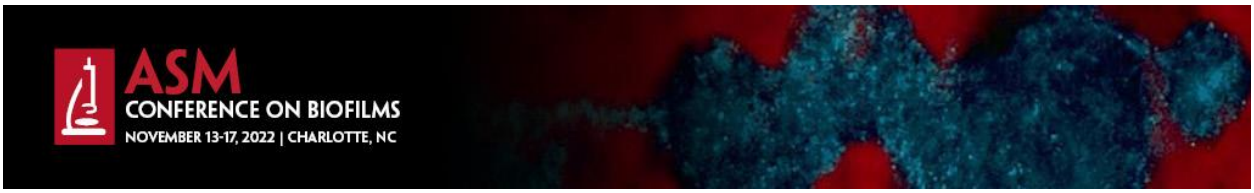

Therapeutic Development from the Study of *Enterococcus faecalis* and *Candida albicans* Bioflms

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Fungal pathogens are a continuing challenge due to a lack of effective antifungals and a rise in both acquired and intrinsic resistance. We have previously described the inhibition of *Candida albicans* virulence following exposure to the 68 amino acid bacteriocin EntV, secreted by *Enterococcus faecalis.* This protein reduces adhesion and biofilm formation, protects *C. elegans* from *C. albicans* infections at sub-nanomolar concentrations, and reduces fungal burden, invasion, and inflammation in a mouse model of oropharyngeal candidiasis (OPC). To optimize EntV as a potential therapeutic and better understand its antifungal features, we obtained an X-ray structure of the EntV pro-peptide, which. identifies six alpha helices enclosing a seventh helix of 16 amino acids (a7). Using the in vitro adhesion and nematode infection assays we demonstrated that the antifungal activity resides entirely in a7, which could be reduced to 12 amino acids that retained full activity in all assays but, interestingly, did not have antibacterial activity. Shorter peptides, down to 10 amino acids, had reduced activity. Using *C. elegans* we demonstrated that the 12 amino acid peptide was also effective against the emerging multidrug resistant pathogen *Candida auris* and *Cryptococcus neoformans*, an agent of fungal meningitis that is very distantly related to *Candida*. Moving to rodents, we found excellent protection in the OPC model, a catheter infection model, and in disseminated disease. The mechanism of action is not yet understood, but these peptides are not toxic to *C. albicans*. To further develop the potential of these peptides, we generated and tested a library of peptide derivatives using high throughput worm screen, identifying several candidates with enhanced activity. Together, these results showcase EntV-derived peptides as promising candidates for antifungal therapeutic development.