



HAL
open science

Development of trained immunity and activation of inflammasomes are promising strategies to combat *Staphylococcus aureus* infection

Emmanuel Chaumond, Elma Lima Leite, Sandrine Péron, Nathalie Daniel, Yann Le Gouar, Aurélie Nicolas, Jordane Ossemond, Arthur Gautron, David Gilot, Vasco Ariston de Carvalho Azevedo, et al.

► To cite this version:

Emmanuel Chaumond, Elma Lima Leite, Sandrine Péron, Nathalie Daniel, Yann Le Gouar, et al.. Development of trained immunity and activation of inflammasomes are promising strategies to combat *Staphylococcus aureus* infection. 18e congrès national de la SFM “ Un monde à explorer ”, Société Française de Microbiologie (SFM), Oct 2023, Rennes, France. hal-04234405

HAL Id: hal-04234405

<https://hal.inrae.fr/hal-04234405>

Submitted on 10 Oct 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License



Société Française
de Microbiologie

MICROBES 2023

18^e CONGRÈS NATIONAL DE LA SFM

4-6
octobre

**LE COUVENT
DES JACOBINS**

CENTRE DES CONGRÈS DE
DE **RENNES** MÉTROPOLE



Déclaration de conflit d'intérêt

Pour cette présentation,
je déclare n'avoir aucun conflit d'intérêt.



INRAE

N. Berkova
SFM 2022

INRAE

Development of trained immunity and activation of inflammasomes are promising strategies to combat *Staphylococcus aureus* infection

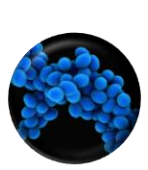
Berkova Nadia

STLO, UMR 1253, INRAE, Rennes

nadejda.berkova@inrae.fr

<https://www6.rennes.inrae.fr/stlo>





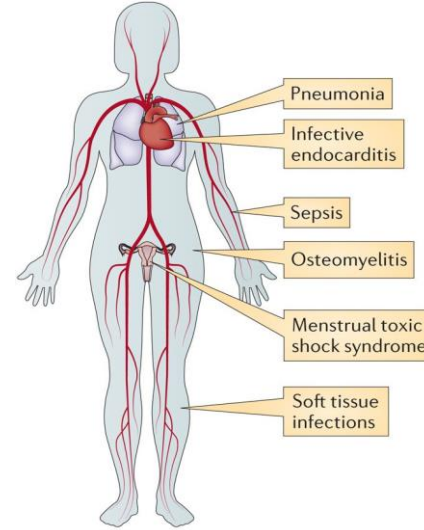
➤ *Staphylococcus aureus* is responsible for a wide range of infections in human and animals

S. aureus-induced diseases represent serious problems, especially during chronic infections

Human Mild skin infections



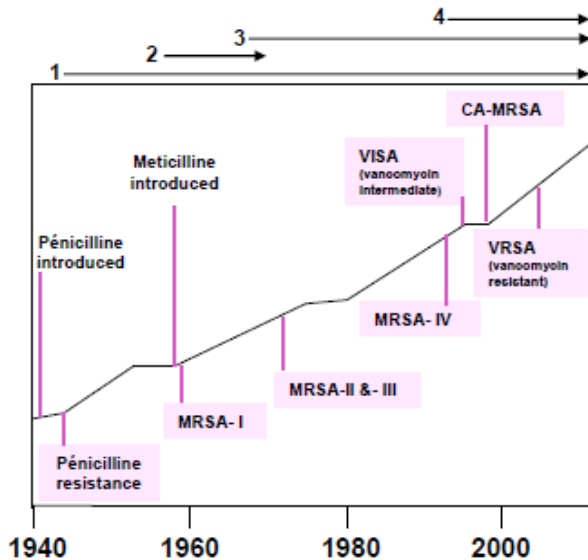
Life-threatening infections



Dairy_cattle: Chronic mastitis



Waves of *S. aureus* resistance



Nature Reviews | Microbiology

Urgent Need



Unraveling Immunity to Strengthen the Host's Defense Against Recurrent *S. aureus* Infection



➤ The compelling reasons to study non-immune cells in host-pathogen dynamics

Site-Specific Defense:

Non-immune cells with an extended lifespan are located in tissues prone to infections

Chronic Infections:

Tissue-residents non-immune cells, contribute to infection persistence by internalizing pathogens

Cellular Crosstalk:

Immune cells & non-immune cells communication shapes a coordinated defense response



Osteomyelitis, often caused by *S. aureus* infections

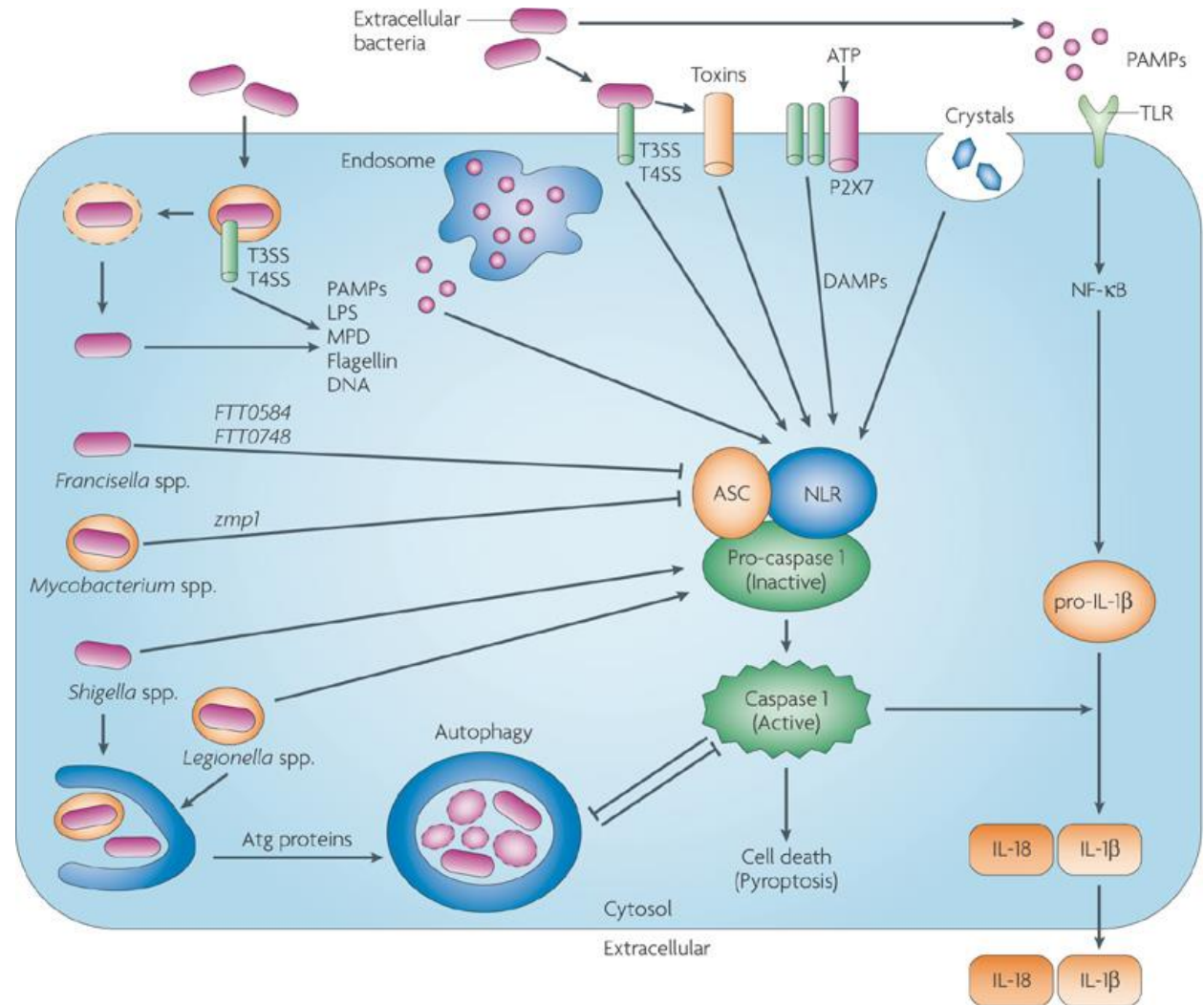


How Osteoblasts Defend Against *S. aureus* Invasion?

➤ INFLAMMASOMES activation as a defense mechanism against infection and injury

Persistent inflammation activates protein complexes, inflammasomes, that are composed of **a sensor (NLR)**, **an adaptor (ASC)**, and **a zymogen procaspase-1**

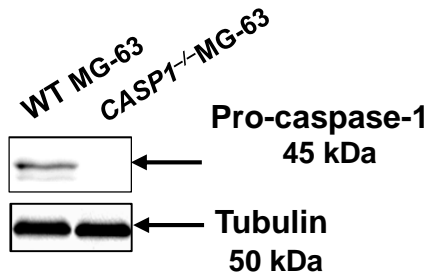
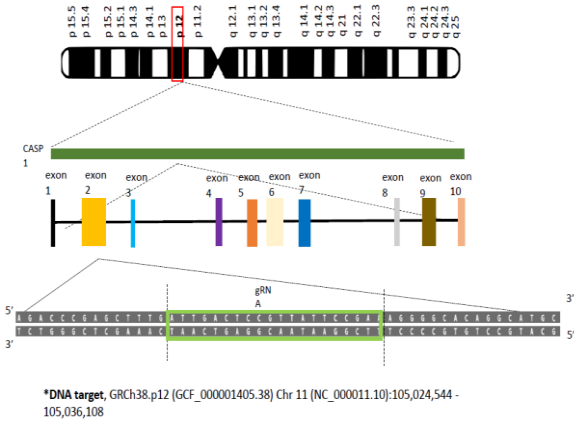
Inflammasomes activate Caspase-1, which proteolytically matures pro-IL-1 β and pro-IL-18



➤ Generation of *CASP1*^{-/-} MG-63 cells using the CRISPR-Cas9 gene editing system

a

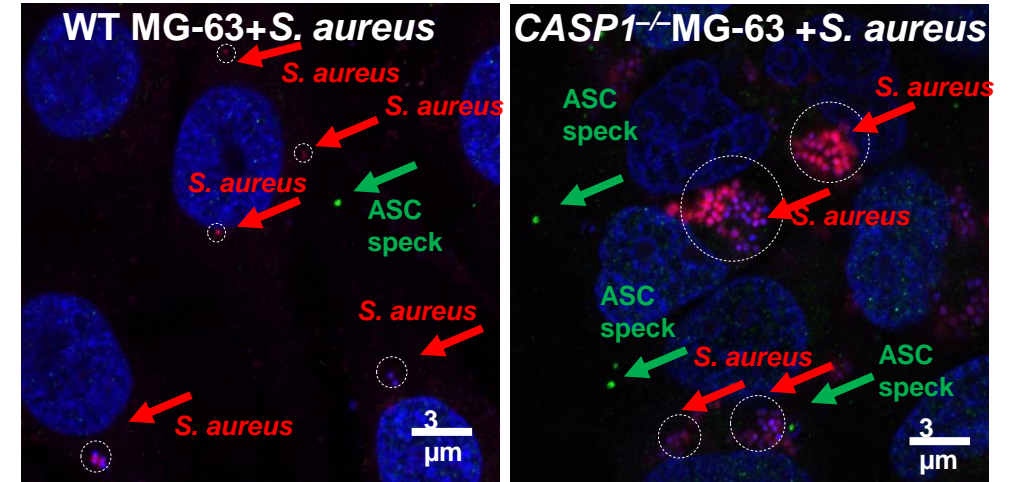
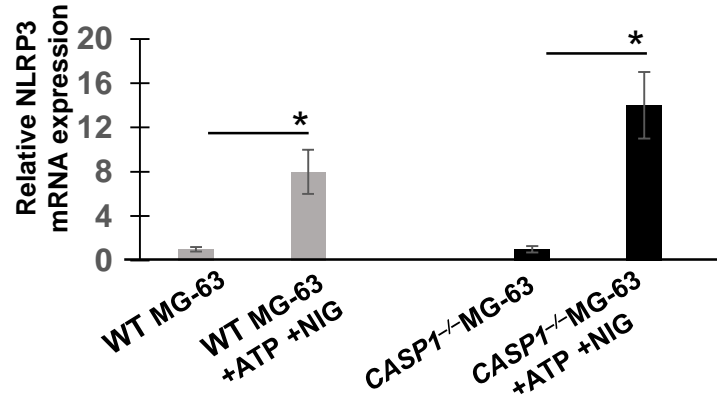
Human Chromosome 11 map depicting the position of Caspase-1



Lack of the 45-kDa band corresponding to pro-caspase-1 in *CASP1*^{-/-} MG-63 cells

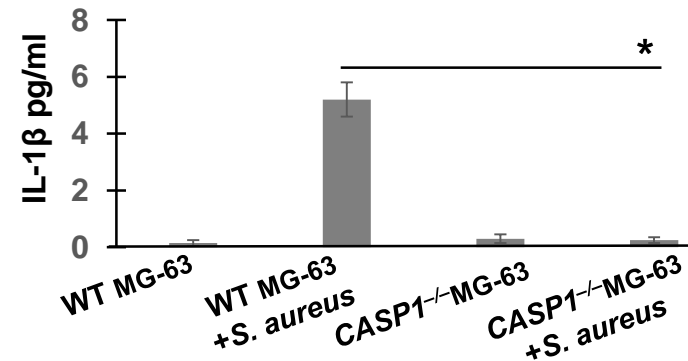
b

WT MG-63 cells and *CASP1*^{-/-} MG-63 clone express NLRP3 and form ASC specks.



c

Lack of IL-1 β production in *CASP1*^{-/-}MG-63 in contrast to WT MG-63 cells (ELISA)



Only WT MG-63 cells produce IL-1 β following exposure to *S. aureus*

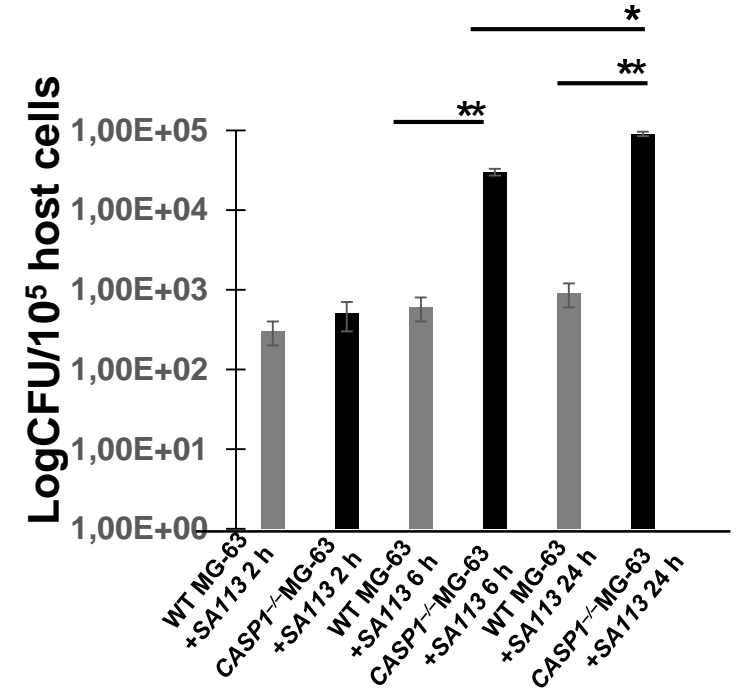
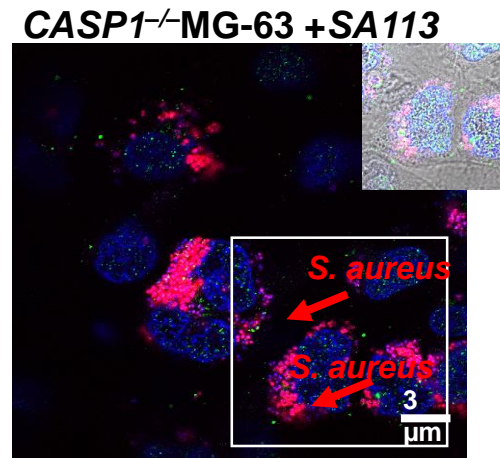
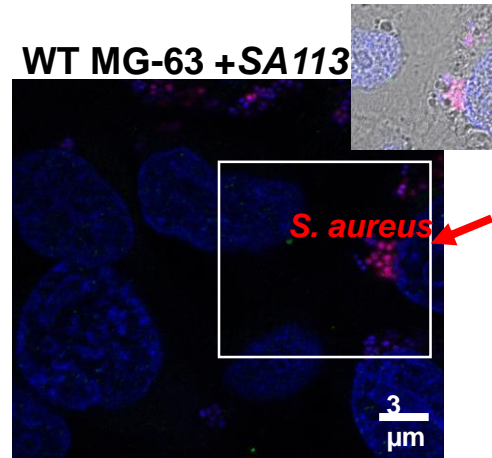
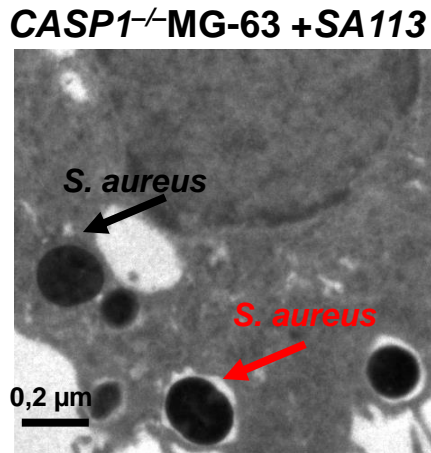
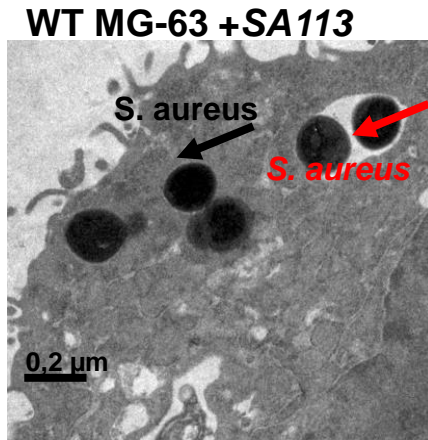
INRAE

N. Berkova
SFM 2022

➤ *S. aureus* clearance by osteoblast-like MG-63 cells depends on caspase-1

2h

Transmission electron micrographs

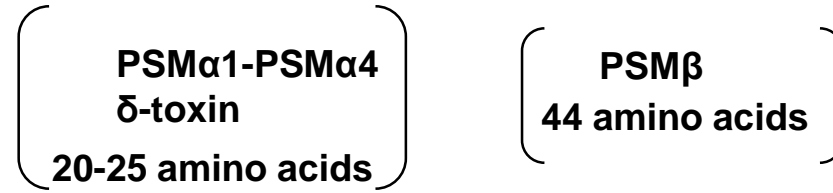


Internalization of *S. aureus* (2h) was not impaired in CASP1^{-/-}MG-63 cells

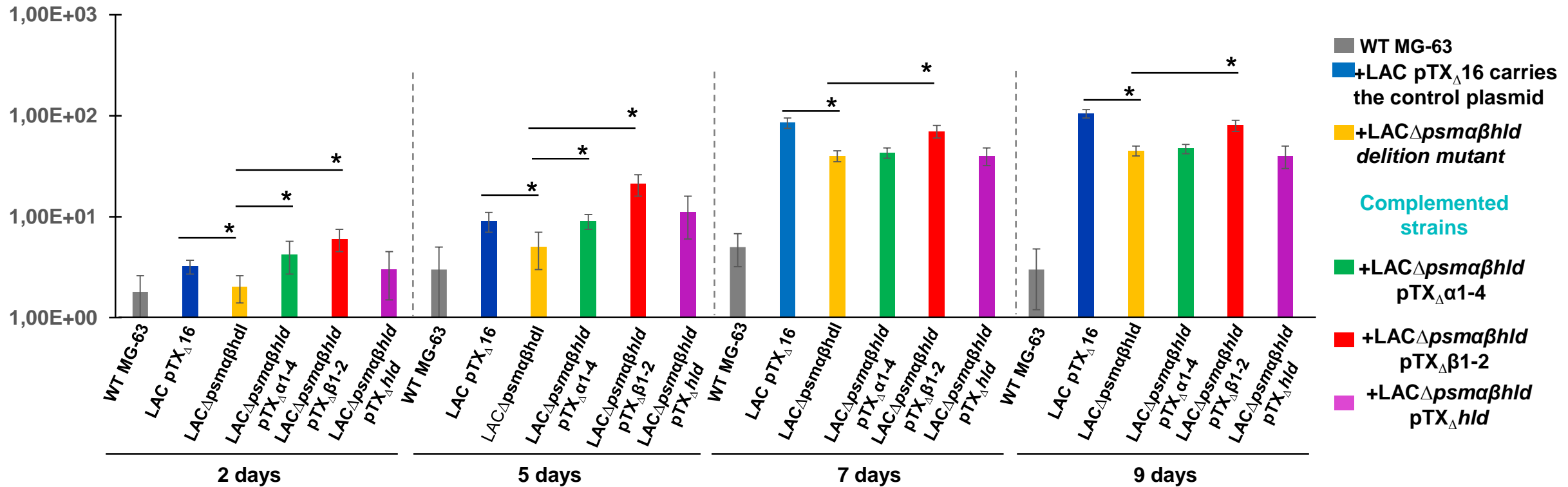
Most internalized bacteria are surrounded by phagosomal/lysosomal membranes, some bacteria are scattered freely in the cytosol

Higher number of intracellular *S. aureus* cells was observed in CASP1^{-/-} MG-63 cells compared to WT MG-63 cells

➤ Phenol-soluble modulins peptides (PSMs) define the virulence potential of *S. aureus*



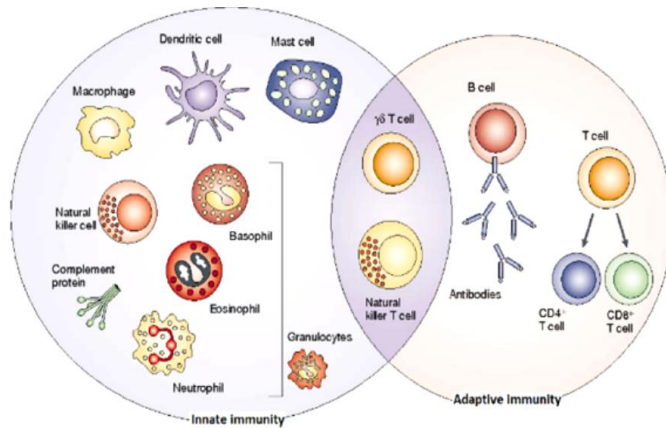
Log IL-1 β pg/ml



S. aureus phenol-soluble modulins stimulate IL-1 β release from infected MG-63 cells

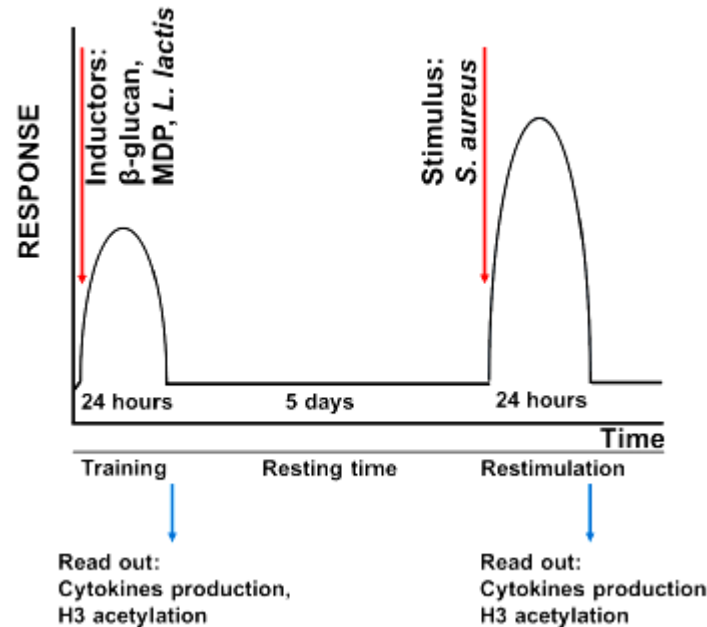
➤ Trained Immunity: shaping host-pathogen interactions through a new paradigm

Traditionally, the immune system has been divided into innate and adaptive components



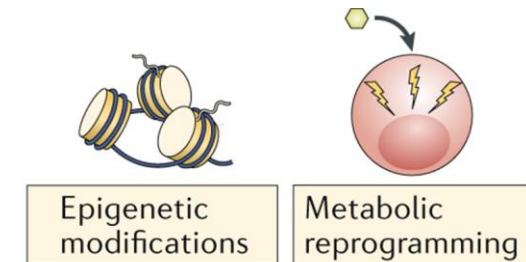
Dranoff, Nat Rev Cancer, 2004

Innate immunity exhibits adaptive traits, termed **innate immune memory** or **trained immunity**, leading to an **enhanced response** after subsequent unrelated challenges



Adapted from Netea *at al.* Science, 2016

The molecular basis of trained immunity involves metabolic and epigenetic changes



Exploring Trained Immunity Potential in Non-Immune Cells against *S. aureus* Infection

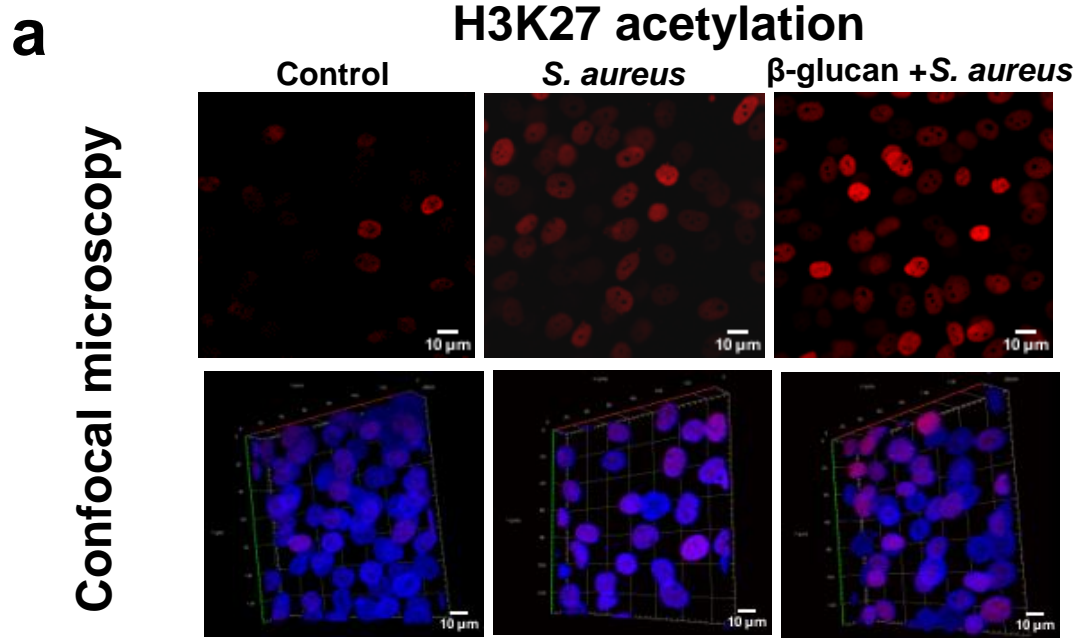
INRAE

N. Berkova
SFM 2022

MG-63, osteoblast-like cells
A549, lung epithelial cells

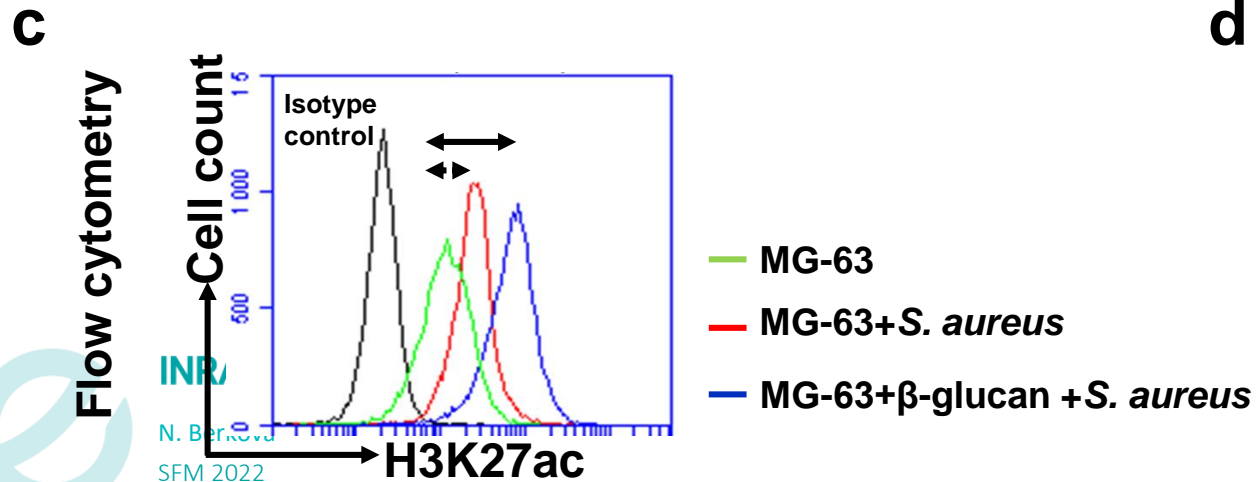
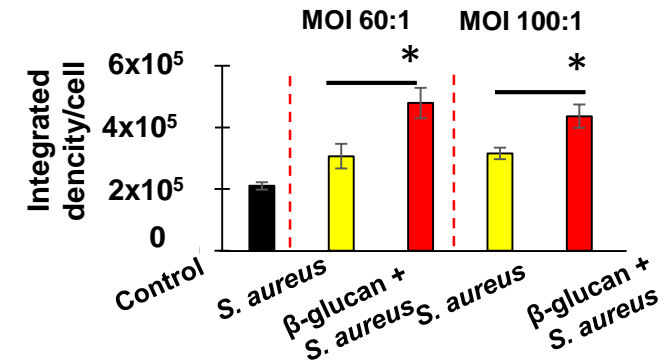
➤ Enhanced H3K27 acetylation in β -glucan-trained cells upon *S. aureus* stimulation, positively correlating with IL-6/IL-8 production

MG-63

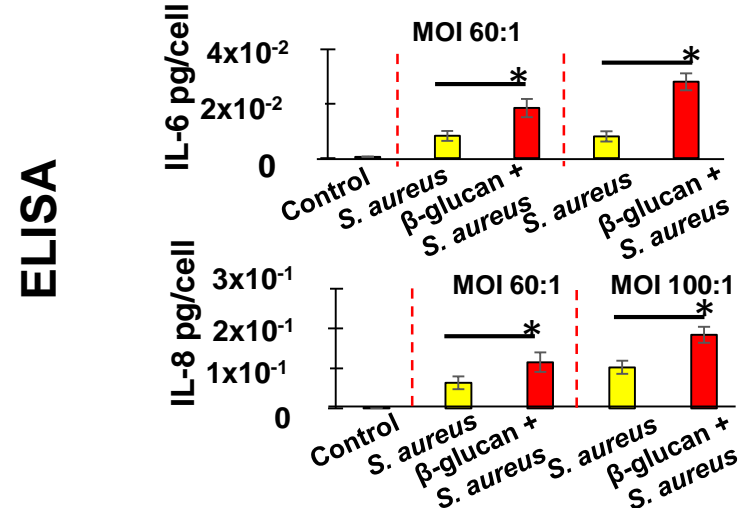


b

Normalized Integrated Density was monitored for comparing H3K27 acetylation



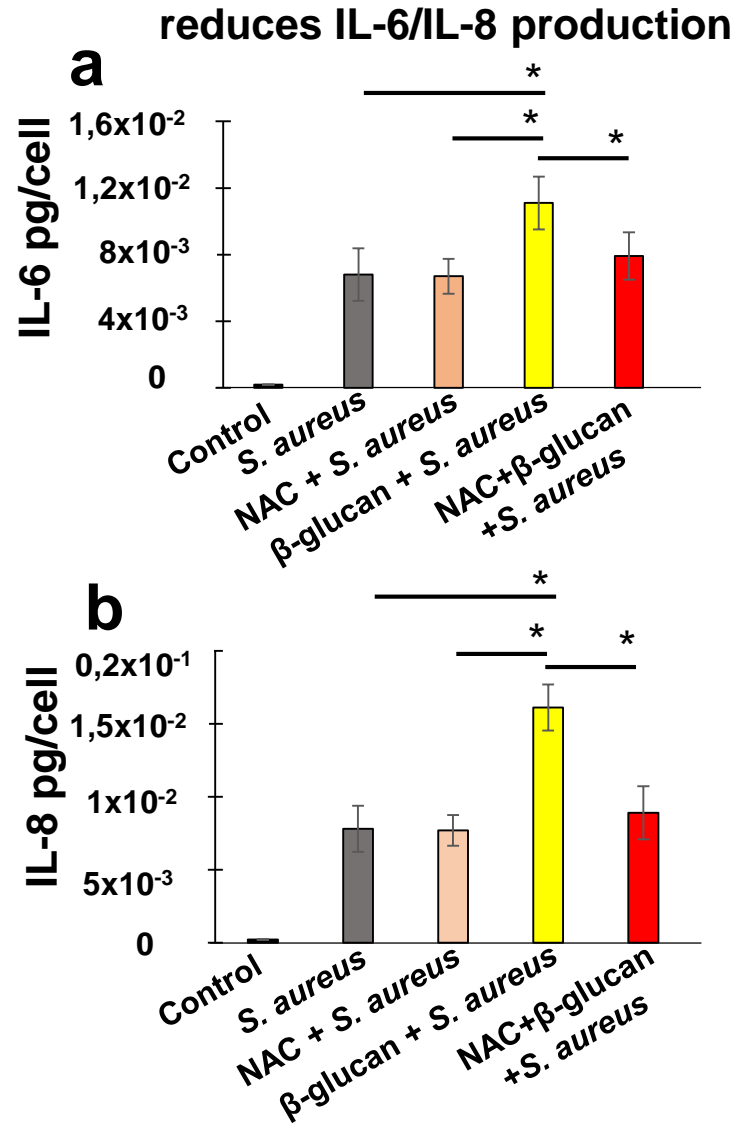
Assessment of IL-6 and IL-8 production



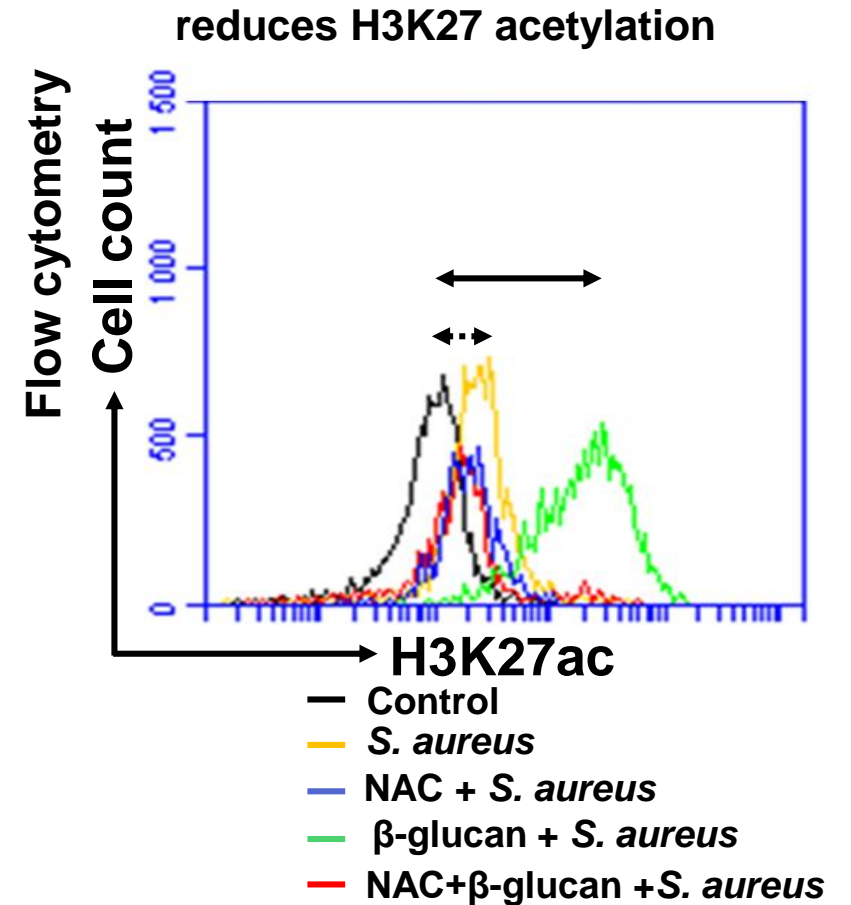
➤ Development of the innate immune memory depends on reactive oxygen species

Pre-treatment of cells with the ROS inhibitor NAC, prior to β -glucan treatment

ELISA



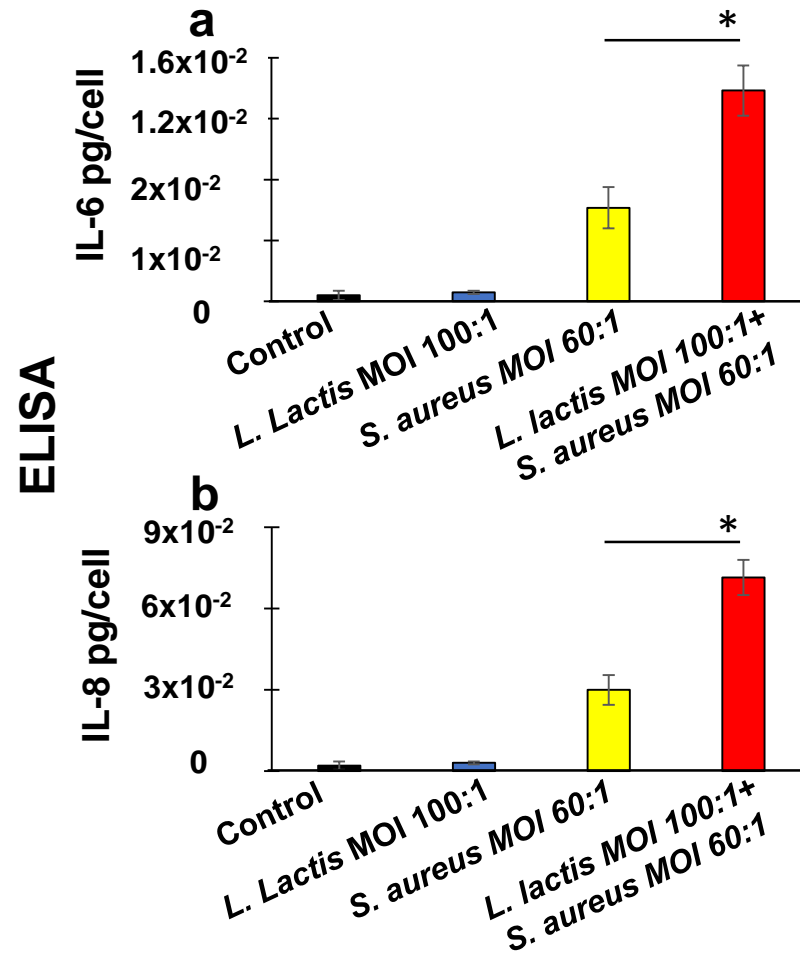
c



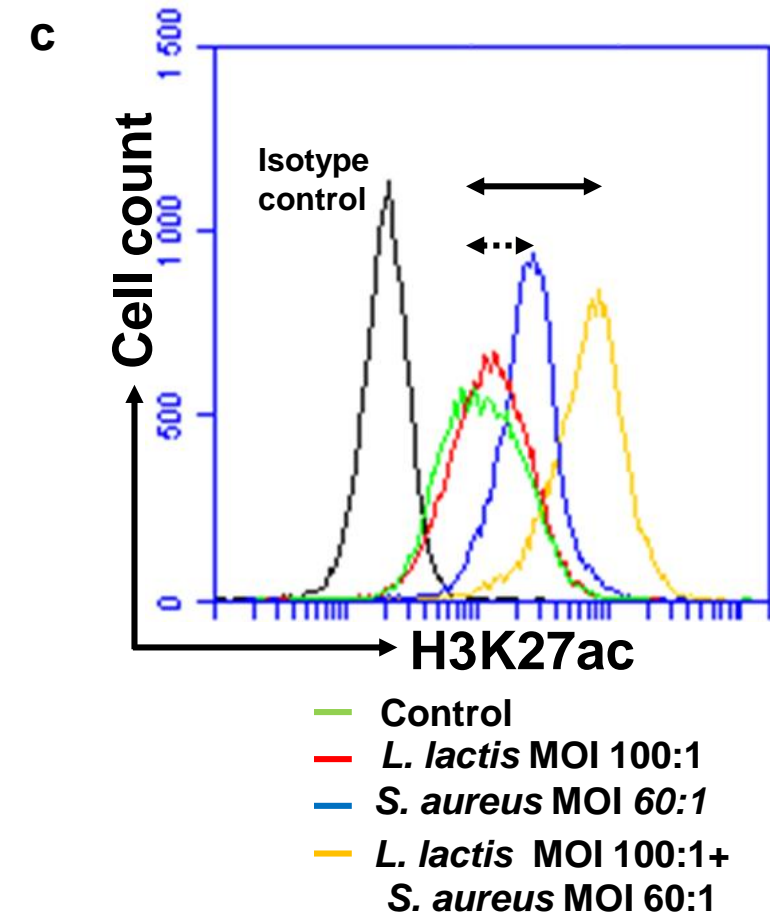
The decrease in IL-6/IL-8 production correlates to the decline in H3K27 acetylation in NAC-pre-treated cells

➤ Cells exposed to *L. lactis* increase IL-6/IL-8 production upon *S. aureus* stimulation, correlating with H3K27 acetylation

Pre-exposure of cells to *L. lactis* increases IL-6 /IL-8 production upon a stimulation with *S. aureus*



Pre-exposure of cells to *L. lactis* increases H3K27 acetylation upon a stimulation with *S. aureus*

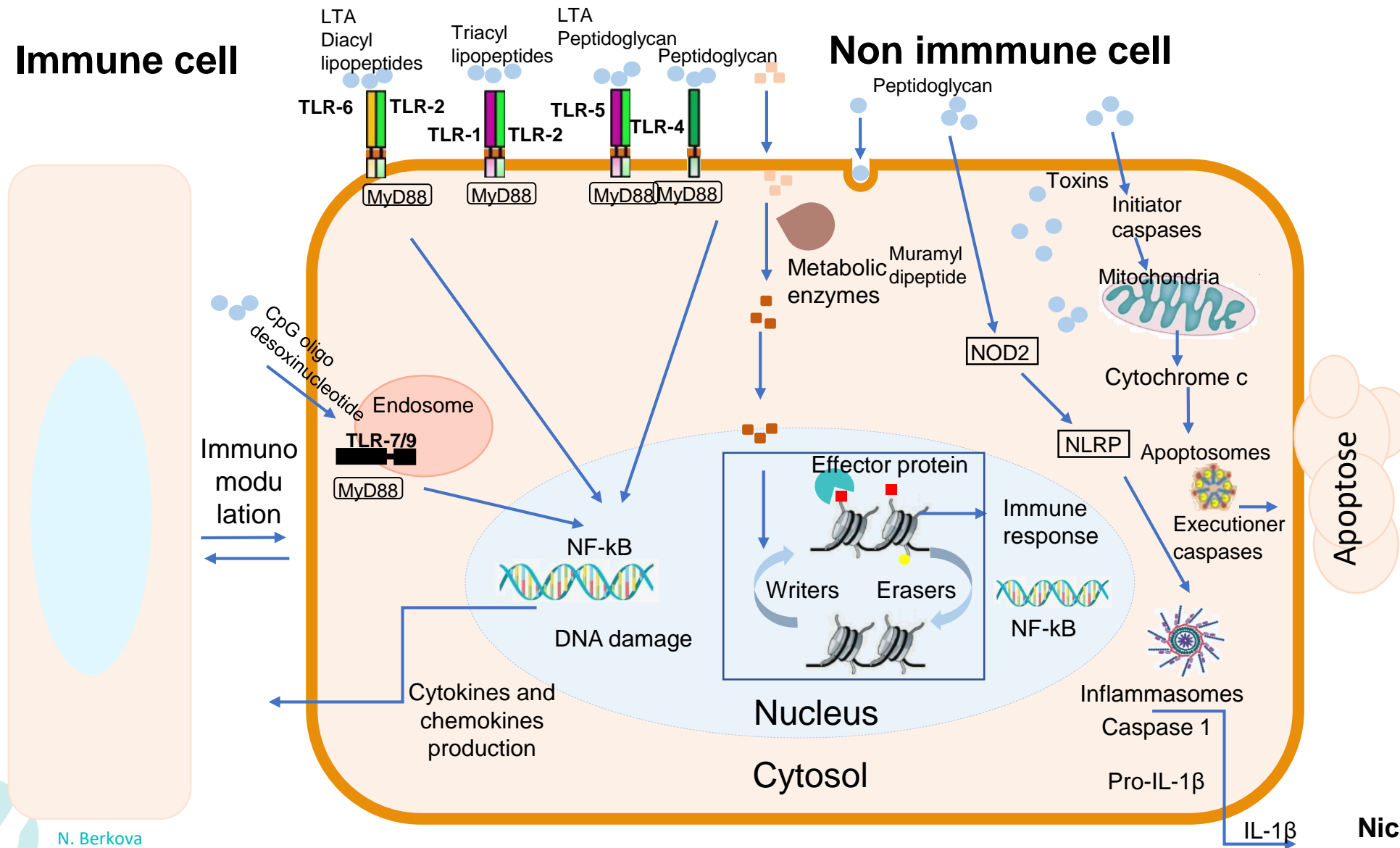


The increase in IL-6/IL-8 production correlates with the rise in H3K27 acetylation in cells pre-treated with *L. lactis*

Lactococcus lactis may be a potential inducer of trained immunity

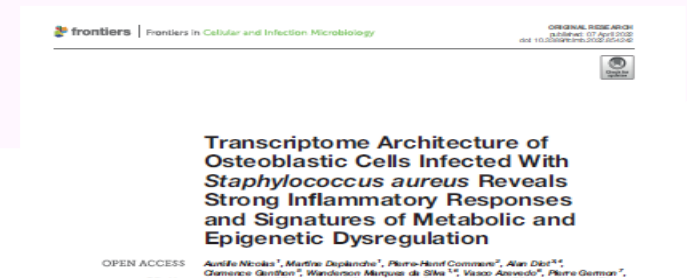
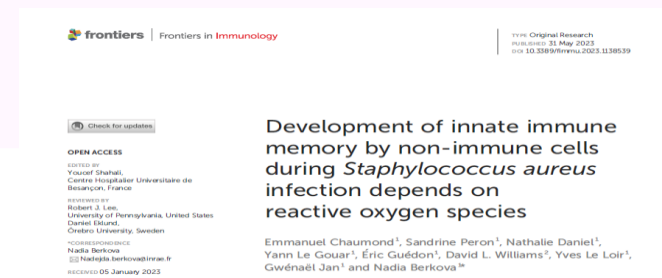
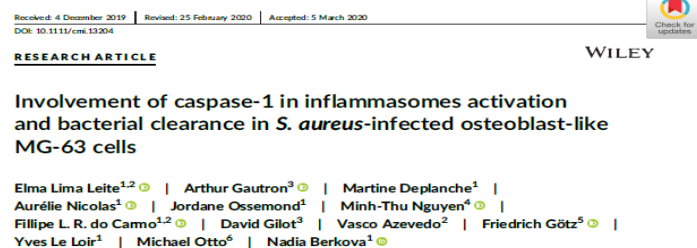
Chaumond et al. Front. Immunol. 2023

➤ Model of the immune, metabolic and epigenetic dysregulated signatures induced by long-term *S. aureus* infection



➤ CONCLUSION

- ❖ Besides structural functions, non-immune cells contribute to the defense response against *S. aureus* through inflammasomes activation
- ❖ The active caspase-1 restricts intracellular replication of *S. aureus* in non-professional phagocytes
- ❖ Non-immune cells develop trained immunity that is at least partially dependent on ROS
- ❖ *L. lactis* may be a potential inducer of trained immunity, suggesting the possibility of using this bacterium as a preventive measure against staphylococcal infections



COLLABORATIONS

THANK YOU FOR YOUR ATTENTION



UMR1253, STLO,
Rennes
Peron S.,
Chamound E.,
Nicolas A.,
Ossemond J.,
Daniel N.,
Le Gouar Y.,
Deplanche M.,
Jan G.,
Julien Jardin,
Guedon E,
Le Loir Y



NIH, Bethesda,
Maryland, USA
Michael Otto



Infectious Disease and
Immunity, East Tennessee
State University, Johnson,
TN, USA
David L. Williams



Universit  Paris-Saclay,
INRAE, AgroParisTech,
Micalis Institute, Jouy-
en-Josas, France
Bierne H



UNIVERSIT  DE
RENNES 1
Universit  de Rennes 1, IGDR,
UMR 6290, Rennes, France
Gautron A, Gilot D



Belo Horizonte
MG university, Brazil
Elma Lima Leite
Fillipe L. R. do
Carmo,
Vasco Azevedo



University of
Tubingen, Germany,
Minh-Thu Nguyen,
Fritz Goetz



Centre International de
Recherche en Infectiologie,
INSERM U1111, CNRS
UMR5308, Universit  Lyon 1,
Frederic Laurent F., Lina G,
Vandenesch F

Intramural Research Program of the National Institute of
Allergy and Infectious Diseases (NIAID), U.S. A, NIH

Deutsche Forschungsgemeinschaft
(DFG) SFB766

ANR-20-CE35-0001
ANR-20-PAMR-0011)



N. Berkova
SFM 2022



Institut de G n tique
& D veloppement de Rennes

Metaprogram INRAE GISA
LONGhealth-MPP10573