JN 22es Journées Nationales d'Infectiologie

Immunomodulation for difficult-to-treat infections

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Conflicts of interest

- Personnal funding + grants from BioMerieux and Merck

What is a “difficult-to-treat infection”?

Difficult-to-treat infections and Resident bugs ?

Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis

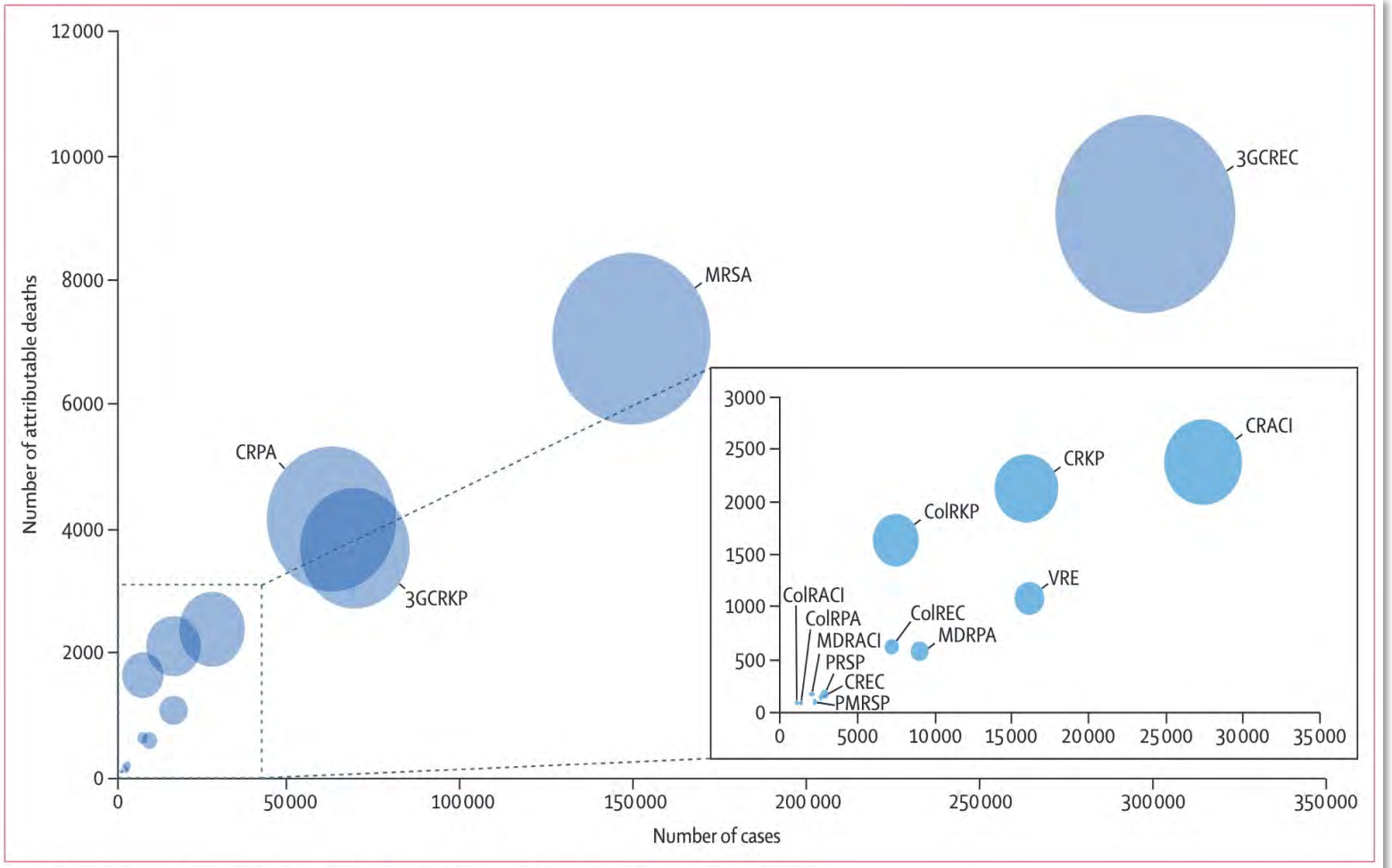


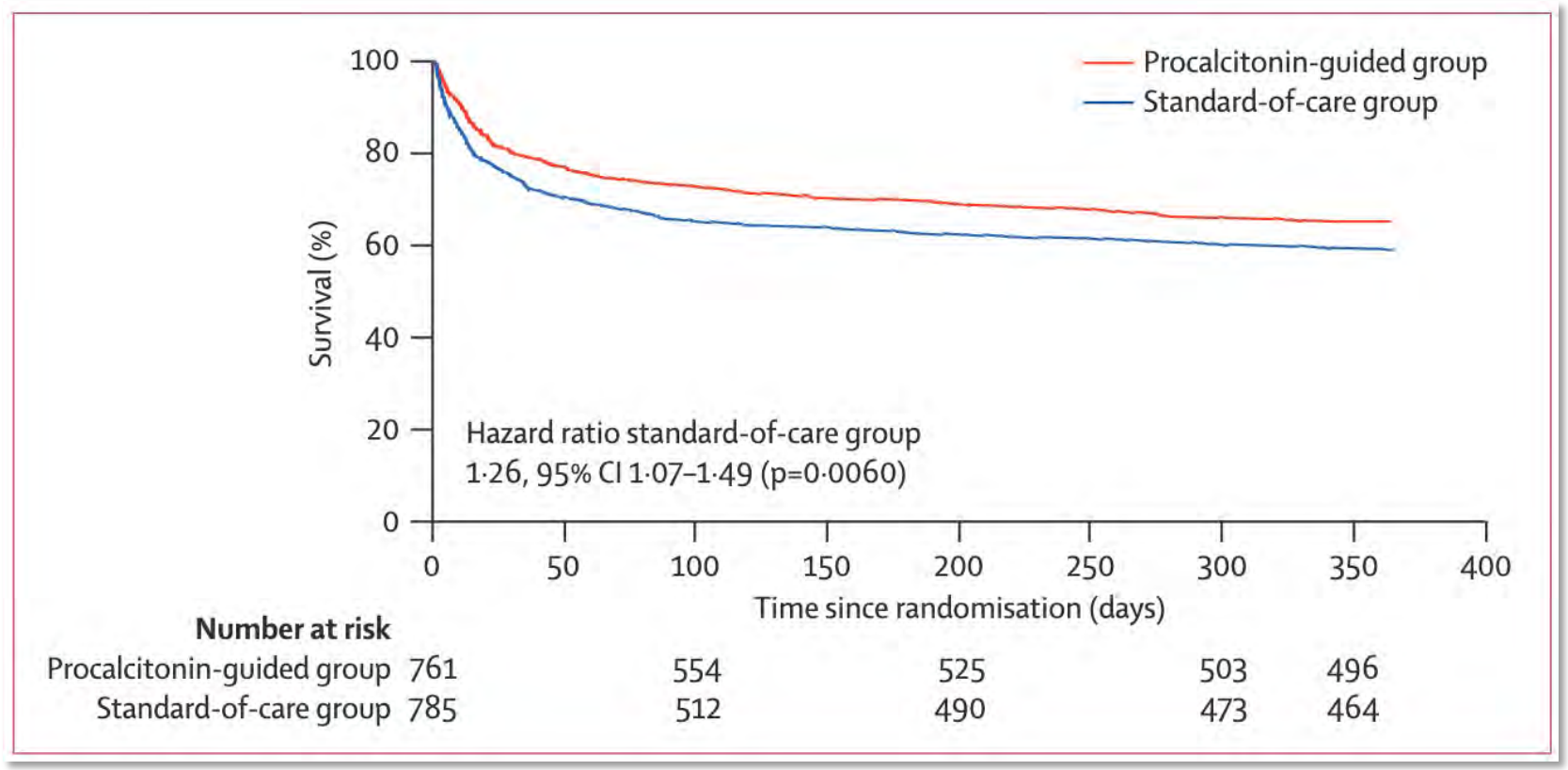
Figure 1: Infections with antibiotic-resistant bacteria, EU and European Economic Area, 2015

Difficult-to-treat infections

Do we need immunotherapies to improve outcomes of patients with “easy-to-treat infections”?

Antimicrobial therapy and the roof of glass

The example of septic shock



De Jong et al. Lancet Infect Dis 2016

Antimicrobial therapy and the roof of glass

The example of hospital-acquired pneumonia

Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial

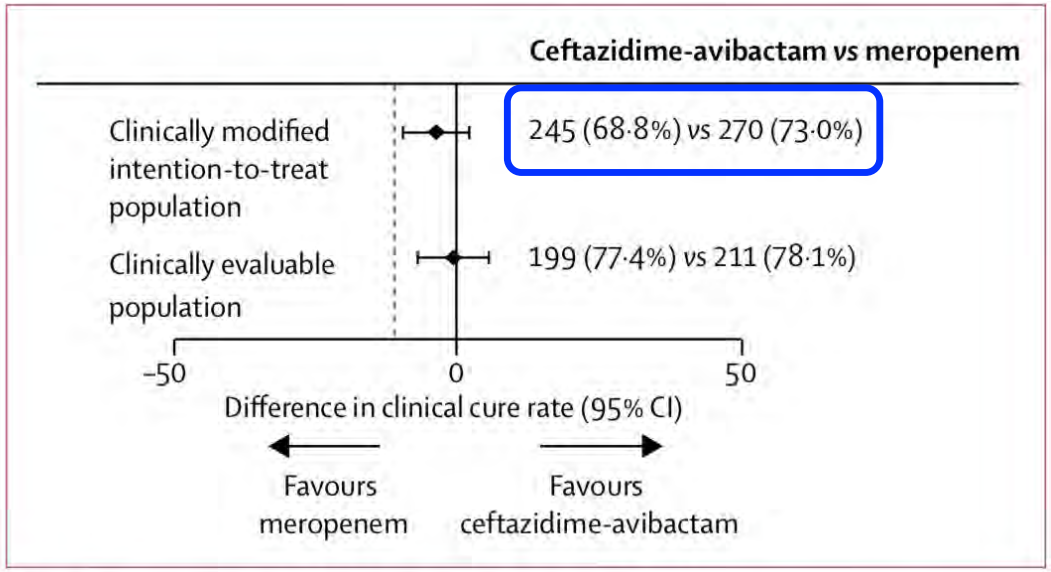


Figure 2: **Clinical cure rates at test-of-cure visit**
Data are number of patients with clinical cure (%). Dashed line indicates non-inferiority margin of −12·5%.

Implementation of French Recommendations for the Prevention and the Treatment of Hospital-acquired Pneumonia: A Cluster-randomized Trial

Roquilly et al. Clin Infect Dis 2020

	Before reco. N=600 patients	After reco. N=669 patients	P-value
Treatment failure	99 (66%)	117 (**75%**)	0.16
Death at day 28	104 (17%)	113 (**17%**)	0.93

Difficult-to-treat infections

Do we need immunotherapies to improve outcomes of patients with "easy-to-treat infections"?

YES

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Box 3. New Terms and Definitions

- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.

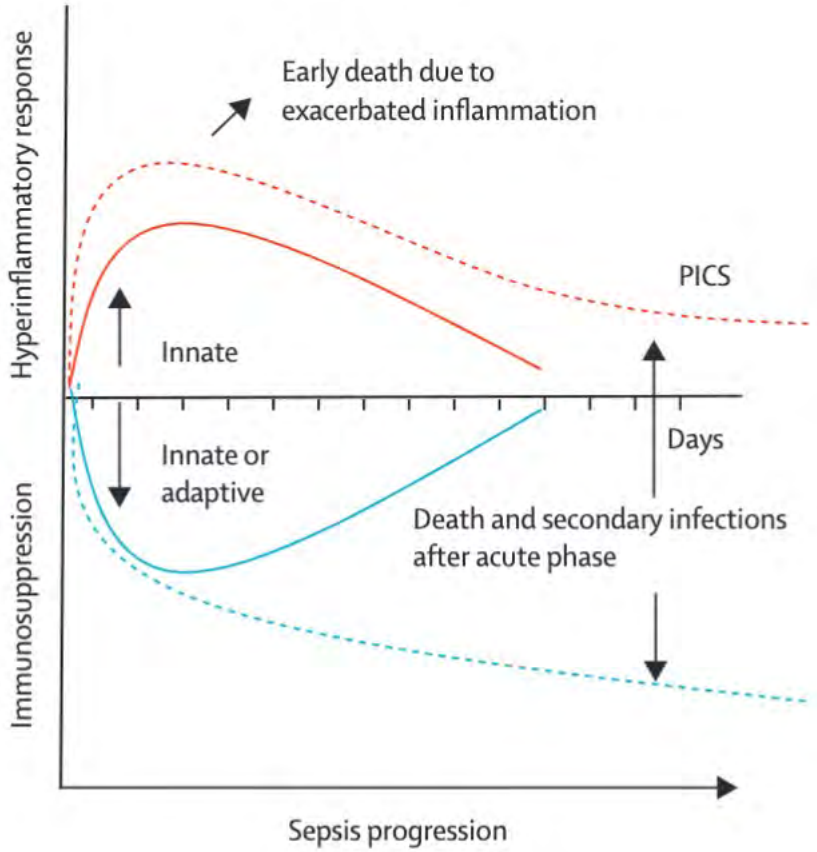
→ **immunotherapy**

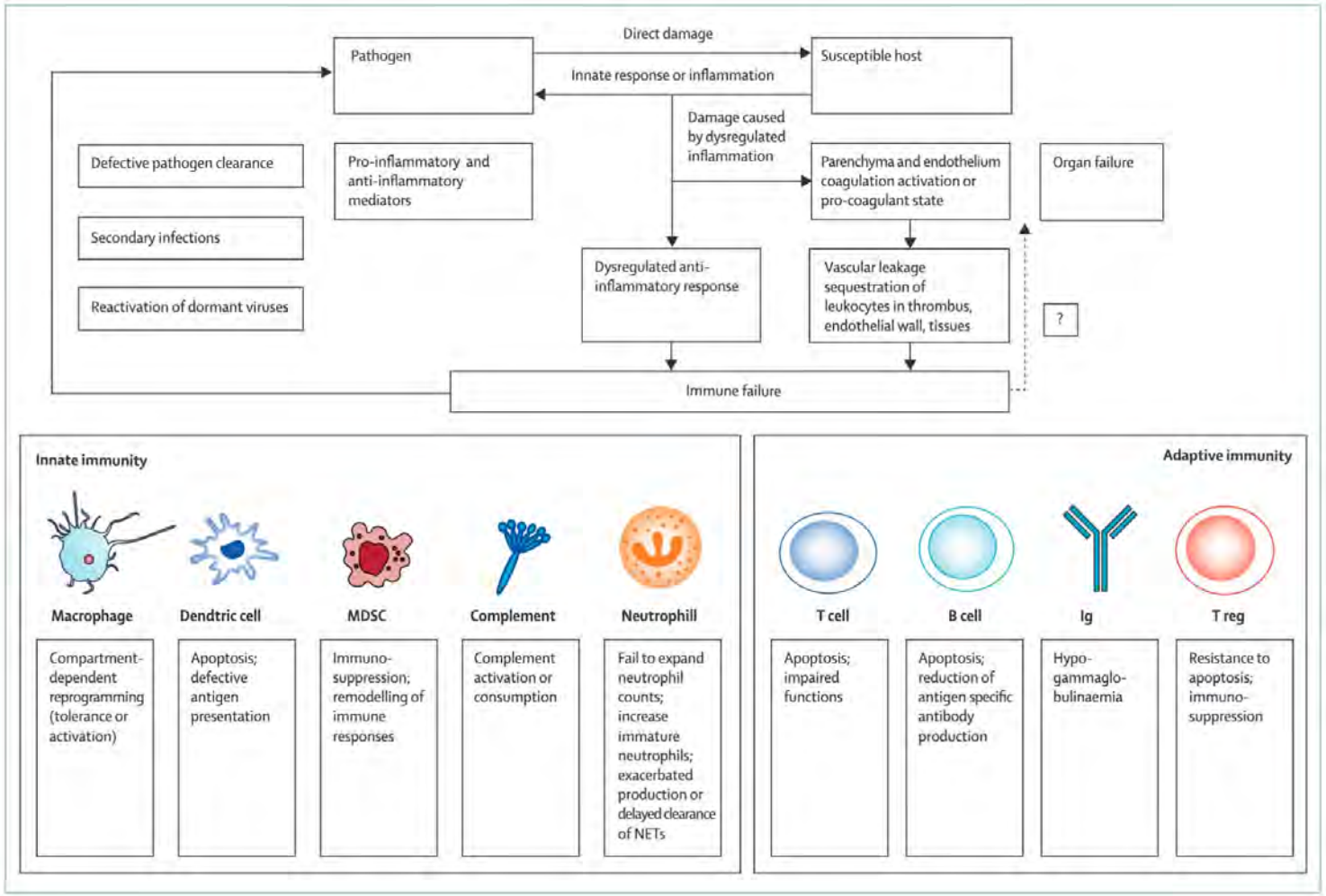
Immune physiology and sepsis

Current gaps in sepsis immunology: new opportunities for translational research

Ignacio Rubio, Marcin F Osuchowski, Manu Shankar-Hari, Tomasz Skirecki, Martin Sebastian Winkler, Gunnar Lachmann, Paul La Rosée, Guillaume Monneret, Fabienne Venet, Michael Bauer, Frank M Brunkhorst, Matthijs Kox, Jean-Marc Cavaillon, Florian Uhle, Markus A Weigand, Stefanie B Flohé, W Joost Wiersinga, Marta Martin-Fernandez, Raquel Almansa, Ignacio Martin-Loeches, Antoni Torres, Evangelos J Giamarellos-Bourboulis, Massimo Girardis, Andrea Cossarizza, Mihai G Netea, Tom van der Poll, André Scherag, Christian Meisel, Joerg C Schefold, Jesús F Bermejo-Martín

Lancet Infect Dis 2020





Immune physiology and (?) sepsis (?)

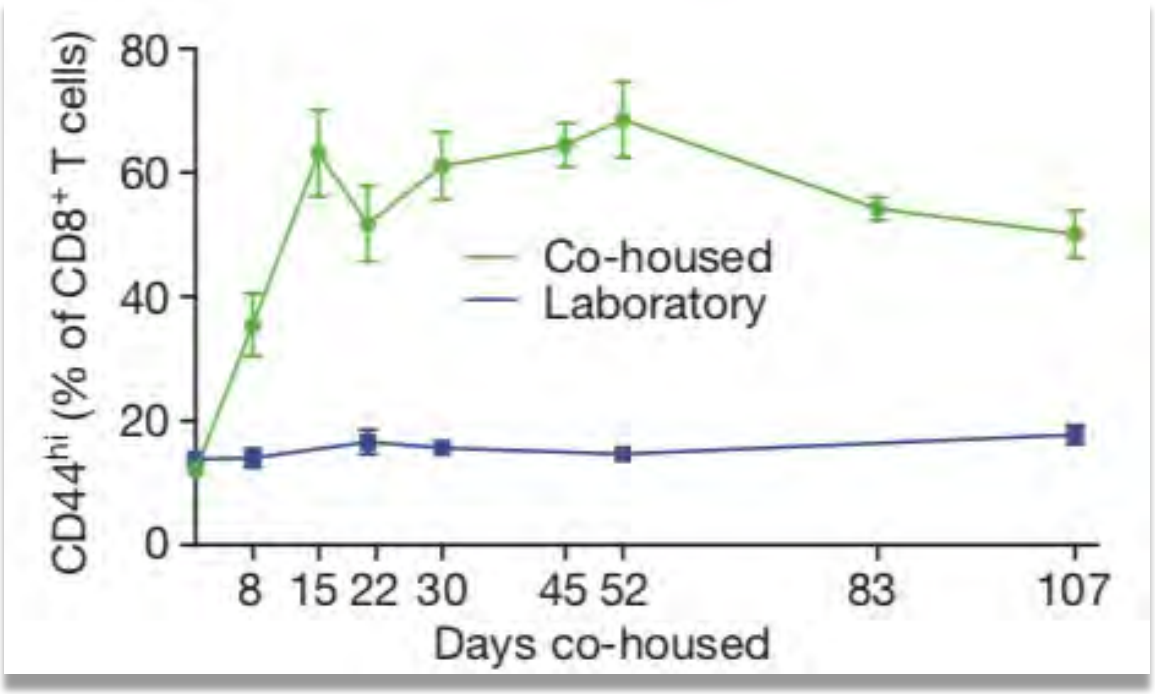
1. **It is critical to differentiate infection of a sterile tissue from mucosal infection**

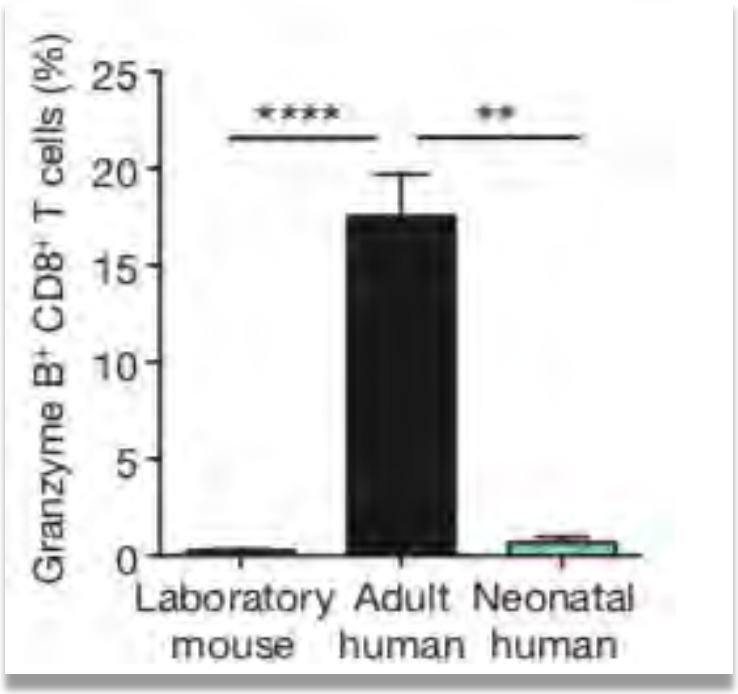
2. Dysbiosis, a refined concept of mucosal infection physiopathology

Roquilly et al. Lancet respir Med 2019

Host-pathogen interactions: a mutual benefit

Ex. Immune competence





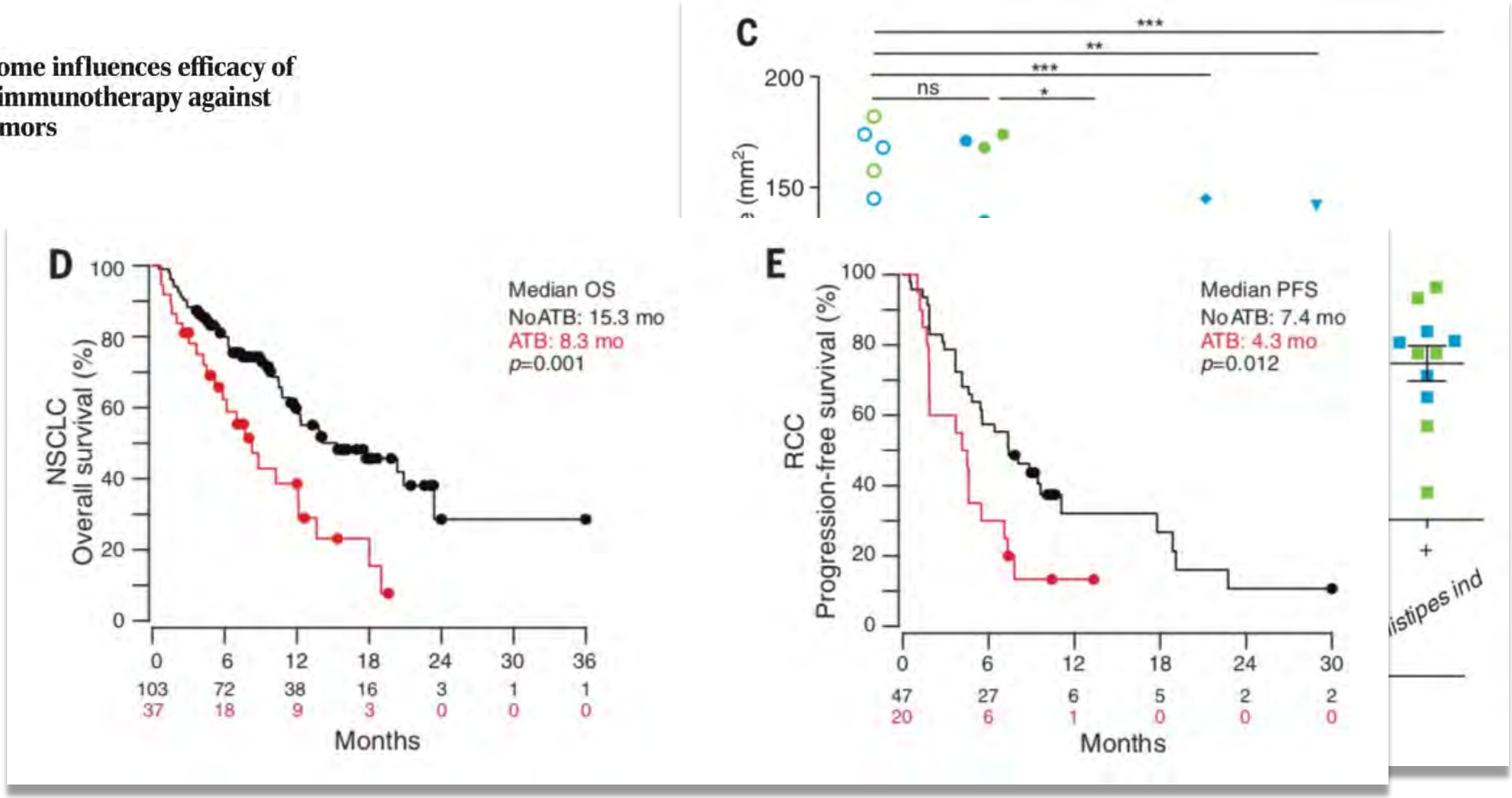
Beura et al. Nature 2016

Host-pathogen interactions: a mutual benefit

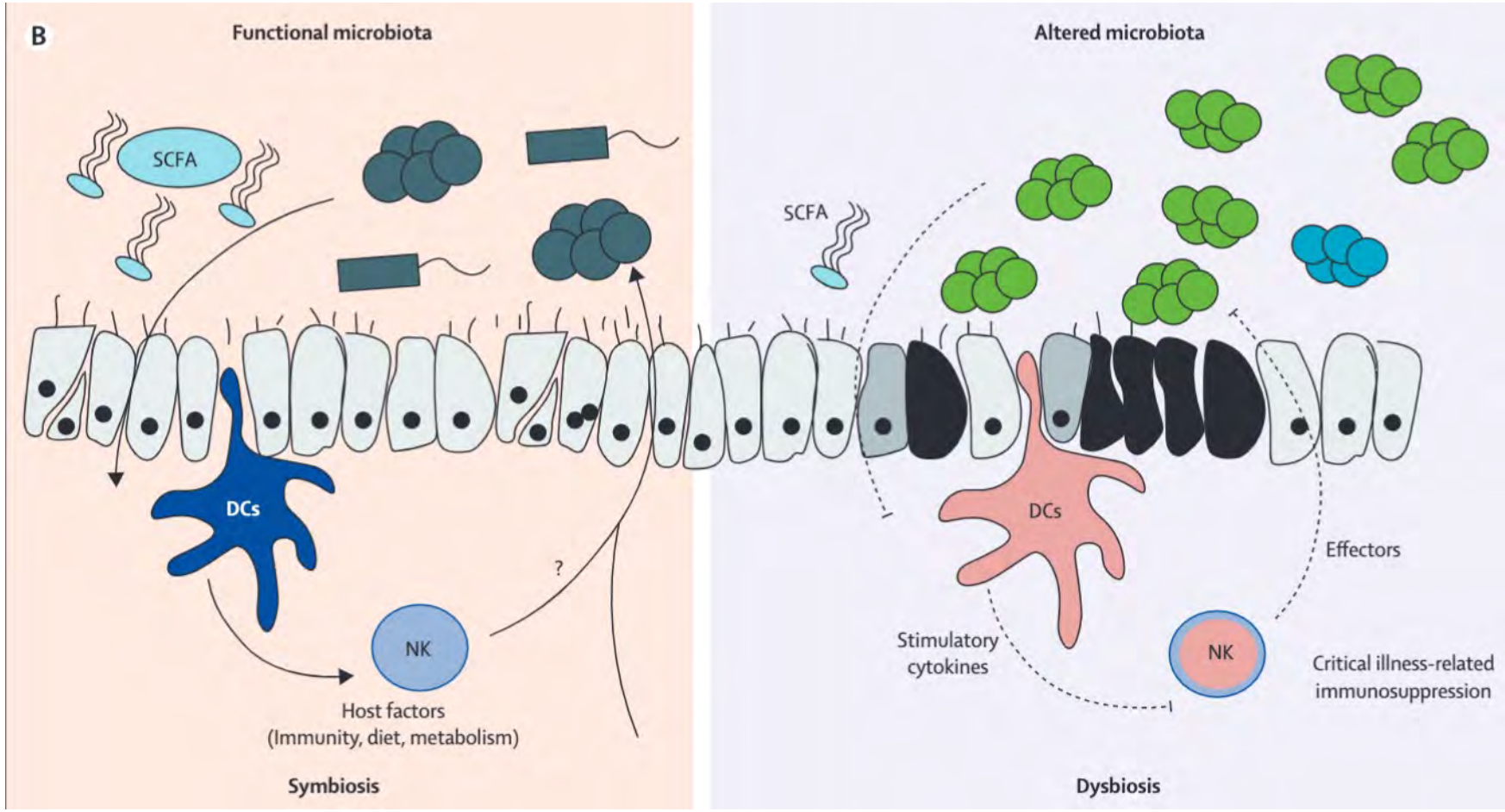
Ex. Immunomudulation by antiobitics

Science

Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors

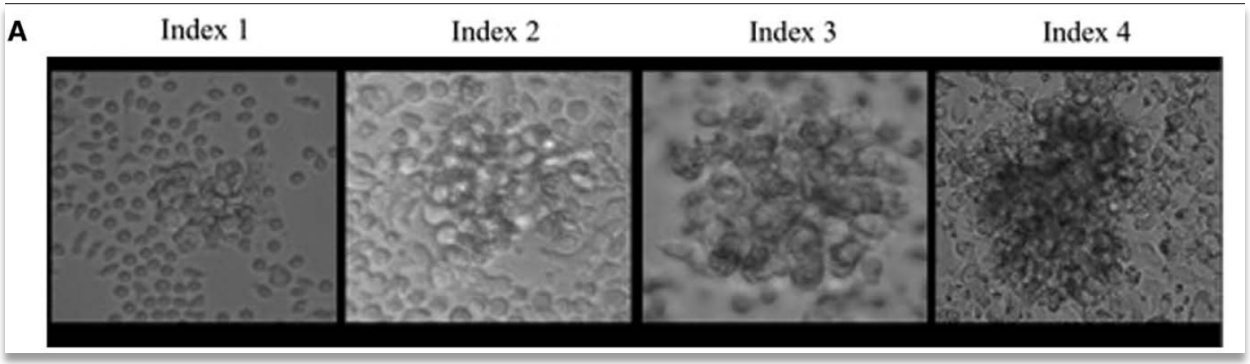


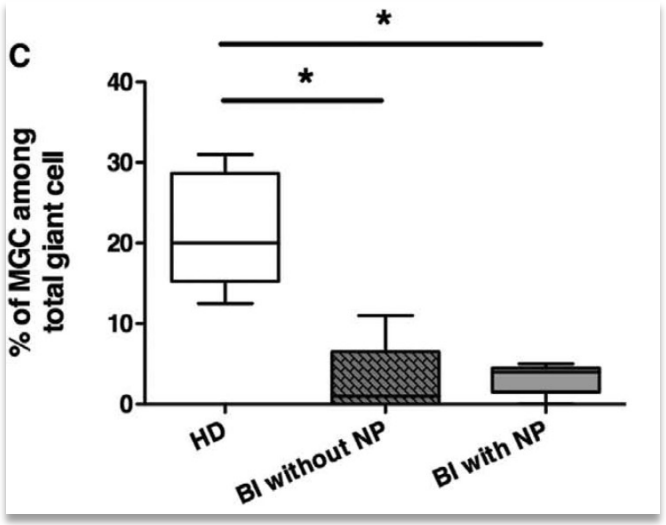
We need more knowledge on the mucosal immunity status before and during mucosal infections to have the full picture

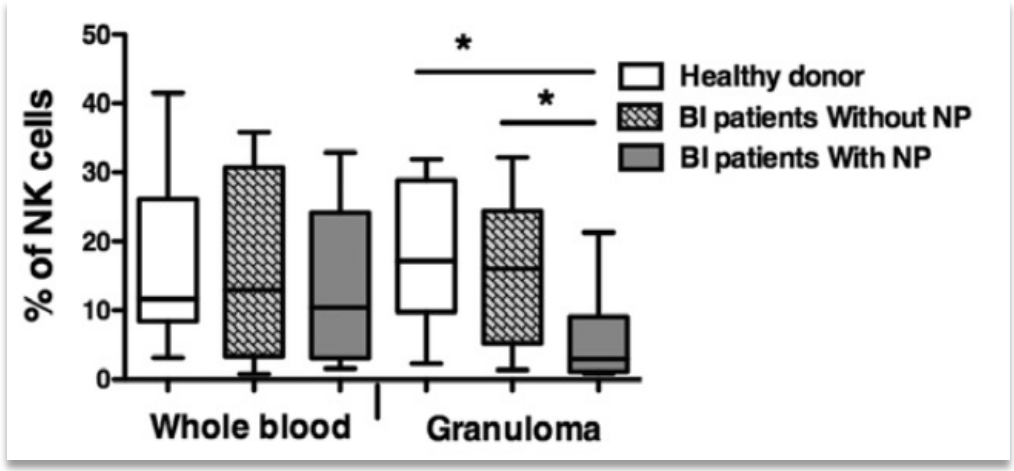


Immunity and hospital-acquired pneumonia

defect in myeloid / NK cells interactions



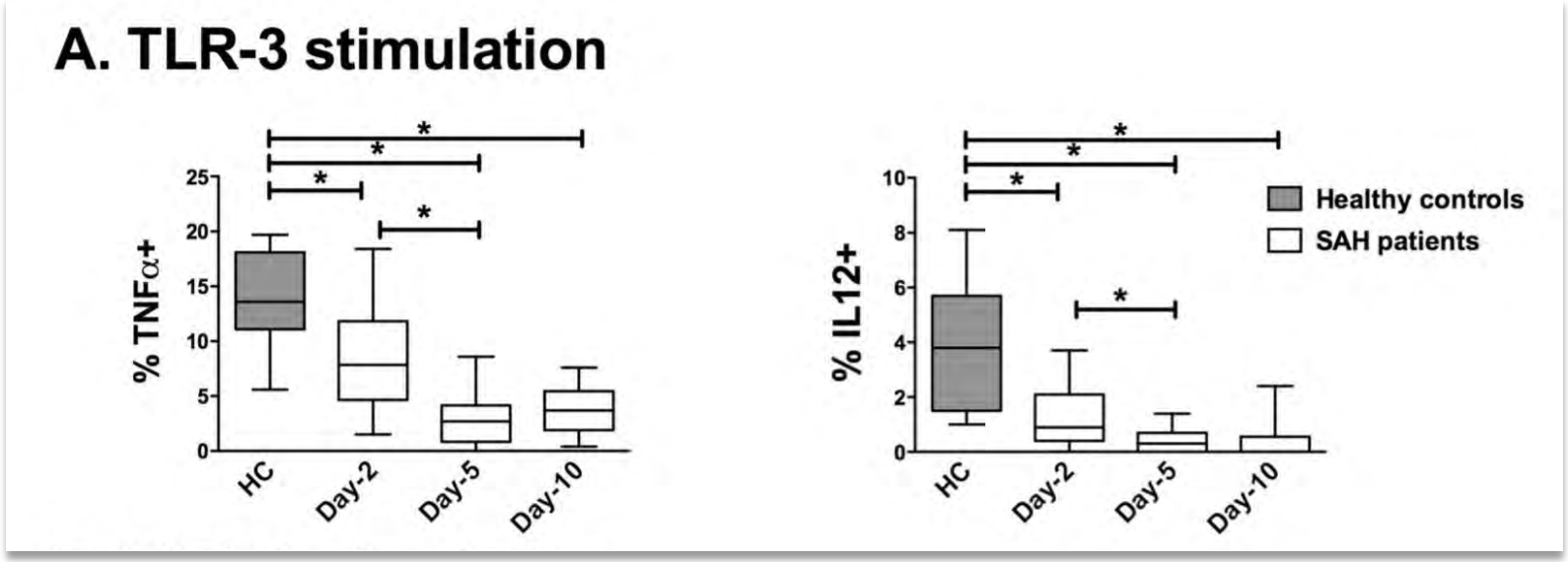




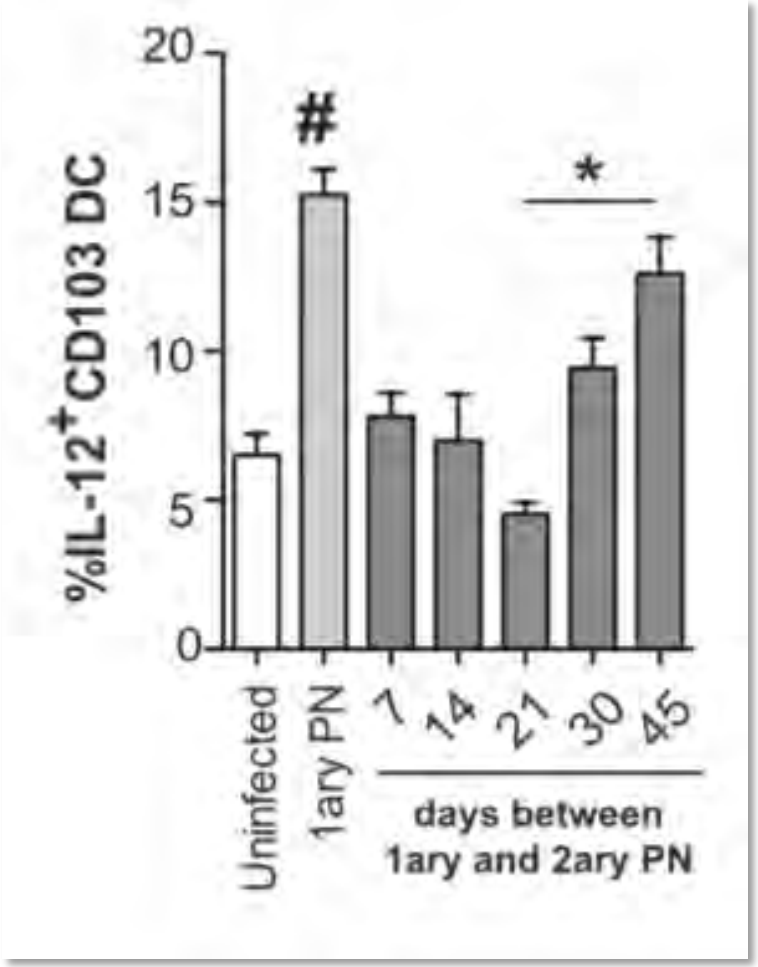
Deknuydt et al. Crit Care Med 2013

Immunity and hospital-acquired pneumonia

Production of IL-12 by DCs is decreased during HAP



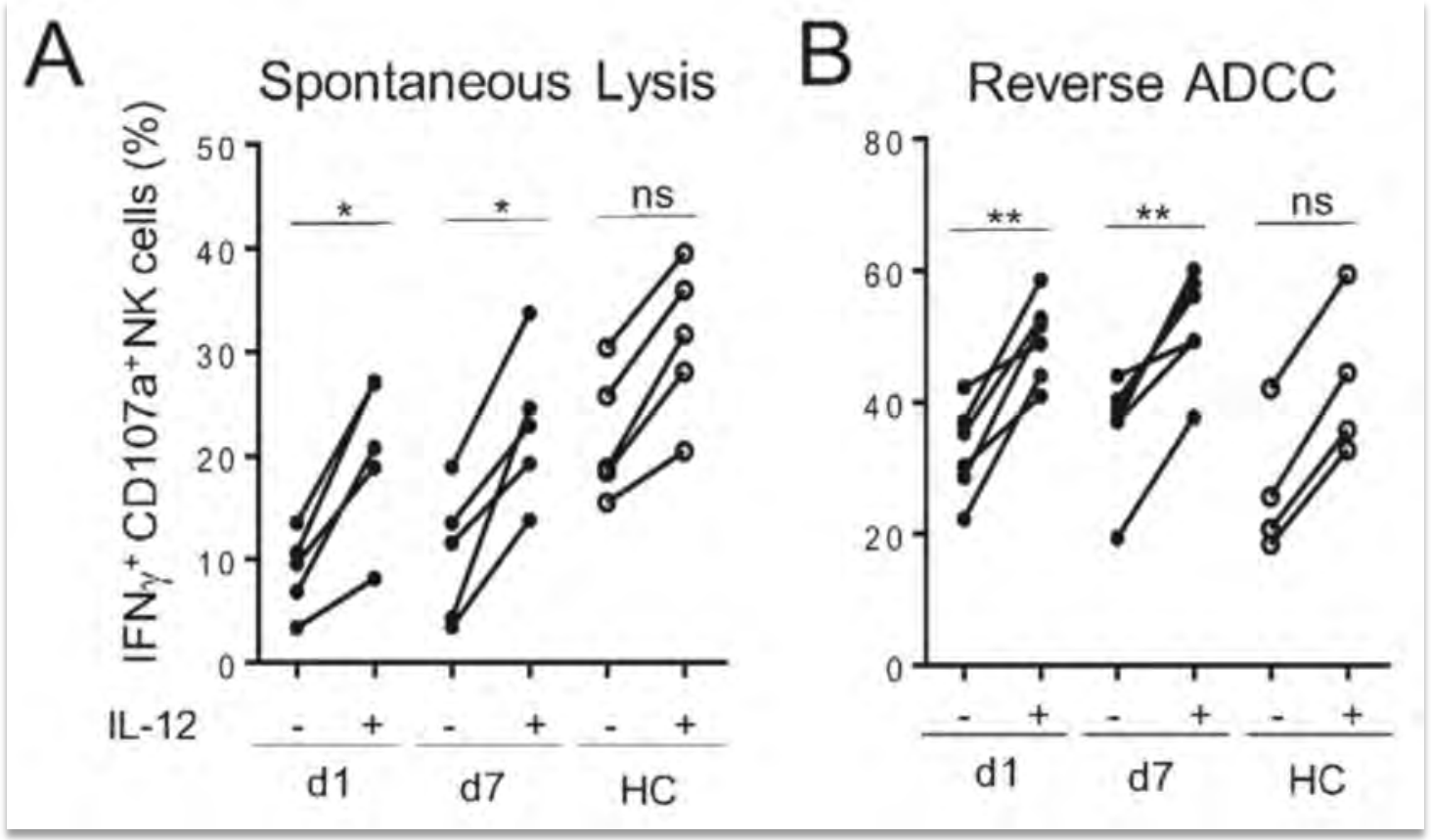
Roquilly et al. PLoS one 2013



Roquilly et al. Immunity 2017

Immunity and hospital-acquired pneumonia

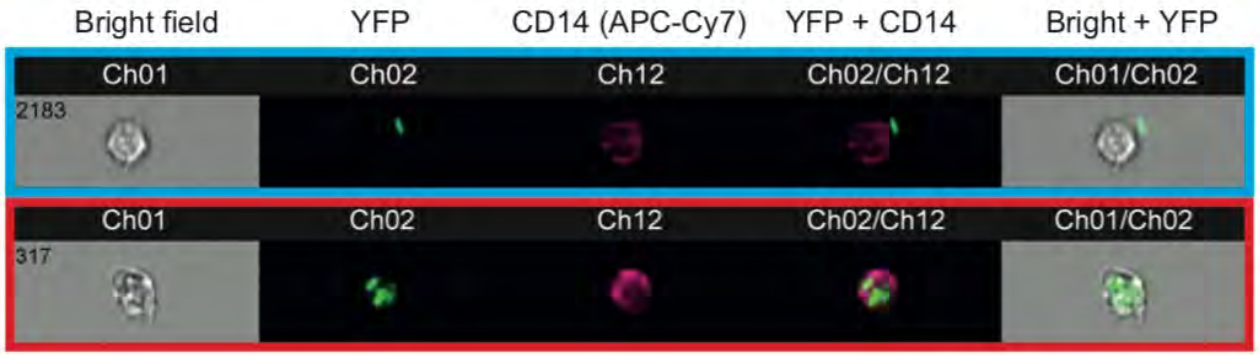
IL12 treatment restored IFNg production by NK cells function in vitro

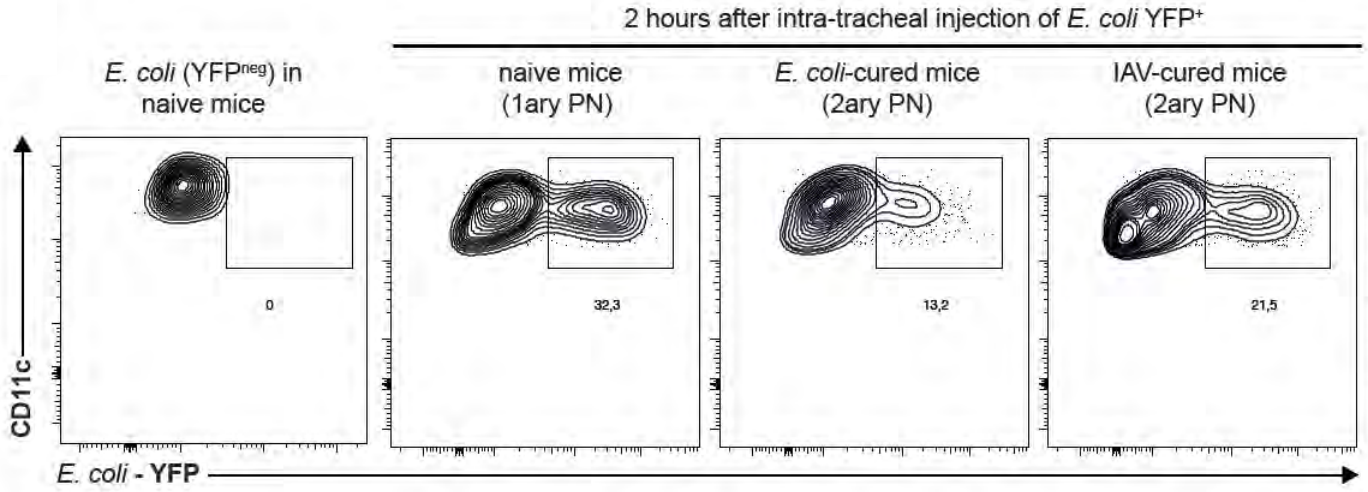


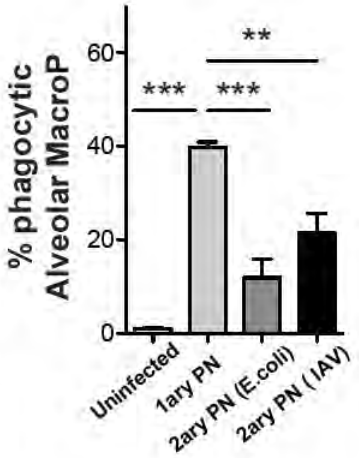
Roquilly et al. Clin Immunol 2015

Immunity and hospital-acquired pneumonia

Capacity of phagocytosis by AM is decreased during HAP

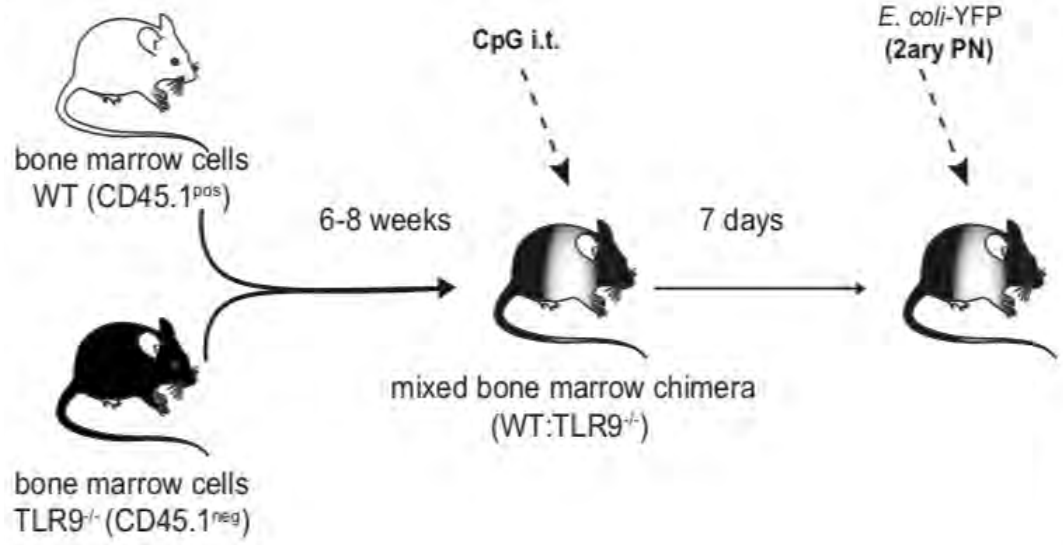


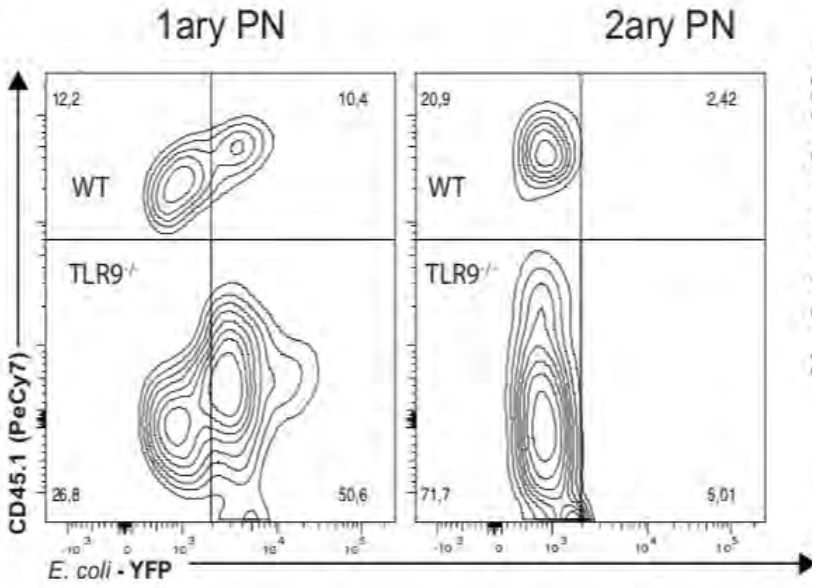


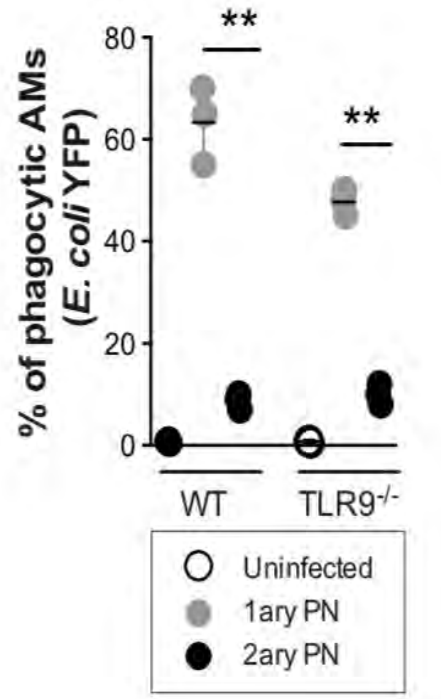


Roquilly et al. Nature Immunol 2020

AMs programming is not induced by the pathogens but by 2ary mediators of the inflammatory response

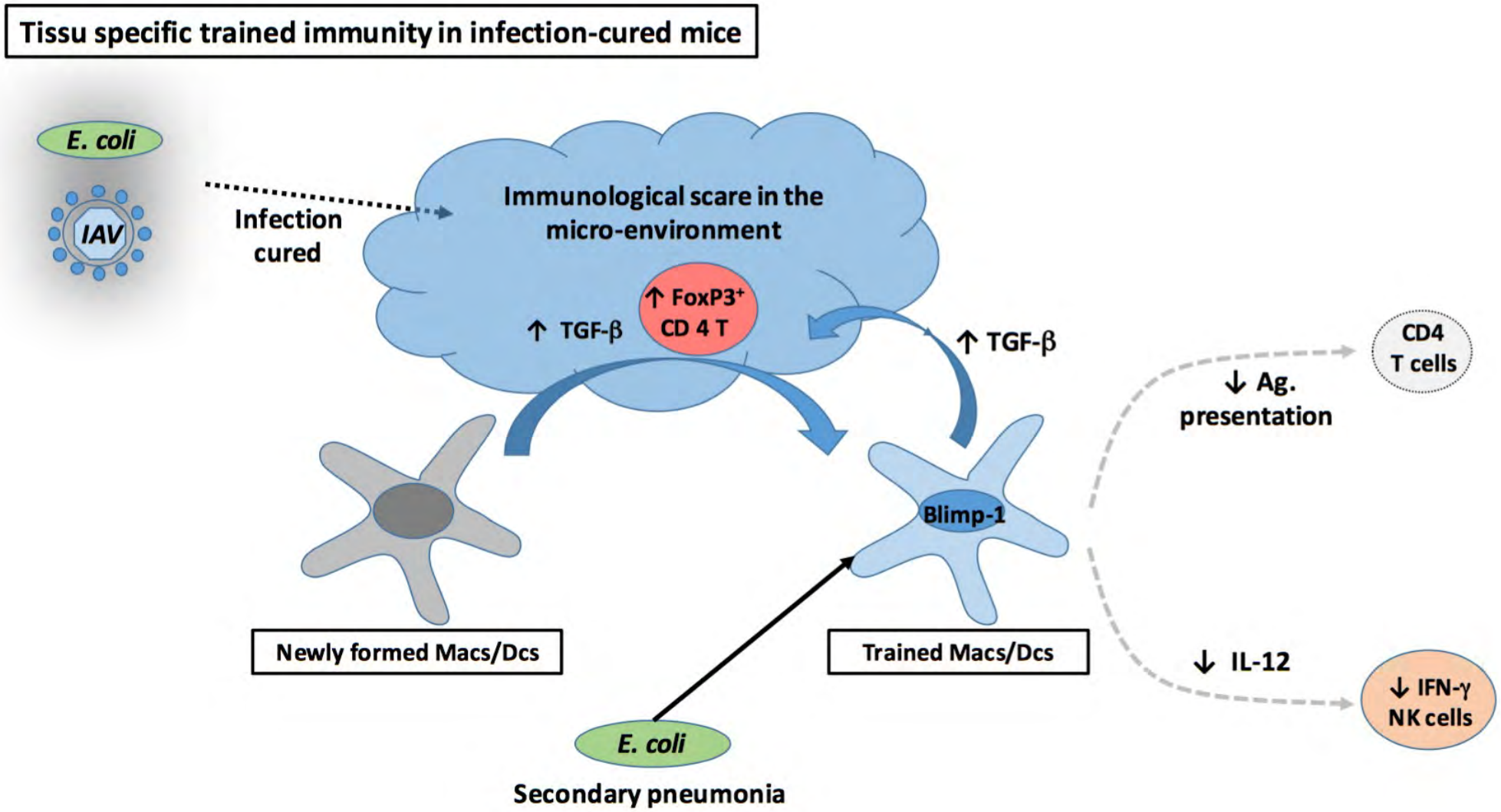






Acquired-immunosuppression during sepsis

An active process



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Treatment of infections

What can immunotherapies currently afford to the clinicians ?

Mucosal immunity

time for a reappraisal of the physiopathology !

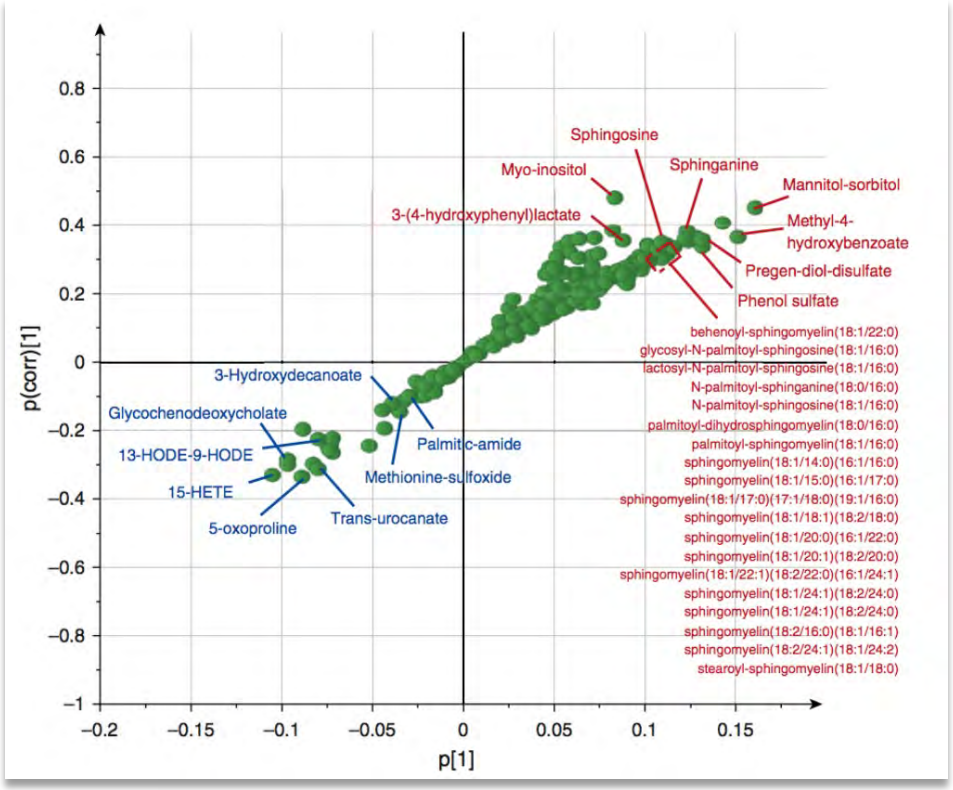
In couples quarrels,

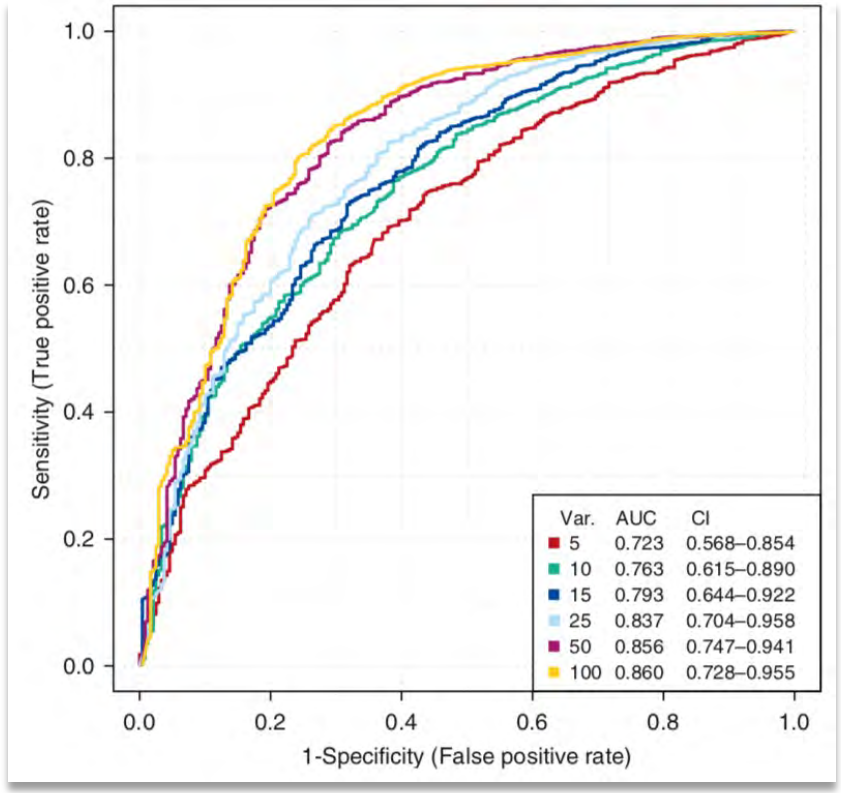
no party is innocent !

Restauration of the symbiosis

Modulation of the microbiome to restore symbiosis

Correction of the bacterial metabolic functions

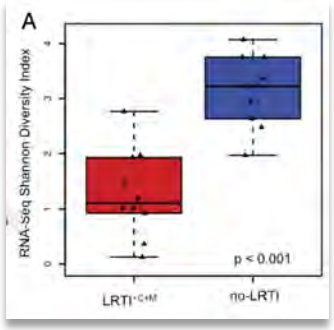




Risk of Mechanical ventilation in children with bronchiolitis *Stewart et al. AJRCCM 2017*

Modulation of the microbiome to restore diversity

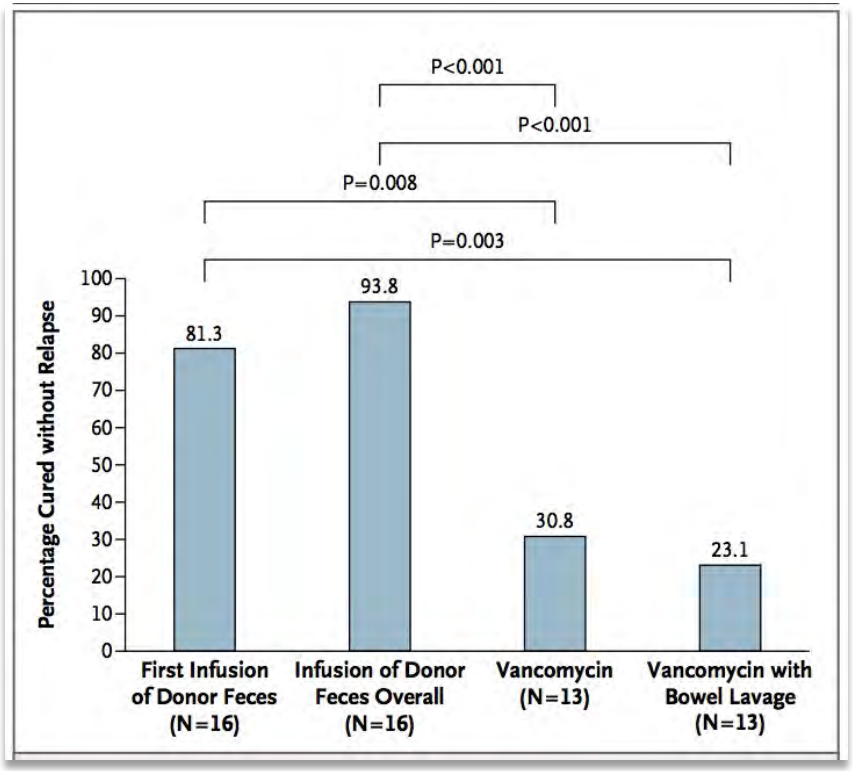
microbiota transplantation to increase diversity



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 31, 2013 VOL. 368 NO. 5

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*



Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial

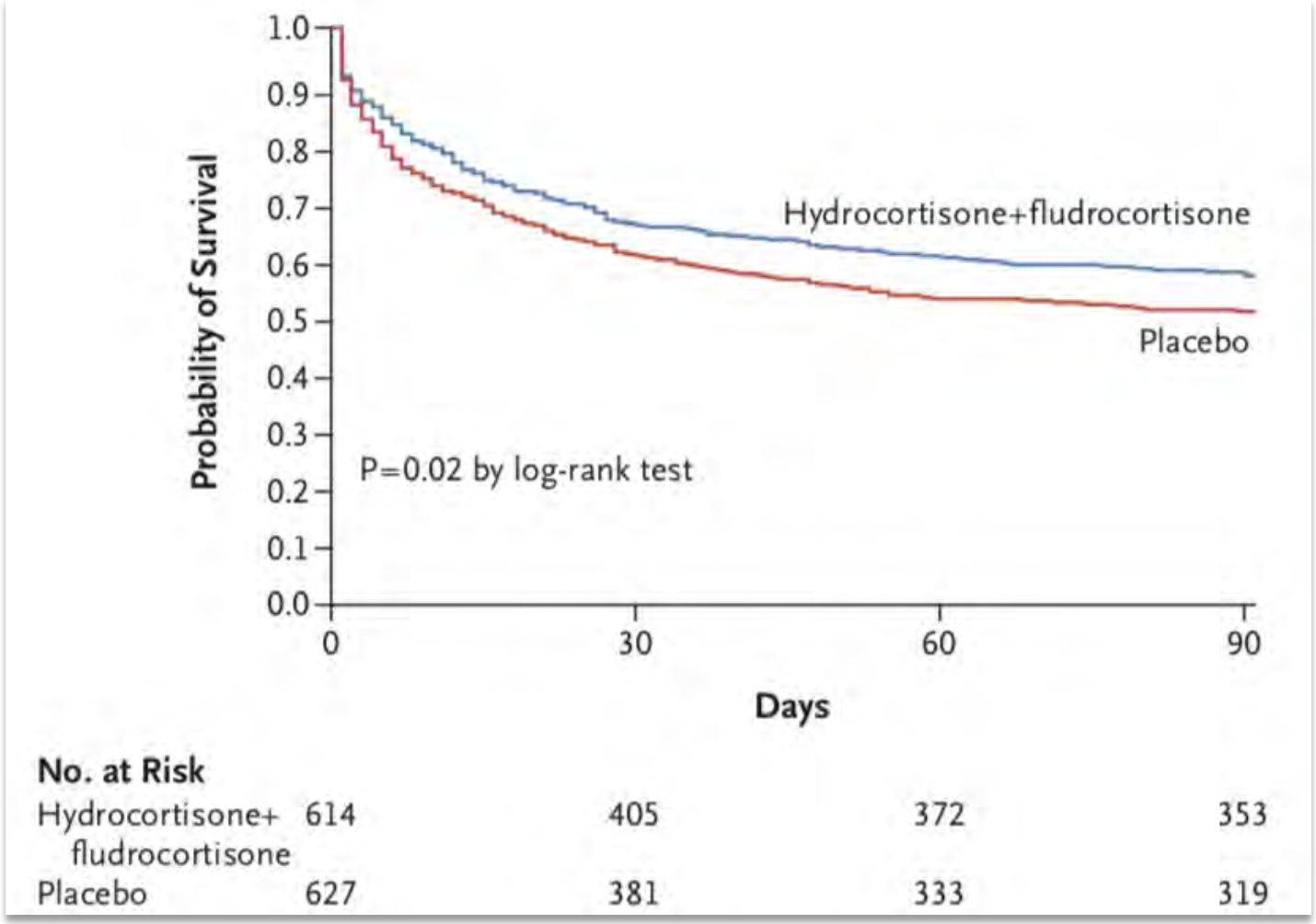
Paul Moayyedi,[1] Michael G. Surette,[1] Peter T. Kim,[2,3] Josie Libertucci,[1] Melanie Wolfe,[1] Catherine Onischi,[3] David Armstrong,[1] John K. Marshall,[1] Zain Kassam,[4] Walter Reinisch,[1] and Christine H. Lee[3]

Table 2. Outcome Measures Comparing Fecal Microbial Transplantation With Placebo

Outcome	Placebo (n = 37)	FMT (n = 38)	*P* value
Clinical remission,[a] n (%)	2 (5)	9 (24)	.03
Clinical response,[b] n (%)	9 (24)	15 (39)	.16
Full Mayo score	6.34	6.09	.42
IBDQ score	149.38	152.13	.44
EQ-5D score	70.07	68.52	.99
CRP, *mg/L* (n = 17 placebo, n = 15 FMT)	3.3 ± 3.4	4.9 ± 5.9	.38
ESR, *mm/h* (n = 17 placebo, n = 15 FMT)	13.1 ± 11.2	15.9 ± 17.0	.59
Proportion with high ESR, n (%)	4 (24)	3 (20)	1.0
Proportion with high CRP, n (%)	5 (29)	2 (13)	.40
Patients with serious adverse events n (%)	2[c] (5)	3[d] (8)	1.0

Immunomodulation: steroids for septic shock

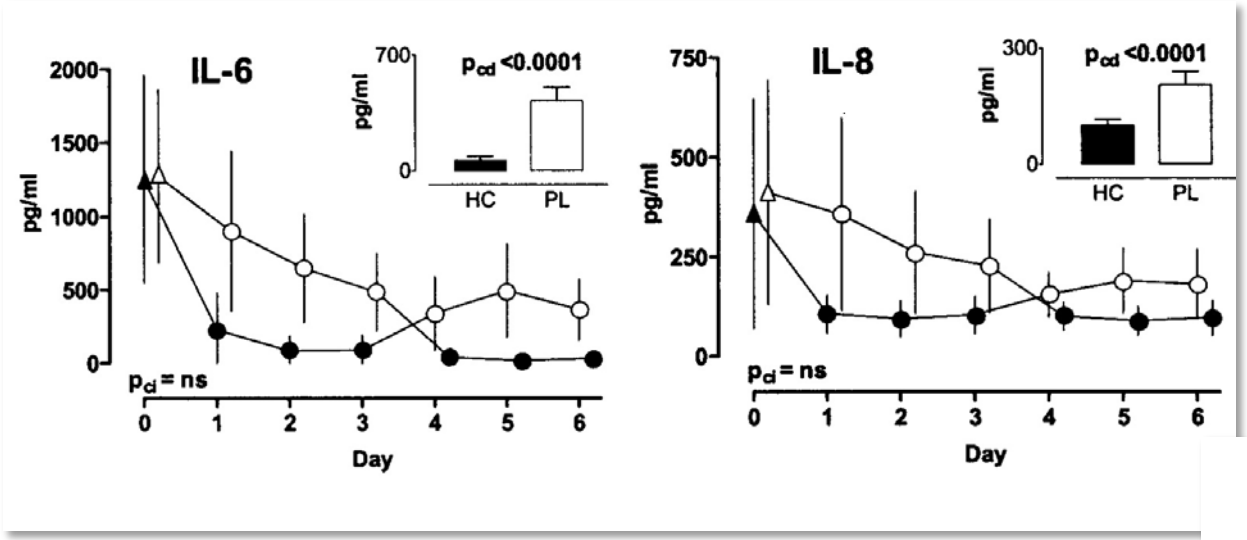
… more than immunosuppressors ?



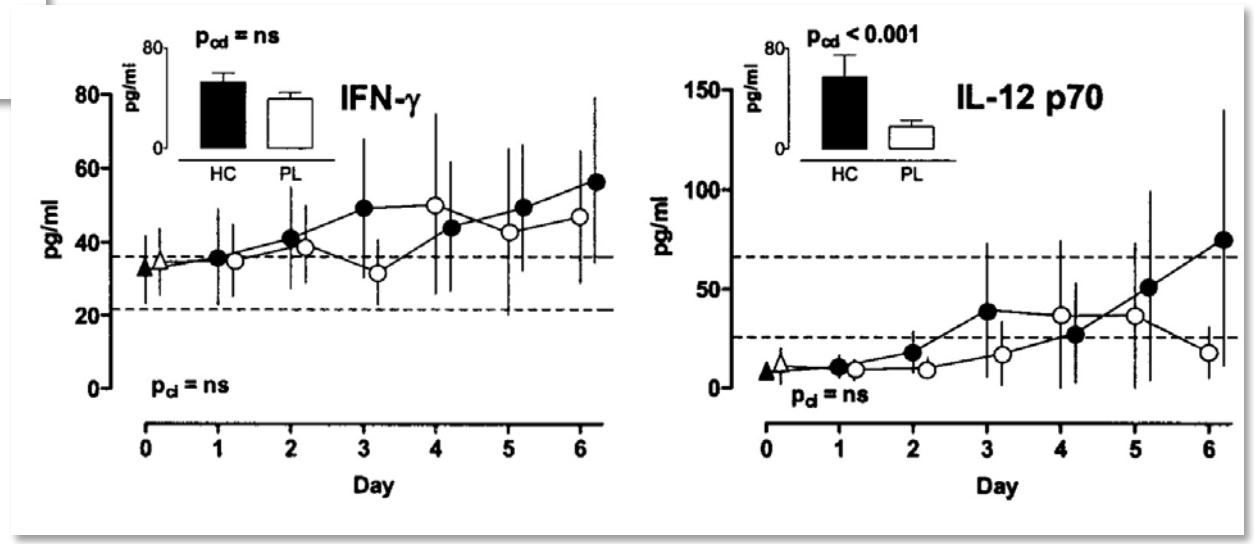
Annane et al. NEJM 2018

Immunomodulation by steroids

… more than immunosuppressors ?



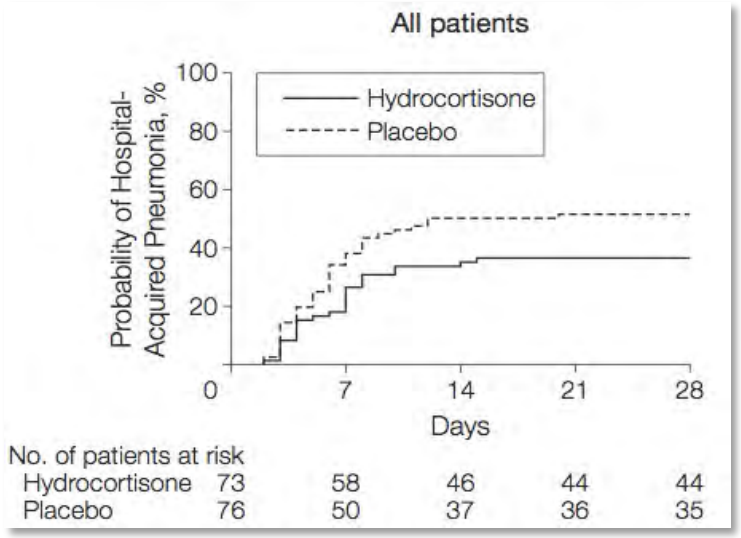
Kel et al. AJRCCM 2003



Immunomodulation by steroids

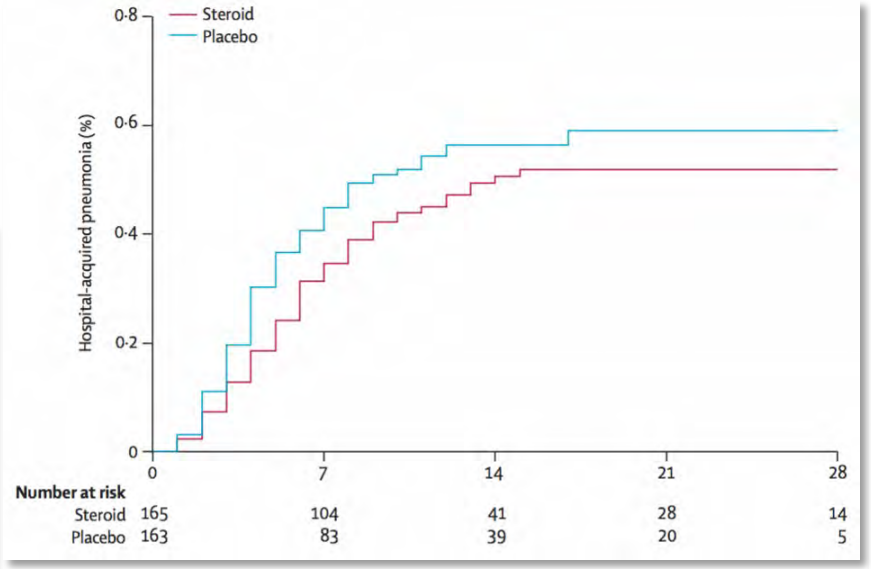
… *more than immunosuppressors ?*

Hydrocortisone Therapy for Patients With Multiple Trauma
The Randomized Controlled HYPOLYTE Study



Roquilly et al.
JAMA 2011

Hydrocortisone and fludrocortisone for prevention of hospital-acquired pneumonia in patients with severe traumatic brain injury (Corti-TC): a double-blind, multicentre phase 3, randomised placebo-controlled trial

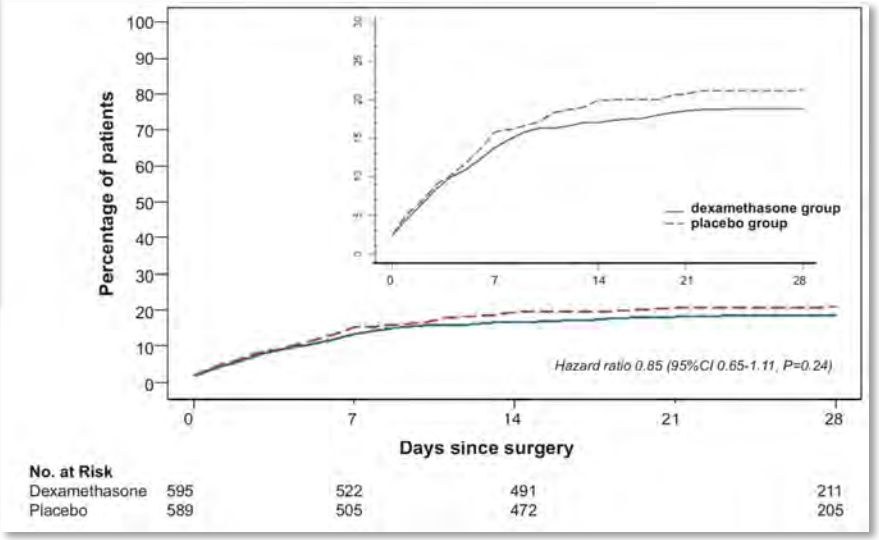


Asehnoune et al.
Lancet Respir Med 2014

RESEARCH

Effect of dexamethasone on complications or all cause mortality after major non-cardiac surgery: multicentre, double blind, randomised controlled trial

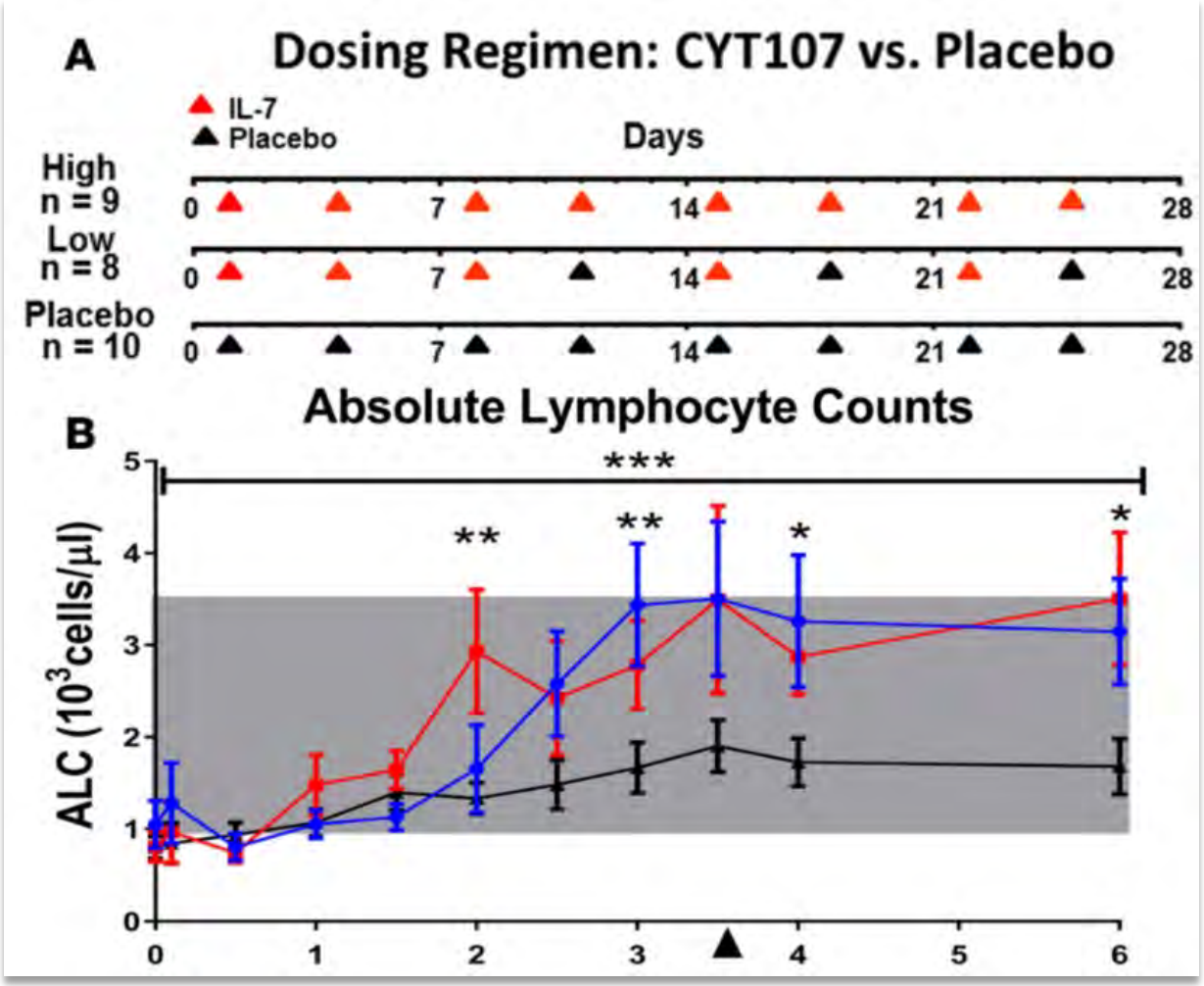
Karim Asehnoune,[1] Charlene Le Moal,[2] Gilles Lebuffe,[3] Marguerite Le Penndu,[1]



Asehnoune et al.
BMJ 2021

Host-targeted approaches for the treatment of infections

Boosting immunity - the future ?



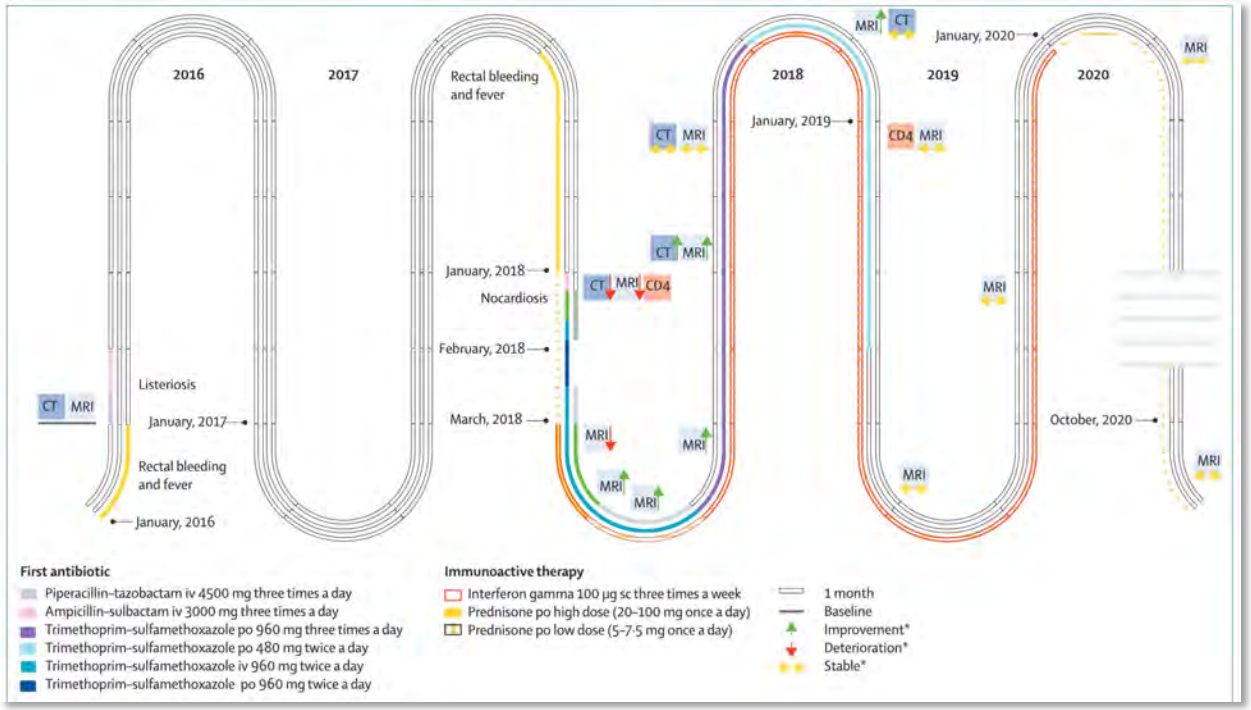
Francois et al. JCI exp 2018

Immunotherapies as a rescue therapy

Interferon-γ (Imukin ®)

Treatment of disseminated nocardiosis: a host–pathogen approach with adjuvant interferon gamma

Thomas Derungs, Fabian Leo, Christoph Loddenkemper, Thomas Schneider

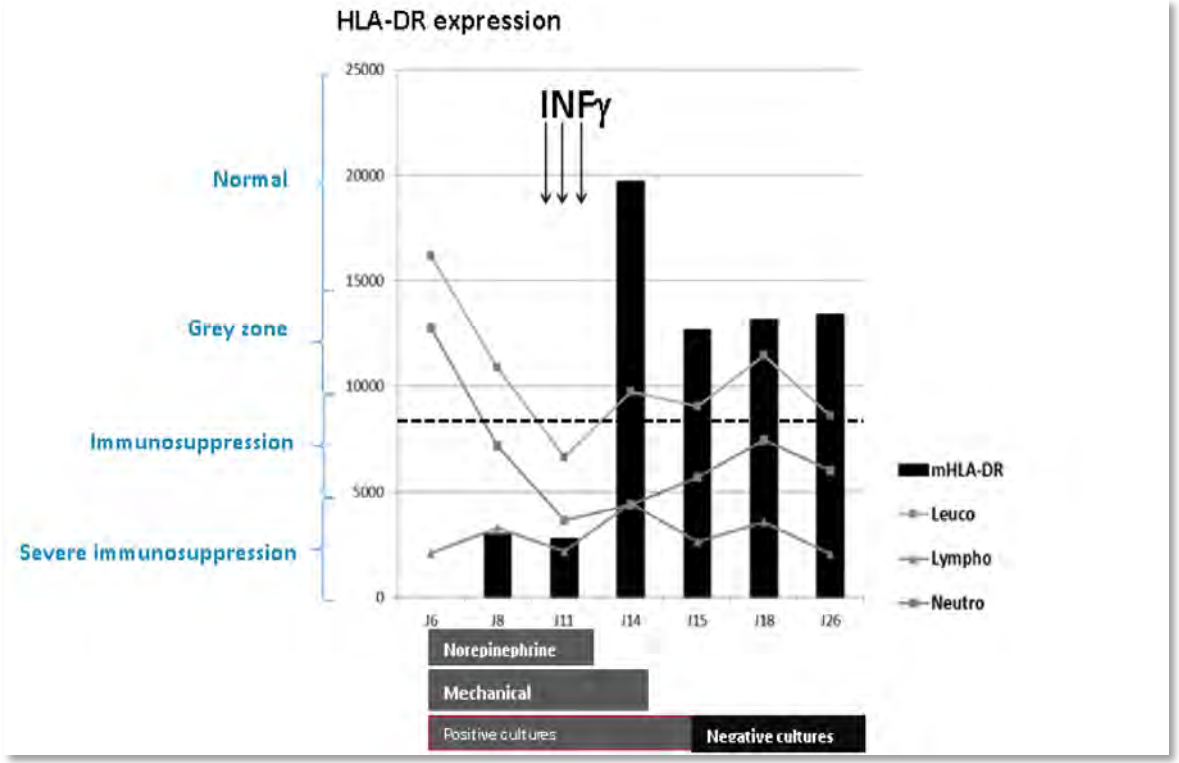


Lancet Infect Dis 2021

RESEARCH ARTICLE Open Access

Multicentric experience with interferon gamma therapy in sepsis induced immunosuppression. A case series

Didier Payen[1,2*], Valerie Faivre[1,2], Jordi Miatello[3,4], Jenneke Leentjens[5], Caren Brumpt[6], Pierre Tissières[3,4], Claire Dupuis[1], Peter Pickkers[7] and Anne Claire Lukaszewicz[1,2]



Host-targeted approaches for the treatment of infections

Boosting immunity - the future ?

rHuIL-12 or rHuIFN-γ for the treatment of HAP in ICU patients

The HAP2 project

Clinical expertise

- Clinical trials
- Immunology
- Access to IBIS & ATLANREA cohorts
- Big data

- **Pr. TORRES**
- Lung infections
- HAP
- VAP

- **Dr KOULENTI**
- HAP
- antibiotic dosage optimisation
- infections from multidrug resistant pathogens

Study treatment provider

Neumedicines

- **Pr NETEA**
- Epigenetic,
- metabolomic
- Trained immunity

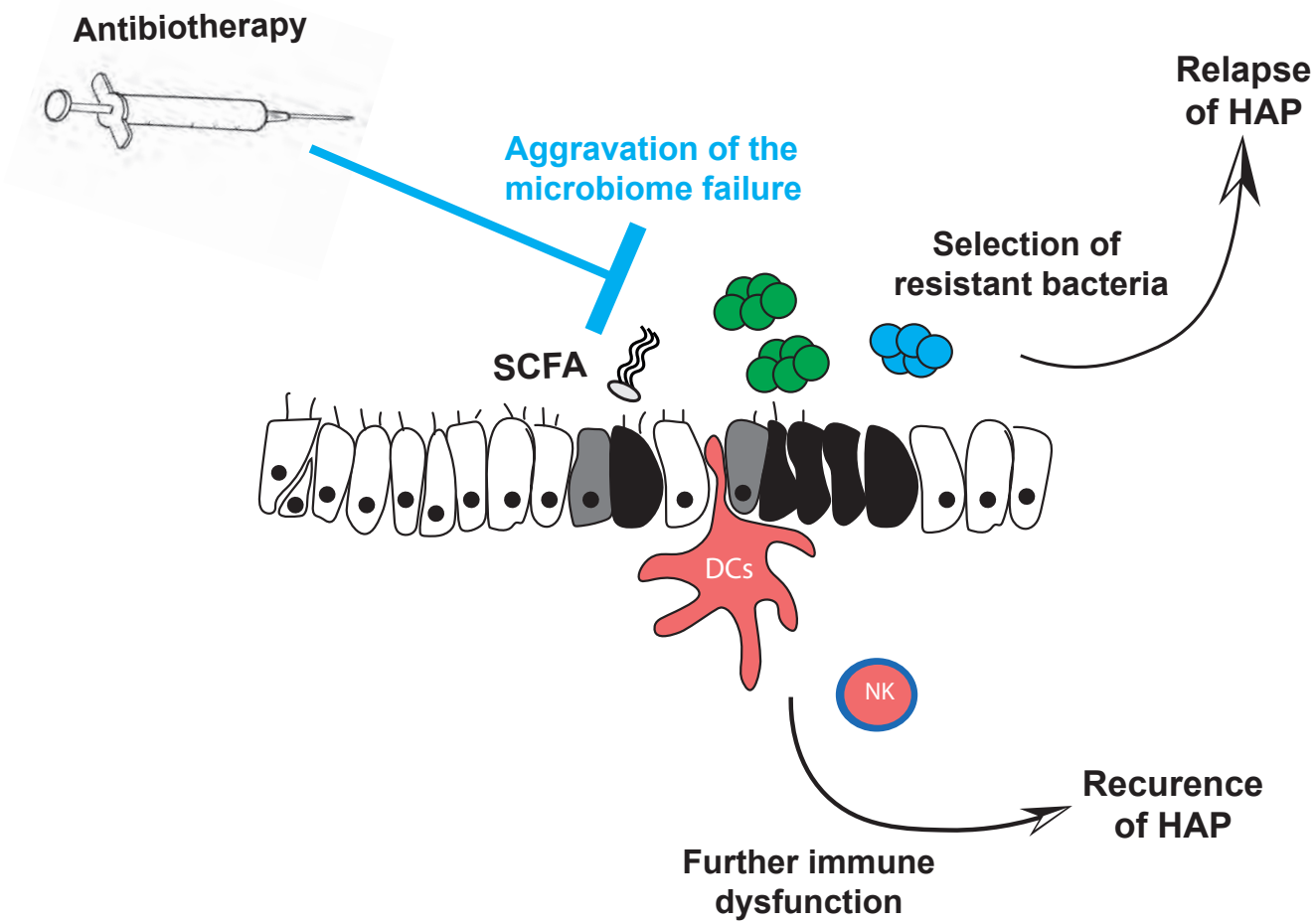
- **Pr BECHER**
- immune-monitoring
- biology of IL-12 superfamily members

- **Dr JOUSSET**
- viral sequencing
- transcriptomic analysis of host response to viral infections

- **Pr DICKSON**
- lung microbiome

Dysbiosis and treatment of mucosal infections

… a therapeutical revolution

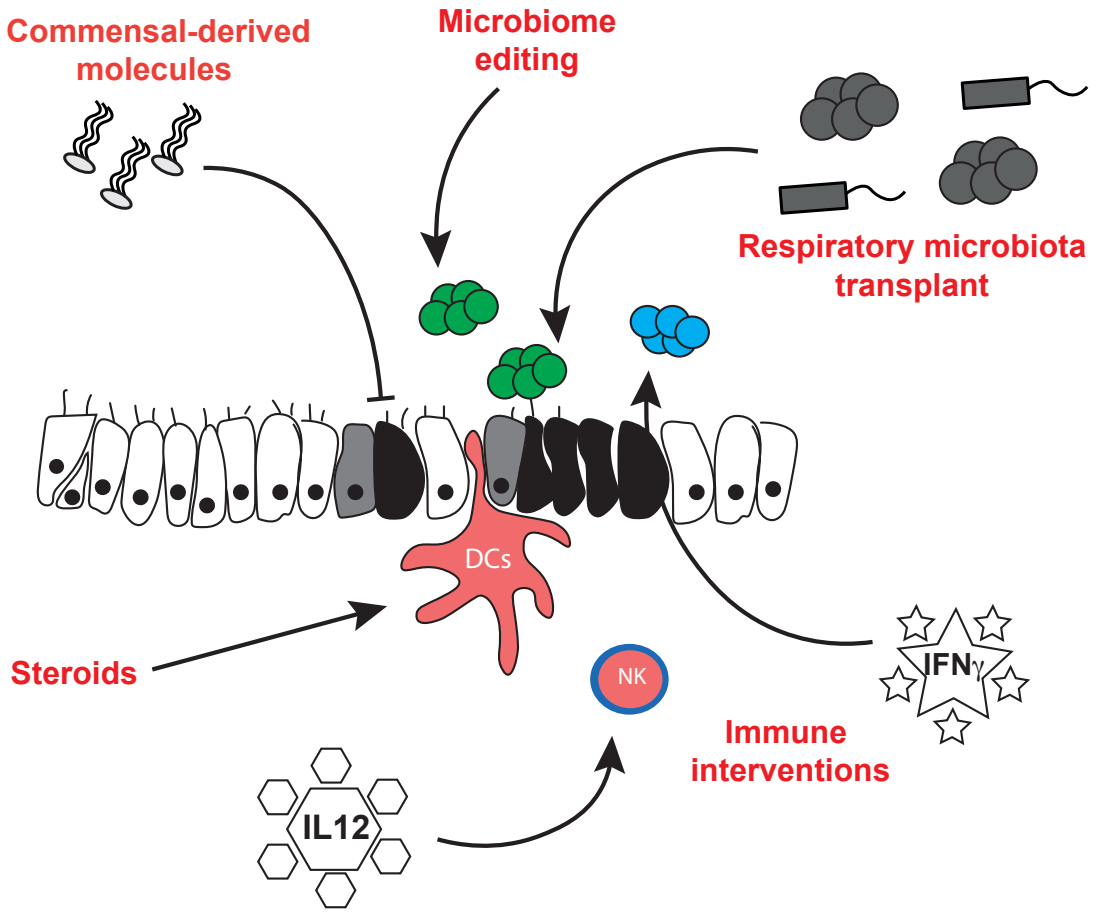


Further reduction of the host-microbes interactions

Roquilly et al. Lancet respir Med 2019

Dysbiosis and treatment of mucosal infections

… a therapeutical revolution

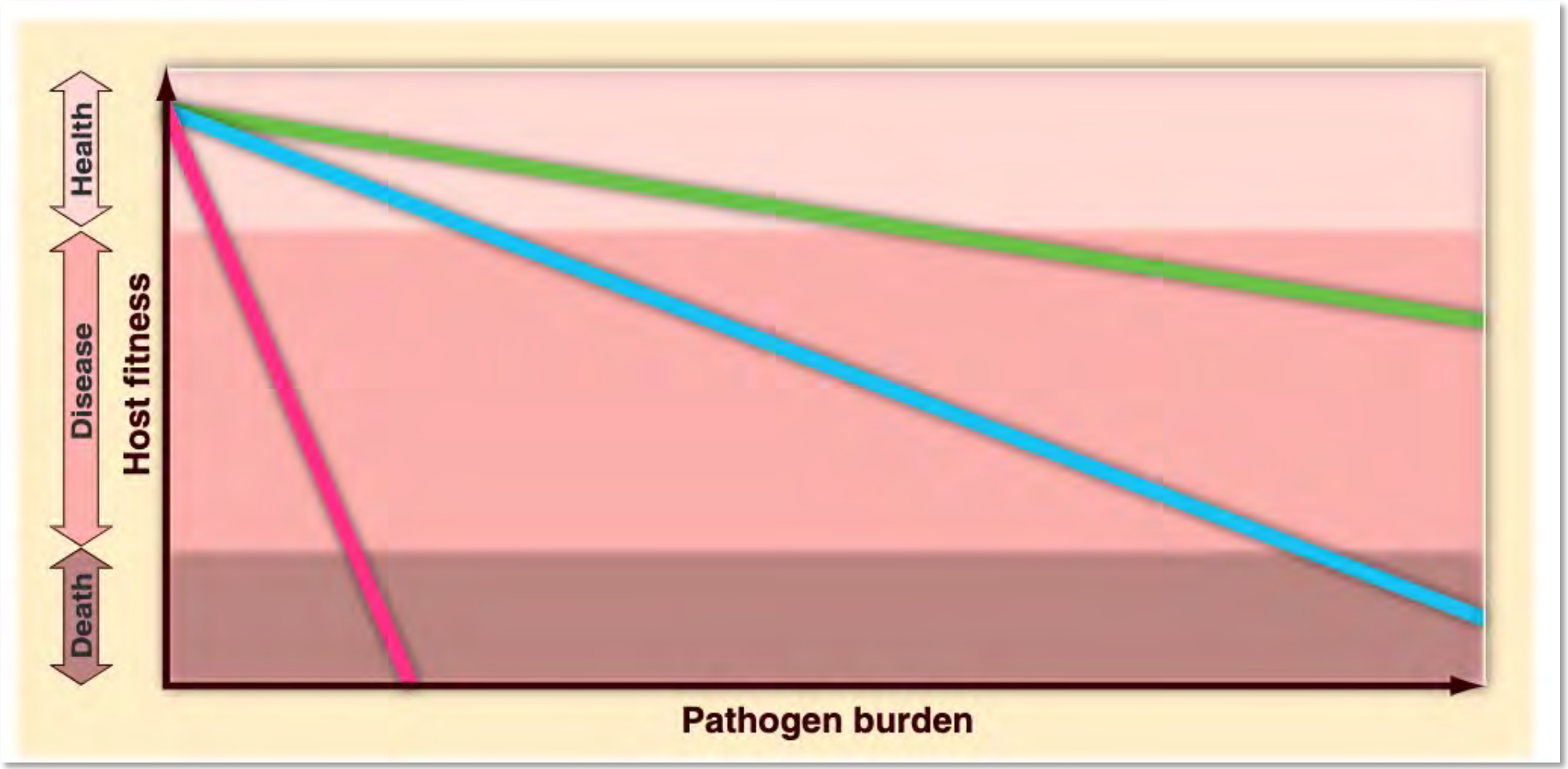


Normalization of the host-microbes interactions

Roquilly et al. Lancet respir Med 2019

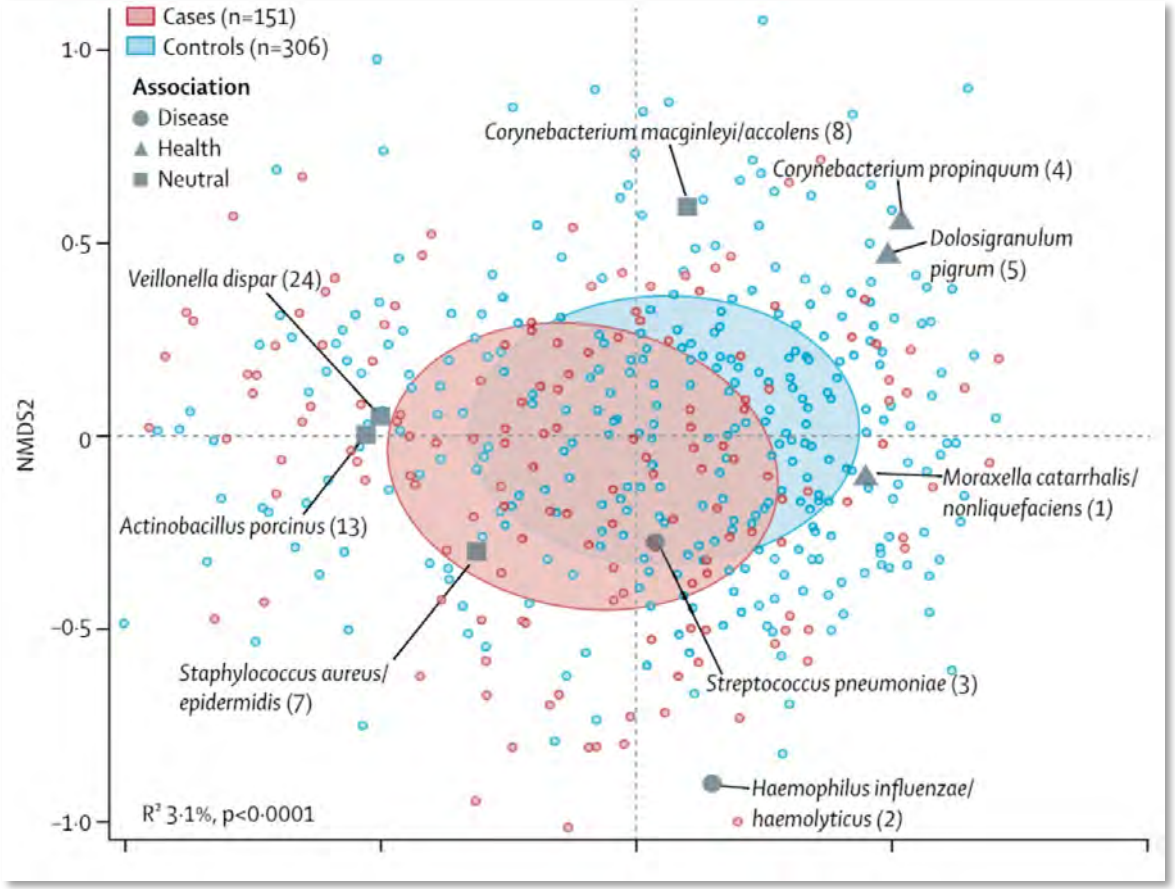
Boosting tolerance or immunity ?

Disease Tolerance as a Defense Strategy
Ruslan Medzhitov, *et al.*
Science **335**, 936 (2012);
DOI: 10.1126/science.1214935

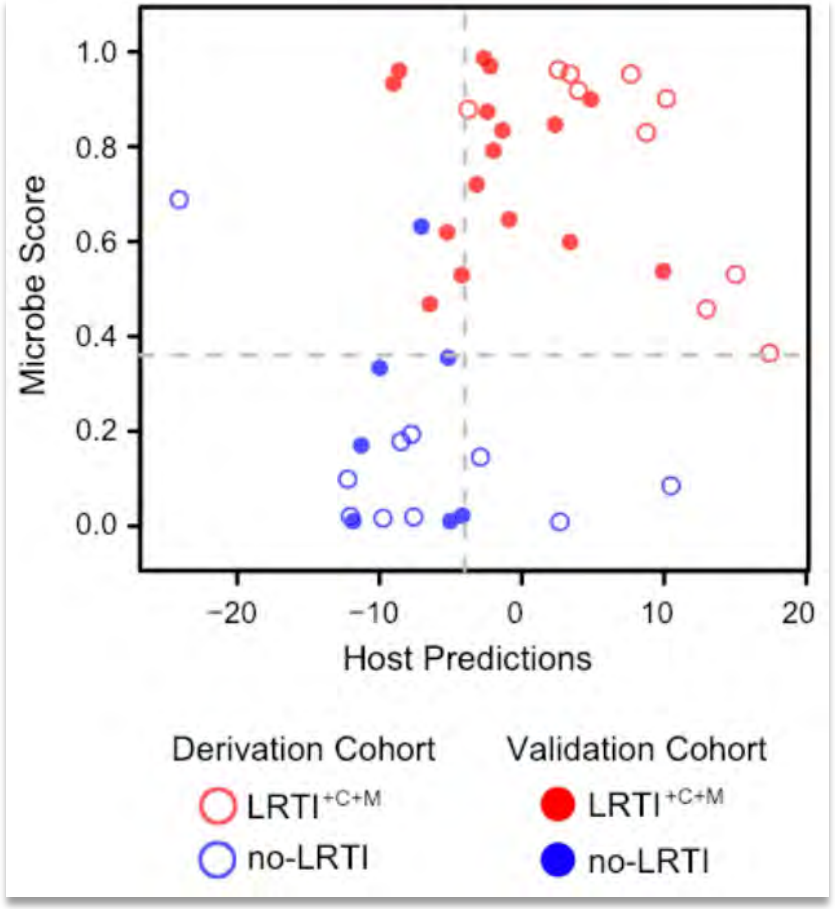


Precision medecine

Integration multi-omics pour biomarqueurs



Man et al. Lancet Respir Med 2019



Langelier PNAS 2018

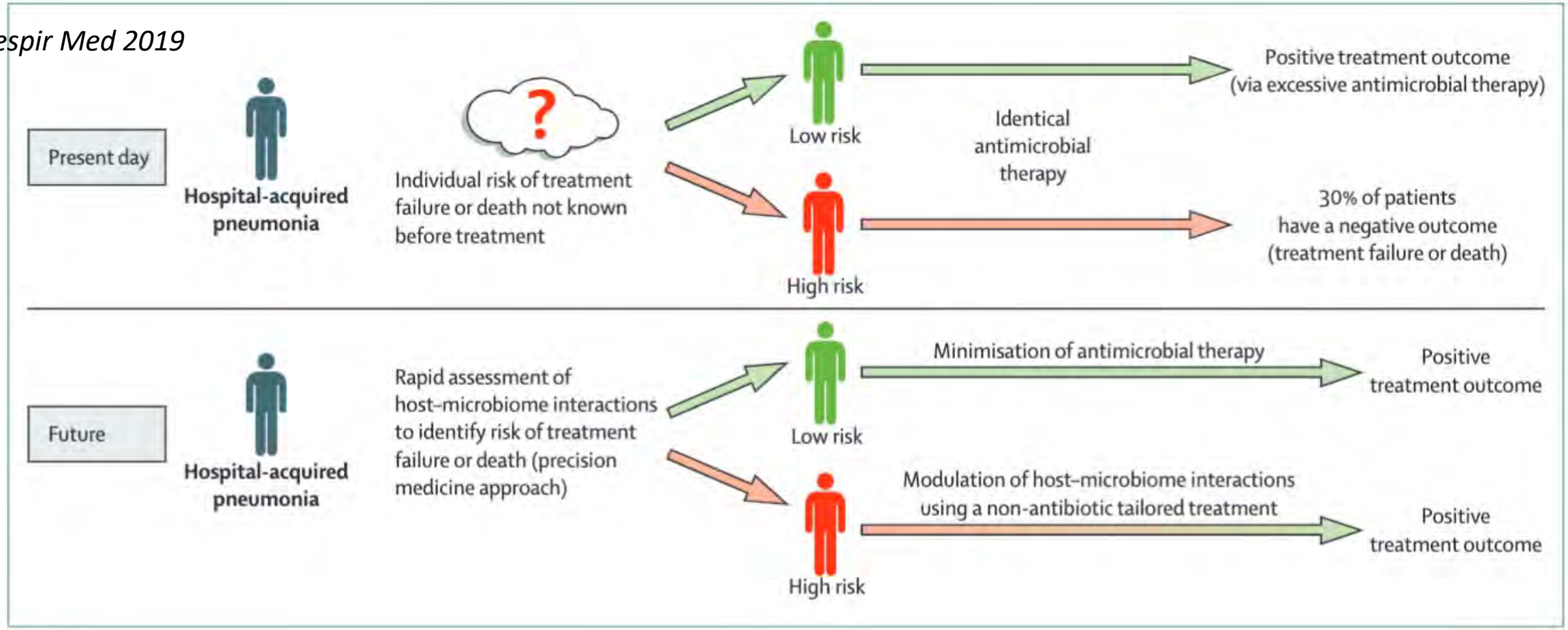
Precision medecine

Integration multi-omics

Pathophysiological role of respiratory dysbiosis in hospital-acquired pneumonia

A Roquilly, A Torres, J A Villadangos, M G Netea, R Dickson, B Becher, K Asehnoune

Lancet Respir Med 2019



Collaboration with
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M. Ashayeripanah

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Cédric Jacqueline (PhD)
Marion Davieau
Tanguy Roman (PhD)
Barbara Misme-Aucouturier (PhD)
Alexis Broquet (PhD)
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