Physiopathologie du Sepsis

DESAR - Avril 2005

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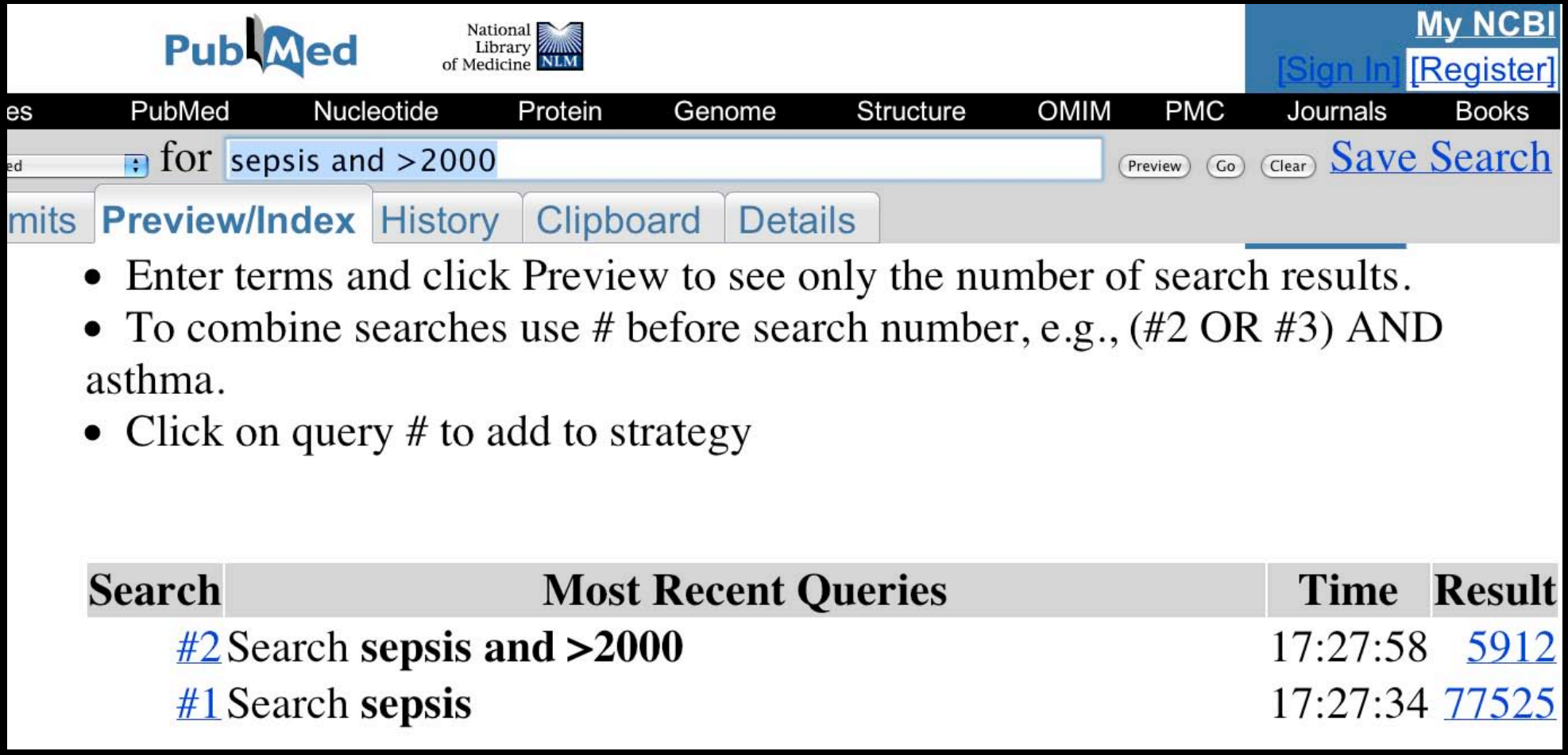
Plan

- Méthodologie (bibliographie)
- Les données épidémiologiques
- Du sepsis vers la défaillance d'organe
- Inflammatoire, Immunité, Coagulation …
- Des pistes …
  - Génétique
  - Système Nerveux et Variabilité de la Réponse
  - Hibernation
  - HMGB-1, MIF, …
  - Autres …

Méthodologie



Méthodologie

Définitions, Epidémiologie

- Angus, Crit Care Med 2001; 29: 1303
- Levy, Crit Care Med 2003; 31: 1250
- Alberti, Am J Respir Crit Care Med 2005; 171: 461
- ***Annane, Lancet 2005; 365: 63***

Physiopathologie et nouvelles pistes

- ***Hotchkiss, New Engl J Med 2003; 348: 138***
- Riedemann, Nat Med 2003; 9: 517
- Matthay, Nat Med 2004; 10: 1161
- Aird, Blood 2003; 101: 3765
- Singer, Lancet 2004; 364: 545
- Vanhorebeek, Lancet 2005; 365: 53

Epidémiologie (Angus, Crit Care Med 2001; 29: 1303)

Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care

Derek C. Angus, MD, MPH, FCCM; Walter T. Linde-Zwirble; Jeffrey Lidicker, MA; Gilles Clermont, MD; Joseph Carcillo, MD; Michael R. Pinsky, MD, FCCM

Objective: To determine the incidence, cost, and outcome of severe sepsis in the United States.

Design: Observational cohort study.

Setting: All nonfederal hospitals (n = 847) in seven U.S. states.

Patients: All patients (n = 192,980) meeting criteria for severe sepsis based on the International Classification of Diseases, Ninth Revision, Clinical Modification.

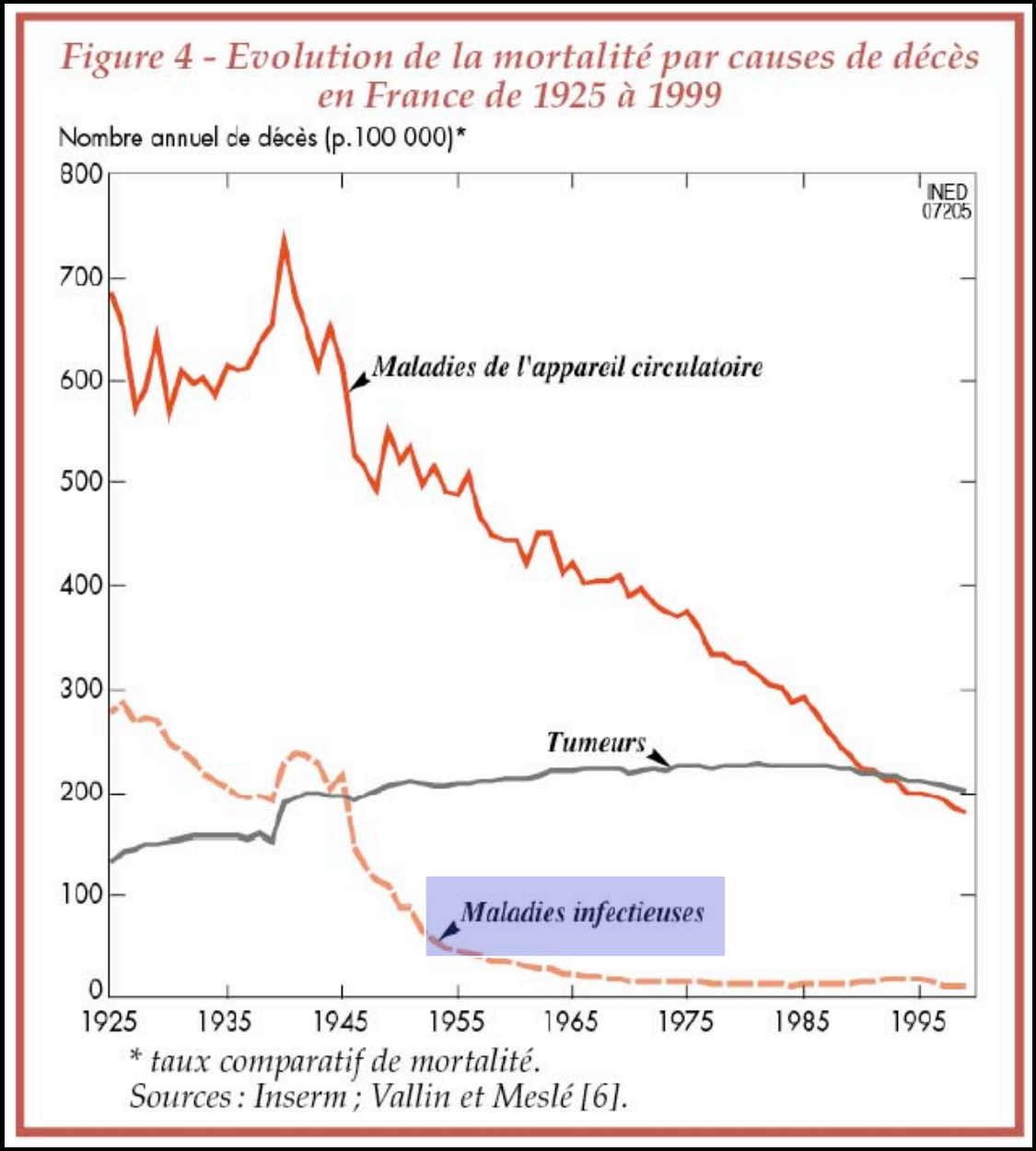
Interventions: None.

Measurements and Main Results: We linked all 1995 state hospital discharge records (n = 6,621,559) from seven large states with population and hospital data from the U.S. Census, the Centers for Disease Control, the Health Care Financing Administration, and the American Hospital Association. We defined severe sepsis as documented infection and acute organ dysfunction using criteria based on the International Classification of Diseases, Ninth Revision, Clinical Modification. We validated these criteria against prospective clinical and physiologic criteria in a subset of five hospitals. We generated national age- and gender-adjusted estimates of incidence, cost, and outcome. We identified 192,980 cases, yielding national estimates of 751,000 cases (3.0 cases per 1,000 population and 2.26 cases per 100 hospital discharges), of whom 383,000 (51.1%) received intensive care and an additional 130,000 (17.3%) were ventilated in an intermediate care unit or cared for in a coronary care unit. Incidence increased >100-fold with age (0.2/1,000 in children to 26.2/1,000 in those >85 yrs old). Mortality was 28.6%, or 215,000 deaths nationally, and also increased with age, from 10% in children to 38.4% in those >85 yrs old. Women had lower age-specific incidence and mortality, but the difference in mortality was explained by differences in underlying disease and the site of infection. The average costs per case were $22,100, with annual total costs of $16.7 billion nationally. Costs were higher in infants, nonsurvivors, intensive care unit patients, surgical patients, and patients with more organ failure. The incidence was projected to increase by 1.5% per annum.

Conclusions: Severe sepsis is a common, expensive, and frequently fatal condition, with as many deaths annually as those from acute myocardial infarction. It is especially common in the elderly and is likely to increase substantially as the U.S. population ages. (Crit Care Med 2001; 29:1303–1310)

215 000 morts/USA : 10% des décès

Epidémiologie du sepsis



◆ Cardio-Vasc

- Prévention
- Physiopath et Définition
  - *ECG*
  - *CPK Tropo*
  - *Thrombose*
  - *Δg rapide (early goal directed)*
  - *Inflammation et Sd Métabolique*
- Traitements adaptés

◆ Cancer

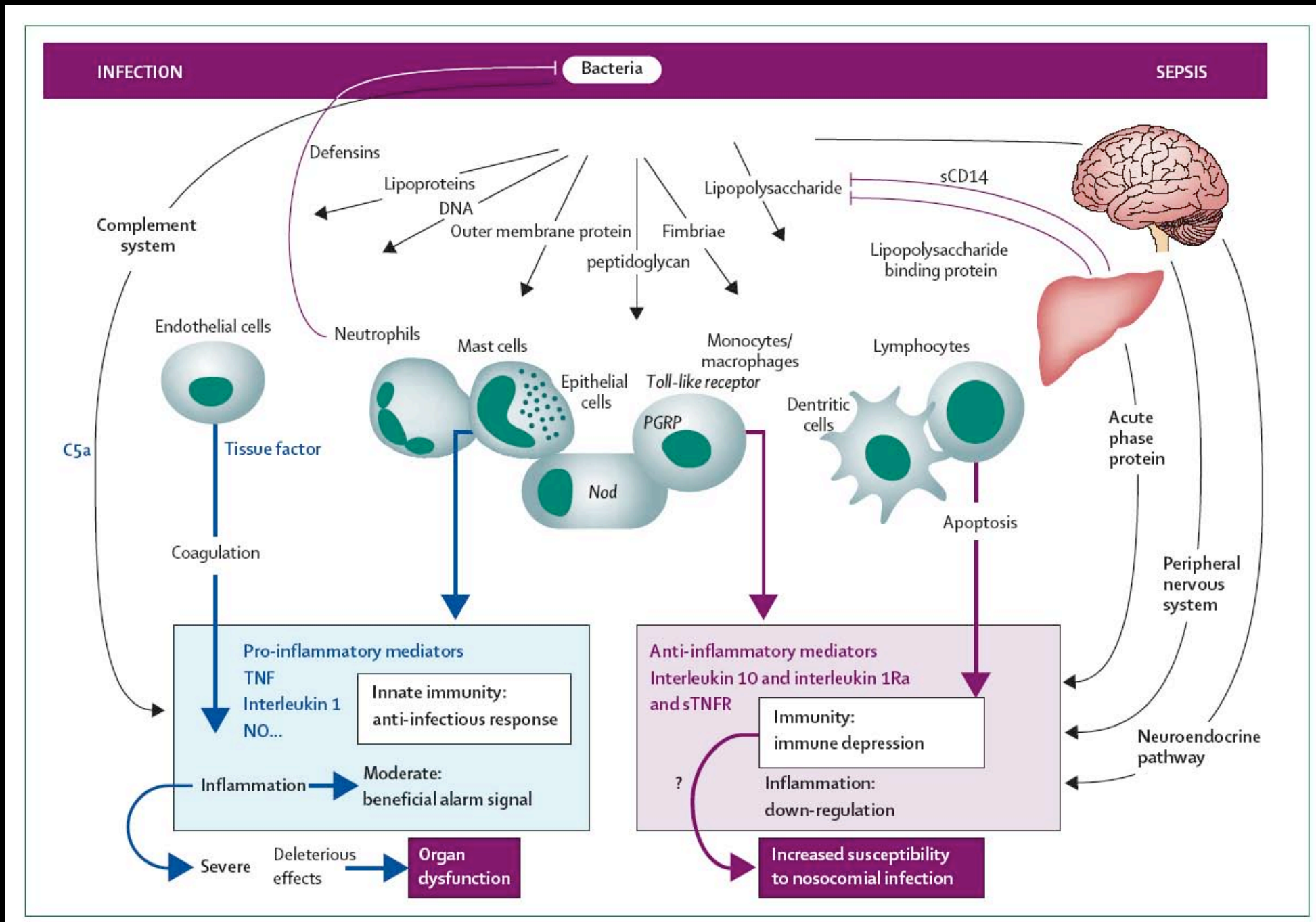
- Prévention
  - *Recul des FDR*
- Δg rapide (dépistage) +++
- Physiopath et Définition
  - *TNM, génétique*
- Traitements adaptés

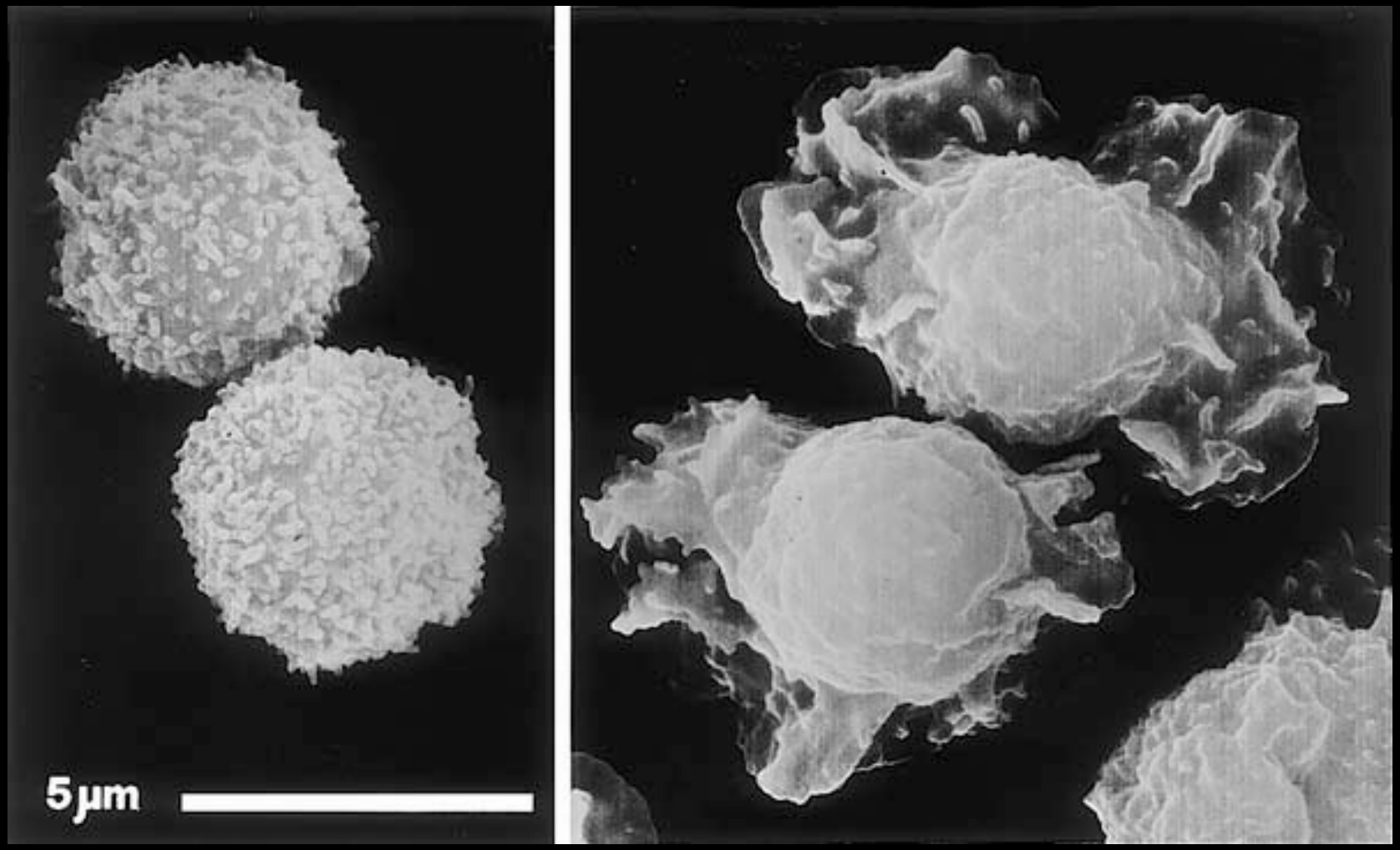
Définitions ?

- 1991 : Conférence de Consensus (Bone)
- 2001 : Nouvelle conférence (Rien de neuf sous le soleil)
  - Pas de physiopathologie claire
  - Hétérogénéité +++ et modèles expérimentaux …
  - Pas de marqueurs biologiques ou trop …
- Concept PIRO

De quoi on meurt au cours du sepsis ?

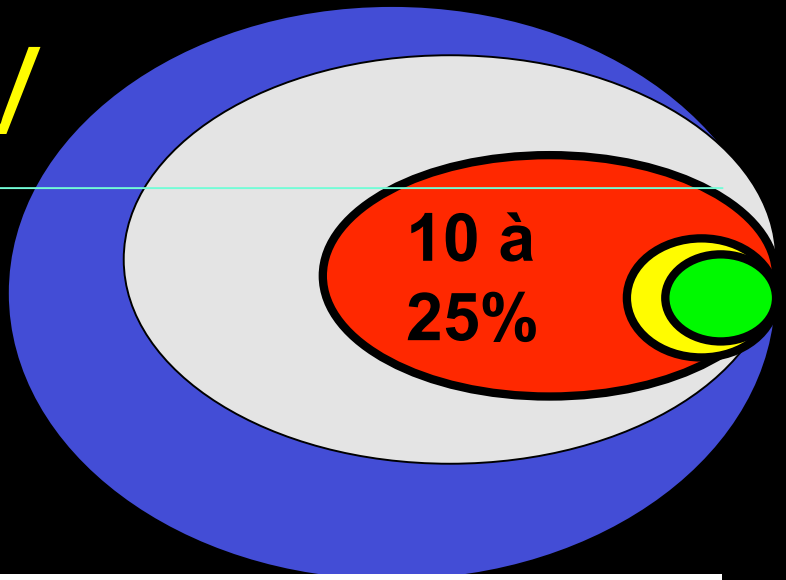
- Autopsies ? On ne meurt pas d'hypoxémie, d'IRA
- Apoptose du système immunitaire
- Functional rather than structural abnormalities
- Limitations ou arrêt de soins …


INFECTION
Bacteria
SEPSIS
Defensins
Lipoproteins
DNA
Outer membrane protein
Fimbriae
peptidoglycan
Lipopolysaccharide
sCD14
Lipopolysaccharide binding protein
Complement system
Endothelial cells
Neutrophils
Mast cells
Epithelial cells
Monocytes/ macrophages
Toll-like receptor
PGRP
Nod
Lymphocytes
Dentritic cells
C5a
Tissue factor
Coagulation
Acute phase protein
Apoptosis
Peripheral nervous system
Neuroendocrine pathway
Pro-inflammatory mediators
TNF
Interleukin 1
NO...
Innate immunity: anti-infectious response
Inflammation
Moderate: beneficial alarm signal
Severe
Deleterious effects
Organ dysfunction
Anti-inflammatory mediators
Interleukin 10 and interleukin 1Ra and sTNFR
Immunity: immune depression
?
Inflammation: down-regulation
Increased susceptibility to nosocomial infection



5 secondes après traitement par LPS

Du Sepsis vers le SDMV



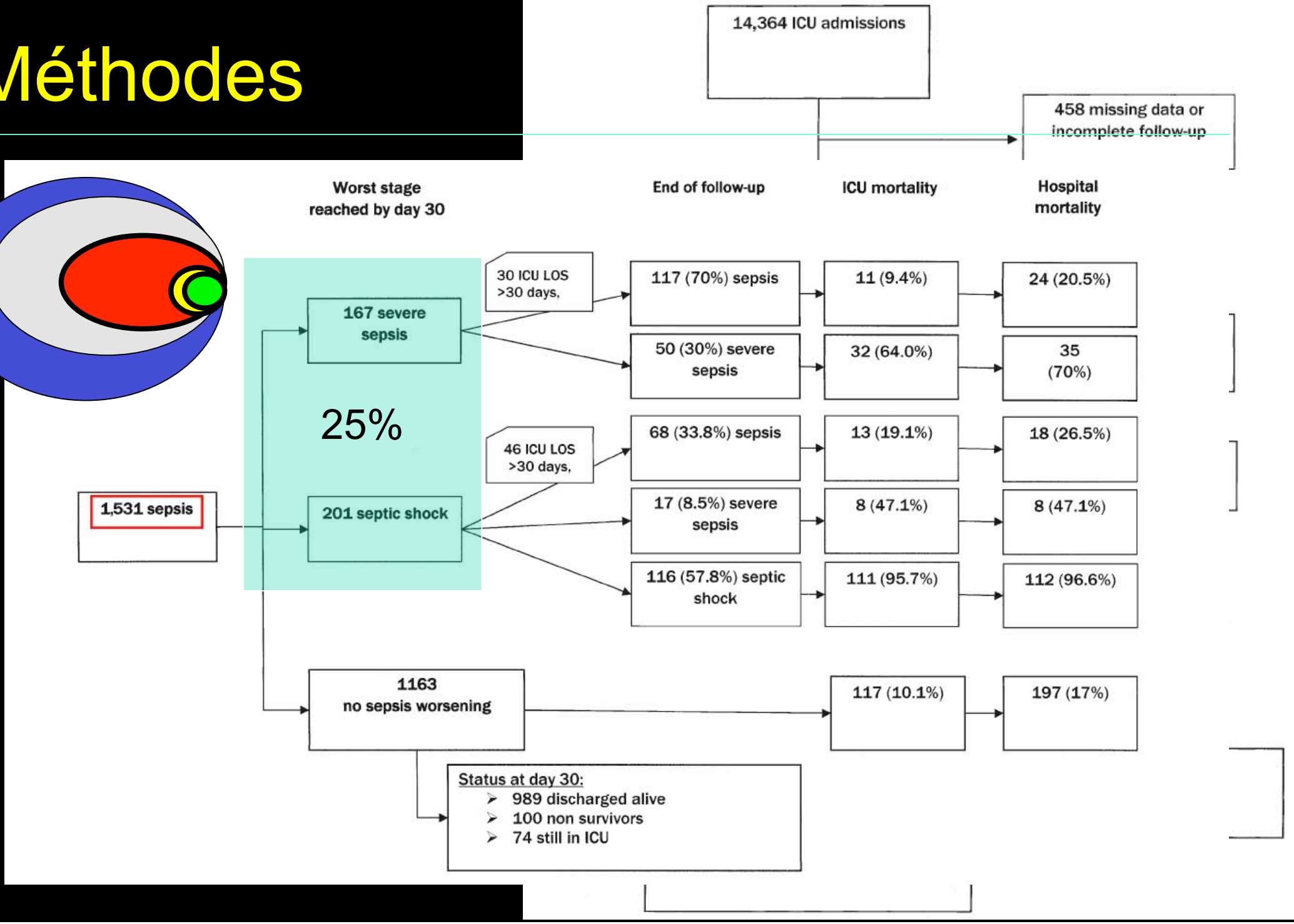
Systemic Inflammatory Response and Progression to Severe Sepsis in Critically Ill Infected Patients

Corinne Alberti, Christian Brun-Buisson, Sylvie Chevret, Massimo Antonelli, Sergey V. Goodman, Claudio Martin, Rui Moreno, Ana R. Ochagavia, Mark Palazzo, Karl Werdan, and Jean Roger Le Gall, for the European Sepsis Study Group

Clinical Epidemiology Unit, Hôpital Robert Debré; Department of Medical Biostatistics, Hôpital Saint-Louis; and Medical Intensive Care Unit, Hôpital Saint-Louis, Assistance Publique—Hôpitaux de Paris, Université Paris VII, Paris; and Medical Intensive Care Unit, Hôpital Henri-Mondor, Assistance Publique-Hôpitaux de Paris, Université Paris XII, Créteil, France; Istituto di Anestesiologia e Rianimazione, Universita Cattolica del Sacro Cuore, Policlinico A. Gemelli, Rome, Italy; General Intensive Care Unit, Department of Anesthesiology and Critical Care Medicine, Hadassah Hebrew University Medical Center, Jerusalem, Israël; Critical Care-Trauma Centre, London Health Sciences Centre, London, Ontario, Canada; Intensive Care Unit, Santo Antonio dos Capuchos Hospital, Lisboa, Portugal; Intensive Care Unit, Parc Tauli Hospital, Red Gina, Spain; Intensive Care Unit, Charing Cross Hospital, London, United Kingdom; and Universitatsklinik und Poliklinik fur Innere Medizin III, Klinikum Krollwitz der Martin-Luther-Universitat Halle-Wittenberg, Halle, Germany

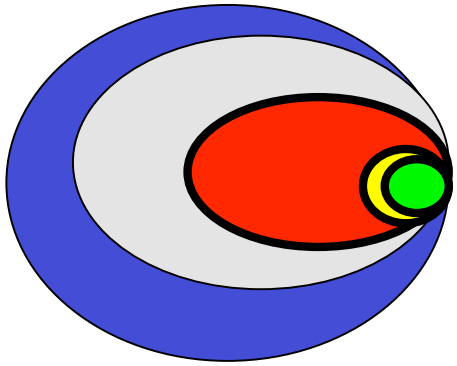
Alberti, Am J Respir Crit Care Med 2005; 171: 461

Méthodes

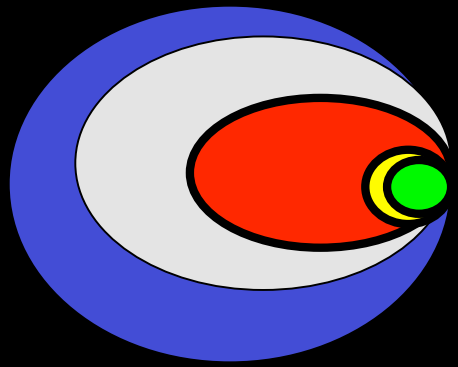

14,364 ICU admissions
458 missing data or incomplete follow-up
Worst stage reached by day 30
End of follow-up
ICU mortality
Hospital mortality
1,531 sepsis
167 severe sepsis
201 septic shock
25%
30 ICU LOS >30 days,
46 ICU LOS >30 days,
117 (70%) sepsis
11 (9.4%)
24 (20.5%)
50 (30%) severe sepsis
32 (64.0%)
35 (70%)
68 (33.8%) sepsis
13 (19.1%)
18 (26.5%)
17 (8.5%) severe sepsis
8 (47.1%)
8 (47.1%)
116 (57.8%) septic shock
111 (95.7%)
112 (96.6%)
1163 no sepsis worsening
117 (10.1%)
197 (17%)
Status at day 30:
989 discharged alive
100 non survivors
74 still in ICU

Du Sepsis vers le SDMV

Age (per year)	1.00 (0.99–1.00)
Male sex	1.07 (0.87–1.32)
Admission category	
Surgical scheduled	1.00
Surgical emergency	0.94 (0.66–1.34)
Medical	0.73 (0.54–0.98)*
Trauma	0.80 (0.53–1.21)†
Comorbidities	
Liver cirrhosis	1.50 (1.07–2.11)*
Chronic respiratory failure	1.16 (0.80–1.69)
Chronic heart failure	1.16 (0.86–1.56)
Chronic renal failure	0.98 (0.70–1.39)
Immunodepression	1.10 (0.87–1.39)
Chronic alcohol abuse	1.02 (0.78–1.35)



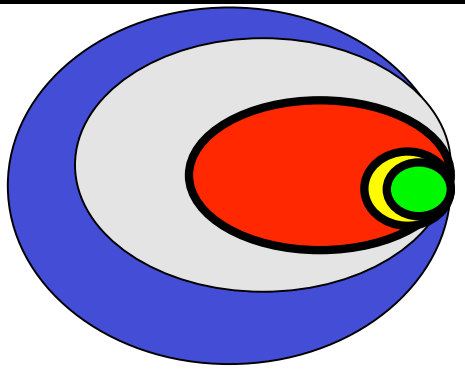
Du Sepsis vers le SDMV



	Physiology	
SIRS criteria		
Hyperthermia/hypothermia	1.80 (1.45–2.23)‡	—§
Tachycardia	1.61 (1.22–2.13)‡	—
Tachypnea or mechanical ventilation	1.70 (1.06–2.71)*	—
Leukocytes < 4,000 or > 12,000	1.23 (1.00–1.51)*	—
> 2 SIRS criteria	1.73 (1.40–2.14)†	—
Physiologic variables		
Temperature > 38.2°C	1.82 (1.49–2.23)‡	1.63 (1.33–1.99)‡
Heart rate > 120/minute	1.63 (1.33–1.99)‡	1.34 (1.09–1.64)‡
Systolic blood pressure < 110 mm Hg	1.71 (1.39–2.10)‡	1.51 (1.23–1.86)‡
Platelet count < 150 × 10^9/L	1.68 (1.37–2.05)‡	1.47 (1.20–1.81)‡
Leukocytes < 4 × 10^9/L	1.72 (1.21–2.45)‡	—
Sodium > 145 mmol/L	1.88 (1.45–2.43)‡	1.51 (1.16–1.95)‡
Bilirubin > 30 μmol/L	1.61 (1.27–2.03)‡	1.35 (1.06–1.72)*
Urea > 15 mmol/L	1.13 (0.91–1.41)†	—

Du Sepsis vers le SDMV

	Characteristics of infection	
Postoperative infection	1.55 (1.11–2.17)‡	
Origin of infection		
Community-acquired	1.00	
Hospital-acquired	1.38 (1.10–1.74)‡	
ICU-acquired	1.38 (1.07–1.79)*	
Source of infection		
Respiratory tract	0.94 (0.76–1.16)	
Pneumonia	1.44 (1.18–1.76)‡	1.47 (1.18–1.82)‡
Digestive tract	1.12 (0.83–1.50)	—
Peritonitis	1.41 (1.01–1.98)*	1.51 (1.07–2.13)*
Urinary tract	0.81 (0.56–1.16)†	—
Primary bacteremia	1.80 (1.18–2.76)‡	1.81 (1.21–2.70)‡
Catheter-related	1.66 (1.04–2.65)*	—
Miscellaneous	1.03 (0.77–1.37)	—
Microorganisms		
Gram-positive cocci	1.36 (1.10–1.68)‡	1.26 (1.02–1.57)*
Escherichia coli and *Proteus*	1.22 (0.91–1.65)†	—
Other *Enterobacteriaceae*	1.44 (1.08–1.93)*	—
Aerobic gram-negative bacilli	1.40 (1.07–1.83)*	1.38 (1.05–1.80)*
Candida and fungi	1.23 (0.85–1.77)†	—



What's next ? Après CHAOS, PIRO

Table 2. The PIRO system for staging sepsis

Domain	Present	Future	Rationale
Predisposition	Premorbid illness with reduced probability of short term survival. Cultural or religious beliefs, age, sex.	Genetic polymorphisms in components of inflammatory response (e.g., TIR, TNF, IL-1, CD14); enhanced understanding of specific interactions between pathogens and host diseases.	In the present, premorbid factors impact on the potential attributable morbidity and mortality of an acute insult; deleterious consequences of insult heavily dependent on genetic predisposition (future).
Insult infection	Culture and sensitivity of infecting pathogens; detection of disease amenable to source control.	Assay of microbial products (LPS, mannan, bacterial DNA); gene transcript profiles.	Specific therapies directed against inciting insult require demonstration and characterization of that insult.
Response	SIRS, other signs of sepsis, shock, CRP.	Nonspecific markers of activated inflammation (e.g., PCT or IL-6) or impaired host responsiveness (e.g., HLA-DR); specific detection of target of therapy (e.g., protein C, TNF, PAF).	Both mortality risk and potential to respond to therapy vary with nonspecific measures of disease severity (e.g., shock); specific mediator-targeted therapy is predicated on presence and activity of mediator.
Organ dysfunction	Organ dysfunction as number of failing organs or composite score (e.g., MODS, SOFA, LODS, PEMOD, PELOD).	Dynamic measures of cellular response to insult—apoptosis, cytopathic hypoxia, cell stress.	Response to preemptive therapy (e.g., targeting microorganism or early mediator) not possible if damage already present; therapies targeting the injurious cellular process require that it be present.

Interactions Hôtes Pathogènes

Interactions Hôtes-Pathogènes

- Limites du modèle endotoxique
- Etude de modèles compartimentalisés
  pneumonie, péritonite, méningite
- Etude en fonction des germes et des souches
- Etude en fonction du statut immunitaire de l ’hôte

Compartimentalisation

- **Macrophage alvéolaire**
  - Recrute les neutrophiles, monocytes et lymphocytes
- **Les bactéries et leurs dérivés (LPS)**
  - reconnus par médiateurs de l'inflammation et l'immunité innée
- Inoculum faible :
  - Macrophages et PMN détruisent les germes
  - Réponse cytokinique est localisée ("compartimentalisée")
- Inoculum fort ou à fort pouvoir pathogène :
  - Débordement des défenses locales : Dommages Collatéraux
- **Désactivation du système monocyte/macrophage**
  - **Immunoparalysie systémique**

What's next ?

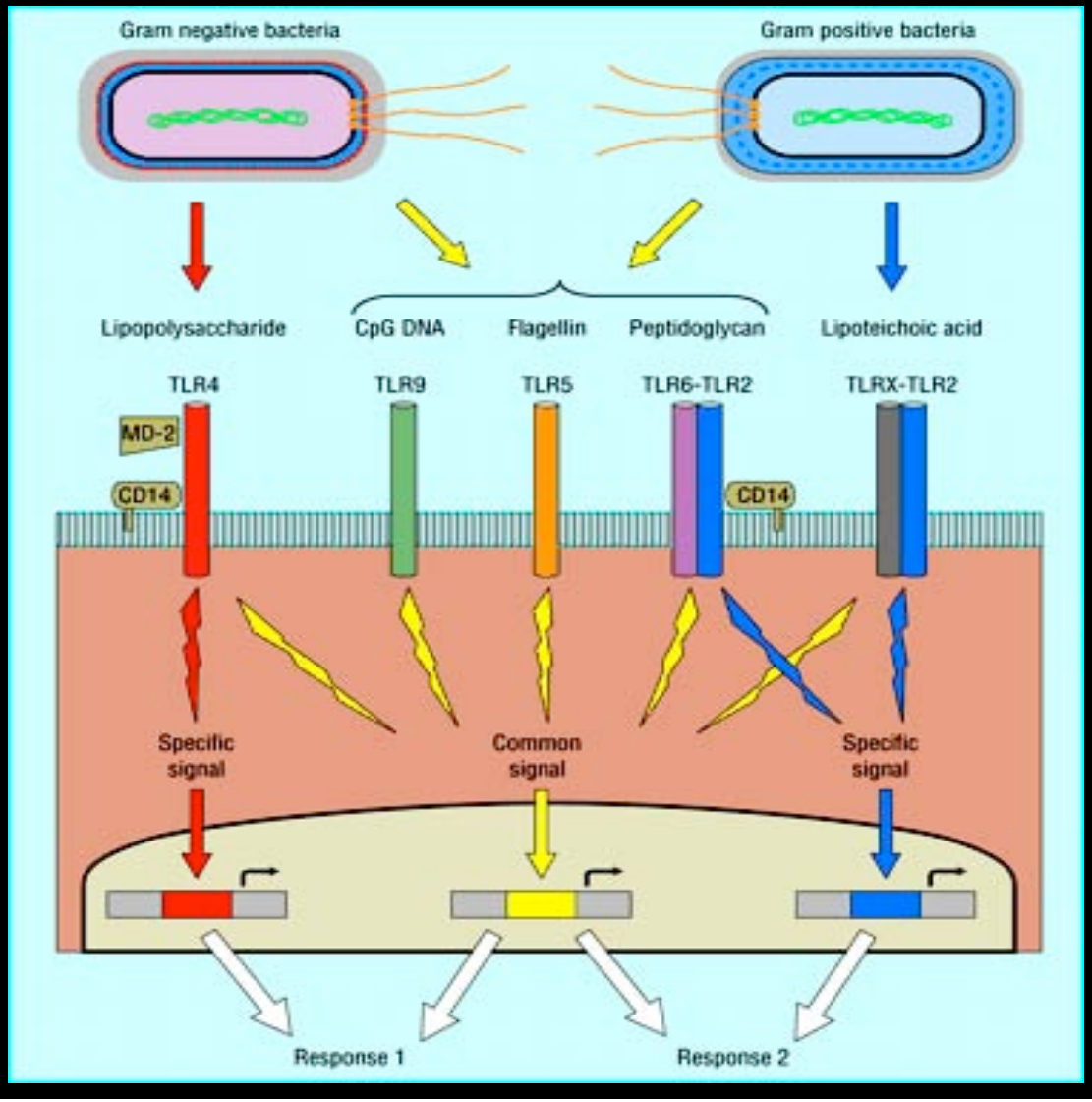
Inflammation
Coagulation
[endothelium]

Immunité

Neuro-endocrine

Métabolique

GENESE DE LA REPONSE INFLAMMATOIRE



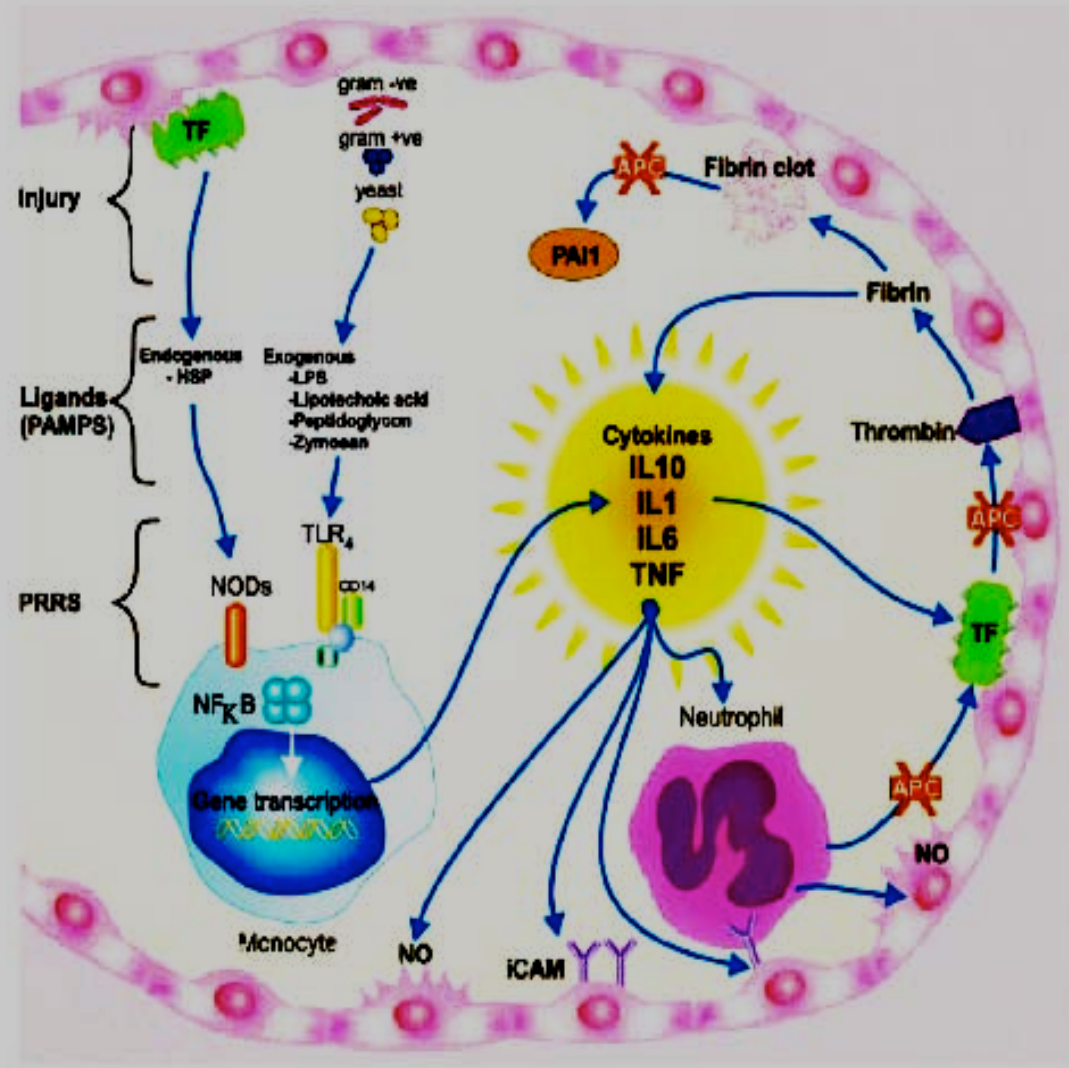
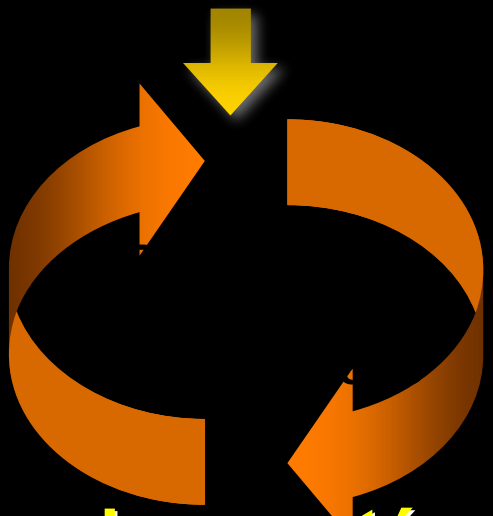


FIGURE 1. A simplified diagram of the innate immune response to infection and tissue injury involving the inflammatory cytokines and the coagulation cascade. –ve = negative; +ve = positive; PAI1 = platelet-activation inhibitor-1; ICAM = intracellular adhesion molecule.

SEPSIS : de la paillasse au Lit

Infection



↑ Coagulation
↓ Fibrinolyse

Limiter l'extension de l'infection

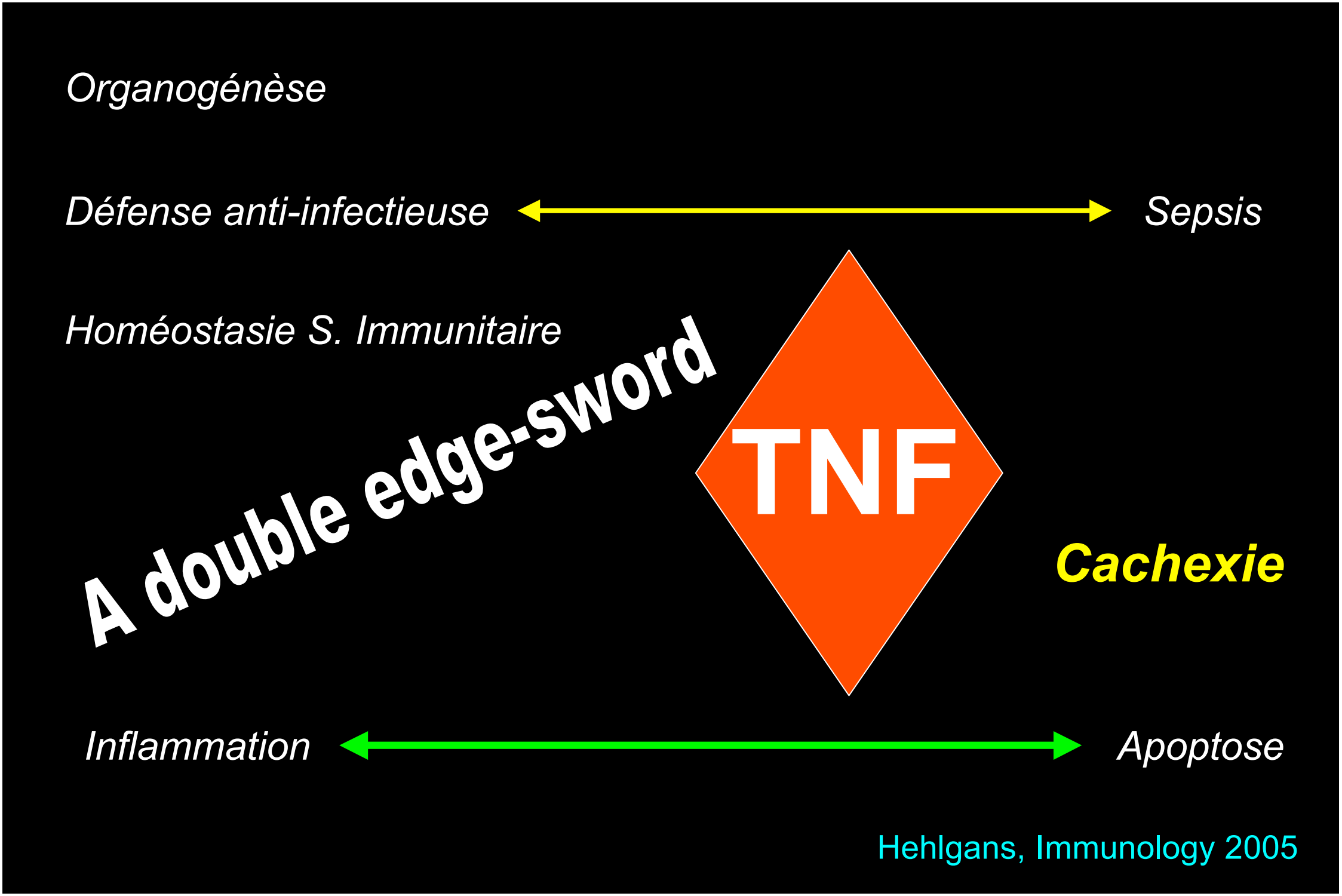
↑ Inflammation

Détruire les bactéries

"Extension systémique"

Sepsis

Définitions cliniques ?


Organogénèse
Défense anti-infectieuse
Sepsis
Homéostasie S. Immunitaire
A double edge-sword
TNF
Cachexie
Inflammation
Apoptose
Hehlgans, Immunology 2005

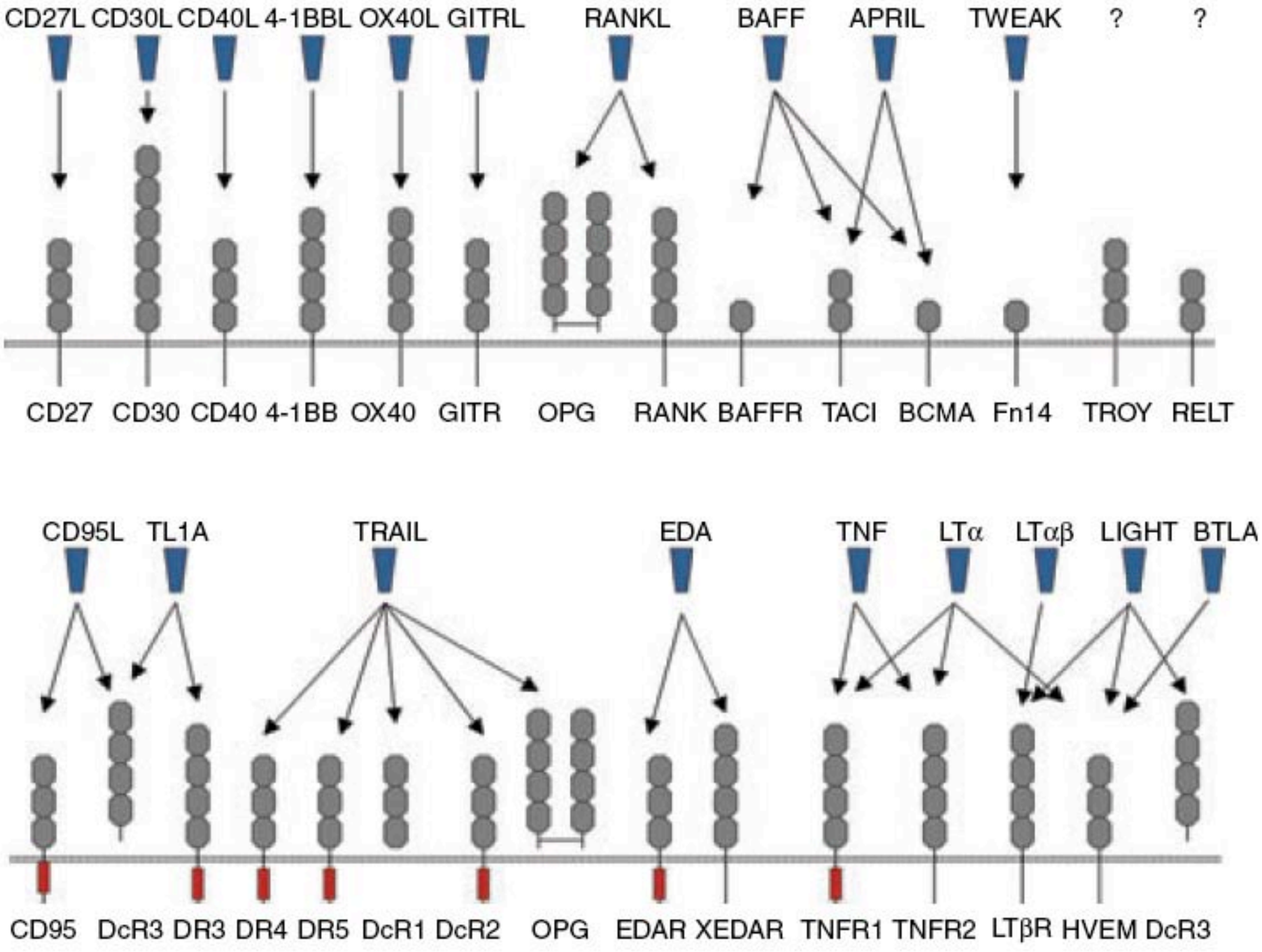
Le TNF, c'est bon !

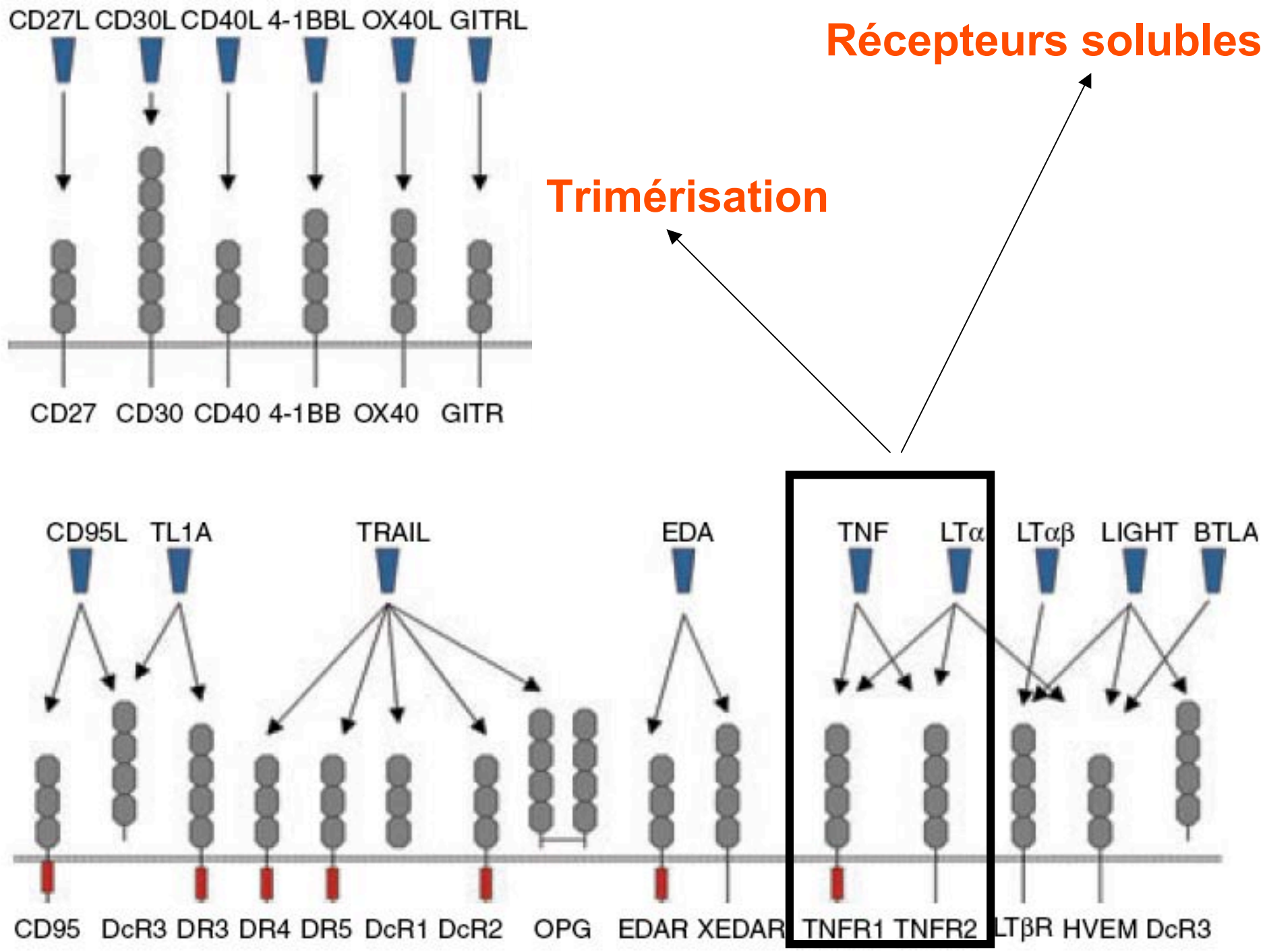
Pas de TNF, défaut de régénération hépatique
Maladies auto-immunes
Susceptibilité aux infections

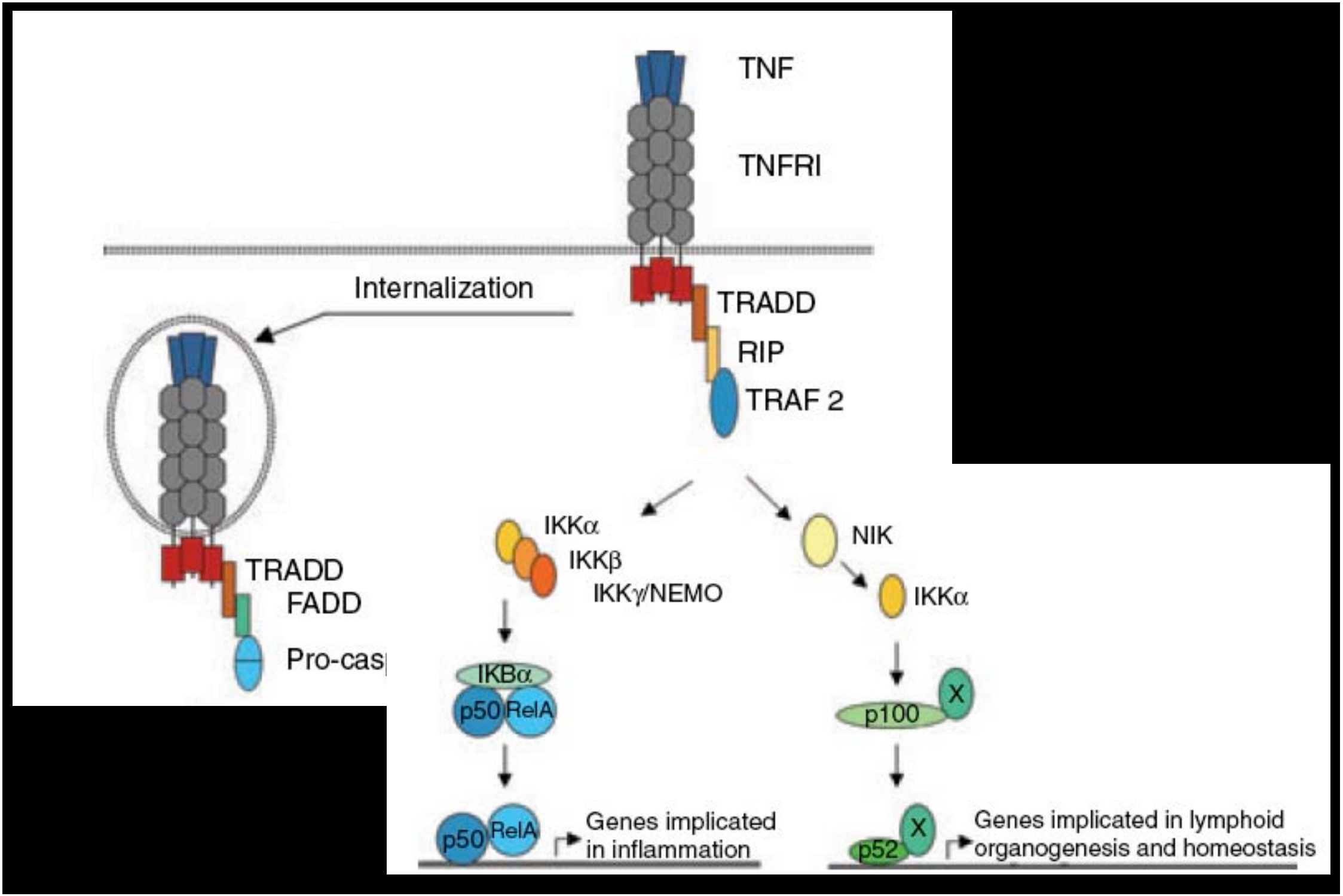
Table 3. Role of TNF/TNFR superfamily members in bacterial infections based on studies using gene targeted mice

Targeted gene	Innate host defence	References
TNFR 1	High susceptibility for: *M. tuberculosis*, BCG, *M. avium*, *S. typhimurium*, *L. monocytogenes*, *L. major*, *T. cruzi*, *T. gondii*	90, 200, 215–217
TNFR2	Slightly higer susceptibility for: *L. monocytogenes*, *Plasmodium berghei* ANKA	97, 206
LTβR	High susceptibility for: *M. tuberculosis*, *L. monocytogenes*	80
TNF	High susceptibility for: *M. tuberculosis*, *S. aureus*, *L. monocytogenes*	198, 215, 218
Fas	High susceptibility for: *L. monocytogenes*	219
LTα	High susceptibility for: *S. aureus*, *M. tuberculosis*	218
LIGHT	Not affected for: *M. tuberculosis*	220

Hehlgans, Immunology 2005


CD27L
CD30L
CD40L
4-1BBL
OX40L
GITRL
RANKL
BAFF
APRIL
TWEAK
?
?
CD27
CD30
CD40
4-1BB
OX40
GITR
OPG
RANK
BAFFR
TACI
BCMA
Fn14
TROY
RELT
CD95L
TL1A
TRAIL
EDA
TNF
LTα
LTαβ
LIGHT
BTLA
CD95
DcR3
DR3
DR4
DR5
DcR1
DcR2
OPG
EDAR
XEDAR
TNFR1
TNFR2
LTβR
HVEM
DcR3

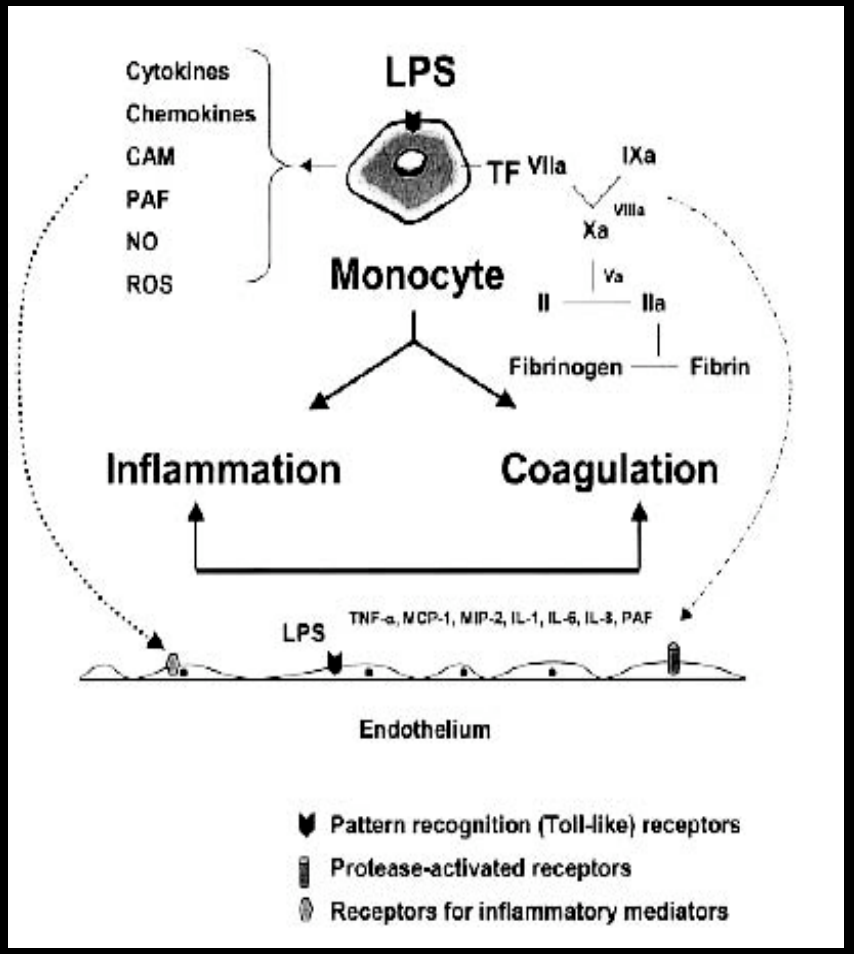

CD27L CD30L CD40L 4-1BBL OX40L GITRL
CD27 CD30 CD40 4-1BB OX40 GITR
Récepteurs solubles
Trimérisation
CD95L TL1A TRAIL EDA TNF LTα LTαβ LIGHT BTLA
CD95 DcR3 DR3 DR4 DR5 DcR1 DcR2 OPG EDAR XEDAR TNFR1 TNFR2 LTβR HVEM DcR3


TNF
TNFRI
Internalization
TRADD
RIP
TRAF 2
TRADD
FADD
Pro-cas
IKKα
IKKβ
IKKγ/NEMO
NIK
IKKα
IKBα
p50
RelA
p100
X
p50
RelA
Genes implicated in inflammation
p52
X
Genes implicated in lymphoid organogenesis and homeostasis

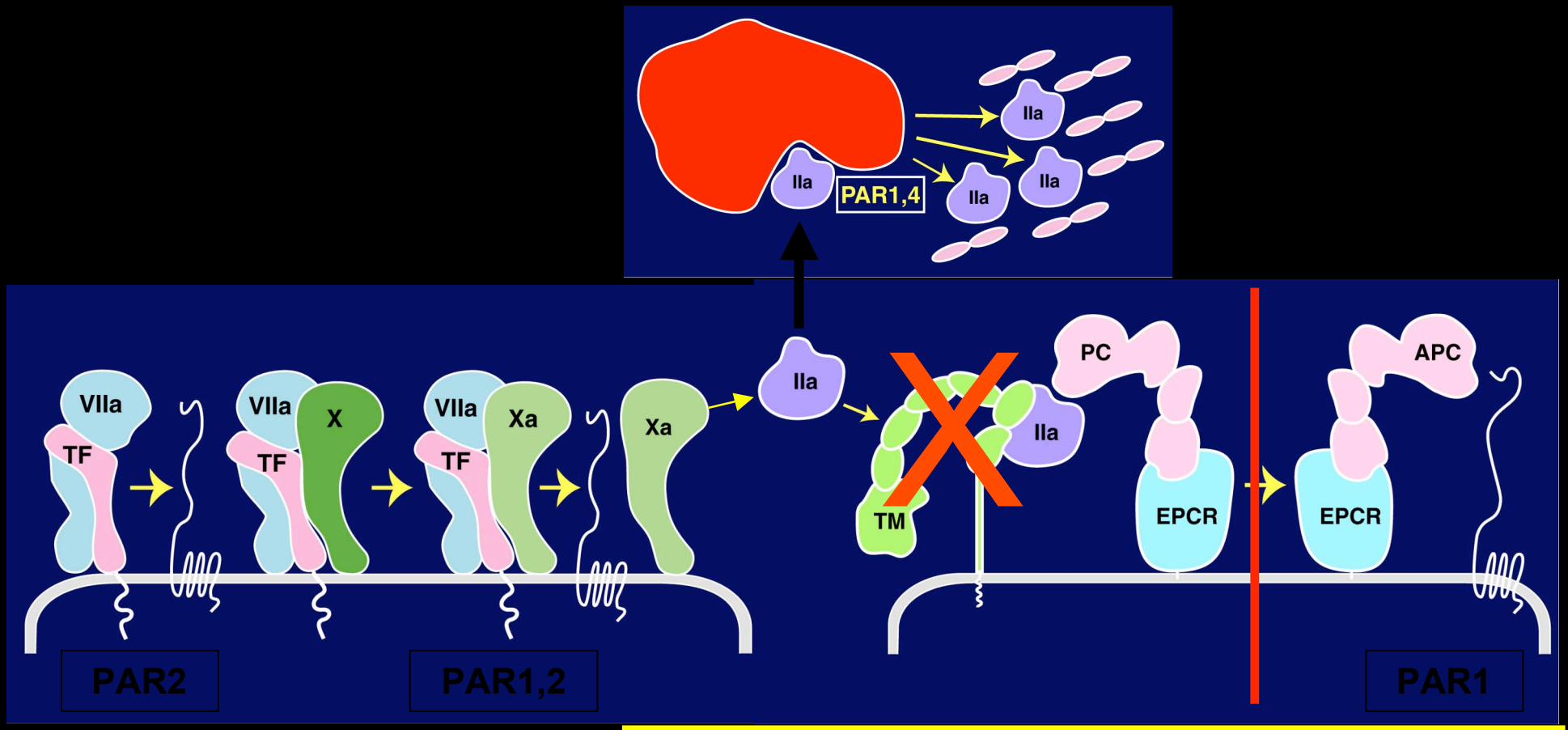
Review article

The role of the endothelium in severe sepsis and multiple organ dysfunction syndrome

William C. Aird



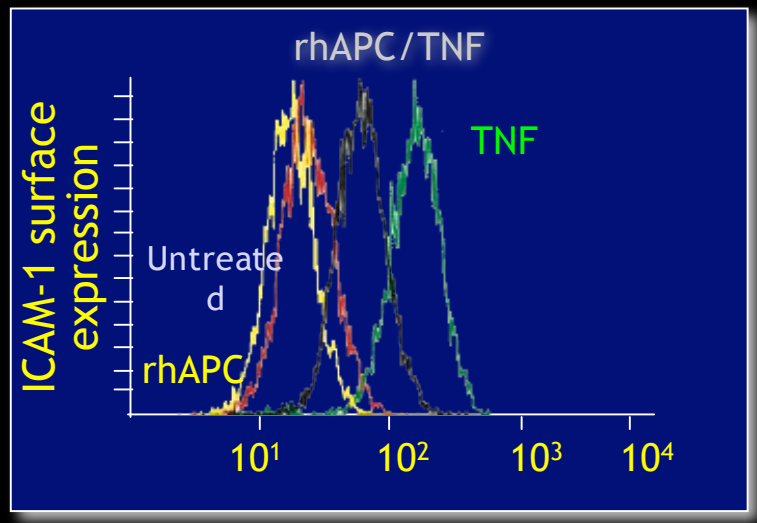
Shift in the Vascular Inflammatory Balance in Severe Sepsis

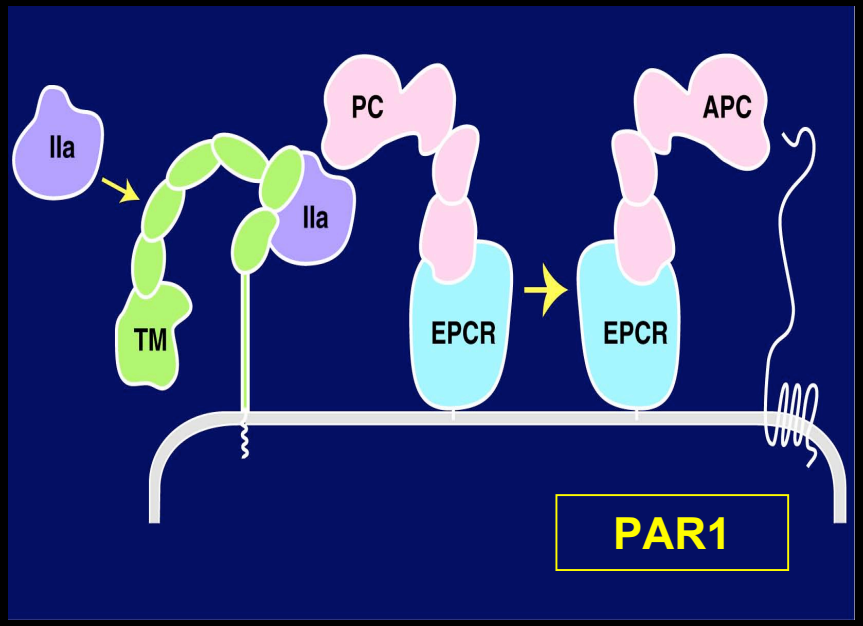


Loss of thrombomodulin disables the endothelial protective APC-PAR1 pathway

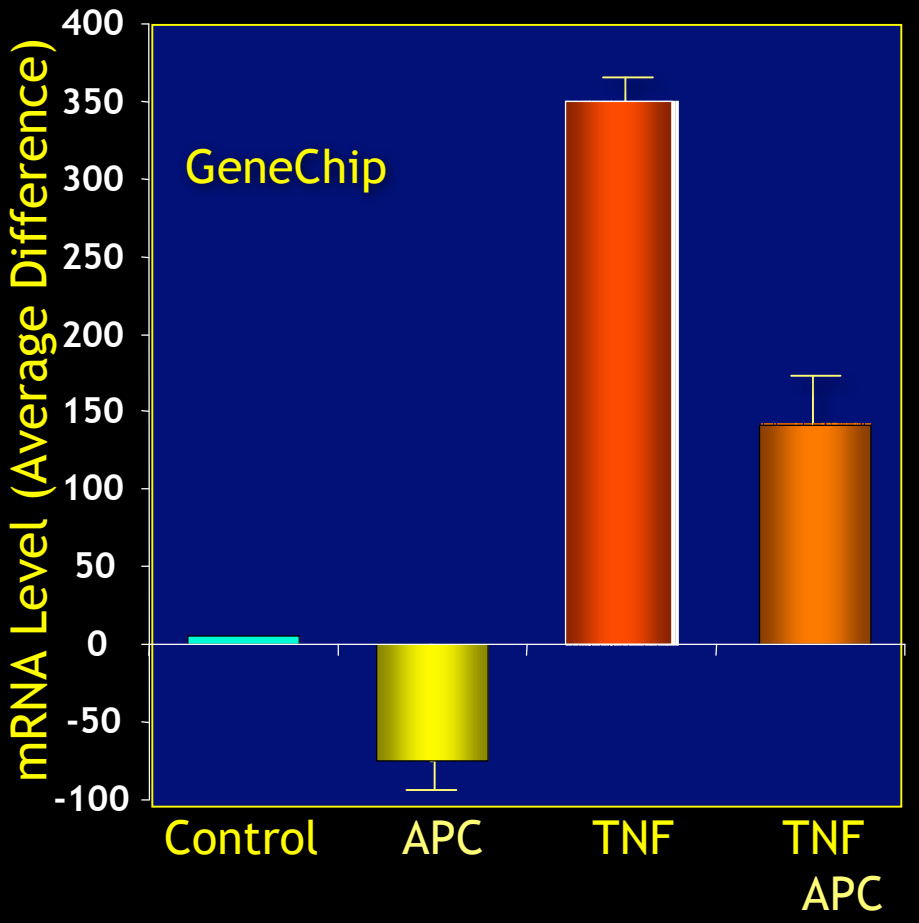
Riewald & Ruf, PNAS 2001

Protective APC-PAR1 Signaling





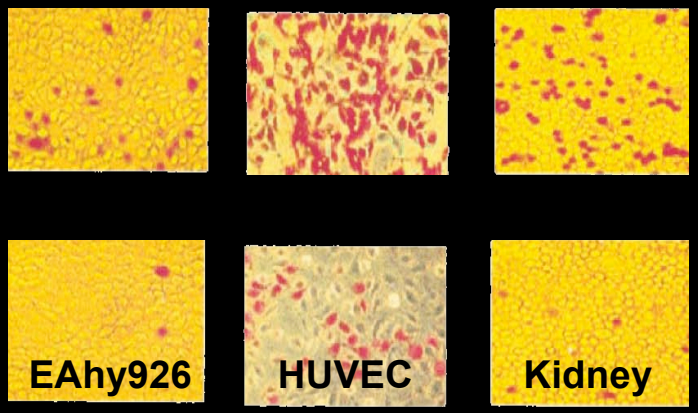
Quiescent Endothelial Cell

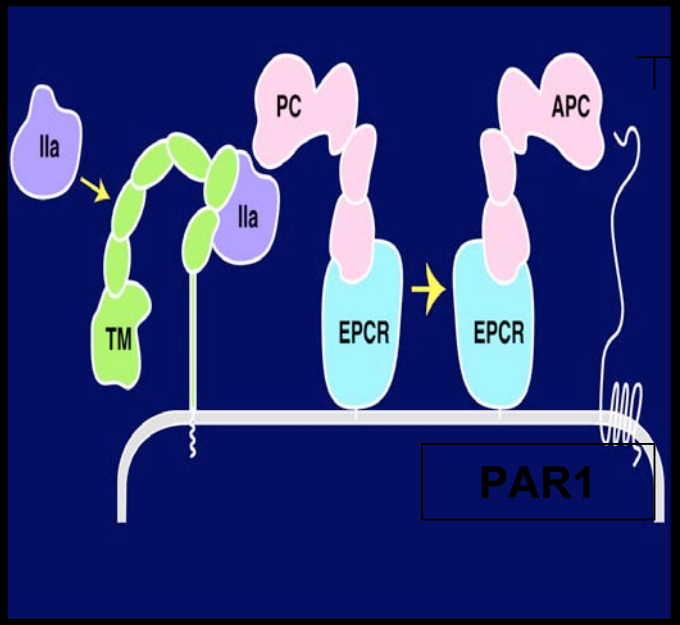


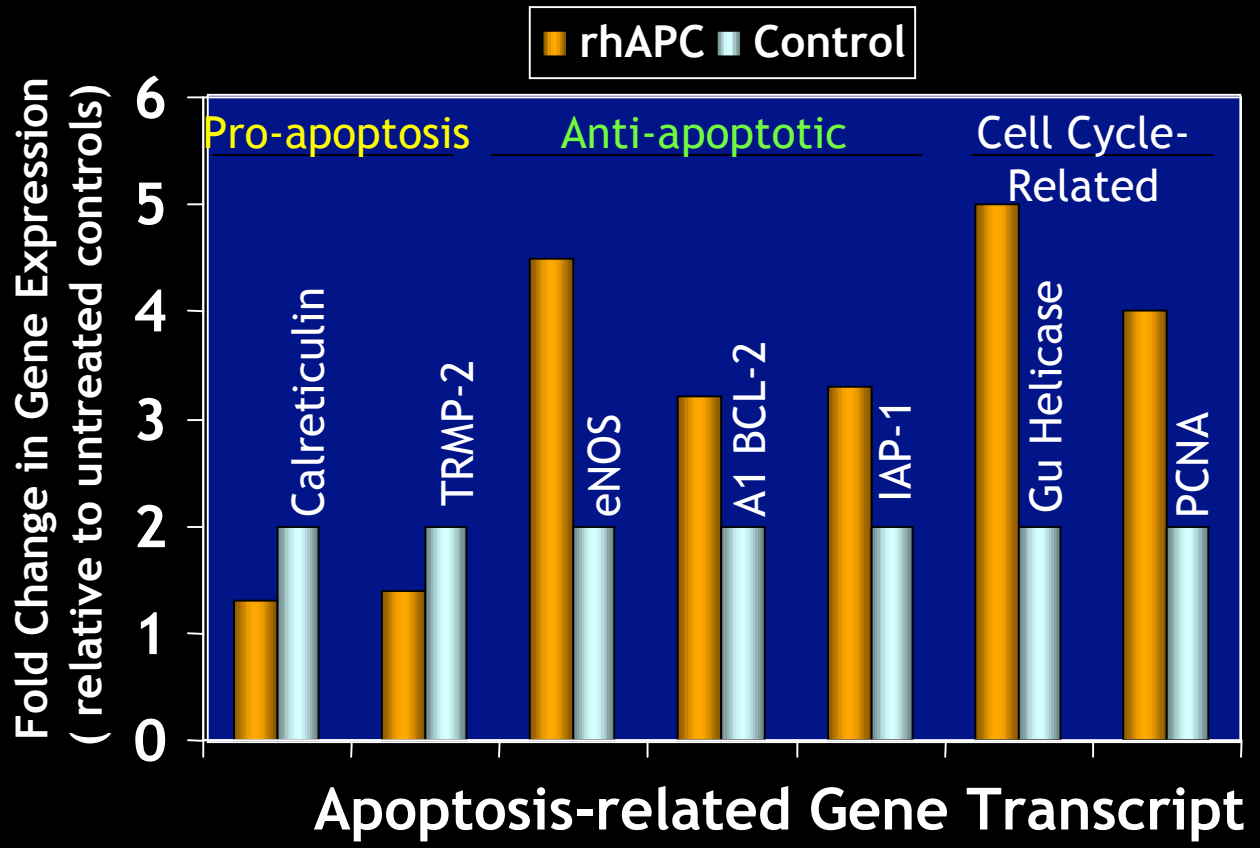
Anti-inflammatory signaling accounted for by PAR1 activation

Joyce et al. *J. Biol. Chem.* 276: 11199, 2001;

Protective APC-PAR1 Signaling





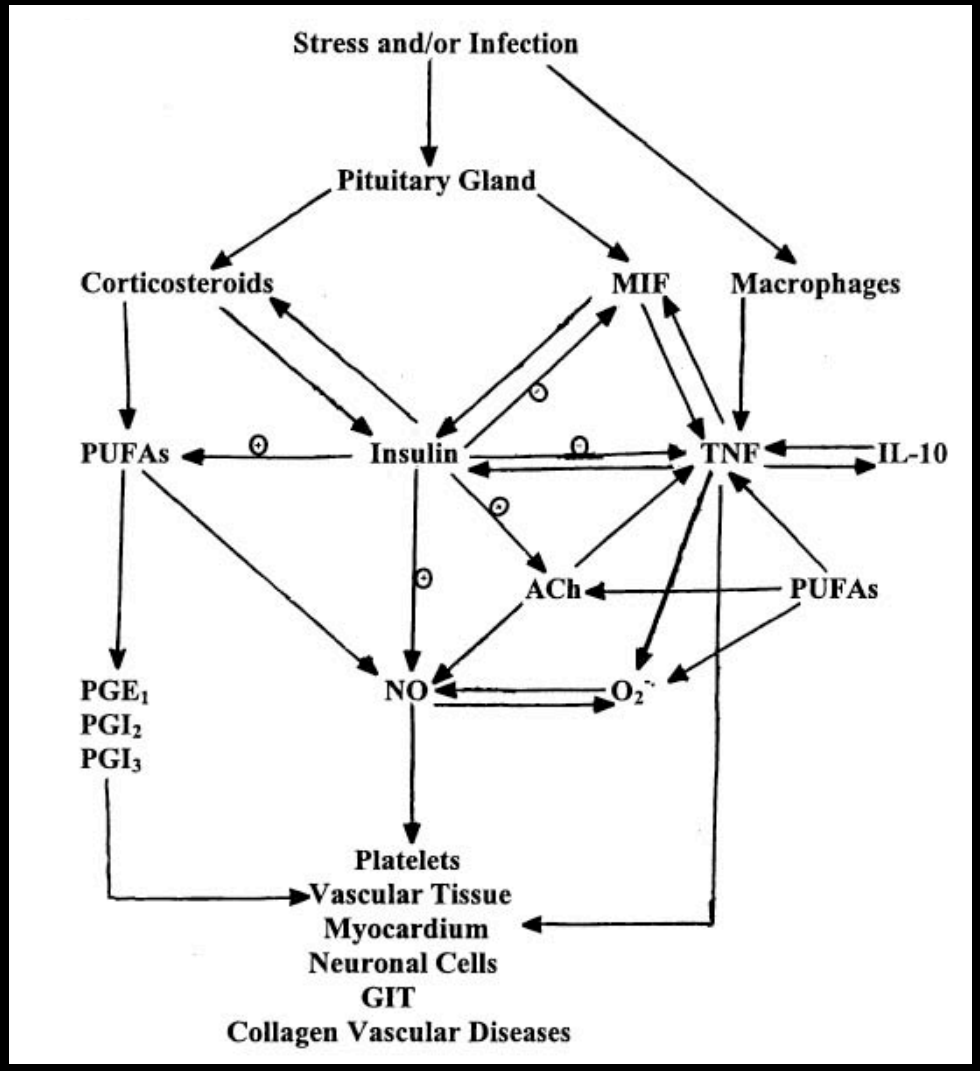


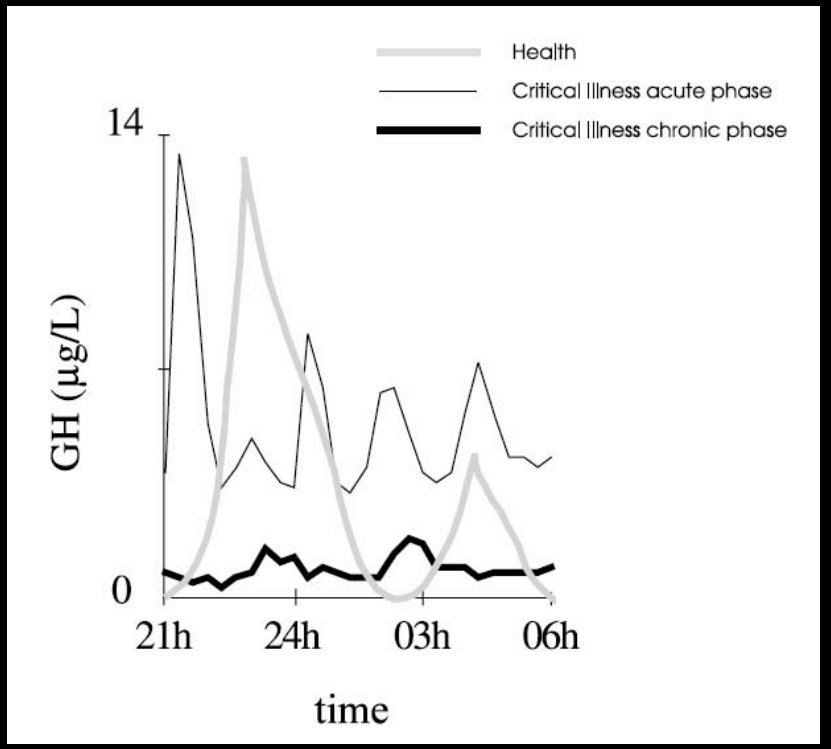
Anti-apoptotic autocrine signaling accounted for by PAR1 activation

Joyce et al. *J. Biol. Chem.* 276: 11199, 2001;
Riewald et al. *Science* 296:1880, 2002

Le Système Neuro-Endocrine

Après une phase primaire, le CHAOS

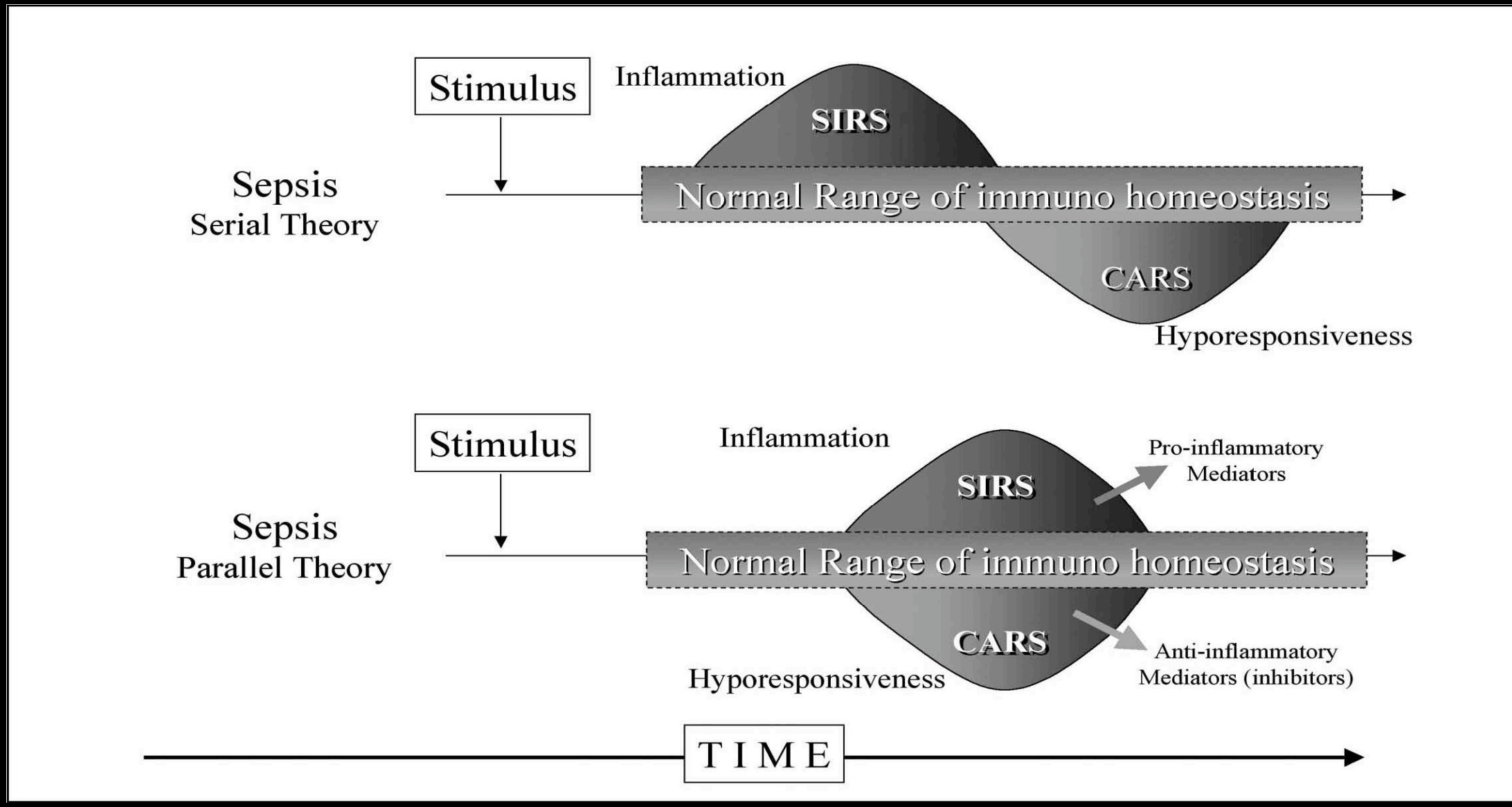




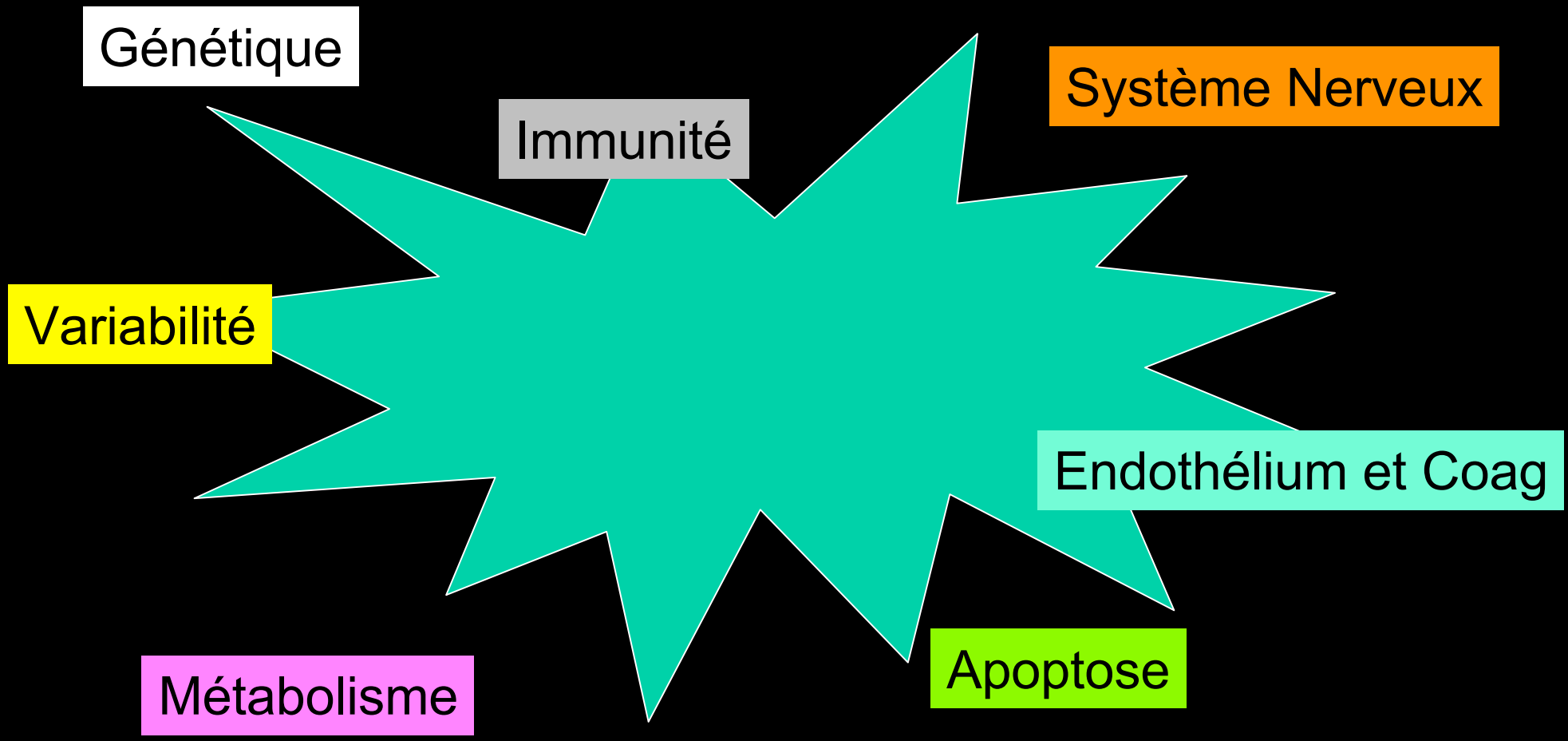
Le Système Neuro-Endocrine

	Disorders	Putative consequences
Cortisol	Impaired synthesis, circadian rhythm Impaired clearance from plasma Impaired transport to tissues Peripheral tissue resistance	Impaired contractile response to α-agonists: contributes to shock Inflammation Organ dysfunction Death
Renin and aldosterone	Shift of aldosterone from renin dependency to adrenocorticotropin dependency with hyper-reninaemia and hypoaldosteronism	Salt loss and hypovolaemia contribute to shock
DHEA, DHEAS	Usually decreased levels—mechanisms unknown?	Unknown
Sex hormones	Androstenedione and oestrogen concentrations are raised. Concentrations of testosterone, luteinising hormone, and follicle stimulating hormone are decreased. Loss of pulsatile secretion of gonadic hormones	Unknown
Thyroid hormones	Loss of pulsatile secretion of thyrotropin, reduced secretion of thyroid stimulating hormone and thyroid hormone secretion, and altered peripheral thyroid hormone metabolism (changes in tissue deiodinase activities), resulting in low circulating T_3 and high rT_3 concentrations and decreased T_4 concentrations	Possibly contribute to muscle protein loss and malnutrition
Vasopressin	Neuronal apoptosis triggered by inducible NO synthase, resulting in impaired vasopressin synthesis and release, mainly in late phase of septic shock	Contributes to shock
Insulin	Cytokines impair transcription of glucose transporter 4 gene and mediate systemic insulin resistance, resulting in hyperglycaemia and high concentrations of circulating insulin	Enhances immune cell and neurone functions. Hyperglycaemia promotes superinfection and polyneuromyopathy, and increases the risk of death
Growth hormones	Loss of pulsatile secretion	Possibly contributes to lean body mass loss and malnutrition

DHEA=dehydroepiandrosterone. DHEAS=dehydroepiandrosterone sulphate.


Stimulus
Inflammation
SIRS
Sepsis
Serial Theory
Normal Range of immuno homeostasis
CARS
Hyporesponsiveness
Stimulus
Inflammation
Pro-inflammatory
Mediators
SIRS
Sepsis
Parallel Theory
Normal Range of immuno homeostasis
CARS
Anti-inflammatory
Mediators (inhibitors)
Hyporesponsiveness
TIME

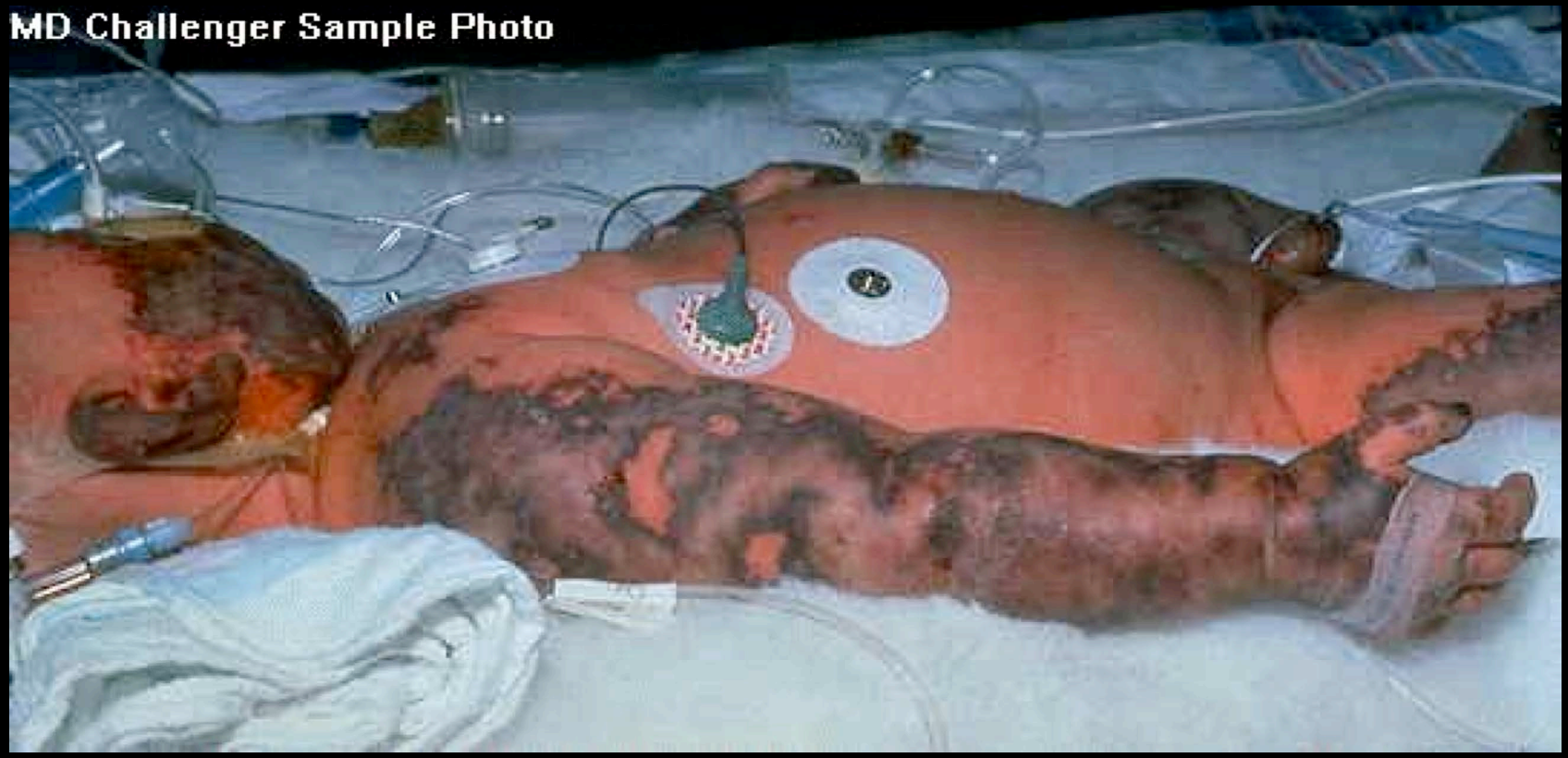
What’s next ?


Génétique
Immunité
Système Nerveux
Variabilité
Endothélium et Coag
Apoptose
Métabolisme

What’s next ?

Génétique

Variabilité


MD Challenger Sample Photo

Polymorphisme génétique de l 'hôte

Nous ne sommes pas égaux devant l 'infection

- **paludisme** — **Nature 1994**
- **meningococcémie** — **J Infect Dis 1996**
- **leishmaniose** — **J Exp Med 1995**

- **choc septique**

Table 6. Predictive Factors of Mortality Using a Multiple Logistic Regression Model

Deceased	Odds Ratio (95% Confidence Interval)	SE	z	P>|z|
Age*	1.46 (1.06-2.00)	0.24	2.32	.02
Derived probability of dying†	1.22 (1.01-1.46)	0.11	2.08	.04
TNF2	3.75 (1.37-10.24)	1.99	2.58	.01

*Odds ratio per 10 years of increase.
†Odds ratio per 10% increase of the Simplified Acute Physiologic Score (SAPS II)–derived probability of dying.

Mira et al. JAMA 1999; 282: 561

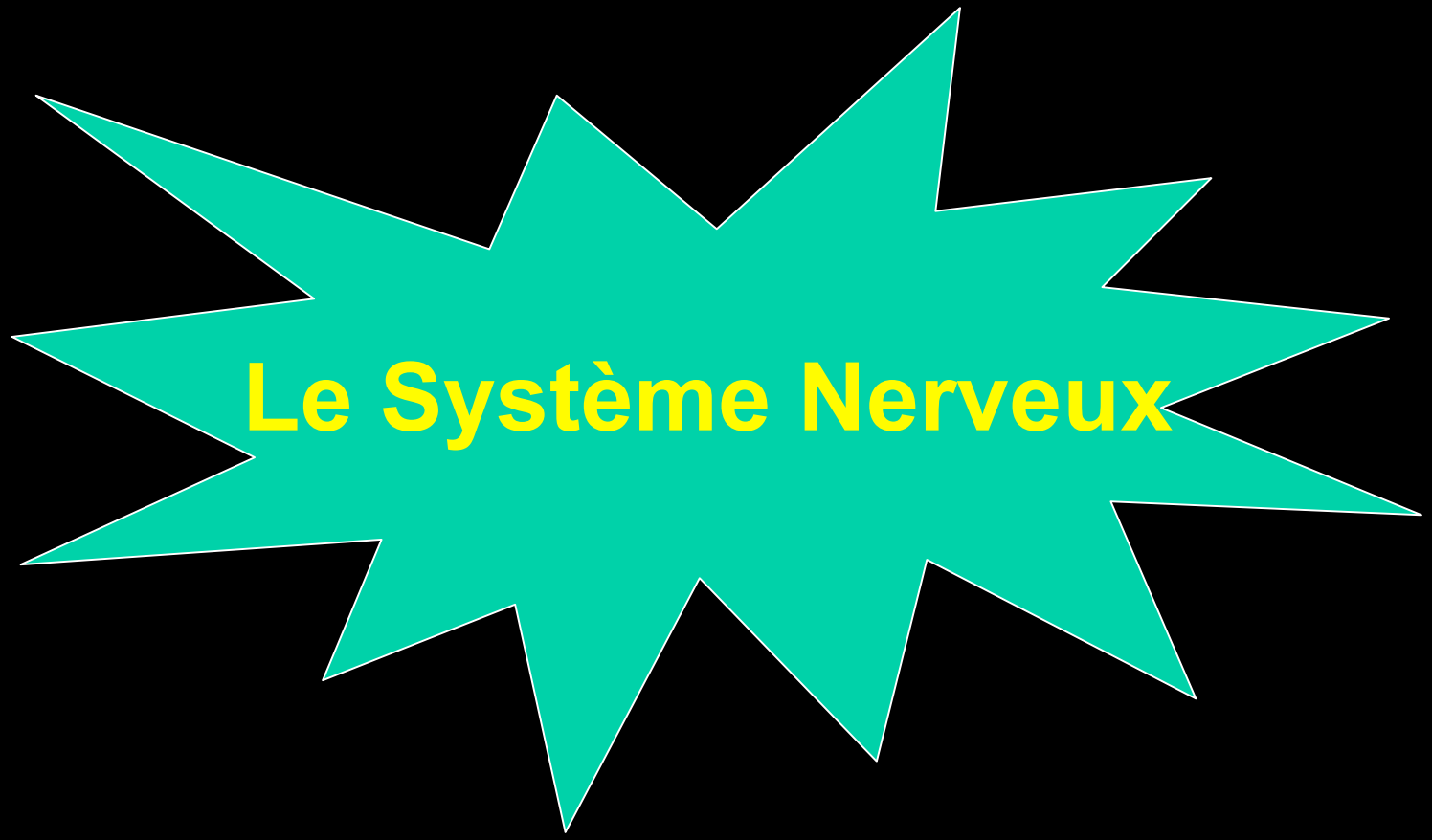
Polymorphisme génétique de l ’hôte

- Petites études
- Peu ou pas de relation genotype/phénotype
- SNPs ou Haplotypes, et association de polymorphismes

- La génétique, c’est beaucoup plus compliqué qu’on le croit …
  - RNAi
  - Régulation épigénétique
  - Modifications post-traductionnelles
  - Protéomique …

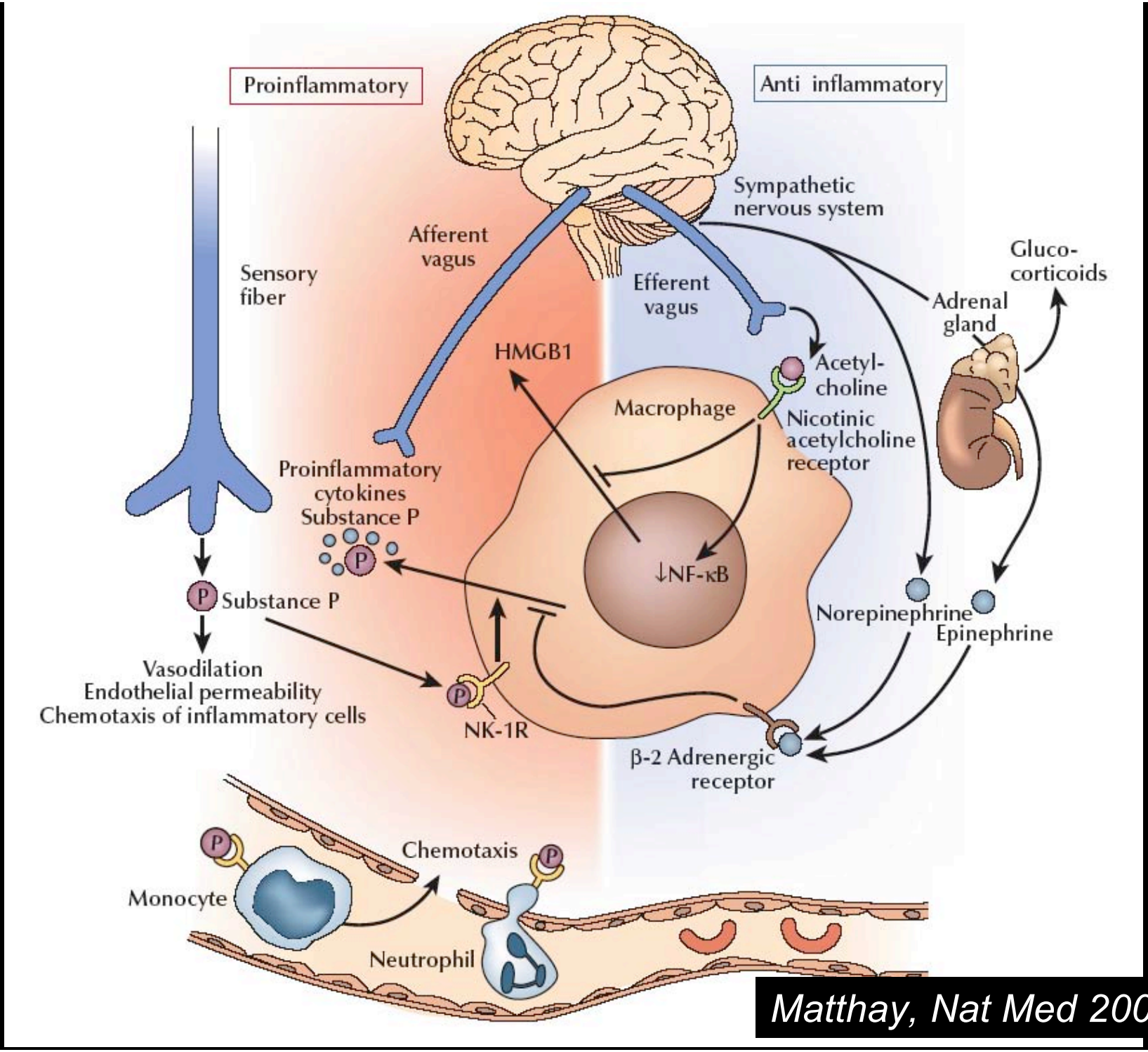
- Impact sur la pratique (quels OR, quelles possibilités d’ITV ?)

What’s next ?



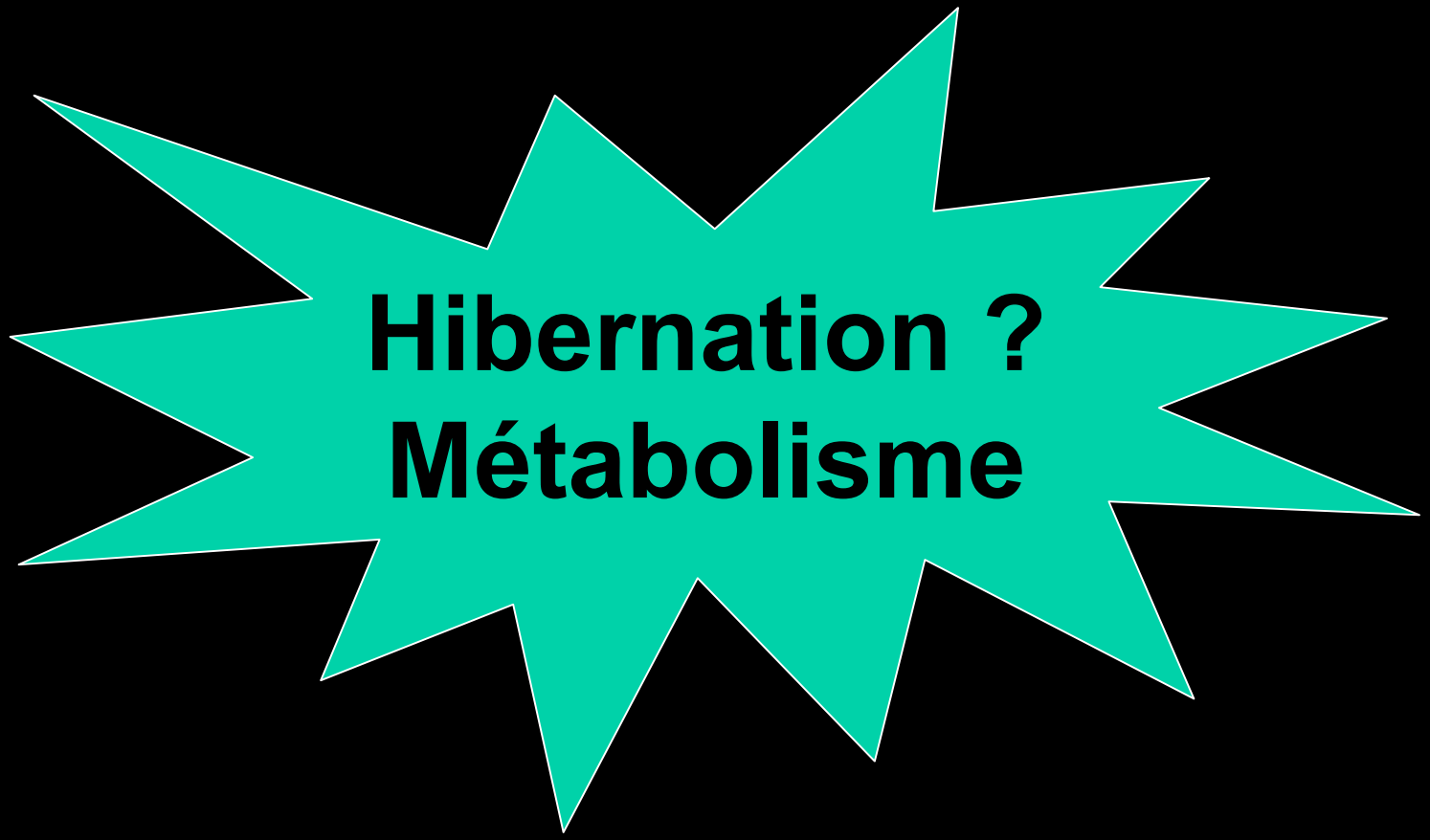
Le Système Nerveux …

- Lésions diffuses du SNC (Apoptose), Sharshar Lancet 2002
- Perte de la variabilité de la réponse S/PS
- Dysfonction Axes Endocriniens
- Dysfonction Axe Neuro-Immuns

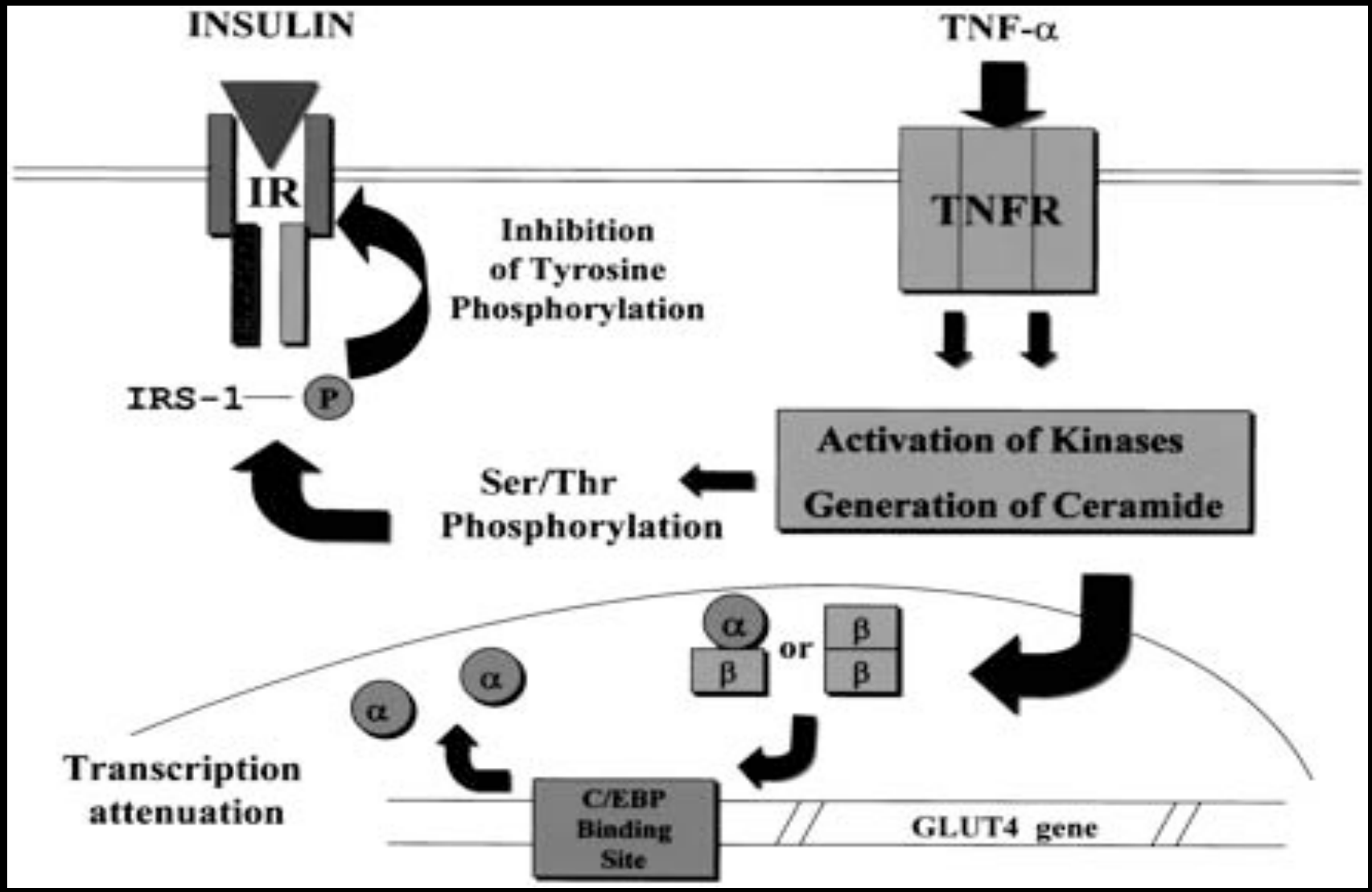


Matthay, Nat Med 2004; 10: 1161

What’s next ?



Tumor Necrosis Factor-–Induced Insulin Resistance in Adipocytes *Qi, Exp Biol Med 2000*



Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation

Mervyn Singer, Vincenzo De Santis, Domenico Vitale, William Jeffcoate

Lancet 2004; 364: 545–48

Bloomsbury Institute of Intensive Care Medicine, Wolfson Institute of Biomedical Research and Department of Medicine, University College London, London, UK (Prof M Singer FRCP, V De Santis MD, D Vitale MD); Department of Anaesthesia, University "La Sapienza", Rome, Italy (V De Santis, D Vitale); and Department of Diabetes and Endocrinology, City Hospital, Nottingham, UK (W Jeffcoate MRCP)

Sepsis and other critical illnesses produce a biphasic inflammatory, immune, hormonal, and metabolic response. The acute phase is marked by an abrupt rise in the secretion of so-called stress hormones with an associated increase in mitochondrial and metabolic activity. The combination of severe inflammation and secondary changes in endocrine profile diminish energy production, metabolic rate, and normal cellular processes, leading to multiple organ dysfunction. This perceived failure of organs might instead be a potentially protective mechanism, because reduced cellular metabolism could increase the chances of survival of cells, and thus organs, in the face of an overwhelming insult. We propose that, first, multiple organ failure induced by critical illness is primarily a functional, rather than structural, abnormality. Indeed, it may not be failure as such, but a potentially protective, reactive mechanism. Second, the decline in organ function is triggered by a decrease in mitochondrial activity and oxidative phosphorylation, leading to reduced cellular metabolism. Third, this effect on mitochondria might be the consequence of acute-phase changes in hormones and inflammatory mediators.

Baisse des capacités métaboliques
NO-dépendente (atteinte du complexe I de la chaîne respiratoire)
Théorie de **l'Hibernation**

- **axe corticotrope stunné**
- **IRM fonctionnelle et dysoxie tissulaire ?**

Association between mitochondrial dysfunction and severity and outcome of septic shock

David Brealey, Michael Brand, Iain Hargreaves, Simon Heales, John Land, Ryszard Smolenski, Nathan A Davies, Chris E Cooper, Mervyn Singer

Lancet 2002; **360:** 219–23

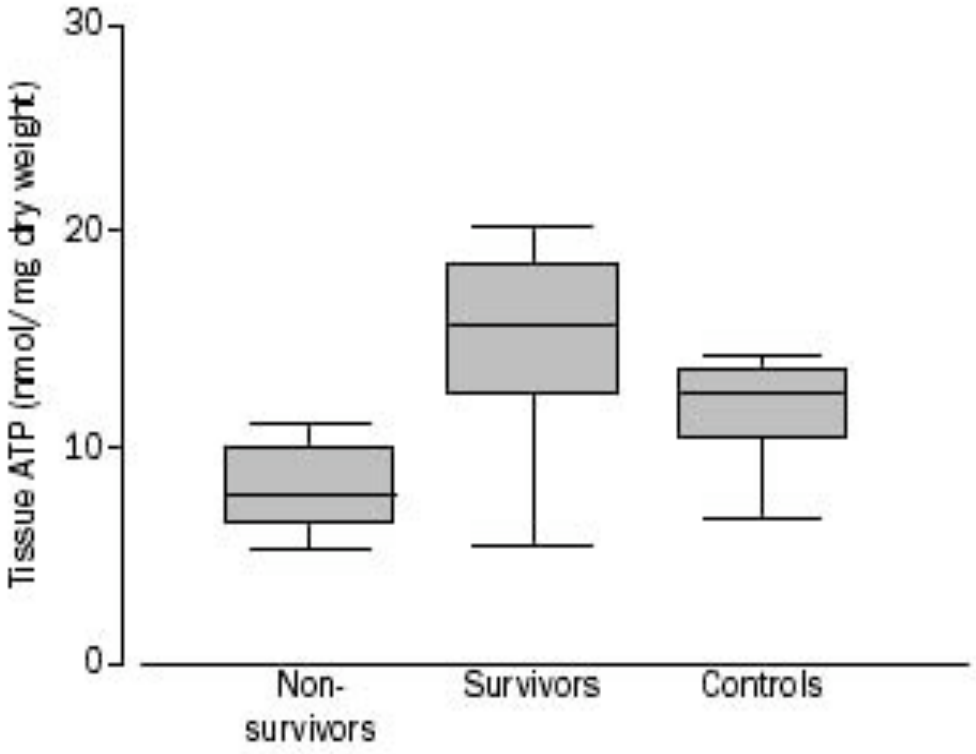


Figure 1: Tissue ATP concentrations in patients with sepsis and in controls
Horizontal lines=medians, boxes=quartiles, whiskers=ranges.

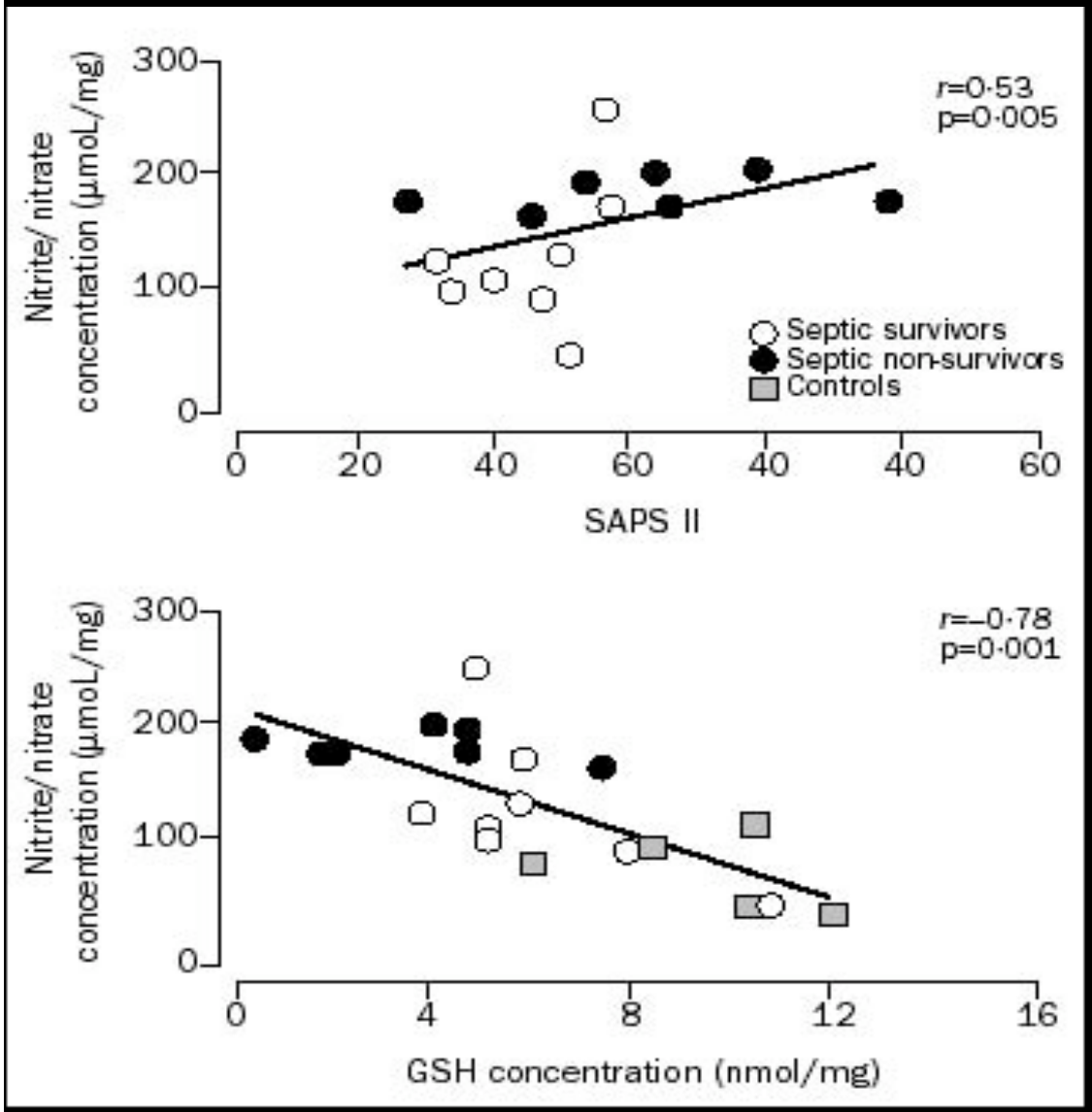
Altération de la respiration mitochondriale dans des modèles de sepsis (Singer et al)

Lancet 2005

Protection of hepatocyte mitochondrial ultrastructure and function by strict blood glucose control with insulin in critically ill patients

Ilse Vanhorebeek, Rita De Vos, Dieter Mesotten, Pieter J Wouters, Christiane De Wolf-Peeters, Greet Van den Berghe

Anomalies du complexe I de la chaine respiratoire
Correction par l'insuline



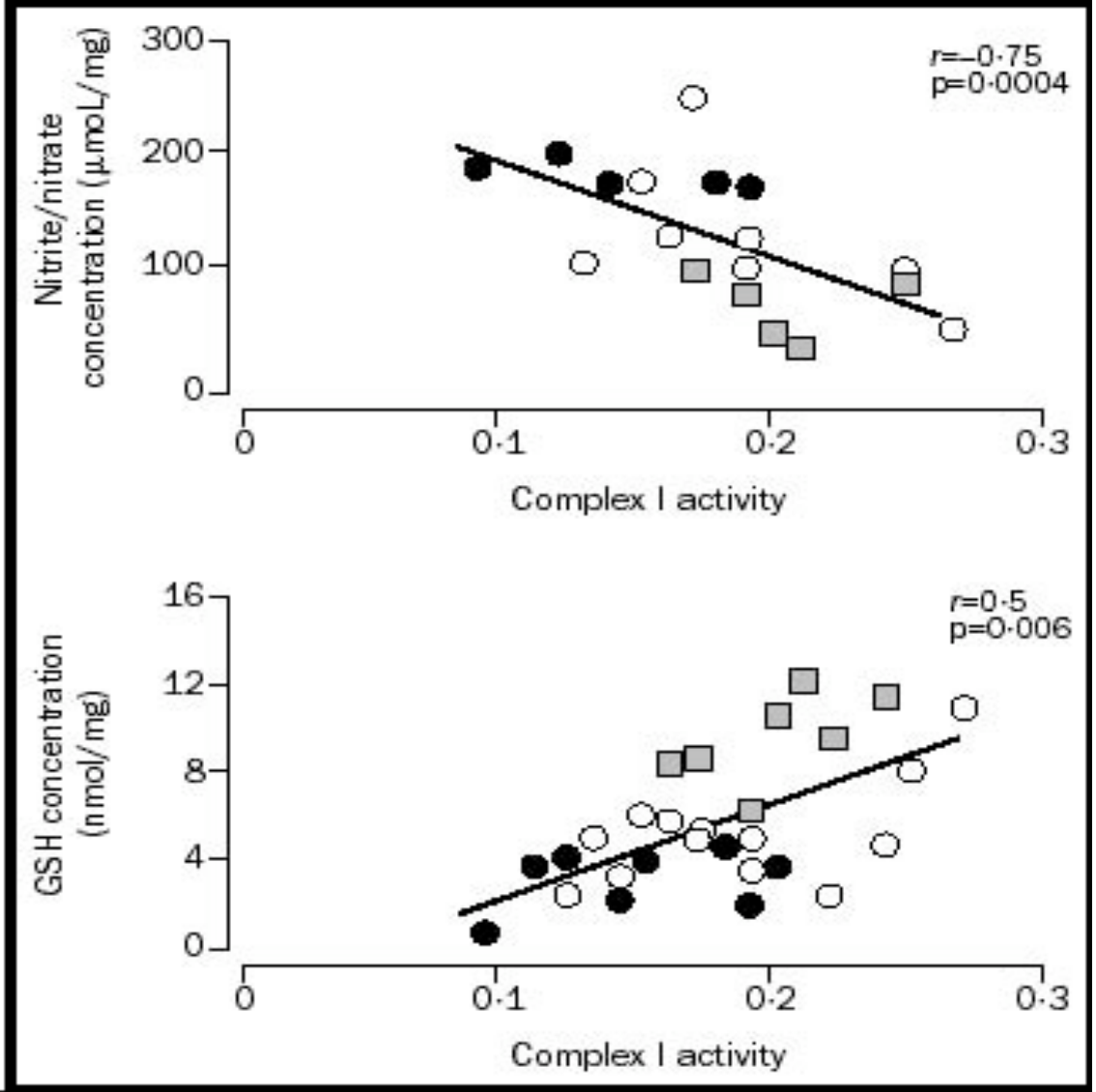
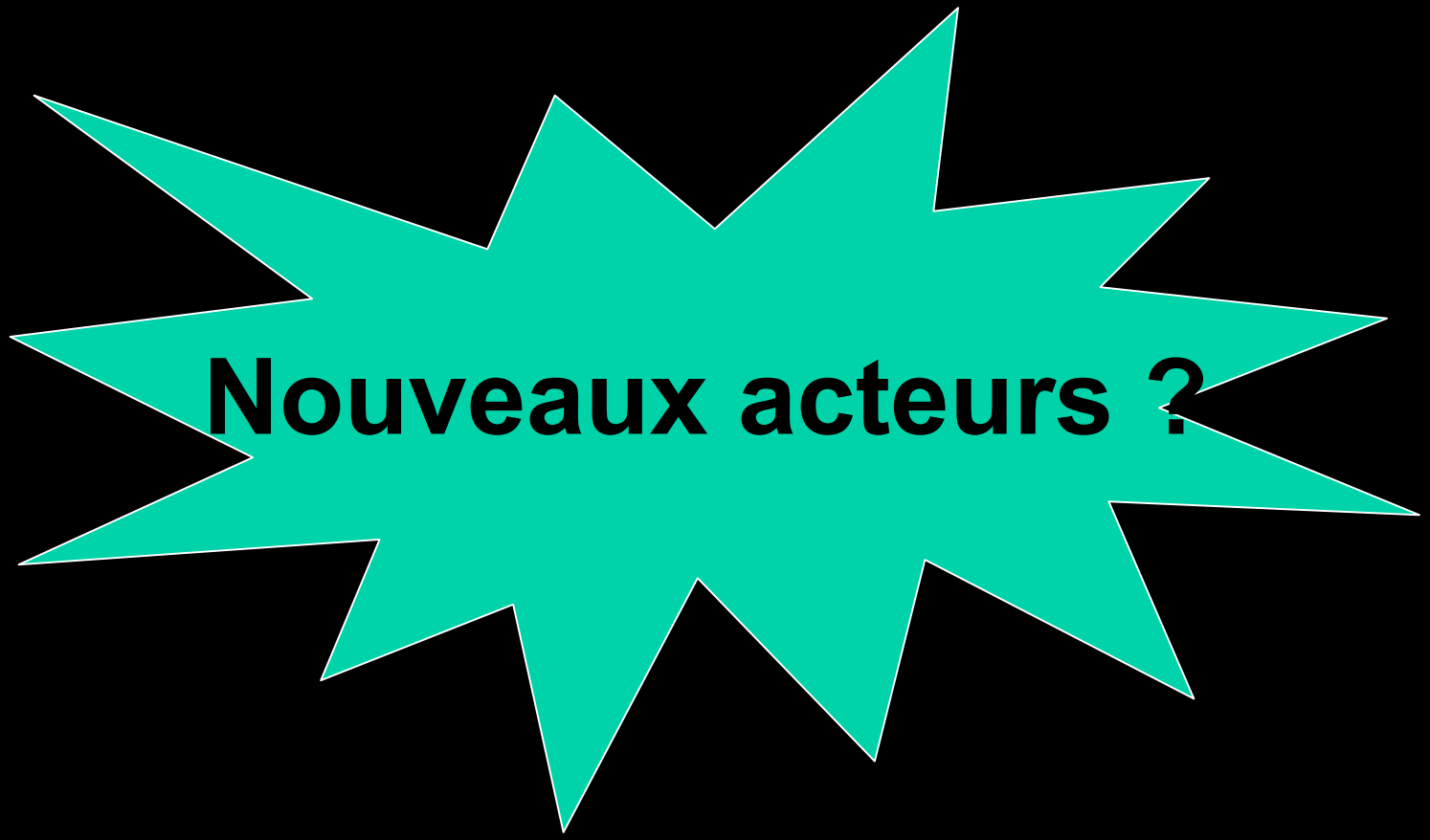
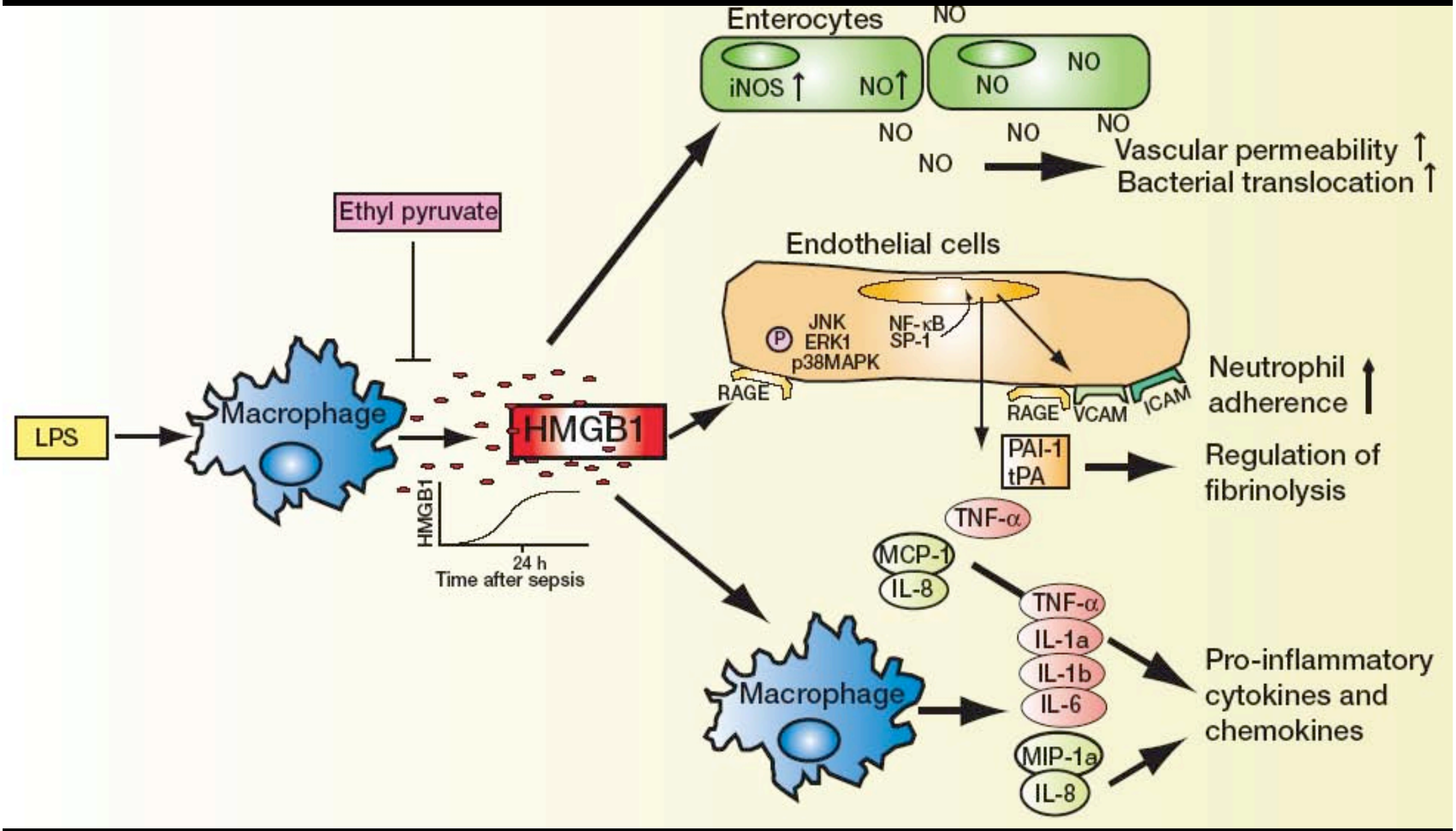


Figure 3: **Correlation between tissue nitrite/nitrate concentration, simplified acute physiology score (SAPS II), tissue reduced glutathione (GSH) concentration, and complex I activity**

What’s next ?

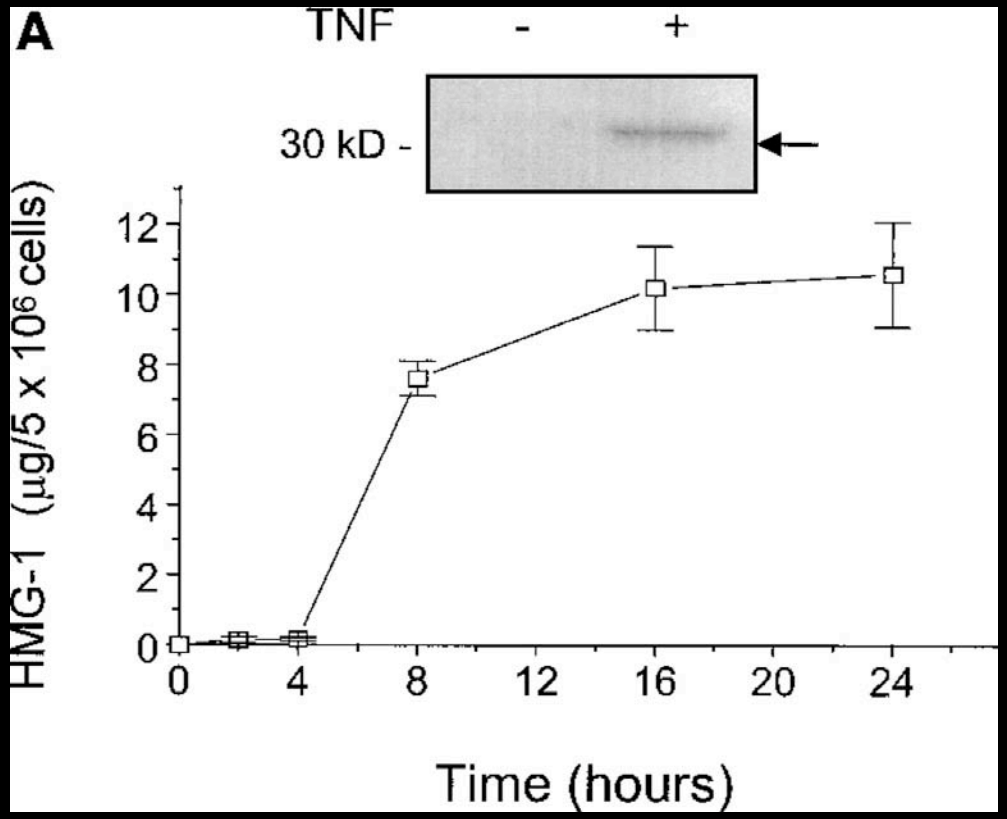


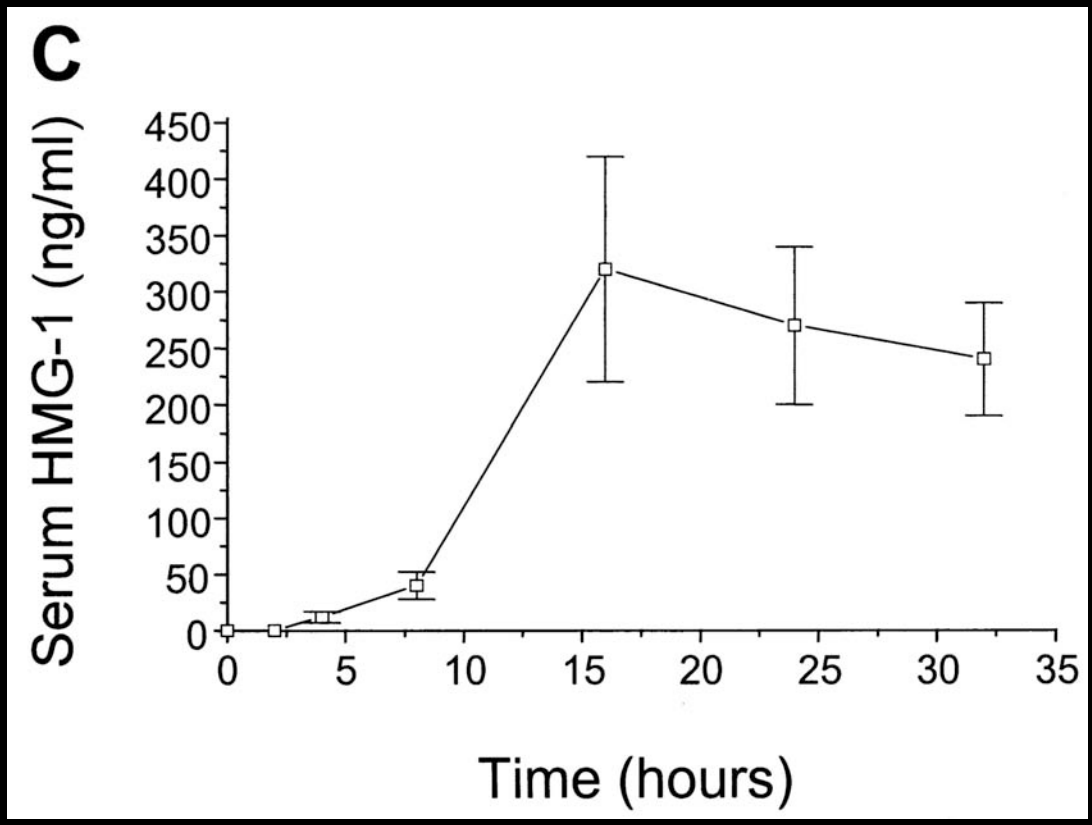
HMGB1


Enterocytes
NO
iNOS ↑
NO↑
NO
NO
NO
NO
NO
NO
Vascular permeability ↑
Bacterial translocation ↑
Ethyl pyruvate
Endothelial cells
JNK
ERK1
p38MAPK
NF-κB
SP-1
RAGE
RAGE
VCAM
ICAM
Neutrophil adherence
LPS
Macrophage
HMGB1
PAI-1
tPA
Regulation of fibrinolysis
HMGB1
24 h
Time after sepsis
TNF-α
MCP-1
IL-8
TNF-α
IL-1a
IL-1b
IL-6
MIP-1a
IL-8
Macrophage
Pro-inflammatory cytokines and chemokines

HMGB1

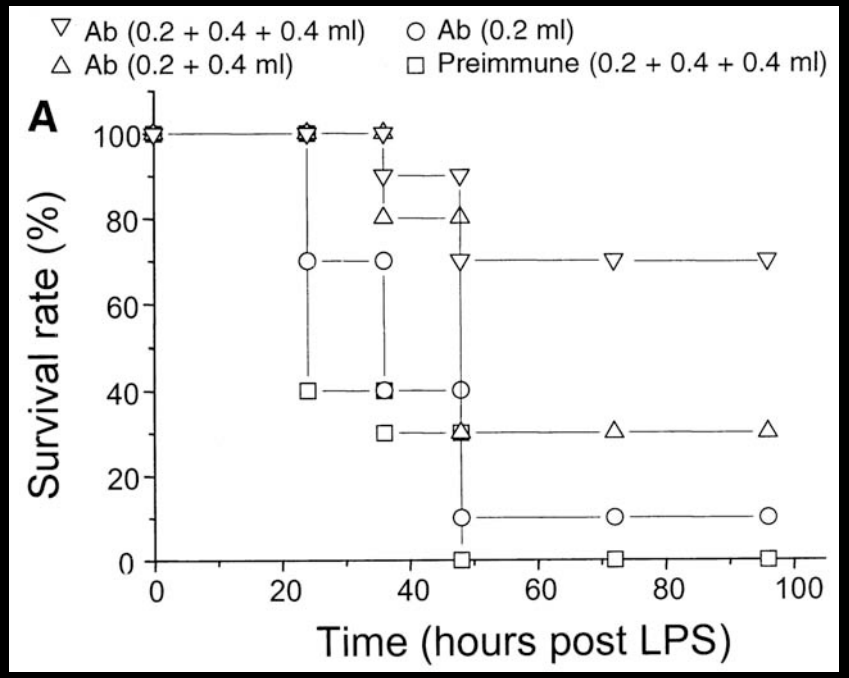
HMG-1 : a late mediator of sepsis …
SDS PAGE …
Protéine nucléaire et membranaire (cascade de la coag.)

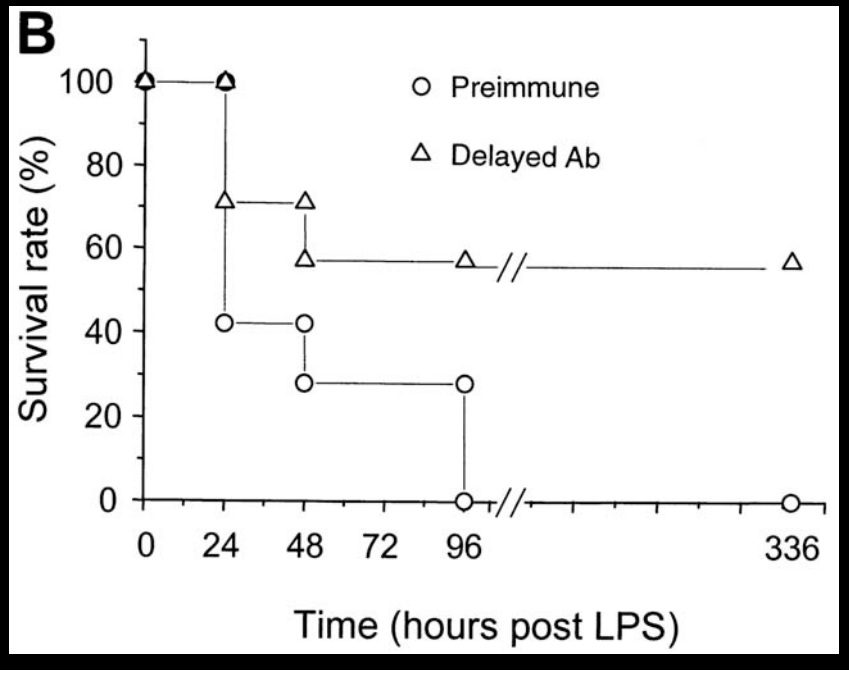


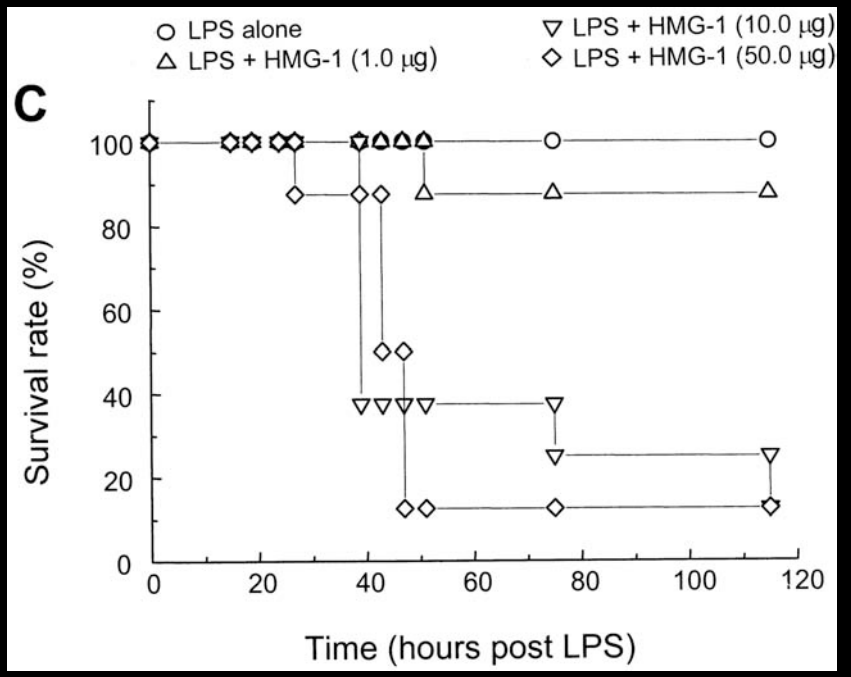


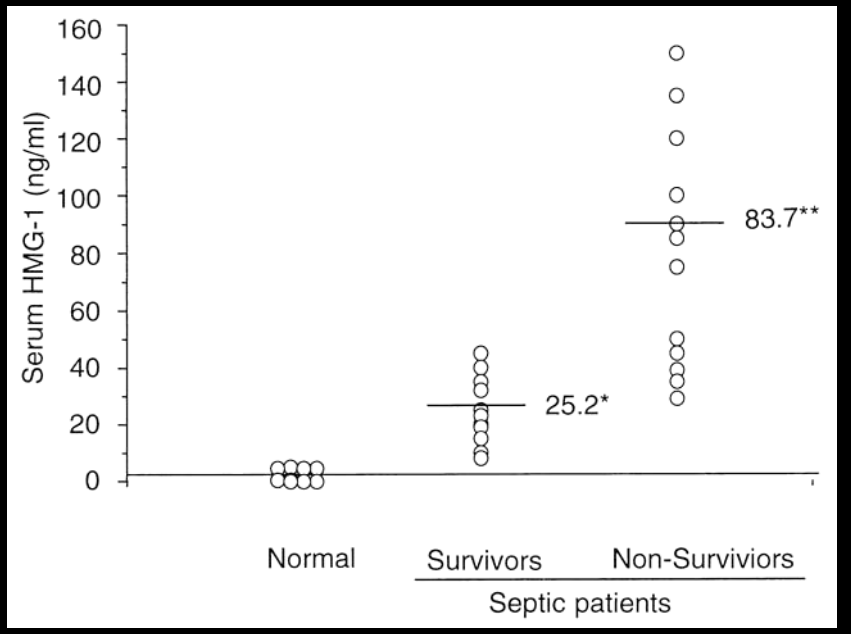
Science 1999; 285: 248

HMG-1

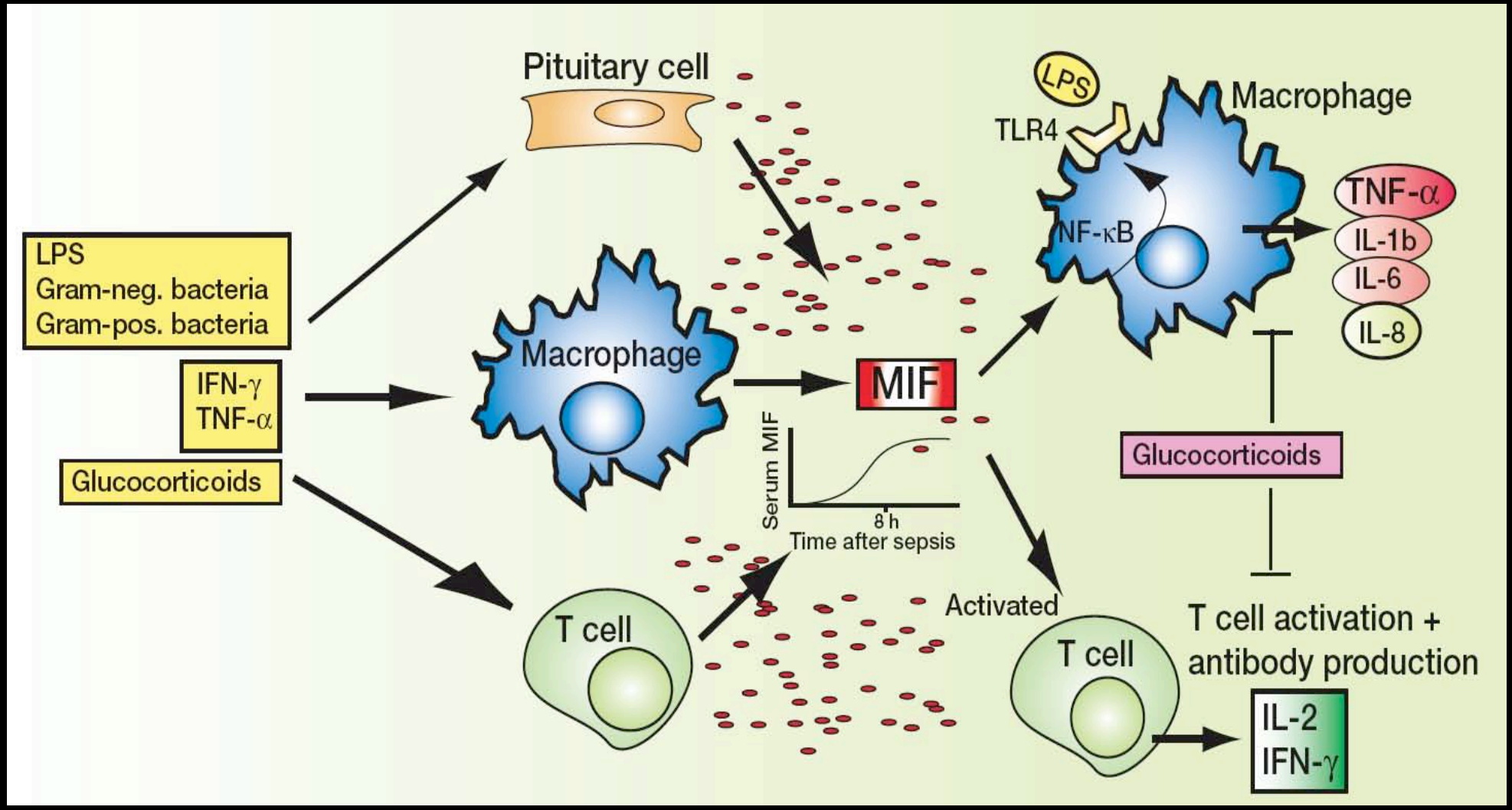

A
Ab (0.2 + 0.4 + 0.4 ml)
Ab (0.2 ml)
Ab (0.2 + 0.4 ml)
Preimmune (0.2 + 0.4 + 0.4 ml)
Survival rate (%)
Time (hours post LPS)


B
Preimmune
Delayed Ab
Survival rate (%)
Time (hours post LPS)


C
LPS alone
LPS + HMG-1 (1.0 μg)
LPS + HMG-1 (10.0 μg)
LPS + HMG-1 (50.0 μg)
Survival rate (%)
Time (hours post LPS)


Serum HMG-1 (ng/ml)
25.2*
83.7**
Normal
Survivors
Non-Survivors
Septic patients

MIF

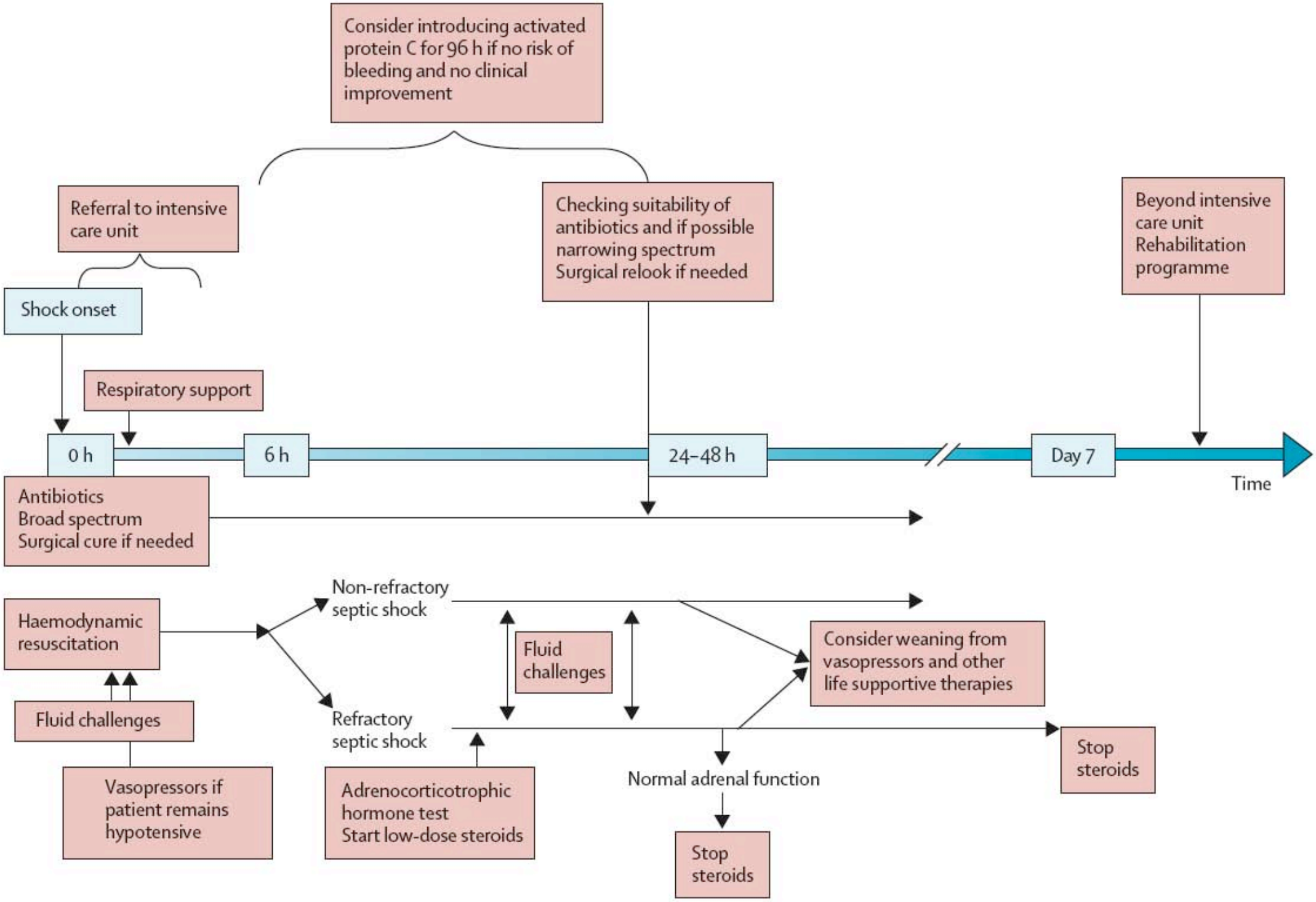

Pituitary cell
LPS
TLR4
Macrophage
TNF-α
IL-1b
IL-6
IL-8
NF-κB
LPS
Gram-neg. bacteria
Gram-pos. bacteria
IFN-γ
TNF-α
Glucocorticoids
Macrophage
MIF
Serum MIF
8 h
Time after sepsis
Glucocorticoids
T cell
Activated
T cell
T cell activation +
antibody production
IL-2
IFN-γ

	Molecules	Development phase
Lipopolysaccharide	Cationic antimicrobial protein 18	Experimental
	Synthetic analogues of lipid A, E5564	Clinical, phase II
	Recombinant human lipoproteins	Experimental
	Monoclonal antibodies to CD14	Clinical, phase I
Late proinflammatory mediators	Antibody to high mobility group box 1,	Experimental
	DNA-binding A box, ethyl pyruvate	Experimental
	Anti-macrophage migration inhibitory factor	Experimental
Complement system cascade	Blockade of either C5a or C5a receptor	Experimental
Apoptosis	Anti-caspase	Experimental
	Blockade of Fas/Fas ligand	
	with Fas receptor fusion protein	Experimental
	Metoclopramide	Experimental
	Over-expression of B-cell lymphoma/leukaemia-2	Experimental
Poly-ADP-ribose synthase	Inhibitors of this target	Experimental
Inducible NO synthase	2-aminopyridines, ONO-1714, polyphenolic flavonoid	Experimental
	antioxidant, aminoguanidine, L-N6-(1-iminoethyl)-lysine	
Autonomic nervous system	Vagal nerve stimulation	Experimental
Others	High mobility group-CoA reductase inhibitors	Experimental
	Blockade of endothelin-receptor	Experimental
	Calpain inhibitors	Experimental
	A_{2A} adenosine receptor agonists	Experimental

Table 6: **Putative future targets and treatments**

Conclusion

Il ne faut pas se tromper
de physiopathologie


Consider introducing activated protein C for 96 h if no risk of bleeding and no clinical improvement
Referral to intensive care unit
Checking suitability of antibiotics and if possible narrowing spectrum
Surgical relook if needed
Beyond intensive care unit
Rehabilitation programme
Shock onset
Respiratory support
0 h
6 h
24–48 h
Day 7
Time
Antibiotics
Broad spectrum
Surgical cure if needed
Haemodynamic resuscitation
Non-refractory septic shock
Fluid challenges
Consider weaning from vasopressors and other life supportive therapies
Fluid challenges
Refractory septic shock
Stop steroids
Vasopressors if patient remains hypotensive
Adrenocorticotrophic hormone test
Start low-dose steroids
Normal adrenal function
Stop steroids

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Matthay, Nat Med 2004; 10: 1161
Singer, Lancet 2004; 364: 545
Vanhorebeek, Lancet 2005; 365: 53