

RÉPONSE CYTOKINIQUE À L'AGRESSION

Jean-Marc Cavaillon
Cytokines & inflammation



jmcavail@pasteur.fr

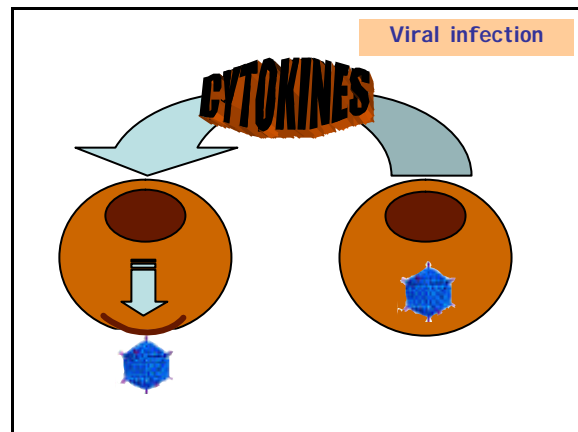


RÉPONSE CYTOKINIQUE À L'AGRESSION

- 1) Les cytokines
- 2) L'induction des cytokines par les agents infectieux
- 1) Le rôle des cytokines contre l'infection
- 2) Mi-ange / mi-démon : l'exemple du sepsis

RÉPONSE CYTOKINIQUE À L'AGRESSION

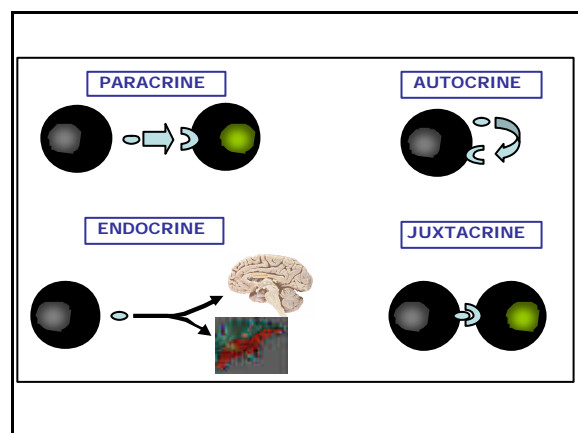
- 1) Les cytokines
- 2) L'induction des cytokines par les agents infectieux
- 1) Le rôle des cytokines contre l'infection
- 2) Mi-ange / mi-démon : l'exemple du sepsis



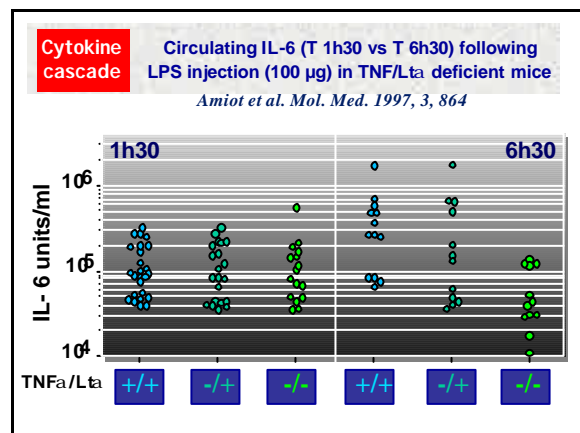
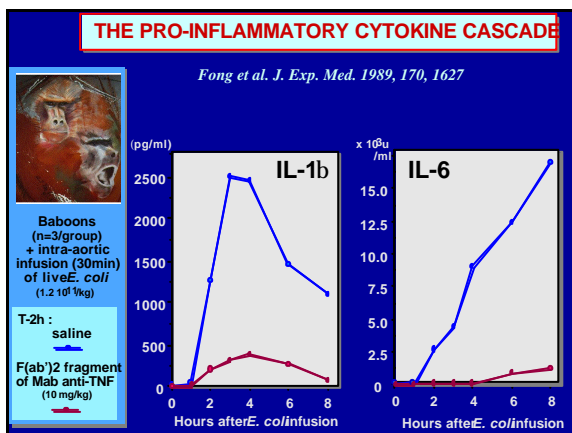
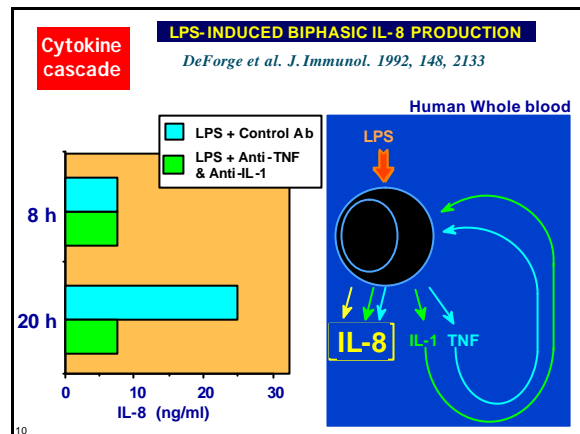
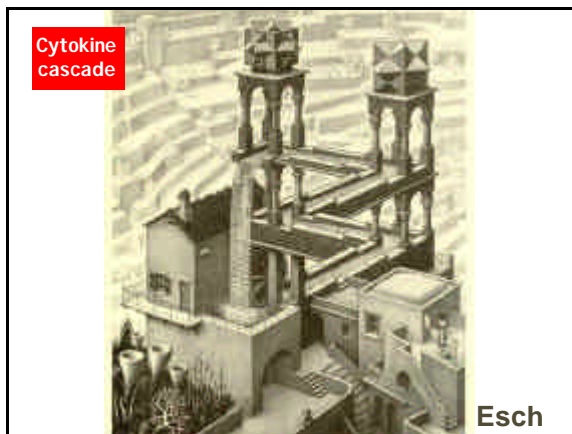
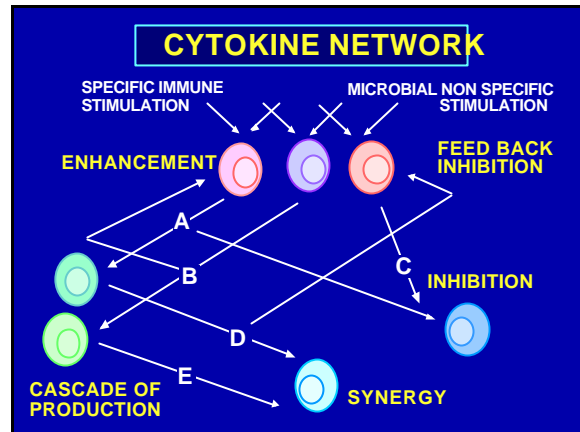
Cytokines

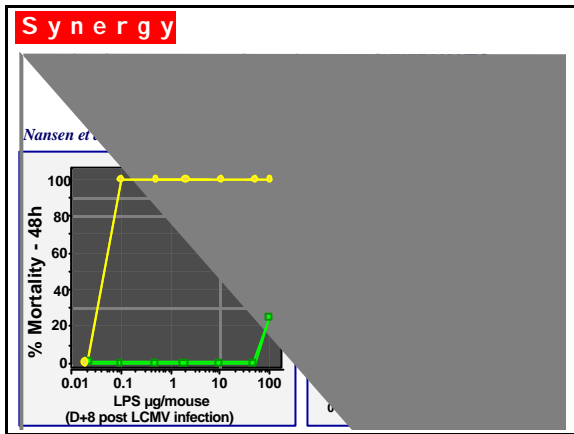
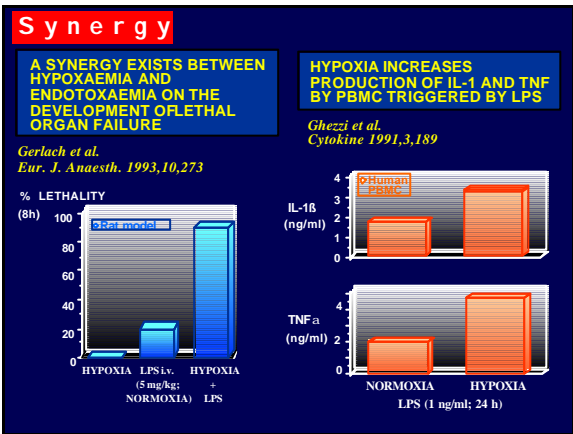
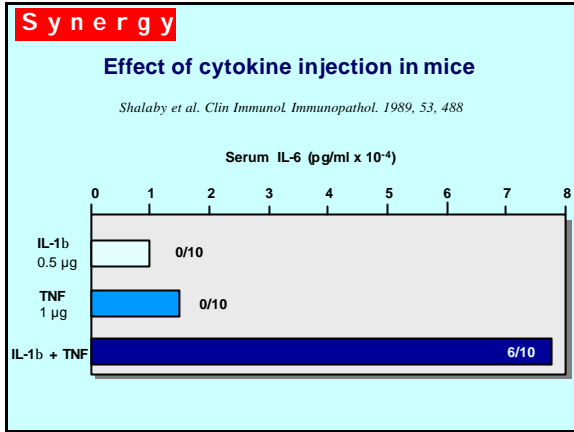
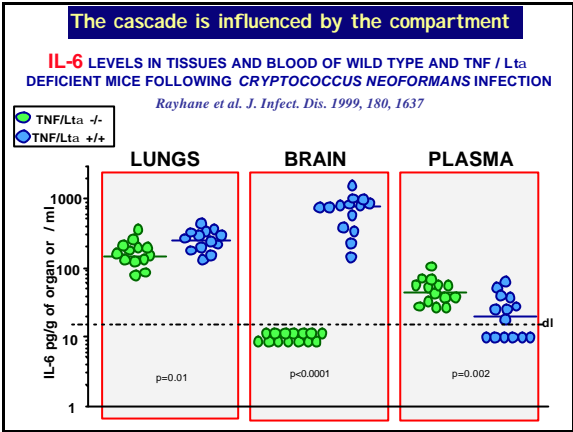
THE WAY TO TALK OF IMMUNE CELLS : AN UNIVERSAL LANGUAGE

CYTOKINES **RECEPTORS**



CYTOKINES	
INTERFERONS	IFN α , IFN β , IFN γ , IFN κ , IFN λ , IFN ω
INTERLEUKINS	IL-1 α , IL-1 β , IL-1 γ , IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17A-E, IL-18, IL-19, IL-20, IL-21, IL-22, IL-23, IL-25, IL-26, IL-27, IL-28, IL-29
COLONY STIMULATING FACTORS	M-CSF, G-CSF, GM-CSF
CHEMOKINES	CCL1, CCL2, CCL3... CCL28 XCL1, XCL2 CXCL1, CXCL2, CXCL3... CXCL16 CX3CL1
TNF family	TNF, Lta, Ltb, NGF, CD27L, CD30L, CD40L, CD137L FasL, LIGHT, TRAIL, RANKL, TWEAK, APRIL, BlyS
TRANSFORMING GROWTH FACTORS	TGF α , TGF β _{1,2,3}
Leukemia Inhibitory Factor (LIF), Cardiotrophin, Oncostatin M, CNTF Migration inhibitory factor (MIF), Stem cell factor (c kit ligand)	

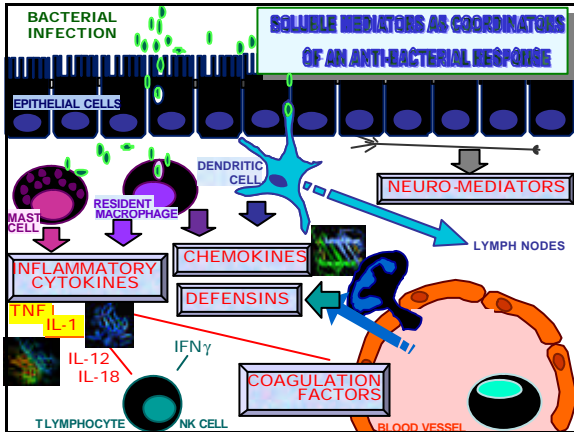


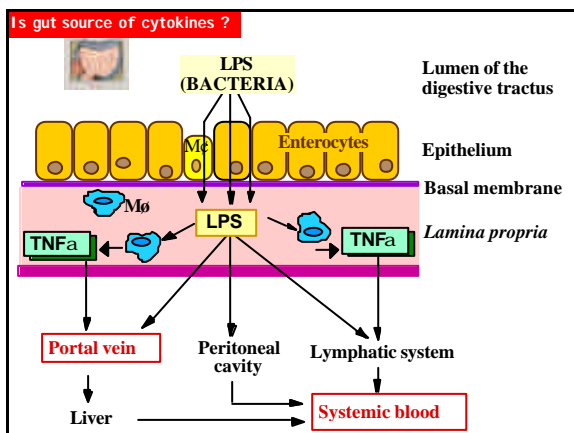
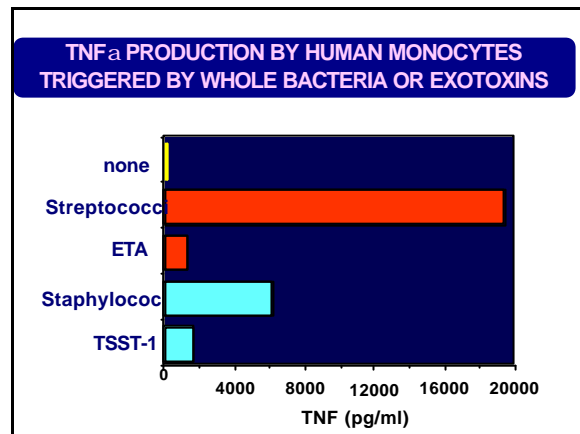
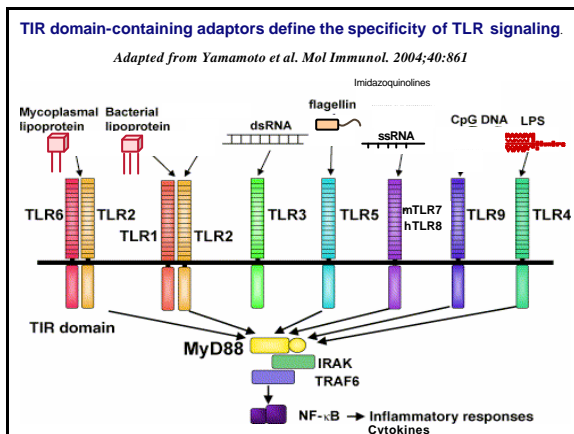
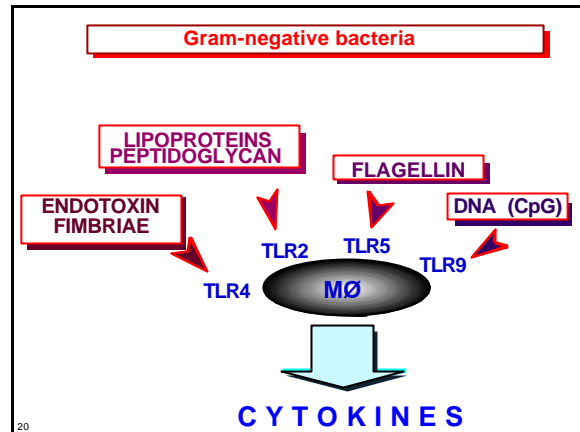
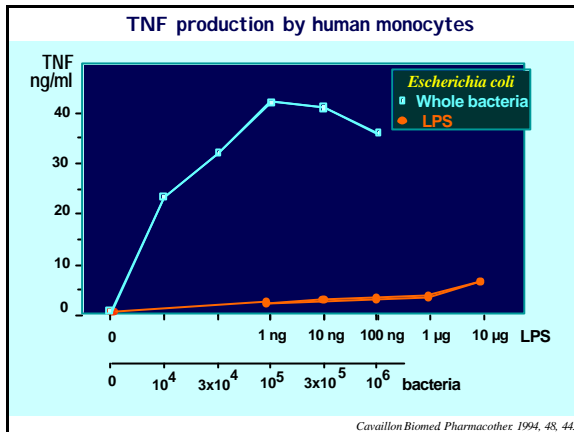


D.E.S.C. Maladies Infectieuses et Transmissibles

RÉPONSE CYTOKINIQUE À L'AGRESSION

- 1) Les cytokines
- 2) L'induction des cytokines par les agents infectieux
- 3) Le rôle des cytokines contre l'infection
- 4) Mi-ange / mi-démon : l'exemple du sepsis



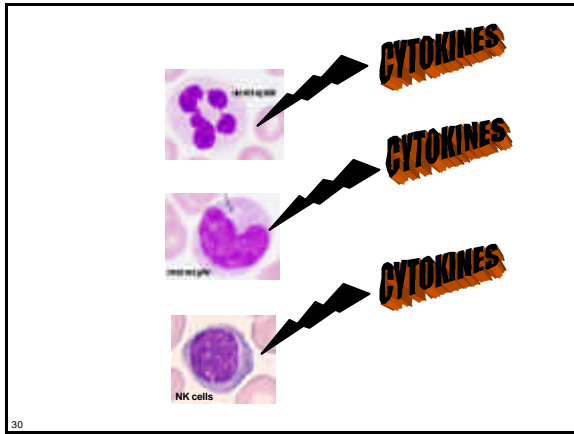
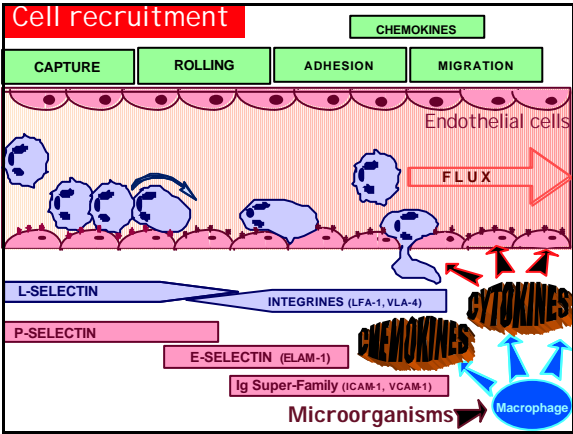
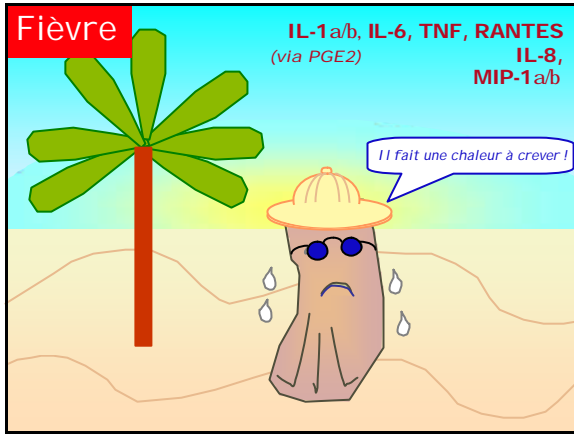
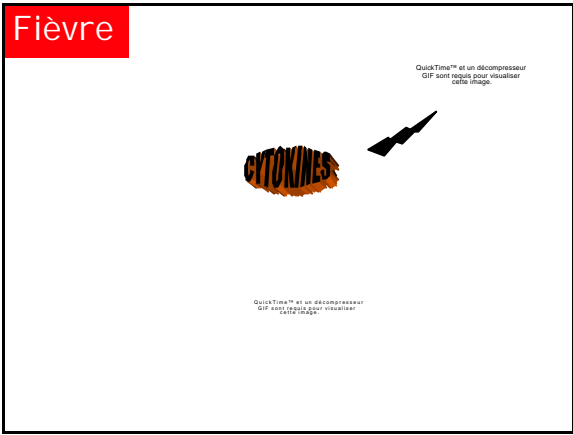
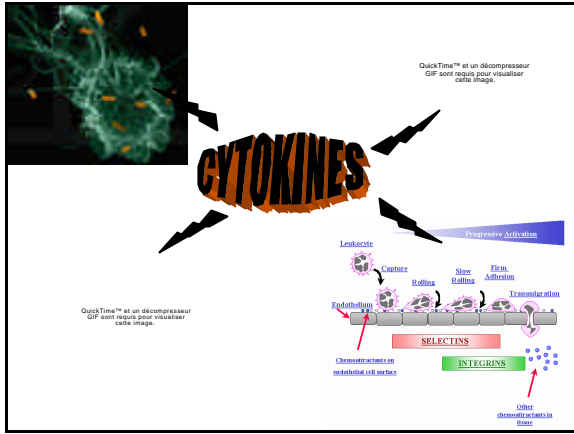
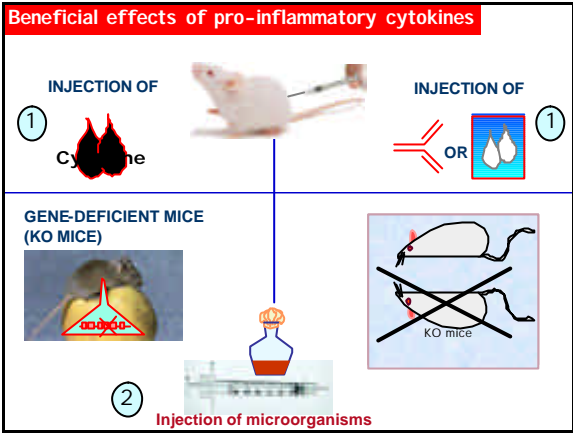


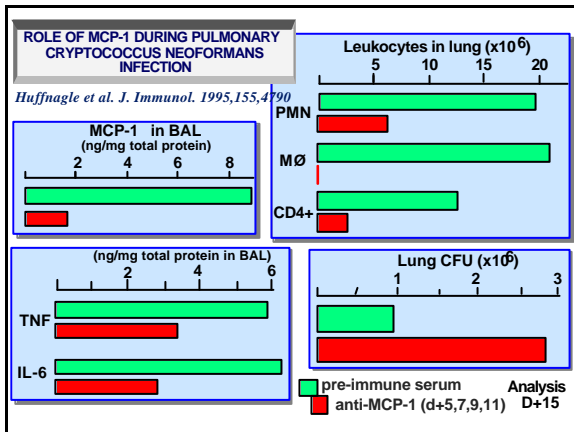
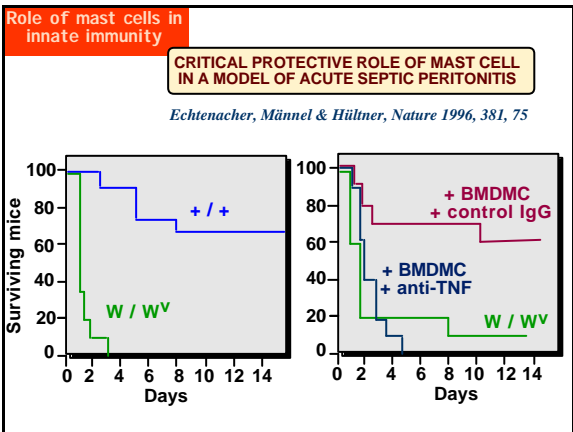
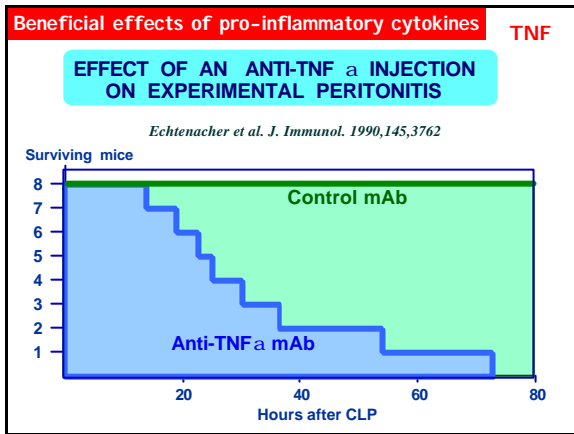
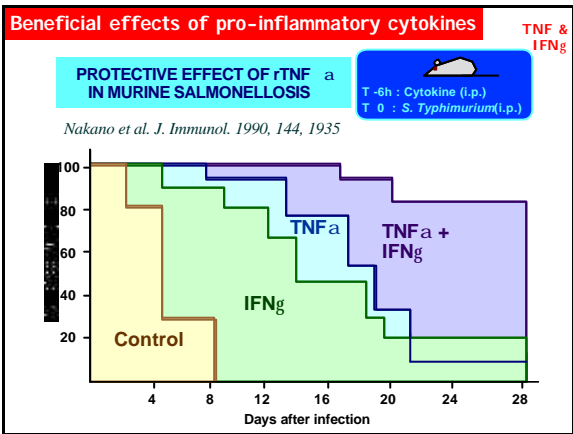
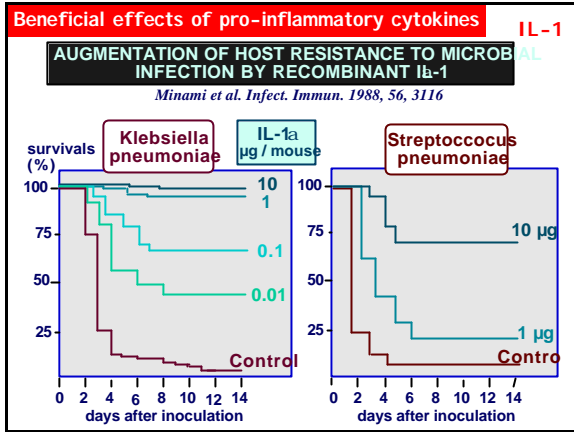
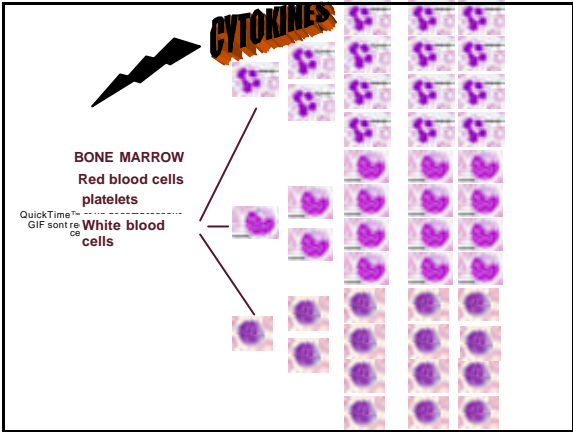
D.E.S.C. Maladies Infectieuses et transmissibles

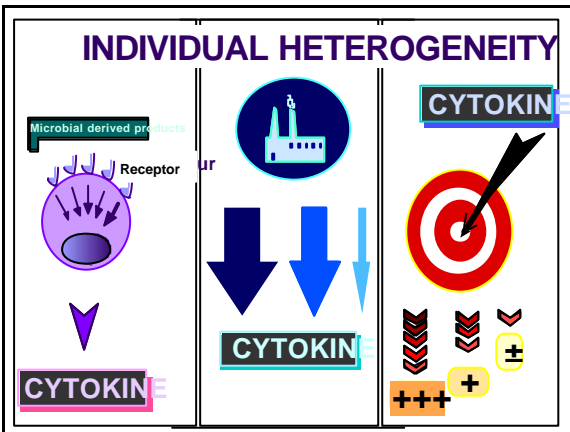
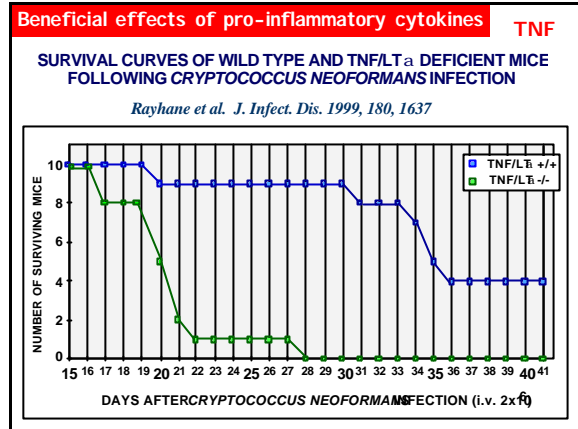
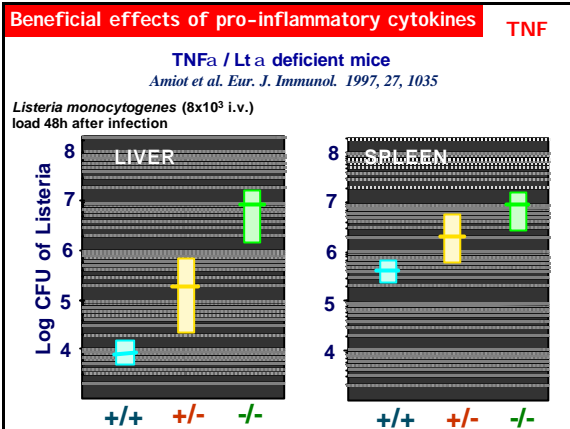
RÉPONSE CYTOKINIQUE À L'AGRESSION

- 1) Les cytokines
- 2) L'induction des cytokines par les agents infectieux

- 1) Le rôle des cytokines contre l'infection
- 2) Mi-ange / mi-démon : l'exemple du sepsis







D.E.S.C. Maladies Infectieuses et transmissibles

RÉPONSE

MISSION

- 1) Les
- 2) L'inc
- 1) Le r
- 2) Mi-

ion sepsis

40

MICE DEFICIENT FOR THE 55 kDa TNF RECEPTOR ARE RESISTANT TO ENDOTOXIC SHOCK YET SUCCOMB TO Listeria monocytogenes INFECTION
Pfeffer et al. Cell 1993, 73, 457

	Survival		
	+/+	-/-	
5 x 10 ⁴ live <i>L. monocytogenes</i>	6/6	1/7	Death Within 6 days
100 μ g LPS *	0/6	6/6	Necrosis of almost all hepatocytes
200 μ g Staphylococcal Enterotoxin B *	0/3	7/8	

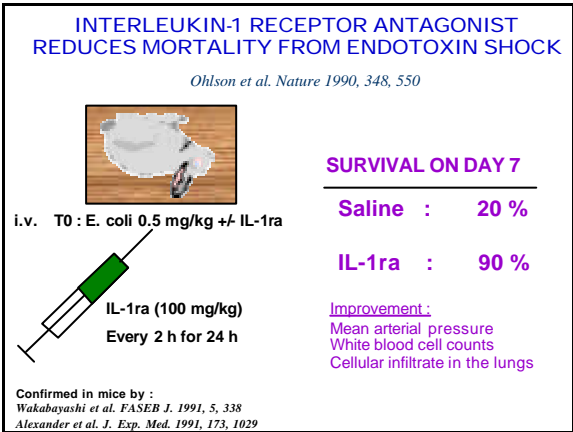
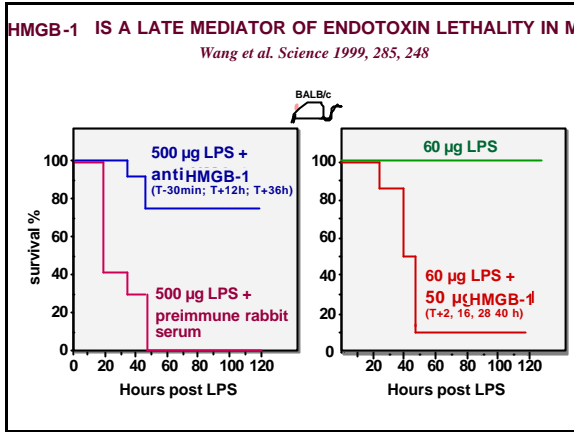
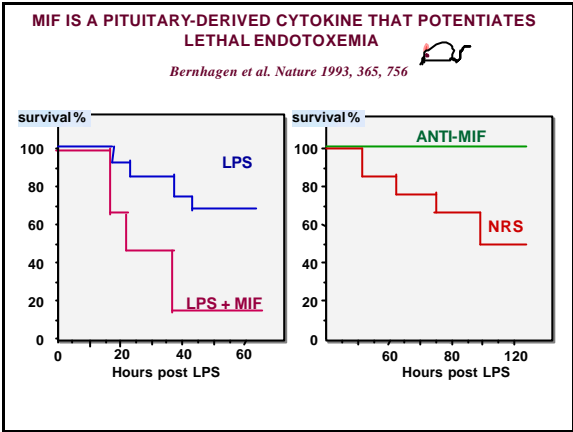
* D-GalNH₂ treated mice

Synergy

EVIDENCE FOR IFN γ AS A MEDIATOR OF THE LETHALITY OF ENDOTOXIN & TNF α
Doherty et al. J. Immunol. 1992, 149, 1666

TNF α	300 μ g/kg	0 % lethality
IFN γ	50,000 U	0 % lethality
TNF α + IFN γ		100 % lethality

ANTI-IFN γ	TNF α
	1 to 4 LD 100 (1400 μ g/kg)
	Protection



PROTECTION INDUCED BY SOLUBLE TNF RECEPTOR
Van Zee et al. *PNAS* 1992, 89, 4845

Baboon

T0 : *E. coli* [LD 100]
Infusion = 30 min

T0 : ± s TNF R
(molar excess x 300)
Infusion = 3 h

	<i>E. coli</i>	<i>E. coli</i> + S TNF R I
TNF (2h)	30 ng/ml	< d.l.
IL-1b (3h)	2.5 ng/ml	0.5 ng/ml
IL-6 (8 h)	20 000 u/ml	9 000 u/ml
Mean arterial pressure	- 56 %	- 29 %
Resuscitation fluid required to maintain hemodynamic stability	163 ml/kg	13 ml/kg

Is TNF responsible of the deleterious effects observed during sepsis ? → **ANTI-TNF STUDIES**

Beutler et al.
Passive immunization against cachectin/tumor necrosis factor protects mice from lethal effects of endotoxin
Science 1985, 229, 869

Tracey et al.
Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia
Nature 1987, 330, 662

8 multicentric double blind against placebo Studies (1990/1998): 4132 patients (1990/1998)

Mortality day : Placebo 41% / anti-TNF 40%

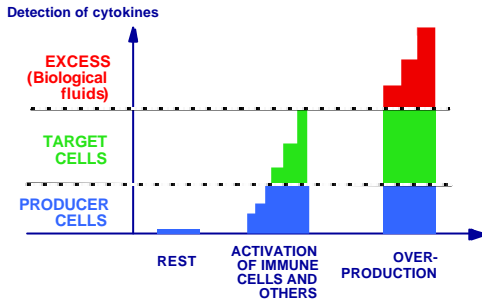
Is IL-12 responsible of the deleterious effects observed during sepsis ?

INVOLVEMENT OF IL-12 IN LPS-DEPENDENT SHOCK BUT NOT IN TNF-DEPENDENT SHOCK
Mattner et al. *Infect. Immun.* 1997, 65, 4734

	% SURVIVAL (350 µg LPS i.p.)	% SURVIVAL (LPS 0.1µg + GalNH ₂ 10 mg)
CONTROLS	12	0
ANTI-IL-12 24, 12 & 1h before LPS challenge	90	0
TNF R - IgG 1h before LPS challenge	70	90

Circulating cytokines : the tip of the iceberg ?

Cavaillon et al. Circ. Shock 1992, 38, 145



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/k, i.e. 3750 X dose given to human volunteers)

Hours after LPS injection	Serum concentration (pg/ml)				
	LPS	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

50

Erasmus MC **6th European Congress of Trauma and Emergency Surgery** September 9-12, 2004

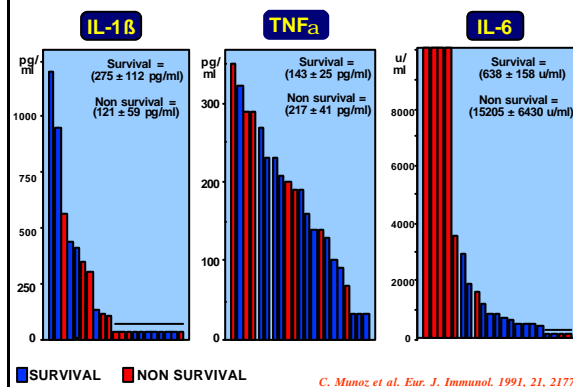
SEPSIS :
an exacerbated production of **anti-inflammatory** cytokines

CIRCULATING CYTOKINES

HUMAN SEPSIS

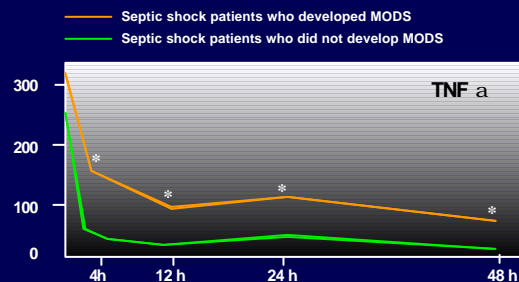
	TNF	1986	Waage et al. Scand. J. Immunol. 24, 739
	IL-1	1988	Girardin et al. N. Engl. J. Med. 319, 397
	IL-6	1989	Waage et al. J. Exp. Med. 169, 33 Hack et al. Blood 74, 1704
	IL-8	1992	Hack et al. Infect. Immun. 60, 2835 Friedland et al. Infect. Immun. 60, 2402
	IL-10	1994	Marchand et al. Lancet 343, 707
	IL-1ra	1994	Rogy et al. J. Am Coll Surg. 178, 132
	TGFβ	1996	Marie et al. Ann. Intern. Med. 125, 520

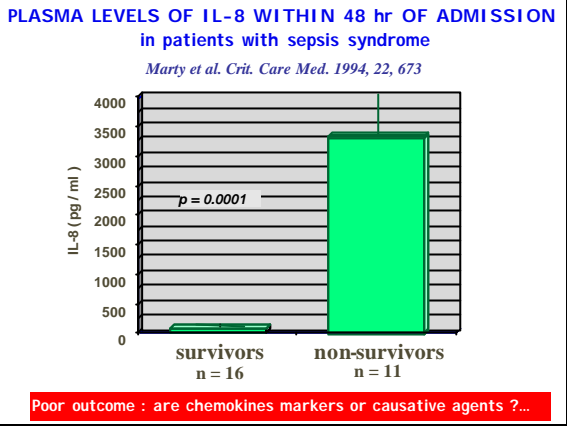
Exacerbated production of pro-inflammatory cytokines



THE PERSISTENCE OF TNF (AND IL-6) IN THE SERUM RATHER THAN THE PEAK LEVELS CORRELATES WITH MODS DEVELOPMENT AND PREDICTS A POOR OUTCOME

Pinsky et al. Chest 1993, 103, 565

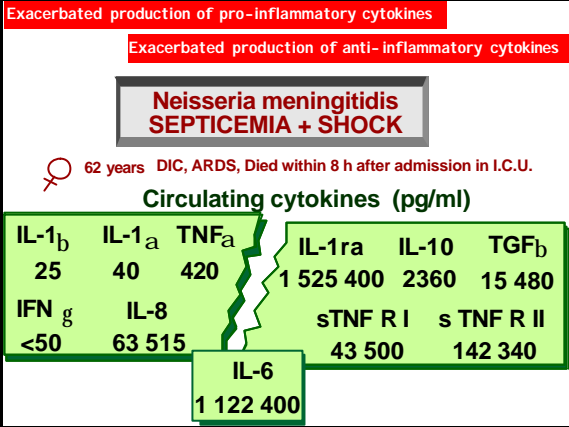
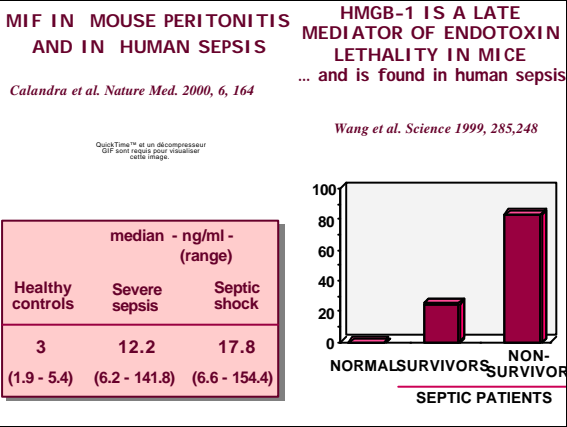




Correlation (r values) between markers at admission
[n = 18 sepsis patients APACHE II = 23 ± 2]

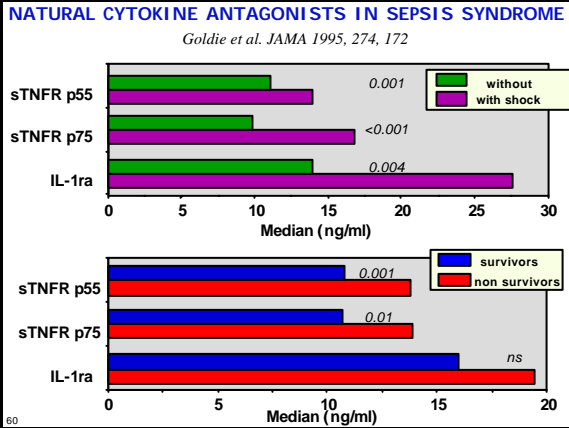
	IL-8	MCP-1	MIP-1b	RANTES	IL-1ra	IL-10	sTNFR II
IL-6	0.80*	0.77*	0.89*	no	0.74*	0.97*	no
IL-8	-	0.99*	0.89*	no	0.80*	0.85*	no
MCP-1	-	-	0.87*	no	0.77*	0.83*	no
MIP-1b	-	-	-	no	0.90*	0.93*	no
RANTES	-	-	-	-	no	no	no
IL-1ra	-	-	-	-	-	0.84*	no

RANTES is inversely correlated with APACHE II score $r = -0.71$, $p = 0.02$



Erasmus MC **6th European Congress of Trauma and Emergency Surgery** September 9-12, 2004

Are anti-inflammatory mediators sufficient to counteract the deleterious effects of pro-inflammatory cytokines ?

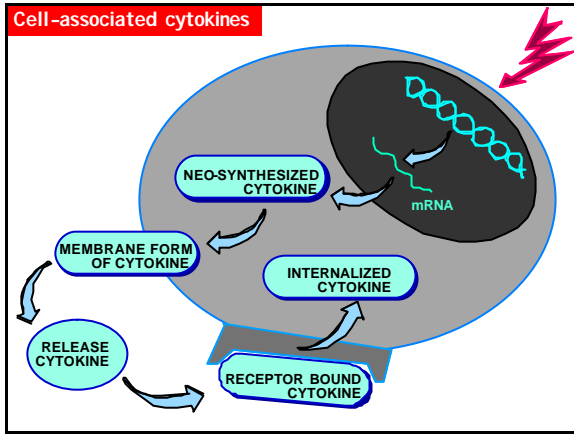
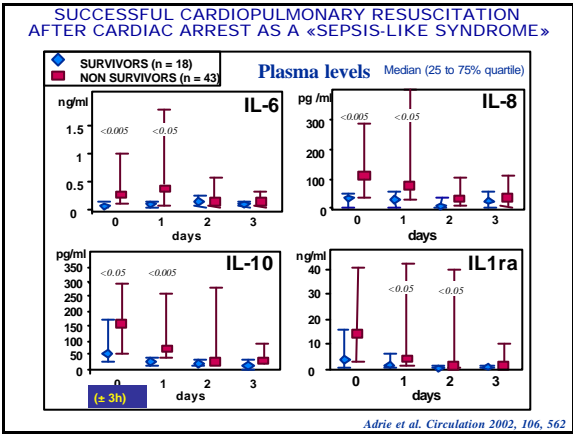
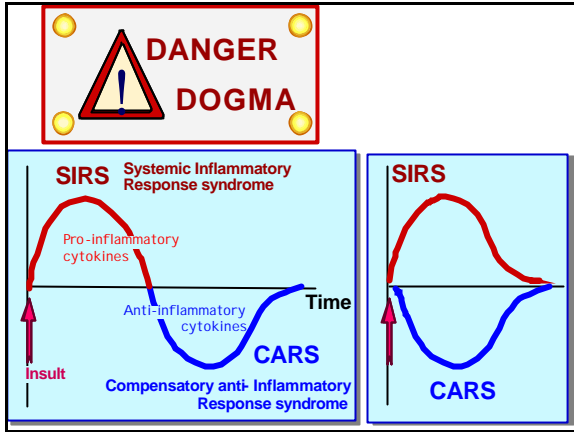


CIRCULATING TNF & sTNFR IN MENINGOCOCCAEMIA
Girardin et al. Immunol. 1992, 76, 20

ON ADMISSION	SURVIVALS (n = 26)	DEATHS (n = 9)	p
TNF	470 pg/ml	(3.1 x) 1466 pg/ml	0.001
sTNF R I	26.3 ng/ml	(1.3 x) 35.4 ng/ml	0.007
sTNF R II	67.8 ng/ml	(1.4 x) 93.3 ng/ml	0.04

CLINICAL DEVELOPMENT OF ARDS
Suter et al. Am. Rev. Resp. Dis. 1992, 145, 1016

IN BAL (pg/ml)	TNF		10 731 ± 5048	x 92.5
	116 ± 36	—		
	sTNF R I	3700 ± 1400	24 600 ± 2600	x 6.6



Cell-associated cytokines **TNF**

MEAN VALUES OF CIRCULATING TNF and MONOCYTE-ASSOCIATED TNF AT THE END OF THE LONGITUDINAL STUDY AMONG SEPTIC PATIENTS

	SURVIVING	NON SURVIVING
Mean day of the last measurement	14 ± 2	10 ± 3
Plasma TNF _a (pg/ml)	17 % (<70-150)	67 % (125 ± 53)
Monocyte - Associated TNF _a pg/10 ⁶ monocytes	67 % (233 ± 67)	100% (372 ± 90)

Munoz et al. Eur. J. Immunol 1991, 21, 2177

