Os jovens cientistas e a evolução da Ciência

I Workshop de Jovens Pesquisadores em Planejamento e Desenvolvimento de Fármacos

Faculdade de Ciências Farmacêuticas – USP
São Paulo, SP
05 de março de 2015

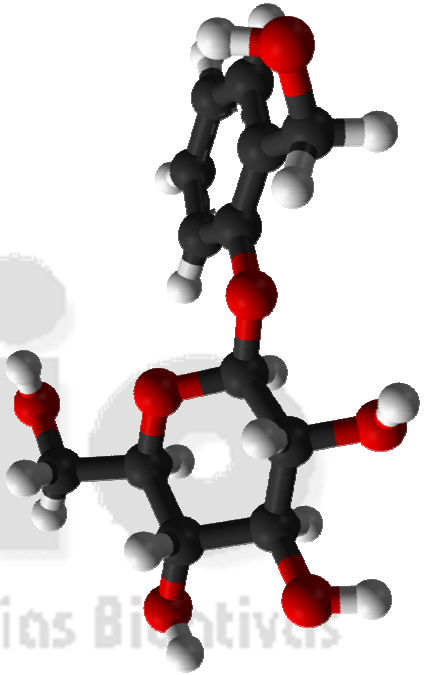
Eliezer J. Barreiro

Professor Titular

Universidade Federal do Rio de Janeiro

Laboratório de Avaliação e Síntese de Substâncias Bioativas

Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos
INCT-INOFAR



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"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

(1854-1912)

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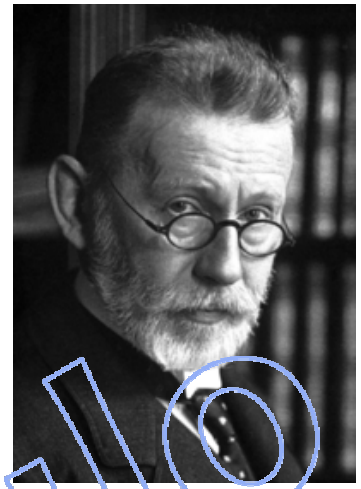
Prêmio de maior reconhecimento científico

medicinal chemistry

Emil Fischer (50)

1852-1919

The Nobel Prize in Chemistry 1902



Paul Ehrlich (54)

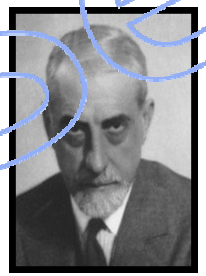
1854-1915

The Nobel Prize in Physiology or Medicine 1908

Daniel Bovet (45)

1907-1992

The Nobel Prize in Physiology or Medicine 1952



Ernest Fourneau (39)

1872-1949

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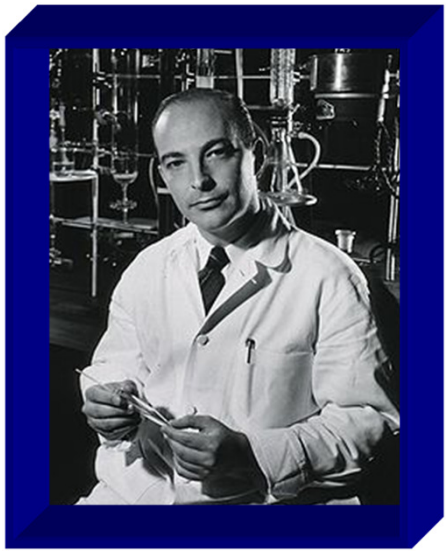


Prêmio Nobel, 1959

1987

The Two Cultures: Chemistry and Biology[1]

Arthur Kornberg

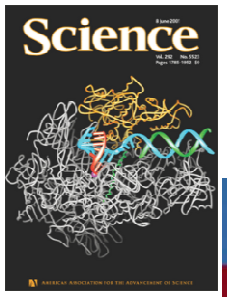
Department of Biochemistry, Stanford University, Stanford, California 94305

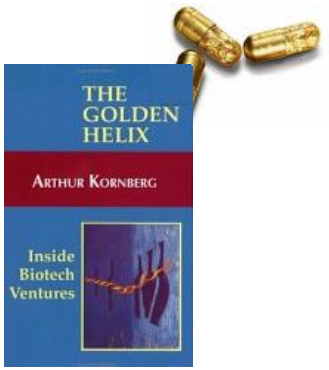
Received July 14, 1987

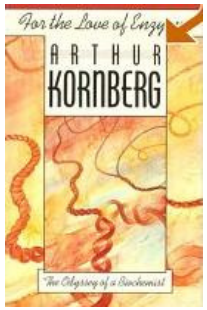
Arthur Kornberg (41)
1918-2007

"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..."

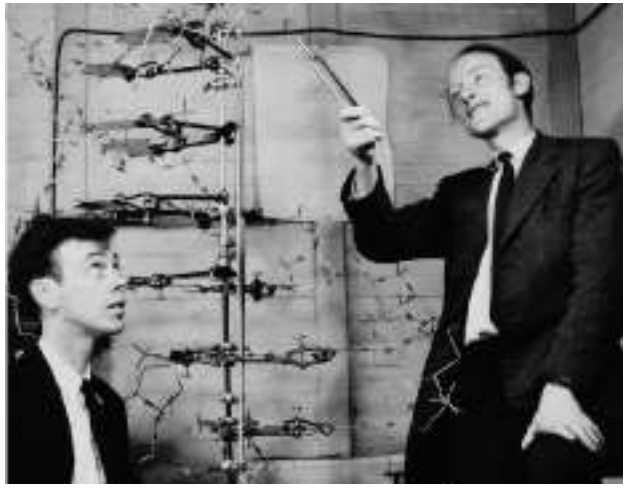


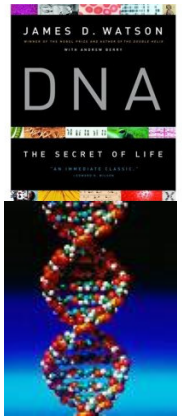




Biochemistry **1987,** *26,* 6888-6891

Uma das maiores conquistas da Ciência através dos tempos...





(62)

Os físicos Crick (46) & Wilkins (46) & o biólogo Watson (34)

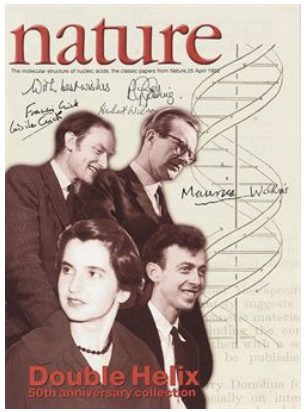
JD Watson & FHC Crick,

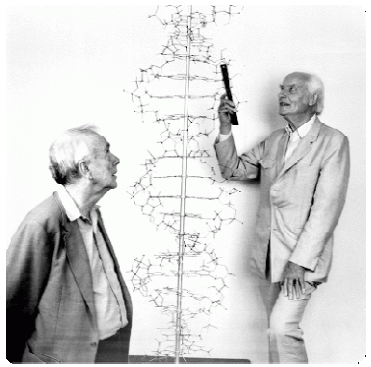
A Structure for Deoxyribose Nucleic Acid,

Nature **1953**, *171*, 737–738 .

Início da Biologia Molecular

The Nobel Prize in Medicine & Physiology 1962





MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

We wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey[1]. They kindly made their manuscript available to us in advance of publication. Their model consists of three inter-twined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion. this structure is unsatisfactory for two reasons:

(1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions. namely, that each chain consists of phosphate diester groups joining ß-D-deoxy-ribofuranose residues with 3',5' linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow righthanded helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions.

Each chain loosely resembles Furberg's[2] model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Furberg's 'standard configuration', the sugar being roughly perpendicular to the attached base. There is a residue on each chain every 3-4 A. in the z-direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 A. The distance of a phosphorus atom from the fibre axis is 10 A. As the phosphates are on the outside, cations have easy access to them.

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so

Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on interatomic distances. We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. *M.* H. F. Wilkins, Dr. R. E. Franklin and their co-workers at King's College, London. One of us (J.D.W.) has been aided by a fellowship from the National Foundation for Infantile Paralysis.

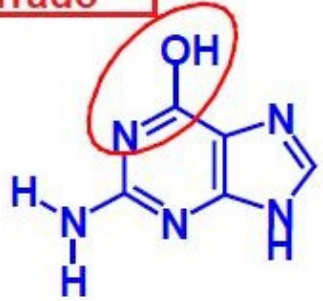
Medical Research Council Unit for the Study of the Molecular Structure of Biological Systems, Cavendish Laboratory, Cambridge. April 2.

J.D. WATSON
F.H. C. CRICK

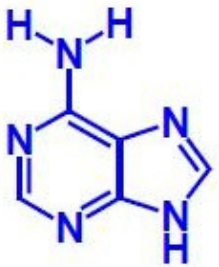
A elucidação da estrutura do DNA

Verão de 1952 Erwin Chagaff critica Farncis Crick & James Watson por ignorarem as estruturas das bases nuclêicas

tautômero errado

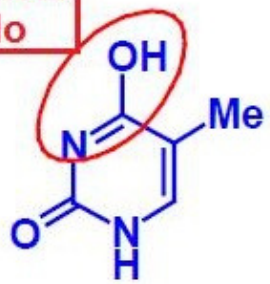


guanine

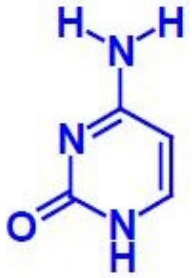


adenine

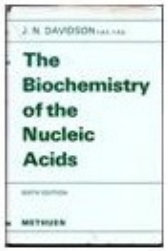
tautômero errado



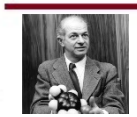
thymine



cytosine



J. N. Davidson, The Biochemistry of Nucleic Acids, London, 1950



Início de 1953: Linus Pauling publica um modelo do DNA com fosfatos

27 de fevereiro de 1953 : Jerry Donohue corrige as fórmulas das bases

28 de fevereiro de 1953: Watson & Crick deduzem o modelo correto do DNA

2 de abril de 1953: Manuscrito foi enviado à Nature; publicado em 25 de abril

Citado por J. Watson and A. Berry, DNA. The Secret of Life, 2003

Vide: H. Kubinyi , Drug research: myths, hype and reality, Nature Rev Drug Discov 2003, 2, 665

Hugo Kubinyi, www.kubinyi.de

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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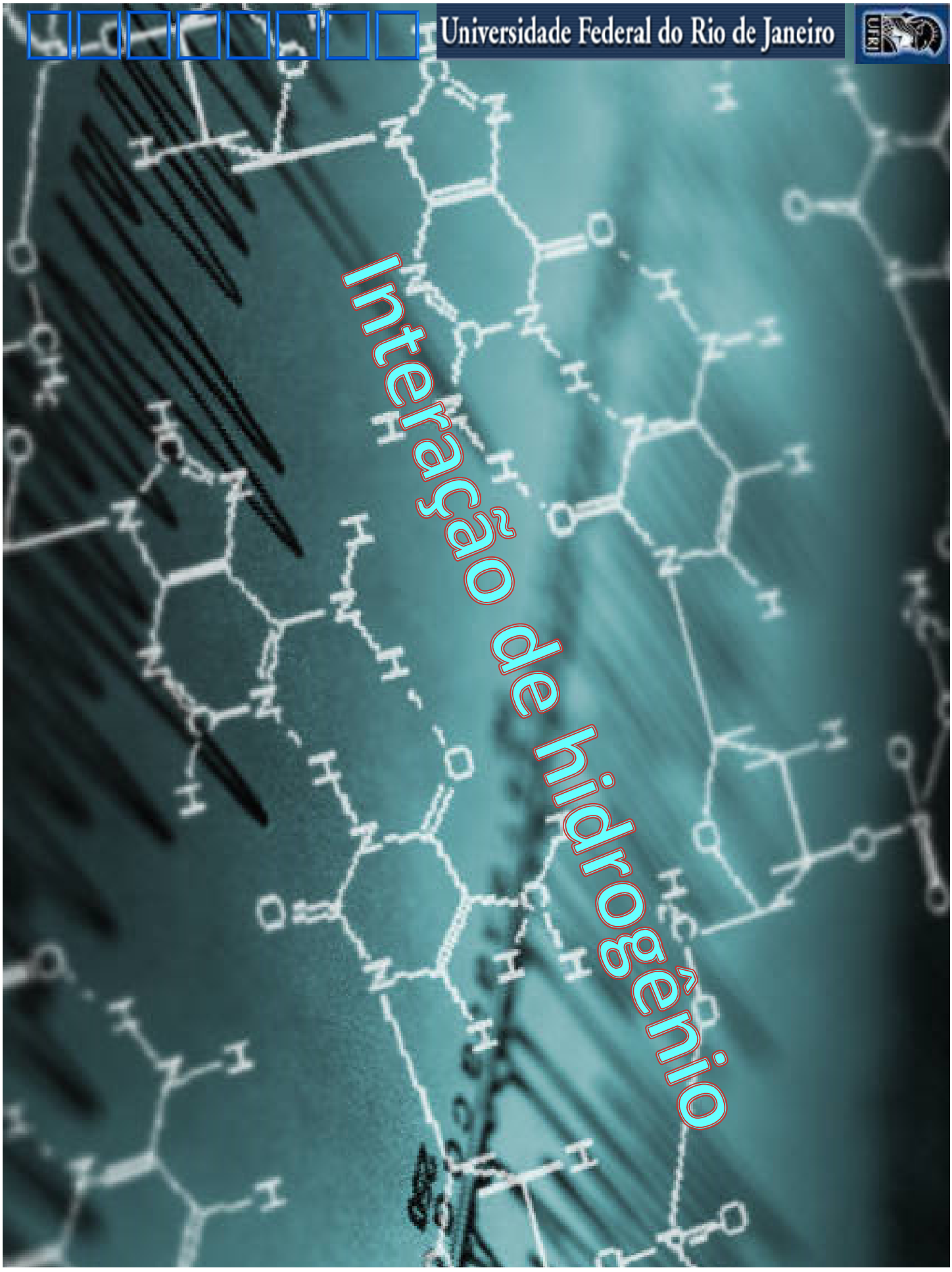
UFRJ
Estação de Mutação
Genômica
Proteômica
Dia Mundial do DNA = 25 de abril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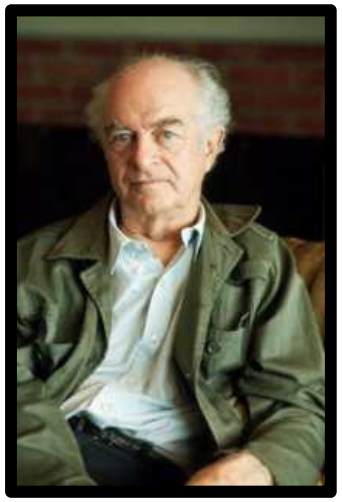
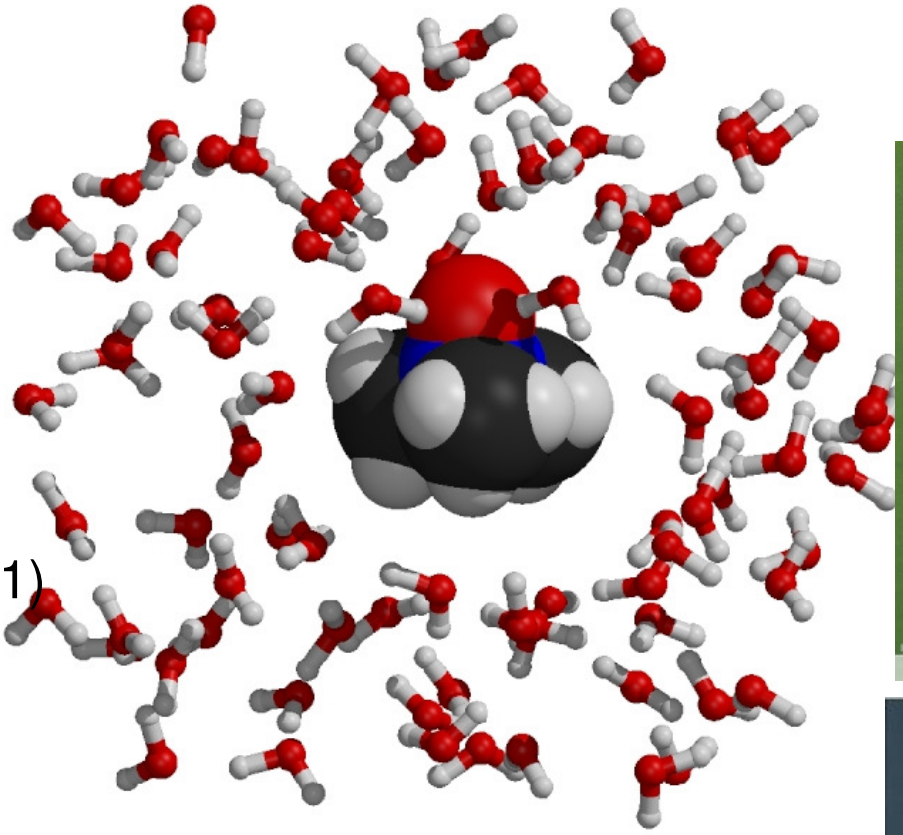
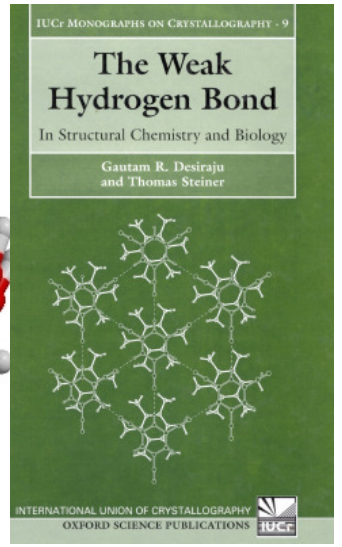
UFRJ
Interação de hidrogênio

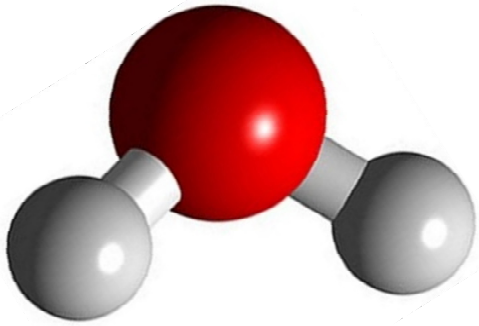
Universidade Federal do Rio de Janeiro



Linus C. Pauling (53, 61)
1901-1994



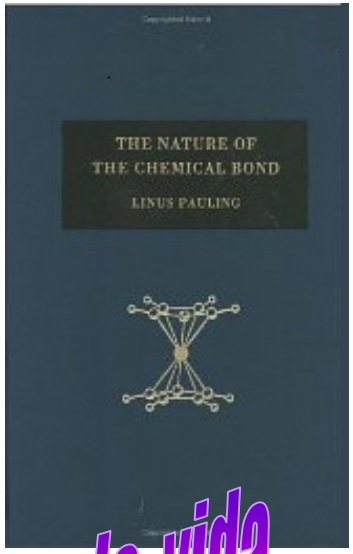




"ligações" de hidrogênio ...

The Nobel Prize in Chemistry 1954

The Nobel Piece Prize in 1962



Moléculas da vida ...

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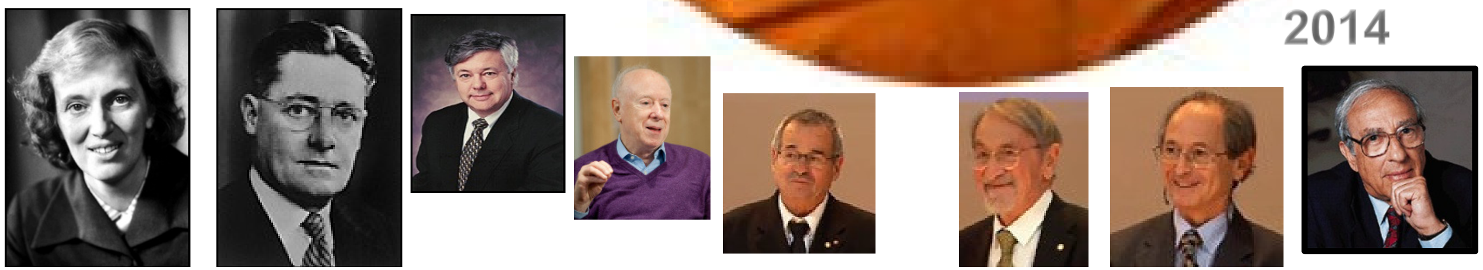
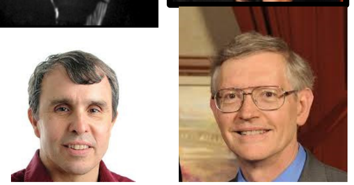
O prêmio Nobel & os fármacos

1902



2014



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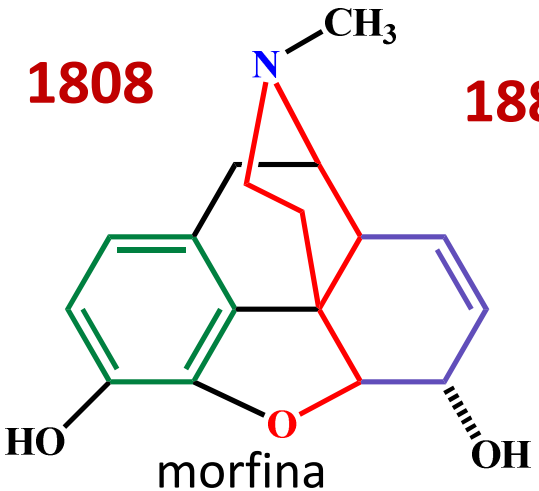
The Nobel Prize in Medicine & Physiology 1982

John Vane (55)
(1927-2004)

Sune Bergström (66)
(1916-2004)

Bengt Samuelsson (48)
(1934)

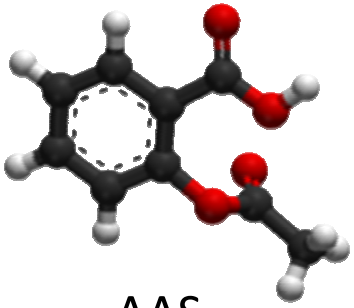
1808



morfina

$C_{17}H_{19}NO_3$

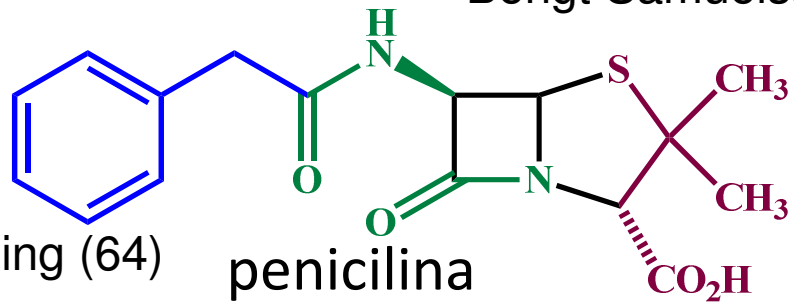
1889



AAS

$C_9H_8O_4$

1929



penicilina

$C_{16}H_{18}N_2O_4S$

Sir Robert Robinson (61)
(1886-1975)

The Nobel Prize in Chemistry 1947

Sir Alexander Fleming (64)
(1881-1955)

The Nobel Prize in Medicine & Physiology 1945

The Nobel Prize in Chemistry 1964

Dorothy C. Hodgkin (54)
(1910-1994)

Howard W. Florey (47)
(1898-1968)

E. Boris Chain (39)
(1906-1979)

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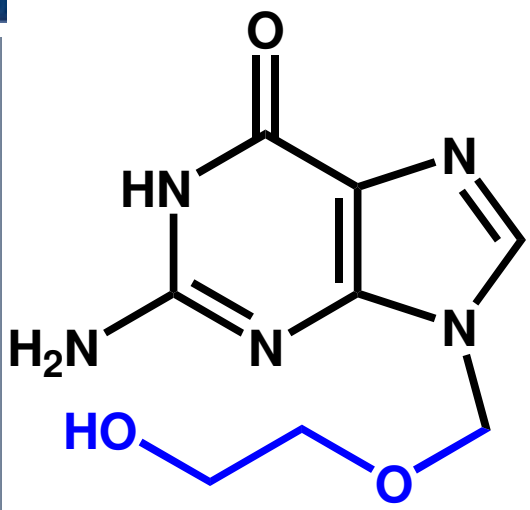
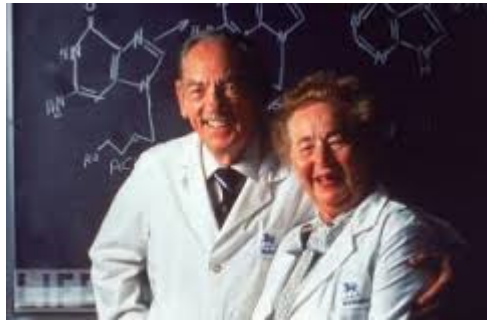


aciclovir



Gertrude B Elion (70)
(1918-1999)

Burroughs Wellcome
(atual GSK)

1988

George Hitchings (83)
(1905-1998)

6-mercaptopurina,
azatioprina,
alopurinol, trimetoprim,
nelarabina

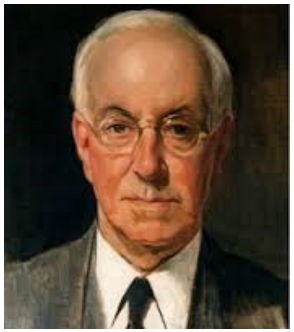
ICI

propranolol

James W. Black (64)
(1924 - 2010)

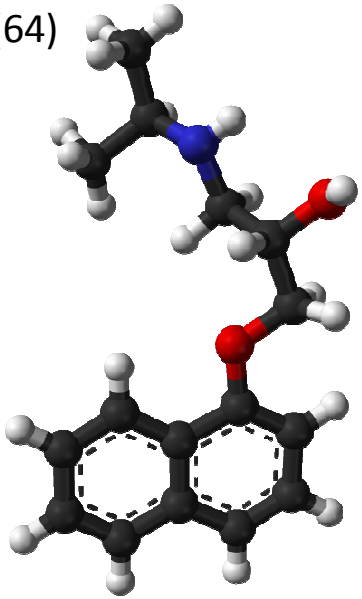
1936

Otto Loewi (63)
(1873-1961)



Henry H Dale (61)
(1875-1968)

Raymond Ahlquist (1914–1983)



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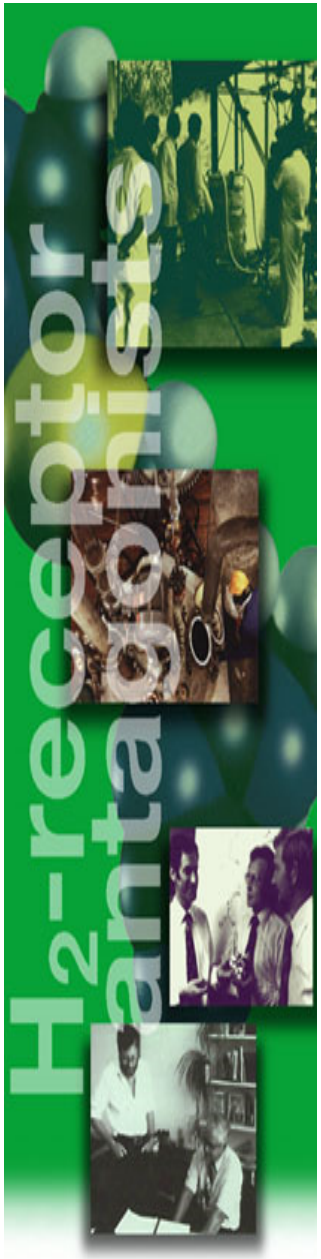


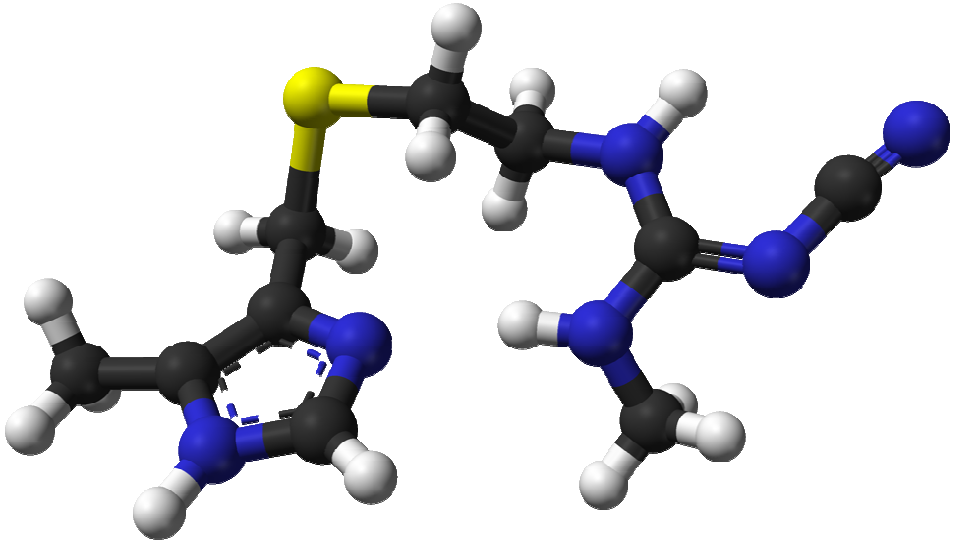
National Historic Chemical Landmarks

AMERICAN CHEMICAL SOCIETY

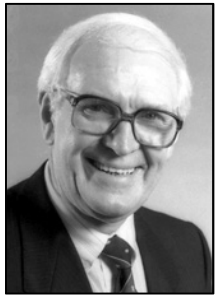
A new era of logical drug design

The research program leading to cimetidine also represented a revolution in the way pharmaceuticals are developed. Traditionally, the development of a new drug would often depend on the fortuitous discovery of a plant or microbial extract that showed some of the required biological activity. Using that first extract as a lead, many similar compounds would be made and tested for pharmacological effectiveness. In many cases, the researchers did not know how the drug worked, so finding an optimal compound was difficult.

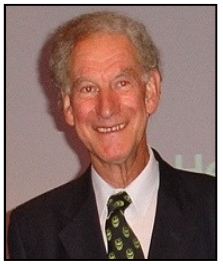
The physiologic approach



1988



James W. Black

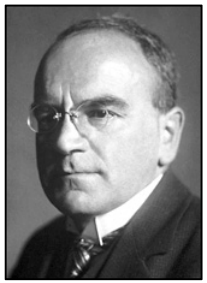


C. Robin Ganellin

John C. Emmett

Graham J. Durant

As estatinas: inovação bilionária

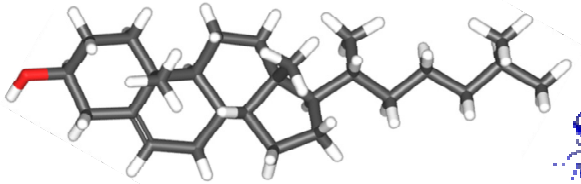


Heinrich Wieland (50)
(1877-1957)

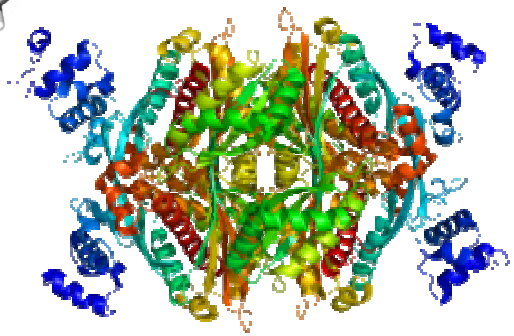
1927

Adolf Windaus (52)
(1876-1959)

1928



colesterol

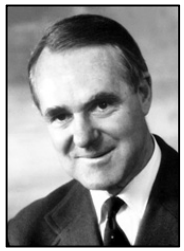


HMGCoAR

1964

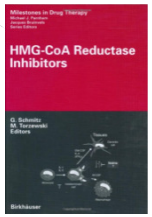
Konrad Bloch (53)
(1912-2000)

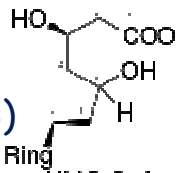
Feodor Lynen (54)
(1911-1979)



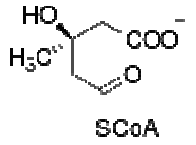
John Cornforth (58)
(1917-2013)

1975

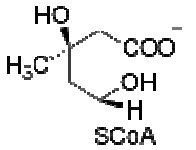




HMG CoA
Reductase Inhibitor



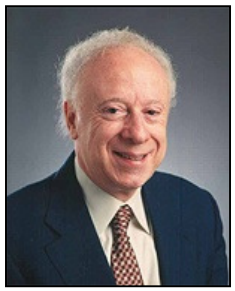
HMG CoA



Mevaldyl CoA transition
state intermediate

1985

LDL



Joseph L Goldstein (45)
(1940)

Michael S Brown (44)
(1941)

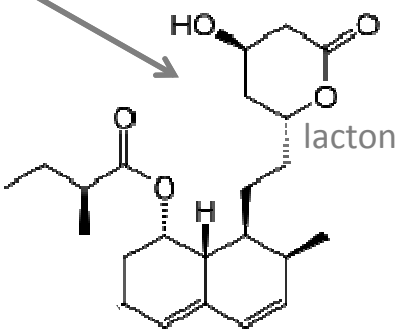
University of Texas, Dallas

Akira Endo
(1933)

Albert Lasker Award
for Clinical
Medical Research, 2008*

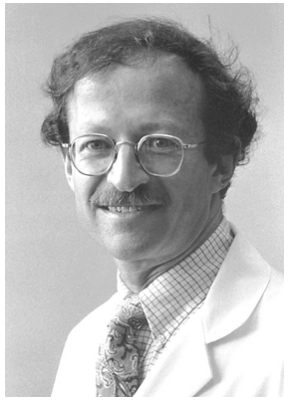
J Med Chem
1985, *28*, 1

Daiichi-Sankyo

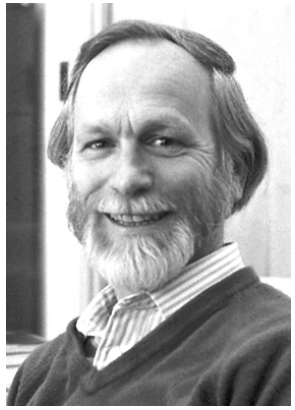


Mevilonina
/compactina

Tinibes: inibidores de TK's



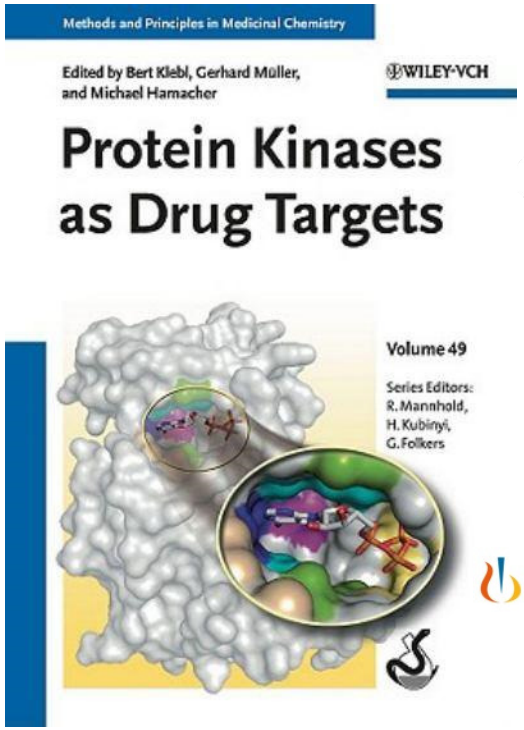
Harold E. Varmus (50)
(1939)

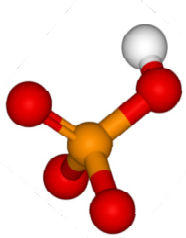


for their discovery of the cellular origin of retroviral oncogenes

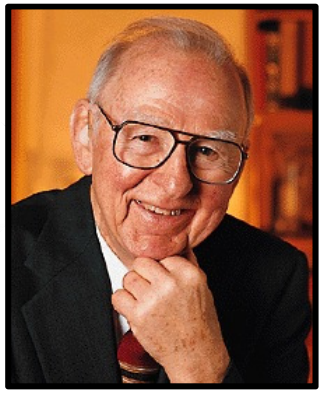
J. Michael Bishop (53)
(1936)

1989



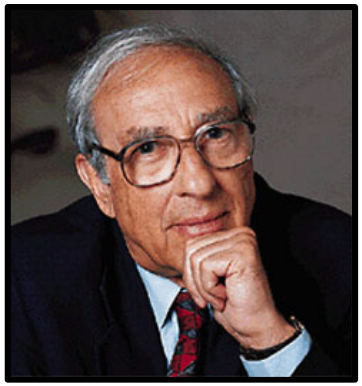


kinoma



Edwin G. Krebs (72)
(1918 –2009)

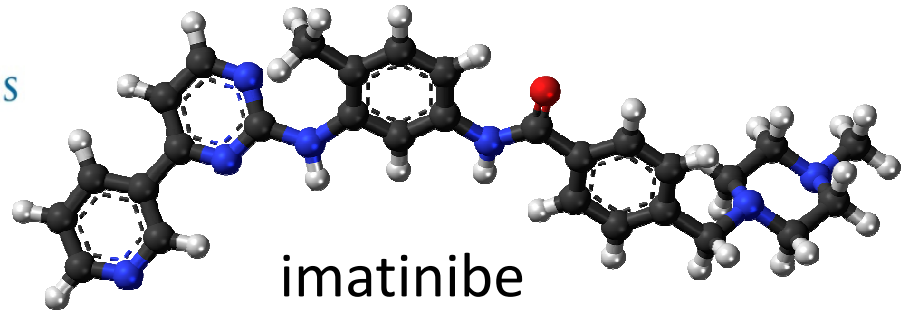
1992



Edmond H. Fischer (72)
(1920)

NOVARTIS

2001



imatinibe

Pasteur´s dictum

Dans les domaines de

l‘observation le hasard

ne favorise que les esprits préparés.

L. Pasteur, Conference, Université de Lille (07 Décembre, 1854)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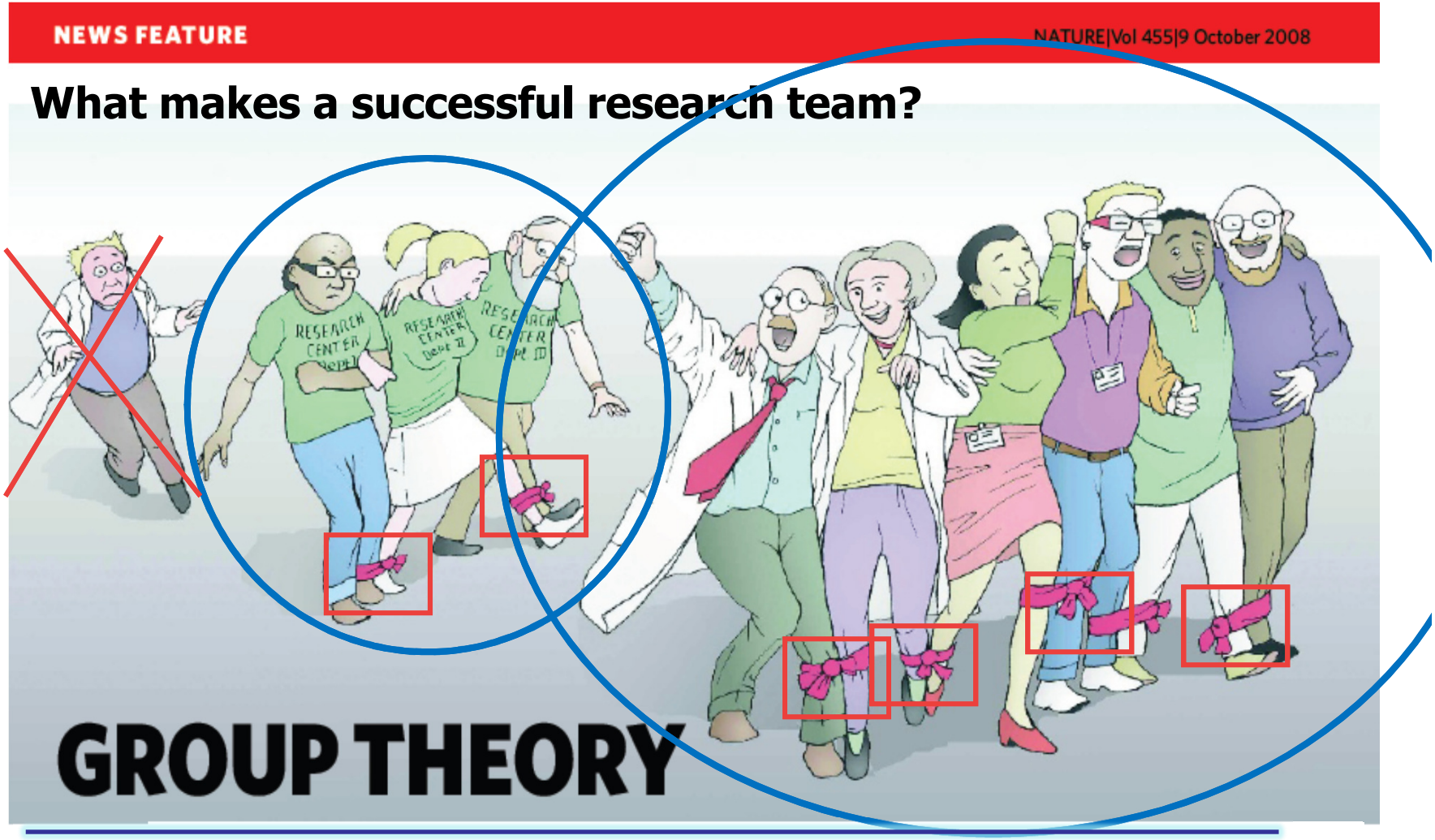
UFRJ
Eficiência...
Competência
Temporança
Competitividade
...não é suficiente!

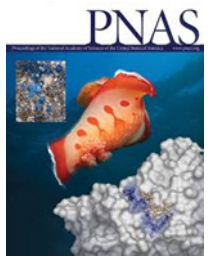
J. Whitfield, *Nature* **2008**, *455*, 720



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.

Prêmio Nobel 1875-2008*

Age dynamics in scientific creativity,
PNAS **2011**, *108*, 18910



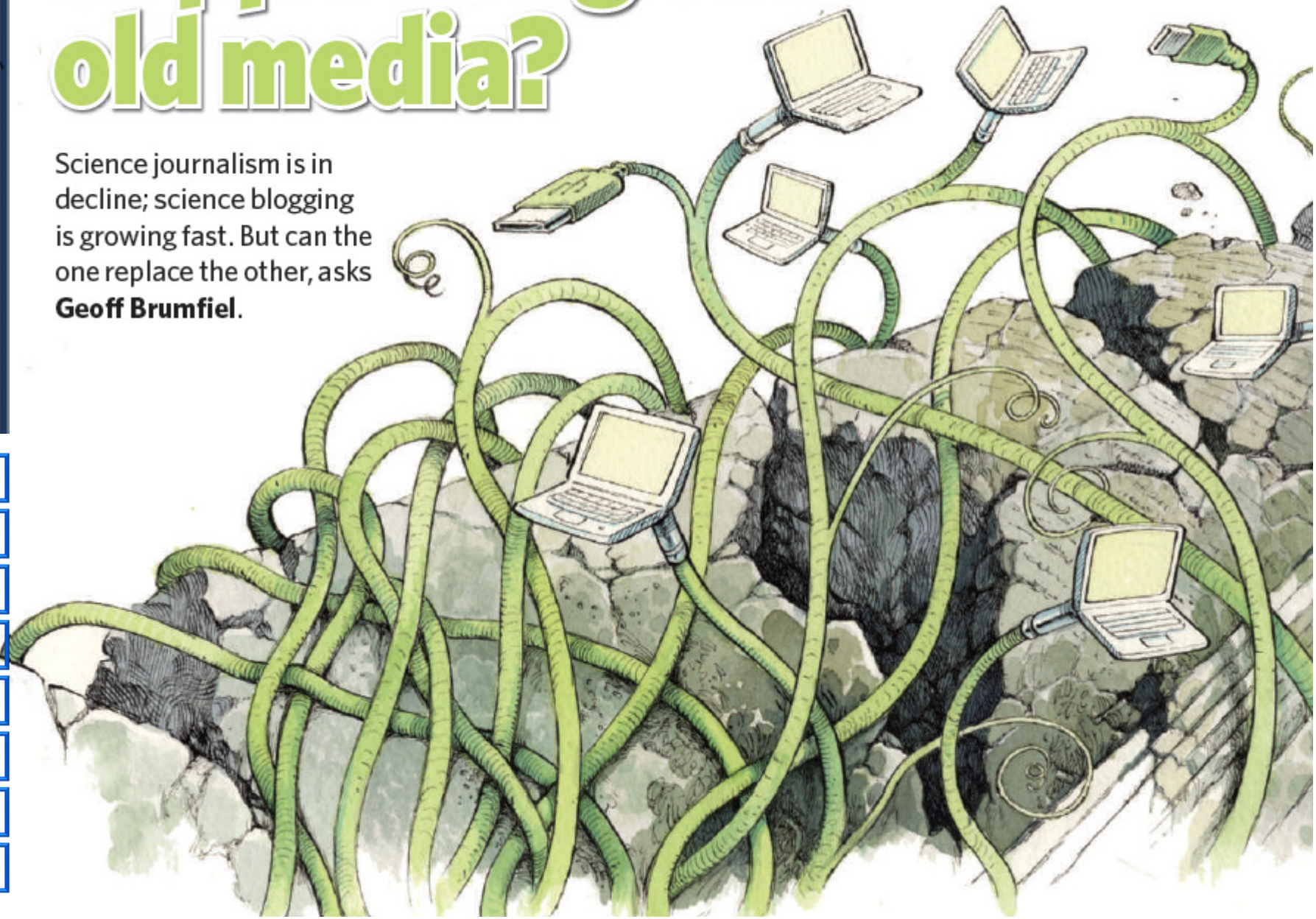
- Bruce A.Weinberg (Dept. of Economics, Ohio St. Un.) & Benjamin F. Jones (Northwestern Un.) estudaram os ganhadores do Prêmio Nobel (525 em 555) de física (182), química (153) e medicina (190) entre 1901 e 2008 (E 835): criatividade e variabilidade;
- < 1905 *ca.* >60% tinham *ca*. 30y (física 1934 = quântica)
  > 1980 *ca.* <19% tinham 40y
- expansão do conhecimento científico, no início do século 20 doutorava-se aos ~26 anos; < teóricos;
- *Quanto conhecimento se precisa ter, em uma área, para fazer-se contribuições científicas relevantes* ?

* Física.net

Nature **2009**, *458*, 274

Supplanting the old media?

Science journalism is in decline; science blogging is growing fast. But can the one replace the other, asks **Geoff Brumfiel**.



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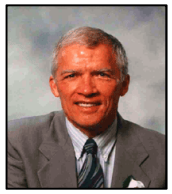
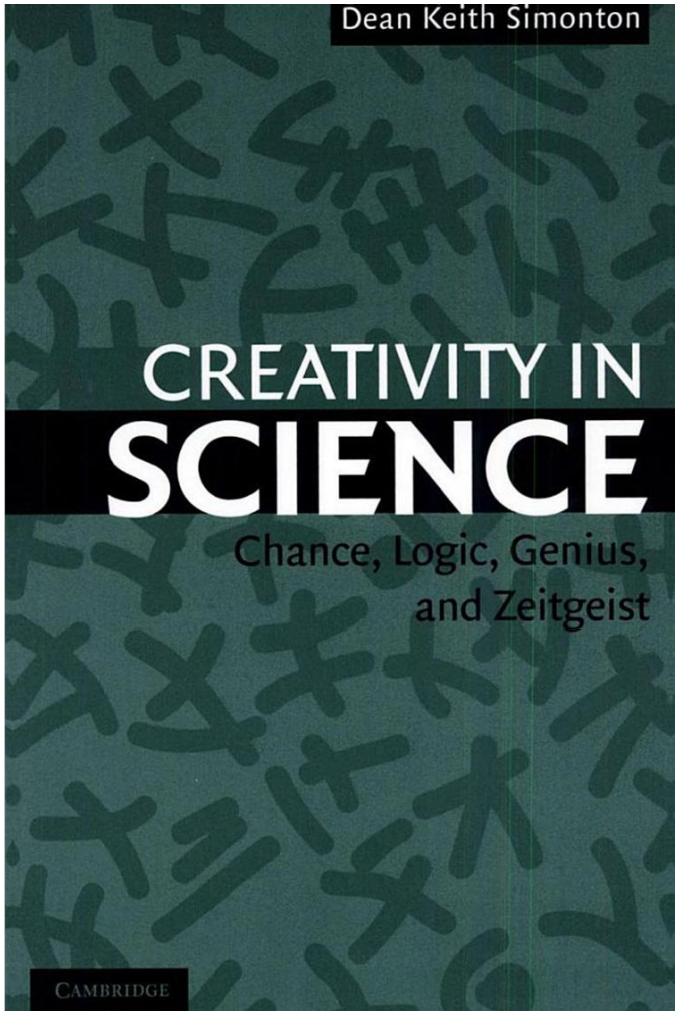


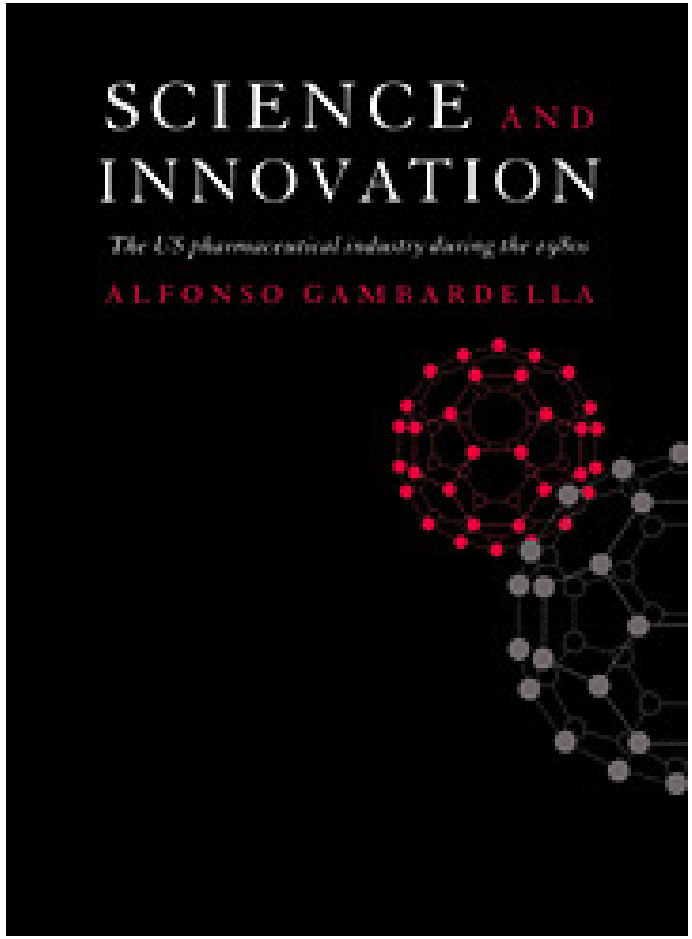
SC=In



Cambridge University Press,
Cambridge UK, 1995

Collaboration Creativity Commercialisation Curiosity Challenging Competitive

=



*S*cience & *C*riativity = *Im*novation!

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D3

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Os medicamentos foram uma das *maiores* invenções do século 20 !

A Química Medicinal

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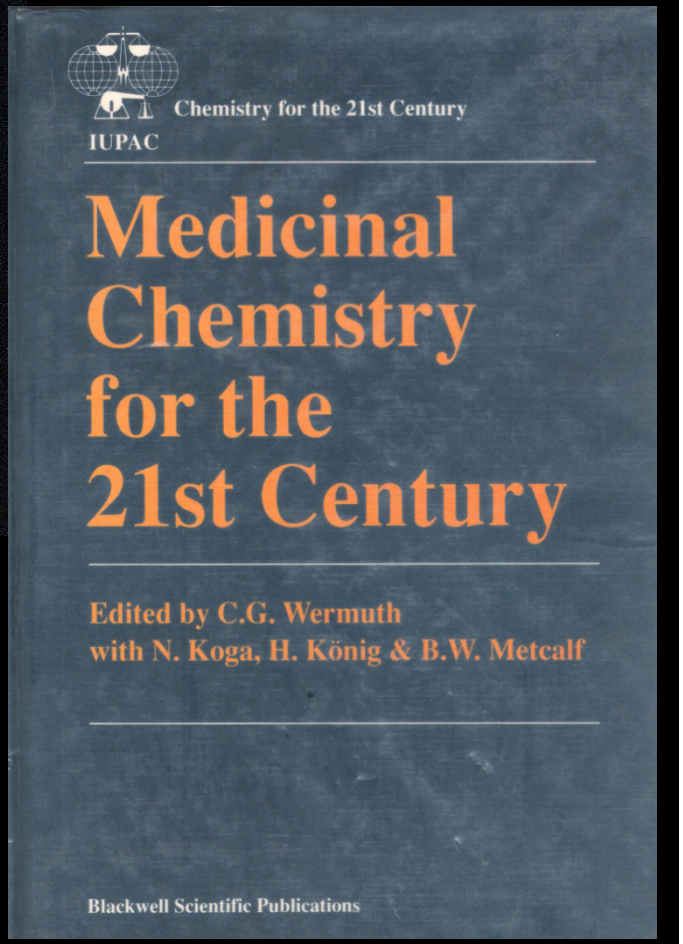
Século 21

Siglo 21

21st Century



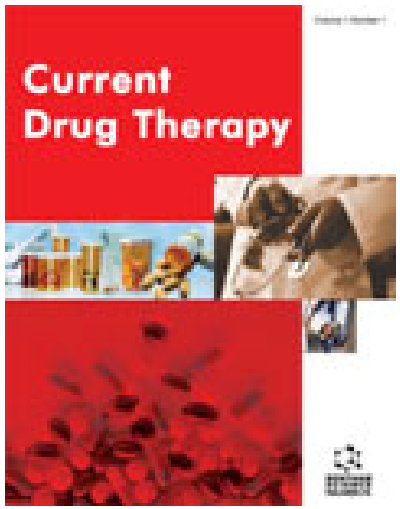
New Insights for Multifactorial Disease Therapy: The Challenge of the Symbiotic Drugs

Eliezer J. Barreiro and Carlos Alberto Manssour Fraga

Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, P.O. Box 68023, 21944-971, Rio de Janeiro, RJ, Brazil.

Abstract: Some physiopathological processes involved in the genesis of diseases could suggest the necessity of designing bioligands or prototypes that aggregate, in only one molecule, dual pharmacodynamical properties, becoming able to be recognized by two elected bioreceptors. This approach can have distinct aspects and, when a novel ligand or a prototype acts in two elected targets belonging to the same biochemical pathway, *e.g.* arachidonic acid cascade, it receives the denomination of dual or mix agent. On the other hand, if these two targets belong to distinct biochemical routes and both are related to the same disease, we can characterize the agents able to modulate it as symbiotic ligands or prototypes. In the present work, we provide some examples and applications of the molecular hybridization concept for the structural design of new symbiotic ligands and prototypes, especially those applied in the treatment of chronic-degenerative disorders.

Key Words: Symbiotic drugs; molecular hybridization; multifactorial diseases; therapeutic innovation; drug design; dual compounds.

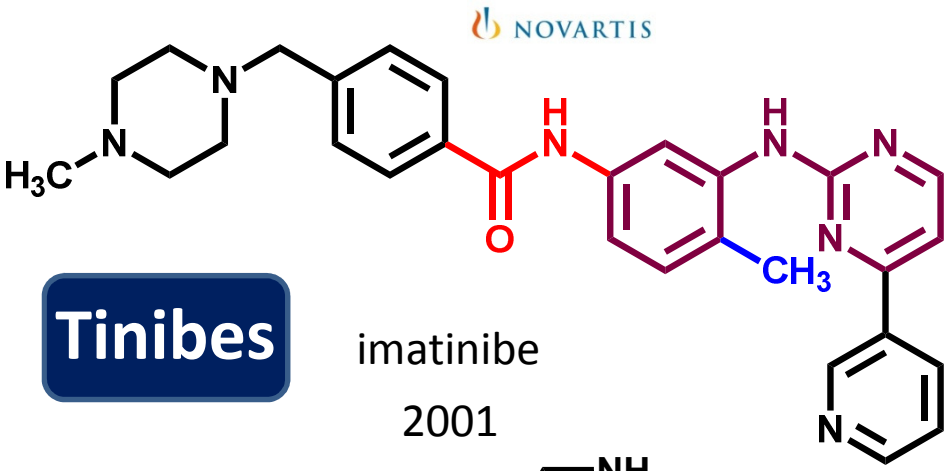


Fármacos simples, não curam doenças complexas!

Fármacos do século 21

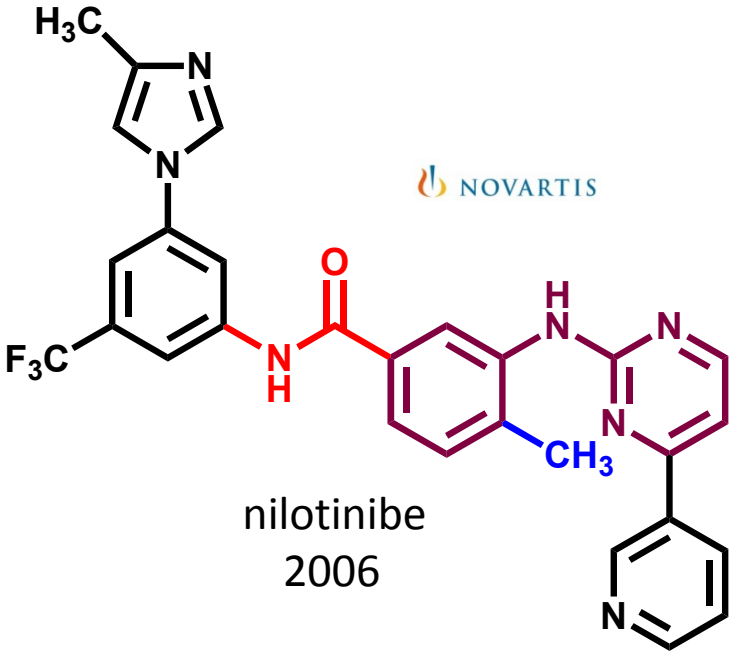
Universidade Federal do Rio de Janeiro

Tinibes



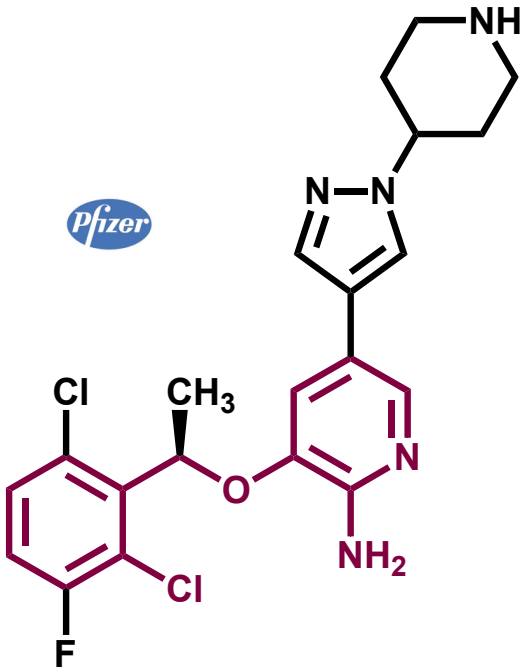
imatinibe

2001



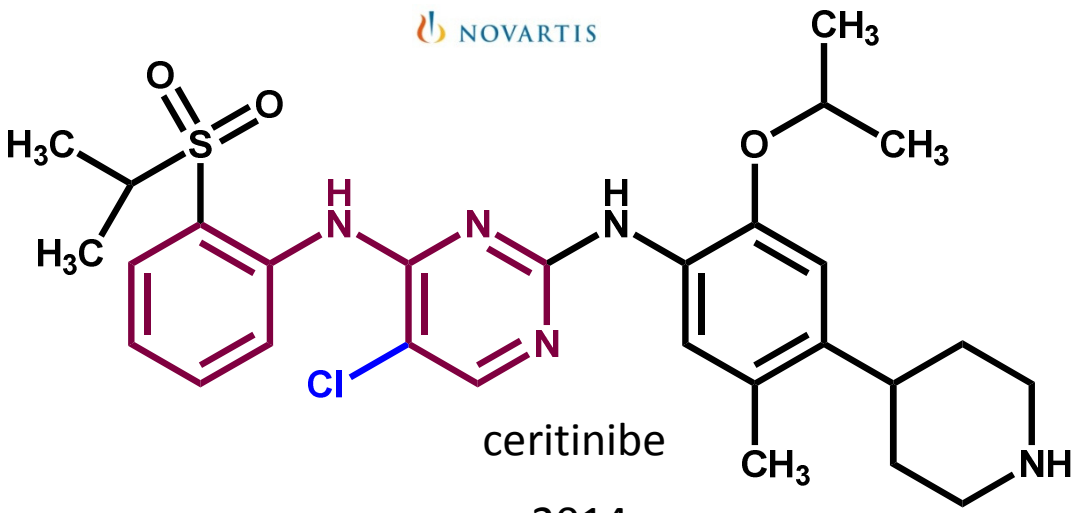
nilotinibe

2006



crizotinibe

2011



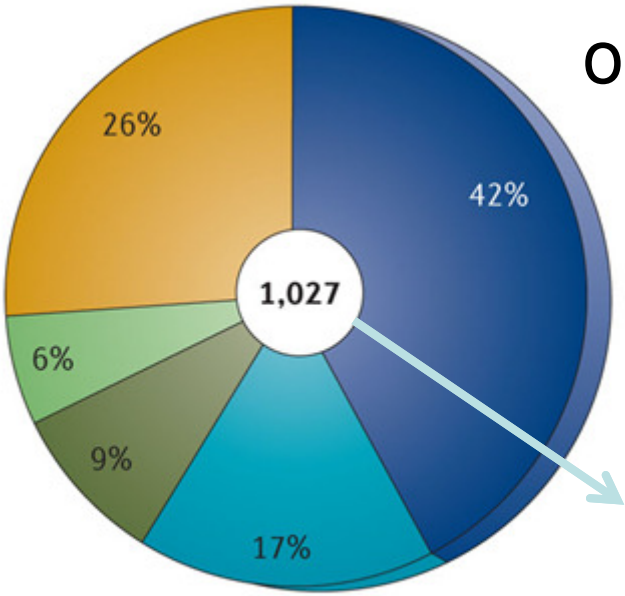
ceritinibe

2014

Novelty in the target landscape of the pharmaceutical industry*

P. Agarwal, P. Sanseau, L. R. Cardon

Nature Rev. Drug Discov. **2013**, *12*, 575–576



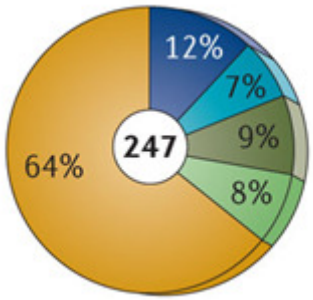
A percentagem dos alvos foi tabulada pelo número de empresas que estão estudando-os (considerando apenas *h*-alvos)

Número total de alvos estudados em programas de pesquisa nas empresas farmacêuticas

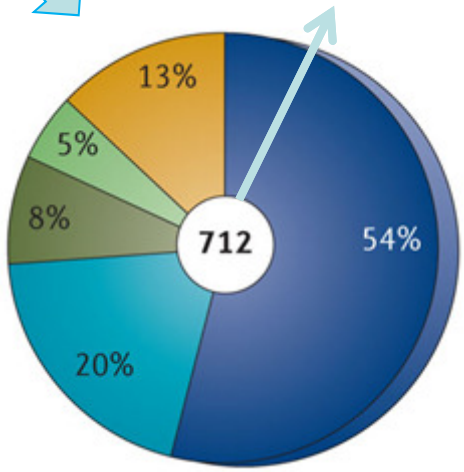
Alvos estudados por muitas organizações

β-sítio da APP-clivagem enzima 1 (BACE1), α7-nAChR, GPR119, mGluR5, H_3R, microtúbulo associado a PTN tau (MAPT)

Alvos estudados por 5 ou mais organizações



247 são alvos "<u>comprovados</u>" (que tem fármaco no mercado)



712 são alvos "<u>novos</u>" (sem fármacos no mercado)

* Pfizer, J& J, Novartis, Bayer, Roche, Merck, Sanofi, GSK, Abbott, AZ,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Medicinal
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fascinante!

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Minicursos

25-29 de janeiro de 2016

Inscrições 01/09/2015

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LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas
2016
Muito obrigado
pela atenção!
Praia do Boqueirão, Saquarema, RJ
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