



# INCT-INO FAR, a Brazilian network for drug design, discovery and development

National Institute of Science and Technology in Drugs and Medicines



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Professor

Universidade Federal do Rio de Janeiro



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



# Summary

- ❖ *Prologue: a brief view of scientific research nowadays & the interdisciplinarity of complex drug discovery (DD) process;*
- ❖ *The pharmaceutical innovation and the role of the university*
- ❖ *The INCT-INO FAR: our mission*
- ❖ *The INCT-INO FAR: Who we are & what we do*
- ❖ *The INCT-INO FAR: Final remarks*
- ❖ *Acknowledgments*



# Prologue...



# The scientific research through the ages...



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



**The physical Crick & the biologist Watson**

JD Watson & FHC Crick, A Structure for Deoxyribosé Nucleic Acid, *Nature* 1953, 171, 737-738.



**The human genome team**

## 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

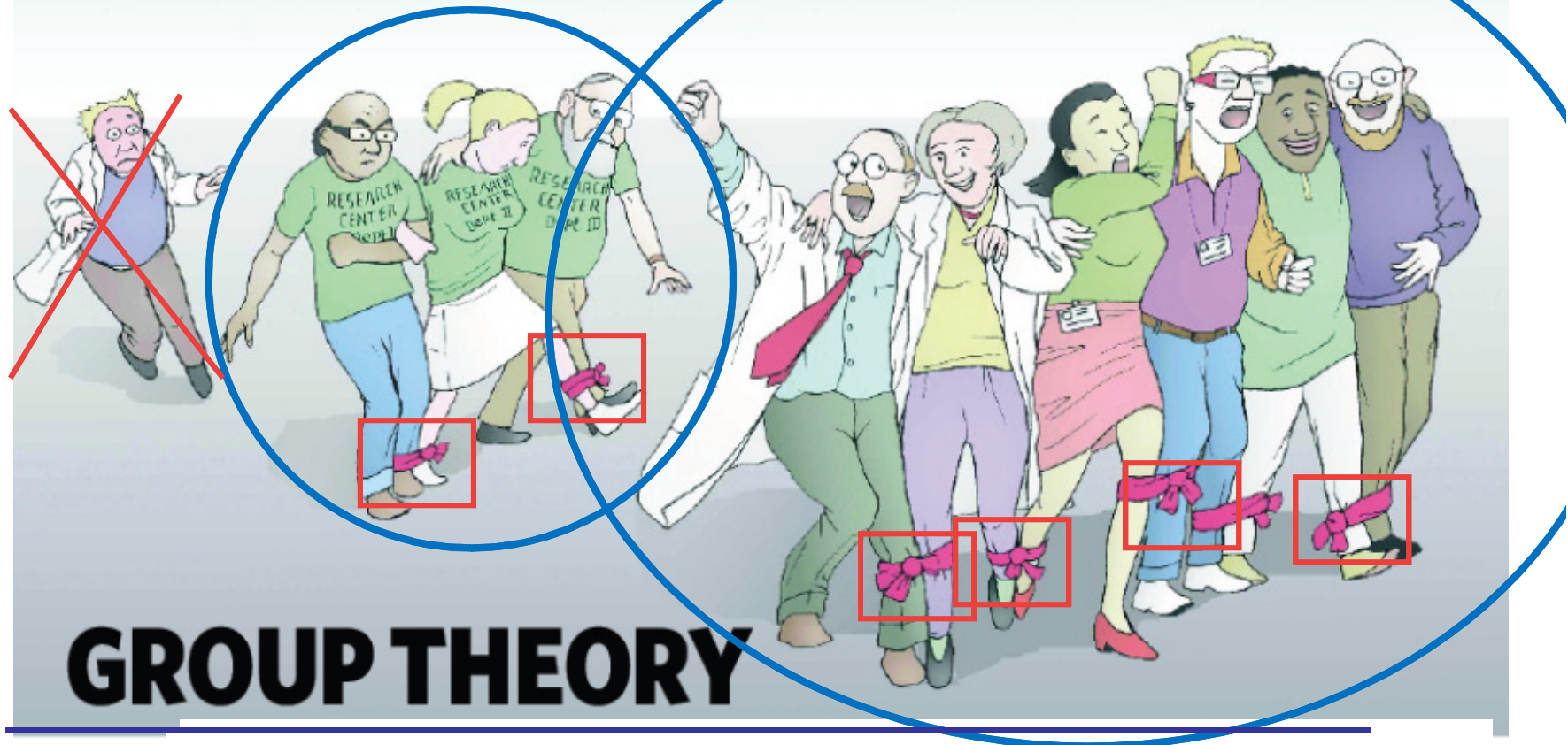




NEWS FEATURE

NATURE|Vol 455|9 October 2008

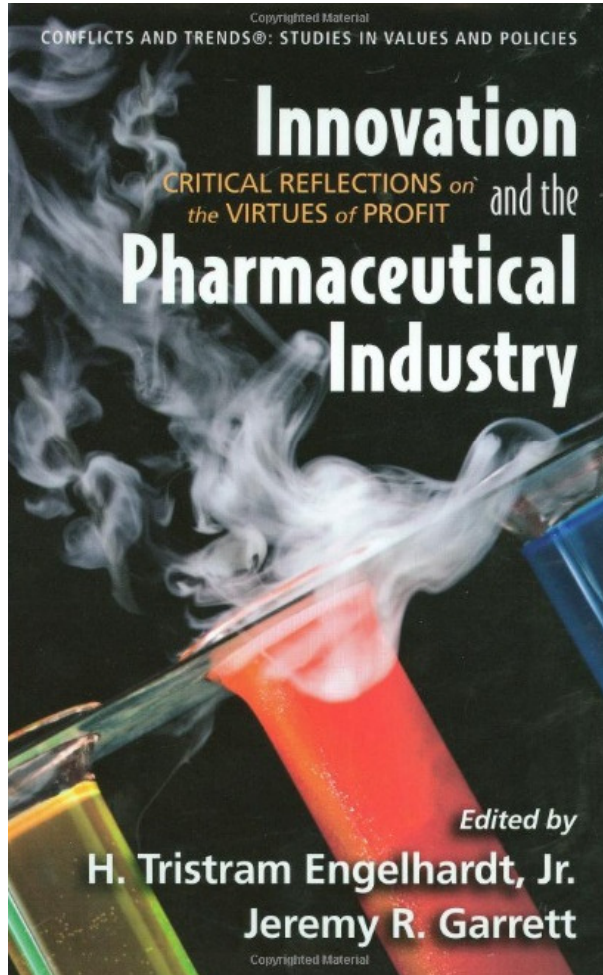
## What makes a successful research team?



W Masona, 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.

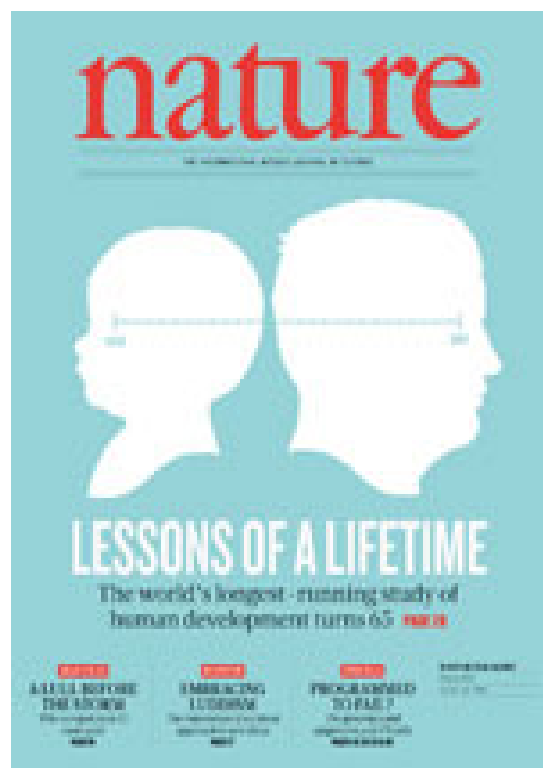


The  
pharmaceutical  
innovation...



**Technological innovation is a process mostly dynamic in industrial activity. This dynamism is accentuated in pharmaceutical innovation which, more than any other, depend on the effective and productive interaction between **Science & Technology.****





2011

PHARMACEUTICALS

# Traditional drug-discovery model ripe for reform

*Academic researchers set to play much greater role in pharmaceutical development.*

BY DANIEL CRESSEY

With drug pipelines running dry and a slew of blockbuster medicines about to lose patent protection, the voices arguing that the traditional drug-development process is too expensive and inefficient to survive are getting louder.

Employing thousands of in-house scientists to develop drug candidates from scratch has turned into a billion-dollar gamble that simply isn't delivering enough profitable products to market. Bernard Munos, founder of the Inno-Think pharmaceutical policy research group in Indianapolis, Indiana, is not alone in believing that the next three years "will probably see an implosion of the old model" of drug discovery.

So what comes next? Cutbacks, certainly: witness Pfizer's dramatic announcement early last month that it will soon close its research site at Sandwich, UK, and slice roughly US\$1.5 billion from its proposed 2012 research and development spend (see *Nature* 470, 154; 2011).



HILTON DEUTSCH/CORBIS

The kit may have improved, but the in-house drug discovery model has changed relatively little.

Nature 2011, 471, 17

Why companies involved in DD fail than succeed at releasing the creative energy of its scientists?

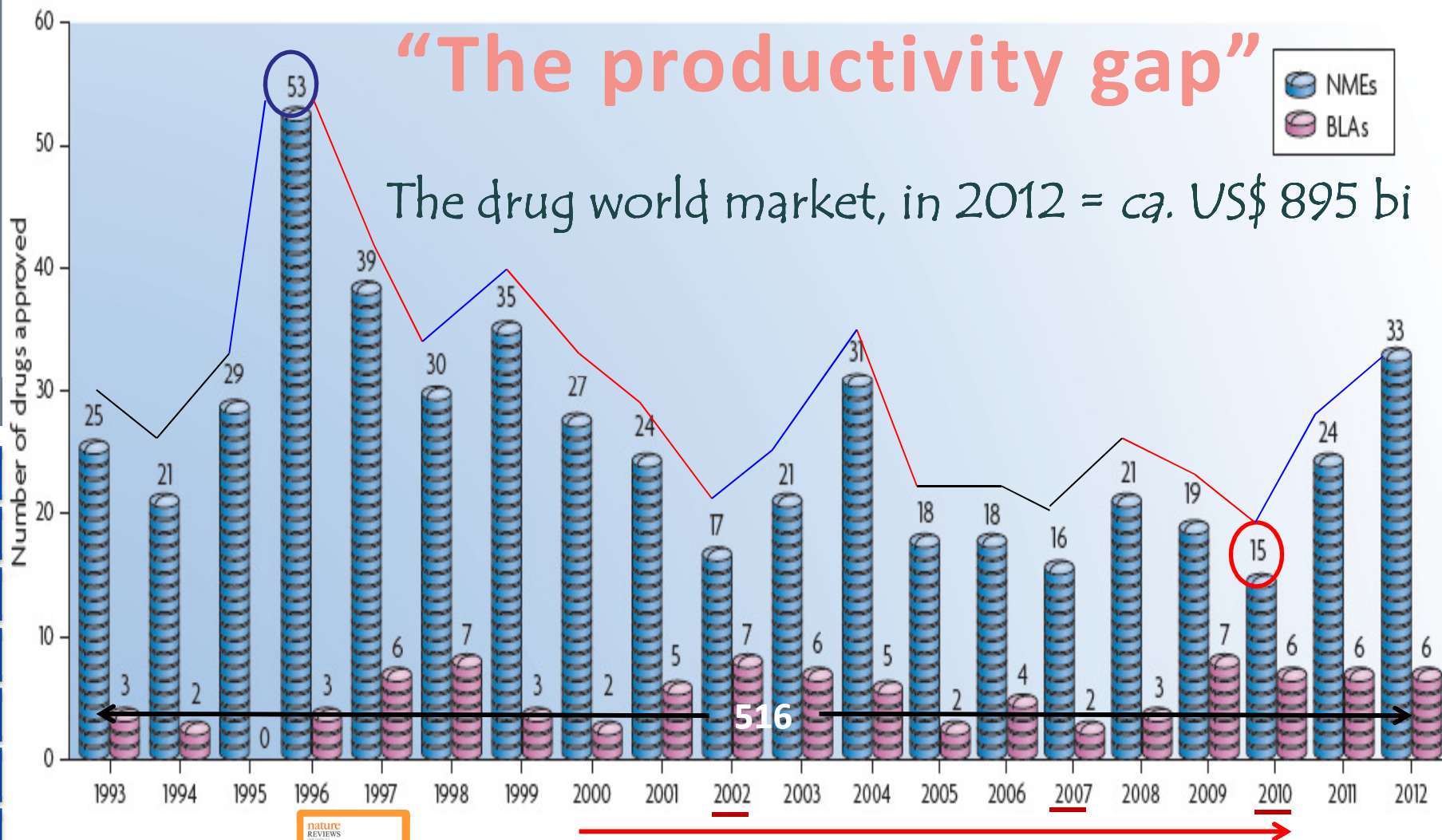
M Abou-Gharbia, WE Childers, Discovery of Innovative Therapeutics: Today's Realities and Tomorrow's Vision. 1. Criticisms Faced by the Pharmaceutical Industry, *J. Med. Chem.* **2013**, 56, 5659; LJS Knutsen, Drug discovery management, small is still beautiful: Why a number of companies get it wrong, *Drug Discov. Today* **2011**, 16, 476.



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# New chemical entities 1993-2012



A. Mullard, 2012 FDA drug approvals, *Nature Rev. Drug Discov.* **2013**, 12, 87.



# Is open innovation the way forward for big pharma?

The current, fully integrated business model of large pharmaceutical companies is increasingly considered to be unsustainable, and so new approaches that engage large and small companies, governments and academic institutions are needed. Could 'open innovation' models that have proved successful in other sectors be fruitfully adopted by the pharmaceutical industry?



J Hunter & S Stephens, *Nature Rev. Drug Discov.* **2010**, *9*, 87

Big  
B Pharma  
P



Innovation process *in-house*

= fully integrated pharmaceutical company

To fully integrated pharmaceutical network

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JW Scannell, A Blanckley, H Boldon, B Warrington, Diagnosing the decline in pharmaceutical R&D efficiency, *Nature Rev. Drug Discov.* **2012**, *11*, 191; M Goldman, Reflections on the Innovative Medicines Initiative, *Nature Rev. Drug Discov.* **2011**, *10*, 321; F Pammolli *et al.*, The productivity crisis in pharmaceutical R&D, *Nature Rev. Drug Discov.* **2011**, *10*, 428 ; M Williams, Productivity Shortfalls in Drug Discovery: Contributions from the Preclinical Sciences? *JPET* **2011**, *336*, 3; SM Paul *et al.*, How to improve R&D productivity: the pharmaceutical industry's grand challenge, *Nature Rev. Drug Discov.* **2010**, *9*, 203; M R Barnes *et al.* Lowering industry firewalls: pre-competitive informatics initiatives in drug discovery, *Nature Rev. Drug Discov.* **2009**, *8*, 701; B Hughes, Harnessing open innovation, *Nature Rev. Drug Discov.* **2009**, *8*, 344; B Munos, Lessons for 60 years of pharmaceutical innovation, *Nature Rev. Drug Discov.* **2009**, *8*, 959.



*The role of  
universities  
in DD*





## 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

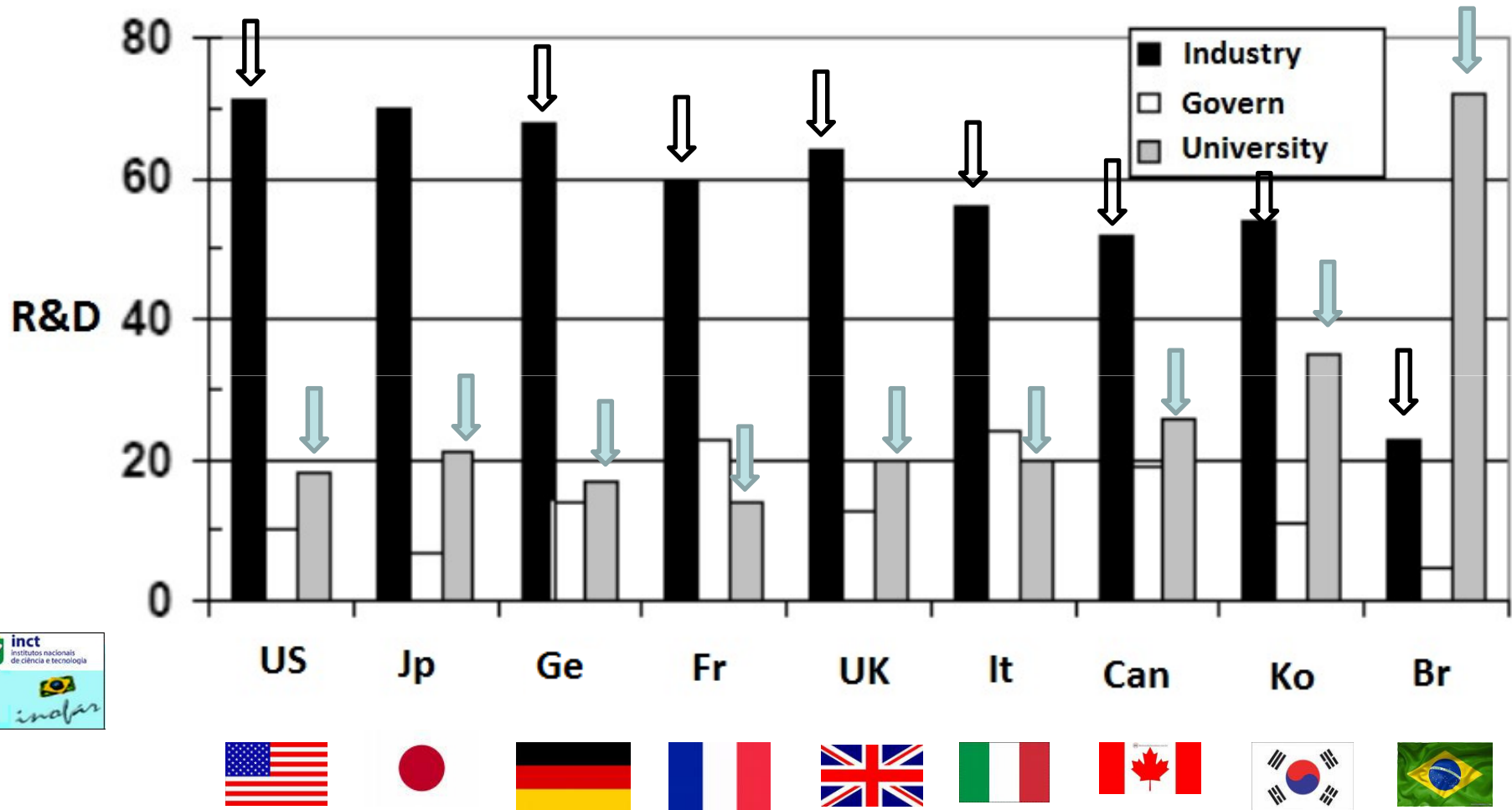
*Inter-alia*: S Laufer, U Holzgrabe, D Steinhilber, Drug Discovery: A modern decathlon, *Angew. Chem. Int. Ed.* **2013**, *52*, 4072; A S Kesselheim, J Avorn, The most transformative drugs of the past 25 years: a survey of physicians, *Nature Rev. Drug Discov.* **2013**, *12*, 425; H Wild, C Huwe, M Lessl, Collaborative Innovation — Regaining the Edge in Drug Discovery, *Angew. Chem. Int. Ed.* **2013**, *52*, 2684; W L Jorgensen, Challenges for Academic Drug Discovery, *Angew. Chem. Int. Ed.* **2012**, *51*, 11680; S Frye et al., US Academic Drug Discovery, *Nature Rev. Drug Discov.* **2011**, *10*, 409; C J Tralau-Stewart et al., Drug Discovery: New models for Industry-Academic partnerships, *Drug Discov. Today* **2009**, *14*, 95; PG Wyatt, The emerging academic drug discovery sector, *Future Med. Chem.* **2009**, *1*, 1013.

“ Without a doubt, a university has a number of unique characteristics that could contribute to making it an ideal environment where drug discovery & medicinal chemistry activities can thrive...There is no doubt that academia can play an important role in drug discovery”

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



# The scientific manpower





 <p>INCT inofar</p>	<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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The National Institutes of Science and Technology (INCT's) program has ambitious and large goals in terms of mobilizing national effort of the best research groups in Brazil, acting at frontier and strategic areas of science, to contribute for sustainable development of the country.



# INCT-INOFAR...





# INCT-INOFAR



inct  
inofar

instituto nacional  
de ciência e tecnologia de Fármacos e Medicamentos

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English



Project CNPq 573.564/2008-6

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

## The Mission

Home

INCT-INOFA

Team

Scientific adviser board  
(SAB)

Research groups

Research people

Useful articles

Publications

Meetings

Videos

- Organize the Brazilian scientific capacity in an effective drug discovery network;
- Support multi-institutional research projects in drug discovery & design;
- Contribute to Brazilian radical & incremental innovation in new & generic drugs;
- Studies in total synthesis of generic drugs & advanced synthetic intermediates and starting materials;
- Contribute to continuous high qualification of students in medicinal chemistry & pharmacology;



Who we are





# INCT-INOFAR



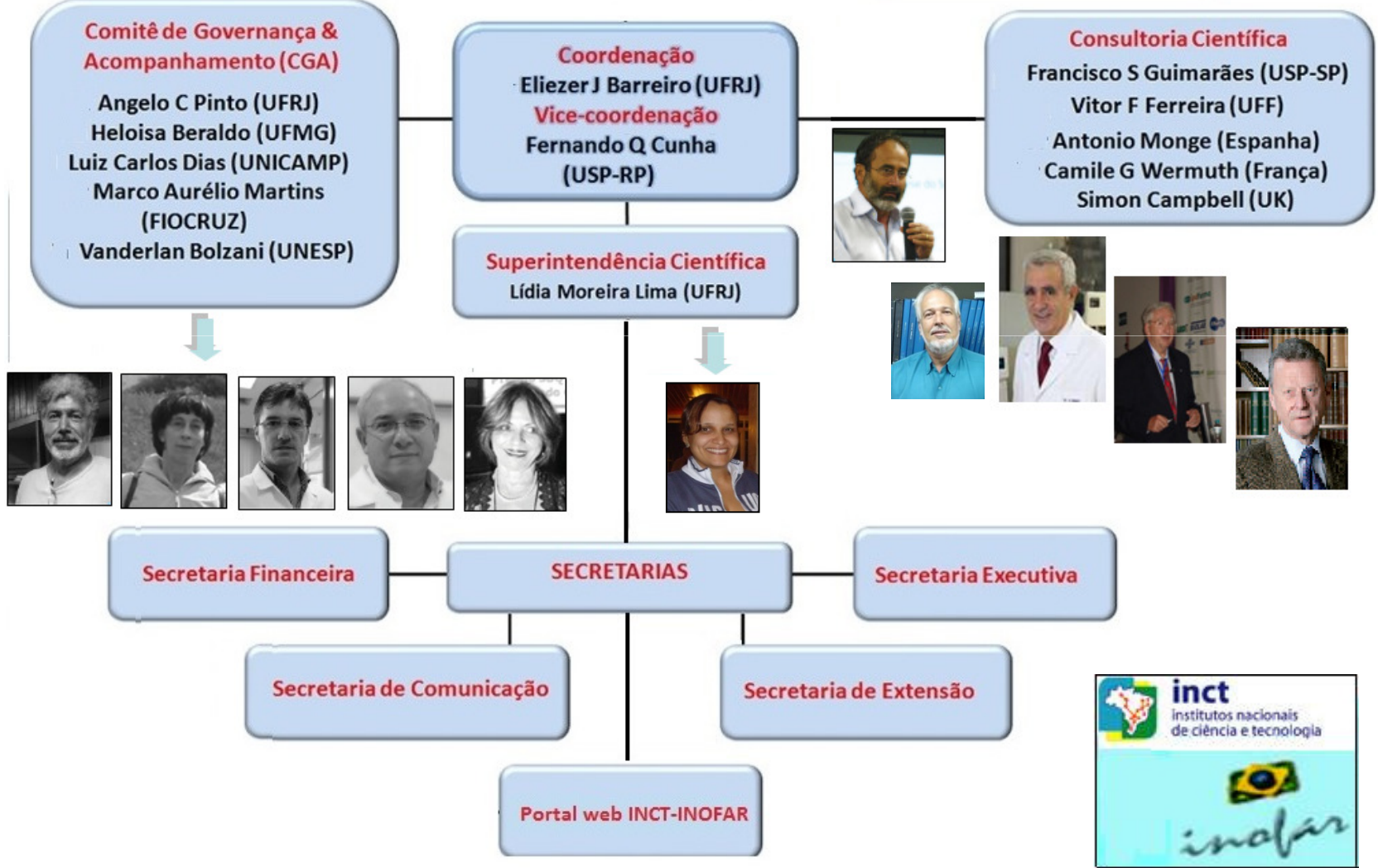
## Governance committee

Innovation in Drugs and Medicines



Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos 

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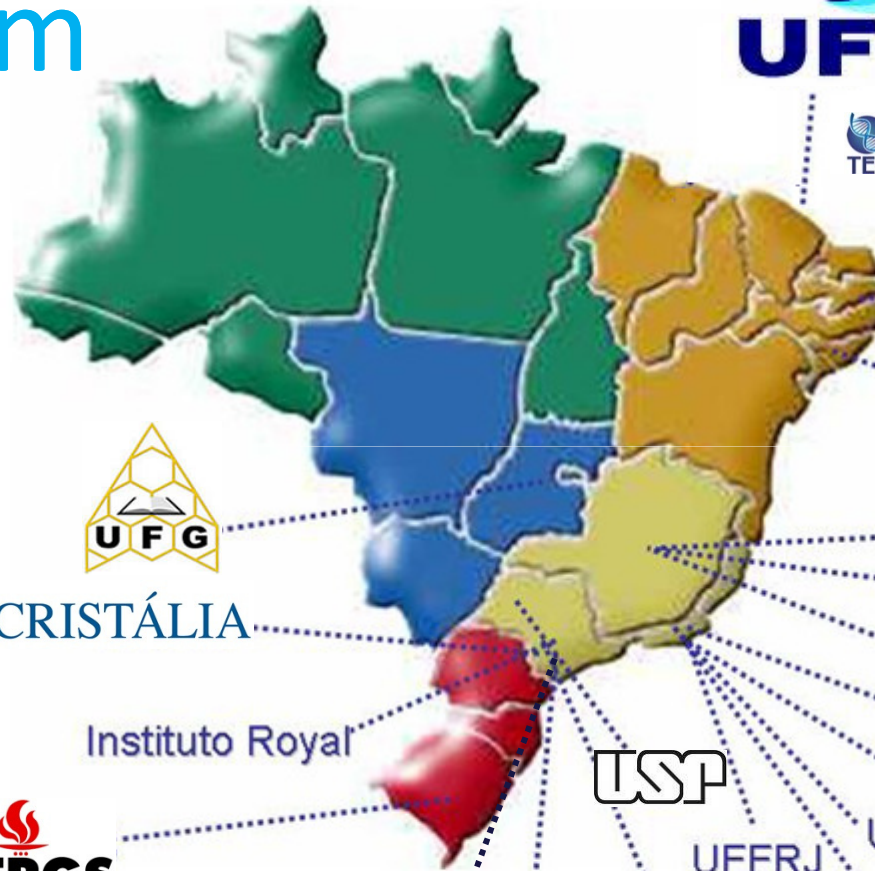

inct  
 institutos nacionais  
 de ciência e tecnologia



# INCT-INO FAR



## The Team



In Vitro Cells



Instituto Royal

UFMG

FIOCRUZ

UFMG

USP

UFRJ



UFRJ



LNCC



unesp

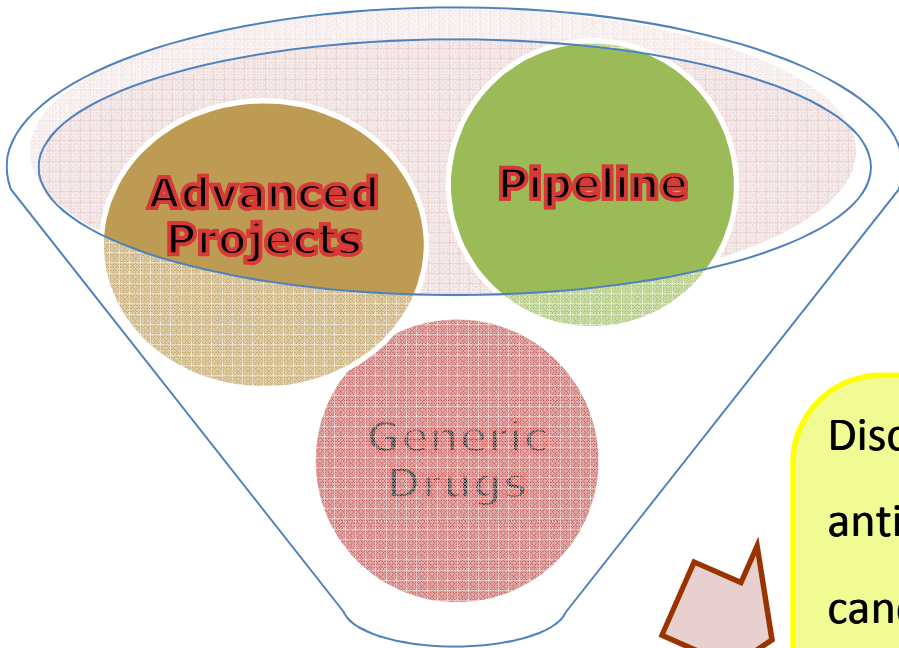




What we do



# Radical *In*novation



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

Discovery of novel anticancer drug candidates designed as novel combretastatin A4 analogues  
LASSBio-UFRJ / FM-UFC  
**BR 10 2012 007619 5**  
**PCT BR 2013 000095**

Study of the anti-inflammatory effect of LASSBio-897 on chronic lung diseases in mice  
Laboratory of Inflammation  
FIOCRUZ, RJ

# Incremental *Innovation*



Generic drugs\*

(BR Low # 9787, 02/10/1999)



In Brazil the market of generic drugs is ca. 23,5% (2012)

Active pharmaceutical ingredients (API's)

> 92%



"The art is to select [generics] that will be winners *versus* ones where there will be enormous competition."

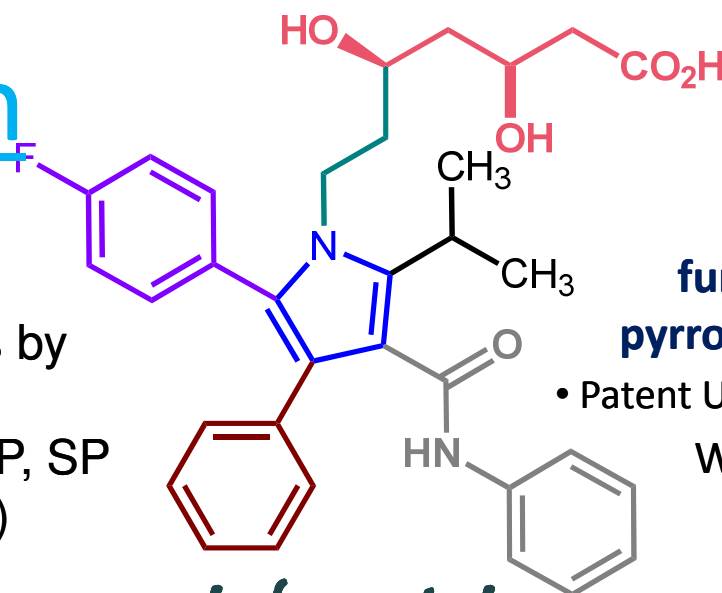
# Incremental *Im*novation



## • Atorvastatin

1991 Lipitor™

- New stereoselective synthesis by Professor **Luiz Carlos Dias** & Dr **Adriano S. Vieira**, UNICAMP, SP (2010) – INPI Patent, 2011 (BR)



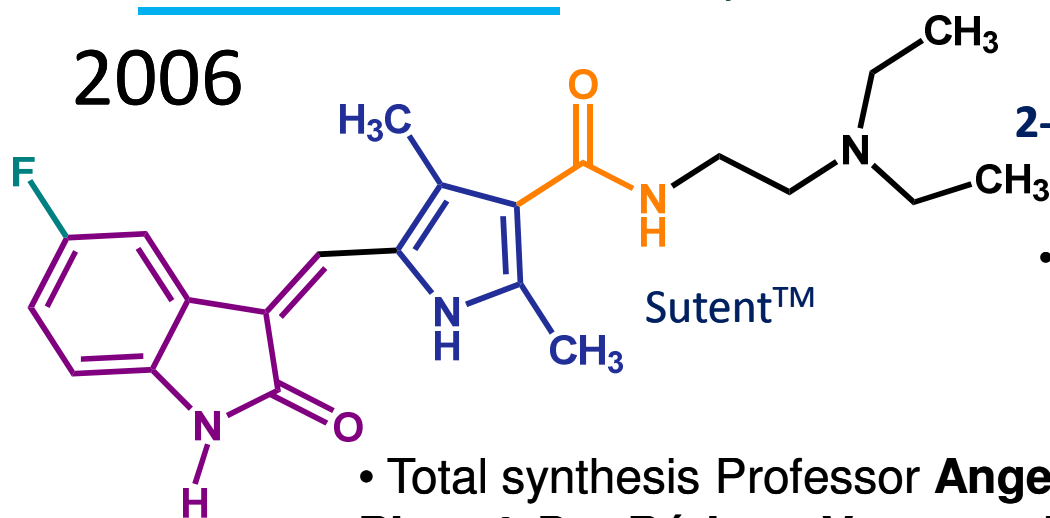
functionalized  
pyrrolheptenoic acid

- Patent US 5273995 Pfizer (1991)

World total sales:  
US\$ > 120 bi  
(1991-2011)

## • Sunitinib *super blockbuster-drug*

2006



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

- \*Patent US 7211600 (2001)

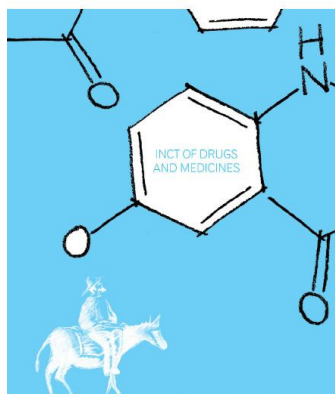
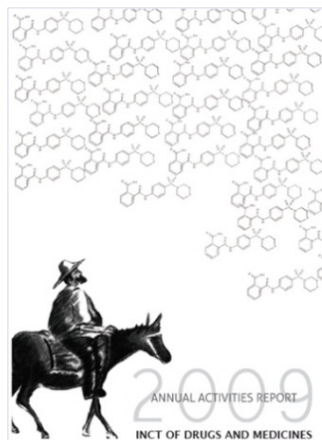
- Multi TK inhibitor indicated to renal carcinoma

- Total synthesis Professor **Angelo da Cunha Pinto** & Dra **Bárbara Vasconcellos da Silva** UFRJ, RJ (**2011**) (BR)

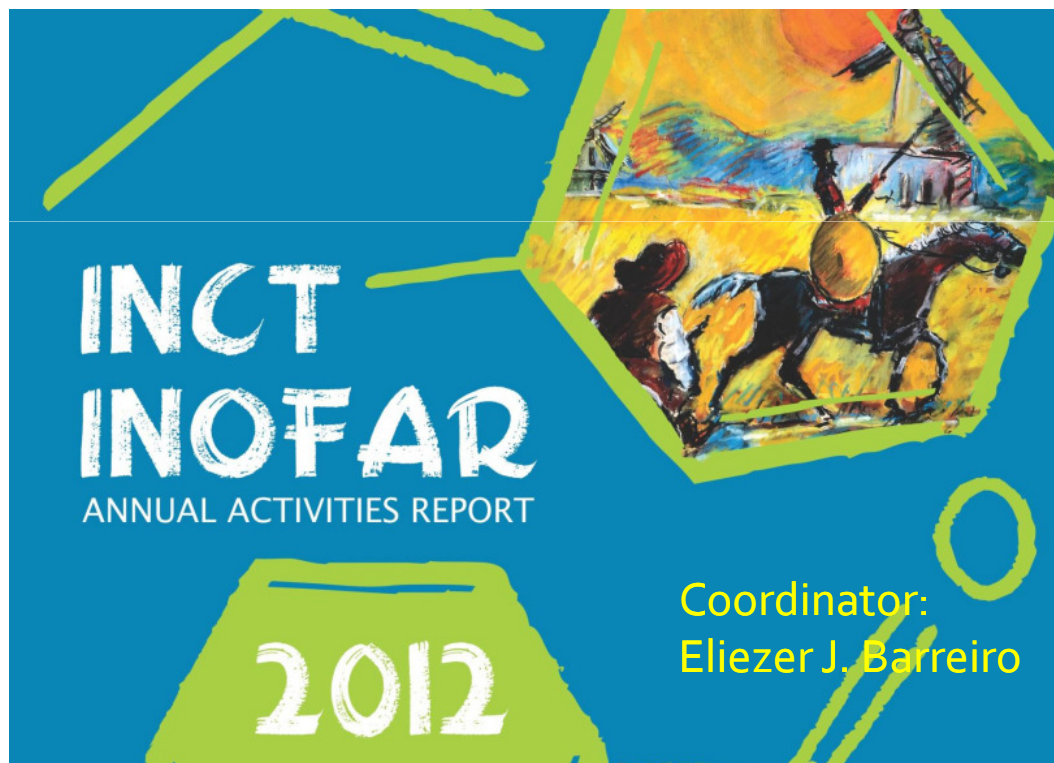
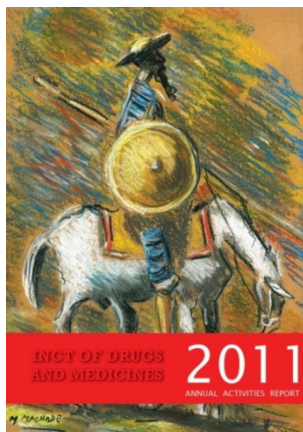
Total sales of tinibs in  
US market: US\$ 18,5 bi  
(2009)



# Annual Activities Report



2010  
ANNUAL ACTIVITIES REPORT



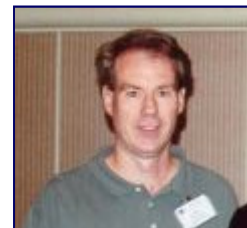
[www.inct-inofar.ccs.ufrj.br/download/aar/2012.pdf](http://www.inct-inofar.ccs.ufrj.br/download/aar/2012.pdf)

# Final remarks

*“For all the efforts to industrialize and automate discovery, history suggests drug discovery is art as well as science and relies heavily on the skill of experienced drug*

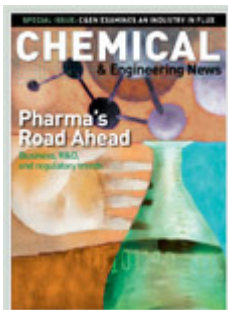
*hunters...”*

**Charles H. Reynolds**



Johnson & Johnson Pharmaceutical Research and Development, Spring House, Pa  
 em *Pharma's Road Ahead* , C&EN Special Issue, Volume 84, number 25, June 19, 2006

**C&EN**  
CHEMICAL & ENGINEERING NEWS





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## Acknowledgments



# Thank you for your attention