

28AB-ISMS16 **Natural Lipopeptide Antibiotic Tripropeptin C Revitalizes and Synergistically Potentiates the Activity of Beta-Lactams against Methicillin-Resistant *Staphylococcus aureus***

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Tripropeptin C (TPPC) is a natural calcium-ion-dependent lipopeptide antibiotic that inhibits peptidoglycan biosynthesis by binding to prenyl pyrophosphate. It displays very potent antimicrobial activity both *in vitro* and in a mouse model of methicillin-resistant *Staphylococcus aureus* (MRSA) septicemia. The combination of TPPC with all classes of beta-lactams tested (including penam, carbapenem, cephem, and oxacephem) showed highly synergistic effects against MRSA strains, but not against methicillin-sensitive *S. aureus* strains. These synergistic effects were observed with both a checkerboard methodology and a time-kill analysis. The TPPC analogue, bis-methyl ester-TPPC, which has neither antimicrobial activity nor the ability to bind prenyl pyrophosphate, also potentiated the activity of beta-lactams. This result indicates that the mechanism of the synergistic activity of TPPC is independent of its binding to prenyl pyrophosphate. Therefore, synergistically enhancing the anti-MRSA activities of TPPC and beta-lactams by combining them is a novel and potentially powerful therapeutic strategy for MRSA infections. In this presentation, we will also discuss its interesting mode of action.