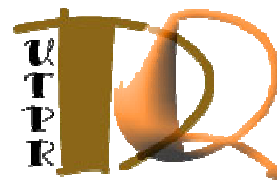




Universidade Federal do Rio de Janeiro

"CELEBRAÇÃO DO ANO INTERNACIONAL DA QUÍMICA NA UFPR"

Departamento de Química – UFPR - 09 de dezembro de 2011



A Química Medicinal

Eliezer J. Barreiro

Professor Titular

Universidade Federal do Rio de Janeiro



Laboratório de Avaliação e Síntese de Substâncias Bioativas

<http://www.farmacia.ufrj.br/lassbio>

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

Programa de Desenvolvimento de Fármacos – ICB-UFRJ





Sumário

- Definição & cronologia histórica da **Química Medicinal**
- Primeiro paradigma da **QuimMed**: Fischer & Ehrlich
- O berço da **QuimMed**: Os pioneiros
- A interdisciplinaridade da **QuimMed**
- A inovação tecnológica em fármacos
- O processo de invenção de fármacos
- Segundo paradigma da **QuimMed**: século 21
- **LASSBio-596**: candidato a novo fármaco antiasmático
- **INCT de Fármacos e Medicamentos (INCT-INO FAR)**
- Missão e equipe do **INCT-INO FAR**
- **INCT-INO FAR** & desafios da inovação radical
- **INCT-INO FAR** & a inovação incremental

Química
e
Medicinal



Química Medicinal

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estuda os fatores moleculares relacionados ao modo de ação dos fármacos, incluindo a compreensão da relação entre a estrutura química e a atividade (SAR), além das propriedades que governam sua absorção, distribuição, metabolismo, eliminação (ADME) e toxicidade.



IUPAC

<http://www.iupac.org>

Chemistry and Human Health Division (VII)

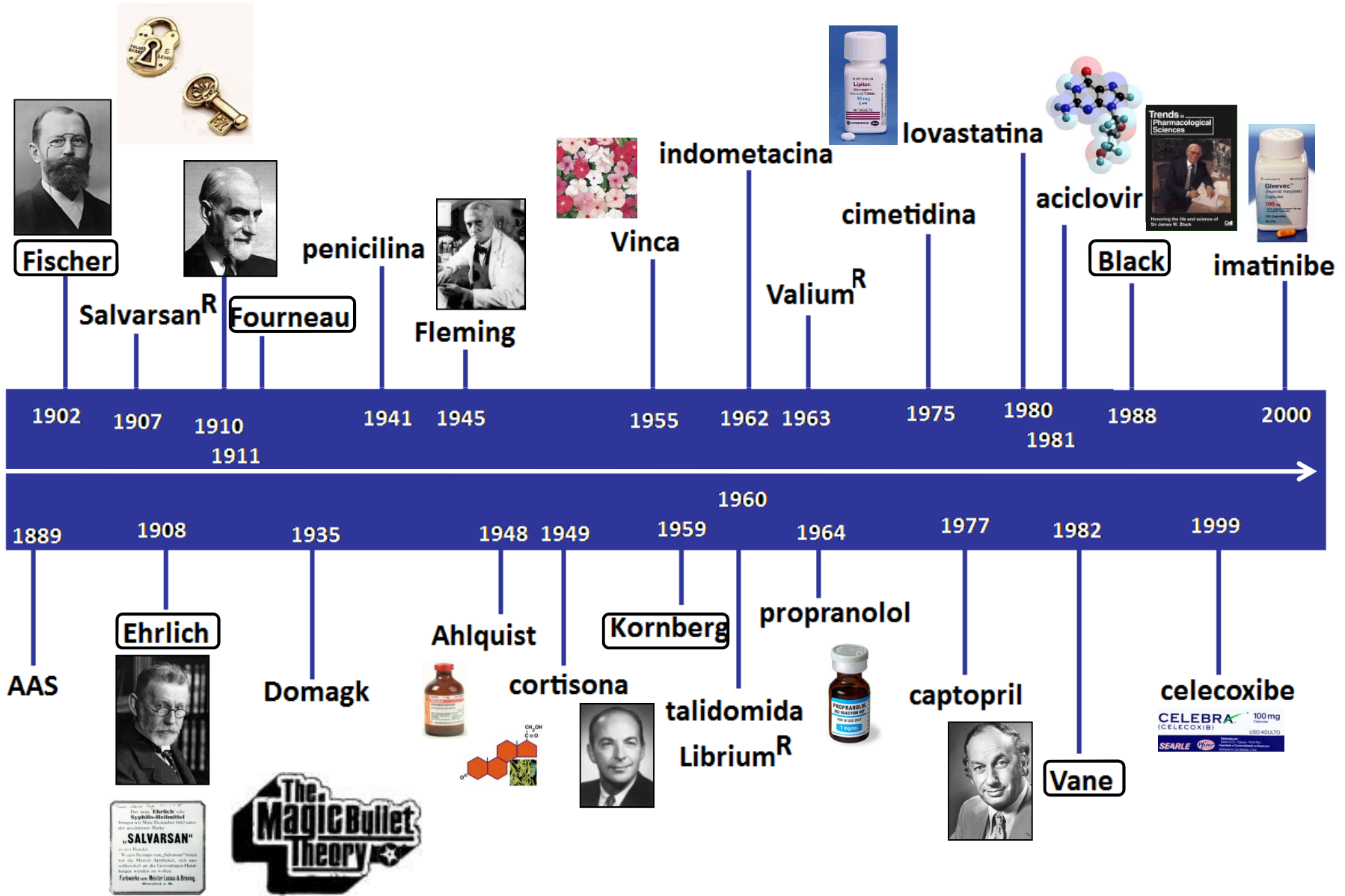
Subcommittee on Medicinal Chemistry and Drug Development.

Eur. J. Med. Chem. 1996, 31, 747

C. R. Ganellin *et al.*, *Eur. J. Med. Chem.* 2000, 35, 163; A. Monge *et al.*, *Eur. J. Med. Chem.* 2000, 35, 1121



Cronologia histórica da Química Medicinal





O paradigma de Ehrlich & Fischer



Emil Fischer

1852-1919

1902

E. Fischer, *Ber. Dtsch. Chem. Ges.* **1890**, 23, 799

LOCK & KEY
CONCEPT



Planejamento racional

Biorreceptor

macrobiomolécula
baseado no sítio de reconhecimento

BSRM

BL-AA

Fármaco

micromolécula

baseado no ligante / análogo-ativo



Paul Ehrlich

1854-1915

1908



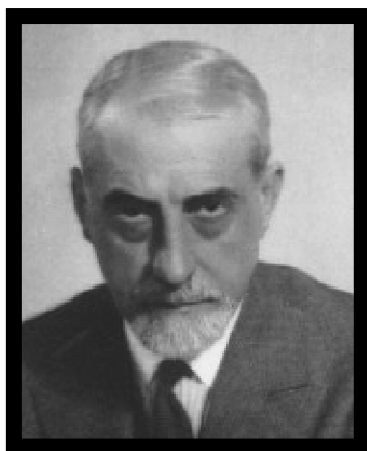
Physiologic
A abordagem fisiológica
approach

one-drug-one-bullet

Primeiro paradigma da Química Medicinal



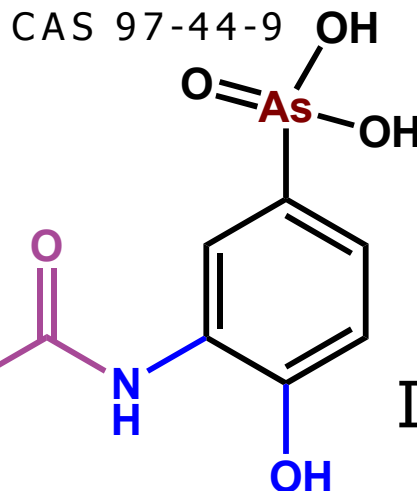
O berço da Química Medicinal



Ernest Fourneau
1872-1949



Stovarsol



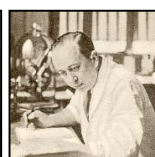
Institut Pasteur (1887)

1911- Laboratoire de Chimie Thérapeutique



Diretor: Emile Roux

1911-1944 – Jacques Tréfouël (1897-1977)
Thérese Tréfouël (1892-1978)
Germaine Benoit (1901-1983)
Federico Nitti (1903-1947)



Daniel Bovet
1907-1992 *

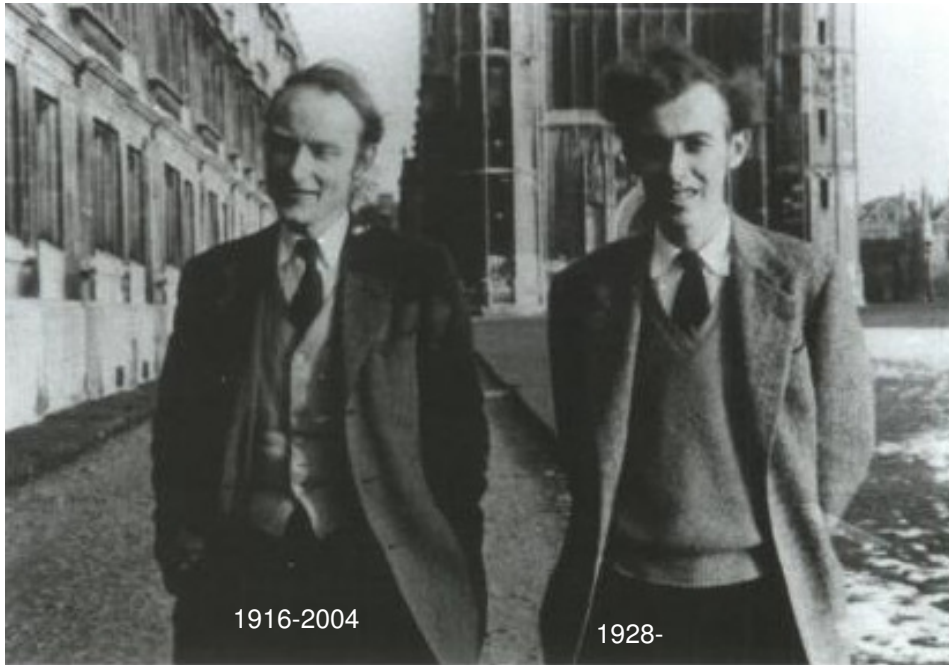
* Farmacêutico suíço
Doutor *h.c.* UFRJ

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

Curare: SAR

J-P Fourneau, « Ernest Fourneau fondateur de la Chimie Pharmaceutique française », *Revue de l'Histoire de la Pharmacie*, t.XXXIV, n° 275, 335-355

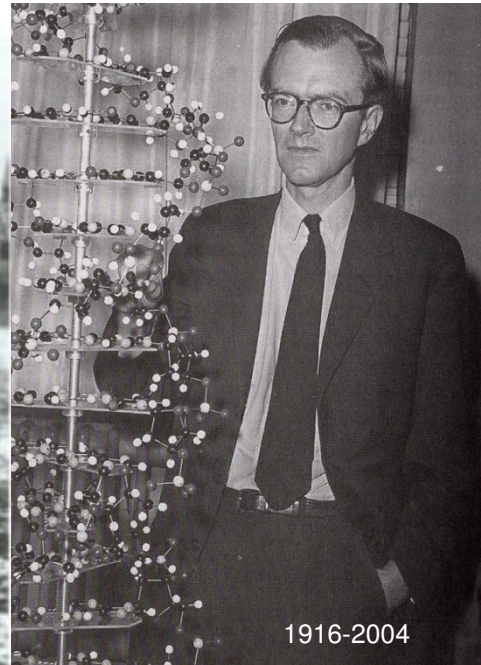
Prêmio Nobel de Fisiologia/Medicina



1916-2004

1928-

Francis Crick and James Watson in Cambridge, England, 1953
(Courtesy of the James D. Watson Special Collection, Cold Spring Harbor Laboratory Archives.
From Watson J.D. 1968, *The Double Helix*. Atheneum Press, New York.)



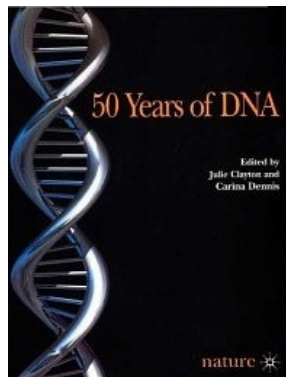
1916-2004

Maurice H. F. Wilkins

1962



O físico Crick, o biólogo Watson & o médico Wilkins



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



Interdisciplinaridade

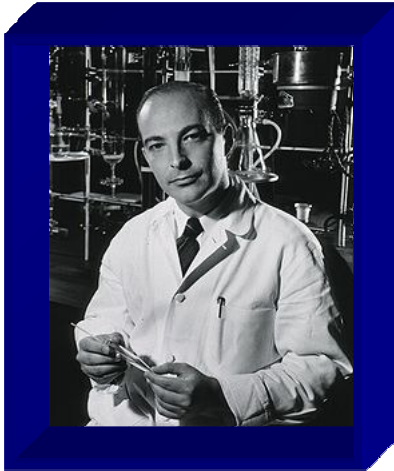
Slide 7

EJB4

Exemplos de extraordinárias conquistas do conhecimento humano deveram-se às associações de capacidades e competências complementares, essenciais à sua consecução: e.g. DNA em publicação de apenas 2 páginas em prestigioso periódico científico que resultou, décadas depois, na era ômica.

JD Watson & FHC Crick, *Nature*, 1953, 171, 737-738

Eliezer J. Barreiro; 04/03/2010



Arthur Kornberg
1918-2007

1
9
8
7

Prêmio Nobel, 1959



The Two Cultures: Chemistry and Biology¹

Arthur Kornberg

Department of Biochemistry, Stanford University, Stanford, California 94305

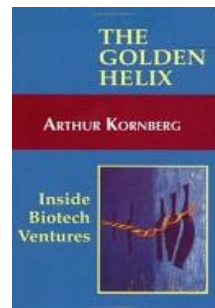
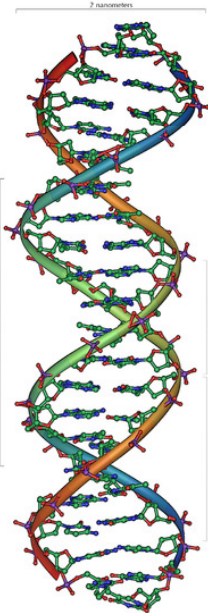
Received July 14, 1987

“Much of life can be understood in rational terms if expressed in the language of chemistry... the

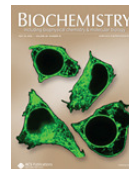
historical roots of chemistry and biology

are intertwined in many places...

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



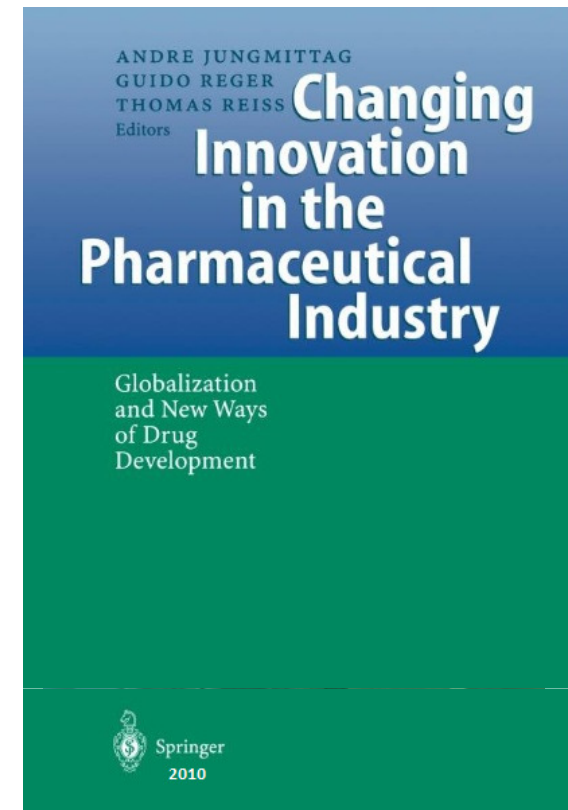
Biochemistry 1987, 26, 6888-6891



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** depende, fortemente, do avanço científico e resulta da descoberta ou da invenção de novos fármacos sendo a principal driving-force da indústria farmacêutica, que faturou *ca.* US\$ 950 bilhões, em 2011.





The drug discovery process...



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



- *Science* **2004**, 303, 1713 (Donald Kennedy Ed)

- Rethinking Drug Discovery
- Surviving the Blockbuster Syndrome
- Orphan Drugs of the Future?
- Protein Kinase Inhibitors: Insights into Drug Design from Structure
- Polyketide and Nonribosomal Peptide Antibiotics: Modularity and Versatility
- Organic Chemistry in Drug Discovery
- The Many Roles of Computation in Drug Discovery
- Drug Delivery Systems: Entering the Mainstream

is scientific research based.

“Science is made of facts, just as houses are made of stones; but a mere collection of facts is no more science than a pile of stones a house” - Henri Poincare, 1902





Universidade Federal do Rio de Janeiro

Química Medicinal



LASSBio

Laboratório de Avaliação e Síntese de Substâncias Bioativas

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

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



Pharmacology
Farmacologia



Molecular
Modelagem
Modeling
Molecular



© 2010



A Química Medicinal

Século 21

Siglo 21

21st Century

Siècle 21



Chemistry for the 21st Century

IUPAC

Medicinal Chemistry for the 21st Century

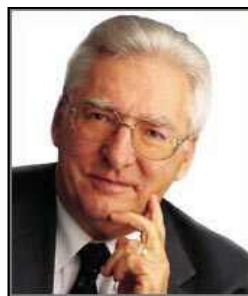
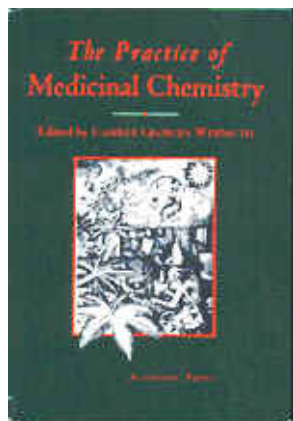
Edited by C.G. Wermuth
with N. Koga, H. König & B.W. Metcalf

Blackwell Scientific Publications



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 compared with monotarget formulations.”



Camille G. Wermuth

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

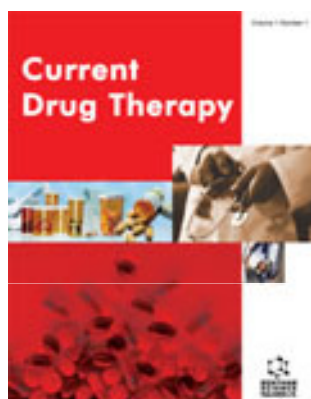


New Insights for Multifactorial Disease Therapy: The Challenge of the Symbiotic Drugs

Eliezer J. Barreiro and Carlos Alberto Manssour Fraga

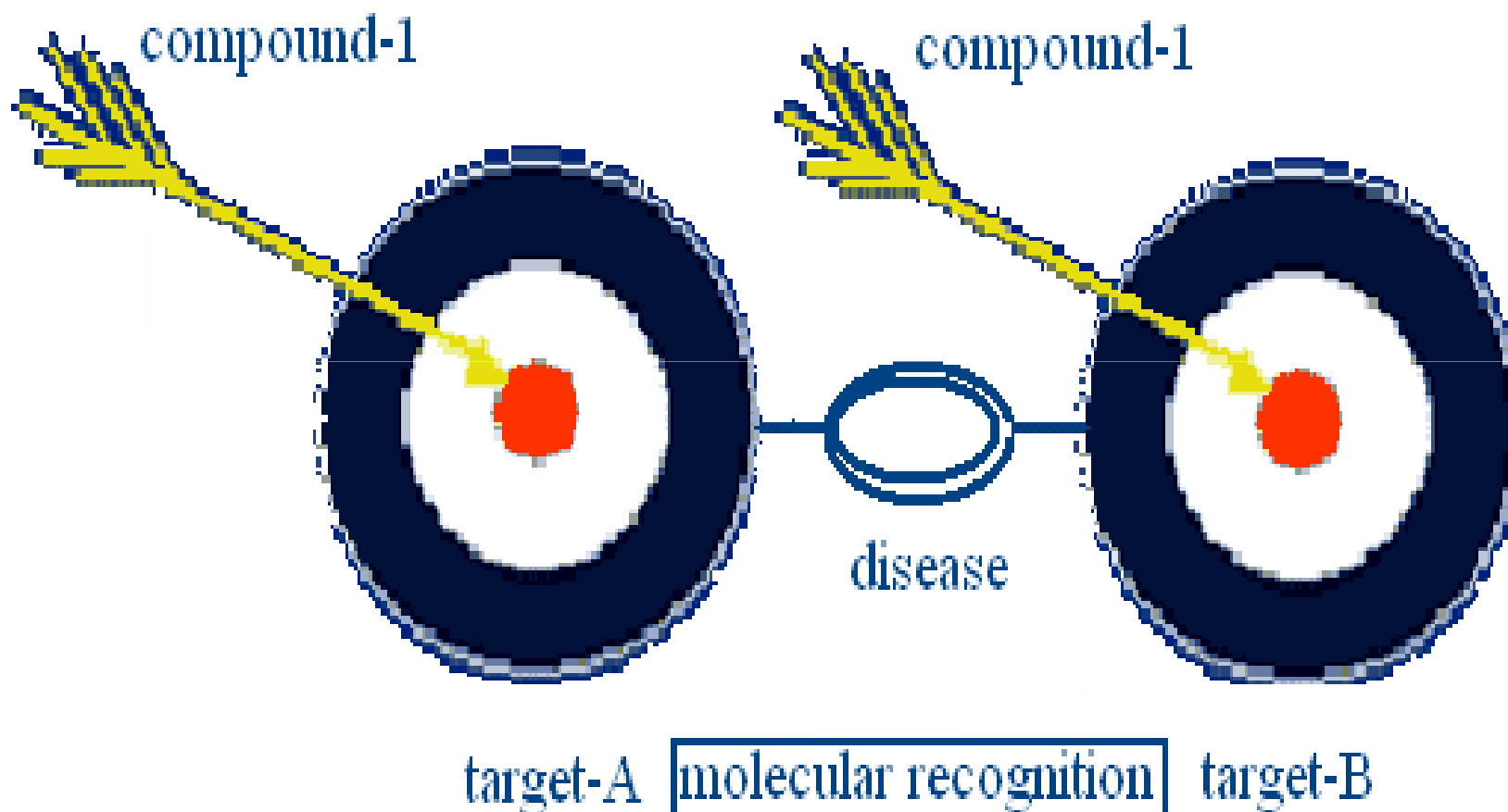
Química Medicinal

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.



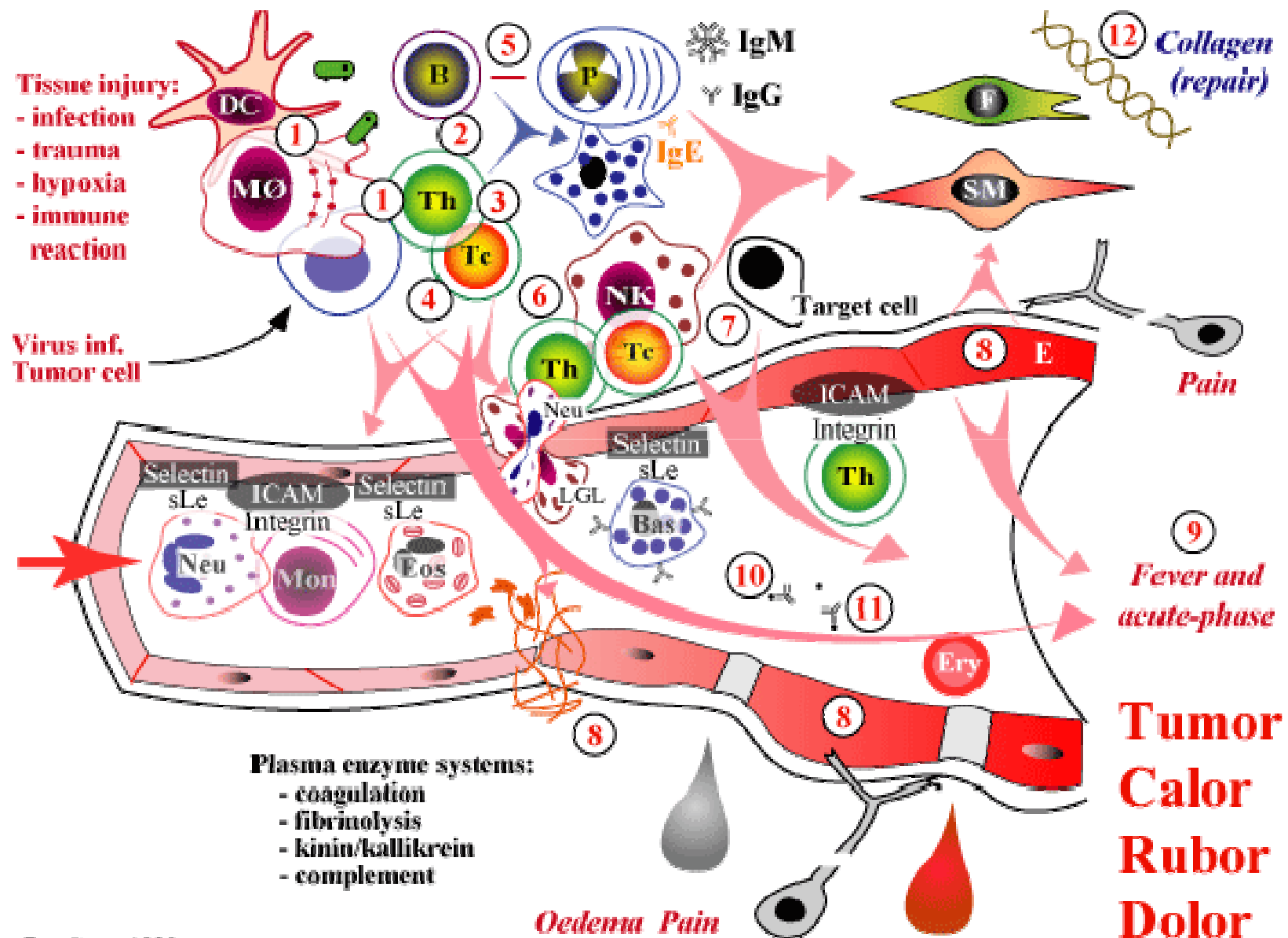
O tratamento de uma patologia multifatorial (e.g. doenças crônicas não transmissíveis, câncer, metabólicas, etc) com fármacos planejados para alvos terapêuticos únicos (Primeiro paradigma da Química Medicinal ou Paradigma de Ehrlich & Fischer) será sempre paliativo! Estas patologias requerem fármacos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

The multiple-target lead design



Segundo paradigma da Química Medicinal

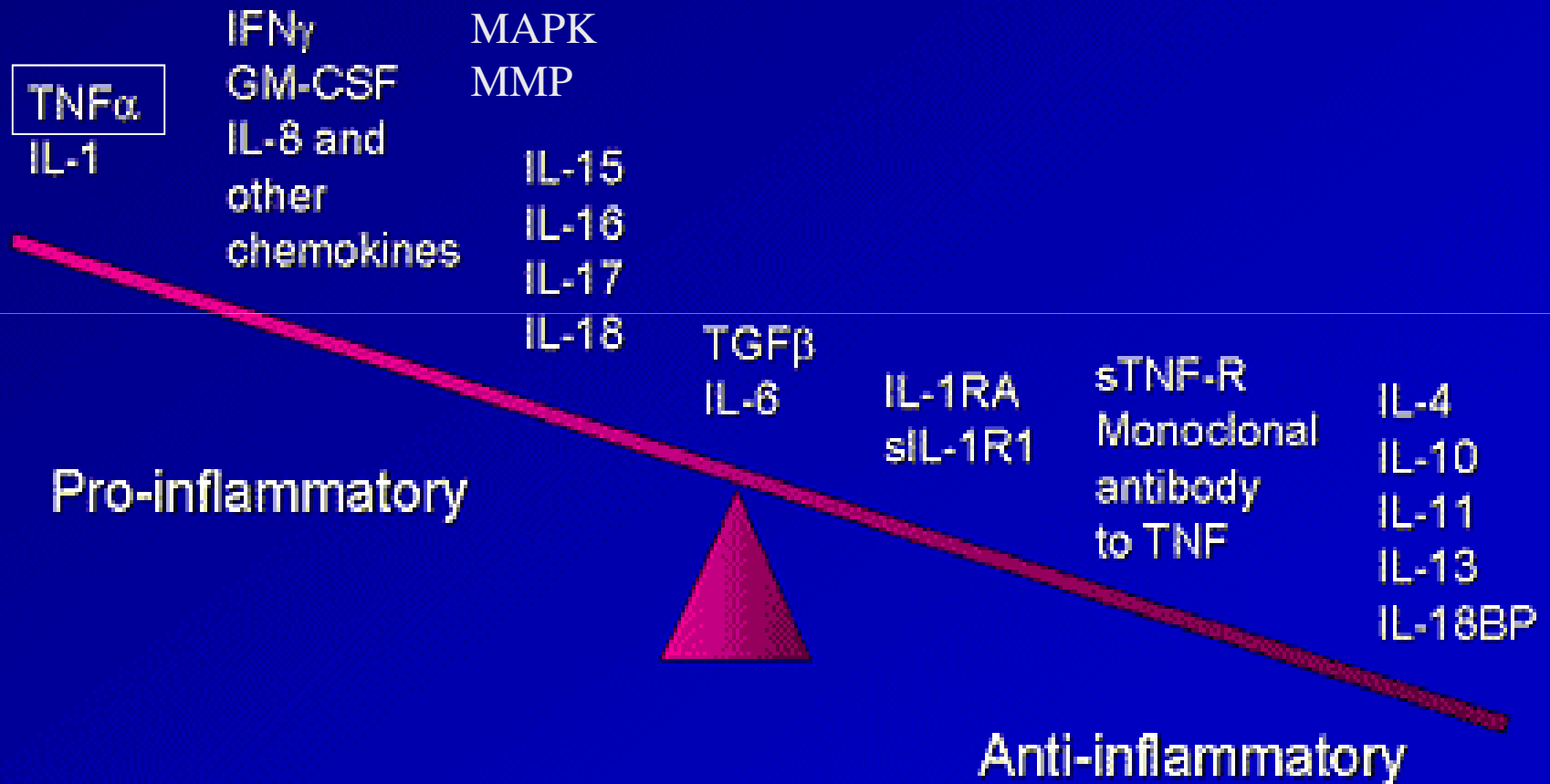
Inflamação: Doença crônica não transmissível



Bendtzen 1999



Role of Cytokines and Cytokine Inhibitors in Chronic Inflammation



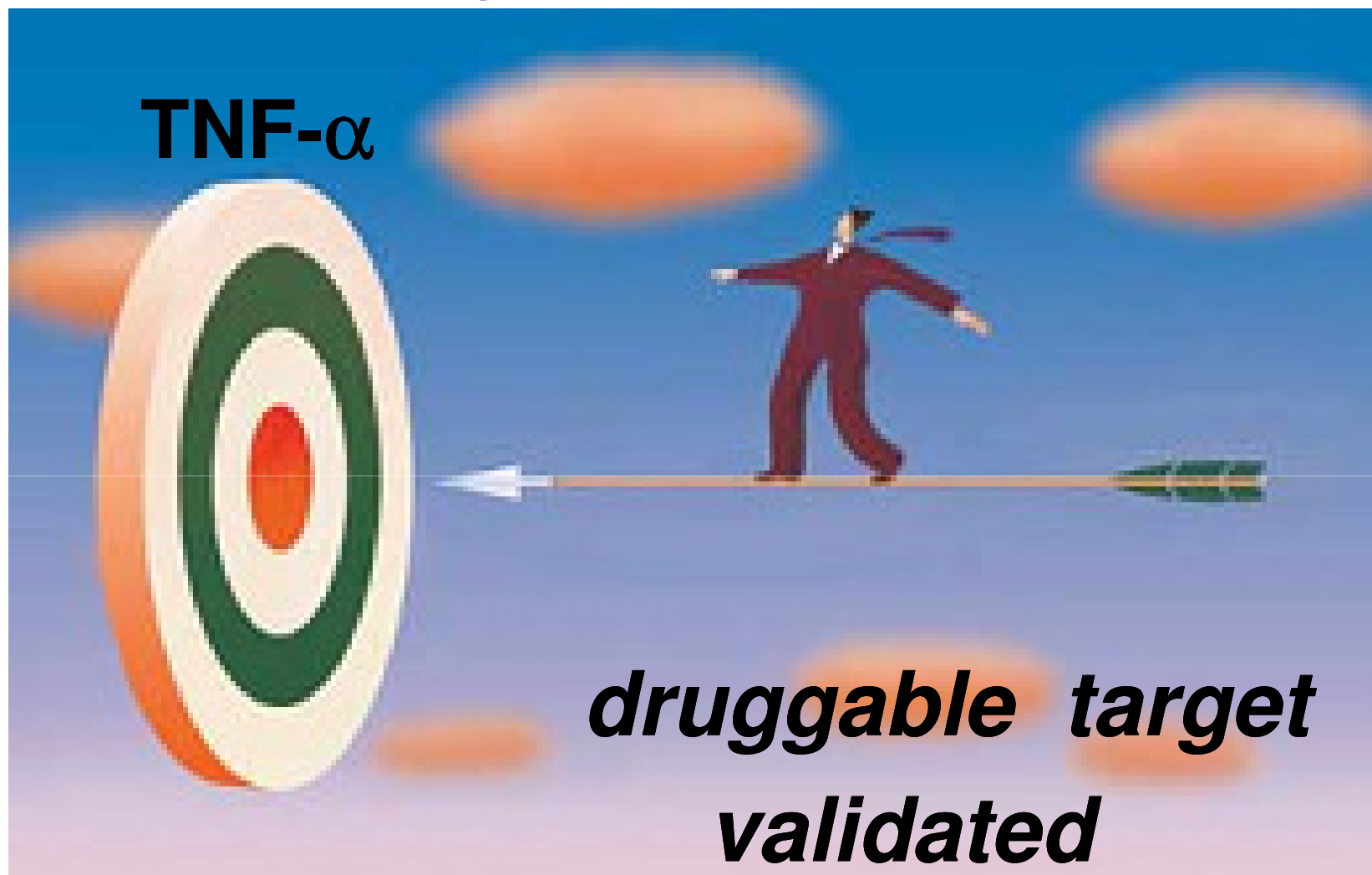
Arend. Arthritis Rheum 2001.

* 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 blockade in RA and other chronic inflammatory diseases, *Curr. Op. Pharmacol.* 2010, 10, 308

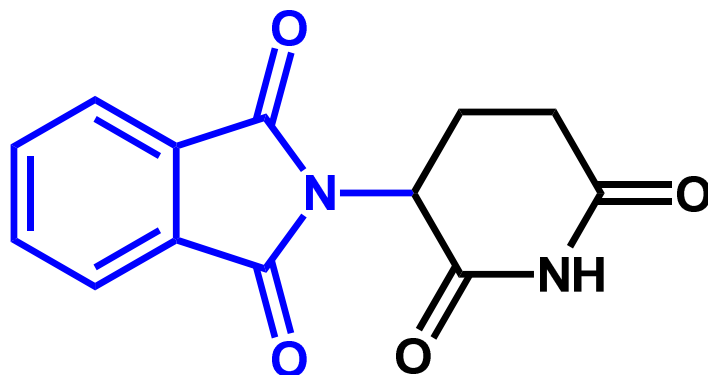


Biofármacos anti-TNF-alfa usados na clínica

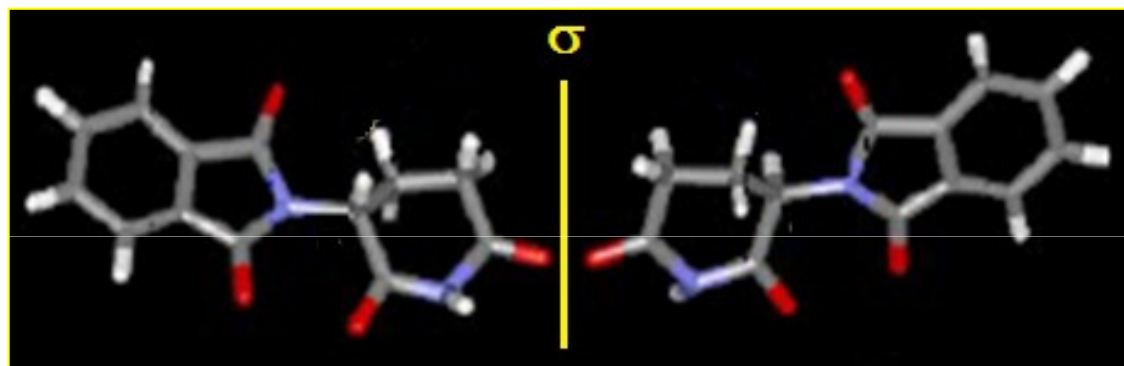
Biofármaco (nome fantasia)	Situação	Forma biológica
Adalimumab Humira ^R	aprovado	anticorpo anti-hTNF ^{a)}
Etanercept Enbrel ^R	aprovado	TNFR2 acoplado a Fc do IgG ^{b)}
Infliximab Remicade ^R	aprovado	anticorpo quimérico anti-hTNF ^{c)}
ISIS 104838	clínico	antisense TNF
Onercept Serono ^R	clínico &	TNFR solúvel p55
CDP 571 Humicade	clínico &	IgG4 anti-TNF humanizado

a) Total de vendas em 2011 : US\$ 6,6 bilhões; b) idem: US\$ 6,5 bilhões; c) idem US\$ 6, 4 bilhões; & Descontinuado;

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



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



Wilhelm Kunz, 1953

Herbert Keller, 1953

CNS, 1957

Frances Kelsey, 1961

Gilla Kaplan, 1991 (TNF- α)

Elisabeth Sampaio, 1997

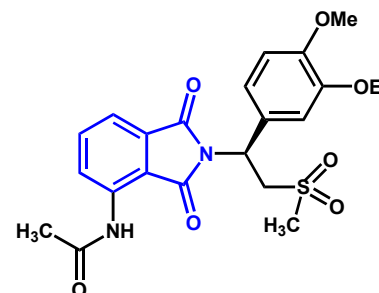
Thalidomide Anti-TNF α

TNF- α IC₅₀ = 200 μ M

Apremilast, Phase II, Celgene (2009)

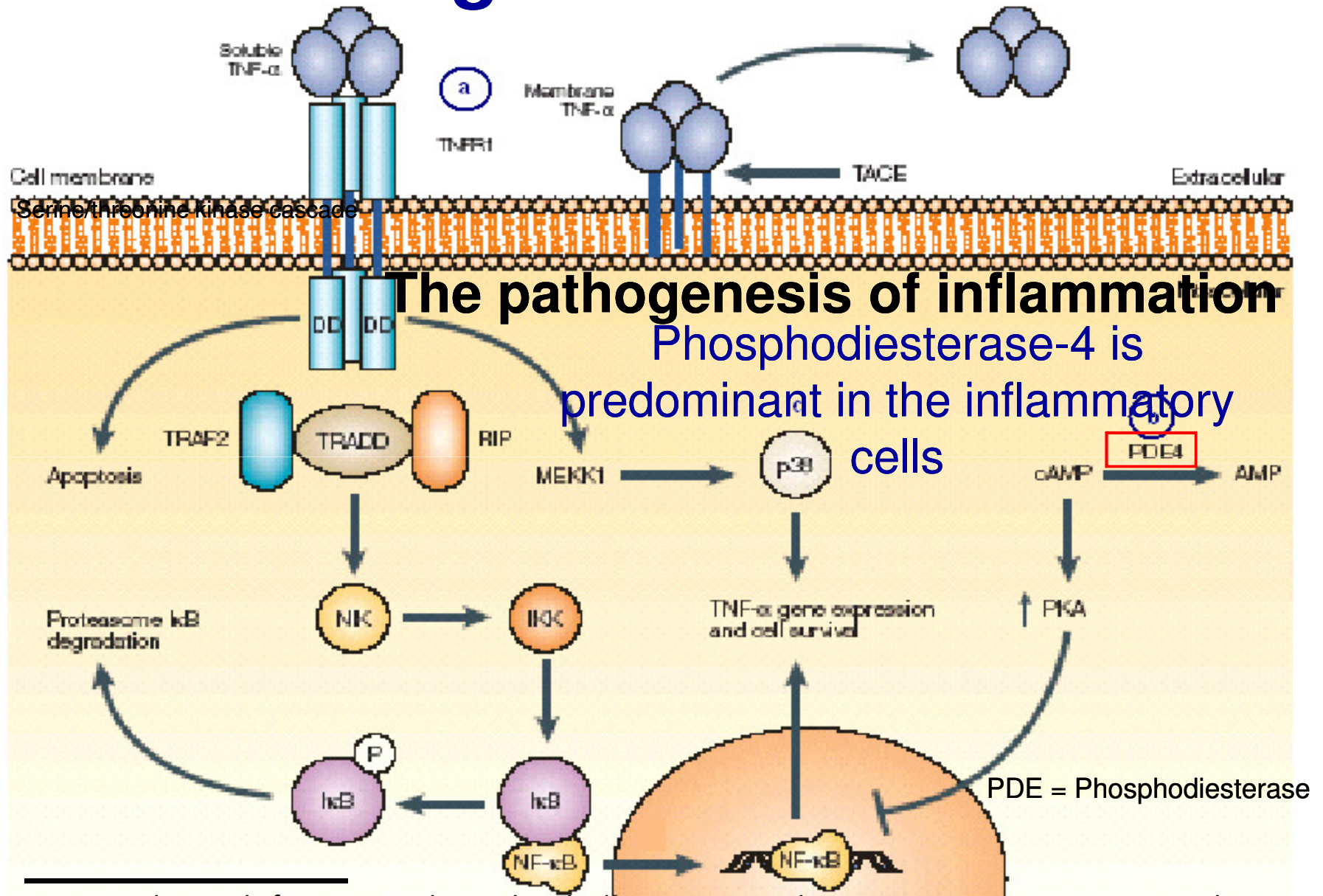
H-W Man *et al.*, *J. Med. Chem.* **2009**, *52*, 1522

FE McCann *et al.*, *Arthritis Res. Ther.* **2010**, *12*, R107





Second Target Election: PDE-4



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

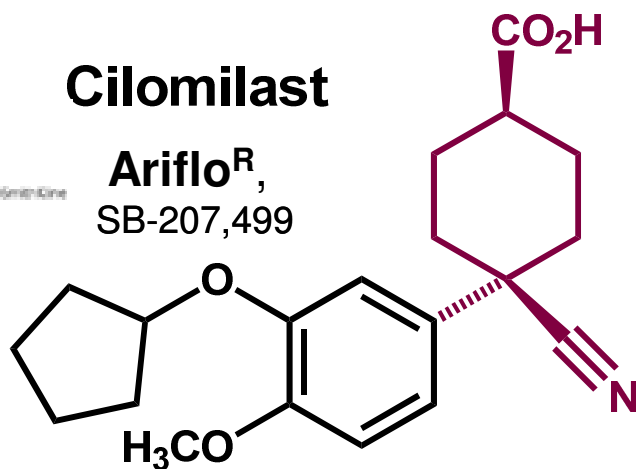


Alvo terapêutico validado

Cilomilast



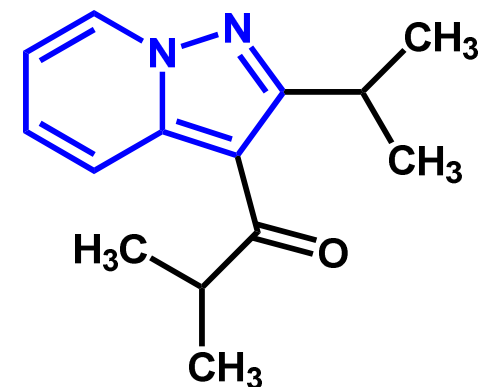
Ariflo^R,
SB-207,499



4-cyano-cyclohexyl carboxylic acid

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

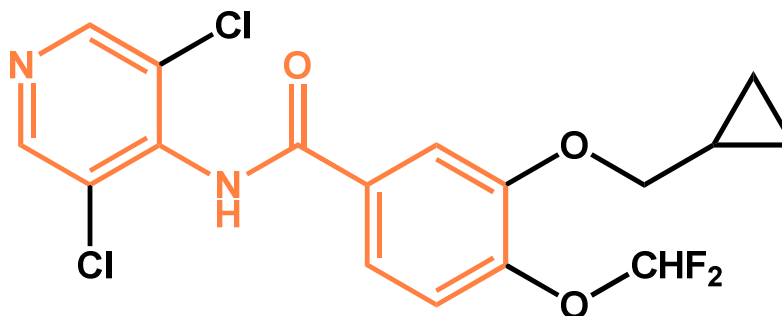
Ibudilast



pyrazolo[1,5-a]pyridine

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

Roflumilast



pyridine-benzamide

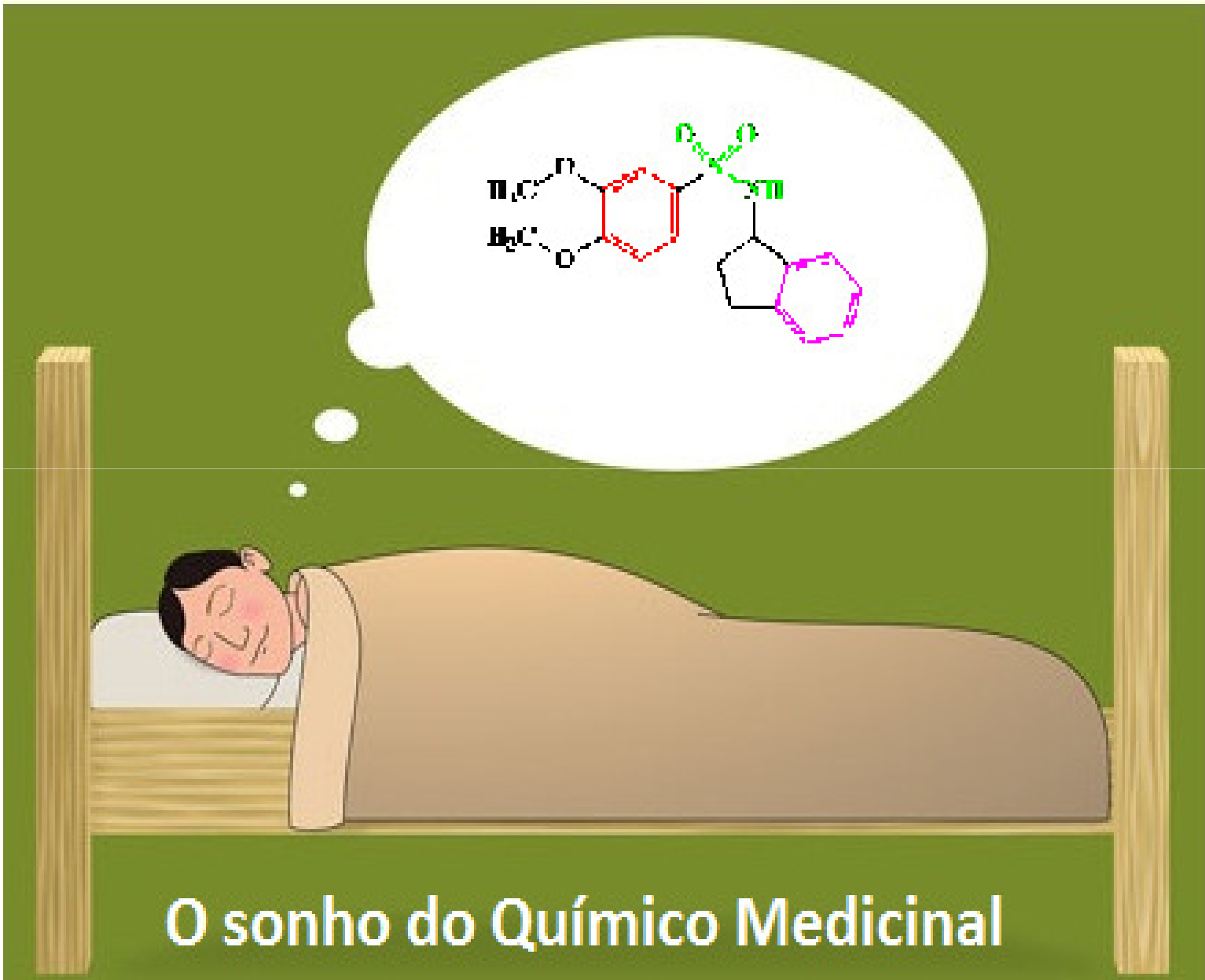
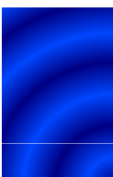
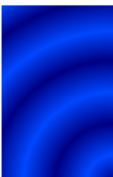
LM Fabbri *et al.*, *Nature Rev Drug Discov* **2010**, *9*, 761



Daxas^R
Aprovado
2011

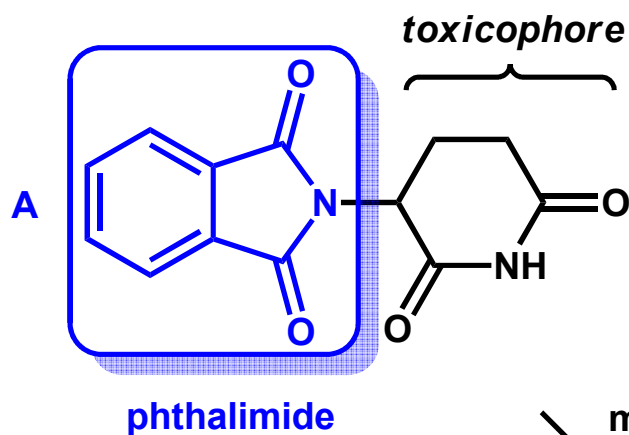


A Kodimuthali, S S L Jabaris, M Pal, Recent advances on phosphodiesterase 4 inhibitors for the treatment of asthma and chronic obstructive pulmonary disease, *J. Med. Chem.* **2008**, *51*, 5471; S. Diamant, D Spina, PDE-4 inhibitors: a novel, targeted therapy for obstructive airways diseases, *Pulmonary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

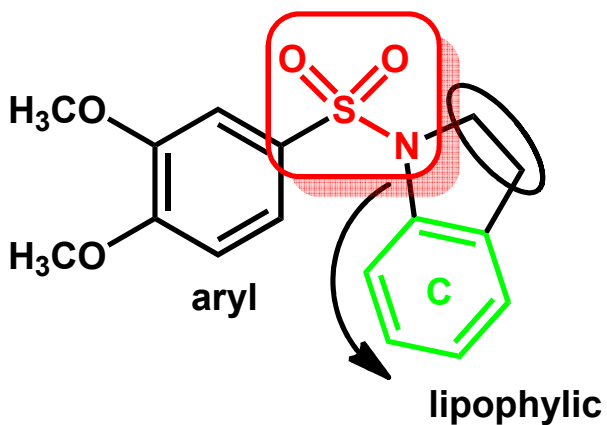
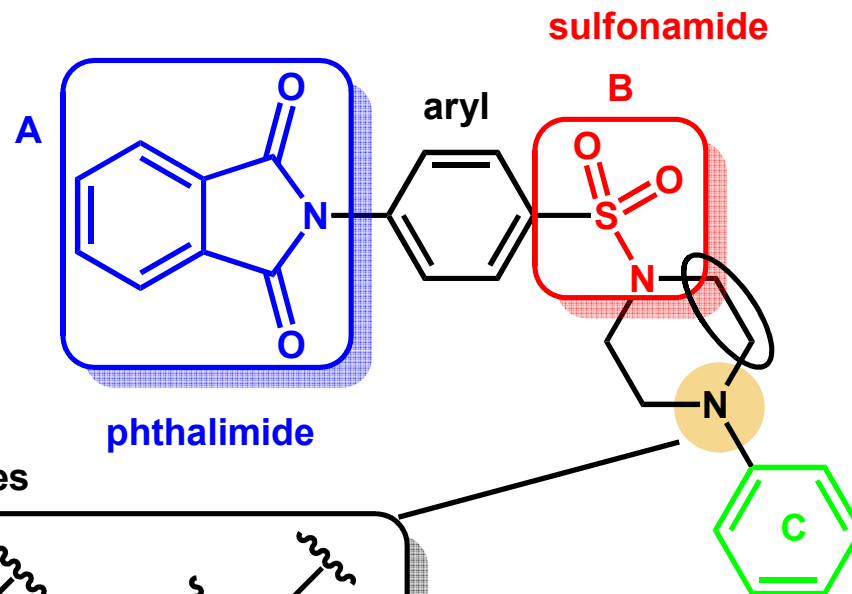


O sonho do Químico Medicinal

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

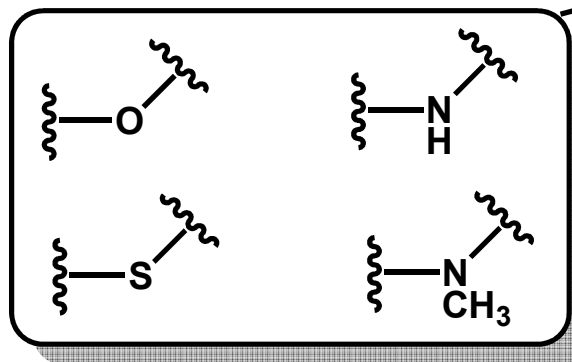


molecular hybridization



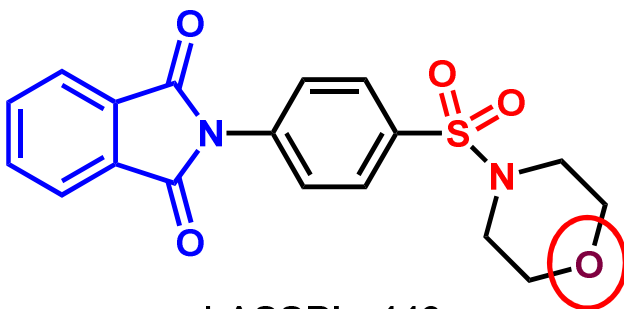
Montana *et al.*, 1998

isosteres

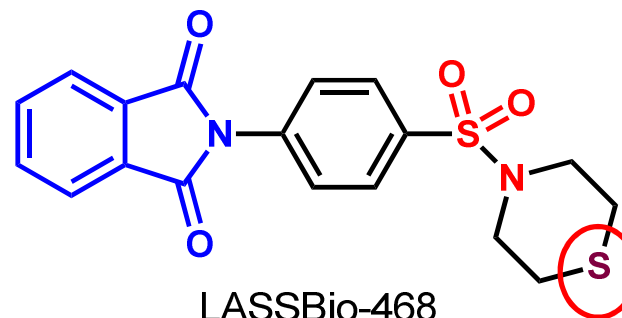




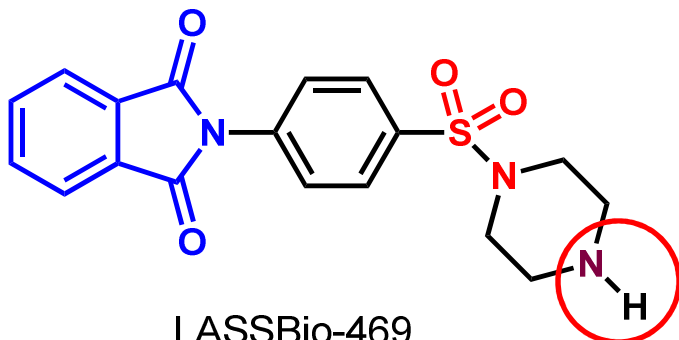
Série Congênere



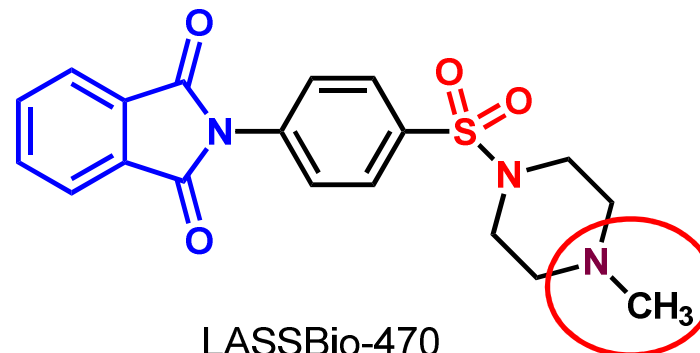
LASSBio-449



LASSBio-468

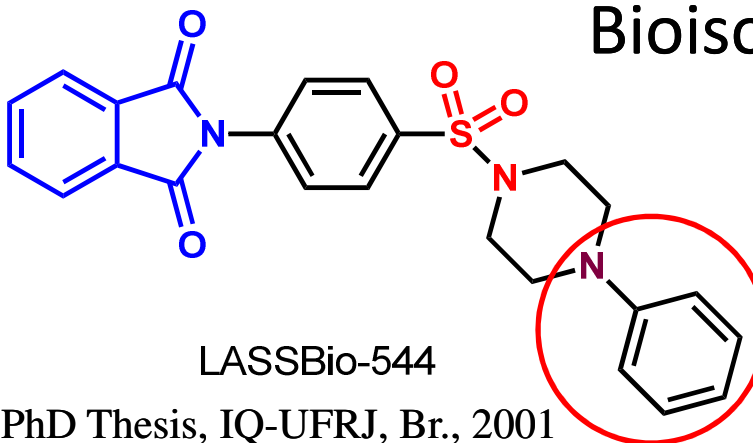


LASSBio-469



LASSBio-470

Bioisosterismo

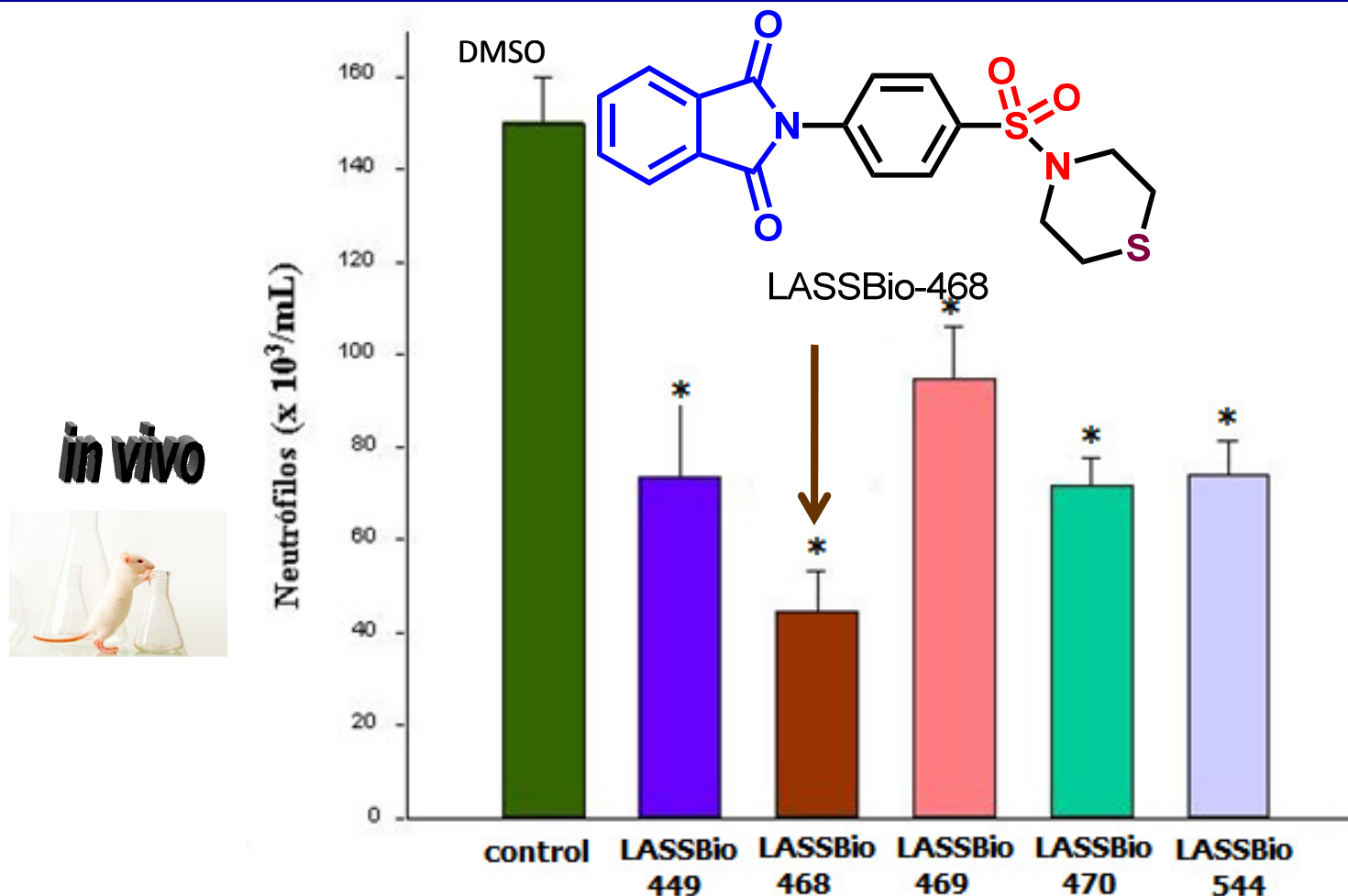


LASSBio-544



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.*)



Results are expressed as means SEM of seven animals.

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

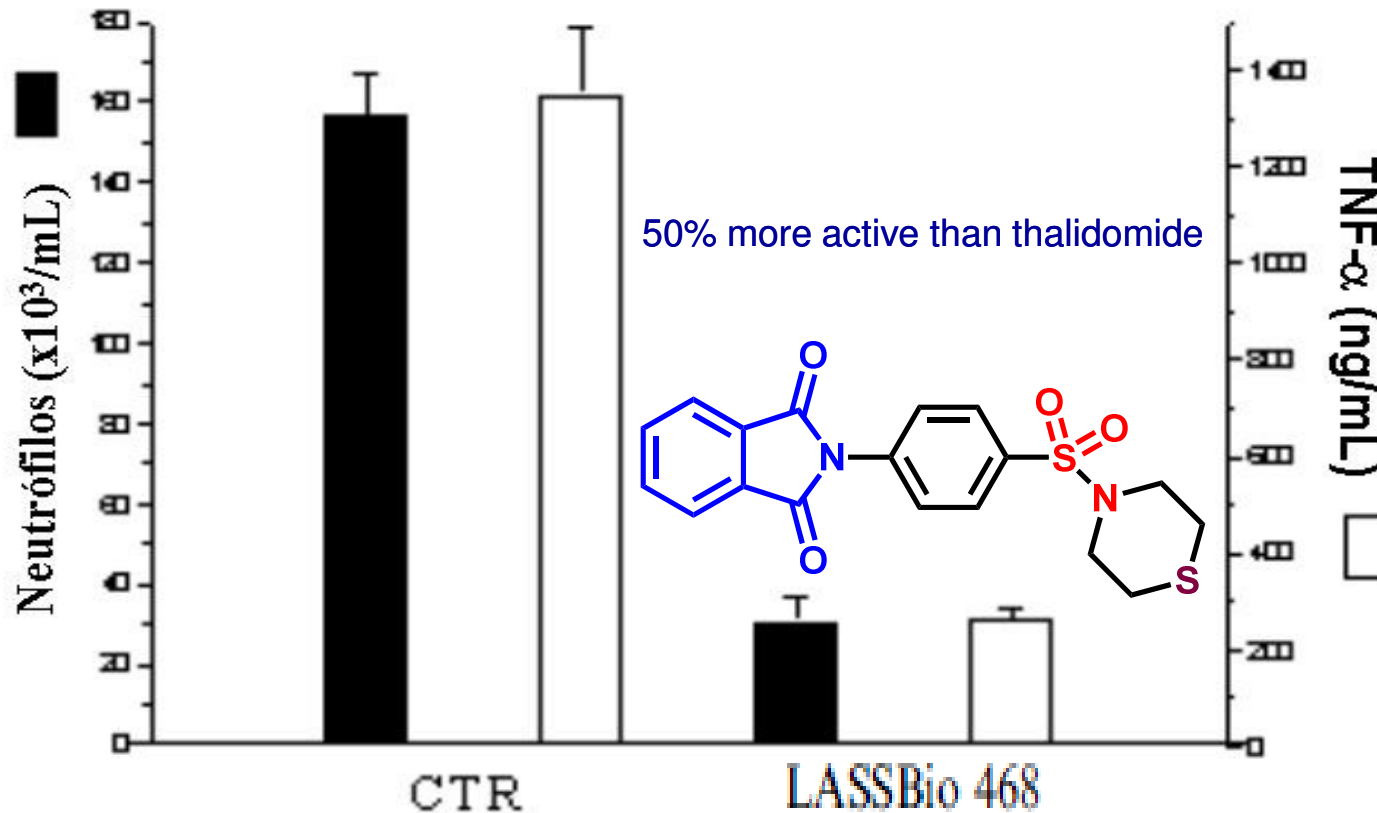
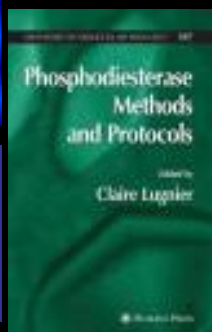
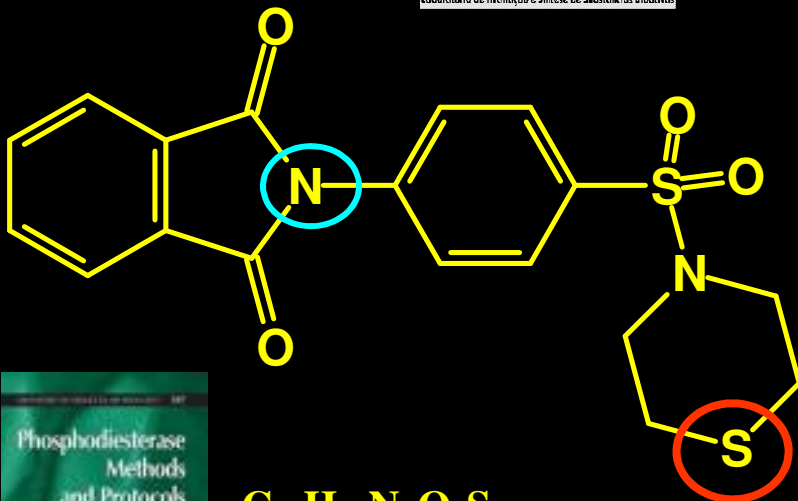


Fig. 1 Effect of LASSBio-468, thalidomide and pentoxifylline on survival BALB/c mice after LPS (500 μ g/mice) administration.



LASSBio 468

TNF- α ED₅₀ 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.

IC₅₀ = 13,5 μ M
cf. PDE-1, 2, 3, 5 > 150 μ M;

Bioorganic & Medicinal Chemistry 10 (2002) 3067–3073

Synthesis and Anti-Inflammatory Activity of Phthalimide Derivatives, Designed as New Thalidomide Analogues

Lidia M. Lima,^{a,b} Paulo Castro,^c Alexandre L. Machado,^c Carlos Alberto M. Fraga,^{a,b} Claire Lugnier,^d Vera Lúcia Gonçalves de Moraes^c and Eliezer J. Barreiro^{a,b,*}

^aLaboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio, <http://www.farmacia.ufrj.br/lassbio>),

Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, Brazil

^bInstituto de Química, Universidade Federal do Rio de Janeiro, Brazil

^cDepartamento de Bioquímica Médica, Universidade Federal do Rio de Janeiro, Brazil

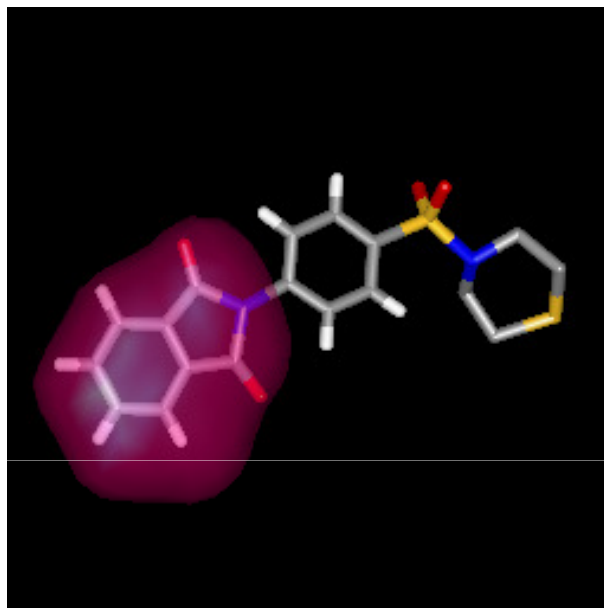
^dCNRS URA 600, IllKirch, France

Received 3 December 2001; accepted 16 January 2002



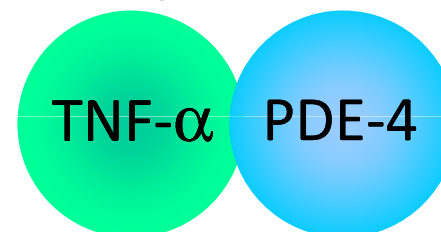


Novo composto-protótipo dual



LASSBio-468

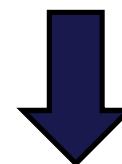
Desenhado por
hibridação molecular



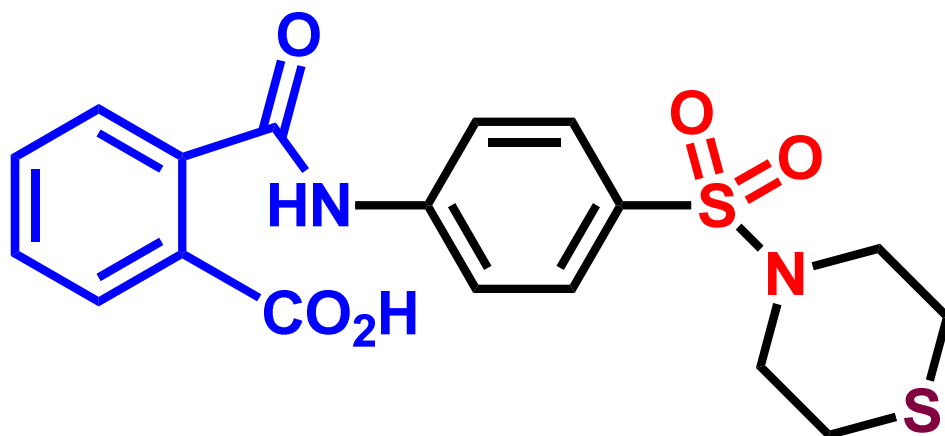
TNF- α ED₅₀ 2,5 mg/Kg

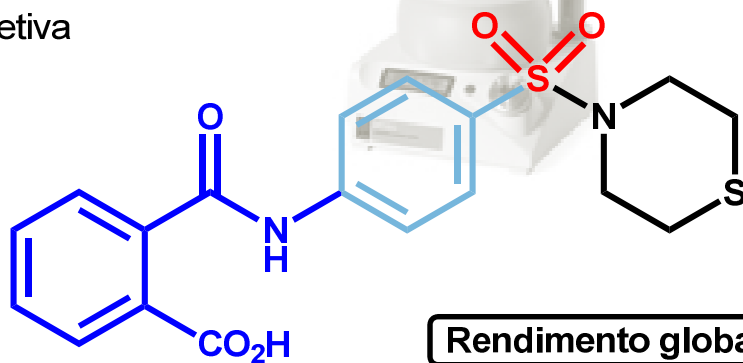
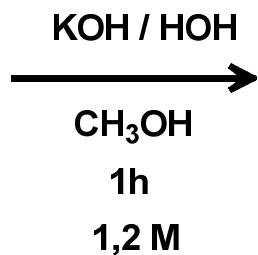
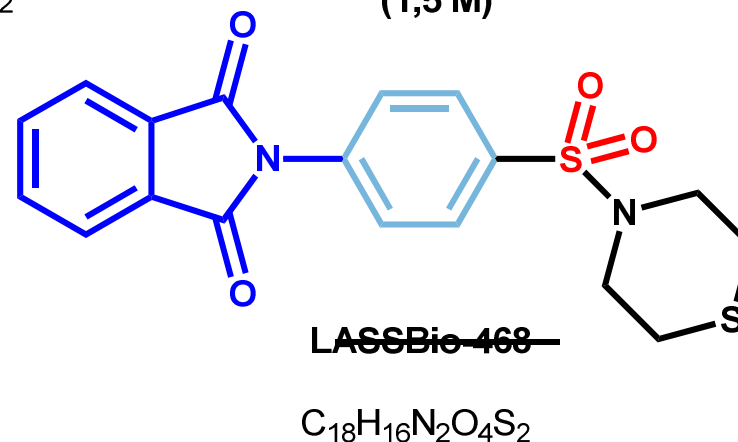
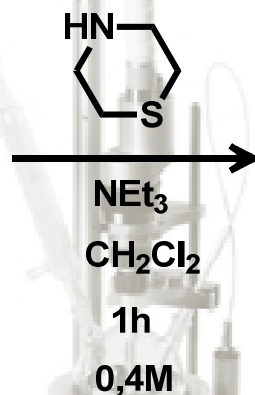
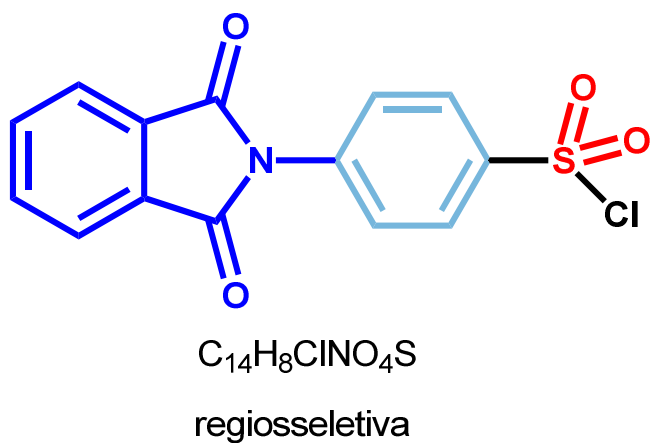
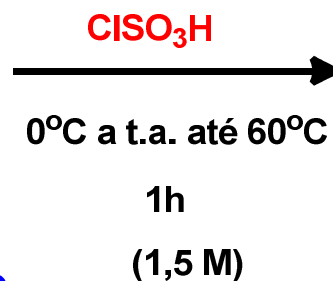
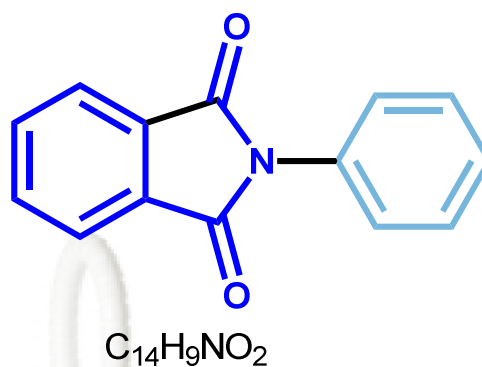
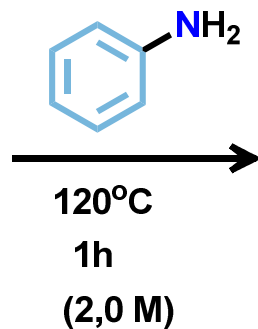
PDE-4 IC₅₀ = 13,6 μ M

Estudos do
metabolismo



LASSBio-596





Rendimento global: 29%

LASSBio-596

$C_{18}H_{18}N_2O_5S_2$

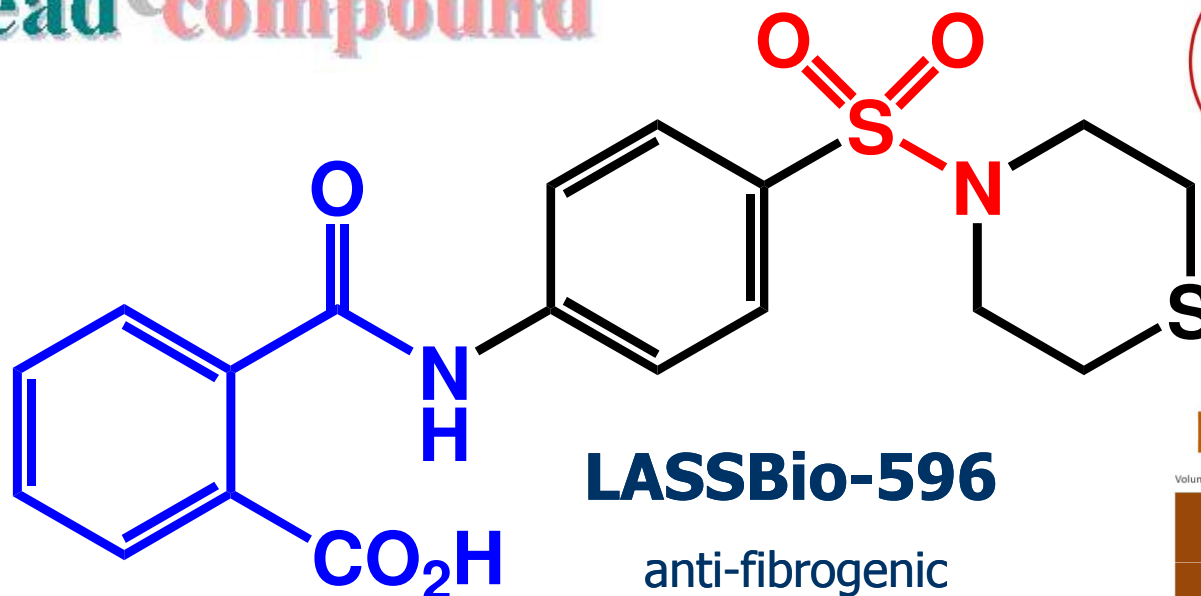
^{13}C , 1H RMN / IV / UV / EM
HPLC
calorimetria diferencial
de varredura (DSC)
CHN
Difração de Raios-X





a
s
t
h
m
a

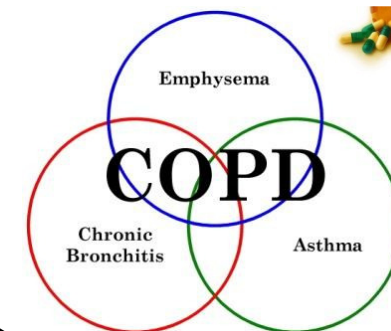
lead compound



LASSBio-596

anti-fibrogenic

Lead Optimization



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 microcystin-LR, *Toxicon* **2011**, *58*, 195.



instituto nacional de Farmacos e Medicamentos
de ciencia e tecnologia

www.inct-inofar.ccs.ufrj.br



Project CNPq 573.564/2008-6

Home

INCT-INOVAR

Team

Scientific adviser board
(SAB)

Research groups

Research people

Useful articles

Publications

Meetings

Videos

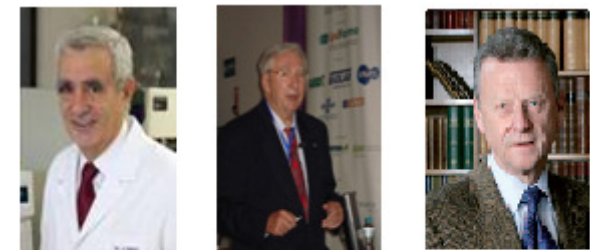
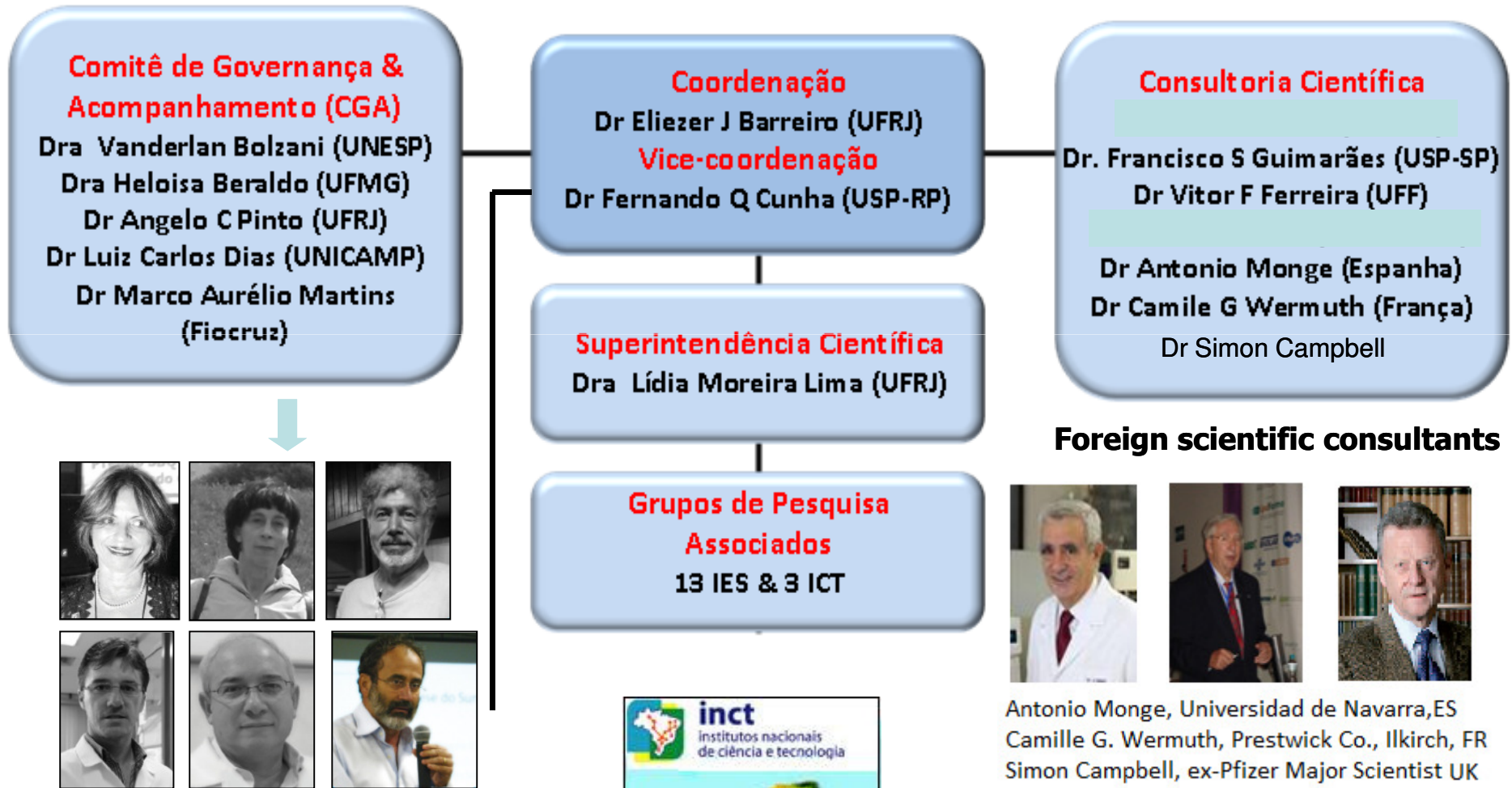
A missao do INCT-INOVAR

- Organizar as competencias cientficas nacionais em uma rede efetiva de pesquisa em farmacos;
- Apoiar projetos de pesquisa cientfica multi-institucionais voltados para novos farmacos;
- Contribuir para a inovaao incremental e radical em novos farmacos e genericos;
- Estudar e desenvolver a sntese total de genericos, intermedirios avanados e matrias-primas;
- Contribuir para a formaao cientfica qualificada de pessoal em qumica medicinal & farmacologia;
- Promover a divulgaao das cincias dos farmacos e dos medicamentos, assim como seu uso racional e seguro;



Governance committee

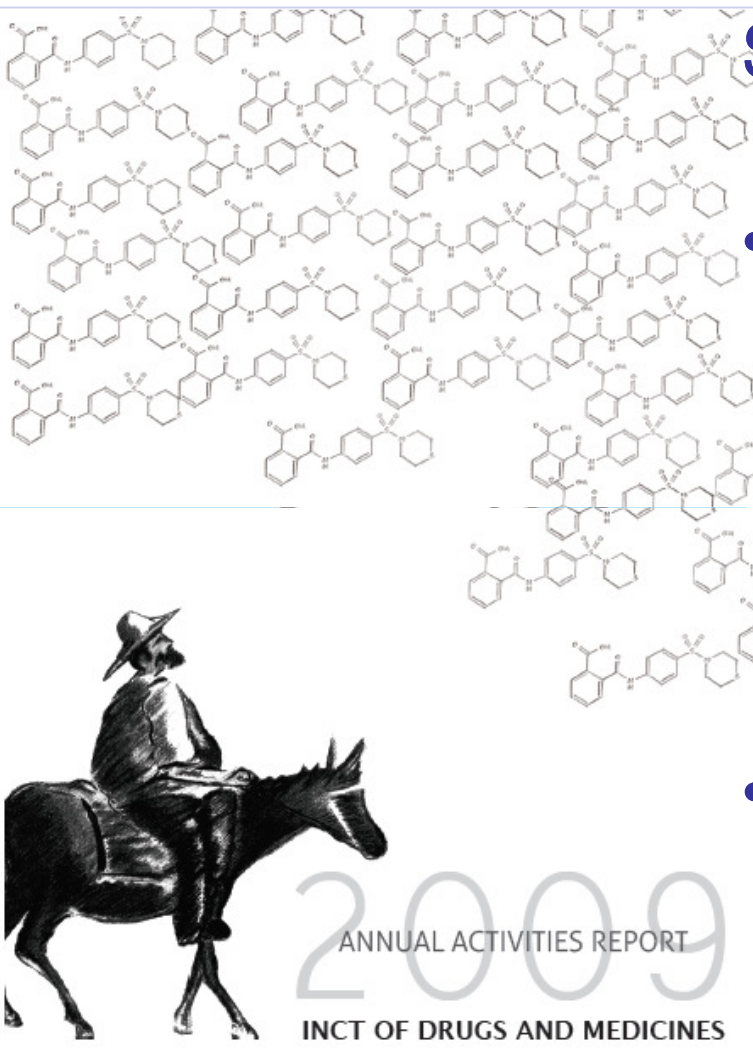
Innovation in Drugs and Medicines



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



Annual Activities Report



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

Subprojetos multi-institucionais & interdisciplinares

- **Inovação radical**
dor, inflamação, asma, SNC, doenças negligenciadas, sistema cardiovascular, anticâncer, metabólicas
- **Inovação incremental**
(fármacos genéricos)
SUS
novas oportunidades

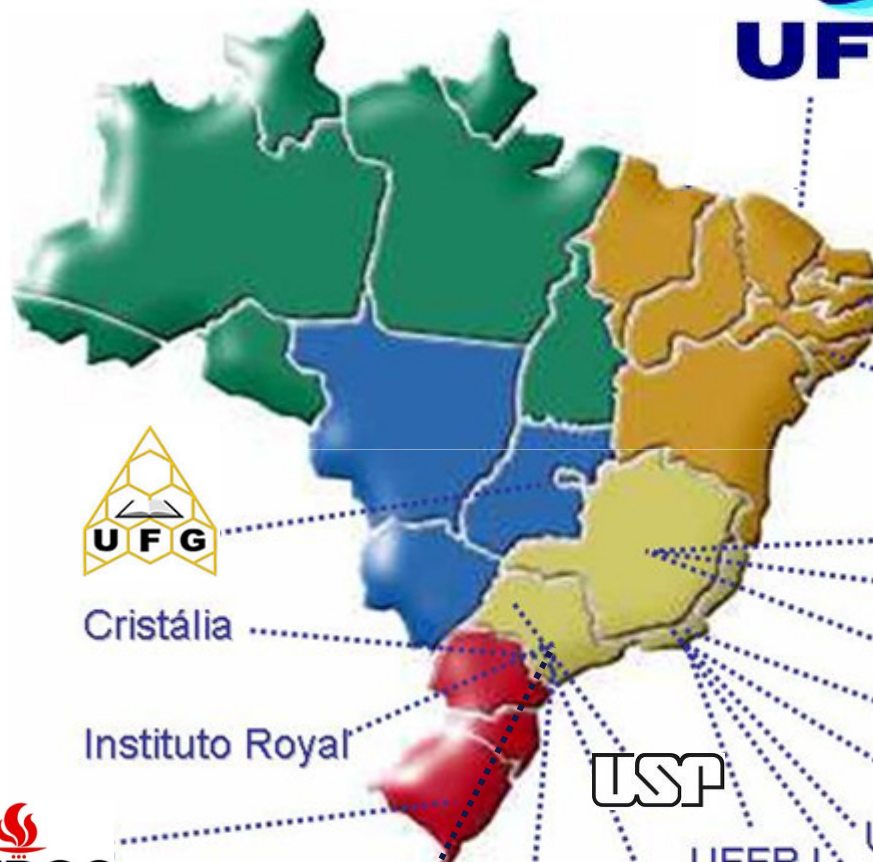
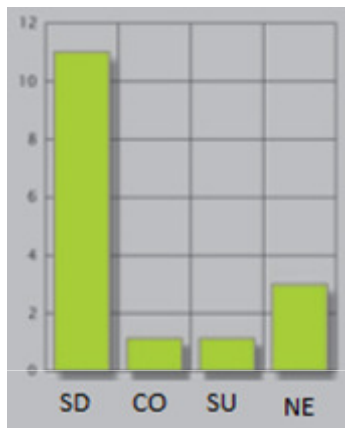
www.inct-inofar.ccs.ufrj.br/download/aar/2010.pdf



INCT-INO FAR



Equipe



Cristália

Instituto Royal

In Vitro Cells

UFMG

FIOCRUZ



UFMG

USP

UFRJ



UFFRJ



UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL



unesp

LNCC





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

Precisamos resolver, com urgência, a grave situação de dependência das importações de farmoquímicos, medicamentos e adjuvantes farmacotécnicos, invertendo o sentido do

Caminho das Índias dos fármacos no Brasil

Inovação incremental

- 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





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]

Patente US 5273995 Pfizer (1991):

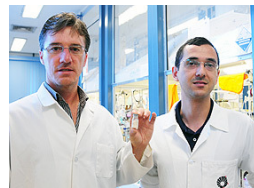
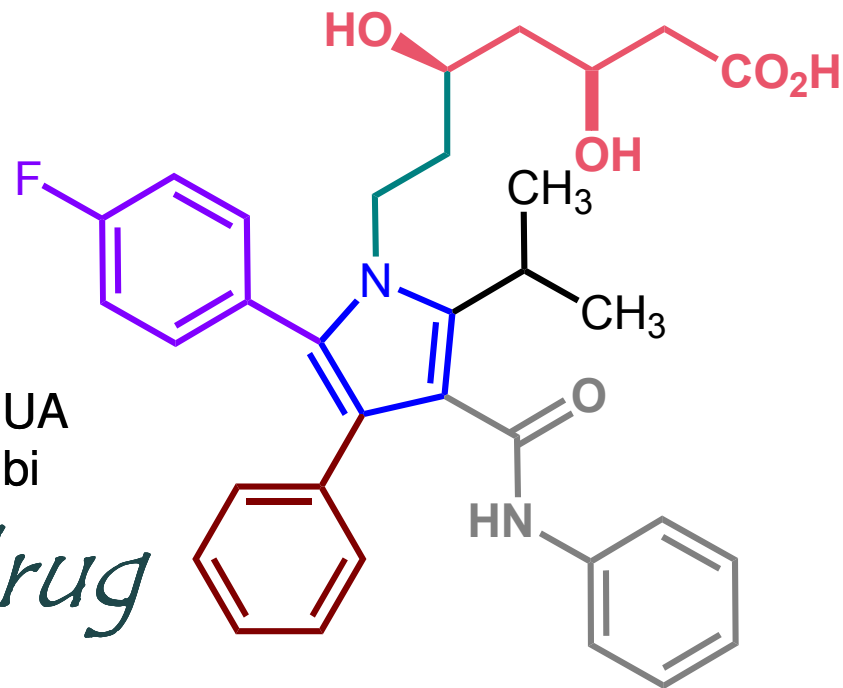
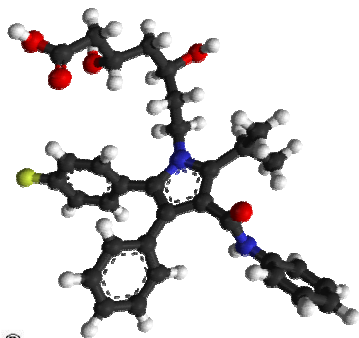
12 etapas = 4,2%

venceu em 30 de novembro de 2011, nos EUA

- Total em vendas mundiais de *ca.* US\$ 100 bi

super blockbuster-drug

- Nova síntese Prof. **Luiz Carlos Dias** & Dr **Adriano S Vieira**, IQ-UNICAMP, em 2010, pelo **INCT-INO FAR**



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

11 etapas = 19,3%

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)

PCT dezembro de 2011



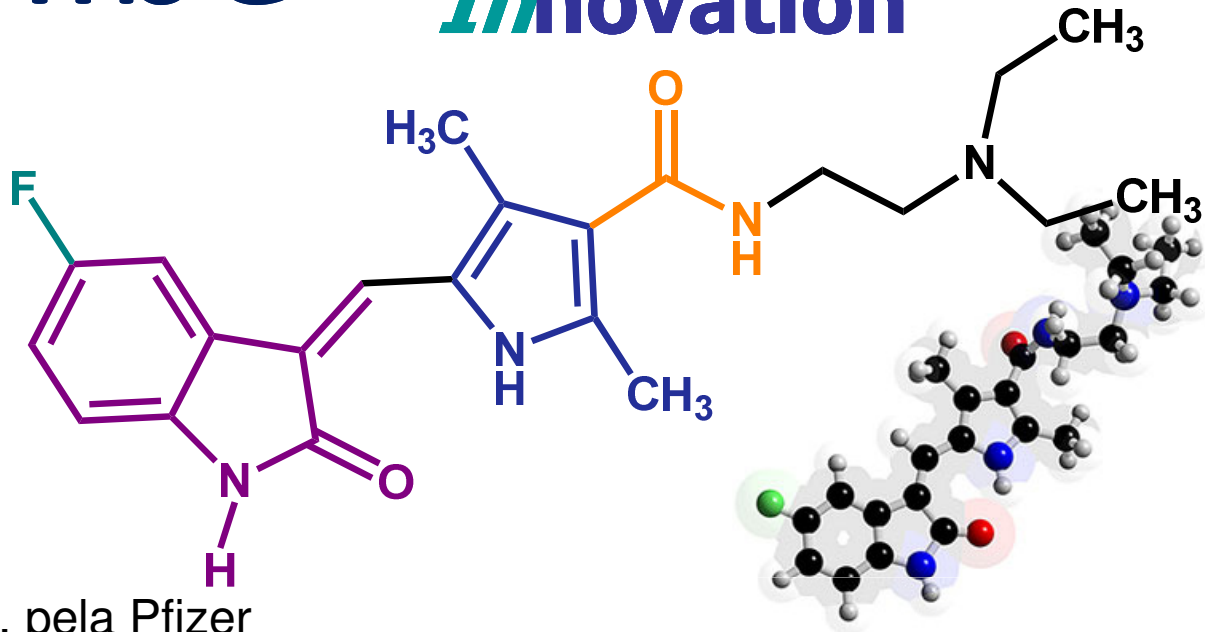
Sunitinibe

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**



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



Pinto & Dr Bárbara Vasconcellos da Silva, IQ-UFRJ, em 2011, pelo INCT-INOVAR

Vendas de tinibes no mercado norte-americano: US\$ 18,5 bi (2009)

Importações *ca.* US\$ 3 milhões/ano

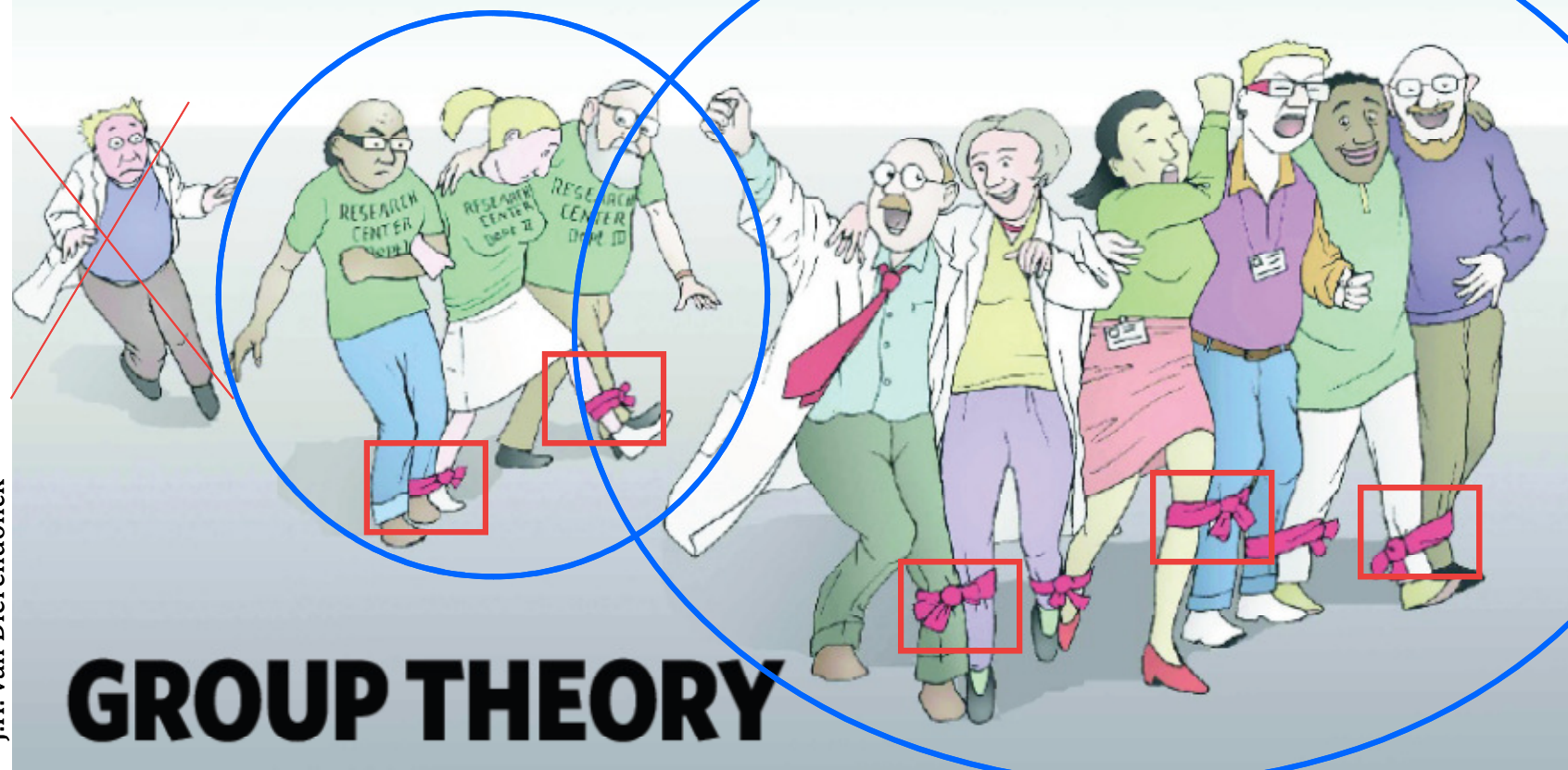
S Aggarwal, *Nature Rev Drug Discov* 2010, 9, 427

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

NEWS FEATURE

NATURE|Vol 455|9 October 2008

O que faz o sucesso de uma equipe ?



J.H. van Dierendonck

GROUP THEORY

What makes a successful team? **John Whitfield** looks at research that uses massive online databases and network analysis to come up with some rules of thumb for productive collaborations.



A equipe do INCT-INO FAR



reunião de avaliação e acompanhamento
Rio de Janeiro, 16 & 17 de novembro de 2011

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

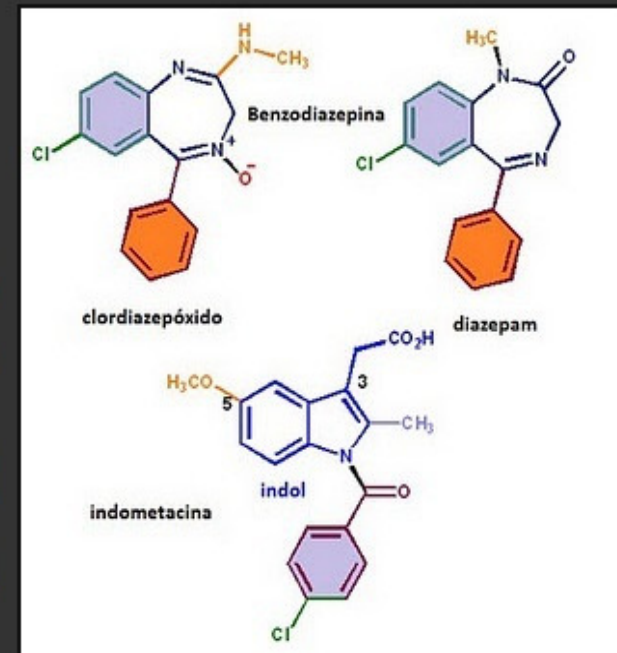
De fármacos e suas descobertas

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.

SÁBADO, 26 DE NOVEMBRO DE 2011

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

Nesta etapa da Linha do Tempo da Química Medicinal: assim nascem os fármacos atingimos a década de 50, a partir de quando surgiram inúmeras inovações terapêuticas significativas, resultado dos avanços importantes observados em várias disciplinas relacionadas à Química ou à Biologia.



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



Corcovado uma das sete novas maravilhas do mundo



Sugar Loaf



Rio-Niterói bridge

Boas Festas!



Copacabana Beach



Copacabana beach view from Sugar Loaf



Sunset at Arpoador Beach

Rio de Janeiro, BR



Maracanã stadium



Barra da Tijuca beach

Obrigado



SBQ

ANO INTERNACIONAL DA QUÍMICA