Lactococcus lactis Induces Trained Immunity in Non-immune Cells During Staphylococcus aureus Infection

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INTERNATIONAL SCIENTIFIC CONFERENCE PROBIOTICS, PREBIOTICS GUT MICROBIOTA AND HEALTH
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Lactococcus lactis induces protective trained immunity in non-immune cells against *Staphylococcus aureus* infection

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INSTITUT CARNOT QUALIMENT

L'INSTITUT agro Rennes Angers

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

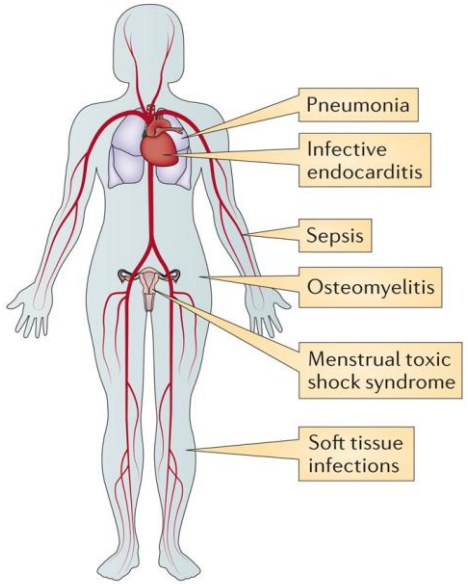
Gram-positive bacterium

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

Human

Mild skin infections

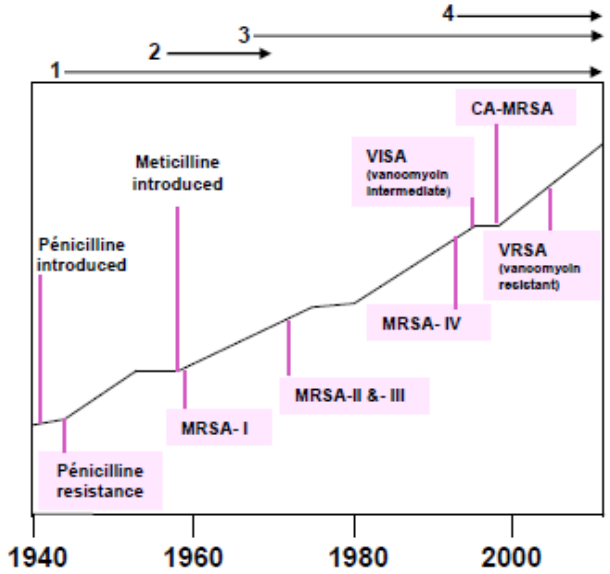
Life-threatening infections



Nature Reviews | Microbiology

Dairy cattle:
Chronic mastitis

Waves of *S. aureus* resistance



Chambers and DeLeo Nat Rev Microbiol 2010

Urgent Need

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

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

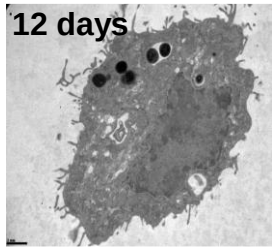
Site-Specific Defense:
Non-immune cells with an extended lifespan are located in tissues prone to infections

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

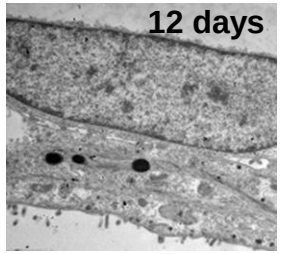
Chronic osteomyelitis

Osteoblasts defend against *S. aureus* Invasion



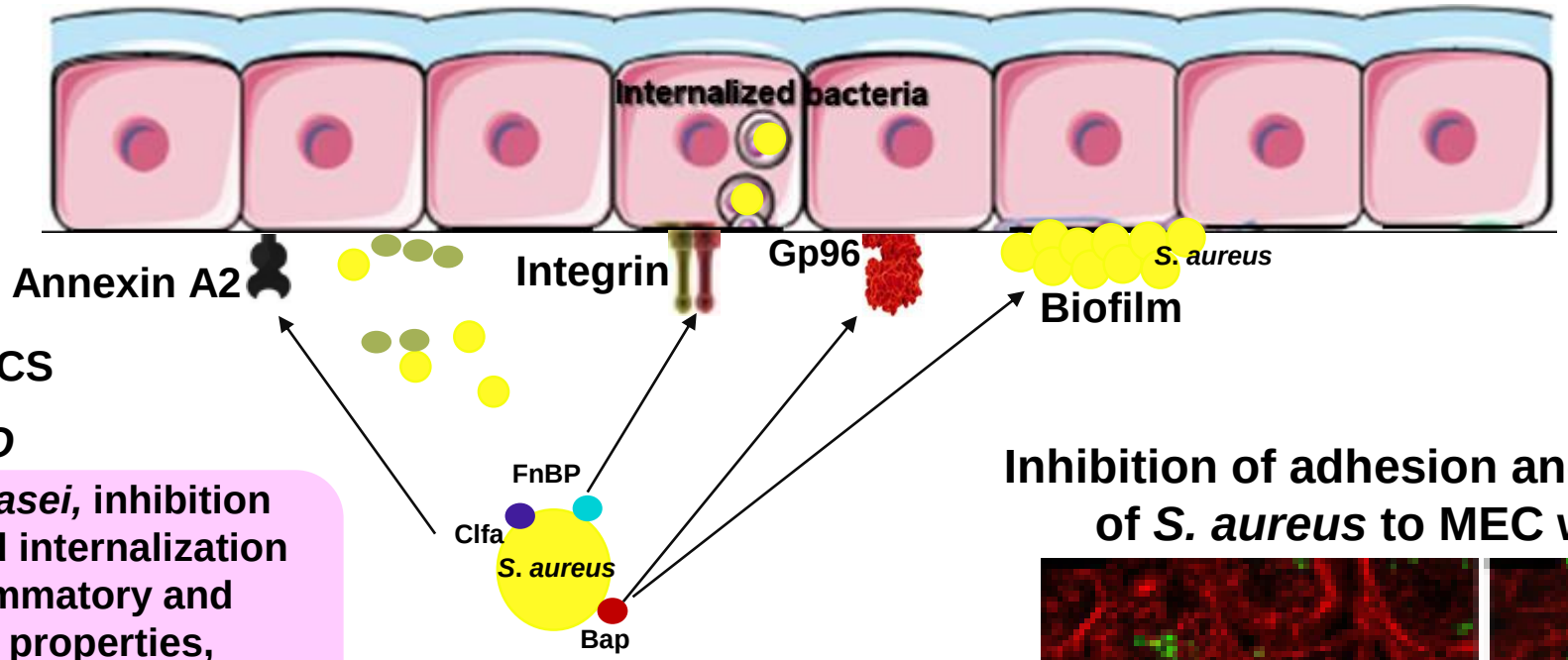
Chronic mastitis

Mammary epithelial cell (MEC) govern immune response against *S. aureus* in the udder



A549, lung cells **MG-63, osteoblast-like cells** **MAC-T, bovine mammary epithelial cell**

Probiotics are "*live microorganisms which, when administered in adequate amounts, confer a health benefit on the host*"



PROBIOTICS

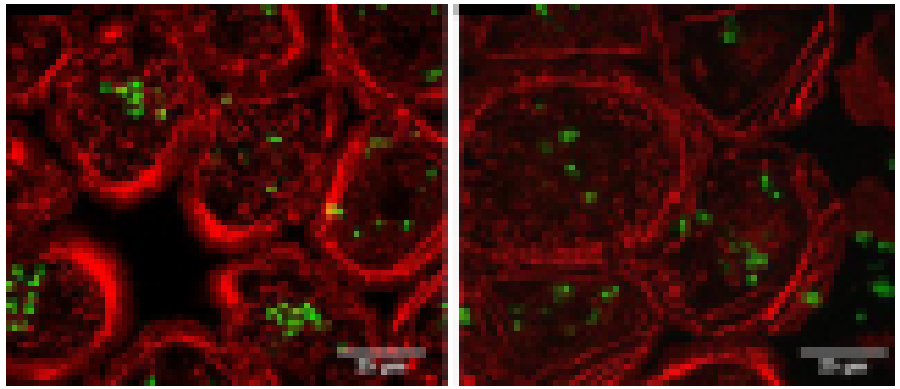
IN VITRO

L. lactis **and** ***Lb. casei,*** **inhibition of an adhesion and internalization**
Lb. casei, **anti-inflammatory and immunomodulatory properties,**
Lb. rhamnosus, **antibiofilm properties**

IN VIVO

Treating clinical mastitis: nisin, ***L. lactis*** **antimicrobial polypeptide**
B. subtilis **lipopetide fengycin abrogates** ***S. aureus*** **colonization: the inhibition of Agr quorum-sensing signalling system**

Inhibition of adhesion and internalization of *S. aureus* to MEC with *L. casei*



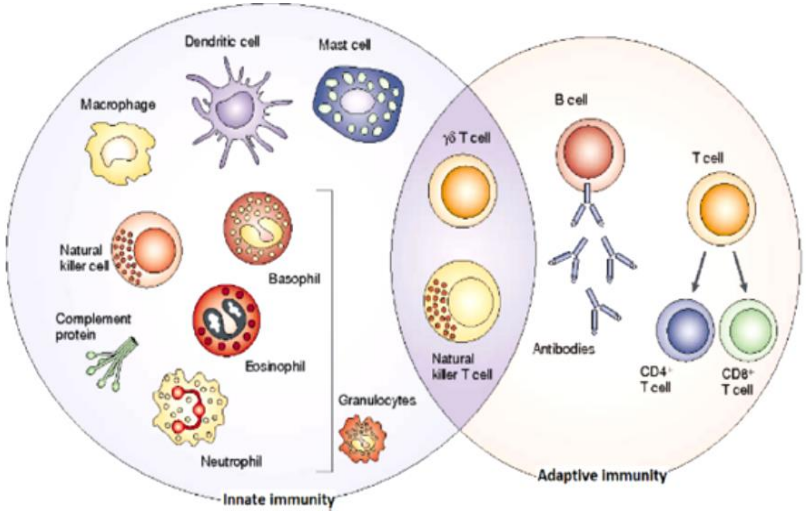
MEC+*S. aureus*

MEC+*S. aureus* +*L. casei*

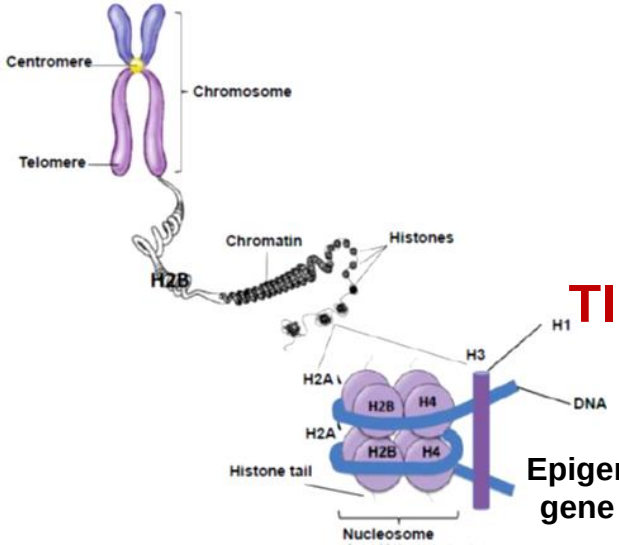
Campos et al., BMC Vet Res. 2022
Touza-Otero et al. Biomed. Pharmacother, 2024
Piewngam *et al*., Nature 2018
Cao *et al*, J. Dairy Sci. 2007
Bouchard *et al*. AEM, 2013

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

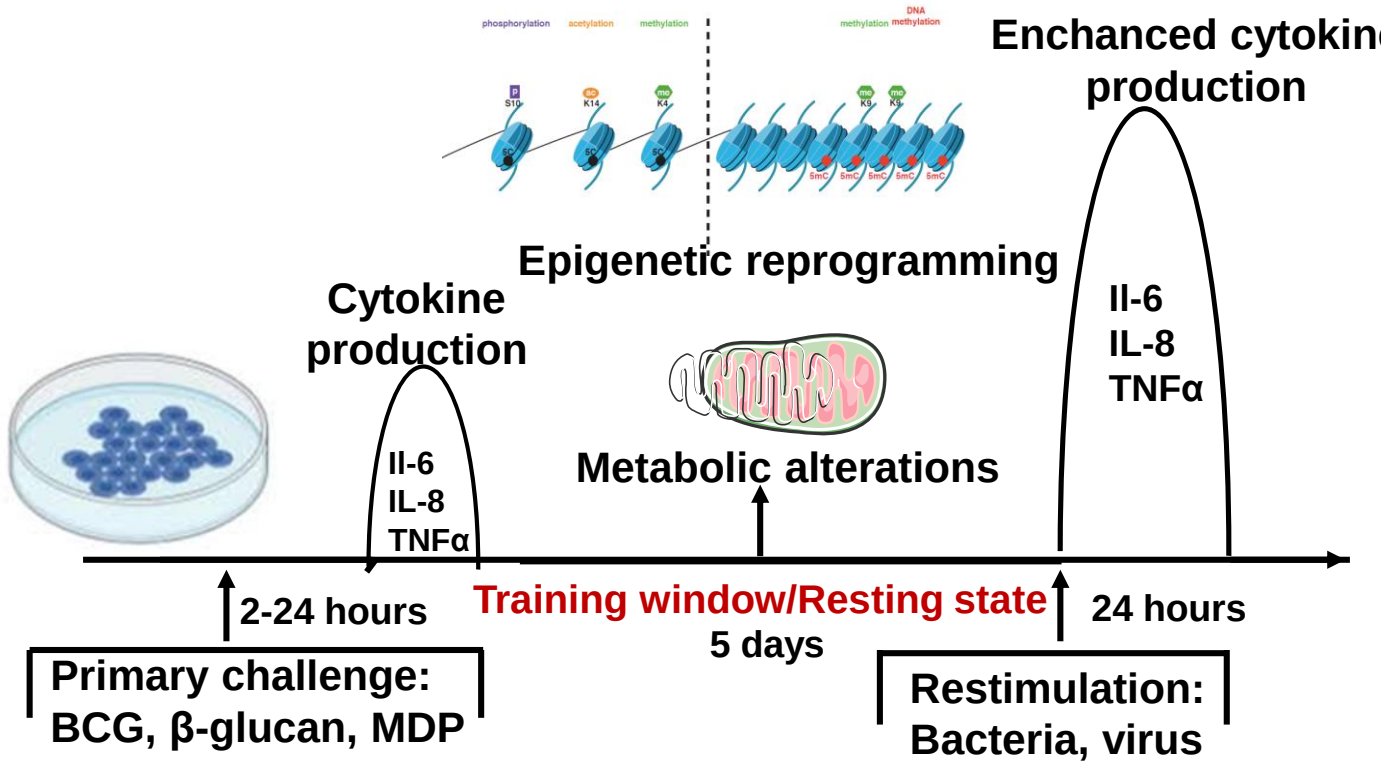
Traditionally, the immune system has been divided into innate and adaptive



Dranoff, Nat Rev Cancer, 2004



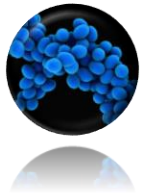
Innate immunity exhibits adaptive traits, termed innate immune memory or trained immunity



TI enhances the immune response to subsequent unrelated challenges through epigenetic reprogramming and metabolism alterations

Epigenetic reprogramming: modifications of the gene expression without altering the gene sequence (DNA methylations, histone modifications, nucleosome remodeling)

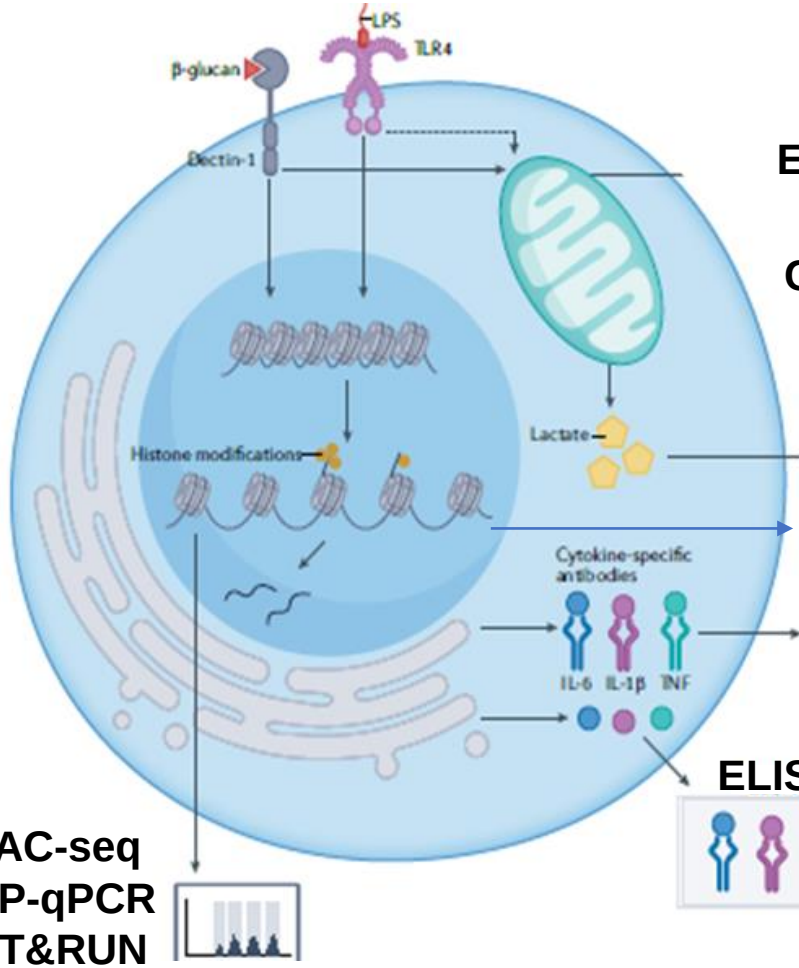
Adapted from Netea *at al.* Science, 2016



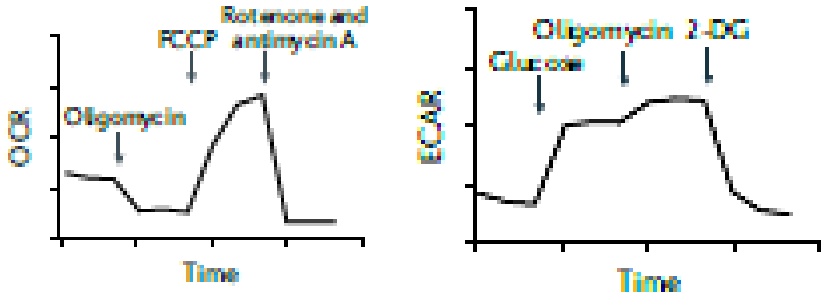
HYPOTHESIS

PROBIOTIC BACTERIA COULD INDUCE TRAINED IMMUNITY IN NON-IMMUNE CELLS IN THE CONTEXT OF *S. aureus* INFECTION

Cellular, molecular, metabolic and epigenetic approaches to studying trained immunity



Extracellular flux

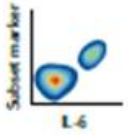


- Trained innate immune cells produce protons via the lactate pathway
  - Extracellular acidification rate (ECAR) as an indicator of glycolysis
  - Oxygen consumption rate (OCR) as an indicator of oxidative phosphorylation

Seahorse XF analysis: mitochondrial functions

Colorimetric analysis

Flow cytometry



Cytokine production
Histone modification

ELISA

Cytokine production

ATAC-seq
ChIP-qPCR
CUT&RUN
CUT&Tag

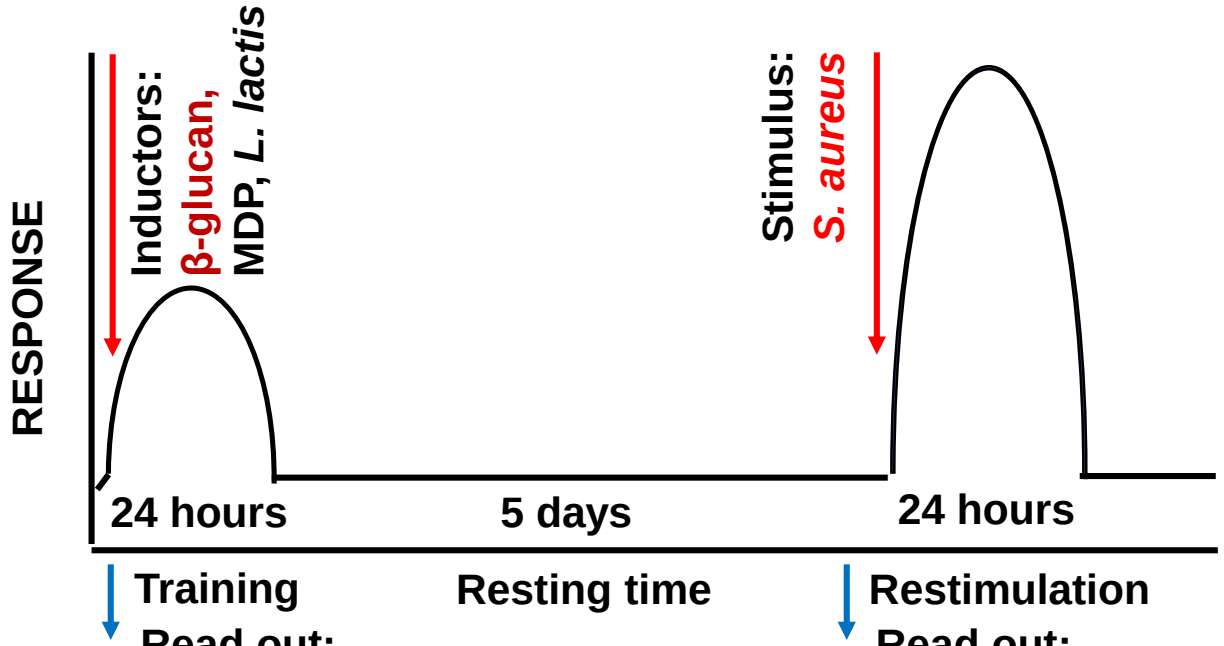
Ochando *et al.*, 2023

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

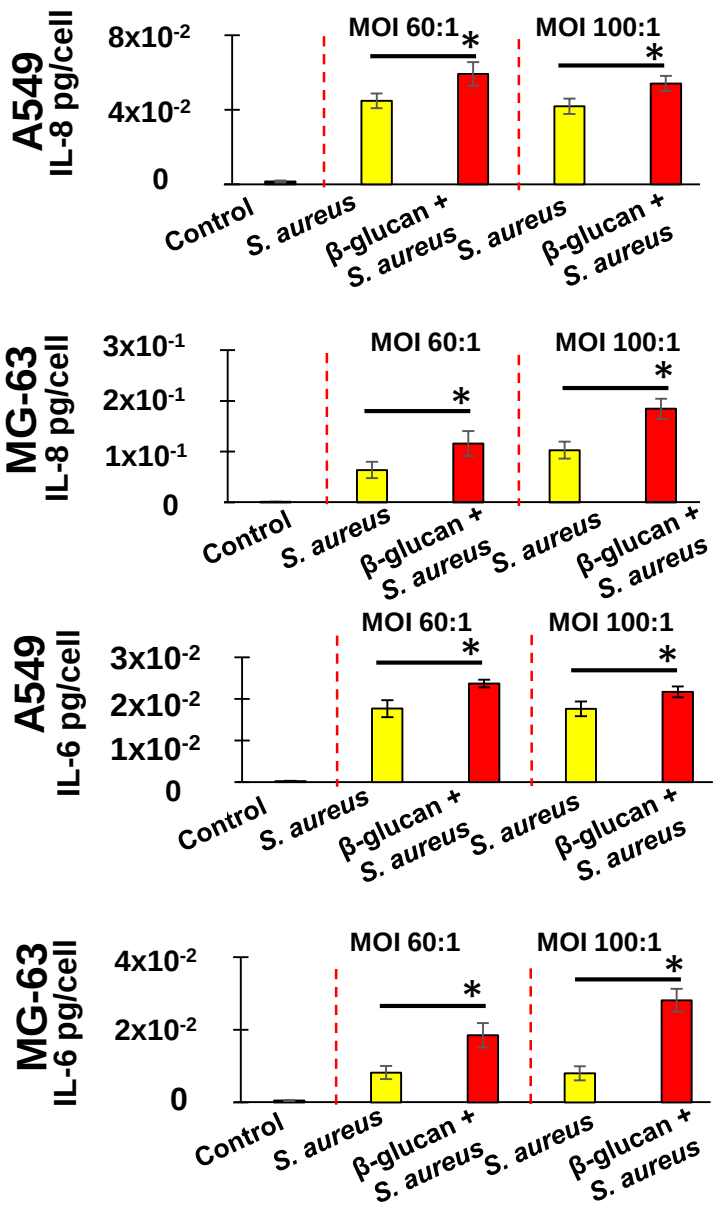
Training of osteoblast-like MG-63 and lung A549 cells increases a subsequent production of IL-6 and IL-8

A

Schematic overview of the trained immunity model



B



Assessment of IL-6 and IL-8 production by ELISA

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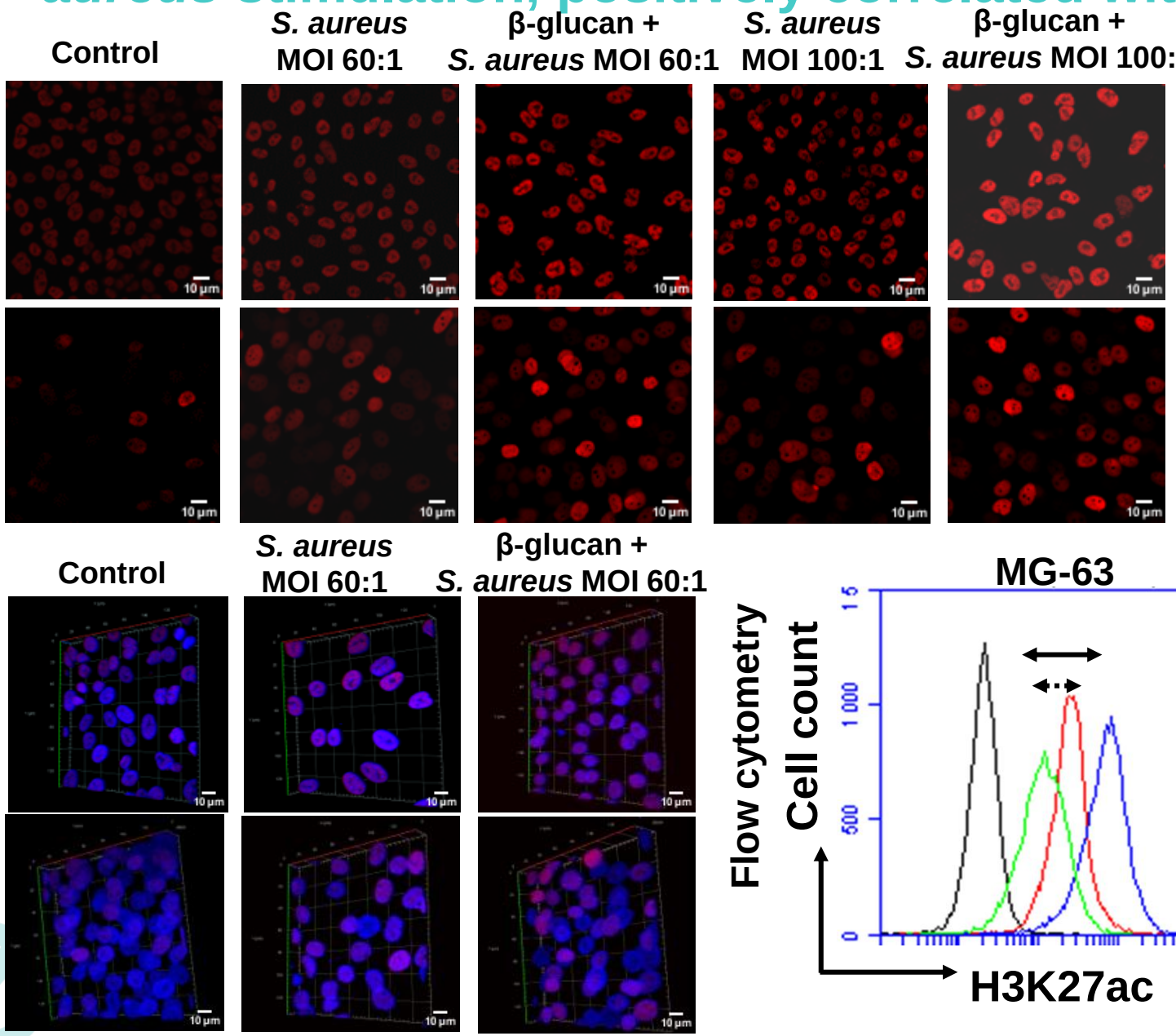
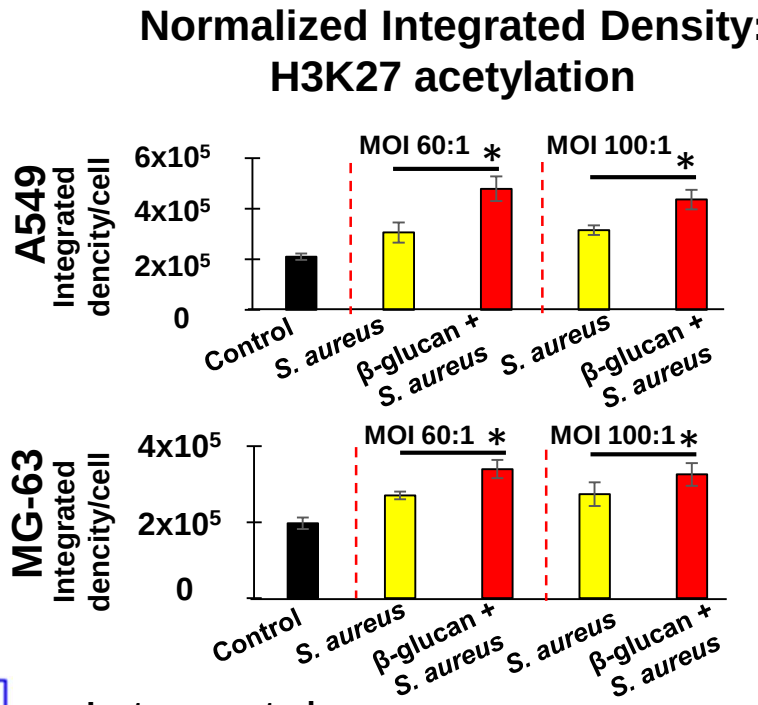
Enhanced H3K27 acetylation in β-glucan-trained cells upon *S. aureus* stimulation, positively correlated with IL-6/IL-8 production

Immunofluorescence confocal microscopy





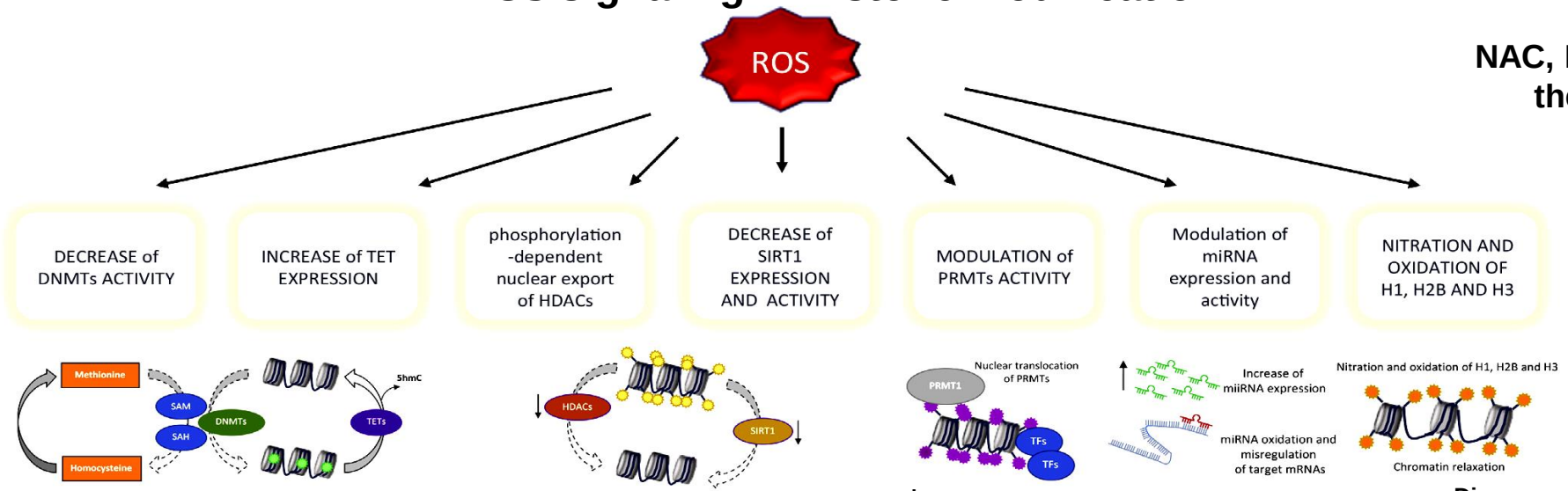
- Isotype control
- MG-63
- MG-63+*S. aureus*
- MG-63+β-glucan +*S. aureus*

develop

Developpment of β-glucan-induced trained immunity in non-immune cells

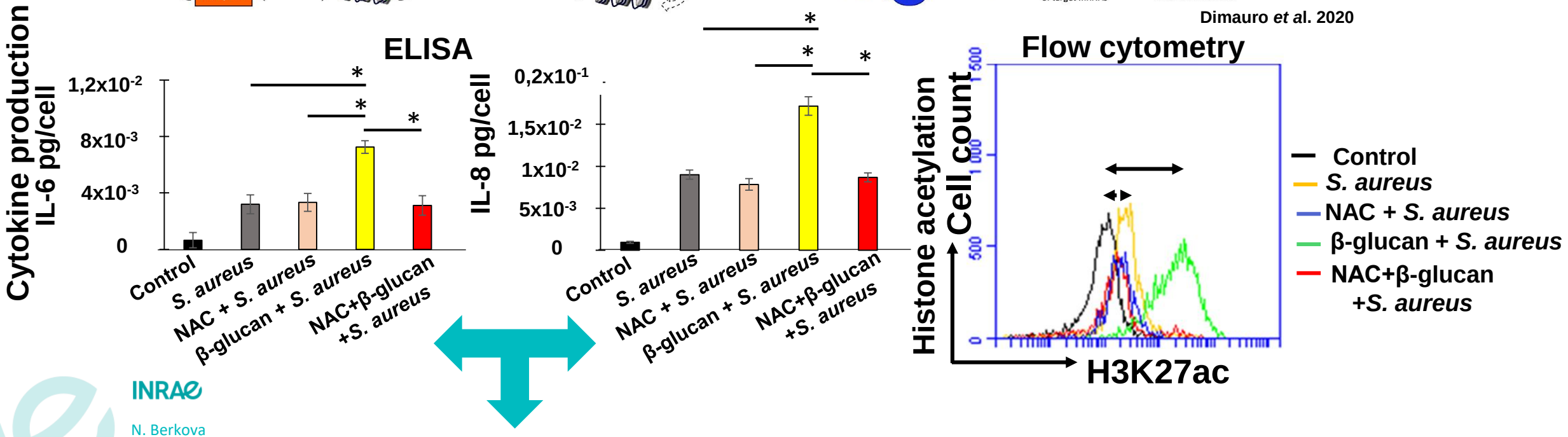
Involvement of ROS in the development of trained immunity

ROS signaling in histone modification



NAC, N-acetyl-l-cysteine, the ROS inhibitor

Dimauro *et al.* 2020



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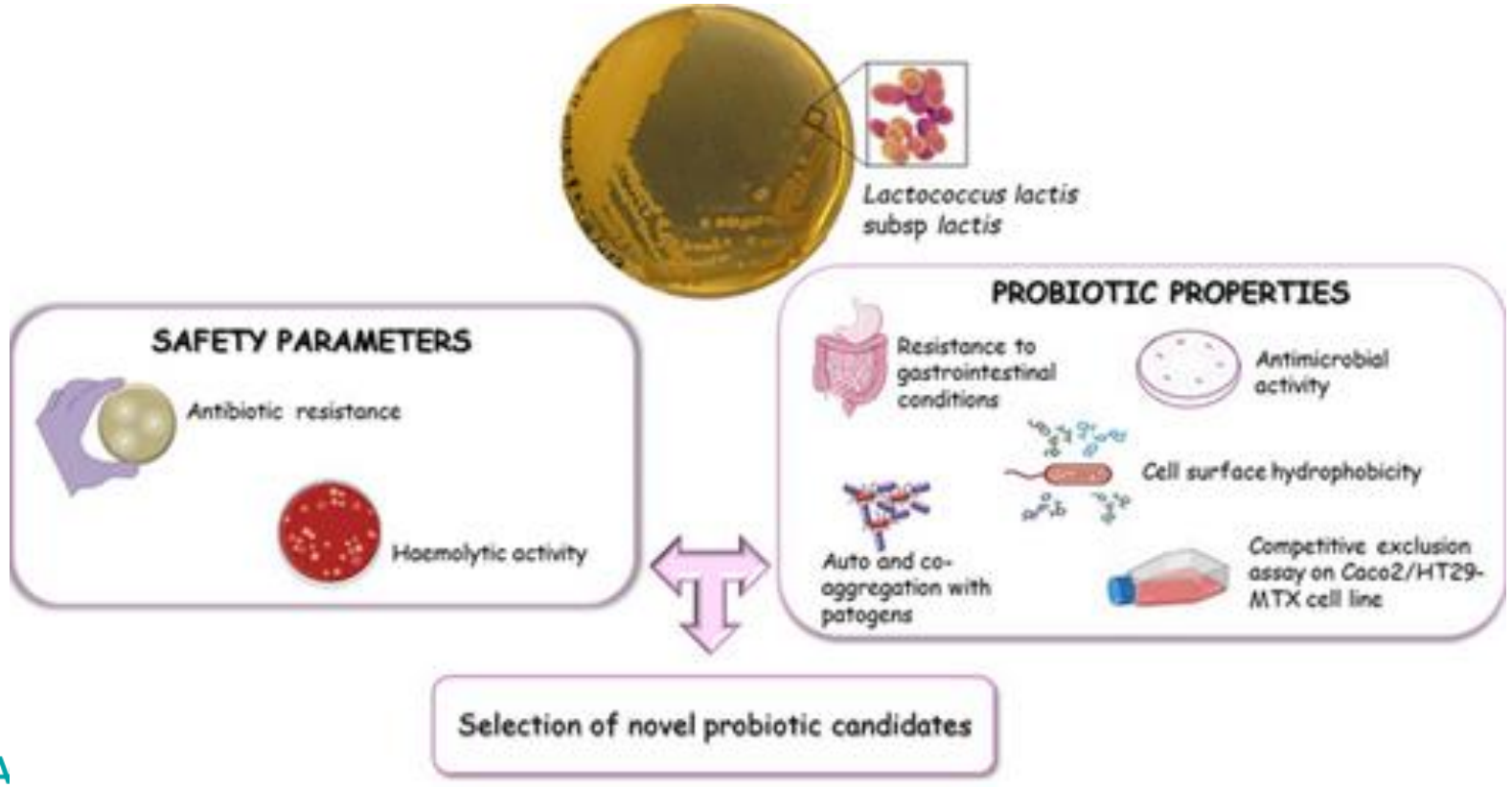
The decrease in IL-6/IL-8 production correlates to the decline in H3K27 acetylation in NAC-pre-treated cells

Probiotic Properties of *Lactococcus lactis*

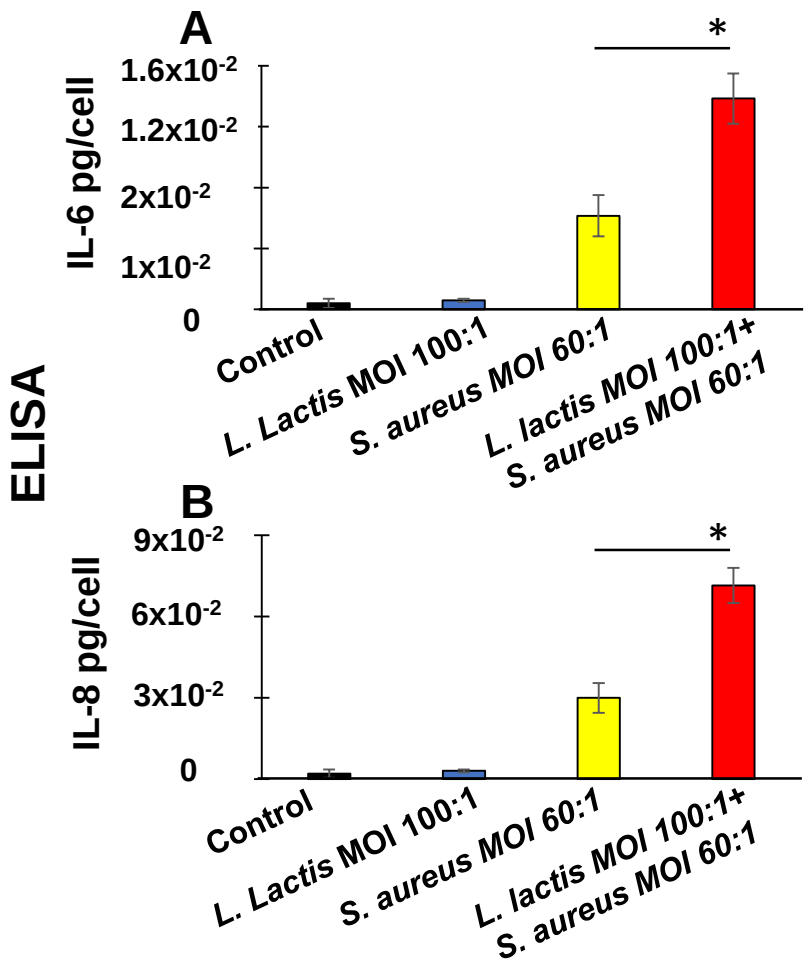
***L. lactis* is a Gram positive bacterium**
***L. Lactis* is found on plant surfaces, animal skin and in the gastrointestinal tracts of animals**
***L. Lactis* is a key actor in the dairy industry as a starter in cheese**
***L. Lactis* is also used as common probiotic for human health**



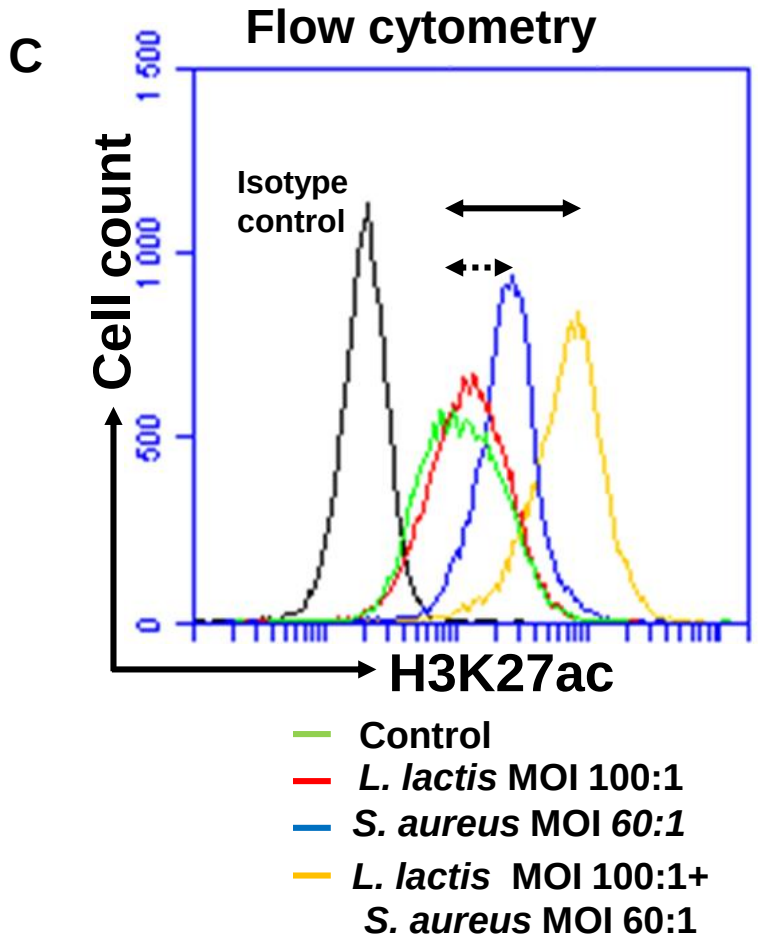
De Chiara et *al*. 2024

Cells exposed to *Lactococcus lactis* MG1363 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*



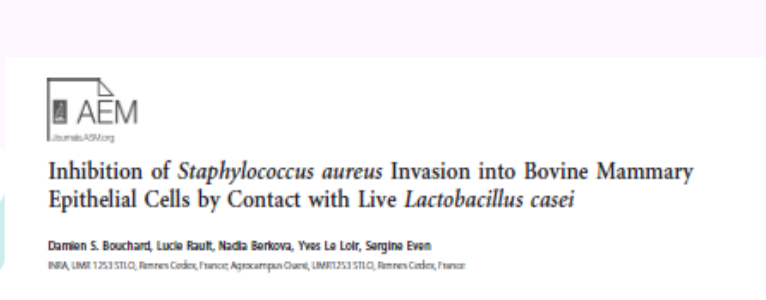
The increase in IL-6/IL-8 production correlates with the rise in H3K27 acetylation in cells pre-treated with *L. lactis*

Lactococcus lactis is a potential inducer of trained immunity

Chaumond et al. Front. Immunol. 2023

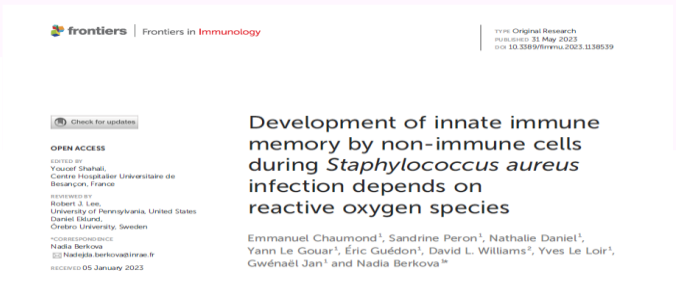
CONCLUSION

- **Besides structural functions, non-immune cells contribute to the defense response against *S. aureus***
- **Non-immune cells develop trained immunity that is at least partially dependent on ROS**
- ***L. lactis* is a potential inducer of trained immunity, suggesting the possibility of using this bacterium as a preventive measure against staphylococcal infections**


AEM

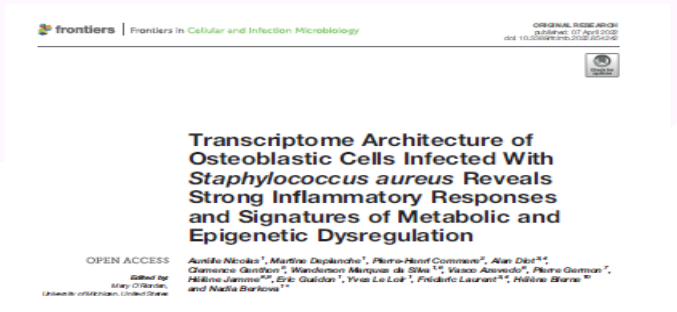
Inhibition of *Staphylococcus aureus* Invasion into Bovine Mammary Epithelial Cells by Contact with Live *Lactobacillus casei*

Damien S. Bouchard, Lucie Rault, Nadia Berkova, Yves Le Loir, Sergine Even


frontiers | Frontiers in Immunology

Development of innate immune memory by non-immune cells during *Staphylococcus aureus* infection depends on reactive oxygen species

Emmanuel Chaumond, Sandrine Peron, Nathalie Daniel, Yann Le Gouar, Éric Guédon, David L. Williams, Yves Le Loir, Gwénaël Jan and Nadia Berkova


frontiers | Frontiers in Cellular and Infection Microbiology

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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Metaprogram INRAE GISA LONGhealth–MPP10573

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