

Ciência, Química Medicinal & Webinários

Webinário Inaugural do Programa de Seminários do LASSBio 2022
10 de janeiro de 2022

Eliezer J. Barreiro



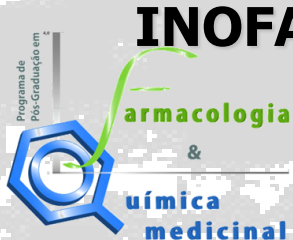
Professor Titular

Laboratório de Avaliação e Síntese de Substâncias Bioativas

Instituto de Ciências Biomédicas

Universidade Federal do Rio de Janeiro

Instituto Nacional de Ciência e Tecnologia em Fármacos e Medicamentos (INCT-INO FAR)



Programa de Pós-Graduação em Farmacologia e Química Medicinal (PPGFQM)



Uma outra possibilidade para hoje...

Louis Pasteur

“No campo da
observação,
o acaso só
acontece para
as mentes
preparadas”.



Conference, Université de Lille (07 Décembre, 1854).

Murphy's Law

V/S



Capt Edward A. Murphy Jr
(1918-1990)

anything can go wrong

It Will Go Wrong

At the Worst Possible Moment...

Uma pergunta para responderem ao final...

1993

Porque são
importantes os
webinários do

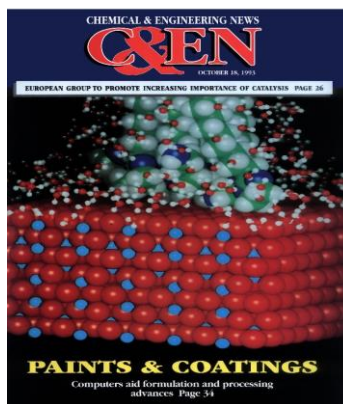


?

1993

NOBEL PRIZE IN CHEMISTRY

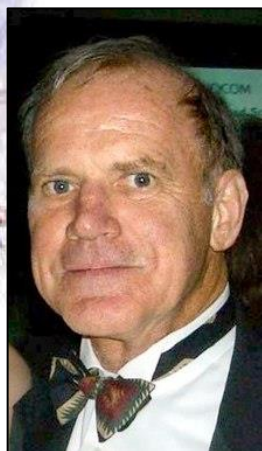
Two biochemists win for DNA work



Chem. Eng. News 1993, 71 (42) 6–7



The 1993 Nobel Prize in Chemistry was awarded last week to two biochemists whose development of chemical methods for manipulating DNA has revolutionized genetic engineering, stimulated basic biochemical research, and opened the door for new applications in industry and medicine. The \$825,000 prize will be shared by American Kary B. Mullis, who now works as a private consultant and writer in La Jolla, Calif., and British-born Canadian Michael Smith, a biochemistry professor and director of the Biotechnology Laboratory at the University of British Columbia, Vancouver.



Kary B. Mullis
(1944-2019)

[UCSF](#)



Michael Smith
(1932-2000)

[J. Biol. Chem.](#)



1993

Prêmio Nobel de Medicina



'Split genes' discovery wins medicine Nobel

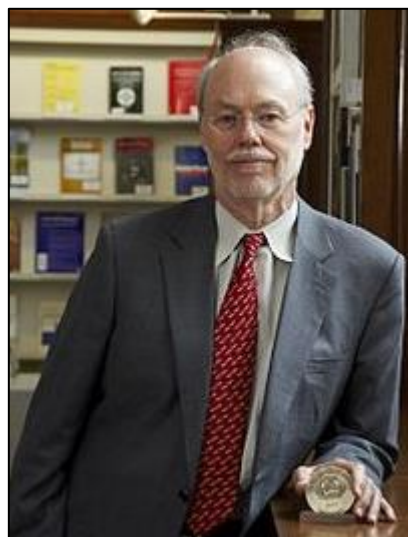
Chem. Eng. News **1993**, 71 (42) 6–7



Richard J. Roberts

(1943-)

[\(Scopus\)](#)



Phillip A. Sharp

(1944-)

[\(Un. Illi.\)](#)



Two U.S. researchers who were educated as chemists won the 1993 Nobel Prize in Physiology or Medicine last week for their discovery that genes can consist of two or more well-separated segments of genetic material (DNA).

British-born Richard J. Roberts and American-born Phillip A. Sharp share the \$842,000 prize for their independent discovery in 1977 of "split genes." Roberts, 50, is a research director at New England Biolabs, a company in Beverly, Mass., that makes restriction enzymes and related products for molecular biology research. Sharp, 49, is a cancer researcher who heads the biology department at Massachusetts Institute of Technology. Both men earned bachelor's and doctorate degrees in chemistry.

***“La science est faite de faits,
tout comme les maisons sont faites de pierres;
mais une simple collection de faits
est pas plus la science
qu'un tas de pierres une maison”***

= “A ciência é feita de fatos,
assim como as casas são feitas de pedras;
mas uma mera coleção de fatos não é ciência,
assim como uma pilha de pedras, não é uma casa.”

Jules Henri Poincaré

(1854-1912)



Holden Thorp



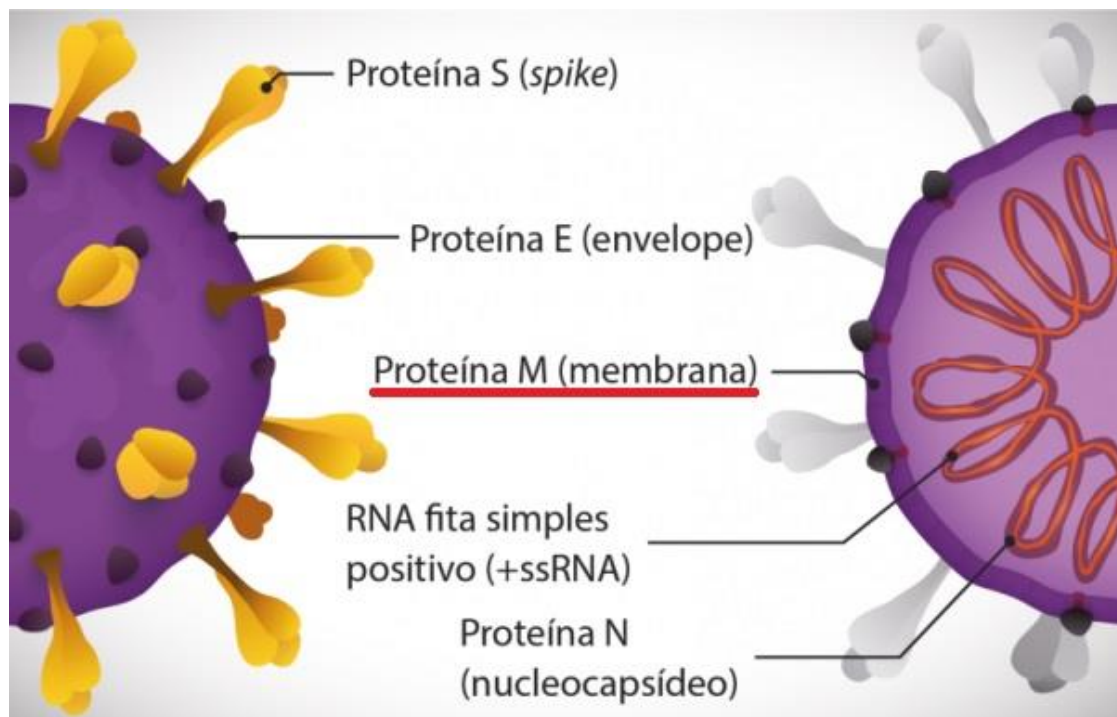
Editor in Chief of



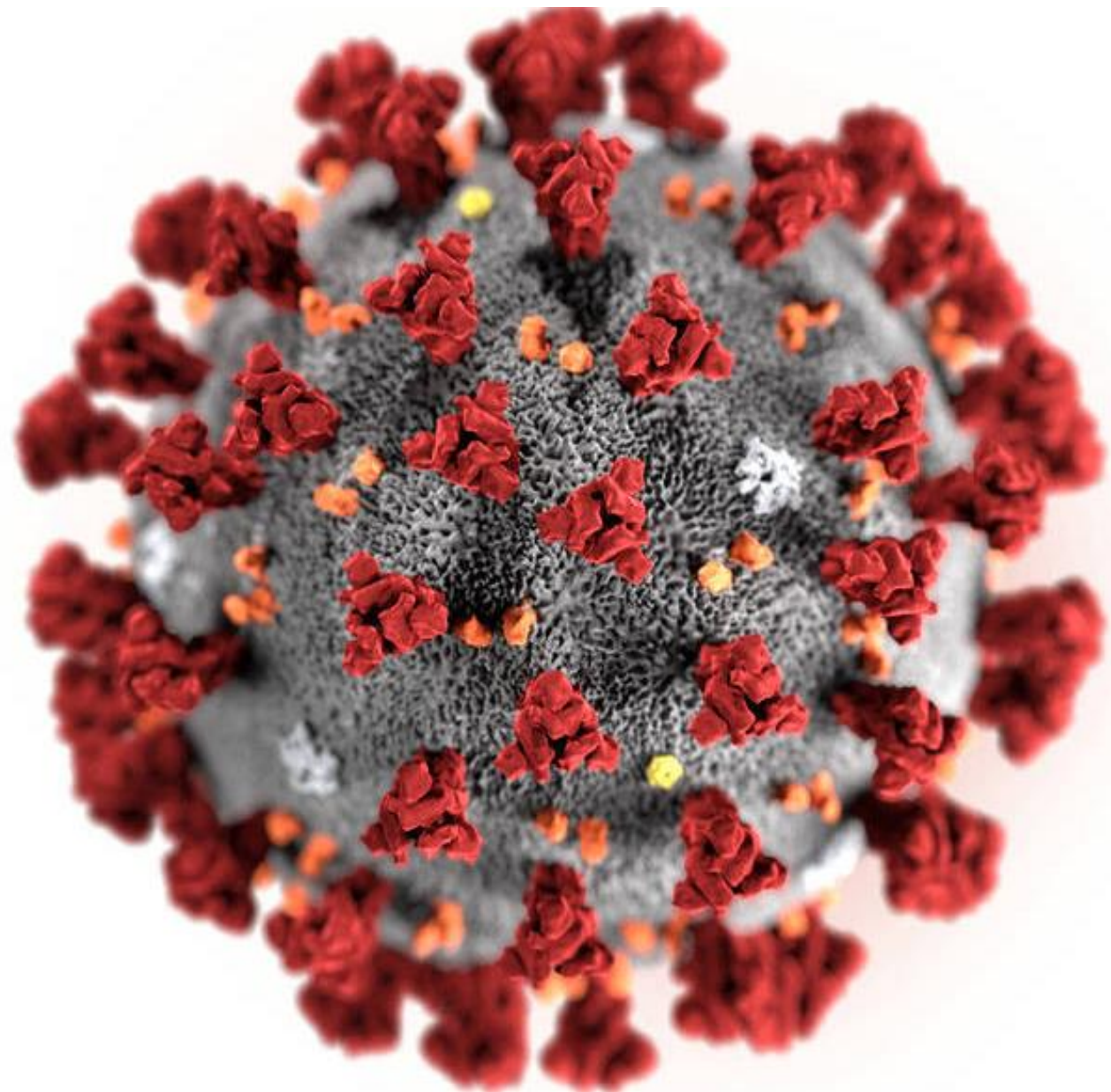
“This is a time when people are thinking about **science** in a way that they never have...
...**Science** really needs to have a strong voice”



Covid-19



estrutura do vírus SARS-CoV-2.



SARS-CoV-2

Post #113



De fármacos e suas descobertas

Pretende-se tratar de temas, opiniões, comentários sobre a Ciência dos Fármacos, seu uso seguro e benefícios. História da descoberta/invenção de fármacos e aspectos da formação qualificada de universitários e pós-graduandos nas Ciências dos Fármacos também são de interesse.

www.ejb-eliezer.blogspot.com

Vide: Remdesevir

terça-feira, 5 de outubro de 2021

Molnupiravir, um anti-viral para tratamento oral da Covid-19?

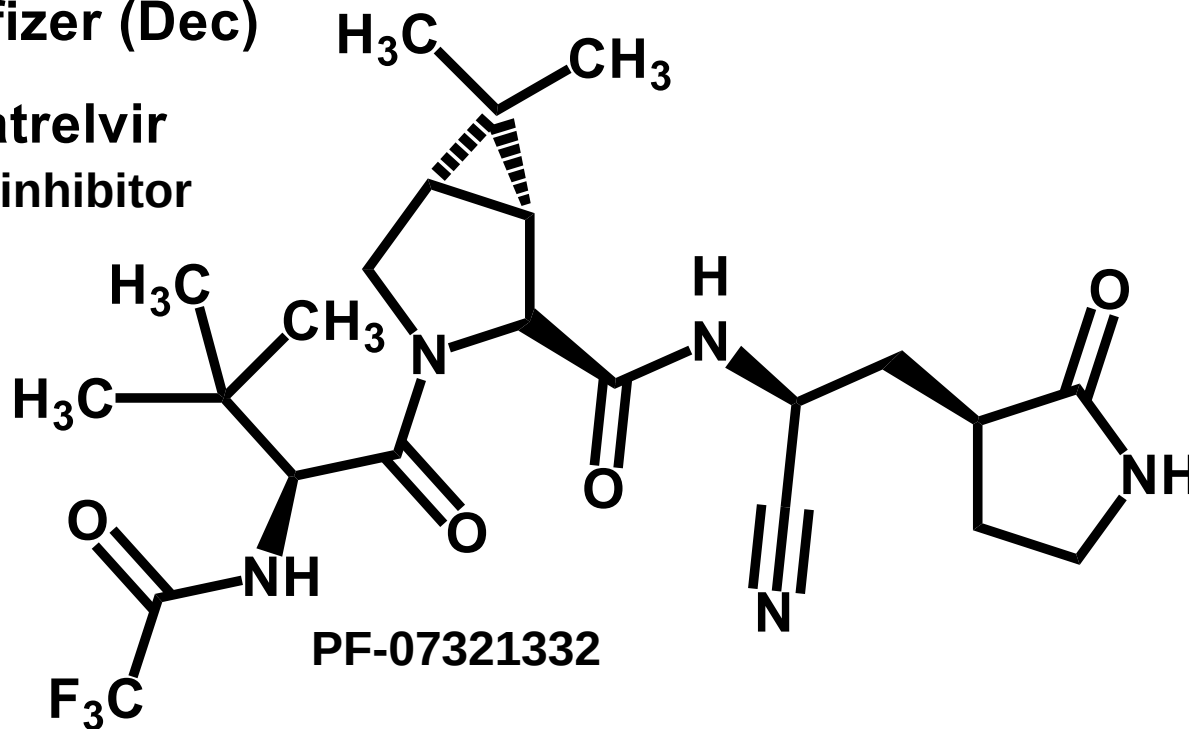
Tenho participado, como convidado, em várias lives de diversas naturezas, neste trágico período que vivemos devido a Covid-19. Promovidas por diferentes fóruns e tratando de aspectos relevantes do processo de inovação farmacêutica, certamente, motivadas por este nosso momento. Concordo com os autores que consideram a inovação farmacêutica uma das mais importantes, dentre aquelas de natureza tecnológicas, e a que mais depende do avanço do conhecimento científico, i.e. da Ciência. O retorno social, em benefícios à sociedade, que os novos medicamentos e as vacinas representam, são hoje bem melhor compreendidos pela sociedade. Tanto que nestes tempos difíceis, Holden Thorp, -Chefe da prestigiosa revista Science, disse em uma entrevista: "This is a time when people are thinking about science in a way that they never have" (A Widener, Science 2020) esta afirmativa dá contornos definitivos ao reconhecimento da importância da Ciência em nossa sociedade contemporânea.

O novo candidato a tratamento antiviral oral COVID-19 da Pfizer reduziu o risco de hospitalização ou morte em 89%

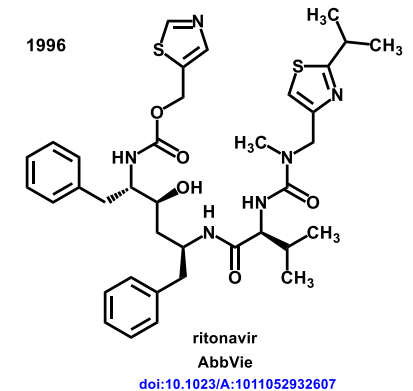
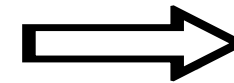
Desenhado como um inibidor covalente da protease SARS-CoV-2-3CL (M^{PRO})

2021 - Pfizer (Dec)

Nirmatrelvir a covalent inhibitor



+ Ritonavir



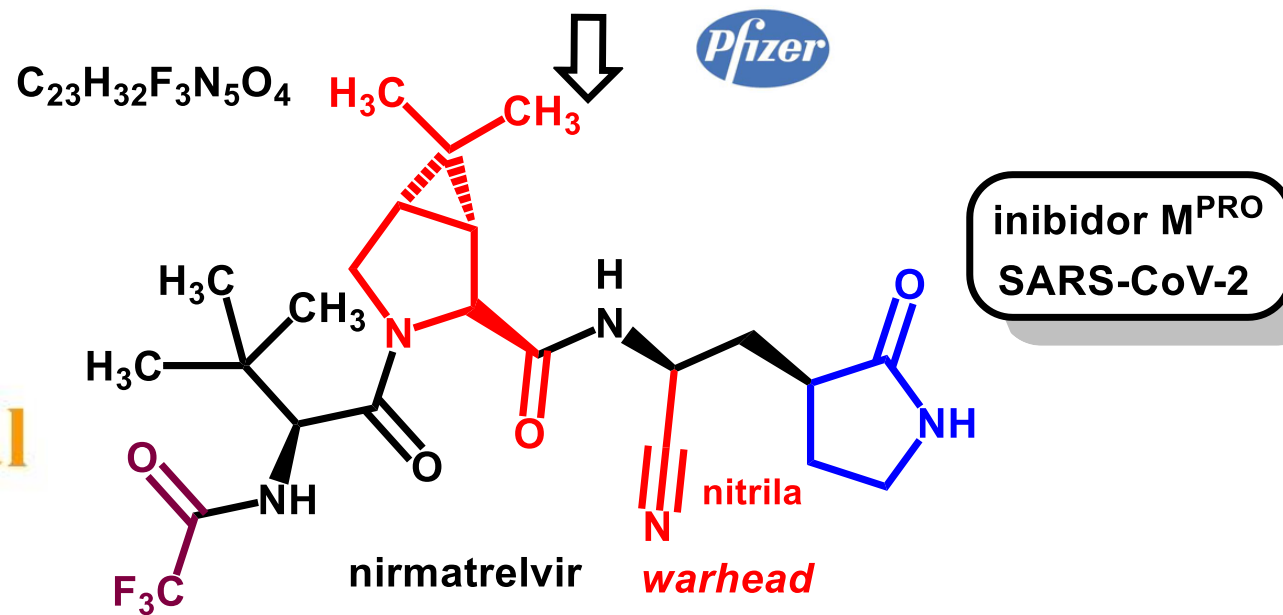
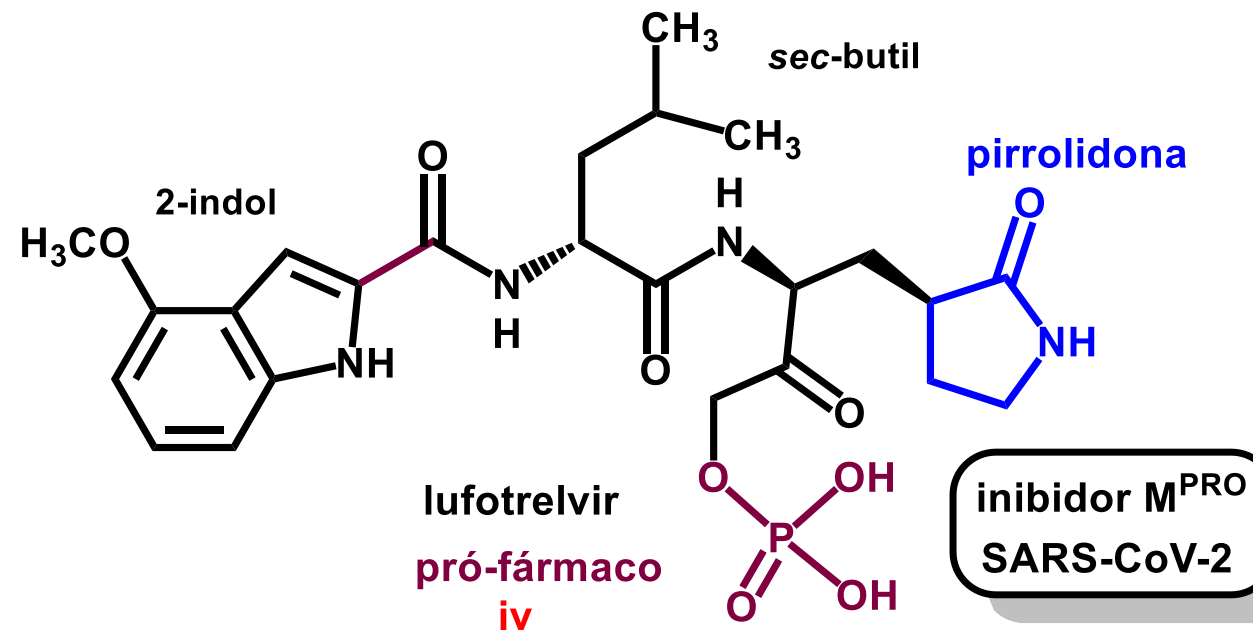
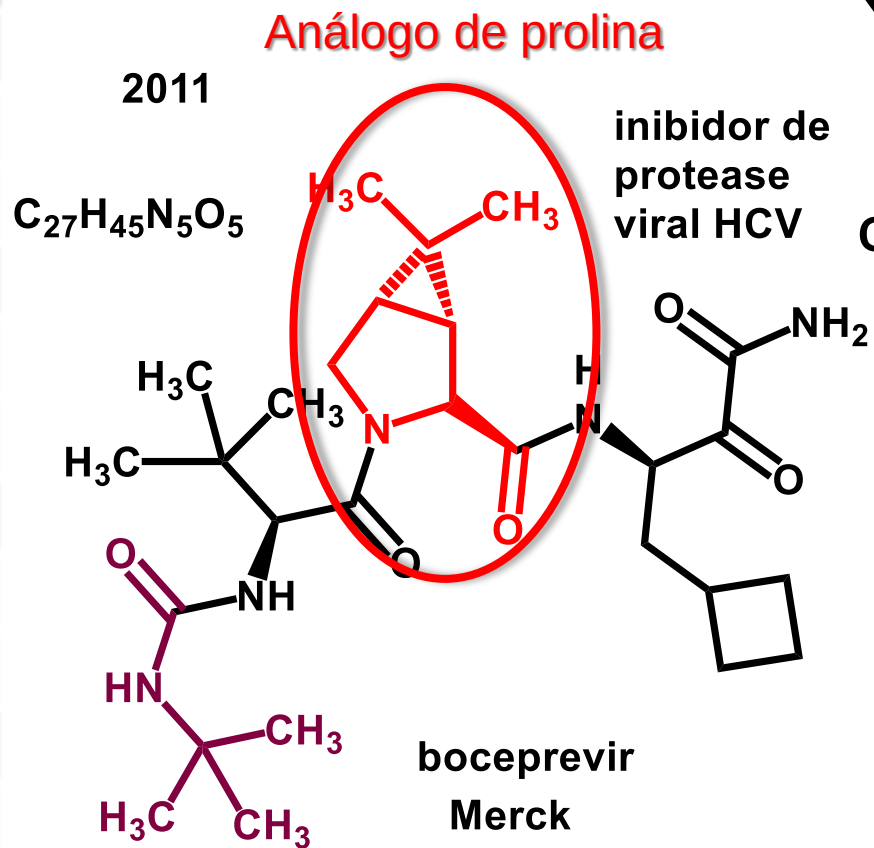
22/12/2021 - FDA

ORAL ANTIVIRAL

PAXLOVID
(PF-07321332; ritonavir)

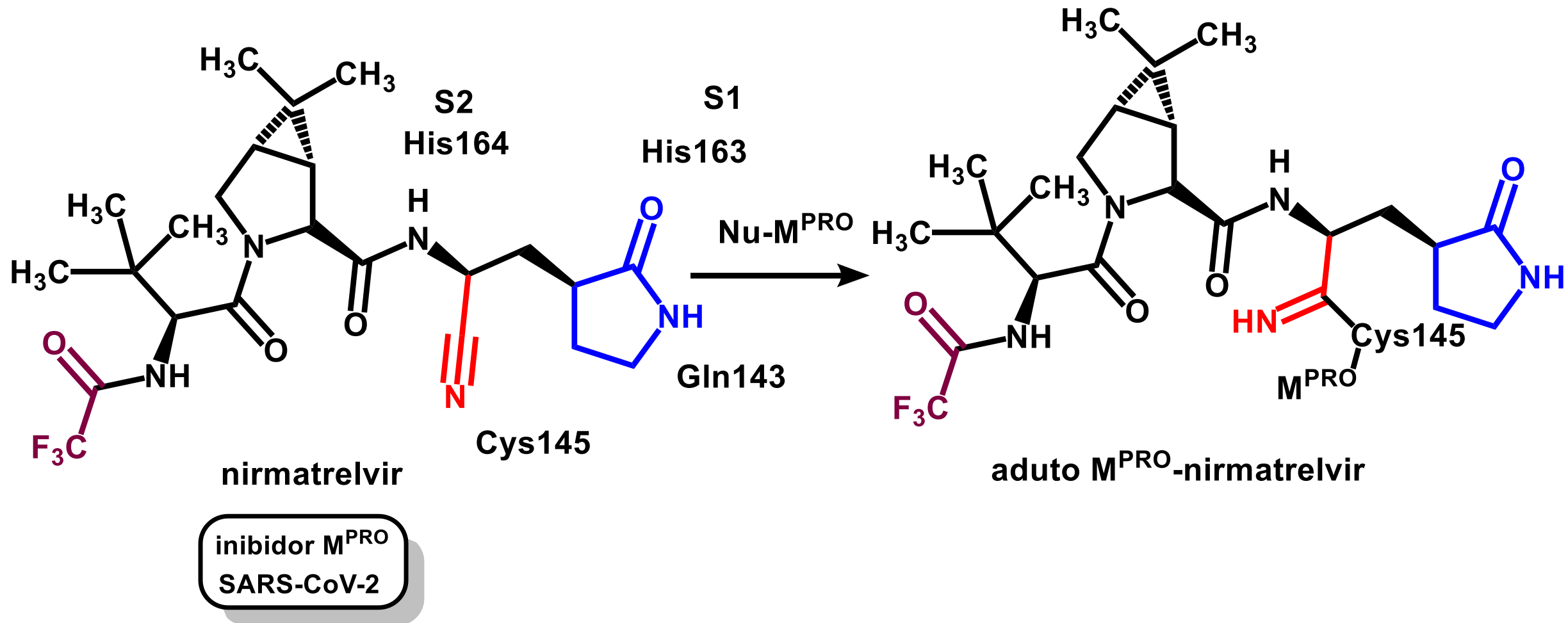
90% EFFECTIVE IN COVID?





Química
med
Medicinal
chem

Mecanismo molecular de inibição da M^{PRO}



SARS-CoV-2 CL-M^{Pro}

PDB:7SI9

Cys145

**Inibição
covalente**

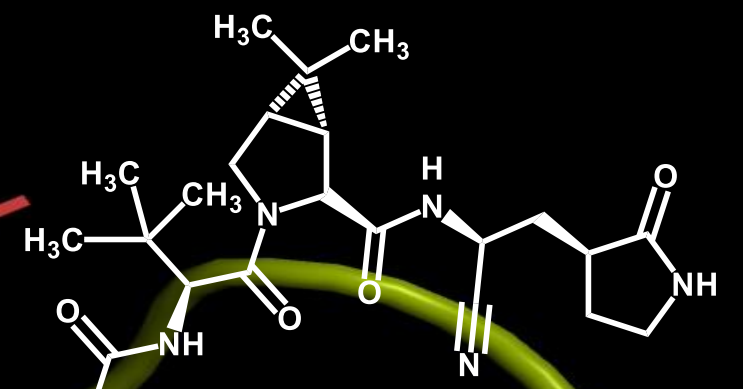
His41

pirrolidona

t-Bu

CF₃

Análogo de
prolina





(1949)

Dennis Liotta

Emory Institute for Drug Development
National Academy of Inventors in 2014

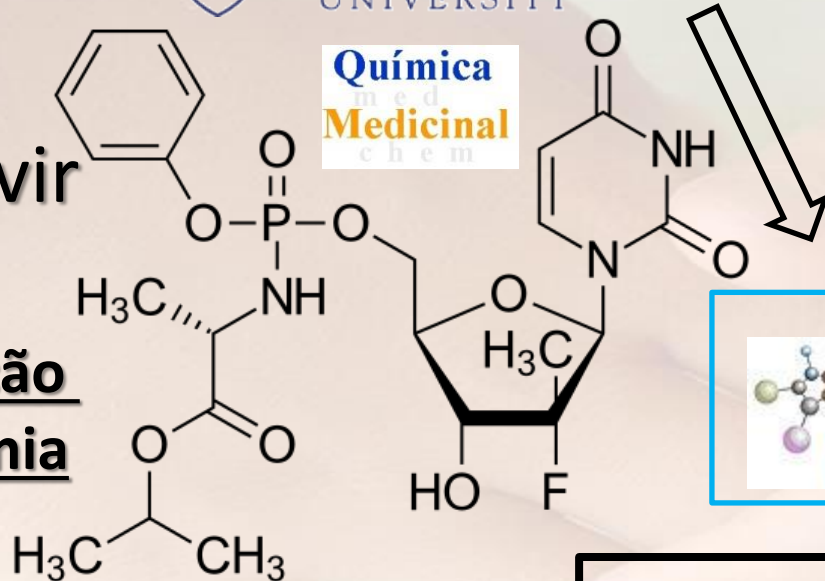


EMORY
UNIVERSITY

Química
med
Medicinal
chem

Sosfobuvir
(SOVALDI®)

Contribuição
da Academia



Inovação Bilionária



2013-2018 - faturamento com fármacos
para HCV atingiu US\$ 58,6 bi



Ledispavir
(Harvoni®)



FDA Oct 2014

The 2016 IUPAC - Richter Prize in Medicinal Chemistry: Dr. Michael J. Sofia.
XXIV European Federation of Medicinal Chemistry International Symposium in
Manchester, UK on 28 August 2016

[2016 IUPAC-G Richter Prize](#)

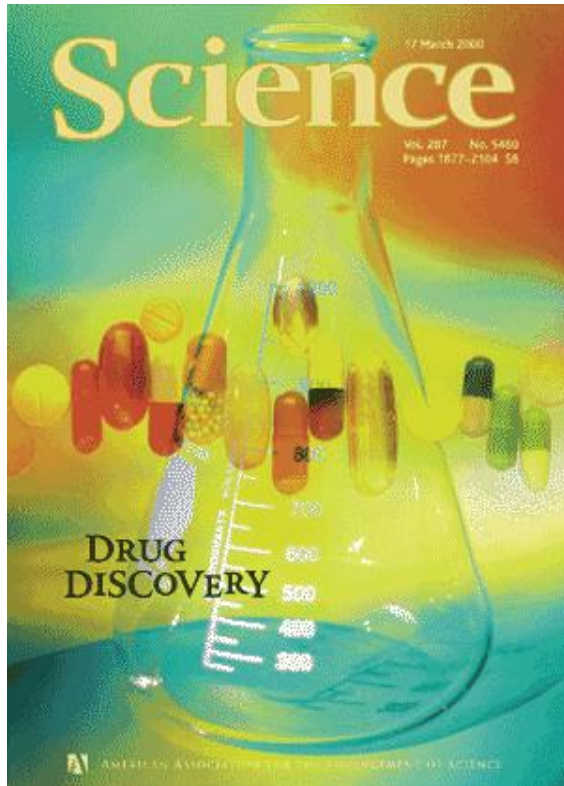
M D Ehlers, Lessons from a recovering academic, *Cell* **2016**, 165, 1043



(1968)

A descoberta de fármacos...

[10.1126/science.287.5460.1951](https://doi.org/10.1126/science.287.5460.1951)



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

[10.1126/science.303.5665.1729](https://doi.org/10.1126/science.303.5665.1729)



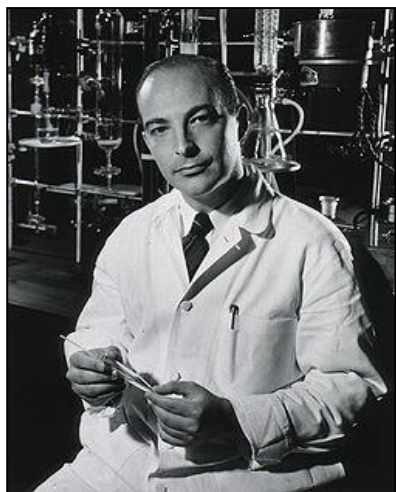
- *Science* **2004**, 303, 1713
(D. Kennedy)

[10.1126/science.309.5735.721](https://doi.org/10.1126/science.309.5735.721)

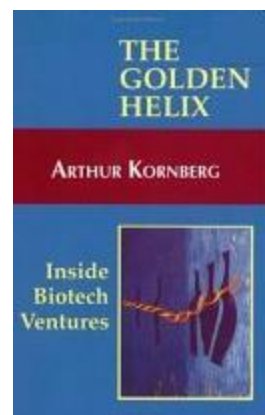
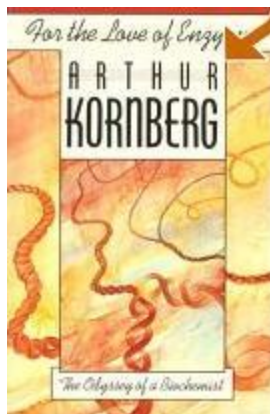


- *Science* **2005**, 309, 721
(J. Mervis)

...depende da pesquisa científica!



Arthur Kornberg (41)
1918-2007



Prêmio Nobel, 1959



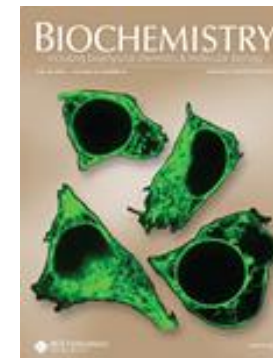
1987

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...



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

medicinal chemistry

...is a chemistry-based discipline, that combines expertise from **chemistry** and **pharmacology** to **design**, **discovery** and synthesize original chemical entities, to therapeutic use. It includes the study of their **metabolism** and the molecular interpretation of their **mode of action** (MoA), including the molecular properties of existing drugs, also.^{a)}

Medicinal Chemistry is a translational discipline concerning the drug discovery process!

^{a)} Adapted from <http://www.chem.qmul.ac.uk/iupac/medchem/>





Assuntos Gerais

Quim. Nova, Vol. 40, No. 6, 694-700, 2017

A EVOLUÇÃO DA QUÍMICA MEDICINAL NO BRASIL: AVANÇOS NOS 40 ANOS DA SOCIEDADE BRASILEIRA DE QUÍMICA*

Antonia Tavares do Amaral^a, Carolina Horta Andrade^b, Arthur E. Kümmerle^c e Rafael V. C. Guido^{d,*}

Recebido em 02/04/2017; aceito em 29/05/2017

Medicinal Chemistry includes the invention, discovery, design, identification, and interpretation of the molecular mechanism of action of biologically active compounds. In addition to the discovery of bioactive molecules investigates drug metabolism and the relationships between chemical structure and biological activity.

In this article, we review the evolution of Medicinal Chemistry in Brazil during the last 40 years and evaluate the impact of the Brazilian contributions in the international context.

Keywords: Medicinal Chemistry; Brazil; Progress; Evolution

<http://dx.doi.org/10.21577/0100-4042.20170075>

[Química Nova, 2017, 40, 694](#)

Química Medicinal

química nova

Volume 40, Número 6, 2017

[Química Nova, 2007, 30, 1456](#)



LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

QUÍMICA MEDICINAL MODERNA: DESAFIOS E CONTRIBUIÇÃO BRASILEIRA

Lídia M. Lima[#]

Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, CP 68006, 21944-910 Rio de Janeiro - RJ, Brasil

MODERN MEDICINAL CHEMISTRY: CHALLENGES AND BRAZILIAN CONTRIBUTION. The main aspects of the modern Medicinal Chemistry, among the classic and industrial paradigms, used in the drug discovery process will be treated. The contribution of the Brazilian science in the knowledge generation in Medicinal Chemistry will be demonstrated, with base in searches accomplished in the portal Web of Science[®] 7.10 and in the directory of groups of research of CNPq.

Keywords: medicinal chemistry; prototype; pharmaceutical industry.

Os medicamentos
foram uma das
***maiores* INVENÇÕES**
do Século 20 !



Química Medicinal

JGB Pedreira, LS Franco, EJ Barreiro, Chemical Intuition in Drug Design and Discovery, *Curr Top Med Chem* **2019**, 19, 1679: doi.org/10.2174/1568026619666190620144142

hora do intervalo



Para conversa....

Os pioneiros Fischer, Ehrlich, Bovet

The Nobel Prize
in Chemistry 1902



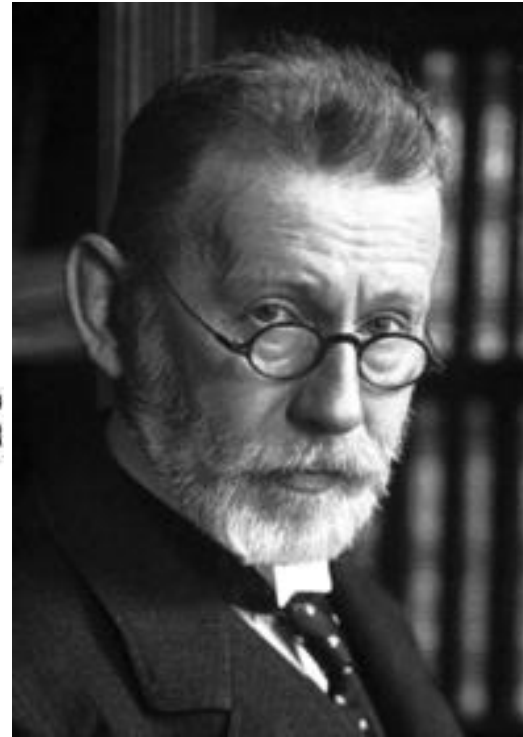
Emil Fischer

1852-1919



LOCK & KEY
CONCEPT

The Nobel Prize in
Physiology or Medicine
1908



Paul Ehrlich

1854-1915



K Strebhardt & A Ullrich, Paul Ehrlich magic bullet concept:
100 years of progress, *Nature Rev. Cancer* **2008**, 8, 473

Química
Medicinal
The Nobel Prize
in Chemistry 1957



Daniel Bovet

1907-1992



III EVQFM



Escola
de Verão
Química Farmacêutica
e Medicinal

Camille G. Wermuth

(1933-2015)

[Chemistry International](#)



Université Louis Pasteur

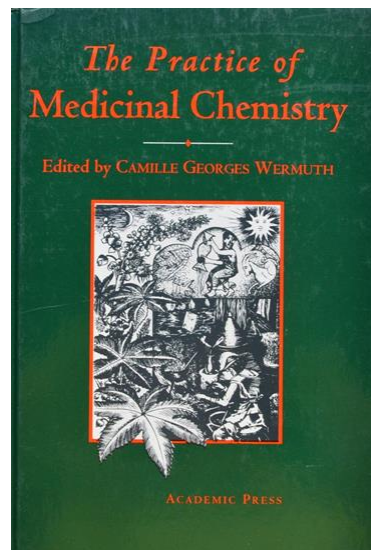
Strasbourg

1969-2002



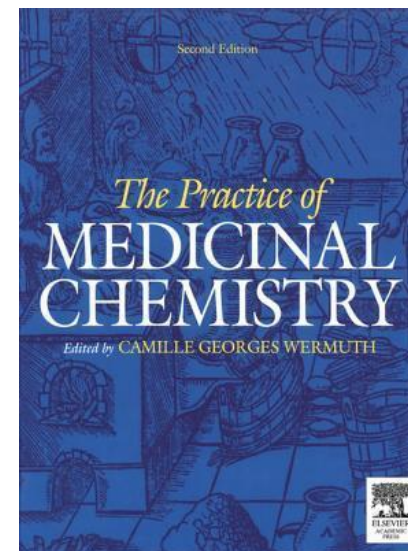
1999 - Prestwick Chemical
Contract Research Organization (CRO)
(Dr Kathleen Clarence Smith)

PRESTWICK CHEMICAL
A medicinal chemistry company

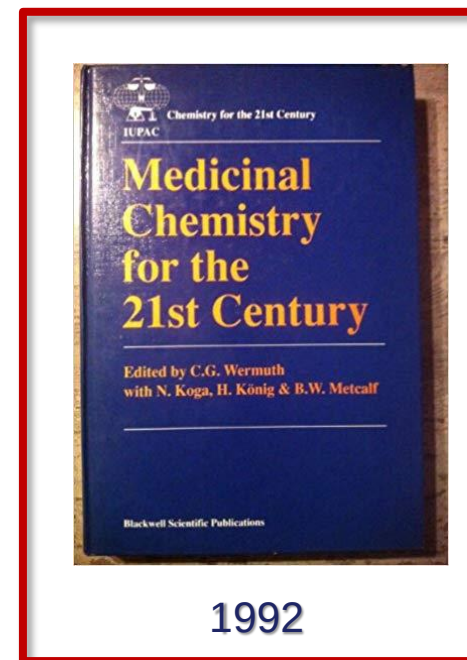


1996

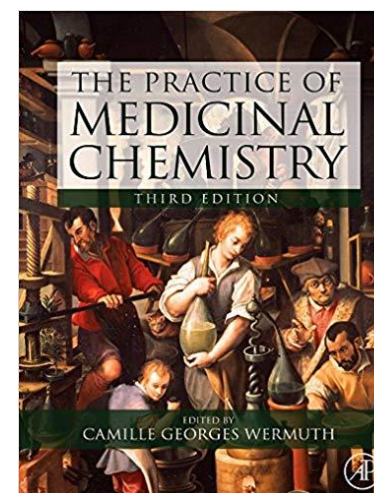
Química
med
Medicinal
chem



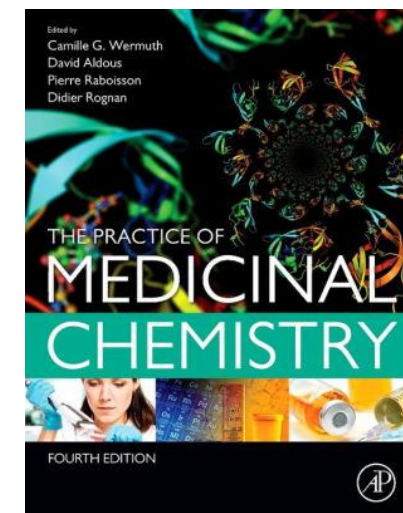
2003



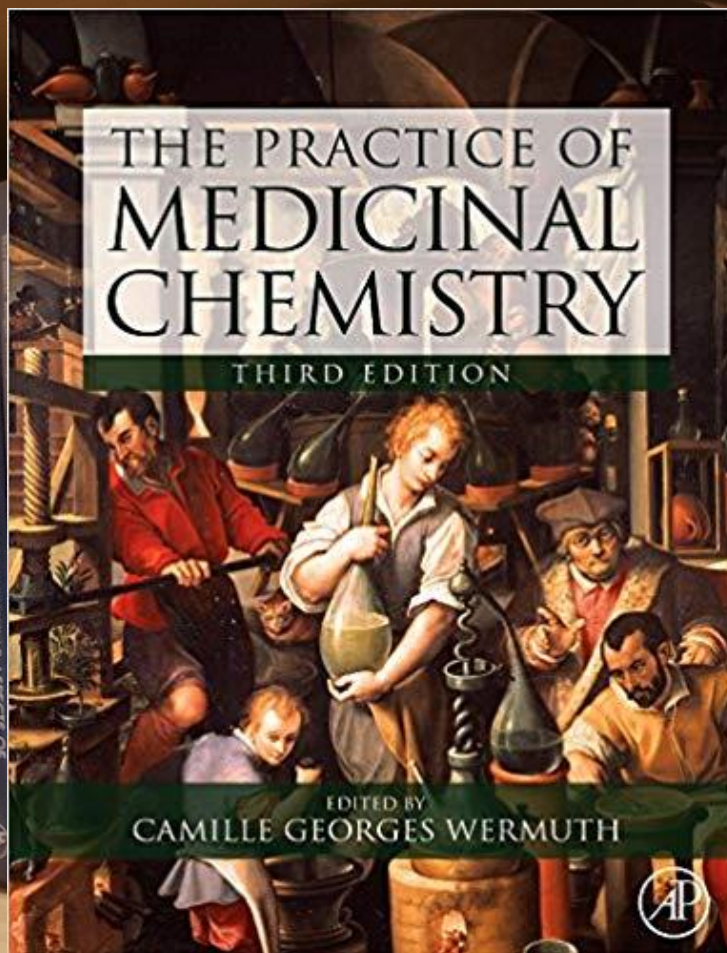
1992



2008



2015

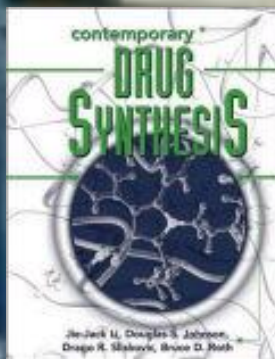


A Maldição de Wermuth

"...In fact,therefore be very careful when starting a new project (in Medicinal Chemistry) and never forget that the worst thing a medicinal chemist can do is to prepare a me-too of an inactive compound!".

Camille G. Wermuth

no Prefácio da 3^a edição do livro "The Practice of Medicinal Chemistry", Elsevier, 2008.



Síntese
Orgânica
NÃO
é Química
Medicinal

■ **224 pesquisadores**
ganharam o Prêmio
Nobel de Medicina
desde 1895-2021



Da esquerda para direita: fila de cima: E Fischer, P Ehrlich, D Bovet, A Fleming, J R Vane;
Fila de baixo: J Black, G B Elion, E G Krebs, B K Kobilka, A Patapoutian

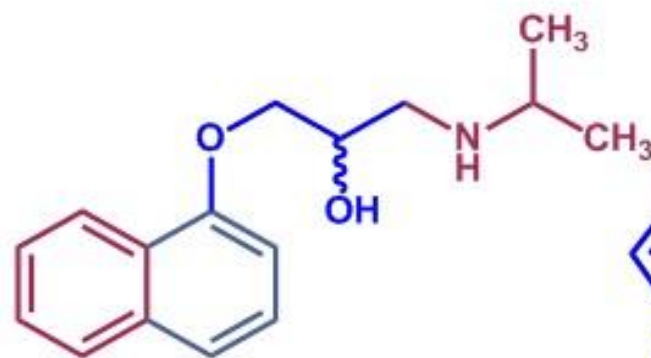


● **187 pesquisadores**
ganharam o Prêmio
Nobel de Química
desde 1901-2021



Inovações Terapêuticas Admiráveis

Química
med
Medicinal
chem



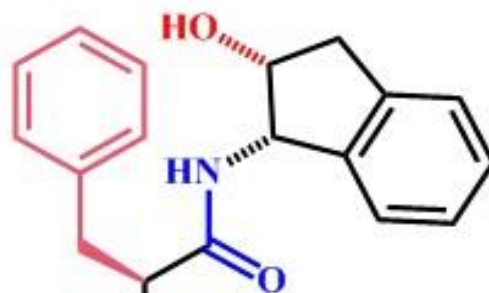
propranolol
1964



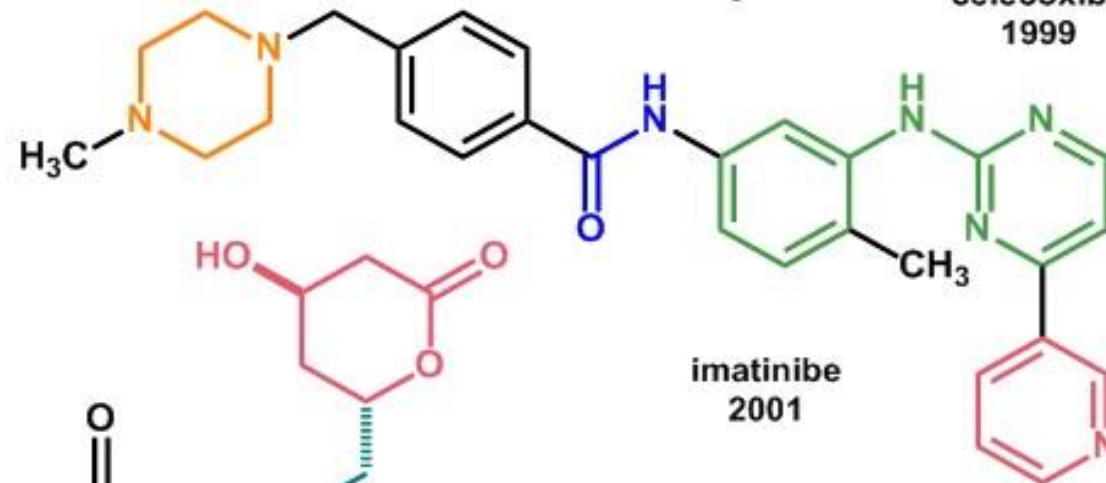
cimetidina
1975



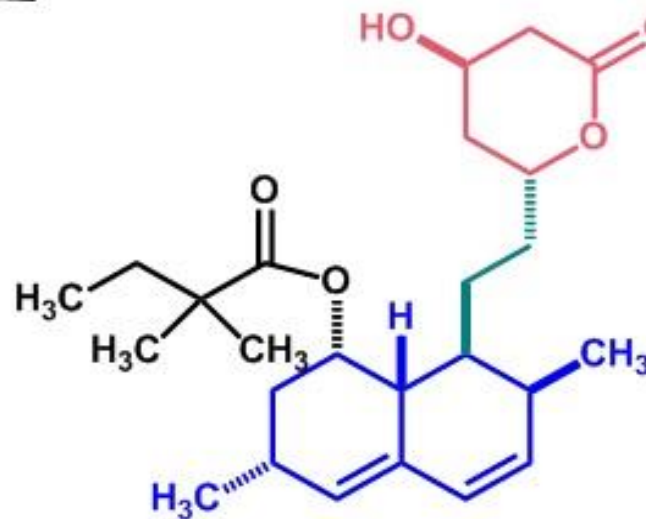
celecoxibe
1999



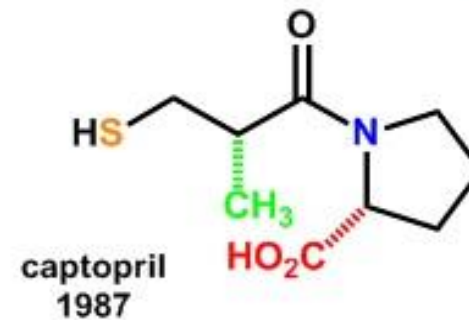
indinavir
1996



imatinibe
2001



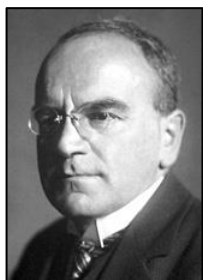
simvastatina
1986



captopril
1987



As estatinas, uma classe terapêutica fascinante



1927

Heinrich Wieland (50)

(1877-1957)



1928

Adolf Windaus (52)

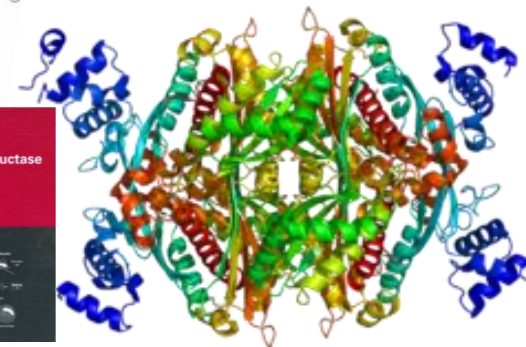
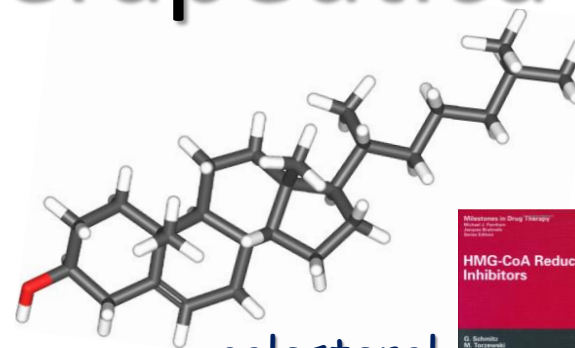
(1876-1959)



1947

Robert Robinson (61)

(1886-1975)



1964

Konrad Bloch (53)

(1912-2000)



Feodor K. Lynen (54)

(1911-1979)



1965

Robert Woodward (48)

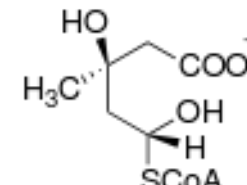
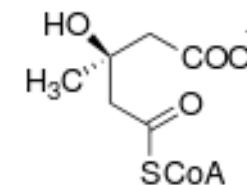
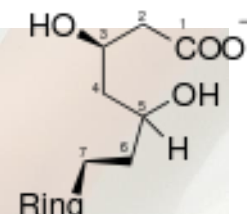
(1917-1979)



1975

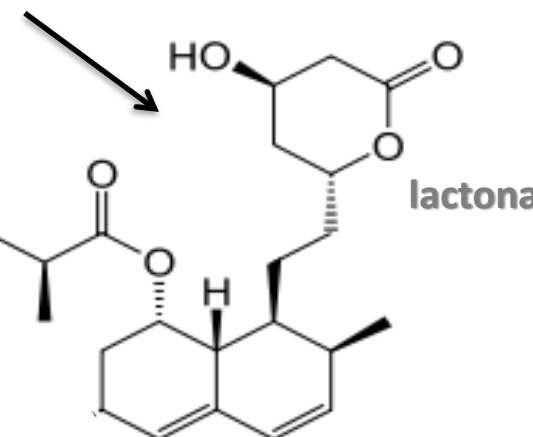
John Cornforth (58)

(1917-2013)



HMG CoA

Mevaldyl CoA transition state intermediate



Mevilonina /compactina



1985

LDL

Joseph L. Goldstein (45)

(1940)

University of Texas, Dallas



1964

Michael S. Brown (44)

(1941)



Dorothy C. Hodgkin (54)

(1910-1994)



Akira Endo

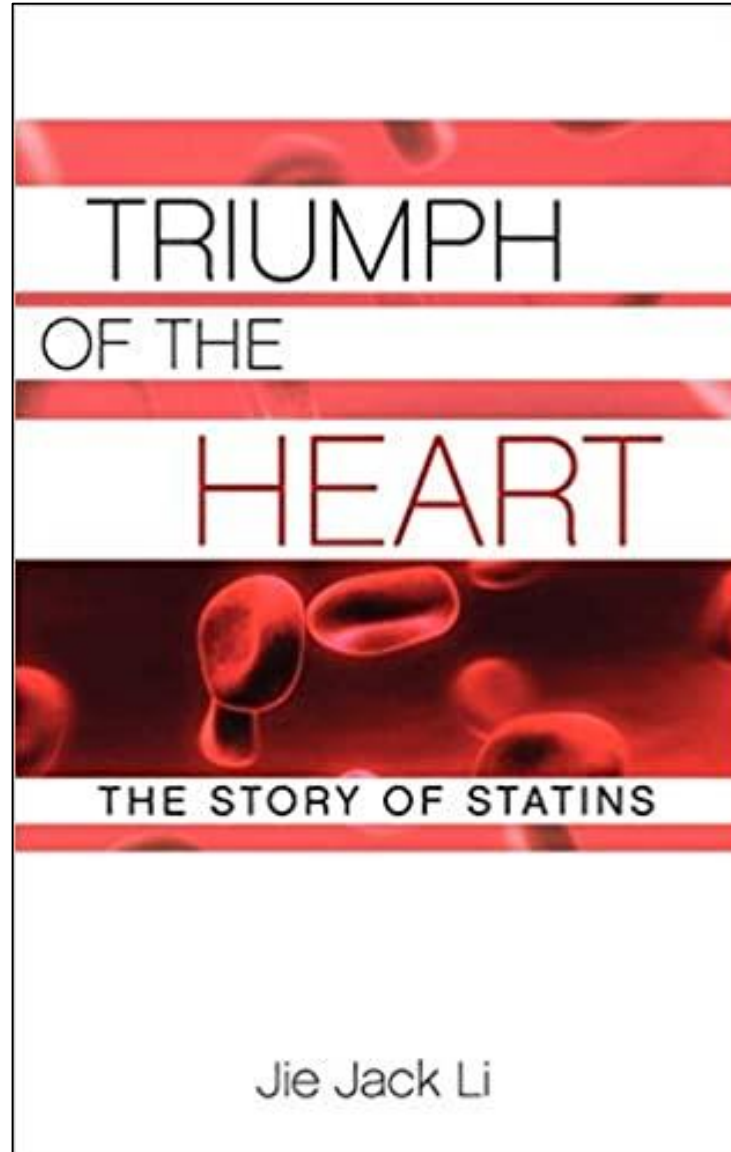
(1933-)

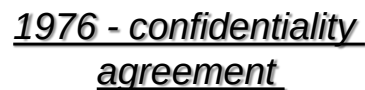
Albert Lasker Award
for Clinical
Medical Research, 2008



J Med Chem
1985, 28, 1







Dr P. Roy Vagelos

(1929-)

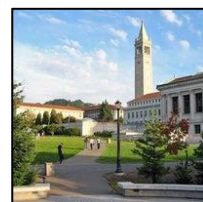
Vice-Presidente Pesquisa
Farmacêutica da Merck
(Presidente & CEO)



1991

atorvastatina

fifth-in-class



Química Medicinal

ZOCOR®
(SIMVASTATIN)

“blockbuster mentality”

1982



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

C. H. Heatcock, Un Berkeley, US

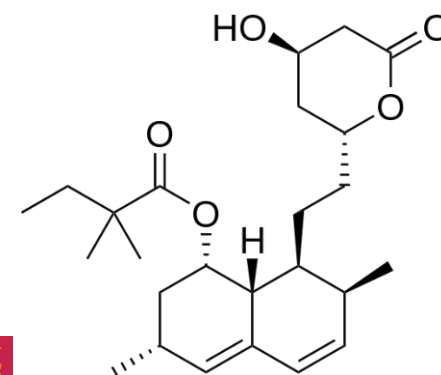


Alfred W. Alberts

Aspergillus terreus



Georg
Albers-Schönberg



simvastatina
first-in-class

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

C. H. Heatcock, Un Berkeley, US

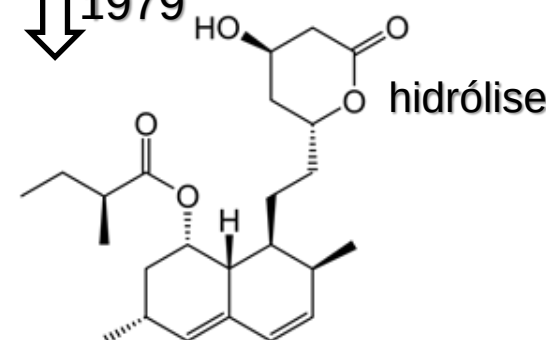


Arthur A. Patchett

**Diretor do Departamento
New Lead Discovery**

Alfred Burger Award 2002

↓ 1979



Aspergillus terreus
lovastatina

A descoberta da lovastatina

> 45 milhões de pessoas usaram estatinas (2005)

Estatinas

Química
med
Medicinal
chem

atorvastatina

ácido (*N*-pirrol)-3,5-di-hidróxi-heptanóico

1991 → 1997



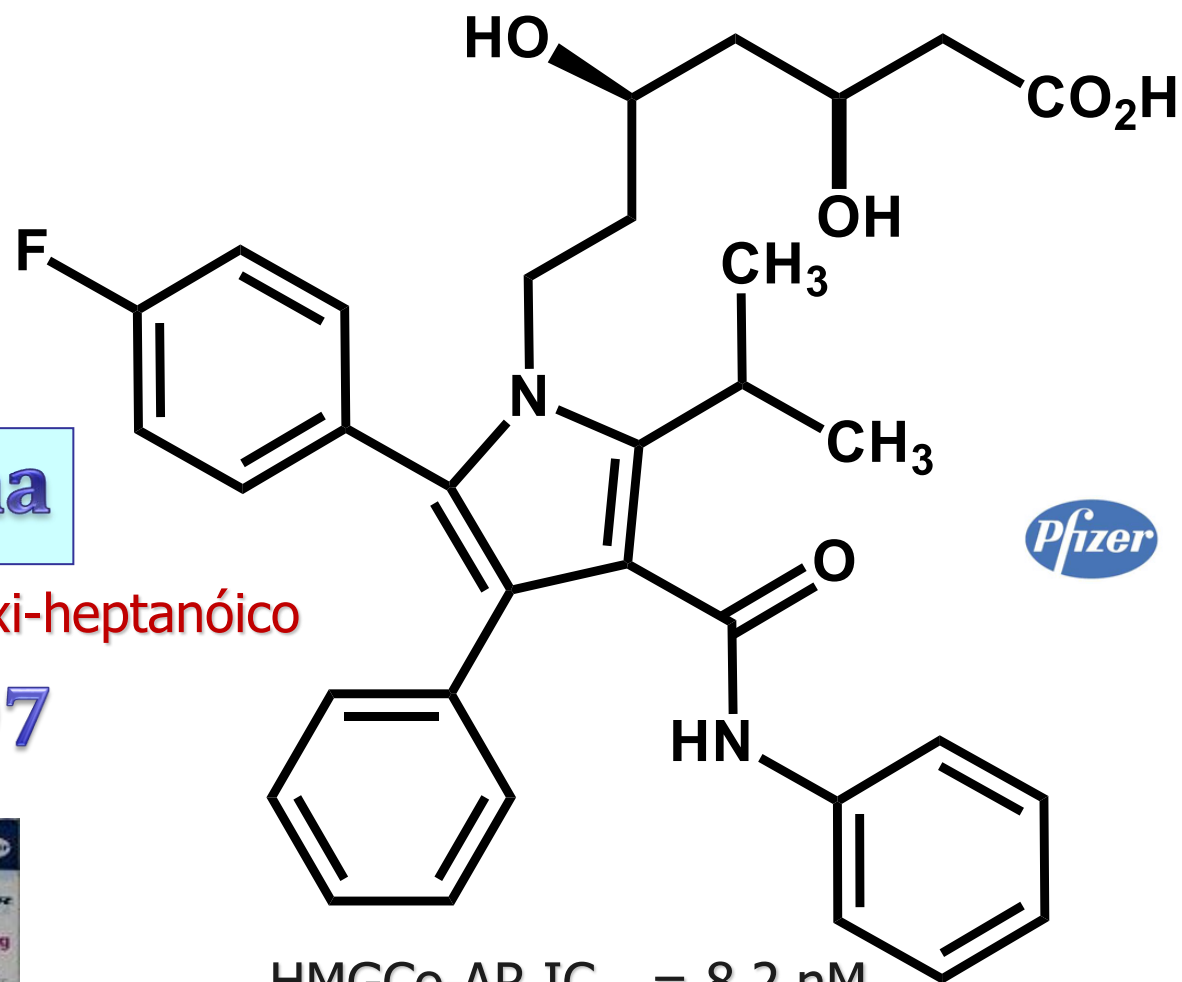
Bruce D Roth

2013 SCI Perkin Medal

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

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

Warner-Lambert



Pfizer



HMGCo-AR IC₅₀ = 8,2 nM

Biodisponibilidade=12%

2005 – US\$ 13 bi; 2011 – US\$ 13,3 bi;

Síntese: *ca.* 200 toneladas/ano
ca. >> 45 milhões de pessoas (2005)



Total de Vendas = *ca.* US\$ 150 bilhões (1991-2011)



TURNING TO TEAMWORK
Drug firms huddle on intractable diseases P12

Pfizer to close UK research site

Drug maker Pfizer is to close its research and development (R&D) facility in Kent, which employs 2,400 people.

<http://www.bbc.co.uk/news/business-12335801>



Pfizer Global Research & Development, Sandwich, UK



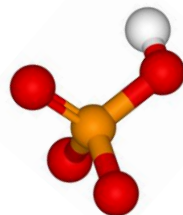
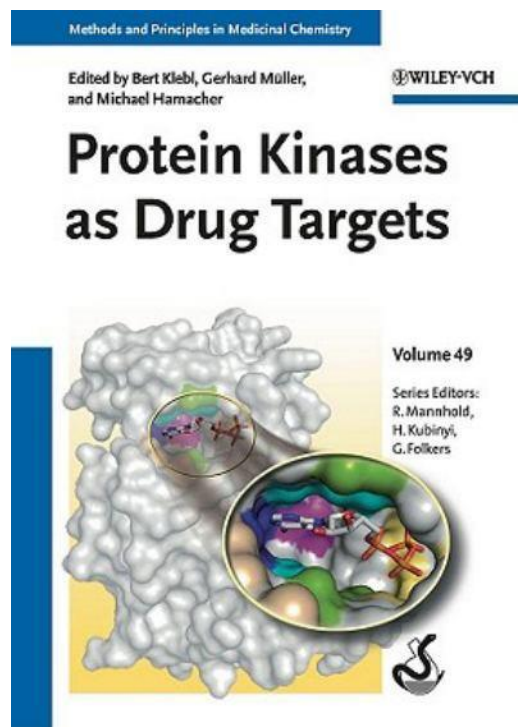
Imatinibe, o primeiro-da-classe “top-1”



Harold E. Varmus (50)
(1939)



1989

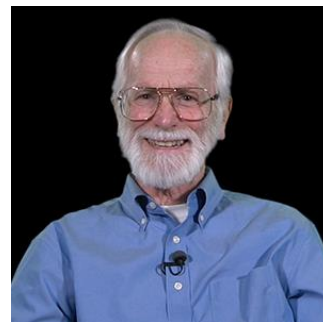


kinoma

Edwin G. Krebs (72)
(1918 –2009)



2001



J. Michael Bishop (53)
(1936)

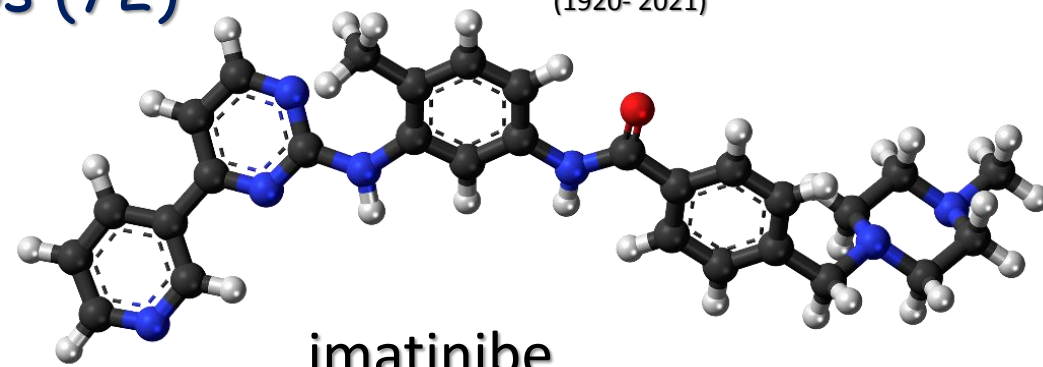
“for their discovery of the cellular origin of retroviral oncogenes”



1992



Edmond H. Fischer (72)
(1920- 2021)



imatinibe

TIMELINE

Protein kinases — the major drug targets of the twenty-first century?

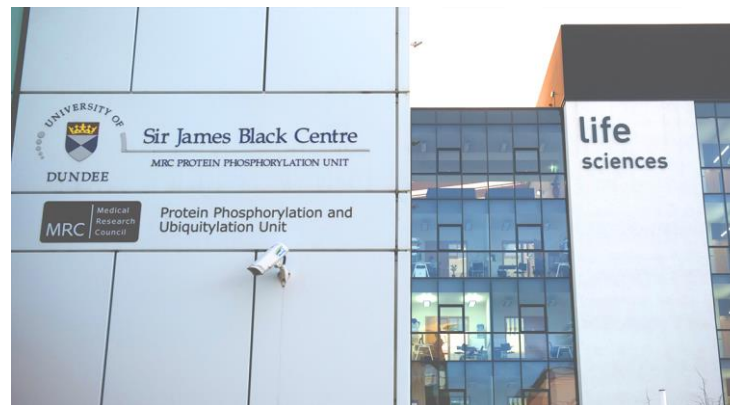
Philip Cohen

NATURE REVIEWS | DRUG DISCOVERY

VOLUME 1 | APRIL 2002 | 309



(1945)

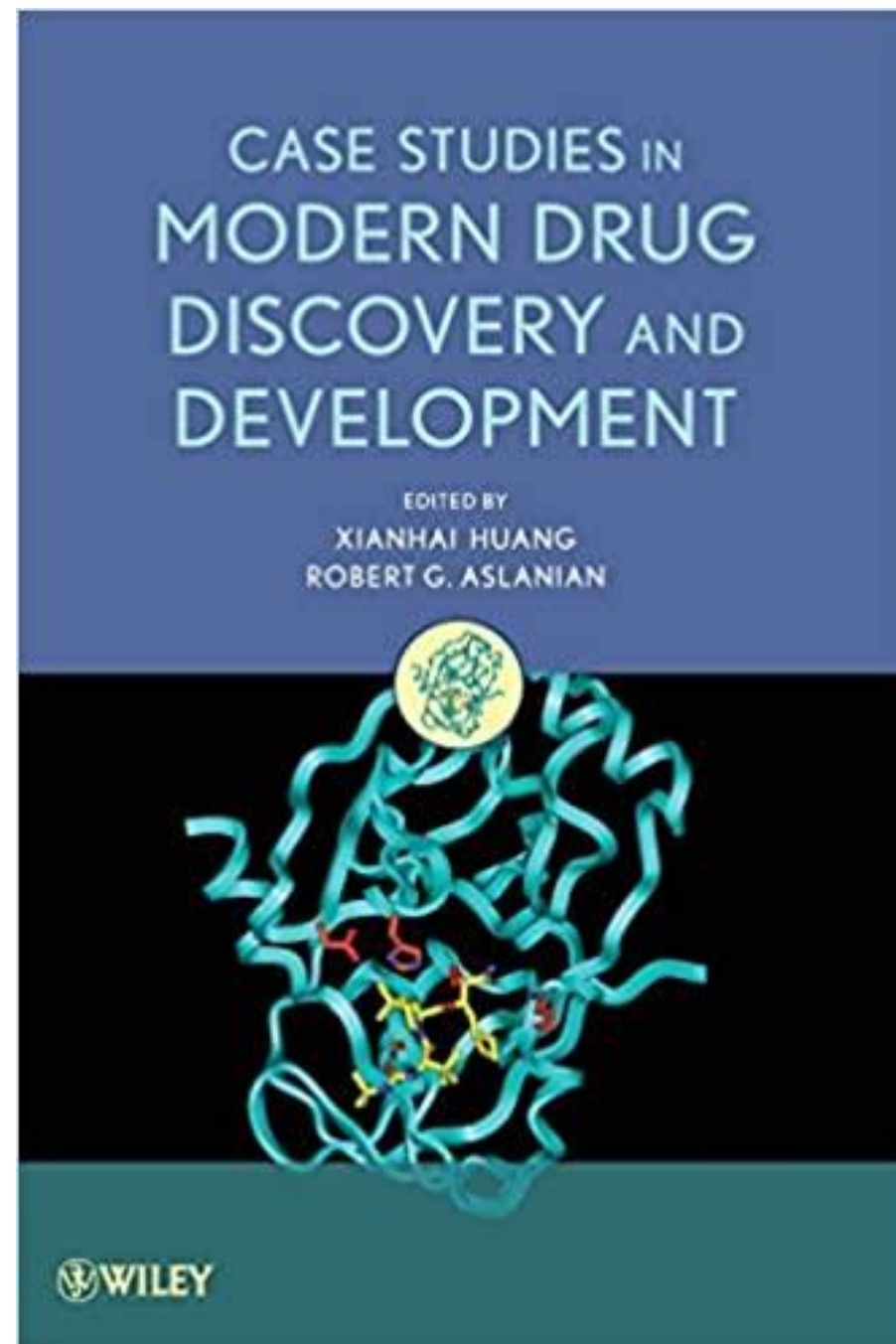


University of Dundee, Scotland





E. J. Barreiro, A. E. Kümmerle, C. A. M. Fraga,
The methylation effect in medicinal chemistry,
Chem Rev **2011**, *111*, 5215.

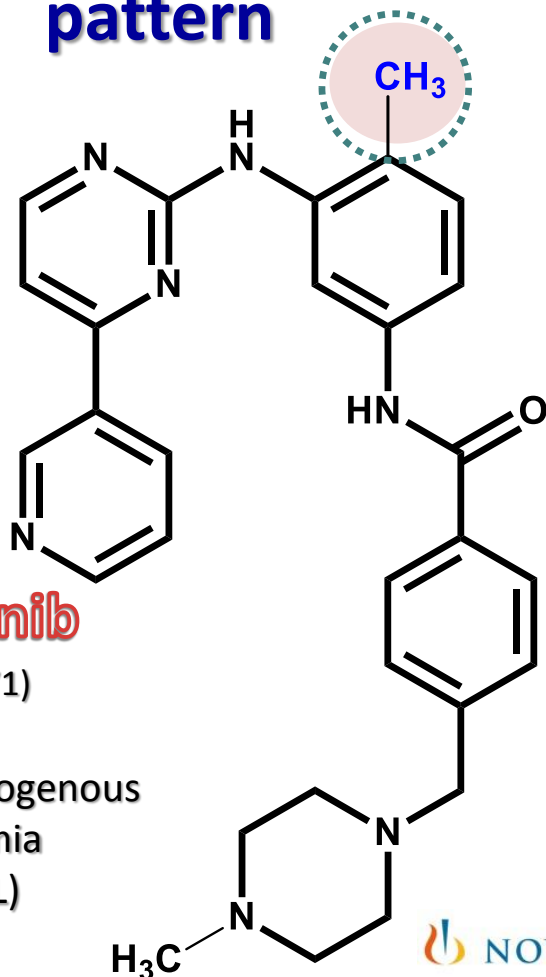


New molecular pattern

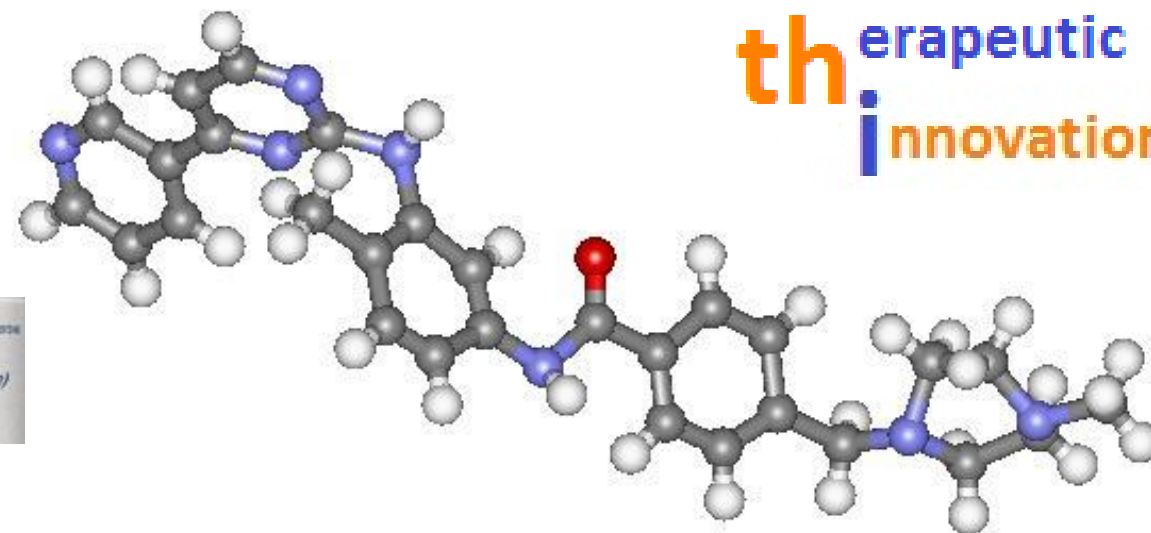
imatinib

(STI571)

chronic myelogenous leukemia (CML)



NOVARTIS



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

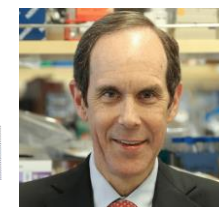
1990 – Jürg Zimmermann

1995 - Compound STI571 ++

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



Nicholas B. Lydon*
(1947)



Brian J. Druker*
(1955)



Charles L. Sawyers**
(1959)

* Blueprint Medicines Inc

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

Awarded with the 2012 Japan Prize in Healthcare and Medical Technology;

** Named in 2011, Thomson Reuters Citation Laureate in Medicine;



Edição Virtual
25 a 28 de
janeiro de 2022

Data limite
para entrega
dos
relatórios
individuais de
atividades de
2021.



REALIZAÇÃO

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

PATROCÍNIO

REDES SOCIAIS

UFRJ

PARTICIPEM

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A história do LASSBio

Revista Virtual de Química

ISSN 1984-6835

Artigo

As Longas Pernas do Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio®): Histórico e Perspectivas

Barreiro, E. J.

Rev. Virtual Quim., 2013, 5 (2), 266-282. Data de publicação na Web: 19 de janeiro de 2013

DOI: [10.5935/1984-6835.20130026](https://doi.org/10.5935/1984-6835.20130026)



http://www.lassbio.icb.ufrj.br/20anos_apresenta.html#

Hora das respostas.

2022



Porque são
importantes os
seminários do



?