

# Bacterial and Host Factors in *Staphylococcus aureus* Septic Arthritis

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligens försvaras i Arvid Carlsson, Academicum, Medicinaregatan 3, torsdagen den 17 oktober 2024, klockan 9:00.

av **Zhicheng Hu**

Fakultetsopponent:

**Professor Andreas Peschel**

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## Avhandlingen baseras på följande delarbeten

- I. **Hu Z.**, Kopparapu P. K., Ebner P., Mohammad M., Lind S., Jarneborn A., Dahlgren C., Schultz M., Deshmukh M., Pullerits R., Nega M., Nguyen M. T., Fei Y., Forsman H., Gotz F., & Jin T. (2022). Phenol-soluble modulins alpha and beta display divergent roles in mice with staphylococcal septic arthritis. *Commun Biol*, 5(1), 910.
- II. **Hu Z.**, Kopparapu P. K., Deshmukh M., Jarneborn A., Gupta P., Ali A., Fei Y., Engdahl C., Pullerits R., Mohammad M., & Jin T. (2023). The Impact of Aging and Toll-like Receptor 2 Deficiency on the Clinical Outcomes of *Staphylococcus aureus* Bacteremia. *J Infect Dis*, 228(3), 332-342.
- III. **Hu Z.**, Deshmukh M., Jarneborn A., Bollmann M., Corciulo C., Ali A., Svensson N.D.M., Engdahl C., Pullerits R., Mohammad M., & Jin T. Anti-RANKL prevents bone erosion in infectious arthritis. *Under revision*

# Bacterial and Host Factors in *Staphylococcus aureus* Septic Arthritis

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## Abstract

The intense battle against *Staphylococcus aureus* (*S. aureus*) infections, along with the ongoing struggle to develop new effective treatments, presents a major challenge for the healthcare system. This highly pathogenic bacteria have a vast range of virulence factors, including phenol-soluble modulins (PSMs) at its disposal. Importantly, *S. aureus* is attributable to a broad spectrum of clinical infections in humans, not least bacteremia and the joint debilitating disease, septic arthritis.

The aim of this thesis was to uncover bacterial virulence factors and host factors that are critical for the progression of septic arthritis induced by *S. aureus*. The thesis also reviews recent therapeutic innovations targeting this challenging disease. Three key papers are included in this thesis, each addressing different aspects of *S. aureus*-induced infections in mouse models.

**Paper I** investigates the role of PSMs, specifically PSM $\alpha$  and PSM $\beta$ , in the development of septic arthritis. The findings demonstrate that PSM $\alpha$  exacerbates systemic infection by impairing neutrophil function, leading to increased bacterial burden and more severe disease outcomes. Conversely, PSM $\beta$  appears to have a protective role, mitigating inflammation and reducing joint damage. These results suggest that targeting PSM $\alpha$  might reduce infection severity, while enhancing PSM $\beta$  activity could offer therapeutic benefits in treating septic arthritis.

**Paper II** explores the impact of aging and Toll-like receptor 2 (TLR2) deficiency on the outcomes of *S. aureus* bacteremia. The study reveals that older mice and those deficient in TLR2 are more susceptible to severe infection outcomes, including higher mortality rates and impaired bacterial clearance. This highlights the crucial role of TLR2 in mediating an effective immune response against *S. aureus*, especially in vulnerable populations like the elderly.

**Paper III** focuses on the mechanism of bone destruction in septic arthritis, particularly the role of osteoclast-mediated bone degradation. The results suggest that combining traditional antibiotic treatment with anti-RANKL therapy, which inhibits osteoclast activity, offers a promising approach to mitigating bone destruction in septic arthritis. This combination therapy could significantly improve treatment outcomes by addressing both infection and the resulting bone damage.

Together, these studies provide a comprehensive understanding of the pathogenic mechanisms of *S. aureus* in septic arthritis and identify potential therapeutic targets to improve treatment outcomes.

**Keywords:** *Staphylococcus aureus*, septic arthritis, PSMs, aging, TLR2, anti-RANKL, mouse.