



Universidade Federal do Rio de Janeiro

# Instituto Nacional de Ciência e Tecnologia em Fármacos e Medicamentos - INCT-

## INOFAR:

### A Química na Saúde

[www.inct-inofar.ccs.ufrj.br](http://www.inct-inofar.ccs.ufrj.br)

Eliezer J. Barreiro

Professor Titular - UFRJ



Laboratório de Avaliação e Síntese de Substâncias Bioativas

<http://www.farmacia.ufrj.br/lassbio>





## ● Preâmbulo introdutório

- ▶ A pesquisa científica contemporânea: *status-quo*;
- ▶ A interdisciplinaridade da ciência e do fármaco;
- ▶ A inovação tecnológica farmacêutica;

## ● O INCT-INOFAR

- ▶ Concepção & missão: *quo-vadis*;
- ▶ Inovação radical em fármacos: a busca por novos protótipos de fármacos (novas entidades químicas = NCE's);
- ▶ Inovação incremental em fármacos: estudo de rotas sintéticas de novos fármacos genéricos (oportunidades & SUS) e de intermediários avançados estratégicos;

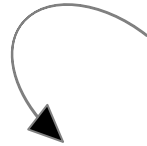




# A pesquisa científica através dos tempos...



**Galileo, Newton, Darwin, & Einstein**



**O físico Crick & e o biólogo Watson**

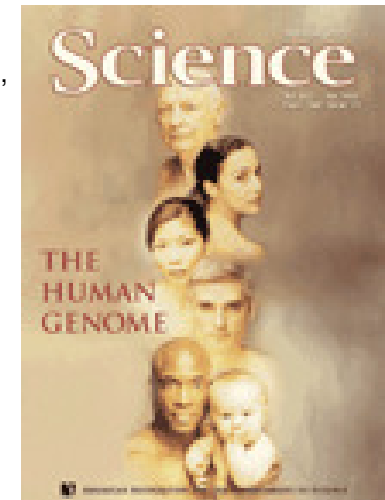


**A equipe do genoma humano.**



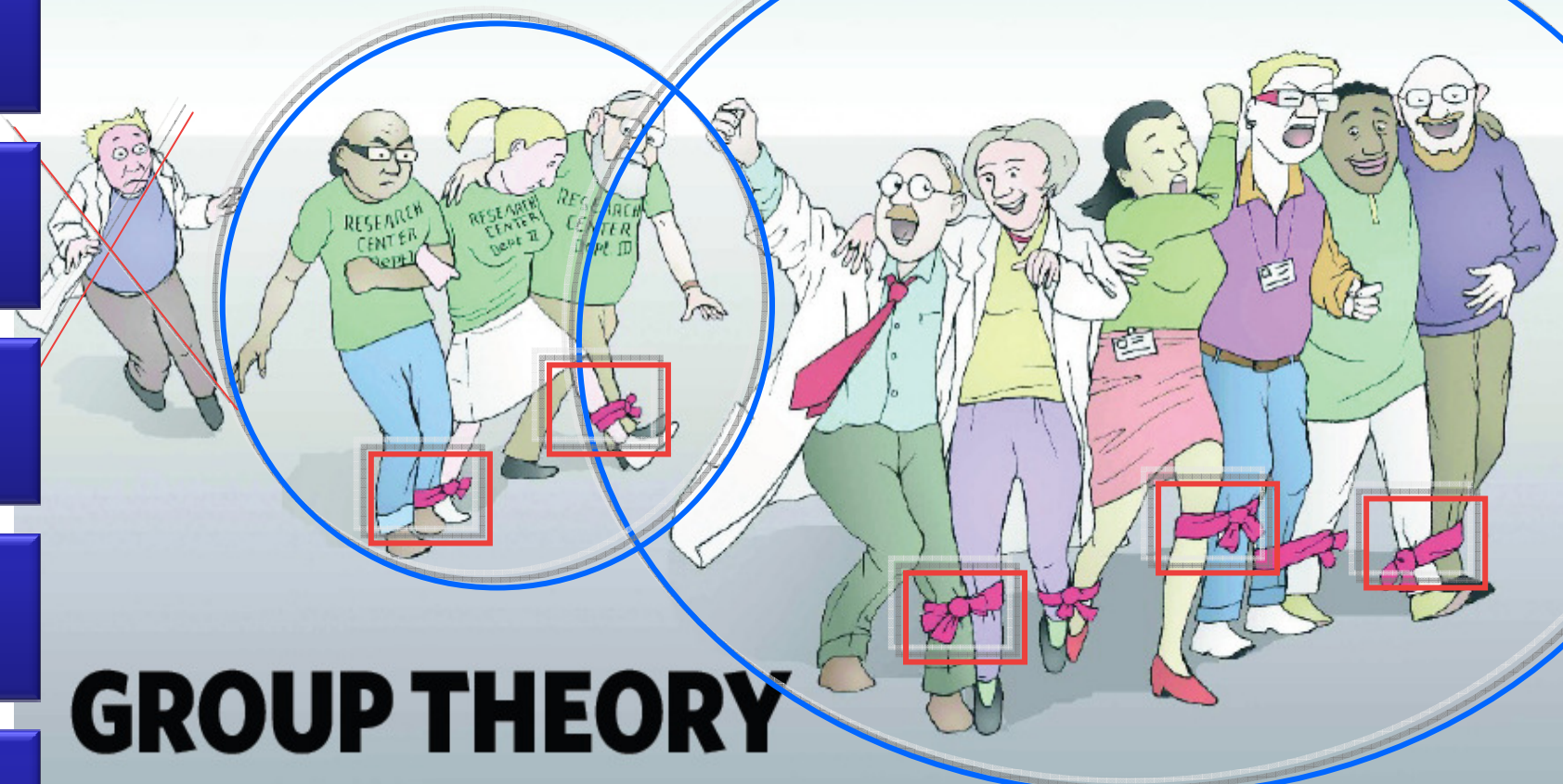
# The Sequence of the Human Genome

J. Craig Venter, Mark D. Adams, Eugene W. Myers, Peter W. Li, Richard J. Mural, Granger G. Sutton, Hamilton O. Smith, Mark Yandell, Cheryl A. Evans, Robert A. Holt, Jeannine D. Gocayne, Peter Amanatides, Richard M. Ballew, Daniel H. Huson, Jennifer Russo Wortman, Qing Zhang, Chinnappa D. Kodira, Xiangqun H. Zheng, Lin Chen, Marian Skupski, Gangadharan Subramanian, Paul D. Thomas, Jinghui Zhang, George L. Gabor Miklos, Catherine Nelson, Samuel Broder, Andrew G. Clark, Joe Nadeau, Victor A. McKusick, Norton Zinder, Arnold J. Levine, Richard J. Roberts, Mel Simon, Carolyn Slayman, Michael Hunkapiller, Randall Bolanos, Arthur Delcher, Ian Dew, Daniel Fasulo, Michael Flanigan, Liliana Florea, Aaron Halpern, Sridhar Hannenhalli, Saul Kravitz, Samuel Levy, Clark Mobarry, Knut Reinert, Karin Remington, Jane Abu-Threideh, Ellen Beasley, Kendra Biddick, Vivien Bonazzi, Rhonda Brandon, Michele Cargill, Ishwar Chandramouliswaran, Rosane Charlab, Kabir Chaturvedi, Zuoming Deng, Valentina Di Francesco, Patrick Dunn, Karen Eilbeck, Carlos Evangelista, Andrei E. Gabrielian, Weiniu Gan, Wangmao Ge, Fangcheng Gong, Zhiping Gu, Ping Guan, Thomas J. Heiman, Maureen E. Higgins, Rui-Ru Ji, Zhaoxi Ke, Karen A. Ketchum, Zhongwu Lai, Yiding Lei, Zhenya Li, Jiayin Li, Yong Liang, Xiaoying Lin, Fu Lu, Gennady V. Merkulov, Natalia Milshina, Helen M. Moore, Ashwinikumar K Naik, Vaibhav A. Narayan, Beena Neelam, Deborah Nusskern, Douglas B. Rusch, Steven Salzberg, Wei Shao, Bixiong Shue, Jingtao Sun, Zhen Yuan Wang, Aihui Wang, Xin Wang, Jian Wang, Ming-Hui Wei, Ron Wides, Chunlin Xiao, Chunhua Yan, Alison Yao, Jane Ye, Ming Zhan, Weiqing Zhang, Hongyu Zhang, Qi Zhao, Liansheng Zheng, Fei Zhong, Wenyan Zhong, Shiaoping C. Zhu, Shaying Zhao, Dennis Gilbert, Suzanna Baumhueter, Gene Spier, Christine Carter, Anibal Cravchik, Trevor Woodage, Feroze Ali, Huijin An, Aderonke Awe, Danita Baldwin, Holly Baden, Mary Barnstead, Ian Barrow, Karen Beeson, Dana Busam, Amy Carver, Angela Center, Ming Lai Cheng, Liz Curry, Steve Danaher, Lionel Davenport, Raymond Desilets, Susanne Dietz, Kristina Dodson, Lisa Doup, Steven Ferreira, Neha Garg, Andres Gluecksmann, Brit Hart, Jason Haynes, Charles Haynes, Cheryl Heiner, Suzanne Hladun, Damon Hostin, Jarrett Houck, Timothy Howland, Chinyere Ibegwam, Jeffery Johnson, Francis Kalush, Lesley Kline, Shashi Koduru, Amy Love, Felecia Mann, David May, Steven McCawley, Tina McIntosh, Ivy McMullen, Mee Moy, Linda Moy, Brian Murphy, Keith Nelson, Cynthia Pfannkoch, Eric Pratts, Vinita Puri, Hina Qureshi, Matthew Reardon, Robert Rodriguez, Yu-Hui Rogers, Deanna Romblad, Bob Ruhfel, Richard Scott, Cynthia Sitter, Michelle Smallwood, Erin Stewart, Renee Strong, Ellen Suh, Reginald Thomas, Ni Ni Tint, Sukyee Tse, Claire Vech, Gary Wang, Jeremy Wetter, Sherita Williams, Monica Williams, Sandra Windsor, Emily Winn-Deen, Keriellen Wolfe, Jayshree Zaveri, Karena Zaveri, Josep F. Abril, Roderic Guigó, Michael J. Campbell, Kimmen V. Sjolander, Brian Karlak, Anish Kejariwal, Huaiyu Mi, Betty Lazareva, Thomas Hatton, Apurva Narechania, Karen Diemer, Anushya Muruganujan, Nan Guo, Shinji Sato, Vineet Bafna, Sorin Istrail, Ross Lippert, Russell Schwartz, Brian Walenz, Shibu Yooseph, David Allen, Anand Basu, James Baxendale, Louis Blick, Marcelo Caminha, John Carnes-Stine, Parris Caulk, Yen-Hui Chiang, My Coyne, Carl Dahlke, Anne Deslattes Mays, Maria Dombroski, Michael Donnelly, Dale Ely, Shiva Esparham, Carl Fosler, Harold Gire, Stephen Glanowski, Kenneth Glasser, Anna Glodek, Mark Gorokhov, Ken Graham, Barry Gropman, Michael Harris, Jeremy Heil, Scott Henderson, Jeffrey Hoover, Donald Jennings, Catherine Jordan, James Jordan, John Kasha, Leonid Kagan, Cheryl Kraft, Alexander Levitsky, Mark Lewis, Xiangjun Liu, John Lopez, Daniel Ma, William Majoros, Joe McDaniel, Sean Murphy, Matthew Newman, Trung Nguyen, Ngoc Nguyen, Marc Nodell, Sue Pan, Jim Peck, Marshall Peterson, William Rowe, Robert Sanders, John Scott, Michael Simpson, Thomas Smith, Arlan Sprague, Timothy Stockwell, Russell Turner, Eli Venter, Mei Wang, Meiyuan Wen, David Wu, Mitchell Wu, Ashley Xia, Ali Zandieh, and Xiaohong Zhu





## What makes a successful research team?



# GROUP THEORY

# Interdisciplinarity

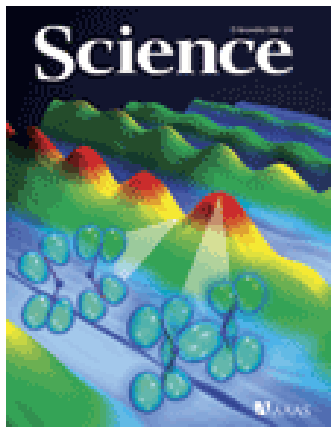
J. Whitfield, *Nature* 2008, 455, 720

“A good scientist is someone who succeeds in getting the various scientific disciplines to work together harmoniously just as the fingers of a hand can function properly only if they work in concert.” P. Janssen

# 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 ambiente de rede.*

## Slide 6

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### EJB15

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

### E4

Eliezer; 22/04/2010



## ● Preâmbulo introdutório

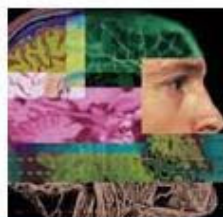
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# the Pharmaceutical Century

TEN DECADES OF DRUG DISCOVERY

ACS PUBLICATIONS  
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[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.



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."*

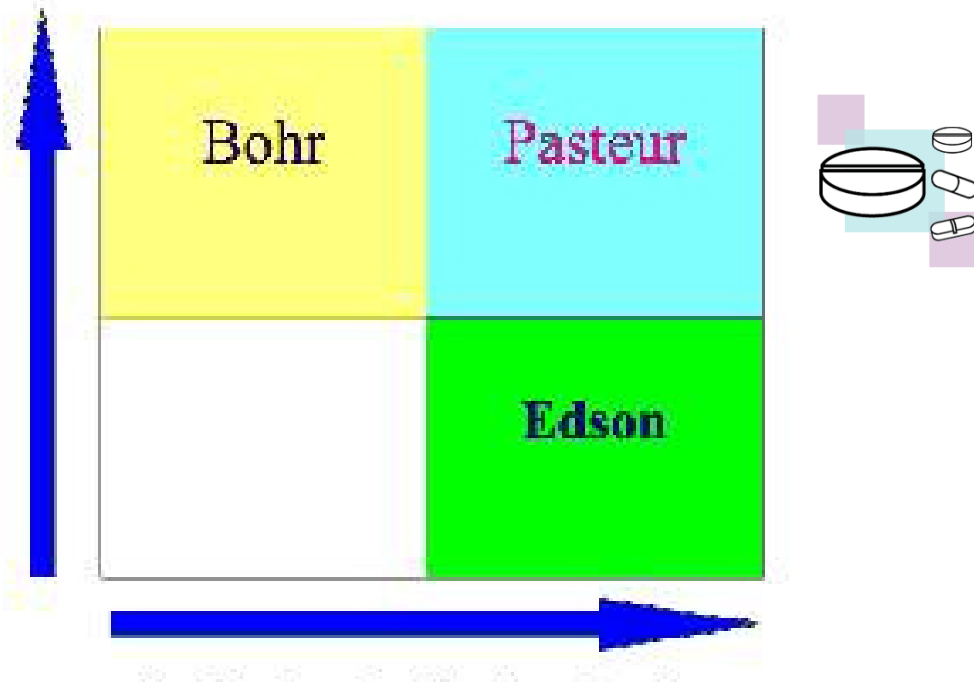
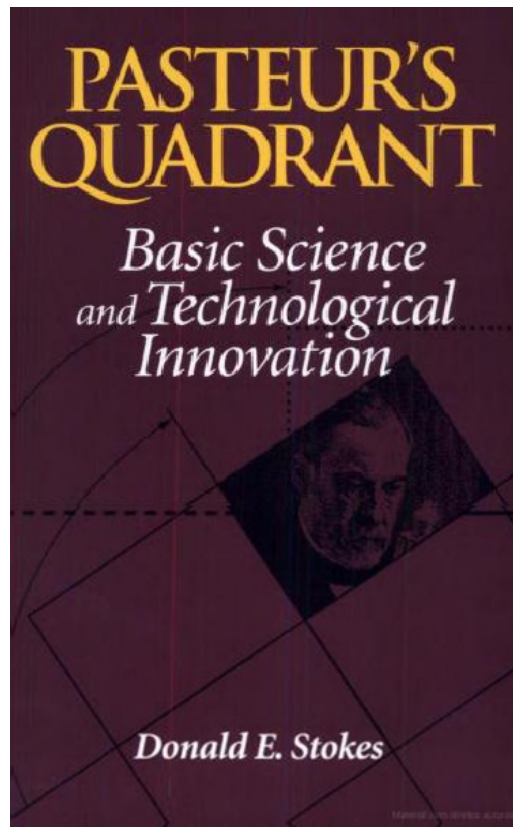
**Slide 8**

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**EJB29**

Eliezer J Barreiro; 02/05/2010

# The production of knowledge



D. E. Stokes; *Pasteur's Quadrant: Basic Science and Technological Innovation*, Book News, Inc., Portland, EUA, 1999.

M. Gibbons *et al.*, *The new production of knowledge: the dynamics of science & research in contemporary societies*, SAGE, London, 1994.

**Slide 9**

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**EJB30**

**The production of knowlegde**

Eliezer J Barreiro; 02/05/2010



Arthur Kornberg

# 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.”*

**Interdisciplinarity**



*Arthur Kornberg*

*Biochemistry 1987, 26, 6888-6891*

**Slide 10**

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**EJB17**

Rio de Janeiro, 05 de março de 2010, Prof. Eliezer J. Barreiro, LASSBio, UFRJ.

Eliezer J. Barreiro; 04/03/2010



A interdisciplinaridade é indispensável

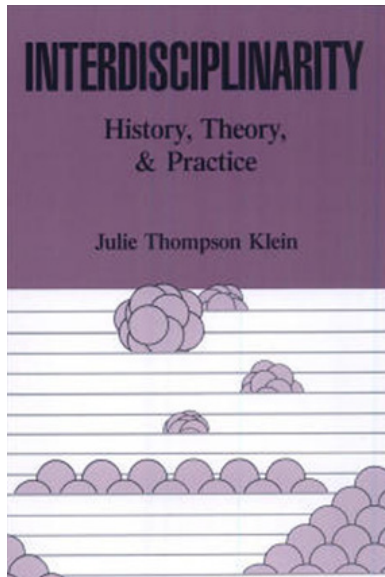
para a solução de problemas

ou desafios complexos !



As ciências dos fármacos são complexas

e diversas: Saúde, Biológicas, Exatas





## ● Preâmbulo introdutório

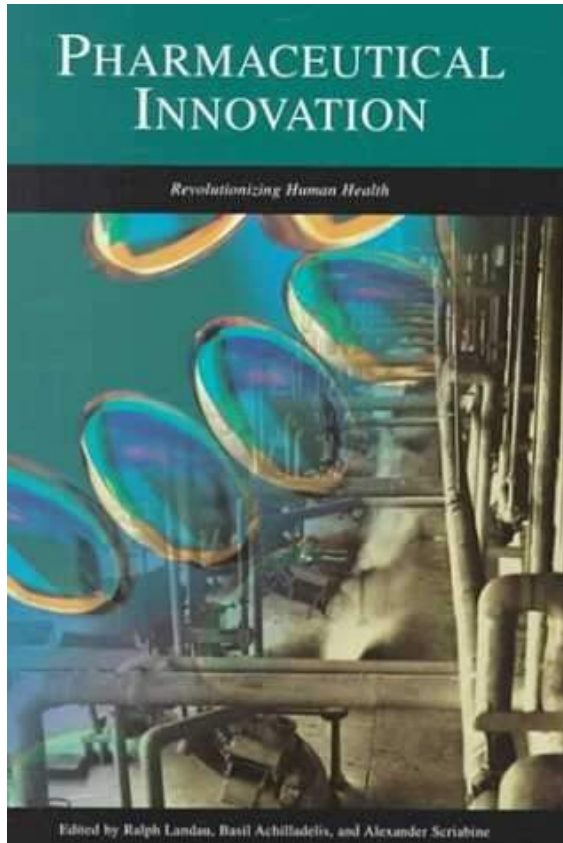
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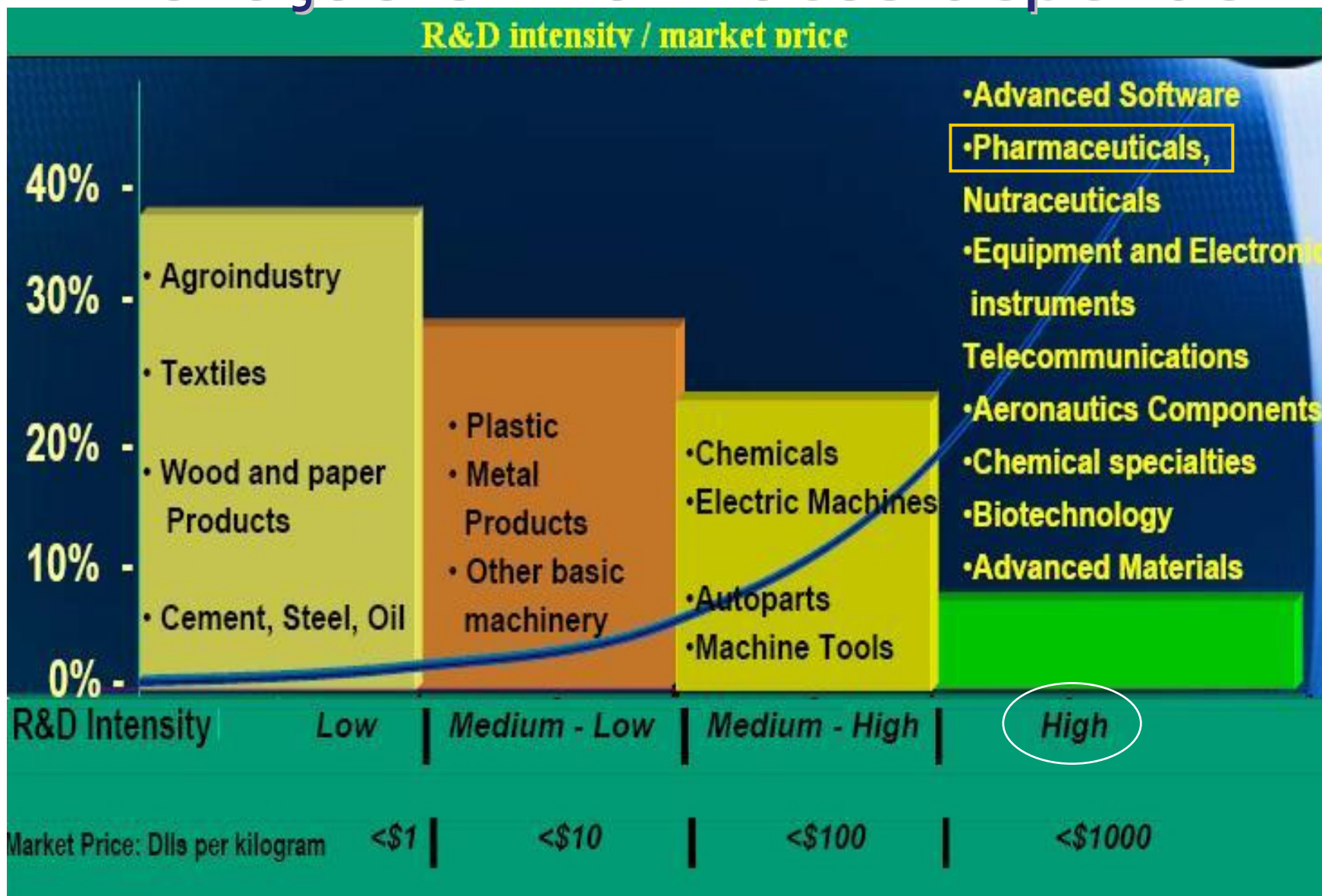




A inovação tecnológica é um dos processos mais dinâmicos da atividade industrial. Este dinamismo se expressa de forma acentuada na inovação tecnológica farmacêutica que, mais do que qualquer outra, depende da efetiva interação entre Ciência & Tecnologia



# A inovação em fármacos depende...



... da pesquisa científica !



# The drug discovery process...



- *Science* **2000**, 287, 1951 (J.Uppenbrink, J.Mervis)

*Science* **2004**, 303, 1713 (Donald Kennedy Ed)

- Rethinking Drug Discovery
- Surviving the Blockbuster Syndrome
- Orphan Drugs of the Future?
- Protein Kinase Inhibitors: Insights into Drug Design from Structure
- Polyketide and Nonribosomal Peptide Antibiotics: Modularity and Versatility
- Organic Chemistry in Drug Discovery
- The Many Roles of Computation in Drug Discovery
- Drug Delivery Systems: Entering the Mainstream

is scientific research based.

“Science is made of facts, just as houses are made of stones; but a mere collection of facts is no more science than a pile of stones a house”



Henri Poincaré, 1902

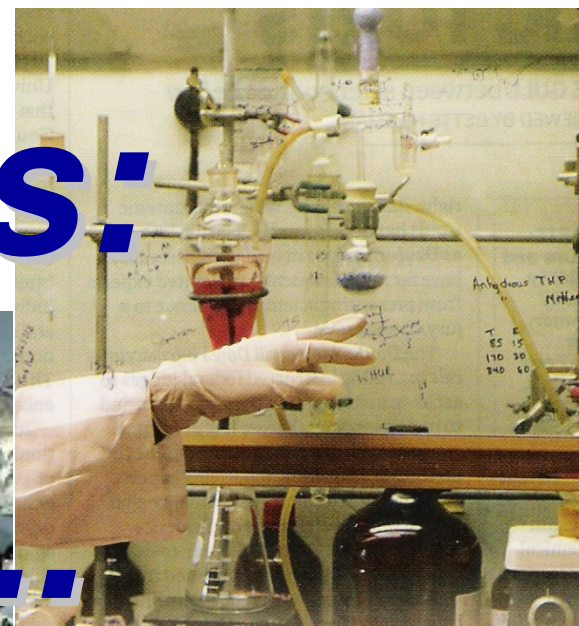
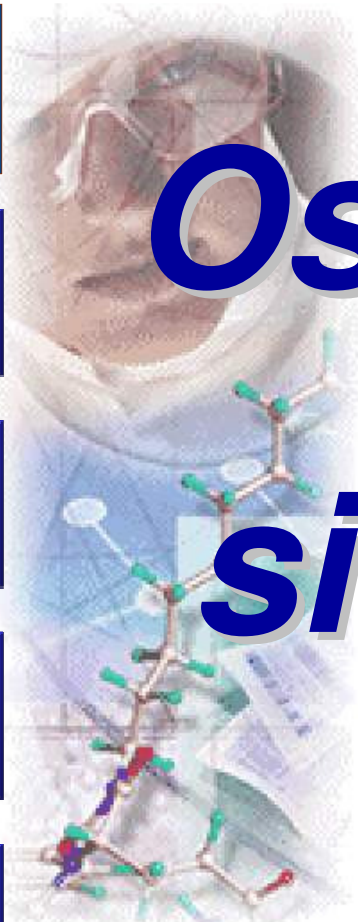


***Os fármacos:***

***sintéticos ...***

**>> 85% do arsenal terapêutico**

**são de fármacos sintéticos ...**





***cimetidina*** ***propranolol***

***captopril***

***celecoxibe***

***estatinas***

***losartana***

***indinavir***

***imatinibe***

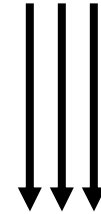
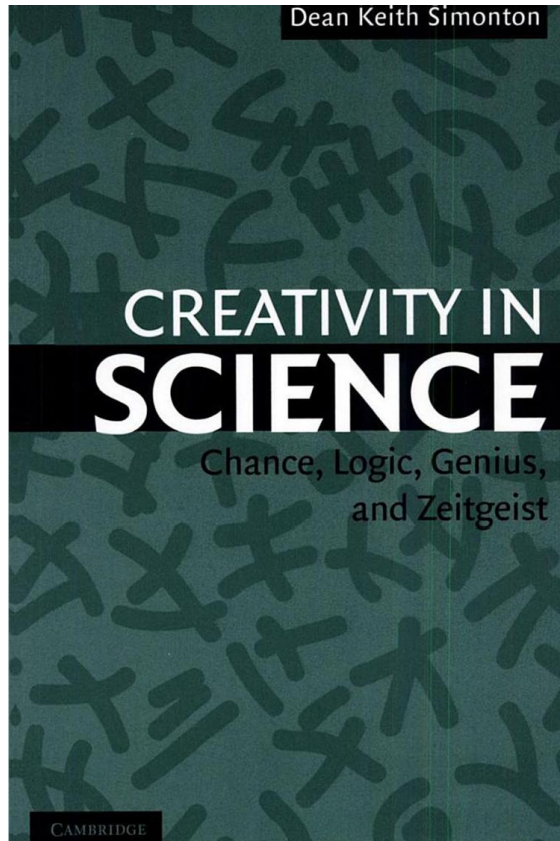
***sildenafil***

***Fármacos  
Inovadores***

***maraviroc***



# Pesquisa & Criatividade



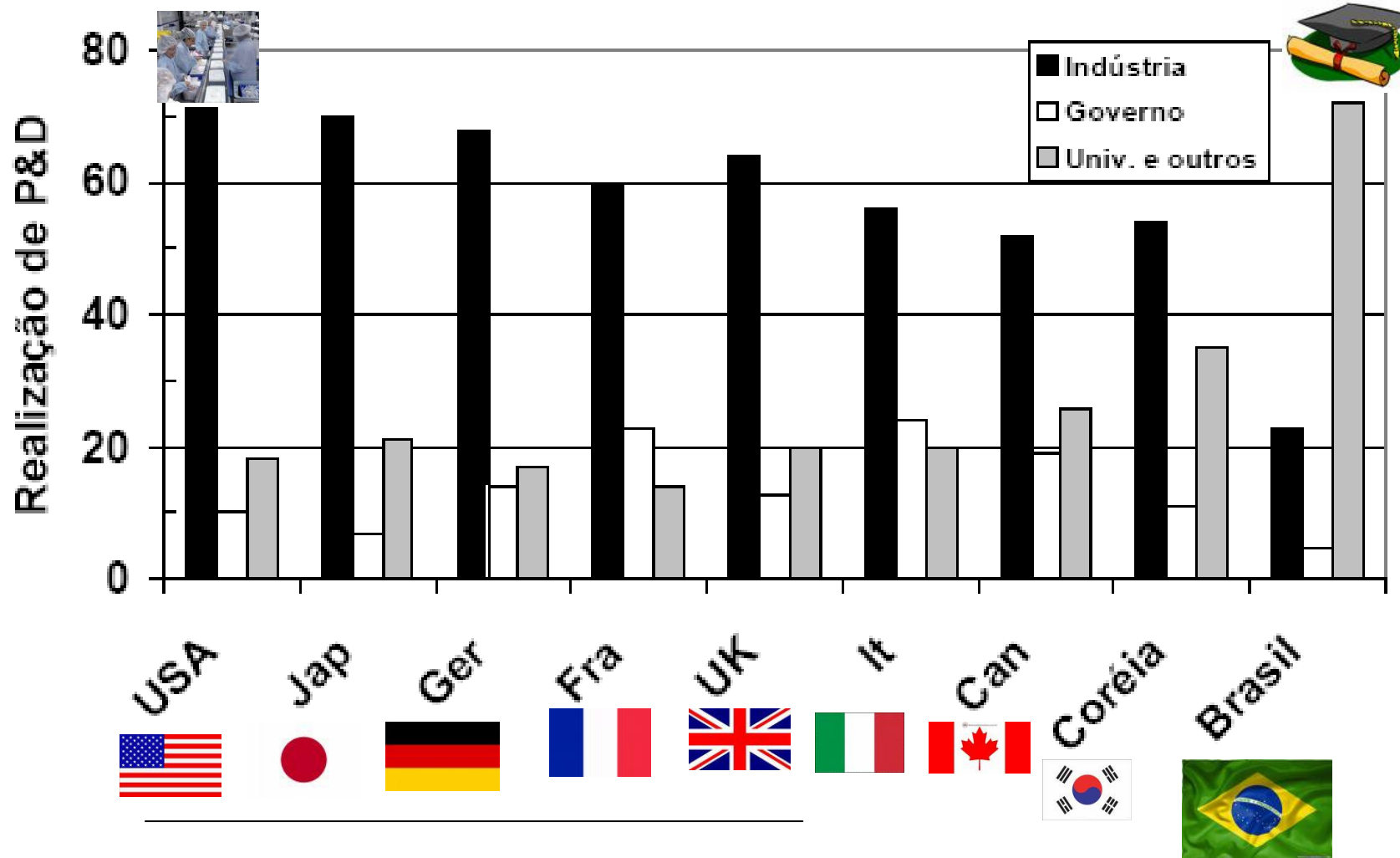
“discoveries and inventions become virtually inevitable (1) as prerequisite kinds of knowledge accumulate in man’s cultural store; (2) as the attention of a sufficient number of investigators is focused on a problem – by emerging social needs, or by developments internal to the particular science, or by both”

Robert K. Merton (1961)

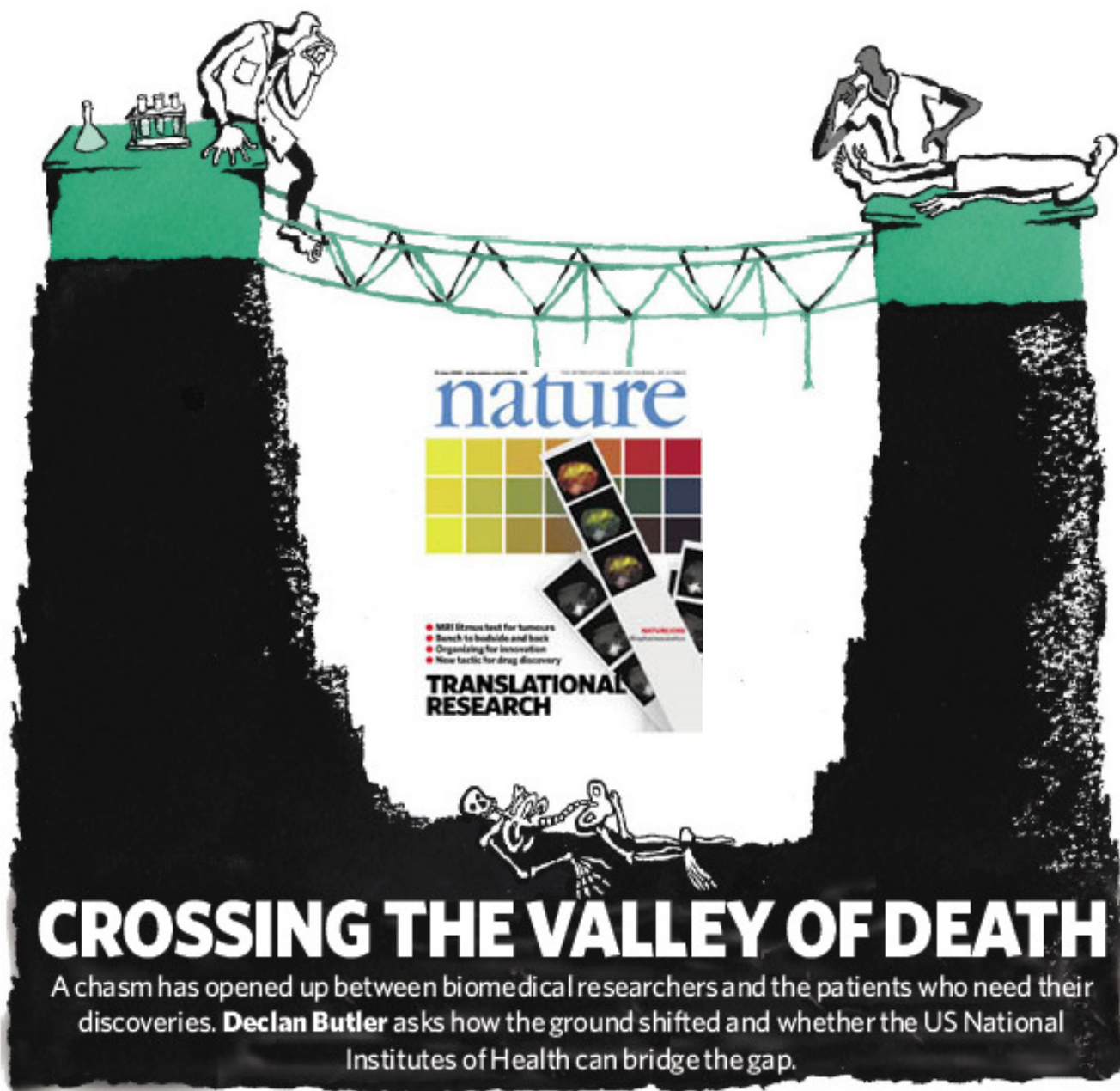
The role of genius in scientific advance. *New Scientist*, 12, 306-308

■ O ambiente propício à criatividade existe, naturalmente, na Academia (= *liberdade acadêmica*), favorecendo a criação do conhecimento novo e a pesquisa científica inovadora !

# Distribuição dos pesquisadores ativos



Adaptado de C. H. Brito Cruz & C. A. Pacheco, "Conhecimento & Inovação: Desafios do Brasil no Século XXI", em [www.inovacao.unicamp.br/report/intc-pacheco-brito.pdf](http://www.inovacao.unicamp.br/report/intc-pacheco-brito.pdf) (2/01/2009)



# CROSSING THE VALLEY OF DEATH

A chasm has opened up between biomedical researchers and the patients who need their discoveries. **Declan Butler** asks how the ground shifted and whether the US National Institutes of Health can bridge the gap.



**Slide 20**

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**EJB32**

**Nature 2008, 453, 840**

Eliezer J Barreiro; 02/05/2010



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- ▶ Apresentação
- ▶ Institutos
- ▶ Notícias
- ▶ Contato

Um dos maiores programas de Ciência e Tecnologia do Brasil

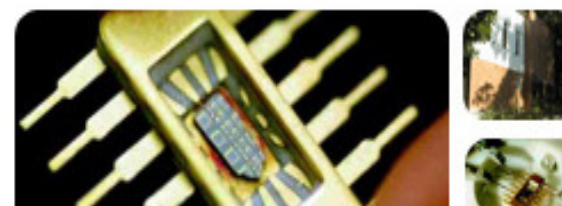
## ▶ Notícias

[Pesquisadores do IICT de Astrofísica publicam 100 artigos em oito meses](#)

[UFMG faz pesquisa pioneira para tratamento da dengue](#)

[IICT de Fixação Biológica de Nitrogênio promove simpósio internacional em setembro](#)

122 projetos INCT's





instituto nacional de Fármacos e Medicamentos  
de ciência e tecnologia

www.inct-inofar.ccs.ufrj.br



Project CNPq 573.564/2008-6

Home

INCT-INOVAR

Team

Scientific adviser board  
(SAB)

Research groups

Research people

Useful articles

Publications

Meetings

Videos

## A missão do INCT-INOVAR

- Organizar as competências científicas nacionais em uma rede efetiva de pesquisa em fármacos;
- Apoiar projetos de pesquisa científica multi-institucionais voltados para novos fármacos;
- Contribuir para a inovação incremental e radical em novos fármacos e genéricos;
- Estudar e desenvolver a síntese total de genéricos, intermediários avançados e matérias-primas;
- Contribuir para a formação científica qualificada de pessoal em química medicinal & farmacologia;
- Promover a divulgação das ciências dos fármacos e dos medicamentos, assim como seu uso racional e seguro;

## Governance committee

## Innovation in Drugs and Medicines

**Comitê de Governança & Acompanhamento (CGA)**  
Dra Vanderlan Bolzani (UNESP)  
Dra Heloisa Beraldo (UFMG)  
Dr Angelo C Pinto (UFRJ)  
Dr Luiz Carlos Dias (UNICAMP)  
Dr Marco Aurélio Martins (Fiocruz)



**Coordenação**  
Dr Eliezer J Barreiro (UFRJ)  
**Vice-coordenação**  
Dr Fernando Q Cunha (USP-RP)

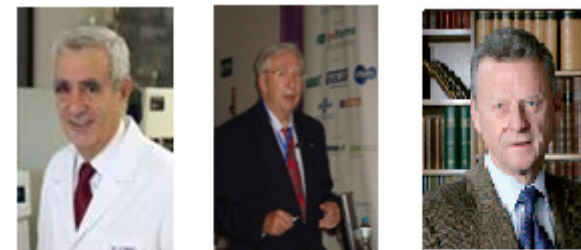
**Superintendência Científica**  
Dra Lídia Moreira Lima (UFRJ)

**Grupos de Pesquisa Associados**  
13 IES & 3 ICT



**Consultoria Científica**  
Dr. Francisco S Guimarães (USP-SP)  
Dr Vitor F Ferreira (UFF)  
Dr Antonio Monge (Espanha)  
Dr Camile G Wermuth (França)  
Dr Simon Campbell

## Foreign scientific consultants

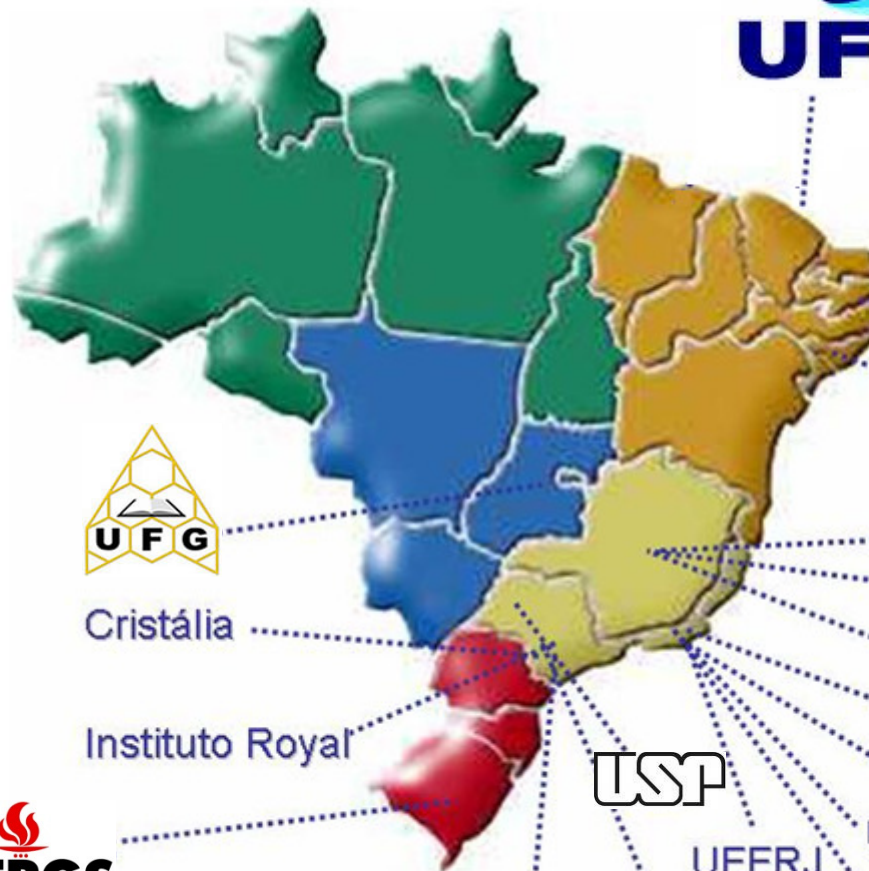


Antonio Monge, Universidad de Navarra, ES  
Camille G. Wermuth, Prestwick Co., Ilkirch, FR  
Simon Campbell, ex-Pfizer Major Scientist UK



# Research partners

## INCT-INO FAR



In Vitro Cells

UFMG

FIOCRUZ

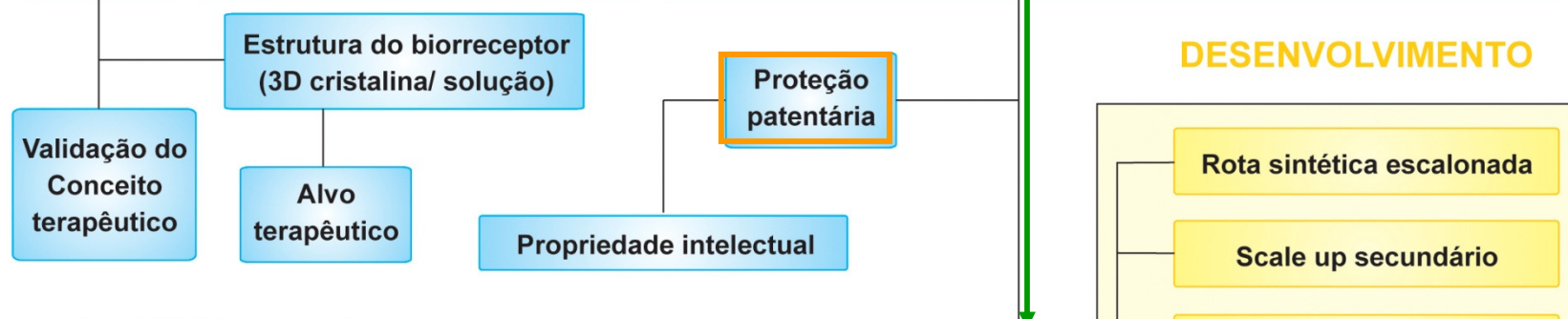
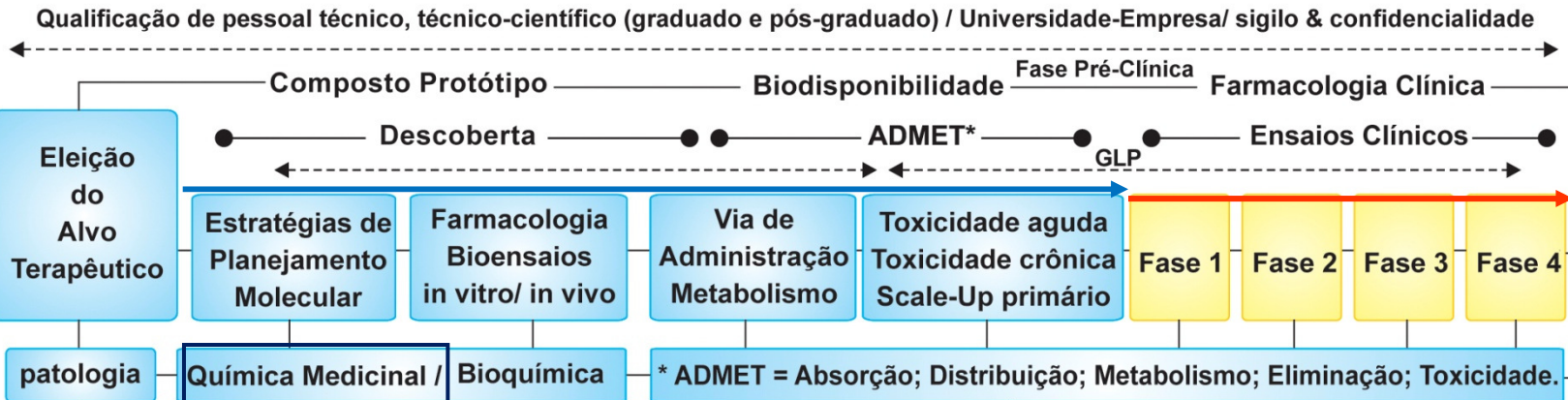
UFMG



UFRJ

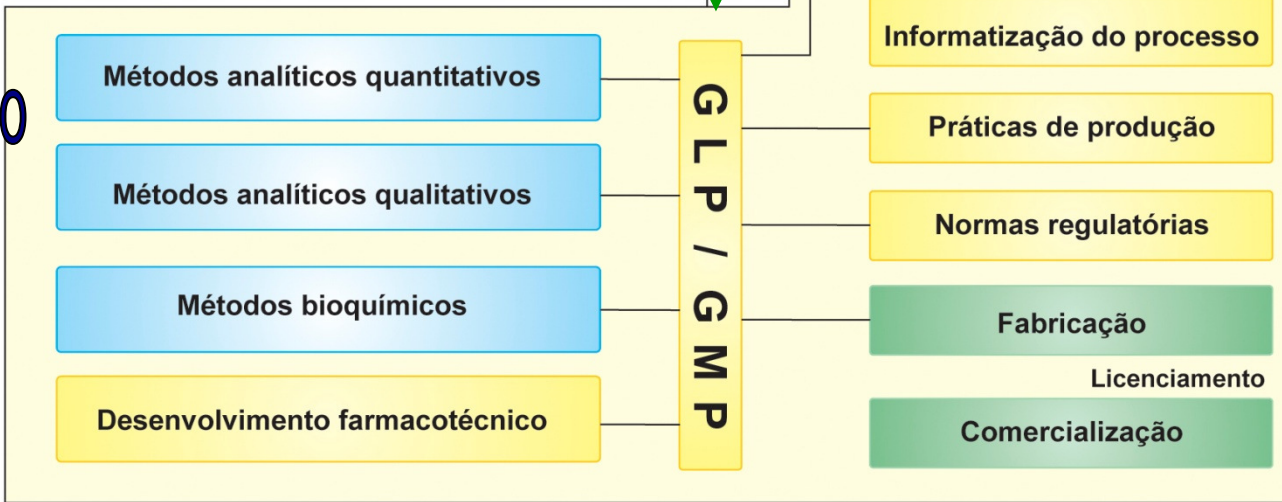
UERJ





**PESQUISA**

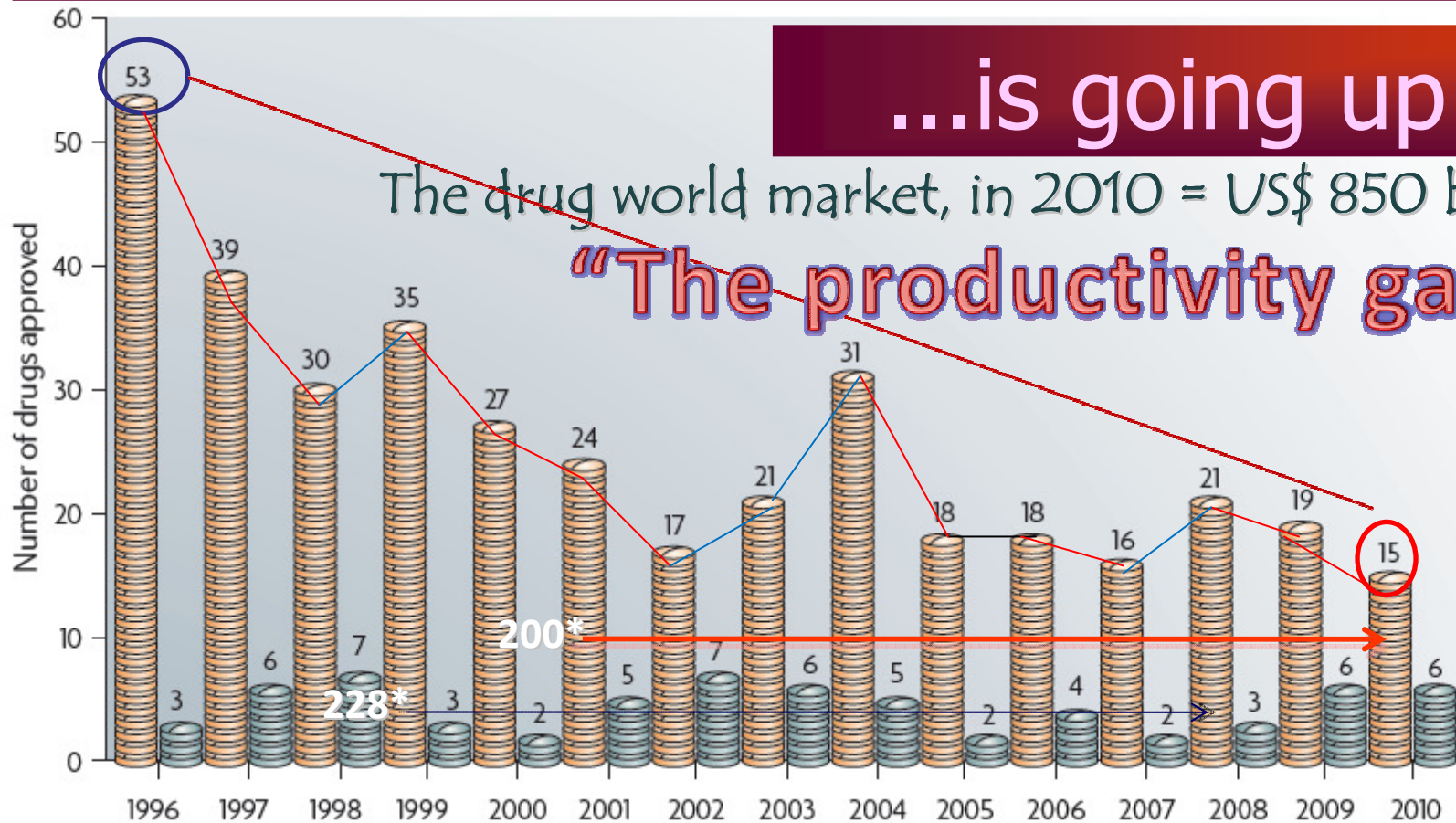
# Cadeia da inovação em Fármacos e Medicamentos





# The Big Pharma innovation crisis...

...is going up !



The drug world market, in 2010 = US\$ 850 bi

“The productivity gap”



\* A. Mullard, 2010 FDA drug approvals, *Nature Rev. Drug Discov.* **2011**, *10*, 82.

“In the 10-year period between 1999 and 2008, the FDA approved 183 small-molecule drugs...”

D Swinney & J Anthony, *Nature Rev. Drug Discov.* **2011**, *10*, 507.

The pharmaceutical industry invest *ca.* 10-15% year in R&D





“...the search for new drugs,  
especially in lead-optimization,  
is an evolutionary process that is  
only like to be successful if new  
methods merge with classical  
Medicinal Chemistry knowledge...  
combinatorial chemistry  
& high-throughput screening  
approaches resulted from  
inappropriate compound selection...”



Hugo Kubinyi



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# Annual Activities Report

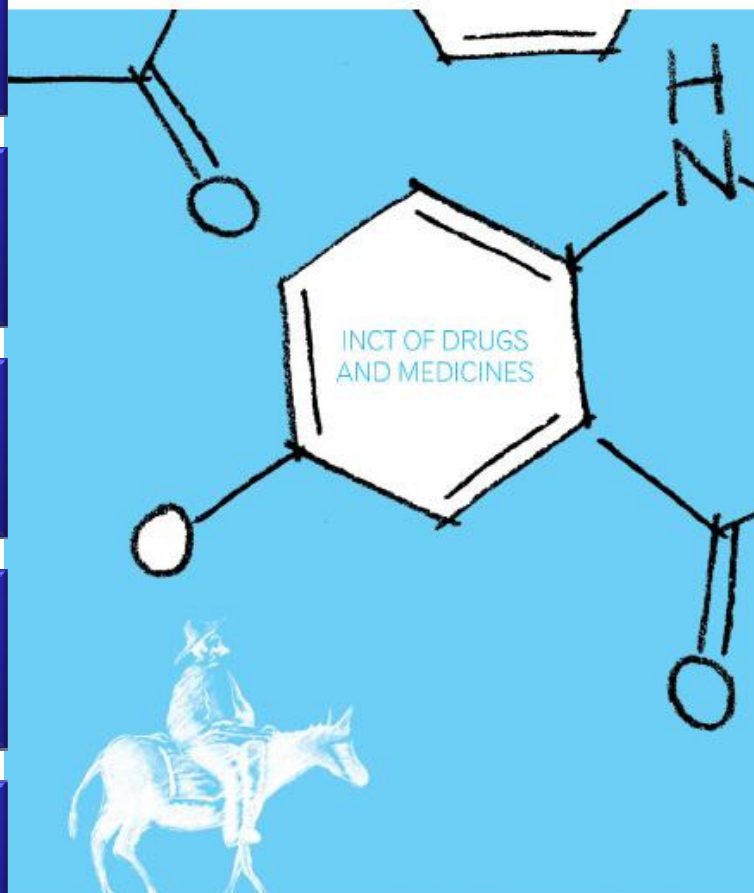
Interdisciplinary & multi-team research projects

- **Radical innovation**

pain, inflammation,  
asthma, CNS,  
neglected diseases,  
cardiovascular system,  
anticancer

- **Incremental innovation**

SUS (BR healthcare)  
new generic drugs



2010

ANNUAL ACTIVITIES REPORT

[www.inct-inofar.ccs.ufrj.br/download/aar/2010.pdf](http://www.inct-inofar.ccs.ufrj.br/download/aar/2010.pdf)



# Radical *Innovation*



## ADVANCED PROJECTS

1. *Development of new anti-asthmatic pharmaceutical prototypes (LASSBio-596).*  
Prof. Patricia Rieken Macedo Rocco (UFRJ) .  
Prof. Lidia Moreira Lima (UFRJ)
2. *Study of functionalized n-phenylpiperazine derivatives as prototypes for the development of new atypical antipsychotics.*  
Prof. Stella Maris Kuze Rates (UFRGS)
3. *Study of the potential anti-inflammatory effect of the LASSBio 897 compound, on silicosis and asthma models.*  
Prof. Patricia Machado Rodrigues e Silva (FIOCRUZ-RJ)  
Prof. Marco Aurelio Martins (FIOCRUZ-RJ)

22%

43%

## INTERMEDIATE PROJECTS

1. *Benzaldehyde Semicarbazone (BS).*  
Prof. Heloisa de Oliveira Beraldo (UFMG)
2. *Therapeutic potential of the new vasodilator compound (LASSBio 1289) in arterial and pulmonary hypertension.*  
Prof. Gisele Zapata Sudo (UFRJ)
3. *Evaluation of antiparasitary activity of a series of semicarbazone and hydrazine-n-acylhydrazone derivatives.*  
Prof. Magna Suzana Alexandre Moreira (UFAL) .
4. *Prospection of Opportunities in New Generic and Innovative New Generic Medications.*  
Prof. Adelaide Maria de Souza Antunes (INPI)
5. *Planning, synthesis and pharmacological evaluation of vectorized and self-organized neuroactive prototypes.*  
Prof. Ricardo Menegatti (UFG)
6. *Planning, synthesis, structural characterization and pharmacological evaluation of new anti-inflammatory, anti-infective, and neuroactive pharmaceutical candidates.*  
Prof. Claudio Viegas Junior (UNIFAL-MG)

Pipeline (except # 4)

## EARLY STAGE PROJECTS

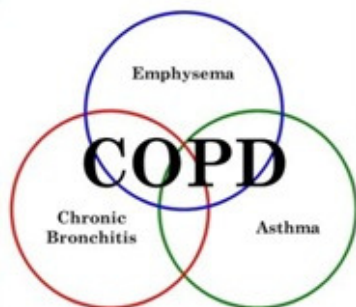
1. *Theoretical Investigation of the Action Mechanism of Dialkylphosphorylhydrazones as Ribose 5-Phosphate Isomerase Enzyme Inhibitors of Trypanosoma cruzi and Plasmodium falciparum.*  
Prof. Carlos Mauricio R. de Sant'Anna (UFRRJ) -
2. *Evaluation of the antitumoral activity of new molecules planned structurally from the imatinib prototype.*  
Prof. Patricia Dias Fernandes (UFRJ)
3. *Triage of new replication inhibitors for the acquired human immunodeficiency virus Type 1 (HIV-1) from the LASSBio Chemical Library.*  
Prof. Luciana Jesus da Costa (UFRJ)
4. *Pharmacological evaluation of new neuroactive Zolpidem derivatives.*  
Prof. Roberto Takashi Sudo (UFRJ)
5. *"In silico" prediction and "in vitro" production through bioconversion of human metabolites of pharmaceutical prototype candidates.*  
Prof. Valeria de Oliveira (UFG)

35%



## Novo candidato a fármaco anti-asmático

# LASSBio-596



$C_{18}H_{18}N_2O_5S_2$

406,4

Log P = 2 / CLogP = 1,80

MR = 103,02

Pre-clinic studies

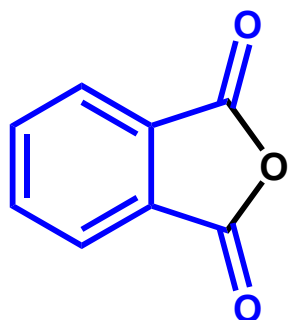
# 2011

PIBR 0208767-7 - 08/11/2002

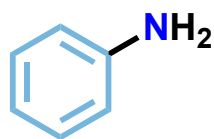
PIBR 0401660-2 - 27/04/2004

Atua por mecanismo farmacológico de ação inédito = Inovação !

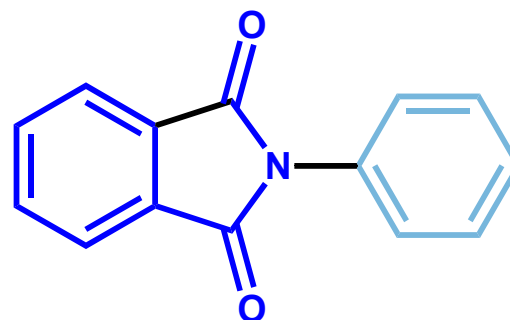
L. M. Lima *et al.*, *Bioorg. Med. Chem. Lett.*, **12**, 1533, 3067 (2002) ; P. R. M. Rocco *et al.*, *Eur. Respir. J.*, **22**, 20 (2003) ; L. M. Lima *et al.*, *Antii-nflamatory & Anti-allergy Agents in Medicinal Chemistry*, **3**, 9 (2004) ; J. V. Bevilaqua *et al.*, *Applied Biochem. Biotechnol.*, **121**, 117 (2005); M. S. Alexandre-Moreira *et al.*, *International Immunopharmacology*, **5**, 485 (2005); H. S. Campos *et al.*, *Braz. J. Med. Biol. Res.*, **39**, 283 (2006) ; L.M. Lima *et al.*, *Anti-inflammatory & Anti-allergy Agents in Medicinal Chemistry*, **5**, 79 (2006)



anidrido ftálico  
 $C_8H_4O_3$



120°C  
1h  
(2M)

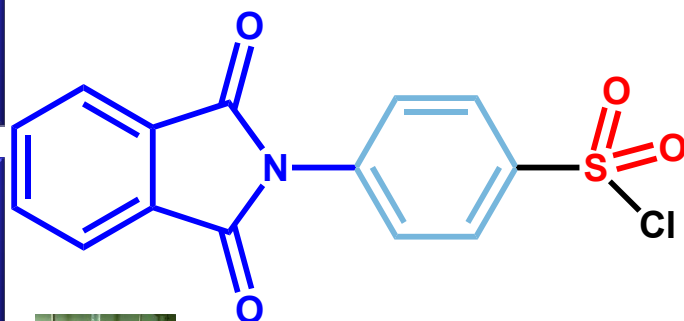


$C_{14}H_9NO_2$

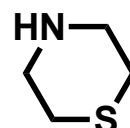
$ClSO_3H$

0°C a t.a. até 60°C

1h  
(1M)



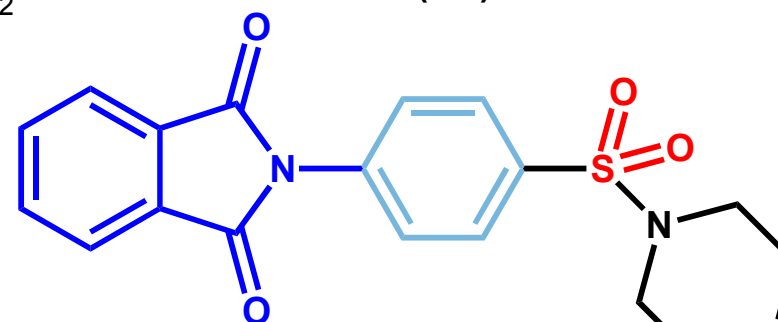
$C_{14}H_8ClNO_4S$



$NEt_3$

$CH_2Cl_2$

1h  
0,4M



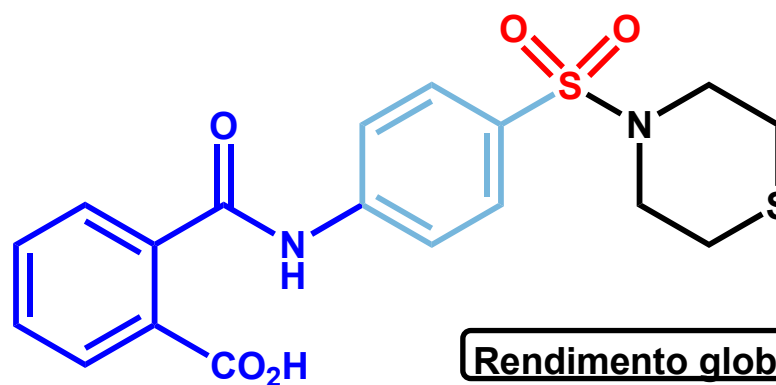
**LASSBio-468**

$C_{18}H_{16}N_2O_4S_2$



KOH / HOH

$CH_3OH$   
1h  
0,35M



**LASSBio-596**

$C_{18}H_{18}N_2O_5S_2$

Rendimento global: 29%



$^{13}C$ ,  $^1H$  RMN / IV / UV / EM  
HPLC

calorimetria diferencial  
de varredura (DSC)

CHN

Difração de Raios-X

**Scale-up**



# RVQ

*Revista Virtual de Química*

ISSN 1984-6835



## LASSBio-596: da descoberta aos ensaios pré-clínicos

Rocco, Patricia R. M.;<sup>a</sup> Xisto, Debora G.;<sup>a</sup> Silva, J. D.;<sup>a</sup> Diniz, Magareth F. F. M.;<sup>b</sup> Almeida, Reinaldo N.;<sup>b</sup> Luciano, Melissa N.;<sup>b</sup> Medeiros, Isac A.;<sup>b</sup> Cavalcanti, Bruno C.;<sup>c</sup> Ferreira, José R. O.;<sup>c</sup> de Moraes, Manoel O.;<sup>c</sup> Costa-Lotufo, Letícia V.;<sup>c</sup> Pessoa, Claudia do Ó;<sup>c</sup> Dalla-Costa, T.;<sup>d\*</sup> Cattani, Vitória B.;<sup>d</sup> Barreiro, Eliezer J.<sup>e</sup>, Lima, Lidia M.<sup>e</sup>

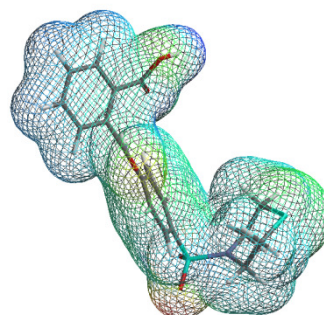
*Rev. Virtual Quim.*, 2010, 2 (1), 10-27. Data de publicação na Web: 30 de agosto de 2010

<http://www.uff.br/rvq>

### Resumo

Neste artigo é revisado a trajetória que vai da descoberta de um novo candidato a fármaco antiasmático, o ácido 2-[4-(1,4-tiazinan-4-ilsulfonil)fenilcarbamoil]benzoico (LASSBio-596), à realização dos primeiros ensaios pré-clínicos, com enfoque nos efeitos de LASSBio-596 em modelo murino de asma aguda e crônica, estudos farmacocinéticos e toxicológicos em roedores e determinação do seu potencial genotóxico e mutagênico.

LASSBio-596





## ● Preâmbulo introdutório

- ▶ A pesquisa científica contemporânea: *status-quo*;
- ▶ A interdisciplinaridade da ciência e do fármaco;
- ▶ A inovação tecnológica farmacêutica;

## ● O INCT-INOFAR

- ▶ Concepção & missão: *quo-vadis*;
- ▶ Inovação radical em fármacos: a busca por novos protótipos de fármacos (novas entidades químicas = NCE's);
- ▶ Inovação incremental em fármacos: estudo de rotas sintéticas de novos fármacos genéricos (oportunidades & SUS) e de intermediários avançados estratégicos;







# Drug Discovery – Editorial

Donald Kennedy  
*Editor-in-Chief*



*Science* 2004, 303, 1717

*"... The process of drug discovery is not only of scientific interest, it entails a fascinating interplay among a variety of economic, social, and political institutions.."*



# O “*Caminho das Índias*” dos nossos fármacos (genéricos!)

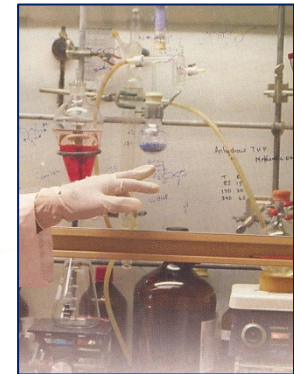
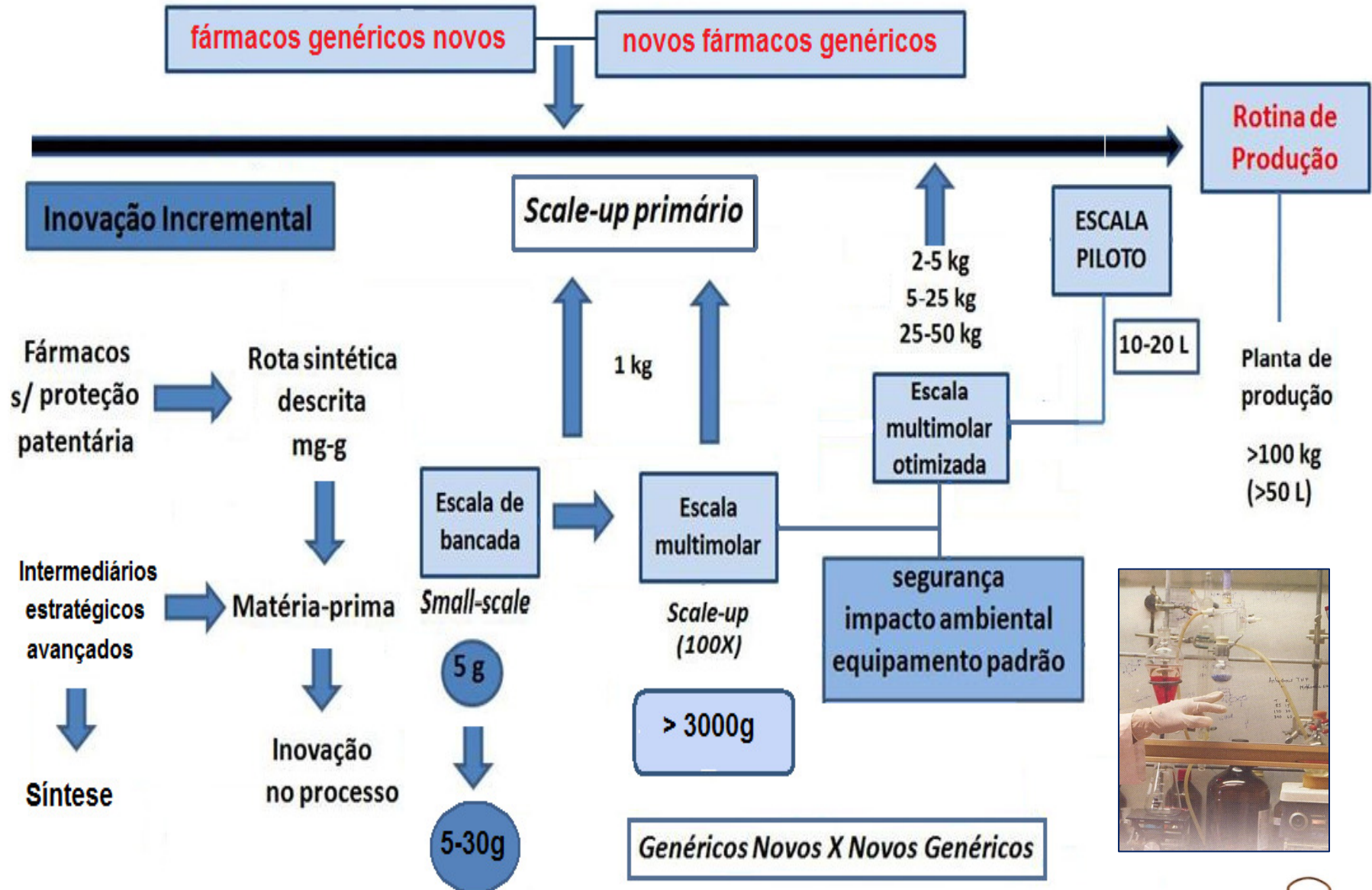
Precisamos resolver, com urgência, a grave situação de dependência das importações de fármacos, invertendo o sentido do *atual Caminho das Índias*...

Biolab Sanus Farmaceutica Ltda  
Cristália Produtos Químicos Farmacêuticos Ltda  
EMS - Sigma Pharma  
Eurofarma Laboratórios Ltda  
Genom Farmacêutica Ltda  
Laboratórios BIOSINTÉTICA  
Laboratório Neo Química Indústria Farmacêutica Ltda  
Laboratório Teuto Brasileiro  
LIBBS Farmacêutica  
Medley S/A Indústria Farmacêutica  
Mantecorp  
Zambon Laboratórios Farmacêuticos Ltda





# Inovação Incremental



❖ O grave gargalo do escalonamento

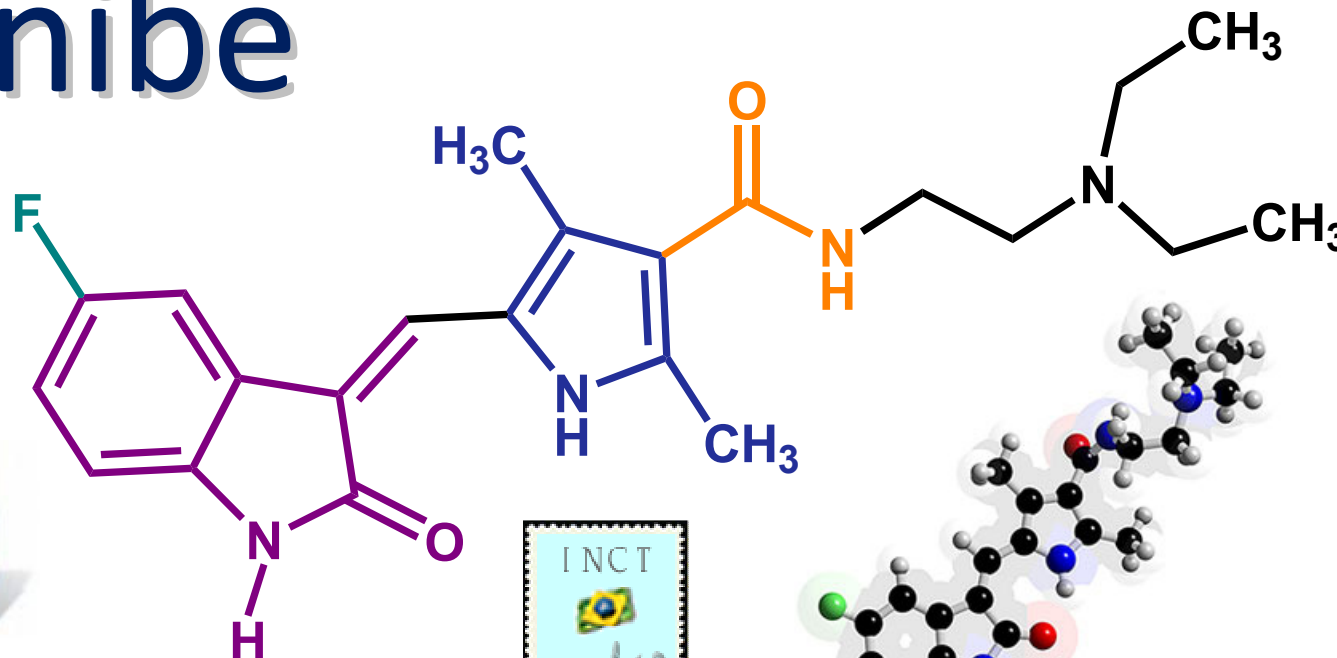




# Sunitinibe

2006

Sutent<sup>R</sup>



- Sintetizado, em 1999, pela Pfizer
- Patente de 2001 (US)
- Inibidor BCR-ABL Tyr-quinase
- Indicado para Ca-estômago/rim
- Nova síntese Prof. Angelo da Cunha Pinto & Dr Bárbara Vasconcelos IQ-UFRJ, **em 2011**, pelo INCT-INOVAR

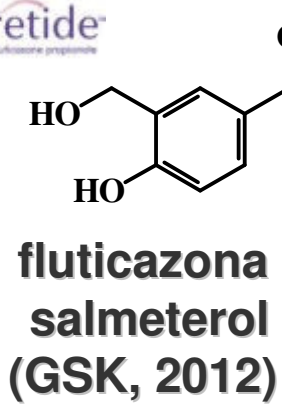
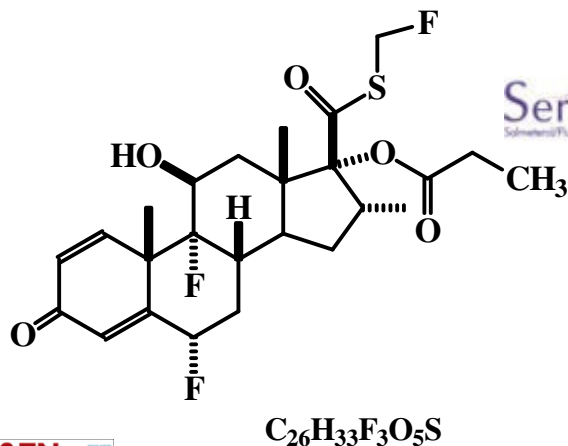
50 mg / 28 caps *ca.* R\$ 20.837,90

Vendas de tinibes no  
mercado  
norte-americano:  
US\$ 18,5 bi (2009)

Importações  
*ca.* US\$ 3 milhões/ano



# Os fármacos *best-seller* em 2010\*



**Clopidogrel (BMS, 2011)**



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

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

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

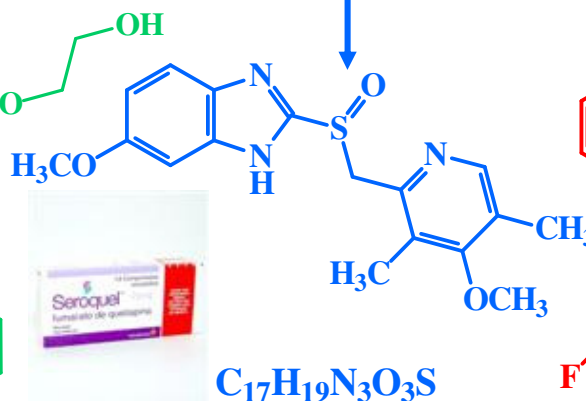
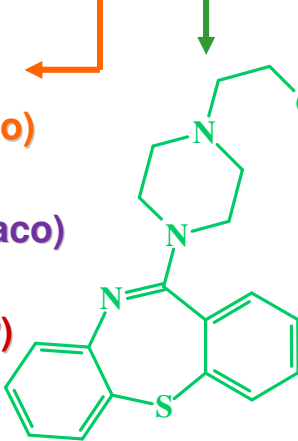
**Olanzapina (Zyprexa<sup>®</sup>, Ely Lilly)**

**Adalimumab (Humira<sup>®</sup>, Abbott)**

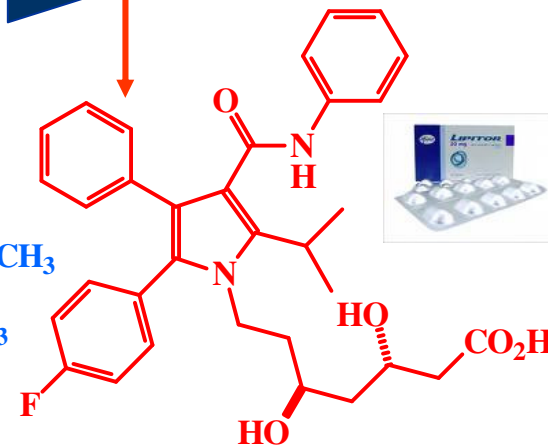
**75,0 (8,7%)**

**Quetiapina (AZ, 2012)**

em US\$ bilhões



**Esomeprazola (AZ)**



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

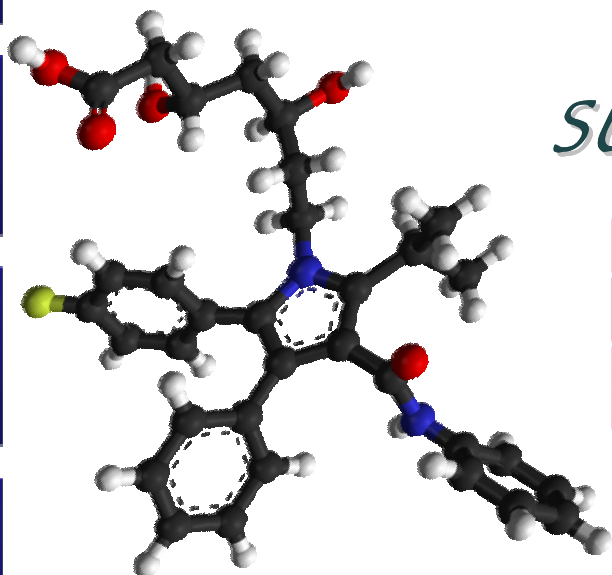
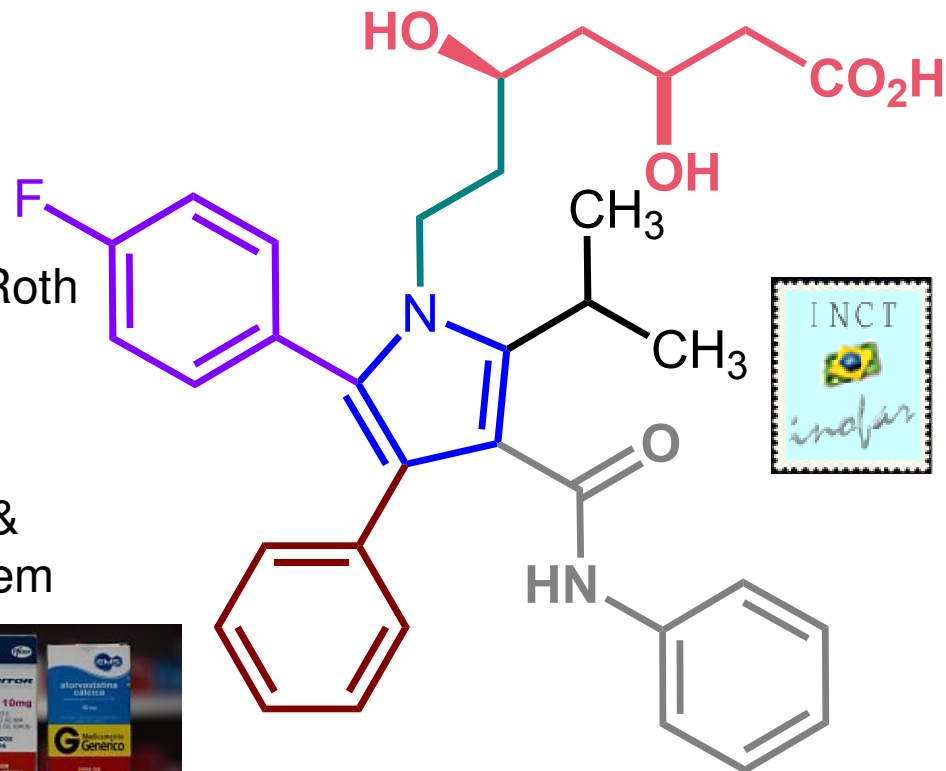
\* R Mullin, *C&EN* 2010 (06/12) 14-21



# Atorvastatina

1991

- Sintetizada, em 1985, por Bruce D. Roth
- Patente US 5273995 Pfizer (1991)
- Nova síntese Prof. Luiz Carlos Dias & Dr Adriano Siqueira, IQ-UNICAMP, em **2010**, pelo INCT-INOVAR



*super blockbuster-drug*

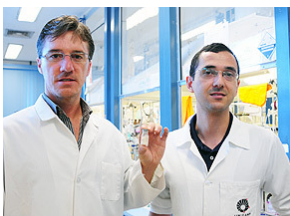
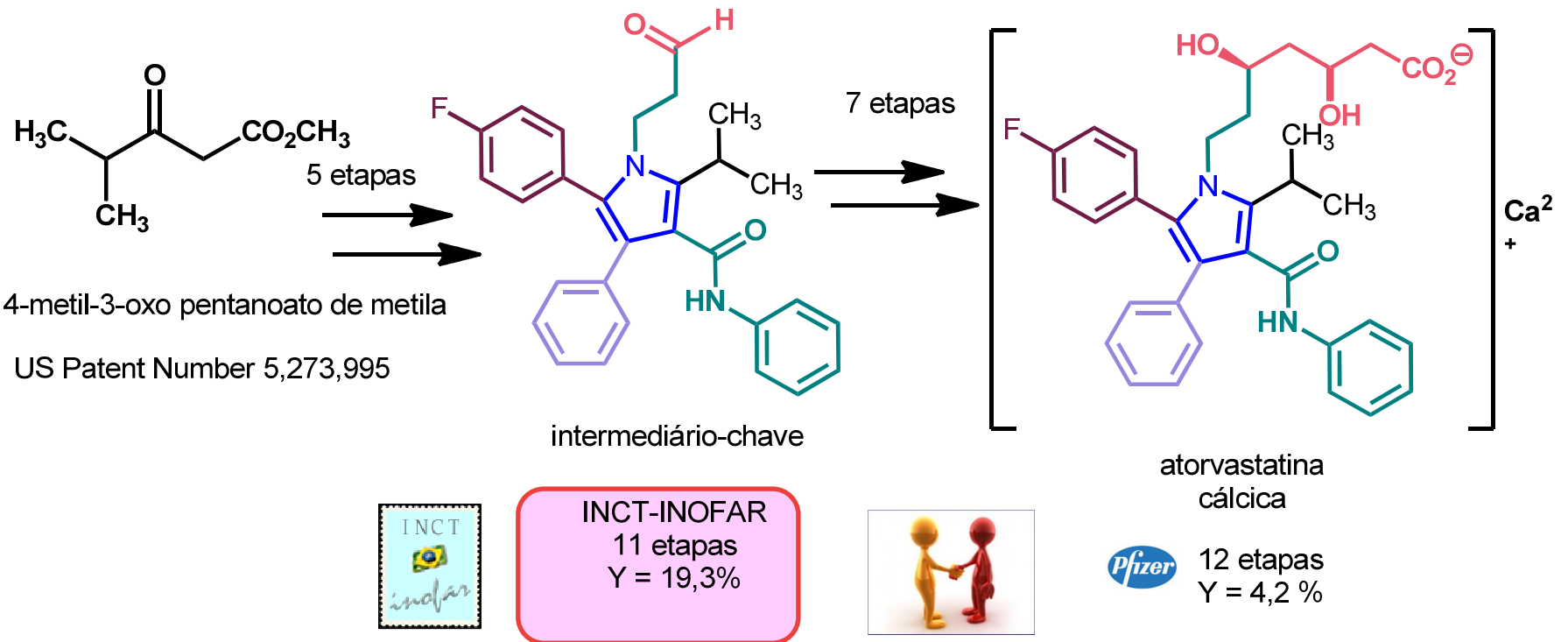


- B. D. Roth, BD (2002). "The discovery and development of atorvastatin, a potent novel hypolipidemic agent", *Prog Med Chem* **2002**, *40*, 1–22
- K. Maggon, "Best-selling human medicines 2002–2004", *Drug Discovery Today* **2005**, *10*, 739–42





# Nova síntese da atorvastatina



O professor Luiz Carlos Dias e o pós-doutorando Adriano Siqueira Vieira: nova rota é mais barata e eficiente

LC Dias, AS Vieira, EJ Barreiro, Processo de obtenção de atorvastatina cálcica utilizando novos intermediários PI 018110015039 (protocolado no INPI, em 25/04/2011)

\* Prof. Luiz Carlos Dias & Dr Adriano V Siqueira, IQ-UNICAMP



# A equipe do INCT-INO FAR



Universidade Federal do Rio de Janeiro, março 2011

Primeira reunião de avaliação e acompanhamento de 2011





# Considerações

# Finais





# Novos arranjos institucionais são necessários

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

07 October 2009 vol 1, issue 1, 95-101

REVIEWS



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

Reviews • POST SCREEN

**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 model

Is

PG Wyatt, The emerging academic drug-discovery sector. *Future Med. Chem.* **2009**, 1, 1013; R Kneller, The importance of new companies for drug discovery: origins of a decade of new drugs. *Nature Rev. Drug Discov.* **2010**, 9, 867; AJ Stevens *et al.*, The role of public-sector research in the discovery of drugs and vaccines. *N. Engl. J. Med.* **2011**, 364, 535.

Is



# Open-Innovation



Henry Chesbrough



“Most innovations fail.  
And companies that don’t  
innovate die”



---

*Big-Pharmas* estão adotando esta estratégia para minimizar sua crise de produtividade. Novos paradigmas de gestão da pesquisa científica para chegar a fármacos inovadores estão em curso de se desenharem.



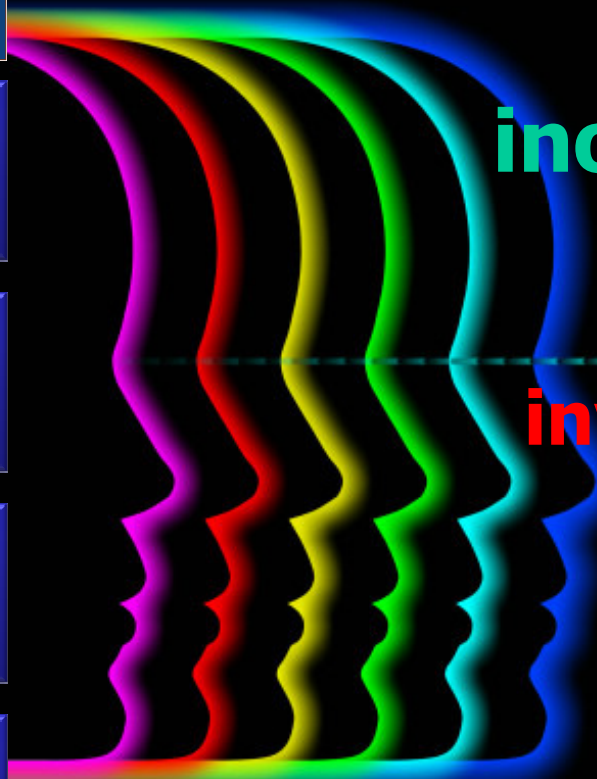
# *Pôle de recherche interdisciplinaire pour le médicament*



Parc d'Innovation d'Illkirch  
Communauté Urbaine de Strasbourg



The effective and productive industry-university interaction in Brazilian pharmaceutical sector is poor, superficial and occasional.



**Nossa capacitação para a**

**inovação no setor de fármacos,**



**exige mais do que**

**investimentos ou parcerias entre**

**universidade, empresa**

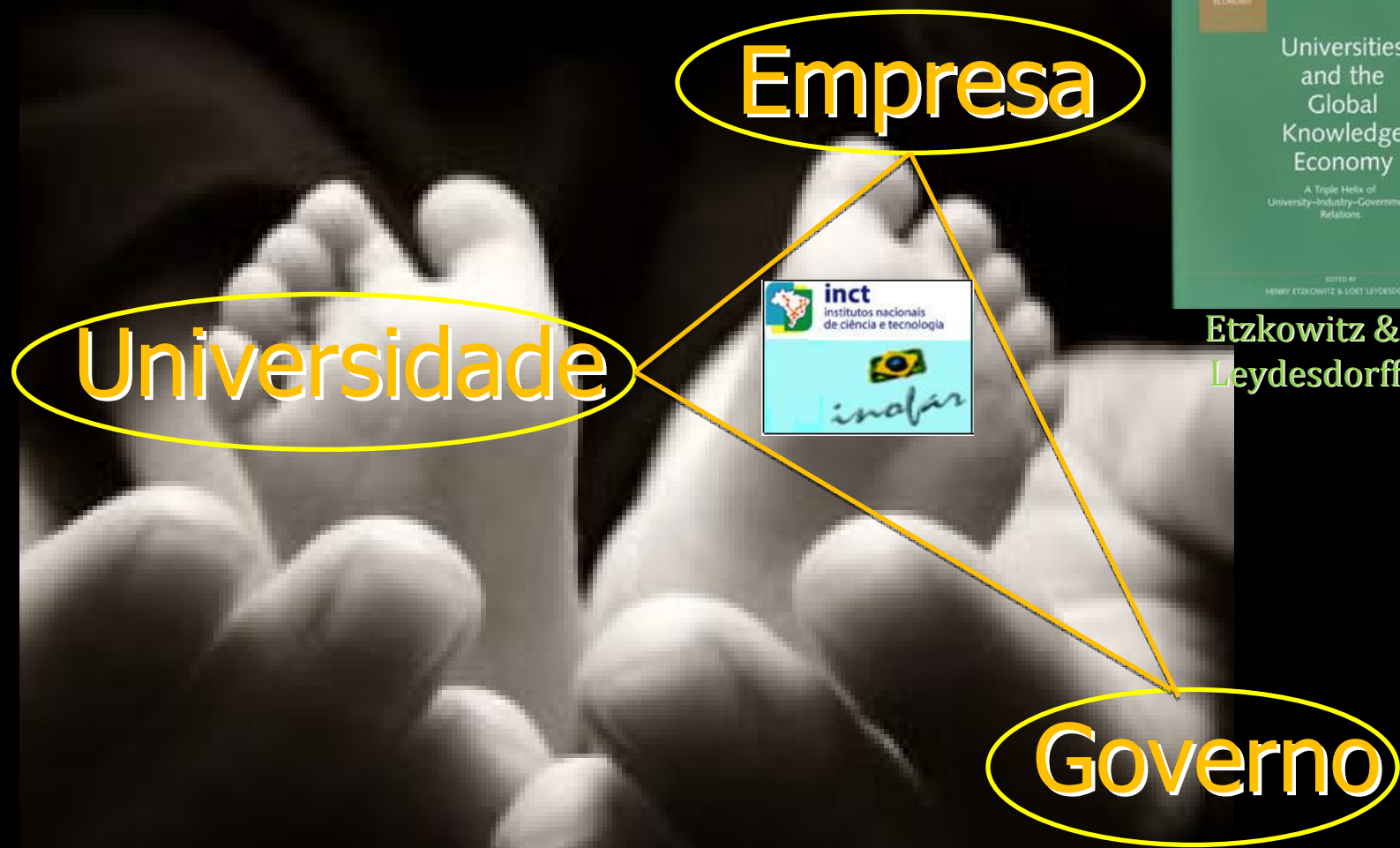
**pública/privada e governo!**

**Exige pessoal qualificado,**

**ações articuladas, integradas,**

**vontade política, superação dos**

***gargalos* e coragem empresarial.**



O estágio atual da inovação  
farmacêutica no Brasil



# UFRJ

A sede do  
**INCT-INO FAR**

[www.inct-inofar.ccs.ufrj.br](http://www.inct-inofar.ccs.ufrj.br)



# Obrigado

	<p>Instituto Nacional de Ciência e Tecnologia</p> <hr/> <p>de Fármacos e Medicamentos</p> <p><a href="http://www.inct-inofar.ccs.ufrj.br">www.inct-inofar.ccs.ufrj.br</a></p>
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