PennState

Applied Biological and
Biosecurity Research Laboratory

Combating Antimicrobial Resistant Organisms Using Bacteriophage Cocktails

Identifying personalized therapeutic phage cocktails against multidrug resistant (MDR) bacterial pathogens

Mission Area:
Innovating Biomedical Engineering for Health Security

Mission Area:
Fighting Antimicrobial Resistance

Type: Prototype Development

Region: Central/South America

Countries: Peru (Phase I)

Status: In Development

Overview

Beginning with a library of characterized phages against each of the ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* spp), this approach aims to identify combinations of phages that produce synergistic growth inhibition in patient-specific clinical isolates, and to provide these cocktails for clinical therapeutic use. The rate limiting step in this therapeutic approach is the time required to screen the library in order to determine the best phages to include in the cocktail. We aim to understand synergistic growth inhibition by various phages in an attempt to shorten the time required to developing an efficacious phage cocktail to any ESKAPE organism.

Objectives / Goals

1. Identifying specific gaps in library coverage (as defined by host range or resistance mechanisms) and using the identity of these gaps for targeted phage harvesting.
2. Understanding the diversity of synergistic mechanisms, and how bacteria develop resistance, may lead to the ability to predict synergies and/or shrink the turnaround for compounding effective therapeutic cocktails, by either better-informing personalized cocktail formulation (currently an exclusively empirical activity) or allowing for the creation of a panel of off-the-shelf population level cocktail products for either therapeutic or prophylactic use

Technical Approach

We hypothesize that the host range and/or genomic composition of a phage isolate may correlate with its ability to be efficaciously combined with other phages in a custom compounded cocktail. If this is true, we may be able to predict synergy in custom compounded cocktails from data that the Navy is already collecting. Moreover, we may identify signatures of synergizable host

ranges (or genomic compositions) that can be screened-for, or selected-for during phage harvesting.

We hypothesize that understanding the spectrum of evolutionary mechanisms that is responsible for phage resistance to synergistic cocktails will allow us to understand and predict synergy. To do this we will perform selection experiments with single phages and synergistic phage cocktails. The resistant strains derived in these selections will also be useful for phage harvesting. Thus, the isolation phages required to compound synergistic cocktails may be aided by studies of bacterial phage resistance.

We hypothesize that a better understanding of phage synergies and concomitant bacterial adaptive mutations for phage resistance may allow for the creation of a panel of optimized cocktails that have broad activity against many different strains. Thus, a better understanding of the parameters of synergistic custom cocktail formulation may allow for the production of rationally generated broad spectrum cocktails that may serve as population level therapeutic products and/or prophylactics.

We hypothesize that clonal phage isolates may experience genetic/phenotypic drift when they are manufactured on "tool" strains. We will explore this explicitly by looking at host range on a culture that is serially passaged in a tool strain. This will allow us to see how adaptation during manufacturing affects host range. Every individual phage burst event produces a population that has adapted to the strain on which it was grown. This adaptation may alter the phage population to variable degrees. A synergistic phage cocktail grown on a target of interest will be compared to those same phages manufactured/grown on a different permissive tool strain.

Partners

Funders:

- The Pennsylvania State University
- United States Navy

Implementation / Scientific:

- Naval Medical Research Unit 6 (NAMRU-6), Lima and Iquitos, Peru
- Naval Medical Research Center, Silver Spring, MD