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INCT-INOFAR, a Brazilian network for drug design, discovery and development

Eliezer J. Barreiro

Professor

www.inct-inofar.ccs.ufrj.br

Projeto CNPq nº 573.564/2008-6 « » FAPERJ nº E-26/170.020/2008

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Summary

- *Prologue: a brief view of scientific research nowadays*
- *The complex drug discovery (DD=D2) process*
- *The pharmaceutical innovation*
- *The possible role of the university in the DD process*
- *The INCT-INOFAR: our mission*
- *The INCT-INOFAR: Who are we?*
- *The INCT-INOFAR: What we did and what we do?*
  - *In radical innovation*
  - *In incremental innovation*
- *Final remarks & Acknowledgments*


Prologue...

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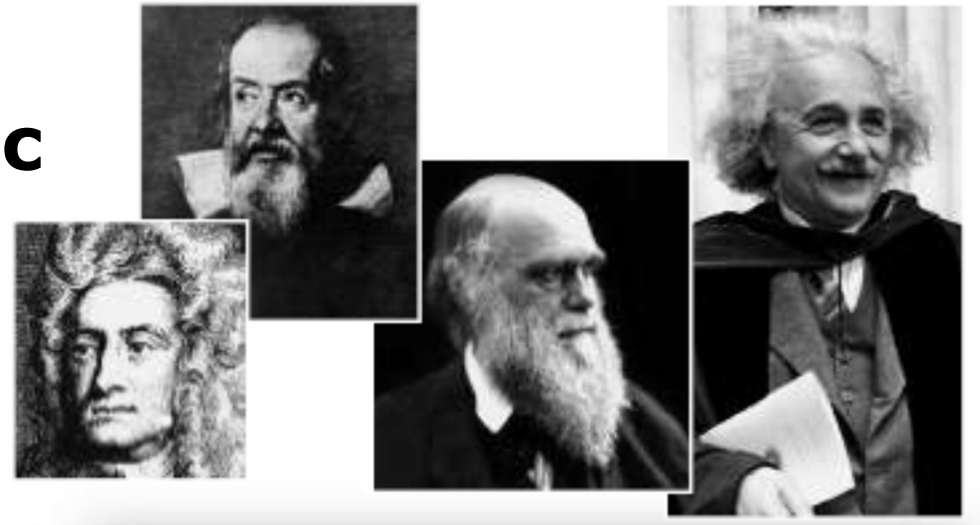
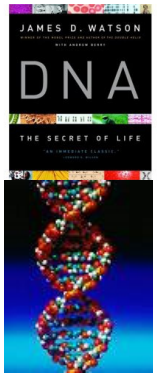
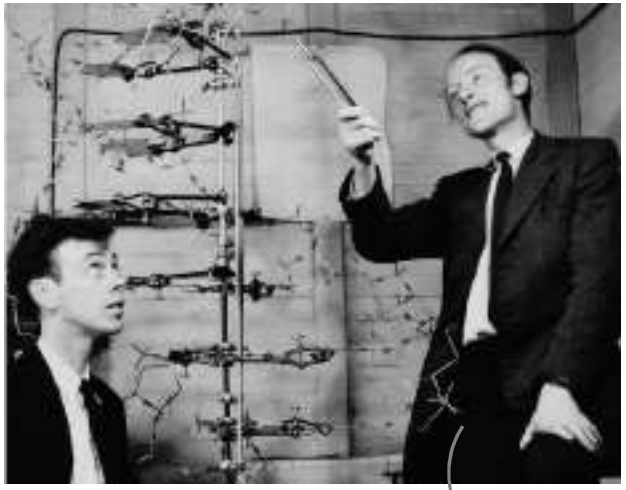
The scientific activity through the ages...



Galileo, Newton, Darwin, & Einstein





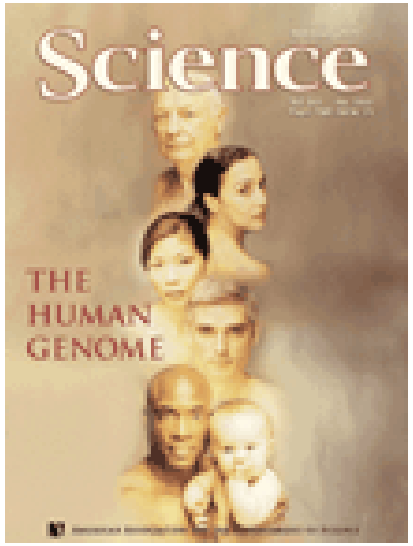
The physical Crick & the biologist Watson

JD Watson & FHC Crick, A Structure for Deoxyribose 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 Ferriera, 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



Science **2001** *291*, 1304-1351 [DOI: 10.1126/science.1058040]

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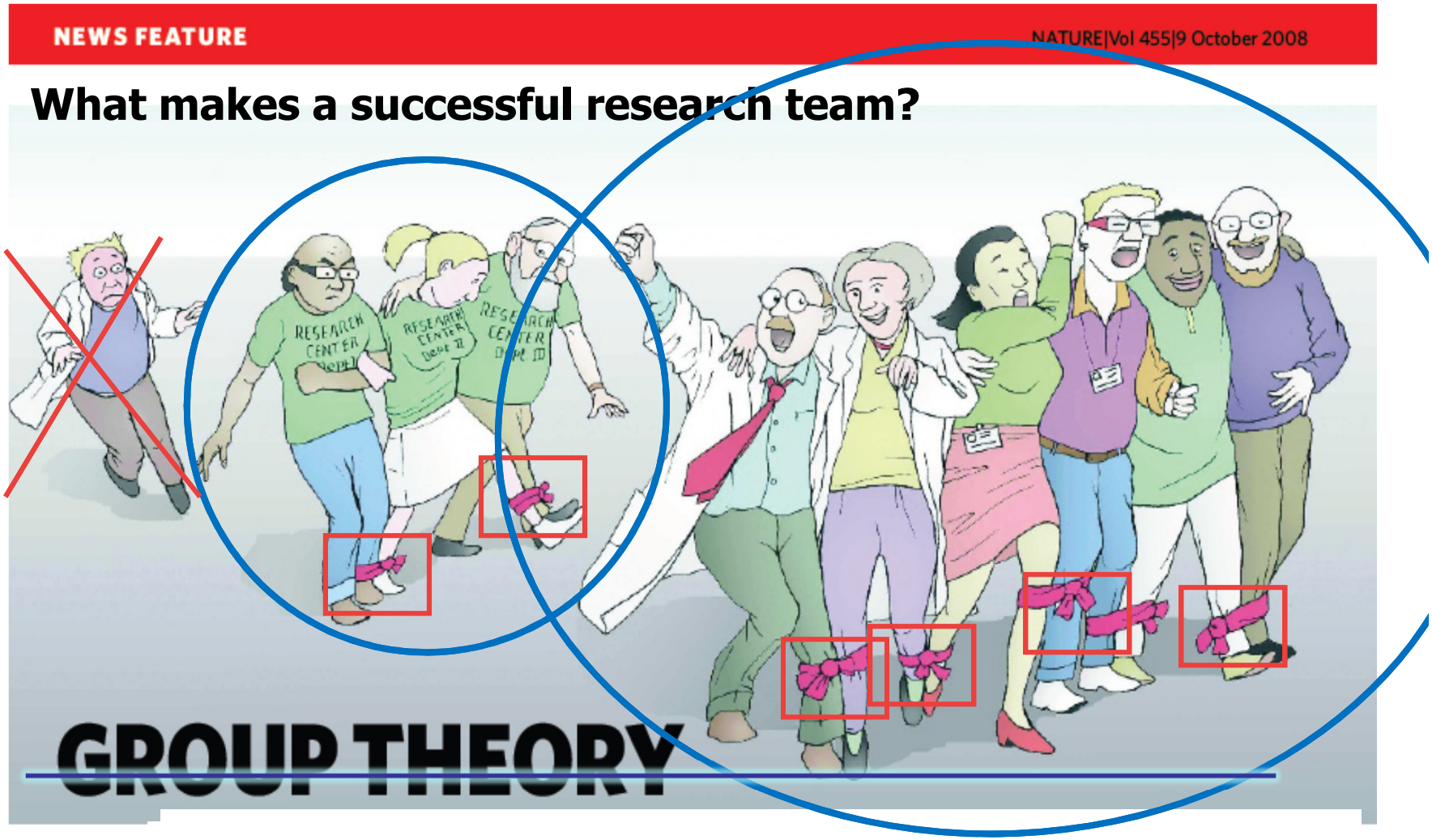
J. Whitfield, *Nature* **2008**, *455*, 720



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.

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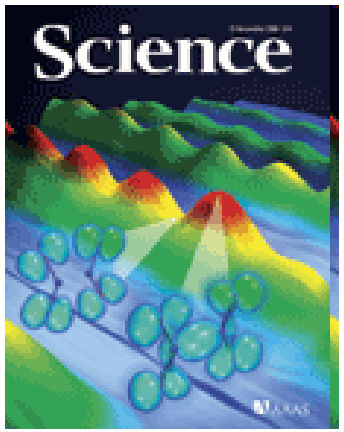
Multi-University Research Teams: Shifting Impact, Geography, and Stratification in Science

Benjamin F. Jones,[1,2]* Stefan Wuchty,[3]* Brian Uzzi[1,3,4]*



SCIENCE VOL 322 21 NOVEMBER 2008 1259

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

The authors demonstrate that scientific research in interdisciplinary teams has an impact on the quality of work, increasing the production of new knowledge really innovative.

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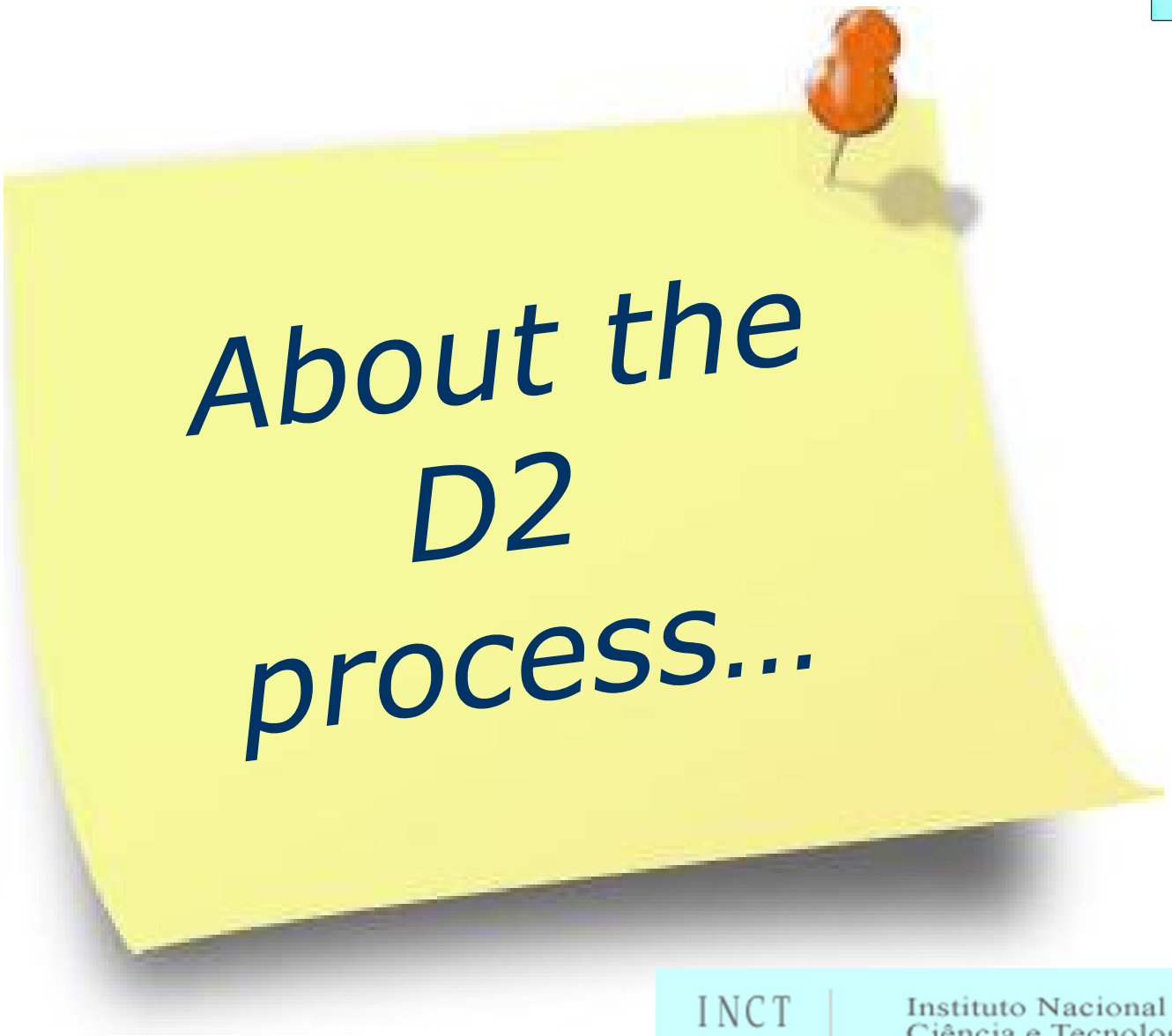
"For all the efforts to industrialize and automate discovery, history suggests drug discovery is art as well as science and relies heavily on the skill of experienced drug hunters..."

Charles H. Reynolds

J&J Pharmaceutical Research and Development, Spring House, Pa

em *Pharma's Road Ahead* , C&EN, Volume 84, Issue 25, June 19, 2006

medicinal chemistry



About the D2 process...

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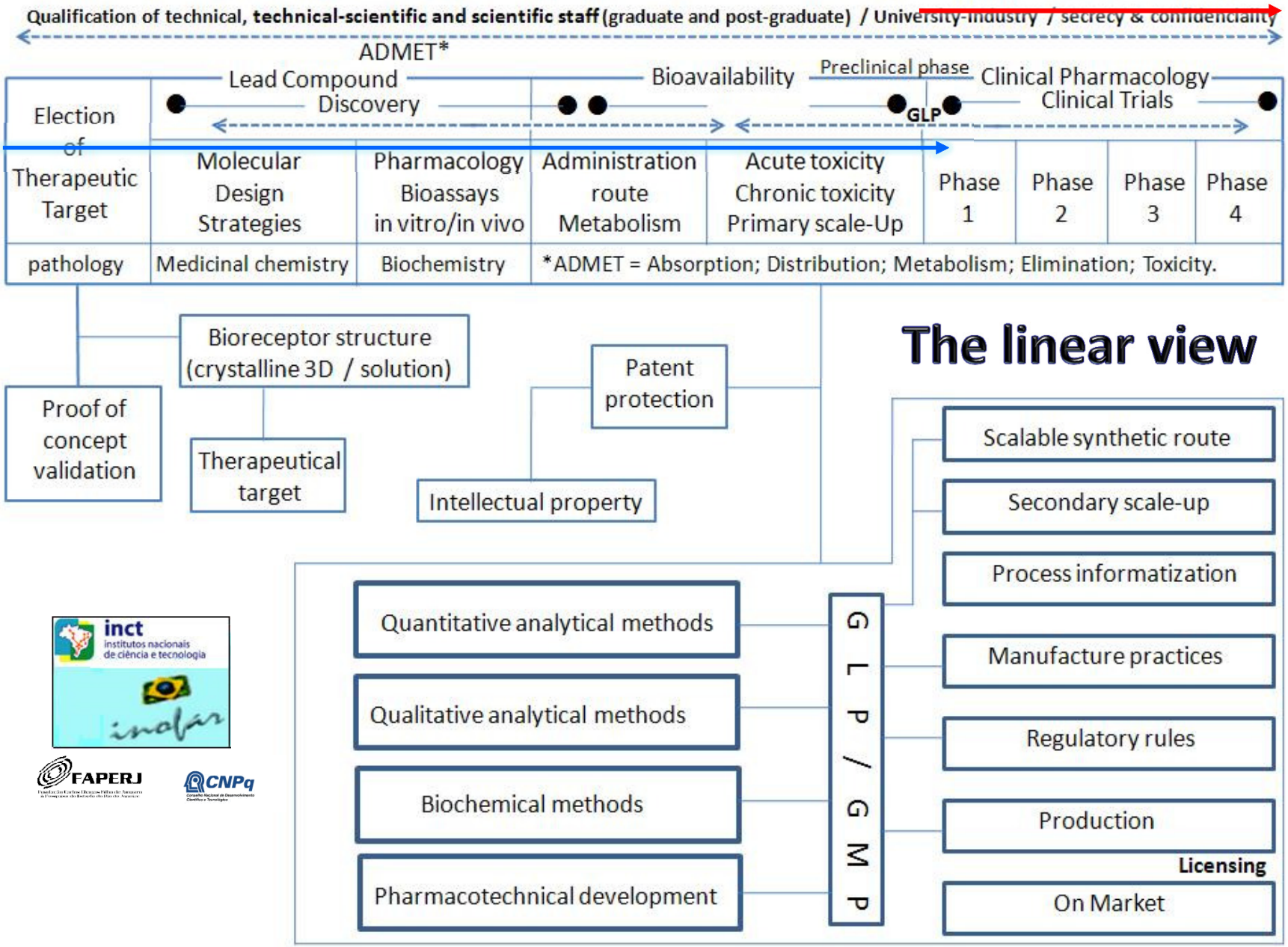
The drug discovery & development process



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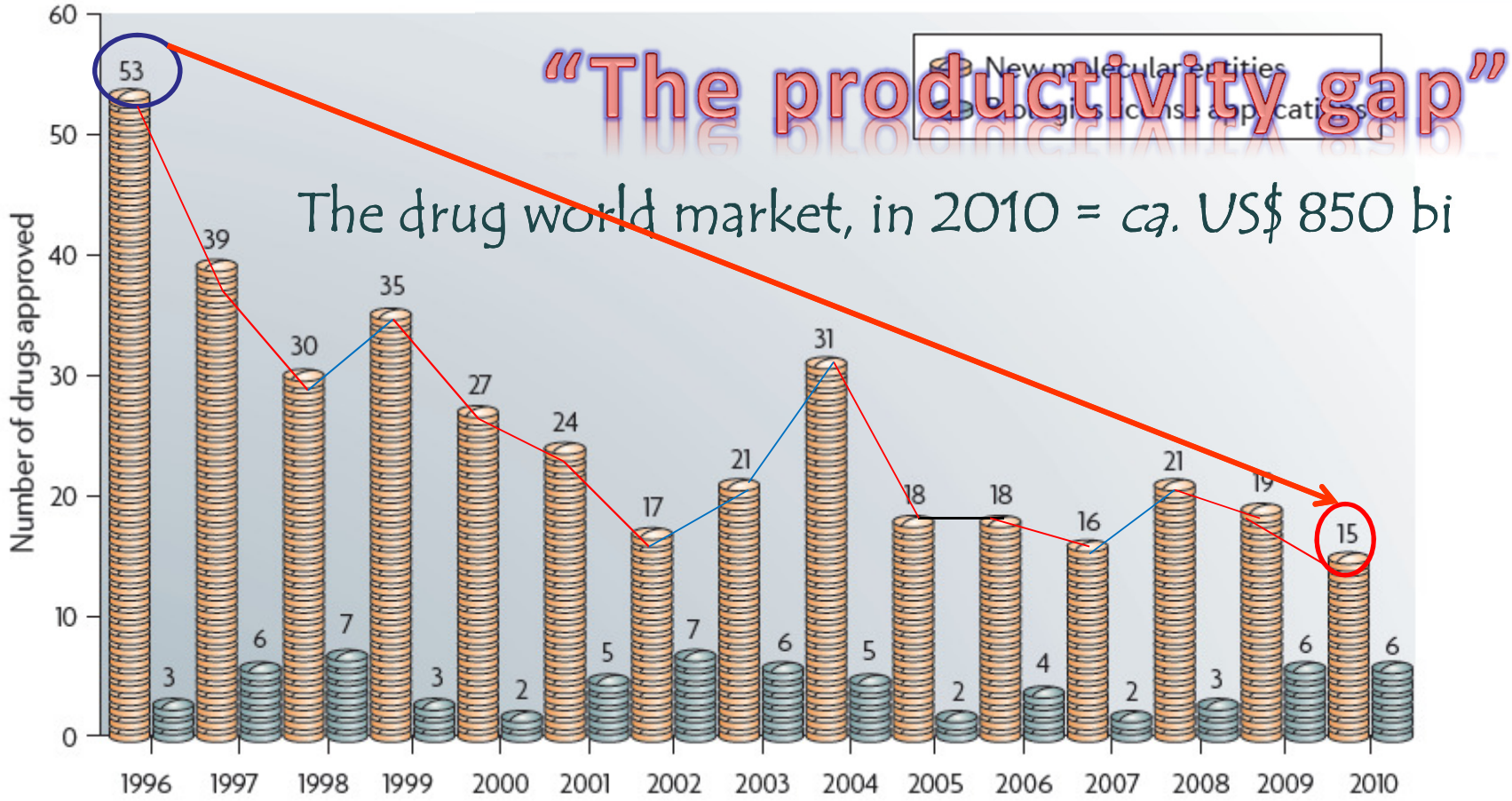
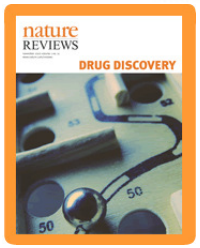
FAPERJ CNPq

The Big Pharma innovation crisis...





* 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, How were new medicines discovered? *Nature Rev. Drug Discov.* **2011**, *10*, 507.

The *Big-Pharma* ...

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; S M Paul *et al*. How to improve R.&D productivity: the pharmaceutical industry's grand challenge, *Nature Rev. Drug Discov.* **2010**, *9*, 203; B Munos, Lessons for 60 years of pharmaceutical innovation, *Nature Rev. Drug Discov*. **2009**, *8*, 959;

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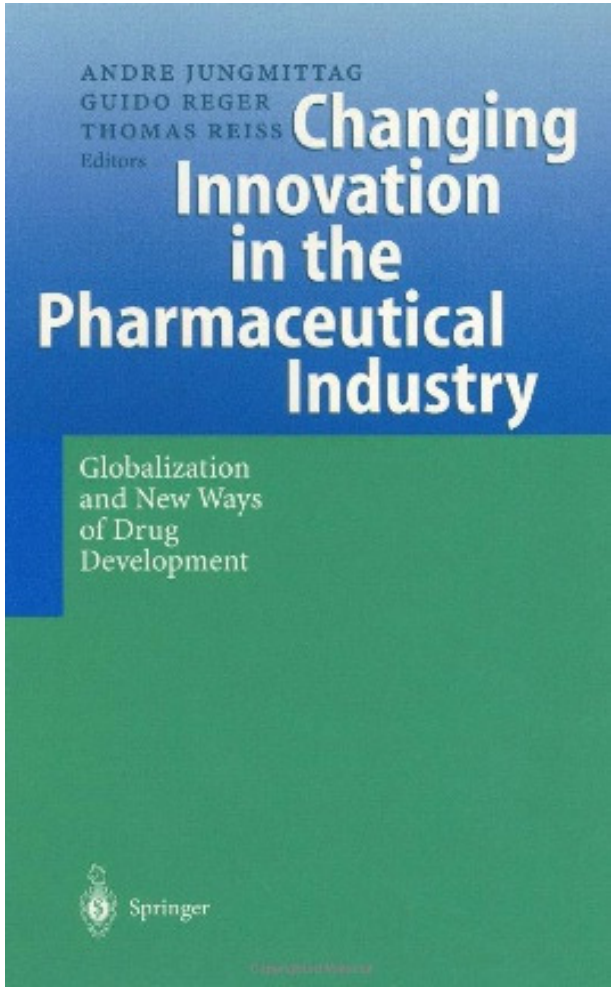

Technological innovation is a process most dynamic in industrial activity.
This dynamism is accentuated in <u>pharmaceutical innovation</u> which, more than any other, depends on the effective and productive interaction between <u>Science & Technology</u>.

The blockbuster sindrome...

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2011

IN FOCUS NEWS

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).

HULTON-DEUTSCH/CORBIS

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

Nature 2011, 471, 17

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The possible role of university in D2 process

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The drug discovery process...

2000

2004

...is completely scientific-based !.

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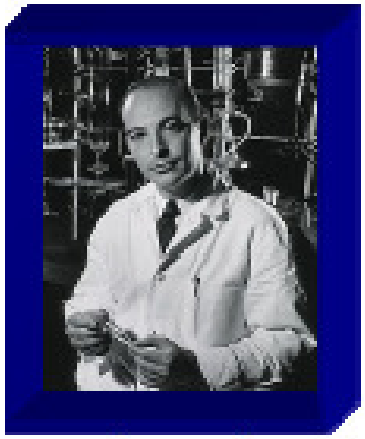
Nobel Prize, 1959

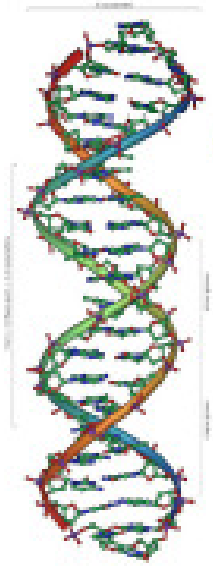


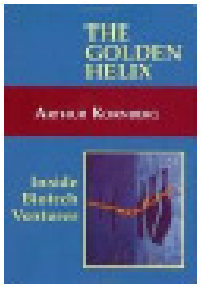
Arthur Kornberg
1918-2007

The Two Cultures: Chemistry and Biology

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..."*

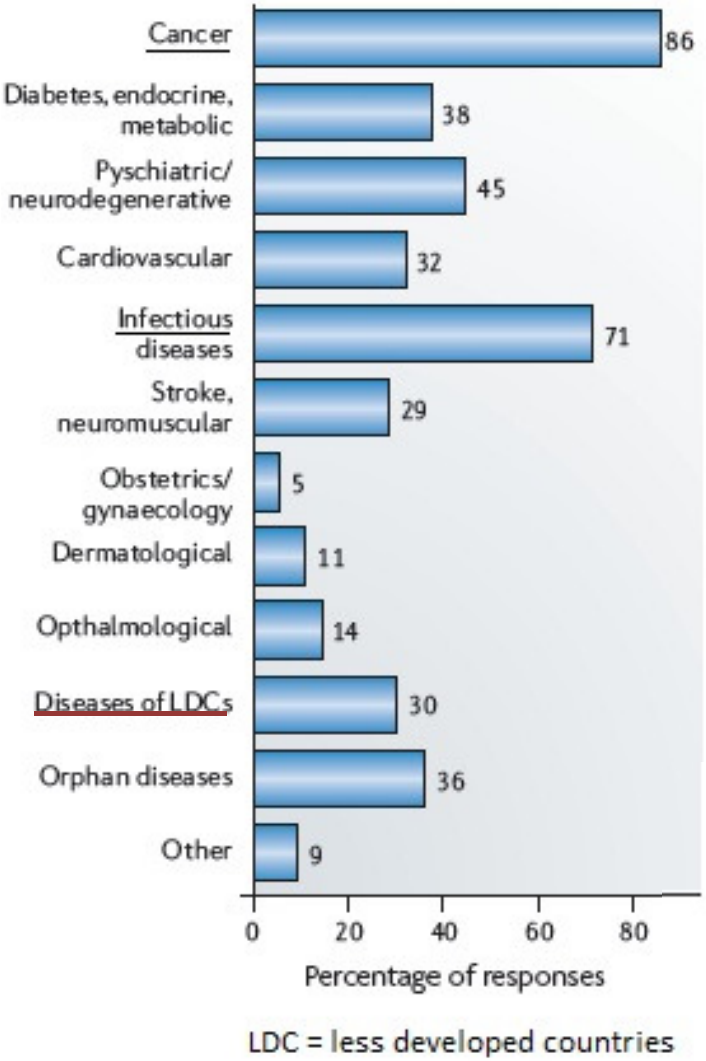
A. Kornberg, **Science and medicine at the millennium**, *Braz J Med Biol Res*, **1997**, *30*, 1379

Biochemistry 1987, *26*, 6888-6891

Interdisciplinarity

US academic drug discovery

Stephen Frye, Marina Crosby, Teresa Edwards and Rudolph Juliano

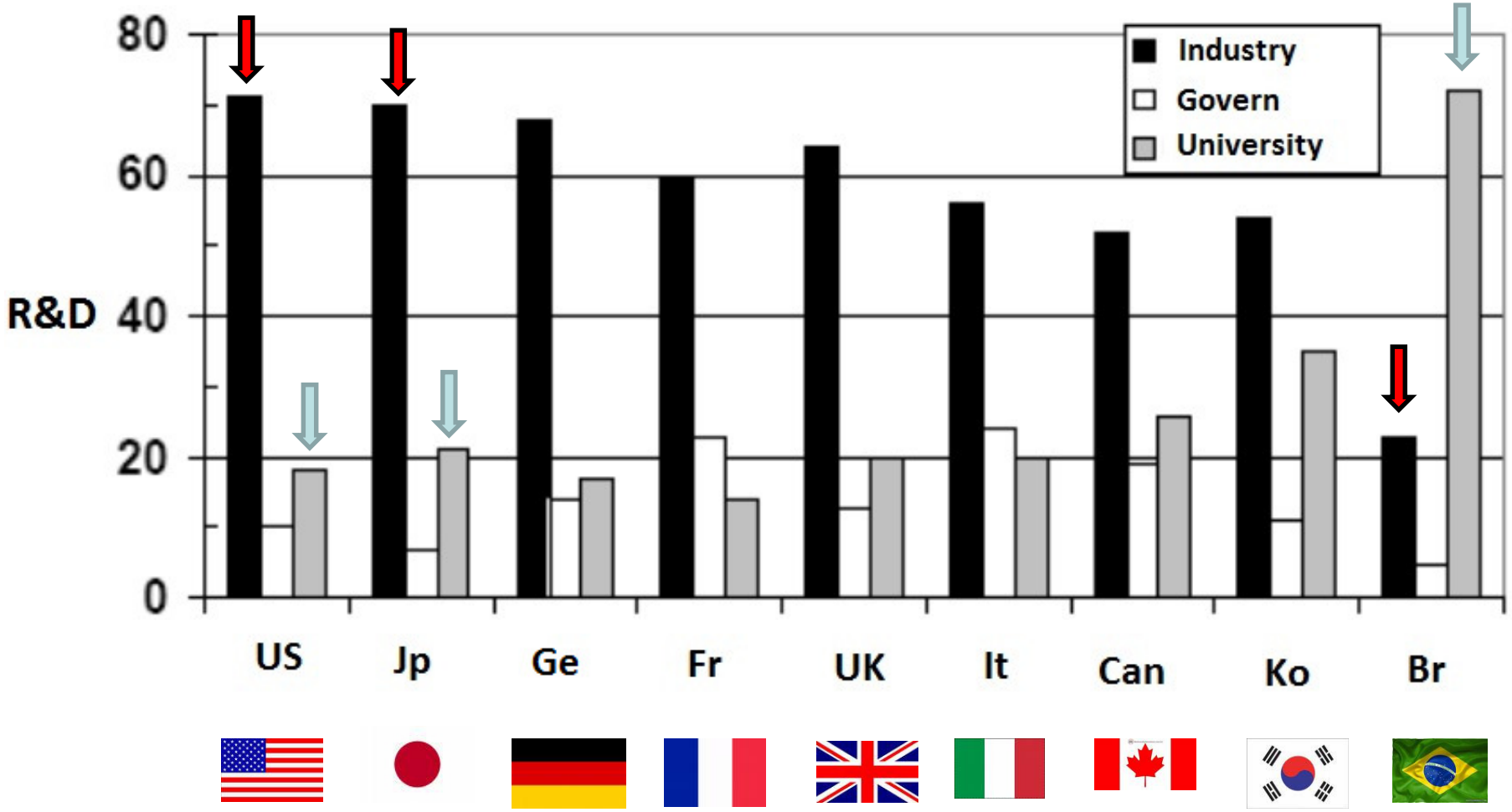


Nature Rev. Drug Discov. **2011**, *10*, 409

The authors identified 78 AI's involved in academic drug discovery (ADD): cancer (86%), infectious diseases (71%) and CNS (45%), metabolic & endocrine diseases (38%), orphan diseases (36%), cardiovascular (32%), diseases of less developed countries (30%)

ADD → **Several targets: PK's, GPCR's**

The scientific manpower



Source: 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 (2/01/2009)

Learning Cycles in Drug Discovery & Development

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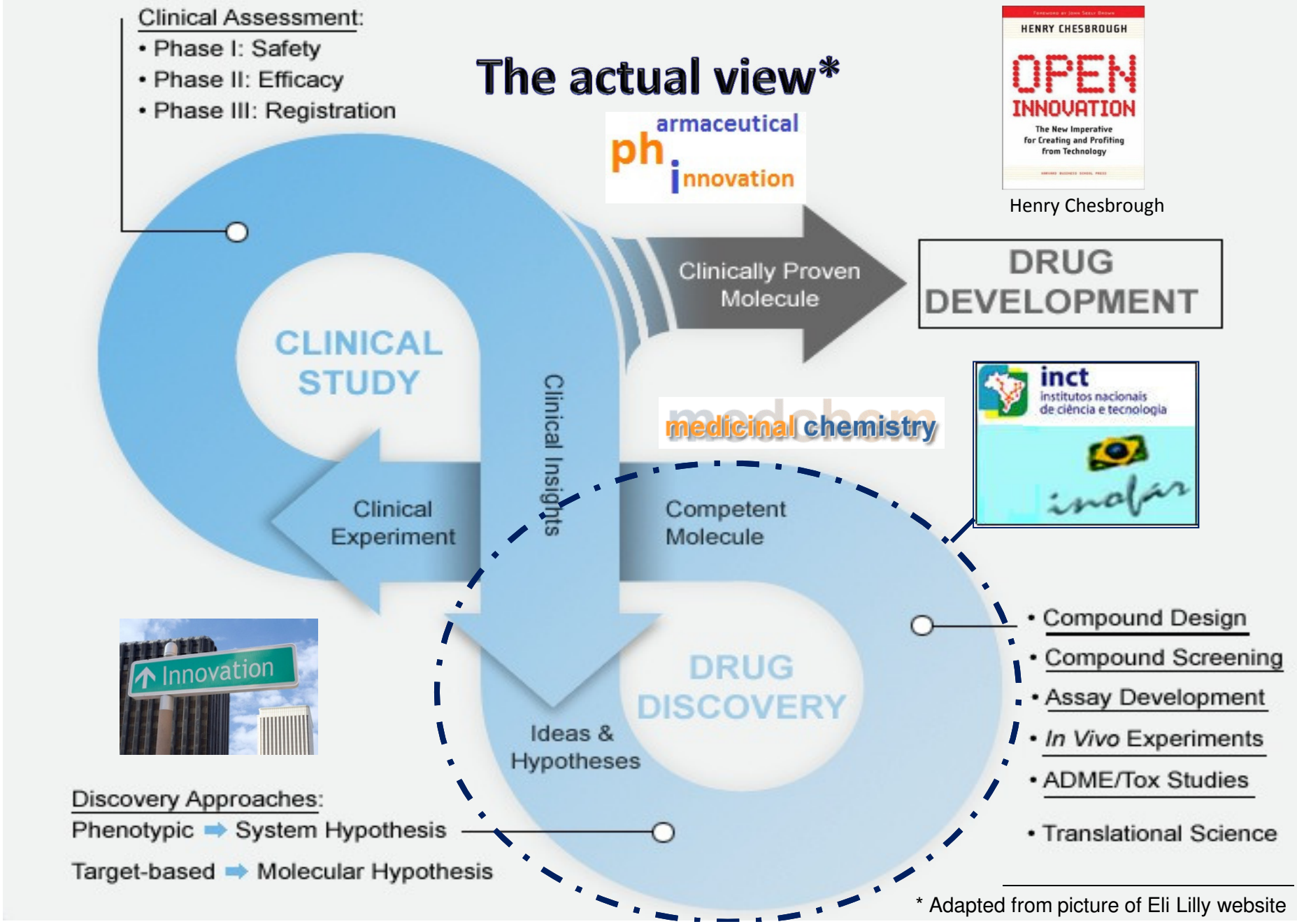

* Adapted from picture of Eli Lilly website

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The mission of INCT-INOFAR

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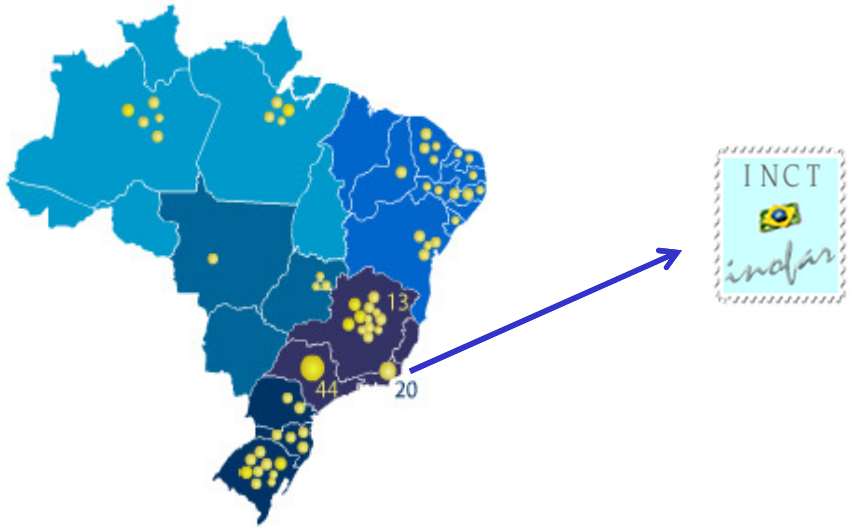
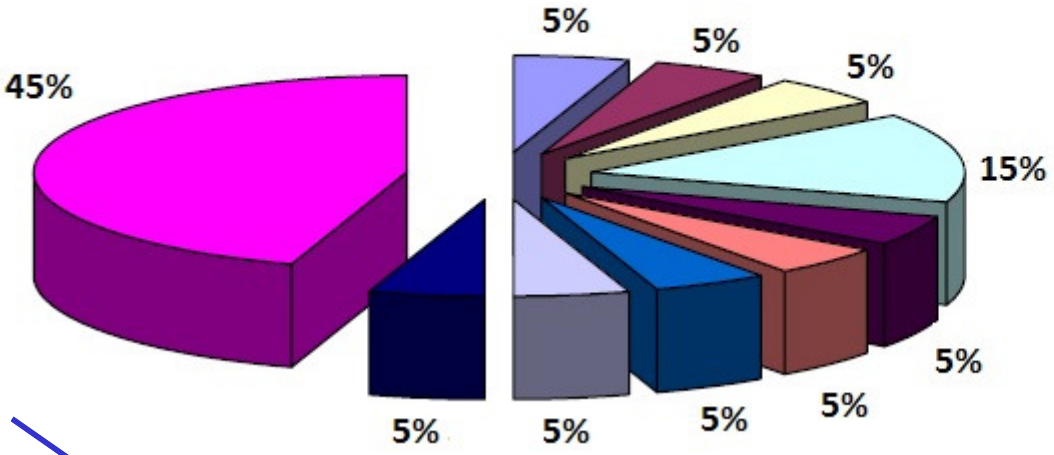
Apresentação | Institutos | Notícias | Contato

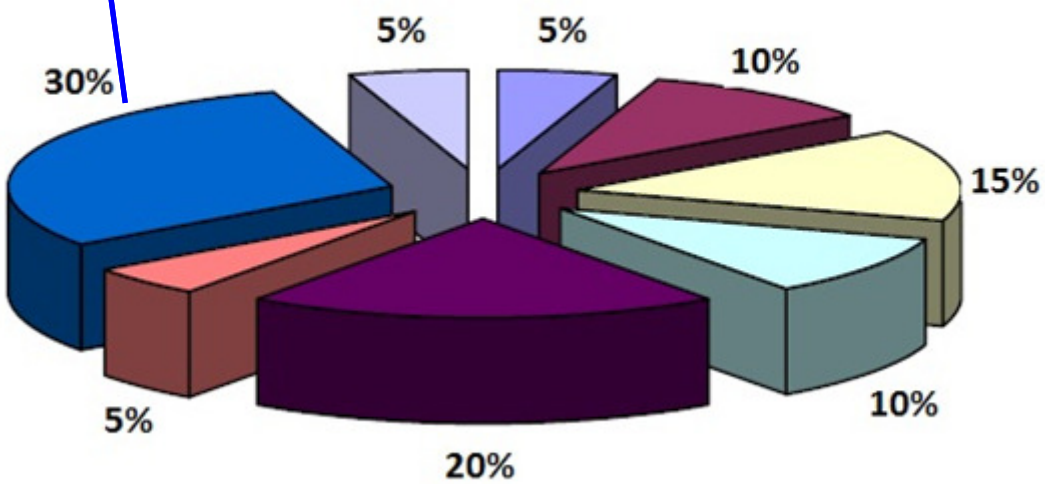
Apresentação



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´s in Rio de Janeiro state





INCT´s in Rio de Janeiro state

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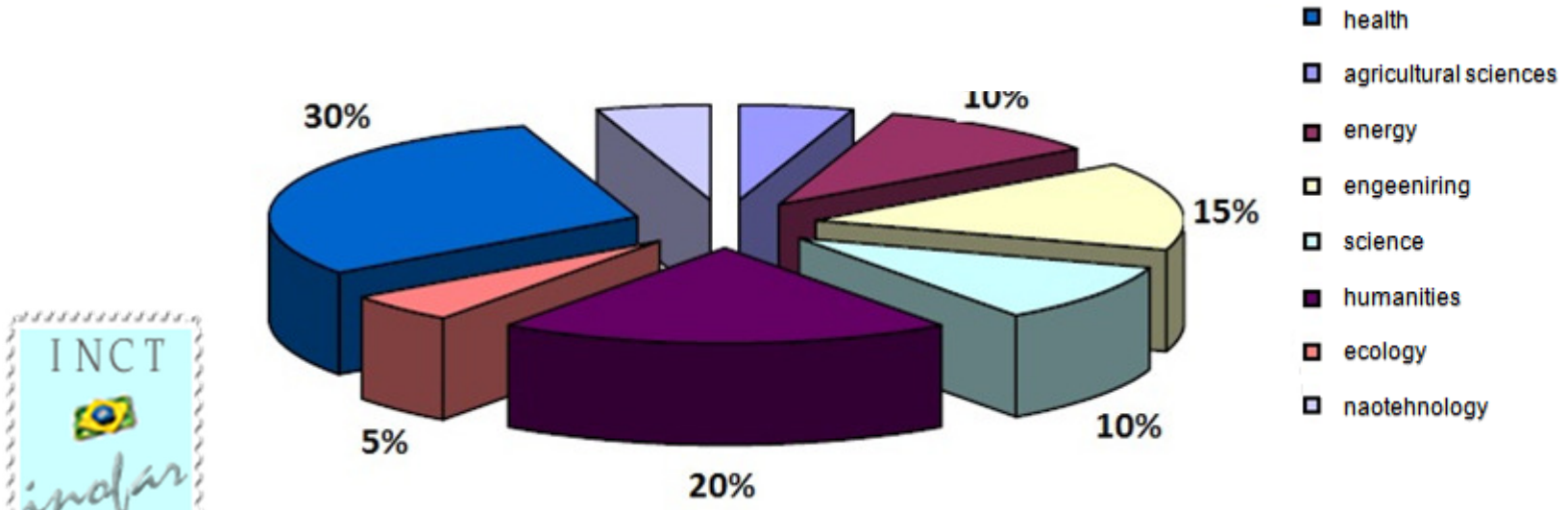
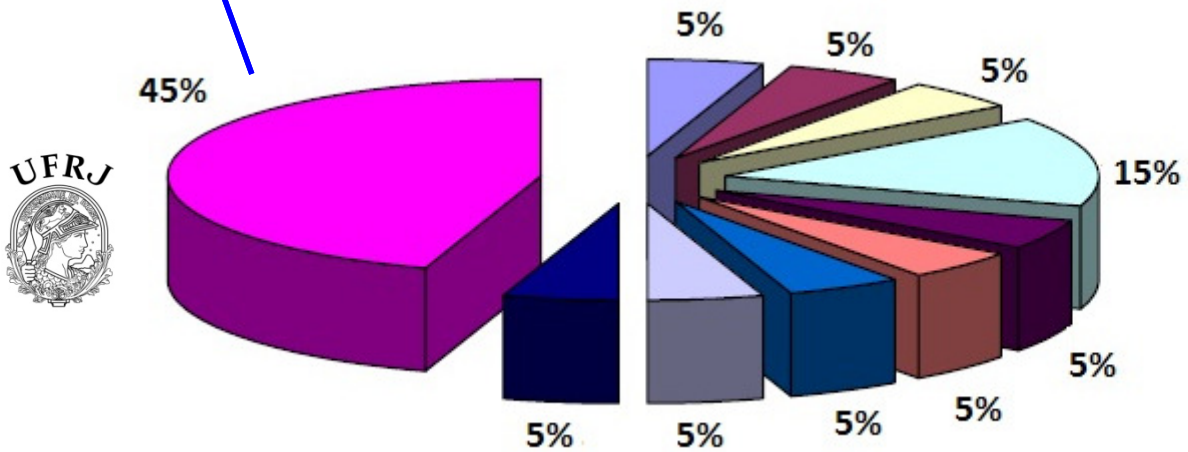


LASSBio®

FAPERJ
Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro



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English

CNPq FAPERJ

Project CNPq 573.564/2008-6

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- Home
- INCT-INOFAR
- Team
- Scientific adviser board (SAB)
- Research groups
- Research people
- Useful articles
- Publications
- Meetings
- Videos

The Mission

- 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;

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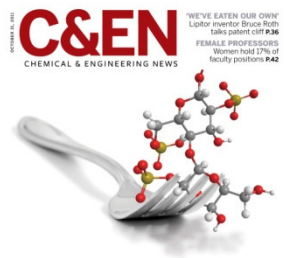
B R I C (SA)

BUSINESS

India's Sun Pharma, Vadodara

INDIA PERSEVERES AS DRUG DISCOVERER



Despite setbacks, the country's drug companies continue to pursue **HOMEGROWN COMPOUNDS**

AMRUTHANAND NAIR, C&EN CONTRIBUTING EDITOR, MUMBAI


Who are we?

INCT-IN*OFAR*

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Governance committee

Innovation in Drugs and Medicines

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Camille G. Wermuth, Prestwick Co., Ilkirch, FR
Simon Campbell, ex-Pfizer Major Scientist UK

medicinal chemistry

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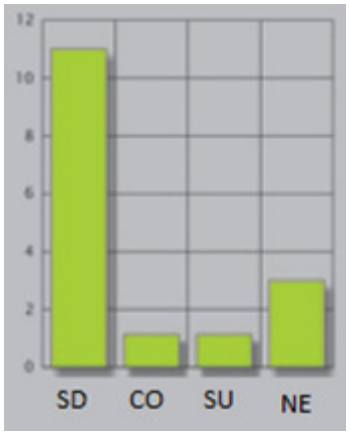
Research partners



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UFAL

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Instituto Royal

UNIFAL-MG

In Vitro Cells

UFMG

FIOCRUZ

UFMG

USP

UFRJ

FIOCRUZ FUNDAÇÃO OSWALDO CRUZ

UERJ

UFFRJ

UFRJ

Ciallyx

LNCC

unesp

UNICAMP

LNCC

UFRRJ

INCT inofar

UFRGS
UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

UNIVERSITÄT TÜBINGEN

UNIVERSIDAD DE LA REPÚBLICA URUGUAY


What we did
and
what we do?

2D Network

To do more!

To do faster!

To do better!

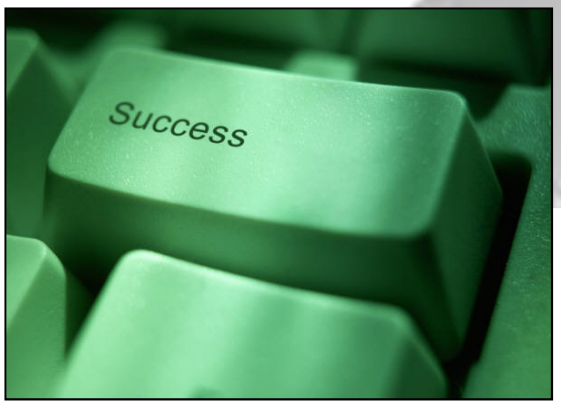
Conditions

To be organized!

To be trustable!

To be a team !

D2



New lead-compounds

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Drug Discovery Today • Volume 14, Numbers 1/2 • January 2009 07 October 2009 vol 1, issue 1, 95-101 REVIEWS

Open innovation

Drug discovery: new models for industry–academic partnerships

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

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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

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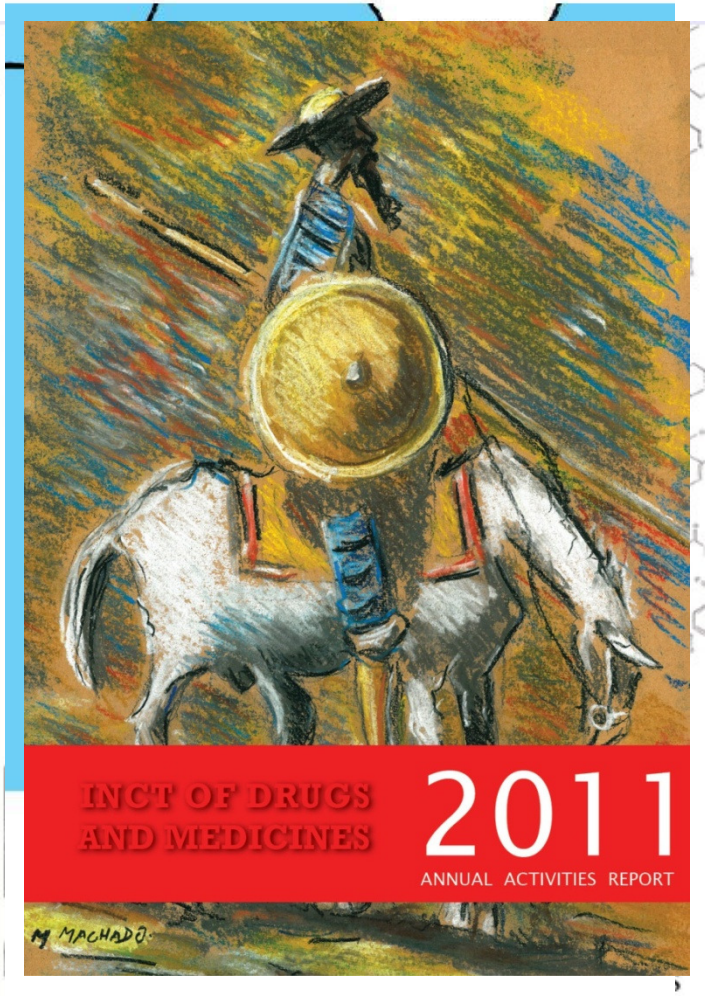
AJ Stevens *et al.,* The role of public-sector research in the discovery of drugs and vaccines. *N. Engl. J. Med.* **2011**, *364*, 535; R Kneller, The importance of new companies for drug discovery: origins of a decade of new drugs. *Nature Rev. Drug Discov.* **2010**, *9*, 867; MR Barnes *et al*., Lowering industry firewalls: pre-competitive informatics iniciatives in drug discovery, *Nature Rev. Drug Discov.* **2009**, *8*, 701; PG Wyatt, The emerging academic drug-discovery sector. *Future Med. Chem.* **2009**, *1*, 1013.

Annual Activities Report



- **Radical innovation**

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

- **Incremental innovation**

  synthesis of new generic drugs

  new synthetic routes to old generic drugs

www.inct-inofar.ccs.ufrj.br/download/aar/2009.pdf
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www.inct-inofar.ccs.ufrj.br/download/aar/2011.pdf

Radical *Inn*ovation

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Study of the anti-inflammatory effect of LASSBio-897 on chronic lung diseases in mice

Laboratory of Inflammation

FIOCRUZ, RJ

Discovery of novel anticancer drug candidates designed as novel combretastatin A4 analogues

LASSBio-UFRJ / FM-UFC

Antileishmanial activity of new *N*-acylhydrazone derivatives and analogues

ICB-UFAL / LASSBio-UFRJ

Discovered y of novel anti-inflammatory drug candidates designed as p38 MAPK inhibitor

FMRP-USP / LASSBio-UFRJ

N-Phenylpiperazine derivatives as prototypes to develop new atypical antipsychotic drugs

FF-UFRGS / LASSBio-UFRJ

Incremental *In*novation

Generic drugs*

In Brazil the market of generic drugs is *ca*. US$ 18 bi (2011)

Active pharmaceutical ingredients (API's)

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

M McCoy, Generic Drugs, *C&EN* **2002** (#13) *80*, 23

Incremental *In*novation

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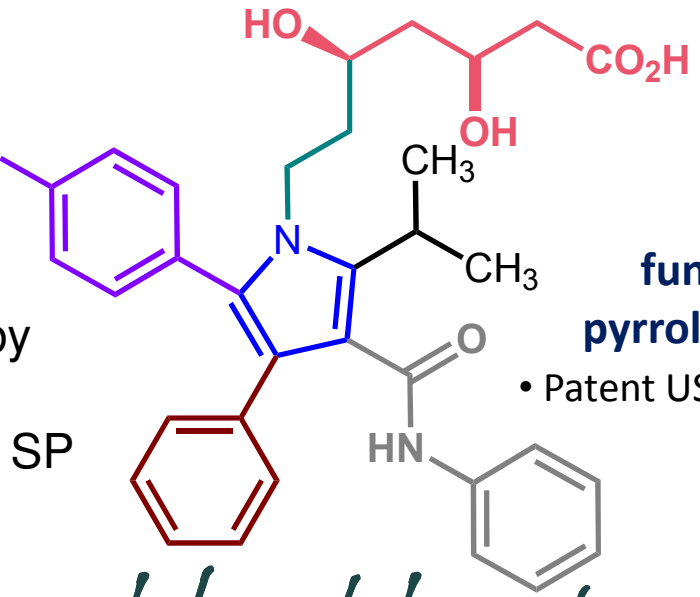
• Atorvastatin

1991 Lipitor™



functionalized pyrrolheptenoic acid

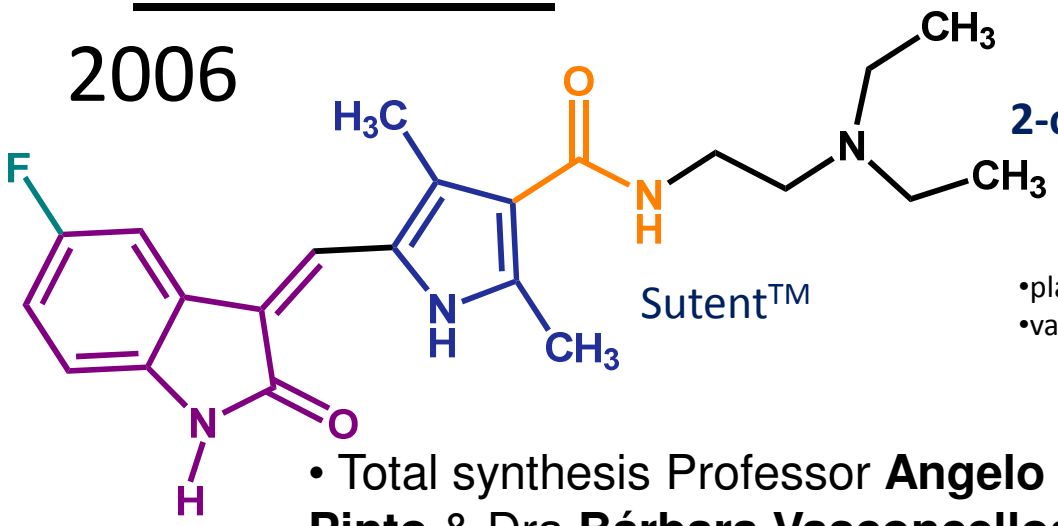
• Patent US 5273995 Pfizer (1991)

•HMGCoAR

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

• Sunitinib *super blockbuster-drug*

2006



Sutent™

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

*Patent US 7211600 (2001)

•platelet-derived growth factor receptor (PDGF-Rs)
•vascular endothelial growth factor receptor (VEGFRs),

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

Total sales of tinibs in US market:

ca.US$ 18,5 bi (2009)

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The INCT-INOFAR team

INCT-INOFAR, 6th Evaluation Meeting

Rio de Janeiro, RJ (BR)

May 15 & 16 , 2012

Projeto CNPq nº 573.564/2008-6 «» FAPERJ nº E-26/170.020/2008

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Final remarks & *Acknowledgements*

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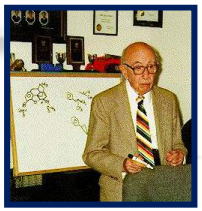
Final remarks

"...The unprecedented increase in human life expectancy, which has almost doubled in a hundred years, is mainly due to drugs and to those who discovered them."



Alfred Burger

In "The practice of medicinal chemistry", Wiley, 1970, p 4

medicinal chemistry

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Thank you for your attention

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