



Universidade Federal do Rio de Janeiro



eliezer © 2016

# O Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos (INCT-INO FAR) e a Interação Universidade-Empresa



II Simpósio Gaúcho de Inovação em Saúde  
& I Encontro do Programa de Pós-Graduação em Ciências Farmacêuticas  
13 de setembro de 2016



## Eliezer J. Barreiro

Professor Titular - UFRJ



Laboratório de Avaliação e Síntese de Substâncias Bioativas

### Laboratório de Avaliação e Síntese de Substâncias Bioativas

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



# 2009



<http://inct.cnpq.br/>



Instituto Nacional de  
Ciência e Tecnologia

de Fármacos e Medicamentos

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

Universidade Federal do Rio de Janeiro

UM DOS MAIORES  
**PROGRAMAS** DE  
CIÊNCIAS E TECNOLOGIA DO  
BRASIL



SAÚDE

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PESQUISE OS  
**INSTITUTOS**  
E SAIBA MAIS  
SOBRE SUAS ATUAÇÕES

# Edital 2014

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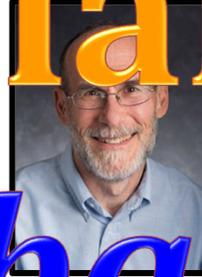
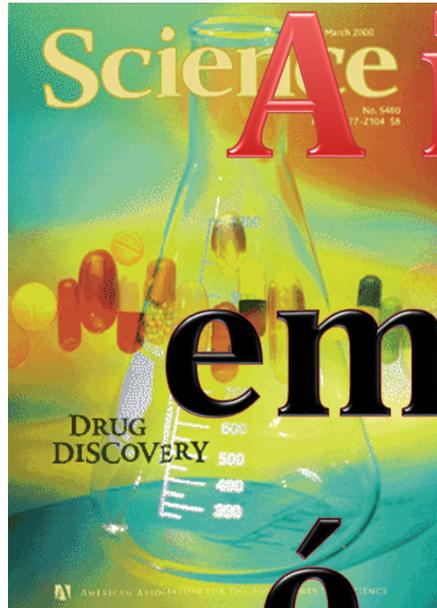
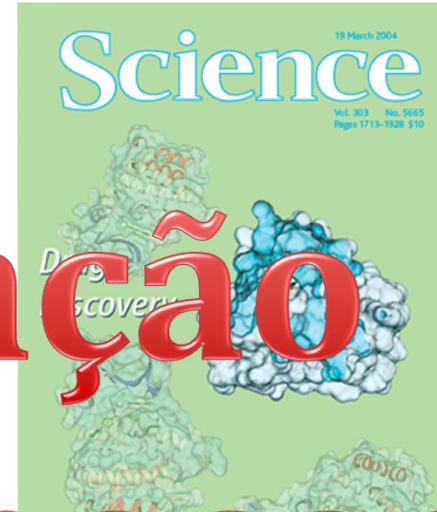
Fale conosco

# Sumário

- ❖ A inovação tecnológica & farmacêutica;
- ❖ O processo de Drug Discovery (DD):
- ❖ A interdisciplinaridade;
- ❖ INCT-INO FAR:
  - ❖ Inovação radical & incremental;
  - ❖ Interação Universidade-Empresa;
  - ❖ Considerações finais.



Innovation



# A inovação

# em fármacos

[OnLine](#)

• *Science* **2004**, 303, 1713

(Donald Kennedy)

# é baseada

• *Science* **2000**, 287, 1951

(Julia Uppenbrink, J. Mervis)

# em Ciência!

• *Science* **2005**, 309, 721

(Jeffrey Mervis)

J Couzin, The Brains Behind Blockbusters,  
*Science* **2005**, 309, 728



# Ciência & Criatividade

As inovações **radicais** tornam-se virtualmente inevitáveis quando: a)



**Ciência + Criatividade = Inovação**

- (2) a atenção de um número suficiente de pesquisadores está voltada para o mesmo problema;
- (3) existam necessidades sociais emergentes, ou por desenvolvimento efetivo da ciência, ou por ambos.

Robert K. Merton



Herbert Marshall McLuhan  
(1911-1980)

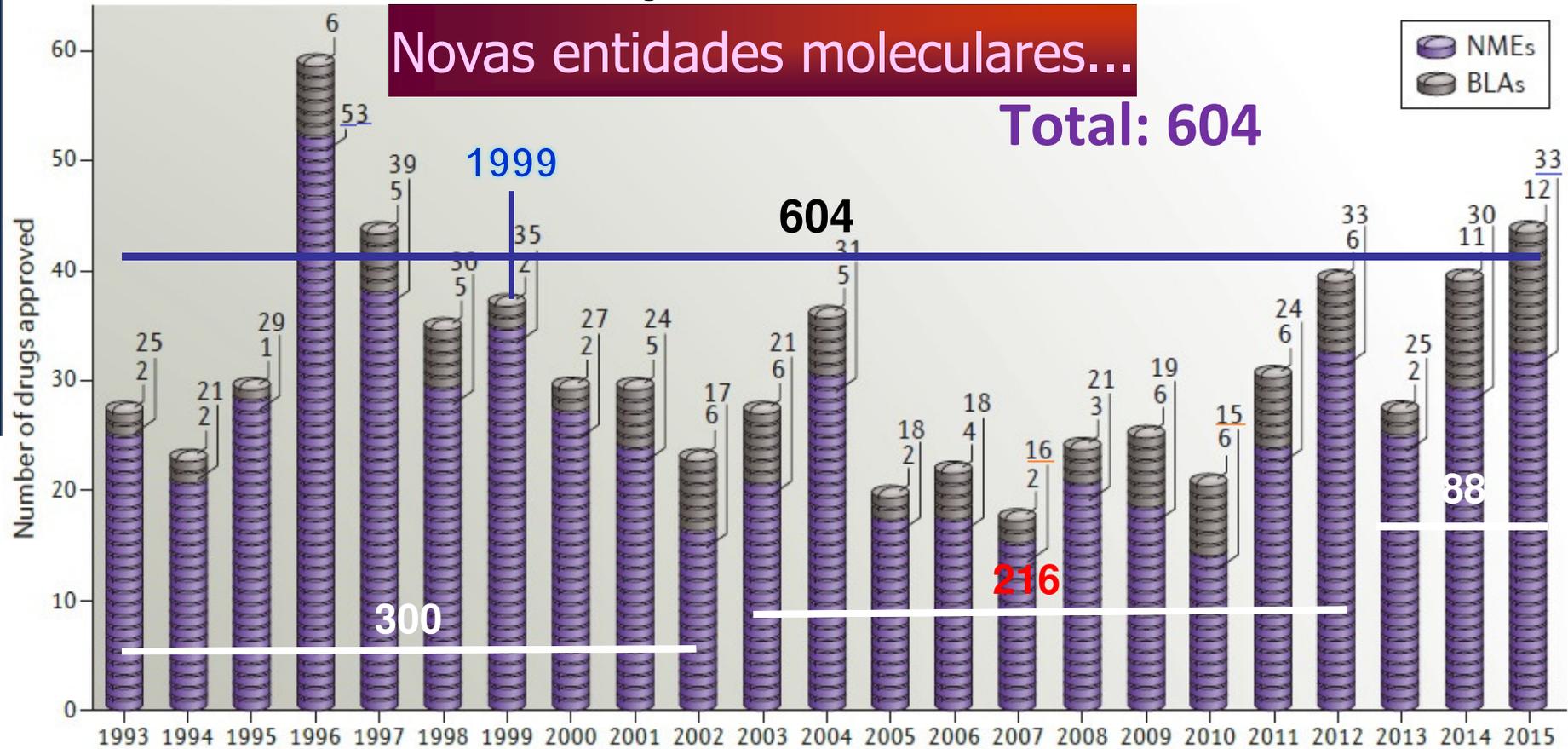
***Aldeia global***

a) The role of genius in scientific advance, *New Scientist* 1961, (#259, Nov 02) 306



Challenges

# As inovações farmacêuticas (1993-2015)



**Novel approvals since 1993.** New molecular entities (NMEs) and Biologics License Applications (BLAs) approved by the Center for Drug Evaluation and Research (CDER) since 1993.



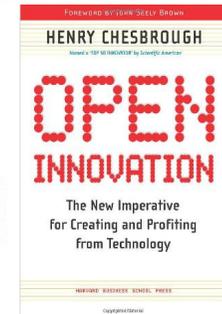
A Mullard, *Nat Rev Drug Discov* 2016, 15, 73



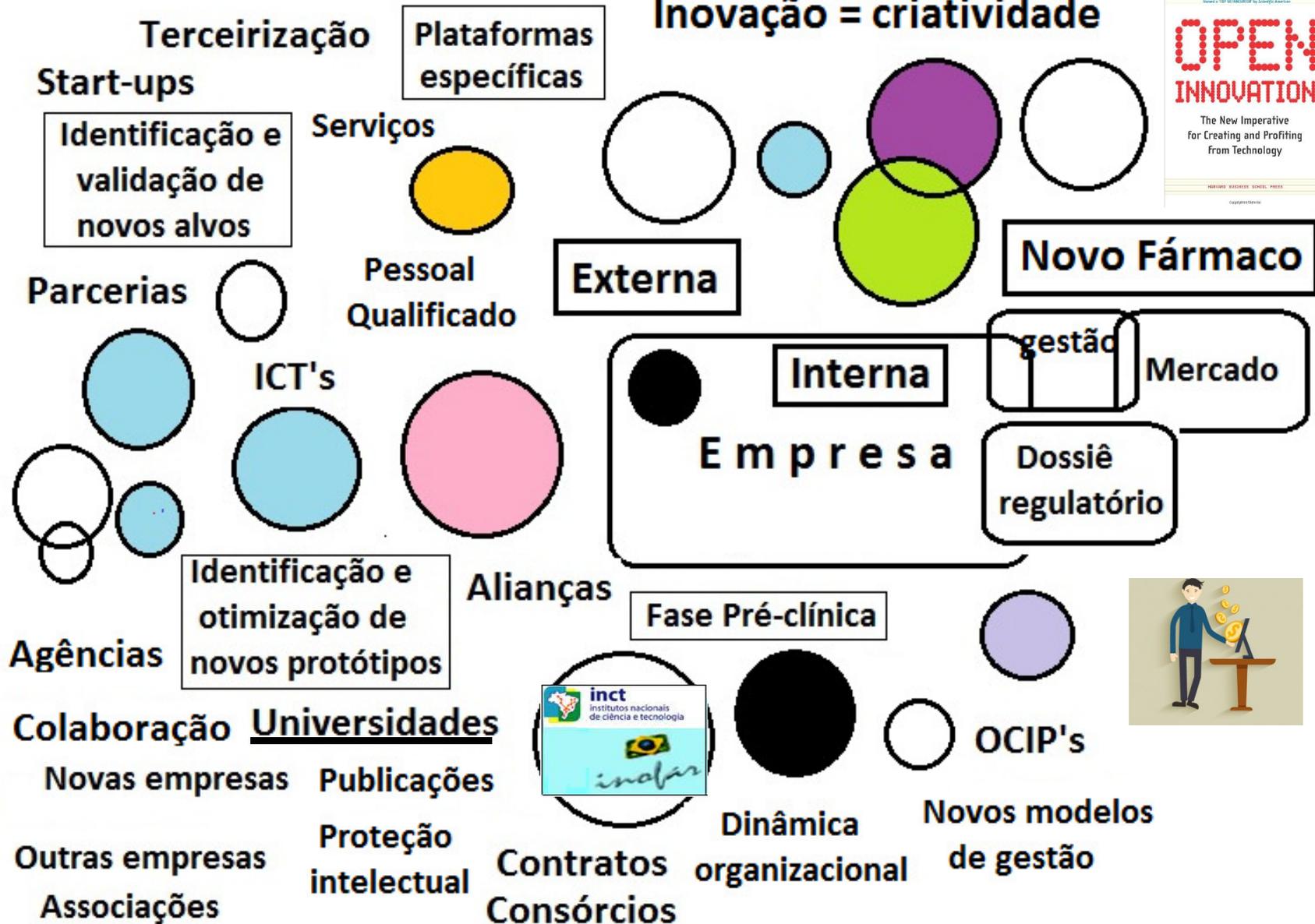
*Big-Pharma*

# A gestão da inovação na indústria farmacêutica

ph <sup>armaceutical</sup> <sub>innovation</sub>



Inovação = criatividade

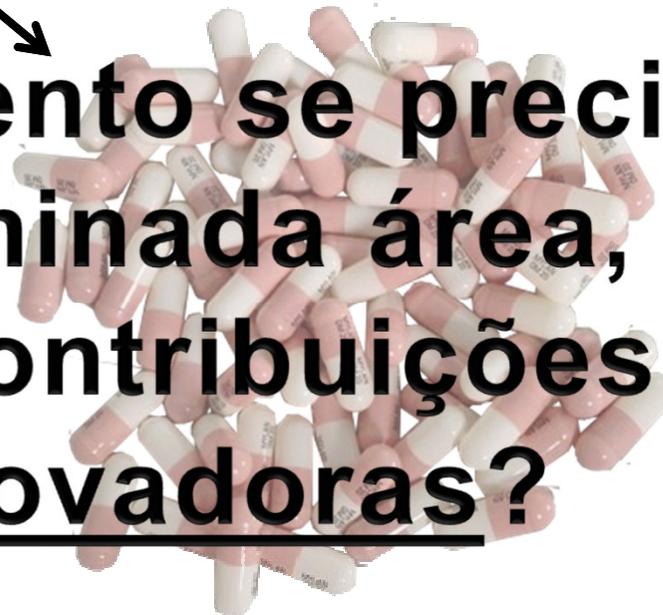




Quais fatores favorecem a inovação?

Inteligência criativa

Quanto conhecimento se precisa, em uma determinada área, para se fazer contribuições científicas inovadoras?





## Drug Discovery in an Academic Setting: Playing to the Strengths

Donna M. Huryn\*

Department of Pharmaceutical Sciences, University of Pittsburgh, 712 Salk Hall, 3501 Terrace Street, Pittsburgh, Pennsylvania 15261, United States

*Inter-alia:* S Hanessian, **Academic–Industrial**

**Collaboration: Toward the Consilience of Two Solitudes,** *ACS Med. Chem. Lett.*, **2016**, *7*, 6;

S Mignani, S Huber, H Tomas, J Rodrigues, J-P Majoral, **Why and how have drug discovery strategies in pharma changed? What are the new mindsets?**, *Drug Discov. Today* **2016**, *21*, 239;

A Gautam, **The changing model of big pharma: impact of key trends**, *Drug Discov. Today* **2016**, *21*, 379 ; M Alvim-Gaston et al. **Open Innovation Drug Discovery (OIDD): A Potential Path to Novel**

**Therapeutic Chemical Space**, *Curr Top Med Chem* **2014**, *14*, 294; KC Nicolaou, **Academic–Industrial Partnerships in Drug Discovery and Development**, *Angew. Chem. Internat. Ed.* **2014**, *53*, 4730;

J M Abou-Gharbia, W E Childers, **Discovery of Innovative Therapeutics: Today’s Realities and Tomorrow’s Vision. 1.Criticisms Faced by the Pharmaceutical Industry**, *J. Med. Chem.* **2013**, *56*, 5659; W L Jorgensen, **Challenges for Academic Drug Discovery**, *Angew. Chem. Int.Ed.* **2012**, *51*, 11680.

*ACS Med. Chem. Lett.* **2013**, *4*, 313

DOI:10.1021/ml400012g

**“There is no doubt that  
academia can play an  
important role in drug  
discovery”**



O mercado mundial em 2015

ca. US\$ 921 bi



*Fármacos Sintéticos*



# Drug Discovery – Editorial

**Donald Kennedy**  
*Editor-in-Chief*

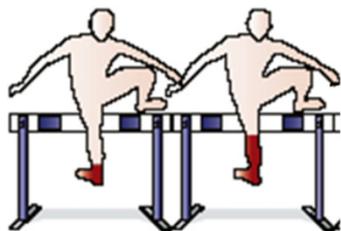


*Science* **2004**, 303, 1717

*"... 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.."*

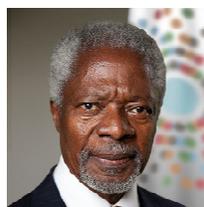
# Declaração da Cúpula do Milênio da Nações Unidas

Nova York, 6 a 8 de setembro de 2000.



## O Projeto do Milênio

Secretário-Geral das Nações Unidas em 2002



**Kofi Annan**

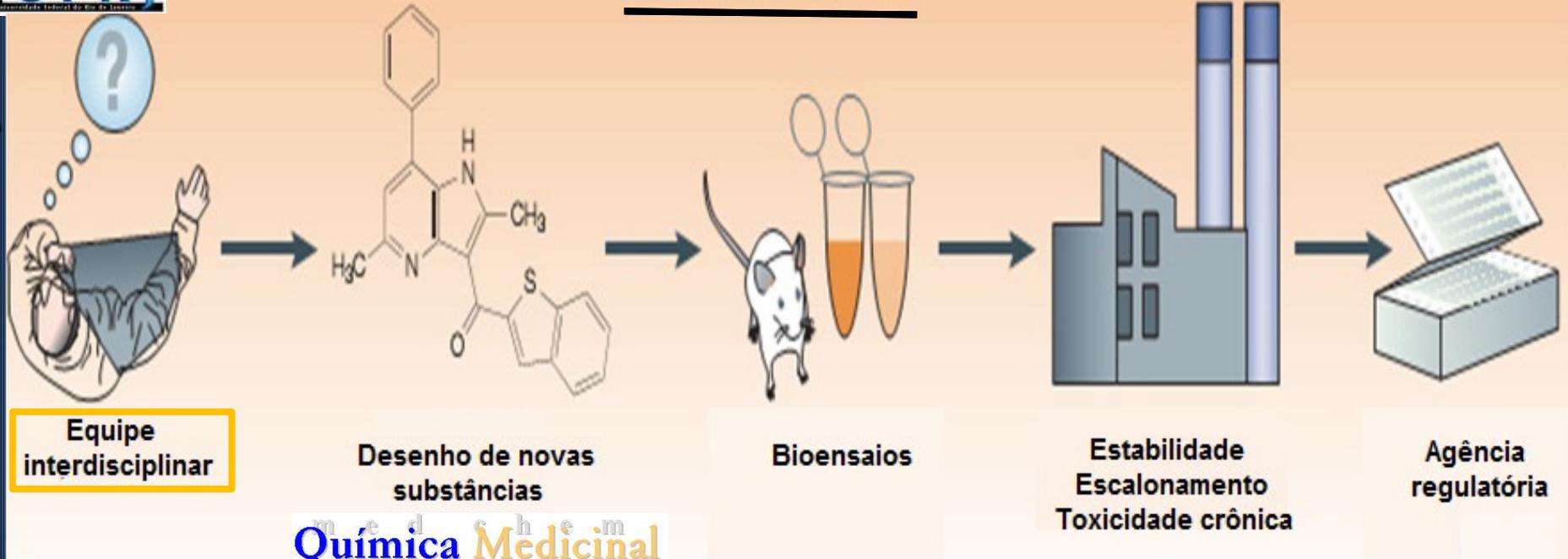
1997-2007



**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 ...”

### Fase pré-clínica

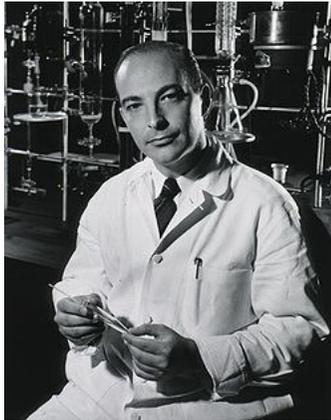


### Fase clínica

O processo de *drug discovery* (D2) é complexo & interdisciplinar...



# Prêmio Nobel, 1959



Arthur Kornberg (41)  
1918-2007

H  
O  
M  
A  
N

## The Two Cultures: Chemistry and Biology<sup>1</sup>



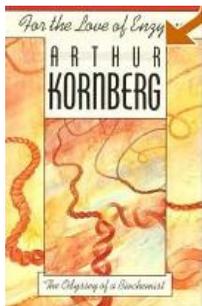
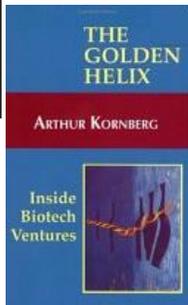
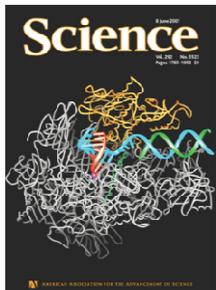
Arthur Kornberg

Department of Biochemistry, Stanford University, Stanford, California 94305

Received July 14, 1987

*“Much of life can be understood in rational terms if expressed in the language of chemistry... the historical roots of chemistry and biology are intertwined in many places...*

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



Biochemistry 1987, 26, 6888-6891

# A *interdisciplinaridade*

é fundamental na  
solução de problemas  
ou desafios complexos !



Para uma adequada  
qualificação interdisciplinar,  
são essenciais  
arranjos institucionais  
& temporais próprios !



Fitoterápicos  
Biofármacos  
Fitofármacos

# Fármacos

↓ IF\*

# Medicamentos

# Pesquisa científica

Inovação radical

**Farmacologia**

\* Indústria farmacêutica

Insumos

M.P.

Tecnologia

Química

Biologia

**Química Medicinal**



<http://inct.cnpq.br/>

|  |   |
|--|---|
|  <p>INCT<br/>inofar</p> | <p>Instituto Nacional de<br/>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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**Edital 2014**

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Project CNPq 573.564/2008-6

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INCT-INOVAR

Team

Scientific adviser board  
(SAB)

Research groups

Research people

Useful articles

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Meetings

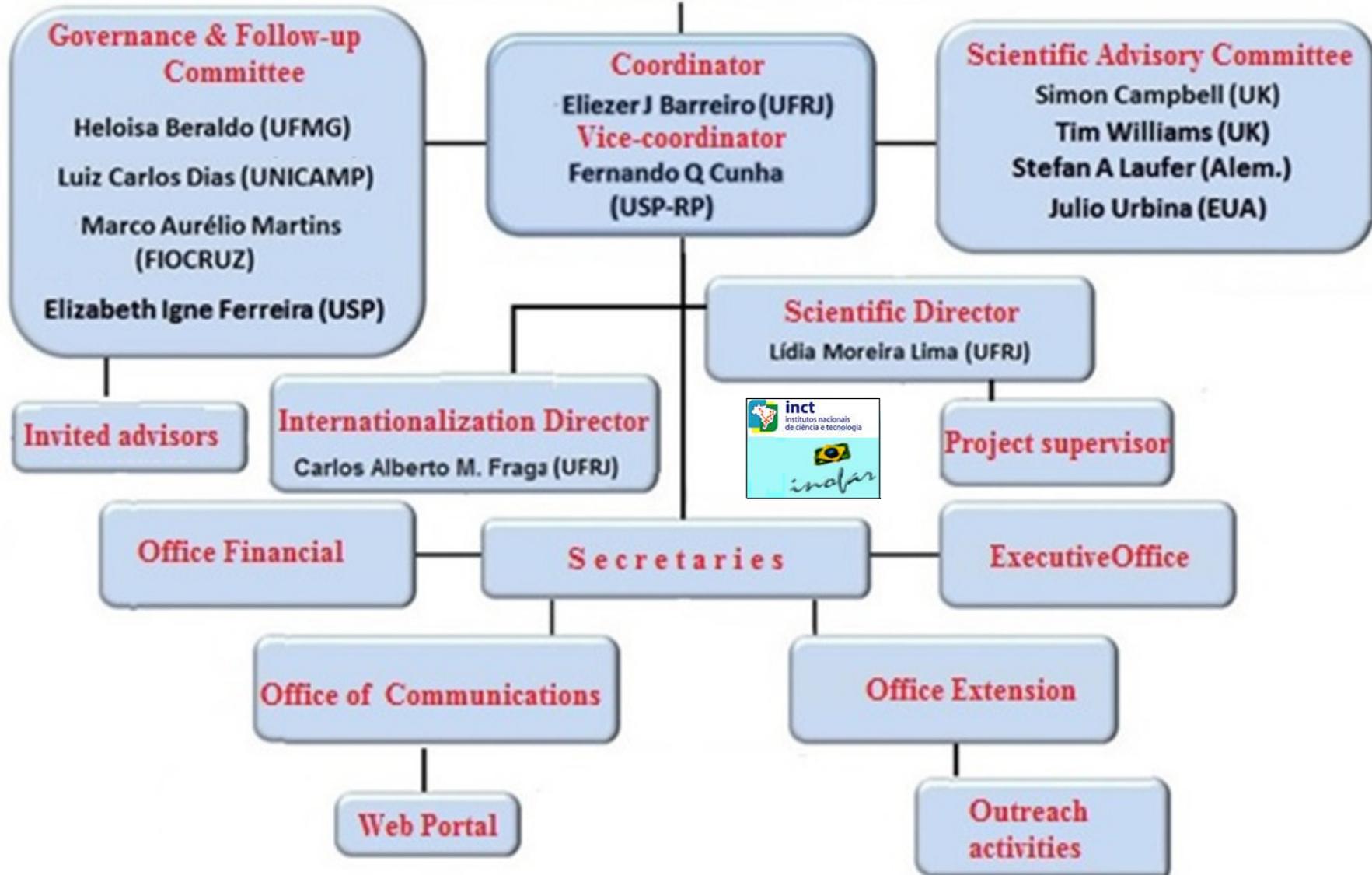
Videos



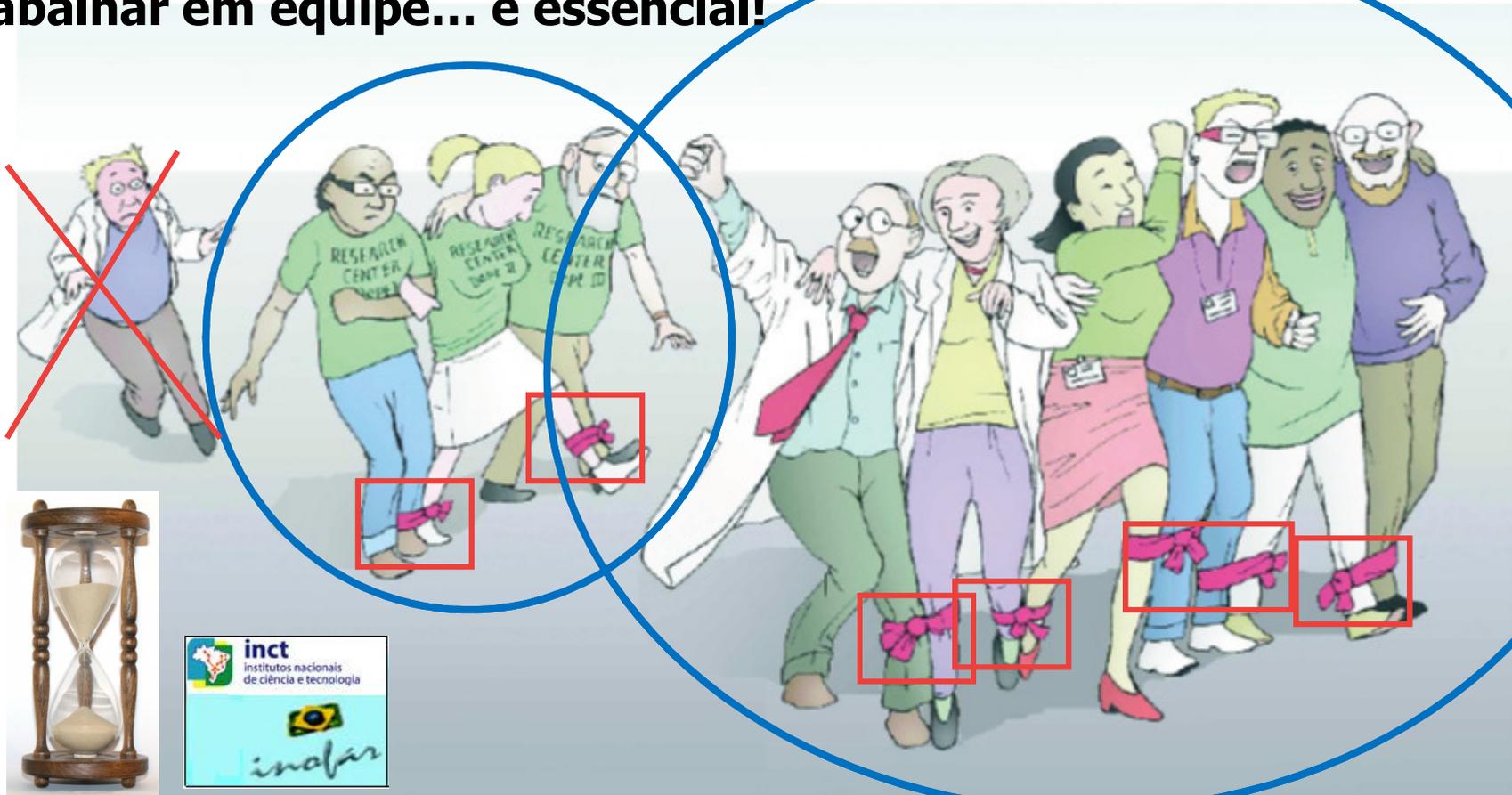
## A missão do INCT-INOVAR

- 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



## Trabalhar em equipe... é essencial!



W Mason, D J Watts, Collaborative learning in networks, *PNAS* **2012**, 109, 764; M Williams, Productivity Shortfalls in Drug Discovery: Contributions from the Preclinical Sciences?, *JPET* **2011**, 336, 3; R Guimera, B Uzzi, J Spiro, L A N Amaral, Team Assembly Mechanisms Determine Collaboration Network Structure and Team Performance, *Science* **2005**, 308, 697.

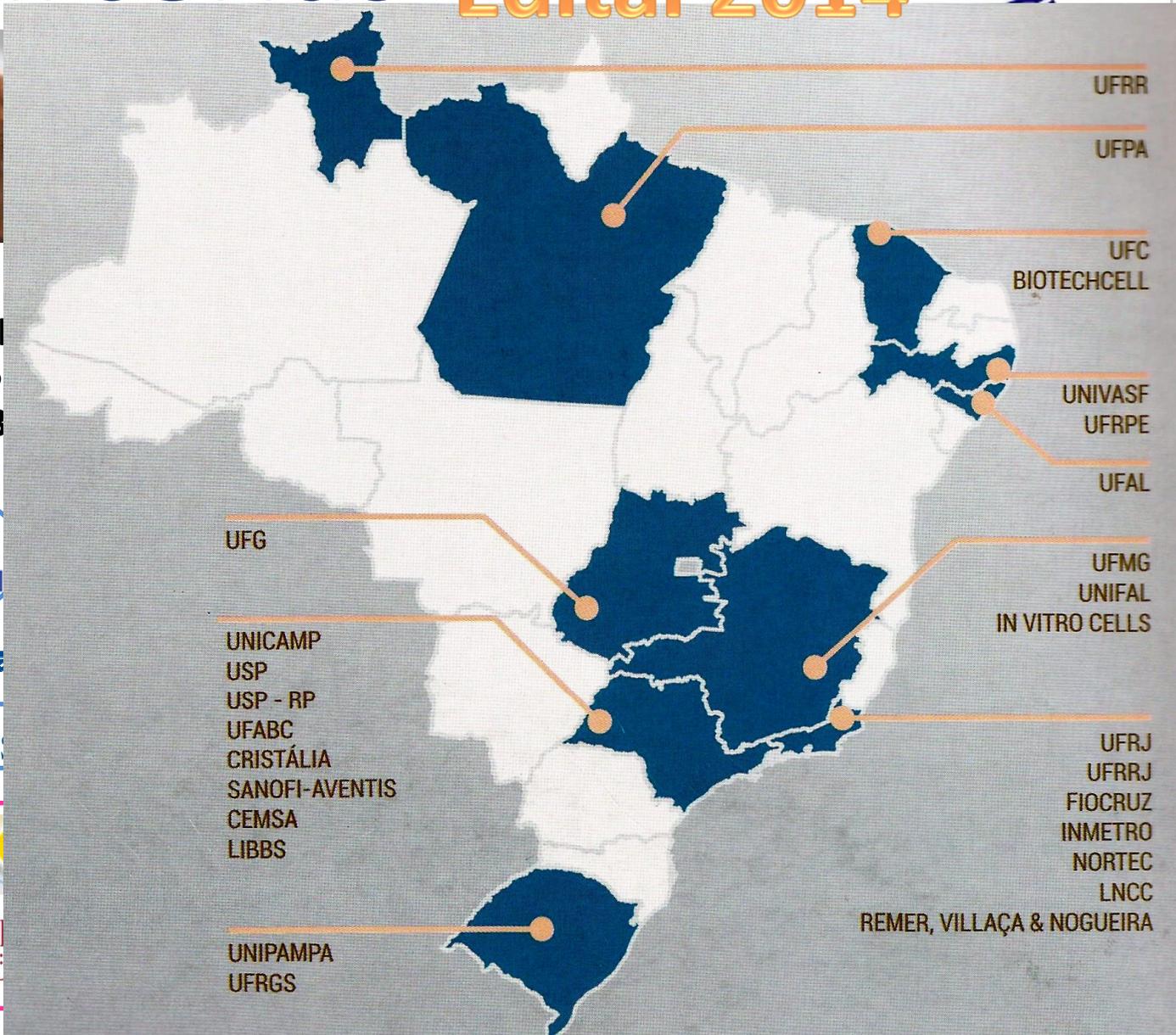
# Parcerias

## INCT-INO FAR

### Edital 2014



30 grupos  
5  
3



UFMG

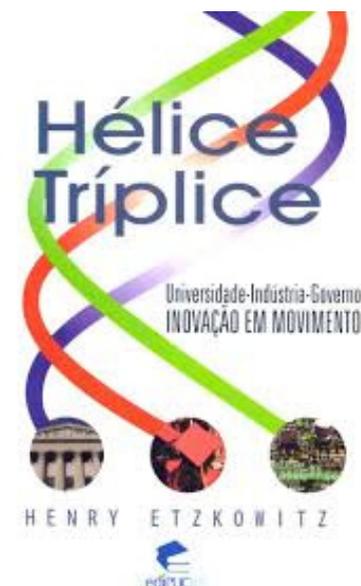
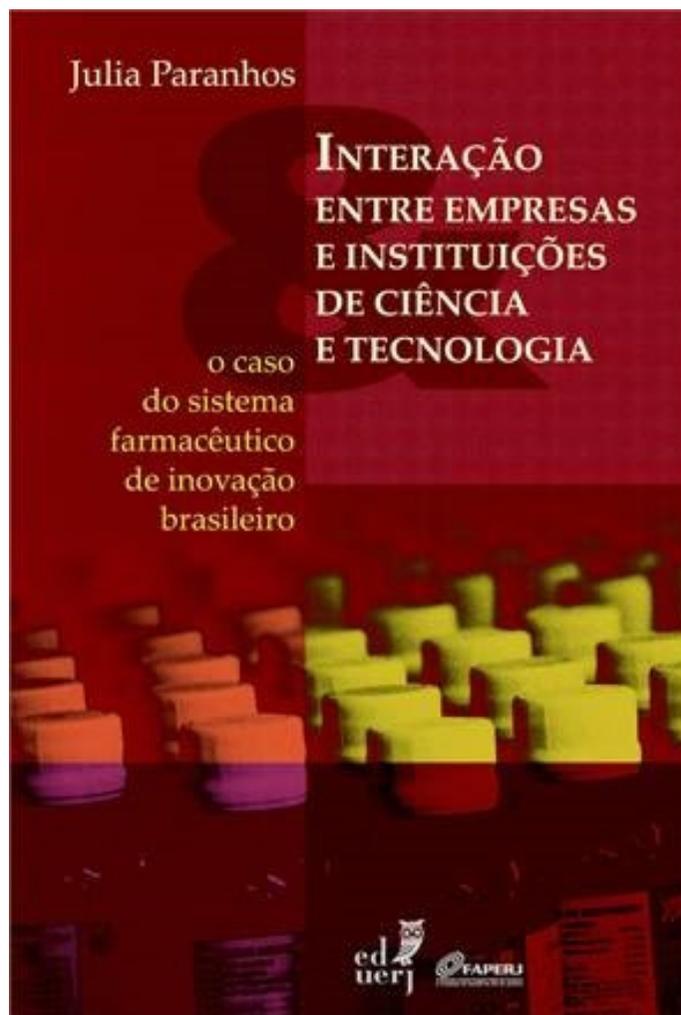




# A tríplice hélice



Dra Julia Paranhos  
Instituto de Economia  
UFRJ



1997

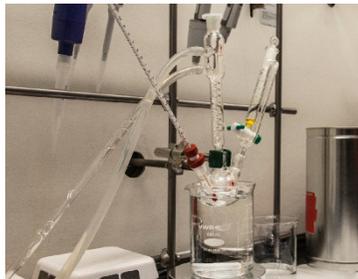


Henry  
Etzkowitz

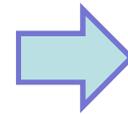


# Síntese de Fármacos: Scale-up

10-100 mg



P&DI



Lab  
scale

10-100 g

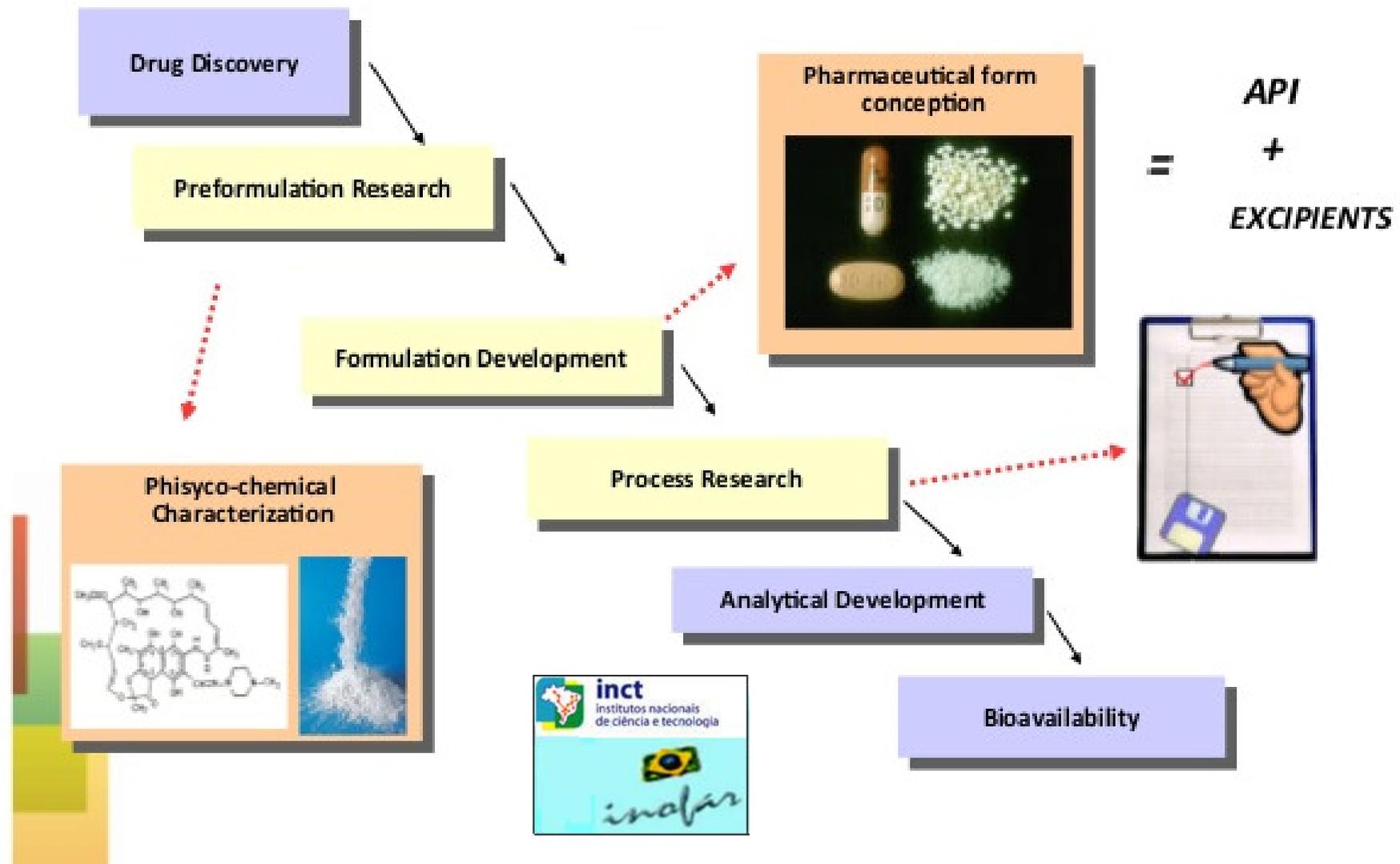


Scale  
-up

1- 5 kg



# Pharmaceutical Development Process



# Desenvolvimento galênico

Formulação

Higroscopicidade

Estabilidade

Dissolução

Excipientes

Rotas de degradação

Calorimetria

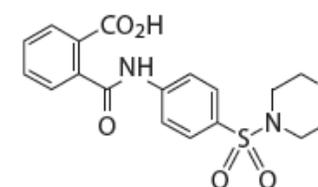


# Potential Inhibitory Effect of LASSBio-596, a New Thalidomide Hybrid, on Inflammatory Corneal Angiogenesis in Rabbits

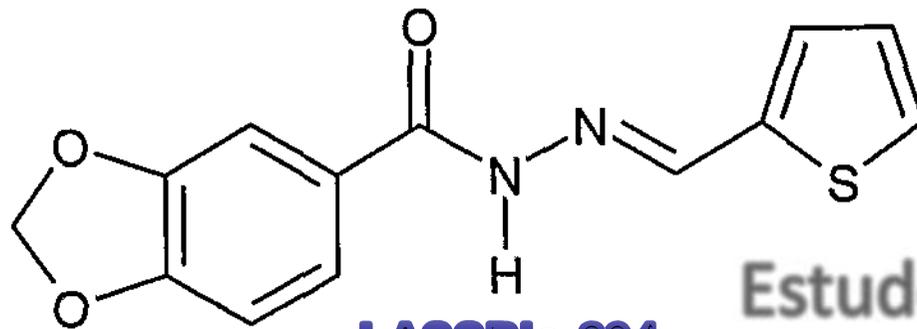
Joao Crispim M.L. Ribeiro<sup>a</sup> Francisco Vagnaldo Fechine<sup>a</sup>  
 Mariana Zaira M.L. Ribeiro<sup>a</sup> Eliezer J. Barreiro<sup>b</sup> Lidia Moreira Lima<sup>b</sup>  
 Nagila M.P.S. Ricardo<sup>a</sup> Maria Elisabete Amaral de Moraes<sup>a</sup>  
 Manoel Odorico de Moraes<sup>a</sup>

<sup>a</sup>Universidade Federal do Ceara, Ceara, e <sup>b</sup>Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

topical application of LASSBio-596 at 1.0% has a potential inhibitory effect on inflammatory corneal angiogenesis in rabbits.



LASSBio-596



**LASBio-294**

7 Kg (ca. 24,5 M)

Estudos pré-clínicos



 CRISTÁLIA



CHN

## Solubility of a New Cardioactive Prototype Drug in Ionic Liquids

Jacqueline Resende de Azevedo, Jean-Jacques Letourneau, Fabienne Espitalier,\* and Maria Inês Ré

Université de Toulouse, Mines-Albi, UMR-CNRS 5302, Centre RAPSODEE, Campus Jarlard, F-81013 Albi CT cedex 09, France

**S** Supporting Information

**ABSTRACT:** Solubility in different solvents is an intrinsic material characteristic for a defined molecule. The solubility of a new cardioactive prototype drug, 3,4-methylenedioxybenzoyl-2-thienylhydrazone (LASSBio-294), was determined in seven different imidazolium based ionic liquids (ILs). The ionic liquids selected were 1-ethyl-3-methylimidazolium methyl phosphonate; 1-ethyl-3-methylimidazolium ethyl phosphonate; 1-ethyl-3-methylimidazolium acetate; 1,3-dimethylimidazolium methyl phosphonate; 1-butyl-3-methylimidazolium acetate; 1-butyl-3-methylimidazolium tetrafluoroborate; and 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide. In addition, solubility data of LASSBio-294 in water and in mixtures of water and ILs were also measured. For all solvents, the concentration of drug in saturated solutions was determined by high performance liquid chromatography (HPLC). Solid–liquid equilibrium measurements were performed in a range of temperatures from 288.15 K to 308.15 K, at atmospheric pressure. From the solubility data it can be concluded that the drug showed sufficient solubility in five of the tested ILs so that these compounds can be suitable for further crystallization studies. The aim of this work is also to discuss and understand the solubility of LASSBio-294 in these alternative solvents. The results indicate that the solubility of the drug is dependent on IL structural variations (cation–anion combinations).



### ■ ACKNOWLEDGMENTS

The authors would like to thank Cristália Ltda. (Itapira, SP, Brazil) for providing the drug LASSBio-294.



Deutsche  
Forschungsgemeinschaft

## INTERNATIONAL ACTIVITIES



<http://www.icepha.de/>

INCT-INOFAR established, on November 18, 2011, a cooperation agreement with the Interdisciplinary Center of Pharmacogenomics and Pharmaceutical Research (ICEPHA) of the University of Tübingen, Germany. Through this deal, we broaden the international scope of INCT-INOFAR and the bases for scientific exchange and the development of innovative research projects in new pharmaceuticals. On the other hand, the agreement establishes the organization of scientific and academic activities, like courses, conferences, symposiums, or lectures, and the exchange of researchers and/or students, as well as the exchange of materials and publications of mutual interest.



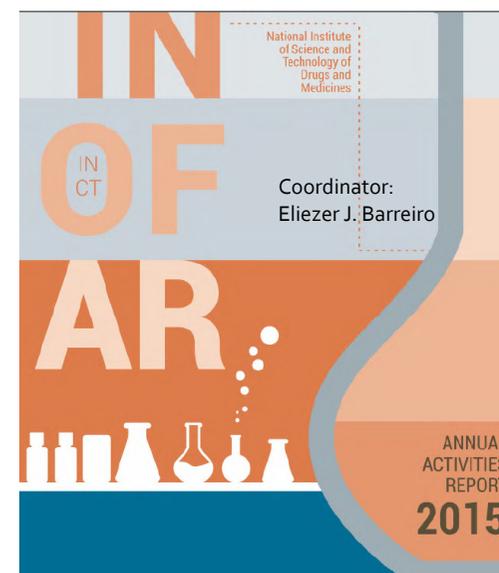
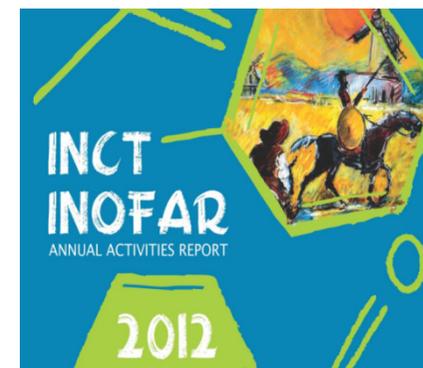
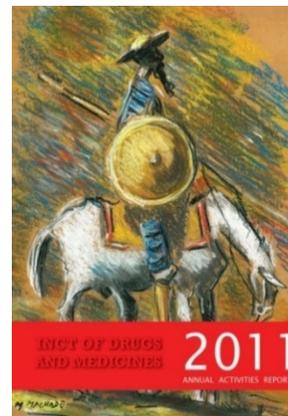
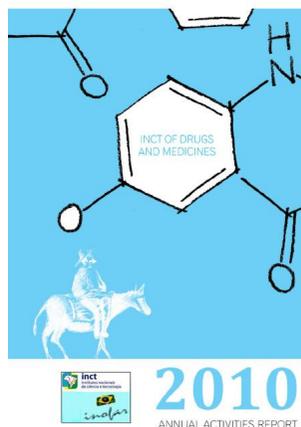
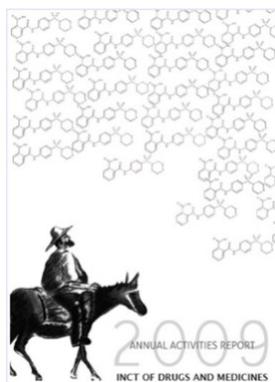
University Council, Federal University of Rio de Janeiro, November, 2011



At the end of 2011, INCT-INOFAR through the Dean of the Federal University of Rio de Janeiro (UFRJ) signed a cooperation agreement with the Interdisciplinary Center for Pharmacogenomics and Pharmaceutical Research (ICEPHA) of the University of Tübingen, Germany, directed by Professor Stefan Laufer.

# Annual Activities Report

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



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Advanced  
Projects



Pipeline



**Antileishmanial** activity of new  
*N*-acylhydrazone derivatives and  
analogues ICB-UFAL / LASSBio-

UFRJ

Studies on design & discovery  
of new **antidiabetes** drug  
candidates.

LASSBio-UFRJ

**BR102013012646-2**

Studies of **anti-**  
**inflammatory** &  
analgesic effect of  
**LASSBio-591**. LASSBio-  
UFRJ/FM-USP,RP

Studies of new  
oncolytic agent, **dual**  
**inhibitor of kinases**

LASSBio-UFRJ

**WO2014113859**

**WO2013142935**

Studies on new  
drug candidate useful  
for **neuropathic pain**  
LASSBio-UFRJ / FM-USP,RP

**WO2012054996**

Bolsas = mobilidade

# Incremental Innovation\*

## \* Atorvastatin

Organic & Biomolecular Chemistry

PAPER

View Article Online  
View Journal | View Issue



Cite this: *Org. Biomol. Chem.*, 2016, 14, 2291

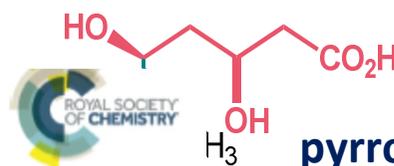
Received 12th December 2015,  
Accepted 29th December 2015  
DOI: 10.1039/c5ob0254g

www.rsc.org/obc

### The total synthesis of calcium atorvastatin†

Luiz C. Dias,<sup>a\*</sup> Adriano S. Vieira<sup>a</sup> and Eliezer J. Barreiro<sup>b</sup>

A practical and convergent asymmetric route to calcium atorvastatin (**1**) is reported. The synthesis of calcium atorvastatin (**1**) was performed using the remote 1,5-*anti* asymmetric induction in the boron-mediated aldol reaction of  $\beta$ -alkoxy methylketone (**4**) with pyrrolic aldehyde (**3**) as a key step. Calcium atorvastatin was obtained from aldehyde (**3**) after 6 steps, with a 41% overall yield.



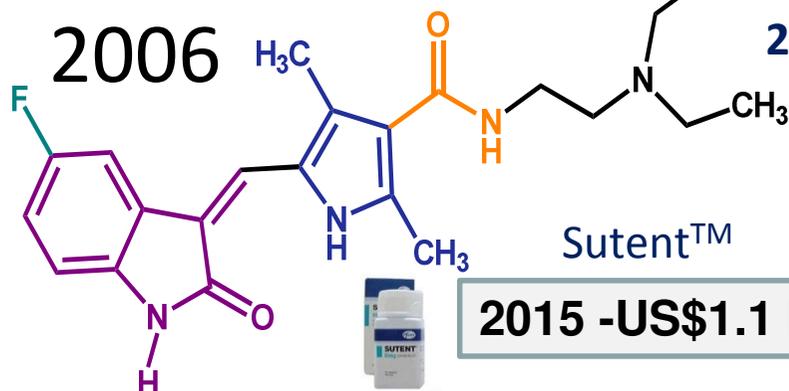
Lipitor™

functionalized  
pyrrolheptanoic acid (5g scale)

• Patent US 5273995 Pfizer (1991)

World total sales:  
US\$ > 150 bi  
(1991-2011)

## \* Sunitinib



2015 - US\$1.1 bi

• Total synthesis Professor **Angelo C. Pinto†** & Dr **Bárbara Vasconcellos da Silva** IQ, UFRJ, RJ (2011) (BR)



Top-1 blockbuster drug

functionalized

2-oxo-1*H*-indol-1*H*-pyrrole-3-carboxamide

\* Patent US 7211600 (2001)

• Multi TK inhibitor indicated to renal carcinoma

The global kinase inhibitors market: 2010 - US\$ 28.1 bi; 2011 - US\$ 29.1 bi The market is expected to reach US\$ 40.2 bi by 2016!

\*

**Fluoxetine** (SSR<sub>i</sub>) & **Quetiapine** (Seroquel™)  
**Valsartan** (Diosan, AT<sub>1</sub>), **Dasatinib** (Bcr-Abl<sub>i</sub>)





# Patente obtida

United States Patent 7,091,238

August 15, 2006

Thienylhydrazon with digitalis-like properties (positive inotropic effects)

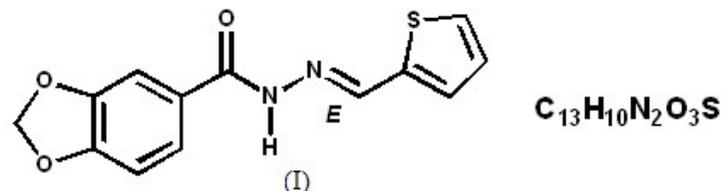
## Abstract

The invention discloses a compound having the formula (I) wherein R.sub.1 is selected from the group consisting of hydrogen, alkyl of 1 to 6 carbon atoms, unsubstituted phenyl, and substituted phenyl; R.sub.2 is selected from the group consisting of H, alkene, un-substituted phenol, and substituted phenyl; and pharmaceutically acceptable salts thereof, having digitalis-like properties. The invention further discloses a novel method to synthesize 3,4-methylenedioxybenzoyl-2-thienylhydrazone (LASSBio-294). LASSBio-294 produces positive inotropic effect on cardiac and skeletal muscle. The invention is useful for the treatment of congestive heart failure and muscle fatigue. It lacks toxic effects seen in digitalis glycosides.



**Inventors:** Sudo; Roberto Takashi (Rio de Janeiro, BR), Albuquerque; Edson X. (Baltimore, MD), Barreiro; Eliezer J. (Rio de Janeiro, BR)  
**Filed:** June 21, 2000  
**PCT Filed:** June 21, 2000  
**PCT No.:** PCT/US00/17024  
**371(c)(1),(2),(4) Date:** April 08, 2004  
**PCT Pub. No.:** WO00/78754  
**PCT Pub. Date:** December 28, 2000

The invention includes the novel chemical compound having the formula (I)



## SUMMARY OF THE INVENTION

There is a great medical need for drugs to treat congestive heart failure. Congestive heart failure is an important cause of mortality and morbidity in the U.S.: over 2.5 million patients are currently diagnosed. Compounds derived from digitalis, which are in the class of cardiac glycosides, are the primary drugs used in the treatment of congestive heart failure, particularly systolic dysfunction. However, digitalis ameliorates congestive heart failure by producing a positive inotropic effect. A positive inotropic agent strengthens the contractility of muscular tissue. Digitalis-derived drugs have the defect of being cardio-toxic and neuro-toxic at doses just above their therapeutic range (Hardman, J. G. and Limbird, L. E., The Pharmaceutical Basis of Therapeutics, 9.sup.th ed. McGraw-Hill New York, 1996, chapter 34). There is a need for drugs that can treat congestive heart failure and are less toxic near their therapeutic range.

## A QUESTÃO DA INOVAÇÃO EM FÁRMACOS NO BRASIL: PROPOSTA DE CRIAÇÃO DO PROGRAMA NACIONAL DE FÁRMACOS (PRONFAR)

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THE QUESTION OF INNOVATIVE DRUGS IN BRAZIL. THE PROPOSAL OF THE PRONFAR CREATION. Medicines are essential instruments to the preservation, maintenance and promotion of Health. The access to the medicine represents an important factor of social inclusion, depending on the availability of the pharmaceutical – active principle contained in the medicine that in 85% of the cases has a synthetic origin. In this scenario the importance of knowing how to make pharmaceuticals and medicines play a significant role in the viability of the autonomous Health politics necessary for the demands of the major Nations. In this context, this work describes concisely the main aspects involved in the interdisciplinary drug discovery process, identifying the possible gorges for the successful development of innovative drugs in Brazil.

Keywords: Pronfar creation; innovative drugs in Brazil.

### Challenges of the Brazilian pharmaceutical industry

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### DESAFIOS DA INDÚSTRIA FARMACÊUTICA BRASILEIRA

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...s and Challenges for Innovation in  
...aceuticals: Now or Never!

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**CONSIDERAÇÕES FINAIS**

**Em Ciência, no que diz respeito ao empenho, ao compromisso, ao esforço, à dedicação, não existe meio termo! Ou você faz a coisa bem feita ou é melhor não fazer.**



THE 8<sup>TH</sup> BRAZILIAN SYMPOSIUM ON  
MEDICINAL CHEMISTRY



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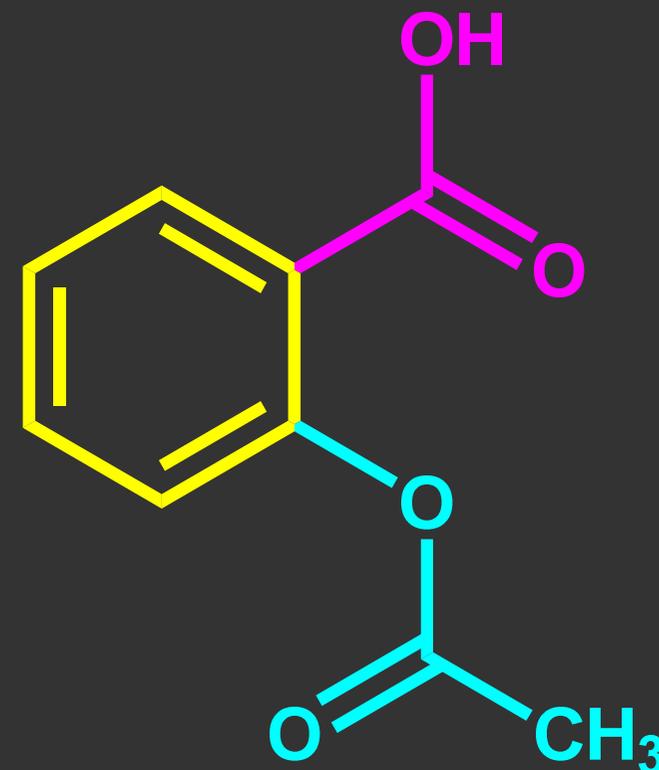
ARMAÇÃO DOS BÚZIOS (RJ) BRAZIL

THE 8<sup>TH</sup> IS COMING UP WITH HIGHLIGHTS IN  
MEDICINAL CHEMISTRY.

# CONVITE

## De fármacos e suas descobertas

Pretende-se tratar de temas, opiniões, comentários sobre a Ciência dos Fármacos, seu uso seguro e benefícios. Aspectos da formação qualificada de universitários e pós-graduandos nas Ciências dos Fármacos também são de interesse.



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# Muito Obrigado

Morro do Corcovado com a estátua do Cristo Redentor, uma das sete maravilhas do mundo moderno.