



UNIVERSIDADE DO ESTADO DO RIO DE JANEIRO

5º WCTI – Workshop de Ciência, Tecnologia e Inovação
Inovação e Saúde
7 de novembro de 2013



**INCT-INOVAR: Rede Brasileira para Desenho,
Descoberta e Desenvolvimento de Medicamentos**

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Instituto Oswaldo Cruz
Fundação Oswaldo Cruz - FIOCRUZ



UNIVERSIDADE DO ESTADO DO RIO DE JANEIRO

**5º WCTI – Workshop de Ciência, Tecnologia e Inovação
Inovação e Saúde**

Sumário

- A prática da inovação em medicamentos: ontem e hoje
 - O papel da academia e do setor produtivo
 - A teoria da rede multidisciplinar
- A experiência do INCT-INOVAR
 - Quem somos
 - O que fazemos

Paul Erlich (1854-1915)



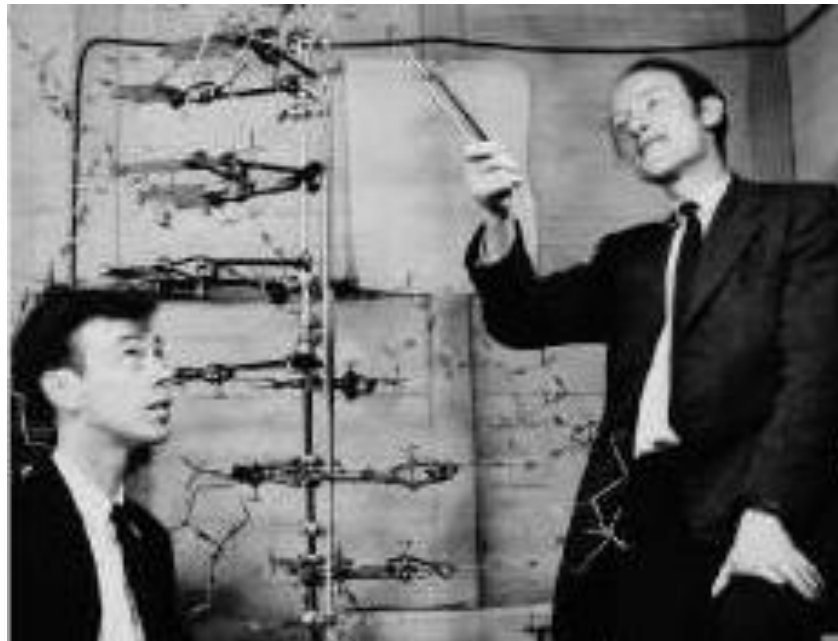
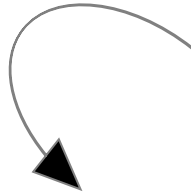
- Prêmio Nobel em Fisiologia e Medicina, 1906
- Médico e cientista
 - Hematologia
 - Imunologia
 - Quimioterapia
- Descobriu Salvarsan – Tratamento da sífilis

“Corpora Non Agunt Nisi Fixate”

“A Substance will not work unless it is bound”



1906, composto
606, Arsfenamina
(Salvarsan)



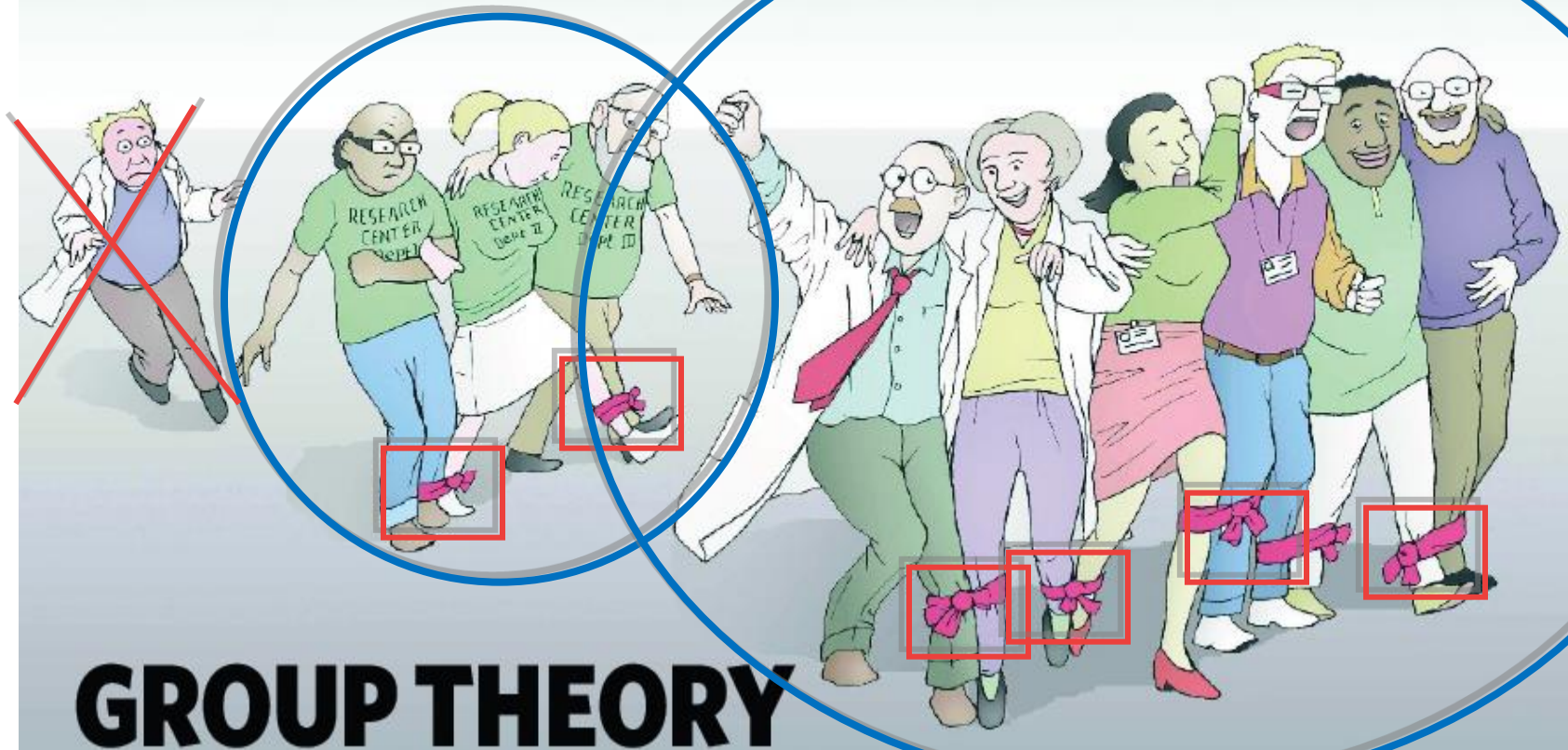
The physical Crick & the biologist Watson

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

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



What makes a successful research team?

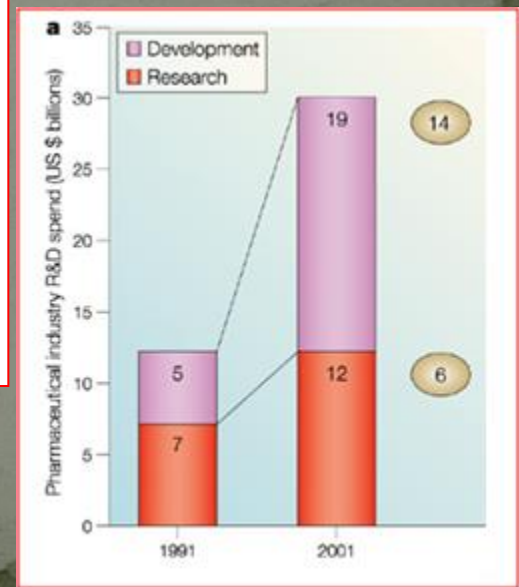
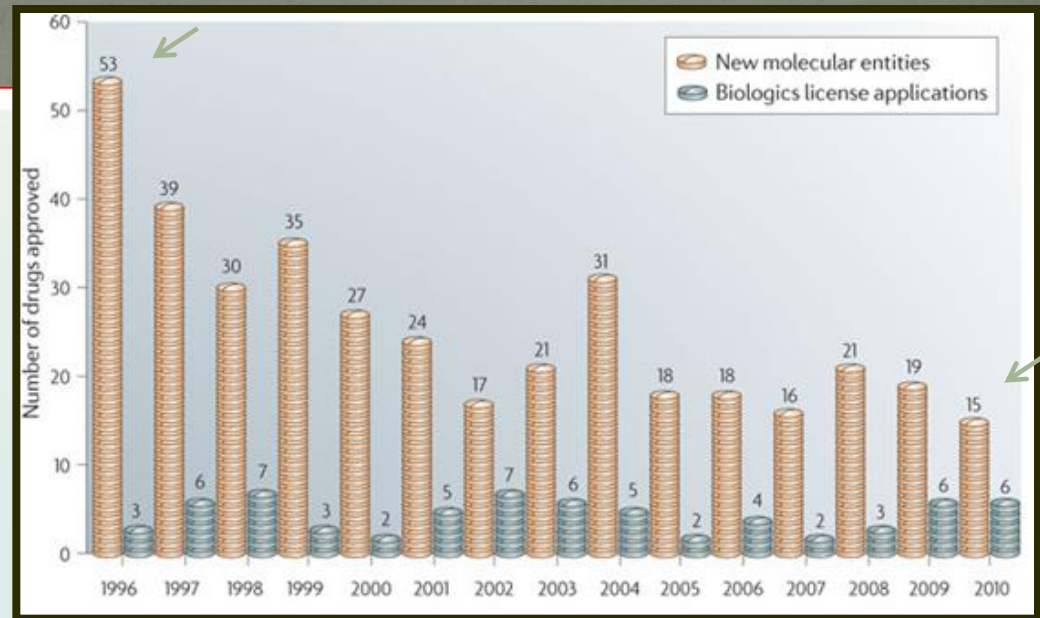
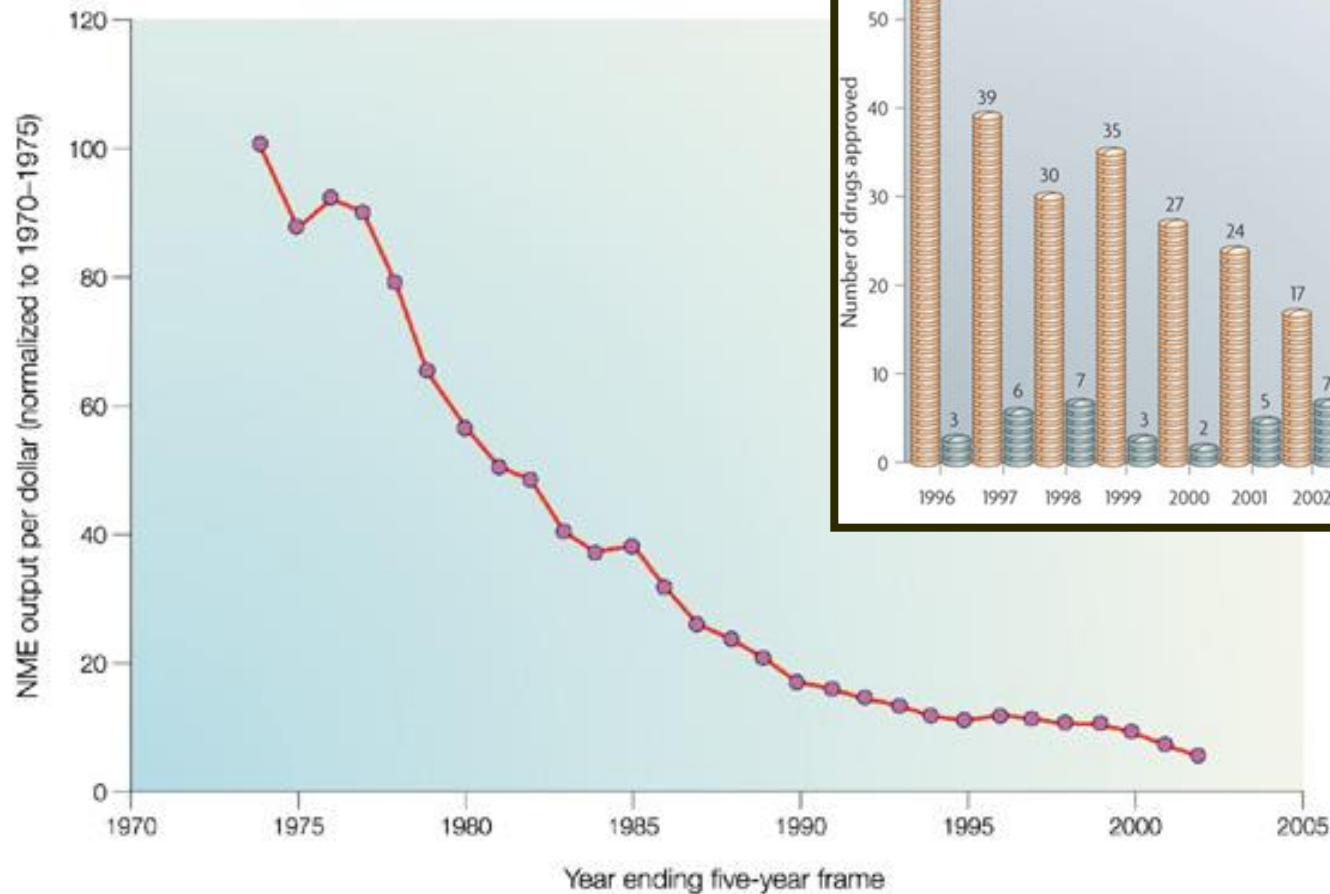


W Masona, D J Watts, Collaborative learning in networks, *PNAS* **2012**, 109, 764; M Williams, Productivity Shortfalls in Drug Discovery: Contributions from the Preclinical Sciences?, *JPET* **2011**, 336, 3; R Guimera, B Uzzi, J Spiro, L A N Amaral, Team Assembly Mechanisms Determine Collaboration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



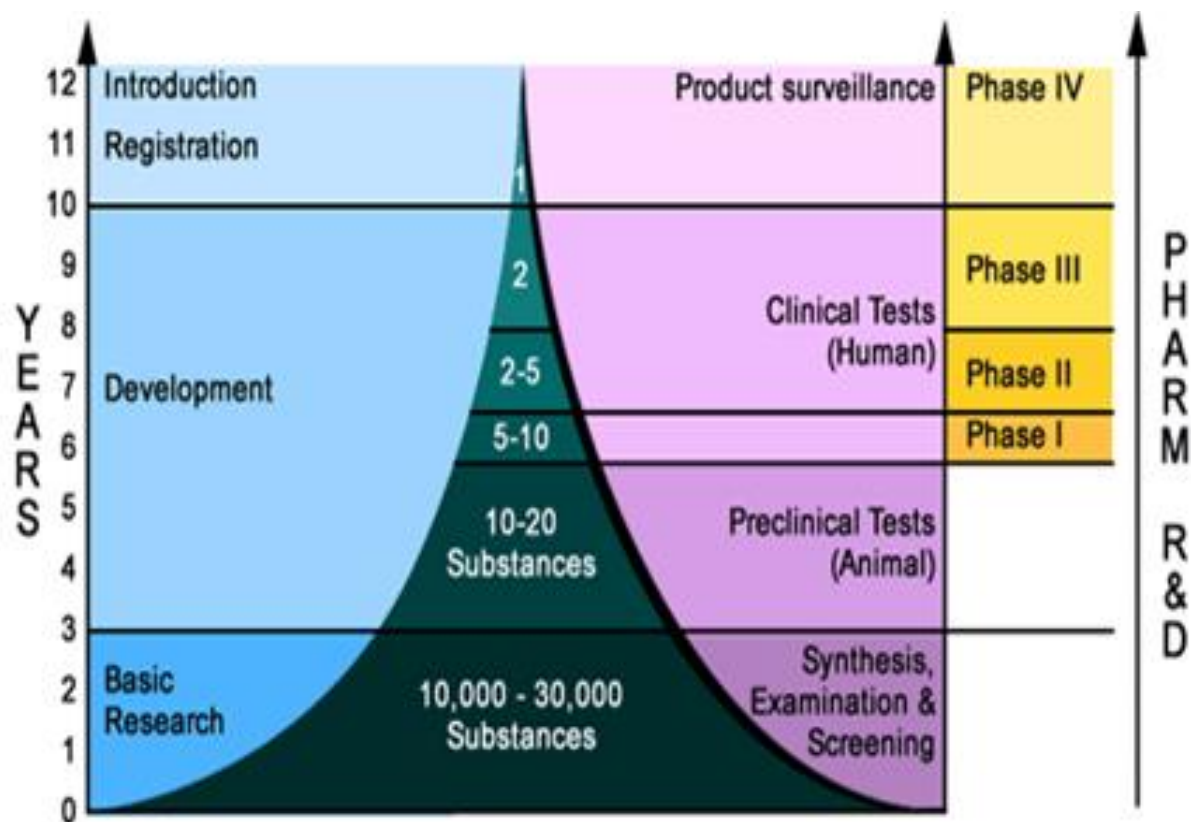
The role of universities in DD

Pesquisa e Desenvolvimento de Novos Fármacos: Sinais de Declínio na Produtividade das “Big-Pharmas”



Booth & Zimmel (2004) Nature Rev. Drug Discovery 3, 451;
A. Mullard (2011) Nature Rev. Drug Discovery 10, 82.

Mercado Farmacêutico Mundial em 2012 (US\$ 962.1 Bi)

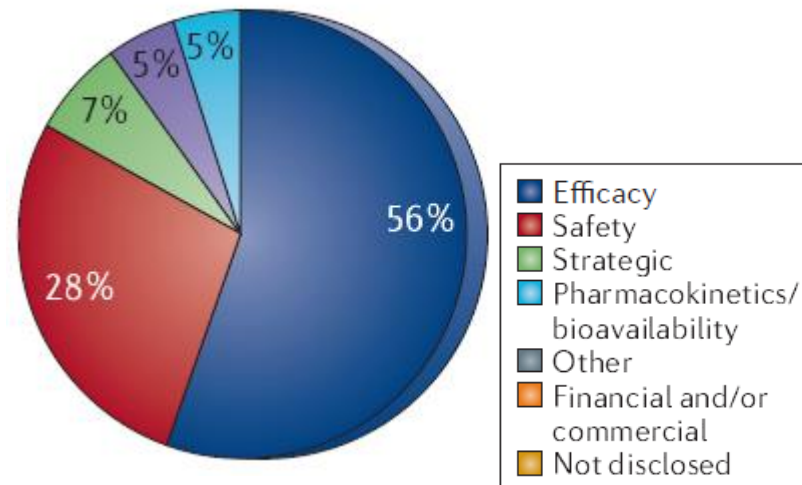


- Inovação Radical
- Inovação Incremental (Me-Better)
- Inovação Aditiva (Me-Too)
- Genéricos

- Pharmaceutical industry faces an enormous challenge in the form of late-stage compound failures.
- 70% of recent failures in Phases 2 and 3 of drug development has to do with problems on efficacy and safety

Principais Razões para Falhas no Desenvolvimento de Fármacos

a Causes of failure

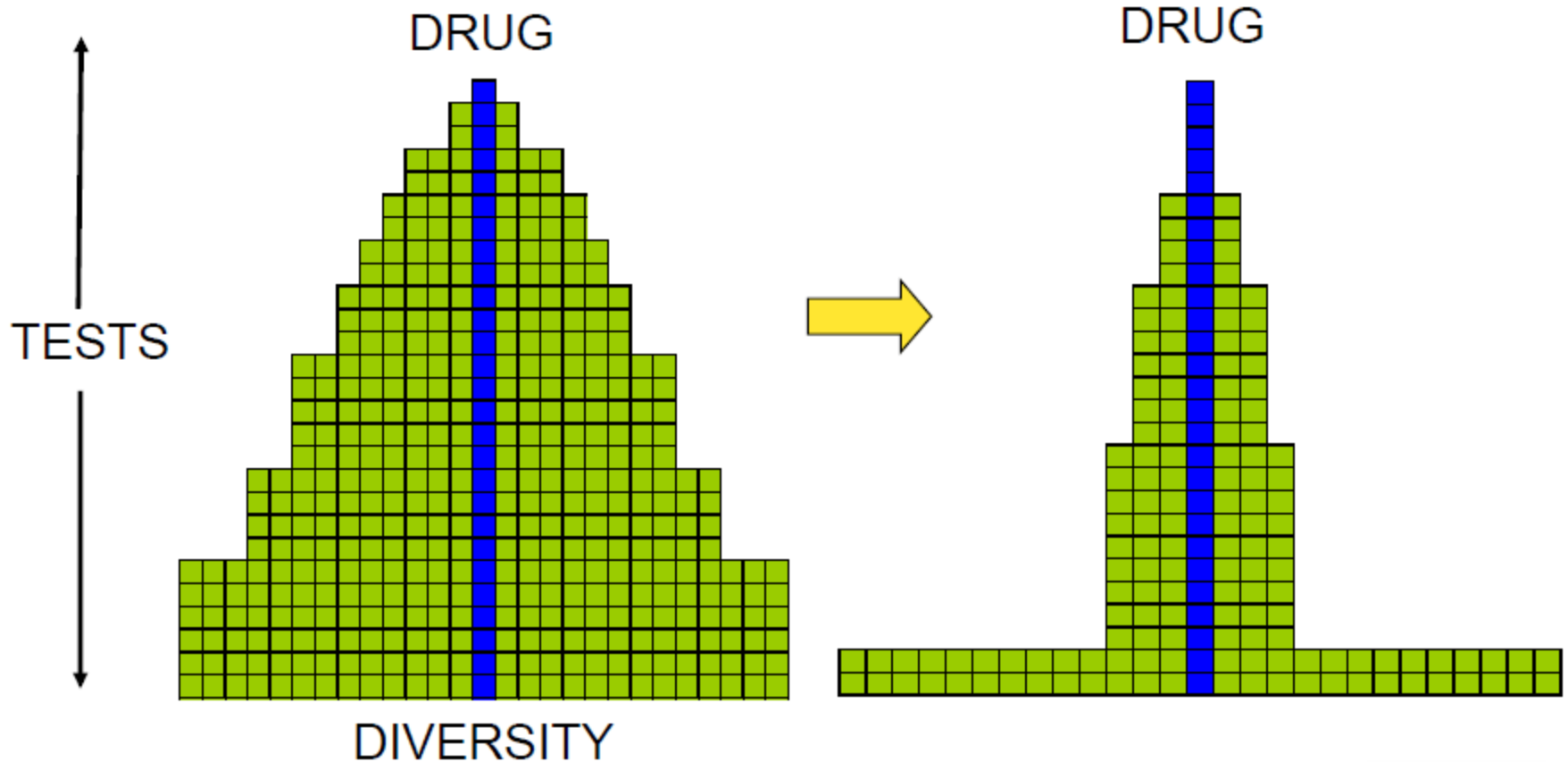


Average preclinical costs for a successful launch is US\$270 million

Paul, S.M. et al. (2010) How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nat. Rev. Drug Discov.* 9, 203–214

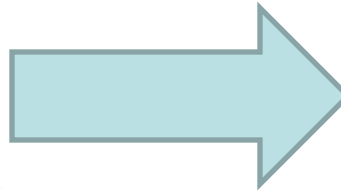
Arrowsmith & Miller (2013) *Nature Rev. Drug Discovery* 12, 569;

Desafios para o Processo de Descoberta de Fármacos

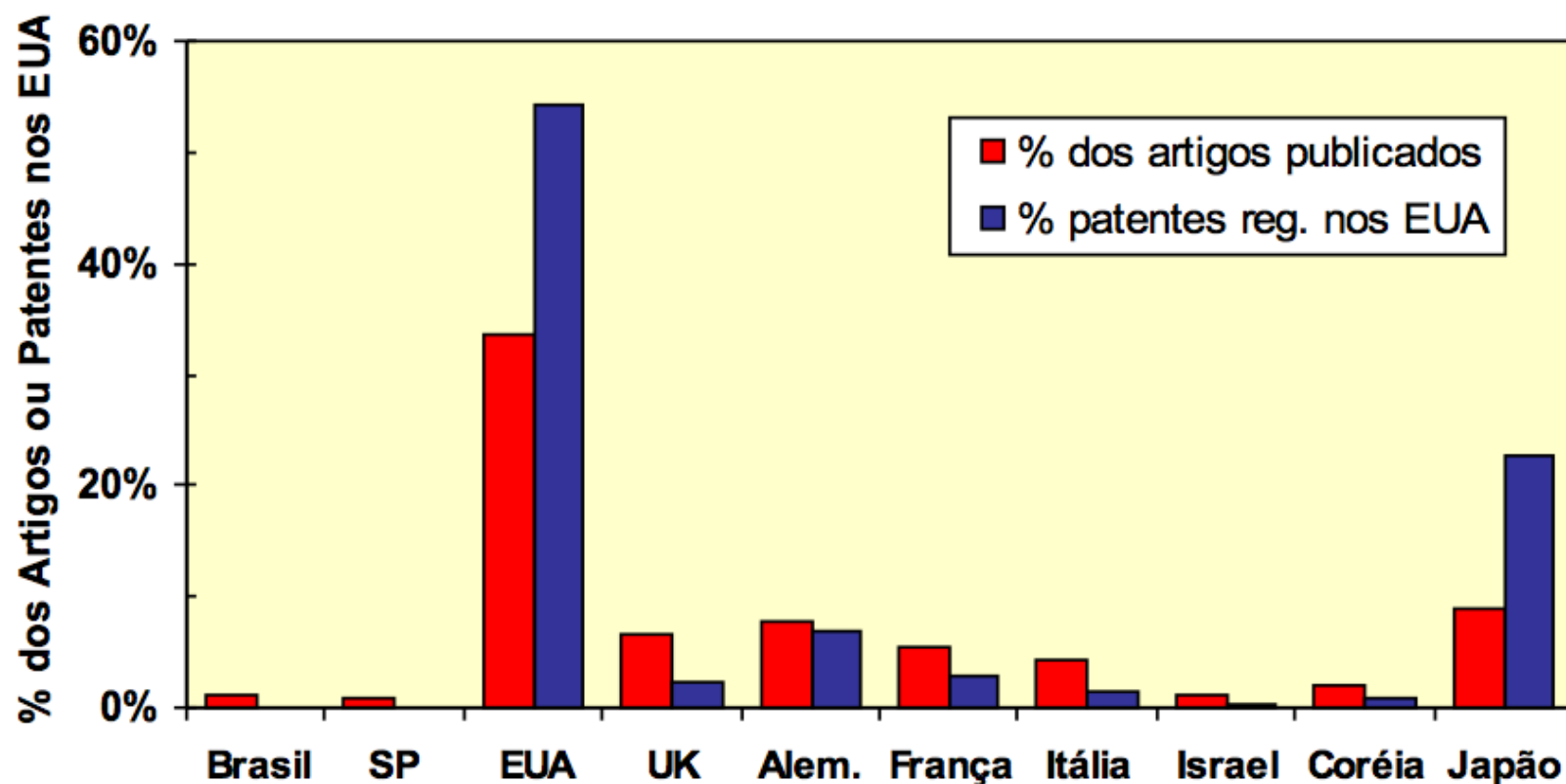


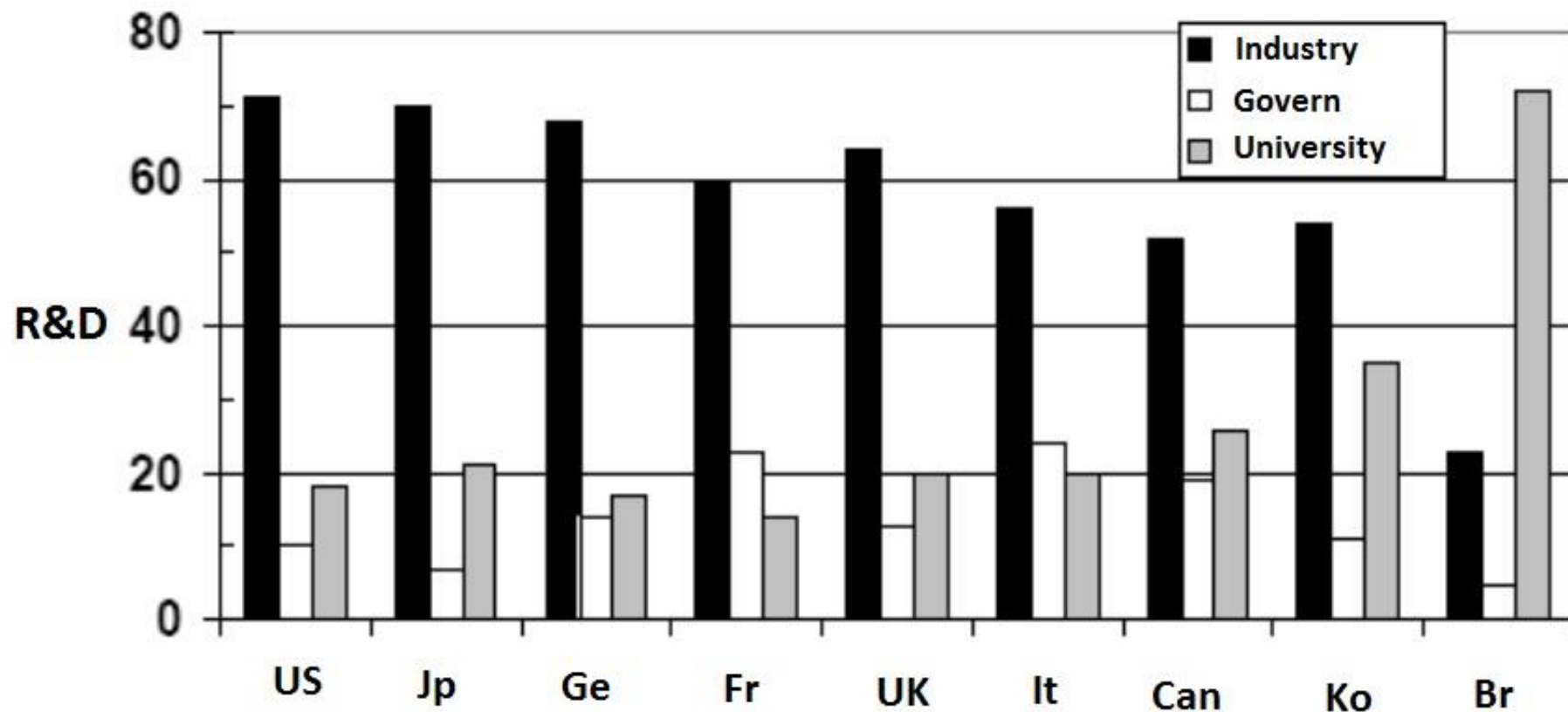
Desafios na Busca por Novos Fármacos: Acelerar o processo/reduzir custos

É como procurar uma agulha no palheiro....



Presença mundial em C&T Artigos e Patentes





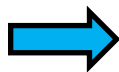
Is open innovation the way forward for big pharma?

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_P Pharma



Innovation process *in-house*

= fully integrated pharmaceutical company

To fully integrated pharmaceutical network

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.



Medicine man

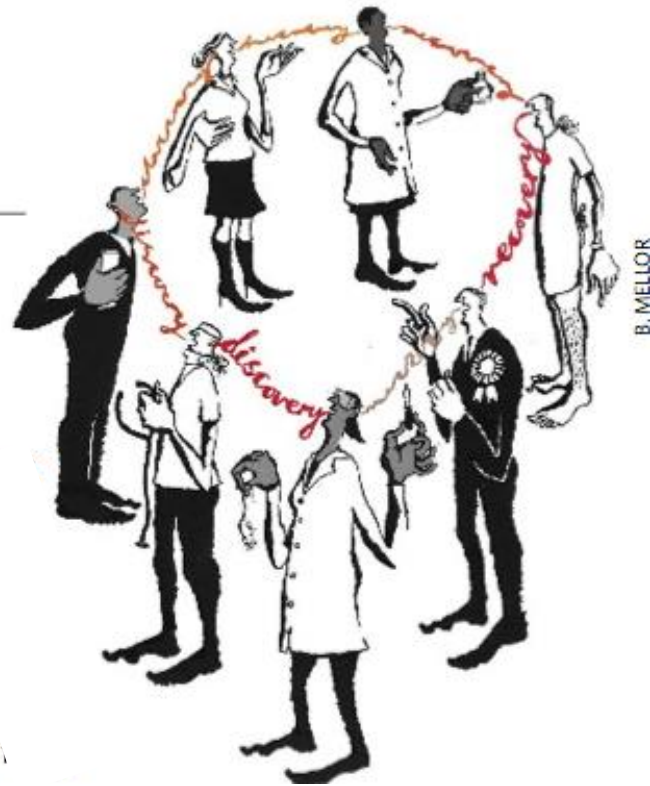
As director of the NIH's bold new translational research centre, Christopher Austin has to show that he can jump-start a tortuous drug-discovery process.

National Center for Advancing Translational Sciences (NCATS)

Funded at US\$575 million last year

Mission: "to get more successful medicines into more patients, more quickly"

“Does anyone in the audience believe that there is something that NCATS is going to do that the industry — thinks is critical and that they are not doing?” he asked. “That is incredible to think that. If you believe that, you believe in fairies



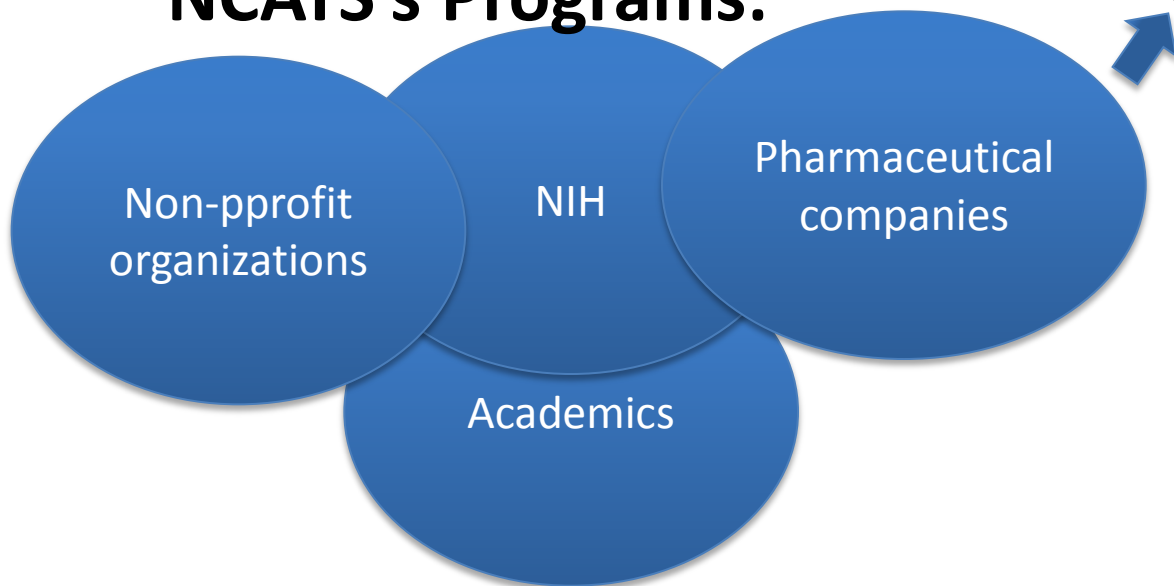
“ The focus will be on overcoming obstacles on the road to drug development, from inadequate toxicology methods to inefficient clinical-trial recruitment, rather than actually producing the drugs”

Christopher Austin

Roy Vagelos

The New York Times front-page story declaring that NIH officials “have decided to start a billion-dollar **government drug development center to help create medicines**” and that to do so Collins was willing to “**cannibalize**” other parts of the NIH.

NCATS's Programs:



- to try to move into clinical testing compounds that show promise against neglected diseases



4 compounds moving into clinical trials in the past 15 months.

- Segundo uso: Substâncias já testadas em humanos mas abandonadas pela big pharma (razões de negócio ou inativas nas doenças investigadas. Tentar outras aplicações.
- Avaliação toxicológica: Desenvolvem chips que mimetizam tecidos humanos com o objetivo de fazer triagem de efeitos tóxicos de fármacos.
- Iniciaram em 2011 a triagem de 10.000 agentes químicos ambientais e todos compostos aprovados contra qualquer doença humana em vias de sinalização, com objetivo de identificar substâncias com efeito tóxico.

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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.



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Project CNPq 573.564/2008-6

Home

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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;



Who we are



Instituto Nacional de
Ciência e Tecnologia

de Fármacos e Medicamentos

www.inct-inofar.ccs.ufrj.br



Governance committee

Innovation in Drugs
and Medicines

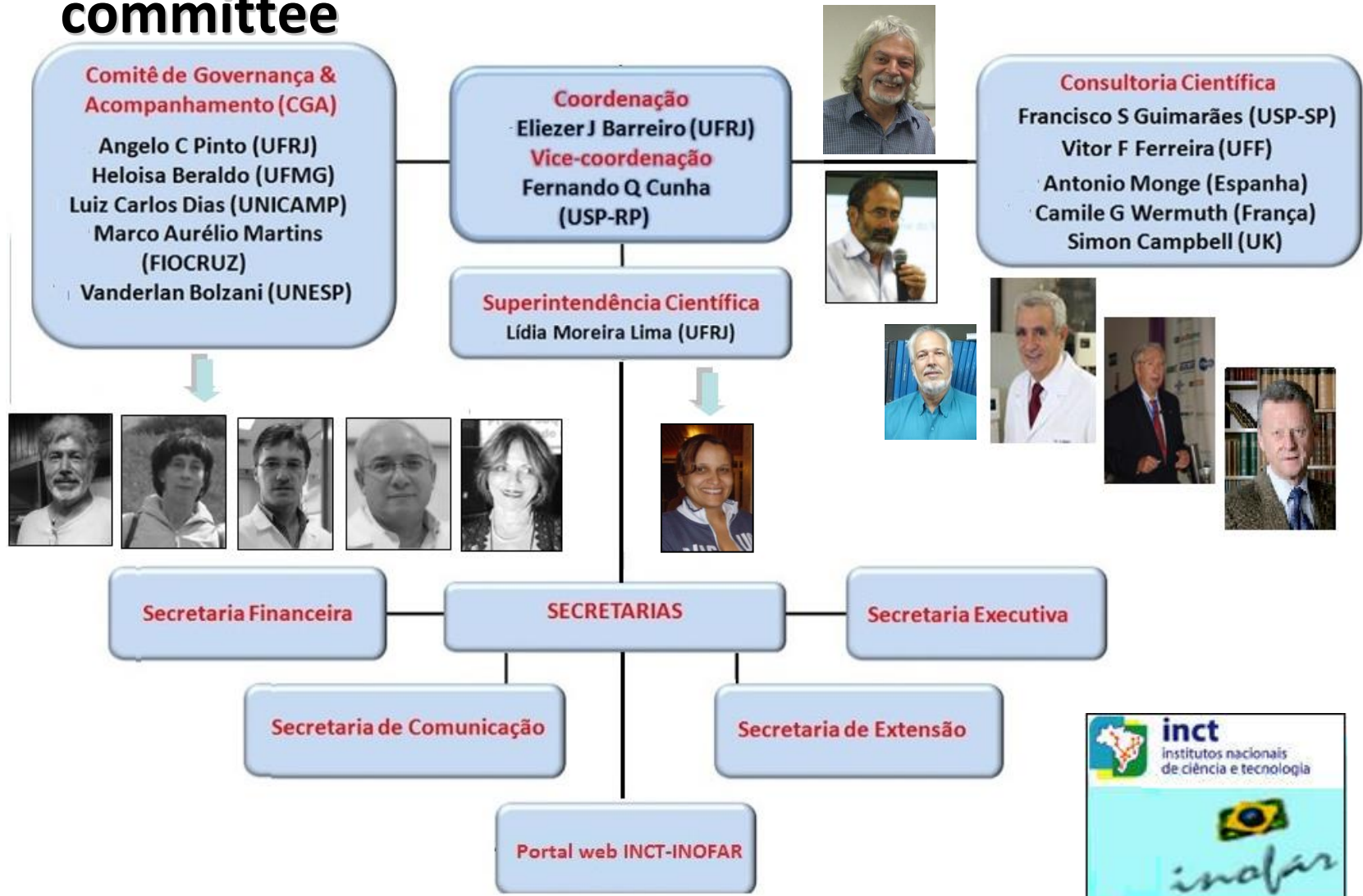


inofar

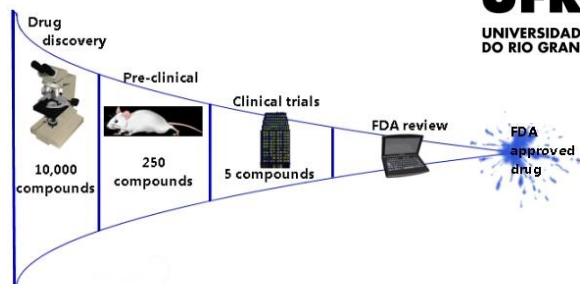
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What we do

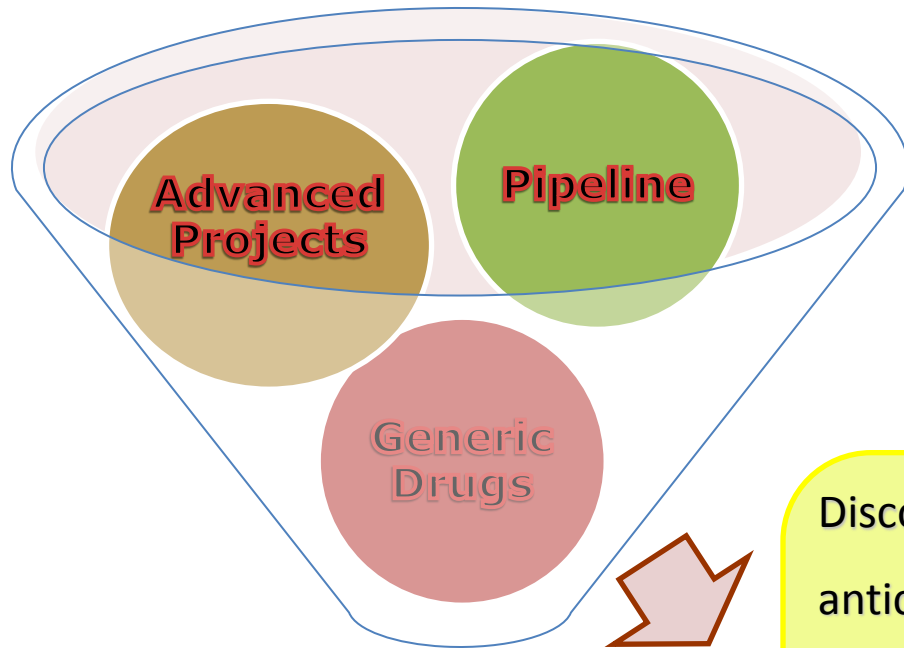


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de Fármacos e Medicamentos

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Radical *Innovation*



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

LASSBio-897 for the
treatment of silicosis

Laboratory of Inflammation

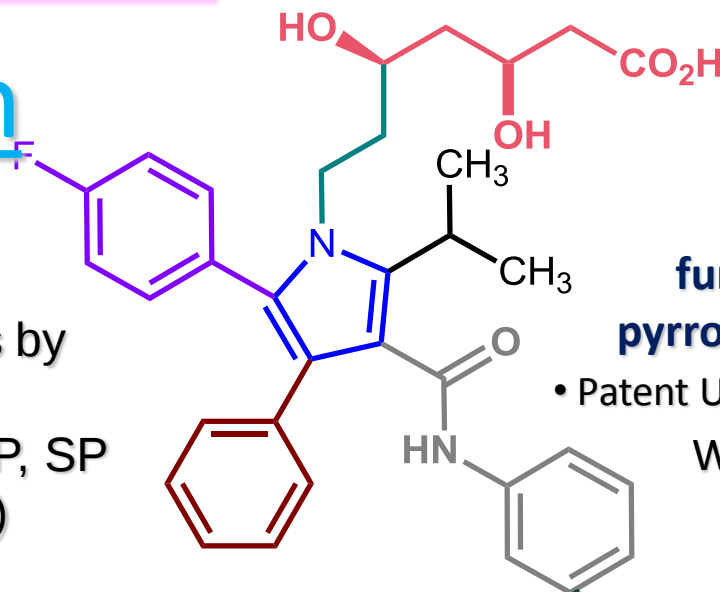
IOC - FIOCRUZ, RJ

Incremental *Innovation*

• Atorvastatin

1991 Lipitor™

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



**functionalized
pyrroleheptenoic acid**

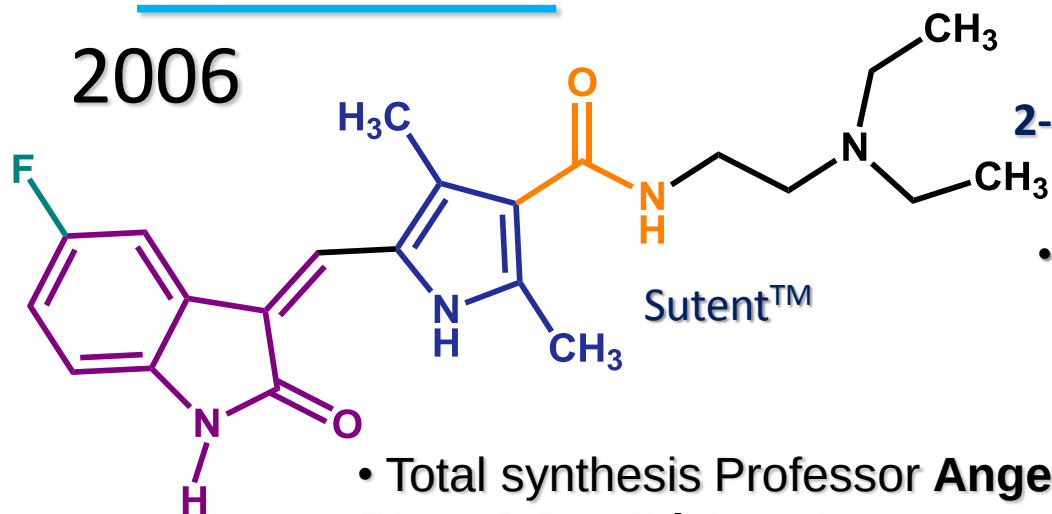
- Patent US 5273995 Pfizer (1991)

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

super blockbuster-drug

• Sunitinib

2006



Sutent™

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

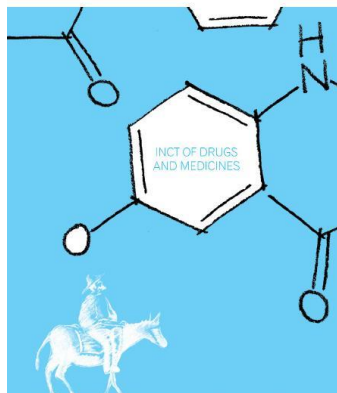
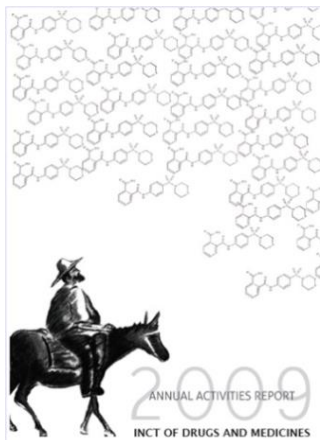
- *Patent US 7211600 (2001)

- Multi TK inhibitor indicated to renal carcinoma

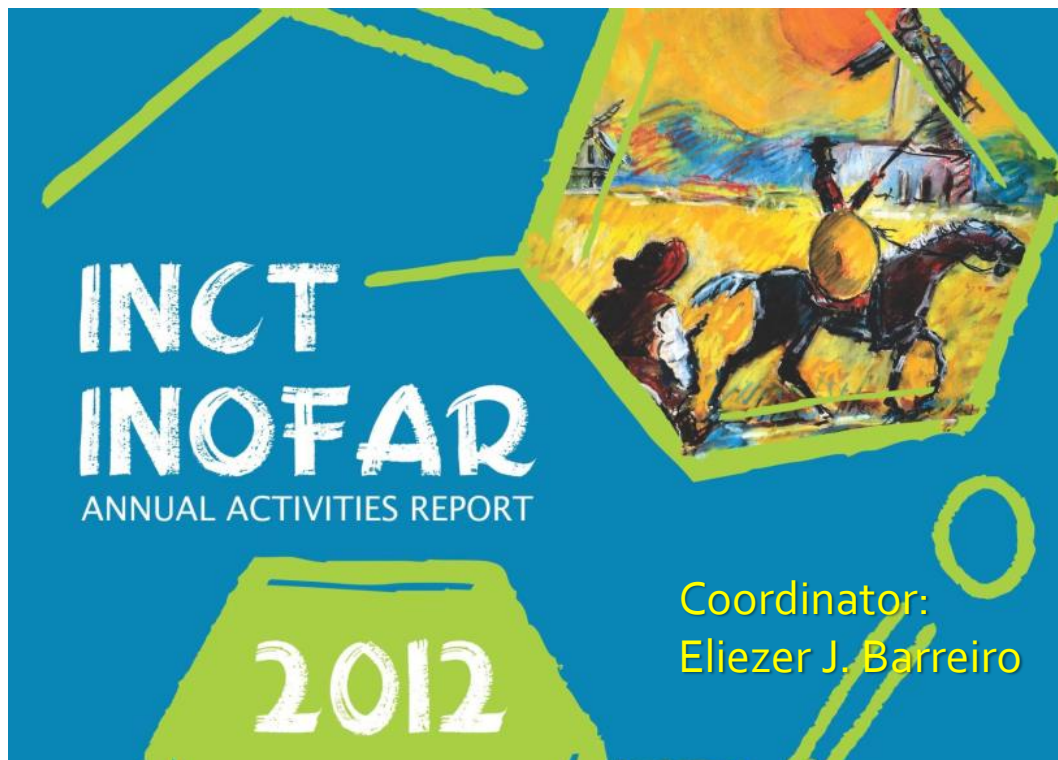
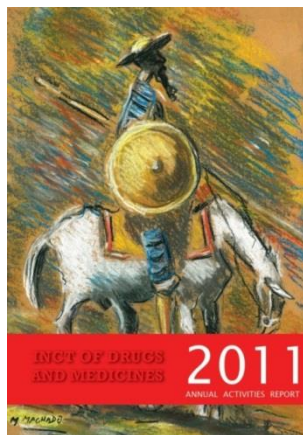
- Total synthesis Professor **Angelo da Cunha Pinto** & Dra **Bárbara Vasconcellos da Silva** UFRJ, RJ (**2011**) (BR)

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

Annual Activities Report



2010
ANNUAL ACTIVITIES REPORT



Coordinator:
Eliezer J. Barreiro

www.inct-inofar.ccs.ufrj.br/download/aar/2012.pdf

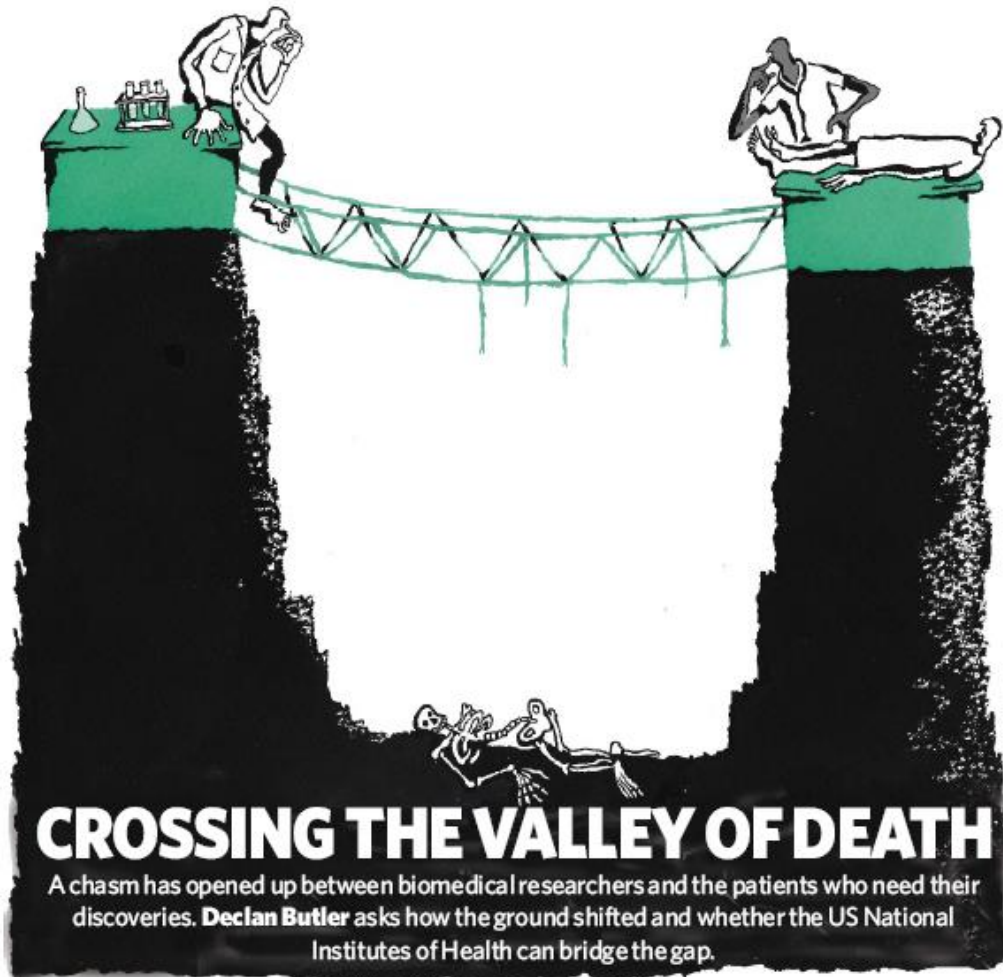
Finalizando....

Desafio: Não se deve buscar fazer o que outros já fazem muito bem, mas fazer o que os outros não pode fazer ou fazem mal;

Desafio: Não se pode negligenciar a importância da ciência básica.



“Cruzando o Vale da Morte”



Butler D (2008) Translational research: crossing the valley of death. *Nature* **453**: 840-842

The hedquarter of
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Acknowledgments



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