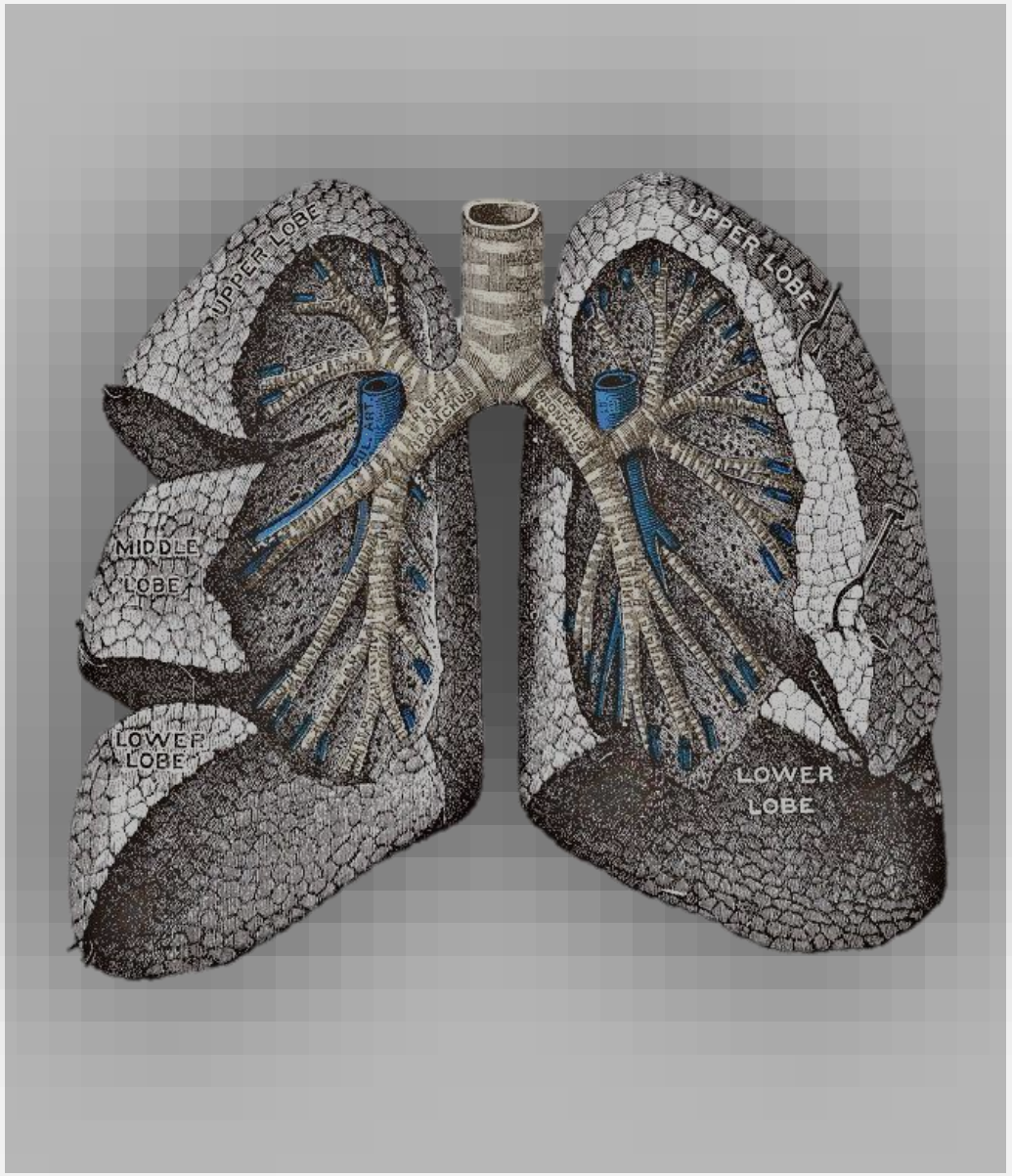


Le système immunitaire, un nouvel organe à monitorer en réanimation ?

Renaud Prével
Médecine Intensive Réanimation

Journées d'Anesthésie
Réanimation Chirurgicale d'Aquitaine

Vendredi 17 novembre 2023

Inserm

Bronchial Remodeling

CHU BDX

Conflits d’intérêt financiers

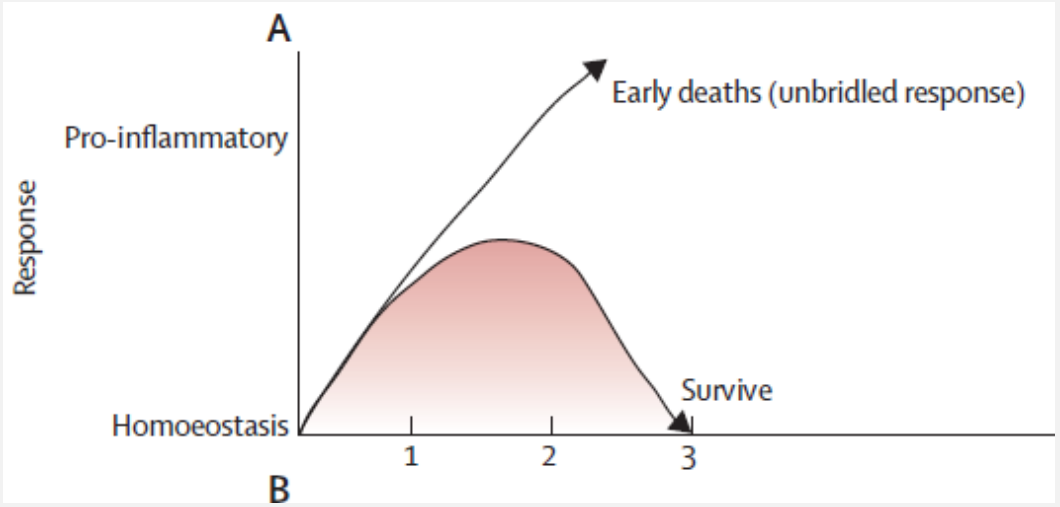
- CSL-Behring : bourse de recherche NETs et COVID
- Gilead : congrès SRLF Paris 2023
- GSK : congrès ERS Milan 2023

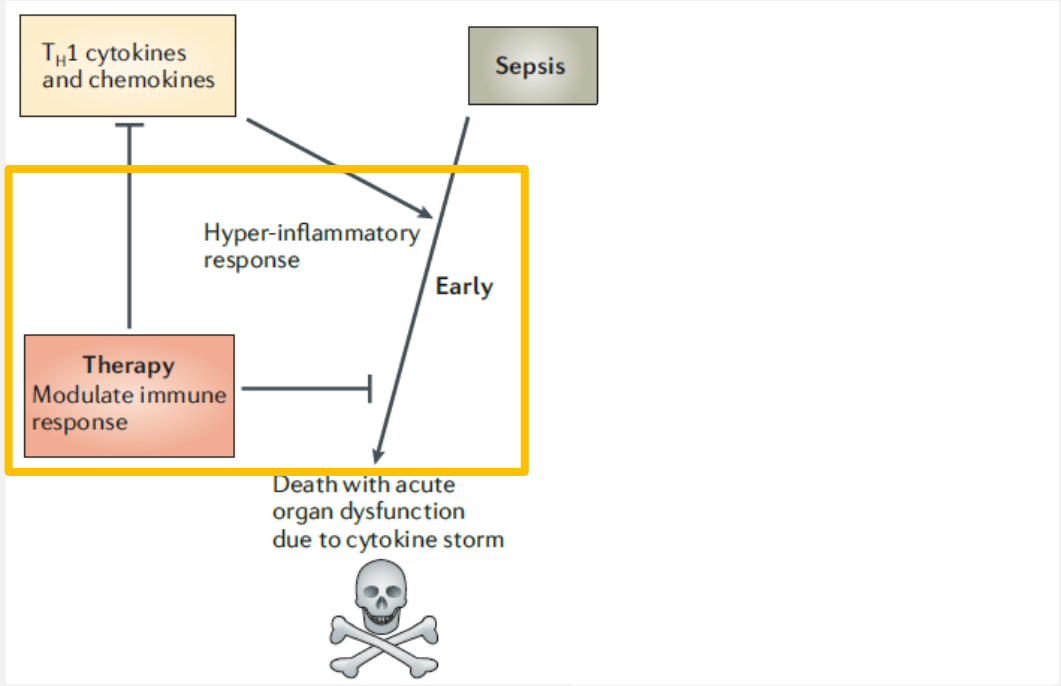
Sepsis : hyperactivation immunitaire

« What differentiates sepsis from infection is

an *aberrant or dysregulated host response*

and the presence of *organ dysfunction*. »



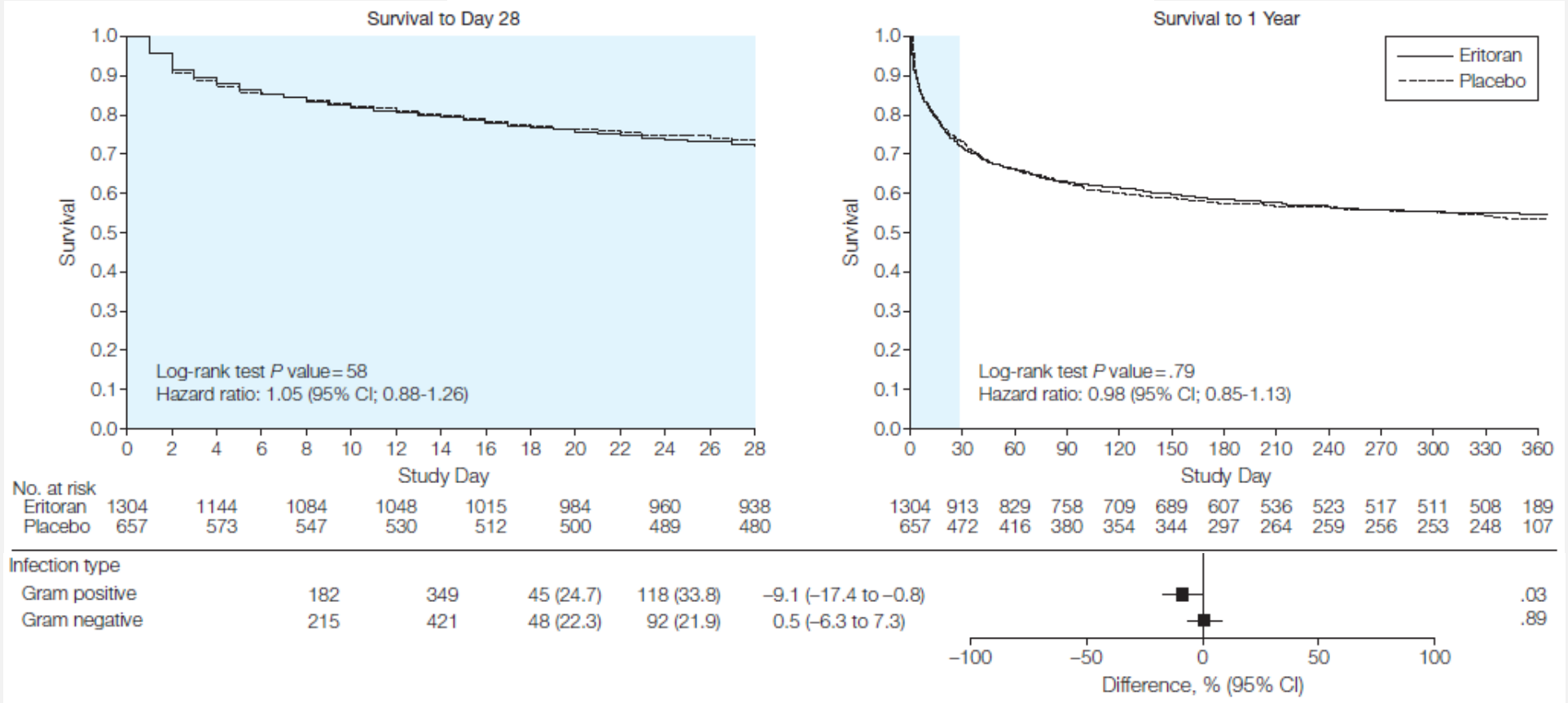


Singer *et al.*, JAMA 2016
Hotchkiss *et al.*, Lancet Infect Dis 2013
Hotchkiss *et al.*, Nat Rev Immunol 2006

Immunomodulation à la phase précoce

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

The ACCESS Randomized Trial

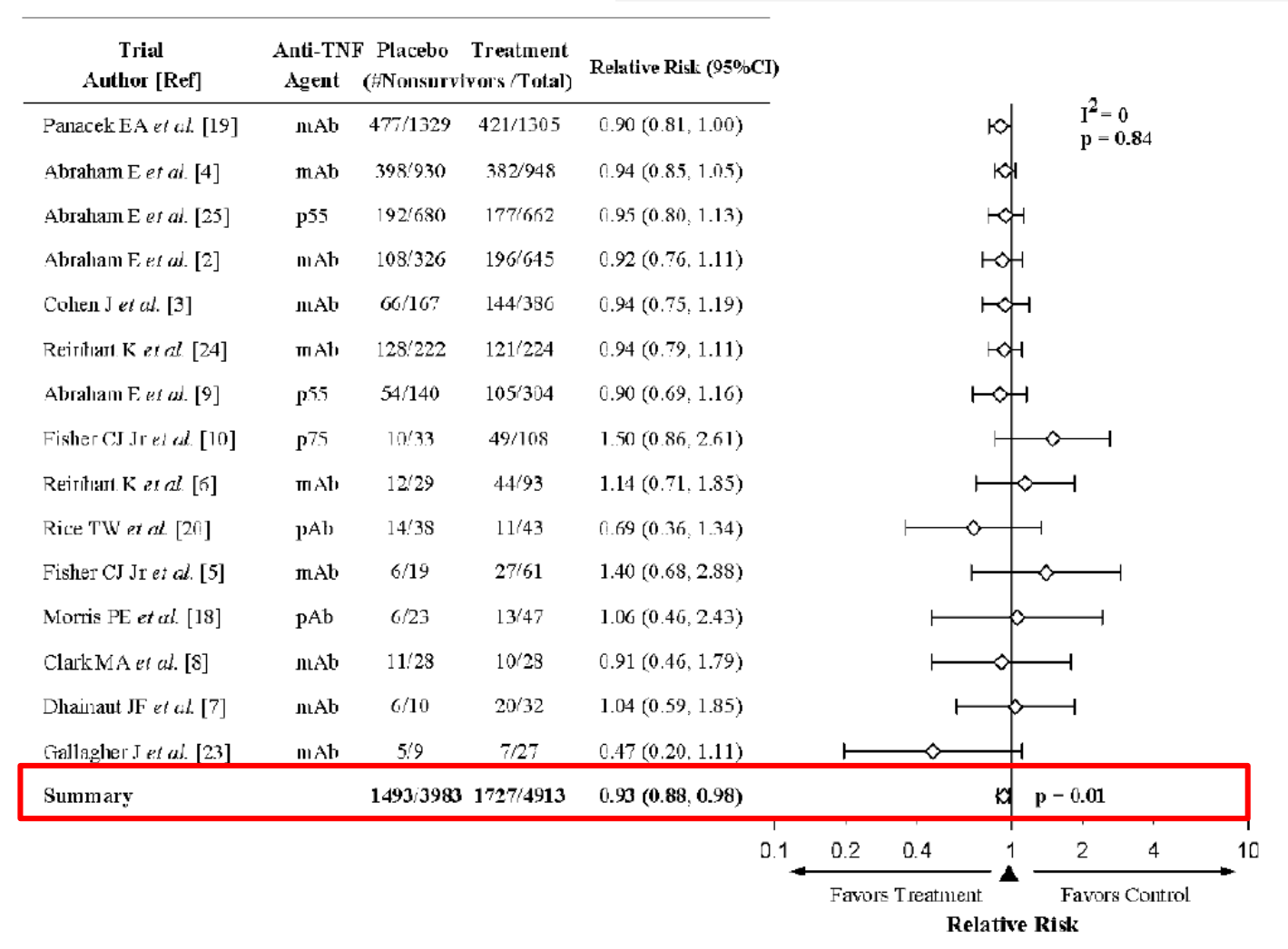


Opal *et al.*, JAMA 2013

Immunomodulation à la phase précoce

Anti-Tumor Necrosis Factor Therapy is Associated with Improved Survival in Clinical Sepsis Trials: A Meta-analysis

Trial Author [Ref]	Anti-TNF Agent	Placebo (#Nonsurvivors /Total)	Treatment	Relative Risk (95%CI)
Panacek EA *et al.* [19]	mAb	477/1329	421/1305	0.90 (0.81, 1.00)
Abraham E *et al.* [4]	mAb	398/930	382/948	0.94 (0.85, 1.05)
Abraham E *et al.* [25]	p55	192/680	177/662	0.95 (0.80, 1.13)
Abraham E *et al.* [2]	mAb	108/326	196/645	0.92 (0.76, 1.11)
Cohen J *et al.* [3]	mAb	66/167	144/386	0.94 (0.75, 1.19)
Reinhart K *et al.* [24]	mAb	128/222	121/224	0.94 (0.79, 1.11)
Abraham E *et al.* [9]	p55	54/140	105/304	0.90 (0.69, 1.16)
Fisher CJ Jr *et al.* [10]	p75	10/33	49/108	1.50 (0.86, 2.61)
Reinhart K *et al.* [6]	mAb	12/29	44/93	1.14 (0.71, 1.85)
Rice TW *et al.* [20]	pAb	14/38	11/43	0.69 (0.36, 1.34)
Fisher CJ Jr *et al.* [5]	mAb	6/19	27/61	1.40 (0.68, 2.88)
Morris PE *et al.* [18]	pAb	6/23	13/47	1.06 (0.46, 2.43)
Clark MA *et al.* [8]	mAb	11/28	10/28	0.91 (0.46, 1.79)
Dhainaut JF *et al.* [7]	mAb	6/10	20/32	1.04 (0.59, 1.85)
Gallagher J *et al.* [23]	mAb	5/9	7/27	0.47 (0.20, 1.11)
Summary		**1493/3983**	**1727/4913**	**0.93 (0.88, 0.98)**



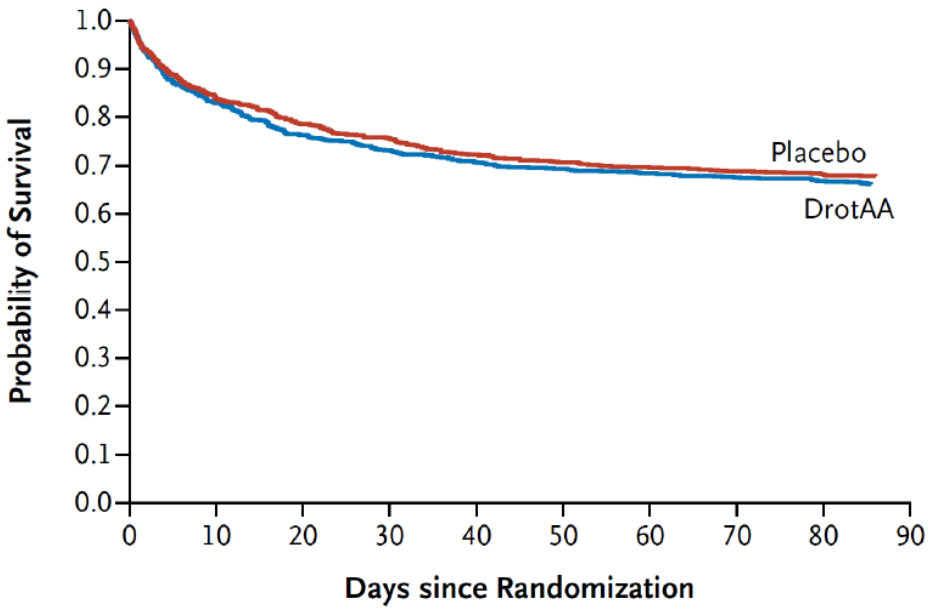
Qiu *et al.*, Crit Care Med 2013

Immunomodulation à la phase précoce

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.*, NEJM 2012

Immunomodulation à la phase précoce

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

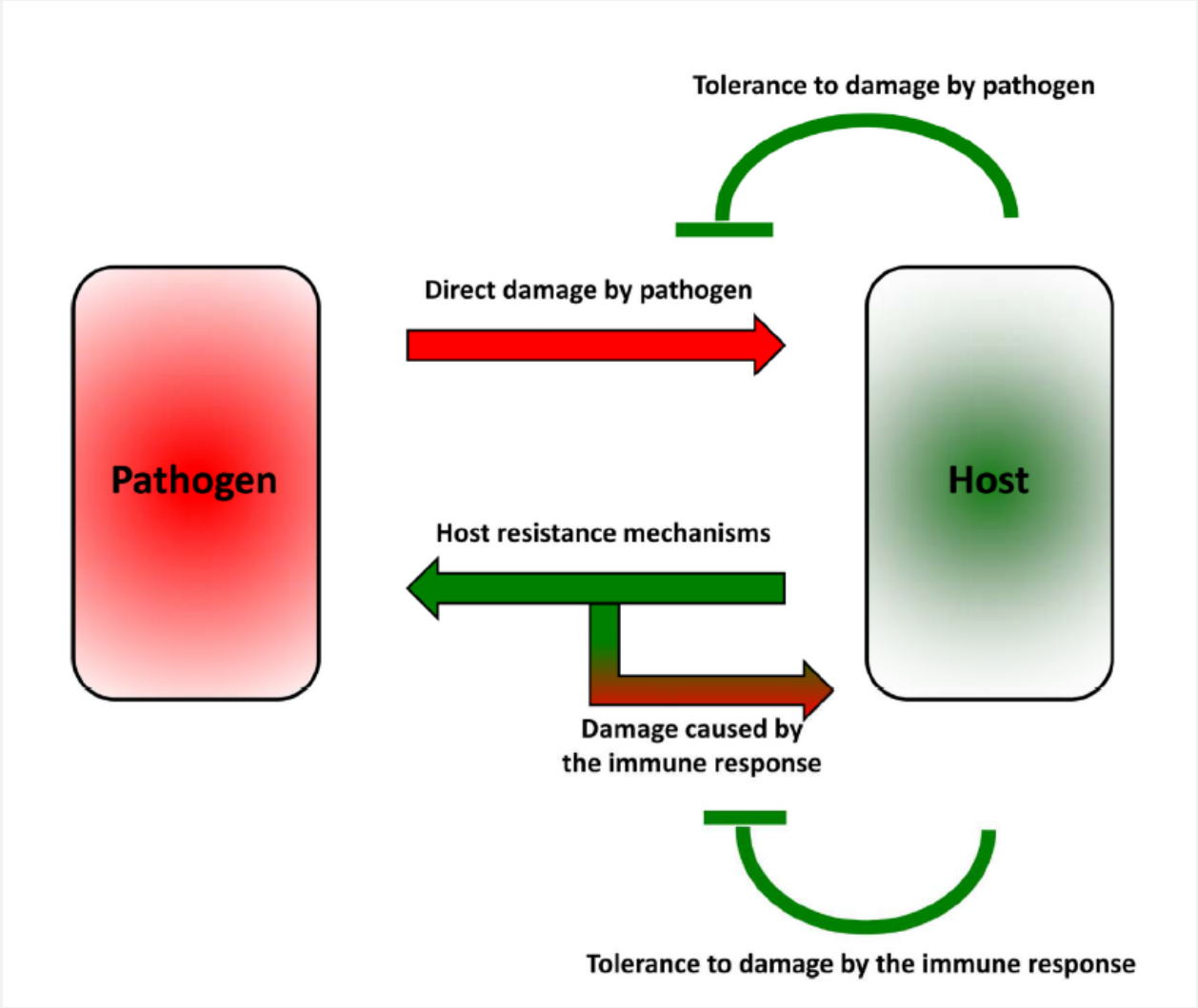
Phase précoce : le vieux débat des corticoïdes

« *We suggest **AGAINST** using IV hydrocortisone to treat septic shock patients **if adequate fluid resuscitation and vasopressor therapy** are able to **restore** hemodynamic **stability*** »

« ***If this is not achievable**, we suggest IV hydrocortisone* »

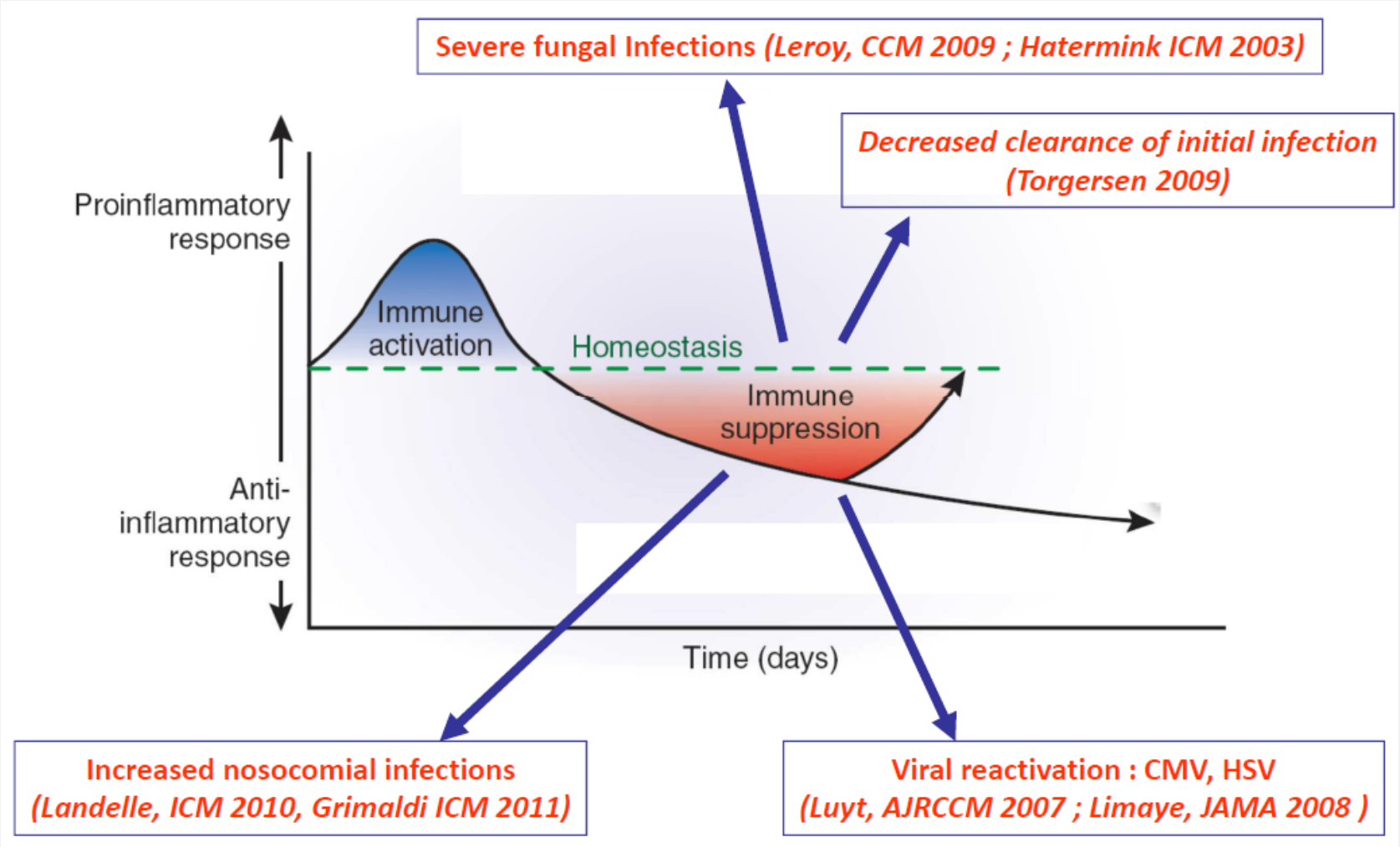
Surviving Sepsis Campaign

Immunorégulation : *host resistance vs disease tolerance*



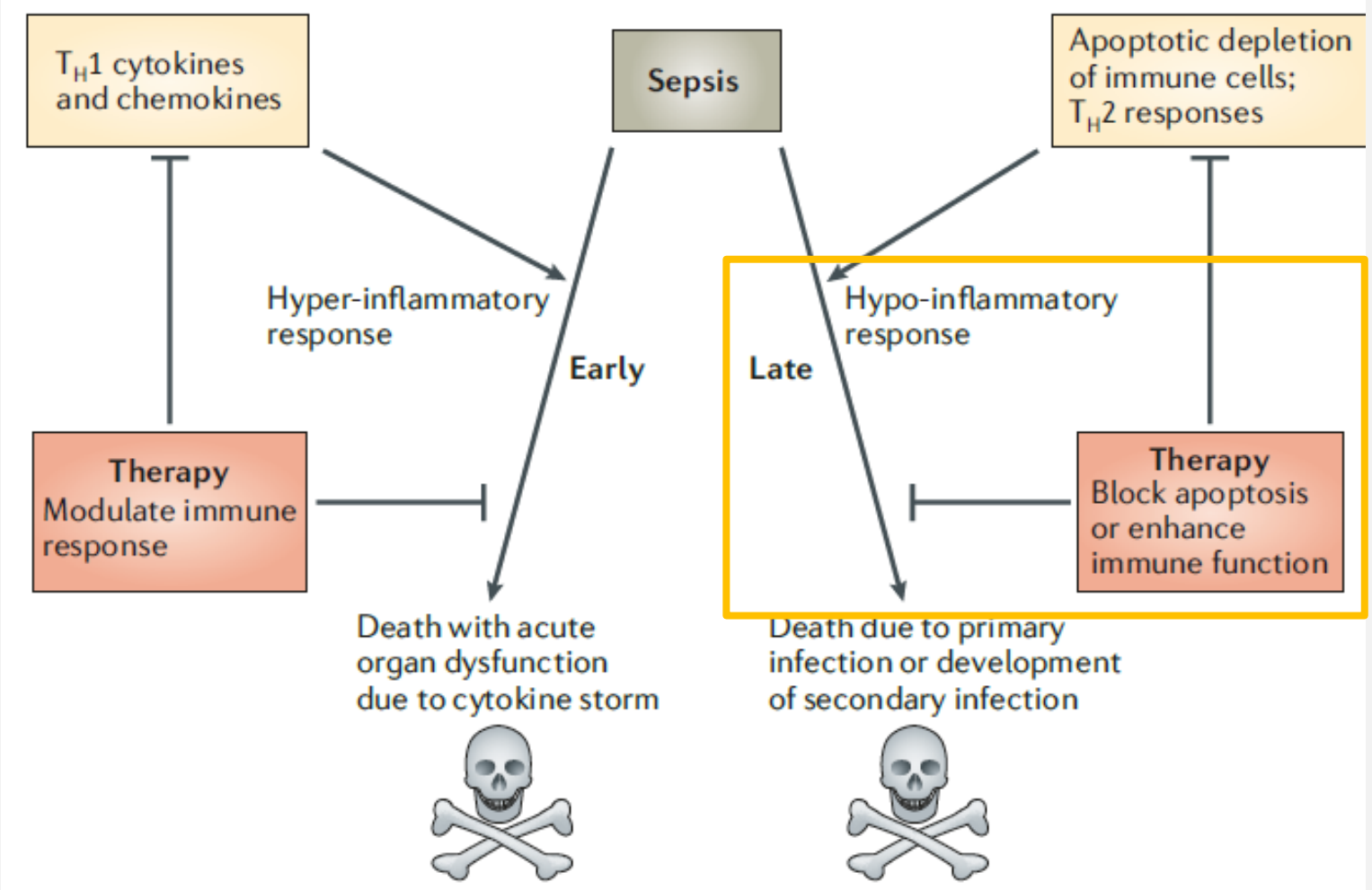
Medzhitov *et al.*, Science 2012

Immunodépression secondaire au sepsis : court terme



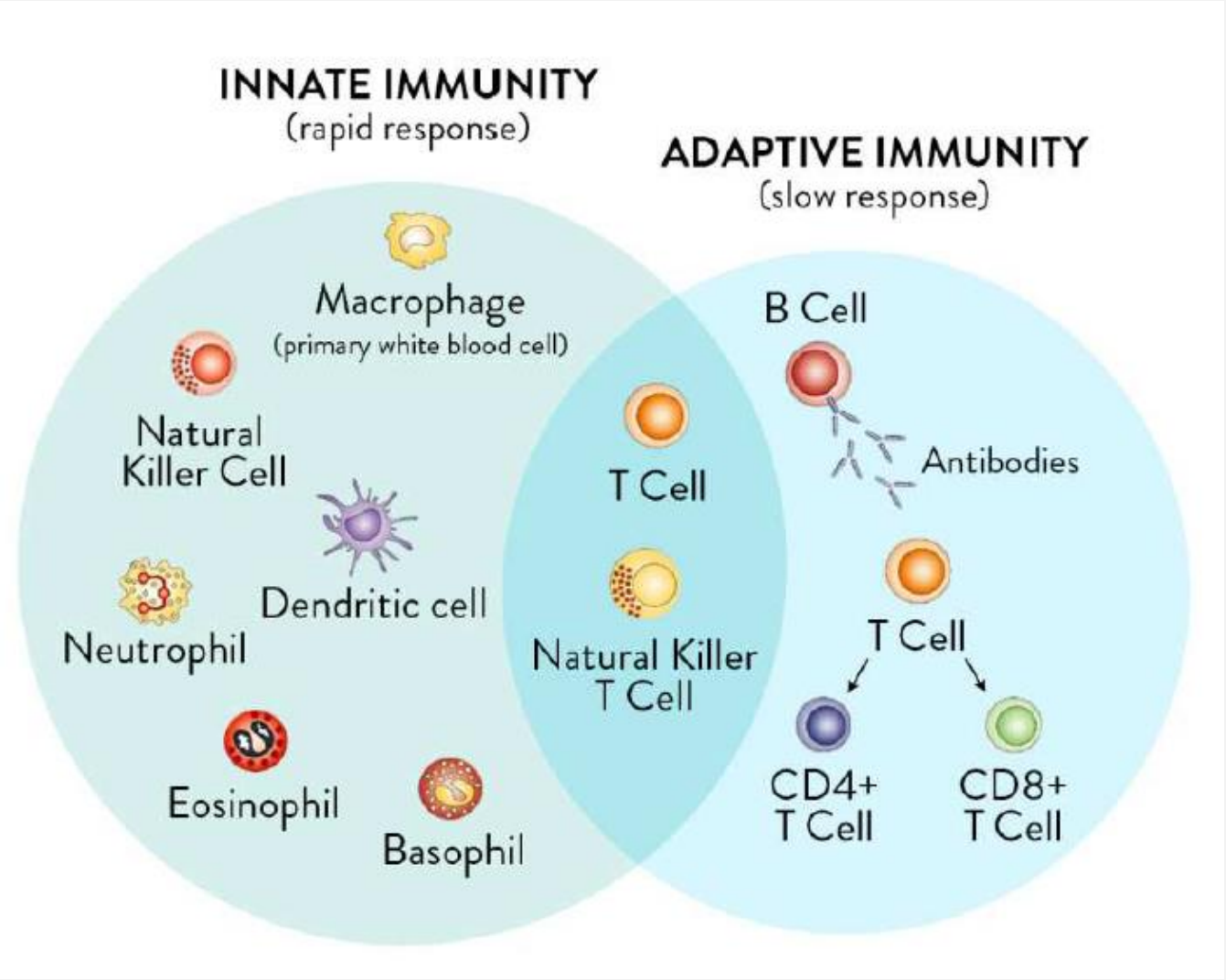
Hotchkiss *et al.*, Nat Medicine 2009

Immunodépression secondaire au sepsis

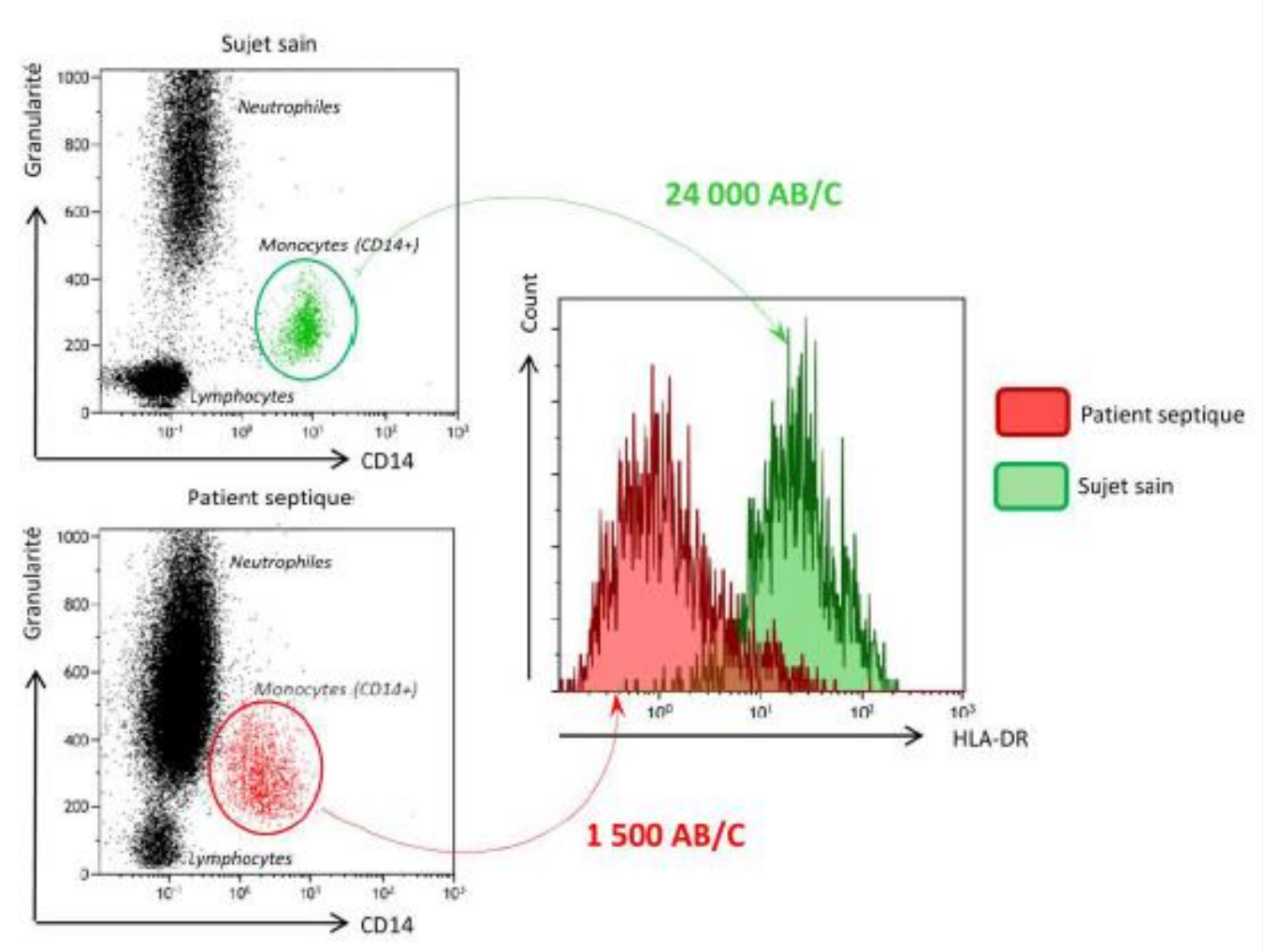


Hotchkiss *et al.*, Nat Rev Immunol 2006

Immunomonitorage : qui regarder ?



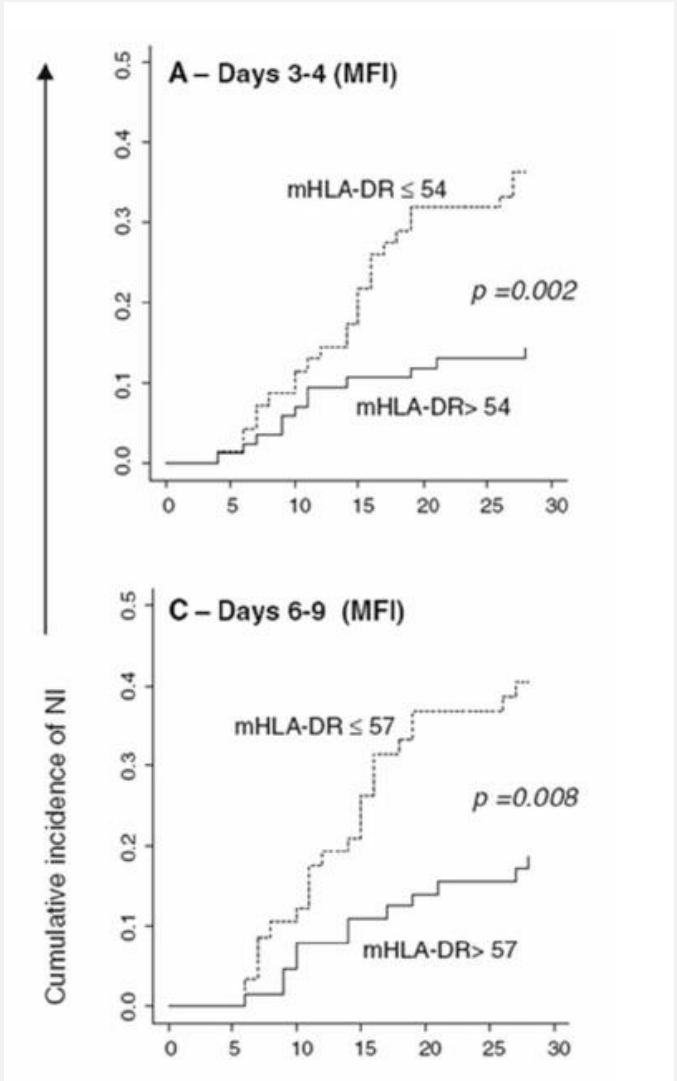
Immunomonitorage : monocytes

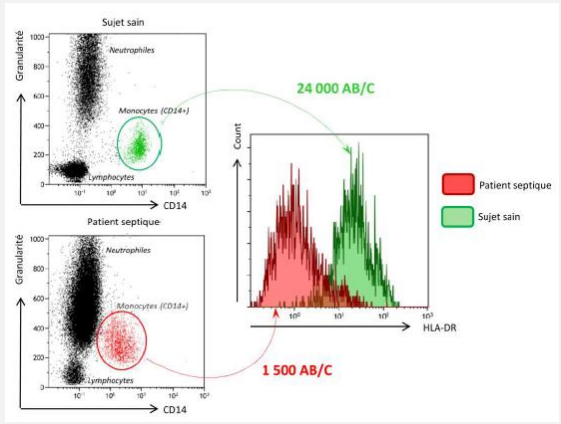


Monneret *et al*., Intensive Care Med 2006
Landelle *et al*., Intensive Care Med 2010

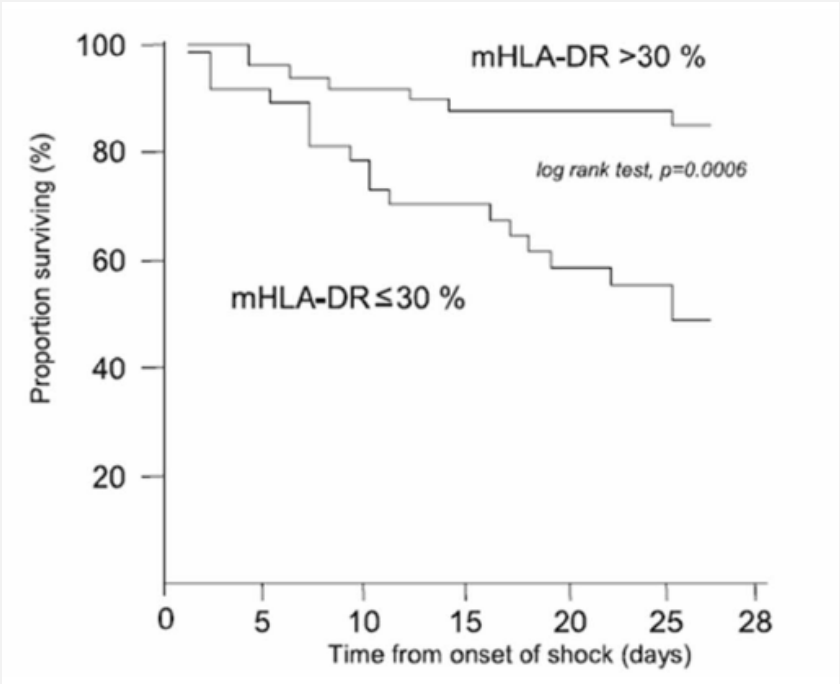
Immunomonitorage : monocytes

Survenue infections nosocomiales



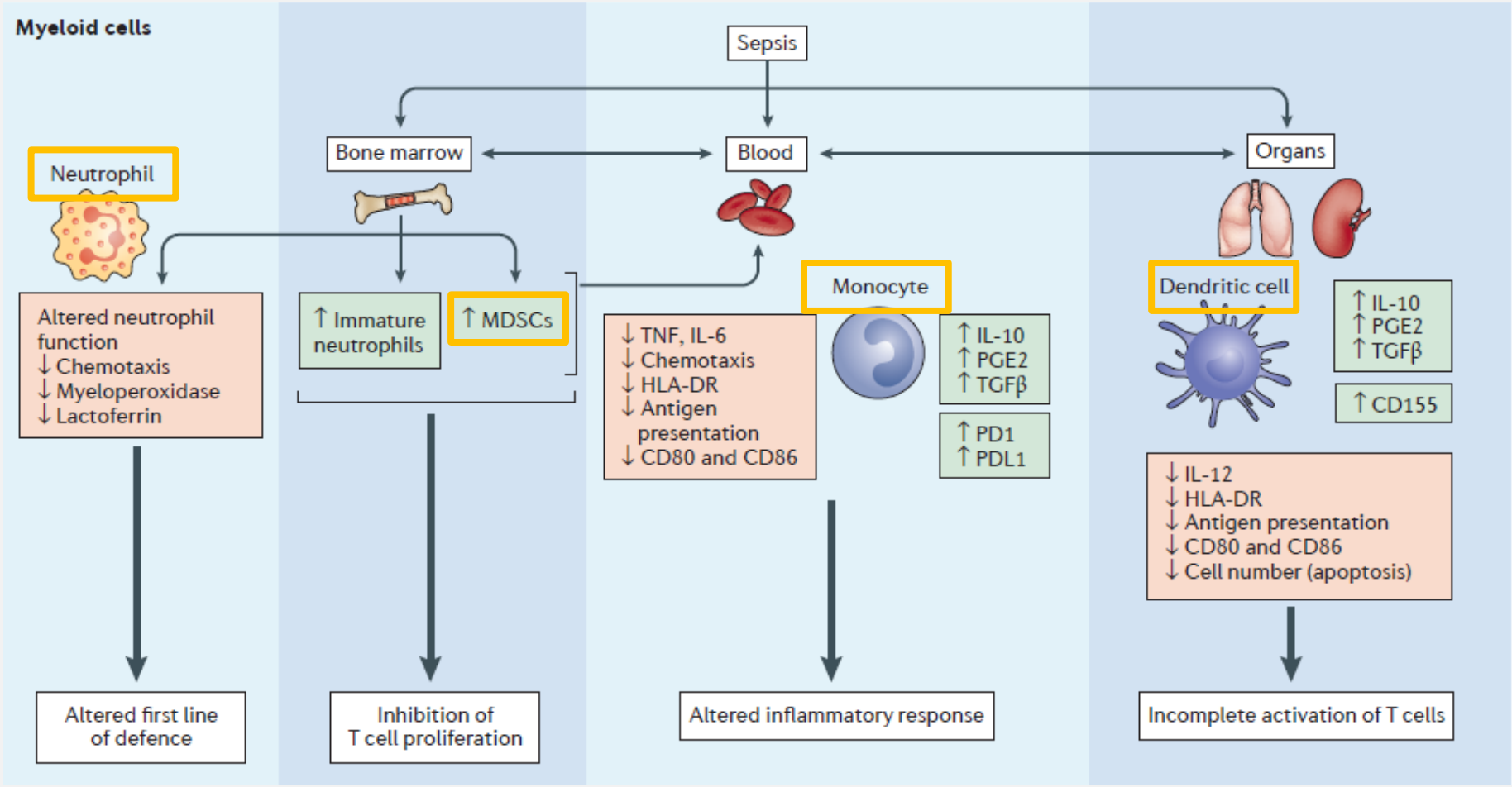


Mortalité J30



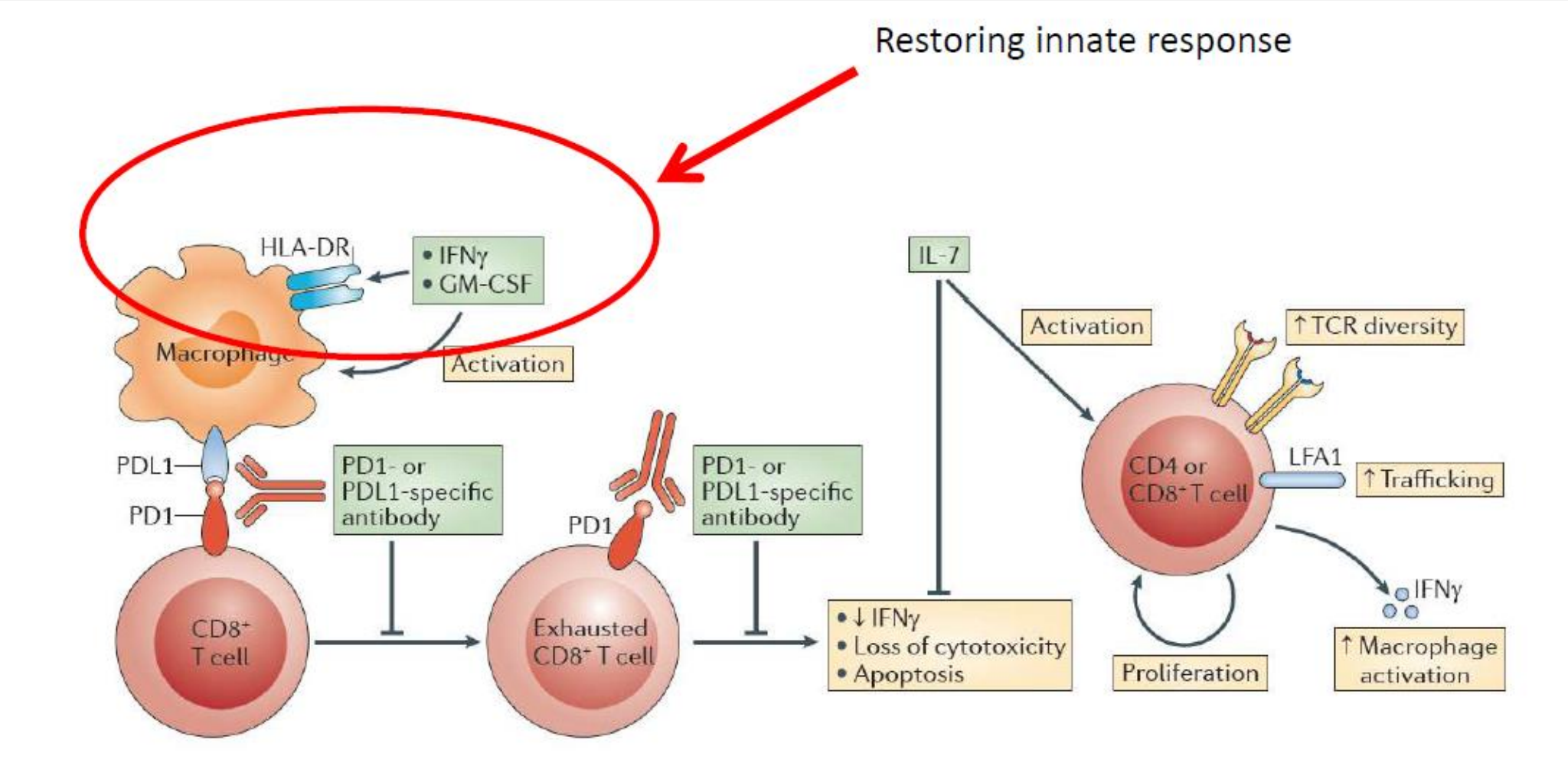
Monneret *et al.*, Intensive Care Med 2006
Landelle *et al.*, Intensive Care Med 2010

Immunomonitorage : immunité innée



Venet *et al.*, Nat Rev Nephrol 2018

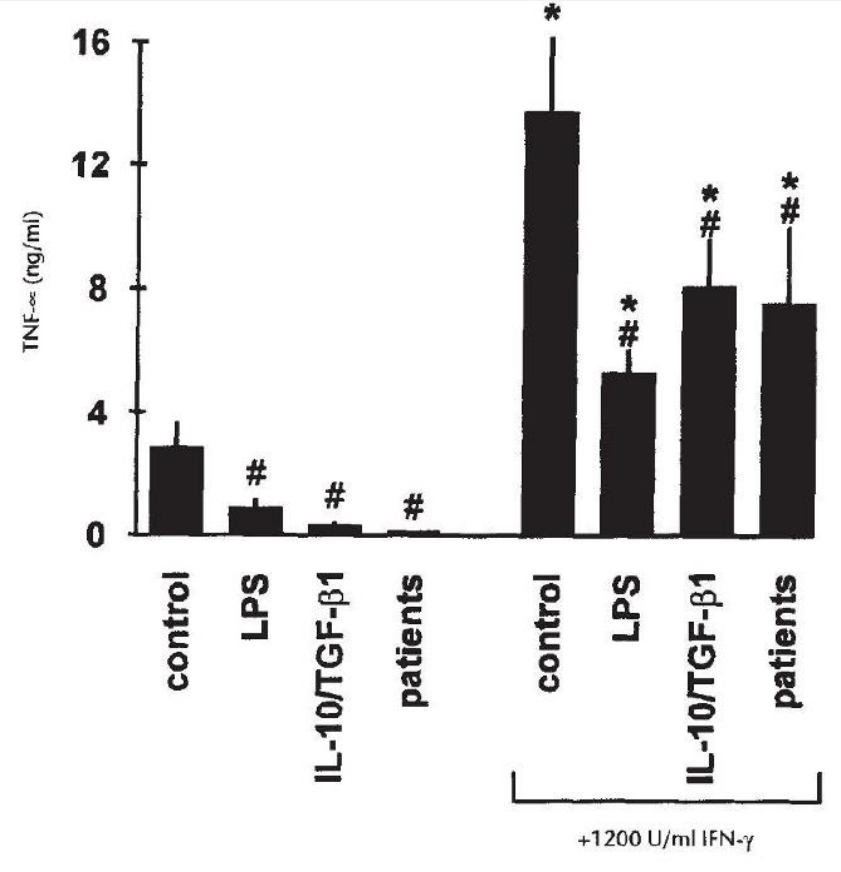
Immunomodulation : immunité innée



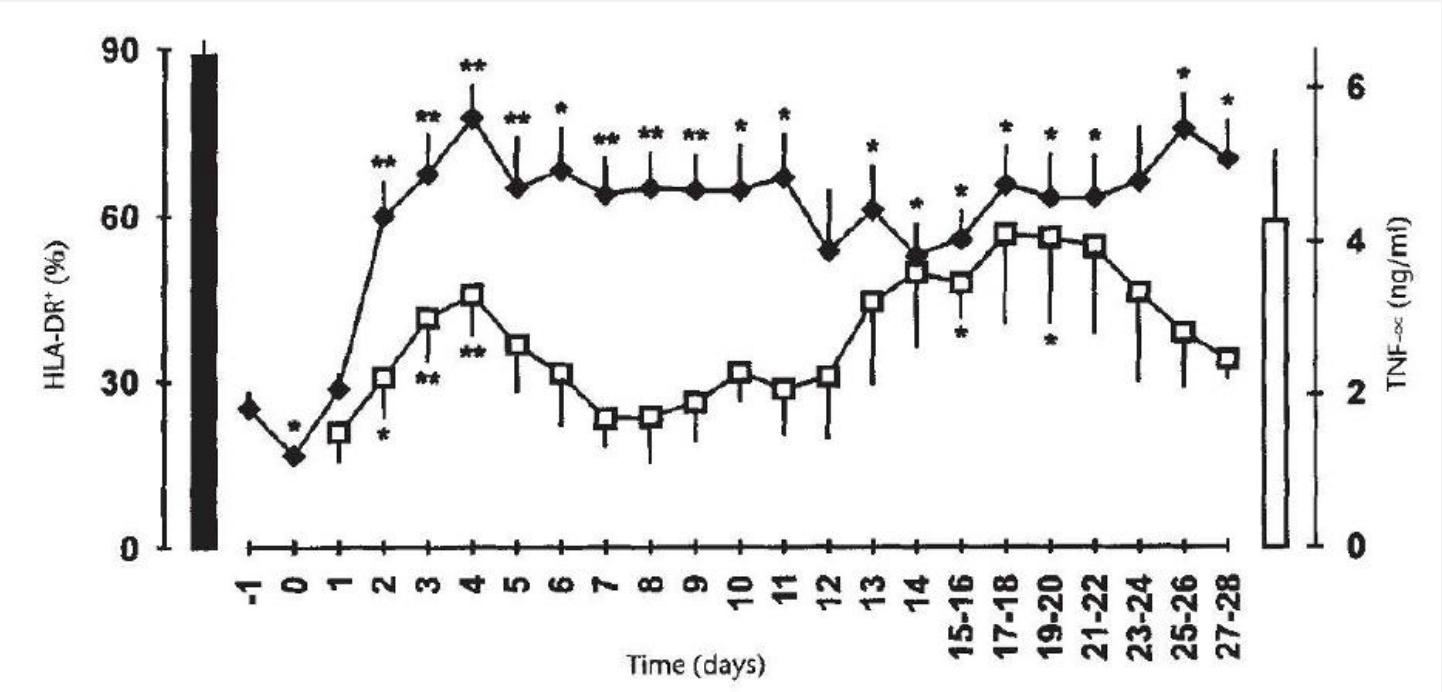
Hotchkiss *et al*., Nat Rev Immunol 2013

Immunomodulation : interféron γ

ex vivo



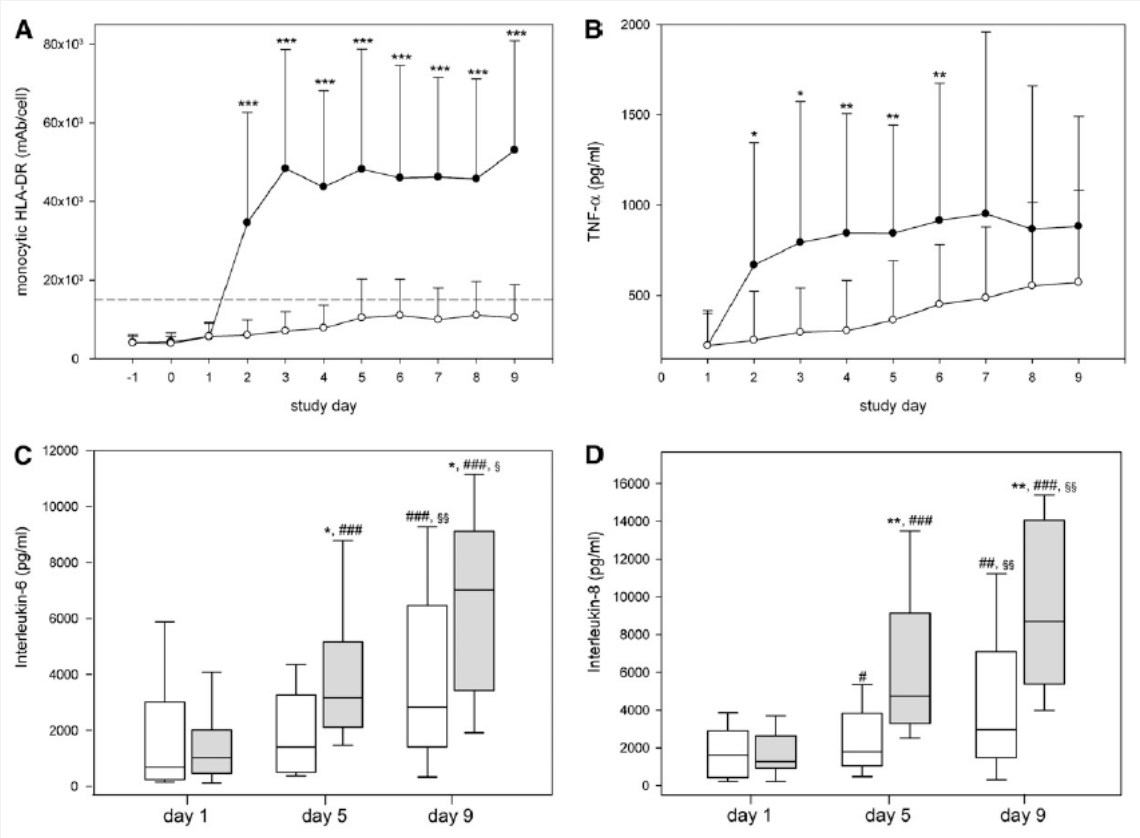
in vivo



Confirmation dans une étude sujets sains avec challenge LPS

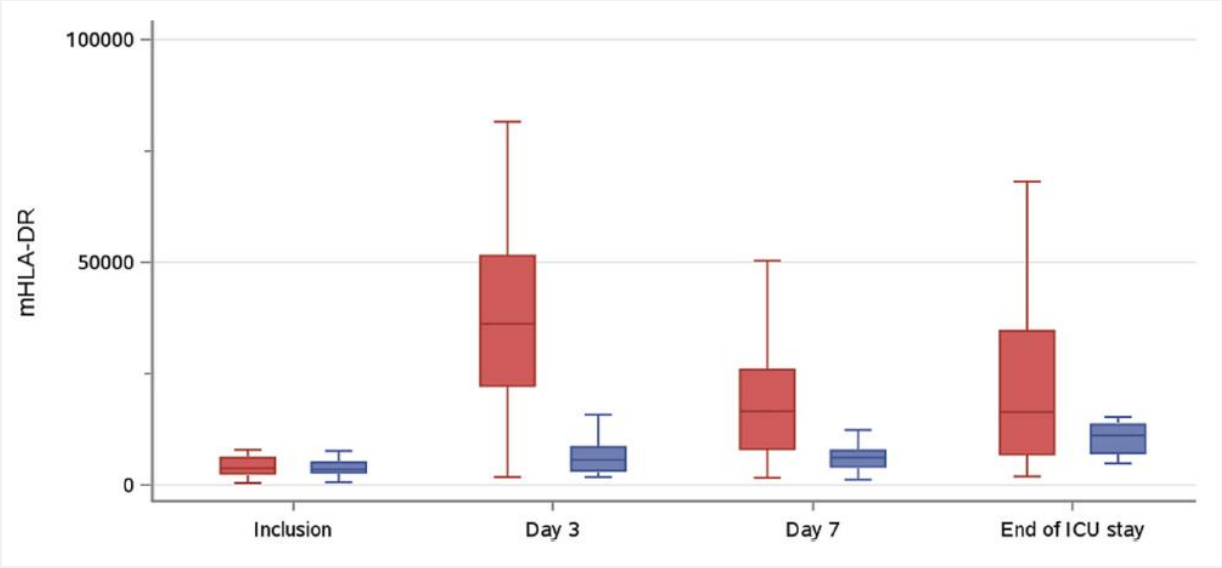
Döcke *et al*., Nat Medicine 1997
Leentjes *et al*., AJRCCM 2012

Immunomodulation : GM-CSF



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).

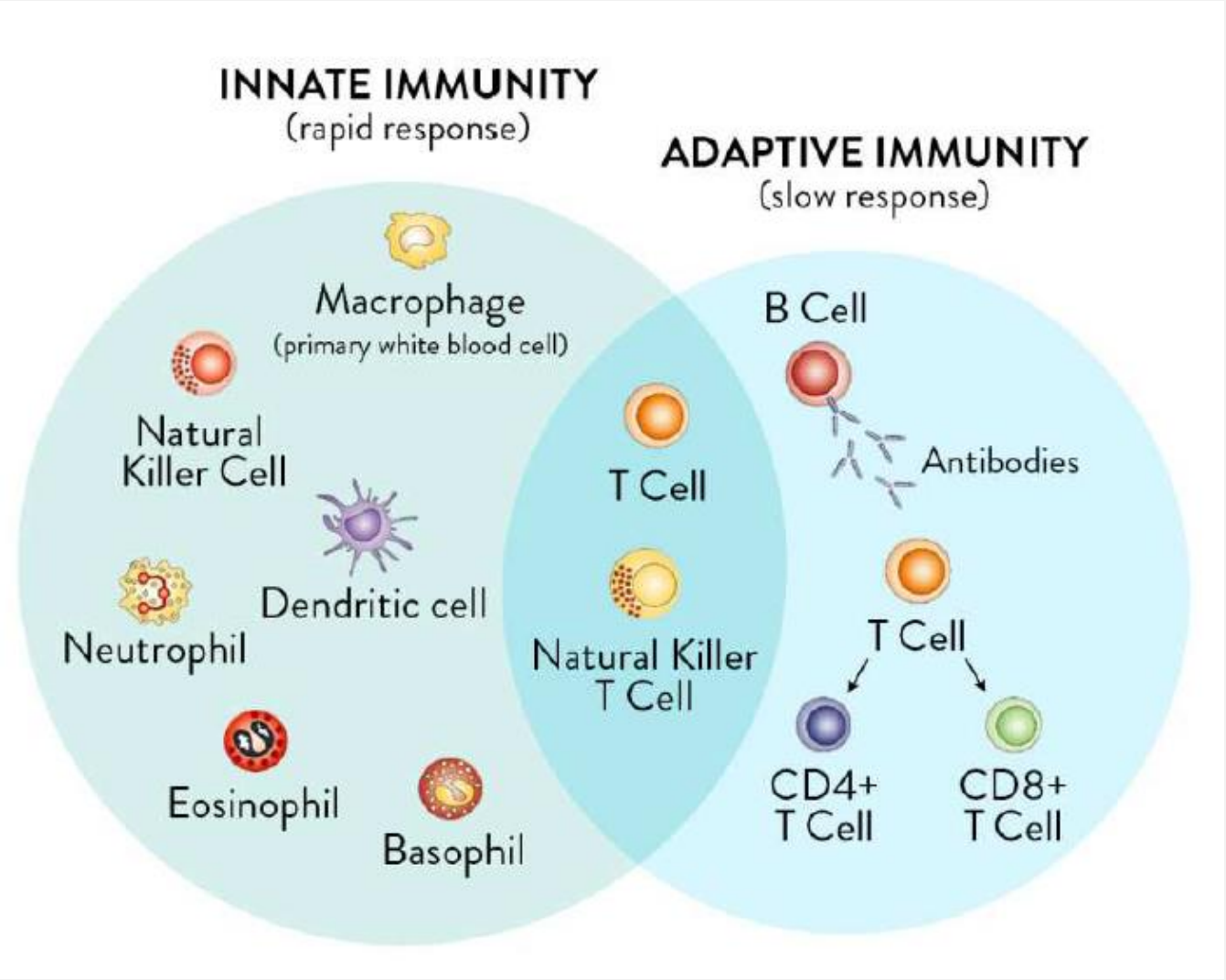


Results: The study was prematurely stopped because of insufficient recruitment. A total of 98 patients were included, 54 in the intervention group and 44 in the placebo group. The two groups were similar except for a higher body mass index and McCabe score in the intervention group. No significant difference was observed between groups regarding ICU-acquired infection (11% vs 11%, $p = 1.000$), 28-day mortality (24% vs 27%,$p = 0.900$), or the number or localization of the ICU infections.

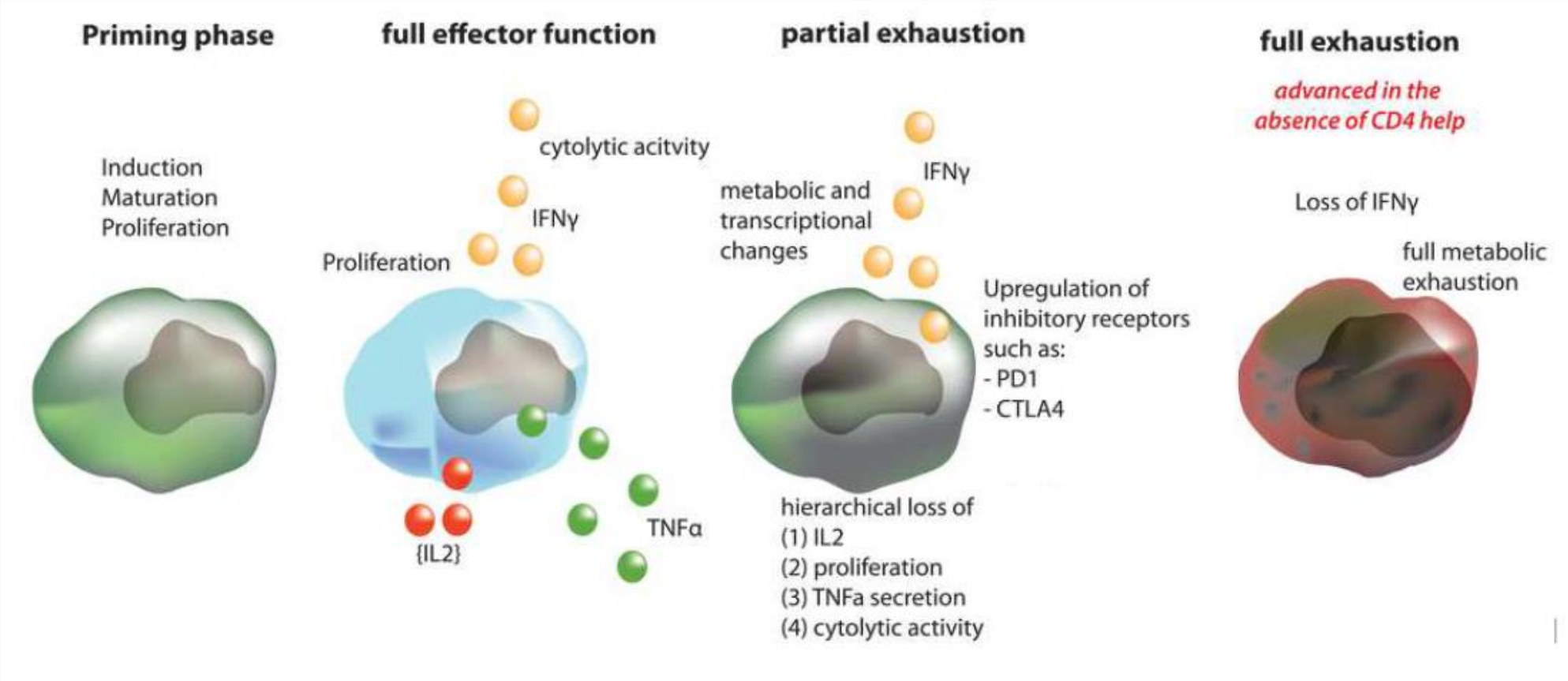
Meisel *et al.*, AJRCCM 2009

Vacheron *et al.*, J Crit Care 2023

Immunomonitorage : qui regarder ?



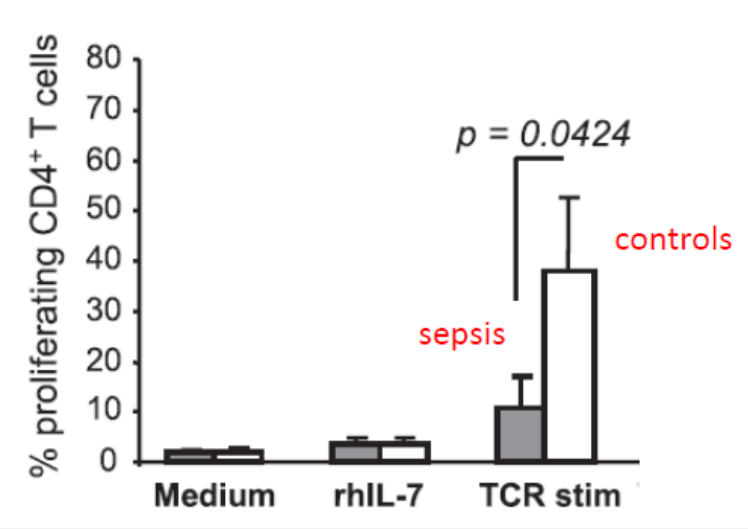
Immunomonitorage : lymphocytes T épuisés



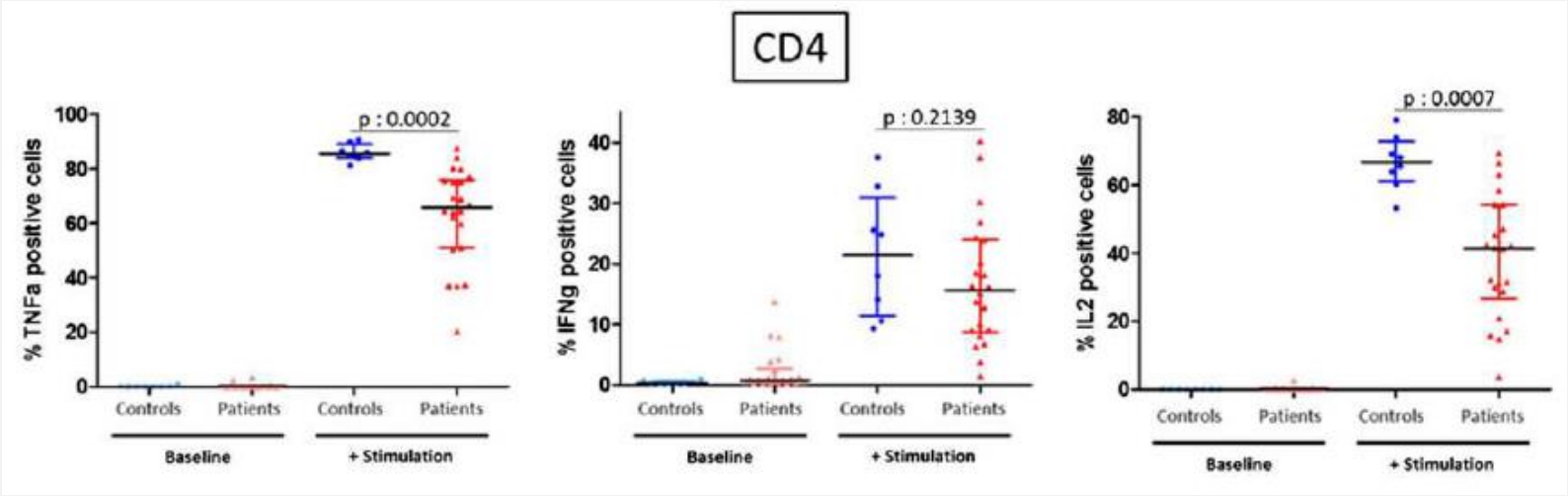
Streeck *et al.*, J Infect Dis 2017

Immunomonitorage : altération fonction LT CD4+

Diminution de la prolifération



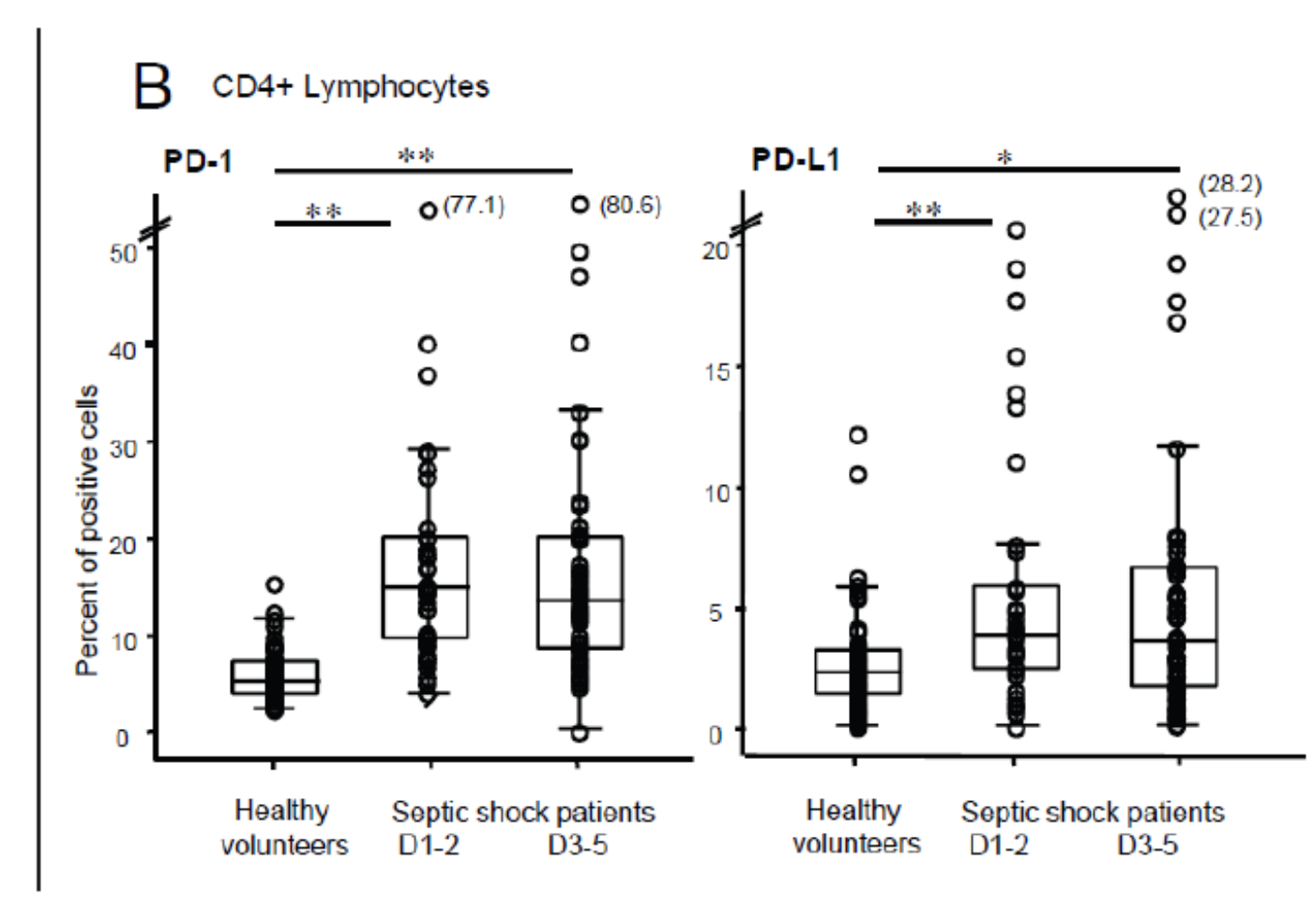
Diminution de la production cytokinique



Venet *et al.*, J Immunol 2012

Letessier *et al.*, Cytokine 2017

Immunomonitorage : points de contrôle immunitaires

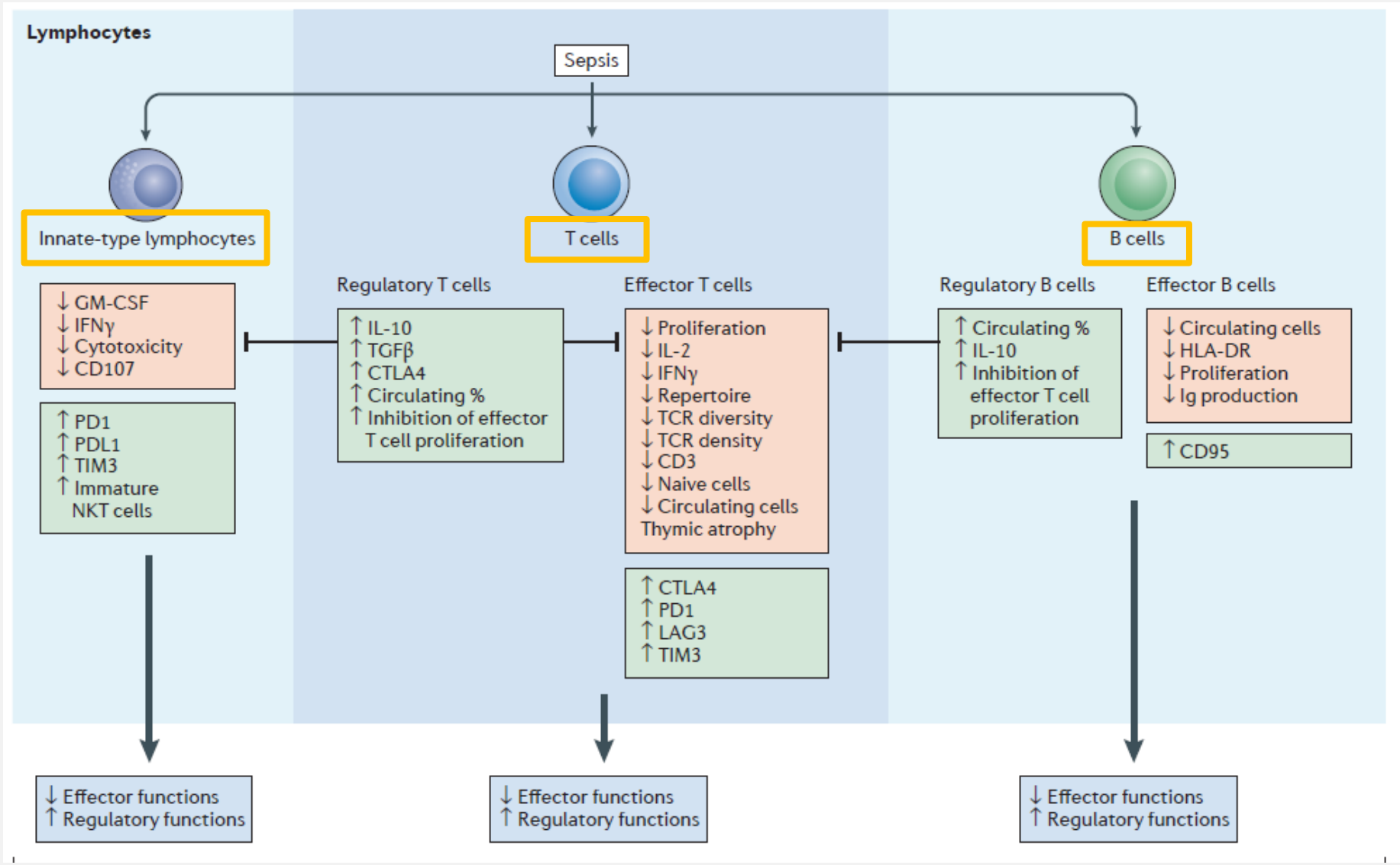


Association

Apoptose lymphocytaire
Infections nosocomiales
Mortalité

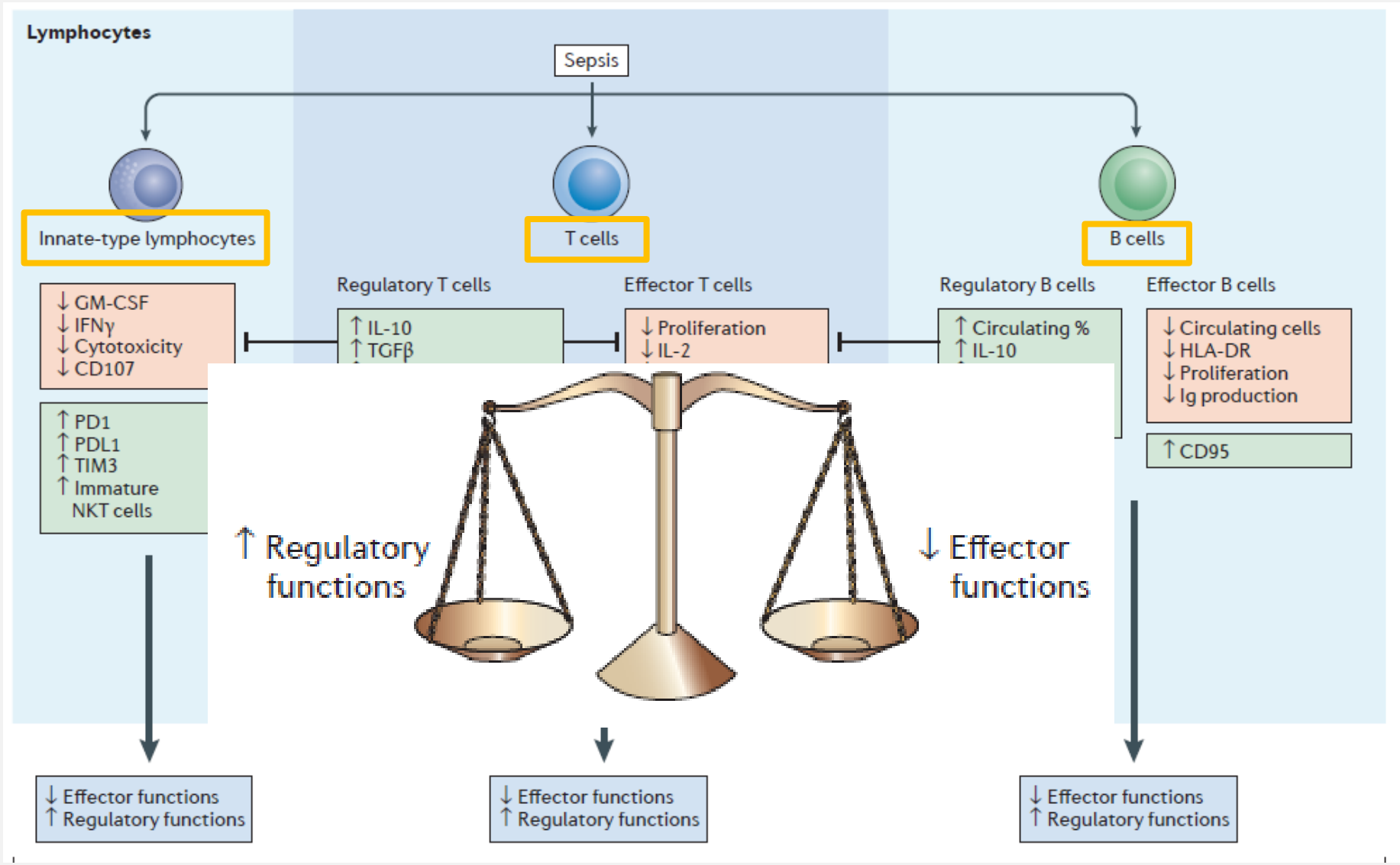
Guignant *et al.*, Crit care 2011

Immunomonitorage : cellules lymphoïdes



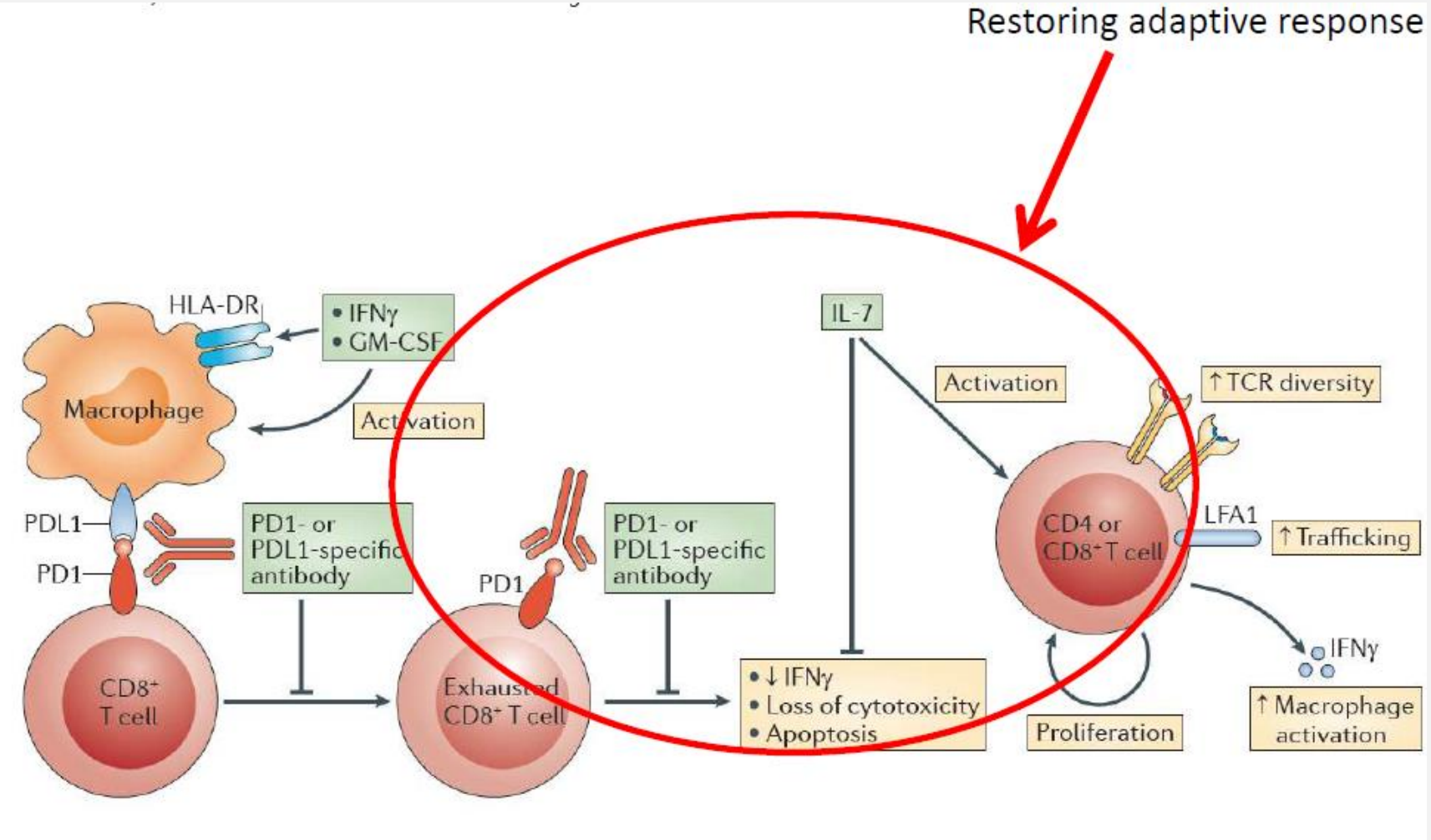
Venet *et al.*, Nat Rev Nephrol 2018

Immunomonitorage : cellules lymphoïdes



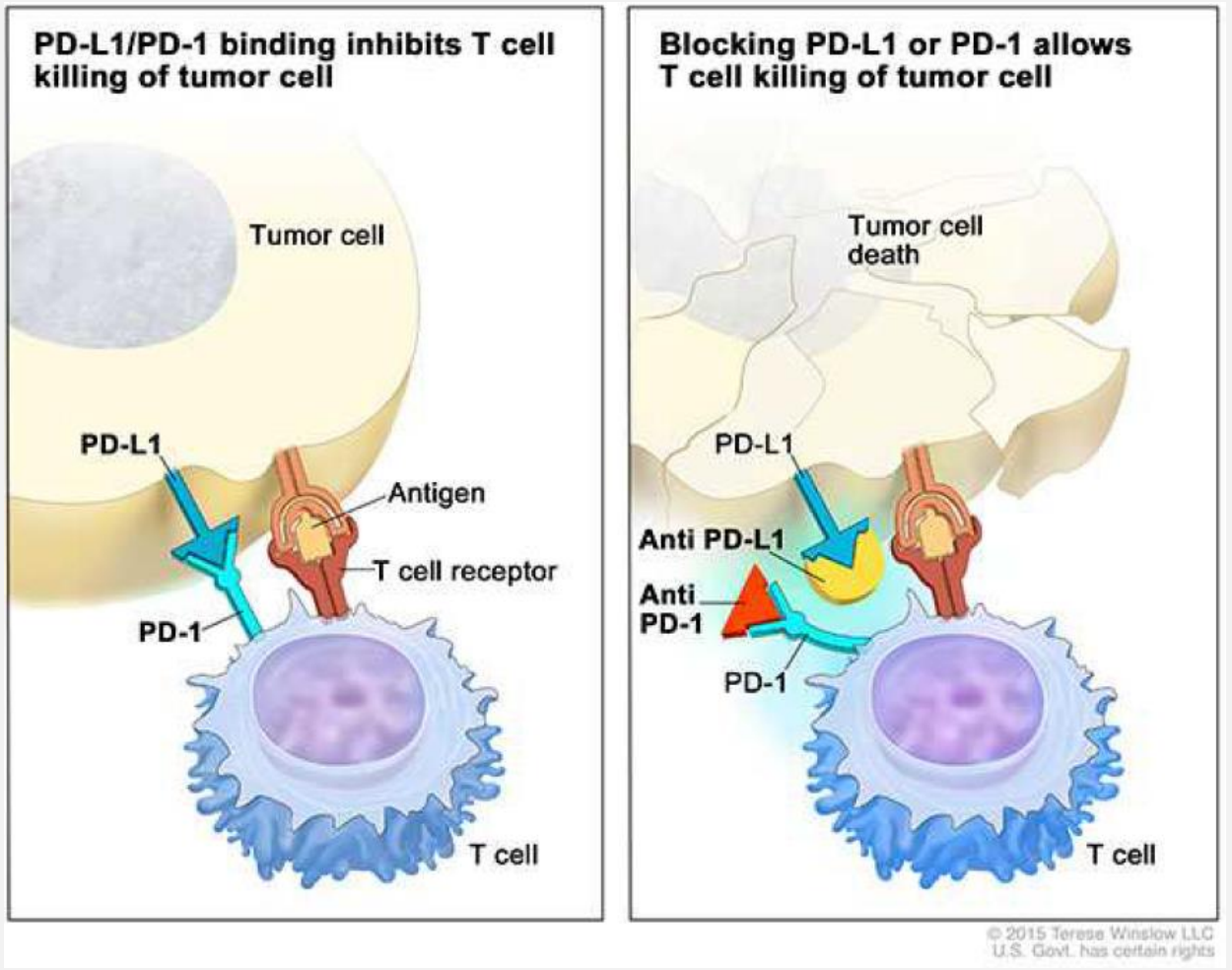
Venet *et al.*, Nat Rev Nephrol 2018

Immunomodulation : immunité adaptative



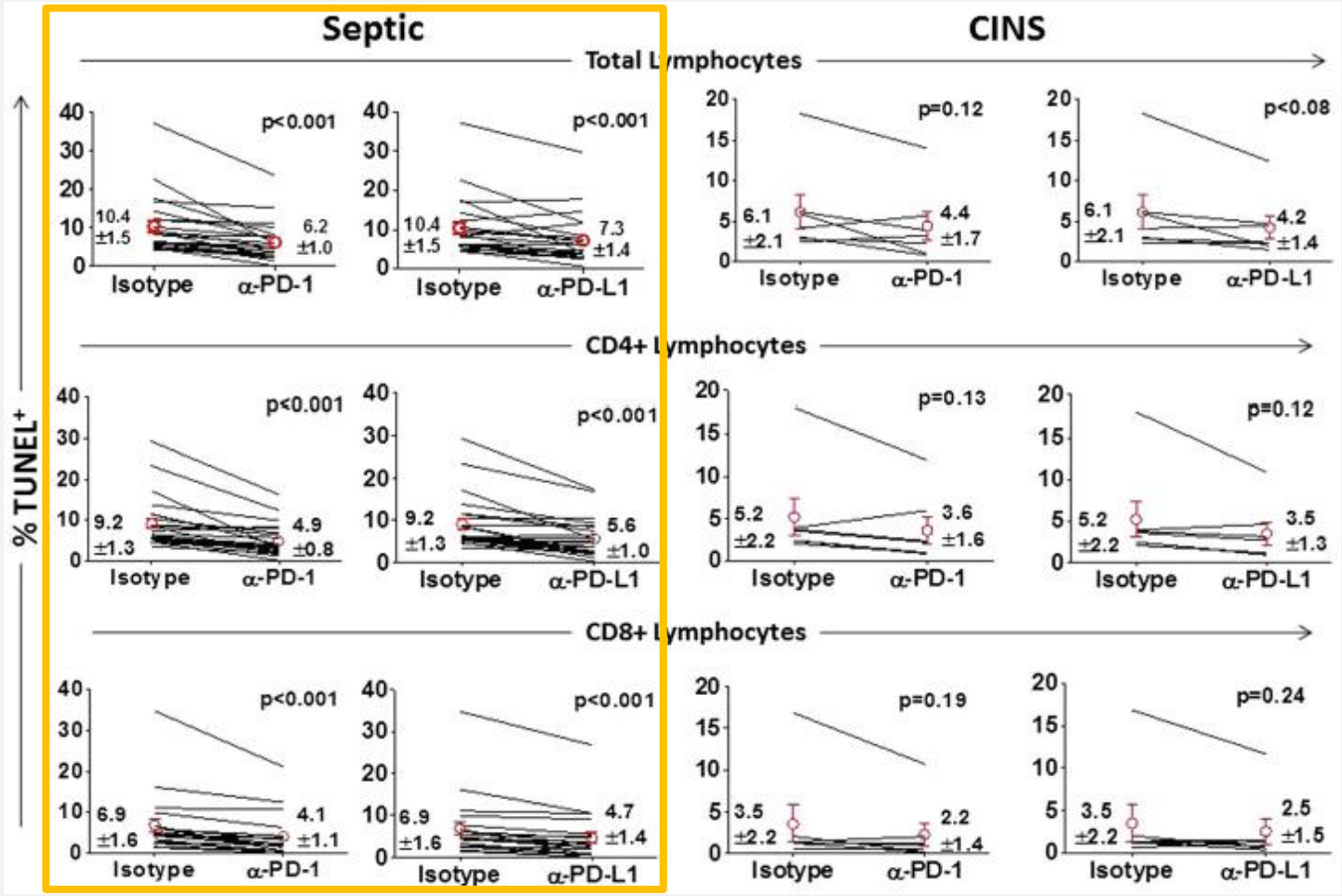
Hotchkiss *et al.*, Nat Rev Immunol 2013

Axe PD-1/PD-L1


PD-L1/PD-1 binding inhibits T cell killing of tumor cell
Tumor cell
PD-L1
Antigen
T cell receptor
PD-1
T cell
Blocking PD-L1 or PD-1 allows T cell killing of tumor cell
Tumor cell death
PD-L1
Anti PD-L1
Anti PD-1
PD-1
T cell
© 2015 Terese Winslow LLC U.S. Govt. has certain rights

Immunomodulation : anti-PD-1/PD-L1 *ex vivo*

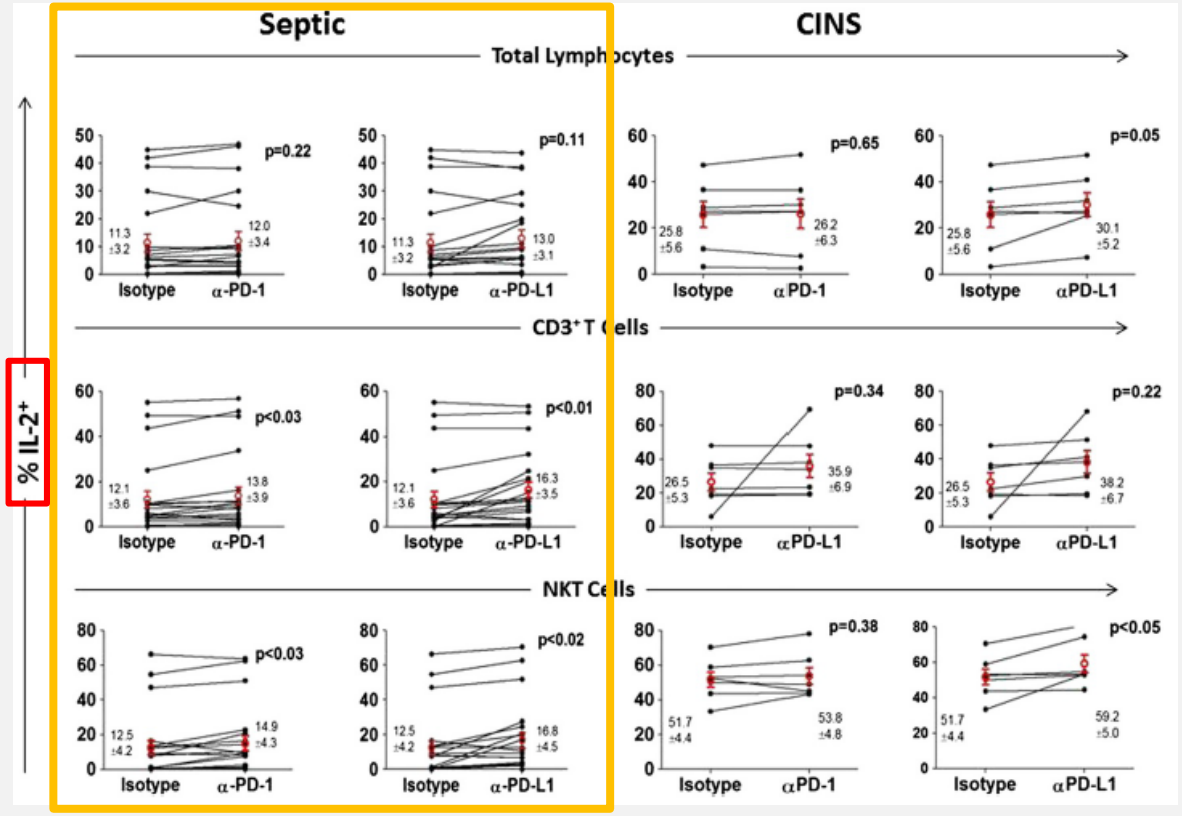
Diminution de l'apoptose

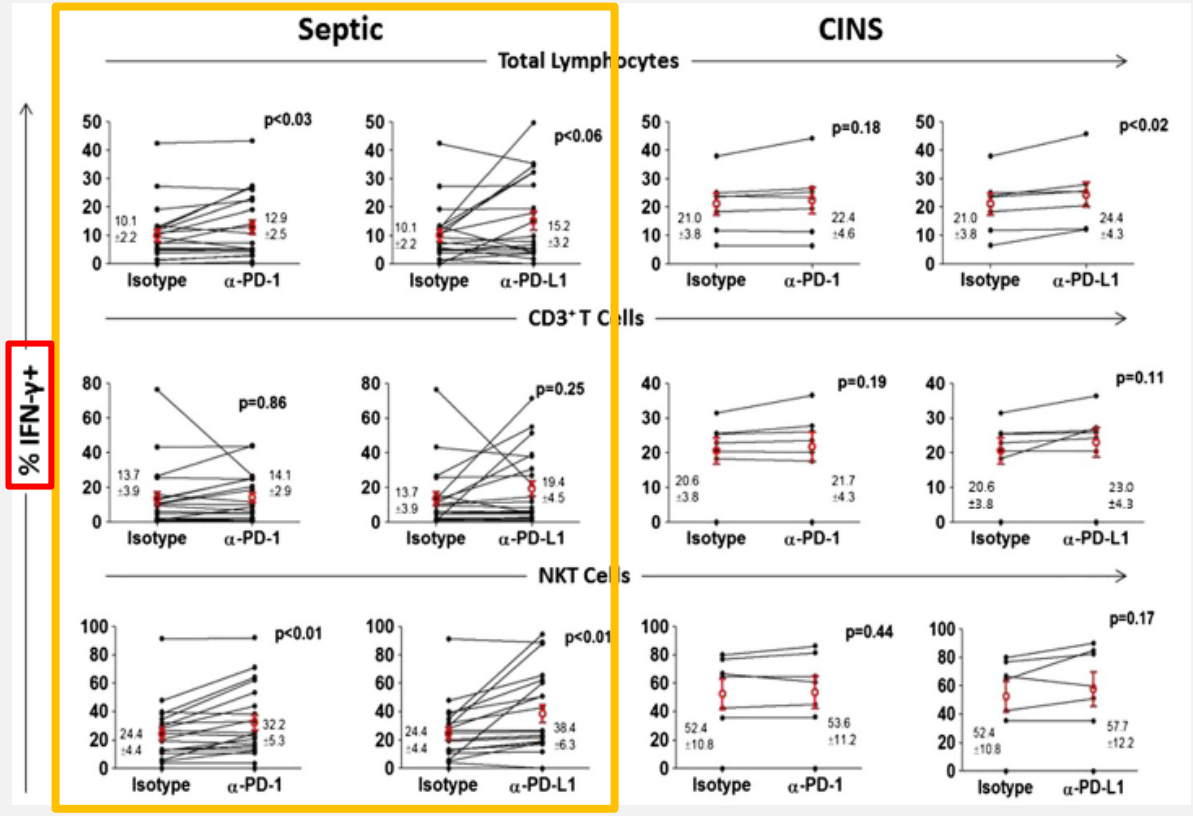


Chang *et al.*, Crit care 2014

Immunomodulation : anti-PD-1/PD-L1 *ex vivo*

Augmentation de la production cytokinique

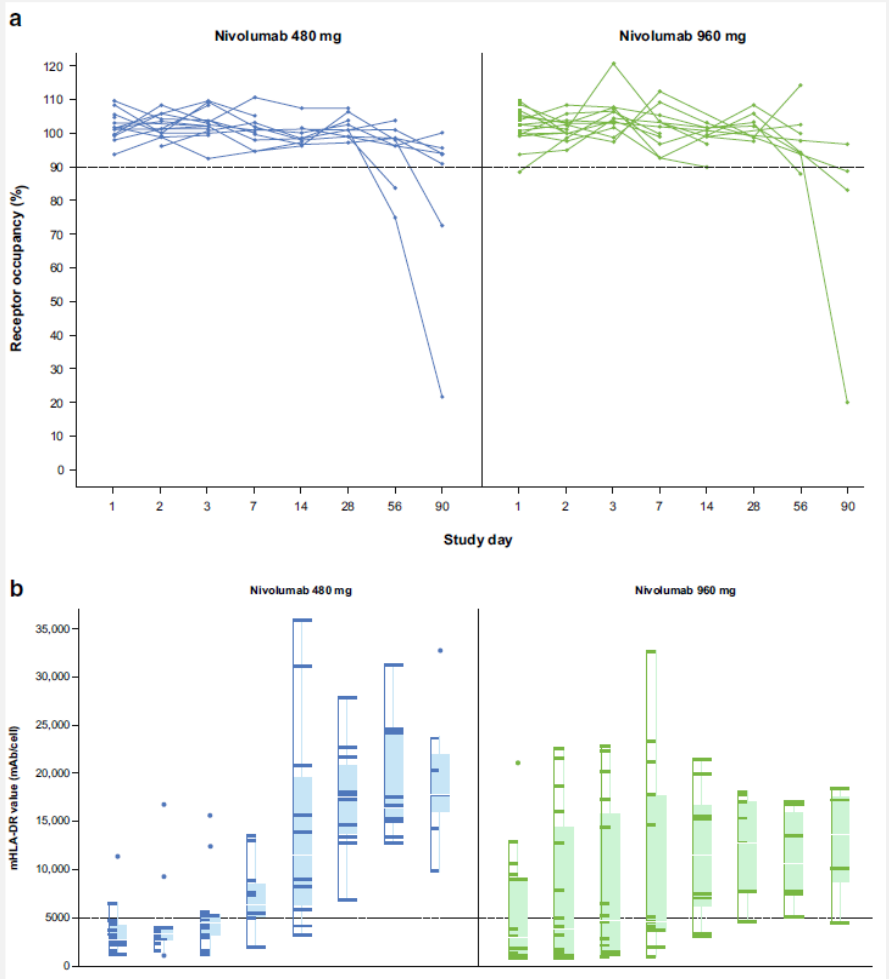




Chang *et al.*, Crit care 2014

Immunomodulation : anti-PD-1/PD-L1 *in vivo*

Anti-PD-1



Hotchkiss *et al*., Intensive Care Med 2019

Anti-PD-L1

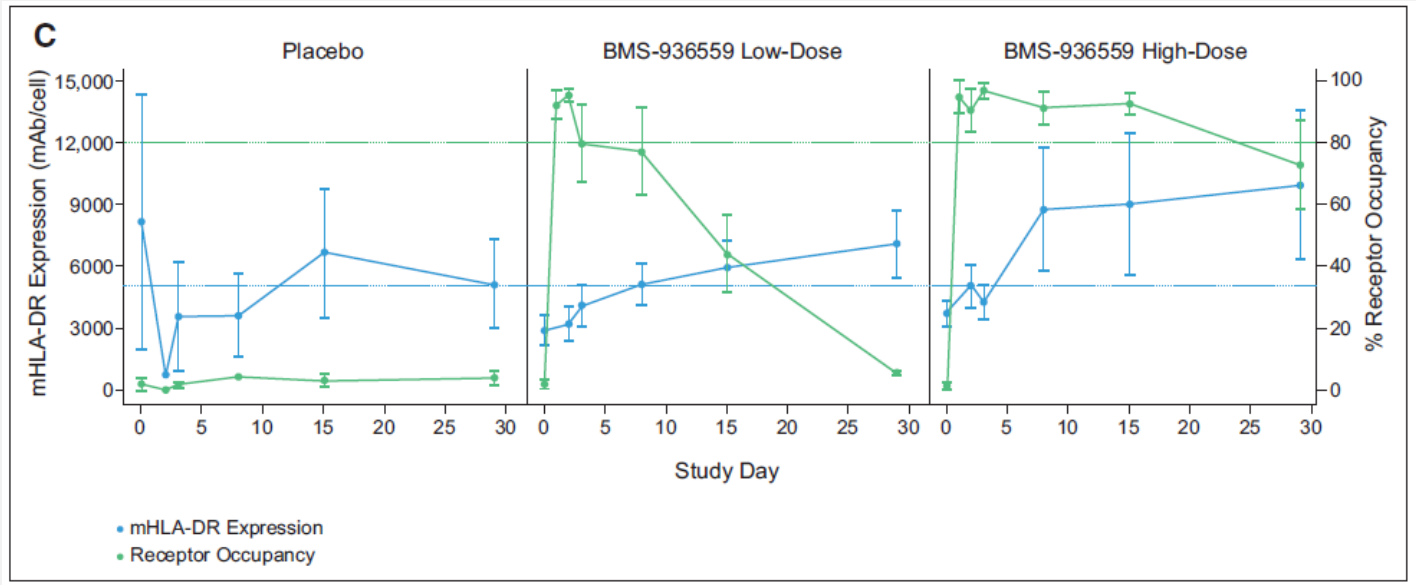
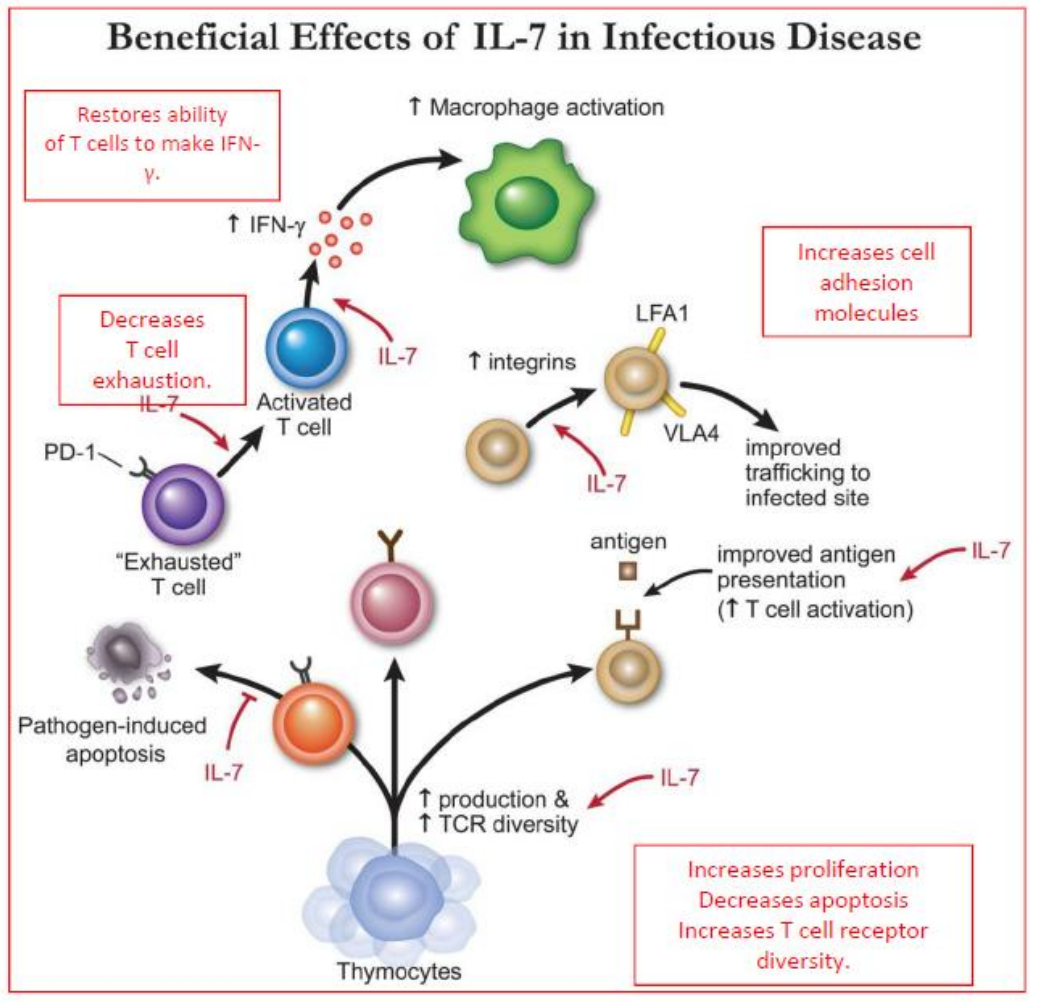


Figure 2. *(Continued)* **C**, Changes in RO and mHLA-DR expression in participants receiving placebo, or 10, 30, and 100 mg dose combined ("low-dose group"), or 300 and 900 mg dose combined ("high-dose group") up to day 29 post-infusion. *Green dashed line* represents 80% RO; *blue dashed line* represents mHLA-DR 5,000 mAb per cell. n/a = not applicable.

Augmentation production IFNγ par LT
Pas d'effet sur compte total lymphocytes
Pas de différence [cytokines]
3-6% *vs* 54% irAEs, aucun sévère

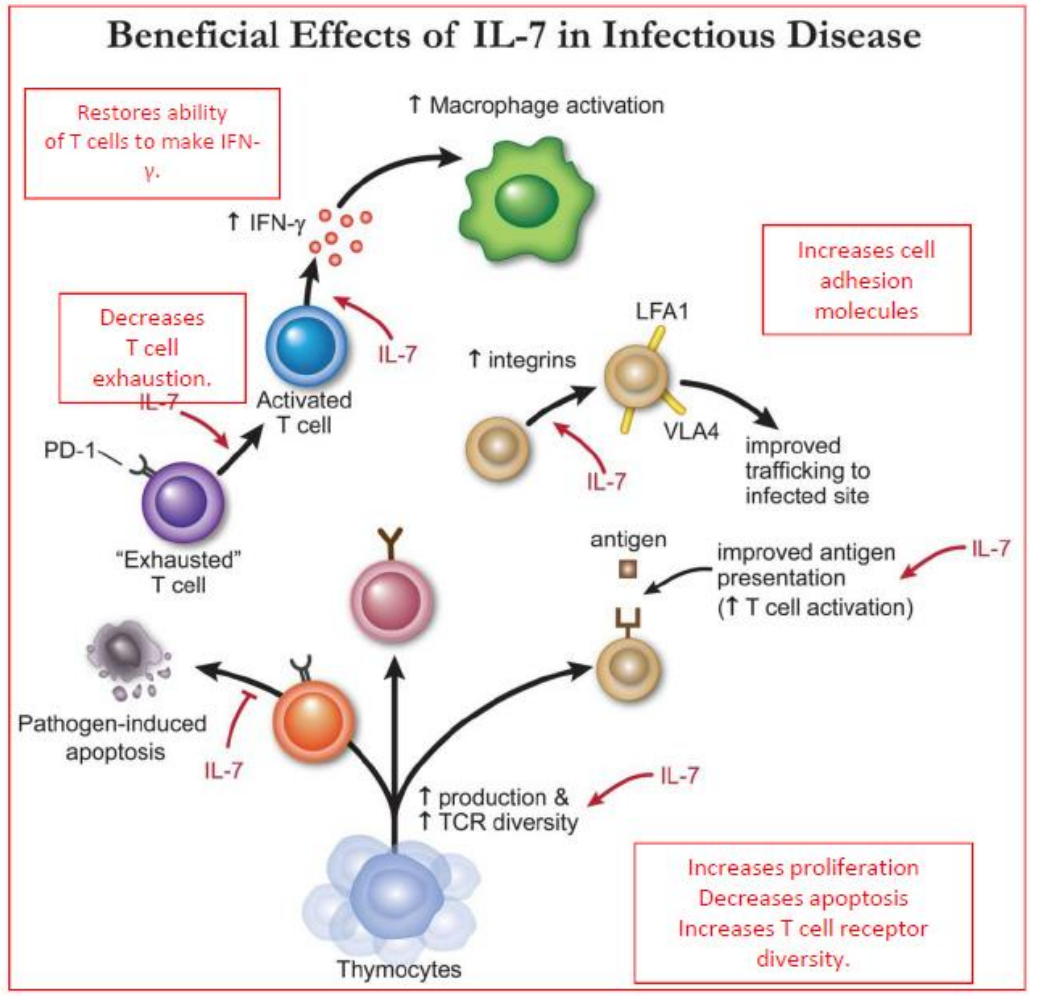
Hotchkiss *et al*., Crit Care Med 2019

Immunomodulation : interleukine-7



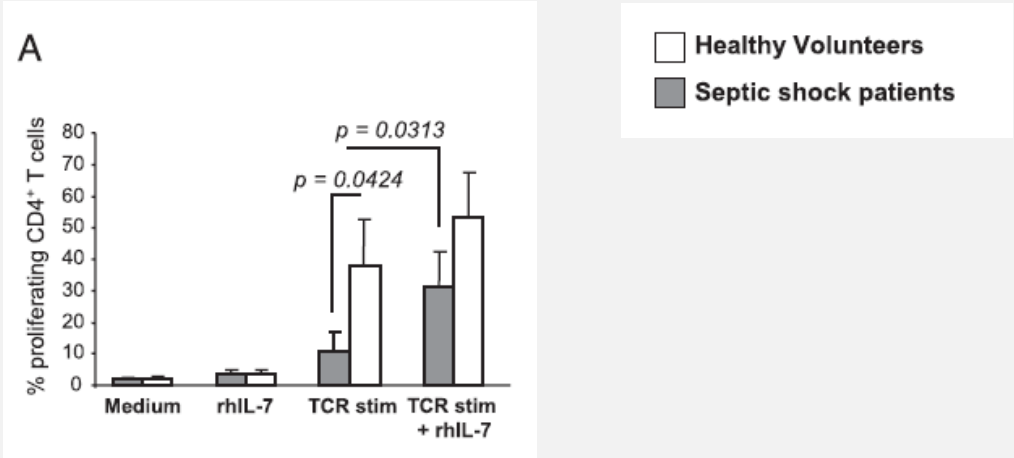
Hotchkiss *et al*., Trends in Mol Med 2014

Immunomodulation : interleukine-7

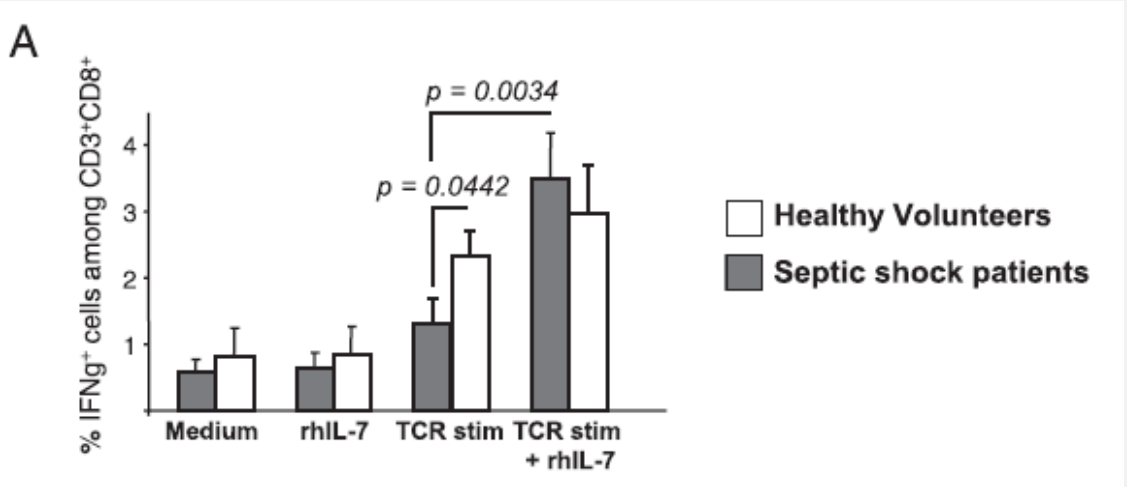


Hotchkiss *et al.*, Trends in Mol Med 2014

Prolifération *ex vivo*



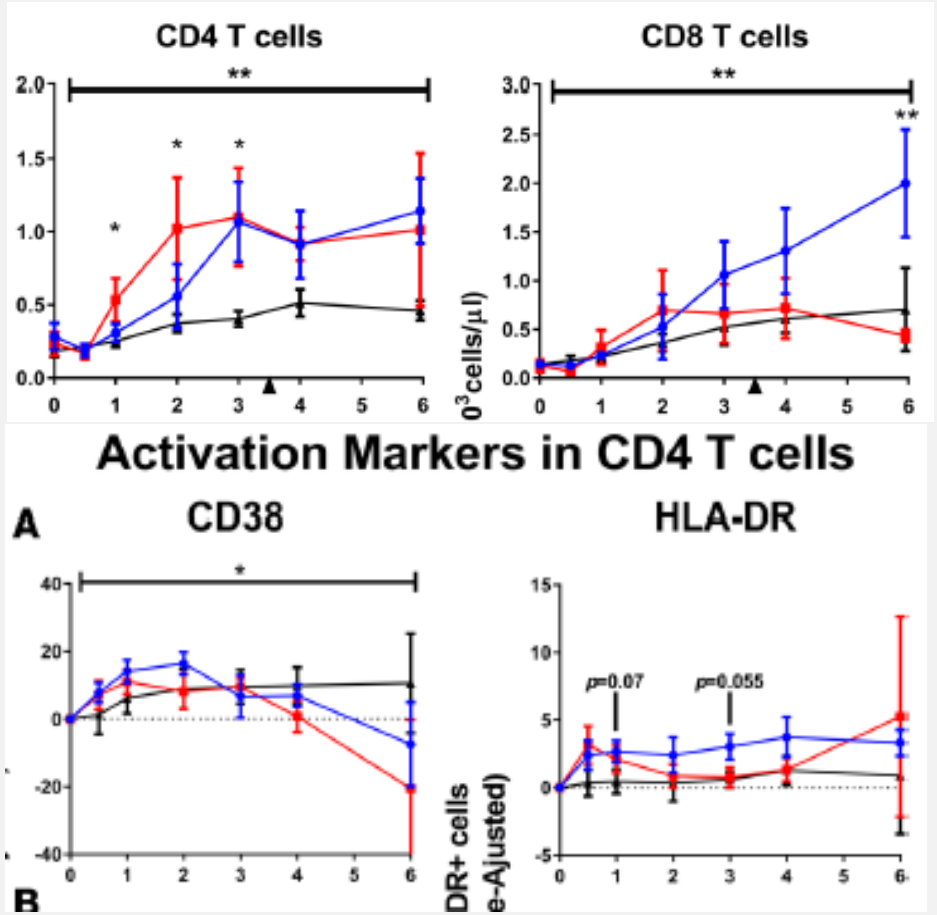
Production cytokinique *ex vivo*



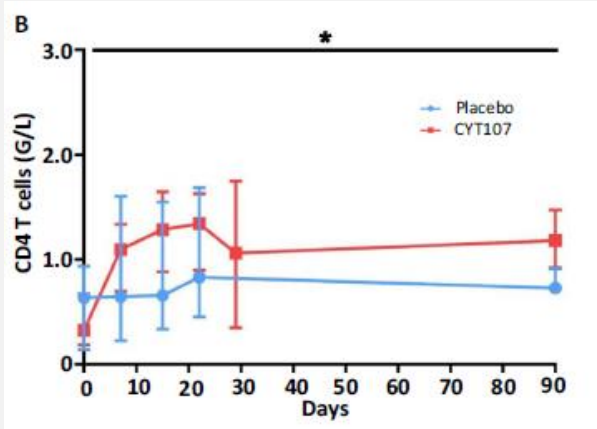
Venet *et al.*, J Immunol 2012

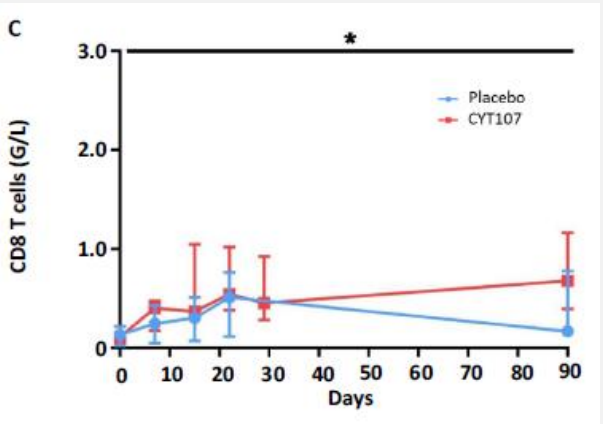
Immunomodulation : interleukine-7 *in vivo*

IM / SC



IV





administration. Three patients treated with CYT107 developed fever and respiratory distress occurring approximately 5–8 h after drug administration. It was the investigators' opinions that the events were possibly drug-related because of the temporal association of occurring following CYT107 administration. Two of the

Pas d'effet indésirable grave

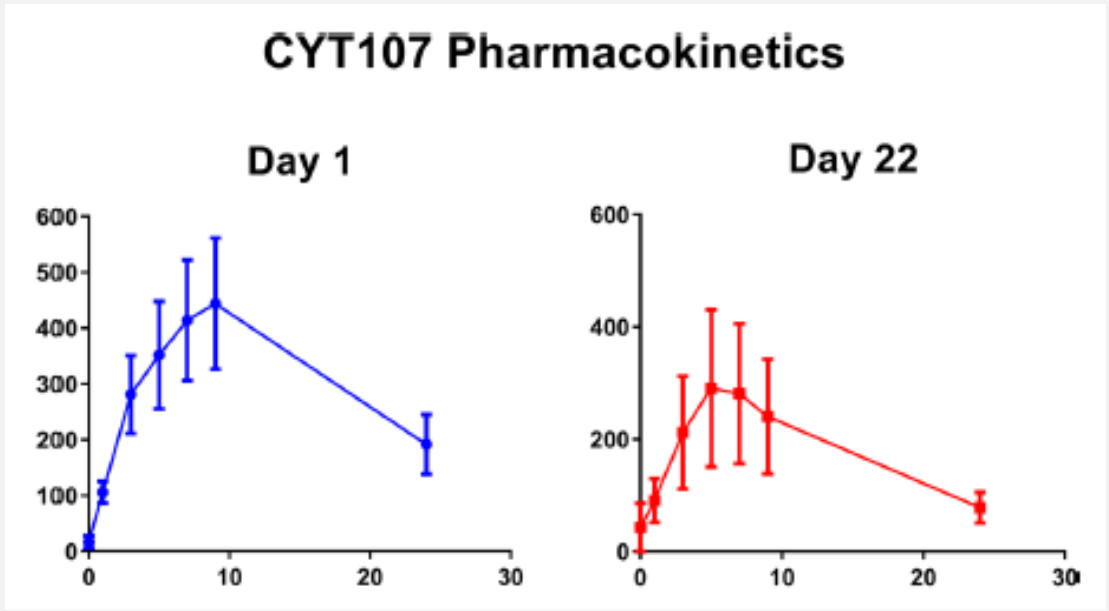
Mortalité : 2/10 placebo *vs* 5/17 groupe rhIL-7

François *et al.*, JCI Insight 2018

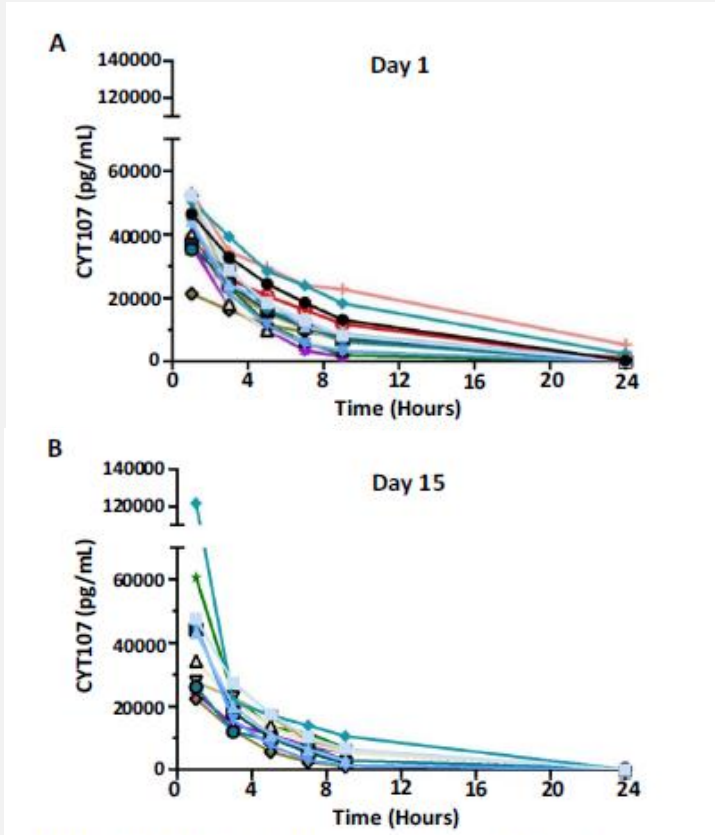
Daix *et al.*, Annals of Intensive Care 2023

Immunomodulation : interleukine-7

IM / SC



IV

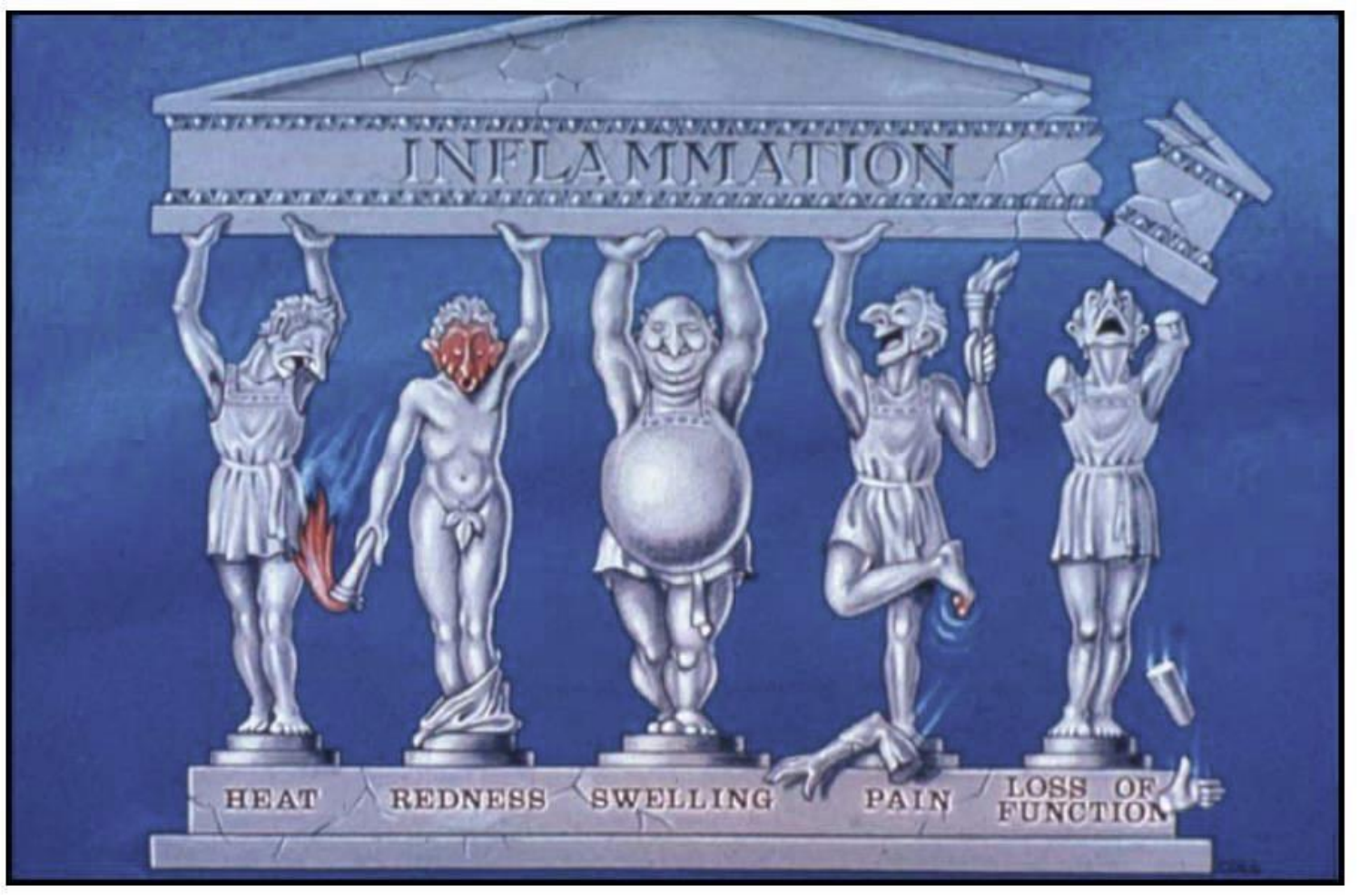


(OSFD). However, intravenous CYT107 produced an approximately 100-fold increase in CYT107 blood concentration compared with intramuscular CYT107. No cytokine storm and no formation of antibodies to CYT107 were observed.

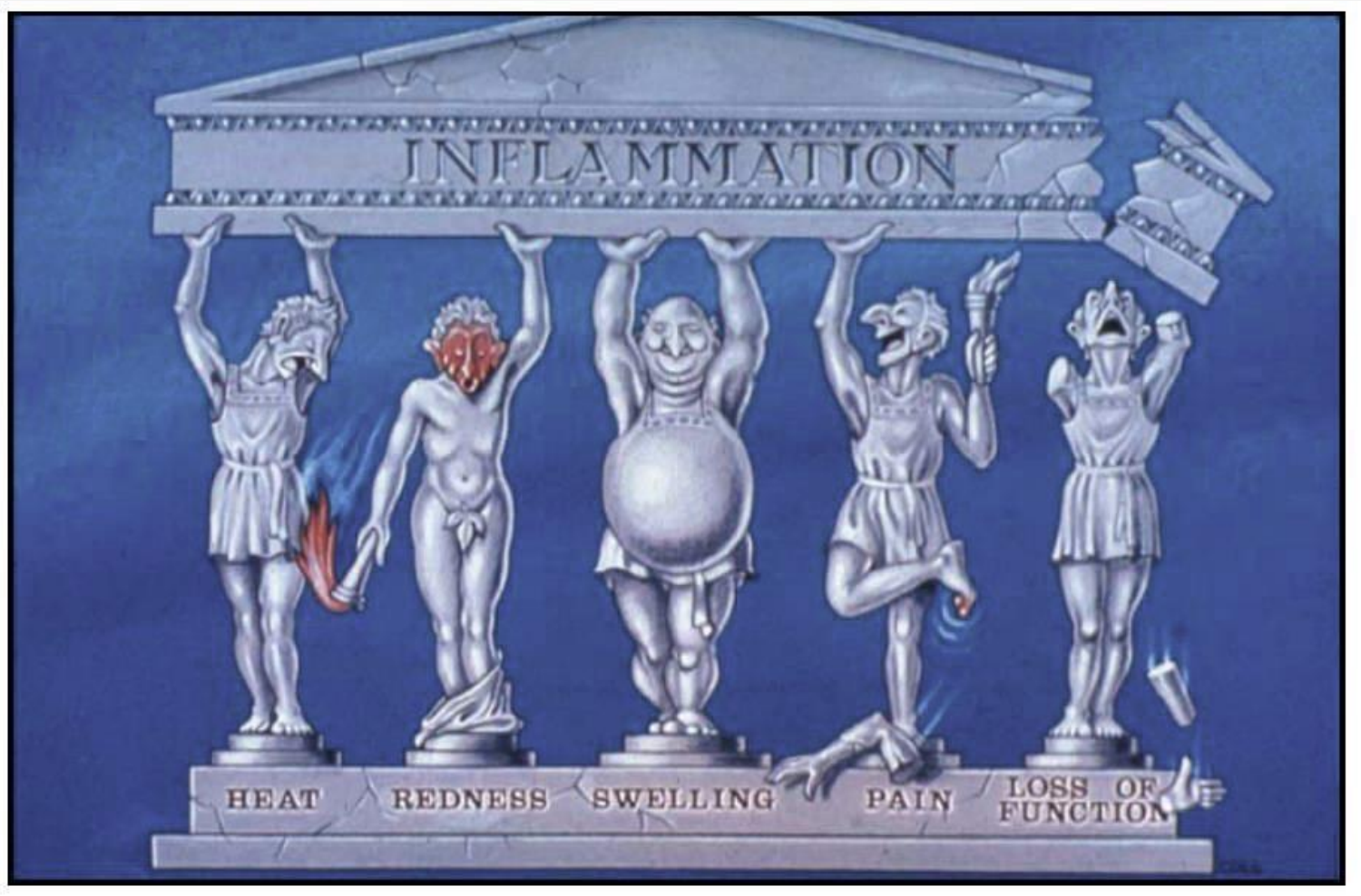
François *et al.*, JCI Insight 2018

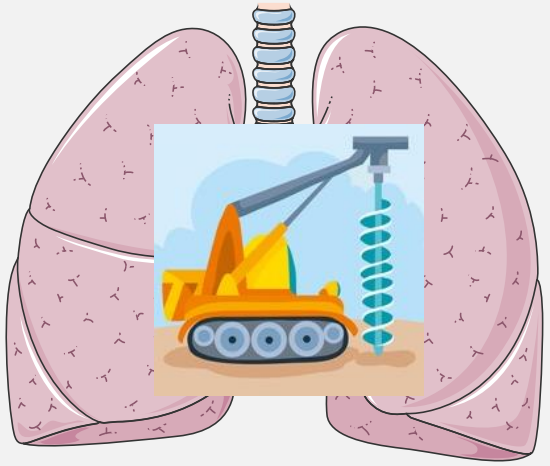
Daix *et al.*, Annals of Intensive Care 2023

Sang circulant *vs* organes

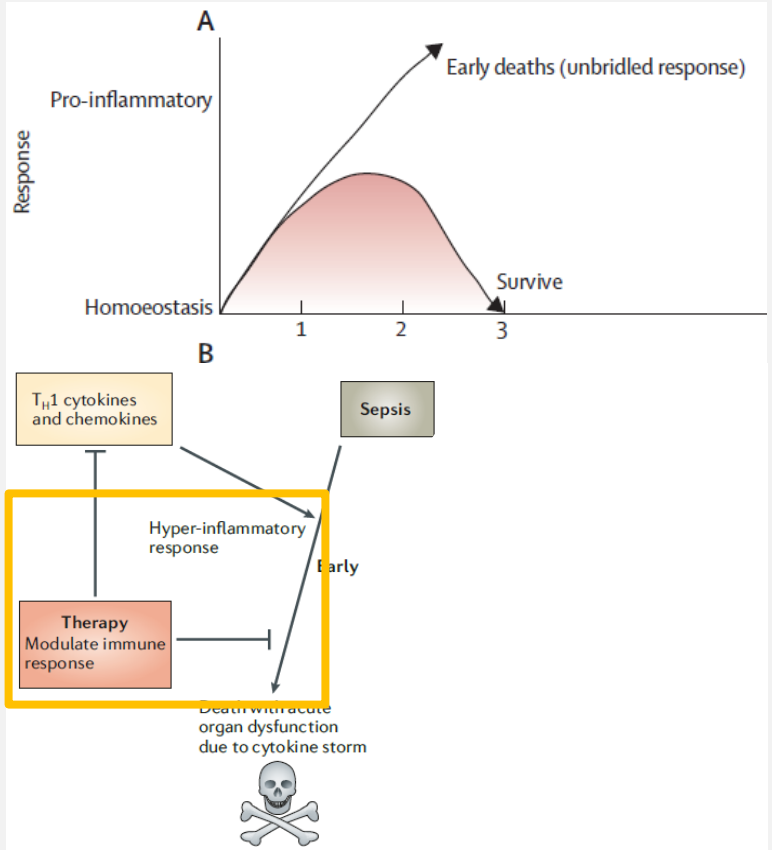


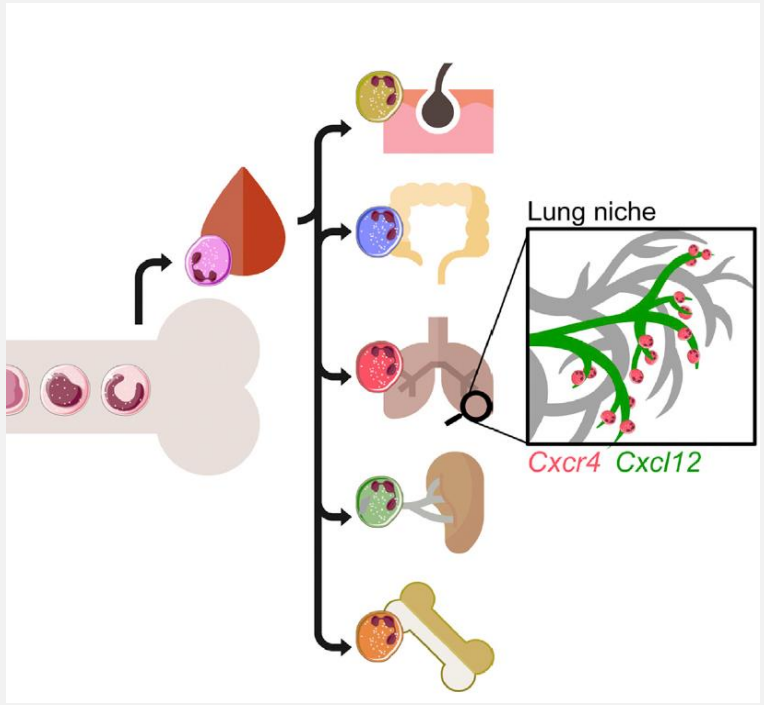
Sang circulant *vs* organes

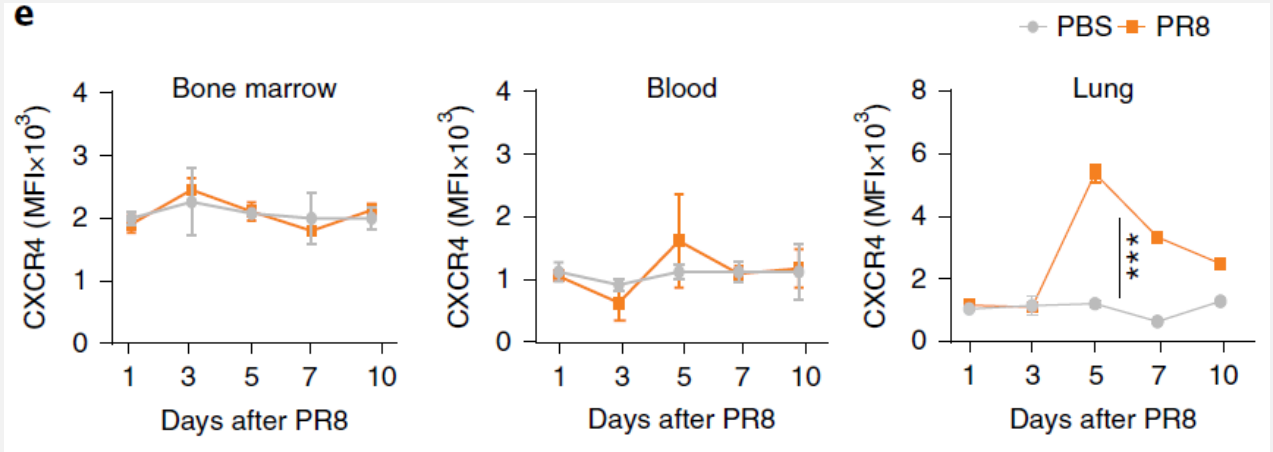




Immunomodulation locale : poumon



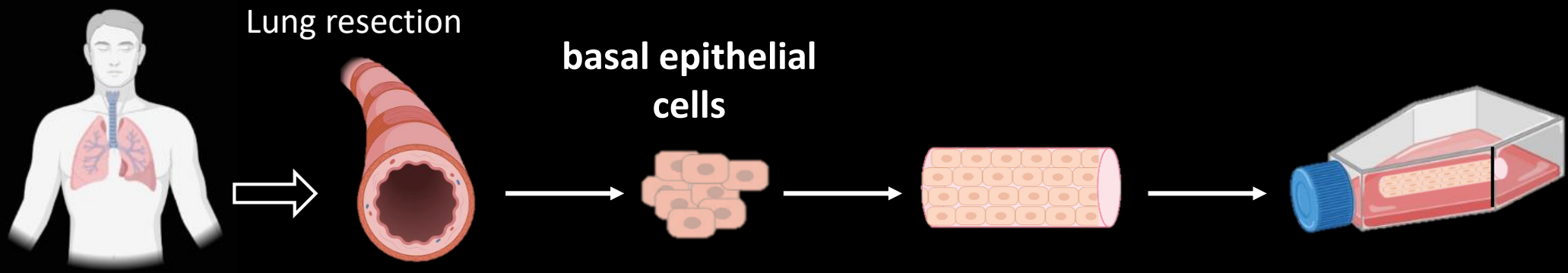


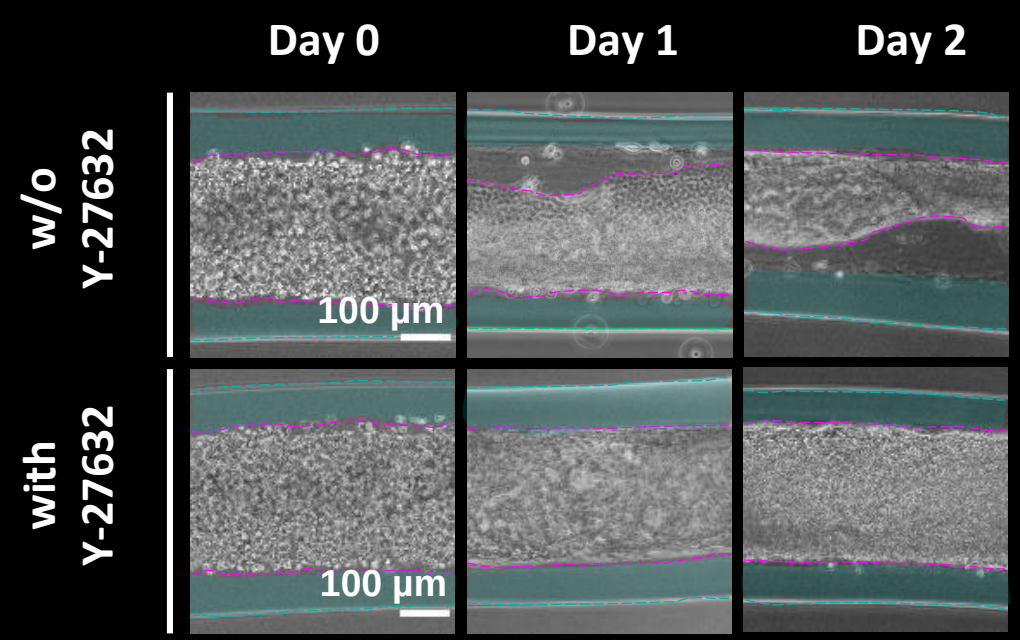


Radermecker *et al.*, Nat Immunol 2019
Ballesteros *et al.*, Cell 2020

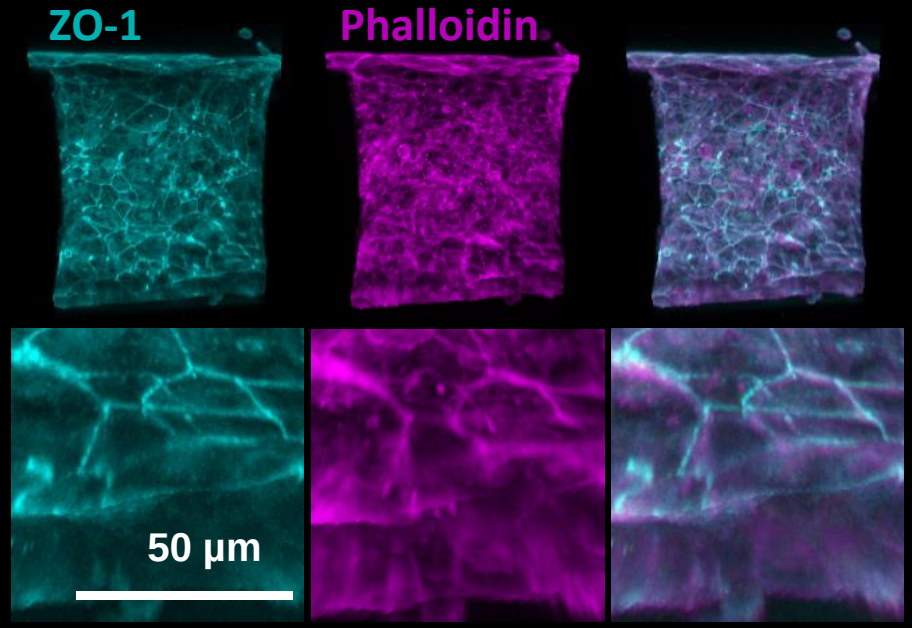
Bronchial Remodeling

Characterizing the bronchioid model over time





Longitudinal section of a 3D view (Day 2)

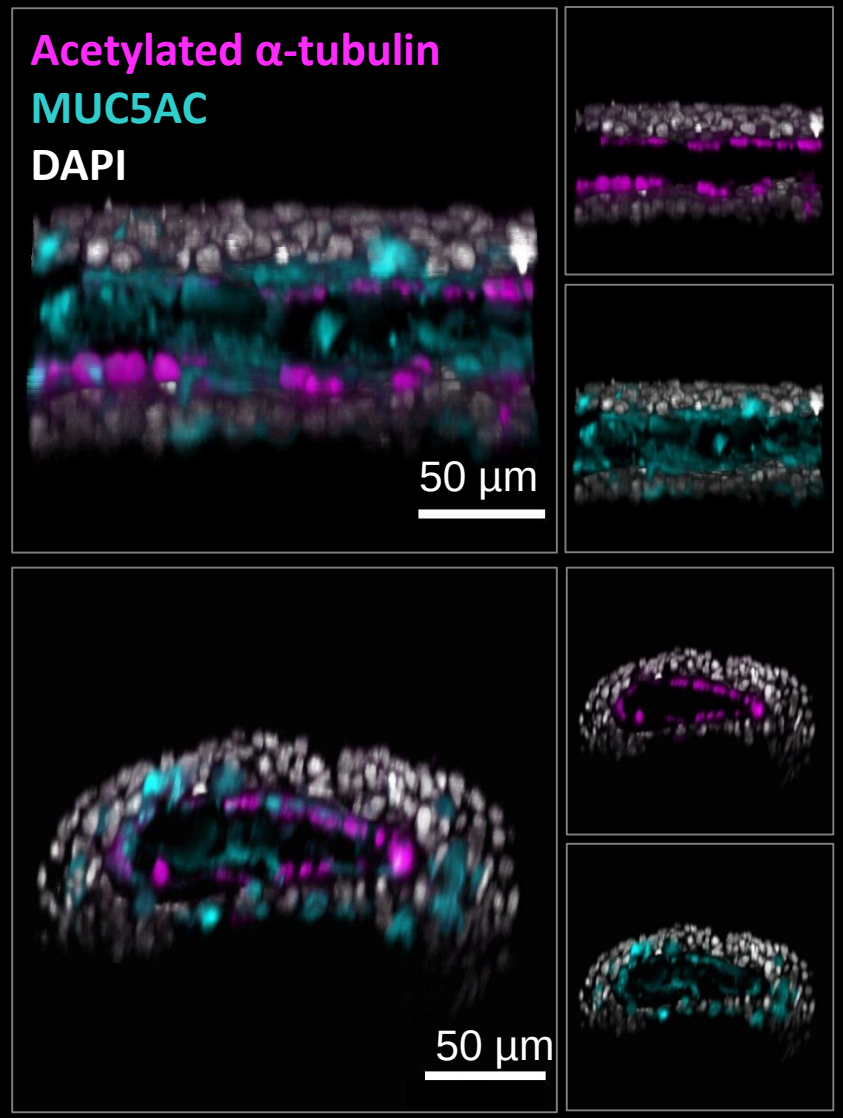


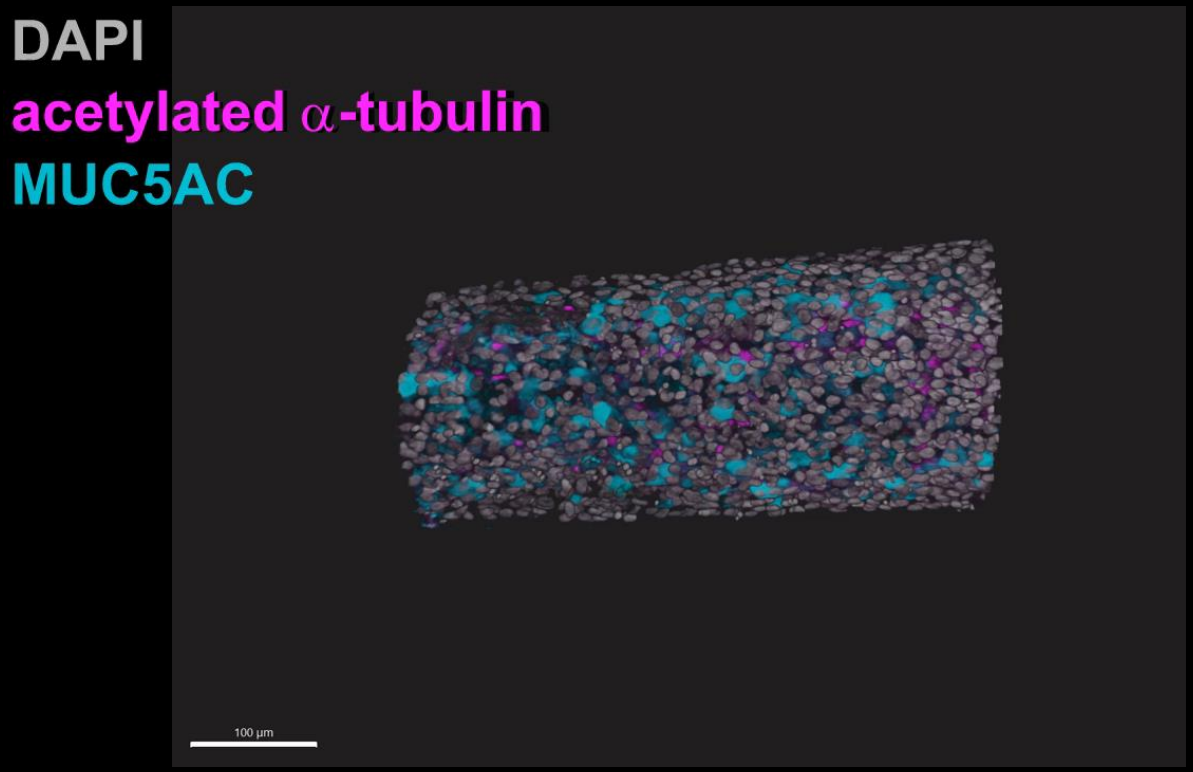
Bronchial Remodeling

Characterizing the bronchioid model over time

Longitudinal

Transversal



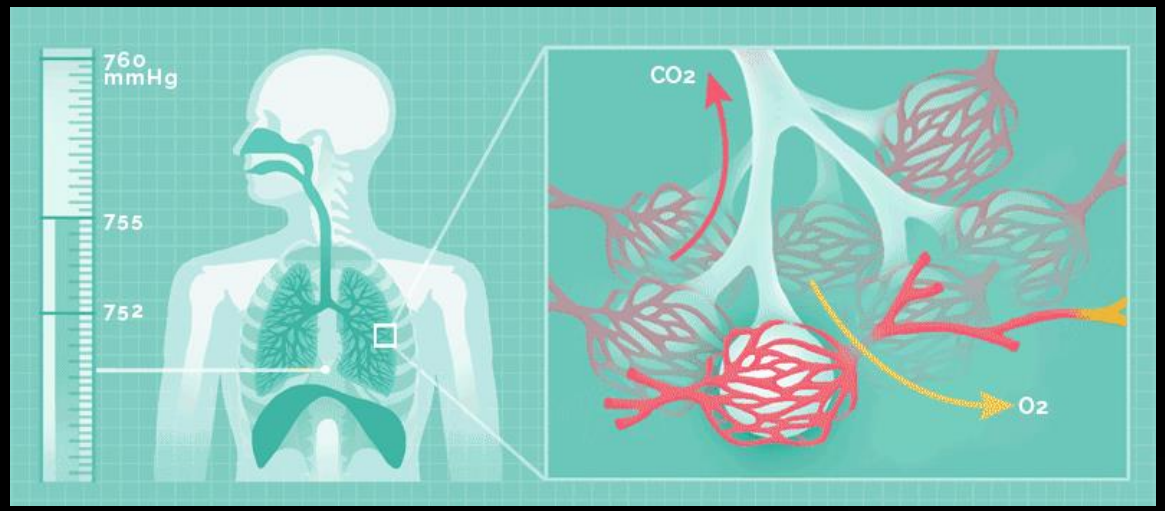


ANR JCJC 2021 Bronchiole Pr I. Dupin
Collaboration CNRS 5298, Drs Nassoy et Recher

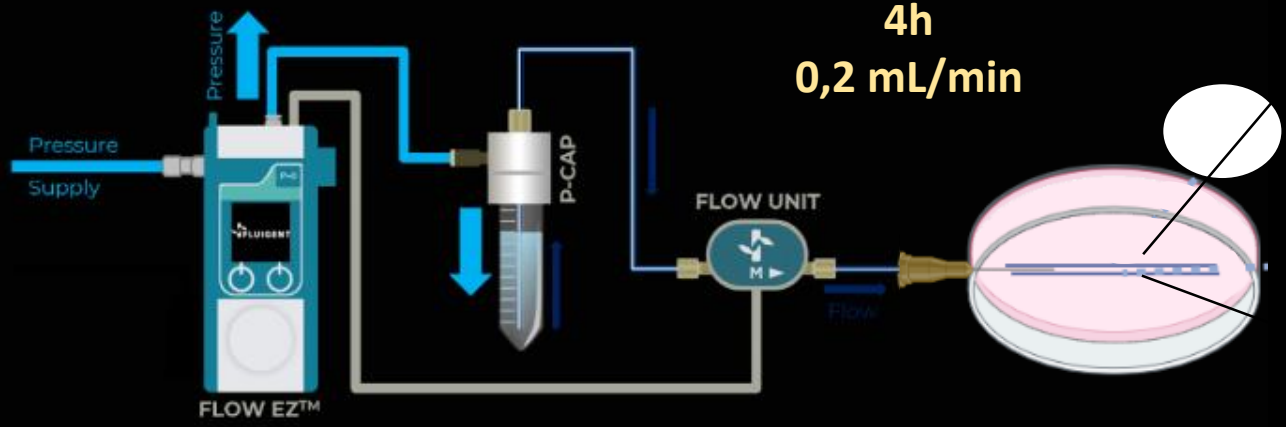
Bronchial Remodeling

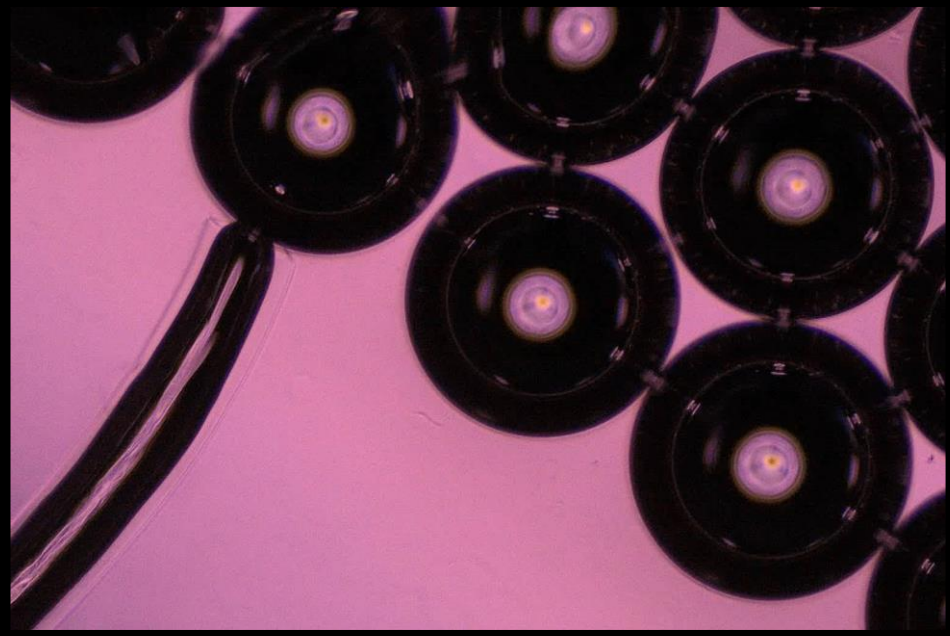
Perfusing the bronchioid with air

http://tabletopwhale.com/2014/10/24/3-different-ways-to-breathe.html



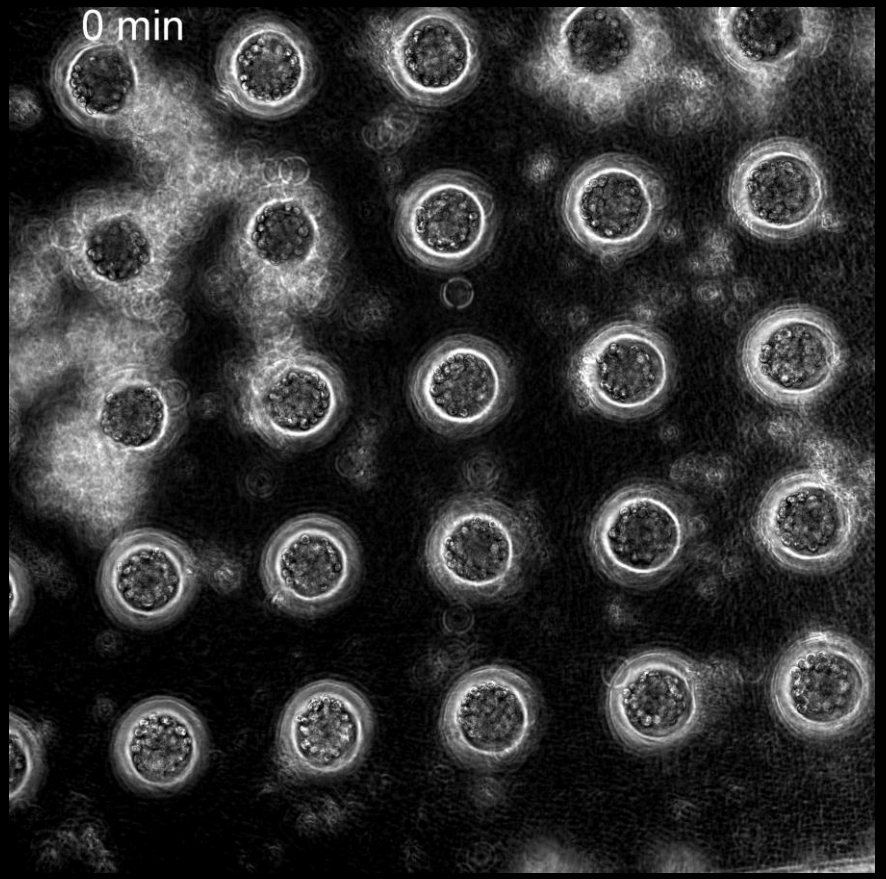
Air perfusion:
4h
0,2 mL/min



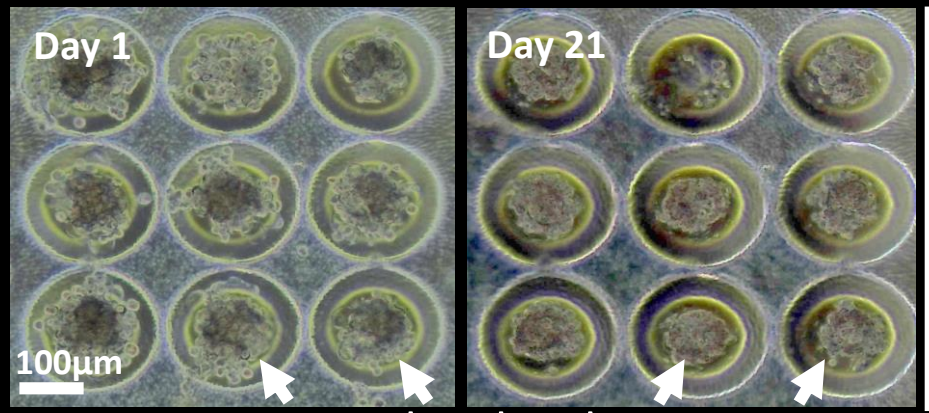


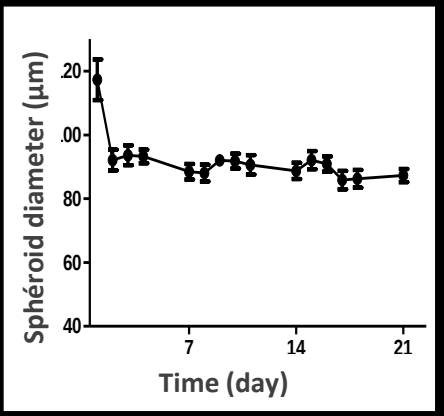
Bronchial Remodeling

Modeling alveoli *in vitro*



Stability over time



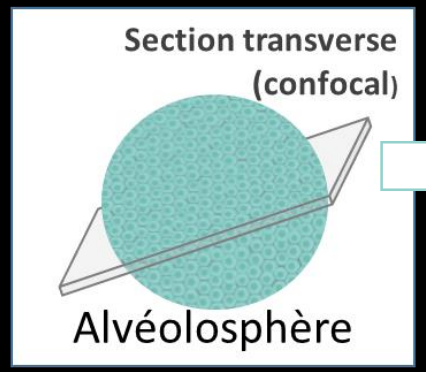


Alveolospheres

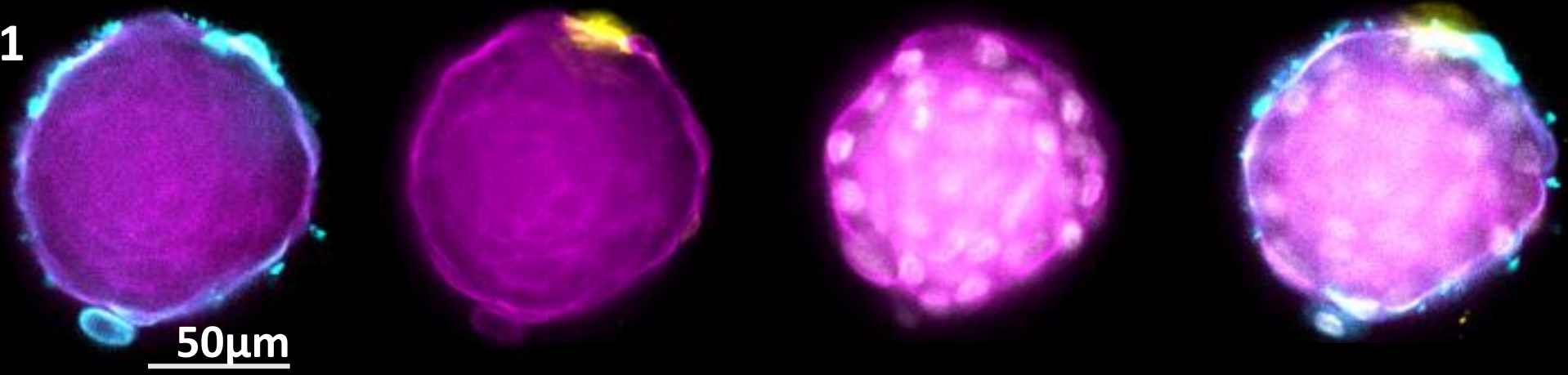
ANR PRCE 2022 Lumen Dr M. Zysman
Collaboration Alvéole

Bronchial Remodeling

Modeling alveoli *in vitro*

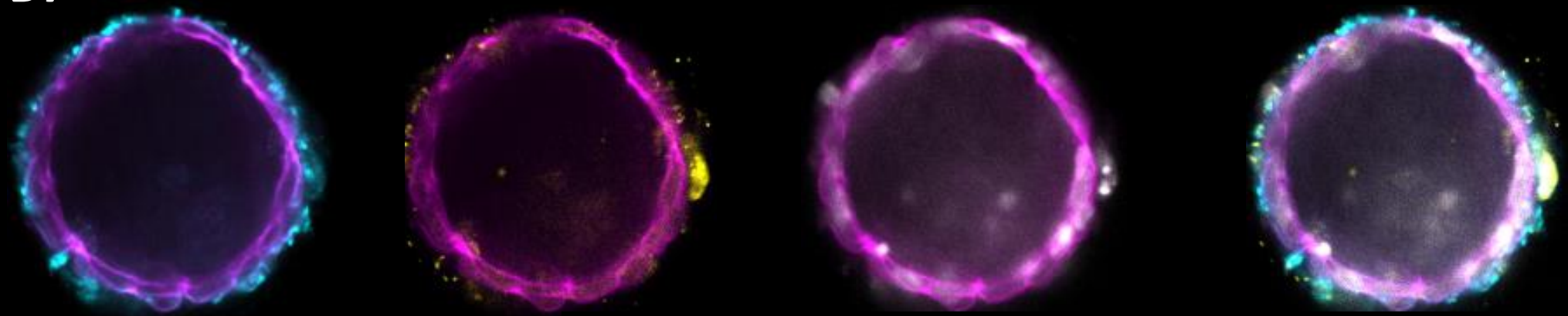


D1

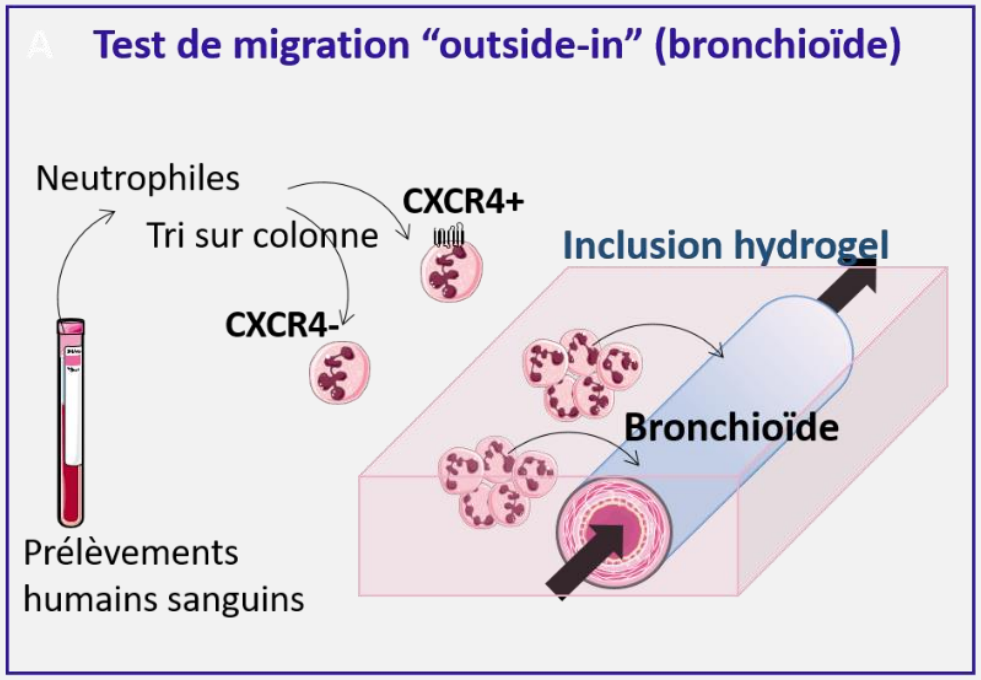


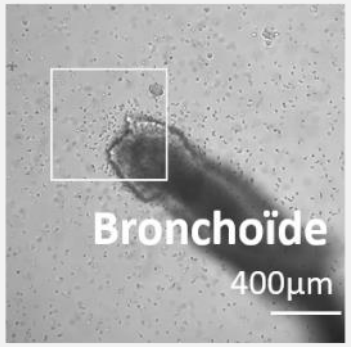
Phalloidine HT1 | Phalloidine HT2 | Phalloidine DAPI | Merged

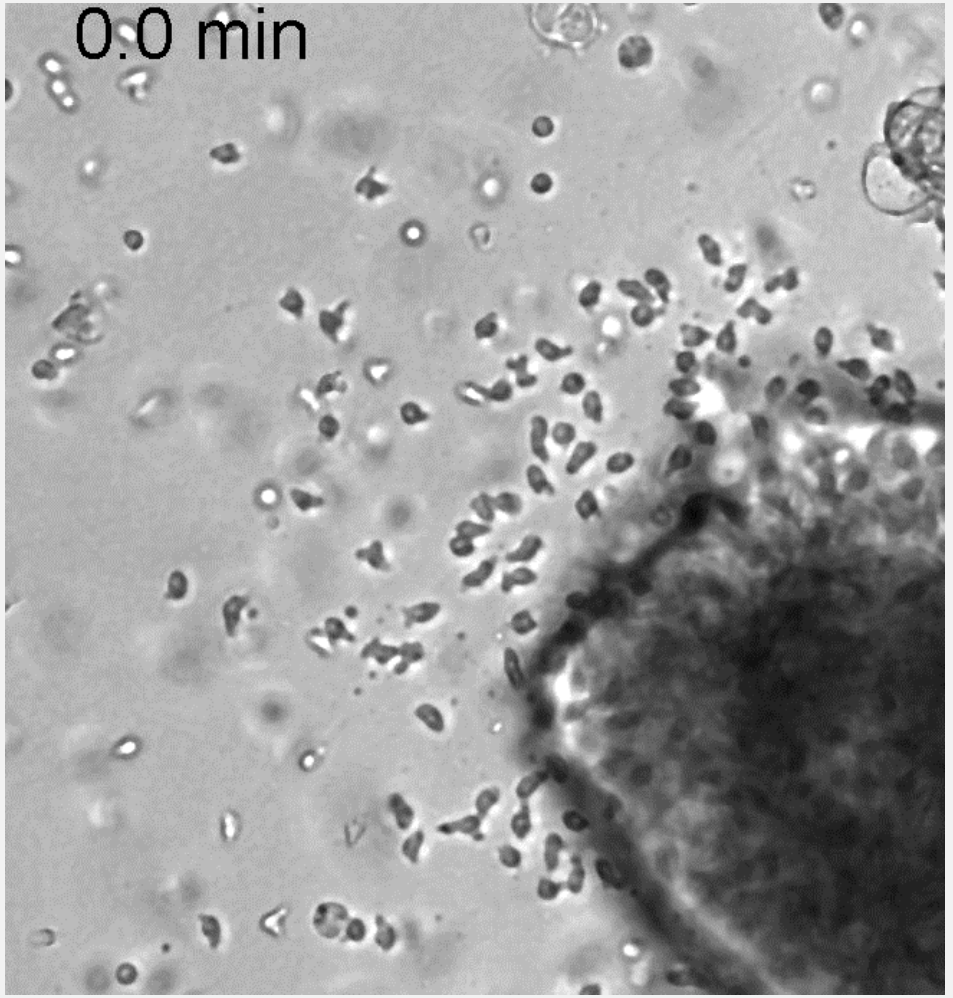
D7



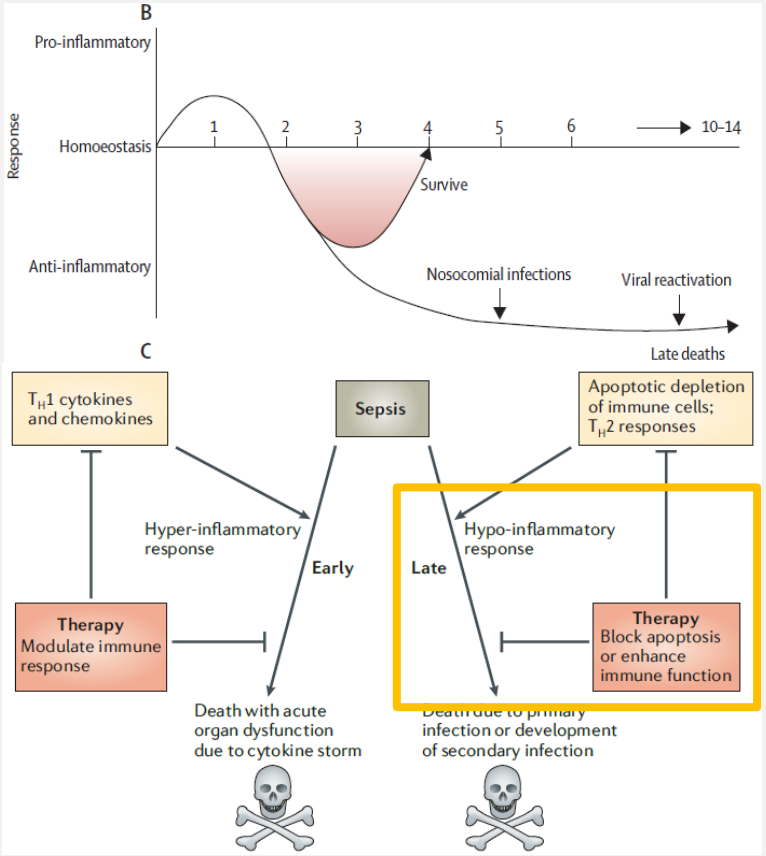
Co-culture organoïdes et neutrophiles





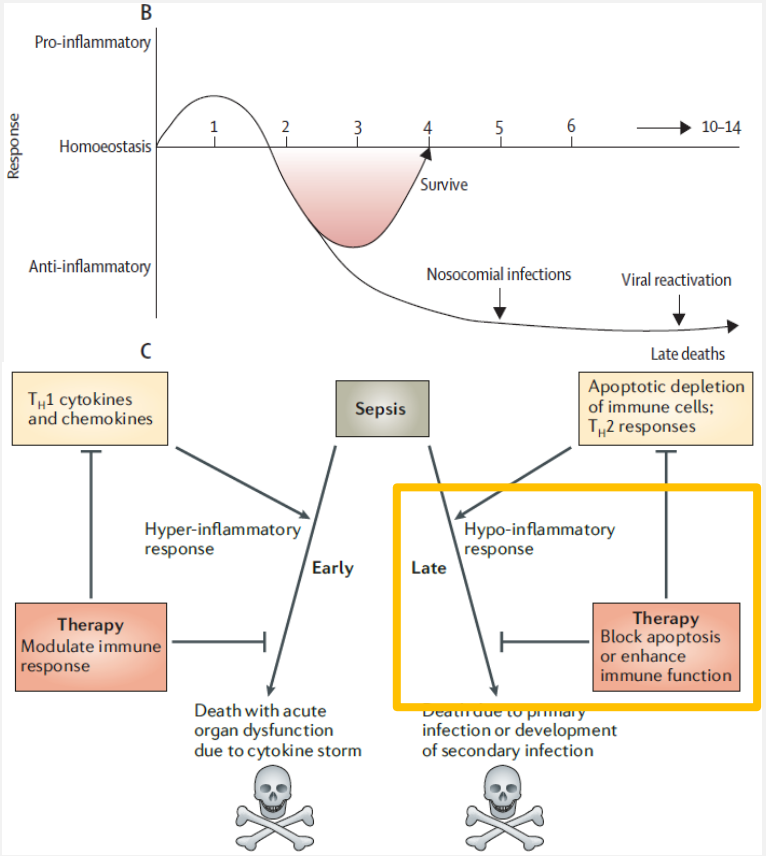


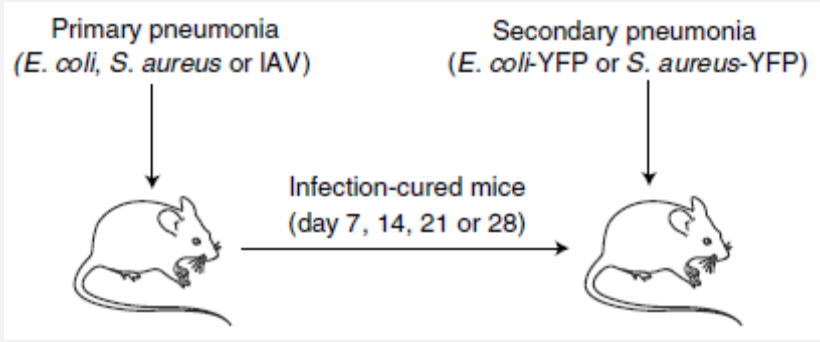
Immunodépression locale : poumon

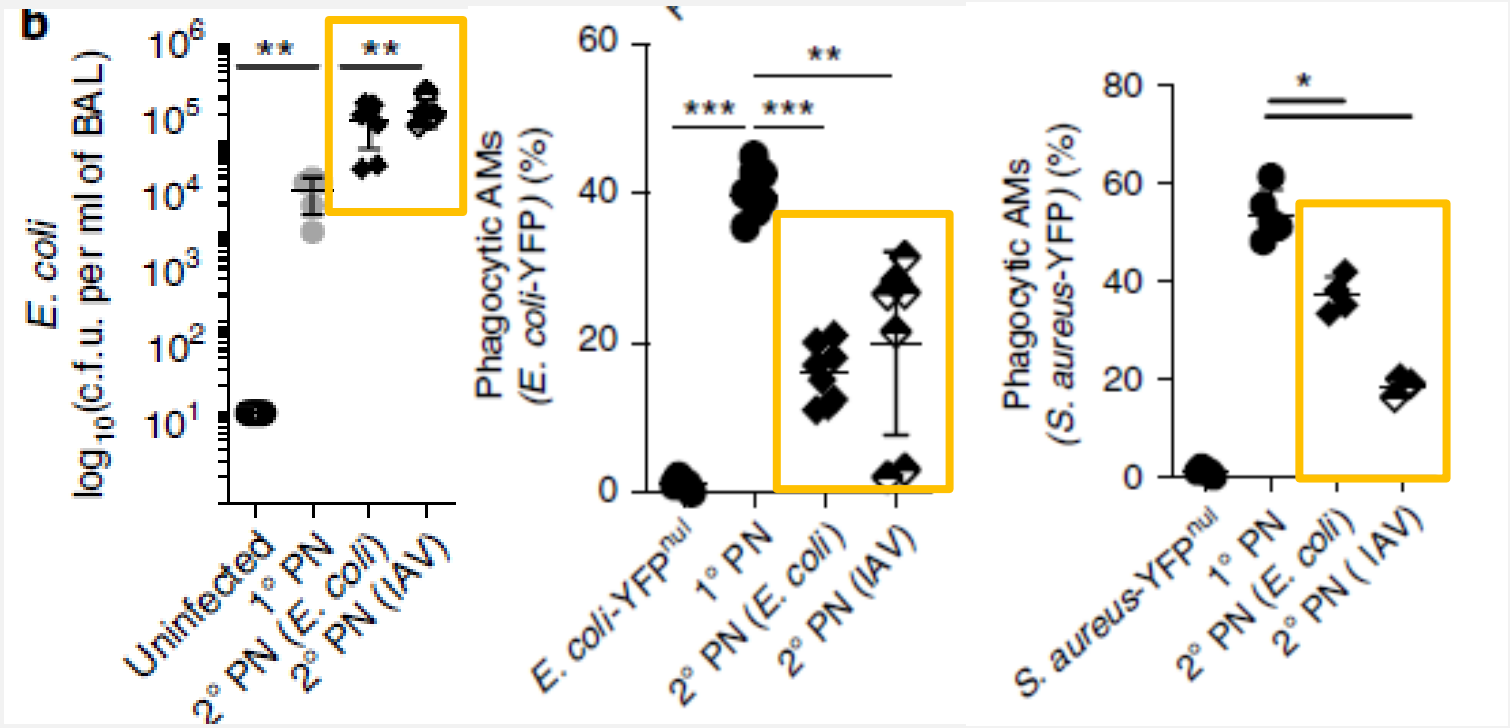


Roquilly *et al.*, Nat Immunol 2020

Immunodépression locale : poumon

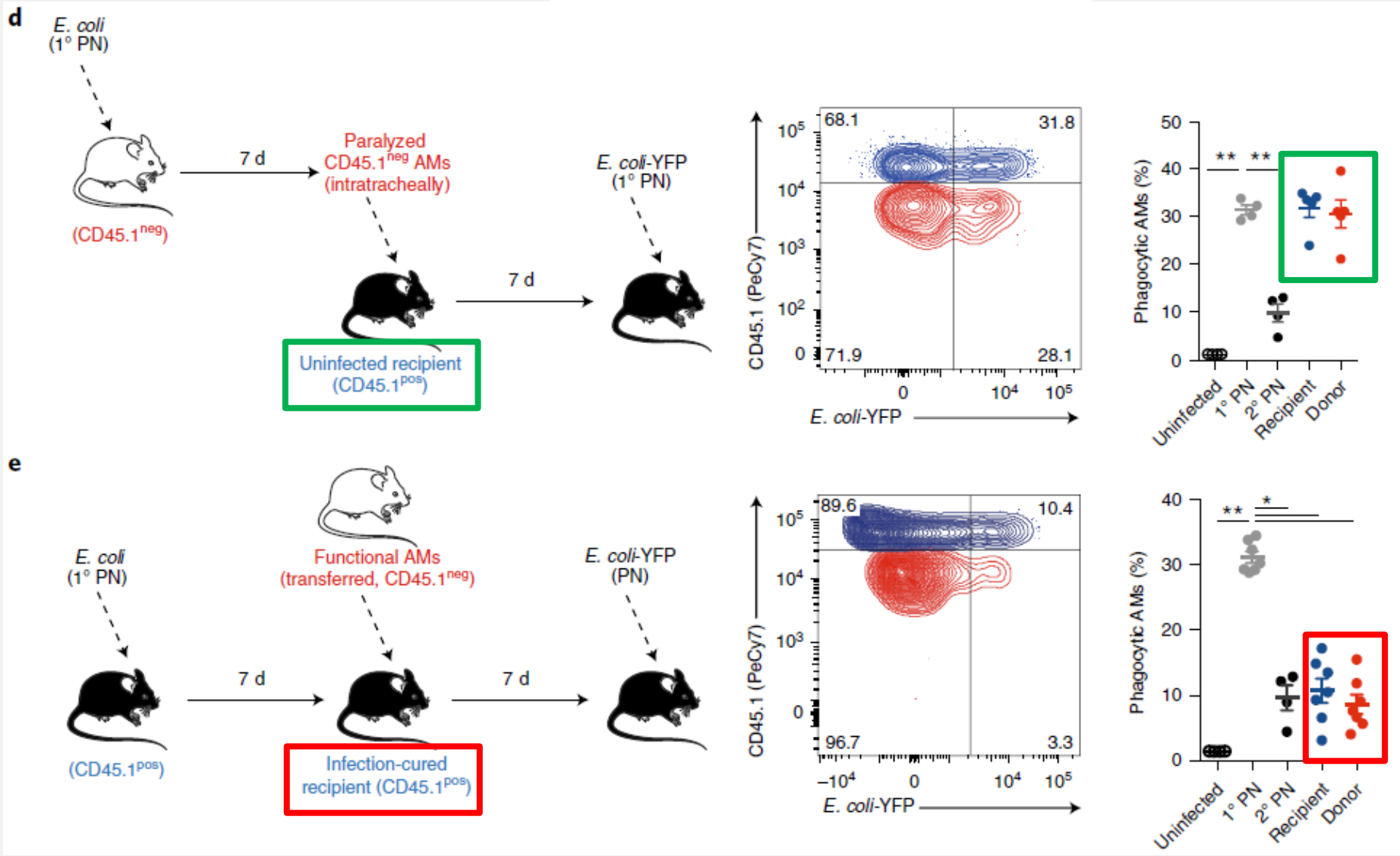






Roquilly *et al.*, Nat Immunol 2020

Immunodépression locale : macrophages alvéolaires



Roquilly *et al.*, Nat Immunol 2020

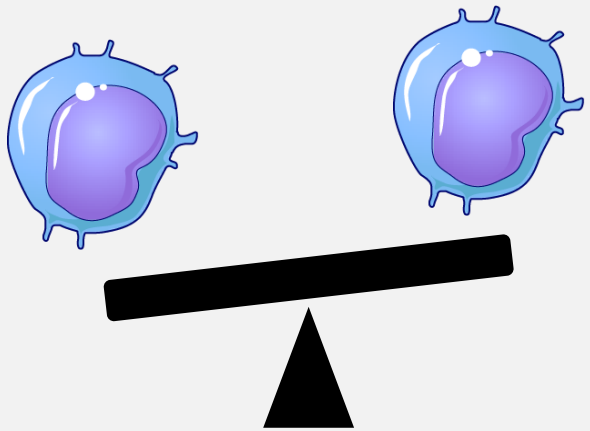
Macrophages alvéolaires anti-inflammatoires

Anti-inflammatoire

Interférons de type I fortes doses (grippe)

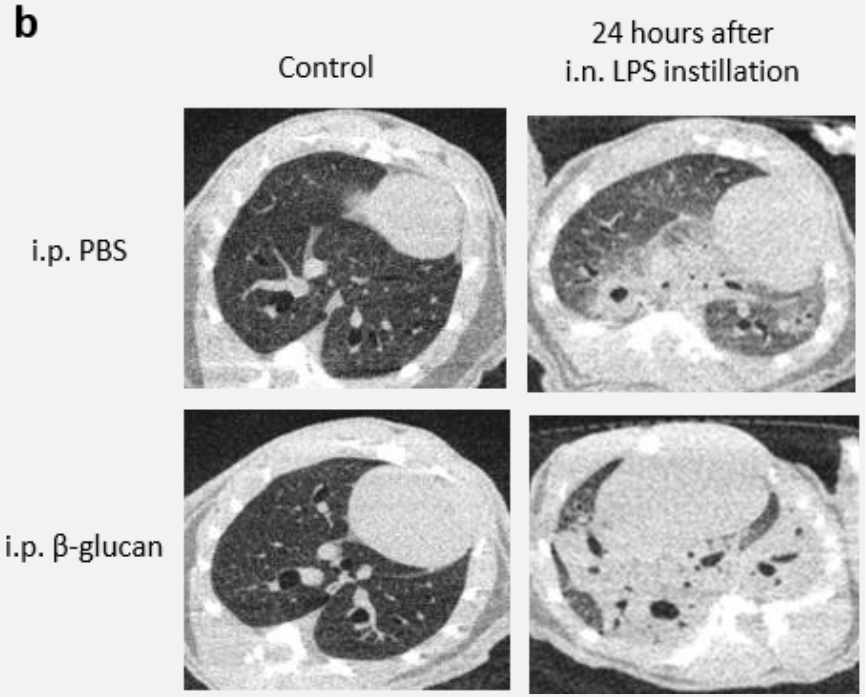
TNF-α fortes doses (LPS systémique)

Micro-environnement
(pneumopathie *E. coli* et *S. aureus*)

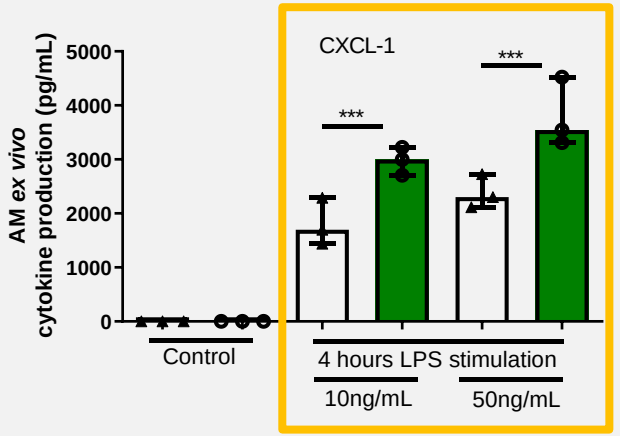


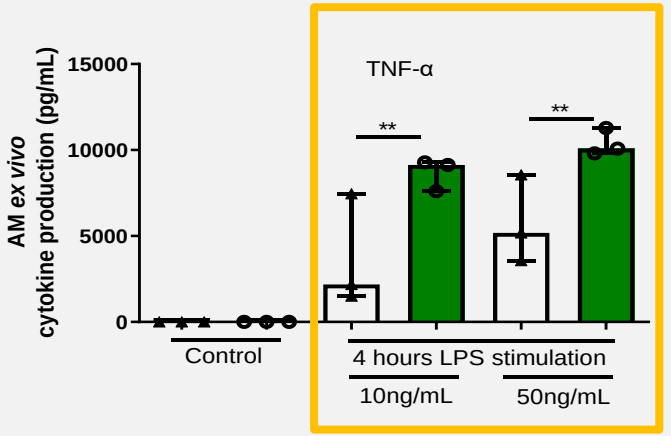
Shahangian *et al.*, J Clin Investig 2009
Nakamura *et al.*, J Clin Investig 2011
Shirey *et al.*, mBio 2019
Mason *et al.*, J Infect Dis 1997
Roquilly *et al.*, Nat Immunol 2020

Immunostimulation des macrophages alvéolaires

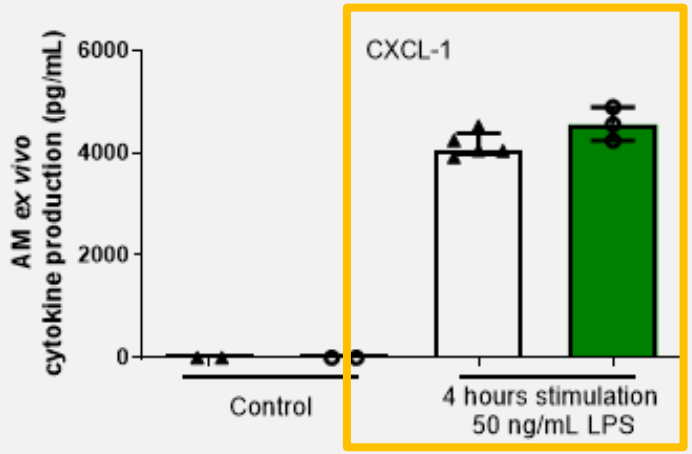


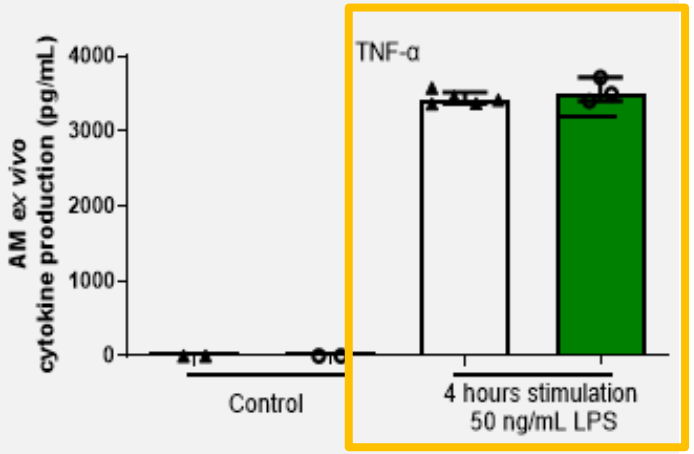
WT





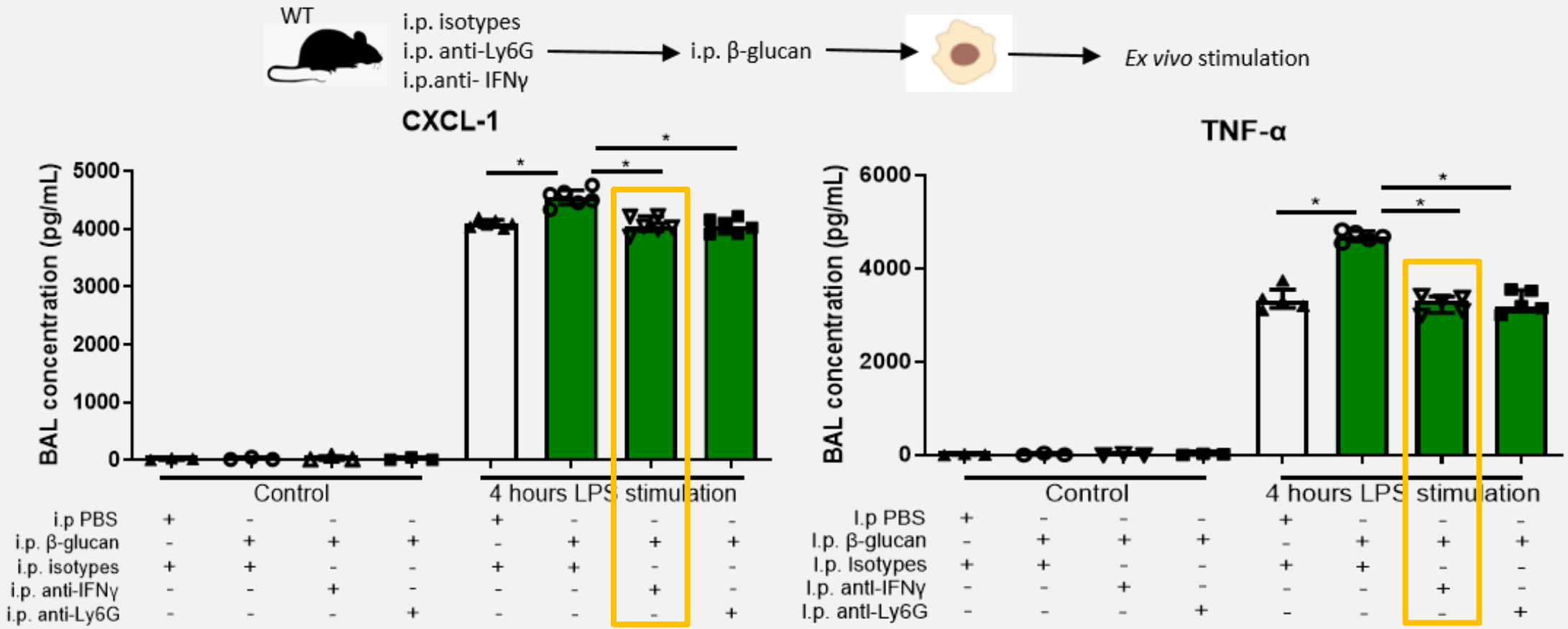
IfngR$^{-/-}$





Prével *et al.*, Unpublished data

Macrophages alvéolaires et IFN γ



Prével *et al.*, Unpublished data

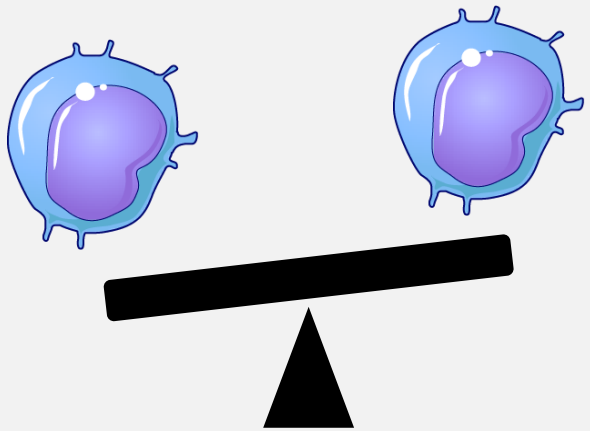
Le retour de l'interféron γ *via* les macrophages alvéolaires

Anti-inflammatoire

Interférons de type I fortes doses (grippe)

TNF-α fortes doses (LPS systémique)

Micro-environnement
(pneumopathie *E. coli* et *S. aureus*)



Pro-inflammatoire

Interférons de type I faibles doses
Faible dose LPS pulmonaire

Interféron γ (type II) faibles doses
β-glucan systémique
S. pneumoniae atténué
Vaccination nasale adénovirus

Shahangian *et al.*, J Clin Investig 2009
Nakamura *et al.*, J Clin Investig 2011
Shirey *et al.*, mBio 2019
Mason *et al.*, J Infect Dis 1997
Roquilly *et al.*, Nat Immunol 2020

Yao *et al.*, Cell 2018
Arafa *et al.*, J Clin Investig 2022
Zahalka *et al.*, Mucosal Immunol 2022
Gu *et al.*, eLife 2021

IFNγ en prévention des PAVM

Patients traumatisés IOT
mHLA-DR sang < 30%
IFN-γ inhalé 100µg * 3/jour (J2-3 pour 7 j)

	Group 1a (n = 11) IFN	Group 1b (n = 10) Placebo	*p* Value
Age, yrs	51 ± 16	47 ± 12	NS
APACHE II score	25.7 ± 5.5	27.4 ± 5.1	NS
ISS	40 ± 16	43 ± 19	NS
Po_2/Fio_2	355 ± 50	374 ± 54	NS
Outcome (deaths)	3/11 (27%)	4/10 (40%)	NS
Incidence of VAP	1/11 (9%)	5/10 (50%)	<.05
Early onset pneumonia	0	1/10 (10%)	
Late onset pneumonia	1/11 (9%)	4/10 (40%)	

	Group 1a (n = 11) IFN		*p* Value	Group 1b (n = 10) Placebo		*p* Value		
	1st BAL	*2nd BAL*	*1st & 2nd 1a*	*1st BAL*	*2nd BAL*	*1st & 2nd 1b*	*1st 1a & 1st 1b*	*1st 1a & 1st 1b*
Total cells in BAL, 10^4/mL	8.9 ± 1.4	8.5 ± 1.09	NS	9.3 ± 1.2	11.8 ± 1.7	NS	NS	<.01
Cell diferential in BAL, %								
Macrophages	73 ± 6	65 ± 6	NS	71 ± 7	66 ± 9	NS	NS	NS
Neutrophils	14 ± 3.2	20 ± 7	NS	14 ± 2.8	19 ± 8	NS	NS	NS
Lymphocytes	11 ± 5	14 ± 4	NS	12 ± 3	12 ± 4	NS	NS	NS
Total protein in BAL, µg/mL	138 ± 31	155 ± 24	NS	147 ± 30	177 ± 29	NS	NS	NS
HLA-DR expression	16.4 ± 5.4	44 ± 12.7	<.0001	19 ± 6	22 ± 6	NS	NS	<.001

Nakos *et al.*, Crit Care Med 2002

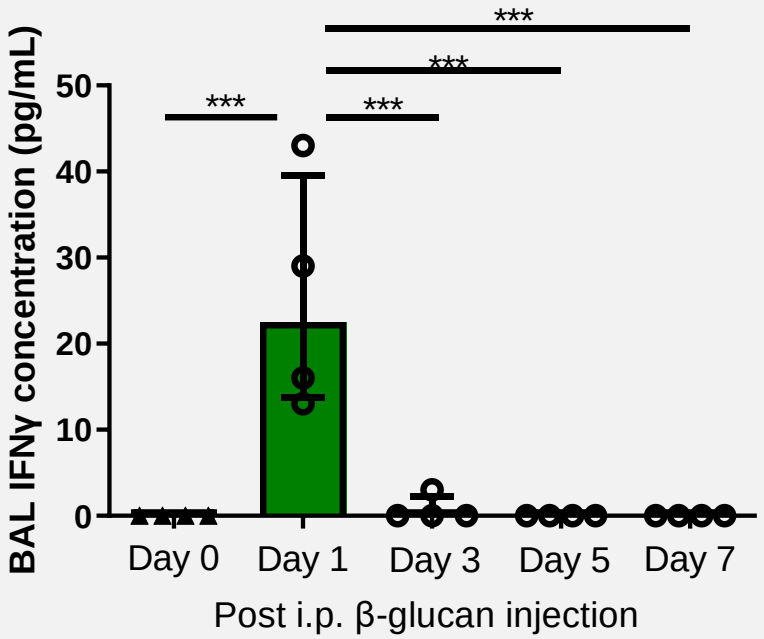
Patients traumatisés 50%, 5% sepsis
IFN-γ SC 100µg/2 jours J1 à J9

	IFNγ	Placebo	HR [95CI]
HAP/ mortalité J28	26/55 (47,3%)	16/53 (30,2%)	1,76 [0,94-3,29]
Mortalité J28	7/55 (12,7%)	9/53 (17%)	0,68 [0,25-1,85]
HAP	19/55 (34,5%)	8/53 (15,1%)	2,06 [0,92-4,57]
			p-value
Effets indésirables graves	24 (43,6%)	17 (31,5%)	0,19

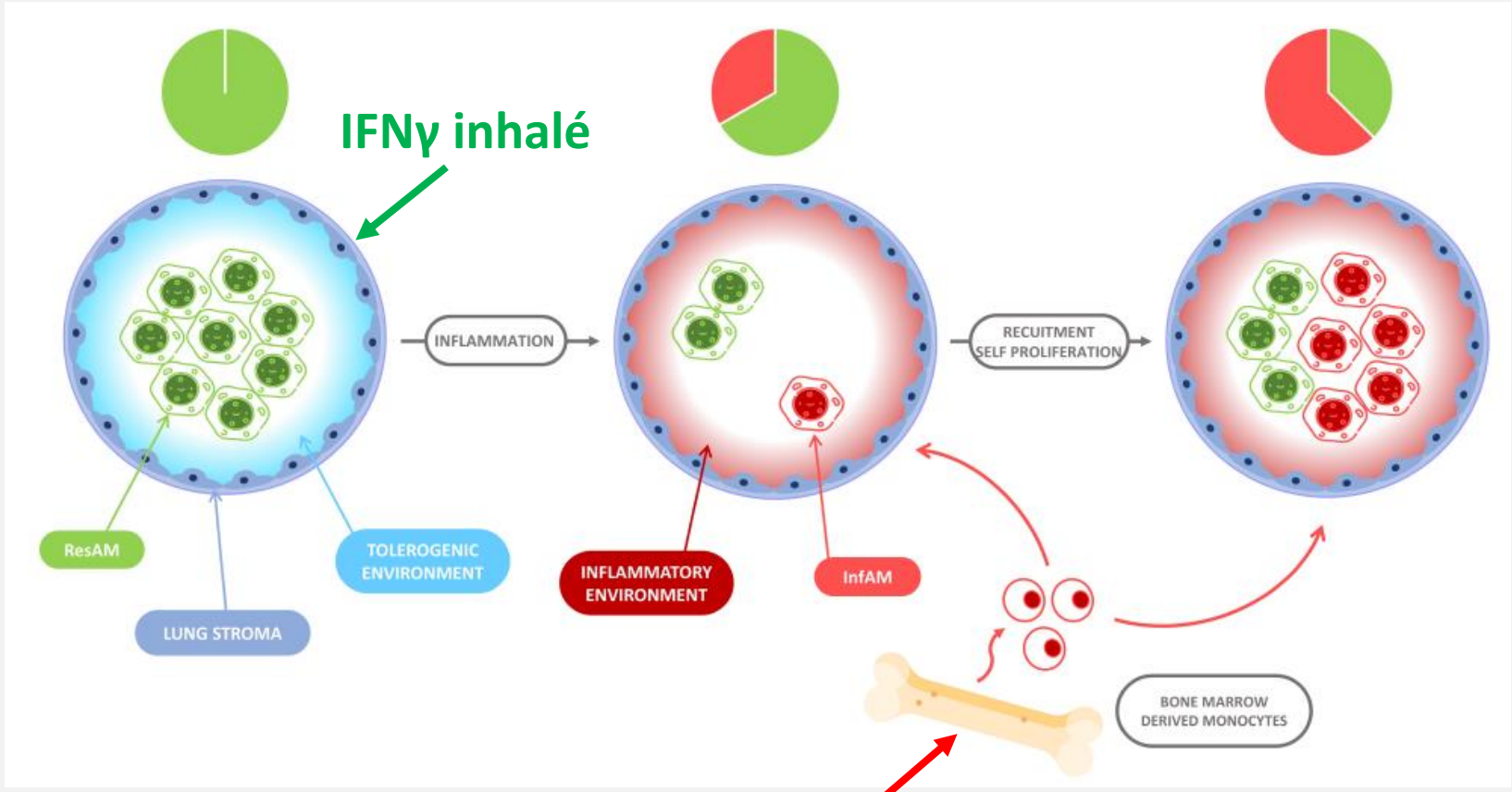
Roquilly *et al.*, Intensive Care Med 2023

Comment expliquer cette différence ?

Dose ?

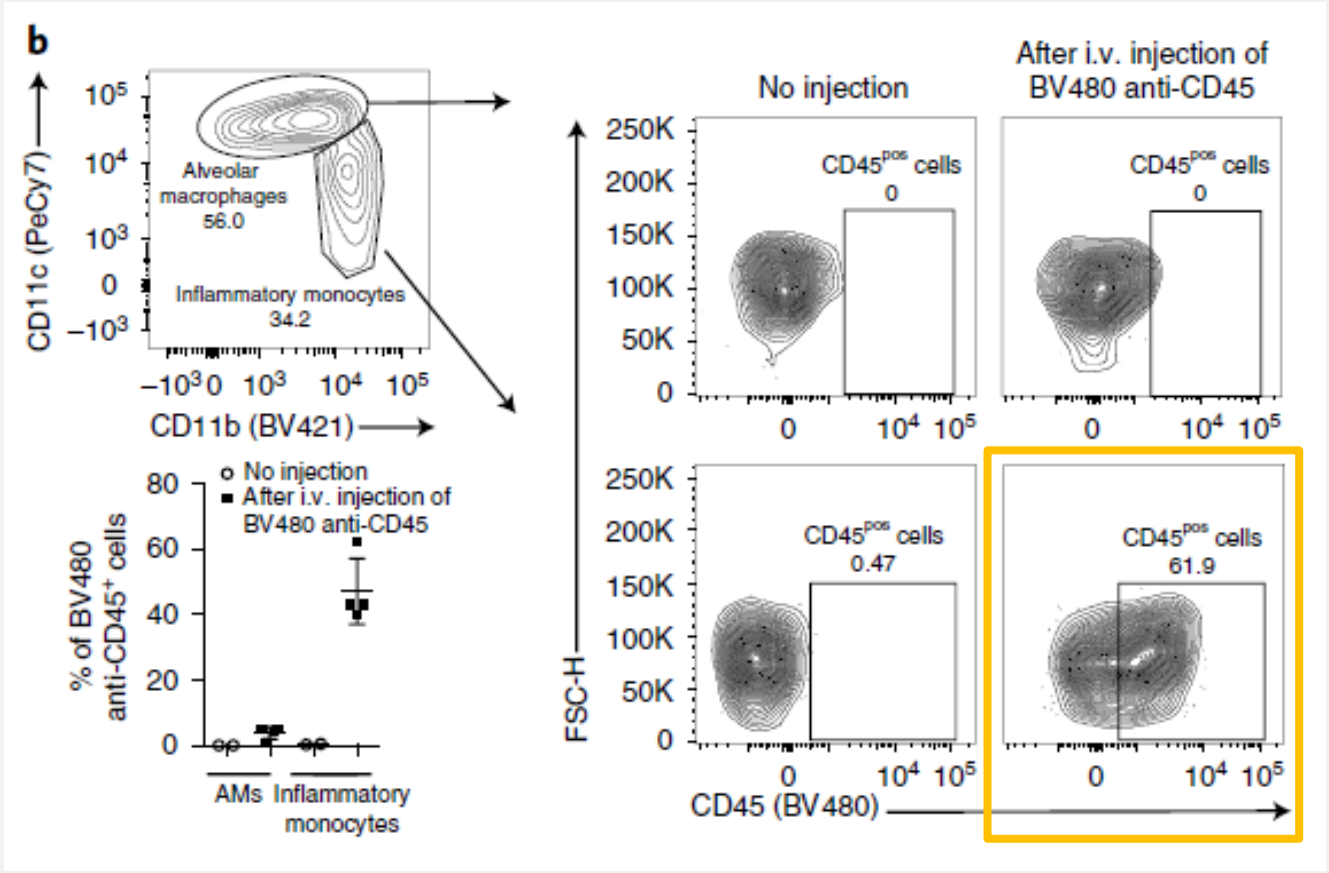


Voie d'administration : AM vs IM ?



Prével *et al.*, Unpublished data
Martin *et al.*, Intensive Care Med 2023

Sélection des patients



Dosage sang circulants mHLA-DR pour inflammation extra-pulmonaire ?

Macrophages alvéolaires / dérivés des monocytes sur LBA ?

Conclusion

Pas (peu : corticoïdes ?) de traitement efficace sur la phase hyperinflammatoire

Choc septique : immunodépression secondaire +/- polytraumatisé

Prise en charge de cette immunodépression induite

- Quels marqueurs ?
- Systémique *vs* organes ?
- Quels objectifs ?

Quel impact à long terme ?

Rôle du microbiote ? Du système neuro-végétatif ?

Développement des cellules souches mésenchymateuses ?

Perspectives

Immunity

Review

The immunology of sepsis

Tom van der Poll,[1,*] Manu Shankar-Hari,[2,3] and W. Joost Wiersinga[1]

Despite more than three decades of research and more than 200 randomized controlled trials, we do not have a single treatment that consistently saves lives in sepsis patients

Van der Poll T. *Immunity* 2021

« *We believe that **single agent** immune-modulatory intervention, as attempted in past sepsis trials, **will probably fail*** »
Delano, J Clin Invest 2016

Perspectives

Immunity

Review

The immunology of sepsis

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Van der Poll T. *Immunity* 2021

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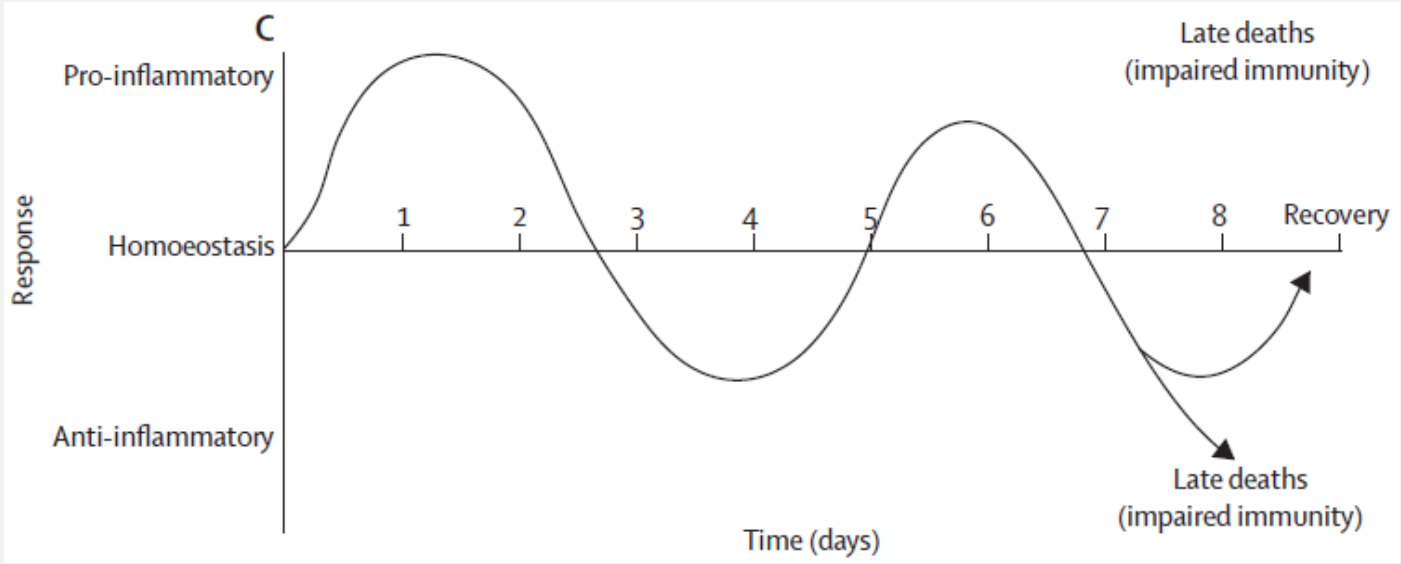
Delano, J Clin Invest 2016

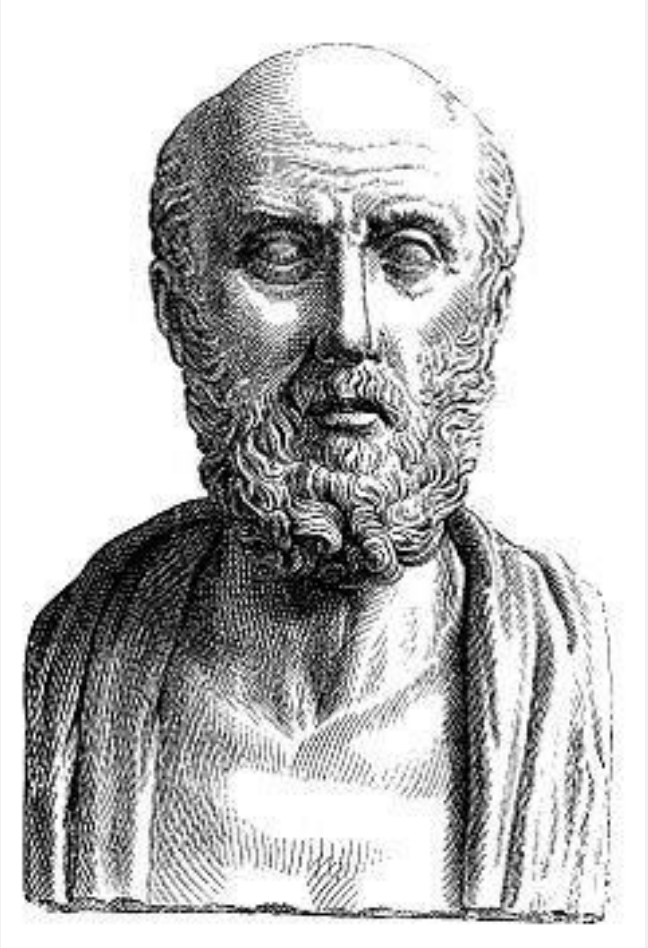
« We should spend **more time learning** how to achieve an accurate diagnosis and **less time searching for a magic bullet** »

Roger C. Bone (1941- 1997)

Perspectives

« *Conversely, the notion of more thorough and rigorous patient selection, coupled with frequent monitoring of immune function and* ***goal-directed immune modulatory therapy involving multiple agents****, may, over time,* ***provide optimal clinical benefit***»
Delano J Clin Invest 2016





Primum non nocere

Divangahi's lab, McGill university

Prof Maziar Divangahi
Dr Leonardo Jurado
Kim Tran
Mina Sadeghi
Julia Chronopoulos
Elizabeth Lapshina
Vera Lynn
Kristina Nikolaou

Former members
Dr Erwan Pernet
Dr Nargis Khan
Dr Eva Kaufman
Dr Shradha Wali
Dr Renata Sindeaux
Alexandre Grant
Thierry Legroux
Carolanne Plourde
Dawn Attride

MEAKINS CHRISTIE

Fonds de recherche Santé Québec

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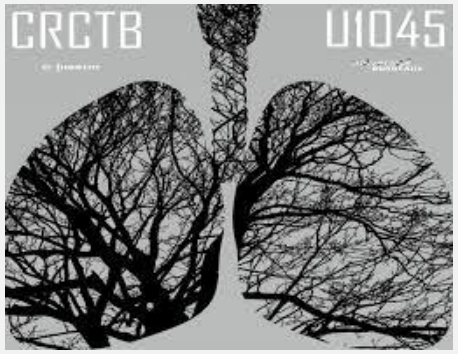
Centre de Recherche Cardio-Thoracique de Bordeaux U1045



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Groupe Micro-mycobiote

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Dr Raphaël Enaud
Dr Sébastien Imbert
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Groupe BPCO

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siRNA

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