

# A inovação radical em fármacos no País, uma perspectiva pessoal



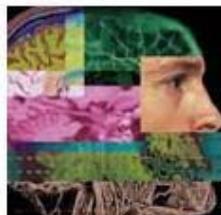
LASSBio®

UFRJ

Eliezer j. Barreiro

Professor Titular

Universidade Federal do Rio de Janeiro



# the Pharmaceutical Century

TEN DECADES OF DRUG DISCOVERY



*Analytical Chemistry* | *Chemical & Engineering News* | *Modern Drug Discovery*  
*Today's Chemist at Work* | *E-Mail Us* | *Electronic Readers Service*

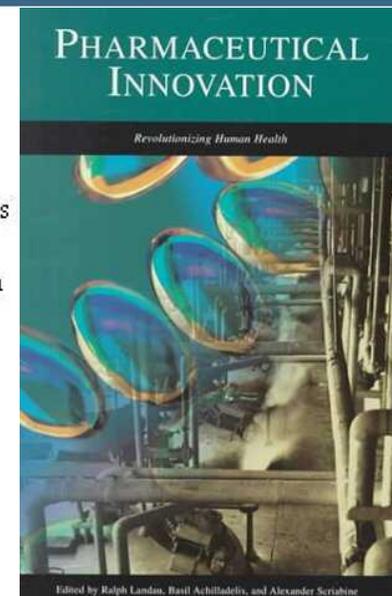
1800s to 1919

We live today in a world of drugs. Drugs for pain, drugs for disease, drugs for allergies, drugs for pleasure, and drugs for mental health. Drugs that have been rationally designed; drugs that have been synthesized in the factory or purified from nature. Drugs fermented and drugs engineered. Drugs that have been clinically tested. Effective. Safe.

Binômio doença-doente



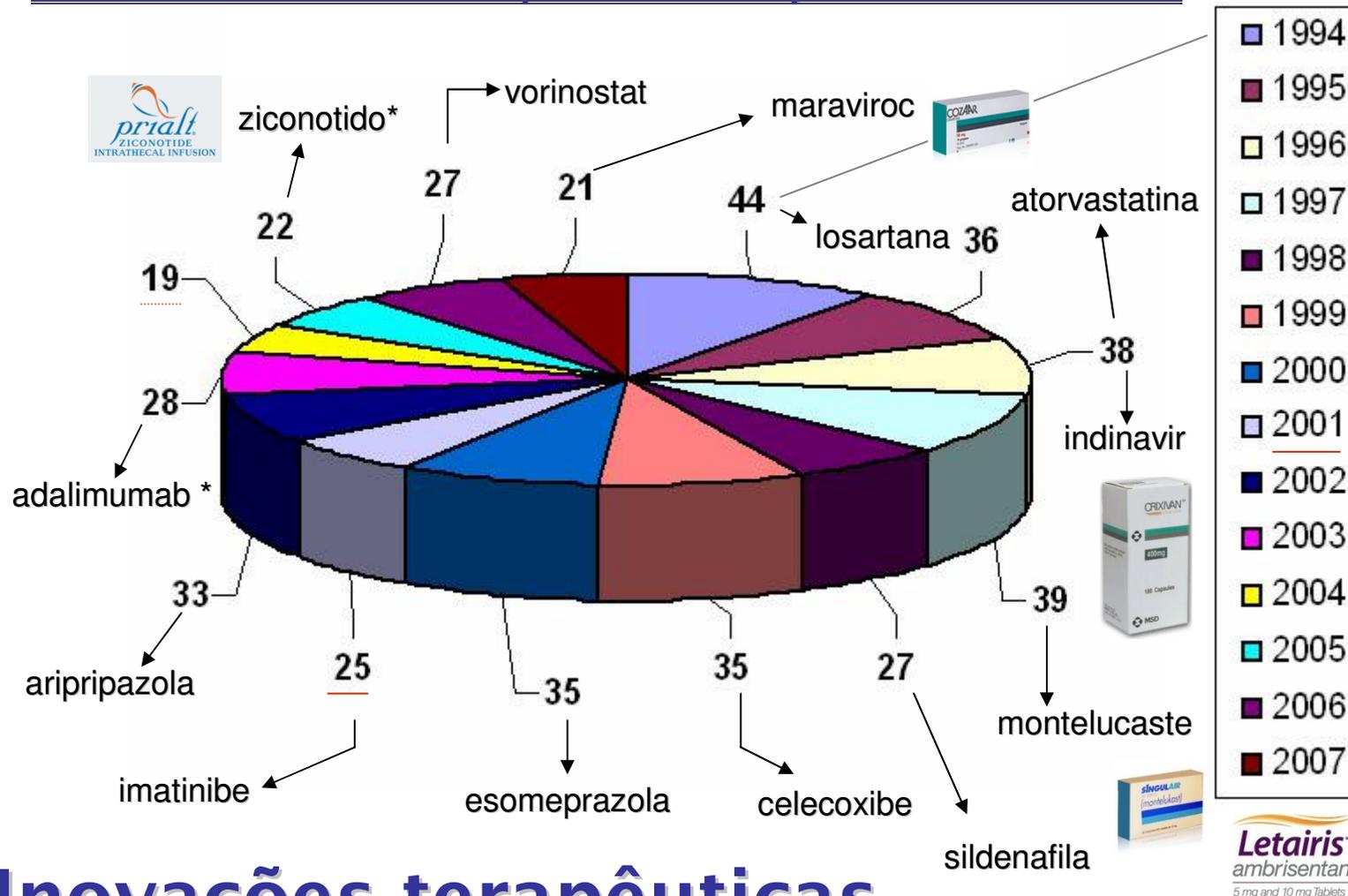
zoom



"We live today in a world of **drugs**. Drugs for **pain**, drugs for **disease**, drugs for **allergies**, drugs for **pleasure**, and drugs for **mental health**. Drugs that have been **rationally designed**; drugs that **have been synthesized** or **purified from nature**. Drugs **fermented** and drugs **engineered**. Drugs that have been clinically tested. Effective. Safe."



# Novos fármacos lançados por ano (1994 – 2007)

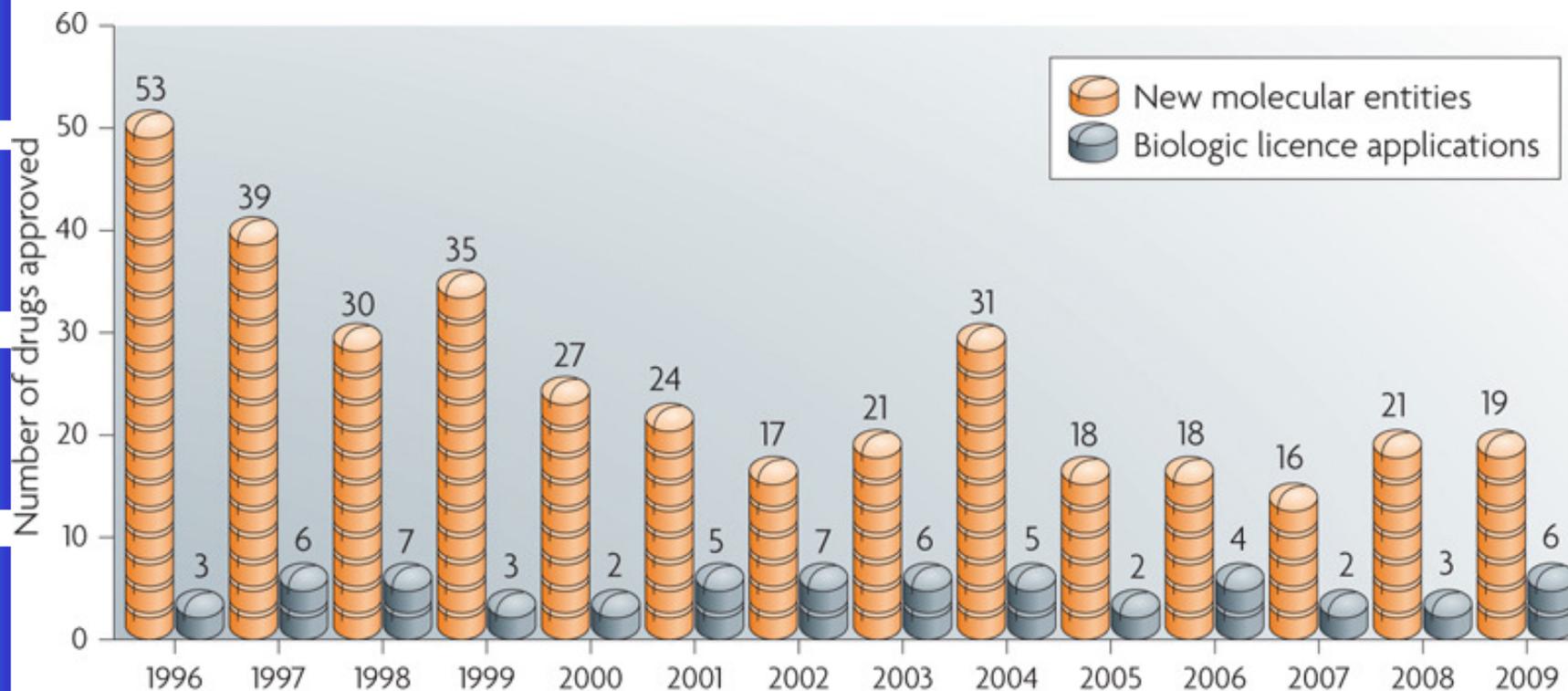


## Inovações terapêuticas

ca. 30 novos fármacos lançados / ano



# Os fármacos inovadores estão mais raros...



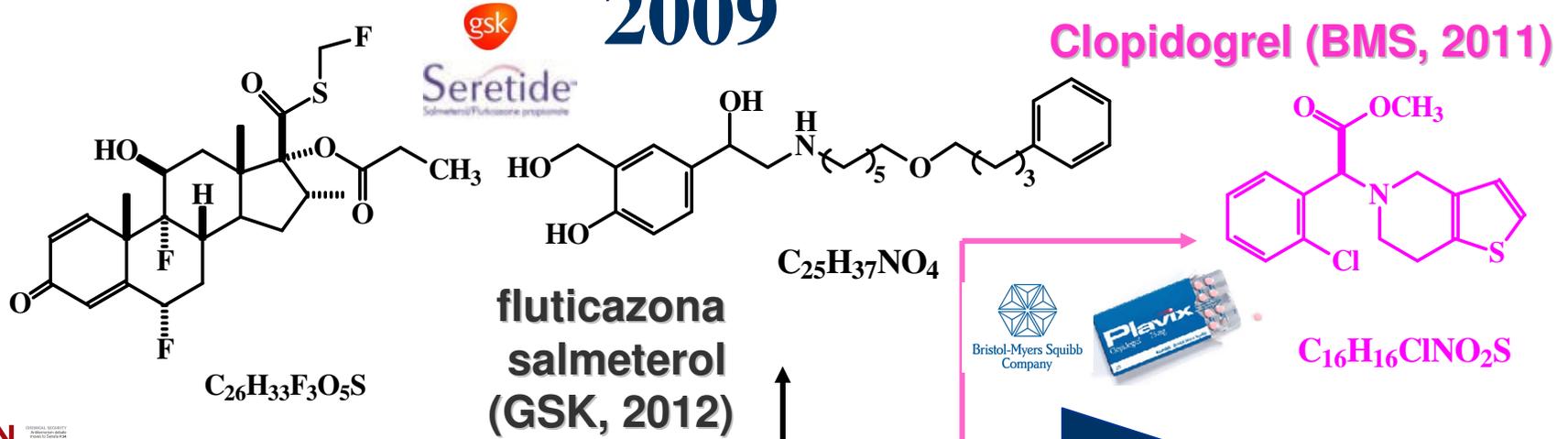
*Ou:* as inovações já não são assim tão inovadoras!



Nature Reviews | Drug Discovery



# Os top-5 fármacos no mercado mundial\* 2009



**Etanercept**  
 (Enbrel<sup>®</sup>, biofármaco)

**Olanzapina**  
 (Zyprexa<sup>®</sup>, AstraZeneca)

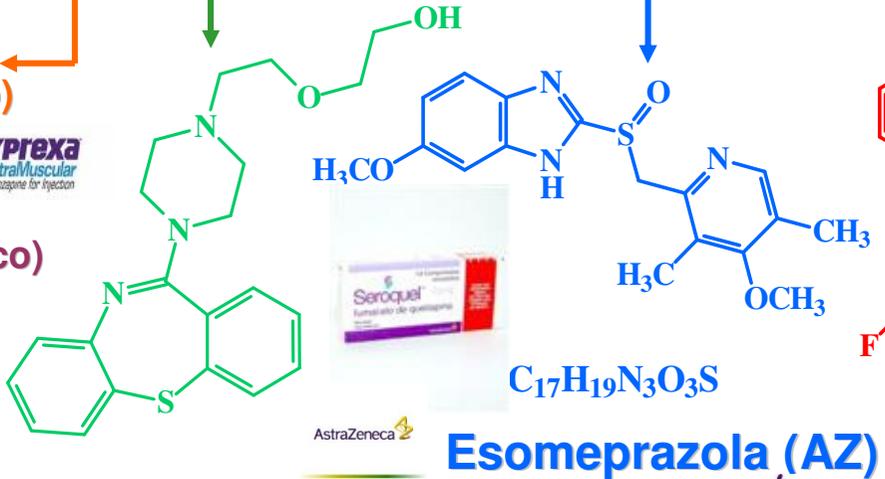
**Infliximabe**  
 (Remicade<sup>®</sup>, biofármaco)

**Montelukast**  
 (Singulair<sup>®</sup>, Merck)

**Rosuvastatina**  
 (Crestor<sup>®</sup>, AZ)

**68,1**  
 (8,2%)

**CRESTOR**  
 rosuvastatin calcium



**Atorvastatina**  
 (Pfizer; 06/2011)

**C<sub>33</sub>H<sub>35</sub>FN<sub>2</sub>O<sub>5</sub>**

**Nexium**  
 (esomeprazole magnesiumum)

**Letron**  
 Pfizer

\* SJ Ainsworth, C&EN 2009 (07/12) 13-21



# • Inovação radical

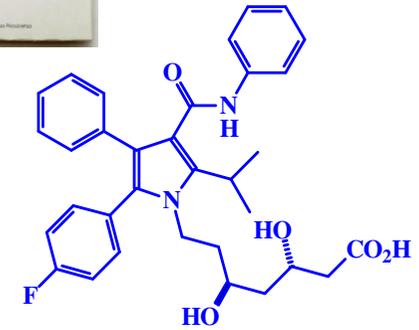
1970 - Akira Endo isola, no Japão, a compactina de fungos

1979 - A. Endo isola a lovastatina de *Monascus ruber*

1980 - A. Patchett (Merck) descobre a lovastatina em *Aspergillus sp.*

1986 - simvastatina, fluvastatina

*me-better*



C<sub>33</sub>H<sub>35</sub>FN<sub>2</sub>O<sub>5</sub>

1999 - rosuvastatina

## ESTATINAS

atorvastatina



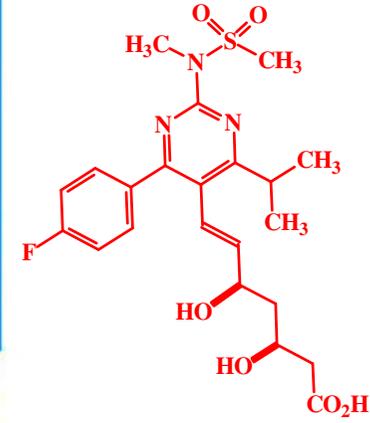
1950 - colesterol plasmático é relacionado ao risco de doenças coronarianas

a estrutura da compactina permite a eleição do alvo: HMG-CoA redutase

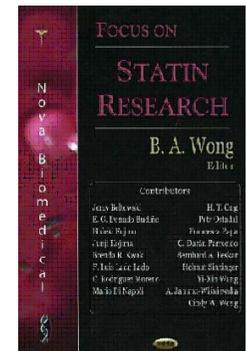
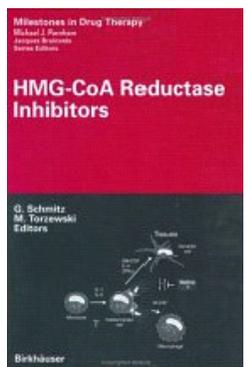
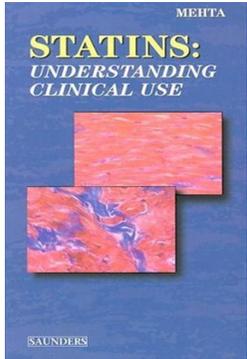


1987 - FDA (EUA) aprova a lovastatina

1993



*me-too*



1988 - pravastatina (estudos do metabolismo da compactina)





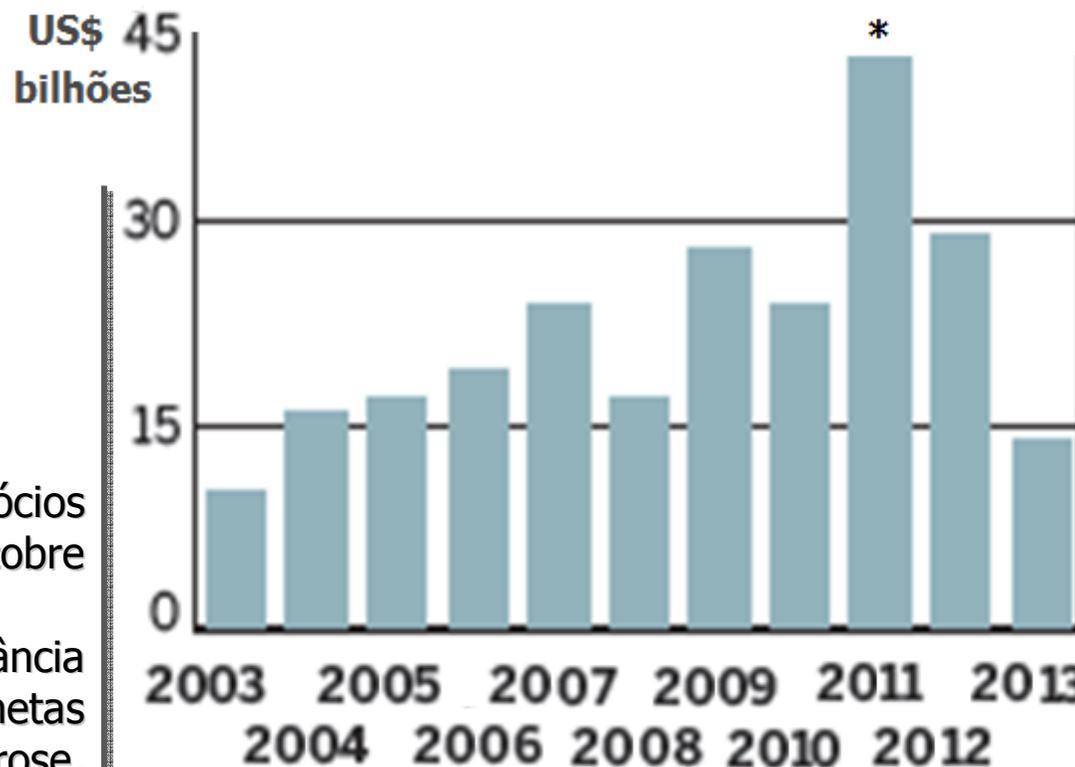
DECEMBER 7, 2009  
**C&EN**  
 CHEMICAL & ENGINEERING NEWS  
 CHEMICAL SECURITY  
 Antiterrorism debate moves to Senate I  
 TRIBOLC  
 Molecular wear and tear unusual systems I



**PHARMA REFORMULATES**  
 Pushing plans to fortify pipelines, profits p.13  
PUBLISHED BY THE AMERICAN CHEMICAL SOCIETY

As estratégias de negócios mudam na IF que descobre moléculas inovadoras: Novas fusões, alternância geográfica, ajustes de metas terapêuticas (osteoporose, sistema respiratório, trombose, esclerose múltipla, altismo, câncer), participação no mercado de medicamentos genéricos (ca. US\$ 80 bi em 2009; Aventis & Medley, BR)

A IF global observará reduções nos oito principais mercados (EUA, Jpn, Fr, Ale, It, Ch, Sp, UK)



\* Três blockbusters perderão proteção patentária: e.g. atorvastatina, clopidogrel & seretide

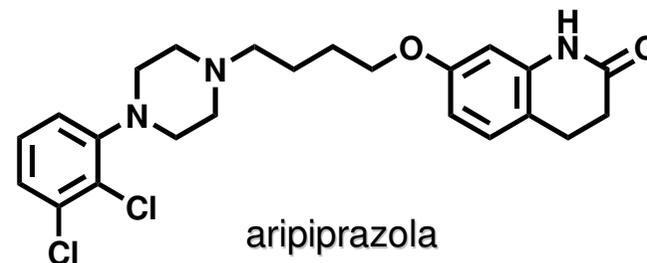
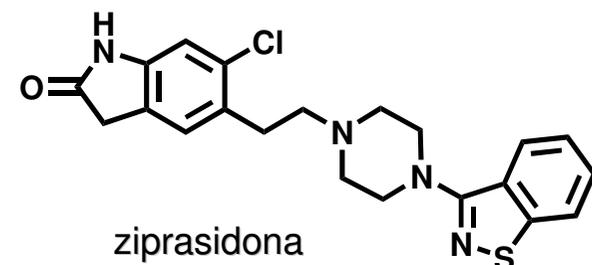
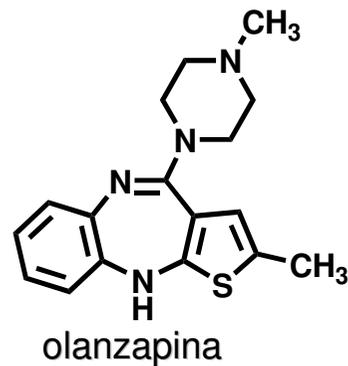
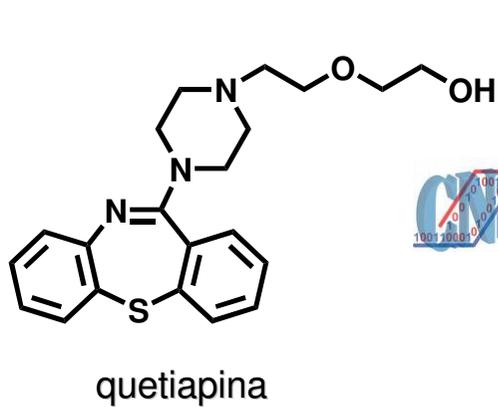
Fonte: SJ Ainsworth, *C&EN* 2009 (07/12) 13-21





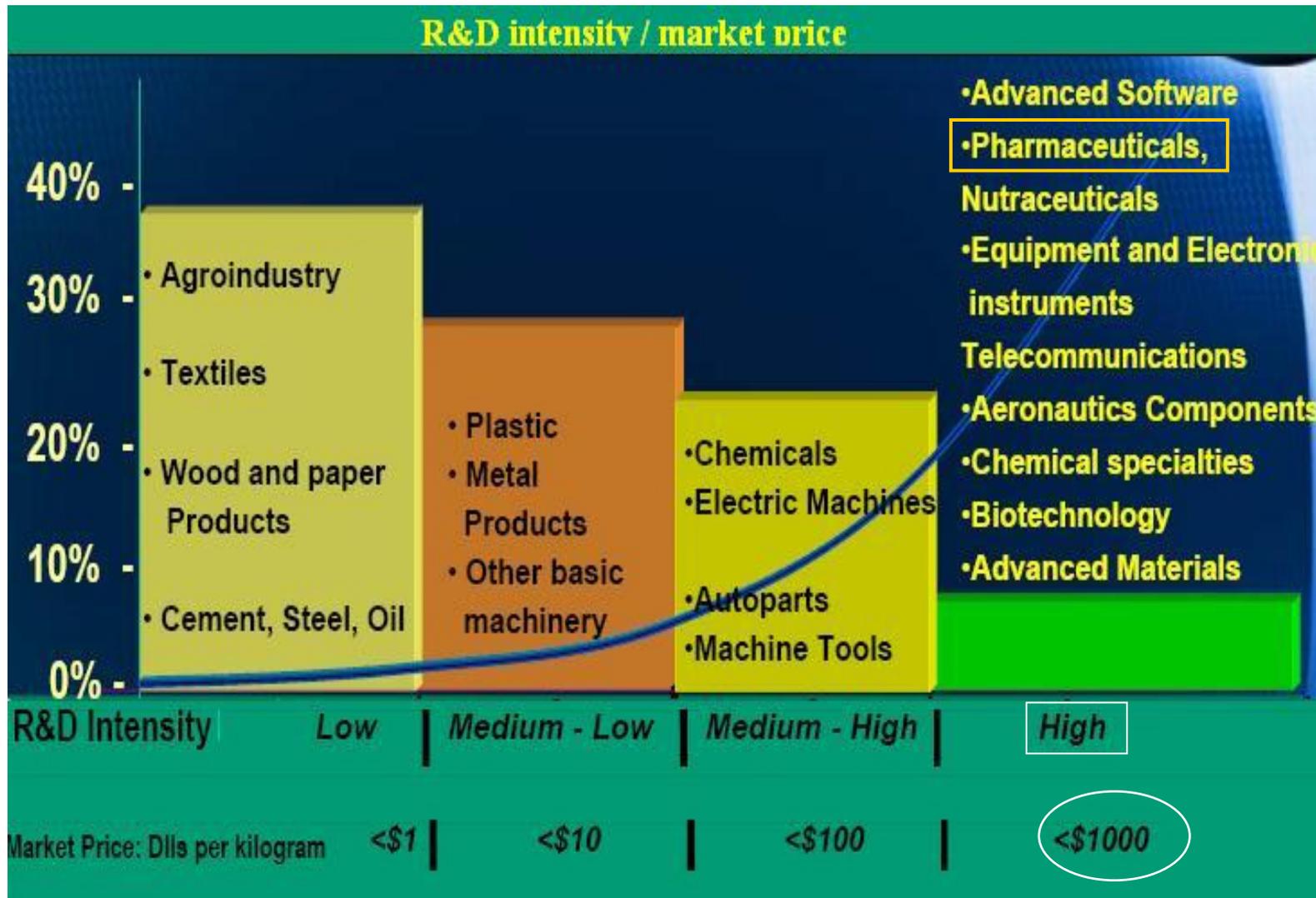
Company	Launched drug	Mechanism of action	2006 sales worldwide (US\$)	Patent expiration
Pfizer	Lipitor	5-HMGCoAR	13,8 billion	2011
Eli Lilly	Zyprexa (olanzapine)	D <sub>2</sub> , 5-HT <sub>2</sub> , M <sub>1-4</sub> , H <sub>1</sub> antagonist	4.3 billion	2011
Pfizer	Geodon (ziprasidone)	D <sub>2</sub> , 5-HT <sub>2</sub> antagonist	0.8 billion	2012
AstraZeneca	Seroquel (quetiapine fumarate)	D <sub>2</sub> , 5-HT <sub>2</sub> , 5-HT <sub>6</sub> , H <sub>1</sub> antagonist	3.6 billion	2012
Bristol-Myers Squibb	Abilify (aripiprazole)	D <sub>2</sub> partial agonist	1.2 billion	2014

5-HT, 5-hydroxytryptamine receptor;  $\alpha$ -2<sub>A</sub>,  $\alpha$ -2<sub>A</sub> adrenoceptor; D<sub>2</sub>, dopamine receptor 2; H<sub>1</sub>, histamine receptor 1; M<sub>1-4</sub>, muscarinic receptors 1-4.



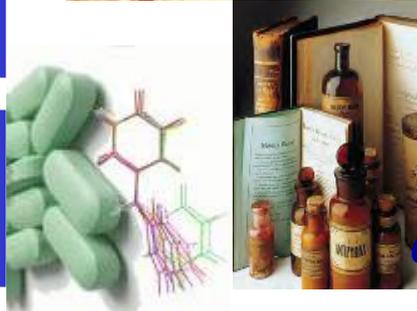
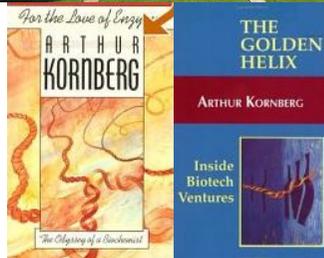
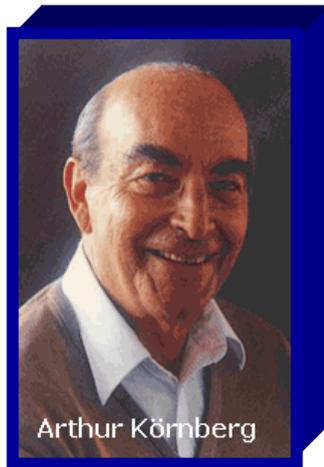


# A inovação em fármacos depende da pesquisa



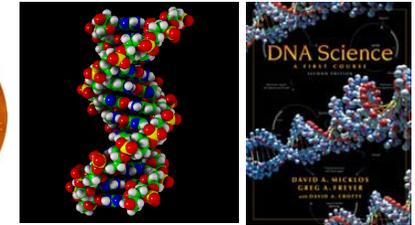
*The New York Times*, 15 de maio de 2007  
O mercado global de patentes é de US\$ 200 bi!

Em 2006, o Brasil ocupava o 48º lugar dentre os inovadores, a Rússia 37ª, o México 45ª, o Chile 47ª, a Índia 58ª e a China 59ª.



# Nobel Prize, 1959

“for their discovery of the mechanisms in the biological synthesis of RNA and DNA”



“We have the paradox of the two cultures,

chemistry and biology,

growing further apart even as they discover more common ground....

Pharmaceutical chemistry was until recently the bastion of organic chemistry... in the search for alternative or superior drugs for the treatment of various diseases.”

Arthur Kornberg

Biochemistry 1987, 26, 6888-6891

Interdisciplinaridade

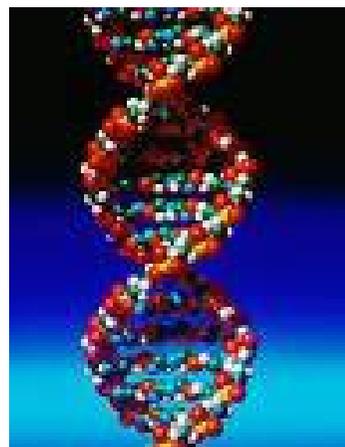
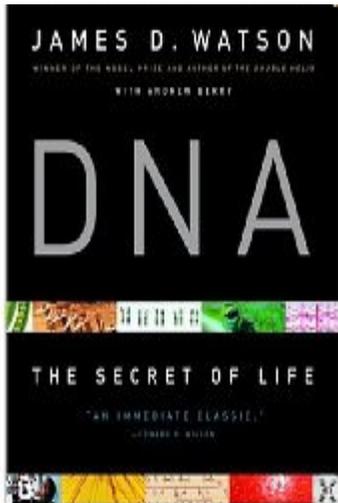
## Slide 11

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### EJB25

Kornberg definiu as bases da interdisciplinaridade das ciências dos fármacos quando antecipou a necessidade de aproximar-se a Química e a Biologia.

Eliezer J. Barreiro; 04/03/2010



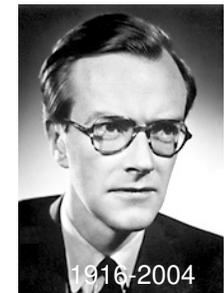
1916-2004

1928-

Francis Crick and James Watson in Cambridge, England, 1953  
(Courtesy of the James D. Watson Special Collection, Cold Spring Harbor Laboratory Archives.  
From Watson J.D. 1968, *The Double Helix*. Atheneum Press, New York.)



1962



1916-2004

Maurice H. F. Wilkins

## *O físico Crick & biólogo Watson*

Watson, JD & Crick, FHC Nature 1953, **171**, 737-738

# Interdisciplinaridade

## Slide 12

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### EJB24

Exemplos de extraordinárias conquistas do conhecimento humano deveram-se às associações de capacidades e competências complementares, essenciais à sua consecução: e.g. DNA em publicação de apenas 2 páginas em prestigioso periódico científico que resultou, décadas depois, na era ômica.

JD Watson & FHC Crick, *Nature*, 1953, 171, 737-738

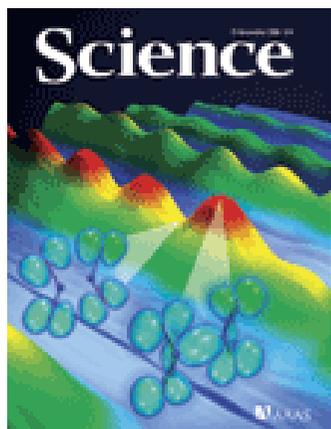
Eliezer J. Barreiro; 04/03/2010



# Multi-University Research Teams: Shifting Impact, Geography, and Stratification in Science



Benjamin F. Jones,<sup>1,2\*</sup> Stefan Wuchty,<sup>3\*</sup> Brian Uzzi<sup>1,3,4\*</sup>



SCIENCE VOL 322 21 NOVEMBER 2008 1259

<sup>1</sup>Kellogg School of Management, Northwestern University, Evanston, IL 60208, USA. <sup>2</sup>National Bureau of Economic Research, Cambridge, MA 02138, USA. <sup>3</sup>Northwestern Institute on Complexity (NICO), Northwestern University, Evanston, IL 60208, USA. <sup>4</sup>Haas School of Business, University of California at Berkeley, Berkeley, CA 94720, USA.

.....  
*A pesquisa científica contemporânea se faz em ambientes de rede.*

## Slide 13

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### EJB22

Para completude em sua atuação com plena formação de M&D,I a PG precisa interagir além de sua própria arena, sem ir de lado mas com decisão.

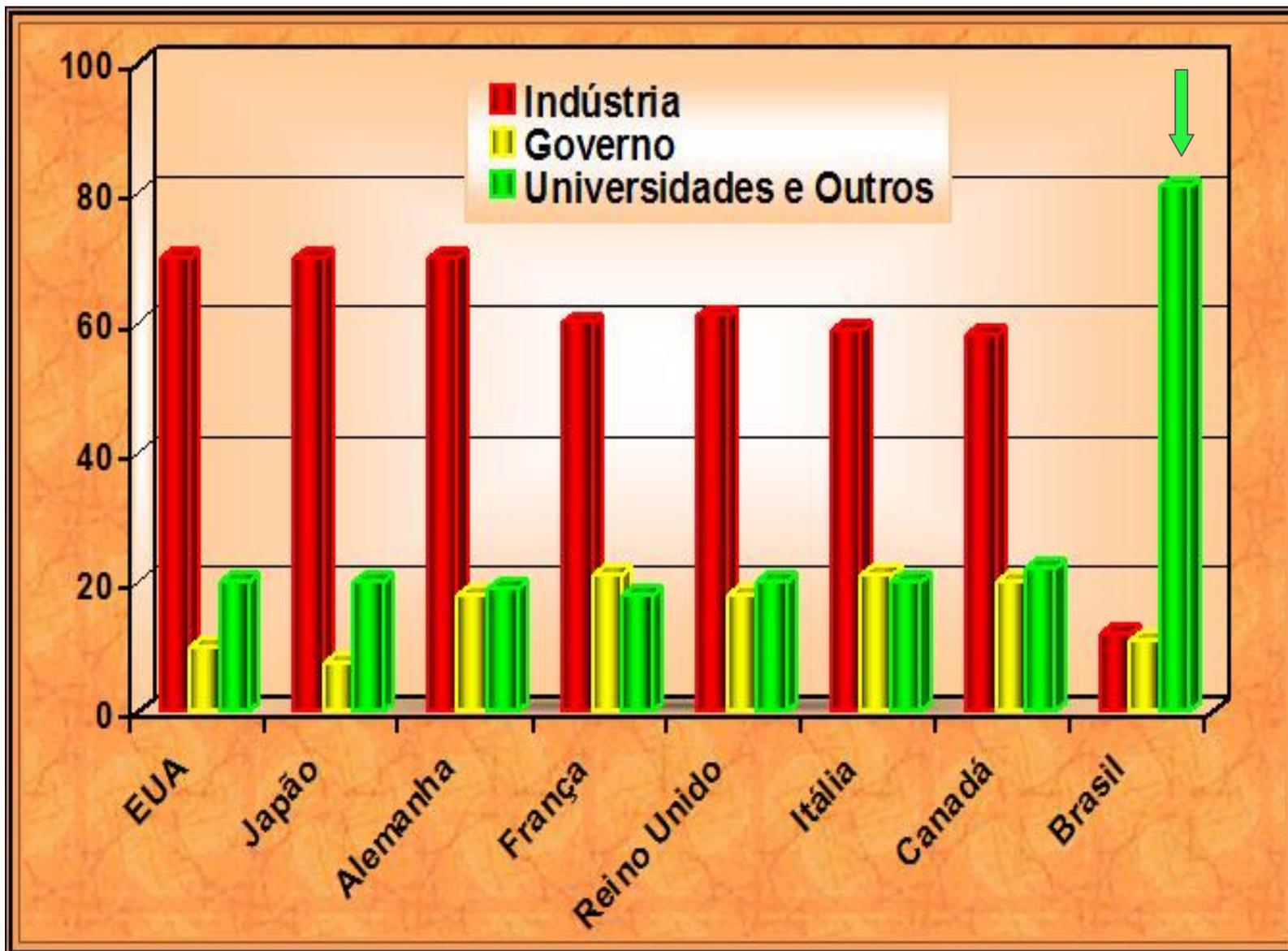
Eliezer J. Barreiro; 04/03/2010

### E1

Eliezer; 22/04/2010

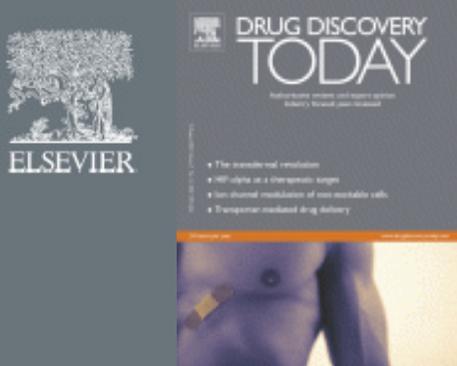


## Aonde se faz a ciência no Brasil ?





Drug Discovery Today • Volume 14, Numbers 1/2 • January 2009



REVIEWS



Universidade

Empresa

Reviews • POST SCREEN

## Drug discovery: new models for industry–academic partnerships

**Cathy J. Tralau-Stewart, Colin A. Wyatt, Dominique E. Kleyn and Alex Ayad**

Drug Discovery Centre and Business Development, Imperial College London SW7 2AZ, UK

The re-focusing of pharmaceutical industry research away from early discovery activities is stimulating the development of novel models of drug discovery, notably involving academia as a 'front end'. In this article the authors explore the drivers of change, the role of new entrants (universities with specialised core facilities) and novel partnership models. If they are to be sustainable and deliver, these new models must be flexible and properly funded by industry or public funding, rewarding all partners for contributions. The introduction of an industry-like process and experienced management teams signals a revolution in discovery that benefits society by improving the value gained from publicly funded research.



## Produção Científica

2,2% conhecimento novo "*falou*" português em 2009 !

> 32.000 publicações em 2009 (*ca.* 10.000 doutores)

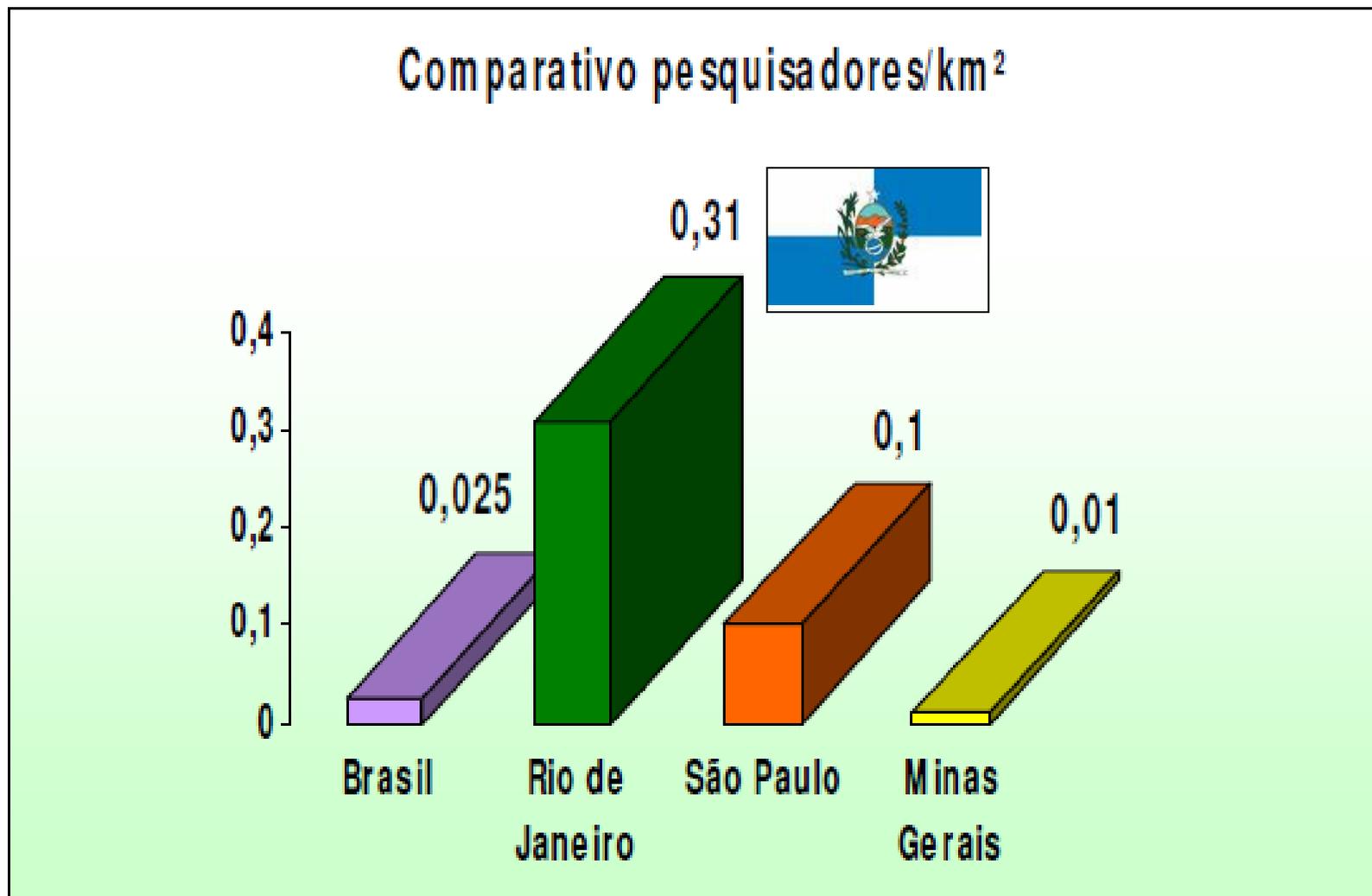


Universidade Federal do Rio de Janeiro (2001-2010) *Scopus*

Ano	2006	2007	2008	2009	2010
Ciências da Vida (Total: 2912)	475	506	551	505	64*
Ciências Exatas (Total: 2947)	493	510	553	528	70*

\* Apenas as duas primeiras semanas

## Capacidade científico-tecnológica do estado do Rio de Janeiro





# Novos Compostos-Protótipos Descobertos no



**LASSBio-585** ←

→ **LASSBio-581**

*Thienylhydrazone with digitalis-like properties  
(positive inotropic effects)*  
August 15, 2006  
Publication Number: 07091238



**Otimização do protótipo**  
Otimização do protótipo Otimização do protótipo





# Novo protótipo de fármaco anti-asmático

## LASSBio-596

Mecanismo



Fase Pré-clínica

Metabolismo

anti-asmático

MR = 103,02



Toxicidade

Farmacocinética

PIBR 0208767-7 - 08/11/2002  
PIBR 0401660-2 - 27/04/2004





*J. Pharmacol. Exper. Ther.* 2001, 299, 558

*Brit. J. Pharmacol.* 2001, 134, 603

Patente

**LASSBio-294**

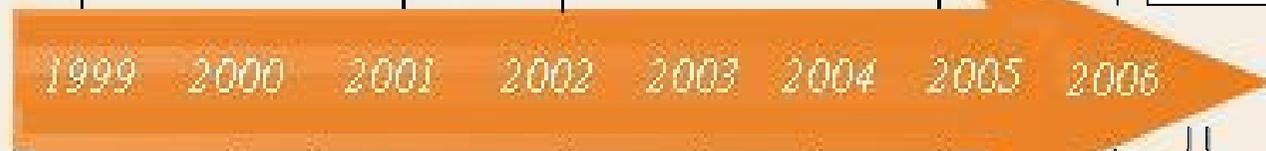
*Brit. J. Pharmacol.* 2002, 135, 293

*Bioorg. Med. Chem.* 2005, 13, 3431



**License agreement**

**USPTO 7.091.238**



**Empresa**

*Pronex 1*

Bioensaios

Tese

Tese



UFRJ

**Otimização**

**pipeline**

*XVI Cong Lat Pharmacol.*

**INPI PI 0403363-9  
PCT 20/08/2005**

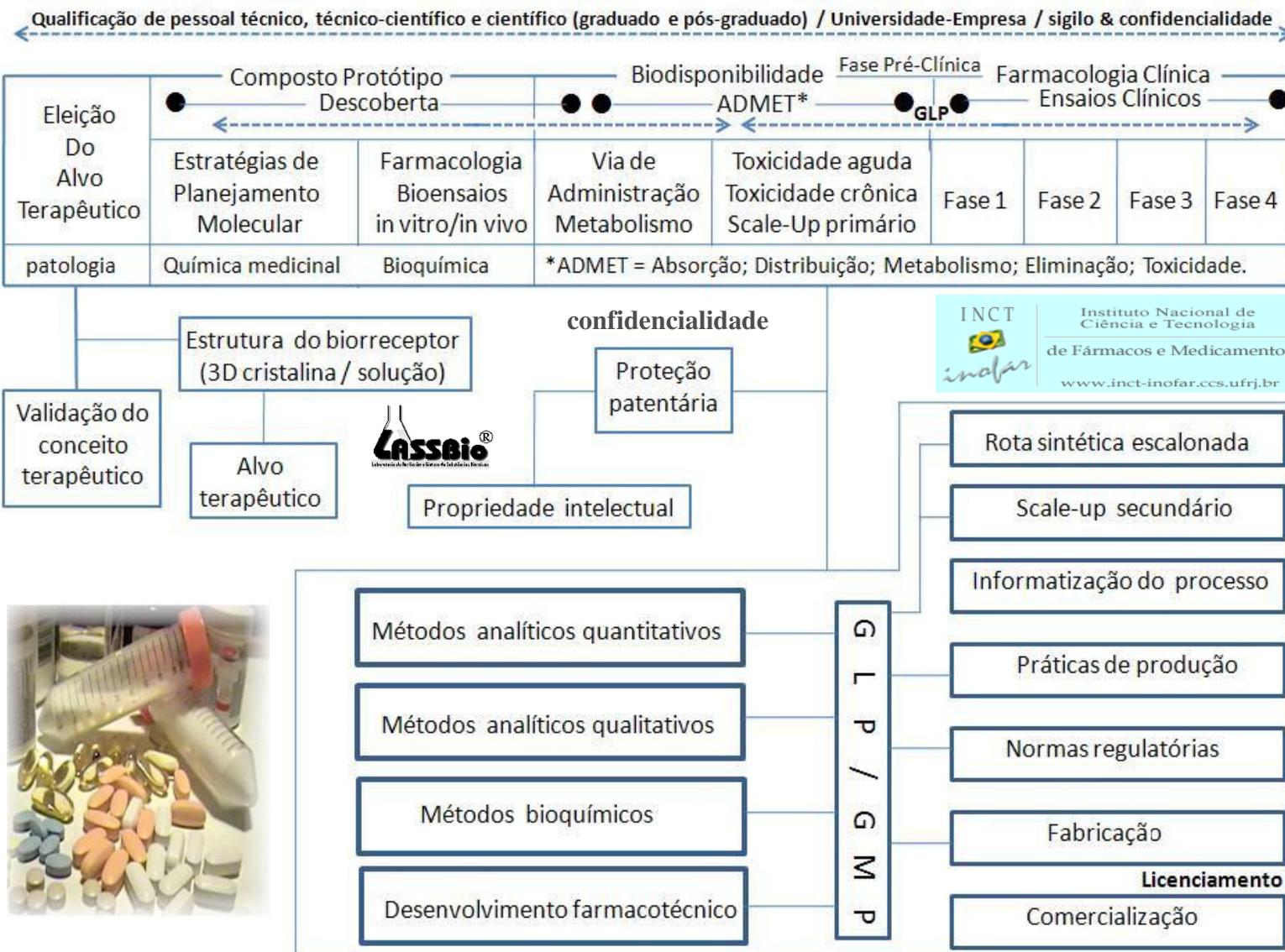
*4th Internat. Congr. Pharm. Sci., Rib. Preto, 2003*

*Eur. J. Med. Chem.* 2000, 35, 187

*Eur. J. Pharmacol.* 2003, 470, 79



# A cadeia de inovação em fármacos




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## Programa de Pós Graduação em Farmacologia e Química Medicinal

29 de abril de 2008

O Instituto de Ciências Biomédicas (ICB) da Universidade Federal do Rio de Janeiro mantém o Programa de Pós-Graduação na modalidade *stricto sensu* que permite obter graus de Mestre e Doutor em Ciências (Farmacologia e Química Medicinal). Os cursos de Mestrado e Doutorado são reconhecidos pela CAPES com conceito 4 e credenciados pelo Conselho Federal de Educação, tendo participações significativas na formação de recursos humanos. O Mestrado e o Doutorado recebem alunos novos regularmente duas vezes ao ano, através de seleções realizadas em fevereiro/março ou julho/agosto.

[SAIBA MAIS]

# Interdisciplinaridade



A recente criação da PG (M&D) em Farmacologia e Química Medicinal ilustra nova perspectiva de horizonte na PG da UFRJ, pois é a primeira com o perfil desta proposta interdisciplinar na AL.I

Eliezer J. Barreiro; 04/03/2010



Química  
Medicinal

**24 a 28 de janeiro de 2011.**

**Inscrições a partir de 01 setembro**  
**[www.farmacia.ufrj.br/lassbio](http://www.farmacia.ufrj.br/lassbio)**



# UFRJ



# Obrigado

pela presença e atenção.

