entre **M**éditerranéen de **M**édecine **M**oléculaire

Inserm U1065

Mechanisms of Sepsis :

From the molecular side to the patient's bedside

Laurent BOYER, DR Inserm, C3M, Nice

Inserm

La science pour la santé

From science to health

chu de Nice

UNIVERSITÉ CÔTE D'AZUR

Axis 1: Mechanisms of sepsis – Improving the understanding of sepsis

Coordinators: Christophe COMBADIERE, Karim ASEHNOUNE, Laurent BOYER

Contributors: Antoine DEWITTE, Catherine WERTS, Fabienne VENET, Philippe BULET, Jean-Marc CAVAILLON, Ala-eddine DEGHMANE, Fanny LANTERNIER, Marie-Elisabeth BOUGNOUX, Jessica QUINTIN, Olivier DUSSURGET, François SCHELCHER, François MEURENS, Renaud TISSIER, Djillali ANNANE.

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Research priorities and proposition for fundings :

Infection & immunity

Microbiology of Sepsis

Nervous system & Sepsis

Organe failure and thrombosis

System biology of Sepsis

Developing new tools and models

Therapeutical targets identification

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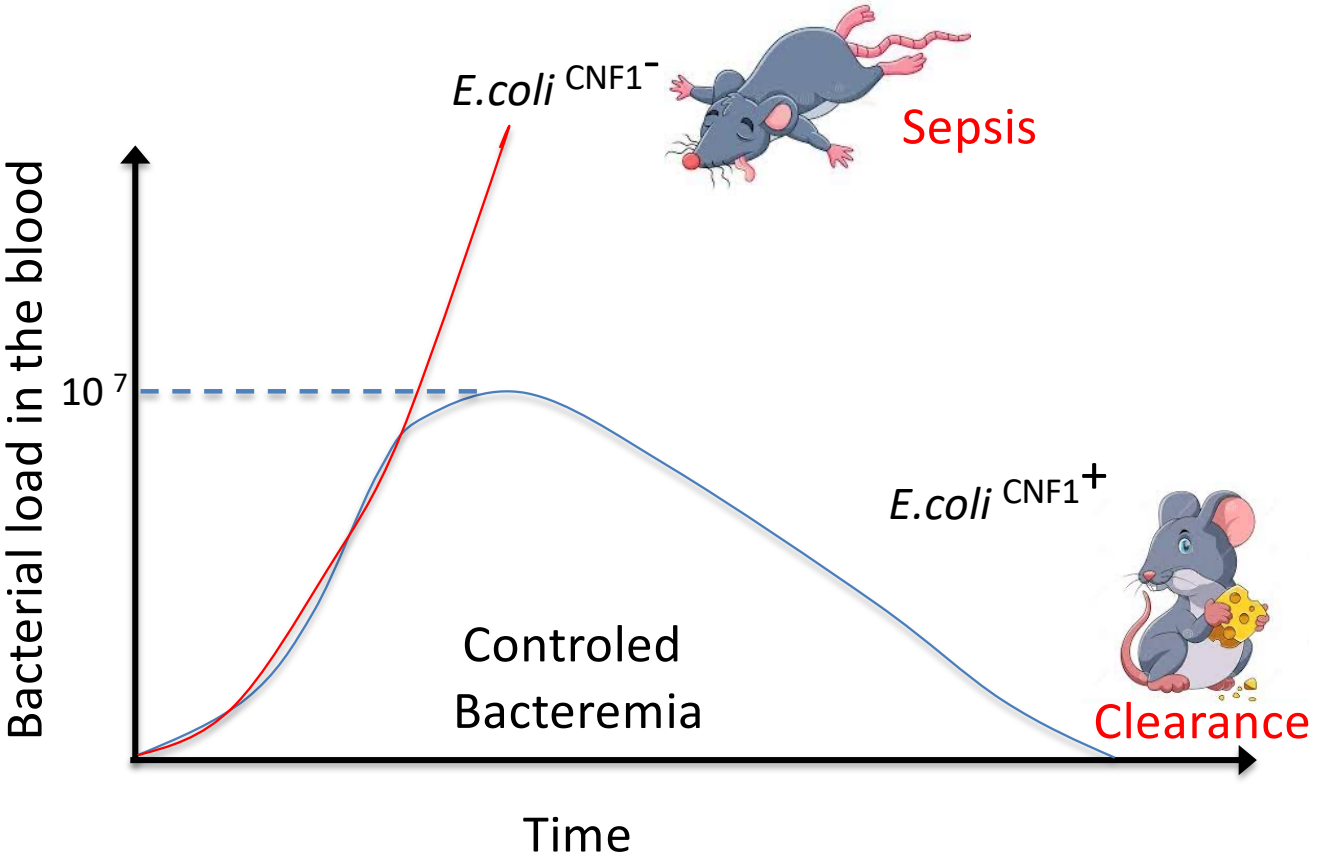
CONGRATS & THANK YOU

A personal perspective:

How we bumped into exploring molecular aspects of sepsis?

The origins: Uropathogenic *Escherichia coli* infections

Trans-uretral infections in mice to determine the role of the CNF1 bacterial virulence factor



Patrick Munro

Unpublishable data, 2012

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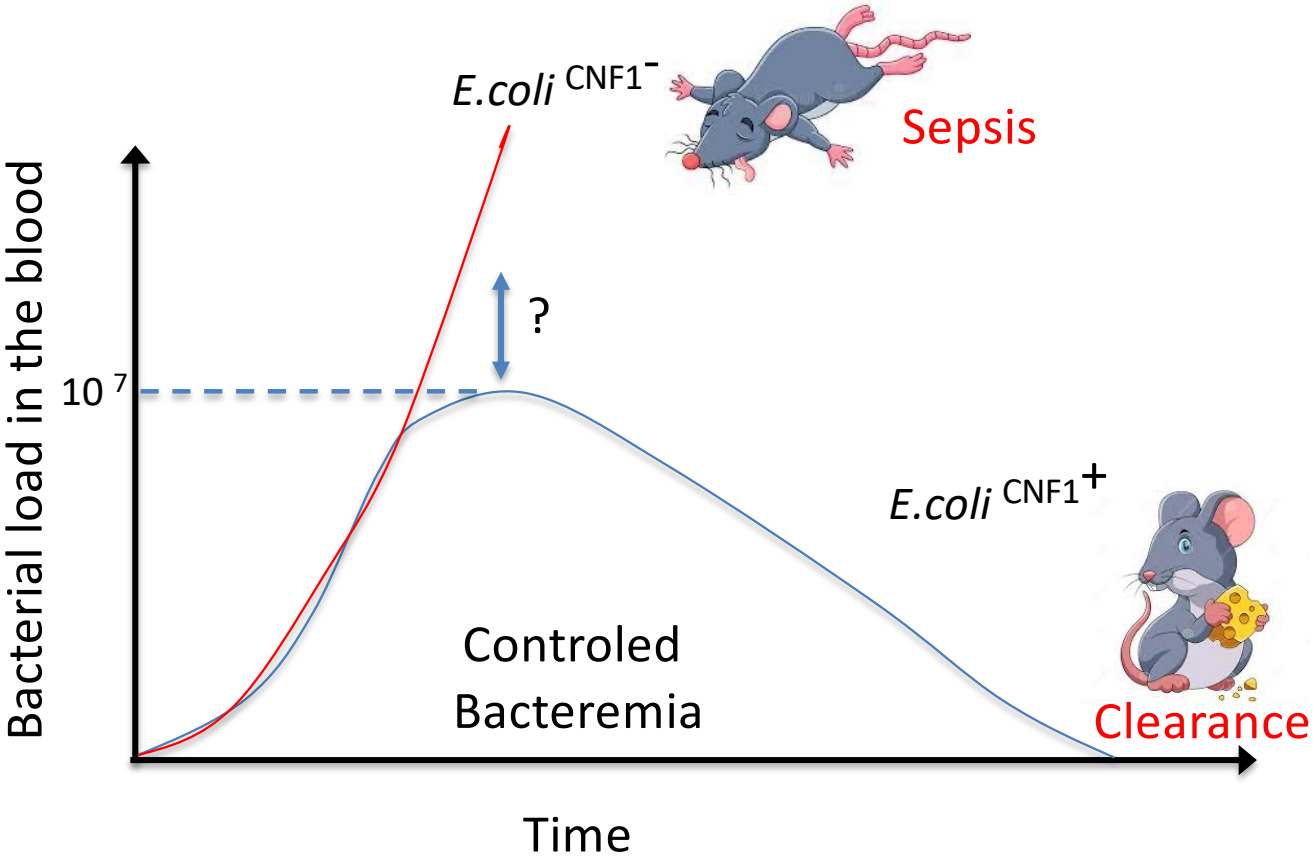

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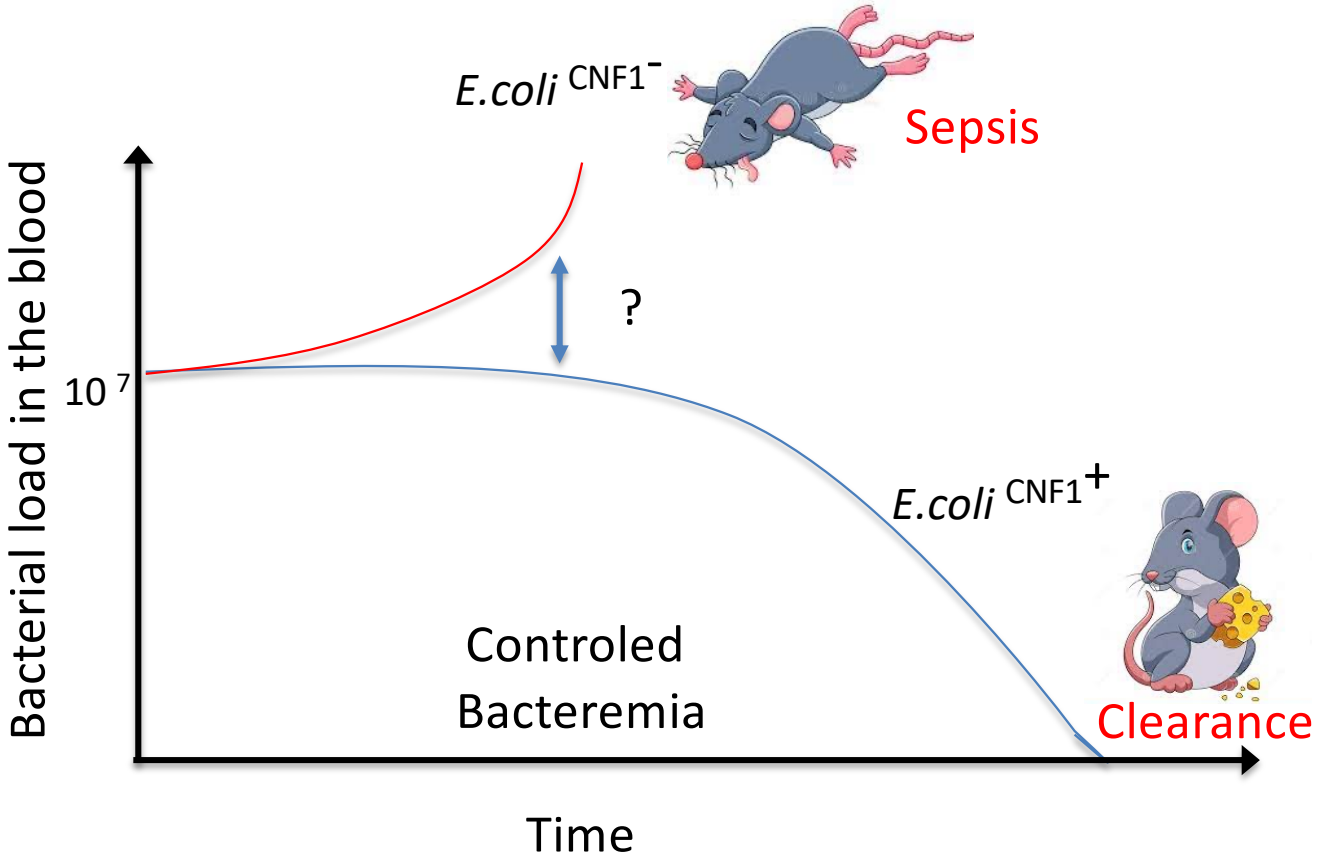

Patrick Munro

Diabaté et al, *PLOS Pathogens,* 2015

What is controling bacterial clearance during bacteremia?

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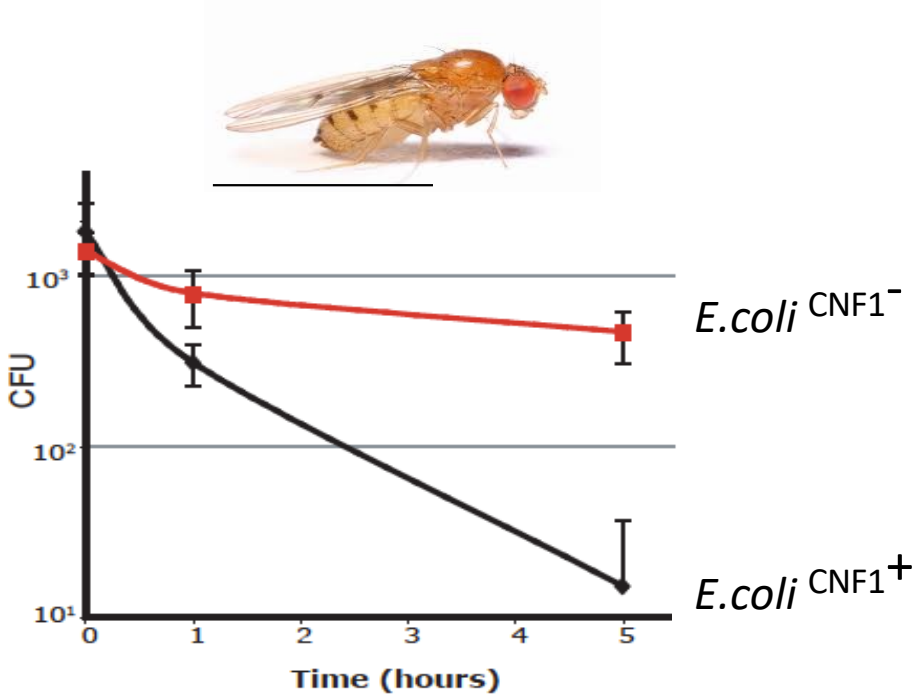
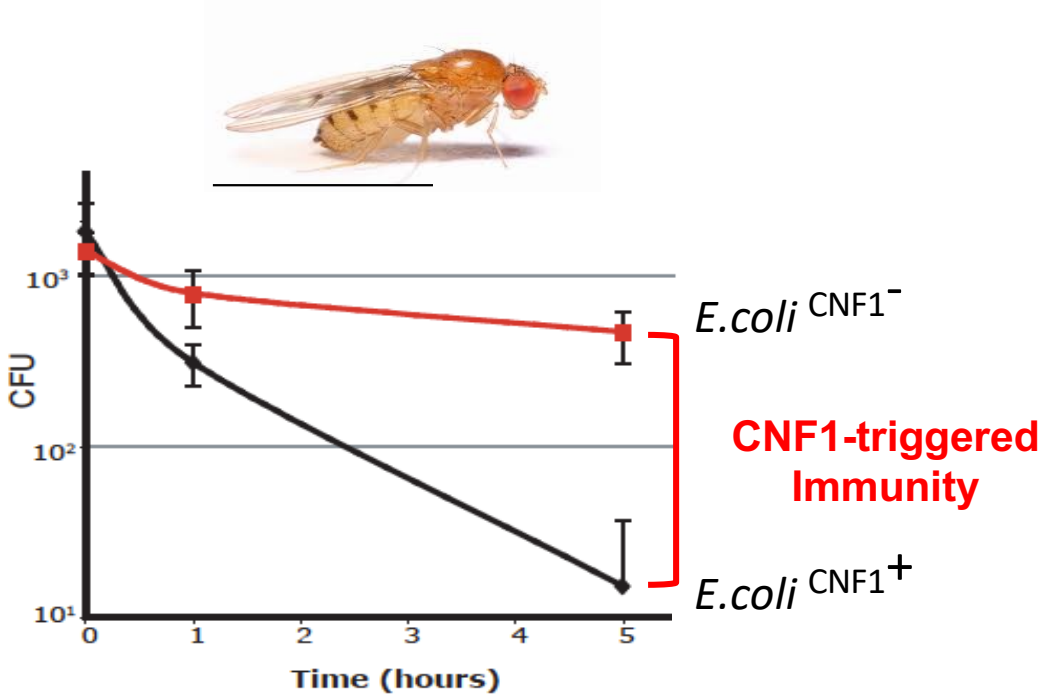
This reminded us about Effector triggered immunity in drosophila

Effector-triggered immunity during drosophila systemic infection



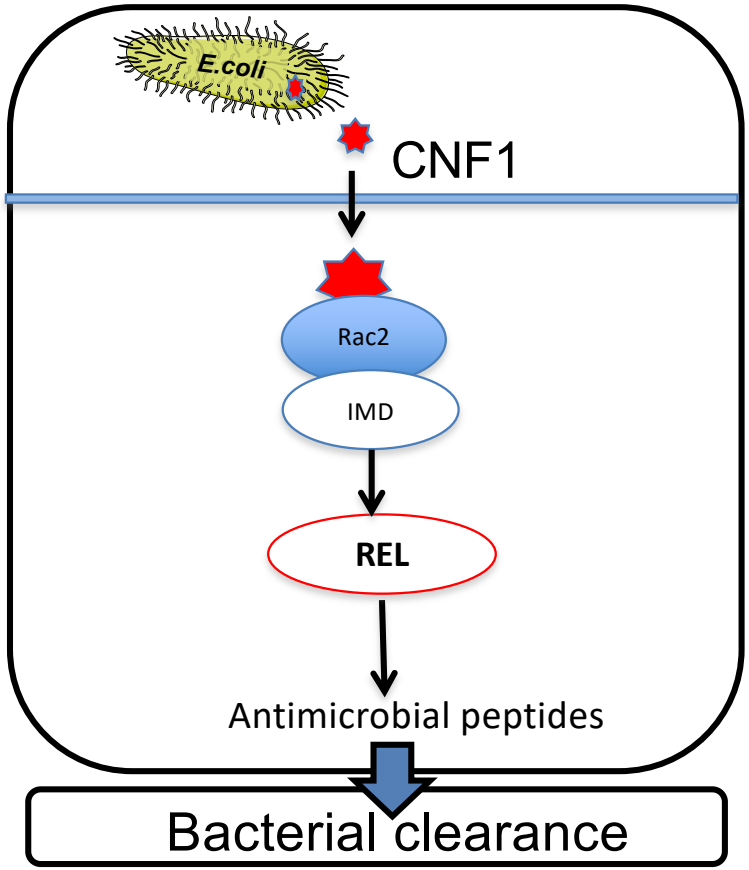
Boyer et al, *Immunity,* 2011

Effector-triggered immunity during drosophila systemic infection



Boyer et al, Immunity, 2011

CNF1 toxin -triggered immunity is related to Effector triggered immunity

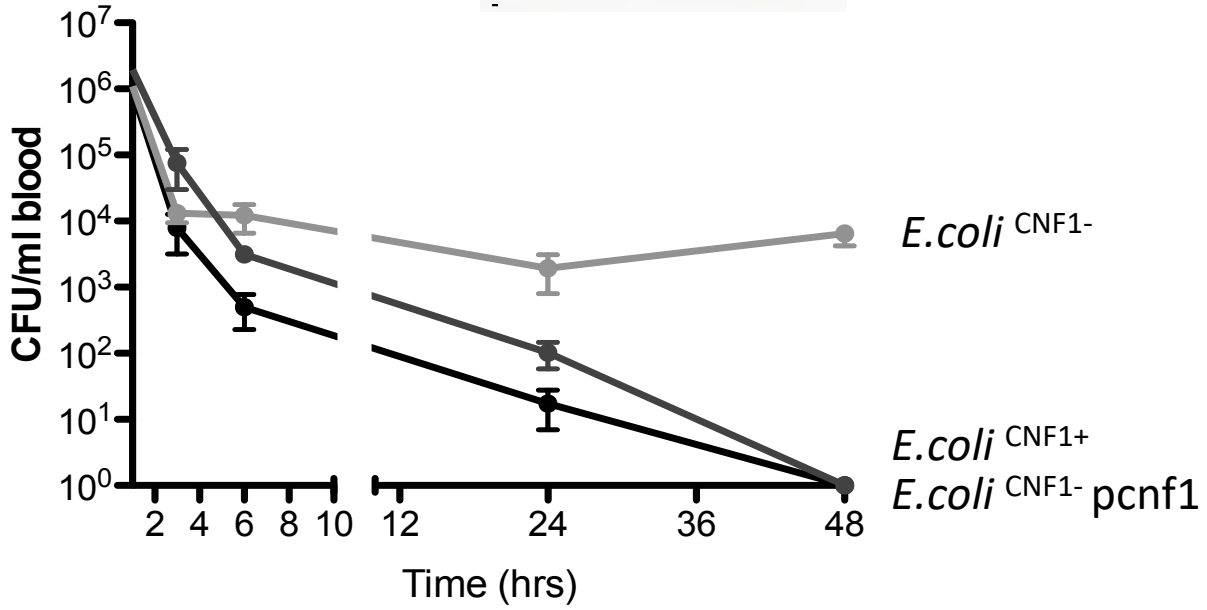


Boyer et al, *Immunity,* 2011

Does effector-triggered immunity controling bacteremia in mice?

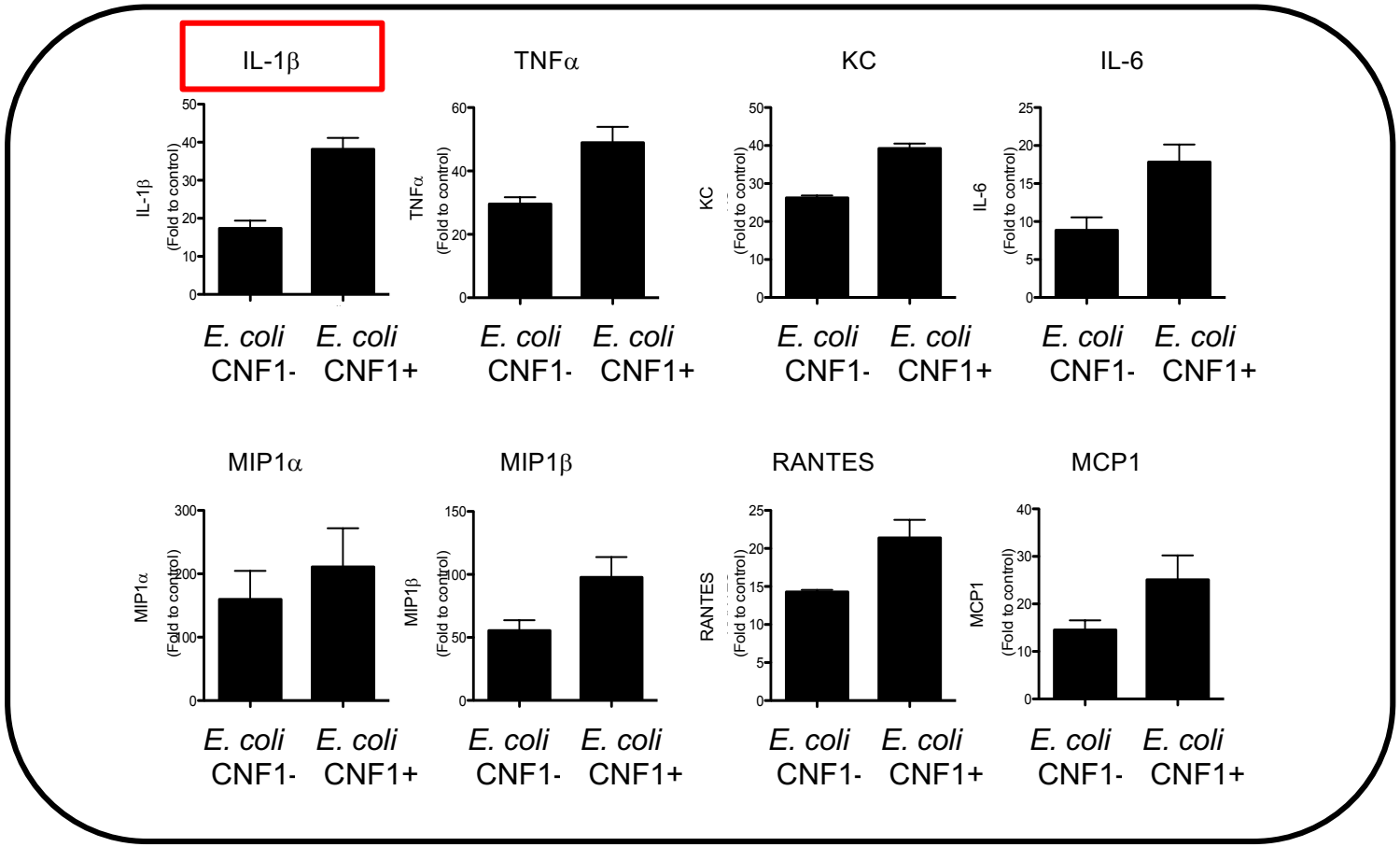
E. coli expressing CNF1 are cleared rapidly during bacteremia

Bacteremia Model: tail vein injection in mice



Diabaté et al, *PLOS Pathogens,* 2015

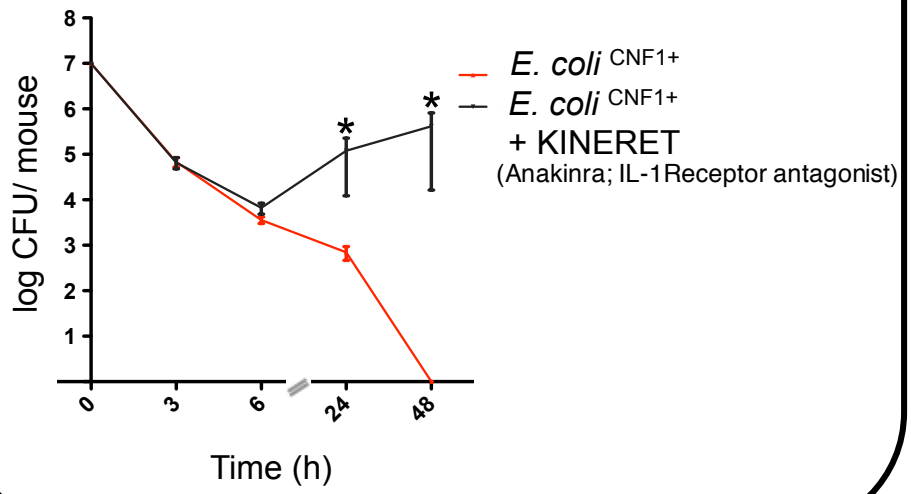
E. coli expressing CNF1 triggers an increased systemic cytokine response during bacteremia



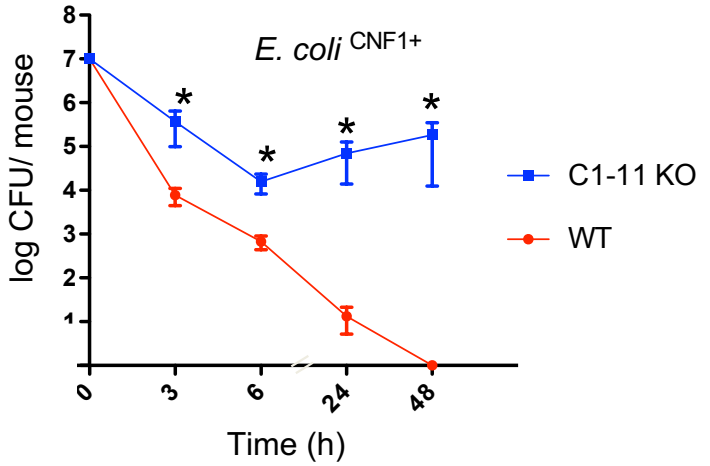
Diabaté et al, *PLOS Pathogens,* 2015

IL-1β signaling is essential for CNF1-triggered bacterial clearance

IL-1R signaling is required for bacterial clearance



Bacterial clearance is blocked in Caspase 1-11 KO mice



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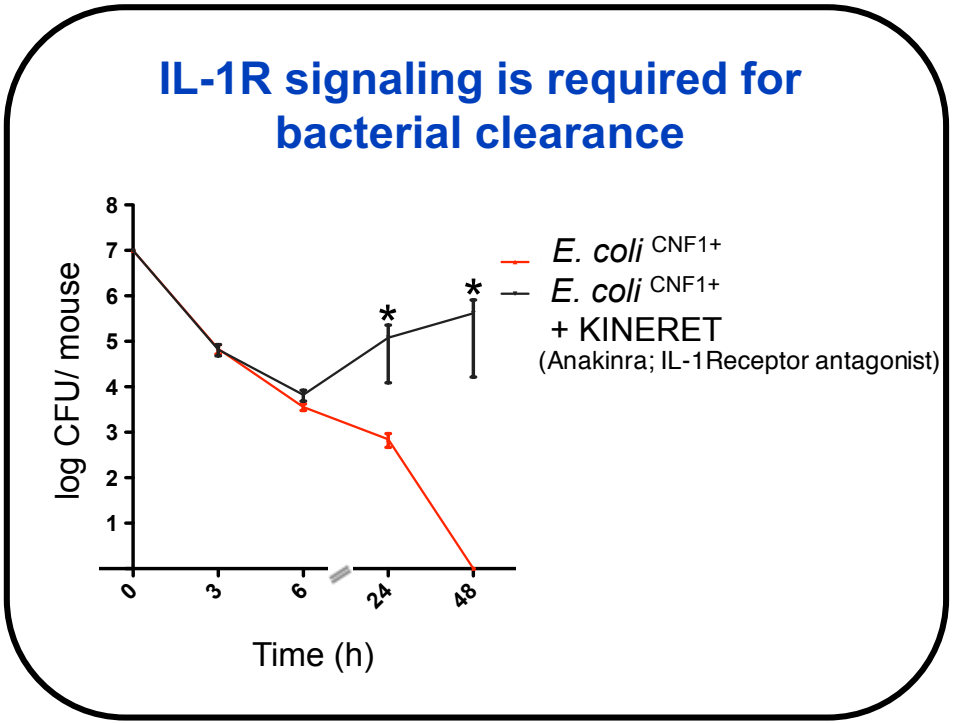
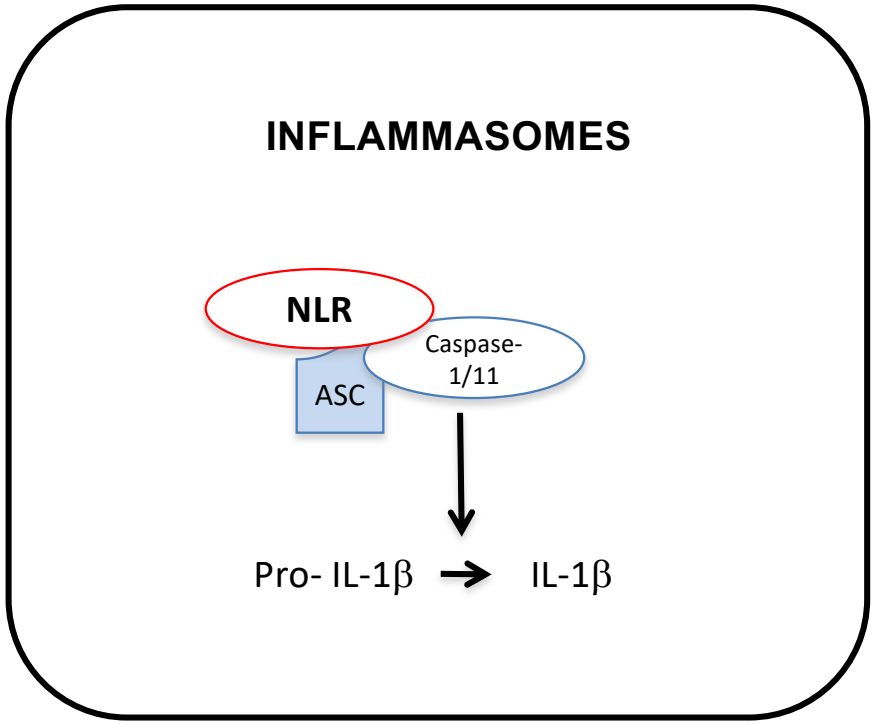
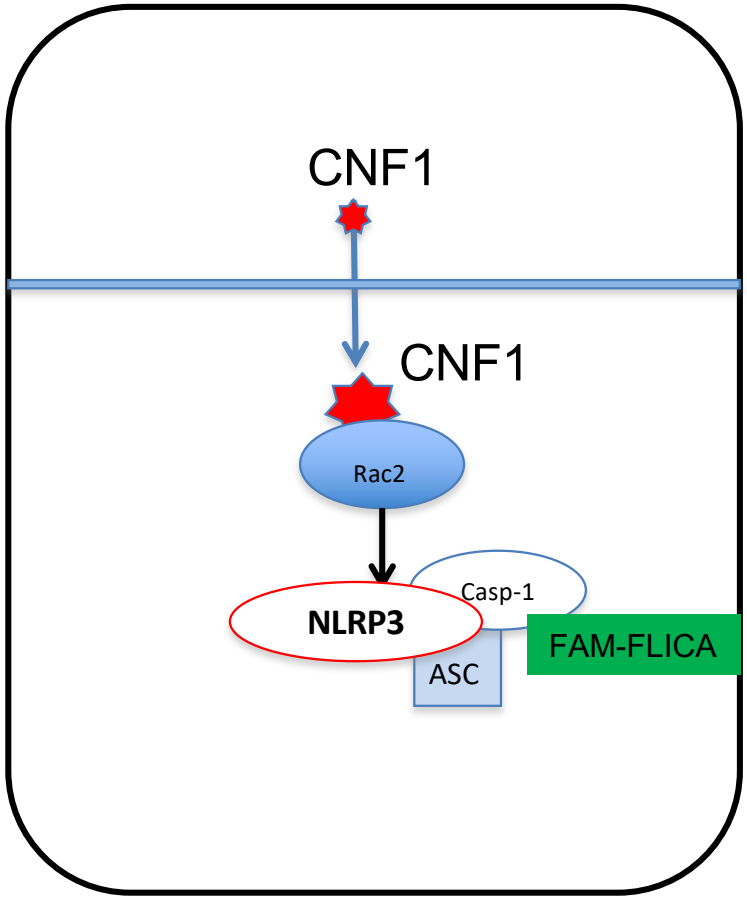




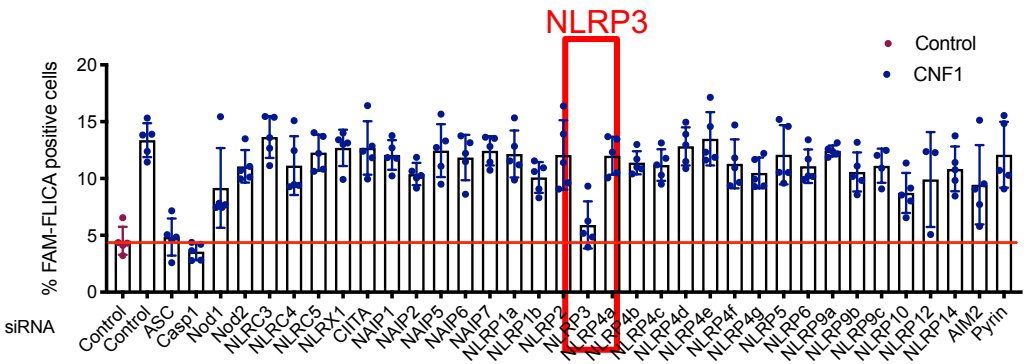
Diabaté et al, *PLOS Pathogens,* 2015

Which NLR is responsible for CNF1-triggered immunity?

NLRP3 is responsible for the detection of the CNF1 toxin



⇒ **RNAi screen of NLRs in macrophages**

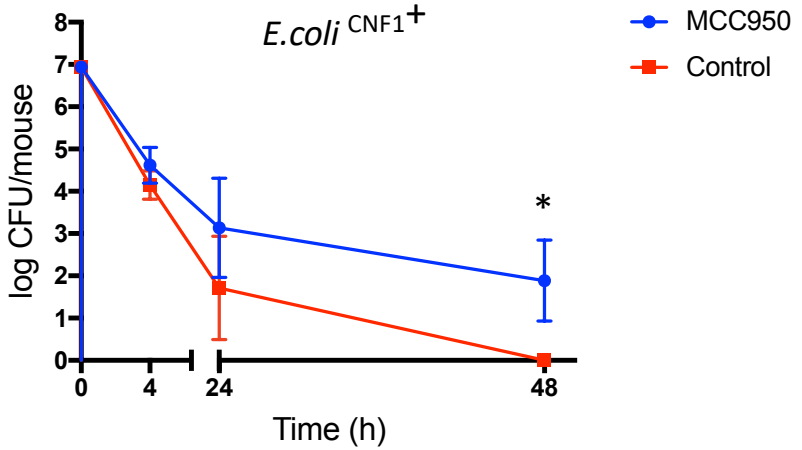


Océane Dufies

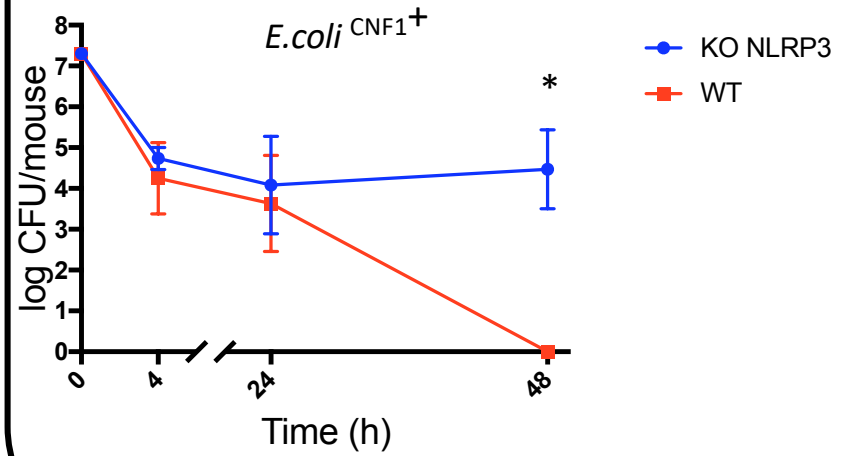
Dufies et al, *Nature Microbiology,* 2021

NLRP3 is essential in controling bacterial clearance during bacteremia

NLRP3 inhibitor MCC950 inhibits the clearing of CNF1+ bacteria



NLRP3 KO mice are deficient in clearing CNF1+ bacteria



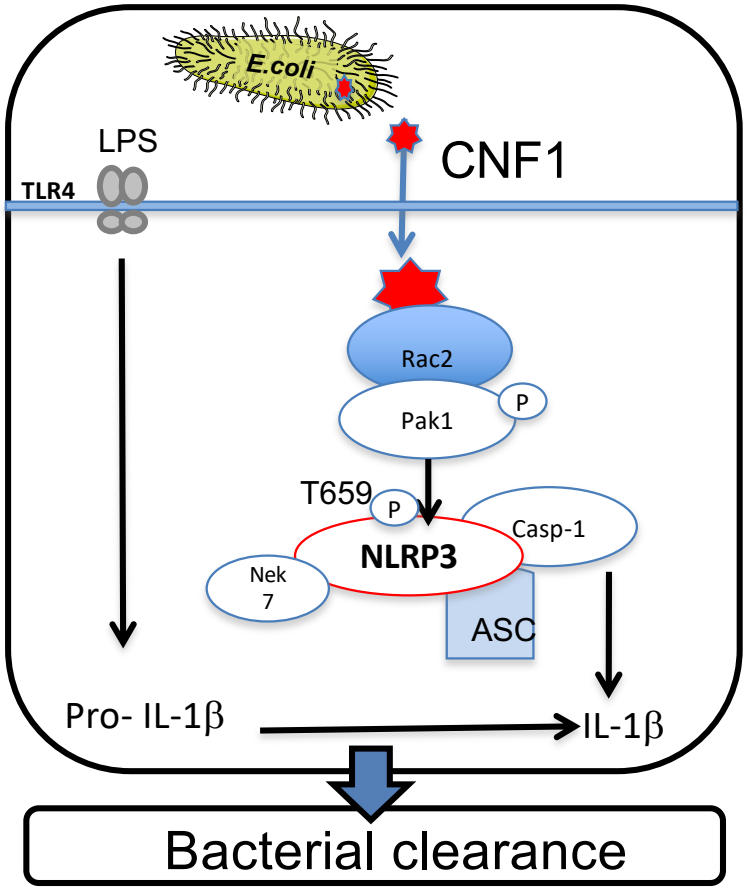
Collab V. Petrilli (CRCL, Lyon)

Océane Dufies

Patrick Munro

Dufies et al, *Nature Microbiology,* 2021

Protective Role of NLRP3 inflammasome during bacteremia in mice



Océane Dufies

Patrick Munro

Raymond Ruimy

Orane Visvikis

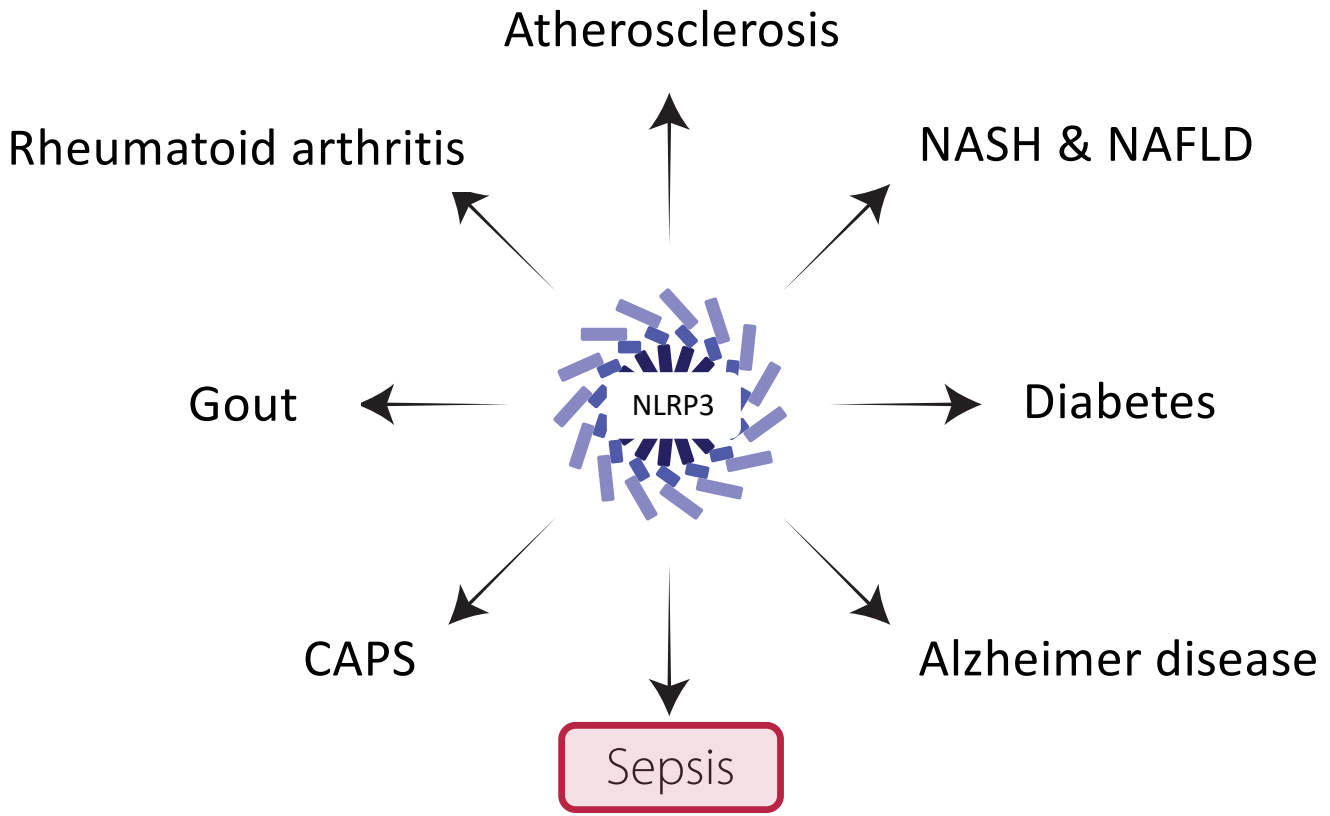
Cédric Torre

Dufies et al, *Nature Microbiology,* 2021

NLRP3 Inflammasome :

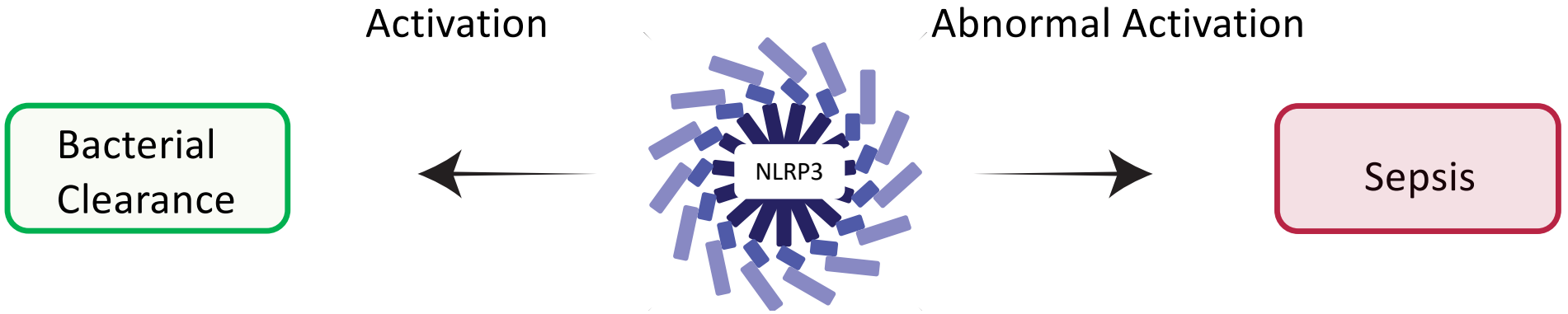
Not always beneficial…

Abnormal activation of the NLRP3 inflammasome is implicated in many diseases



Fusco et al., 2020

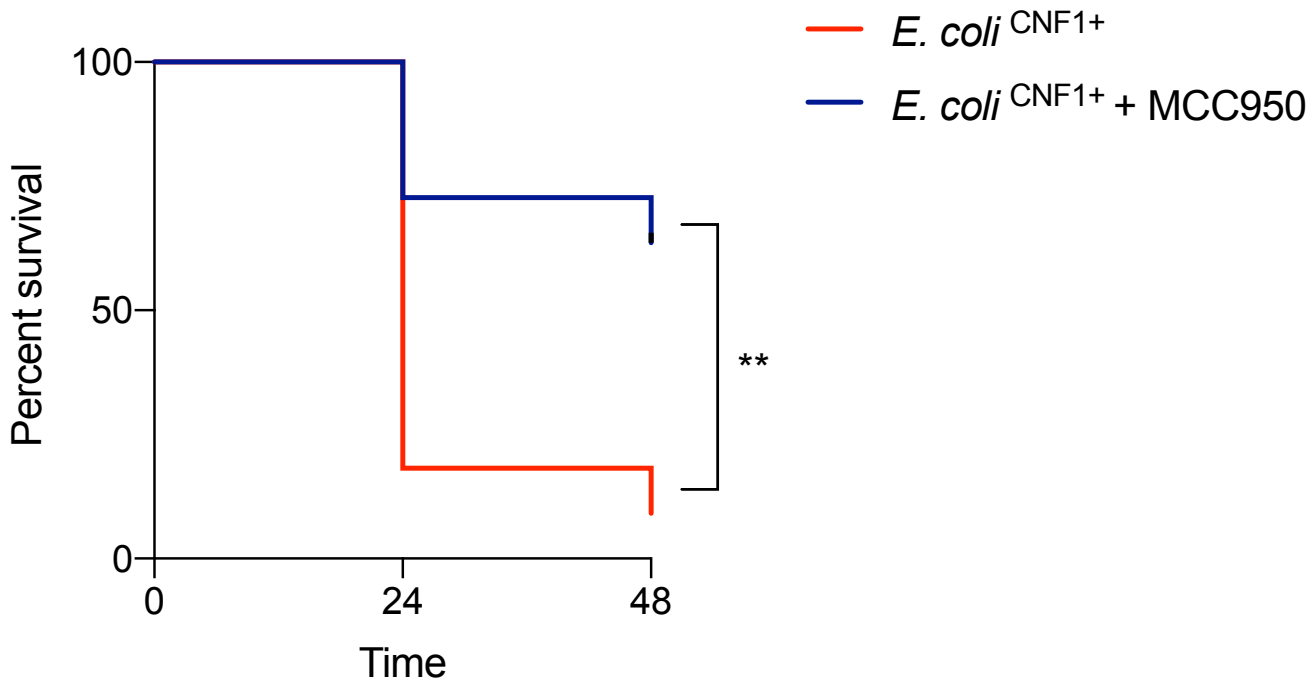
NLRP3 inflammasome activation status controls the switch from controlled bacteremia to Sepsis ?



NLPR3 inhibition protects from Sepsis in high dose infections

Bacteremia Model: tail vein injection in mice

Sepsis: 10^8 CFU/mice



Unpublished data, 2012

Deleterious role of the NLRP3 inflamasome during Sepsis

Bacteremia Model: tail vein injection in mice

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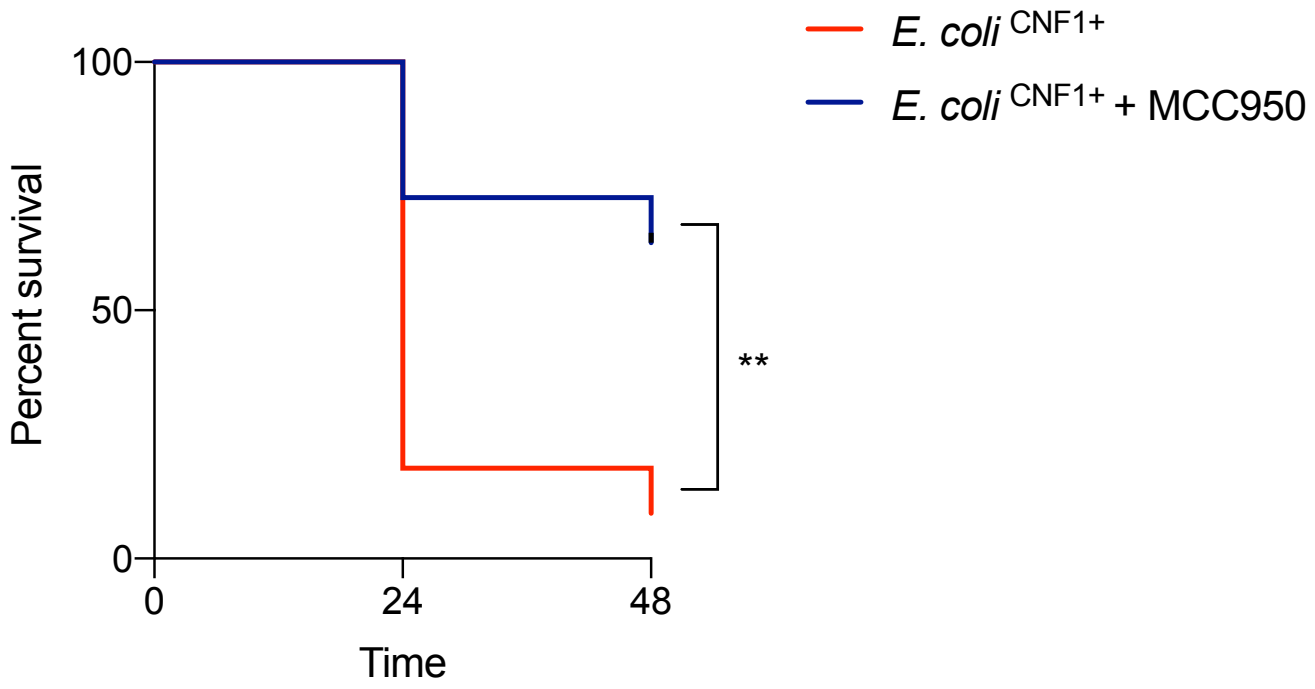

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Should the NLRP3 inflammasome be activated or inhibited to treat bacteremic patients?

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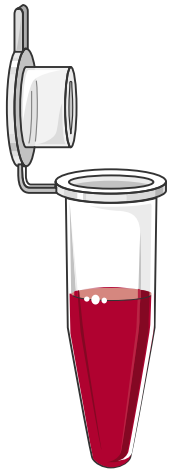
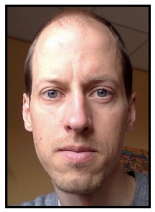
It is necessary to determine the activation status of NLRP3 for each bacteremic patients

Measuring inflammasome activation in the circulating leukocytes of patients with Bacteremia with or without Sepsis?



Patient's whole Blood

Immunophenotyping & Caspase-1 activation monitoring (FAM-FLICA) using flow cytometry



Johan Courjon Renaud Scussel Michel Carles

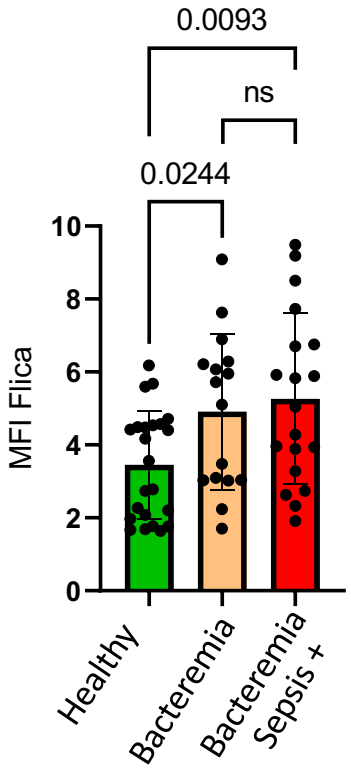
Collaboration F. Venet (HCL, Lyon) et B. Py (CIRI, Lyon)

Trial registration: ClinicalTrials.gov NCT03869593

Non-Classical monocytes and Eosinophils have an increased FAM-FLICA Signal during Bacteremia

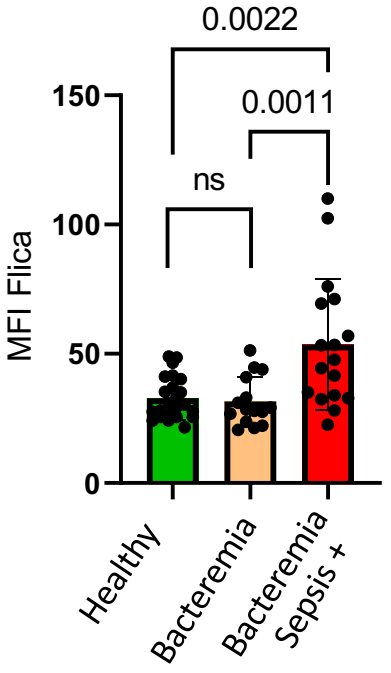
Non-classical monocytes

($CD14^{dim}CD16^{+}$)



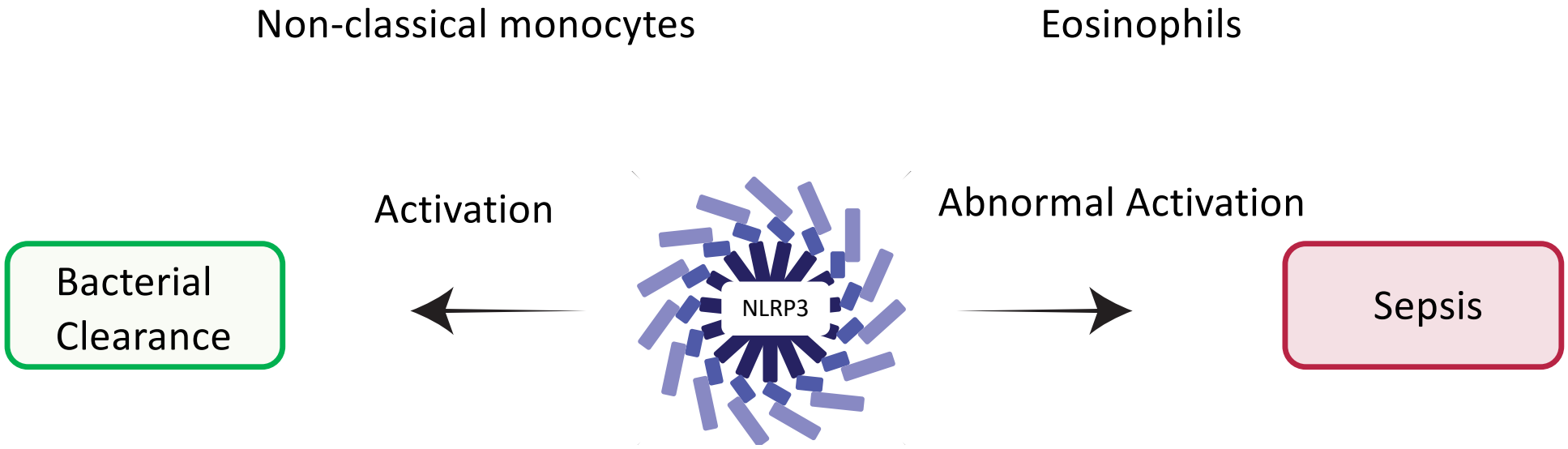
Eosinophils

($CD66b^{+}CD16^{dim}Siglec8^{+}$)



In progress, n=19/group, Sepsis= SOFA ≥ 2

Hypothesis


Non-classical monocytes
Eosinophils
Activation
Abnormal Activation
Bacterial Clearance
NLRP3
Sepsis

Acknowledgments

C3M Team #6 MICROBIAL VIRULENCE AND INFLAMMATORY SIGNALING

C3M, Team 2
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C3M, Team 3
S. Marchetti
E. Verhoeyen

C3M, Team 12
T. Passeron
S. Rocchi

C3M, Team 13
L. Yvan Charvet

C3M Facilities

LP2M, Nice
S. Ivanov

UGent, Belgium
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IPBS, Toulouse
E. Meunier

CIRI, Lyon
T. Henry
B. Py

CRCL, Lyon
V. Petrilli

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DÉPARTEMENT DES ALPES-MARITIMES

Thank you for your attention