

KKU International Teaching Platform

UNIVERSITÉ PIERRE & MARIE CURIE
L'EXCELLENCE À PARIS

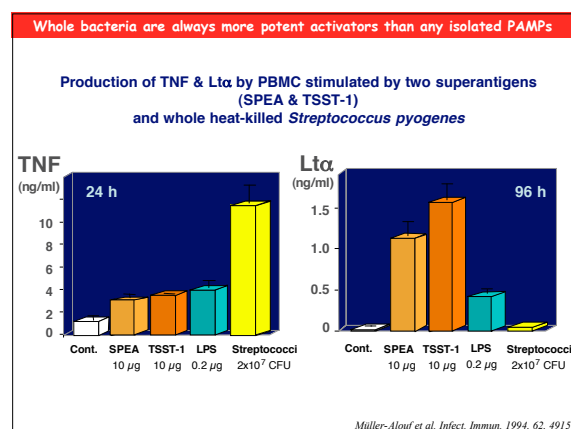
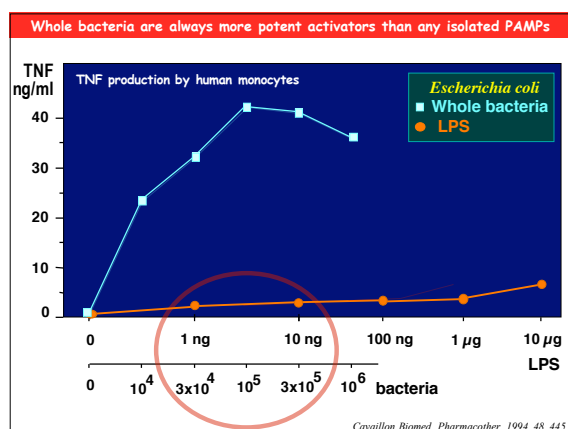
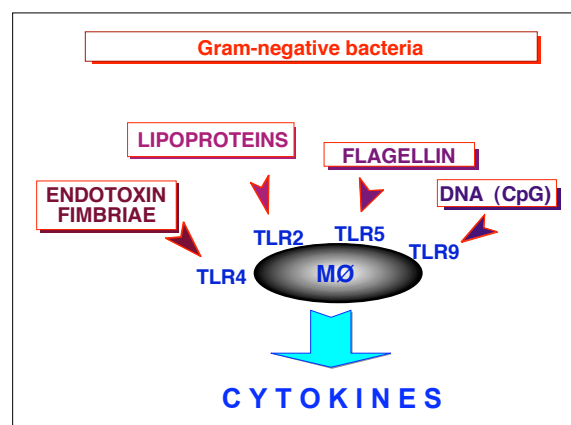
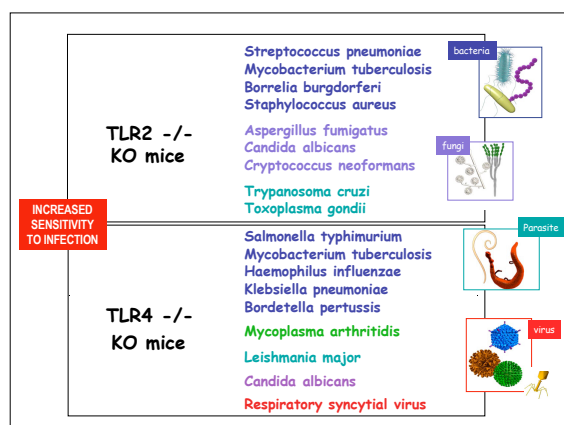
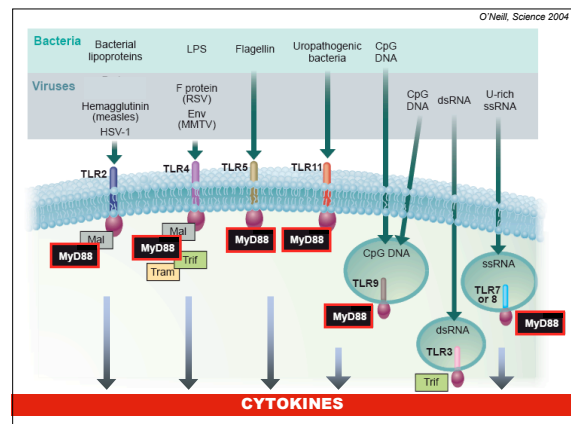
Khon Kaen University

Cytokines and infectious diseases

- 1/ INDUCTION OF CYTOKINES BY MICROBIAL PRODUCTS
- 2/ CO-FACTORS & SYNERGY
- 3/ INFECTION & Th1 / Th2 PROFILE
- 4/ ANTI-INFECTIOUS PROPERTIES OF CYTOKINES
- 5/ EXACERBATED PRODUCTION & DELETERIOUS EFFECTS
- 6/ STRATEGIES OF PATHOGENS TO COUNTERACT CYTOKINES
- 7/ MODULATION BY NATURAL PRODUCTS

Jean-Marc Cavaillon
Unit Cytokines & Inflammation

INSTITUT PASTEUR



IN VIVO ?

SHOCK AND MULTIPLE ORGAN DYSFUNCTION AFTER SELF-ADMINISTRATION OF SALMONELLA ENDOTOXIN

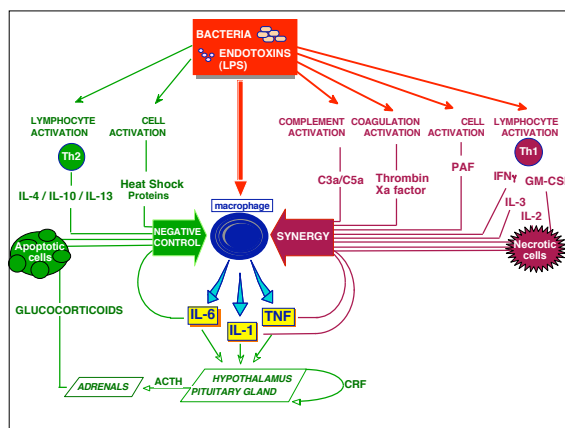
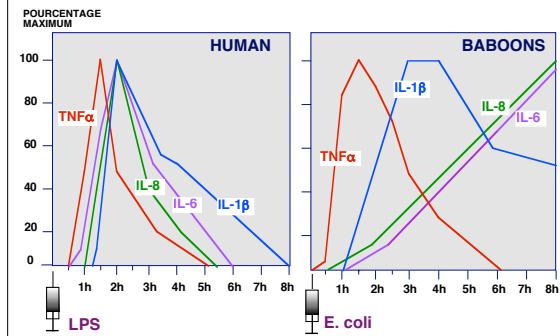
Taveira da Silva et al. N. Engl. J. Med. 1993, 328, 1457

1 mg LPS (15 µg/kg, i.e. 3750 X dose given to human volunteers)

Hours after LPS injection	LPS	Serum concentration (pg/ml)			
		TNF ELISA	TNF Bioassay	IL-6	IL-8
3.6	nd	14 630	9157	nd	nd
6.8	38	147	17	263 510	16 410
11.5	< 5	nd	nd	51 910	3 190

IN VIVO ?

KINETICS OF CYTOKINES FOLLOWING LPS OR BACTERIA INJECTIONS

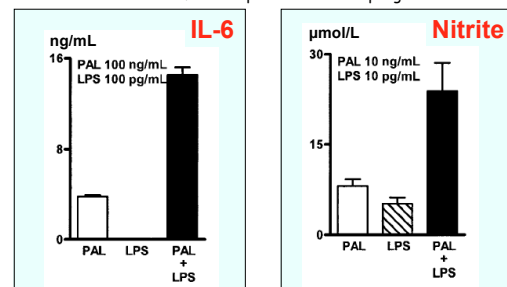


SYNERGY BETWEEN PAMPs

Peptidoglycan-associated lipoprotein (PAL) has synergy with LPS

Liang et al. J. Infect. Dis. 2005, 191, 939

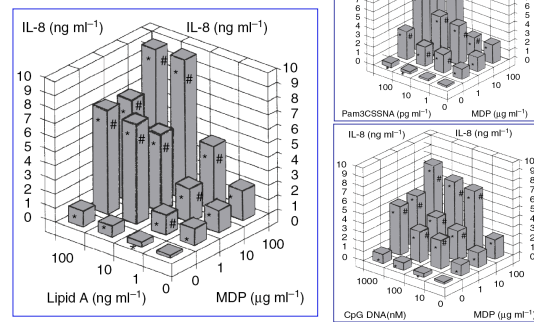
Activation of mouse peritoneal macrophages



SYNERGY BETWEEN PAMPs

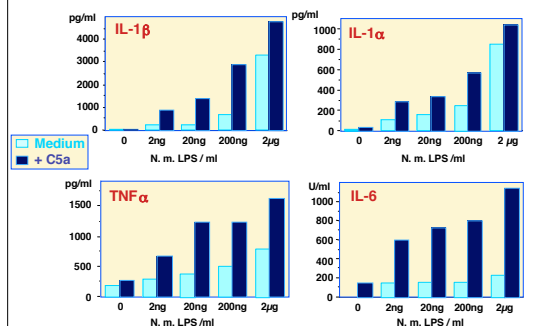
Synergy between MDP and TLR2, TLR4 and TLR9 ligands

Huehara et al. Cell. Microbiol. 2004

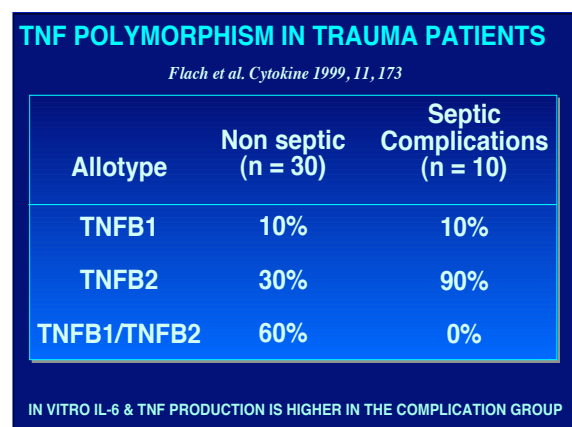
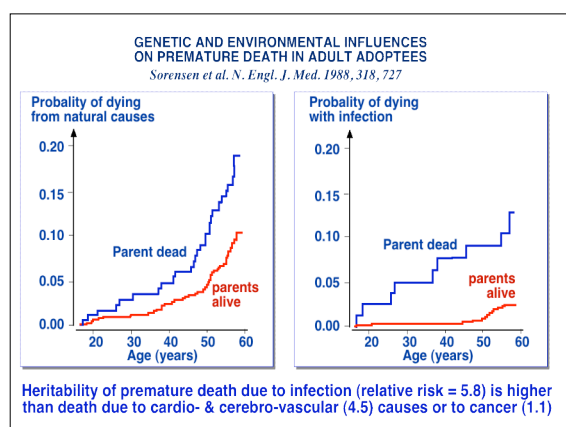
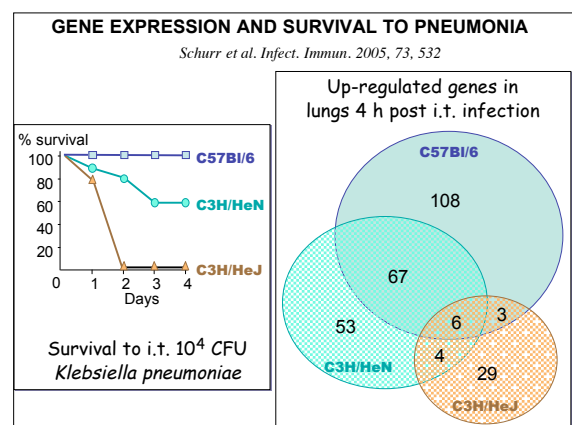
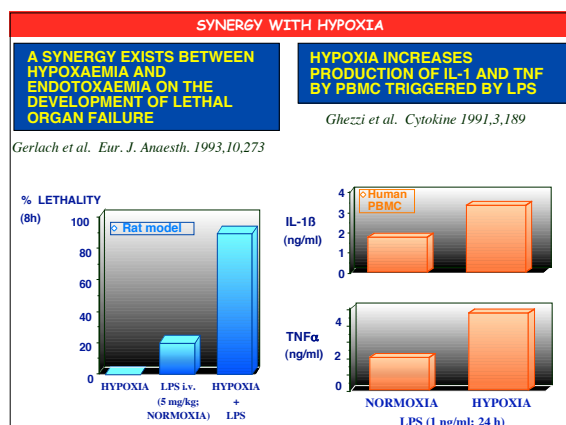
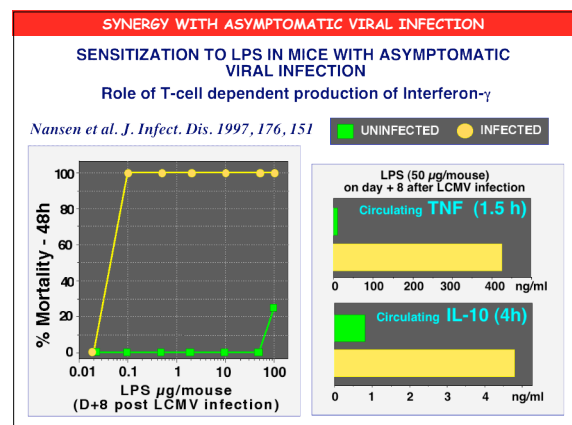
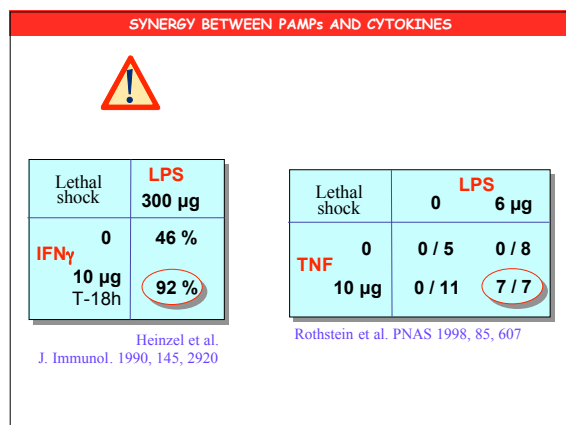


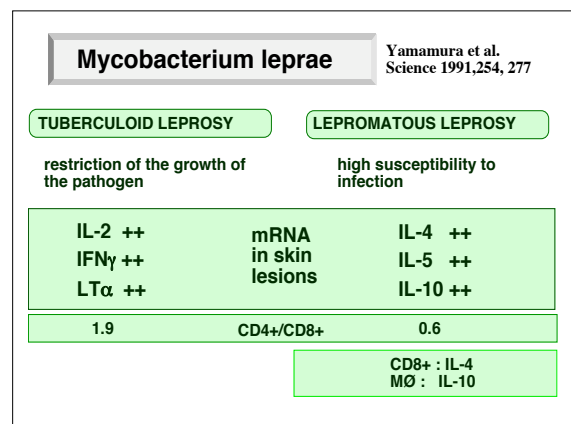
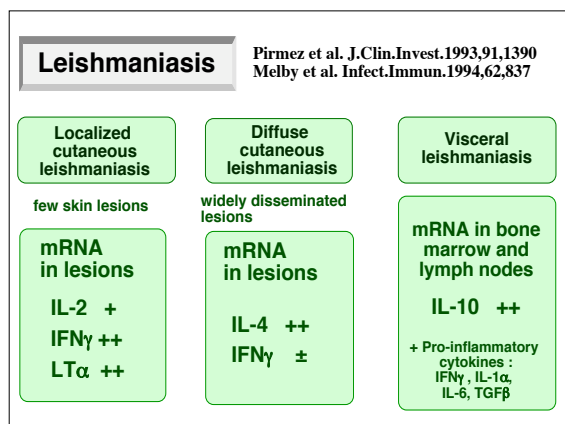
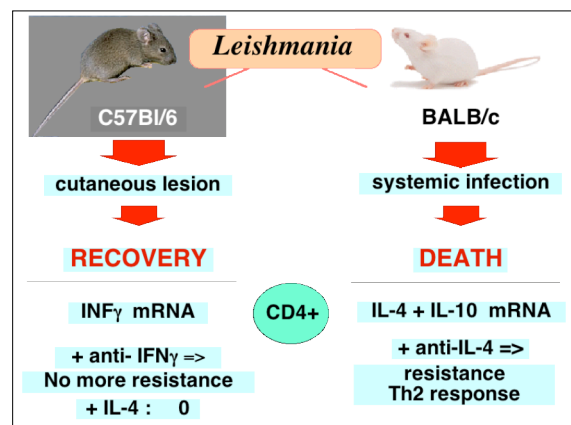
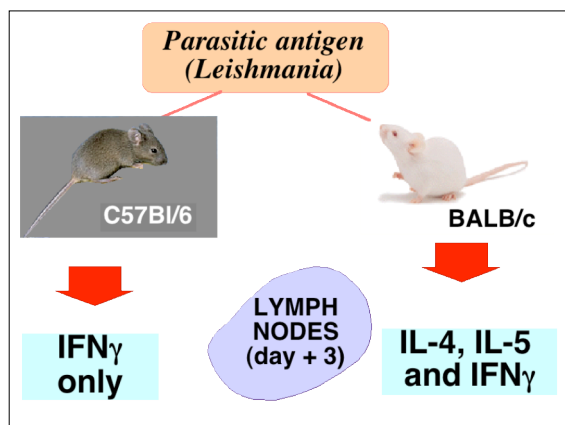
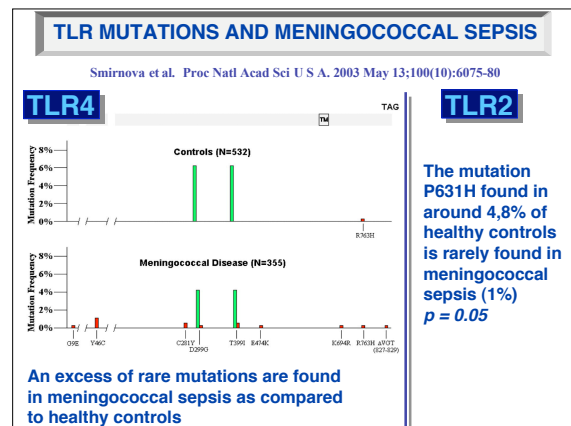
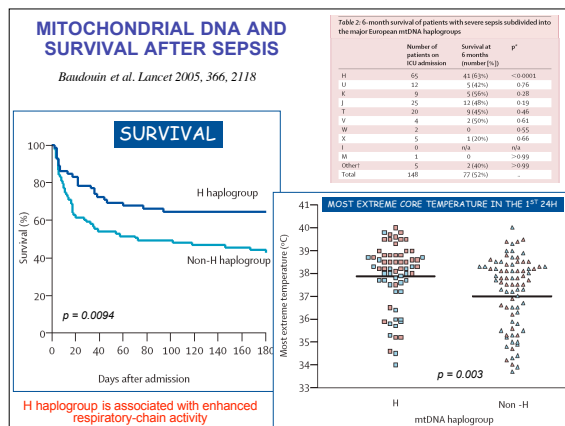
SYNERGY WITH ANAPHYLATOXIN C5α

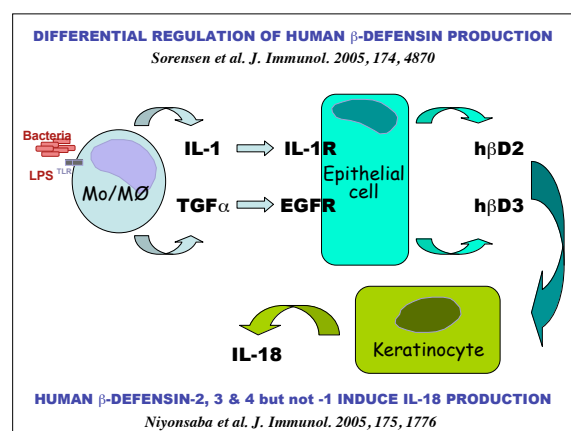
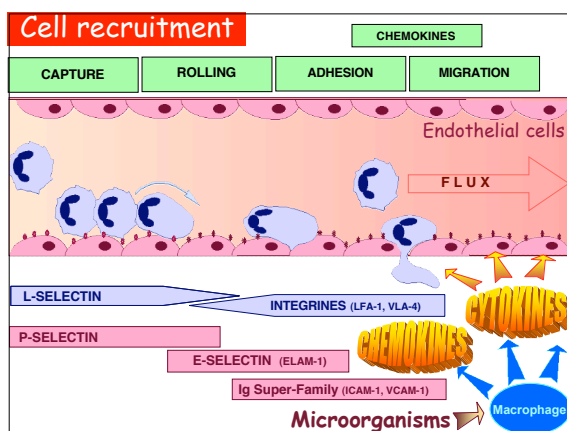
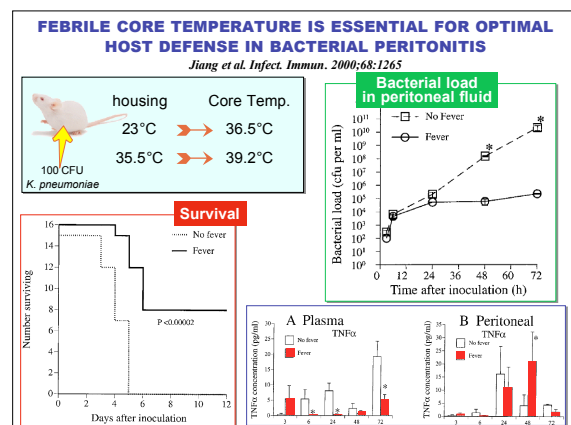
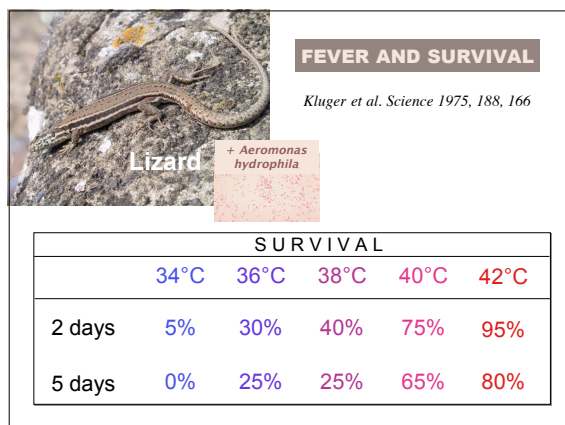
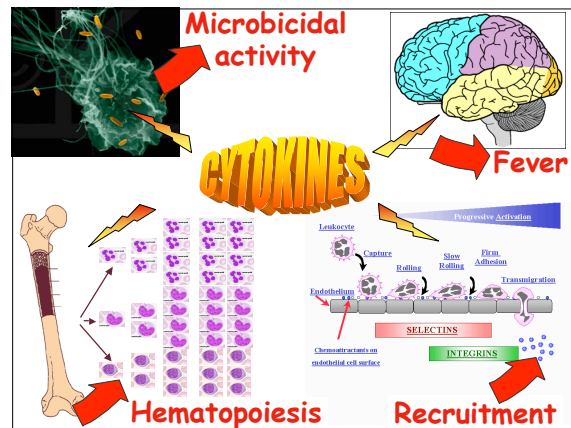
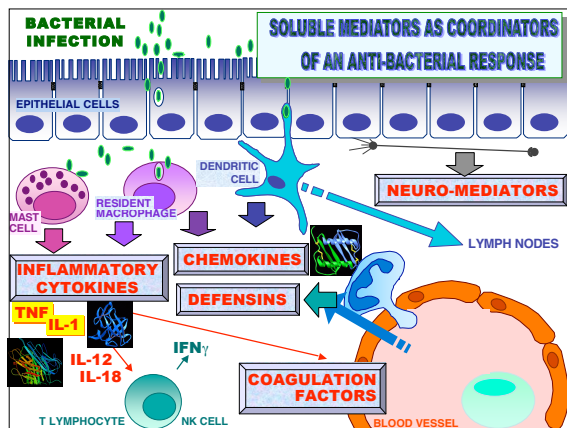
Recombinant C5α enhances IL-1 and TNF release by LPS-stimulated monocytes and macrophages

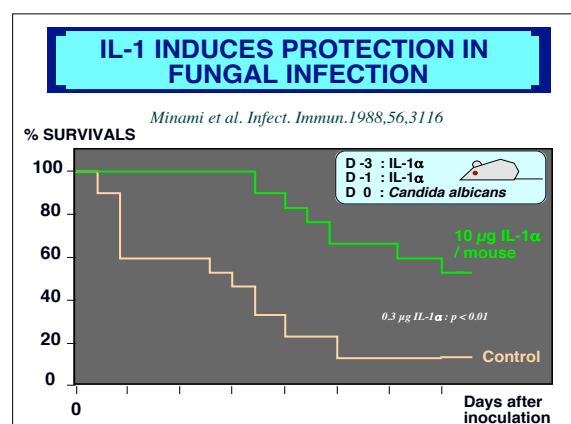
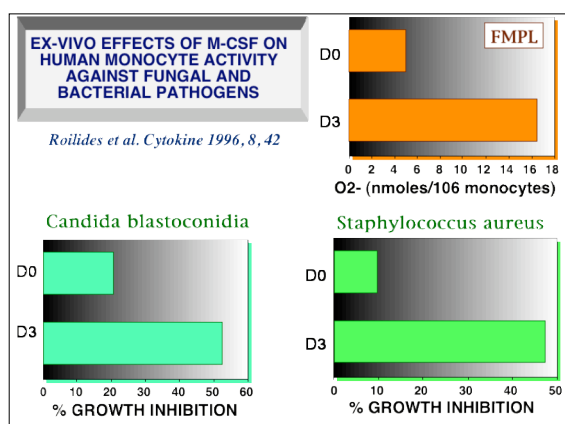
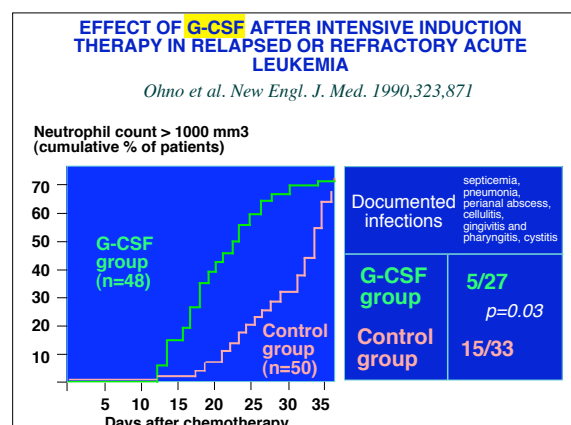
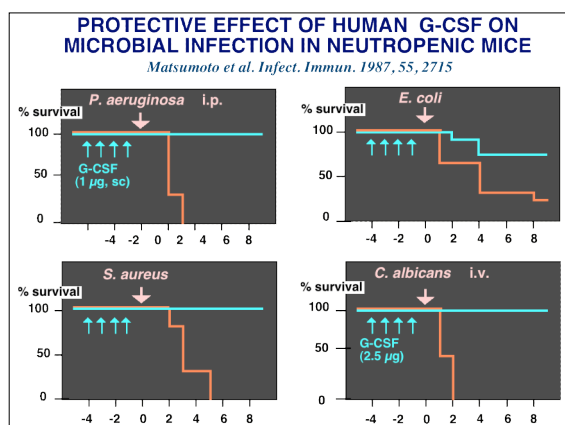
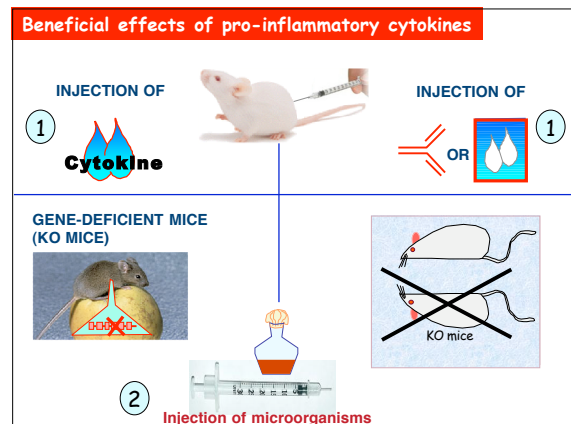
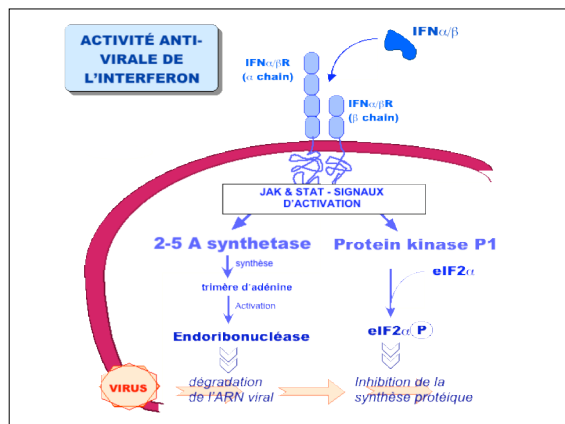


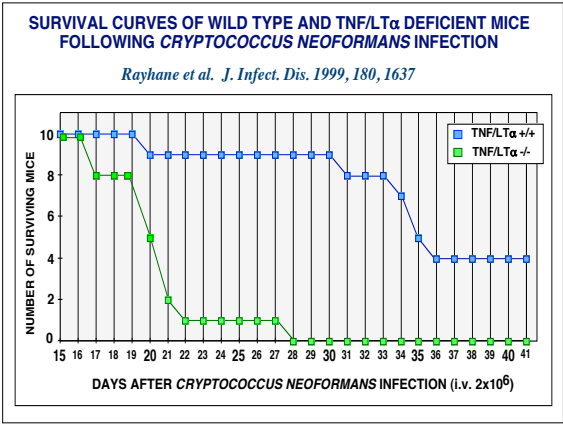
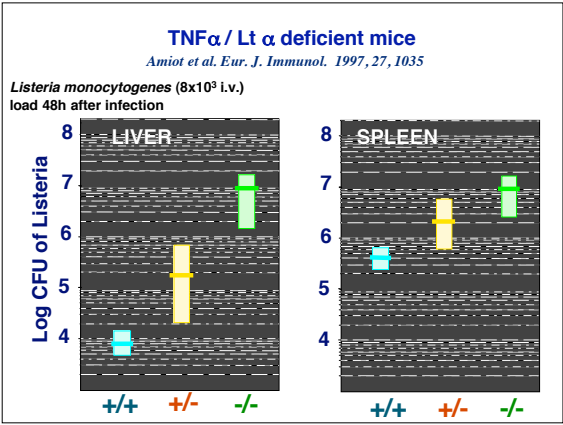
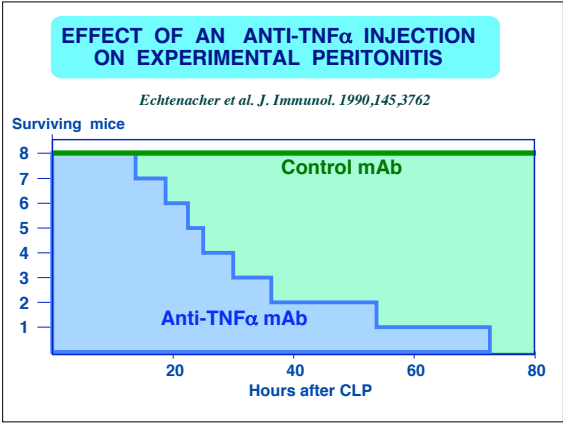
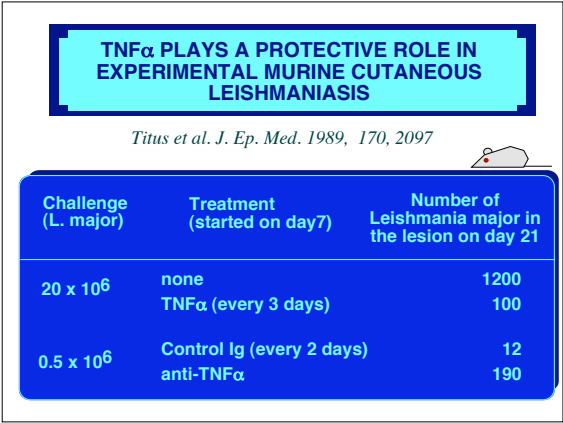
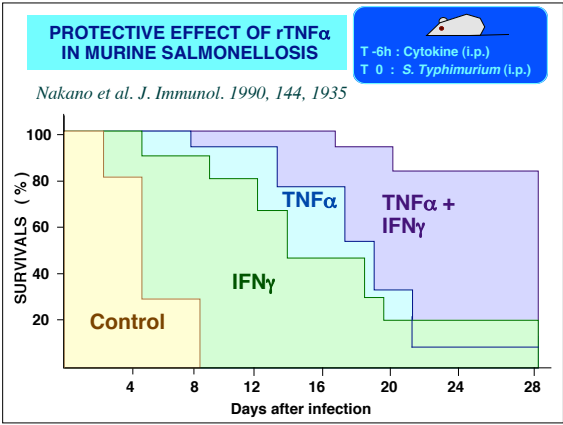
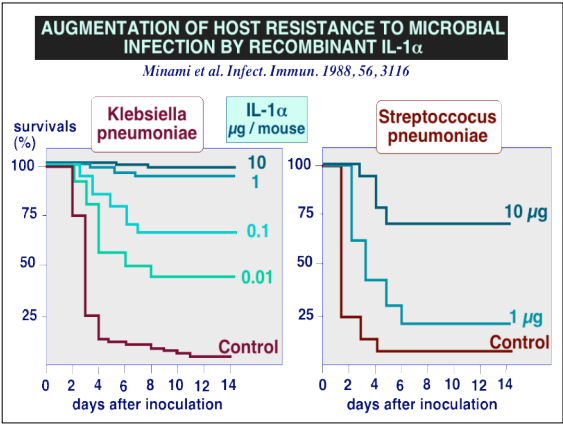
Cavillon et al. Eur. J. Immunol. 1990, 20, 253

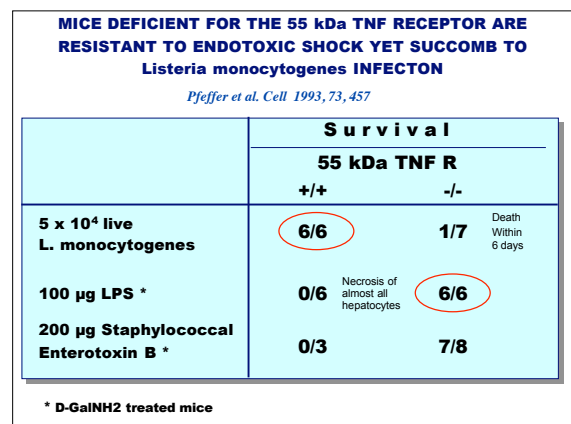
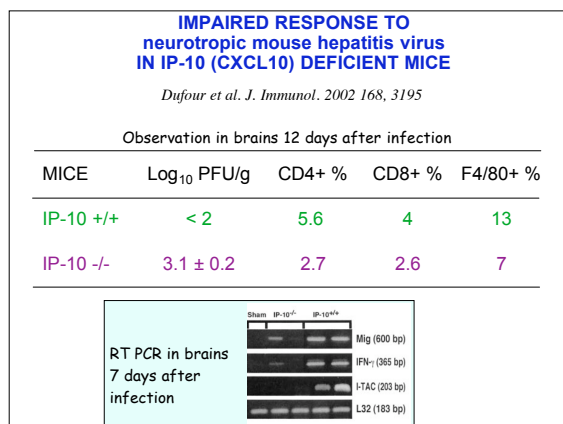
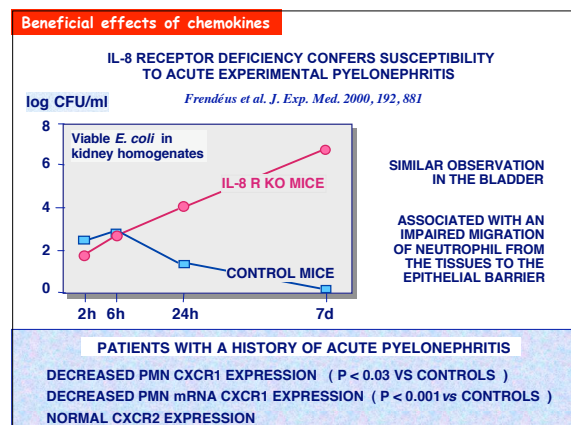
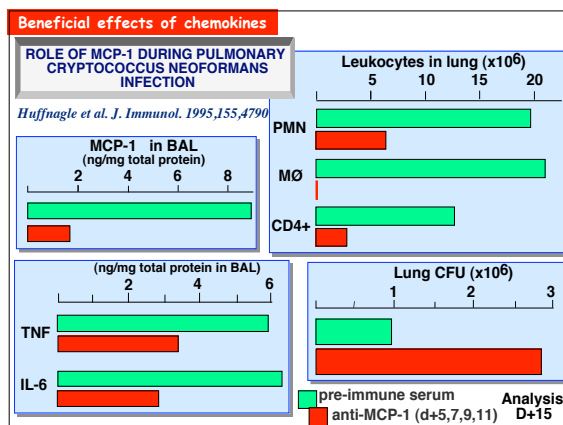
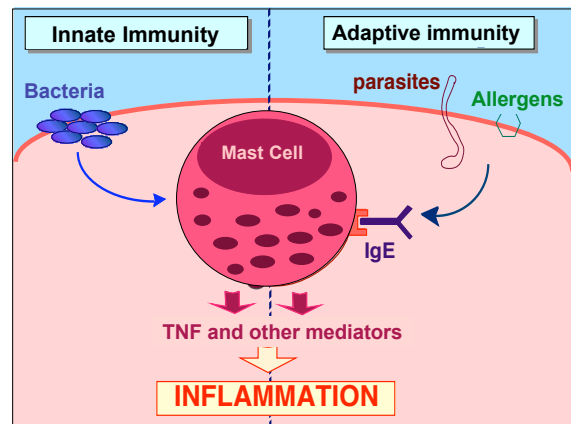
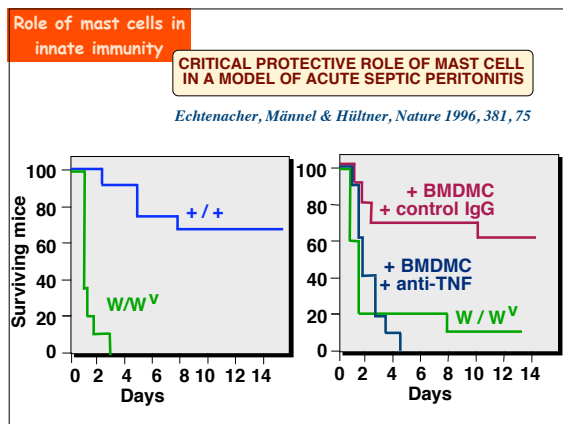


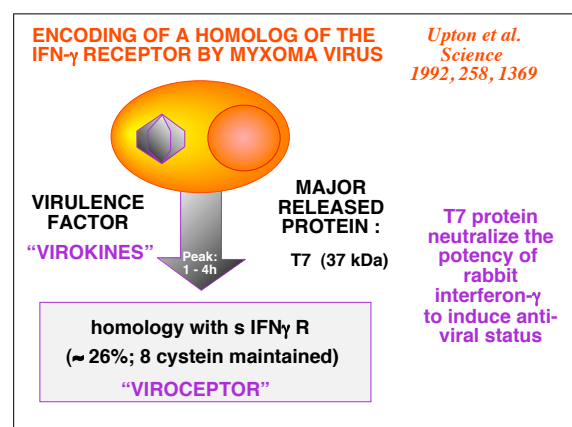
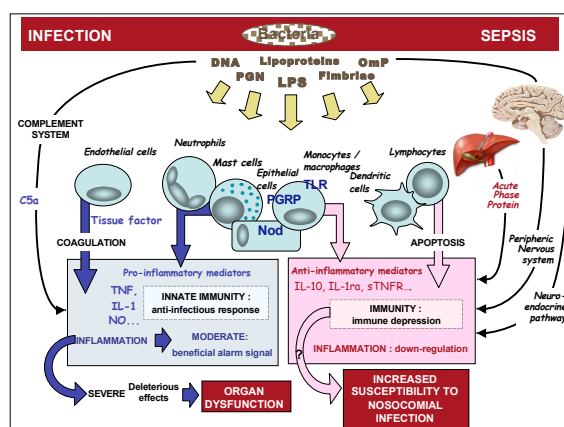
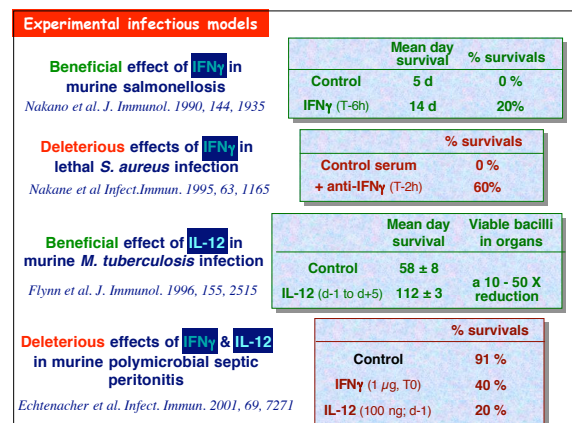
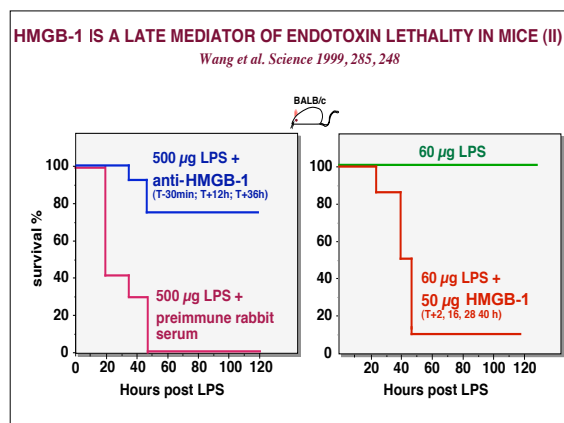
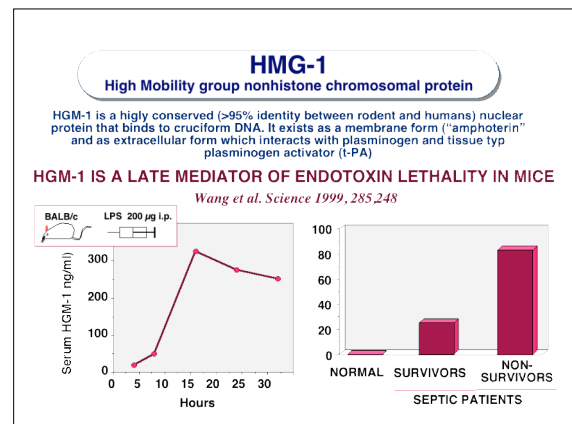
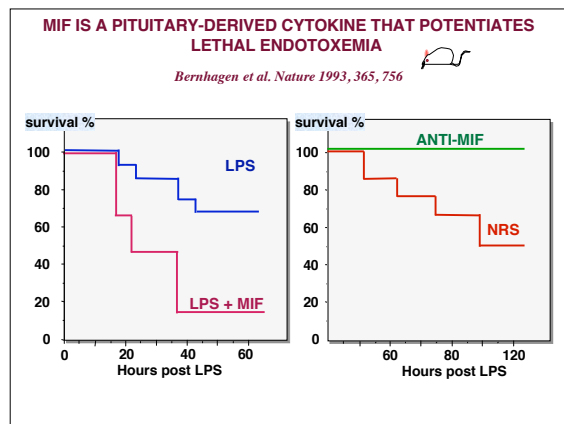


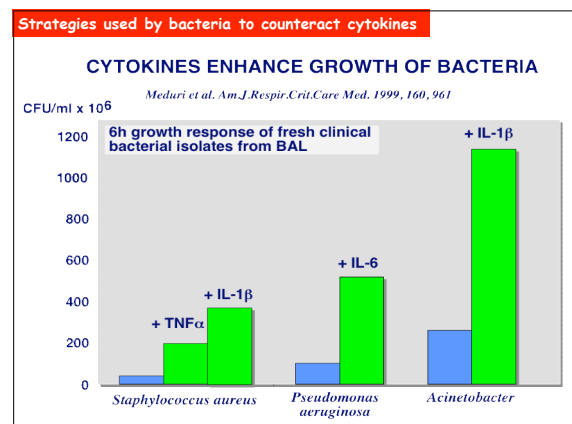
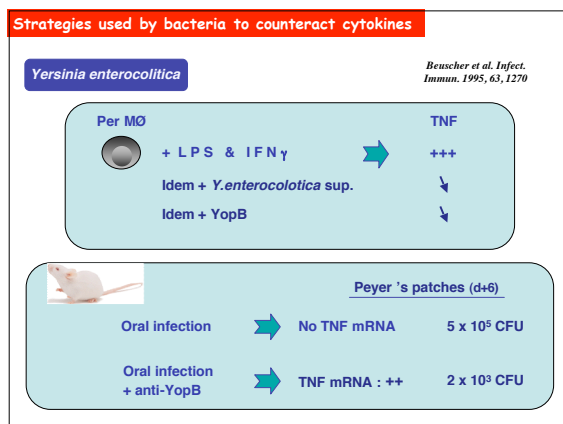
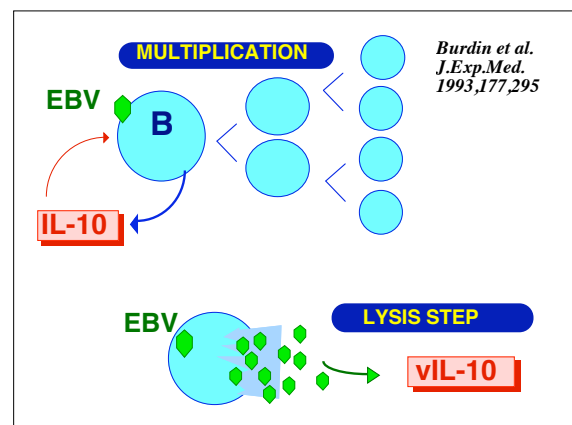
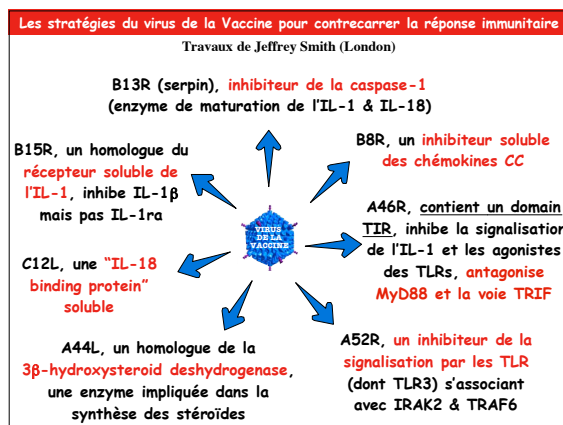
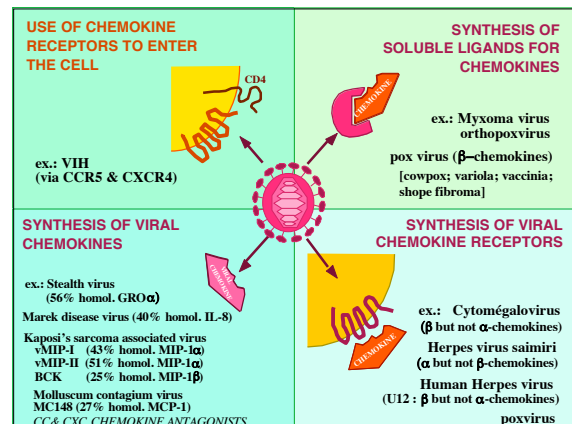
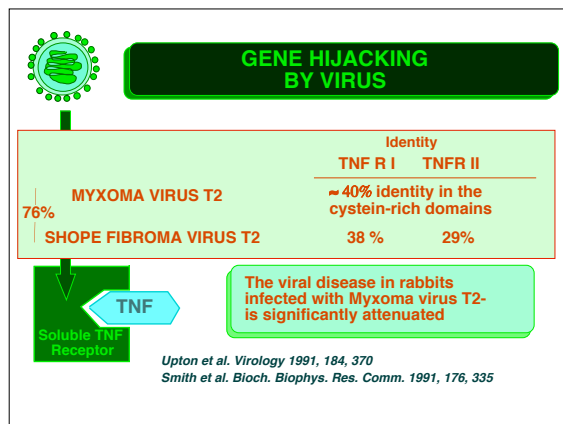












INACTIVATION OF MEMBRANE TNF α BY GINGIPAINS FROM *Porphyromonas gingivalis*

Mezyk-Kopeck *et al. Infect Immun.* 2005; 73: 1506-14.

Gingipains are cysteine proteinases produced by *Porphyromonas gingivalis*, a major causative bacterium of adult periodontitis. They consist of arginine-specific (HRgpA and RgpB) and lysine-specific (Kgp) proteinases.

Flow cytometric analysis of membrane TNF α expressing cells

Counts

Ctrl

HRgpA

RgpB

Kgp

w/o gingipains

Fluorescence Intensity

INACTIVATION OF IL-8 BY *Streptococcus pyogenes*

Edwards et al. *J. Infect. Dis.* 2005, 192, 783

LETHAL NECROTIZING FASCIITIS CAUSED BY *S. pyogenes* IS CHARACTERIZED BY A PAUCITY OF NEUTROPHILS AT THE SITE OF INFECTION

In vitro neutrophil migration in response to IL-8 and IL-8 cleaved by supernatants from *S. pyogenes* H292

Condition	No. of neutrophils ($\times 10^2$)
H292 only	~3
IL-8 only	~27
IL-8 + H292	~5

IL-8 cleavage by supernatants from *S. pyogenes* H292

Native IL-8 **Inactivated IL-8**

EVASION OF TLR5 BY FLAGELLATED BACTERIA

Andersen-Nissen et al. PNAS. 2005, 102, 9247

Luciferase activity in CHO expressing human TLR5

Bacterium	% Fold Induction
<i>Salmonella typhimurium</i>	100
<i>Salmonella typhi</i>	70
<i>Shigella flexneri</i>	75
<i>Pseudomonas aeruginosa</i>	70
<i>Listeria monocytogenes</i>	85
<i>Serratia marcescens</i>	105
<i>Legionella pneumophila</i>	75
<i>Escherichia coli</i>	110

Two monomers of Flagellin

Mutations occurred in 89-96 region, known to be important for TLR5 recognition

Salmonella typhimurium, Salmonella typhi, Shigella flexneri, Pseudomonas aeruginosa, Listeria monocytogenes, Serratia marcescens, Legionella pneumophila, Escherichia coli, Bartonella bacilliformis, Rhizobium meliloti, Campylobacter jejuni, Helicobacter pylori

Convex, Concave, 89-96, 411

Number of publications related to (plant or natural products)
+ cytokine + infection

The bar chart displays the annual number of publications from 1988 to 2006. The y-axis represents the number of publications, ranging from 0 to 120 in increments of 20. The x-axis shows the years. The data shows a steady increase in publications over time, with a notable spike in 2004 reaching approximately 115 publications, followed by a decrease in 2005 and 2006.

Year	Number of Publications
1988	5
1989	4
1990	4
1991	5
1992	8
1993	8
1994	10
1995	16
1996	8
1997	15
1998	13
1999	20
2000	17
2001	28
2002	30
2003	50
2004	115
2005	85
2006	40

Compound A

Compound A (CpdA, or 2-(4-(4-cyanophenyl)-2-chloro-N-methyl-ethylammonium chloride), is a stable analogue of the biogenic phenyl acridine precursor found in the Nambian shrub *Salsola arbuscula* Boissier (9, 10).

In vivo anti-inflammatory effect in a zymosan-induced inflamed paw mouse model

Group	Pretreatment	Difference zymosan-PBS	P value compared with ethanol group
1	PBS	2.02 ± 0.30	0.381 (NS)
2	Ethanol	1.89 ± 0.23	
3	DEX	1.20 ± 0.39	0.0017 (**)
4	CpdA	1.07 ± 0.42	0.0007 (***)

Mice were injected i.c. with zymosan in the footpad, and swelling was determined at 24 after the injection.

Effect of compound A on TNF-induced IL-6 Production by TC10 endothelial cells

DEX	CpdA	TNF	pg/ml IL-6
-	-	+	~100
+	-	+	~10
-	+	+	~10
+	+	+	~140
-	-	-	~90
+	-	-	~10
-	+	-	~10
+	+	-	~10

Inhibition of TNF and NO production by mangiferin (from *Mangifera indica*)

Garrido et al. Pharmacol. Res. 2004, 50, 165

Effect of *per os* administration of *Mangifera indica* extract (V) and mangiferin (M) (10 - 200 µg/kg) for 7 days on LPS-induced TNF (T=60 min)

in vivo

Group	TNF (ng ml⁻¹)
CTR	~1
V000	~2
V100	~35
V500	~25
V1000	~15*
V5000	~12*
M100	~10*
M500	~8*
M1000	~5*
DM000	~2*

(B)

Effect of mangiferin (M: 1-200 µg/ml) on LPS (± IFN)-induced TNF and nitrite production by RAW 264 M/D

in vitro

Group	TNF (pg ml⁻¹)
CTR	~10
M000	~10
LPS	~1050
LPS+IFN	~1000
M100+LPS+IFN	~1100
M500+LPS+IFN	~850*
M1000+LPS+IFN	~700*
M2000+LPS+IFN	~550*
DE+M1000+LPS+IFN	~400*

(A)

TNF mRNA expression (T=30 min) in lungs and liver after LPS injection

Dexa M20 M100 V1000 V500 LPS CTR

Lung

Liver

G-3-PDH

in vitro

Effect of mangiferin (M: 1-200 µg/ml) on LPS (± IFN)-induced TNF and nitrite production by RAW 264 M/D

NO

Group	NO (µM)
CTR	~1
M100	~5
M500	~4
LPS	~24
LPS+IFN	~22
M100+LPS+IFN	~22
M500+LPS+IFN	~20*
M1000+LPS+IFN	~18*
M2000+LPS+IFN	~15*
LNMW+M1000+LPS+IFN	~5*

(B)

