Universidade Federal do Rio de Janeiro

Seminários VDEPI

Complexo Tecnológico de Medicamentos
Farmanguinhos / Fiocruz

2011 SBQ ANO INTERNACIONAL DA QUÍMICA

"A QUÍMICA MEDICINAL E A INOVAÇÃO EM FÁRMACOS:

o papel do INCT- INOFAR"

Eliezer J. Barreiro

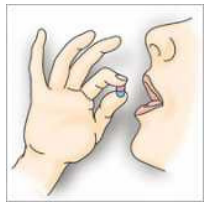
Professor Titular
U F R J

Laboratório de Avaliação e Síntese de Substâncias Bioativas

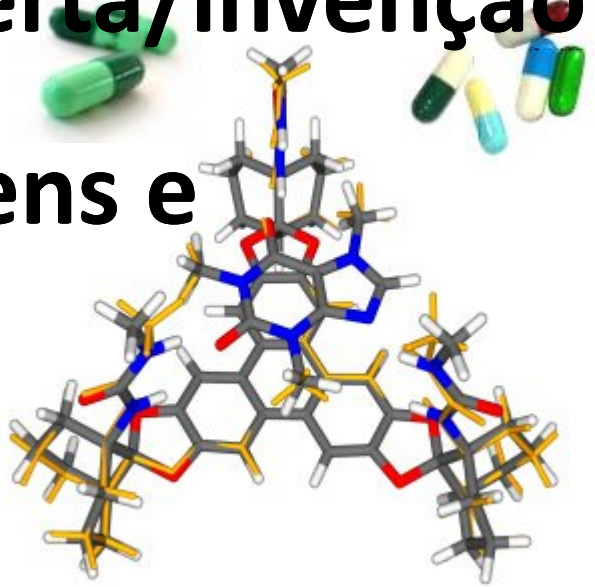
Instituto Nacional de Ciência e Tecnologia
de Fármacos e Medicamentos
INCT-INOFAR

Universidade Federal do Rio de Janeiro

Química Medicinal

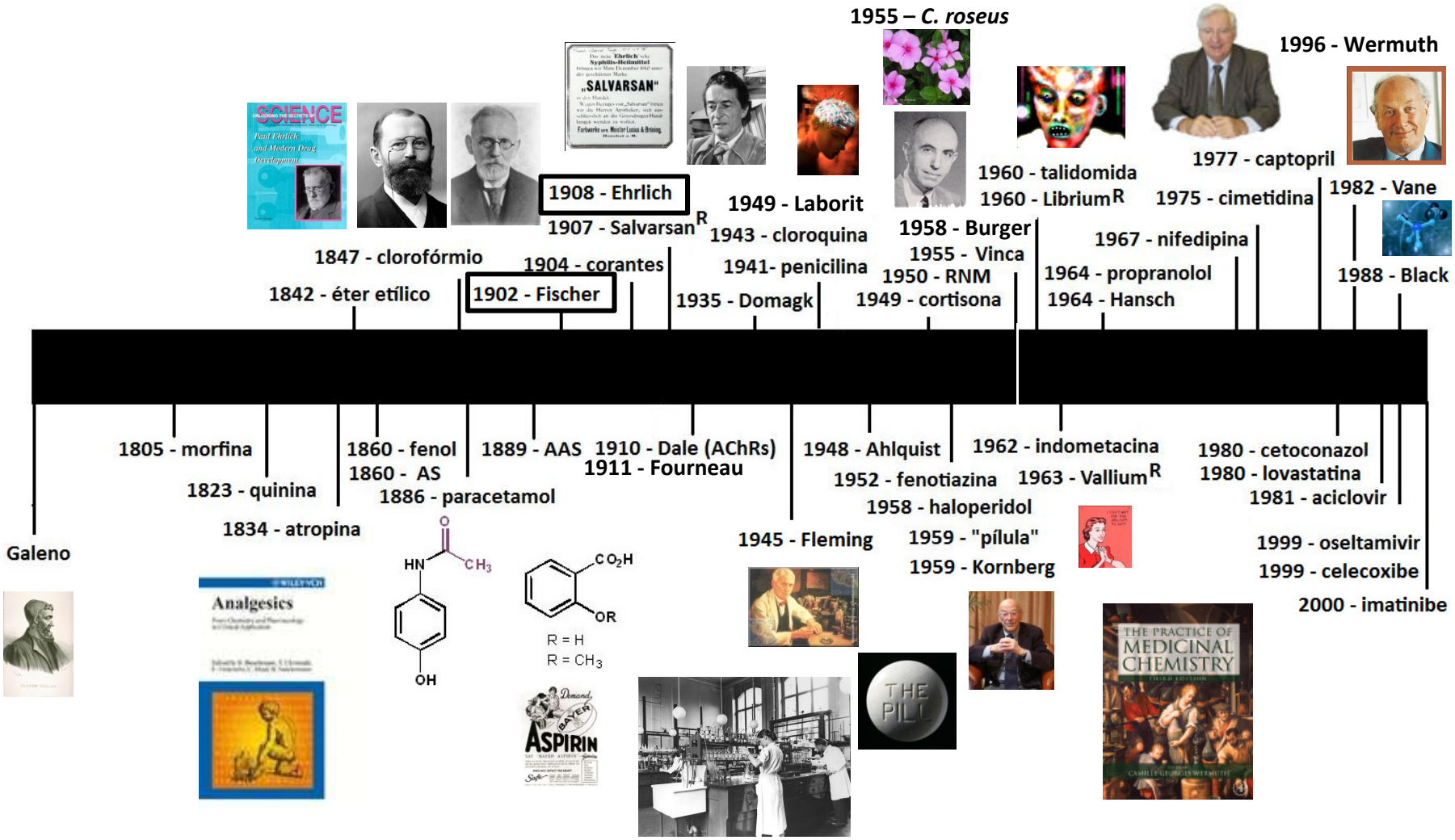


A Química Medicinal estuda as razões moleculares da ação dos fármacos, sua descoberta/invenção empregando abordagens e estratégias interativas multidisciplinares.



Universidade Federal do Rio de Janeiro

Cronologia histórica da Química Medicinal



Paradigma de Ehrlich & Fischer: Primeiro Paradigma da Química Medicinal

LASSBio®

http://ejb-eliezer.blogspot.com

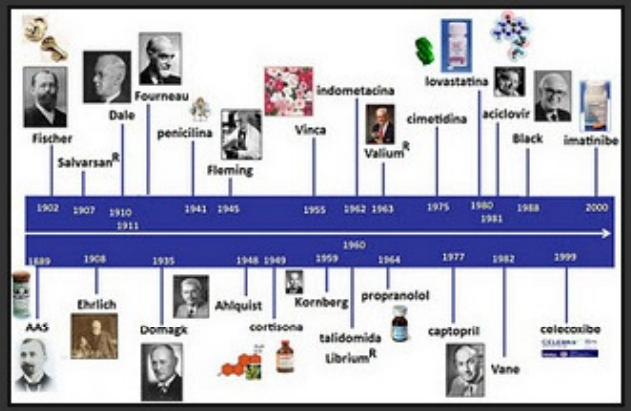
De fármacos e suas descobertas

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

http://ejb-eliezer.blogspot.com

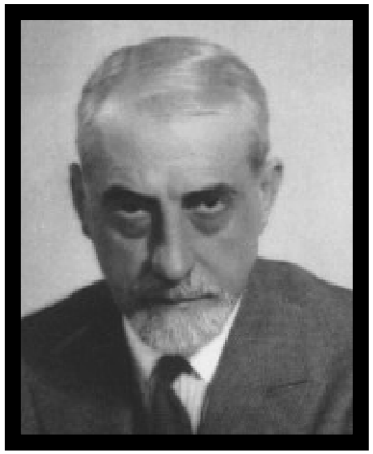
SEGUNDA-FEIRA, 14 DE NOVEMBRO DE 2011

A Linha do Tempo da Química Medicinal: assim nascem os fármacos (III)



A descoberta da penicilina promoveu o desenvolvimento da quimioterapia e inúmeros e diversos antibióticos se somam na composição do atual arsenal terapêutico. Além da diversidade química destas substâncias bioativas, em termos moleculares, vários são seus os mecanismos farmacológicos de ação. Ao lado dos antibióticos, outros fármacos são classificados como qumioterápicos e entre estes estão os fármacos oncológicos, onde se encontram os antibióticos anti-câncer, como as antraciclínas, e destacam-se a daunomicina (daunorubicina) descoberta nos laboratórios Farmitalia na cidade de Milão, Itália, por Aurelio Di Marco, em 1962, isolada do fungo *Streptomyces peucetius* e seu derivado 14-hidroxilado, adriamicina, que podem ser consideradas as moléculas pioneiras desta classe de agentes oncológicos.

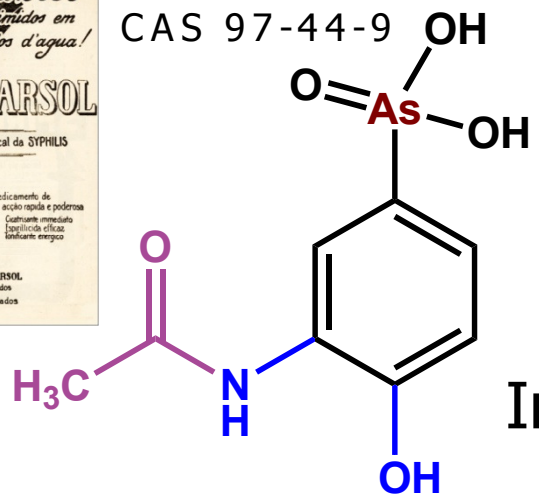
O berço da Química Medicinal



Ernest Fourneau
1872-1949

Stovarsol

CAS 97-44-9



Institut Pasteur (1887)

1911- Laboratoire de Chimie Thérapeutique

Diretor: Emile Roux

SOME ASPECTS OF THE RELATIONSHIP BETWEEN CHEMICAL CONSTITUTION AND CURARE-LIKE ACTIVITY

By Daniel Bovet*
Istituto Superiore di Sanita, Rome, Italy

Definition

Historical Background. Curarizing substances represent a group of pharmacodynamic agents whose effects reproduce those of different types of Indian curare and its active principles (d-tubocurarine, C-toxiferine, C-curarine I).

Ann. NY Acad. Sci. 1951, 54, 407-437

Daniel Bovet
1907-1992 *

*Farmacêutico suiço
Doutor *h.c.* UFRJ

Prêmio Nobel de Fisiologia/Medicina
1957
anti-histamínicos
(sulfonamidas)

Curare: SAR

J-P Fourneau, « Ernest Fourneau foundateur de la Chimie Pharmaceutique française », *Revue de l'Histoire de la Pharmacie*, t.XXXIV, nº 275, 335-355

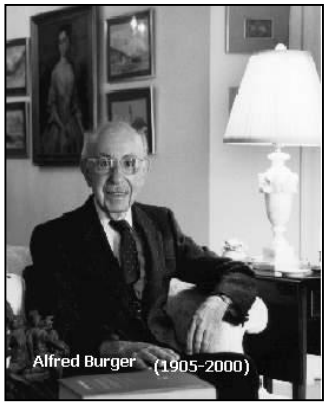
Drug Design and Development. A Realistic Appraisal*

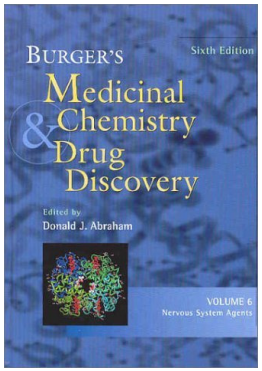
Alfred Burger

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901. *Received December 29, 1976*

J. Med Chem. **1978**, *21*, 1

The discovery of new biologically–therapeutically active structures continues to depend on screening and on isolated observations of unexpected drug metabolites and drug activities. The selection of therapeutically improved and useful chemicals requires molecular modification. Refinements in intuitive and physicochemical methodology can provide shortcuts in random choices and permit extrapolations of some facets of activity with a variable degree of accuracy. The final decisions concerning the usefulness of a drug remain in the domain of experimental and clinical pharmacology.





Prof. Alfred Burger

(1904-2000)

University of Virginia

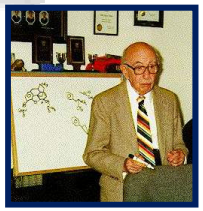
EUA

1958 – fundou o Journal of the Medicinal and Pharmaceutical Chemistry → depois Journal of Medicinal Chemistry

---

"An Editor's Commentary on the Birth of a Journal", *J. Med. Chem.* **1991**,*34*, 2-6

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

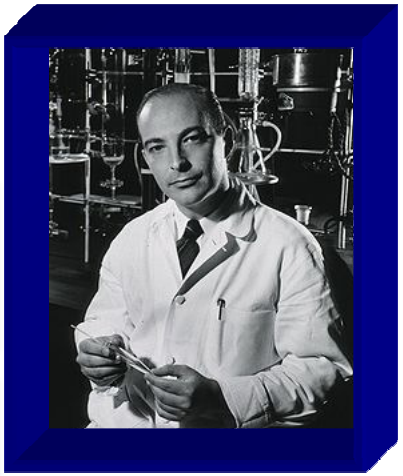


Alfred Burger

em "The practice of medicinal chemistry", Wiley, 1970, p. 4.

EJB2

UFRJ



Arthur Kornberg
1918-2007

Prêmio Nobel, 1959

The Two Cultures: Chemistry and Biology[1]

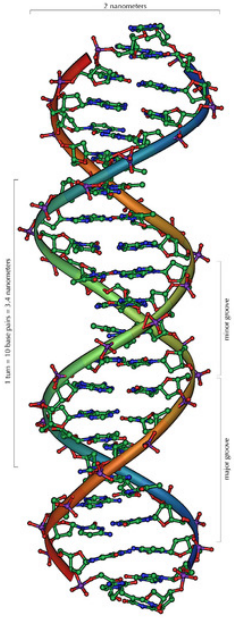
1987

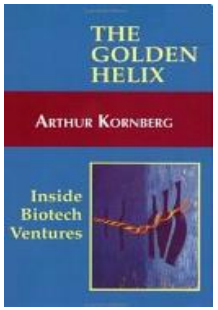
Interdisciplinaridade

Department of Biochemistry, Stanford University, Stanford, California 94305

Received July 14, 1987

"Much of life can be understood in rational terms if expressed in the language of chemistry... the historical roots of chemistry and biology are intertwined in many places…





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

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

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

LASSBio®

Slide 8

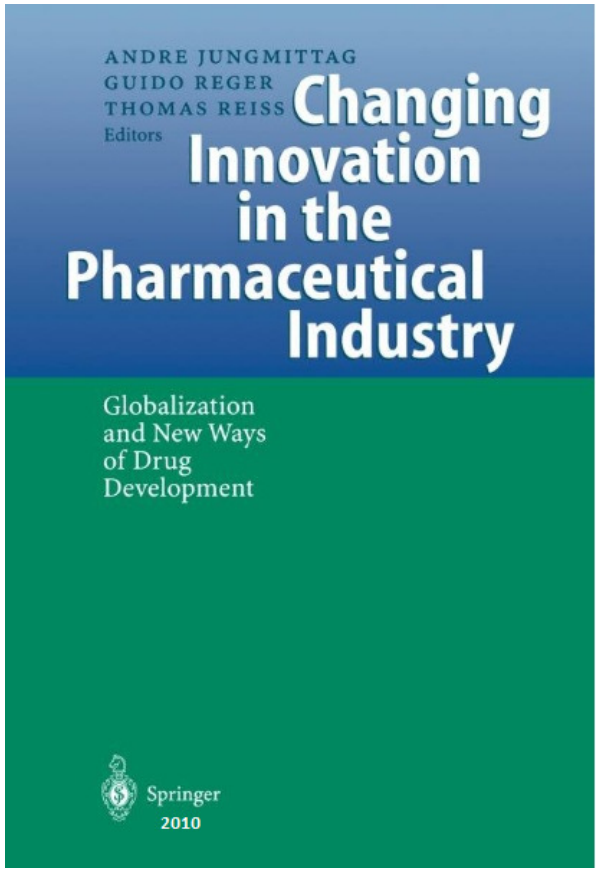
EJB2

Kornberg definiu as bases da interdisciplinaridade das ciências dos fármacos quando antecipou a necessidade de aproximar-se a Química e a Biologia.

Eliezer J. Barreiro; 04/03/2010

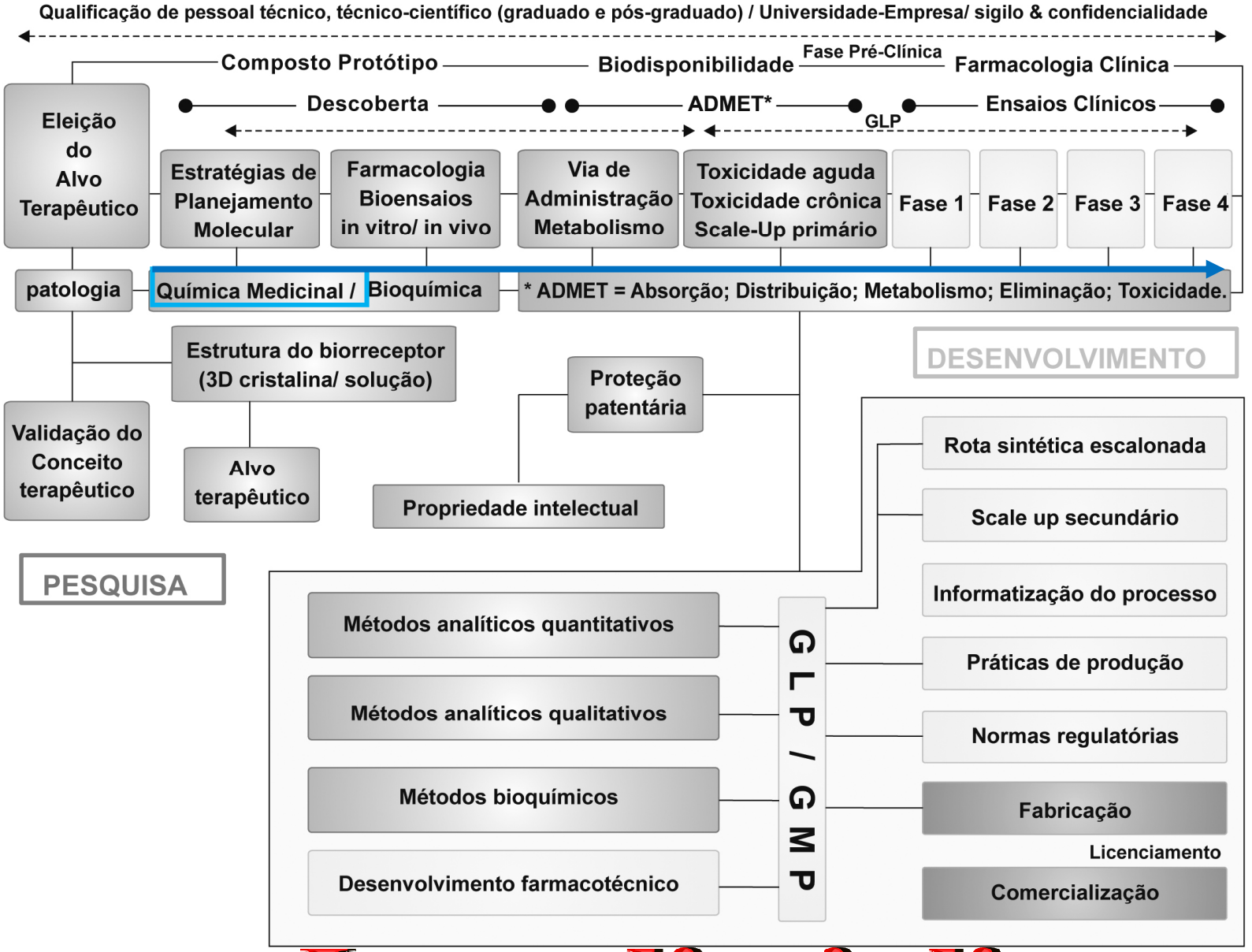
Universidade Federal do Rio de Janeiro

A inovação tecnológica é um dos processos mais dinâmicos da atividade industrial. Este dinamismo se expressa de forma acentuada na inovação tecnológica farmacêutica que, mais do que qualquer outra, depende da efetiva interação entre Ciência & Tecnologia.



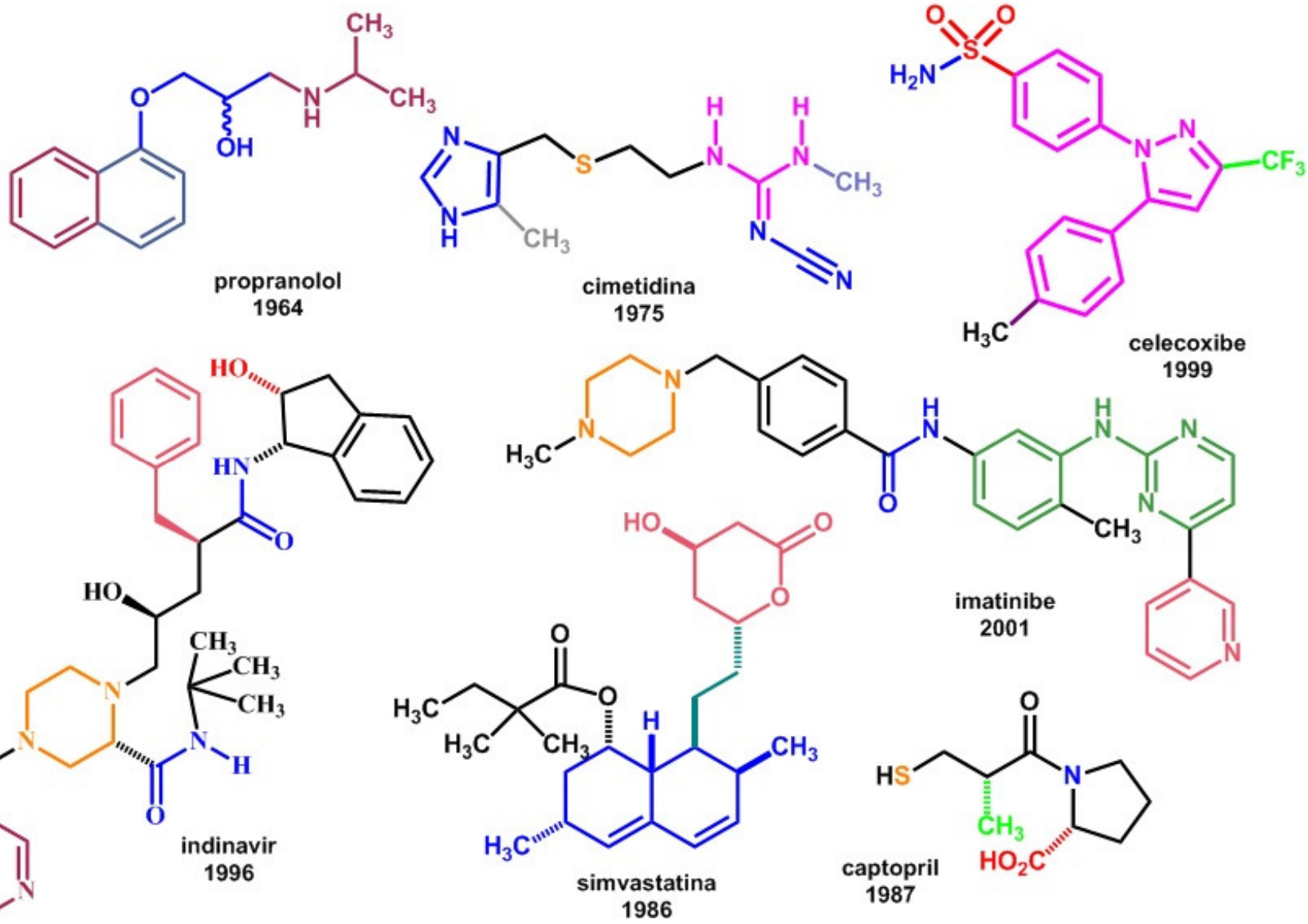
A **inovação farmacêutica** é produto da *descoberta* ou da *invenção e* o principal *driving-force* da indústria farmacêutica que *desenvolve* fármacos e que faturou US$ 850 bilhões, em 2010.

A cadeia de inovação radical de fármacos



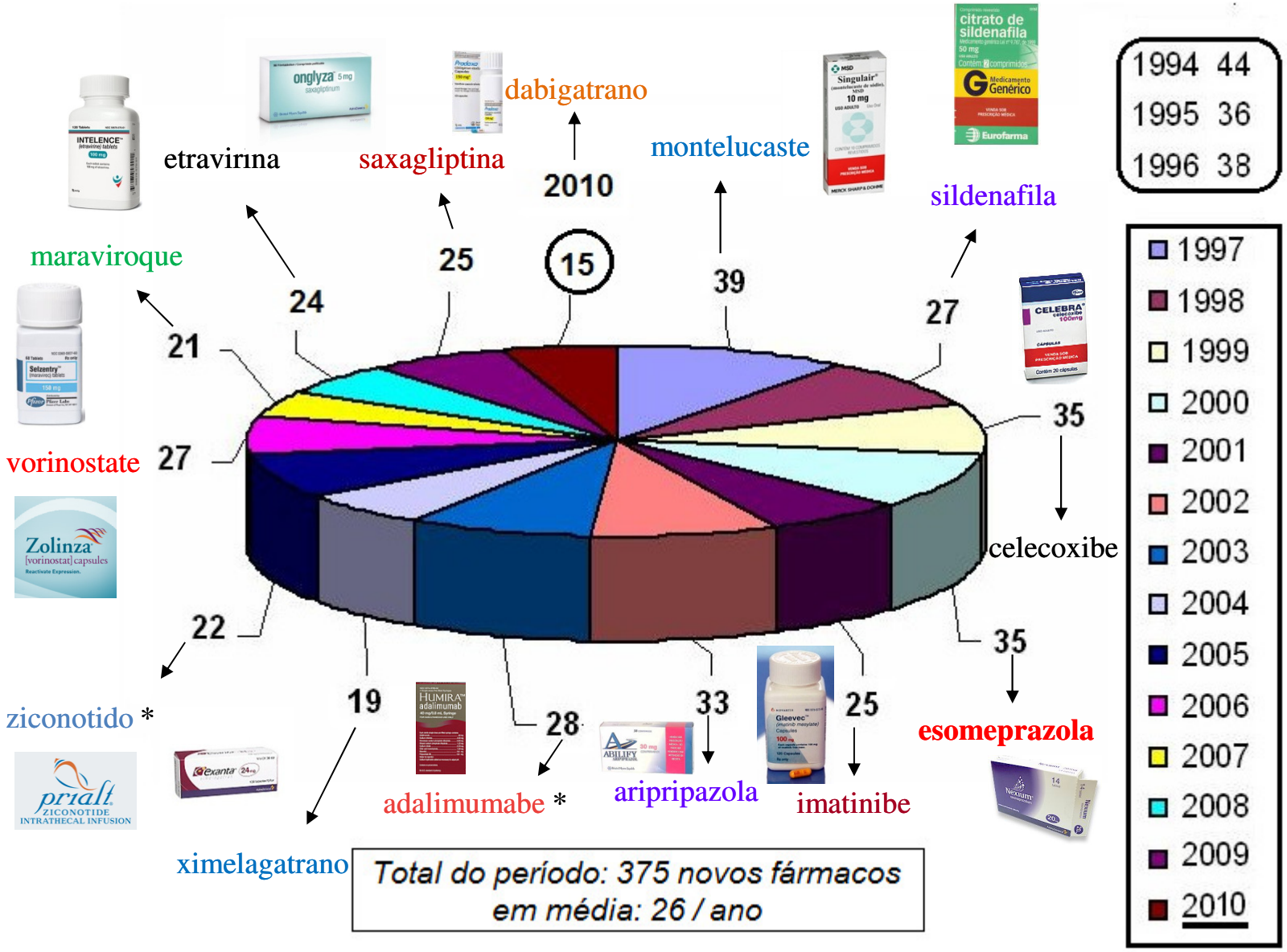
Interdisciplinar

Alguns fármacos inovadores



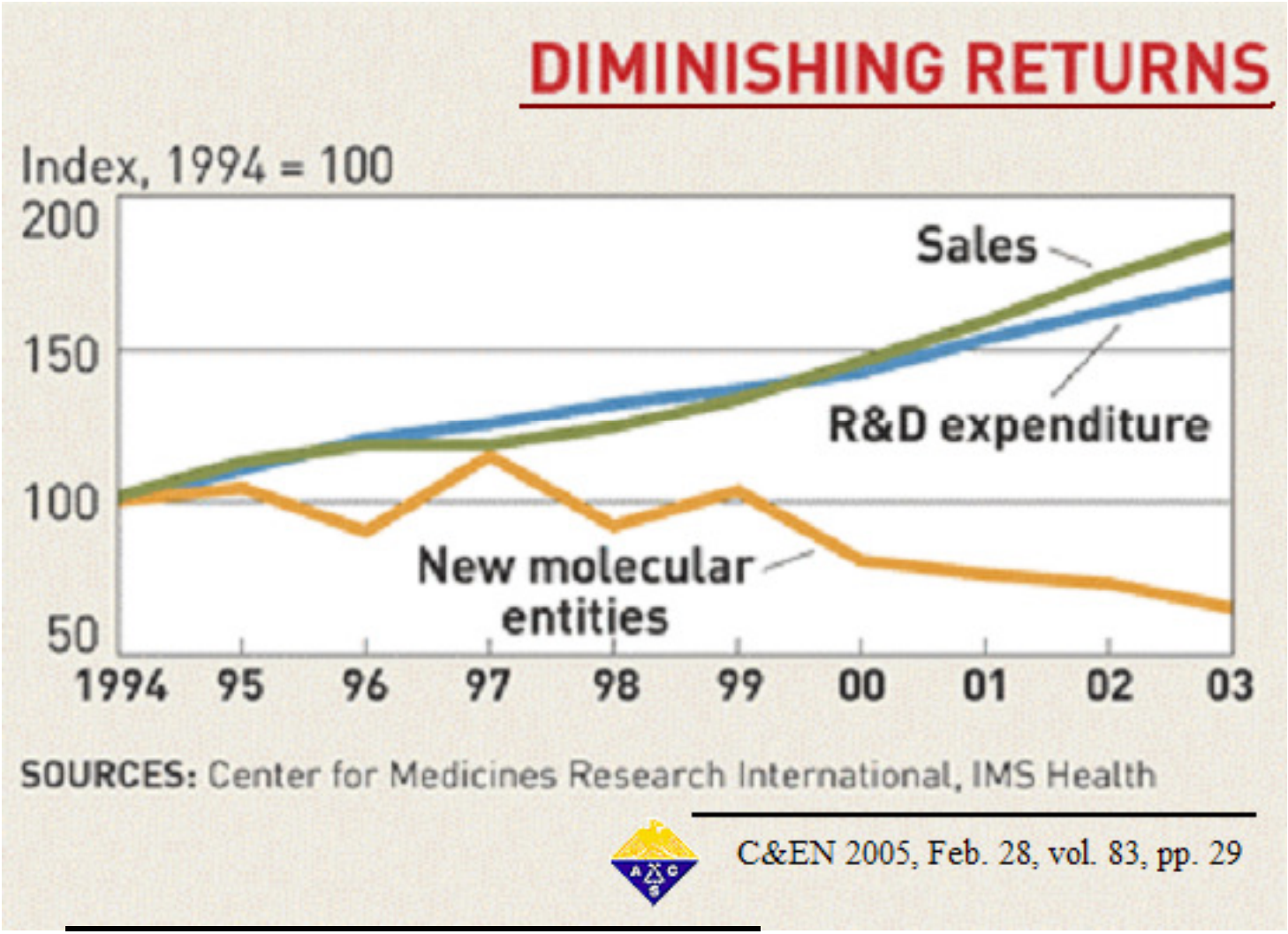
Universidade Federal do Rio de Janeiro

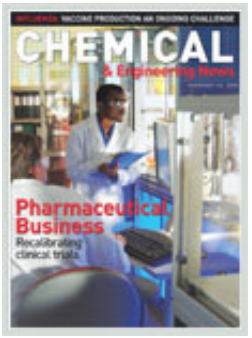
Novos fármacos



A IF que inova em fármacos investe 10-15% do faturamento em P&D

Crise de produtividade na Bigpharma

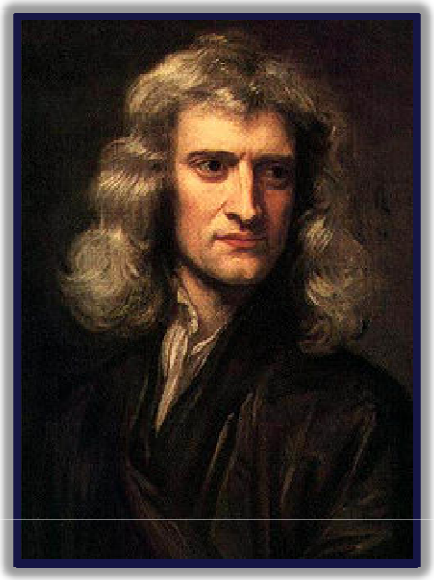




O investimento em PD&I teria sido *ca.* US$ 85 bilhões (2010)!

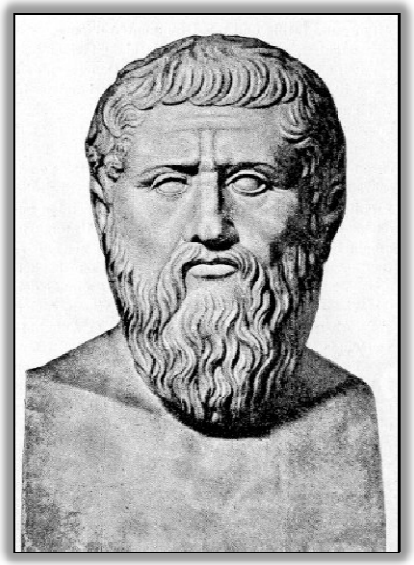
A. Mullard, 2010 FDA drug approvals, *Nat. Rev. Drug Discov.* **2011**, *10*, 82 (doi: 10.1038/nrd3370)

O que tinham em comum estes gênios?



Sir Isaac Newton
(1643-1727)

1667



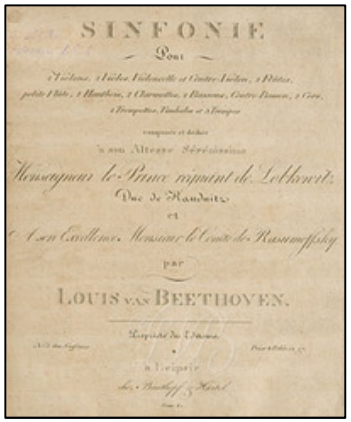
Platão
(428-347 aC)

A Republica

Leonardo da Vinci
(1452-1519)

A Santa Ceia

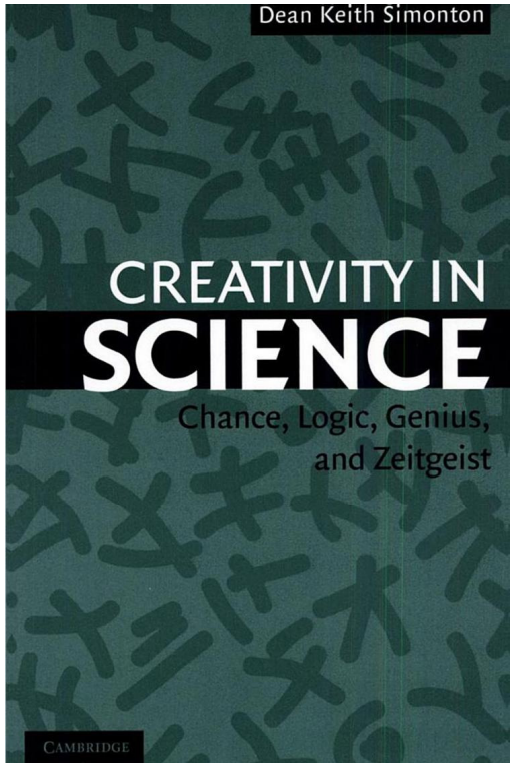
Ludwig van Beethoven
(1770-1827)



Sinfonia nº 5

D Keith Simonton

Inovação & Criatividade



http://psychology.ucdavis.edu/Simonton

Scientific creativity is a topic addressed by many distinct disciplines or what have been termed *metasciences*

The most important of these metasciences are the history of science, the philosophy of science, the sociology of science, and the psychology of science. Not surprisingly, each of these metasciences has a somewhat distinctive outlook on the phenomenon. Part of the disciplinary variation may result simply from contrasts in methodological techniques and substantive interests. Where historians prefer narratives, philosophers favor analyses. While sociologists like to discuss institutions, psychologists like to look at individuals. Nonetheless, some of the differences among the metasciences are also based on the essential fact that scientific creativity can be examined from four principal perspectives: logic, genius, chance, and zeitgeist.

- O ambiente propício à criatividade existe, *naturalmente*, na Academia, favorecendo a produção do conhecimento novo e a pesquisa científica inovadora !

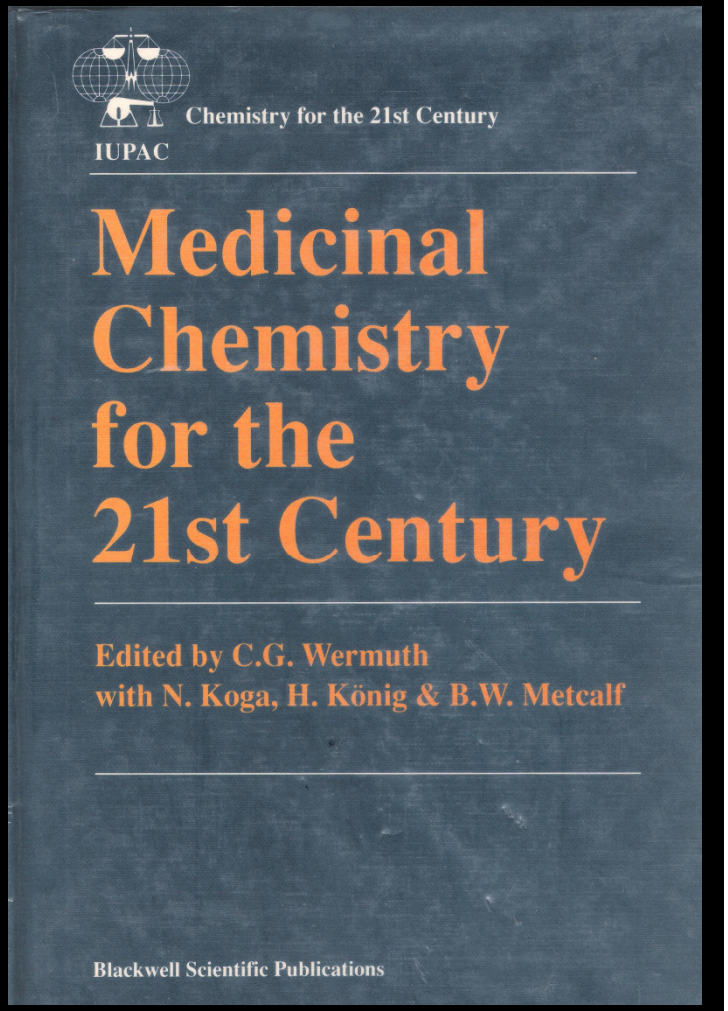
A Química Medicinal

Século 21

Siglo 21

21st Century

Siécle 21



Criatividade inovadora *MedChem*

Current Drug Therapy, 2008, *3*, 000-000

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

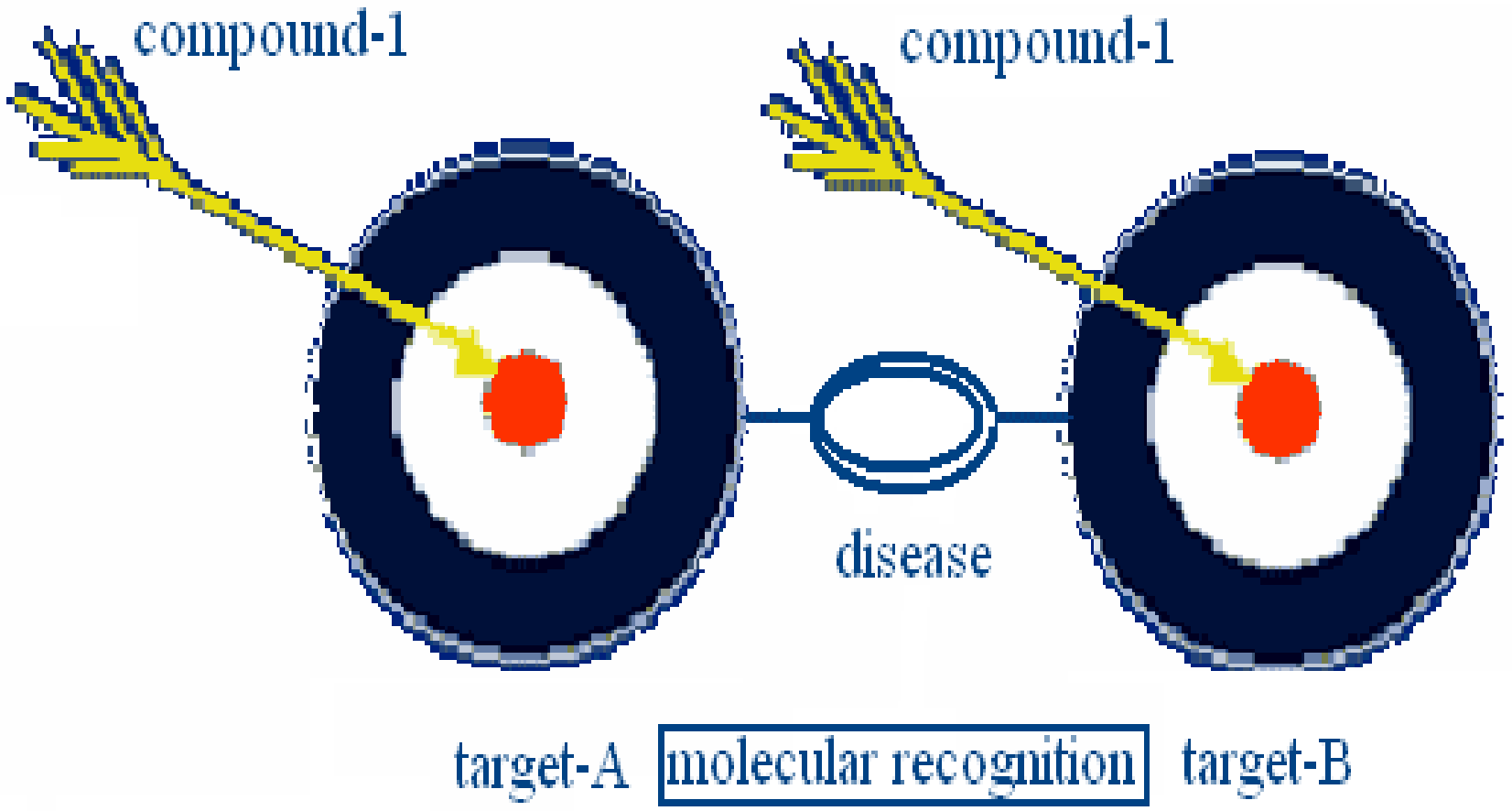
Eliezer J. Barreiro and Carlos Alberto Manssour Fraga

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.

Química Medicinal

O tratamento de uma patologia multifatorial (*e.g.* doenças crônicas não transmissíveis, câncer, metabólicas, etc) com fármacos planejados para *alvos terapêuticos únicos* (*Primeiro paradigma da Química Medicinal* ou *Paradigma de Ehrlich & Fischer*) será sempre paliativo! Estas patologias requerem fármacos multi-alvos, *i.e.* duplos, mixtos, múltiplos ou simbióticos.

The multiple-target lead design

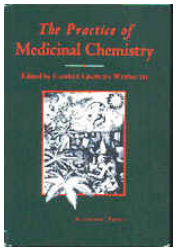


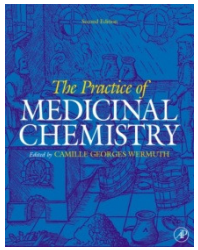
Segundo paradigma da Química Medicinal

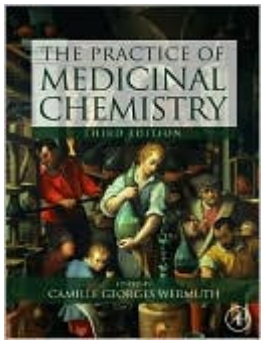
Universidade Federal do Rio de Janeiro

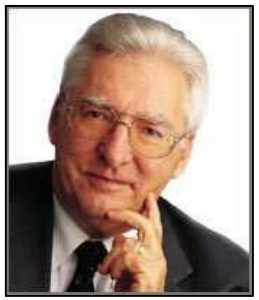
Química Medicinal

" ... the preparation of dual- or multiple-ligands on an almost rational basis is now conceivable and it can be expected that many of these molecules will yield drugs of superior clinical value ..."









Camille G. Wermuth

Drug Discov. Today **2004**, *9*, 826

LASSBio®

Universidade Federal do Rio de Janeiro

Química Medicinal

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

LASSBio

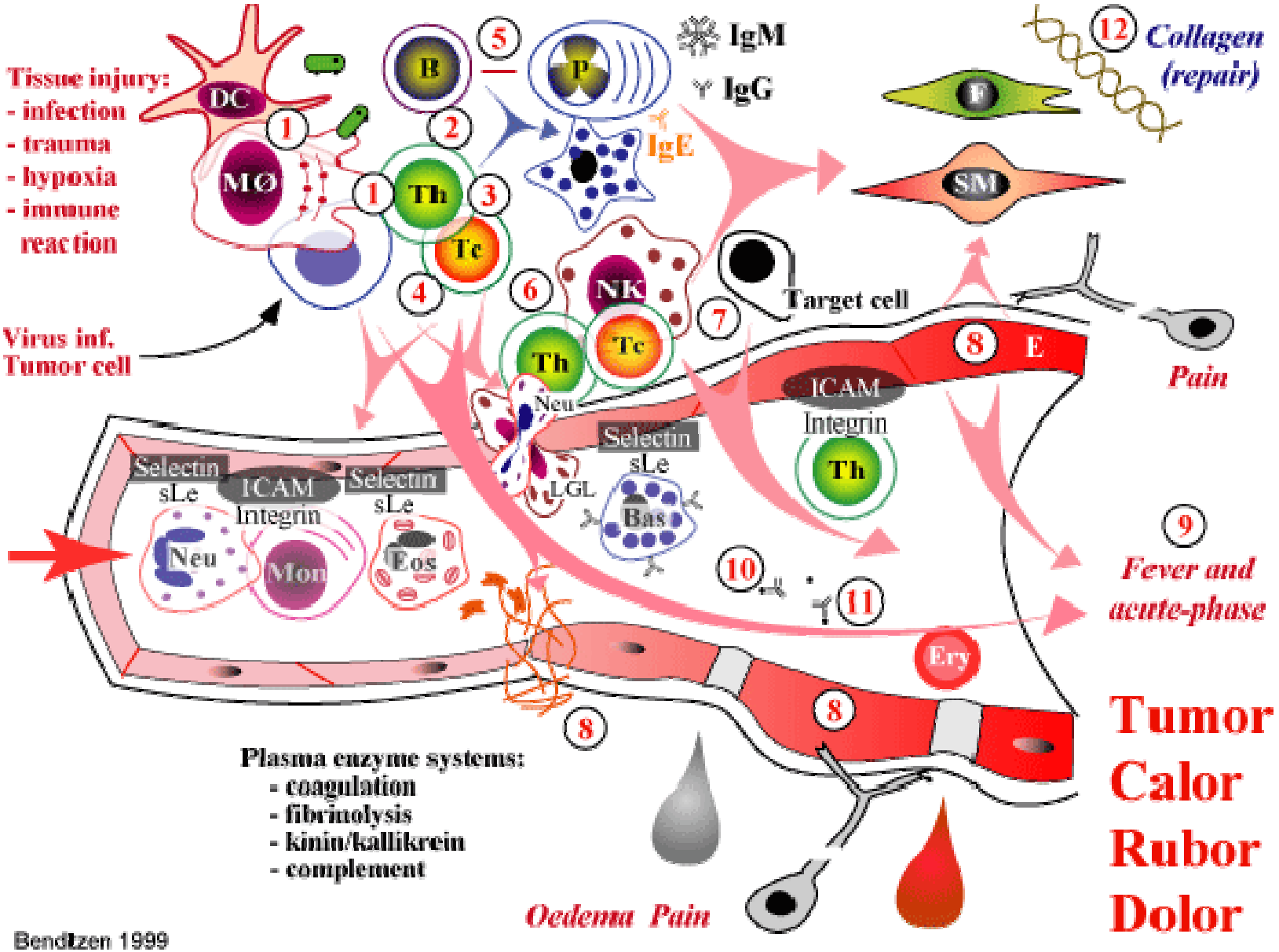
Laboratório de Avaliação e Síntese de Substâncias Bioativas

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

Pharmacology
Farmacologia

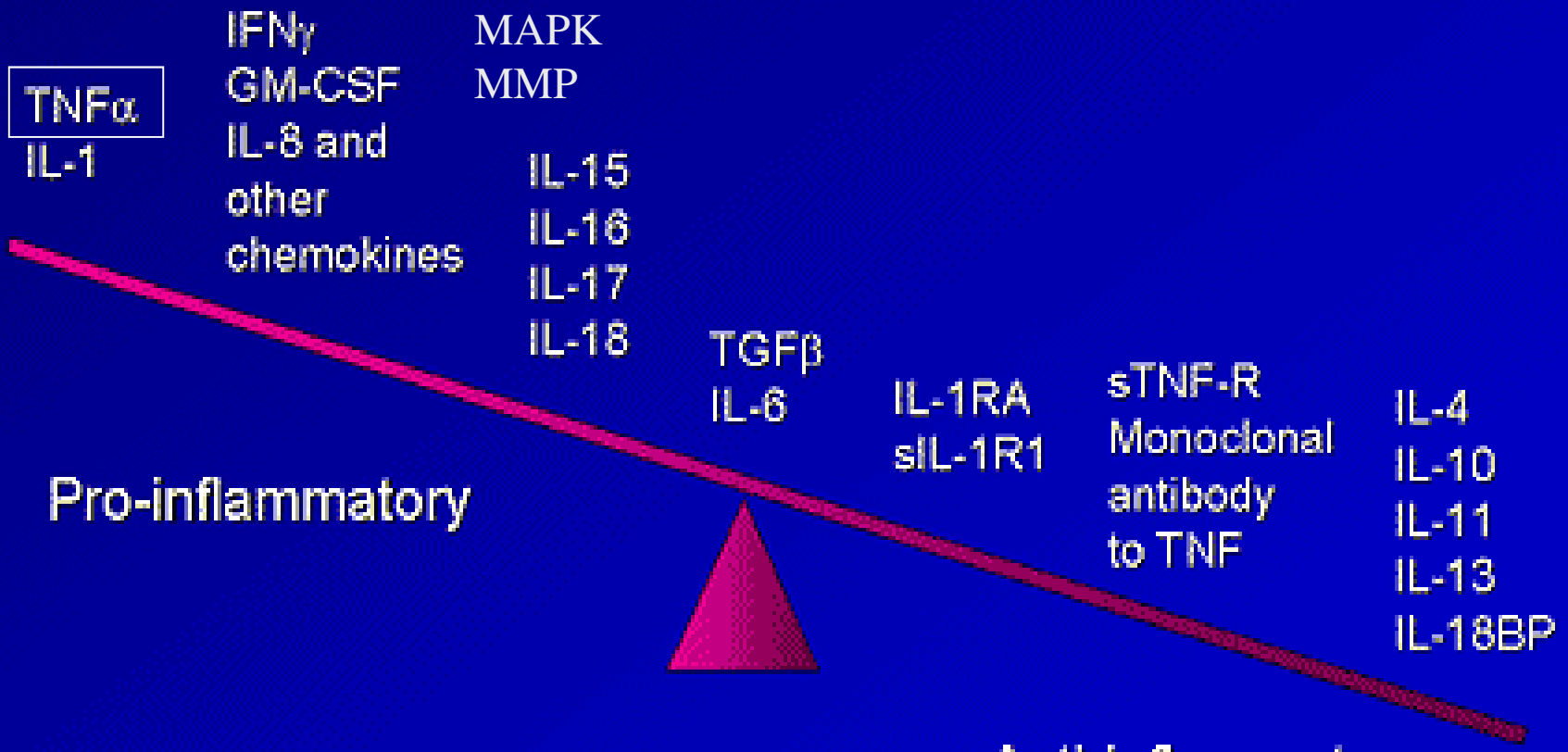
Molecular
Modelagem
Modeling
Molecular

Inflamação: Doença crônica não transmissível



Universidade Federal do Rio de Janeiro

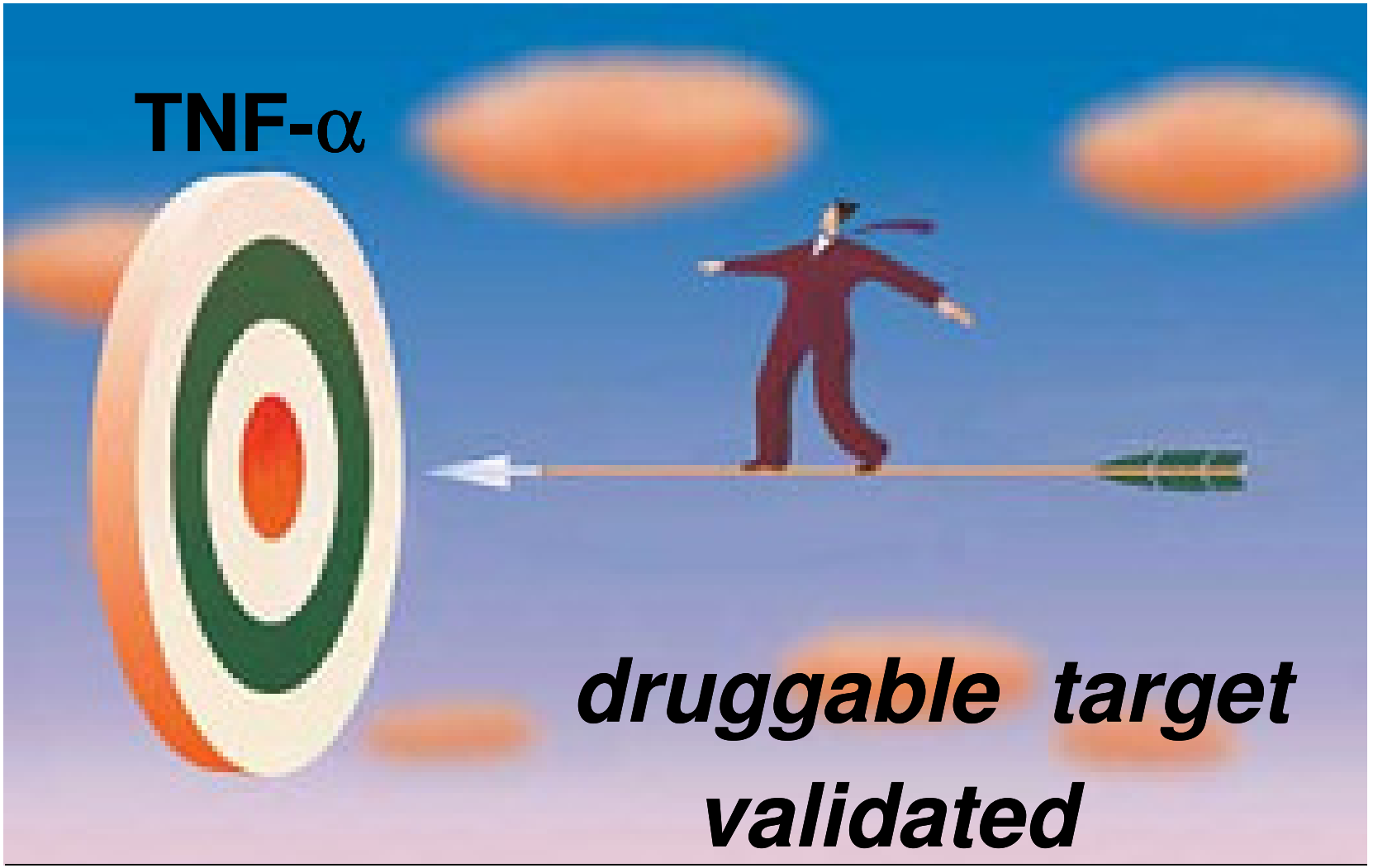
Role of Cytokines and Cytokine Inhibitors in Chronic Inflammation



Arend. *Arthritis Rheum* 2001.

* TNF-α = Tumor necrosis factor-alpha

The Target Election: TNF-α



TNF-α is a cytokine that appears rapidly in response to inflammatory injury

PC Taylor, Pharmacology of TNF blockde in RA and other chronic inflammatory diseases, *Curr. Op. Pharmacol.* **2010**, *10*, 308

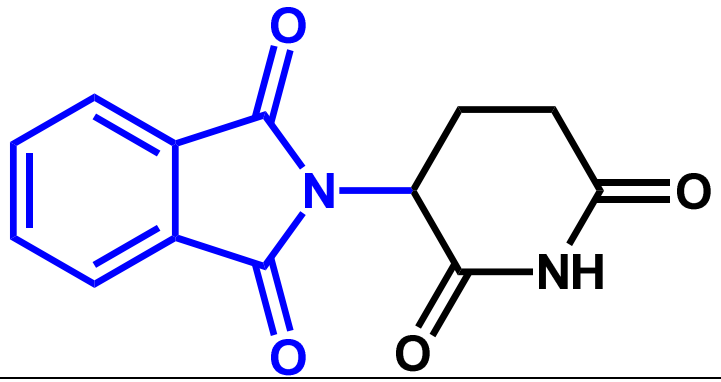
Anti-TNFα Therapies

*Protein-based anti-TNF-alpha Therapies in Clinical Use**

Drug	Status	Biological Form
Etanercept	approved	soluble TNFR2 coupled to Fc portion of IgG
Infliximab	approved	chimeric anti-human TNF antibodie
Adalimumab	approved	anti-human TNF antibodie
ISIS 104838	clinical	TNF anti-sense
Onercept	clinical	soluble p55 TNFR
Humicade	clinical	anti-TNF humanised IgG4

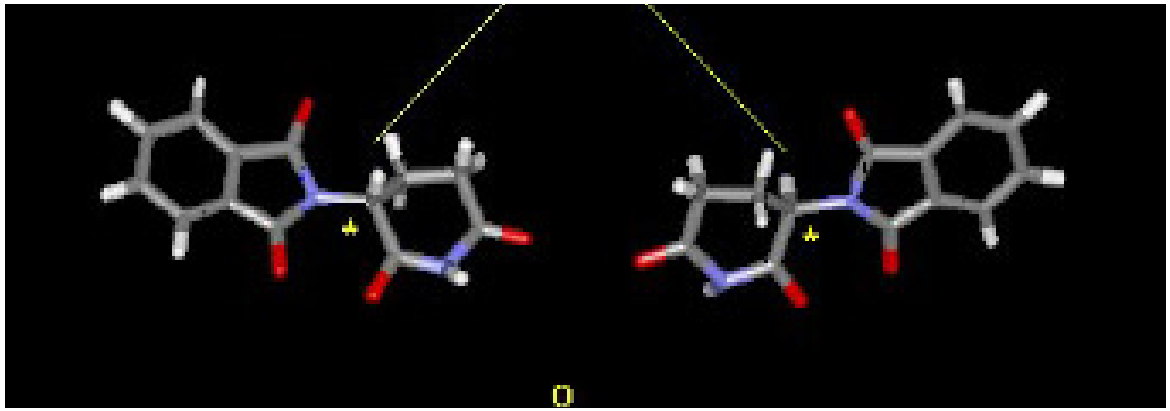
PC Taylor, Pharmacology of TNF blockade in rheumatoid arthritis and other chronic inflammatory diseases, *Curr. Op. Pharmacol*. **2010**, *10*, 308

* protein-based injectable anti-TNFα therapies (biopharmaceuticals)



medicinal chemistry

2-(2,6-dioxo-3-piperidinyl)-1*H*-isoindole-1,3(2*H*)-dione



Thalidomide

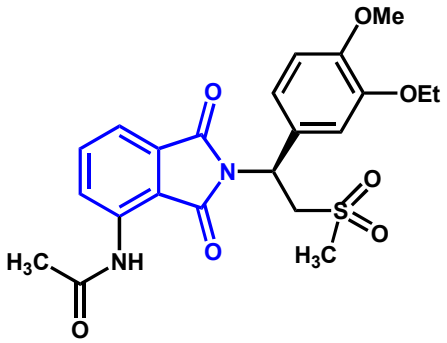
Anti-TNFα

TNF-α IC_{50} = 200 μM

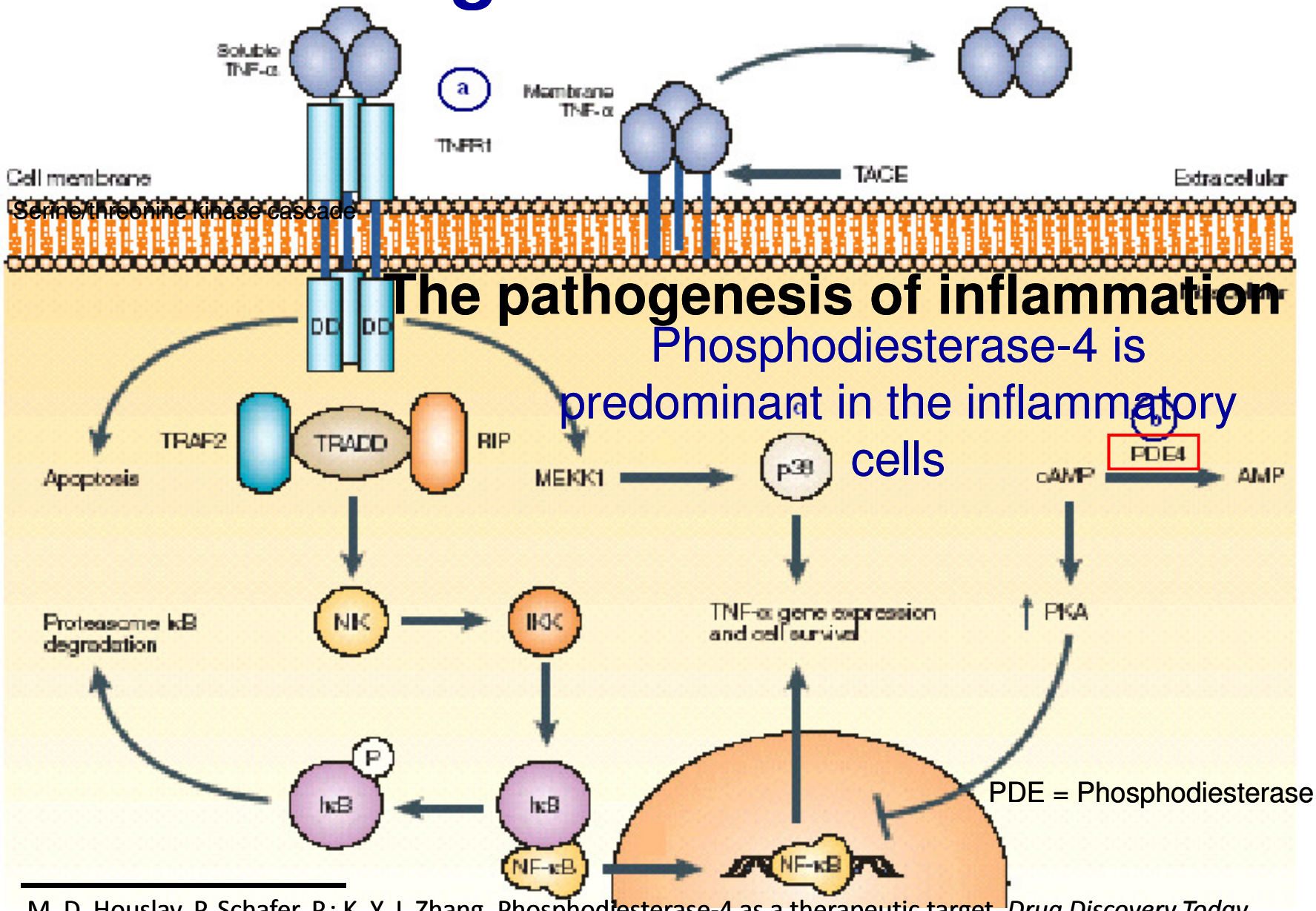
Wilhelm Kunz, 1953
Herbert Keller, 1953
CNS, 1957
Frances Kelsey, 1961
Gilla Kaplan, 1991 (TNF-α)
Elisabeth Sampaio,1997

Apremilast, Phase II, Celgene (2009)

H-W Man *et al.*, *J. Med. Chem.* **2009,** *52,* 1522
FE McCann *et al.*, *Arthritis Res. Ther.* **2010,** *12,* R107



Second Target Election:PDE-4



The pathogenesis of inflammation

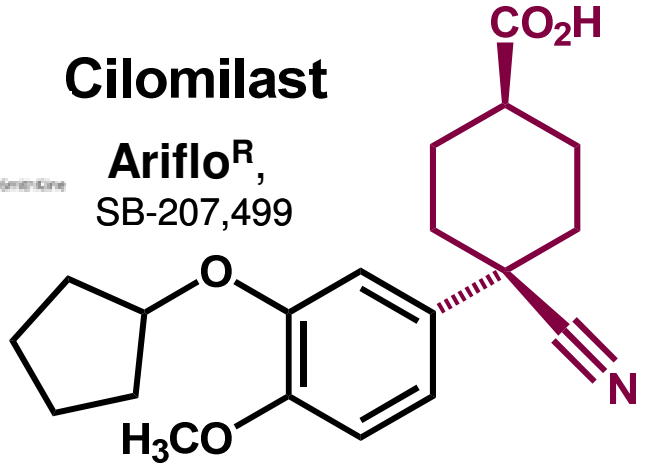
Phosphodiesterase-4 is predominant in the inflammatory cells

M. D. Houslay, P. Schafer, P.; K. Y. J. Zhang, Phosphodiesterase-4 as a therapeutic target, *Drug Discovery Today* **2005**, *10,* 1503; B. J. Lipworth, Phosphodiesterase-4 inhibitors for asthma and chronic obstructive pulmonary disease, *Lancet* **2005**, *365*, 167

Alvo terapêutico validado

Cilomilast

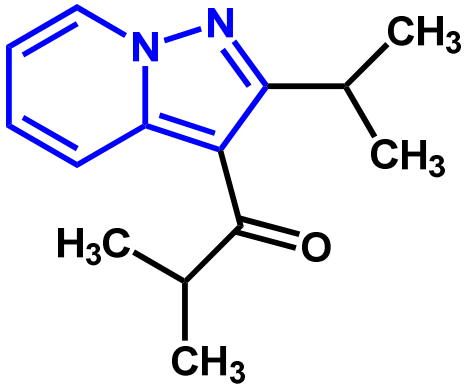
Ariflo^{R},
SB-207,499



4-cyano-cyclohexyl carboxylic acid

SB Christensen *et al., J. Med.Chem*. **1998**, *41*, 821

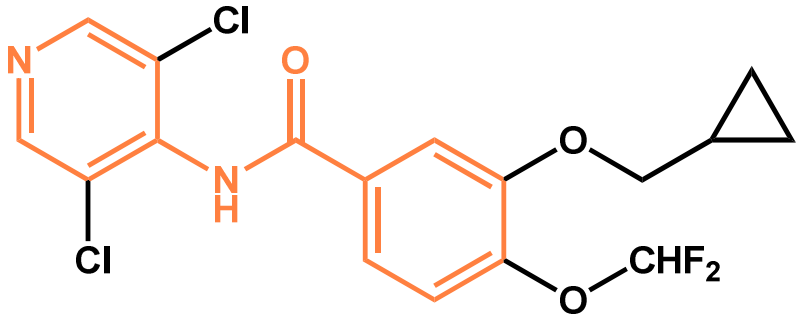
Ibudilast



pyrazolo[1,5-*a*]pyridine

Z Huang *et al*., *Life Sciences* **2006**, *78*, 2663

Roflumilast

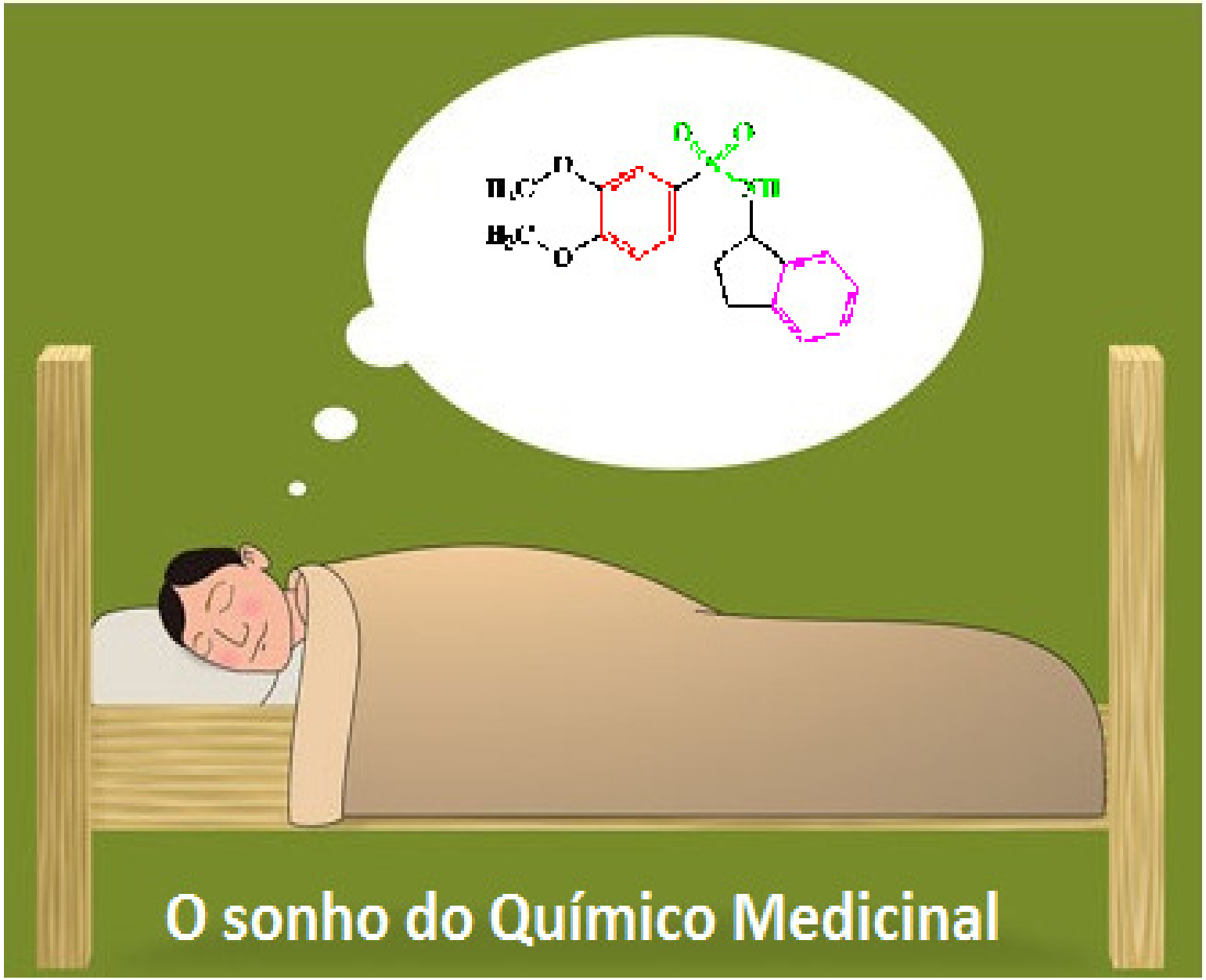


Daxas^{R}
Aprovado
2011

pyridine-benzamide

LM Fabbri *et al*., *Nature Rev Drug Discov* **2010**, *9*, 761

A Kodimuthali, S S L Jabaris, M Pal, Recent advances on phosphodiesterase 4 inhibitors for the treatment of asthma and chronic obstructive pulmonary disease, *J*. Med. Chem. **2008**, *51*, 5471; S. Diamant, D Spina, PDE-4 inhibitors: a novel , targeted therapy for obstructive airways diseases, *Pulmonary Pharmacol. Ther.* **2011**, *24*, 353.


O sonho do Químico Medicinal

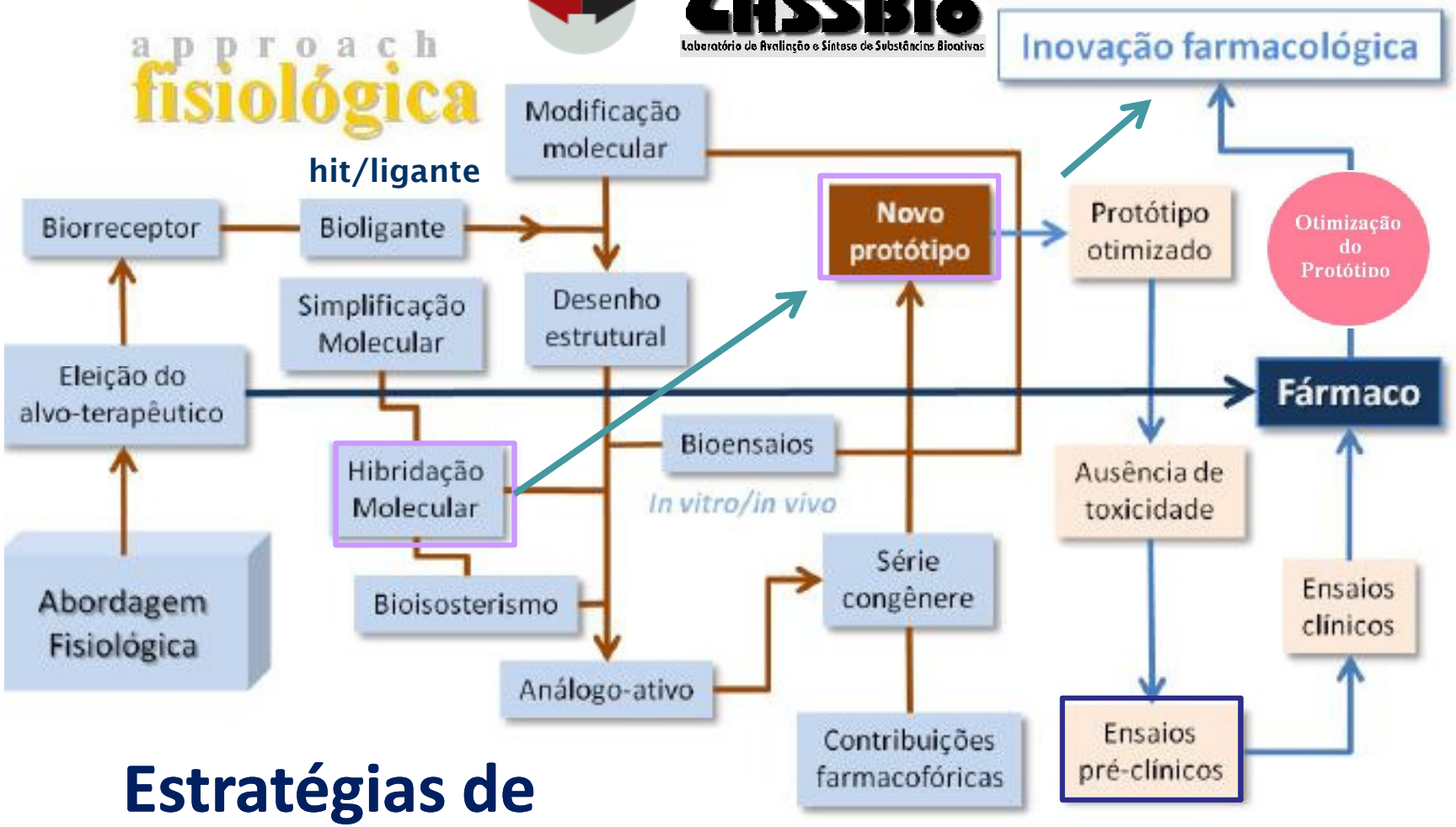
Universidade Federal do Rio de Janeiro

Physiologic approach

A abordagem fisiológica

Química Medicinal

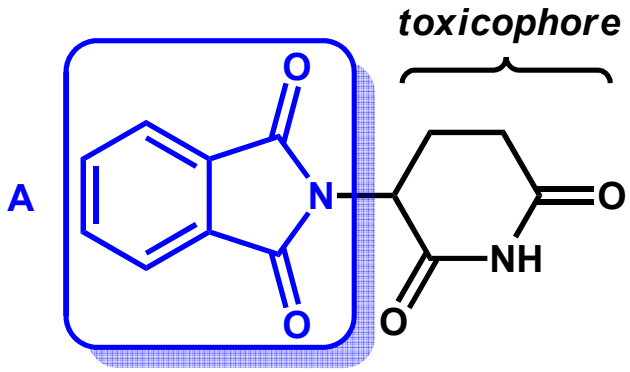
LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas



Estratégias de *desenho* molecular

validação precoce do alvo-terapêutico

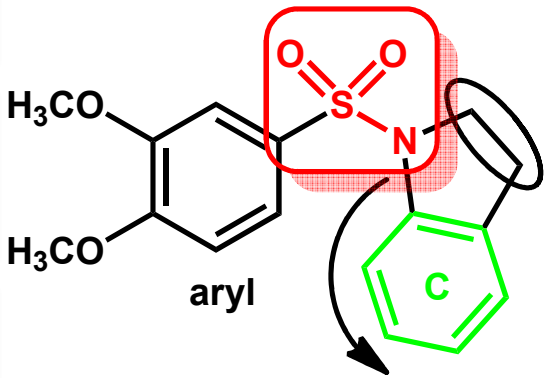
The design of new dual agent with anti-TNFα activity & PDE-4i



phthalimide

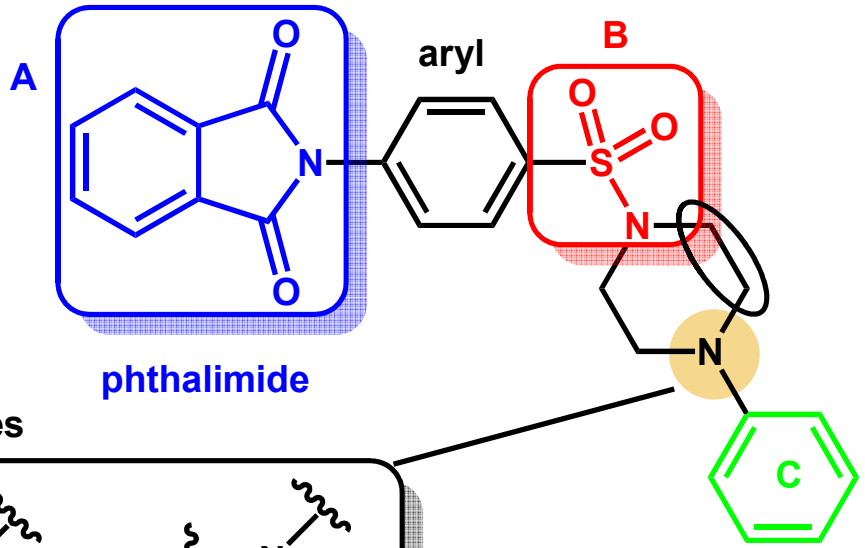
molecular hybridization

B sulfonamide



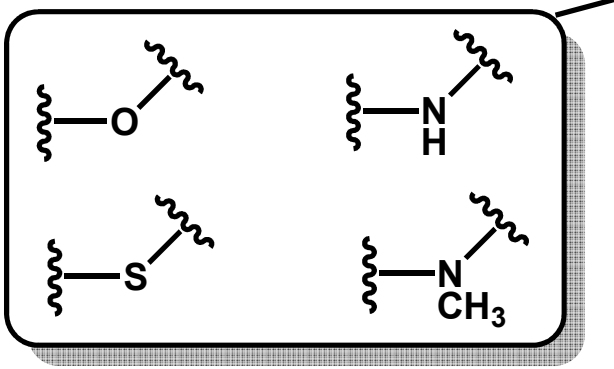
lipophylic

Montana *et al*., 1998



phthalimide

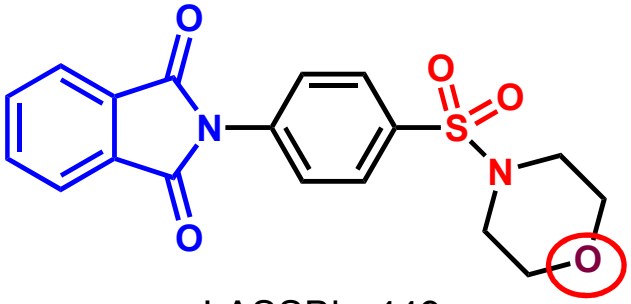
isosteres



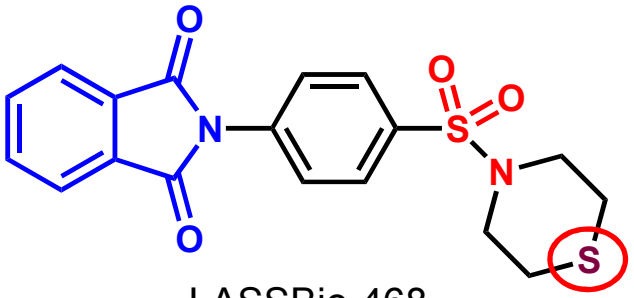
σ, π, RM

Drug Design

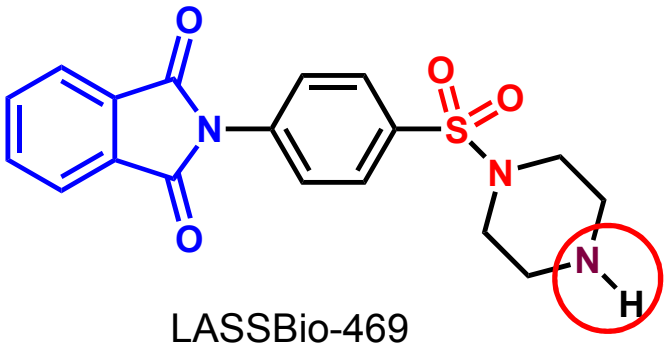
Série Congênere



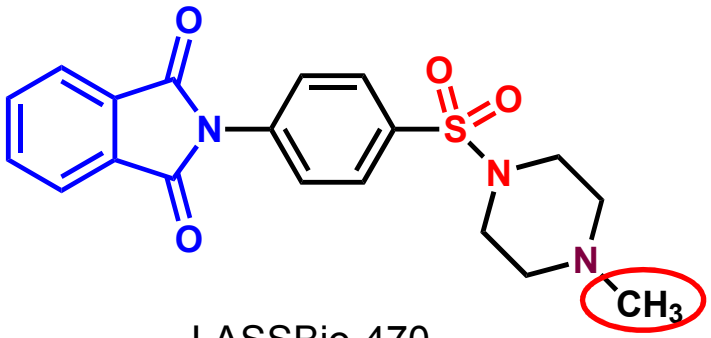
LASSBio-449



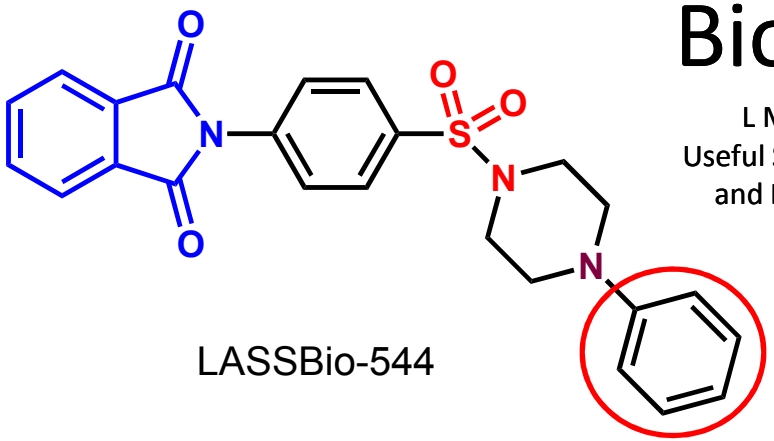
LASSBio-468



LASSBio-469



LASSBio-470



LASSBio-544

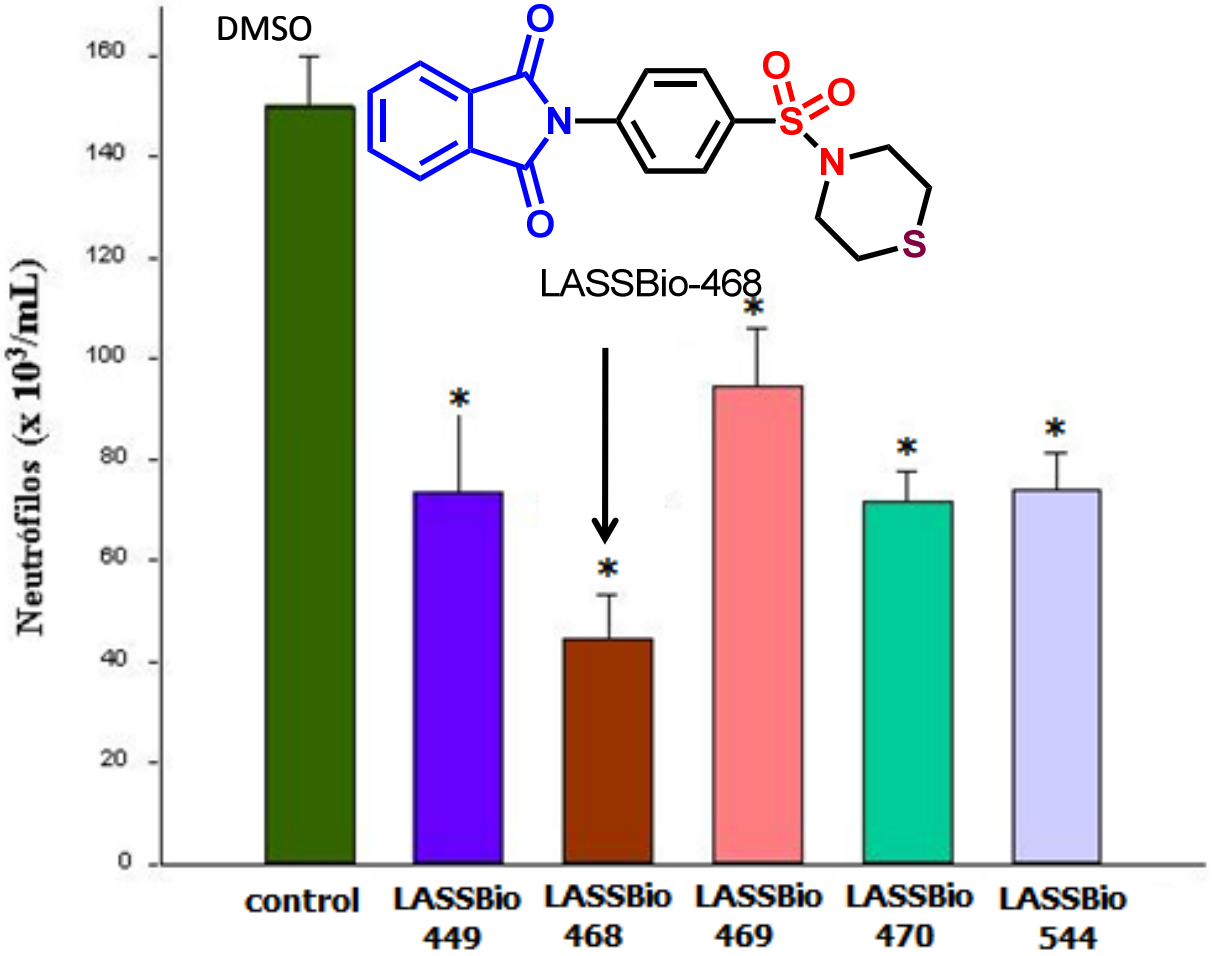
Bioisosterismo

L M Lima, EJ Barreiro, Bioisosterism: A Useful Strategy for Molecular Modification and Drug Design, *Cur. Med. Chem.* **2005**, *12*, 23

Lidia M. Lima (LASSBio), PhD Thesis, IQ-UFRJ, Br., 2001

Effect of new compounds and thalidomide on neutrophils influx, induced by LPS into BALB/c of mice lungs (10 mg/kg, DMSO; i.p.)

in vivo



Results are expressed as means SEM of seven animals.

Vera G Koatz
IBqM, Universidade Federal do Rio de Janeiro

Effect of compound LASSBio 468 (50 mg/kg, i.p.) on TNF-α levels and neutrophils influx (BALB/c of mice lungs)

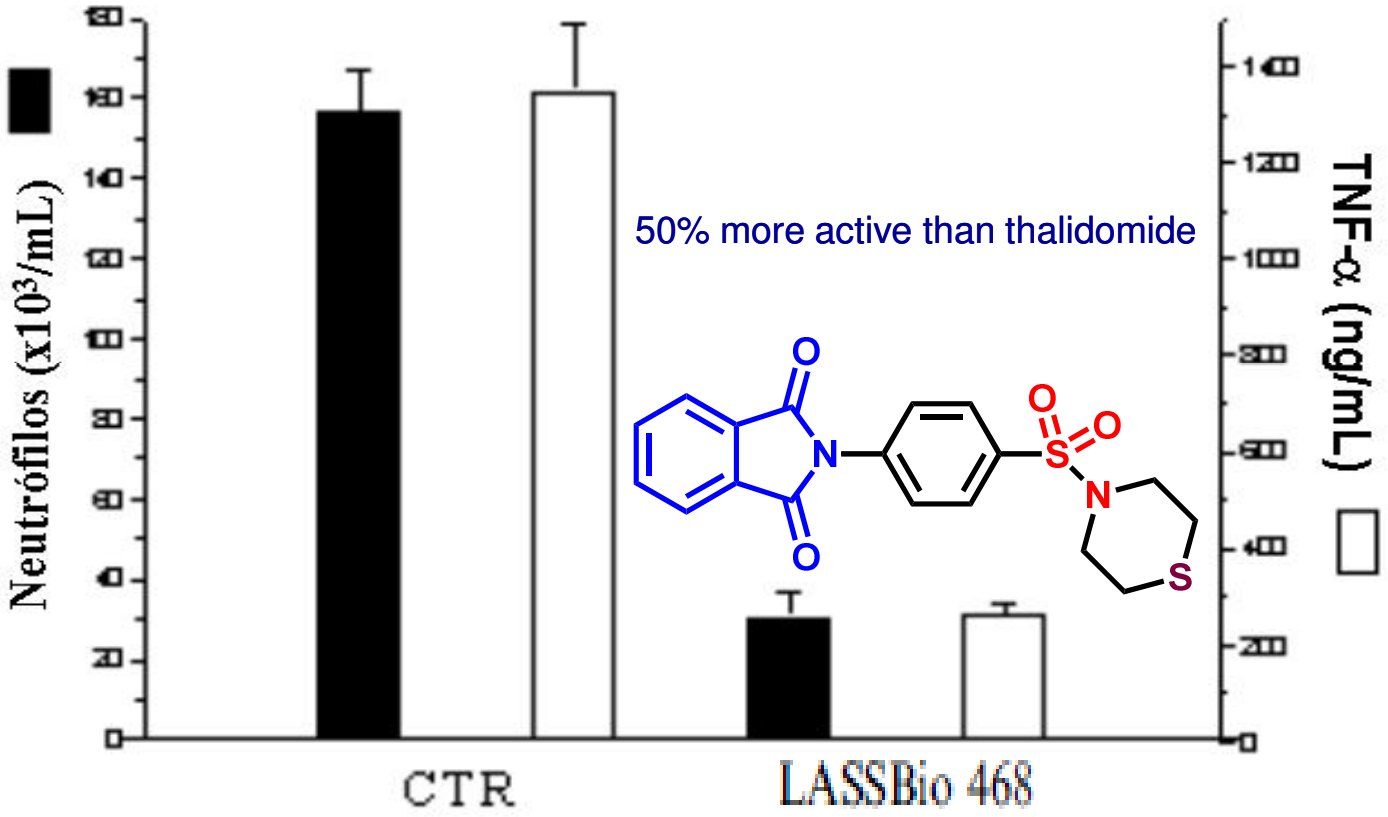
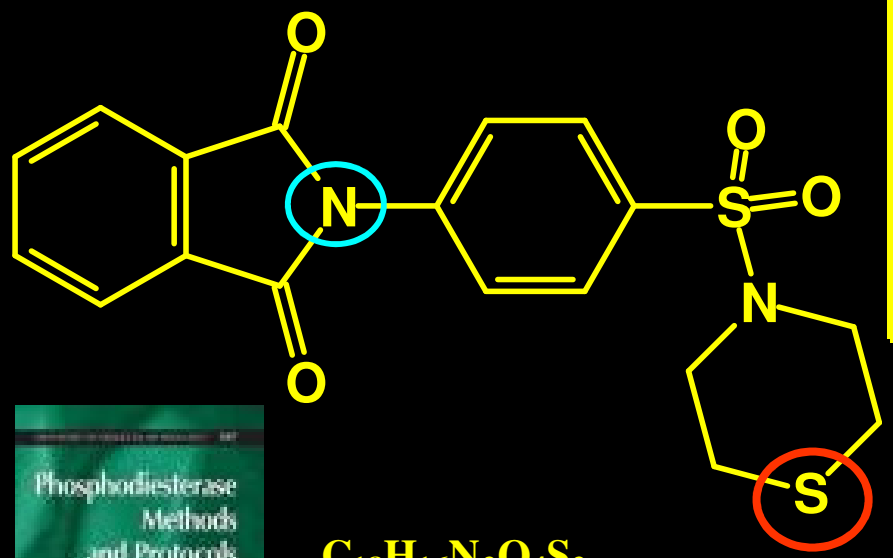


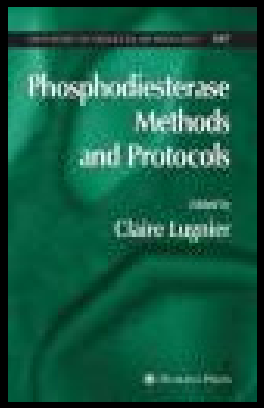
Fig. . Effect of LASSBio-468, thalidomide and pentoxifylline on survival BALB/c mice after LPS (500 µg/mice) administration.

Vera G Koatz
IBqM, Universidade Federal do Rio de Janeiro

Universidade Federal do Rio de Janeiro



$C_{18}H_{16}N_2O_4S_2$



LASSBio 468

TNF-α ED_{50} 2,5 mg/Kg

lead compound

PDE-4 inhibitor

Dr **Claire** **Lugnier** (CAPES-COFECUB; LASSBio-Strasbourg)
Université Louis Pasteur, Strasbourg, FR.
Laboratoire de Pharmacologie et de Physicochimie des Interactions Cellulaires et Moléculaires.

IC_{50} = 13,5μM

cf. PDE-1, 2, 3, > 150 μM;

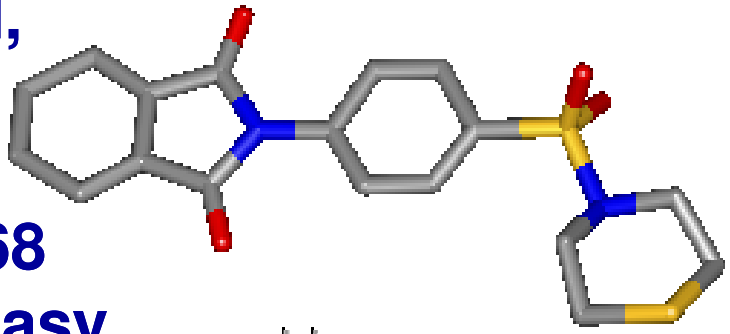
a) L. M. Lima *et al.*, "Synthesis and Anti-inflammatory Activity of Phthalimide Derivatives, Designed as New Thalidomide Analogues", *Bioorg. Med. Chem.* 2002, 10, 3067;

b) M. S. Alexandre-Moreira *et al.*, "LASSBio-468: a New achiral Thalidomide Analogue which Modulates TNF-α and NO Production and Inhibit Endotoxic Shock and Arthritis in Animal Model", *International Immunopharmacology* 2005, 5, 485.

LASSBio-468

A new dual anti-inflammatory agent

LASSBio-468 is a new dual-target anti-inflammatory lead-compound, active at TNF-α production and with inhibitory activity on PDE-4, as originally planned. LASSBio-468 is structurally simple derivative, easy to synthesized at good overall yield and 0.5 M scale. This new achiral compound presents immunomodulatory activity without anti-proliferative effect, in contrast to THLD. LASSBio-468 is an useful lead-compound to treatment of chronicle inflammatory disorders as rheumatoid arthritis and shock septic syndrome.

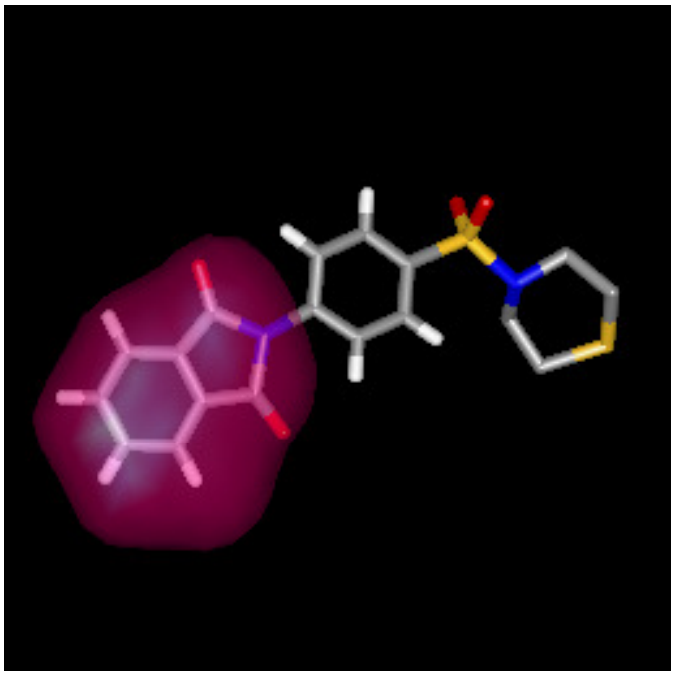


L. M. Lima *et al*., "Synthesis and Anti-inflammatory Activity of Phthalimide Derivatives, Designed as New Thalidomide Analogues", *Bioorg. Med. Chem*. **2002**, *10*, 3067; A. L. Machado *et al*., "Design, Synthesis and anti-inflammatory activity of novel phthalimide derivatives, structurally related to thalidomide", *Bioorg. Med. Chem. Lett*. **2005**, *15*, 1169

Universidade Federal do Rio de Janeiro

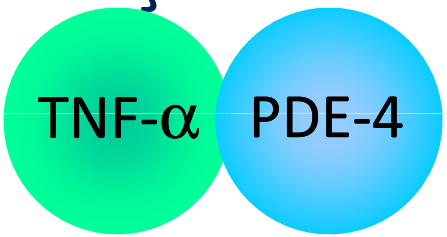
Química Medicinal

The discovery of new dual lead-compounds



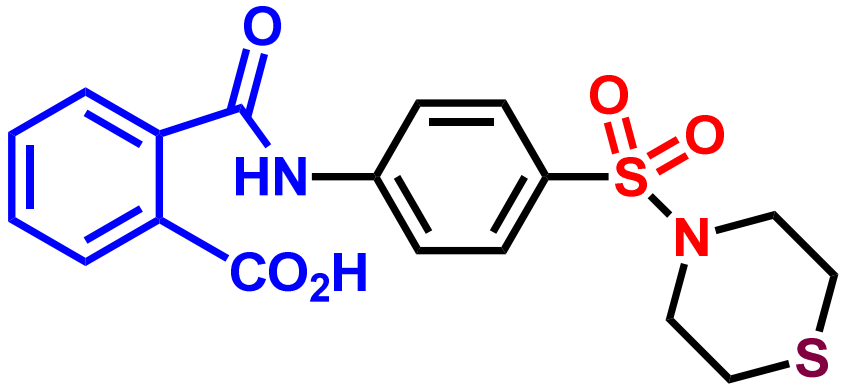
LASSBio-468

Desenhado por hibridação molecular



TNF-α ED_{50} 2,5 mg/Kg

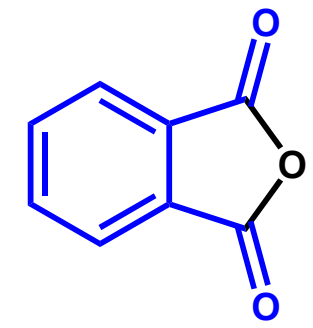
PDE-4 IC_{50} = 13,6 µM



Metabolism studies

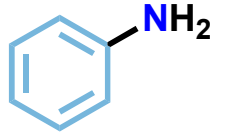
LASSBio-596

L. M. Lima, P. Castro, A. L. Machado, C. A. M. Fraga, C. Lugnier, V. L. G. Moraes, E. J. Barreiro, *Synthesis and Anti-inflammatory activity of Phthalimide Derivatives, Designed as New Thalidomide Analogues, Bioorg. Med. Chem*. **2002**, *10*, 3067.



anidrido ftálico

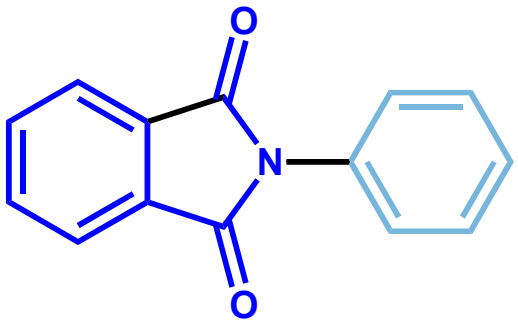
$C_8H_4O_3$



120°C

1h

(2M)



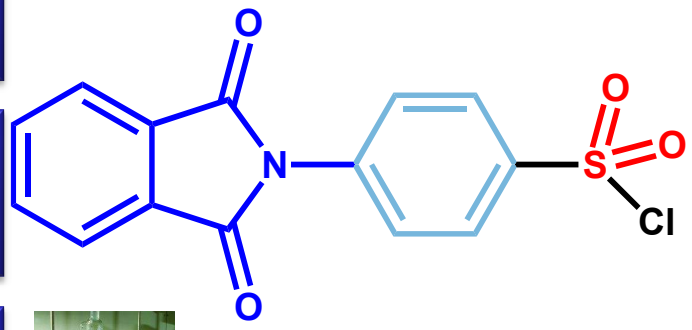
$C_{14}H_9NO_2$

$ClSO_3H$

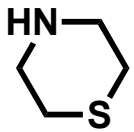
0°C a t.a. até 60°C

1h

(1M)



$C_{14}H_8ClNO_4S$

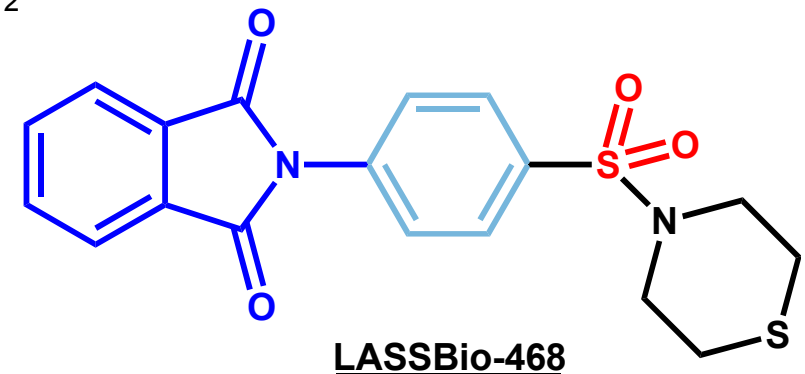


NEt_3

CH_2Cl_2

1h

0,4M



LASSBio-468

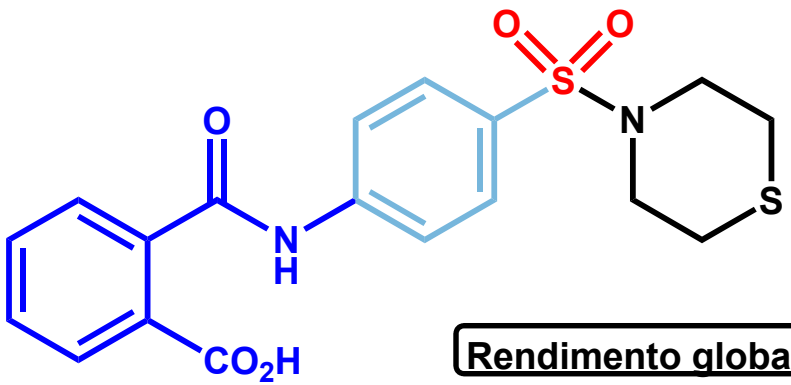
$C_{18}H_{16}N_2O_4S_2$

KOH / HOH

CH_3OH

1h

0,35M



LASSBio-596

$C_{18}H_{18}N_2O_5S_2$

Rendimento global: 29%

^{13}C, ^{1}H RMN / IV / UV / EM

HPLC

calorimetria diferencial de varredura (DSC)

CHN

Difração de Raios-X

RVq Revista Virtual de Química

ISSN 1984-6835

LASSBio-596: da descoberta aos ensaios pré-clínicos

Rocco, Patricia R. M.;[a] Xisto, Debora G.;[a] Silva, J. D.;[a] Diniz, Magareth F. F. M.;[b] Almeida, Reinaldo N.;[b] Luciano, Melissa N.;[b] Medeiros, Isac A.;[b] Cavalcanti, Bruno C.;[c] Ferreira, José R. O.;[c] de Moraes, Manoel O.;[c] Costa-Lotufo, Letícia V.;[c] Pessoa, Claudia do Ó;[c] Dalla-Costa, T.;[d]* Cattani, Vitória B.;[d] Barreiro, Eliezer J.[e], Lima, Lidia M.[e]

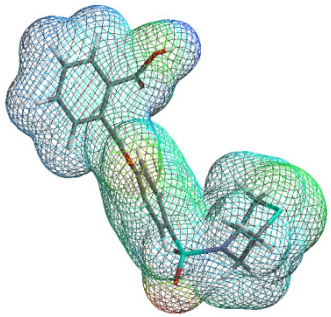
Rev. Virtual Quim., **2010**, *2* (1), 10-27. Data de publicação na Web: 30 de agosto de 2010

http://www.uff.br/rvq

Resumo

Neste artigo é revisado a trajetória que vai da descoberta de um novo candidato a fármaco antiasmático, o ácido 2-[4-(1,4-tiazinan-4-ilsulfonil)fenilcarbamoil]benzoico (LASSBio-596), à realização dos primeiros ensaios pré-clínicos, com enfoque nos efeitos de LASSBio-596 em modelo murino de asma aguda e crônica, estudos farmacocinéticos e toxicológicos em roedores e determinação do seu potencial genotóxico e mutagênico.

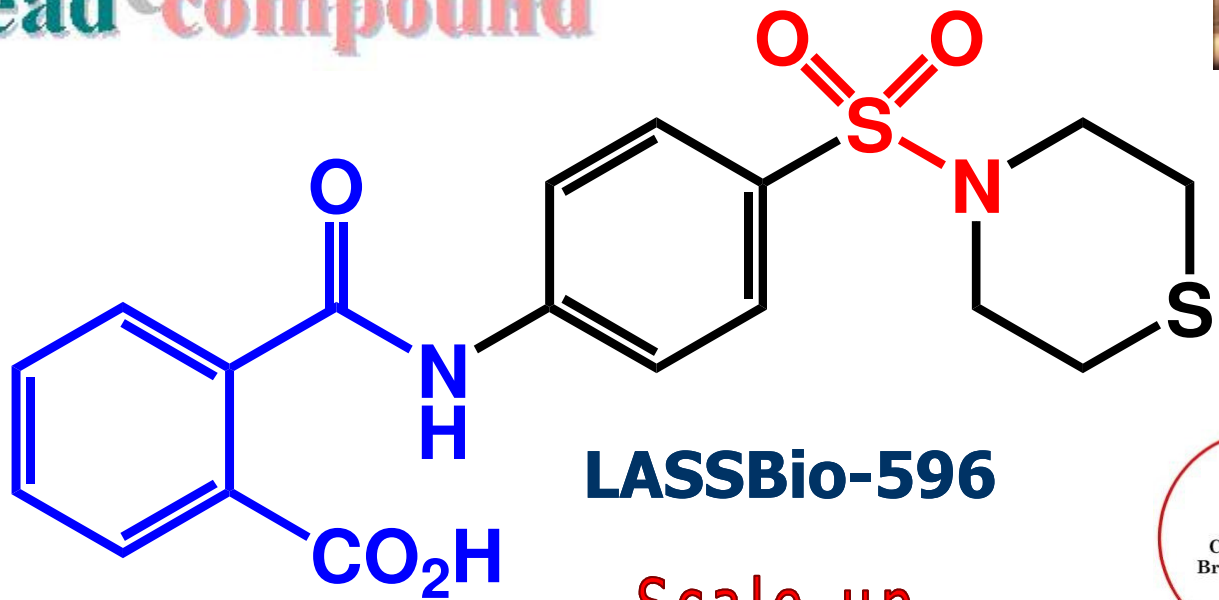
LASSBio-596



Universidade Federal do Rio de Janeiro

lead compound

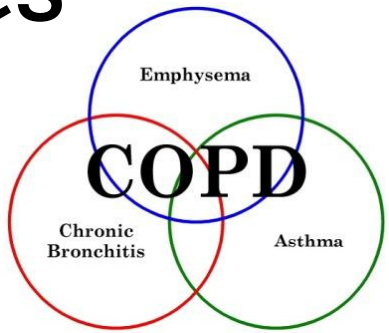
asthma



LASSBio-596

Scale-up

Lead Optimization



anti-fibrogenic

INCT inofar — Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos — www.inct-inofar.ccs.ufrj.br

L. M. Lima *et al*., Synthesis and Anti-inflammatory Activity of Phthalimide Derivatives, Designed as New Thalidomide Analogues, *Bioorg. Med. Chem*. **2002**, *10,* 3067; A. L. Machado *et al.*, Design, Synthesis and anti-inflammatory activity of novel phthalimide derivatives, structurally related to thalidomide, *Bioorg. Med. Chem. Lett***. 2005***, 15***,*** 1169; M. S. Alexandre-Moreira *et al*., LASSBio-468: a New achiral Thalidomide Analogue which Modulates TNF-α and NO Production and Inhibit Endotoxic Shock and Arthritis in Animal Model*, Internat. Immunopharmacol.* **2005**, *5*, 485; L. M. Lima, N. M. de Lima, Contribuição do LASSBio no desenvolvimento de novos candidatos a protótipos de fármacos antiasmáticos*, Rev. Virtual Quim*. **2009**, *1*, 35; R.M.P. Rocco *et al*., LASSBio-596: da descoberta aos ensaios pré-clínicos, *Rev. Virtual Quim*. **2010**, *2*, 10; G.M.C. Carvalho *et al*., Can LASSBio-596 and dexamethasone treat acute lung and liver inflammation induced by microcystin-LR?, *Toxicon* **2010**, *56*, 604; N.V. Casquilho *et al*., LASSBio-596 *per os* avoids pulmonary and hepatic inflammation induced by microscystin-LR, *Toxicon* **2011**, *58*, 195.

LASSBio®

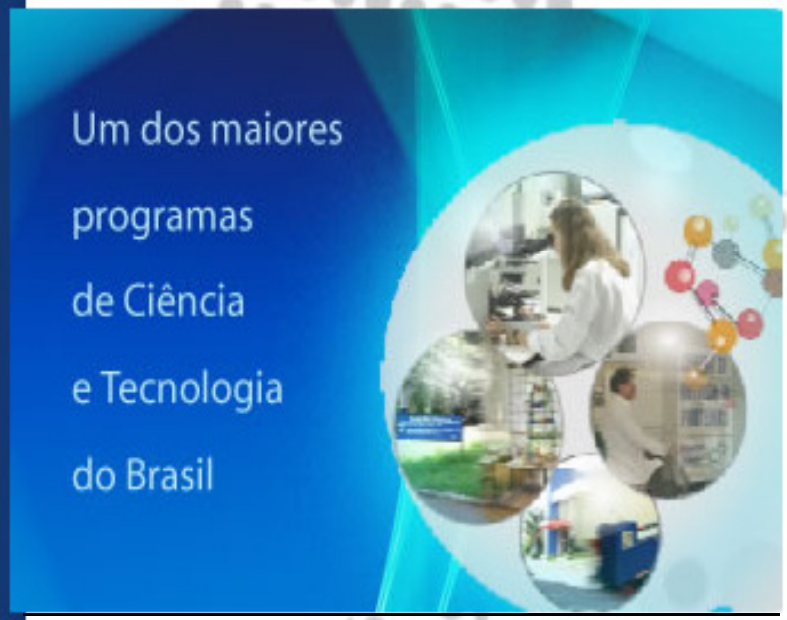
Ministério da Ciência e Tecnologia

BRASIL

inct
institutos nacionais
de ciência e tecnologia

CNPq

Apresentação | Institutos | Notícias | Contato

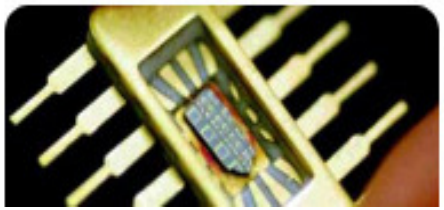


Notícias

Pesquisadores do IINCT de Astrofísica publicam 100 artigos em oito meses

UFMG faz pesquisa pioneira para tratamento da dengue

IINCT de Fixação Biológica de Nitrogênio promove simpósio internacional em setembro



Universidade Federal do Rio de Janeiro

inct inofar

instituto nacional de ciência e tecnologia de Fármacos e Medicamentos

www.inct-inofar.ccs.ufrj.br

CNPq FAPERJ

Project CNPq 573.564/2008-6

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

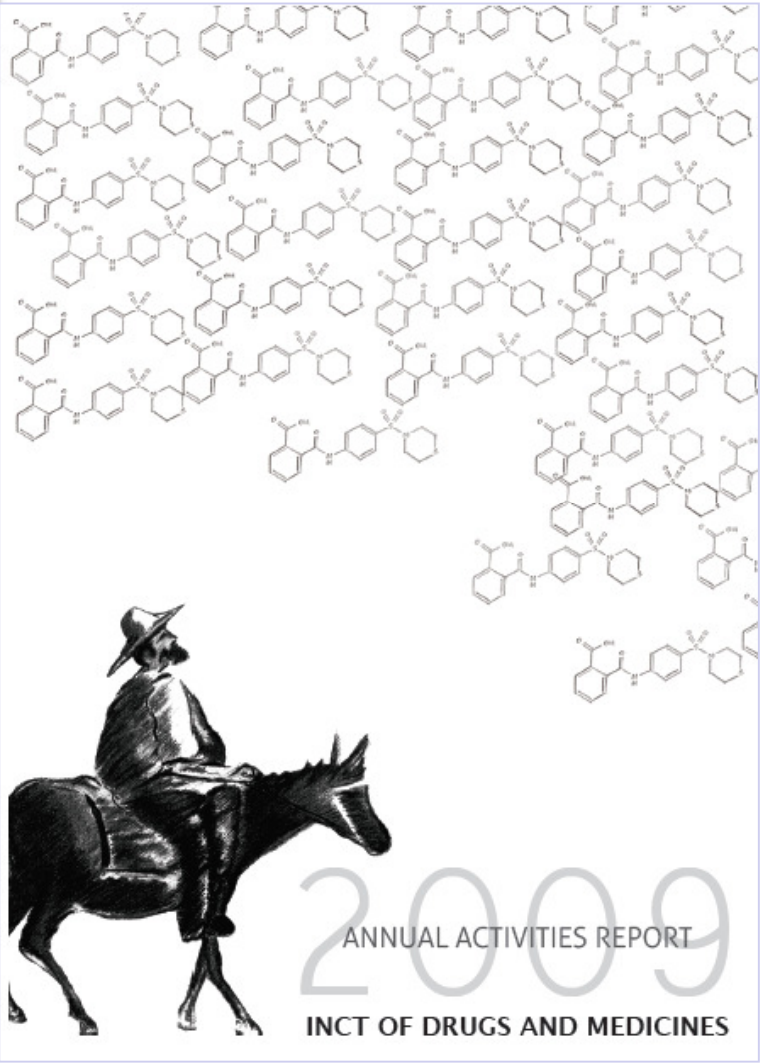
Farmácia

A missão do INCT-INOFAR

- Organizar as competências científicas nacionais em uma rede efetiva de pesquisa em fármacos;
- Apoiar projetos de pesquisa científica multi-institucionais voltados para novos fármacos;
- Contribuir para a inovação incremental e radical em novos fármacos e genéricos;
- Estudar e desenvolver a síntese total de genéricos, intermediários avançados e matérias-primas;
- Contribuir para a formação científica qualificada de pessoal em química medicinal & farmacologia;
- Promover a divulgação das ciências dos fármacos e dos medicamentos, assim como seu uso racional e seguro;

Universidade Federal do Rio de Janeiro

Annual Activities Report



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

Interdisciplinar & multi-team research projects

- **Radical innovation**
  pain, inflammation, asthma, CNS, neglected diseases, cardiovascular system, anticancer
- **Incremental innovation**
  SUS (BR healthcare)
  new generic drugs

www.inct-inofar.ccs.ufrj.br/download/aar/2010.pdf

Universidade Federal do Rio de Janeiro

INCT-INOFAR

Governance committee

Innovation in Drugs and Medicines

Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos

www.inct-inofar.ccs.ufrj.br

Comitê de Governança & Acompanhamento (CGA)
Dra Vanderlan Bolzani (UNESP)
Dra Heloisa Beraldo (UFMG)
Dr Angelo C Pinto (UFRJ)
Dr Luiz Carlos Dias (UNICAMP)
Dr Marco Aurélio Martins (Fiocruz)






Coordenação
Dr Eliezer J Barreiro (UFRJ)
Vice-coordenação
Dr Fernando Q Cunha (USP-RP)

Superintendência Científica
Dra Lídia Moreira Lima (UFRJ)

Grupos de Pesquisa Associados
13 IES & 3 ICT

Consultoria Científica
Dr. Francisco S Guimarães (USP-SP)
Dr Vitor F Ferreira (UFF)
Dr Antonio Monge (Espanha)
Dr Camile G Wermuth (França)
Dr Simon Campbell

inct institutos nacionais de ciência e tecnologia

inofar

Foreign scientific consultants

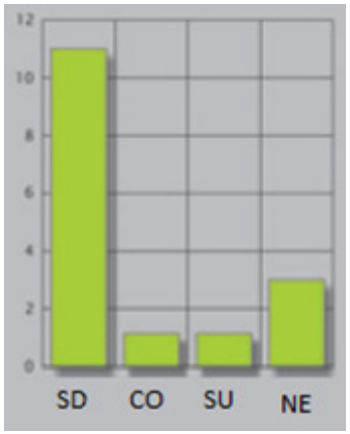


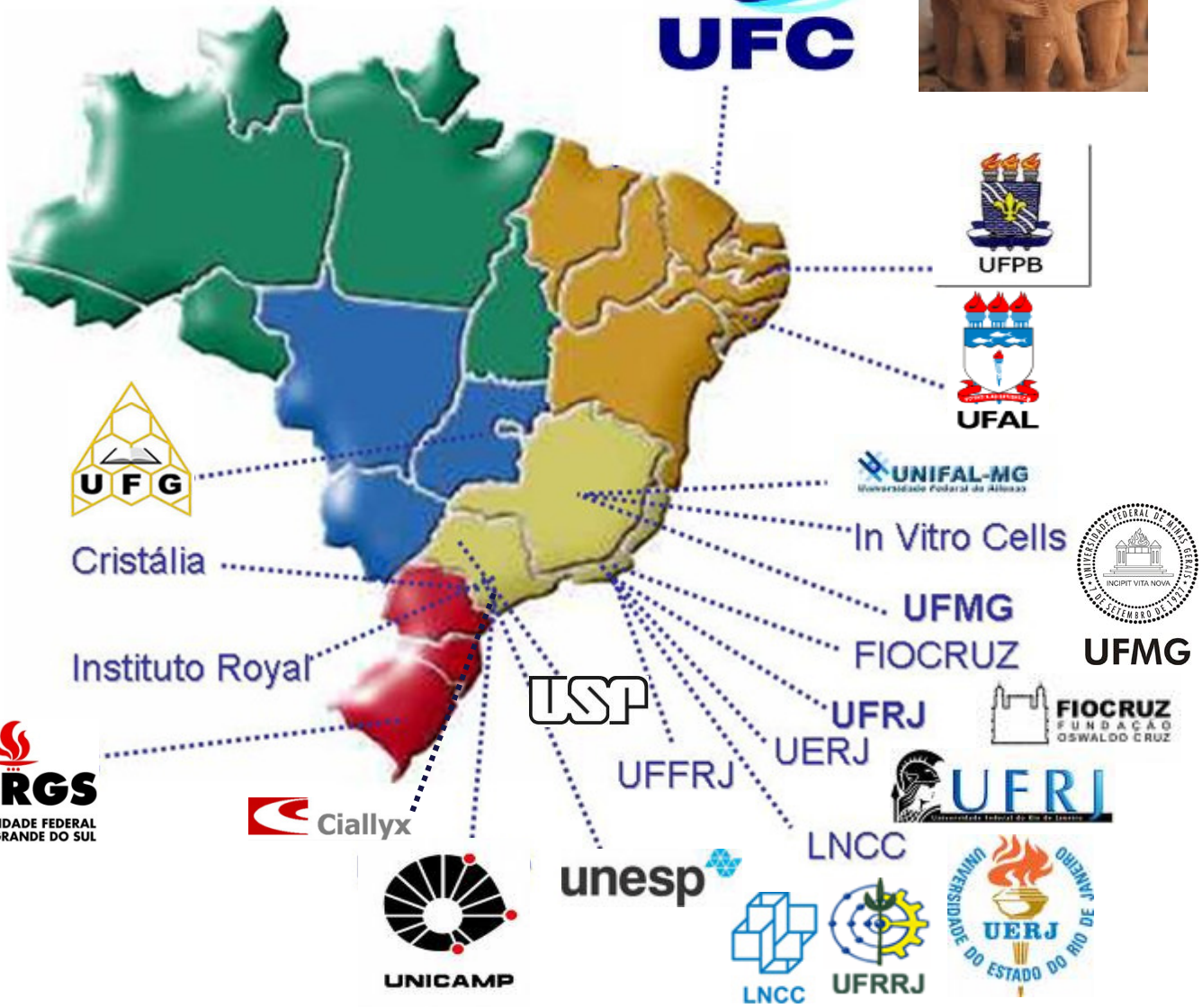
Antonio Monge, Universidad de Navarra,ES
Camille G. Wermuth, Prestwick Co., Ilkirch, FR
Simon Campbell, ex-Pfizer Major Scientist UK

Universidade Federal do Rio de Janeiro

INCT-INOFAR

Research partners





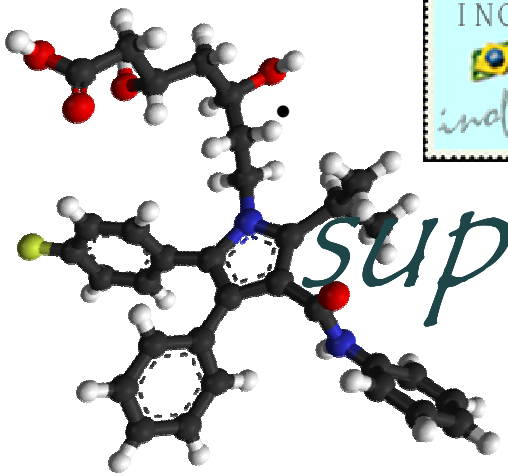
Atorvastatina

Incremental *In*novation

1991

- Sintetizada, em 1985, por Bruce Roth
[B. D. Roth, "The discovery and development of atorvastatin, a potent novel hypolipidemic agent", Prog. Med. Chem. **2002**, *40*, 1–22]
Patente US 5273995 Pfizer (1991):
12 etapas = 4,2%
- Nova síntese Prof. **Luiz Carlos Dias** & Dr **Adriano S Vieira**, IQ-UNICAMP, em **2010**, pelo **INCT-INOFAR:**

O professor Luiz Carlos Dias e o pós-doutorando Adriano Siqueira Vieira: nova rota é mais barata e eficiente



11 etapas = 19,3%

super blockbuster-drug

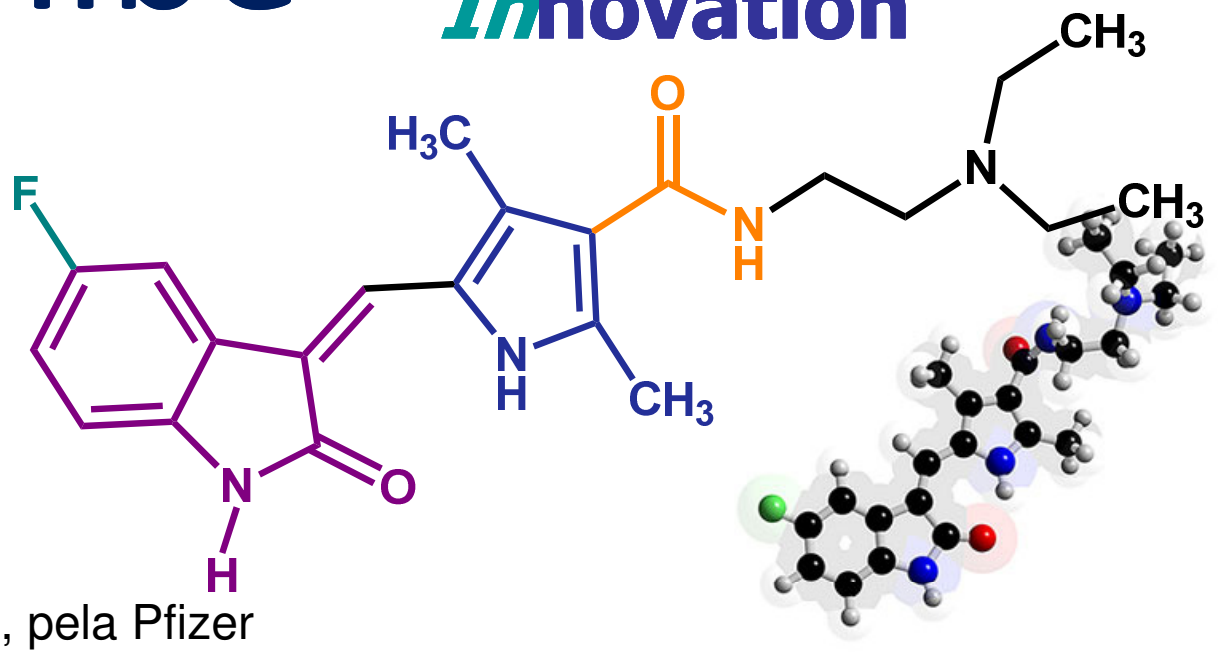
LC Dias, A S Vieira, EJ Barreiro, Processo de obtenção de atorvastatina cálcica utilizando novos intermediários
*PI 018110015039 (*protocolado no INPI, em 25/04/2011)

Sunitinibe

Incremental *In*novation

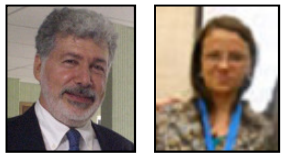
2006

Sutent^{R}



- Sintetizado, em 1999, pela Pfizer
- Patente de 2001 (US)
- Inibidor BCR–ABL Tyr-quinase
- Indicado para Ca-estômago/rim
- Nova síntese Prof. **Angelo da Cunha Pinto** & Dr **Bárbara Vasconcellos da Silva**, IQ-UFRJ, **em 2011**, pelo INCT-INOFAR

50 mg / 28 caps *ca.* R$ 20.837,90



Vendas de tinibes no mercado norte-americano:

US$ 18,5 bi (2009)

Importações

ca. US$ 3 milhões/ano

S Aggarwal, *Nature Rev Drug Discov* **2010**, *9*, 427

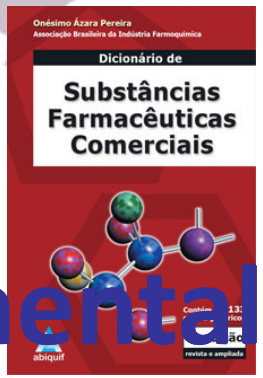
O "*Caminho das Índias*" dos nossos fármacos (genéricos!)

Precisamos resolver, com urgência, a grave dependência de importações de fármacos, invertendo o sentido do *atual Caminho das Índias* !

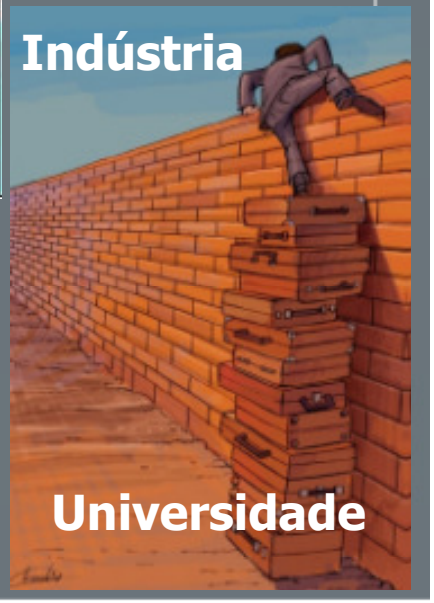
EJ Barreiro & CAM Fraga, A Questão da inovação em fármacos no Brasil: proposta de criação do Programa Nacional de Fármacos (PRONFAR) ***Quim. Nova* 2005, *28*, Supl. S56-S63**

Biolab Sanus Farmaceutica Ltda
Cristália Produtos Químicos Farmacêuticos Ltda
EMS - Sigma Pharma
Eurofarma Laboratórios Ltda
Genom Farmacêutica Ltda
Laboratórios BIOSINTÉTICA
Laboratório Neo Química Indústria Farmacêutica Ltda
Laboratório Teuto Brasileiro
LIBBS Farmacêutica
Medley S/A Indústria Farmacêutica
Mantecorp
Zambon Laboratórios Farmacêuticos Ltda

Inovação incemental



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



Drug discovery: new models for industry–academic partnerships

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

Drug Discovery Centre and Business Development, Imperial College London SW7 2AZ, UK

The re-focusing of pharmaceutical industry research away from early discovery activities is stimulating the development of novel models of drug discovery, notably involving academia as a 'front end'. In this article the authors explore the drivers of change, the role of new entrants (universities with specialised core facilities) and novel partnership models. If they are to be sustainable and deliver, these new models must be flexible and properly funded by industry or public funding, rewarding all partners for

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

Universidade Federal do Rio de Janeiro

A equipe do INCT-INOFAR

V reunião de avaliação e acompanhamento

Rio de Janeiro, 16 & 17 de novembro de 2011

Química Medicinal

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

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

Pfizer

" ...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..."

The Role of the Medicinal Chemist in Drug Discovery – Then and Now, *Nature Rev. Drug Disc.* **2004**, *3*, 853.

Universidade Federal do Rio de Janeiro

Obrigado

Rio2016

2011
SBQ
ANO INTERNACIONAL DA QUÍMICA

LASSBio®

FAPERJ

CNPq
Conselho Nacional de Desenvolvimento Científico e Tecnológico

CCS
CENTRO DE CIÊNCIAS DA SAÚDE
UNIVERSIDADE FEDERAL DO RIO DE JANEIRO