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2022 SEA Symposium Abstract

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Systematic overexpression of genes encoded by mycobacteriophage Waterfoul reveals novel inhibitors of mycobacterial growth

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Bacteriophages represent an enormous reservoir of novel genes, many of which are unrelated to existing entries in public databases and cannot be assigned a predicted function. Characterization of these genes can provide important insights into the intricacies of phage-host interactions and may offer new strategies to manipulate bacterial growth and behavior. Overexpression is a useful tool in the study of gene-mediated effects, and we describe here the construction of a plasmid-based overexpression library of a complete set of genes for Waterfoul, a mycobacteriophage closely related to those infecting clinically important strains of *Mycobacterium tuberculosis* and/or *Mycobacterium abscessus*. The arrayed Waterfoul gene library was systematically screened in a plate-based cytotoxicity assay, identifying a diverse set of 32 Waterfoul gene products capable of inhibiting growth of the host Mycobacterium smegmatis and providing a first look at the frequency and distribution of cytotoxic products encoded within a single mycobacteriophage genome. Several of these Waterfoul gene products were observed to confer potent anti-mycobacterial effects, making them interesting candidates for follow-up mechanistic studies.