

THE GRADUATE COLLEGE OF THE  
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

# Maliha Rahman

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE  
GRADUATE COLLEGE  
*Graduate Pharmaceutical Sciences*



***Monday, July 10, 2017, 9:00 am***  
College of Pharmacy Building, Room 339

PHAGE-LIKE CHROMOSOMAL ISLANDS, VIRULENCE, AND  
DAPTOMYCIN RESISTANCE IN STREPTOCOCCUS ANGINOSUS

COMMITTEE IN CHARGE: W. Michael McShan, Ph.D., Chair; Nathan Shankar,  
Ph.D.; Michael A. Ihnat, Ph.D.; Randle M. Gallucci, Ph.D.; David W. Dyer, Ph.D.

**ABSTRACT:** *Streptococcus anginosus* is an important cause of internal organ abscesses, meningitis, female genital tract infection, neonatal sepsis, and bacteremia even though they are part of human oral flora. It was difficult to identify this bacteria to the species level until recently so it is not a well-studied pathogen. The genome of daptomycin-resistant strain J4206, originally isolated from a patient suffering from breakthrough bacteremia and septic shock, was sequenced and compared to daptomycin sensitive strains SA1 and J4211 genomes. The circular J4206 genome contains multiple mobile genetic elements, including transposons, integrative conjugative elements and a phage-like chromosomal island SanCI. Daptomycin resistance involves multiple alterations in the cell membrane and cell wall, and this comparative genomic study has identified unique features involved in cell surface modification in J4206 that may contribute to resistance. Genome sequencing of *S. anginosus* identified a phage-like chromosomal island (SanCI) integrated into the DNA mismatch repair operon. In *S. pyogenes*, related chromosomal islands (SpyCI) integrated into the same operon confer a mutator phenotype as well as alter global gene regulation, including the increased expression of many virulence factors. We hypothesized that SanCI will also alter global transcription patterns and virulence in *S. anginosus*. The SanCI was introduced into a SanCI-free *S. anginosus* strain (J4211) by natural transformation. To provide a selectable marker for transformation, gene *strA*, encoding a predicted transcriptional regulator, was replaced with the gene conferring erythromycin resistance (*ermB*), which after transfer created strain OKSan3. A functional copy of *strA* was then returned to this derivative of J4211, creating strain OKSan4. RNA sequencing (RNA-seq) of strains J4211, OKSan4 and OKSan3 confirmed that the addition of the SanCI altered *S. anginosus* global transcription patterns with altered expression of virulence, competence and survival factor genes and also genes involved in carbohydrate, amino acid and nucleotide metabolism. The result of this study along with our previous studies in *S. pyogenes* demonstrate that streptococcal chromosomal islands are a unique class of virulence factors that improve the fitness of their host cell by altering global transcription patterns and increasing virulence.