Genetically engineered phages for therapeutics: proceed with caution

To the Editor — Barring a few hiccups, phage therapy may soon be at the forefront of treatment for deadly bacterial infections caused by multi-drug-resistant bacteria. Although the potential for clinical application has existed since their discovery a century ago, these nanoparticles have not yet achieved success as a full-blown antimicrobial therapy. This is perhaps because, thus far, preclinical and clinical studies have provided little evidence of robust efficacy. The recent treatment of a *Mycobacterium abscessus* infection in a 15-year-old teenager with cystic fibrosis using a three-phage cocktail has revolutionized the way we look at phage therapy today¹. In this ground-breaking study showcasing the clinical implications of basic research, the patient recovered from multi-drug-resistant, disseminated mycobacterial infection after treatment with genetically engineered phages whose repressor genes were removed. While this is the first therapeutic application of phages to treat mycobacterial infection and the first approach to use genetically engineered phages, it also raises a concern. There is no control over the potential release of such genetically engineered phages into the environment when they are used as a therapy.

Lysogeny is the mode by which a phage increases its survivability when the conditions are unfavorable. In this phase, the phage persists in a dormant state in the bacterial host². The phage may switch

from this lysogenic state to the lytic cycle to generate progeny phages, killing the host cell in the process. Lysogenic phages — which do not kill the host bacteria — cannot be used for antimicrobial therapy, which explains why the authors genetically engineered the phages *ZoeJ* and *BPs* to obtain obligate lytic phages for clinical application. However, questions remain regarding the effects of releasing such genetically engineered lytic phages, during and after the treatment, into the environment. The authors tested the effects of their phages on a small set of bacterial hosts and found no evidence of non-specific killing. However, this was but a limited test of the range of hosts for the phages and their impact, which does not lend itself to definitively conclude that these engineered phages have a restricted host range. Such a conclusion would require a rigorous and comprehensive set of tests conducted against more diverse bacterial hosts.

With increasingly rapid advances in phage therapy, the use of genetically engineered phages will need to be scrutinized very carefully, as they may influence bacterial community dynamics, genome evolution and ecosystem biogeochemistry³. The question therefore arises as to whether the concerns associated with the use of genetically engineered microorganisms should also be applied to genetically engineered bacteriophages? While phages cannot directly infect

humans, plants or animals, they may adversely affect these organisms by altering their associated microbiota.

It is estimated that there are 10^{31} phages on Earth⁴. Nature's selection pressures and survival of the fittest are highly efficient tools that have generated a rich repertoire of competitive bacteriophages belonging to both lysogenic and 'obligate lytic' types in the environment⁵. These existing phages could be exploited for their therapeutic potential. In this manner, we may overcome the need for genetically engineered bacteriophages and limit their release into the environment. □

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Competing interests

The authors declare no competing interests