CHALLENGES FACED IN THE PLANNING, DEPLOYMENT, AND ADOPTION OF A LAYERED MEDICAL DEFENSE STRATEGY

Combinations Of Novel Bacteriophage Are Efficacious Against Mdr Pseudomonas Aeruginosa And Restore Sensitivity To Carbapenem Antibiotics

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The recurring threat of antibiotic resistance in bacteria has rendered entire classes of drugs ineffective, creating pathogens that are virtually untreatable. As an alternative therapeutic option, the utility of lytic bacteriophage (phage) has received renewed attention. Following propagation within their specific bacterial host, phage are released from the cell in a viral burst, killing the infected bacterium. The Gram-negative ESKAPE bacterium Pseudomonas aeruginosa has become a pathogen of urgent concern due its extensive multi-drug resistance (MDR) profile, high occurrence in wound infections suffered by warfighters serving abroad, and widespread incidences in hospital-acquired infections throughout the United States. Despite the reported efficacy of phage therapy for eradicating P. aeruginosa infections, concerns remain about spontaneous resistance that may arise allowing it to evade viral infection. This may, in turn, result in a fitness tradeoff, re-sensitizing the bacterium to antibiotic treatment. When combined, phage and antibiotics together may produce synergistic effects, providing possibilities for novel layered medical countermeasures against the pathogen.

Environmental screening and phage enrichment has yielded three novel lytic viruses capable of infecting the MDR P. aeruginosa strain PA01. Co-administration of each phage with a panel of thirty antibiotics produced varying combinations with growth inhibition of bacteria, including several β-lactam drugs to which the strain is resistant to. Notably, this was observed with both imipenem and meropenem, which were both ineffective as stand-alone treatments. A combination cocktail of all three phages was completely inhibitory to growth, even without antibiotics. The same 3x phage cocktail also disrupted PA01 biofilms, reducing biomass by over 75% compared to untreated biofilms. Further, the phage cocktail demonstrated broad efficacy as well, capable of infecting 33 out of 100 diverse clinical isolate strains of P. aeruginosa.

Together, these results indicate a promising approach for designing layered medical countermeasures to overcome antibiotic resistance against recalcitrant, MDR bacteria such as P. aeruginosa. Combination therapy, either by synergistic phage-antibiotic pairings, or by phage cocktails, presents a means of controlling mutations that can allow for bacteria to gain a competitive edge.