# 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.


# Déclaration de conflit d'intérêt

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

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

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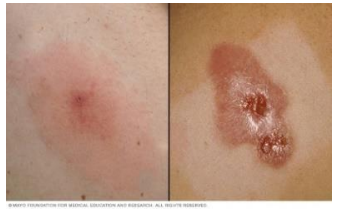
# *Staphylococcus aureus* is responsible for a wide range of infections in human and animals

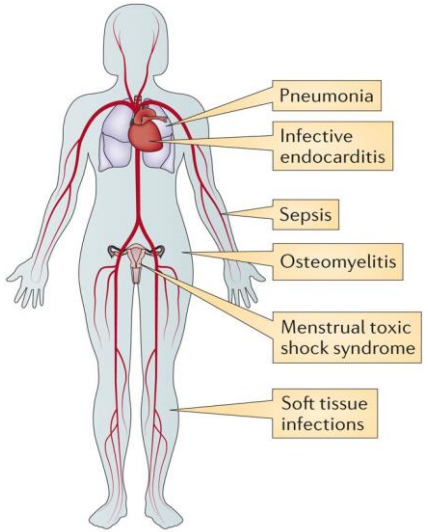
**_S. aureus_-induced diseases represent serious problems, especially during chronic infections**

**Human**

**Mild skin infections**



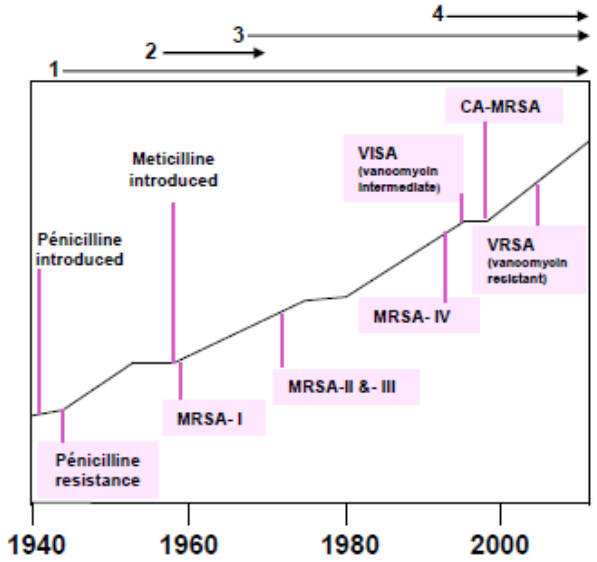
**Life-threatening infections**




Nature Reviews | Microbiology

**Dairy cattle:**
**Chronic mastitis**

**Waves of *S. aureus* resistance**




Chambers and DeLeo Nat Rev Microbiol 2010

**Urgent Need**

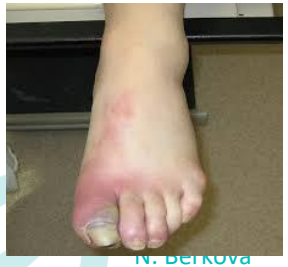
**Unraveling Immunity to Strengthen the Host's Defense Against Recurrent *S. aureus* Infection**

# 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



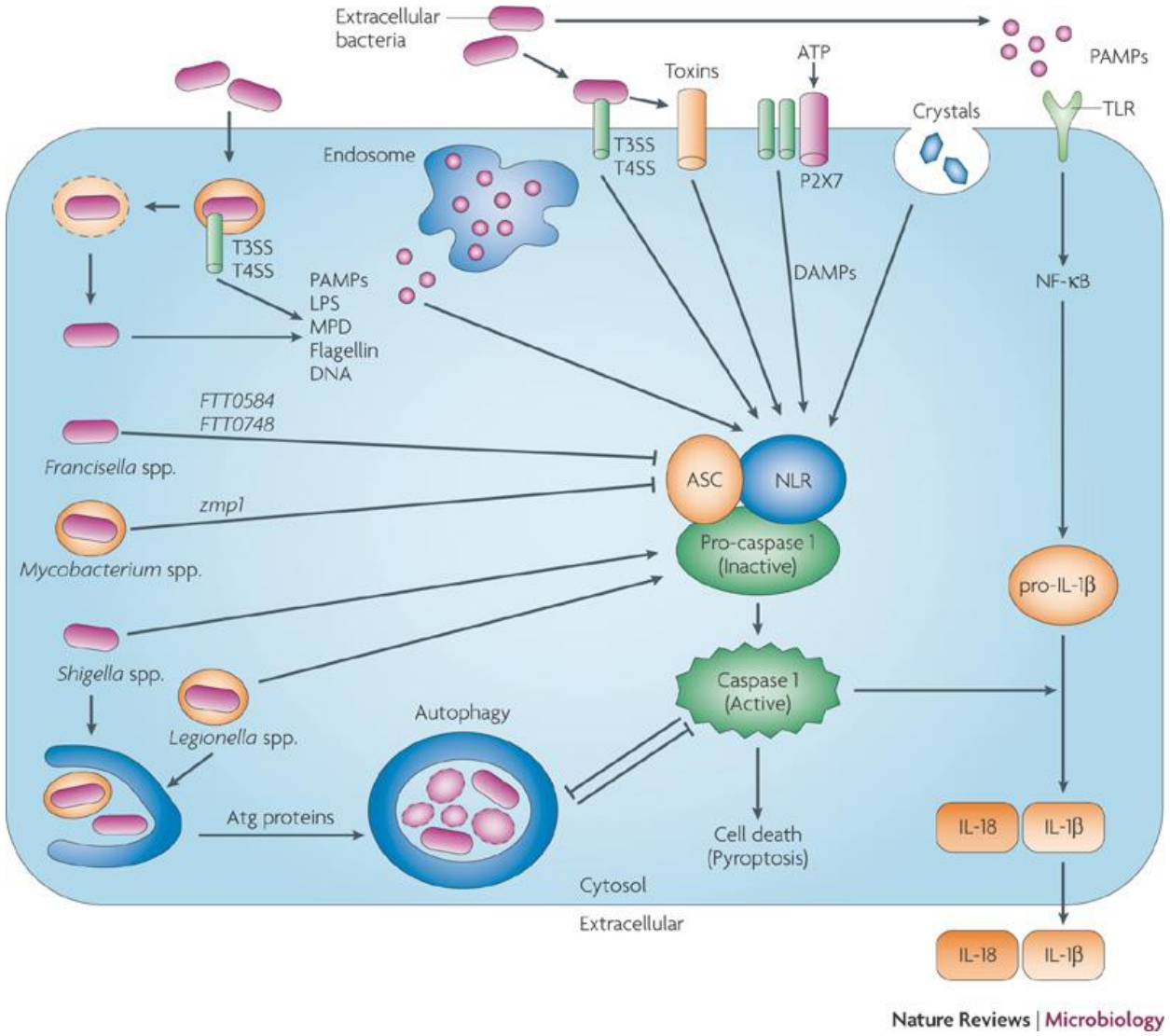
**Osteomyelitis, often caused by *S. aureus* infections**

**How Osteoblasts Defend Against *S. aureus* Invasion?**

# INFLAMMASOMES activation as a defense mechanism against infection and injury

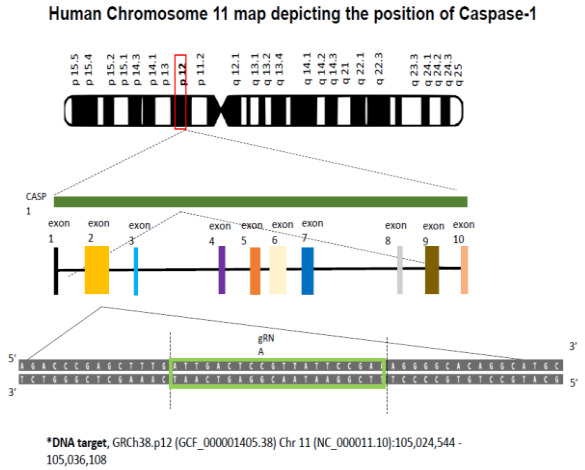
**Persistent inflammation activates protein complexes, inflammasomes, that are composed of a sensor (NLR), an adaptor (ASC), and a zymogen procaspase-1**

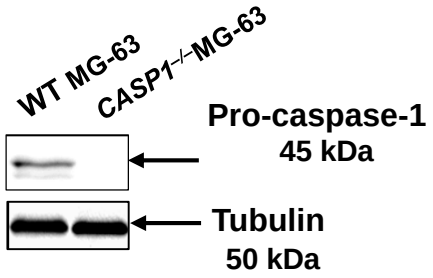
**Inflammasomes activate Caspase-1, which proteolytically matures pro-IL-1β and pro-IL-18**



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

**a**

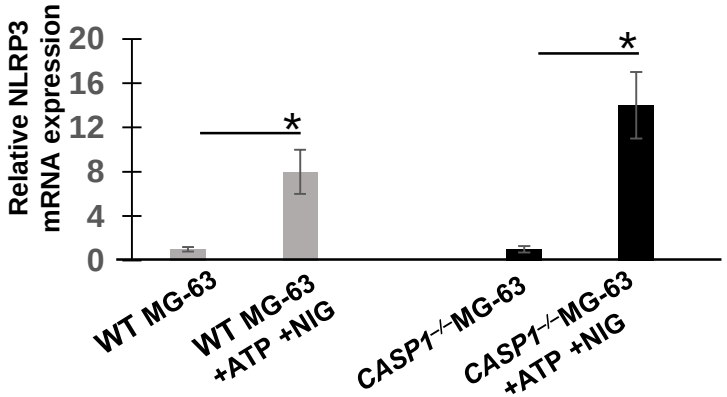


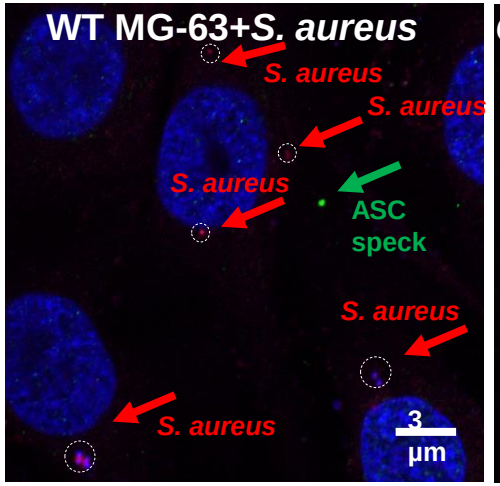



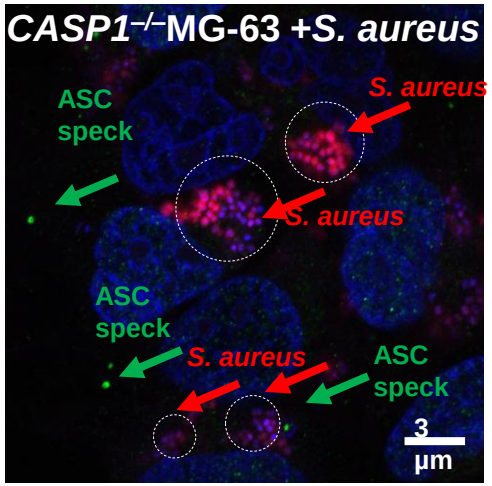

**Lack of the 45-kDa band corresponding to pro-caspase-1 in CASP1$^{-/-}$ MG-63 cells**

**b**

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

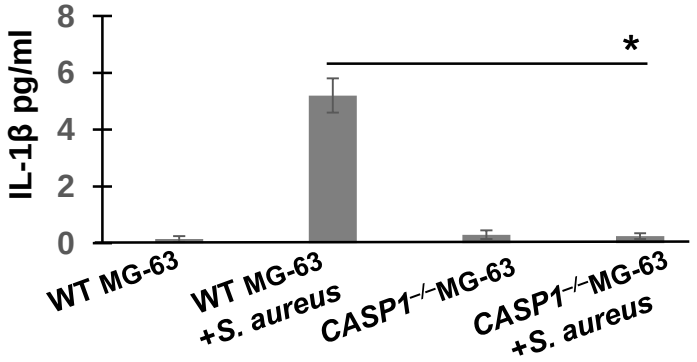



**c**

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



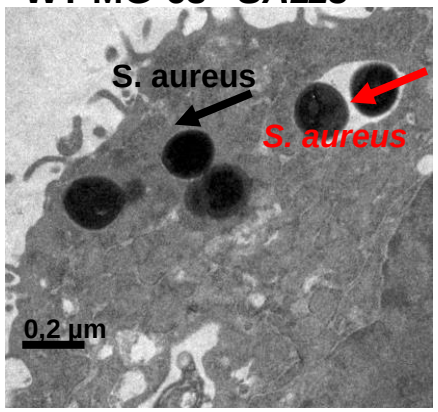

**Only WT MG-63 cells produce IL-1β following exposure to *S. aureus***

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

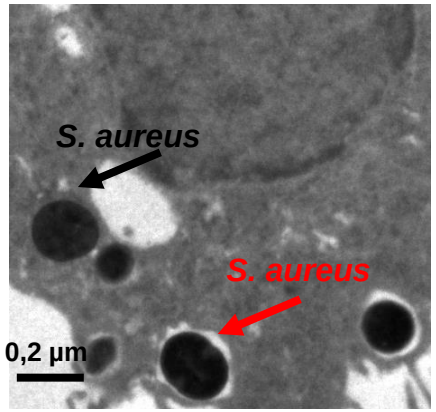
2h

Transmission electron micrographs

WT MG-63 +*SA113*

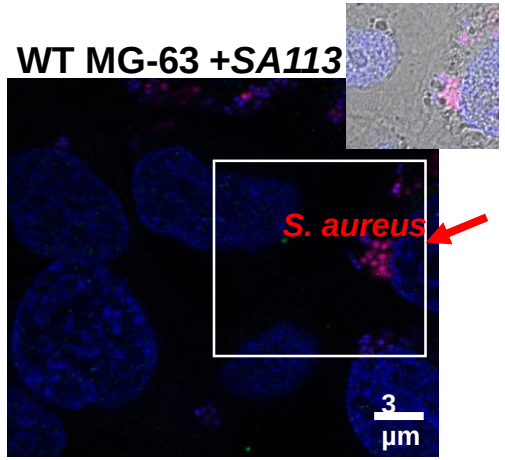



*CASP1*$^{-/-}$MG-63 +*SA113*

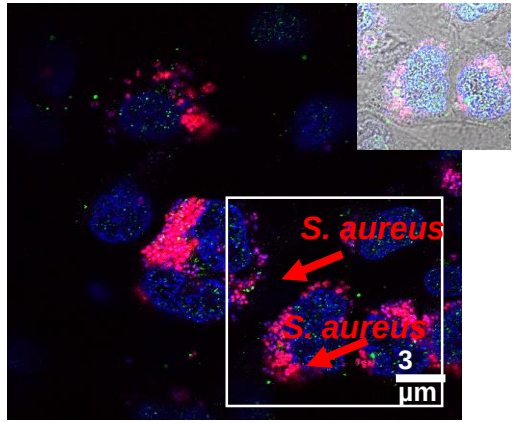



Most internalized bacteria are surrounded by phagosomal/lysosomal membranes, some bacteria are scattered freely in the cytosol

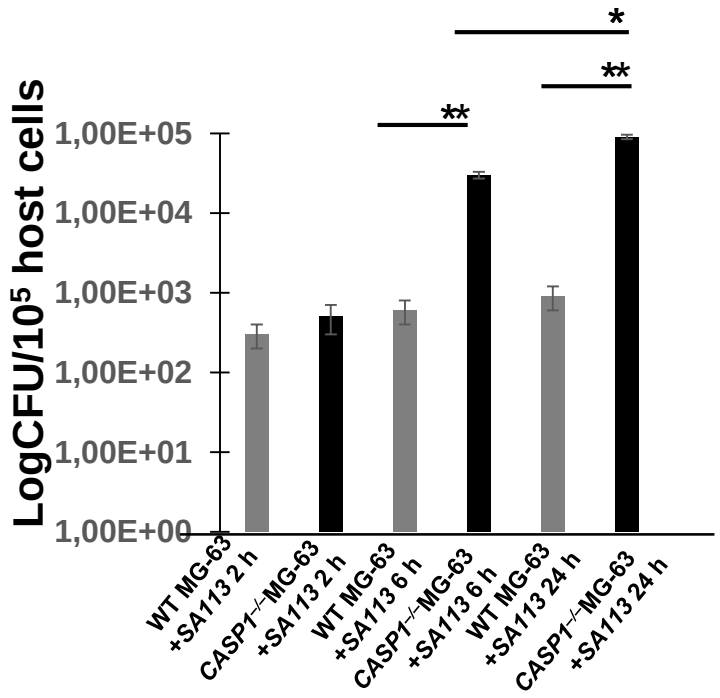
WT MG-63 +*SA113*




*CASP1*$^{-/-}$MG-63 +*SA113*




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

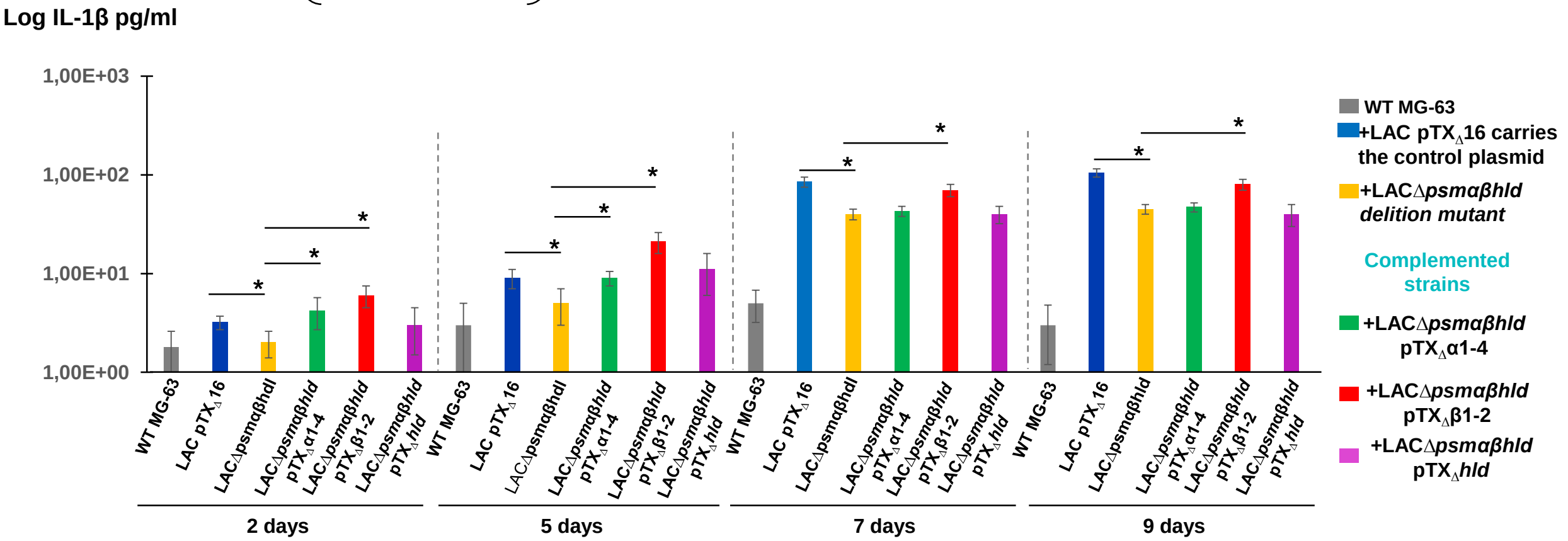



Internalization of *S. aureus* (2h) was not impaired in CASP1$^{-/-}$MG-63 cells

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

**PSMα1-PSMα4**
**δ-toxin**
**20-25 amino acids**

**PSMβ**
**44 amino acids**



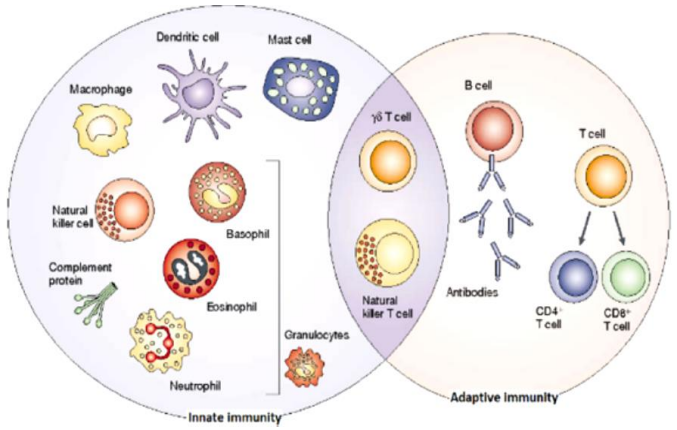

***S. aureus* phenol-soluble modulins stimulate IL-1β release from infected MG-63 cells**

Elma Lima Leite *et al*. Cell. Microbiol., 2020

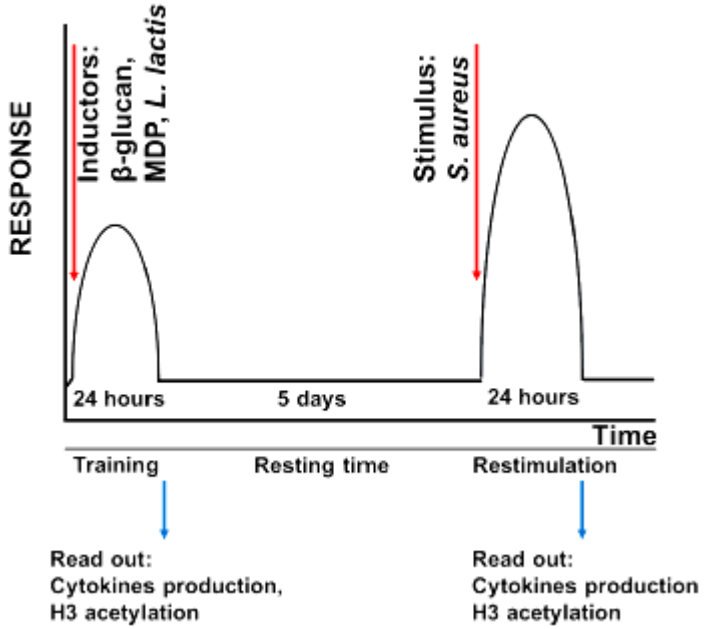
# Trained Immunity: shaping host-pathogen interactions through a new paradigm

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

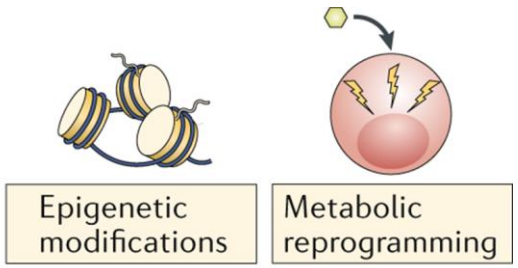
**Innate immunity exhibits adaptive traits, termed innate immune memory or trained immunity, leading to an enhanced response after subsequent unrelated challenges**




Dranoff, Nat Rev Cancer, 2004




**The molecular basis of trained immunity involves metabolic and epigenetic changes**




**Adapted from Netea *at al.* Science, 2016**

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

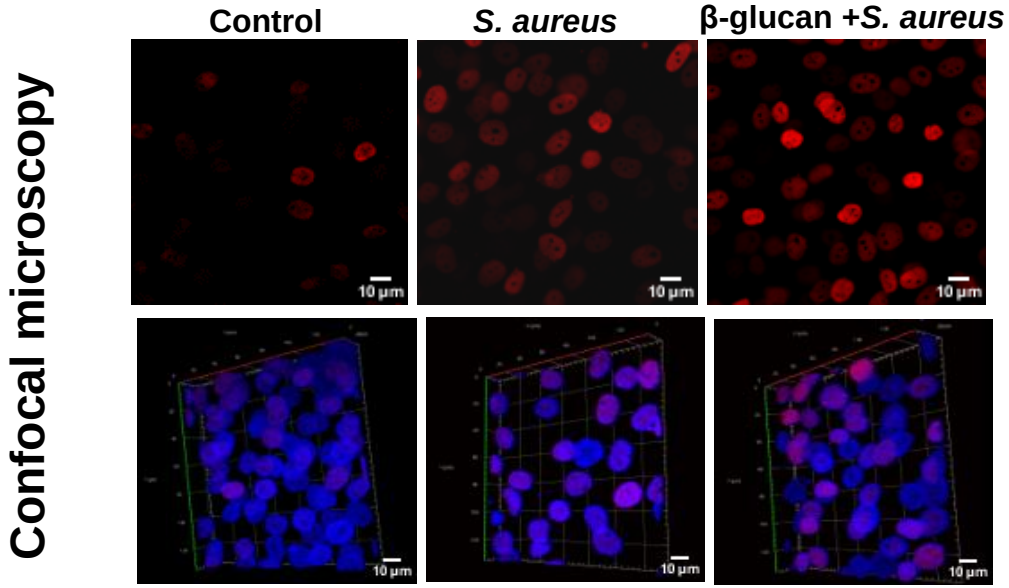
**MG-63, osteoblast-like cells**
**A549, lung epithelial cells**

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

**MG-63**

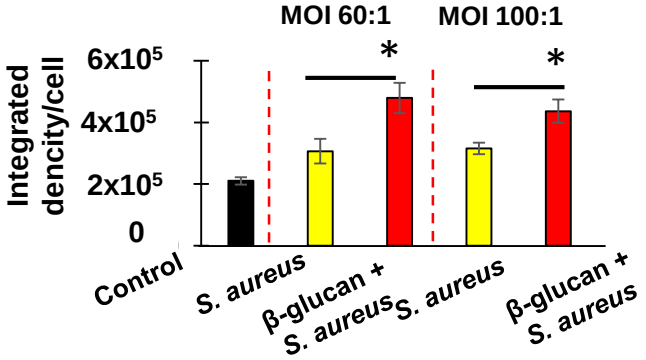
**a**

## H3K27 acetylation

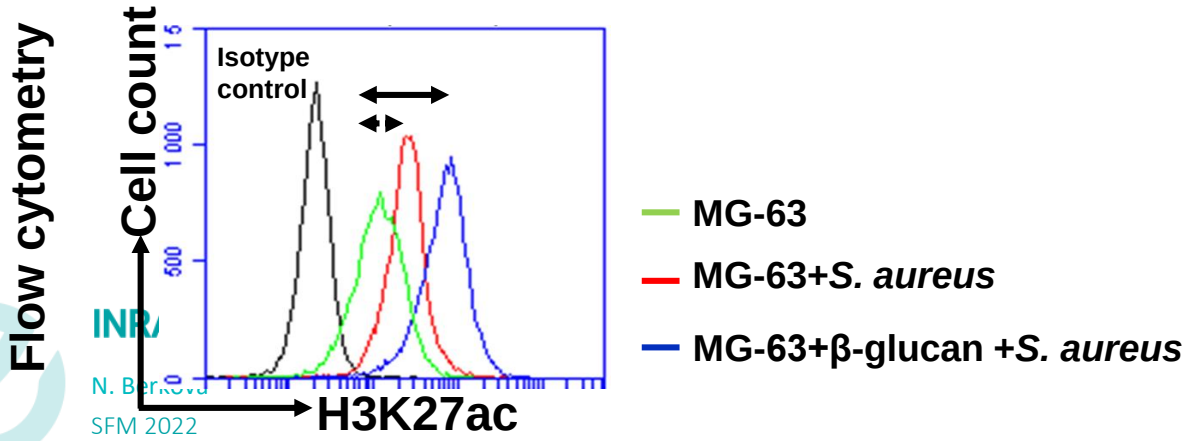



**b**

## Normalized Integrated Density was monitored for comparing H3K27 acetylation

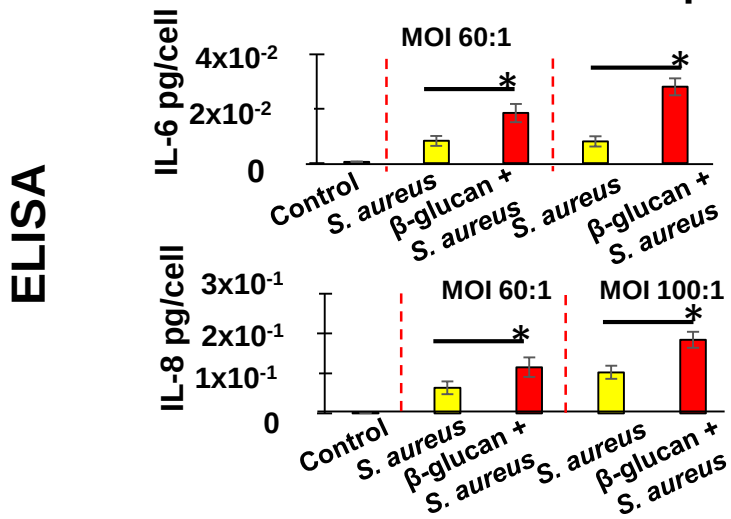



**c**




**d**

## Assessment of IL-6 and IL-8 production

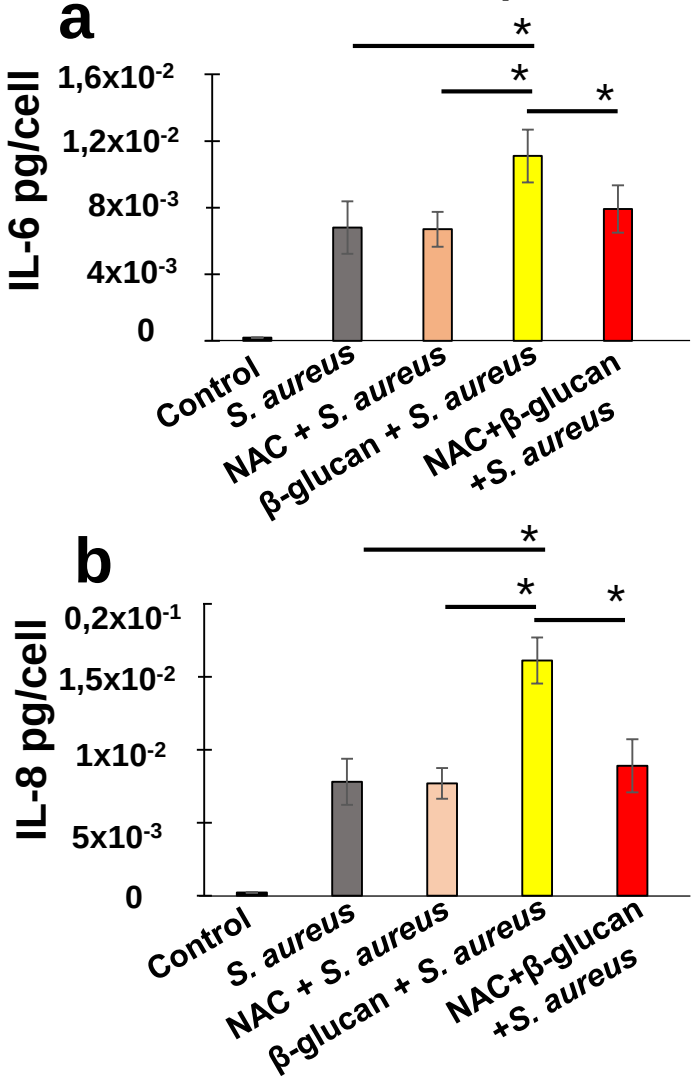


# Development of the innate immune memory depends on reactive oxygen species

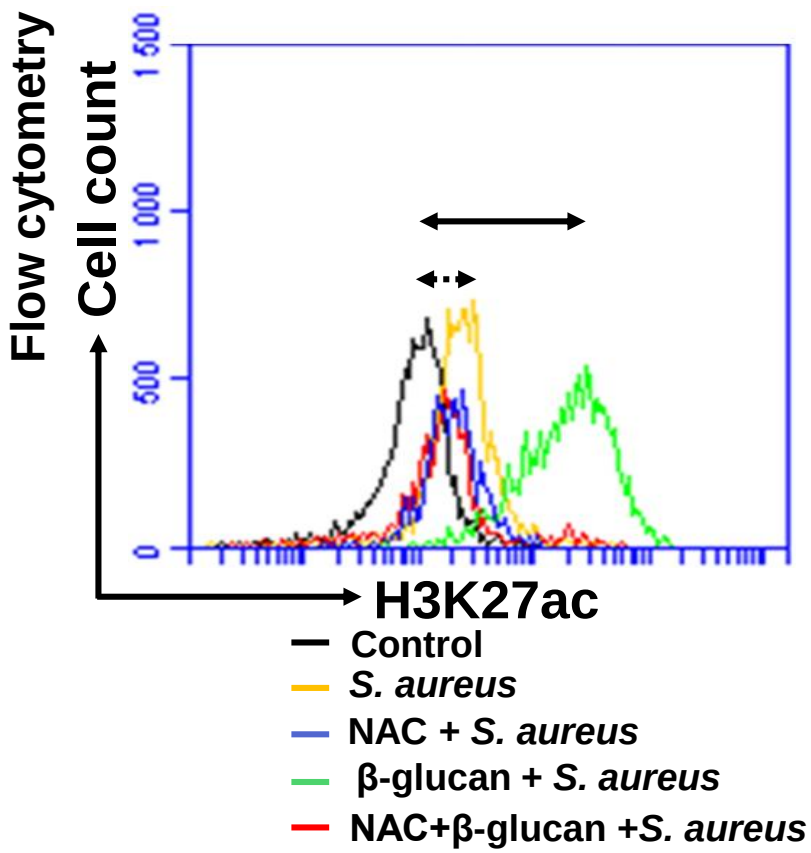
**Pre-treatment of cells with the ROS inhibitor NAC, prior to β-glucan treatment**

**reduces IL-6/IL-8 production**

ELISA



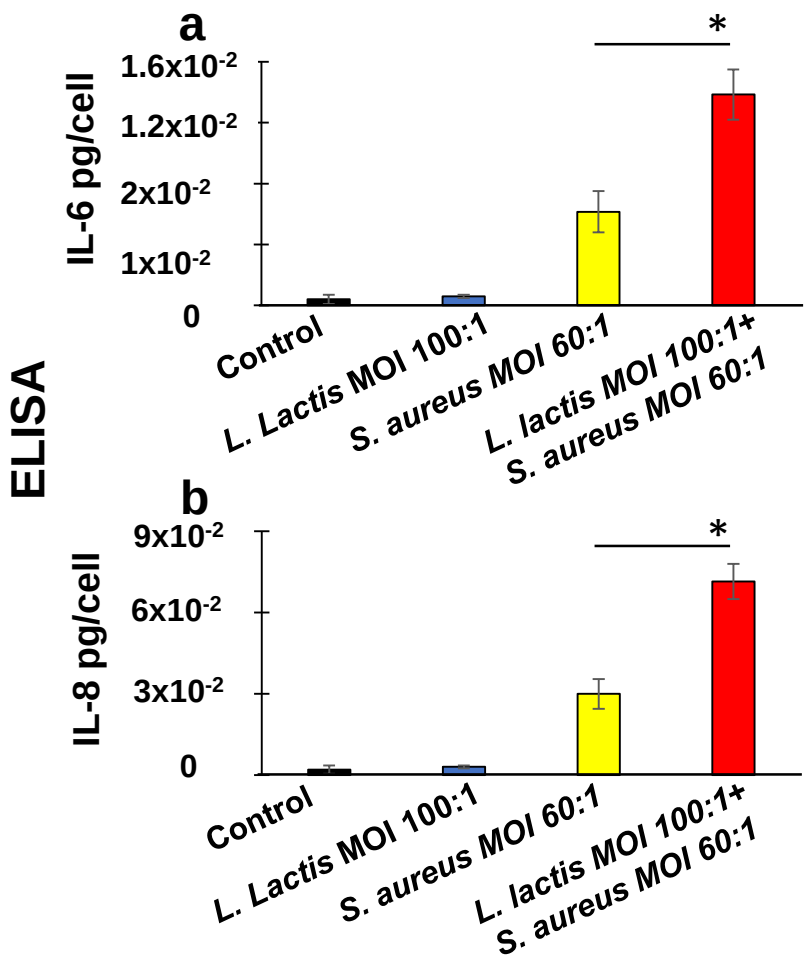

**reduces H3K27 acetylation**



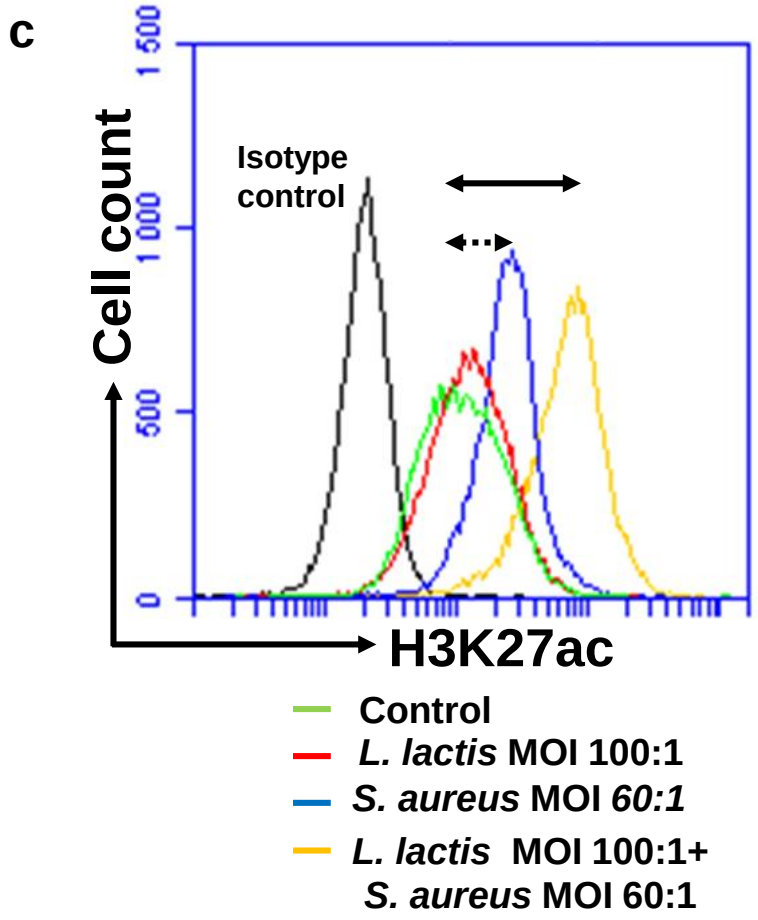

**The decrease in IL-6/IL-8 production correlates to the decline in H3K27 acetylation in NAC-pre-treated cells**

# 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***

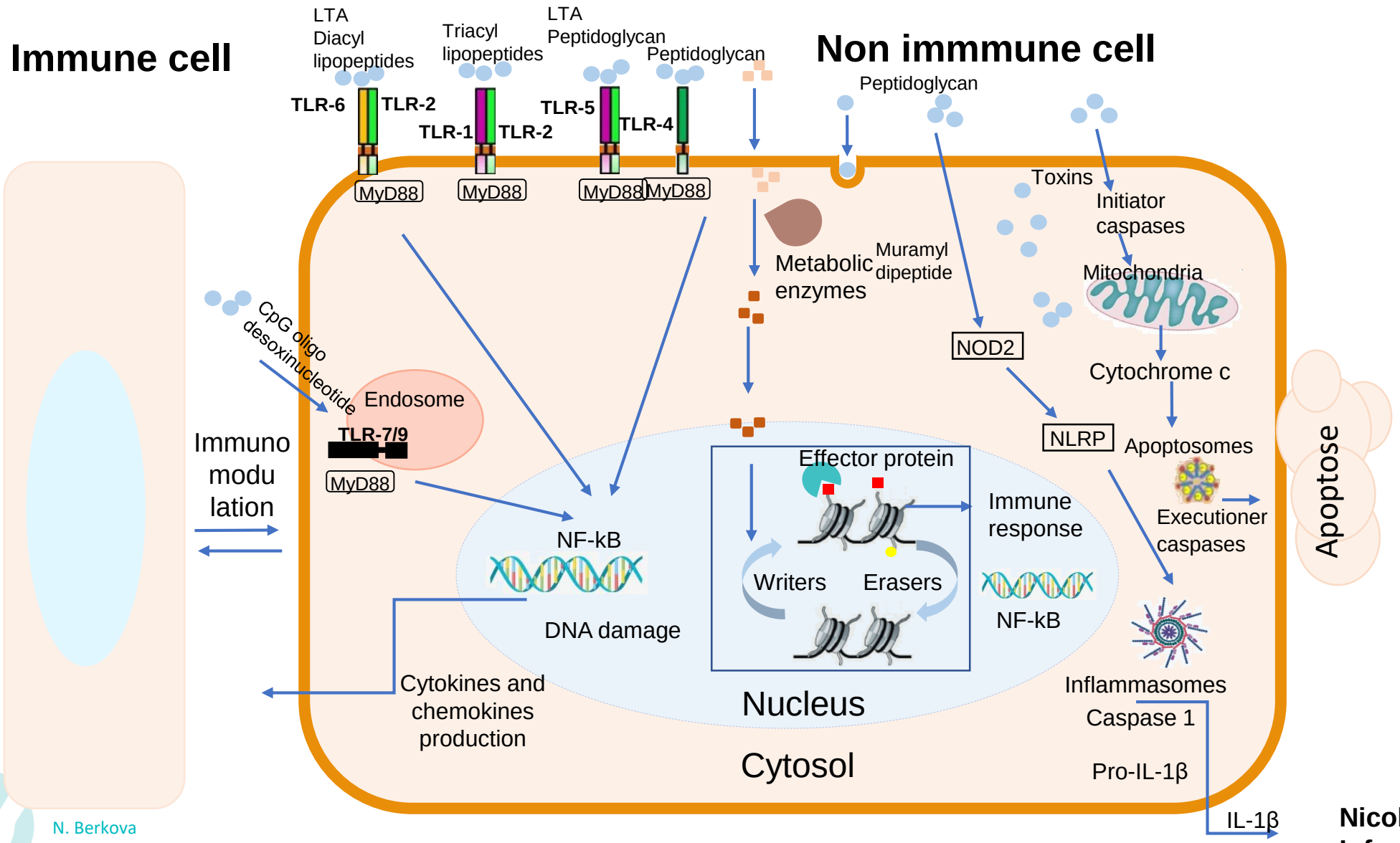



**The increase in IL-6/IL-8 production correlates with the rise in H3K27 acetylation in cells pre-treated with *L. lactis***

***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

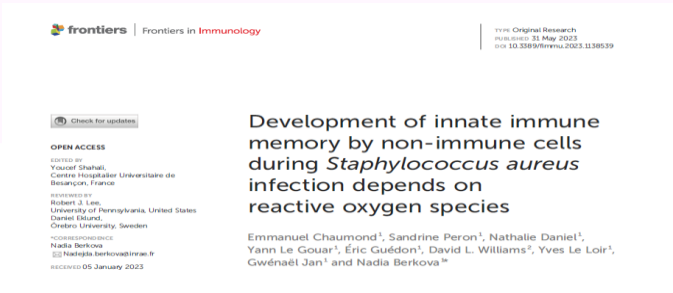


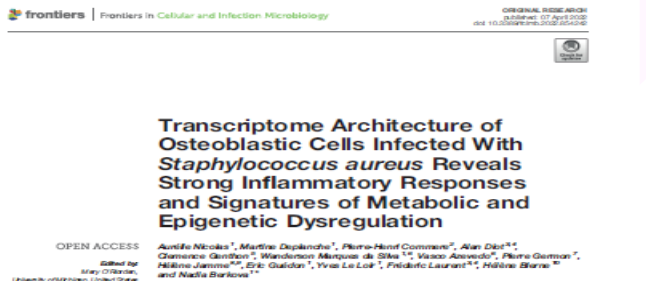

Nicolas *et al*. Front Cell Infect Microbiol., 2022

# 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**


Received: 4 December 2019 | Revised: 25 February 2020 | Accepted: 5 March 2020
DOI: 10.1111/cmi.13204
RESEARCH ARTICLE
WILEY
Involvement of caspase-1 in inflammasomes activation and bacterial clearance in *S. aureus*-infected osteoblast-like MG-63 cells
Elma Lima Leite[1,2] | Arthur Gautron[3] | Martine Deplanche[1] | Aurélie Nicolas[1] | Jordane Ossemond[1] | Minh-Thu Nguyen[4] | Fillipe L. R. do Carmo[1,2] | David Gilot[3] | Vasco Azevedo[2] | Friedrich Götz[5] | Yves Le Loir[1] | Michael Otto[6] | Nadia Berkova[1]


frontiers | Frontiers in Immunology
TYPE Original Research
PUBLISHED 31 May 2023
DOI 10.3389/fimmu.2023.1138539
OPEN ACCESS
Development of innate immune memory by non-immune cells during *Staphylococcus aureus* infection depends on reactive oxygen species
Emmanuel Chaumond[1], Sandrine Peron[1], Nathalie Daniel[1], Yann Le Gouar[1], Éric Guédon[1], David L. Williams[2], Yves Le Loir[1], Gwénaël Jan[1] and Nadia Berkova[1]*


frontiers | Frontiers in Cellular and Infection Microbiology
OPEN ACCESS
Transcriptome Architecture of Osteoblastic Cells Infected With *Staphylococcus aureus* Reveals Strong Inflammatory Responses and Signatures of Metabolic and Epigenetic Dysregulation

# COLLABORATIONS

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