À Lyon depuis 1996 !

AER

ACTUALITÉS EN RÉANIMATION
Médecine Intensive, Surveillance Continue
et Urgences Graves

23 et 24 novembre 2017

Immunomodulation et sepsis : Actualités 2017

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

CRICS-TRIGGERSEP

Flow Division
Immunology
Department

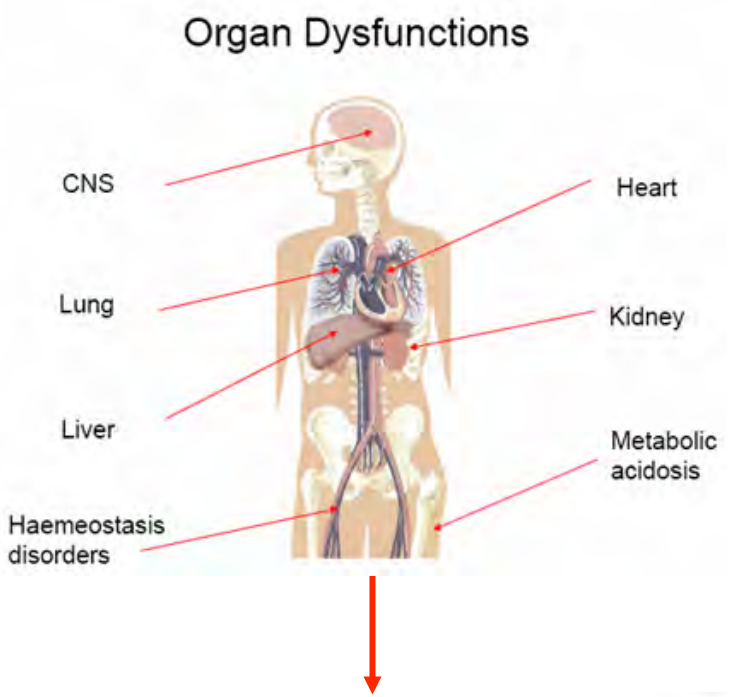
Lyon 1

Hospices Civils de Lyon

BIOMÉRIEUX

Sepsis-3 definition

Uncontrolled Inflammatory response



Decreased arterial pressure
Shock
Multiple organ failure

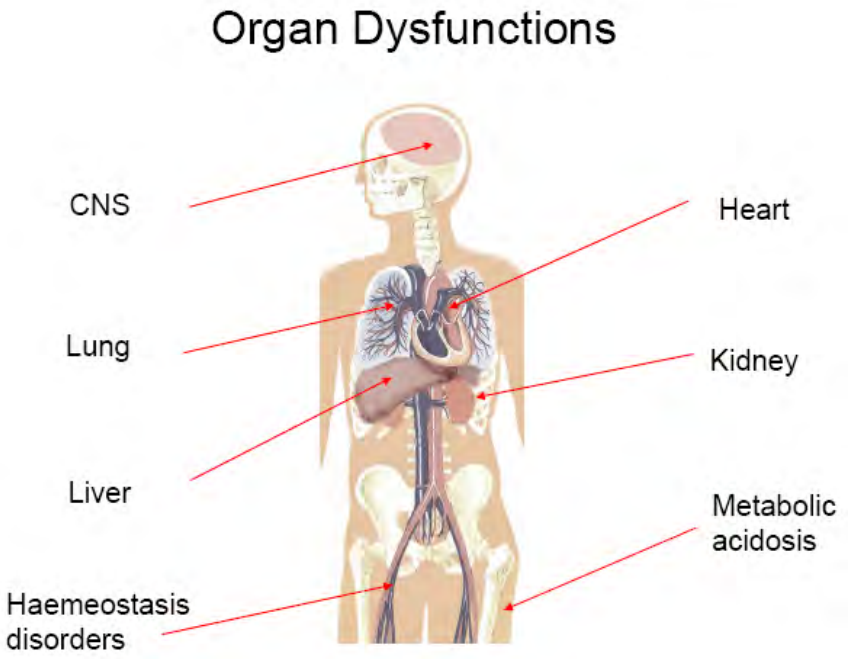
REVISED DEFINITIONS

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

Immunomodulation: first attempts

Uncontrolled inflammatory response



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

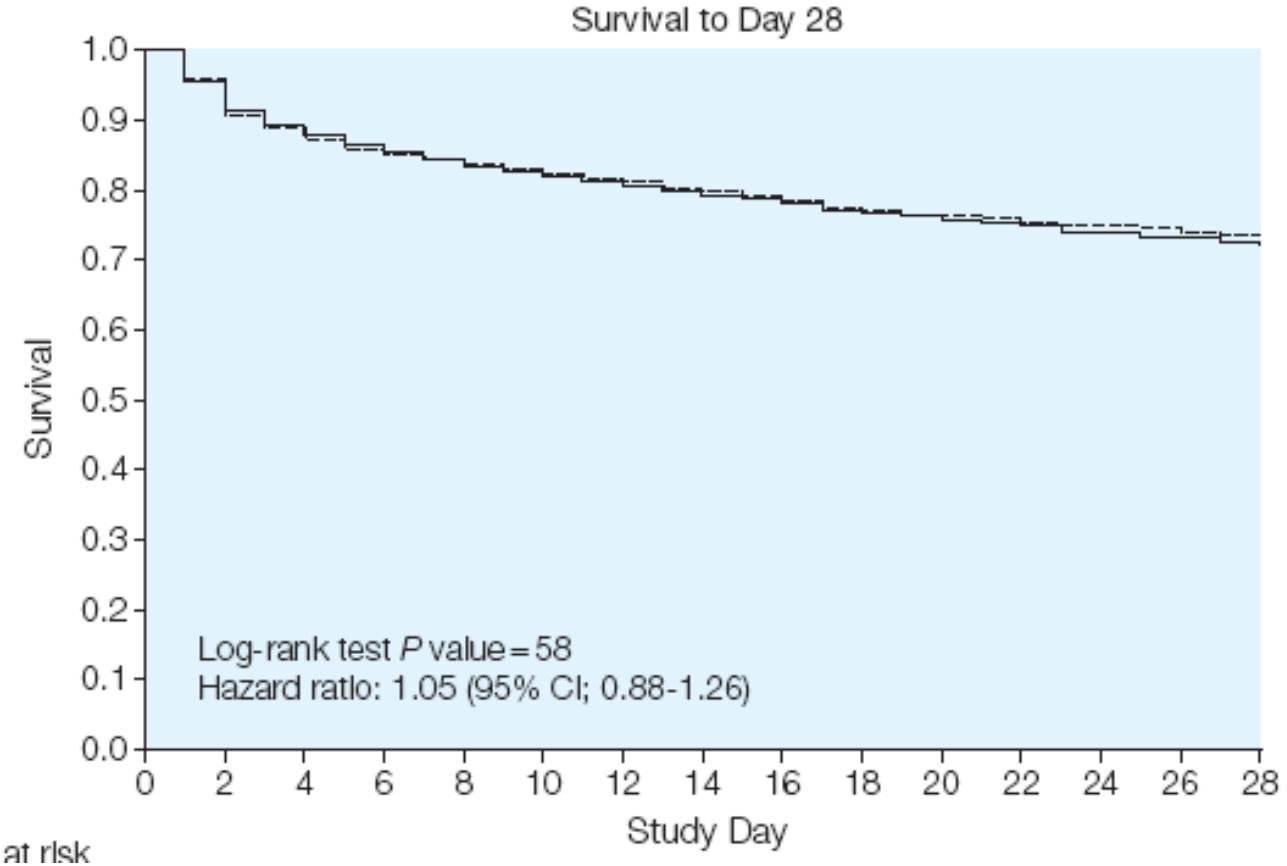
Failure of clinical trials testing anti-inflammatory therapies

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 (high doses) …	9 …	1267 …	35 …	39 …
Total	33	12034	**38**	**38**

Zeni et al, Crit Care Med, 1997

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

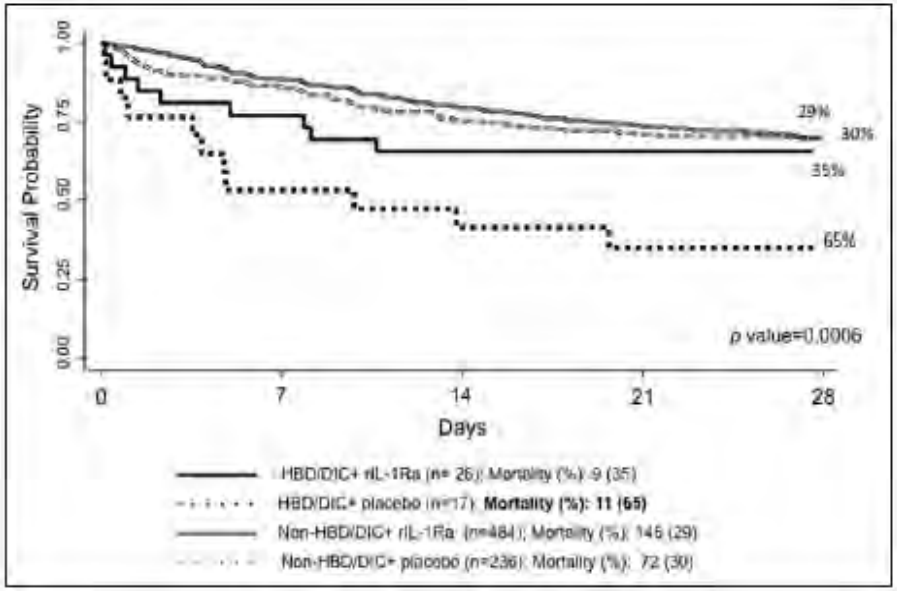
Still a room for blocking inflammation ?

Eichacker, P.Q. et al. Risk and the efficacy of antiinflammatory agents: retrospective and confirmatory studies of sepsis. ***Am J Respir Crit Care Med* 2002.**

Panacek, E.A. et al. Afelimomab in patients with severe sepsis and elevated interleukin-6 levels. ***Crit Care Med 2004***

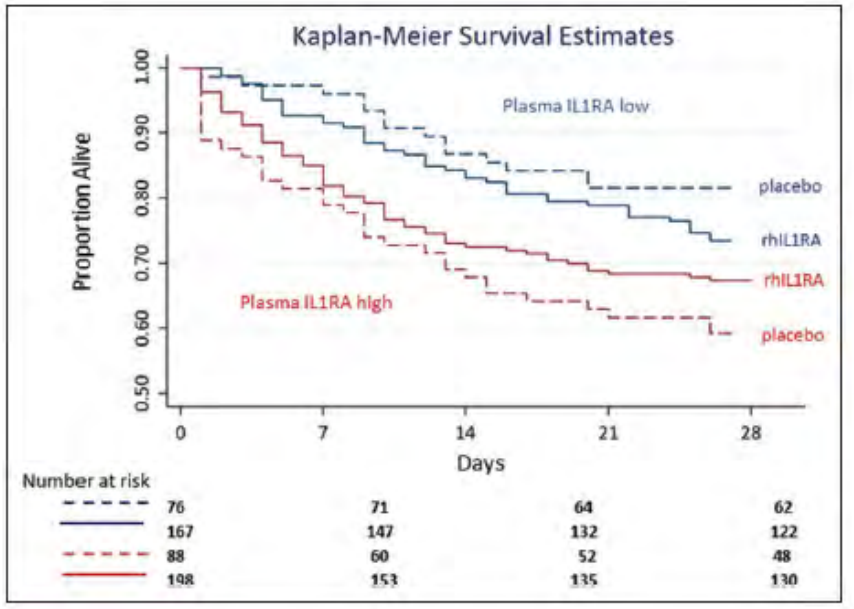
From IL1-RA trials (***JAMA 1994, CCM 1997***):

MAS



Shakoory B et al., CCM 2016

IL1-RA measurments



Meyer NL et al., CCM 2017

Still a room for blocking inflammation ?

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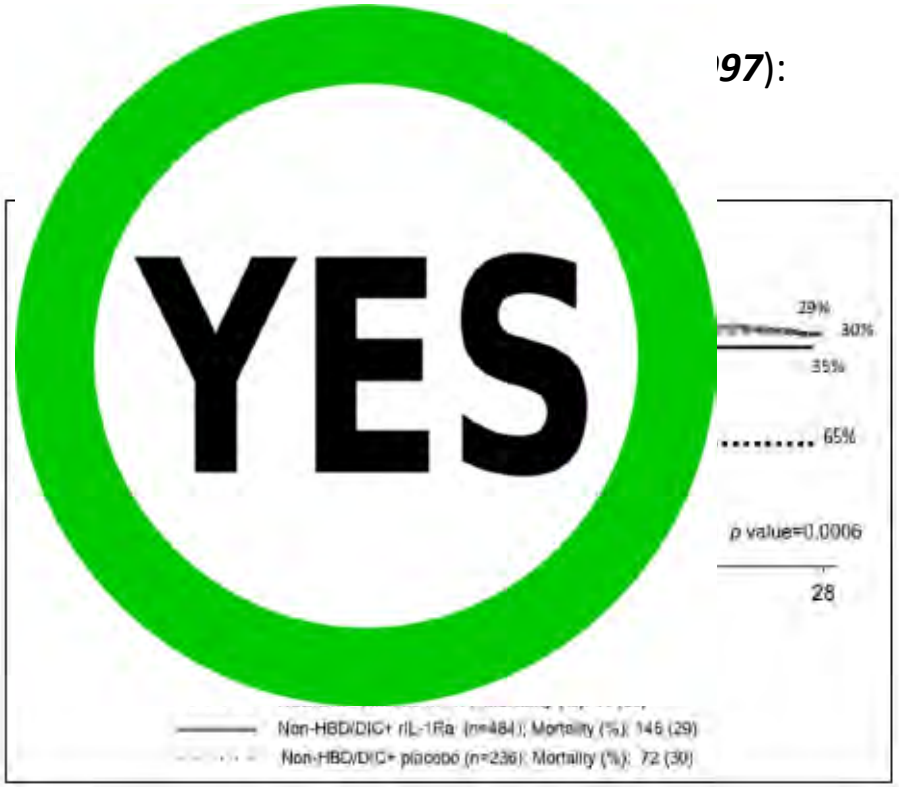
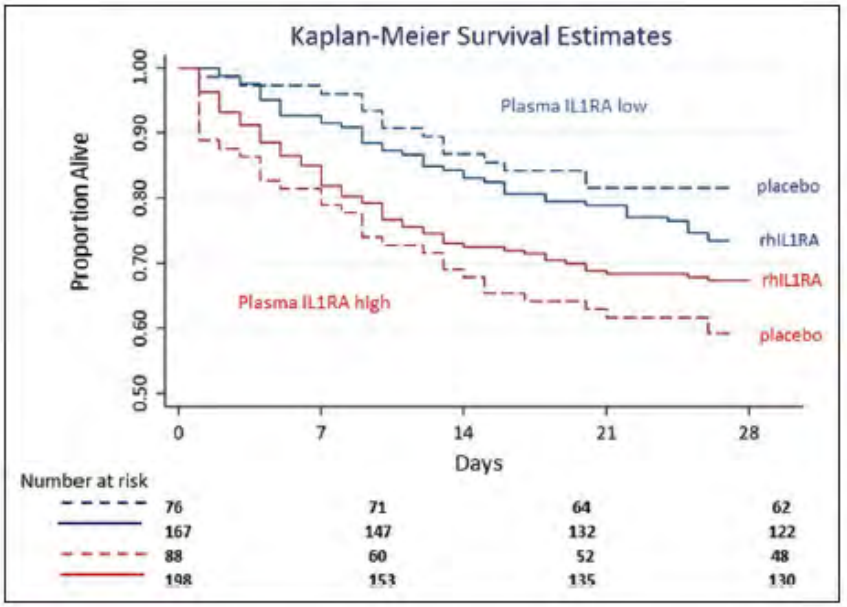


Shakoory B et al., CCM 2016

IL1-RA measurments



Meyer NL et al., CCM 2017

Still a room for blocking inflammation ?

Eichacker, P.Q. et al. Risk and the efficacy of antiinflammatory agents: retrospective and confirmatory studies of sepsis. ***Am J Respir Crit Care Med* 2002.**

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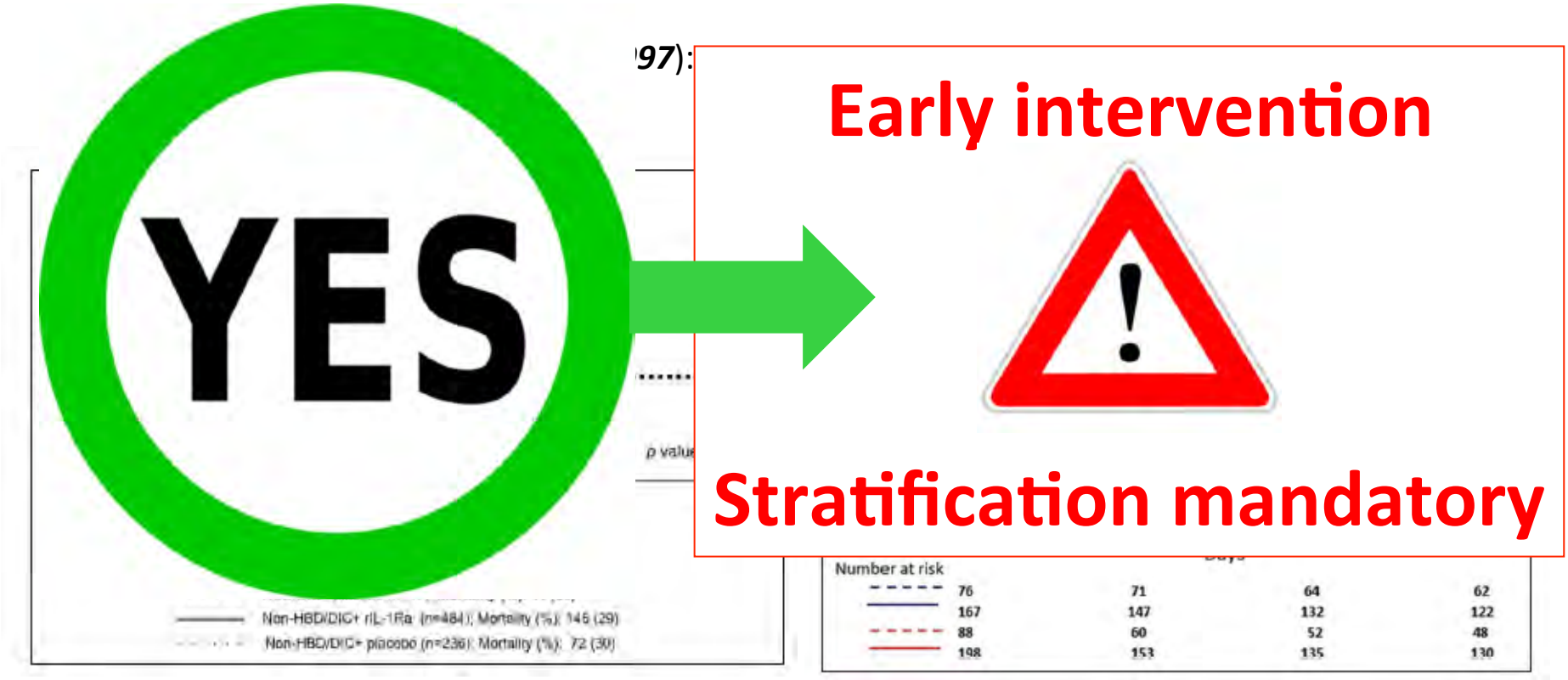
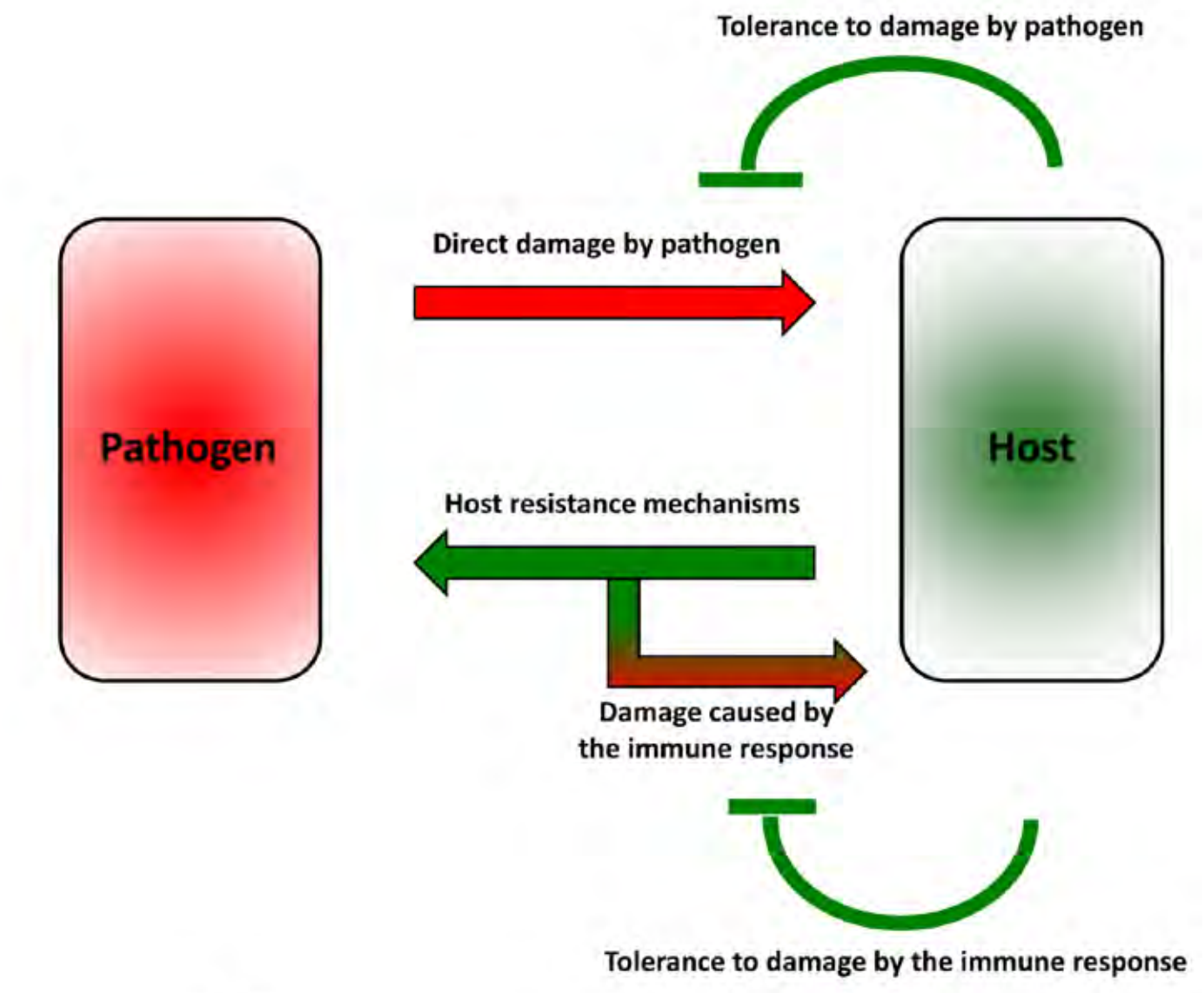


Shakoory B et al., CCM 2016

Meyer NL et al., CCM 2017

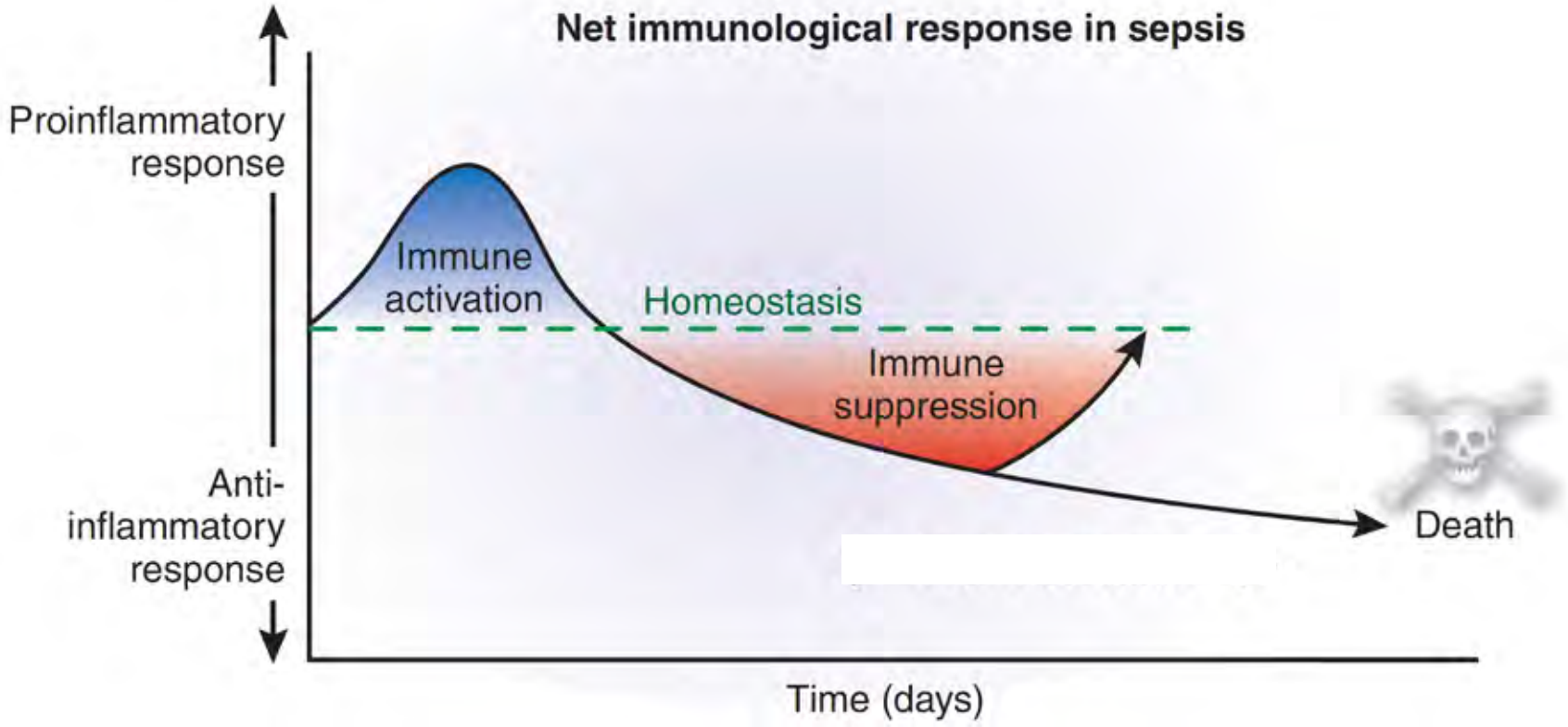


Medzhitov et al., Science 2012

The sepsis-induced immunosuppression hypothesis

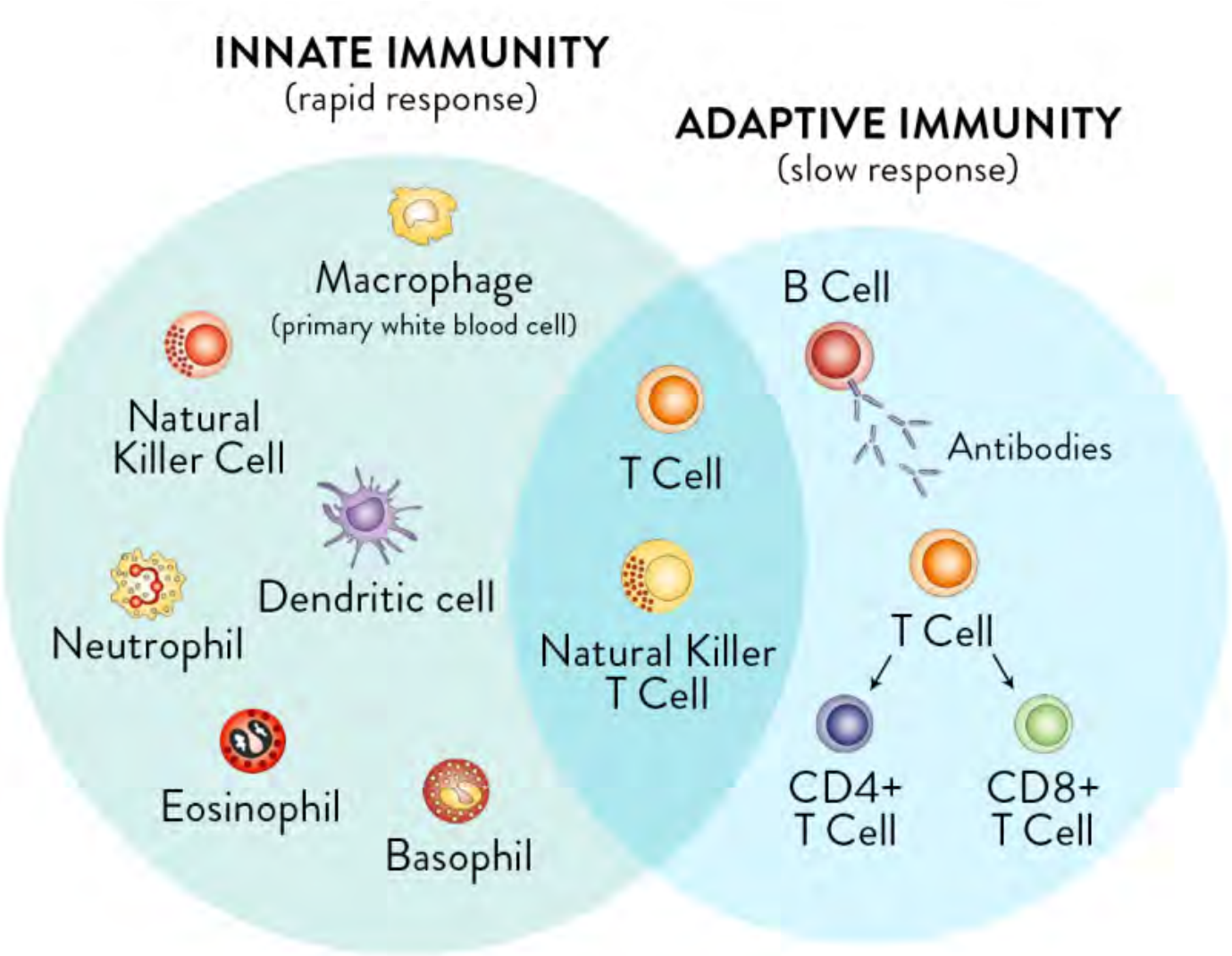
Tilting toward immunosuppression

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

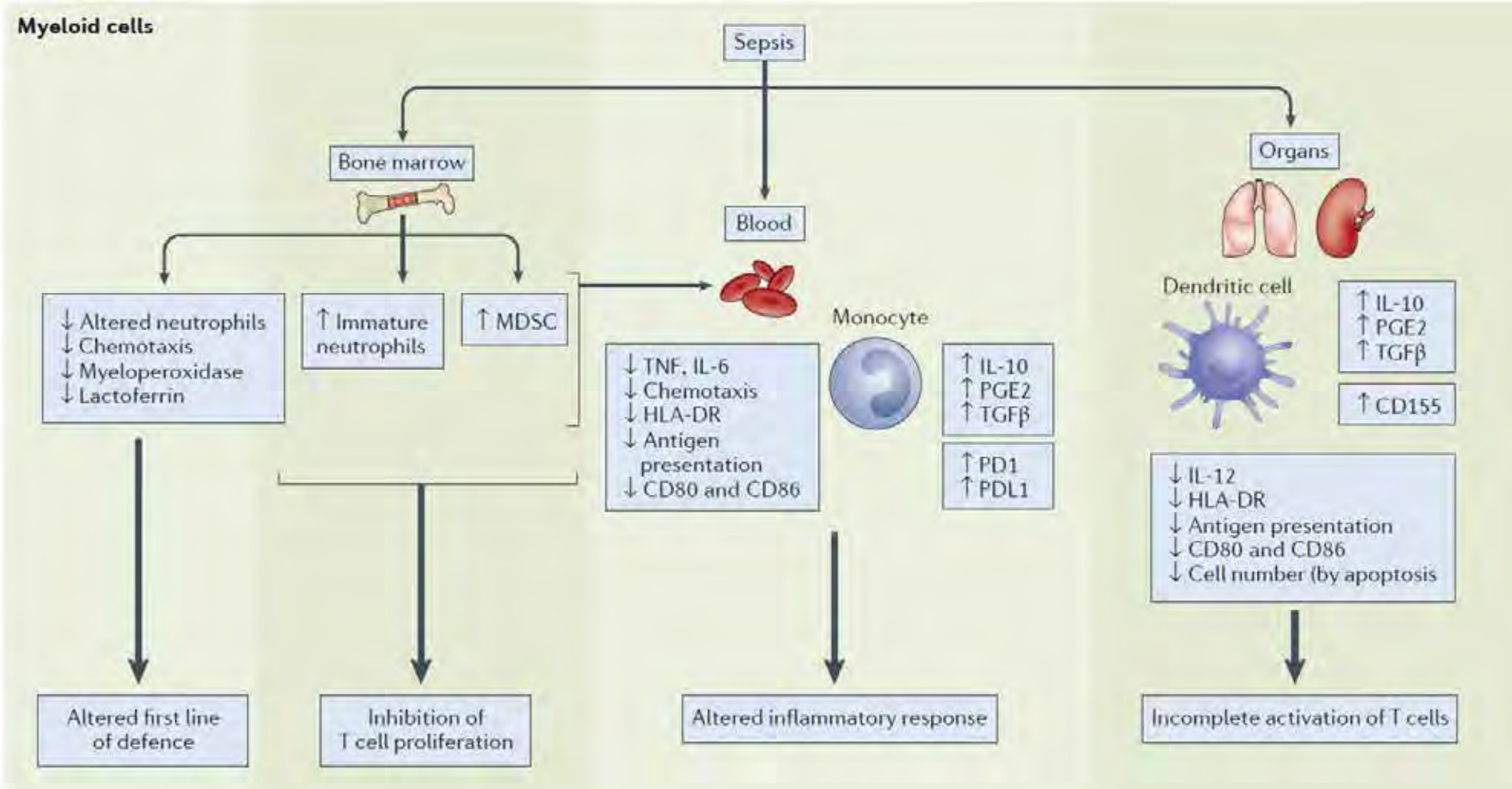


nature medicine

Do septic patients present immune alterations ?



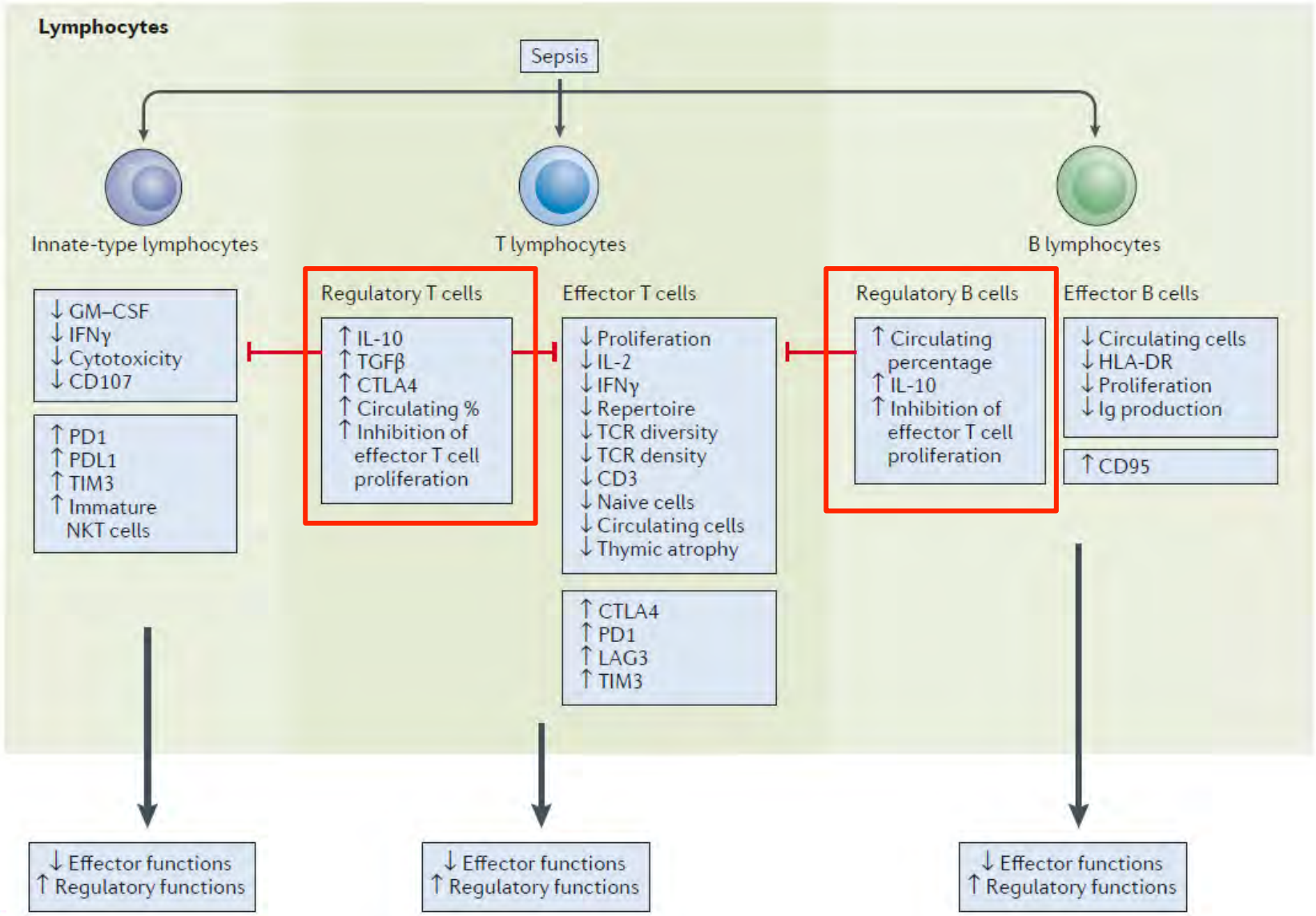
Myeloid cells (summary)



nature REVIEWS

Venet & Monneret, 2018

Lymphoid cells (summary)



nature REVIEWS

Venet & Monneret, 2018

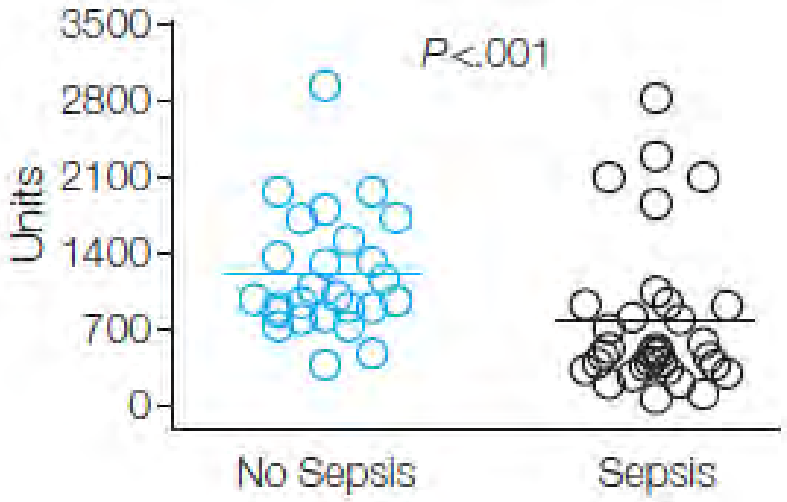
What about (lymphoid) organs ?

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)

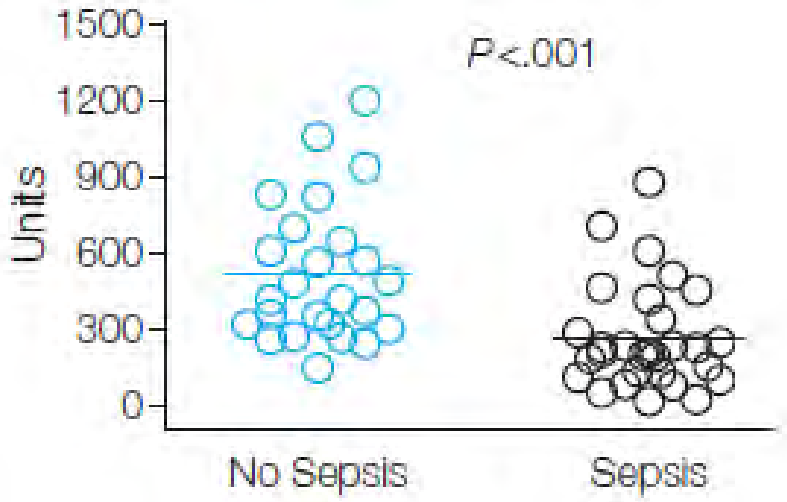
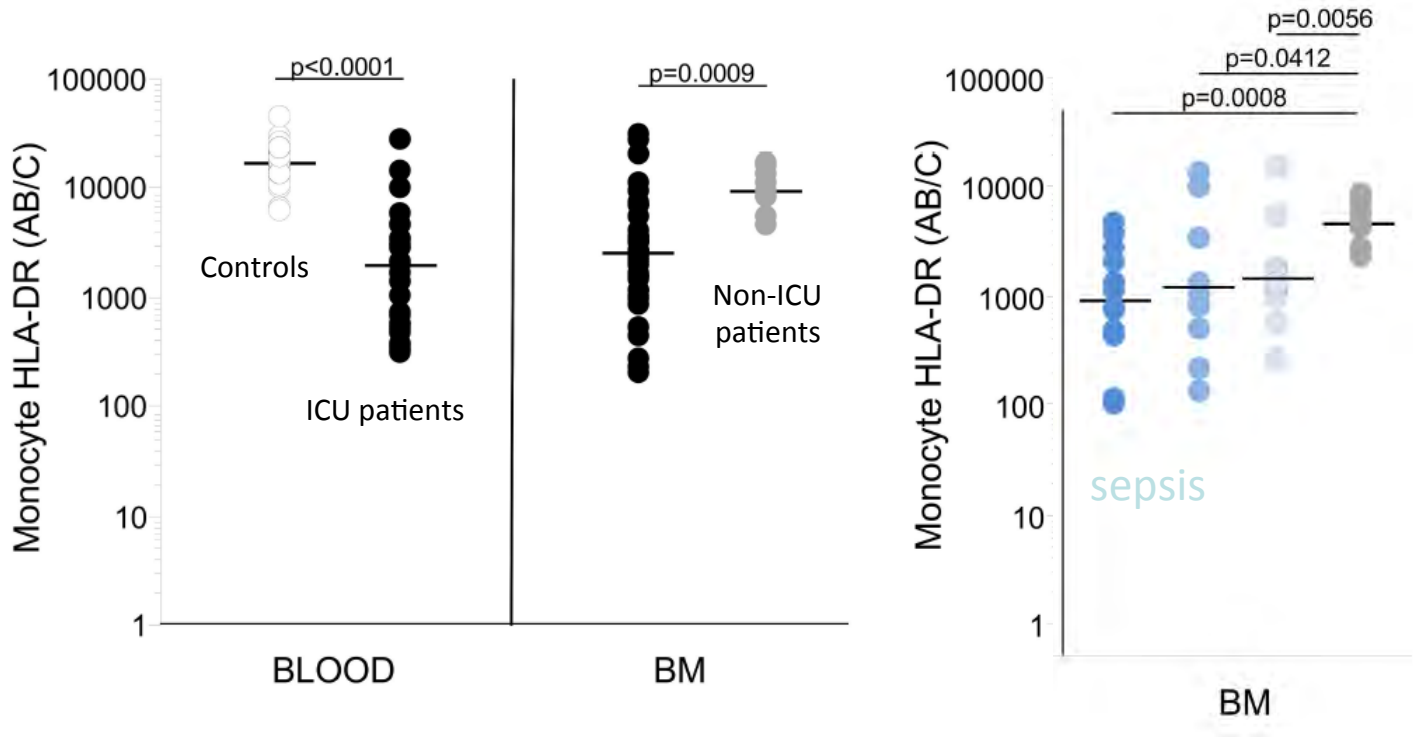


Figure 3. Expression of Cell Surface Receptors on Splenic Antigen-Presenting Cells and Tissue Macrophages

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

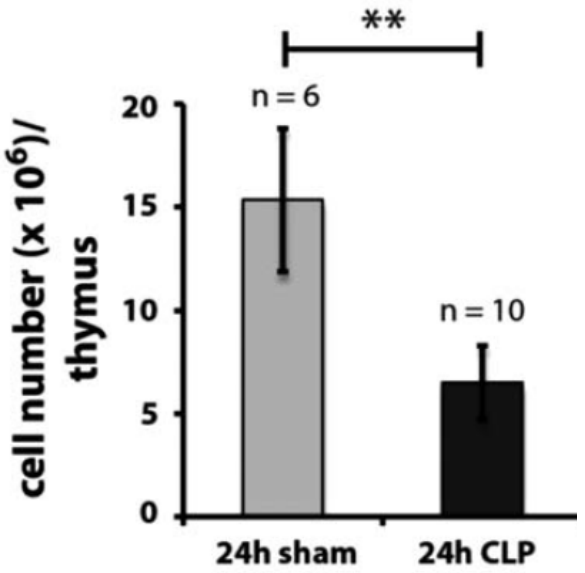
Faivre et al., 2016

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*†

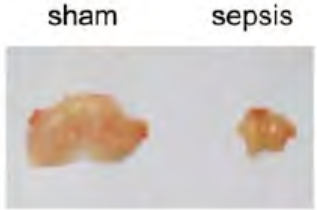
SHOCK, Vol. 48, No. 2, pp. 215–226, 2017

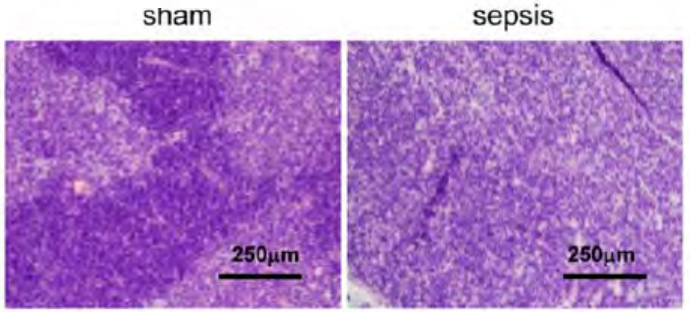


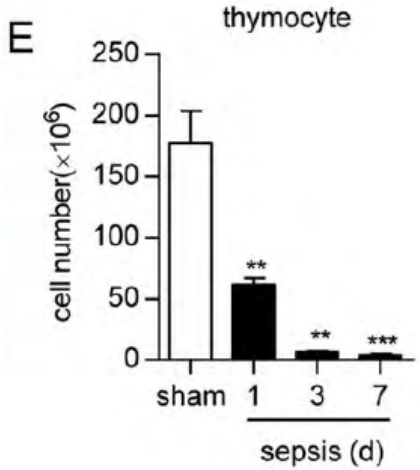
Sepsis-Induced Thymic Atrophy Is Associated with Defects in Early Lymphopoiesis

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]

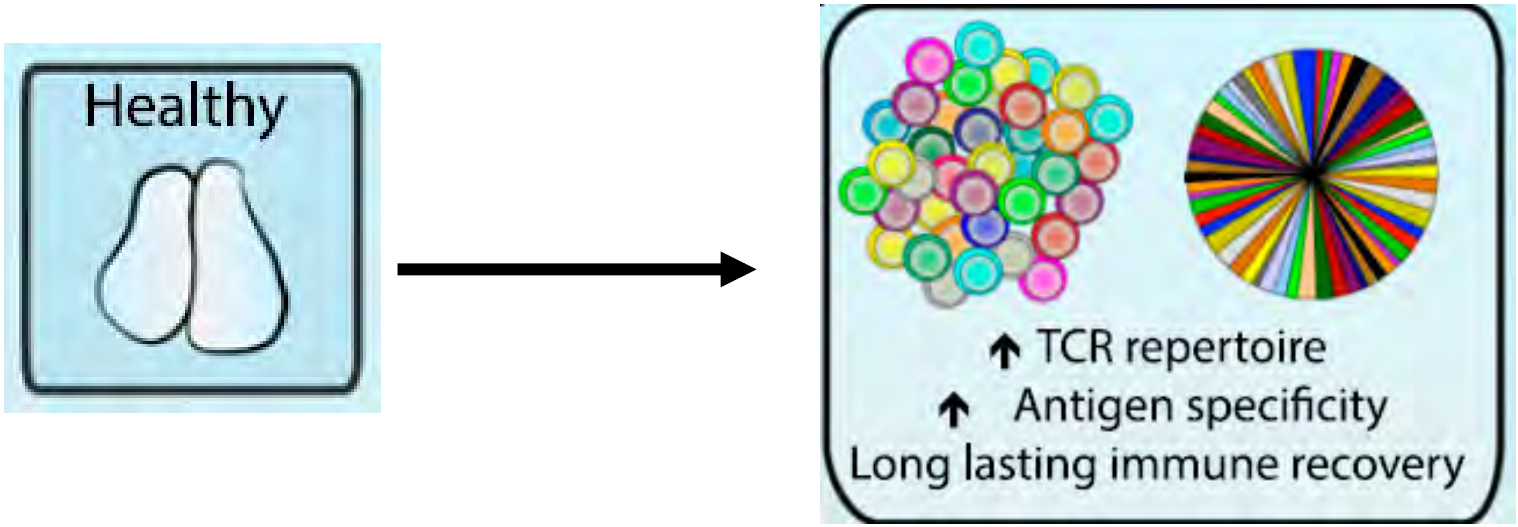
STEM CELLS 2016;34:2902–2915



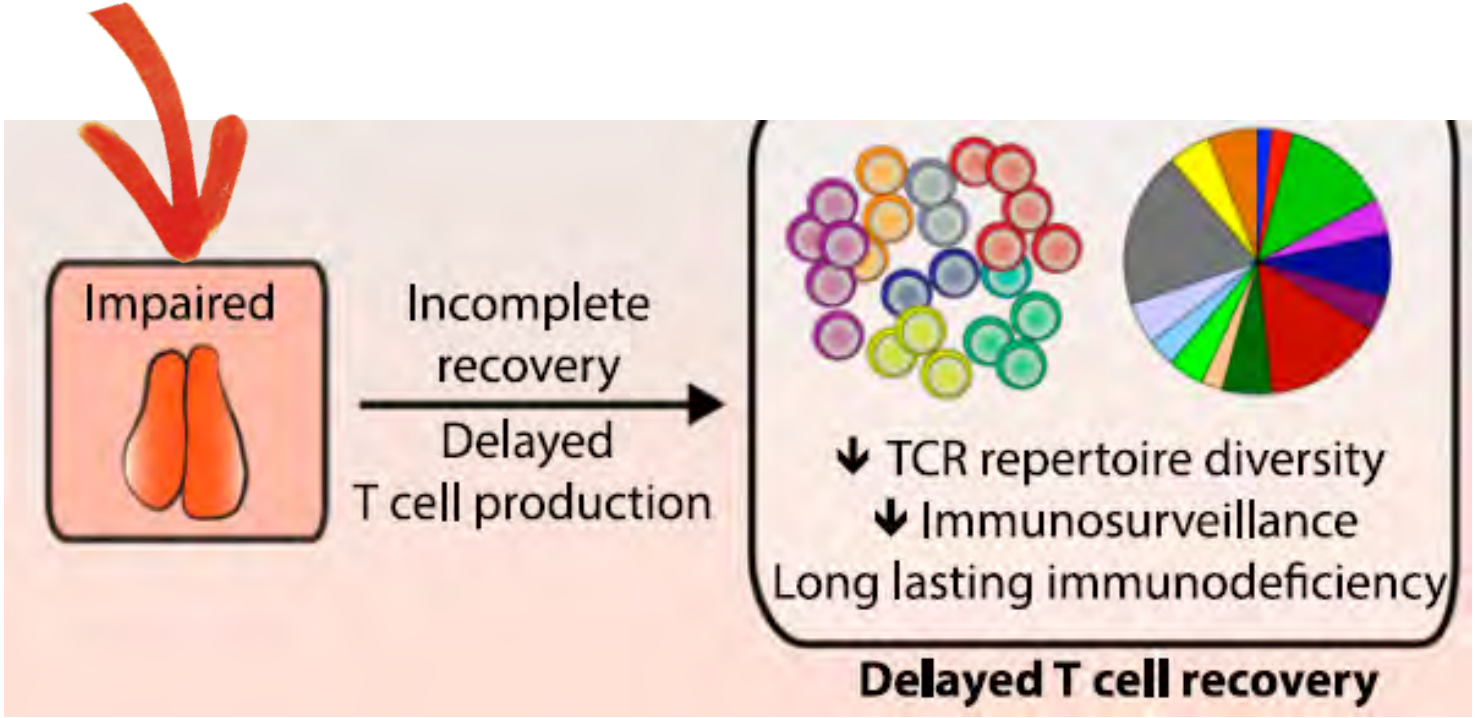




STEM CELLS

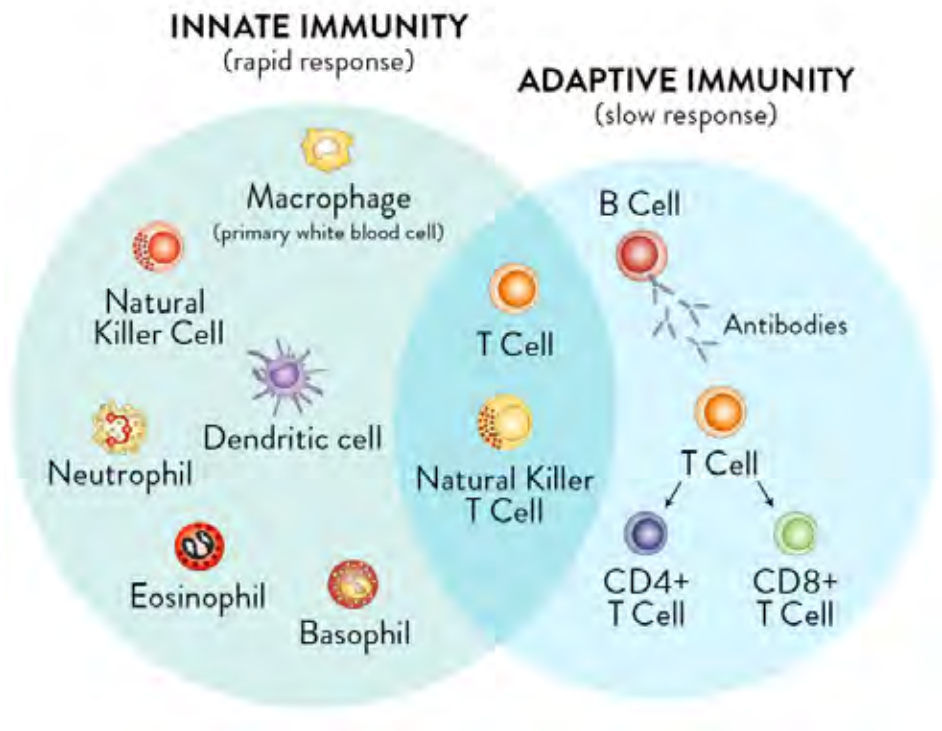


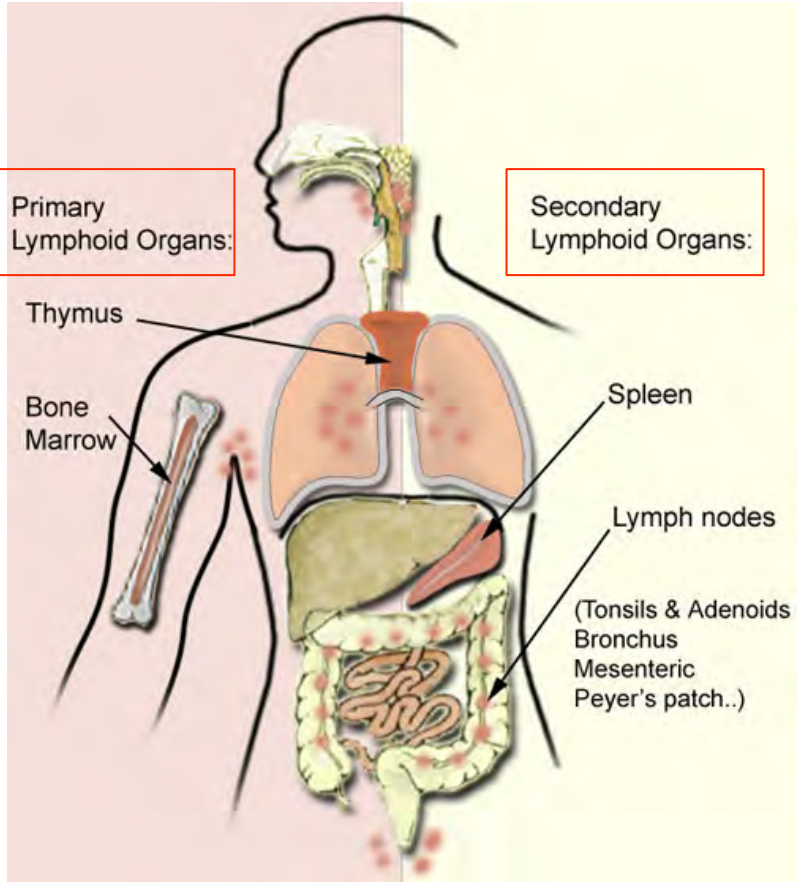
SEPSIS



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

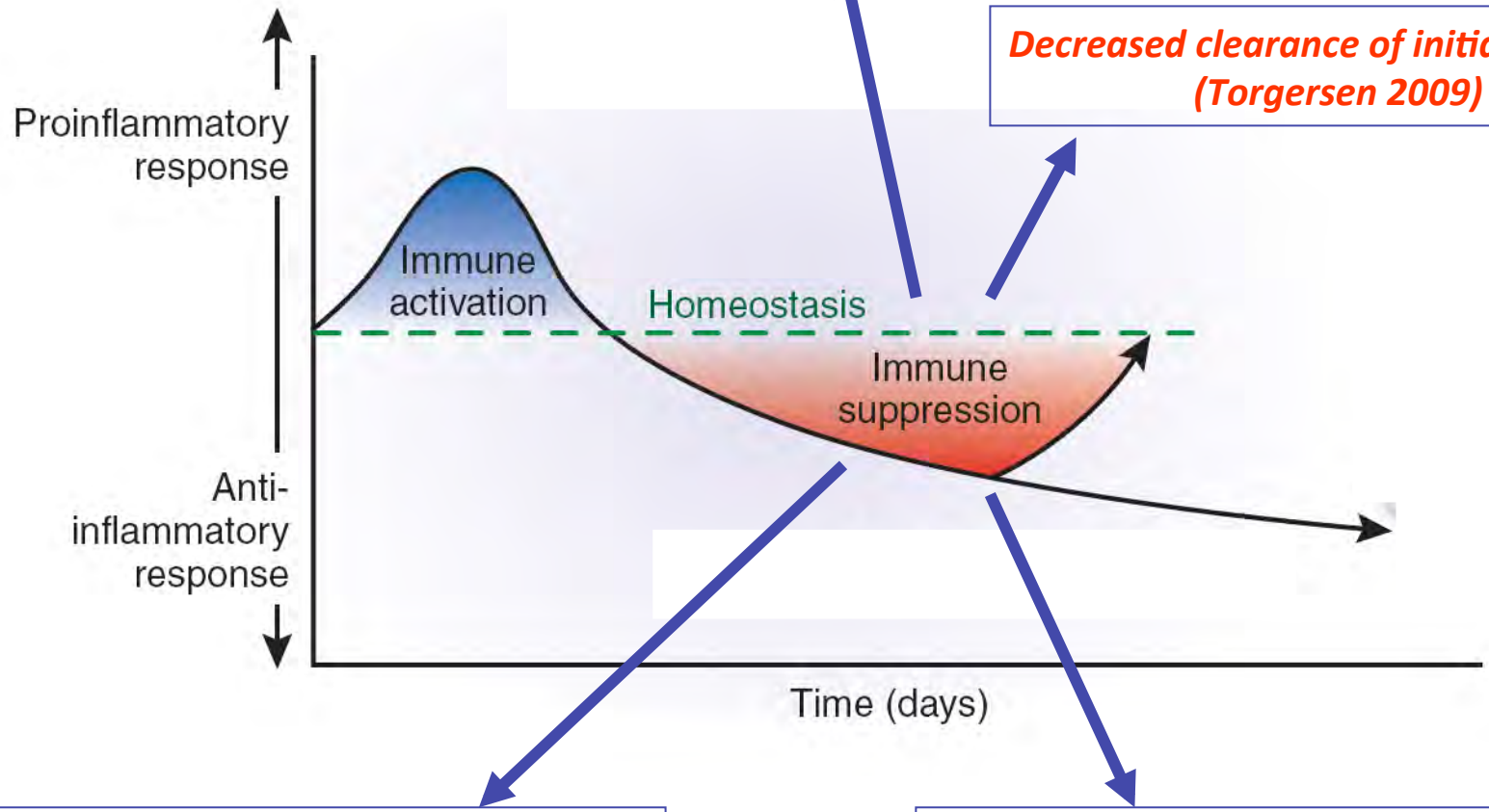
Summary


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..)

Consequences of sepsis-induced immunosuppression

Severe fungal Infections *(Leroy, CCM 2009 ; Hatermink ICM 2003)*

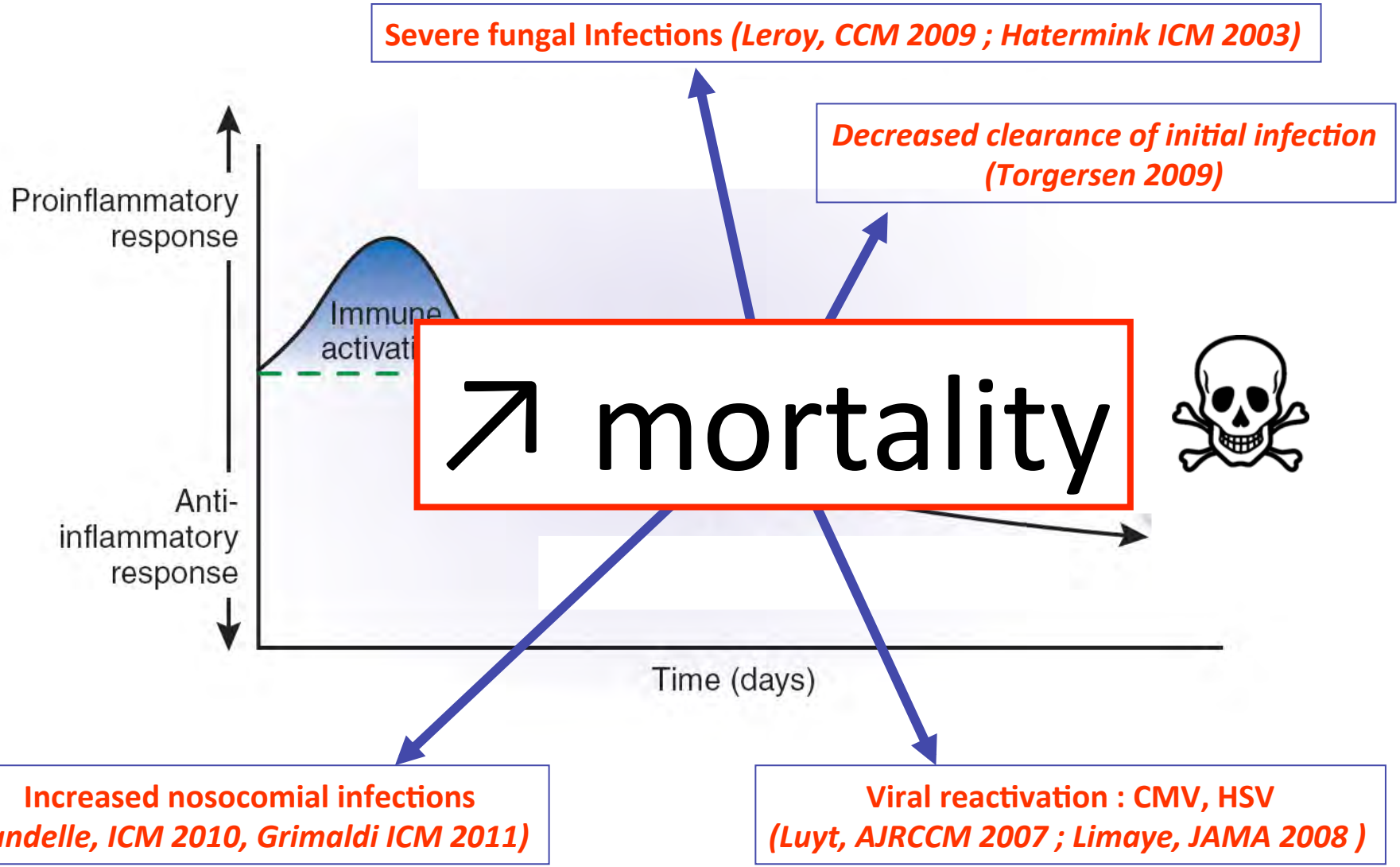
Decreased clearance of initial infection (Torgersen 2009)



Increased nosocomial infections *(Landelle, ICM 2010, Grimaldi ICM 2011)*

Viral reactivation : CMV, HSV *(Luyt, AJRCCM 2007 ; Limaye, JAMA 2008)*

Consequences of sepsis-induced immunosuppression



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

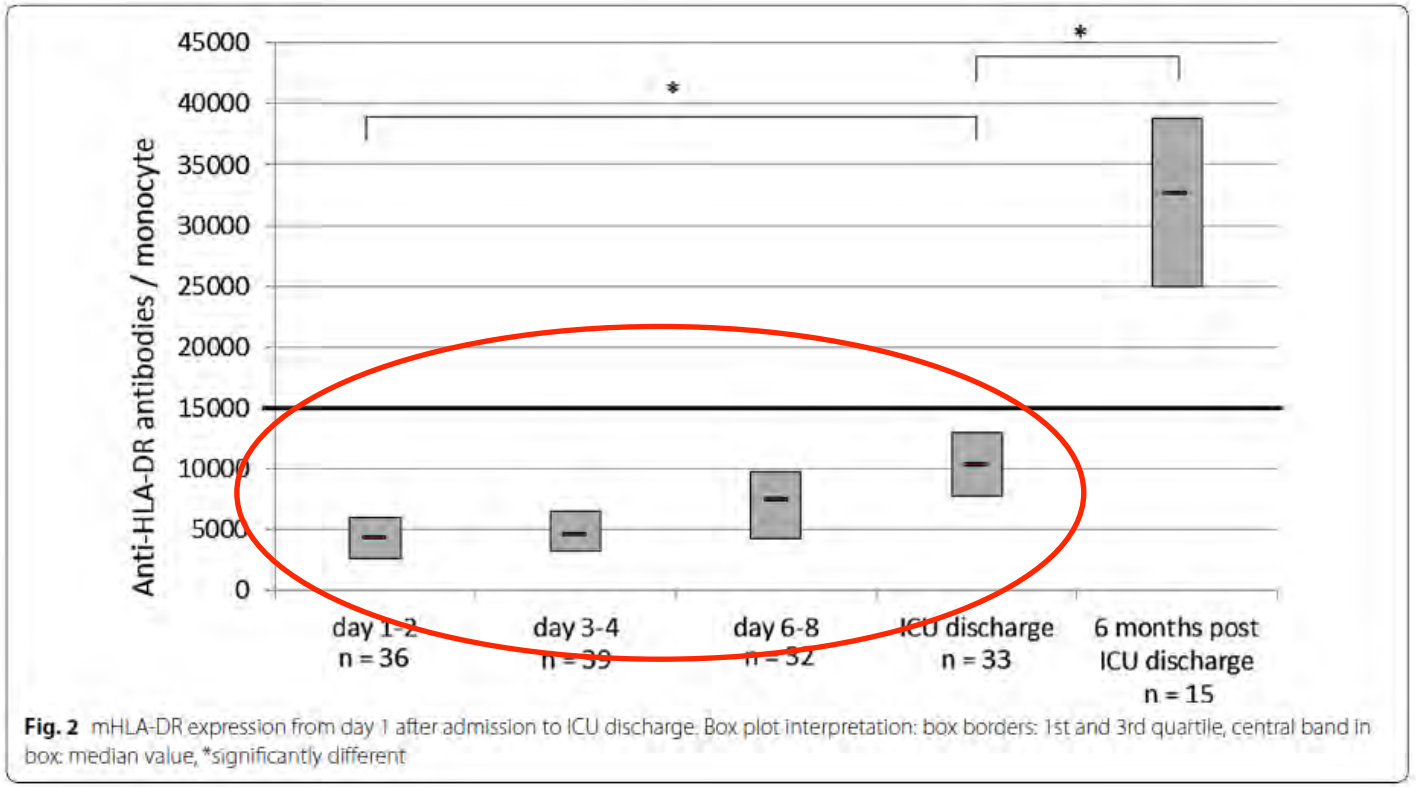


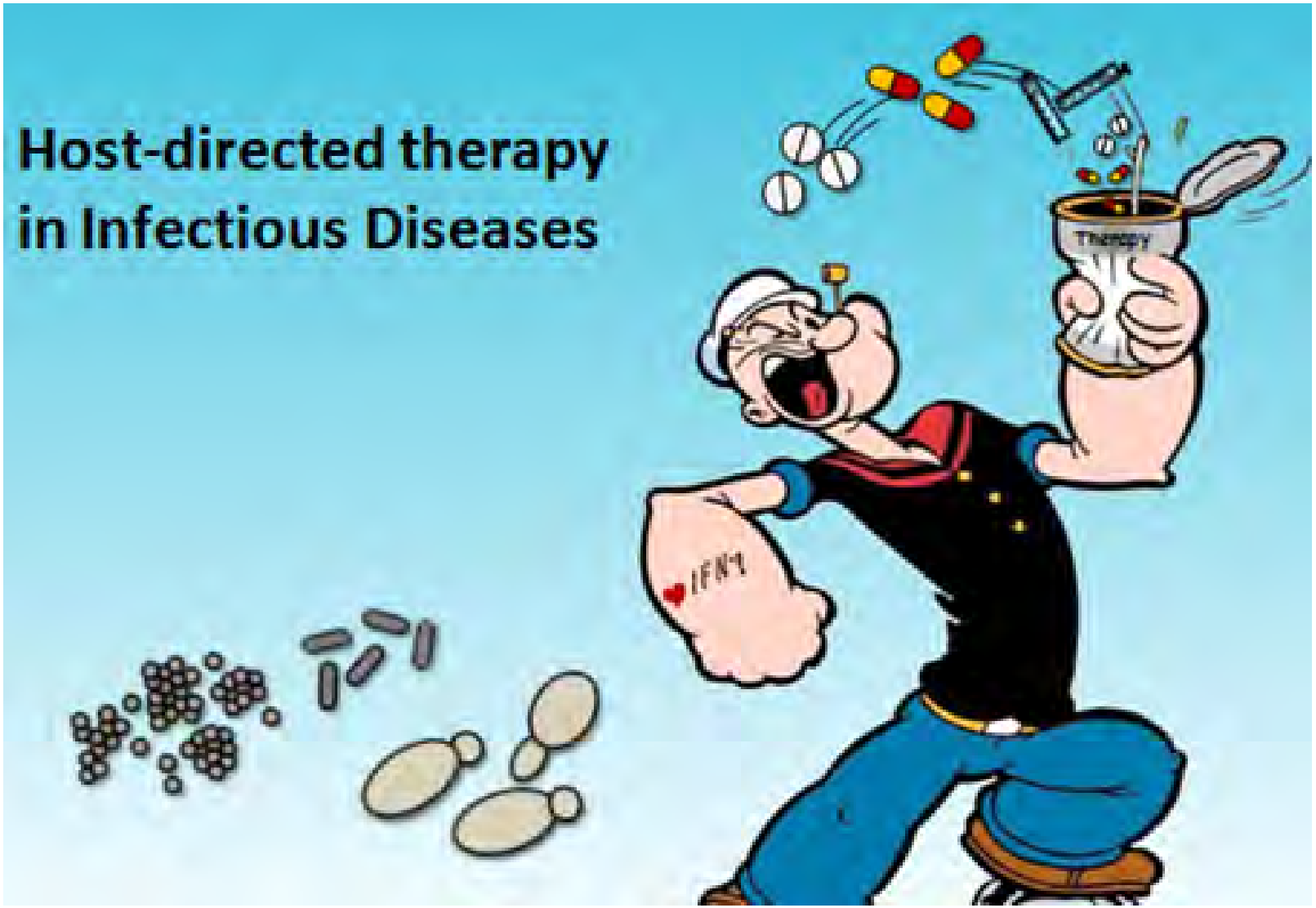
Fig. 2 mHLA-DR expression from day 1 after admission to ICU discharge. Box plot interpretation: box borders: 1st and 3rd quartile, central band in box: median value, *significantly different

Median discharge = 11 days

Annals of Intensive Care

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

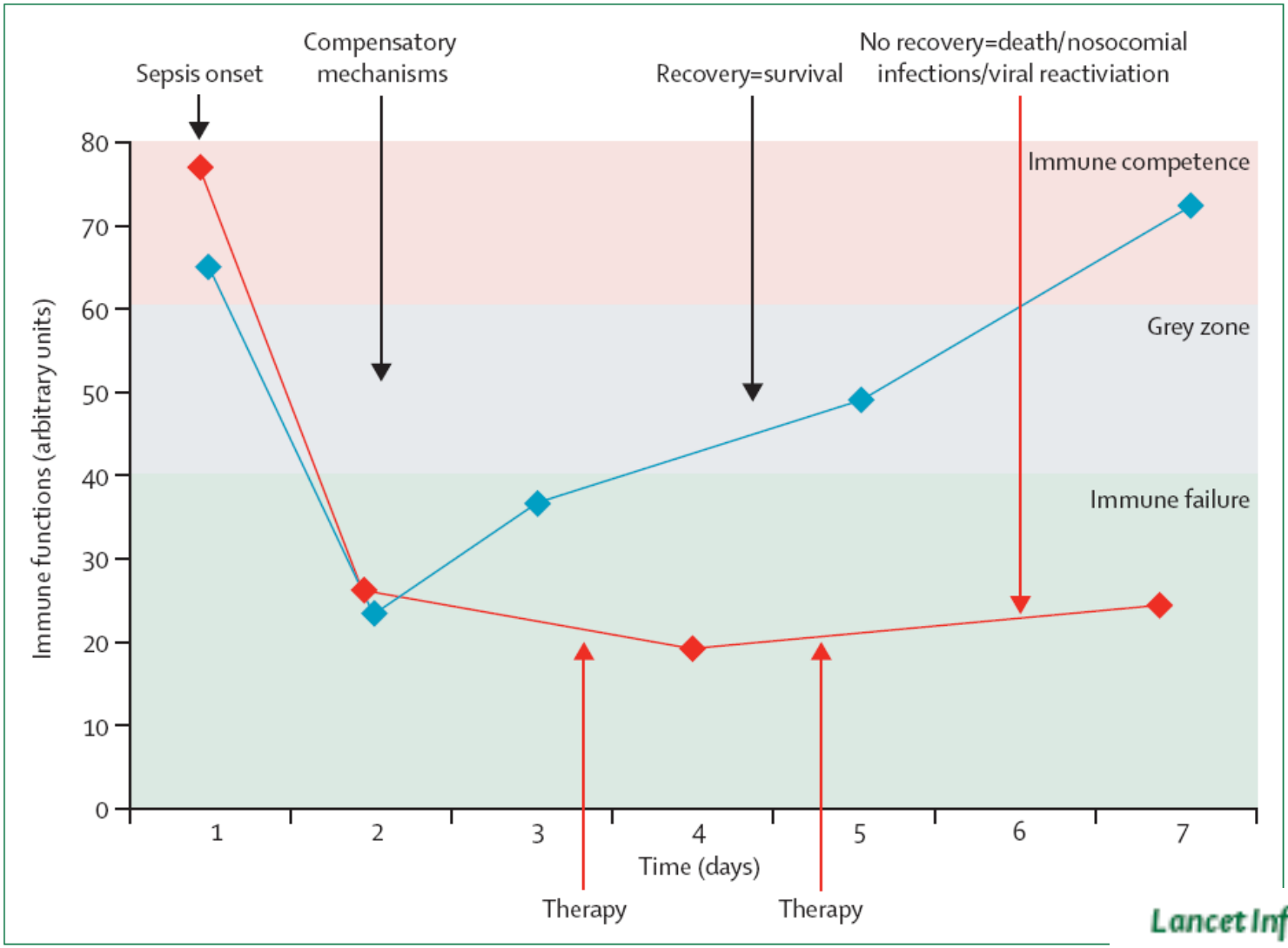
Immunostimulation in sepsis



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



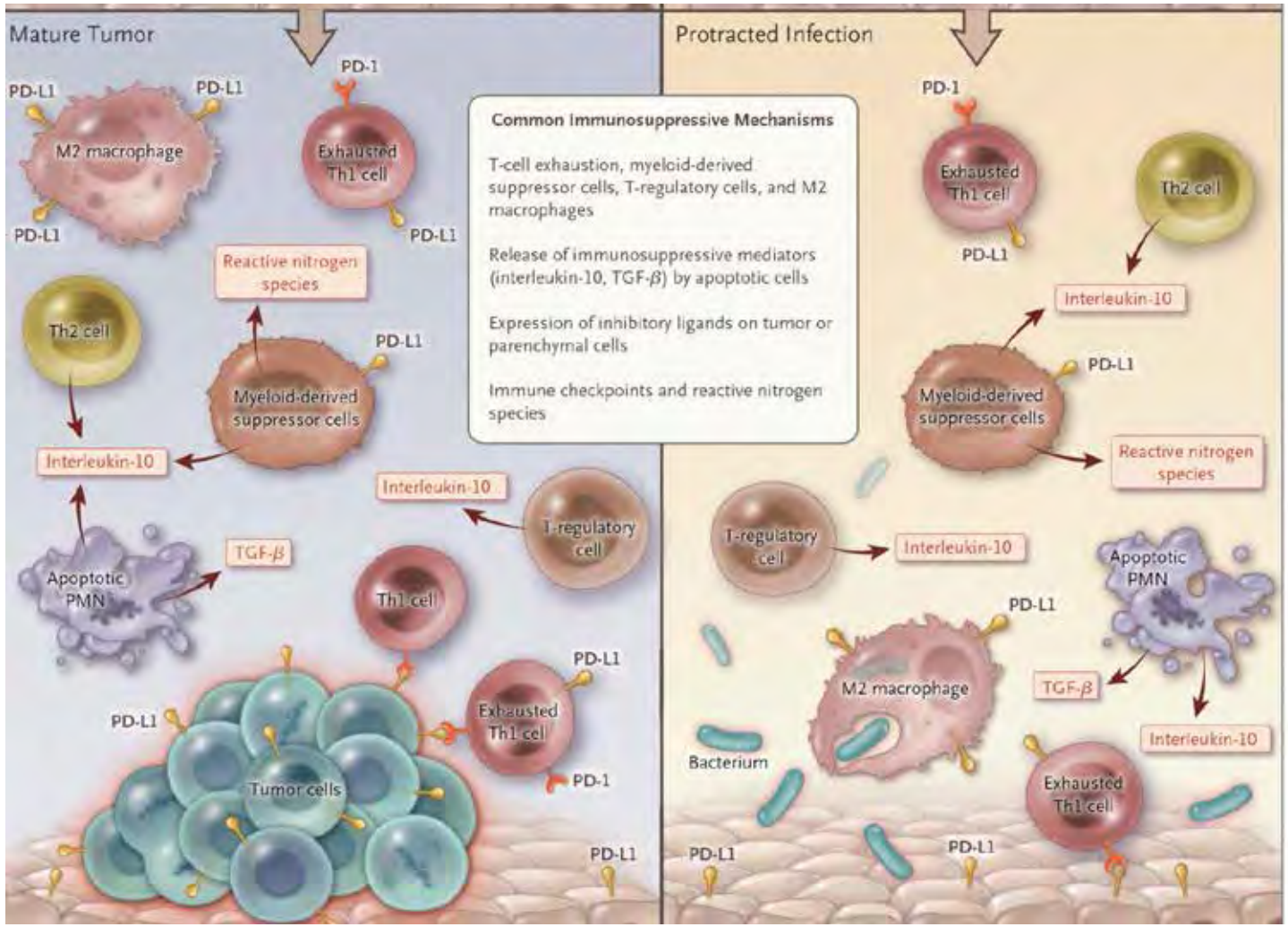
Lancet Infect Dis 2013; 13: 260–68

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.



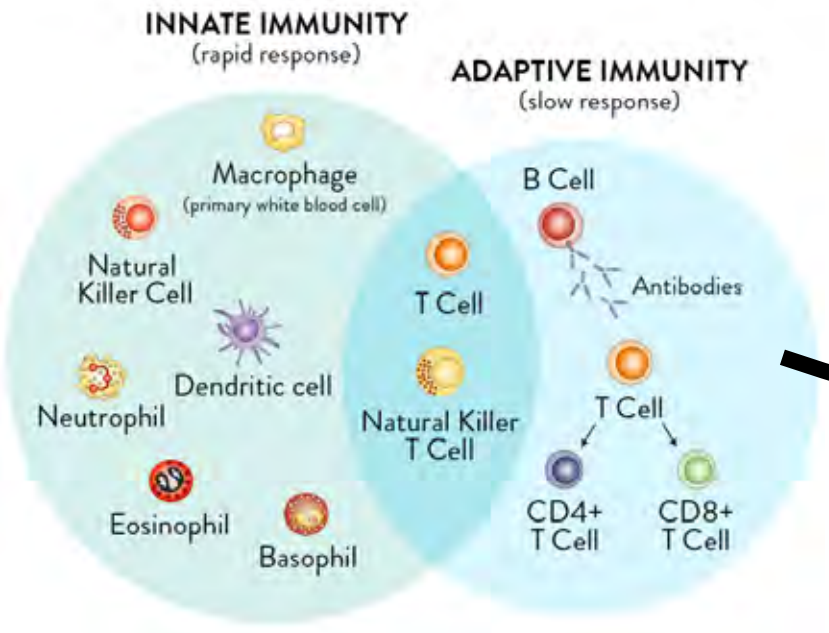
Principles of immunotherapy

Antibiotics ⟶

Principles of immunotherapy

Antibiotics ⟶

Rejuvenate / stimulate immune cells



Principles of immunotherapy

Compelling preclinical results in sepsis:

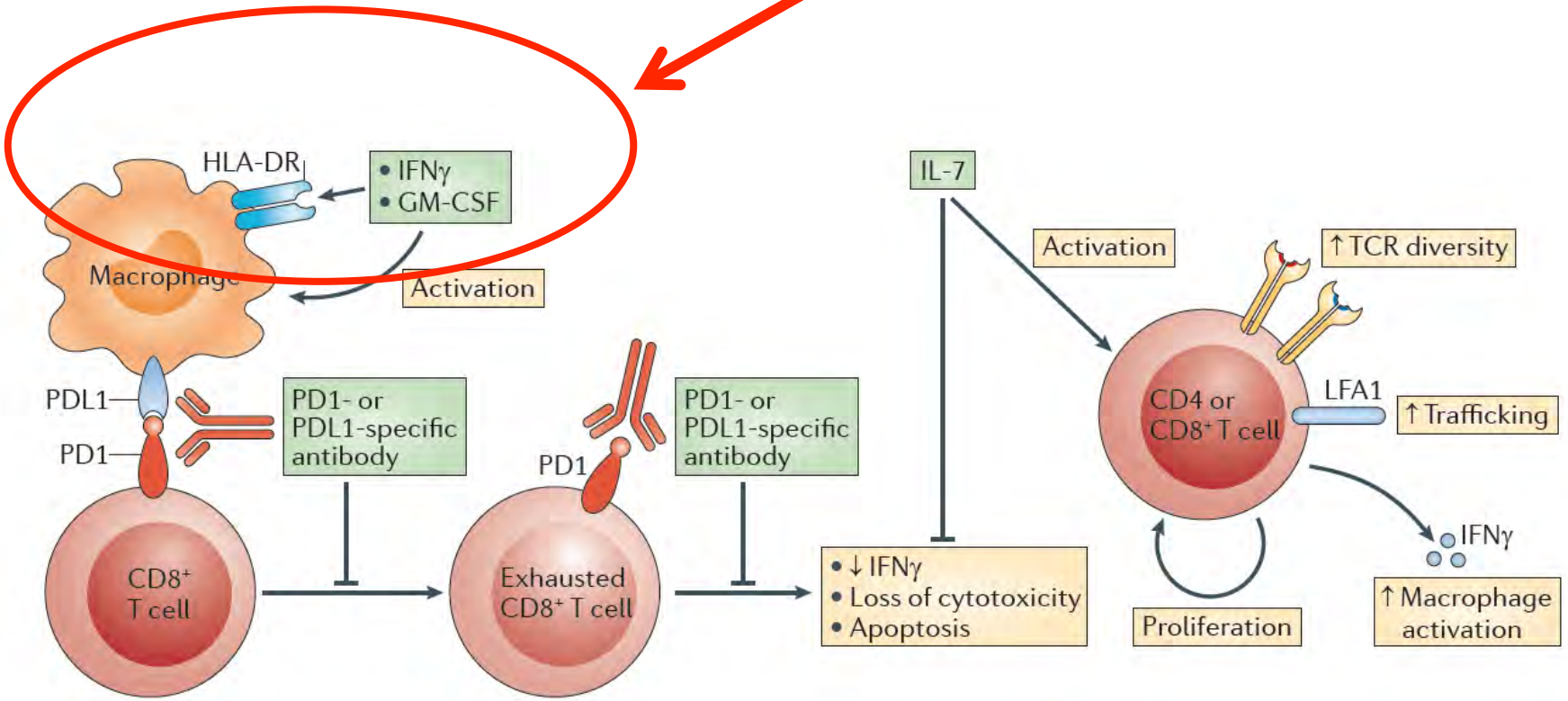
- Improves bacterial clearance and mortality in mice

- Restores immune functions ex-vivo in human cells

Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

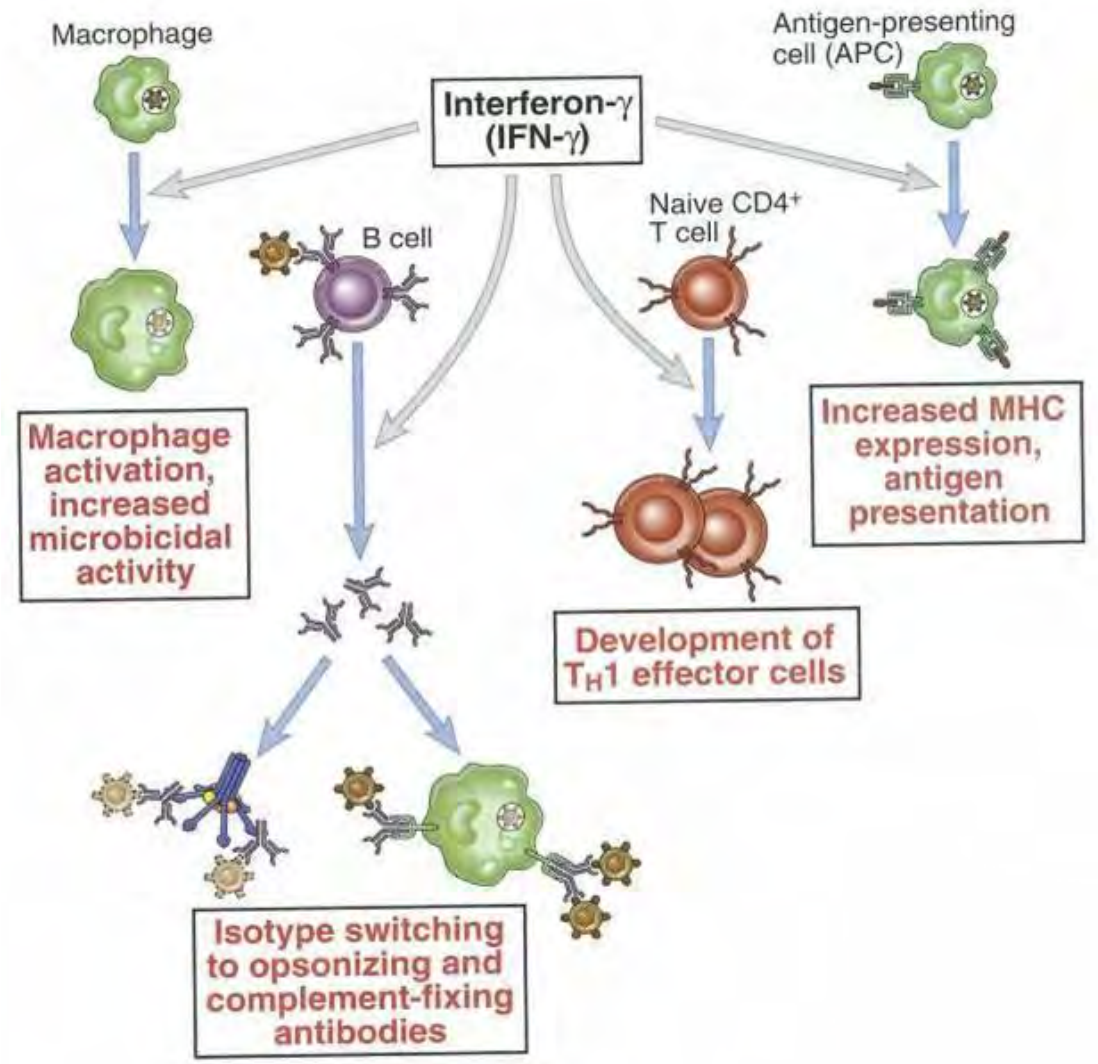
Richard S. Hotchkiss[1], Guillaume Monneret[2] and Didier Payen[3]

Restoring innate response



NATURE REVIEWS | IMMUNOLOGY 2013

1. INTERFERON - γ (IMUKIN)



Docke WD et al. Nat Med. 1997;3:678-81
Monocyte deactivation in septic patients: restoration by IFN-gamma treatment

9 patients severe sepsis

↓

HLA-DR < 30 %
(2 consecutive days)

↓

Interferon-gamma

Mortality 33 %

Non randomized

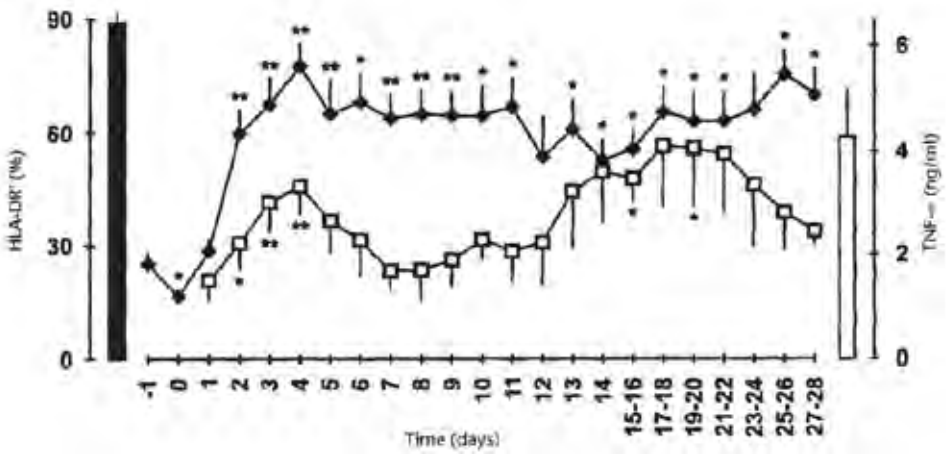
26 patients severe sepsis

↓

HLA-DR < 30 %
(2 consecutive days)

↓

Mortality 58 %



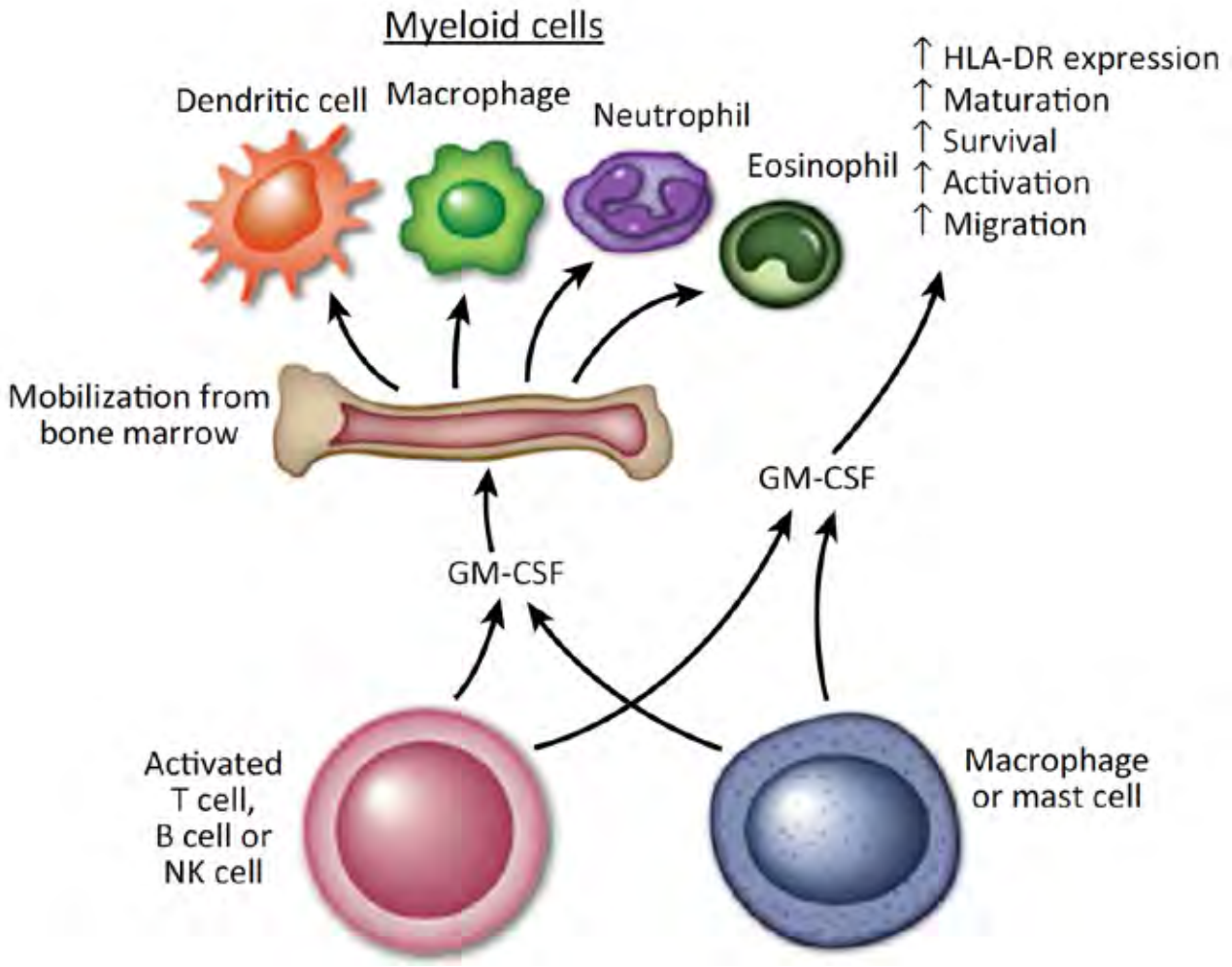
nature medicine

Case reports (successful)

- Nakos et al., CCM 2002 (nosocomial infections in trauma)
- Luckasewicz et al., CCM 2009 (nosocomial)
- Delsing et al, BMC Infectious Diseases 2014 (fungal infections)
- Nalos et al., AJRCCM 2012 (staph sepsis)
- Mezidi et al., Minerva Anesth 2014 (fungal infection)
- Grimaldi et al., Lancet infect Dis 2017 (mucormycosis)

Current trial in fungal infections (Netea, Nijmingen) – non randomized

2. GM-CSF (Leukine)

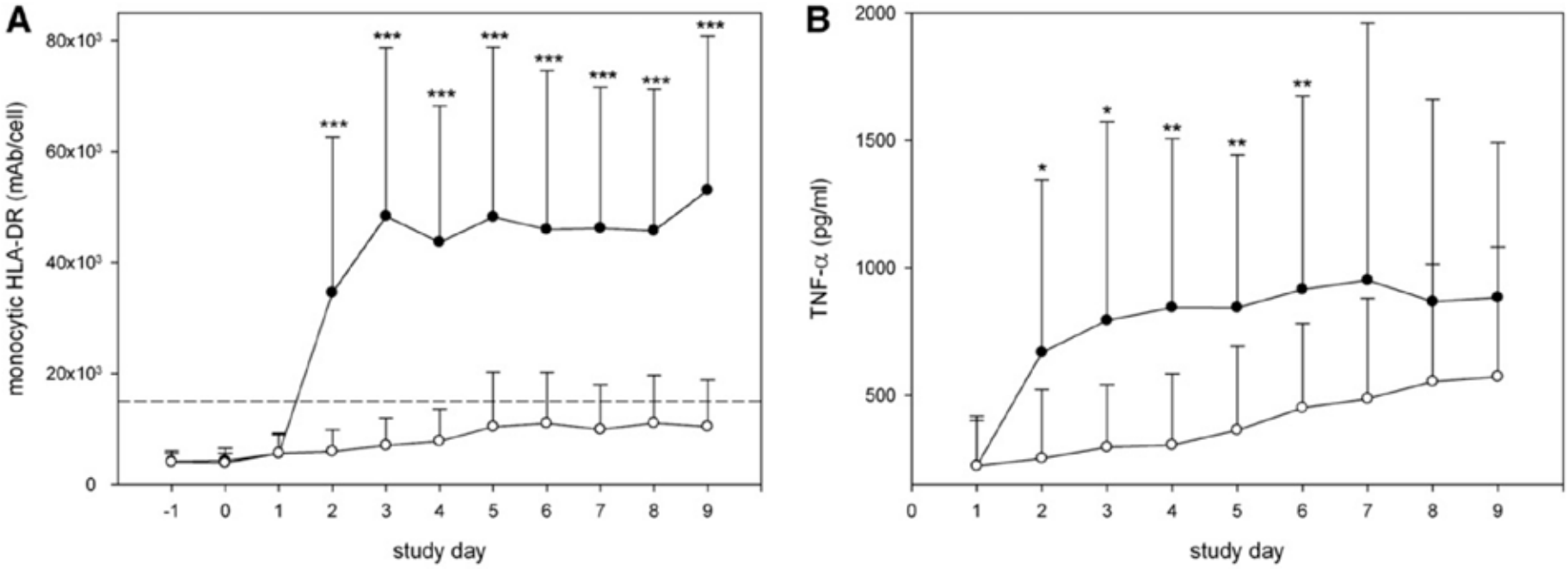


Trends in Molecular Medicine, April 2014, Vol. 20, No. 4

Granulocyte–Macrophage Colony-stimulating Factor to Reverse Sepsis-associated Immunosuppression

A Double-Blind, Randomized, Placebo-controlled Multicenter Trial

Christian Meisel[1]*, Joerg C. Schefold[2]*, Rene Pschowski[2], Tycho Baumann[1], Katrin Hetzger[1], Jan Gregor[3], Steffen Weber-Carstens[4], Dietrich Hasper[2], Didier Keh[4], Heidrun Zuckermann[3], Petra Reinke[2,5], and Hans-Dieter Volk[1,5]

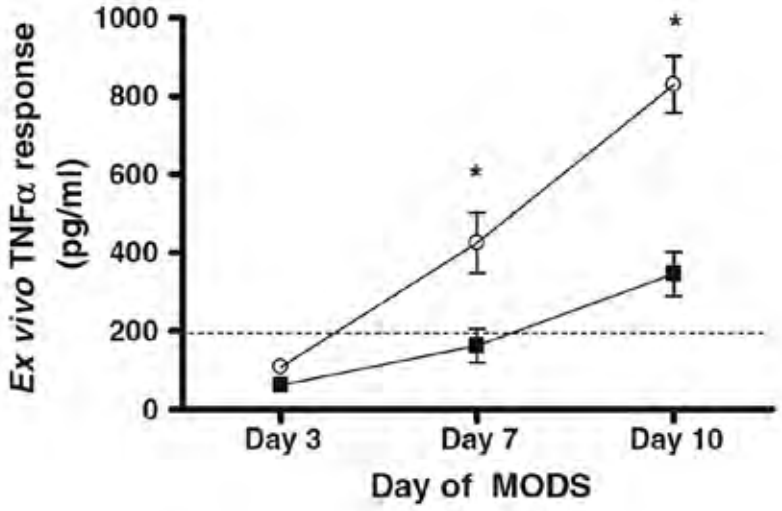


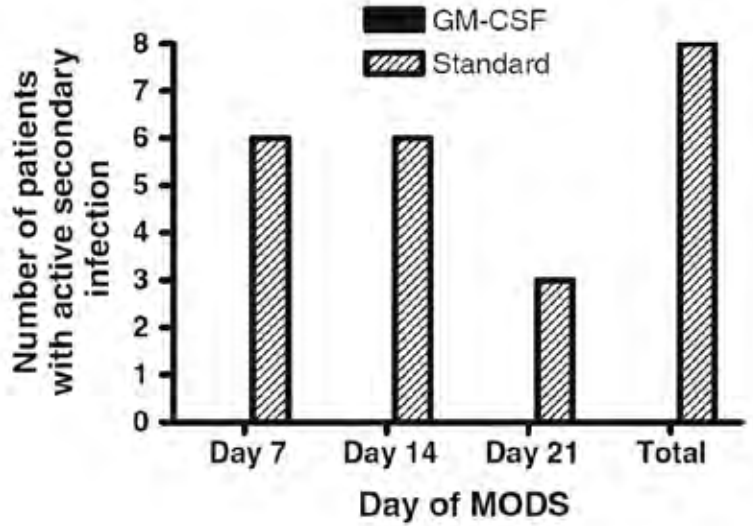
- No adverse effects
- Significantly shorter time of ventilation (148 vs 208 h, p=0.04)
- shorter length of intra-hospital stay (59 vs 69 days)
- shorter length of ICU stay (41 vs 52)
- 28-day mortality not different (trial not powered for mortality)

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 180 2009

Mark W. Hall
Nina L. Knatz
Carol Vetterly
Steven Tomarello
Mark D. Wewers
Hans Dieter Volk
Joseph A. Carcillo

Immunoparalysis and nosocomial infection in children with multiple organ dysfunction syndrome

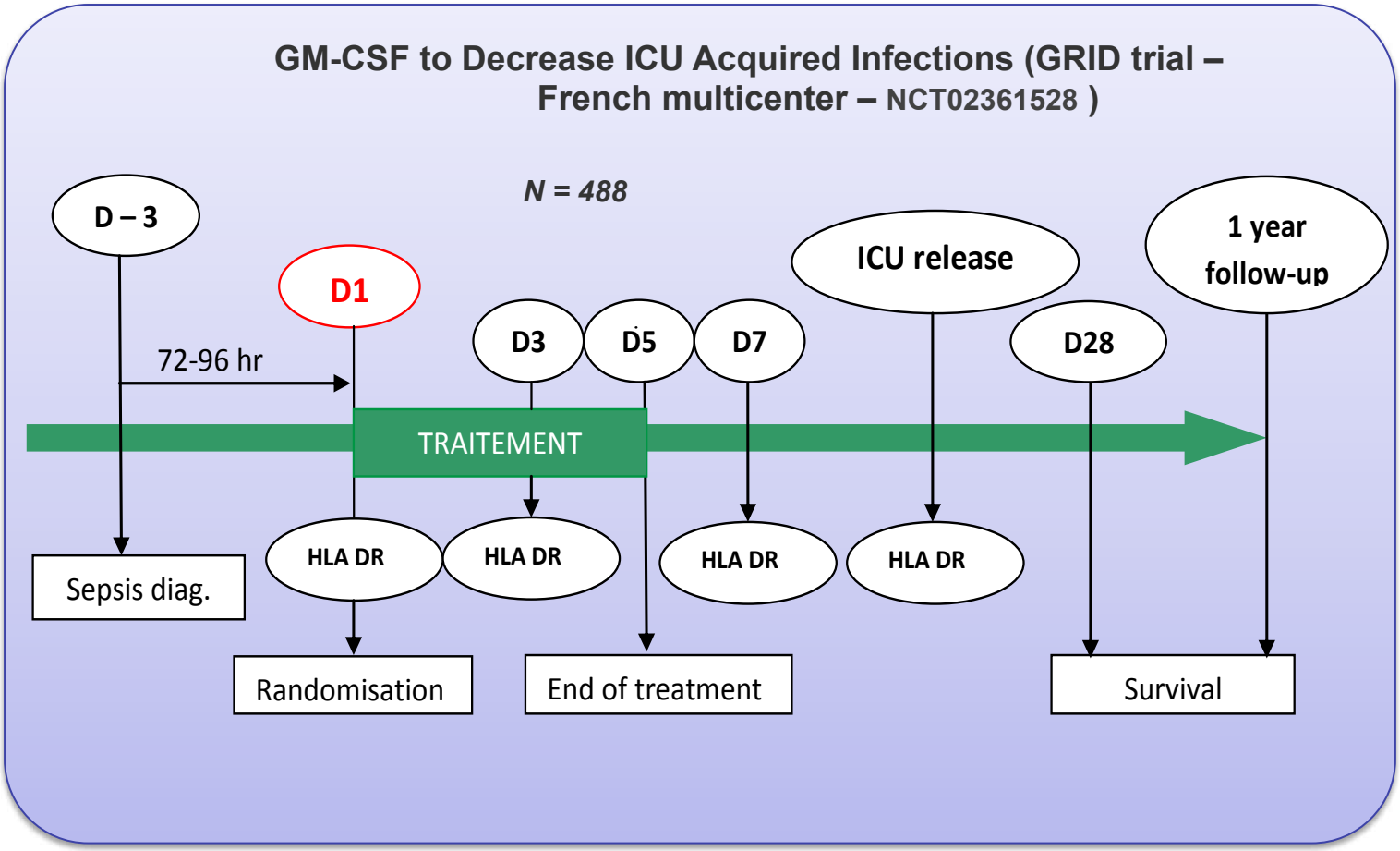




Absence of nosocomial Infections on GM-CSF

Intensive Care Med (2011) 37:525–532

The GRID study



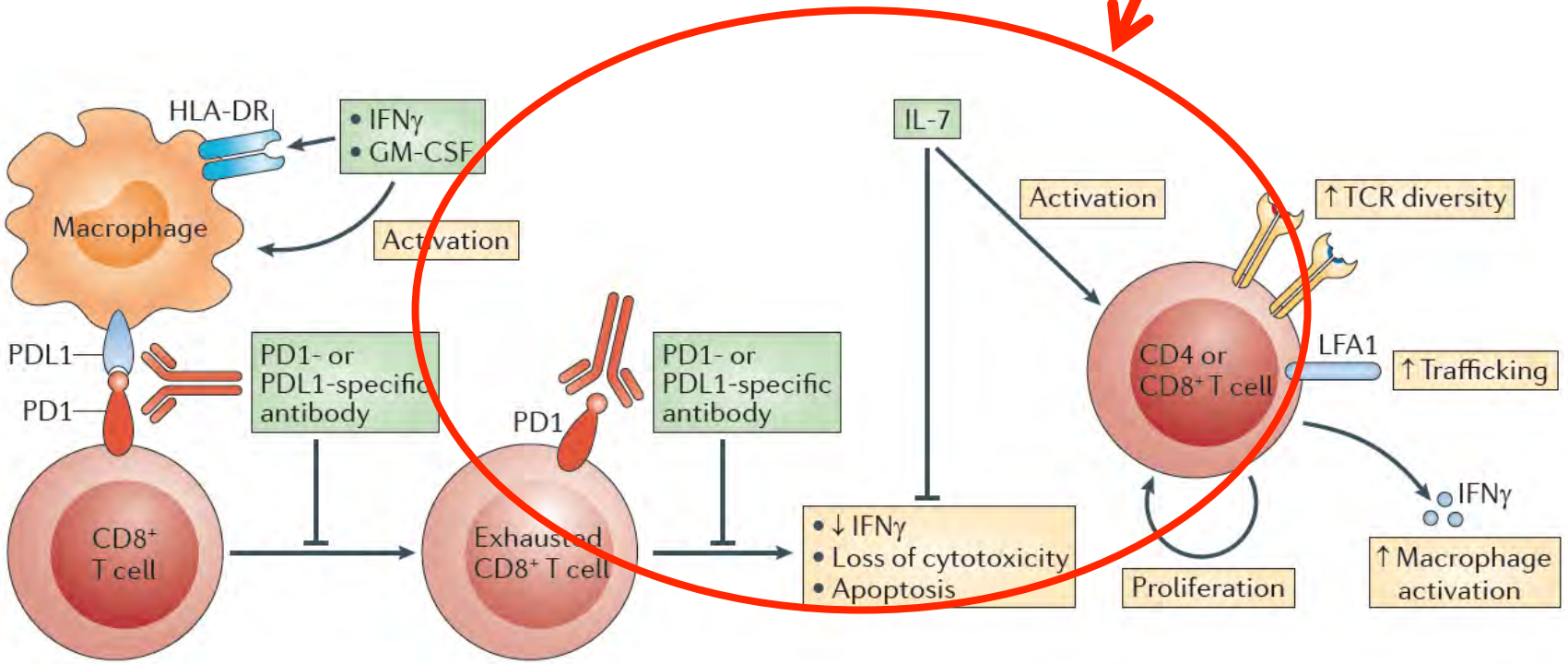
Trial ended by promoter at 100 patients

Results to be published in 2018

Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

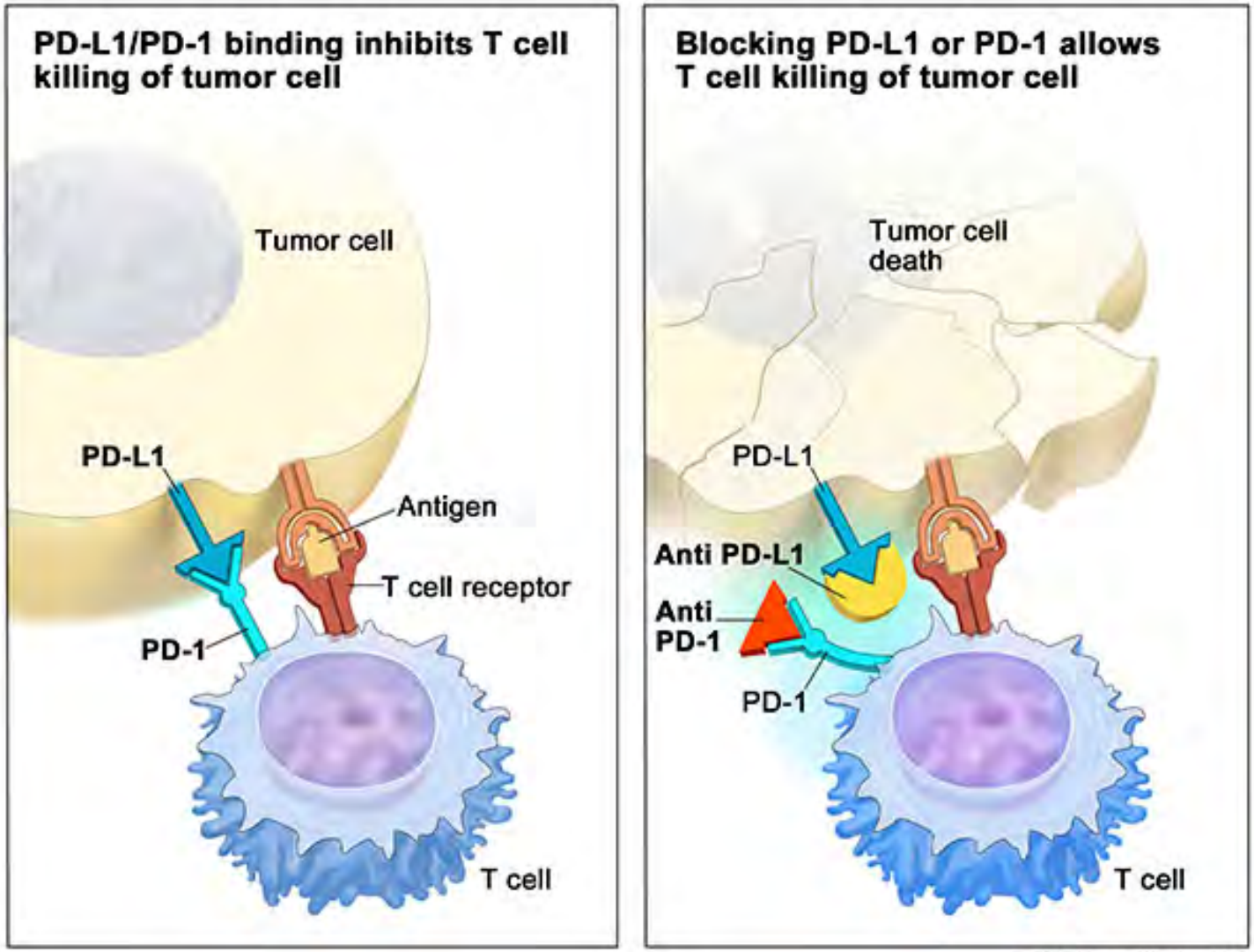
Richard S. Hotchkiss[1], Guillaume Monneret[2] and Didier Payen[3]

Restoring adaptive response



NATURE REVIEWS | IMMUNOLOGY 2013

3. Anti-PD1 / Anti-PD-L1



International Journal of
Molecular Sciences

MDPI

Review

Targeting Immune Cell Checkpoints during Sepsis

Naeem K. Patil [1,*], Yin Guo [1], Liming Luan [1] and Edward R. Sherwood [1,2]

Table 2. Summary of clinical studies showing alterations in expression of various immune checkpoints during sepsis.

Reference	Sample Size	Alterations in Expression of Immune Checkpoints	Any Other Major Clinical Findings
Guignant et al., 2011 [43]	64 Patients, prospective study	Increased PD-1 and PD-L1 on $CD4^+$ T cells, and higher PD-L1/PD-L2 on monocytes	- Impaired lymphocyte proliferation - Findings correlated with increased nosocomial infections and mortality
Zhang et al., 2011 [44]	19 Patients, prospective study	Increased PD-1 and $CD4^+$ and $CD8^+$ T cells, and higher PD-L1 on monocytes	- Increased T and B lymphocytes apoptosis
Boomer et al., 2011 [23]	Postmortem study, 40 patients	• Increased PD-1 on CD4+ and CD8+ on splenic T cells • Increased PD-L1 and HVEM on lung tissue • Increased PD-L1/PD-L2 on splenic dendritic cells	- Depletion of $CD4^+$ and $CD8^+$ and HLA-DR+ cells in spleen and lung - Decreased IL-7 receptor alpha on splenic T cells
Boomer et al., 2012 [57]	24 Patients, prospective study	• Increased PD-L1 on splenic dendritic cells, and CTLA-4 on $CD4^+$, $CD8^+$ T cells • Increased TIM-3, LAG-3 on splenic $CD4^+$ T cells	Impaired splenic T cell function (as measured by decreased IFN-γ production upon ex vivo stimulation of cells)
Shubin et al., 2013 [58]	24 Patients, prospective study	Increased BTLA on circulating $CD4^+$ T cells	Increased BTLA correlated with increased mortality
Yang et al., 2013 [59]	26 Patients (12-sepsis,14-severe sepsis)	Increased TIM-3 mRNA in PBMC's in sepsis patients as compared to severe sepsis patients	None
Chang et al., 2014 [45]	43 Patients, Prospective study	• Increased PD-1 and decreased PD-L1 on $CD8^+$ T cells • Increased PD-L1 on monocytes	- Decreased IFN-γ and Il-12 production by CD8+ T cells upon ex vivo stimulation - Increased PD-1 expression on $CD8^+$ T cells correlated with increased rate of secondary infections
Ren et al., 2015 [60]	Prospective study; 40-sepsis and42-severe sepsis patients18-septic shock pateints	• Increased TIM-3 on monocytes of septic shock patients • Decreased plasma soluble TIM-3 levels in septic shock patients	Decreased soluble TIM-3 levels correlated with increased mortality
Patera et al., 2016 [24]	17 Pateints, prospective study	• Increased PD-L1 on suppressor neutrophils • Increased PD-1 on $CD4^+$ T cells and NK cells	- Impaired neutrophil, monocyte and NK cell function - Impaired $CD8^+$ T cell function

Nivolumab plus interferon-γ in the treatment of intractable mucormycosis

Acquired immunosuppression is an important complication of major trauma and might contribute to the development of severe fungal infections in these patients. Here, we describe a patient with extensive abdominal mucormycosis unresponsive to conventional therapy who was treated successfully with immunostimulating drugs.

A previously healthy 30-year old woman sustained pelvic and femur fractures, extensive soft-tissue abdominal and pelvic damage, pulmonary contusion, and second-degree burns in the terrorist bombing in Brussels in March, 2016. The patient's early hospital course was complicated by sepsis, femur osteomyelitis, and deep wound infections with multi-drug-resistant Enterobacteriaceae. On day 15 after admission to the intensive care unit, results of CT analysis showed gastric and splenic necrosis (figure); gastric biopsy results available on day 18 revealed invasive mucormycosis, and treatment was started with liposomal amphotericin-B and posaconazole.

Figure: Abdominal CT scan
CT scan with contrast, showing place of infarcement of splenic parenchyma (S), gas in the splenic pseudocysts (arrowhead), and gastric intramural gas (arrow)

On day 22, gastrectomy and splenectomy were done; pathology showed invasive mucormycosis in the stomach and spleen with extension into peritoneal and vascular structures, but additional debridement was not feasible. Because of the poor prognosis and immunosuppression, as shown by a low absolute lymphocyte count, low monocyte HLA-DR expression and increased expression of programmed death-1 (PD-1) on T-cells (appendix), immunoadjuvant therapy with interferon-γ (Immukine, Boehringer, Brussels, Belgium; 100 μg three times weekly for five doses) was started on day 28, followed by a single 250 mg dose of nivolumab (Opdivo, BMS, Braine l'Alleud, Belgium) on day 30. Subsequent immunological examinations showed increases in absolute lymphocyte count, monocyte HLA-DR expression, and CD8 T-cells, and decreased T-cell PD-1 expression (appendix). The patient improved slowly, and repeat CT scans showed no residual infection. The patient was discharged from the intensive care unit 80 days after admission.

This patient, with well documented fungal sepsis, showed typical features of post-aggression immunosuppression involving defective innate and adaptive immunity.[1,2] Interferon-γ and the anti-PD-1 monoclonal antibody nivolumab reversed these defects. Interferon-γ restores monocyte function and has been used as rescue therapy for life-threatening fungal infections in patients not responding to conventional treatment.[1,3] Nivolumab binds to PD-1, blocks interaction with its ligands, PD-L1 and PD-L2, and releases PD-1 pathway-mediated inhibition of T-cell proliferation and cytokine production. Anti-PD-1 has shown activity in animal models of fungal sepsis and in patients with chronic hepatitis C virus infection.[4] A phase I clinical trial of nivolumab in the treatment of severe sepsis is about to begin (NCT02960854).

Combination immunotherapy has been proposed as a possible advance in sepsis treatment.[5] To our knowledge, this is the first report showing efficacy of such an approach in a patient with life-threatening fungal infection unresponsive to conventional therapy.

FGI has research support funding from Bristol Myers Squibb, the maker of nivolumab, and is also doing clinical trials with anti-PD-L1, an immunotherapy drug made by Bristol Myers Squibb, for sepsis. All other authors declare no competing interests. The patient provided consent for publication of this letter.

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1 Netea MG, Joosten LA, van der Meer JW, Kullberg BJ, van de Veerdonk FL. Immune defence against Candida fungal infections. *Nat Rev Immunol* 2015; **15**: 630–42.
2 Kullberg BJ, van de Veerdonk F, Netea MG. Immunotherapy: a potential adjunctive treatment for fungal infection. *Curr Opin Infect Dis* 2014; **27**: 515–16.
3 Delsing CE, Gresnigt MS, Leentjens J, et al. Interferon-gamma as adjunctive immunotherapy for invasive fungal infections: a case series. *BMC Infect Dis* 2014; **14**: 166.
4 Attanasio J, Wherry EJ. Costimulatory and coinhibitory receptor pathways in infectious disease. *Immunity* 2016; **44**: 1052–68.
5 Hotchkiss RS, Opal S. Immunotherapy for sepsis—a new approach against an ancient foe. *N Engl J Med* 2010; **363**: 87–89.

Early ICU course:

- Acute Lung Injury
- Osteomyelitis
- Deep wound infection
- MDR enterobacteria
- Mucormycosis

Low levels of mHLA-DR
High levels of PD1 on Tcells

Immunkin (IFNg)
Nivolumab (anti PD-1)

THE LANCET
Infectious Diseases

Current trials

ANTI PD-1 / ANTI-PD-L1

Two Phase 1b/2a, randomized, double-blinded, placebo-controlled, multicenter study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics:

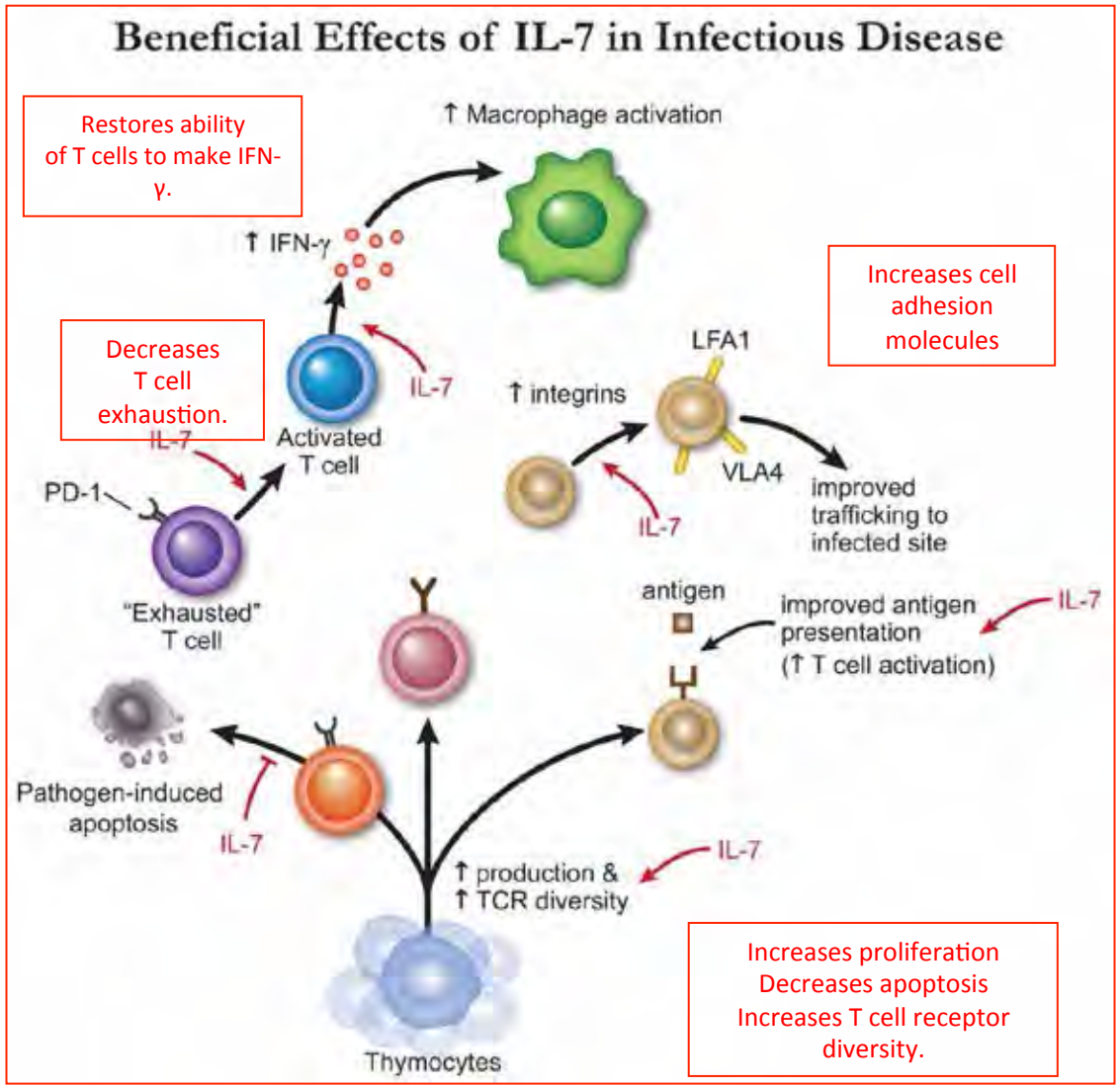
- Nivolumab (anti-PD1, NCT02960854)
- BMS-936559 (anti-PD-L1, NCT02576457)

Next trial in preparation : PD-1 (international multicenter, randomized trial)

4. 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.

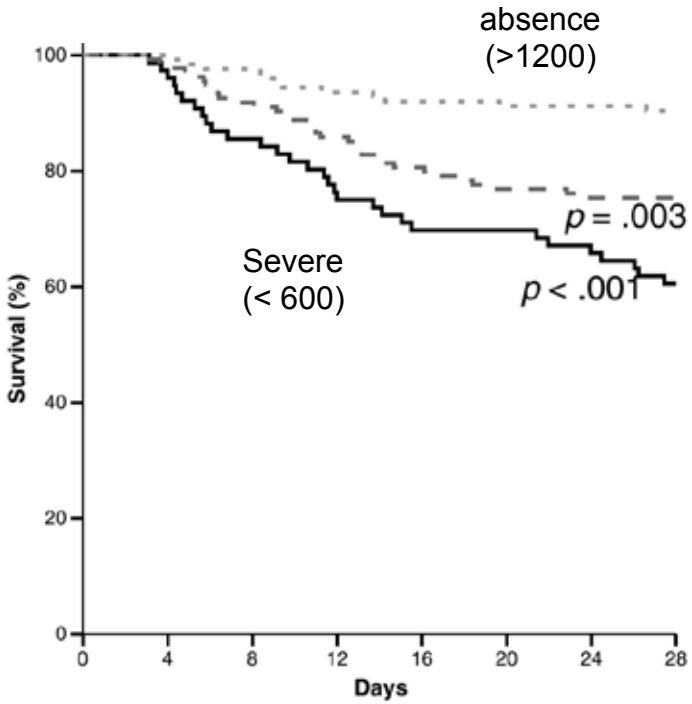


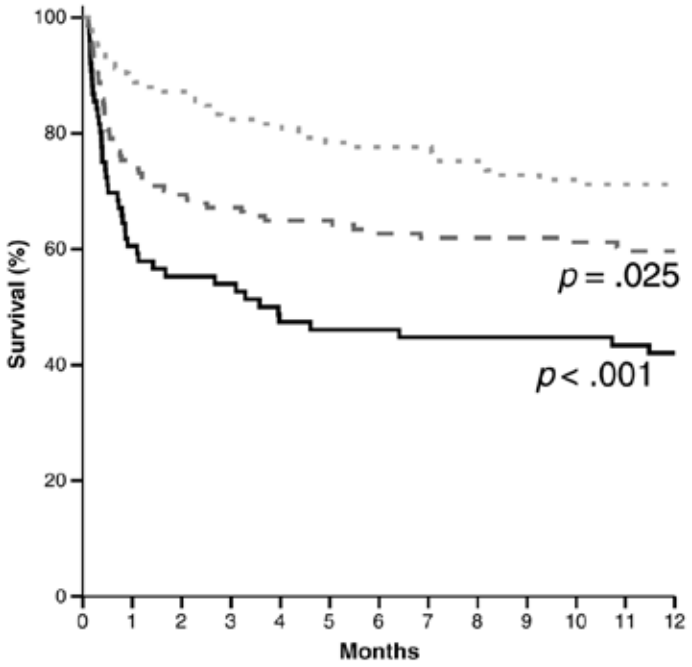
Trends in Molecular Medicine, April 2014, Vol. 20, No. 4

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

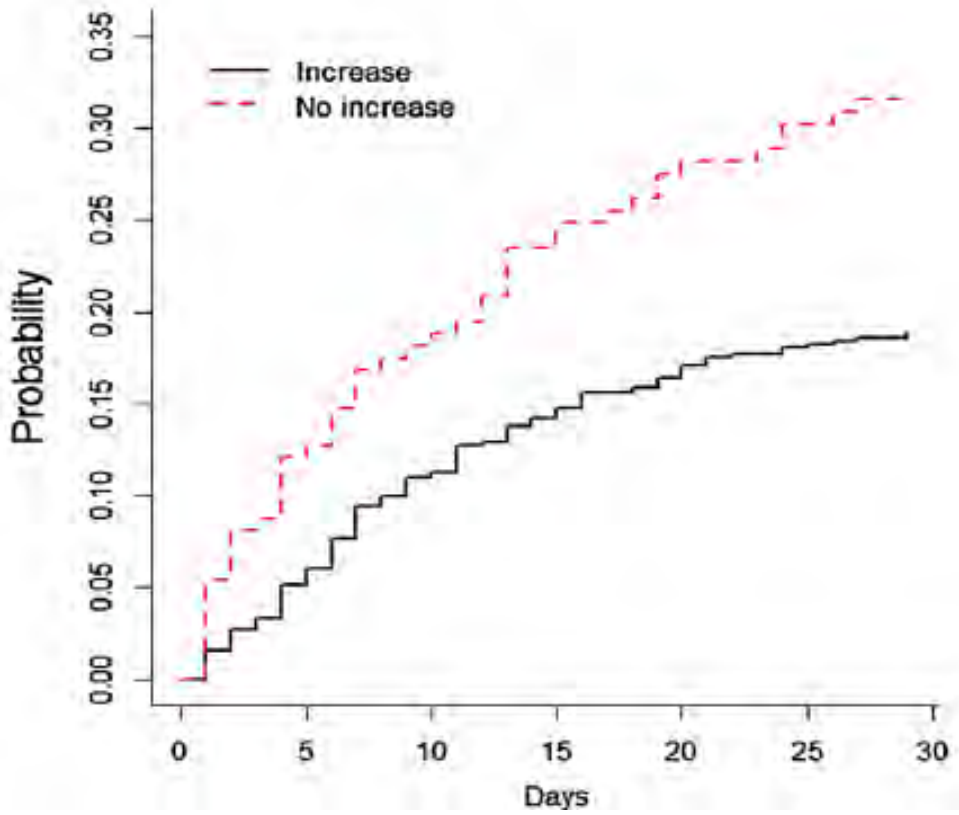




SHOCK, Vol. 42, No. 5, pp. 383–391, 2014

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

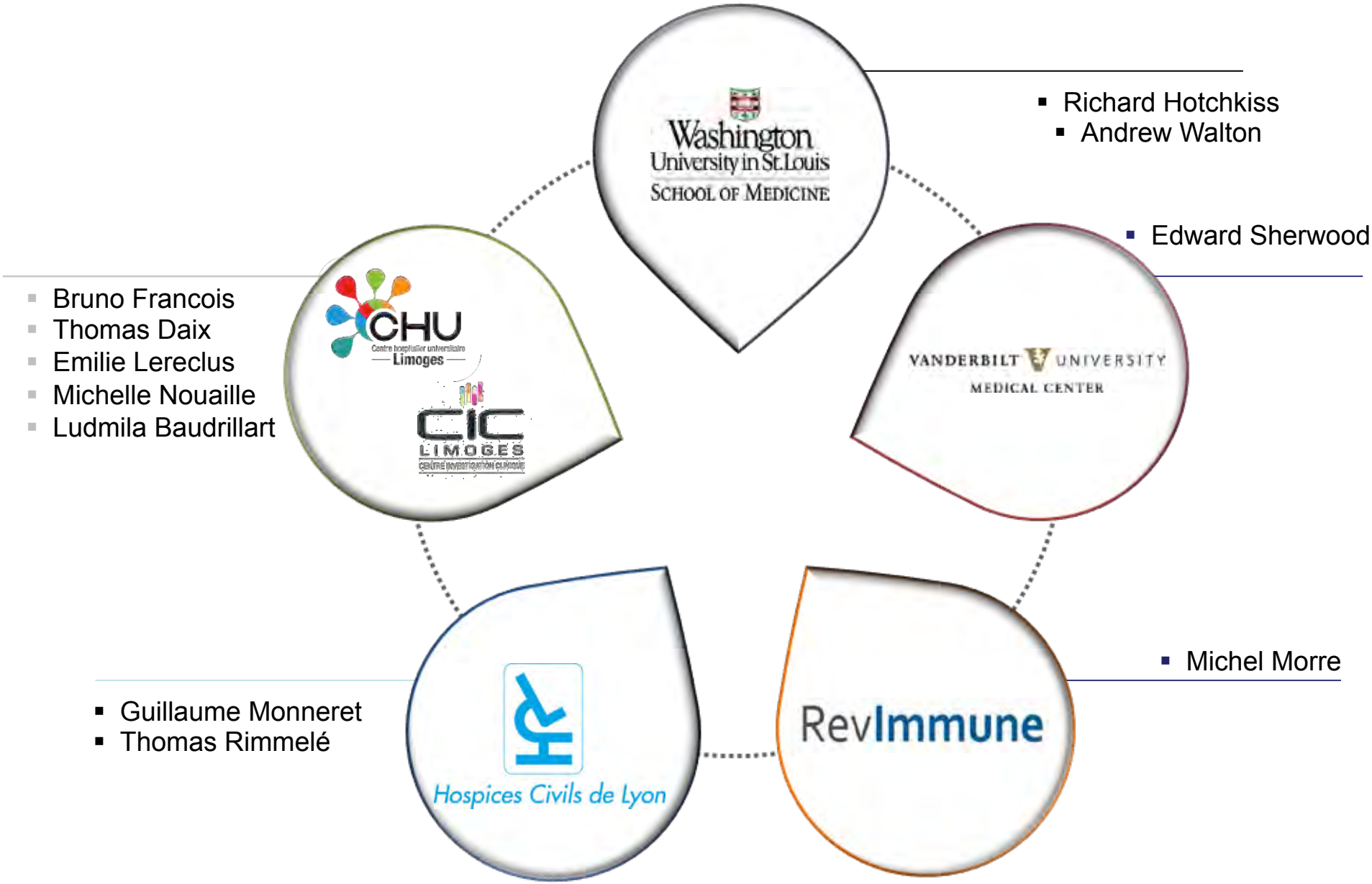
Ly increase between baseline and day 3



Annals of Intensive Care

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

The IRIS trial (to be submitted)



- Richard Hotchkiss
- Andrew Walton
- Edward Sherwood
- Bruno Francois
- Thomas Daix
- Emilie Lereclus
- Michelle Nouaille
- Ludmila Baudrillart
- Michel Morre
- Guillaume Monneret
- Thomas Rimmelé

Immunostimulation (summary)

- Preclinical results in sepsis : +++

- Several clinical cases : +++

- First trials promising (no adverse “cytokine storm”)

- GRID (GM-CSF) & IRIS (IL-7) : to be published in 2018

- Anti-PD-1 : to be started in 2018

=> Awaiting good news from multicenter RCT

CANCER IMMUNOLOGY

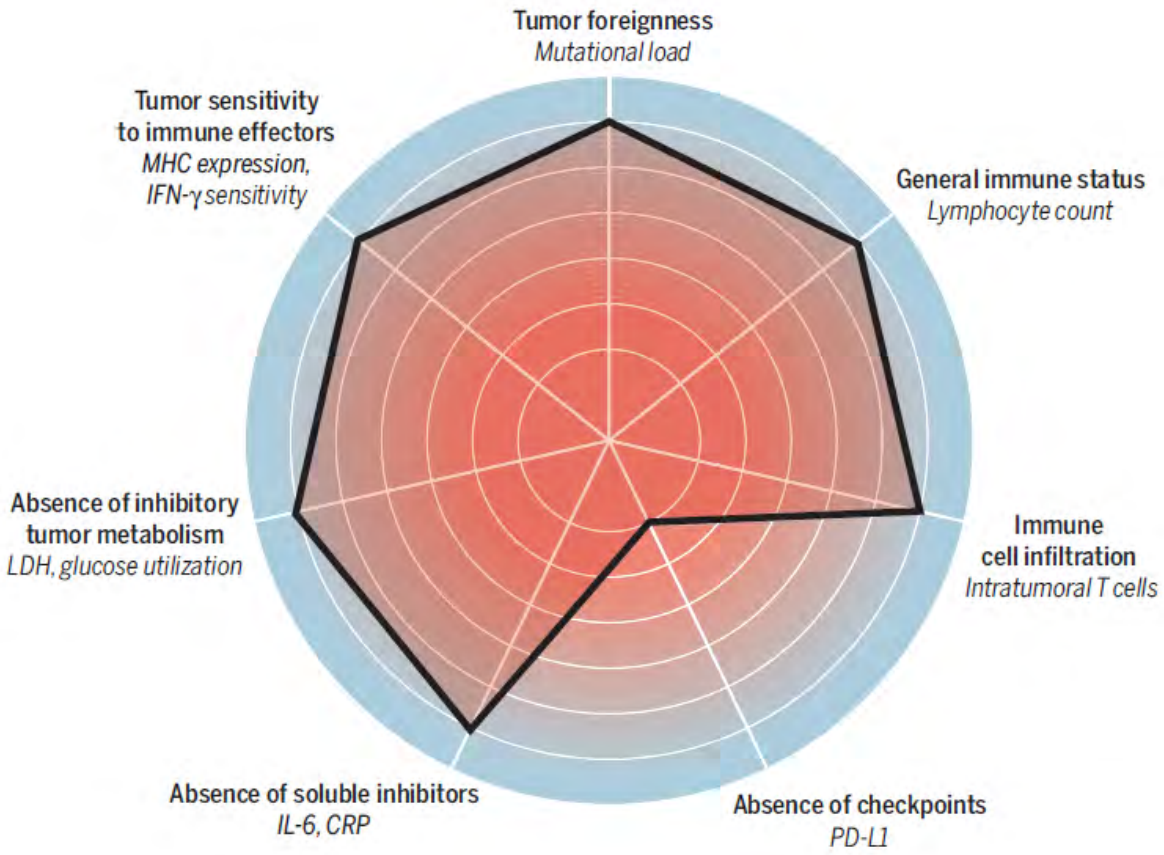
The "cancer immunogram"

Visualizing the state of cancer–immune system interactions may spur personalized therapy

By **Christian U. Blank,[1,2] John B. Haanen,[1,2] Antoni Ribas,[3] Ton N. Schumacher[2]**

Science
2016
AAAS

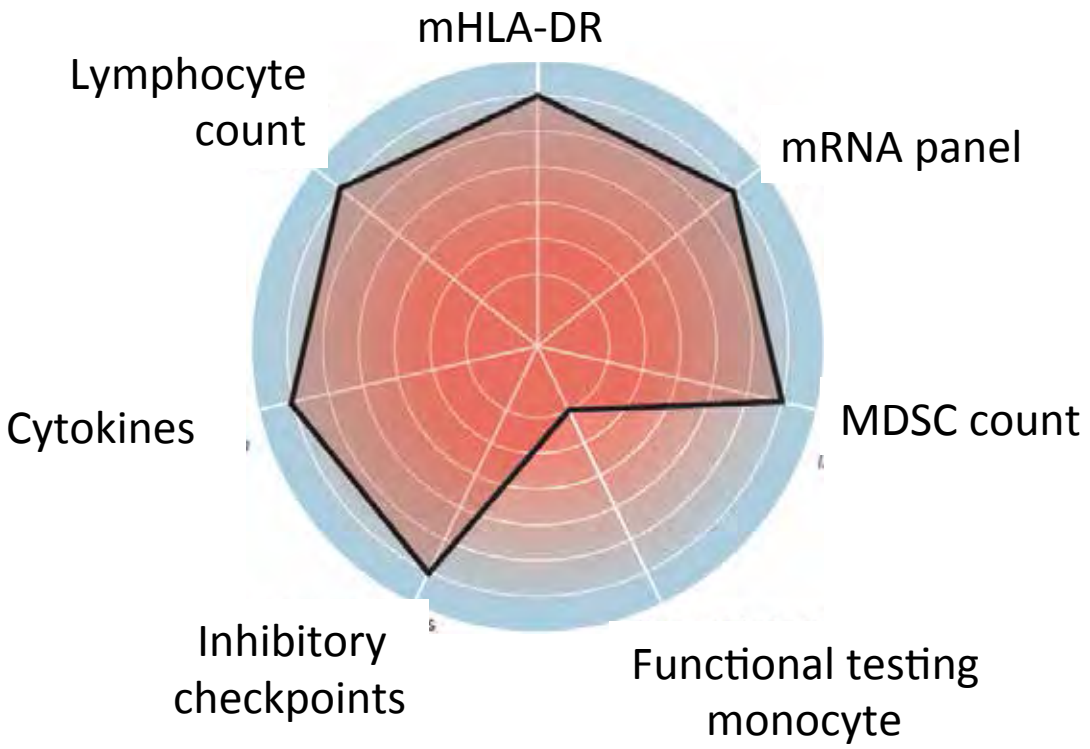
"Seven parameter classes may constitute a reasonable initial framework for building such an immunogram..."



"...a cancer immunogram... does make it possible to... discuss treatment options in a more refined and personalized manner..."

The future? => The « sepsis immunogram »

*"...a **sepsis** immunogram... does make it possible to... discuss treatment options in a more refined and personalized manner..."*



(meningococcemia ≠ immunosenescence ≠ diabetes)
+ impact of biotherapies

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