THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Kimberly McCullor

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

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College of Pharmacy Building | Room 230

Bacteriophage and Phage-Like Elements of Clinically Important Streptococci: Role in Horizontal Gene Transfer and Enhanced Virulence

Committee in Charge: William M. McShan, PhD; Allison F. Gillaspy, PhD
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ABSTRACT: *Streptococcus pneumoniae* and *Streptococcus pyogenes* remain significant pathogens world-wide. *S. pneumoniae* alone accounts for an estimated 3.7 million cases of severe infections globally in children, even with pneumococcal vaccines. The role bacteriophages and phage-like elements play in contributing to the robustness of these pathogens through facilitating genetic diversity and by altering expression remains understudied and was the focus of this project through genome sequencing and phylogenetic analysis of high efficiency transducing *S. pyogenes* lytic bacteriophage A25 and investigating the role of phage-like element SpnCI (**S**treptococcus **pn**eumoniae **c**hromosomal **i**sland) in altering phenotypes including enhanced virulence in *S. pneumoniae*.

A25 sequencing unexpectedly revealed a genome organization that was similar to *S. pyogenes* prophages. In addition to similar modular organization, A25 contained a residual lambdoid-like regulatory module that was included within a region containing high homology with prophages from strains MGAS10270, MGAS315, and MGAS10570, indicating an escape from lysogeny. Escape had ramifications on A25 host range as strains containing high homology prophages, were rendered resistant to A25 infection via superinfection immunity. Phylogenetic analysis demonstrated close relatedness to other phages employing less stringent *pac*-type DNA packaging mechanisms. Lower packaging stringency plus the ability to shield successful transductants from A25-specific lysis in strains containing high homology prophages likely explains A25's high efficiency transduction capabilities.

SpnCI enhanced virulence in infection model *Galleria mellonella* causing significantly higher amounts of mortality (80% compared to 50% in SpnCI null infections) and morbidity (1.6 mean health score compared to 3.8 score in SpnCI null infections) and was found to alter transcription leading to lower expression of capsule. Throughout growth, SpnCI remained integrated within a shared promoter region of heavy metal transporter gene *corA* and gene involved in nucleotide excision repair (NER) *uvrA*. This enhanced susceptibility to UV, indicating attenuation of NER function. SpnCI disseminated utilizing resident prophage structure and lytic function demonstrating the ability to move in a transformation- independent manner.

Overall, the study demonstrates the contribution of phage and phage-like mobile genetic elements in enhancing the robustness of pathogens *S. pyogenes* and *S. pneumoniae* by facilitating genetic diversity through transduction or through modulating gene expression leading to enhanced virulence.