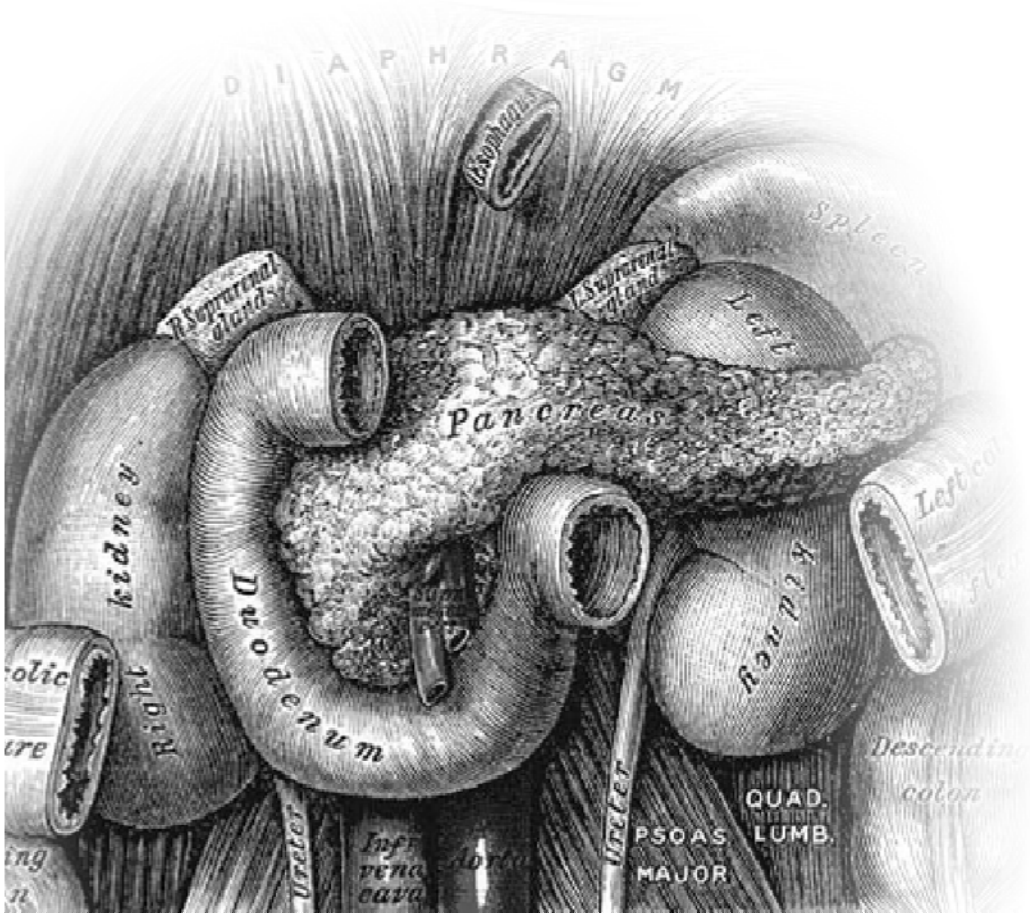
Paper de les citocines i altres mediadors en la PA greu



Daniel Closa Autet
CSIC, IDIBAPS, Hospital Clínic
Barcelona

ACUTE PANCREATITIS:

A CONSIDERATION OF PANCREATIC HEMORRHAGE, HEMORRHAGIC, SUPPURATIVE, AND GANGRENOUS PANCREATITIS, AND OF DISSEMINATED FAT-NECROSIS.

The Middleton-Goldsmith Lecture for 1889.

BY

REGINALD H. FITZ, M.D.,

Shattuck Professor of Pathological Anatomy in Harvard University, and Physician to the Massachusetts General Hospital.

BOSTON

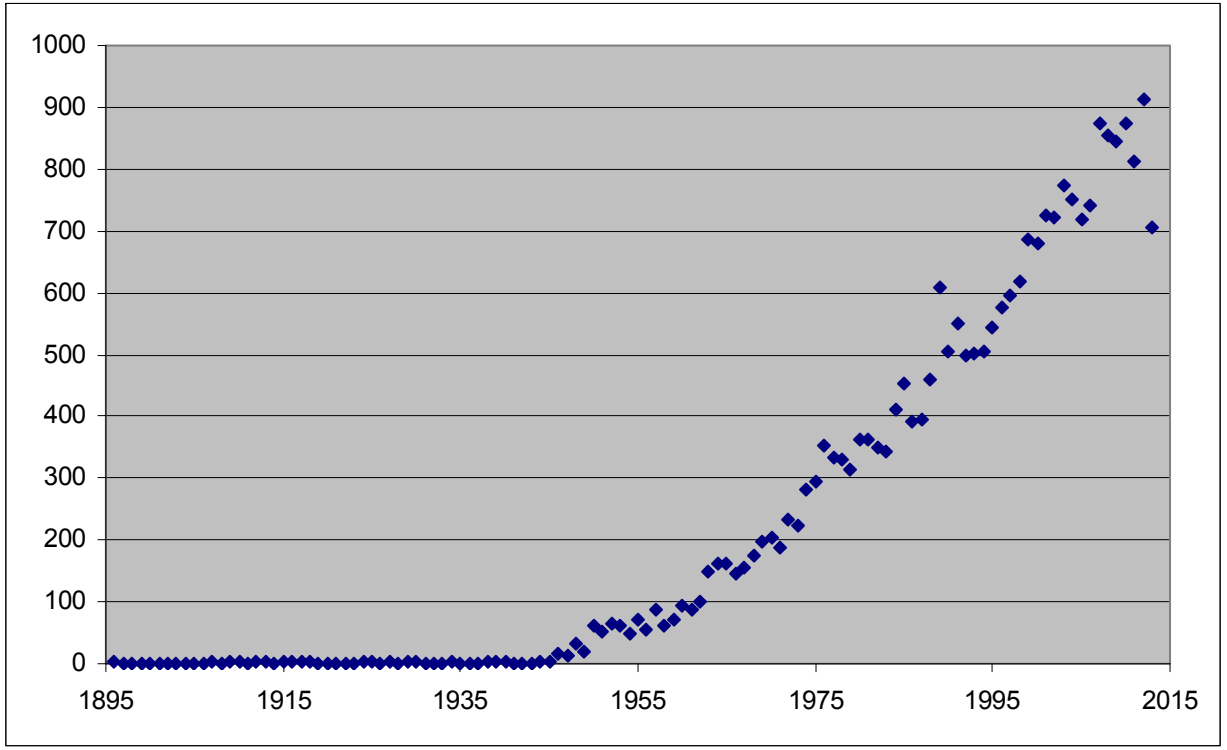
CUPPLES AND HURD, PUBLISHERS

The Algonquin Press

1889

“Acute pancreatitis”

25675 articles (1896-2013)



BRITISH MEDICAL JOURNAL:

BEING THE JOURNAL OF THE BRITISH MEDICAL ASSOCIATION.

EDITED FOR THE ASSOCIATION BY ERNEST HART.

LONDON: SATURDAY, JULY 4, 1896.

CLINICAL LECTURE
ON A
CASE OF ACUTE PANCREATITIS.

Delivered at the Middlesex Hospital

By W. CAYLEY, M.D., F.R.C.P.,
Physician to the Hospital.

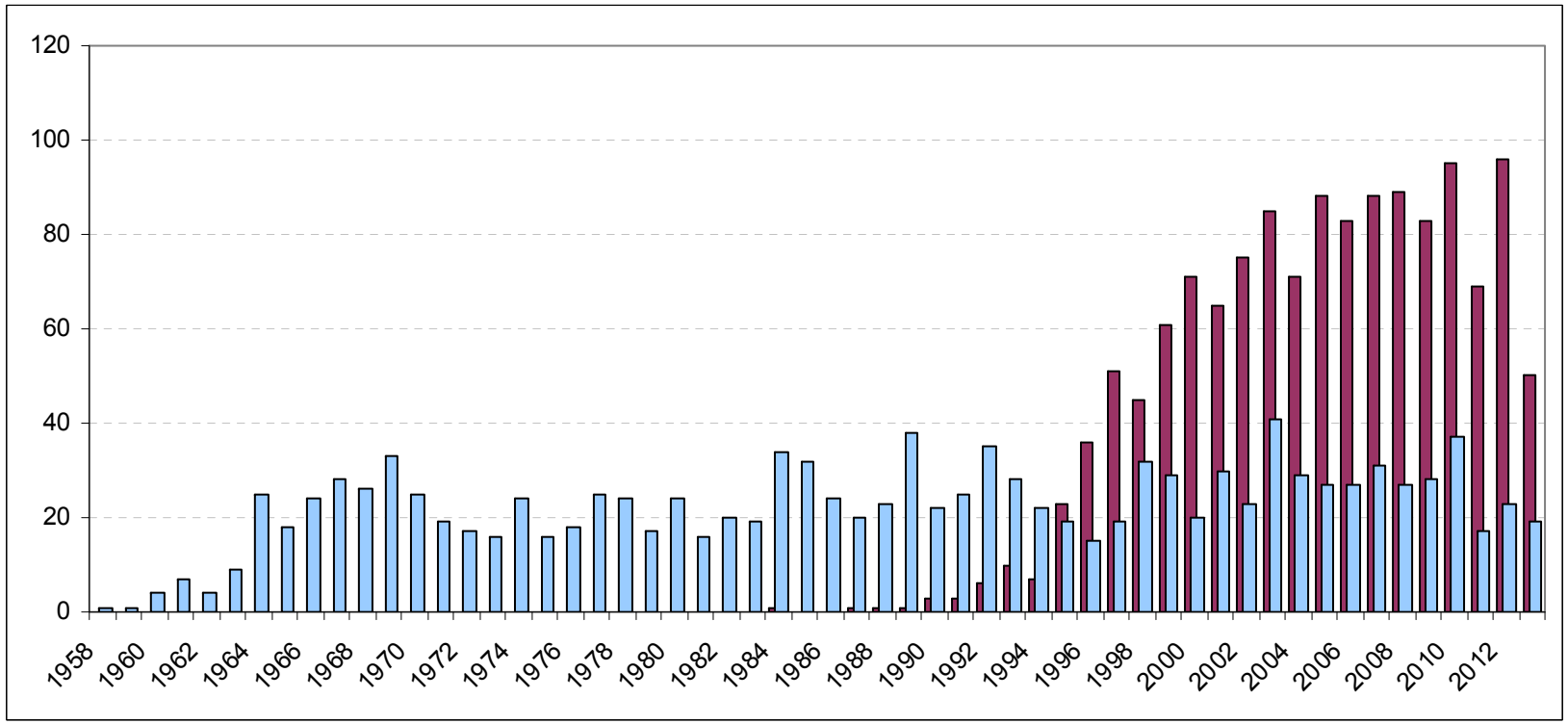
The characteristic symptoms, then, of the disease are these—epigastric pain and tenderness, which may as in this case be at first only of moderate intensity, and resemble the pain of gastric catarrh, but may be very severe from the outset; then vomiting, but the vomit does not present the characters of the regurgitant vomiting of intestinal obstruction. There is usually constipation, but sometimes diarrhœa; there may be fulness or swelling in the epigastrium, but no general distension or any signs of the presence of gas in the abdominal cavity. The tenderness is mostly limited to the epigastric region. Fever is inconstant, and with the collapse the temperature falls. The fatal collapse may set in as early as the second day, more commonly on the third or fourth.

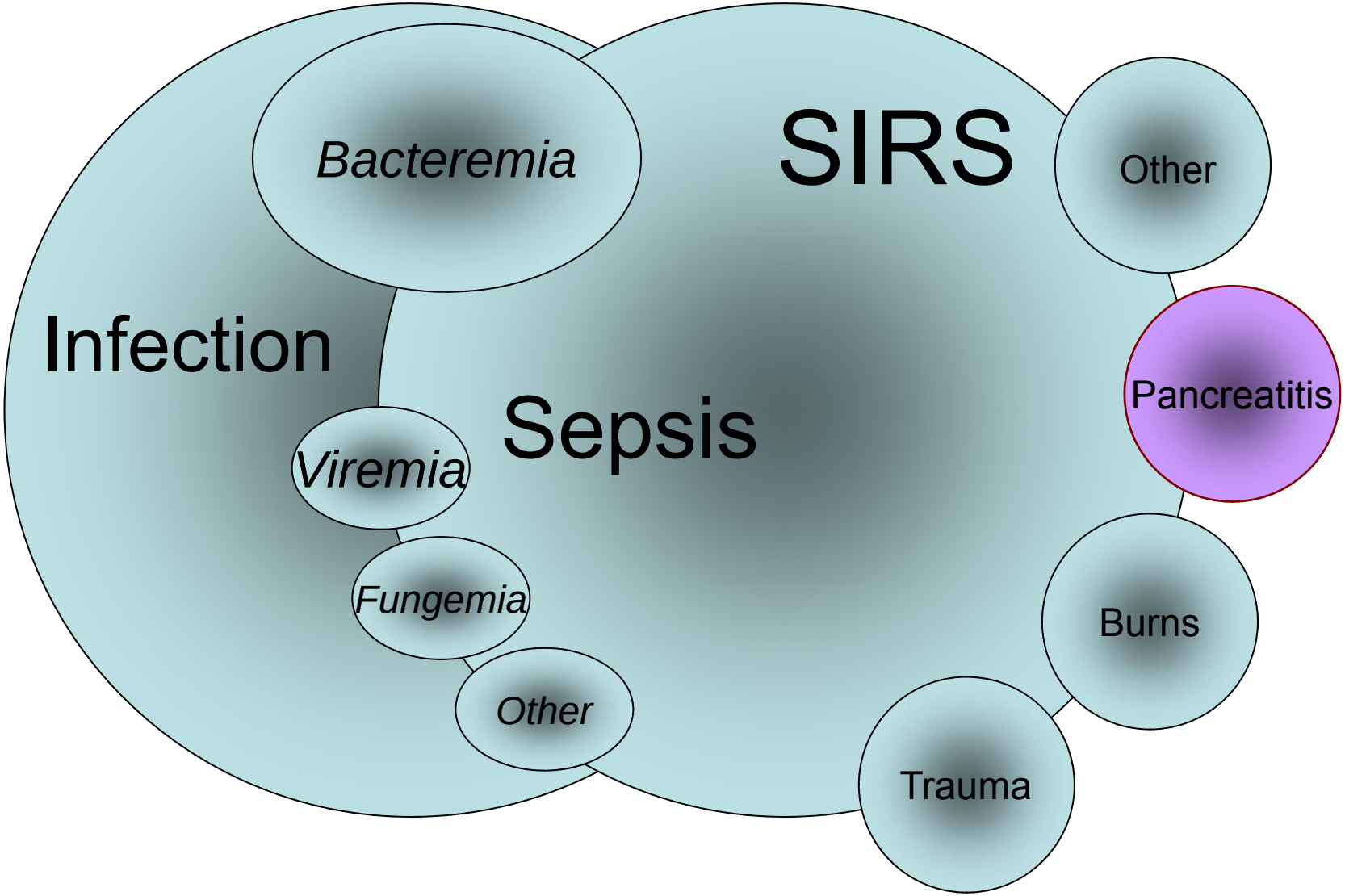
The last point to be considered is the treatment, about which there is little to be said. We have no means of controlling an acute internal infective inflammation; we can only aim at counteracting the effects and obviating the tendency to death.

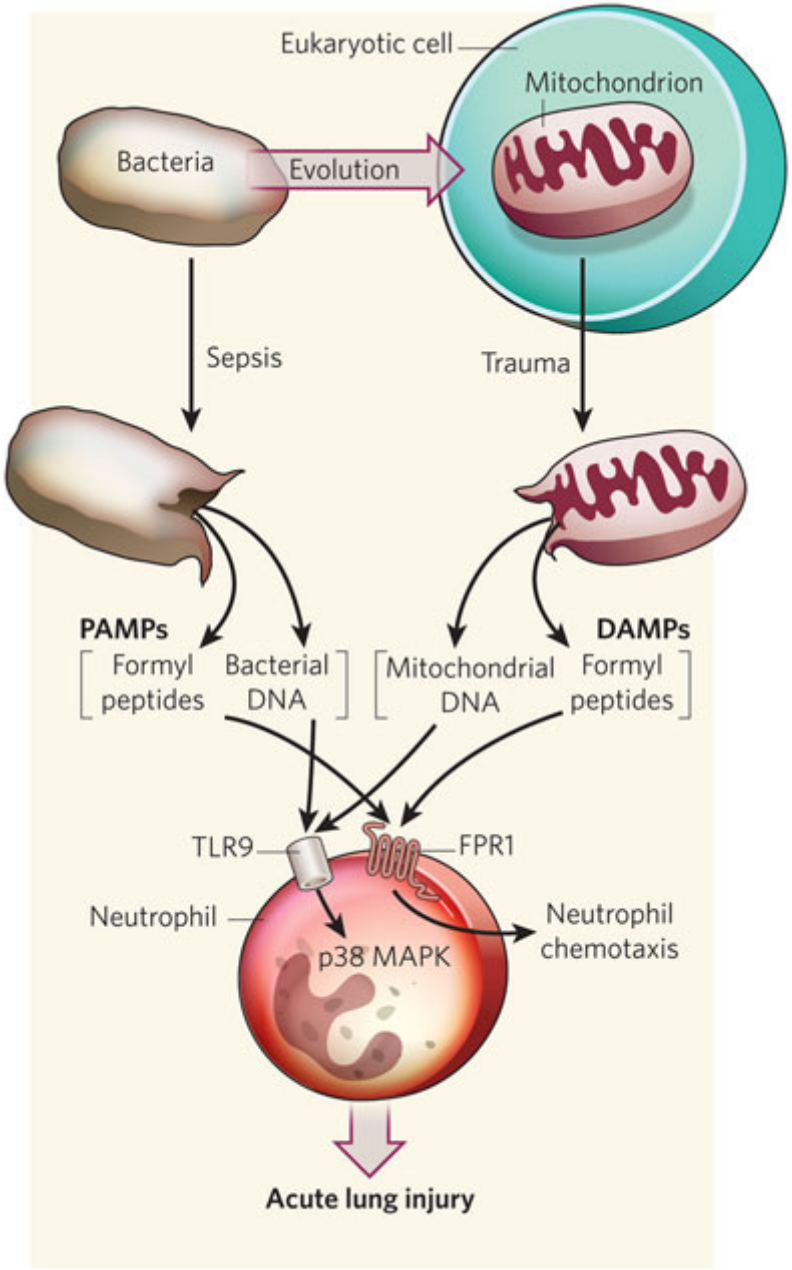
The fatal collapse in these cases is probably to be attributed to interference with the functions of the great sympathetic ganglia and consequent vasomotor paralysis of the mesenteric vessels and the draining into them of a large part of the blood, together with cardiac inhibition, and the only chance would be to tide the patient over this dangerous period and give time for the inflammation to subside or become limited; in the suppurative or even the gangrenous form this appears to take place. We must then use those means which are usually employed to combat collapse, alcoholic stimulants administered by the mouth or rectum, hypodermic injections of ether and strychnine, morphine to relieve pain; we might perhaps with advantage have recourse to these other remedies

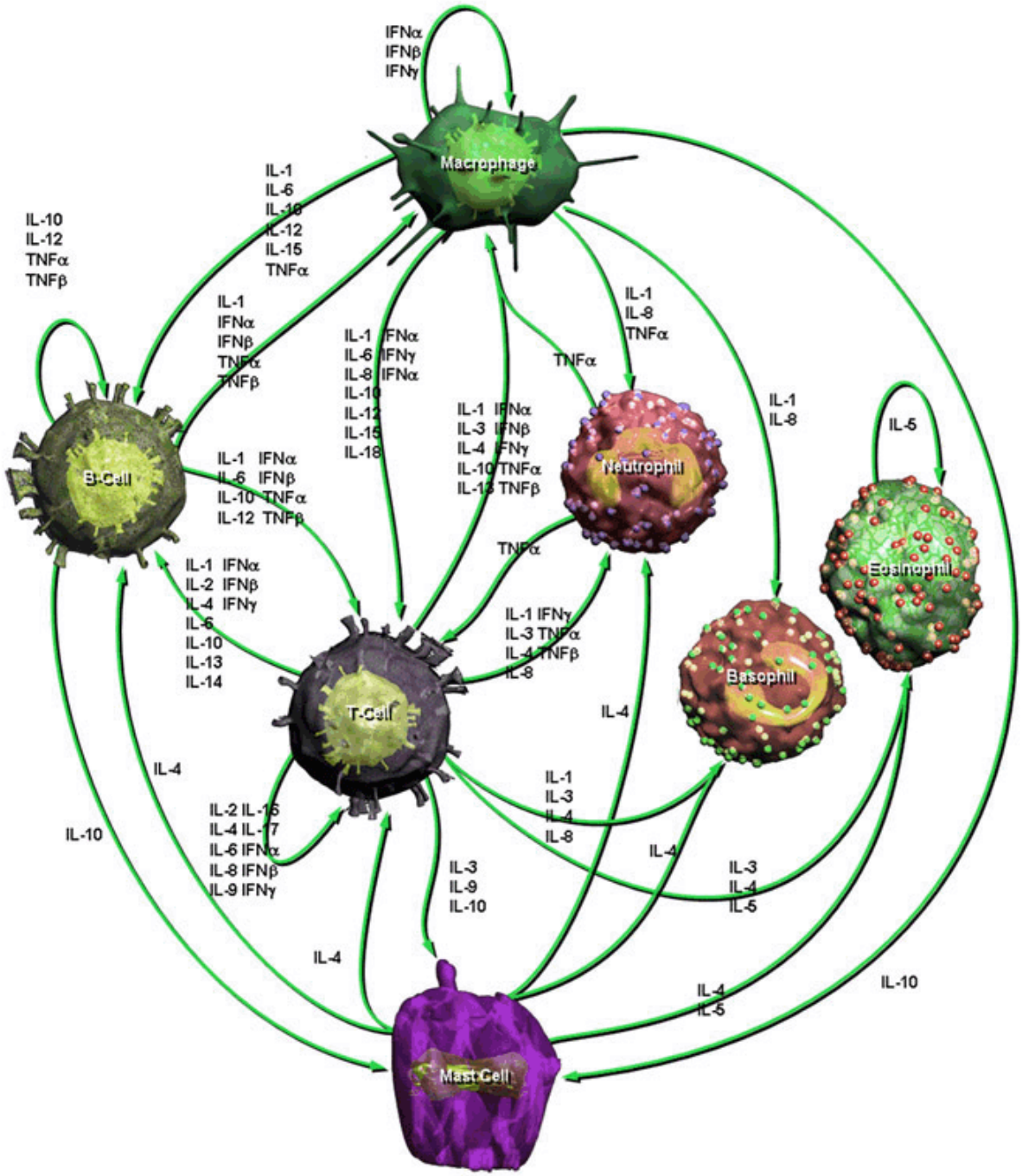
AP + protease inhibitors

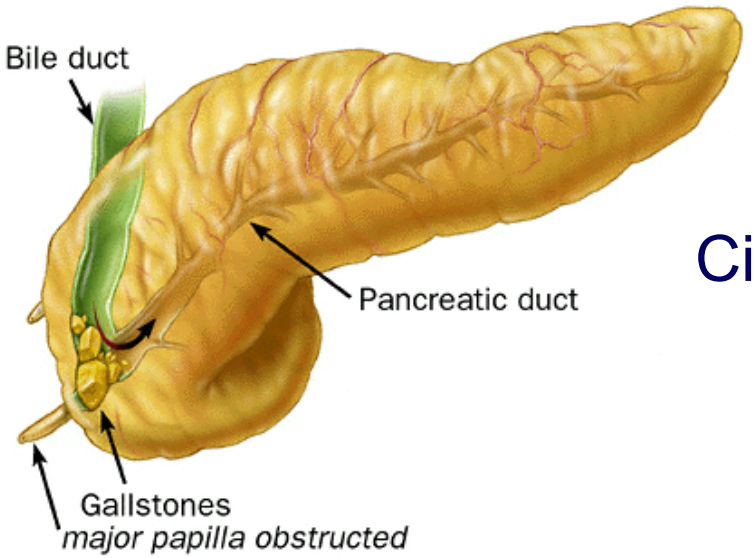
AP + cytokines




Bacteremia
SIRS
Other
Infection
Pancreatitis
Sepsis
Viremia
Fungemia
Burns
Other
Trauma


Eukaryotic cell
Mitochondrion
Bacteria
Evolution
Sepsis
Trauma
PAMPs
Formyl peptides
Bacterial DNA
Mitochondrial DNA
Formyl peptides
DAMPs
TLR9
FPR1
Neutrophil
p38 MAPK
Neutrophil chemotaxis
Acute lung injury


IFNα
IFNβ
IFNγ
Macrophage
IL-1
IL-6
IL-10
IL-12
IL-15
TNFα
IL-10
IL-12
TNFα
TNFβ
IL-1
IFNα
IFNβ
TNFα
TNFβ
IL-1 IFNα
IL-6 IFNγ
IL-8 IFNα
IL-10
IL-12
IL-15
IL-18
IL-1
IL-8
TNFα
TNFα
IL-1 IFNα
IL-3 IFNβ
IL-4 IFNγ
IL-10 TNFα
IL-12 TNFβ
IL-1
IL-8
IL-5
B-Cell
IL-1 IFNα
IL-6 IFNβ
IL-10 TNFα
IL-12 TNFβ
Neutrophil
Eosinophil
TNFα
IL-1 IFNα
IL-2 IFNβ
IL-4 IFNγ
IL-6
IL-10
IL-13
IL-14
IL-1 IFNγ
IL-3 TNFα
IL-4 TNFβ
IL-8
T-Cell
Basophil
IL-4
IL-4
IL-1
IL-3
IL-4
IL-8
IL-10
IL-2 IL-15
IL-4 IL-17
IL-6 IFNα
IL-8 IFNβ
IL-9 IFNγ
IL-4
IL-3
IL-9
IL-10
IL-3
IL-4
IL-5
IL-4
IL-4
IL-5
IL-10
Mast Cell



Pancreatic enzymes

Lipase
Amilase
Trypsin
Phospholipase

Citokines

TNFα
IL-1β
IL-4
IL-6
IL-8
IL-10
IL-11
IL-18
IL-22

Chemokines

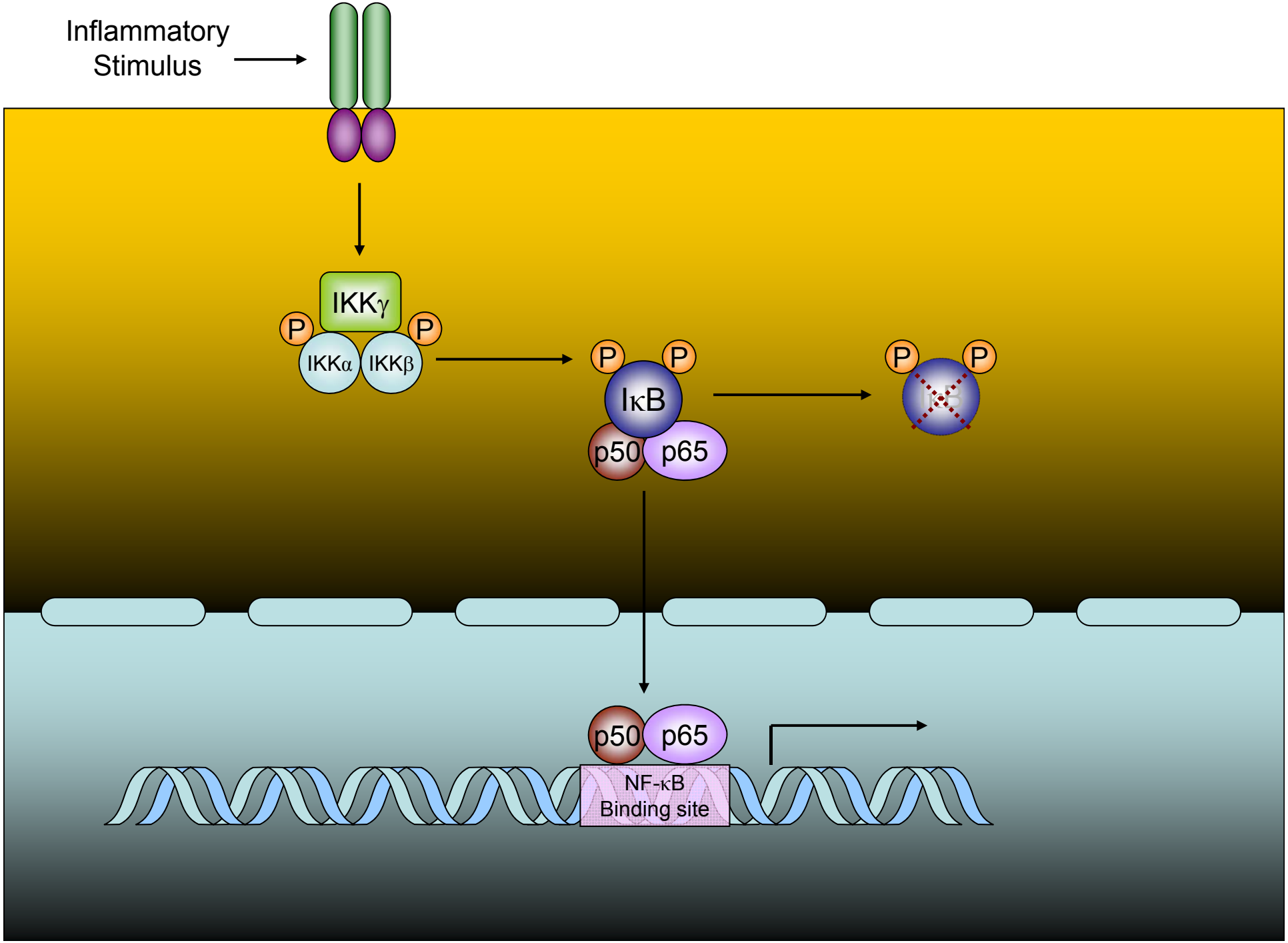
MCP-1
CINC
MIP-2
RANTES

Eicosanoids

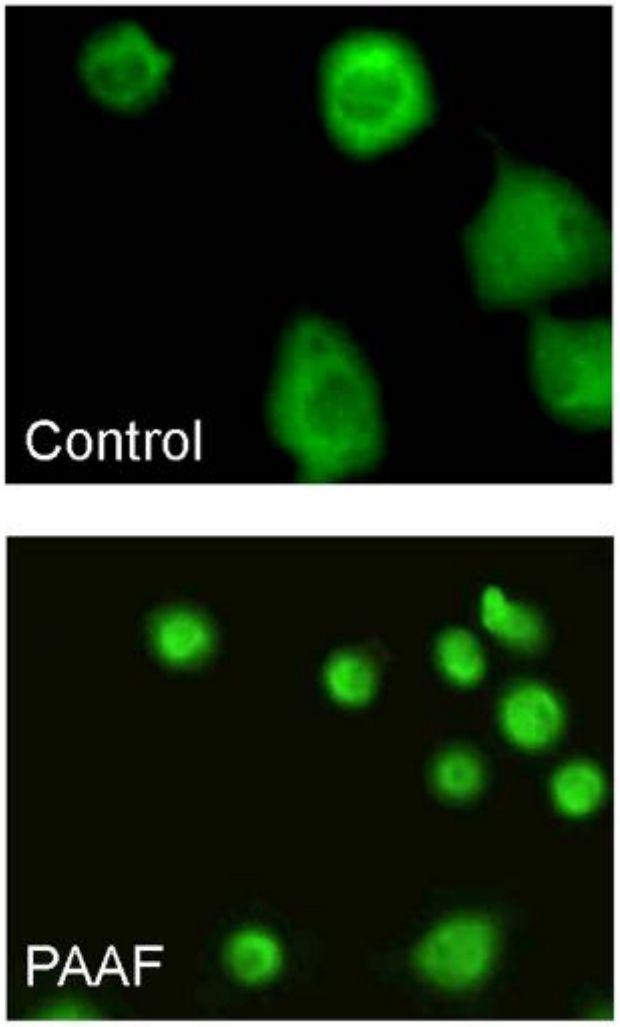
PGE2
LTB4
TXA2
PGI2
15dPGJ2

Free radicals

XOD / O_2^-
NO


Inflammatory
Stimulus
IKKγ
P
P
IKKα
IKKβ
P
P
IκB
p50
p65
P
P
p50
p65
NF-κB
Binding site

NFκB en macròfags



(alguns) Gens induibles per NFκB

IL-1α
IL-1β
IL-2
IL-6
IL-8
IL-9
IL-11
IL-13
IL-15
TNFα
IFNβ
TNFα Receptor
IL-2 Receptor

M-CSF
G-CSF
IGM-CSF
PDGFβ
VEGF

CCL2
CCL11
CCL15
CXCL5
CCR7

COX-2
12-LOX
HOX
iNOS
SOD-2
MMP9
PLC
GSTP1

ICAM-1
E-Selectina
P-Selectina
VCAM-1

CRP
ApoC
BDKRB1
OPRM1
CD48
CD69
MYC
STAT5
VIM
CCND1
KLK3
.....
.....

(alguns) Gens induibles per NFκB

IL-1α
IL-1β
IL-2
IL-6
IL-8
IL-9
IL-11
IL-13
IL-15
TNFα
IFNβ
TNFα Receptor
IL-2 Receptor

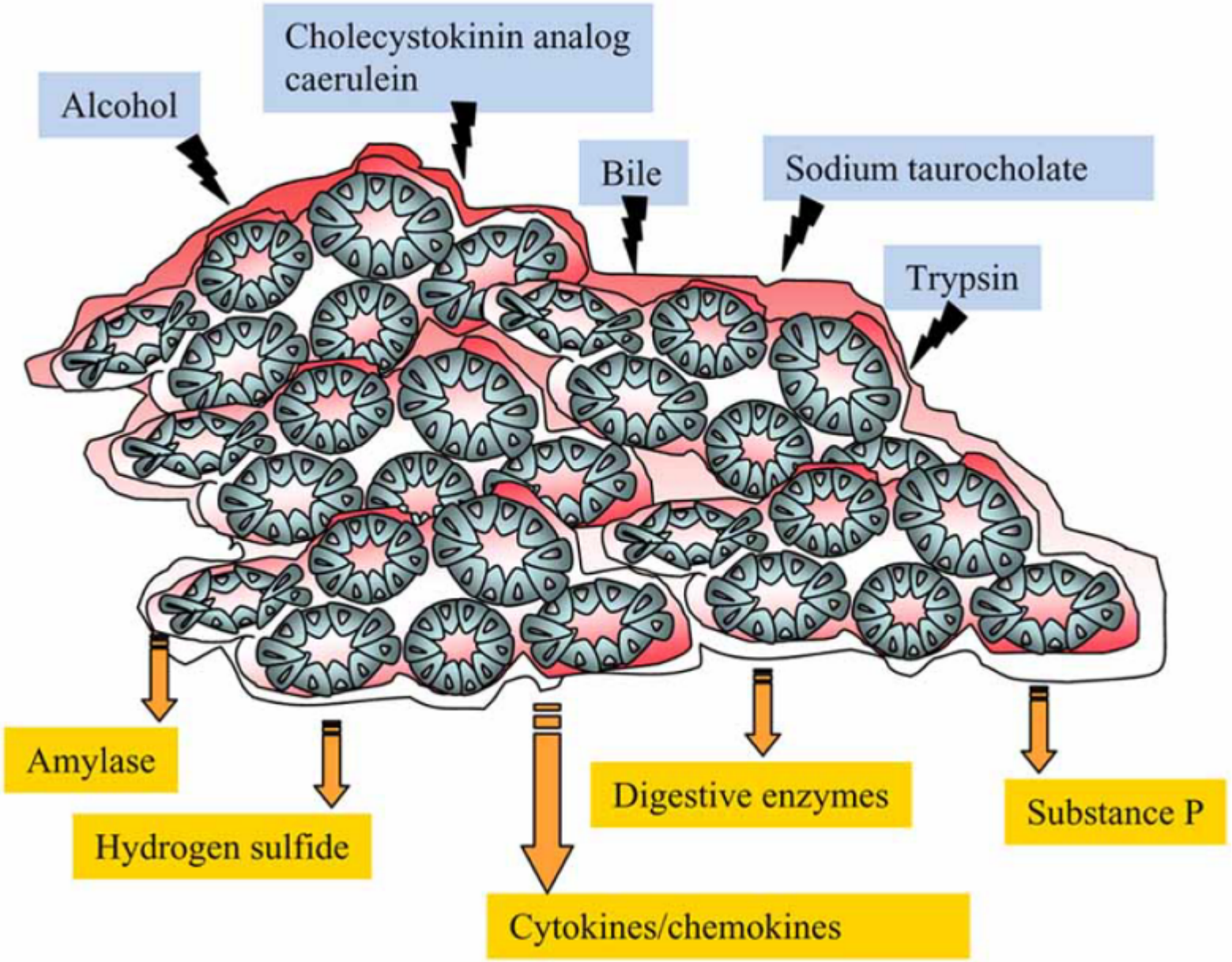
M-CSF
G-CSF
IGM-CSF
PDGFβ
VEGF

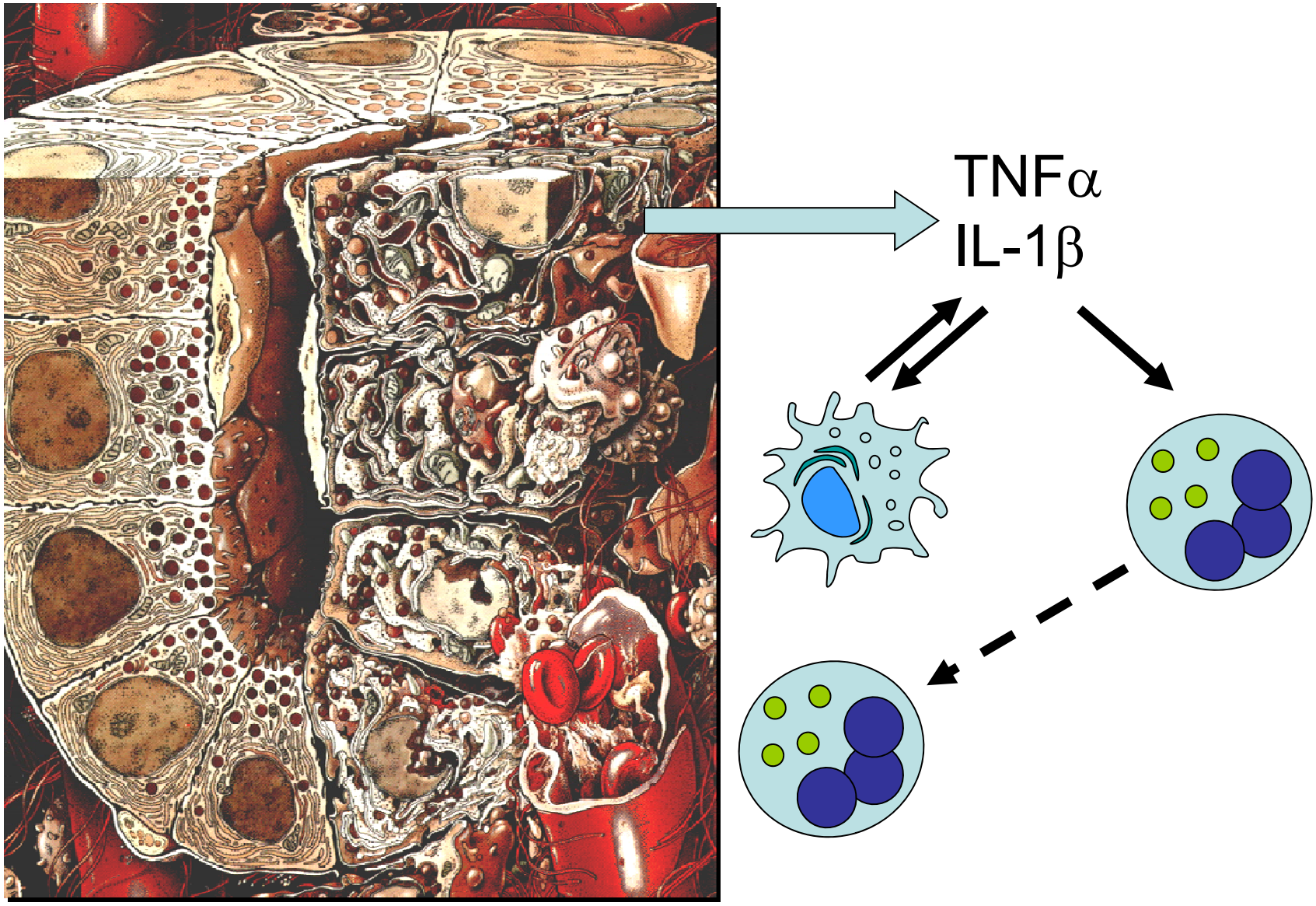
CCL2
CCL11
CCL15
CXCL5
CCR7

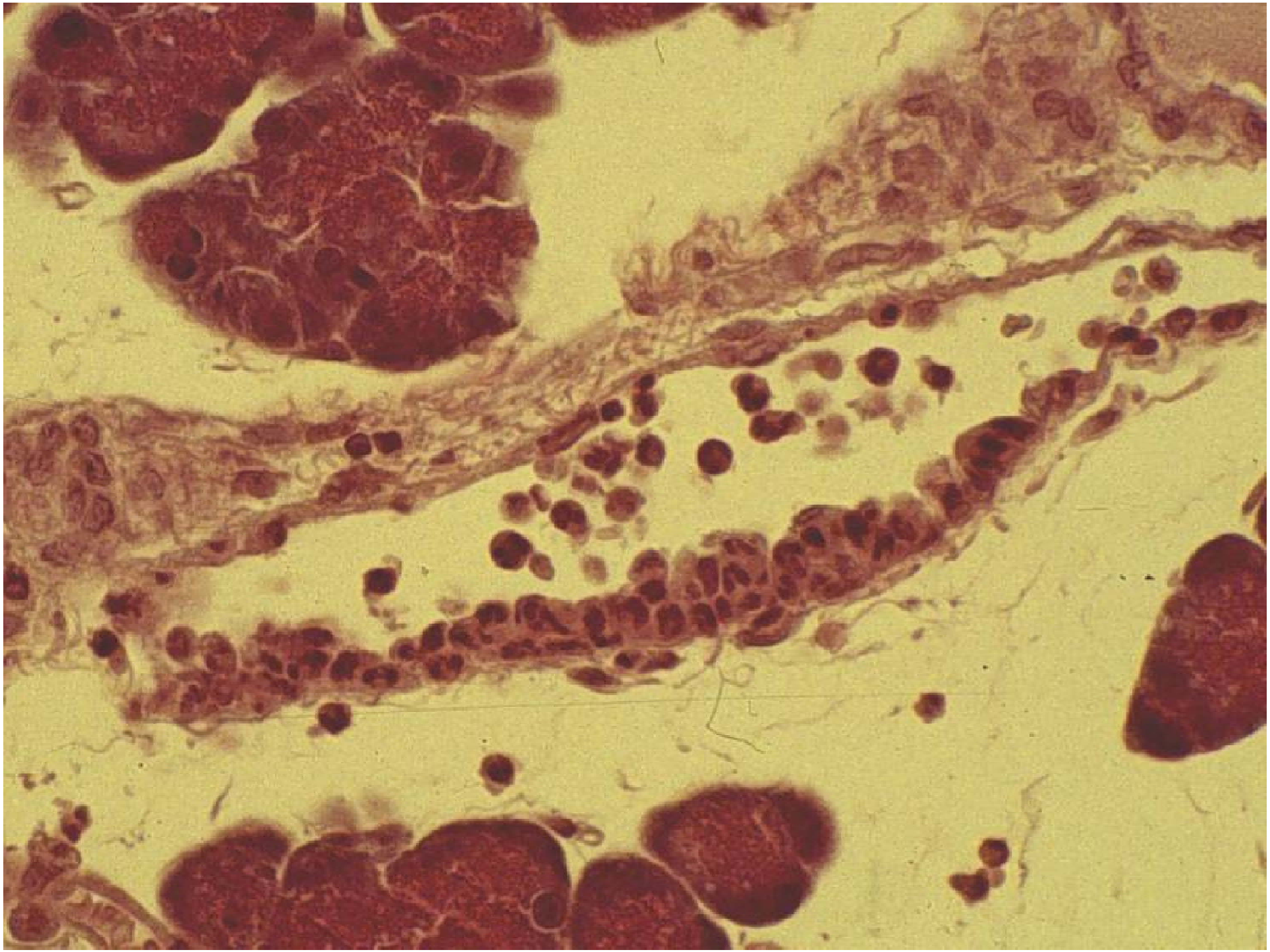
COX-2
12-LOX
HOX
iNOS
SOD-2
MMP9
PLC
GSTP1

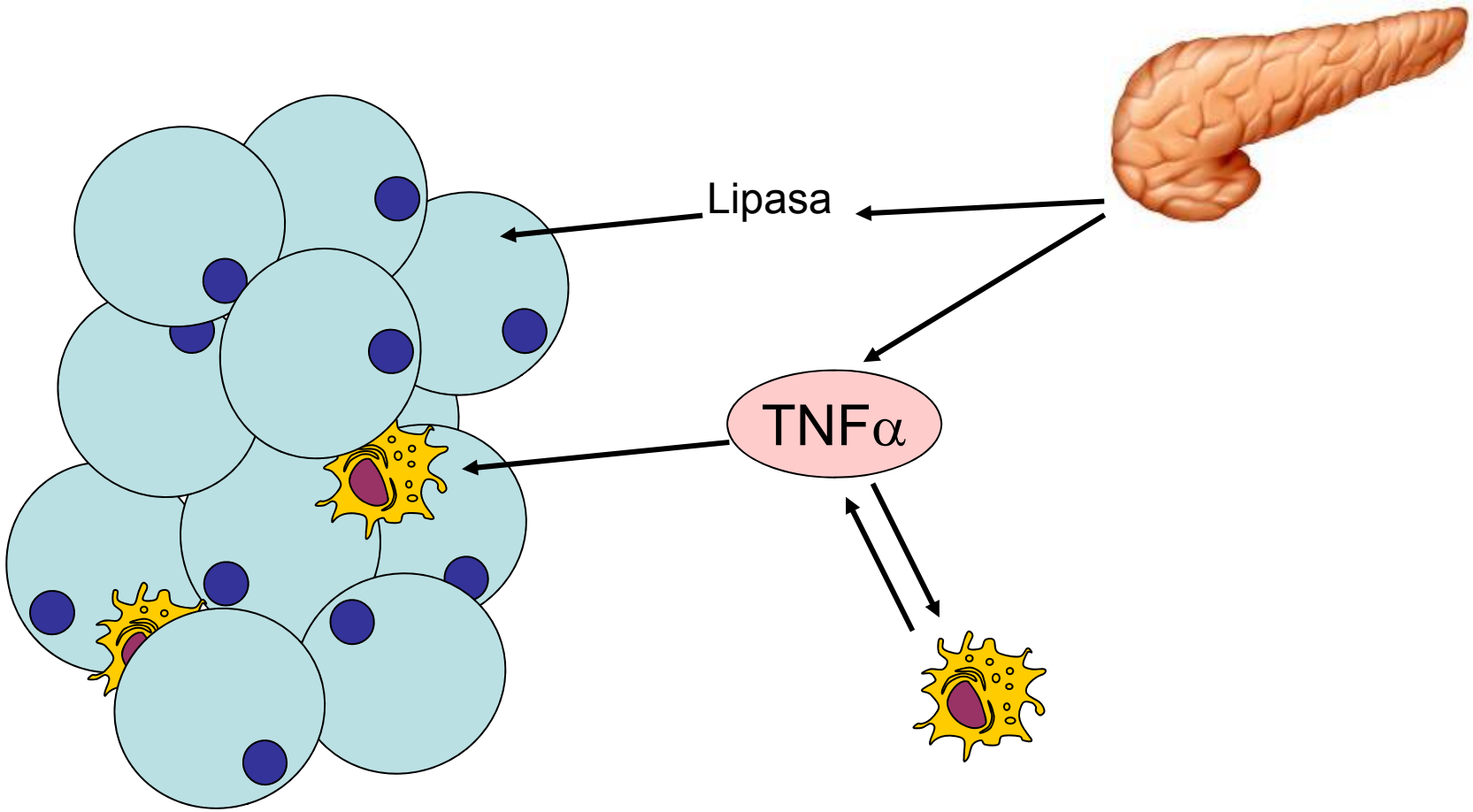
ICAM-1
E-Selectina
P-Selectina
VCAM-1

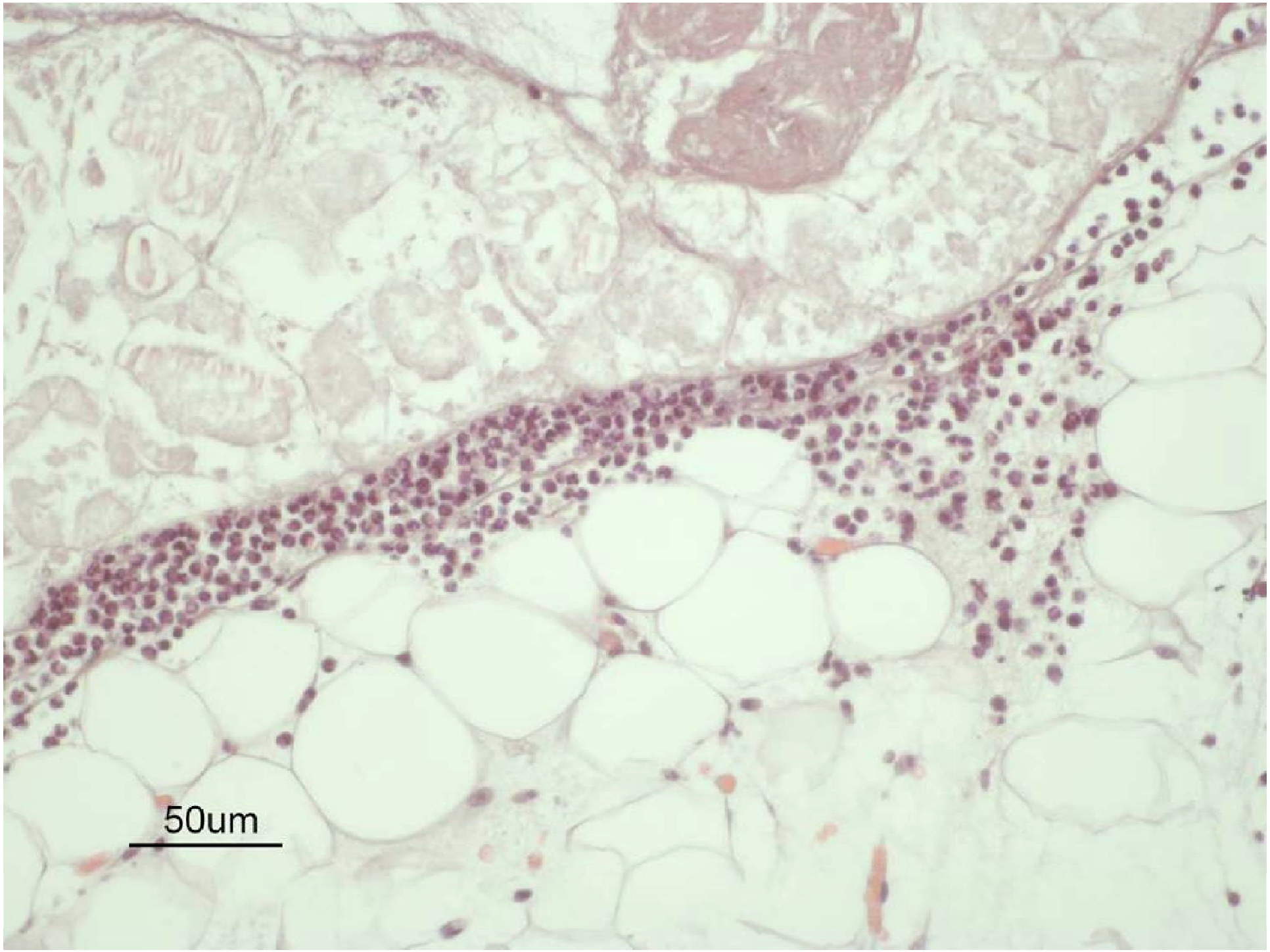
CRP
ApoC
BDKRB1
OPRM1
CD48
CD69
MYC
STAT5
VIM
CCND1
KLK3
.....
.....

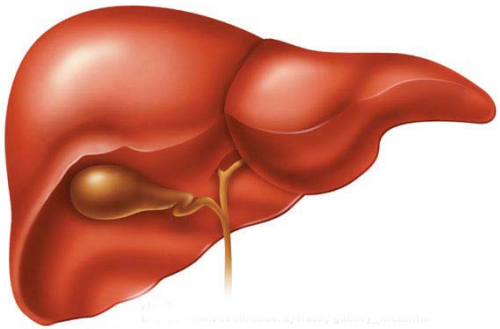

Cholecystokinin analog caerulein
Alcohol
Bile
Sodium taurocholate
Trypsin
Amylase
Hydrogen sulfide
Cytokines/chemokines
Digestive enzymes
Substance P

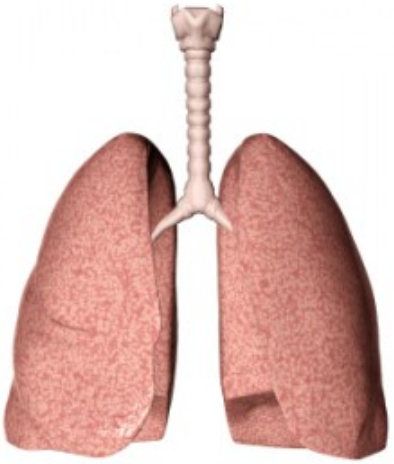

TNFα
IL-1β




Lipasa
TNFα

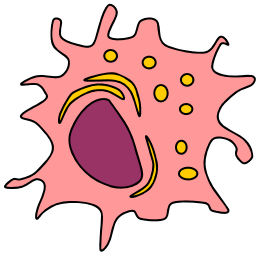

50um

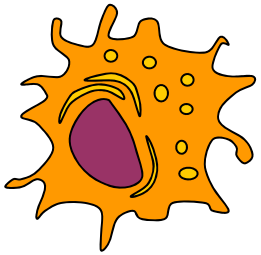


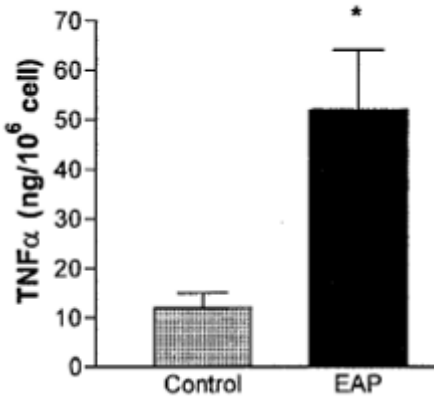


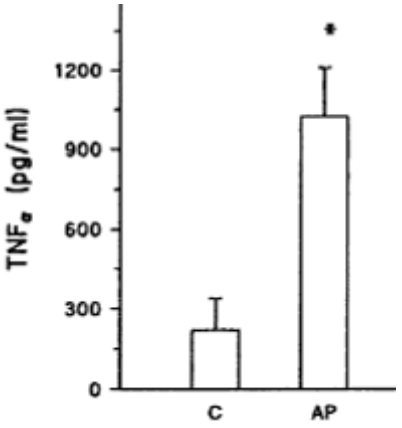
Kupffer cells

Alveolar macrophages





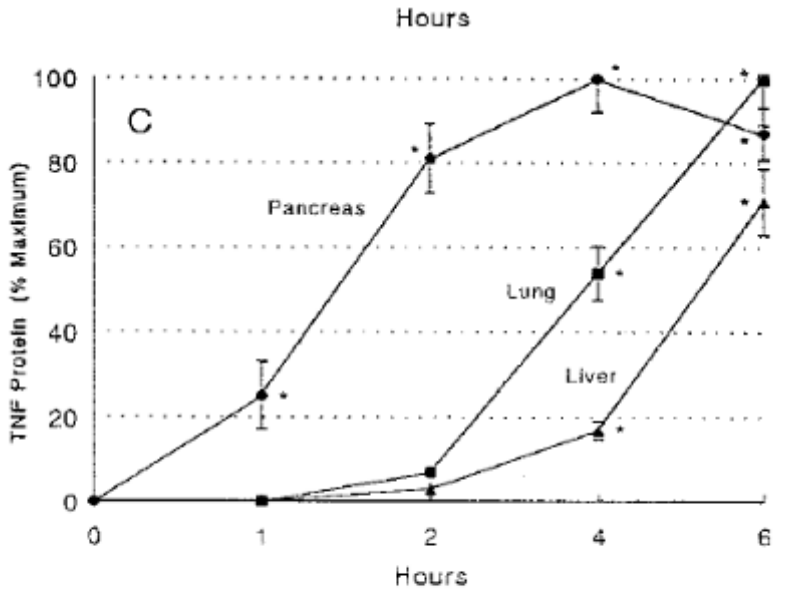




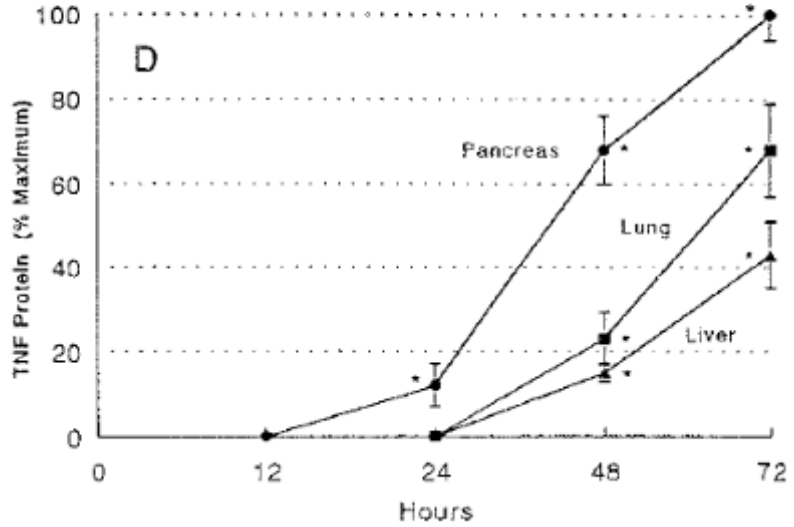
Folch et al. *Dig Dis Sci.* 2000;45:1535-44

Closa D, Sabater L, et al. *Ann Surg*. 1999; 229:230-6.

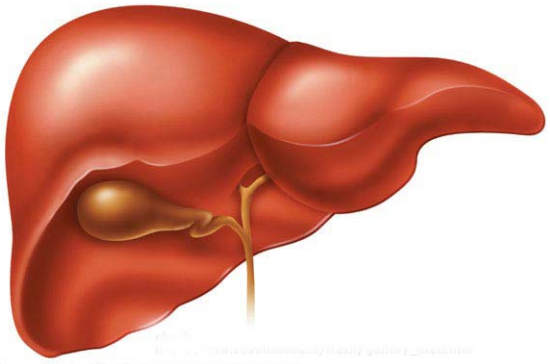
Ceruleïna (ratolí)



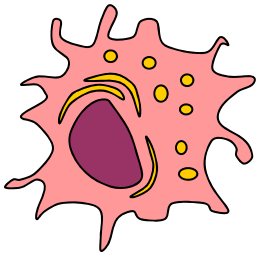
CDE (ratolí)



Norman JG, et al. *Dig Dis Sci.* 1997;42:1783-8.



Kupffer cells



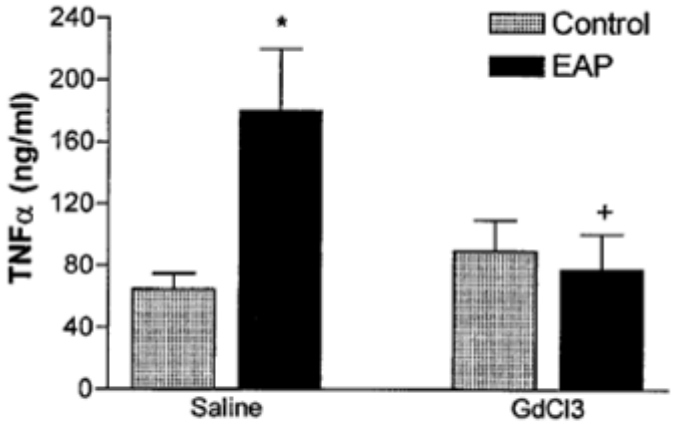
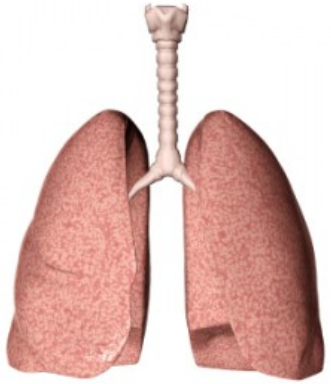
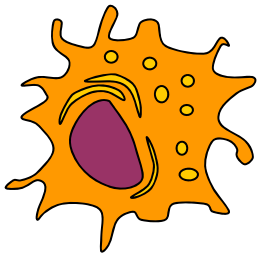


Fig 4. Serum levels of TNF-α. Induction of pancreatitis results in an increase in serum levels of TNF-α. Kupffer cell inhibition with $GdCl_3$ abolishes the increase of serum levels of TNF-α.

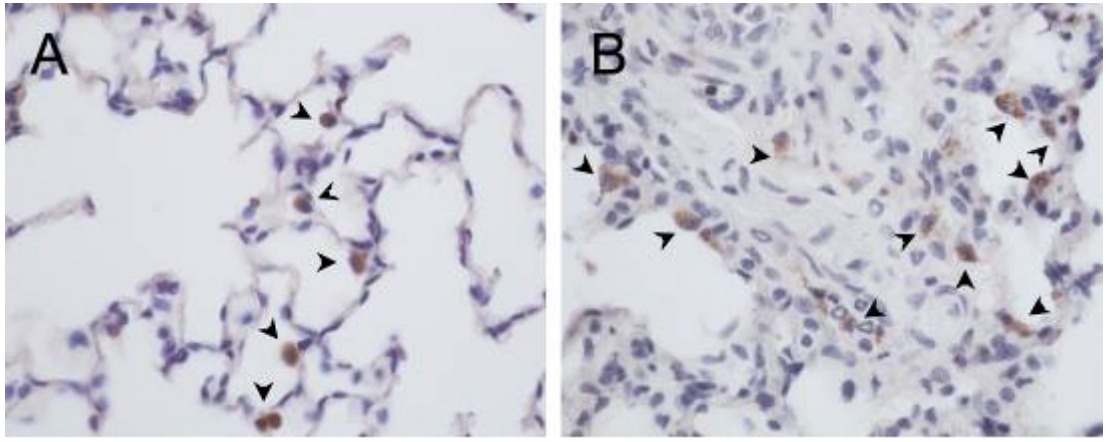
Folch et al. *Dig. Dis. Scienc.* 45, 8:1535-1544 (2000)

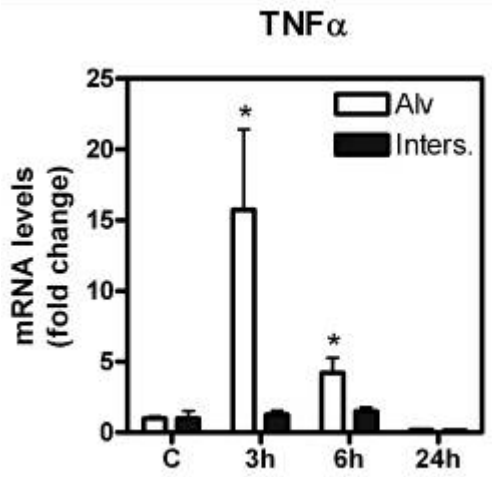


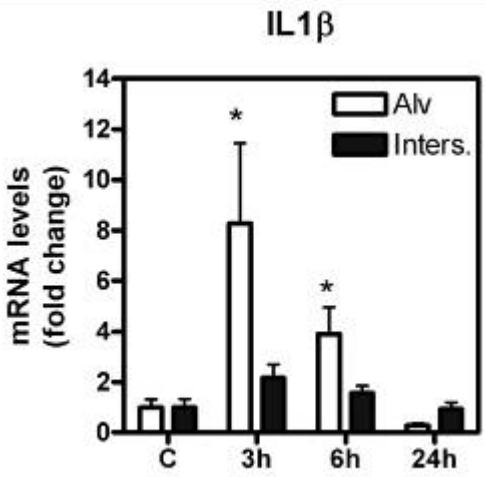


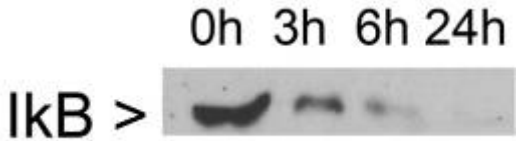
Control AP

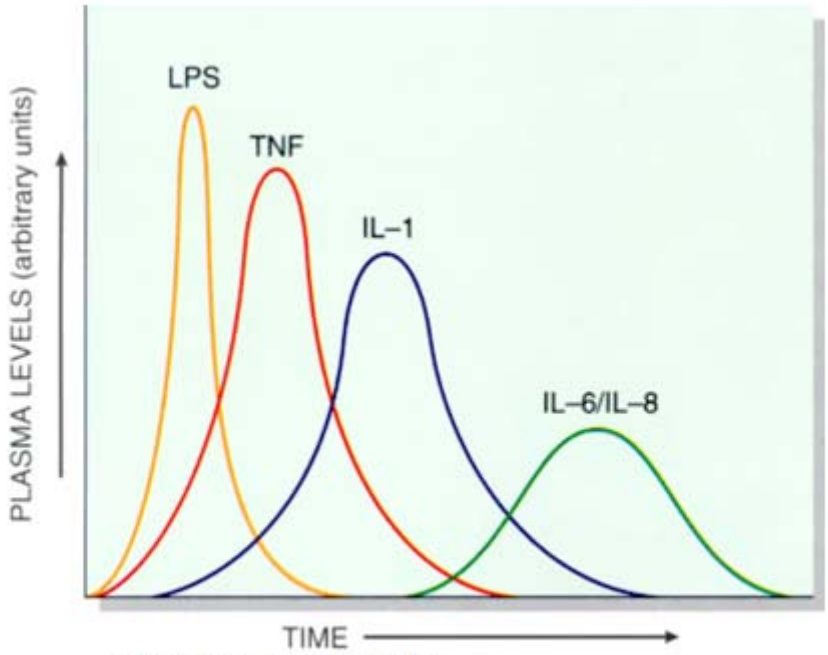
Anti CD68



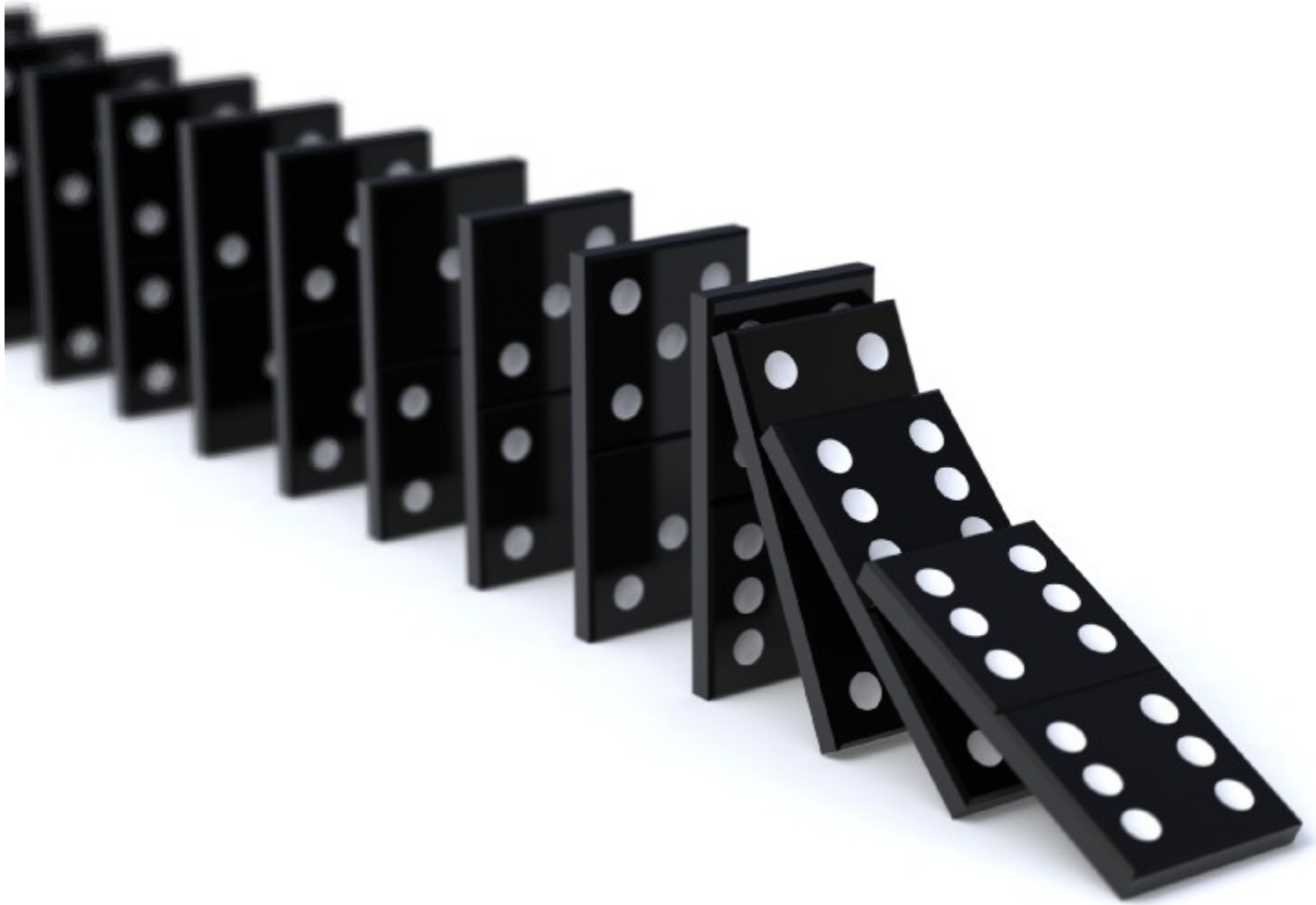


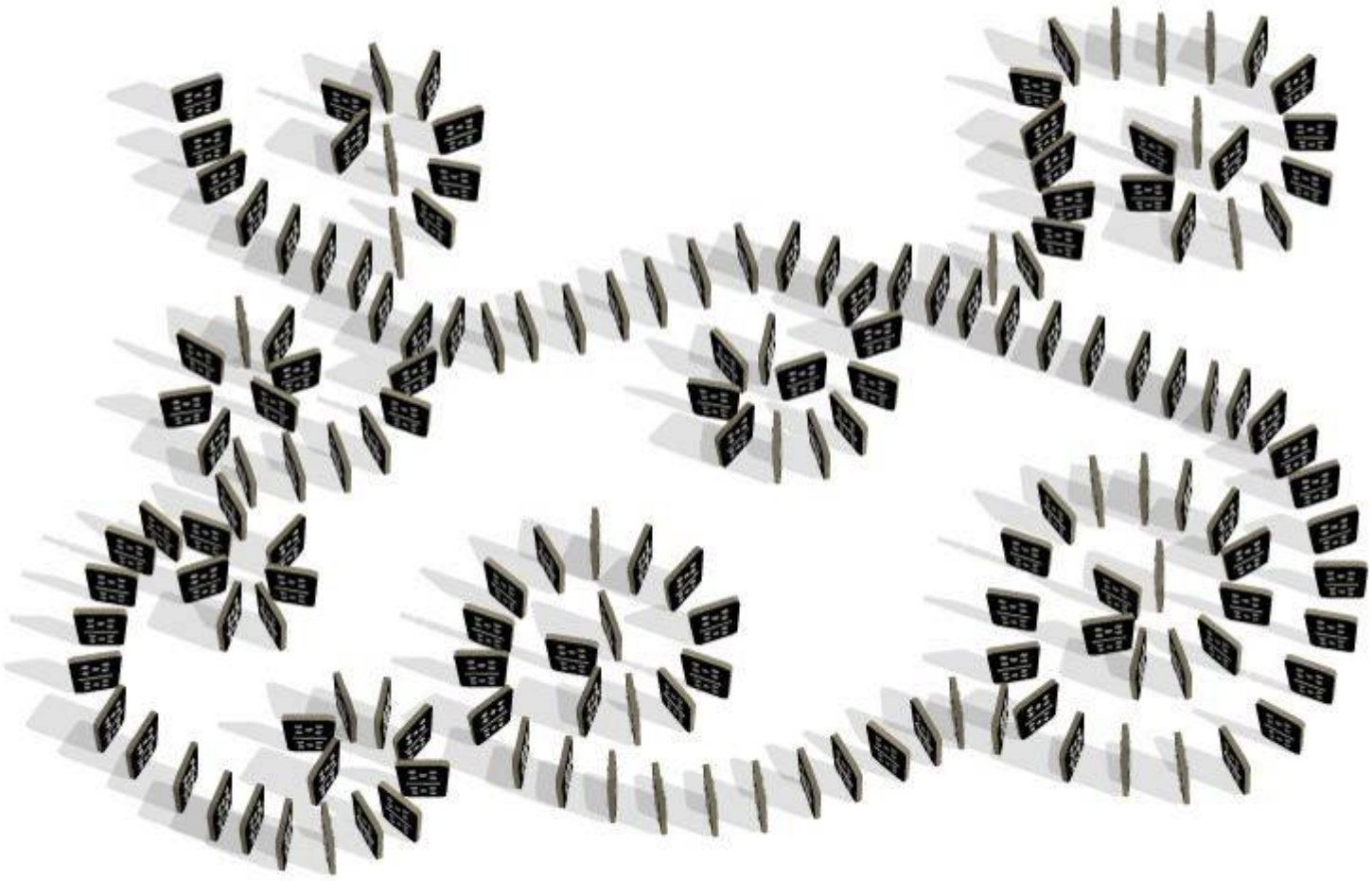






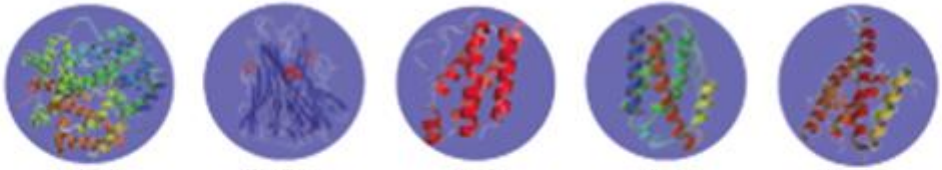
Cytokine cascade





Pro-inflamatory Cytokines : stimulate the immune system

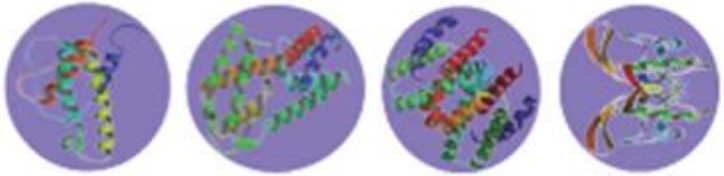
Th1



INF-γ TNF-α IL-2 IL-6 IL-12

Anti-inflamatory Cytokines : supress the immune system

Th2

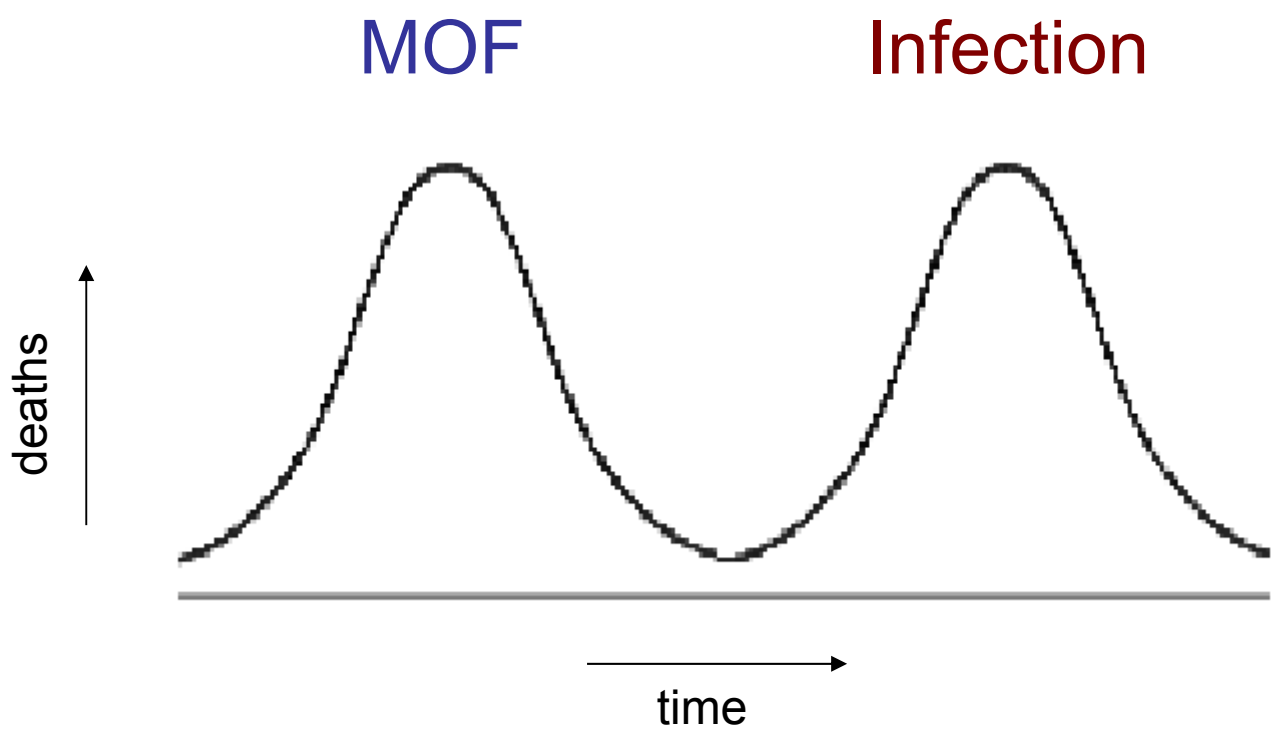


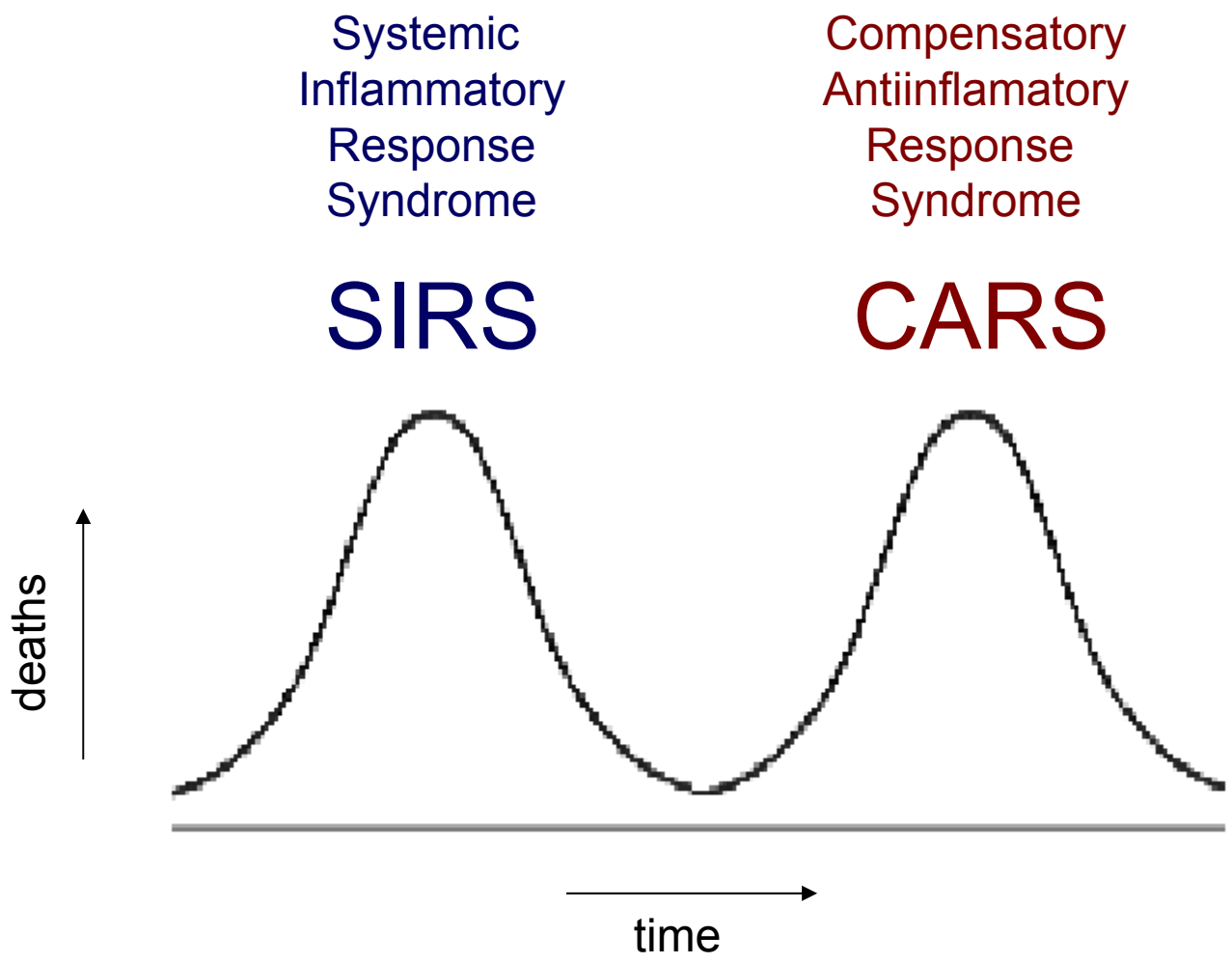
IL-4 IL-5 IL-10 TGF-β

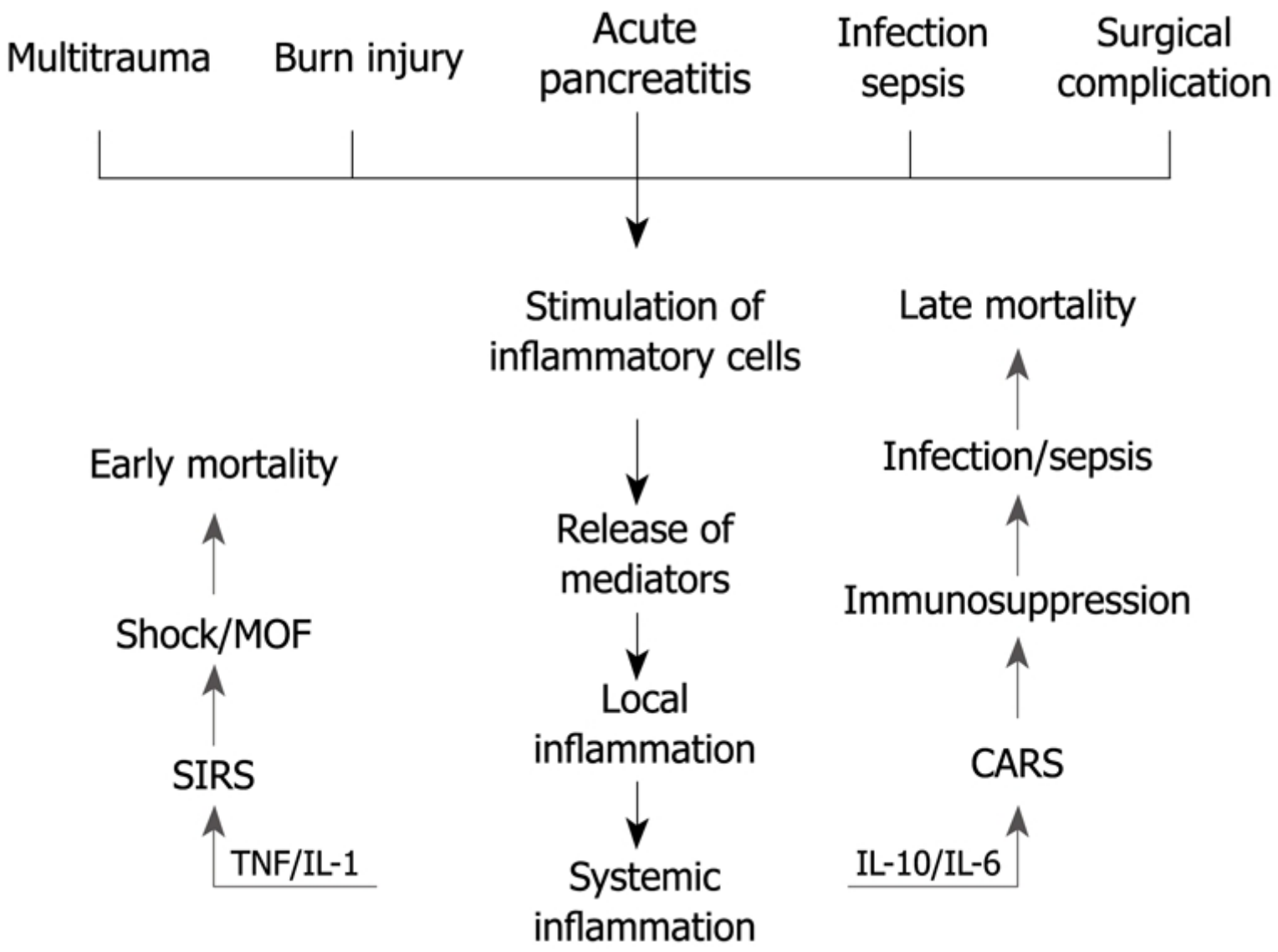
Crystallography derived from RCSB Protein Data Bank.[1]

Pharmacological treatment of acute pancreatitis: Overview of drugs tested in animal experimental models and clinical trials

Name	Mechanism	Effect in animal models	Result in human trials
Somatostatin	Inhibition of pancreatic secretion	No reduced mortality	No reduced mortality
Octreotid	Inhibition of pancreatic secretion	No effect (divergent results)	No reduced mortality
Gabexate mesilate	Protease inhibitor	Reduced histology score	Maybe reduced mortality
N-acetyl-cysteine	Reduction of oxidative stress	Reduced severity	No reduced mortality
Nitrogen oxide	Improvement of micro-circulation	Reduced edema	No published trials
Steroids	Non-specific anti-inflammatory	Reduced mortality	No published trials
PAF inhibitor	Specific anti-inflammatory	No reduced mortality	No reduced mortality
Antibiotics	Antibacterial	-	Reduced mortality
Probiotics	Prevention of colonization of the gut	-	No reduced mortality

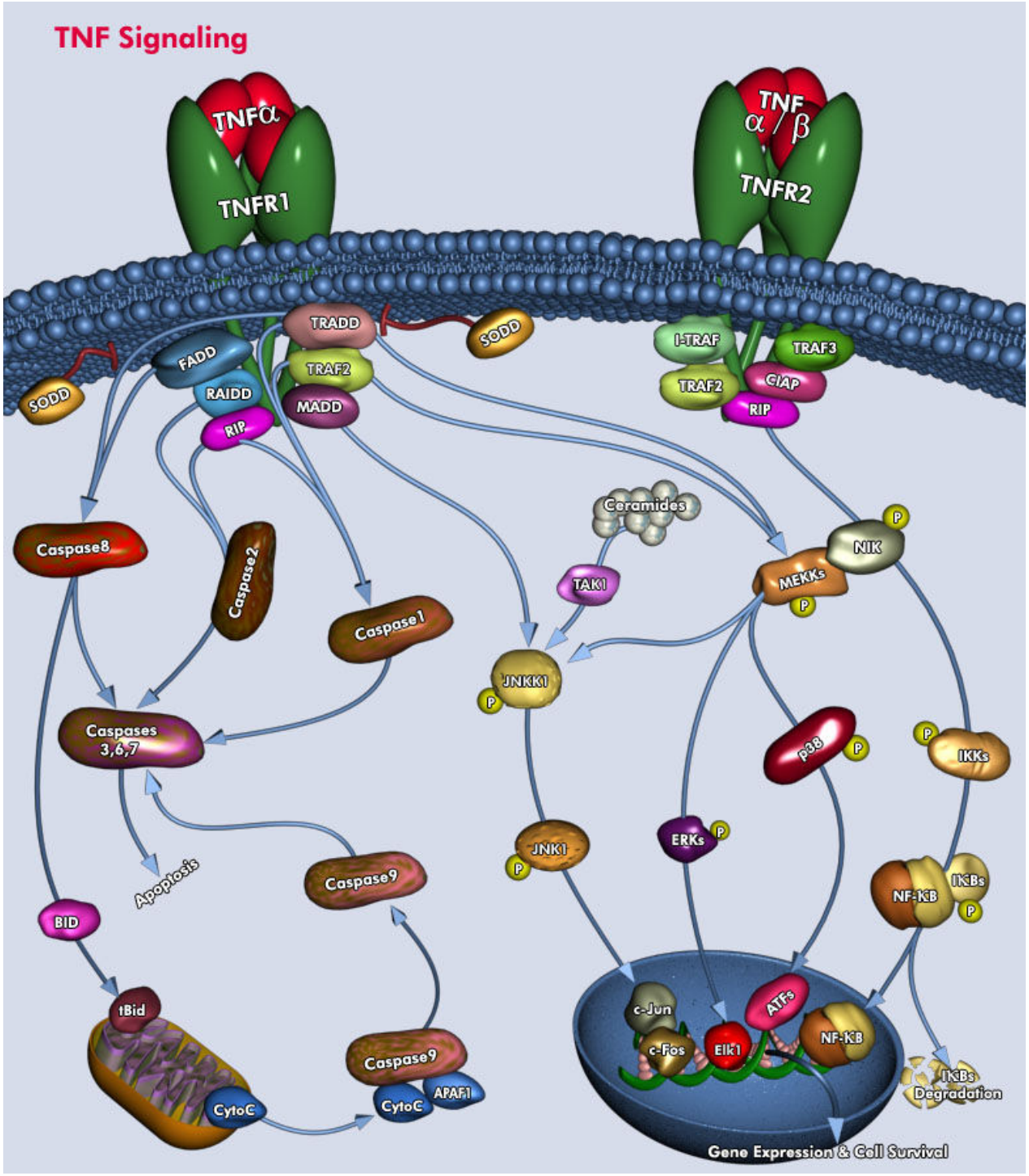

MOF
Infection
deaths
time

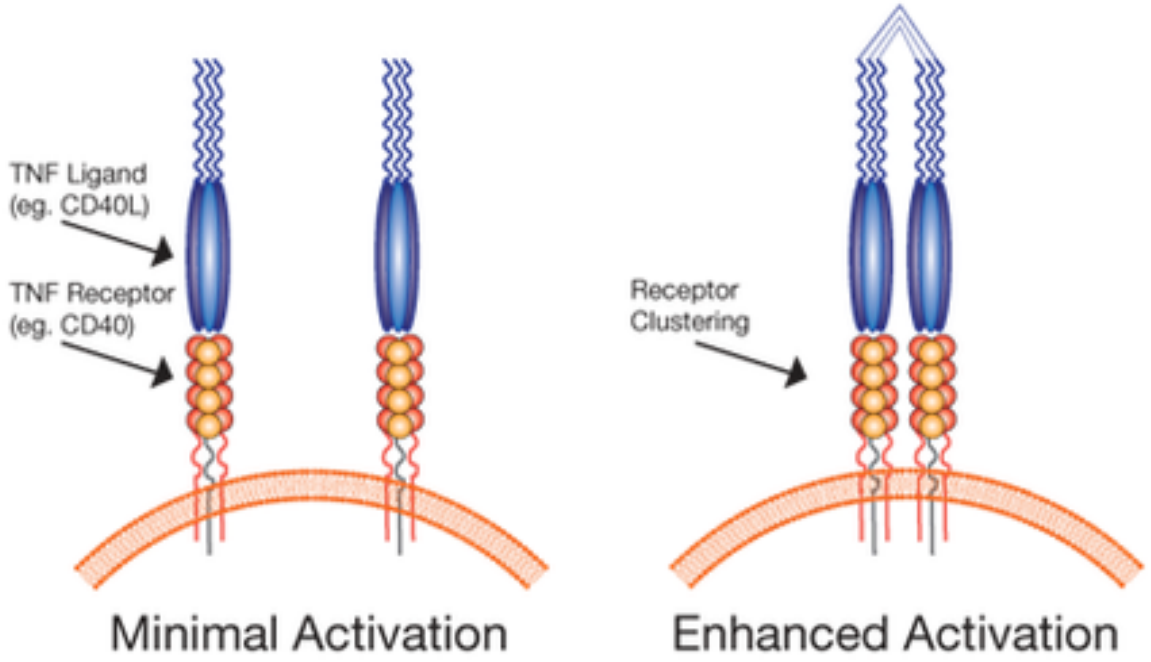

Systemic
Inflammatory
Response
Syndrome
Compensatory
Antiinflamatory
Response
Syndrome
SIRS
CARS
deaths
time

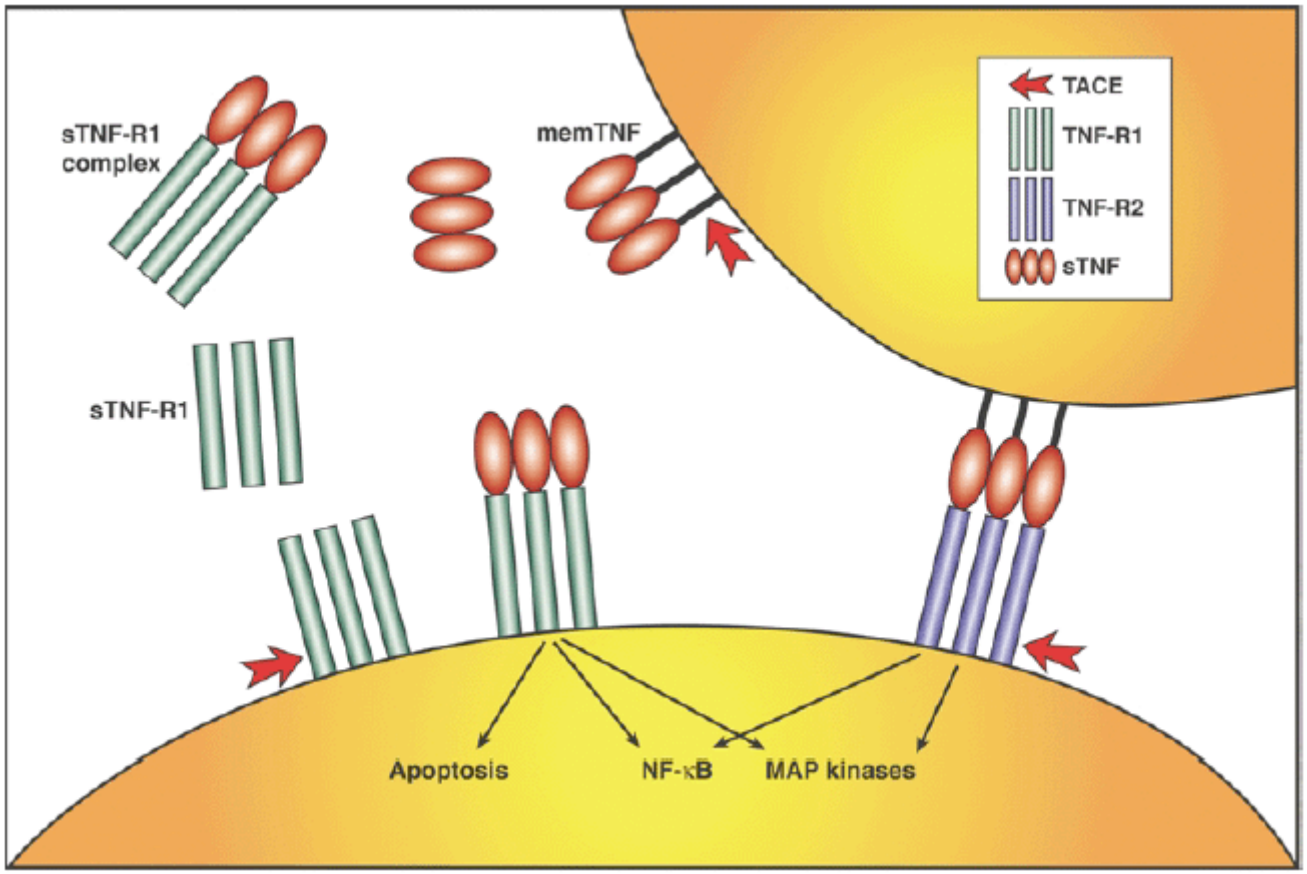

Multitrauma
Burn injury
Acute pancreatitis
Infection sepsis
Surgical complication
Stimulation of inflammatory cells
Release of mediators
Local inflammation
Systemic inflammation
Early mortality
Shock/MOF
SIRS
TNF/IL-1
Late mortality
Infection/sepsis
Immunosuppression
CARS
IL-10/IL-6

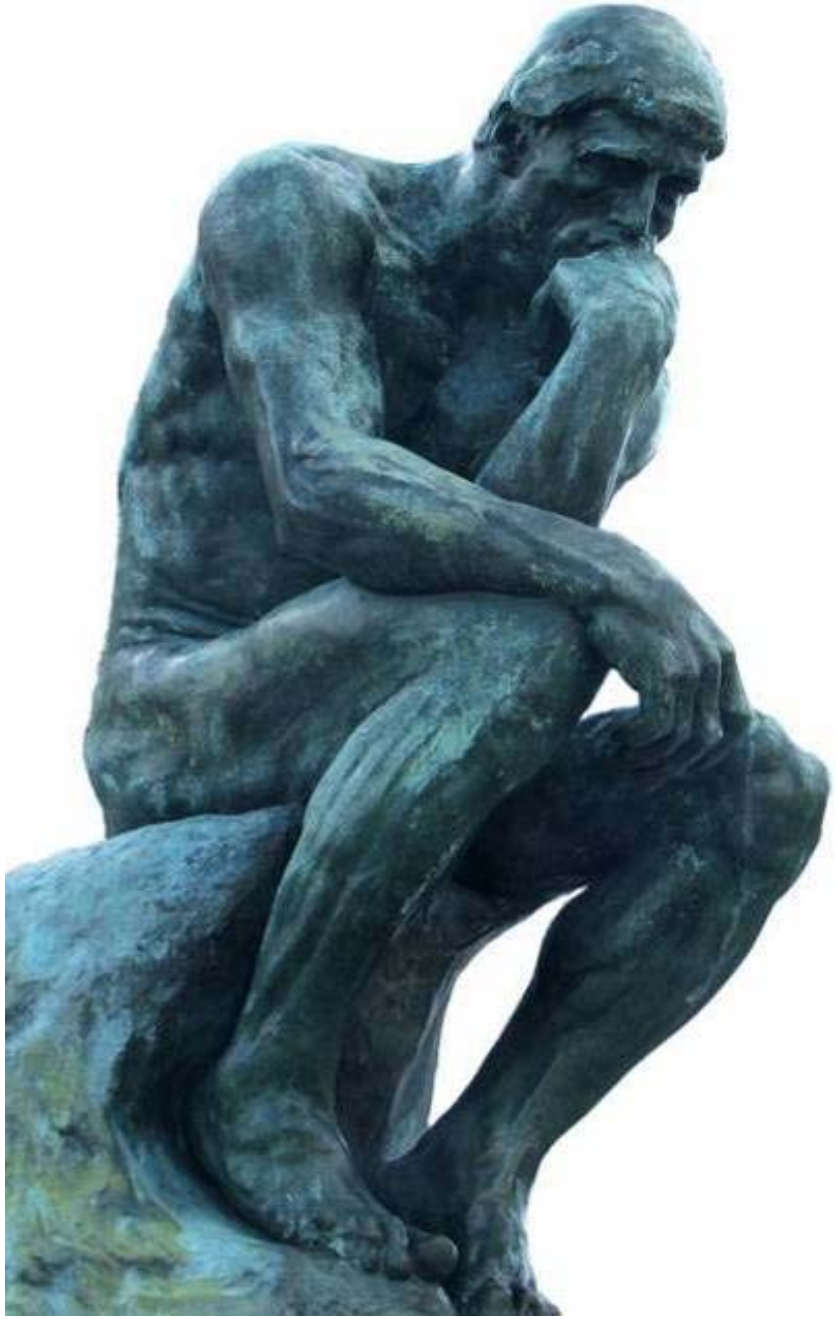
Marcadors pronóstic?

No	"Acceptable"
IL1β IL11 TNFα	IL6 IL8 IL10 IL17

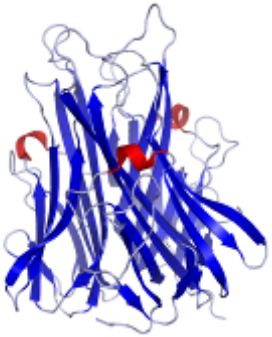

TNF Signaling
TNFα
TNFR1
TNF α / β
TNFR2
TRADD
SODD
FADD
TRAF2
RAIDD
MADD
RIP
SODD
I-TRAF
TRAF3
TRAF2
cIAP
RIP
Ceramides
TAK1
NIK
MEKKs
Caspase8
Caspase2
Caspase1
JNKK1
Caspases 3,6,7
p38
IKKs
JNK1
ERKs
Apoptosis
Caspase9
NF-KB
IKBs
BID
tBid
c-Jun
ATFs
c-Fos
Elk1
NF-KB
Caspase9
CytoC
CytoC
APAF1
IKBs Degradation
Gene Expression & Cell Survival


TNF Ligand
(eg. CD40L)
TNF Receptor
(eg. CD40)
Minimal Activation
Receptor
Clustering
Enhanced Activation

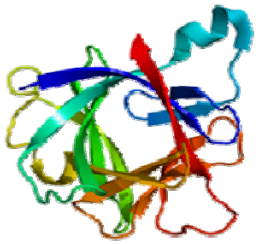

sTNF-R1
complex
memTNF
TACE
TNF-R1
TNF-R2
sTNF
sTNF-R1
Apoptosis
NF-κB
MAP kinases



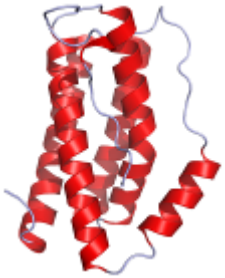
TNFα



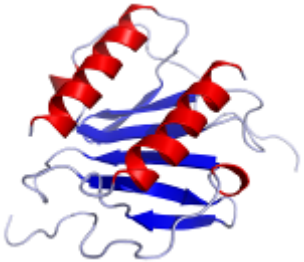
IL-1β



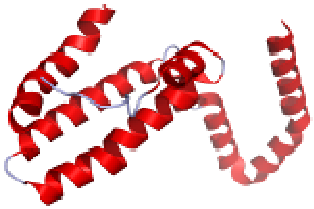
IL-6



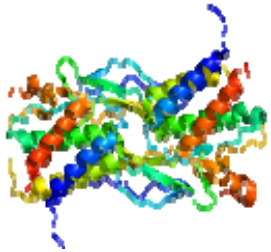
IL-8



IL-10

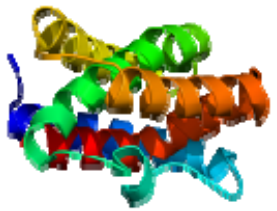


IL-15



IL-17

IL-22



IL-?