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Unleashing the power of inflammasomes and trained immunity: promising strategies in the fight against *Staphylococcus aureus* infection

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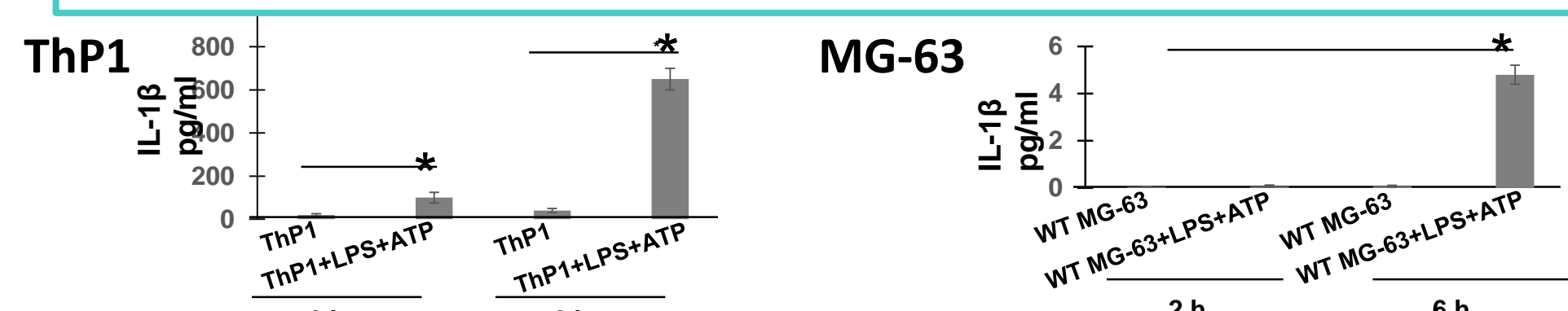
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CONTEXT & AIM

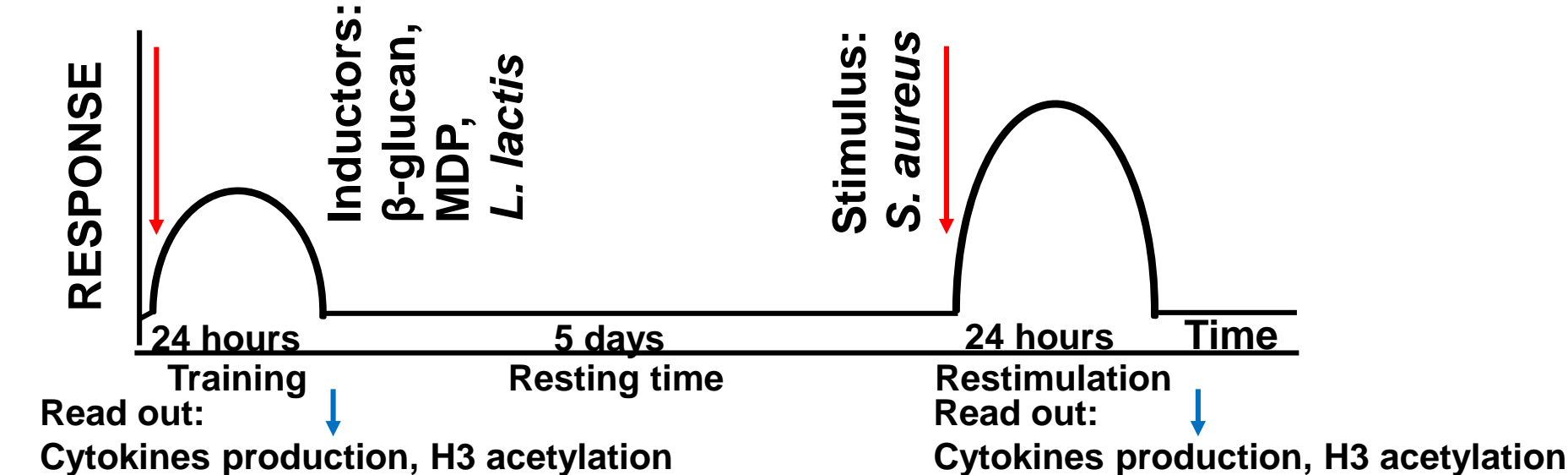
- The inflammasome is a signaling platform that assembles upon danger signal or pathogen recognition, activating downstream proteases like Caspase-1 and Caspase-11 to mature pro-IL-1 β , pro-IL-18, and pro-IL-33.
- Staphylococcus aureus* is a gram-positive bacterium that can cause several fatal infections, which are prone to recurrence. The quorum-sensing system in *S. aureus* (Agr) regulates the expression of PSMs encoding genes.
- Trained immunity (TI) enhances the immune response to subsequent unrelated challenges through epigenetic reprogramming of transcriptional pathways and alteration of cell metabolism.
- Our objectives include a comparison of IL-1 β production by monocyte-like ThP1 cells vs osteoblast-like MG-63 cells and comprehending the role of inflammasomes effector, caspase-1, investigating the development of TI in non-immune cells.

Monocyte-like ThP1 cells produced a higher amount of IL-1 β vs osteoblast-like MG-63 cells

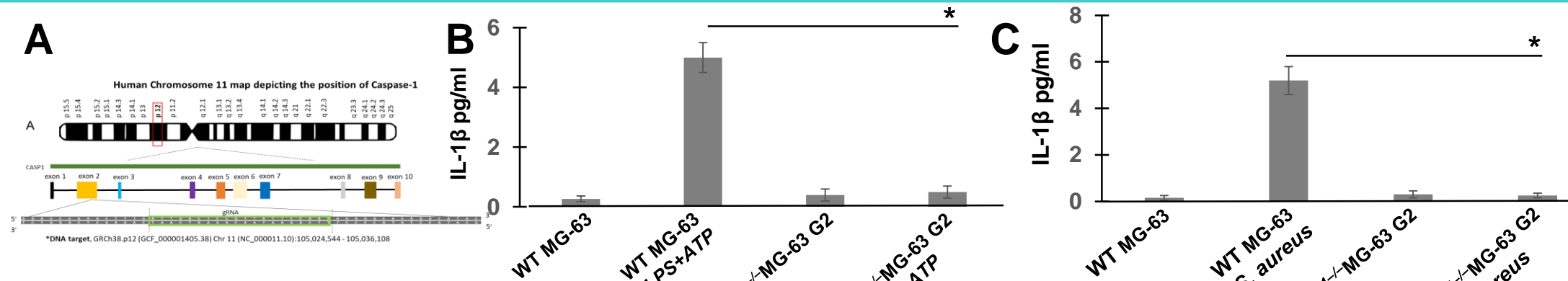


RESULTS

Schematic overview of the innate immune memory model



Generation of CASP1^{-/-} MG-63 cells using the CRISPR-Cas9

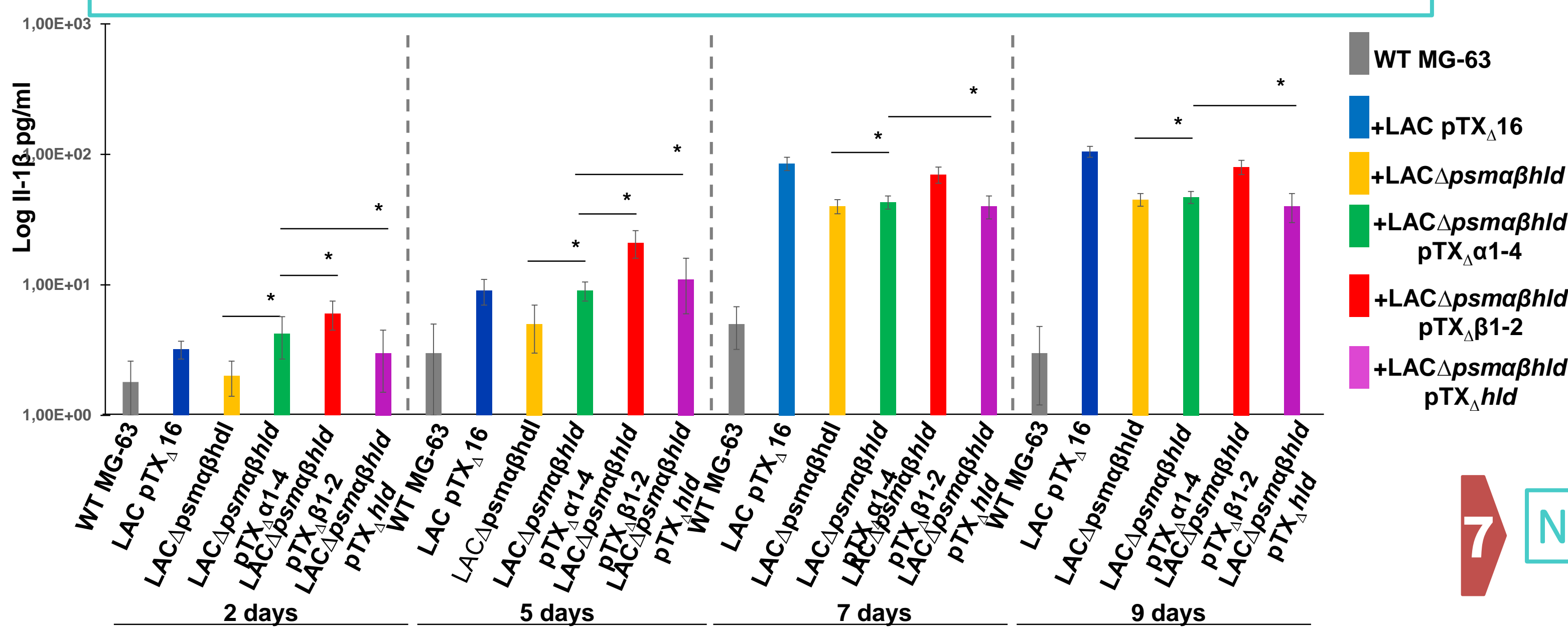


A. Generation of CASP1^{-/-} MG-63 cells targeting exon 2 of the CASP1 gene

B. Assessment of NLRP3 mRNA levels in WT MG-63 and CASP1^{-/-} MG-63 cells (RT-qPCR).

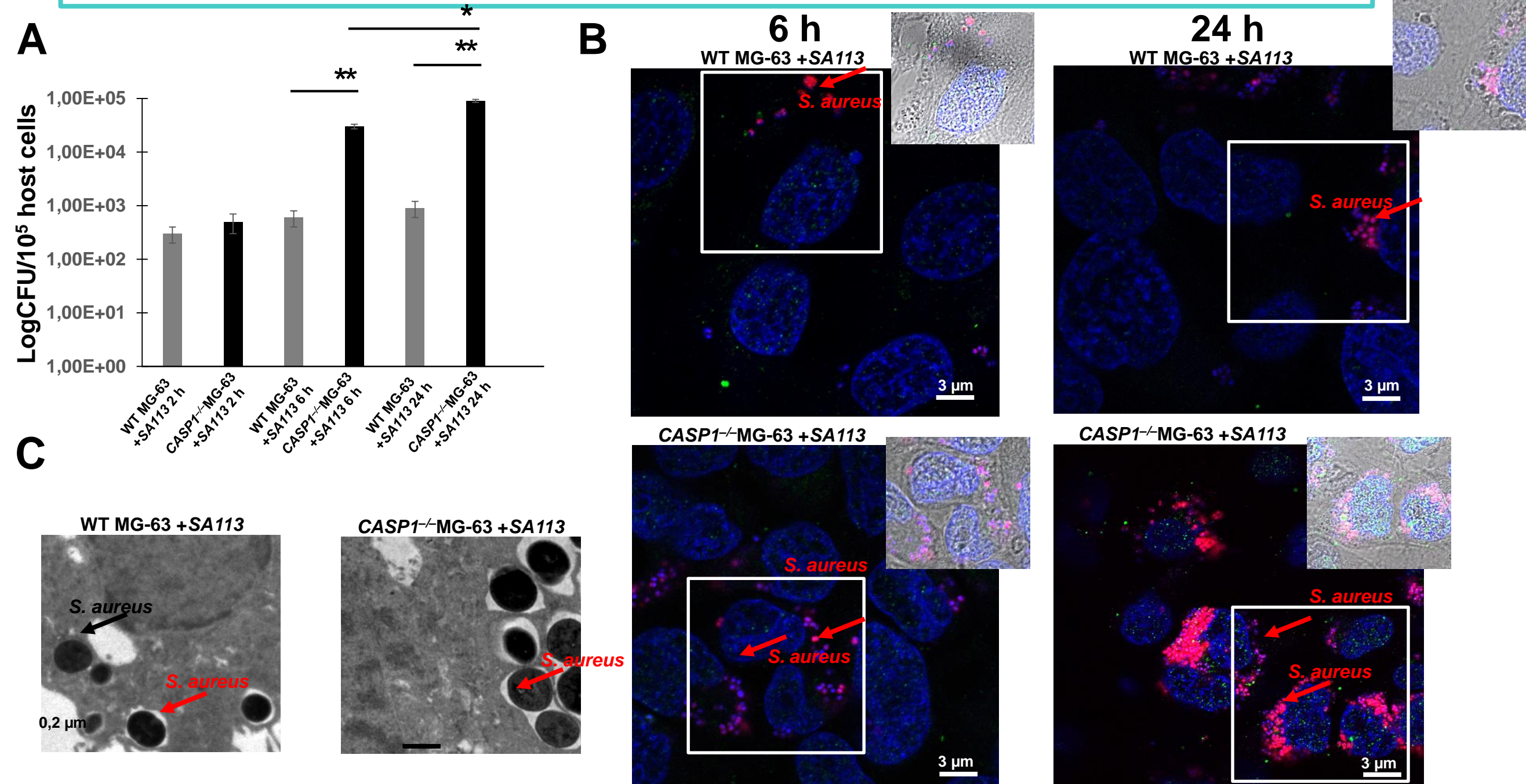
D. Assessment of the level of IL-1 β in cell supernatants (ELISA)

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



Exposure of MG-63 cells to USA300 LAC (pTXΔ16), which carries the control plasmid, the deletion mutant LACΔpsmaβhid (pTXΔ16), and the complemented strains

Involvement of caspase-1 in bacterial clearance

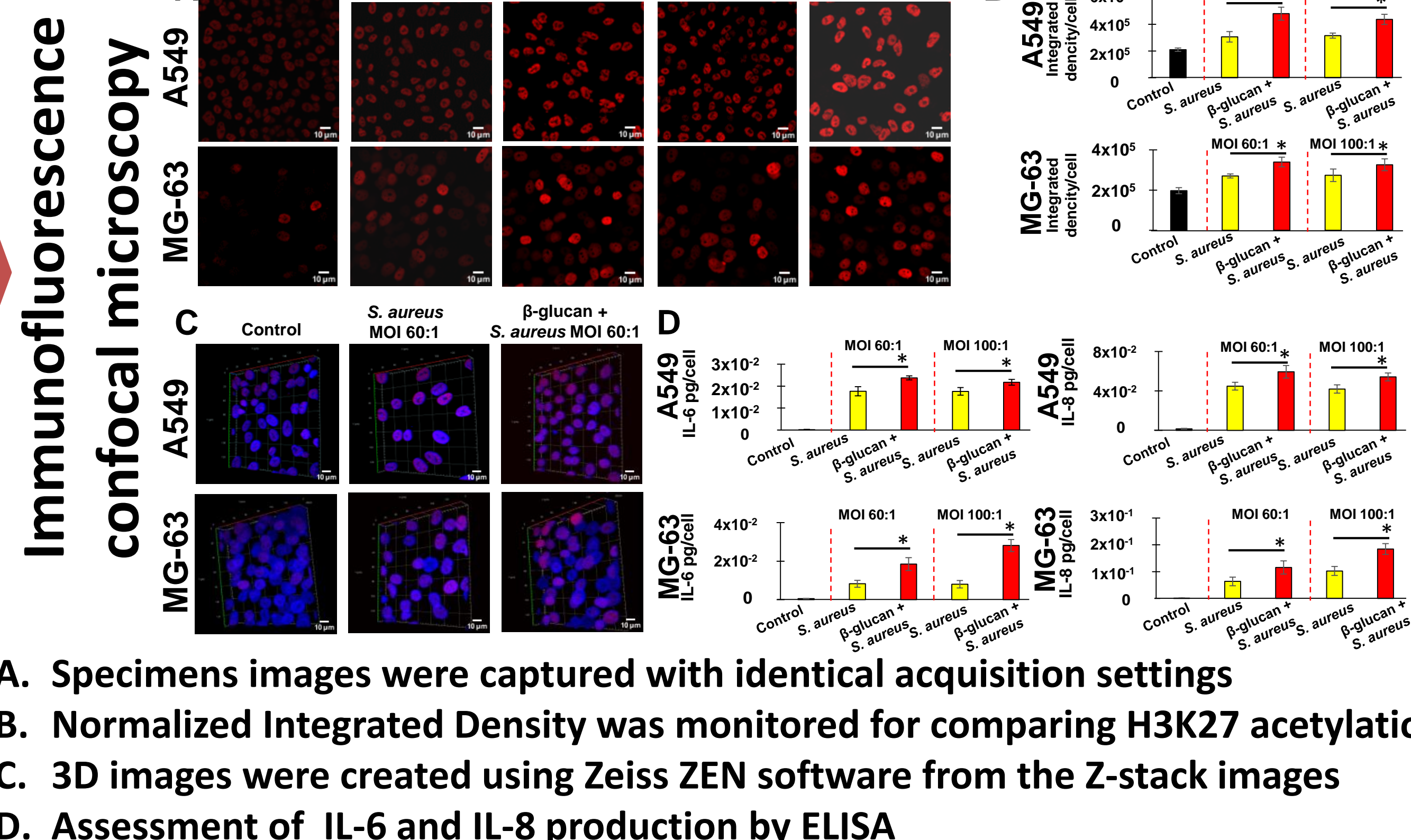


A. Exposure of WT MG-63 or CASP1^{-/-} MG-63 cells to a *S. aureus* SA113 strain

B. Exposure of WT MG-63 or CASP1^{-/-} MG-63 cells to *S. aureus* SA113 (red) Staining with anti-PYCARD antibody (green)

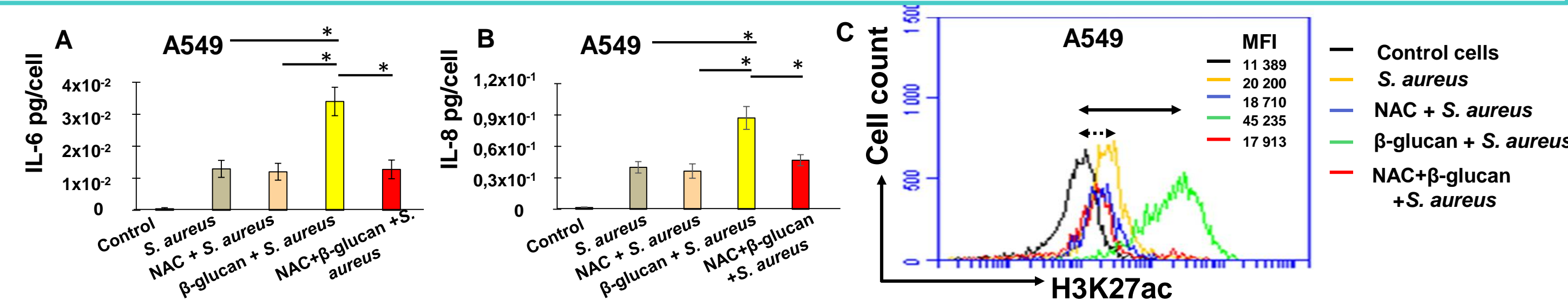
C. Transmission electron micrographs of cells infected with SA113 strain

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



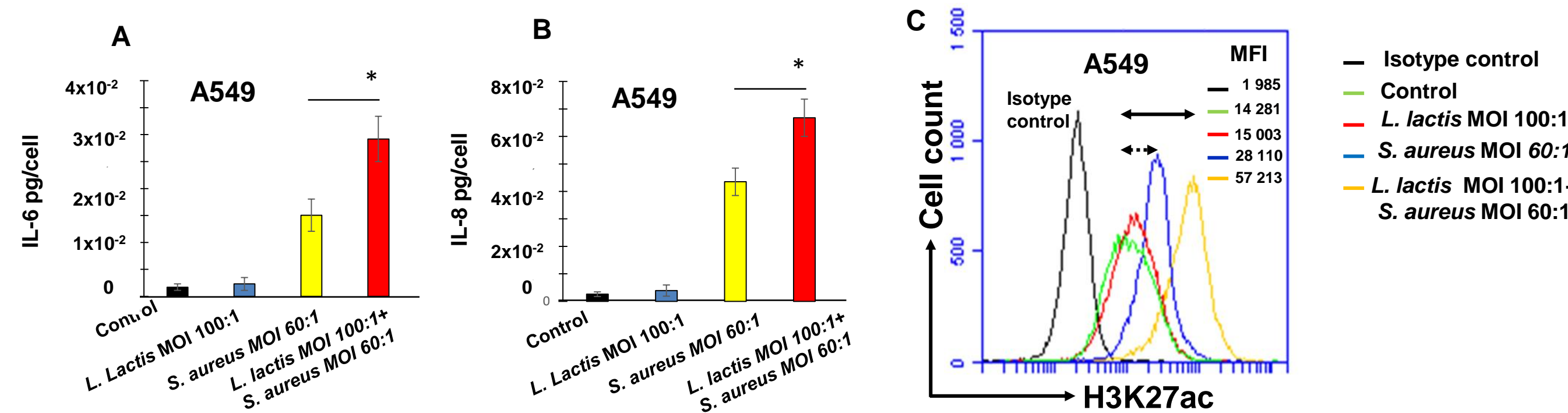
- Specimens images were captured with identical acquisition settings
- Normalized Integrated Density was monitored for comparing H3K27 acetylation
- 3D images were created using Zeiss ZEN software from the Z-stack images
- Assessment of IL-6 and IL-8 production by ELISA

NAC addition before β-glucan-pretreatment reduces IL-6/IL-8 production



- Assessment of IL-6 and IL-8 production by ELISA in NAC-pretreated cells upon *S. aureus* stimulation
- Flow cytometry analysis of treated cells

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



- Assessment of IL-6 and IL-8 production by ELISA in cells exposed to *L. lactis* before *S. aureus* infection
- Flow cytometry analysis of treated cells

CONCLUSION

- Non-immune cells induce an immune response against *S. aureus* through inflammasomes activation and processing of IL-1 β
- Inflammasomes related IL-1 β production by infected osteoblast-like cells appears to be dependent on PSM β among PSMs
- The active caspase-1 restrict intracellular replication of *S. aureus* in non-professional phagocytes
- Besides structural functions and tissue homeostasis, non-immune cells contribute to the defense response in infected hosts
- The development of TI in non-immune cells is partially dependent on ROS production
- L. lactis* may be a potential inducer of the innate immune system in non-immune cells, suggesting the possibility of using this food-grade lactic acid bacterium with probiotic properties before surgery as a preventive measure against staphylococcal infection