Uncovering new targets for the fight against MRSA infections: Targeting Polyamine Detoxification.

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Introduction

- Antibiotic-resistant bacterial infections are increasing in occurrence, in 2018 alone, 14,000 Canadians died due to antimicrobial resistant pathogens.
- MRSA is the leading cause of hospital and community-acquired infections worldwide.
- Bacteria are continually developing new resistance mechanisms towards last-resort antibiotics increasing the need for the development of new treatment strategies.
- Polyamines are small polycationic molecules produced by all forms of life, and their concentrations increase at infection sites.
- The most prevalent community-acquired MRSA strain USA300 shows resistance to exogenous polyamines, while these compounds are toxic to other strains.
- This unique resistance, stemming from polyamine detoxification systems that are not fully known, is thought to enhance the virulence of this strain, thus contributing to its prevalence.

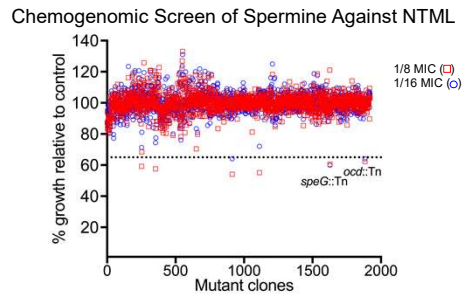
Objectives

- We hypothesized that disrupting USA300's unique resistance to polyamines will increase susceptibility to these compounds, prevent polyamine-induced antibiotic resistance, and improve antibiotic treatment outcomes.
- Our work aims to identify previously unknown polyamine detoxification systems in MRSA to serve as novel antibiotic targets and discover inhibitors of these systems.

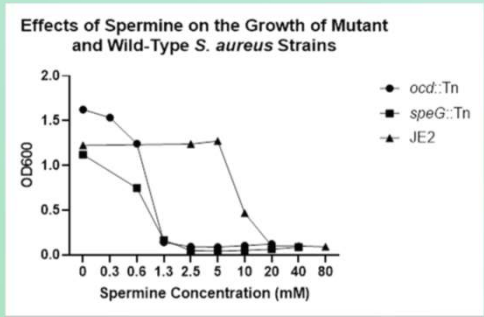
Methods

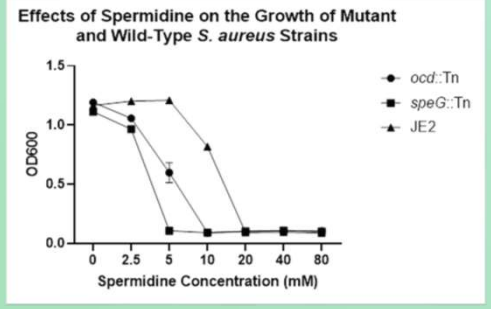
- We determined the MICs of polyamines against USA300 using the broth microdilution method.
- We performed a genome-wide screen to identify targets involved in polyamine resistance.
- We tested mutants of the identified targets in a *Galleria mellonella* infection model to evaluate their *in vivo* relevance.
- We studied the interaction between polyamines and antibiotics against USA300 using checkerboard assays.

Results

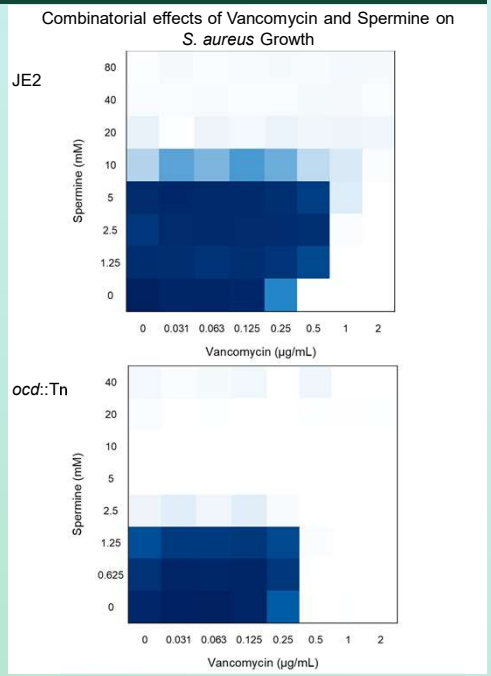


- A genome-wide screen identified new factors involved in polyamine resistance mechanisms. Those of primary interest include *speG* and *ocd*.

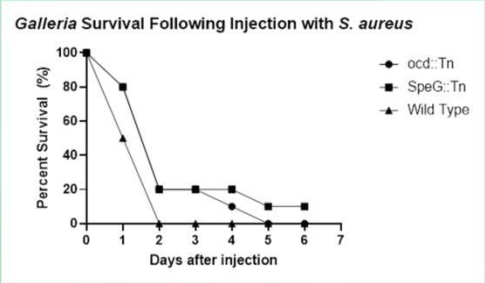




- Mutants with disruptions in *speG* and *ocd* are more susceptible to spermidine and spermine than the wild-type strain.



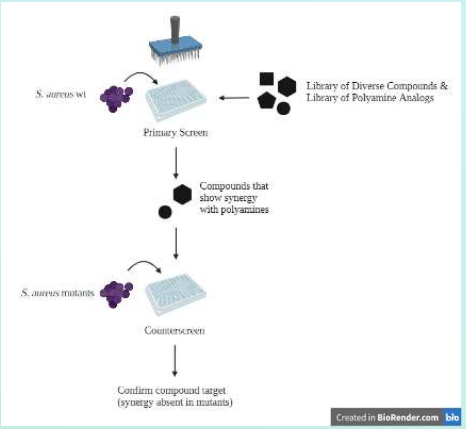
- Polyamines increased resistance against clinically relevant antibiotics in the wild-type strain, but not in *ocd* and *speG* mutants.



- *ocd and speG* mutants are slightly less virulent in the *Galleria* infection model compared to the wild-type strain.

Conclusions/Future Directions

- Polyamines increase resistance and provide a protective effect against certain antibiotics used to treat MRSA.
- We have Identified new mechanisms of polyamine resistance in MRSA that can serve as new targets for antibiotic therapy and are currently screening for this.



- Workflow for the discovery of an inhibitor of polyamine detoxifying systems in *S. aureus*. Image created with BioRender.com

Significance

- This study reveals novel drug targets that will provide new potential therapeutic solutions to multidrug-resistant *S. aureus* infections.

Acknowledgements

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