Next-Generation Engineered Peptide Antibiotics

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INTRODUCTION: Bacteria predominantly exist as multicellular communities known as biofilms that are estimated to cause at least 65% of all human infections, and demonstrate increased adaptive resistance to conventional antibiotics. Currently, there are no available drugs that effectively target bacterial biofilms. Certain molecules, such as host defense peptides and nitric oxide, are produced as part of the innate immune system of humans and virtually every other multicellular organism on Earth. These natural antibiotics have evolved to fight off infections and therefore constitute excellent templates for the design and discovery of next-generation anti-biofilm therapeutics. OBJECTIVES: To engineer novel antimicrobial therapeutics based on molecules of the human innate immune system. MATERIALS AND METHODS: We designed and generated novel, synthetic anti-biofilm agents derived from naturally occurring host defense peptides. Using high-throughput peptide synthesis technology and biofilm microplate and flow cell microfluidics assays, we have turned host defense peptides that exhibit modest activity against biofilms into potent anti-biofilm agents. In addition, the structure of nitric oxide (NO) was chemically modified to generate cyclic nitroxide molecules with enhanced biophysical and biological functionalities. DISCUSSION AND RESULTS: Using this approach, we have identified synthetic peptides with clinically relevant anti-biofilm properties including peptides that: i) act in a broad-spectrum manner; ii) work by interfering with the phosphorylated nucleotide ppGpp that operates as a communication signal in bacteria; iii) potentiate the activity of different classes of conventional antibiotics commonly used in the clinic that are inefficient in the treatment of biofilms when used in stand-alone therapy; iv) exhibit activity in vivo, as they conferred protection in several animal models against otherwise lethal Pseudomonas aeruginosa biofilm infections. Moreover, NO was modified into cyclic nitroxides that also eradicated pre-formed biofilms grown in flow cells, and synergized with fluoroquinolones against biofilms. CONCLUSION: Using natural molecules of the innate immune system as templates, we have been able to generate synthetic anti-biofilm therapeutics with great clinical potential.

Keywords: Antibiotic discovery, Peptides, Synthetic Biology