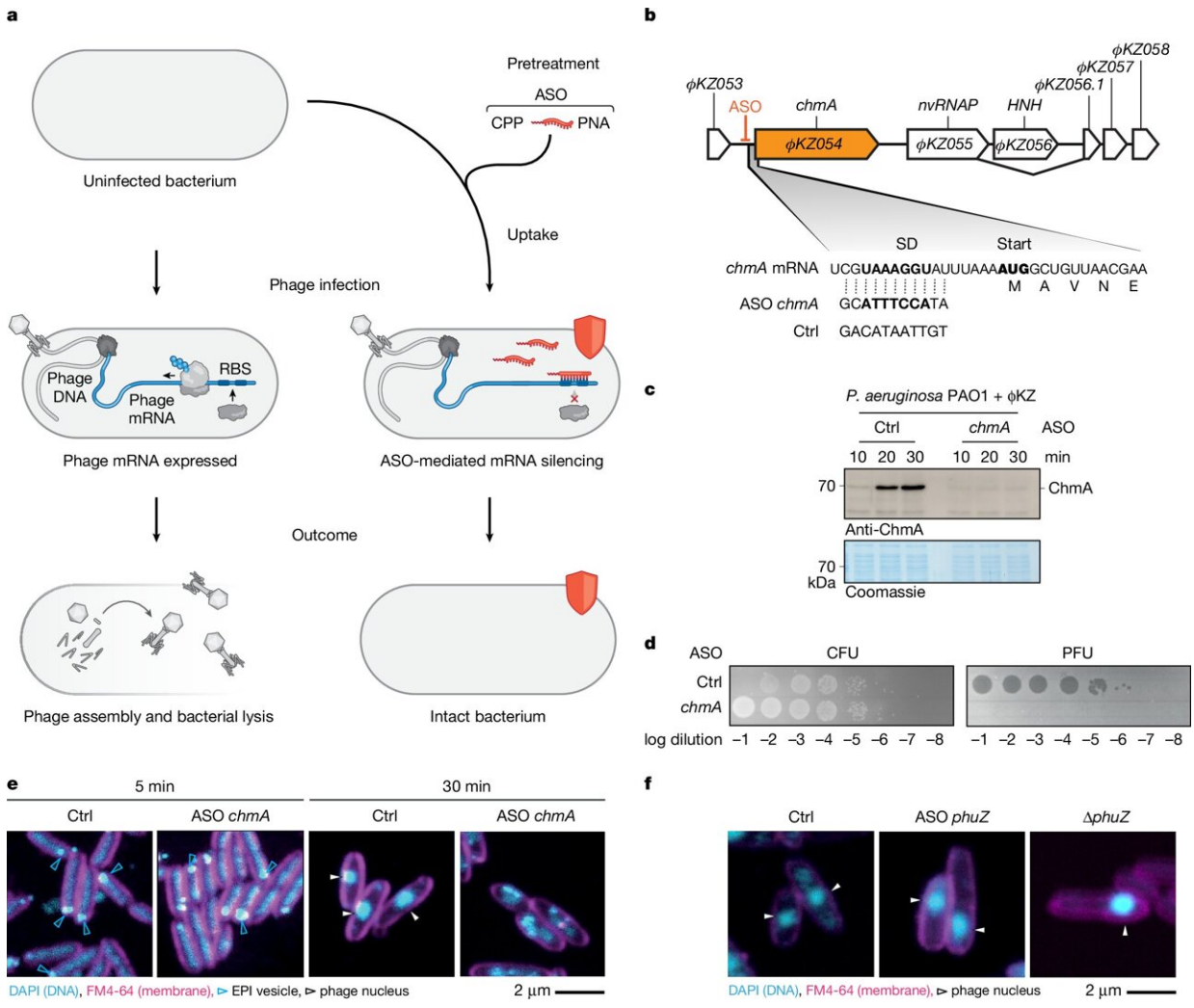
RNA technology 'hacks' into phage replication, offering new insights into molecular interactions

September 10 2025, by Andreas Fischer



ASOs silence ΦKZ transcripts in Pseudomonas. Credit: *Nature* (2025). DOI: 10.1038/s41586-025-09499-6

Bacteriophages, or phages for short, are viruses that infect bacteria. Using phages therapeutically could be very useful in fighting antibiotic-resistant pathogens, but the molecular interactions between phages and host bacteria are not yet sufficiently understood. Jörg Vogel's research group at the Helmholtz Institute for RNA-based Infection Research (HIRI) and the Institute of Molecular Infection Biology (IMIB) in Würzburg has now succeeded in specifically interfering with phage reproduction using a molecular tool called antisense oligomers (ASOs).

According to the researchers, this innovative RNA technology offers new insights into the molecular world of phages and is expected to advance the development of future therapeutic applications. The study has been published in the journal *Nature*.

Like humans, bacteria have to cope with viruses—known as bacteriophages, or phages for short. Phages invade bacteria, hijack their cellular machinery, multiply, and cause the bacterial cell to burst. This releases new phages, which then go on to infect other bacteria. Phages are harmless to humans because they target only bacteria. They are also quite selective: Most phages are specialized in infecting specific host bacteria, including bacterial pathogens.

"By attacking and decimating pathogens, phages protect our health as a side effect—in a kind of covert operation, so to speak. Harnessing their therapeutic potential, especially against the backdrop of increasing antibiotic resistance, would be a game changer," says Jörg Vogel, lead author of the study.

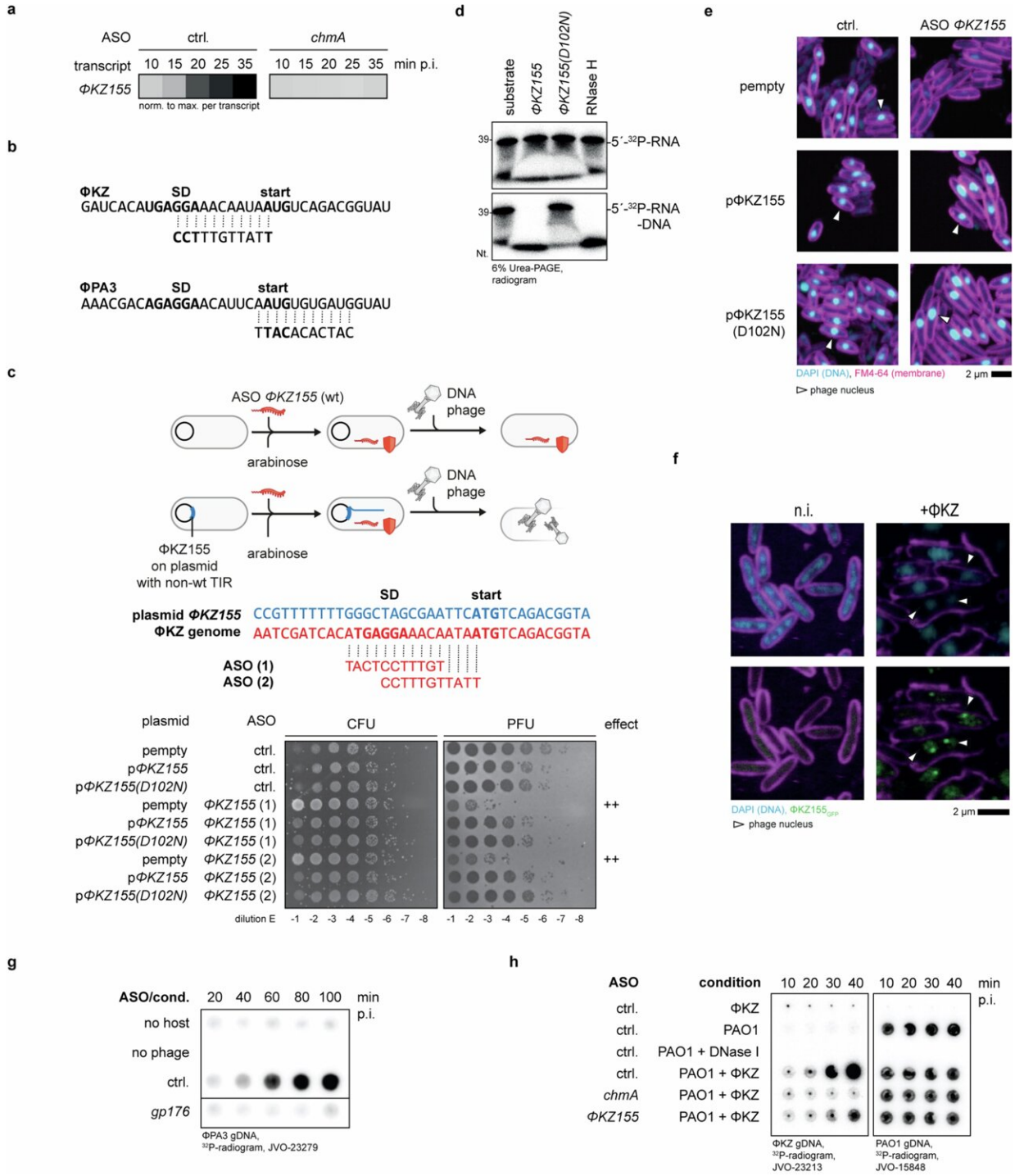
Vogel is the founding director of the Helmholtz Institute for RNA-based Infection Research (HIRI) in Würzburg, a site of the Braunschweig Helmholtz Center for Infection Research (HZI) in cooperation with the

Julius-Maximilians-Universität Würzburg (JMU). He also heads the Institute of Molecular Infection Biology (IMIB) at the JMU Medical Faculty.

Molecular tool introduced—phage manipulated

"In order to use phages therapeutically, we need a much better understanding of the molecular interaction between phages and host bacteria," says Milan Gerovac, the study's first author. Gerovac was a postdoc in Vogel's laboratory and now runs the junior research group Complexes in Phage-Infected Cells at the HZI.

"Not much is known about this. One reason being that phages protect their genetic material from cellular defense systems of the bacteria with a kind of protective shield. Unfortunately, this shield is also quite effective against common molecular investigation methods."



I ΦKZ155 involvement in the phage replication cycle. Credit: *Nature* (2025). DOI: 10.1038/s41586-025-09499-6

To decipher the molecular phage-host relationship, they need a new approach—and that is exactly what the HIRI researchers did in their current study. With an innovative RNA-based molecular tool known as antisense oligomers (ASOs), they succeeded in interfering specifically with the phage reproduction cycle.

"The ASOs introduced into the bacterial cell switched off the synthesis of specific phage proteins at a key point," Gerovac explains. "We were able to 'hack' into phage replication with the ASOs, so to speak."

ASOs can be synthesized in a lab to bind precisely to specific sites on messenger RNA (mRNA), which transmits information from the genome to the protein synthesis machinery. The ASOs act as a stumbling block at the starting point of protein production; the mRNA can no longer be read, so protein synthesis does not begin. Antibacterial ASOs, also known as programmable antibiotics or asobiotics, have been studied for some time in Vogel's laboratory.

"Since ASOs are known to inhibit protein synthesis in bacteria, we suspected that they could also do so in phages. This is because phages reproduce with the help of the host bacteria's cellular machinery," says Vogel. "And we were absolutely right."

In focus: A jumbo phage that kills hospital germs

Using ASO technology, the researchers successfully prevented phage propagation in various phage-bacteria pairs, demonstrating that the approach is broadly applicable. Their research focused on a jumbo phage called ΦKZ that could potentially treat dangerous infections of wounds, airways, and lungs caused by the hospital germ Pseudomonas aeruginosa.

"Jumbo phages have a very large genome," Gerovac explains. "With the

help of ASOs, we were able to systematically switch off the synthesis of a large number of phage proteins. Using this knock-down screening approach, we identified previously unknown proteins central to phage propagation."

The researchers hope that ASO technology will be widely used in phage research to better understand the fundamental molecular mechanisms of phages and advance the development of new therapeutic approaches in the fight against bacterial pathogens.

More information: Milan Gerovac et al, Programmable antisense oligomers for phage functional genomics, *Nature* (2025). DOI: 10.1038/s41586-025-09499-6

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