

Abstract

Mycobacteriophages: Diversity, Dynamics, and Therapy [†]

Graham F. Hatfull *

Department of Biological Sciences, University of Pittsburgh, Pittsburgh, PA 15260, USA; gfh@pitt.edu

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Abstract: Bacteriophages—viruses that infect bacteria—are the most numerous biological entities in the biosphere. The phage population is not only vast but dynamic and old, and perhaps not surprisingly, highly diverse genetically. We are exploring and defining this biological diversity by isolating and genomically characterizing individual phages, and through comparative genomic analyses. The development of large integrated research-education programs, such as the Science Education Alliance Phage Hunters Advancing Genomics and Evolutionary Science (SEA-PHAGES) program, have established a large collection of 15,500 individual phages—all isolated on bacterial hosts within the phylum Actinobacteria—of which over 3000 are fully sequenced. These genomes are highly diverse genetically, even if isolated on the same bacterial strain, and are richly populated in genes of unknown function. We propose that many of these genes are involved in the dynamic relationships between bacteria and their viruses, either promoting or countering viral defense systems, or denying competing phages the opportunity to superinfect infected cells. Examples of these include prophage-mediated defense systems in which integrated prophages of temperate viruses lysogenically express genes that prevent attack by unrelated (heterotypic) phages. These systems are prevalent among temperate phages and can act with exquisite specificity in their defense profiles. Phages can also encode their own counter-defense systems to negate the functions of these prophage-mediated defenses. These contributions to microbial dynamics dictate the phage susceptibility profiles of individual strains of pathogenic bacteria, adding complexity to the prospects for the broad therapeutic use of phages against bacterial infections. However, we have shown that the administration of a three-phage cocktail engineered and personalized to a specific highly antibiotic-resistant strain of *Mycobacterium abscessus* contributes to substantial clinical improvement.

Keywords: bacteriophage; viral diversity; phage therapy



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