

As Ciências Farmacêuticas dos Fármacos & a Química Medicinal



I Seminário de Ciências Farmacêuticas, UFJF/Campus de Governador Valadares, MG



Eliezer J. Barreiro



Universidade Federal do Rio de Janeiro

Professor Titular

Laboratório de Avaliação e Síntese de Substâncias Bioativas

Química
med
Medicinal
chem



www.farmacia.ufrj.br/lassbio

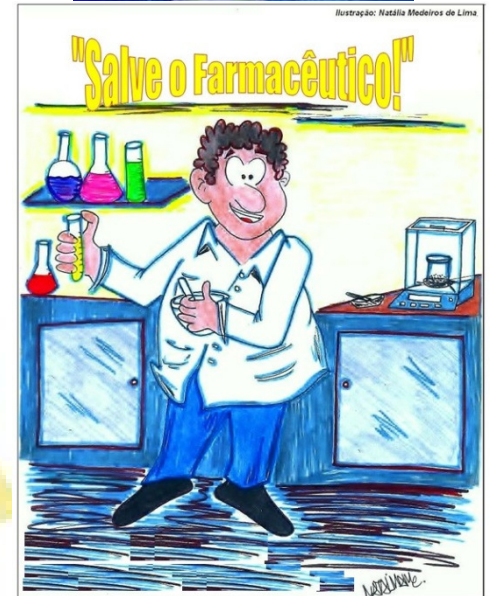


S U M Á R I

- As Ciências Farmacêuticas através dos tempos
- Os idos tempos da farmacognosia...
- A importância dos fármacos e medicamentos
- O *berço* da Química Medicinal
- A complexa interdisciplinaridade da cadeia de inovação em fármacos e medicamentos
- Química Medicinal: Como *nascem* os fármacos?
- A inovação farmacêutica e o conhecimento científico
 - AAS, penicilina e propranolol: fármacos marcantes
- Uma invenção bilionária: as estatinas
- Como agem os fármacos?
- Os fármacos do século 21: multi-alvos
- Os inibidores de tirosina-quinase: os tinibes
 - Um breve exemplo de “*casa*”
- Considerações finais



As Ciências Farmacêuticas



AS Ciências Farmacêuticas

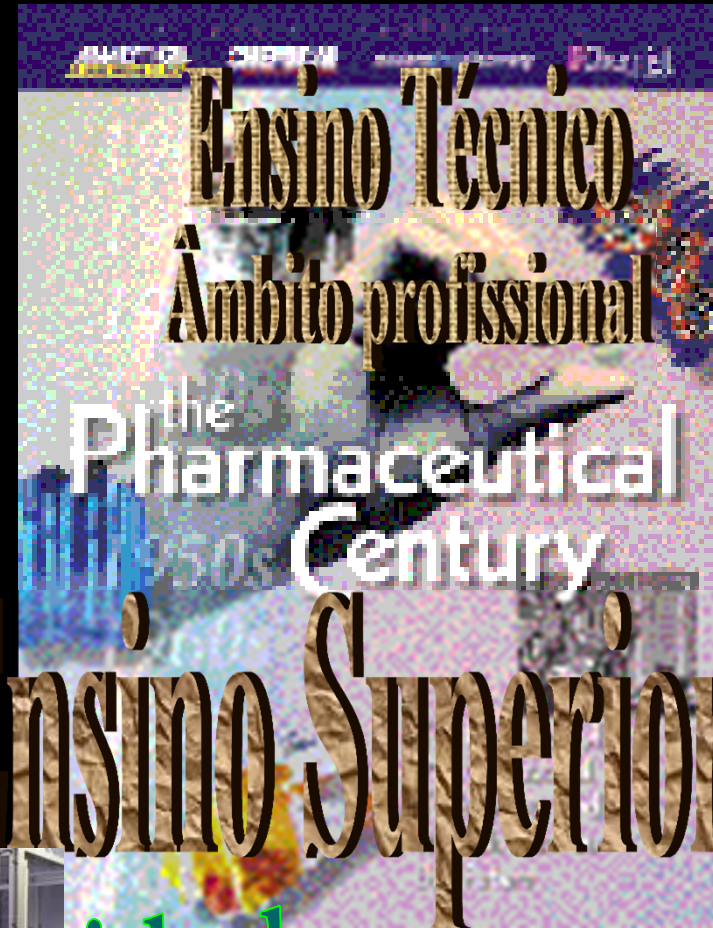


Século 21

Siglo 21

21th Century

Siècle 21



Interdisciplinaridade





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Os idos tempos da Farmacognosia...

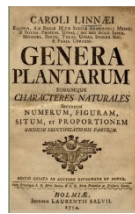


Antoine Laurent de Jussieu
1748-1832

Os vegetais e sua
"ordem admirável"

1811

Farmacognosia



1789



François Magendie
1783-1855



Formulaire
1827

Fisiologia experimental



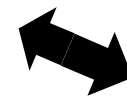
Farmacologia



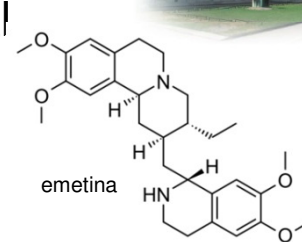
Pierre-Jean Robiquet
1780-1840



Joseph B Caventou
1795-1877



alcalóides

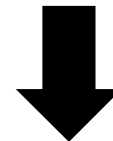


Pierre Joseph Pelletier
1788-1842



1788-1842

Substâncias puras



Fitoquímica



Química de PN

é uma ciência multidisciplinar que contempla o estudo das propriedades físicas, químicas, bioquímicas e biológicas dos fármacos ou dos fármacos potenciais de origem natural assim como busca novos fármacos a partir de fontes naturais (Soc. Bras. Farmacognosia)



Declaração da Cúpula do Milênio da Nações Unidas

Nova Iorque, 6 a 8 de setembro de 2000



O Projeto do Milênio

Secretaria-Geral das Nações Unidas em 2002

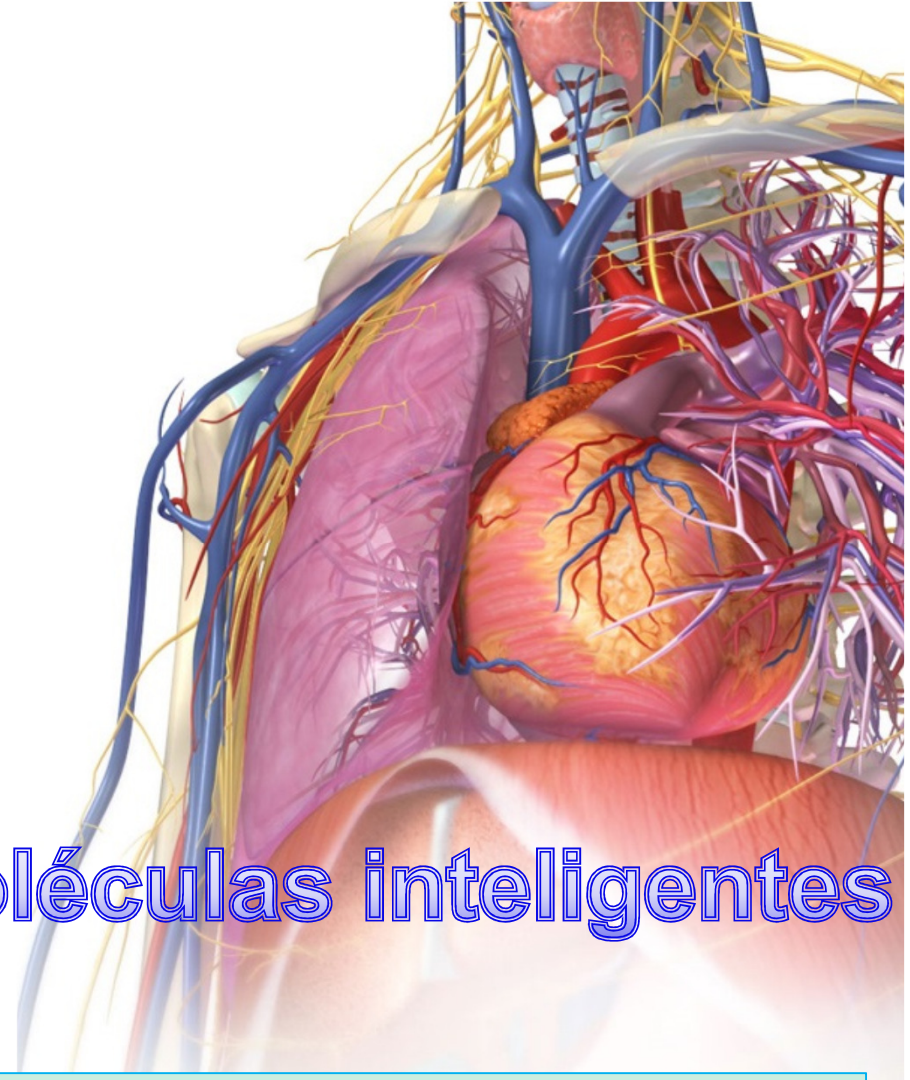
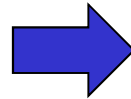


2015



“...Países em desenvolvimento provavelmente continuarão imersos na pobreza, a menos que possam fazer o que países desenvolvidos fizeram para atingir o crescimento sustentável: **incorporar ciência, tecnologia e inovação** em suas estratégias econômicas ...”

A complexidade da fisiologia...



Os fármacos são moléculas inteligentes



Os medicamentos foram uma das maiores invenções do século 20

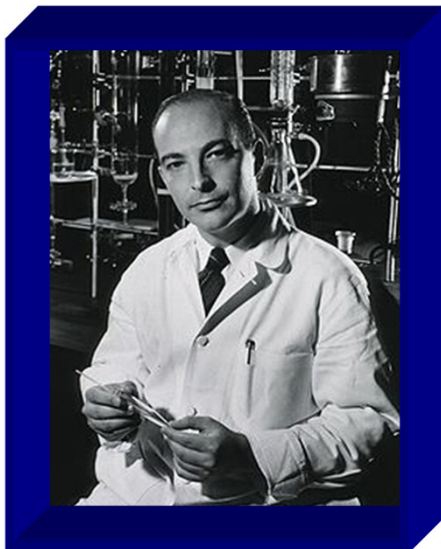




interdisciplinaridade

Farmacognosia
Biofísica Bioquímica Genética
Parasitologia Síntese Orgânica Enzimologia
Química Geral Espectroscopia Computação Física
Bioinformática Toxicologia Imunologia Fitoquímica
Farmacotécnica Química Analítica Físico-Química
Biologia estrutural Química Geral Química Orgânica
Bioinorgânica Química Inorgânica Fisiologia
Bioestatística Microbiologia Biologia molecular
Farmacogenômica Cálculo Química Computacional
Bioorgânica Farmacologia





Arthur Kornberg
1918-2007

FOR
MAN

Prêmio Nobel, 1959



The Two Cultures: Chemistry and Biology¹

Arthur Kornberg

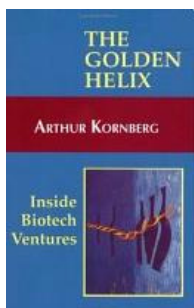
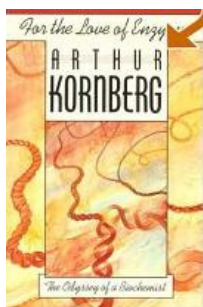
Department of Biochemistry, Stanford University, Stanford, California 94305

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...

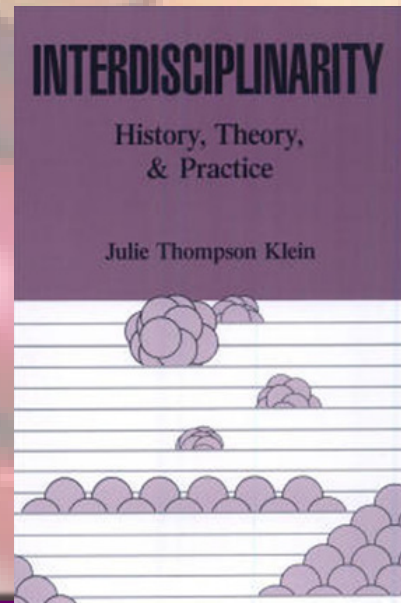


Química Medicinal was until recently the bastion of organic chemistry... in the search for alternative or superior drugs for the treatment of various diseases...”



Biochemistry 1987, 26, 6888-6891

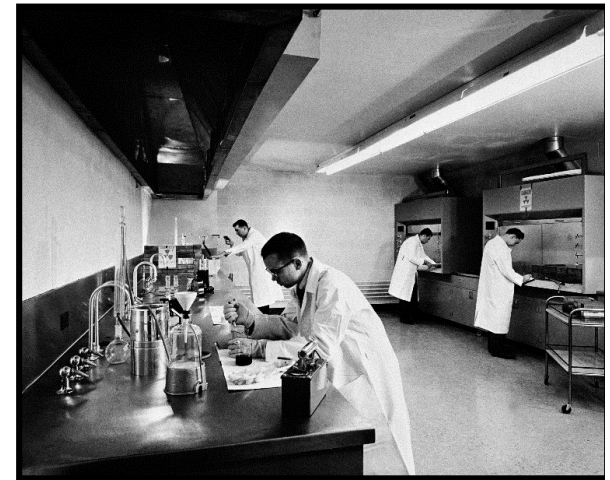
A **interdisciplinaridade**
exige novos arranjos institucionais
& temporais para adequada
qualificação profissional !



A cadeia de inovação em fármacos é complexa e interdisciplinar!

Formação científica....

Existem fortes e inúmeras evidências de que a formação científica do atual universitário, está apequenando-se de mais a mais, com perdas das características de curso superior de base científica, para tornar-se curso de nível técnico!





Como se inventa uma molécula?



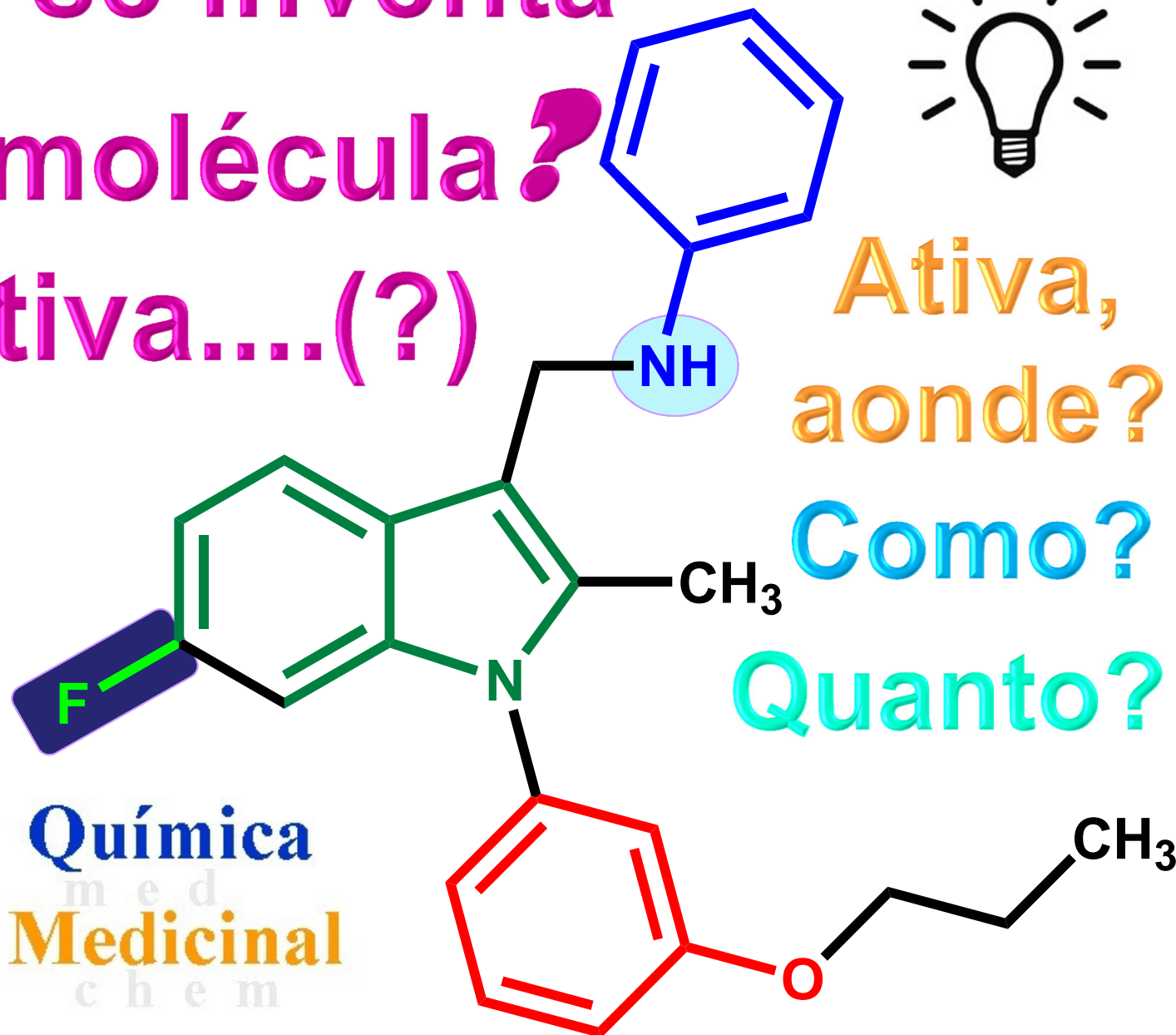
Bioativa....(?)

Ativa,
aonde?

Como?

Quanto?

S
O
C
N
X
H



Química
med
Medicinal
chem



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THE ROLE OF THE MEDICINAL CHEMIST IN DRUG DISCOVERY — THEN AND NOW

Química Medicinal

Joseph G. Lombardino* and John A. Lowe III[‡]



Joseph G. Lombardino



2011- ACS Award in Industrial Chemistry (ziprazidone)



“ ...medicinal chemists

today live in exciting times...

their work can have a beneficial effect on millions of suffering patients – surely an important motivating factor for any scientist...”

Joseph G. Lombardino & John A. Lowe, III

The Role of the Medicinal Chemist in Drug Discovery – Then and Now,

Nature Rev. Drug Disc. **2004**, 3, 853.





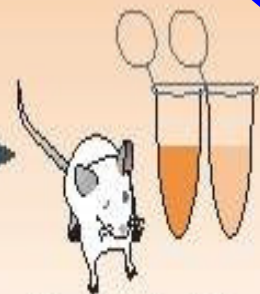
Preclinical studies



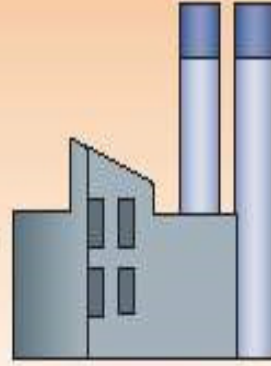
Research team formed and objectives set



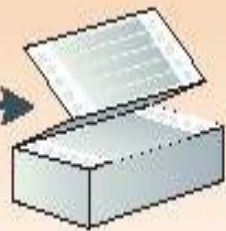
Novel chemicals synthesized



Chemicals tested for efficacy and safety in test tubes and animals. Results used to choose drug candidate.



Formulation, stability scale-up synthesis, chronic safety in animals



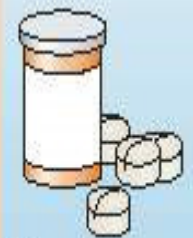
Company files Investigational New Drug (IND) application with FDA

Química Medicinal

Clinical studies



O processo de descoberta/invenção & desenvolvimento de fármacos é complexo...



Drug is approved for marketing

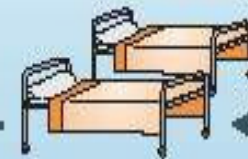
ANVISA

FDA

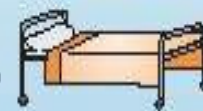
FDA reviews NDA



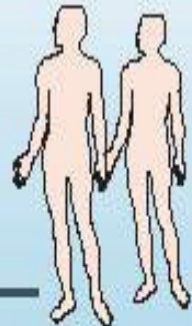
Company files New Drug Application (NDA)



Phase III: large clinical trials in many patients



Phase II: studies in patients (efficacy)



Phase I: studies in healthy humans (toleration)



O berço da Química Medicinal



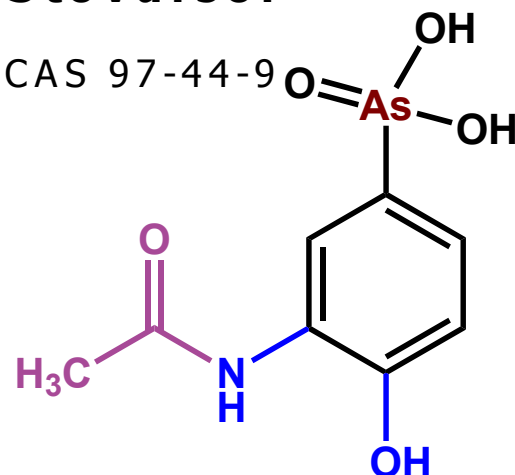
Ernest Fourneau
1872-1949

[Biografia de Fourneau](#)



Stovarsol

CAS 97-44-9



Institut Pasteur (1887)



1911- Laboratoire de Chimie Thérapeutique

Institut Pasteur (Pierre Paul Emile Roux)

1^o *paper* sobre SAR
Curare and Curare-like Agents.

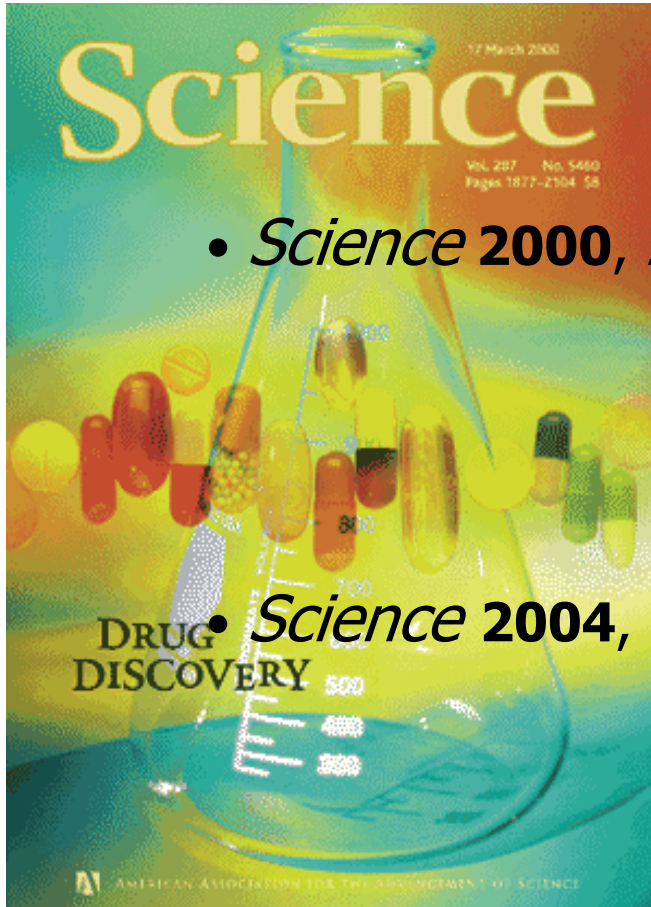
Prêmio Nobel de
Fisiologia/Medicina
1957



Daniel Bovet
1907-1992 *
Sulfonamidas,
anti-histamínicos.



A inovação farmacêutica...



- *Science* **2000**, 287, 1951 (J. Uppenbrink, J. Mervis)



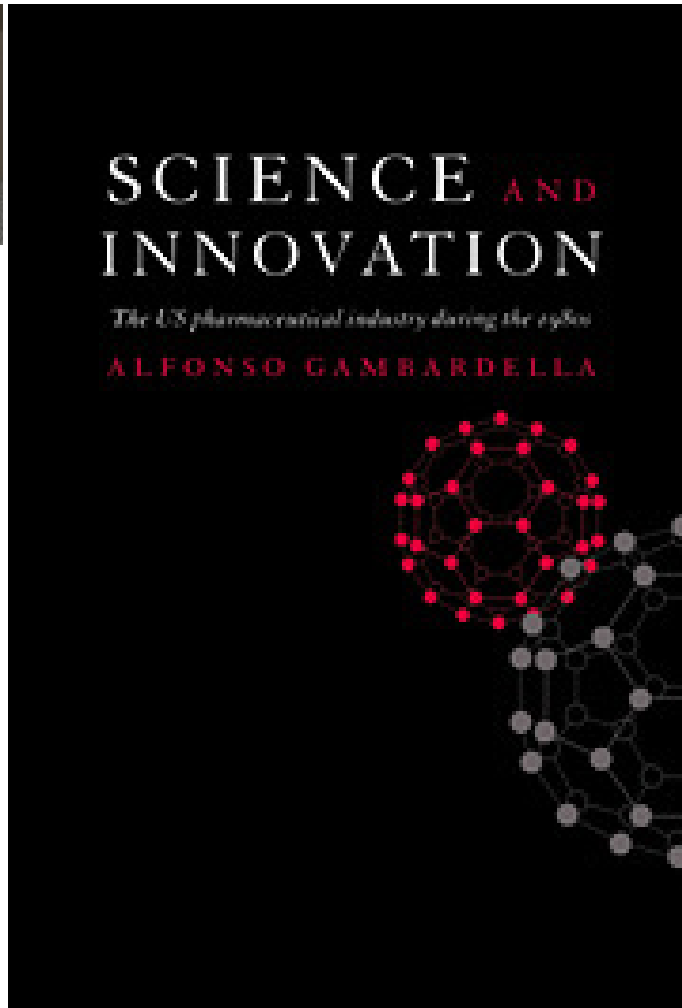
- *Science* **2004**, 303, 1713 (D. Kennedy)



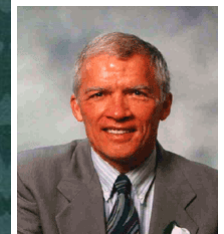
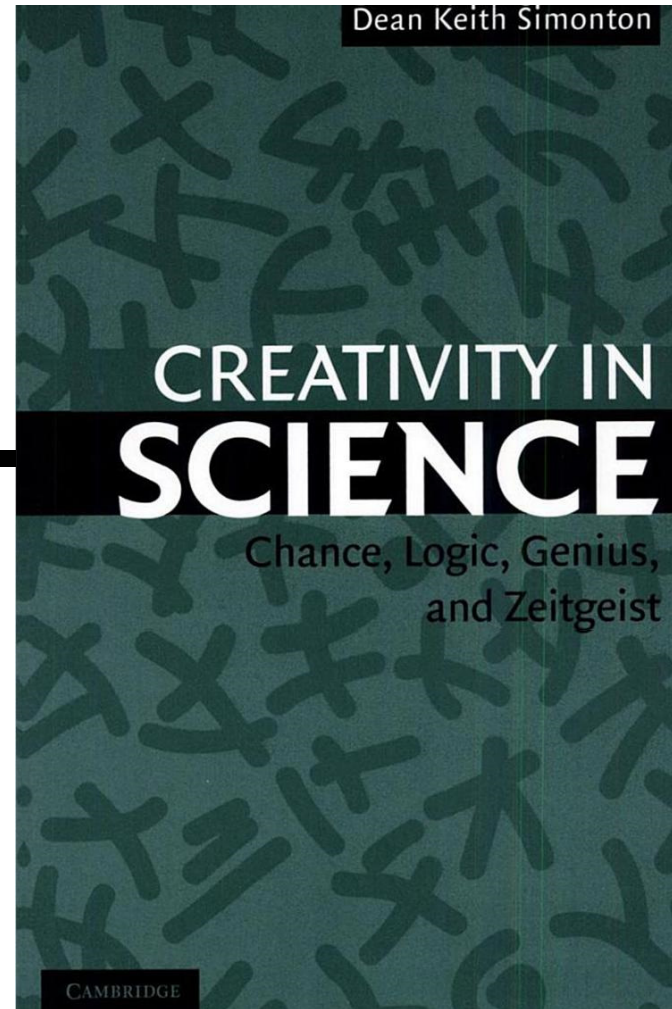
...depende do conhecimento científico!



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Cambridge University Press,
Cambridge UK, 1995



Ciência & Criatividade = Inovação !

Os fármacos e o Nobel !

1982



John R. Vane
(1927-2004)

http://nobelprize.org/nobel_prizes/medicine/laureates/1982/vane-autobio.html



Sune K. Bergström

(1916-2004)

http://nobelprize.org/nobel_prizes/medicine/laureates/1982/bergstrom-autobio.html

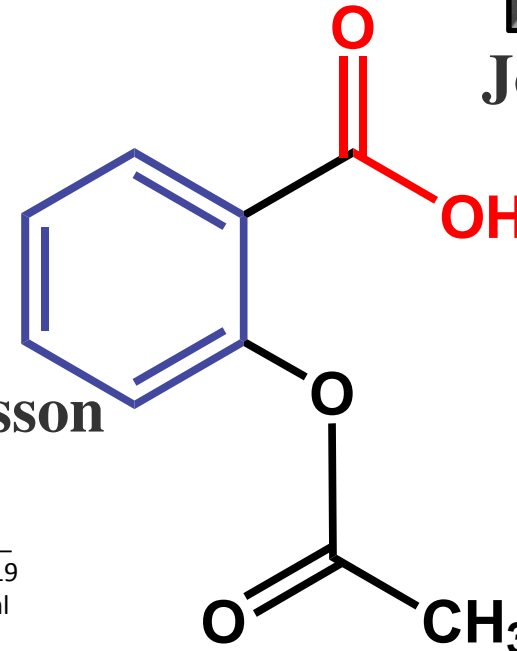


Bengt I. Samuelsson

(1934-)

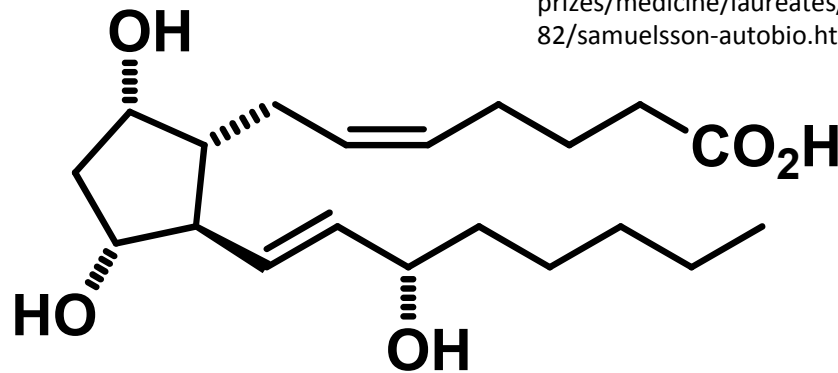
http://nobelprize.org/nobel_prizes/medicine/laureates/1982/samuelsson-autobio.html

Ácido acetilsalicílico



$C_9H_8O_4$

AAS



Prostaglandina $F_{2\alpha}$

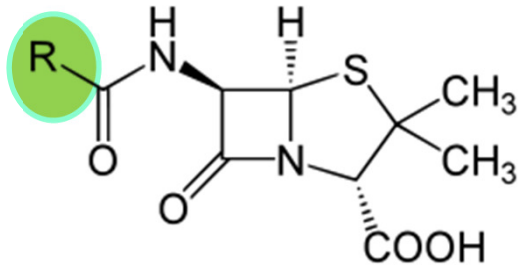
1889 ➡ 1982

Molécula salva-vidas...

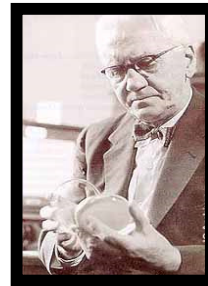
Antibióticos β-lactâmicos



- 1877 – L. Pasteur
- 1897 - Ernest Duchesne, Lyon
- 1928 – A Fleming, Londres
- 1939 – Florey & Chain
- 1943 – RB Woodward, R Robinson
- 1945 - Dorothy C. Hodgkin
- 1948 – Patente de processo
- 1957 – John Sheehan, MIT



Penicilina



Alexander Fleming

1881-1955



Howard W. Florey

1898-1968



Dorothy C. Hodgkin

1910-1994

MD Vargas, *Rev Virtual Quim* **2012**, 4, 85

antibioticoterapia

O acaso ajuda a sorte



Fungos



E. Boris Chain

1906-1979

1945



1964



EB Chain *et al.*,
Lancet **1940**, 2, 226



Inovações farmacêuticas marcantes

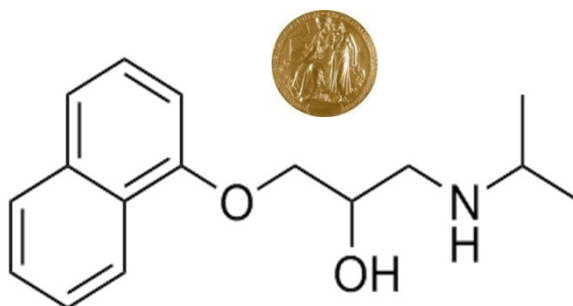
Século XX

1964

propranolol
 cimetidina
 captopril
 omeprazola
imatinibe

paclitaxel
 lovastatina
 penicilina

1942



Química
 medicinal
 Medicinal
 chem

Paradigma inicial

Mono-alvo

século XX

século XXI

2011

crizotinibe

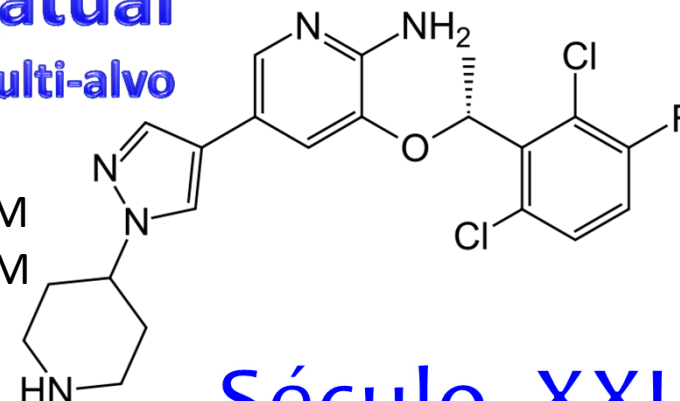
Paradigma atual

Multi-alvo

Inibidor duplo

C-MET TK $IC_{50} = 8 \text{ nM}$

ALK $IC_{50} = 20 \text{ nM}$



AT Shaw, U Yasothan, P Kirkpatrick,
 Crizotinib, *Nature Rev Drug Discov*
 2011, 10, 897

Século XXI



EJ Barreiro, CAM Fraga, New Insights for multifactorial disease therapy: the challenge of multifactorial drugs, *Curr Drug Therapy* 2008, 3, 1; JL Medina-Franco, MA Giulianotti, GS Welmaker, RA Houghten, Shifting from the single to the multitarget paradigm in drug discovery, *Drug Discov Today* 2013, 18, 495;



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Am J Physiol 1948, 153, 586



Raymond Ahlquist (1914)

A STUDY OF THE ADRENOTROPIC RECEPTORS

RAYMOND P. AHLQUIST

From the Department of Pharmacology, University of Georgia School of Medicine

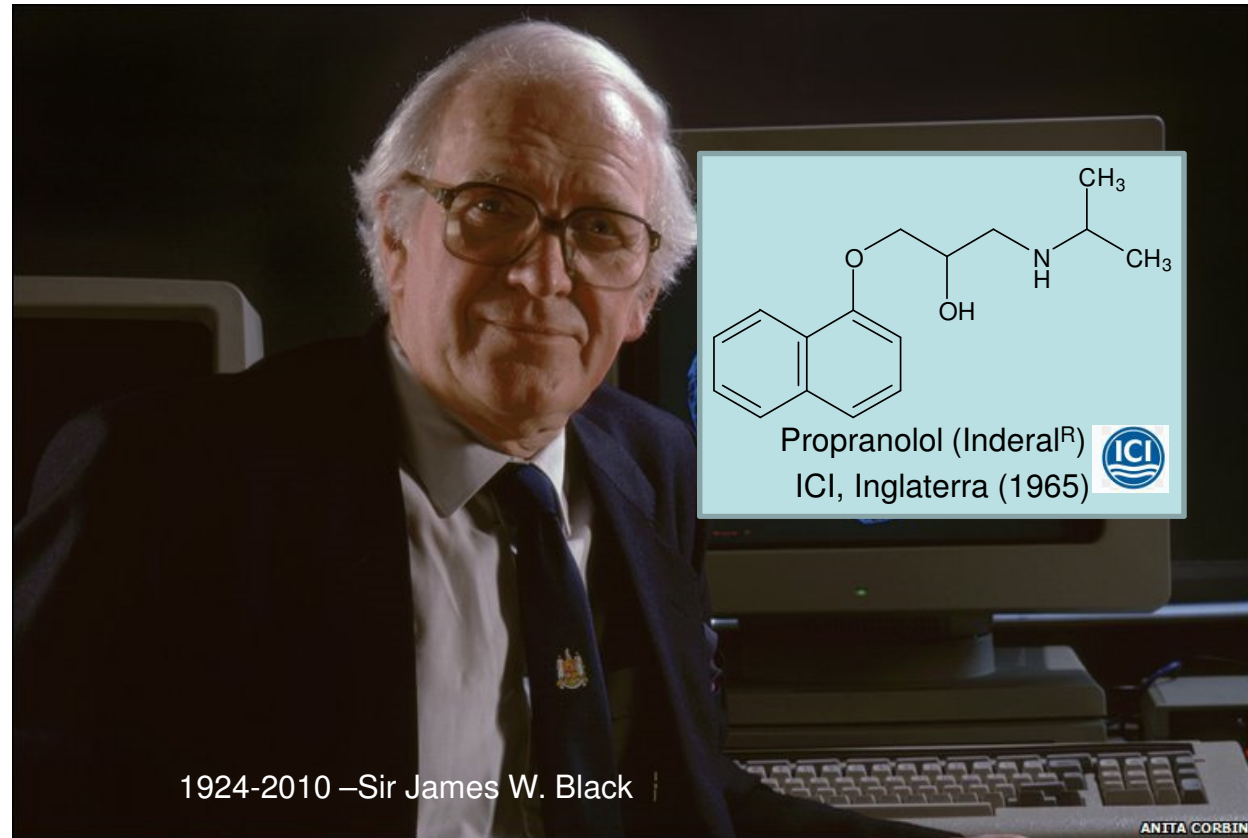
AUGUSTA, GEORGIA



1905 – Henry Dale



**Premio Nobel
1988**



1924-2010 – Sir James W. Black

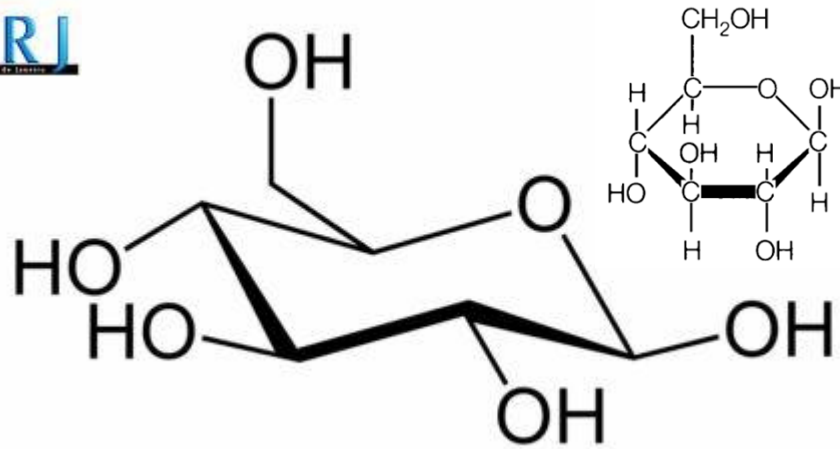
ANITA CORBIN

R Ganellin, W Duncan, Obituary James Black (1924-2010), *Nature* **2010**, 464, 1292; CPPage, J Schaffhausen, NP Shankley, The scientific legacy of Sir James W. Black, *TIPS* **2011**, 32, 181;



Como agem os fármacos



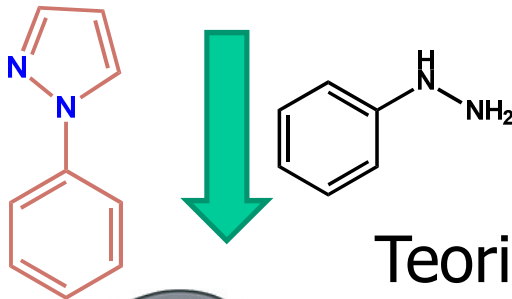
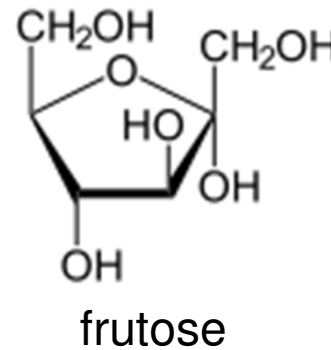


The Nobel Prize in Chemistry 1902
Emil Fischer



Emil Fischer
1852-1919

Glicose



Teoria da chave-fechadura

Complementaridade molecular

Reconhecimento molecular

Interação fármaco-biorreceptor



Química Medicinal





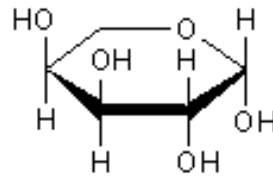
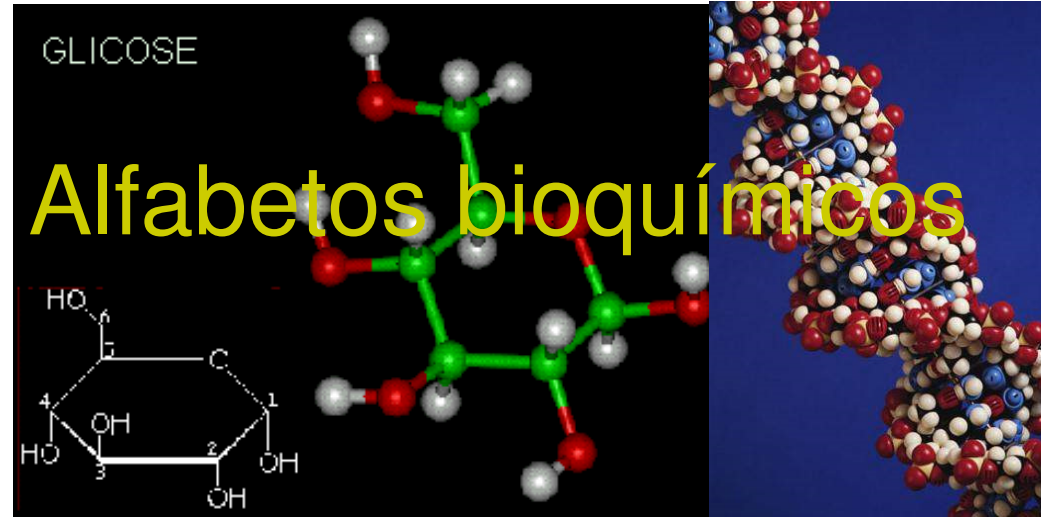
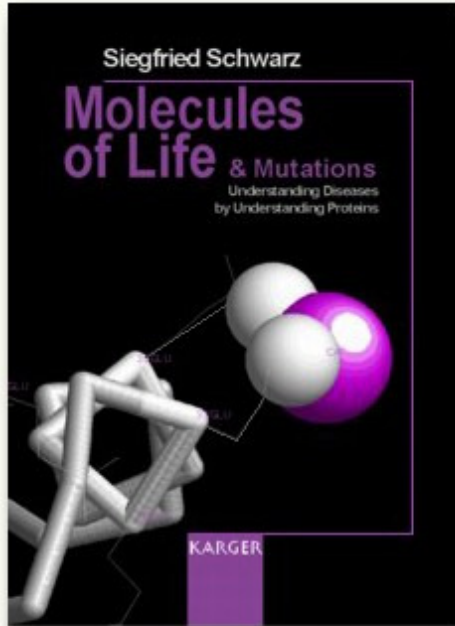
Os fármacos atuam em alvos terapêuticos...

Química Medicinal

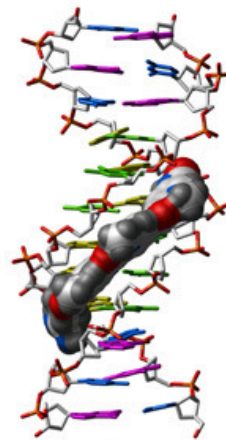
... os biorreceptores.



* J. Drews, "Editorial: What's in a number?", *Nature Rev. Drug Discov.* **2006**, *5*, 975;
J. Drews & S. Ryser, Classic drug targets, *Nature Biotechnol.* **1997**, *15*, 1318;
& J.P. Overington, A-L Bissan & A.L. Hopkins, *Nature Rev. Drug Discov.* **2006**, *5*, 993;
Estes autores estimam em 324 os biorreceptores de todos os fármacos contemporâneos.



β -L-Arabinose



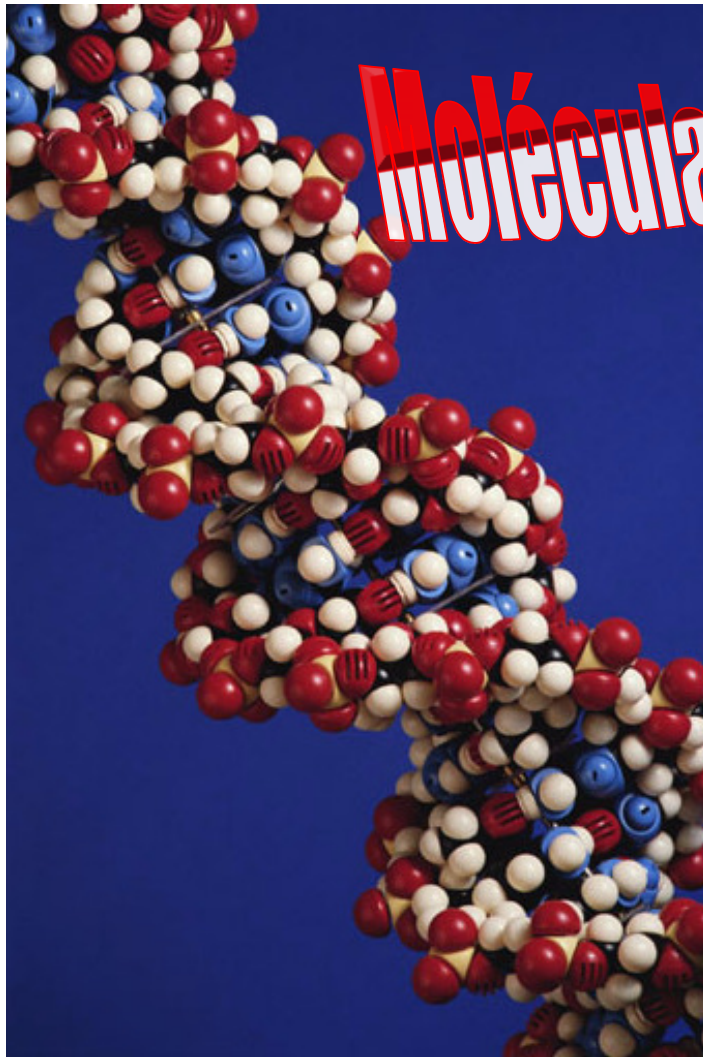
Model Compound Bound to the Minor Groove of a DNA Molecule

Carboídratos

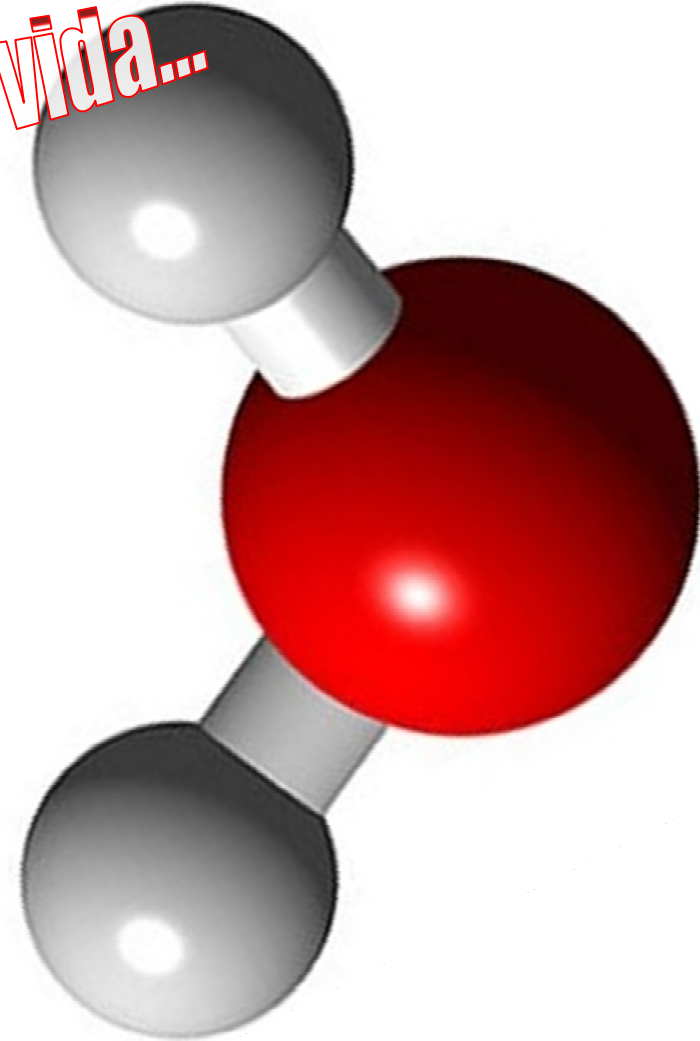
Lipídeos

ácidos nucleícos

proteínas

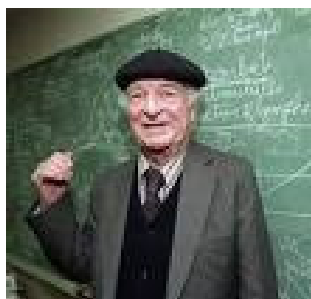
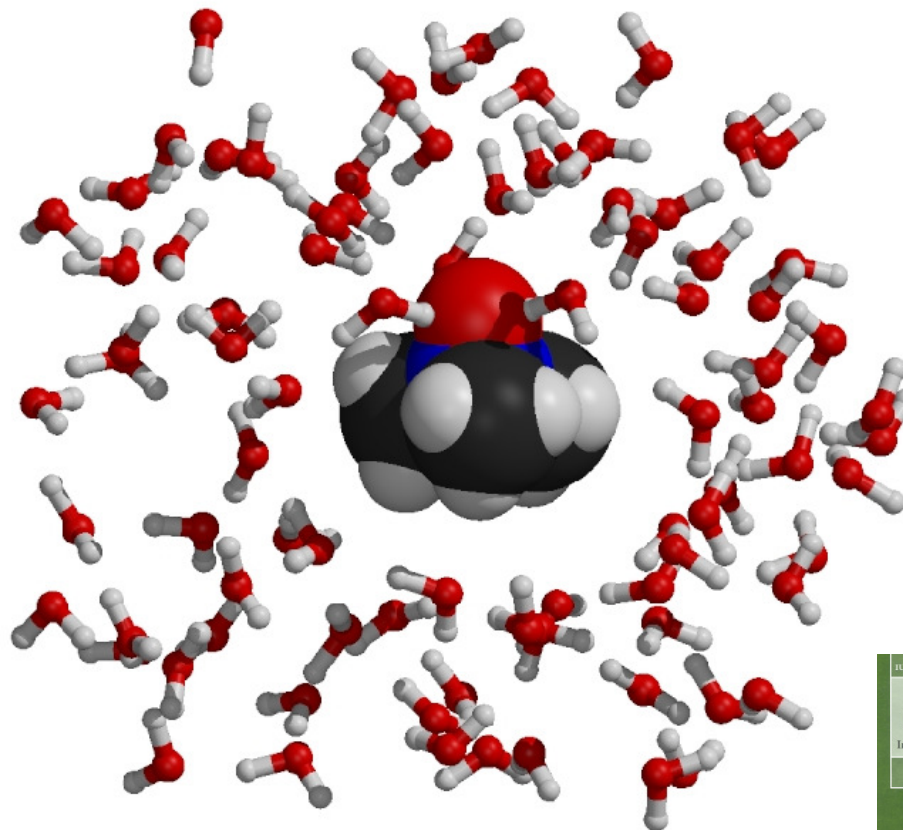
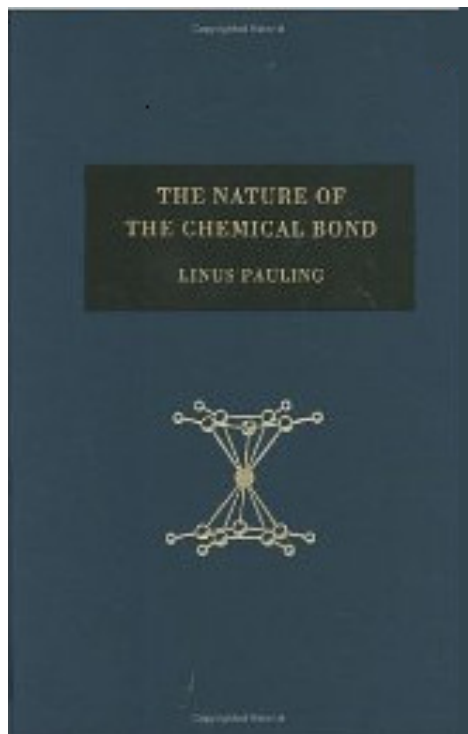


Moléculas da vida...



O que têm em comum?

A importância das “ligações” frágeis...

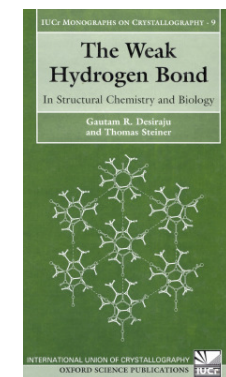


Linus C. Pauling
1901-1994

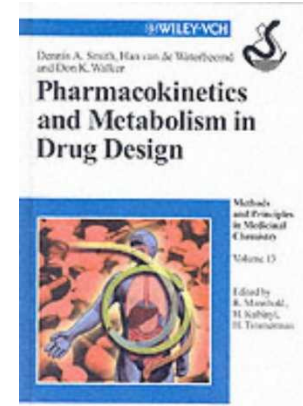
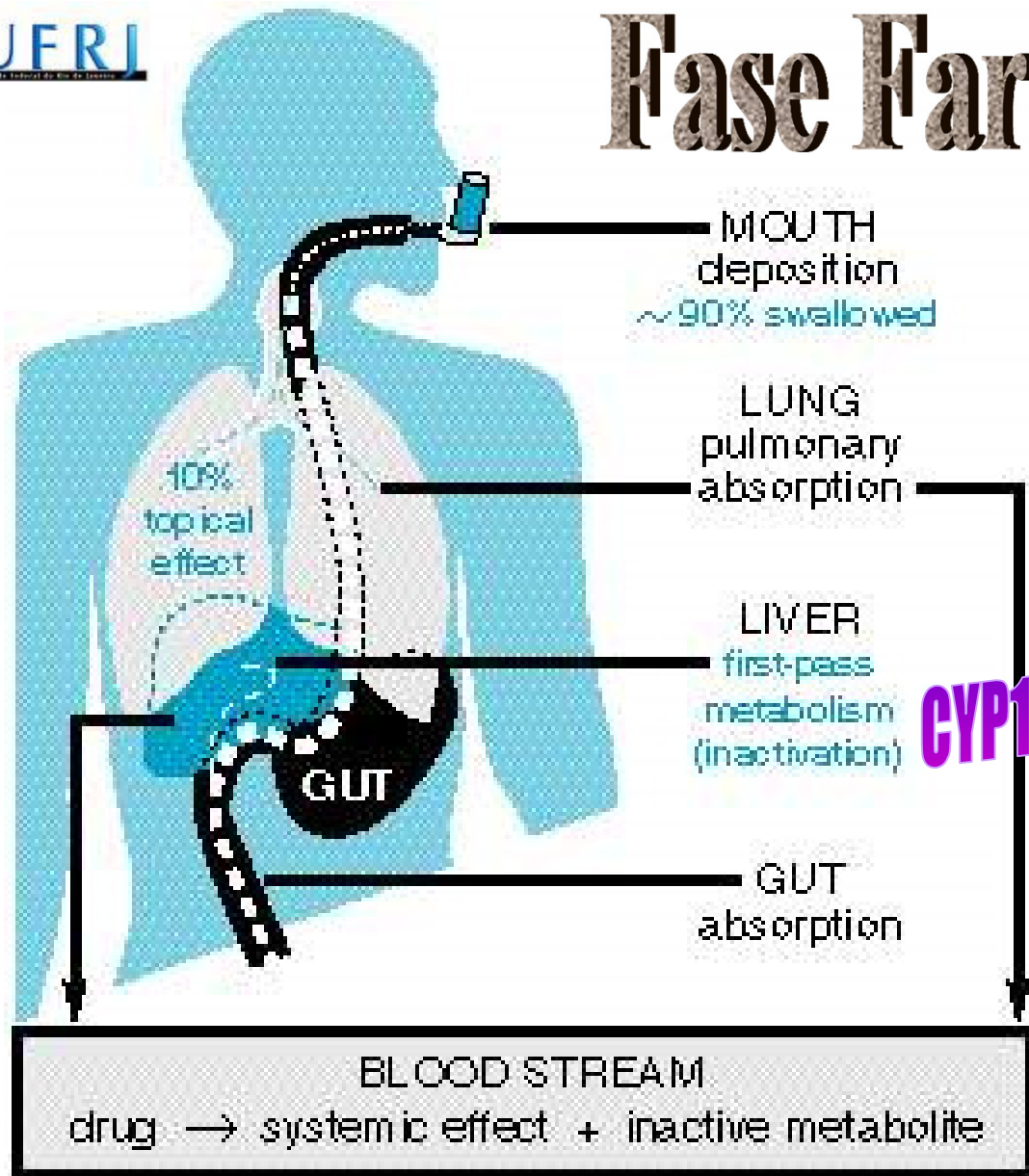
1954, 1962



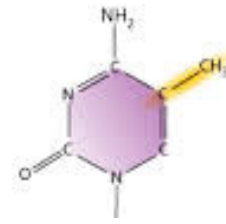
“ligações”
de hidrogênio ...



Fase Farmacocinética



CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4

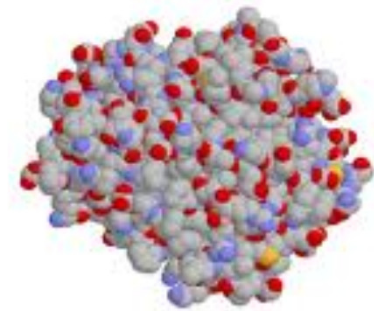
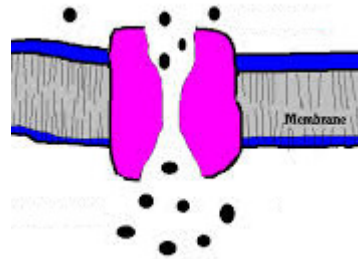
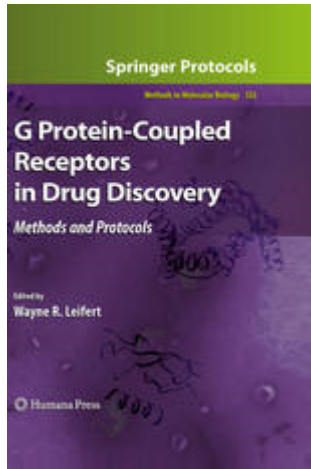
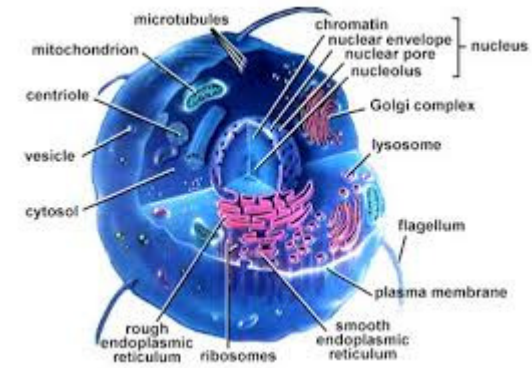
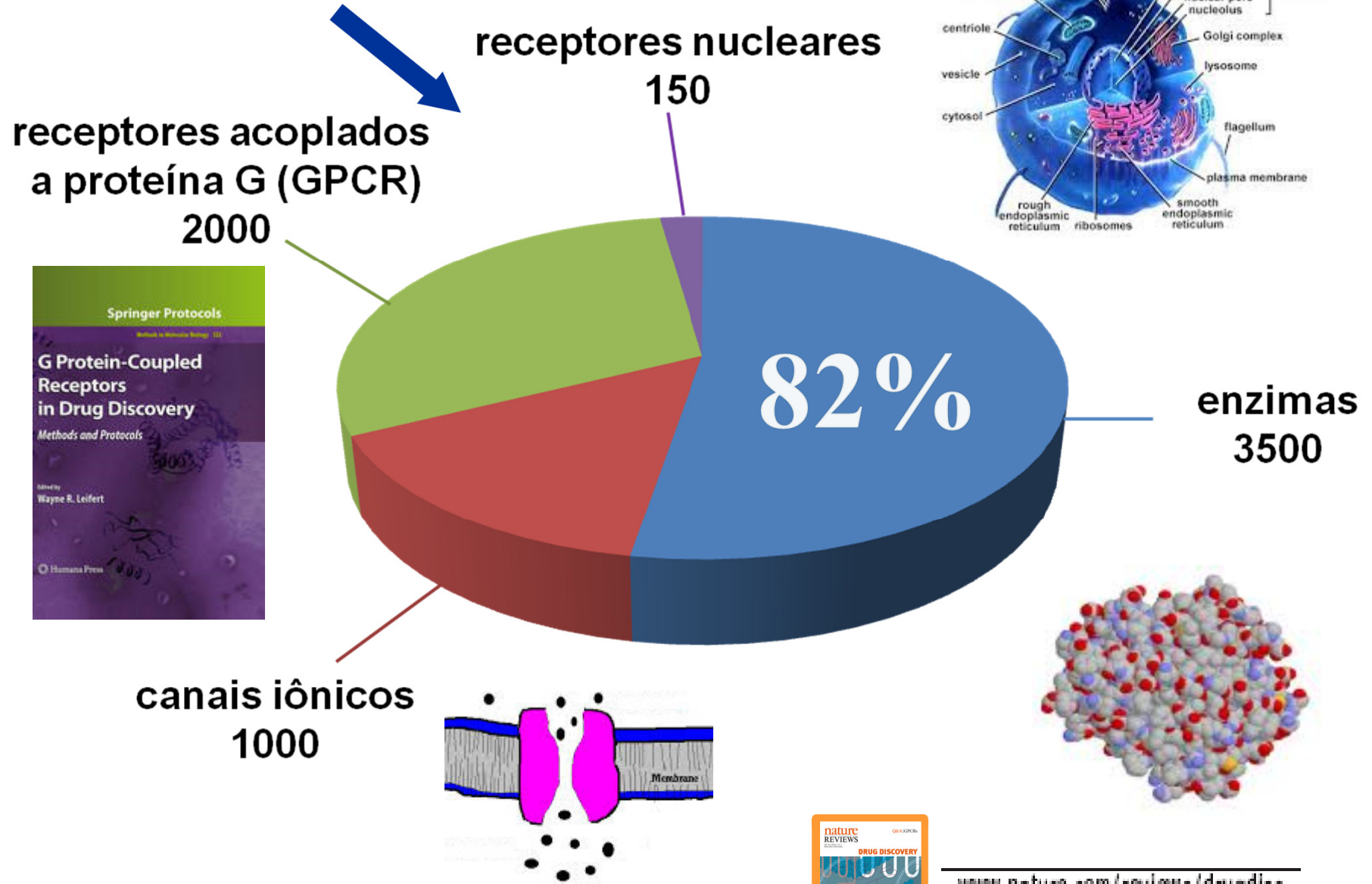


DNA methylation is the addition of a methyl group (M) to the DNA base cytosine (C).

Como os fármacos *acham* os receptores?



A maioria dos biorreceptores dos fármacos contemporâneos são enzimas ...



www.nature.com/reviews/drugdisc
Hopkins, A. L. & Groom, C. R. The druggable genome. *Nature Rev. Drug Discov.* 1, 727-30 (2002).

The Nobel Prize in Chemistry 2012

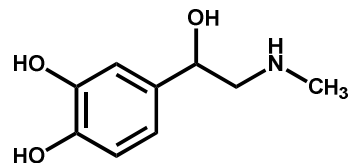


Photo: U. Montan
Robert J. Lefkowitz



Photo: U. Montan
Brian K. Kobilka



- a) Howard Hughes Medical Institute and Duke University Medical Center, Durham, NC, USA
- b) Stanford University School of Medicine, Stanford, CA, USA

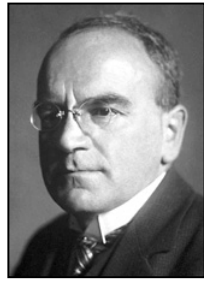
“for studies of G-protein-coupled receptors”



Universidade Federal do Rio de Janeiro



Uma inovação bilionária: as estatinas



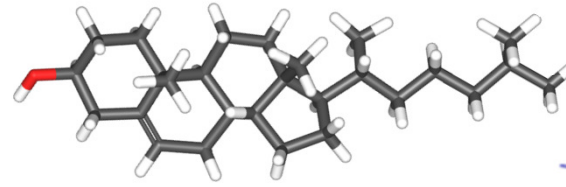
Heinrich Wieland
1877-1957

1927



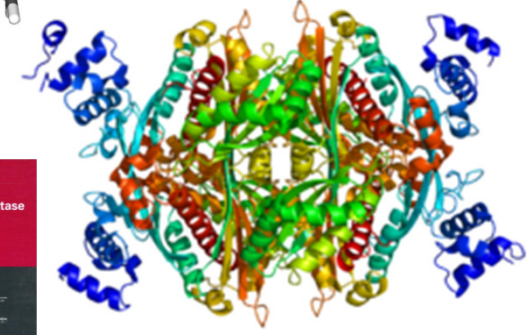
Adolf OR Windaus 1975
1876-1959

1928



colesterol

1951



HMGCoAR



1964



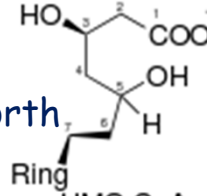
Konrad Bloch
1912-2000



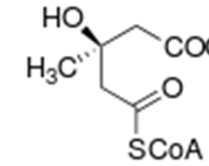
Feodor FK Lynen
1911-1979



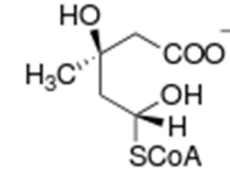
John Cornforth
1917-2013



HMG CoA
Reductase inhibitor



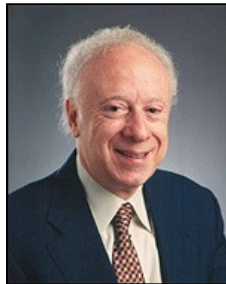
HMG CoA



Mevaldyl CoA transition
state intermediate

1985

LDL



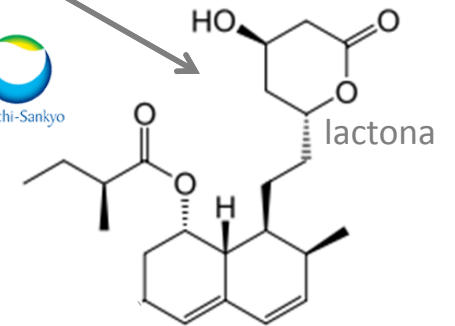
Joseph L Goldstein Michael S Brown
University of Texas, Dallas



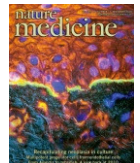
J Med Chem
1985, 28, 1



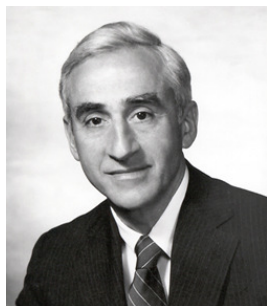
Akira Endo
Albert Lasker Award
for Clinical
Medical Research, 2008*



Mevilonina
/compactina



* A Endo, A gift from nature: the birth of the statins, *Nature Medicine* 2008, 14, 26



Dr P. Roy Vagelos

Vice-Presidente Pesquisa
Farmacêutica da Merck
(Presidente & CEO)

1976 - confidentiality agreement



Alfred W. Alberts



Georg
Albers-Schönberg



Arthur A. Patchett
Diretor do Departamento
New Lead Discovery
Alfred Burger Award 2002



1991



atorvastatina

fifth-in-class



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Volume 47

Sponsored by the Division of Medicinal Chemistry
of the American Chemical Society

Editor in Chief: MANOJ C. DESAI



therapeutic
innovation

1982

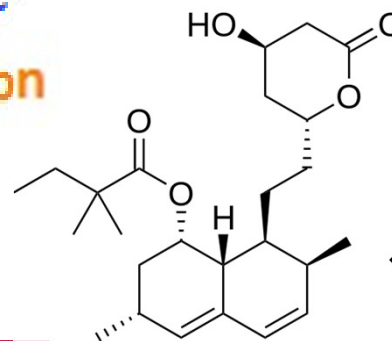
ZOCOR®
(SIMVASTATIN)

“blockbuster mentality”

Química
med
Medicinal
chem



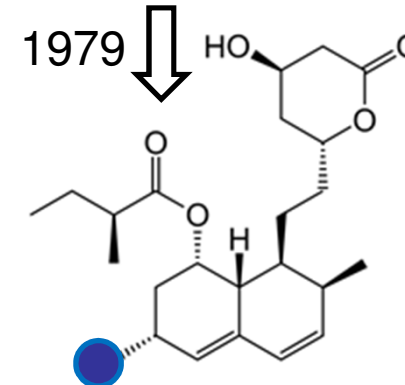
J. Med. Chem. **1986**, 29, 849



simvastatina
first-in-class



1979



Aspergillus terreus
lovastatina

[A descoberta da lovastatina](#)

> 45 milhões de pessoas usaram estatinas (2005)

Atorvastatina



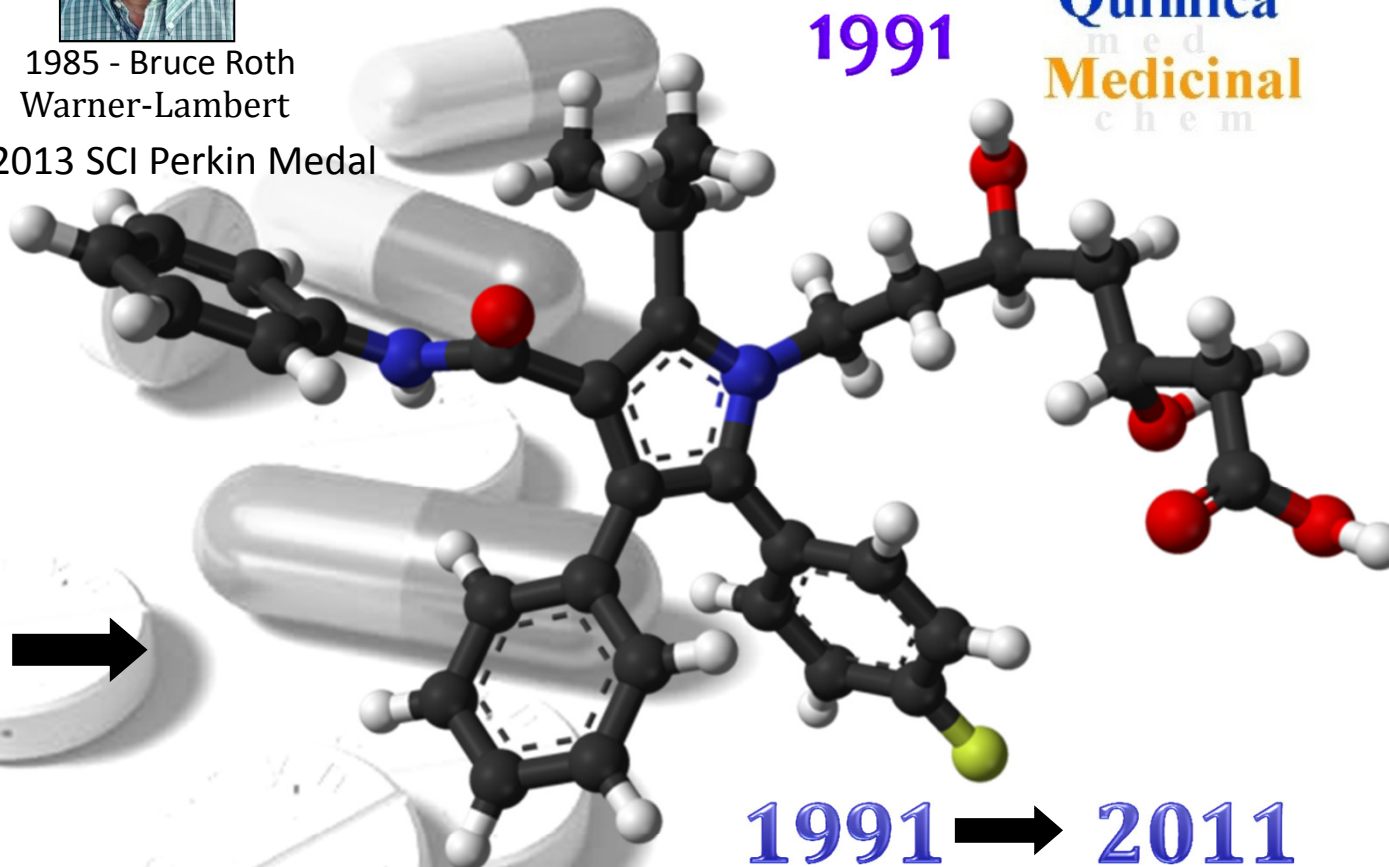
1985 - Bruce Roth
Warner-Lambert

2013 SCI Perkin Medal

Estatinas

Química
med
Medicinal
chem

1991



1991 → 2011

ácido (*N*-pirrol)-3,5-di-hidróxi-heptanóico
Síntese: ca. 200 toneladas/ano HMGCo-AR IC₅₀ = 8,2 nM



**Fármaco recordista mundial em vendas:
US\$ 150 bilhões**

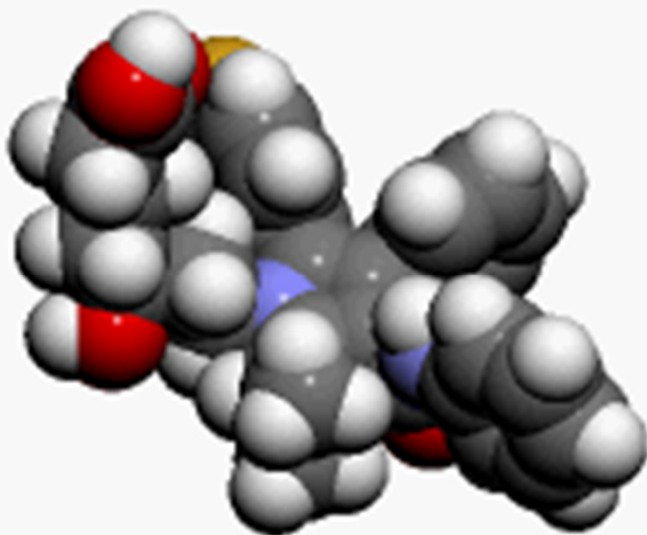
B. D. Roth, *Progr. Med. Chem.* **2002**, *40*, 1-22

B. D. Roth, et al., *J. Med. Chem.* **1990**, *33*, 21-31

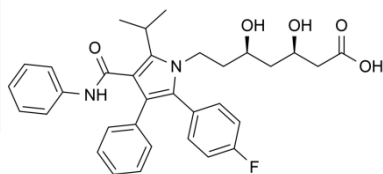
Atorvastatina

sintetizada em 1985, por Bruce D. Roth,
na Parke-Davis Warner-Lambert Co.
Patent US 5273995 Pfizer (1991)

19 etapas; 5% rendimento



O maior *bestseller* da história da indústria farmacêutica mundial



**Estudo de rotas de síntese,
a partir de intermediários
primários de menor custo,
de fármacos genéricos**



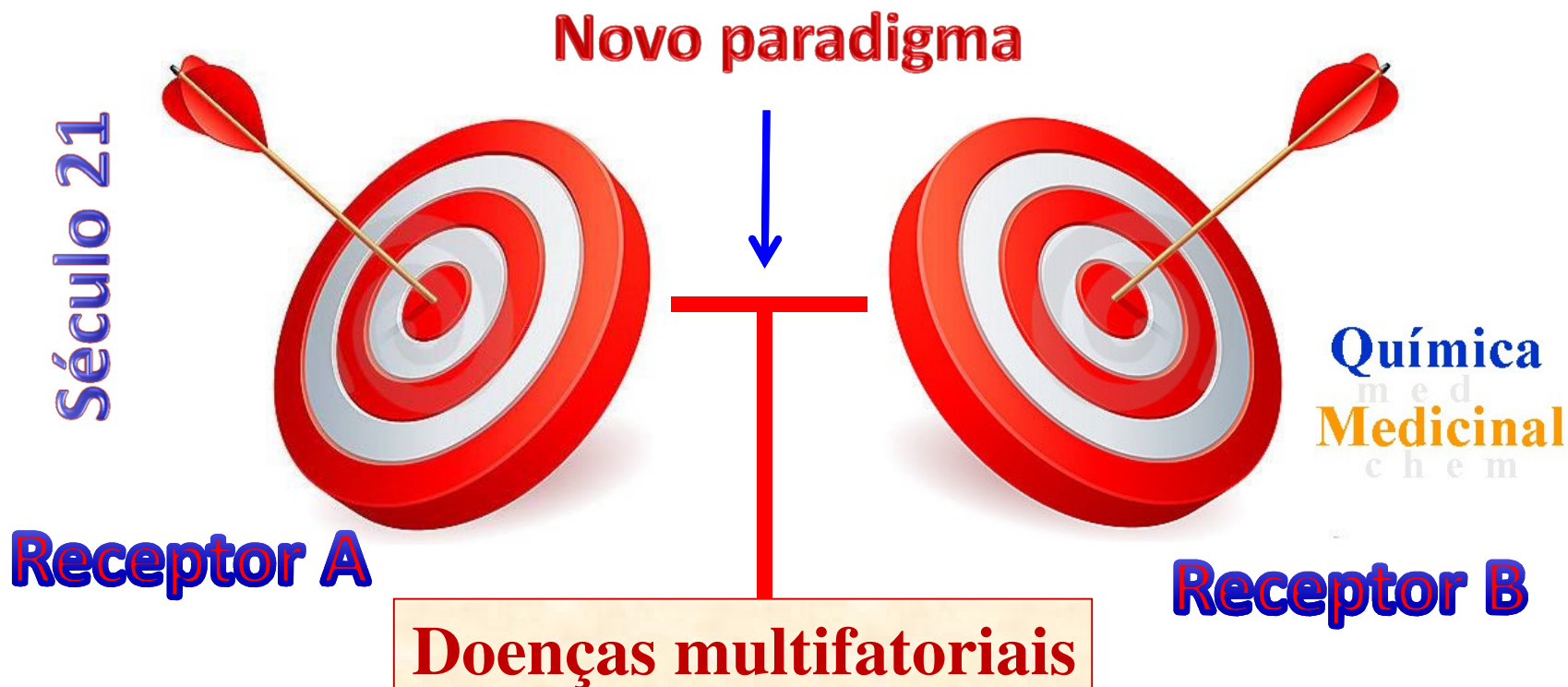
Professor Luiz Carlos Dias
& Dr Adriano Siqueira Vieira
IQ, UNICAMP

18 etapas; 19% rendimento; 5g escala

- INPI Patente 018110015039, 2011 (BR)
Nova rota de síntese da atorvastatina
cálcica usando novos intermediários (25/04)

INCT-INOFAR: www.inct-inofar.ccs.ufrj.br

Fármacos do século 21



O desenho racional de fármacos multi-alvos depende da capacidade de combinarem-se padrões farmacofóricos múltiplos, capazes de terem reconhecimento molecular pelos receptores envolvidos na patologia multifatorial.

JL Medina-Franco et al. Shifting from the single to the multitarget paradigm in drug discovery, *Drug Discov. Today* **2013**, *18*, 495; C Hiller, J Kühhorn, P Gmeiner, Class A G-Protein-Coupled Receptor (GPCR) Dimers and Bivalent Ligands, *J. Med. Chem.* **2013**, *56*, 6542; G Phillips, M Salmon, Bifunctional compounds for the treatment of COPD, *Annu. Rev. Med. Chem.* **2012**, *47*, 209; S Reardon, A world of chronic disease, *Science* **2011**, *333*, 558.

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

Eliezer J. Barreiro and Carlos Alberto Manssour Fraga

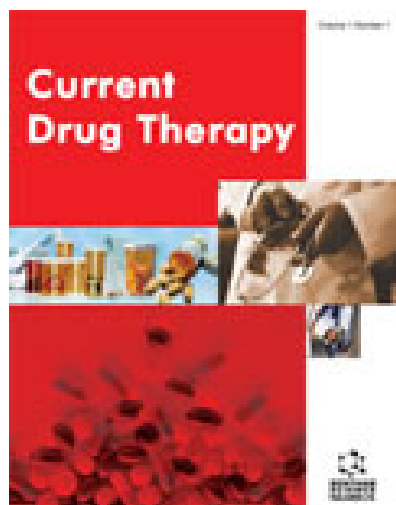


Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, P.O. Box 68023, 21944-971, Rio de Janeiro, RJ, Brazil.



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!***



Química
m e d
Medicinal
c h e m

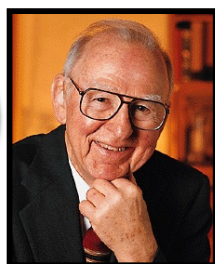
Inibidores de tirosina-quinases (TK)



Edmond H Fischer



1992

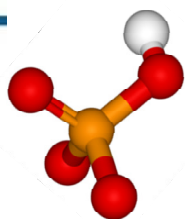


Edwin G Krebs
(1918 –2009)

Methods and Principles in Medicinal Chemistry
Edited by Bert Klebl, Gerhard Müller,
and Michael Hamacher

WILEY-VCH

Protein Kinases as Drug Targets

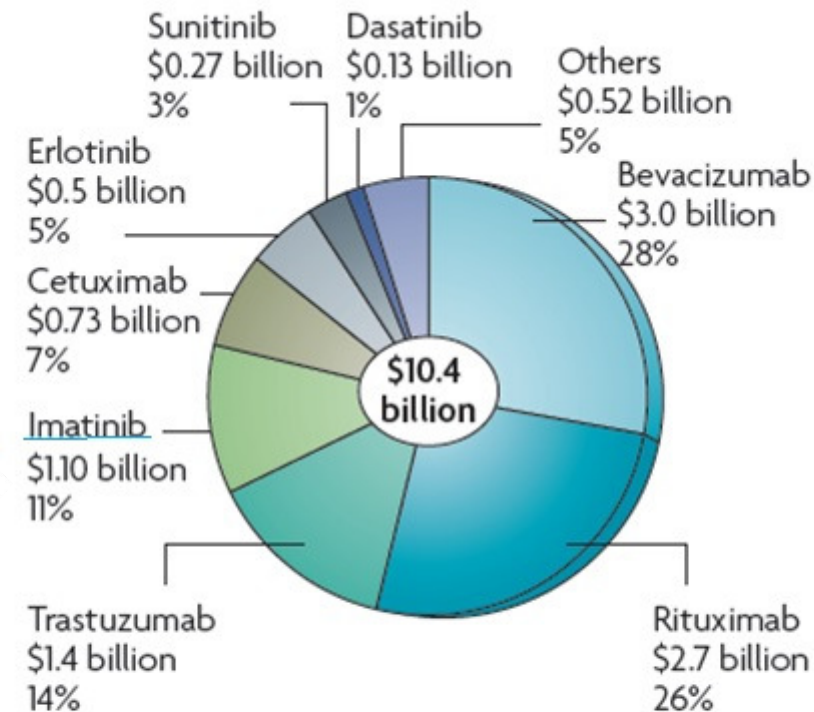


quinoma



Volume 49
Series Editors:
R. Mannhold,
H. Kubinyi,
G. Folkers

Targeted therapies



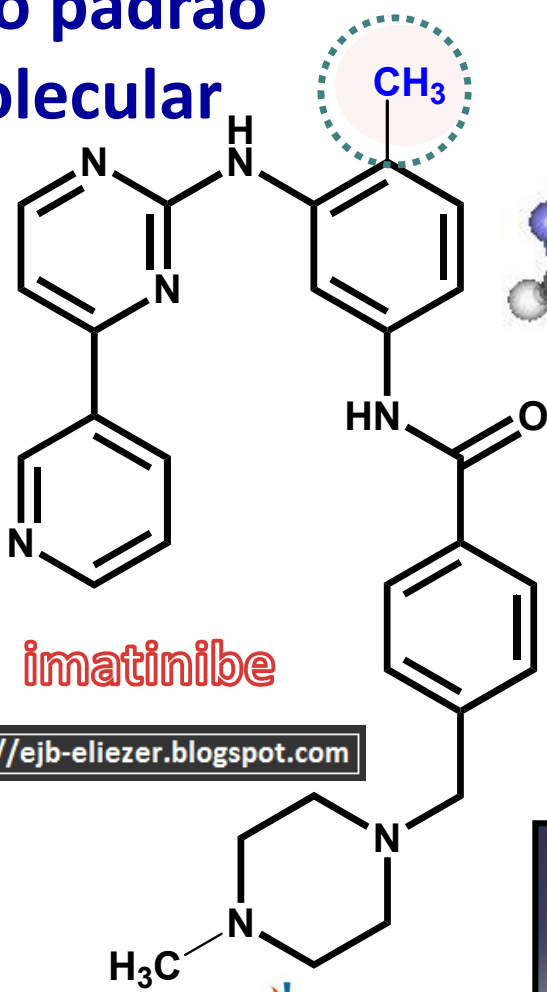
Market for targeted cancer therapies. US sales of targeted therapies share of the US market based on 2009 sales.

Sources: company reports

Vendas mundiais do imatinibe (2009): US\$ 3,95 bi

S. Aggarwal, Targeted cancer therapies, *Nature Rev. Drug Discov.* **2010**, 9, 427; P. Cohen, Timeline: **Protein kinases** — the major drug targets of the twenty-first century? *Nature Rev. Drug Discov.* **2002**, 1, 309.

Novo padrão molecular



imatinibe

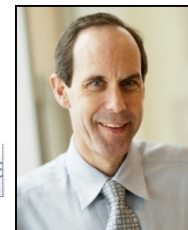
<http://ejb-eliezer.blogspot.com>

Leucemia mielóide
crônica
(CML)

imatinibe



Nicholas B. Lydon
Blueprint Medicines Inc*



Brian J. Druker*
Blueprint Medicines Inc

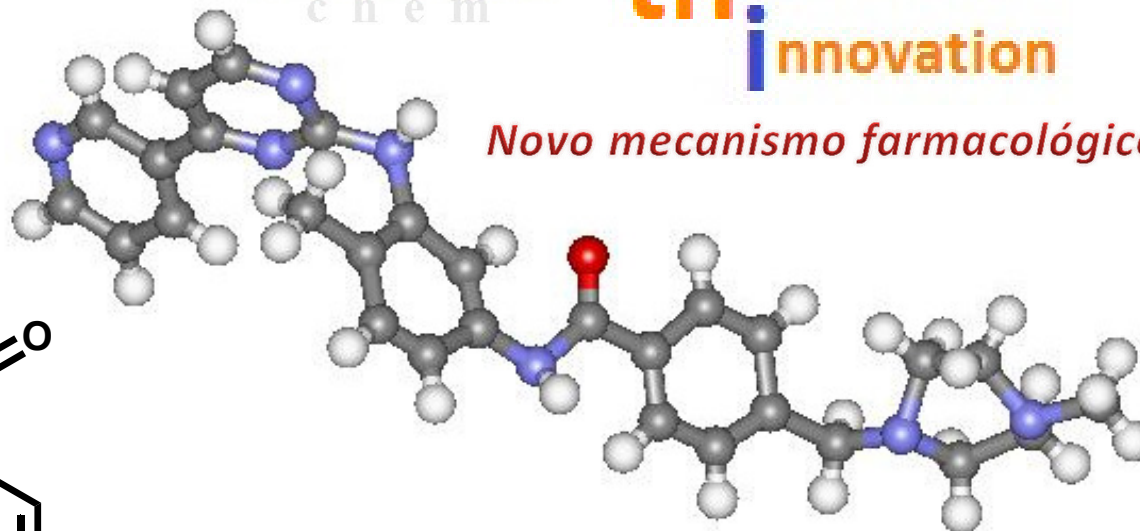


Charles L. Sawyers**
Blueprint Medicines Inc

Química
med
Medicinal
chem

th
erapeutic
i
nnovation

Novo mecanismo farmacológico



1988 – Nicholas Lydon, Brian J. Druker
& Charles L Sawyers &

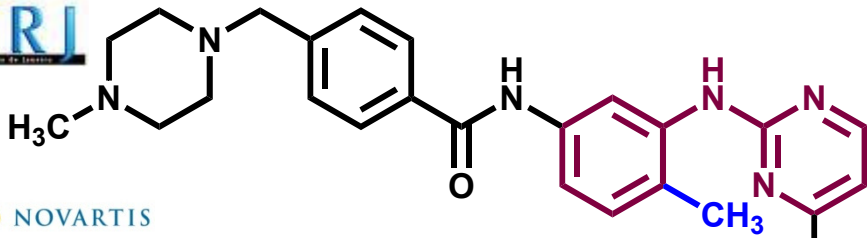
1995 - Composto STI571 ++

2001 – Imatinibe (Gleevec^R, [Novartis](#))[[link](#)]

& 2009 - Lasker Foundation Clinical Award (*J. Clin. Invest.* **2009**, *119*, 2863)

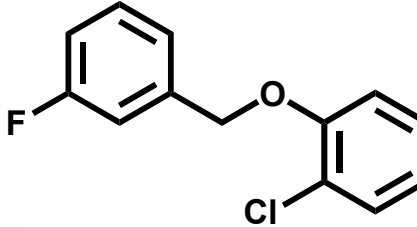
* B. J. Druker has been awarded with the 2012 Japan Prize in Healthcare and Medical Technology;

** C. L. Sawyers was named in 2011, Thomson Reuters Citation Laureate in Medicine;



NOVARTIS

imatinib
2001

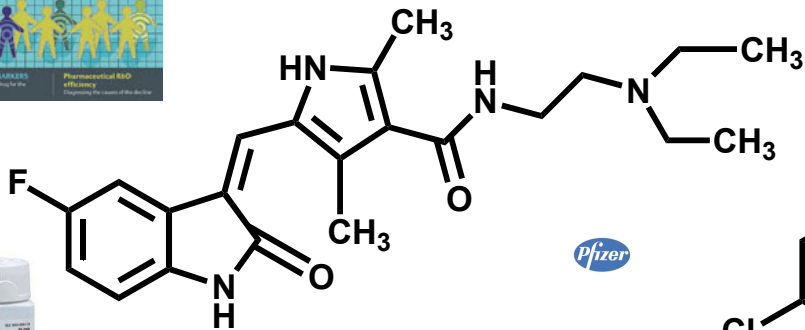


therapeutic
innovation



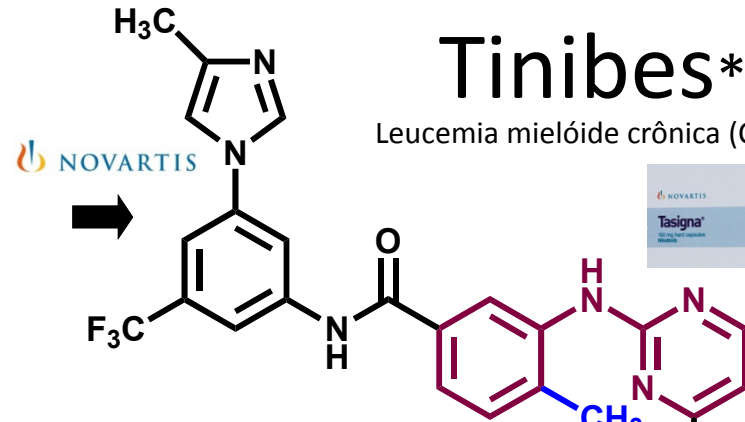
gsk

lapatinib
2007



Pfizer

sunitinib
2006

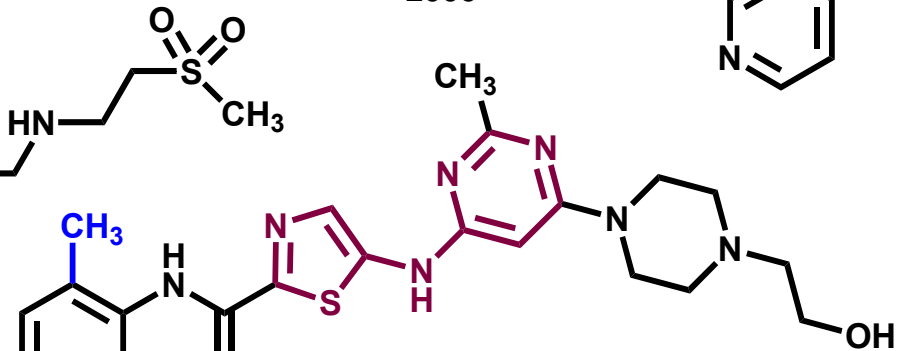


NOVARTIS

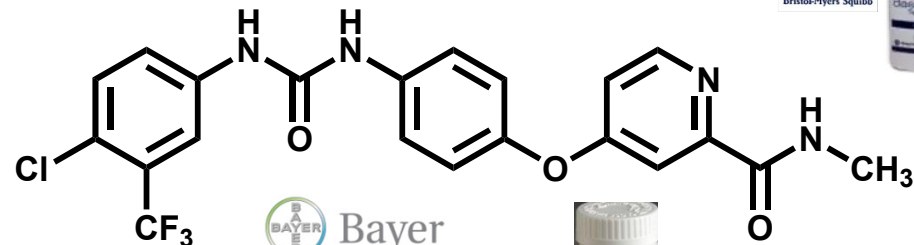
nilotinib
2006

Tinibes*

Leucemia mielóide crônica (CML) &



dasatinib
2007



Bayer

sorafenib
2007



2011- crizotinibe
2012- bosutinibe

Pfizer

• Mercado EUA (2009): US\$ 18,5 bi *

<http://ejb-eliezer.blogspot.com>

• S Aggarwal, *Nature Rev Drug Discov* 2010, 9, 427
& R Ren, *Nature Rev Cancer* 2005, 5, 172



Universidade Federal do Rio de Janeiro



Cidade Universitária, ilha do Fundão,
Rio de Janeiro, RJ

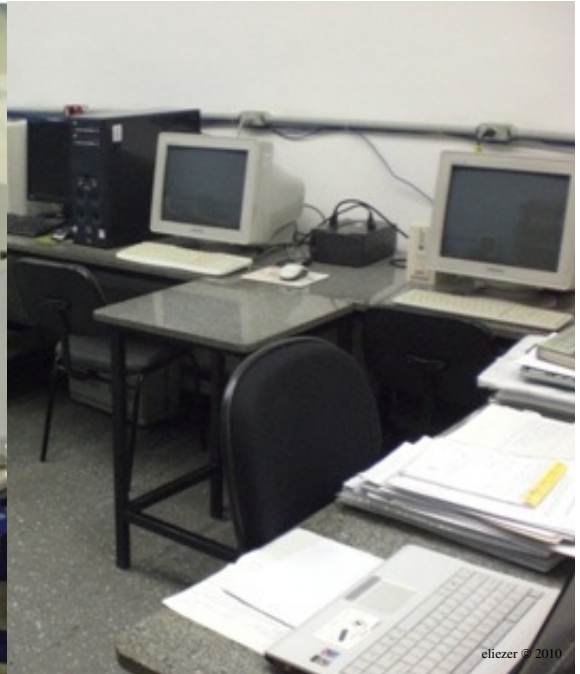
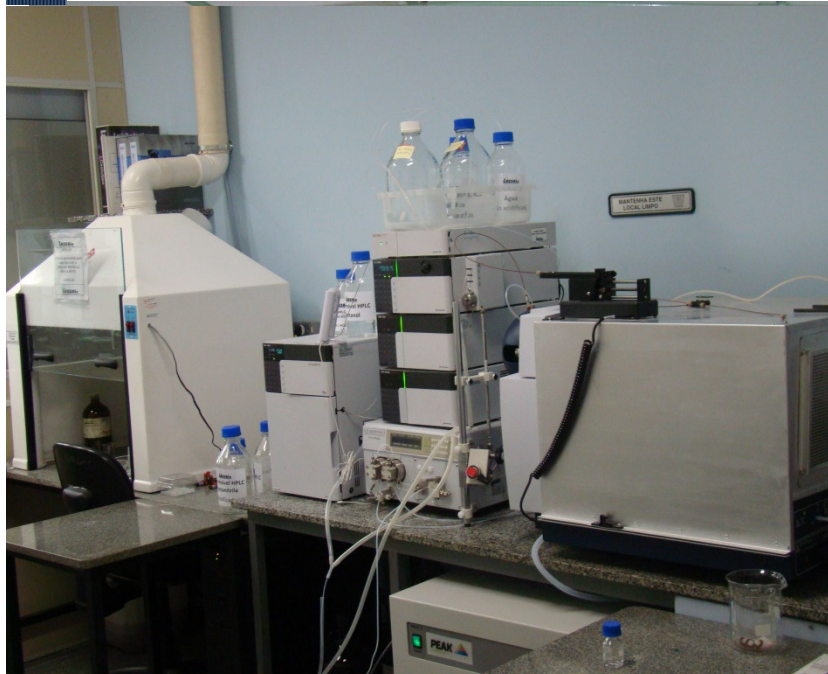


Química Medicinal
Pharmacology
Farmacologia

LASSBIO

Laboratório de Avaliação e Síntese de Substâncias Bioativas

Creado em 19/04/1994 Laboratório de Avaliação e Síntese de Substâncias Bioativas



“...**discovery** *consists* of seeing
what everybody else **has seen**
and **thinking** what
no body else
has not thought...”



1937

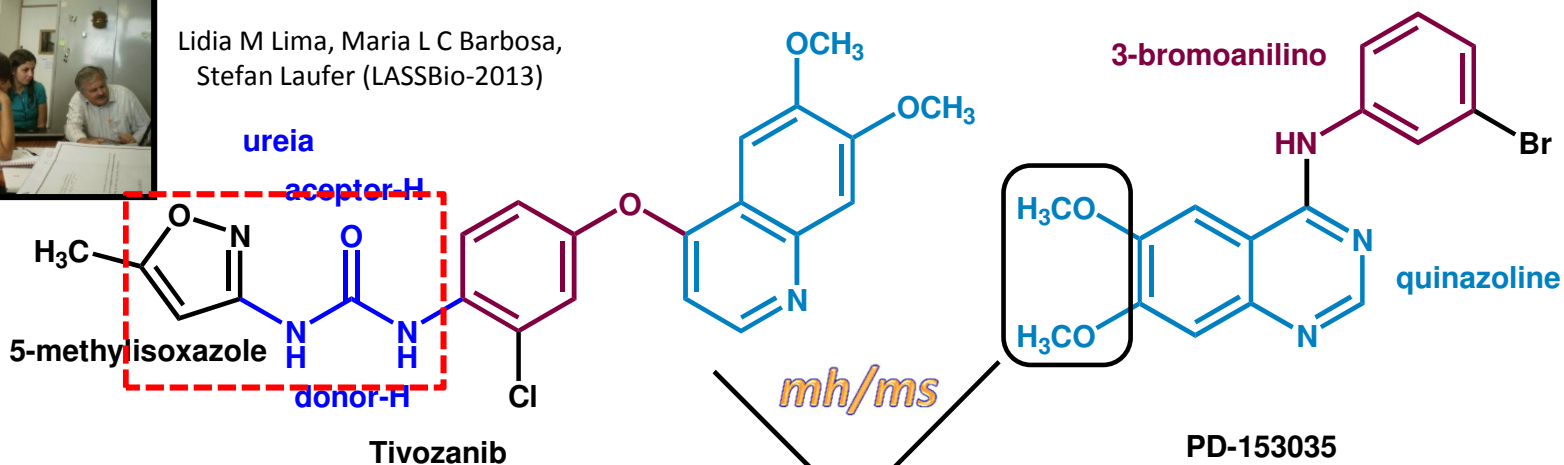


Albert Szent-Györgyi (1893-1986)

Novos tinibes duais

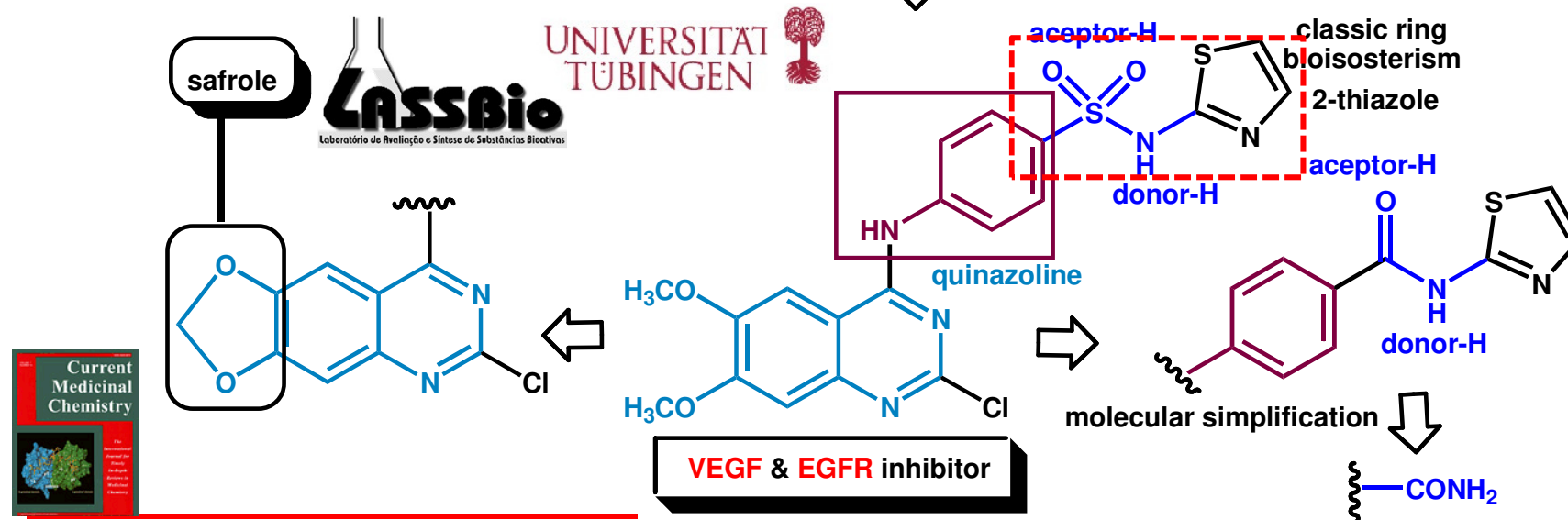


Lidia M Lima, Maria L C Barbosa,
Stefan Laufer (LASSBio-2013)



oral **VEGF** receptor tyrosine kinase inhibitor

inhibits tyrosine kinase activity of the **EGFR**



C Viegas Jr et al., Molecular Hybridization: a useful tool in the design of new drugs prototypes, *Curr. Med. Chem.* **2007**, *14*, 103; M L C Barbosa, L M Lima, R Tesch, C M R Sant'Anna, F Totzke, M HG Kubbutat, C Schächtele, S A Laufer, E J Barreiro, Novel 2-chloro-4-anilino-quinazoline derivatives as EGFR and VEGFR-2 dual inhibitors, *Eur J Med Chem* **2014**, *71*, 1-14.

Novel 2-chloro-4-anilino-quinazoline derivatives as EGFR and VEGFR-2 dual inhibitors

Maria Leticia de Castro Barbosa^{a,b}, Lídia Moreira Lima^{a,b}, Roberta Tesch^a, Carlos Mauricio R. Sant'Anna^c, Frank Totzke^d, Michael H.G. Kubbutat^d, Christoph Schächtele^d, Stefan A. Laufer^e, Eliezer J. Barreiro^{a,b,*}

^a Laboratory of Evaluation and Synthesis of Bioactive Substances (LASSBio), Federal University of Rio de Janeiro, P.O. Box 68024, 21944-971 Rio de Janeiro, RJ, Brazil¹

^b Graduate Program of Chemistry (PGQu), Chemistry Institute, Federal University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil

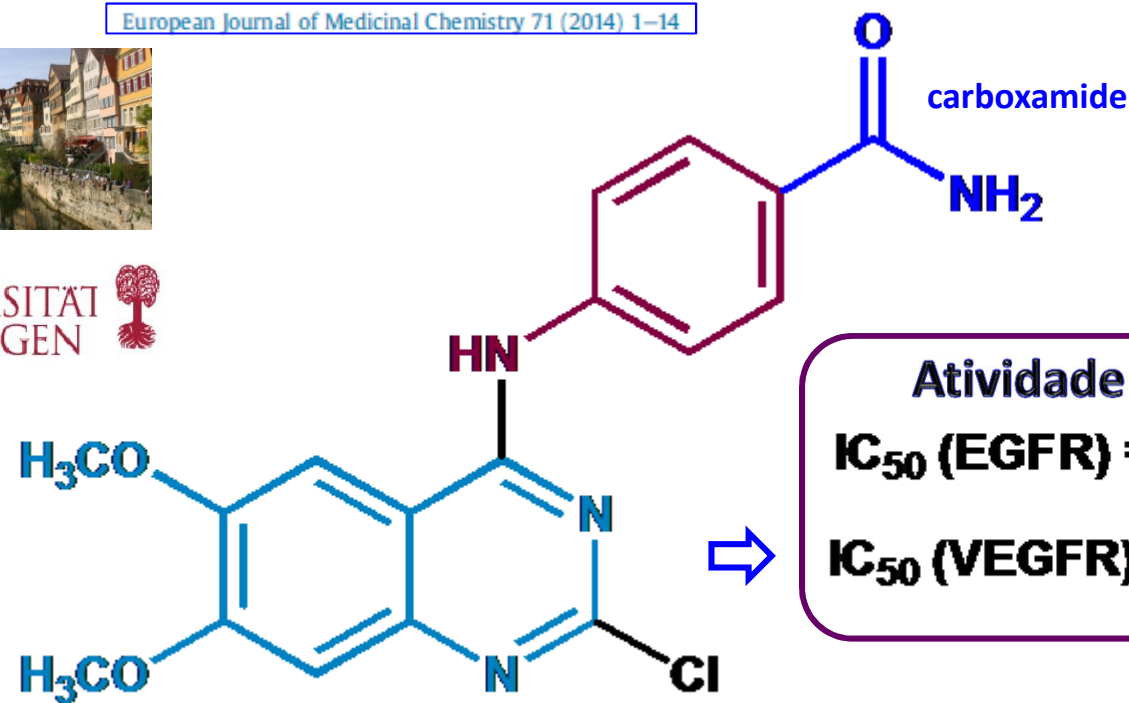
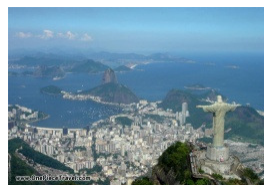
^c Department of Chemistry, Federal Rural University of Rio de Janeiro (UFRRJ), Seropédica, RJ, Brazil

^d ProQinase GmbH, Freiburg, Germany

^e Department of Pharmaceutical/Medicinal Chemistry, Institute of Pharmacy, Eberhard-Karls-University Tübingen, Tübingen, Germany



European Journal of Medicinal Chemistry 71 (2014) 1–14



Atividade dual
IC₅₀ (EGFR) = 0,90 μM
IC₅₀ (VEGFR) = 1,17 μM

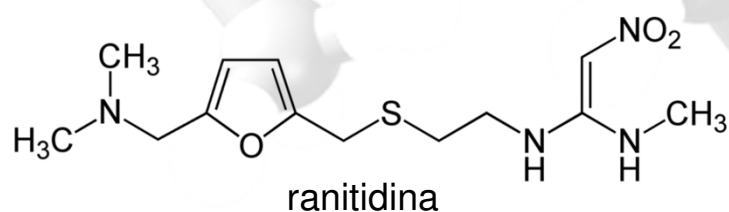
Novel molecular pattern
with EGFR/VEGFR dual
activity!

LASSBio-1630

Depósito de patente no INPI

MLC Barbosa, Novos derivados quinazolinícos funcionalizados inibidores duais das tirosina cinases receptoras EGFR & VEGFR-2, Tese de Doutorado, Instituto de Química, UFRJ, 2013.

“... when it comes to drug discovery you’re not trying to make complicated molecules, but make molecules that will be effective ...”



Barry J. Price

Research Director Glaxo (1967-1995)



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Original article Volume 71, 7 January 2014, Pages 1-14

Novel 2-chloro-4-anilino-quinazoline derivatives as EGFR and VEGFR-2 dual inhibitors

Maria Leticia de Castro Barbosa^{a, b}, Lídia Moreira Lima^{a, b}, Roberta Tesch^a, Carlos Mauricio R. Sant'Anna^c, Frank Totzke^d, Michael H.G. Kubbutat^d, Christoph Schächtele^d, Stefan A. Laufer^e, Eliezer J. Barreiro^{a, b}   

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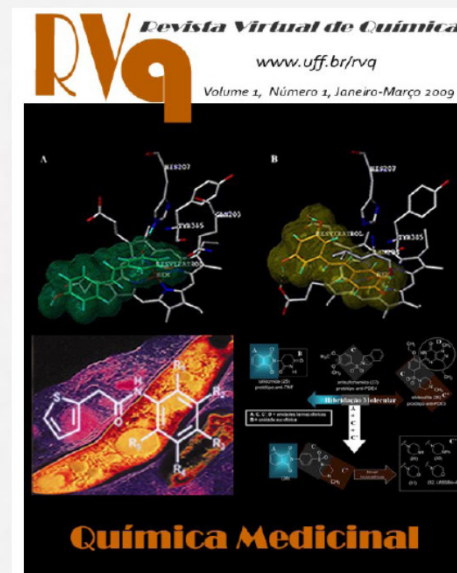
Maria Leticia de Castro Barbosa | Lídia Moreira Lima

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Medicinal
é *simplesmente*
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Epílogo Obrigado.

"Meditai se só as nações fortes podem fazer Ciência

ou se é a Ciência que as fazem fortes"



Oswaldo Cruz

1872-1917



Praia do Boqueirão, Saquarema, RJ



Universidade Federal do Rio de Janeiro

Obrigado.

ejbarreiro@ccsdecania.ufrj.br



Cristo Redentor, uma das sete maravilhas do mundo moderno