

The Phage Manifesto

It is critical that NIH and NSF develop plans for a major expansion of research in phage biology. Bacteriophages are key factors in microbial pathogenesis, major tools in biotechnology, integral components in global ecology, and, potentially, a powerful weapon against the rising tide of drug-resistant bacterial pathogens and microbial bioweapons. Unfortunately, there are few laboratories ready to engage any of these issues. Classical phage biology, supported by many NIH and NSF grants, dominated molecular biology into the 1970's and generated much of its core knowledge base. Now support for phage biology has been reduced to a mere handful of grants, mostly to principal investigators already late in their careers. The scheduled extinction of the NIH study section responsible for most phage biology grant proposals merely puts a end to an era of unabated decline in bacteriophage research.

Many factors contributed to this decline, including the highly visible exodus from the field of many prominent scientists who viewed phage as powerful experimental tools and means to an end, rather than an intrinsically important component of modern microbiology. In any case, there are very few young scientists with training in phage biology, and fewer still being trained, especially in the United States. Thus, although the general scientific community thinks that phage biology is a mature field, the reality is that very little is known about any bacteriophages outside of a few classic systems. In a real sense, the new phage biology that is needed for progress in such diverse areas as bacterial genomics, marine ecology, microbial pathogenesis and phage-based therapeutics lacks a fundamental base, because we do not know that our detailed knowledge of the classic coliphages can be extended to phages of other bacteria. In fact, recent results suggest otherwise. Recently, a *Bordetella* phage was described which apparently uses an HIV-type reverse transcriptase to mutagenize its own tail fiber gene (*Science* **295**:2091). Classically, filamentous phages were thought to be exclusively virulent until it was shown that active cholera derives from the induction of an M13-like prophage of *V. cholerae* (*Science* **272**:5270). The shiga-like toxin of hemorrhagic *E. coli* turns out to be a phage protein and its release is caused by phage lysis (*Molec. Microbiol.* **44**:957). These and other developments suggest that our knowledge of bacteriophages is an inch wide and a mile deep.

The NIH, NSF and other national funding agencies are the only forces capable of attracting young scientists to phage biology, which is in a kind of potentially still-born infancy. Concrete steps would be *to promulgate RFAs in aspects of phage biology of many different bacterial genera* and *to assign the responsibility for research proposals in bacteriophage biology to new peer review entities with appropriate expertise*. Failure to take action will cause serious delays in developing a component of modern microbiology critical to our understand of bacterial pathogenesis and ecology. Moreover, public perception is primed to appreciate bacteriophage as an ally, and a natural one at that, in the struggle against bacterial disease and bioterrorism. Phage biology, once a great American intellectual province, should languish no more.