

Porque não falam português os nossos fármacos – Parte 2

XXIV Semana da Farmácia
Faculdade de Farmácia - novembro de 2006

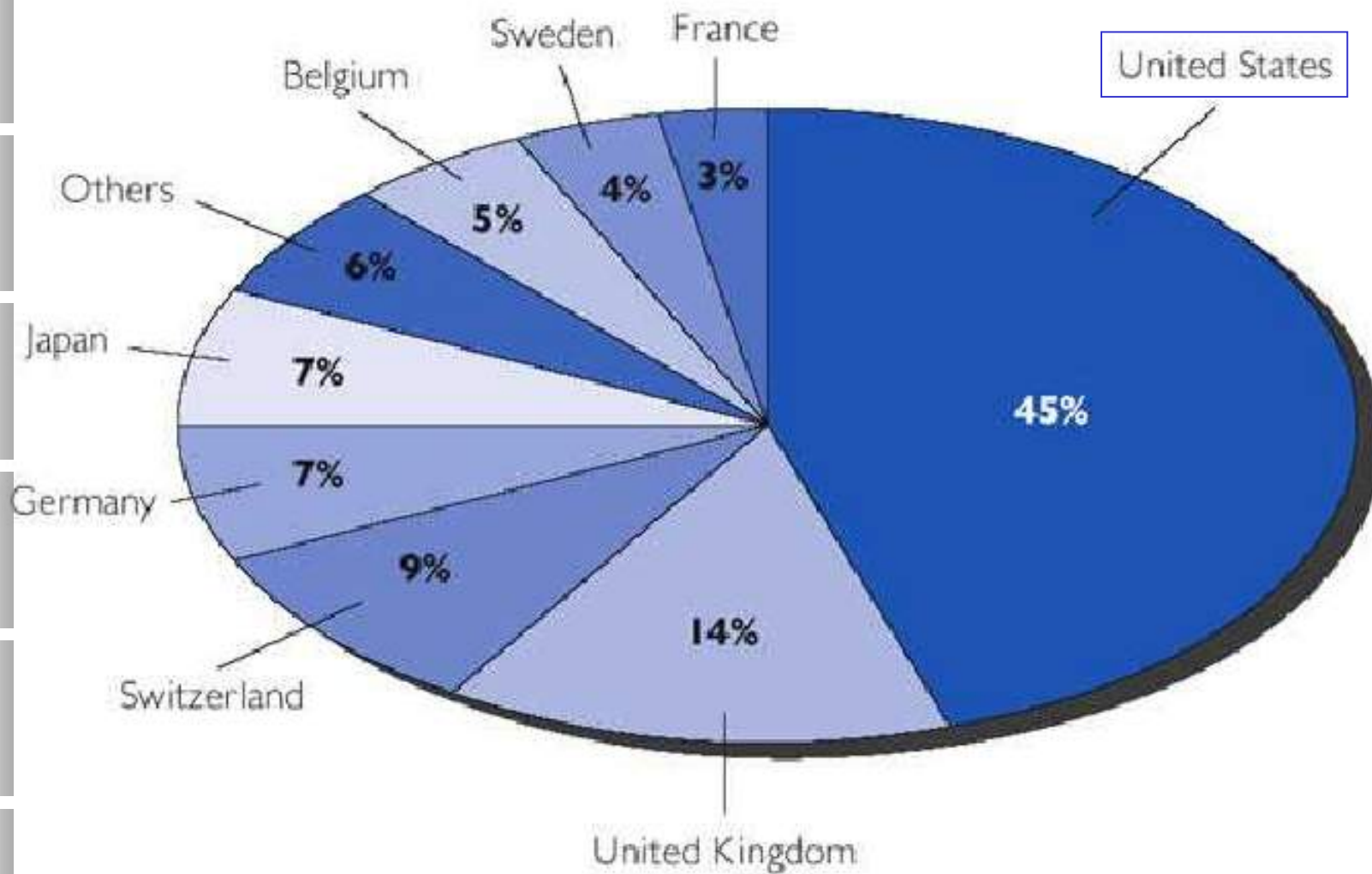
Eliezer J. Barreiro
UFRJ

Laboratório de Avaliação e Síntese de Substâncias Bioativas



Universidade Federal do Rio de Janeiro

Descobridores de Fármacos



Pharmaceuticals are forecast to outpace chemicals in 2004-05

Chemical industry excluding pharmaceuticals

Chemical industry including pharmaceuticals

Consumer products

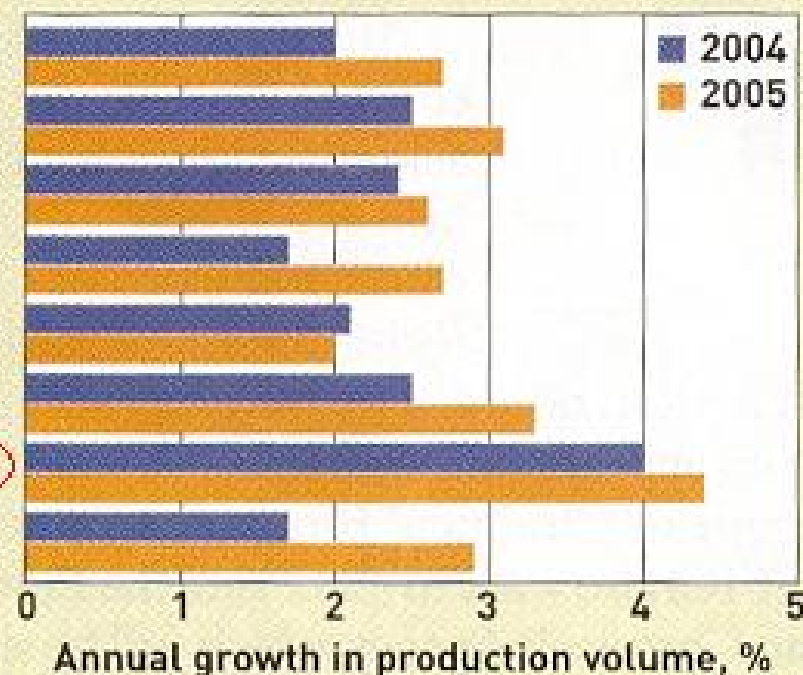
Fine & specialty chemicals

Inorganic basic chemicals

Petrochemicals

Pharmaceuticals

Polymers



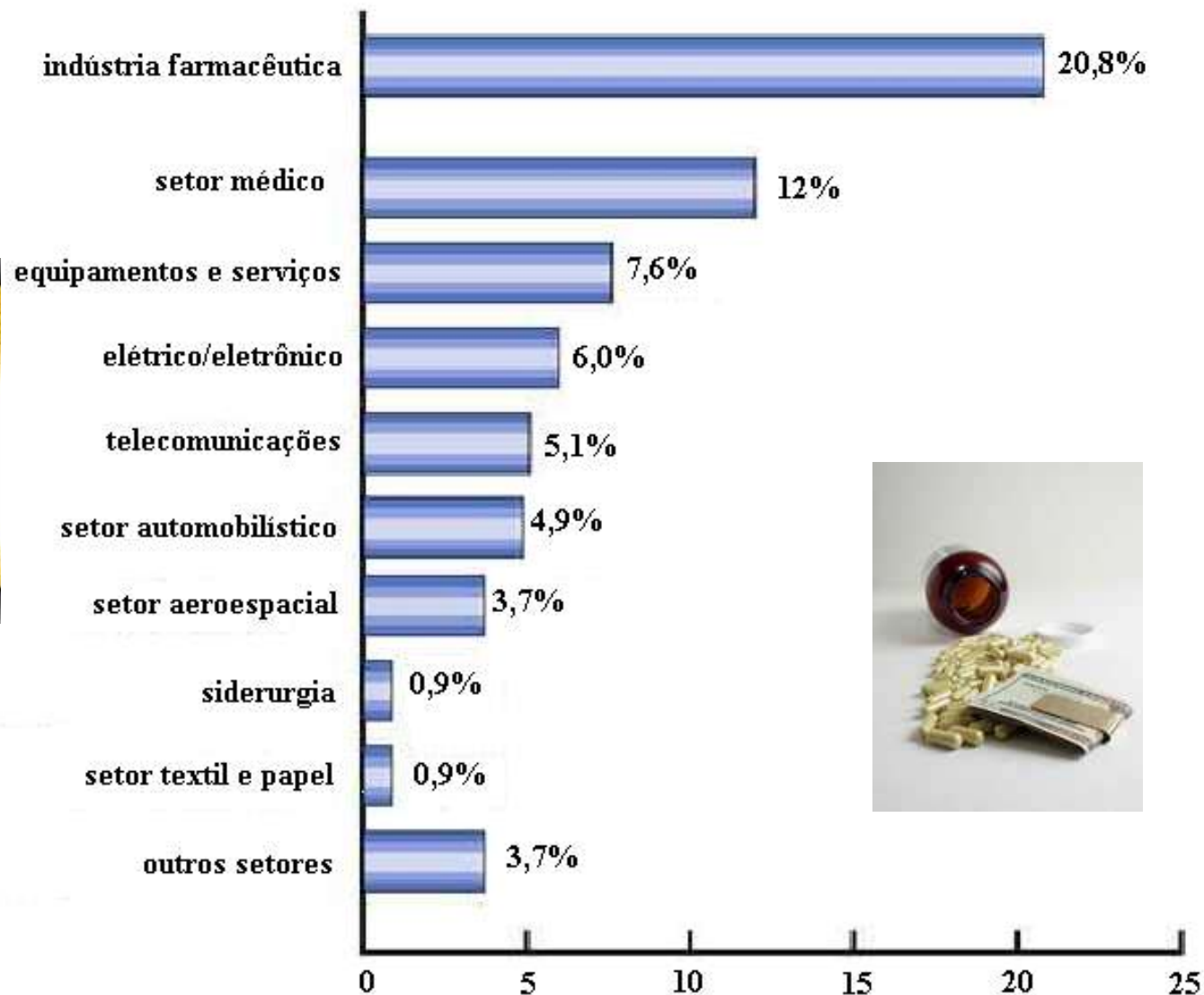
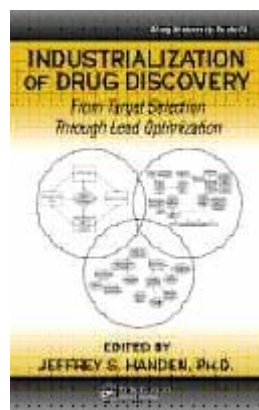
SOURCE: European
Chemical Industry Council

C&EN, 2005

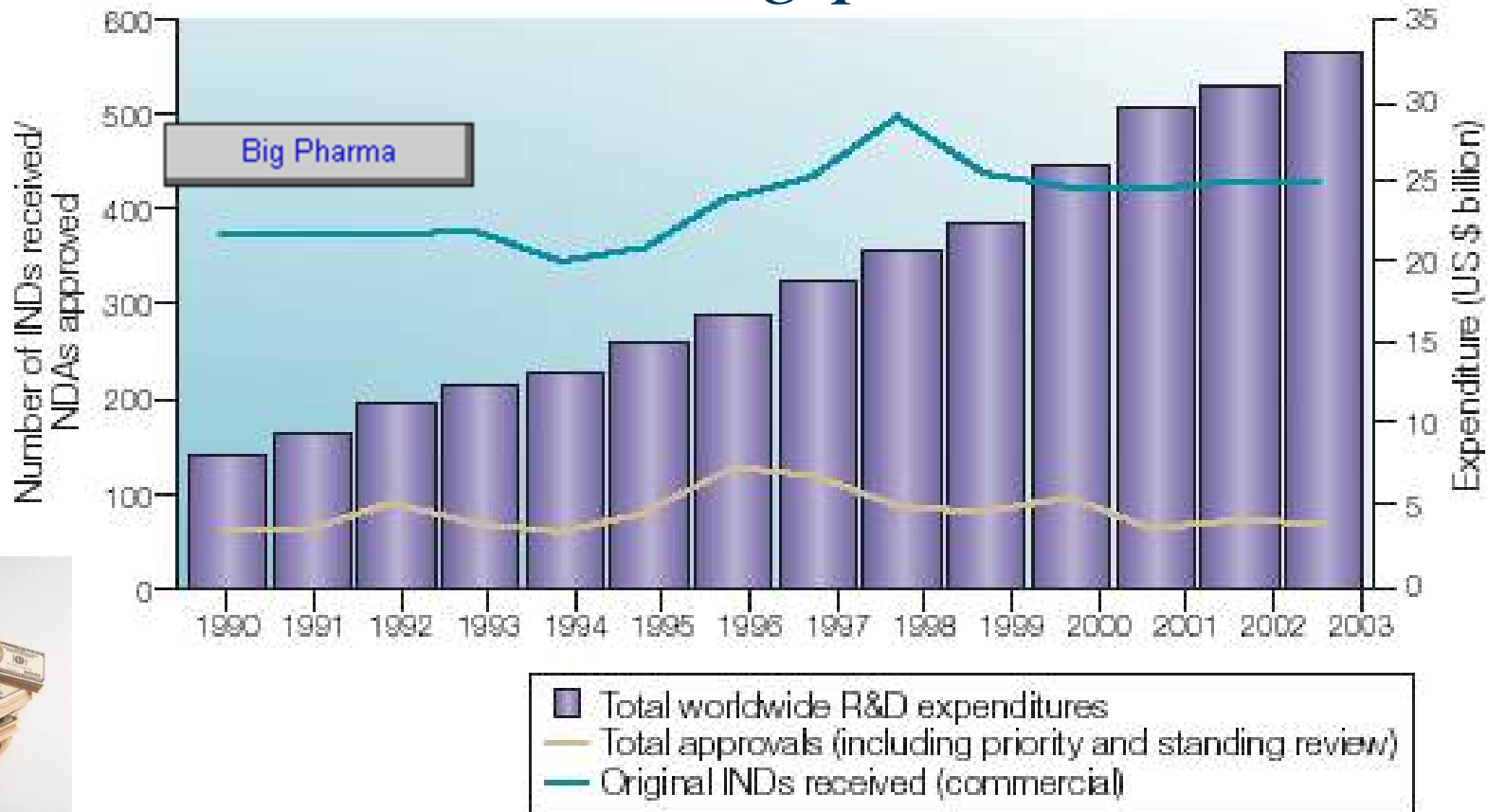


Percentagem do faturamento investida em R&D/setores industriais

(1998)



Gastos em P&D nas *Big-pharmas*



**J.A. DiMasi, R.W. Hansen, H.G. Grabowsky, *J. Health Economics* 2003, 22, 151;
J. A. DiMasi *et al.*, “The Cost of Innovation in the Pharmaceutical Industry” *J. Health Economics* 1991, 10, 107.**

Tufts University Center for the Study of Drug Development (Boston, EUA)

O preço da inovação...!?



Available online at www.sciencedirect.com

SCIENCE @ DIRECT®

Journal of Health Economics 22 (2003) 151–185

www.elsevier.com/locate/econbase

JOURNAL OF
HEALTH
ECONOMICS

The price of innovation: new estimates of drug development costs

Joseph A. DiMasi^{a,*}, Ronald W. Hansen^b, Henry G. Grabowski^c

^a Tufts Center for the Study of Drug Development, Tufts University, 192 South Street, Boston, MA 02111, USA

^b Administration, University of Rochester, Rochester, NY, USA
^c Economics, Duke University, Durham, NC, USA

Received 24 May 2002; accepted 28 October 2002

1: [Health Aff \(Millwood\)](#). 2006 Mar-Apr;25(2):420-8.

Estimating the cost of new drug development: is it really 802 million dollars?

Adams CP, Brantner VV.

Bureau of Economics, Federal Trade Commission, in Washington, DC, USA. cadams@ftc.gov

This paper replicates the drug development cost estimates of Joseph DiMasi and colleagues ("The Price of Innovation"), using their published cost estimates along with information on success rates and durations from a publicly available data set. For drugs entering human clinical trials for the first time between 1989 and 2002, the paper estimated the cost per new drug to be 868 million dollars. However, our estimates vary from around 500 million dollars to more than 2,000 million dollars, depending on the therapy or the developing firm.

PMID: 16522582 [PubMed - indexed for MEDLINE]

randomly selected new drugs were obtained from a survey were used to estimate the average pre-tax cost of new drug development during testing were linked to the costs of commercialization. The estimated average out-of-pocket cost per new drug is \$1.3 billion, which is higher than the point of marketing approval re-approval cost estimate of US\$ 802 million (2000 dollar study with a similar methodology, total capitalized cost of \$1.3 billion at a discount rate of 7.4% above general price inflation).

Keywords: Innovation; R&D cost; Pharmaceutical industry; Discount rate; Technical success rates

Tufts Center for the Study of Drug Development

Research Update: [After Years of Declining R&D Productivity, Drug Development Is Poised to Take Off](#)

Who We Are

The Tufts Center for the Study of Drug Development is an independent, academic, non-profit research group affiliated with Tufts University. Founded in 1976, Tufts CSDD is internationally recognized for its scholarly analyses and thoughtful commentary on pharmaceutical issues. Tufts CSDD's mission is to provide strategic information for drug developers, regulators, and policy makers on improving the quality and efficiency of pharmaceutical development, research, and utilization.



From The Director



Kenneth I. Kaitin, Ph.D.

Welcome to the Tufts Center. I invite you to learn more about us.

[Read More >>](#)

33rd Annual Postgraduate Course in Clinical Pharmacology, Drug Development, and Regulation

*Feb. 6-10, 2006 * Four Seasons Hotel * Boston, MA*



Now in its 33rd year, Tufts CSDD's highly acclaimed, five-day *Postgraduate Course* provides advanced instruction in practical and technical problem solving in the areas of clinical pharmacology, drug development, clinical trial design, and new drug regulation. Our 2006 program includes several new presentations, which will focus on vaccines, patient recruitment, informed consent, investigative site challenges, and portfolio management

TUFTS

--Please Choose--

[About Us](#)

[Research](#)

[Publications](#)

[Information Services](#)

[Institute for Professional Development](#)

[Become a Tufts CSDD Sponsor](#)

[News & Events](#)

[Links](#)



Home | Contact | Site Map
Online Impact Reports

Participate in Tufts CSDD Survey: *Measuring Company's Hiring Needs of Clinical Study Personnel*

[\(click here to access\)](#)

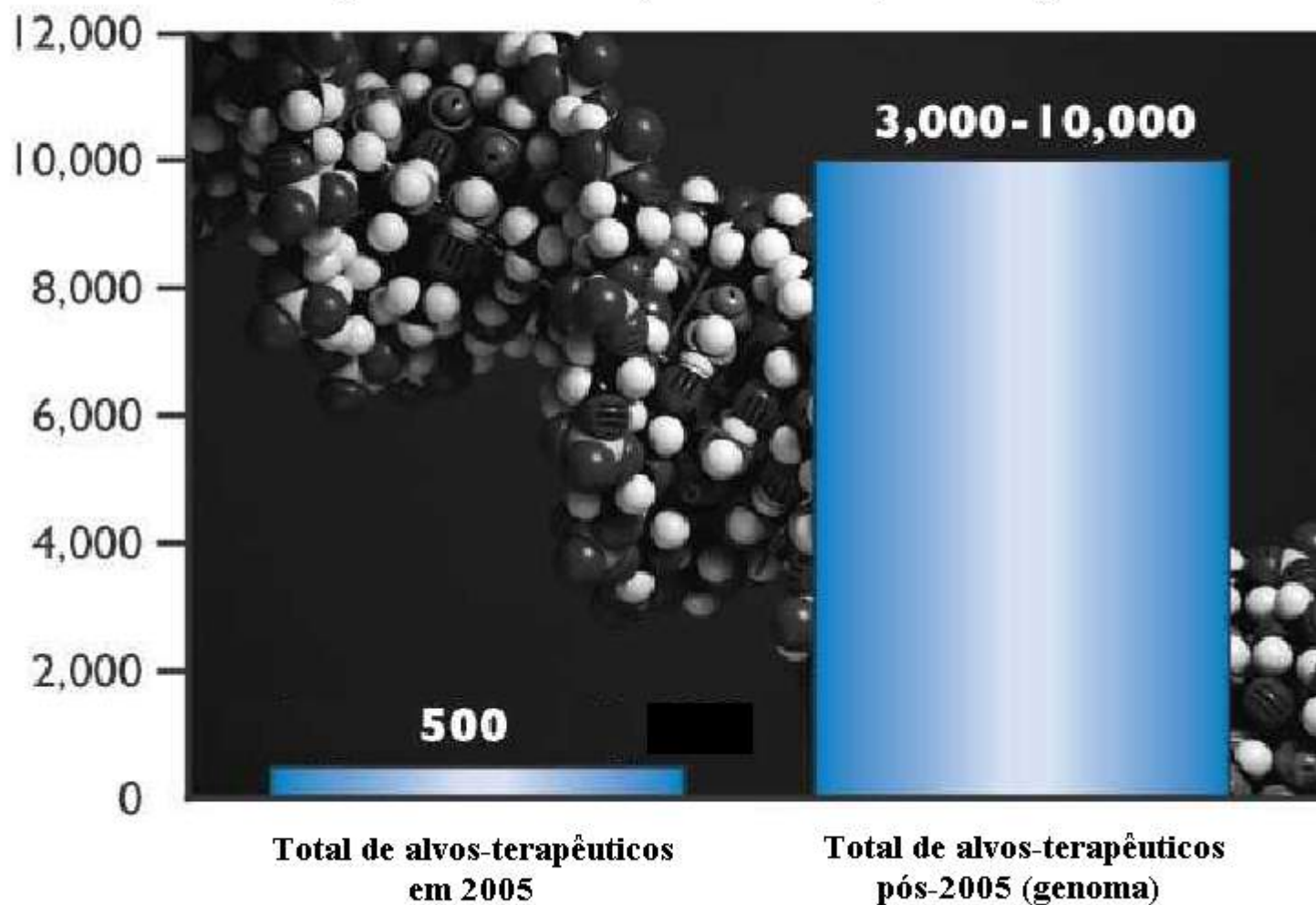

Internet

O custo da descoberta de um novo fármaco

não atinge US\$ 800 milhões ...!

Alvos-terapêuticos possíveis para novos fármacos

Oportunidades para inovação terapêutica



Big-Pharma e gastos com tecnologia da informação

- indústria aeroespacial
- indústria automobilística
- indústria química
- setor de embalagens
- computadores e correlatos
- indústria de petróleo
- indústria farmacêutica
- outros



Bioinformática

Nota: 500 empresas de tecnologia da informação foram consultadas; 23 empresas químicas e 25 indústrias farmacêuticas; Fonte: AMR Research (C&EN, ACS, 2004)

“...Change is in the air for drug discovery... the excitement of this interdisciplinary field at a time of transition ...”

**J. Uppenbrink & J. Mervis (Eds.),
Science 287, 1951 (2000)
(*Special Issue*)**



Drug Discovery

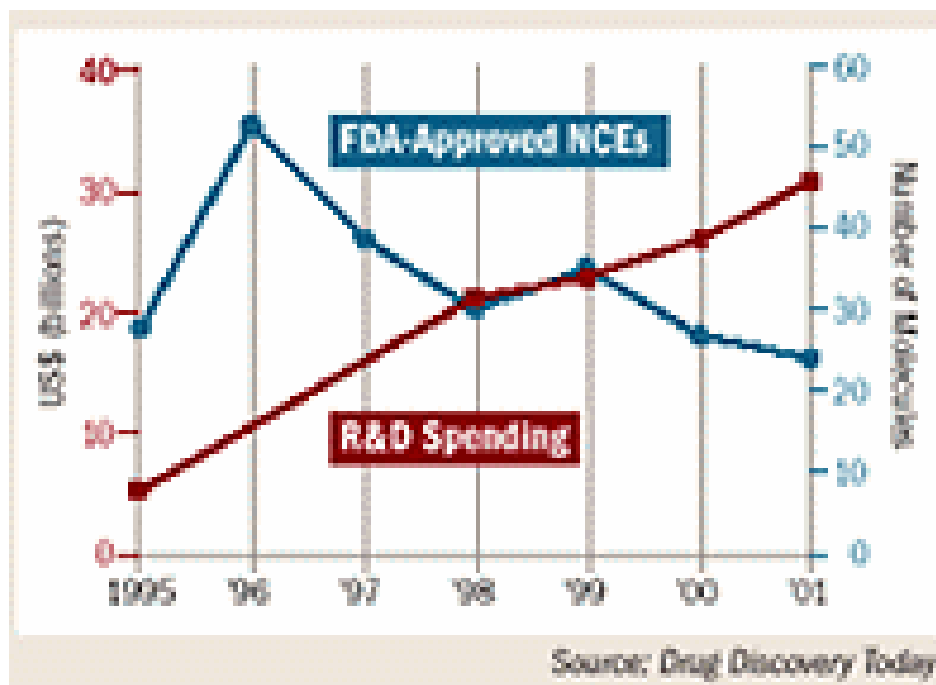
Drug Discovery

Donald Kennedy, *Editor-in-Chief*

Drug Discovery – Editorial

Science 2004, 303, 1717

“..The rate of introduction of new chemical entities has slowed despite the wealth of new technologies...”



Science

Moving Beyond 'Me-Too'

L. M. Jarvis
C&EN October 9, 2006
Volume 84 (41), 42

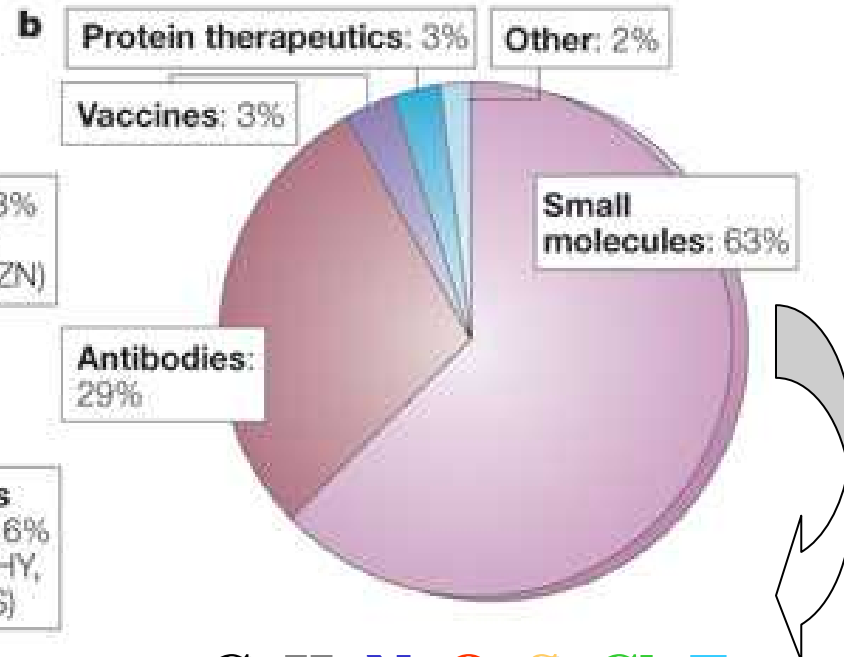
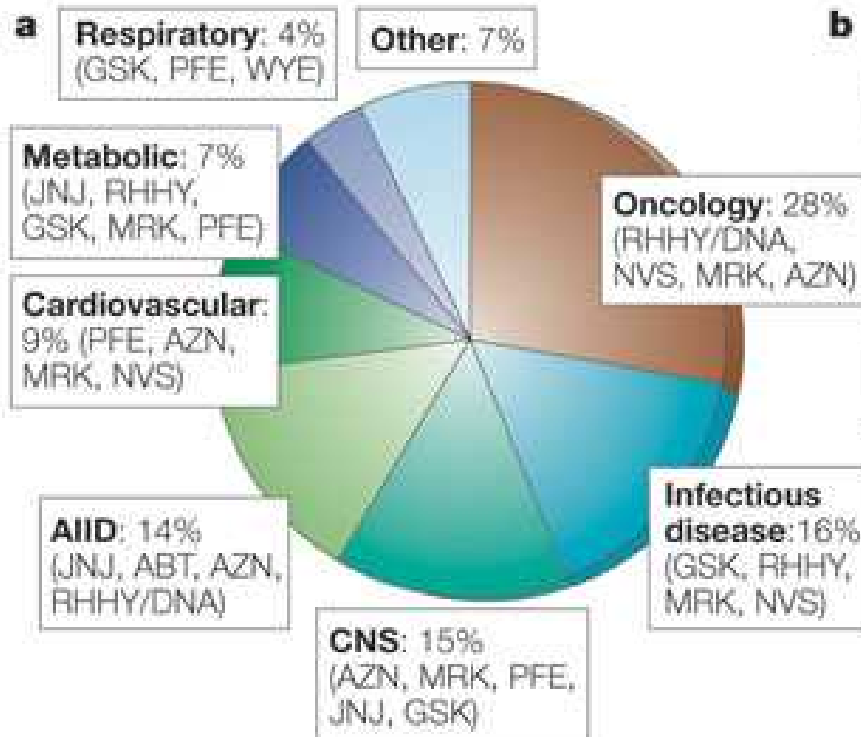
“...the pharmaceutical industry's declining productivity, ...penchant for me-too products...”

“ ...the four drugs that are going to drive sales growth at AstraZeneca between 2005 and 2011 are all essentially me-too products...”:

- the chronic obstructive pulmonary disease (COPD) treatment Symbicort^R, is a combination of *two older drugs* formoterol (long-acting β_2 -adrenoceptor agonist) & budesonide (glucocorticoid).
- the schizophrenia drug Seroquel^R (quetiapine, mixed 5-HT₂/D2 antagonist) has a better side-effect profile than other drugs in its class, but is not hugely innovative.
- the antiulcerant Nexium^R (esomeprazole) is a follow-on to Prilosec^R (omeprazole) and is generally considered a life-cycle extension product.
- the anticholesterol drug Crestor^R (rosuvastatin, 5-HMG inhibitor) is yet another statin albeit an extremely potent one.



Caçadores de moléculas...



C, H, N, O, S, Cl, F

PM ~ < 500

Copyright © 2005 Nature Publishing Group
Nature Reviews | Drug Discovery

pipeline



e-mail of Eliezer J. Barreiro

De: Kyle Kuhn - Paramount BioCapital Investments, LLC
Para: eliezer@pharma.ufrj.br
Cc: eliezer@ufrj.br
Data: 26/08/2006 11:01
Assunto: Phthalimide derivative LASSBio-552



Dr. Barreiro,

My name is Kyle Kuhn, I represent a *biopharmaceutical investment firm called Paramount BioCapital Investments, LLC*. My job here at Paramount is to identify promising therapeutic technologies, and explore potential investment and/or licensing opportunities.

I recently saw a summary of some information you presented at the recent International Symposium on Nitric Oxide, Cytokines and Inflammation, in Malbourne, and I would like to learn more about compound LASSBio-552.


I would like to know the development status of this compound, as well as any plans for its continued development. *I would also like to know the IP status for this technology.* Any additional information you can provide would be very helpful.

It may be more convenient to speak over the phone. If you would like to provide a number, and suggest a convenient time, I would be happy to give you a call. Alternatively, my contact information is provided below, please feel free to contact me at your convenience. I look forward to hearing from you.

Best regards,
Kyle Kuhn

Biotechnology Venture Capital Analyst
Paramount BioCapital Investments, LLC
787 Seventh Avenue - New York, NY 10019 -Tel: 212.554.4315 -Fax: 212.554.4490
e-mail: KKuhn@Paramountbio.com

Os caçadores...

Endereço  http://www.paramountbio.com/content/index.html



Links

Norton AntiVirus



Google

 estments



Settings



PARAMOUNT
BIOSCIENCES

www.paramountbio.com

Our mission is to
identify, evaluate and
assess a broad
spectrum of cutting-
edge medical
technologies and seek
to capture innovations
with significant
commercial potential.



Paramount is a prolific founder of development biotech companies.

Headquarters:

New York Office

787 7th Avenue
48th Floor
NY, NY 10019

California Office

23046 Avenida de la Carlota
Suite 360
Laguna Hills, CA 92653

North Carolina Office

100-A Eastwood Center
Suite 117
Wilmington, NC 28403

Cambridge Office

124 Mt. Auburn Street
University Place, Harvard
Square
Suite 200 North
Cambridge, MA 02138

London Office

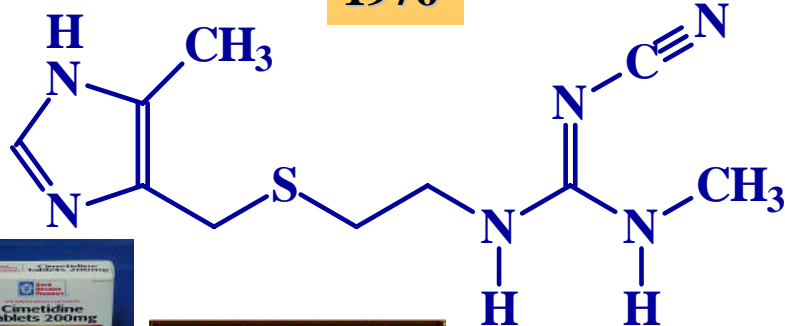
Building 3, Chiswick Park
566 Chiswick High Road
London
W4 5YA
United Kingdom



1976

1981

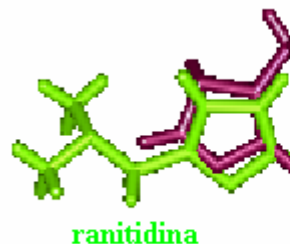
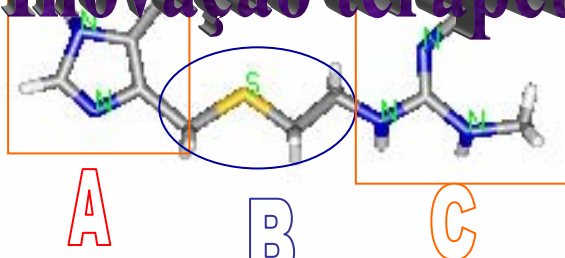
me-too



Cimetidina

Robin Ganellin *et al.*, 1974
US 3950333 1974, 1976 - SK&F
Brit. J. Pharmacol. **53**, 435 (1975).

Inovação terapêutica



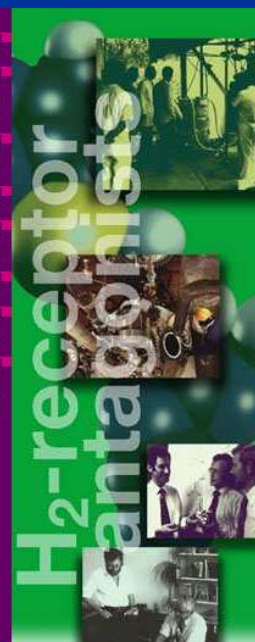
Endereço <http://acswebcontent.acs.org/landmarks/tagamet/newera.html>

National Historic Chemical Landmarks

AMERICAN CHEMICAL SOCIETY
Science That Matters

Search Contact Us Site Map chemistry.org

Home
About the Landmarks Program
Frontiers of Knowledge
Medical Miracles
Industrial Advances
New Products
Cradles of Chemistry
Action! Take Part & Nominate

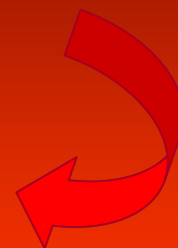


A new era of logical drug design

The research program leading to cimetidine also represented a revolution in the way pharmaceuticals are developed. Traditionally, the development of a new drug would often depend on the fortuitous discovery of a plant or microbial extract that showed some of the required biological activity. Using that first extract as a lead, many similar compounds would be made and tested for pharmacological effectiveness. In many cases, the researchers did not know how the drug worked, so finding an optimal compound was difficult.

The development of cimetidine was radically different: it was one of the first drugs to be designed logically from first principles. SK&F's multidisciplinary research team first looked at the physiological cause of acid secretion. They confirmed that a molecule found in the body called histamine triggers the release of acid when it binds to a specific receptor (now called the H_2 -receptor) in the stomach lining. Their aim was to find a molecule that successfully competed with histamine in combining with the receptor, but then blocked, rather than stimulated, acid release. Such a molecule was called a histamine H_2 -receptor antagonist and represented a new class of drugs.

Using a step by step analysis of structural and physical properties, the team made a series of histamine-based molecules, which were then tested for antagonist activity using carefully designed pharmacological assays. Today, this approach of rational drug design underpins the discovery programs of many major pharmaceutical companies.



Chifre d'affaires (2003): US\$ 29,0 bilhões
(crescimento vegetativo 10%/ano)

Investimentos R&D: US\$ 4,4 bilhão

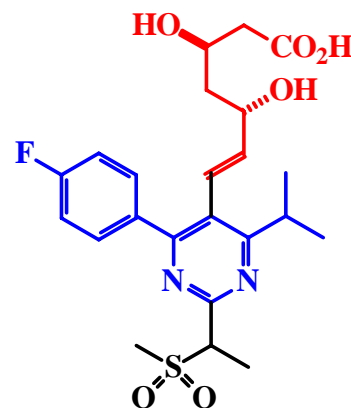
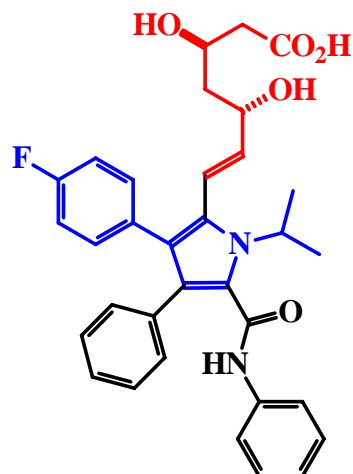
Pipeline: 53 projetos em fase pré-clínica
148 projetos em desenvolvimento:
83 NCE's, 20 vacinas, 45 produtos

A estratégia do *me-too* continua...

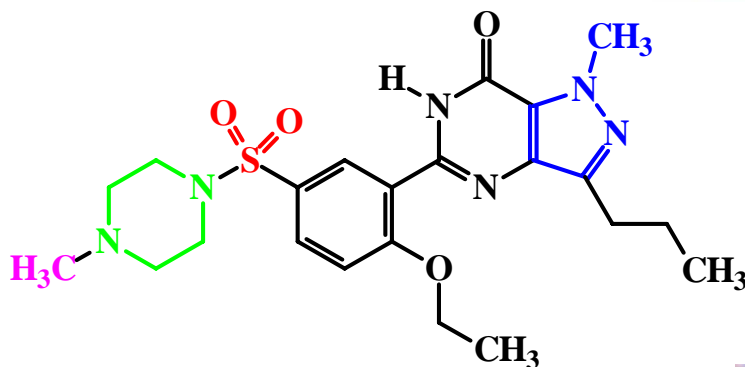
me-too



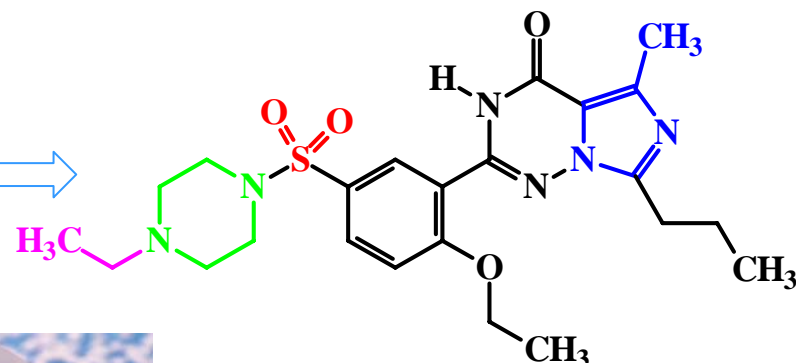
atorvastatina



rosuvastatina



sildenafil

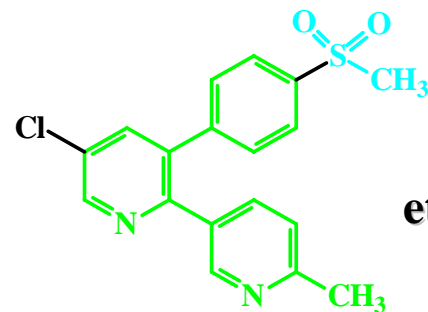
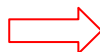
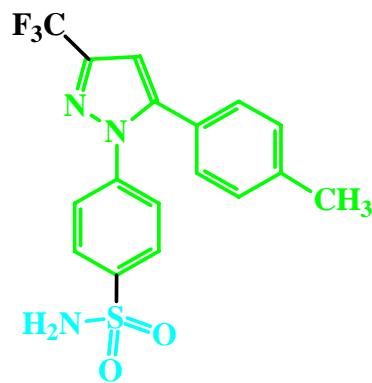


vardenafil



A estratégia do *me – too*...


celecoxib
1999



etoricoxib
2002



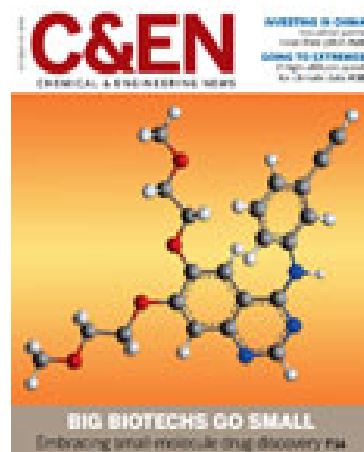
Losing Their Religion

L. M. Jarvis

C&EN October 30, 2006

Volume 84 (44), 14-20

Biotechs take a more "agnostic approach" to drug discovery by expanding into small molecules

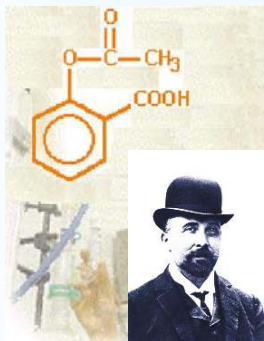


GAINING ACCESS Big biotech firms have struck a number of small-molecule deals over the past 12 months

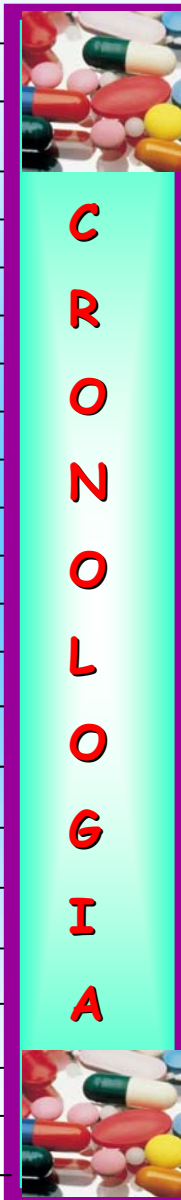
COMPANY	PARTNER	DETAILS
Serono	Newron Pharmaceuticals	License for safinamide, a central nervous system drug in Phase III trials
Biogen Idec	UCB	License for CDP323, an inhibitor of α 4-integrin
Genentech	CGI Pharmaceuticals	Alliance to develop kinase inhibitors for an undisclosed oncology target
Amgen	Predix (Epix)	Collaboration to develop S1P1 modulators for autoimmune diseases
Genentech	Inotek	Alliance to develop inhibitors of poly (ADP-ribose) polymerase for cancer indications
Amgen	ProStrakan	License for preclinical compounds for renal disease
Genentech	Piamed	Collaboration to develop oncology drugs targeting PI-3 kinase
Serono	Rigel	License for Rigel's aurora kinase program, including a lead oncology candidate

SOURCE: Company websites

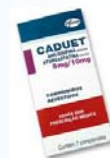
Cronologia da Descoberta de Fármacos



AAS *	1889
barbitúricos	1923
cloroquina	1934
sulfonamidas	1935
penicilina	1942
nitrofurano	1952
progesterona	1953
talidomida	1954
haloperidol	1958
verapamil	1962
indometacina	1963
propranolol	1964
salbutamol	1968
prostaglandinas	1970
oxamniquina	1970
nifedipina	1975
cimetidina	1976
atenolol	1976
captopril	1977
oxicams	1980
praziquantel	1980
aciclovir	1981



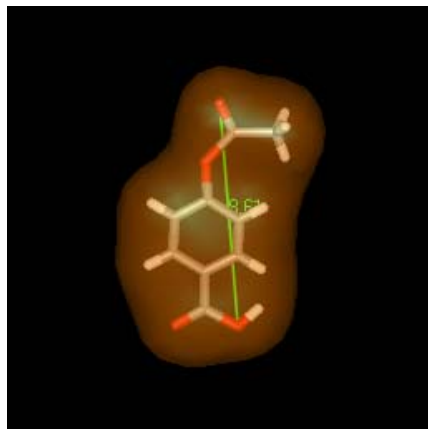
1981	ranitidina
1985	misoprostol
1985	mefloquina
1987	azidovudina
1987	lovastatina
1989	ozagrel
1989	mifepristona
1989	fluoxetina
1990	salmeterol, amlodipina
1993	tacrina, fanciclovir
1995	indinavir, saquinavir
1996	docetaxel, atorvastatina
1996	zileuton, efavirenz, olanzapina
1997	zafirlukast, montelukast
1998	infliximab
1999	celecoxib orlistat sildenafil
2000	galantamina rofecoxib
2001	imatinib
2002	apomorfina, etoricoxib
2003	varденаfil, gefitinibid, aripiprazola
2004	rosuvastatina, rofecoxib
2005	pregabalin, Caduet ^R
2006	risperidona, vorinostat (Zolynza ^R)



Everyone is searching for drugs

Editorial overview
Alan Cuthbert

Current Opinion in Pharmacology 2004, **4**, 487

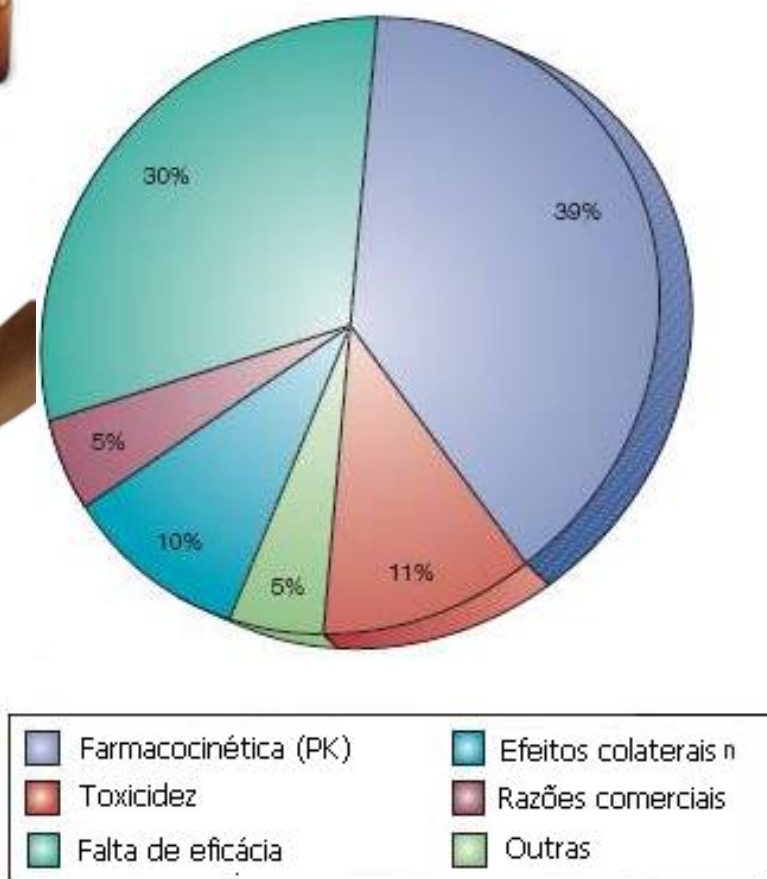
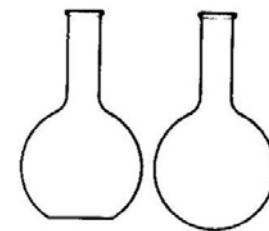


Big-pharma
&
Small
molecules





Principais gargalos do processo de descoberta de novos fármacos





Os gargalos da inovação na indústria farmacêutica

Drug Information Journal, Vol. 30, pp. 97-107, 1996
Printed in the USA. All rights reserved.

0092-8615/96
Copyright © 1996 Drug Information Association Inc.

INNOVATION DEFICIT IN THE PHARMACEUTICAL INDUSTRY

JÜRGEN DREWS, MD

President, International Research

STEFAN RYSER, PhD

Scientific Assistant to the President, International Research

Hoffmann-La Roche Inc., Nutley, New Jersey

Novos fármacos

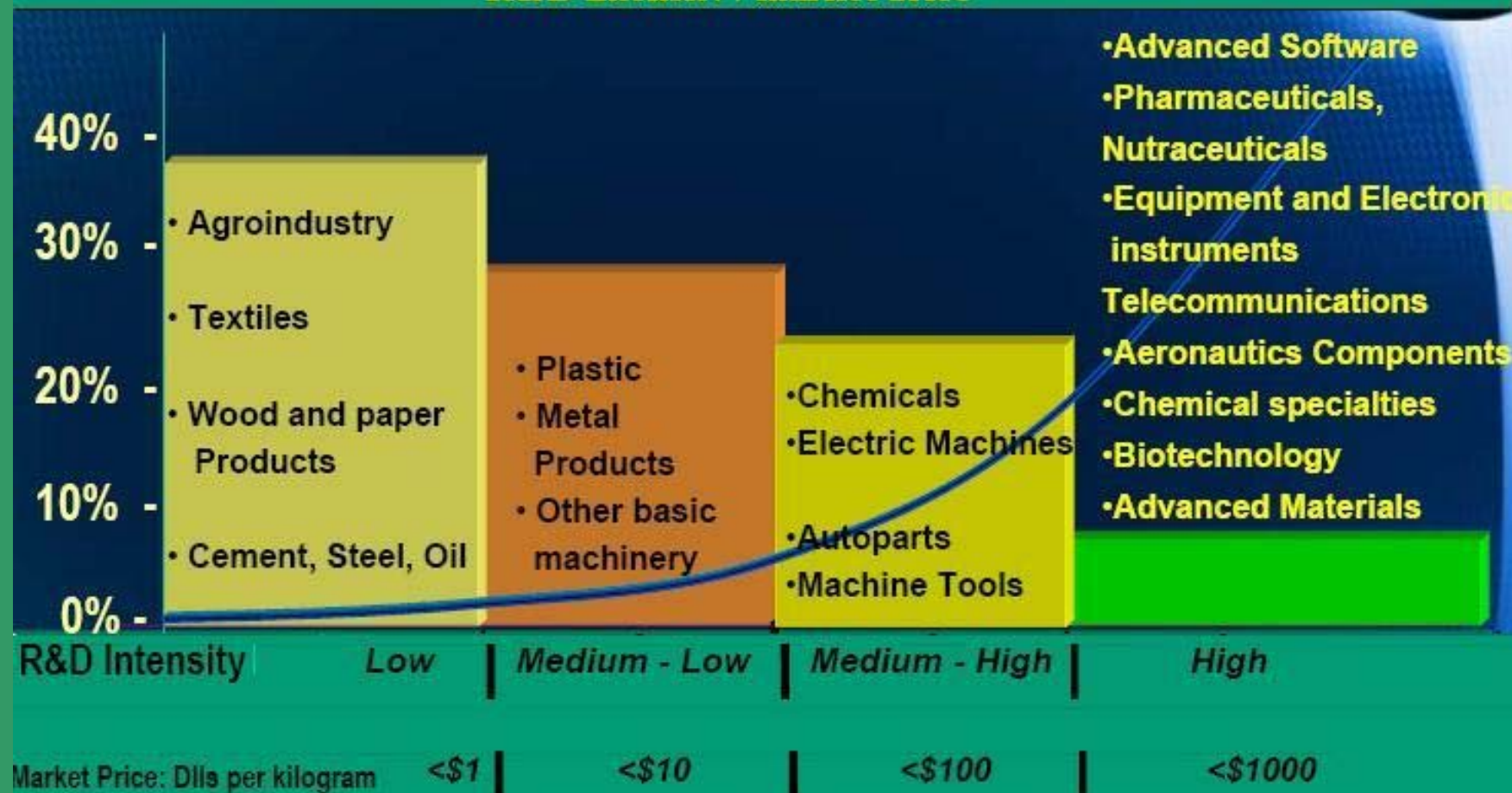
1990 – 1994 = 215

1995 – 1999 = 207

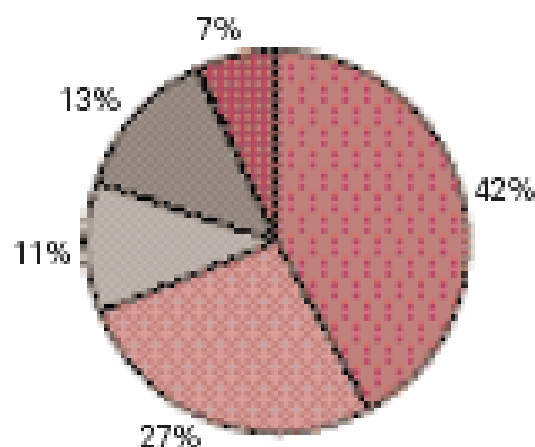
2000 – 2004 = 162



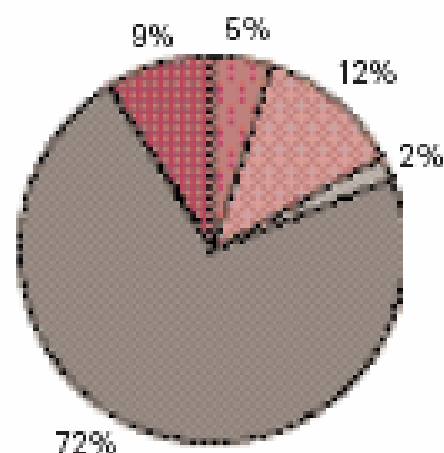
R&D intensity / market price








Mercado mundial de medicamentos (US\$406 bilhões em 2002)



População mundial (seis bilhões de pessoas em meados de 2001)



-  América do Norte
-  Europa
-  Japão
-  África, Ásia e Oriente Médio
-  América Latina

Fontes: IMS Health / Population Reference Bureau |

Declaração da Cúpula do Milênio da Nações Unidas, Nova York, 6 a 8 de setembro de 2000



O Projeto do Milênio
Secretário-Geral das Nações Unidas em 2002

2015

“....Países em desenvolvimento provavelmente continuarão imersos na pobreza a menos que possam fazer o que países desenvolvidos fizeram para atingir o crescimento sustentável: ***incorporar ciência, tecnologia e inovação*** em suas estratégias econômicas ... ”



Fármacos e medicamentos são instrumentos essenciais à assistência farmacêutica, eficiente e segura à população sendo, portanto, agentes de efetiva inclusão social, imprescindíveis ao pleno exercício da soberania da Nação.



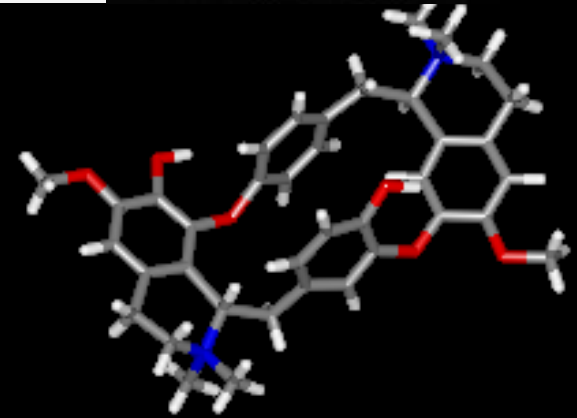
Os fármacos & nós.....



Curare

Fármaco dos Índios

Bloqueadores ganglionares

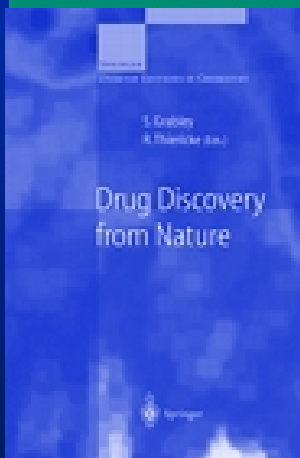


d-tubocurarina

Chondrodendron tomentosum



Patrimônio genético brasileiro



Inovações terapêuticas



M. O. Rocha e Silva
1910-1983



S. H. Ferreira
1934-

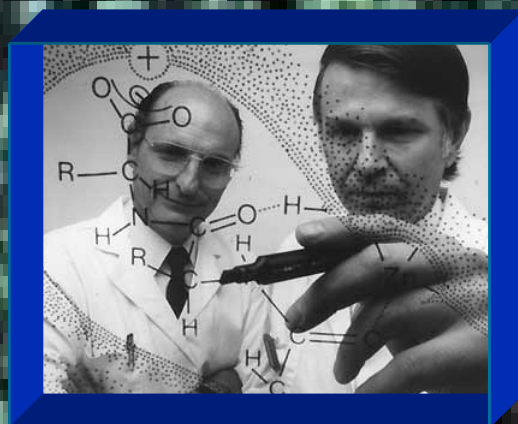
S.H. Ferreira, A Bradykinin-potentiating factor (BFP) present in the venom of *Bothrops jararaca*, *Brit. J. Pharmacol.* 1965, 24, 163.



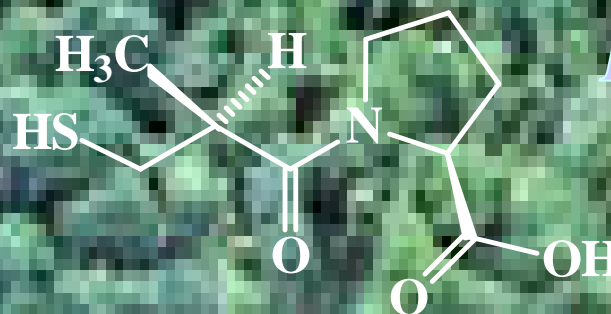
**Descoberta do sistema
renina-angiotensina
(RAS)**



**Inibidor
ECA**



D. W. Cushman & M. A. Ondetti



**Captopril
(Capoten[®])**



M. A. Ondetti, D. W. Cushman & B. Rubin, *Chronicles of Drug Discovery*, vol. 2, J.S. Bindra & D. Lednicer, Eds., Wiley, Nova Iorque, 1983, p. 1-32

Anti-hipertensivos inibidores da enzima conversora

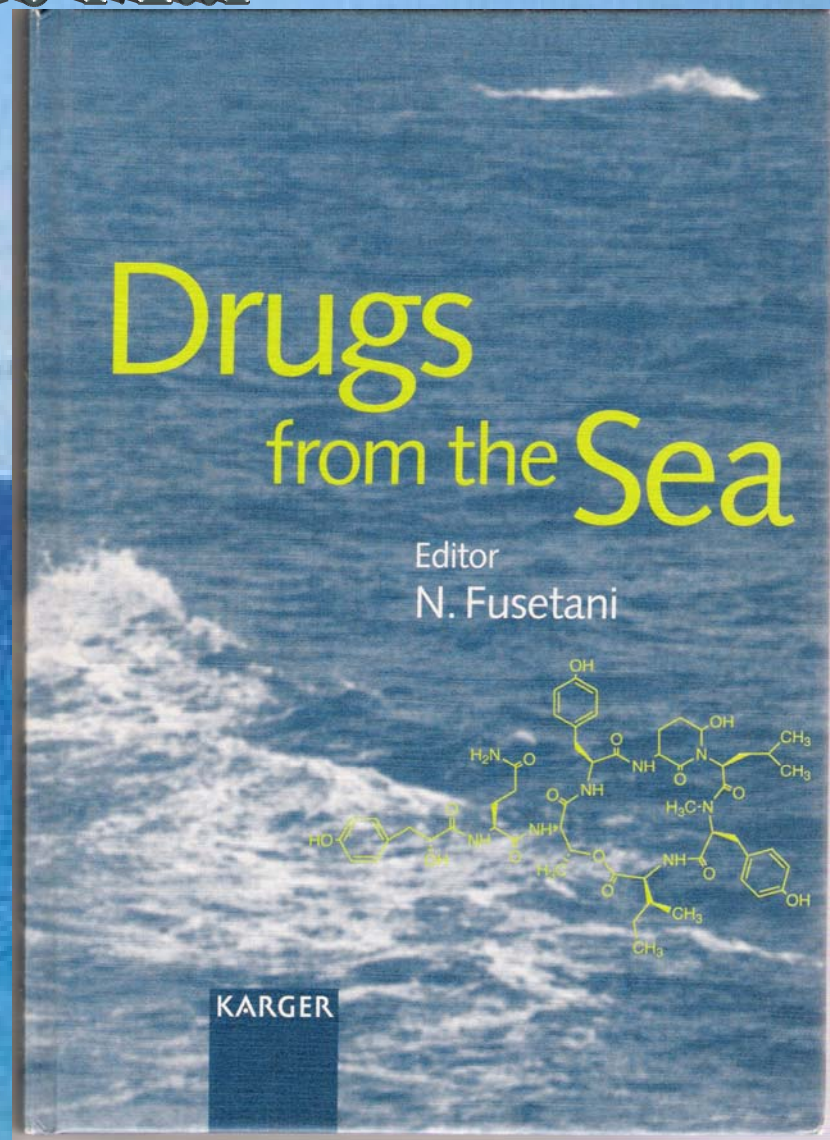
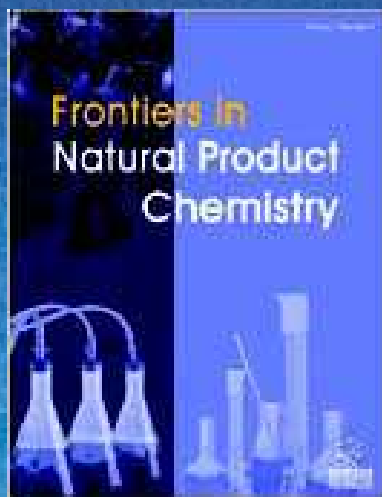
Compound	Company	Target	Protease class
Captopril	Bristol-Myers Squibb	ACE	Metallo
Enalapril	Merck		
Lisinopril	AstraZeneca		
Trandolapril	Abbott		
Zofenopril	Menarini group		
Ramipril	Aventis		
Moexipril	Boehringer Mannheim		
Imidapril	Trinity Pharmaceuticals		
Perindopril	Daiichi Pharmaceutical, Servier/Solvay		
Qinapril	Pfizer		
Fosinopril	Bristol-Myers Squibb		
Benazepril	Novartis		
Cilazapril	Roche		



Produtos Naturais do Mar



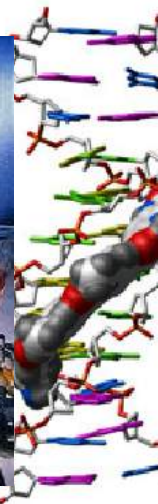
N. Fusetani



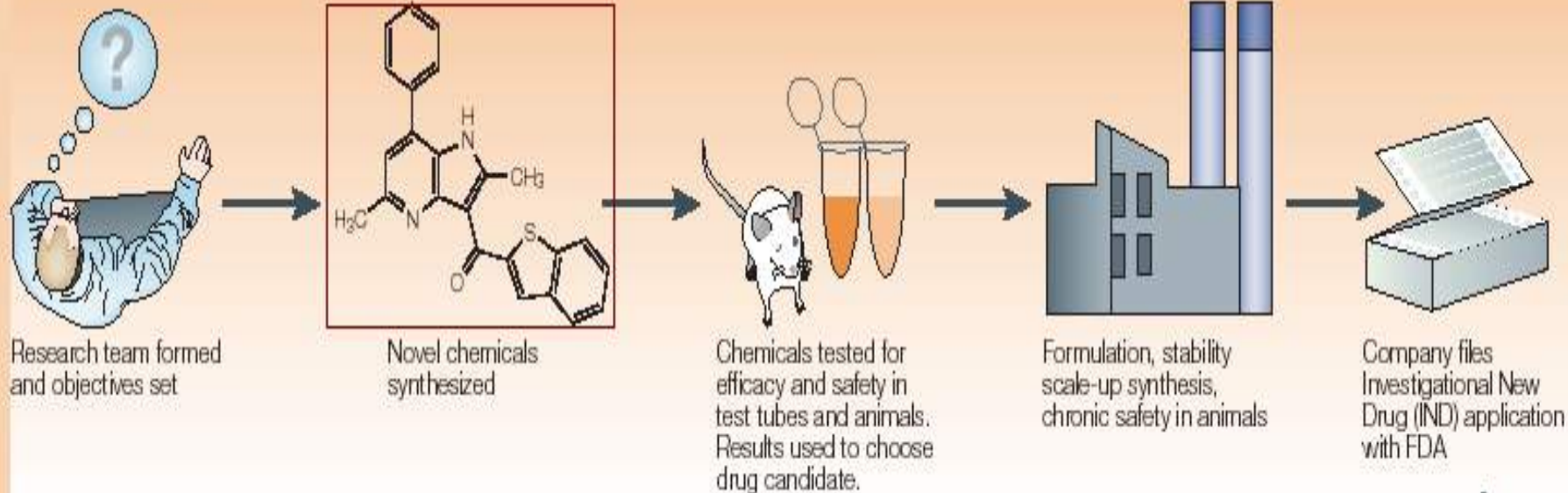
Produtos Naturais Marinhos em Ensaios Clínicos

Composto	Organismo	Fase	Doença
KRN7000	Porifera	I	câncer
IPL-567	Porifera	I	inflamação
methopetrosin	Celenterata	I	inflamação
GST-21	nemertea	I	Alzheimer
Dolastatina 10	molusco	II	câncer
LU-103793	molusco	I	câncer
Ziconitido	molusco	III	dôr
Briostatina	Briozoa	II	câncer
Didemnina B	Urocordarta	II	câncer
Ecteinascidina 743	Urocordata	II	câncer
Esqualamina	Cordata	I	câncer

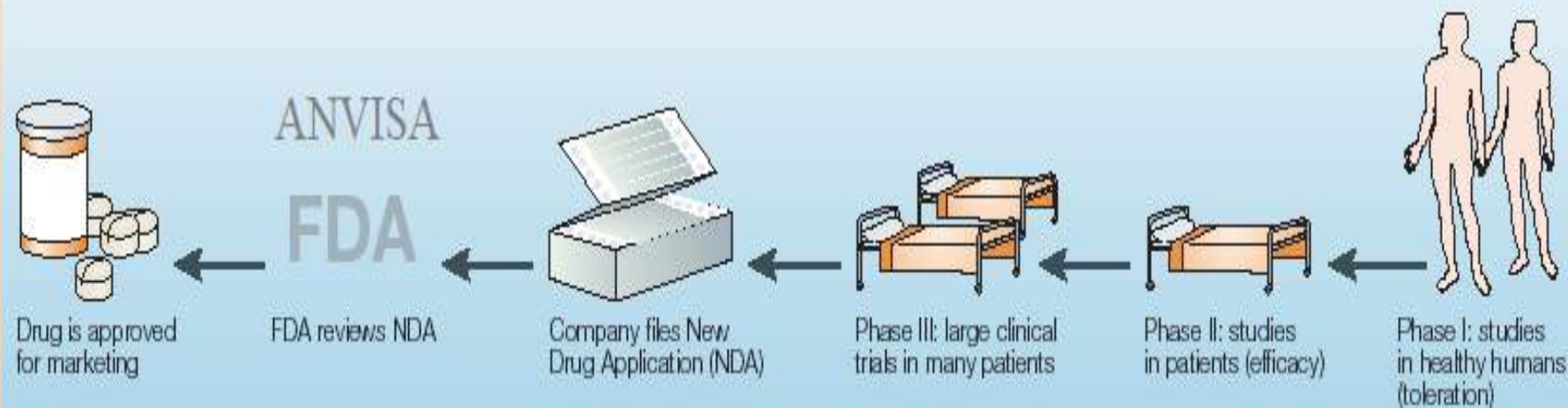
Como se descobrem
os fármacos?



Preclinical studies



Clinical studies



Química

A Química Medicinal é uma disciplina que estuda os aspectos relacionados à descoberta, invenção e preparação de substâncias bioativas,

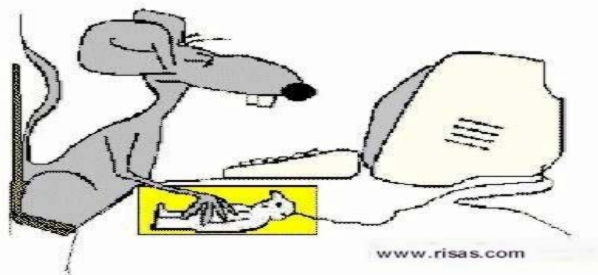
Medicinal

de interesse terapêutico, i.e. fármacos.

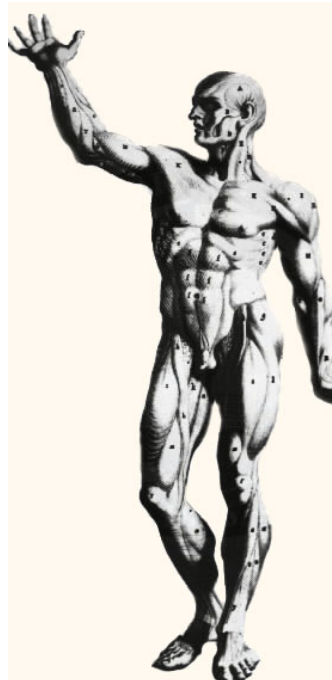
Estuda os fatores moleculares do modo de ação dos fármacos, incluindo a compreensão

da relação entre a estrutura química e a atividade terapêutica, absorção, distribuição, metabolismo, eliminação e toxicidade.

medicinal chemistry

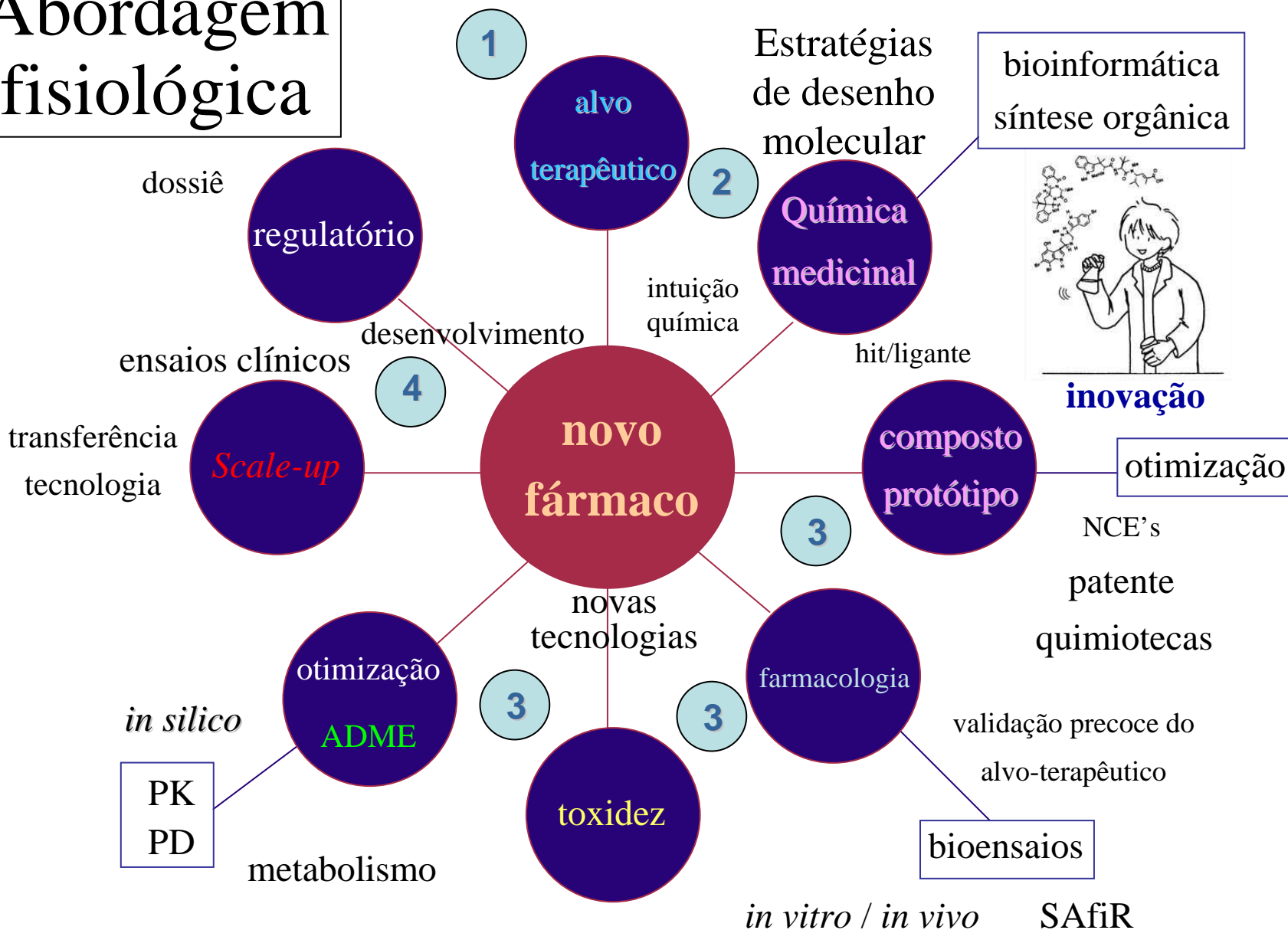


Lactic Acid Bacteria
Computer Aided Drug Design



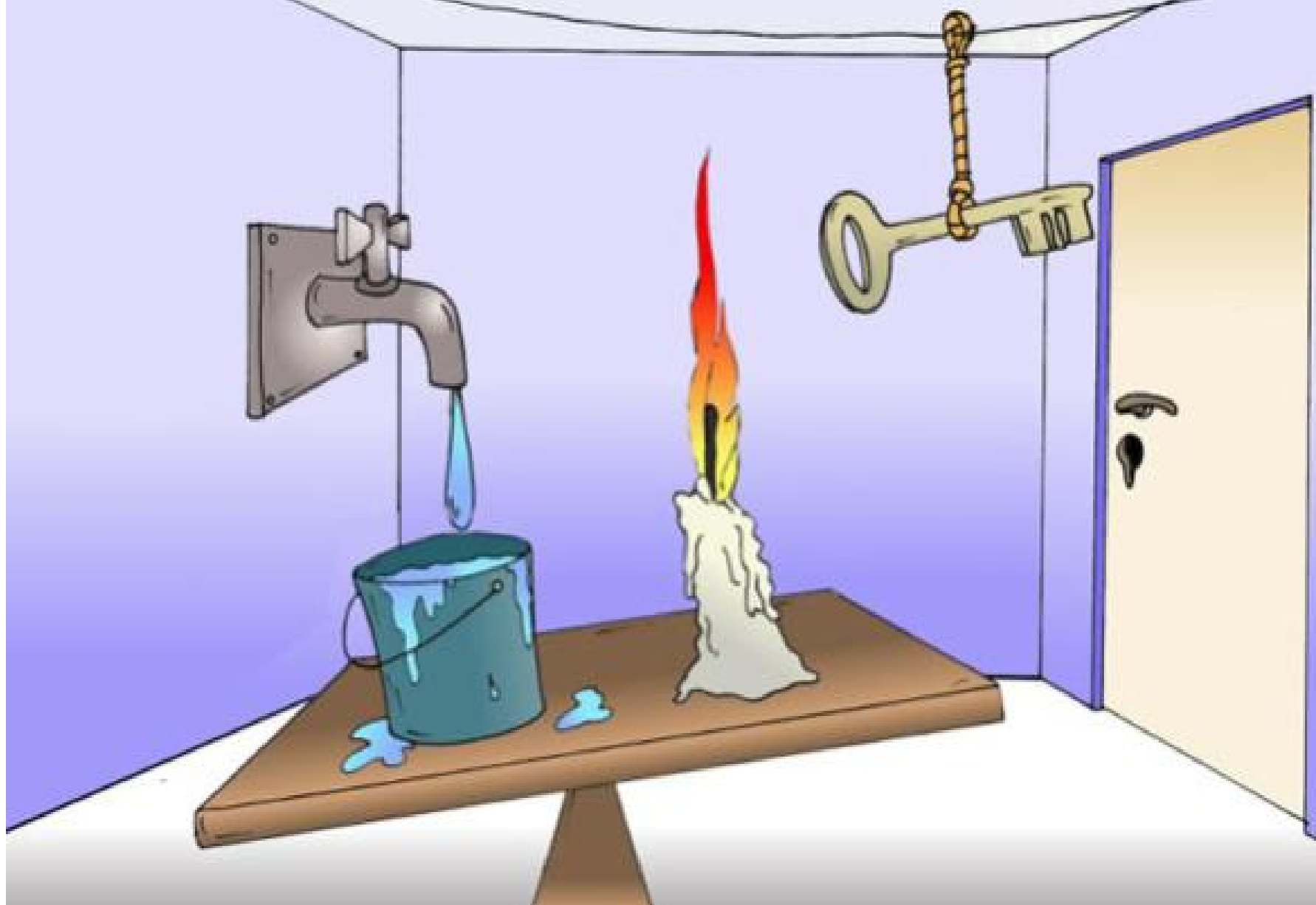
Interdisciplinaridade

Abordagem fisiológica





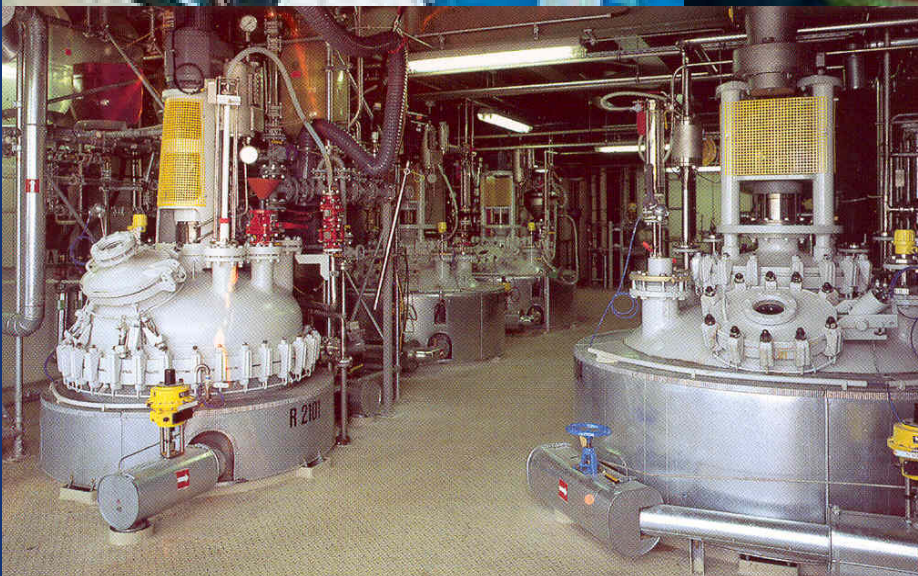
O processo racional da descoberta de fármacos





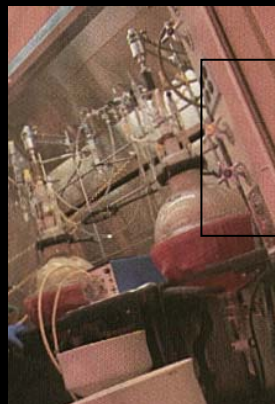
equipe





Fármacos sintéticos

Características dos Fármacos



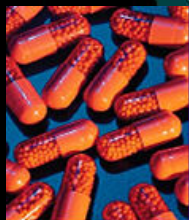
Heterocíclicos
62%



N 95%

S 28%

O 18%



Não-heterocíclicos
38%

HJ Roth et al., 1988

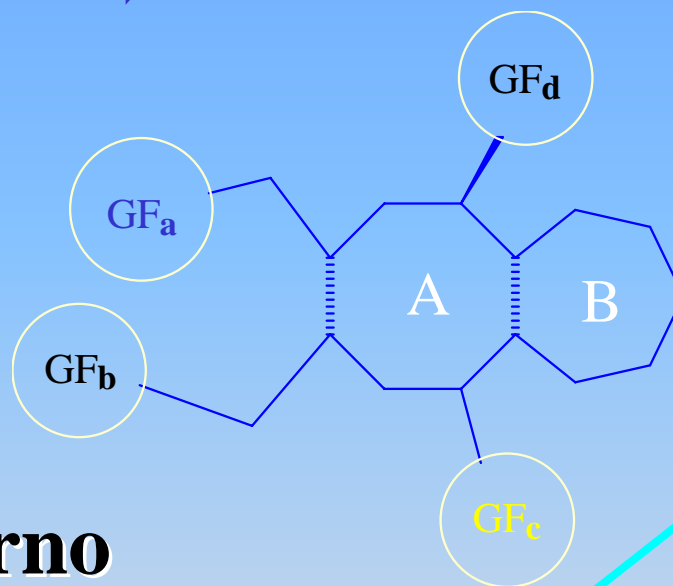
Paradigma antigo

**Composto
Sintético**

**Atividade
Biológica**

C, H, O, N, S, Cl, F

Análise elementar > 100%



**Produto
Natural**

Paradigma moderno

**Atividade
Farmacológica
(Fármaco)**

**Novo
Composto
Sintético**

Protótipo

ED₅₀