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New trends in anti-inflammatory drugs

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http://www.lassbio.icb.ufrj.br/

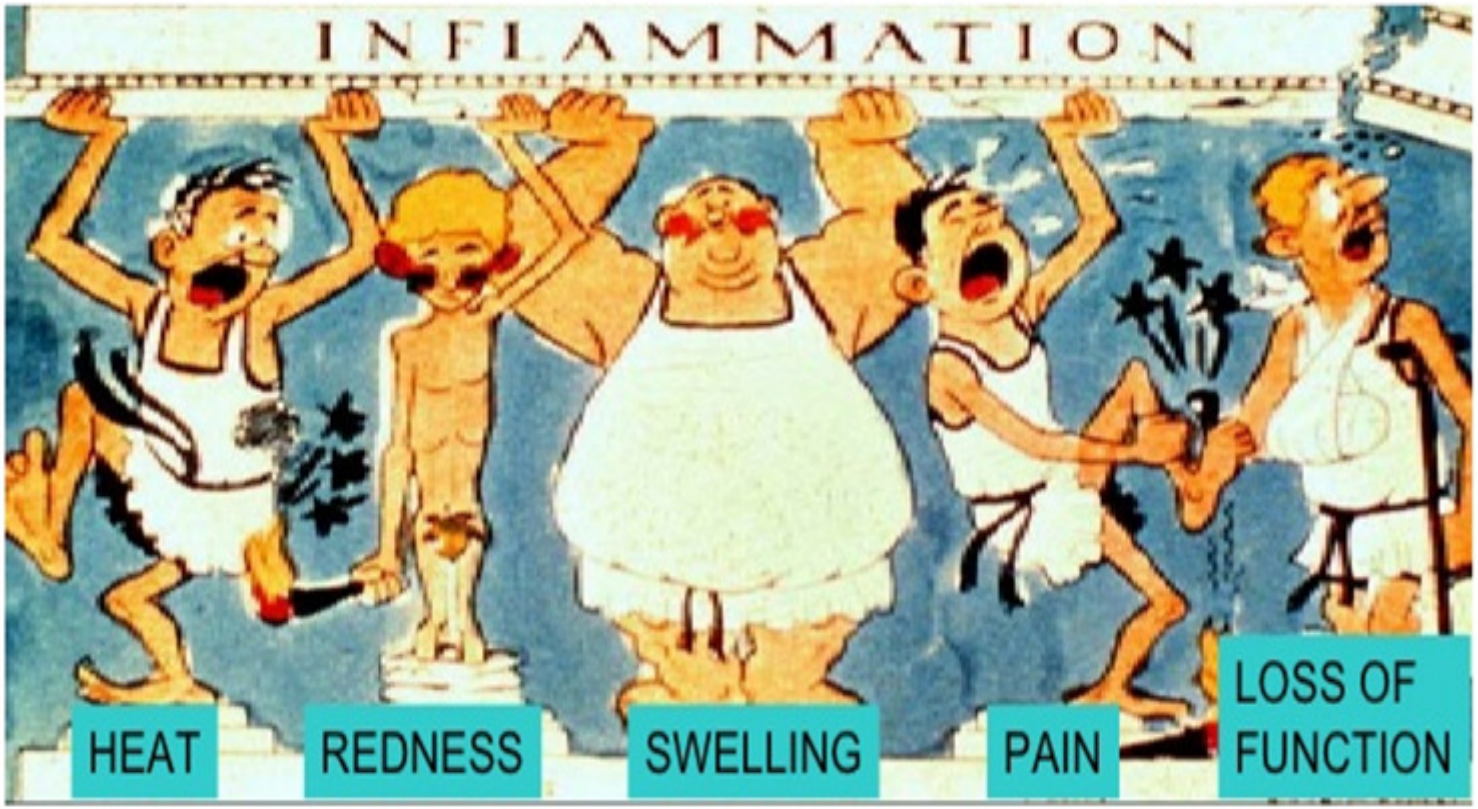
Institute of Biomedial Sciences

Talk Contents

- The inflammatory process: a brief view
- Small Molecules
  - The timeline of anti-inflammatory drugs (AID)
- Targets
  - From COX-1 to kinases
  - Phosphodiesterase-4 (PDE-4) inhibitors
  - Anti-TNFα biopharmaceuticals
- Multi-target drugs: *in-house* results, LASSBio-468, new dual DMARD candidate
- Concluding remarks

SIGNS AND SYMPTOMS OF INFLAMMATION

The inflammatory response can be either acute or chronic, but the local reactions signals are described as the cardinal signs & symptoms of inflammation.



Acute inflammation involves:

alteration of vascular caliber
(vasodilatation leads to increased blood flow)

changes of microvasculature
(increased permeability for plasma protein and cells)

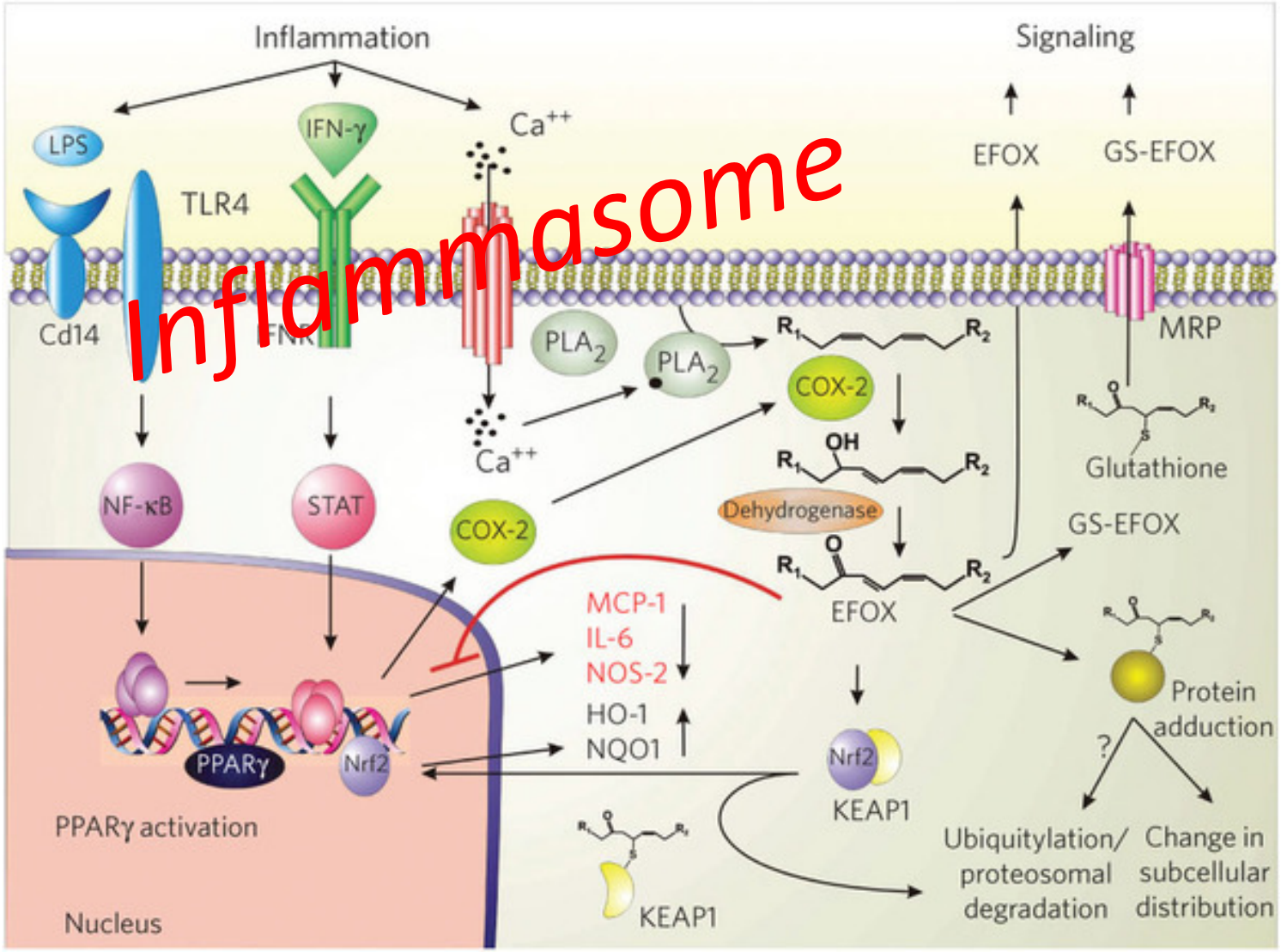
emigration of leukocytes from microcirculation
(leukocyte activation leads to elimination of offending agent)

It can be controlled by several AI drugs, including glicocorticoids and NSAI agents

The chronic inflammatory diseases

- Rheumatoid arthritis (RA)
- Inflammatory bowel disease
- Psoriasis
- Alzheimer disease (AND)
- Atherosclerosis
- Stroke / heart attack
- COPD / asthma
- Septic shock
- Cancer

The mediators of the inflammatory process



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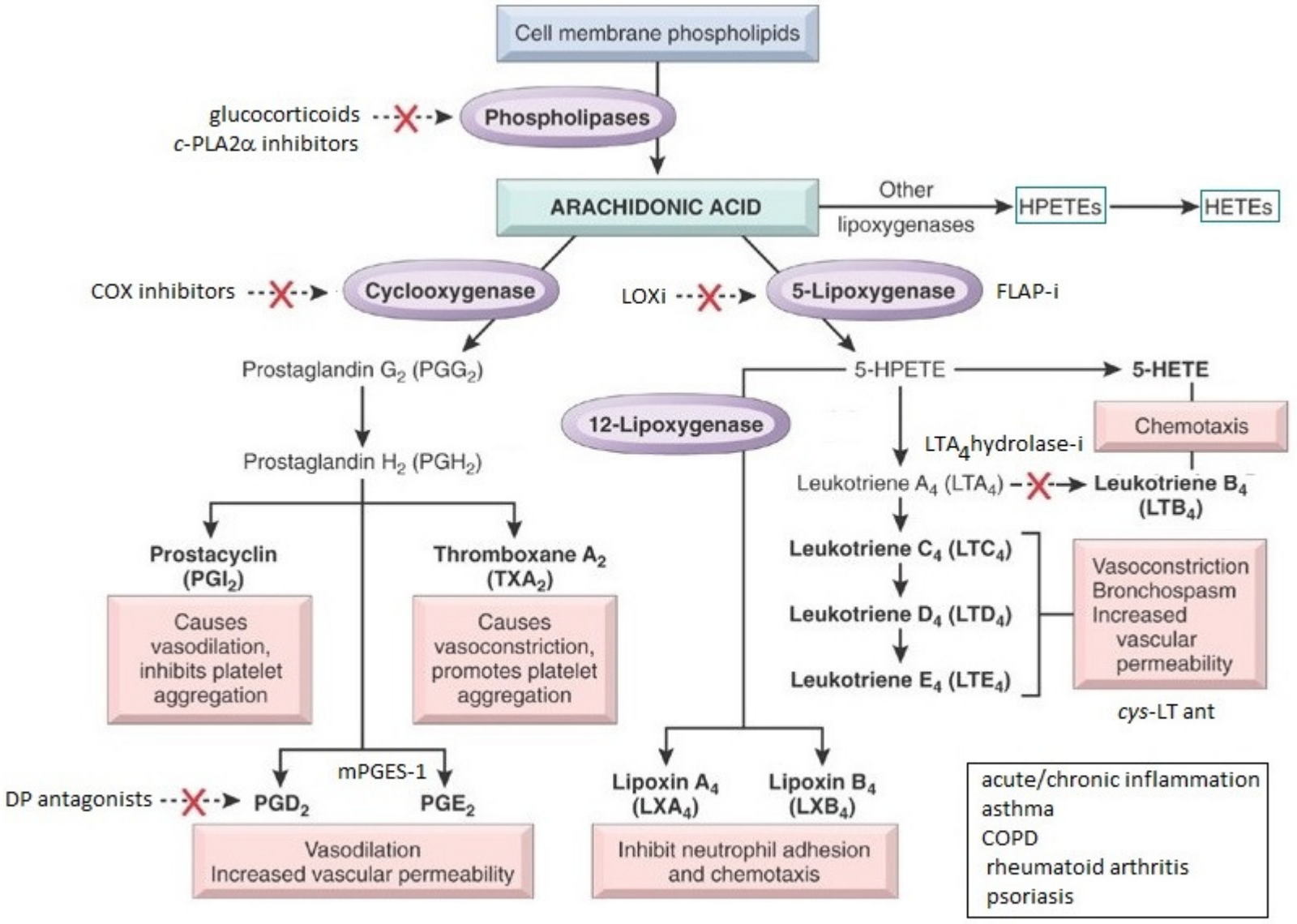
The inflammatory response is multifactorial!

The arachidonic acid cascade & inflammation



Adapted from Robbins & Cotran´s Pathological Basis of Disease, 8th Ed., Kumar et al (eds), Elsevier, Philadelphia (2010)

The enzymatic inhibition promotes the accumulation of the substrate !

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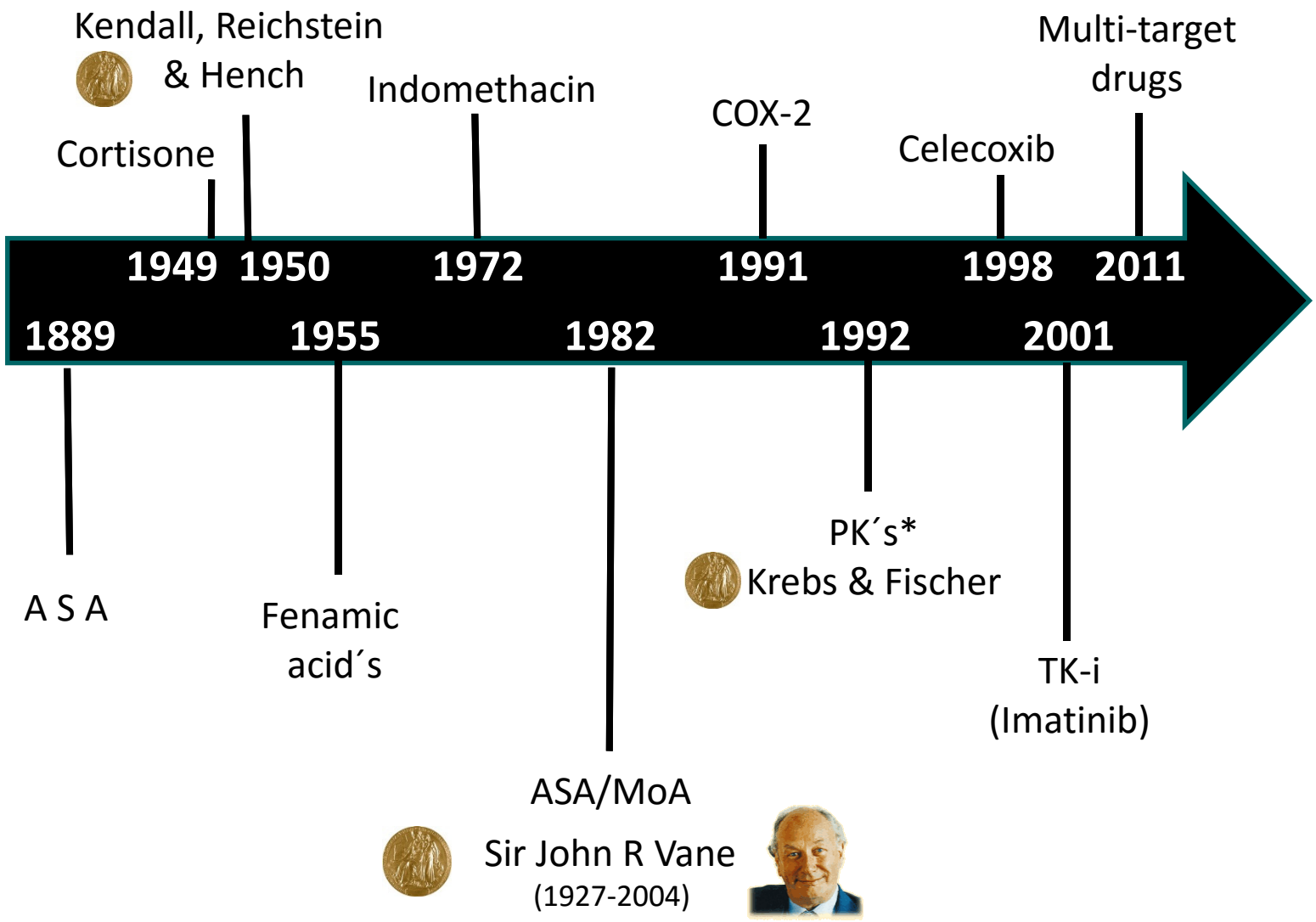
Small Molecules

medicinal chemistry

The timeline of AID´s

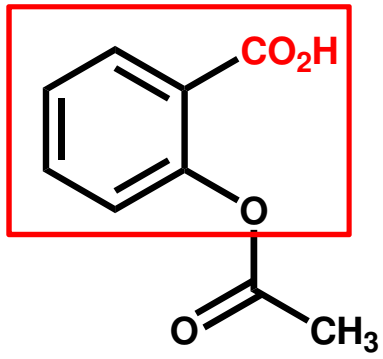


* P Cohen, DR Alessi, Kinase drug discovery--what's next in the field?, *ACS Chem Biol.* **2013**, *8*, 96

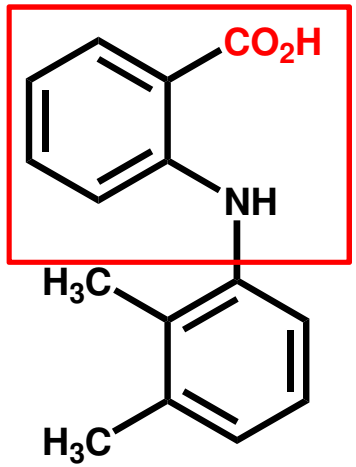
The beginning...

Parke Davis Co. 1960 → 1964

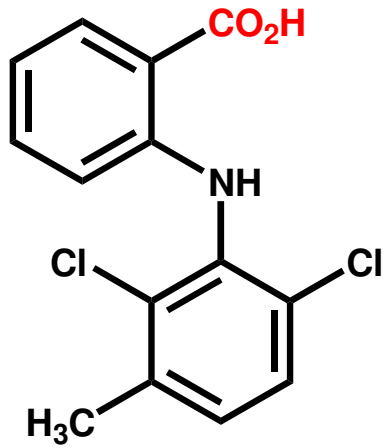
Claude Winder



ASA

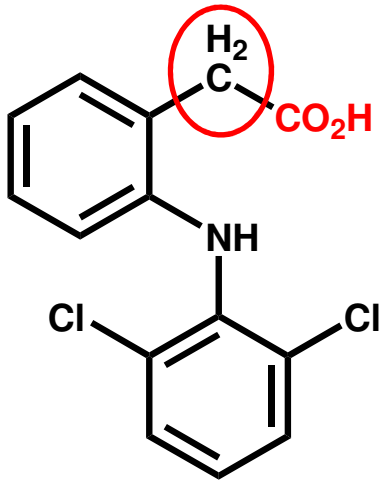


Mefenamic acid



Meclofenamic acid

Ciba-Geigy
(Novartis)



Diclofenac

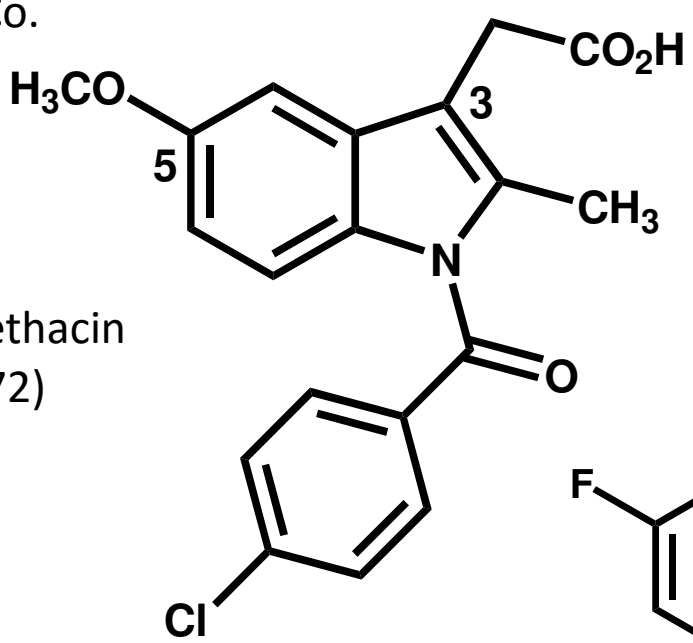
1973

Phenyl acetic class

C-linear homologue

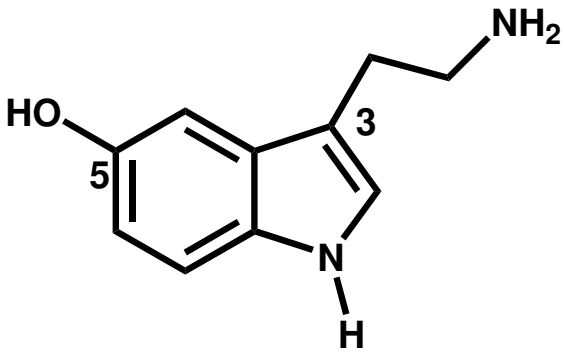
From COX-1 to kinases

Merck Co.

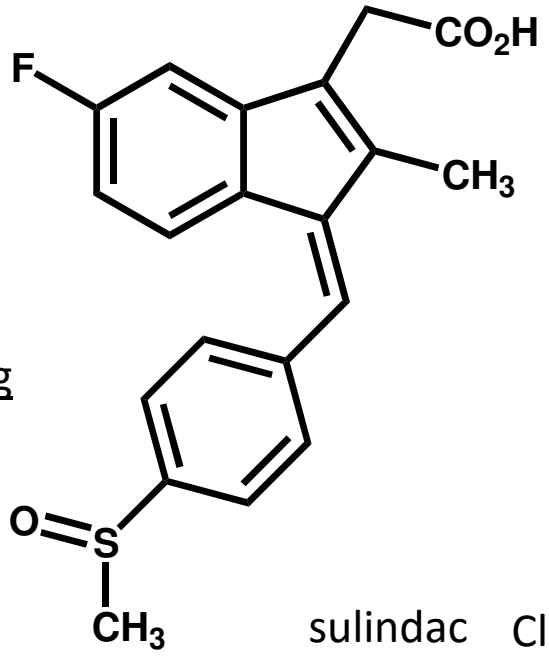


indomethacin
(1972)

T Y Shen
(1924)



serotonin



sulindac Clinoril®

<u>non-steroidal anti-inflammatory drug</u>

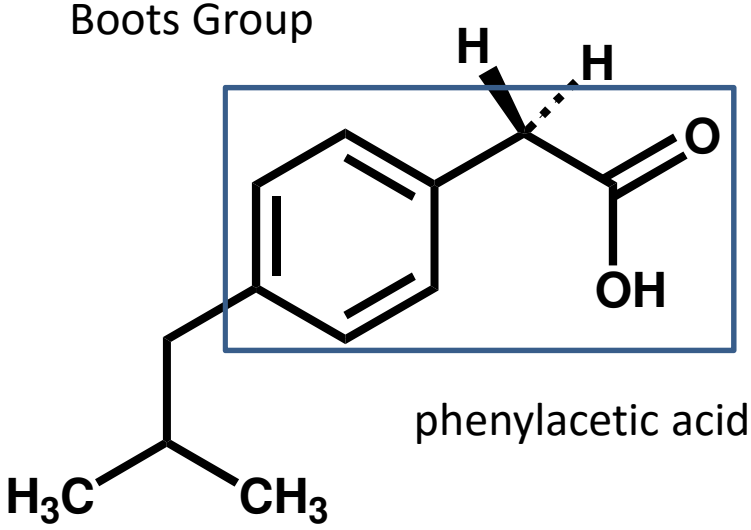
Sulindac is a prodrug

(1980)

K P Townsend, D Praticò, Novel therapeutic opportunities for Alzheimer's disease: focus on nonsteroidal anti-inflammatory drugs, *The FASEB Journal*, **2005**, *19*, 1592

From COX-1 to kinases

Boots Group



phenylacetic acid

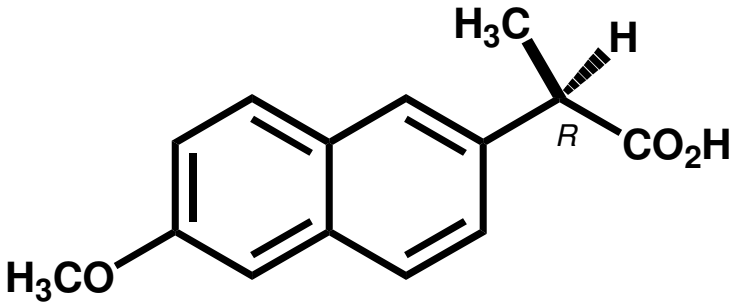
Ibufenac

Syntex
(Ian T Harrison)

Stewart Adams

Ibuprofen *

Six times more active
than ibufenac



Naproxen (1976)

Over **t**he **c**ounter (OTC) drug

α-Aryl propionic acid
Profen´s class
C_1-branched homologue

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* S S Adams, R Cob, *Prog. Med. Chem.* **1967**, *5*, 59.

EJ Barreiro, AE Kummerle, CAM Fraga, The methylation effect in medicinal chemistry, *Chem. Rev.* **2011**, *111*, 5215.

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All these initial AI drugs

have been discovered

under poor understanding of the

underlying inflammatory mechanisms!

medicinal chemistry

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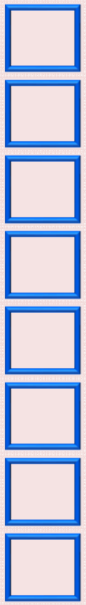
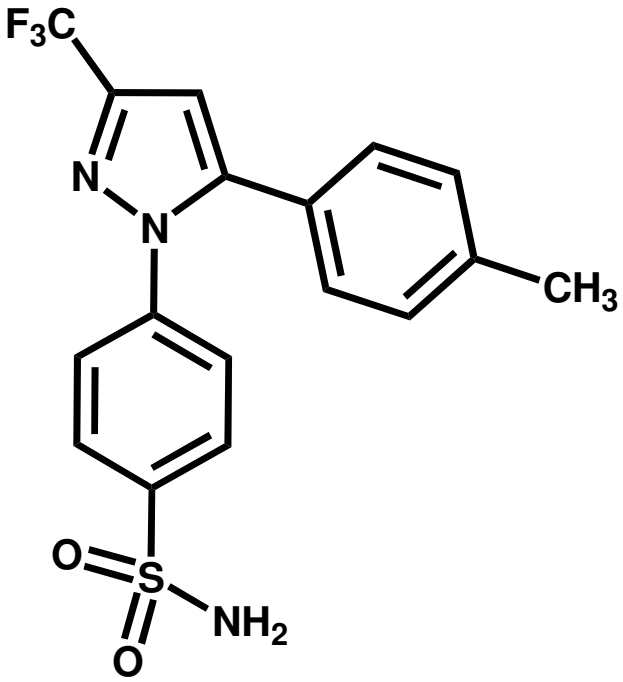


T a r g e t s

From COX-1 to kinases

Pfizer (Searle Co., 1993)

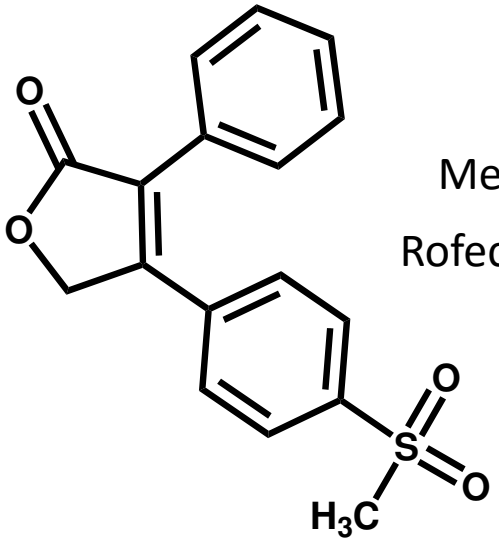


Celecoxib (1998)

The first COX-2 selective nonsteroidal anti-inflammatory drug

COX-2

Discovered in 1991 by
Daniel L. Simmons
Brigham Young University



Merck Co.

Rofecoxib (1999)

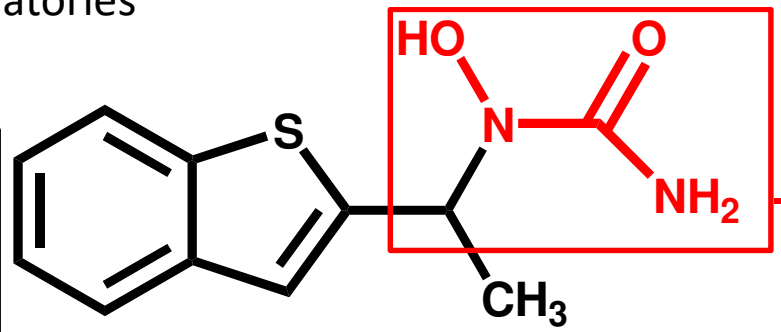
2004 - withdrawn for safety concerns
(use increase the risk of heart attack & stroke)

From COX-1 to kinases

Abbott Laboratories

1996

SRS-A — LTB_4, LTC_4, LTD_4, LTE_4



Zileuton (Zyflo^R)

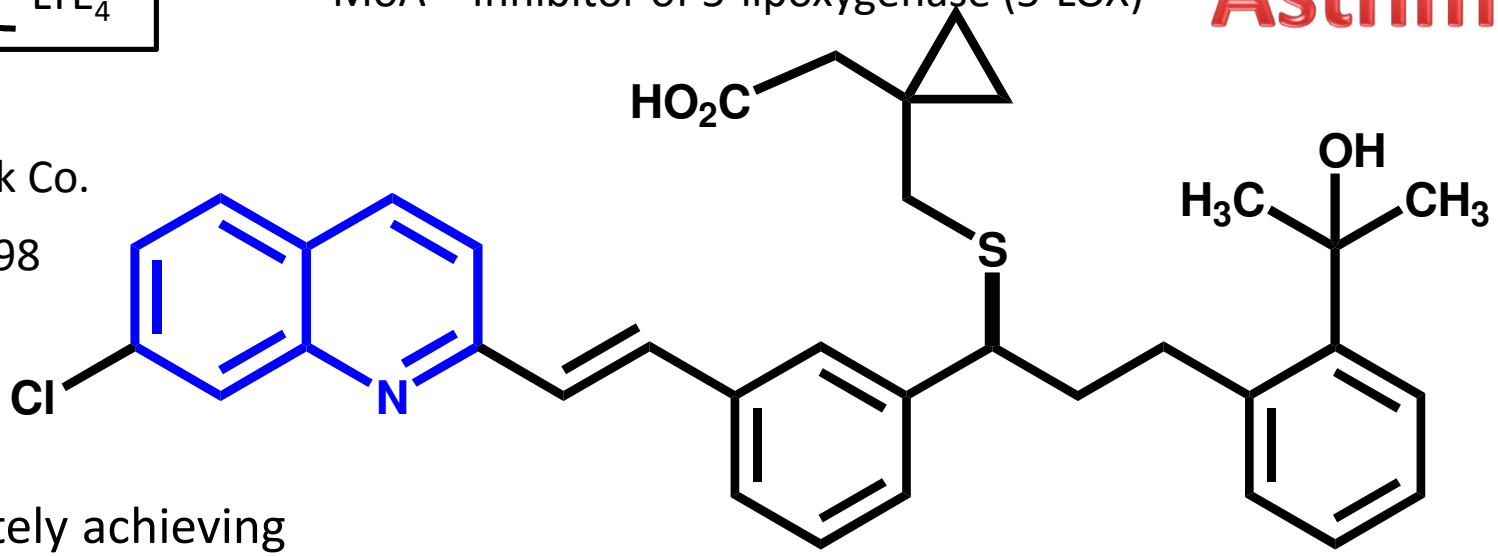
Hydroxamic acid scaffold

MoA = Inhibitor of 5-lipoxygenase (5-LOX)

Asthma

Merck Co.

1998

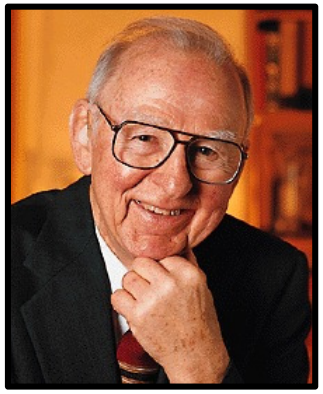


Ultimately achieving blockbuster status

*Monte*lukast (Singulair^R)

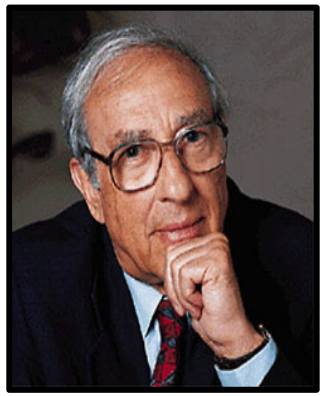
MoA = *cys*-leukotriene receptor antagonist (LTRant)

From COX-1 to kinases



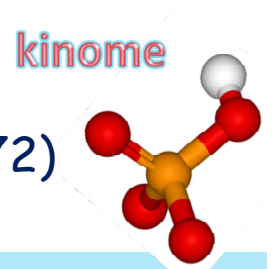
Edwin G. Krebs (72)
(1918 –2009)

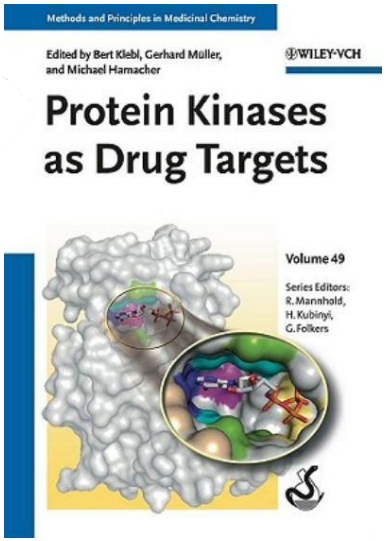
1992

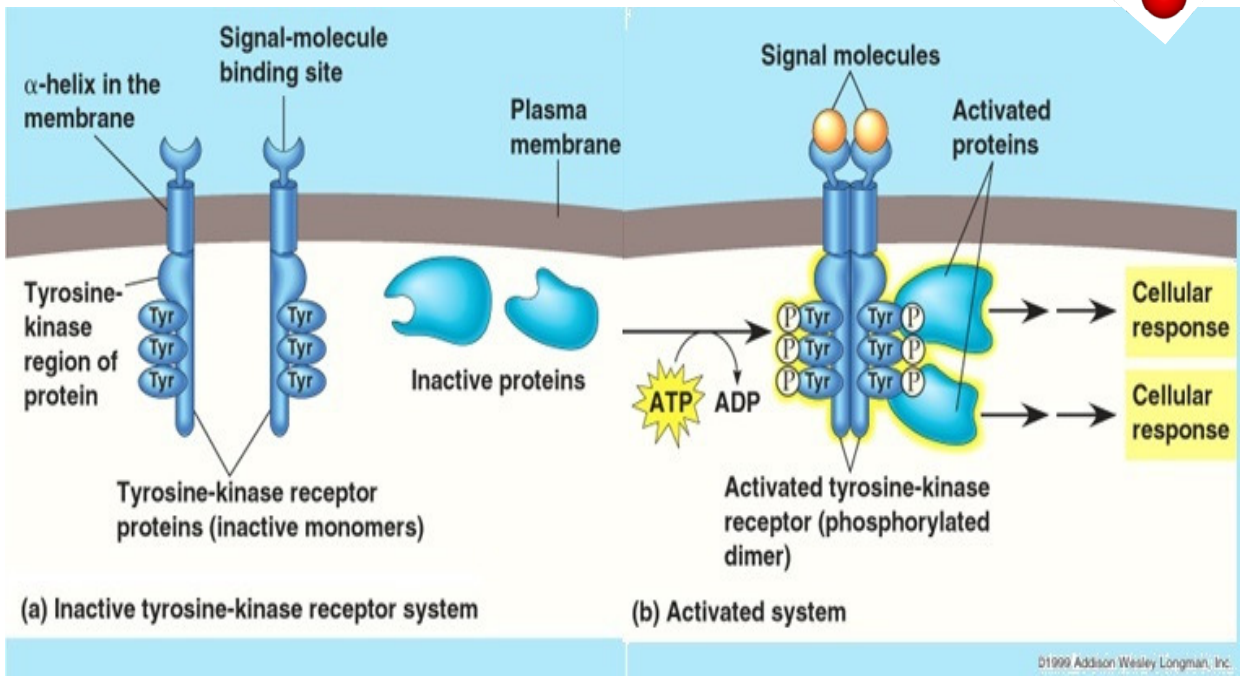


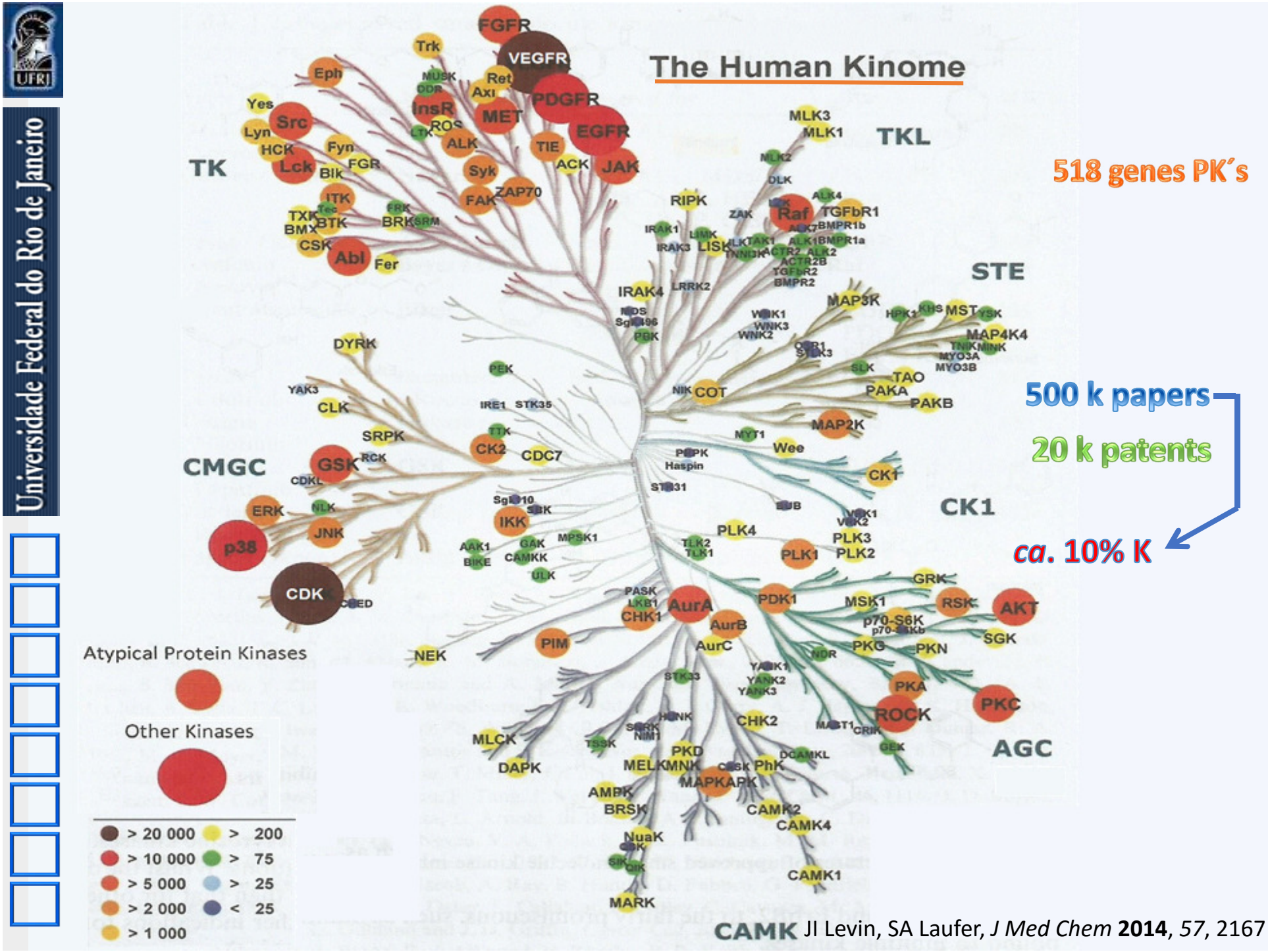
Edmond H. Fischer (72)
(1920)

"… for describing how reversible phosphorylation works as a switch to activate proteins and regulate various cellular processes."









CAMK JI Levin, SA Laufer, *J Med Chem* **2014**, *57*, 2167

Kinase inhibitors as anti-inflammatory drugs

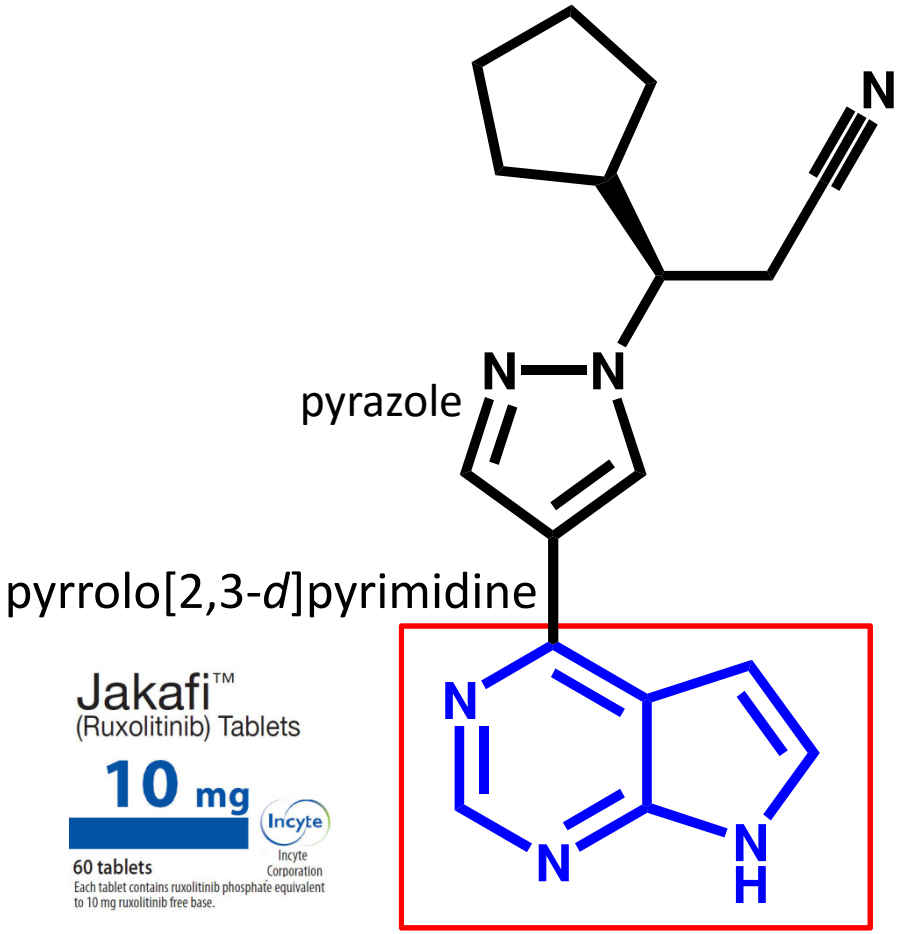
Agent	Targets for therapeutic activity	Indication/Phase
Tofacitinib	JAK3/JAK1/JAK2	RA/Phase III Psoriasis/Phase II
Ruxolitinib	JAK1/JAK2	Psoriasis/Phase II
VX-509	JAK3	RA/Phase II
R-348	JAK3	RA/Phase I
INCB-028050	JAK1/JAK2	RA/Phase II
Lestaurtinib	FLT3/TrkA/JAK2	AML/Phase III
AC-430	JAK2	Psoriasis/Phase II RA/Phase I

Adapted from A Kontzias, A Lawrence, M Gradina, J J O´Shea, Kinase inhibitors in the treatment of immune-mediated disease, *Med Rep.* **2012**, *4*, 5.

From COX-1 to kinases

Incyte Pharmaceuticals and Novartis

FDA Approval 2011



Ruxolitinib

$C_{17}H_{18}N_6$

John J O´Shea
Immunologist from NIH, described the significance of JAK3 inhibition as AI target

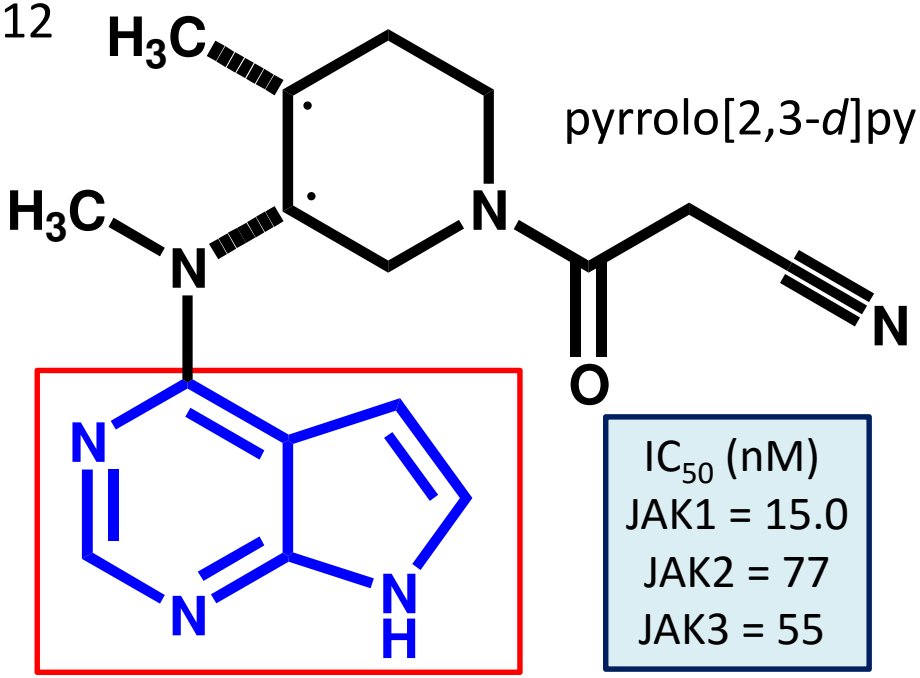
JAK1/JAK2-selective inhibitor

IC_{50} (nM)
JAK1 = 6.4
JAK2 = 8.8
JAK3 = 487

RA
Myelofibrosis (progressive)
& plaque psoriasis

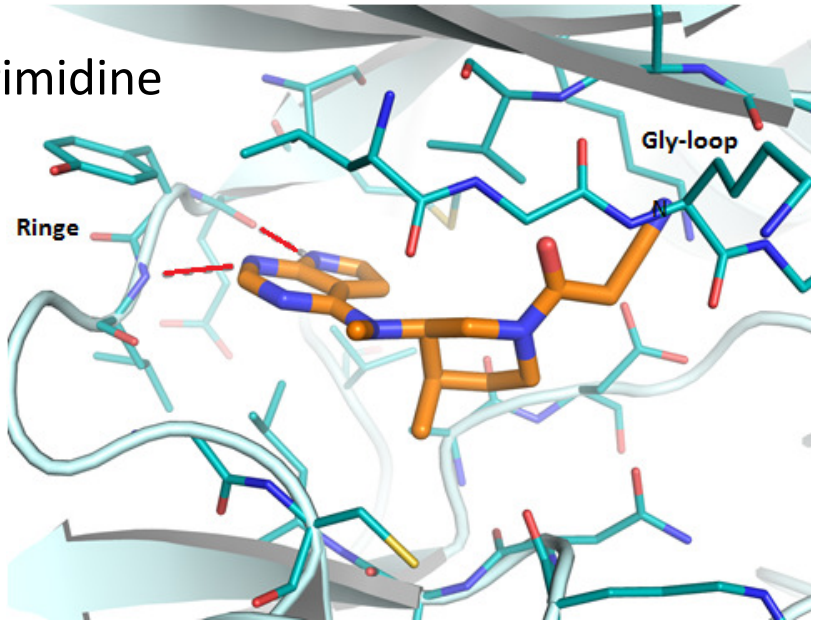
Pfizer
2012

From COX-1 to kinases



pyrrolo[2,3-*d*]pyrimidine

IC_{50} (nM)
JAK1 = 15.0
JAK2 = 77
JAK3 = 55



Crystal Structure of CP-690,550 in the JAK3 active site showing hinge binding

J J O´Shea et al, *J Med Chem* **2008**, *51*, 8012.

Xeljanz™ (tofacitinib tablets) 5 mg* 60 Tablets

Tofacitinib *
(CP-690,550)

JAK1/JAK3-selective inhibitor

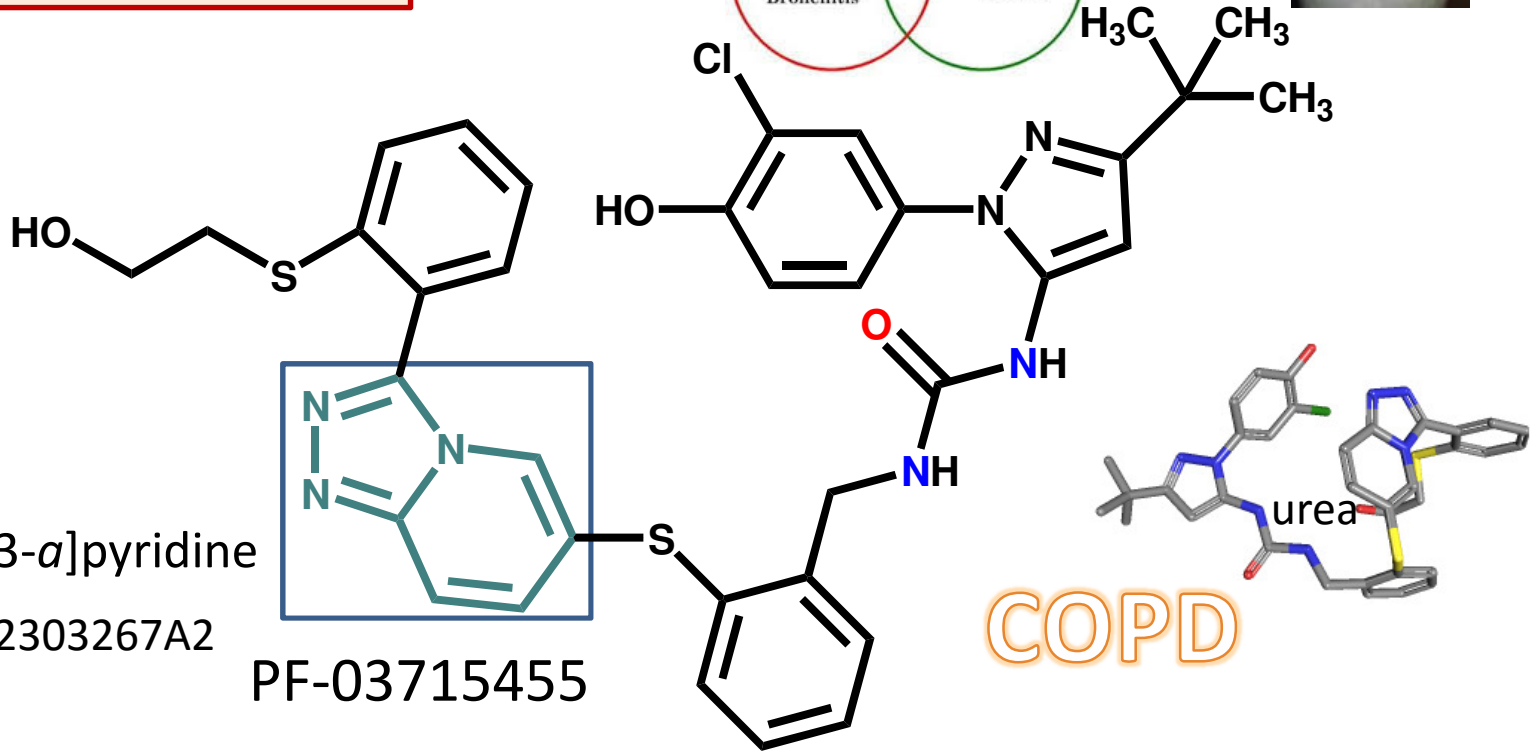
* approved by FDA, in 2012, for the treatment of RA and it is in clinical Phase II studies for the treatment chronic plaque psoriasis (prevention of organ transplant rejection)

M Skynner et al., Janus Kinases –Just another kinase or a paradigm shift for the treatment of autoimmune disease?, in Anti-inflammatory drug discovery, J I Levin, S A Laufer (eds), RSC Publishing 2012, pp. 211-254.

From COX-1 to kinases

Pfizer

European Respiratory Society
Annual Congress 2013



triazolo[4,3-*a*]pyridine

Patent EP2303267A2

PF-03715455

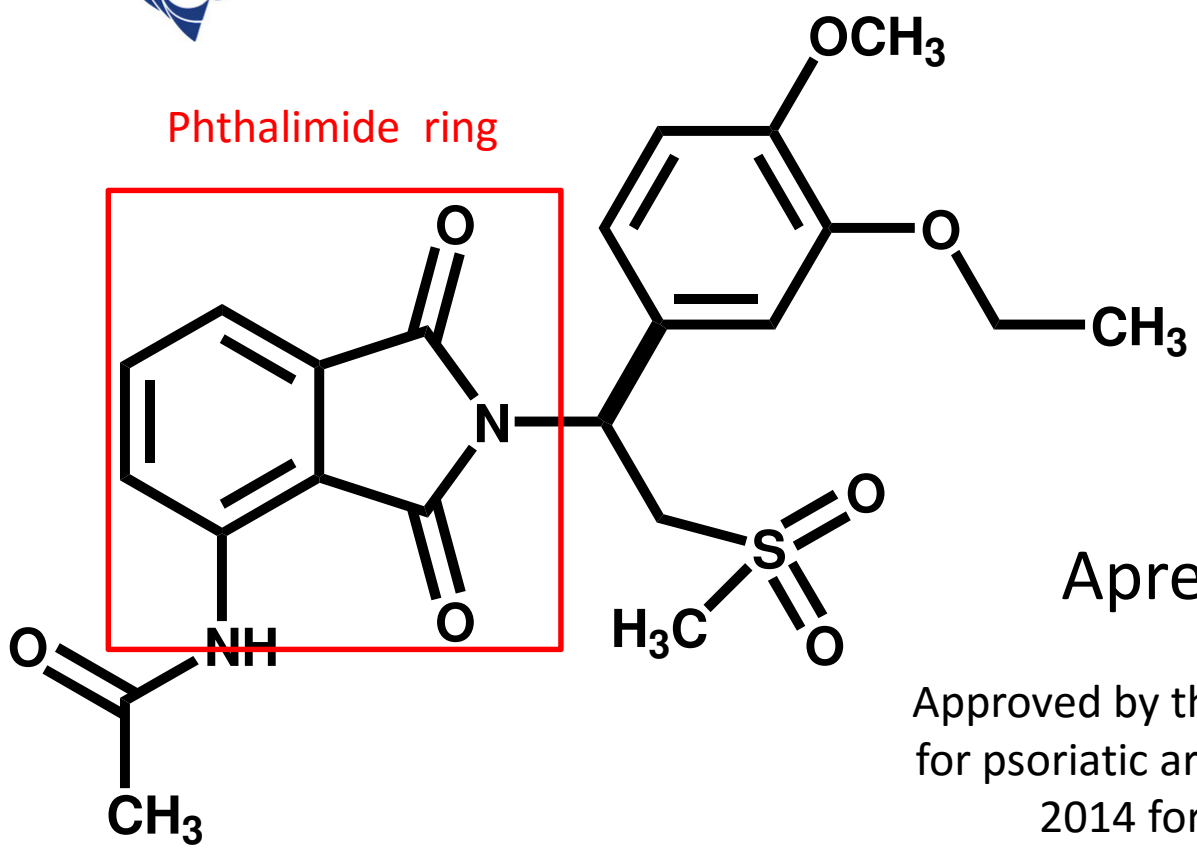
An <u>inhaled</u> **p38 mitogen-activated protein (MAP) kinases** Inhibitors for the treatment of moderate & severe chronic obstructive pulmonary disease (COPD)

In 2015, annual sales of kinases drugs are anticipated to US$20 billion

Phosphodiestarease-4 (PDE-4) inhibitor

Celgene 2014

Phthalimide ring



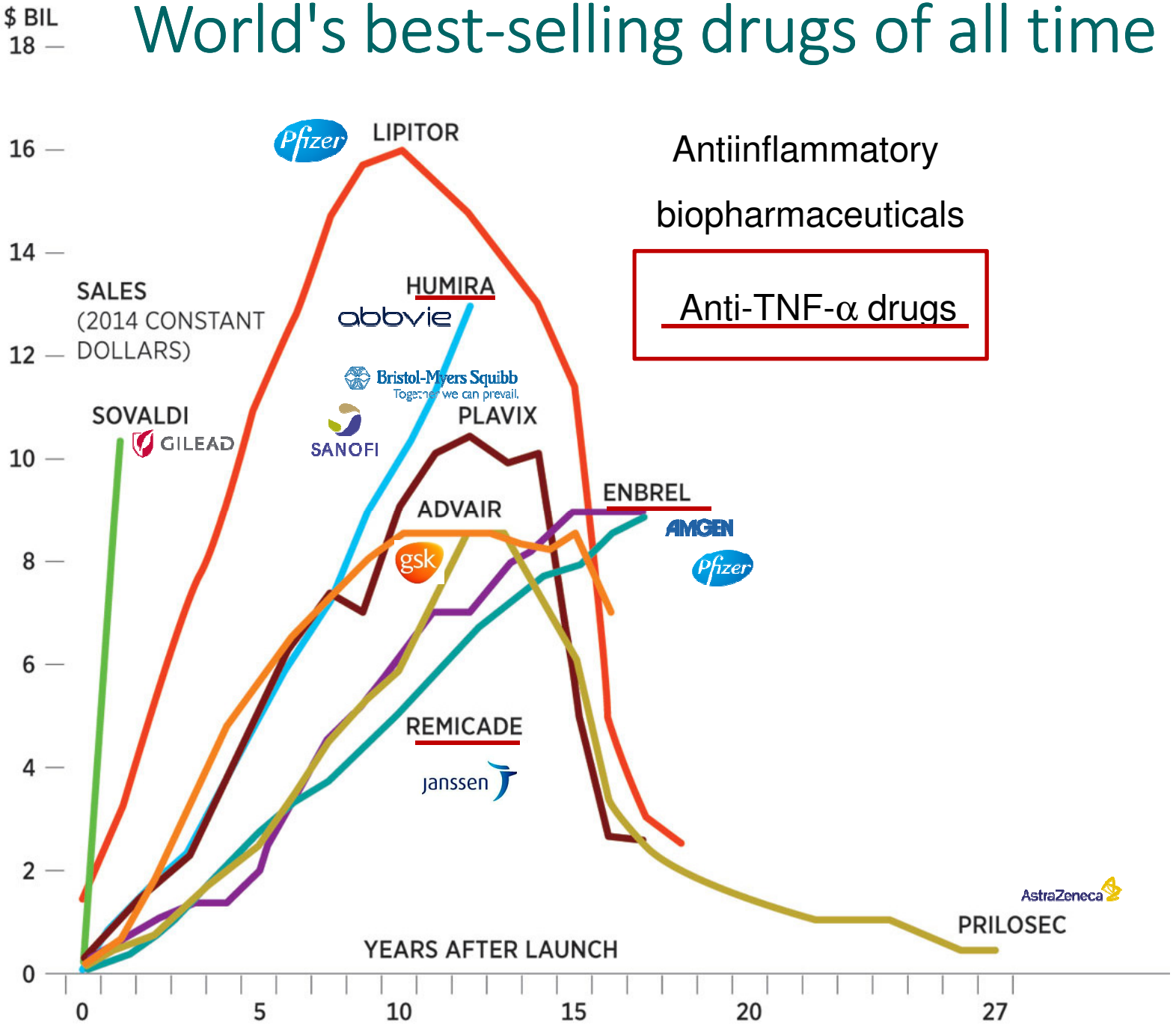
Apremilast

Approved by the FDA in March, **2014**, for psoriatic arthritis & in September, 2014 for plaque arthritis.

Roflumilast (2010;Daxas^{R}) is a second drug that acts as a selective inhibitor PDE-4 used for COPD control

P Berstein, AS Laufer, *Annu. Rept. Med. Chem*. **2015**, *50*, 0000

World's best-selling drugs of all time



Antiinflammatory biopharmaceuticals

Anti-TNF-α drugs

Anti-TNF-α Biopharmaceuticals

*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

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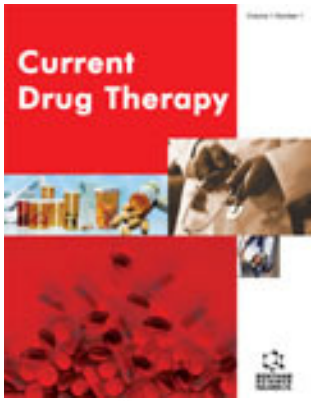
Could be effective a single target drug in the treatment of multifactorial diseases?

Current Drug Therapy, 2008, *3*, 000-000 1

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.



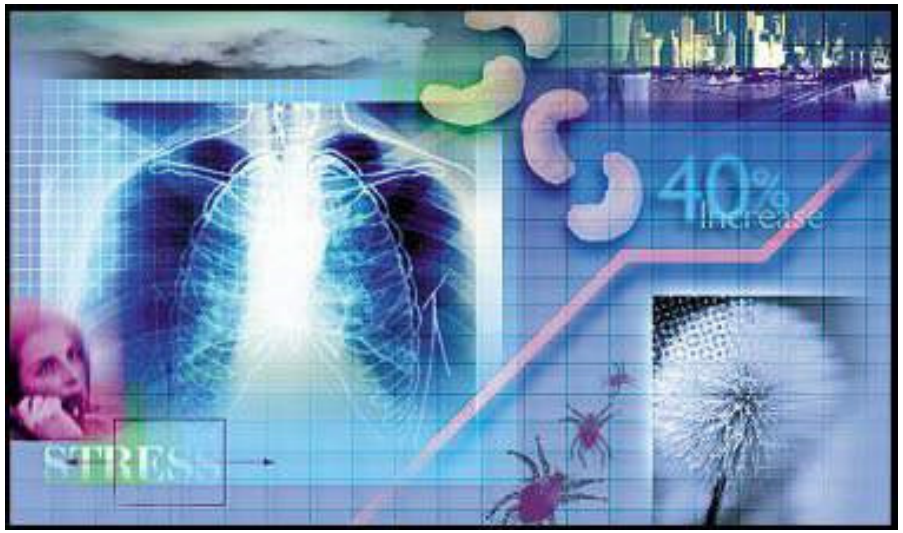
The treatment of multifactorial diseases (*e.g.* inflammatory chronic diseases), with drugs designed for a single therapeutic target, will always palliative!

These disorders require multi-target drugs as dual agents.

A simple drug don't work well in complex diseases

Multi-target drug: in-house results

LASSBio-468, new dual candidate



LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

medicinal chemistry

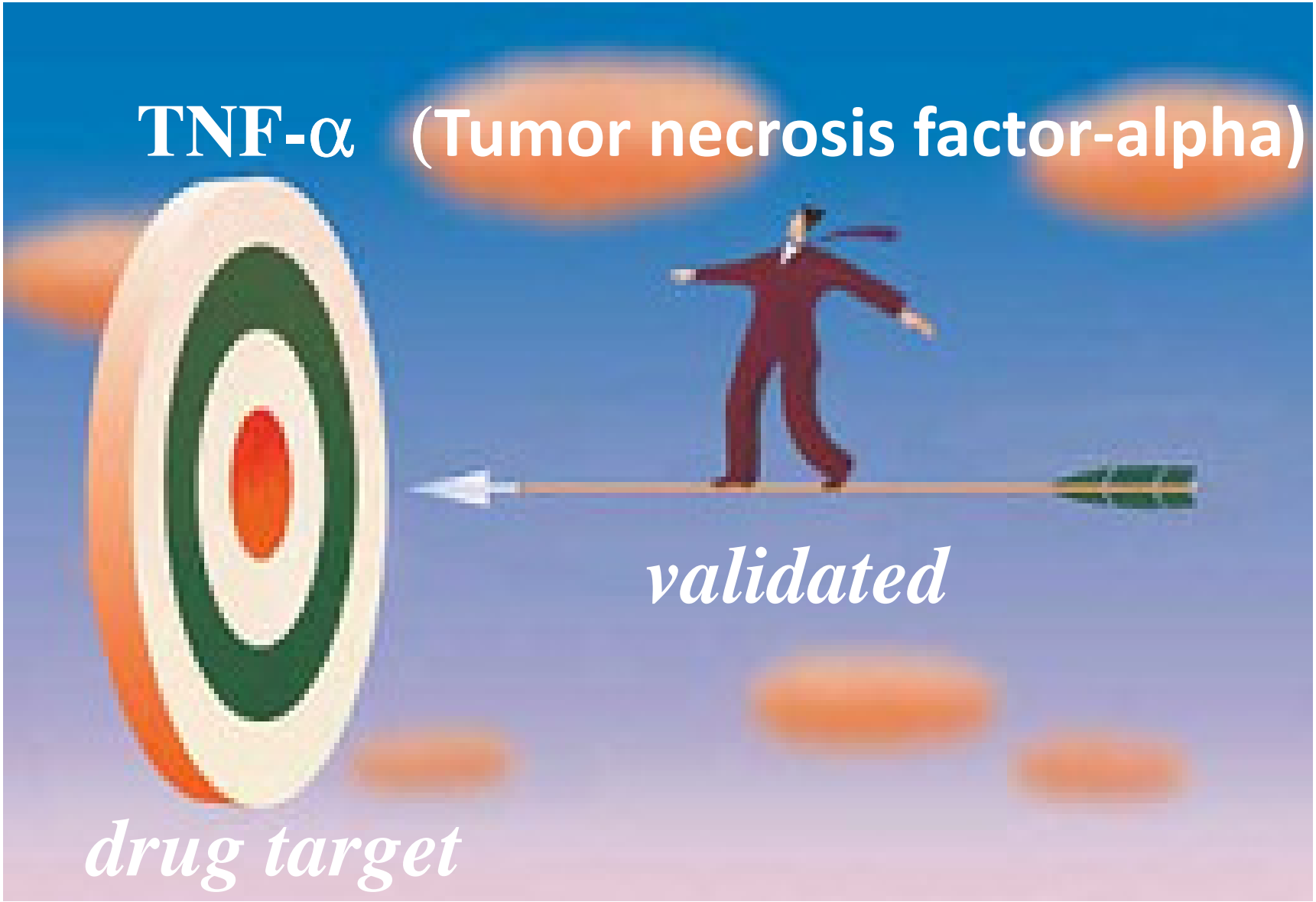
Inflammatory disease

New dual anti-inflammatory lead drug-candidate

Multifactorial disorder

- **Phosphodiesterase inhibitor (PDE-4i)**

& TNF-α modulator activity

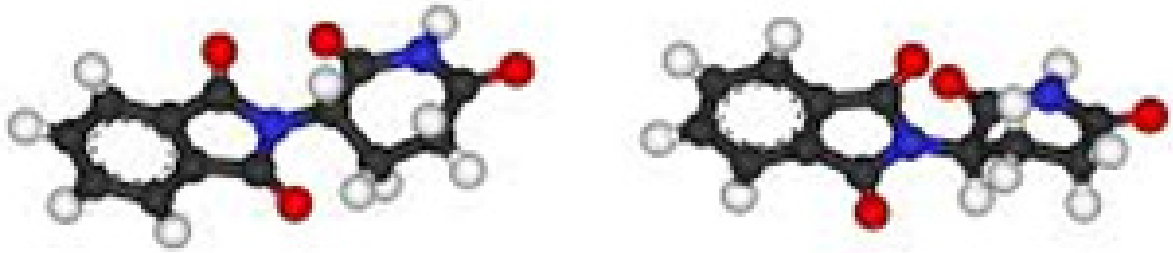


TNF-α is a pleiotropic cytokine with important pro-inflammatory functions

MLC Barbosa et al., Therapeutic approaches for tumor necrosis factor inhibition, *Braz. J. Pharm. Sci.* **2011**, *47*, 427.

The first pharmacophoric scaffold

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

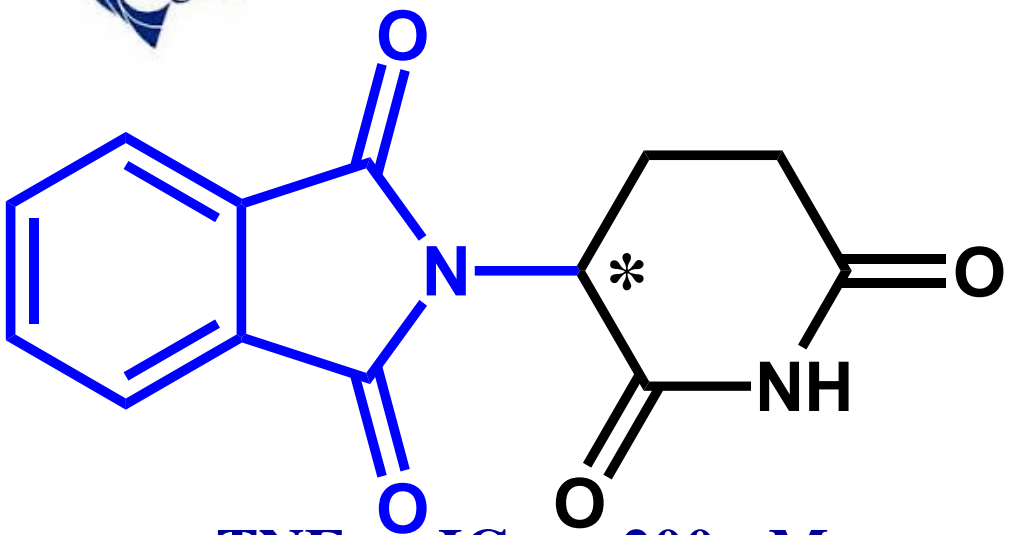


THALOMID (thalidomide) Capsules

Celgene

Thalidomide (THLD)

Oral TNF-α inhibitor



TNF-α IC_{50} = 200 μM

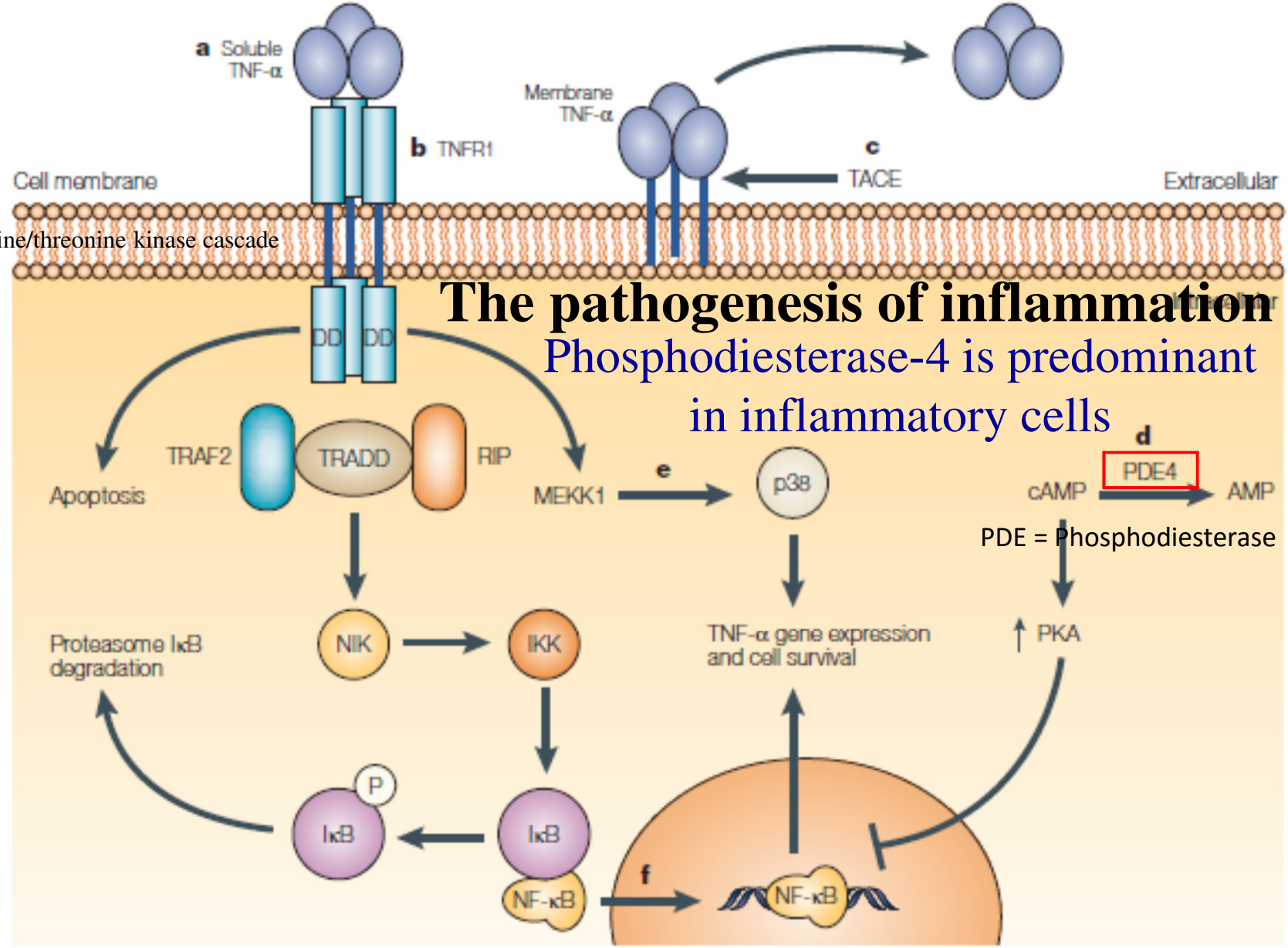
medicinal chemistry

Advantages of small molecule

- Convenient non-injectable
- Facilitate tissue penetration
- Possible once a day dosing
- Reduced immunosupression
- Easier synthesis lower costs

V Richmond et al., Small Molecules as Anti-TNF Drugs, *Curr Med Chem.* **2015**, *22*, 2920

The Second Target Election: PDE



From: MA Palladino et al., *Nat Rev.Drug Discov* **2003**, *2*, 736

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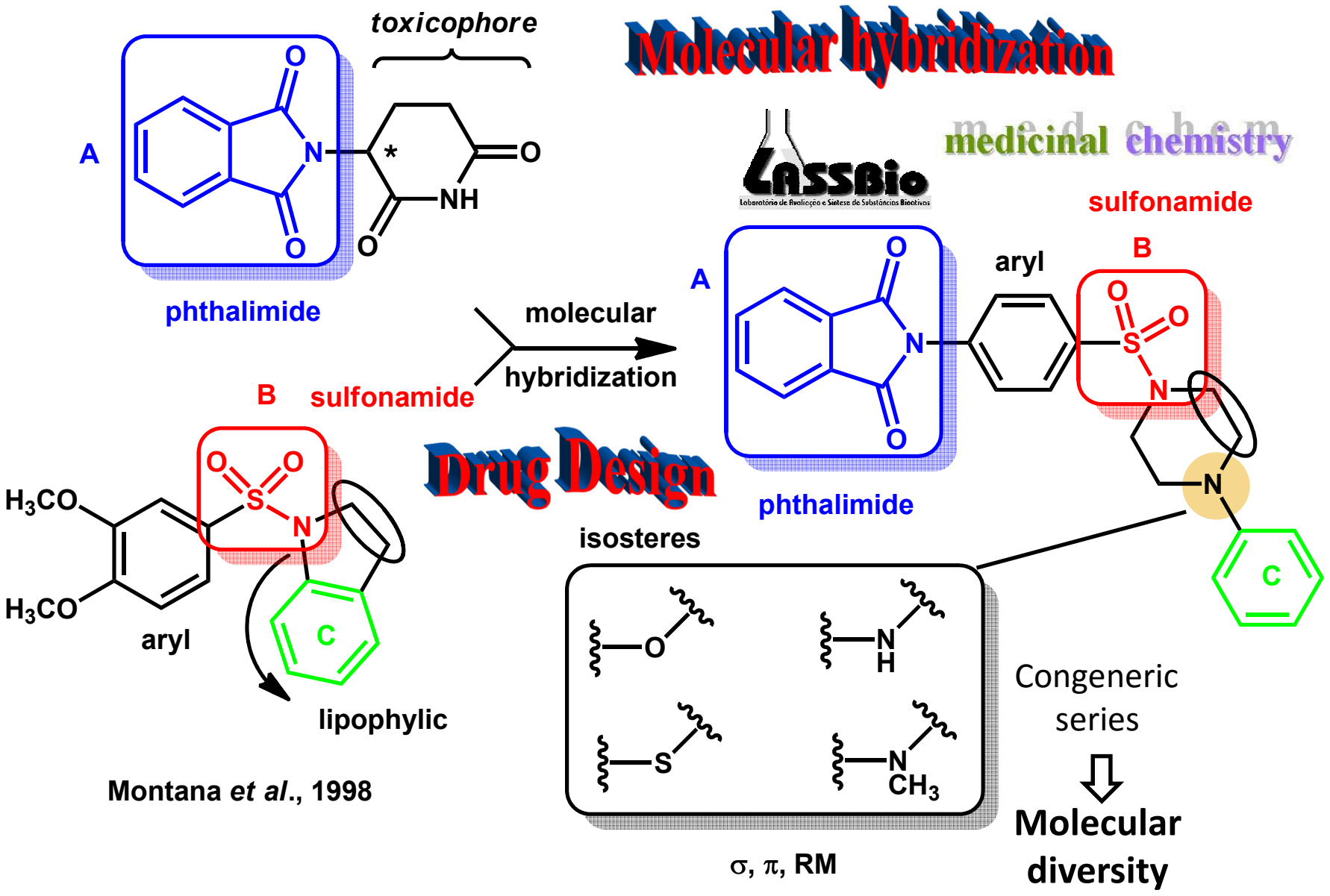
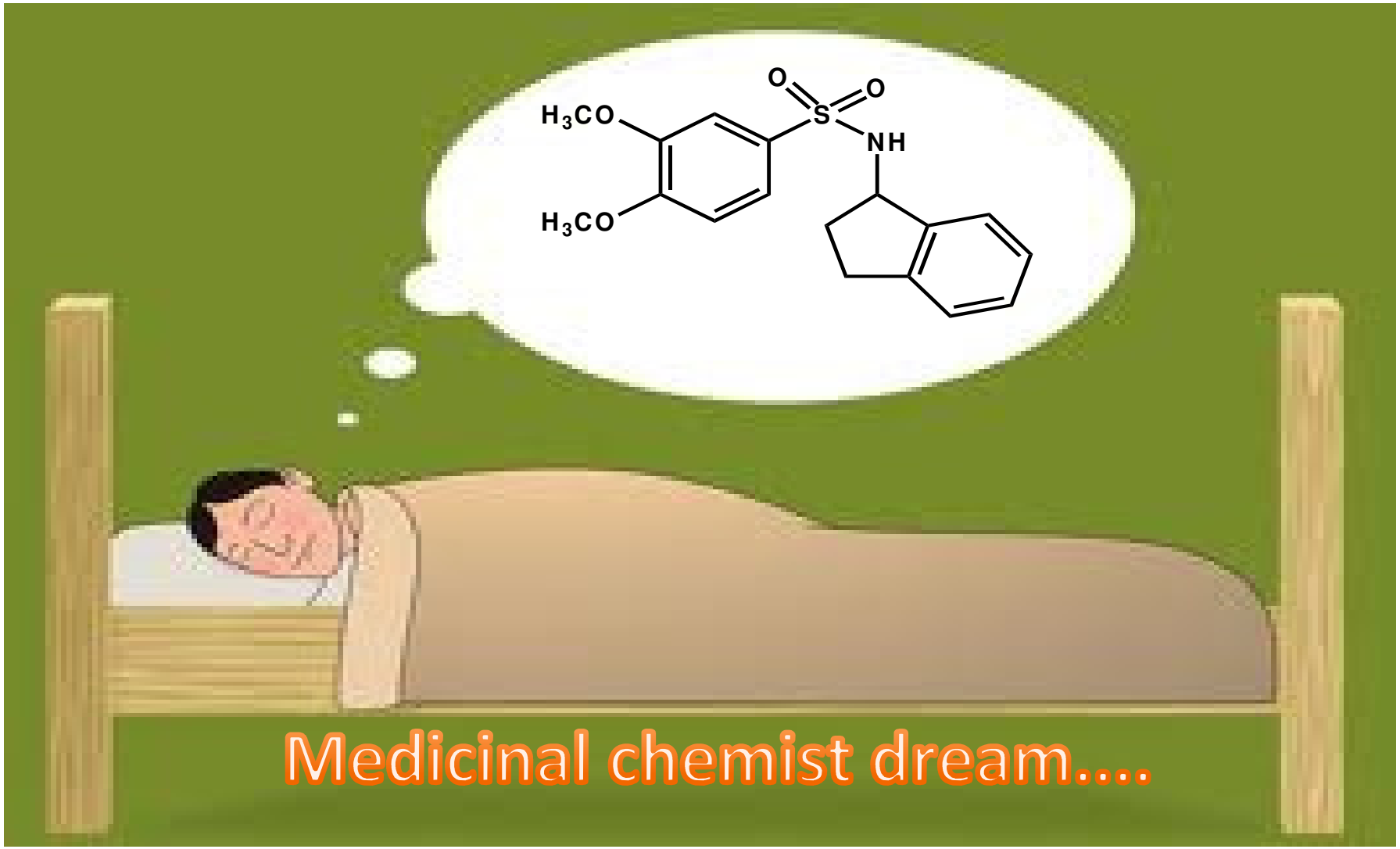
Chemical Intuition

medicinal chemistry

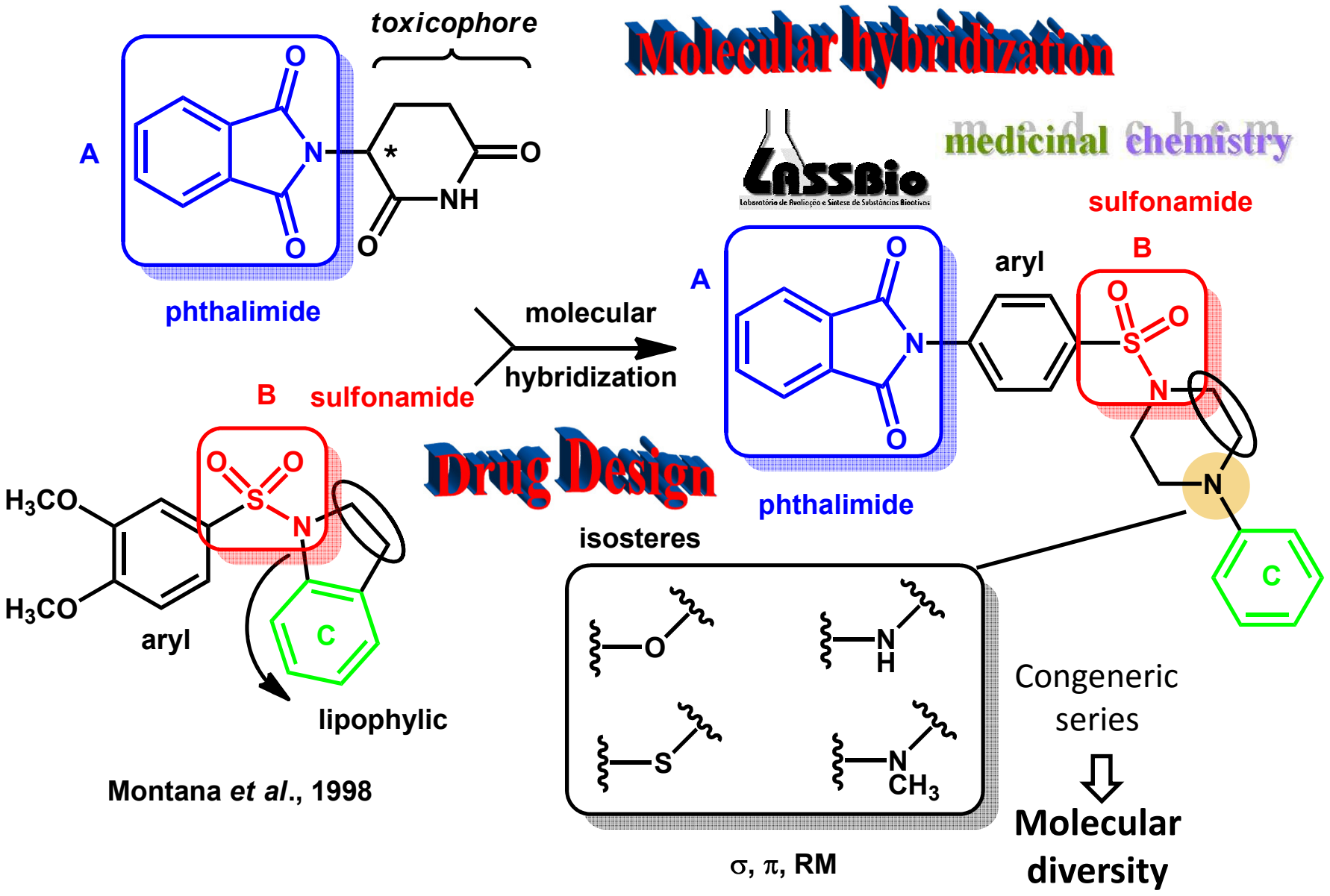
The molecular design of new dual agent: anti-TNFα & PDE-4i



C Viegas Jr, A Danuello, VS Bolsani, EJ Barreiro, CAM Fraga, **Molecular Hybridization**: A useful tool in the design of new drug prototypes, *Curr Med Chem* **2007**, *14*, 1829

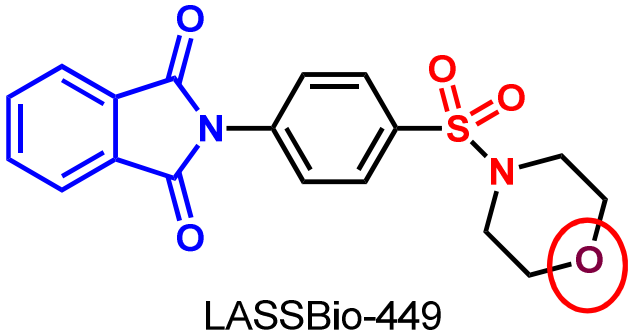

O
O
S
NH
H3CO
H3CO
Medicinal chemist dream....

The molecular design of new dual agent: anti-TNFα & PDE-4i

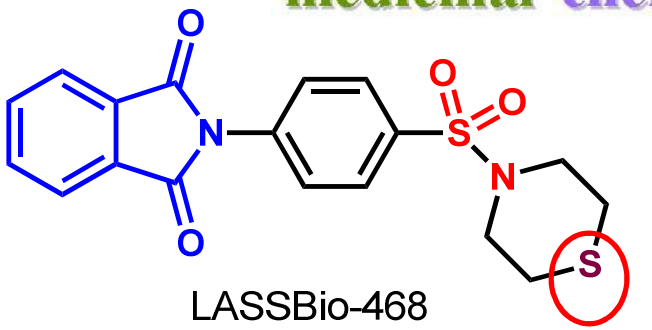


C Viegas Jr, A Danuello, VS Bolsani, EJ Barreiro, CAM Fraga, **Molecular Hybridization**: A useful tool in the design of new drug prototypes, *Curr Med Chem* **2007**, *14*, 1829

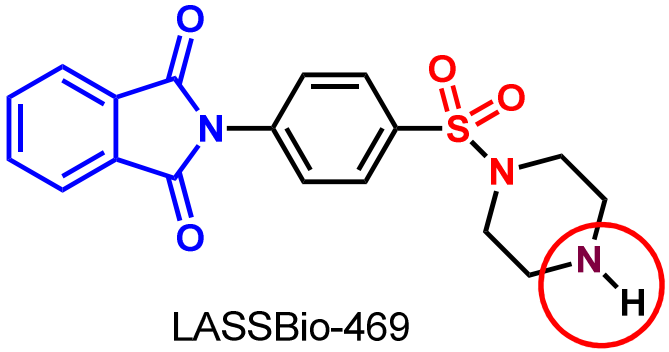
Congeneric series



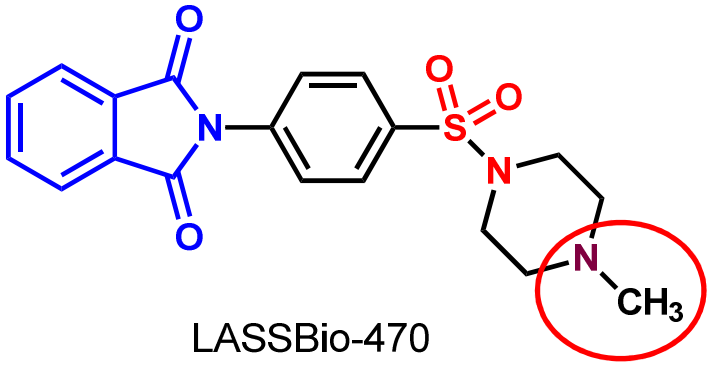
LASSBio-449



LASSBio-468

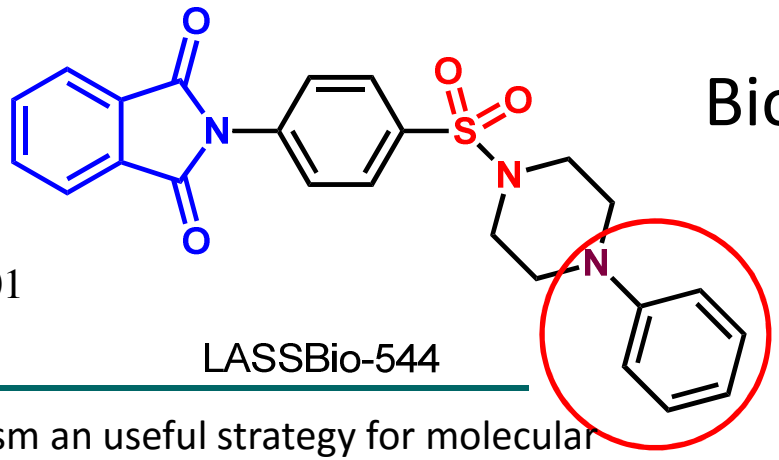


LASSBio-469



LASSBio-470

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



LASSBio-544

Bioisosterism

LM Lima, EJ Barreiro, Bioisosterism an useful strategy for molecular modification and drug design, *Curr.Med.Chem.***2005**, *12*, 23

Synthesis of congeneric series

Universidade Federal do Rio de Janeiro

phthalic anhydride
$C_8H_4O_3$

120°C
1 hr
2.0 M

$C_{14}H_9NO_2$

$ClSO_3H$
0°C to rt, then 60°C
1 hr
1.0 M

$C_{14}H_8ClNO_4S$

NEt_3
CH_2Cl_2
1 hr
0.4 M

LASSBio-544
69%

LASSBio-469
58%

LASSBio-449
65%

LASSBio-470
67%

LASSBio-468
72%

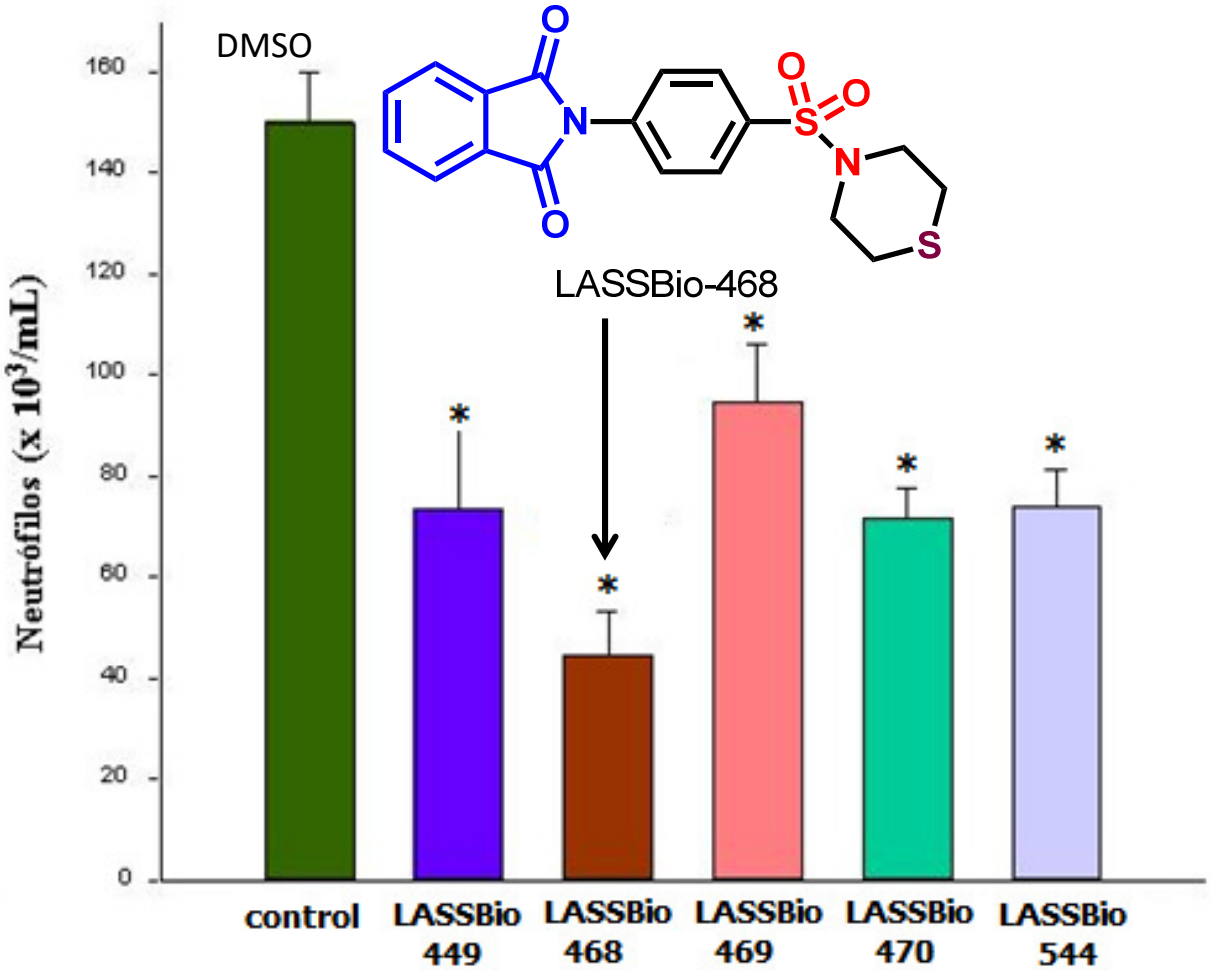
Overall yield: *ca.* 25%
(~ 0.5 M, 200 g)

$C_{18}H_{16}N_2O_4S_2$
M.W. = 388.45

Lidia M. Lima, PhD Thesis, IQ-UFRJ,2001

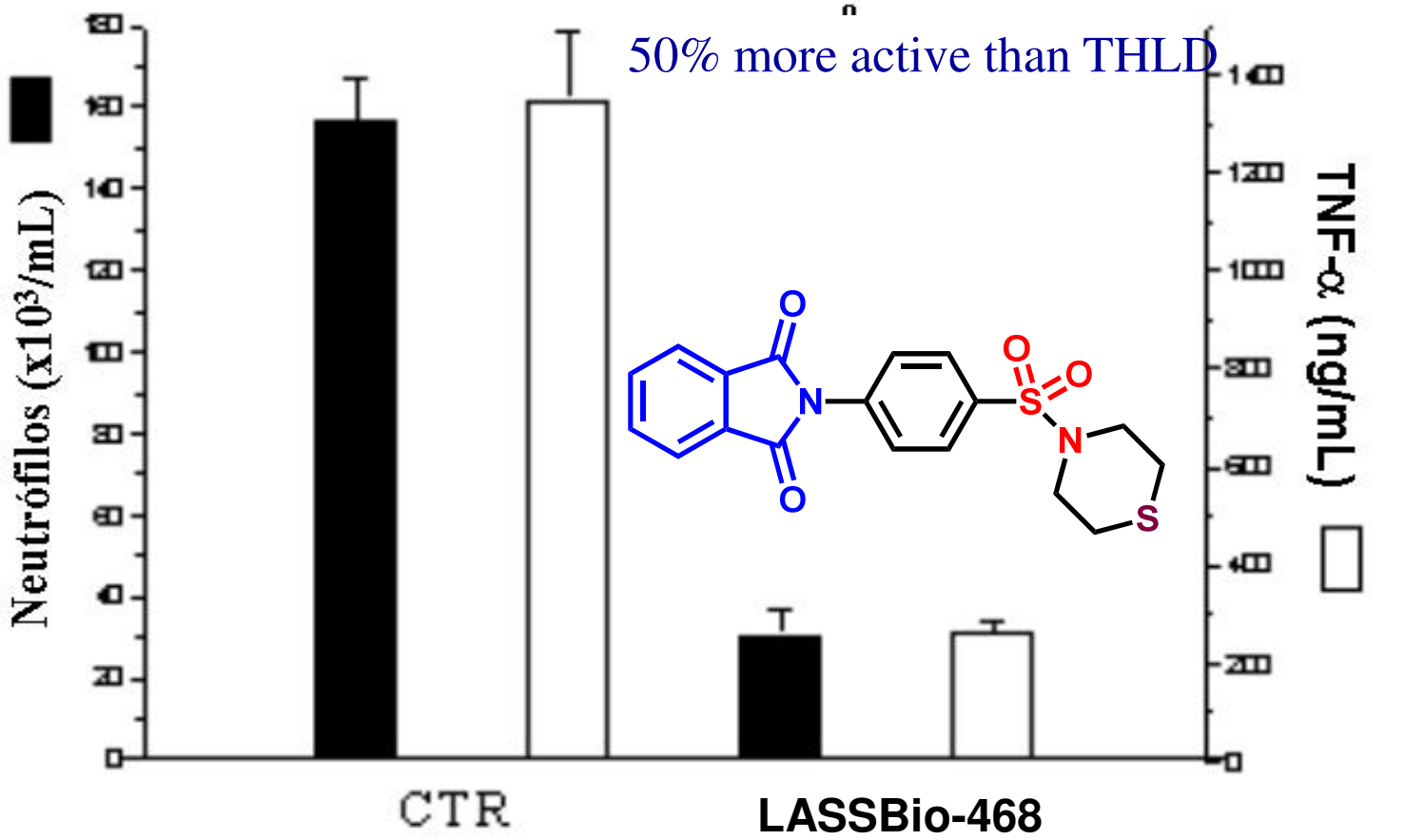
Effect of new compounds and thalidomide on neutrophils influx, induced by LPS into BALB/c of mice lungs (10 mg/kg, DMSO; ip)

in vivo



Results are expressed as means SEM of seven animals.

Effect of compound LASSBio 468 (50 mg/kg, ip) on TNF-α levels and neutrophils influx (BALB/c; lung exudate)



Inhibition of the production of TNF-α promote the elevation of intracellular levels of cyclic 3',5'-adenosine monophosphate (cAMP) in leukocytes, associated with inhibition of PDE-4 activity.*

* DO Procopio, MM Teixeira, MM Camargo, LR Travassos, MA Ferguson, IC Almeida, RT Gazzinelli, Differential inhibitory mechanism of cyclic AMP on TNF-α and IL-12 synthesis by macrophages exposed to microbial stimuli. *Br. J. Pharmacol.***1999**, *127*, 1195

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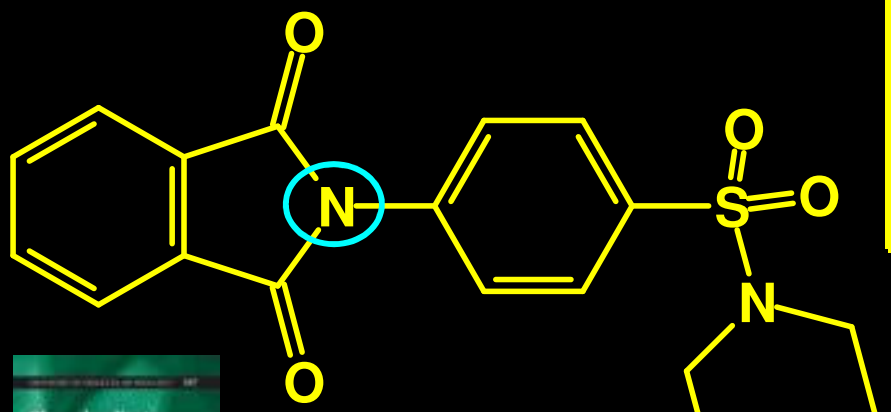
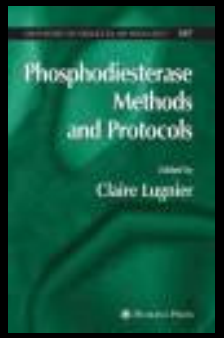




$C_{18}H_{16}N_2O_4S_2$

LASSBio 468

TNF-α ED_{50} 2.5 mg/Kg

lead compound

PDE-4 inhibitor

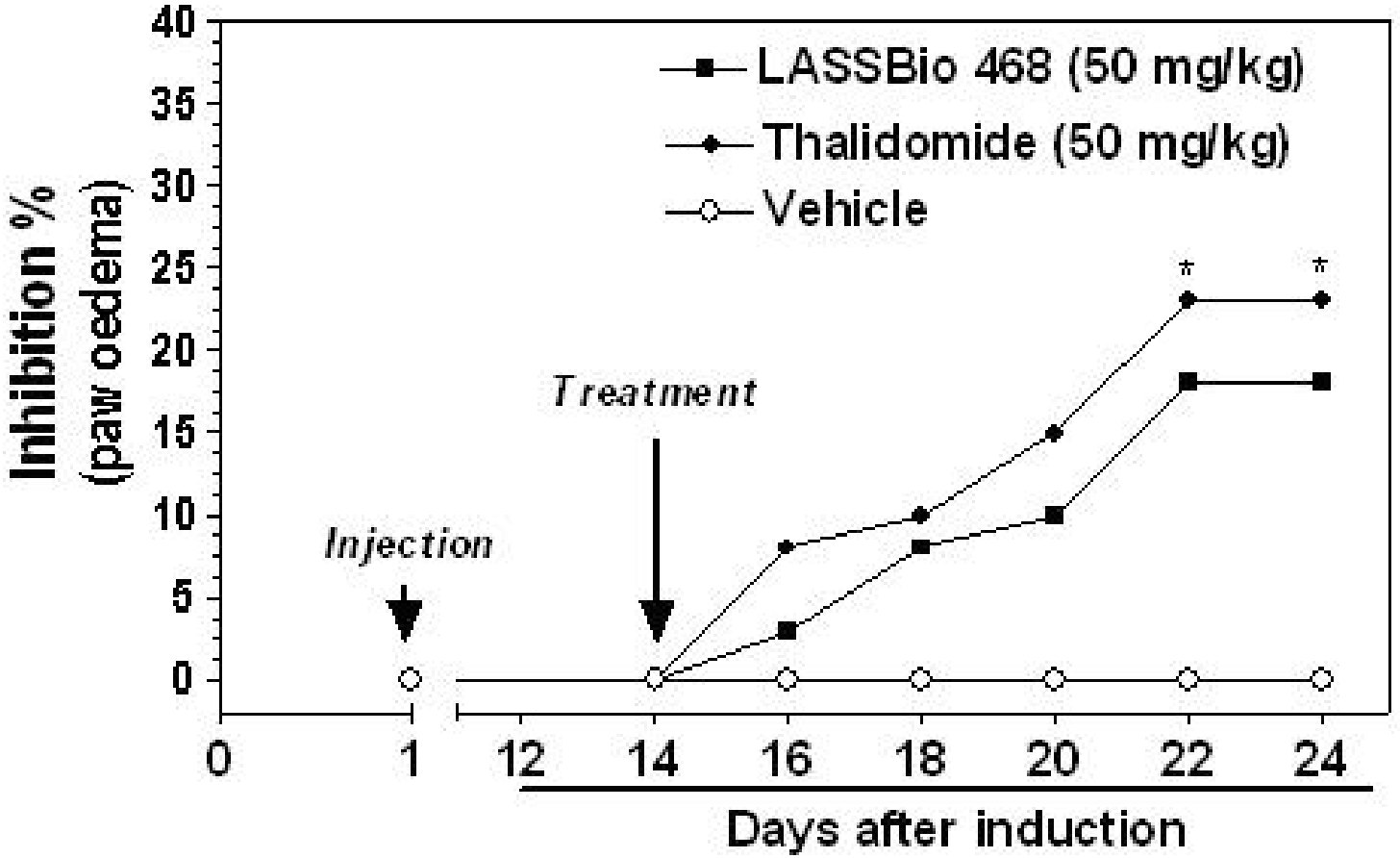
Dr Claire Lugnier (CAPES-COFECUB; LASSBio-Strasbourg)
Université Louis Pasteur, Strasbourg, FR.
Laboratoire de Pharmacologie et de Physicochimie des Interactions Cellulaires et Moléculaires.

IC_{50} = 30.1 μM

cf. PDE-1, 2, 3, >> 150 μM;

L M Lima et al., Synthesis and Anti-inflammatory Activity of Phthalimide Derivatives, Designed as New Thalidomide Analogues, *Bioorg. Med. Chem.* **2002**, *10*, 3067; 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; LM Lima, CAM Fraga, VLG Koatz, EJ Barreiro, Thalidomide and Analogs as Anti-Inflammatory and Immunomodulator Drug Candidates, *Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry*, **2006**, *5*, 79; L M Lima, N M de Lima, *Rev. Virtual Quim.* **2009**, *1*, 35;

Effect of the treatment with LASSBio-468 (50 mg/kg po) on hind paw edema in adjuvant-induced arthritis (AiA-model) (*Mycobacterium tuberculosis*) in rats

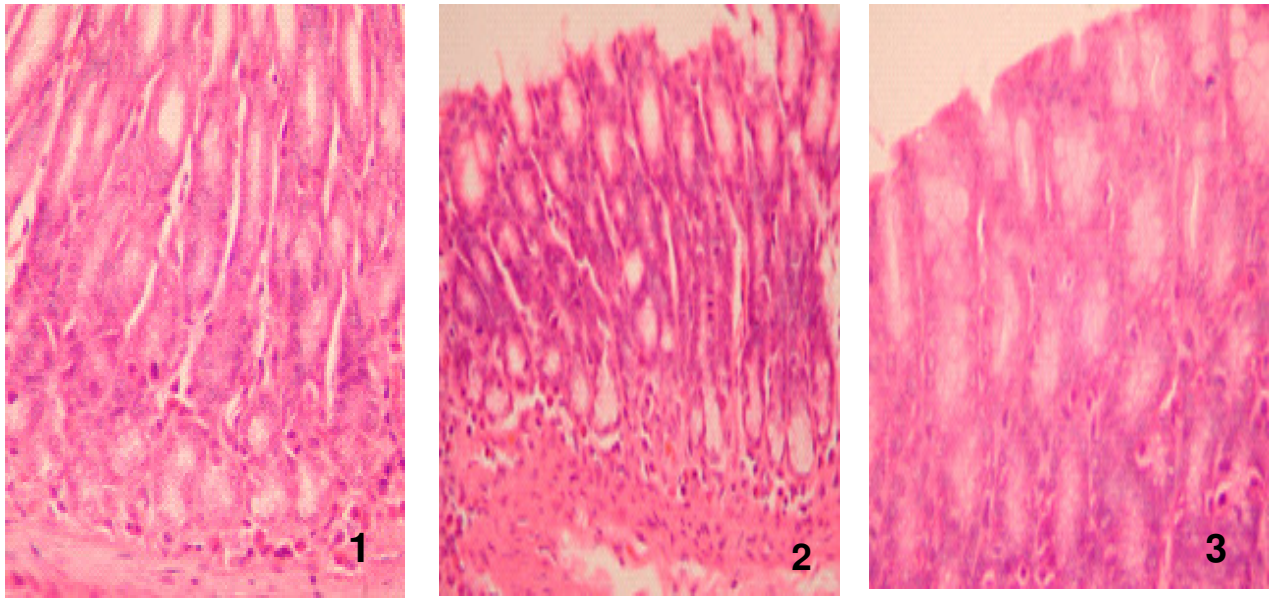


23%

18%

Dr Magna Suzana Alexandre-Moreira
LASSBio, Universidade Federal do Rio de Janeiro

Histopathological results



(1) Photomicrography of granulomatous hepatitis in the control animals (HE – 100X);
(2) Animals treated with thalidomide (HE – 100X);
(3) Animals treated with LASSBio 468 (HE – 200X);

*** A positive control was performed *M. tuberculosum*.**

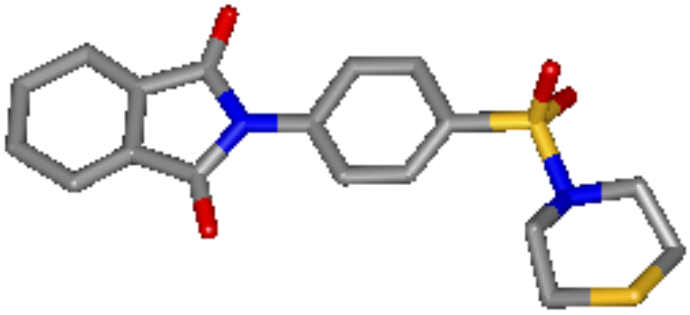
LASSBio-468 has a protective effect on inflamation development mediated by immunomodulatory macrophage activity

Christina M Takyia
ICB, Universidade Federal do Rio de Janeiro

LASSBio-468

A new DMARD lead-candidate

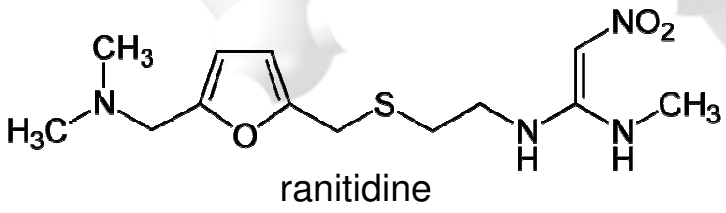
LASSBio-468 is a new dual anti-inflammatory agent (DMARD), active at TNF-α production with inhibitory activity on PDE-4.



This new achiral compound is an immunomodulator lead, without proliferative activity in the concavalin-A mitogen assay, in contrast to TLDH. It is an useful lead to therapy of rheumatoid arthritis & septic shock 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; AL Machado *et al.*, Design, Synthesis and anti-inflammatory activity of novel phthalimide derivatives, structurally related to thalidomide, *Bioorg. Med. Chem. Lett*. 2005*, 15*, 1169.

"… when it comes to drug discovery you're not trying to make complicated molecules, but make molecules that will be effective … "



ranitidine

Barry J. Price

Research Director Glaxo (1967-1995)

Concluding remarks

- Inflammation is so broad that, there remains both need and opportunity for new, distinctive, and successful small molecule agents, including selective multitarget candidates.

- Several recent potential new targets for AI drugs were identified as *m*-PGES-1, *c*PLA2a, LTA_4-hydrolase, from eicosanoids class; from kinases are MK2, Sik kinase, Janus kinases (JAKS), IKKβ, Bruton´s tyrosin kinase (Btk), p38 MAPK inhibitors. GPCR´s also represents an important pathway to develop new AI agents acting as CCR1, CCR2 & CB2 agonists.

- The discovery of the integral role of the *Inflammasome* in driving inflammatory processes, has now led to efforts to directly block its formation and actions and represents an important pathway to control inflammatory disorders, including chronic ones.


“ ...medicinal chemists today live in exciting times...
their work can have a beneficial effect on millions of
suffering patients – surely an important motivating
factor for any scientist...”
Joseph G. Lombardino & John A. Lowe, III
The Role of the Medicinal Chemist in Drug Discovery – Then and Now,
Nature Rev. Drug Disc. 2004, 3, 853.
[doi:10.1038/nrd1523]
medicinal chemistry

Acknowledgements

Thank to my Colleagues of LASSBio
and to all students & postdocs


Dra Lídia M. Lima


Dr. Carlos A. M. Fraga

CNPq
Conselho Nacional de Desenvolvimento Científico e Tecnológico

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Conferences

Short-courses

Thank you

UFRJ XXII Escola de Verão LASSBio

em Química Farmacêutica e Medicinal

January 25-29, 2016

Inscriptions

www.evqfm.com.br

LASSBio

Laboratório de Avaliação e Síntese de Substâncias Bioativas