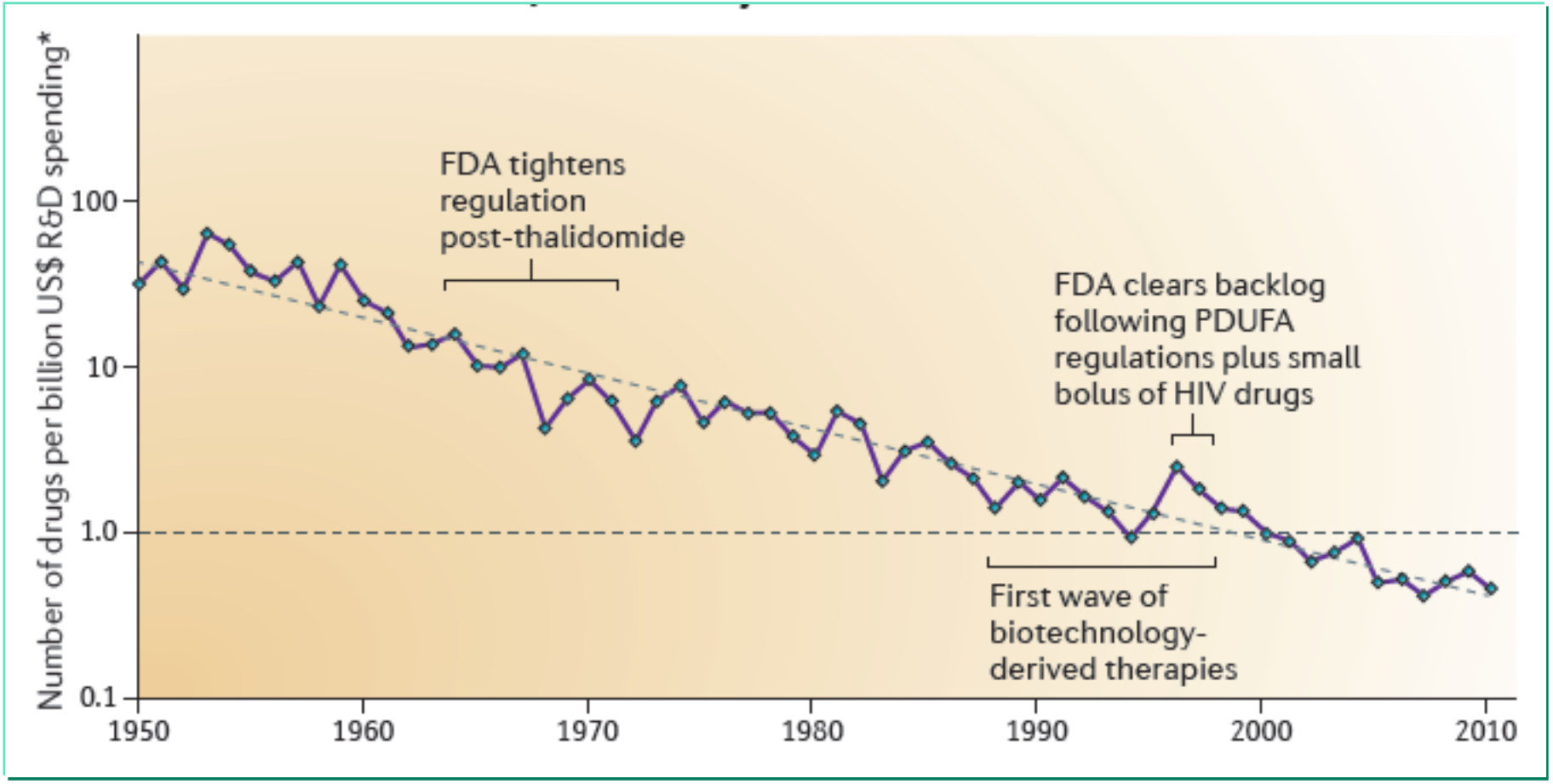
All values inflation adjusted to 2013.
Sources: EvaluatePharma; US Food and Drug Administration (FDA); Boston Consulting Group (BCG) analysis

U. Schulze, M. Baedeker, Yen Ting Chen, D. Greber, R&D productivity: on the comeback trail, Nature Reviews Drug Discovery 13, 331–33, (2014)

Pharmaceutical Industry – Changing Climate

Eroom's Law in pharmaceutical R&D.

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

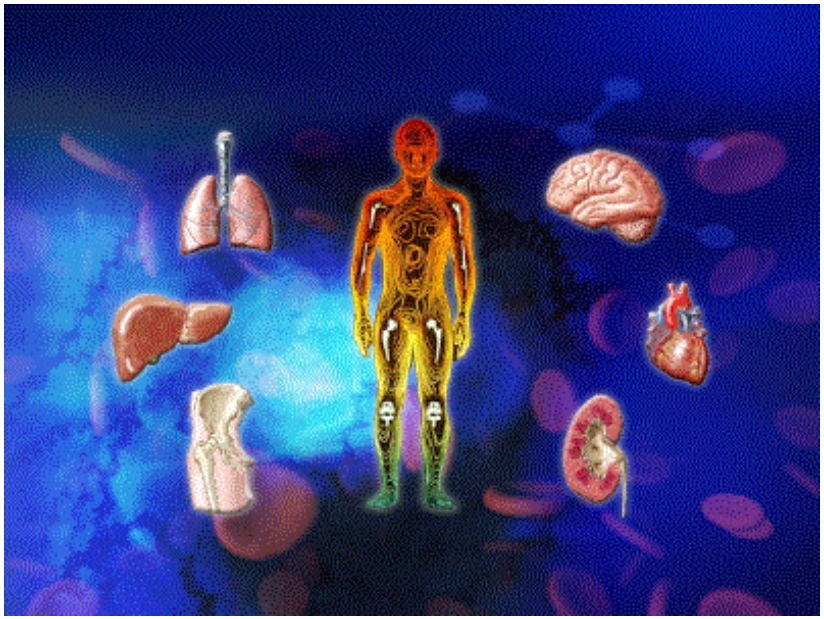


The number of new drugs approved by the US Food and Drug Administration (FDA) per billion US dollars (inflation-adjusted) spent on research and development (R&D) has halved roughly every 9 years.

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.

The Changing Climate in Pharmaceutical Research

The human body is complex



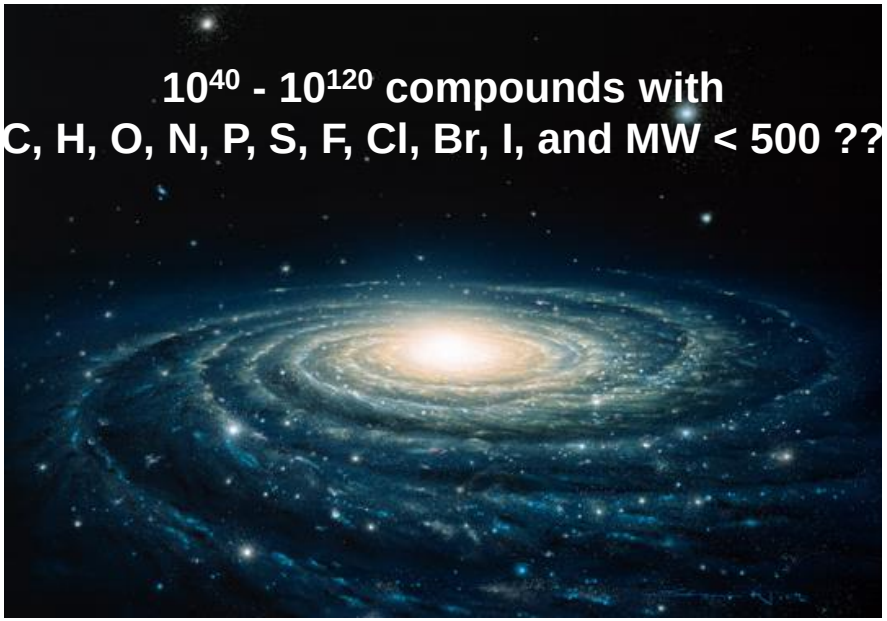
100 organs,
1500 different cell types,
10.000 diseases

- **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

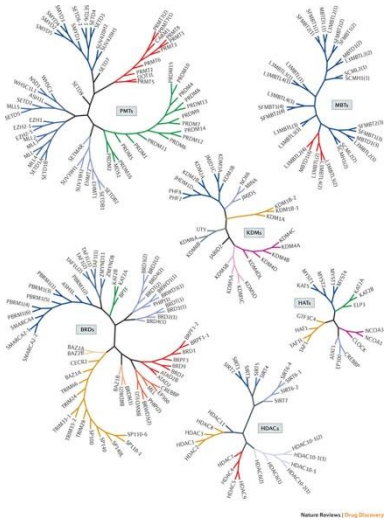
Pharmaceutical Industry – The R & D Process

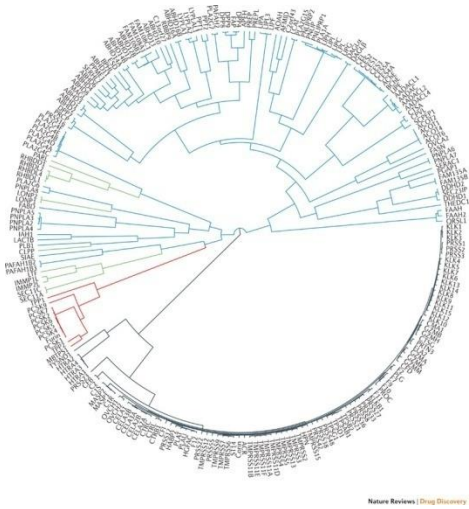
Chemogenomics

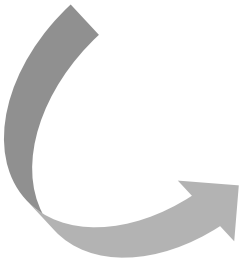
Cemical Universe

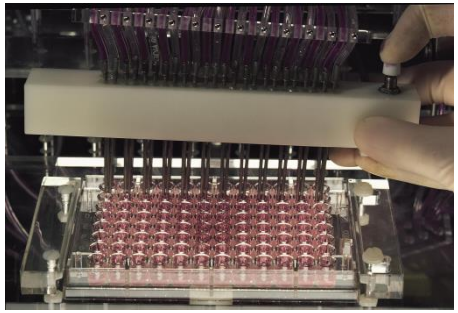


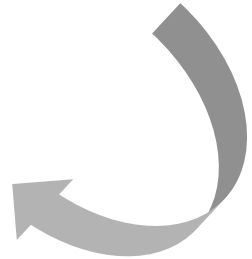
Target Universe



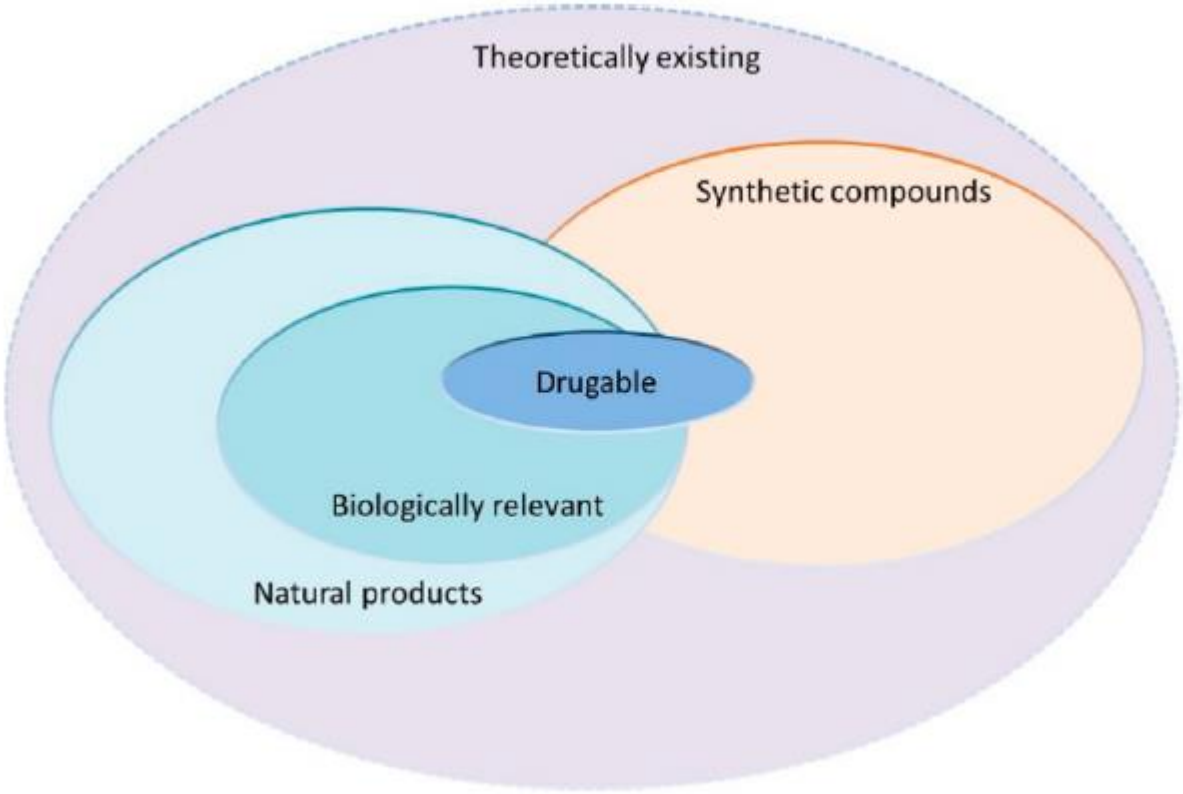








Venn diagram of the distribution of commonly used libraries in chemical space



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

Technological Inputs into Drug Research & Development

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




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

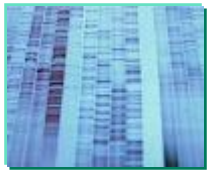
100 compounds per chemist per year

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

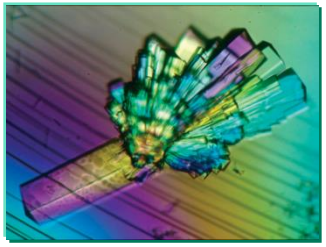
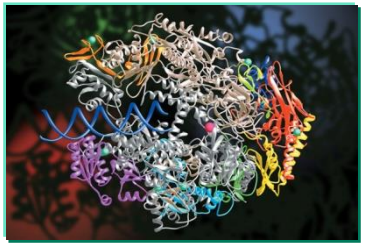
Genomics

x 1.000.000.000 faster

Technological Inputs into Drug Research & Development

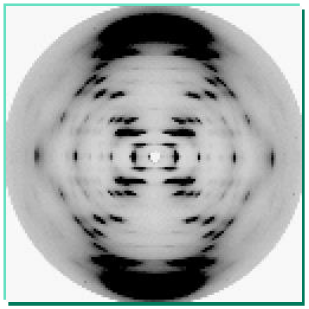
X-ray Crystallography



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

1st Protein X-ray Structures



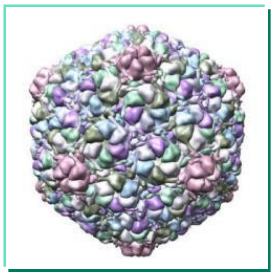
Structure-Based Design

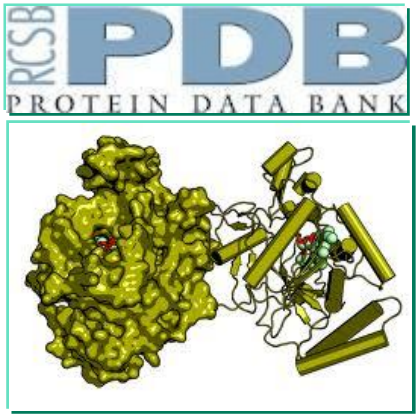
x 1.000 faster calculation

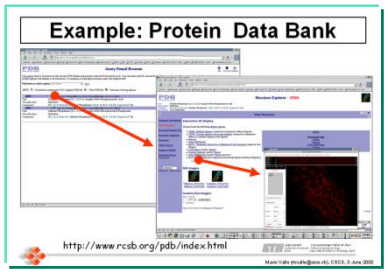
R & D Performance: Drug Discovery Technologies

Technological Inputs into Drug Research & Development

Three Dimensional Protein Structures



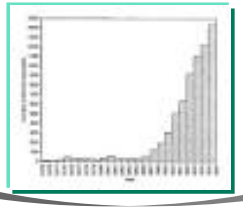




1970s | 1980s | 1990s | 2000s | 2010s

Some 100s Structures

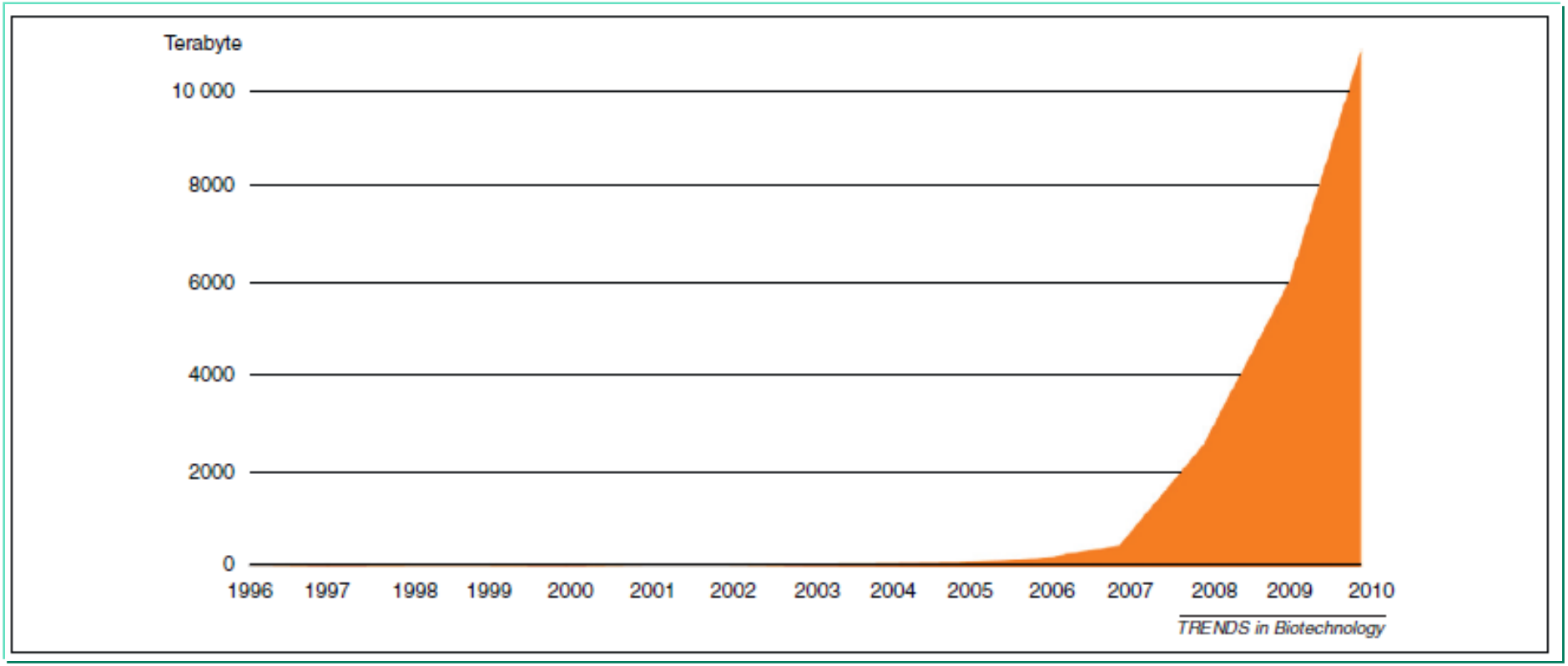
> 50.000 Structures



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).

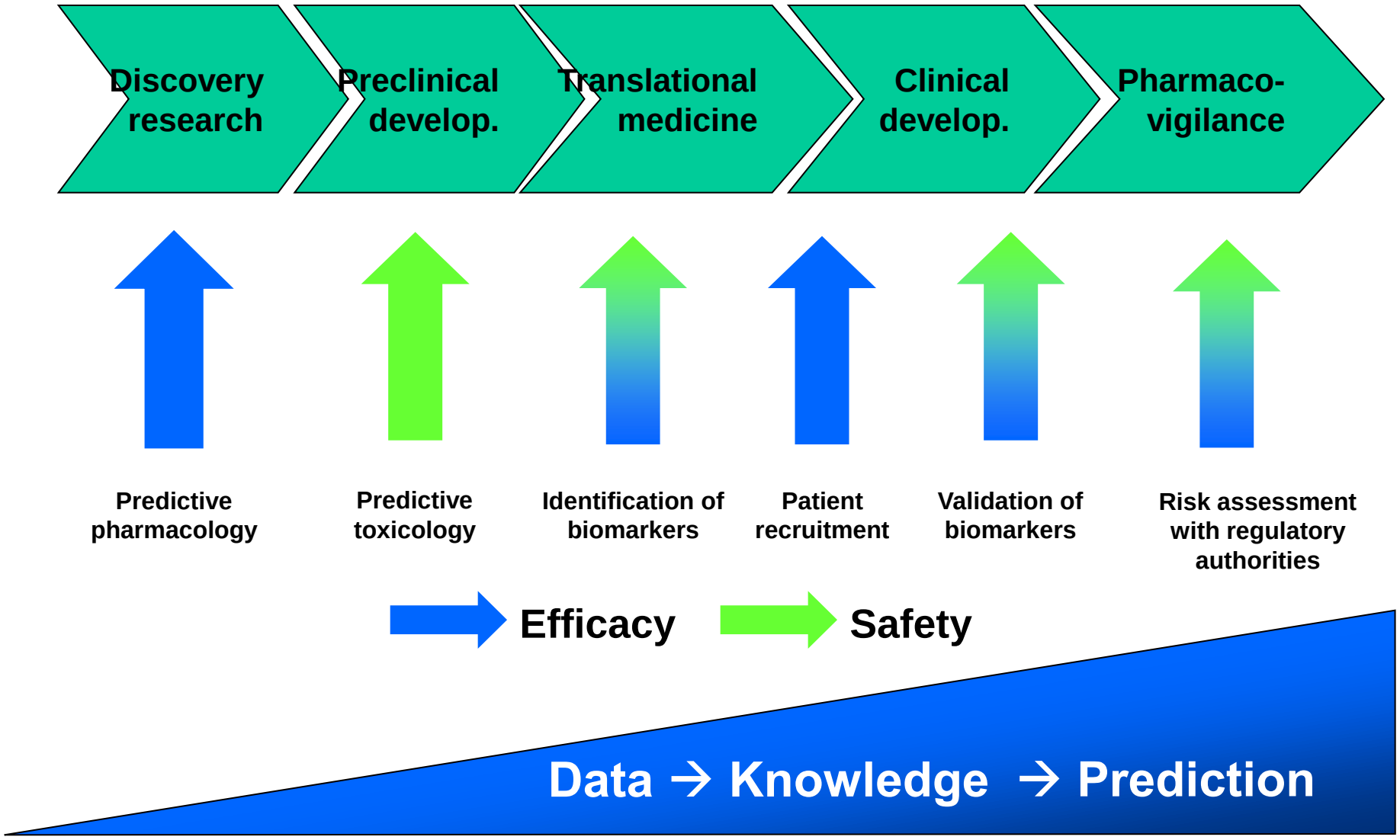
Potential outcome of new technologies

- 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

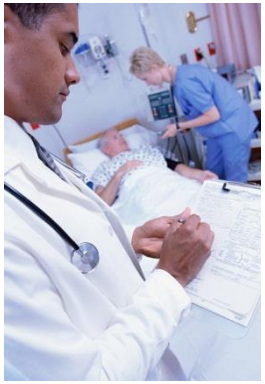
Pharmaceutical Industry – The R & D Process

Key R&D bottlenecks to overcome



EFFICACY in Pharmacology

TRANSLATIONAL MEDICINE



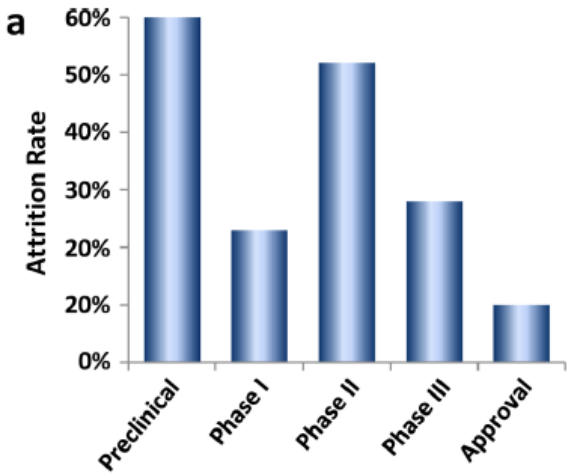
Preclinical models that are more predictive of clinical efficacy and safety

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

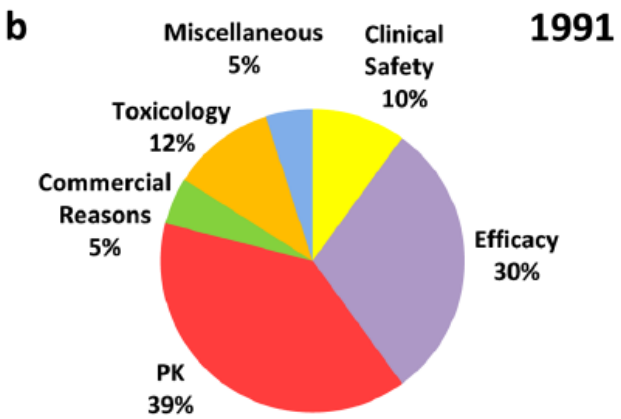
Nothing

Clinical attrition statistics

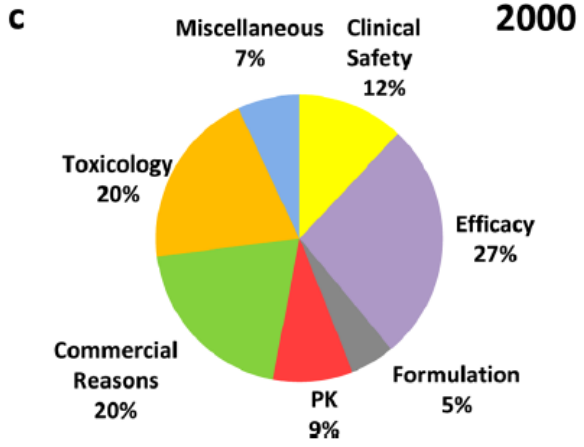
Attrition rate by stage of development



Reasons for clinical failure in 1991



Reasons for clinical failure in 2000



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 – The R & D Process

Drug Research was and is…

…the Search for a Needle in a Haystack

Pharmaceutical Industry – The R & D Process

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

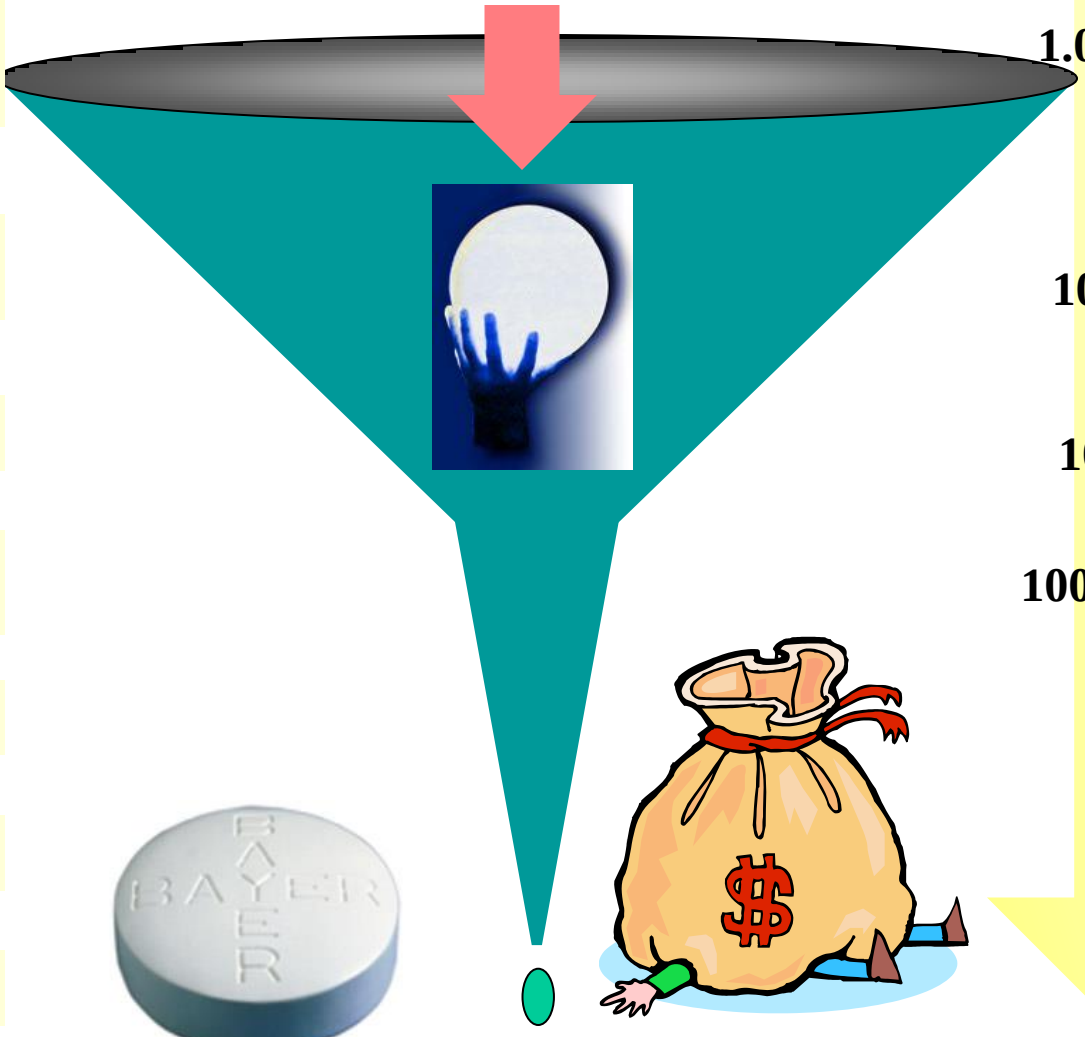
An optimized lead is no candidate

A candidate is not a drug

A drug is not a success

A successful drug is luck!

10^{100} Chemical Space of Organic Molecules



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10s

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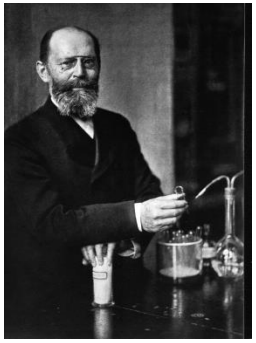
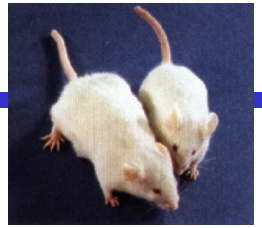
Pharmaceutical Industry – The R & D Process

The Evolution of Drug Discovery Strategies

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





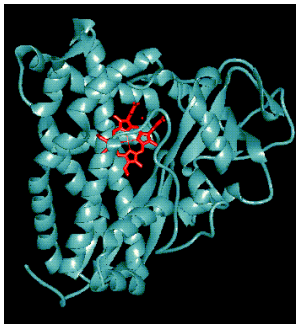
1900

- *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

- Progress in biochmistry and
- Structural biology

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



1985

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

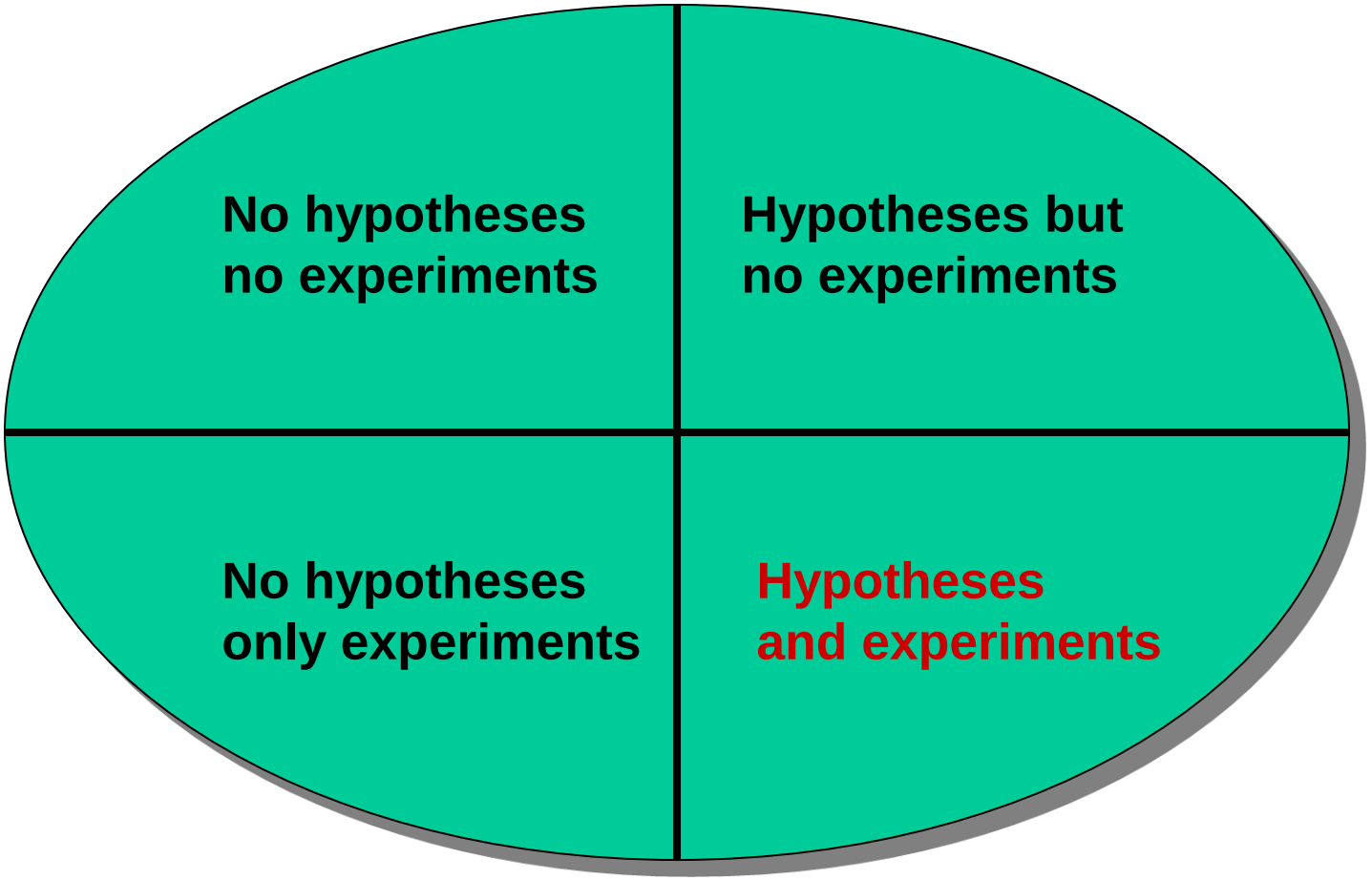
- High throughput screening programs

1995

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

- screening of > 100.000 compounds/day
- timeconsuming and expensive process
- Many hits and too few leads
- low diversity of many libraries: large series of similar in house cpds, chemical catalog series,...
- low drug likeness

Four Possible Strategies in Research



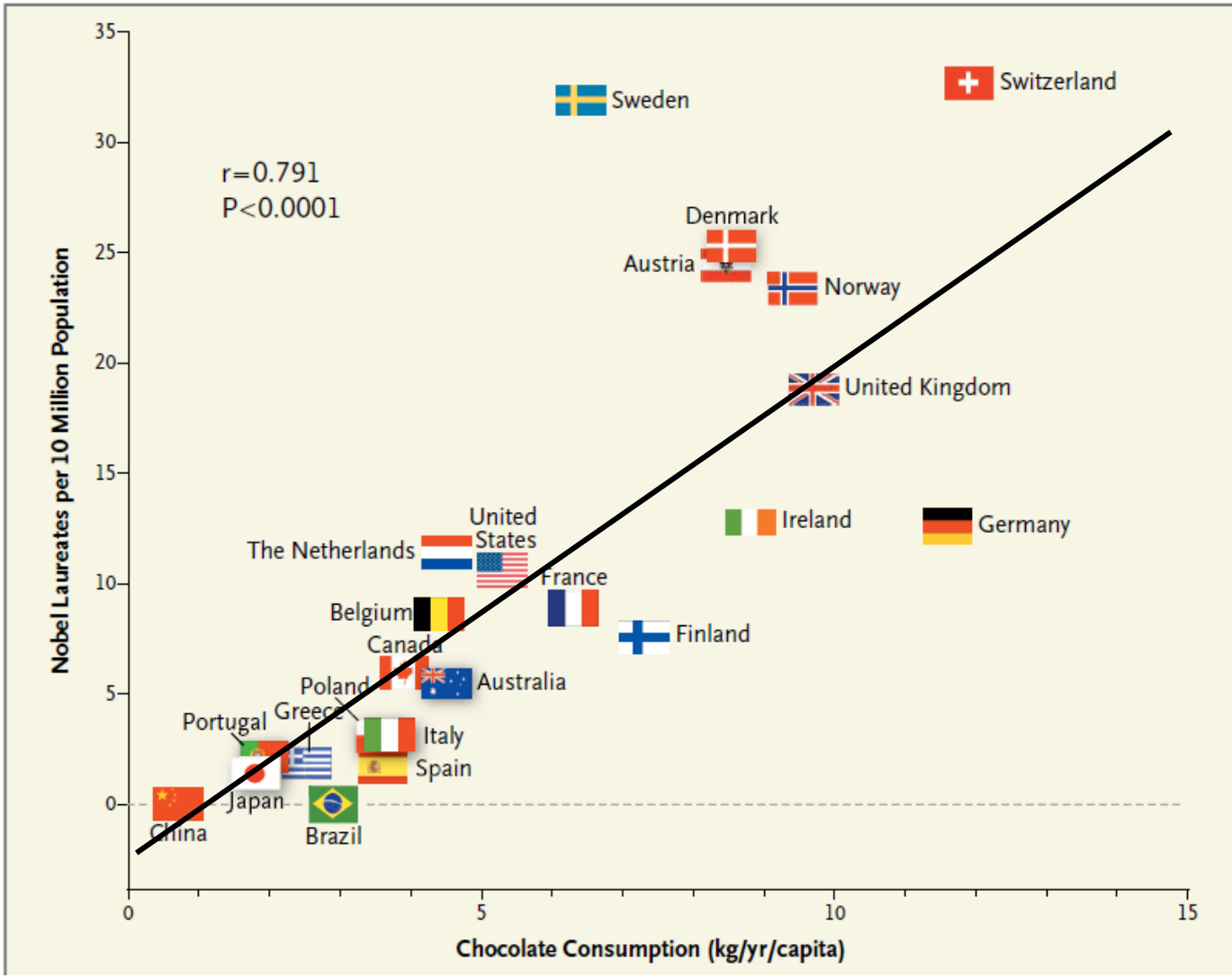
Rolf Zinkernagel (Nobel prize in Medicine 1996)

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,

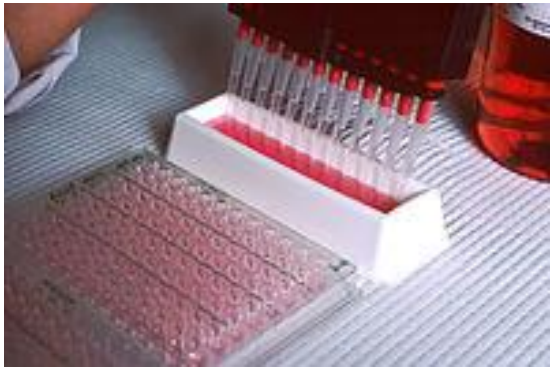
and it closely correlates with the number of Nobel laureates in each country.



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

The early days of drug discovery at Grünenthal (1990)

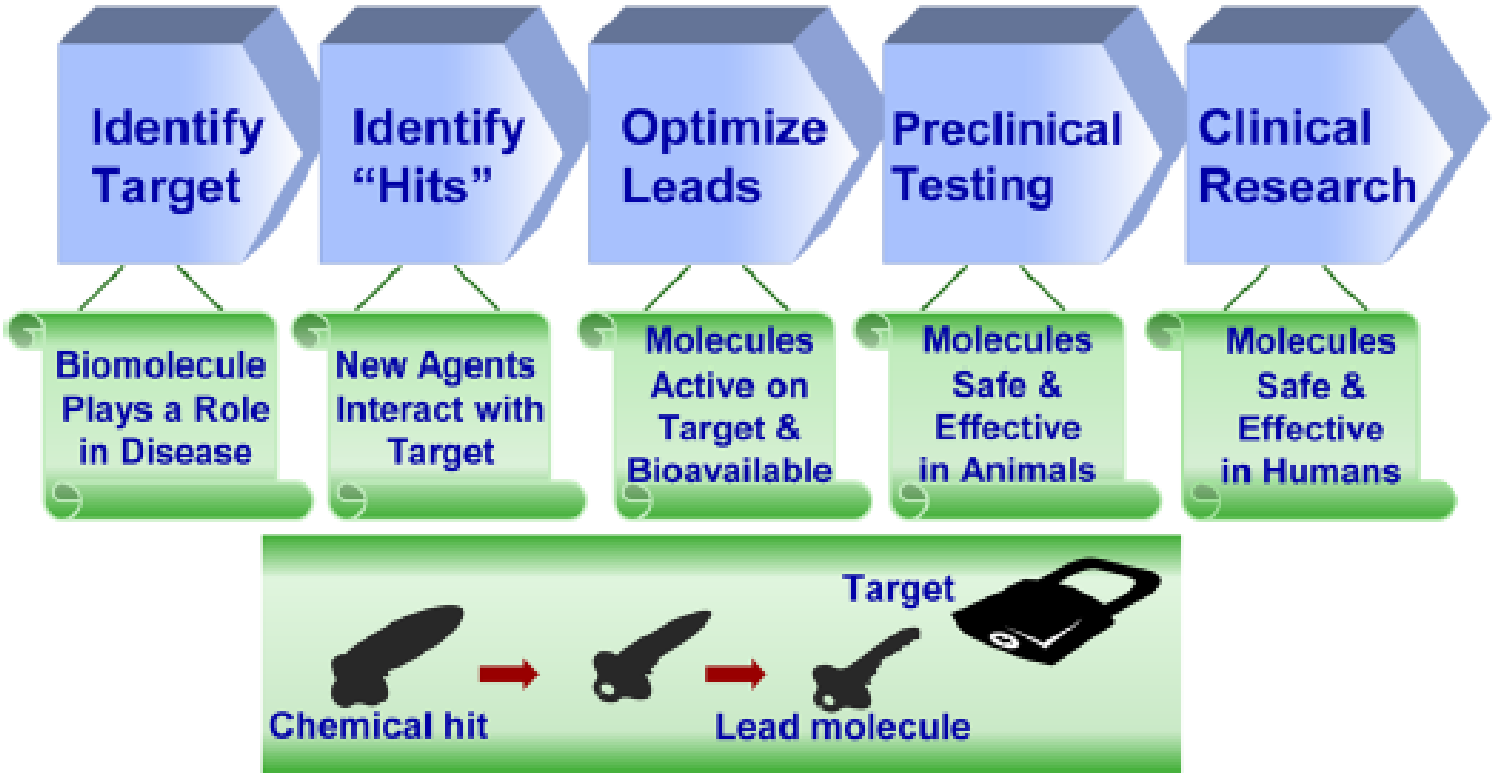
***in vivo* activity**
Writhing Mouse
ED_{50}, oral



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

Pharmaceutical Industry – The R & D Process

Drug discovery process



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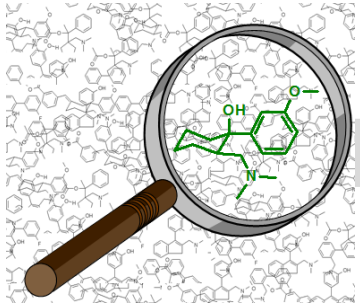
Advantages of early *in vivo* testing

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

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

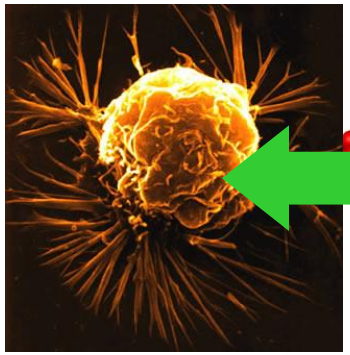
- *Focus on building disease models - for many years an area neglected in favour of for instance multi-chemistry.*
- *Use modern integrated screening directly on animals, including both behaviour and various analyte parameters.*
- ***Synthesize carefully selected substances and test them all on animals.***

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.

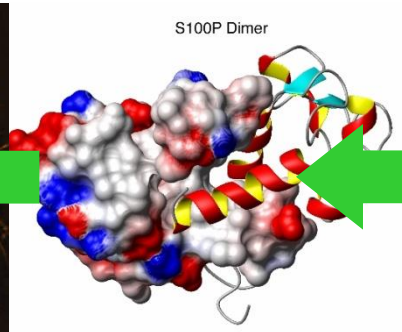
The Future of Medicinal Chemistry & Medicinal Chemists

in vivo Pharmacology

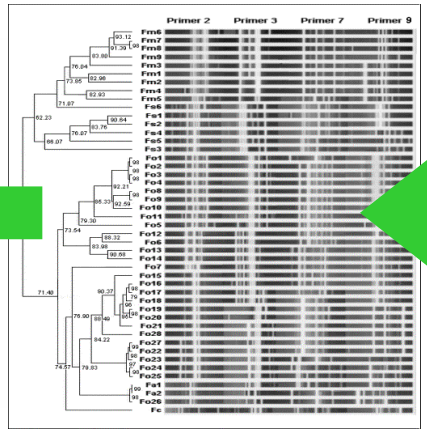
The Future of Medicinal Chemistry & Medicinal Chemists



Cell Structure and Function

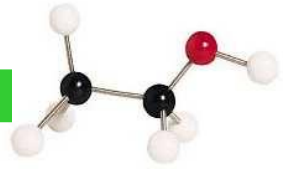


Proteine

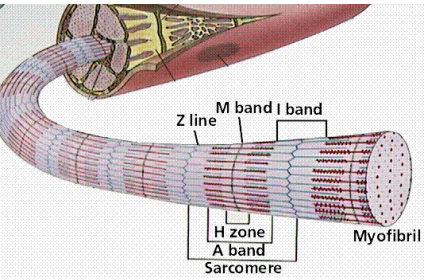


Genome

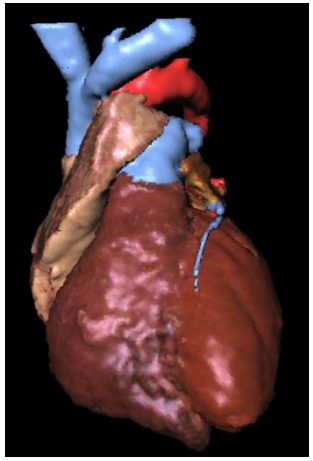
Gene



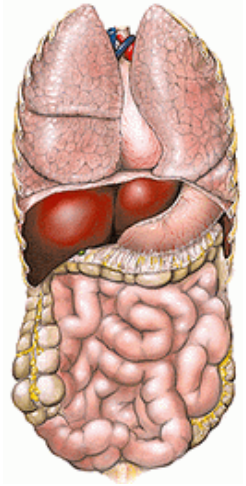
Molecule



Tissue Structure and Function



Organ Structure and Function



Organ System

Organism

The Future of Medicinal Chemistry & Medicinal Chemists

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

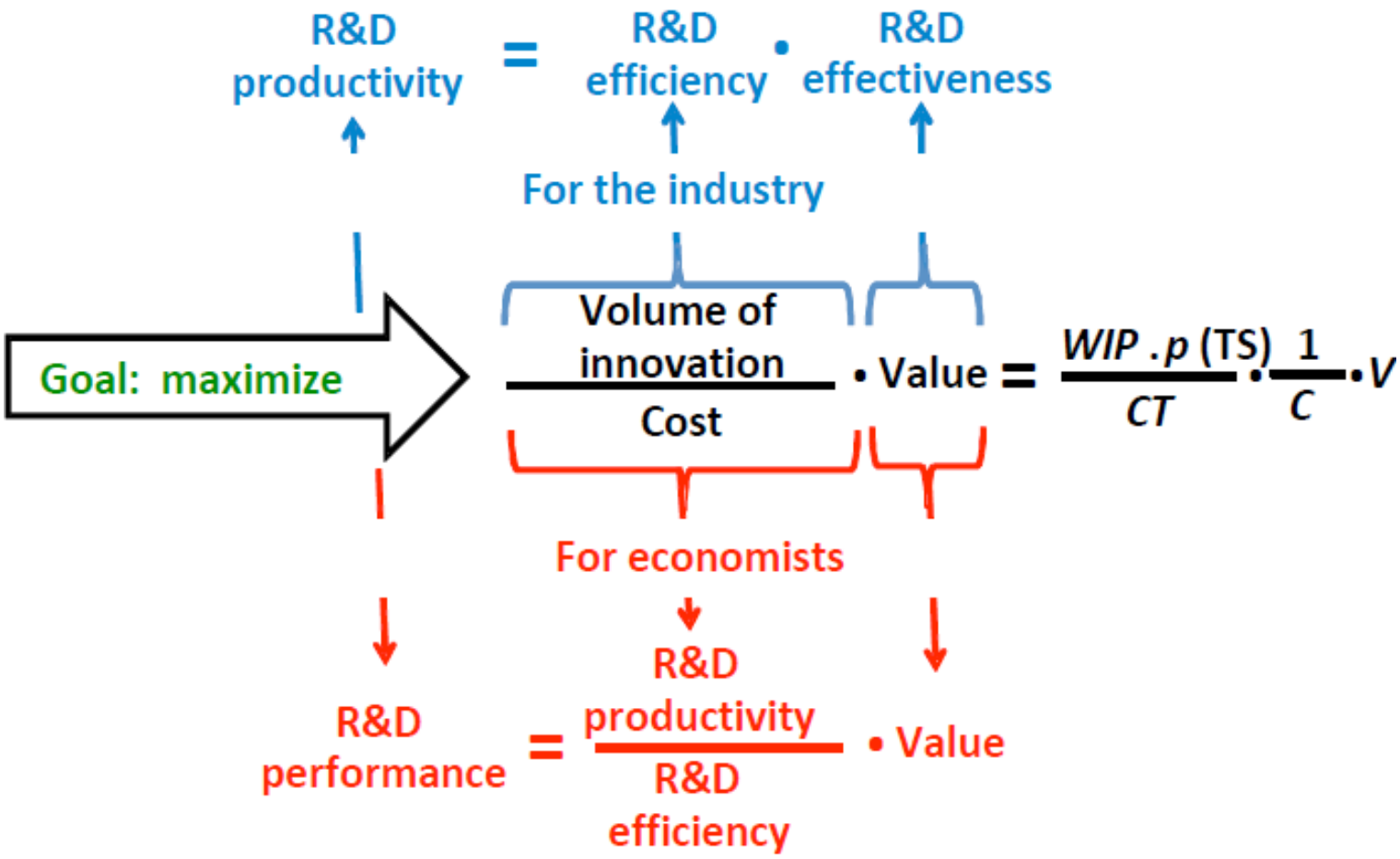
ABSTRACT: In the United States, medicinal chemists continue to face job insecurity and high rates of unemployment. The situation is unlikely to improve in the near future. Is there a light at the end of the tunnel? Is there anything we can do to revitalize our community? The answer may be right in front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

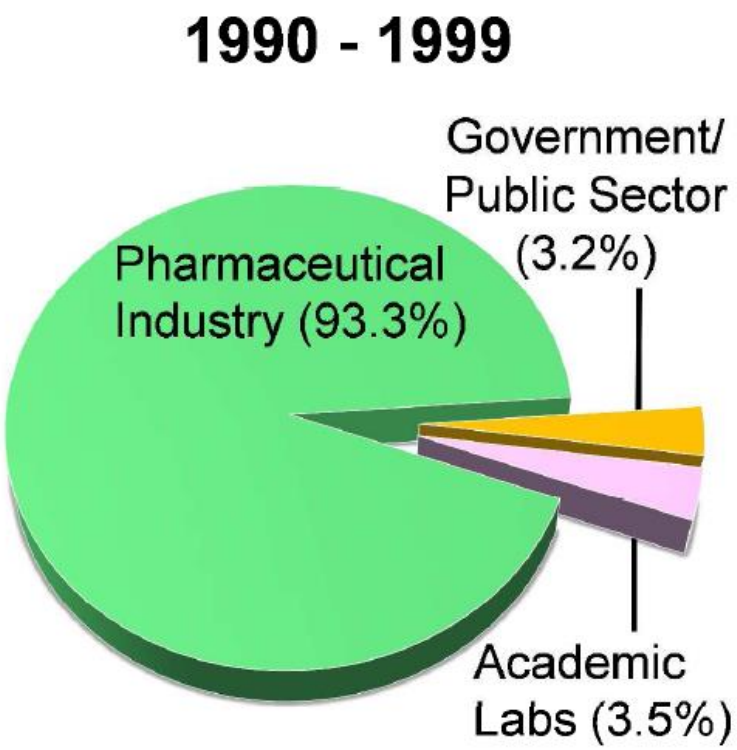
- …Steve Jobs once said, "*When you grow up, you tend to get told that the world is the way it is, and your life is just to live your life inside the world. Try not to bash into the walls too much. Try to have a nice family life. Have fun, save a little money*."
- Computers and drugs are not quite the same, but his statement captures the current mind-set of many medicinal chemists…

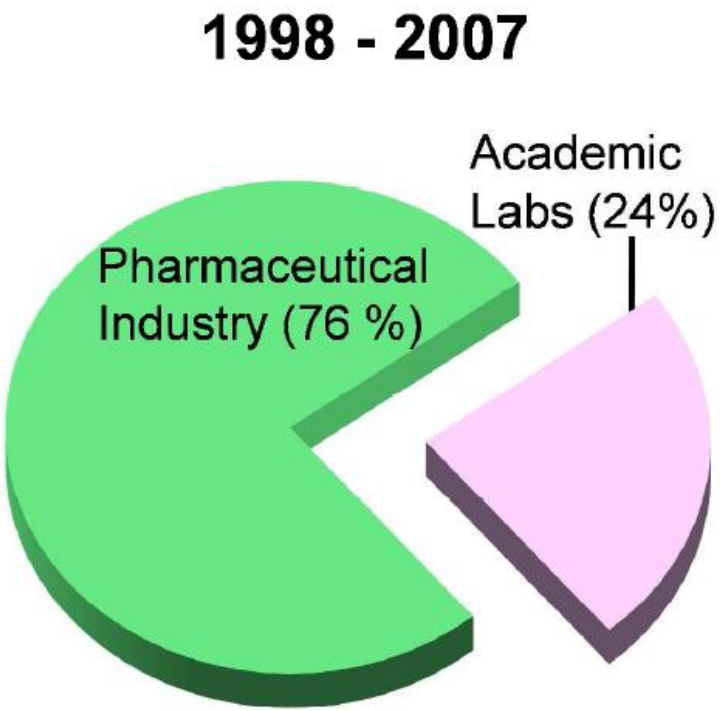
Takashi Tsukamoto, Tough Times for Medicinal Chemists: Are We to Blame?, ACS Med. Chem. Lett. 2013, 4, 369−370

R&D Performance and Productivity



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)