Using Bacteriophages to Reverse Antibiotic Resistance of Pathogens (Ramot)

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Technology

A Novel complex of engineered phages that deliver uniquely programmed CRISPR-Cas constructs into bacteria to reverse their antibiotic resistance.

The Need & Solution

The increasing threat of pathogen resistance to antibiotics requires the development of novel antimicrobial strategies. Bacterial pathogens evolve to overcome the therapeutic effect of antibiotics simply because antibiotics kill bacteria that are not resistant to them. This selective pressure that kills sensitive bacteria but not antibiotic-resistant bacteria is applied in each use of antibiotics. Currently, there is no approach that exerts selection pressure, which counteracts the selective pressure formed by antibiotics, i.e., a selection pressure that favorably changes the ratio of antibiotic-sensitive pathogens over antibiotic-resistant pathogens. Applying such a selection pressure will actively increase ratio of antibiotic-sensitive bacteria, and treat the core problem of antibiotic-resistance formation rather than its symptoms. Here we propose a genetic strategy that aims to sensitize bacteria to antibiotics and selectively kill antibiotic-resistant bacteria. We will use temperate phages to deliver a functional CRISPR-Cas system into the genome of antibiotic-resistant bacteria. The delivered CRISPR-Cas system will be programmed to destroy both antibiotic resistance-conferring plasmids and genetically modified lytic phages. This linkage between antibiotic-sensitization and protection from lytic phages is a key feature of the strategy. It allows programming of lytic phages to kill only antibiotic-resistant bacteria while protecting antibiotic-sensitized bacteria.

Potential Applications

This proposed technology has several potential human clinical applications, for addressing antibiotic resistance in human bacterial pathogens, by applying a constant selective pressure that will force bacteria to select for maintaining antibiotic sensitivity genetic properties. The first product developed from this technology is a “superphage spray product” aimed as a biological disinfectant for significantly lowering the percentage of antibiotic-resistant bacteria in hospital settings, in particular on hands of medical personnel.

Stage of Development: POC in non-pathogenic bacteria

Patents: One US granted patent (number 8,865,158) and one pending patent application

Supporting Publications

Yosef, I., Manor, M., Kiro, R., and Qimron, U. (2015) Temperate and lytic bacteriophages programmed to sensitize and kill antibiotic-resistant bacteria. Proceedings of the National Academy of Sciences USA, in press, 2015.
Edgar, R., Friedman, N., Molshanski-Mor, S. and Qimron, U. (2011) Reversing Bacterial Resistance to Antibiotics by Phage-Mediated Delivery of Dominant Sensitive Genes. Appl Environ Microbiol.
Jermy, A. (2012) Antimicrobials: Reversing resistance with phage. Nat Rev Microbiol, 10, 83.
Lukits A (2012) A New Weapon in the Fight Against Superbugs. The Wall Street Journal 17/1/2012.

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