# **GraXRS-Dependent Resistance of Staphylococcus aureus to Human Osteoarthritic Synovial Fluid**

## **Abstract**

Osteoarthritis is the most prevalent joint disease in the United States, with many patients requiring surgical replacement of the affected joint. The number of joint arthroplasty procedures performed each year is increasing, and infection is a leading cause of implant failure. *Staphylococcus aureus* is the most frequently isolated organism associated with periprosthetic joint infections of the knee or hip, and due to the emergence of antibiotic-resistant strains, treatment options are limited. Here, we show that synovial fluid from osteoarthritic patients is iron restrictive toward *S. aureus* and, for strains representing the clonal lineages USA100, USA200, USA400, and USA600, bactericidal. Remarkably, community-associated methicillin-resistant *S. aureus* (CA-MRSA) strain USA300-LAC was highly resistant to synovial fluid killing but could be sensitized to killing by mutation of the GraXRS regulatory system and GraXRS-regulated *mprF* gene or by small-molecule inhibition of GraR. Thus, we propose the GraXRS-VraFG regulatory system and *mprF* as targets for future therapeutics for treatment of *S. aureus* bone and joint infections.**IMPORTANCE** Osteoarthritis, a degenerative disease that results in the breakdown of joint cartilage and underlying bone, is the most prevalent joint disease in the United States. Surgical intervention, including total joint replacement, is a clinically effective procedure that can help to restore the patient's quality of life. Unfortunately, joint replacement procedures come with a risk of infection that is estimated to occur in 1 to 2% of cases, and periprosthetic joint infection (PJI) is a leading cause of implant failure, requiring revision surgery. *Staphylococcus aureus* is well known for its ability to cause PJIs and was found to be the most frequently isolated organism from PJIs of the knee or hip. Antibiotic-resistant strains can often limit treatment options. In this study, we demonstrate that the MRSA strain LAC can resist killing and grow in human synovial fluid from osteoarthritic knees. Furthermore, we show that the GraXRS regulatory system is required for the displayed synovial fluid resistance. We further demonstrate that a small-molecule inhibitor of GraR sensitizes LAC to synovial fluid, validating the Gra system as a therapeutic target for the treatment of PJIs in humans.

**Keywords:** GraXRS; MRSA; S. aureus; Staphylococcus aureus; cationic peptides; infection; iron; joint; osteoarthritis; synovial fluid.

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