THE BIG WIDE WORLD OF BACTERIOPHAGES: WHAT ARE THEY AND HOW DID THEY GET TO BE THAT WAY?

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Bacteriophages are the most numerous biological entries in the biosphere, and outnumber all other forms of life added together. Genomic characterization of just 500 of the approximately 10^{31} particles shows them to encompass enormous genetic diversity and to be replete with genes that have not been found elsewhere. Phages thus offer the largest reservoir of unexplored genes in the biosphere.

We have determined the sequences of 60 mycobacteriophages all of which share a common bacterial host. These are highly – although not uniformly – diverse and have genomes that are characteristically structured with mosaic architectures. Each genome can thus be considered as a unique arrangement of a set of modules that are shared among the population. The evolutionary mechanisms giving rise to this population are unlikely to involve targeted recombination mechanisms and probably involve illegitimate recombination in which there is little preference for the participating molecules or positions within them.

We know little about the functions of the vast majority of phage genes although we have recently developed methods that will help to elucidate them. Functions can be predicted from a small number of genes that do match known database entries, although many of these are surprises, since they have not been found previously in phage genomes. The roles of these in phage growth are unclear.

We have focused on the genomic characterization of mycobacteriophages in the belief that they can readily be exploited for understanding and manipulating their bacterial hosts including *Mycobacterium tuberculosis*. We have devised a large set of phage-derived tools such as integration vectors, recombineering systems, and transposon delivery vehicles, as well learning novel insights into mycobacterial physiology such as biofilm formation.

Finally, mycobacteriophages show considerable promise as tools for clinical microbiology of *M. tuberculosis*, especially in the development of diagnostic tools that can accurately and rapidly report the drug susceptibility profiles of clinical tuberculosis specimens. A variety of recombinant phages have been constructed and are currently being evaluated for this purpose.