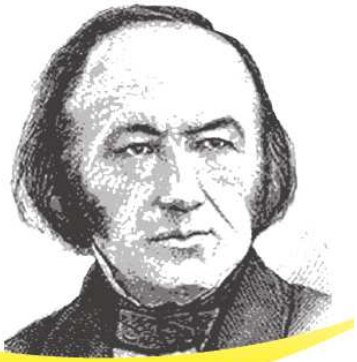
JEUDI 16 NOVEMBRE 2017
UFR Médecine Paris 7 Diderot,
site Xavier-Bichat - Paris 18ème

60ème journée de l'hôpital Claude-Bernard



Immunoparalysie post-sepsis : mythe ou réalité ?

Guillaume Monneret

Hôp. E. Herriot / Hospices Civils de Lyon
EA 7426 - Pathophysiology of Injury-Induced Immunosuppression - U. Lyon 1
ISPB (School of Pharmacy) – U. Lyon 1

Lyon 1

Hospices Civils de Lyon

Flow Division
Immunology Department

CRICS-TRIGGERSEP
Clinical Research in Intensive Care and Sepsis
TRIal Group for Global Evaluation and Research in SEPsis
F-CRIN Network

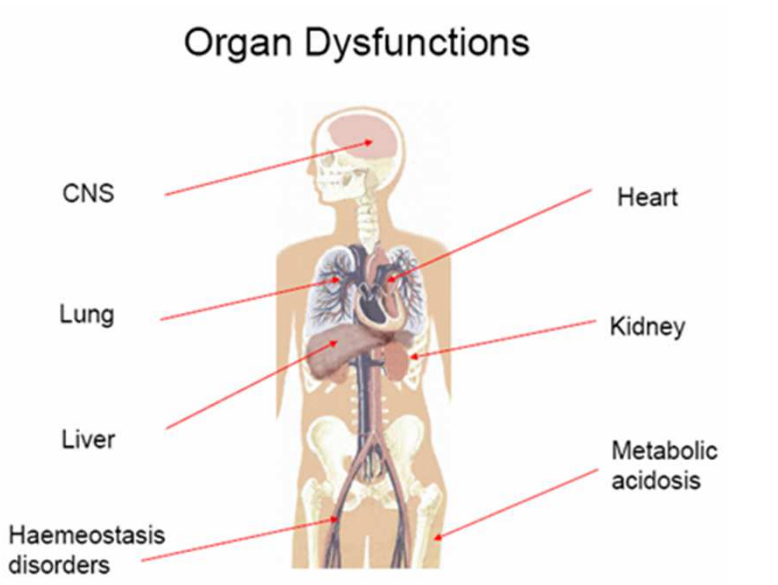
BIOMÉRIEUX

Questions

1. Les raisons du mythe ?
2. Mythe ou réalité ?
3. Immunostimulation est-elle une chimère ?

Sepsis definition

Uncontrolled Inflammatory response →



Decreased arterial pressure
Shock
Multiple organ failure

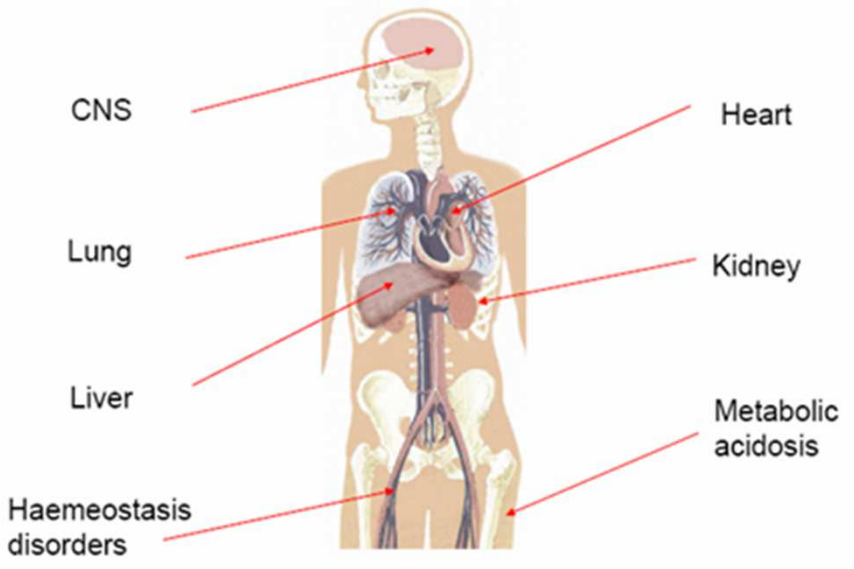
REVISED DEFINITIONS

Sepsis	Life threatening organ dysfunction* caused by a dysregulated host response to infection
Septic shock	Sepsis and vasopressor therapy needed to increase mean arterial pressure to ≥65 mm Hg and lactate to >2 mmol/L despite adequate fluid resuscitation

Singer et al., JAMA 2016

Sepsis treatment

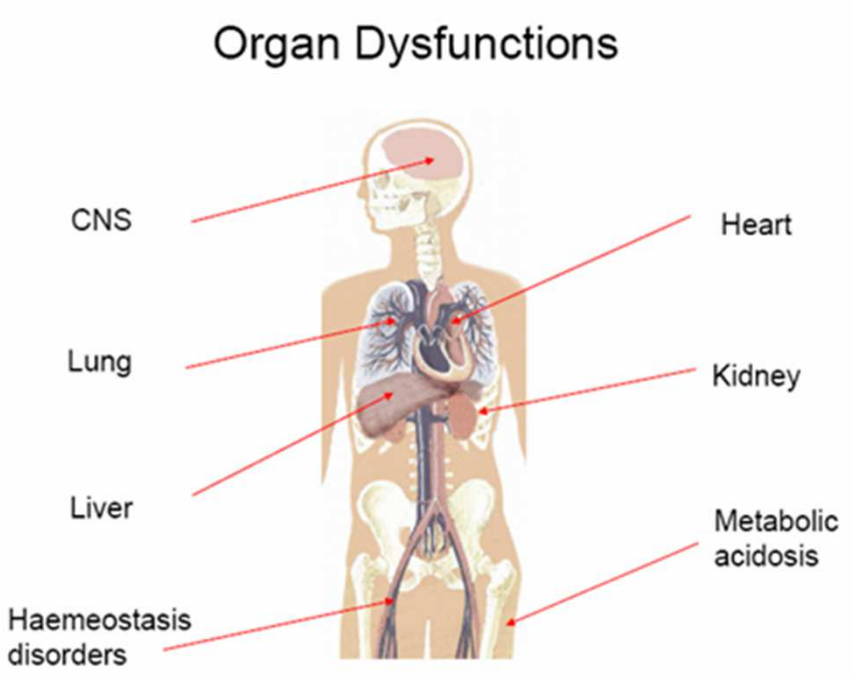
Uncontrolled Inflammatory response



Early treatment :
Antibiotherapy
(+ surgery when appropriate)
Agressive vascular resuscitation
Vasoactive agents

Decreased arterial pressure
Shock
Multiple organ failure

Uncontrolled Inflammatory response

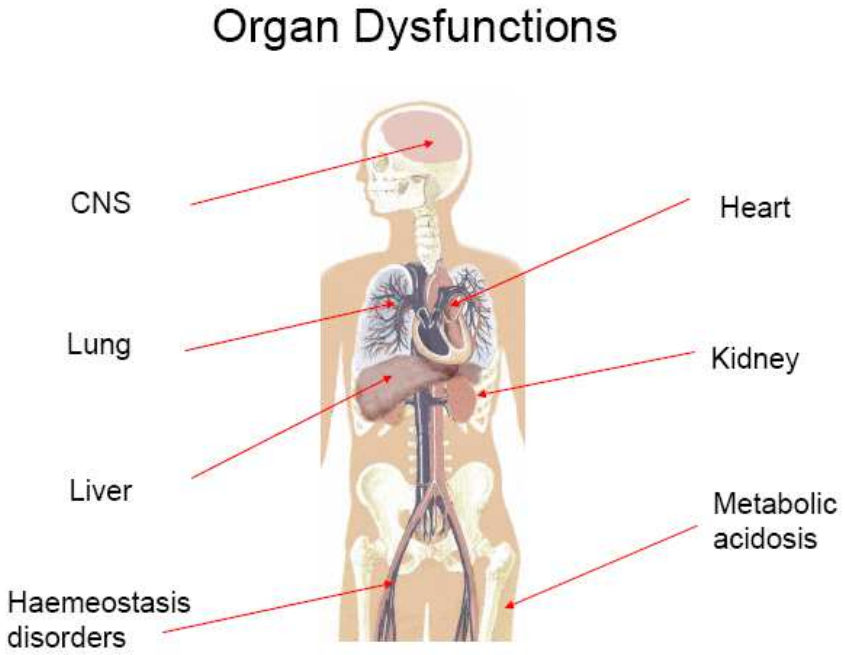


Adjunctive therapy

Early treatment :
Antibiotherapy
Agressive vascular resuscitation
Vasoactive agents

Decreased arterial pressure
Shock
Multiple organ failure

Uncontrolled inflammatory response



Adjunctive therapy in addition to symptomatic treatments : <u>anti-inflammatory drugs</u>

Failure of clinical trials testing anti-inflammatory therapies

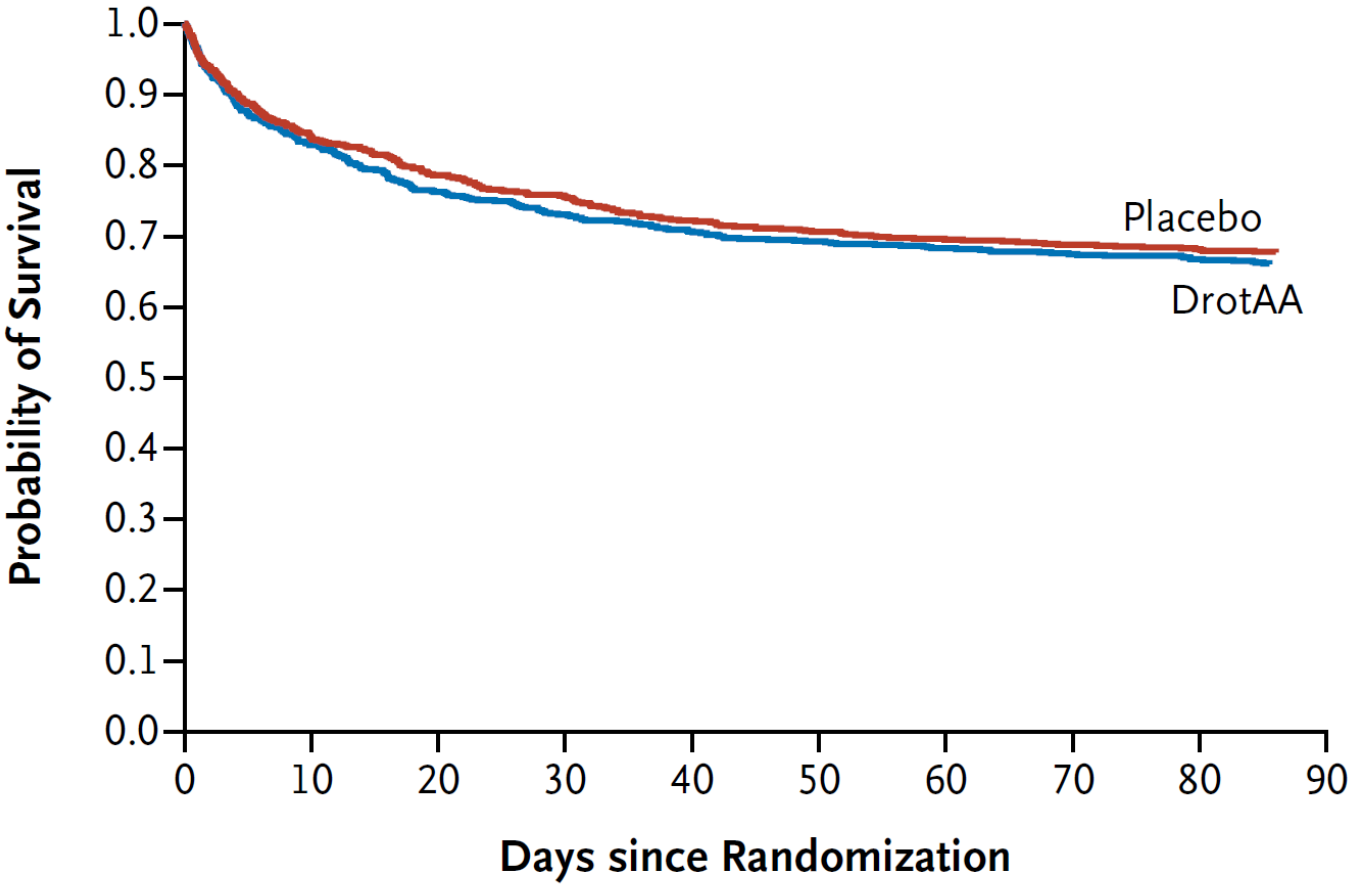
Drug	Number of studies	Number of patients	Mortality (%)	
			Placebo	Drug
Anti-endotoxine	4	2010	35	35
Anti-bradykinine	2	755	36	39
Anti-PAF	2	870	50	45
Anti-TNF	8	4132	41	40
R solubles TNF	2	688	38	40
AINS	3	514	40	37
Steroids	9	1267	35	39
(high doses)	…	…	…	…
…				
Total	33	12034	**38**	**38**

Zeni et al, Crit Care Med, 1997

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 31, 2012 VOL. 366 NO. 22

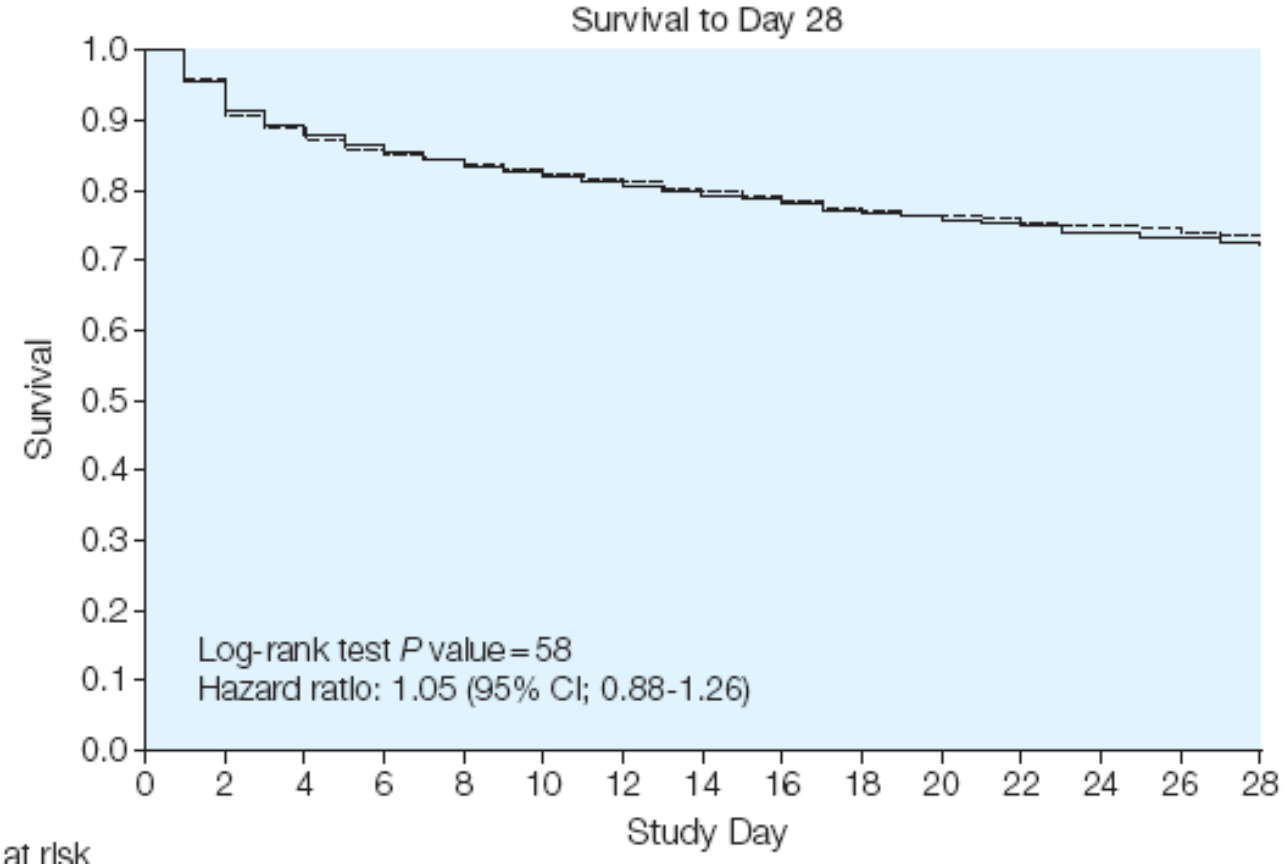
Drotrecogin Alfa (Activated) in Adults with Septic Shock



Ranieri et al. 2012

Effect of Eritoran, an Antagonist of MD2-TLR4, on Mortality in Patients With Severe Sepsis

The ACCESS Randomized Trial



JAMA The Journal of the American Medical Association

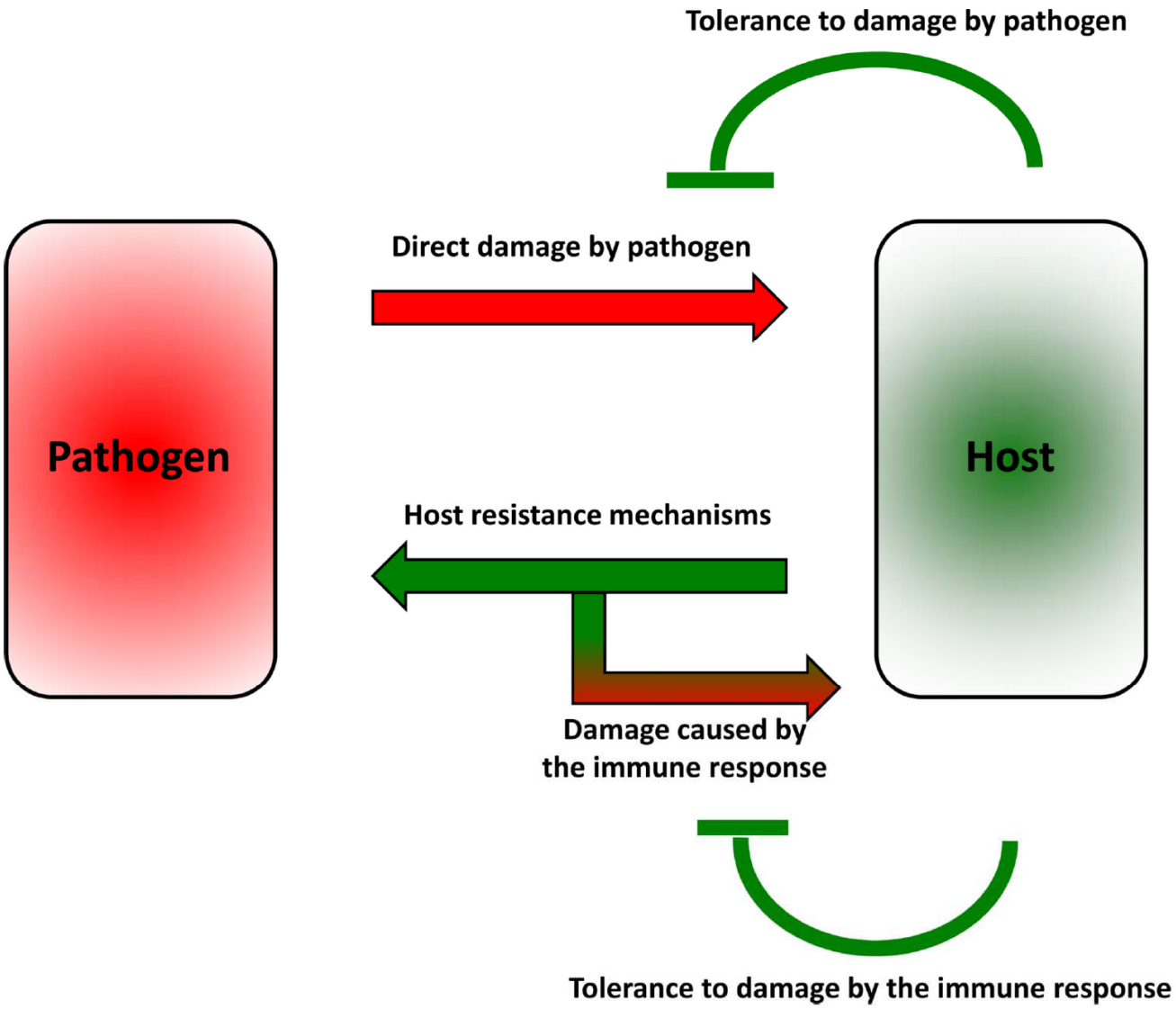
Opal et al. 2013

Seeds for a new paradigm

Meakins JL, Pietsch JB, Bubenick O, Kelly R, Rode H, Gordon J, MacLean LD: **Delayed hypersensitivity: indicator of acquired failure of host defenses in sepsis and trauma**.
Ann Surg 1977, **186**(3):241-250.

Munoz C, Carlet J, Fitting C, Misset B, Bleriot JP, Cavaillon JM: **Dysregulation of in vitro cytokine production by monocytes during sepsis**.
J Clin Invest 1991, **88**(5):1747-1754

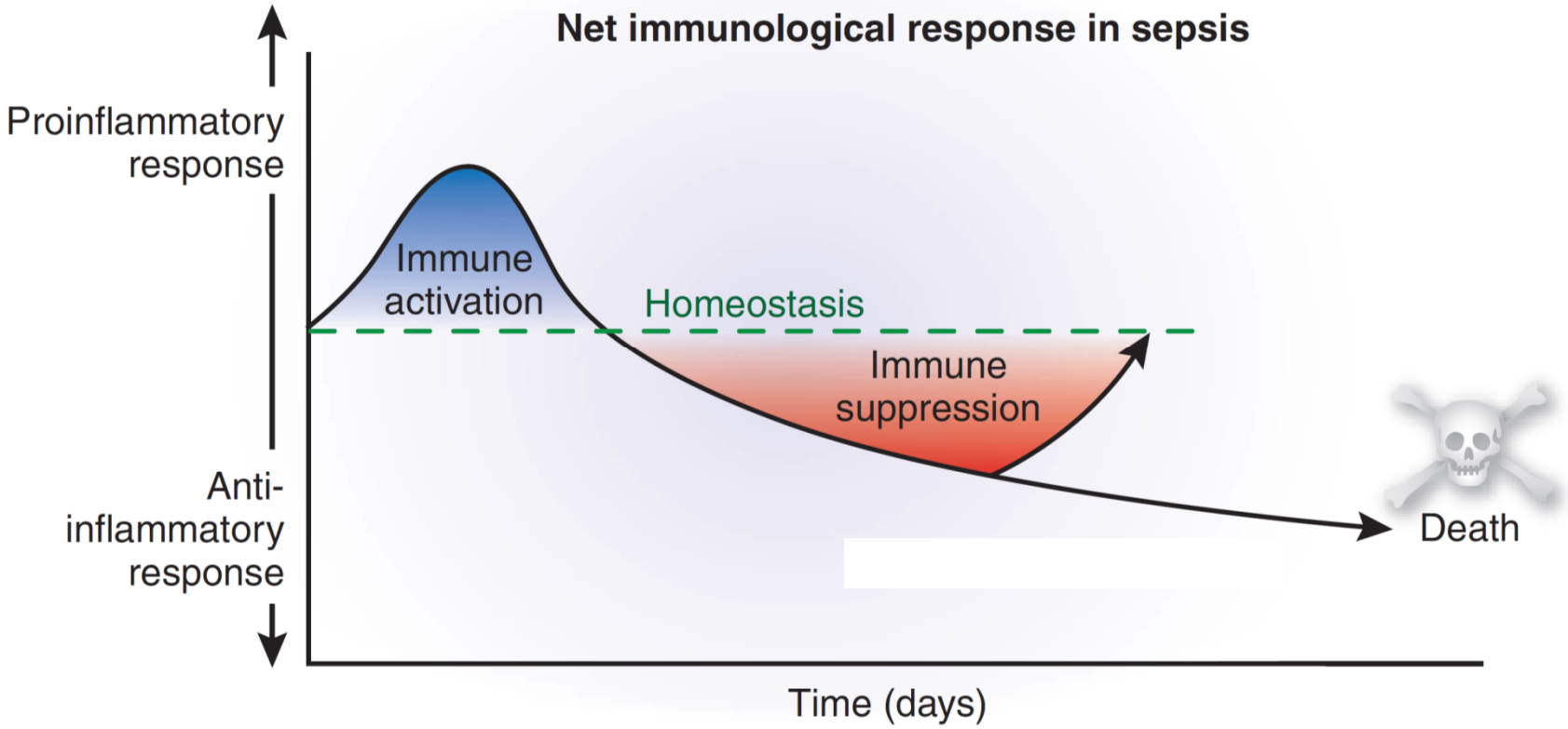
Hotchkiss RS, Swanson PE, Freeman BD, Tinsley KW, Cobb JP, Matuschak GM, Buchman TG, Karl IE: **Apoptotic cell death in patients with sepsis, shock, and multiple organ dysfunction**.
Crit Care Med 1999, **27**(7):1230-1251.



Medzhitov et al., Science 2012

Tilting toward immunosuppression

Richard S Hotchkiss, Craig M Coopersmith, Jonathan E McDunn & Thomas A Ferguson

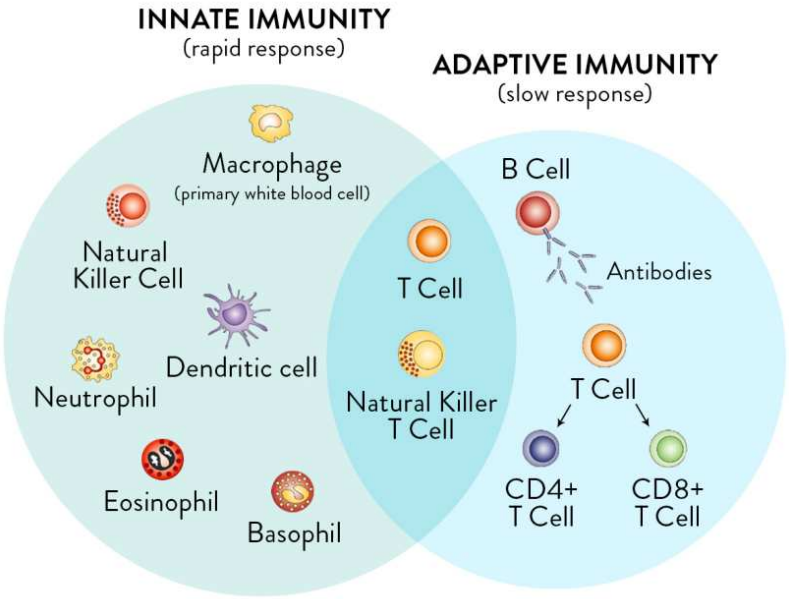


nature medicine

2009

Are septic patients really immunosuppressed ?

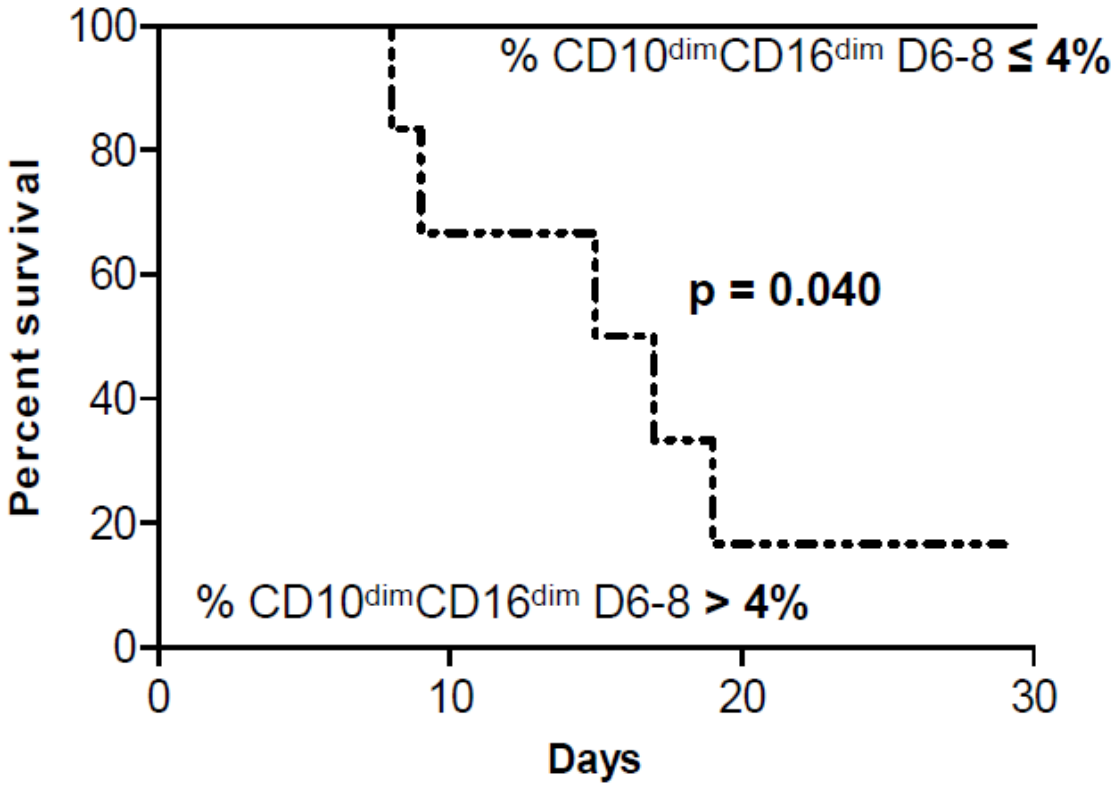
Do septic patients present immune alterations ?



Marked alterations of neutrophil functions during sepsis-induced immunosuppression

Julie Demaret,[*,†] *Fabienne Venet,*[*,†] *Arnaud Friggeri,*[‡] *Marie-Angélique Cazalis,*[§] *Jonathan Plassais,*[§] *Laurent Jallades,*[¶] *Christophe Malcus,** *Françoise Poitevin-Later,** *Julien Textoris,*[§,‖] *Alain Lepape,*[‡] *and Guillaume Monneret*[*,†,1]

At day 7, persitence of elevated % of immature neutrophils
Is associated with 28-day mortality



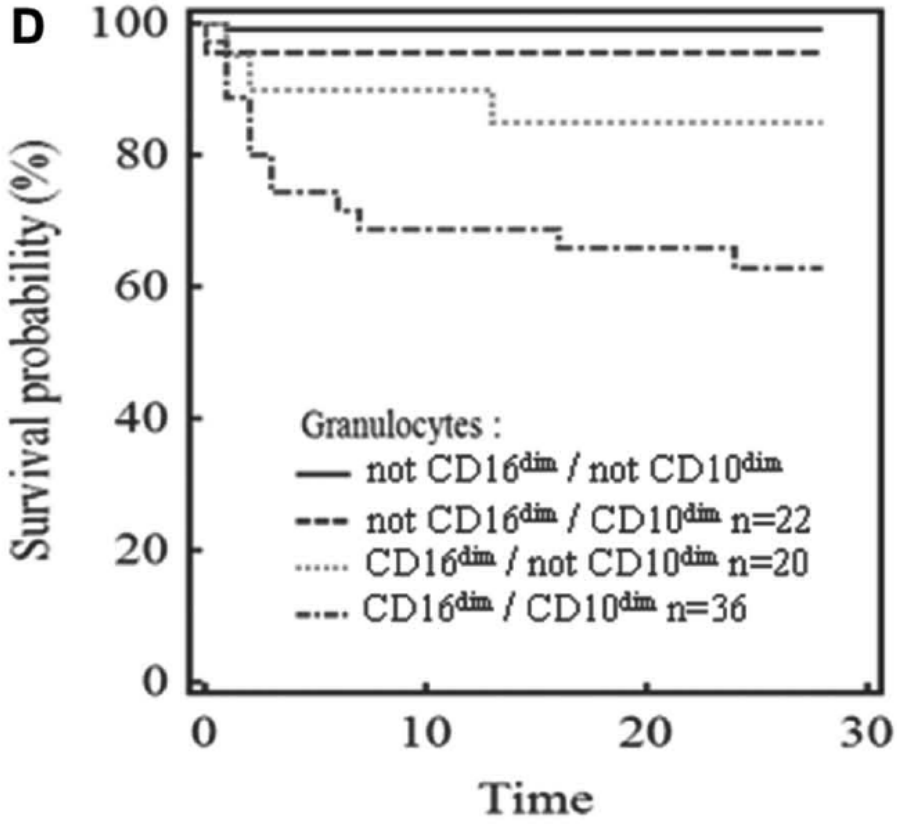
JLB
Volume 98, December 2015 *Journal of Leukocyte Biology*

Circulating Immature Granulocytes With T-Cell Killing Functions Predict Sepsis Deterioration*

Estelle Guérin, MD[1]; Marie Orabona, MD[2]; Marie-Astrid Raquil, MD, PhD[3]; Bruno Giraudeau, MD, PhD[4]; Rémy Bellier, MD[2]; Sébastien Gibot, MD, PhD[5]; Marie-Christine Béné, MD, PhD[6]; Francis Lacombe, MD, PhD[7]; Nathalie Droin, PhD[3]; Eric Solary, MD, PhD[3]; Philippe Vignon, MD, PhD[2,8]; Jean Feuillard, MD, PhD[1]; Bruno François, MD[2,8]

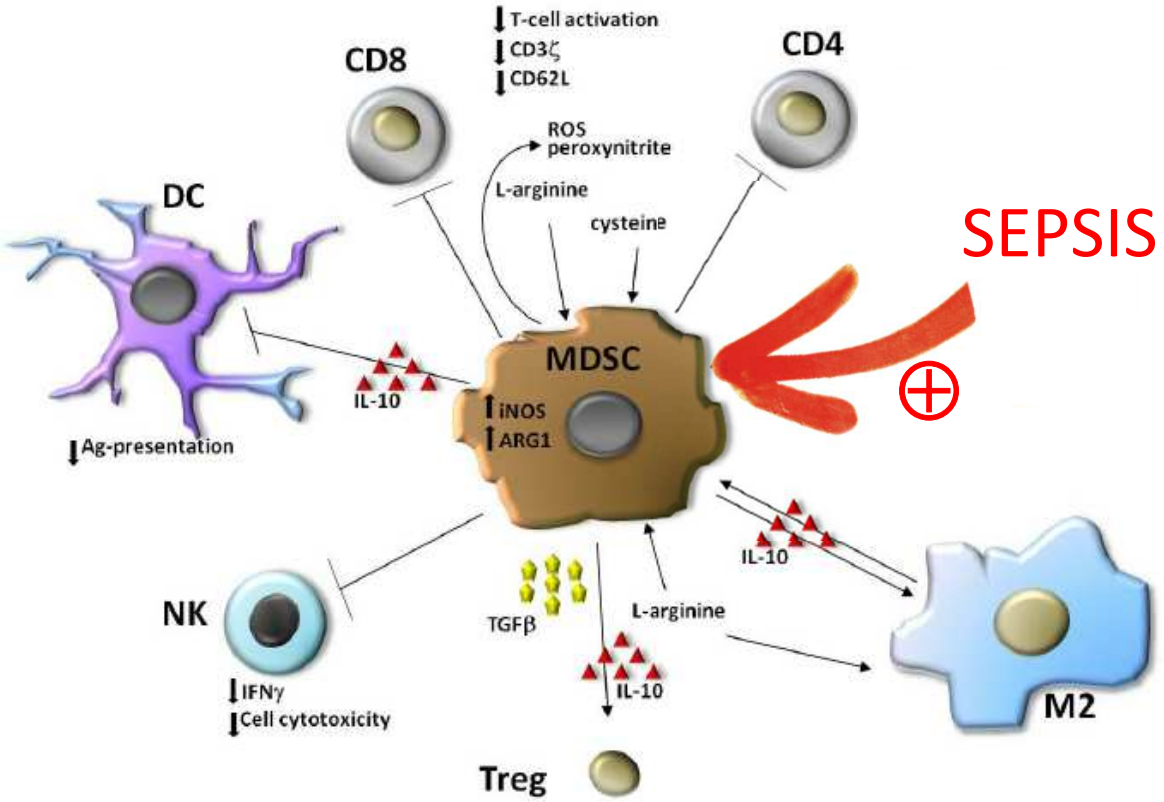
Critical Care Medicine

September 2014 • Volume 42 • Number 9



→ MDSC ?

MDSC: novel cells of interest in sepsis



<u>Animal models</u>

Landoni 2016, Clinical Science

Llitjos 2016, J Pathol

McPeak 2017, Infect Immun

McPeak 2017, J Leuko Biol

<u>Clinics</u>

Janols 2014, J Leuko Biol

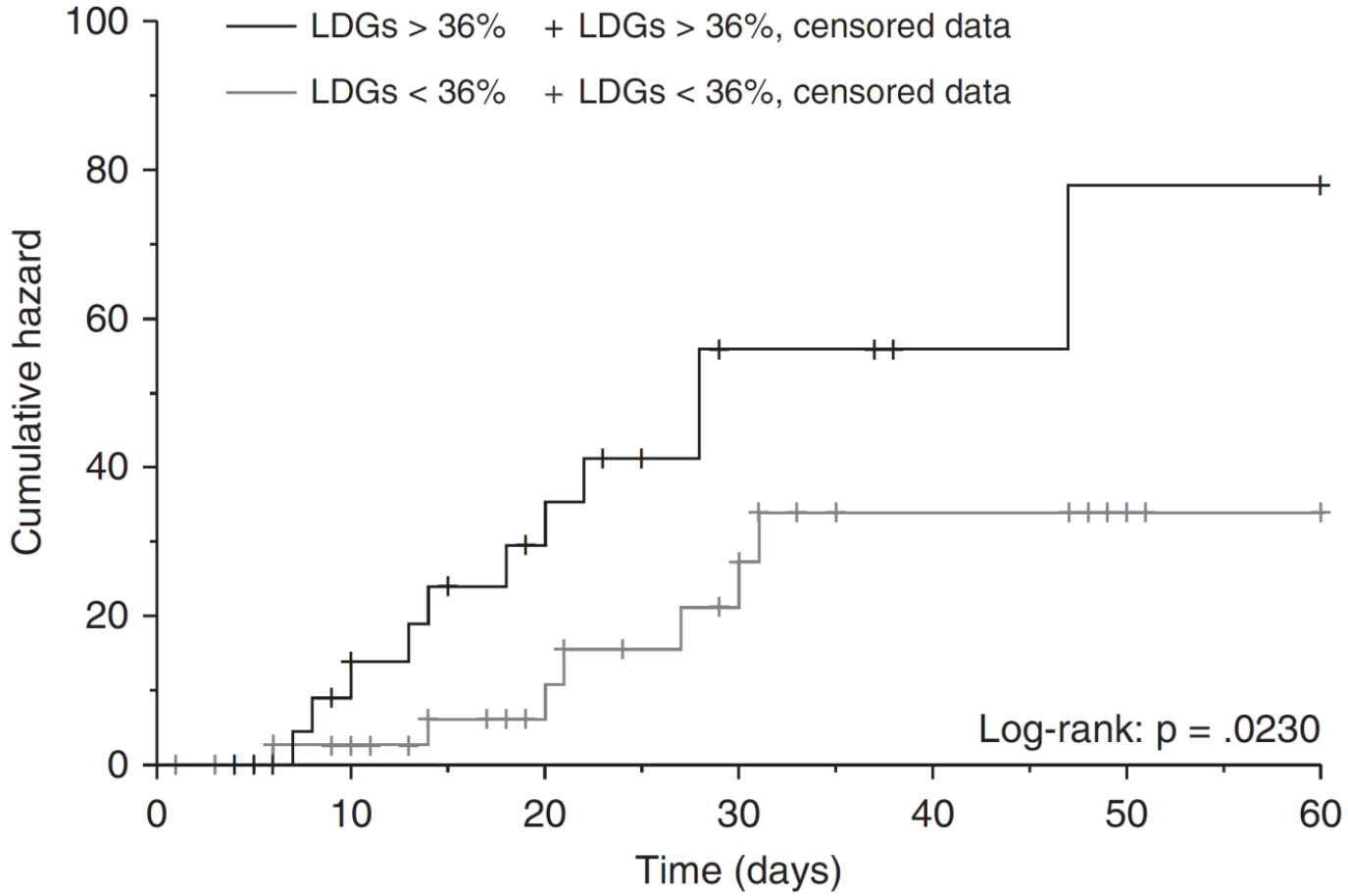
Mathias 2017, Annals Surg

Bernsmeier 2017, Gut

Early Expansion of Circulating Granulocytic Myeloid-derived Suppressor Cells Predicts Development of Nosocomial Infections in Patients with Sepsis

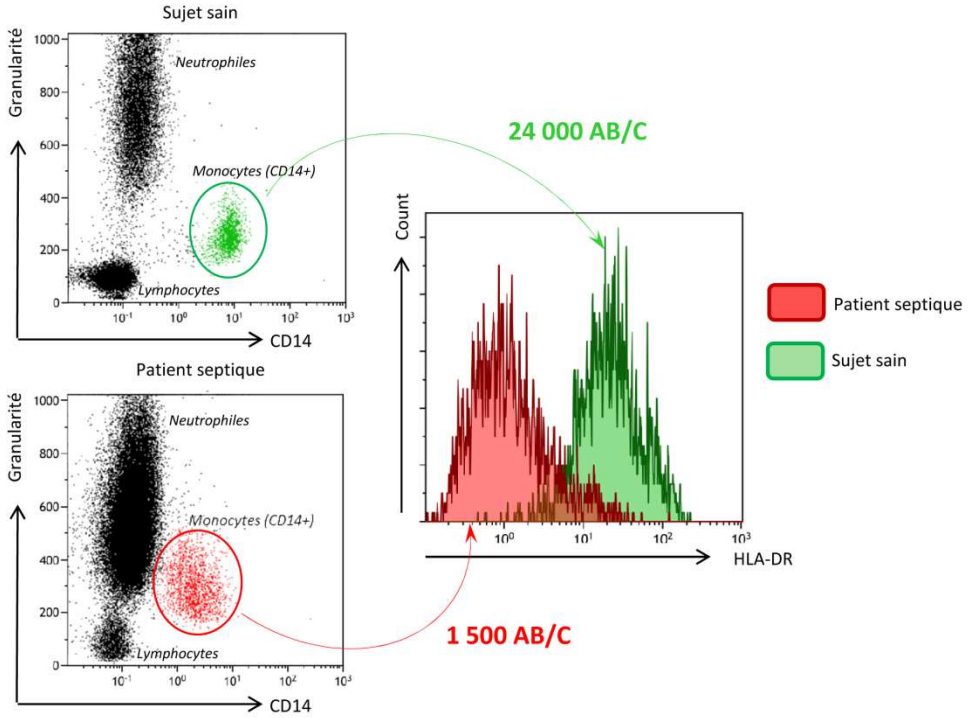
Fabrice Uhel[1,2,3,4], Imane Azzaoui[3,4], Murielle Grégoire[3,4], Céline Pangault[3,4], Joelle Dulong[3,4], Jean-Marc Tadié[1,2,3,4], Arnaud Gacouin[1,2], Christophe Camus[1,2], Luc Cynober[5,6], Thierry Fest[3,4], Yves Le Tulzo[1,2,3,4], Mikael Roussel[3,4], and Karin Tarte[3,4]

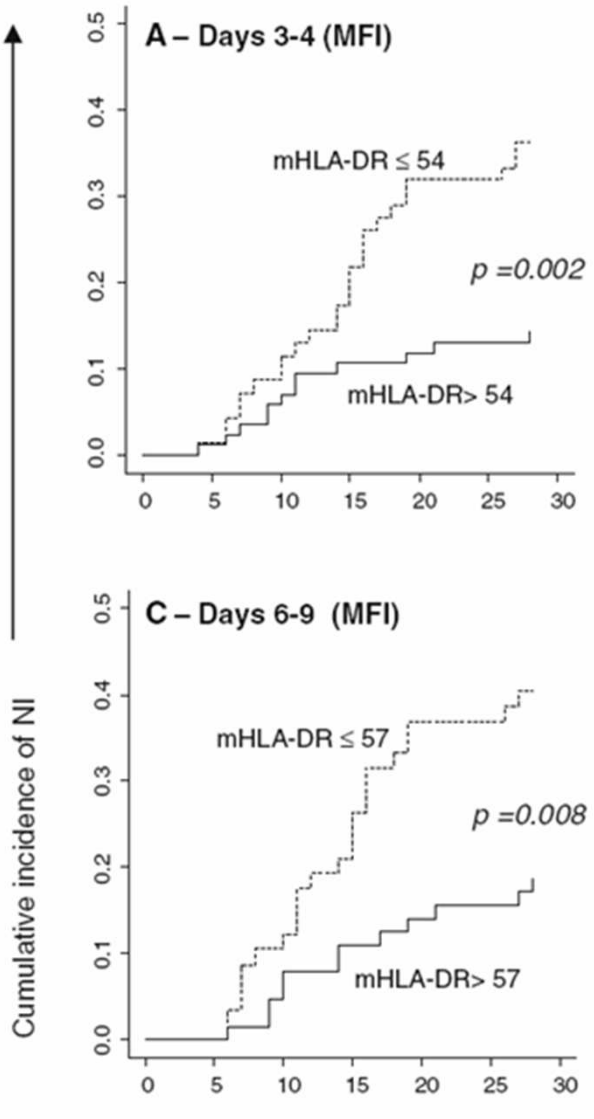
American Journal of Respiratory and Critical Care Medicine®
2017
We help the world breathe®
AJRCCM



Low monocyte human leukocyte antigen-DR is independently associated with nosocomial infections after septic shock

Landelle et al., 2010



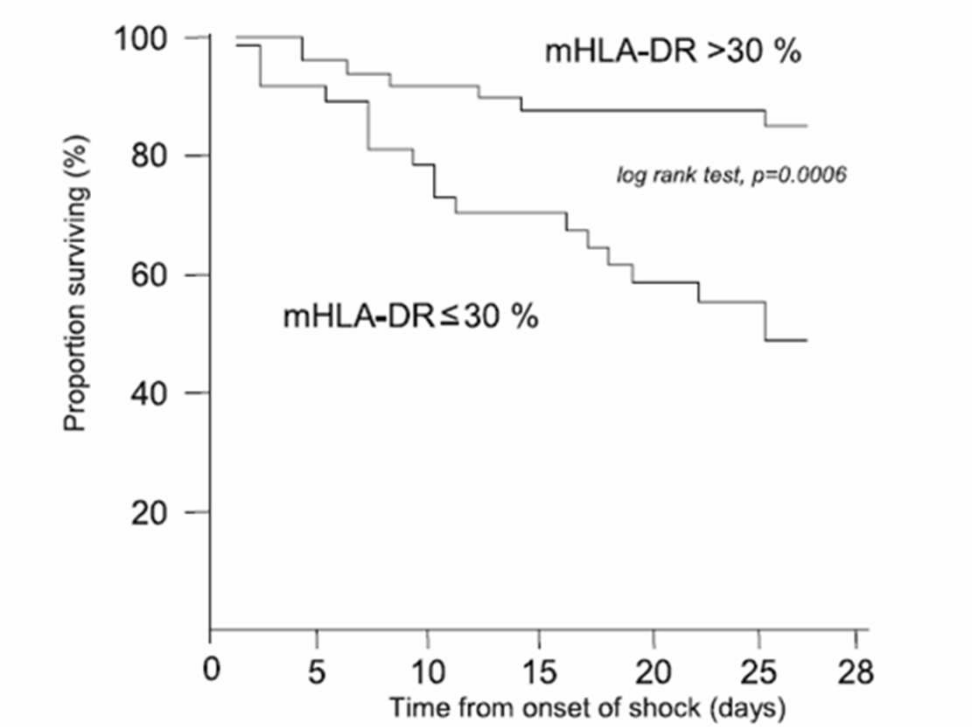


- Multivariate analysis (including usual confounding factors):
SOFA, SAPSII, Intubation, catheterization
- Competitive risks analysis

Persisting low monocyte human leukocyte antigen-DR expression predicts mortality in septic shock

INTENSIVE CARE MEDICINE

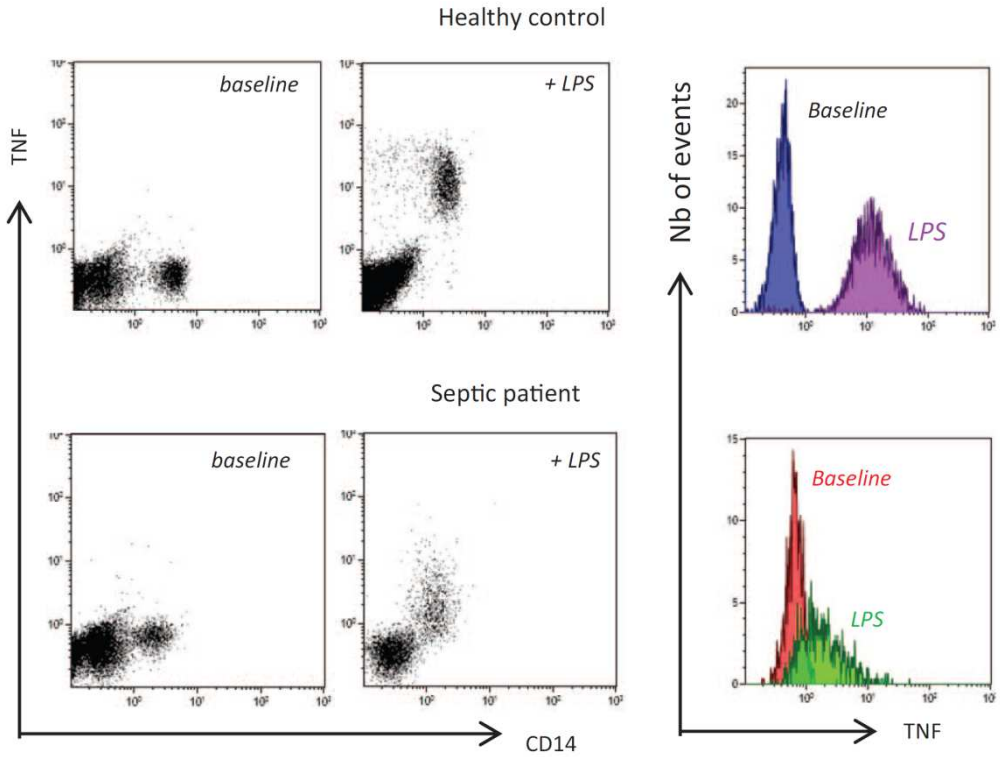
Survival curves stratified on mHLA-DR at 30 % at days 3-4 (n = 120 patients)

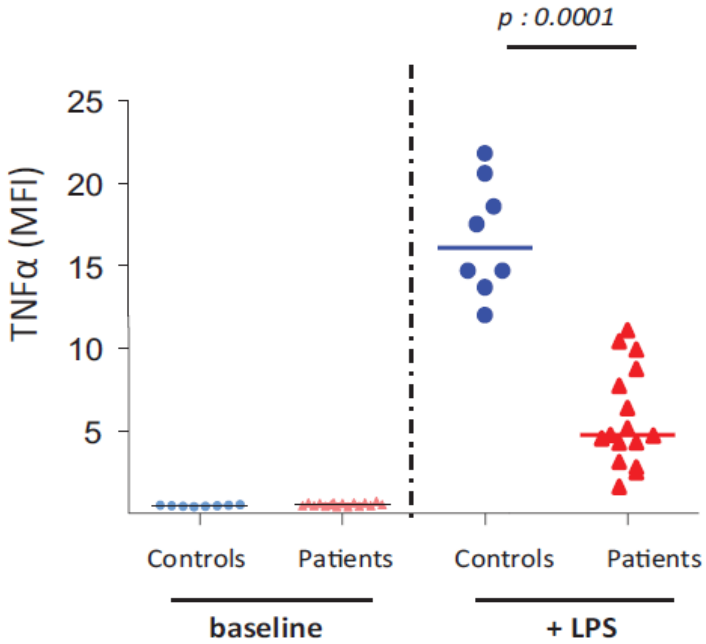


Multivariate analysis : mHLA-DR is an independent predictor of mortality (OR = 9) (after adjustment for usual clinical confounders : SAPS II, SOFA, comorbidities…)

Monneret et al., 2006

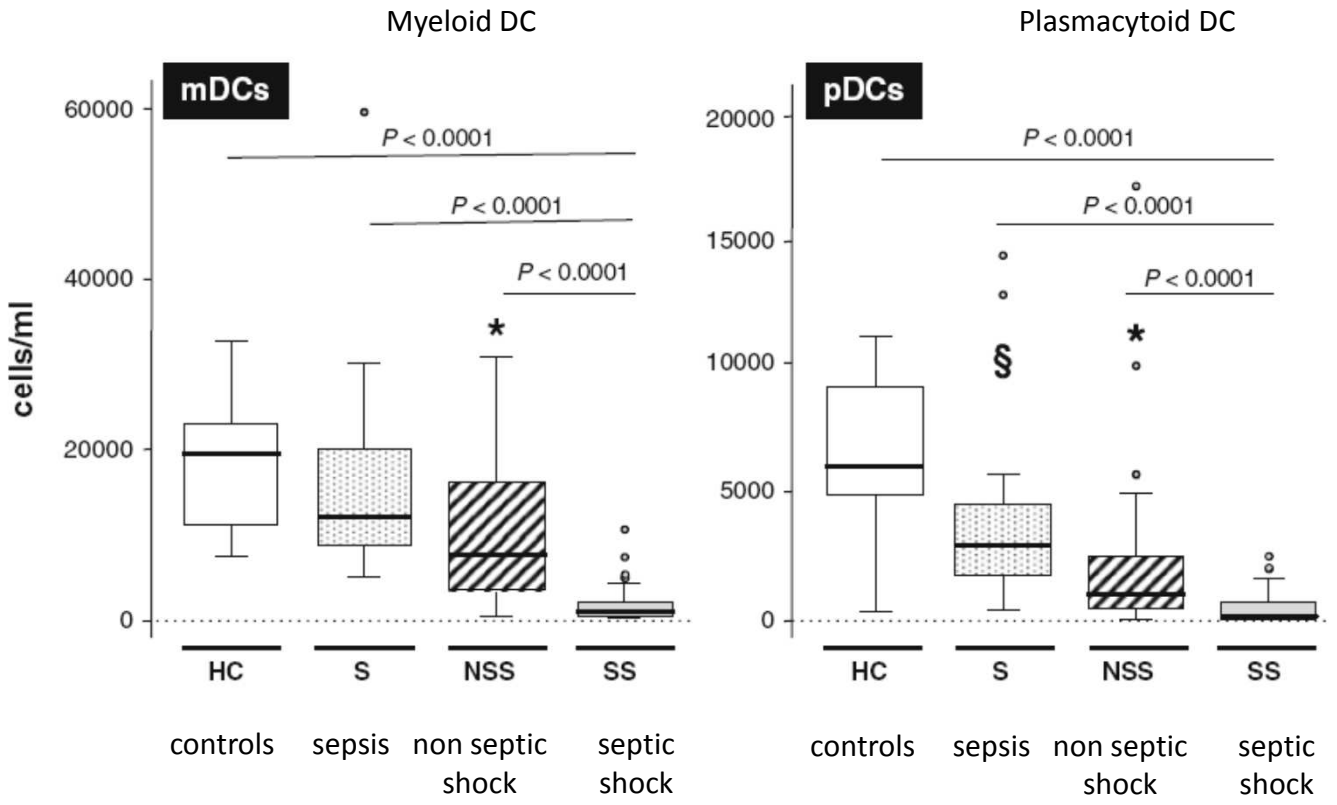
NOVEL APPROACH IN MONOCYTE INTRACELLULAR TNF MEASUREMENT: APPLICATION TO SEPSIS-INDUCED IMMUNE ALTERATIONS





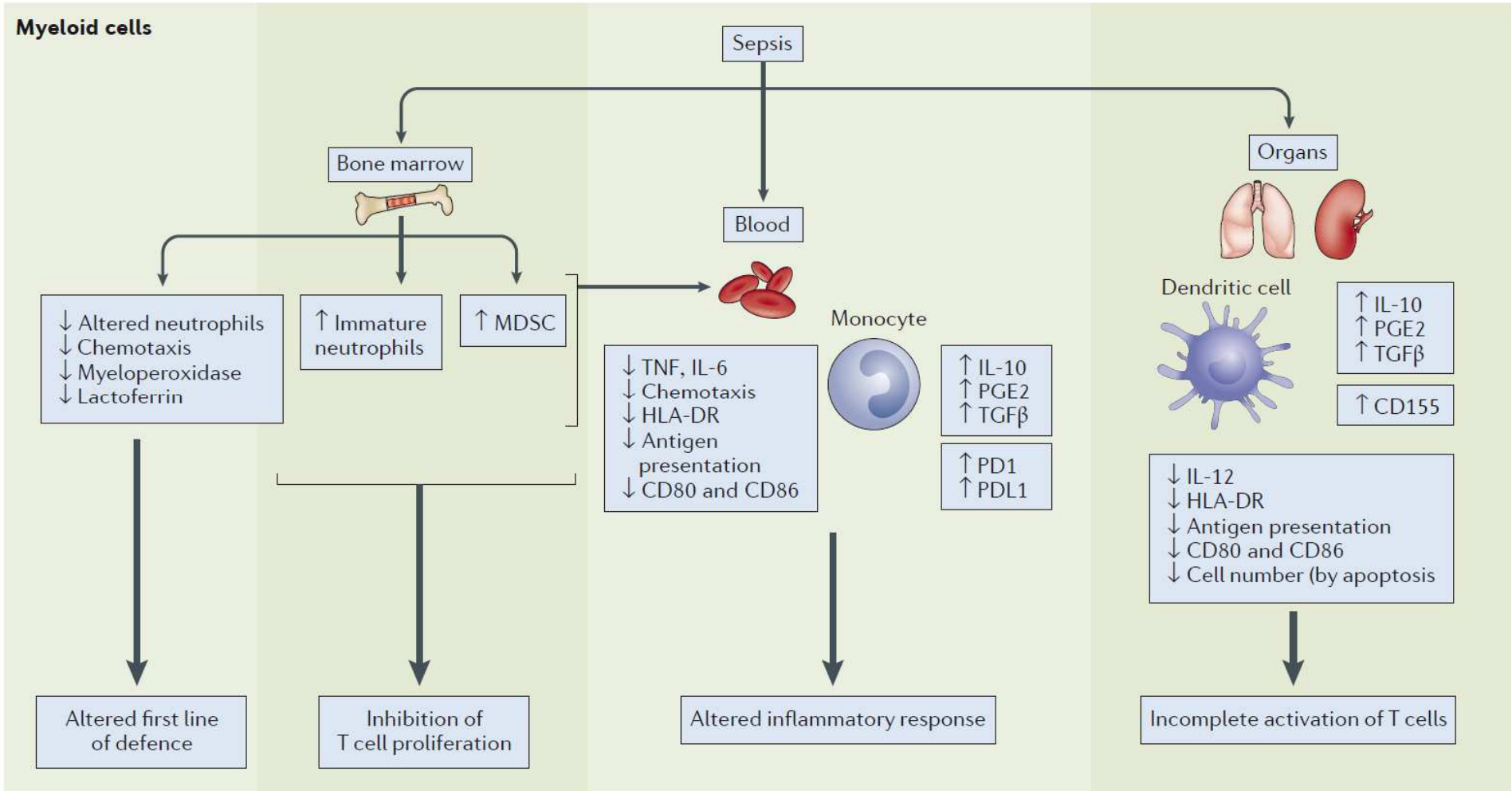
SHOCK, Vol. 47, No. 3, pp. 318–322, 2017

Profound and persistent decrease of circulating dendritic cells is associated with ICU-acquired infection in patients with septic shock



Grimaldi et al., 2009

Myeloid cells (summary)

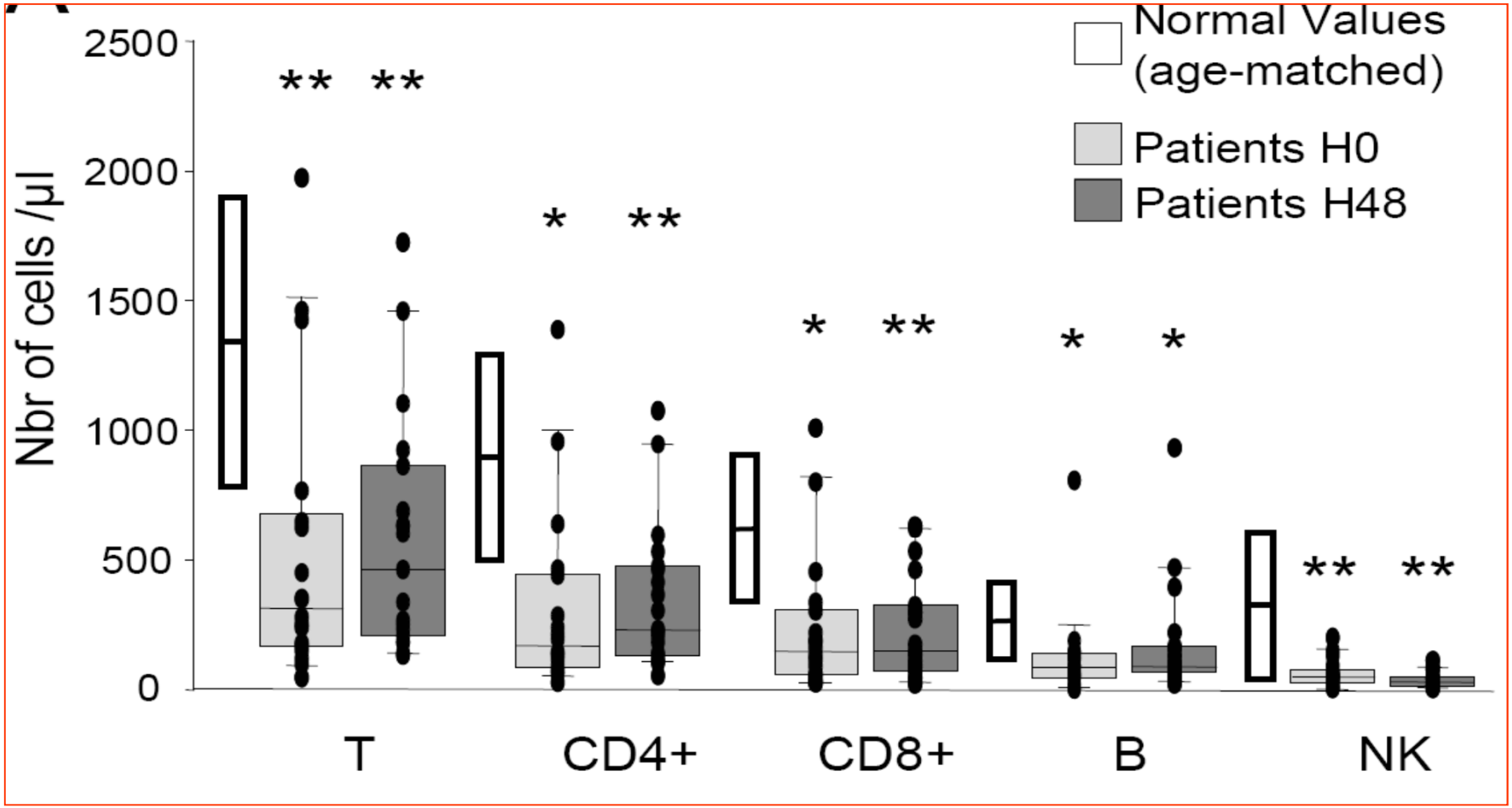


nature REVIEWS

Venet & Monneret, 2018

EARLY ASSESSMENT OF LEUKOCYTE ALTERATIONS AT DIAGNOSIS OF SEPTIC SHOCK

Fabienne Venet,* Fanny Davin,† Caroline Guignant,‡ Audrey Larue,† Marie-Angélique Cazalis,† Romain Darbon,† Caroline Allombert,† Bruno Mougin,† Christophe Malcus,‡ Françoise Poitevin-Later,‡ Alain Lepape,*§ and Guillaume Monneret*‡

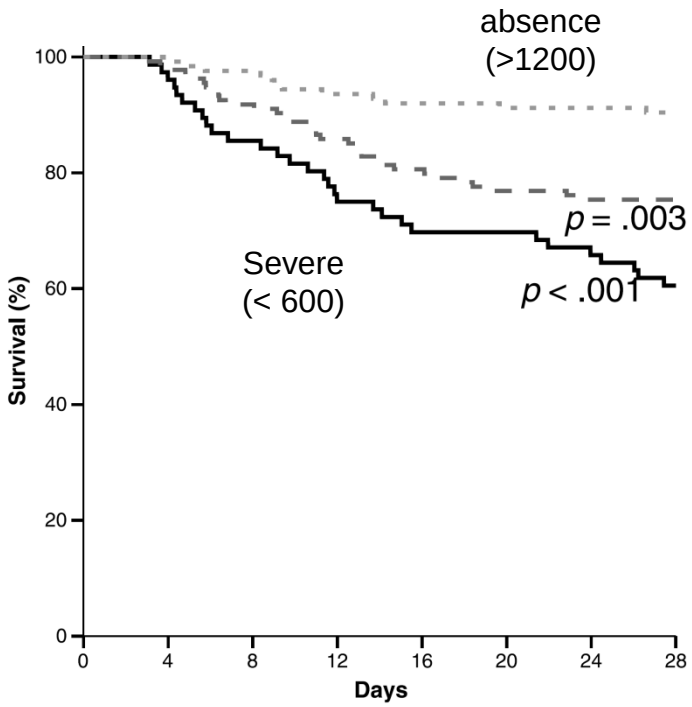


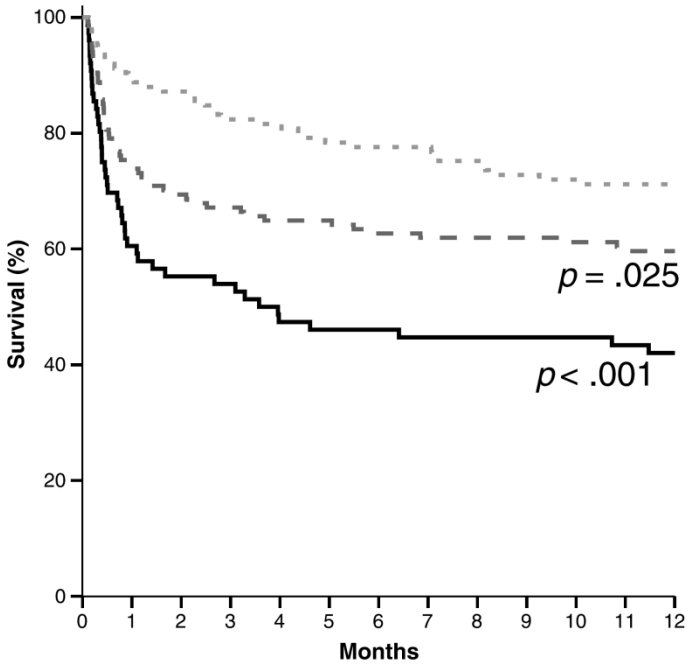
SHOCK, Vol. 34, No. 4, pp. 358–364, 2010

PERSISTENT LYMPHOPENIA AFTER DIAGNOSIS OF SEPSIS PREDICTS MORTALITY

Anne M. Drewry,* Navdeep Samra,† Lee P. Skrupky,‡ Brian M. Fuller,*§ Stephanie M. Compton,* and Richard S. Hotchkiss*†

=> Day 4 total lymphocyte count

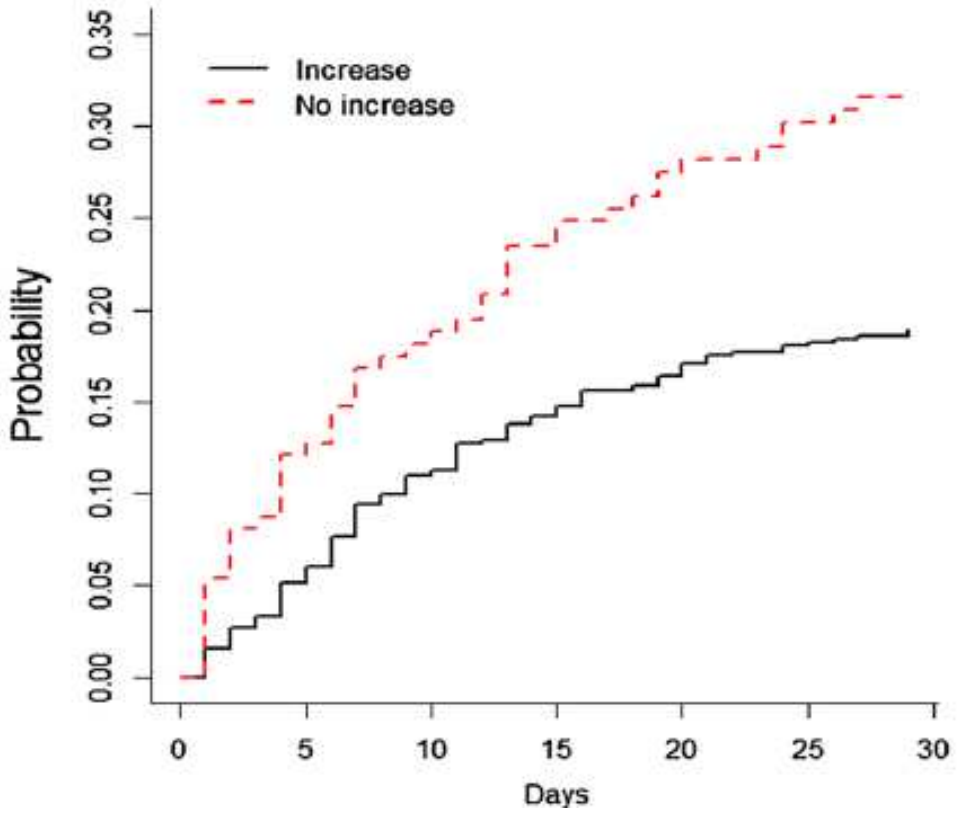




SHOCK, Vol. 42, No. 5, pp. 383–391, 2014

Persistent lymphopenia is a risk factor for ICU-acquired infections and for death in ICU patients with sustained hypotension at admission

Ly increase between baseline and day 3

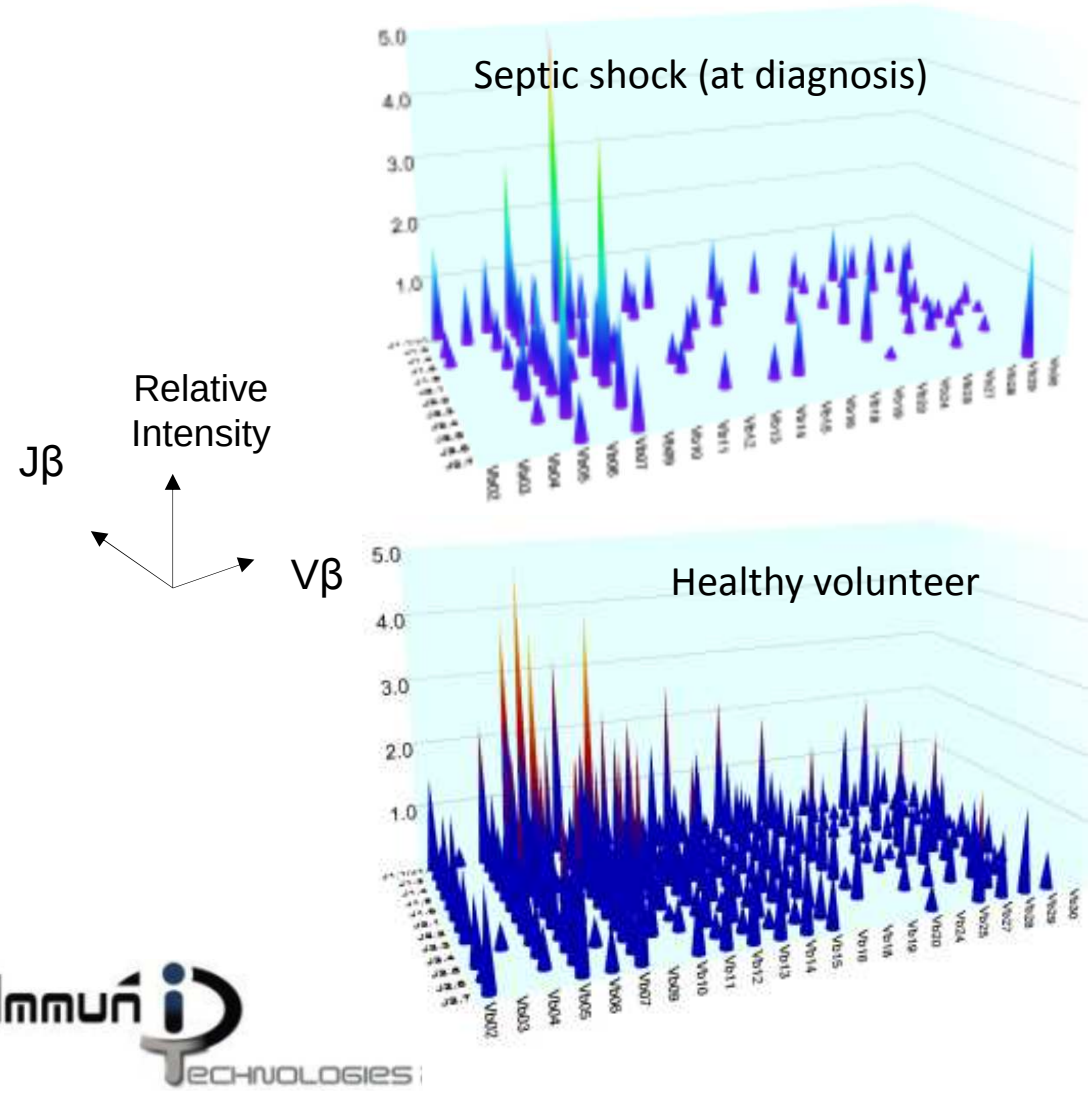


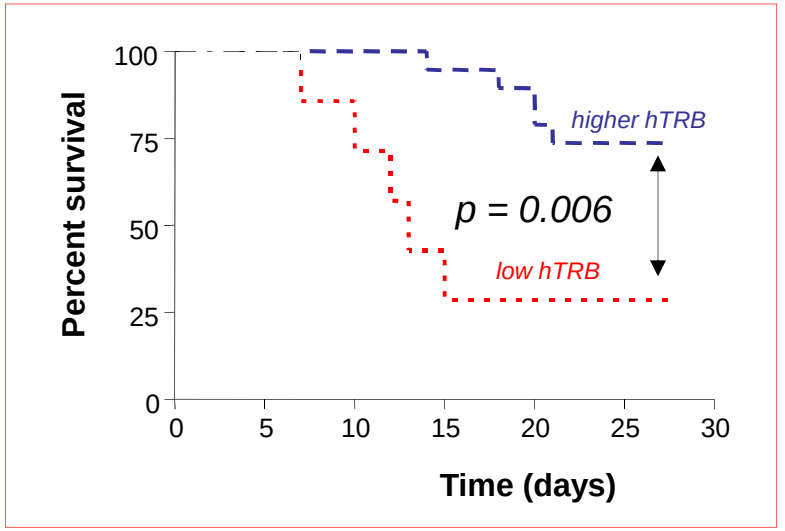
Annals of Intensive Care

Adrie *et al. Ann. Intensive Care (2017) 7:30*

Marked decreased TCR diversity independently of lymphopenia

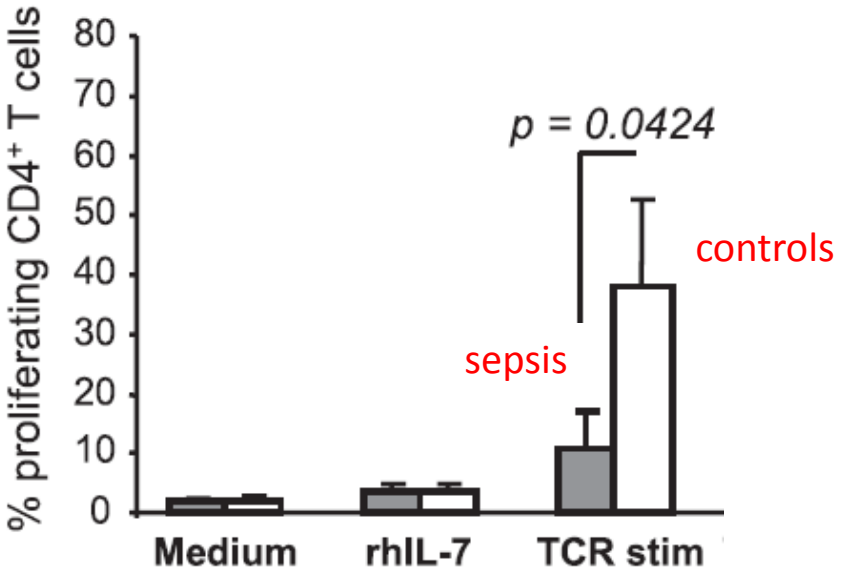
(hTRB VJ combinatorial diversity assessed by qRT-PCR)



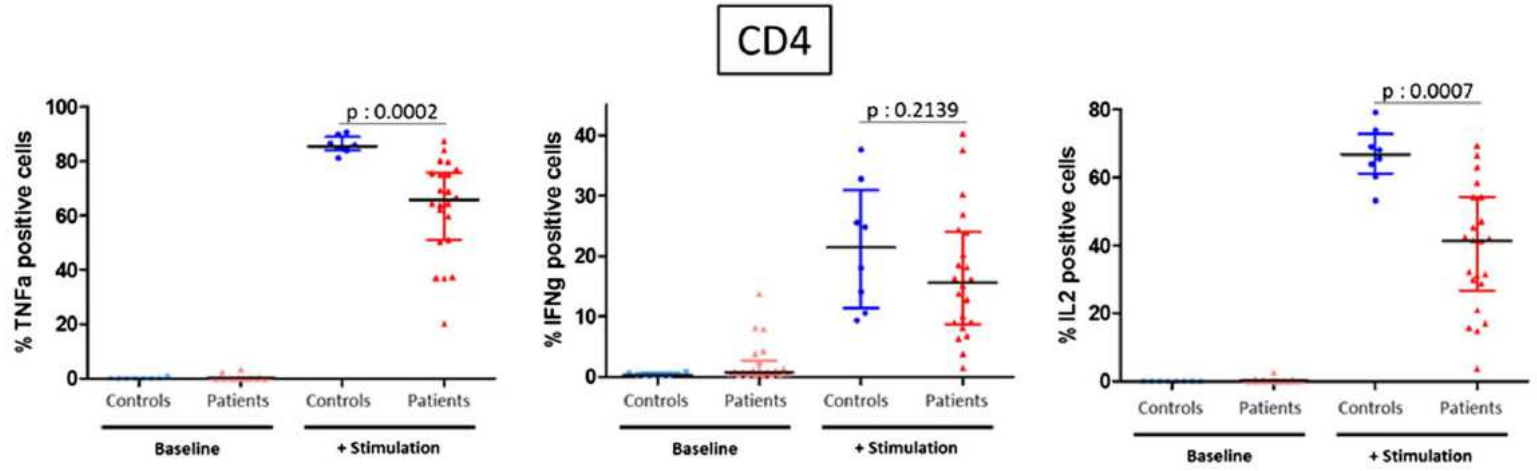


Venet et al., Crit Care Medicine (2013)

Loss of lymphocyte fonctions: proliferation / cytokine release

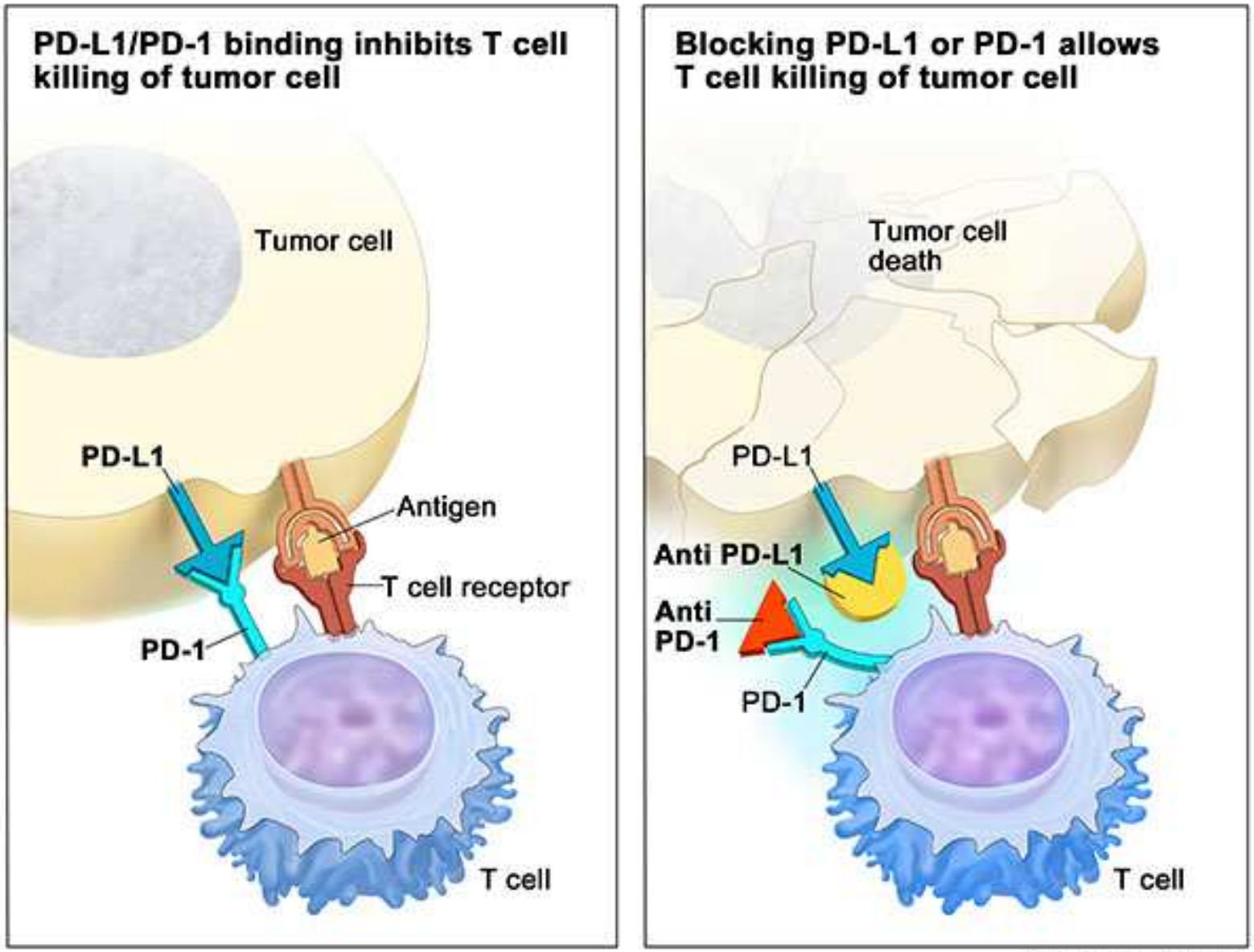


Venet et al., J Immunol 2012



Letessier et al., Cytokine 2017

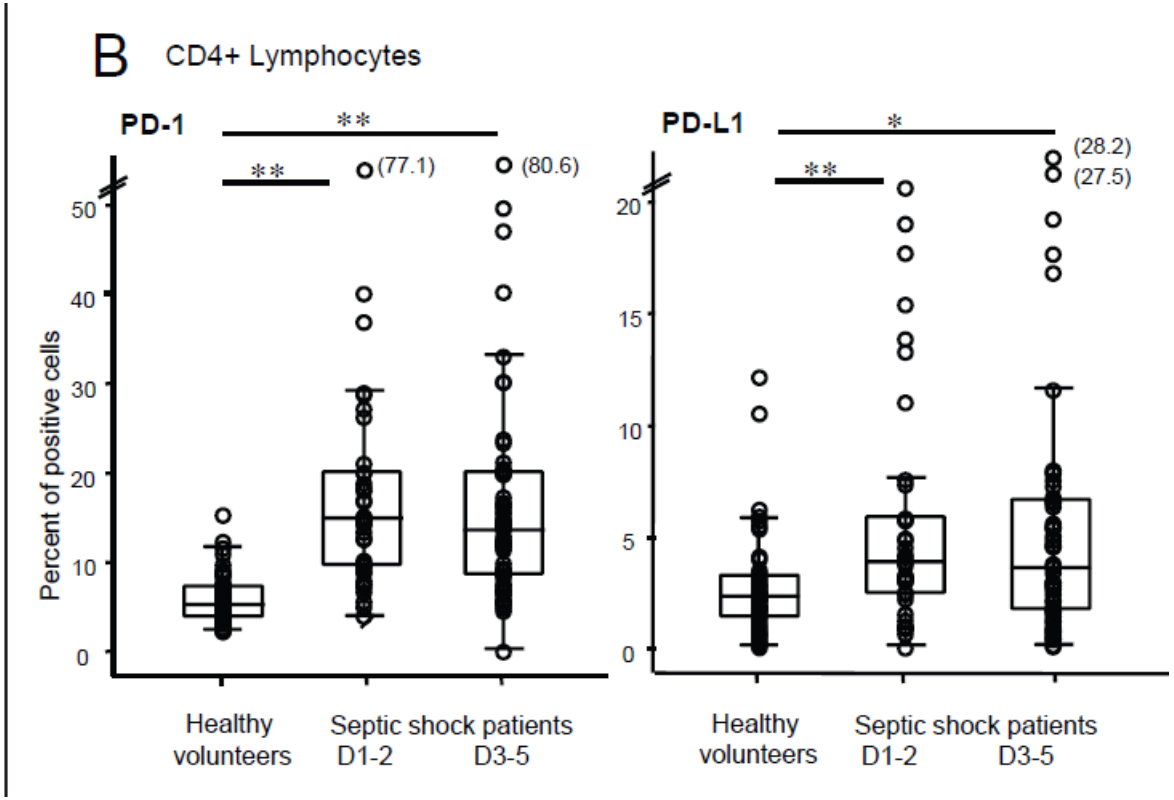
Incrased inhibitory checkpoints



Programmed death-1 levels correlate with increased mortality, nosocomial infection and immune dysfunctions in septic shock patients

Caroline Guignant[1], Alain Lepape[2], Xin Huang[3], Hakim Kherouf[1], Laure Denis[4], Françoise Poitevin[1], Christophe Malcus[1], Aurélie Chéron[5], Bernard Allaouchiche[5], François Gueyffier[6], Alfred Ayala[3], Guillaume Monneret[1*†] and Fabienne Venet[1†]

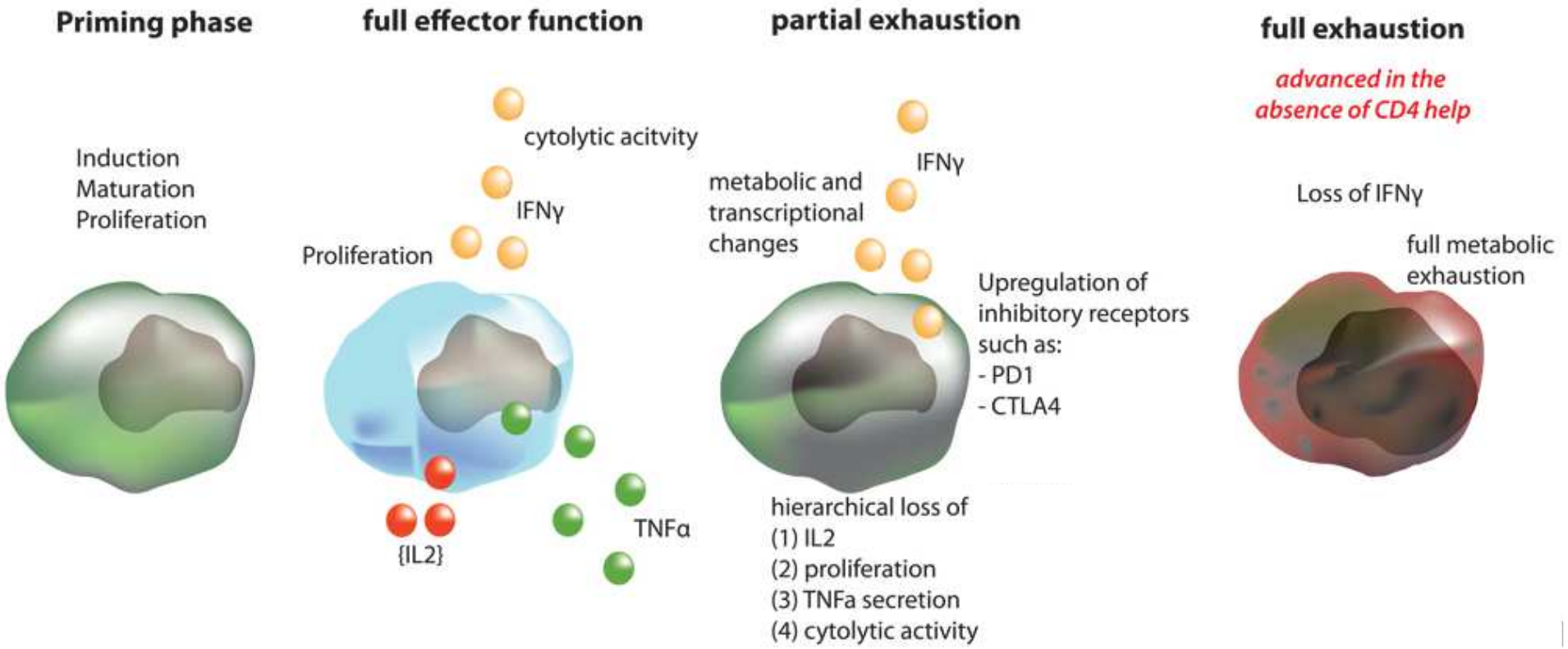
CRITICAL CARE
2011



Associated with:

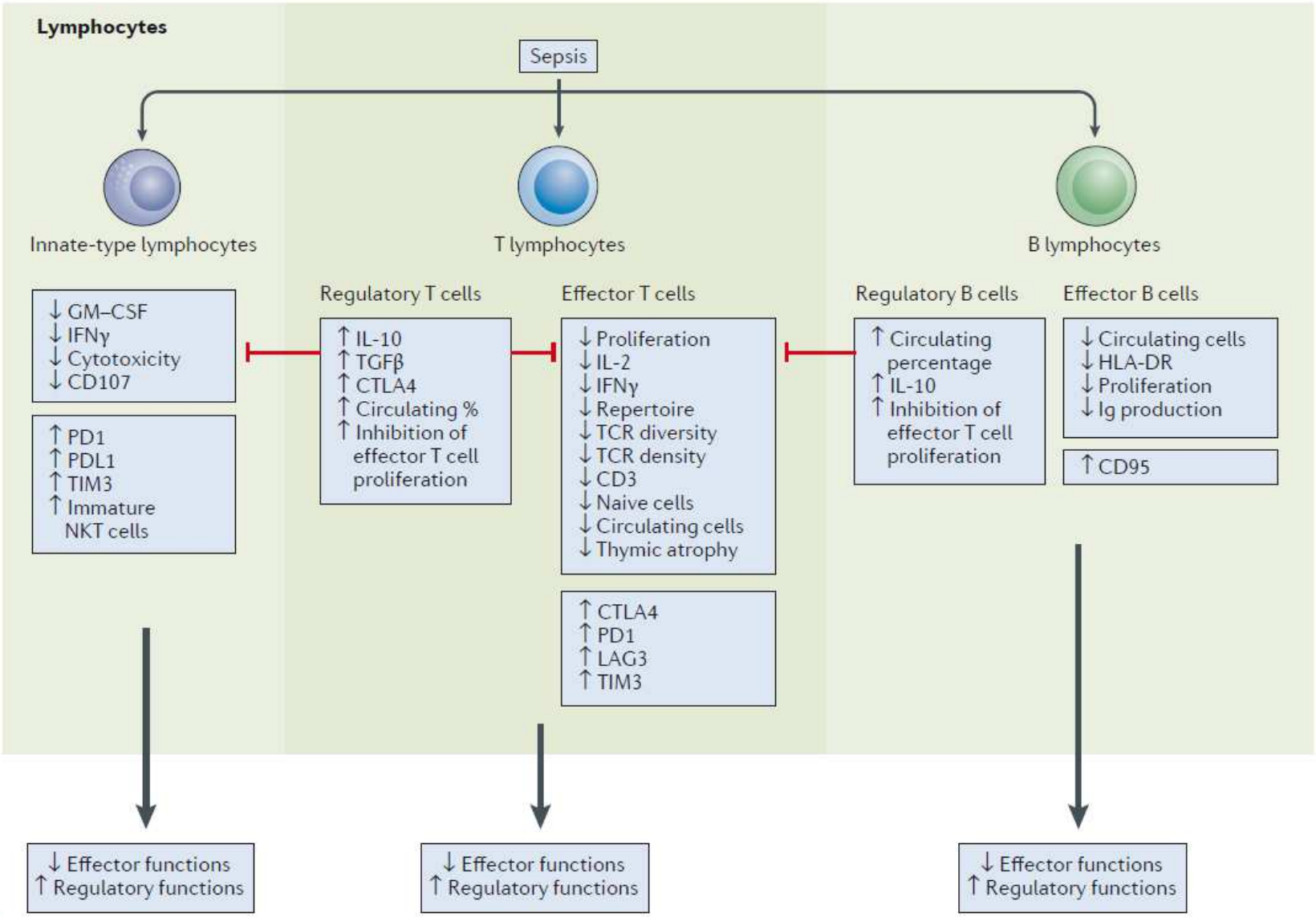
- 28-day mortality
- Nosocomial infection
- Decreased proliferation

The « exhausted » lymphocyte phenotype in sepsis



Streeck, J Infect Dis. 2010

Lymphoid cells (summary)



nature REVIEWS

Venet & Monneret, 2018

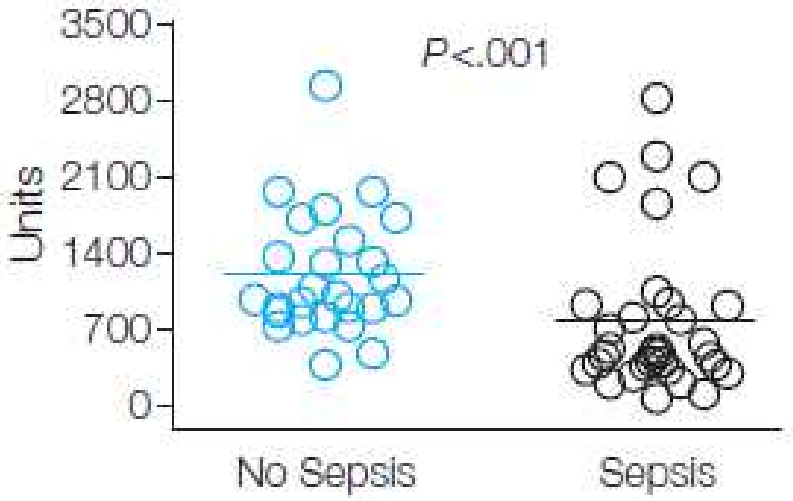
What about (lymphoid) organs ?

Immunosuppression in Patients Who Die of Sepsis and Multiple Organ Failure

CARING FOR THE CRITICALLY ILL PATIENT

Boomer et al. JAMA, December 21, 2011—Vol 306, No. 23

Blood



Macrophages (lung, spleen)

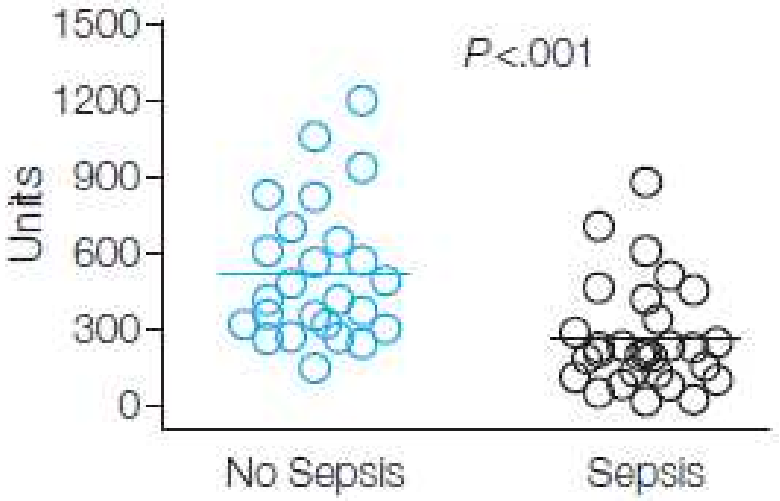
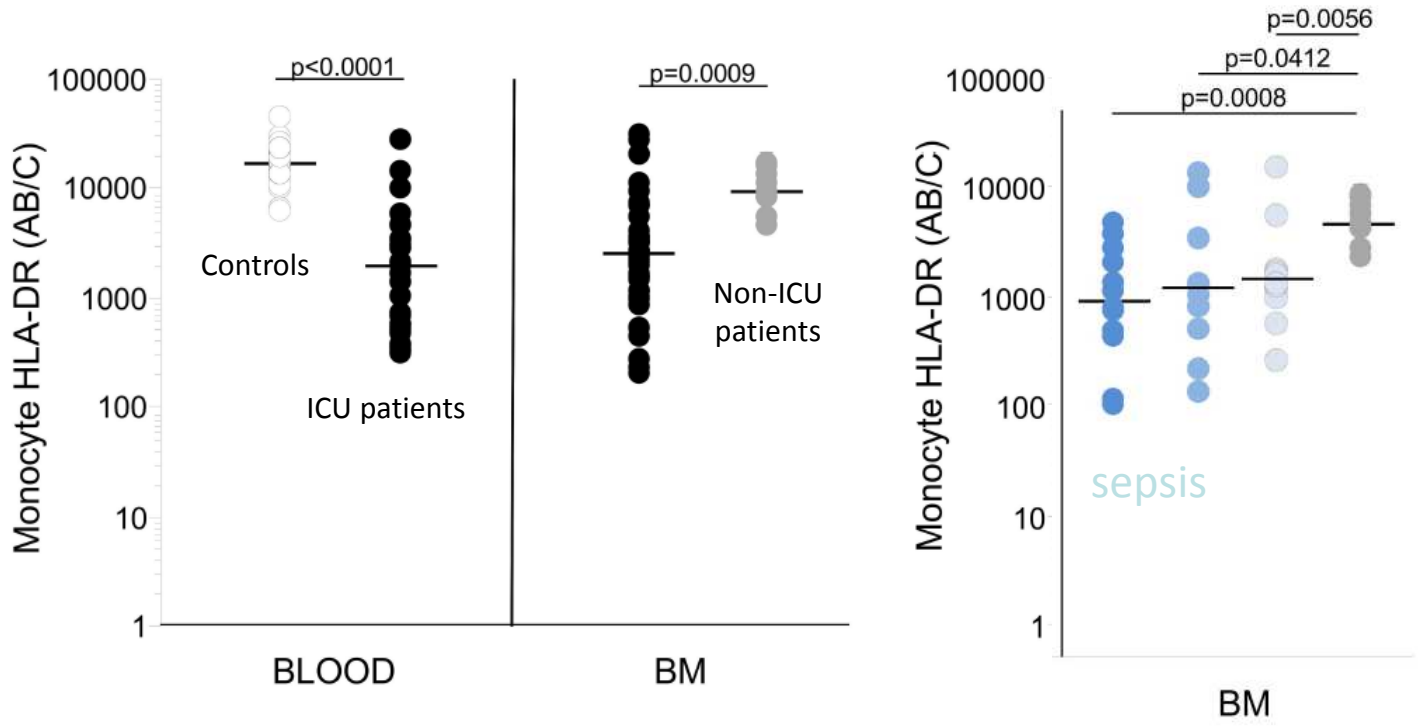


Figure 3. Expression of Cell Surface Receptors on Splenic Antigen-Presenting Cells and Tissue Macrophages

Lymphoid organs are also affected (post-mortem biopsy) : spleen, lungs (+ circulating blood)

Downregulation of Blood Monocyte HLA-DR in ICU Patients Is Also Present in Bone Marrow Cells



PLOS ONE

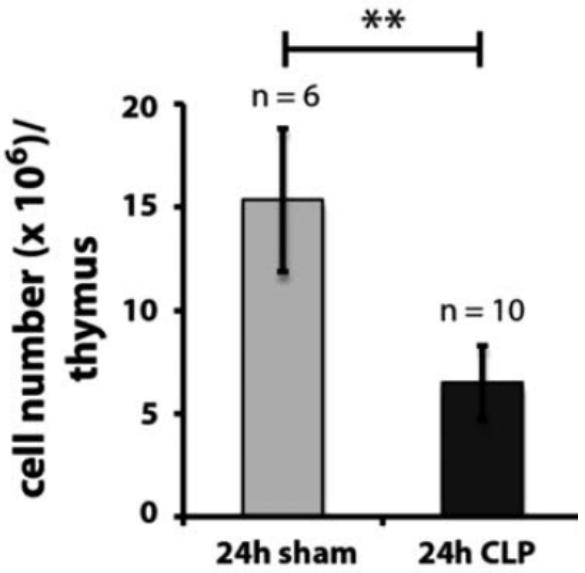
Faivre et al., 2016

Thymus

APOPTOTIC DIMINUTION OF IMMATURE SINGLE AND DOUBLE POSITIVE THYMOCYTE SUBPOPULATIONS CONTRIBUTES TO THYMUS INVOLUTION DURING MURINE POLYMICROBIAL SEPSIS

Christoph Netzer,[*] Tilo Knape,[†] Laura Kuchler,[*] Andreas Weigert,[*] Kai Zacharowski,[‡] Waltraud Pfeilschifter,[§] Gregory Sempowski,[||] Michael J. Parnham,[†] Bernhard Brüne,[*†] and Andreas von Knethen[*†]

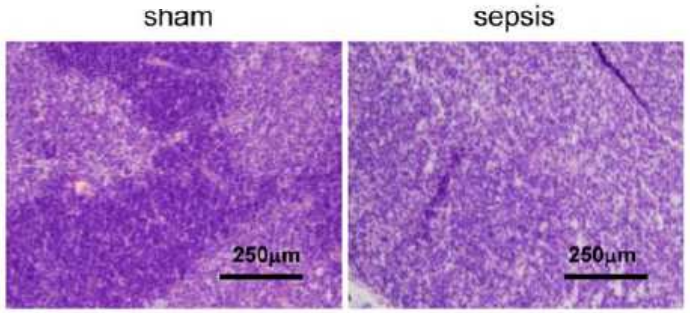
SHOCK, Vol. 48, No. 2, pp. 215–226, 2017

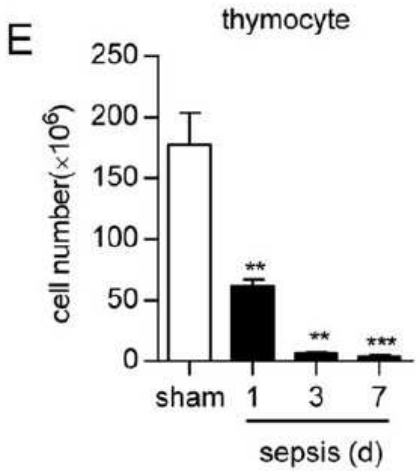


Sepsis-Induced Thymic Atrophy Is Associated with Defects in Early Lymphopoiesis

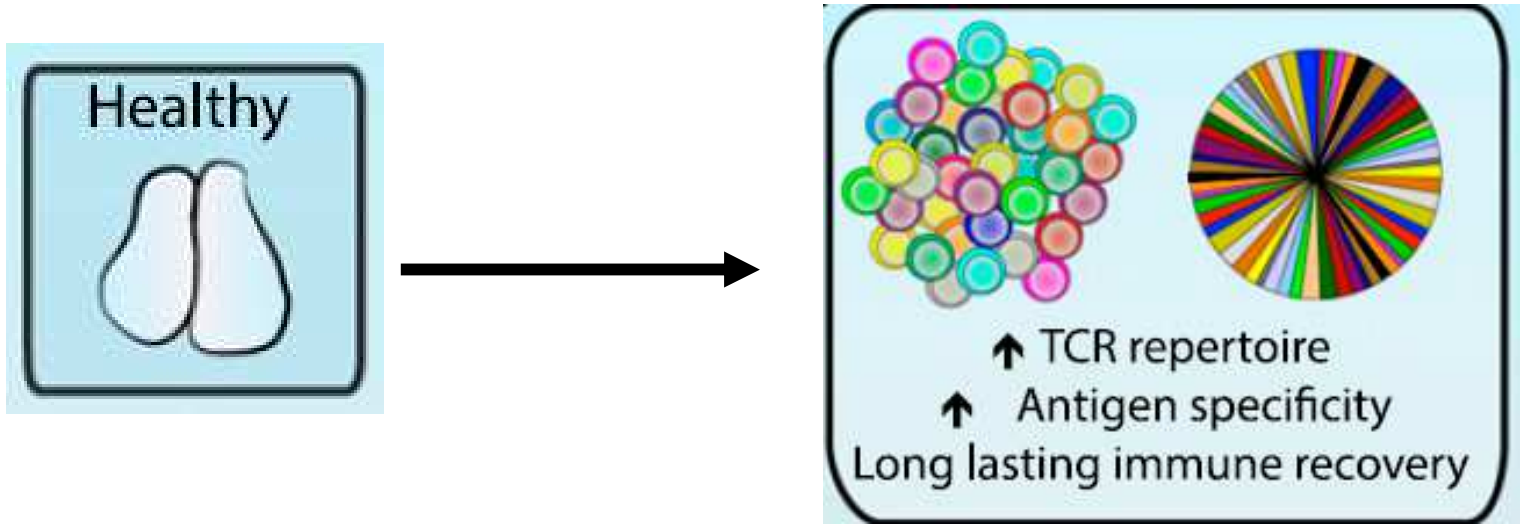
STEM CELLS 2016;34:2902–2915

YAXIAN KONG,[a,b] YAJIE LI,[a,b] WEIMEI ZHANG,[a,b] SHAOXIN YUAN,[a,b] RENÉ WINKLER,[c] ULRIKE KRÖHNERT,[c] JUNYAN HAN,[a,b] TAO LIN,[a,b] YU ZHOU,[d] PENG MIAO,[e] BEIBEI WANG,[a,b] JIANPING ZHANG,[a,b] ZHENGYA YU,[e] YU ZHANG,[d] CHRISTIAN KOSAN,[c] HUI ZENG[a,b]

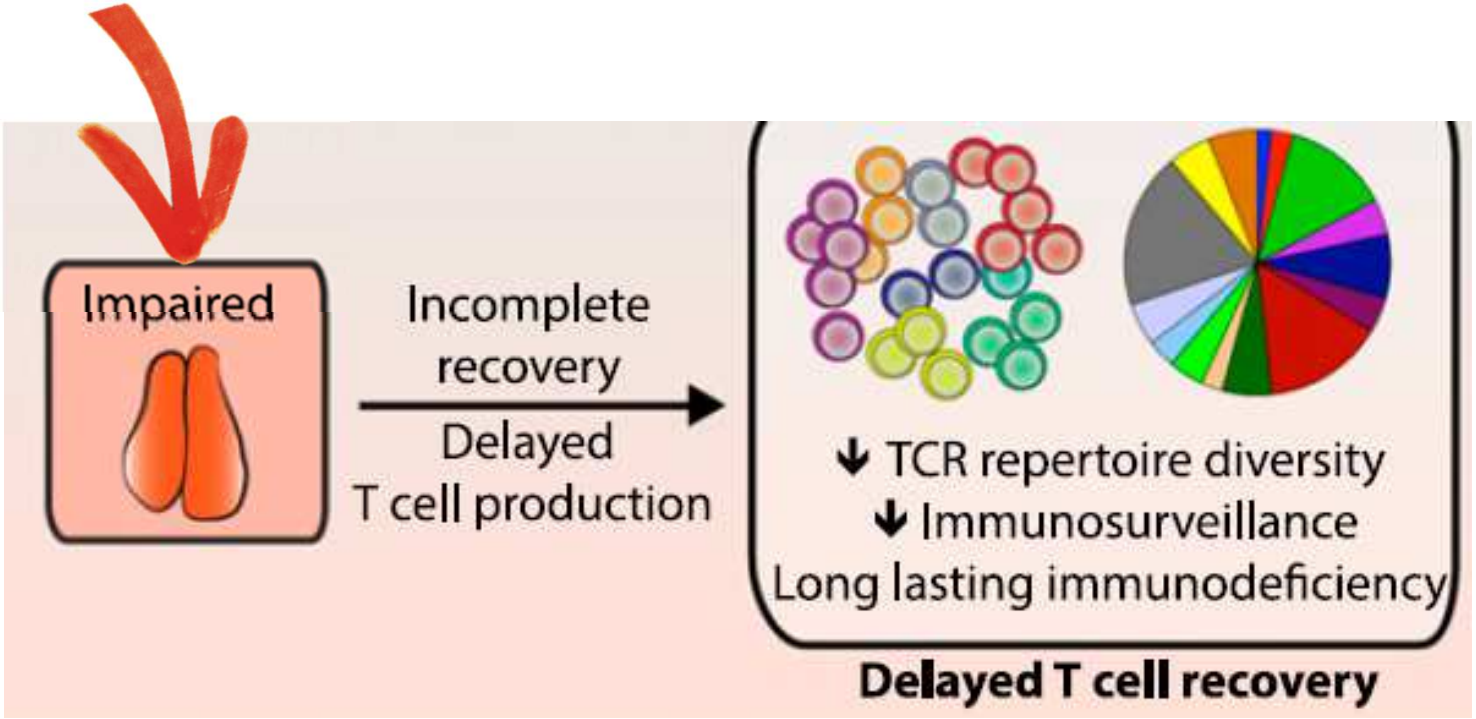




STEM CELLS

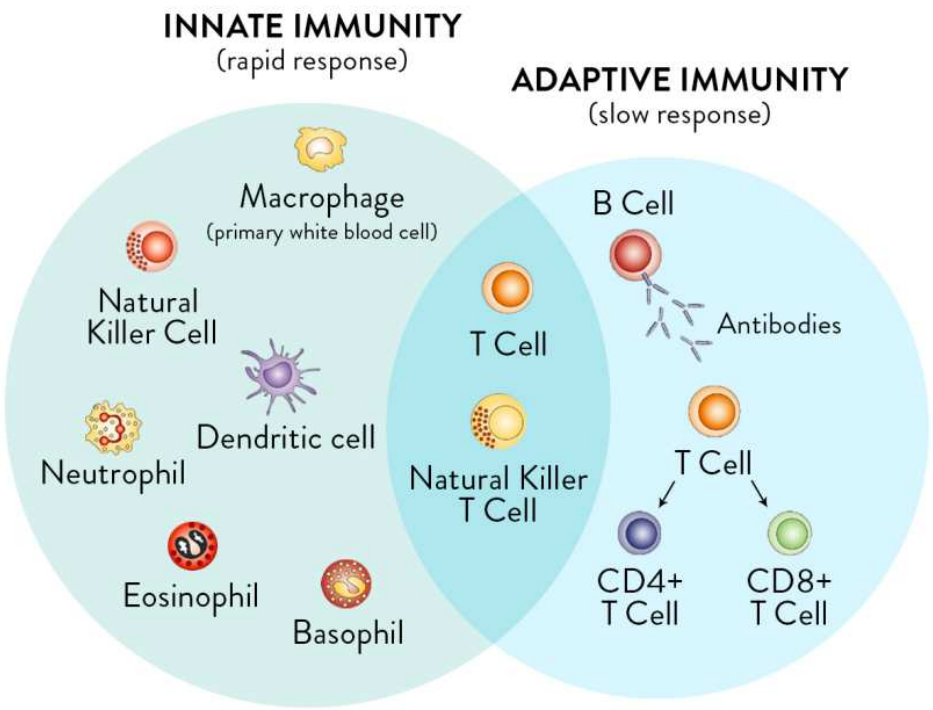


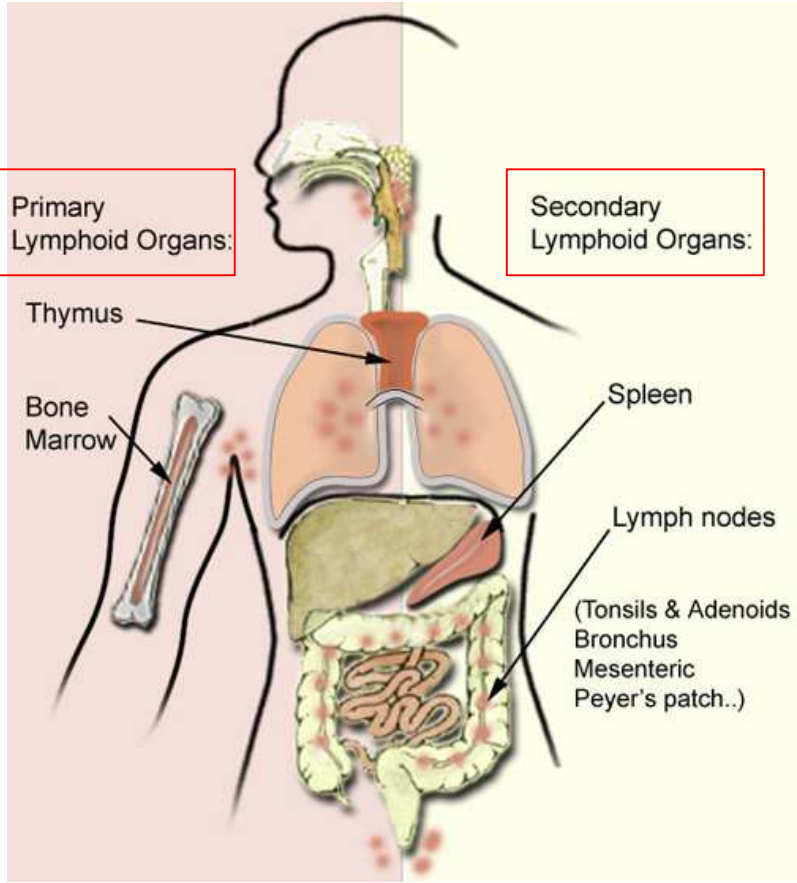
SEPSIS



Adapted from Chaudhry HS, J Immunol 2017

Summary


INNATE IMMUNITY
(rapid response)
ADAPTIVE IMMUNITY
(slow response)
Macrophage
(primary white blood cell)
Natural
Killer Cell
Dendritic cell
Neutrophil
Eosinophil
Basophil
T Cell
Natural Killer
T Cell
B Cell
Antibodies
T Cell
CD4+
T Cell
CD8+
T Cell


Primary
Lymphoid Organs:
Thymus
Bone
Marrow
Secondary
Lymphoid Organs:
Spleen
Lymph nodes
(Tonsils & Adenoids
Bronchus
Mesenteric
Peyer's patch..)

Summary


INNATE IMMUN
(rapid response)
Macrophage
(primary white blood c
Natural
Killer Cell
Dendritic cell
Neutrophil
Eosinophil
Basophil
Sorry...
TEMPORARILY
OUT OF
SERVICE
Secondary
Lymphoid Organs:
Spleen
Lymph nodes
(Tonsils & Adenoids
Bronchus
Mesenteric
Peyer's patch..)

Definition of immunosuppression

Immunosuppression is defined by the association

altered immune function + increased risk for infections

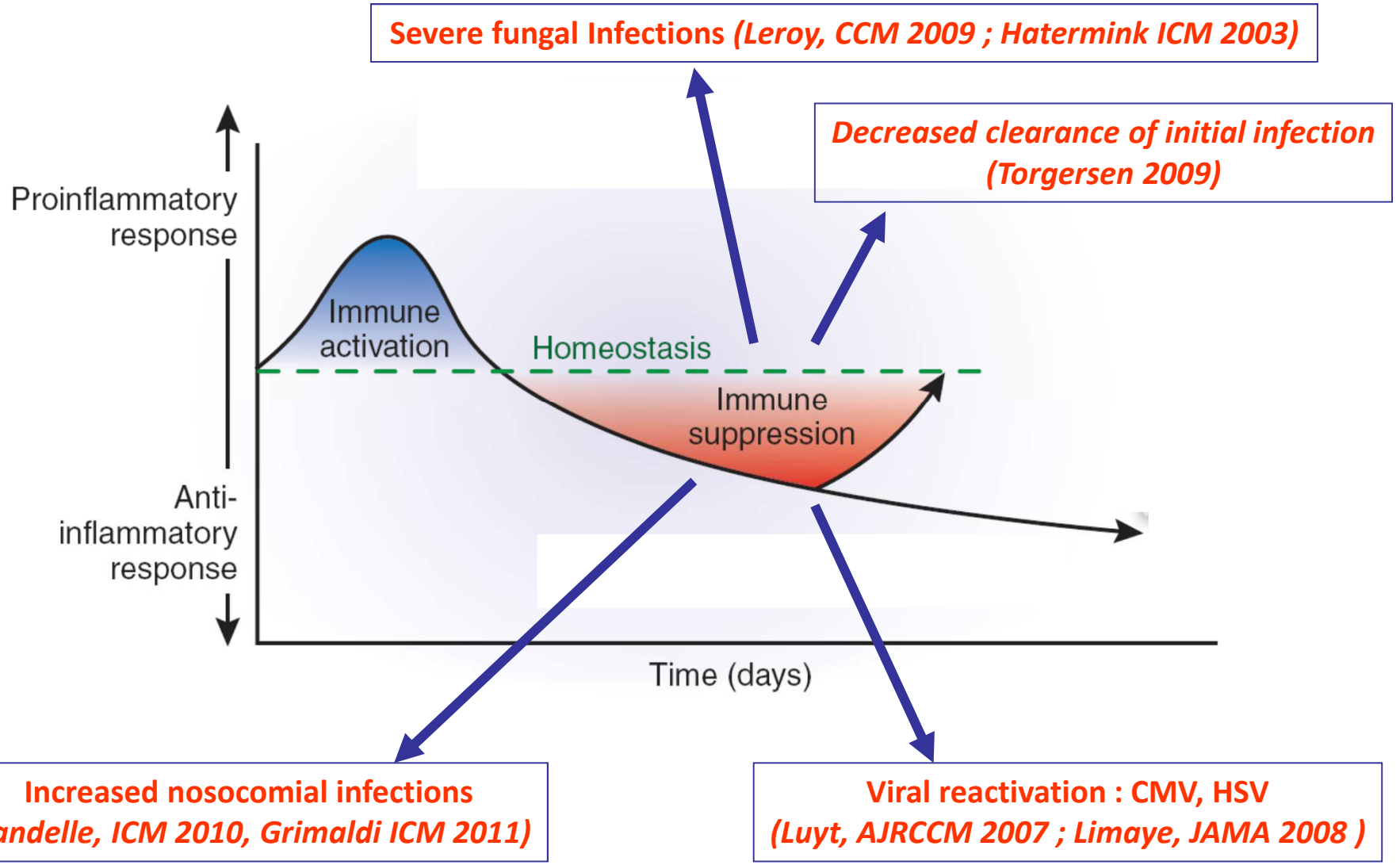
- Quantitative and /or qualitative
- Whatever the fonction
- Whatever the cause

(i.e., immune system's ability to fight infections is compromised or entirely absent)

Does this definition fit with septic patients ?

	Number	Functionality	Association with increased secondary infections
Neutrophils / MDSC	↑	↓	**Yes** (and mortality)
Monocytes	=	↓	**Yes** (and mortality)
DC	↓	↓	**Yes** (and mortality)
lymphocytes	↓	↓	**Yes** (and mortality)

Consequences of sepsis-induced immunosuppression



According to definition

septic patients are immunosuppressed

According to definition

septic patients are immunosuppressed

Immunodépression induite par le sepsis

Assessment of sepsis-induced immunosuppression at ICU discharge and 6 months after ICU discharge

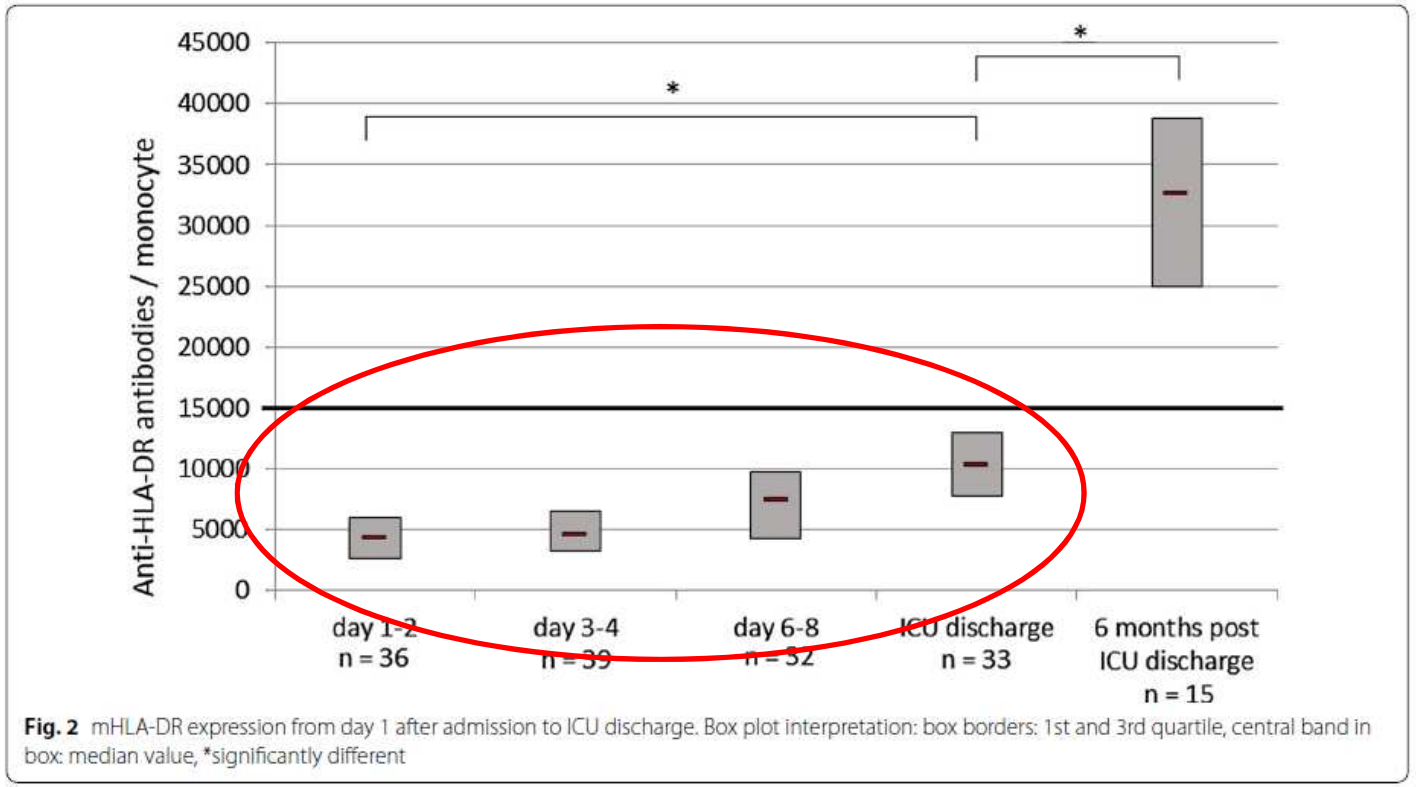


Fig. 2 mHLA-DR expression from day 1 after admission to ICU discharge. Box plot interpretation: box borders: 1st and 3rd quartile, central band in box: median value, *significantly different

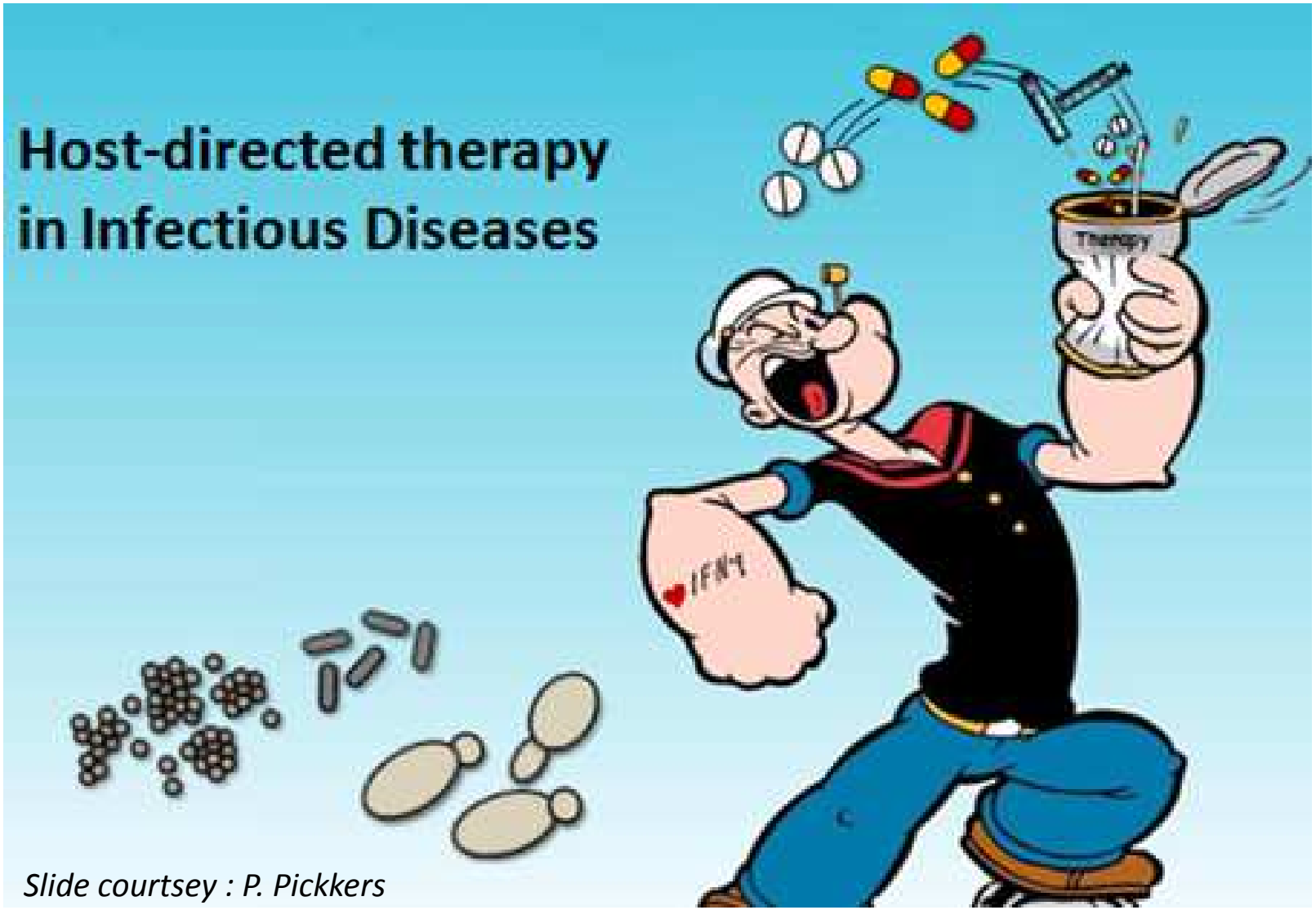
Median discharge = 11 days

Annals of Intensive Care

Zorio *et al. Ann. Intensive Care (2017) 7:80*

Immunostimulation et sepsis = chimère ?

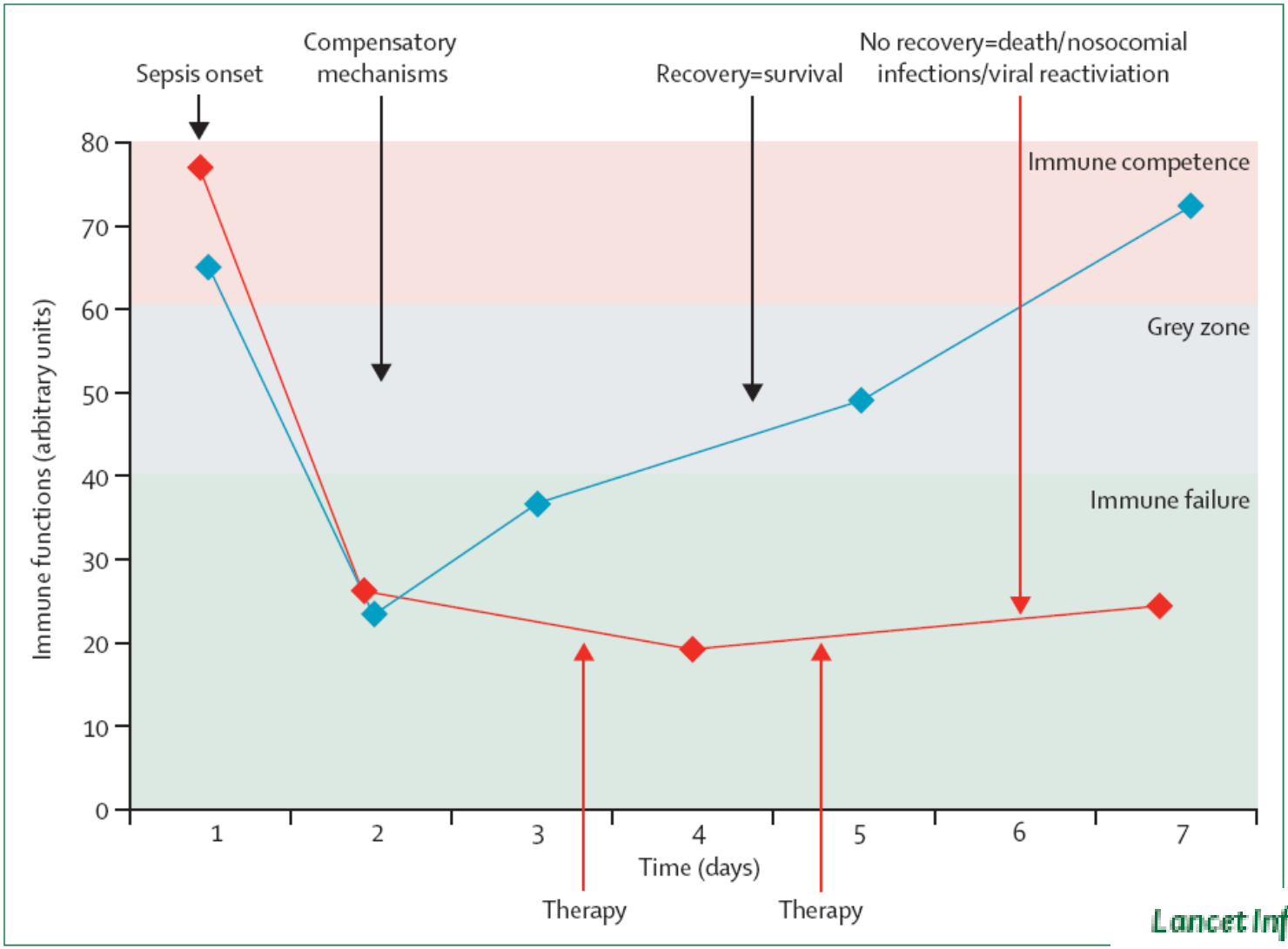
Projet séduisant, mais irréalisable ; idée vaine qui n'est que le produit de l'imagination (http://www.larousse.fr)



Slide courtsey : P. Pickkers

Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach

Richard S Hotchkiss. Guillaume Monneret. Didier Paven



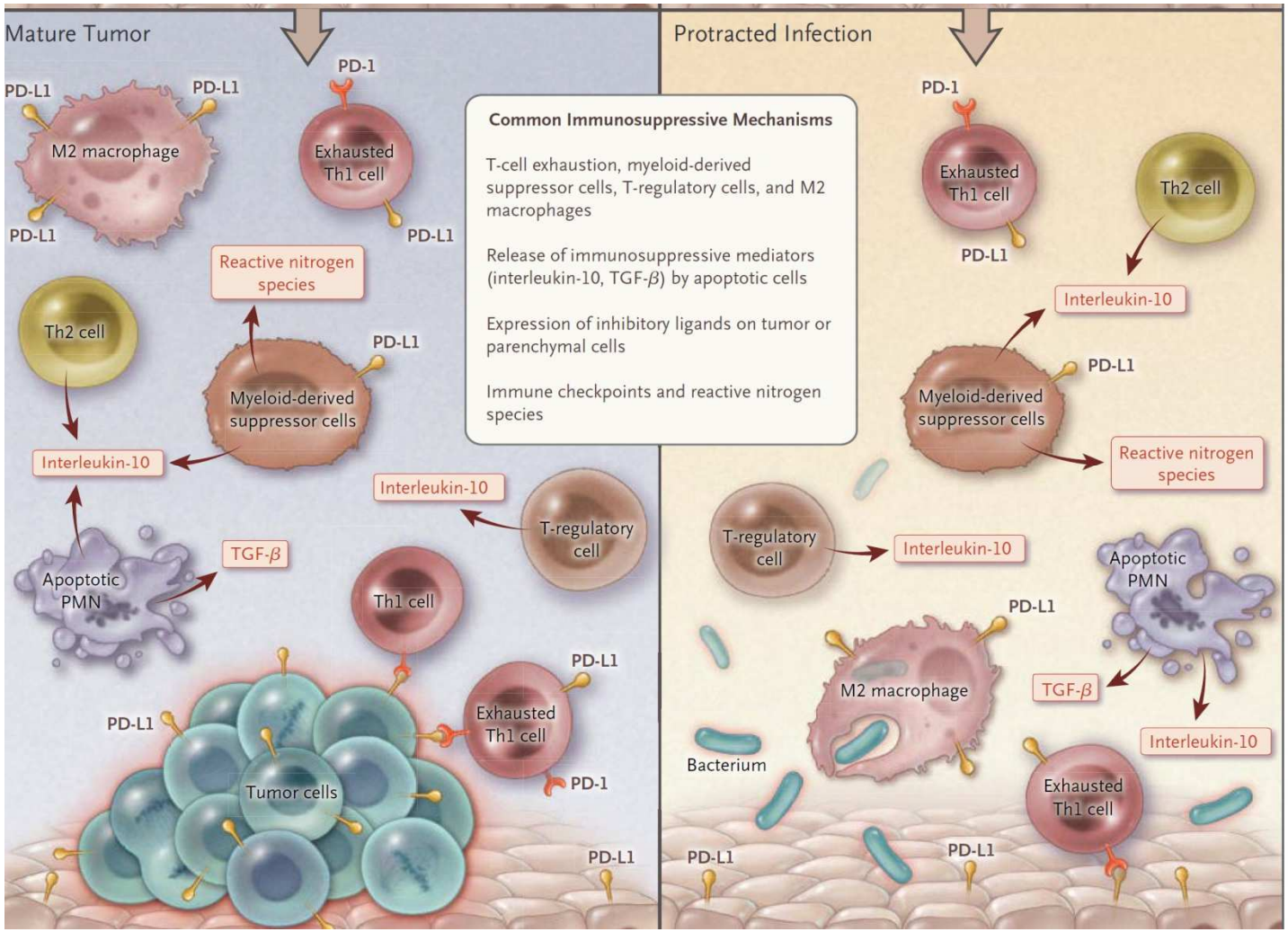
Lancet Infect Dis 2013; 13: 260–68

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor*

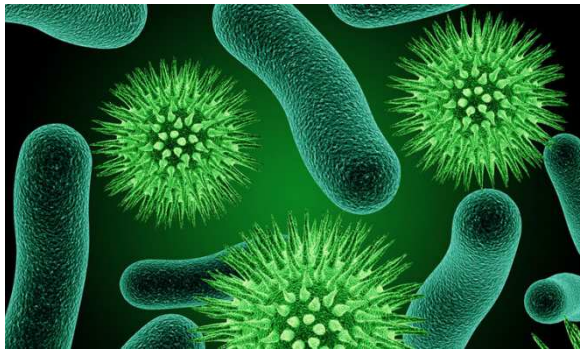
Parallels between Cancer and Infectious Disease

Richard S. Hotchkiss, M.D., and Lyle L. Moldawer, Ph.D.



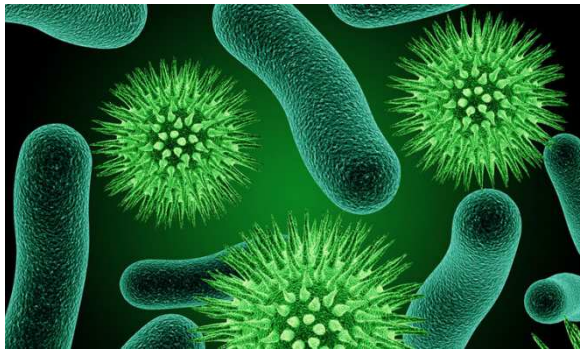
Principles of immunotherapy

Antibiotics

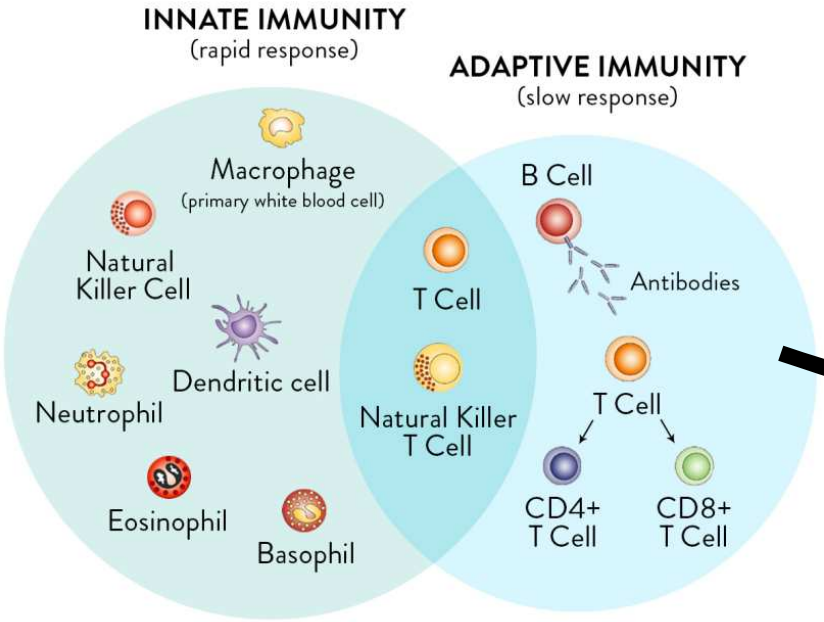


Principles of immunotherapy

Antibiotics ⟶



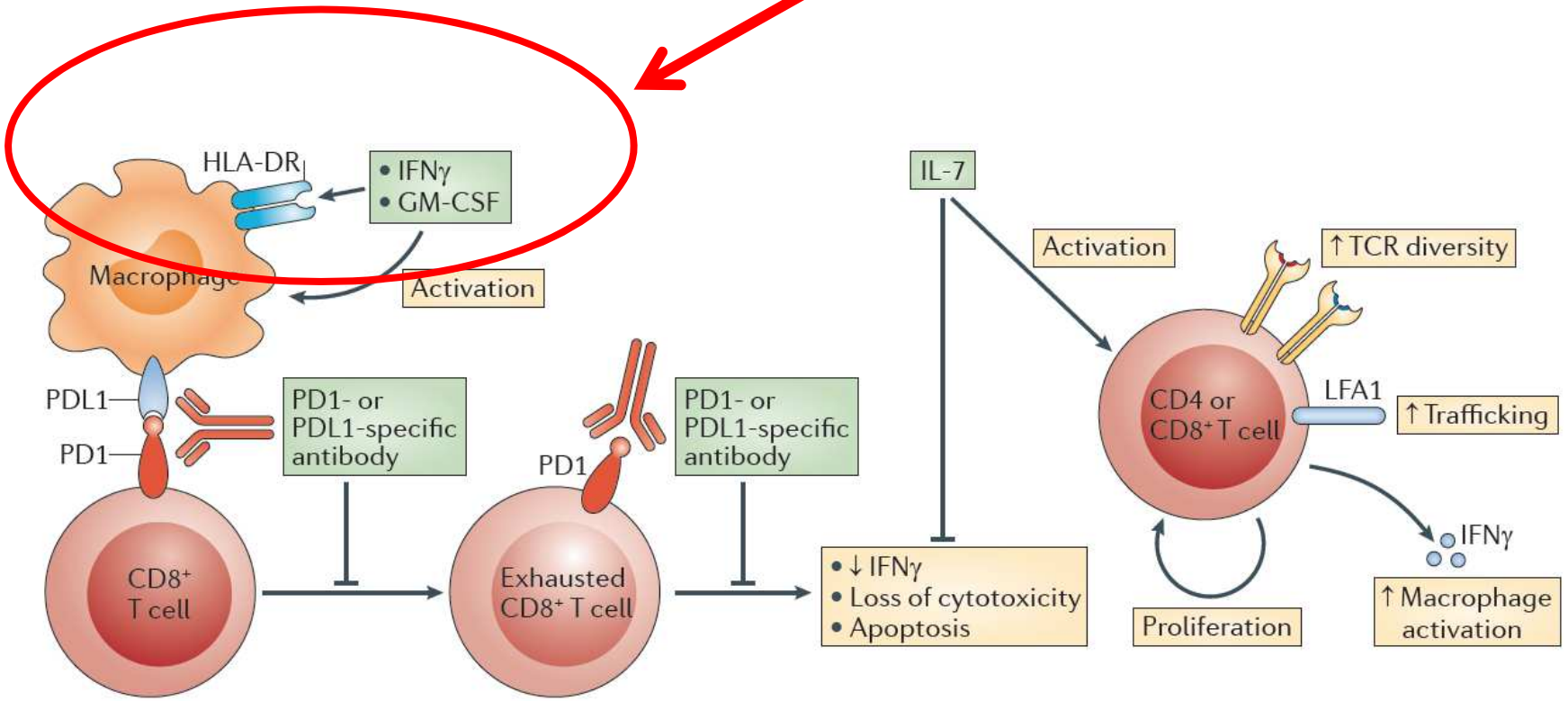
Rejuvenate / stimulate immune cells



Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

Richard S. Hotchkiss[1], Guillaume Monneret[2] and Didier Payen[3]

Restoring innate response

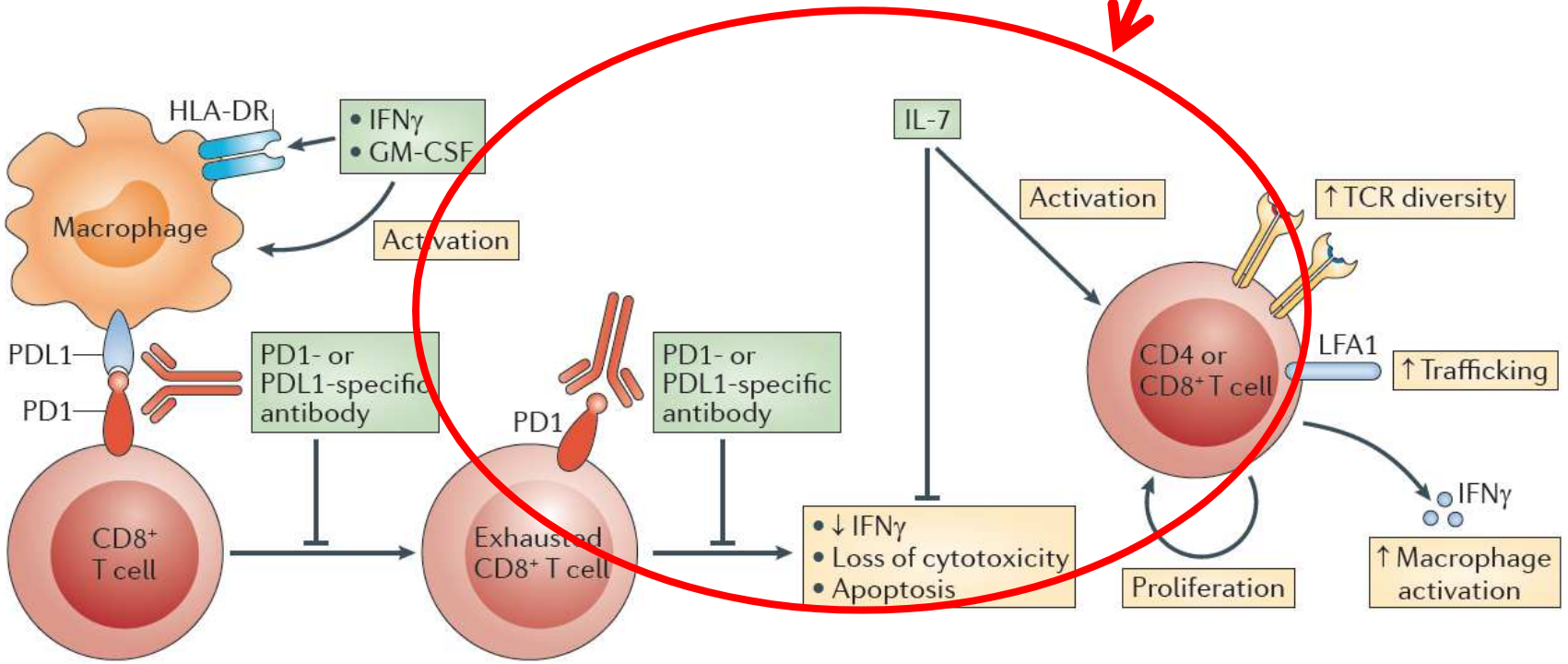


NATURE REVIEWS | IMMUNOLOGY 2013

Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

Richard S. Hotchkiss[1], Guillaume Monneret[2] and Didier Payen[3]

Restoring adaptive response



NATURE REVIEWS | IMMUNOLOGY 2013

Current trials

GRID (NCT02361528) 

GRID study - GM-CSF trial in septic shock (PHRC national, CHLS). Septic shock patients with the lowest mHLA-DR values will receive either a placebo or GM-CSF. Evaluation criteria: decreased rate of HAI in GM-CSF-treated group. 488 patients to be included (NCT02361528).

 IRIS-7 (NCT02640807) 

IRIS 7B study - rhIL-7 in septic shock (phase II trial, Prof. R. Hotchkiss, St-Louis, USA). rhIL-7 in patients with severe lymphopenia after septic shock. Evaluation criteria: safety issues, restoration of immune functions (lymphocyte count, mHLA-DR). 30 patients to be included (NCT02640807). A phase III study is ready to start once first study will be completed (350 patients).

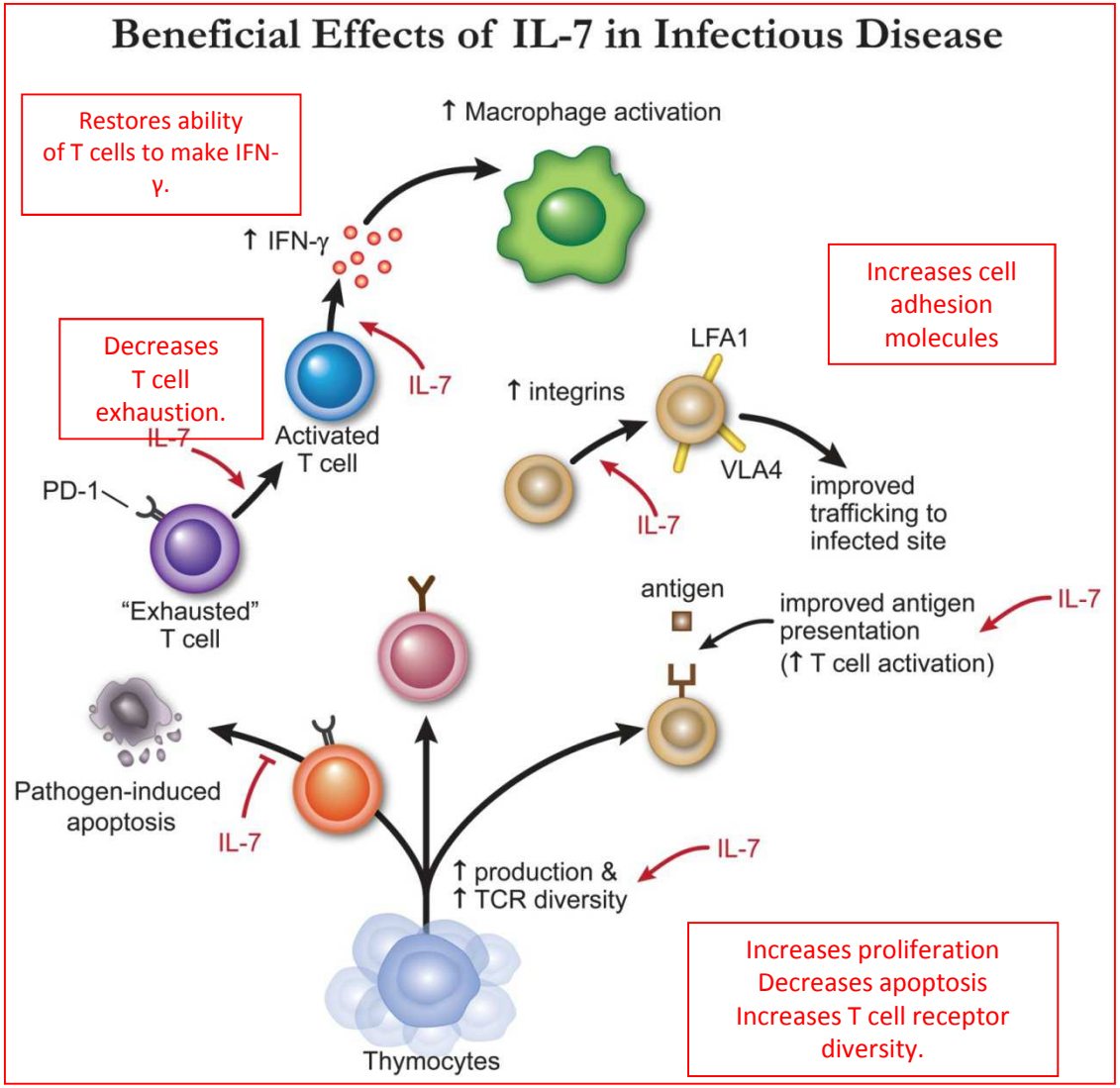
 ANTI PD-1

A Phase 1b/2a, Randomized, Double-Blinded, Placebo-Controlled, Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of BMS-936559 in Subjects With Severe Sepsis (13 centers, 220 patients to be included)

IL-7

IL-7 acts at multiple levels to improve functionality of CD4 and CD8 T cells and secondarily adaptive immunity.

IL-7 offers a new approach to infectious disease.



Trends in Molecular Medicine, April 2014, Vol. 20, No. 4

Chimère ou réel espoir ?

LYON, F
EA 7426
« Pathophysiology of Injury-induced Immunosuppression »