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ASO-based functional genomics reveals new phenotypes of essential genes in nucleus-forming jumbo phages

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Jumbo phages with large genomes (200-600 kb) are fascinating models to study RNA translocation across membranes and intracellular structures. Many such jumbo phages including the *Pseudomonas* phage phiKZ build and replicate with an intracellular structure in the infected bacterium, the so-called phage nucleus. This protects their genome from cytosolic phage defense proteins, but it also necessitates phage mRNA export into the host cytosol for translation by host ribosomes. The mRNA export machinery is currently unknown, and functional screens have been severely hampered by the general genetic inaccessibility of nucleus-forming jumbo phages. To overcome this limitation, we have introduced non-genetic mRNA knockdown using exogenous delivery of programmable antisense oligomers (ASOs) to silence genes of both DNA and RNA phages (Gerovac M et al. 2025). A systematic screen of core and accessory genes of phage ΦKZ, coupled to RNA-sequencing and microscopy analyses, has discovered previously unrecognised proteins that are essential for phage propagation and that, upon silencing, elicit distinct phenotypes at the level of the phage and host response. I will give an update on where we stand with microbial ASO technology in general and with nucleus-forming phages in particular.

Reference #1

Gerovac M, Buhlmann L, Zhu Y, Đurica-Mitić S, Rech V, Carien S, Gräfenhan T, Popella L, Vogel J (2025)

Programmable antisense oligomers for phage functional genomics
Nature 646(8087):1195-1203

Reference #2

Reference #3

Author: VOGEL, Jörg (1 Helmholtz Institute for RNA-based Infection Research (HIRI), 2 University of Würzburg)

Presenter: VOGEL, Jörg (1 Helmholtz Institute for RNA-based Infection Research (HIRI), 2 University of Würzburg)

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