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ANTIMICROBIALS

Reversing resistance with phage

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The threat from antibiotic resistance has seen interest in phage therapy rekindled in recent years. Writing in *Applied and Environmental Microbiology*, Edgar *et al.* provide proof-of-principle for using phages to deliver dominant-sensitive genes into bacteria to reverse resistance.

Traditional approaches to phage therapy rely on the ability of viruses to kill their bacterial prey. However, narrow host range and the ability of bacteria to become resistant to infection mean that in practice, using phage to replace antibiotics is currently not feasible. An alternative approach has been to use phage in combination with antibiotics. For instance, it has been shown that using phage to disrupt the SOS response in bacteria can lead to heightened sensitivity to a range of antibiotics.

Edgar *et al.* sought to use phage to reverse resistance to streptomycin, an antibiotic that targets the 30S ribosomal subunit of both Gram-positive and Gram-negative bacteria. The authors isolated strains of *Escherichia coli* K12 that were resistant to streptomycin owing to mutations in *rpsL*, which encodes a conserved 30S ribosomal component, and transformed them with plasmids that contained a copy of the wild-type *rpsL* gene. They observed a ~tenfold decrease in the minimum inhibitory concentration (MIC) of streptomycin needed to block growth, indicating that the presence of *rpsL* confers streptomycin sensitivity in a dominant manner. The authors then engineered *rpsL* into phage λ as part of a resistance cassette, and a streptomycin-resistant strain was lysogenized with the phage to allow incorporation of wild-type *rpsL* into the bacterial genome. The resultant strain exhibited a tenfold decrease in MIC for streptomycin. Furthermore, if two copies of the *rpsL* gene, one wild type and one containing numerous silent mutations to avoid recombination, were engineered into the phage, this dropped even further to levels comparable with streptomycin-susceptible strains. Importantly, if viruses were engineered to introduce wild-type copies of *gyrA*, the product of which forms part of the enzyme gyrase, the authors were able to reverse resistance to the antibiotic nalidixic acid.

Taken together, these data suggest that provided that a dominant-sensitive gene can be identified, this approach may be viable for use with a range of antibiotics to which bacteria have evolved resistance.

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ORIGINAL RESEARCH PAPER Edgar, R. *et al.* Reversing bacterial resistance to antibiotics by phage-mediated delivery of dominant sensitive genes. *Appl. Environ. Microbiol.* 23 Nov 2011 (doi:10.1128/AEM.05741-11)
FURTHER READING Lu, T. K. & Collins, J. J. Engineered bacteriophage targeting gene networks as adjuvants for antibiotic therapy. *Proc. Natl Acad. Sci. USA* **106**, 4629–4634 (2009)

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