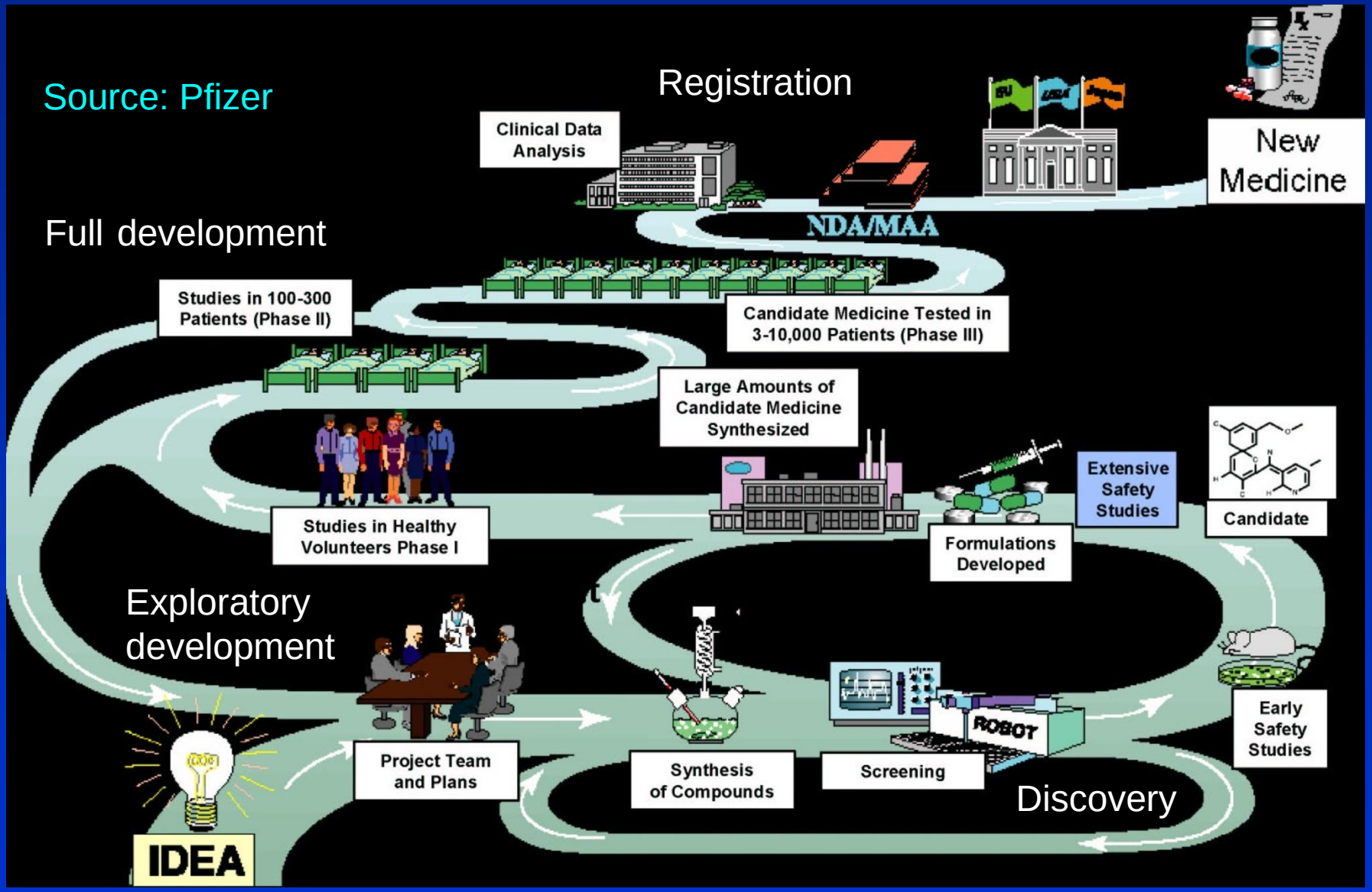
Adapt and Survive: the Changing Face of R&D in the Pharmaceutical Industry and its Impact on Cheminformatics

Dr. Wendy A. Warr

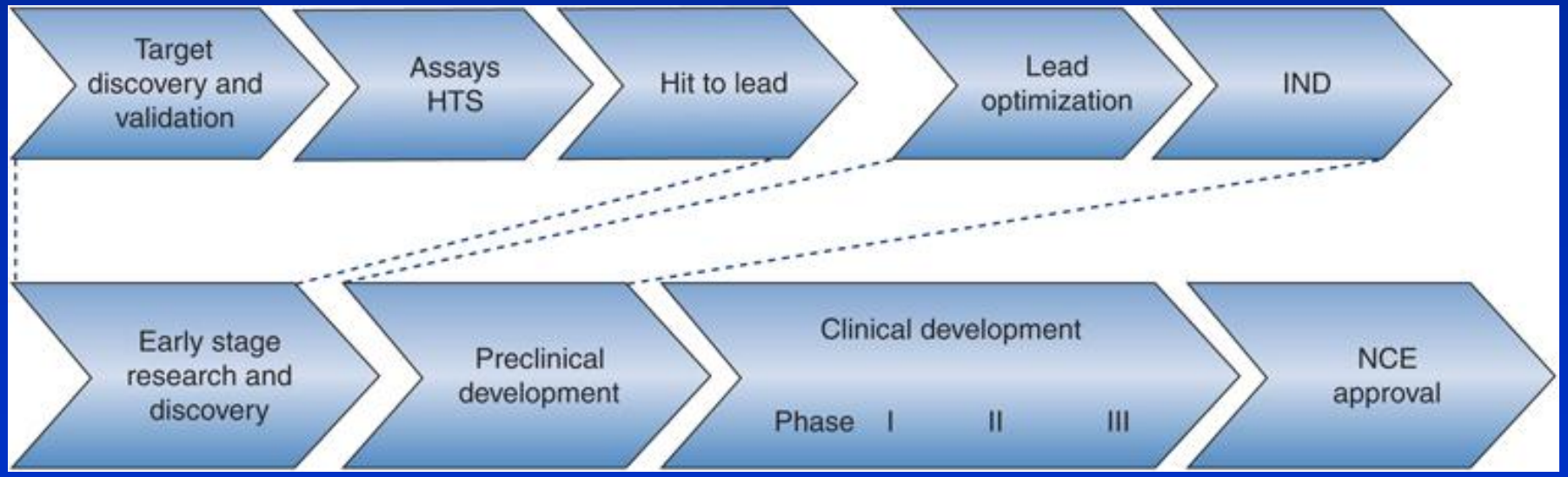
http://www.warr.com

The Long Road to a New Medicine



Wendy Warr & Associates

Drug Discovery and Development



US005723765A

United States Patent [19]

Oliver et al.

[11] Patent Number: 5,723,765

[45] Date of Patent: Mar. 3, 1998

[54] **CONTROL OF PLANT GENE EXPRESSION**

[75] Inventors: **Melvin John Oliver**, Lubbock; **Jerry Edwin Quisenberry**, Idalou; **Norma Lee Glover Trolinder**, Quanah, all of Tex.; **Don Lee Keim**, Leland, Miss.

[73] Assignees: **Delta and Pine Land Co.**, Scott, Miss.; **The United States of America as represented by the Secretary of Agriculture**, Washington, D.C.

[21] Appl. No.: **477,559**

[22] Filed: **Jun. 7, 1995**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 283,604, Aug. 1, 1994, abandoned.

[51] **Int. Cl.**[6] **C12N 15/29**; C12N 15/82; A01H 4/00; A01H 5/00

[52] **U.S. Cl.** **800/205**; 800/250; 536/24.1; 536/23.6; 536/24.5; 435/320.1; 435/240.4; 435/172.3

[58] **Field of Search** 536/24.1, 23.6, 536/24.5; 435/320.1, 240.4, 172.3; 800/205, 250

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,959,317	9/1990	Sauer	435/172.3
5,159,135	10/1992	Umbeck	800/205
5,217,889	6/1993	Ronisson et al.	435/172.3
5,231,019	7/1993	Paszkowski et al.	435/172.3
5,244,802	9/1993	Rangaa	435/240.5
5,270,201	12/1993	Richards et al.	435/240.4
5,304,730	4/1994	Lawson et al.	800/205
5,352,605	10/1994	Fraley et al.	435/240.4

FOREIGN PATENT DOCUMENTS

131623	3/1991	European Pat. Off. .
9008826	8/1990	WIPO .
9109957	7/1991	WIPO .
9403619	2/1994	WIPO .

OTHER PUBLICATIONS

Schena et al. A steroid-inducible gene expression system for plant cells. Proc. Natl. Acad. Sci. USA. vol. 88. pp. 10421–10425. Dec. 1991.

Gatz et al. Regulation of a modified CaMV 35s promoter by the TN10–encoded Tet repressor in transgenic tobacco. Mol. Gen. Genet. (1991) 227:229–237.

Bayley et al. Exchange of gene activity in transgenic plants catalyzed by the Cre–lox site–specific recombination system. Plant Molecular Biology 18: 353–361, 1992.

Galau et al. Cotton Lea4(D19) and LeaA2(D132) Group 1 Lea Genes Encoding Water Stress–Related Proteins Containing a 20–Amino Acid Motif. Plant Physiol. (1992) 99, 783–788.

Barthelemy et al. The Expression of Saporin, a Ribosome–inactivating Protein from the Plant Saponaria officinalis, in *Escherichia coli*. J. Biol. Chem. vol. 268, No. 9, p. 6546548, Mar. 1993.

Lanzer, Michael and Bujard, Hermann. "Promoters largely determine the efficiency of repressor action." *Proc. Natl. Acad. Sci. USA*, 85: 8973–8977 (1988).

Araki, Kimi et al., *Site–specific recombination of a transgene in fertilized eggs by transient expression of Cre recombinase*, Proc. Natl. Acad. Sci. USA. 92(1):160–164 (1995).

Medberry, Scott L., et al., *Intro–chromosomal rearrangements generated by Cre–lox site–specific recombination*, Nucleic Acids Research, 23(3):485–490 (1995).

Chapman, Sean, Kavanagh, Tony and Baulcombe, David. "Potato virus X as a vector for gene expression in plants." *The Plant Journal*, 2(4):549–557 (1992).

Odell, Joan T., et al., *Seed–Specific Gene Activation Mediated by the Cre/lox Site–Specific Recombination System*, Plant Physiol., 106:447–458 (Oct. 2, 1994).

Qin, Minmin, et al., *Cre recombinase–mediated site–specific recombination between plant chromosomes*, Proc. Natl. Acad. Sci. USA. 91:1706–1710 (1994).

Sauer, Brian. *Manipulation of Transgenes by Site–Specific Recombination: Use of Cre Recombinase*, Methods in Enzymology, 225:890–900 (1993).

Barinaga, Marcia. "Knockout mice: round two." *Science*, 265:26–28 (1994).

Gu, Hua, Marth, Jamey D. Orban, Paul C., Mossmann, Horst and Rajewsky, Klaus, "Deletion of a DNA of a polymerase B gene segment in T cells using cell type–specific gene targeting." *Science*, 265:103–106 (1994).

(List continued on next page.)

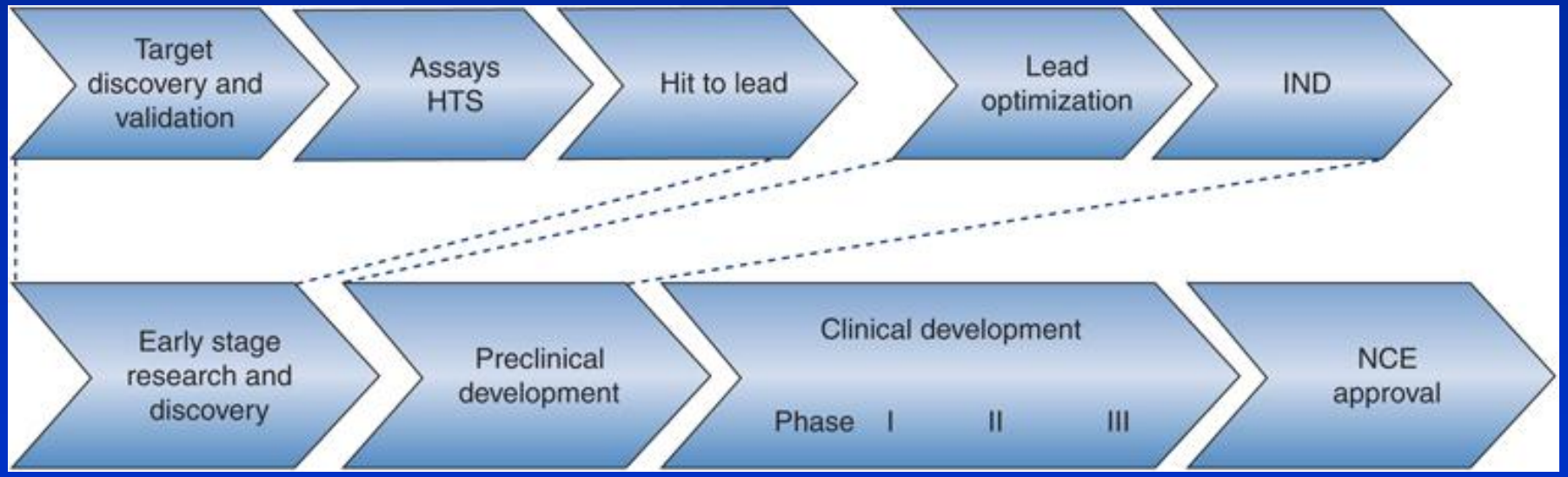
Primary Examiner—Douglas W. Robinson
Assistant Examiner—Thomas Haas
Attorney, Agent, or Firm—Rothwell, Figg, Ernst & Kurz

[57] **ABSTRACT**

A method for making a genetically modified plant comprising regenerating a whole plant from a plant cell that has been transfected with DNA sequences comprising a first gene whose expression results in an altered plant phenotype linked to a transiently active promoter, the gene and promoter being separated by a blocking sequence flanked on either side by specific excision sequences, a second gene that encodes a recombinase specific for the specific excision sequences linked to a repressible promoter, and a third gene that encodes the repressor specific for the repressible promoter. Also a method for making a genetically modified hybrid plant by hybridizing a first plant regenerated from a plant cell that has been transfected with DNA sequences comprising a first gene whose expression results in an altered plant phenotype linked to a transiently active promoter, the gene and promoter being separated by a blocking sequence flanked on either side by specific excision sequences to a second plant regenerated from a second plant cell that has been transfected with DNA sequences comprising a second gene that encodes a recombinase specific for the specific excision sequences linked to a promoter that is active during seed germination, and growing a hybrid plant from the hybrid seed. Plant cells, plant tissues, plant seed and whole plants containing the above DNA sequences are also claimed.

55 Claims, No Drawings

Drug Discovery and Development



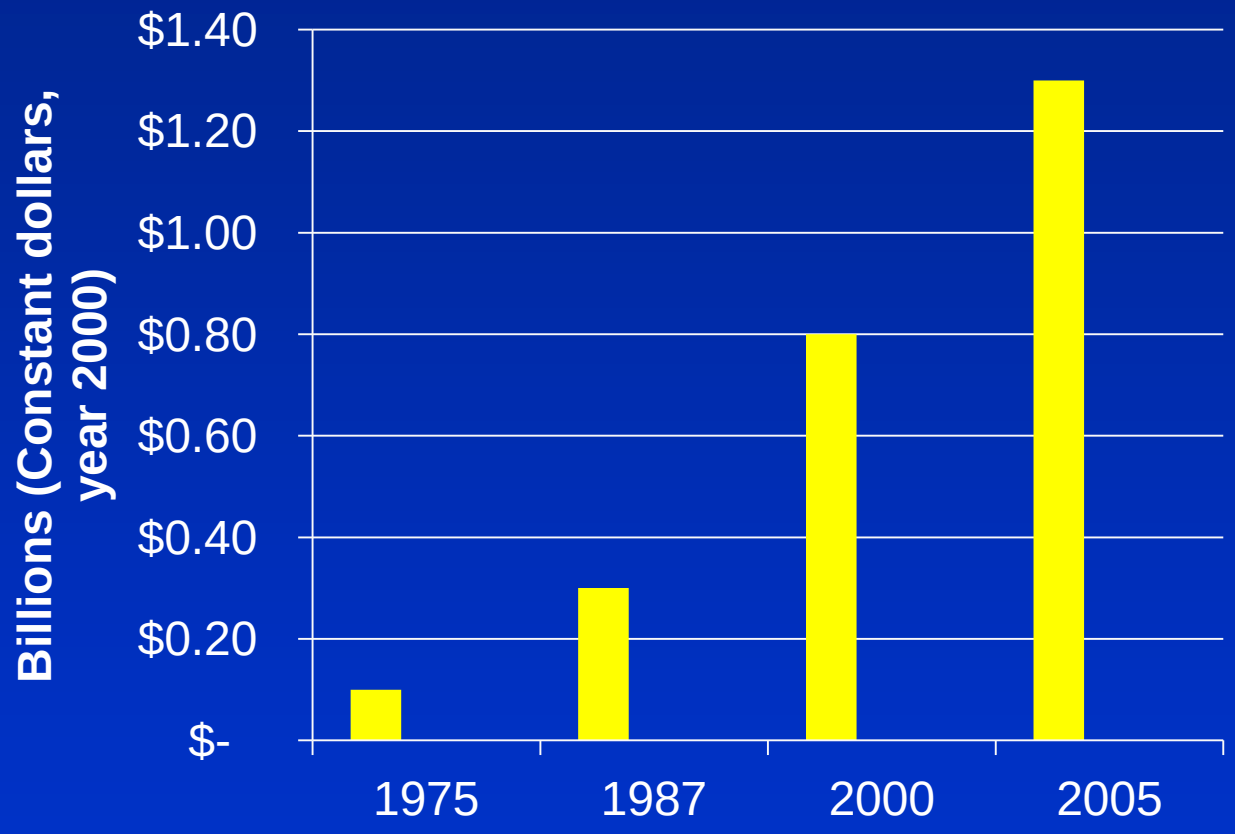
From Concept to Product: 10-15 Years

Target identification and validation	Months/years
Lead identification	4-6 months
Lead optimization	4-6 months
Preclinical development	4-6 months
Phase I	18 months
Phase II	12-24 months
Phase III	2-3 years
FDA review and scale up to manufacturing	6-24 months

Attrition

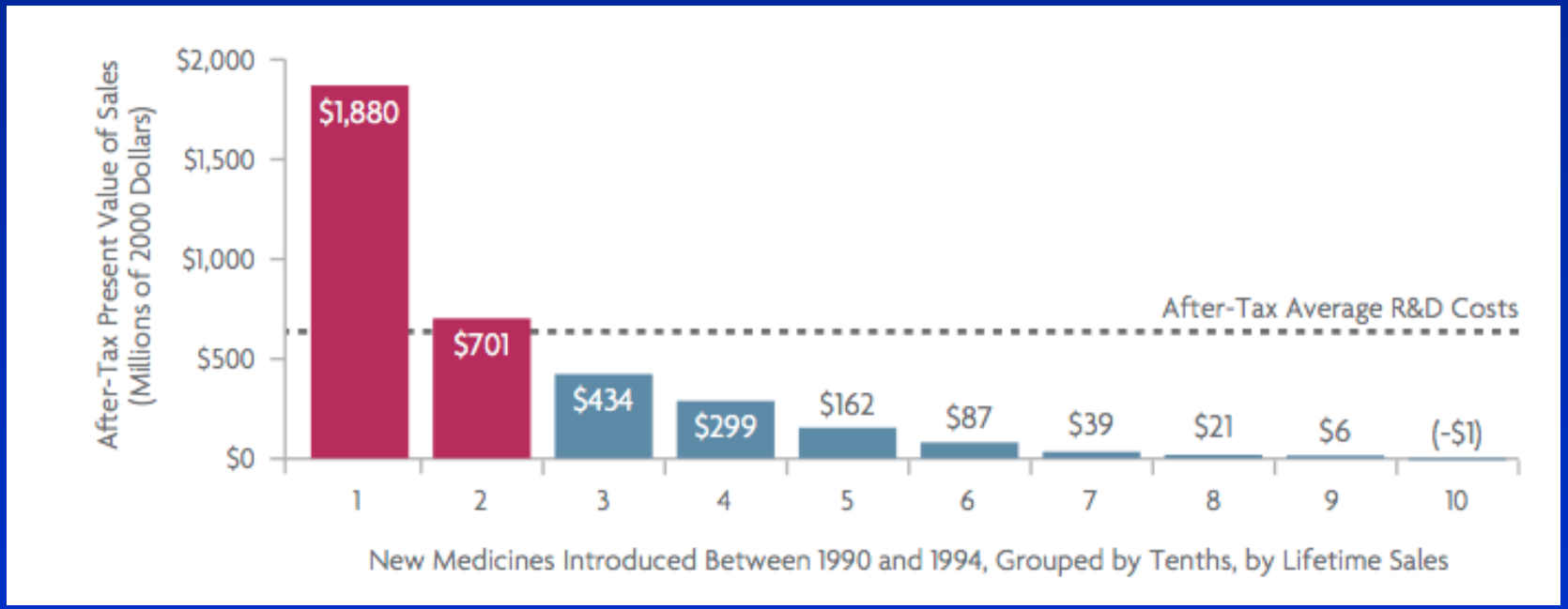
Stage	Compounds In	Compounds Out
Lead identification	Up to 50,000	100-200
Lead optimization	100-200	20
Preclinical	20	1-5
Phase I	1-5	1-3
Phase II	1-3	1-2
Phase III	1-2	1

The Cost



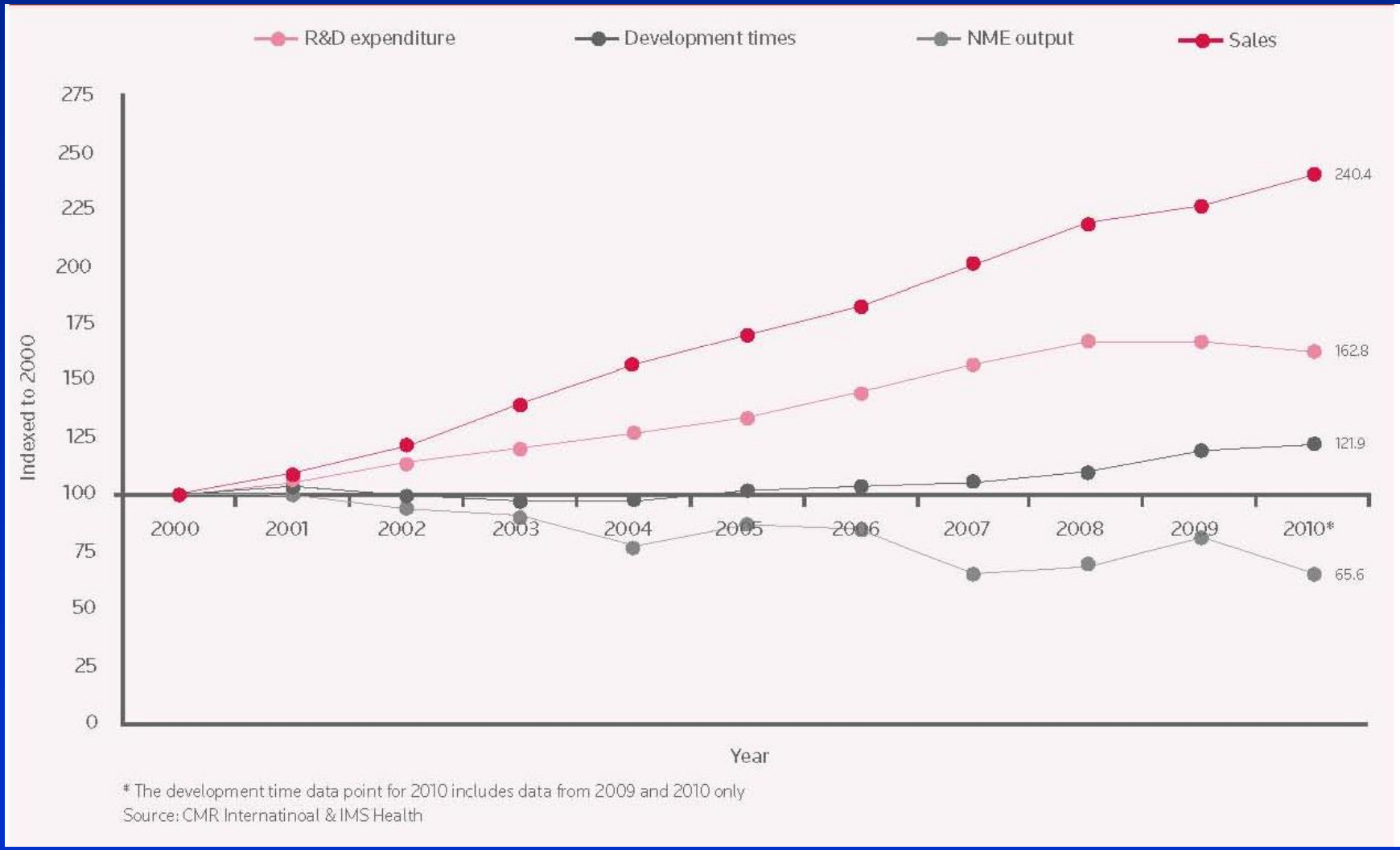
Source: DiMasi, Grabowski. *Managerial and Decision Economics* **2007**, *28*, 469-479

Only Two in Ten Approved Drugs Produce Revenues That Exceed Average R&D Costs

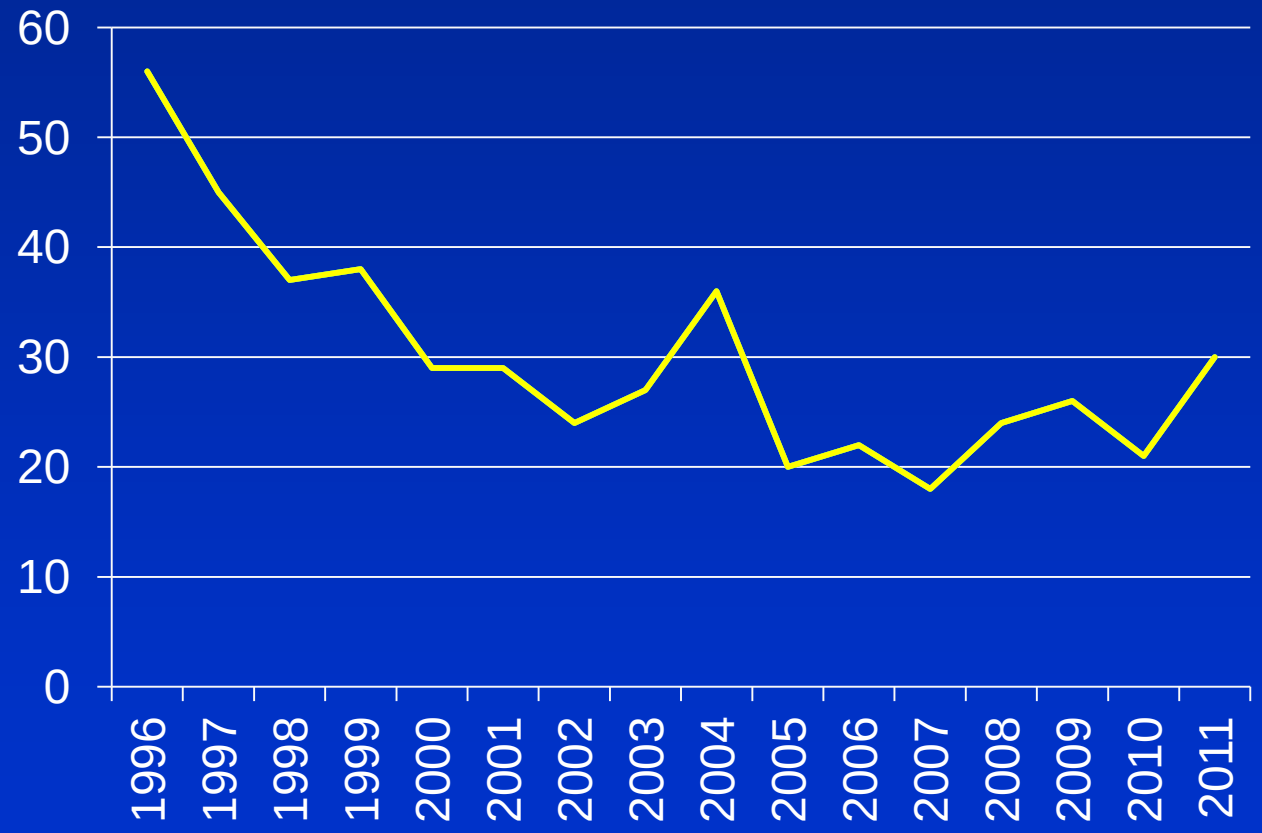


Source: Vernon, Golec, DiMasi. *Health Economics Letters* 2009

Pharmaceutical Industry Productivity 2000-2010



Number of New Molecular Entities Approved

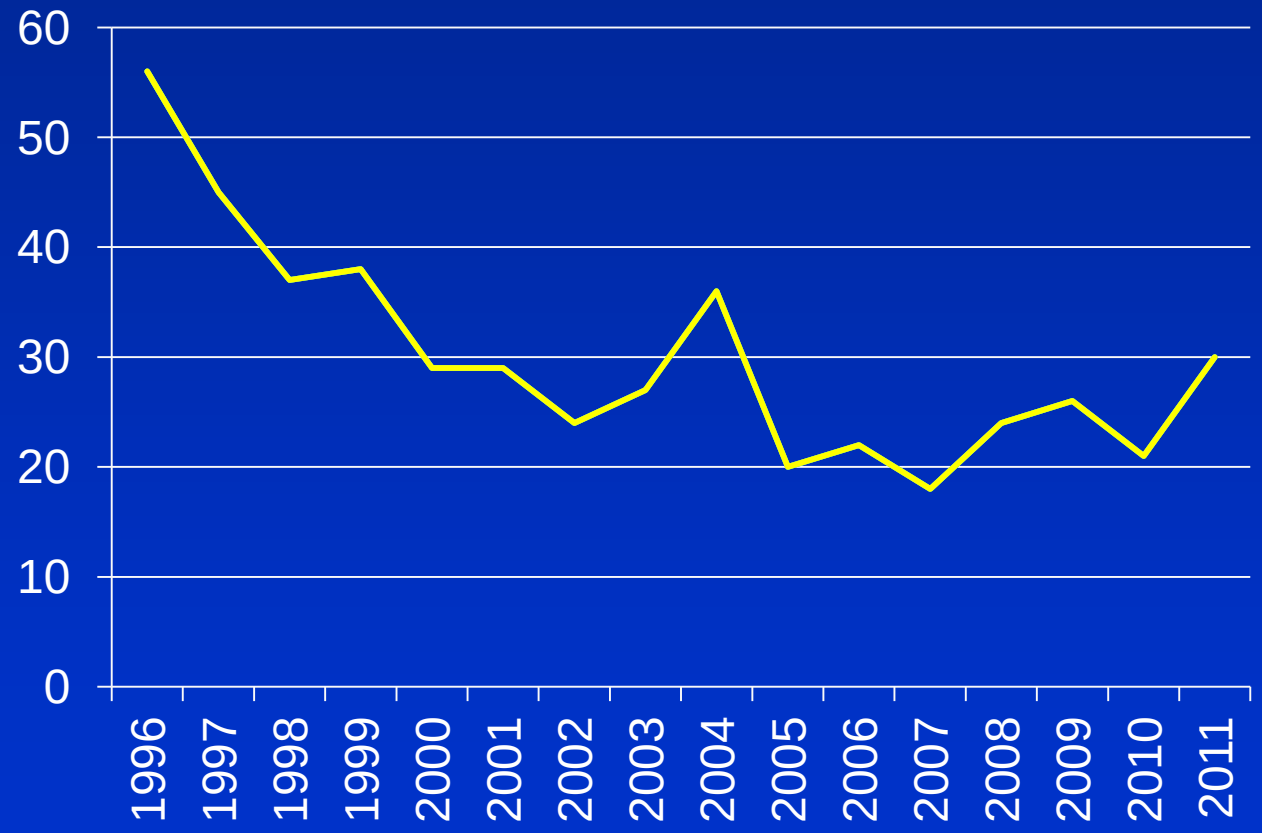


Wendy Warr & Associates

Why the Fall in Numbers of New Chemical Entities?

- Easiest drugs already found
- Companies ultra-cautious about withdrawals
- Disruption from mergers
- Or is it just the normal cycle?

Number of New Molecular Entities Approved



Wendy Warr & Associates

Investment in R&D

- R&D spending by drug companies in the US fell by $1.2 billion in 2011
- US venture capital investment in biotech fell by 43% in the first quarter of 2012
- National Institutes of Health budget will not rise in 2013

“One of the most frustrating things is that people who bring you sugared drinks and potato chips have a higher multiple than an industry that will save your life.”

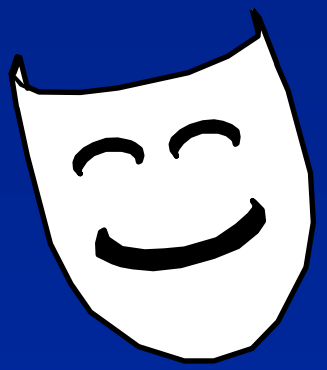
Chris Viehbacher, CEO, Sanofi

Measuring Return from Investment in R&D

- 10/12 top pharma saw internal rate of return (IRR) fall from 11.8% in 2010 to 8.4% in 2011
- Cost of bringing a drug to market increased by 21%
- Number of compounds in late stage development decreased from 23 to 18

Source: Deloitte and Thomson Reuters

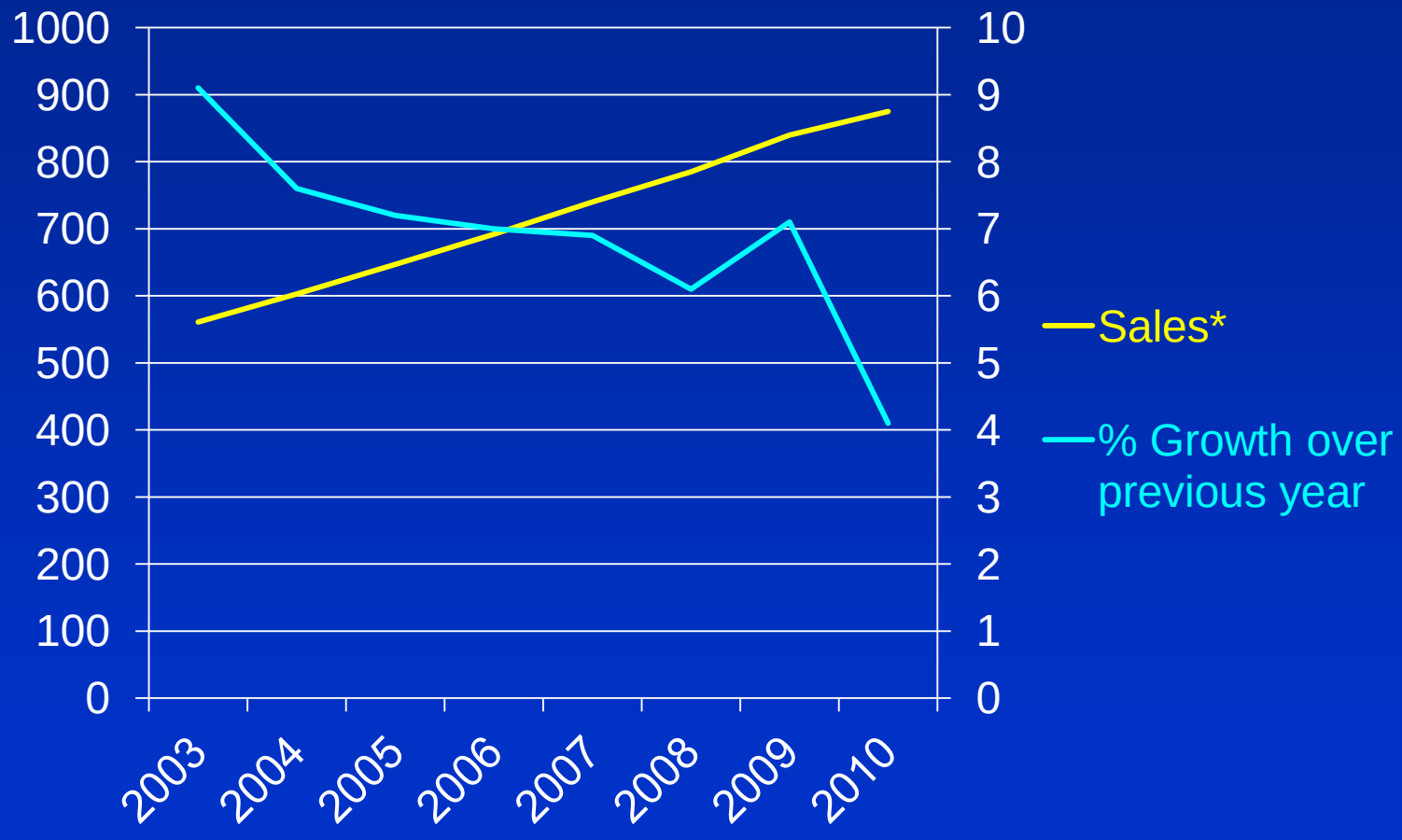
Measuring Return from Investment in R&D



- More value from product commercialization than lost from late-stage failures
- Non-R&D costs have declined; higher operating margin
- To combat high costs in future, R&D organizations will share capabilities in non-competitive R&D areas

Source: Deloitte and Thomson Reuters

Global Pharmaceutical Market



*Constant $ in billions based on Q410

Threats to the Industry

- CAGR in sales falling
- Generic competition (“the patent cliff”)
- Price pressures
- Crowded markets
- Increasing R&D budgets
- Declining productivity

The Solution?

- Mergers and acquisitions
- Cost cutting
- Restructuring
- Diversification
- In-licensing
- Alliances and outsourcing
- Target emerging markets
- Personalized medicine
- Portfolio management techniques
- Life cycle management

Consolidation: Pharma

Pfizer now comprises the following companies:

- Warner Lambert (Agouron, Farmitalia, Jouvenal, Parke-Davis)
- Pharmacia (Monsanto, Searle, Sugen, Upjohn)
- Wyeth (American Cyanamid, American Home Products, A.H.Robins, Genetic Institute)

Source: Bill Town

Consolidation: Cheminformatics

Acclerys now comprises the following former companies:

MSI (Biodesign, Cambridge Molecular Design, Polygen, Biosym, BioCad), Synopsys, Oxford Molecular (Biostructure, CAChe, Chemical Design, HDI, PSI (Fein Marquart), GCG, Intelligenetics, Cambridge Combinatorial), Synomics, SciTegic, Symyx (MDL (ORAC, OHS)), Contur Software AB

Source: Bill Town

M&As: the Impact on Productivity

- Rationalization needed after merger
  - TAs, research sites, conflicting informatics
- Disruption
- Momentum lost in research
- Entrenched camps develop
- Decision making loses objectivity
- Growth is largely from cost savings
- Benefits of scale not proven beyond a certain size
- M&As are self-limiting

Product Lifecycle Management

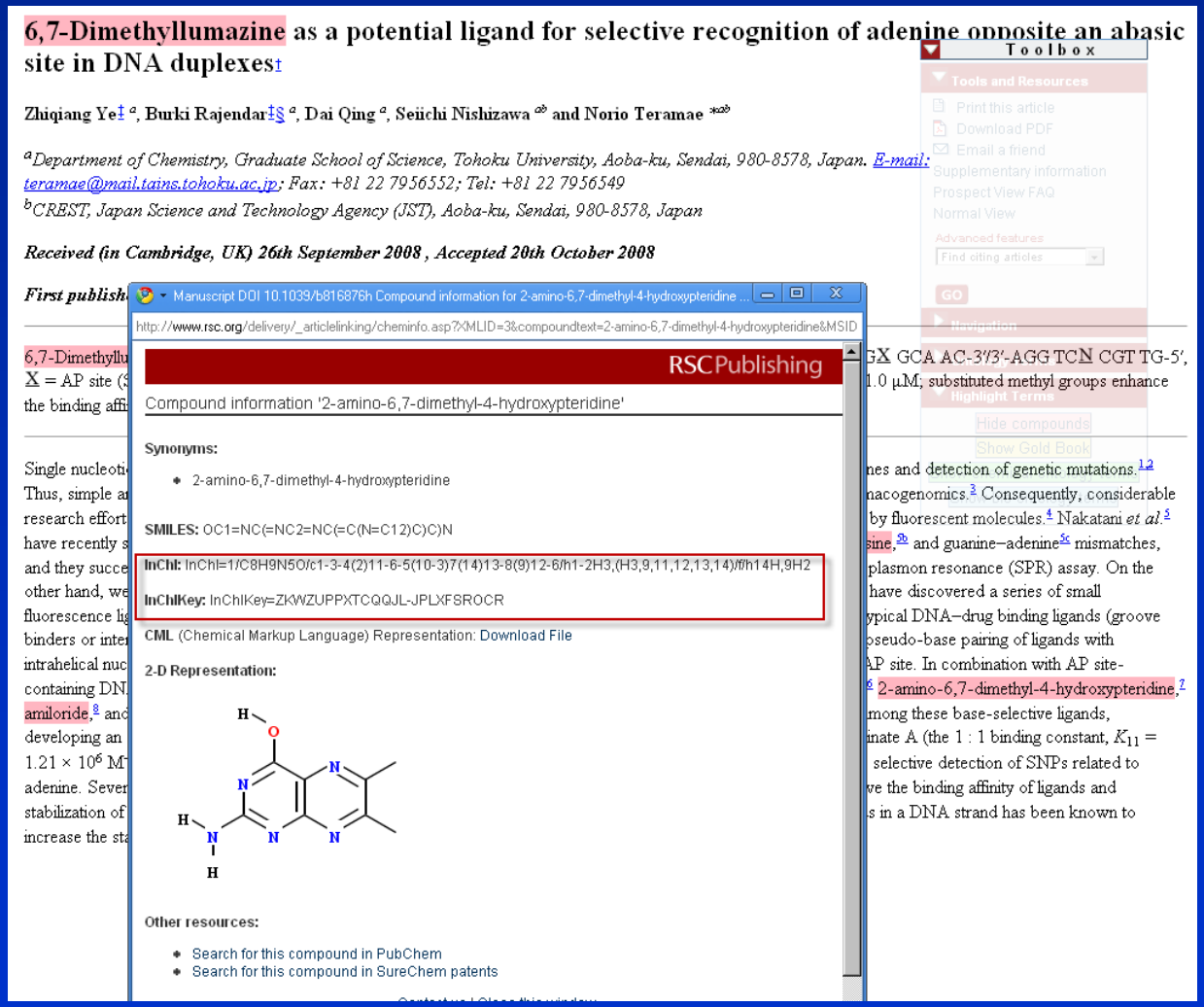
- New indications
- Reformulations
- Combination drugs
- Rx to OTC
- Branded generics
- Mergers and acquisitions
- Alliances
- Pricing
- Patent protection strategies
- New markets
- Refocusing R&D spend
- Reducing development time
- Branding and rebranding

Making R& D More Virtual

- Semantic technologies
- Computer-aided molecule design
- Predictive biosimulation
  - virtual cells, organs, animals
  - complete digital model of man

Source: Steve Arlington, Pricewaterhouse Coopers

RSC Prospect



6,7-Dimethyllumazine as a potential ligand for selective recognition of adenine opposite an abasic site in DNA duplexes†

Zhiqiang Ye‡ [a], Burki Rajendar‡§ [a], Dai Qing [a], Seiichi Nishizawa [ab] and Norio Teramae *[ab]

[a]Department of Chemistry, Graduate School of Science, Tohoku University, Aoba-ku, Sendai, 980-8578, Japan. E-mail: teramae@mail.tains.tohoku.ac.jp; Fax: +81 22 7956552; Tel: +81 22 7956549

[b]CREST, Japan Science and Technology Agency (JST), Aoba-ku, Sendai, 980-8578, Japan

Received (in Cambridge, UK) 26th September 2008 , Accepted 20th October 2008

First publish

Manuscript DOI 10.1039/b816876h Compound information for 2-amino-6,7-dimethyl-4-hydroxypteridine ...

http://www.rsc.org/delivery/_articlelinking/cheminfo.asp?XMLID=3&compoundtext=2-amino-6,7-dimethyl-4-hydroxypteridine&MSID

RSC Publishing

Compound information '2-amino-6,7-dimethyl-4-hydroxypteridine'

Synonyms:

- 2-amino-6,7-dimethyl-4-hydroxypteridine

SMILES: OC1=NC(=NC2=NC(=C(N=C12)C)C)N

InChI: InChI=1/C8H9N5O/c1-3-4(2)11-6-5(10-3)7(14)13-8(9)12-6/h1-2H3,(H3,9,11,12,13,14)/f/h14H,9H2

InChIKey: InChIKey=ZKWZUPPXTCQQJL-JPLXFSROCR

CML (Chemical Markup Language) Representation: Download File

2-D Representation:

Other resources:

- Search for this compound in PubChem
- Search for this compound in SureChem patents

Toolbox

Tools and Resources

Print this article

Download PDF

Email a friend

Supplementary information

Prospect View FAQ

Normal View

Advanced features

Find citing articles

GO

Navigation

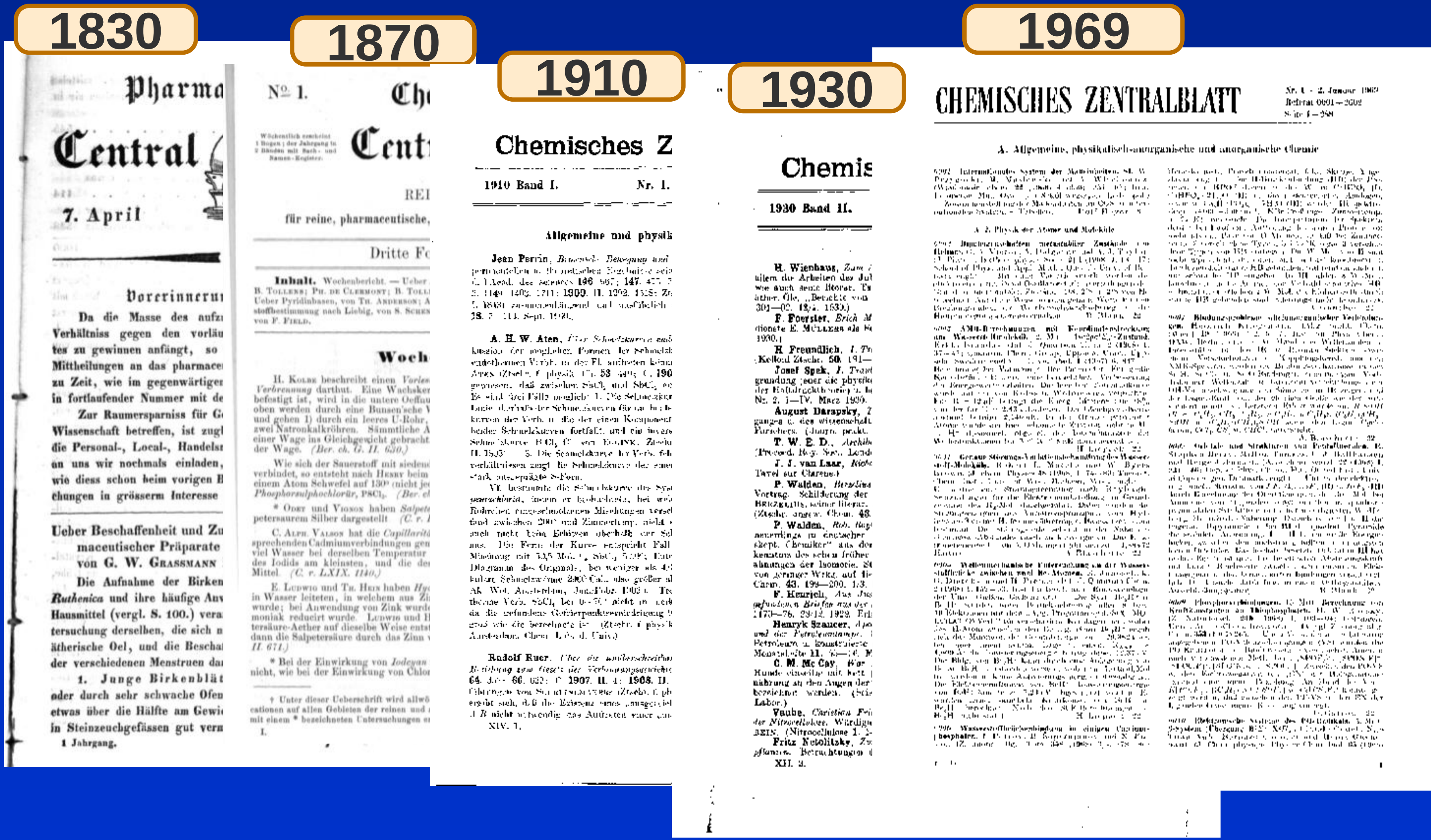
Highlight Terms

Hide compounds

Show Gold Book

Wendy Warr & Associates

A Challenge for OCR



Wendy Warr & Associates

Source: InfoChem

“Article of the Future”

Improvement of the anodic bioelectrocatalytic activity of mixed culture biofilms by a simple co - Windows Internet Explorer

http://www.articleofthefuture.com/S0956566308004417/#compound-item1

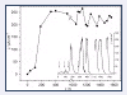
Improvement of the anodic bioelectrocatalytic activity…

PDF (6 pages) E-mail Export More Display mode

View other article » Take our survey »

Outline Show thumbnails Article top

Research highlights
Abstract
1. Introduction
2. Experimental
2.1. General conditions
2.2. Chemicals and electrodes
2.3. Half-cell electrochemical experiments
2.4. Fuel cell experiments
2.5. Metabolic analysis
2.6. Phylogenetic analysis of the mixed culture biofilms
2.7. Scanning electron microscopy
2.8. Substrate solutions
2.9. Biofilm growth and electrochemical biofilm acclimatization



2.10. G. sulfurreducens biofilm electrodes
3. Results and discussion
3.1. Primary and secondary biofilm formation

Biosensors and Bioelectronics

Volume 24, Issue 1, December 2008, Pages 1006-1011

Improvement of the anodic bioelectrocatalytic activity of mixed culture biofilms by a simple consecutive electrochemical selection procedure

Ying Liu [a], Falk Harnisch [a], Katja Fricke [a], Rabea Sietmann [b], Uwe Schröder [a,*]

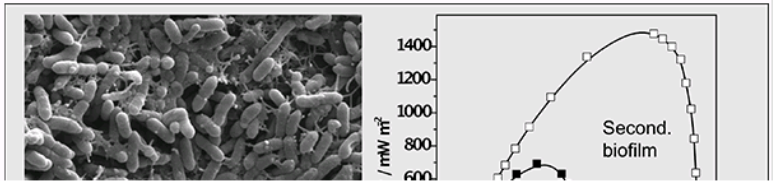
* Corresponding author. Tel.: +49 3834 864330; fax: +49 3834 864451.

[a] Institute of Biochemistry, University of Greifswald, Felix-Hausdorff-Strasse 4, 17487 Greifswald, Germany

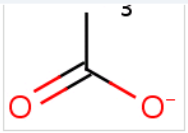
[b] Institute of Microbiology, University of Greifswald, Friedrich-Ludwig-Jahn-Strasse 15a, 17487 Greifswald, Germany

Research highlights

- Electroactive biofilms can be directly evolved from natural inoculums such as wastewater, but their original electrocatalytic performance is limited;
- The catalytic performance of the primary electroactive biofilms can be improved by a simple procedure;
- In this procedure primary electroactive biofilms are used as inoculum for the formation of secondary biofilms.
- The performance increase from primary to secondary biofilms was found to be up to 100%.



Sidebar content: Compound information (9)



Reaxys Registry Number

1901470

Molecular Formula

$C_2H_3O_2$

CAS Registry Number

71-50-1, 2887-46-9, 72063-59-3, 84148-57-2

Linear Structure Formula

$CH_3C(O)O^{(1-)}$

Chemical Name

acetate , acetate anion, acetate ion, acatate, acetic acid; deprotonated form, anhydrous acetate, (1S,3R)-acetate

Molecular Weight

59.0446

Type of Substance

acyclic

InChi Key

QTBSBXVTEAMEQO-UHFFFAOYSA-M

Open in Reaxys
Print
Open in new window

previous 1 of 9 (view all) next

Done Internet 100%

Wendy Warr & Associates

Making R& D More Virtual

- Semantic technologies
- Computer-aided molecule design
- Predictive biosimulation
  - virtual cells, organs, animals
  - complete digital model of man

Source: Steve Arlington, Pricewaterhouse Coopers

Rational Drug Design

- Receptor structure unknown, ligand structures unknown
- Receptor known, ligand known
- Receptor known, ligand unknown
- Receptor unknown, ligands known

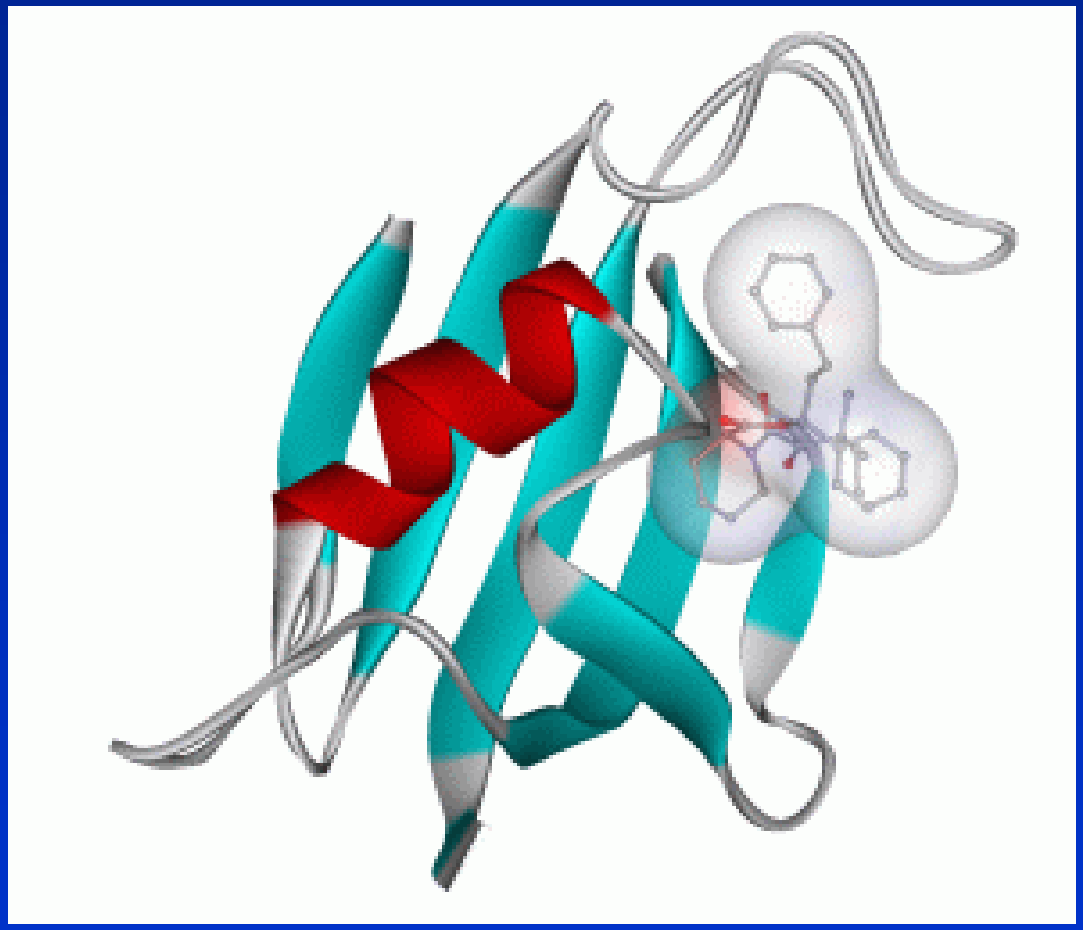
Rational Drug Design

- Receptor structure unknown, ligand structures unknown
- Receptor known, ligand known
- Receptor known, ligand unknown
- Receptor unknown, ligands known

Rational Drug Design

- Receptor structure unknown, ligand structures unknown
- Receptor known, ligand known
- Receptor known, ligand unknown
- Receptor unknown, ligands known

Docking a Ligand in a Protein

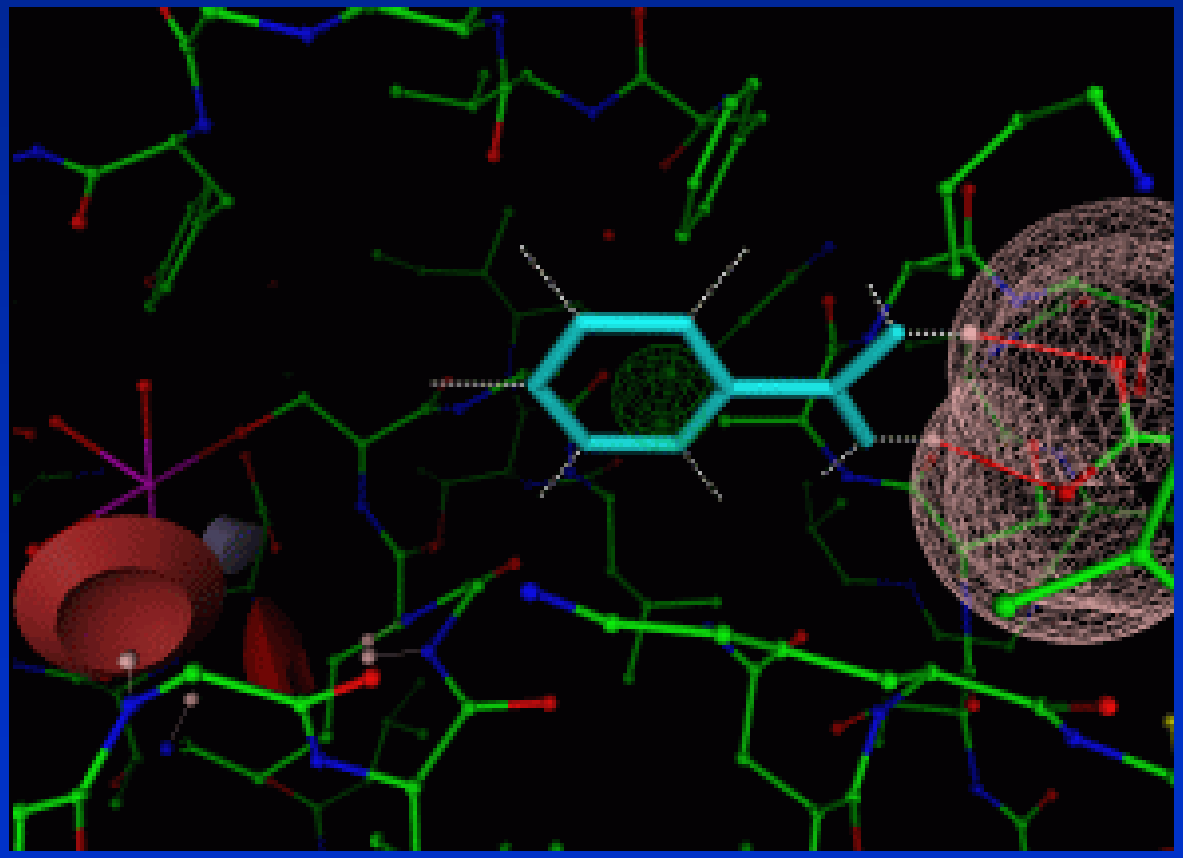


Source: Cambridge Crystallographic Data Centre

Rational Drug Design

- Receptor structure unknown, ligand structures unknown
- Receptor known, ligand known
- Receptor known, ligand unknown
- Receptor unknown, ligands known

De novo Drug Design

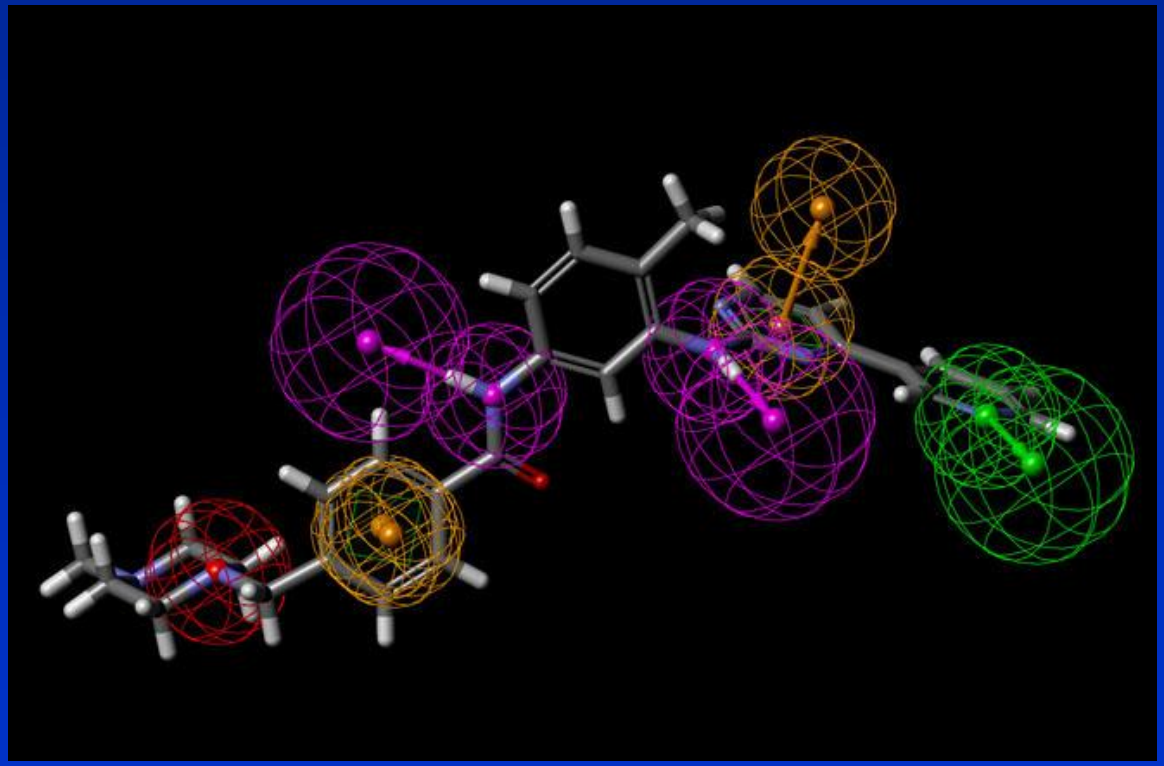


Source: SimBioSys

Rational Drug Design

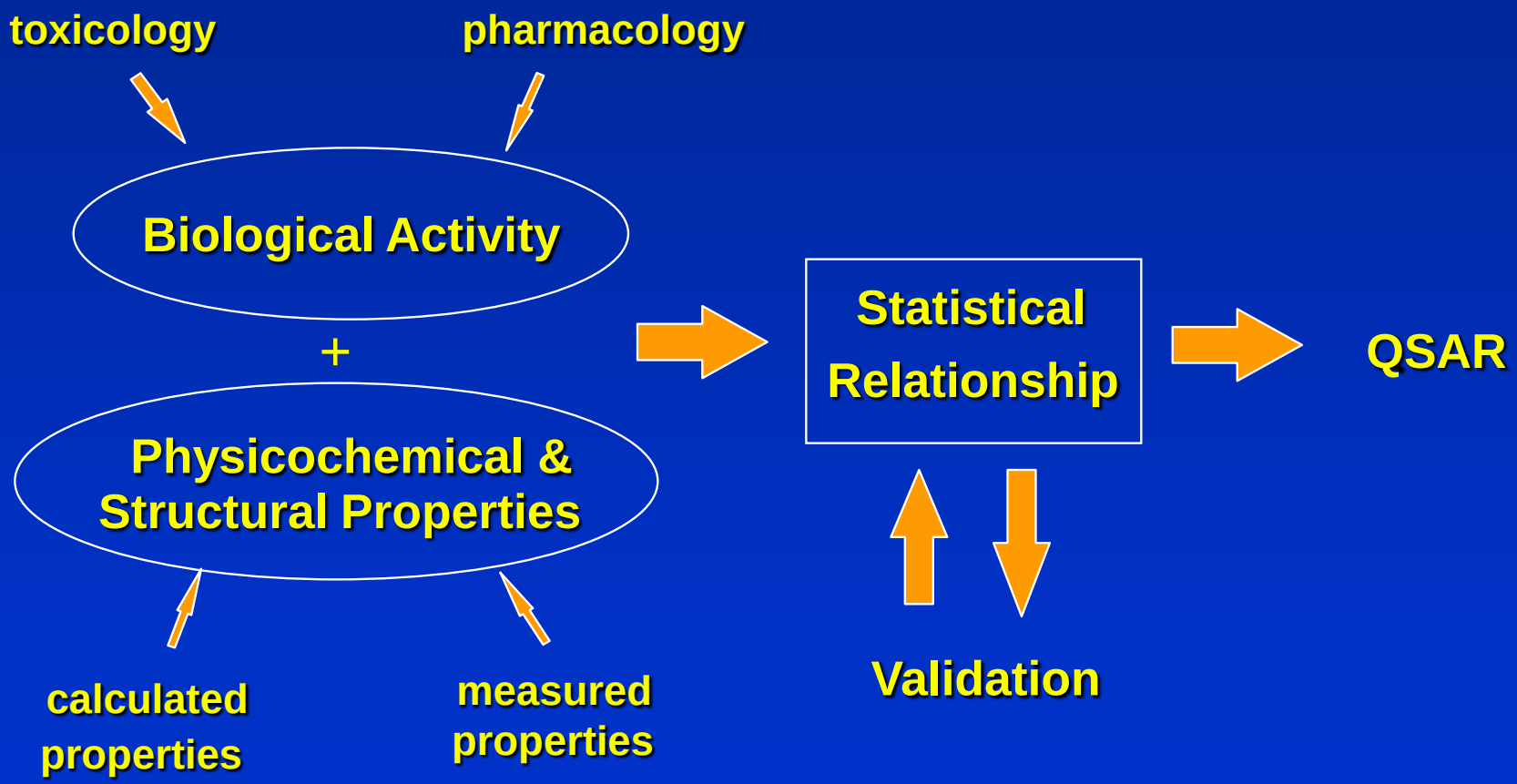
- Receptor structure unknown, ligand structures unknown
- Receptor known, ligand known
- Receptor known, ligand unknown
- Receptor unknown, ligands known

Pharmacophore Model

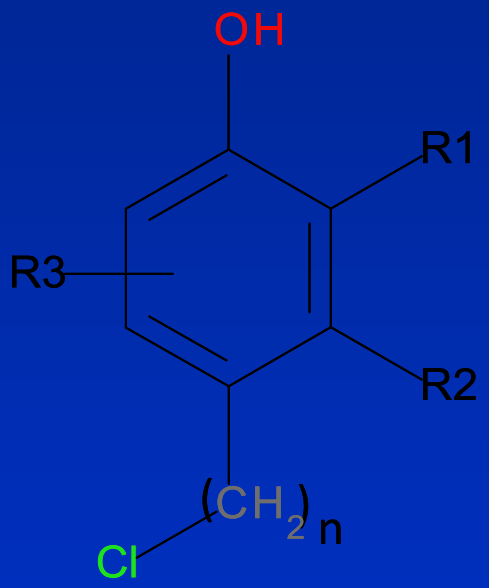


Source: Accelrys

Quantitative Structure Activity Relationships (QSAR)



A Markush Structure



Substituent variation

R1 = methyl or ethyl

Homology variation

R2 = alkyl

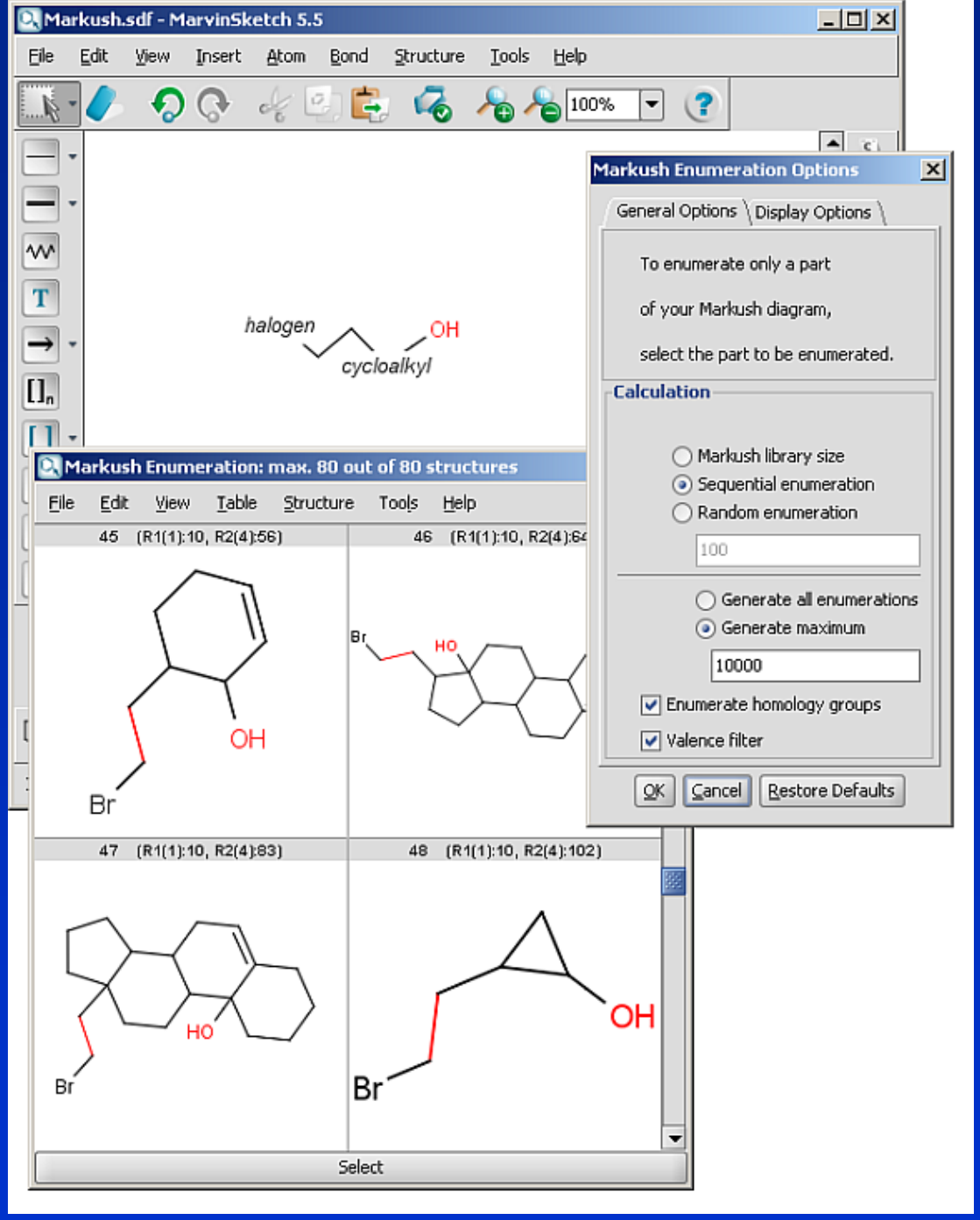
Position variation

R3 = amino

Frequency variation

n = 1-3

Source: Digital Chemistry



Source:
ChemAxon

Drug Discovery in the 1970s

Drug Discovery in the 1970s

- Unplanned innovation
- Serendipity
- Drugs based on natural products
- Chemists used intuition
- Random screening
- Linear workflow
- Informatics only peripheral

Advances of the 1990s

- The human genome project
- Genomics
- Proteomics
- Growth in knowledge of protein structures
  - X-ray crystallography
  - NMR
  - homology modeling
- High throughput screening (HTS)
- Combinatorial chemistry
- Bioinformatics and cheminformatics

Drug Discovery Today

- Start with knowledge of a biological target
  - and maybe a known protein structure
- Screen the fewest compounds needed
- Vast quantities of data
- Informatics is of strategic importance
- Informatics supports decision making
- Multi-disciplinary teams share knowledge
- “Fail early”: predict druglikeness

Changing strategies

- Pharma 1.0
  - Blockbuster model
  - Focus on top line
- Pharma 2.0
  - Strategies addressed in this talk
  - Focus on bottom line
- Pharma 3.0
  - Delivering health outcomes
  - Being customer-centric
  - Being payer-insightful

Source: Carolyn Buck Luce, Ernst &Young