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Alternatives to antibiotics for multidrug-resistant infections and inflammation

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Introduction:

The inexorable increase in multidrug-resistant infections combined with a decrease in the new antibiotic discovery and the lack of compounds to treat recalcitrant high-density infections, such as those associated with chronic biofilm and abscess infections, is creating a potential crisis in human medicine. According to the US CDC, biofilms represent two-thirds of all hospital infections, infecting devices and causing chronic infections of the lung, bladder, wounds, oral cavity, urinary and respiratory tracts, skin, etc. They are very difficult to treat due to their multi-drug adaptive resistance to antibiotics and the fact that no agent has been introduced into human medicine to specifically address biofilm infections. Thus it is imperative to consider alternatives to conventional antibiotics for treating such infections. Cationic host defense (antimicrobial) peptides are produced by virtually all organisms, ranging from plants and insects to humans, as a major part of their innate defenses against infection. They are a key component of innate immunity and have multiple mechanisms that enable them to deal with infections and inflammation including an ability to favorably modulate the innate immune system and distinct antibiotic and anti-biofilm activities. We have defined a class of peptides that act against biofilms formed by multiple species of bacteria in a manner that is independent of activity vs. planktonic bacteria. We have now developed novel anti-biofilm peptides that (i) kill multiple species of bacteria in biofilms (MBEC <1?g/ml), including the most fearsome antibiotic-resistant pathogens in our society (collectively termed ESKAPE pathogens) and other major clinically relevant Gram-negative and Gram-positive bacteria, (ii) work synergistically with antibiotics against multiple bacterial species and in animal model infections and (iii) are effective in animal models of high density biofilm and abscess infections. Structure-activity relationships studies showed no major overlap between anti-biofilm and antimicrobial (vs. planktonic bacteria) activities and indeed organisms completely resistant to antibiotic peptides can still be treated with anti-biofilm peptides. The action of such peptides is dependent on their ability to trigger the degradation of the nucleotide stress signal ppGpp. Some of these peptides have additional advantages in addressing the inflammatory sequelae of chronic infections, in that they can boost protective innate immunity while suppressing potentially harmful inflammation/sepsis.