Marianne O Poulsen et al., J Microb Biochem Technol 2018, Volume: 10
DOI: 10.4172/1948-5948-C2-040

12th World Congress on

Biotechnology and Microbiology

June 28-29, 2018 | Amsterdam, Netherlands

Caenorhabditis elegans as a simple *in vivo* model for combinatorial therapy with thioridazine and dicloxacillin against infections with methicillin-resistant *Staphylococcus aureus*

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The shortage of drugs active against methicillin-resistant *Staphylococcus aureus* (MRSA) is a growing clinical problem. *In vitro* studies indicate that the phenothiazine thioridazine (TZ) might enhance the activity of the β-lactam antibiotic dicloxacillin (DCX) to a level where MRSA is killed, but positive *in vivo* studies have yet to be performed. We have introduced *Caenorhabditis elegans* infected by MRSA as an *in vivo* model to test the effect of TZ as a helper drug in combination with DCX. Because TZ is an anthelmintic, initial experiments were carried out to define the thresholds of toxicity, determined by larval development, and induction of stress-response markers. No measurable stress effects were observed at the concentrations below 64 mg/L TZ. Of seven tested MRSA strains the most pathogenic strain (ATCC 33591) was chosen for treatment analysis. Full-grown *C. elegans* were exposed to the test strain for three days and subsequently treated with 8 mg/L DCX and 8 mg/L TZ for two days. This resulted in a 14-fold reduction in the intestinal MRSA load as compared with untreated controls. Each drug alone resulted in a two to threefold reduction in MRSA load. In conclusion, we have proved *C. elegans* as a simple model for testing synergy between TZ and DCX against MRSA. Moreover, we have shown that TZ enhances the activity of DCX in a simple *in vivo* host model as *C. elegans* leading to a decrease of bacterial load of MRSA in the nematode gut and intestine.

Biography

Marianne O Poulsen is pursuing her PhD from Southern University of Denmark, Odense, Denmark. She is currently working at Odense University Hospital, Odense, Denmark and has published five papers.

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