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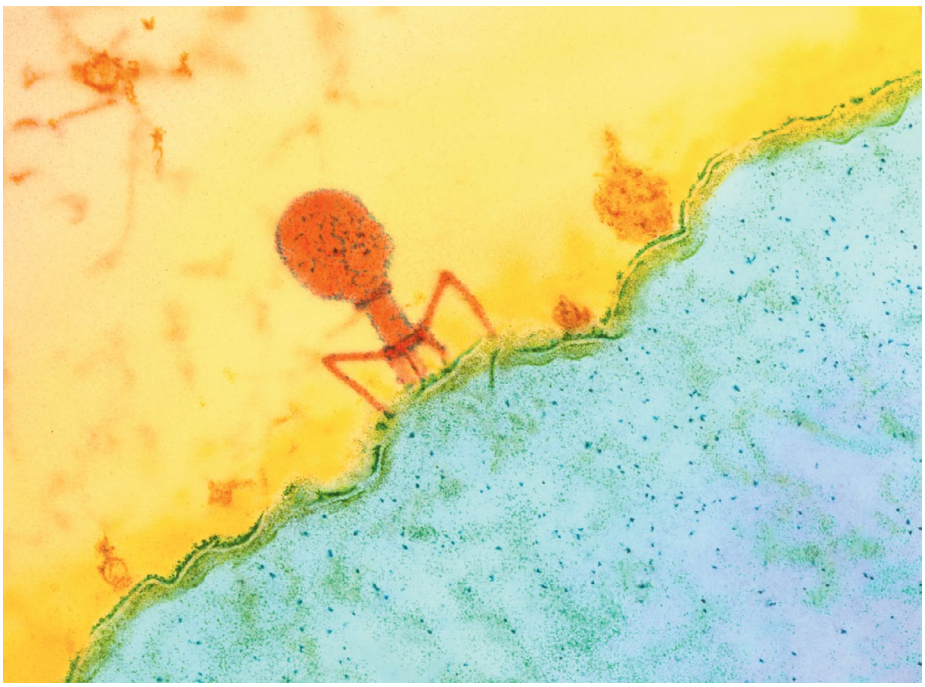
The phage–bacteria arms race

In this issue of *Nature Structural & Molecular Biology*, we are publishing two studies investigating the mechanisms of how bacteria fight phage invasion, and how phages fight back.



Colored transmission electron micrograph of T4 bacteriophage infecting *E. Coli*.

On our February cover, we feature a colored transmission electron micrograph of a T4 bacteriophage virus attacking an *Escherichia coli* bacterium — images such as this are admittedly among the most spectacular pieces of data ever acquired. We chose this image to illustrate two papers published in this issue, both around the theme of the phage–bacteria arms race. Bacteria and archaea use CRISPR–Cas systems as a defense mechanism targeting foreign nucleic acid sequences and thus protecting them from phage or foreign plasmid invasion. In response, phages developed anti-CRISPR (Acr) proteins that target and inhibit CRISPR–Cas systems. A wide variety of Acrs have been identified, targeting different CRISPR–Cas systems through different mechanisms, of broad interest. In the first study we feature in this issue, Yu et al. investigate the mechanism of inhibition of bacterial Cas activity by the anti-Cas9 protein AcrIIA27, showing that this Acr inhibits Cas9 activity via interaction with the scaffold RNA. Additionally, the authors develop an RNA truncation optimization strategy that has the potential to improve genome editing. Another tool in the bacterial anti-phage defense arsenal are retrons, prokaryotic reverse transcriptase systems. In the second study highlighted, Jasnauskaitė et al. find that the *E. coli* retron Eco2 is triggered by phage nuclease activity to act as an antiviral by cutting tRNAs and shutting down translation, which brings phage replication to a halt. This study demonstrates the potential of minimal retron systems, such as Eco2, as a tool in retron-based genome engineering systems.

In addition to the interest in mechanisms underlying phage–bacteria interactions as a source of new tools for genome engineering, phage-based therapies have garnered much attention and investment (B. Johnson, *Nat. Biotechnol.* **41**, 438–440; 2023) in recent years. Their potential has long been known, since Félix d'Herelle first discovered bacteriophages, associated with dysentery, and proposed they be used as therapeutic agents against bacterial infections more than one hundred years ago (F. d'Herelle, *C. R. Acad. Sci.* **165**, 373–375; 1917). With either their natural, or engineered, selectivity for specific bacterial strains, phage-based therapies promise to remove infectious bacteria without harming the beneficial microbiome. This is an exciting field of both basic and applied research that we will be following with great attention in upcoming years and hope to continue to feature in our pages.

In this issue, we are also publishing a study from Nagahata, Kato, Yamada et al. providing structural insight into CRISPR–Cas9 evolution. By analyzing cryo-electron microscopy structures of four phylogenetically diverse RNA-guided nucleases, in complex with their guide RNA and target DNA, the authors characterized successive structural changes to RNA-guided nucleases associated with their function in adaptive immune systems. We are also excited to feature a Review from Pindi and Palermo titled *Computation and deep-learning-driven advances in CRISPR genome editing*, in which the authors discuss how different computational and modeling tools can be applied to engineering and improving CRISPR systems. In this insightful Review, the authors also reflect on both the challenges of applying these computational tools, as well as the insight they can bring to understanding the mechanisms underlying how CRISPR systems work. The continued investment and interest of both scientific and biotechnology communities in CRISPR-based systems for genome engineering signals the strength and excitement in the field. As editors, we are similarly excited to see what new tools and therapeutic avenues will open in the years to come.

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