

Persistent NLRP3 inflammasome activation is associated with delayed immunosuppression in septic patients

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*Team NLRP3 Inflammasome and Immune response to sepsis
Team EA7426 Pathophysiology of injury-induced immunosuppression*

Under the supervision of Pr Monneret & Pr Venet



Université Claude Bernard Lyon 1



Centre
International
de Recherche
en Infectiologie

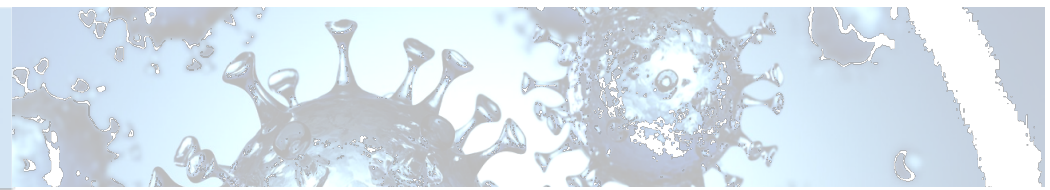


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en Pharmacie des Hôpitaux de Lyon »

Sepsis definition



Introduction

Materials and Methods

Results

Discussion

SEPSIS DEFINITION

LIFE-THREATENING ORGAN DYSFUNCTION



CAUSED BY



DYSREGULATED HOST RESPONSE TO INFECTION

1st cause of death in ICU

In 2017 ~ 50 million cases of sepsis worldwide
11 million sepsis-related deaths

Rudd et al. Lancet 2020



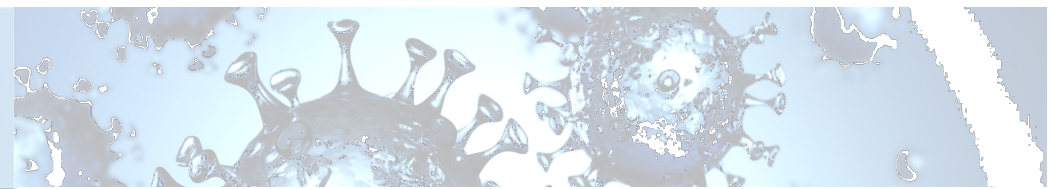
The NEW ENGLAND JOURNAL of MEDICINE

Recognizing Sepsis as a Global Health Priority — A WHO Resolution

Konrad Reinhart, M.D., Ron Daniels, M.D., Niranjana Kissoon, M.D., Flavia R. Machado, M.D., Ph.D.,
Raymond D. Schachter, L.L.B., and Simon Finfer, M.D.

This article was published on June 28, 2017,

Immune response to sepsis

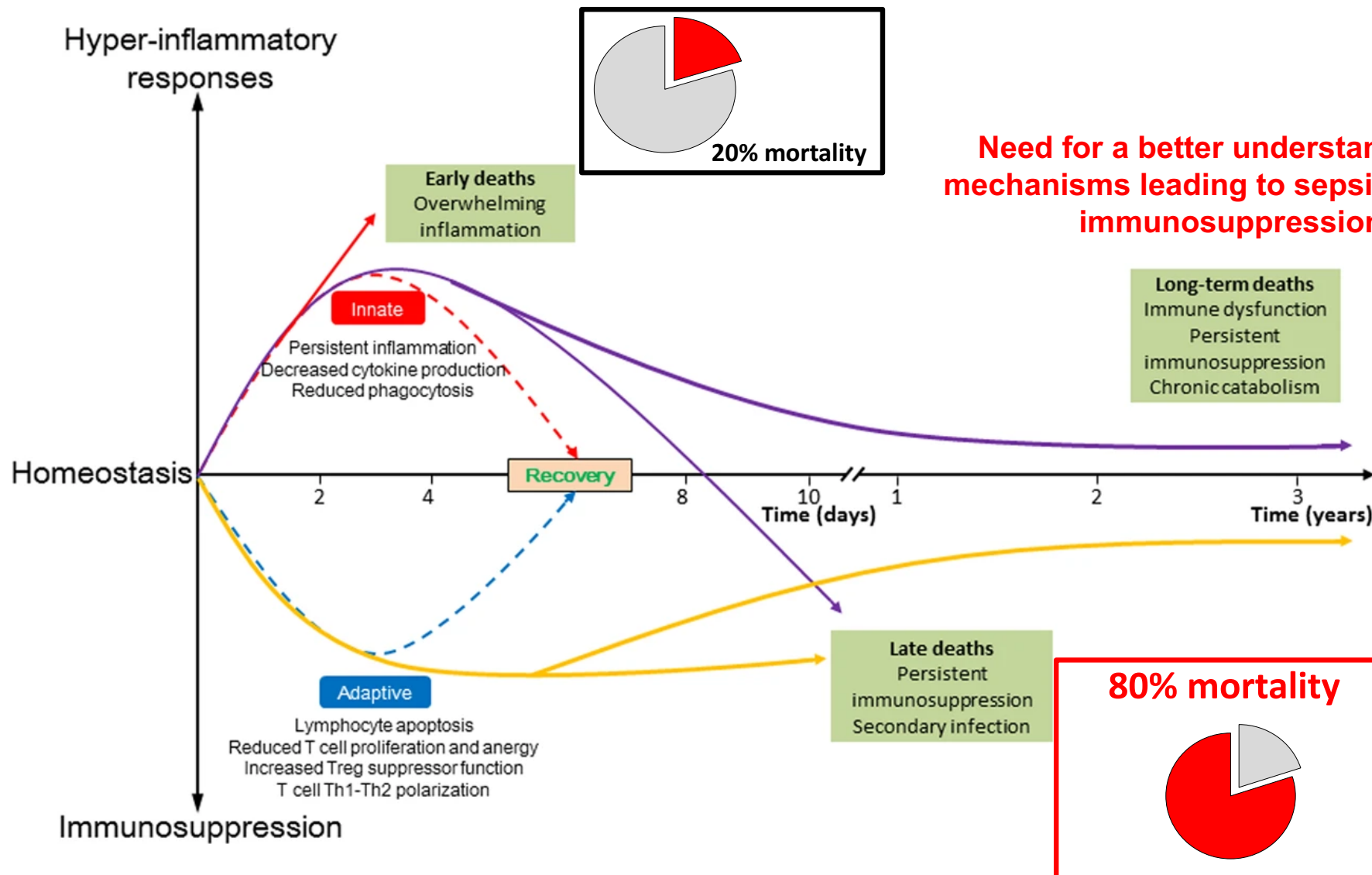


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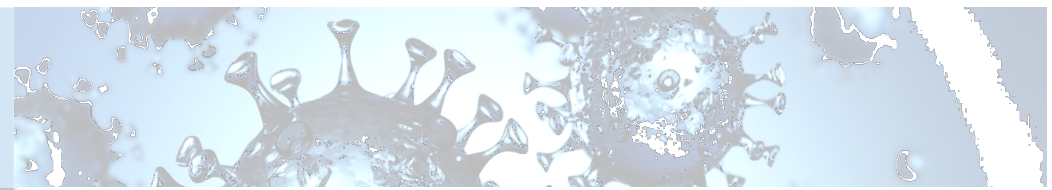
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Need for a better understanding of mechanisms leading to sepsis-induced immunosuppression

Inflammation & immune alterations

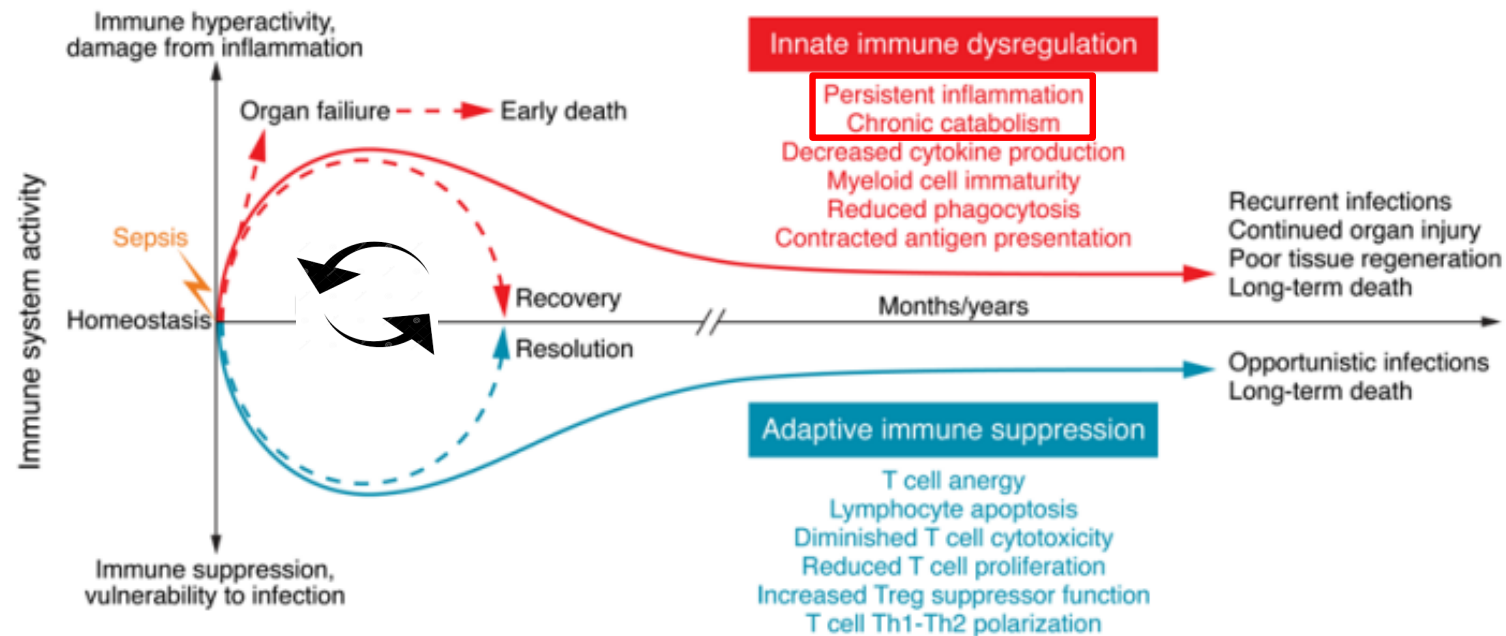


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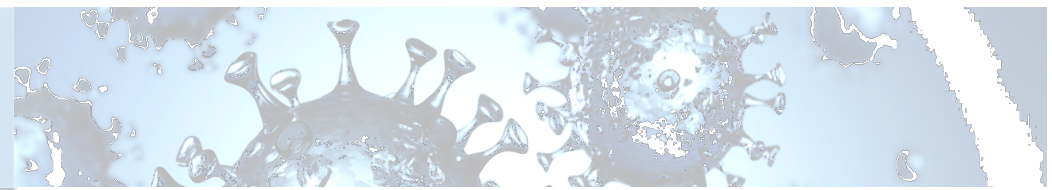
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NRLP3 inflammasome

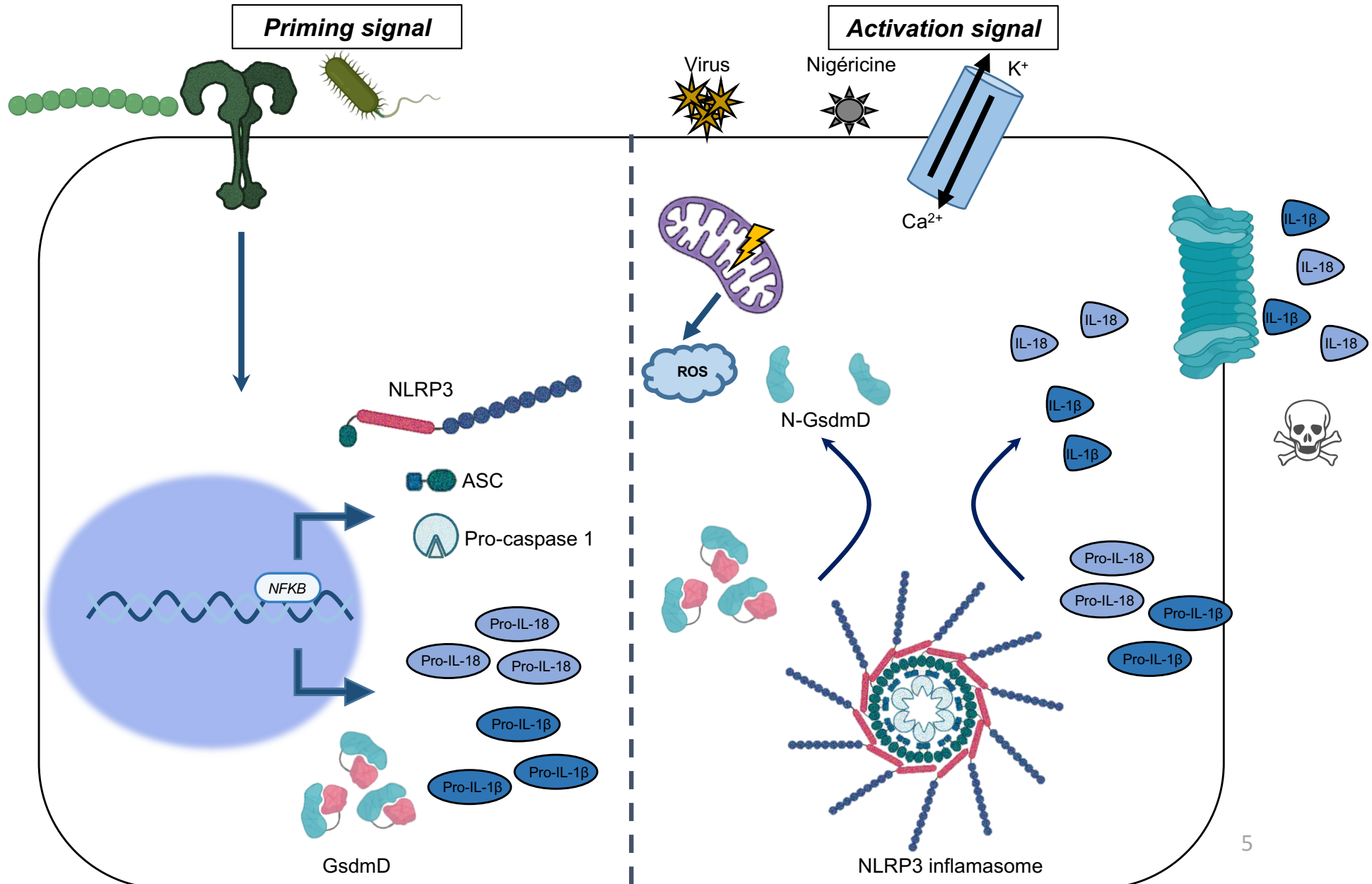


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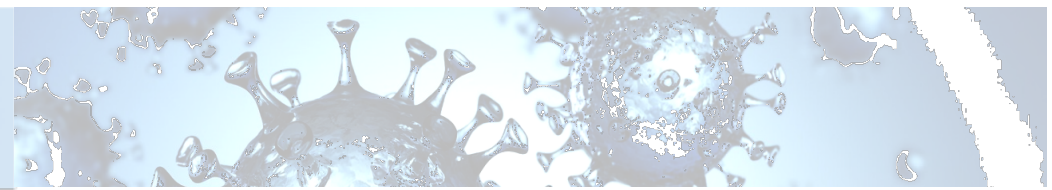
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Link between MDSC & NLRP3 inflammasome



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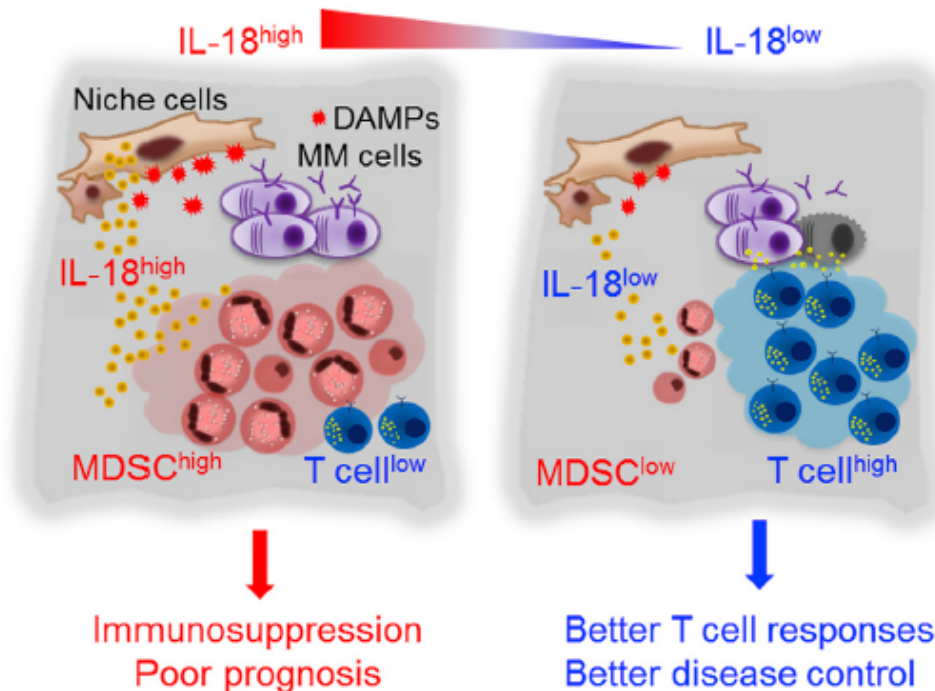
Discussion

Cancer Cell

Dysregulated IL-18 Is a Key Driver of Immunosuppression and a Possible Therapeutic Target in the Multiple Myeloma Microenvironment

Kyohei Nakamura,¹ Sahar Kassem,² Alice Cleynen,³ Marie-Lorraine Chretien,^{2,4} Camille Guillerey,^{1,5} Eva Maria Putz,¹ Tobias Bald,¹ Irmgard Förster,⁶ Slavica Vuckovic,^{5,7} Geoffrey R. Hill,⁷ Seth L. Masters,^{8,9} Marta Chesi,¹⁰ P. Leif Bergsagel,¹⁰ Hervé Avet-Loiseau,^{2,11} Ludovic Martinet,^{2,12,*} and Mark J. Smyth^{1,5,12,13,*}

Cancer Cell 33, 634–648, April 9, 2018



IL-18 Enhances Immunosuppressive Responses by Promoting Differentiation into Monocytic Myeloid-Derived Suppressor Cells

Hui Xuan Lim,* Hye-Jin Hong,* Daeho Cho,[†] and Tae Sung Kim* *J Immunol* 2014

Targeting tumor-derived NLRP3 reduces melanoma progression by limiting MDSCs expansion

Isak W. Tengesdal^{a,b}, Dinoop R. Menon^c, Douglas G. Osborne^c, Charles P. Neff^a, Nicholas E. Powers^a, Fabia Gamboni^a, Adolfo G. Mauro^d, Angelo D'Alessandro^e, Davide Stefanoni^e, Morkos A. Henen^{a,f}, Taylor S. Mills^g, Dennis M. De Graaf^{a,b}, Tania Azam^a, Beat Vogeli^e, Brent E. Palmer^a, Eric M. Pietras^g, James DeGregori^h, Aik-Choon Tan^h, Leo A. B. Joosten^h, Mayumi Fujita^{c,1}, Charles A. Dinarello^{a,b,1}, and Carlo Marchetti^{a,1}

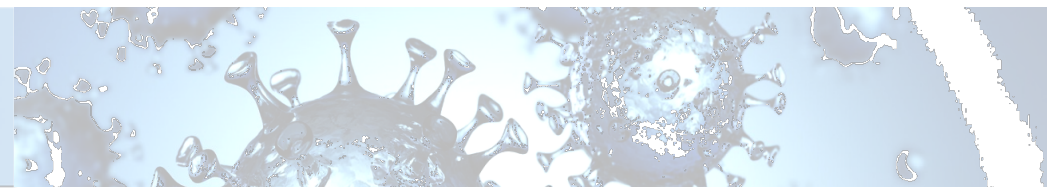
Proceedings of the National Academy of Sciences, 2021

NLRP3 signaling drives macrophage-induced adaptive immune suppression in pancreatic carcinoma

Donnele Daley,^{1,*} Vishnu R. Mani,^{1,*} Navyatha Mohan,¹ Neha Akkad,¹ Gautam S.D. Balasubramania Pandian,¹ Shivraj Savadkar,¹ Ki Buom Lee,¹ Alejandro Torres-Hernandez,¹ Berk Aykut,¹ Brian Diskin,¹ Wei Wang,¹ Mohammad S. Farooq,¹ Arif I. Mahmud,¹ Gregor Werba,¹ Eduardo J. Morales,¹ Sarah Lall,¹ Benjamin J. Wadowski,¹ Amanda G. Rubin,¹ Matthew E. Berman,¹ Rajkishen Narayanan,¹ Mautin Hundeyin,¹ and George Miller^{1,2}

J. Exp. Med. 2017

Hypothesis and methodology



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Hypothesis :

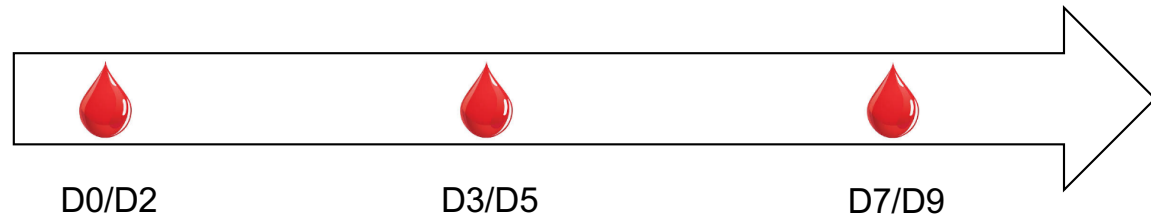


Prospective work

ICU Admission



COVID-19 & Septic shock
Controls

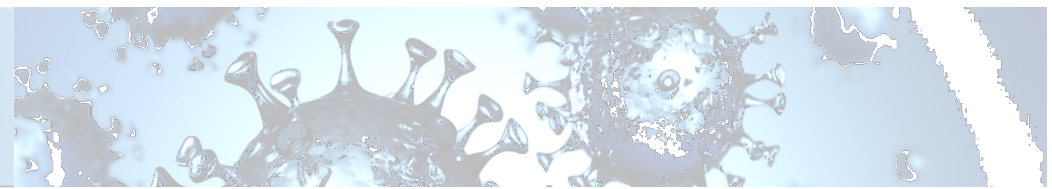


Retrospective work

The REAnimation Low Immune Status Markers (REALISM) project: a protocol for broad characterisation and follow-up of injury-induced immunosuppression in intensive care unit (ICU) critically ill patients

Mary-Luz Rol^{1, 2}, Fabienne Venet^{2, 3}, Thomas Rimmelé^{2, 4}, Virginie Moucadel⁵, Pierre Cortez⁶, Laurence Quemeneur⁷, David Gardiner¹³, Andrew Griffiths⁸, Alexandre Pachot^{2, 5},  Julien Textoris^{2, 4, 5}, Guillaume Monneret^{2, 3} On behalf of the REALISM study group

Prospective study methodology



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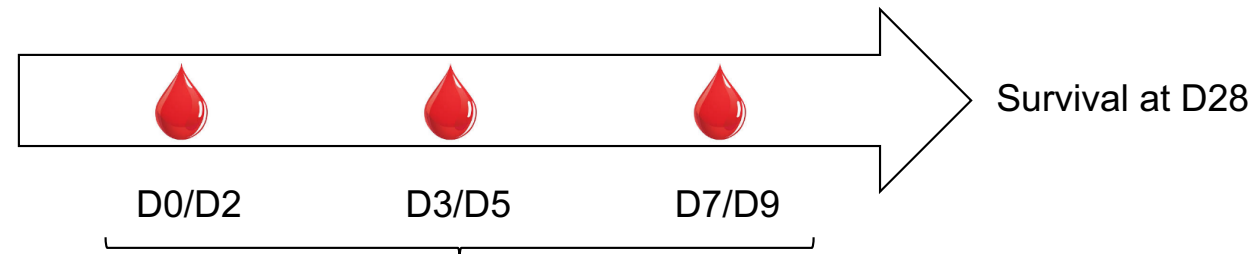
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ICU Admission



n= 15 Controls
n= 15 COVID-19 ICU patients
n= 17 septic shock patients



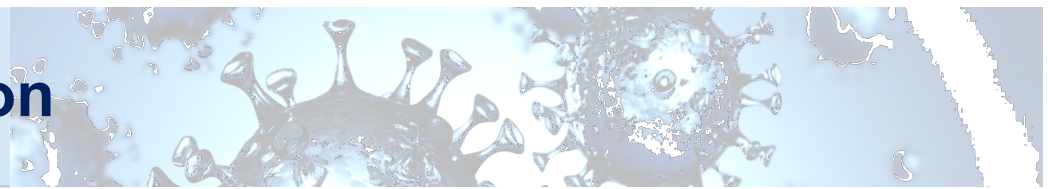
Sepsis-induced immune alterations

- mHLA-DR expression → m-MDSC
- LOX1⁺ PMN-MDSC

NLRP3 inflammasome activation

- Plasma cytokines: IL-1 β , IL-18
- Related: IL-1RIs & IL-1Ra

Inflammation & immunosuppression

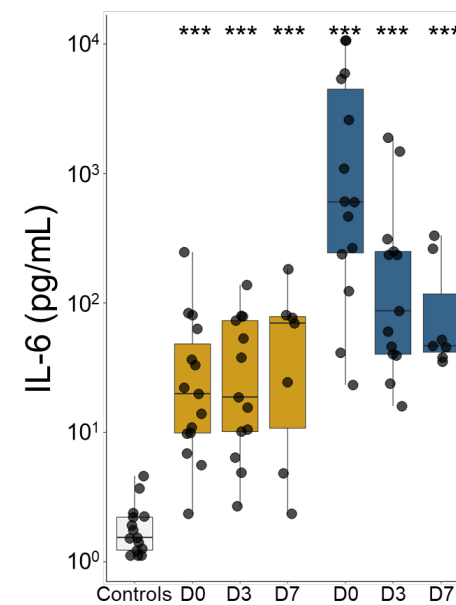
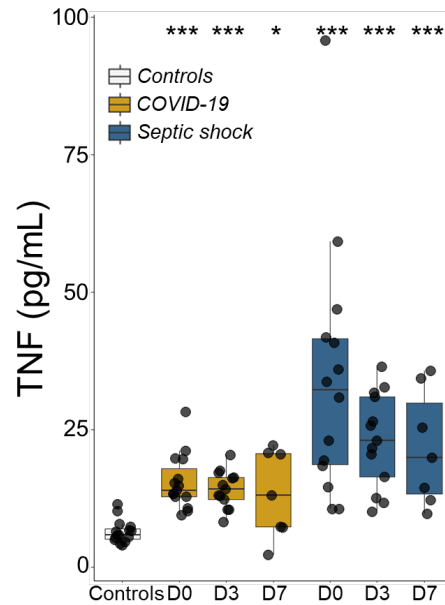


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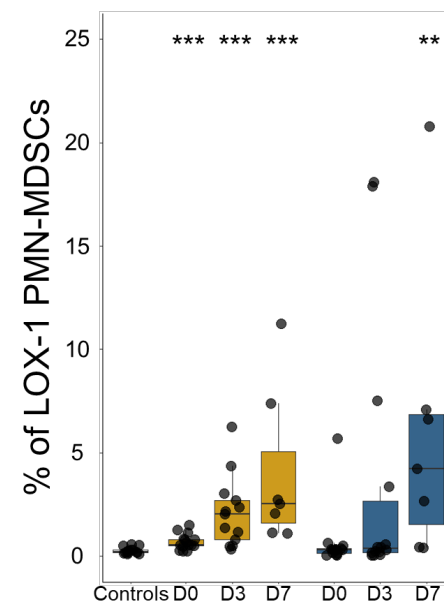
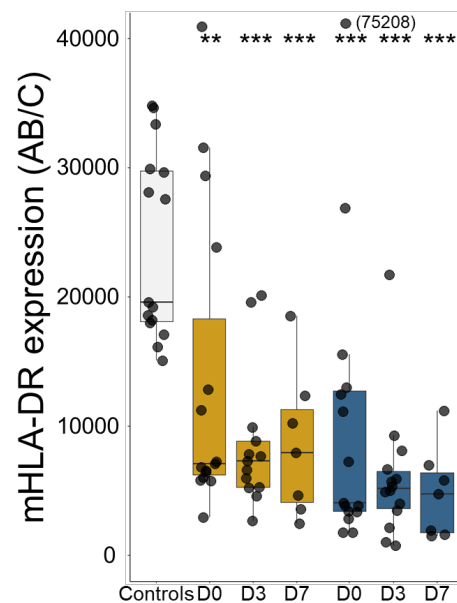
Discussion

Early inflammatory response



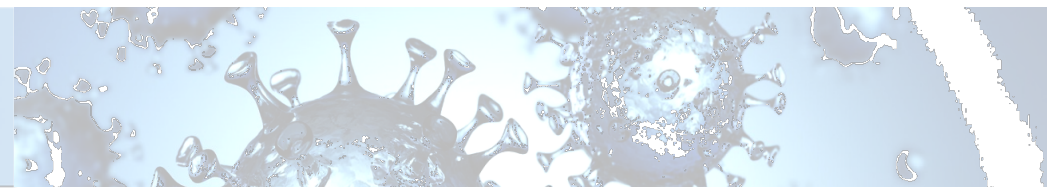
Standard parameters of septic patients :
 ✓ **Hyperinflammation**
 ✓ **Immunosuppression**

Delayed immune alterations



* p < 0.05
 ** p < 0.01
 *** p < 0.001
 Mann-Whitney U test

NLRP3 inflammasome activation

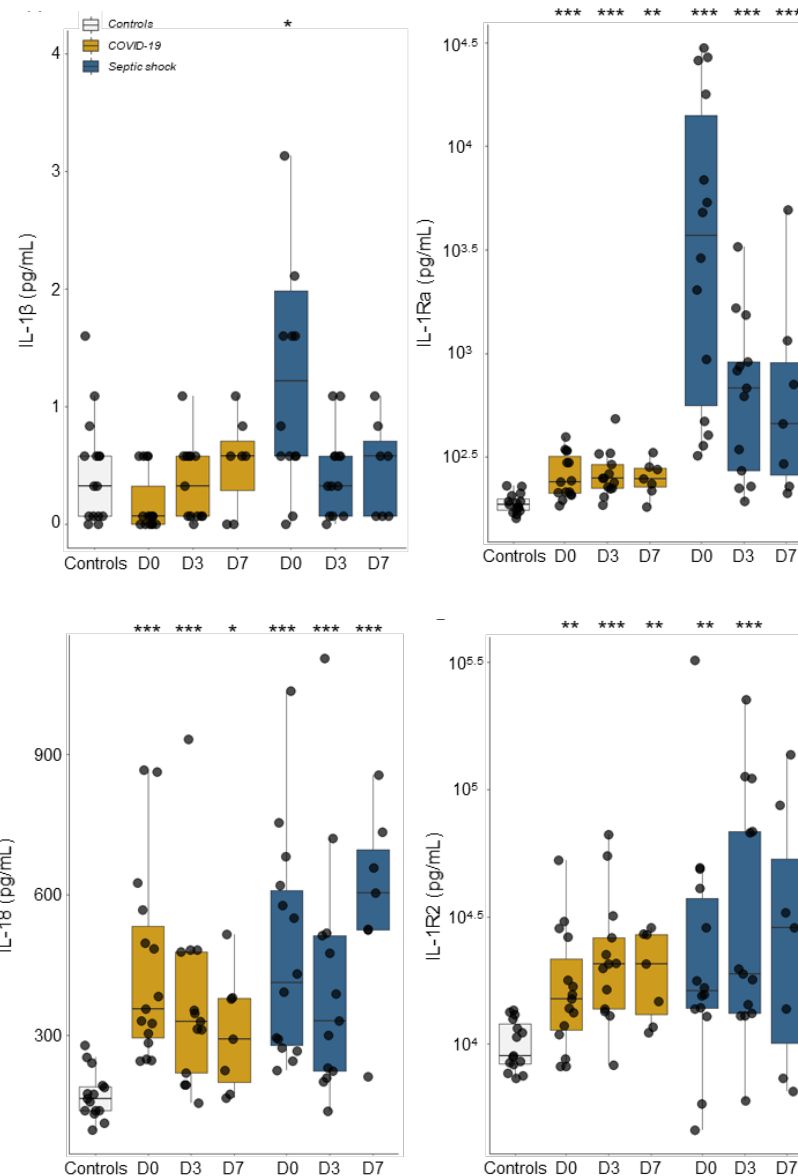


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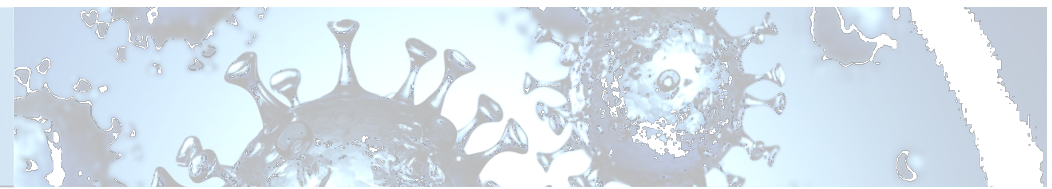


Hyperactivation of NLRP3 inflammasome

Correlations persistent NLRP3 inflammation and immunosuppression at D7 :

- IL-18 & LOX-1 PMN-MDSCs : $r=0.57$, $p=0.059$
- IL-1R2 & mHLA-DR : $r=-0.66$, $p=0.012$

Persistent NLRP3 inflammasome activation is associated with immune alterations

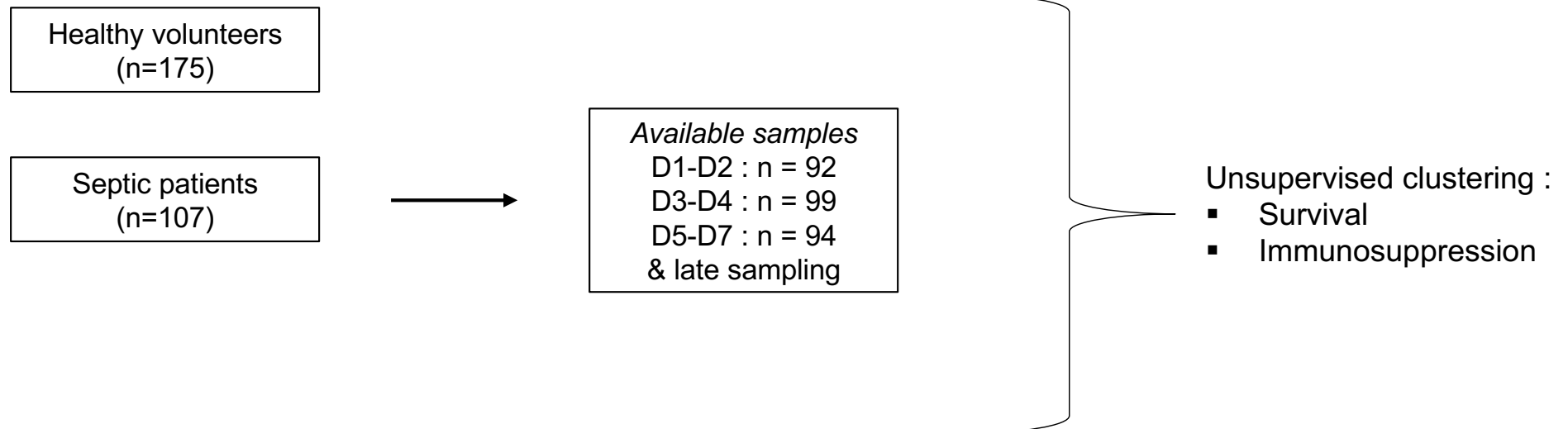


The REAnimation Low Immune Status Markers (REALISM) project: a protocol for broad characterisation and follow-up of injury-induced immunosuppression in intensive care unit (ICU) critically ill patients

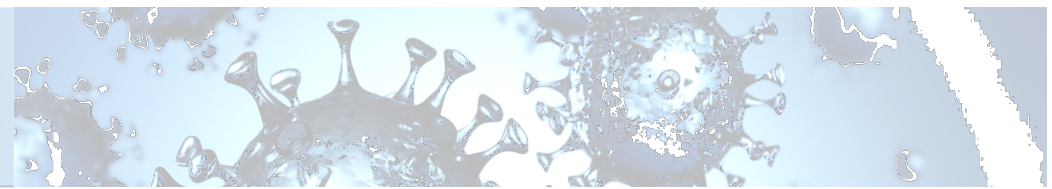
Mary-Luz Rol^{1, 2}, Fabienne Venet^{2, 3}, Thomas Rimmelé^{2, 4}, Virginie Mouchadel⁵, Pierre Cortez⁶, Laurence Quemeneur⁷, David Gardiner¹³, Andrew Griffiths⁸, Alexandre Pachot^{2, 5},  Julien Textoris^{2, 4, 5}, Guillaume Monneret^{2, 3} On behalf of the REALISM study group

Immune alterations characterization :

- Broad transcriptomic analysis → NLRP3 related genes : **IL-1R2**



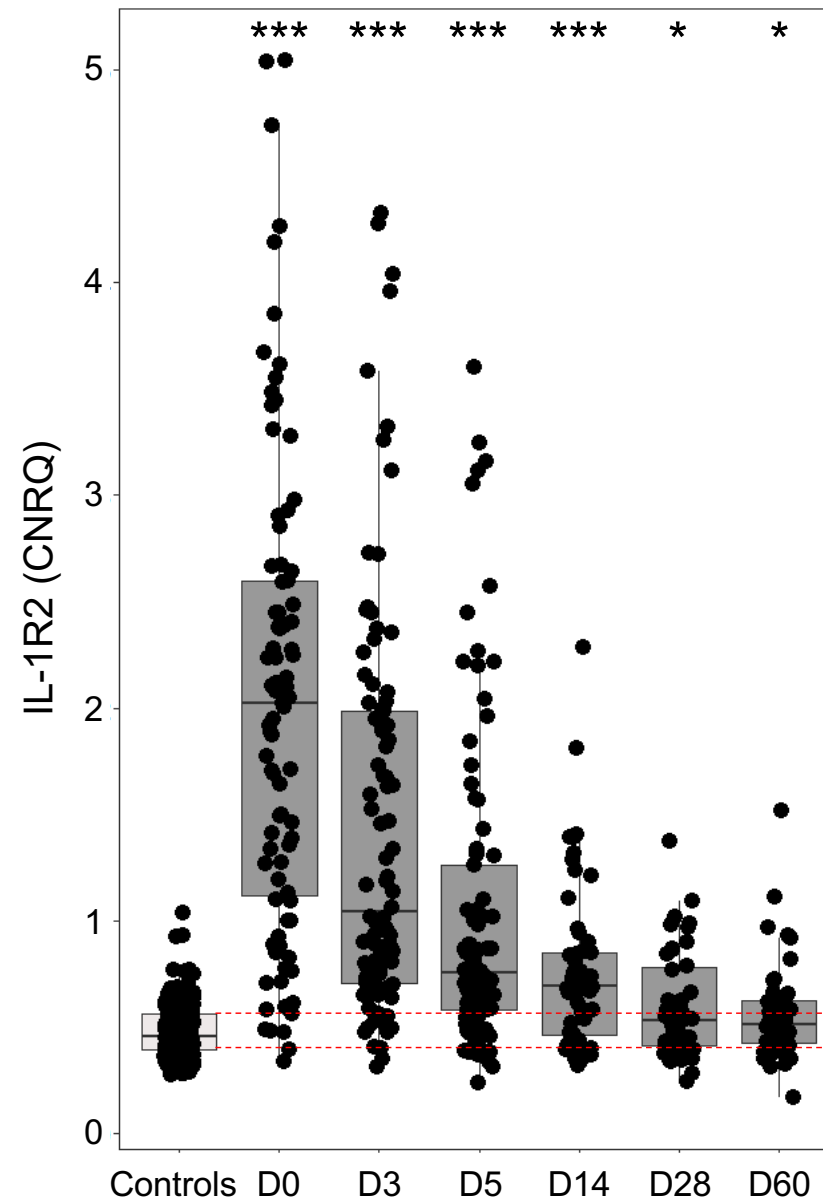
IL-1R2 kinetic



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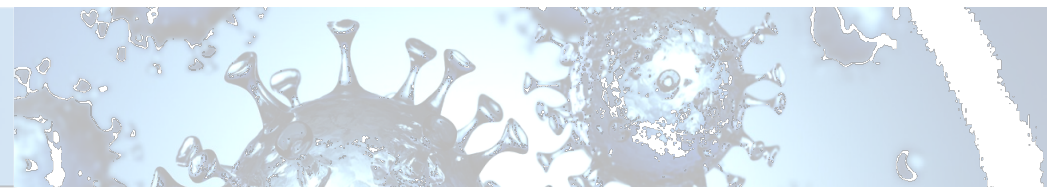
Results

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mRNA data similar to those
observed with the plasma
protein

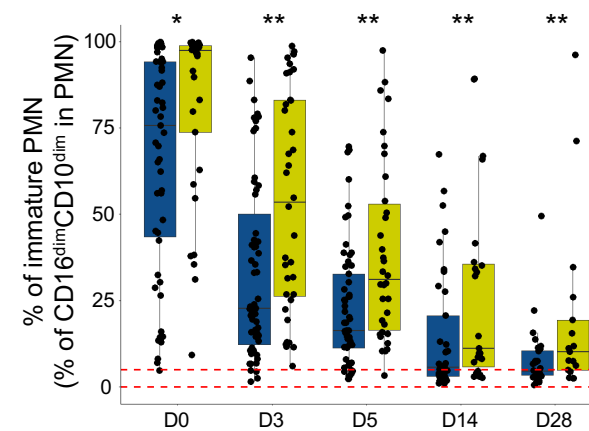
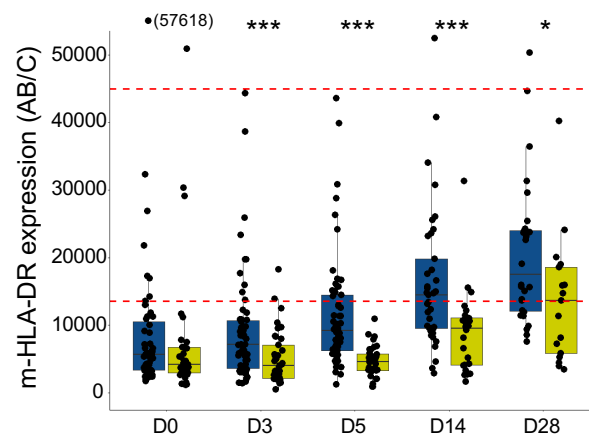
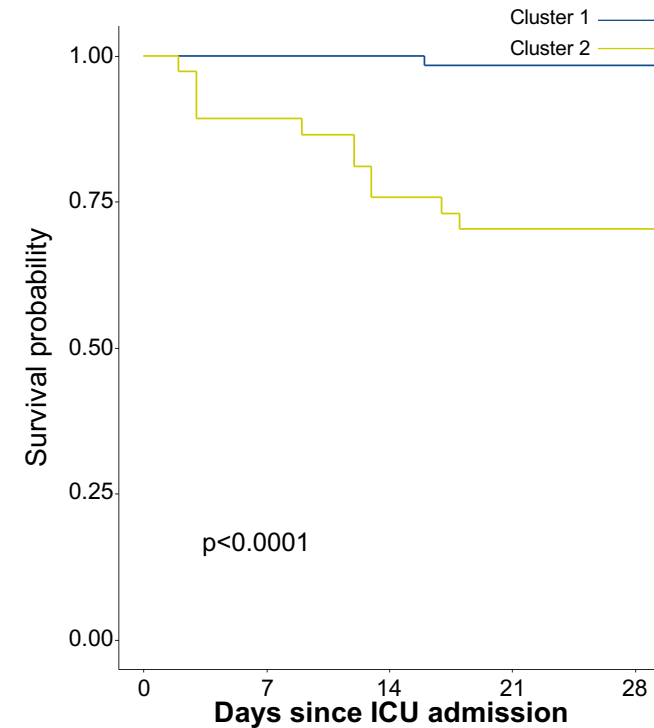
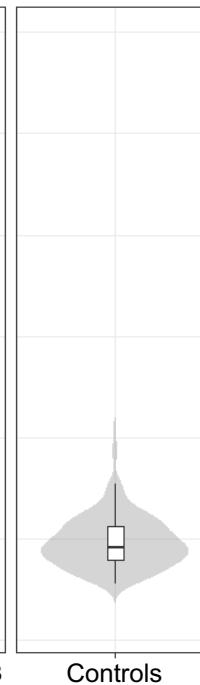
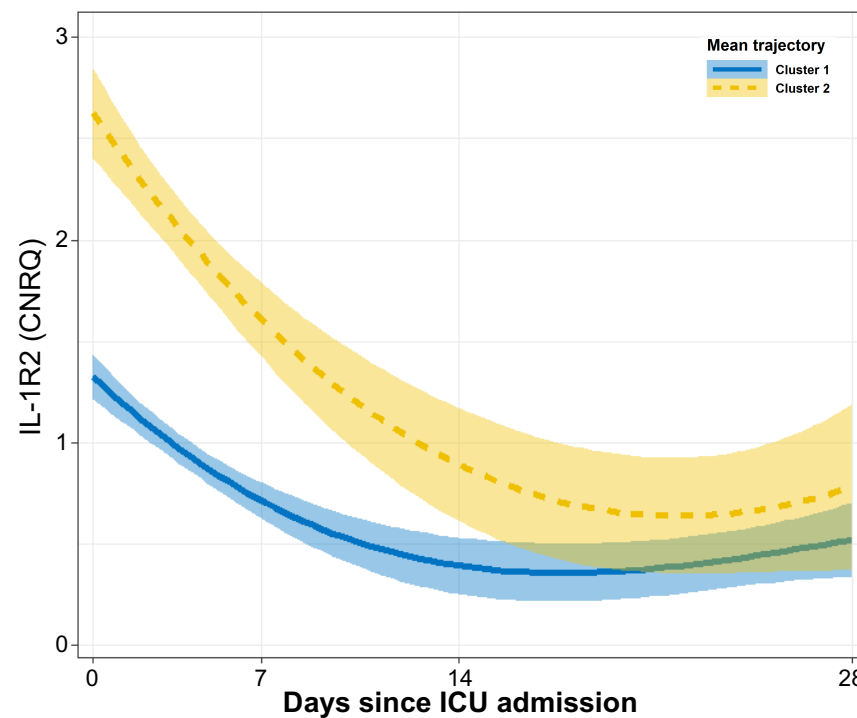
NLRP3 inflammasome activation



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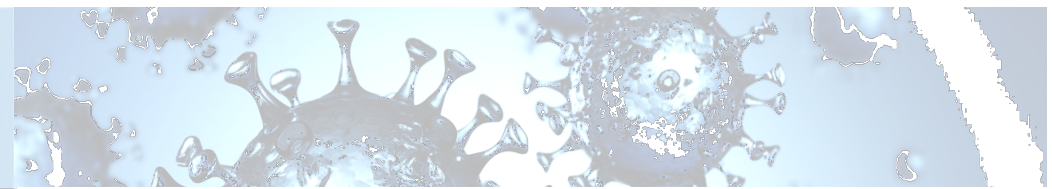
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* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$
Mann-Whitney U test

Conclusion



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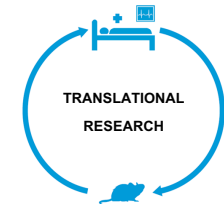
Conclusion

NLRP3 inflammasome **activation** and its **persistence** : associated with **marked immunosuppression** and **increased mortality rates**.



Results **submitted for publication**

Perspectives



Identifying endotypes → could hold important **clinical implications** for the **management of sepsis**

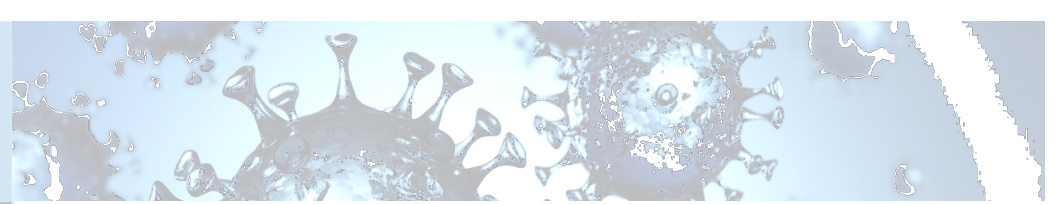
Pathophysiological explorations : Mice models of sepsis

- **NLRP3 KO mice**
- Mice treated with **inflammasome inhibitors**



Repurposing **therapies** focused on this inflammatory pathway

Contributors and Collaborations



Immunology Lab – Hospices Civils de Lyon

Pr G Monneret	Dr C Lombard
Dr C Malcus	Dr S Viel
Dr R Pescarmona	Dr L Garnier
Dr E Micoud	M Perret
Team of technicians	M Villard

Intensive Care Units Hospices Civils de Lyon

Pr AC Lukaszewics	Pr H Yonis
Pr T Rimmelé	Pr F Wallet
Pr L Argaud	Pr V Piriou
Pr M Cour	Pr F Dailler
Pr JC Richard	Dr MC Delignette
Dr F Bidar	Research Nurses

Team « Inflammasome NLRP3 and Immune Response to Sepsis, CIRI, Inserm U1111, CNRS, UMR5308, ENS, UCBL1

Dr B Py	Romane Riou
Pr F Venet	Louise Courcol
Dr M Gossez	Clara Vigneron

Patients and their families

INSERM U1111, CNRS
UMR5308
Dr T Henry

Centre d'Investigation Clinique
CIC 1407 Inserm - HCL
M Buisson - I Boussaha
M Ndiaye - Research Nurses

CRCL, INSERM, UMR
1052, CNRS 5286
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INSERM U1065, C3M
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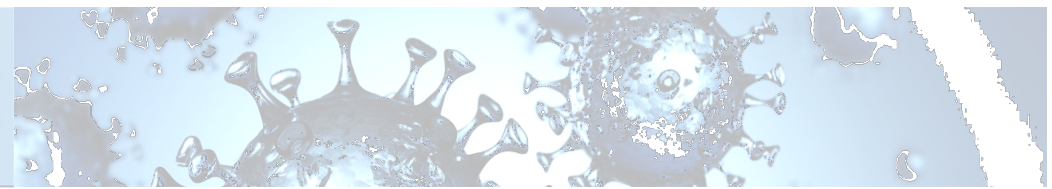
Dr E Peronnet
Dr MA Cazalis
Dr V Cheynet
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M Bodinier



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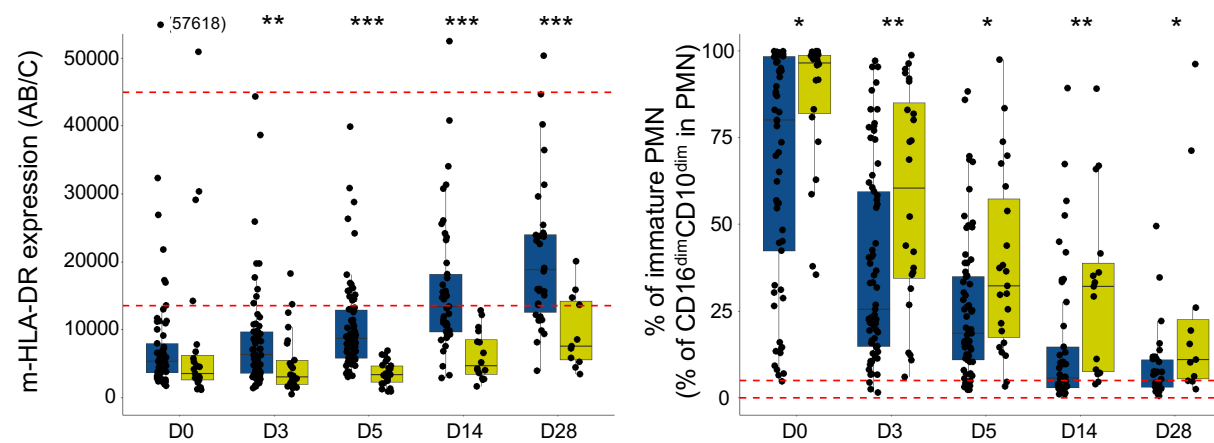
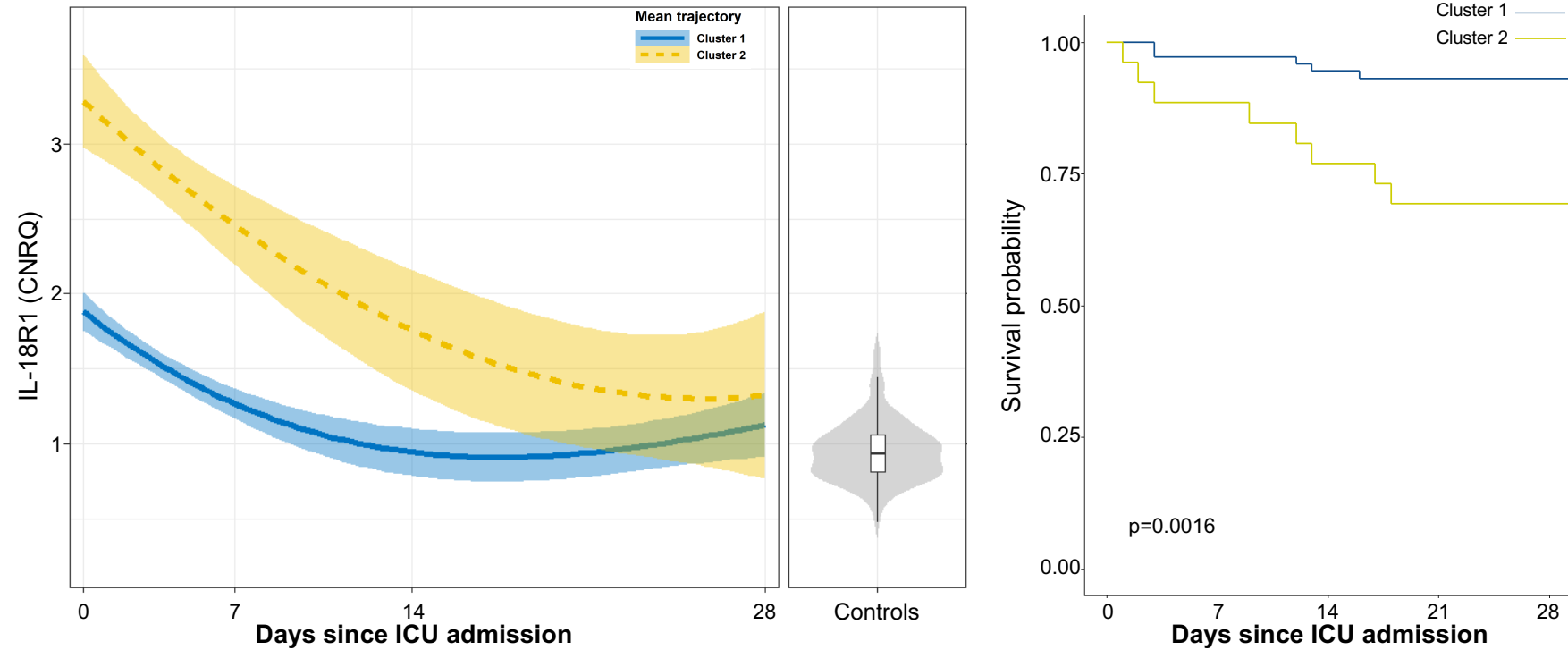
NLRP3 inflammasome activation



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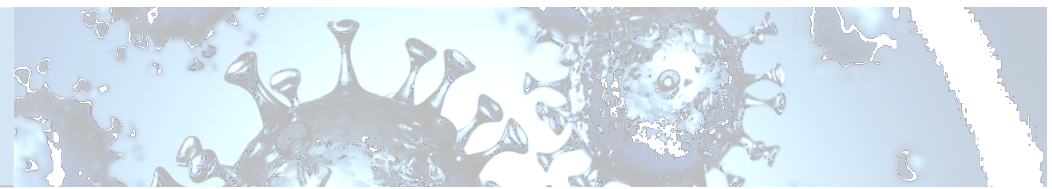
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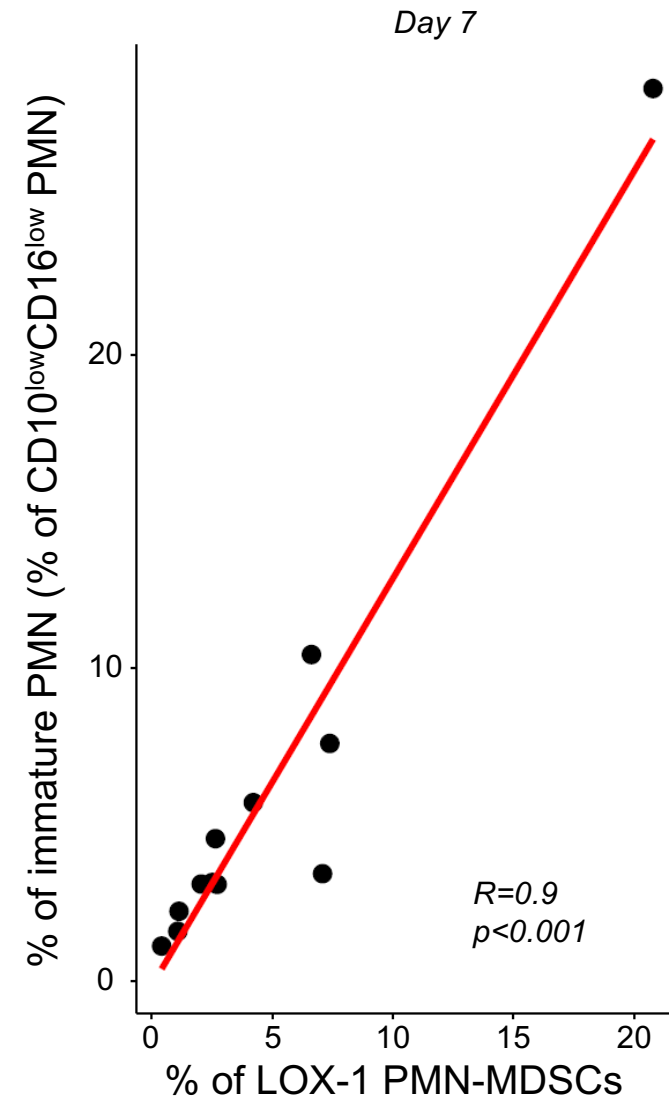
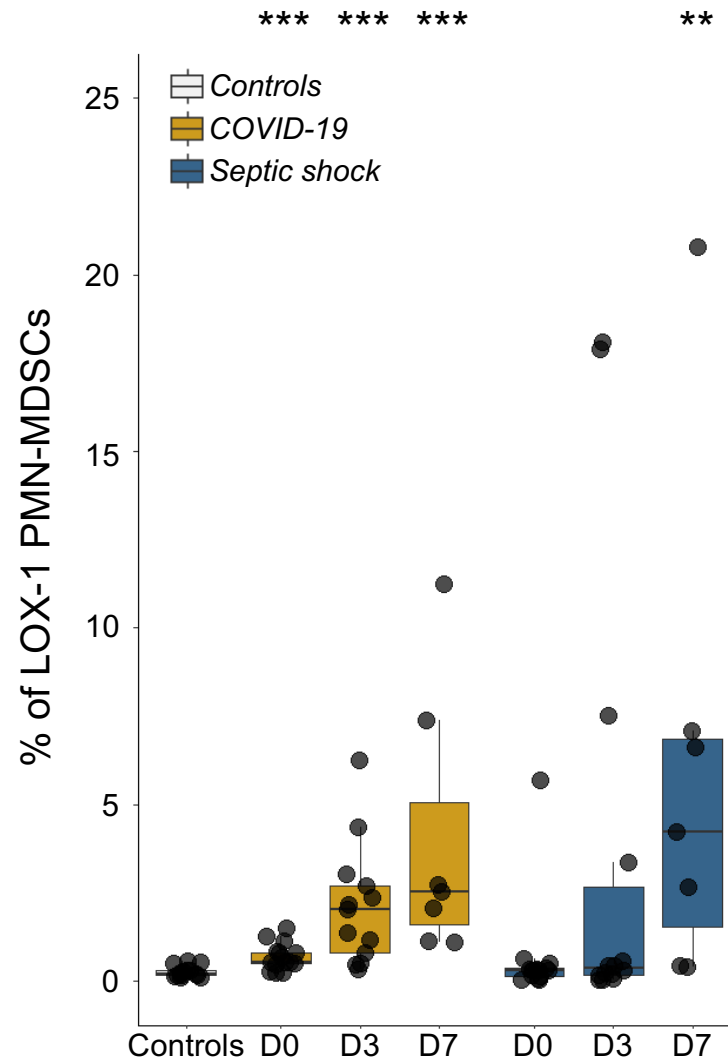
Parallels between LOX-1 PMN-MDSCs and immature PMN



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