To be or Not be Virulent as a Nucleus-forming Phage

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Jumbo phages encode hundreds of uncharacterized factors that orchestrate host takeover and stress responses. Yet, our understanding of which of these proteins engage in stable interactions with the host gene expression machinery remains limited. Many of these factors lack sequence similarity and have poorly predictable structures, hindering computational annotation of functions and prediction of interaction partners. At the same time these factors represent a playground for discoveries.

Our goal is to map the complexes formed between phage factors and host RNA polymerases and ribosomes to uncover novel mechanisms of host takeover at the level of gene expression and cellular stress response. Using gradient fractionation coupled to proteomics, we previously identified a ΦKZ phage factor, ΦKZ014, that targets the ribosome in *Pseudomonas* cells to boost phage replication (Gerovac et al. 2024, Wannasrichan et al. 2025). We now extend this approach to additional jumbo phages that form a phage nucleus, including e.g. *Escherichia* phage Goslarvirus and others and compare the insights on the phage and host sides.

Subsequently, we functionally characterise these factors and explore the complex replication cycle of the *Chimalliviridae* family by integrating transcriptomics and structure-based interaction predictions, as well as knockdowns (Gerovac et al., 2025). Furthermore, we characterise their contribution to phage replication under stress conditions. Here, we realised that these phages can share a replication cycle where the hosts are not lysed and can outgrow into a colony (Dougherty et al. 2026). Together, our findings reveal previously unknown interfaces and regulatory pathways exploited by jumbo phages, offering potential strategies to combat antimicrobial resistance.