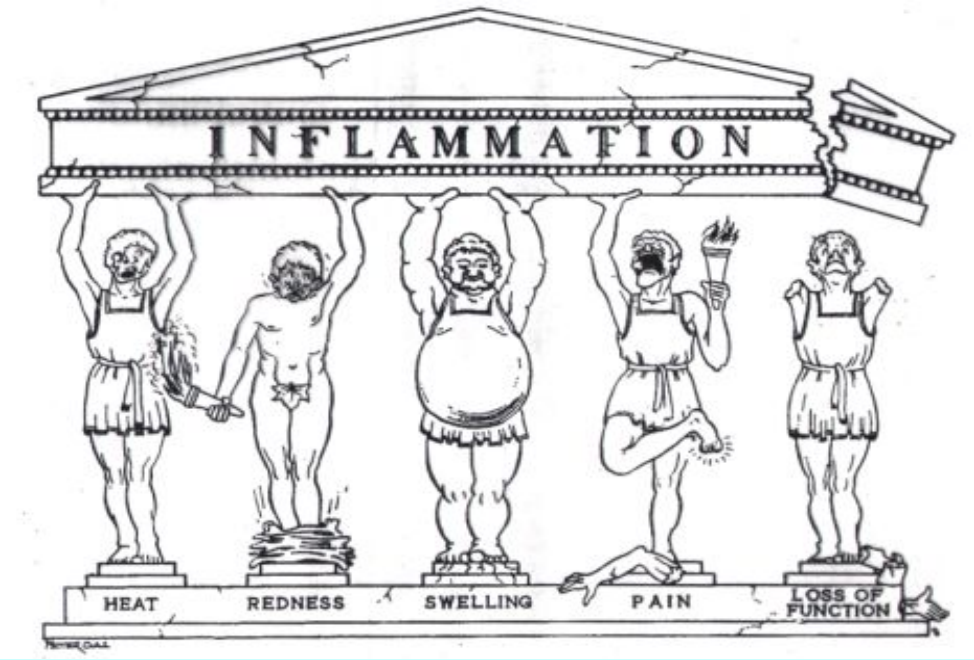
PROCESSO INFIAMMATORIO

Successione di modificazioni che avvengono in un tessuto vivente in risposta alla lesione, purché questa non sia di grado tale da distruggere la struttura e la vitalità del tessuto

- L'infiammazione è fondamentalmente una **risposta protettiva**, il cui scopo ultimo è liberare l'organismo dalla causa iniziale della lesione cellulare (es. microbi, tossine) e dalle conseguenze di tale lesione (es. cellule e tessuti necrotici).

- Tuttavia infiammazione e riparazione possono essere potenzialmente dannose.

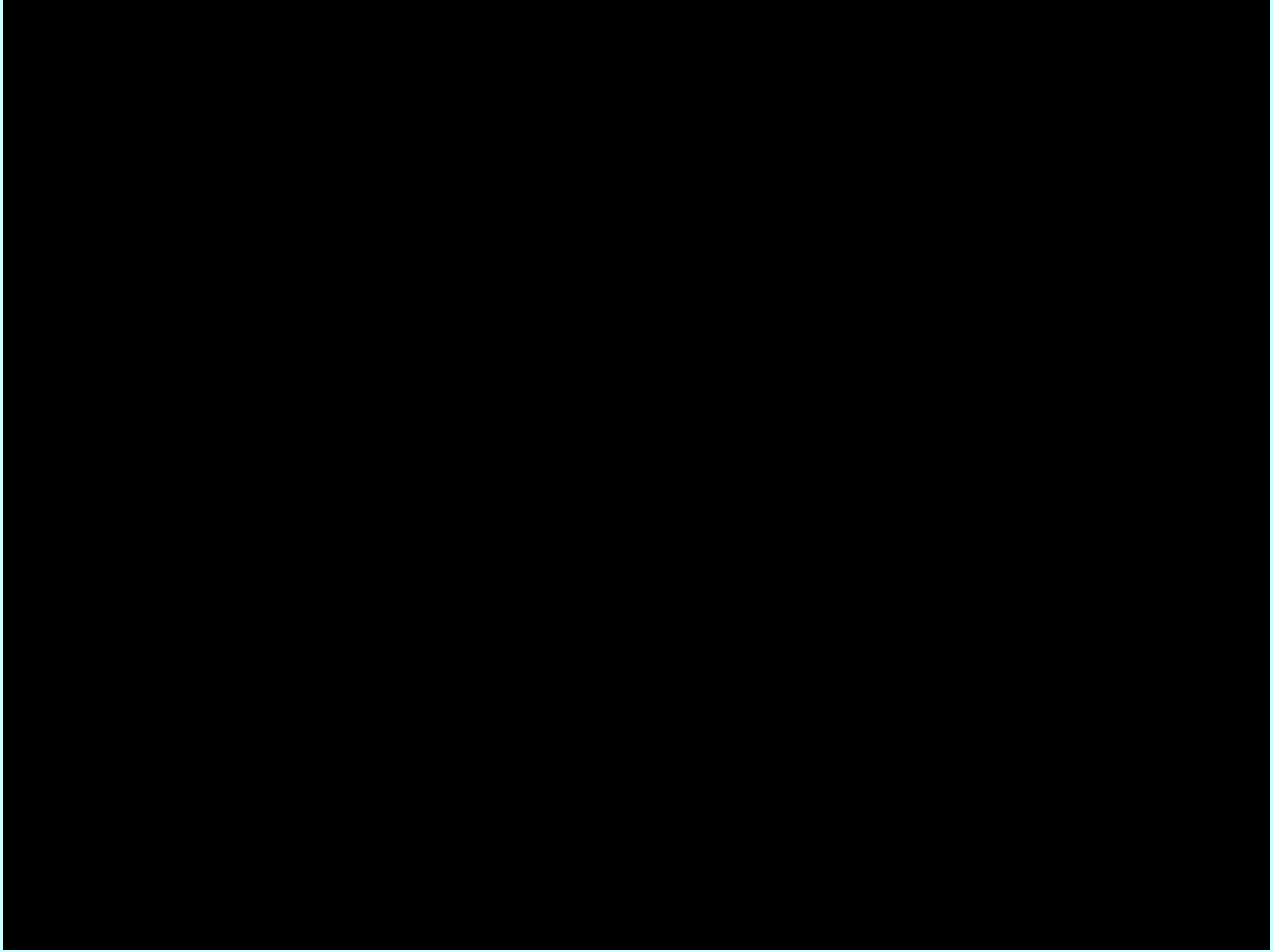


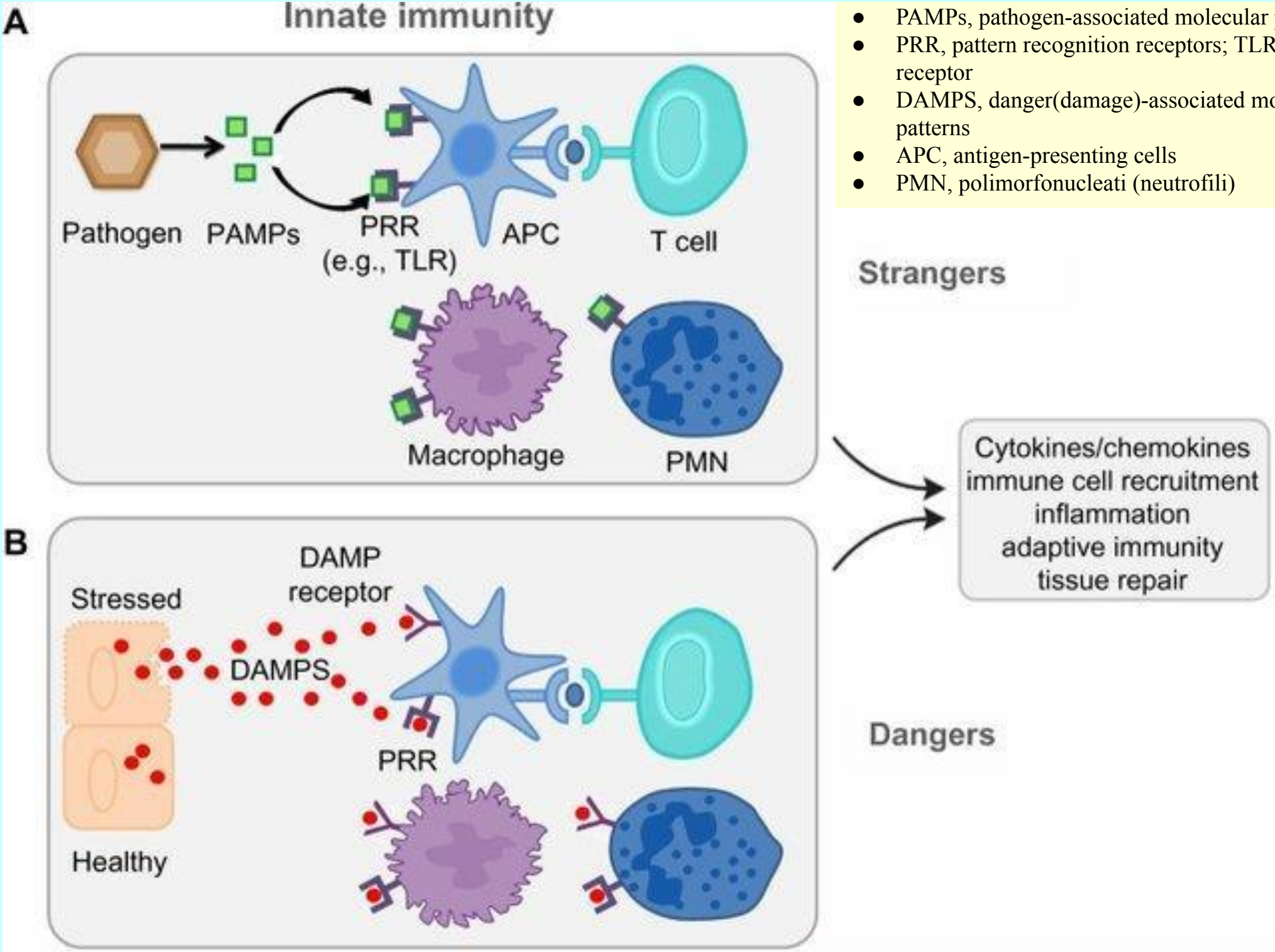
CENNI STORICI

- 3000 a.C. Papiro egizio – Descrizione delle caratteristiche cliniche dell'infiammazione
- I secolo d.C. Celso – Individuò i 4 segni cardinali dell'infiammazione: **RUBOR, TUMOR, CALOR, DOLOR**
- 1793 John Hunter – l'infiammazione non è una malattia, ma una risposta aspecifica che ha un effetto salutare sull'ospite
- 1844 Virchow – Individua un quinto segno clinico: **FUNCTIO LAESA**
- 1882 Elie Metchnikoff – Scoprì il processo e il ruolo della **FAGOCITOSI**
- 1908 Paul Erlich ed Elie Metchnikoff – Premio Nobel per lo sviluppo della teoria dell'immunità umorale (**Ruolo degli anticorpi**)
- 1927 Sir Thomas Lewis affermò che sostanze chimiche, ad esempio l'istamina, mediano le alterazioni vascolari legate all'infiammazione (**Ruolo dei mediatori chimici**)

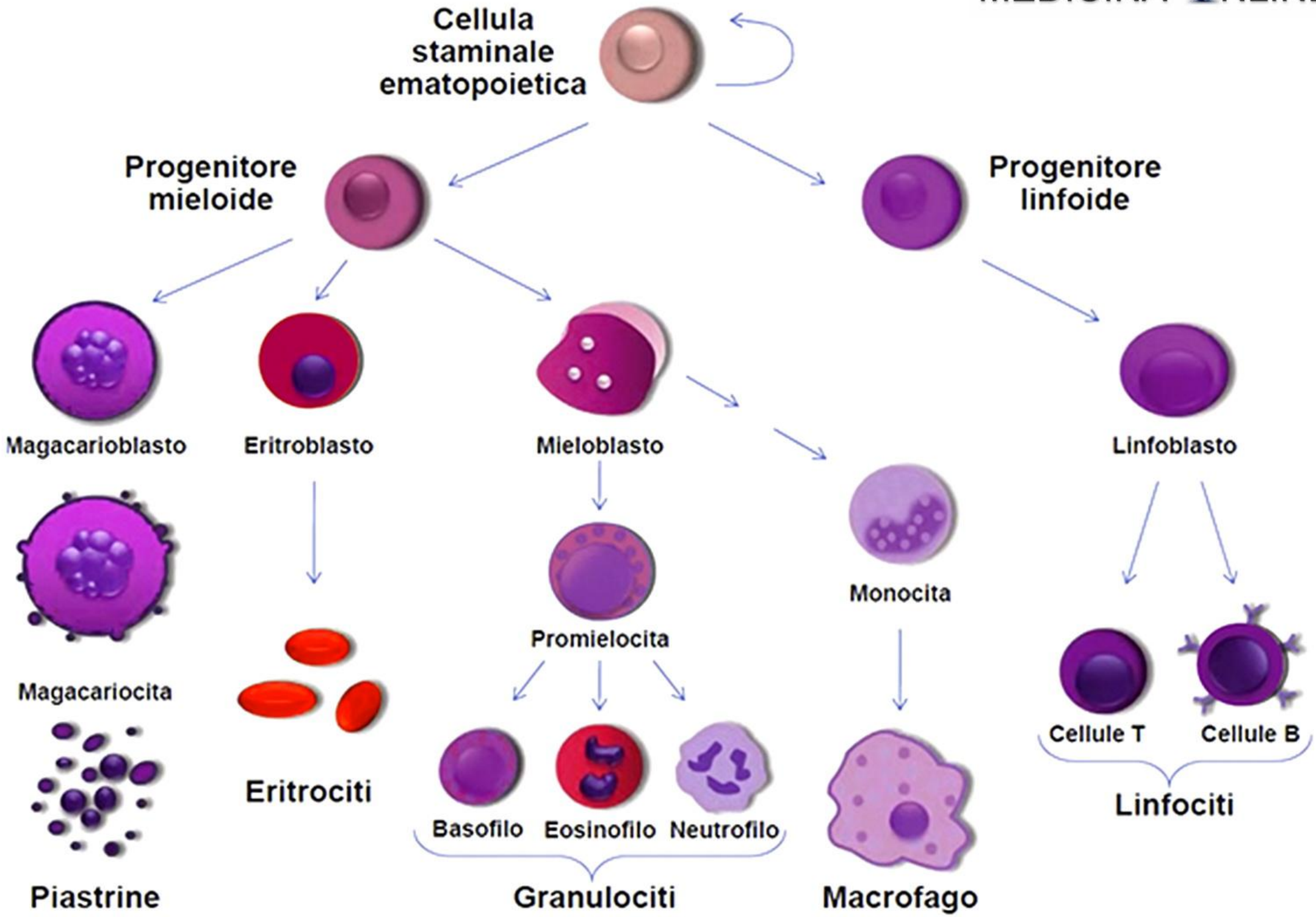
STIMOLI DELL'INFIAMMAZIONE

- Infezioni (batteriche, virali, parassitiche) e tossine microbiche
- Traumi (superficiali e profondi)
- Agenti fisici e chimici (lesione termica, irradiazione, alcune sostanze chimiche ambientali)
- Necrosi tissutale (da qualsiasi causa)
- Corpi estranei (schegge, sporcizia, fili di sutura)
- Reazioni immunitarie (o di ipersensibilità)



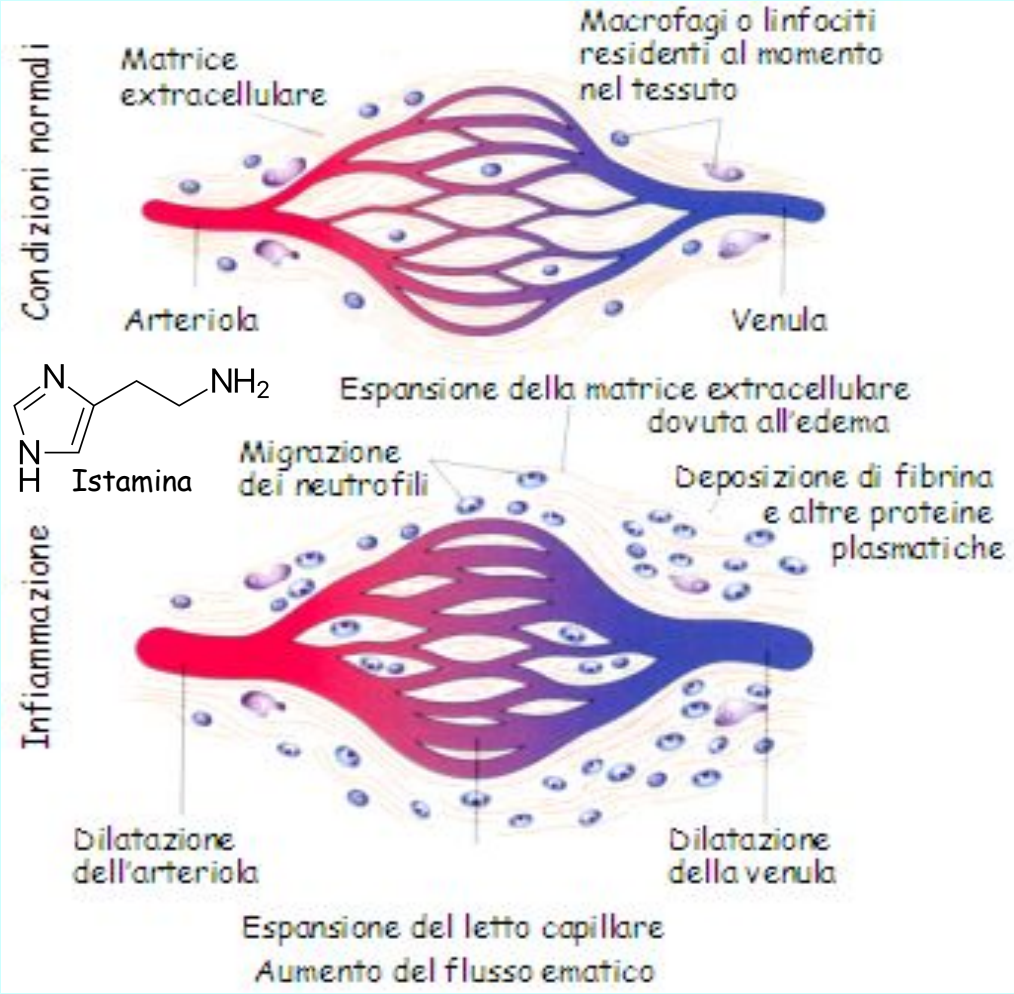


- PAMPs, pathogen-associated molecular patterns
- PRR, pattern recognition receptors; TLR, toll-like receptor
- DAMPS, danger(damage)-associated molecular patterns
- APC, antigen-presenting cells
- PMN, polimorfonucleati (neutrofili)



INFIAMMAZIONE ACUTA

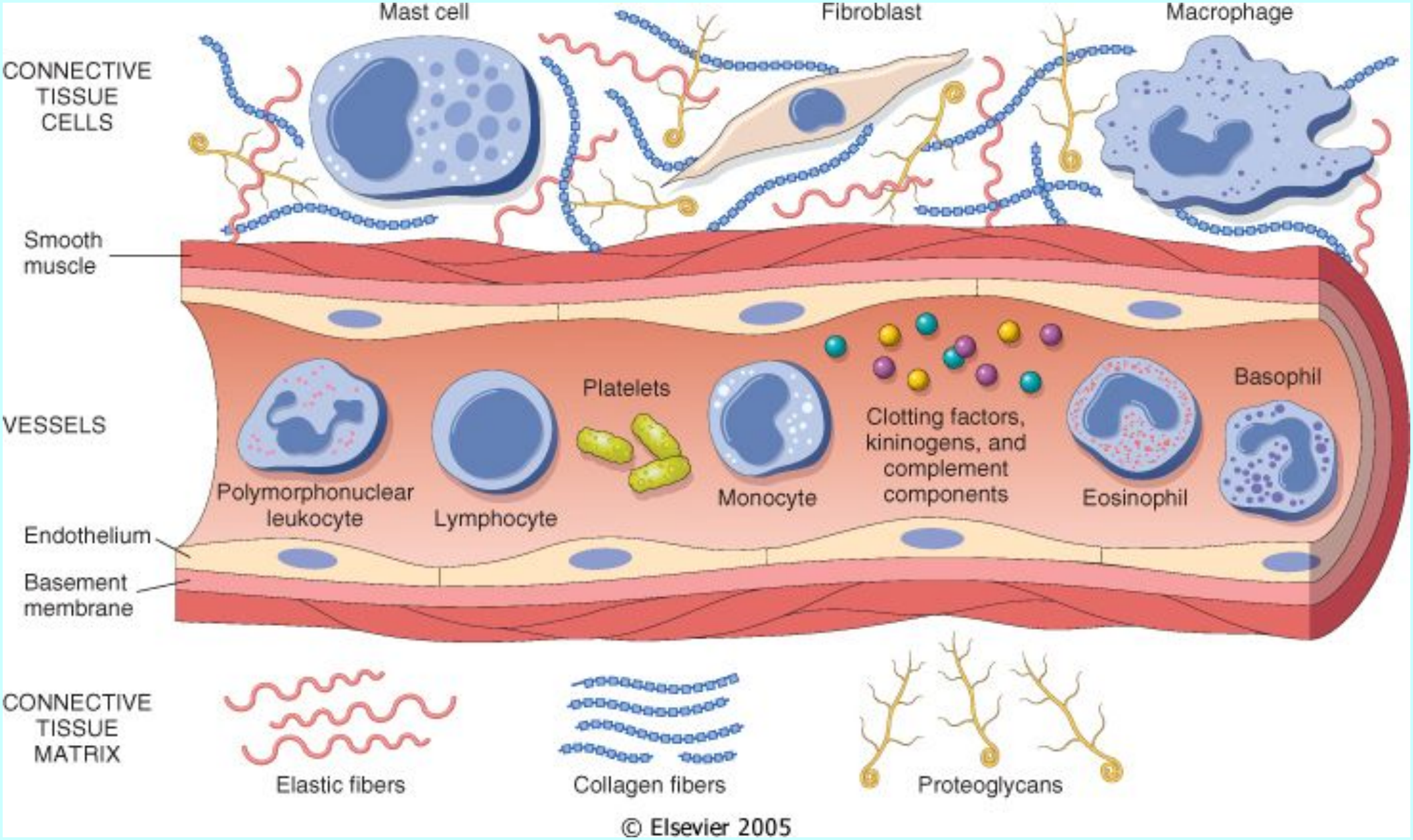
Risposta rapida ad un agente lesivo che serve a portare nella sede della lesione i mediatori della difesa dell'ospite, leucociti e proteine plasmatiche.



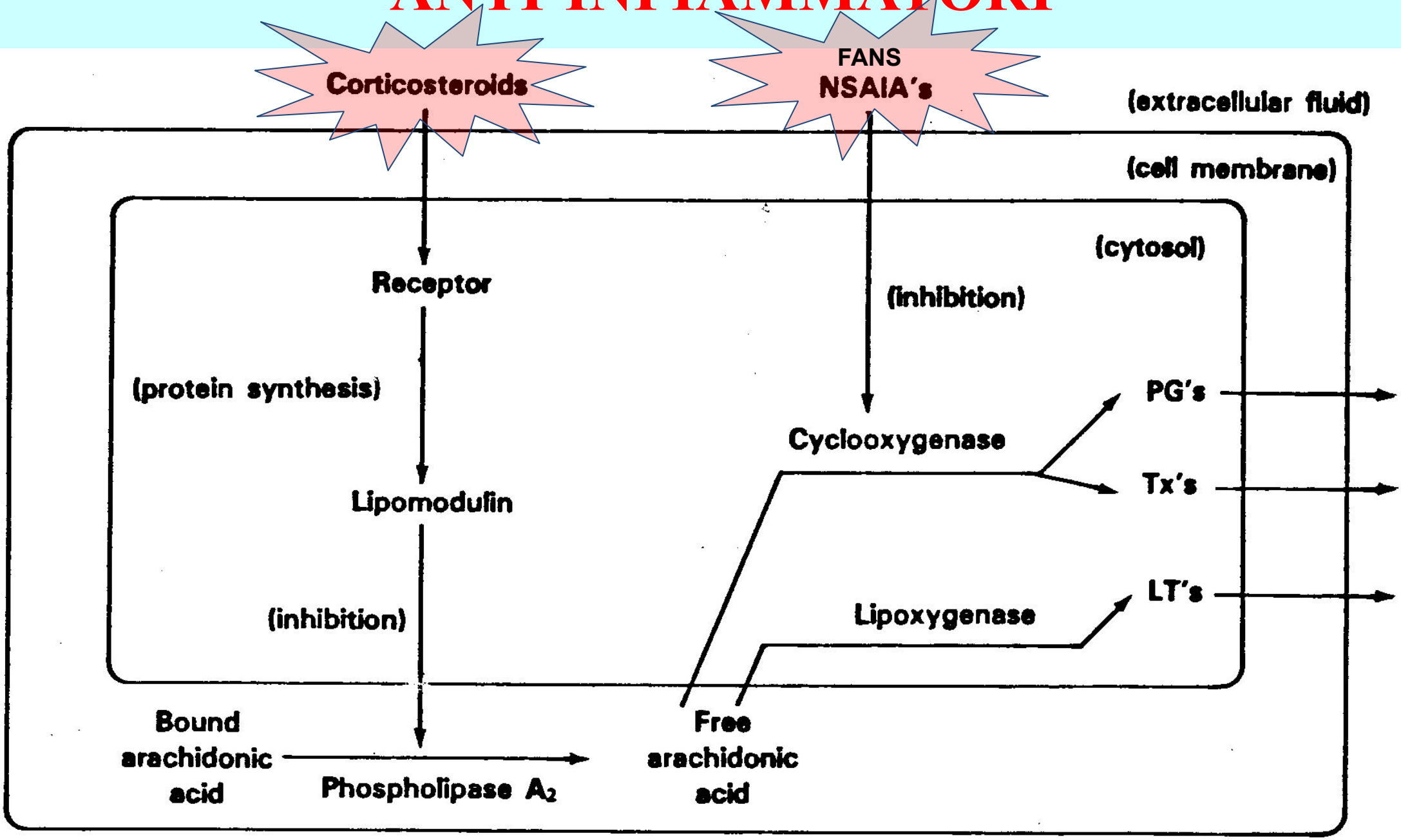
Ha 3 componenti principali:

- Alterazioni del calibro vascolare che determinano un aumento del flusso ematico
- Modificazioni strutturali nella microvascolarizzazione che consentono alle proteine plasmatiche e ai leucociti di lasciare il circolo
- Fuoriuscita dei leucociti dal microcircolo, accumulo in sede di lesione e attivazione per l'eliminazione dell'agente lesivo

PROTAGONISTI DELL'INFIAMMAZIONE



ANTI-INFIAMMATORI



Cellular events in the inhibitory action of NSAIA's and corticosteroids on arachidonic acid metabolism (modified from reference 22). PG = prostaglandin; LT = leukotriene; Tx = thromboxane; NSAIA = non-steroidal anti-inflammatory agents.

FANS = Farmaci anti-infiammatori Non-Steroidei

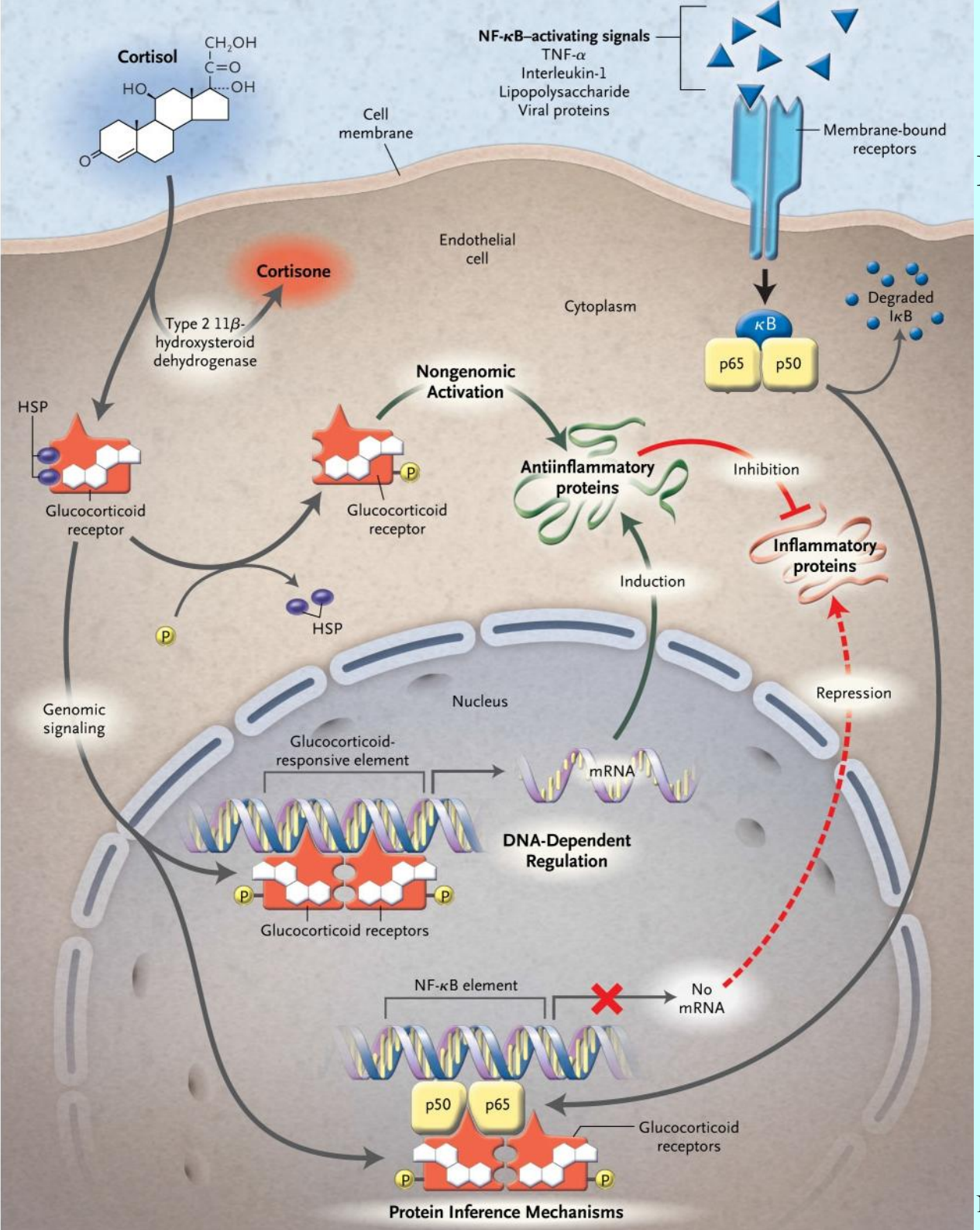
CORTICOSTEROIDI

RECETTORE GLUCOCORTICOIDI

Azioni genomiche:
Transattivazione e transrepressione

Interazione con altri fattori di trascrizione (NF-κB)

Azioni non-genomiche:
Interazione con recettori di membrana e secondi messaggeri



N Engl J Med 353;16 (2005)

MECCANISMI ALLA BASE DELL'ATTIVITÀ ANTIINFIAMMATORIA DEI GLUCOCORTICOIDI

- **Riduzione dell'espressione di citochine pro-infiammatorie quali interferone-γ, interleuchine IL-1 e IL-6, fattore di necrosi tumorale α (TNF-α) e fattore stimolante le colonie (CSF), tutti fattori coinvolti nelle risposte del sistema immunitario**
- **Riduzione dell'espressione della COX-2 (ciclossigenasi-2) e della iNOS (ossido nitrico sintasi inducibile) con conseguente inibizione della produzione e del rilascio di altri mediatori dell'infiammazione tra cui prostaglandine, leucotrieni, istamina**
- **Riduzione dell'espressione del gene della collagenasi, un importante enzima coinvolto nell'infiammazione**
- **Stimolazione della produzione della lipocortina-1 (annessina) che inibisce l'attività della fosfolipasi A2 che interviene nella cascata dell'acido arachidonico**

CORTICOSTEROIDI

Trascrizione di IκB e transrepressione di NFκB e activator protein 1 (c-Jun e fos)

Induzione e attivazione di Annessina I (lipocortina)

Induzione di MAPK fosfatase 1

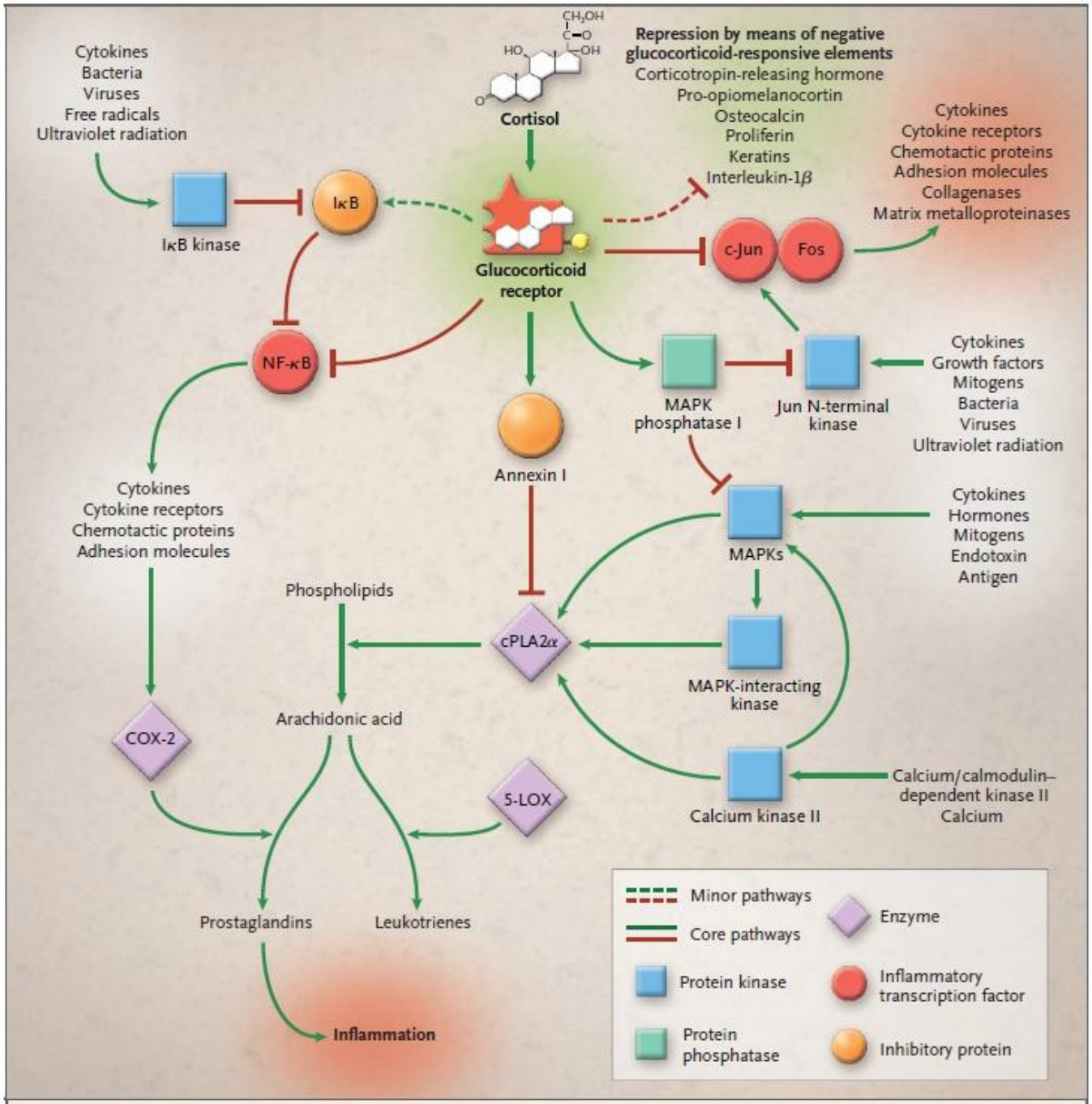
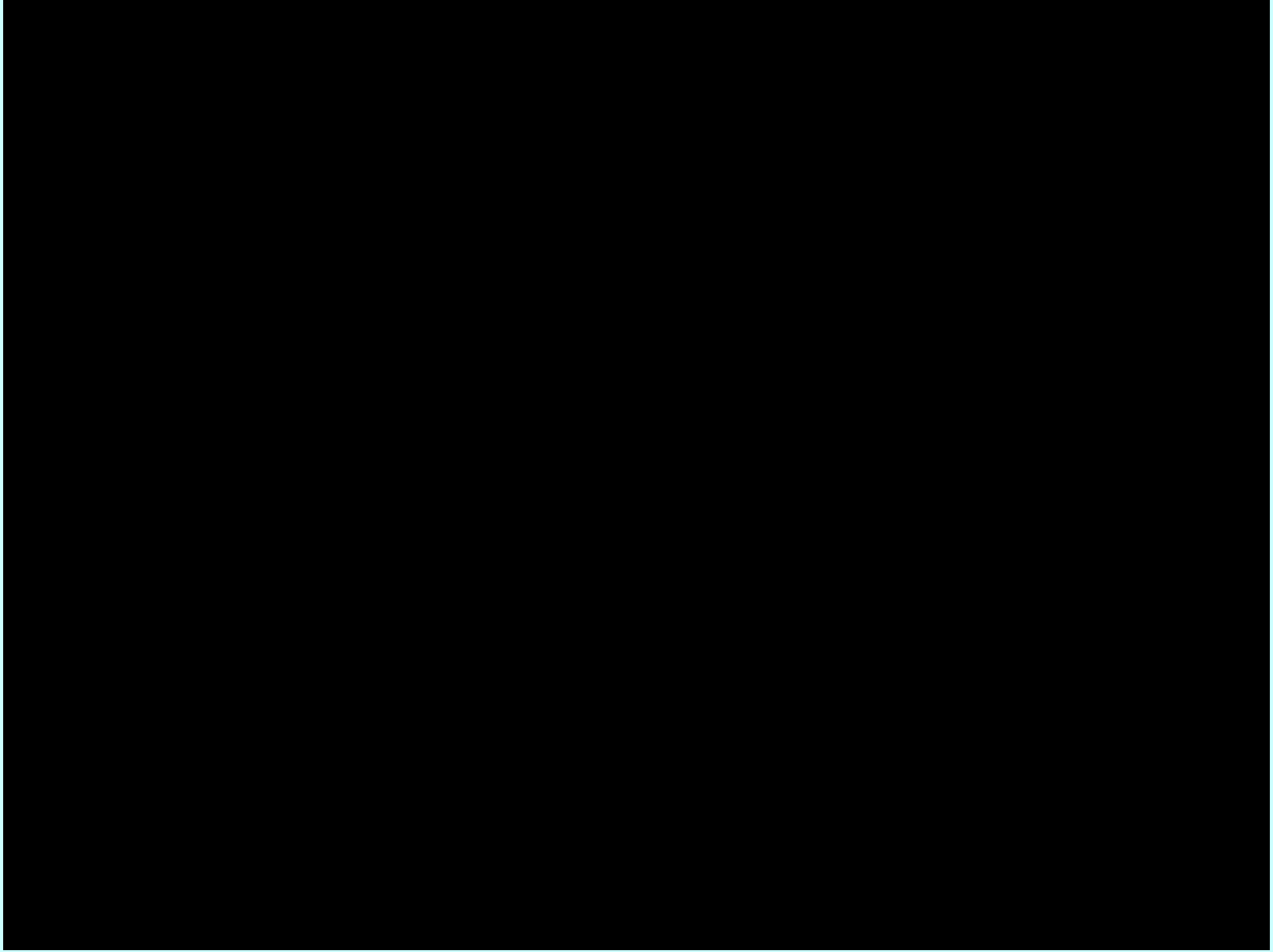


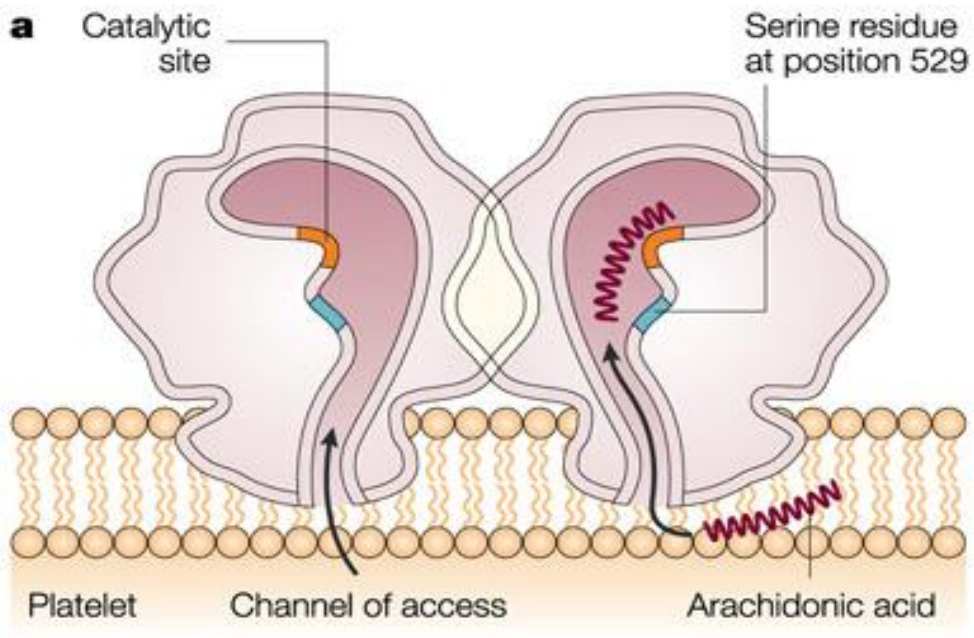
Figure 4. Partial Molecular Architecture Underlying the Glucocorticoid-Induced Antagonism of Inflammation.

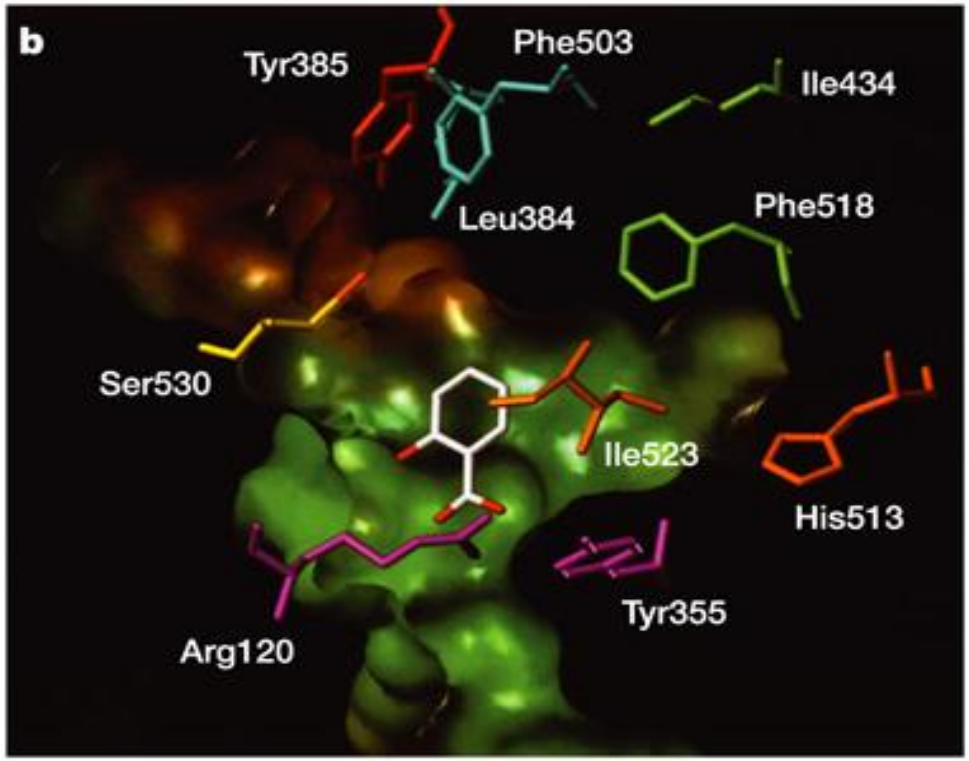
Inflammatory pathways are characterized by positive feedback loops (i.e., cytokines activate NF-κB, which in turn stimulates the synthesis of more cytokines) and by redundancy (i.e., cytokines also activate c-Jun–Fos). The glucocorticoid receptor inhibits these pathways at multiple points by directly blocking the transcription of inflammatory proteins by NF-κB and activator protein 1 and by inducing the expression of antiinflammatory proteins such as IκB, annexin I, and MAPK phosphatase I. 5-LOX denotes 5-lipoxygenase, and COX-2 cyclooxygenase 2. Red lines denote inhibition, and black arrows activation. An interactive version of this figure is available with the full text of the article at www.nejm.org.

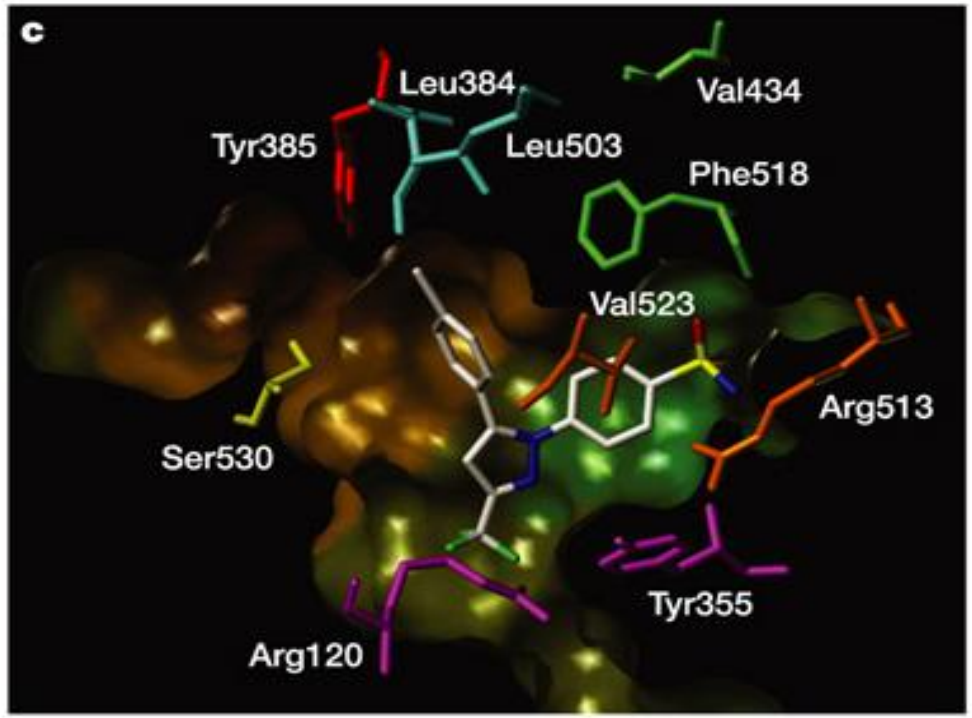
N Engl J Med 353;16 (2005)



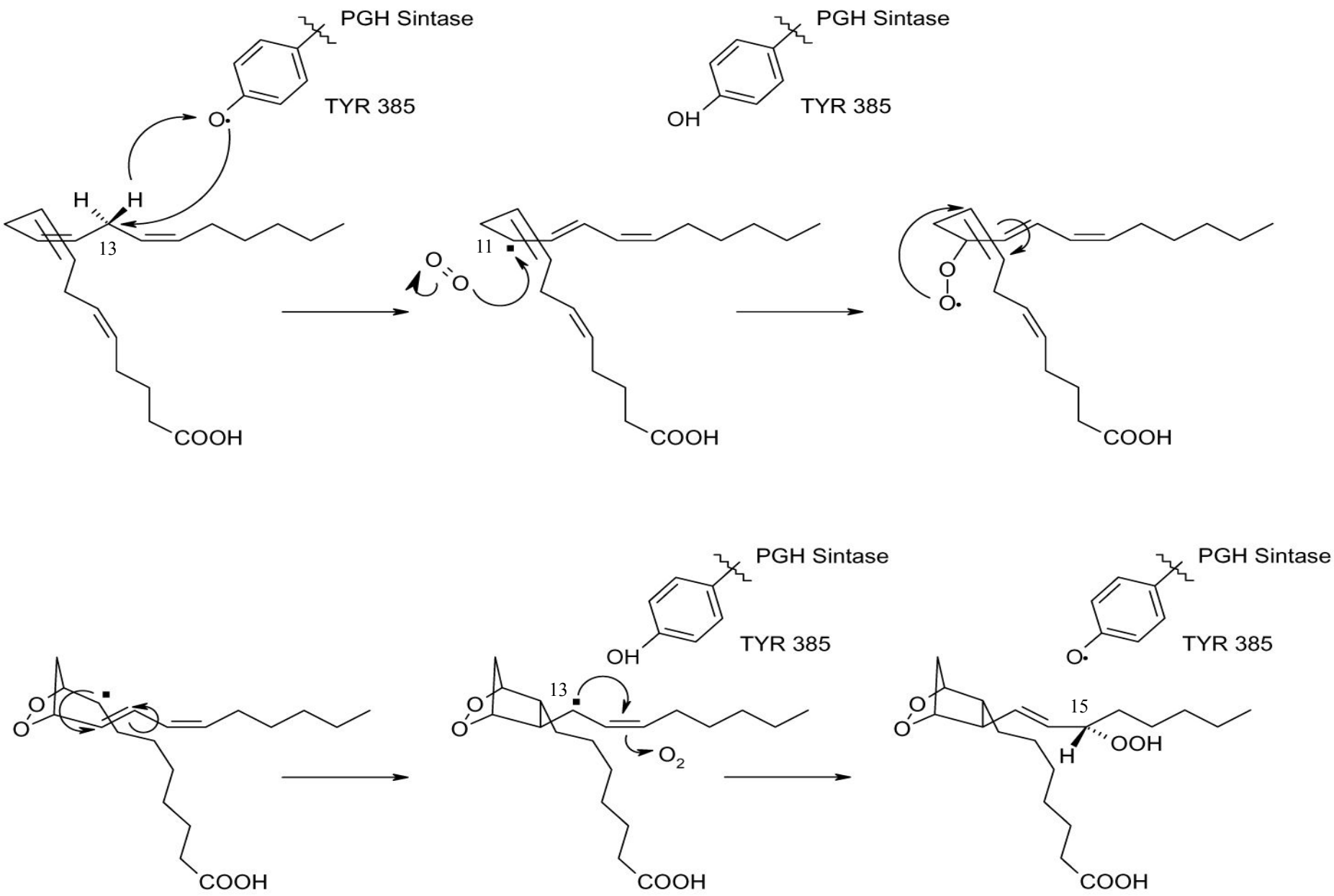
CICLOSSIGENASE

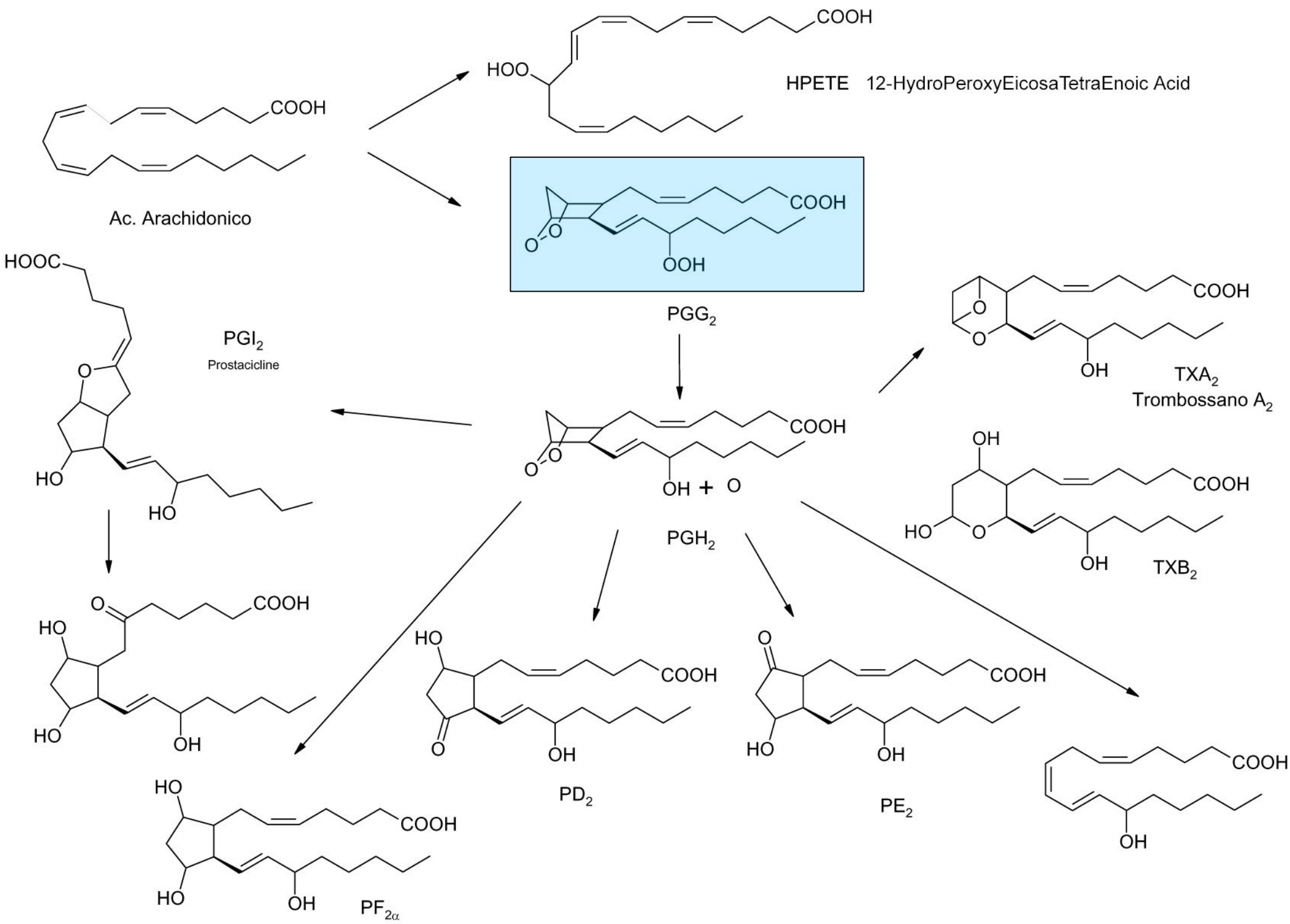






SINTESI DELLE PROSTAGLANDINE




COOH
HOO
HPETE 12-HydroPeroxyEicosaTetraEnoic Acid
Ac. Arachidonico
COOH
O
O
OOH
PGG2
HOOC
PGI2
Prostacicline
HO
HO
COOH
OH + O
PGH2
COOH
OH
TXA2
Trombossano A2
OH
COOH
HO
O
OH
TXB2
O
COOH
HO
HO
OH
HO
COOH
O
OH
PD2
HO
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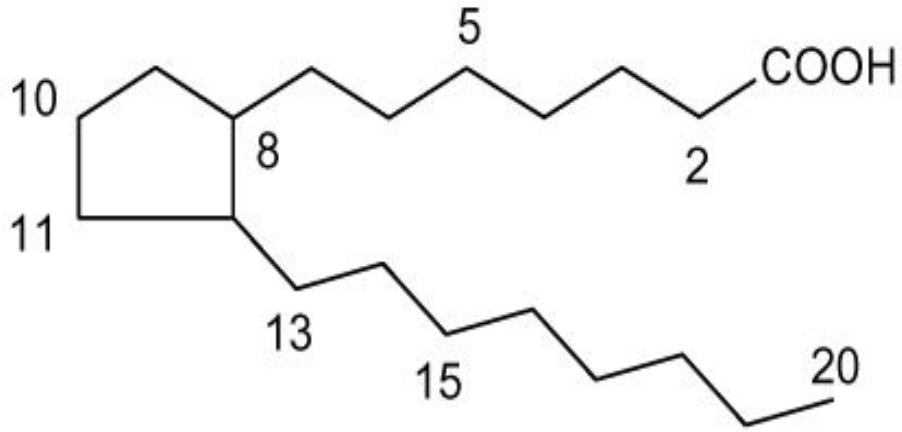
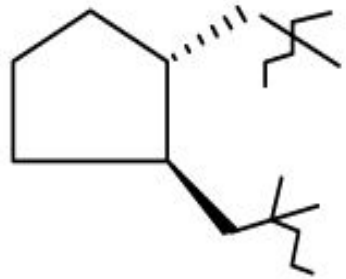
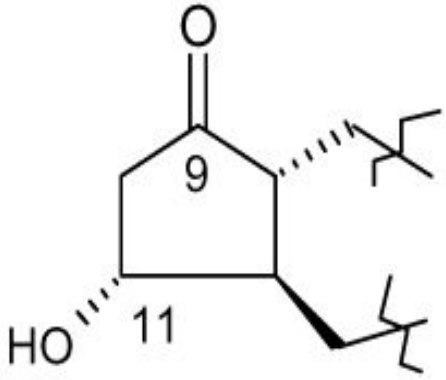
OH
PE2
COOH
OH
HO
COOH
HO
OH
PF2α



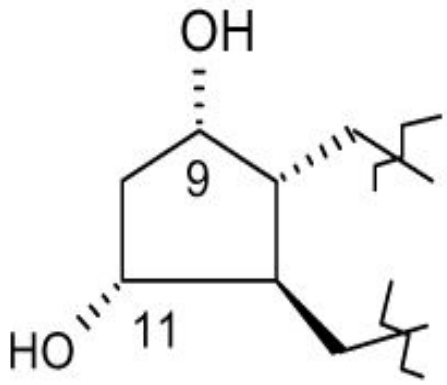
ACIDO PROSTANOICO



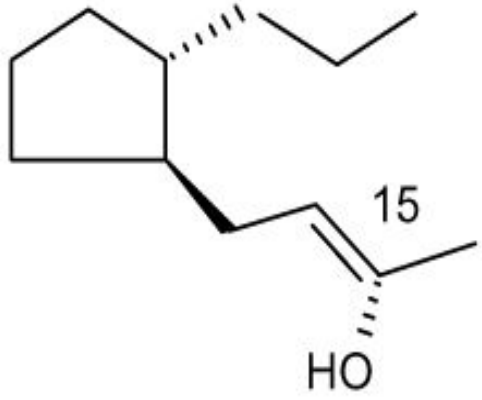
Prostaglandine naturali



Serie E



Serie Fα



nelle naturali OH in 15 conf. α = S

Nature Reviews Drug Discovery **2**; 879-890 (2003); doi:10.1038/nrd1225

COX-2 AND BEYOND: APPROACHES TO PROSTAGLANDIN INHIBITION IN HUMAN DISEASE

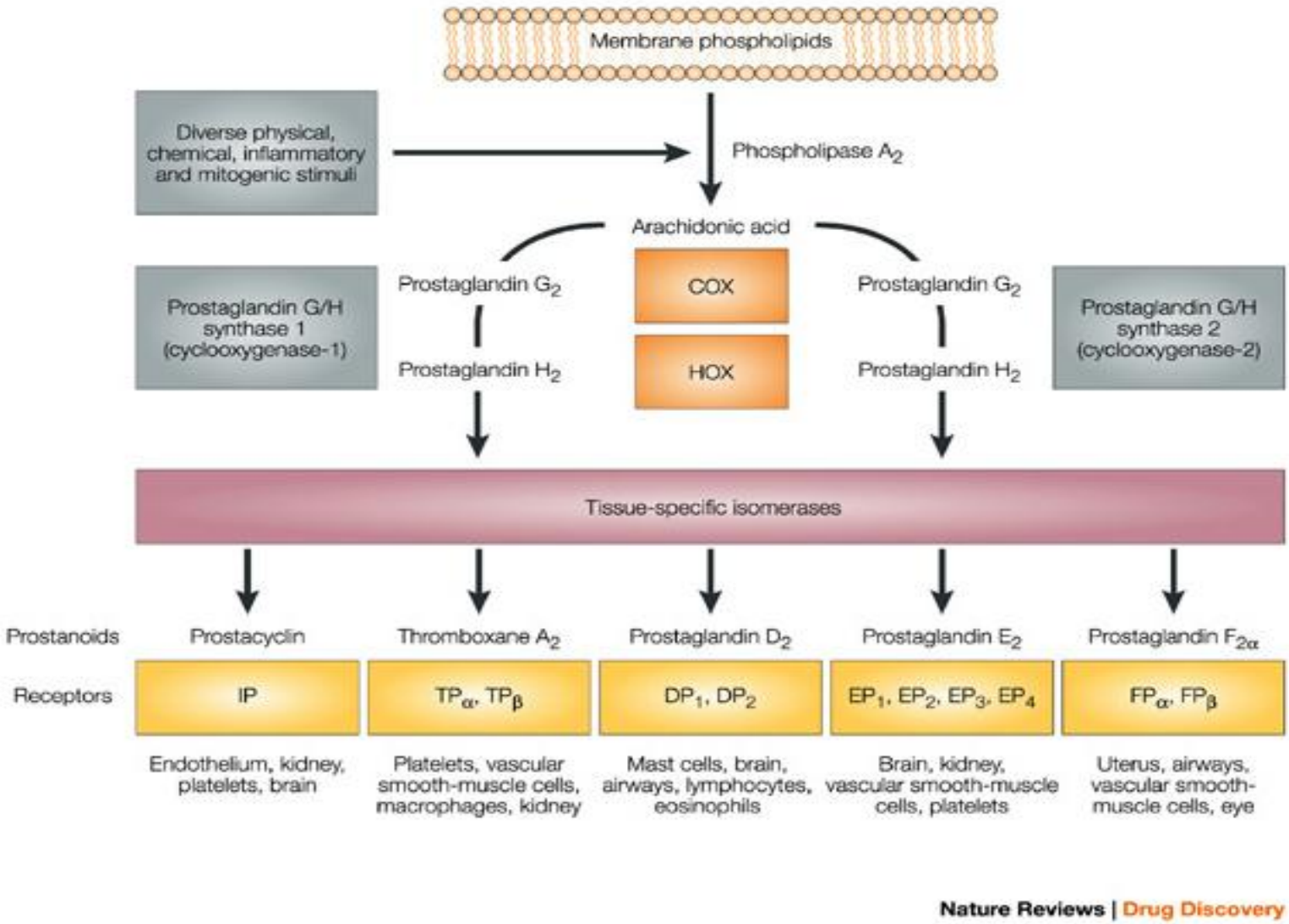


Figure 2 | **Prostaglandin biosynthetic cascade.** Nonspecific physical and chemical stimuli mobilize release of arachidonic acid from the sn-2 position of membrane phospholipids, permitting metabolism by PGG_2/H_2 synthases. These enzymes possess both cyclooxygenase (COX) and hydroperoxidase (HOX) activities and catalyze the sequential formation of prostaglandin (PG) endoperoxides. These are then further metabolized by isomerases and synthases (for example PGE synthases), which are expressed with some tissue specificity and generate distinct PGs. These activate distinct G protein coupled receptors which derive from an ancestral E prostanoid (EP) receptor with one exception. The DP_2 (also known as CRTH2) belongs to the fMLP receptor superfamily. Adapted with permission from Ref. 16 © Massachusetts Medical Society (2001). COX, cyclooxygenase; DP, PGD_2 receptor; EP, PGE_2 receptor; FP, PGF_2 receptor; HOX, hydroperoxidase; IP, PGI_2 receptor; TP, TxA_2 receptor.

Table 25–1 Eicosanoid Receptors

RECEPTOR	PRIMARY LIGAND	SECONDARY LIGAND	PRIMARY COUPLING	MAJOR PHENOTYPE IN KNOCKOUT MICE
DP_1	PGD_2		↑ cAMP (G_s)	↓ Allergic asthma
$DP_2/CHRT_2$	PGD_2	15d-PGJ_2?	↑ $Ca^{2+}{}_i$ (G_i)	?
EP_1	PGE_2		PLC ($G_?$)	Decreased response of colon to carcinogens
EP_2	PGE_2		↑ cAMP	Impaired ovulation and fertilization; salt sensitive hypertension
EP_{3A-D}	PGE_2		↓ cAMP (G_i) ↑ cAMP (G_s) ↑ PLC (G_q)	Resistance to pyrogens
EP_4	PGE_2		↑ cAMP (G_s)	Patent ductus arteriosus
$FP_{A,B}$	$PGF_{2\alpha}$	IsoP?	PLC (G_q)	Failure of parturition
IP	PGI_2	PGE_2	↑ cAMP (G_s)	↑ Thrombotic response, ↓ response to vascular injury
$TP_{\alpha,\beta}$	TxA_2	IsoPs	↑ PLC (G_q, G_i, $G_{12/13}$, G_{16})	↑ Bleeding time, ↑ response to vascular injury
BLT_1	LTB_4		G_{16}, G_i	Some suppression of inflammatory response
BLT_2	LTB_4	12(*S*)-HETE 12(*R*)-HETE	G_q-like, G_i-like, G_z-like	?
$CysLT_1$	LTD_4	LTC_4/LTE_4	↑ PLC (G_q)	↓ Innate and adaptive immune vascular permeability response, ↑ pulmonary inflammatory and fibrotic response
$CysLT_2$	LTC_4/LTD_4	LTE_4	↑ PLC (G_q)	↓ Pulmonary inflammatory and fibrotic response

This table lists the major classes of eicosanoid receptors and their signaling characteristics. Splice variants are indicated where appropriate. Major phenotypes in knockout mouse models are listed.

ABBREVIATIONS: $Ca^{2+}{}_i$, cytosolic Ca^{2+}; cAMP, cyclic AMP; PLC, phospholipase C (activation leads to increased cellular inositol phosphate and diacyl glycerol generation and increased $Ca^{2+}{}_i$); IsoPs, isopostanes; DP_2 is a member of the fMLP receptor superfamily; fMLP, formyl-methionyl-leucyl-phenylalanine. *See* text for other abbreviations.

SINTESI DEI LEUCOTRIENI

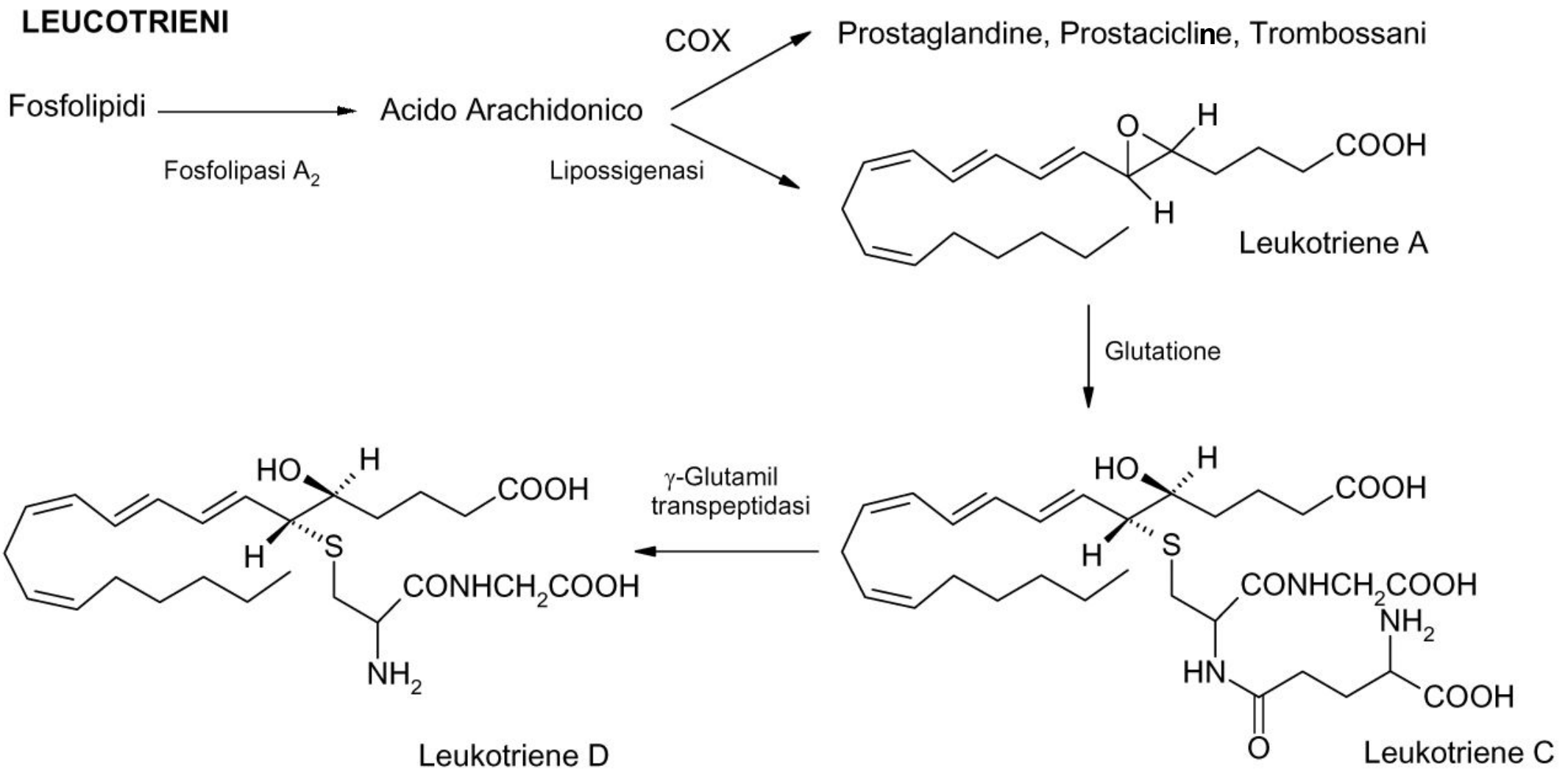
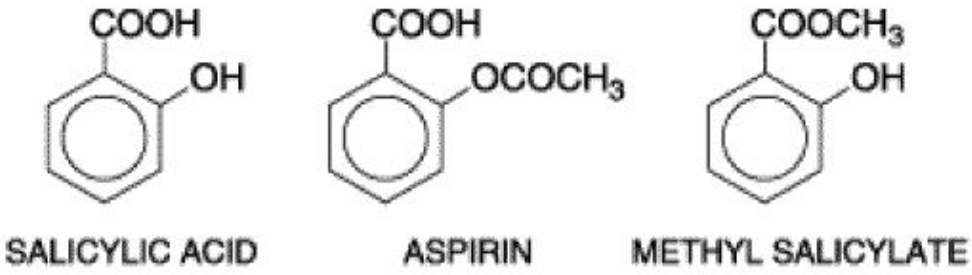
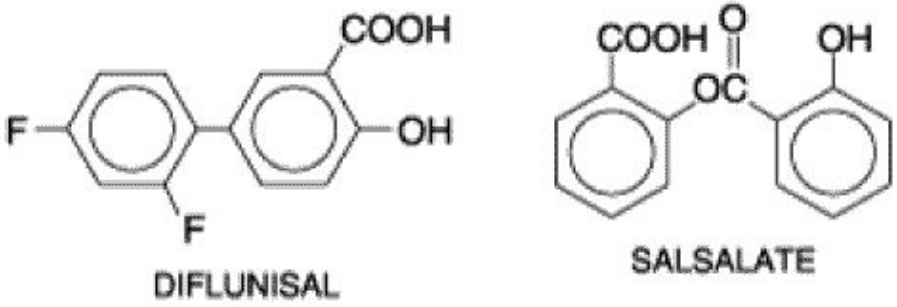
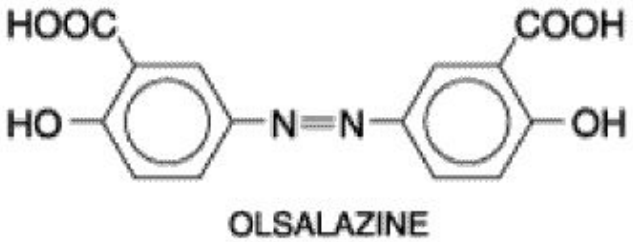


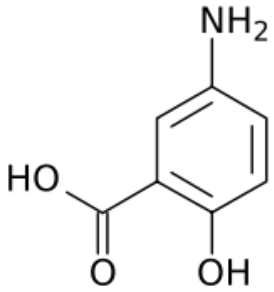
Figure 26–1

SALICILATI

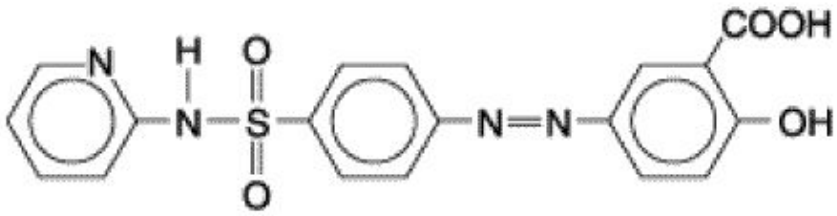








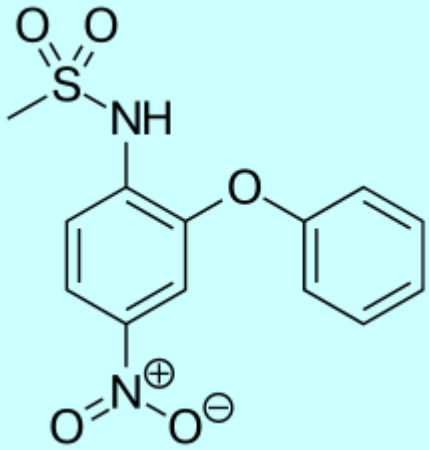
MESALAZINE



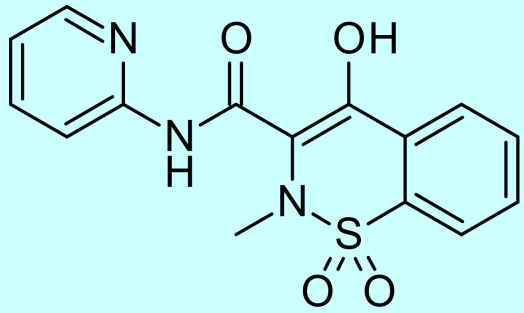
SULFASALAZINE

Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

FANS (NSAID)



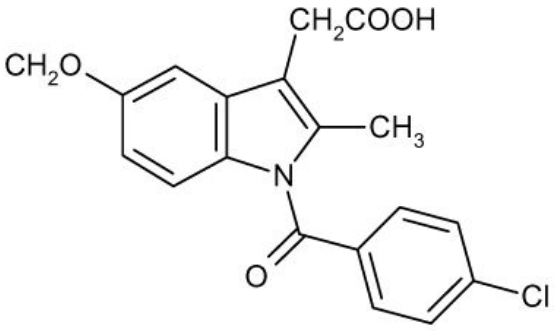
SOLFONILIDICI
NIMESULIDE (AULIN)



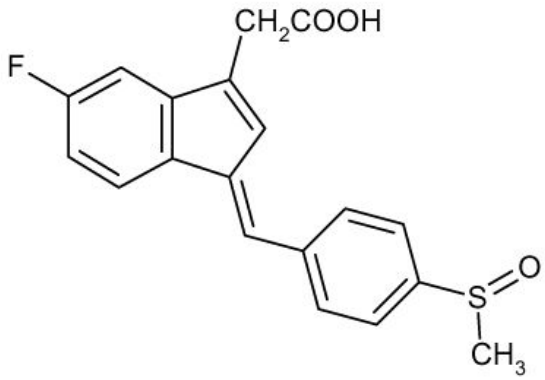
DERIVATI DI ACIDI ENOLICI
(OXICAM)
PIROXICAM (FELDENE)

FANS (NSAID)

DERIVATI INDOLICI

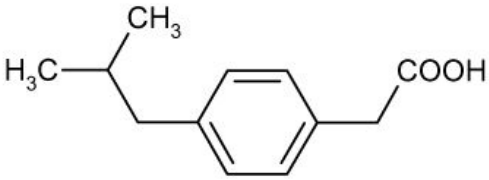


INDOMETACINA

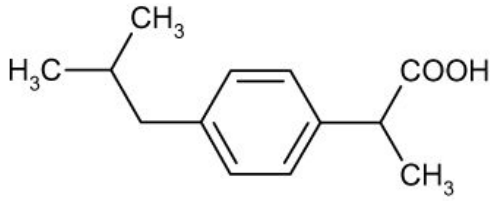


SULINDAC

ACIDI FENILACETICI E FENILPROPRIONICI

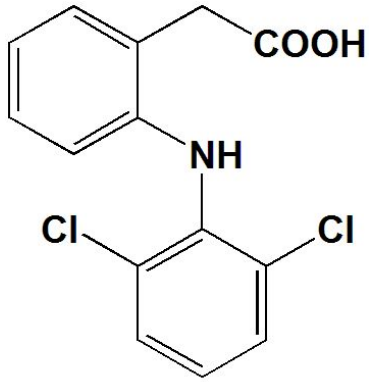


IBUFENAC



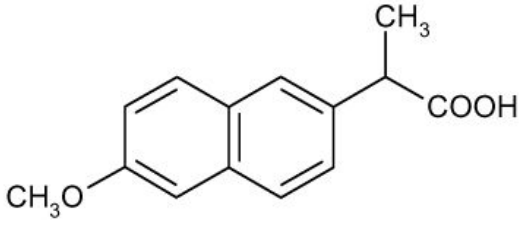
IBUPROFEN

MOMENT
BRUFEN
CIBALGINA
ACTIGRIP

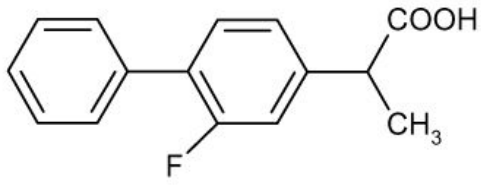


diclofenac

VOLTAREN
DICLOREUM



NAPROXEN
MOMENDOL



FLURBIPROFEN

BENACTIV GOLA
FROBEN
OCUFEN
TANTUM ACTIV GOLA

Table 26–2 Common and Shared Side Effects of NSAIDs	
SYSTEM	**MANIFESTATIONS**
GI (side effects decreased with COX-2–selective drugs)	Abdominal pain
	Nausea
	Anorexia
	Gastric erosions/ulcers
	Anemia
	GI hemorrhage
	Perforation
	Diarrhea
Renal	Salt and water retention
	Edema, worsening of renal function in renal/cardiac and cirrhotic patients
	Decreased effectiveness of antihypertensive medications
	Decreased effectiveness of diuretic medications
	Decreased urate excretion (especially with aspirin)
	Hyperkalemia
CNS	Headache
	Vertigo
	Dizziness
	Confusion
	Depression
	Lowering of seizure threshold
	Hyperventilation (salicylates)
Platelets (side effects absent with COX-2–selective drugs)	Inhibited platelet activation
	Propensity for bruising
	Increased risk of hemorrhage
Uterus	Prolongation of gestation
	Inhibit labor
Hypersensitivity	Vasomotor rhinitis
	Angioneurotic edema
	Asthma
	Urticaria
	Flushing
	Hypotension
	Shock
Vascular	Closure of ductus arteriosus

COX-1 & COX-2

Proc. Natl. Acad. Sci. USA
Vol. 88, pp. 2692–2696, April 1991
Biochemistry

Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing

(cyclooxygenase/Rous sarcoma virus/immediate-early gene/pp60$^{v\text{-}src}$)

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Contributed by R. L. Erikson, December 26, 1990

ABSTRACT **Rous sarcoma virus was shown to induce in chicken embryo fibroblasts (CEF) a 4.1-kilobase mRNA (designated CEF-147) encoding a 603-amino acid protein. Analysis of the protein sequence showed that it shared 59% amino acid identity with sheep prostaglandin G/H synthase, the enzyme that catalyzes the rate-limiting steps in the production of prostaglandins. Significant differences, at both the protein and mRNA levels, existed between the *src* oncogene product-inducible prostaglandin synthase and the protein isolated and cloned from sheep seminal vesicle, suggesting that the *src*-inducible prostaglandin synthase may be a new form of the enzyme. A distinguishing feature of *src*-inducible prostaglandin synthase mRNA is its low abundance in nonproliferating chicken embryo fibroblasts and its relatively high abundance in *src*-transformed cells. Additionally, the majority of the *src*-inducible prostaglandin synthase RNA present in nonproliferating cells was found to be nonfunctional because of the presence of an unspliced intron that separated the signal peptide from the remainder of the protein. Upon mitogenic stimulation, this intron was removed, resulting in the induction of fully-spliced CEF-147 mRNA.**

ies have been done on the relationship of prostaglandin synthesis and cell division, and it is now well established that many mitogens induce PGHS activity (4–11). Significantly, it has also been shown that some nonsteroidal antiinflammatory drugs exert antiproliferative and antitumor activities *in vitro* and *in vivo*, suggesting that PGHS plays an important role in regulating or promoting cell proliferation in some normal and neoplastically transformed cells (12–15).

RSV-inducible prostaglandin synthase encoded by the CEF-147 cDNA showed several important features that distinguished it from the only form of the enzyme thus far cloned, which was first isolated from sheep seminal vesicles (this sheep form is hereafter termed $PGHS_{ov}$) (16–18) and later cloned by cross-hybridization techniques in mouse (19) and human (20). The pp60$^{v\text{-}src}$-inducible form we term "$miPGHS_{ch}$" for mitogen-inducible $PGHS_{chicken}$.

Of the cDNAs isolated that encode $miPGHS_{ch}$, several contained a 553-base-pair (bp) unspliced intron located 17 amino aids from the amino terminus, which prohibited translation of the sequence. Northern blots showed that the majority of $miPGHS_{ch}$ mRNA in contact-inhibited, nontransformed CEF grown in low serum contained this intron and

COX-1 & COX-2

Proc. Natl. Acad. Sci. USA
Vol. 89, pp. 7384–7388, August 1992
Pharmacology

Human cyclooxygenase-2 cDNA

(prostaglandins/gene expression/angiogenesis/inflammation)

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Communicated by Philip Needleman, May 1, 1992

ABSTRACT **Cyclooxygenase (Cox), also known as prostaglandin (PG) H synthase (EC 1.14.99.1), catalyzes the rate-limiting step in the formation of inflammatory PGs. A major regulatory step in PG biosynthesis is at the level of Cox: growth factors, cytokines, and tumor promoters induce Cox activity. We have cloned the second form of the Cox gene (Cox-2) from human umbilical vein endothelial cells (HUVEC). The cDNA encodes a polypeptide of 604 amino acids that is 61% identical to the previously isolated human Cox-1 polypeptide. *In vitro* translation of the human (h)Cox-2 transcript in rabbit reticulocyte lysates resulted in the synthesis of a 70-kDa protein that is immunoprecipitated by antiserum to ovine Cox. Expression of the hCox-2 open reading frame in Cos-7 monkey kidney cells results in the elaboration of cyclooxygenase activity. hCox-2 cDNA hybridizes to a 4.5-kilobase mRNA species in HUVEC, whereas the hCox-1 cDNA hybridizes to 3- and 5.3-kilobase species. Both Cox-1 and Cox-2 mRNAs are expressed in HUVEC, vascular smooth muscle cells, monocytes, and fibroblasts. Cox-2 mRNA was preferentially induced by phorbol 12-myristate 13-acetate and lipopolysaccharide in human endothelial cells and monocytes. Together, these data demonstrate that the Cox enzyme is encoded by at least two genes that are expressed and differentially regulated in a variety of cell types. High-level induction of the hCox-2 transcript in mesenchymal-derived inflammatory cells suggests a role in inflammatory conditions.**

umbilical vein endothelial cells (HUVEC), we demonstrated that IL-1, an inhibitor of endothelial growth, induces the 3-kb Cox mRNA in a time- and dose-dependent manner (12). In contrast, heparin-binding growth factor 1 (HBGF-1), a potent mitogen for HUVEC, suppresses the Cox mRNA levels (13).

Recently, several cDNAs that are homologous to the Cox gene were cloned. Xie *et al.* (14) reported the cloning of a *src*-inducible cDNA, termed CEF-147; the 70-kDa deduced polypeptide encoded by the CEF-147 cDNA is homologous (59% identity) to the ovine, murine, and human Cox-1 sequences. In addition, Herschman and colleagues (15) reported the characterization of a 4.5-kb PMA-inducible immediate-early transcript, termed TIS10, from 3T3 cells. The murine TIS10 polypeptide also possessed significant (59%) sequence identity to the known Cox-1 sequences but was more closely related (82% identity) to the chicken Cox-2 (CEF147) polypeptide. While the deduced polypeptide sequences of these cDNAs contain amino acid residues essential for Cox enzyme activity, expression of these cDNAs into enzymatically active Cox protein has not been reported. Furthermore, the expression of the TIS10 mRNA was detected only in 3T3 and rat-1 cells (15).

In this communication, we describe the cloning, sequencing, and expression of human Cox-2 (hCox-2) cDNA from endothelial cells.† We also demonstrate that both hCox-1 and hCox-2 genes are expressed by a variety of normal cell types and are regulated differentially.

COX-1
COX-2

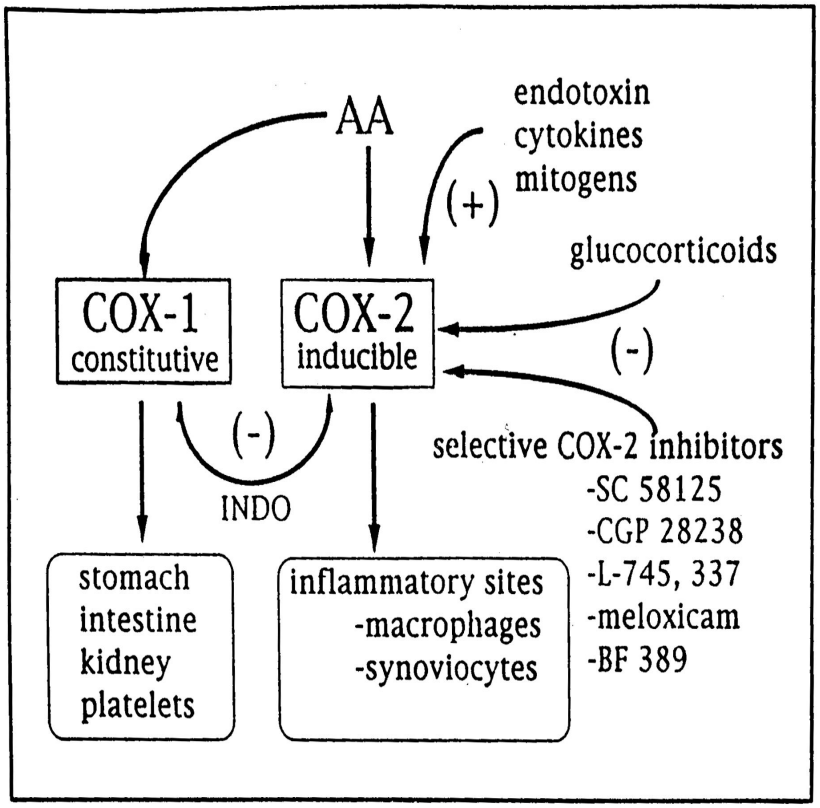
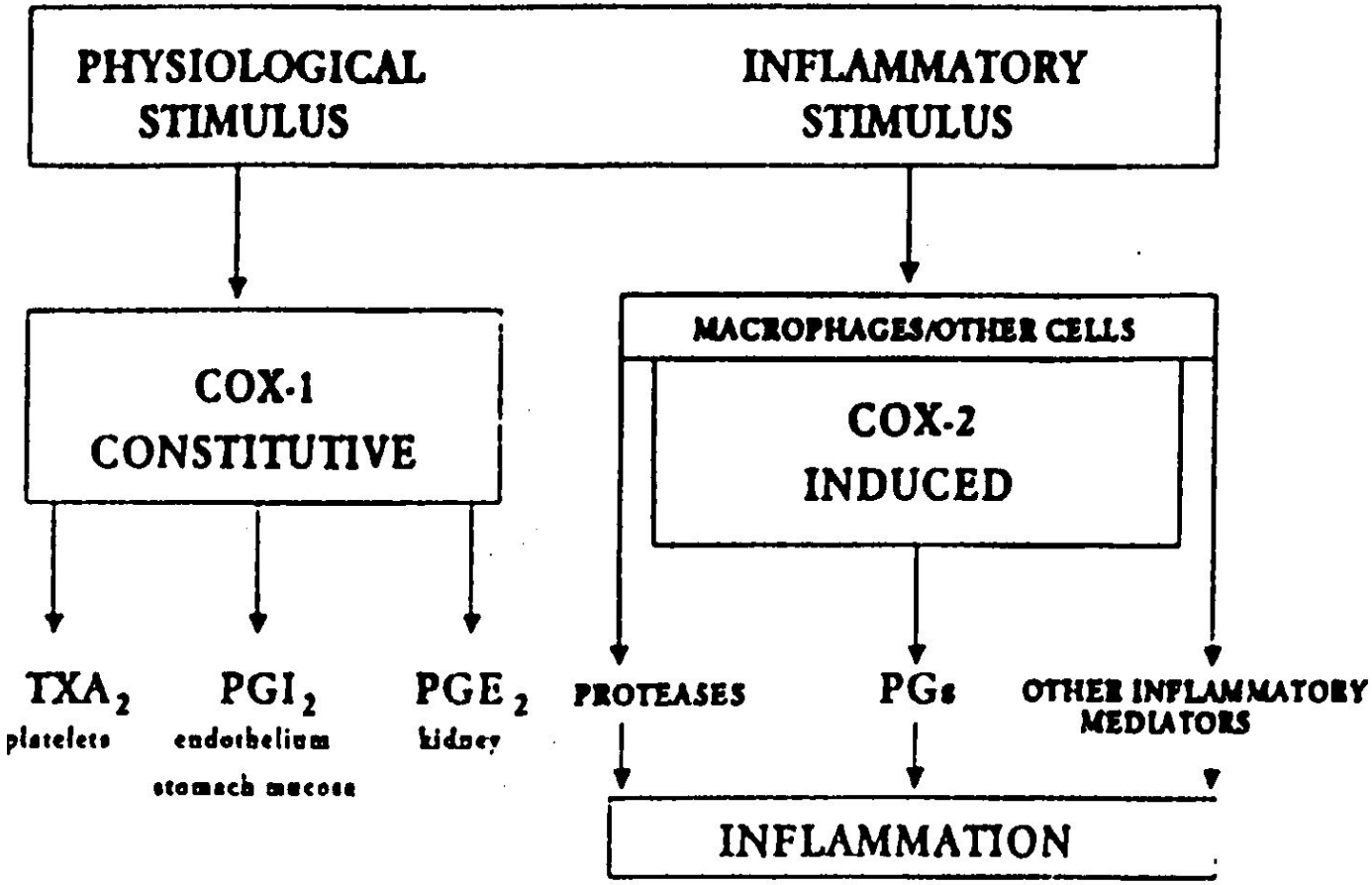
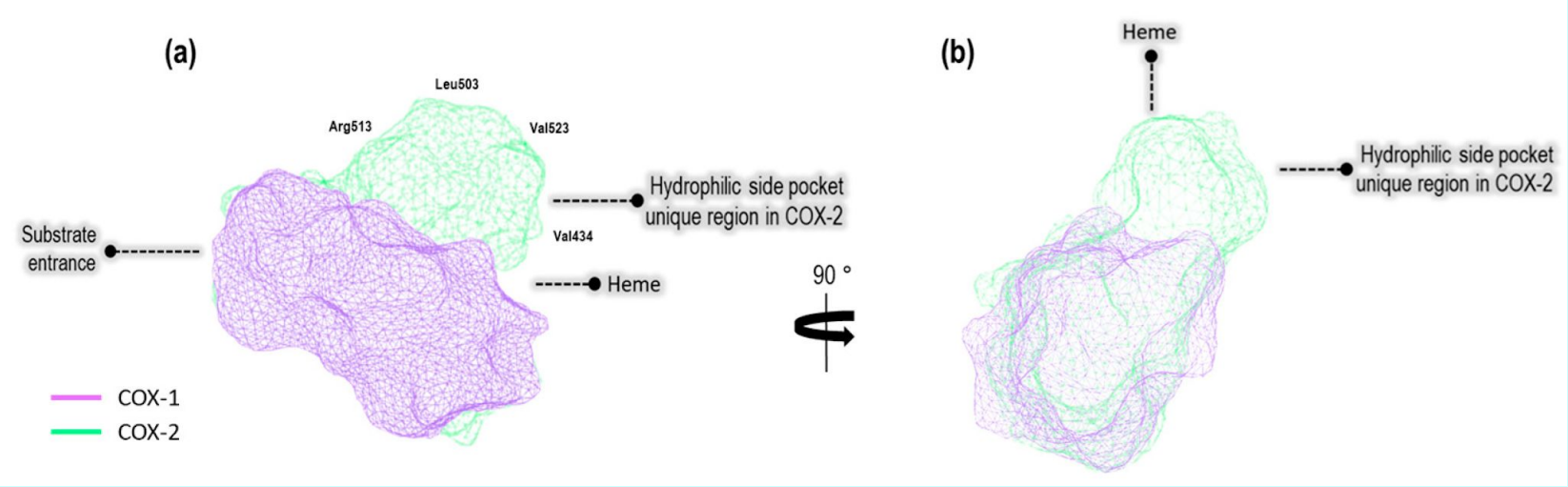


Fig. 2. Pathways of constitutive and inducible cyclooxygenase enzymes.

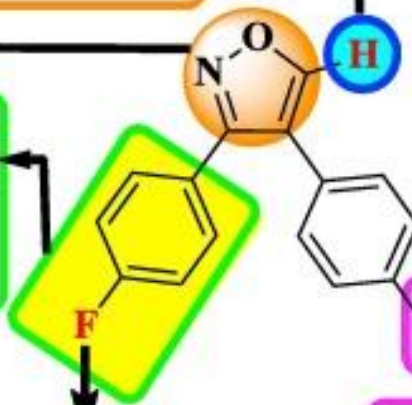


COXIB



Mono- and bicyclic compounds possessing two vicinal aryl moieties on the central heterocyclic ring system represent a major class of selective COX-2 inhibitors

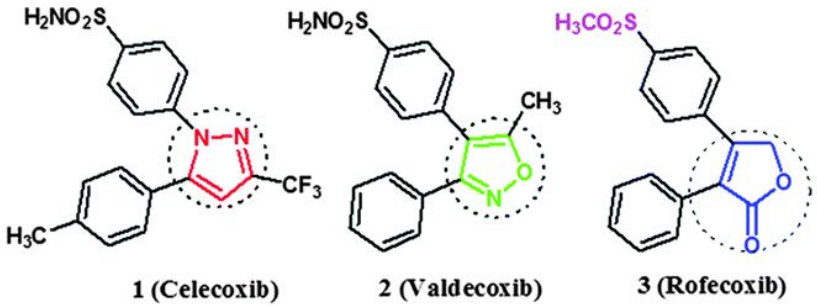
the 3,4-diaryl-substituted isoxazoles possessing a small substituent like H and Me displayed high COX-2 inhibition affinity



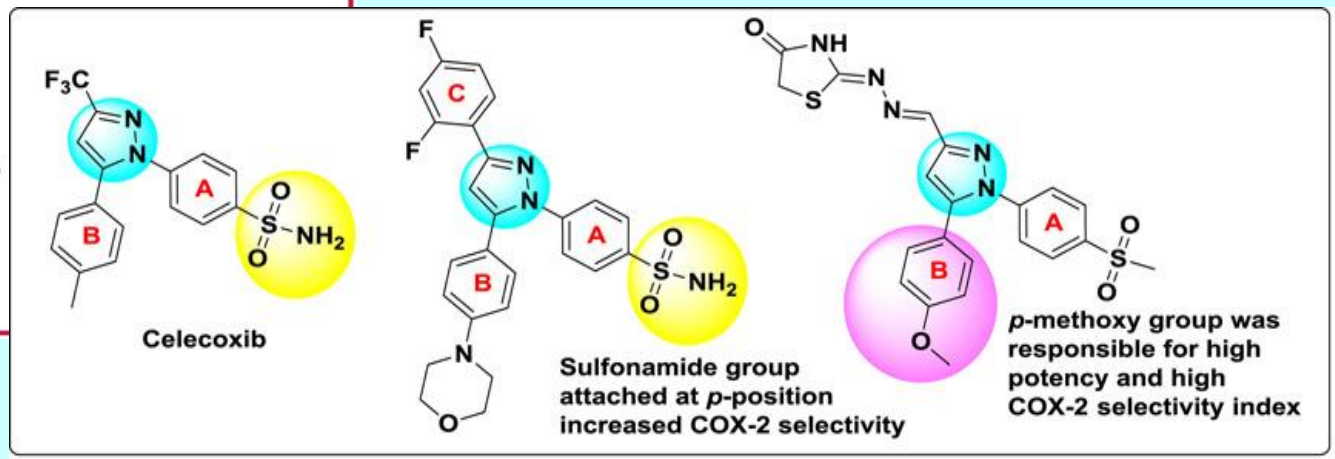
The introduction of a 4-fluorophenyl substituent resulted in retained high COX-2 affinity

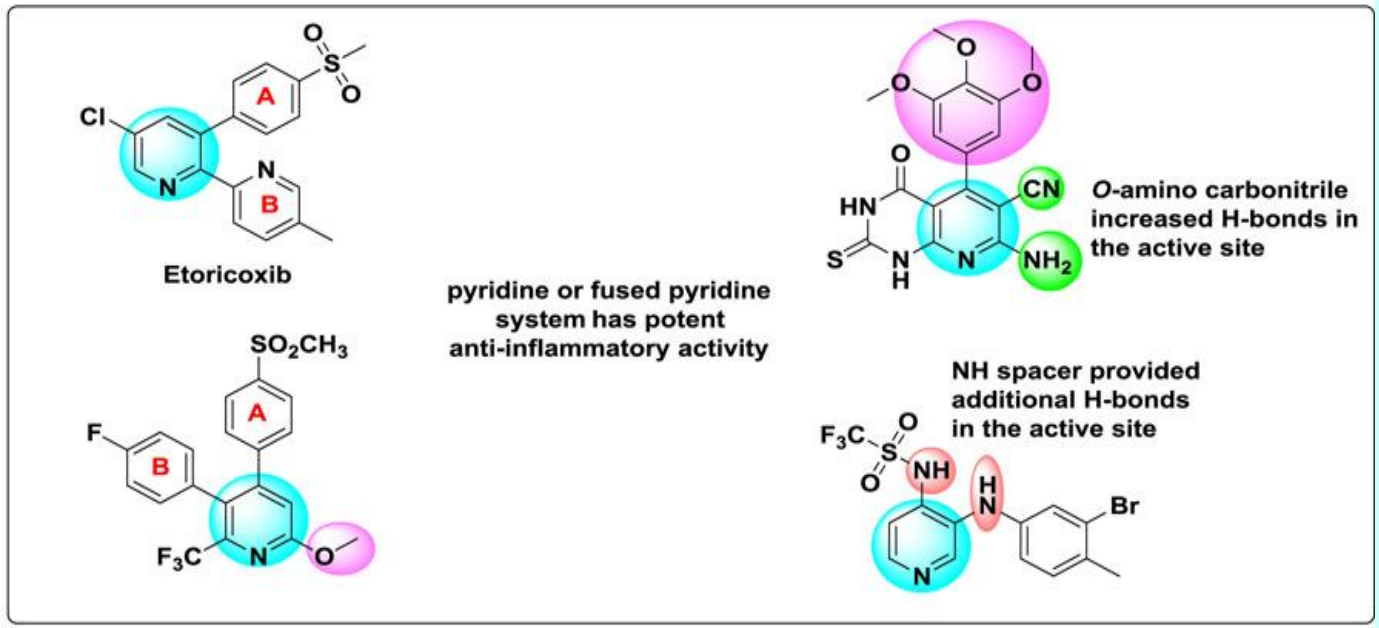
The presence of electron withdrawing groups like "F" favours selective and potent COX-2 inhibitory activity

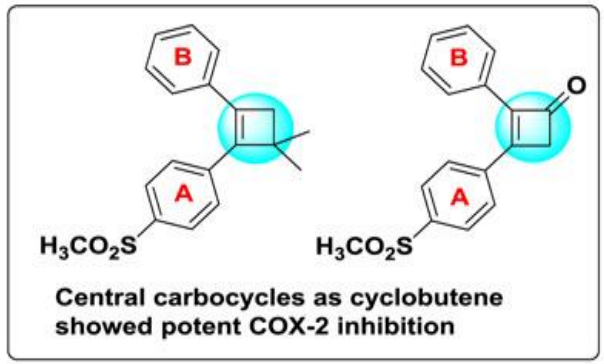
Compounds having SO_2NH_2 groups at *para* position were found to be the most selective COX-2 inhibitors

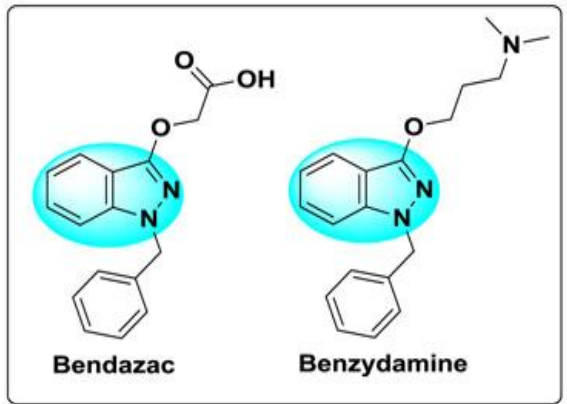

1 (Celecoxib)
2 (Valdecoxib)
3 (Rofecoxib)

COXIB


Celecoxib
Sulfonamide group attached at p-position increased COX-2 selectivity
p-methoxy group was responsible for high potency and high COX-2 selectivity index


Etoricoxib
pyridine or fused pyridine system has potent anti-inflammatory activity
O-amino carbonitrile increased H-bonds in the active site
NH spacer provided additional H-bonds in the active site


Central carbocycles as cyclobutene showed potent COX-2 inhibition


Bendazac
Benzydamine

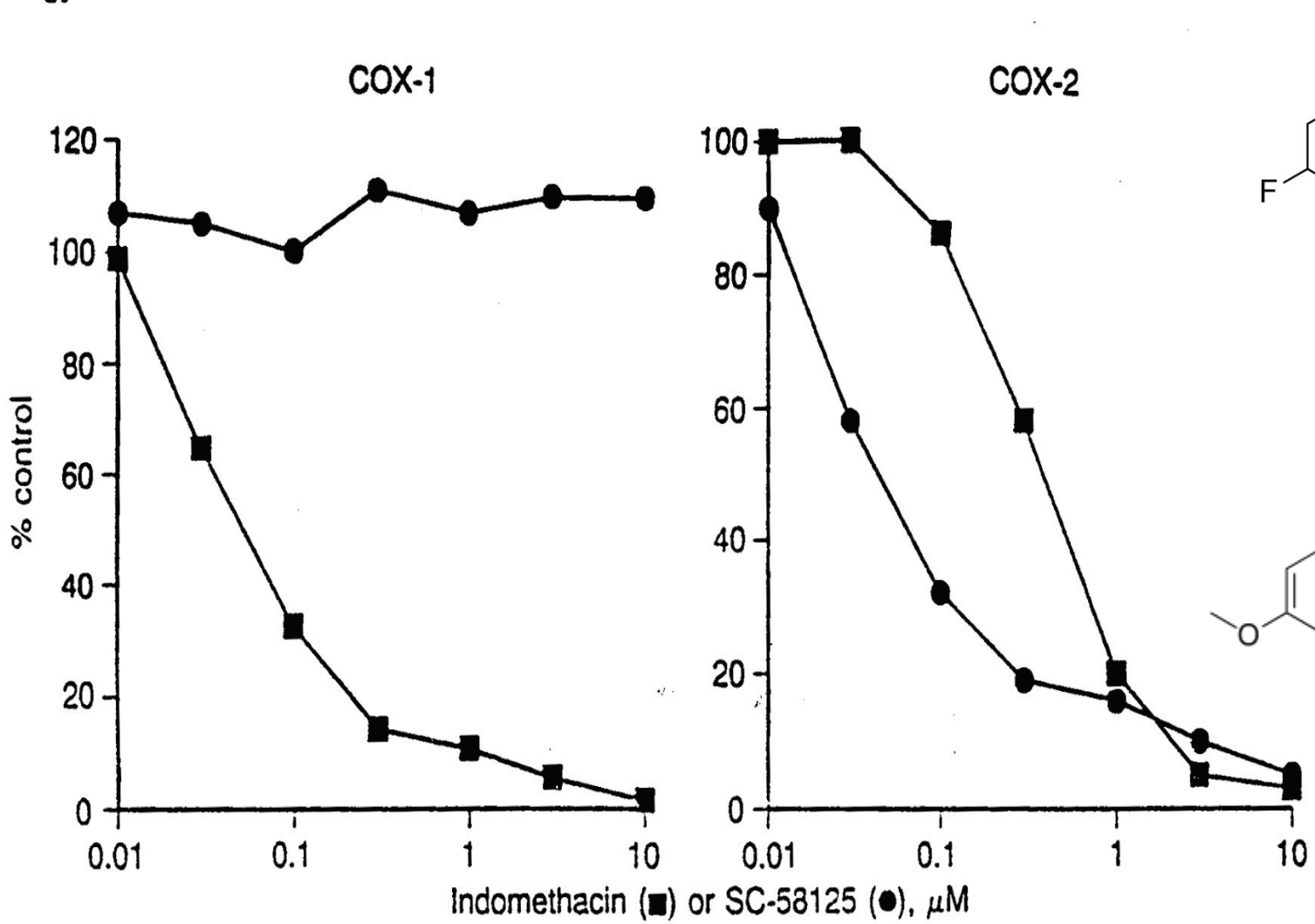
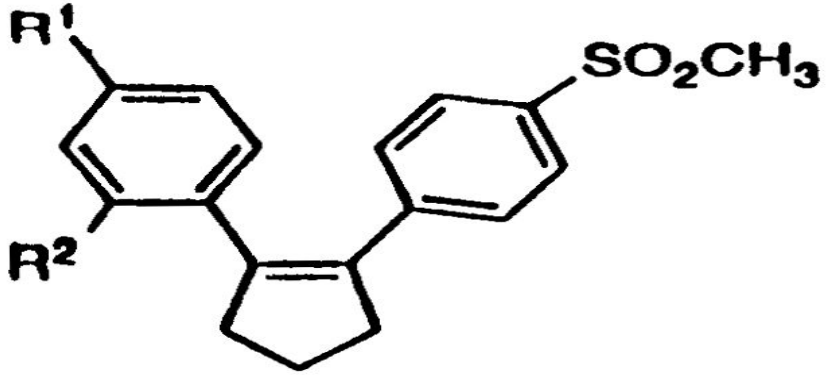


FIG. 4. SC-58125 selectively inhibits COX-2 versus COX-1. Mouse COX-1 and COX-2 were engineered into the baculovirus expression vector pVL1393; expression of COX protein was determined by assessing PG synthetic capability in homogenates from cells incubated 3 days with COX-1 or COX-2 baculovirus-infected Sf9 cells. Indomethacin (■) or SC-58125 (●) (0.001–10 μM) was preincubated with homogenates (2–10 μg of protein) for 10 min prior to addition of arachidonic acid (10 μM). PGE_2 formed during a 10-min incubation was detected by ELISA (Cayman Chemicals, Ann Arbor, MI).

Cyclopentene Cyclooxygenase Inhibitors



			IC$_{50}$ (μM)			
compd[a]	R^1	R^2	COX-1[b]	COX-2[b]	n[c]	selectivity
1a	F	H	>100	0.026	11	>3800
1b	OCH_3	H	9.92	0.005	3	1980
1c	Cl	H	>100	0.003	4	>33,000
1d	CH_3	H	>100	0.003	2	>33,000
1e	H	H	>100	2.25	2	>44
1f	CF_3	H	>100	0.865	2	>120
1g	Cl	Cl	>100	0.053	2	>1900
1h	CN	H	>100	77.9	3	>1.3
1i	CH_2OH	H	>100	3.20	1	>31
1j	CH_2OCH_3	H	>100	6.60	2	>15
1k	SCH_3	H	>100	0.221	4	>450
1l	F	CH_3	>100	0.075	3	>1300
NS-398			>10	0.01	3	>1000
indomethacin			0.2	1.2	10	0.167

[a] See ref 20. [b] See ref 21. [c] Number of assays conducted.

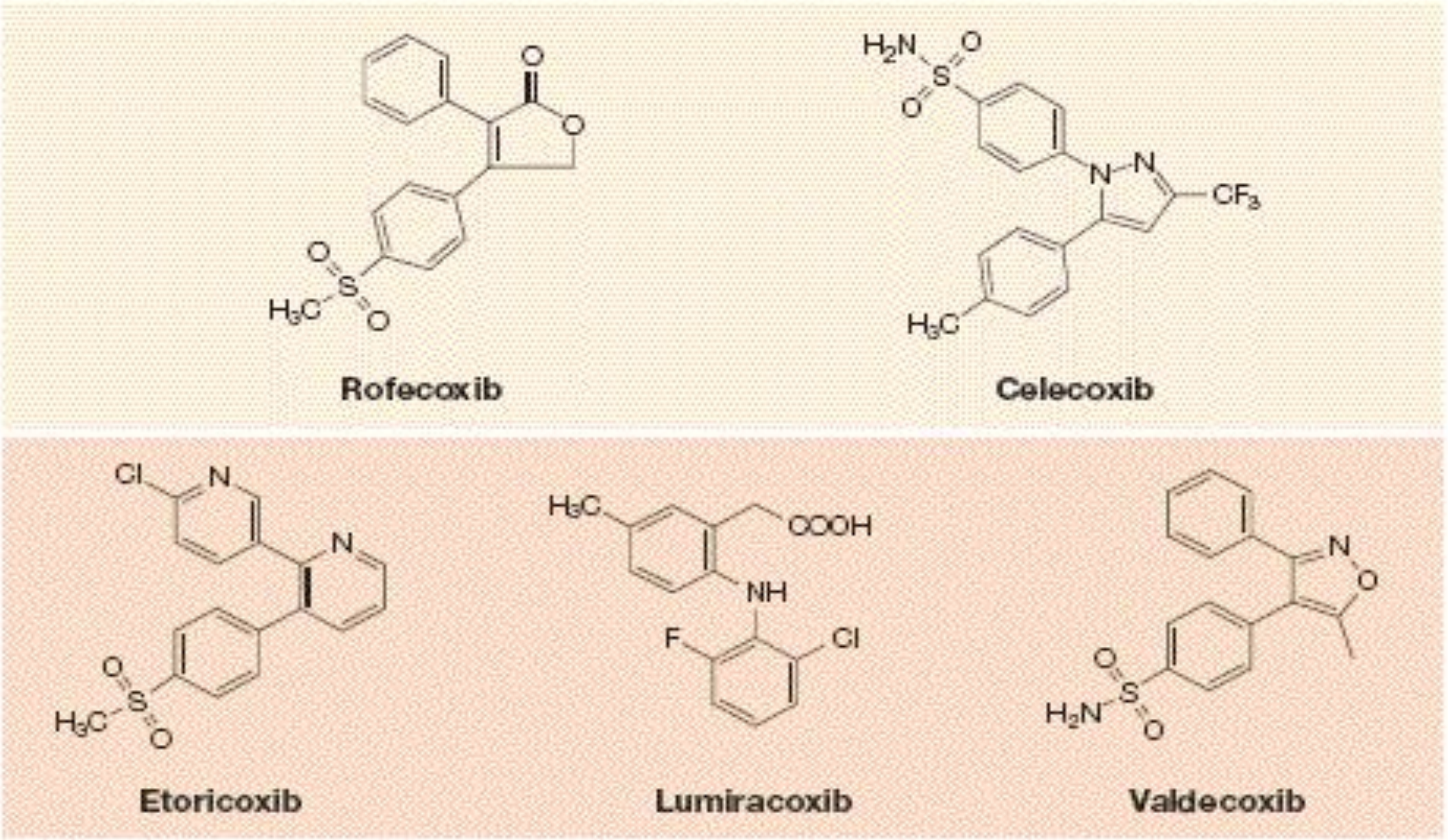


Figure 3 | **Selective inhibitors of COX-2.** The structures of first-generation (that is, rofecoxib and celecoxib) and second-generation (that is, etoricoxib, lumiracoxib and valdecoxib), purpose-designed selective inhibitors of cyclooxygenase-2 (COX-2).

VIGOR

COMPARISON OF UPPER GASTROINTESTINAL TOXICITY OF ROFECOXIB AND NAPROXEN IN PATIENTS WITH RHEUMATOID ARTHRITIS

CLAIRE BOMBARDIER, M.D., LOREN LAINE, M.D., ALISE REICIN, M.D., DEBORAH SHAPIRO, DR.P.H., RUBEN BURGOS-VARGAS, M.D., BARRY DAVIS, M.D., PH.D., RICHARD DAY, M.D., MARCOS BOSI FERRAZ, M.D., PH.D., CHRISTOPHER J. HAWKEY, M.D., MARC C. HOCHBERG, M.D., TORE K. KVIEN, M.D., AND THOMAS J. SCHNITZER, M.D., PH.D., FOR THE VIGOR STUDY GROUP

ABSTRACT

Background Each year, clinical upper gastrointestinal events occur in 2 to 4 percent of patients who are taking nonselective nonsteroidal antiinflammatory drugs (NSAIDs). We assessed whether rofecoxib, a selective inhibitor of cyclooxygenase-2, would be associated with a lower incidence of clinically important upper gastrointestinal events than is the nonselective NSAID naproxen among patients with rheumatoid arthritis.

Methods We randomly assigned 8076 patients who were at least 50 years of age (or at least 40 years of age and receiving long-term glucocorticoid therapy) and who had rheumatoid arthritis to receive either 50 mg of rofecoxib daily or 500 mg of naproxen twice daily. The primary end point was confirmed clinical upper gastrointestinal events (gastroduodenal perforation or obstruction, upper gastrointestinal bleeding, and symptomatic gastroduodenal ulcers).

Conclusions In patients with rheumatoid arthritis, treatment with rofecoxib, a selective inhibitor of cyclooxygenase-2, is associated with significantly fewer clinically important upper gastrointestinal events than treatment with naproxen, a nonselective inhibitor. (N Engl J Med 2000;343:1520-8.)

[Timeline: The Rise and Fall of Vioxx]

Gastrointestinal Toxicity With Celecoxib vs Nonsteroidal Anti-inflammatory Drugs for Osteoarthritis and Rheumatoid Arthritis

The CLASS Study: A Randomized Controlled Trial

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Theodore Pincus, MD
Andrew Whelton, MD
Robert Makuch, PhD
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James B. Lefkowith, MD
Kenneth M. Verburg, PhD
G. Steven Geis, PhD, MD

Context Conventional nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with a spectrum of toxic effects, notably gastrointestinal (GI) effects, because of inhibition of cyclooxygenase (COX)-1. Whether COX-2–specific inhibitors are associated with fewer clinical GI toxic effects is unknown.

Objective To determine whether celecoxib, a COX-2–specific inhibitor, is associated with a lower incidence of significant upper GI toxic effects and other adverse effects compared with conventional NSAIDs.

Design The Celecoxib Long-term Arthritis Safety Study (CLASS), a double-blind, randomized controlled trial conducted from September 1998 to March 2000.

Setting Three hundred eighty-six clinical sites in the United States and Canada.

Participants A total of 8059 patients (≥18 years old) with osteoarthritis (OA) or rheumatoid arthritis (RA) were enrolled in the study, and 7968 received at least 1 dose of study drug. A total of 4573 patients (57%) received treatment for 6 months.

Interventions Patients were randomly assigned to receive celecoxib, 400 mg twice per day (2 and 4 times the maximum RA and OA dosages, respectively; n=3987); ibuprofen, 800 mg 3 times per day (n=1985); or diclofenac, 75 mg twice per day (n=1996). Aspirin use for cardiovascular prophylaxis (≤325 mg/d) was permitted.

Main Outcome Measures Incidence of prospectively defined symptomatic upper GI ulcers and ulcer complications (bleeding, perforation, and obstruction) and other adverse effects during the 6-month treatment period.

Results For all patients, the annualized incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers for celecoxib vs NSAIDs were 0.76% vs 1.45% (P=.09) and 2.08% vs 3.54% (P=.02), respectively. For patients not taking aspirin, the annualized incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers for celecoxib vs NSAIDs were 0.44% vs 1.27% (P=.04) and 1.40% vs 2.91% (P=.02). For patients taking aspirin, the annualized incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers for celecoxib vs NSAIDs were 2.01% vs 2.12% (P=.92) and 4.70% vs 6.00% (P=.49). Fewer celecoxib-treated patients than NSAID-treated patients experienced chronic GI blood loss, GI intolerance, hepatotoxicity, or renal toxicity. No difference was noted in the incidence of cardiovascular events between celecoxib and NSAIDs, irrespective of aspirin use.

Conclusions In this study, celecoxib, at dosages greater than those indicated clinically, was associated with a lower incidence of symptomatic ulcers and ulcer complications combined, as well as other clinically important toxic effects, compared with NSAIDs at standard dosages. The decrease in upper GI toxicity was strongest among patients not taking aspirin concomitantly.

JAMA. 2000;284:1247-1255 www.jama.com

FOR PATIENTS WITH MUSCULOskeletal disorders, conventional nonsteroidal anti-inflammatory drugs (NSAIDs) are a mainstay of clinical care.[1-3] Well-established limitations of NSAID therapy, however, include the risk of developing significant injury to the upper gastrointestinal (GI) tract.[4-10] The annualized incidence rate of symptomatic GI ulcers and ulcer complications in NSAID users ranges from 2% to 4% (1%-2% for ulcer complications alone).[11-15] NSAID-related ulcer complications are estimated to lead to

For editorial comment see p 1297.

Author Affiliations and Financial Disclosures are listed at the end of this article.
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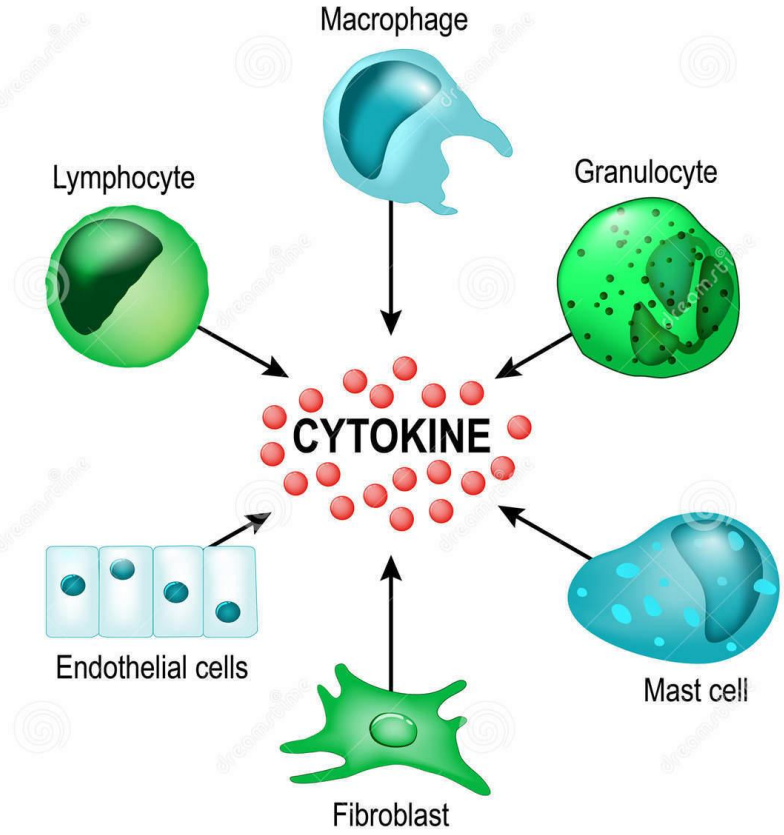
Table 4. Adverse Effects During the 6-Month Treatment Period*

Adverse Effects	All Patients: Celecoxib Group (n = 3987)	All Patients: NSAID Group (n = 3981)	Patients Not Taking Aspirin: Celecoxib Group (n = 3154)	Patients Not Taking Aspirin: NSAID Group (n = 3169)
Gastrointestinal				
Dyspepsia	575 (14.4)	640 (16.1)†	427 (13.5)	496 (15.7)†
Abdominal pain	387 (9.7)	522 (13.1)†	286 (9.1)	395 (12.5)†
Diarrhea	373 (9.4)	392 (9.8)	288 (9.1)	293 (9.2)
Nausea	277 (6.9)	370 (9.3)†	213 (6.8)	277 (8.7)†
Constipation	68 (1.7)	234 (5.9)†	48 (1.5)	172 (5.4)†
Total	**1250** (31.4)	**1465** (36.8)†	**942** (29.9)	**1127** (35.6)†
Withdrawals	345 (8.7)	427 (10.7)†	252 (8.0)	321 (10.1)†
Hepatic				
Elevated serum ALT	23 (0.6)	88 (2.2)†	18 (0.6)	68 (2.1)†
Elevated serum AST	18 (0.5)	73 (1.8)†	13 (0.4)	60 (1.9)†
Total	**24** (0.6)	**93** (2.3)†	**18** (0.6)	**72** (2.3)†
Withdrawals	2 (<0.1)	46 (1.2)†	2 (<0.1)	36 (1.1)†
Bleeding-related				
Anemia	81 (2.0)	175 (4.4)†	59 (1.9)	123 (3.9)†
Ecchymosis	28 (0.7)	32 (0.8)	22 (0.7)	26 (0.8)
Hematochezia	17 (0.4)	40 (1.0)†	11 (0.3)	29 (0.9)†
Total	**123** (3.1)	**238** (6.0)†	**90** (2.9)	**171** (5.4)†
Withdrawals	16 (0.4)	26 (0.7)	13 (0.4)	19 (0.6)
Renal				
Peripheral edema	113 (2.8)	138 (3.5)	90 (2.9)	108 (3.4)
Hypertension	66 (1.7)	90 (2.3)†	50 (1.6)	65 (2.1)
Increased creatinine level	28 (0.7)	48 (1.2)†	20 (0.6)	33 (1.0)
Total	**200** (5.0)	**263** (6.6)†	**155** (4.9)	**198** (6.2)†
Withdrawals	44 (1.1)	41 (1.0)	37 (1.2)	32 (1.0)
Cardiovascular				
Cerebrovascular accident	5 (0.1)	10 (0.3)	3 (<0.1)	5 (0.2)
Myocardial infarction	10 (0.3)	11 (0.3)	3 (<0.1)	4 (0.1)
Angina	24 (0.6)	22 (0.6)	10 (0.3)	7 (0.2)
Total	**37** (0.9)	**39** (1.0)	**16** (0.5)	**14** (0.4)
Withdrawals	12 (0.3)	13 (0.3)	9 (0.3)	5 (0.2)
Cutaneous				
Rash	218 (5.5)	103 (2.6)†	180 (5.7)	91 (2.9)†
Pruritus	91 (2.3)	59 (1.5)†	72 (2.3)	44 (1.4)†
Urticaria	22 (0.6)	14 (0.4)	18 (0.6)	13 (0.4)
Total	**298** (7.5)	**163** (4.1)†	**241** (7.6)	**136** (4.3)†
Withdrawals	109 (2.7)	49 (1.2)†	92 (2.9)	43 (1.4)†

*Data are given as No. (%) of patients. Categories are nonadditive; patients may have experienced more than 1 adverse event in each category. NSAID indicates nonsteroidal anti-inflammatory drug; ALT, alanine aminotransferase; and AST, aspartate aminotransferase.
†P≤.05 vs celecoxib group.

CITOCHINE E CHEMOCHINE

La fase effettrice dei meccanismi aspecifici di difesa e dell'immunità mediata dai linfociti T nei confronti di microrganismi esterni, come virus e batteri, è in gran parte mediata da proteine con azione di tipo ormonale, denominate **CITOCHINE**

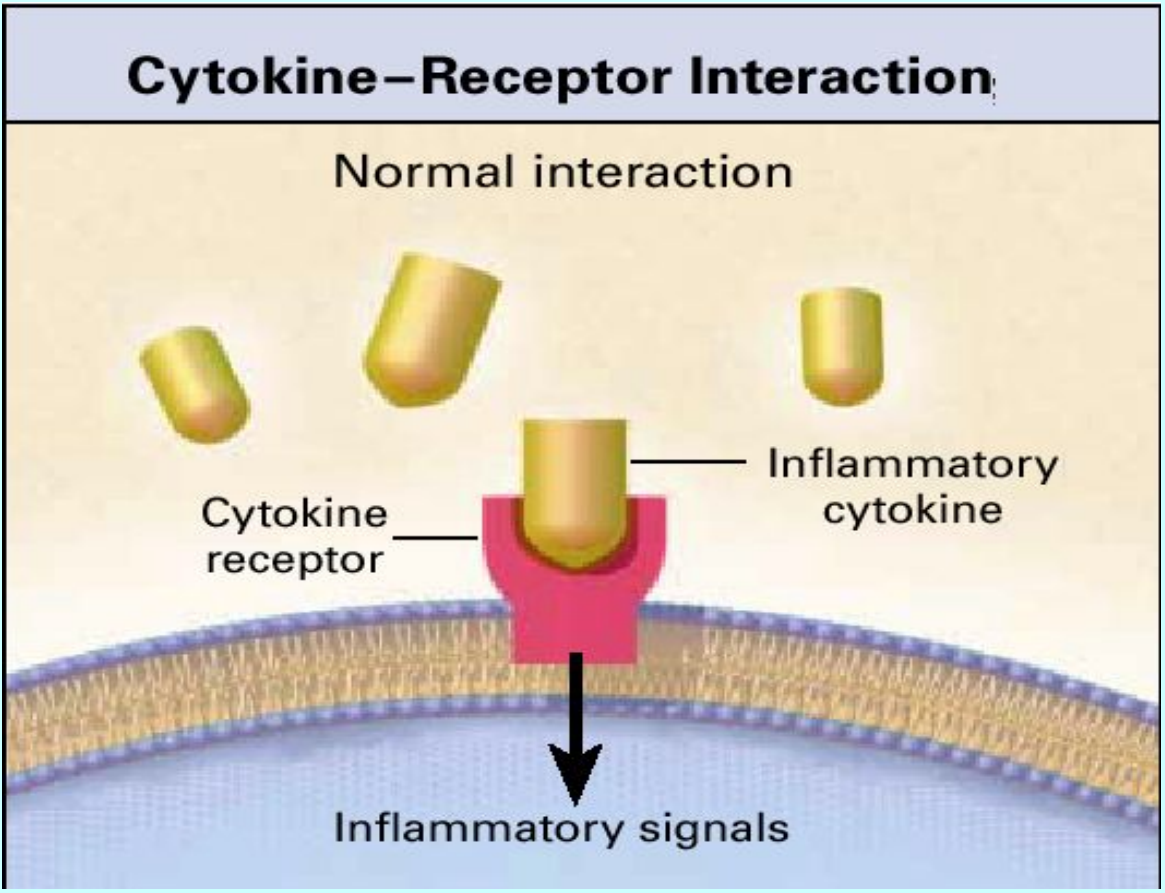


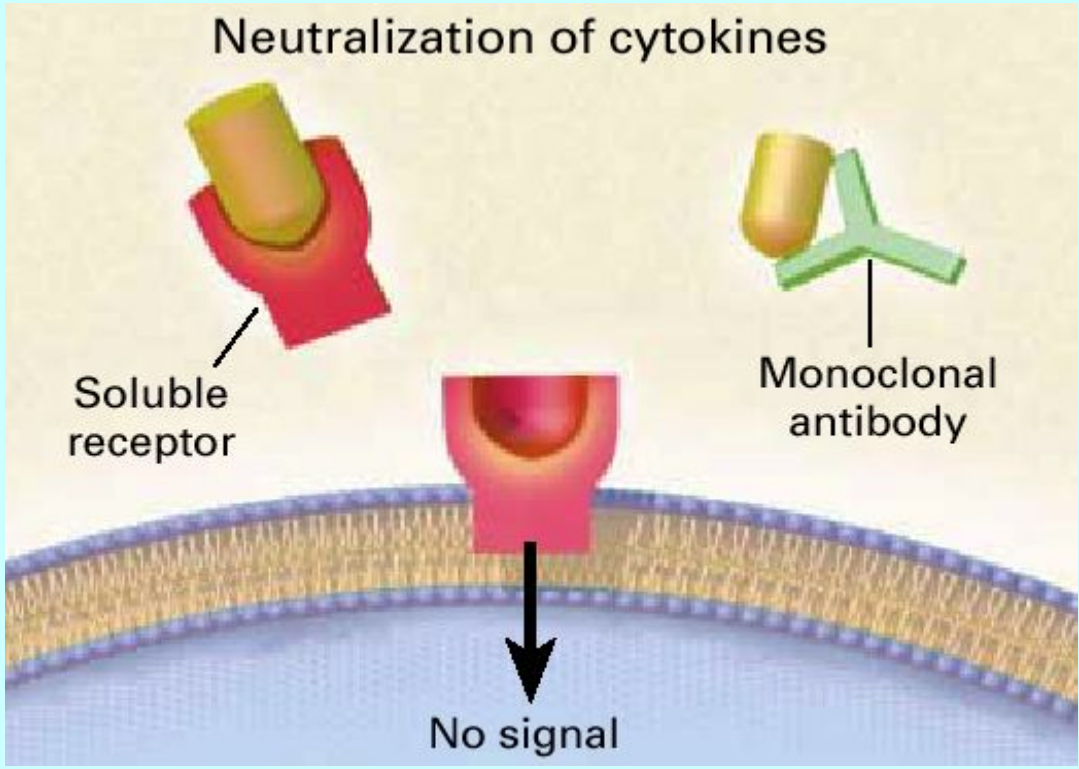
Le citochine attivano la risposta infiammatoria

CARATTERISTICHE GENERALI DELLE CITOCHINE

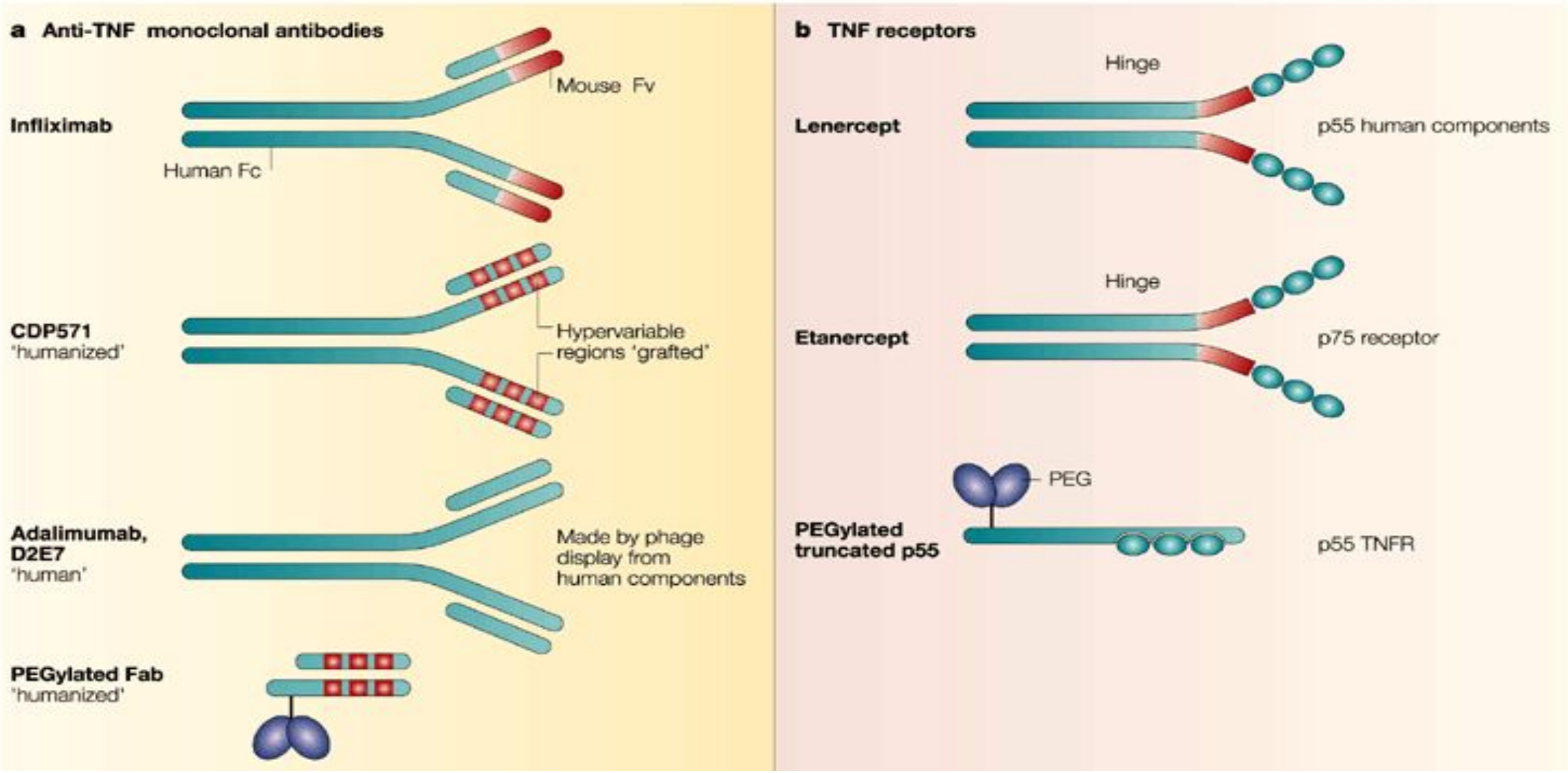
- Le citochine sono piccole proteine (circa 25 KDa) con funzione di regolazione sulle risposte immunitarie e infiammatorie. Interleuchine (IL), Chemochine, Interferone γ, Trasforming Grow Factor ß (TGF-ß), Tumor Necrosis Factor (TNF)
- Sono riconosciute da recettori specifici presenti sulla cellula bersaglio
- Sono secrete da diversi tipi di cellule (prevalentemente macrofagi e linfociti T)
- La secrezione delle citochine non è costitutiva, ma indotta per un breve periodo

FARMACI BIOLOGICI ANTI-TNF



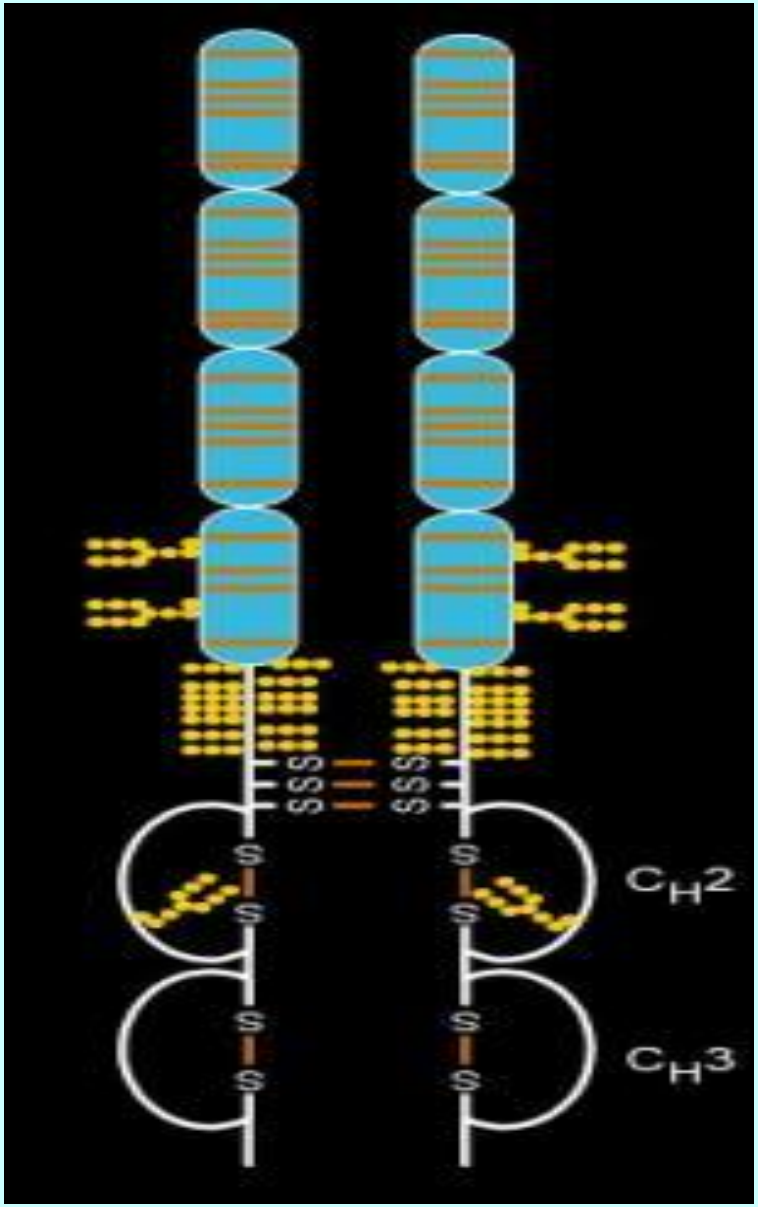


FARMACI BIOLOGICI ANTI-TNF



a) Monoclonal antibodies. **Infliximab** is 'chimeric' — it is three-quarters human (constant region; Fc) and one-quarter mouse (variable region; Fv) (sold as Remicade by Centocor/J&J, Schering-Plough). **CDP571** (Celltech) is 'humanized' — it is a human antibody with grafted mouse hypervariable regions. **D2E7** (Abbott Laboratories) is 'human' — it is made by phage display from human components. The **PEGylated Fab** is produced by Celltech (Pharmacia).
b) TNF receptors (TNFRs). **Lenercept** (Roche) is a human TNFR p55 dimer that is fused to human IgG Fc. **Etanercept** is a human TNFR p75 dimer that is fused to human IgG Fc (sold as Enbrel; Wyeth/Immunex). The **PEGylated truncated human TNFR p55 monomer** is produced by Amgen. PEG, polyethylene glycol; TNF, tumour-necrosis factor.

ETANERCEPT (Enbrel)



L'etanercept è un farmaco per il trattamento di malattie a carattere autoimmunitario che agisce interferendo con l'attività del TNF.

L’etanercept è una proteina di fusione, ottenuta tramite tecniche del DNA ricombinante, ottenuta dall'unione del recettore umano p75 per il fattore TNF-α con la frazione Fc dell’immunoglobulina umana IgG1. La proteina funziona da recettore solubile per il TNF-α e possiede un’affinità di legame per il TNF-α più alta di quella degli altri recettori solubili.
È una molecola complessa, dall'alto peso molecolare, circa 150 KDa, che si lega al TNFα andando ad inibire la sua attività nel processo evolutivo dell'infiammazione, sia nell'uomo che negli animali.
È un farmaco indicato per la cura della psoriasi, dell’artrite psoriasica dell’artrite reumatoide, della spondilite anchilosante e, potenzialmente, da qualsiasi altro processo mediato dal TNFα.

SVANTAGGI

- Costo (Etanercept 10.000 €/anno, Infliximab 13.000-18.000 €/anno, Adalimumab 14.000 €/anno, 2015)
- Ricomparsa dei sintomi alla sospensione
- Problemi con il sistema immunitario in caso di particolari infezioni e alcuni tumori.
- Analisi dati a lungo termine (sia per efficacia che per eventi indesiderati)